Studies Towards the Total Synthesis of Tagetitoxin

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I, Amandeep Kaur Sandhu, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Tagetitoxin is a phytotoxin which was isolated in 1981 from the plant pathogenic bacterium, *Pseudomonas syringae* pv. *tagetis*. It is an inhibitor of chloroplast and bacterial RNA polymerases, but more importantly, it is the only known natural product which is a selective inhibitor of eukaryotic RNA polymerase III. Synthesis of this compound would therefore be useful for biologists studying transcription. The proposed structure of tagetitoxin is highly functionalised and consists of two bridged heterocyclic rings, however the absolute configuration is not known and other ambiguities remain. Recently, the validity of this structure has been challenged and has provided further motivation for its synthesis.

Our initial route to form the tagetitoxin core involved employing a carbene-mediated ring expansion strategy which had been successfully tested on monocyclic substrates. We planned to form the ring expansion precursor, a 1,3-oxathiolane, from the corresponding *tert*-butyl β-hydroxysulfide using a novel reaction developed in our group. Methodology work was carried out on simpler substrates in order to investigate the scope of this reaction. It was found that this reaction worked well on substrates containing a range of functional groups and moderate to good yields were obtained in general. Although this provided a basis for the final stages of the synthesis, many difficulties were encountered during the initial stages which led to an alternative strategy being adopted.

During other work in the group, the first synthesis of the bicyclic tagetitoxin core was achieved *via* the cyclisation of a thiol onto an electrophilic ketoester. This strategy was thus employed in approaches to an analogue of the natural product, decarboxytagetitoxin, and tagetitoxin itself. Starting from a carbohydrate precursor, an advanced intermediate for the synthesis of decarboxytagetitoxin was prepared, although time constraints prevented completion of the synthesis. Difficulties in forming a diol intermediate through Payne rearrangement meant that only limited progress was made towards the synthesis of tagetitoxin.

Sabh te vadaa Satgur Nanak
jin kal rakhee meree

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ਮੈ ਵੱਧ ਤੋ ਵੱਧ ਧੰਨਵਾਦ ਕਰਦੀ ਹਾਂ ਧੰਨ ਧੰਨ ਸ੍ਰੀ ਗੁਰੂ ਗ੍ਰੰਥ ਸਾਹਿਬ ਜੀ ਦਾ ਜਿਨਾਂ ਦੀ ਕ੍ਰਿਪਾ ਨਾਲ ਮੈ ਪੀ. ਐਚ. ਡੀ. ਨੂੰ ਪੂਰਾ ਕੀਤਾ ਹੈ । ਇਸ ਤੋ ਬਾਅਦ ਮੈ ਧੰਨਵਾਦ ਕਰਦੀ ਹਾਂ ਸੰਤ ਬਾਬਾ ਮਾਨ ਸਿੰਘ ਜੀ ਦਾ ਜਿਨਾਂ ਨੇ ਮੈਨੂੰ ਗੁਰੂ ਗ੍ਰੰਥ ਸਾਹਿਬ ਜੀ ਨਾਲ ਜੋੜਿਆ ।ਉਨਾਂ ਦੇ ਬਚਨਾਂ ਦਾ ਸਦਕਾ ਮੈ ਇਸ ਡਿਗਰੀ ਨੂੰ ਪੂਰਾ ਕੀਤਾ ।

ABBREVIATIONS

A	adenine
AA	asymmetric aminohydroxylation
ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
abs.	absolute
AIBN	azobisisobutyronitrile
app.	apparent
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
***n*-Bu**	*n*-butyl
***t*-Bu**	*t*-butyl
Bz	benzoyl
C	cytosine
Cbz	carboxybenzyl
CI	chemical ionisation
COSY	correlation spectroscopy
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	dichlorodicyanoquinone
DEPT	distortionless enhancement by polarisation transfer
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide

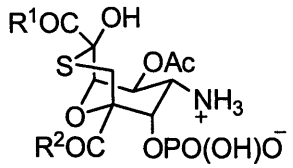
DNA	deoxyribonucleic acid
dppf	1,1′-bis(diphenylphosphino)ferrocene
ee	enantiomeric excess
EI	electron ionisation
eq	equivalent
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
G	guanine
HMBC	heteronuclear multiple bond connectivity
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra red
L	ligand
LDA	lithium diisopropylamide
***m*-CPBA**	*meta*-chloroperoxybenzoic acid
Me	methyl
mRNA	messenger RNA
Ms	methylsulfonyl
MS	mass spectrometry
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NTP	nucleoside triphosphate
Nu	nucleophile
o/n	over night
PG	protecting group
Ph	phenyl
PHAL	phthalazine

PMB	*para*-methoxybenzyl
PMBz	*para*-methoxybenzoyl
PMP	*para*-methoxyphenyl
PNP	*para*-nitrophenyl
Pol	polymerase
Pr	propyl
R	alkyl
RNA	ribonucleic acid
rRNA	ribosomal RNA
RT	room temperature
SAE	Sharpless asymmetric epoxidation
sat.	saturated
SM	starting material
snRNA	small nuclear RNA
T	thymine
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
TOF	time of flight
tRNA	transfer RNA
Ts	*para*-toluenesulfonyl
U	uracil
UTP	uridine triphosphate

CONTENTS

1. INTRODUCTION

Tagetitoxin **1** (Figure 1) is a highly functionalised natural product which is produced by a pathogenic bacterium. It is proposed to consist of two bridged heterocyclic rings; an oxathiane in the boat conformation and a tetrahydropyran in the chair conformation. Certain ambiguities, however, exist concerning the structure of tagetitoxin and recently its structural validity has been challenged. These issues can only be resolved upon the completion of its synthesis.



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

Figure 1: Tagetitoxin

From a biological point of view, tagetitoxin is an inhibitor of bacterial and chloroplast RNA polymerases, but most significantly, it is the only known natural product shown to selectively inhibit RNA polymerase III in eukaryotes. These enzymes play a prominent role in RNA transcription. Although, tagetitoxin is commercially available, its high cost is a limiting factor for molecular biologists studying its effects on the transcription process. In this respect, the synthesis of this compound would be beneficial to the biological community.

In order to appreciate the inhibitory effects of tagetitoxin, the process of transcription and the roles of the RNA polymerases will be discussed.

1.1 Transcription

During transcription, genetic information is transferred from DNA to RNA. The main types of RNA are;

- mRNA - this acts as a mobile copy of the genetic information and is translated to form polypeptides and, eventually, proteins.

- rRNA - a key component of ribosomes, where translation of mRNA to polypeptides takes place.
- tRNA - responsible for bringing a specific amino acid to the ribosome, which is subsequently transferred to the growing polypeptide chain.

Initially, transcription in prokaryotes will be examined, followed by the more complicated transcription processes in eukaryotic cells.

1.1.1 Transcription in prokaryotes

Prokaryotic transcription occurs in the cytoplasm of the cell, and is carried out by the enzyme RNA polymerase. RNA polymerase from *E. coli* is the most studied enzyme in this group. It consists of five subunits, including a polypeptide known as the σ-factor. The latter is instrumental in bringing about the initiation of transcription by recognising a promoter site on the gene.[1] Promoter sites are chemical triggers containing certain base sequences which "switch on" the desired gene and provide a binding site for the enzyme. In prokaryotes there is a promoter sequence (at −10 base units), which usually consists of the nucleotide sequence TATAAT, and is referred to as the Pribnow box.[1] This is a crucial component in the initiation of transcription in prokaryotes. It is at this region where the DNA helix unwinds and where the polymerase can access the strand of DNA to be copied. Once the enzyme is bound to the DNA template, the σ-factor is responsible for stabilising the resulting complex.

As RNA polymerase moves along the DNA template (from the 3′ to 5′ direction), the latter is temporarily unwound to expose the bases. RNA polymerase constructs RNA by assembling a strand of base pairs complementary to those on the DNA. This is known as the elongation phase. An important point to note here is that if the base adenine is exposed on the DNA molecule, the complementary base pair on the RNA strand will be uracil, not thymine, as the latter is not found in RNA.[2] RNA polymerase catalyses the polymerisation reaction:

$$RNA_n + NTP \rightarrow RNA_{n+1} + PP_i$$

The RNA chain is constructed *via* reaction of the 3′ hydroxyl group of the previously

incorporated nucleotide with the α-phosphate of the incoming nucleoside triphosphate (NTP) (Figure 2). Pyrophosphate (PP_i), which is released during the reaction, is subsequently hydrolysed to the inorganic phosphate (P_i), by the enzyme pyrophosphatase. The free energy released during this hydrolysis step drives polymerisation forward, making it virtually irreversible.[3]

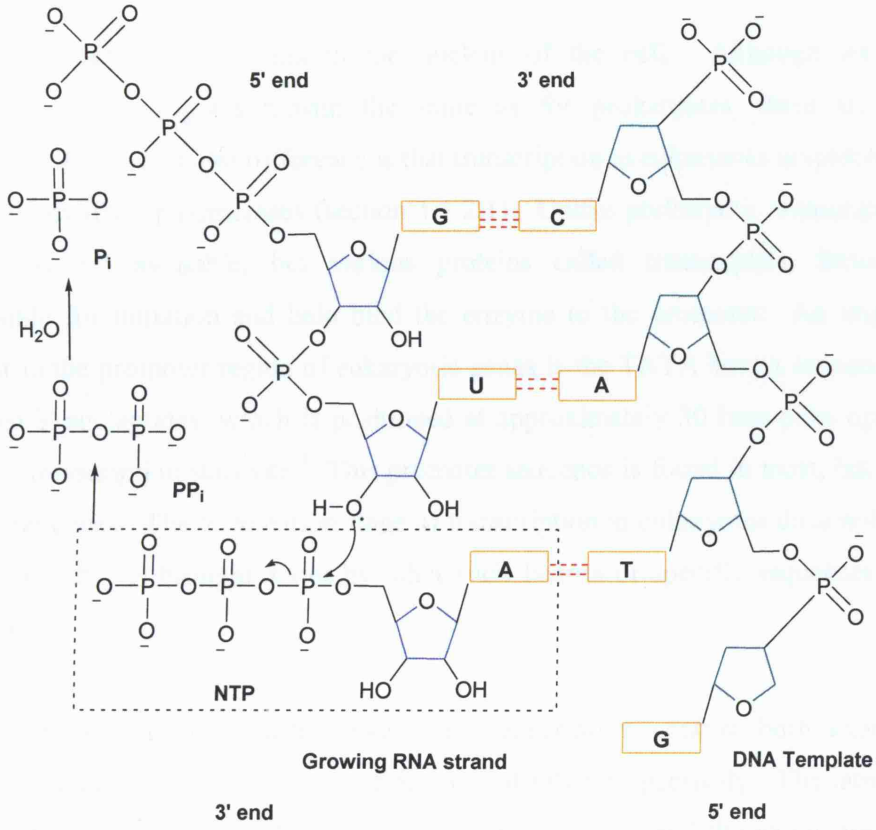


Figure 2: RNA polymerisation

RNA polymerases can incorporate between 20-50 nucleotides per second into a growing RNA molecule. In order to do this the enzyme has to remain attached to the DNA over long sections of the template. However the enzyme-template interaction must be weak enough so that enzyme can move from nucleotide to nucleotide on the template. The σ-factor is released during the elongation phase, following a conformational change of the enzyme. This allows the interaction between the polymerase and DNA template to become "loose" so the enzyme can move along the template with ease.[1] Phosphate bond cleavage as the NTPs are incorporated into the RNA chain provides the energy necessary to facilitate the movement of the enzyme.[3]

Termination of transcription occurs when RNA polymerase reaches a specific base sequence on the DNA template, and may be facilitated by an additional protein called the ρ-factor. The polymerase then releases the newly formed RNA chain and dissociates itself from the DNA template

1.1.2 Transcription in eukaryotes

Eukaryotic transcription occurs in the nucleus of the cell. Although the main principles of transcription remain the same as for prokaryotes, there are some disparities. The first major difference is that transcription in eukaryotes is catalysed by three distinct RNA polymerases (section 1.1.2.1). Unlike prokaryotic transcription, a σ-factor is not available, but various proteins called transcription factors are responsible for initiation and help bind the enzyme to the promoter. An important element in the promoter region of eukaryotic genes is the TATA box; a sequence rich in A and T nucleotides, which is positioned at approximately 30 base pairs upstream from the transcription start site.[4] This promoter sequence is found in most, but not all eukaryotic genes. The termination stage of transcription in eukaryotes does not utilise the ρ-factor, but is brought about by other such factors or specific sequences in the DNA template.

RNA transcripts formed during eukaryotic transcription contain both exons and introns, which are coding and non-coding parts of DNA respectively. The introns are removed from the primary RNA molecule during splicing, and the exons are joined together. The presence of introns in prokaryotic RNA is much rarer. Eukaryotic mRNA also requires further post transcriptional modifications, such as the respective capping and polyadenylation of the 5′ and 3′ ends of the molecule.[5] The benefits of these adaptations include protection from degradation of mRNA by exonucleases and stability during translation.

1.1.2.1 RNA polymerases

There are three types of RNA polymerases found in the nucleus of eukaryotic cells:[3]

1. **RNA polymerase I** – synthesises large ribosomal RNAs.

2. **RNA polymerase II** – responsible for the formation of mRNAs and most small nuclear (sn) RNAs.
3. **RNA polymerase III** – forms a range of low molecular weight RNAs including tRNA, 5S ribosomal RNAs and some snRNAs.

The three polymerases are inhibited, to varying degrees, by the toxin α-amanitin. In mammals, for example, RNA polymerase II is the most affected enzyme with 25 ng/mL of α-amanitin causing 50% inhibition. RNA polymerase III exhibits intermediate resistance (50% inhibition at 20 μg/mL), but RNA polymerase I is completely resistant up to a concentration of 400 μg/mL of the toxin.[6] This varying resistance is used as a diagnostic tool for determining which enzyme is responsible for the transcription of various RNA molecules.[7]

The RNA polymerases typically consist of 12-17 subunits; two of these are large (M_r = 120 000-220 000), while the rest are small (M_r <50 000).[4] Some of these subunits are unique to a particular polymerase, whilst others may be common to all three. The active site is positioned at the bottom of a catalytic pocket which is formed between the two large subunits. Mg^{2+} ions are also present in the active site and are involved in catalysing all the reactions that take place.[8]

The genes that are transcribed by RNA polymerases I, II and III are termed class I, II and III genes respectively. A transcription factor which is used by all three RNA polymerases is the TATA binding-protein (TBP). This is employed regardless of whether or not there is a TATA box present in the promoter. Prior to the transcription of each class of gene, the TBP binds with various TAFs (TBP associated factors) to form a complex, for example, SL1, TFIID or TFIIIB (Figure 3).[7] These complexes are ultimately responsible for recruiting the polymerase in question to the DNA template.

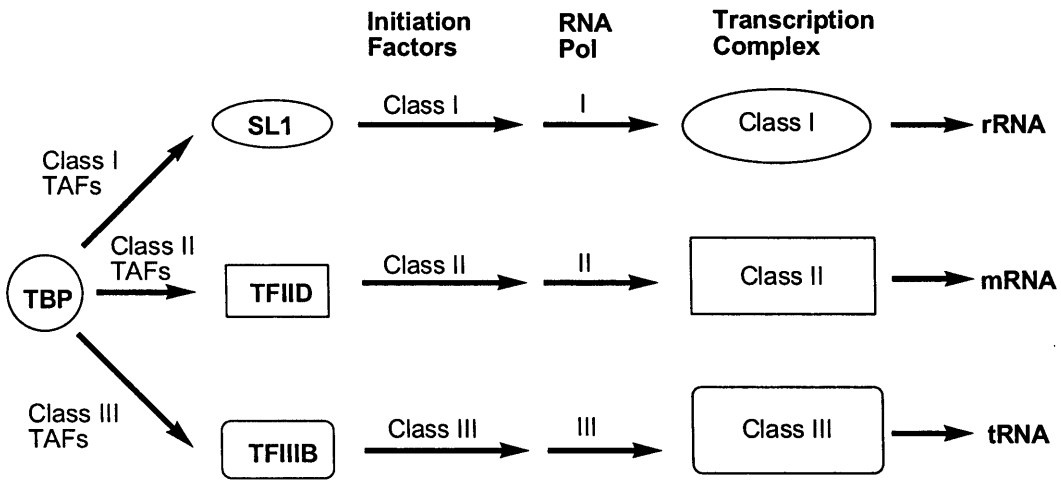


Figure 3: Transcription of class I, II and III genes

1.1.2.1.1 RNA polymerases I and II

RNA polymerase I consists of 12 subunits and is responsible for 50-70% of all nuclear transcription.[4] It does not require a TATA box to be present in the promoter, but instead relies on a sequence in the gene called the UCS (upstream control sequence). This essentially binds the transcription factors UBF (upstream binding factor) and SL1 which in turn recruit the polymerase. Termination occurs with the aid of the transcription factor TTF-1, which is specific for this polymerase.[9,10]

RNA polymerase II is the most studied of the eukaryotic polymerases, probably because it transcribes all protein-coding genes. This also consists of 12 subunits. Transcription is initiated when various transcription factors, including TFIID, bind to the TATA box. This, in turn, enables RNA polymerase II to bind to the template. In cases where there is no TATA box in the promoter region, binding of TFIID still takes place, albeit without sequence specificity, and facilitates initiation. During the elongation stage, additional proteins called elongation factors are present. These prevent the RNA polymerase from pausing along the template. Termination is believed to occur when the enzyme reaches the sequence AAUAAA or a GC rich sequence.[4] It has also been suggested that termination is brought about by a pausing process.[11]

Recently, greater insight into the mechanism of transcription by RNA polymerase II

has been attained due to the pioneering work of Roger Kornberg, who was awarded the Nobel Prize for Chemistry in 2006.[12] Studies by Kornberg *et al.* have provided the X-ray structure of RNA polymerase II at 2.8 Å resolution.[13] In addition, images of the enzyme as part of an elongation complex,[14] and of other functionally significant complexes during the transcription process, have been published.[15] This research has revealed the clearest images of RNA polymerase II to date, providing enhanced understanding of both its structural complexity and the manner in which it presides over transcription.

1.1.2.1.2 RNA Polymerase III

RNA polymerase III is the largest and most complex of the eukaryotic RNA polymerases, consisting of 17 subunits with an aggregate molecular weight of 600-700 kD.[7] Ten of these subunits are unique, two are also found in RNA pol I, and five are common to all three polymerases.[8] The enzyme is involved in approximately 10% of all nuclear transcription.[4]

As previously mentioned, RNA pol III is responsible for the formation of small RNA molecules, namely tRNA and 5S ribosomal RNA, which are required during protein synthesis. 5S rRNA is approximately 120 nucleotides long and is found associated with the large sub-unit of ribosomes in all eukaryotic organisms. tRNAs are typically 70-90 nucleotides in length and are required during the translation process.[7]

In contrast to the other eukaryotic polymerases, the promoter elements required for initiation by pol III are generally found within the gene that is to be transcribed, rather than upstream.[16] This type of promoter element is called an ICR (internal control region). However, upstream promoter sequences for RNA pol III are known, for example, the mammalian U6 snRNA gene which has an upstream TATA box.[7] Mixed type promoters, which contain both internal and external elements, have also been identified in various yeast species.[8]

The promoter for the 5S rRNA gene contains an internal promoter element known as the C-box (Figure 4, (a)). The transcription factor TFIIIA first binds to this region, followed by TFIIIC. The presence of the latter then brings in TFIIIB, which in turn is

responsible for enlisting the polymerase.[7] The initiation of tRNA gene transcription is similar, except the promoter consists of an A-box and B-box to which TFIIIC binds, and TFIIIA is not required (Figure 4, (b)).

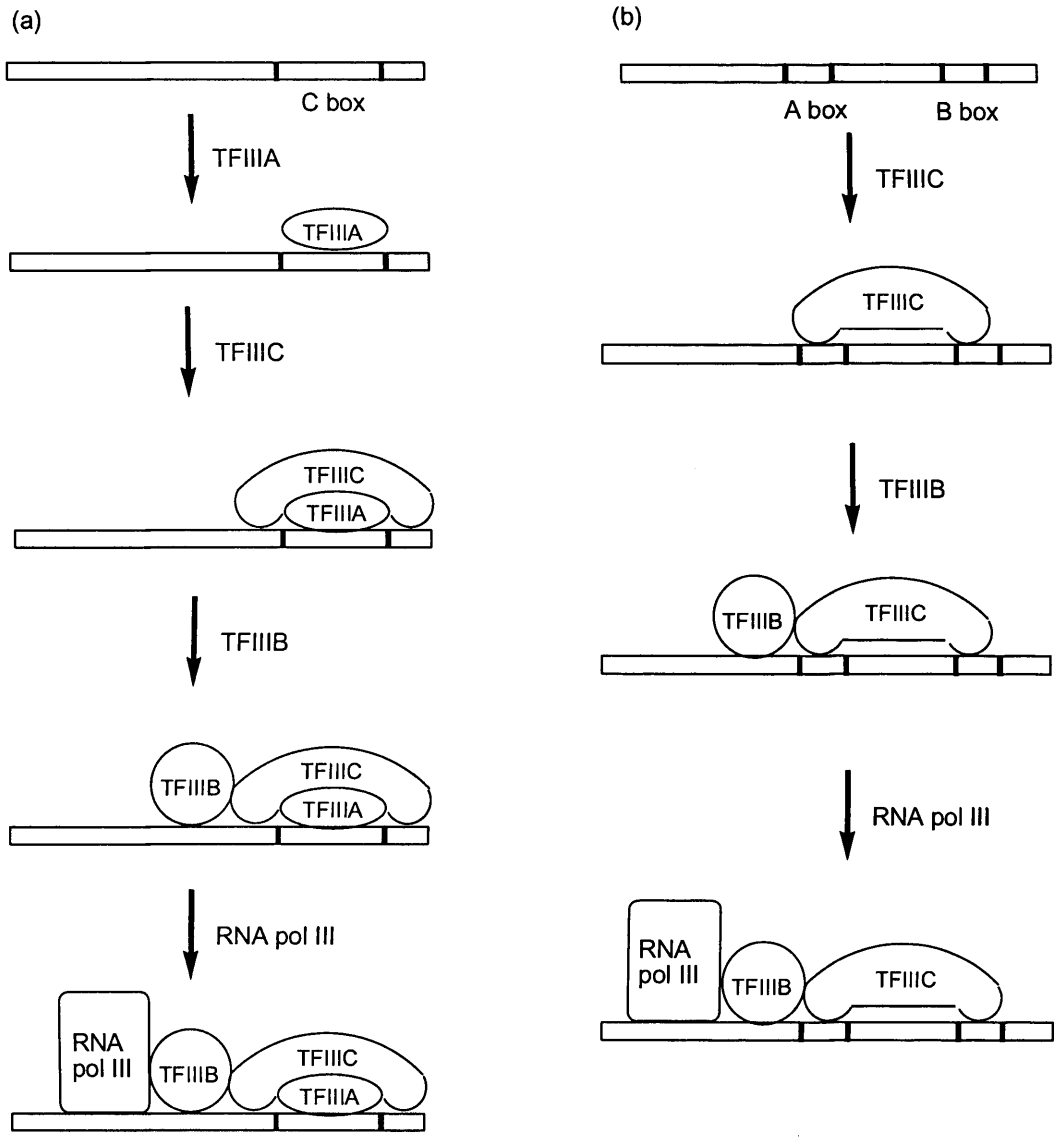


Figure 4: Transcription complex formation on (a) 5S rRNA genes and (b) tRNA genes

No elongation factors have been identified for RNA polymerase III, even though the enzyme can pause at certain points on the template. It has been suggested that one of the subunits of the enzyme plays a part in resuming transcription when it pauses.[17]

Termination of transcription occurs when a sequence of at least 4 T-residues is

reached.[9,18] Transcription of the gene can be reinitiated after termination as the transcription factors which assemble during initiation remain bound to the template. This allows multiple-round transcription to occur with great efficiency. It has also been reported that the template is bent, bringing the initiation and termination sites closer together and thus improving the ease of reinitiation.[8]

1.2 Tagetitoxin

1.2.1 Isolation and structure elucidation

Tagetitoxin was first isolated from the plant pathogenic bacterium *Pseudomonas syringae* pv. *tagetis* in 1981.[19] The liquid cultures of the bacterium were first precipitated in methanol then extracted with organic solvent. Gel filtration followed by anion exchange and partition chromatography provided the natural product.

Mitchell and Hart determined the molecular weight of tagetitoxin to be 435 using field desorption mass spectrometry.[20] It was suggested on the basis of ^{1}H, ^{13}C, ^{31}P NMR studies and TLC staining that the toxin contained carboxyl groups, three hydroxyl groups, an amine, a phosphate ester and a sulfur atom as part of a thiol or thioether moiety. A radioactive double-labelling experiment showed the phosphorus to sulfur ratio to be one to one. Analysis of proton and carbon NMR spectra suggested that the molecular formula was $C_{11}H_{18}NO_{13}PS$ and that the molecule existed as the cyclic hemithioketal **2** (Figure 5).

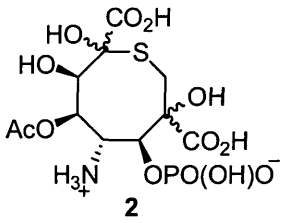


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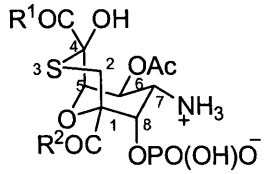
Figure 5: First proposed structure of tagetitoxin

This structure was revised in 1989 as more advanced MS and NMR data suggested that the compound was more likely to exist as two bridged heterocyclic rings.[21] FAB mass spectrostometry showed that (MH^+) was 417.0361 and the molecular formula was amended to $C_{11}H_{17}N_2O_{11}PS$. Other key differences to the first predicted structure were

that just one hydroxyl group was believed to be present rather than three, and the presence of an amide and ether moiety were also acknowledged. Analysis of the data favoured structure **1a**, a substituted 9-oxa-3-thiabicyclo[3.3.1]nonane (Figure 6).



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

Figure 6: Revised structure of tagetitoxin **1**

A strong NOE was observed between the protons on C-2 and the axial proton on C-7, suggesting that they are in close proximity. The coupling constant between the protons on C-6 and C-7 showed the dihedral angle to be 180°, indicating a true diaxial interrelationship. ^{13}C-^{1}H long range shift correlation data was also obtained and indicated a correlation between C-4 and the two protons on C-2. Such associations were also observed between the carbon of the carbonyl moiety at C-1 and the proton on C-8, and between the carbon atom of the acetyl carbonyl group and the protons on C-5 and C-6. A strong correlation was also found to exist between the carbonyl carbon atom at C-4 and the proton on C-5.

The position of the carboxylic acid and amide functionalities is ambiguous, although the authors favour the position of the amide at C-4 (**1a**) rather than at C-1 (**1b**) due to the lower chemical shift of this signal (171.2 ppm) in the carbon NMR spectrum, compared to that of C-1 (174.5 ppm). The stereochemistry at C-4 is also unassigned, and the absolute configuration of tagetitoxin is unknown.

A recent publication, however, has stated that the bicyclic structure shown above is incorrect and questions the purity of the tagetitoxin sample that was analysed. Gronwald *et al.* claim that they have isolated a tagetitoxin fraction of higher purity than in previous cases.[22] Various analyses of Gronwald *et al.*'s tagetitoxin sample showed significant discrepancies with the structure proposed by Mitchell *et al.* TLC staining of the tagetitoxin sample, for example, suggested that a primary amine was

not present, although the presence of a phosphate ester was confirmed. The previous indication that the structure contained an amine was accredited to the presence of ninhydrin-reactive contaminants.

Another major point of disagreement is that Gronwald *et al.* declared the molecular weight of tagetitoxin to be 678, as determined by positive ion electrospray ionisation (ESI) mass spectrometry, which showed an ion corresponding to MH^+ at 679.5216. ESI TOF mass spectrometry on the TLC spot of their tagetitoxin sample also showed an ion with m/z = 679, as did a sample of commercially available tagetitoxin. Although an observed ion with m/z = 417.3316 was considered to be a fragment of the molecular ion, this was not believed to be the case for the ion at m/z = 417.0361 observed by Mitchell and co-workers, which Gronwald *et al.* claim is a result of contamination.

The proton and carbon NMR spectra of Gronwald *et al.*'s tagetitoxin sample were similar to those previously obtained except for some extra peaks. These were found at 1.75 and 2.53 pm in the proton spectrum, and 23.23 and 181.45 ppm in the carbon spectrum. The general similarity between the NMR spectra led the authors to conclude that the extra mass which is associated with a molecular weight of 678, may be "accounted for by the presence of atoms (oxygen, nitrogen, sulfur) and exchangeable protons that are not detected by 1D NMR." 2D NMR experiments were also conducted. Although there was evidence that the COSY, TOCSY and HMQC spectra agreed to some extent with Mitchell *et al.*'s proposed structure, HMBC analysis of the sample appeared to indicate that this structure was incorrect.

Undoubtedly, this investigation of Gronwald *et al.* has raised questions concerning the validity of the proposed structure of tagetitoxin. However, there are certain aspects of this study which may be considered with some apprehension. Although, this is not mentioned in the publication, the extra peaks which were observed in the 1D NMR spectra may be due to ammonium acetate which was used as an eluent during purification. Looking at the reproduced proton spectrum provided, these peaks are much larger than the other tagetitoxin-assigned peaks.

In addition, an alternative structure based on their data has not been suggested, nor has

a molecular formula been put forward, despite the acquisition of HRMS data. The authors have acknowledged that elemental analysis is required, but there have been no further reports of this. Due to the lack of this information, the synthesis of tagetitoxin will be based on the structure proposed by Mitchell *et al.* Although many unanswered questions remain, the uncertainty surrounding the structure of tagetitoxin provides a strong motivation to complete its synthesis.

1.2.2 Biological activity

Tagetitoxin is a specific inhibitor of RNA polymerase III in a wide range of eukaryotes, as well as bacterial RNA polymerase.[23] Experiments on *Xenopus laevis* oocytes showed that RNA pol III was affected to a greater extent than the other RNA polymerases. RNA pol III directed transcription, in various sources, is inhibited by tagetitoxin concentrations of just 0.3-3.0 μM. RNA pol II, however, is generally much less sensitive to the toxin. Tagetitoxin concentrations greater than 100 μM were required to have any inhibitory effect on nuclear RNA pol II from wheatgerm.[24]

Chloroplast RNA polymerase, which is distinct from the three RNA polymerases found in the nucleus of eukaryotic cells, is also inhibited by tagetitoxin. This gives rise to the effect of apical chlorosis in plants, whereby leaves at the apex lose their colour and appear bleached. Application of 20 ng of the toxin to the stems of marigold and zinnia plants resulted in apical chlorosis after 2-3 days.[20] The toxin appears to affect new chlorophyll accumulation rather than existing chlorophyll levels and prevents proplastids from developing into mature chloroplasts.[25] It has been observed that tagetitoxin specifically reduced the incorporation of [^{3}H] uridine into RNA in an isolated chloroplast.[23] When it was added to transcriptionally active chloroplast protein extracts, it directly inhibited the incorporation of [^{32}P] UTP into RNA.

Chloroplast RNA polymerase and bacterial RNA polymerase from *E.coli* are inhibited by a tagetitoxin concentration of less than 1 μM.[24] Tagetitoxin also inhibits *in vitro* transcription directed by RNA polymerase from the cyanobacterium Anabaena 7120, and has been shown to affect RNA polymerase found in the strains of the bacterium from which the toxin itself is produced.[24] It may be that the tagetitoxin is metabolised into a non-toxic form in *Pseudomonas syringae* pv. *tagetis*, thus preventing the

bacterium from poisoning itself. RNA polymerases from the two bacteriophages, SP6 and T7 appear to be unaffected by the toxin even at a concentration of 1 mM.[24] However, the structure of RNA polymerase found in these organisms is different to that of RNA polymerase found in *E. coli*.[26]

The inhibitory effect of tagetitoxin on chloroplast RNA polymerase has led to its application as a plant growth regulator.[27] Tagetitoxin is also being sold under the commercial name Tagetin™ for RNA polymerase and transcription studies, at a cost of £149 for 12 μg (February 2008).[28] The synthesis of this natural product would benefit molecular biologists studying transcription greatly as it would allow larger quantities of this natural product to be obtained at a more reasonable price, and open up possibilities for forming analogues with different activities.

1.2.2.1 Mechanism of inhibition

Attempts have been made to clarify the mechanism by which tagetitoxin acts as an inhibitor and although this has not been fully established, important insights have been made. The mechanism of inhibition is believed to be similar for the various RNA polymerases that are affected.

Tagetitoxin appears to increase the stability of the intrinsic pausing of RNA polymerase III along the DNA template during the elongation stage of transcription.[29] The pattern of this pausing varies for different class III genes. This may be due to the fact that the number and stability of intrinsic pause sites along each type of template differs from gene to gene. For example, it was found that transcription of the U6 snRNA gene is less sensitive to inhibition than for the 5S rRNA gene.[23] As the concentration of tagetitoxin was increased, the amount of full-length transcript produced decreased and there was an increase in the amount of shorter, low molecular weight transcripts. In the absence of tagetitoxin, the short RNA transcripts could be elongated further to form full-length transcripts in the majority of cases. This indicates that the effects of pausing are usually reversible.

Further evidence which shows that tagetitoxin interferes with the elongation process is provided by Matthews and Durbin.[30] Their studies on RNA polymerase from *E. coli*

showed that the toxin can interact with the ternary complex, which consists of the RNA polymerase core enzyme, DNA template and the nascent RNA molecule. Studies on *E. coli* RNA polymerase have also shown that tagetitoxin is not a competitive inhibitor of nucleotides. This is supported by the work of Corda *et al.* on spinach chloroplasts which revealed that tagetitoxin did not interfere with phosphodiester bond formation, nor did it compete with nucleotides to bind to the RNA polymerase active site.[31] Another explanation for the inhibitory effect of tagetitoxin was that it may enhance the binding of oligonucleotides to the elongation complex.[30] This in turn may impede the rate at which oligonucleotides are released and result in a lower rate of product formation. The movement of the enzyme along the DNA template may also be affected in a similar manner to RNA pol II inhibition by α-amanitin, which is believed to prevent the enzyme from translocating along the template.[32]

Although these studies provided some insight into the inhibitory effect of tagetitoxin, it was acknowledged that they still did not provide a clear explanation of the actual mode of action. Recently, Vassylyev and co-workers published the structure of bacterial RNA polymerase from *Thermus thermophilus* in a complex with tagetitoxin at a resolution of 2.4 Å.[33] Unfortunately, this resolution is not sufficient to establish the exact structure of tagetitoxin and therefore resolve the controversy surrounding this issue (section 1.2.1). Nevertheless, the X-ray structure shows that tagetitoxin binds near the active site of the enzyme. The interaction of tagetitoxin with the enzyme is brought about *via* hydrogen bonds between of 9 of the toxin's oxygen atoms with protein side chains of the enzyme. Inhibition is thought to occur by tagetitoxin stabilising the RNA polymerase in a non-productive state during NTP entry into the active site. This causes all catalytic activity of the enzyme to decrease.

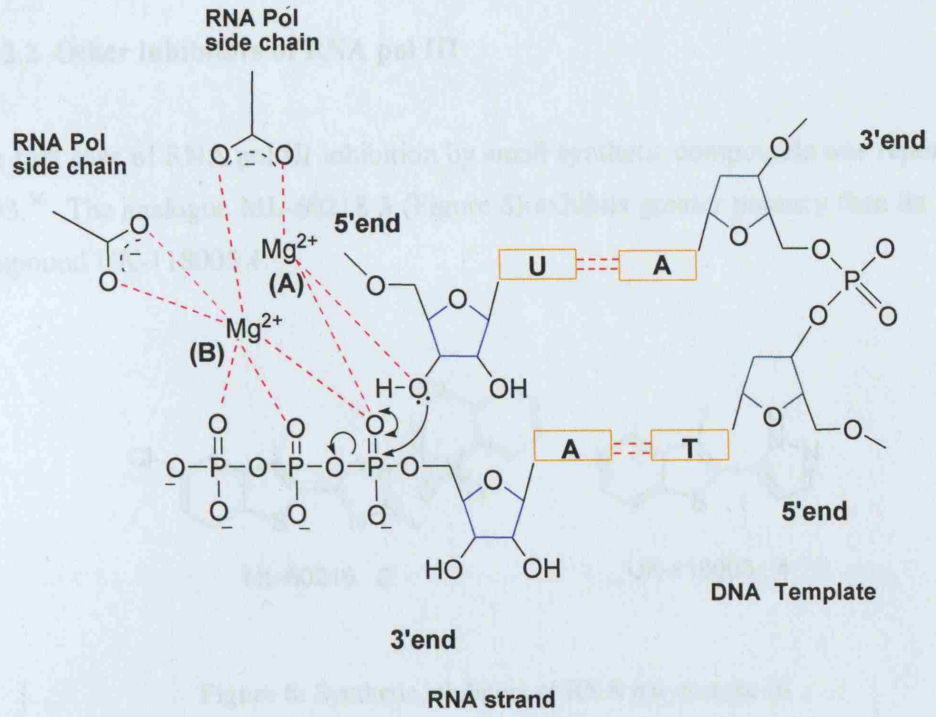
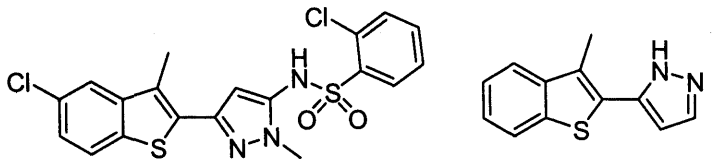


Figure 7: Role of Mg^{2+} ions in RNA synthesis

During RNA synthesis, two Mg^{2+} ions are believed to be involved in the formation of the phosphodiester bond beween the incoming NTP and the 3′ OH terminal of the RNA chain. One of these ions (ion A) coordinates to the 3′ hydroxyl moiety and the α-phosphate of NTP (Figure 7), making nucleophilic attack by the former easier.[34,35] The other ion (ion B) coordinates to all three of the phosphates on the NTP, and in conjunction with ion A, helps to stabilise a pentavalent transition state which results. In the tagetitoxin-RNA polymerase complex examined by Vassylyev *et al.*, a third Mg^{2+} ion (tMg) was also observed. This was coordinated to the phosphate group present in tagetitoxin and to two active site residues of the enzyme. As ion B is usually bound to one of these active site residues, the tMg ion weakens the binding of ion B with the enzyme, which in turn disturbs the optimal geometry of ions A and B in the pentavalent transition state, leading to lower catalytic activity. Although the tMg ion weakens the interaction of the enzyme with ion B, homology modelling studies showed that it increased the affinity of the enzyme for ion A. This may be responsible for stabilising the enzyme in an inactive state which in turn increases pausing along the template and disrupts translocation.

1.2.2.2 Other inhibitors of RNA pol III

The first case of RNA pol III inhibition by small synthetic compounds was reported in 2003.[36] The analogue ML-60218 **3** (Figure 8) exhibits greater potency than its parent compound UK-118005 **4**.



ML-60218 **3** UK-118005 **4**

Figure 8: Synthetic inhibitors of RNA polymerase III

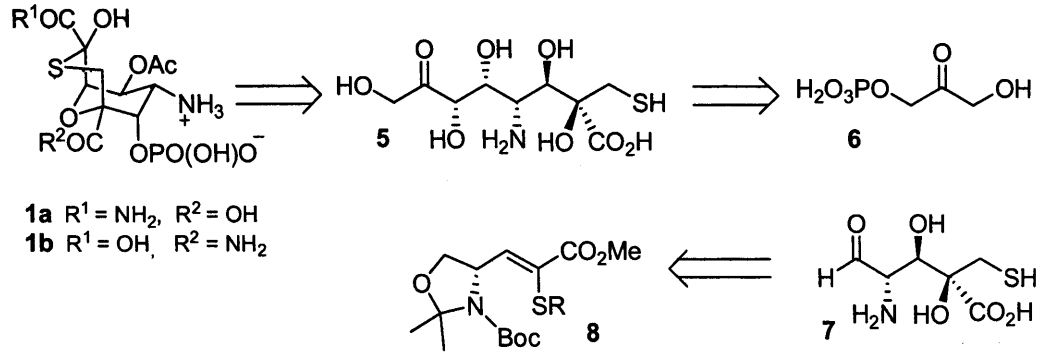
These compounds have not been tested on RNA polymerases I and II, so it is not yet known whether the inhibition of RNA pol III is selective, although results suggest that UK-118005 is not a general inhibitor.

1.2.3 Previous synthetic attempts

To date, only two other groups have reported their attempts to synthesise tagetitoxin in the literature.

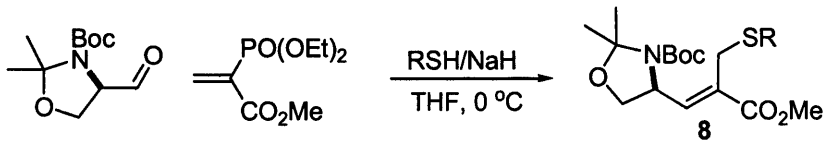
1.2.3.1 Sammakia's approach

Sammakia *et al.* planned to synthesise the natural product *via* an enzymatic coupling of the aldehyde **7** with the dihydroxyacetone phosphate **6** (Scheme 1).[37] It was envisaged that the cyclisation of the linear precursor **5** would give tagetitoxin.



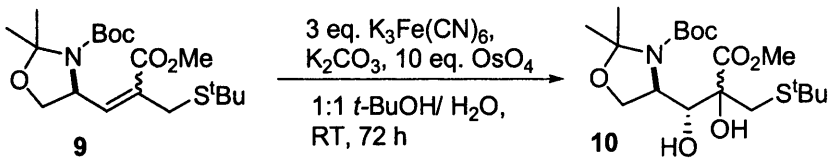
Scheme 1: Sammakia *et al.*'s strategy to synthesise tagetitoxin **1**.

The authors prepared the alkene **8** *via* the one-pot synthesis shown in Scheme 2.



Scheme 2: Formation of alkene **8**

It was envisaged that dihydroxylation of **8** followed by hydrolysis of the oxazolidinone and oxidation of the resulting primary alcohol to the aldehyde, would lead to **7**. However, the subsequent dihydroxylation step also led to the oxidation of the protected thiol. It was found that the degree of sulfur oxidation was dependent on the nature of the thiol protecting group and the co-oxidant used in the dihydroxylation. Electron-withdrawing substituents on the thiol, as well as sterically bulky groups decreased the rate of sulfur oxidation. The best yield of sulfide product **10** (50-63%) was obtained when the starting thiol **9** was protected with a *tert*-butyl group and the dihydroxylation was carried out using the Yamamoto procedure (Scheme 3).

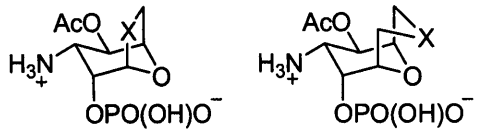


Scheme 3: Dihydroxylation of thiol **9**

The diastereomeric ratio of the product **10** was 25:1, with the major isomer being the one required for the rest of the synthesis. No further developments have since been reported.

1.2.3.2 Furneaux's approach

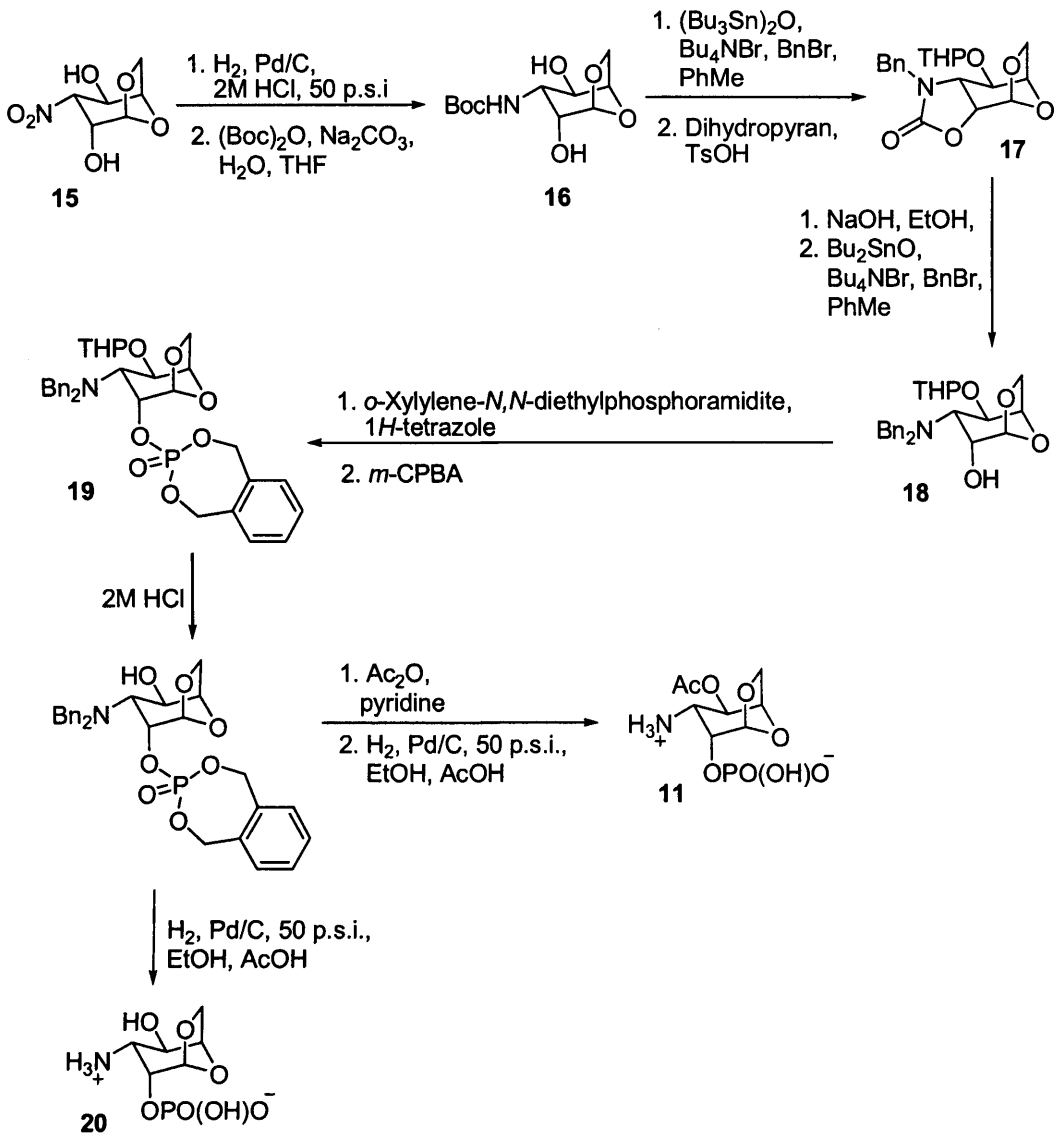
Furneaux *et al.* were interested in making analogues of tagetitoxin of the types shown in Figure 9.[38] D-Sugars were chosen as the building blocks for the syntheses due to their ready availability.



11 X= O
12 X= S
13 X= O
14 X= S

Figure 9: Furneaux *et al.'s* synthetic targets

The analogue **11** was successfully synthesised *via* the synthetic route shown in Scheme 4.

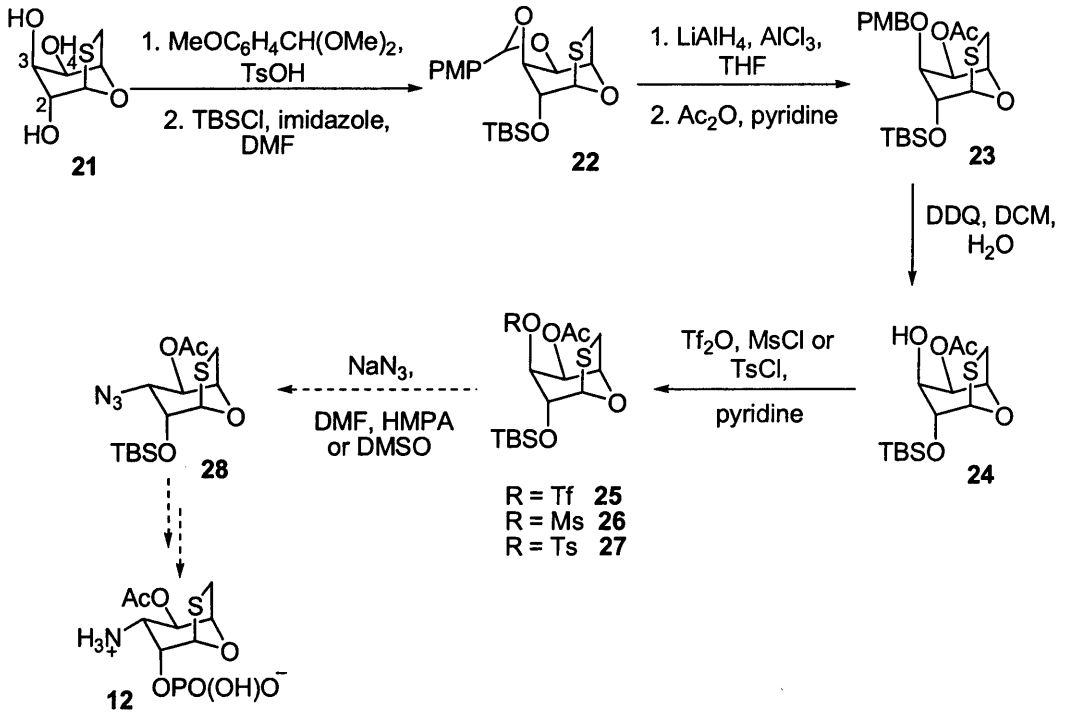


Scheme 4: Synthesis of analogue **11**

Hydrogenation of 1,6-anhydro-3-deoxy-3-nitro-D-gulose **15**, followed by treatment with Boc anhydride gave the diol **16**. This was subsequently converted to the cyclic carbamate **17**. The latter was then opened under basic conditions and the tertiary amine **18** was formed upon addition of dibutyltin oxide, tetrabutylammonium bromide and benzyl bromide. Phosphitylation, followed by oxidation to the phosphate using *m*-CPBA gave **19**. Removal of the THP protecting group with acid, acetylation of the resulting alcohol and hydrogenation produced the analogue **11**. Analogue **20** was formed in a similar manner. The final step of this synthesis afforded both analogues in quantitative yield, however neither of these analogues were biologically active when

applied to various weeds at 1000 g/ha.* It has been suggested that thiosugars tend to be more biologically active than their oxygen counterparts,[39] so it is possible that the analogue **12** would exhibit biological activity.

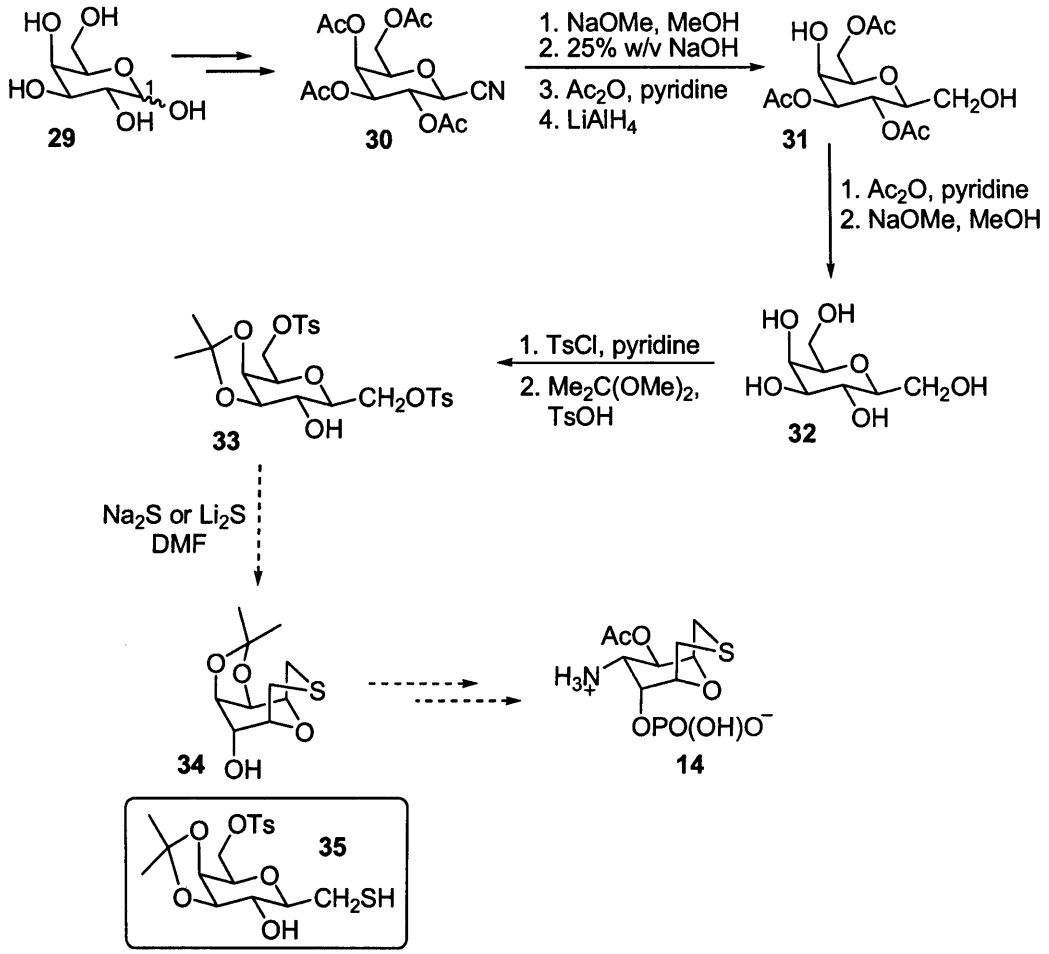
An alternative synthetic route was attempted which could also provide access to the sulfur analogue **12** (Scheme 5). The underlying strategy was to selectively functionalise the hydroxyl groups at C-2 and C-4 of compound **21**, and to introduce a good leaving group (triflate, mesylate or tosylate) at C-3. Attack of sodium azide at C-3 would displace the leaving group, and thereby introduce a nitrogen functionality which could be converted to an amine. The C-2 and C-4 hydroxyls were successfully functionalised with a TBS ether and acetate group respectively to give **23**, *via* the formation of intermediate **22**. Removal of the *para*-methoxybenzyl ether afforded **24**. The introduction of the leaving group to give **25**, **26** and **27** was also achieved, but its subsequent displacement by sodium azide to form the product **28** was unsuccessful. This was accredited to the steric hindrance provided by the TBS group to the incoming nucleophile.



Scheme 5: Attempted synthesis of analogue **12**

* *Avena fatua* (wild oat), *Setaria viridis* (green foxtail), *Amaranthus reteroflexus* (redroot pigweed) and *Chenopdium album* (fat hen) were the weeds tested.

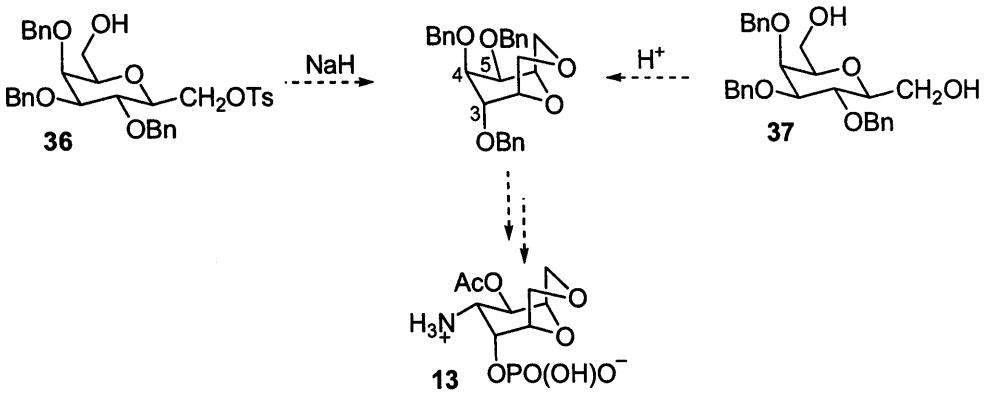
Attempts to make the analogue **14**, which bears a closer resemblance to the proposed structure of tagetitoxin, were also unsuccessful. It was hoped that a one carbon extension at C-1 on D-galactopyranose **29** and eventual ring closure would give the desired product (Scheme 6). D-Galactopyranose **29** was converted to **30**. This led to **31**, *via* the formation of a δ-lactone which was subsequently reduced. Acetylation, then treatment with sodium methoxide afforded **32**, which was then modified to give **33**. The cyclic product **34**, however, was not obtained despite treatment of **33** with sodium sulfide or lithium sulfide in DMF. The only product isolated was the thiol **35**.



Scheme 6: Attempt to form analogue **14**

It was thought that the bulky isopropylidene protecting group could be preventing the ring closure, so benzyl groups were used to protect the alcohol functionalities at C-3, C-4 and C-5, in an attempt to form the analogue **13** (Scheme 7). This modification did

not lead to the desired cyclisation as a complex mixture was obtained when **36** was treated with sodium hydride. Acid catalysed cyclodehydration of **37** was also attempted to no avail as only starting material was recovered. Reaction with triphenylphosphine and diethyl azodicarboxylate gave the same result.

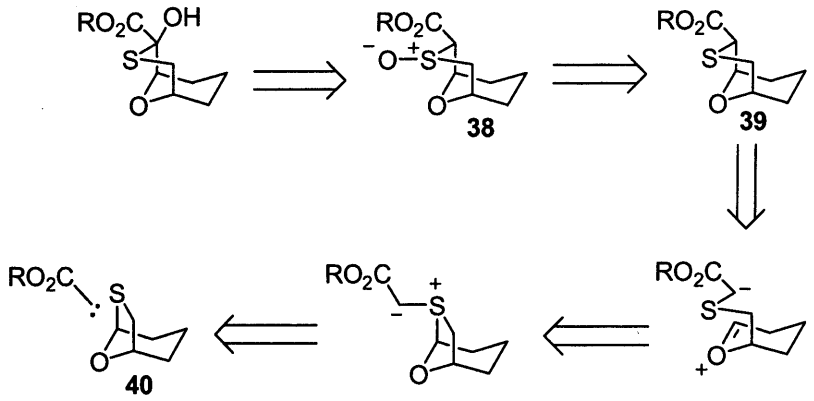


Scheme 7: Attempt to form analogue **13**

1.2.3.3 Previous work in the Porter Group

1.2.3.3.1 Ring expansion strategy

A possible way to synthesise the tagetitoxin core is by ring expansion of a bridged bicyclic 1,3-oxathiolane, such as **40**, *via* the insertion of a carbene into the C-S bond (Scheme 8).

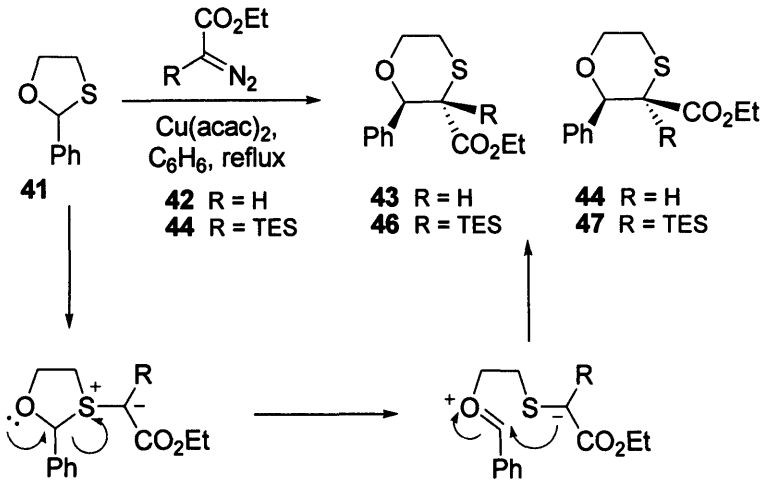


Scheme 8: Ring expansion strategy to form bicylic tagetitoxin core

The hydroxyl functionality could be introduced *via* a Pummerer reaction on the sulfoxide **38** or by hydroxylation of the enolate of ester **39**.

1.2.3.3.2 Ring expansion of monocyclic substrates

Previous synthetic studies in our group[40,41] investigated the scope of a ring expansion reaction on monocyclic substrates such as 2-phenyl-1,3-oxathiolane **41** (Scheme 9), as bridged bicyclic systems were not readily available.



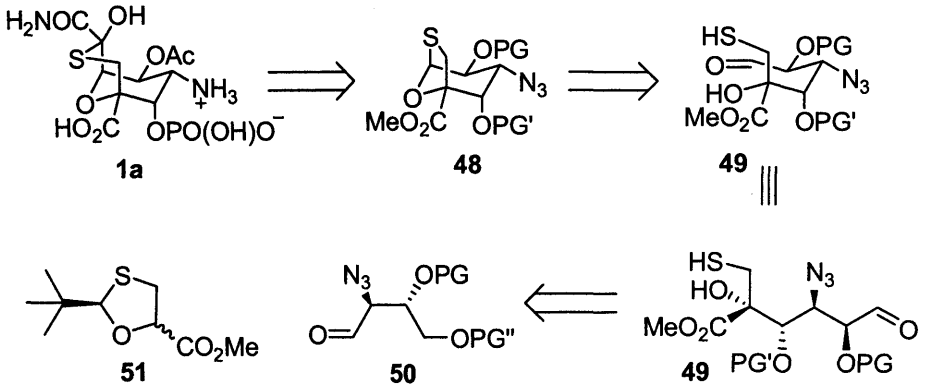
Scheme 9: Ring expansion of 1,3-oxathiolane **41**

Ethyl diazoacetate **42**, in the presence of a copper catalyst, gave a poor yield (19%) of the 1,4-oxathianes **43** and **44** in a 2:1 ratio. An appreciable amount of starting material was also recovered which led to a larger quantity of **42** being used to drive the reaction to completion. However, the inability of **42** to discriminate between the sulfur atom in the product and the starting material, led to unwanted side products. In contrast, the use of ethyl (triethylsilyl)diazoacetate **43** afforded a good yield (67%) of **46** and **47** in an 8:1 ratio. The reaction also worked well on other 2-aryl-1,3-oxathiolanes, producing both good yields and high diastereomeric ratios, whereas an isobutyl substituent at the 2-position gave poor results. Desilylation was effectively carried out using TBAF.

1.2.3.3.3 Aldol approach to ring expansion precursor

The results of the methodological study on monocyclic substrates were to be applied to

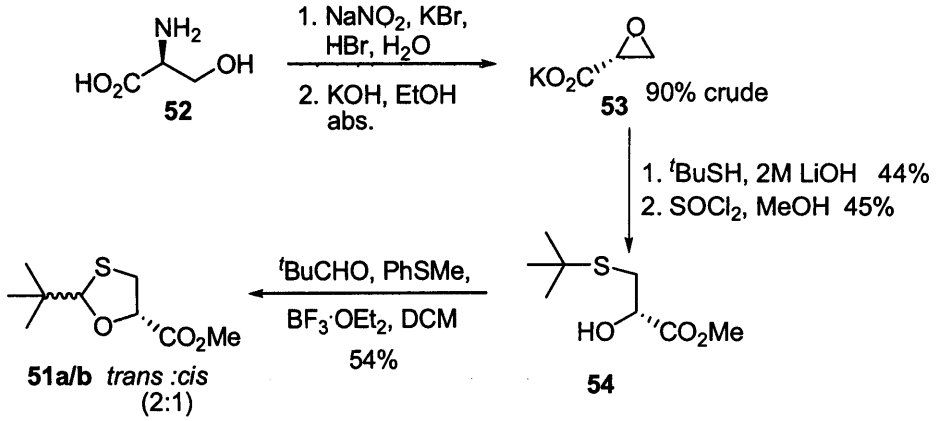
the synthesis of tagetitoxin, where ring expansion of **48** (Scheme 10) would give the core structure of the natural product.



Scheme 10: Strategy to form tagetitoxin **1a** from oxathiolane **51**

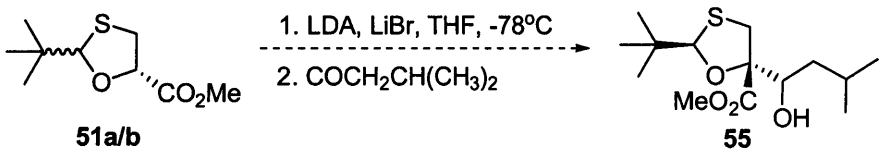
It was envisaged that an aldol reaction between the oxathiolane **51** and azidoaldehyde **50** would give 5-hydroxy-6-mercaptohexanal **49** *via* the formation of the *E*-enolate. Intramolecular acid-catalysed thioacetal formation could then in turn give the ring expansion precursor **48**.

The synthesis of the oxathiolane ester **51** was attempted by following the route shown in Scheme 11.[42] Potassium glycidate **53** was obtained from L-serine **52** *via* a diazotisation reaction followed by treatment with potassium hydroxide. Ring opening of the epoxide with *tert*-butyl thiol followed by esterification gave **54**. A novel oxathiolane forming reaction gave the 1,3-oxathiolane **51a/b** as a 2:1 (*trans*:*cis*) mixture of diastereomers.



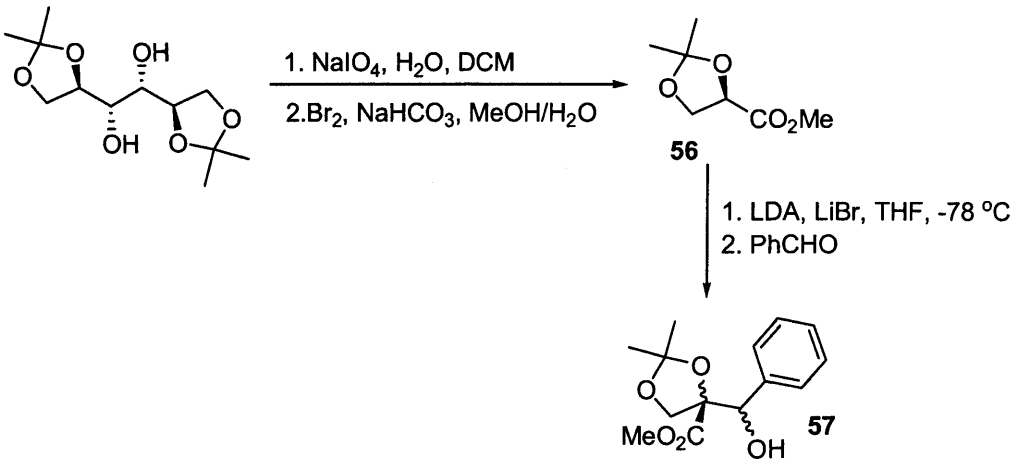
Scheme 11: Formation of oxathiolane **51a/b**

The *trans* isomer was required for the aldol reaction with azidoaldehyde, but it was not possible to separate this from the unwanted *cis* isomer. Nevertheless, the feasibility of the proposed aldol reaction was tested on the mixture of oxathiolanes using isobutyraldehyde (Scheme 12). Instead of forming the desired product **55**, decomposition of the starting material occurred. The reaction was also carried out using benzaldehyde, but gave the same result.



Scheme 12: Attempted aldol reaction of **51a/b** with isobutyraldehyde

It was believed that the thioether functionality present was causing substrate decomposition *via* β-elimination. In order to test this hypothesis, the aldol reaction was carried out with the dioxolane ester substrate **56** (Scheme 13).

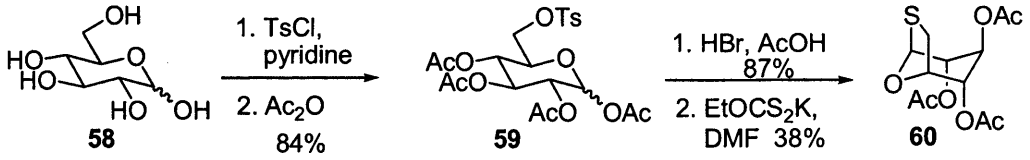


Scheme 13: Aldol reaction of **56** with benzaldehyde

The product **57** was obtained as a mixture of diastereomers, albeit in low yield. This result supports the argument that the sulfur atom was the cause of the unsuccessful aldol reaction depicted in Scheme 12. Therefore, it was realised that the synthetic route to tagetitoxin, described in Scheme 10, was not going to be feasible and an alternative strategy was required.

1.2.3.3.4 Ring expansion of bicyclic substrates

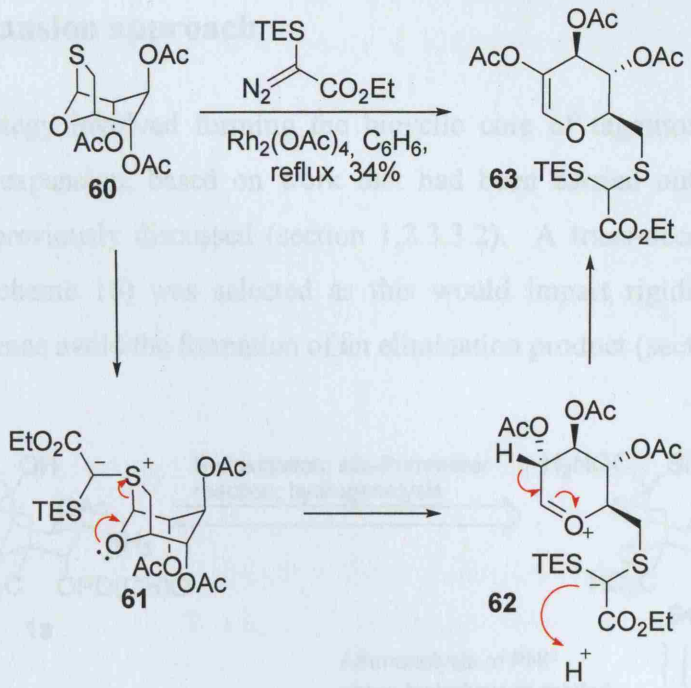
Ring expansion was also attempted on a bicyclic compound such as **60**. This substrate was synthesised from D-glucose **58** (Scheme 14).[43] Tosylation of the primary alcohol, followed by acetylation of the remaining hydroxyl groups gave **59**. Reaction with hydrogen bromide, followed by treatment with potassium ethylxanthate salt afforded **60**.



Scheme 14: Synthesis of **60** from D-glucose **58**

When this substrate was subjected to ring expansion conditions (Scheme 15), the elimination product **63** was formed. A possible explanation for this result is that following formation of the sulfur ylid, **61** undergoes a ring-flip to give **62**. This gives

rise to an axial proton β to the oxygen which can be eliminated to give the enol ether **63**.



Scheme 15: Formation of **63**

Therefore, it was recognised that a bicyclic substrate such as **60** was not a suitable precursor for ring expansion and required suitable modification to prevent ring-flipping.

1.3 Aims of the research project

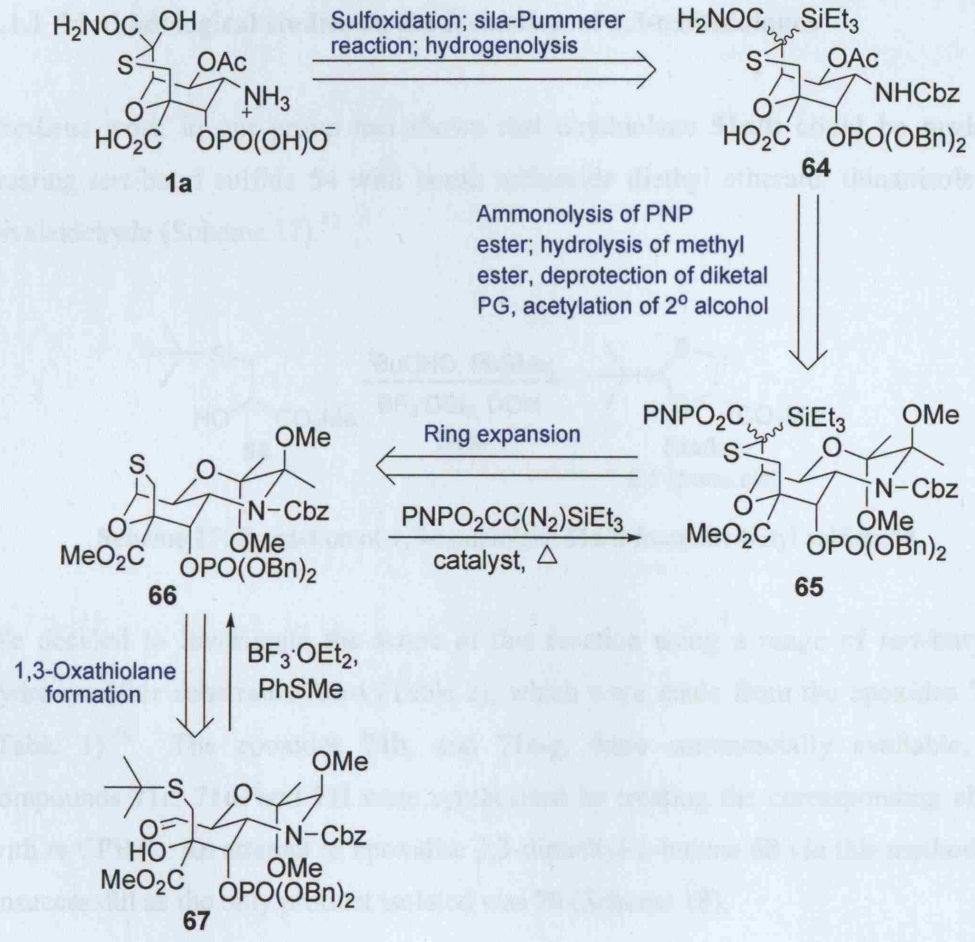
The aim of this project is to synthesise tagetitoxin *via* a flexible route which will allow the preparation of analogues. There are numerous factors which make the synthesis of this compound appealing;

- The controversy and debate surrounding its structure should be resolved on completion of its synthesis.
- A successful synthetic route to this natural product will be highly beneficial to molecular biologists studying transcription.
- From a synthetic point of view, its highly functionalised structure makes it a challenging target.
- There are no previous synthetic routes to this compound.

2. RESULTS & DISCUSSION

2.1 Ring expansion approach

Our initial strategy involved forming the bicyclic core of tagetitoxin *via* carbene-mediated ring expansion, based on work that had been carried out on monocyclic substrates, as previously discussed (section 1.2.3.3.2). A trans-decalin type system such as **66** (Scheme 16) was selected as this would impart rigidity, prevent ring flipping, and hence avoid the formation of an elimination product (section 1.2.3.3.4).



Scheme 16: Retrosynthesis of tagetitoxin **1a** from hydroxysulfide **67**

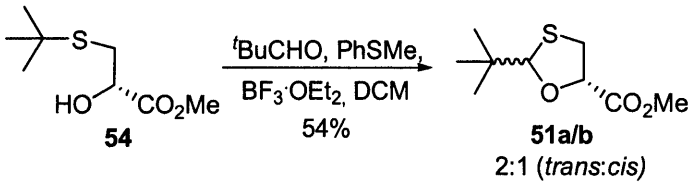
Tagetitoxin **1a** would be derived from the ring-expanded product **65** following ammonolysis of the PNP ester to give the amide and hydrolysis of the methyl ester to give the acid. Cleavage of the diketal protecting group and protection of the resulting

secondary alcohol as an acetate would lead to **64**. Finally, the hemithioacetal would be installed by means of sulfoxidation and a sila-Pummerer reaction, and the benzyl protecting groups on the phosphate moiety would be removed by hydrogenolysis in liquid ammonia.

The ring expansion precursor, **66** would in turn be formed from **67** *via* the intramolecular variant of a novel reaction which was discovered in our group. Before starting our synthetic route towards tagetitoxin, we decided to investigate this reaction in more detail.

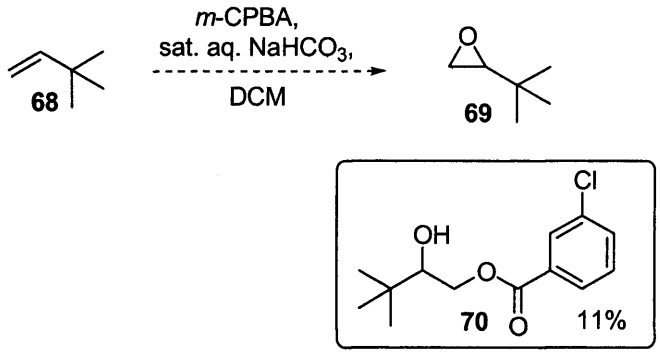
2.1.1 Methodological studies on the formation of 1,3-oxathiolanes

Previous work in our group had shown that oxathiolane **51a/b** could be made by treating *tert*-butyl sulfide **54** with boron trifluoride diethyl etherate, thioanisole and pivalaldehyde (Scheme 17).[42]



Scheme 17: Formation of 1,3-oxathiolane **51a/b** from *tert*-butyl sulfide **54**

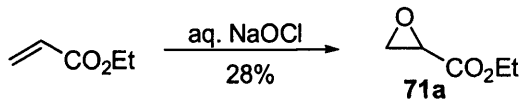
We decided to investigate the scope of this reaction using a range of *tert*-butyl β-hydroxysulfide substrates **73a-i** (Table 2), which were made from the epoxides **71a-i** (Table 1).[44] The epoxides **71b**, and **71e-g**, were commercially available, and compounds **71c**, **71d**, and **71i** were synthesised by treating the corresponding alkene with *m*-CPBA. An attempt to epoxidise 3,3-dimethyl-1-butene **68** *via* this method was unsuccessful as the only product isolated was **70** (Scheme 18).



Scheme 18: Attempted epoxidation of alkene **68**

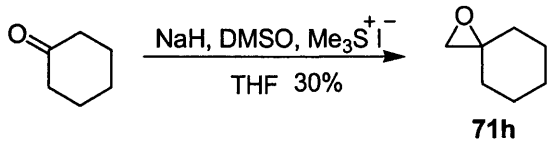
It seems that the epoxide **69** was initially formed but was then ring-opened by *meta*-chlorobenzoic acid. The epoxide **69** is also expected to be quite volatile and this may be the reason why it was not isolated.

The epoxide **71a** was formed by reacting ethyl acrylate with bleach[45] (Scheme 19).



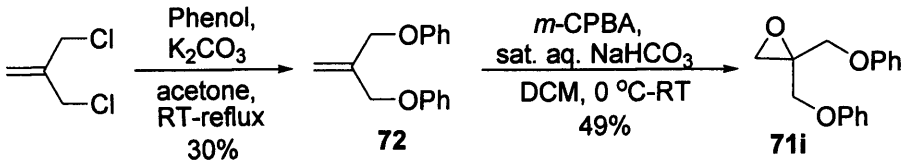
Scheme 19: Formation of ethyl glycidate **71a**

The disubstituted oxirane **71h** was made from cyclohexanone *via* methylene transfer by dimethylsulfonium methylide (Scheme 20).[46] The latter was formed *in situ* by reaction of the conjugate base of DMSO and trimethylsulfonium iodide.



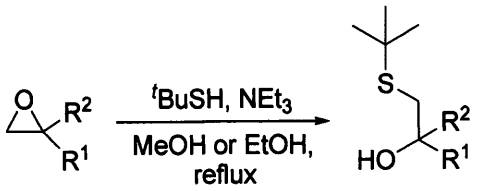
Scheme 20: Formation of disubstituted epoxide **71h**

The epoxide **71i** was synthesised from the alkene **72**, which was formed from 3-chloro-2-chloromethyl propene (Scheme 21).[47]



Scheme 21: Preparation of **71i**

The ring opening of most of the epoxides was carried out with *tert*-butyl thiol and triethylamine (Scheme 22).[48]



71a-i **73a-i**

Scheme 22: Ring-opening of epoxides **71a-i** with *tert*-butyl thiol

Substrate	R^1	R^2	Time/ h	Yield (%)
71a	CO_2Et	H	2	27[a]
71b	*n*-C_3H_7	H	5	77
71c	CH_2Ph	H	2.5	72
71d	CH_2OPh	H	o/n	97
71e	CH_2OBn	H	21	53
71f	$CH_2OCH_2CH{=}CH_2$	H	2.5	80
71g	$(CH_2)_6CH{=}CH_2$	H	2.5	93
71h	-$(CH_2)_5$-		6	48
71i	CH_2OPh	CH_2OPh	2.5	93

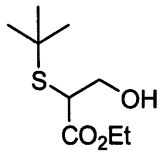
[a]Sodium ethoxide was used in place of triethylamine

Table 1: Results of epoxide ring-opening with *tert*-butyl thiol

The results of the ring-opening reaction (Table 1) generally gave good yields, the best yield being that for the phenoxy substrate **71d**. Most of the reactions proceeded cleanly, giving mainly product and few impurities.

It was not possible to form the ester product **73a** using this method. An unidentifiable mixture of products was obtained when 0.5-1.0 eq. of triethylamine was used and

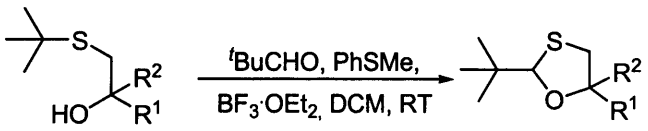
when the quantity of triethylamine was reduced further, only starting material was recovered. The substitution of triethylamine with sodium bicarbonate was also investigated[49] but again, the desired product was not isolated. **73a** was eventually formed using 0.1 equivalents of sodium ethoxide and *tert*-butyl thiol in ethanol, albeit in a poor yield. Several side-products, in addition to the desired compound **73a**, were also formed. One of these was identified as **74** (Figure 10), which is the result of *tert*-butyl thiol attacking the more substituted carbon of the epoxide ring.



74

Figure 10: Side-product formed upon ring-opening of epoxide **71a**

The *tert*-butyl β-hydroxysulfides **73a-i** were subjected to the oxathiolane forming conditions (Scheme 23), the results of which are shown in Table 2. The ratios of the two diastereomers were determined by measuring the relative intensity of peaks in the proton NMR spectra. The major diastereomer for **75a-g** was identified by NOE experiments (Figure 11).



73a-i **75a-i**

Scheme 23: Formation of 1,3-oxathiolanes **75a-i**

Substrate	R^1	R^2	Time/ h	Crude ratio (*cis*:*trans*)	Yield/ % (*cis*:*trans*)[a]
73a	CO_2Et	H	4	1:2.2	67 (1:2.4)
73b	*n*-C_3H_7	H	4	2.5:1	15[b]
73c	CH_2Ph	H	22	3.8:1	47 (3.8:1)
73d	CH_2OPh	H	5	2.7:1	74 (2.2:1)
73e	CH_2OBn	H	24	3:1	82 (2.7:1)
73f	$CH_2OCH_2CH{=}CH_2$	H	25	2.9:1	36 (2.8:1)
73g	$(CH_2)_6CH{=}CH_2$	H	5	3.7:1	12 (14:1)
73h	-$(CH_2)_5$-		22	–	Pure product not obtained
73i	CH_2OPh	CH_2OPh	23	–	91

[a] Ratio of diastereomers following purification.

[b] Only the major *cis*-isomer was isolated as it was not possible to obtain a clean sample of the *trans*-isomer

Table 2: Results of the oxathiolane forming reaction

The ester **75a** was formed in good yield as well as the compounds containing a benzyl or phenyl ether (**75d, 75e, 75i**), with **75i** being produced with the best yield overall. This result also shows that the reaction is not limited to secondary alcohol substrates. The *n*-propyl and benzyl-substituted compounds **75b** and **75c** were obtained in markedly lower yields, although the poor yield obtained for **75b** could be due in part to the high volatility of the product. It was not possible to obtain a clean sample of **75h** despite repeated purification attempts by flash chromatography. This was due to difficulty in separating the product from non-polar impurities.

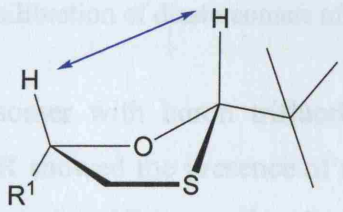
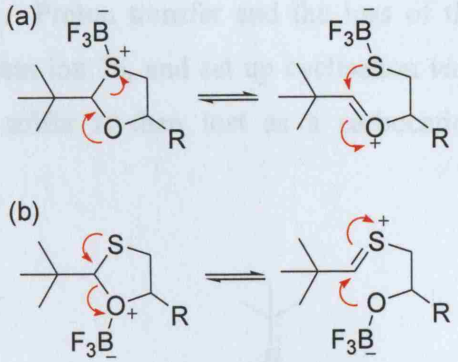


Figure 11: Nuclear Overhauser enhancement in **75b-g**

NOE measurements showed that the *cis*-isomer was the predominant isomer for oxathiolanes **75b-g** (Figure 11) whilst the *trans*-isomer was the major product for the

ester product **75a**. With the aim of discovering whether the product ratios were thermodynamically controlled, attempts were made to determine which of the two diastereomers of **75b** was more thermodynamically stable. It has been shown that diastereomers of 2,5-disubstituted 1,3-oxathiolanes exist in equilibrium and can be interconverted by boron trifluoride diethyl etherate.[50] This equilibration may occur *via* formation of an oxonium ion (Scheme 24, (a)) or a sulfonium species (Scheme 24, (b)). Hence, the thermodynamic product could be established by subjecting the minor isomer to boron trifluoride diethyl etherate and monitoring whether or not the major isomer was produced.



Scheme 24: Formation of (a) oxonium and (b) sulfonium intermediates

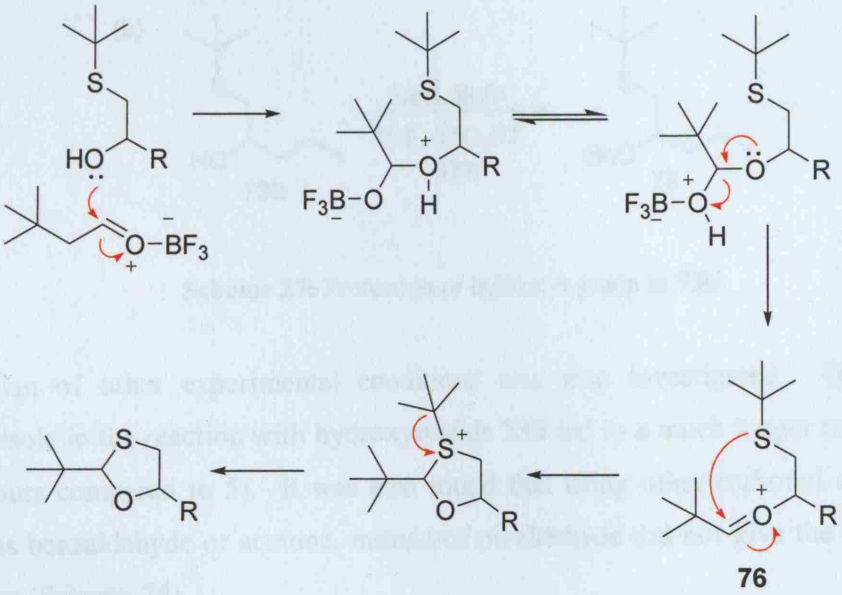
As **75b** was the only product for which one diastereomer could be isolated cleanly, it was selected as the test substrate.

Scheme 25: Equilibration of diastereomers of oxathiolane **75b**

On treatment of the *trans*-isomer with boron trifluoride diethyl etherate in DCM (Scheme 25), the proton NMR showed the presence of a singlet corresponding to the proton on C-2 in the *cis*-isomer in addition to the signal for the same proton in the *trans*-isomer. The ratio of these peaks was 3.3:1, in favour of the *cis*-isomer. However, extensive decomposition also occurred, and the other peaks corresponding to the *cis*-isomer could not be identified definitively; thus the evidence for the *cis*-isomer being the thermodynamic product should be regarded as uncertain.

Nevertheless our results are in agreement with studies carried out by Keskinen *et al.*, which show that the *cis*-product is the more stable diastereomer in 2,5-dialkyl-1,3-oxathiolanes.[50] The predominant *trans*-isomer for the ester product **75a** also has literature precedent, as the synthesis of methyl 2-methyl-1,3-oxathiolane-5-carboxylate by Teodori *et al.* from the corresponding hydroxythiol gave the *trans*-isomer as the major product.[51]

A viable mechanism for the oxathiolane forming reaction is shown in Scheme 26. The boron trifluoride complex activates pivaldehyde which is then attacked by the hydroxyl moiety of the sulfide. Proton transfer and the loss of the complexed oxygen atom would give the oxonium ion **76**, and set up cyclisation *via* the sulfur atom. The *tert*-butyl group on the sulfur is then lost as a carbocation which is scavenged by thioanisole.

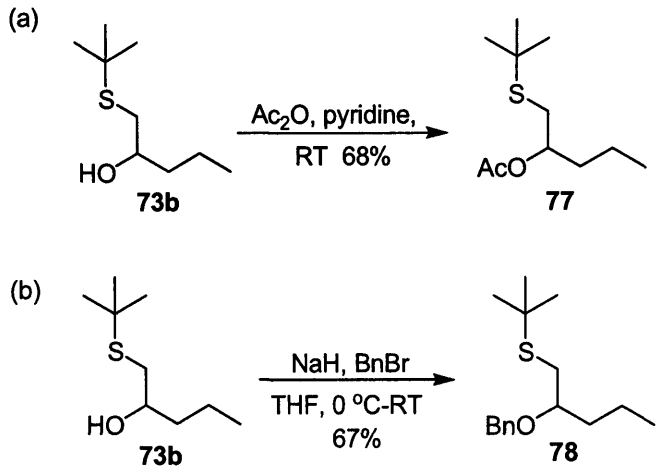


Scheme 26: Proposed mechanism of oxathiolane forming reaction

Alternatively, loss of the *tert*-butyl group from the sulfur atom could occur prior to the condensation reaction with pivalaldehyde. However, when a control reaction was carried out without using pivalaldehyde,[44] only starting material was recovered, suggesting that this alternative explanation was not viable.

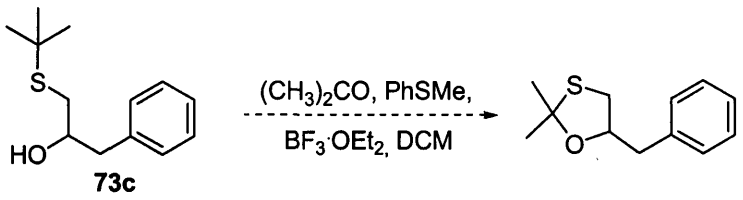
In order to test further the mechanism shown in Scheme 26, the hydroxyl group of **73b**

was protected with an acetyl functionality (Scheme 27, (a)) and with a benzyl group (Scheme 27, (b)) to give the products **77** and **78** respectively. Subjection of the protected compounds to boron trifluoride diethyl etherate, thioanisole and pivalaldehyde was expected to give starting material if the reaction occurred *via* the proposed mechanism. When **77** and **78** were subjected to oxathiolane forming conditions, a complex mixture was obtained in both cases but no oxathiolane was present. As it was not possible to identify the compounds which made up the mixture, the results are inconclusive.



Scheme 27: Protection of hydroxyl group in **73b**

Variation of other experimental conditions was also investigated. Omission of thioanisole in the reaction with hydroxysulfide **73d** led to a much longer reaction time (40 hours compared to 5). It was also found that using other carbonyl compounds, such as benzaldehyde or acetone, instead of pivaldehyde did not give the oxathiolane product (Scheme 28).



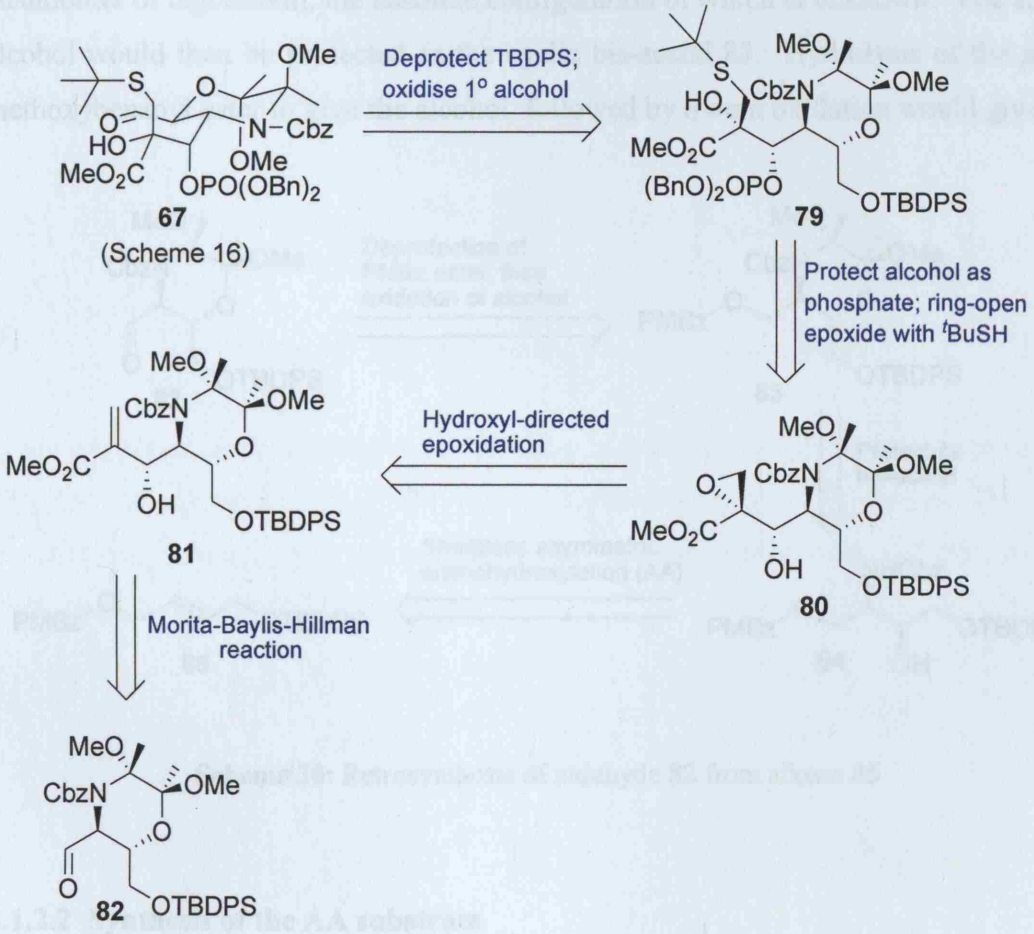
Scheme 28: Attempted oxathiolane formation using acetone

In conclusion, the oxathiolane forming reaction was shown to be successful for a wide range of substrates and the limitations of this reaction were acknowledged.

2.1.2 Synthesis of ring expansion precursor

2.1.2.1 Strategy & retrosynthesis

The ring expansion and 1,3-oxathiolane methodology provided a good basis for the latter stages of our proposed strategy to form tagetitoxin. The remainder of our intended synthetic route is outlined in Scheme 29.

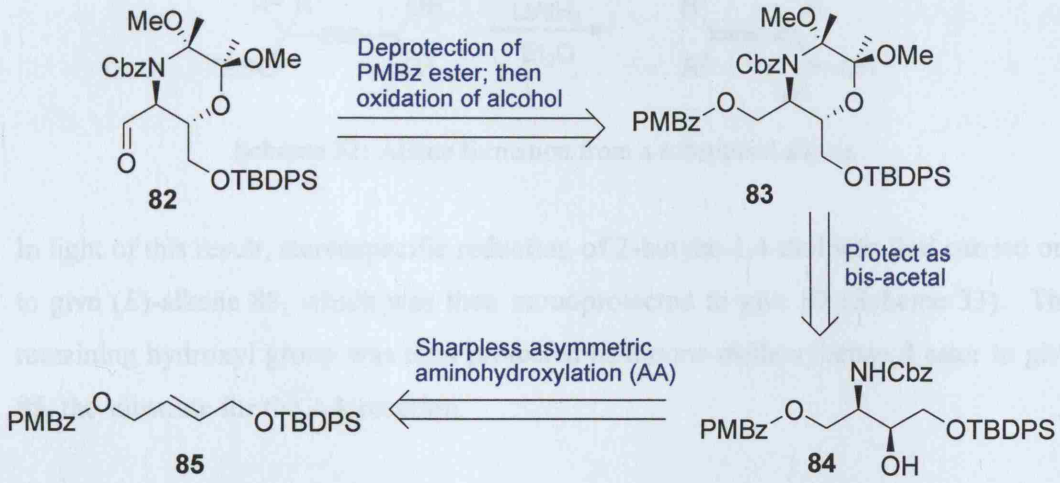


Scheme 29: Retrosynthesis of hydroxysulfide **67** from aldehyde **82**

The aldehyde **67** would be formed from **79** following removal of the TBDPS silyl ether and oxidation of the resulting primary alcohol. The sulfide **79** would in turn be formed by ring-opening of the epoxide **80** with *tert*-butyl thiol, as previously seen in

the methodology work to form *tert*-butyl β-hydroxysulfides. Epoxidation of the alkene **81** would be achieved upon treatment with TBHP in the presence of titanium tetraisopropoxide as a catalyst.[52] Finally, the alkene **81** would be the product of a Morita-Baylis-Hillman reaction of aldehyde **82** with methyl acrylate.[53] Aldehyde **82** was therefore the first key synthetic target of this route to tagetitoxin.

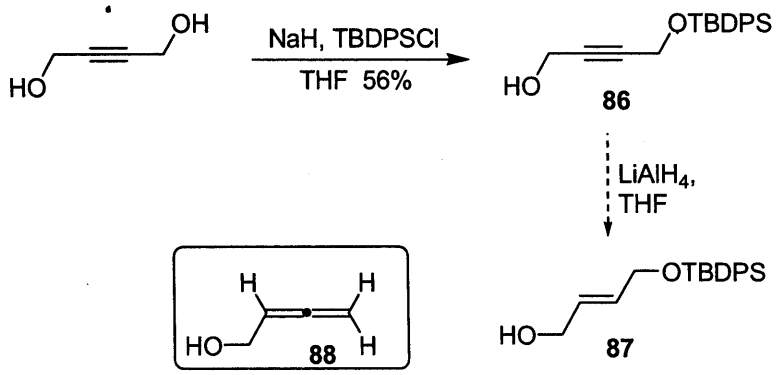
It was envisaged that the aldehyde **82** could be synthesised *via* the route shown in Scheme 30. The vicinal amino alcohol **84** would be constructed *via* Sharpless asymmetric aminohydroxylation (AA) of alkene **85**. The enantiomer formed would depend on the chiral ligand used, imparting the flexibility to synthesise either enantiomer of tagetitoxin, the absolute configuration of which is unknown. The amino alcohol would then be protected as the cyclic bis-acetal **83**. Hydrolysis of the *para*-methoxybenzoyl ester to give the alcohol, followed by Swern oxidation would give **82**.



Scheme 30: Retrosynthesis of aldehyde **82** from alkene **85**

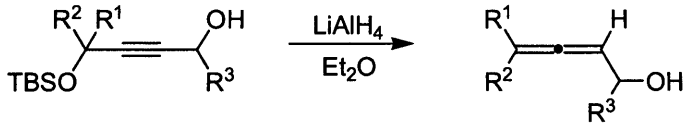
2.1.2.2 Synthesis of the AA substrate

In order to obtain alkene **85**, we initially attempted to form the alkene **87** by monosilylation of 2-butyne-1,4-diol, followed by stereospecific reduction with lithium aluminium hydride (Scheme 31). Although the protection of the alkyne was successful, the subsequent reduction was not, as only the TBDPS-OH moiety and a trace amount of the allene **88** was observed.



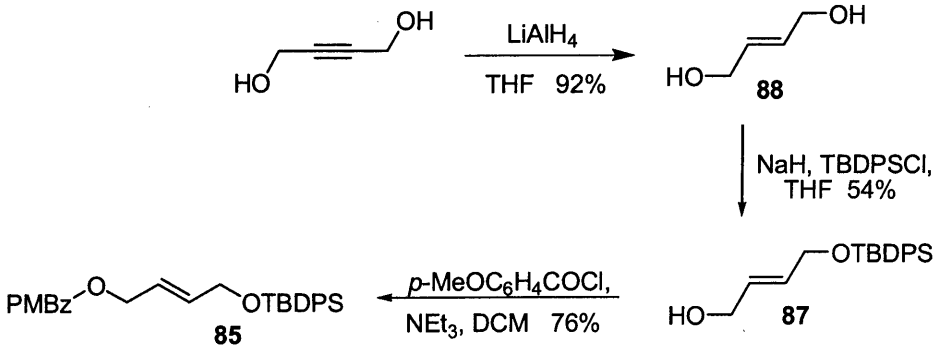
Scheme 31: Attempted formation of alkene **87**

It appears that the hydride attacked the triple bond of the alkyne **86**, forming the allene **88** and displaced the OTBDPS group in the process. Compounds such as **86** have been reported to form allenes when treated with lithium aluminium hydride (Scheme 32).[54]



Scheme 32: Allene formation from a substituted alkyne

In light of this result, stereospecific reduction of 2-butyne-1,4-diol was first carried out to give (*E*)-alkene **88**, which was then monoprotected to give **87** (Scheme 33). The remaining hydroxyl group was then protected as a *para*-methoxybenzoyl ester to give **85**, the substrate for the AA reaction.

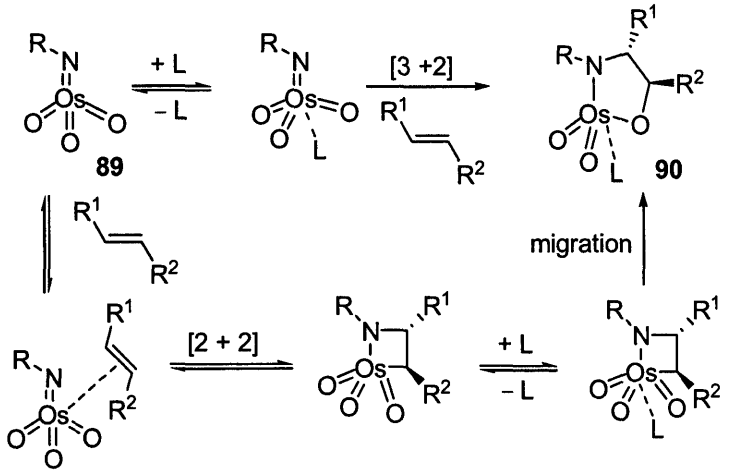


Scheme 33: Formation of AA substrate **85**

2.1.2.3 Overview of the AA reaction[55,56]

The active catalyst of the AA reaction consists of *Cinchona* alkaloid derived ligands and an osmium species. A stoichiometric source of nitrogen provides the amino moiety and acts as a co-oxidant. The enantioselectivity observed is due to the chiral ligands on the catalyst. These also affect the regioselectivity and increase the rate of the reaction.

The first step in the reaction is the deprotonation of the nitrogen source to form the corresponding alkali metal salt, which in turn forms a complex with the osmium species. This imidoxoosmium(VIII) species **89** gives rise to an azaglycolate intermediate **90**, after the addition of the alkene substrate and coordination of the ligand. Two possible pathways have been suggested for the generation of **90**, which differ in the order of alkene addition and ligand coordination, as well as the mode of alkene addition (Scheme 34). The first pathway resembles the mechanism of the dihydroxylation of alkenes with osmium tetraoxide. Here, the ligand first coordinates to the osmium atom in **89** and [3 + 2] syn addition of the alkene follows to give **90**.

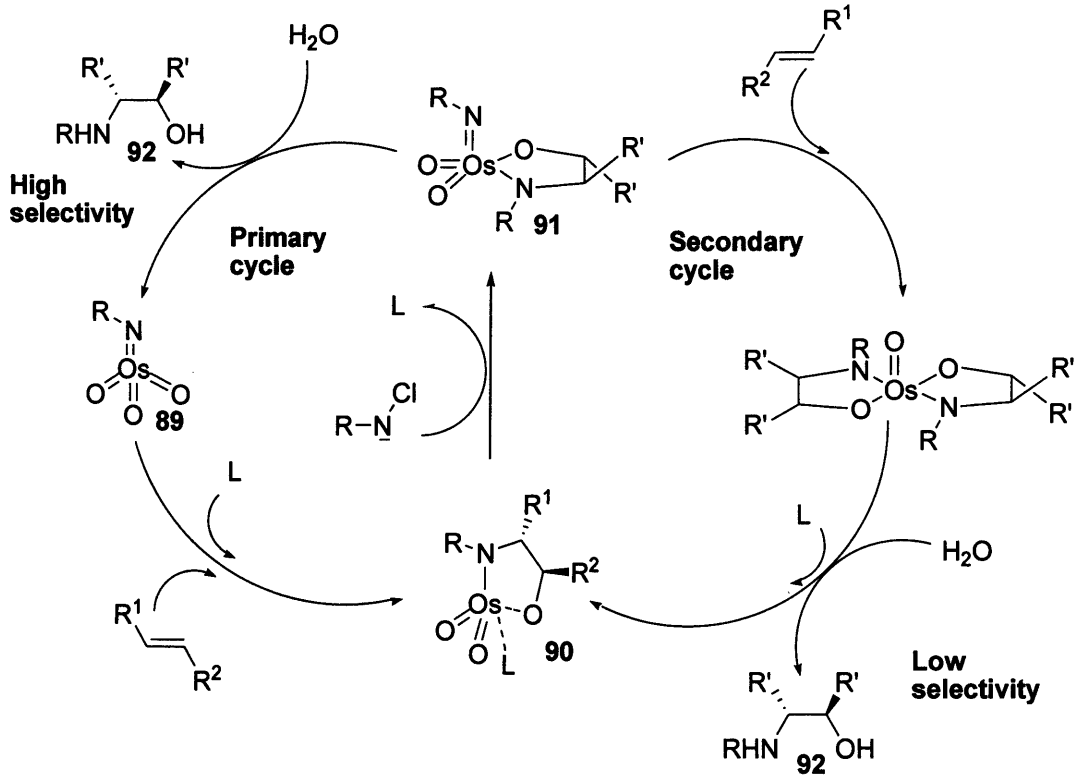


Scheme 34: Possible pathways to form azaglycolate **90**

The alternative possibility mirrors a suggested mechanism of the Sharpless asymmetric dihydroxylation reaction, whereby the imidotrioxoosmium species **89** undergoes [2 + 2] addition, prior to coordination of the ligand, and the azaglycolate **90** is formed after

bond migration. However, due to various experimental and theoretical work that has been carried out,[57-59] the [3 +2] pathway is favoured over the [2 +2] alternative for the dihydroxylation procedure. Despite this precedent, further investigation into the mechanism of the AA reaction is needed to ascertain the exact route along which it proceeds.

Following its formation from the imidotrioxoosmium complex **89**, it is postulated that the azaglycolate **90** is oxidised by the nitrogen source to give the intermediate **91** (Scheme 35). This is then hydrolysed to give the product **92** in high selectivity, and regenerates **89**. It is possible that hydrolysis can occur prior to oxidation, but either alternative produces the product in high selectivity. Intermediate **91**, however, can also undergo addition of a second molecule of alkene and thus enter a secondary catalytic cycle. Unlike in the primary cycle, the addition of the second molecule of alkene is not with the coordination of the chiral ligand, so the product **92** is formed with low selectivity. Therefore, in order to obtain the aminohydroxylation product with high selectivity, the primary catalytic cycle must dominate the secondary cycle. This is achieved by carrying out the reaction in aqueous solvent mixtures, thus enabling intermediate **91** to be efficiently hydrolysed.



Scheme 35: Catalytic cycles of the AA reaction

2.1.2.4 Selection of the AA substrate; influence on regioselectivity

Alkene **85** was chosen as the substrate for the aminohydroxylation reaction as it was reported to give good regioselectivity.[60] The Janda model[60] shows that the regioselectivity of the AA reaction depends on the nature of the substrate and how it fits into the U-shaped binding pocket of the ligand-osmium complex (Figure 12 (a)). If R^1 is a *para*-methoxybenzoyl ester and R^2 is a TBDPS ether, the regioselectivity shown in Figure 12 (b) is observed. This is because there are favourable aryl-aryl interactions between the *para*-methoxy benzene ring and the ligand. The *para*-methoxy substituent further enhances these interactions as it is a π-donor,[55] so this portion of the alkene would be attracted towards the catalytic pocket. The bulky TBDPS group, however, prefers to point away from the sterically hindered pocket. Therefore, having both the *para*-methoxybenzoyl ester and TBDPS ether as substituents on the alkene would strongly favour the desired regioselectivity.

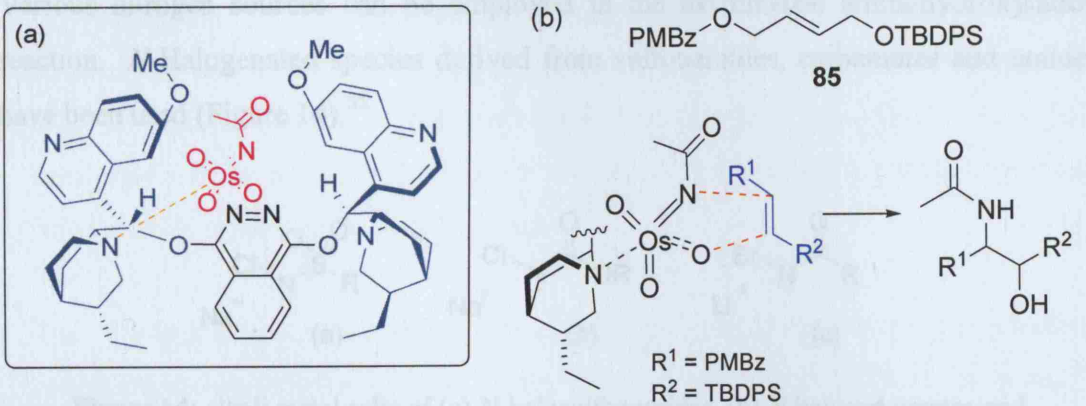


Figure 12: (a) Osmium complex with the ligand $(DHQD)_2PHAL$
(b) Favoured regioselectivity for alkene **85**

We decided to synthesise both enantiomers of the aminohydroxylation product as both would be required to calculate the enantiomeric excess. At this point, it did not matter which enantiomer was made as either would lead to one of the enantiomers of tagetitoxin, the absolute configuration of which is unknown. The ligand $(DHQD)_2PHAL$ would give enantiomer **93a** as it favours addition from the β-face of the alkene, whereas $(DHQ)_2PHAL$ would give the opposite enantiomer **93b** as it directs addition from the α-face (Figure 13).

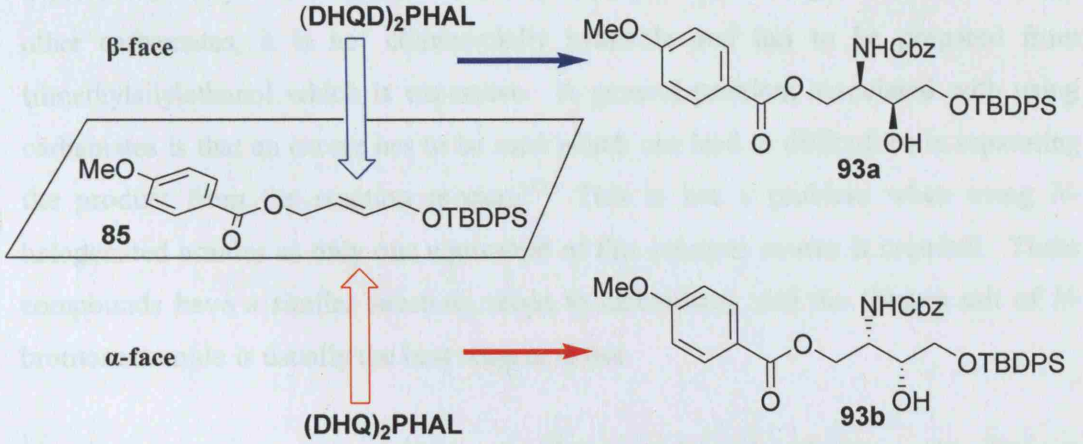


Figure 13: Rationale for the formation of either enantiomer of AA product from alkene **85**

2.1.2.5 Selection of the nitrogen source

Various nitrogen sources can be employed in the asymmetric aminohydroxylation reaction. *N*-Halogenated species derived from sulfonamides, carbamates and amides have been used (Figure 14).[55]

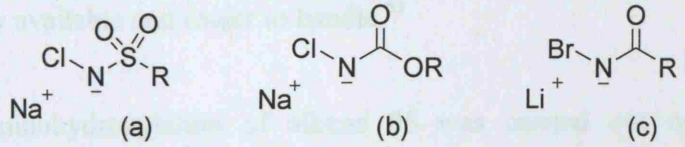


Figure 14: alkali metal salts of (a) *N*-halosulfonamides, (b) *N*-halocarbamates and (c) *N*-haloamides

Chloramine-T (TsN(Na)Cl) is the most frequently used sulfonamide reagent as it is commercially available and inexpensive. In comparison, chloramine-M (MsN(Na)Cl) generally gives higher regio- and enantio-selectivities as well as higher yields, but has to be prepared. The disadvantages of using sulfonamides are that they are difficult to deprotect and have a limited substrate scope. Carbamates have a wider substrate scope and can be deprotected fairly easily under mild conditions. The carbamate nitrogen sources which are usually used are ethyl, benzyl, *tert*-butyl and 2-(trimethylsilyl)ethyl (Teoc) carbamate. The latter is regarded as the superior reagent as it gives the best yields, regio- and enantioselectivities and fastest reaction rates. It can also be

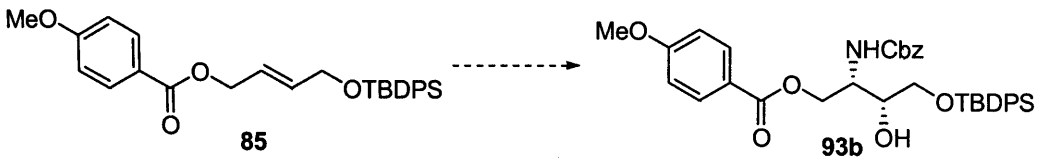
deprotected easily with fluoride.[61] The only drawback of this reagent is that, unlike the other carbamates, it is not commercially available and has to be prepared from trimethylsilylethanol which is expensive. A general problem associated with using carbamates is that an excess has to be used which can lead to difficulties in separating the product from the reaction mixture.[55] This is not a problem when using *N*-halogenated amides as only one equivalent of this nitrogen source is required. These compounds have a similar substrate scope to carbamates, and the lithium salt of *N*-bromoacetamide is usually the best reagent to use.

For the aminohydroxylation of **85** we decided to use benzyl carbamate as the nitrogen source, as it was shown to work well on a range of substrates and the carbamate protecting group could be easily removed later on in the synthesis.

2.1.2.6 Aminohydroxylation with benzyl carbamate

Carbamates are usually converted to the corresponding chloramine salt *in situ* by reaction with *tert*-butyl hypochlorite and sodium hydroxide.[62] However we decided to use 1,3-dichloro-5,5-dimethylhydantoin instead of *tert*-butyl hypochlorite as it has been shown to be a good substitute for the latter with the added benefits of being commercially available and easier to handle.[63]

Thus the aminohydroxylation of alkene **85** was carried out under the reaction conditions shown in Scheme 36 with 1 mol% of the osmium catalyst and the ligand.[63] The vicinal amino alcohol was not isolated and 66% of starting material was recovered after 24 hours. A trace amount of an unidentifiable product or mixture was also isolated. The reaction was repeated using 5 mol% of the osmium catalyst and 6 mol% of the ligand, the relative quantities used by Janda *et al.*[60] This did not improve the result as 68% of starting material was recovered after 28 hours and there was no indication that the product **93b** had been formed.



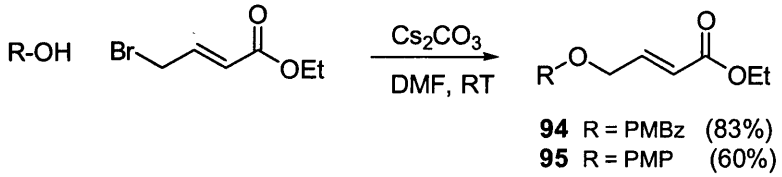
Reagents and conditions: $K_2O_4Os.2H_2O$, NaOH, $(DHQ)_2PHAL$, 1,3-dichloro-5,5-dimethylhydantoin, $CbzNH_2$, $^nPrOH/H_2O$ (1:1), RT

Scheme 36: Attempted AA reaction of **85** with benzyl carbamate

These results led us to use *N*-bromoacetamide, as this reagent had been shown to react successfully with alkene **85** to form the desired product in 59% yield using $(DHQD)_2PHAL$ as the ligand.[60] We envisaged that if this modification gave a successful result, we could subsequently replace the acetyl protecting group on the nitrogen with the more labile Cbz moiety.

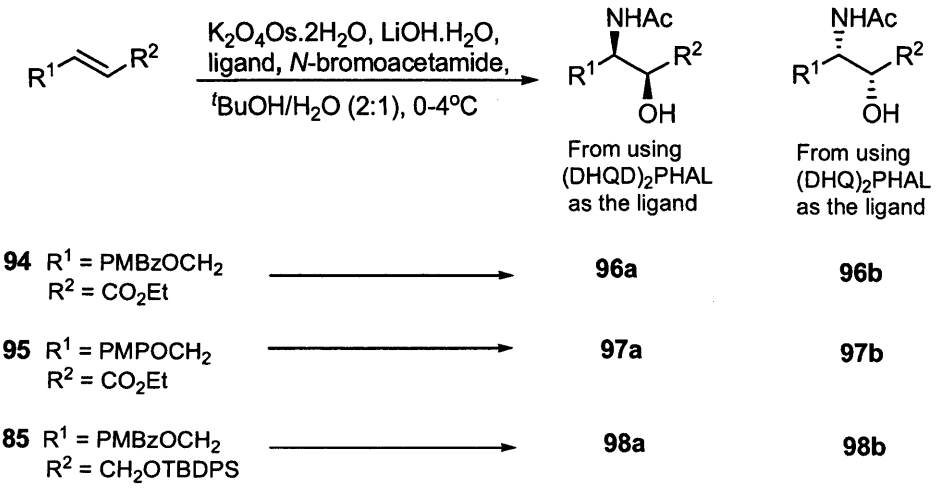
2.1.2.7 Aminohydroxylation with *N*-bromoacetamide

We decided to carry out the AA reaction on the two ester substrates **94** and **95**, previously reported by Janda,[60] as well as the silyl substrate **85**, in order to assess which gave the most useful results. The ester substrates **94** and **95** were formed by reacting the corresponding alcohol with ethyl 4-bromocrotonate (Scheme 37).



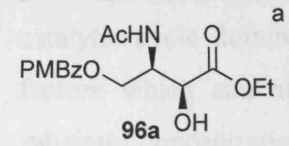
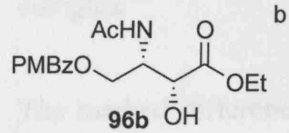
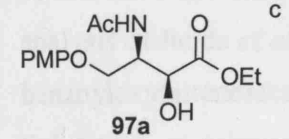
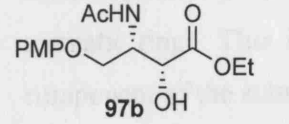
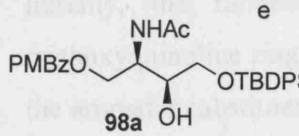
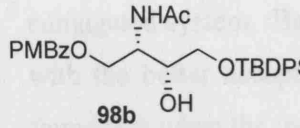
Scheme 37: Formation of ethyl ester AA substrates **94** and **95**

The desired regioselectivity of the AA is also favoured for these substrates as the aryl component will have attractive interactions with the aromatic rings of the catalyst, as has previously been explained (section 2.1.2.4). The AA reaction was carried out using both $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$, in order to form both enantiomers of the amino alcohol product for each substrate (Scheme 38).[64]



Scheme 38: AA reaction with *N*-bromacetamide

The AA reaction with the PMBz/ethyl ester substrate **94** afforded the products **96a** and **96b** in good regioselectivity, excellent enantioselectivity after recrystallisation and moderate yields (Table 3). In comparison, results for the products **97a** and **97b** were poorer in terms of the regioselectivity, although the enantioselectivity was similar. The yields were also lower as it was difficult to separate the regioisomers during recrystallisation. The products **98a** and **98b** were formed as only the desired regioisomer and in good enantioselectivity from the TBDPS/PMBz ester substrate **85**.

AA Product	Yield (columned/ recrystallised)/%	ee (columned/ recrystallised)/ %	Regioselectivity (crude/ columned)
a  **96a**	56/47	81.6/98.4	42:1/20:1
b  **96b**	56/43	90.1/99.5	25:1/10.7:1
c  **97a**	37/14	>89.0/>93.9	13.5:1/15.3:1
d  **97b**	41/22	>90.0/99.3	8.7:1/8:1
e  **98a**	48/41	92[f]	Desired regioisomer only
 **98b**	43/40	88[f]	Desired regiosiomer only

The corresponding diols were also isolated (yields in brackets) [a] **96c** (5%), [b]**96d** (7%), [c]**97c** (7%), [d]**97d** (7%), [e]**98c** (8%); [f]The ee after recrystallisation is given.

Table 3: Results of the AA reaction with *N*-bromoacetamide

In addition to the aminohydroxylation products, a small amount of the dihydroxylation product was also isolated from most of the aminohydroxylation reactions. The presence of an osmium(VIII) species, such as the tetraoxide, leads to the formation of dihydroxylation product. Although osmium(VI) was used in the reactions, it is

possible to form osmium tetroxide *in situ*, *via* hydrolysis of the imidotrioxosmium species **89**. Reduction of the amount of water in the solvent mixture is recommended in order to avoid this, but as water is also important in order to ensure that the primary catalytic cycle dominates (see section 2.1.2.3), a compromise must be met. Other factors which can affect the amount of dihydroxylation product formed are the substrate concentration, the ligand:osmium ratio and rate of addition of the osmium complex.[55]

The marked difference in regioselectivity observed from using the PMBz/ethyl ester substrate **94** and the PMP/ethyl ester substrate **95** may be explained by a more detailed analysis of Janda *et al.*'s rationalisation. Ojima *et al.* have reported that, in general, 4-benzoyloxybutenoates show higher regioselectivity than 4-benzyloxybutenoates.[65] Substrates containing the *O*-benzoyl moiety, such as **94**, give higher regio- and enantioselectivity when there is an electron donating group in the 4-position of the aromatic ring. This is a result of there being stronger interactions between the aryl component of the substrate with the 6-methoxyquinoline portion of the ligand.

Initially, the rationale behind this was attributed to the fact that the 6-methoxyquinoline ring is electron rich and therefore behaves as an electron donor, and the aromatic substituent on the substrate acts as an acceptor. The aromatic ring in 4-benzoyloxybutenoates has a superior π-electron accepting ability than the aromatic ring in 4-benzyloxybutenoates as the carbonyl group in the former provides a conjugated system. Based on this theory, a stronger interaction should, therefore, form with the better acceptor or the more electron deficient ring. However, the authors found that when the methoxy group on the 4-benzoyloxy ring was replaced with a nitro moiety, the aromatic-aromatic interactions between the ligand and substrate were weaker. This led to the realisation that dipole-dipole interactions between the aromatic rings play a significant part. The 6-methoxyquinoline rings in the ligand are also polarised and have opposite dipoles to one another. When the substrate approaches the U-shaped binding pocket of the ligand-osmium catalytic complex, there will be a greater attractive interaction if the aromatic ring also has a strong dipole. This in turn will lead to higher regioselectivity in accordance with Janda's model. The direction of the dipole in the substrate does not matter as it only has to interact with one of the 6-methoxyquinoline rings.

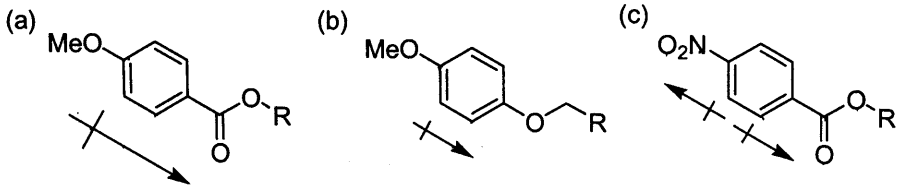


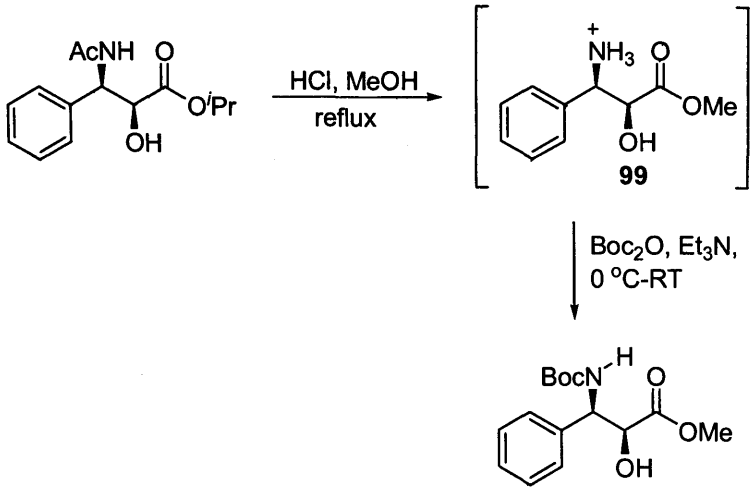
Figure 15: Relative strength and direction of dipoles in substituted benzyl and benzoyl functionalities

With a 4-methoxybenzoyl substituent, a strong dipole exists as the electrons are polarised in the direction of the carbonyl group (Figure 15, (a)). This effect is not as pronounced in the 4-methoxybenzyl moiety (Figure 15, (b)) which lacks the electron withdrawing power of a carbonyl group. In the case of the 4-nitro substituted benzoyloxy compound (Figure 15, (c)), the dipole moments arising from both electron withdrawing substituents are effectively cancelled out. As the 4-methoxybenzyl substituent has a poorer dipole than its 4-methoxybenzoyl counterpart, its interaction with the aromatic ring of the ligand is weaker, and therefore the AA reaction with this substrate has an inferior regioselectivity.

Alkene **85** was favoured as the substrate with which to continue the rest of the synthesis as it gave only the desired regioisomer of the amino alcohols **98a** and **98b** in good enantioselectivity, and meant that fewer manipulations were required to form aldehyde **82**. However, before a final decision was made, it was important to see if the AA products from the three alkene substrates would be suitable for the next step of synthesis; replacement of the *N*-acetyl moiety.

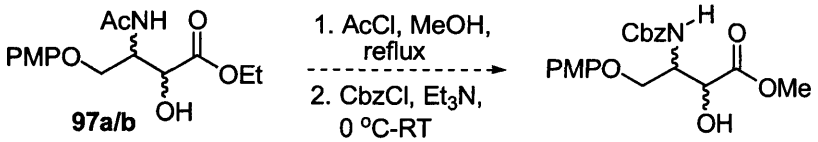
2.1.2.8 Replacement of the *N*-acetyl group

Although the *N*-acetyl group present in the AA products would be able to withstand a variety of reaction conditions, it could be a problem to deprotect in the later stages of the synthesis. The harsh deprotection conditions usually used for hydrolysis of an acetamide, refluxing in HCl,[66] would almost certainly be detrimental to other more sensitive moieties present. Therefore, we sought to substitute the acetyl protecting group on the nitrogen with the more labile carbamate, as was originally intended.



Scheme 39: Lee *et al.*'s method of replacing an *N*-acetyl moiety with an *N*-Boc group

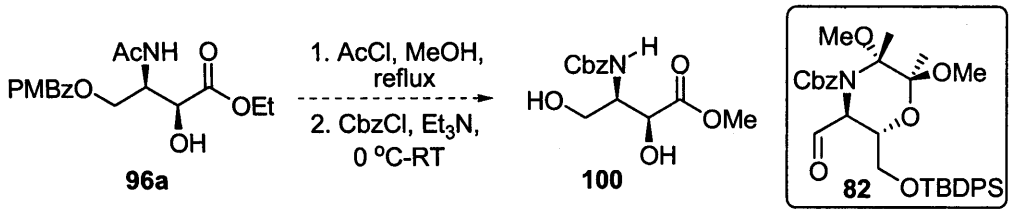
Lee *et al.* have successfully replaced an *N*-acetyl group with an *N*-Boc group *via* the protonated free amine intermediate **99** (Scheme 39).[67] We considered implementing this strategy to replace the *N*-acetyl group in the AA product with the *N*-Cbz functionality. The reaction was first tested on a mixture of both enantiomers† of the AA product **97a/b** (Scheme 40) as this was most suited to the acidic conditions required compared to the other substrates. Unfortunately, no product was isolated.



Scheme 40: Attempted replacement of *N*-acetyl group in **97a/b** with *N*-Cbz group using the protocol of Lee *et al.*

The reaction was also attempted using the PMBz/ethyl ester product **96a** (Scheme 41), although with this compound, the PMBz ester would also be cleaved under the acidic conditions to give the diol **100**. This could be converted to the aldehyde **82**, if the possibility of lactone formation was avoided.

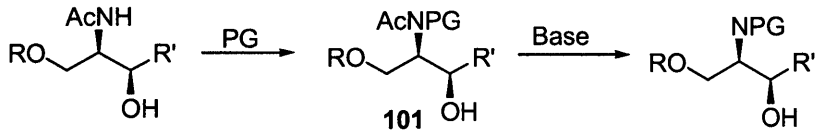
† There was not a substantial amount of either enantiomer available at the time of the reaction.



Scheme 41: Attempted replacement of *N*-acetyl group in **96a** with *N*-Cbz group

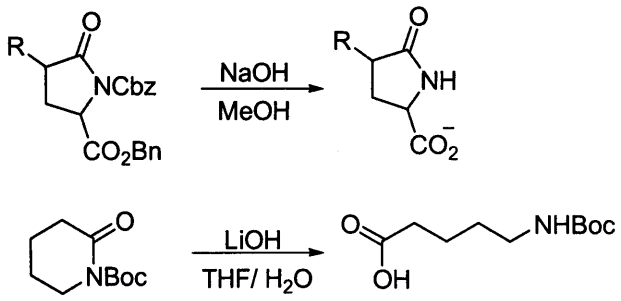
The reaction was also unsuccessful with this substrate as no identifiable product was isolated.

An alternative approach was to convert the *N*-acetyl group to a mixed imide such as **101** upon treatment with another nitrogen protecting group and then selectively cleave the *N*-acetyl bond with base (Scheme 42). The formation of the imide makes cleavage of the acetyl moiety easier as the carbonyl group is more prone to attack by nucleophiles. This method has been successful in converting *N*-acetyl and *N*-benzoyl amino acids to *N*-Boc amino acids.[68]



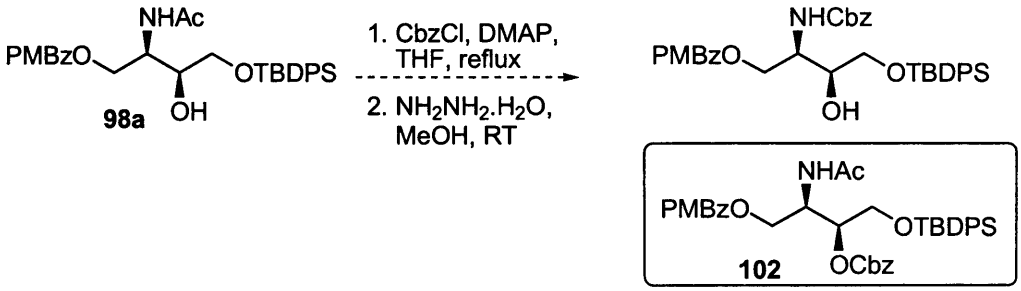
Scheme 42: Replacement of N-acetyl group *via* mixed imide formation

An *N*-Cbz group could also be implemented in this manner, although it has been recognised that cleavage of the *N*-Cbz bond maybe more likely than that of the *N*-acetyl bond.[69] Furthermore, experiments have shown that when Cbz protected lactams were subjected to hydrolysis or methanolysis conditions, the Cbz group was cleaved rather than the amide bond (Scheme 43).[70] In contrast, Boc protected lactams were cleaved at the amide bond under similar conditions.[69]



Scheme 43: Hydrolysis of *N*-Cbz and *N*-Boc protected lactams

Despite the precedent that this type of reaction may be better suited to having a Boc functionality as the other nitrogen protecting group, it was decided that the reaction would first be attempted with benzyl chloroformate. For this conversion, the PMBz/TBDPS AA product **98a** was selected as it was compatible with reaction conditions and was the favoured substrate (see section 2.1.2.7). We decided to proceed using the enantiomer formed from the ligand $(DHQD)_2PHAL$, as the latter gave slightly better results in terms of enantioselectivity and was cheaper than $(DHQ)_2PHAL$.

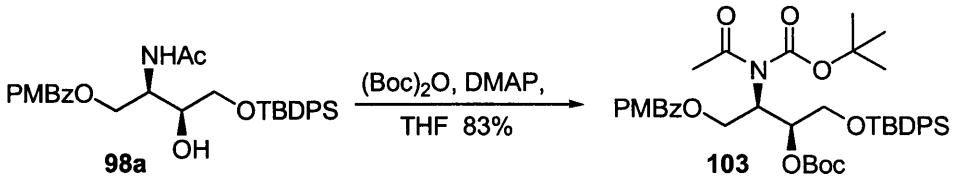


Scheme 44: Attempt to replace *N*-acetyl group in **98a** with *N*-Cbz using mixed imide procedure

Upon treatment of **98a** with benzyl chloroformate, followed by hydrazine monohydrate, no deacetylation occurred and the alcohol was protected instead to give the carbonate **102** (Scheme 44). This was confirmed by mass spectrometry as a molecular ion with a mass of 692 was detected, corresponding to MNa^+.

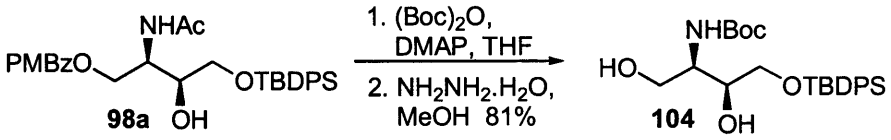
The reaction of **98a** with Boc anhydride was carried out, but analogously to the Cbz

carbonate **102**, the only product isolated was the Boc carbonate. To get around this problem, a larger excess of Boc anhydride was used in order to protect the amide as well as the alcohol. By increasing the number of equivalents of Boc anhydride used, from 2 to 6, the mixed imide **103** was obtained (Scheme 45).



Scheme 45: Mixed imide formation using Boc anhydride

A one-pot reaction was then implemented, whereby following Boc protection, the acetyl functionality and the Boc carbonate were successfully cleaved using hydrazine monohydrate (Scheme 46). Unexpectedly, the PMBz ester was also removed, leading to the diol **104**. Acetamide cleavage under these conditions has been successfully carried out in the presence of methyl, ethyl and benzyl esters, with only a small amount of ester hydrolysis taking place, if any.[68] Therefore, it was surprising to see that diol **104** was the only product isolated.

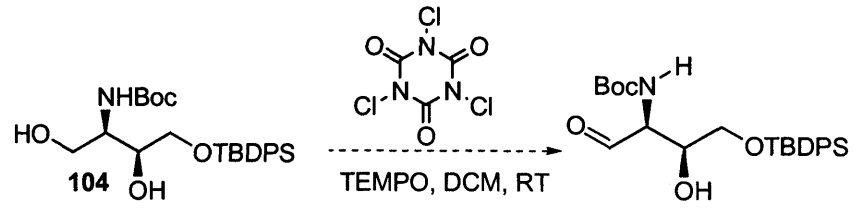


Scheme 46: One-pot mixed imide formation and cleavage of *N*-acetyl group

Excess hydrazine was used in order to quench any surplus Boc anhydride in the reaction mixture. In the interest of avoiding the cleavage of the PMBz ester, the excess of hydrazine was reduced from 6 to 4 eq, but this resulted in an incomplete reaction, with a substantial amount of the mixed imide **103** remaining. Thus, the hydrolysis of the ester was unavoidable.

The selective oxidation of the primary alcohol of **104** was attempted using trichlorocyanuric acid and TEMPO (Scheme 47), a technique which was fruitful for a

similar substrate.[71] Unfortunately, although no starting material remained, there was little evidence that the product had been formed. There are other protocols for the selective oxidation of primary alcohols, such as TEMPO with sodium bromite[72] or NCS,[73] but these were not investigated as we felt that it would be beneficial to explore a more promising strategy which had been established during other work in our group.



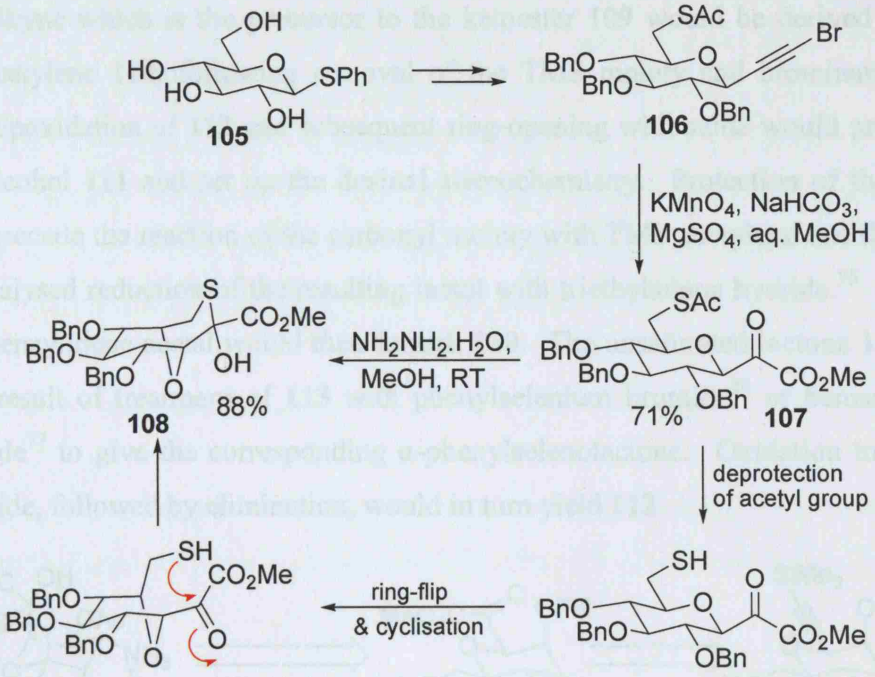
Scheme 47: Attempted oxidation of primary alcohol in **104**

2.1.3 Conclusions on the ring expansion route

Failure to carry out the AA reaction with benzyl carbamate in order to obtain a Cbz protected amine functionality, led to a problematic start to this synthetic route. The AA reaction was successfully carried out using *N*-bromoacetamide and we hoped to replace the acetamide with a Cbz-protected amine, but this was not possible. Although the acetyl moiety was eventually replaced with a Boc group, unexpected cleavage of the PMBz ester created further difficulties. The cumbersome nature of this route led us to adopt a different strategy.

2.2 Cyclisation of a thiol onto an α-ketoester

Julien Plet, another PhD student in the group, carried out the first synthesis of the tagetitoxin core on a partially functionalised carbohydrate substrate.[43,74] The key reaction by which this was achieved was the cyclisation of a thiol onto an electrophilic α-ketoester. Phenyl-1-thio-β-D-glucopyranoside **105** was derived from D-glucose and subsequently converted to bromoalkyne **106** (Scheme 48). Oxidation to the α-ketoester **107** was achieved using potassium permanganate in methanol. Finally, cyclisation occurred upon deprotection of the thioacetate with hydrazine monohydrate, to give the bicyclic core of tagetitoxin **108** as a single stereoisomer.



Scheme 48: Formation of the bicyclic core of tagetitoxin from **105**

After the sulfur is deprotected, the compound undergoes a ring-flip to the boat conformation and then cyclises to form the hemithioacetal. The tetrahydropyran ring of **108** adopts a boat conformation, due to the presence of the three equatorial benzyl groups, whereas the oxathiane ring is in the chair conformation.

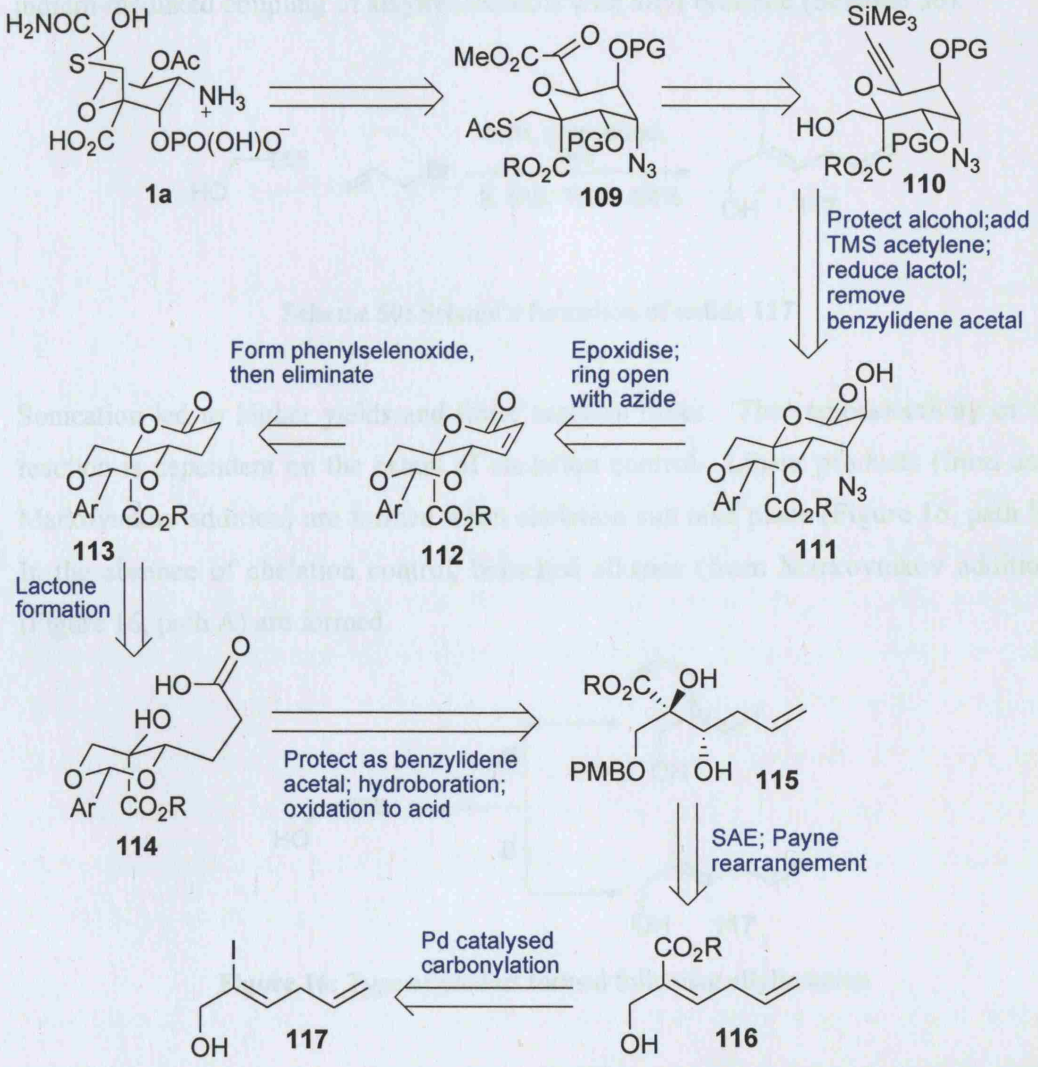
The promising precedent set by this work led us to adopt this strategy in our synthetic work towards tagetitoxin.

2.2.1 Towards tagetitoxin

2.2.1.1 Strategy & retrosynthesis

We initially decided to apply this strategy to a non-carbohydrate based route as it would provide a versatile method to form either enantiomer of tagetitoxin. With carbohydrates, one is more or less limited to one enantiomer (usually the D-sugar) which is the cheapest starting material available. As the retrosynthetic scheme shows (Scheme 49), the final stages of the synthesis would be implemented by the cyclisation

of the deprotected thioacetate onto the ketoester as previously discussed. The bromoalkyne which is the precursor to the ketoester **109** would be derived from the TMS acetylene **110**, following removal of the TMS moiety and bromination using NBS. Epoxidation of **112** and subsequent ring-opening with azide would provide the azido-alcohol **111** and set up the desired stereochemistry. Protection of the alcohol would precede the reaction of the carbonyl moiety with TMS acetylene and the Lewis-acid catalysed reduction of the resulting lactol with triethylsilane hydride.[75] Cleavage of the benzylidene acetal would then furnish **110**. The unsaturated lactone **112** would be the result of treatment of **113** with phenylselenium bromide[76] or benzeneselenic anhydride[77] to give the corresponding α-phenylselenolactone. Oxidation to give the selenoxide, followed by elimination, would in turn yield **112**.

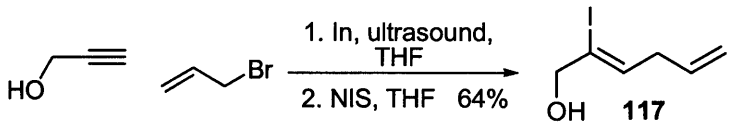


Scheme 49: Retrosynthesis of tagetitoxin **1a** from iodide **117**

The lactone **113** would be formed *via* the intramolecular cyclisation of the alcohol in **114** onto the acid, which would be the product of hydroboration of the alkene **115** followed by oxidation. Protecting the secondary alcohol in **115** as a benzylidene acetal with the PMB ether moiety would leave the tertiary alcohol free for cyclisation. Finally, the diol **115** would be formed after palladium catalysed carbonylation of the iodide **117** to give **116**, which would then undergo Sharpless asymmetric epoxidation and a Payne rearrangement with *para*-methoxybenzyl alcohol.

2.2.1.2 Allyindation approach

Schmid has developed a short route to the iodide **117** and related compounds, *via* the indium-mediated coupling of alkynyl alcohols with allyl bromide (Scheme 50).[78]



Scheme 50: Schmid's formation of iodide **117**

Sonication led to higher yields and faster reaction times. The regioselectivity of the reaction is dependent on the extent of chelation control. Linear products (from anti-Markovnikov addition) are formed when chelation can take place (Figure 16, path B). In the absence of chelation control, branched alkenes (from Markovnikov addition) (Figure 16, path A) are formed.

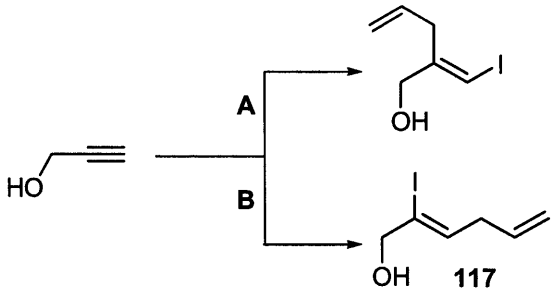
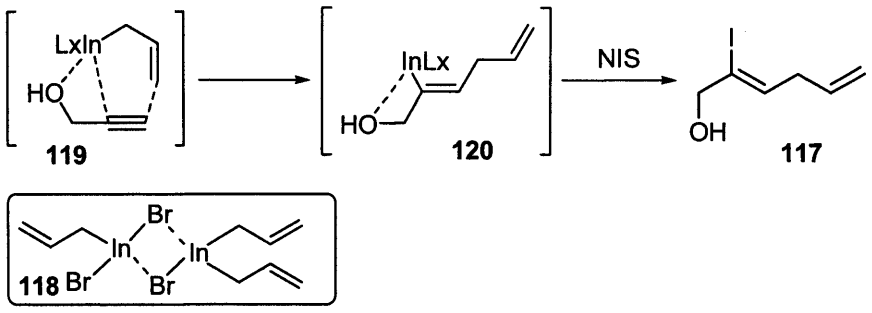


Figure 16: Type of product formed following allylindation

The level of chelation control depends on the distance between the alcohol group and the alkyne. The closer the alcohol is to the triple bond, the better the chance of

chelation. Thus, the linear product **117** is expected when the alkyne is propargyl alcohol.

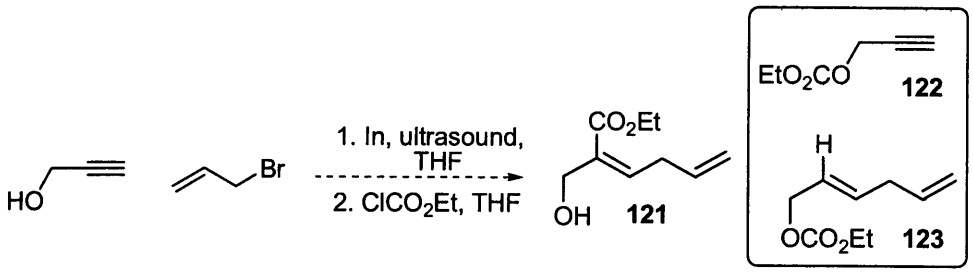
It is proposed that the indium forms the indium sesquibromide complex **118** with allyl bromide *in situ*. This can then chelate with the propargylic alcohol to form a four-membered transition state **119** as shown (Scheme 51). *N*-Iodosuccinimide then quenches intermediate **120** to give the iodide **117**.



Scheme 51: Formation of iodide **117** *via* chelation control

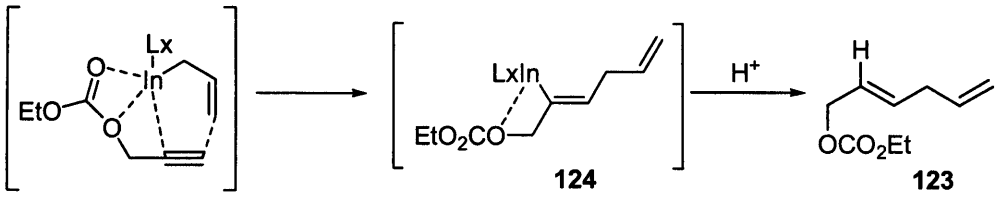
This reaction, therefore, had promise to provide quick and easy access to the iodide **117**. In our hands, the product was formed under the above conditions, as determined by NMR spectroscopy. However, it was not possible to separate the product from a persistent impurity which was unidentified and always present. Alternative sources of electrophilic iodine, such as ICl and I_2 were also tried but did not give better results. In fact, with ICl, a greater amount of the impurity was produced. The best result was obtained when the reaction was carried out on 112 mg of propargyl alcohol with NIS. Although a slight amount of the impurity was present, the material could be taken through to the next stage. However, when the same conditions were applied to 228 mg of propargylic alcohol, there was a considerable deterioration of the results as a significant amount of the impurity was present compared to the product. The lack of reproducible results and inability to form reasonable quantities of the iodide meant that we had to revise our approach.

We attempted to quench the intermediate **120** with ethyl chloroformate rather than an iodide source in the hope that unsaturated ester **121** could be formed directly (Scheme 52).



Scheme 52: Attempt to form unsaturated ester **121** *via* allylindation

A 1:4 mixture of the carbonates **122** and **123** was obtained instead. It is likely that compound **123** is formed from the quenching of a vinylindium species with HCl which is formed *in situ* (Scheme 53). The vinylindium species **124** may be formed by chelation-controlled coupling of an allylindium with the propargyl carbonate; alternatively, the allylindation and protodemetallation may precede carbonate formation.



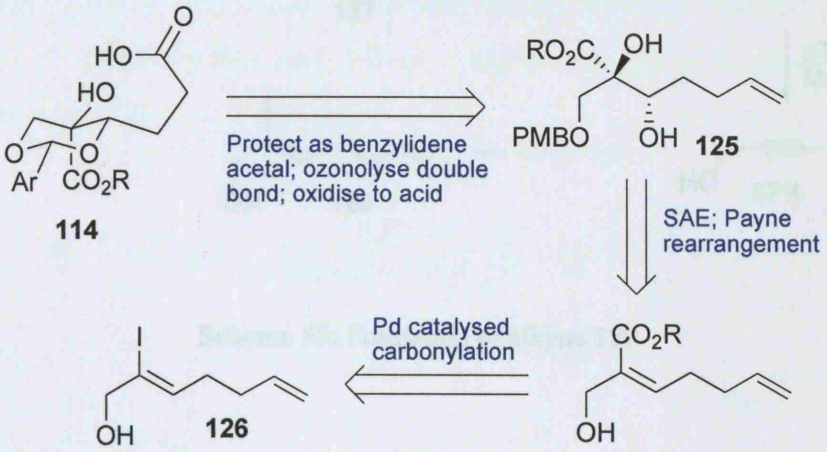
Scheme 53: Proposed explanation for the formation of carbonate **123**

The lack of success with allyindation led us to investigate an alternative route to the acid **114**.

2.2.1.3 Coupling between acetylide and bromoalkene approach

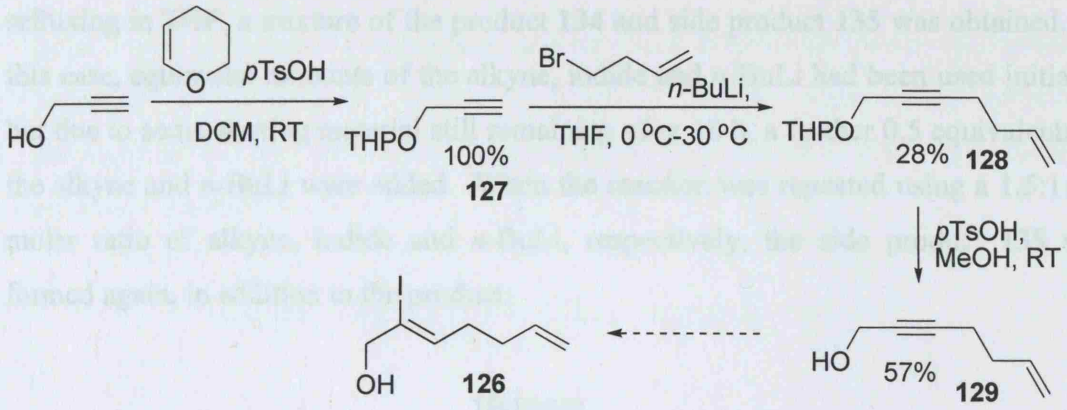
The strategy to from acid **114** was slightly amended in the sense that iodide **126** would be used instead of iodide **117** (Scheme 54). Formation of iodide **126** was to be achieved *via* the reaction of an acetylide anion with a bromoalkene. We decided to use 4-bromobutene, rather than allyl bromide, in order to avoid the possibility of the resulting enyne becoming conjugated under the basic conditions. The extra carbon atom in the alkene chain meant that the acid **114** would be formed from the ozonolysis

and oxidation of alkene **125**, rather than hydroboration followed by oxidation as was initially intended.



Scheme 54: Retrosynthesis of acid **114** from iodide **126**

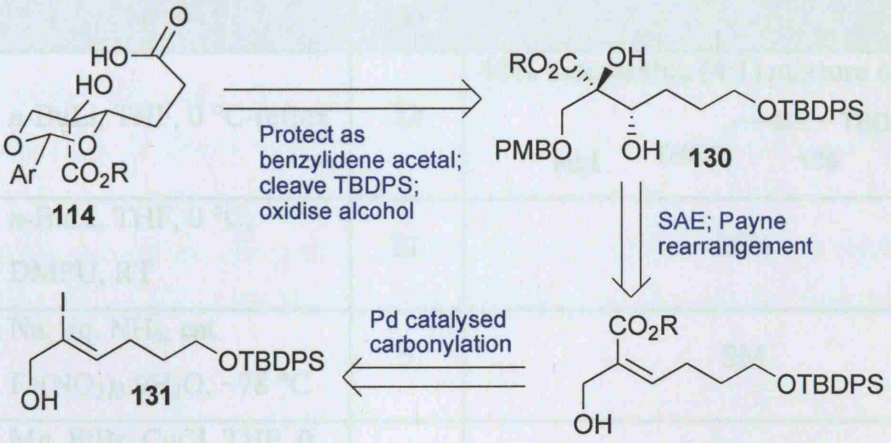
Propargyl alcohol was protected as the THP ether **127** in quantitative yield (Scheme 55). Deprotonation with *n*-BuLi formed the acetylide anion, which effected nucleophilic substitution on 4-bromobut-1-ene, to give **128**. The low yield obtained was a result of the reaction not going to completion. A considerable amount of starting material still remained in the reaction mixture after 76 h. The reaction was repeated and heated at reflux for 42 h, but again, the starting material was not fully converted and product was obtained in a similar 24% yield. In another attempt to drive the reaction to completion, DMPU was added as it is a dipolar aprotic solvent and promotes S_N2 reactions. However, no improvement in the conversion of starting material, and consequently the yield of product, was observed. The coupled product **128** was subsequently treated with mild acid to remove the THP protecting group and give **129**. The iodide **126** could then have been formed *via* hydroalumination of **129**, followed by quenching with iodine, but the unsatisfactory yields encountered in the initial stage led us to pursue another route.



Scheme 55: Formation of alkyne **129**

2.2.1.4 Coupling between acetylide and bromoalcohol approach

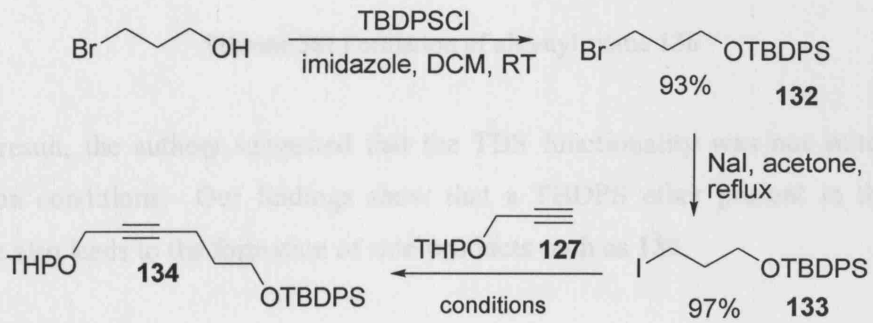
Rather than coupling the alkyne **127** with a bromoalkene, it could also be coupled with a protected bromoalcohol. Referring to the retrosynthesis, acid **114** could be obtained by the deprotection of the silyl ether in diol **130**, followed by oxidation (Scheme 56).



Scheme 56: Retrosynthesis of acid **114** from iodide **131**

3-Bromopropan-1-ol was protected as the TBDPS ether **132** and the Finkelstein reaction was used to obtain the iodide **133** (Scheme 57). The subsequent alkylation of the acetylene **127** to form **134** was problematic. A range of reaction conditions were investigated, the best results of which are shown in Table 4. By just using *n*-BuLi and

refluxing in THF, a mixture of the product **134** and side product **135** was obtained. In this case, equimolar amounts of the alkyne, iodide and *n*-BuLi had been used initially, but due to some starting material still remaining after 18 h, a further 0.5 equivalents of the alkyne and *n*-BuLi were added. When the reaction was repeated using a 1.5:1:1.3 molar ratio of alkyne, iodide and *n*-BuLi, respectively, the side product **135** was formed again, in addition to the product.



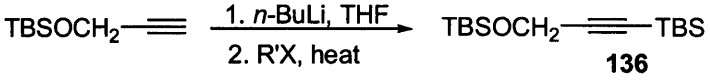
Scheme 57: Formation of alkyne **134**

Entry	Reaction conditions	Time /h	Best result
1	*n*-BuLi, THF, 0 °C-reflux	22	40% inseparable (4:1) mixture of product and THPO–≡–TBDPS **135**
2	*n*-BuLi, THF, 0 °C; DMPU, RT	21	26%
3	Na, liq. NH_3, cat. $Fe(NO_3)_3.9H_2O$, −78 °C	5	SM
4	Mg, EtBr, CuCl, THF, 0 °C-RT-50 °C	77	SM
5	NaH, DMSO, RT	22	SM
6	MeLi·LiBr, THF, DMSO	21	59%

Table 4: Results for the alkylation of acetylene **127** with iodide **133**

Alkylations of terminal acetylenes have been reported to proceed in excellent yields

under these conditions.[79] Moreover, they are said to proceed cleanly and without formation of side-products. However, it was found that when a silyl protected propargyl alcohol was used, the alkynyl silane **136** was formed, as part of a mixture of products (Scheme 58).

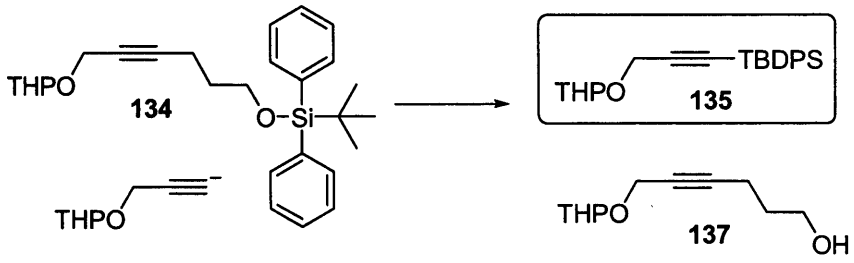


Scheme 58: Formation of alkynyl silane **136**

As a result, the authors suggested that the TBS functionality was not suited to the reaction conditions. Our findings show that a TBDPS ether present in the halide source also leads to the formation of side-products such as **136**.

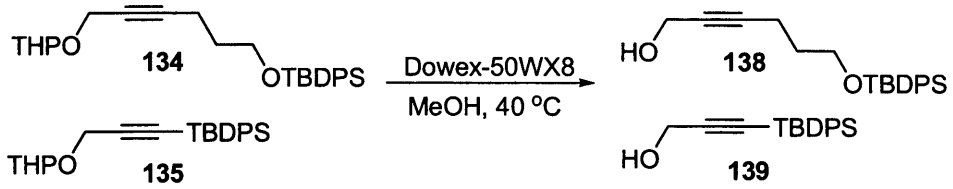
Next, DMPU (Table 4, entry 2) was added to the reaction mixture. The conversion of starting material to product was still poor with a product yield of 26%, although no side product **135** was observed. In this case equimolar amounts of alkyne, iodide and *n*-BuLi were used. When the reaction was repeated with having a slight excess of the alkyne and/or *n*-BuLi, similar yields were obtained, and the side product **135** was still absent. However, when a greater excess of the alkyne and *n*-BuLi (4 and 3.6 eq respectively) were added, both the product and side product were obtained in 2:1 ratio. It appears that the alkynyl silane **135** does not form as easily in the presence of DMPU.

The occurrence of the side product **135** may be due to the excess of the alkynyl anion attacking the silicon of the TBDPS ether and displacing the alcohol moiety (Scheme 59).



Scheme 59: Formation of side product **135**

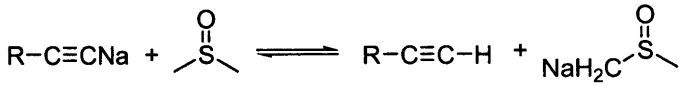
This result is surprising as the silicon atom is so sterically hindered. The TLC of the reaction mixture showed that a polar compound, likely to be the alcohol **137**, was present due to a spot on the baseline. When the product and side product mixture were heated in methanol with acidic exchange resin[80] (Scheme 60), it was possible to separate the alcohol **139** in order to confirm the structure of side product **135** by NMR spectroscopy.



Scheme 60: Formation of alcohols **138** and **139**

The classical method of forming acetylide anions with sodium amide (Table 4, entry 3) was also attempted, but only starting material was obtained each time. The same result was obtained using the Grignard procedure (Table 4, entry 4).

Alkylations of acetylenes have also been successfully carried out with sodium hydride and DMSO[81] which, as an aprotic dipolar solvent, promotes S_N2 reactions. However, a problem with using these conditions is that DMSO can be deprotonated by the acetylide anion that is formed, which can lead to alkylation of the solvent rather than the acetylene (Scheme 61).[82,83]



Scheme 61: Metallation of DMSO

The position of the equilibrium depends on the relative acidities of the acetylene and DMSO. As DMSO is fairly acidic, the acetylene must also be sufficiently acidic in order to prevent metallation of the solvent.[79] Terminal acetylenes which contain a phenyl **140** or diethoxymethane **141** group are more acidic than those containing a simple alkyl chain **143**, for example (Figure 17).[82]

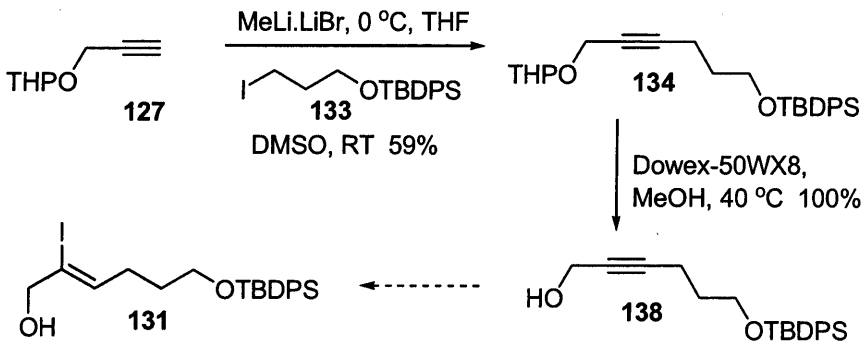
$$\underset{\mathbf{140}}{Ph-C\equiv C-H} = \underset{\mathbf{141}}{(EtO)_2CH-C\equiv C-H} > \underset{\mathbf{142}}{ROCH_2-C\equiv C-H} > RO(CH_2)_2-C\equiv C-H > \underset{\mathbf{143}}{R-C\equiv C-H}$$

Figure 17: Relative acidities of various alkynes in DMSO

This is a result of an inductive stabilising effect which these groups exert on the resulting acetylene anion after deprotonation. Acetylenes of the type **142** are also quite acidic and alkylations of acetylenes where R is a THP group have been successfully carried out in DMSO.[82] It appears that the presence of a propargylic oxygen atom is an influencing factor with regard to the degree of stabilisation and therefore, the acidity, of the acetylene.

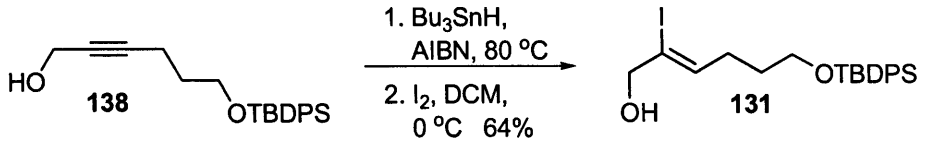
Thus, THP alkyne **127** was treated with sodium hydride in DMSO (Table 4, entry 5) under the same conditions employed by Rollinson *et al.*[84] Unfortunately, only starting material was obtained. By changing the base to methyllithium, as a complex with lithium bromide (Table 4, entry 6), a satisfactory result was achieved, giving the alkylated acetylene **134** in 59% yield.

The THP ether was then deprotected with acidic resin[80] to give the alcohol **138** (Scheme 62). Direct conversion of **138** to the iodide **131** was attempted by carrying out hydroalumination to form a vinylaluminium species which could then be quenched with iodine. Using DIBAL[85] no product formation was observed. When a mixture of $LiAlH_4$ and $AlCl_3$ [86] was employed, some product was formed but could not be isolated from impurities. In addition, this result was not reproducible.



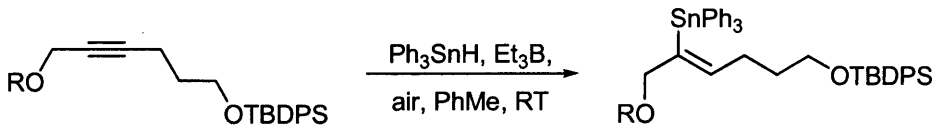
Scheme 62: Formation of alkyne **138**

These inadequate results led us to investigate forming the iodide **131** *via* the corresponding stannane. The one-pot stannylation and iodination procedure[87,88] depicted in Scheme 63 furnished **131** in a reasonable yield.



Scheme 63: Formation of iodide **131**

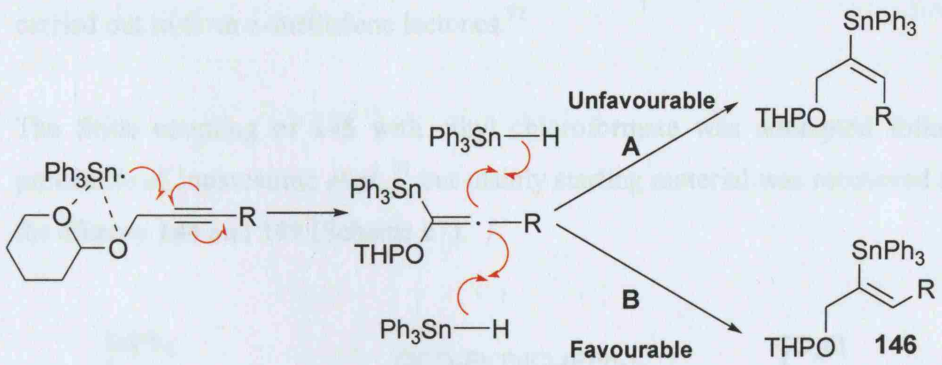
Vinyl stannane formation with triphenyltin hydride and triethylborane was also investigated. Reaction with the alcohol **138** gave a disappointing 9% of isolated product **144** (Scheme 64 (a)). 41% of a 1.1:1 mixture of the product and starting material (which was co-eluted during column chromatography) was also obtained. When the THP protected alkyne **134** was subjected to the same conditions, considerably more product was formed than with the propargyl alcohol **138**, as determined by the crude NMR (Scheme 64 (b)). However, starting material still remained and it was not possible to separate the latter from the product **145** using column chromatography. A vast improvement was made to this situation by increasing the concentration at which the reaction was carried out from 0.1 M, as stated in the literature,[89] to 1.0 M (Scheme 64 (c)). This alteration not only gave full conversion of starting material, but also reduced the time of the reaction from at least 18 h to just over 1 h.



(a) R = H; concentration = 0.1 M; 9% of product **144** (and 41% of 1.1:1 mixture of product **144** and SM **138**)
(b) R = THP; concentration = 0.1 M; inseparable (50:50) mixture of product **145** and SM **134**
(c) R = THP; concentration = 1.0 M; 99% of product **145**; regioselectivity: >85% (crude); >90% (columned)

Scheme 64: Results of hydrostannylation with triphenyltin hydride

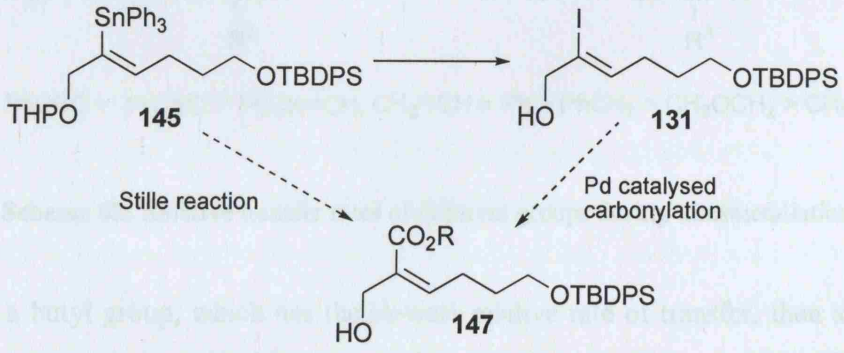
The excellent regioselectivity[‡] observed is due to the coordination of the propargylic oxygen atom to the triphenyltin radical (Scheme 65). Coordination of the THP oxygen to the tin radical may also occur.[88,90]



Scheme 65: Rationale for observed regioselectivity in hydrostannylation reaction

In the final step, hydrogen abstraction may occur *cis* to the triphenyltin moiety (path A) or *cis* to the THP ether (path B). The latter is more favourable as there is less steric hindrance for the incoming stannane, so the regioisomer **146** dominates.

The next target in the synthesis was formation of the unsaturated ester **147**. This could be achieved by converting **145** to the iodide **131**, followed by palladium catalysed carbonylation with carbon monoxide (Scheme 66). However, we decided to investigate an alternative approach, whereby **147** could be formed *via* a Stille reaction of **145** with a chloroformate. This route was not only beneficial in that it had one less synthetic step but also avoided the use of a poisonous gas.

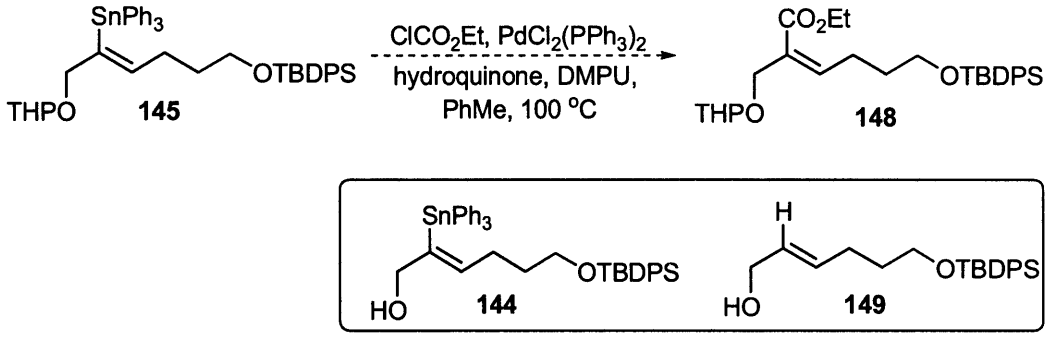


Scheme 66: Routes to the unsaturated ester **147**

[‡] The regiochemistry of the vinyl stannane products was validated by NOE experiments.

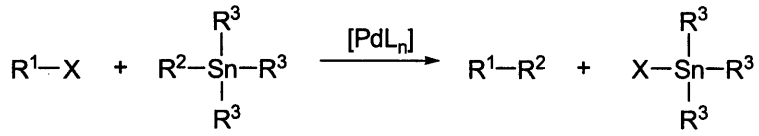
A palladium catalysed cross coupling reaction of vinyl stannanes with chloroformates and carbamoyl chlorides has been reported which provided the corresponding esters and amides in good yields.[91] An intramolecular version of this reaction has also been carried out to form α-methylene lactones.[92]

The Stille coupling of **145** with ethyl chloroformate was attempted following the procedure of Jousseaume *et al.*,[91] but mainly starting material was recovered as well as the alkenes **144** and **149** (Scheme 67).



Scheme 67: Attempted Stille coupling of stannane **145** with ethyl chloroformate

This led us to examine the use of the tributyltin analogue of **145** instead. Stille's studies on the cross coupling between organostannanes and acid chlorides revealed that in the transmetallation step, the rate of transfer of the different groups on tin varies (Scheme 68).[93,94]



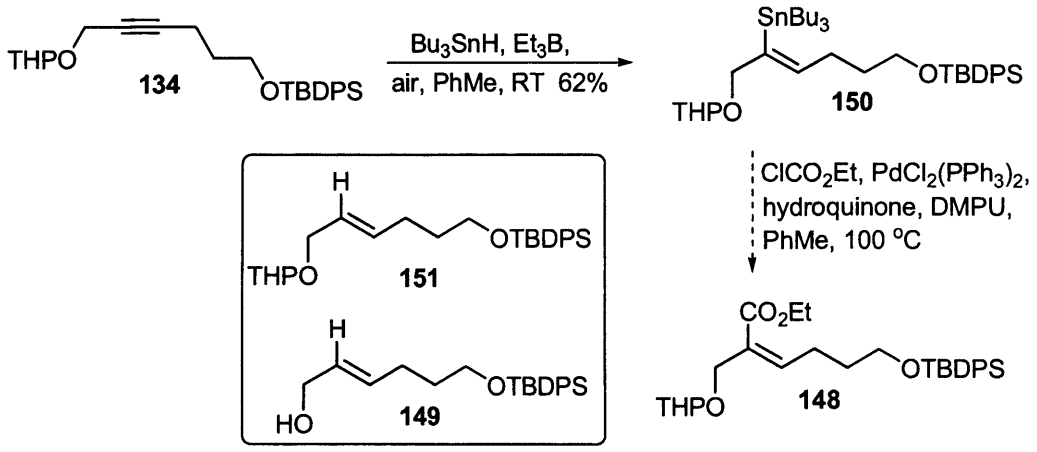
R^2 = PhC≡C > PrC≡C > PhCH=CH, CH_2=CH > Ph > $PhCH_2$ > CH_3OCH_2 > CH_3 > Bu

Scheme 68: Relative transfer rates of different groups during transmetallation

If R^3 is a butyl group, which has the slowest relative rate of transfer, then any other group on the tin is more likely to be transferred to the palladium complex. Therefore, for the tributyltin counterpart of **145**, the transfer of the alkene moiety to ethyl

chloroformate should occur more readily and result in the desired product.

The tributyltin intermediate **150** was prepared in an analogous manner to **145** *via* triethylborane initiated radical hydrostannylation, albeit in a lower yield (Scheme 69). The regioselectivity (>70% in crude mixture and >80% following purification) was also poorer than for the triphenyltin compound.

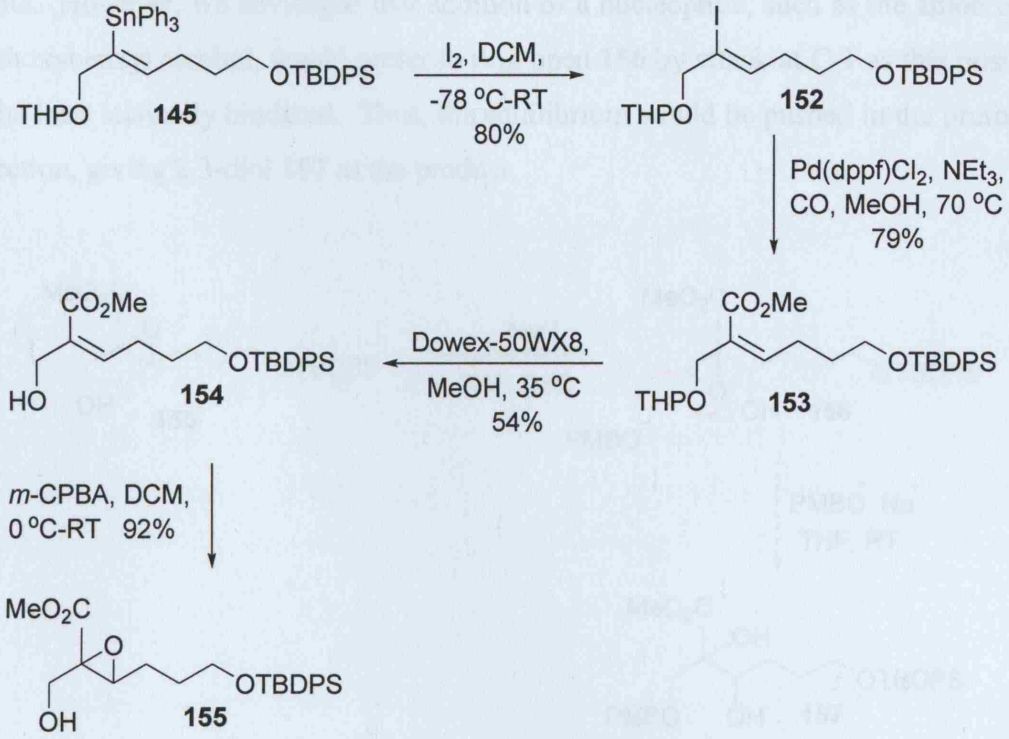


Scheme 69: Attempted Stille reaction of stannane **150** with ethyl chloroformate

Subsequent exposure of this substrate to the cross coupling conditions as before, did not result in product formation (Scheme 69). Although there was little starting material left, alkenes **149** and **151** were formed. A possible cause for the production of these compounds was that the ethyl chloroformate may have been contaminated with HCl. The reaction was repeated using freshly distilled ethyl chloroformate, but no improvement was seen. These results meant that we had to pursue the route *via* the iodide as previously described.

The iodination[95] of **145** proceeded in good yield to give **152** (Scheme 70) and this was converted to the unsaturated ester **153** *via* palladium-catalysed carbonylation. Initially, *trans*-dichlorobis(triphenylphosphine)palladium(II) was employed as the catalyst,[96] but it was difficult to separate this from the product during purification and the reaction had to be heated for 84 h before all the starting material was consumed. By using 1,1′ bis(diphenylphosphino)ferrocenepalladium(II) chloride instead,[97] not only was pure product isolated in good yield (79%), but the reaction time was reduced to 5 h.

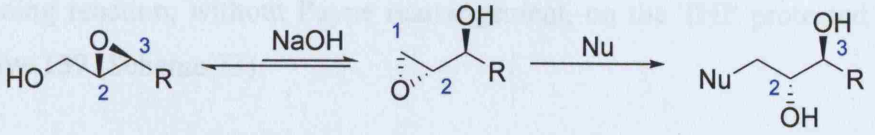
Deprotection of the THP ether afforded **154**, which was epoxidised to give **155**, the substrate for the proposed Payne rearrangement. At this stage, we decided to form the racemic epoxide. If the Payne rearrangement was successful then, the epoxide would later be formed stereoselectively *via* Sharpless asymmetric epoxidation.



Scheme 70: Formation of epoxide **155** from stannane **145**

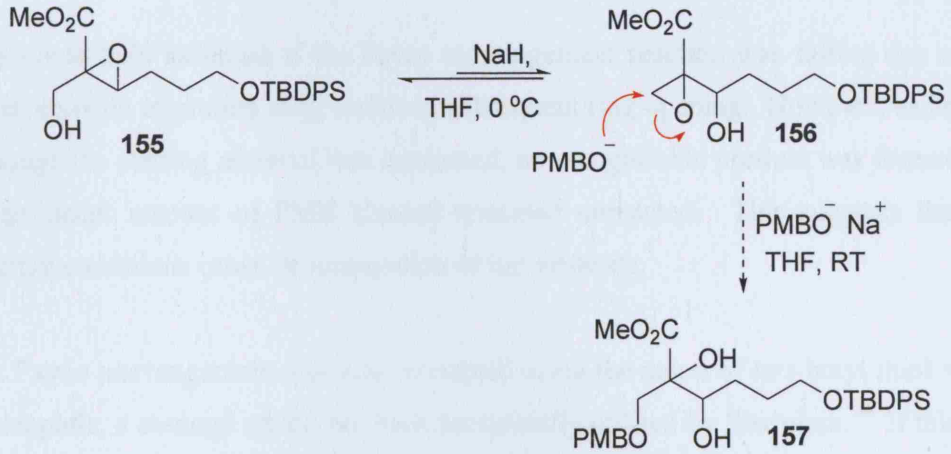
2.2.1.5 Payne Rearrangement

The Payne rearrangement of 2,3-epoxy alcohols to 1,2-epoxy alcohols proceeds under basic conditions and can be used to initiate nucleophilic attack at C-1 of the former (Scheme 71).[98,99] From a trans-epoxide a 2,3-anti diol is formed as shown.



Scheme 71: Payne rearrangement

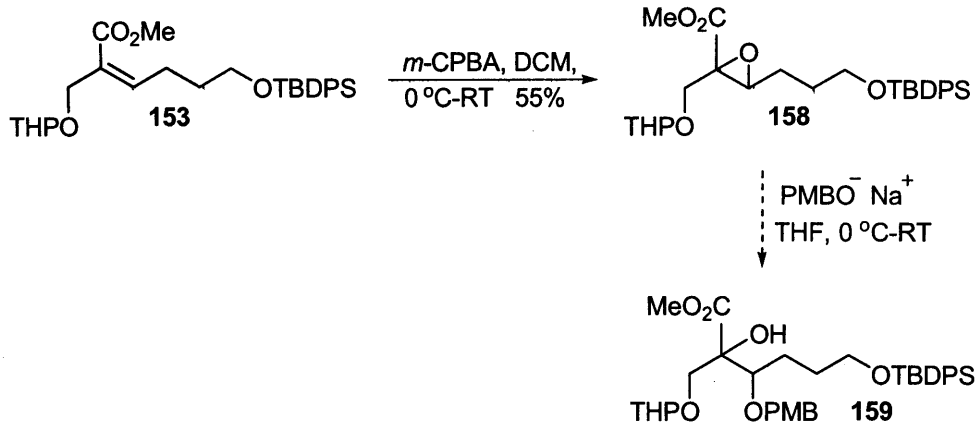
We aimed to exploit this rearrangement to form the diol **157** (Scheme 72). Sodium hydride would be used to deprotonate the alcohol in **155**, which would then cyclise round to form the 1,2-epoxide **156** and ring open the original 2,3-epoxide in the process. These two forms would exist in equilibrium, with the 2,3-epoxide being favoured as, being the more substituted oxirane, it is the most thermodynamically stable. However, we envisaged that addition of a nucleophile, such as the anion of *p*-methoxybenzyl alcohol, would prefer to ring open **156** by attack at C-1 as this position is the least sterically hindered. Thus, the equilibrium would be pushed in the preferred direction, giving 2,3-diol **157** as the product.



Scheme 72: Payne rearrangement strategy to form diol **157**

Unfortunately, despite several attempts, no product was isolated. The starting material was rapidly consumed in each case, but it was not being converted into the desired product. Moreover, there was no evidence of any incorporation of the PMB alcohol, which was usually recovered in considerable amounts after column chromatography. Additionally, there were also signs that the silyl ether had been cleaved.

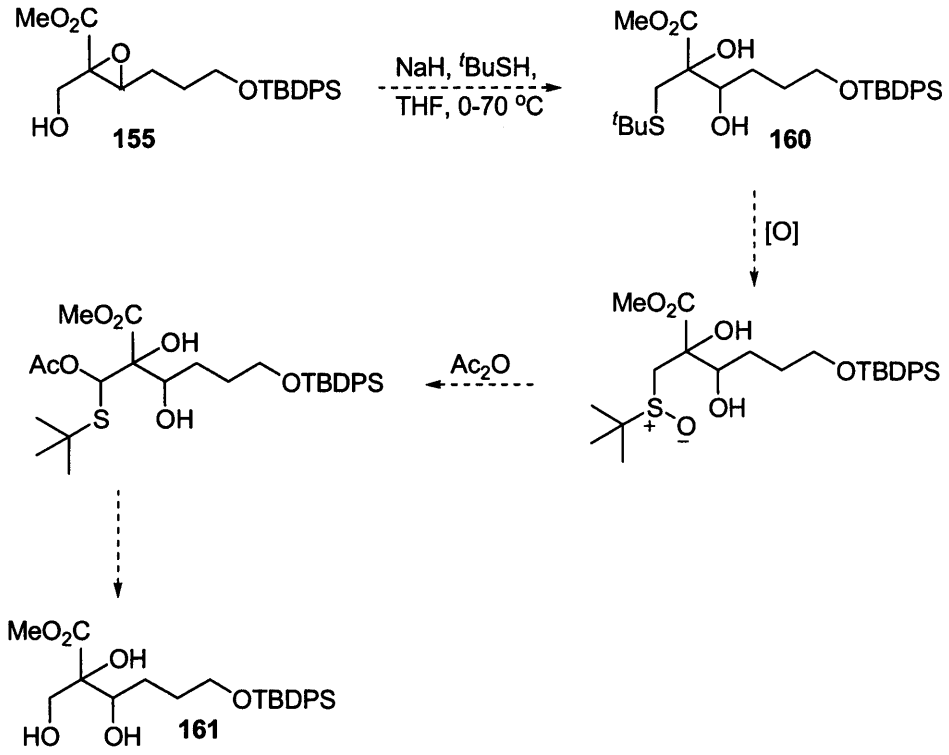
In light of these findings, we thought that it would be worthwhile to attempt a simpler ring opening reaction, without Payne rearrangement, on the THP protected substrate **158** to give **159** (Scheme 73).



Scheme 73: Attempted ring-opening of epoxide **158** with PMB alcohol

This could help ascertain if the Payne rearrangement reaction was failing due to the initial epoxide migration step, or due to subsequent ring opening. However, as before, although the starting material was consumed, no recognisable product was formed and a significant amount of PMB alcohol remained unreacted. This suggests that the reaction conditions cause decomposition of the substrate.

The Payne rearrangement was also attempted using the anion of *tert*-butyl thiol as the nucleophile, a strategy which has been successfully utilised by Sharpless.[99] If this was successful, the product **160** could be transformed into **161**, *via* a Pummerer reaction (Scheme 74). Unfortunately, the reaction using *tert*-butyl thiol was also unsuccessful.



Scheme 74: Strategy to form triol **161** *via* Payne rearrangement with *tert*-butyl thiol

In light of these results, and due to time implications, we decided that it would be more beneficial to stop work on tagetitoxin and start the synthesis of its analogue, decarboxytagetitoxin.

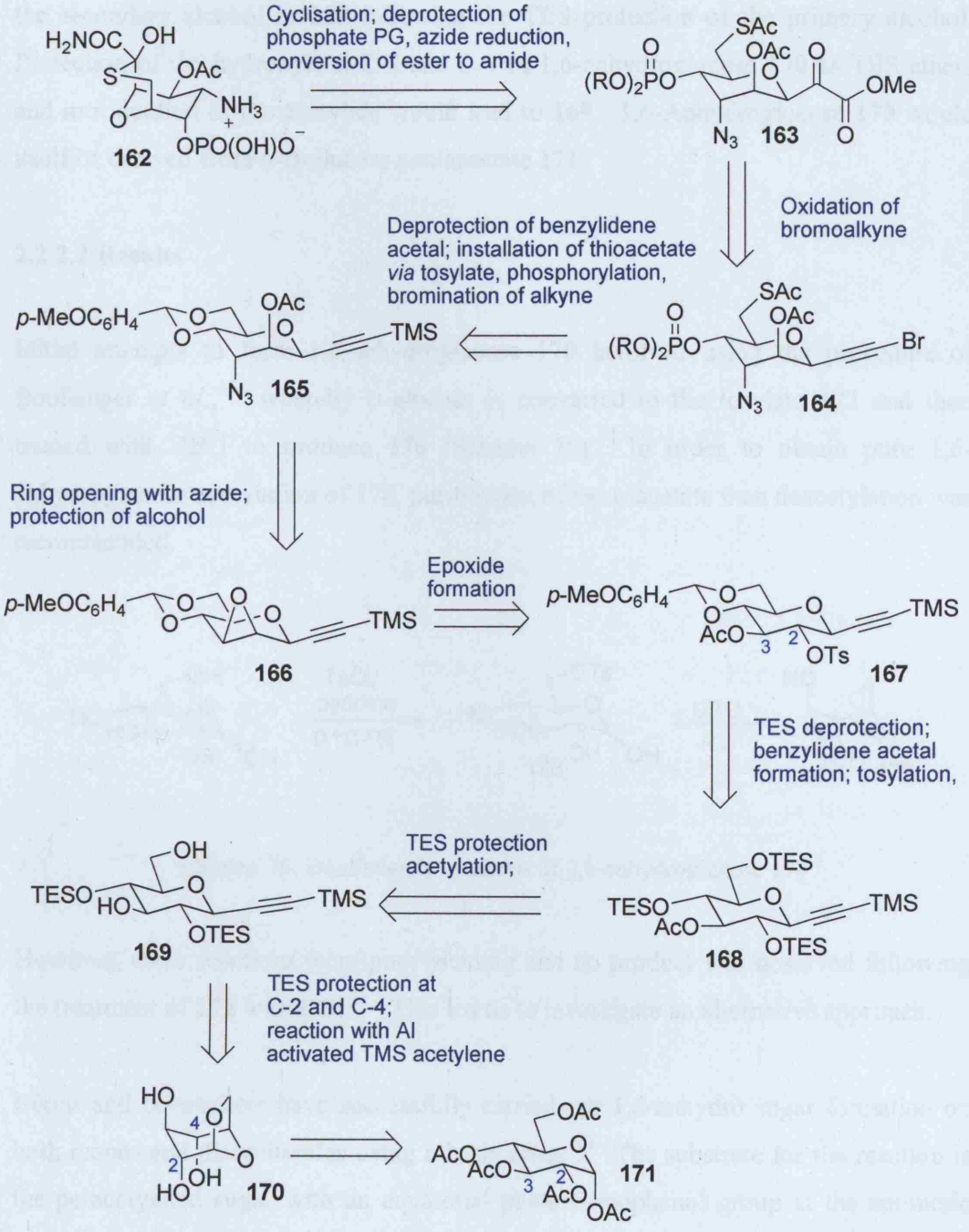
2.2.2. Towards decarboxytagetitoxin

2.2.2.1 Strategy & retrosynthesis

For the synthesis of decarboxytagetitoxin **162**, we adopted a carbohydrate-based approach (Scheme 75). Our starting point was α-D-glucose pentaacetate **171** which meant that inversion of the stereocentres at C-2 and C-3 was necessary to obtain the *altro* configuration of the product. The installation of an amine at C-3 was also required. In order to achieve this, we planned to form a 2,3-β-epoxide, which would then undergo diaxial ring-opening with azide. Formation of the epoxide would be implemented by selective tosylation at O-2.

The stategy to form the bicyclic core *via* cyclisation of a thiol onto an α-ketoester was

to be implemented as before. The ketoester **163** would be the result of oxidation of the bromoalkyne **164**. This in turn would be formed from **165** following removal of the benzylidene acetal, conversion of the primary alcohol to the thioacetate and then phosphorylation of the secondary alcohol.



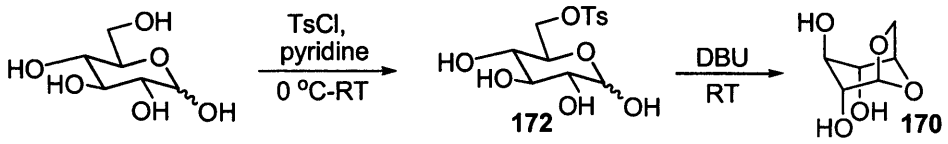
Scheme 75: Retrosynthesis of decarboxytagetitoxin **162**

Ring-opening of the β-epoxide **166** with azide followed by protection of the alcohol to

give the acetate would lead to **165**. Removal of the three TES groups in **168** and formation of a benzylidene acetal would leave only one free hydroxyl group which could be activated as the tosylate. Deprotection of the acetyl group at C-3 in **167** would result in an oxyanion which would cyclise round to form the epoxide by displacing the tosylate at C-2. The acetate **168** would be prepared from acetylation of the secondary alcohol in **169** following the TES protection of the primary alcohol. Protection of the hydroxyls at C-2 and C-4 of 1,6-anhydroglucose **170** as TES ethers and introduction of the acetylide would lead to **169**. 1,6-Anhydroglucose **170** would itself be derived from α-D-glucose pentaacetate **171**.

2.2.2.2 Results

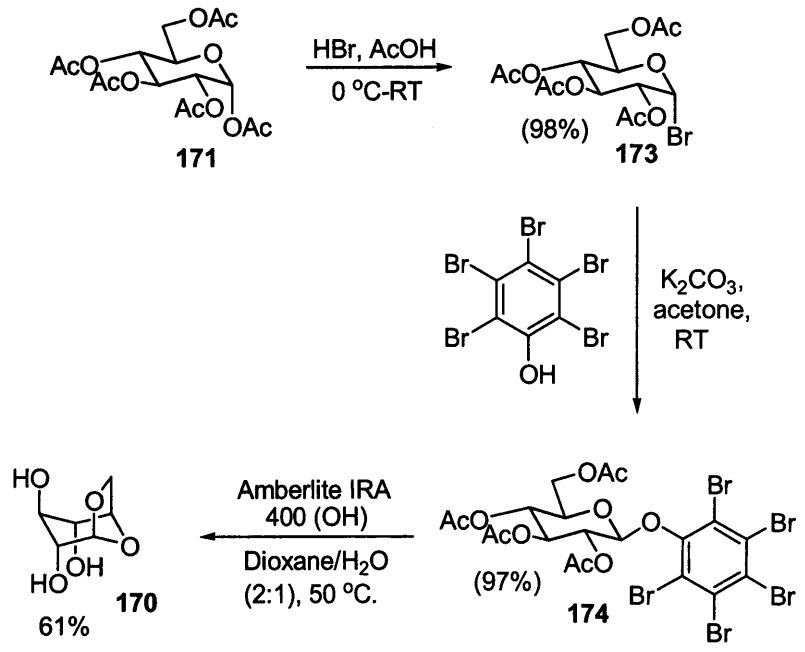
Initial attempts to form 1,6-anhydroglucose **170** involved using the procedure of Boullanger *et al.*,[100] whereby D-glucose is converted to the tosylate **172** and then treated with DBU to produce **170** (Scheme 76). In order to obtain pure 1,6-anhydroglucose acetylation of **170**, purification of the triacetate then deacetylation was recommended.



Scheme 76: Boullanger's synthesis of 1,6-anhydroglucose **170**

However, these reactions were poor yielding and no product was observed following the treatment of **172** with DBU. This led us to investigate an alternative approach.

Boons and co-workers have successfully carried out 1,6-anhydro sugar formation on both mono- and disaccharides using a basic resin.[101] The substrate for the reaction is the peracetylated sugar with an equatorial pentabromophenol group at the anomeric position.

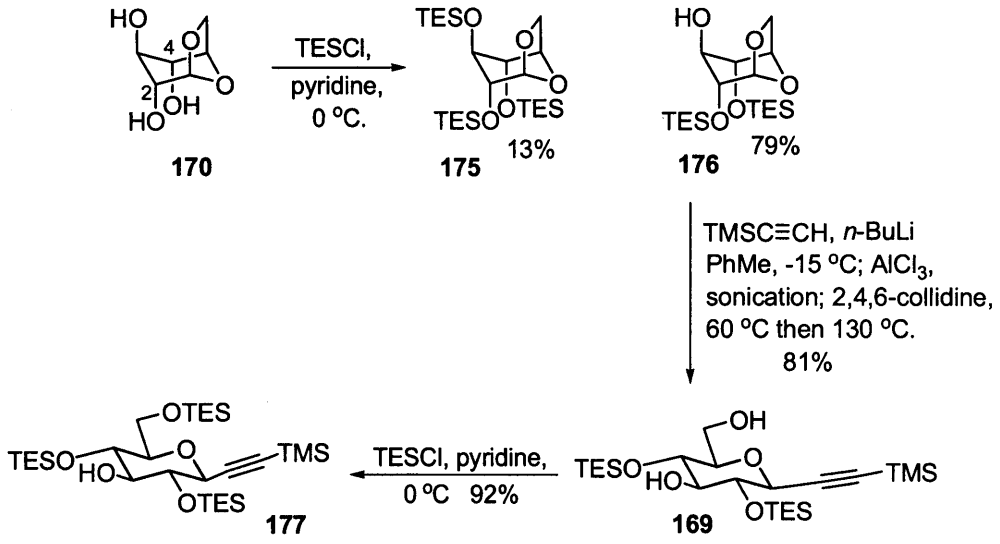


Scheme 77: Formation of 1,6-anhydroglucose **170** from glucose pentaacetate **171**

The anomeric bromide **173** was prepared by treatment of commercially available α-D-glucose pentaacetate **171** with hydrogen bromide/acetic acid solution (Scheme 77). The literature procedure for formation of the pentabromophenyl glycoside **174** involves the use of sodium pentabromophenoxide, which is prepared beforehand from pentabromophenol and sodium methoxide.[102] However, in our hands, the reaction proceeded more efficiently using a mixture of potassium carbonate and pentabromophenol, which forms the phenoxide salt *in situ*. In addition, the pentabromophenyl glycoside **174** was often of adequate quality after the work-up procedure to be taken through to the next step without recrystallisation. Formation of 1,6-anhydroglucose **170** was then carried out using basic Amberlite resin. On some occasions, the 1,6-anhydroglucose product was obtained in an acceptable quality to warrant no further purification following filtration and solvent removal. If some impurities remained, the product was purified quite easily by column chromatography.

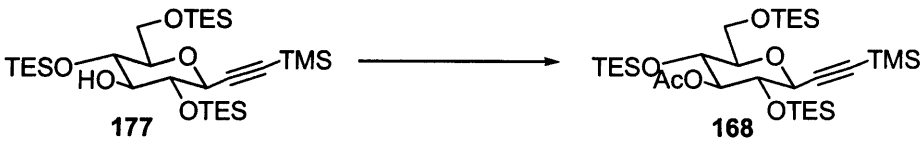
Next, the hydroxyls at C-2 and C-4 were protected as silyl ethers to give **176** in 79% yield (Scheme 78).[103] Additionally, a small amount of the tri-silylated compound **175** was formed. The 1,3-dioxolane ring of **176** was then opened with lithium (trimethylsilyl)acetylide and aluminium chloride to give **169**.[103] The modified

conditions developed by Julien Plet were used,[43] in which the reaction mixture is sonicated during reaction of the lithium acetylide with the aluminium chloride. Freshly sublimed aluminium chloride was found to be necessary for high yields in this process. Subsequently, the primary alcohol was also protected with triethylsilyl chloride to give **177** in 92% yield after purification.



Scheme 78: Synthesis of alcohol **177**

Surprisingly, the protection of the secondary alcohol in **177** to form the acetate **168** (Scheme 79) was non-trivial. Standard acetylation procedures, such as acetic anhydride with pyridine or triethylamine (Table 5, entries 1 and 2) failed to convert any starting material.

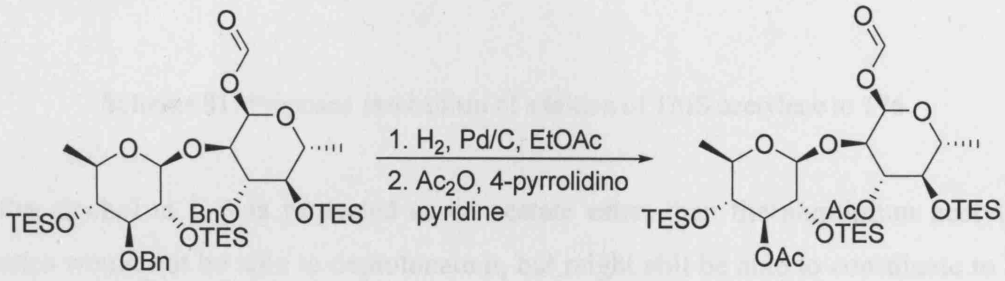


Scheme 79: Acetylation of alcohol **177**

Entry	Conditions	Result
1	Ac_2O, pyridine, DCM, RT	SM
2	Ac_2O, Et_3N, DCM, RT	SM
3	AcCl, pyridine, DCM, RT	SM
4	Ac_2O, DMAP, pyridine, RT	SM
5	Ac_2O, $^nBu_3P$, Et_3N, DCM, RT	SM
6	Ac_2O, 4-pyrrolidinopyridine, Et_3N, RT	70% product

Table 5: Reaction conditions and results of the acetylation of alcohol **177**

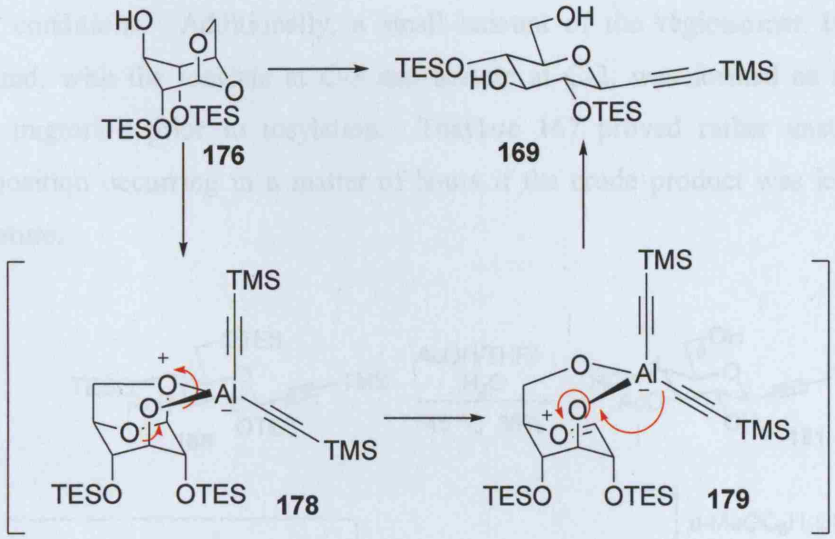
Using the more reactive acetyl chloride (Table 5, entry 3) also had no effect. When DMAP was added to catalyse the reaction (Table 5, entry 4), once again, mainly starting material remained after 19 h. Tributylphosphine (Table 5, entry 5) which has been reported to be more effective than DMAP in some acylation reactions,[104] gave a similar result. Our attention then turned to 4-pyrrolidinopyridine, which has been used by Smith and co-workers to acylate a secondary alcohol between two TES groups in a carbohydrate substrate (Scheme 80).[105]



Scheme 80: Smith's acetylation of a secondary alcohol using 4-pyrrolidinopyridine

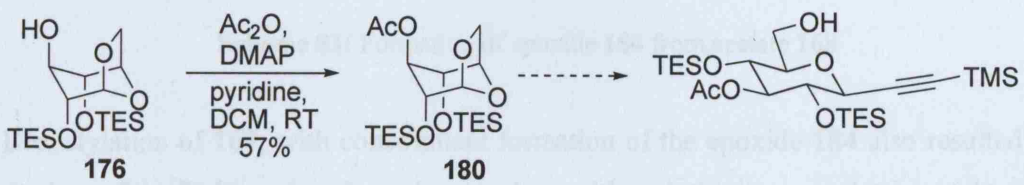
This catalyst was found to be the most effective for acylation of unreactive alcohols compared to other 4-substituted pyridines.[106] Thankfully, the acetylation of **177**, catalysed by 4-pyrrolidinopyridine was successful (Table 5, entry 6), giving a yield of 70% after optimisation. Some understanding of the reason for the low reactivity of alcohol **177** can be gained from the fact that it has a higher R_f on TLC than the acetate **168**. This suggests that the hydroxyl group is effectively sterically shielded by the flanking TES groups.

During our attempts to acylate **177**, we also considered the introduction of the acetate ester at C-3 at an earlier stage, prior to the alkynylation of **176**. The mechanism proposed by Vassella *et al.*, suggests that the aluminium trichloride forms a $Al(C{\equiv}C{-}TMS)_3$ species **178** with the lithium TMS acetylene (Scheme 81).[107] This deprotonates the alcohol at C-3 and coordinates to the oxygen in the 1,3-dioxolane bridge through aluminium. The subsequent formation of the oxonium ion **179** and migration of a TMS acetylene moiety gives the product **169**.



Scheme 81: Proposed mechanism of addition of TMS acetylene to **176**

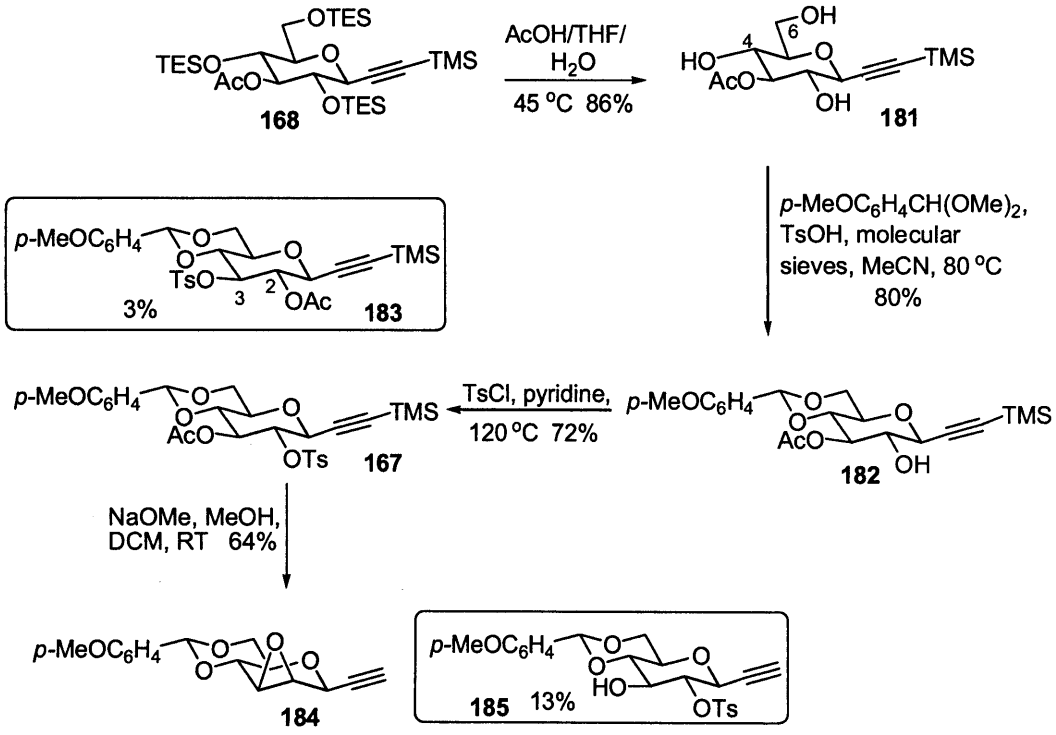
If the alcohol at C-3 is protected as an acetate ester, then the aluminium acetylide species would not be able to deprotonate it, but might still be able to coordinate to the oxygen at C-3. It would also be expected to coordinate to the oxygen in the 1,3-dioxolane bridge as before, hence there was a possibility that the reaction could still be successful for the acetylated substrate.



Scheme 82: Synthesis of acetate **180**

This, however, was not the case as **180** failed to react under these conditions (Scheme 82). The presence of a free alcohol at C-3 is therefore required for the alkynylation to succeed.

The acylated product **168** was treated with a mixture of acetic acid, THF and water in order to remove the TES protecting groups to give the triol **181** (Scheme 83). Protection of the C-4 and C-6 hydroxyls as the *p*-methoxybenzylidene acetal provided **182**, and the remaining alcohol was activated as the tosylate, a reaction which required forcing conditions. Additionally, a small amount of the regioisomer **183** of this compound, with the tosylate at C-3 and acetate at C-2, was formed as a result of acetate migration prior to tosylation. Tosylate **167** proved rather unstable, with decomposition occurring in a matter of hours if the crude product was left at room temperature.

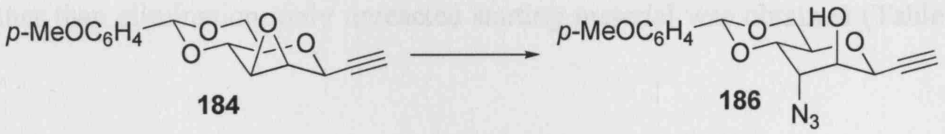


Scheme 83: Formation of epoxide **184** from acetate **168**

Deacetylation of **167**, with concomitant formation of the epoxide **184** also resulted in the loss of the TMS moiety from the acetylene, although this was not detrimental to the rest of the synthesis. The amount of base added was significant; a small amount gave

an incomplete reaction but a large excess led to some deprotection of the benzylidene acetal group. The best result was obtained using 5 eq. of base to give epoxide **166** in 64% yield as well as 13% of the diol monotosylate **185**. The latter could then be re-subjected to the same conditions to form more of the epoxide.

Ring-opening of the epoxide **184** with azide was expected to occur with high regioselectivity at C-3 to give the product **186** (Scheme 84). However, this reaction was problematic. Standard azidation methods, such as sodium azide and ammonium chloride (Table 6, entries 1 and 2) resulted in the deprotection of the benzylidene acetal protecting group in some of the starting material. This has been observed for other 4,6-*O*-benzylidene derivatives and is a result of the acidity of ammonium chloride.[108]



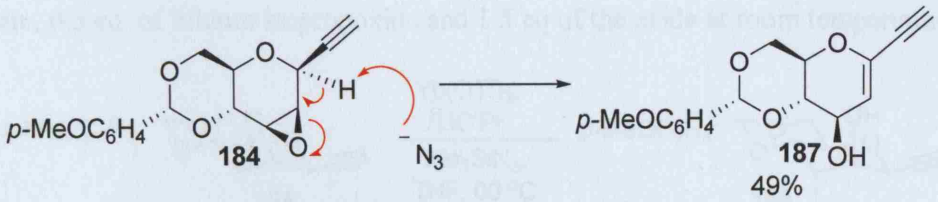
Scheme 84: Ring-opening of epoxide **184** with azide

Entry	Conditions	Result
1	NaN_3, NH_4Cl, MeOH/H_2O (7:1), DCM, 80 °C	Some deprotection of acetal & a 1:1.7 mixture of product and unidentifiable compound.
2	NaN_3, NH_4Cl, $MeOCH_2CH_2OH/H_2O$ (5:1), 140 °C	Deprotection of acetal & unidentifiable mixture of compounds.
3	NaN_3, DMF, 90 °C	Elimination product **187** (49%)
4	NaN_3, DMF, RT	SM
5	NaN_3, CF_3CH_2OH, RT	SM
6	NaN_3, Oxone®, MeCN/H_2O (9:1), DCM, RT	Deprotection of acetal
7	Me_3SiN_3, $BF_3{\cdot}OEt_2$, DCM, RT	Deprotection of acetal
8	Me_3SiN_3, $Yb(OTf)_3$, LiO^iPr, THF, 60 °C	product **186** (79%)

Table 6: Reaction conditions and results of epoxide ring-opening reaction

A small amount of product was formed using the conditions outlined in entry 1, but it was part of an inseparable mixture with an unidentifiable compound.

Heating the epoxide **184** with sodium azide in DMF (Table 6, entry 3), gave the enyne elimination product **187** (Scheme 85).



Scheme 85: Formation of enyne elimination product **187**

However, when the reaction was carried out at RT, in order to favour substitution rather than elimination, only unreacted starting material was obtained (Table 6, entry 4).

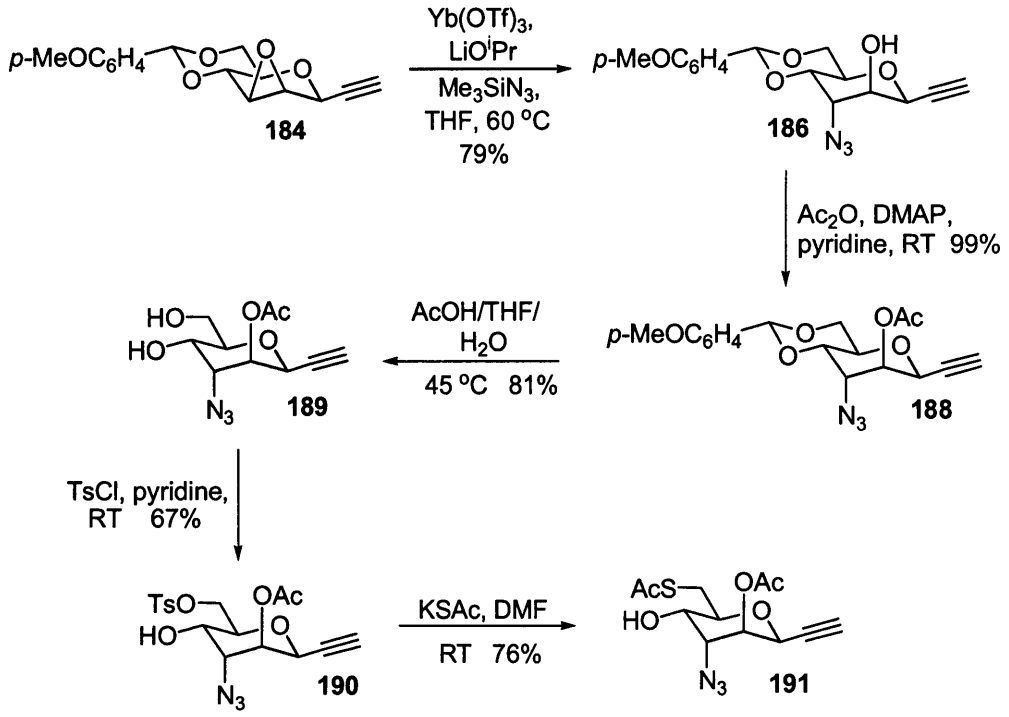
Next, the reaction was carried out in trifluoroethanol (TFE) (Table 6, entry 5), which was expected, as a strongly H-bonding solvent, to promote epoxide ring-opening.[109] Unfortunately, the epoxide was only sparingly soluble in this solvent and starting material was recovered.

Sabitha and co-workers have successfully carried out ring-opening of epoxides with sodium azide using Oxone®.[110] Application of this methodology to epoxide **184**, however, resulted in deprotection of the benzylidene acetal, (Table 6, entry 6) which is attributed to the mildly acidic nature of Oxone®.

Use of an organic source of azide was also investigated. Trimethylsilyl azide was used in conjunction with boron trifluoride diethyl etherate (Table 6, entry 7), a combination which has been shown to form azido alcohols from epoxides in carbohydrate systems.[111] Once again, appreciable benzylidene acetal cleavage was observed. This is probably a result of the Lewis acid coordinating to one of the oxygen atoms in the acetal ring and thereby promoting hydrolysis.

Eventually we had success using a combination of ytterbium triflate and lithium

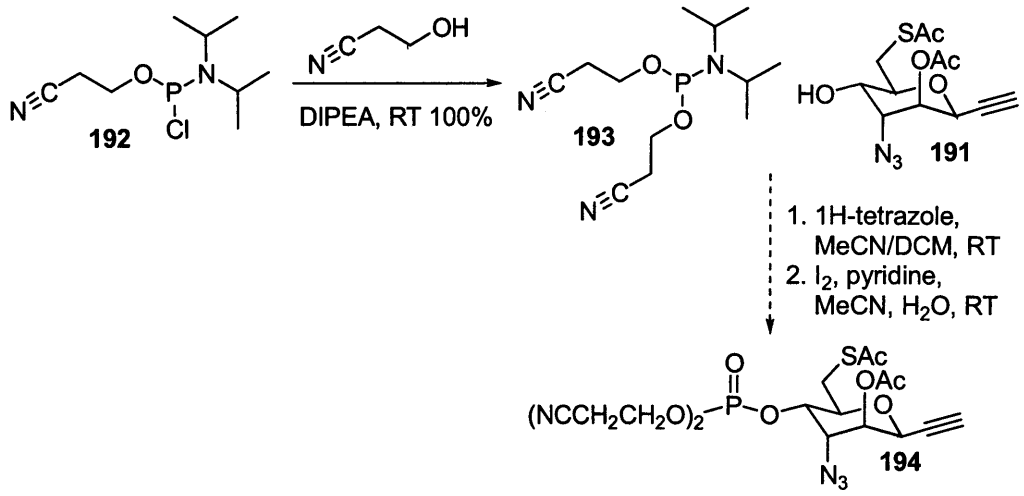
isopropoxide (Table 6, entry 8). In this procedure, developed by Yamamoto *et al.*,[112] ytterbium isopropoxide is formed *in situ*, and activates the epoxide for nucleophilic attack. The best yield was obtained using 0.6 eq. of ytterbium triflate, 1.8 eq. of lithium isopropoxide and 3 eq. of trimethylsilyl azide at 60 °C. These conditions are considerably more forcing than those reported by Yamamoto (0.1 eq. of ytterbium triflate, 0.3 eq. of lithium isopropoxide and 1.5 eq of the azide at room temperature).



Scheme 86: Synthesis of thioacetate **191** from epoxide **184**

The secondary alcohol in **186** was then acylated to give **188**, and the *para*-methoxybenzylidene acetal was cleaved under acidic conditions (Scheme 86). The resulting diol **189** was then converted to **190** by activation of the primary alcohol as the tosylate. The latter was then displaced with potassium thioacetate to afford **191** in 76% yield.

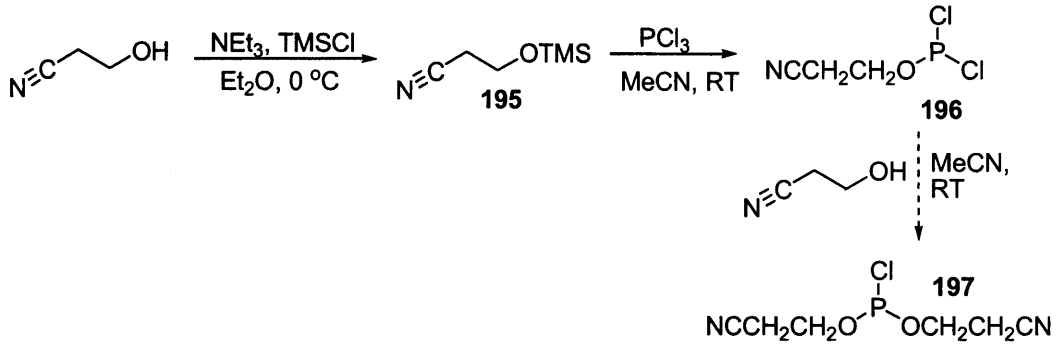
Phosphorylation of the secondary alcohol in **191** was initially attempted using the phosphoramidite **193** which was prepared from the commercially available chloride **192** and 3-hydroxypropionitrile (Scheme 87).[113] The aim was to form a phosphite first, which would then be oxidised to the phosphate **194** with iodine.[114] Unfortunately, no product was isolated and some starting material was recovered.



Scheme 87: Attempted phosphorylation of thioacetate **191**

The reaction was repeated using larger excesses of tetrazole (4-5 equivalents, instead of 2.2) and the phosphoramidite (3.1 eq., instead of 1.1 eq.) but none of the desired product was formed.

Our attention then turned to another phosphorylating reagent, di(2-cyanoethyl)phosphochloridite **197**, which has been used in the synthesis of a polyphosphorylated natural product.[115] We attempted to synthesise this reagent from 3-hydroxypropionitrile as shown in Scheme 88.

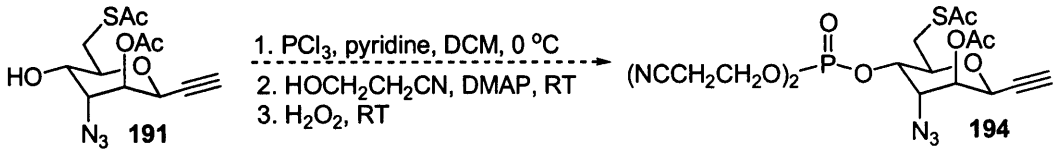


Scheme 88: Attempted preparation of di(2-cyanoethyl)phosphochloridite **197**

Although the protection of 3-hydroxypropionitrile with TMSCl was successful, conversion of the resulting silyl ether **195** to the di(2-cyanoethyl)phosphochloridite

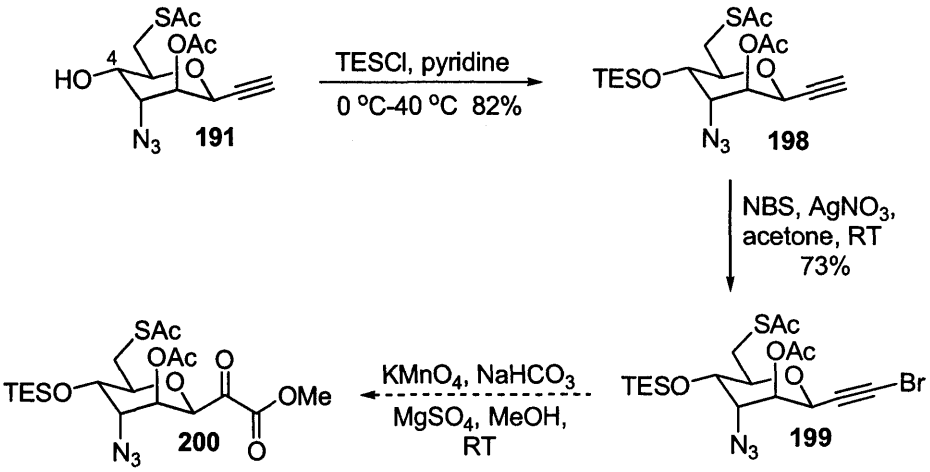
197 was not achieved. Instead, the phosphodichloridite **196** was formed, and was assigned on the basis of a peak in the ^{31}P NMR spectrum at 180 ppm which corresponds to phosphodichloridites. An attempt to form **197** from this compound *via* treatment with more alcohol failed. The ^{31}P NMR of the resulting residue showed that none of the dichloro- compound **196** remained, but peaks at 8 and 10 ppm which correspond to phosphates were present, rather than a peak at approximately 150 ppm, which would have been expected for the desired monochlorophosphite product.

An alternative approach to phosphorylation of the secondary alcohol was to treat **191** with phosphorus trichloride and then to displace the remaining chloride moieties with 3-hydroxypropionitrile, followed by oxidation to the phosphate **194** (Scheme 89). This method has been put to use by Evans and co-workers with good results,[116] but was not successful in our case, despite using freshly distilled phosphorus trichloride.



Scheme 89: Attempt to phosphorylate **191** using Evans' protocol

Lack of progress in the phosphorylation step and time constraints led to a slight revision of our strategy as we endeavoured to form the bicyclic core of tagetitoxin prior to the installation of the phosphate at C-4.



Scheme 90: Synthesis of bromoalkyne **199**

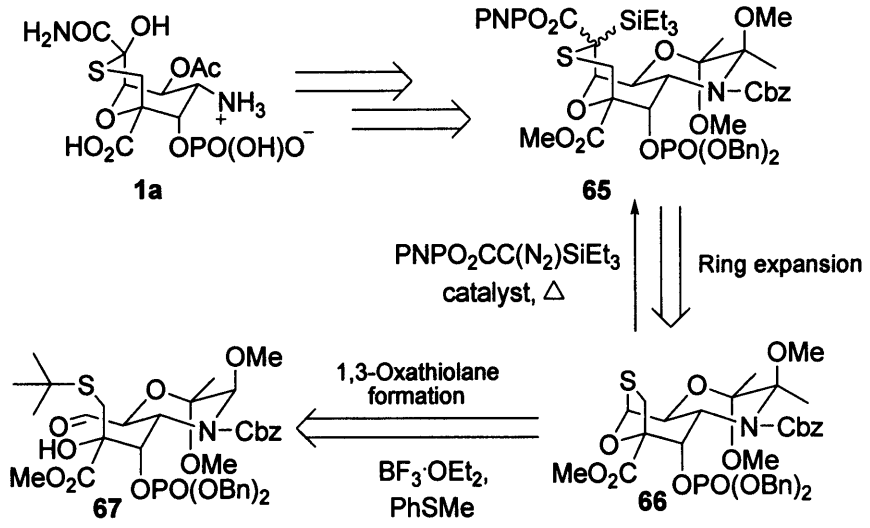
The hydroxyl at C-4 was protected as a silyl ether to give **198** (Scheme 90). Unlike previous protections of alcohols with TES chloride which went to completion within a few hours at 0 °C, this reaction was extremely sluggish. A considerable excess of the silyl chloride was added and the temperature was increased from 0 °C to RT and eventually 40 °C. This suggests that the alcohol at C-4 is unreactive and may be the reason why phosphorylation was also unsuccessful. Next, the bromoalkyne **199** was formed upon treatment of **198** with NBS and silver nitrate. The subsequent oxidation to the ketoester **200** was expected to be precarious as previous experience with related substrates had shown that the potassium permanganate needed to be added slowly in small portions for the reaction to be successful.[43] Addition of too much potassium permanganate would lead to decomposition of the substrate, and as this reaction was to be carried out on the last remaining 7 mg of **199**, extra care was taken. Unfortunately, the reaction was not successful on this scale and resulted in the decomposition of starting material.

Time constraints prevented further work on the synthesis of decarboxytagetitoxin, but this synthetic route is being investigated further by Dr. Anne Mortimer.

3. CONCLUSIONS & FUTURE WORK

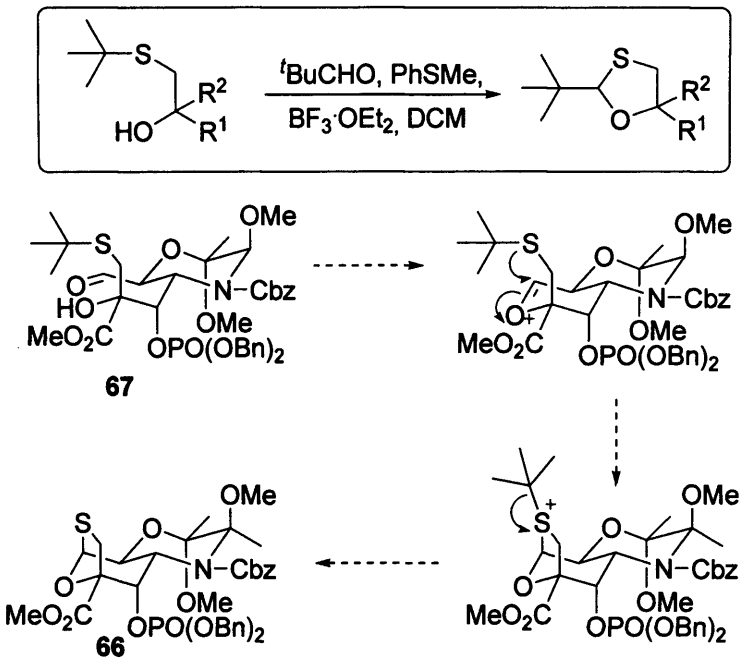
The aim of this project was to synthesise tagetitoxin, the only known natural product which is a selective inhibitor of RNA polymerase III. Not only would synthesis of this compound be useful to biologists studying transcription, but would also assist in verifying its highly intriguing structure.

Our initial strategy to form the bicyclic core involved carrying out a ring expansion reaction of the 1,3-oxathiolane **66** to the 1,4-oxathiane **65** (Scheme 91), a method which had previously been established in our group for monocyclic substrates.



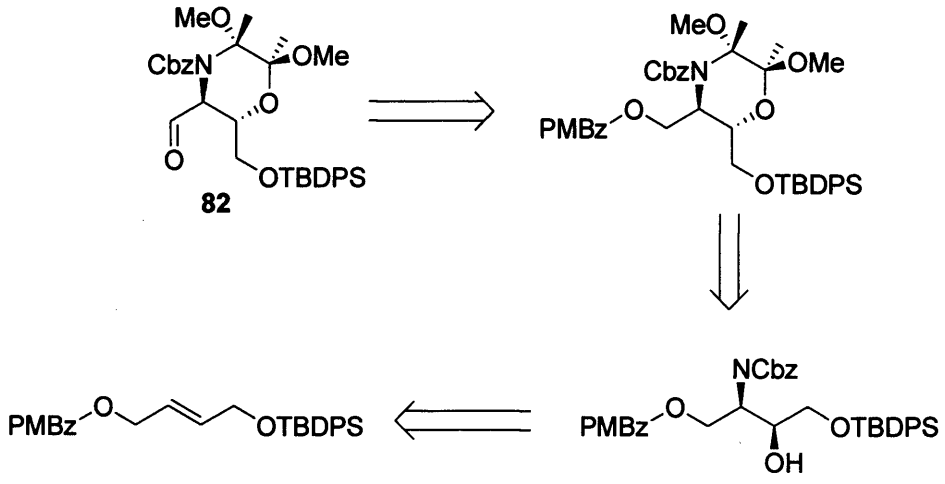
Scheme 91: Ring expansion strategy to form tagetitoxin **1a**

The ring expansion precursor **66** would in turn be formed *via* the intramolecular version of a novel 1,3-oxathiolane forming reaction, also discovered in our group. Methodological studies on this reaction showed it to be successful on a range of substrates and we hoped that it would also lead to the formation of **66** from **67** (Scheme 92).



Scheme 92: Proposed formation of **66** *via* intramolecular version of oxathiolane forming reaction

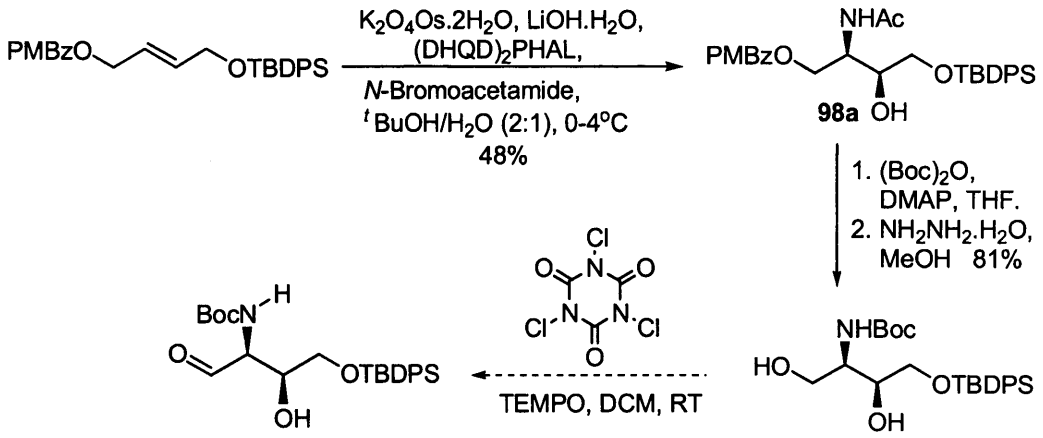
However problems were encountered during the early stages of the proposed route to **67**. The first main synthetic intermediate was the aldehyde **82** which we planned to form using Sharpless asymmetric aminohydroxylation (Scheme 93).



Scheme 93: Strategy to form aldehyde **82**

Failure in carrying out the AA reaction, using benzyl carbamate as a nitrogen source, ultimately caused us to abandon this route. Although the AA reaction was successfully

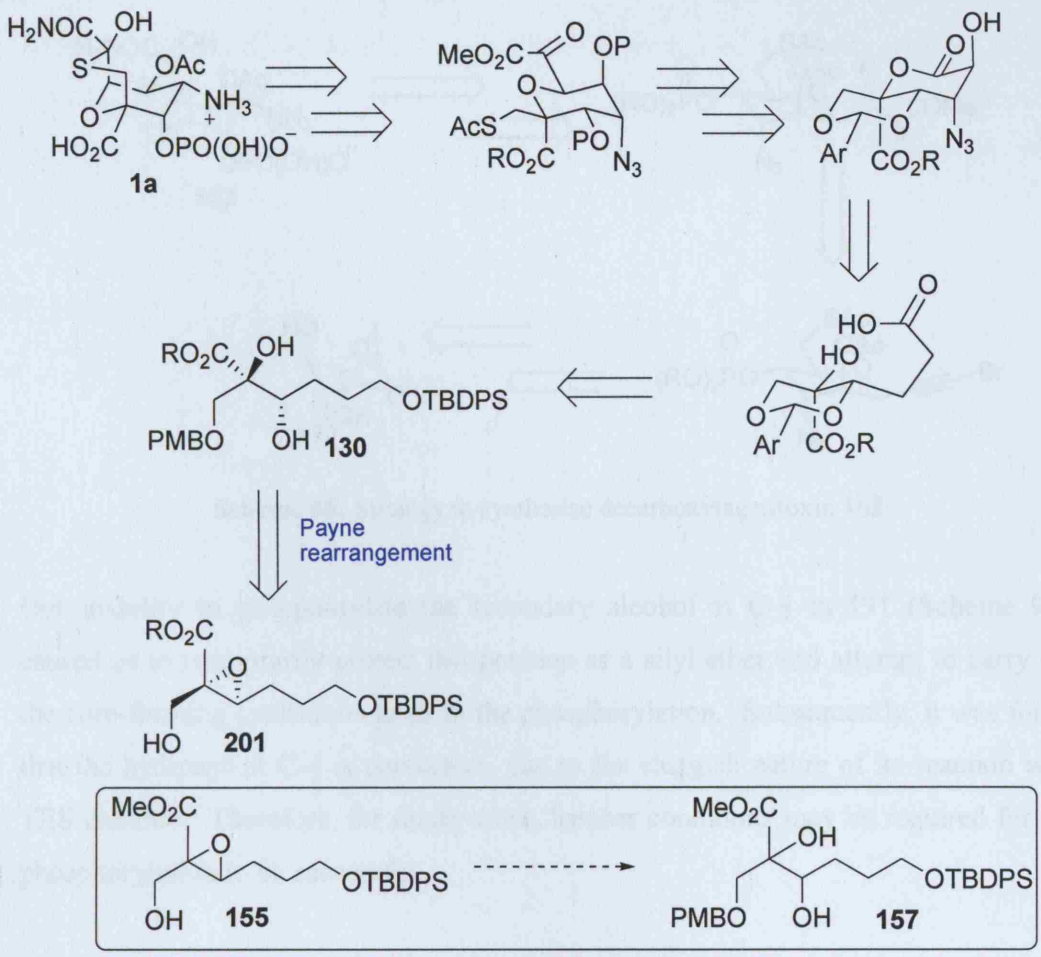
carried out using *N*-bromoacetamide to give **98a** (scheme 94), attempts to replace the acetyl protecting group with the more labile Cbz group, as originally intended, were not fruitful. Eventually, the acetyl group was replaced by a Boc functionality, but the concurrent removal of the PMB ester moiety meant that this synthesis was becoming unwieldy.



Scheme 94: AA reaction with *N*-bromoacetamide and replacement of *N*-acetyl group

At this point, the first synthesis of the tagetitoxin core was carried out in the group. The hemithioacetal moiety was formed *via* the cylisation of a thiol onto an electrophilic ketoester, and provided a promising new strategy.

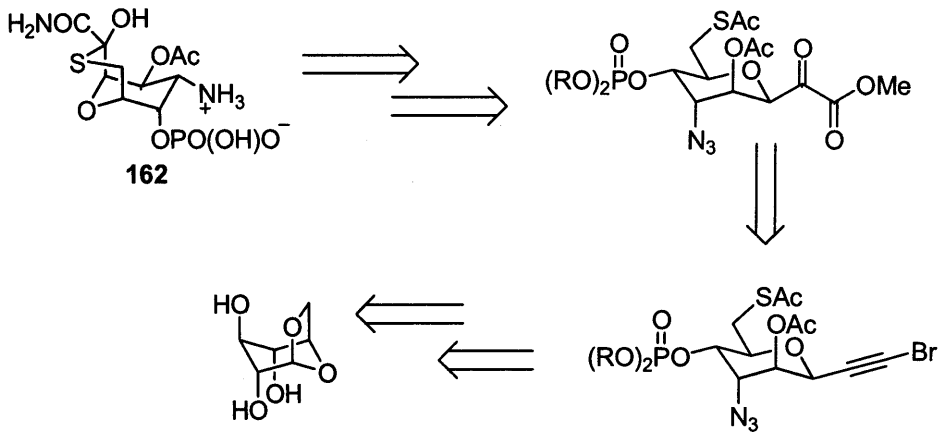
Based on this idea, routes towards tagetitoxin and its analogue, decarboxytagetitoxin, were investigated. The plan to synthesise tagetitoxin involved forming the diol **130** *via* the Payne rearrangement of the epoxide **201** with *para*-methoxybenzyl alcohol (Scheme 95).



Scheme 95: Strategy to form tagetitoxin **1a** *via* Payne rearrangement of epoxide **201**

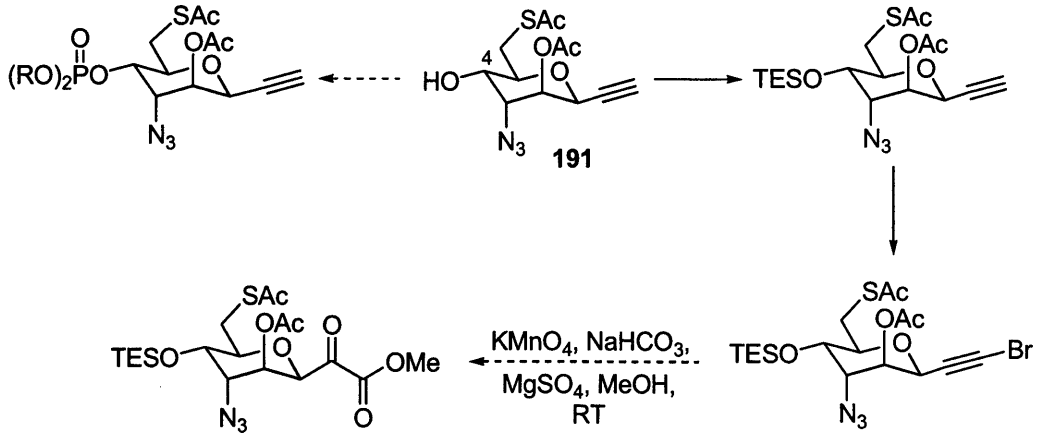
The Payne rearrangement was first tested on the racemic substrate **155**, but was unsuccessful as the product **157** was not formed. It appeared that the reaction conditions appeared to cause decomposition of the epoxide substrate. This was most likely due to the methyl ester group present.

For the synthesis of decarboxytagetitoxin **162** we embarked on a carbohydrate-based approach (Scheme 96)



Scheme 96: Strategy to synthesise decarboxytagetitoxin **162**

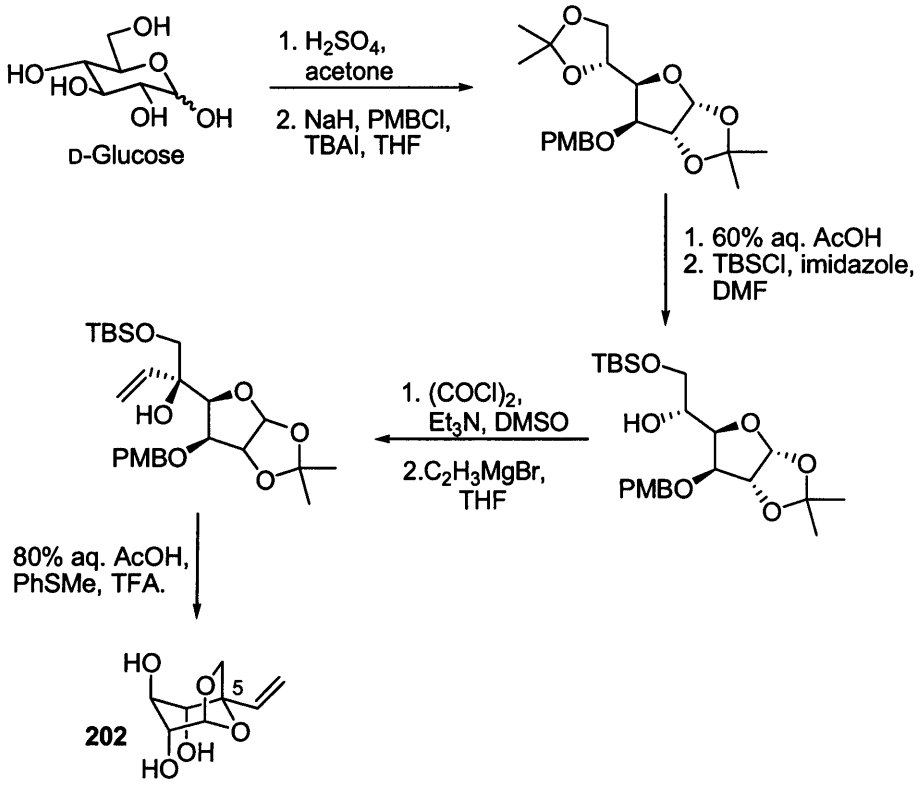
Our inability to phosphorylate the secondary alcohol at C-4 in **191** (Scheme 97), caused us to temporarily protect this position as a silyl ether and attempt to carry out the core-forming cyclisation prior to the phosphorylation. Subsequently, it was found that the hydroxyl at C-4 is unreactive, due to the sluggish nature of its reaction with TES chloride. Therefore, for future work, harsher conditions may be required for the phosphorylation to be successful.



Scheme 97: Latter stages of synthetic route to decarboxytagetitoxin

Time constraints and consequently, a shortage of material meant that the synthesis of decarboxytagetitoxin could not be completed during this project. However, this work is being continued in the group and we are optimistic that it will be completed in the near future.

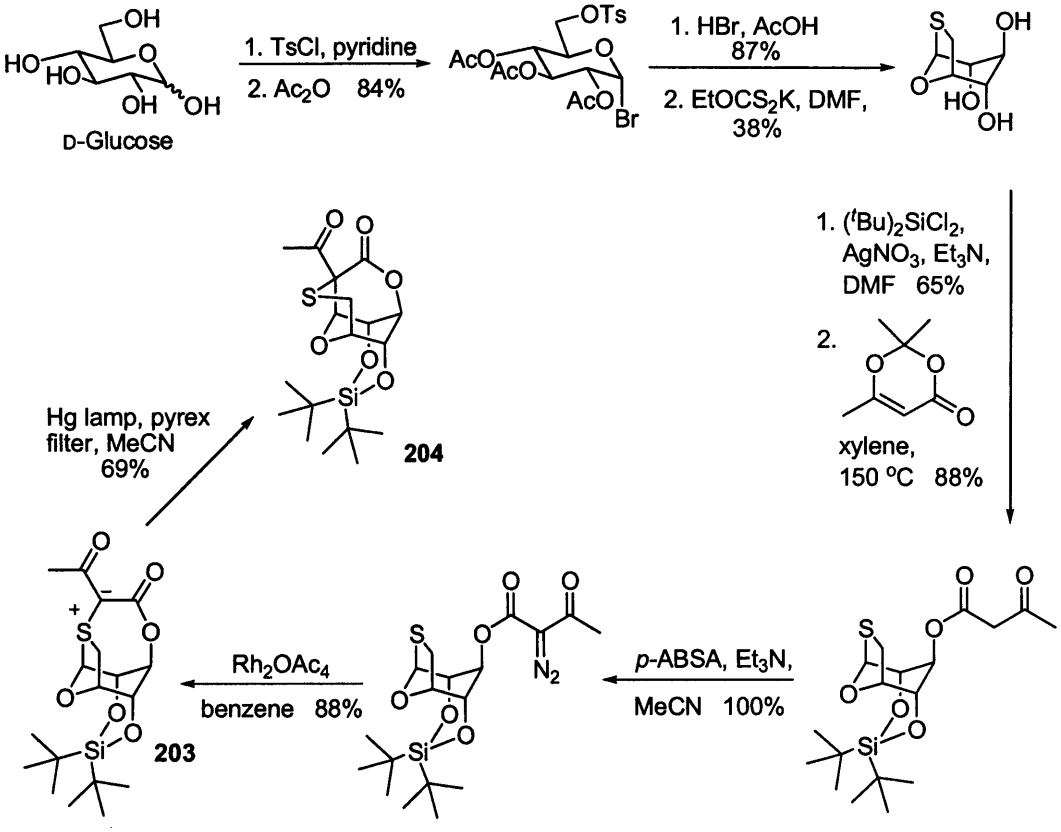
Based on this route, the synthesis of tagetitoxin is also being carried out by Moussa Sehailia, another PhD student in the group. The key difference in this approach is the presence of a vinyl group at C-5 in **202** (Scheme 98), which can be converted into a carboxylic acid in the final stages.



Scheme 98: Formation of anhydrosugar **202**

Following the formation of the anhydrosugar **202**, the remainder of the synthesis is analogous to that of decarboxytagetitoxin.

The formation of the bicyclic core of tagetitoxin *via* rearrangement of the ylid **203** (Scheme 99) is also being investigated by Dr. Anne Mortimer.



Scheme 99: Formation of tagetitoxin core *via* ring expansion

The ylid **203** was remarkably stable and was isolated by column chromatography. Its rearrangement to give **204** was achieved photochemically, validating our original original ring expansion concept as a method for the synthesis of the tagetitoxin skeleton.

4. Experimental

For reactions carried out in anhydrous conditions, all glassware was flame-dried prior to use and allowed to cool to RT *in vacuo*. The reactions were then carried out under an argon atmosphere. THF, DCM, Et_2O, toluene, hexane and MeCN for reactions were obtained from the UCL Chemistry anhydrous solvent system, whereby solvents are dried by passing through alumina columns under nitrogen. Anhydrous methanol and DMF from Romil, and anhydrous isopropanol from Acros were used as supplied. DMSO, pyridine, triethylamine, and *N*-ethyldiisopropylamine were distilled from calcium hydride. Acetone and 3-hydroxypropionitrile were distilled from molecular sieves. Ethanol was dried by stirring with magnesium turnings and iodide, heating to reflux, then distillation.[117]

p-Toluenesulfonyl chloride was recrystallised from toluene and petroleum ether (bp: 40-60 °C) prior to use. NBS was recrystallised from boiling water and dried over P_2O_5, in accordance with the method described by Dauben and McCoy.[118] Ethyl 4-bromocrotonate was purified by column chromatography (SiO_2, 2% EtOAc in petroleum ether) prior to use. Dowex-50Wx8 resin was activated as the acidic form by washing with 6M HCl, then H_2O, until the washings were neutral.

N-Bromoacetamide was prepared according to a literature procedure.[119] Lithium isopropoxide was prepared by dropwise addition of *n*-BuLi (1.6M in hexanes, 5 mmol) to anhydrous isopropanol (5 mmol), cooled in an ice-bath. The solution was stirred at RT for 35 min then concentrated *in vacuo*. The resulting white solid was dried under high vacuum then stored under argon.

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

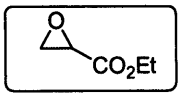
For column chromatography, BDH silica gel (40-63 μm) was used. TLC was carried out on aluminium plates pre-coated with Merck silica gel (60 F_{254}) which were visualised using UV at 254 nm or by staining with vanillin or potassium permanganate. Solvents were removed using a Buchi rotary evaporator.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

^{1}H NMR spectra were recorded on Bruker AMX-300, AMX-400 and AVANCE 500 MHz spectrometers. The signals are assigned as s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, tt = triplet of triplets, td = triplet of doublets, ddt = doublet of doublets of triplets, dtd = doublet of triplets of doublets, q = quartet, dq = doublet of quartets, m = multiplet. ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz and 125 MHz on a Bruker AMX-300, AMX 400 and AVANCE-500 spectrometers, respectively. ^{1}H COSY, ^{13}C DEPT, HMQC and HMBC experiments were used to aid peak assignments and determine structures when required. Chemical shifts (δ), in parts per million, are referenced to the residual solvent peak, except for spectra in D_2O which are referenced to internal 1,4-dioxan.

IR spectra were recorded on a SHIMADZU FT-IR 8700 instrument and a Perkin Elmer Precisely Spectrum 100 FT-IR spectrometer with ATR. Mass spectra and high resolution mass spectra were recorded by Mr John Hill and Dr Lisa Harris on Micromass 70-SE and MAT 900XP instruments.

Melting points were measured using a Reichert-Jung Thermovar instrument. Optical rotations were measured on an AA Series Automatic Polarimeter (POLAAR 2000). Elemental analyses were carried out by Mrs Jill Maxwell. HPLC data was obtained using the ProStar/ Dynamax 2.4 software package and Varian HPLC hardware. Daicel Chiralpak AD columns (2.1 mm × 150 mm) were used.

Ethyl oxirane carboxylate 71a



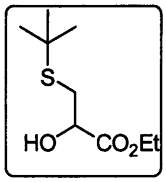
Sodium hypochlorite solution[§] (5% aq., 133 mL, 98 mmol) was cooled to 5-8 °C. Ethyl acrylate (7.6 mL, 70 mmol) was added in one portion and the resulting mixture was stirred for 6 h at RT. The organic material was extracted with DCM (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was distilled[45] (bp: 94-96 °C, 50 mmHg; Lit:[120] 88-90 °C, 60 mmHg) to give the product **71a** as a colourless oil (2.24 g, 28%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (3H, t, *J* 7.1 Hz, $CO_2CH_2C\underline{H}_3$), 2.91 (1H, dd, *J* 6.5, 4.1 Hz, 1 of $C\underline{H}_2OCH$), 2.94 (1H, dd, *J* 6.5, 2.5 Hz, 1 of $C\underline{H}_2OCH$), 3.40 (1H, dd, *J* 4.1, 2.5 Hz, $C\underline{H}CO_2Et$), 4.15-4.30 (2H, m, $CO_2C\underline{H}_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 46.3 ($\underline{C}H_2OCH$), 47.4 ($CH_2O\underline{C}H$), 61.6 ($\underline{C}H_2CH_3$), 169.2 (C=O).

ν_{max}/cm^{-1} (film): 2987 (C-H), 1731 (C=O), 1205, 1031.

Ethyl 3-(*tert*-butylsulfanyl)-2-hydroxypropanoate 73a



A solution of sodium ethoxide was prepared by adding sodium (11.9 mg, 0.5 mmol) to dry ethanol (0.26 mL) at 0-5 °C. *tert*-Butylthiol (0.43 mL, 3.8 mmol) was then added and the resultant solution was stirred for 30 min at RT. A solution of ethyl oxirane carboxylate **71a** (400 mg, 3.4 mmol) in dry ethanol (6.9 mL) was added dropwise, and the mixture was heated to reflux for 2 h. Water (10 mL) was added and the ethanol removed *in vacuo*. The organic material was then extracted with diethyl ether (2 × 10 mL). The organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 15% EtOAc in petroleum ether) gave the product **73a** as a yellow oil (193 mg, 27%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.32 (9H, s, $(CH_3)_3C$), 2.85 (1H, dd, *J* 13.0, 5.8 Hz, 1 of SCH_2), 3.02 (1H, dd, *J* 13.0, 4.3 Hz, 1 of SCH_2),

[§] Evans Extra Bleach solution was used.

4.26 (2H, q, *J* 7.1 Hz, $C\underline{H}_2CH_3$), 4.37-4.40 (1H, m, $CH_2C\underline{H}(OH)$).

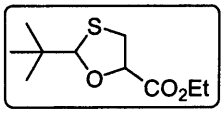
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 ($CH_2\underline{C}H_3$), 30.9 ($(\underline{C}H_3)_3C$), 33.0 (SCH_2), 42.4 ($(CH_3)_3\underline{C}$), 62.0 ($\underline{C}H_2CH_3$), 69.9 ($CH_2\underline{C}H(OH)$), 173.1 (C=O).

ν_{max}/cm^{-1} (film): 3444 (O-H), 2962 (C-H), 2931 (C-H), 2902 (C-H), 1732 (C=O), 1461.

m/z (CI+, CH_4): 207 (MH^+, 10%), 188 (11), 151 (100), 133 (81), 105 (25).

HRMS (CI+, CH_4): $C_9H_{19}O_2S$ (MH^+) requires: 207.1055; found: 207.1048; error: 3.4 ppm.

Ethyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate 75a



Pivalaldehyde (0.06 mL, 0.5 mmol), thioanisole (0.06 mL, 0.5 mmol) and boron trifluoride diethyl etherate complex (0.13 mL, 1.1 mmol) were added to a solution of ethyl 3-(*tert*-butylsulfanyl)-2-hydroxypropanoate **73a** (109 mg, 0.53 mmol) in dry DCM (1.3 mL). The mixture was stirred for 4 h at RT and then quenched with sat. aq. $NaHCO_3$ (5 mL). The organic material was extracted with DCM (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture of diastereomers (1:2.2, *cis:trans*). Purification by column chromatography (SiO_2, 1% EtOAc in petroleum ether) gave the product **75a**, an oil, (77 mg, 67%) as a mixture of the two isomers (1:2.4, *cis*: *trans*).

^{1}H NMR (500 MHz, $CDCl_3$): *trans* isomer δ 0.99 (9H, s, $(CH_3)_3C$), 1.23-1.31 (3H, m, $CH_2C\underline{H}_3$), 3.12 (1H, dd, *J* 10.7, 6.6 Hz, 1 of SCH_2), 3.24-3.28 (1H, m, 1 of SCH_2), 4.18-4.28 (2H, m, $C\underline{H}_2CH_3$), 4.94 (1H, dd, *J* 6.6, 2.5 Hz, $CH_2C\underline{H}CO_2Et$), 5.23 (1H, s, $(CH_3)_3CC\underline{H}$).

cis isomer δ 1.02 (9H, s, $(CH_3)_3C$), 1.23-1.31 (3H, m, $CH_2C\underline{H}_3$), 2.99 (1H, dd, *J* 10.4, 9.0 Hz, 1 of SCH_2), 3.22-3.25 (1H, m, 1 of SCH_2), 4.18-4.28 (2H, m, $C\underline{H}_2CH_3$), 4.47 (1H, dd, *J* 9.0, 5.8 Hz, $CH_2C\underline{H}CO_2Et$), 4.99 (1H, s, $(CH_3)_3CC\underline{H}$).

^{13}C NMR (75 MHz, $CDCl_3$): *trans* isomer δ 14.2 ($CH_2\underline{C}H_3$), 25.7 ($\underline{C}H_3)_3C$), 34.3 (SCH_2), 35.7 ($(CH_3)_3\underline{C}$), 61.5 ($\underline{C}H_2CH_3$), 80.6 ($\underline{C}HCO_2Et$), 95.9 ($(CH_3)_3C\underline{C}H$), 170.9 (C=O).

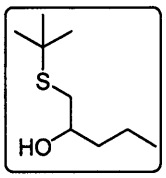
cis isomer δ 14.2 ($CH_2\underline{C}H_3$), 25.9 ($\underline{C}H_3)_3C$), 34.7 (SCH_2), 35.4 ($(CH_3)_3\underline{C}$), 61.5 ($C\underline{H}_2CH_3$), 80.9 ($\underline{C}HCO_2Et$), 96.4 ($(CH_3)_3C\underline{C}H$), 169.2 (C=O).

ν_{max}/cm^{-1} (film): 2957 (C-H), 2868 (C-H), 1744 (C=O), 1364, 1186, 1144.

m/z (CI+, CH_4): 219 (MH^+, 16%), 203 (10), 161 (81), 149 (24), 133 (100), 101 (41).

HRMS (CI+, CH_4): $C_{10}H_{19}O_3S$ (MH^+) requires: 219.1055; found: 219.1056; error: 0.7 ppm.

1-(*tert*-Butylsulfanyl)pentan-2-ol 73b



tert-Butylthiol (1.46 mL, 13.0 mmol) and triethylamine (0.91 mL, 6.5 mmol) were added to a solution of 1,2-epoxypentane (1.12 g, 13.0 mmol) in methanol (130 mL). The mixture was heated to reflux for 5 h, allowed to cool and concentrated *in vacuo*. Column chromatography (SiO_2, 5% EtOAc in petroleum ether) afforded the product **73b** as a colourless oil (1.76 g, 77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, broad t, *J* 7.0 Hz, $CH_2C\underline{H}_3$), 1.32 (9H, s, $(CH_3)_3C$), 1.37-1.53 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 2.35 (1H, s, OH), 2.50 (1H, dd, *J* 12.8, 8.6 Hz, 1 of SCH_2), 2.76 (1H, dd, *J* 12.7, 3.6 Hz, 1 of SCH_2), 3.61-3.69 (1H, m, C<u>H</u>OH).

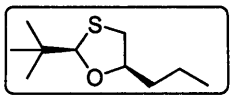
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 19.0 ($\underline{C}H_2CH_3$), 31.1 (($\underline{C}H_3)_3C$), 36.6 ($\underline{C}H_2CH_2CH_3$), 38.7 (SCH_2), 42.4 (($CH_3)_3\underline{C}$), 69.8 (<u>C</u>HOH).

ν_{max}/cm^{-1} (film): 3385 (O-H), 2929 (C-H), 2872 (C-H), 1460, 1363, 1163.

m/z (EI): 176 (M^+, 93%), 133 (43), 119 (52), 104 (100), 103 (96).

HRMS (EI): $C_9H_{20}OS$ (M^+) requires: 176.1235; found: 176.1239; error: 2.2 ppm

***cis*-2-*tert*-Butyl-5-propyl-1,3-oxathiolane 75b**



Pivalaldehyde (0.41 mL, 3.74 mmol), thioanisole (0.44 mL, 3.74 mmol) and boron trifluoride diethyl etherate (0.95 mL, 7.48 mmol) were added to a solution of 1-(*tert*-butylsulfanyl)pentan-2-ol **73b** (659 mg, 3.74 mmol) in dry DCM (9.4 mL). The resulting mixture was stirred at RT for 4 h, then quenched with sat. aq. $NaHCO_3$ (10 mL) and the organic material extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in*

vacuo to give the crude product as a mixture of two diastereomers (2.5:1, *cis:trans*). Purification by column chromatography (SiO_2, hexane) gave *cis*-2-*tert*-butyl-5-propyl-1,3-oxathiolane **75b** as a colourless oil (104 mg, 15%).**

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, broad t, *J* 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 0.95 (9H, s, $(CH_3)_3C$), 1.33-1.50 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.53-1.60 (1H, m, 1 of $C\underline{H}_2CH_2CH_3$), 1.68-1.75 (1H, m, 1 of $C\underline{H}_2CH_2CH_3$), 2.47 (1H, app. t, *J* 9.9 Hz, 1 of SCH_2), 2.94 (1H, dd, *J* 9.8, 4.7, 1 of SCH_2), 3.83-3.88 (1H, m, CHO), 4.90 (1H, s, $(CH_3)_3CC\underline{H}$)).

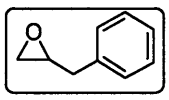
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 ($CH_2CH_2\underline{C}H_3$), 19.6 ($CH_2\underline{C}H_2CH_3$), 25.8 ($(\underline{C}H_3)_3C$), 35.1 ($(CH_3)_3\underline{C}$), 35.9 ($\underline{C}H_2CH_2CH_3$), 36.9 (SCH_2), 84.0 (CHO), 95.4 ($(CH_3)_3C\underline{C}H$).

ν_{max}/cm^{-1} (film): 2957 (C-H), 2930 (C-H), 2864 (C-H), 1479, 1464, 1362.

m/z (EI): 188 (M^+, 23%), 131 (100), 103 (31).

HRMS (EI): $C_{10}H_{20}OS$ (M^+) requires: 188.1235; found: 188.1238; error: 1.5 ppm.

Benzyloxirane[121] 71c



Allylbenzene (1.02 g, 8.63 mmol) was dissolved in DCM (10 mL) and cooled to 0 °C. *m*-CPBA (70-75%, 2.34 g, *ca.* 9.49 mmol) was added to the solution and the resulting mixture was stirred for 4 h at RT. Sat. aq. $NaHCO_3$ (15 mL) was added to the reaction mixture and the organic material extracted with DCM (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and the solution concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% EtOAc in petroleum ether) gave the product **71c** as a colourless oil (874 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (1H, dd, *J* 5.0, 2.7 Hz, 1 of $C\underline{H}_2Ph$), 2.79-2.86 (2H, m, 1 of $C\underline{H}_2Ph$ and 1 of CH_2O), 2.94 (1H, dd, *J* 14.5, 5.6 Hz, 1 of CH_2O), 3.14-3.19 (1H, m, $C\underline{H}CH_2Ph$), 7.25-7.32 (5H, m, aryl).

^{13}C NMR (75 MHz, $CDCl_3$): δ 38.8 ($\underline{C}H_2Ph$), 46.9 (CH_2O), 52.5 ($\underline{C}HCH_2Ph$), 126.7 (aryl-*para*), 128.6 (aryl-*ortho*), 129.0 (aryl-*meta*), 137.2 (aryl-*ipso*).

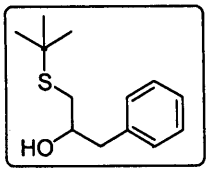
ν_{max}/cm^{-1} (film): 3028 (C-H), 2991 (C-H), 2918 (C-H), 1497, 1454, 1404, 1258.

m/z (EI): 134 (M^+, 80), 105 (64), 105 (64), 104 (64), 91 (100).

HRMS (EI): $C_9H_{10}O$ (M^+) requires: 134.0732; found: 134.0733; error: 1.3 ppm.

** It was not possible to isolate a clean sample of the *trans* isomer.

1-(*tert*-Butylsulfanyl)-3-phenylpropan-2-ol 73c



tert-Butylthiol (0.29 mL, 2.5 mmol) and triethylamine (0.35 mL, 2.5 mmol) were added to a solution of 2-benzyloxirane **71c** (341 mg, 2.54 mmol) in ethanol (25 mL). The mixture was heated to reflux for 2.5 h, cooled to RT and concentrated *in vacuo*. Column chromatography (SiO_2, 5% EtOAc in petroleum ether) gave the product **73c** as a colourless oil (408 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (9H, s, $(CH_3)_3C$), 2.26 (1H, broad s, OH), 2.58 (1H, dd, *J* 12.8, 7.8 Hz, 1 of $C\underline{H}_2Ph$), 2.75 (1H, dd, *J* 12.8, 4.4 Hz, 1 of $C\underline{H}_2Ph$), 2.84 (2H, app. d, *J* 6.4 Hz, SCH_2), 3.87-3.96 (1H, m, $C\underline{H}(OH)$), 7.20-7.26 (3H, m, aryl), 7.29-7.35 (2H, m, aryl).

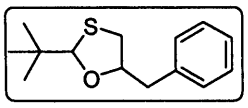
^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1 ($(\underline{C}H_3)_3C$), 35.6 ($\underline{C}H_2Ph$), 42.5 ($(CH_3)_3\underline{C}$), 42.9 (SCH_2), 71.3 (CH(OH)), 126.6 (aryl-*para)*, 128.5 (aryl-*ortho*), 129.4 (aryl-*meta*), 138.0 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 3418 (O-H), 2899 (C-H), 2864 (C-H), 1456, 1366, 1163, 1032.

m/z (EI): 224 (M^+, 21%), 206 (100), 150 (83), 133 (70), 117 (100).

HRMS (EI): $C_{13}H_{20}OS$ (M^+) requires: 224.1235; found: 224.1239; error: 1.8 ppm.

5-Benzyl-2-*tert*-butyl-1,3-oxathiolane 75c



Pivalaldehyde (0.13 mL, 1.2 mmol), thioanisole (0.14 mL, 1.2 mmol) and boron trifluoride diethyl etherate (0.30 mL, 2.4 mmol) were added to a solution of 1-(*tert*-butylsulfanyl)-3-phenylpropan-2-ol **73c** (215 mg, 1.18 mmol) in dry DCM (3 mL), and the stirred for 18 h at RT. The reaction mixture was quenched with sat aq. $NaHCO_3$ (10 mL) and the organic material extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture of diastereomers (3.8:1, *cis*:*trans*). Purification by column chromatography (SiO_2, petroleum ether) gave the product **75c**, an oil, as a mixture of both diastereomers (3.8:1, *cis*:*trans*, 131 mg, 47%).

^{1}H NMR (500 MHz, $CDCl_3$): *cis*-isomer δ 0.96 (9H, s, $(CH_3)_3C$), 2.56 (1H, app. t, *J*

9.9 Hz, 1 of $C\underline{H}_2Ph$), 2.85-2.89 (2H, m, 1 of $C\underline{H}_2Ph$ and 1 of SCH_2), 3.11 (1H, dd, *J* 13.8, 6.2 Hz, 1 of SCH_2), 4.06-4.11 (1H, m, CHO), 4.92 (1H, s, $(CH_3)_3CC\underline{H}$), 7.19-7.24 (3H, m, aryl), 7.26-7.30 (2H, m, aryl).

trans-isomer δ 0.96 (9H, s, $(C\underline{H}_3)_3C$), 2.77-2.83 (2H, m, $C\underline{H}_2Ph$), 2.85-2.89 (1H, m, 1 of SCH_2), 2.99 (1H, dd, *J* 13.5, 6.1 Hz, 1 of SCH_2), 4.57-4.59 (1H, m, CHO), 5.04 (1H, s, $(CH_3)_3CC\underline{H}$), 7.19-7.24 (3H, m, aryl), 7.26-7.30 (2H, m, aryl).

^{13}C NMR (75 MHz, $CDCl_3$): *cis*-isomer δ 25.8 ($(\underline{C}H_3)_3C$), 35.9 ($(CH_3)_3\underline{C}$), 36.6 ($\underline{C}H_2Ph$), 40.1 (SCH_2), 84.4 (CHO), 95.4 ($(CH_3)_3C\underline{C}H$), 126.5 (aryl-*para*), 128.4 (aryl-*ortho)*, 129.4 (aryl-*meta*), 137.9 (aryl-*ipso*).

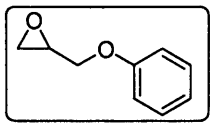
trans-isomer δ 25.9 ($(\underline{C}H_3)_3C$), 35.2 ($(CH_3)_3\underline{C}$), 36.6 ($\underline{C}H_2Ph$), 39.2 (SCH_2), 84.3 (CHO), 94.6 ($(CH_3)_3C\underline{C}H$), 126.5 (aryl-*para*), 128.5 (aryl-*ortho*), 129.3 (aryl-*meta*), 138.1 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 2930 (C-H), 2864 (C-H), 1497, 1479, 1454, 1362, 1182, 1076.

m/z (CI+, CH_4): 237 (MH^+, 7%), 211 (10), 151 (55), 117 (100), 91 (50).

HRMS (CI+, CH_4): $C_{14}H_{21}OS$ (MH^+) requires: 237.1313; found: 237.1314; error: 0.5 ppm.

(Phenoxymethyl)oxirane 71d



A solution of (allyloxy)benzene (2.03 g, 15.1 mmol) in DCM (20 mL) was cooled to 0 °C. *m*-CPBA (70-75%, 12.3 g, *ca.* 50 mmol) and sat. aq. $NaHCO_3$ (20 mL) were added to the cooled solution and the resulting mixture stirred for 4 h. The mixture was then filtered through Celite® and washed with brine (50 mL). The organic material was extracted with DCM (3 × 20 mL) and the combined organic extracts dried ($MgSO_4$). The crude product was concentrated and then purified by column chromatography (SiO_2, 7% EtOAc in petroleum ether) to give the product **71d**[122] as a colourless oil (931 mg, 41%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76 (1H, dd, *J* 4.9, 2.7 Hz, 1 of $C\underline{H}_2OCHCH_2$), 2.91 (1H, app. t, *J* 4.5 Hz, 1 of $C\underline{H}_2OCHCH_2$), 3.34-3.39 (1H, m, $CH_2OC\underline{H}CH_2$), 3.97 (1H, dd, *J* 11.0, 5.6 Hz, 1 of $C\underline{H}_2OPh$), 4.22 (1H, dd, *J* 11.0, 3.2 Hz, 1 of $C\underline{H}_2OPh$), 6.90-7.00 (3H, m, aryl), 7.26-7.33 (2H, m, aryl).

^{13}C NMR (75 MHz, $CDCl_3$): δ 44.8 ($\underline{C}H_2(O)CHCH_2$), 50.2 ($CH_2(O)\underline{C}HCH_2$), 68.7

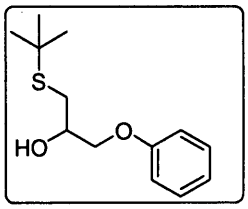
($\underline{C}H_2OPh$), 114.6 (aryl-*ortho*), 121.3 (aryl-*para*), 129.5 (aryl-*meta*), 158.5 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 3002 (C-H), 2926 (C-H), 1587, 1495, 1243, 1040.

m/z (CI+, CH_4): 151 (MH^+, 29%), 150 (M^+, 81), 133 (65), 121 (100), 107 (31), 77 (15)

HRMS (CI+, CH_4): $C_9H_{11}O_2$ (MH^+) requires: 151.0759; found: 151.0754; error: 3.0 ppm.

1-(*tert*-Butylsulfanyl)-3-phenoxypropan-2-ol 73d



tert-Butylthiol (0.29 mL, 2.60 mmol) and triethylamine (0.36 mL, 2.60 mmol) were added to a solution of 2-(phenoxymethyl)oxirane **71d** (390 mg, 2.60 mmol) in ethanol (26 mL), and the mixture was heated to reflux for 18 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 5% EtOAc in petroleum ether) to give the product **73d** as a yellow oil (606 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (9H, s, $(CH_3)_3C$), 2.51 (1H, broad s, OH), 2.78 (1H, dd, *J* 13.0, 6.9 Hz, 1 of SCH_2), 2.89 (1H, dd, *J* 13.0, 5.6 Hz, 1 of SCH_2), 3.97-4.14 (3H, m, both OCH_2 and $C\underline{H}(OH)$), 6.90-6.99 (3H, m, aryl), 7.26-7.32 (2H, m, aryl).

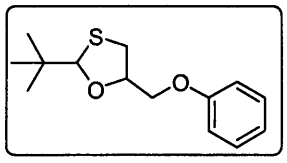
^{13}C NMR (300 MHz, $CDCl_3$): δ 31.0 ($(\underline{C}H_3)_3C$), 32.3 (SCH_2), 42.7 ($(CH_3)_3\underline{C}$), 69.3 (CH(OH)), 70.6 (OCH_2), 114.6 (aryl-*ortho*), 121.2 (aryl-*para*), 129.5 (aryl-*meta*), 158.5 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 3395 (O-H), 2926 (C-H), 2864 (C-H), 1601, 1495, 1245.

m/z (EI): 240 (M^+, 20%), 222 (22), 149 (29), 133 (49), 94 (100).

HRMS (EI): $C_{13}H_{20}O_2S$ (M^+) requires: 240.1184; found: 240.1186; error: 0.9 ppm.

2-*tert*-Butyl-5-(phenoxymethyl)-1,3-oxathiolane 75d



Pivalaldehyde (0.11 mL, 1.0 mmol), thioanisole (0.12 mL, 1.0 mmol) and boron

trifluoride diethyl etherate (0.26 mL, 2.0 mmol) were added to a solution of 1-*(tert*-butylsulfanyl)-3-phenoxypropan-2-ol **73d** (245 mg, 1.02 mmol) in dry DCM (2.55 mL) and stirred for 5 h at RT. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL) and the organic material was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to give a crude mixture of both diastereomers (2.7:1, *cis:trans*). Purification by column chromatography (SiO_2, petroleum ether) gave an inseparable mixture of both diastereomers (2.2:1, *cis:trans*) of the product **75d** as a colourless oil (189 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$): *cis*-isomer δ 0.97 (9H, s, $(CH_3)_3C$), 2.79 (1H, app. t, *J* 9.6 Hz, 1 of SCH_2), 3.11 (1H, dd, *J* 10.3, 5.2 Hz, 1 of SCH_2), 4.05 (1H, dd, *J* 9.8, 5.6 Hz, 1 of $C\underline{H}_2OPh$), 4.19 (1H, dd, *J* 9.8, 5.3, 1 of $C\underline{H}_2OPh$), 4.29-4.34 (1H, m, CHO), 5.00 (1H, s, $(CH_3)_3CC\underline{H}$), 6.89-6.96 (3H, m, aryl), 7.25-7.29 (2H, m, aryl).

trans-isomer δ 0.97 (9H, s, $(CH_3)_3C$), 3.03 (1H, dd, *J* 10.8, 4.3 Hz, 1 of SCH_2), 3.05-3.11 (1H, m, 1 of SCH_2), 3.99 (1H, dd, *J* 9.4, 6.8 Hz, 1 of $C\underline{H}_2OPh$), 4.03-4.08 (1H, m, 1 of $C\underline{H}_2OPh$), 4.72-4.77 (1H, m, CHO), 5.00 (1H, s, $(CH_3)_3CC\underline{H}$), 6.89-6.96 (3H, m, aryl), 7.25-7.29 (2H, m, aryl).

^{13}C NMR (75 MHz, $CDCl_3$): *cis*-isomer δ 25.9 ($(\underline{C}H_3)_3C$), 34.4 (SCH_2), 35.2 ($(CH_3)_3\underline{C}$) 68.6 (CH_2O), 81.7 (CHO), 96.1 ($(CH_3)_3C\underline{C}H$), 114.7 (aryl-*ortho*), 121.1 (aryl-*para*), 129.5 (aryl-*meta*), 158.6 (aryl-*ipso*).

trans-isomer δ 25.9 ($(\underline{C}H_3)_3C$), 34.2 (SCH_2), 36.1 ($(CH_3)_3\underline{C}$), 67.6 (CH_2O), 81.2 (CHO), 95.4 ($(CH_3)_3C\underline{C}H$), 114.7 (aryl-*ortho*), 121.1 (aryl-*para*), 129.5 (aryl-*meta*), 158.6 (aryl-*ipso*).

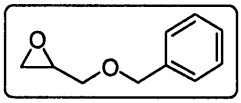
ν_{max}/cm^{-1} ($CDCl_3$): 2957 (C-H), 2870 (C-H), 1599, 1497, 1244, 1049, 908.

m/z (FAB+): 253 (MH^+, 23%), 252 (M^+, 30), 195 (100), 154 (56) 137 (33).

HRMS (FAB+): $C_{14}H_{21}O_2S$ (MH^+) requires: 253.1262; found: 253.1254; error: 3.4 ppm.

Elemental analysis: $C_{14}H_{20}O_2S$ requires: C 66.6, H 8.0; found: C 66.8, H 8.0%.

Benzyloxymethyloxirane 71e



Allyl benzyl ether (2.10 g, 14.2 mmol) was dissolved in DCM (20 mL), and the

solution was cooled to 0 °C. *m*-CPBA (70-75%, 5.2 g, *ca.* 21.3 mmol) and sat. aq. $NaHCO_3$ (20 mL) were added and the resulting mixture was stirred for 20 h at RT. The mixture was then filtered through Celite® and the filtrate was washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4% EtOAc in petroleum ether) gave the product **71e**[123] as a colourless oil (422 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (1H, dd, *J* 5.0, 2.7 Hz, 1 of $C\underline{H}_2(O)CH$), 2.81 (1H, app. t, *J* 4.6 Hz, 1 of $C\underline{H}_2(O)CH$), 3.18-3.21 (1H, m, $CH_2(O)C\underline{H}$), 3.44 (1H, dd, *J* 11.4, 5.9 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 3.77 (1H, dd, *J* 11.4, 3.0 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 4.56 (1H, d, *J* 11.9 Hz, 1 of $C\underline{H}_2Ph$), 4.62 (1H, d, *J* 11.9 Hz, 1 of $C\underline{H}_2Ph$), 7.26-7.36 (5H, m, aryl).

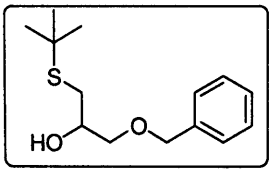
^{13}C NMR (75 MHz, $CDCl_3$): δ 44.3 ($\underline{C}H_2(O)CH$), 50.9 ($CH_2(O)\underline{C}H$), 70.8 ($\underline{C}H_2OCH_2Ph$), 73.3 ($\underline{C}H_2Ph$), 127.8 (aryl-*ortho* and *para*), 128.5 (aryl-*meta*), 137.9 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 3030 (C-H), 2999 (C-H), 2862 (C-H), 1722, 1452, 1097.

m/z (CI+, CH_4): 165 (MH^+, 16%), 164 (M^+, 100), 106 (72), 92 (65).

HRMS (CI+, CH_4): $C_{10}H_{13}O_2$ (MH^+) requires: 165.0916; found: 165.0919; error: 1.8 ppm.

1-(Benzyloxy)-3-(*tert*-butylsulfanyl)propan-2-ol 73e



Triethylamine (0.15 mL, 1.07 mmol) and *tert*-butyl thiol (0.17 mL, 1.54 mmol) were added to a solution of 2-(benzyloxymethyloxirane) **71e** (252 mg, 1.54 mmol) in methanol (15 mL) and the mixture was heated to reflux for 21 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, 5% EtOAc in petroleum ether) to give the product **73e** as an oil (206 mg, 53%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (9H, s, $(CH_3)_3C$), 2.40 (1H , broad s, OH), 2.67 (1H, dd, *J* 12.8, 7.1 Hz, 1 of SCH_2), 2.75 (1H, dd, *J* 12.8, 5.9 Hz, 1 of SCH_2), 3.49 (1H, dd, *J* 9.6, 6.3 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 3.58 (1H, dd, *J* 9.6, 4.0 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 3.87-3.95 (1H, m, $C\underline{H}(OH)$), 4.57 (2H, s, $C\underline{H}_2Ph$), 7.27-7.38 (5H, m, aryl).

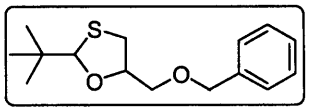
^{13}C NMR (75 MHz, $CDCl_3$): δ 31.0 (($\underline{C}H_3)_3C$), 32.3 (SCH_2), 42.4 (($CH_3)_3\underline{C}$), 69.7 (CH(OH)), 73.1 ($\underline{C}H_2OCH_2Ph$), 73.5 ($\underline{C}H_2Ph$), 127.8 (aryl-*ortho* and *para*), 128.5 (aryl-*meta*), 137.9 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 3443 (O-H), 2961 (C-H), 2924 (C-H), 2862 (C-H), 2899 (C-H), 1454, 1364.

m/z (CI+, CH_4): 255 (MH^+, 32%), 236 (100), 199 (20), 181 (69), 147 (40), 124 (16).

HRMS (CI+, CH_4): $C_{14}H_{23}O_2S$ (MH^+) requires: 255.1419; found: 255.1412; error: 2.5 ppm.

5-(Benzyloxymethyl)-2-*tert*-butyl-1,3-oxathiolane 75e



Pivalaldehyde (0.05 mL, 0.46 mmol), thioanisole (0.06 mL, 0.46 mmol) and boron trifluoride diethyl etherate (0.12 mL, 0.93 mmol) were added to a solution of 1-(benzyloxy)-3-(*tert*-butylsulfanyl)propan-2-ol **73e** (118 mg, 0.46 mmol) in dry DCM (1.2 mL). The mixture was stirred for 24 h at RT, then sat. aq. $NaHCO_3$ (5 mL) was added. The organic material was extracted with DCM (2 × 10 mL) and the organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the crude product was obtained as a mixture of diastereomers (3:1, *cis:trans*). Column chromatography (SiO_2, hexane) afforded both isomers of the product **75e** as an oil (2.7:1, *cis:trans*, 101 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$): *cis*-isomer δ 0.97 (9H, s, $(CH_3)_3C$), 2.65 (1H, app. t, *J* 9.8 Hz, 1 of SCH_2), 2.99 (1H, dd, *J* 10.1, 5.2 Hz, 1 of SCH_2), 3.60 (1H, dd, *J* 10.4, 4.7 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 3.67 (1H, dd, *J* 10.4 5.7 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 4.12-4.17 (1H, m, CHO), 4.55-4.62 (2H, m, $C\underline{H}_2Ph$), 4.97 (1H, s, $(CH_3)_3CC\underline{H}$), 7.31-7.37 (5H, m, aryl).

trans-isomer δ 0.96 (9H, s, $(CH_3)_3C$), 2.90 (1H, dd, *J* 10.7, 4.6 Hz, 1 of SCH_2), 2.99 (1H, dd, *J* 10.7, 5.9 Hz, 1 of SCH_2), 3.49 (1H, dd, *J* 9.8, 6.2 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 3.55 (1H, dd, *J* 9.8, 5.8 Hz, 1 of $C\underline{H}_2OCH_2Ph$), 4.55-4.62 (3H, m, $C\underline{H}_2Ph$ and CHO), 4.93 (1H, s, $(CH_3)_3CC\underline{H}$), 7.31-7.37 (5H, m, aryl).

^{13}C NMR (75 MHz, $CDCl_3$): *cis*-isomer δ 25.9 (($\underline{C}H_3)_3C$), 34.3 (SCH_2), 35.1 (($CH_3)_3\underline{C}$), 70.9 ($\underline{C}H_2OCH_2Ph$), 73.5 ($\underline{C}H_2Ph$), 82.9 (CHO), 96.0 (($CH_3)_3C\underline{C}H$), 127.7 (aryl-*ortho* and *para*), 128.4 (aryl-*meta*), 138.1 (aryl-*ipso*).

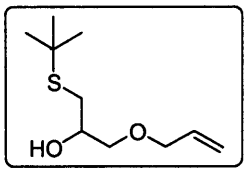
trans-isomer δ 25.9 ((<u>C</u>H$_3$)$_3$C), 34.1 (SCH$_2$), 36.0 ((CH$_3$)$_3$<u>C</u>), 70.0 (<u>C</u>H$_2$OCH$_2$Ph), 73.4 (<u>C</u>H$_2$Ph), 82.0 (CHO), 95.3 ((CH$_3$)$_3$C<u>C</u>H), 127.7 (aryl-*ortho* and *para*), 128.4 (aryl-*meta*), 138.1 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 2955 (C-H), 2864 (C-H), 1479, 1454, 1364, 1090.

m/z (CI+, CH$_4$): 271 (61%), 267 (MH$^+$, 15), 209 (100), 181 (43), 103 (14).

HRMS (CI+, CH$_4$): C$_{15}$H$_{23}$O$_2$S (MH$^+$) requires: 267.1419; found: 267.1410; error: 3.3 ppm.

1-(Allyloxy)-3-(*tert*-butylsulfanyl)propan-2-ol 73f



Triethylamine (1.3 mL, 1.4 mmol) and *tert*-butyl thiol (1.5 mL, 13.4 mmol) were added to a solution of 2-(allyloxy)oxirane (1.53g, 13.4 mmol) in methanol (134 mL), and the mixture was heated to reflux for 2.5 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO$_2$, 10% EtOAc in petroleum ether) to give the product **73f** as an oil (2.19g, 80%).

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.32 (9H, s, (CH$_3$)$_3$C), 2.46-2.62 (1H, broad s, OH), 2.66 (1H, dd, *J* 12.8, 7.0 Hz, 1 of SCH$_2$), 2.74 (1H, dd, *J* 12.8, 5.9 Hz, 1 of SCH$_2$), 3.44 (1H, dd, *J* 9.6, 6.4 Hz, 1 of HOCHC<u>H</u>$_2$O), 3.54 (1H, dd, *J* 9.6, 4.0 Hz, 1 of HOCHC<u>H</u>$_2$O), 3.84-3.92 (1H, m, C<u>H</u>(OH)), 4.01-4.04 (2H, m, C<u>H</u>$_2$CH=CH$_2$), 5.17-5.31 (2H, m, CH=C<u>H</u>$_2$), 5.84-5.97 (1H, m, C<u>H</u>=CH$_2$).

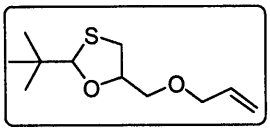
^{13}C NMR (75 MHz, CDCl$_3$): δ 31.0 ((<u>C</u>H$_3$)$_3$C), 32.3 (SCH$_2$), 42.4 ((CH$_3$)$_3$<u>C</u>), 69.7 (CH(OH)), 72.3 (HOCH<u>C</u>H$_2$O), 73.0 (<u>C</u>H$_2$CH=CH$_2$), 117.3 (CH=<u>C</u>H$_2$), 134.5 (<u>C</u>H=CH$_2$).

ν_{max}/cm^{-1} (film): 3445 (O-H), 2961 (C-H), 2899 (C-H), 2862 (C-H), 1645 (C=C), 1460, 1366.

m/z (CI+, CH$_4$): 205 (MH$^+$, 10%), 187 (18), 159 (20), 149 (45), 131 (100), 97 (38).

HRMS (CI+, CH$_4$): C$_{10}$H$_{21}$O$_2$S (MH$^+$) requires: 205.1262; found: 205.1259; error: 1.8 ppm.

5-(Allyloxymethyl)-2-*tert*-butyl-1,3-oxathiolane 75f



Pivalaldehyde (0.60 mL, 5.53 mmol), thioanisole (0.65mL, 5.53 mmol) and boron trifluoride diethyl etherate (1.40 mL, 11.1 mmol) were added to a solution of 1-(allyloxy)-3-(*tert*-butylsulfanyl)propan-2-ol **73f** (1.13g, 5.53 mmol) in dry DCM (13.8 mL). The resulting mixture was stirred for 25 h at RT, then sat. aq. $NaHCO_3$ (15 mL) was added. The organic material was extracted with DCM (3 × 15 mL), and the combined organic extracts washed with brine (15 mL) then dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a crude mixture of diastereomers (2.9:1, *cis:trans*). Purification by column chromatography (SiO_2, hexane) gave the product **75f**, an oil, as a mixture of diastereomers (2.8:1, *cis:trans*, 426 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$): *cis*-isomer δ 0.96 (9H, s, $(CH_3)_3C$), 2.63 (1H, app. t, *J* 9.8 Hz, 1 of SCH_2), 2.98 (1H, dd, *J* 10.1, 5.2 Hz, 1 of SCH_2), 3.56 (1H, dd, *J* 10.5, 4.8 Hz, 1 of $OCHCH_2O$), 3.64 (1H, dd, *J* 10.5, 5.7 Hz, 1 of $OCHCH_2O$), 4.02-4.05 (2H, m, $CH_2CH=CH_2$), 4.08-4.13 (1H, m, CHO), 4.95 (1H, s, $(CH_3)_3CCH$), 5.16-5.29 (2H, m, $CH=CH_2$), 5.84-5.92 (1H, m, $CH=CH_2$).

trans-isomer δ 0.96 (9H, s, $(CH_3)_3C$), 2.89 (1H, dd, *J* 10.7, 4.7 Hz, 1 of SCH_2), 2.98 (1H, dd, *J* 10.7, 5.9 Hz, 1 of SCH_2), 3.46 (1H, dd, *J* 9.9, 6.3 Hz, 1 of $OCHCH_2O$), 3.51 (1H, dd, *J* 9.9, 5.7 Hz, 1 of $OCHCH_2O$), 4.00-4.02 (2H, m, $CH_2CH=C$), 4.51-4.55 (1H, m, CHO), 4.94 (1H, s, $(CH_3)_3CCH$), 5.16-5.29 (2H, m, $CH=CH_2$), 5.84-5.92 (1H, m, $CH=CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): *cis*-isomer δ 25.9 ($(CH_3)_3C$), 34.4 (SCH_2), 35.1 ($(CH_3)_3C$), 70.9 ($OCHCH_2O$), 72.5 ($CH_2CH=CH_2$), 82.9 ($OCHCH_2O$), 96.0 ($(CH_3)_3CCH$), 117.2 ($CH=CH_2$), 134.6 ($CH=CH_2$).

trans-isomer δ 25.9 ($(CH_3)_3C$), 34.1 (SCH_2), 36.0 ($(CH_3)_3C$), 70.1 ($OCHCH_2O$), 72.4 ($CH_2CH=CH_2$), 82.0 ($OCHCH_2O$), 95.3 ($(CH_3)_3CCH$), 117.2 ($CH=CH_2$), 134.6 ($CH=CH_2$).

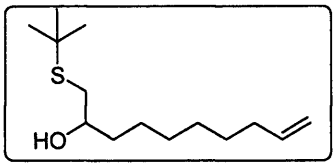
ν_{max}/cm^{-1} (film): 2955 (C-H), 2951 (C-H), 2926 (C-H), 1724, 1641 (C=C), 1479, 1464.

m/z (CI+, CH_4): 235 (10%), 217 (MH^+, 10), 203 (11), 159 (100), 131 (41), 103 (37), 97 (98).

HRMS (CI+, CH_4): $C_{11}H_{21}O_2S$ (MH^+) requires: 217.1262; found: 217.1265; error: 1.2

ppm.

1-(*tert*-Butylsulfanyl)dec-9-en-2-ol 73g



tert-Butylthiol (0.84 mL, 7.46 mmol) and triethylamine (1.04 mL, 7.46 mmol) were added to a solution of 1,2–epoxy-9-decene (1.15 g, 7.46 mmol) in ethanol (75 mL). The mixture was heated to reflux for 2.5 h, cooled to RT and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in petroleum ether) gave the product **73g** as a pale yellow oil (1.69 g, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31-1.40 (10H, m, $(C\underline{H}_2)_5CH_2CH{=}CH_2$), 1.33 (9H, s, $(CH_3)_3C$), 2.00-2.07 (2H, m, $C\underline{H}_2CH{=}CH_2$), 2.50 (1H, dd, *J* 12.8, 8.6 Hz, 1 of SCH_2), 2.77 (1H, dd, *J* 12.8, 3.6 Hz, 1 of SCH_2), 3.59-3.67 (1H, m, C<u>H</u>OH), 4.90-5.02 (2H, m, $CH{=}C\underline{H}_2$), 5.80 (1H, ddt, *J* 17.0, 10.3, 6.7 Hz, $C\underline{H}{=}CH_2$).

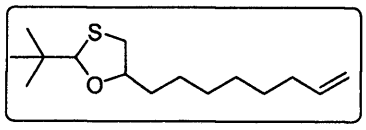
^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 28.9, 29.0, 29.5 ($(\underline{C}H_2)_4CH_2CH{=}CH_2$), 31.2 ($(\underline{C}H_3)_3C$), 33.8, 36.6, 36.7 ($SCH_2$, $\underline{C}H_2(CH_2)_4$, $\underline{C}H_2CH{=}CH_2$), 42.4 ($(CH_3)_3\underline{C}$), 70.0 (CH(OH)), 114.2 ($CH{=}\underline{C}H_2$), 139.15 ($\underline{C}H{=}CH_2$).

ν_{max}/cm^{-1} (film): 3404 (O-H), 2928 (C-H), 2856 (C-H), 1639 (C=C), 1458, 1364, 1163.

m/z (FAB+): 245 (MH^+, 100%), 227 (23), 187 (25), 171 (68).

HRMS (FAB+): $C_{14}H_{29}OS$ (MH^+) requires: 245.1939; found: 245.1928; error: 4.6 ppm.

2-*tert*-Butyl-5-(oct-7-enyl)-1,3-oxathiolane 75g



Pivalaldehyde (0.19 mL, 1.72 mmol), thioanisole (0.20 mL, 1.72 mmol) and boron trifluoride diethyl etherate (0.44 mL, 3.44 mmol) were added to a solution of 1-(*tert*-butylsulfanyl)dec-9-en-2-ol **73g** (420 mg, 1.72 mmol) in dry DCM (4.3 mL). The mixture was stirred at RT overnight, then sat. aq. $NaHCO_3$ (10 mL) was added. The organic material was extracted with DCM (3 × 10 mL) and the combined organic

extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solution was concentrated *in vacuo* to give a crude mixture of diastereomers (3.7:1, *cis:trans*). Purification by column chromatography (SiO_2, petroleum ether) gave the product **75g**, an oil, (53 mg, 12%) as a 14:1 *cis:trans* ratio of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) (major isomer only): δ 0.97 (9H, s, $(CH_3)_3C$), 1.25-1.79 (10H, m, $(C\underline{H}_2)_5CH_2CH=CH_2$), 2.02-2.07 (2H, m, $C\underline{H}_2CH=CH_2$), 2.49 (1H, app. t, *J* 9.9 Hz, 1 of SCH_2), 2.96 (1H, dd, *J* 9.8, 4.7 Hz, 1 of SCH_2), 3.83-3.90 (1H, m, CHO), 4.92 (1H, s, $(CH_3)_3CC\underline{H}$), 4.94-5.02 (2H, m, $CH=C\underline{H}_2$), 5.81 (1H, ddt, *J* 17.0, 10.3, 6.7 Hz, $C\underline{H}=CH_2$).

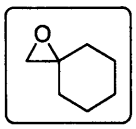
^{13}C NMR (75 MHz, $CDCl_3$) (major isomer only): δ 25.8 ($(\underline{C}H_3)_3C$), 26.2, 28.8, 29.0, 29.5 (4 of $(\underline{C}H_2)_5CH_2CH=CH_2$), 33.7, 33.8, 36.9 (1 of $(\underline{C}H_2)_5CH_2CH=CH_2$, SCH_2, $\underline{C}H_2CH=CH_2$), 35.1 ($(CH_3)_3\underline{C}$), 84.2 (CHO), 95.4 ($(CH_3)_3C\underline{C}H$), 114.2 ($CH=\underline{C}H_2$), 139.1 ($\underline{C}H=CH$).

ν_{max}/cm^{-1} (film): 2928 (C-H), 2856 (C-H), 1641 (C=C), 1479, 1362, 1072.

m/z (CI+, CH_4): 257 (MH^+, 15%), 239 (13), 199 (80), 171 (100), 137 (31).

HRMS (CI+, CH_4): $C_{15}H_{29}OS$ (MH^+) requires: 257.1939; found: 257.1934; error: 2.1

1,1-Oxaspiro[2.5]octane 71h



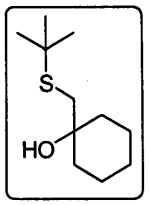
Sodium hydride (60% dispersion in mineral oil, 346 mg, 5.1 mmol) was washed with hexane under argon. Dry DMSO (5.1 mL) was added and the mixture was heated at 70-75 °C for 20 min. After allowing the mixture to cool to RT, dry THF (5.2 mL) was added and the mixture was cooled in an ice-salt bath to 0 °C. A solution of trimethylsulfonium iodide (1.25 g, 6.1 mmol) in dry DMSO (5.2 mL) was then added dropwise. The resultant solution was stirred for 5 min before the addition of cyclohexanone (0.53 mL, 5.1 mmol). Stirring was continued for 10 min, then the solution was allowed to warm to RT and stirred for a further 35 min. The reaction mixture was diluted with H_2O (60 mL), and the organic material extracted with Et_2O (3 × 30 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated.[124] Purification by column chromatography (SiO_2, 2% EtOAc in petroleum ether) gave the product **71h**[125] as a yellow oil (175 mg, 30%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46-1.63 (8H, m, cyclohexane), 1.67-1.80 (2H, m,

cyclohexane), 2.59 (2H, s, (O)CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 25.3, 33.6 (cyclohexane CH_2), 54.5 (C(O)$\underline{C}H_2$), 59.0 ((CH_2)$_3\underline{C}$(O).

1-(*tert*-Butylsulfanylmethyl)cyclohexanol 73h



tert-Butylthiol (0.26 mL, 2.32 mmol) and triethylamine (0.16 mL, 1.16 mmol) were added to a solution of 1,1-oxaspiro[2.5]octane **71h** (260 mg, 2.32 mmol) in methanol (23 mL) and the resultant solution was heated to reflux for 3 h. The reaction mixture was then cooled to RT and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 8% EtOAc in petroleum ether) gave the product **73h** as a white crystalline solid (225.4 mg, 48%).

mp: 29-32 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23-1.70 (10H, m, cyclohexane), 1.32 (9H, s, (CH_3)$_3$C), 1.73-2.18 (1H, broad s, OH), 2.65 (2H, s, SCH_2).

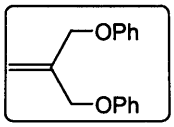
^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2 (cyclohexane), 25.7 (cyclohexane), 31.0 (($\underline{C}H_3$)$_3$C), 37.3 (cyclohexane), 41.4 (SCH_2), 42.0 ((CH_3)$_3\underline{C}$), 69.9 ((CH_2)$_3\underline{C}$OH).

ν_{max}/cm^{-1} (KBr): 3470 (O-H), 2934 (C-H), 2860 (C-H), 1460, 1448, 1364.

m/z (EI): 210 (13), 202 (M^+, 8%), 104 (100), 99 (96).

HRMS (EI): $C_{11}H_{22}OS$ (M^+) requires: 202.1391; found: 202.1386; error: 2.5 ppm.

1,1-Di(phenoxymethyl)ethene[47] 72



Phenol (4.97g, 52.8 mmol) was dissolved in acetone (60 mL). Potassium carbonate (7.30 g, 52.8 mmol) was added and the resultant slurry was stirred at RT for 15 min. 3-Chloro-2-(chloromethyl)propene (2.78 mL, 24.0 mmol) was then added and the mixture was heated to reflux for 22 h. The reaction mixture was allowed to cool, then diluted with H_2O (70 mL). The organic material was extracted with Et_2O (2 × 60 mL), and the organic extracts were washed with brine (60 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1% EtOAc in hexane) gave the product **72** (1.71g, 30%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): 4.66 (4H, s, C$\underline{H_2}$OPh), 5.42-5.44 (2H, m, CH_2=C), 6.94-6.99 (6H, m, aryl), 7.26-7.32 (4H, m, aryl).

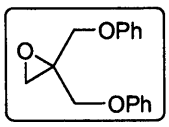
^{13}C NMR (75 MHz, $CDCl_3$): δ 68.6 (C$\underline{H_2}$OPh), 114.8 (aryl-*ortho*), 115.7 ($\underline{C}H_2$=C), 121.0 (aryl-*para*), 129.5 (aryl-*meta*), 140.5 (CH_2=$\underline{C}$), 158.6 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 3067, 3040, 2916 (C-H), 2866 (C-H), 1599 (C=C), 1587, 1495.

m/z (FAB+): 241(MH^+, 16%), 240 (M^+, 42), 307 (13), 154 (39).

HRMS (FAB+): $C_{16}H_{17}O_2$ (MH^+) requires: 241.1229; found: 241.1232; error: 1.5 ppm.

1,1-Di(phenoxymethyl)oxirane 71i



1,1 Di(phenoxymethyl)ethene **72** (802 mg, 3.3 mmol) was dissolved in DCM (8 mL) and the solution was cooled to 0 °C in an ice/salt bath. *m*-CPBA (70-75%, 902 mg, *ca.* 3.7 mmol) and sat. aq. $NaHCO_3$ (5 mL) were added and the resulting mixture was stirred for 5 hours at RT. The mixture was cooled to 0 °C and further *m*-CPBA (70-75%, 902 mg, *ca.* 3.7 mmol) was added. The mixture was stirred at RT for 21 h then additional *m*-CPBA (70-75%, 902 mg, *ca.* 3.7 mmol) and sat. aq. $NaHCO_3$ (2 mL) were added. After further stirring at RT for 3 h, the reaction mixture was filtered through Celite® and the filtrate was washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 6% EtOAc in petroleum ether) afforded the product **71i** as an oil (415 mg, 49%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (2H, s, CH_2(O)C), 4.23 (2H, d, *J* 10.6 Hz, 2 of C$\underline{H_2}$OPh), 4.28 (2H, d, *J* 10.6 Hz, 2 of C$\underline{H_2}$OPh) 6.92-7.01 (6H, m, aryl), 7.26-7.33 (4H, m, aryl).

^{13}C NMR (75 MHz, $CDCl_3$): δ 49.5 ($\underline{C}H_2$OC), 56.9 ($\underline{C}O(CH_2)_3$), 68.0 ($\underline{C}H_2$OPh), 114.7 (aryl-*ortho*), 121.4 (aryl-*para*), 129.5 (aryl-*meta*), 158.5 (aryl-*ipso*).

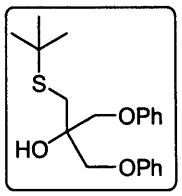
ν_{max}/cm^{-1} (film): 3057 (C-H), 3040 (C-H), 2930 (C-H), 1587, 1497, 1242.

m/z (CI+, CH_4): 257 (MH^+, 19%), 256 (M^+, 100), 185 (23), 183 (29), 181 (29), 173 (67), 133 (11).

HRMS (CI+, CH_4): $C_{16}H_{17}O_3$ (MH^+) requires: 257.1178; found: 257.1169; error: 3.3

ppm.

2-(*tert*-Butylsulfanylmethyl)-1,3-diphenoxy-propan-2-ol 73i



Triethylamine (0.1 mL, 0.7 mmol) and *tert*-butylthiol (0.11 mL, 1.0 mmol) were added to a solution of 1,1-di(phenoxymethyl)oxirane **71i** (257 mg, 1.0 mmol), and the resulting mixture was heated to reflux for 2.5 h. The reaction mixture was then allowed to cool to RT and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 2.5% EtOAc in petroleum ether) gave the product **73i** as a white solid (321 mg, 92%)

mp: 68-70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (9H, s, $(CH_3)_3C$), 3.04 (2H, s, SCH_2), 4.11 (4H, s, 2 × $C\underline{H}_2OPh$), 6.94-6.98 (6H, m, aryl), 7.26-7.31 (4H, m, aryl).

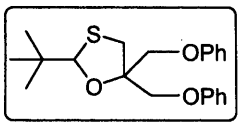
^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9 ($(\underline{C}H_3)_3C$), 33.3 (SCH_2), 42.6 ($(CH_3)_3\underline{C}$), 70.0 ($\underline{C}H_2OPh$), 72.8 (CH(OH)), 114.7 (aryl-*ortho*), 121.2 (aryl-*para*), 129.5 (aryl-*meta*), 158.5 (aryl-*ipso*).

ν_{max}/cm^{-1} (KBr): 3377 (O-H), 2951 (C-H), 2932 (C-H), 2924 (C-H), 1599, 1590, 1497.

m/z (EI): 346 (M^+, 13%), 235 (100), 179 (46), 131 (65), 107 (84), 94 (58).

HRMS (EI): $C_{20}H_{26}O_3S$ (M^+) requires: 346.1603; found: 346.1610; error: 2.1 ppm.

2-*tert*-Butyl-5,5-di(phenoxymethyl)-1,3-oxathiolane 75i



Pivalaldehyde (0.05 mL, 0.48 mmol), thioanisole (0.06 mL, 0.48 mmol) and boron trifluoride diethyl etherate (0.12 mL, 0.96 mmol) were added to a solution of 2-(*tert*-butylsulfanylmethyl)-1,3-diphenoxy-propan-2-ol **73i** (166 mg, 0.48 mmol) in dry DCM (1.2 mL). The reaction mixture was stirred for 23 h at RT, and then sat. aq. $NaHCO_3$ (5 mL) was added. The organic material was extracted with DCM (2 × 10 mL) and the organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, hexane)

afforded the product **75i** as a colourless oil (155 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (9H, s, $(CH_3)_3C$), 3.13 (1H, d, *J* 11.4 Hz, 1 of SCH_2), 3.27 (1H, d, *J* 11.4 Hz, 1 of SCH_2), 4.13 (1H, d, *J* 9.4 Hz, 1 of $C\underline{H}_2OPh$), 4.19 (1H, d, *J* 9.4 Hz, 1 of $C\underline{H}_2OPh$), 4.21 (2H, s, $C\underline{H}_2OPh$), 5.08 (1H, s, $(CH_3)_3CC\underline{H}$), 6.92-6.80 (6H, m, aryl), 7.26-7.30 (4H, m, aryl).

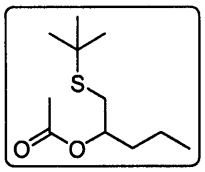
^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 ($(\underline{C}H_3)_3C$), 35.2 (SCH_2), 35.4 ($(CH_3)_3\underline{C}$), 67.6 ($\underline{C}H_2OPh$), 69.0 ($\underline{C}H_2OPh$), 87.8 ($\underline{C}(O)(CH_2)_3$), 96.1 ($(CH_3)_3C\underline{C}H$), 114.8 (aryl), 114.9 (aryl), 121.1 (aryl), 129.5 (aryl), 158.7 (aryl-*ipso*), 158.8 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 2955 (C-H), 2932 (C-H), 1599, 1587, 1497, 1244.

m/z (EI): 358 (M^+, 50%), 301 (100), 145 (98), 107 (53), 94 (30).

HRMS (EI): $C_{21}H_{26}O_3S$ (M^+) requires: 358.1603; found: 358.1592; error: 2.9 ppm.

1-(*tert*-Butylsulfanyl)pentan-2-yl acetate 77



Acetic anhydride (0.16 mL, 1.7 mmol) was added to a solution of 1-(*tert*-butylsulfanyl)pentan-2-ol **73b** (246 mg, 1.40 mmol) in dry pyridine (1.5 mL) at 0 °C and stirred for 24 h at RT. The mixture was then diluted with EtOAc (7 mL), washed with 2M HCl (7 mL), sat. aq. $CuSO_4$ (7 mL), sat. aq. $NaHCO_3$ (7 mL), brine (7 mL) and dried ($MgSO_4$). Concentration *in vacuo*, and purification by column chromatography (SiO_2, 5% EtOAc in petroleum ether) gave the product **77** as a colourless oil (208 mg, 68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* 7.3 Hz, $CH_2C\underline{H}_3$), 1.22-1.46 (2H, m, $C\underline{H}_2CH_3$), 1.32 (9H, s, $(CH_3)_3C$), 1.51-1.73 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.06 (3H, s, $O{=}CCH_3$), 2.64 (1H, dd, *J* 13.0, 6.7 Hz, 1 of SCH_2), 2.73 (1H, dd, *J* 13.0, 5.8 Hz, 1 of SCH_2), 4.90-4.98 (1H, m, $C\underline{H}OAc$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($CH_2\underline{C}H_3$), 18.6 ($C\underline{H}_2CH_3$), 21.2 ($O{=}C\underline{C}H_3$), 31.0 ($(\underline{C}H_3)_3C$), 32.2 ($\underline{C}H_2CH_2CH_3$), 35.3 (SCH_2), 42.4 ($(CH_3)_3\underline{C}$), 73.7 ($\underline{C}HOAc$)), 170.8 (C=O).

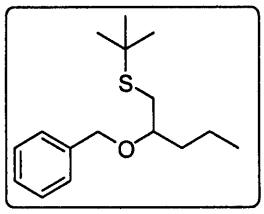
ν_{max}/cm^{-1} (film): 2961 (C-H), 2941 (C-H), 1740 (C=O), 1460, 1366, 1240.

m/z (FAB+): 241 (MNa^+, 81%), 176 (100).

HRMS (FAB+): $C_{11}H_{22}O_2SNa$ (MNa^+) requires: 241.1238; found: 241.1227; error: 4.7

ppm.

2-Benzyloxy-1-(*tert*-butylsulfanyl)pentane 78



Sodium hydride (60% dispersion in mineral oil, 121 mg, 3.02 mmol) was washed with hexane under argon. Dry THF (1.3 mL) was added and the resulting slurry was cooled to 0 °C. A solution of 1-(*tert*-butylsulfanyl)pentan-2-ol **73b** (242 mg, 1.37 mmol) in dry THF (1.4 mL) was added dropwise and the mixture was stirred for 30 min. Benzyl bromide (0.18 mL, 1.8 mmol) was then added dropwise and the mixture was stirred for 45 min at 0 °C and then at RT overnight. The reaction mixture was then diluted with Et_2O (20 mL), and washed with aq. 1M NH_4Cl (10 mL) and brine (15 mL), then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2, 1% EtOAc in petroleum ether) gave the product **78** (246 mg, 67%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.28-1.70 (13H, m, $(CH_3)_3C$ and $C\underline{H}_2C\underline{H}_2CH_3$), 2.64 (1H, dd, *J* 12.2, 7.0 Hz, 1 of SCH_2), 2.78 (1H, dd, J 12.2, 5.1 Hz, 1 of SCH_2), 3.49-3.60 (1H, m, CHO), 4.52 (1H, d, *J* 11.5 Hz, 1 of $PhC\underline{H}_2$), 4.65 (1H, d, *J* 11.6 Hz, 1 of $PhC\underline{H}_2$), 7.21-7.39 (5H, m, aryl).

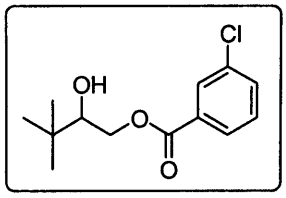
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 18.6 ($\underline{C}H_2CH_3$), 30.9 ($(\underline{C}H_3)_3C$), 32.3 ($\underline{C}H_2CH_2CH_3$), 36.3 (SCH_2), 42.0 ($(CH_3)_3\underline{C}$), 71.5 ($Ph\underline{C}H_2$), 78.7 (CHO), 127.5 (aryl), 127.8 (aryl), 128.3 (aryl), 138.7 (aryl-*ipso*).

ν_{max}/cm^{-1} (film): 2959 (C-H), 2932 (C-H), 2870 (C-H), 1456, 1364, 1094.

m/z (EI): 266 (M^+, 25%), 193 (47), 159 (72), 103 (73), 91 (100).

HRMS (EI): $C_{16}H_{26}OS$ (M^+) requires: 266.1704; found: 266.1705; error: 0.4 ppm.

2-Hydroxy-3,3-dimethylbutyl 3-chlorobenzoate 70



3,3-Dimethylbutene (2.05 g, 24.4 mmol) was dissolved in DCM (30 mL) and the solution was cooled to 0 °C. Sodium bicarbonate (30 mL) and *m*-CPBA (70-75%, 12.0 g, *ca.* 73.1 mmol) were added and the resultant mixture was stirred overnight. The mixture was then filtered through Celite® and the organic material extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7% EtOAc in petroleum ether) gave 2-hydroxy-3,3-dimethylbutyl 3-chlorobenzoate **70** as a yellow oil (709 mg, 11%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (9H, s, $(CH_3)_3C$), 2.09-2.28 (1H, broad s, OH), 3.66 (1H, dd, *J* 8.9, 2.4 Hz, (C<u>H</u>(OH)), 4.25 (1H, dd, *J* 11.4, 8.9 Hz, 1 of CH_2), 4.53 (1H, dd, *J* 11.4, 2.4 Hz, 1 of CH_2), 7.36-7.42 (1H, m, aryl), 7.52-7.56 (1H, m, aryl), 7.92-7.95 (1H, m, aryl), 8.02-8.03 (1H, m, aryl).

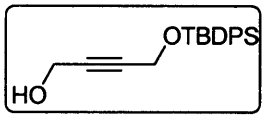
^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 ($(\underline{C}H_3)_3C$), 26.3 ($(CH_3)_3\underline{C}$), 34.1 (C(OH)), 67.4 (CH_2), 127.3 (aryl), 129.7 (aryl), 129.8 (aryl), 131.7 (aryl-*ipso*), 133.2 (aryl), 134.6 (aryl-*ipso*), 165.8 (C=O).

ν_{max}/cm^{-1} (film): 3502 (O-H), 2960 (C-H), 2872 (C-H), 1725 (C=O), 1428, 1259, 1133, 1073.

m/z (FAB+): 259 (MH^+ (^{37}Cl), 6%), 257 (MH^+ (^{35}Cl), 14), 219 (6), 154 (100).

HRMS (FAB+): $C_{13}H_{18}O_3{}^{35}Cl$ (MH^+) requires: 257.0944; found: 257.0948; error: 1.2 ppm.

4-(*tert*-Butyldiphenylsilanyloxy)but-2-yn-1-ol 86



Sodium hydride (60% dispersion in mineral oil, 604 mg, 15.1 mmol) was washed with hexane under argon then suspended in dry THF (17.7 mL). A solution of 2-butyne-1,4-diol (1.50 g, 17.4 mmol) in dry THF (20.5 mL) was added dropwise. The resulting mixture was heated at 35 °C for 3 h. A solution of TBDPSCl (3.0 mL, 11.6 mmol) in

dry THF (13.6 mL) was then added and the mixture was stirred for 19 h at RT. The reaction mixture was then diluted with Et_2O (100 mL) and washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*.[126] Purification by column chromatography (SiO_2, 12% EtOAc in petroleum ether) gave the product **86**[127] as a pale yellow oil (2.12 g, 56%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (9H, s, $(C(CH_3)_3)$, 1.43 (1H, broad s, OH), 4.20 (2H, t, *J* 1.8 Hz, $C{\equiv}C\underline{CH_2}OSi$), 4.36 (2H, t, *J* 1.8 Hz, $C{\equiv}C\underline{CH_2}OH$), 7.37-7.48 (6H, m, aryl-*para* and *meta*), 7.70-7.74 (4H, m, aryl-*ortho*).

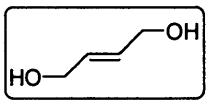
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 ($\underline{C}(CH_3)_3$), 26.7 ($C(\underline{C}H_3)_3$), 51.2 (CH_2OSi), 52.7 (CH_2OH), 83.5 ($C{\equiv}\underline{C}CH_2OSi$), 84.3 ($C{\equiv}\underline{C}CH_2OH$), 127.7 (aryl-*meta*), 129.8 (aryl-*para*), 133.1 (aryl-*ipso*), 135.7 (aryl-*ortho*).

ν_{max}/cm^{-1} (film): 3354 (O-H), 3071, 2930 (C-H), 2858 (C-H), 1589, 1472, 1427, 1373.

m/z (CI+, CH_4): 325 (MH^+, 41%), 307 (100), 267 (98), 247 (68), 229 (62), 199 (80), 179 (38), 139 (77).

HRMS (CI+, CH_4): $C_{20}H_{24}OSi$ (MH^+) requires: 325.1624; found: 325.1624; error: 0 ppm.

(*E*)-But-2-ene-1,4-diol[128] 88



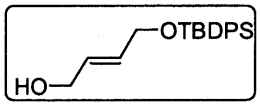
Dry THF (33 mL) was added to lithium aluminium hydride (944 mg, 24.9 mmol) under argon and the resultant slurry was cooled to 0 °C. A solution of 2-butyne-1,4-diol (1.02 g, 11.9 mmol) in dry THF (26 mL) was added dropwise. The reaction mixture was allowed to warm to RT and was then heated to reflux for 2 h. After the reaction mixture had been allowed to cool to RT it was placed in an ice bath and aq. 3M NaOH was added dropwise until no more effervescence occurred. 3M HCl was then added dropwise until the reaction mixture was neutral, as judged by universal indicator paper. Et_2O (80 mL) was then added followed by silica gel (7.5 g), and the resulting mixture was concentrated *in vacuo*. Column chromatography (SiO_2, 5% MeOH in Et_2O) afforded the product **88** as a yellow oil (950 mg, 91%).

^{1}H NMR (300 MHz, CD_3OD): δ 4.05-4.06 (4H, m, CH_2), 4.88 (2H, s, OH), 5.80-5.82 (2H, m, HC=CH).

^{13}C NMR (75 MHz, CD_3OD): δ 63.1 (CH_2), 131.3 (C=C).

ν_{max}/cm^{-1} (film): 3265 (O-H), 2868 (C-H), 1651, 1633, 1418, 1371, 1086, 976.

(*E*)-4-(*tert*-Butyldiphenylsilanyloxy)but-2-en-1-ol 87



Sodium hydride (60% dispersion in mineral oil, 1.98 g, 49.1 mmol) was washed with hexane under argon then suspended in dry THF (98 mL). The resulting slurry was cooled to 0 °C in an ice-bath, then a solution of (*E*)-but-2-ene-1,4-diol **88** (4.33 g, 49.14 mmol) in dry THF (49 mL) was added dropwise. The mixture was stirred at RT for 30 min. A solution of TBDPSCl (11.6 mL, 44.67 mmol) in dry THF (45 mL) was added dropwise and the mixture was stirred at RT for 22 h. The reaction mixture was then diluted with Et_2O (450 mL) and washed with sat. aq. $NaHCO_3$ (150 mL) and brine (150 mL). The organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*.[126] Purification by column chromatography (SiO_2, 15% EtOAc in petroleum ether) gave the product **87**[129] (7.81 g, 54%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (9H, s, $(C(CH_3)_3)$, 1.44 (1H, broad s, OH), 4.13-4.16 (2H, m, CH_2OSi), 4.21-4.24 (2H, m, $C\underline{H}_2OH$), 5.74-5.83 (1H, m, $C=C\underline{H}CH_2OSi$), 5.88-5.98 (1H, m, $C=C\underline{H}CH_2OH$), 7.35-7.46 (6H, m, aryl-*para* and *meta*), 7.66-7.70 (4H, m, aryl-*ortho*).

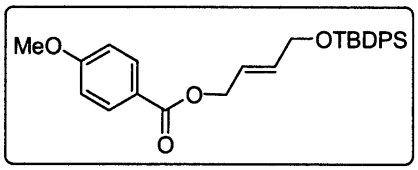
^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2 ($\underline{C}(CH_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 63.3 (CH_2OSi), 63.8 (CH_2OH), 127.7 (aryl-*meta*) 128.8 ($C=\underline{C}HCH_2OSi$), 129.7 (aryl-*para*), 130.7 ($C=\underline{C}HCH_2OH$), 133.6 (aryl-*ipso*), 135.6 (aryl-*ortho*).

ν_{max}/cm^{-1} (film): 3333 (O-H), 2930 (C-H), 2856 (C-H), 1589, 1558, 1472, 1427.

m/z (FAB+): 349 (MNa^+, 33%), 326 (M^+, 13), 199 (55), 176 (100).

HRMS (FAB+): $C_{20}H_{26}O_2SiNa$ (MNa^+) requires: 349.1600; found: 349.1614; error: 4.1 ppm.

(*E*)-4-(*tert*-Butyldiphenylsilanyloxy)but-2-enyl 4-methoxybenzoate[60] 85



A solution of (*E*)-4-(*tert*-butyldiphenylsilanyloxy)but-2-en-1-ol **87** (249 mg, 0.76 mmol) and triethylamine (0.12 mL, 0.84 mmol) in dry DCM (2.2 mL) was added

dropwise to a solution of 4-methoxybenzoyl chloride (143 mg, 0.84 mmol) in dry DCM (2 mL) at 0 °C. The mixture was stirred at RT for 18 h, diluted with DCM (10 mL) and washed with 1M HCl (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in petroleum ether) gave the product **85** (268 mg, 76%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (9H, s, $C(CH_3)_3$), 3.87 (3H, s, OCH_3), 4.22-4.26 (2H, m, C=CHC<u>H</u>$_2$OSi), 4.77-4.82 (2H, m, $ArCO_2C\underline{H}_2CH$=C), 5.88-6.02 (2H, m, <u>H</u>C=C<u>H</u>), 6.91-6.94 (2H, m, aryl-PMBz), 7.35-7.44 (6H, m, aryl-TBDPS), 7.67-7.69 (4H, m, aryl-TBDPS), 7.99-8.04 (2H, m, aryl-PMBz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (<u>C</u>$(CH_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 55.4 (OCH_3), 63.6 (CH_2OSi), 64.7 ($ArCO_2C\underline{H}_2$), 113.6 (aryl-*ortho* to OMe) 122.7 (aryl-*ipso* to C=O), 123.9 (<u>C</u>=C), 127.7 (aryl-*meta* to Si), 129.7 (aryl-*para* to Si), 131.7 (aryl-*meta* to OMe), 133.4 (C=<u>C</u>), 133.5 (aryl-*ipso* to Si), 135.6 (aryl-*ortho* to Si), 163.4 (aryl-*ipso* to OMe), 166.1 (C=O).

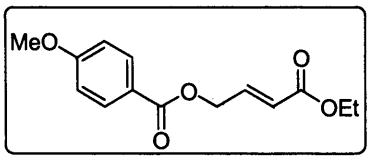
ν_{max}/cm^{-1} (film): 2932 (C-H), 2856 (C-H), 1717 (C=O), 1607 (C=C), 1512, 1427, 1257.

m/z (FAB+): 483 (MNa^+, 100%), 333 (25), 199 (19), 176 (50).

HRMS (FAB+): $C_{28}H_{32}O_4SiNa$ (MNa^+) requires: 483.1968; found: 483.1968; error: 0 ppm.

Elemental analysis: $C_{28}H_{32}O_4Si$ requires: C 73.0, H 7.0; found: C 72.8, H 7.0%.

Ethyl *(E)*-4-(4-methoxybenzoyloxy)-2-butenoate[60] 94



4-Methoxybenzoic acid (812 mg, 5.34 mmol) was added to a suspension of caesium carbonate (1.76 g, 5.39 mmol) in dry DMF (10.7 mL). After the resultant mixture had been stirred for 20 min at RT, ethyl 4-bromocrotonate (0.75 mL, 5.18 mmol) was added and stirring was continued for 22 h. H_2O (80 mL) was added and the organic material extracted with EtOAc (2 × 50 mL). The combined organic extracts were then washed with H_2O (50 mL), brine (50 mL) and dried ($MgSO_4$). Removal of solvent *in vacuo* and purification by column chromatography (SiO_2, 5% EtOAc in petroleum

ether) gave the product **94** (1.13g, 83%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* 7.2 Hz, $CH_2\underline{CH_3}$), 3.86 (3H, s. OCH_3), 4.21 (2H, q, *J* 7.1 Hz, $\underline{CH_2}CH_3$), 4.96 (2H, dd, *J* 4.5, 2.0 Hz, $\underline{CH_2}CH{=}C$), 6.11 (1H, dt, *J* 15.8, 2.0 Hz, $CH_2CH{=}\underline{CH}$), 6.91-6.96 (2H, m, aryl-*ortho* to OMe), 7.05 (1H, dt, *J* 15.8, 4.5 Hz, $CH_2\underline{CH}{=}CH$), 8.00-8.05 (2H, m, aryl-*meta* to OMe).

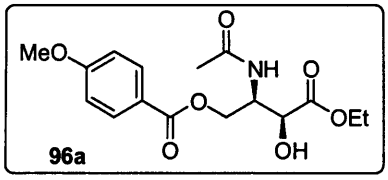
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (CH_3), 55.5 (OCH_3), 60.6 ($\underline{C}H_2CH_3$), 62.7 ($\underline{C}H_2CH{=}CH$), 113.8 (aryl-*ortho* to OMe), 121.9 (aryl-*ipso* to C=O), 122.1 ($C{=}\underline{C}HCO_2Et$), 131.8 (aryl-*meta* to OMe), 141.5 ($CH_2\underline{C}H{=}CH$), 163.7 (aryl-*ipso* to OMe), 165.8 (C=O), 165.9 (C=O).

ν_{max}/cm^{-1} (film): 2980 (C-H), 2937 (C-H), 1717 (C=O), 1607, 1512, 1258.

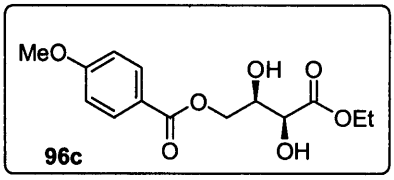
m/z (EI): 265 (MH^+, 35%), 264 (70), 152 (55), 136 (94), 119 (100), 92 (61).

HRMS (EI): $C_{14}H_{16}O_5$ (M^+) requires: 264.0998; found: 264.1002; error: 1.5 ppm.

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate 96a and ethyl (2*S*,3*R*)-2,3-hydroxy-4-(4-methoxybenzoyloxy)butanoate 96c



96a



96c

Potassium osmate dihydrate (16.9 mg, 0.05 mmol) was added to a solution of lithium hydroxide monohydrate (39.2 mg, 0.93 mmol) in H_2O (2.7 mL). *tert*-Butanol (5.4 mL) was then added, followed by $(DHQD)_2PHAL$ (42.8 mg, 0.06 mmol). The mixture was stirred for 20 min until a homogeneous solution was obtained. A 1:1 mixture of *tert*-butanol/ H_2O (4.2 mL) was added and the mixture was cooled in an ice bath to 0-5 °C. *N*-Bromoacetamide (139 mg, 1.01 mmol) was then added in one portion. After 5 min, a solution of ethyl (*E*)-4-(4-methoxybenzoyloxy)-2-butenoate **94** (242 mg, 0.916 mmol) in *tert*-butanol (1.4 mL) was added. The bright yellow/orange reaction mixture was stirred for 6 h in the ice bath, then stored in a freezer overnight. Once the reaction mixture had defrosted, it was stirred for a further 4 h in an ice bath at 0-5 °C. After allowing the reaction mixture to warm to RT, Na_2SO_3 (460 mg) was added and stirring was continued for 1 h. H_2O (20 mL) was then added and the organic material extracted with DCM (3 ×10 mL). The combined organic extracts were washed with H_2O (50 mL) and then brine (50 mL) before being dried ($MgSO_4$).[64] The solvent was removed *in vacuo* to give the crude product as a mixture of regioisomers (42:1 in

favour of the desired compound). Purification by column chromatography (SiO_2, 50%-66% EtOAc in petroleum ether) gave the product, a 20:1 mixture of regiosiomers, as a white solid (174 mg, 56%). The material was then recrystallised from EtOAc/hexane (2:1) to give the product **96a**, a white crystalline solid, as the desired regioisomer (145 mg, 47%).

mp 143-145 °C

$[\alpha]_D^{15}$ = +44.2 (*c* 0.33 in $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 1.96 (3H, s, $C\underline{H}_3C(O)NH$), 3.35 (1H, broad s, OH), 3.86 (3H, s, OCH_3), 4.23 (1H, dq, *J* 10.7, 7.1 Hz, 1 of $C\underline{H}_2CH_3$), 4.26 (1H, dq, *J* 10.7, 7.2 Hz, 1 of $C\underline{H}_2CH_3$), 4.38 (1H, dd, *J* 11.1, 7.3 Hz, 1 of $ArCO_2C\underline{H}_2$), 4.39 (1H, d, *J* 1.8 Hz, C<u>H</u>(OH)), 4.44 (1H, dd, *J* 11.1, 6.7 Hz, 1 of $ArCO_2C\underline{H}_2$), 4.82 (1H, dtd, *J* 9.1, 7.0, 2.1 Hz, AcNHC<u>H</u>), 5.91 (1H, d, *J* 9.4 Hz, NH), 6.92 (2H, d, *J* 9.0 Hz, aryl-*ortho* to OMe), 7.99 (2H, d, *J* 8.9 Hz, aryl-*meta* to OMe).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 ($CH_2\underline{C}H_3$), 23.1 ($\underline{C}H_3CONH$), 50.2 (C(OH)H), 55.4 (OCH_3), 62.5, 62.8 ($\underline{C}H_2CHNHAc$ and $\underline{C}H_2CH_3$), 69.3 (<u>C</u>HNHAc), 113.6 (aryl-*ortho* to OMe), 121.8 (aryl-*ipso* to C=O), 131.7 (aryl-*meta* to OMe), 163.5 (aryl-*ipso* to OMe), 166.1 ($Ar\underline{C}O_2$), 169.7 (NHCO), 173.7 ($\underline{C}O_2Et$).

ν_{max}/cm^{-1} (KBr): 3337 (OH), 1736 (C=O), 1720 (C=O), 1651, 1607, 1558.

m/z (FAB+): 362 (MNa^+, 10%), 349 (20), 326 (60), 199 (65), 177 (94), 176 (100), 173 (92).

HRMS (FAB+): $C_{16}H_{21}O_7NNa$ (MNa^+) requires: 362.1216; found: 362.1223; error: 2.0 ppm.

HPLC (Chiralpak AD; 85:15 Hexane/*i*PrOH; 0.5 mL/min): t_R (minor) = 4.85 min, t_R (major) = 6.45 min. After column chromatography ee: 81.6%; after recrystallisation ee: 98.4%.

Further elution gave the dihydroxylation product **96c** as an oil (17 mg, 5%).

$[\alpha]_D^{21}$ = +14.2 (*c* 0.12 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$), 2.55 (1H, broad s, $CH_2CH(O\underline{H})$), 3.17 (1H, broad s, $CH(O\underline{H})CO_2Et$), 3.84 (3H, s, OCH_3), 4.26-4.30 (4H, m, $OC\underline{H}_2CH_3$ and 2 × C<u>H</u>(OH)), 4.40 (1H, dd, *J* 11.5, 5.6 Hz, 1 of $C\underline{H}_2CH(OH)$), 4.49 (1H, dd, *J* 11.5, 6.9 Hz, 1 of $C\underline{H}_2CH(OH)$), 6.90 (2H, d, *J* 8.8 Hz, aryl-*ortho* to OMe),

7.99 (2H, d, *J* 8.8 Hz, aryl-*meta* to OMe).

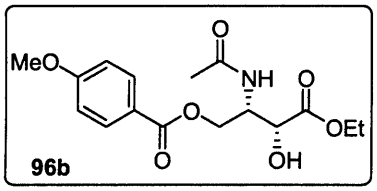
^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 55.4 (OCH_3), 62.4 ($\underline{C}H_2CH_3$), 65.2 ($\underline{C}H_2CH(OH)$), 70.6 ($CH_2\underline{C}H(OH)$), 70.9 ($\underline{C}H(OH)CO_2Et$), 113.7 (aryl-*ortho* to OMe), 122.0 (aryl-*ipso* to C=O), 131.8 (aryl-*meta* to OMe), 163.5 (aryl-*ipso* to OMe), 166.1 ($Ar\underline{C}O_2$), 172.7 ($\underline{C}O_2Et$).

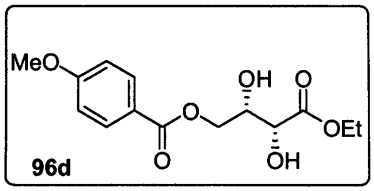
ν_{max}/cm^{-1} ($CHCl_3$ cast): 3472 (O-H), 2974 (C-H), 1713 (C=O), 1607, 1513 1259, 1170.

m/z (FAB+): 321 (MNa^+, 61%), 283 (9), 199 (13), 177 (94), 176 (100).

HRMS (FAB+): $C_{14}H_{18}O_7Na$ (MNa^+) requires: 321.0950; found: 321.0957; error: 2.1 ppm.

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate 96b and ethyl (2*R*,3*S*)-2,3-hydroxy-4-(4-methoxybenzoyloxy)butanoate 96d





Potassium osmate dihydrate (13.2 mg, 0.04 mmol) was added to a solution of lithium hydroxide monohydrate (30.8 mg, 0.73 mmol) in H_2O (2.2 mL). *tert*-Butanol (4.4 mL) was added to the solution followed by $(DHQ)_2PHAL$ (33.6 mg, 0.04 mmol). The mixture was stirred for 10 min until a homogeneous solution was obtained. A 1:1 mixture of *tert*-butanol/H_2O (3.3 mL) was added and the mixture was cooled in an ice bath to 0-5 °C. *N*-Bromoacetamide (109 mg, 0.79 mmol) was then added in one portion. After 5 min, a solution of ethyl (*E*)-4-(4-methoxybenzoyloxy)-2-butenoate **94** (190 mg, 0.72 mmol) in *tert*-butanol (1.1 mL) was added. The bright yellow/orange reaction mixture was stirred for 7 h 30 min in the ice bath, then stored in a freezer overnight. Once the reaction mixture had defrosted it was stirred for a further 6 h 30 min in an ice-bath at 0-5 °C. After allowing the reaction mixture to warm to RT, Na_2SO_3 (350 mg) was added and stirring was continued for a further 1 h. H_2O (20 mL) was then added and the organic material was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with H_2O (50 mL) and then brine (50 mL) before being dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as a mixture of regioisomers (25:1 in favour of the desired compound). Purification by column chromatography (SiO_2, 50%-66% EtOAc in petroleum ether)

gave the product, a 10.7:1 mixture of regioisomers, as a white solid (174 mg, 56%). This material was then recrystallised from EtOAc/hexane (2:1) to give the product **96b**, a white crystalline solid, as a single regioisomer (104 mg, 43%).

mp 143-145 °C

$[\alpha]_D^{16} = -52.6$ (*c* 0.33 in $CHCl_3$).

NMR data is consistent with that for the enantiomer **96a**.

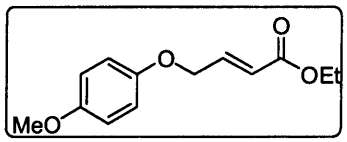
HPLC (Chiralpak AD; 85:15 Hexane/*i*PrOH; 0.5 mL/min): t_R (minor) = 4.77 min, t_R (major) = 6.55 min. After column chromatography ee: 90.1%; after recrystallisation ee: 99.5%.

Further elution gave the dihydroxylation product **96d** as an oil (18 mg, 7%).

$[\alpha]_D^{21} = -8.3$ (*c* 0.39 in $CHCl_3$).

NMR data is consistent with that for the enantiomer **96c**.

Ethyl (*E*)-4-(4-methoxyphenoxy)but-2-enoate[60] 95



4-Methoxyphenol (1.32 g, 10.7 mmol) was added to a suspension of caesium carbonate (3.50 g, 10.8 mmol) in dry DMF (21.3 mL). The resultant mixture was stirred for 30 min at RT before ethyl 4-bromocrotonate (1.5 mL, 10.4 mmol) was added. Stirring was then continued for a further 20 h. H_2O (150 mL) was added and the organic material extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with H_2O (60 mL), brine (60 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo*, followed by column chromatography (SiO_2, 4% EtOAc in petroleum ether) afforded the product **95** as an oil (1.47 g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 3.77 (3H, s, OCH_3), 4.21 (2H, q, *J* 7.1 Hz, $C\underline{H}_2CH_3$), 4.64 (2H, dd, *J* 4.0, 2.1 Hz, $C\underline{H}_2CH{=}CH$), 6.19 (1H, dt, *J* 15.8, 2.1 Hz, $CH_2CH{=}C\underline{H}$), 6.84 (4H, s, aryl), 7.07 (1H, dt, *J* 15.8, 4.1 Hz, $CH_2C\underline{H}{=}CH$).

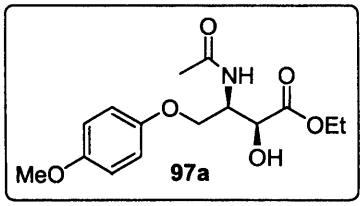
^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 ($CH_2\underline{C}H_3$), 55.7 (OCH_3), 60.5, 67.2 ($\underline{C}H_2CH_3$ and $\underline{C}H_2CH{=}CH$), 114.7, 115.7 (aryl-*ortho* and *meta* to OMe), 121.9 ($CH{=}\underline{C}HCO_2Et$), 142.8 ($\underline{C}H{=}CHCO_2Et$), 152.3, 154.3 (aryl-*ipso*), 166.1 ($\underline{C}O_2Et$).

ν_{max}/cm^{-1} (film): 2986 (C-H), 2907 (C-H), 2835 (C-H), 1717 (C=O), 1666 (C=C), 1506.

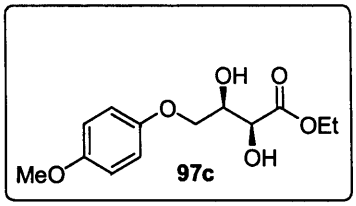
m/z (FAB+): 237 (MH^+, 100%), 191 (9), 155 (64).

HRMS (FAB+): $C_{13}H_{17}O_4$ (MH^+) requires: 237.1127; found: 237.1122; error: 2.0 ppm.

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate 97a and ethyl (2*S*,3*R*)-2,3-hydroxy-4-(4-methoxyphenoxy)butanoate 97c



97a



97c

Potassium osmate dihydrate (15.9 mg, 0.04 mmol) was added to a solution of lithium hydroxide monohydrate (36.9 mg, 0.88 mmol) in H_2O (2.6 mL). *tert*-Butanol (5.2 mL) was then added, followed by $(DHQD)_2PHAL$ (40.3 mg, 0.05 mmol). The resultant mixture was stirred for 10 min before a 1:1 mixture of *tert*-butanol/ H_2O (3.9 mL) was added. After cooling in an ice-bath for 25 min, *N*-bromoacetamide (131 mg, 0.95 mmol) was added. After 5 min, a solution of ethyl (*E*)-4-(4-methoxyphenoxy)but-2-enoate **95** (204 mg, 0.863 mmol) in *tert*-butanol (1.3 mL) was added and the solution was stirred for 7 h at 0-5 °C. The reaction mixture was then stored in a freezer overnight. Once it was defrosted, the reaction mixture was stirred for a futher 4 h in an ice bath at 0-5 °C. After the reaction mixture had been allowed to warm to RT, Na_2SO_3 (420 mg) was added and stirring continued for a further 1 h. Addition of H_2O (20 mL) preceded the extraction of the organic material with DCM (3 × 10 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude product as a mixture of regioisomers (13.5:1 in favour of the desired compound). Purification by column chromatography (SiO_2, 50% EtOAc in petroleum ether) afforded the product, a 15.3:1 mixture of regioisomers, as a white solid (99 mg, 37%). Following recrystallisation from EtOAc/hexane (3:2), the product **97a**, a white crystalline solid, was obtained as a single regioisomer (38 mg, 14%).

mp 107-109 °C

$[\alpha]_D^{21} = +7.6$ (*c* 0.43 in $CHCl_3$) (Lit.[130] $[\alpha]_D = +1.04$ (*c* 5.0 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$), 1.99 (3H, s, CH_3CONH), 3.25 (1H, broad s, OH), 3.76 (3H, s, OCH_3), 3.97 (1H, dd, *J* 9.3, 7.8 Hz, 1 of $ArOC\underline{H}_2$), 4.07 (1H, dd, *J* 9.3, 4.9 Hz, 1 of $ArOC\underline{H}_2$), 4.26 (1H, dq, *J* 10.8, 7.1 Hz, 1 of $C\underline{H}_2CH_3$), 4.30 (1H, dq, *J* 10.8, 7.1 Hz, 1 of $C\underline{H}_2CH_3$), 4.53 (1H, broad s, C<u>H</u>OH), 4.70-4.76 (1H, m, C<u>H</u>NH), 5.92 (1H, d, *J* 9.2 Hz, NH), 6.81-6.87 (4H, m, aryl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 23.2 ($\underline{C}H_3CONH$), 50.5 (CHNH), 55.7 (OCH_3), 62.5, 66.7 ($O\underline{C}H_2CH_3$ and $\underline{C}H_2CHNH$), 69.0 (CHOH), 114.7, 115.7 (aryl-*ortho* and *meta* to OMe), 152.3, 154.3 (aryl-*ipso*), 169.8 (NHCO), 173.4 ($\underline{C}O_2Et$).

ν_{max}/cm^{-1} (KBr): 3344, 3238 (O-H), 1713 (C=O ester), 1655 (C=O amide), 1522, 1244.

m/z (CI+, CH_4): 312 (MH^+, 4%), 188 (100), 124 (20), 91 (19).

HRMS (CI+, CH_4): $C_{15}H_{22}O_6N$ (MH^+) requires: 312.1447; found: 312.1449; error: 0.7 ppm.

Elemental analysis: $C_{15}H_{21}O_6N$ requires: C 57.35, H 6.7, N 4.5; found: C 57.1, H 6.8, N 4.2%.

HPLC (Chiralpak AD; 85:15 Hexane/*i*PrOH; 0.5 mL/min): t_R (minor) = 4.98 min, t_R (major) = 5.24 min. After column chromatography ee: >89.0%; after recrystallisation ee: >93.9%.

Further elution gave the dihydroxylation product **97c** as a white solid (20 mg, 7%).

mp 68-69 °C

$[\alpha]_D^{23}$ = +2.2 (*c* 0.55 in $CHCl_3$).[††]

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 2.48 (1H, broad s, $CH_2CH(O\underline{H})$), 3.16 (1H, broad s, $CH(O\underline{H})CO_2Et$), 3.75 (3H, s, OCH_3), 4.02 (1H, dd, *J* 9.4, 6.0 Hz, 1 of $ArOC\underline{H}_2$), 4.05 (1H, dd, *J* 9.4, 6.4 Hz, 1 of $ArOC\underline{H}_2$), 4.28-4.30 (1H, m, $CH_2C\underline{H}(OH)$), 4.30 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 4.35 (1H, d, *J* 2.0 Hz, $C\underline{H}(OH)CO_2Et$), 6.79-6.86 (4H, m, aryl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 55.7 (OCH_3), 62.3 ($\underline{C}H_2CH_3$), 69.0 ($\underline{C}H_2CH(OH)$), 70.6, 70.7 ($CH_2\underline{C}H(OH)$ and $\underline{C}H(OH)CO_2Et$), 114.7, 115.6 (aryl-*ortho* and *meta* to OMe), 152.5, 154.2 (aryl-*ipso*), 173.0 ($\underline{C}O_2Et$).

ν_{max}/cm^{-1} (solid): 3399 (O-H), 2957 (C-H), 2936 (C-H), 1765 (C=O), 1511, 1231,

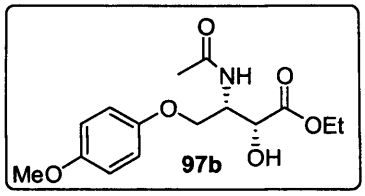
[††] The optical rotation was measured from a sample of the compound from another experiment (which had been carried out on a larger scale).

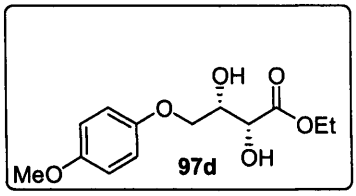
1049.

m/z (FAB+): 293 (MNa^+, 100%), 283 (16), 199 (17), 176 (19).

HRMS (FAB+): $C_{13}H_{18}O_7Na$ (MNa^+) requires: 293.1001; found: 293.1004; error: 1.1 ppm.

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate 97b and ethyl (2*R*,3*S*)-2,3-hydroxy-4-(4-methoxyphenoxy)butanoate 97d





Potassium osmate dihydrate (14.6 mg, 0.04 mmol) was added to a solution of lithium hydroxide monohydrate (33.9 mg, 0.807 mmol) in H_2O (2.4 mL). *tert*-Butanol (4.8 mL) was then added, followed by $(DHQ)_2PHAL$ (37 mg, 0.05 mmol). The resultant mixture was stirred for 10 min before a 1:1 mixture of *tert*-butanol/ H_2O (3.6 mL) was added. After cooling in an ice-bath for 15 min, *N*-bromoacetamide (120 mg, 0.87 mmol) was added. After 5 min, a solution of ethyl (*E*)-4-(4-methoxyphenoxy)but-2-enoate **95** (187 mg, 0.79 mmol) in *tert*-butanol (1.2 mL) was added and the solution was stirred for a further 8 h at 0-5 °C. The reaction mixture was then stored in a freezer overnight. Once the reaction mixture was defrosted, it was stirred for a further 4 h in an ice-bath at 0-5 °C. After the reaction mixture had been allowed to warm to RT, Na_2SO_3 (420 mg) was added and stirring continued for a further 1 h. Addition of H_2O (20 mL) preceded the extraction of the organic material with DCM (3 × 10 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude product as a mixture of regioisomers (8.7:1 in favour of desired compound). Purification by column chromatography (SiO_2, 50% EtOAc in petroleum ether) afforded the product, an 8:1 mixture of regioisomers, as a white solid (101 mg, 41%). Following recrystallisation from EtOAc/hexane (3:2), the product **97b**, a white crystalline solid, was obtained as a single regioisomer (54 mg, 22%).

mp 107-109 °C

$[\alpha]_D^{23} = -13.8$ (*c* 0.16 in $CHCl_3$).

NMR data is consistent with that for the enantiomer **97a**.

HPLC (Chiralpak AD; 85:15 Hexane/*i*PrOH; 0.5 mL/min): t_R (major) = 4.90 min, t_R (minor) = 5.98 min. After column chromatography ee: >90.0%; After recrystallisation ee: 99.3%.

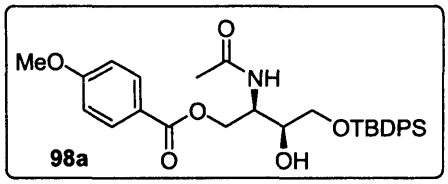
Further elution gave the dihydroxylation product **97d** as a white solid (20 mg, 7%).

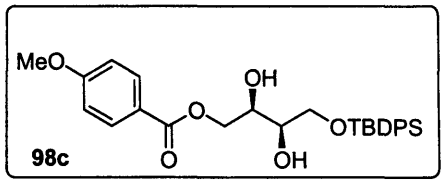
mp 68-69 °C

$[\alpha]_D^{23} = -6.2$ (*c* 0.63 in $CHCl_3$).

NMR data is consistent with that for the enantiomer **97c**.

(2*R*,3*S*)-2-Acetamido-4-(*tert*-butyldiphenylsilanyloxy)-3-hydroxybutyl 4-methoxybenzoate 98a and (2*R*,3*S*)-2,3-hydroxy-4-(*tert*-butyldiphenylsilanyloxy)butyl 4-methoxybenzoate 98c





Potassium osmate dihydrate (73 mg, 0.198 mmol) was added to a solution of lithium hydroxide monohydrate (169 mg, 4.03 mmol) in H_2O (12 mL). *tert*-Butanol (24 mL) was added to the solution followed by $(DHQD)_2PHAL$ (185 mg, 0.24 mmol). The mixture was stirred for 10 min until a homogeneous solution was obtained. A 1:1 mixture of *tert*-butanol/ H_2O (18 mL) was added and the mixture was cooled in an ice bath at 0-5 °C for 15 min. *N*-Bromoacetamide (600 mg, 4.35 mmol) was then added in one portion. After 5 min, a solution of (*E*)-4-(*tert*-butyldiphenylsilanyloxy)but-2-enyl 4-methoxybenzoate **85** (1.82 g, 3.95 mmol) in *tert*-butanol (6 mL) was added. The green reaction mixture was stirred for 7 h 45 min in the ice bath. It was then stored overnight in a freezer. Once the reaction mixture was defrosted, it was stirred for a further 2 h in an ice bath at 0-5 °C, before, again, being stored in a freezer overnight. Stirring at 0-5 °C was continued for an additional 7 h after the reaction mixture was defrosted. After allowing the reaction mixture to warm to RT, Na_2SO_3 (1.98 g) was added and stirring was continued for a further 1 h. H_2O (120 mL) was then added and the organic material was extracted with DCM (3 × 60 mL). The combined organic extracts were washed with H_2O (100 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as the desired regioisomer. Purification by column chromatography (SiO_2, 40% EtOAc in petroleum ether) gave the product **98a**

as a white solid (1.02 g, 48%). The product **98a** was then recrystallised from EtOAc/ hexane (1:1) (873 mg, 41%,) to give a white crystalline solid.

mp 137-139 °C

$[\alpha]_D^{21} = +9.7$ (*c* 1.01 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (9H, s, $C(CH_3)_3$), 1.92 (3H, s, $C\underline{H}_3CONH$), 3.00 (1H, broad s, OH), 3.60 (1H, dd, *J* 10.3, 8.2 Hz, 1 of CH_2OSi), 3.68 (1H, dd, *J* 10.3, 4.9 Hz, 1 of CH_2OSi), 3.87 (3H, s, OCH_3), 3.92-3.95 (1H, m, $C\underline{H}NH$), 4.27-4.42 (3H, m, CH_2CO_2 and $C\underline{H}OH$), 5.88 (1H, d, *J* 8.3 Hz, NH), 6.92 (2H, d, *J* 8.8 Hz, aryl-PMBz), 7.35- 7.44 (6H, m, aryl-TBDPS), 7.62-7.64 (4H, m, aryl-TBDPS), 7.96 (2H, d, *J* 8.8 Hz, aryl-PMBz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 ($\underline{C}(CH_3)_3$), 23.2 ($\underline{C}H_3CONH$), 26.9 ($C(\underline{C}H_3)_3$), 48.9 (CHNH), 55.5 (OCH_3), 63.3 ($\underline{C}H_2CO_2$), 64.8 (CH_2OSi), 69.9 (CHOH), 113.7 (aryl-*ortho* to OMe), 122.1 (aryl-*ipso* to C=O), 127.8 (aryl-*meta* to Si), 130.0 (aryl-*para* to Si), 131.8 (aryl-*meta* to OMe), 132.8 (aryl-*ipso* to Si), 135.5 (aryl-*ortho* to Si), 163.6 (aryl-*ipso* to OMe), 166.4 ($Ar\underline{C}O_2$), 170.2 (CONH).

ν_{max}/cm^{-1} (KBr): 3420 (O-H), 2934 (C-H), 2860 (C-H), 1705 (C=O ester), 1663 (C=O amide), 1607 , 1512, 1259, 1113.

m/z (FAB+): 558 (MNa^+, 14%), 326 (21), 199 (32), 176 (100), 173 (70).

HRMS (FAB+): $C_{30}H_{37}O_6NSiNa$ (MNa^+) requires: 558.2288; found: 558.2280; error: 1.5 ppm.

The ee was determined by preparing the Mosher ester of the recrystallised product **98a** in accordance with the procedure of Ward and Rhee:[131]

Dry DMF (2 μL, 29 μmol) was added to a solution of (*R*)-(+)-MTPA (5.9 mg, 25.2 μmol) in dry hexane (1 mL) at RT, followed by oxalyl chloride (10 μL, 114 μmol). A white precipitate was formed and stirring at RT was continued for 2 h. The mixture was filtered then concentrated *in vacuo*. A solution of the alcohol **98a** (4 mg, 7.5 μmol), triethylamine (3 μL, 22 μmol), and DMAP (a small crystal, *ca.* 1 mg) in $CDCl_3$ (100 μL) was added to the residue, and the mixture was stirred for 3 h at RT. ^{1}H NMR showed complete conversion into the diastereomeric Mosher ester. (Excess of other reagents also present).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (9H, s, $C(CH_3)_3$), 1.85 (3H, s, CH_3CONH), 3.45 (3H, s, CH_3OCCF_3), 3.72 (1H, dd, *J* 11.3, 5.1 Hz, 1 of CH_2OSi), 3.78 (1H, dd, *J* 11.3,

5.5 Hz, 1 of CH_2OSi), 3.84 (3H, s, aryl-$OC\underline{H}_3$), 4.16 (1H, dd, *J* 11.4, 6.1 Hz, 1 of $ArCO_2C\underline{H}_2$), 4.28 (1H, dd, *J* 11.4, 5.8 Hz, 1 of $ArCO_2C\underline{H}_2$), 4.77-4.82 (1H, m, C<u>H</u>NH), 5.24 (1H, app. q, *J* 5.1 Hz, C<u>H</u>CH_2OSi), 5.63 (1H, d, *J* 9.3 Hz, NH), 6.89 (2H, d, *J* 9.0 Hz, aryl-PMBz), 7.26-7.61 (10H + 5H, m, aryl-TBDPS and aryl-C(OMe)(CF_3)),‡‡ 7.93 (2H, d, *J* 9.0 Hz, aryl-PMBz).

^{19}F NMR (300 MHz, $CDCl_3$): δ −71.8, −71.7, −71.4

The ee was determined to be 92% by measuring the ratio of the peak for (C<u>H</u>NH) in the major diastereoisomer at at 4.77-4.82 ppm and the peak for (C<u>H</u>NH) in the minor diastereoisomer at 4.57-4.62 ppm

Further elution gave the dihydroxylation product **98c** as an oil (178 mg, 8%).

$[\alpha]_D^{21}$ = +2.0 (*c* 0.60 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05 (9H, s, $C(CH_3)_3$), 2.72 (1H, broad s, OH), 2.85 (1H, broad s, OH), 3.77-3.82 (3H, m, CH_2OSi and C<u>H</u>(OH)CH_2OSi), 3.85 (3H, s, OCH_3), 4.03 (1H, broad s, $CO_2CH_2C\underline{H}(OH)$), 4.35 (1H, dd, *J* 11.5, 6.3 Hz, 1 of CO_2CH_2), 4.39 (1H, dd, *J* 11.5, 5.4 Hz, 1 of CO_2CH_2), 6.89 (2H, d, *J* 8.9 Hz, aryl-PMBz), 7.36-7.40 (6H, m, aryl-TBDPS), 7.62-7.65 (4H, m, aryl-TBDPS), 7.96 (2H, d, *J* 8.9 Hz, aryl-PMBz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2 ($\underline{C}(CH_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 55.4 (OCH_3), 65.6 (CH_2OSi and $CO_2\underline{C}H_2$), 70.0 (<u>C</u>H(OH)CH_2OSi), 70.9 ($CO_2CH_2\underline{C}H(OH)$), 113.6 (aryl-*ortho* to OMe), 122.2 (aryl-*ipso* to C=O), 127.8 (aryl-*meta* to Si), 130.0 (aryl-*para* to Si), 131.8 (aryl-*meta* to OMe), 132.6, 132.7 (aryl-*ipso* to Si), 135.5 (aryl-*ortho* to Si), 163.5 (aryl-*ipso* to OMe), 166.4 (C=O).

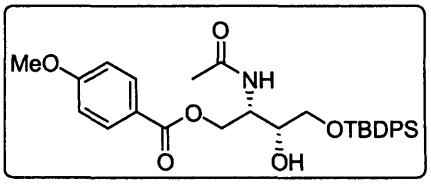
ν_{max}/cm^{-1} ($CHCl_3$ cast): 3454 (O-H), 2933 (C-H), 2858 (C-H), 1713 (C=O), 1607, 1258, 1113.

m/z (FAB+): 517 (MNa^+, 13%), 329 (39), 286 (15), 199 (26), 176 (100).

HRMS (FAB+): $C_{28}H_{34}O_6SiNa$ (MNa^+) requires: 517.2022; found: 517.20123; error: 1.9 ppm.

‡‡ Includes aromatic protons from excess MTPA/ MTPACl/ MTPA anhydride

(2*S*,3*R*)-2-Acetamido-4-(*tert*-butyldiphenylsilanyloxy)-3-hydroxybutyl 4-methoxybenzoate 98b



Potassium osmate dihydrate (15.8 mg, 0.04 mmol) was added to a solution of lithium hydroxide monohydrate (36.7 mg, 0.87 mmol) in H_2O (2.6 mL). *tert*-Butanol (5.2 mL) was added to the solution followed by $(DHQ)_2PHAL$ (40.1 mg, 0.05 mmol). The mixture was stirred for 10 min until a homogeneous solution was obtained. A 1:1 mixture of *tert*-butanol/ H_2O (3.9 mL) was added and the mixture was cooled in an ice bath at 0-5 °C for 15 min. *N*-Bromoacetamide (130.2 mg, 0.944 mmol) was added in one portion. After 5 min, a solution of (*E*)-4-(*tert*-butyldiphenylsilanyloxy)but-2-enyl 4-methoxybenzoate **85** (395 mg, 0.858 mmol) in *tert*-butanol (1.3 mL) was added. The green reaction mixture was stirred for 7 h 40 min in the ice bath, then stored in a freezer overnight. Once the reaction mixture had defrosted, stirring was continued for a further 7 h 25 min in an ice-bath at 0-5 °C. After allowing the reaction mixture to warm to RT, Na_2SO_3 (430 mg) was added and stirring was continued for a further 1 h. H_2O (20 mL) was then added and the organic material was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with H_2O (30 mL) and then brine (20 ml) before being dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude product as the desired regioisomer. Purification by column chromatography (SiO_2, 40% EtOAc in petroleum ether) gave the product **98b** as a white solid (199 mg, 43%). Recrystallisation from EtOAc/hexane (1:1) afforded the product **98b** as white crystalline solid (185 mg, 40%).

mp 137-139 °C

$[\alpha]_D^{18} = -15.2$ (*c* 0.89 in $CHCl_3$).

NMR data is consistent with that for the enantiomer **98a**.

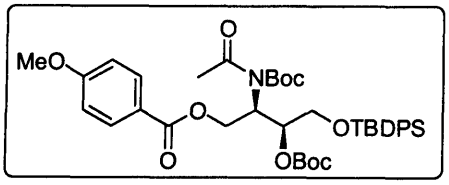
The ee was determined by preparing the Mosher ester of **98b** in accordance with the procedure of Ward and Rhee (as previously described for **98a**).[131] ^1H NMR showed complete conversion into the diastereomeric Mosher ester. (Excess of other reagents also present).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (9H, s, $C(CH_3)_3$), 1.79 (3H, s, CH_3CONH), 3.50 (3H, s, CH_3OCCF_3), 3.80-3.87 (2H, m, CH_2OSi), 3.78 (1H, dd, *J* 11.3, 5.5 Hz, 1 of CH_2OSi), 3.83 (3H, s, aryl-OCH_3), 3.93 (1H, dd, *J* 11.3, 6.9 Hz, 1 of $ArCO_2CH_2$), 4.16 (1H, dd, *J* 11.3, 6.3 Hz, 1 of $ArCO_2CH_2$), 4.57-4.62 (1H, m, CHNH), 5.44 (1H, d, *J* 9.4 Hz, NH), 5.49-5.52 (1H, m, $CHCH_2OSi$), 6.88 (2H, d, *J* 9.0 Hz, aryl-PMBz), 7.25-7.62 (10H + 5H, m, aryl-TBDPS and aryl-C(OMe)(CF_3)),[§§] 7.91 (2H, d, *J* 9.0 Hz, aryl-PMBz).

^{19}F NMR (300 MHz, $CDCl_3$): δ −71.8, −71.7, −71.0

The ee was determined to be 88% by measuring the ratio of the peak for (CHNH) in the major diastereoisomer at 4.57-4.62 ppm and the peak for (CHNH) in the minor diastereoisomer at 4.77-4.82 ppm .

(2*R*,3*S*)-2-(*N*-(*tert*-butoxycarbonyl)acetamido)-3-(*tert*-butoxycarbonyloxy)-4-(*tert*-butyldiphenylsilanyloxy)butyl 4-methoxybenzoate 103



Acetamide **98a** (200 mg, 0.37 mmol) was dissolved in dry THF (1.3 mL). DMAP (9.0 mg, 74 μmol) and di-*tert*-butyl dicarbonate (485 mg, 2.22 mmol) were added and the solution heated to reflux for 21 h. After allowing the mixture to cool to RT, DCM (30 mL) was added, and the solution washed with 1M HCl (15 mL), sat. aq. $NaHCO_3$ (15 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo*, followed by column chromatography (SiO_2, 10%-20% EtOAc in petroleum ether) afforded the title compound **103** as a viscous oil (226 mg, 83%).

$[\alpha]_D^{16} = -70.7$ (*c* 0.21 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (9H, s, $(CH_3)_3CSi$), 1.45 (9H, s, $(CH_3)_3CO$), 1.50 (9H, s, $(CH_3)_3CO$), 2.44 (3H, s, CH_3CON), 3.79-3.85 (1H, m, 1 of CH_2OSi), 3.83 (3H, s, OCH_3), 3.92 (1H, dd, *J* 11.8, 2.4 Hz, 1 of CH_2OSi), 4.52 (1H, broad s, 1 of $ArCO_2CH_2$), 4.68-4.73 (1H, m, 1 of $ArCO_2CH_2$), 5.38 (2H, broad s, CHN and $CHOCO_2$), 6.85 (2H, d, *J* 8.9 Hz, aryl-PMBz), 7.33-7.44 (6H, m, aryl-TBDPS), 7.68-

[§§] also includes aromatic protons from excess MTPA/ MTPACl/ MTPA anhydride

7.71 (4H, m, aryl-TBDPS), 7.89 (2H, d, *J* 8.9 Hz, aryl-PMBz).

^{1}H NMR (400 MHz, $CDCl_3$) at 55 °C: δ 1.08 (9H, s, $(CH_3)_3CSi$), 1.45 (9H, s, $(CH_3)_3CO$), 1.51 (9H, s, $(CH_3)_3CO$), 2.43 (3H, s, CH_3CON), 3.79-3.85 (1H, m, 1 of CH_2OSi), 3.84 (3H, s, OCH_3), 3.95 (1H, dd, *J* 11.7, 3.1 Hz, 1 of CH_2OSi), 4.54 (1H, dd, *J* 11.4, 5.4 Hz, 1 of $ArCO_2C\underline{H}_2$), 4.71 (1H, dd, *J* 11.4, 7.6 Hz, 1 of $ArCO_2C\underline{H}_2$), 5.28 (1H, broad s, CHN), 5.36-5.40 (1H, m, $CHOCO_2$)), 6.85 (2H, d, *J* 8.9 Hz, aryl-PMBz), 7.32-7.42 (6H, m, aryl-TBDPS), 7.68-7.71 (4H, m, aryl-TBDPS), 7.89 (2H, d, *J* 8.9 Hz, aryl-PMBz).

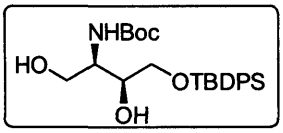
^{13}C NMR (100 MHz, $CDCl_3$) at 25 °C: δ 19.2 ($(CH_3)_3\underline{C}Si$), 26.7 ($(\underline{C}H_3)_3CO$), 27.7, 27.8 ($(\underline{C}H_3)_3CSi$ and $(\underline{C}H_3)_3CO$), 54.4 (broad, CHN), 55.4 (OCH_3), 62.6 ($\underline{C}H_2CO_2Ar$), 63.6 ($\underline{C}H_2OSi$), 74.8 ($\underline{C}HOBoc$), 81.8, 83.8 ($NCO_2\underline{C}(CH_3)_3$ and $OCO_2\underline{C}(CH_3)_3$), 113.6 (aryl-*ortho* to OMe), 122.2 (aryl-*ipso* to C=O), 127.7 (aryl-*meta* to Si), 129.7 (aryl-*para* to Si), 131.6 (aryl-*meta* to OMe), 132.9, 133.1 (aryl-*ipso* to Si and $N\underline{C}O_2C(CH_3)_3$), 135.6 (aryl-*ortho* to Si), 153.0 ($O\underline{C}O_2C(CH_3)_3$), 163.4 (aryl-*ipso* to OMe), 165.6 ($Ar\underline{C}O_2$), 173.6 ($CH_3\underline{C}ON$).

ν_{max}/cm^{-1} (film): 2978 (C-H), 2932 (C-H), 1742 (C=O), 1717 (C=O), 1607, 1256.

m/z (FAB+): 758 (MNa^+, 100%), 558 (96), 197 (10).

HRMS (FAB+): $C_{40}H_{53}O_{10}NSiNa$ (MNa^+) requires: 758.3363; found: 758.3349; error: 1.6 ppm.

(2*R*,3*S*)-2-(*tert*-butoxycarbonylamino)-4-(*tert*-butyldiphenylsilanyloxy)butane-1,3-diol 104



To a solution of acetamide **98a** (206 mg, 385 μmol) in dry THF (1.3 mL), was added DMAP (9.4 mg, 77 μmol) and di-*tert*-butyl dicarbonate (336 mg, 1.54 mmol). The mixture was heated to reflux for 22 h, then allowed to cool to RT. MeOH (1.3 mL) was added, followed by hydrazine monohydrate (0.11 mL, 2.31 mmol) and the mixture was stirred at RT for 3 h, then heated to reflux for 19 h. Further hydrazine monohydrate (40 μL, 840 μmol) was added and heating continued for 4 h. The mixture was then allowed to cool to RT, diluted with DCM (30 mL), and washed with 1M HCl (15 mL), aq. 1M $CuSO_4$ soln. (15 mL), and aq. 1M $NaHCO_3$ soln. (15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by

column chromatography (SiO_2, 50% EtOAc in petroleum ether) gave the title compound **104** as a colourless oil (143 mg, 81%).

$[\alpha]_D^{21} = -276$ (*c* 0.05 in $CHCl_3$).

^{1}H NMR (400 MHz, CD_3OD): δ 1.04 (9H, s, $(CH_3)_3CSi$), 1.42 (9H, s, $OC(CH_3)_3$), 3.55-3.66 (4H, m, $C\underline{H}_2CHNH$ and CH_2OSi), 3.84-3.88 (1H, broad m, ($C\underline{H}NHCO_2$), 3.95-3.98 (1H, broad $C\underline{H}OH$), 5.48 (1H, s, NH), 7.37-7.44 (6H, m, aryl), 7.67-7.70 (4H, m, aryl).

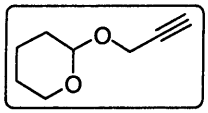
^{13}C NMR (100 MHz, CD_3OD): δ 20.0 ($(CH_3)_3\underline{C}Si$), 27.4 ($(\underline{C}H_3)_3CSi$), 28.8 ($OC(\underline{C}H_3)_3$), 54.1 (CHNH), 54.8 (CHNH-minor rotamer), 62.8 (CH_2OSi), 66.0 (CH_2OH), 71.1 (CH(OH)), 80.2 ($O\underline{C}(CH_3)_3$), 128.8 (aryl-*meta* to Si), 130.9 (aryl-*para* to Si), 134.6 (aryl-*ipso* to Si), 136.7 (aryl-*ortho* to Si), 158.2 (C=O).

ν_{max}/cm^{-1} (film): 3449 (O-H), 2939 (C-H), 1697 (C=O), 1504, 1111, 702.

m/z (CI+, CH_4): 460 (MH^+, 42%), 361 (23), 360 (100), 302 (28), 282 (16).

HRMS (CI+, CH_4): $C_{25}H_{38}O_5NSi$ (MH+) requires: 460.2514; found: 460.2510; error: 0.9 ppm.

Prop-2-ynyl-2-oxytetrahydropyran[132] 127



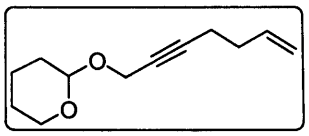
3,4-Dihydro-2*H*-pyran (18.1 mL, 200 mmol) was added to a solution of propargyl alcohol (8.00 g, 143 mmol) in dry DCM (280 mL) and the mixture was cooled to 0 °C in an ice-bath. *p*-Toluenesulfonic acid (272 mg, 1.43 mmol) was added and stirring continued at RT for 24 h. The mixture was diluted with Et_2O (300 mL) and washed with a mixture of brine (30 mL), sat. aq. $NaHCO_3$ (30 mL), and H_2O (40 mL). The organic layer was washed with further brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 2% EtOAc in petroleum ether) gave the product **127** as a colourless oil (19.9 g, quantitative).

^{1}H NMR (500 MHz, $CDCl_3$): 1.48-1.64 (4H, m, THP), 1.69-1.75 (2H, m, THP), 2.39 (1H, t, *J* 2.4 Hz, C≡CH), 3.49-3.54 (1H, m, 1 of $C\underline{H}_2O$-THP), 3.82 (1H, ddd, *J* 11.7, 9.2, 3.0 Hz, 1 of $C\underline{H}_2O$-THP), 4.21 (1H, dd, *J* 15.7, 2.4 Hz, 1 of $C\underline{H}_2C{\equiv}CH$), 4.27 (1H, dd, *J* 15.7, 2.4 Hz, 1 of $C\underline{H}_2C{\equiv}CH$), 4.80 (1H, t, *J* 3.4 Hz, $C\underline{H}OCH_2{\equiv}CH$).

^{13}C NMR (75 MHz, $CDCl_3$): 19.0 (THP), 25.3 (THP), 30.2 (THP), 54.0 ($\underline{C}H_2O$- THP), 62.0 ($\underline{C}H_2C{\equiv}CH$), 74.0 ($C{\equiv}\underline{C}H$), 79.8 ($\underline{C}{\equiv}CH$), 96.8 ($\underline{C}HOCH_2{\equiv}CH$).

ν_{max}/cm^{-1} (film): 3294, 2947 (C-H), 2870 (C-H), 1204, 1119, 1026.

2-(Hept-6-en-2-ynyloxy)-tetrahydro-2*H*-pyran 128



Prop-2-ynyloxytetrahydropyran **127** (1.09 g, 7.77 mmol) was dissolved in dry THF (26 mL) and cooled to 0 °C in an ice-bath. *n*-BuLi (1.6M in hexane, 4.9 mL, 7.77 mmol) was added dropwise and the brown mixture was stirred for 1 h at 0 °C. A solution of 4-bromo-1-butene (0.79 mL, 7.77 mmol) in dry THF (8 mL) was then added and the mixture was stirred at 30 °C for 76 h. After cooling to 0 °C, H_2O (2 mL) was added and the reaction mixture was poured into a mixture of brine (30 mL) and Et_2O (50 mL). The organic material was extracted with further Et_2O (2 × 25 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 5% EtOAc in petroleum ether) gave the product **128** (420 mg, 28%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49-1.65 (4H, m, THP), 1.69-1.89 (2H, m, THP), 2.23-2.33 (4H, m, C≡CC$\underline{H_2}$C$\underline{H_2}$), 3.49-3.55 (1H, m, 1 of C$\underline{H_2}$(O)-THP), 3.83 (1H, ddd, *J* 11.8, 9.1, 3.1 Hz, 1 of C$\underline{H_2}$(O)-THP), 4.20 (1H, dt, *J* 15.3, 2.0 Hz, 1 of OCH_2C≡C), 4.28 (1H, dt, *J* 15.3, 2.0 Hz, 1 of OCH_2C≡C), 4.81 (1H, t, *J* 3.4 Hz, C$\underline{H}$OCH_2C≡C), 5.01 (1H, d, *J* 10.3 Hz, 1.2 Hz, 1 of CH=C$\underline{H_2}$), 5.07 (1H, d, *J* 17.2 Hz, 1.5 Hz, 1 of CH=C$\underline{H_2}$), 5.84 (1H, ddt, *J* 16.8, 10.2, 6.4 Hz, C$\underline{H}$=CH_2).

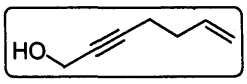
^{13}C NMR (100 MHz, $CDCl_3$): 18.7 (C$\underline{H_2}$CH=CH_2), 19.1 (THP), 25.4 (THP), 30.3 (THP), 32.8 (C≡C$\underline{C}$$H_2CH_2$), 54.5 (O$CH_2$), 62.0 ($\underline{C}$$H_2$(O)-THP), 76.2 (OC$H_2$$\underline{C}$≡C), 85.8 (C≡$\underline{C}CH_2CH_2$), 96.6 ($\underline{C}HOCH_2$C≡C), 115.6 (CH=$\underline{C}$$H_2$), 136.9 ($\underline{C}$H=C$H_2$).

ν_{max}/cm^{-1} (film): 2939 (C-H), 2870 (C-H), 1643 (C=C), 1443, 1119, 1026.

m/z (CI+, isobutane): 203 (25%), 195 (MH^+, 42), 185 (35), 125 (100), 119 (51), 107 (65), 99(37), 86 (86).

HRMS (CI+, isobutane): $C_{12}H_{19}O_2$ (MH+) requires: 195.1385; found: 195.1380; error: 2.7 ppm.

Hept-6-ene-2yn-1-ol 129



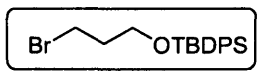
p-Toluenesulfonic acid (1.6 mg, 8.3 μmol) was added to a solution of 2-(hept-6-en-2-ynyloxy)-tetrahydro-2*H*-pyran **128** (107 mg, 550 μmol) in dry MeOH (1 mL). After stirring the mixture at RT for 1 h, H_2O (1 mL) was added, and the organic material was extracted with Et_2O (3 × 5 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography afforded the product **129**[133] (35 mg, 57%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (1H, broad s, OH), 2.22-2.33 (4H, m, C≡CH_2CH_2), 4.24 (2H, broad s, $C\underline{H}_2OH$), 5.02 (1H, d, *J* 10.0 Hz, 1 of CH=$C\underline{H}_2$), 5.07 (1H, dd, *J* 17.0, 1.4 Hz, 1 of CH=$C\underline{H}_2$),*** 5.84 (1H, ddt, *J* 16.8, 10.3, 6.4 Hz, $C\underline{H}$=CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 18.6 (C≡$C\underline{C}H_2CH_2$), 32.7 ($\underline{C}H_2CH$=CH_2), 51.4 (CH_2OH), 78.8 (C≡$\underline{C}CH_2CH_2$), 85.7 ($\underline{C}$≡CCH_2CH_2), 115.7 (CH=$\underline{C}H_2$), 136.8 ($\underline{C}H$=CH_2).

ν_{max}/cm^{-1} (film): 3348 (O-H), 2924 (C-H), 2870 (C-H), 1643 (C=C), 1435, 1011.

***tert*-Butyl (3-bromopropoxy)diphenylsilane**[134] **132**



Imidazole (8.90 g, 131 mmol) and TBDPSCl (13.4 mL, 52.2 mmol) were added to a solution of 3-bromopropanol (7.26g, 52.2 mmol) in dry DCM (100 mL). The mixture was stirred at RT for 18 h. H_2O (400 mL) was added, the layers separated and the organic material was extracted with further DCM (2 × 250 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 4% EtOAc in petroleum ether) gave the product **132** as an oil (18.2 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 2.06 (2H, quintet, *J* 6.5 Hz, $C\underline{H}_2CH_2OSi$), 3.57 (2H, t, *J* 6.6 Hz, CH_2Br), 3.76 (2H, t, *J* 5.7 Hz, CH_2OSi), 7.35-7.43 (6H, m, aryl-TBDPS), 7.64-7.66 (4H, m, aryl-TBDPS).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3 ($\underline{C}(CH_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 30.6 ($\underline{C}H_2CH_2OSi$),

*** There is overlap between the two methylene signals.

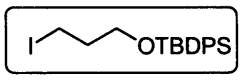
35.5 (CH_2Br), 61.4 (CH_2OSi), 127.7 (aryl-*meta*), 129.7 (aryl-*para*), 133.6 (aryl-*ipso*), 135.6 (aryl-*ortho*).

ν_{max}/cm^{-1} (film): 3071, 2932 (C-H), 2855 (C-H), 1427, 1111, 702.

m/z (FAB+): 379 (MH^+ (^{81}Br), 12%), 377 (MH^+ (^{79}Br), 15), 329 (50), 261 (53), 201 (29), 176 (100).

HRMS (FAB+): $C_{19}H_{26}O^{79}BrSi$ (MH^+) requires: 377.0936; found: 377.0923; error: 3.5 ppm.

tert-Butyl (3-iodopropoxy)diphenylsilane[134] 133



Sodium iodide (20.9 g, 139 mmol) was added to a solution of *tert*-butyl (3-bromopropoxy)diphenylsilane **132** (17.5 g, 46.5 mmol) in acetone (260 mL). The mixture was heated to reflux for 23 h, cooled to RT and diluted with DCM (420 mL). After washing with H_2O (250 mL), then 1M $Na_2S_2O_3$ aq. soln (250 mL), the organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the product **133** (19.1 g, 97%) as a yellow oil which required no further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (9H, s, $C(CH_3)_3$), 2.00-2.09 (2H, m, $C\underline{H}_2CH_2OSi$), 3.35 (2H, t, *J* 6.8 Hz, CH_2I), 3.71 (2H, t, *J* 5.7 Hz, CH_2OSi), 7.37-7.47 (6H, m, aryl-TBDPS), 7.66-7.69 (4H, m, aryl-TBDPS).

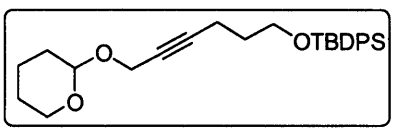
^{13}C NMR (100 MHz, $CDCl_3$): δ 3.4 (CH_2I), 19.3 ($\underline{C}(CH_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 36.2 ($\underline{C}H_2CH_2OSi$), 63.2 (CH_2OSi), 127.7 (aryl-*meta*), 129.7 (aryl-*para*), 133.6 (aryl-*ipso*), 135.6 (aryl-*ortho*).

ν_{max}/cm^{-1} (film): 2930 (C-H), 2856 (C-H), 1472, 1427, 1113, 700.

m/z (CI+, CH_4): 425 (MH^+, 12%), 367 (75), 347 (97), 241 (56), 191 (100).

HRMS (CI+, CH_4): $C_{19}H_{26}OISi$ (MH^+) requires: 425.0798; found: 425.0710; error: 0.5 ppm.

tert-Butyldiphenyl(6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynyloxy)silane 134



Prop-2-ynyloxytetrahydropyran **127** (15.7 g, 112 mmol) was dissolved in dry THF (48

mL) and cooled to 0 °C in an ice-bath. Methyl lithium lithium bromide complex (1.5M in Et_2O, 64.7 mL, 97.1 mmol) was added dropwise and stirring at 0 °C was continued for 1 h. *tert*-Butyl (3-iodopropoxy)diphenylsilane **133** (41.2 g, 97.1 mmol) was then added, followed by dry DMSO (242 mL) and the mixture stirred at RT for 20 h. After cooling to 0 °C, H_2O (150 mL) was slowly added, followed by Et_2O (500 mL). The organic layer was then washed with a 1:1 mixture of brine and H_2O (3 × 300 mL), dried ($MgSO_4$) and concentrated. Column chromatography (SiO_2, 2% EtOAc in petroleum ether), followed by Kugelrohr distillation (110 °C/(2 mmHg)) gave the product **134** (24.89 g, 59%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (9H, s, $C(CH_3)_3$), 1.48-1.63 (4H, m, THP), 1.67-1.85 (4H, m, $C\underline{H}_2CH_2OSi$ and THP), 2.36 (2H, tt, *J* 7.2, 2.2 Hz, $C{\equiv}CC\underline{H}_2CH_2$), 3.47-3.52 (1H, m, 1 of $C\underline{H}_2O$-THP), 3.71 (2H, t, *J* 6.0 Hz, CH_2OSi), 3.82 (1H, dd, *J* 11.8, 9.0, 3.0 Hz, 1 of $C\underline{H}_2O$-THP), 4.15 (1H, dt, *J* 15.2, 2.2 Hz, 1 of $OCH_2C{\equiv}C$), 4.25 (1H, dt, *J* 15.2, 2.2 Hz, 1 of $OCH_2C{\equiv}C$), 4.77 (1H, t, *J* 3.5 Hz, OCHO), 7.34-7.42 (6H, m, aryl), 7.63-7.65 (4H, m, aryl).

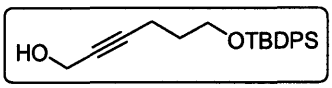
^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4 ($\underline{C}H_2CH_2OSi$), 19.1 (THP), 19.2 ($\underline{C}(CH_3)_3$), 25.4 (THP), 26.8 ($C(\underline{C}H_3)_3$), 30.3 (THP), 31.5 ($C{\equiv}C\underline{C}H_2CH_2$), 54.6 ($O\underline{C}H_2C{\equiv}C$), 62.0 ($CH_2O$-THP), 62.4 ($CH_2OSi$), 75.9 ($OCH_2\underline{C}{\equiv}C$), 86.2 ($OCH_2C{\equiv}\underline{C}$), 96.7 (OCHO), 127.6 (aryl-*meta*), 129.6 (aryl-*para*), 133.8 (aryl-*ipso*), 135.6 (aryl-*ortho*).

ν_{max}/cm^{-1} (film): 2941 (C-H), 2856 (C-H), 1427, 1113, 1022, 702.

m/z (FAB+): 459 (MNa^+, 100%), 217 (14), 199 (33), 197 (34).

HRMS (FAB+): $C_{27}H_{36}O_3SiNa$ (MNa^+) requires: 459.2331; found: 459.2340; error: 1.9 ppm.

6-(*tert*-Butyldiphenylsilanyloxy)hex-2-yn-1-ol 138



Dowex-50Wx8 resin (H^+ form, 2.5 g) was added to a solution of *tert*-butyldiphenyl(6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynyloxy)silane **134** (248 mg, 567 μmol) in MeOH (5 mL) and the mixture was heated at 40 °C for 5 h. The resin was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc in petroleum ether) afforded the product **138**[135] (200 mg, quantitative) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (9H, s, $C(CH_3)_3$), 1.43 (1H, broad s, OH), 1.72-

1.79 (2H, m, $C\underline{H}_2CH_2OSi$), 2.37 (2H, tt, *J* 7.1, 2.2 Hz, $C{\equiv}CC\underline{H}_2CH_2$), 3.74 (2H, t, *J* 6.0 Hz, CH_2OSi), 4.20 (2H, t, *J* 2.2 Hz, $C\underline{H}_2OH$), 7.36-7.46 (6H, m, aryl), 7.65-7.69 (4H, m, aryl).

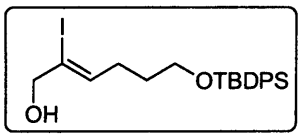
^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3 ($C{\equiv}C\underline{C}H_2CH_2$), 19.2 ($\underline{C}(CH_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 31.4 ($\underline{C}H_2CH_2OSi$), 51.4 ($CH_2OH$), 62.3 ($CH_2OSi$), 78.5 ($OCH_2\underline{C}{\equiv}C$), 86.1 ($OCH_2C{\equiv}\underline{C}$), 127.6 (aryl-*meta*), 129.6 (aryl-*para*), 133.8 (aryl-*ipso*), 135.6 (aryl-*ortho*).

ν_{max}/cm^{-1} (film): 3333 (O-H), 2934 (C-H), 2856 (C-H), 1427, 1111, 700.

m/z (FAB+): 375 (MNa^+, 45%), 326 (15), 199 (23), 176 (100), 173 (55).

HRMS (FAB+): $C_{22}H_{28}O_2SiNa$ (MNa^+) requires: 375.1756; found: 375.1767; error: 2.9 ppm.

(*Z*)-6-(*tert*-Butyldiphenylsilanyloxy)-2-iodo-hex-2-en-1-ol 131



Azobisisobutyronitrile (0.5 mg, 3 μmol) and tributyltin hydride (79 μL, 298 μmol) were added to 6-(*tert*-butyldiphenylsilanyloxy)hex-2-yn-1-ol **138** (105 mg, 298 μmol) and the resulting mixture was heated at 60 °C for 3 h. The temperature was then increased to 75 °C and heating continued for a further 90 min. The reaction mixture was then cooled to 0 °C in an ice-bath and diluted with dry DCM (0.9 mL). Iodine (90.8 mg, 358 μmol) was added and stirring continued at 0 °C for 75 min. Sat. aq. $NaHCO_3$ (6 mL) and aq. 1M $Na_2S_2O_3$ (4 mL) were added and the organic material was extracted with DCM (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and the concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4% EtOAc in petroleum ether) gave the product **131** (92 mg, 64%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 1.63-1.69 (2H, m, $C\underline{H}_2CH_2OSi$), 1.80 (1H, t, *J* 6.7 Hz, OH), 2.23-2.28 (2H, m, $C{=}CHC\underline{H}_2$), 3.67 (2H, t, *J* 6.2 Hz, CH_2OSi), 4.19 (2H, dd, *J* 6.7, 0.9 Hz, $C\underline{H}_2OH$), 5.85 (1H, tt, *J* 6.8, 1.3 Hz, C=CH), 7.35-7.45 (6H, m, aryl), 7.62-7.67 (4H, m, aryl).

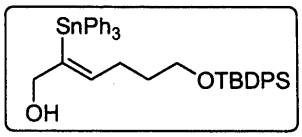
^{13}C NMR (125 MHz, $CDCl_3$): δ 19.2 ($\underline{C}(CH_3)_3$), 26.9 ($C(\underline{C}H_3)_3$), 31.0 ($C{=}CH\underline{C}H_2$), 32.3 ($\underline{C}H_2CH_2OSi$), 63.1 (CH_2OSi), 71.7 (CH_2OH), 108.4 ($\underline{C}{=}CH$), 127.6 (aryl-*para*), 129.6 (aryl-*meta*), 133.9 (aryl-*ipso*), 135.6 (aryl-*ortho*), 136.1 ($C{=}\underline{C}H$).

ν_{max}/cm^{-1} (film): 3379 (O-H), 2932 (C-H), 2855 (C-H), 1666 (C=C), 1427, 1111, 702.

m/z (FAB+): 503 (MNa^+, 100%), 375 (11), 286 (3), 176 (100), 197 (6).

HRMS (FAB+): $C_{22}H_{29}O_2SiINa$ (MNa^+) requires: 503.0879; found: 503.0884; error: 1.0 ppm.

(*Z*)-6-(*tert*-Butyldiphenylsilanyloxy)-2-(triphenylstannyl)-hex-2-en-1-ol 144



Triphenyltin hydride (167 mg, 477 μmol) was added to 6-(*tert*-butyldiphenylsilanyloxy)-hex-2-yn-1-ol **138** (112 mg, 318 μmol), followed by dry toluene (4.5 mL). Triethylborane solution (1.0M in hexane, 48 μL, 48 μmol) was then added dropwise and air (5 mL) was injected into the flask. The reaction mixture was stirred at RT for 43 h. H_2O (15 mL) was added and the organic material extracted with EtOAc (3 × 15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 4% EtOAc in petroleum ether) gave the product **144** (20 mg, 9%) as an oil and a 1.1:1 mixture of the product and SM (93 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (9H, s, $C(CH_3)_3$), 1.33 (1H, t, *J* 6.0 Hz, OH), 1.44-1.50 (2H, m, $C\underline{H}_2CH_2OSi$), 2.10-2.14 (2H, m, $C{=}CHC\underline{H}_2$), 3.32 (2H, t, *J* 6.5 Hz, CH_2OSi), 4.27 (2H, d, *J* 5.4 Hz, $C\underline{H}_2OH$), 6.46 (1H, t, *J* 7.3 Hz, C=CH), 7.30-7.40 (15H, m, aryl), 7.52-7.58 (10H, m, aryl).

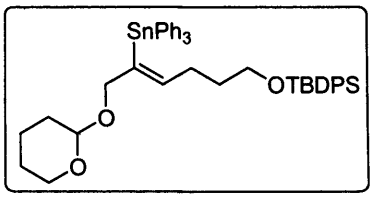
^{13}C NMR (125 MHz, $CDCl_3$): δ 19.1 ($\underline{C}(CH_3)_3$), 26.8 ($C(\underline{C}H_3)_3$), 31.5 ($C{=}CH\underline{C}H_2$), 32.4 ($\underline{C}H_2CH_2OSi$), 63.2 (CH_2OSi), 70.0 (CH_2OH), 127.5 (aryl-*meta* to Si), 128.5 (aryl-Sn), 128.9 (aryl-Sn), 129.5 (aryl-*para* to Si), 133.9 (aryl-*ipso* to Si), 135.5 (aryl-*ortho* to Si), 137.0 (aryl-Sn), 138.9 (aryl-*ipso* to Sn), 140.8 ($\underline{C}{=}CH$) , 144.6 ($C{=}\underline{C}H$).

ν_{max}/cm^{-1} (film): 3441 (O-H), 2932 (C-H), 2855 (C-H), 1620 (C=C), 1427, 1111, 702.

m/z (FAB+): 727 (MNa^+, 66%), 351 (100), 291 (45), 197 (36).

HRMS (FAB+): $C_{40}H_{44}O_2SnSiNa$ (MNa^+) requires: 727.2030; found: 727.2013; error: 2.4 ppm.

(*Z*)-6-*tert*-Butyldiphenyl(6-(tetrahydro-2*H*-pyran-2-yloxy)-5-(triphenylstannyl)-hex-4-enyloxy)silane 145



Triphenyltin hydride (7.07 mL, 27.7 mmol) was added to a solution of *tert*-butyldiphenyl(6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynyloxy)silane **134** (9.30 g, 21.30 mmol) in dry toluene (21 mL). Triethylborane (1.0M solution in hexanes, 2.10 mL, 2.13 mmol) was added dropwise and air (200 mL) was injected into the reaction flask. The reaction mixture was stirred at RT for 80 min. H_2O (400 mL) was added and the organic material extracted with EtOAc (3 × 450 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a 1:>85% mixture of regiosiomers. Column chromatography (SiO_2, 20%-50% DCM in petroleum ether) afforded the product **145**, an oil, as a 1:>90% mixture of regioisomers (16.6 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) major regioisomer: δ 0.94 (9H, s, $C(CH_3)_3$), 1.18-1.66 (8H, m, THP and $C\underline{H}_2CH_2OSi$), 2.08-2.15 (2H, m, $C=CHC\underline{H}_2$), 3.26-3.34 (3H, m, CH_2OSi and 1 of $C\underline{H}_2O$-THP), 3.62 (1H, ddd, *J* 11.5, 9.3, 3.2 Hz, 1 of $C\underline{H}_2O$-THP), 4.06 (1H, d, *J* 11.2 Hz, 1 of $C\underline{H}_2C=CH$), 4.19 (1H, t, *J* 3.2 Hz, OCHO), 4.37 (1H, d, *J* 11.2 Hz, 1 of $C\underline{H}_2C=CH$), 6.51 (1H, t, *J* 7.3 Hz, C=CH), 7.27-7.40 (15H, m, aryl), 7.51-7.57 (10H, m, aryl).

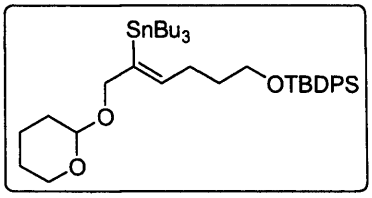
^{13}C NMR (125 MHz, $CDCl_3$) major regioisomer: δ 19.0 (THP), 19.1 ($\underline{C}(CH_3)_3$), 25.4 (THP) 26.8 ($C(\underline{C}H_3)_3$), 30.1 (THP), 31.2 ($C=CH\underline{C}H_2$), 32.5 ($\underline{C}H_2CH_2OSi$), 61.7 ($\underline{C}H_2O$-THP), 63.2 (CH_2OSi), 74.1 ($\underline{C}H_2C=CH$), 97.7 (OCHO), 127.5 (aryl-*ortho* to Si), 128.3 (aryl-Sn), 128.7 (aryl-Sn), 129.4 (aryl-*meta* to Si), 133.9 (aryl-*ipso* to Si), 135.5 (aryl-*para* to Si), 137.0 (aryl-Sn), 138.1, 139.4 (aryl-*ipso* to Sn and $\underline{C}=CH$), 145.8 ($C=\underline{C}H$).

ν_{max}/cm^{-1} (film): 2932 (C-H), 2855 (C-H), 1628 (C=C), 1427, 1111, 702.

m/z (FAB+): 811 (MNa^+, 100%), 351 (92), 289 (33), 197 (50).

HRMS (FAB+): $C_{45}H_{52}O_3SnSiNa$ (MNa^+) requires: 811.2605; found: 811.2584; error: 2.7 ppm.

(*Z*)-6-*tert*-Butyldiphenyl(6-(tetrahydro-2*H*-pyran-2-yloxy)-5-(tributylstannyl)-hex-4-enyloxy)silane 150



Tributyltin hydride (0.42 mL, 1.58 mmol) was added to *tert*-butyldiphenyl(6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynyloxy)silane **134** (460 mg, 1.05 mmol), followed by dry toluene (1.1 mL). Triethylborane (1.0M solution in hexanes, 0.11 mL, 0.105 mmol) was then added, and air (12 mL) was injected into the reaction flask. The mixture was stirred at RT for 20 h. Additional triethylborane (1.0M solution in hexanes, 50 μL, 47.7 μmol) was added and the mixture stirred for a further 2 h. H_2O (20 mL) was added, the organic material extracted with EtOAc (3 × 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a 1:>70% mixture of regiosiomers. Purification by column chromatography (SiO_2, 20% DCM in petroleum ether) afforded the title compound **150**, a pale yellow oil, as a 1:>80% mixture of regioisomers (472 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) major regioisomer: δ 0.84-0.92 (18H, m, ^{n}Bu), 1.03 (9H, s, $C(CH_3)_3$), 1.24-1.71 (17H, m, ^{n}Bu, THP and $C\underline{H}_2CH_2OSi$), 2.09-2.14 (2H, m, $C=CHC\underline{H}_2$), 3.44-3.49 (1H, m, 1 of $C\underline{H}_2O$-THP), 3.64 (2H, t, *J* 6.4 Hz, CH_2OSi), 3.83 (1H, ddd, *J* 11.1, 8.5, 5.2 Hz, 1 of $C\underline{H}_2O$-THP), 3.96 (1H, d, *J* 10.7 Hz, 1 of $C\underline{H}_2C=CH$), 4.25 (1H, d, *J* 10.8 Hz, 1 of $C\underline{H}_2C=CH$), 4.57 (1H, t, *J* 3.5 Hz, OCHO), 6.21 (1H, t, *J* 7.2 Hz, C=CH), 7.34-7.42 (6H, m, aryl), 7.64 (4H, m, aryl).

^{13}C NMR (125 MHz, $CDCl_3$) major regioisomer: δ 10.3 (^{n}Bu), 13.7 (^{n}Bu), 19.2 ($\underline{C}(CH_3)_3$), 19.5 (THP), 25.5 (THP) 26.8 ($C(\underline{C}H_3)_3$), 27.4 (^{n}Bu), 29.2 (^{n}Bu), 30.7 (THP), 31.0 ($C=CH\underline{C}H_2$), 33.0 ($\underline{C}H_2CH_2OSi$), 62.0 ($\underline{C}H_2O$-THP), 63.7 (CH_2OSi), 74.8 ($\underline{C}H_2C=CH$), 97.4 (OCHO), 127.6 (aryl-*meta*), 129.5 (aryl-*para*), 133.9 (aryl-*ipso*), 135.5 (aryl-*ortho*), 140.4 ($\underline{C}=CH$), 142.3 ($C=\underline{C}H$).

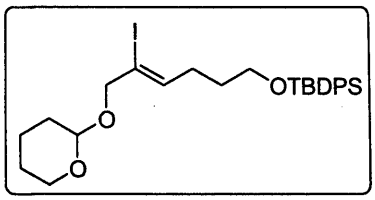
ν_{max}/cm^{-1} (film): 2932 (C-H), 2855 (C-H), 1620 (C=C), 1458, 1111, 1026, 702.

m/z (FAB+): 751 (MNa^+, 2%), 671 (55), 585 (24), 335 (60), 291 (35), 251 (50), 179 (100).

HRMS (FAB+): $C_{39}H_{64}O_3SnSi$ (MNa^+) requires: 751.3544; found: 751.3556; error:

1.6 ppm.

(*Z*)-*tert*-Butyl(5-iodo-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-enyloxy)diphenylsilane 152



Stannane **145** (3.94 g, 5.00 mmol) was dissolved in dry DCM (50 mL) and cooled to −78 °C in a dry ice/acetone bath. Iodine (1.52 g, 6.00 mmol) was added and stirring at −78 °C was continued for 15 min. The reaction mixture was then allowed to warm to RT and stirred for 30 min. The mixture was concentrated *in vacuo* and the residue purified by column chromatography (SiO_2, 2% EtOAc in petroleum ether) to give the product **152** as a pale yellow oil (2.25 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (9H, s, $C(CH_3)_3$), 1.52-1.90 (8H, m, THP and $C\underline{H}_2CH_2OSi$), 2.26-2.31 (2H, m, $C=CHC\underline{H}_2$), 3.49-3.54 (1H, m, 1 of $C\underline{H}_2O$-THP), 3.68 (2H, t, *J* 6.2 Hz, CH_2OSi), 3.89 (1H, ddd, *J* 11.8, 8.8, 3.1 Hz, 1 of $C\underline{H}_2O$-THP), 4.18 (1H, dd, *J* 12.9, 0.8 Hz, 1 of $C=CCH_2O$), 4.32 (1H, dd, *J* 12.9, 1.2 Hz, 1 of $C=CCH_2O$), 4.66 (1H, t, *J* 3.4 Hz, OCHO), 5.89 (1H, t, *J* 6.8 Hz, C=CH), 7.36-7.46 (6H, m, aryl), 7.66-7.69 (4H, m, aryl).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (THP), 19.2 ($\underline{C}(CH_3)_3$), 25.4 (THP), 26.9 ($C(\underline{C}H_3)_3$), 30.4 (THP), 31.1 ($\underline{C}H_2CH_2OSi$), 32.5 ($C=CH\underline{C}$), 62.1($\underline{C}H_2O$-THP), 63.2 (CH_2OSi), 74.7 ($\underline{C}H_2C=C$), 96.9 (OCHO), 104.3 ($CH_2\underline{C}=C$), 127.6 (aryl-*meta*), 129.6 (aryl-*para*), 133.9 (aryl-*ipso*), 135.6 (aryl-*ortho*), 137.6 ($CH_2C=\underline{C}$).

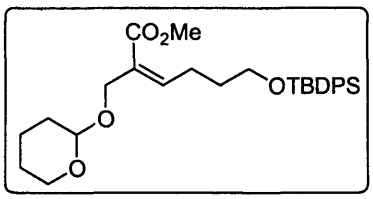
ν_{max}/cm^{-1} (film): 3071, 2932 (C-H), 2855 (C-H), 1651 (C=C), 1466, 1427, 1111.

m/z (FAB+): 587 (MNa^+, 100%), 541 (15), 472 (64).

HRMS (FAB+): $C_{27}H_{37}O_3SiINa$ (MNa^+) requires: 587.1454; found: 587.1449; error: 0.9 ppm.

Elemental analysis: $C_{27}H_{37}O_3SiI$ requires: C 56.7, H 6.4; found C 57.1, H 6.5%.

(*Z*)-Methyl 6-(*tert*-butyldiphenylsilanyloxy)-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)hex-2-enoate 153



Triethylamine (1.12 mL, 8.02 mmol) was added to a solution of iodide **152** (1.51 g, 2.67 mmol) in dry MeOH (41 mL). The solution was then placed under an atmosphere of carbon monoxide, and 1,1'bis(diphenylphosphino)ferrocene palladium (II) chloride complex with DCM (244 mg, 267 μmol) was added. Carbon monoxide was bubbled through the reaction mixture for 15 min, after which it was placed under a balloon containing carbon monoxide. The reaction mixture was stirred at RT for 1 h, then at 25 °C for 30 min. More carbon monoxide was bubbled through the reaction mixture and heating was resumed at 50 °C for 50 min, then 65 °C for 80 min. The reaction mixture was diluted with Et_2O (30 mL) and washed with 3M HCl (20 mL). The organic material was extracted with DCM (2 × 40 mL) and the organic extracts were filtered through Celite®. The filtrate was concentrated *in vacuo*, and the residue purified by column chromatography (SiO_2, 6% EtOAc in petroleum ether) to give the product **153** (1.05 g, 79%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 1.48-1.60 (4H, m, THP), 1.66-1.83 (4H, m, THP and $C\underline{H}_2CH_2OSi$), 2.61 (2H, app. q, *J* 7.5 Hz, C=CHC$\underline{H}_2$), 3.47-3.51 (1H, m, 1 of C$\underline{H}_2$O-THP), 3.67 (2H, t, *J* 6.3 Hz, CH_2OSi), 3.72 (3H, s, OCH_3), 3.84 (1H, ddd, *J* 11.5, 8.6, 2.9 Hz, 1 of C$\underline{H}_2$O-THP), 4.09 (1H, dd, *J* 12.3, 1.0 Hz, 1 of C=CCH_2O), 4.36 (1H, dd, *J* 12.3, 1.1 Hz, 1 of C=CCH_2O), 4.64 (1H, t, *J* 3.5 Hz, OCHO), 6.21 (1H, t, *J* 7.4 Hz, C=CH), 7.35- 7.41 (6H, m, aryl), 7.64-7.66 (4H, m, aryl).

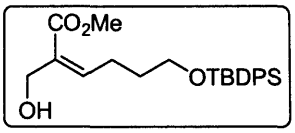
^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1 (THP), 19.2 (C(CH_3)$_3$), 25.4 (THP), 26.1 ($\underline{C}H_2CH_2OSi$), 26.9 (C($\underline{C}H_3$)$_3$), 30.4 (THP), 32.1 (C=CH$\underline{C}$), 51.3 (OCH_3), 62.1 ($\underline{C}H_2$O THP), 63.4 (CH_2OSi), 68.1 ($\underline{C}H_2$C=C), 97.9 (OCHO), 127.4 (aryl-*meta*), 128.6 (C=CH) 129.6 (aryl-*para*), 133.9 (aryl-*ipso*), 135.5 (aryl-*ortho*), 145.3 (C=$\underline{C}$H), 167.1 (C=O).

ν_{max}/cm^{-1} (film): 2941 (C-H), 2856 (C-H), 1720 (C=O), 1651 (C=C), 1427, 1202, 1113.

m/z (FAB+): 519 (MNa^+, 19%), 326 (16), 199 (35), 176 (100).

HRMS (FAB+): $C_{29}H_{40}O_5SiNa$ (MNa^+) requires: 519.2543; found: 519.2548; error: 1.0 ppm.

(*Z*)-Methyl 6-(*tert*-butyldiphenylsilanyloxy)-2-(hydroxymethyl)hex-2-enoate 154



Dowex-50Wx8 resin (H^+ form, 7.00 g) was added to a solution of ester **153** (781 mg, 1.57 mmol) in MeOH (20 mL). The mixture was heated at 32 °C for 4 h. The resin was filtered off and the filtrate concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2% EtOAc in petroleum ether) gave recovered starting material (279 mg, 43%) followed by the product **154** (290 mg, 45%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (9H, s, $C(CH_3)_3$), 1.68-1.74 (2H, m, $C\underline{H}_2CH_2OSi$), 2.29-2.37 (1H, broad s, OH), 2.64 (2H, q, *J* 7.5 Hz, $C=CHC\underline{H}_2$), 3.70 (2H, t, *J* 6.3 Hz, CH_2OSi), 3.75 (3H, s, OCH_3), 4.20 (2H, s, $C\underline{H}_2OH$), 6.23 (1H, t, *J* 7.4 Hz, C=CH), 7.36-7.43 (6H, m, aryl), 7.66-7.68 (4H, m, aryl).

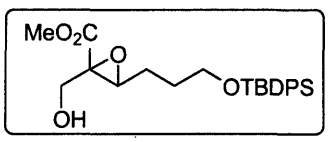
^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 ($\underline{C}(CH_3)_3$), 26.2 ($\underline{C}H_2CH_2OSi$), 26.7 ($C(\underline{C}H_3)_3$), 32.0 ($C=CH\underline{C}$), 51.5 (OCH_3), 63.4 (CH_2OSi), 65.2 (CH_2OH), 127.7 (aryl-*meta*), 129.6 (aryl-*para*), 130.7 ($\underline{C}=CH$), 133.8 (aryl-*ipso*), 135.6 (aryl-*ortho*), 146.0 ($C=\underline{C}H$), 167.5 (C=O).

ν_{max}/cm^{-1} (film): 3435 (O-H), 3071, 2932 (C-H), 2856 (C-H), 1724 (C=O), 1649 (C=C), 1429, 1113.

m/z (FAB+): 435 (MNa^+, 42%), 395 (20), 213(36), 199 (100), 197 (97), 183 (40).

HRMS (FAB+): $C_{24}H_{32}O_4SiNa$ (MNa^+) requires: 435.1968; found: 435.1958; error: 2.1 ppm.

(3-(3-(*tert*-butyldiphenylsilanyloxy)propyl)oxiran-2-yl)methanol 155



(*Z*)-Methyl 6-(*tert*-butyldiphenylsilanyloxy)-2-(hydroxymethyl)hex-2-enoate **154** (194 mg, 0.470 mmol) was dissolved in DCM (1 mL) and cooled to 0 °C in an ice-bath. *m*-CPBA (70-75%, 139 mg, *ca.* 0.56 mmol) was added and the mixture was stirred at RT for 25 h. The reaction mixture was then cooled to 0 °C and further *m*-CPBA (70-75%,

27 mg, *ca.* 0.11 mmol) was added. Stirring at RT was continued for 16 h, then sat. aq. $NaHCO_3$ (5 mL) was added and the organic material extracted with DCM (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 10%-20% EtOAc in petroleum ether) gave the product **155** as an oil (186 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (9H, s, $C(CH_3)_3$), 1.62-1.76 (4H, m, CH_2CH_2OSi), 3.19 (1H, t, *J* 6.0 Hz, $CH(O)CH_2$) 3.64-3.69 (2H, m, CH_2OSi), 3.75 (3H, s, OCH_3), 3.77 (1H, d, *J* 12.6 Hz, 1 of CH_2OH), 4.06 (1H, d, *J* 12.5 Hz, 1 of CH_2OH), 7.34-7.42 (6H, m, aryl), 7.62-7.65 (4H, m, aryl).

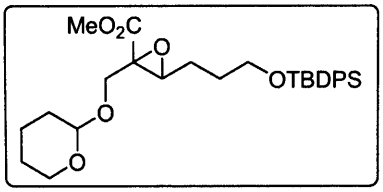
^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 ($C(CH_3)_3$), 24.5 (CH_2CH_2OSi), 26.9 ($C(CH_3)_3$), 29.1 ($CH(O)CH_2$), 52.6 (OCH_3), 60.4 (MeO_2C) 62.8 (CH_2OSi), 63.1 (CH_2OH), 127.7 (aryl-*meta*), 129.7 (aryl-*para*), 133.7 (aryl-*ipso*), 135.5 (aryl-*ortho*), 169.1 (C=O).

ν_{max}/cm^{-1} (film): 3485 (O-H), 2932 (C-H), 2858 (C-H), 1736 (C=O), 1427, 1094.

m/z (FAB+): 429 (MNa^+, 9%), 307(35), 289 (17), 154 (100).

HRMS (FAB+): $C_{24}H_{32}O_5SiNa$ (MNa^+) requires: 429.2097; found: 429.2083; error: 3.1 ppm.

tert-Butyldiphenyl(3-(3-(tetrahydro-2*H*-pyran-yloxy)methyl)oxiran-2-yl)propoxy)silane 158



Alkene **153** (310 mg, 0.62 mmol) was dissolved in DCM (1.2 mL) and cooled to 0 °C in an ice-bath. *m*-CPBA (70-75 %, 185 mg, *ca.* 0.75 mmol) was added and the resulting mixture was stirred at RT for 1 h. The mixture was then cooled to 0 °C and further *m*-CPBA (70-75%, 185 mg, *ca.* 0.75 mmol) was added. Stirring was resumed at RT for 23 h after which time sat. aq. $NaHCO_3$ (10 mL) was added, and the organic material extracted with DCM (2 × 15 mL). The organic extracts were dried ($MgSO_4$), filtered through Celite® and the filtrate concentrated *in vacuo*. Column chromatography (SiO_2, 2%-4% EtOAc in petroleum ether) gave the product **158**, an oil, as a 1:1.3 mixture of diastereomers (177 mg, 55%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (9H + 9H, s, $C(CH_3)_3$, both diastereomers), 1.47-1.82 (10H +10H, m, 6 of THP and $CH_2CH_2CH_2OSi$, both diastereomers), 3.04 (1H, t, *J*

6.1 Hz, C<u>H</u>$(CH_2)_3OSi$, minor), 3.13 (1H, t, *J* 6.0 Hz, C<u>H</u>$(CH_2)_3OSi$, major), 3.37 (1H, d, *J* 11.7 Hz, 1 of THPC<u>H</u>$_2O$, minor), 3.46-3.51 (1H + 1H, m, 1 of CH_2C<u>H</u>$_2O$-THP, both diastereomers), 3.62-3.70 (2H + 2H, m, CH_2OSi, both diastereomers), 3.72 (1H, d, *J* 11.8 Hz, 1 of THPC<u>H</u>$_2O$, major), 3.74 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.78-3.84 (1H +1H, m, 1 of CH_2C<u>H</u>$_2O$-THP, both diastereomers), 4.10 (1H, d, *J* 11.7 Hz, 1 of THPOC<u>H</u>$_2$, major), 4.41 (1H, d, *J* 11.7 Hz, 1 of THPOC<u>H</u>$_2$, minor), 4.62 (1H, t, *J* 3.3 Hz, OCHO, major), 4.70 (1H, t, *J* 3.3 Hz, OCHO, minor), 7.34-7.42 (6H + 6H, m, aryl, both diastereomers), 7.62-7.63 (4H + 4H, m, aryl, both diastereomers).

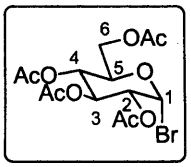
^{13}C NMR (125 MHz, $CDCl_3$): δ 18.8 (THP, major), 18.9 (THP, minor), 19.2 (<u>C</u>$(CH_3)_3$, both diastereomers), 24.6 (<u>C</u>H_2CH_2OSi, minor), 24.8 (<u>C</u>H_2CH_2OSi, major), 25.3 (THP, both diastereomers), 26.8 ($C(\underline{C}H_3)_3$, both diastereomers), 29.0 (CH<u>C</u>H_2, minor), 29.1 (CH<u>C</u>H_2, major), 30.2 (THP, both diastereomers), 52.4 (OCH_3, major), 52.5 (OCH_3, major), 59.6 (<u>C</u>HCH_2, both diasteromers), 61.7 ($CH_2\underline{C}H_2O$-THP, both diastereomers), 62.6 (THPOCH_2<u>C</u>, major), 63.0 (THPOCH_2<u>C</u>, minor), 63.1 (CH_2OSi, major), 63.2 (CH_2OSi, minor), 67.2 (THPO<u>C</u>H_2, minor), 67.8 (THPO<u>C</u>H_2, major), 98.1 (OCHO, minor), 98.9 (OCHO, major), 127.6 (aryl-*meta*, both diasteromers), 129.6 (aryl-*para*, both diastereomers), 133.7 (aryl-*ipso*, both diastereomers), 135.5 (aryl-*ortho*, both diastereomers), 168.7 (C=O, minor), 168.9 (C=O, major).

ν_{max}/cm^{-1} (film): 2941 (C-H), 2856 (C-H), 1738 (C=O), 1429, 1094.

m/z (FAB+): 513 (MH^+, 20%), 455 (29), 351 (100), 293 (45), 199 (59), 154 (58).

HRMS (FAB+): $C_{29}H_{41}O_6Si$ (MH^+) requires: 513.2672; found: 513.2662; error: 2.0 ppm.

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide[136] 173



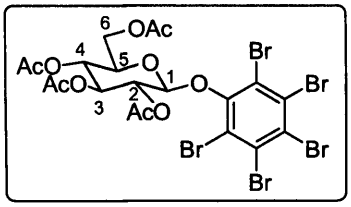
α-D-Glucose pentaacetate (15.0 g, 38.4 mmol) was added to acetic acid (40 mL) and the solution was cooled to 0 °C in an ice-bath. Hydrogen bromide (33% solution in acetic acid, 29.9 mL, 173 mmol) was added dropwise. The mixture was then fitted with a condenser, allowed to warm to RT and stirred for 17 h. The volatile material was removed *in vacuo*, and Et_2O (400 mL) was added. The solution was washed with H_2O (200 mL), sat. aq. $NaHCO_3$ (200 mL) and brine (200 mL), and dried ($MgSO_4$).

Removal of the solvent *in vacuo* gave the product **173** as a white crystalline solid (15.5 g, 98%) which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02 (3H, s, CH_3CO), 2.03 ((3H, s, CH_3CO), 2.08 (2 × 3H, s, CH_3CO), 4.10-4.13 (1H, m, 1 of H-C(6)), 4.26-4.33 (2H, m, H-C(5) and 1 of H-C(6)), 4.82 (1H, dd, *J* 10.0 Hz, 4.1 Hz, H-C(2)), 5.14 (1H, t, *J* 9.8 Hz, H-C(4)), 5.54 (1H, t, *J* 9.8 Hz, H-C(3)), 6.59 (1H, d, *J* 4.0 Hz, H-C(1)).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8, 19.9 ($\underline{C}H_3CO$), 60.4 (C-6), 66.5 (C-4), 69.5, 69.8 (C-2 and C-3), 71.7 (C-5), 86.5 (C-1), 168.7, 169.0, 169.0, 170.0 (C=O).

Pentabromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside 174



Acetone (75 mL) was added to pentabromophenol (18.3 g, 37.6 mmol), followed by potassium carbonate (5.19 g, 37.55 mmol), and the mixture was stirred at RT for 30 min. A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **173** (15.4 g, 37.6 mmol) in acetone (37 mL) was then added and the mixture was stirred for a further 16 h. H_2O (400 mL) was added and the organic material extracted with EtOAc (2 × 250 mL). After drying the organic extracts ($MgSO_4$), the solvent was removed *in vacuo* to give the product **174**[102] as a white solid (29.88 g, 97%) which was then recrystallised for characterisation from MeOH.

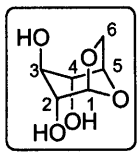
mp 204-206 °C (Lit. 197-198 °C)

$[\alpha]_D^{21} = -7.8$ (*c* 0.81 in $CHCl_3$) Lit. $[\alpha]_D^{25} = -6$ (*c* 1.0 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01 (2 × 3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.09 (3H, s, CH_3CO), 3.61 (1H, ddd, *J* 10.0, 4.8, 2.7 Hz, H-C(5)), 4.02 (1H, dd, *J* 12.3, 2.7 Hz, 1 of H-C(6)), 4.19 (1H, dd, *J* 12.4, 4.8Hz, 1 of H-C(6)), 5.17 (1H, t, *J* 9.7 Hz, H-C(4)), 5.27 (1H, t, *J* 9.4 Hz, H-C(3)), 5.36 (1H, d, *J* 7.8 Hz, H-C(1)), 5.41 (1H, dd, *J* 9.4, 7.8 Hz, H-C(2)).

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.5, 20.6, 20.6, 20.8 ($\underline{C}H_3C(O)$), 61.4 (C-6), 68.2, 71.4, 72.3, 72.5 (C-2, C-3, C-4, C-5), 100.1 (C-1), 122.2 (aryl), 126.0 (aryl), 128.7 (aryl), 150.2 (aryl-*ipso*), 169.2, 169.3, 170.2, 170.4 (C=O).

1,6-Anhydro-β-D-glucopyranose[101] 70



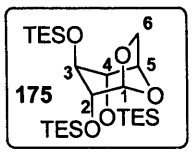
Dioxane (200 mL) was added to pentabromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **174** (20.8 g, 25.4 mL), followed by H_2O (100 mL). To the resulting suspension, Amberlite IRA 400 (OH^- form, 200 g) was added and the mixture heated to 50 °C with stirring for 24 h. Further resin (50 g) was added and heating continued for 16 h. The mixture was allowed to cool to RT and the resin was filtered and washed with dioxane/H_2O. The combined washings were concentrated *in vacuo* to give a white solid which was purified by column chromatography (SiO_2, 10% MeOH in DCM) to give the product **170** (2.51 g, 61%) as a white solid.

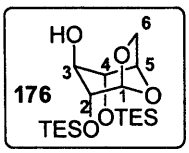
$[\alpha]_D^{23} = -71.3$ (*c* 0.23 in H_2O) Lit. $[\alpha]_D^{24} = -64.2$ (*c* 2.0 in H_2O).

^{1}H NMR (500 MHz, D_2O): δ 3.5-3.55 (1H, m, H-C(2)), 3.69-3.72 (2H, m, H-C(3) and H-C(4)), 3.78 (1H, dd, *J* 7.7, 5.8 Hz, 1 of H-C(6)), 4.12 (1H, dd, *J* 7.7, 1.0 Hz, 1 of H-C(6)), 4.65 (1H, dd, *J* 5.8, 1.4 Hz, H-C(5)), 5.48 (1H, s, H-C(1)).

^{13}C NMR (125 MHz, D_2O): δ 65.9 (C-6), 70.9 (C-2), 71.5, 73.2 (C-3 and C-4), 76.9 (C-5), 102.1 (C-1).

1,6-Anhydro-2,3,4-tris-*O*-(triethylsilanyl)-β-D-glucopyranose 175 and 1,6-Anhydro-2,4-bis-*O*-(triethylsilanyl)-β-D-glucopyranose[103] 176





To 1,6-anhydro-β-D-glucopyranose **170** (1.84 g, 11.35 mmol), dry pyridine (11.4 mL) was added and the solution was cooled to 0 °C in an ice bath. TESCl (3.81 mL, 22.7 mmol) was then dropwise. A white precipitate was formed and the mixture was stirred for 4 h at 0 °C. Petroleum ether (20 mL) was then added and the mixture was washed with 1M HCl (2 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4% EtOAc in petroleum ether) first gave the trisilyl ether compound **175** as a yellow oil (570 mg, 13%).

$[\alpha]_D^{23} = -30.2$ (*c* 1.95 in $CHCl_3$) Lit. $[\alpha]_D^{25} = -24.7$ (*c* 1.1 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.56-0.65 (18H, m, C<u>H</u>$_2$Si), 0.93-0.98 (18H, m, C<u>H</u>$_3$CH$_2$Si), 3.40 (1H, broad s, H-C(2)), 3.47 (1H, broad s, H-C(4)), 3.58 (1H, quintet, *J* 1.6 Hz, H-C(3)), 3.63 (1H, app. t, *J* 6.4, 1 of H-C(6)), 4.07 (1H, dd, *J* 6.8, Hz, 0.9 Hz, 1 of H-C(6)), 4.34 (1H, broad d, *J* 5.1 Hz, H-C(5)), 5.25 (1H, s, H-C(1)).

^{13}C NMR (125 MHz, $CDCl_3$): δ 4.8, 4.9 (CH_2Si), 6.8, 6.9 (<u>C</u>H$_3$CH$_2$Si), 64.7 (C-6), 71.9 (C-2), 72.9 (C-4), 75.2 (C-3), 76.7 (C-5), 102.2 (C-1).

ν_{max}/cm^{-1} ($CDCl_3$ cast): 2954 (C-H), 2878 (C-H), 1459, 1238, 1104.

m/z (FAB+): 527 (MNa^+, 100%), 505 (30), 373 (45), 288 (91), 217 (33), 199 (64), 176 (74).

HRMS (FAB+): $C_{24}H_{52}O_5Si_3$ (MNa^+) requires 527.3020; found: 527.3010; error: 1.9 ppm.

Further elution afforded the diprotected product **176** as a yellow oil (3.49 g, 79%).

$[\alpha]_D^{21} = -28.4$ (*c* 1.58 in $CHCl_3$) Lit. $[\alpha]_D^{25} = -24.7$ (*c* 1.1 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.56-0.67 (12H, m, C<u>H</u>$_2$Si), 0.95-0.99 (18H, m, C<u>H</u>$_3$CH$_2$Si), 2.11 (1H, broad d, *J* 5.6 Hz, OH), 3.44 (1H, d, *J* 3.6 Hz, H-C(4)), 3.50-3.55 (2H, m, H-C(2) and H-C(3)), 3.67 (1H, dd, *J* 7.4, 5.2 Hz, 1 of H-C(6)), 3.87 (1H, d, *J* 7.4 Hz, 1 of H-C(6)), 4.39 (1H, d, *J* 4.7 Hz, H-C(5)), 5.29 (1H, s, H-C(1)).

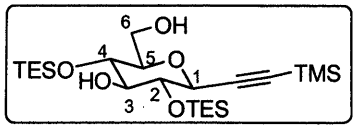
^{13}C NMR (100 MHz, $CDCl_3$): δ 4.7 (CH_2Si), 6.7, 6.8 (<u>C</u>H$_3$CH$_2$Si), 66.4 (C-6), 73.7 (C-2), 74.0 (C-4), 75.6 (C-3), 78.1 (C-5), 103.5 (C-1).

ν_{max}/cm^{-1} ($CDCl_3$ cast): 3460 (O-H), 2955 (C-H), 2878 (C-H), 1634, 1460, 1240, 1107.

m/z (FAB+): 391 (MH^+, 100%), 361 (26), 315 (48), 301 (90), 259 (20), 190 (30).

HRMS (FAB+): $C_{18}H_{39}O_5Si_2$ (MH^+) requires: 391.2336; found: 391.2329; error: 1.9 ppm.

1-(2,4-Bis-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne[103] 169



Trimethylsilyl acetylene (3.52 mL, 24.90 mmol) was dissolved in dry toluene (21 mL) and cooled to −15 °C in an ice/acetone/dry ice bath. *n*BuLi (1.6M in hexanes, 15.6 mL, 24.90 mmol) was added dropwise, which led to the formation of a white precipitate. Stirring was continued at RT for 40 min. Dropwise addition of dry THF

(1.8 mL) resulted in the reaction mixture returning to a colourless solution, which was then added dropwise to a suspension of freshly sublimed $AlCl_3$ (3.32 g, 24.90 mmol) in dry toluene (16 mL). The suspension was heated at 50 °C in an ultrasound bath for 2 h 30 min. The mixture was then heated at 60 °C, without sonication, and a solution of 1,6-anhydro-2,4-bis-*O*-(triethylsilanyl)-β-D-glucopyranose **176** (2.43 g, 6.22 mmol) and 2,4,6-trimethylpyridine (0.55 mL, 6.84 mmol) in dry toluene (3.8 mL) was added dropwise. The dark brown reaction mixture was heated at 130 °C for 16 h, cooled to 0 °C and poured into an ice-cold H_2O/1M HCl (2:1, 180 mL). The organic material was extracted with EtOAc (4 × 120 mL) and the organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4% EtOAc in petroleum ether) afforded the title compound **169** as a yellow oil (2.46 g, 81%).

$[\alpha]_D^{20} = -7.6$ (*c* 0.47 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.16 (9H, s, $Si(CH_3)_3$), 0.57-0.72 (12H, m, $C\underline{H}_2Si$), 0.92-0.99 (18H, m, $C\underline{H}_3CH_2Si$), 2.01 (1H, broad s, HO-C(6)), 2.13 (1H, d, *J* 3.2 Hz, HO-C(3)), 3.23 (1H, ddd, *J* 9.3, 5.5, 2.7 Hz, H-C(5)), 3.31 (1H, td, *J* 8.6, 3.1 Hz, H-C(3)), 3.44-3.48 (2H, m, H-C(2) and H-C(4)),[†††] 3.62-3.66 (1H, m, 1 of H-C(6)), 3.83 (1H, broad d, *J* 11.8 Hz, 1 of H-C(6)), 3.91 (1H, d, *J* 9.5 Hz, H-C(1)).

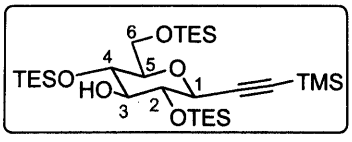
^{13}C NMR (100 MHz, $CDCl_3$): δ −0.32 ($Si(CH_3)_3$), 5.1 (CH_2Si), 6.9 ($\underline{C}H_3CH_2Si$), 62.2 (C-6), 71.0 (C-1), 71.5 (C-5), 75.3 (C-2), 79.4 (C-4), 80.3 (C-3), 91.1 ($C\equiv\underline{C}Si(CH_3)_3$), 102.5 ($\underline{C}\equiv CSi(CH_3)_3$).

ν_{max}/cm^{-1} (film): 3545 (O-H), 2955 (C-H), 2878 (C-H), 1252, 1144, 1088.

m/z (FAB+): 489 (MH^+, 100%), 459 (20), 307 (25), 255 (43), 154 (96).

HRMS (FAB+): $C_{23}H_{49}O_5Si_3$ (MH^+) requires: 489.2888; found: 489.2892; error: 0.9 ppm.

1-(2,4,6-Tris-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne 177



1-(2,4-Bis-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne **169** (158 mg, 320 μmol) and dry pyridine (41 μL, 510 μmol) were dissolved in dry DCM (0.23

[†††] Overlapping triplets

mL) and cooled to 0 °C in an ice-bath. Dropwise addition of triethylchlorosilane (57 μL, 340 μmol) resulted in the formation of a precipitate, and the resulting mixture was stirred for 150 min at 0 °C. Petroleum ether (4 mL) was added and the mixture washed with 1M HCl (2 × 3 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 2% EtOAc in petroleum ether) afforded the product **177** as a yellow oil (177 mg, 92%).

$[\alpha]_D^{21} = -5.3$ (*c* 0.19 in $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (9H, s, $Si(CH_3)_3$), 0.59-0.74 (18H, m, CH_2Si), 0.93-1.01 (27H, m, $C\underline{H}_3CH_2Si$), 2.12 (1H, d, *J* 2.9 Hz, HO-C(3)), 3.17 (1H, ddd, *J* 9.3, 5.1, 1.7 Hz, H-C(5)), 3.30 (1H, td, *J* 11.3, 2.7 Hz, H-C(3)), 3.43-3.50 (2H, m, H-C(2) and H-C(4)), 3.71 (1H, dd, *J* 11.6, 5.1 Hz, 1 of H-C(6)), 3.85-3.88 (2H, m, *J* 11.8 Hz, 1 of H-C(6) and H-C(1)).

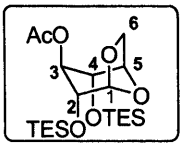
^{13}C NMR (100 MHz, $CDCl_3$): δ −0.36 ($Si(CH_3)_3$), 5.1 (CH_2Si), 5.4 (CH_2Si), 6.8 ($\underline{C}H_3CH_2Si$), 6.9 ($\underline{C}H_3CH_2Si$), 62.5 (C-6), 70.6 (C-1), 71.2 (C-5), 75.3 (C-2), 79.5 (C-4), 81.5 (C-3), 90.3 ($C\equiv\underline{C}Si(CH_3)_3$), 103.0 ($\underline{C}\equiv CSi(CH_3)_3$).

ν_{max}/cm^{-1} (film): 3616 (O-H), 2953 (C-H), 2876 (C-H), 1460, 1416, 1240.

m/z (FAB+): 603 (MH^+, 23%), 573 (39), 453 (38), 301 (68), 255 (100), 205 (43), 171 (65).

HRMS (FAB+): $C_{29}H_{63}O_5Si_4$ (MH^+) requires: 603.3752; found: 603.3743; error: 1.6 ppm.

1,6-Anhydro-2,4-bis-*O*-(triethylsilanyl)-3-*O*-acetyl-β-D-glucopyranose 180



1,6-Anhydro-2,4-bis-*O*-(triethylsilanyl)-β-D-glucopyranose **176** (239 mg, 0.61 mmol), was dissolved in dry pyridine (1.1 mL). Acetic anhydride (120 μL 1.22 mmol) and DMAP (15 mg) were added and the solution was stirred at RT for 18 h. The reaction mixture was then diluted with DCM (20 mL) and washed with 1M HCl (16 mL), then sat. aq. $NaHCO_3$ (16 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* followed by column chromatography of the residue (SiO_2, 6% EtOAc in petroleum ether) afforded the product **180** as an oil (150 mg, 57%).

$[\alpha]_D^{21} = -73.1$ (*c* 0.76 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.58-0.64 (12H, m, CH_2Si), 0.92-0.96 (18H, m, $C\underline{H}_3CH_2Si$), 2.06 (3H, s, CH_3CO), 3.41 (1H, broad s, H-C(2)), 3.47 (1H, broad s, H-C(3)), 3.67 (1H, dd, *J* 7.3, 5.8 Hz, 1 of H-C(6)), 3.89 (1H, dd, *J* 7.3, 0.6 Hz, 1 of H-C(6)), 4.39 (1H, broad d, *J* 6.2 Hz, H-C(5)), 4.67 (1H, t, *J* 1.5 Hz, H-C(4)), 5.27 (1H, broad s, H-C(1)).

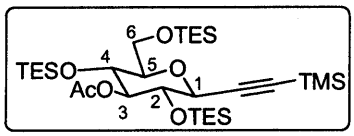
^{13}C NMR (100 MHz, $CDCl_3$): δ 4.5 (CH_2Si), 6.7 ($\underline{C}H_3CH_2Si$), 21.1 ($\underline{C}H_3CO$), 65.1 (C-6), 69.8 (C-2), 70.5 (C-3), 75.5 (C-4), 76.9 (C-5), 102.2 (C-1), 169.4 (C=O).

ν_{max}/cm^{-1} (film): 2955 (C-H), 2877 (C-H), 1752 (C=O), 1225, 1101, 1003.

m/z (FAB+): 455 (MNa^+, 43%), 403 (20), 301 (15), 213 (15), 174 (19), 145 (100), 115 (70).

HRMS (FAB+): $C_{20}H_{40}O_6Si_2Na$ (MNa^+) requires: 455.2261; found: 455.2252; error: 2.0 ppm.

1-(3-*O*-Acetyl-2,4,6-tris-*O*-(triethylsilanyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne 168



Acetic anhydride (2.92 mL, 31.0 mmol), triethylamine (1.39 mL, 31.0 mmol) and 4-pyrrolidinopyridine (287 mg, 1.94 mmol) were added to alcohol **177** (4.67 g, 7.74 mmol) under argon. The resultant mixture was stirred at RT for 15 h. DCM (150 mL) was added and the mixture washed with 1M HCl (200 mL), then sat. aq. $NaHCO_3$ (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 25% DCM in petroleum ether) gave the product **168** as a yellow oil (3.50 g, 70%).

$[\alpha]_D^{20} = -15.0$ (*c* 2.2 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.14 (9H, s, $Si(CH_3)_3$), 0.54-0.65 (18H, m, CH_2Si), 0.90-0.97 (27H, m, $C\underline{H}_3CH_2Si$), 2.11 (3H, s, CH_3CO), 3.19 (1H, ddd, *J* 9.3, 4.0, 1.8 Hz, H-C(5)), 3.57 (1H, t, *J* 9.2 Hz, H-C(2)), 3.67 (1H, t, *J* 9.3 Hz, H-C(4)), 3.72 (1H, dd, *J* 11.7, 4.1 Hz, 1 of H-C(6)), 3.81 (1H, dd, *J* 11.7, 1.8 Hz, 1 of H-C(6)), 3.92 (1H, d, *J* 9.4 Hz, H-C(1)), 4.91 (1H, t, *J* 9.1 Hz, H-C(3)).

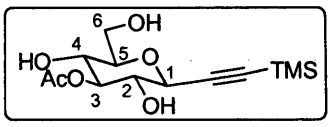
^{13}C NMR (100 MHz, $CDCl_3$): δ −0.43 ($Si(CH_3)_3$), 4.6 (CH_2Si), 5.4 (CH_2Si), 6.8 ($\underline{C}H_3CH_2Si$), 21.7 ($\underline{C}H_3C(O)$), 61.9 (C-6), 68.9 (C-4), 71.5 (C-1), 73.6 (C-2), 79.2 (C-3), 80.7 (C-5), 90.8 ($C\equiv\underline{C}Si(CH_3)_3$), 102.8 ($\underline{C}\equiv CSi(CH_3)_3$), 169.7 (C=O).

ν_{max}/cm^{-1} (film): 2955 (C-H), 2878 (C-H), 1755 (C=O), 1460, 1225, 1109.

m/z (CI+, CH_4): 645 (MH^+, 5%), 615 (20), 453 (100), 321 (22), 145 (47), 115 (35).

HRMS (CI+, CH_4): $C_{31}H_{65}O_6Si_4$ (MH^+) requires: 645.3858; found: 645.3856; error: 0.4 ppm.

1-(3-*O*-acetyl-β-D-glucopyranosyl)-2-trimethylsilanylethyne 181



Acetate **168** (1.42 g, 2.19 mmol) was dissolved in THF (7.5 mL). H_2O (22 mL) and acetic acid (44 mL) were added and the mixture heated at 45 °C for 2h. The mixture was concentrated *in vacuo*, then re-dissolved in EtOAc (50 mL) and washed with sat. aq. $NaHCO_3$ (2 × 50 mL). The organic material was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (SiO_2, 5% MeOH in DCM), to give the product **181** as a white solid (589 mg, 89%).

mp 69-71 °C.

$[\alpha]_D^{20} = -50.9$ (*c* 0.71 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.18 (9H, s, $Si(CH_3)_3$), 2.16 (3H, s, CH_3CO), 2.16 (1H, broad s, HO-C(6)), 2.53 (1H, broad s, HO-C(2)), 2.87 (1H, broad s, HO-C(4)), 3.36 (1H, ddd, *J* 9.6, 4.7, 3.3 Hz, H-C(5)), 3.60 (1H, t, *J* 9.5 Hz, H-C(2)), 3.65 (1H, t, *J* 9.5 Hz, H-C(4)), 3.79 (1H, dd, *J* 12.1, 4.7 Hz, 1 of H-C(6)), 3.91 (1H, dd, *J* 12.1, 3.3 Hz, 1 of H-C(6)), 4.04 (1H, d, *J* 9.6 Hz, H-C(1)), 4.83 (1H, t, *J* 9.3 Hz, H-C(3)).

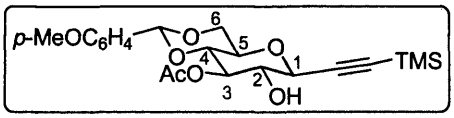
^{13}C NMR (100 MHz, $CDCl_3$): δ −0.27 ($Si(CH_3)_3$), 21.1 ($\underline{C}H_3C(O)$), 62.2 (C-6), 69.3 (C-4), 71.4 (C-1), 72.3 (C-2), 79.2 (C-3), 79.7 (C-5), 92.9 ($C{\equiv}\underline{C}Si(CH_3)_3$), 100.2 ($\underline{C}{\equiv}CSi(CH_3)_3$), 172.8 (C=O).

ν_{max}/cm^{-1} (neat solid): 3390 (O-H), 2958 (C-H), 2897 (C-H), 1720 (C=O), 1247, 1085, 1028.

m/z (CI+, CH_4): 303 (MH^+, 21%), 225 (50), 209 (38), 153 (90), 117 (76), 99 (100).

HRMS (CI+, CH_4): $C_{13}H_{23}O_6Si$ (MH^+) requires: 303.1264; found: 303.1269; error: 1.6 ppm.

1-(3-*O*-Acetyl-4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosyl)-2-trimethylsilanylethyne 182



4Å Molecular sieves, *p*-toluenesulfonic acid (5.6 mg, 294 μmol) and 4-methoxybenzaldehyde dimethyl acetal (121 μL, 710 μmol) were added to a solution of triol **181** (89.5 mg, 296 μmol) in dry acetonitrile. The mixture was heated to reflux for 18 h. After cooling to RT, a few drops of triethylamine were added and the mixture was filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by column chromatography (SiO_2, 1:1:0.01 DCM/ toluene/NEt_3, then 20:1:1:0.01 DCM/toluene/MeOH/NEt_3) to give the product **182** as a white foamy solid (99 mg, 80%).

mp 83-85 °C.

$[\alpha]_D^{22} = -83.9$ (*c* 0.57 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.18 (9H, s, $Si(CH_3)_3$), 2.10 (3H, s, CH_3CO), 2.82 (1H, broad d, *J* 3.9 Hz, OH), 3.47 (1H, dt, *J* 9.7, 4.9 Hz, H-C(5)), 3.60 (1H, t, *J* 9.5 Hz, H-C(4)), 3.66-3.73 (2H, m, H-C(2) and 1 of H-C(6))), 3.76 (3H, s, OCH_3), 4.11 (1H, d, *J* 9.6 Hz, H-C(1)), 4.31 (1H, dd, *J* 10.5, 4.9 Hz, 1 of H-C(6)), 5.11 (1H, t, *J* 9.4 Hz, H-C(3)), 5.41 (1H, s, CHO_2), 6.85 (2H, d, *J* 8.8 Hz, aryl), 7.33 (2H, d, *J* 8.7 Hz, aryl).

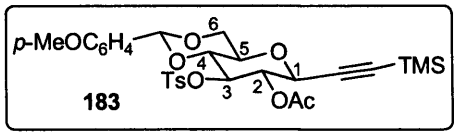
^{13}C NMR (100 MHz, $CDCl_3$): δ −0.27 ($Si(CH_3)_3$), 21.1 ($\underline{C}H_3C(O)$), 55.3 (OCH_3), 68.4 (C-6), 70.8 (C-5)), 72.2 (C-1), 73.4 (C-2), 74.8 (C-3), 78.2 (C-4), 92.8 ($C\equiv\underline{C}Si(CH_3)_3$), 100.1 ($\underline{C}\equiv CSi(CH_3)_3$), 101.4 ($CHO_2$), 113.6 (aryl-*ortho* to OMe), 127.5 (aryl-*meta* to OMe), 129.3 (aryl-*ipso* to CHO_2), 160.1 (aryl-*ipso* to OMe) 171.4 (C=O)

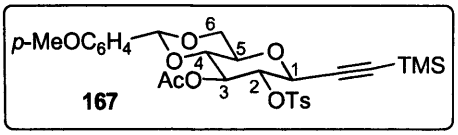
ν_{max}/cm^{-1} (neat solid): 3479 (O-H), 2959 (C-H), 2878 (C-H), 1725 (C=O), 1518, 1247, 1029.

m/z (EI): 420 (M^+, 26%), 241 (8), 179 (21), 136 (100), 121 (34).

HRMS (EI): $C_{21}H_{28}O_7Si$ (M^+) requires: 420.1549; found: 420.1557; error: 1.9 ppm.

1-(2-*O*-Acetyl-4,6-*O*-(4-methoxybenzylidene)-3-*O*-(4-toluenesulfonyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne 183 and 1-(3-*O*-Acetyl-4,6-*O*-(4-methoxybenzylidene)-2-*O*-(4-toluenesulfonyl)-β-D-glucopyranosyl)-2-trimethylsilanylethyne 167





Alcohol **182** (91 mg, 216 μmol) was dissolved in dry pyridine (0.5 mL) and cooled to 0 °C in an ice-bath. *p*-Toluenesulfonyl chloride (49.5 mg, 260 μmol) was added and the solution was stirred at RT for 6 h. The mixture was then cooled to 0 °C and additional *p*-toluenesulfonyl chloride (124 mg, 650 μmol) was added. The mixture was heated at 40 °C for 18 h. A further amount of *p*-toluenesulfonyl chloride (54 mg, 283 μmol) was added and the mixture was heated to reflux for 5 h. After allowing the mixture to cool to RT, DCM (5 mL) was added and the solution was washed with 1M HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), H_2O (10 mL), then dried ($MgSO_4$). Removal of solvent *in vacuo*, and column chromatography of the resulting residue (SiO_2, 6%-10% EtOAc in petroleum ether) gave the compound **183** (3.3 mg, 3%) as white solid.

mp 133-135 °C

$[\alpha]_D^{22} = -14.5$ (*c* 1.18 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.19 (9H, s, $Si(CH_3)_3$), 2.07 (3H, s, CH_3CO), 2.29 (3H, s, $C\underline{H}_3$-aryl), 3.45 (1H, td, *J* 9.7, 5.0 Hz, H-C(5)), 3.62 (1H, t, *J* 9.5 Hz, H-C(4)), 3.69 (1H, t, *J* 10.4 Hz, 1 of H-C(6)), 3.82 (3H, s, OCH_3), 4.24 (1H, d, *J* 9.9 Hz, H-C(1)), 4.31 (1H, dd, *J* 10.7, 5.0 Hz, 1 of H-C(6)), 4.88 (1H, t, *J* 9.5 Hz, H-C(3)), 5.24 (1H, t, *J* 9.6 Hz, H-C(2)), 5.31 (1H, s, CHO_2), 6.85 (2H, d, *J* 8.8 Hz, aryl-PMBz), 7.00 (2H, d, *J* 8.2 Hz, aryl-OTs), 7.21 (2H, d, *J* 8.7 Hz, aryl-PMBz), 7.65 (2H, d, *J* 8.3 Hz, aryl-OTs).

^{13}C NMR (125 MHz, $CDCl_3$): δ −0.56 ($Si(CH_3)_3$), 20.5 ($\underline{C}H_3CO$), 21.6 ($\underline{C}H_3$-aryl) 55.3 (OCH_3), 68.3 (C-6), 69.8 (C-1), 70.9 (C-5), 71.0 (C-2) 78.1 (C-4), 79.7 (C-3), 93.4 ($C\equiv\underline{C}Si(CH_3)_3$), 98.3 ($\underline{C}\equiv CSi(CH_3)_3$), 101.5 ($CHO_2$), 113.6 (aryl-*ortho* to OMe), 127.5 (aryl), 127.9 (aryl), 129.0 (aryl-*ipso* to CHO_2), 129.3 (aryl), 134.0 (aryl-*ipso* to SO_3), 144.3 (aryl-*ipso* to Me), 160.1 (aryl-*ipso* to OMe) 168.9 (C=O).

ν_{max}/cm^{-1} (neat solid): 2960 (C-H), 2929 (C-H), 1758 (C=O), 1616, 1366, 1250, 1172.

m/z (CI+, CH_4): 575 (MH^+, 51%), 421 (15), 179 (22), 137 (100), 91 (60).

HRMS (CI+, CH_4): $C_{28}H_{35}O_9SSi$ (MH^+) requires: 575.1771; found: 575.1781; error:

1.7 ppm.

Further elution afforded the product **167** as a white solid (89 mg, 72%).

mp 157-159 °C.

$[\alpha]_D^{18} = -75.9$ (*c* 0.81 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.20 (9H, s, $Si(CH_3)_3$), 1.86 (3H, s, CH_3CO), 2.41 (3H, s, $C\underline{H}_3$-aryl), 3.46 (1H, td, *J* 9.7, 5.0 Hz, H-C(5)), 3.58 (1H, t, *J* 9.6 Hz, H-C(4)), 3.71 (1H, t, *J* 10.3 Hz, 1 of H-C(6)), 3.75 (3H, s, OCH_3), 4.26 (1H, d, *J* 9.7 Hz, H-C(1)), 4.32 (1H, dd, *J* 10.5, 4.9 Hz, 1 of H-C(6)), 4.87 (1H, t, *J* 9.5 Hz, H-C(2)), 5.31 (1H, t, *J* 9.5 Hz, H-C(3)), 5.39 (1H, s, CHO_2), 6.83 (2H, d, *J* 8.8 Hz, aryl-PMBz), 7.28-7.31 (4H, m, 2 of aryl-OTs and 2 of aryl-PMBz), 7.80 (2H, d, *J* 8.3 Hz, aryl-OTs).

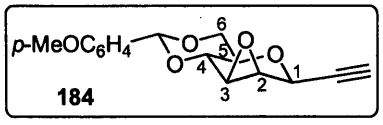
^{13}C NMR (125 MHz, $CDCl_3$): δ −0.47 ($Si(CH_3)_3$), 20.6 ($\underline{C}H_3CO$), 21.6 ($\underline{C}H_3$-aryl) 55.3 (OCH_3), 68.2 (C-6), 70.0 (C-1), 70.8 (C-5), 71.5 (C-3), 78.1 (C-2), 78.4 (C-4), 94.0 ($C\equiv\underline{C}Si(CH_3)_3$), 98.3 ($\underline{C}\equiv CSi(CH_3)_3$), 101.4 ($CHO_2$), 113.6 (aryl-*ortho* to OMe), 127.4 (aryl), 127.8 (aryl), 129.1 (aryl-*ipso* to CHO_2), 129.6 (aryl), 134.4 (aryl-*ipso* to SO_3), 144.8 (aryl-*ipso* to Me), 160.1 (aryl-*ipso* to OMe) 169.8 (C=O).

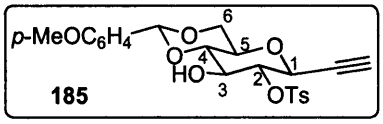
ν_{max}/cm^{-1} (KBr): 2961 (C-H), 2885 (C-H), 1751 (C=O), 1518, 1369.

***m/z* (ESI+):** 575 (MH^+, 100%), 509 (50), 457 (49), 435 (71), 323 (30), 321 (43).

HRMS (ESI+): $C_{28}H_{35}O_9SSi$ MH^+ requires: 575.1771; found: 575.1764; error: 1.2 ppm.

(2,3-Anhydro-4,6-*O*-(4-methoxybenzylidene)-β-D-mannopyranosyl)ethyne 184 and (4,6-*O*-(4-methoxybenzylidene)-2-*O*-(4-toluenesulfonyl)-β-D-glucopyranosyl)ethyne 185





Sodium methoxide (1.5 M in methanol, 0.77 mL, 1.15 mmol), was added to a solution of tosylate **167** (210 mg, 383 μmol) in dry DCM (3.0 mL). The resulting mixture was stirred at RT for 17 h. Additional sodium methoxide (1.5 M in methanol, 0.5 mL, 0.75 mmol) was added and stirring was continued for 18 h at RT. DCM (10 mL) was added and the organic layer was washed with 1M HCl (12 mL), H_2O (12 mL), and dried ($MgSO_4$). Removal of the solvent *in vacuo*, followed by purification of the residue by column chromatography (SiO_2, 10% EtOAc in petroleum ether) gave the epoxide **184**

(70 mg, 64%) as a white solid.

mp 182-184 °C.

$[\alpha]_D^{21} = -34.7$ (*c* 0.18 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.59 (1H, d, *J* 2.2 Hz, C≡CH), 3.21 (1H, td, *J* 9.9, 4.7 Hz, H-C(5)), 3.33 (1H, d, *J* 3.5 Hz, H-C(2)), 3.52 (1H, d, *J* 3.6 Hz, H-C(3)), 3.71-3.75 (2H, m, H-C(4) and 1 of H-C(6)), 3.79 (3H, s, OCH_3), 4.26 (1H, dd, *J* 10.5, 4.7 Hz, 1 of H-C(6)), 4.74 (1H, t, *J* 1.6 Hz, H-C(1)), 5.51 (1H, s, CHO_2), 6.89 (2H, d, *J* 8.7 Hz, aryl), 7.39 (2H, d, *J* 8.7 Hz, aryl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 52.0 (C-2), 54.9 (C-3), 55.3 ($O\underline{C}H_3$), 65.8 (C-1), 69.1 (C-6), 69.9 (C-5), 74.4 (C-4), 74.9 (C≡$\underline{C}$H), 77.8 ($\underline{C}$≡CH), 102.4 (CHO_2), 113.7 (aryl-*ortho* to OMe), 127.4 (aryl-*meta* to OMe), 129.3 (aryl-*ipso* to CHO_2), 160.3 (aryl-*ipso* to OMe).

ν_{max}/cm^{-1} (neat solid): 3258, 2924 (C-H), 2899 (C-H), 1617, 1516, 1249, 1106, 1084.

m/z (CI+, CH_4): 289 (MH^+, 14%), 181 (30), 153 (15), 136 (100), 109 (24), 95 (13).

HRMS (CI+, CH_4): $C_{16}H_{17}O_5$ (MH^+) requires: 289.1076; Found: 289.1071; Error: 1.9 ppm.

Further elution at 20% EtOAc in petroleum ether afforded the compound **185** (14.8 mg, 13%) as a white solid.

mp 137-139 °C.

$[\alpha]_D^{22} = -55.4$ (*c* 0.85 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41 (1H, s, C≡CH), 2.42 (3H,s, $C\underline{H}_3$-aryl), 3.02 (1H, broad s, OH), 3.39 (1H, td, *J* 9.8, 5.0 Hz, H-C(5)), 3.53 (1H, t, *J* 9.4 Hz, H-C(4)), 3.68 (1H, t, *J* 10.3 Hz, 1 of H-C(6)), 3.77 (3H, s, OCH_3), 3.88 (1H, broad t, *J* 9.0 Hz, H-C(3)), 4.18 (1H, dd, *J* 9.8, 2.1 Hz, H-C(1)), 4.30 (1H, dd, *J* 10.5, 5.0 Hz, 1 of H-C(6)), 4.62 (1H, t, *J* 9.7 Hz, H-C(2)), 5.45 (1H, s, CH_2O), 6.85 (2H, d, *J* 8.8 Hz, aryl-PMBz), 7.31 (2H, m, aryl-OTs), 7.36 (2H, d, *J* 8.8 Hz, aryl-PMBz), 7.85 (2H, d, *J* 8.4 Hz, aryl-OTs).

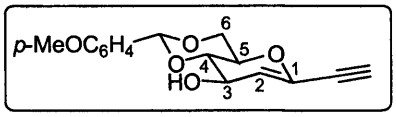
^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7 ($\underline{C}H_3$-aryl) 55.3 (OCH_3), 68.2 (C-6), 68.7 (C-1), 70.5 (C-5), 72.6 (C-3), 75.8 (C≡$\underline{C}$H), 77.6 ($\underline{C}$≡CH), 79.9 (C-4), 81.6 (C-2), 101.8 (CHO_2), 113.7 (aryl-*ortho* to OMe), 127.5 (aryl), 128.4 (aryl), 129.1 (aryl-*ipso* to CHO_2), 129.6 (aryl), 133.4 (aryl-*ipso* to SO_3), 145.3 (aryl-*ipso* to Me), 160.3 (aryl-*ipso* to OMe).

ν_{max}/cm^{-1} (neat solid): 3273, 2875 (C-H), 1616, 1522, 1364, 1258, 1173.

m/z (FAB+): 483 (MNa^+, 9%), 329 (27), 199 (19), 176 (100), 154 (20).

HRMS (FAB+): $C_{23}H_{24}O_8SNa$ (MNa^+) requires: 483.1872; found: 483.1877; error: 1.0 ppm.

3,7-Anhydro-1,3,4-trideoxy-6,8-*O*-(4-methoxybenzylidene)-D-*arabino*-oct-3-en-1-ynitol 187



Sodium azide (56 mg, 867 μmol) was added to a solution of epoxide **184** (50 mg, 173 μmol) in dry DMF (1.7 mL) and heated at 90 °C for 90 min. The mixture was diluted with EtOAc (10 mL), washed with H_2O (2 × 15 mL), brine (15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography (SiO_2, 20% EtOAc in petroleum ether) afforded the title compound **187** (23 mg, 49%) as a white solid.

mp 139-141 °C.

$[\alpha]_D^{22}$ = +3.2 (*c* 0.44 in $CHCl_3$).

to OMe), 136.8 (aryl-*ipso* to CHO_2), 160.3 (aryl-*ipso* to OMe).

^{1}H NMR (500 MHz, C_6D_6): δ 1.59 (1H, broad s, OH), 2.39 (1H, dd, *J* 0.8, 0.4 Hz, C≡CH), 3.24 (3H, s, OCH_3), 3.41 (1H, app. t, *J* 10.3 Hz, 1 of H-C(6)), 3.46 (1H, dd, *J* 10.1, 7.7 Hz, H-C(4)), 3.58 (1H, td, *J* 10.2, 5.3 Hz, H-C(5)), 4.05 (1H, dd, *J* 10.4, 5.3 Hz, 1 of H-C(6)), 4.15 (1H, broad d, *J* 6.5 Hz, H-C(3)), 5.17 (1H, s, H-C(2)), 5.17 (1H, s, CHO_2),‡‡‡ 6.80 (2H, d, *J* 8.9 Hz, aryl), 7.45 (2H, dd, *J* 8.9, 0.5 Hz, aryl).

^{13}C NMR (125 MHz, C_6D_6): δ 54.7 (OCH_3), 67.1 (C-3), 68.0 (C-6), 69.3 (C-5), 77.5 (C≡CH), 77.9 (C≡CH), 79.8 (C-4), 101.8 (CHO_2), 112.0 (C-2), 113.7 (aryl-*ortho* to OMe), 128.5 (aryl-*meta* to OMe), 130.4 (aryl-*ipso* to CHO_2), 160.6 (aryl-*ipso* to OMe).

In $CDCl_3$, the singlets corresponding to H-C(2) and CHO_2 could be seen as two distinct signals (but the H-C(4) and H-C(6) peaks became a multiplet at 3.84 ppm).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (1H, broad s, OH), 2.98 (1H, s, C≡CH), 3.75-3.84 (2H, m, H-C(4) and 1 of H-C(6)), 3.79 (3H, s, OCH_3), 3.95 (1H, td, *J* 10.2, 5.3 Hz, H-C(5)), 4.37 (1H, dd, *J* 10.6, 5.2 Hz, 1 of H-C(6)), 4.51 (1H, broad d, *J* 7.4 Hz, H-C(3)), 5.26 (1H, d, *J* 2.4 Hz, H-C(2)), 5.54 (1H, s, CHO_2), 6.88 (2H, d, *J* 8.8 Hz,

‡‡‡ This signal overlaps with the peak corresponding to H-C(2).

aryl), 7.40 (2H, d, *J* 8.7 Hz, aryl)

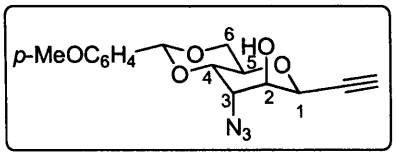
^{13}C NMR (125 MHz, $CDCl_3$): δ 55.3 (OCH_3), 66.9 (C-3), 68.1 (C-6), 68.9 (C-5), 77.0 (C≡CH), 77.6 (C≡CH), 79.7 (C-4), 101.8 (CHO_2), 110.9 (C-2), 113.7 (aryl- *ortho* to OMe), 127.5 (aryl-*meta*

ν_{max}/cm^{-1} ($CHCl_3$ cast): 3275 (O-H), 2924 (C-H), 1636, 1518.

m/z (CI+, CH_4): 289 (MH^+, 100%), 271 (88), 201 (40), 137 (35), 135 (37), 123 (44).

HRMS (CI+, CH_4): $C_{16}H_{16}O_5$ MH^+ requires: 289.1021; found: 289.1015; error: 2.0 ppm.

(3-Azido-3-deoxy-4,6-*O*-(4-methoxybenzylidene)-β-D-altropyranosyl)ethyne 186



Dry THF (2.0 mL) was added to ytterbium (III) triflate (43 mg, 80 μmol) and lithium isopropoxide (16 mg, 240 μmol), followed by epoxide **184** (77 mg, 267 μmol) and dry DCM (3.0 mL). Trimethylsilyl azide (71 μL, 534 μmol), was added and the mixture was heated at 45 °C for 15 h. The temperature was increased to 65 °C and heating continued for another 24 h. The reaction mixture was cooled to RT and further lithium isopropoxide (16 mg, 240 μmol), ytterbium (III) triflate (43 mg, 80 μmol) and trimethylsilyl azide (30 μL, 226 μmol) were added and heating at 65 °C was continued for a further 16 h. The mixture was cooled to RT and diluted with DCM (20 mL). 1M HCl (14 mL) was added, the layers separated and the organic material extracted with further DCM (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10%-20% EtOAc in petroleum ether) afforded the product **186** as a white solid (70 mg, 79%).

mp 134-136 °C.

$[\alpha]_D^{22} = -65.7$ (*c* 0.83 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.47 (1H, broad s, OH), 2.59 (1H, d, *J* 2.2 Hz, C≡CH), 3.75 (1H, t, *J* 10.3 Hz, 1 of H-C(6)), 3.78 (3H, s, OCH_3), 3.81 (1H, broad d, *J* 2.5 Hz, H-C(2)), 3.94 (1H, td, *J* 10.0, 5.1 Hz, H-C(5)), 4.14 (1H, dd, *J* 9.5, 3.2 Hz, H-C(4)), 4.20 (1H, t, *J* 3.3 Hz, H-C(3)), 4.29 (1H, dd, *J* 10.4, 5.0 Hz, 1 of H-C(6)), 4.58 (1H, t, *J* 1.7 Hz, H-C(1)), 5.52 (1H, s, CHO_2), 6.88 (2H, d, *J* 8.8 Hz, aryl), 7.35 (2H, d, *J* 8.8 Hz, aryl).

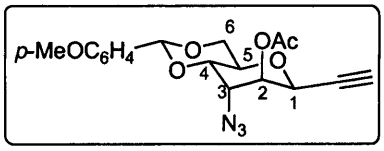
^{13}C NMR (125 MHz, $CDCl_3$): δ 55.3 (OCH_3), 59.8 (C-3), 67.3, 67.4 (C-1 and C-5), 68.6 (C-6), 71.1 (C-2), 75.7 (C-4), 76.3 (C≡CH), 78.2 (C≡CH), 102.3 (CHO_2), 113.7 (aryl-*ortho* to OMe), 127.4 (aryl-*meta* to OMe), 129.4 (aryl-*ipso* to CHO_2), 160.3 (aryl-*ipso* to OMe).

ν_{max}/cm^{-1} ($CHCl_3$ cast): 3437 (O-H), 2920 (C-H), 2114 (N≡N), 1616, 1518, 1385.

m/z (ESI+): 333 (25) 332 (MH^+, 100%), 267 (11), 233 (6), 169 (5).

HRMS (ESI+): $C_{16}H_{18}O_5N_3$ (MH^+) requires: 332.1247; found: 332.1241; error: 1.6 ppm.

(2-*O*-Acetyl-3-azido-3-deoxy-4,6-*O*-(4-methoxybenzylidene)-β-D-altropyranosyl)ethyne 188



To a solution of azide **186** (17.3 mg, 52 μmol) in dry pyridine (0.1 mL), were added acetic anhydride (10 μL, 104 μmol) and DMAP (1.3 mg, 10 μmol). The resulting solution was stirred at RT for 15 h. The reaction mixture was then diluted with DCM (5 mL) and washed with 1M HCl (8 mL), then sat. aq. $NaHCO_3$ (8 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 8% EtOAc in petroleum ether) afforded the product **188** as a white solid (19 mg, 99%). mp 138-140 °C.

$[\alpha]_D^{18} = -92.1$ (*c* 0.51 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19 (3H, s, CH_3CO), 2.48 (1H, d, *J* 2.2 Hz, C≡CH), 3.74-3.82 (1H, m, 1 of H-C(6)), 3.78 (3H, s, OCH_3), 3.99 (1H, td, *J* 9.6, 5.0 Hz, H-C(5)), 4.04 (1H, dd, *J* 9.5, 3.1 Hz, H-C(4)), 4.10 (1H, t, *J* 3.2 Hz, H-C(3)), 4.31 (1H, dd, *J* 10.6, 4.9 Hz, 1 of H-C(6)), 4.64 (1H, t, *J* 1.8 Hz, H-C(1)), 5.05 (1H, dd, *J* 3.4, 1.6 Hz, H-C(2)), 5.52 (1H, s, CHO_2), 6.87 (2H, d, *J* 8.8 Hz, aryl), 7.38 (2H, d, *J* 8.7 Hz, aryl).

^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7 (CH_3CO), 55.3 (OCH_3), 58.2 (C-3), 65.6 (C-1), 67.1 (C-5), 68.6 (C-6), 70.9 (C-2), 75.4 (C≡CH), 76.1 (C-4), 77.2 (C≡CH), 102.3 (CHO_2), 113.7 (aryl-*ortho* to OMe), 127.4 (aryl-*meta* to OMe), 129.2 (aryl-*ipso* to CHO_2), 160.3 (aryl-*ipso* to OMe), 169.5 (C=O).

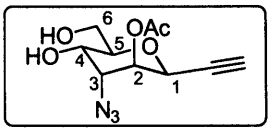
ν_{max}/cm^{-1} ($CHCl_3$ cast): 2928 (C-H), 2870 (C-H), 2125 (N≡N), 1749 (C=O), 1249,

1220.

m/z (FAB+): 375 (16%), 374 (MH^+, 13), 329 (74), 307 (53), 176 (100), 155 (86).

HRMS (FAB+): $C_{18}H_{20}O_6N_3$ (MH^+) requires: 374.1352; found: 374.1359; error: 2.0 ppm.

(2-*O*-Acetyl-3-azido-3-deoxy-β-D-altropyranosyl)ethyne 189



THF (0.7 mL), H_2O (2.1 mL) and acetic acid (4.1 mL) were added to acetate **188** (118 mg, 316 μmol) and the resultant mixture was heated to 45 °C for 4 h. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (15 mL), washed with sat. aq. $NaHCO_3$ (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 5% MeOH in DCM) gave the product **189** as a white solid (65 mg, 81%).

mp 118-120 °C.

$[\alpha]_D^{21} = -143.2$ (*c* 0.16 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (1H, broad s, HO-C(6)), 2.16 (3H, s, CH_3CO), 2.46 (1H, d, *J* 2.3 Hz, C≡CH), 2.53 (1H, broad d, *J* 6.3 Hz, HO-C(4)), 3.64-3.67 (1H, m, H-C(5)), 3.82-3.91 (2H, m, both of H-C(6)), 4.03-4.05 (2H, m, H-C(3) and H-C(4)), 4.60 (1H, t, *J* 1.9 Hz, H-C(1)), 5.08 (1H, dd, *J* 3.0, 1.6 Hz, H-C(2)).

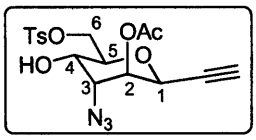
^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7 ($\underline{C}H_3C(O)$), 61.4, 64.8 (C-3 and C-4), 62.7 (C-6), 65.5 (C-1), 70.9 (C-2), 75.8 (C≡$\underline{C}$H), 77.2 ($\underline{C}$≡CH), 169.8 (C=O).

ν_{max}/cm^{-1} ($CHCl_3$ cast): 3410 (O-H), 2924 (C-H), 2114 (N≡N), 1744 (C=O), 1227, 1081.

§§§

§§§ Despite numerous attempts, it was not possible to obtain a mass spectrum of this compound.

(2-*O*-Acetyl-3-azido-3-deoxy-6-*O*-(4-toluenesulfonyl)-β-D-altropyranosyl)ethyne 190



p-Toluenesulfonyl chloride (73 mg, 382 μmol) was added to diol **189** (65 mg, 255 μmol), followed by dry pyridine (1.0 mL). The solution was stirred at RT for 25 h, after which time additional *p*-toluenesulfonyl chloride (24 mg, 126 μmol) was added, and the solution was stirred for a further 23 h. DCM (10 mL) was then added and the reaction mixture washed with 1M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*, followed by column chromatography (SiO_2, 30% EtOAc in petroleum ether) gave the product **190** as a white solid (70 mg, 67%).

mp 48-50 °C.

$[\alpha]_D^{22} = -55.0$ (*c* 0.40 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (3H, s, CH_3CO), 2.42 (1H, d, *J* 2.3 Hz, C≡CH), 2.43 (3H, s, CH_3-aryl), 2.90 (1H, broad s, OH), 3.73-3.76 (1H, m, H-C(5)), 4.02-4.08 (2H, m, H-C(3) and H-C(4)), 4.19 (1H, dd, *J* 11.6, 2.0 Hz, 1 of H-C(6)), 4.36 (1H, dd, *J* 11.6, 4.0 Hz, 1 of H-C(6)), 4.50 (1H, t, *J* 1.9 Hz, H-C(1)), 5.03 (1H, dd, *J* 3.1, 1.6 Hz, H-C(2)), 7.33 (2H, d, *J* 8.0 Hz, aryl), 7.78 (2H, d, *J* 8.3 Hz, aryl).

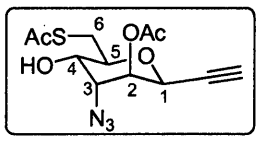
^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8 ($\underline{C}H_3CO$), 21.7 (CH_3-aryl), 61.2, 64.2 (C-3 and C-4), 65.1 (C-1), 68.9 (C-6), 70.8 (C-2), 74.4 (C-5), 75.2 (C≡$\underline{C}$H), 77.4 ($\underline{C}$≡CH), 128.0 (aryl), 130.0 (ary), 132.4 (aryl-*ipso* to SO_3), 145.3 (aryl-*ipso* to Me), 169.8 (C=O).

ν_{max}/cm^{-1} ($CHCl_3$ cast): 3447 (O-H), 2926 (C-H), 2116 (N≡N), 1747 (C=O), 1358, 1175.

m/z (CI+, CH_4): 410 (MH^+, 25%), 322 (40), 238 (100), 150 (98), 122 (51), 96 (74).

HRMS (CI+, CH_4): $C_{17}H_{20}O_7N_3S$ (MH^+) requires: 410.1022; found: 410.1029; error: 1.7 ppm.

(2-*O*-Acetyl-6-*S*-acetyl-3-azido-3-deoxy-6-thio-β-D-altropyranosyl)ethyne 191



Potassium thioacetate (36 mg, 312 μmol) was added to a solution of tosylate **190** (64

mg, 156 μmol) in dry DMF (1.5 mL). The solution was stirred for 17 h at RT, after which EtOAc was added (10 mL). The solution was washed with H_2O (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc in petroeum ether) gave the product **191** as a yellow oil (37 mg, 76%).

$[\alpha]_D^{20} = -70.3$ (*c* 0.31 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (3H, s, CH_3CO), 2.39 (3H, s, $CH_3C(O)S$), 2.43 (1H, d, *J* 2.3 Hz, C≡CH), 3.21 (1H, dd, *J* 14.9, 3.4 Hz, 1 of H-C(6)), 3.33 (1H, dd, *J* 14.9, 4.2 Hz, 1 of H-C(6)), 3.48 (1H, broad d, *J* 4.9 Hz, OH), 3.69-3.71 (1H, m, H-C(4)), 3.83 (1H, td, *J* 7.7, 3.8 Hz, H-C(5)), 4.02 (1H, t, *J* 3.5 Hz, H-C(3)), 4.54 (1H, t, *J* 1.8 Hz, H-C(1)), 5.01 (1H, dd, *J* 3.5, 1.5 Hz, H-C(2)).

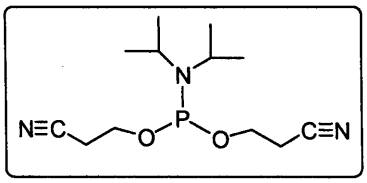
^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8 ($\underline{C}H_3C(O)$), 30.5 ($CH_3C(O)S$), 31.0 (C-6), 60.9, 66.3 (C-3 and C-4), 65.0 (C-1), 70.9 (C-2), 74.8 (C-5), 75.0 (C≡$\underline{C}$H), 77.7 ($\underline{C}$≡CH), 169.8 (C=O), 199.7 (SC=O).

ν_{max}/cm^{-1} ($CHCl_3$ cast): 3470 (O-H), 2924 (C-H), 2872 (C-H), 2112 (N≡N), 1747 (C=O), 1693 (SC=O), 1225, 1113.

m/z (CI+, CH_4): 314 (MH^+, 100%), 288 (35), 226 (47), 184 (75), 138 (89).

HRMS (CI+, CH_4): $C_{12}H_{16}O_5N_3S$ (MH^+) requires: 314.0811; found: 314.0805; error: 1.8 ppm.

Bis(2-cyanoethyloxy)(diisopropylamino)phosphane[113] 193



N-ethyldiisopropylamine (0.22 mL, 1.27 mmol) was added to 2-cyanoethyl diisopropylchlorophosphoramidite (0.19 mL, 0.85 mmol), then 3- hydroxypropionitrile (0.12 mL, 1.69 mmol) was added dropwise. The resulting suspension was stirred at RT for 6 h 30 min. DCM was added (5 mL), followed by sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the organic material was extracted with further DCM (2 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 75% Et_2O in petroleum ether) gave the product **193** as a colourless oil (229 mg, quantitative).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (12H, d, *J* 6.8 Hz, $NCH(C\underline{H}_3)_2$), 2.64 (4H, t, *J* 6.3

Hz, 2 × $CH_2C{\equiv}N$), 3.78-3.82 (2H, m, CH_2O), 3.86-3.90 (2H, m, CH_2O).

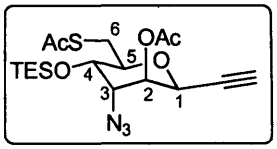
^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4 ($\underline{C}H_2C{\equiv}N$), 24.6 ($NCH(\underline{C}H_3)_2$), 43.2, 43.3 ($N\underline{C}H(CH_3)_2$), 58.4, 58.5 ($CH_2O$), 117.8 (C≡N).

ν_{max}/cm^{-1} (film): 2970 (C-H), 2934 (C-H), 2883 (C-H), 2253 (C≡N), 1464, 1365, 1182.

m/z (CI+, CH_4): 272 (MH^+, 100%), 256 (12), 201 (46), 171 (12).

HRMS (CI+, CH_4): $C_{12}H_{23}O_2N_3P$ (MH^+) requires: 272.1528; found: 272.1533; error: 1.8 ppm.

(2-*O*-Acetyl-6-*S*-acetyl-3-azido-3-deoxy-6-thio-4-*O*-(triethylsilanyl)-β-D-altropyranosyl)ethyne 198



Alcohol **191** (11.5mg, 36.7 μmol) was dissolved in dry pyridine (0.2 mL) and cooled to 0 °C in an ice-bath. TESCl (32 μL, 185 μmol) was added dropwise and the resulting suspension was stirred for 2h 30 min at 0 °C. Further TESCl (50 μL, 289 μL) was then added and the mixture stirred at RT for 18 h, and then at 35-40 °C for a further 1 h. Petroleum ether (5 mL) was added and the solution washed with 1M HCl (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, 5% EtOAc in petroleum ether) afforded the product **198** as a pale yellow oil (13 mg, 82%).

$[\alpha]_D^{15}$ = +33.0 (*c* 0.45 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.64-0.69 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.99 (9H, t, *J* 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 2.15 (3H, s, CH_3CO), 2.33 (3H, s, $CH_3C(O)S$), 2.42 (1H, d, *J* 2.2 Hz, C≡CH), 2.75 (1H, dd, *J* 13.6, 9.5 Hz, 1 of H-C(6)), 3.60 (1H, dd, *J* 13.6, 2.7 Hz, 1 of H-C(6)), 3.72 (1H, td, *J* 9.3, 2.7 Hz, H-C(5)), 3.85-3.86 (1H, broad m, H-C(4)), 3.87 (1H, t, *J* 3.3 Hz, H-C(3)),**** 4.50 (1H, t, *J* 1.9 Hz, H-C(1)), 4.98 (1H, dd, *J* 3.3, 1.6 Hz, H-C(2)).

^{13}C NMR (125 MHz, $CDCl_3$): δ 4.8 ($Si(\underline{C}H_2CH_3)_3$), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 20.7 ($\underline{C}H_3C(O)$), 30.5 ($\underline{C}H_3C(O)S$), 31.2 (C-6), 61.6 (C-4), 64.9 (C-1), 70.0 (C-3), 71.4 (C-2), 75.0 (C-5), 76.0 (C≡$\underline{C}$H), 77.6 ($\underline{C}{\equiv}CH$), 169.7 (C=O), 195.0 (SC=O).

ν_{max}/cm^{-1} ($CHCl_3$ cast): 2955 (C-H), 2912 (C-H), 2880 (C-H), 2112 (N≡N), 1753

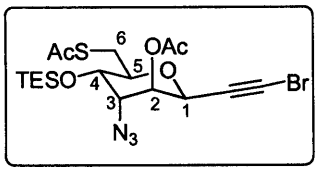
**** There is some overlap with the H-C(4) proton

(C=O), 1693 (SC=O), 1225, 1123.

m/z (FAB+): 428 (MH^+, 30%), 398 (15), 307 (44), 154 (100).

HRMS (FAB+): $C_{18}H_{30}O_5N_3SSi$ (MH^+) requires: 428.1675; found: 428.1682; error: 1.5 ppm.

1-(2-*O*-Acetyl-6-*S*-acetyl-3-azido-3-deoxy-6-thio-4-*O*-(triethylsilanyl)-β-D-altropyranosyl)-2-bromoethyne 199



Silver nitrate (1.7 mg, 10.3 μmol) and *N*-bromosuccinimide (7.0 mg, 38.6 μmol) were added to alkyne **198** (11 mg, 25.7 μmol), followed by dry acetone (1.0 mL). The reaction mixture was stirred at RT for 16 h, diluted with Et_2O (15 mL) and filtered through Celite®. The filtrate was concentrated *in vacuo* and the residue was redissolved in Et_2O (20 mL), washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc in petroleum ether) gavethe product **199** as a pale yellow oil (9.5 mg, 73%).

$[\alpha]_D^{18} = +5.1$ (*c* 0.28 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.62-0.68 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.99 (9H, t, *J* 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 2.16 (3H, s, CH_3CO), 2.33 (3H, s, $CH_3C(O)S$), 2.74 (1H, dd, *J* 13.6, 9.5 Hz, 1 of H-C(6)), 3.60 (1H, dd, *J* 13.6, 2.7 Hz, 1 of H-C(6)), 3.71 (1H, td, *J* 9.2, 2.6 Hz, H-C(5)), 3.83-3.87 (2H, m, H-C(3) and H-C(4)), 4.52 (1H, d, *J* 1.4 Hz, H-C(1)), 4.94 (1H, dd, *J* 3.1, 1.5 Hz, H-C(2)).

^{13}C NMR (125 MHz, $CDCl_3$): δ 4.8 ($Si(\underline{C}H_2CH_3)_3$), 6.7 ($Si(CH_2\underline{C}H_3)_3$), 20.7 ($\underline{C}H_3CO$), 30.5 ($\underline{C}H_3C(O)S$), 31.2 (C-6), 47.8 ($C\equiv\underline{C}Br$), 61.6 (C-4), 65.9 (C-1), 70.0 (C-3), 71.5 (C-2), 74.2 ($\underline{C}\equiv CBr$), 76.0 (C-5), 169.7 (C=O), 195.0 (SC=O).

ν_{max}/cm^{-1} ($CHCl_3$ cast): 2947 (C-H), 2932 (C-H), 2110 (N≡N), 1755 (C=O), 1693 (SC=O), 1221, 1084.

m/z (FAB+): 508 (MH^+ (^{81}Br) 65%), 506 (MH^+ (^{79}Br) 60), 293 (36), 273 (45), 257 (52), 152 (100).

HRMS (FAB+): $C_{18}H_{29}O_5N_3SSi^{79}Br$ (MH^+) requires: 506.0781; found: 506.0771; error: 1.9 ppm.

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APPENDIX

HPLC Data

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate **96a**
-after column
-recrystallised

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate **96b**
-after column
-recrystallised

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate **97a**
-after column
-recrystallised

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate **97b**
-after column
-recrystallised

HPLC Data

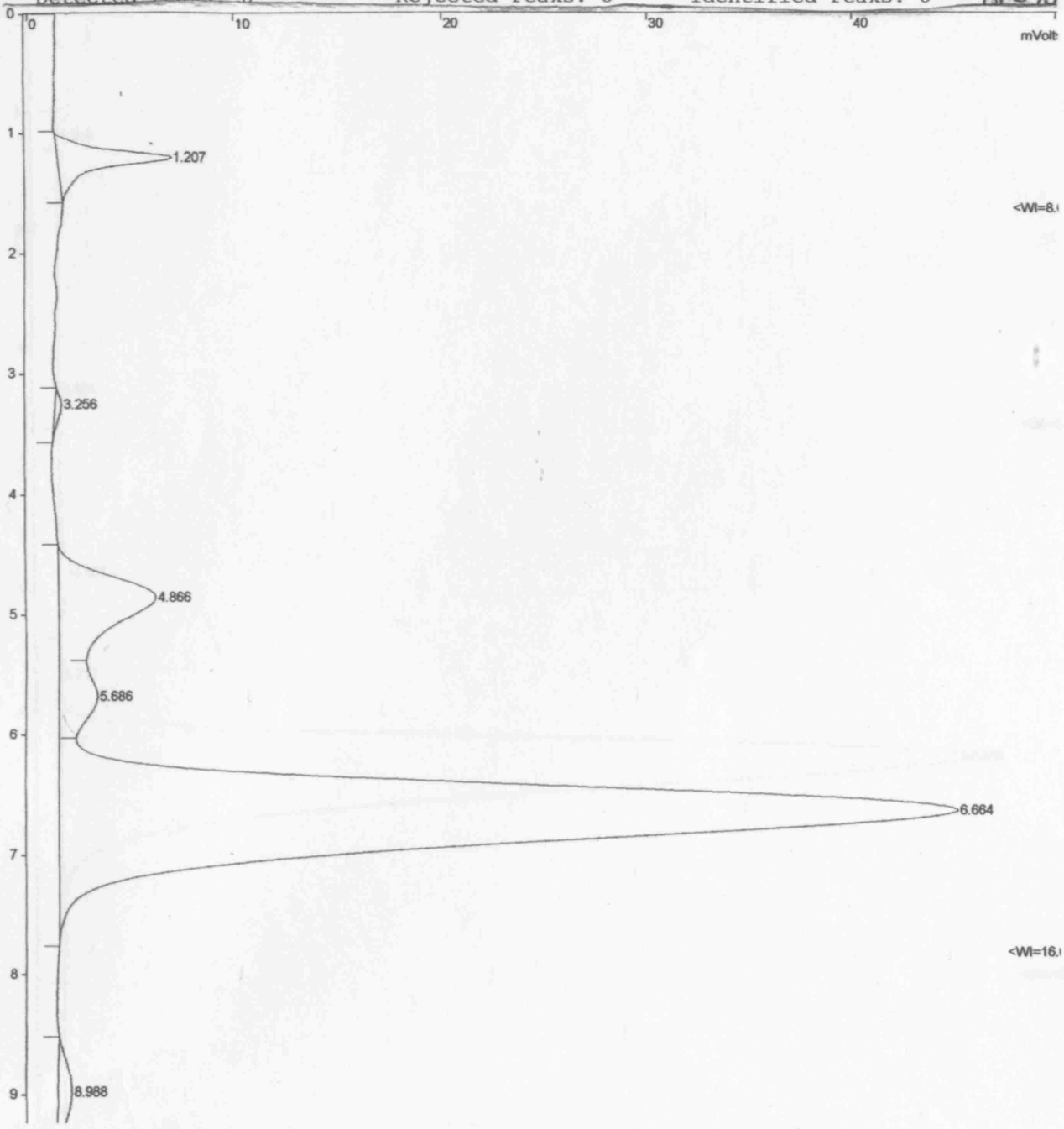
Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate **96a** (after column)

```
Operator    : Amandeep                  Detector Type: ProStar/Dynamax (2 Volts)
Workstation:                            Bus Address  : 24
Instrument : 218 System                 Sample Rate  : 5.00 Hz
Channel    : 1 = UV                     Run Time     : 9.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode          : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		3.3425	1.207	0.000	56414	BB	8.2	
2		0.2381	3.256	0.000	4018	BB	10.1	
3		8.4087	4.866	0.000	141922	BV	27.4	←
4		3.4523	5.686	0.000	58269	VV	43.8	
5		83.1518	6.664	0.000	1403437	VB	29.7	←
6		1.4067	8.988	0.000	23742	BB	32.7	
	Totals:	100.0001		0.000	1687802			

$$\frac{1403437 - 141922}{1403437 + 141922} \times 100 = 81.6\%$$

```
Total Unidentified Counts :    1687801 counts

Detected Peaks: 6          Rejected Peaks: 0          Identified Peaks: 0
```



HPLC Data

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate **96a** (recrystallised)

Operator : Amandeep
Workstation:
Instrument : 218 System
Channel : 1 = UV

Detector Type: ProStar/DynaMax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 9.980 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

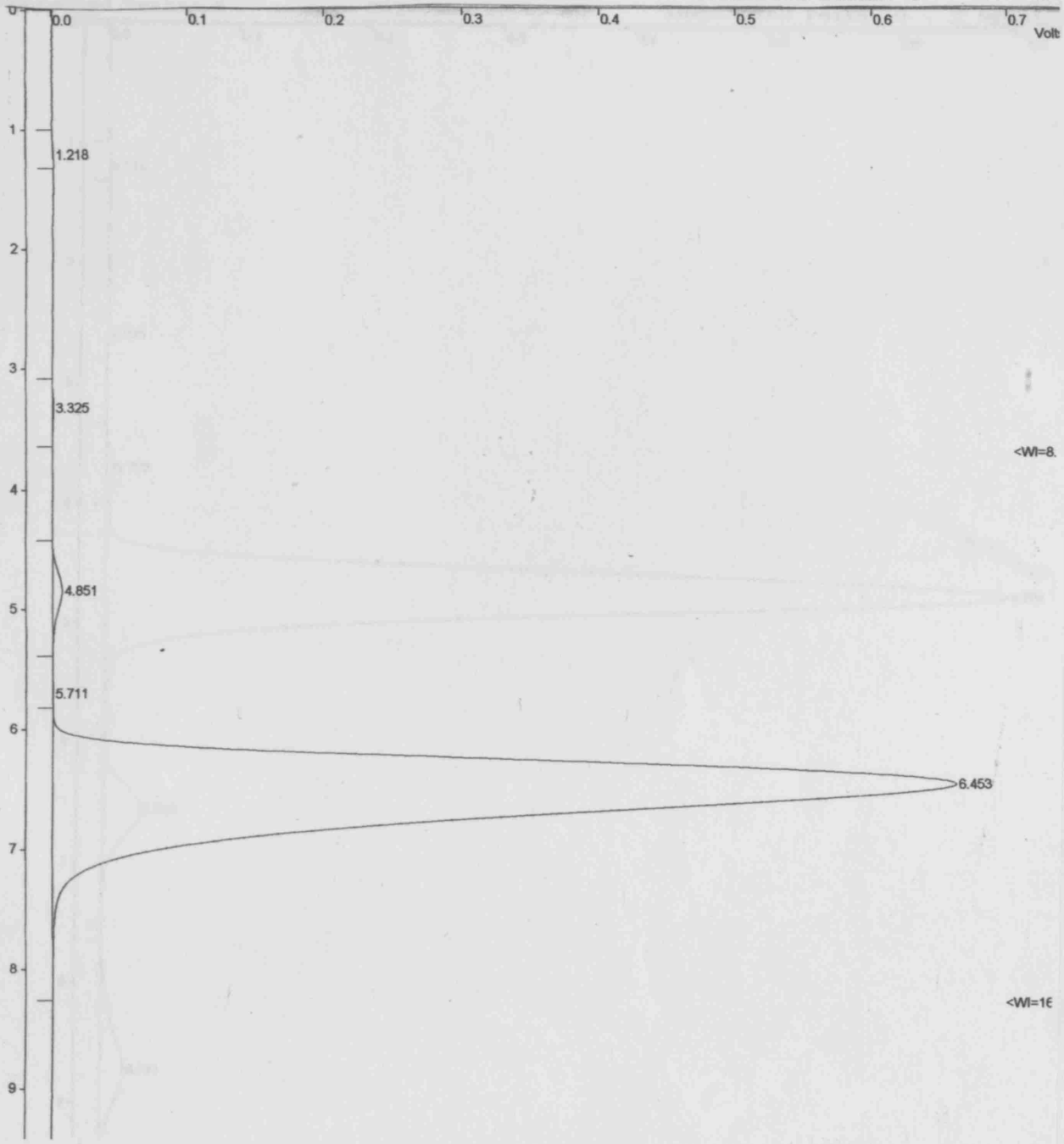
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.0248	1.218	0.000	5187	BB	0.0	
2		0.0715	3.325	0.000	14934	BB	16.5	
3		0.8047	4.851	0.000	168187	BV	0.0 ←	
4		0.0056	5.711	0.000	1180	TS	0.0	
5		99.0934	6.453	0.000	20710786	VB	28.8 ←	
	Totals:	100.0000		0.000	20900274			

Total Unidentified Counts : 20900274 counts

$\frac{20710786-168187}{20710786+168187} \times 100 = 98.4\%$

Detected Peaks: 5 Rejected Peaks: 0 Identified Peaks: 0



HPLC Data

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate **96b** (after column)

Operator : Amandeep
Workstation:
Instrument : 218 System
Channel : 1 = UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 9.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

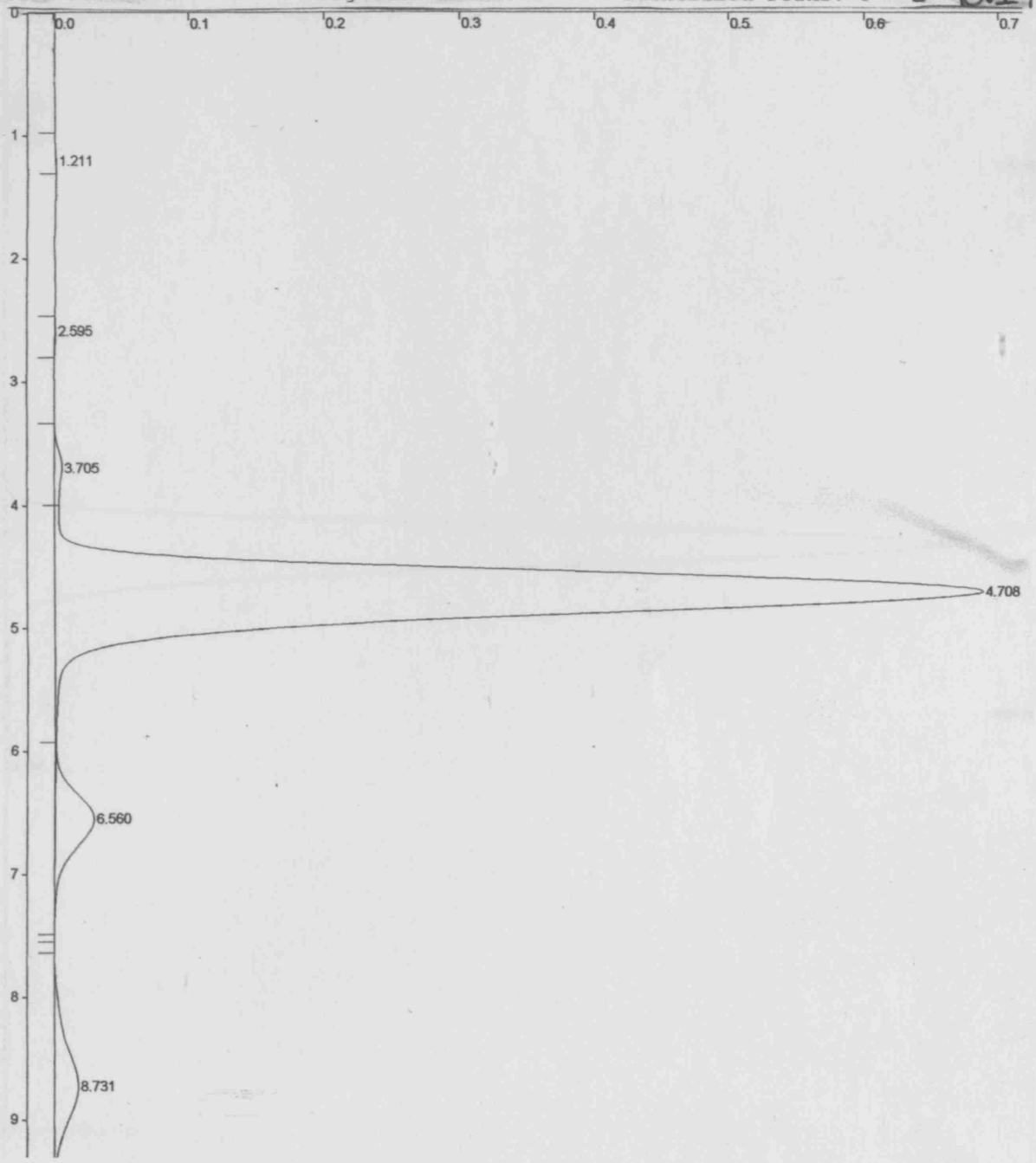
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.0316	1.211	0.000	5925	BB	0.0	
2		0.0312	2.595	0.000	5848	BB	8.5	
3		0.6768	3.705	0.000	126800	BV	18.2	
4		90.2682	4.708	0.000	16912656	VB	22.7 ←	
5		4.7166	6.560	0.000	883702	TS	0.0 ←	
6		4.2755	8.731	0.000	801066	BB	39.8	
	Totals:	99.9999		0.000	18735997			

$\frac{16912656 - 883702}{16912656 + 883702} \times 100 = 90.1\%$

Total Unidentified Counts : 18735996 counts

Detected Peaks: 6 Rejected Peaks: 0 Identified Peaks: 0



HPLC Data

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxybenzoyloxy)butanoate **96b** (recrystallised)

Operator : Amandeep
Workstation:
Instrument : 218 System
Channel : 1 = UV
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 9.987 min

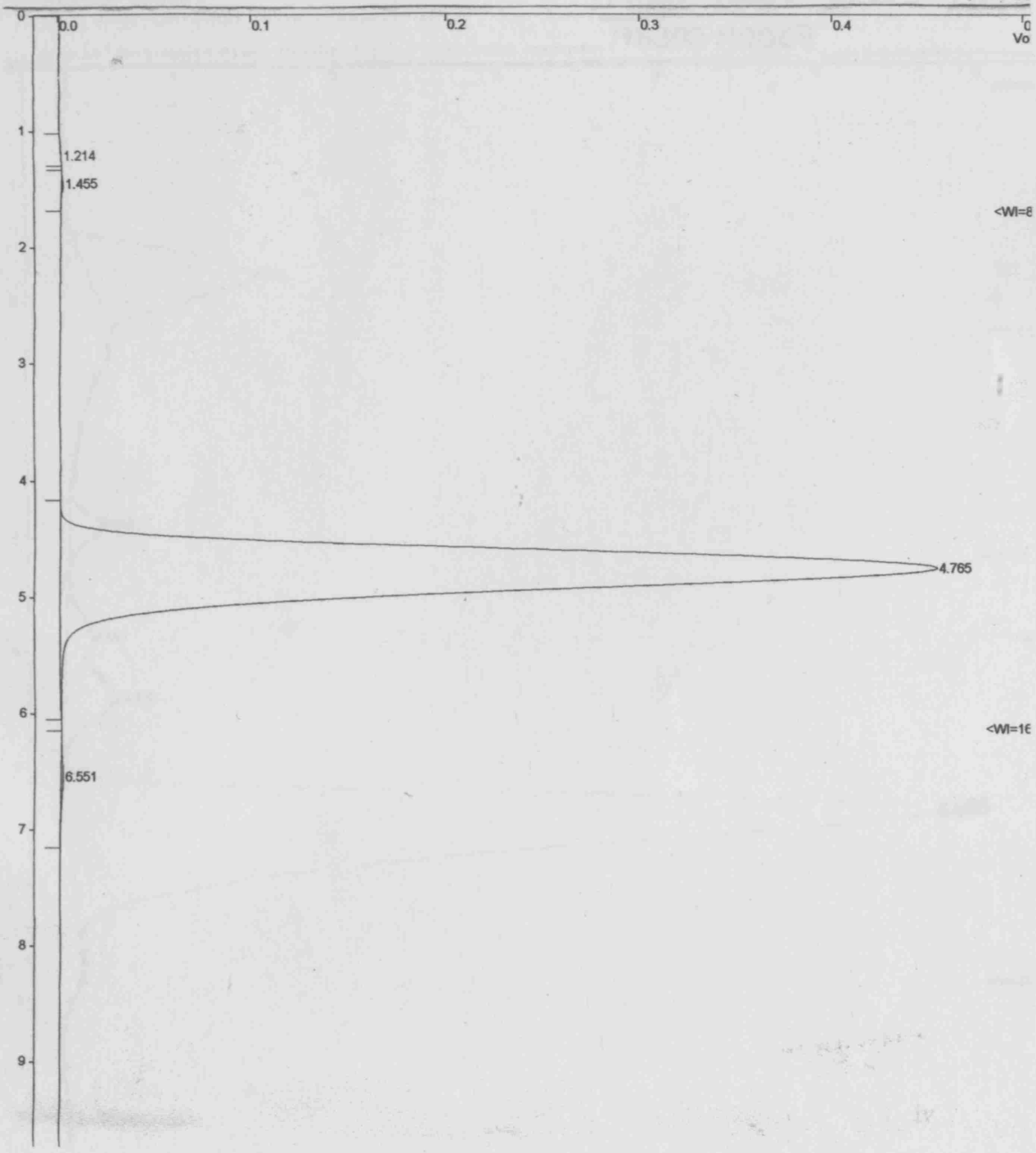
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.0449	1.214	0.000	4863	BB	0.0	
2		0.0560	1.455	0.000	6071	BB	7.9	
3		99.6272	4.765	0.000	10800454	BB	22.2 ←	
4		0.2719	6.551	0.000	29481	BB	24.3 ←	
	Totals:	100.0000		0.000	10840869			

Total Unidentified Counts : 10840869 counts

$$\frac{10800454 - 29481}{10800454 + 29481} \times 100 = 99.5$$



HPLC Data

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate 97a (after column)

Operator : Amandeep
Workstation:
Instrument : 218 System
Channel : 1 - UV
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 9.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

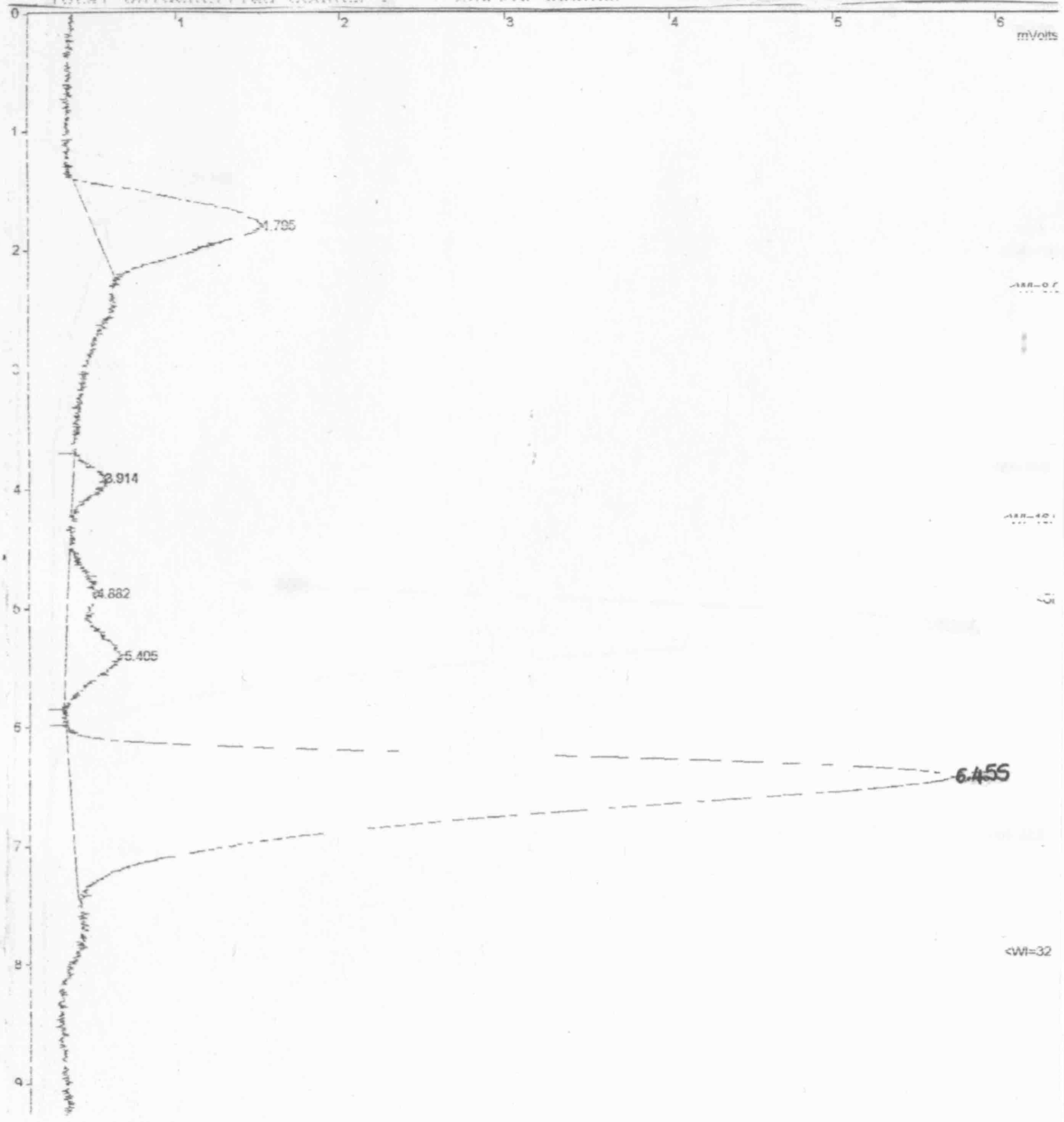
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result (%)	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		13.0629	1.795	0.000	29260	BB	33.7	
2		1.5161	3.914	0.000	3400	BB	14.2	
3		1.3514	4.882	0.000	3027	BV	8.0	U
4		4.4677	**5.405**	0.000	**10007**	VB	22.6	U ←
5		79.6000	**6.453**	0.000	**178300**	BB	31.0	U ←
	Totals:	100.0001		0.000	223994			

Status Codes:
U - User-defined peak endpoint(s)

$$\frac{178300 - 10007}{178300 + 10007} \times 100 = 7899$$

Total Unidentified Counts : 223995 counts



HPLC Data

Ethyl (2*S*,3*R*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate **97a** (recrystallised)

Operator : Amandeep
Workstation:
Instrument : 218 System
Channel : 1 - UV
Detector Type: ProStar/Dynamax (2 volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 9.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

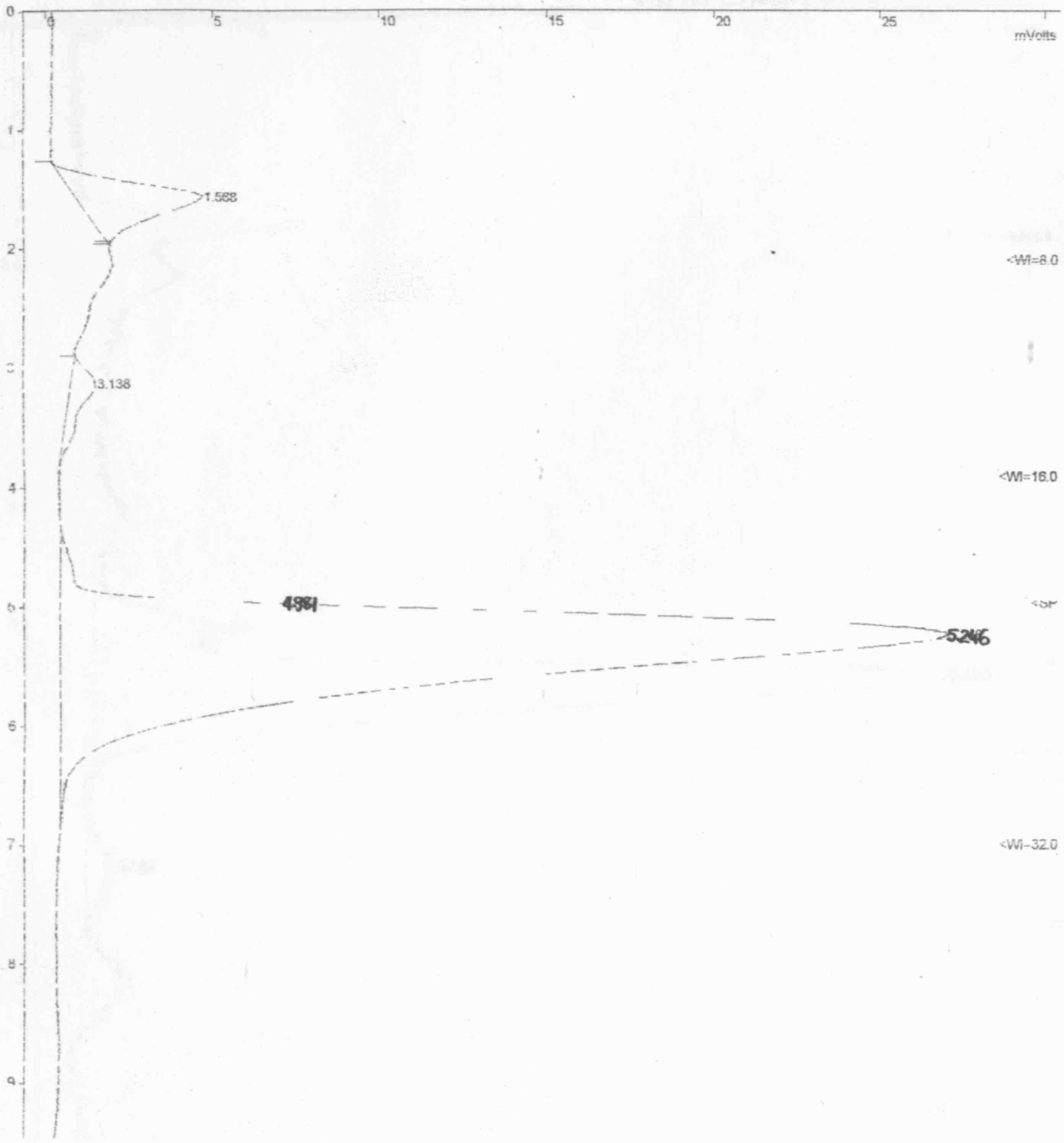
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result (%)	Rel. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		6.6242	1.568	0.000	71678	BV	23.9	
2		1.7779	3.138	0.000	19234	BB	10.3	
3		2.7965	4.981	0.000	30152	BV	9.0 ←	
4		88.8117	5.246	0.000	961002	VB	33.7 ←	
	Totals:	100.0000		0.000	1082066			

Total Unidentified Counts : 1082067 counts

$\frac{961002 - 30152}{961002 + 30152} \times 100 = > 93.9$

Detected Peaks: 5 Rejected Peaks: 1 Identified Peaks: 0



HPLC Data

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate 97b (after column)

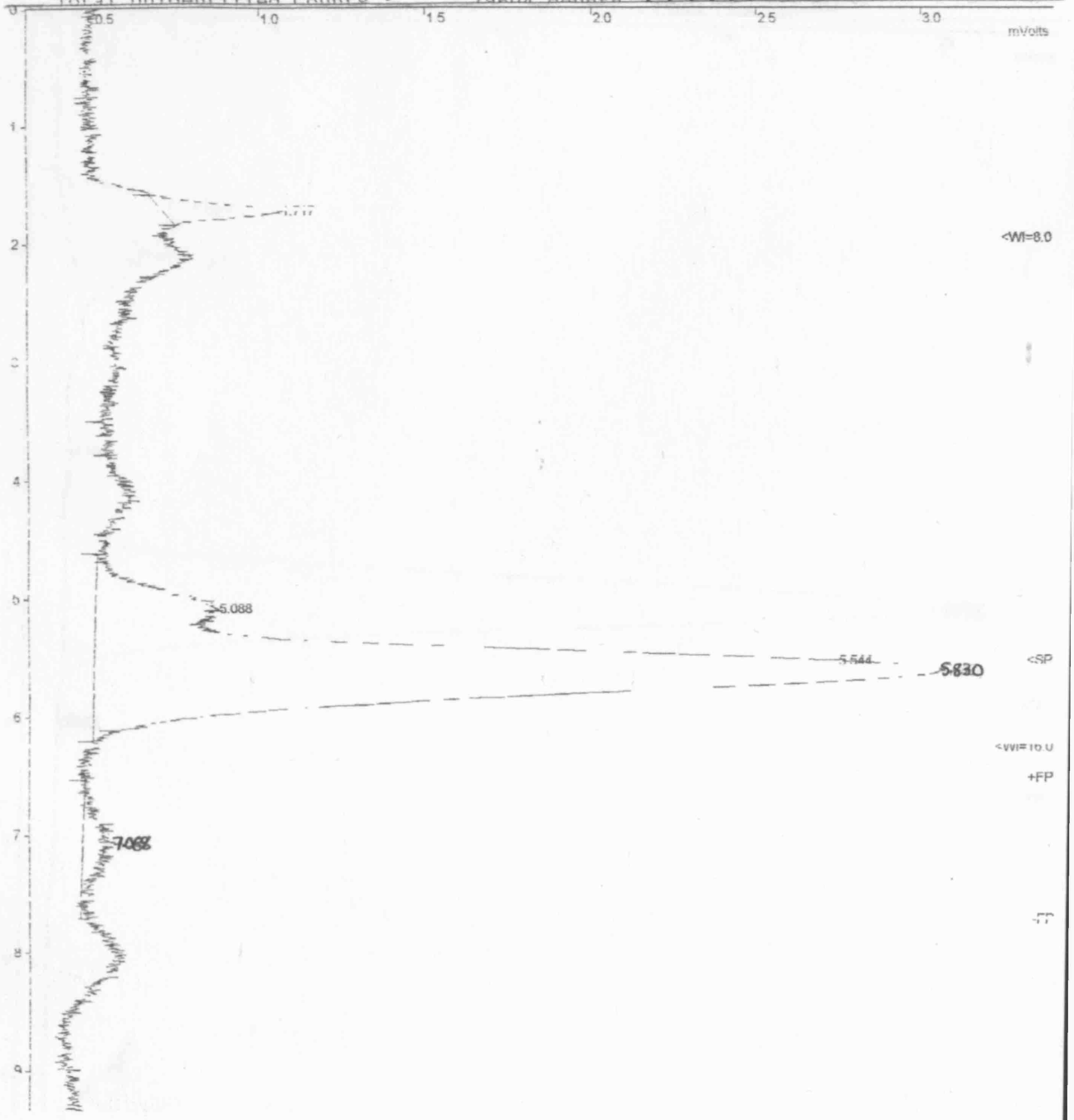
```
Operator    : Amandeep                  Detector Type: ProStar/Dynamax (2 Volts)
Workstation:                            Bus Address  : 24
Instrument : 218 System                 Sample Rate  : 5.00 Hz
Channel    : 1 - UV                     Run Time     : 9.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode          : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result (%)	Rel. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		3.5031	1.717	0.000	2789	BB	7.8	
2		3.0720	2.088	0.000	4073	BV	11.9	U
3		27.3949	5.544	0.000	21799	VV	8.0	U
4		60.2722	5.630	0.000	47979	VB	23.0	U ←
5		3.1678	7.068	0.000	2522	BB	4.9	←
	Totals:	100.0000		0.000	79604			

Status Codes:
U - User-defined peak endpoint(s)

$$\frac{47979-2522}{47979+2522} \times 100 = >90\%$$

Total Unidentified Counts : 79604 counts



HPLC Data

Ethyl (2*R*,3*S*)-3-acetamido-2-hydroxy-4-(4-methoxyphenoxy)butanoate **97b** (recrystallised)

Operator : Administrator — Detector Type: ProStar/Dynamax (2 Volts)
Workstation:
Instrument : 218 System — Bus Address : 24
Channel : 1 - UV — Sample Rate : 5.00 Hz
Run Time : 9.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result (%)	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		9.4016	1.624	0.000	66133	BV	18.2	
2		2.5005	2.048	0.000	17594	VV	6.0	
3		2.6012	2.101	0.000	18299	VB	46.2	
4		2.6247	3.683	0.000	18463	BV	2.6	U
5		82.6964	4.898	0.000	581712	BB	28.2	U ←
6		0.2956	5.982	0.000	2081	BB	0.5	←
	Totals:	100.0000		0.000	703431			

Status Codes:
U - User-defined peak endpoint(s)

$$\frac{581712-2081}{581712+2081} \times 100 = 99.3\%$$