Novel Rearrangement of Sulfur Ylides and Application to the Synthesis of Tagetitoxin

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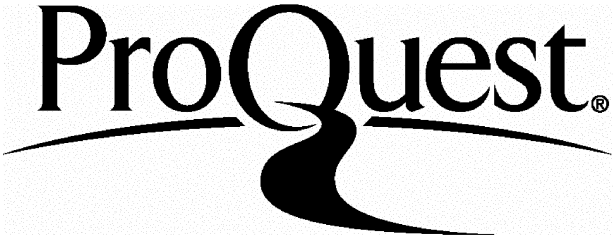

ABSTRACT

This thesis presents the work undertaken towards the total synthesis of tagetitoxin. This phytotoxin was isolated in 1981 from a strain of *Pseudomonas syringae* bacteria, and was shown to specifically inhibit eukaryotic RNA polymerase III from a broad phylogenetic range. A structure has been proposed for tagetitoxin as a highly functionalised 9-oxa-3-thiabicyclo[3.3.1]nonane, but some ambiguity still remains over its absolute configuration and the position of carbonyl substituents. A synthetic route would allow to confirm or revise the proposed structure, provide a possible entry to analogues and increase supplies of the toxin for biological studies on transcription mechanism.

A novel one-carbon ring expansion of 1,3-oxathiolanes was developed in view of constructing the core structure of tagetitoxin. A series of model substrates were successfully converted to the corresponding 1,4-oxathianes using ethyl (triethylsilanyl)diazoacetate and a copper catalyst. The reaction is expected to occur *via* an intermediate sulfur ylide, which rearranges to give the ring-expanded product. This methodology will be applied to a fully functionalised bicyclic precursor to assemble the tagetitoxin frame.

Synthetic studies are described towards the synthesis of the precursor. An aldol reaction between methyl 1,3-oxathiolane-5-carboxylate and a protected 2-azido-3,4-dihydroxybutanal was envisaged to form a functionalised branched 5-mercaptomethyl-5-hydroxypentanal. Intramolecular thioacetal formation would give the fully substituted bicyclic substrate for ring-expansion.

Three approaches to the azidoaldehyde fragment were carried out, which were based on regioselective azide opening of chiral epoxyalcohols. The methyl 1,3-oxathiolane-5-carboxylate fragment was derived from L-serine, using a one pot cyclisation / sulfur deprotection reaction. Model reactions however showed that the enolate of the 1,3-oxathiolane ester was not stable under aldol conditions, possibly due to β-elimination of the sulfur.

A ma famille

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[O]: oxidation
A: adenine
abs.: absolute
acac: acetylacetonate
Ad: adamantyl
AD: asymmetric dihydroxylation
addn.: addition
Alloc: allyloxycarbonyl
anh.: anhydrous
aq.: aqueous
Ar: aromatic
B: Lewis base
BHT: 2,6-di-*tert*-butyl-4-methylphenyl
Bn: benzyl
Boc: *tert*-butyloxycarbonyl
BOM: benzyloxymethyl
C: cytosine
cap: caprolactamate
cat.: catalyst/catalytic
CIP: Cahn-Ingold-Prelog
DAHP: dihydroxyacetone phosphate
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE: dichloroethane
DCM: dichloromethane
DDQ: dichlorodicyanoquinone
de: diastereoisomeric excess
DEAD: diethylazodicarboxylate
DET: diethyl tartrate
DHP: dihydropyran2-yl
DIBAL: diisobutylaluminium hydride
DIPEA: ethyldiisopropylamine
DMAD: dimethylacetylenedicarboxylate
DMAP: dimethylaminopyridine
DMF: *N,N*-dimethylformamide
DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO: dimethylsulfoxide
DNA: deoxyribonucleic acid
DOSP: *N*-(*p*-dodecylphenylsulfonyl) prolinate
E.Coli: Escherichia Coli
EDG: electron-donating group
ee: enantiomeric excess
EWG: electron-withdrawing group
FAB: Fast Atom Bombardment
G: guanine
hfacac: hexafluoroacetylacetonate
HMPA: hexamethylphosphoramide
ibid.: ibidem
IC_{50}: inhibitory concentration
imid.: imidazole
L: ligand
LA: Lewis Acid
LDA: lithium *N,N*-diisopropylamide
LG: leaving group
M: molar/metal
***m*-CPBA**: *m*-chloroperbenzoic acid
MEOX: methyl 2-oxazolidinone-4-carboxylate
MEPY: methyl pyrrolidone-5-carboxylate
MMTr: monomethoxytrityl, or monomethoxytriphenylmethyl
MPPIM: 4-methyl 1-(3-phenyl propanoyl)-2-oxyimidazolidinyl-4-carboxylate
mRNA: messenger RNA
MS: Mass Spectrometry
Ms: mesyl
NMI: *N*-methylimidazole
NMR: Nuclear Magnetic Resonance
NOE: Nuclear Overhauser Effect
Nps: (2-nitrophenyl)sulfenyl
Nu: nucleophile
o/n: overnight

oct: octane
P: protecting group
pfb: perfluorobuyrate
phtal-: phtalimido
P_i: inorganic phosphate
PMB: *p*-methoxybenzyl
Pol: polymerase
PP_i: pyrophosphate
py.: pyridine
quant.: quantitative
Red-Al: sodium bis(2-methoxyethoxy) aluminium hydride
RNA: Ribonucleic acid
rRNA: ribosomal RNA
rt: room temperature
s: second/singlet
SAE: Sharpless Asymmetric Epoxidation
sat.: saturated
SM: starting material
T: thymine
TAS-F: tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBACl: tetra-*n*-butylammonium chloride
TBAF: tetra-*n*-butylammonium fluoride
TBDMS/TBS: *tert*-butyldimethylsilyl
TBDPS: *tert*-butyldiphenylsilyl
TBHP: *tert*-butylhydroperoxide
TEMPO: 2,2,6,6-tetramethyl piperidinyloxyl
TES: triethylsilyl
TF: transcription factor
Tf: triflic; trifluoromethanesulfonic
THF: tetrahydrofuran
THP: tetrahydropyran-2-yl
TMS: trimethylsilyl
Tr: trityl, triphenylmethyl
tRNA: transfer RNA
Troc: 2,2,2-trichloroethoxycarbonyl
Ts or ***p*-Ts**: tosyl; *p*-toluenesulfonic
U: uracil
UTP: uraciltriphosphate

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I Introduction

I-1 Protein synthesis

I-1.1 General overview[1,2]

The nature of a living organism is determined by its genes. The information contained in these genes varies between different organisms, as well as between the different genes of a same organism. Gene expression is the sequence of processes by which the genetic information is used to produce macromolecules, including proteins, which will in turn constitute a unique organism. The first step in the process of protein synthesis is known as DNA transcription and occurs in the cell nucleus. A portion of DNA constituting a gene is used as a template to synthesise the corresponding RNA molecule. Although RNA has properties of its own within the cell, some of it is translated into a protein in a set of reactions that occur on a ribosome: this is the second and final step in protein synthesis, known as RNA translation (**Figure 1**[3]).

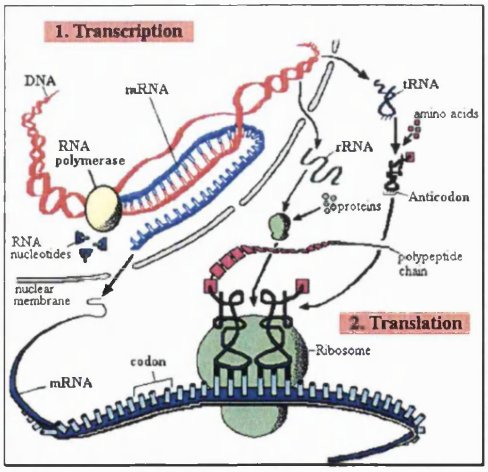


Figure 1: Protein synthesis

[1] Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J.D. *Molecular Biology of the Cell*, 4th ed., Garland Publishing Inc., **2002**, Ch. 6.
[2] White, R. J. *Gene Transcription, Mechanism and Control*, Blackwell Science Ltd.; **2001**, Ch 1.
[3] Reproduced by permission of Access Excellence @ the National Health Museum. Copyright 1999. All rights reserved.

Protein synthesis can thus be summarised by the sequence:

$$\textbf{DNA} \xrightarrow{\text{transcription}} \textbf{RNA} \xrightarrow{\text{translation}} \textbf{PROTEIN}.$$

DNA is a linear polymer made of four different deoxyribonucleotides *via* phosphodiester linkages between the 5' carbon of one deoxyribose group and the 3' carbon of the next. The nucleotides contain the nucleic bases adenine (A), guanine (G), cytosine (C) and thymine (T) (**Figure 2**).

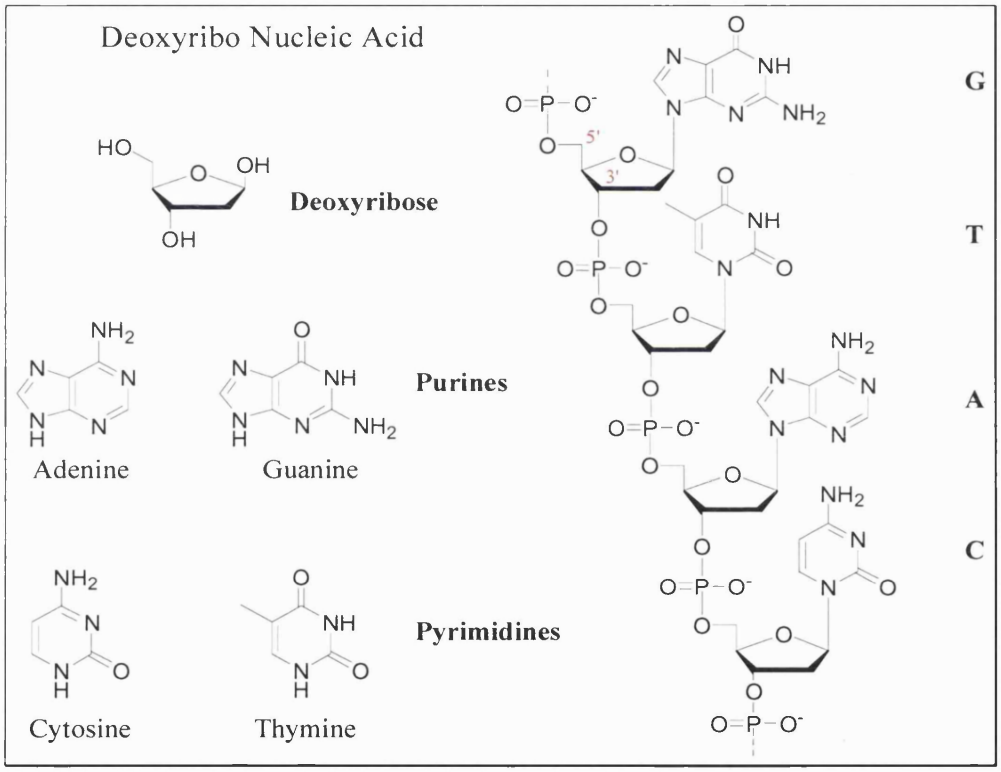


Figure 2: The building blocks of DNA and structure of a DNA strand

Nuclear DNA exists as a double-stranded helix, each polymeric chain being associated to a complementary chain of the same size orientated in the opposite direction. This pairing results from hydrogen bonds between A and T on the one hand, and C and G on the other, which are called Watson-Crick interactions (**Figure 3**).

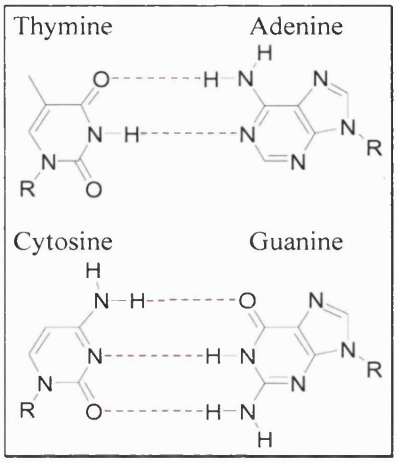


Figure 3: The Watson-Crick base pairs

Like DNA, the RNA polymer is made of a sugar phosphate backbone bearing nucleic bases, however there are chemical and structural differences between the two (**Figure 4**). Base pairing between strands is similar to that in DNA, except that adenine pairs with uracil (U) instead of thymine, which is exclusively used in DNA. The A-U pair, like the A-T pair, has two hydrogen bonds. The RNA backbone is composed of alternating ribose sugars and phosphate groups. Unlike the 2'-deoxyribose used in DNA, ribose has a hydroxyl group attached to the 2' carbon. This "extra" hydroxyl group influences the secondary structure. Although cellular RNA is almost always single-stranded, the RNA chains can take a variety of shapes, allowing for some RNA molecules to have catalytic or structural functions.

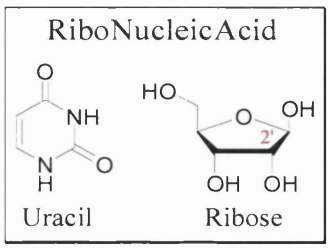


Figure 4: Structures of uracil and ribose, as found in RNA

RNA molecules exist in several types, each having a specific function in the synthesis of proteins:

- messenger RNA (mRNA) is the product of DNA transcription which carries the information for protein synthesis,
- transfer RNA (tRNA) is attached to the amino-acids which will be used to synthesise the protein and "reads" the mRNA sequence,
- ribosomal RNA (rRNA) is the main constituent of ribosomes, which catalyse protein synthesis,
- other types of RNA have catalytic or structural functions.

I-1.2 DNA transcription[4]

RNA synthesis by DNA transcription requires RNA polymerase enzymes. These enzymes are similar in overall structure in both prokaryotes and eukaryotes.

Transcription proceeds in three different phases:

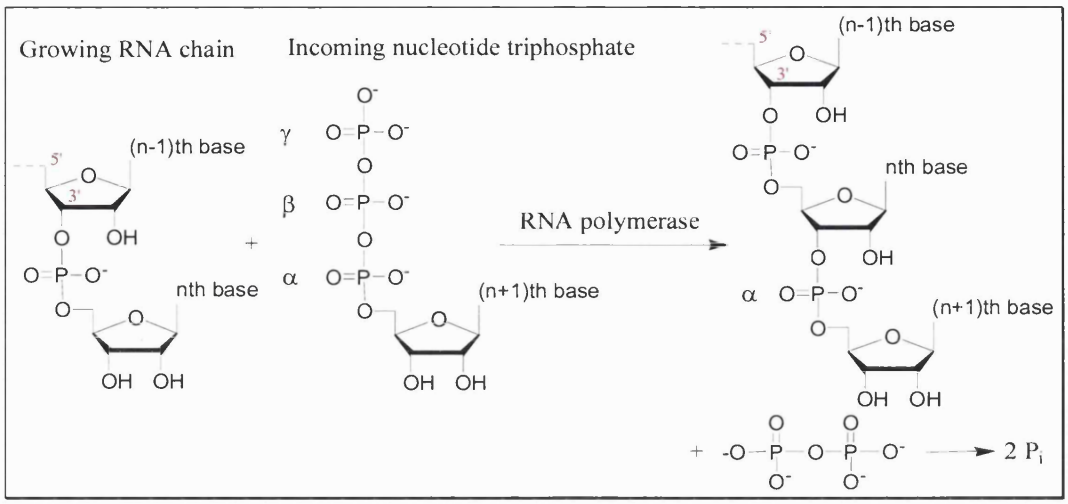
- **initiation** (binding of RNA polymerase to template DNA),
- **elongation** (formation of the polynucleotide),
- **termination** (release of the enzyme and RNA from the DNA template).

Random collisions between RNA polymerase and DNA lead to **initiation** if they occur at a specific region on the DNA called the promoter. This region contains sequence elements that can fit in one or more sites on the RNA polymerase.

[4] Szekely, M. *From DNA to protein*, Macmillan Press Ltd.; **1980**, Ch.3.

In the somewhat simpler case of bacterial RNA polymerase, a subunit called the σ factor is largely responsible for promoter recognition. At first the enzyme is tightly bound to a DNA segment of about 75 base pairs, typically extending from about 55 nucleotides in advance of and 20 nucleotides past the first nucleotide to be copied. However, the structure of this first "closed complex" is not suitable for insertion and base pairing of a ribonucleotide with the corresponding nucleotide in the template. A distortion of the DNA double helix over a dozen base pairs enables the enzyme to come in contact with the bases on one of the strands, thus forming an "open complex", ready for transcription of the template.

The insertion of the first nucleotide (which is almost always a purine) completes the phase of initiation, and the **elongation** of the RNA chain begins. Along with the change in the template conformation to form an open complex, the enzyme is also altered to bind more loosely to the DNA strand, thus allowing motion along the template. This conformational change is achieved by dissociation of the σ factor, after the first ten or so nucleotides of RNA have been synthesised. The mechanism of elongation of the polynucleotide chain then proceeds at a higher speed, by joining the α-phosphate group of the incoming nucleotide triphosphate *via* a phosphodiester linkage to the 3' hydroxyl of the preceding nucleotide (**Scheme 1**). The β- and γ-phosphate groups are released as pyrophosphate (PP_i), which is then cleaved to yield two molecules of inorganic phosphate (P_i). Thus the synthesis of RNA follows the 5' to 3' direction, the 5'-terminal nucleotide of the chain retaining its triphosphate group.



Scheme 1: Elongation of the RNA transcript

Termination of transcription also occurs at specific sites. Several cases have been observed where the termination factor can be a protein (known as the ρ-factor), or a structural feature at the termination site. For example, most bacterial genes have termination signals consisting of A-T nucleotide pairs preceded by a two-fold symmetric DNA sequence, which will result in a transcript RNA folded into a hairpin. This secondary structure will in turn affect the shape of the polymerase, straining the DNA/RNA hybrid. Moreover, the RNA transcript of the termination signal will consist of a U-A sequence, bound to the DNA strand through weaker Watson Crick interactions than if it were C or G (2 hydrogen bonds per complementary base pair *vs.* 3). The result will be the release of the RNA transcript by dissociation of the DNA/RNA hybrid, reformation of the DNA double helix and release of the RNA polymerase.

Whereas prokaryotes have a single type of RNA polymerase to mediate transcription, three different types exist in eukaryotic cells. The three polymerases can be distinguished by their relative sensitivity to the fungal octapeptidic toxin α-amanitin and each of them is active on a distinct set of genes:

- RNA polymerase I synthesises the large rRNAs, and is insensitive to α-amanitin;
- RNA polymerase II synthesises mRNA, and is inhibited by α-amanitin at 1μg/ml;[5]
- RNA polymerase III synthesises a range of small, stable RNAs, including tRNA as well as the smallest rRNA (5S rRNA), and is moderately sensitive to α-amanitin (inhibited at 10μg/ml).[5]

The DNA templates transcribed by polymerases I, II and III are referred to as class I, II or III genes, respectively. Class II genes are by far the most diverse set, since they encode for mRNA, which in turn is translated into all the proteins of a given species.

All three polymerases consist of two large polypeptide subunits and about six to ten smaller ones. Some are specific to an individual polymerase, but all share substantial homology, including with the prokaryotic polymerase. Typically the two largest polypeptides form a core enzyme with a few smaller ones that is capable of randomly transcribing any DNA sequence into its RNA copy: the eukaryotic polymerases on their own cannot recognise genes. Specificity is conferred by additional proteins called transcription factors. These bind to target sequences, either directly or *via* other transcription factors, assembling complexes in order to recruit the polymerase to the promoter site.

[5] Latchman, D. *Gene Regulation: A Eukaryotic Perspective*, 4th ed., Nelson Thomas Ltd.; **2002**, Ch. 3, p37.

I-1.3 RNA polymerase III[2]

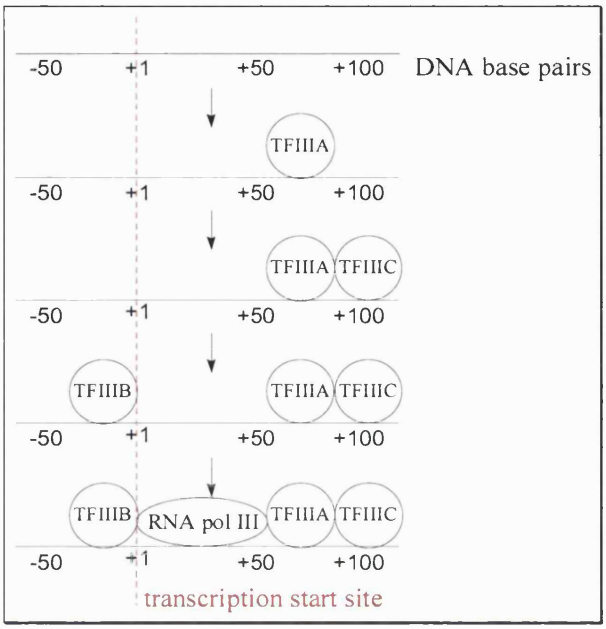
Of the three eukaryotic RNA polymerases, polymerase III is the largest and most complex, consisting of 17 subunits. It is thought to be responsible for *ca.* 10% of nuclear transcription.

One of the unusual features in the transcription of class III genes is that most promoters used by polymerase III are situated within the transcribed region, whereas class I and II gene promoters are always upstream, as is also the case in prokaryotes.

This type of downstream promoter was first observed in the study of genes encoding 5S rRNA. In this case, the promoter is constituted of three internal elements, which are recognised by a first transcription factor TFIIIA. Although the structure and size (number of amino acid residues) of TFIIIA vary between species, a common feature is the presence of zinc fingers, *i.e.* tandem zinc-dependent DNA binding domains, allowing for recognition of DNA across an extended site. TFIIIA then serves as an adaptor to recruit another transcription factor, TFIIIC, which has otherwise little affinity for the 5S rRNA gene. Subsequently, TFIIIC recruits a further transcription factor TFIIIB, forming a stable transcription complex, which remains stable through cell divisions. This complex then promotes the binding of RNA polymerase III at the transcriptional start site, by protein-protein interaction with TFIIIB (**Scheme 2**).

Other class III genes (*e.g.* tRNA genes) have slightly different promoter types and TFIIIA is not always required to recruit TFIIIC. However, TFIIIB always plays a critical role through the binding of the RNA polymerase III.

[2] White, R. J. *Gene Transcription, Mechanism and Control*, Blackwell Science Ltd.; **2001**, Ch 1.



Scheme 2: Transcription initiation by RNA polymerase III at the 5S rRNA gene promoter

As discussed earlier, the closed complex formed at the start site by the transcription factors, RNA polymerase III and the DNA is not suitable for nucleotide insertion. Polymerase III melts the DNA helix around the initiation site, forming a strand-separated open promoter complex, or transcription bubble, which allows the enzyme to move along the gene.

However, elongation does not proceed at a uniform rate, due to pausing of the transcription complex at internal sites. No elongation factors have been identified for polymerase III, unlike polymerases I and II. They may not be necessary because of the smaller size of class III genes. Alternatively, because polymerase III has more subunits than the other RNA polymerases, it is possible that one or more of the polymerase III specific subunits performs the functions carried out by independent elongation factors in the other polymerases. Recent studies also suggest that the reactivation of the elongation complex after pausing could involve trailing RNA polymerases, since the elongation phase can involve multiple RNA polymerases moving one after another

along the same DNA molecule.[6] Thus it would seem the trailing polymerases promote elongation of arrested complexes by translocating them forward. This cooperative mechanism is expected to work particularly well with higly active genes (*i.e.* genes expressed at a high rate), such as rRNA and tRNA genes transcribed by polymerase III. Whereas polymerases I and II require additional factors to terminate transcription, polymerase III recognises clusters of T residues as termination signals. After an initial round of transcription, polymerase III can be recycled without being released from the template, due to the stability of the pre-initiation complex. Multiple round transcriptions are therefore possible and occur at a greater rate, allowing for the efficient production of RNA transcripts necessary to the further processing of the genetic information.

I-2 Tagetitoxin

I-2.1 Origin and proposed structure

Tagetitoxin is a toxin produced by the phytopathogenic bacterium *Pseudomonas syringae* pv. *tagetis*. In 1981, Mitchell and Durbin isolated, purified and characterised tagetitoxin from liquid cultures of the organism.[7] Chemical and spectroscopic data first allowed them to propose an overall structure **1** in 1983, as an 8-membered ring thioether (**Figure 5**).[8] Field-desorption mass spectrometry demonstrated a molecular weight of 435, consistent with the molecular formula $C_{11}H_{18}NO_{13}PS$.

[6] Epshtein, V.; Nudler, E. *Science* **2003**, *300*, 801.
[7] Mitchell, R.E.; Durbin, R.D. *Physiol. Plant Pathol.* **1981**, *18*, 157.
[8] Mitchell, R.E.; Hart, P.A. *Phytochemistry* **1983**, *22*, 1425.

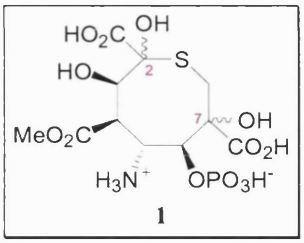


Figure 5: First proposed structure of tagetitoxin

In 1989, new MS and NMR data for tagetitoxin led to the revision of the structure proposed initially. The oxygenated functional groups were identified as acetyl, phosphate, carboxylic acid, carboxamide and two oxygens in either hydroxyl or ether groups. Further MS analysis also gave a different result for the molecular formula: FAB mass spectrometry indicated $(M+H)^+$=417.0361, consistent with $C_{11}H_{17}N_2O_{11}PS$. This molecular formula, along with the absence confirmed by NMR of C-C multiple bonds indicated a bicyclic structure. NOE experiments also showed a definite spatial proximity between the methylene protons α to the sulfur atom and the proton α to the ammonium group. This proximity would be highly unlikely in a monocyclic structure such as **1**, whereas a rigid bicyclic frame would allow for such an NOE effect to be observed. In view of these conclusions, the two possible bicyclic ring structures **2** and **3** were proposed (**Figure 6**).[9] The dihedral angles deduced from the coupling constants between the protons on the four consecutive tertiary carbons showed the protons on C-6 and C-7 to be in a true diaxial interrelationship. This was deemed unlikely in the constrained 7-membered ring **3**, and therefore the substituted 9-oxa-3-thiabicyclo[3.3.1]nonane **2** was favoured by the authors.

[9] Mitchell, R.E.; Coddington, J.M.; Young, H. *Tetrahedron Lett.* **1989**, *30*, 501.

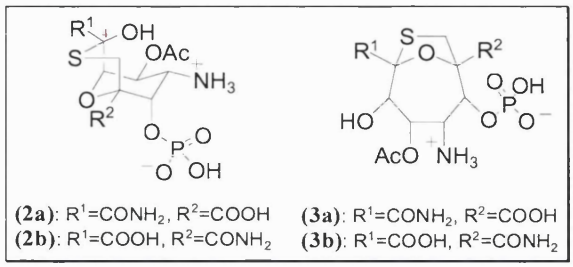


Figure 6: Revised structures of tagetitoxin

The exact position of the carboxamide functionality is not definitive from this data, but is expected to be at C-4 based on chemical shift. All the stereocenters were defined by the data except C-4, although the authors anticipated a boat conformation for the oxathiane ring bearing the hydroxyl and the amide substitutents in axial and equatorial positions respectively. The absolute stereochemistry has not been determined since single crystals suitable for X-ray analysis could not be obtained.

I-2.2 Biological activity

Several species of *Pseudomonas* bacteria produce phytopathogenic toxins, which cause leaf chlorosis.[10] However, tagetitoxin exhibits a different type of activity to most of these toxins, causing apical chlorosis in several host plants (*e.g.* zinnia, marigold, wheat): chloroplast development and chlorophyll accumulation are prevented in growing tissues, whereas mature tissues seem unaffected.[7] The production of tagetitoxin from a selected strain of *Pseudomonas syringae* pv. *tagetis* and its use as a plant-growth regulator have been patented.[11,12]

[10] Kelman, A., *Plant Disease*, Academic Press, **1979**, Vol. IV, 181-202.
[7] Mitchell, R.E.; Durbin, R.D. *Physiol. Plant Pathol.* **1981**, *18*, 157.
[11] Durbin, R.D.; Lukens, J.H.; Uchytil, T.F.; Rhodehamel, N., U.S. Patent, 4,874,706, **1989**.
[12] Tagetitoxin is commercially available as Tagetin™ Inhibitor from Epicentre Technologies, Madison, WI, USA, and distributed in the UK by Cambio Ltd., Cambridge.

The toxin was shown to inhibit *in vitro* and *in organello* chloroplast RNA polymerase, as well as *in vitro E.Coli* RNA polymerase.[13] Tagetitoxin appeared to reduce the incorporation of [^{3}H]uridine into RNA in isolated chloroplasts. The effect observed *in vitro* proved even more acute, and the incorporation of [^{32}P]UTP was virtually abolished at a tagetitoxin concentration of 10 μM. This result suggests that the chloroplast envelope might present a partial barrier for tagetitoxin.

It was also found that tagetitoxin specifically inhibited eukaryotic nuclear RNA polymerase III from a broad phylogenetic range (including vertebrates, insects and yeast) at levels similar to that required for the inhibition of *E.Coli* RNA polymerase.[14] However RNA synthesis directed by other nuclear enzymes was either not significantly inhibited (RNA polymerase II from wheat germ nuclei), or unaffected (RNA polymerases from bacteriophage SP6 or T7).

It was suggested that the sensitivity of *in vitro* RNA synthesis to tagetitoxin depends on the type of RNA polymerase. Although chloroplast RNA polymerase has not been definitively characterised, there is evidence to suggest that it resembles the RNA polymerase of *E. Coli*[15] and one of the chloroplast RNA polymerase subunits exhibits σ-like activity.[16] Moreover, analogies have been found between chloroplast promoter elements and typical prokaryotic promoters.[17] However, the RNA polymerases from

[13] Matthews, D.E.; Durbin, R.D. *J. Biol. Chem.* **1990**, *265*, 493.
[14] Steinberg, T.H.; Matthews, D.E; Durbin, R.D.; Burgess, R.R. *J. Biol. Chem.* **1990**, *265*, 499.
[15] (a) Sijben-Müller, G.; Hallick, R. B.; Alt, J.; Westoff, P.; Herrmann, R. G. *Nucleic Acids Res.* **1986**, *14*, 1029. (b) Ohyama, K.; Fukuzawa, H.; Kohchi, T.; Shirai, H.; Sano, T.; Sano, S.; Umesono, K.; Shiki, T.; Takeuchi, M.; Chang, Z.; Aota, S.; Inokuchi, H.; Ozeki, H. *Nature* **1986**, *322*, 572. (c) Shinozaki, K.; Ohme, M.; Tanaka, M.; Wadasugi, T.; Hayshida, N.; Matsubayasha, T.; Zaita, N.; Chynwongse, J.; Obokata, J.; Yanaguchi-Shinozaki, K.; Ohto, C.; Torazawa, K.; Meng, B. Y.; Sugita, M.; Deno, H.; Kamogashira, T.; Yamama, K.; Kusuda, J.; Takaiwa, F.; Kata, A.; Tahdoh, N.; Shimada, H.; Sugiura, M. *EMBO J.* **1986**, *5*, 2043. (d) Hudson, G. S.; Holton, T. A.; Whitfeld, P. R.; Bottomley, W. *J. Mol. Biol.* **1988**, *200*, 639.
[16] (a) Bulow, S.; Link, G. *Plant Mol. Biol.* **1988**, *10*, 349. (b) Lerbs, S.; Brautigam, E.; Mache, R. *Mol. Gen. Genet.* **1988**, *211*, 459.
[17] (a) Gruissem, W.; Zurawski, G. *EMBO J.* **1985**, *4*, 3375. (b) Hanley-Bowdoin, L.; Chua, N. H. *Trends, Biochem. Sci.* **1987**, *12*, 67.

bacteriophage SP6 or T7 which appeared completely insensitive to tagetitoxin, are very different from *E. Coli* RNA polymerase and consist of a single polypeptide.[18]

A study of the mechanism of inhibition showed that tagetitoxin inhibits the elongation phase of the transcription cycle during promoter-directed transcription by yeast RNA polymerase III.[19] It was suggested that the toxin enhanced pausing of the transcription complex at intrinsic pause sites along the DNA template, resulting in slow RNA release and increased appearance of low molecular weight discrete RNAs at the expense of full-length products. However, the tagetitoxin-enhanced pause pattern is distinct for each type of class III gene. This might result from the binding of transcription factors within the transcribed sequence of class III genes. Indeed the presence of these transcription factors is a known cause for intrinsic pausing during the elongation phase. It was observed that the transcription of vertebrate U6 snRNA gene, which does not require internal factor binding, was less sensitive to tagetitoxin than the transcription of vertebrate 5S rRNA and tRNA genes where such transcription factors (TFIIIA and TFIIIC, and TFIIIC respectively) are internally bound and stable through several rounds of transcription.

Further mechanistic studies on *E. Coli* suggested that tagetitoxin affects the ternary complex consisting of RNA polymerase core enzyme, DNA template and nascent RNA chain.[20] Although the exact mechanism of inhibition is still unknown, a separate study on the spinach chloroplast RNA polymerase showed that the toxin does not compete with nucleotide substrates for binding to the RNA polymerase, nor does it affect

[18] Butler, E. T.; Chamberlain, M. J. *J. Biol. Chem.* **1982**, *257*, 5772.
[19] Steinberg, T.H.; Burgess, R.R. *J. Biol. Chem.* **1992**, *267*, 20204.
[20] Matthews, D.E.; Durbin, R.D. *Biochemistry* **1994**, *33*, 11987.

phosphodiester bond formation.[21] The authors proposed alternative hypotheses based on the similarity observed for inhibition of RNA polymerase II by α-amanitin. Tagetitoxin could enhance the binding of the nascent oligonucleotide to the enzyme-template complex, thus reducing the rate of oligonucleotide release; or it might interfere with translocation of the catalytic active centre with respect to the 3'-OH of the nascent transcript.

Although the exact mode of action of tagetitoxin has not yet been elucidated, its unique specificity for RNA polymerase III (complementary to that of *α*-amanitin for RNA polymerase II) has made it a widely used tool in the biological community for the study of DNA transcription, for example in identifying and characterising new promoters.[22] Recent developments on a genetic approach utilising the yeast *Saccharomyces cerevisiae* led to the identification of two synthetic small molecules which also inhibited RNA polymerase III (**Table 1**).[23]

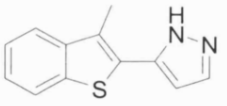
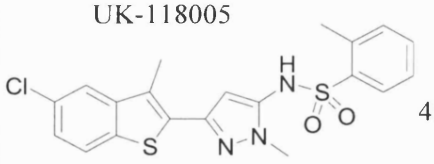
Compound/Structure	Mol Wt	Pol III IC_{50} (μM)*		% inhibition at 200 μM**		
		S. cerevisiae	Human	*S. cerevisiae*	*C. albicans*	Human
 UK-118005	214.3	200	100	62	38	62
 ML-60218	452.4	32	27	88	94	90
	* : whole-cell assay; ** : in vitro assay from subcellular extract					

Table 1: Structures and IC_{50} of UK-118005 and analogue ML-60218

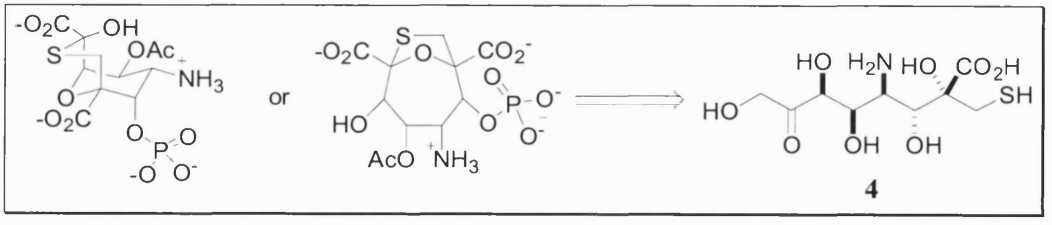
[21] Corda, Y.; Soulie, J.-M.; Job, D. *C. R. Acad. Sci., Sér. III* **1992**, *314*, 613, and references cited therein.
[22] Kapoor, S., Suzuki, J.Y.; Sugiura, M. *Plant J.* **1997**, *11*, 327.
[23] Wu, L.; Pan, J.; Thoroddsen, V.; Wysong, D. R.; Blackman, R. K.; Bulawa, C. E.; Gould, A. E.; Ocain, T. D.; Dick, L. R.; Errada, P.; Dorr, P. K.; Parkinson, T.; Wood, T.; Kornitzer, D.; Weissman, Z.; Willis, I. M.; McGovern, K. *Eukaryotic Cell* **2003**, *2*, 256.

UK-118005 and its analogue ML-60218 proved to be broad spectrum inhibitors having antifungal activity, and showing potency against RNA polymerase III-mediated transcription in systems derived from the yeast *Candida albicans* as well as human cells. This tends to confirm that RNA polymerase III is tractable to inhibition by small molecules, such as tagetitoxin. However, these new inhibitors have not yet been tested against RNA polymerases I and II, therefore selectivity for RNA polymerase III has not been established. Tagetitoxin thus remains the only known specific inhibitor of RNA polymerase III.

I-2.3 Precedent for the synthesis of Tagetitoxin

Despite its isolation dating back twenty years, only two approaches towards the synthesis of tagetitoxin or analogues have been reported.

Sammakia *et al.*[24] have described a putative route to a fully functionalised precursor **4**, which would allow the synthesis of either proposed structure of tagetitoxin by cyclisation (**Scheme 3**).



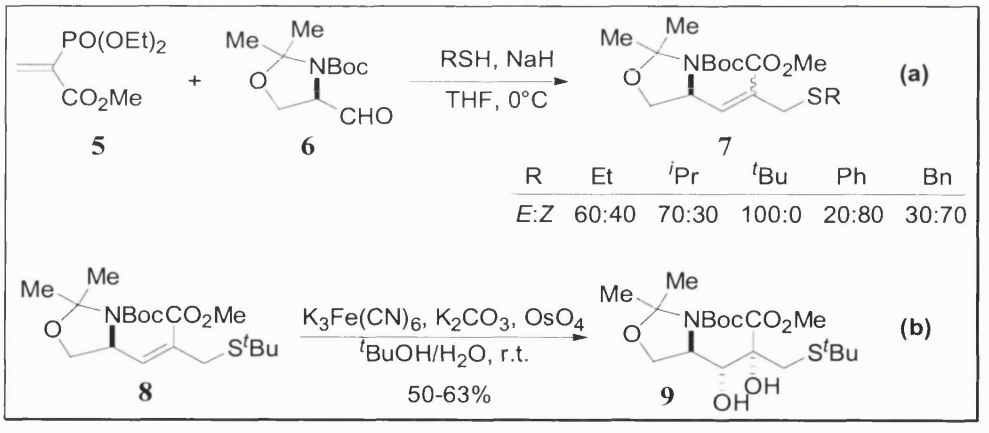
Scheme 3: Sammakia's proposed linear precursor to tagetitoxin

[24] Sammakia, T.; Hurley, T.B.; Sammond, D.M.; Smith, R.S.; Sobolov, S.B.; Oeschger, T.R. *Tetrahedron Lett.* **1996**, *37*, 4427, and references cited therein.

The scope of olefin dihydroxylation in the presence of sulfides as well as the relative rates of oxidation of various classes of sulfides had been examined using the Yamamoto ferricyanide/osmium tetroxide procedure and AD-mix. It appeared that electron-withdrawing substituents and steric hindrance in the vicinity of the sulfur atom retarded the rate of sulfur oxidation and allowed for olefin dihydroxylation to proceed preferentially.

The authors intended to exploit this sulfide-hindrance strategy for the dihydroxylation of oxazolidine olefins **7**, obtained by condensation of phosphonate **5** with oxazolidine aldehyde **6** and a variety of thiols (**Scheme 4, (a)**).[25] The alkyl thiols exhibited moderate to excellent *E* selectivity (with the *tert*-butylthiol affording the *E*-alkene as a single isomer), whereas the aryl thiols favoured the formation of the *Z* isomer.

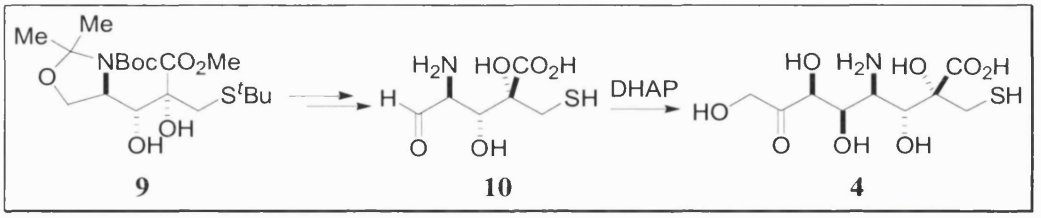
The resulting electron-deficient and sterically hindered α,β-unsaturated esters gave poor results with AD-mix, which led to oxidation to the sulfoxide predominantly. The most synthetically useful result was obtained for the *tert*-butyl protected substrate **8** using Yamamoto's conditions, and afforded a 25:1 diastereoisomeric ratio of diol **9** in moderate yield (**Scheme 4, (b)**).



Scheme 4: Dihydroxylation approach

[25] Semmelhack, M.F.; Tomesch, J.C.; Czarney, M.; Boettger, S. *J. Org. Chem.* **1978,** *43*, 1259.

No further progress has since been reported by Sammakia and co-workers on this strategy, which was expected to afford aldehyde **10** *via* hydrolysis of the oxazolidine followed by selective oxidation of the primary alcohol and thiol deprotection. Enzymatic coupling with dihydroxyacetone phosphate (DHAP) had been envisaged to form the linear precursor **4** to tagetitoxin (**Scheme 5**).



Scheme 5: Sammakia's strategy to tagetitoxin precursor

A different carbohydrate-based approach was pursued by Furneaux *et al.*, in which the synthesis of tagetitoxin analogues **11** and **12** (X=O, S) from D-sugars was attempted (**Figure 7**), based on the herbicidal activity exhibited by structurally related 1,6-anhydro-D-hexose derivatives.[26]

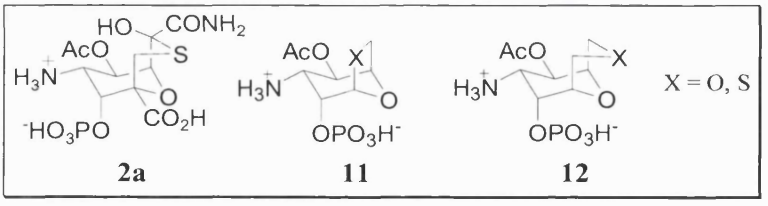
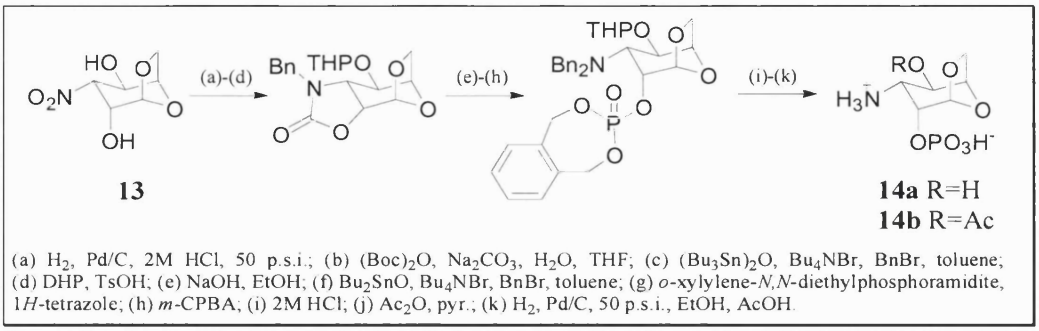


Figure 7: Sugar analogues of tagetitoxin

Two routes were designed to obtain analogues **11**. The first route was based on orthogonal protection of 1,6-anhydro-3-deoxy-3-nitro-D-gulose **13**, which provided the desired stereochemistry for the *cis*-amino phosphonate functionality encountered in the target molecule (**Scheme 6**).

[26] Dent, B.R.; Furneaux, R.H.; Gainsford, G.J.; Lynch, G.P. *Tetrahedron* **1999**, *55*, 6977, and references cited therein.

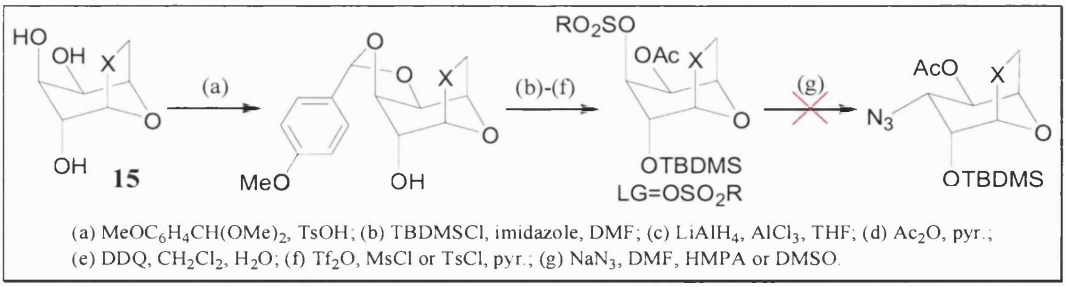


(a) H_2, Pd/C, 2M HCl, 50 p.s.i.; (b) $(Boc)_2O$, Na_2CO_3, H_2O, THF; (c) $(Bu_3Sn)_2O$, Bu_4NBr, BnBr, toluene; (d) DHP, TsOH; (e) NaOH, EtOH; (f) Bu_2SnO, Bu_4NBr, BnBr, toluene; (g) *o*-xylylene-*N,N*-diethylphosphoramidite, 1*H*-tetrazole; (h) *m*-CPBA; (i) 2M HCl; (j) Ac_2O, pyr.; (k) H_2, Pd/C, 50 p.s.i., EtOH, AcOH.

Scheme 6: Synthesis of D-gulose-derived analogues

Reduction of the nitro group, followed by temporary protection of the amino-alcohol as *N*-benzyloxazolidinone allowed THP- protection at C-4. Cleavage of the carbamate left the alcohol at C-2 ready for phosphitylation and oxidation. Deprotection of the THP ether at C-4 (along with acetylation in one case), of the dibenzylamine at C-3 and of the phosphotriester afforded two analogues of tagetitoxin **14a** and **14b** (X=O). Analogues **14a** and **14b** were tested for bioactivity, but neither of them showed any significant activity.[27]

The synthesis of further type **11** analogues (X=O,S) was attempted by a second route, where O-2 and O-4 of 1,6-anhydro-D-galactose **15** were functionalised differentially, and a leaving group was introduced at C-3 to allow azide substitution with inversion of configuration (**Scheme 7**). However, the nucleophilic substitution did not occur, possibly due to the bulky silyl substituent at O-2.

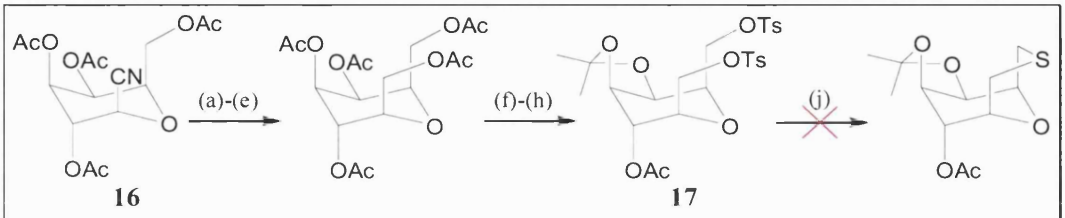


(a) $MeOC_6H_4CH(OMe)_2$, TsOH; (b) TBDMSCl, imidazole, DMF; (c) $LiAlH_4$, $AlCl_3$, THF; (d) Ac_2O, pyr.; (e) DDQ, CH_2Cl_2, H_2O; (f) Tf_2O, MsCl or TsCl, pyr.; (g) NaN_3, DMF, HMPA or DMSO.

Scheme 7: Attempted synthesis of D-galactose-derived analogues

[27] The substrates were applied at 1000 g/ha on the following agriculturally important weeds: *Avena fatua* (wild oat), *Setaria viridis* (green foxtail), *Amaranthus retroflexus* (redroot pigweed) or *Chenopodiu album* (fat hen).

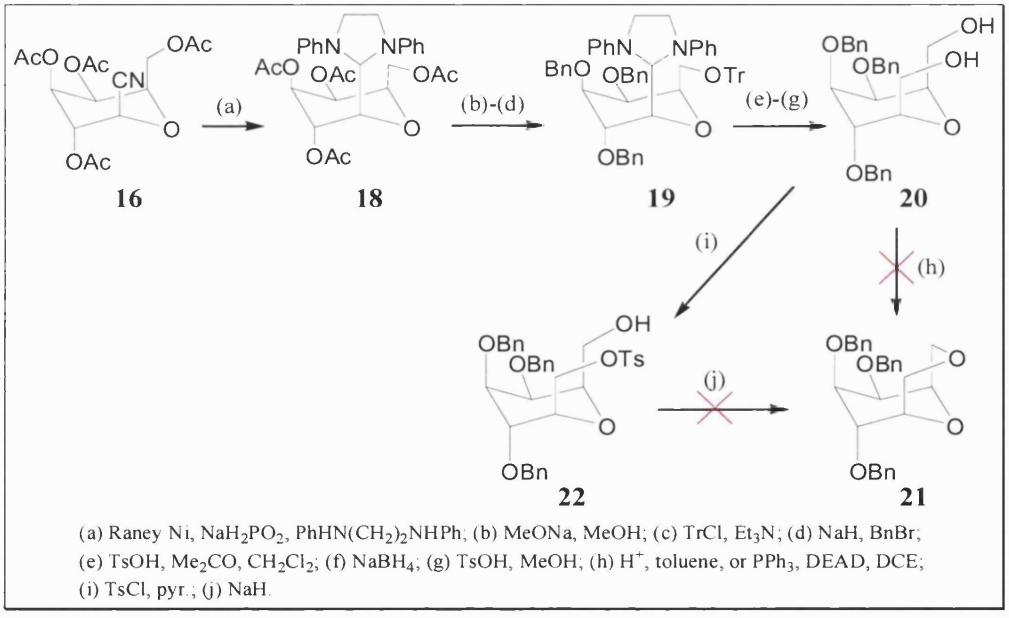
Analogues of type **12** were thought to be accessible from D-galactopyranose (**Scheme 8**). One-carbon chain elongation at C-1 was achieved *via* hydrolysis and reduction of the β-nitrile derivative of D-galactose pentaacetate **16,** but no ring-closure between the carbon at C-1 and C-7 was observed when the ditosylated substrate **17** was treated with various sulfides in an attempt to synthesise analogues with X=S.



(a) MeONa, MeOH; (b) 25% w/v NaOH; (c) Ac_2O, pyr.; (d) $LiAlH_4$; (e) Ac_2O, pyr.; (f) MeONa, MeOH; (g) TsCl, pyr.; (h) $Me_2C(OMe)_2$, TsOH; (i) Ac_2O, pyr.; (j) Li_2S or Na_2S, DMF.

Scheme 8: Attempted synthesis of bicyclic oxathiane analogues

A modified approach was chosen, which would remove any steric constraints from the bulky isopropylidene protecting group thought to affect the ring closure (**Scheme 9**). This was applied to form type **12** analogues with X=O.



(a) Raney Ni, NaH_2PO_2, $PhHN(CH_2)_2NHPh$; (b) MeONa, MeOH; (c) TrCl, Et_3N; (d) NaH, BnBr; (e) TsOH, Me_2CO, CH_2Cl_2; (f) $NaBH_4$; (g) TsOH, MeOH; (h) H^+, toluene, or PPh_3, DEAD, DCE; (i) TsCl, pyr.; (j) NaH.

Scheme 9: Attempted synthesis of bicyclic dioxane analogues

Imidazolidine **18** was derived from β-nitrile **16** by reductive hydrolysis and trapping of the resulting aldehyde with diphenylethylenediamine. Deacetylation and protection of the primary alcohol as a trityl ether was followed by perbenzylation of the remaining secondary alcohols to provide the orthogonally protected substrate **19**. Unmasking of the aldehyde under acidic conditions, borohydride reduction and trityl deprotection afforded the diol **20**. Attempts to cyclise **20** by acid-catalysed dehydration to form dioxane analogue **21**, or under Mitsunobu conditions were unsuccessful, as well as sodium hydride treatment of the monotosylate **22**.

This report highlighted the limitations and difficulties inherent to carbohydrate chemistry as far as the differentiation of hydroxyl groups is concerned. Since the absolute configuration of tagetitoxin has not been determined to this date, the access to both enantiomers of the natural product or any analogue would be limited by the availability of the unnatural sugars.

I-2.4 Aims of the project

The aim of the work presented in this thesis is to develop synthetic methodology which will enable the unique skeleton of tagetitoxin to be assembled, and ultimately to achieve the first total synthesis of tagetitoxin. Indeed it makes for an intriguing synthetic target thanks to (i) the possibility of confirming its structure by total synthesis; and (ii) its unique biological activity as a specific inhibitor for RNA polymerase III. A concise synthetic route to tagetitoxin would give access to larger quantities of the compound for biological research and allow the synthesis of analogues to study the mechanism of

action. Such analogues could be tested as potential herbicides[26] or antibacterial agents.[28]

[26] Dent, B.R.; Furneaux, R.H.; Gainsford, G.J.; Lynch, G.P. *Tetrahedron* **1999**, *55*, 6977.
[28] Strath, M.; Scottfinnigan, T.; Gardner, M.; Williamson, D.; Wilson, I. *Trans. R. Soc. Trop. Med. Hyg.* **1993**, *87*, 21.

I-3 Some aspects of carbene chemistry and recent uses in organic synthesis

Since the early work of Curtius[29] and Staudinger,[30] carbenes have become increasingly important intermediates, finding applications in such diverse fields as photosensitive magnetic materials[31] and ligands for transition-metal catalysis.[32] Carbenes were re-introduced into synthetic organic chemistry in 1954 by Doering,[33] and since then many more synthetically useful transformations have been developed. In the last 10 years, the understanding of carbene chemistry has advanced dramatically with the preparation of persistent triplet diarylcarbenes[34] and the isolation of heteroatom-substituted singlet carbenes.[35]

I-3.1 The carbene species

Carbenes are neutral compounds defying the octet rule, since they feature a divalent carbon atom with only six electrons in its valence shell. The carbon atom can be either linear (*sp*-hybridised carbene centre) or bent (sp^2 hybridisation), although the latter is more frequent and the resulting frontier orbitals are σ and p_π.

Four electronic configurations can result (**Figure 8**): a triplet state ($\sigma^1 p_\pi^1$, **23**) where the two non-bonding electrons are in two different orbitals with parallel spins; two different singlet states (σ^2 and p_π^2, **24** and **25**) where the two electrons are paired in the same

[29] Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1885**, *8*, 2377.
[30] Staudinger, H.; Kupfer, O. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 501.
[31] Tomioka, H. *Pure Appl. Chem.* **2003**, *75*, 1041.
[32] Merceron-Saffon, N.; Baceiredo, A.; Gornitzka, H.; Bertrand, G. *Science* **2003**, *301*, 1223.
[33] Doering, W. v. E.; Hoffman, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162.
[34] Tomioka, H. *Acc. Chem. Res.* **1997**, *30*, 315.
[35] Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

orbital and σ^2 is generally more stable than p_π^2; and an excited singlet state ($\sigma^1 p_\pi^1$, **26**) where the two non-bonding electrons are in two different orbitals with antiparallel spins.[35]

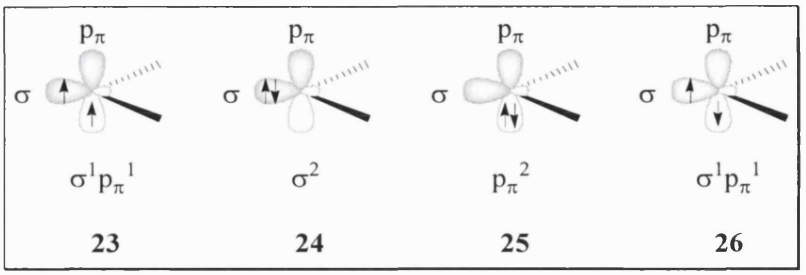


Figure 8: Electronic configurations of carbenes

The reactivity of carbenes is determined by their ground-state spin multiplicity.[36] Singlet carbenes possess a filled and a vacant orbital, and therefore exhibit an ambiphilic character. They show extremely high reactivity and are capable of reacting with very inert sites, such as C-H bonds. On the other hand, triplet carbenes have two singly occupied orbitals and are generally regarded as diradicals.

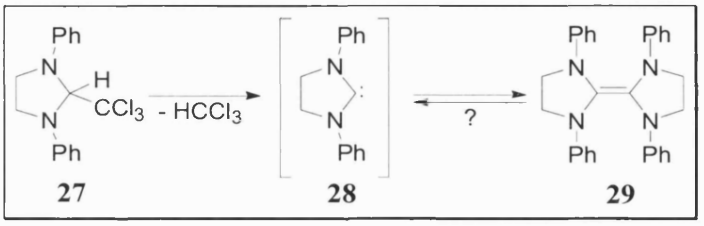
I-3.2 Generation of stable carbenes

The high reactivity of carbene species makes them inherently unstable. Stabilisation by electronic and steric effects have been developed, albeit with greater success for singlet carbenes.[37]

Singlet carbenes bearing two electron-donating groups were initially synthesised by thermal methods. In the early 1960s, Wanzlick tried to prepare the 1,3-diphenylimidazolidin-2-ylidene **28** from **27** by thermal elimination of chloroform

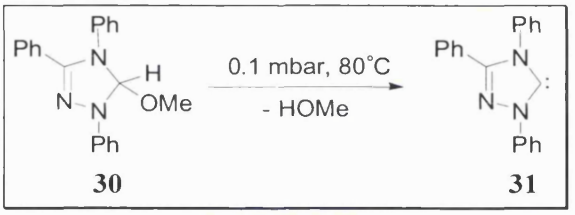
[35] Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.
[36] Schuster, G. B. *Adv. Phys. Org. Chem.* **1986**, *22*, 311.
[37] For a discussion on stable carbenes, see Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674.

(**Scheme 10**).[38] Indeed he believed that the stability of carbenes could be enhanced by the presence of amino substituents. Only the dimeric product **29** was isolated, but recent results by Denk and coworkers seem to provide evidence for an equilibrium between the dimer and two carbene units **28**.[39]



Scheme 10: First synthesis of a stable singlet carbene

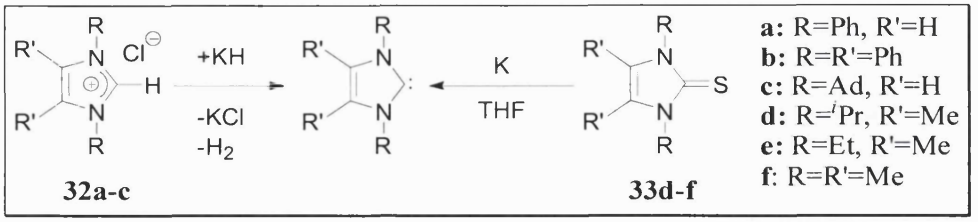
Similarly, thermal elimination of methanol *in vacuo* from triazole **30** afforded the first commercially available carbene **31 (Scheme 11)**.[40]



Scheme 11: Singlet carbene from the triazole series

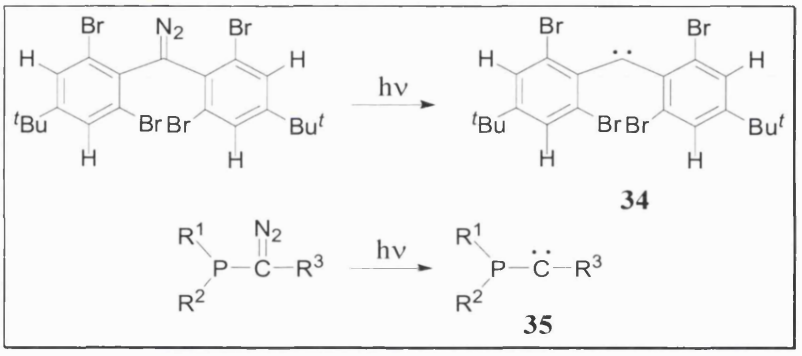
Deprotonation of imidazolium salts **32 a-c** can be achieved with potassium *tert*-butoxide used as a base[41] or as a catalyst added to sodium or potassium hydride,[42] to give the corresponding imidazol-2-ylidenes (**Scheme 12**). Alternatively, alkyl-substituted N-heterocyclic carbenes can be obtained by reduction of imidazol-2(3*H*)-thiones **33 d-f** with potassium in boiling THF.[43]

[38] (a) Wanzlick, H. W.; Kleiner, H., J. *Angew. Chem.* **1961**, *73*, 493. (b) Wanzlick, H. W. *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 75. (c) Wanzlick, H. W.; Esser, F.; Kleiner, H. J. *Chem. Ber.* **1963**, *96*, 1208.
[39] Denk, M. K.; Hatano, K.; Ma, M. *Tetrahedron Lett.* **1999**, *40*, 2057.
[40] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021.
[41] (a) Wanzlick, H. W.; Schönherr, H. J. *Liebigs Ann. Chem.* **1970**, *731*, 1768. (b) Schönherr, H. J.; Wanzlick, H. W. *Chem. Ber.* **1970**, *103*, 1037.
[42] Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
[43] Kuhn, N.; Kratz, T. *Synthesis* **1993**, 561.



Scheme 12: Imidazole-derived carbenes

Photolysis of a diazo precursor is another classical route to free carbenes, which has been used to access stable triplet carbenes bearing bulky aryl substituents.[34] Indeed , the most stable triplet carbene known to date (**34**) is indefinitely stable at 130 K and has a half-life of 16 s at room temperature (**Scheme 13**).[44] A similar method can be used to access stable phosphinocarbenes **35**.[35]



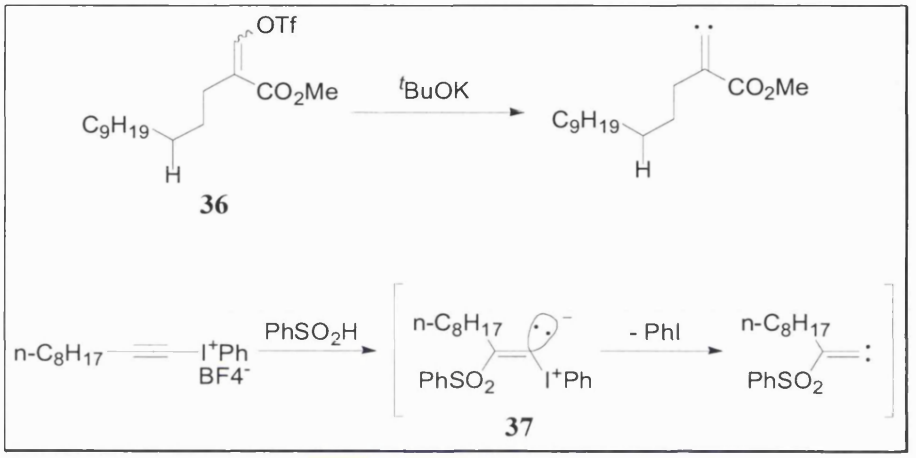
Scheme 13: Synthesis of carbenes by photolysis of a diazo precursor

The stable species described in this section are by nature unreactive. Free carbenes however have been increasingly used as reactive synthetic intermediates.

[34] Tomioka, H. *Acc. Chem. Res.* **1997**, *30*, 315.
[44] (a) Tomioka, H.; Watanabe, T.; Hirai, K.; Furukawa, K.; Takui, T.; Itoh, K. *J. Am. Chem. Soc.* **1995**, *117*, 6376. (b) Tomioka, H.; Hattori, M.; T.; Hirai, K.;Mutara, S. *J. Am. Chem. Soc.* **1996**, *118*, 8723.
[35] Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

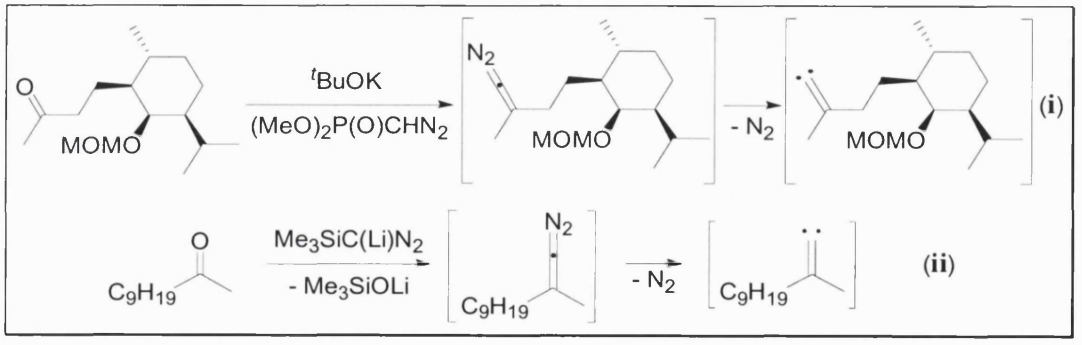
I-3.3 Generation and synthetic use of free carbenes

Alkylidene carbenes, although not stable, are important synthetic intermediates,[45] used in particular in 1,5 C-H insertion reactions. They can be generated in the free form by base-promoted α-elimination of enol triflates **36**[46] or addition-elimination of alkynyliodonium salts **37** (**Scheme 14**).[47]



Scheme 14: Synthesis of alkylidene carbenes by α-elimination

Other methods of preparation involve the extrusion of nitrogen from 1-diazoalkenes, using modifications of the Wadsworth-Emmons reaction (**i**),[48] or the Peterson olefination (**ii**) (**Scheme 15**).[49]



Scheme 15: Synthesis of alkylidene carbenes by nitrogen extrusion

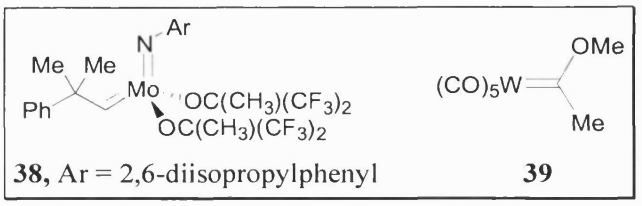
[45] Kirmse, W. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1164.
[46] Ohira, S.; Yamasaki, K.; Yamato, M.; Nakayama, M. *Tetrahedron Lett.* **1995**, *36*, 8843.
[47] Stang, P. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 274 and references cited therein.
[48] Ohira, S.; Yoshihara, N.; Hasegawa, T. *Chem. Lett.* **1998**, 739.
[49] Ohira, S.; Okai, K.; Moritani. T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.

I-3.4 Generation of metal carbenes

The use of free carbenes in organic chemistry is limited, due to their high reactivity and general lack of selectivity towards functionalised organic compounds. Metal carbenes, where the reactive species is complexed to a ligand-bearing metal, offer a more stable alternative, in which reactivity and selectivity can potentially be influenced by the nature of the metal and its ligands.[50]

Transition-metal carbene complexes are generally divided into two classes, "Schrock-type" carbene complexes and "Fischer-type" carbene complexes.[51] In Schrock carbene complexes the carbon atom is nucleophilic and often part of a methylene or alkylidene group. The metal is in a relatively high oxidation state (usually d^0), with strong donor ligands.[52] Fischer carbene complexes however, are electrophilic at the carbon centre and the metal is in a low oxidation state. The most widely studied Fischer carbenes are derived from Group 6 metals, Cr, Mo and W. Numerous applications have been developed including benzannulation, cyclopropanation, C-H insertion and Pauson-Khand reaction.[53] Typical examples of Schrock and Fischer carbene complexes are shown in **Figure 9**: molybdenum complex **38** is a Schrock catalyst for olefin ring-closing metathesis, **39** is the first fully characterised heteroatom-stabilised metal carbene complex, as reported by Fischer.[54]

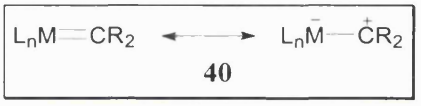
[50] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
[51] (a) Herndon, J. W. *Coord. Chem. Rev.* **2000**, *206-207*, 237. (b) Synthetic applications of metal carbene complexes, including olefin metathesis in Herndon, J. W. *Coord. Chem. Rev.* **2003**, *243*, 3. (c) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Sausalito, 2nd ed., **1999**, Ch. 6.
[52] For a recent review on the synthesis of Schrock carbenes see Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145.
[53] Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591.
[54] Fischer, E.O.; Maasböl, A. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 580.



38, Ar = 2,6-diisopropylphenyl **39**

Figure 9: Schrock and Fischer carbenes

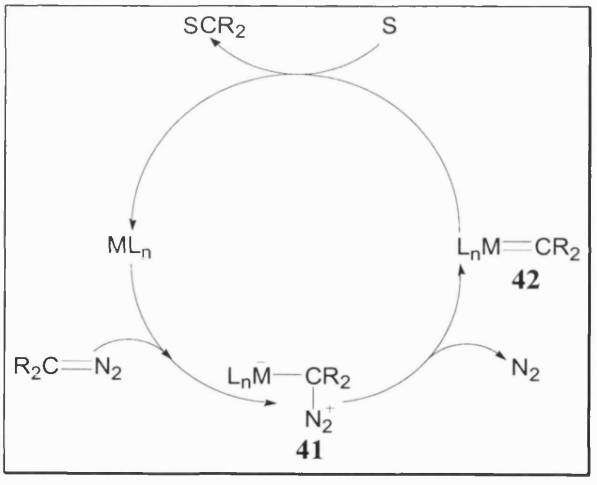
Between the two bonding extremes represented by Schrock and Fischer carbenes lie a variety of related metal carbenes sharing common structural and reactivity features. The following sections will focus on transient electrophilic metal carbenes **40**, obtained by transition metal-catalysed decomposition of diazocompounds (**Figure 10**).[55,56]



40

Figure 10

In a typical catalytic cycle and depending on the coordination of the metal centre, the Lewis acidic[57] transition-metal complexes can react as electrophiles with diazo compounds (**Scheme 16**), to form an adduct **41**



Scheme 16: Transition metal-catalysed decomposition of diazocompounds

[55] The existence of a copper carbene was first suggested by Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376.
[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.
[57] Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

Back-donation of electron density from the metal and concomitant loss of nitrogen forms the metal-stabilised carbene **42**. Transfer of the carbene entity to an electron-rich substrate S completes the catalytic cycle by regenerating the metal catalyst.

Metal catalysis in the decomposition of diazo compounds has evolved considerably over almost a century,[58] progressing from the use of insoluble copper bronze and cupric sulfate until the 1960s to the first soluble copper chelates such as copper(II) bis(acetylacetonate)[59] as well as trialkyl and triaryl phosphite copper(I) catalysts.[60]

Further work by Nozaki, Noyori and co-workers laid the groundwork for effective asymmetric induction with the preparation and use of chiral copper chelates for cyclopropanation reactions.[61] In addition to this, other stable transition metals were shown to catalyse carbenoid reactions.[62] In particular, palladium(II) acetate[63] and rhodium(II) acetate[64] were introduced in the 1970s as alternatives to copper catalysts for carbenoid transformations.

I-3.5 Synthetic transformations involving metal carbenes

Thanks to their versatility and the potential for varying reactivity by the use of different transition metals, metal carbenes have found increasingly diverse uses in synthetic organic chemistry. This section highlights three major synthetic transformations based

[58] Silberrad, O.; Roy, C.S. *J. Chem. Soc.* **1906**, *89*, 179.
[59] Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R . *Tetrahedron Lett.* **1966**, 59.
[60] Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135.
[61] (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5329. (b) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655. (c) Noyori, R.; Takaya, H.; Nakanishi, Y.; Nozaki, H. *Can. J. Chem.* **1969**, *24*, 3655.
[62] (a) Fisher, E. O.; Dötz, K. H. *Chem. Ber.* **1970**, *103*, 1273. (b) Dötz, K. H.; Fisher, E. O. *Ibid.* **1972**, *105*, 1356.
[63] Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.* **1972**, *13*, 1465.
[64] Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, Ph. *Synthesis* **1976**, 600.

on the reaction of metal carbenes: cycloaddition reactions and in particular cyclopropanation; insertion reactions and ylide formation.

I-3.5.1 Cyclopropanation and other cycloadditions

Cyclopropanation of olefins is a widely studied reactions in organic chemistry.[65] The discovery of stable metal carbenes and their compatibility for stereospecific cyclopropanation led the way for the evolution of catalytic methods. Indeed, most initial mechanistic studies of carbenoid transformations were based on cyclopropanation.[66] Transition metal-catalysed decomposition of a diazocompound resulting in addition to alkenes has since become a method of choice. Catalytic systems and diazo-precursors have been developed for both inter- and intramolecular versions of the process, and the control of selectivity encompasses regioselection, diastereoselection and enantioselection.[56]

The most common diazocompounds for cyclopropanation are α-diazoesters **43**,[67,68] but other derivatives bearing one electron-withdrawing group (**44-47**, **Figure 11**) have been used.[69]

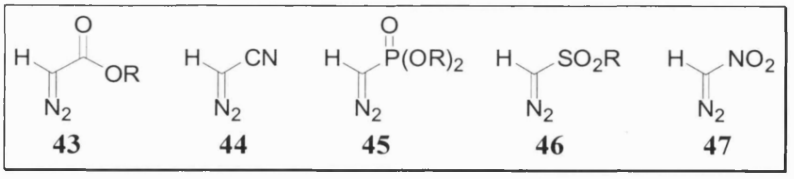
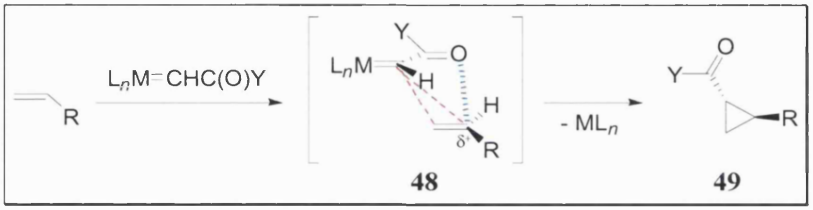


Figure 11: Common classes of diazo reagents

[65] A Web of Knowledge search for "cyclopropanation" covering 1990-2004 returned 2288 entries.
[66] Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348.
[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.
[67] Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1.
[68] Doyle, M. P.; Forbes, D. C. *Chem. Rev.*, **1998**, *98*, 911.
[69] (**44**): Felpin, F.-X.; Doris, E.; Wagner, A.; Valleix, A.; Rousseau, B.; Mioskowski, C. *J. Org. Chem.* **2001**, *66*, 305. (**45**): Lewis, R. T.; Motherwell, W. B. *Tetrahedron Lett.* **1998**, *29*, 5033. (**46**): Padwa, A.; Wannamaker, M. W.; Dyszlewski, A. D. *J. Org. Chem.* **1987**, *52*, 4760. (**47**): O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1991**, *56*, 2258.

The postulated mechanism of cyclopropanation with metal carbenes derived from α-diazocarbonyls proceeds by initial association of the olefin π-bond with the electrophilic carbon of the metal carbene, followed by σ-bond formation and displacement of the catalyst. The developing positive charge on the original alkene is stabilised by the nucleophilic carbonyl oxygen in transition structure **48**, leading to the 1,2-disubstituted cyclopropane **49**. The predominant *trans* stereoselectivity observed with α-diazocarbonyls can be enhanced by increasing the size of the Y group and the nucleophilicity of the carbonyl group (**Scheme 17**).[66]

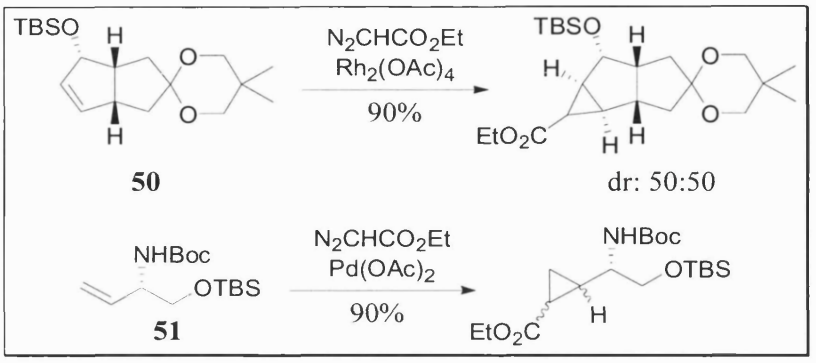


Scheme 17: Regio- and stereoselectivity of the cyclopropanation reaction

Among the catalysts developed for cyclopropanation, those derived from Rh, Ru, Co and Cu react faster with electron-rich alkenes, whereas Pd metal carbenes give the best results for electron-deficient substrates.[70]

Although cyclopropanations of relatively rigid systems such as **50** exhibit good facial selectivity, the relative stereocontrol for the stereogenic centre bearing the carbonyl group can be modest.[71] In acyclic chiral alkene systems such as **51**, all four possible diastereoisomers were obtained on treatment with ethyl diazoacetate and palladium acetate (**Scheme 18**).[72]

[66] Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348.
[70] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
[71] Piers, E.; Moss, N. *Tetrahedron Lett.* **1985**, *26*, 2735.
[72] Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ofune, Y. *J. Org. Chem.* **1991**, *56*, 4167.



Scheme 18: Examples of poor stereoselectivity in cyclopropanation reactions

In order to overcome these restrictions, extensive work on the development of chiral catalysts has been carried out over the years, and a wide range of metal complexes are now available to achieve the desired transformations with high enantio- and diastereoselectivity. As a general rule, copper-based catalysts are most efficient for the preparation of *trans* isomers, whereas cobalt-based catalysts exhibit *cis* selectivity. Rhodium and ruthenium-based catalysts, however efficient, suffer from lower enantio- and diastereoisomeric ratio, or from a somewhat narrower scope. The developments in catalysts for stereoselective cyclopropanation have been extensively reviewed,[70] and some examples are presented in **Figure 12** for the cyclopropanation of styrene.[73]

[70] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977, and references cited therein.

[73] **(52)**: Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726 and Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430. **(53)**: Park, S.-B.; Murata, K.; Matsumoto, H.; Nishiyama, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2487. **(54)**: Stoop, R. M.; Bauer, C.; Setz, P.; Wörle, M.; Wong, T. Y. H.; Mezzetti, A. *Organometalics* **1999**, *18*, 5691 and Bachmann, S.; Furler, M.; Mezzetti, A. *Organometalics* **2001**, *20*, 2102. **(55)**: Fukuda, T.; Katsuki, T. *Synlett* **1995**, 825 and Fukuda, T.; Katsuki, T. *Tetrahedron* **1997**, *53*, 7201. **(56)**: Ishitani, H.; Achiwa, K. *Synlett* **1997**, 781.

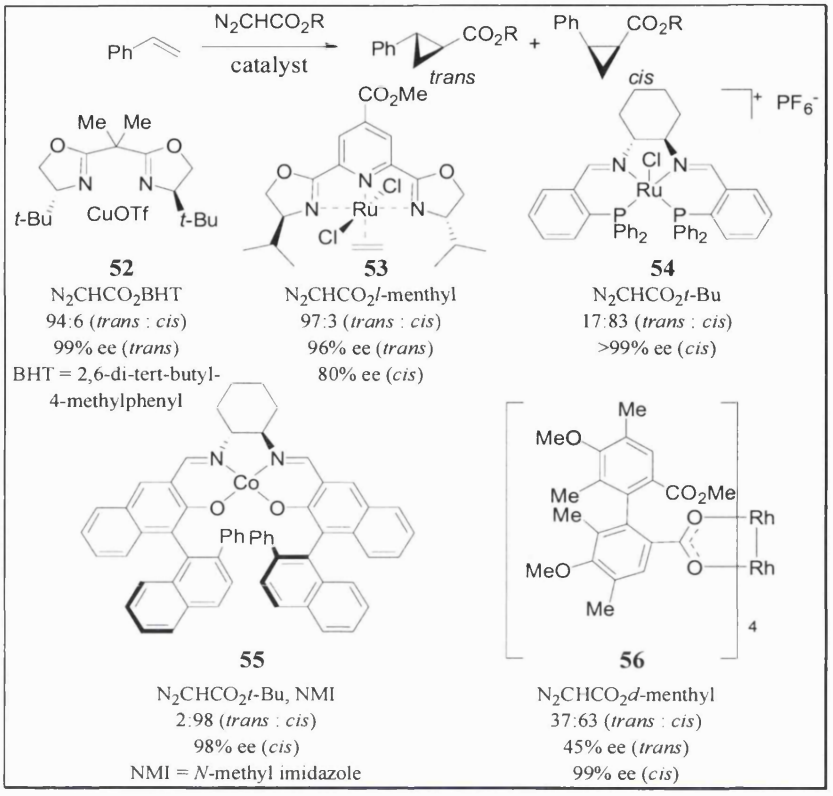
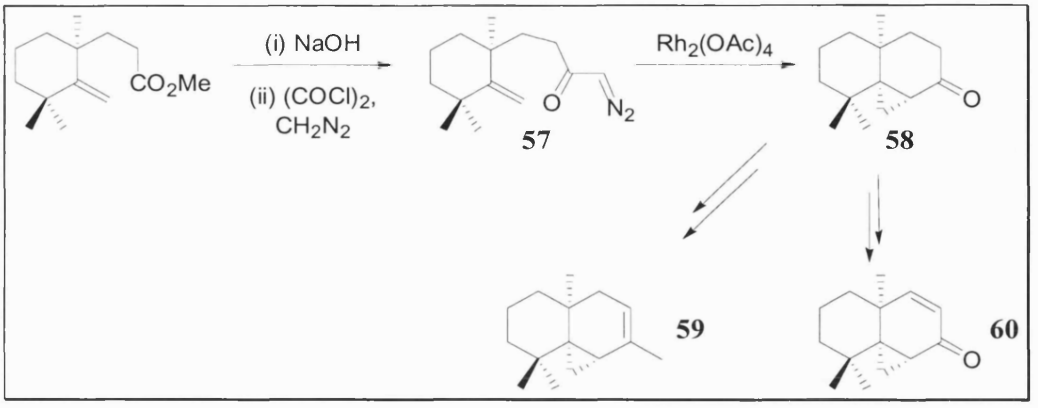


Figure 12: Examples of catalysts for enantioselective cyclopropanation

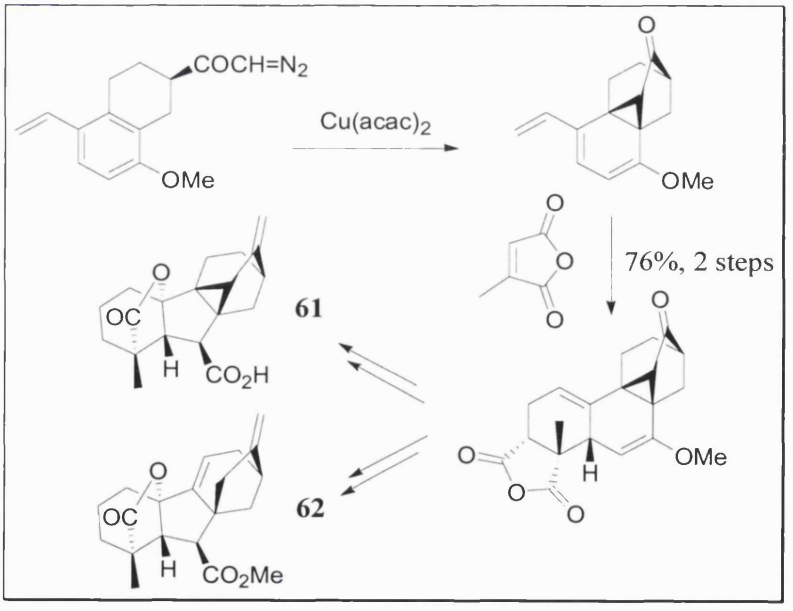
When the diazo unit and the alkene are part of the same molecule, an intramolecular cyclopropanation is possible, leading to a bicyclic product. Moreover, when forming five- or six-membered rings, a single diastereoisomer is frequently obtained. This strategy has been widely used to synthesise terpenes. For example, the cyclopropane dihydromayurone **58** was formed as a single diastereoisomer from diazoketone **57** using a rhodium catalyst, and could be converted into sesquiterpenes thujopsene **59** and mayurone **60** (**Scheme 19**).[74]

[74] Srikrishna, A.; Anebouselvy, K. *J. Org. Chem.* **2001**, *66*, 7102, and references cited therein.



Scheme 19: Intramolecular cyclopropanation in sesquiterpene synthesis

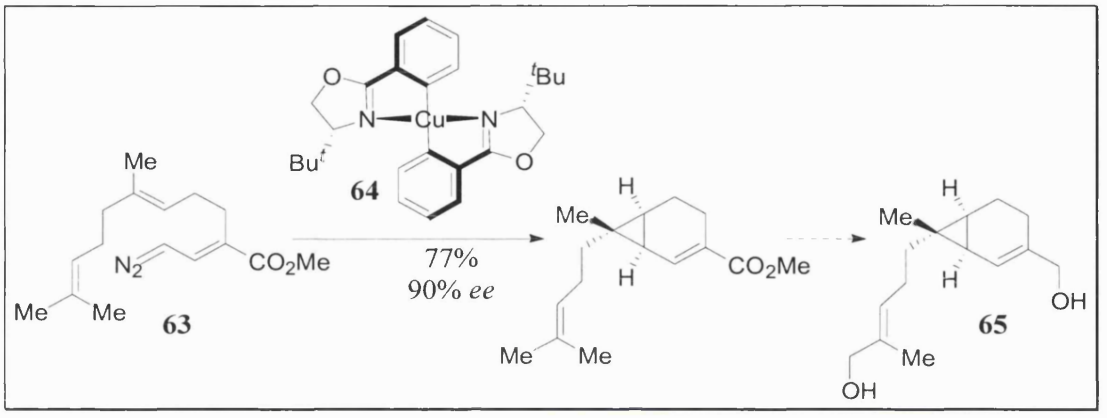
An illustration of the use of intramolecular cyclopropanation for the construction of the complex scaffolds present in natural products is the synthesis of gibberellin derivatives **61** and **62** by Mander, in an intramolecular version of the Buchner reaction (**Scheme 20**).[75] In this case, the use of a copper catalyst was necessary in order to minimise the formation of C-H insertion products, otherwise observed with rhodium catalysts.



Scheme 20: Synthesis of gibberellins *via* intramolecular Buchner reaction

In the intramolecular cyclopropanation as well as in the intermolecular version, catalysts are constantly being developed to access enantiopure substrates starting from achiral

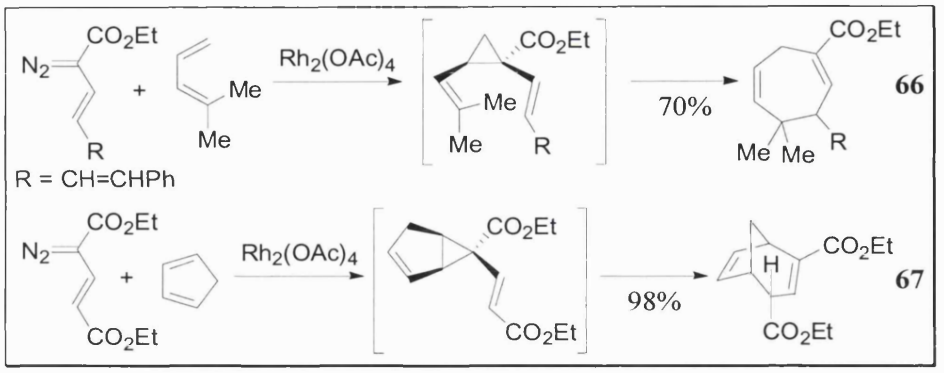
precursors. In the following example of the synthesis of sirenin **65**, Corey's bis-oxazoline **64** (related to the well known copper semicorrin **52**) achieved the intramolecular cyclopropanation of the γ-diazocarbonyl **63** with 90% *ee*, where copper semicorrin **52** only gave 60% *ee* (**Scheme 21**).[76]



Scheme 21: Corey's enantioselective synthesis of sirenin

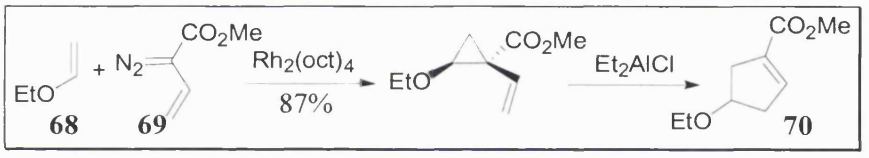
Substituted cyclopropanes, such as vinyl cyclopropanes, are prone to rearrangements due to their inherent strain. Therefore cyclopropanation has been used in conjunction with subsequent sigmatropic rearrangements to afford products of formal cycloaddition.[77] For example, the reaction of vinyldiazoacetates with dienes gives *cis*-1,2-divinylcyclopropanes, which can undergo facile [3,3]-sigmatropic Cope rearrangement, and the sequence amounts to a [3+4]-cycloaddition. **Scheme 22** shows two examples where this formal cycloaddition was used to access 1,4-cycloheptadiene **66**[78] and bicyclic diene **67**.[79]

[75] King, G. R.; Mander, L. N.; Monck, N. J. T.; Morris, J. C.; Zhang, H. *J. Am. Chem. Soc.* **1997**, *119*, 3828.
[76] Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745.
[77] For a review of transition metal-catalysed cycloadditions, see Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
[78] Davies. H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817.
[79] Davies. H. M. L.; Smith, H. D.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853.



Scheme 22: Tandem cyclopropanation-Cope rearrangement

Similarly, a formal [3+2]-cycloaddition resulted from the reaction of vinyl ethers **68** with carbenes derived from vinyldiazoacetates **69**. Subsequent Lewis acid-catalysed rearrangement provided entry to substituted cyclopentene compounds **70** (**Scheme 23**).[80]

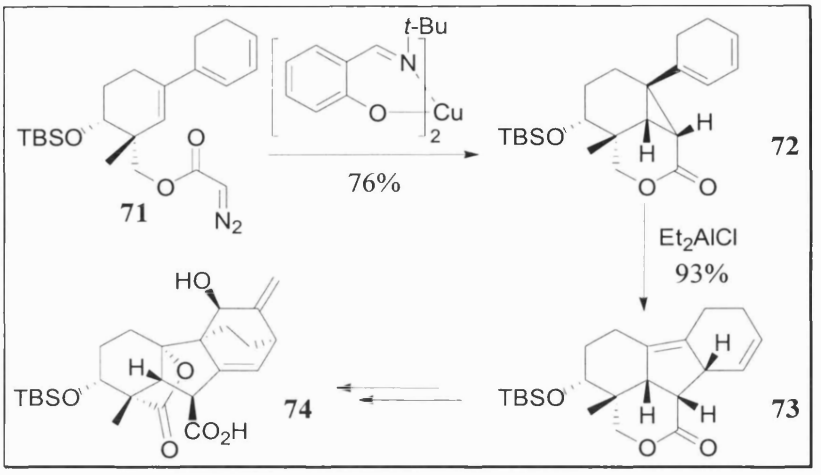


Scheme 23: Formal [3+2]-cycloaddition

Corey used a strategy combining intramolecular diene cyclopropanation and vinylcyclopropane-cyclopentene rearrangement in his synthesis of antheridic acid **74** (**Scheme 24**).[81] The copper-catalysed cyclopropanation of the diazoacetate **71** afforded the fused tricyclic lactone **72** bearing a vinylic cyclopropane, which rearranged to the desired cyclopentene-containing precursor **73** upon treatment with a Lewis acid.

[80] (a) Davies. H. M. L.; Hu, B. *Tetrahedron Lett.* **1992**, *33*, 453. (b) Davies. H. M. L.; Hu, B. *J. Org. Chem.*, **1992**, *57*, 3186. (c) Davies. H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535.

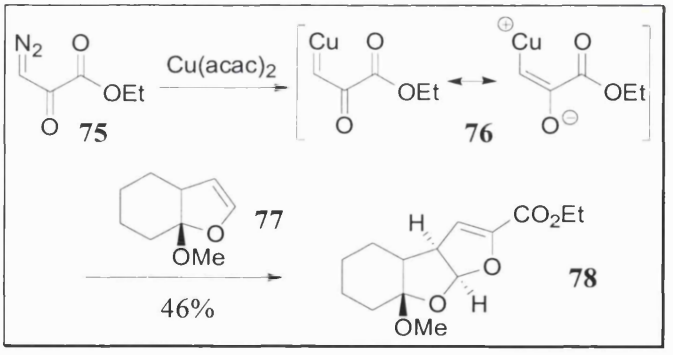
[81] Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025.



Scheme 24: Corey's synthesis of antheridic acid

Metal carbenes have also found widespread use in other cycloaddition reactions.

α-Ketocarbenes are 1,3-dipoles, which can react with electron-rich olefins leading to five-membered rings in a [3+2]-cycloaddition. Alonso and Wenkert showed that the copper carbenoid **76** derived from ethyl diazopyruvate **75** and copper(II) acetylacetonate could add stereoselectively to dihydrofuran **77**, thus forming the tricyclic adduct **78** (**Scheme 25**).[82]



Scheme 25: 1,3-Dipolar ketocarbene addition

Cyclopropanation of alkenes and other cycloadditions involving metal-catalysed decomposition of diazocompounds have many parallels to related reactions of stable

[82] (a) Alonso, M. E.; Jano, P.; Hernandez, M. I.; Greenberg, R. S.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 3047. (b) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sanchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021.

carbene complexes. However, the next two sections deal with reactions of synthetic importance which are specific to metal-catalysed decomposition of diazocompounds, namely insertion reactions and ylide formation.

I-3.5.2 C-H and X-H insertion

Metal carbenes generated by transition metal-catalysed decomposition of diazocompounds have proved to be versatile reagents in insertion reactions into single bonds (**Scheme 26**).

Scheme 26: General scheme for insertion reaction

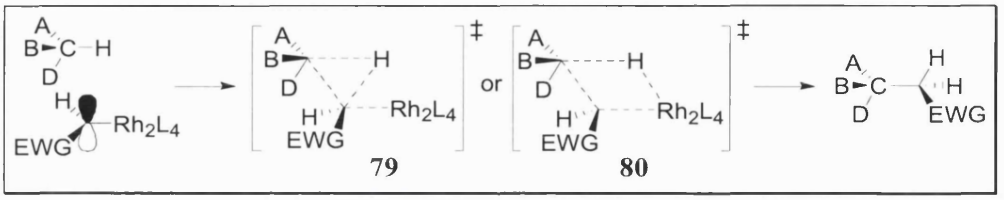
Depending on the polarity of the X-H bond, insertion reactions differ in their mechanism. Low polarity C-H and Si-H bonds undergo insertion in a concerted process, retaining the stereochemical information at the carbon atom in the case of the C-H insertion.[83] Due to the highly polarised nature of O-H, N-H and S-H bonds, the corresponding carbene insertion reactions are almost certainly stepwise processes better described as ylide transformations.[56,67]

In the accepted mechanism for C-H insertion of catalytically-generated metal carbenes (**Scheme 27**),[84] overlap of the vacant *p* orbital on the metal carbene with the σ orbital of

[83] Taber, D. F.; Petty, E. H.; Ramon, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.
[67] Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1.
[84] Doyle, M. P. "Metal Carbene Complexes in Organic Synthesis: Diazodecomposition- Insertion and Ylide Chemistry" in *Comprehensive Organometallic Chemistry II*; Hegedus, L. S.. Ed.; Pergamon Press, New York, **1995**; Vol. 12, Ch. 5.2.

the C-H bond initiates the process. Experimental data on reactions catalysed by dirhodium (II) compounds support the existence of a transition state **79** where the new C-C and C-H bonds form as the ligated metal dissociates.

Another hypothesis favours a different transition-state **80** in which hydrogen is transferred on to the rhodium catalyst.[85]



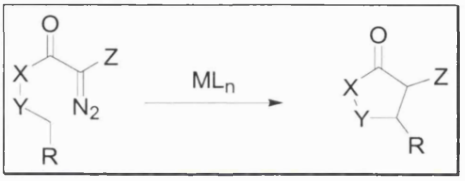
Scheme 27: Mechanism for C-H insertion with Rh(II) catalysts

According to this model, the electrophilicity of the carbene centre will influence the distance from the C-H bond at which C-C bond formation occurs. If the carbene is very electrophilic, *i.e.* the ligands have increased electron-withdrawing character, bond formation can take place at a greater distance and result in lower selectivity. By decreasing electron withdrawal, the transition state occurs later and selectivity is enhanced. Generally, activation of a C-H bond can be influenced electronically, and will preferentially occur at sites that can stabilise build-up of a positive charge. Therefore the presence of an adjacent heteroatom will activate the C-H bond for insertion,[86] whereas electron-withdrawing groups such as esters are inhibiting.[87] Steric and conformational factors can also influence the outcome of the reaction, and the balance between these factors results in improved regiocontrol. This modulation of reactivity of the metal carbene as well as the substrate opens possibilities for selective C-H insertions which was frequently lacking in the same reaction with "free" carbenes.

[85] Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.
[86] (a) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (b) Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1749.
[87] Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

Due to the limitations initially encountered in intermolecular C-H insertion reactions,[56,88] intramolecular reactions have been studied more extensively. It was expected that entropic effects would improve the chemoselectivity of the process, minimising competing cyclopropanation, carbene dimerisation and C-H insertion at undesired centres.

Most intramolecular transformations involve α-diazocarbonyl compounds (**Scheme 28**): β-keto-α-diazoesters, -phosphonates and -sulfones afford cyclopentanone derivatives (X = Y = CH_2, Z = CO_2Et, $PO(OR')_2$, SO_2Ar); diazoacetates, diazoacetoacetates and diazomalonates form γ-lactones (X = O, Y = CH_2, Z = H, $COCH_3$, CO_2R'); 3-alkoxy-1-diazoacetates produce 2(3*H*)-dihydrofuranones (X = CH_2, Y = O, Z = H).



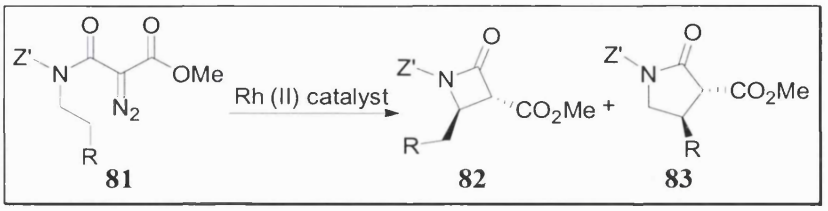
Scheme 28: Intramolecular C-H insertion

The formation of five-membered rings is highly favoured over other ring-sizes, and reactivity increases with increasing alkyl substitution at the carbon centre: 1° C-H << 2° C-H < 3° C-H.[89]

In the case of acyclic diazoacetamides **81**, competition between the formation of β-lactams **82** and γ-lactams **82** makes regiocontrol a more difficult issue, and mixtures of products are commonly observed (**Scheme 29**). β-Lactam formation is typically favoured due to the activating adjacent nitrogen atom,[90] and can be formed selectively

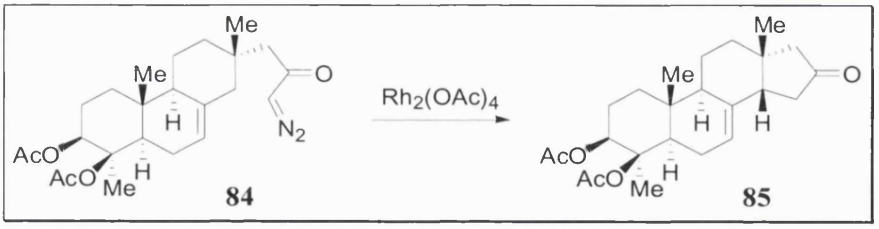
[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.
[88] Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
[89] Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686, and references cited therein.
[90] Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

when the amide is protected with a bulky *tert*-butyl group (Z' = $C(CH_3)_3$). However γ-lactams can be obtained as the sole insertion product when the amide nitrogen is protected with a *p*-nitrophenyl group (Z' = *p*-$NO_2C_6H_4$).



Scheme 29: Competition between β-lactam and γ-lactam formation

Rhodium catalysts, and in particular $Rh_2(OAc)_4$, have generally proven more efficient and selective than traditional copper catalysts for C-H insertion. In their synthesis of the 16-keto steroid **85**, Wenkert and co-workers observed a 60% conversion of the precursor **84** using $Rh_2(OAc)_4$, where $CuSO_4$ had given poor yields (**Scheme 30**).[91]

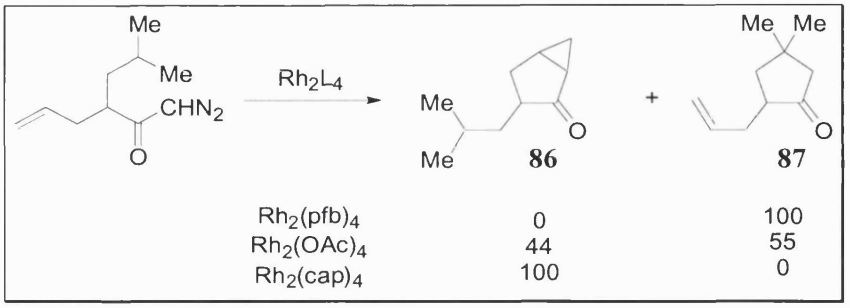


Scheme 30: Rh(II)-catalysed C-H insertion

In competitive intramolecular transformations of diazocompounds catalysed by rhodium complexes, the choice of ligands is crucial since they can switch reaction preference. In the following example (**Scheme 31**), and relative to unselective $Rh_2(OAc)_4$, use of dirhodium (II) perfluorobutyrate $Rh_2(pfb)_4$ affords insertion product **87** exclusively, whereas dirhodium (II) caprolactamate $Rh_2(cap)_4$ is selective for cyclopropanation product **86**.[92]

[91] Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pelliciari, R. *J. Org. Chem.* **1982**, *47*, 3242.

[92] (a) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.



Scheme 31: Catalyst-dependent chemoselectivity for C-H insertion

Asymmetric induction is made possible in insertion reactions because the chiral catalyst undergoes release of the carbene only in the transition state of the product-forming step.[68] The prolific development of chiral catalysts for metal-carbenoid transformations has benefited C-H insertion reactions, and since the first report of asymmetric induction by McKervey,[93] selective systems have been identified using mostly rhodium (II) complexes.[90] Among these, the second-generation imidazolidinone catalyst $Rh_2(MPPIM)_4$ **88** has proved very efficient in the asymmetric synthesis of 4-substituted γ-butyrolactones (**Figure 13**).[94]

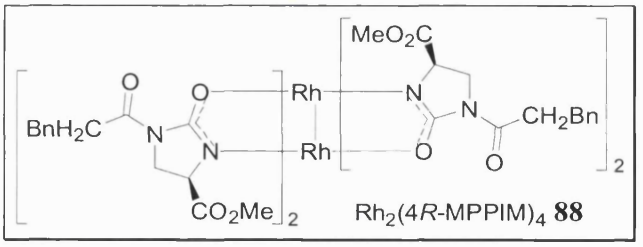
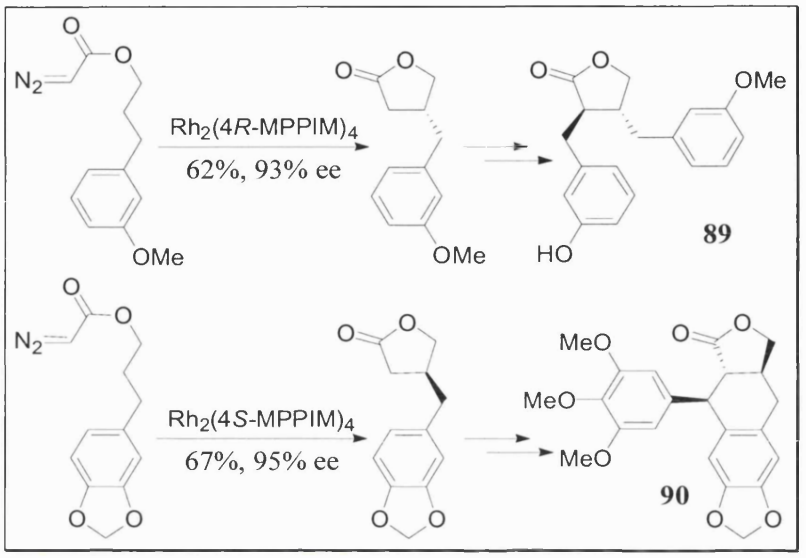


Figure 13: Doyle's imidazolidinone catalyst $Rh_2(MPPIM)_4$

The excellent regio- and stereocontrol observed with this type of catalyst is thought to stem from the restricted access available to the reacting carbenoid centre due to the pendant acyl chains on the chiral ligand. This selectivity has been used in the syntheses

[68] Doyle, M. P.; Forbes, D. C. *Chem. Rev.*, **1998**, *98*, 911.
[93] Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361.
[90] Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
[94] Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146.

of various lignans[95] such as enterolactone **89**[96] and isodeoxypodophyllotoxin **90** (**Scheme 32**).[94]



Scheme 32: Enantioselective synthesis of lignan lactones

Over the past few years, major progress has been achieved in intermolecular C-H insertion reactions. Although this type of reaction was previously considered of little synthetic utility due to its poor selectivity and competitive carbene dimerisation, Davies and co-workers have shown that a particular type of diazocompound allowed the intermolecular insertion to take place in a very chemoselective and enantiocontrolled fashion.[97] In addition to the electron-withdrawing group, capable of enhancing the carbenoid electrophilicity, donor / acceptor-substituted carbenoids such as **91** (**Figure 14**) possess an electron-donating functionality, which stabilises the carbenoid through resonance. The resulting intermediate is therefore less prone to dimer formation.[98]

[95] For a review on lignan lactones and their properties, see Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75.
[96] Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L.; Bode, J. W.; Simonsen, S. H.; Lynch, V. *J. Org. Chem.* **1995**, *60*, 6654.
[94] Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146.
[97] (a) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *47*, 617. (b) Davies, H. M. L. *J. Mol. Catal.* **2002**, *189*, 125.
[98] Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.*, **2000**, *122*, 6897.

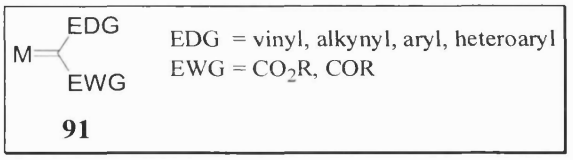
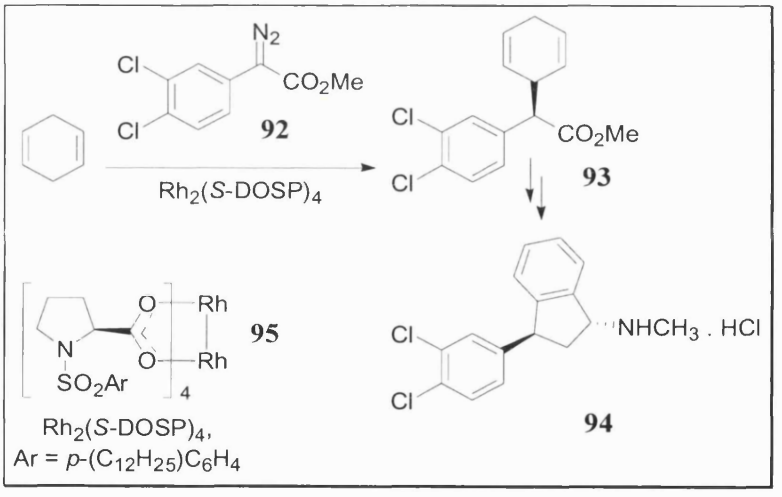


Figure 14: Donor/acceptor-substituted metal carbenes

An example of the synthetic utility of the intermolecular C-H insertion is shown in **Scheme 33**, with the recent enantioselective synthesis of the potent monoamine re-uptake inhibitor (+)-indatraline **94**.[99] The reaction of dichlorophenyldiazoacetate **92** with 1,4-cyclohexadiene catalysed by the prolinate complex Rh_2(*S*-DOSP)$_4$ **95** afforded γ,δ-unsaturated ester **93** in 83% yield and 93% ee. This chemoselectivity for C-H insertion is in sharp contrast with the reaction of acceptor-substituted carbenoids, which formed significant amounts of cyclopropanation products when reacted with 1,4 dienes.[100]



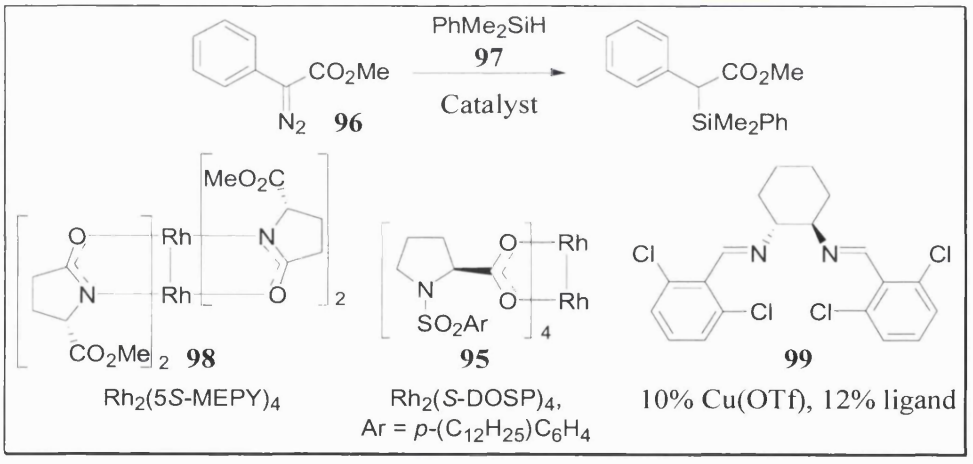
Scheme 33: Synthesis of (+)-indatraline *via* intermolecular C-H insertion

Si-H insertion is thought to proceed *via* a mechanism similar to that of C-H insertion.[101] The higher reactivity of the Si-H bond towards insertion allows selective intermolecular

[99] Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951.
[100] (a) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (b) Müller, P.; Tohill, S. *Tetrahedron Lett.* **2000**, *56*, 1725.
[101] Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

processes that are more restricted in C-H insertion to occur. However, this higher reactivity implies an earlier transition state, thus limiting catalyst control of enantioselectivity.

The first example of a rhodium (II) catalysed reaction of diazoesters with silanes resulting in the formation of α-silylcarbonyl compounds by Si-H insertion was reported by Doyle and co-workers in 1988.[102] Research efforts have been directed towards the development of metal catalysts to address the issue of enantiocontrol.[103] The Si-H insertion of phenyldiazoacetate **96** with phenyldimethylsilane **97** was shown to proceed with moderate to good enantioselectivity with $Rh_2(5S\text{-MEPY})_4$ **98** (47% ee),[104] $Rh_2(S\text{-DOSP})_4$ **95** (85% ee)[105] as well as some copper(I) catalysts associated with chiral C_2-symmetric Schiff base ligands **99** (83% ee) (**Scheme 34**).[106]



Scheme 34: Catalysts for enantioselective Si-H insertion

While the development of catalysts for Si-H insertion is still ongoing, the effects of silicon substituents on enantiocontrol are still to be investigated.

[102] Bagheri, V. B.; Doyle, M. P.; Taunton, J.; Claxton, E. E. *J. Org. Chem.* **1988**, *53*, 6158.
[103] For a parallel approach to catalyst screening, see Buck, R. T.; Coe, D. M.; Drysdale, M. J.; Ferris, L.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Sanghera, J. B. *Tetrahedron: Asymmetry* **2003**, *14*, 791.
[104] Buck, R. T.; Doyle, M. P.; Drysdale, M. J.; Ferris, L.; Forbes, D. C.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Zhou, Q.-L. *Tetrahedron Lett.* **1996**, *37*, 7631.
[105] Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tetrahedron Lett.* **1997**, *38*, 1741.
[106] Dakin, L. A.; Schaus, S. E.; Jacobsen, E. N.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 8947.

I-3.5.3 Ylide formation

Ylides **100** are species bear opposite charges on adjacent atoms (X, with X=O, N, S, P, Se...) (**Figure 15**).

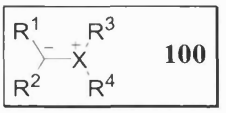
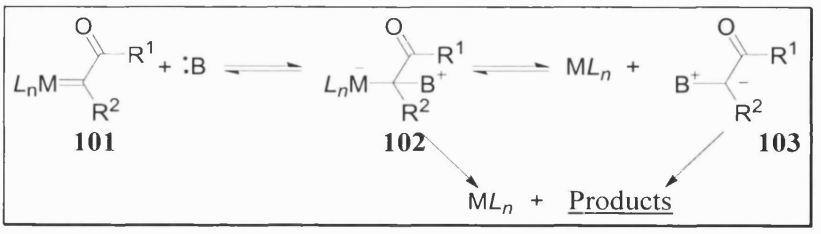


Figure 15: General structure of ylides

Carbenoid entry into ylides has proved a successful alternative to the methods for preparing ylides involving the deprotonation of onium ions by a strong base,[107] or the desilylation of α-silyl onium ions by fluoride ions.[108] As discussed earlier, metal carbenes **101** derived from α-diazocarbonyl compounds are highly electrophilic. They can therefore readily undergo nucleophilic addition of an available Lewis base, typically a heteroatom-substituted organic substrate, to form adducts **102**. These can in turn either dissociate from the catalytically active metal species (forming the free ylide **103** or rearrangement products), or revert to the metal carbene and Lewis base. Generally, the metal-carbon bond of the stabilised adduct **102** is weaker than the newly formed carbon-Lewis base bond, and therefore breaks preferentially (**Scheme 35**).



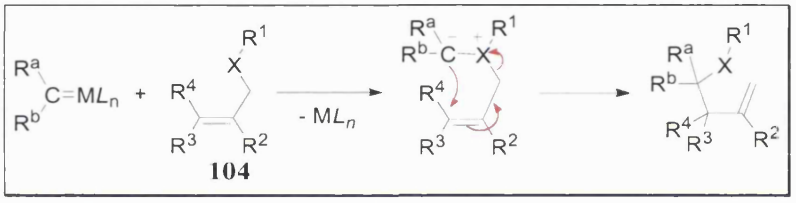
Scheme 35: Generation of ylides from metal carbenes

Nucleophilic species that are known to trap carbenes in this fashion include ethers, thioethers, amine and halides, along with sp^2- or sp-hybridised heteroatoms, as found in aldehyde, ester, ketone, imine, thiocarbonyl and nitrile functional groups.[109]

[107] Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2112.
[108] Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.
[109] Padwa, A.; Hornbuckle, S.F. *Chem. Rev.* **1991**, *91*, 263.

Ylides are highly reactive intermediates and are known to undergo a broad range of inter- and intramolecular reactions: [2,3]-sigmatropic rearrangement of allyl-substituted ylides, [1,2]-insertion or Stevens rearrangement and β-elimination. In the case of sp^2- or *sp*-hybridised heteroatoms, dipolar cycloaddition is also possible.

The symmetry-allowed [2,3]-sigmatropic rearrangement is a facile bond reorganisation process for catalytically-generated ylides derived from allylic (or propargylic) substrates **104**.[110] When the unsaturated bond bears substituents, allylic transposition provides evidence that the reaction proceeds *via* an ylide, rather than direct C-X insertion (**Scheme 36**).[50]

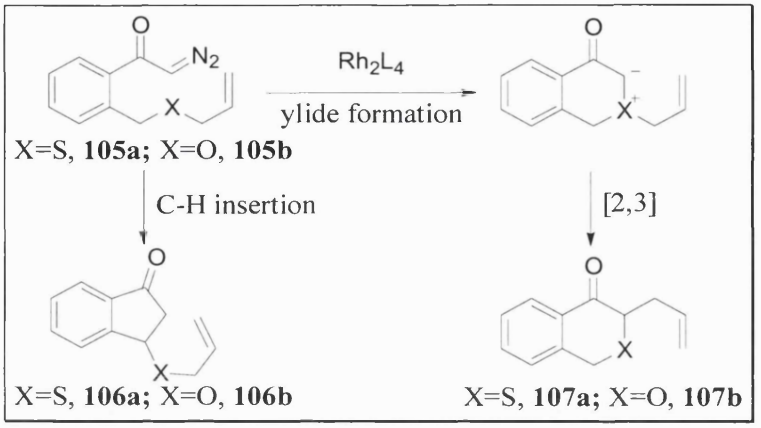


Scheme 36: [2,3]-Sigmatropic rearrangement of allylic ylides

In comparative experiments, allylic sulfides **105a** (X=S) showed a greater tendency towards Rh(II)-catalysed ylide formation and subsequent [2,3]-sigmatropic rearrangement than the corresponding allylic ethers **105b** (X=O), for which C-H insertion was the major competing pathway. In the latter case, a ratio of 1:1 of rearrangement product **107b** /C-H insertion product **106b** was observed (**Scheme 37**), whereas the reaction of allylic sulfide afforded a 9:1 ratio in favour of the rearrangement product **107a**.[111] The prevalence of sulfonium ylides compared to oxonium ylides is probably due to the presence of p_π-d_π interaction which helps stabilise the charge on the

[110] Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781.
[50] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
[111] Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817.

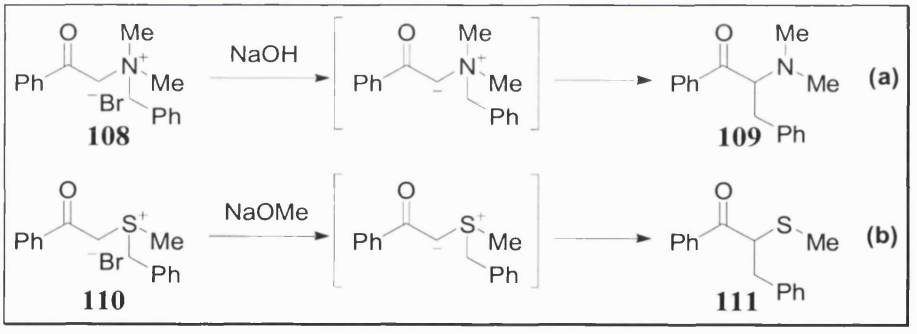
sulfur atom, and is consistent with the relative nucleophilicities of the two heteroatoms.[112]



Scheme 37: Selectivity in ylide formation

Among the broad range of reactions involving ylides, [1,2]-shift has been shown to occur with a variety of substrates.

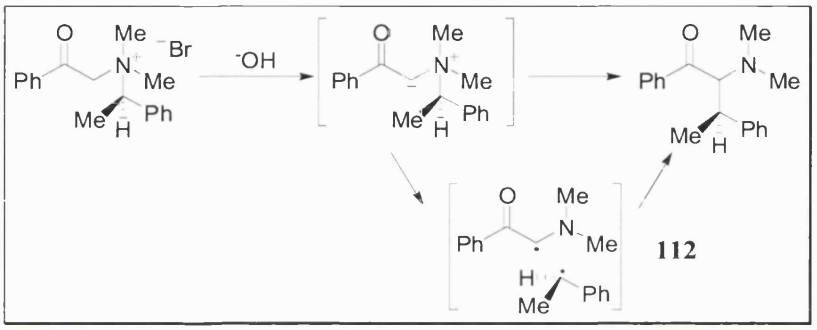
The first example was reported in 1928 by Stevens *et al.*, who observed the conversion of ammonium bromide **108** to α-benzyl amine **109** in basic medium (**Scheme 38, (a)**).[113] The sulfonium bromide **110** was shown to exhibit the same reactivity, giving the corresponding sulfide **111** when treated with sodium methoxide (**Scheme 38, (b)**).[114]



Scheme 38: Stevens rearrangement of ylides

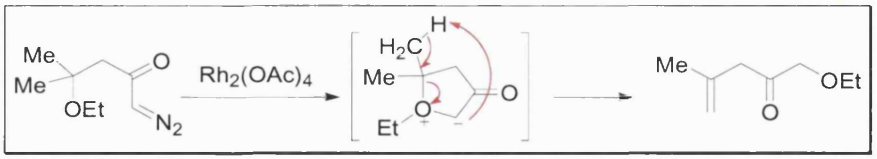
[112] Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.
[113] Stevens, T.S.; Creighton, E.M.; Gordon, A.B.; McNicol, M. *J. Chem. Soc.* **1928**, 3193.
[114] Stevens, T.S.; Thomson, T. *J. Chem. Soc.* **1932**, 69.

Ollis investigated the reaction and demonstrated that it proceeded *via* radical pair intermediates **112** and subsequent rapid recombination within the solvent cage.[115] This is consistent with the Woodward/Hoffmann rules of conservation of orbital symmetry, which forbid a concerted [1,2]-shift, and accounts for the high degree of retention of configuration usually observed for the reaction (**Scheme 39**).



Scheme 39: Homolytic mechanism for the Stevens rearrangement

In addition to [2,3]- and [1,2]-rearrangements, ammonium, oxonium and sulfonium ylides which possess a β-hydrogen can undergo β-elimination to form an alkene and the corresponding amine, ether or sulfide. In the case of oxonium ylides, it has been shown that this reaction does not involve radical intermediates, and probably proceeds *via* intramolecular abstraction of the β-hydrogen by the negatively charged carbanion of the ylide as illustrated in **Scheme 40**.[116]



Scheme 40: β-Elimination of oxonium ylides

[115] (a) Ollis, W.D.; Rey, M.; Sutherland, I.O. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1009. (b) Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1049.
[116] (a) Crackett, P. H.; Sayer, P.; Stoodley, R. J.; Greengrass, C. W. *J. Chem. Soc., Perkin. Trans. 1* **1991**, 1235.(b) Iwamura, H.; Imahashi, Y.; Kushida, K.; Aoki, K.; Satoh, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1690.

Carbonyl ylides **113** are transient dipolar reaction intermediates which exhibit allyl-type resonance (**Figure 16**),[117] and can undergo a range of 1,3-dipolar cycloaddition reactions.

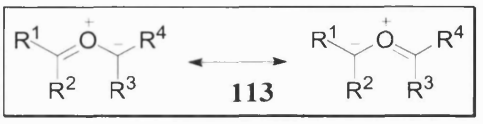
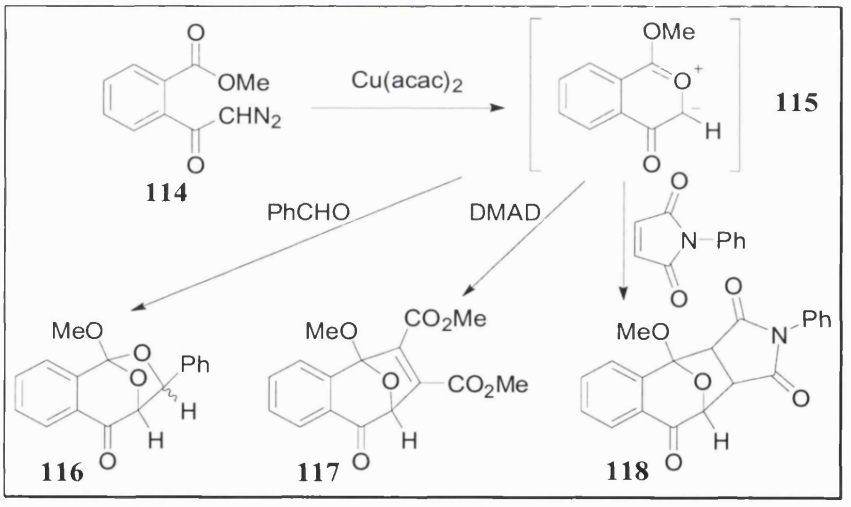


Figure 16: Allyl-type resonance in carbonyl ylides

The intramolecular metal-catalysed generation of carbonyl ylides from α-diazocarbonyl reagents has proved a facile process and has been used in tandem with inter- and intramolecular 1,3-dipolar cycloadditions in order to access highly substituted heterocycles.[109] A typical example involves treatment of *o*-(methoxycarbonyl)-α-diazoacetophenone **114** with catalytic copper(II) acetylacetonate and subsequent trapping of the carbonyl ylide dipole **115** with a variety of dipolarophiles such as benzaldehyde, dimethylacetylenedicarboxylate (DMAD), or *N*-phenylmaleimide to give cycloadducts **116**, **117**, and **118** respectively (**Scheme 41**).[118]



Scheme 41: Tandem carbonyl ylide/dipolar cycloaddition

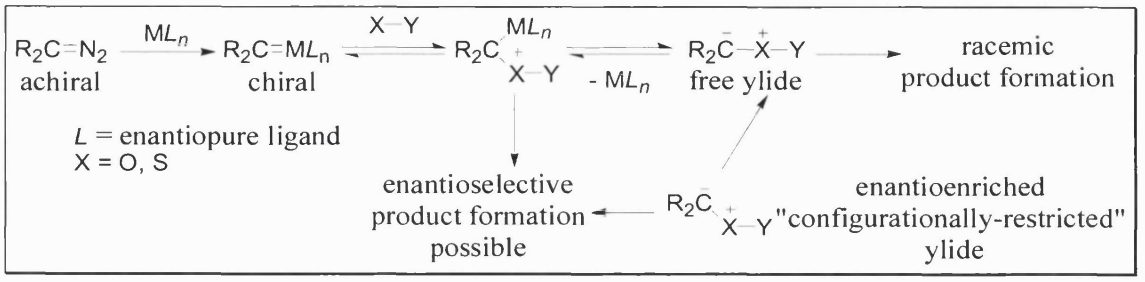
[117] Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 2513.
[109] Padwa, A.; Hornbuckle, S.F. *Chem. Rev.* **1991**, *91*, 263.
[118] Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1266, and references cited therein.

In the absence of dipolarophile, transient carbonyl ylides may generally undergo proton transfer as another possible route to stable products. This process was first reported by Büchi and co-workers in 1953,[119] and has been shown to occur in an intramolecular fashion.[120]

Given the wealth of chemical transformations accessible to ylides – and more generally to metal carbenes, it is not surprising to observe mixtures of products from competing processes. Control of chemoselectivity by choice of the appropriate catalyst and diazocarbonyl compound has significantly increased the viability of ylides as synthetic intermediates. A number of reviews illustrate the advances in selective transformations owing to the continuous development of catalytic systems.[121] The same factors also have profound effects on enantioselectivity in reactions employing chiral catalysts. Despite the significant progess achieved in enantioselective C=C, C-H or X-H insertion of metal carbenoids, ylide transformations present a more difficult case.

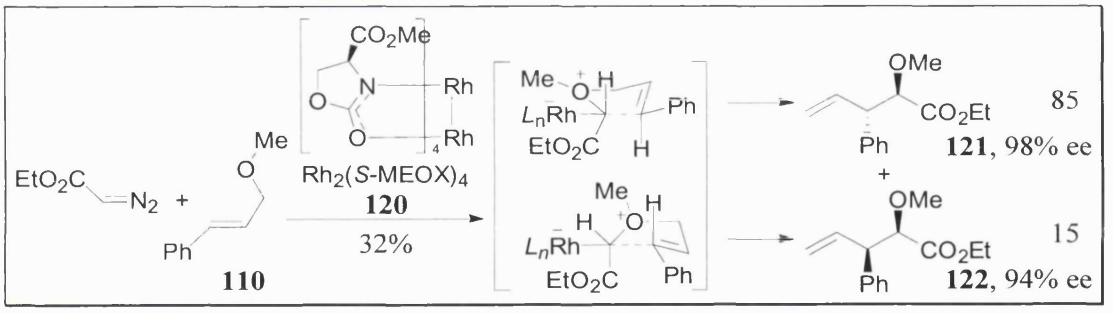
Asymmetric induction using a chiral catalyst is generally conditional to the metal remaining associated with the ylide during the subsequent transformation. As mentioned previously, the catalyst is likely to dissociate because of the relative M-C and X-C bond strengths. The remaining free ylide is unlikely to trigger asymmetric induction, unless it is able to retain a "chiral" configuration, for example at the sulfur centre (**Scheme 42**).[50]

[119] Kharasch, M.S.; Rudy, T.; Nudenberg, W.; Büchi, G. *J. Org. Chem.* **1953**, *18*, 1030.
[120] Lottes, A.; Landgrebe, J. A.; Larsen, K. *Tetrahedron Lett.* **1989**, 4089.
[121] (a) Merlic, C. A.; Zechman. A. L. *Synthesis* **2003**, *8*, 1137. (b) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617*, 98.
[50] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.



Scheme 42: Asymmetric induction in ylide transformations

In the following example, Doyle obtained up to 98% ee in the enantioselective intermolecular oxonium ylide formation / sigmatropic rearrangement of allylic ether **119**, using a chiral rhodium(II) carboxamidate **120**. In this case, the observation of a significant catalyst-dependent diastereoselectivity (using $Rh_2(OAc)_4$ gave 17:83 **121**:**122**) implicates the presence of a catalyst-associated ylide in the product-forming step (**Scheme 43**).[122]



Scheme 43: Diastereoselective tandem ylide formation/[2,3]-sigmatropic rearrangement

[122] Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653.

II Results and Discussion

II-1 Strategy for the synthesis of the tagetitoxin core structure

II-1.1 Retrosynthetic analysis

The aim of this project was to design an efficient route to tagetitoxin (proposed structure **2a**) using known reactions as well as new methodology (**Figure 17**).

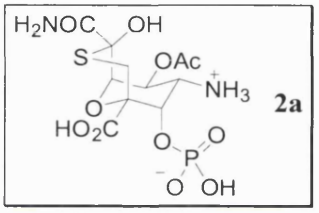
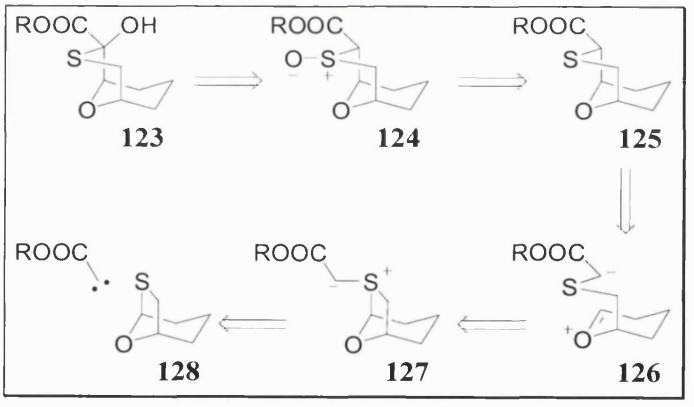


Figure 17: Target structure of tagetitoxin

In the first instance, we considered the core structure **123**: a bridged bicyclic 1,4-oxathiane bearing carbonyl and hydroxyl functionalities α to the sulfur atom. This might be derived from a sulfoxide such as **124** using a Pummerer reaction, or by hydroxylation of the enolate of ester **125** (**Scheme 44**).

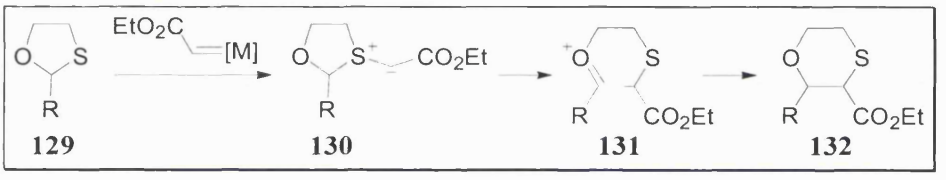


Scheme 44: Retrosynthesis of the core structure of tagetitoxin

Retrosynthetic disconnection of the C-C bond α to the ester unmasks intermediate **126**, bearing an ester enolate and oxonium ion, which can be derived from the rearrangement of bicyclic sulfur ylide **127**. This substrate could be synthesised from a carbene and

bridged bicyclic 1,3-oxathiolane **128**. The sequence **128-125** amounts to a formal insertion of the carbene into the C-S bond, and overall a one-carbon ring expansion of the 5-membered ring to the corresponding 6-membered ring.

In order to simplify the problem, we consider the monocyclic substrate **129** (**Scheme 45**). The ring expansion reaction is expected to proceed *via* generation of the sulfur ylide **130** when the 1,3-oxathiolane **129** is treated with a metal carbene derived from ethyl diazoacetate. O-assisted ring opening should give zwitterion **131**, which can reclose to form the desired 1,4-oxathiane **132**. An alternative to this putative mechanism would be a Stevens-type homolytic rearrangement.[123]



Scheme 45: Putative heterolytic mechanism of ring expansion

At the start of our studies there were no reports of ring expansion reaction of cyclic *O,S*-acetals. However, several related examples of ring expansion of sulfur-containing heterocycles and *O,O*- and *N,O*-acetals, as well as [1,2]-shifts of *O,S*-acetals had been described,[56] which supported the feasibility of the proposed reaction.

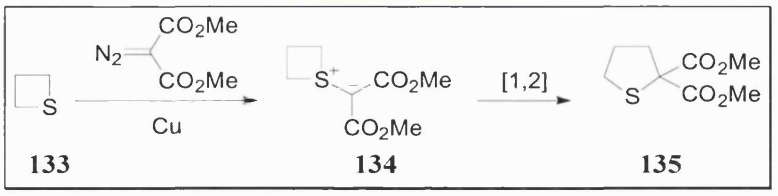
II-1.2 Precedent for ring expansion in sulfur ylide chemistry

Ring expansions of sulfur-containing cycles have been achieved *via* [1,2] shift processes of sulfur ylides. The reaction of thietane **133** with dimethyldiazomalonate formed the

[123] (a) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1009. (b) Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1049. (c) Marko, I. E. *The Stevens and Related Rearrangements* in *Comprehensive Organic Synthesis*, Trost, B. M. and Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 3, p. 913.

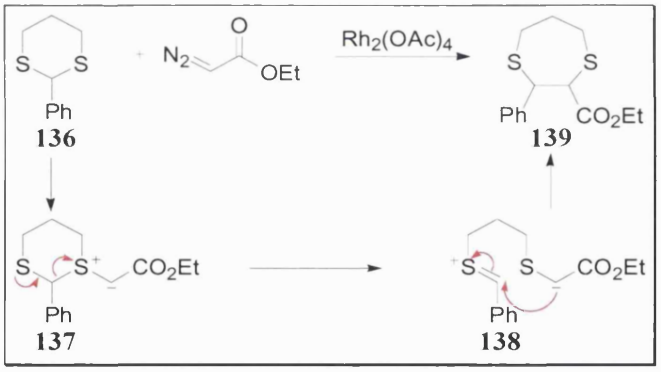
[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.

ylide **134**, which underwent Stevens rearrangement to give tetrahydrothiophene **135** in 26% yield (**Scheme 46**).[124]



Scheme 46: Ring expansion of thietane

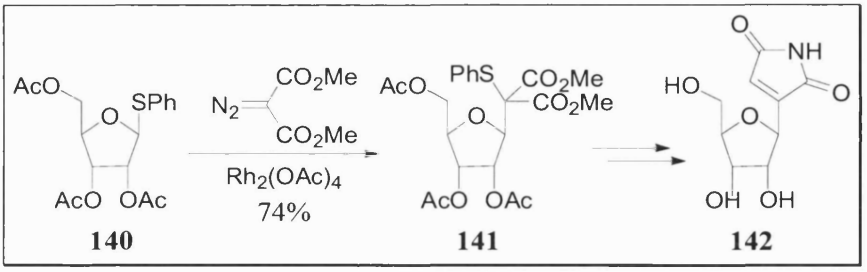
More closely related to our proposed reaction are rearrangements where the ylide is formed from an acetal. Doyle has reported the formation of ring-expanded [1,2]-insertion product **139** from dithiane **136** (**Scheme 47**).[125] A heterolytic mechanism was proposed for the ring expansion, where neighbouring-group participation may facilitate breakage of the ylide C-S bond (**137**) to form the aryl-stabilised sulfonium ion **138**.



Scheme 47: Ring expansion of a dithiane substrate

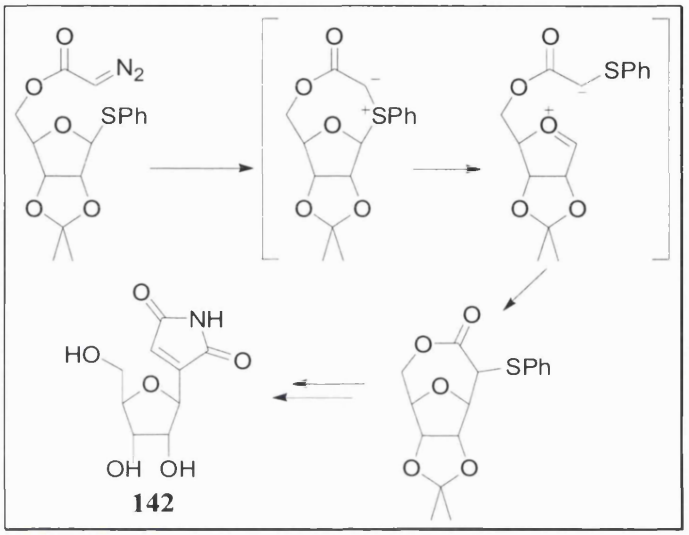
Tandem ylide-formation / [1,2]-shift has been used by Kametani and co-workers[126] as a stereoselective method for C-glycosylation. C-glycoside **141** derived from thioglycoside **140** served as the key intermediate for the synthesis of (+)-showdomycin **142** (**Scheme 48**).

[124] Ando, W.; Koudo, S.; Nakayama, K.; Ichibori, K; Kohoda, H.; Yamato, H.; Imai, I.; Nakaido, S.; Migira, T. *J. Am. Chem. Soc.* **1972**, *94*, 3870.
[125] Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
[126] Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010.



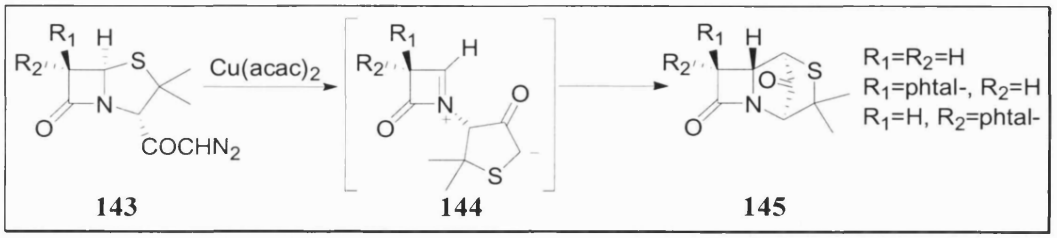
Scheme 48: Rearrangement of *O,S*-acetal in the synthesis of showdomycin

Kim reported an intramolecular approach for the same target (**Scheme 49**).[127]



Scheme 49: Intramolecular rearrangement of *O,S*-acetal in the synthesis of showdomycin

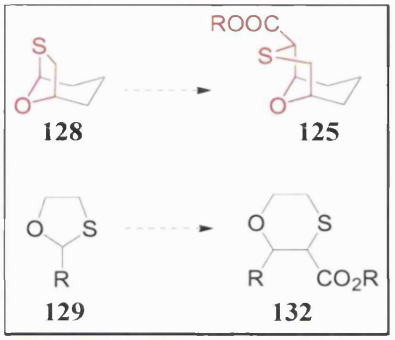
The copper-catalysed ring expansion of fused *N,S*-acetals was described by Mak *et al.* in their approach to carbapenems.[128] Decomposition of *β*-lactam diazoketones **143** formed the tricyclic products **145** in good yields (**Scheme 50**). The inversion of stereochemistry observed at the lactam bridge is consistent with an iminium ion intermediate **144**.



Scheme 50: Ring expansion of *N,S*-acetal in a penicillin derivative

[127] Kim, G. C.; Kang, S. W.; Kim, S. N. *Tetrahedron Lett.* **1993**, *34*, 7627.
[128] Mak, C. P.; Baumann, K.; Mayerl, F.; Mayerl, C.; Fliri, H. *Heterocycles* **1982**, *19*, 1647, and references cited therein.

In light of these successful examples of tandem ylide formation / [1,2]-shift from *S,S*-*O,S*- and *N,S*-acetals, we decided to investigate our proposed strategy for the synthesis of the core structure of tagetitoxin **125**, *via* a 1,3-oxathiolane precursor **128**. However such bridged bicyclic oxathiolanes are not easily accessible, therefore methodology studies were carried out using monocyclic oxathiolane **129** to test the feasibility of the ring expansion (**Scheme 51**).



Scheme 51: Suitable substrates for methodology studies

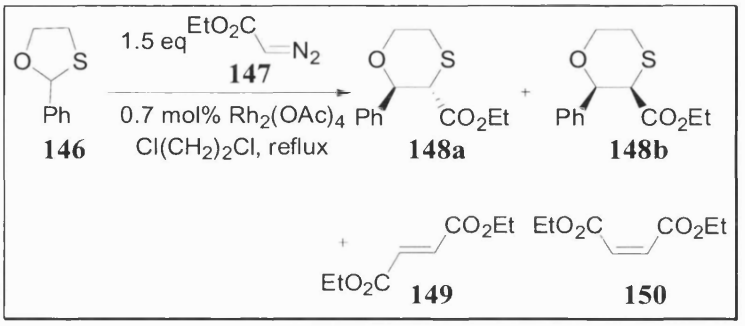
II-2 Carbene-mediated ring expansion of 1,3-oxathiolanes

II-2.1 Previous work in the Porter Group[129]

The starting point for the preliminary study of this novel ring expansion was the choice of 2-phenyl-1,3-oxathiolane **146** as a readily accessible substrate,[130] and its reaction with ethyl diazoacetate **147** (**Scheme 52**). Previous work by Doyle *et al.*[126] on carbene-mediated reactions provided an initial set of conditions, rhodium acetate dimer being chosen as the catalyst. Although the ring expansion products **148a** and **148b** were

[129] Ioannou, M. M. Sci. Thesis, **2000**, UCL.
[130] Kipnis, F.; Ornfelt, J. *J. Am. Chem. Soc.* **1949**, *79*, 3555.
[126] Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.

observed,[131] the reaction did not go to completion and competing self reaction of the diazoacetate gave diethyl fumarate **149** and diethyl maleate **150**.[132]



Scheme 52: Ring expansion using Doyle's conditions

Minimisation of dimerisation could be achieved by slow addition of ethyl diazoacetate, but the conversion was still not complete (*ca.* 30% residual starting material). A change of catalyst and solvent was investigated, and copper(II) acetylacetonate ($Cu(acac)_2$) was chosen since its use for the generation of metal carbenes had been reported.[133] The ring expanded products **148a** and **148b** were isolated in 19% combined yield when 2-phenyl-1,3-oxathiolane **146** was treated with 1.2 eq of ethyl diazoacetate and 11 mol% catalyst in refluxing benzene. These reaction conditions were tested on a range of other monothioacetal substrates **151-155** (**Figure 18**).

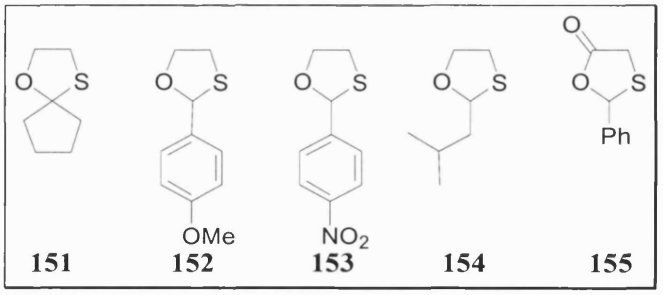
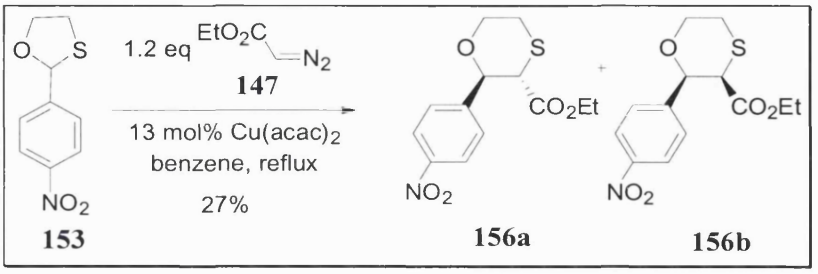


Figure 18: Initial substrates for ring expansion

[131] Characteristic signals were observed on the ^1H NMR spectrum of the reaction mixture, but the products could not be isolated.
[132] Grundmann, C. *Annalen* **1938**, 2936.
[133] Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R. *Tetrahedron Lett.* **1966**, 59.

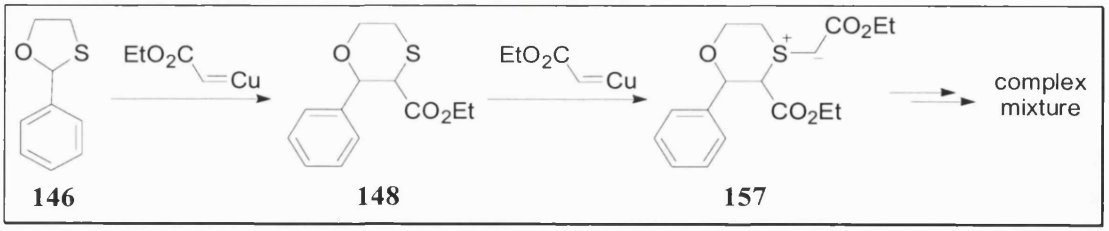
Among these, only 2-(4-nitrophenyl)-1,3-oxathiolane **153** successfully underwent ring expansion to give a 3.5:1:1 mixture of starting material: *trans*-isomer **156a**: *cis*-isomer **156b** (**Scheme 53**).



Scheme 53: Ring expansion of 2-(4-nitrophenyl)-1,3-oxathiolane

Other substrates were unreactive under the chosen conditions, or led to complex mixtures of unidentified products.

In order to drive the reaction to completion, an excess of ethyl diazoacetate was used for the ring expansion of 2-phenyl-1,3-oxathiolane **146**. Along with the formation of diethyl maleate and diethyl fumarate, this resulted in degradation of the oxathiane products. A possible course would be the generation of an ylide **157** from the reaction of the oxathiane sulfur with the metal carbene, followed by further transformations (**Scheme 54**).



Scheme 54: Possible degradation of oxathiane in the presence of excess EDA

Trimethylsilyldiazomethane (**158**, TMS-diazomethane) (**Figure 19**) was used as a commercially available alternative carbene precursor, following recent reports showing

its marked efficiency in metal-catalysed ylide formation and [2,3]-sigmatropic rearrangements of allylsulfonium ylides.[134] Moreover the self-reaction of TMS-diazomethane leading to alkene formation was reported to be slower than that of ethyl diazoacetate.[135]

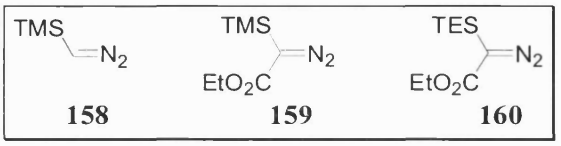
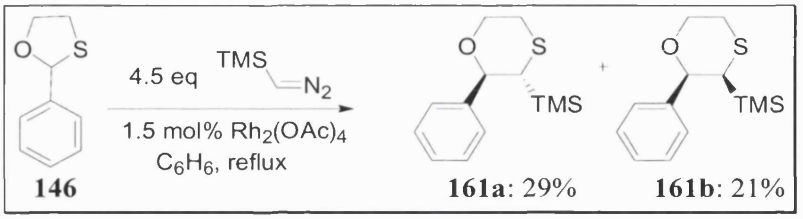


Figure 19: Diazocompounds used for ring expansion

Ring expansion was achieved for the three 2-aryl-1,3-oxathiolanes **146**, **152** and **153** using 4.5 eq of TMS-diazomethane and 1.5 mol% of rhodium acetate dimer in benzene. 2-Phenyl-3-trimethylsilyl-1,4-oxathianes **161a** and **161b** were isolated in 29% and 21% yield respectively (**Scheme 55**). Importantly, the use of an excess of TMS-diazomethane to drive the reaction to completion did not result in product degradation or formation of alkene by-products.



Scheme 55: Ring expansions using TMS-diazomethane

This advantage of the silyl reagent, combined with the need to introduce a carbonyl group α to sulfur (which is present in the target molecule) led us to consider the use of a silylated diazoester in the ring expansion reaction.

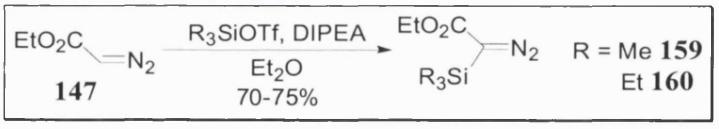
[134] (a) Carter, D. S.; van Vranken, D. L. *Tetrahedron Lett.* **1999**, *40*, 1617. (b) Aggarwal, V. K.; Ferrara, M.; Hainz. R.; Spey, S. E. *Tetrahedron Lett.* **1999**, *40*, 8923.
[135] Crow,W.D.; Gosney, I.; Ormiston, R.A. *J. Chem. Soc., Chem. Commun.* **1983**, 643.

II-2.2 Model studies on the ring-expansion reaction[136]

II-2.2.1 Ring expansion using ethyl TMS-diazoacetate

First reported by Schöllkopf in 1967,[137] silylated diazoesters have recently found use in a range of transition metal catalysed reactions, including intermolecular cyclopropanation,[138] cyclopropenation,[139] carbonyl ylide formation,[140] oxazole synthesis,[16b,141] N-H insertion[142] and deoxygenation of epoxides.[143] In addition, a range of intramolecular reactions of silylated diazoesters have been reported, including insertion into C-H bonds[144] and reactions with tethered alkenes[145] and alkynes.[146]

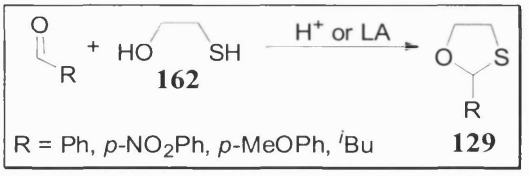
Ethyl (trimethylsilyl)diazoacetate (**159**, ethyl TMS-diazoacetate) and its triethylsilyl (TES-) analogue **160** (**Figure 19**) are readily prepared by reaction of ethyl diazoacetate with the corresponding trialkylsilyl trifluoromethanesulfonate (triflate) in the presence of Hünig's base (**Scheme 56**).[147]



Scheme 56: Synthesis of silylated diazoesters

[136] Ioannou, M.; Porter, M. J., Saez, F. *Chem. Commun.* **2002**, 346.
[137] Schöllkopf, U.; Rieber, N. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 884.
[138] (a) Maas, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993**, *49*, 851. (b) Maas, G.; Alt, M.; Mayer, D.; Bergsträsser, U.; Sklenak, S.; Xavier P.; Apeloig, Y. *Organometallics* **2001**, *20*, 4607. (c) Braddock, D. C.; Badine, D. M.; Gottschalk, T.; Matsuno, A. *Synlett* **2003**, 345.
[139] (a) Maier, G.; Volz, D.; Neudert, J. *Synthesis* **1992**, 561. (b) Arrowood, T. L.; Kass, S. R. *Tetrahedron* **1999**, *55*, 6739.
[140] (a) Alt, M.; Maas, G. *Chem. Ber.* **1994**, *127*, 1537. (b) Alt, M.; Maas, G. *Tetrahedron* **1994**, *50*, 7435. (c) Bolm, C.; Saladin, S.; Kasyan, A. *Org. Lett.* **2002**, *4*, 4631.
[16b] Lerbs, S.; Brautigam, E.; Mache, R. *Mol. Gen. Genet.* **1988**, *211*, 459.
[141] Ducept, P. C.; Marsden, S. P. *Synlett* **2000**, 692.
[142] Bolm, C.; Kasyan, A.; Drauz, K.; Günther, K.; Raabe, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2288.
[143] Bolm, C.; Kasyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Günther, K.; Wagner, C. *Org. Lett.* **2002**, *4*, 2265.
[144] (a) Kablean, S. N.; Marsden, S. P.; Craig, A. M. *Tetrahedron Lett.* **1998**, *39*, 5109. (b) Marsden, S. P.; Pang, W.-K. *Tetrahedron Lett.* **1998**, *39*, 6077. (c) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765. (d) Müller, P.; Lacrampe, F.; Bernardinelli, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1503.
[145] Maas, G.; Krebs, F.; Werle, T.; Gettwert, V.; Striegler, R. *Eur. J. Org. Chem.* **1999**, 1939.
[146] Gettwert, V.; Krebs, F.; Maas, G. *Eur. J. Org. Chem.* **1999**, 1213.
[147] (a) Emde, H.; Simchen, G. *Liebigs Ann. Chem.* **1983**, 816. (b) Allspach, T.; Gümbel, H.; Regitz, M. *J. Organomet. Chem.* **1985**, *290*, 33.

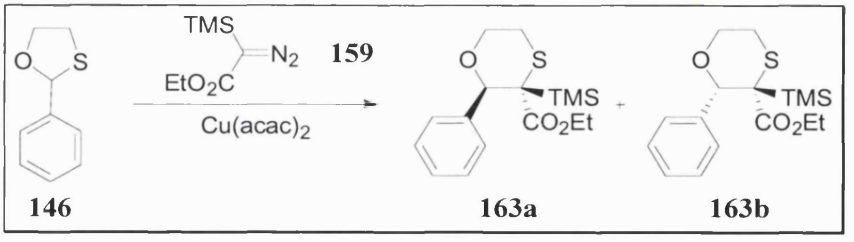
The 1,3-oxathiolane substrates **129** used for the model studies were synthesised by acid-catalysed condensation of the corresponding aldehyde with mercaptoethanol **162** (**Scheme 57**).[131] When *p*-toluenesulfonic acid was used, azeotropic removal of water under Dean and Stark conditions was required. Alternatively, Lewis acids such as zinc chloride and *N*-bromosuccinimide have been shown to promote the condensation.[148]



Scheme 57: Synthesis of 1,3-oxathiolanes

This project started with the study of the ring expansion of the model compound **146** to give a diastereoisomeric mixture of **163a** and **163b** (**Scheme 58**). Throughout this discussion, the isomers **163a** and **163b** will be referred to as *cis* and *trans* oxathiane esters respectively.

The reaction conditions were similar to those described in the previous section for the reaction with ethyl diazoacetate, using 1.2 eq of ethyl TMS-diazoacetate as the carbene precursor and 10 mol% of $Cu(acac)_2$ as the catalyst.



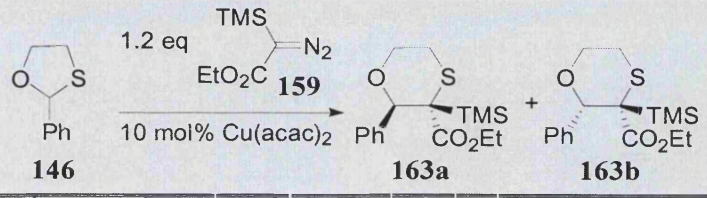
Scheme 58: Ring expansion using ethyl TMS-diazoacetate

Different temperatures and solvents were examined, as well as different modes of addition of the reagents in order to optimise the conversion. Diastereoselectivity was monitored by comparison of the characteristic singlets of 2-H of both oxathiane isomers

[131] Kipnis, F.; Ornfelt, J. *J. Am. Chem. Soc.* **1949**, *79*, 3555.
[148] Lewis acid-catalysed synthesis: Karimi, B.; Seradj, H. *Synlett* **2000**, *6*, 805; Kazahaya, K.; Hamada, N.; Ito, S.; Sato, T. *Synlett* **2002**, *9*, 1535. *N*-Bromosuccinimide-mediated oxathioacetalisation: Kamal, A.; Chouhan, G.; Ahmed, K. *Tet. Lett.* **2002**, *43*, 6947.

in the ^{1}H NMR spectra. Indeed, NOE experiments had previously been carried out on theses products to assign the stereochemistry. The chemical shift of 2-H was shown to be further downfield for *cis* product **163a** (δ = 5.43 ppm), than for the *trans* isomer **163b** (δ = 4.78 ppm).

The results of these experiments are shown in the table below:



146 **163a** **163b**

Entry	Solvent	T (°C)	Reaction time	Composition of crude	Yield	Comments
1	benzene	75	18h	3:2 **163a**:**163b**	60% crude	-
2	benzene	80	5h	3:1.5:1 **163a**:**163b**:SM	67% crude 6% *cis*	*cis* recryst. from EtOH
3	toluene	110	6h	SM and desilylated	-	-
4	benzene	60	48h	SM and desilylated	-	-
5	benzene	80	18h	At 3h 3:2:1 **163a**:**163b**:SM	-	Slow addn of diazo **159**

Table 2: Initial studies on 2-phenyl-1,3-oxathiolane

Although the reaction of **146** in the standard conditions was not complete, the ring-expansion products were formed in a 3:2 **163a**:**163b** ratio (entry 1). Separation of the products was attempted but recrystallisation in ethanol afforded only a small amount (6%) of **163a** (entry 2).

Toluene was tested as an alternative solvent to try and drive the reaction to completion by heating it at a higher temperature (entry 3). The reaction was monitored by ^{1}H NMR every 2h: after 6h starting material was recovered along with what appeared to be desilylated ring-expansion products.

As these conditions proved too harsh, the reaction was carried out at 60°C in benzene for a longer time (entry 5). After 2 days the reaction had not gone to completion and the products started to decompose.

A different procedure was tried, where ethyl TMS-diazoacetate was added slowly to the refluxing mixture of **146** and catalyst in benzene (entry 6). Monitoring of the reaction showed a promising 1:3:2 SM:*cis*:*trans* mixture after 3h but the reaction boiled dry when left overnight.

This series of experiments showed that dry benzene seemed to be a suitable solvent and that the reaction could be carried out at reflux temperature. Slow addition of the diazoacetate was also adopted for the procedure. Doyle reported that the catalytic species in copper-catalysed metal carbene formation was in fact a Cu(I) complex.[56] An excess of the diazo compound is thus required to reduce the initial Cu(II) catalyst to the active species. The Cu(I) complex then generates the metal carbene using another equivalent of diazo compound as shown in the general mechanism for metal carbene formation discussed previously (**I-3.3, Scheme 16, p. 37**).

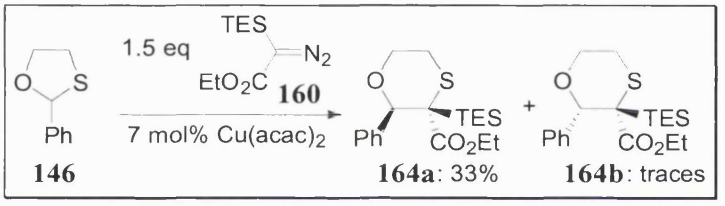
II-2.2.2 Ring expansion using ethyl TES-diazoacetate

The steric bulk of the TMS- group was expected to favour an equatorial position in the oxathiane products. However, the ratios of diastereoisomers observed in this first set of experiments show that neither the *cis* or *trans* isomer was particularly favoured. Moreover desilylation of the ring expanded products had been observed when longer reaction times or higher temperatures had been used. Hence ethyl

[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.

(triethylsilyl)diazoacetate (ethyl TES-diazoacetate) (**160**) was used as an alternative silyl group less susceptible to desilylation.[149] It was also thought that the bulkier TES derivative might induce diastereoselectivity due to steric factors.

Ring expansion was observed when 2-phenyl-1,3-oxathiolane **146** was treated with ethyl TES-diazoacetate in the conditions adopted previously (**Scheme 59**). Although the reaction went to completion, the isolated yield after flash-chromatography on deactivated neutral alumina was only 33%.



Scheme 59: Ring expansion with TES-diazoacetate

The relative stereochemistry of compounds **164a** and **164b** (R=Ph) was assigned using one-dimensional NMR experiments (^{1}H spectra and NOE). For both compounds, the coupling constants for the CH_2CH_2 portion of the six-membered ring were consistent with the adoption of a chair conformation. In the NOE experiments carried out on the major isomer **164a** (**Figure 20**) irradiation of the *ortho*-protons of the phenyl ring generated an enhancement of the axial proton at C-6 and the triethylsilyl group. This is consistent with an axial position of the aromatic substituent, and a relative stereochemistry of the TES and phenyl groups to be *cis*. Therefore in this structure both the phenyl group and the ethyl ester occupy axial positions, the bulky silyl group residing equatorially.

[149] The higher stability of TES-diazoacetate compared to that of TMS-diazoacetate was illustrated by the possibility to purify the TES- derivative by flash chromatography on deactivated alumina.

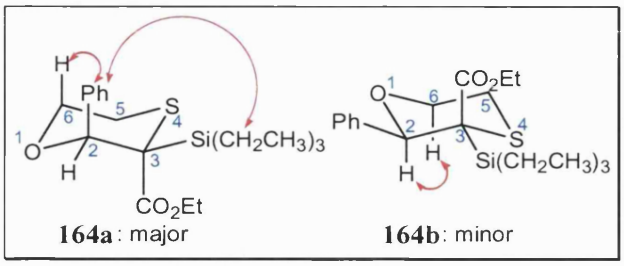


Figure 20: Stereochemistry of ring expanded products by NOE

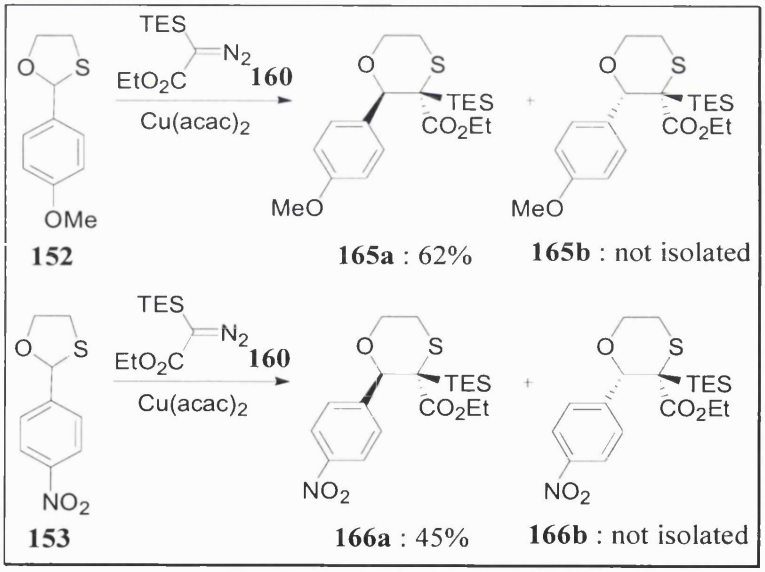
In the NOE spectrum of **164b**, a positive enhancement was observed between the axial C-6 proton and the benzylic proton, indicating an equatorial position of the phenyl group. This is consistent with a *trans* relative stereochemistry for the minor isomer. The chemical shift for the characteristic proton at C-2 was more upfield (δ=4.87ppm) than for the *trans* isomer (δ=5.60ppm). This relative order in the chemical shifts of the diastereoisomers was assumed to be the same for all the structurally related substrates studied in this project and was used to assign tentatively the stereochemistry of the six-membered ring products.

Although the conversion was complete, the isolated yield of the ring expansion of 2-phenyl-1,3-oxathiolane **146** was low. A possible explanation is that decomposition might occur during purification, although no desilylated product or other decomposition products were isolated. A comparative experiment was carried out to probe this hypothesis: ring expansion of 2-phenyl-1,3-oxathiolane **146** was carried out and the crude mixture was divided in three equal parts. This mixture was mainly composed of the *cis* oxathiane isomer **164a**, with traces of remaining starting material. Each aliquot was purified by flash chromatography on a different medium. The results are shown in **table 3**.

Purification medium	Isolated yield
Silica	30%
Deactivated alumina	30%
Florisil®	72%

Table 3: Optimisation of the method of purification

Despite the relative stability of the TES group, the hypothesis of decomposition was supported by this experiment: only Florisil® was tolerated for flash-chromatography without significant losses of material. Consequently it was used in all further experiments, allowing the isolation of the *cis* isomers of 1,4-oxathiane **165a** and 1,4-oxathiane **166a** in good yields (**Scheme 60**).

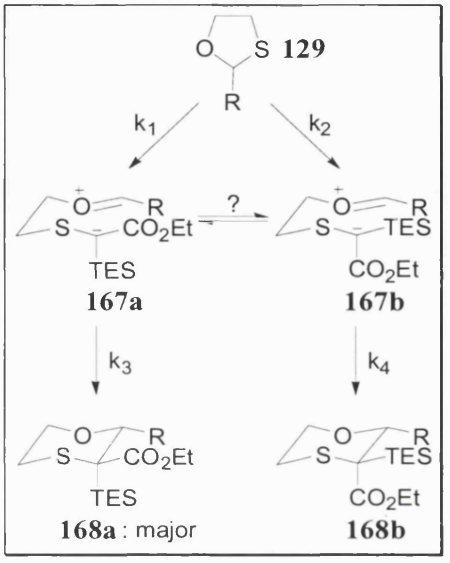


Scheme 60: Optimised ring expansion of aryl oxathiolanes

The results previously discussed showed that ethyl TES-diazoacetate **160** was a better candidate for the ring expansion reaction than ethyl TMS-diazoacetate **159**. Despite longer reaction times, the conversion was notably improved, up to completion in most cases. This may be related to an increased stability (and somewhat lower reactivity) of the silylated compound due to larger alkyl groups. Moreover the ring expansion

appeared to be diastereoselective, a single isomer of the oxathiane products being formed preferentially which we identified to be the *cis* isomer on the basis of NMR data.

The mechanism proposed for the ring expansion reaction involves ring closure of the zwitterion **167** to form the oxathiane ring (**Scheme 61**).



Scheme 61: Kinetic control of diastereoselectivity

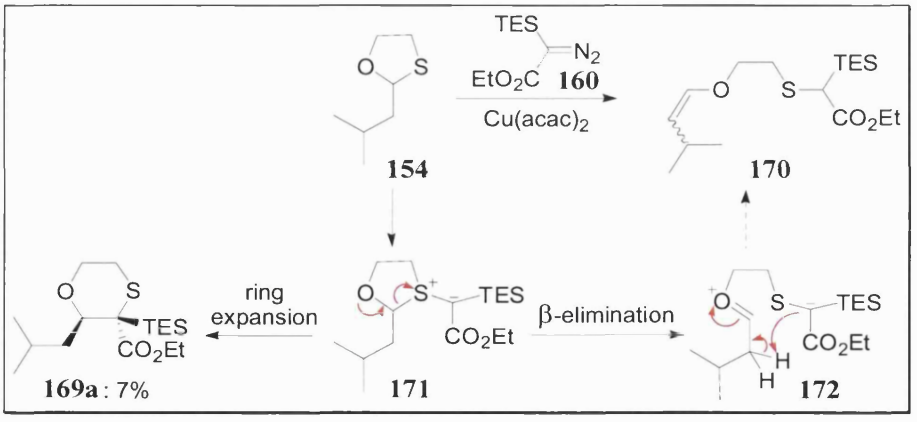
Since the C-C bond formation is unlikely to be reversible under the reaction conditions, the diastereoselectivity observed would be kinetically controlled.[150] Assuming a preferred chair-like conformation for the zwitterionic species, the *cis* and *trans* diastereoisomers **168a** and **168b** would result from ring closure of the intermediates **167a** and **167b**, the less favoured zwittterion **167a** (silyl substituent in axial position) giving rise to the major isomer **168a**. If the interconversion between **167a** and **167b** is possible, the ratio of oxathianes **168a** and **168b** will depend on the rate constants for ring closure, k_3 and k_4. If the interconversion does not occur (*i.e.* if the ring closure is fast), then the ratio of oxathianes **168a** and **168b** will depend on k_1 and k_2. Further mechanistic and kinetic studies are necessary to understand and possibly control the

[150] This could be confirmed by subjecting the isolated *cis* isomer to the ring expansion conditions.

diastereoisomeric outcome of the ring expansion, but these are complicated by the multiple processes involved in the formation of the zwitterion species: generation of the metal carbene, ylide formation through loss of the copper catalyst, and breaking of the C-S bond.

II-2.2.3 Ring expansion of alkyl oxathiolanes

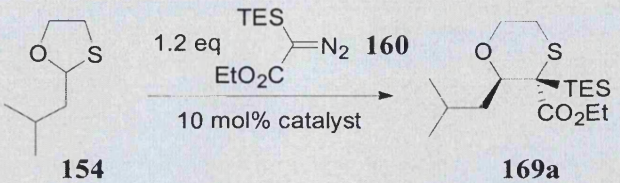
The ring expansion of 2-isobutyl-1,3-oxathiolane **154** under the optimised conditions used for the aryl substrates was complete after 2h and afforded the *cis* product **169a** only, which was isolated in 7% yield.[151] However, this result could not be reproduced and the formation of a mixture of the (*E*)- and (*Z*)-isomers of enol ether **170** was observed instead (**Scheme 62**). These products are thought to result from a rearrangement of ylide **171** or zwitterion **172** to form the stable enol ether. This is made possible by the presence of a hydrogen atom β to the oxonium ion, unlike the 2-aryl-1,3-oxathiolanes.



Scheme 62: Possible mechanism for enol ether formation

[151] The stereochemistry was also confirmed by 2D NMR noesy experiments, and was concordant with the chemical shift hypothesis used to determine the stereochemistry of this series of substrates.

The reaction of 2-isobutyl-1,3-oxathiolane **154** was studied in more detail to try and find a set of conditions which would favour the ring expansion. **Table 4** shows the results of these optimisation attempts, where different catalysts, solvent or procedure were tested.



154 **169a**

Entry	Catalyst	Solvent, T (°C)	Reaction time	Composition of crude	Comments
1	$Cu(acac)_2$	CH_2Cl_2 reflux	5h	SM	-
2	$Cu(acac)_2$	benzene reflux	24h	mainly **170** traces of **169a**	Degassed solvent
3	$Rh_2(OAc)_4$	benzene reflux	40h	SM	-
4	$Cu(hfacac)_2$	benzene reflux	24h	mainly **170** traces of **169a**	-
5	$Cu(MeCN)_4PF_6$	benzene reflux	2.5h	1:1 **169a**:SM	30% **169a**
6	$Cu(MeCN)_4PF_6$	benzene reflux	18h	decomposed	-

Table 4: Methodology on the ring expansion of 2-isobutyl-1,3-oxathiolane

The use of dichloromethane as the solvent in reactions involving the formation of metal carbenes had been reported.[56] When used for the ring expansion of **154**, no reaction occurred.

Although the reaction had previously been carried out under inert atmosphere, air sensitivity of the active catalyst was thought to be a possible detrimental factor. The reaction was carried out using degassed benzene (entry 2), all other conditions being unchanged. Traces of the desired product were observed, but the enol ether was still the major product.

[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.

Various catalysts were investigated. Rhodium acetate dimer had already been used in preliminary studies. However it failed to promote the ring expansion reaction of 2-isobutyl-1,3-oxathiolane using ethyl TES-diazoacetate in refluxing benzene (entry 3). Copper(II) hexafluoroacetylacetonate ($Cu(hfacac)_2$) has been described as more reactive than $Cu(acac)_2$ in the formation of metal carbenes.[56] It proved inefficient for the ring expansion of **154** (entry 4).

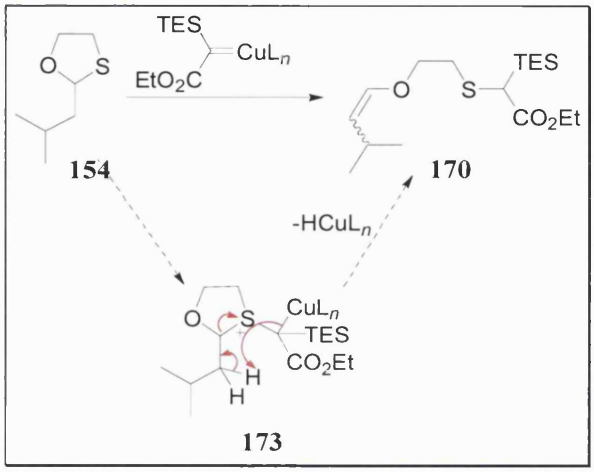
Considering that the active species involved in the formation of a metal carbene is a Cu(I) complex, a Cu(I) catalyst was tested. The reaction was carried out with commercially available tetrakis(acetonitrile) copper(I) hexafluorophosphate ($Cu(MeCN)_4PF_6$) (entry 5). After 2.5 h a 1:1 mixture of starting material and desired product was formed, from which we could isolate **169a** in 30% yield. In this instance the *cis* isomer was not observed. Attempts to drive the reaction to completion using longer reaction time resulted in degradation of the reaction mixture (entry 6).

This series of experiments showed that benzene remained the solvent of choice for the ring expansion reaction. $Cu(MeCN)_4PF_6$ proved to be a suitable Cu(I) source, more selective for the reaction of 2-isobutyl-1,3-oxathiolane **154** than Cu(II) catalysts (e.g. $Cu(acac)_2$). Indeed no enol ether formation was observed. Degassing of the solvent was also adopted, due to the air-sensitivity of $Cu(MeCN)_4PF_6$.

The catalyst-dependence observed for the ring expansion of 2-isobutyl-1,3-oxathiolane contradicts the mechanism proposed in **scheme 45**, where the ring-opened enol ether results from hydrogen abstraction by the free ylide. Instead the β-hydrogen might be abstracted by the metal carbene adduct **173**, depending on the basicity of the carbene

[56] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York **1998**.

centre, which in turn would depend on the nature of the ligands on the metal (**Scheme 63**).



Scheme 63: **Catalyst-selective enol ether formation**

$Cu(MeCN)_4PF_6$ was tested for the ring expansion of two 2-aryl substrates (**146** and **153**), as well as two new substrates, namely 1,3-oxathiolane **174** and 2-*tert*-butyl-1,3-oxathiolane **175** (**Figure 21**).

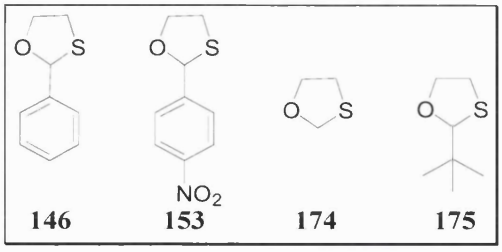


Figure 21: Aryl and alkyl substrates for Cu(I)-catalysed ring expansion

The aim of this series of experiments was to study the efficiency of the catalyst on different substrates to find a set of general conditions. It also allowed us to examine the reactivity of other 1,3-oxathiolanes not bearing any hydrogen β to the oxygen atom. The results are presented in **table 5**.

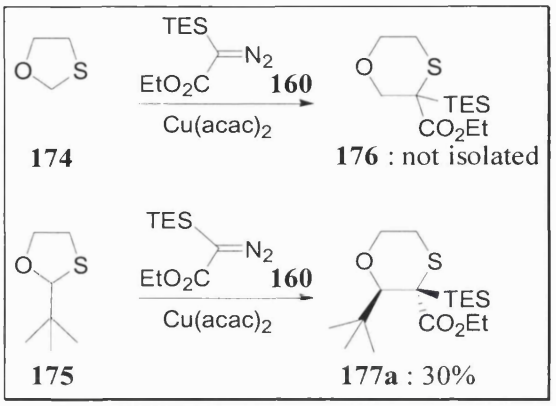
Entry	Substrate	Solvent, T (°C)	Reaction time	Composition of crude	Yield	Comments
1	**146**	benzene reflux	18h	1:1 **163a**:SM	-	Not purified
2	**153**	benzene reflux	8h	1:3 **166a**:SM	-	Not purified
3	**174**	benzene reflux	2.5h	**176**	-	Decomposed before isolation
4	**175**	benzene reflux	4h	1:1.5 **176a**:SM	12% **176a**	*trans* not observed

Table 5: Ring expansions using $Cu(MeCN)_4PF_6$

When the ring expansion of 2-phenyl-1,3-oxathiolane **146** was attempted with $Cu(MeCN)_4PF_6$ as the catalyst, a 1:1 SM:**163a** mixture was obtained after 2h but the reaction did not go any further (entry 1). Similarly, the reaction of 2-(4-nitrophenyl)-1,3-oxathiolane **153** stopped after reaching a ratio of 3:1 SM:**166a** mixture (entry 2).

1,3-Oxathiolane **174** underwent successful ring expansion (entry 3) to give ethyl 3-TES-1,4-oxathiane-3-carboxylate **176** as the sole product, but it decomposed before isolation (**Scheme 64**). Unfortunately this result could not be reproduced, the reaction either leading to an unidentified mixture of products, or not occurring at all.

The ring expansion reaction of 2-*tert*-butyl-1,3-oxathiolane **175** did not go to completion, but an isomer of the desired product was isolated in 12% yield (entry 4) (**Scheme 64**). This isomer was tentatively assigned as the *cis* isomer **177a** on the basis of the chemical shift of H-2 and the general diastereoselectivity observed in the series of substrates studied so far.

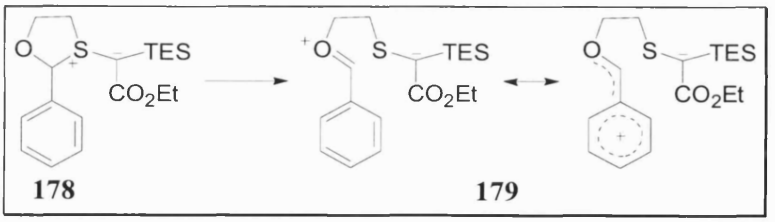


Scheme 64: Ring expansion of alkyl substrates

Although the rate of ring expansion of 2-aryl-1,3-oxathiolanes seems to be faster in the first hours of the reaction using $Cu(MeCN)_4PF_6$, it does not generally go to completion. This could possibly be due to the high sensitivity of the catalyst towards moisture and air, making it prone to poisoning.

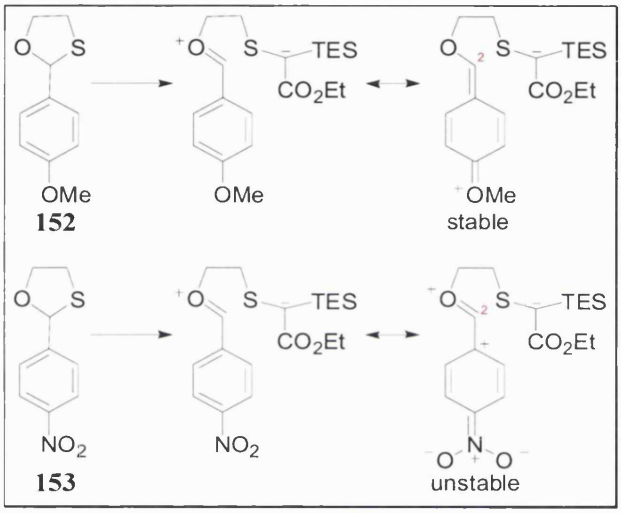
It was shown that the ring expansion of the 2-alkyl substrates **174** and **175** could be achieved with this catalyst, although the results were difficult to reproduce.

Aryl and alkyl substrates seem to exhibit a different reactivity thus might need different sets of conditions to undergo efficient ring expansion and afford the corresponding 1,4-oxathianes. A possible explanation for the higher reactivity of 2-aryl-1,3-oxathiolanes is the stabilisation of the intermediate oxonium zwitterion **179** by conjugation with the aromatic substituent, which could favour the cleavage of the C-S bond of the intermediate ylide **178** and subsequent rearrangement against different reaction pathways (**Scheme 65**).



Scheme 65: Stabilisation of the oxonium intermediate by the aromatic ring

However the electronic influence of the substituents present on the aromatic ring on the reaction is unclear. Both the electron-donating 2-(4-methoxyphenyl)-1,3-oxathiolane **152** and the electron-withdrawing 2-(4-nitrophenyl)-1,3-oxathiolane **153** underwent ring expansion to afford the corresponding *cis* oxathianes in comparable yields despite the fact that the 4-methoxy- group can further stabilise the oxonium ion by resonance whereas the 4-nitro-functionality is expected to destabilise the oxonium ion by creating an adjacent positive charge (**Scheme 66**).



Scheme 66: Electronic effects in the 2-aryl-1,3-oxathiolanes

Further studies are necessary to fully understand the effects of substitution on the ring expansion reaction of 1,3-oxathiolanes.

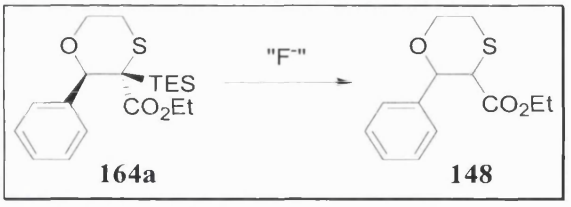
II-2.2.4 Desilylation of ring expanded products

So far, we have shown a route of entry to 1,4-oxathianes *via* copper-mediated ring expansion of 1,3-oxathiolanes using a silylated diazoacetate, and expect to apply this methodology to the synthesis of the natural product tagetitoxin. However, the target

molecule does not bear a silyl functionality on the oxathiane ring. Therefore several methods of desilylation of the ring-expanded products were investigated.

The carbon-silicon bond is strong enough for trialkylsilyl groups to survive a wide variety of synthetic transformations, but it can be selectively cleaved using mild conditions. In particular, the hard nucleophilic fluoride group is often used to remove silicon groups, the driving force for the transformation being the formation of strong Si–F bonds (582 kJ mol^{-1} compared to 340 kJ mol^{-1} for a typical carbon-carbon bond). The increased bond length between silicon and carbon (1.89 Å compared to 1.54 Å C-C) also enables hard nucleophiles (in particular F^-) to react at sterically hindered silicon centres.[152]

Pure *cis* 1,4-oxathiane **164a** was subjected to desilylation conditions using a variety of fluoride anion sources (**Scheme 67**). The results are summarised in **Table 6**.



Scheme 67: Desilylation using fluoride

Entry	Reagents	Solvent, T (°C)	Time	Composition of crude	Yield
1	TBAF.xH_2O	THF, 0°C	0.5h	1:1 *trans:cis*	quantitative
2	NH_4F	MeOH, reflux	1h	1:1 *trans:cis*	quantitative
3	TBACl.xH_2O, KF	MeCN, 50°C	0.5h	1.5:1 *trans:cis*	quantitative
4	TBACl.xH_2O, KF	MeCN, 0°C	0.5h	1.5:1 *trans:cis*	quantitative
5	TAS-F	DCM, -10°C	0.5h	2:1 *trans:cis*	quantitative

Table 6: Desilylation of ring-expanded products

[152] *Advanced Organic Chemistry*, Carey and Sundberg, 3rd Ed., Plenum.

In all cases desilylation proceeded readily, giving quantitative yields of ethyl 2-phenyl-1,4-oxathiane-3-carboxylate **148**. However, no synthetically useful diastereoselectivity was observed using tetra-*n*-butylammonium fluoride hydrate (entry 1) or ammonium fluoride (entry 2).

The detrimental effects of solvation on the nucleophilicity and basicity of the fluoride anion have led to the development of sources of active fluoride, including anhydrous tetra-alkylammonium fluorides[153] and potassium fluoride in the presence of crown ether.[154] However these can present practical disadvantages: anhydrous TBAF is difficult to obtain (it involves hydrofluoric acid neutralisation of aqueous ammonium hydroxide) and is very hygroscopic; whereas the removal of crown ethers can prove difficult. Therefore more convenient sources of "naked" fluoride were investigated in an attempt to modify the diastereoselectivity of the reaction.

In solution tetra-*n*-butylammonium chloride and potassium fluoride dihydrate (entries 3-4) are thought to generate *in situ* an equilibrium concentration of soluble ammonium fluoride, which shows reactivity comparable to those of anhydrous tetra-alkylammonium fluorides and potassium fluoride / crown ether. [155]

TAS-F (tris(dimethylamino)sulfonium difluorotrimethylsilicate, entry 5) is a hypervalent silicon salt, which is a source of highly nucleophilic fluoride anion. [156] It has proved a mild and effective reagent for the deprotection of base- and/or acid-sensitive silyl ethers[157] and the cleavage of Si-C bonds for the formation of "naked" cyclopentadienyl anions.[158]

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[153] (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. (b) Kuwajima, M.; Murofushi, T.; Nakamura, E. *Synthesis* **1972**, 602.

[154] (a) Liotta, C. L.; Harris, H. P. *J. Am. Chem. Soc.* **1974**, *96*, 2250. (b) Liotta, C. L.; Grisdale, E. E. *Tet. Lett.*, **1975** 2405.

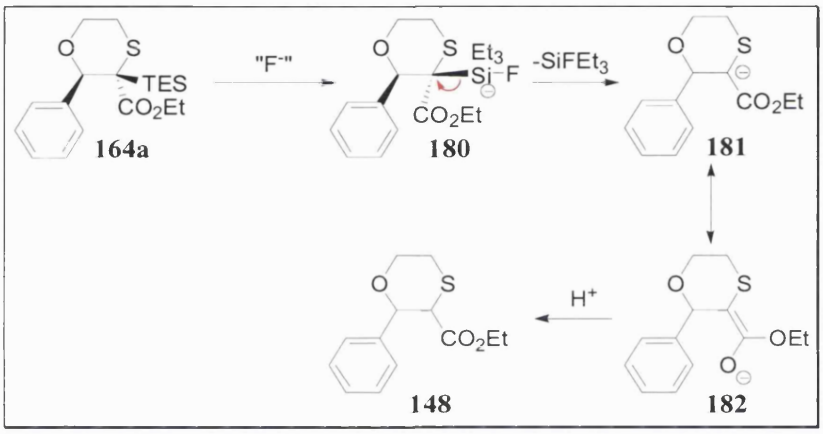
[155] Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

[156] Middleton, W. J. *Org. Syn CV 7*, 258, and references cited therein.

[157] Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

[158] Wessel, J.; Behrens, U.; Lork, E.; Mews, R. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 443.

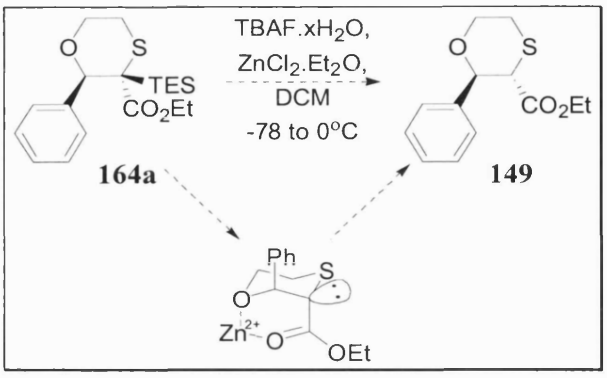
The use of these active fluoride reagents brought little improvement to the diastereoselectivity of the desilylation reaction, with at best a 2:1 ratio in favour of the *trans* isomer being obtained (entry 5). Although the nucleophilicity of the fluoride anion might be enhanced and the adduct **180** formed faster, subsequent cleavage of the carbon silicon bond presumably forms planar carbanion **181**. Protonation in the reaction medium (entries 1-4) or upon work up (entry 5) can thus occur on either face, leading to partial epimerisation at C-3 (**Scheme 68**).



Scheme 68: Partial epimerisation during desilylation

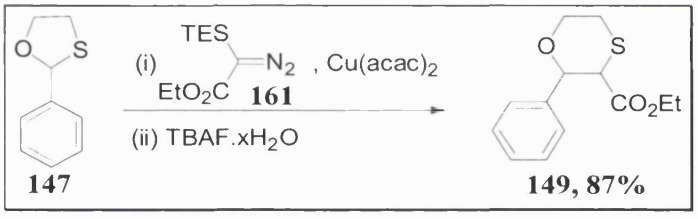
In an attempt to retain the stereochemistry at C-3, stoichiometric zinc chloride etherate complex was added to the substrate prior to treatment with tetra-*n*-butylammonium fluoride hydrate. It was hoped the divalent cation would chelate both the oxathiane oxygen and the carbonyl oxygen, thus favouring a *cis* relationship between the oxathiane C-O bond and the ester which would lead to the *trans* oxathiane after protonation (**Scheme 69**). Unfortunately no reaction was observed, possibly due to inactivation of the zinc reagent by the tetrabutylammonium hydroxide present in commercial TBAF.[159]

[159] (a) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429. (b) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216. (c) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.



Scheme 69: Attempted diastereoselective desilylation

In light of the ease of desilylation, the two-step sequence converting 1,3-oxathiolanes to 1,4-oxathianes could be further optimised by treating the ring expansion reaction mixture with tetra-*n*-butylammonium fluoride prior to isolation (**Scheme 70**). The one-pot process afforded 87% overall yield.[160]



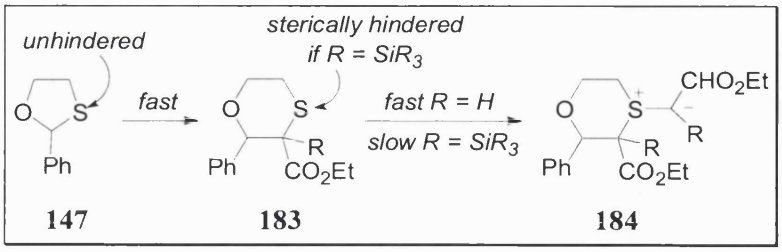
Scheme 70: One-pot ring expansion / desilylation

II-2.2.5 Conclusions on the ring expansion

We have developed an efficient method for the ring expansion of 2-substituted 1,3-oxathiolanes. The poor yields observed when ethyl diazoacetate was used as a carbene source for this reaction are partly due to its tendency to form alkene by-products and to its lack of discrimination between the sulfur atoms in starting material and product (**Scheme 71**, R=H). The complete conversion and high yields observed when the same

[160] The reaction of 2-phenyl-1,3-oxathiolane **147** with ethyl diazoacetate gave 19% of the ring-expanded product in our initial studies (see II-2.1).

substrates are treated with silylated diazoacetates are indicative of an attenuation of both these problems, and we ascribe both effects to the steric bulk of the silyl group. Thus reaction of the bulky silylated metal carbene with the sterically hindered sulfur of 1,4-oxathiane **183** (R=$SiEt_3$) is expected to be markedly slower than its reaction with the starting material, 1,3-oxathiolane **147**.

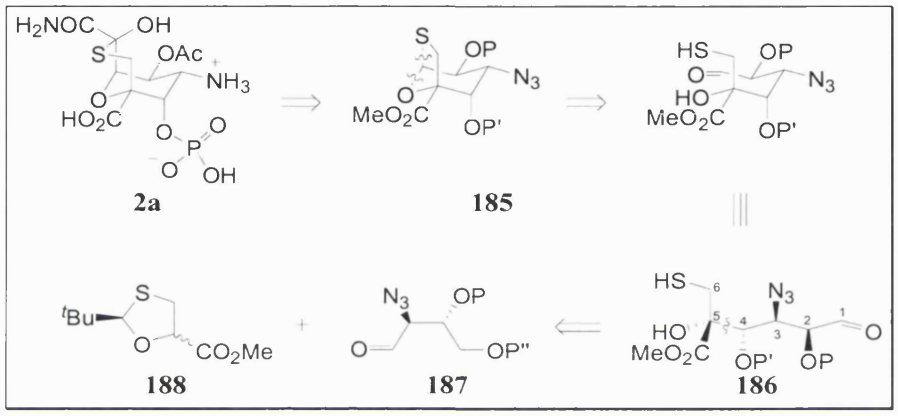


Scheme 71: Optimisation of the ring expansion using steric factors

II-3 Studies towards the synthesis of a tagetitoxin precursor

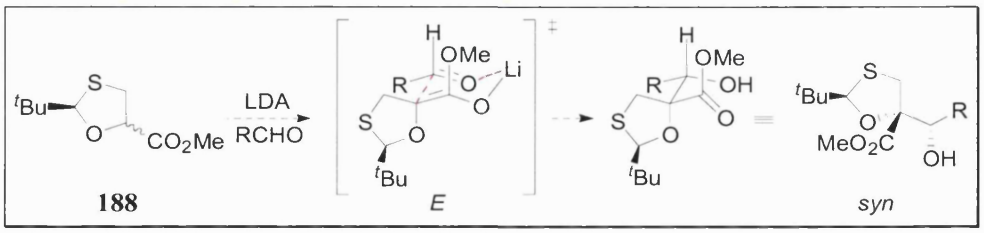
II-3.1 Retrosynthetic analysis

Having proved the feasibility of the one carbon ring expansion of oxathiolanes, we needed to devise a synthesis for the substituted bicyclic precursor **185** to tagetitoxin (**Scheme 72**).



Scheme 72: Retrosynthesis of the fully substituted tagetitoxin precursor

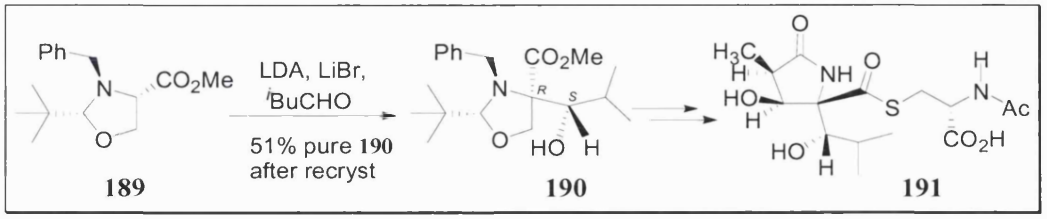
The bridged bicyclic oxathiolane **185** could result from an intramolecular acid-catalysed thioacetalisation of 5-hydroxy-6-mercaptohexanal **186**. The required *syn* diastereoselectivity between the C-4 hydroxy and the C-5 ester could be set up *via* an aldol reaction. Treatment of oxathiolane ester **188** with LDA in THF should form the *E*-enolate predominantly due to chelation with the oxathiolane oxygen.[161] The *tert*-butyl group is expected to direct approach of azidoaldehyde **187** from the *si* face of the enolate to afford the correct enantiomer (**Scheme 73**).



Scheme 73: Envisaged enantio- and diastereocontrol of the aldol-type reaction

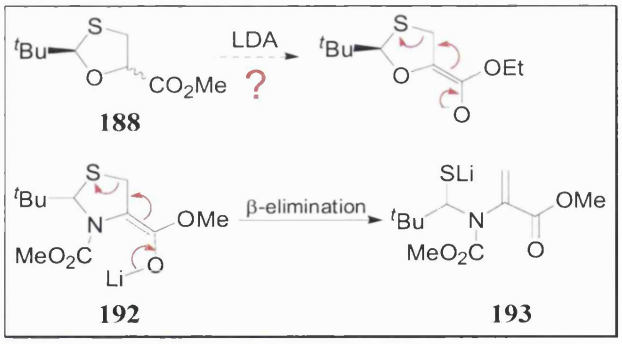
[161] Ireland, R. E.; Wipf, P.; Armstrong, J. D. III *J. Org Chem.* **1991**, *56*, 650.

Such stereocontrol in aldol reactions had been achieved by Corey and Reichard in their synthesis of the microbial agent lactacystin **191** (**Scheme 74**).[162] The *cis*-oxazolidine derivative **189** derived from *N*-benzylserine methyl ester was reacted with isobutyraldehyde to afford **190** as a single isomer.



Scheme 74: Stereoselective aldol in Corey's synthesis of lactacystin

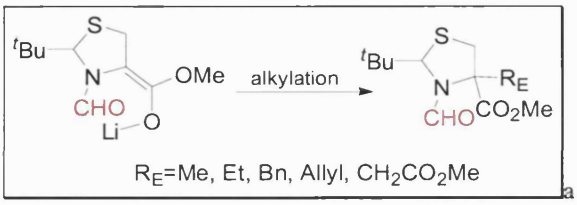
We were aware of a risk of competing *β*-elimination of the ester enolate under aldol conditions, due to the presence of the sulfur atom in our system **188**. Indeed, Seebach showed in his extensive studies on the concept of "Self-Regeneration of Stereocentres"[163] that lithium enolates of carbamate protected thiazolidines **192** were not stable under standard aldol or alkylation conditions, and yielded the elimination products **193** predominantly (**Scheme 75**).[164]



Scheme 75: Competitive *β*-elimination in sulfur-containing ester enolates

[162] Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677.
[163] For a review, see Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708.
[164] (a) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315. (b) Seebach, D.; Jeanguenat, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291.

On the other hand, Pattenden observed that replacement of the carbamate by a formyl protecting group increased the enolate stability sufficiently to perform alkylation reactions (**Scheme 76**).[165]

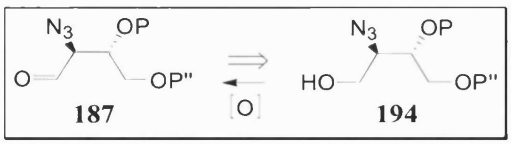


Scheme 76: Alkylation of cysteine derivatives using a formyl protecting group

It was unclear how the presence of an oxygen instead of the nitrogen would influence the stability of the enolate. Moreover we were unaware of any example of related chemistry of *O,S*-acetal enolates. Our efforts were therefore focused on the syntheses of azidoaldehyde **187** and oxathiolane ester **188.**

II-3.2 Synthesis of the azidoaldehyde

One of the envisaged ways to obtain the aldehyde **187** chosen in our strategy for the synthesis of the precursor to tagetitoxin was by oxidation of the corresponding primary alcohol **194** (**Scheme 77**). Therefore we needed to find an efficient entry to such a 2-azido-1,3,4-triol derivative.

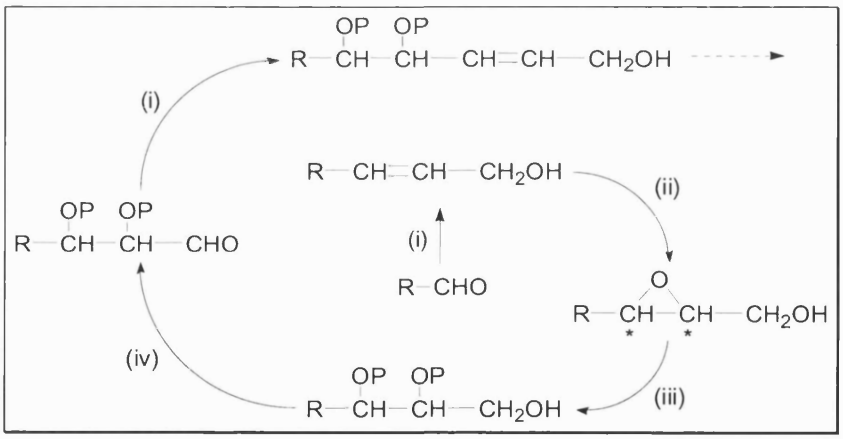


Scheme 77: Trihydroxylated precursor to azidoaldehyde **X**

[165] Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131.

Following renewed interest in the synthesis of carbohydrate and polyhydroxylated natural products in the 1980s, various approaches had been developed for the stereospecific construction of polyols, which relied on the stereo- and regiochemical control of nucleophilic additions to 2,3-epoxyalcohol derivatives.[166,167,168] Masamune and Sharpless reported a systematic iterative approach suitable for the construction of a range of polyhydroxylated substrates, the efficiency of which was demonstrated in the synthesis of L-hexoses.[169]

The strategy consists of a linear two-carbon chain extension achieved in four stages: (i) homologation of an aldehyde to the corresponding allylic alcohol: (ii) Sharpless asymmetric epoxidation of the allylic alcohol; (iii) stereospecific and regioselective nucleophilic opening of the epoxide; (iv) oxidation of the primary alcohol to the corresponding aldehyde. This series of reaction is then repeated to afford the desired chain length (**Scheme 78**).[170]



Scheme 78: Iterative two-carbon extension cycle

[166] Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1378, and references cited therein.

[167] (a) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371. (b) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083. (c) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1983**, *48*, 5083.

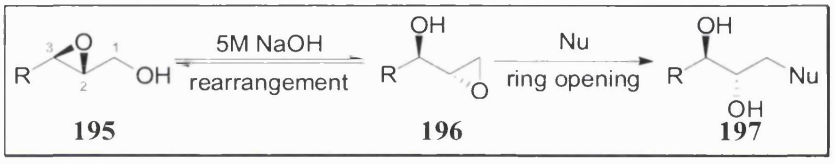
[168] Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.

[169] (a) Ko, S., Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A. III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949. (b)) Ko, S., Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A. III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.

[170] Nicolaou, K.C.; Sorensen, E. J. *Classics in total synthesis*, VCH mbH; **1996**, Ch. 19, p. 293.

We decided to apply the above strategy to construct the desired 2-azido-3,4-hydroxyaldehyde **194**, using an azide for the nucleophilic ring-opening of the epoxide. The systematic study by Sharpless and co-workers of selective transformations of 2,3-epoxyalcohol derivatives using a range of nucleophiles provided insight into the issue of discrimination between the three possible reactive sites for nucleophilic substitution.

Strategies for the C-1 selective nucleophilic substitution exploit the Payne rearrangement of 2,3-epoxyalcohol **195** under basic conditions, by using the 1,2-epoxide **196** for nucleophilic ring-opening (**Scheme 79**).[171]

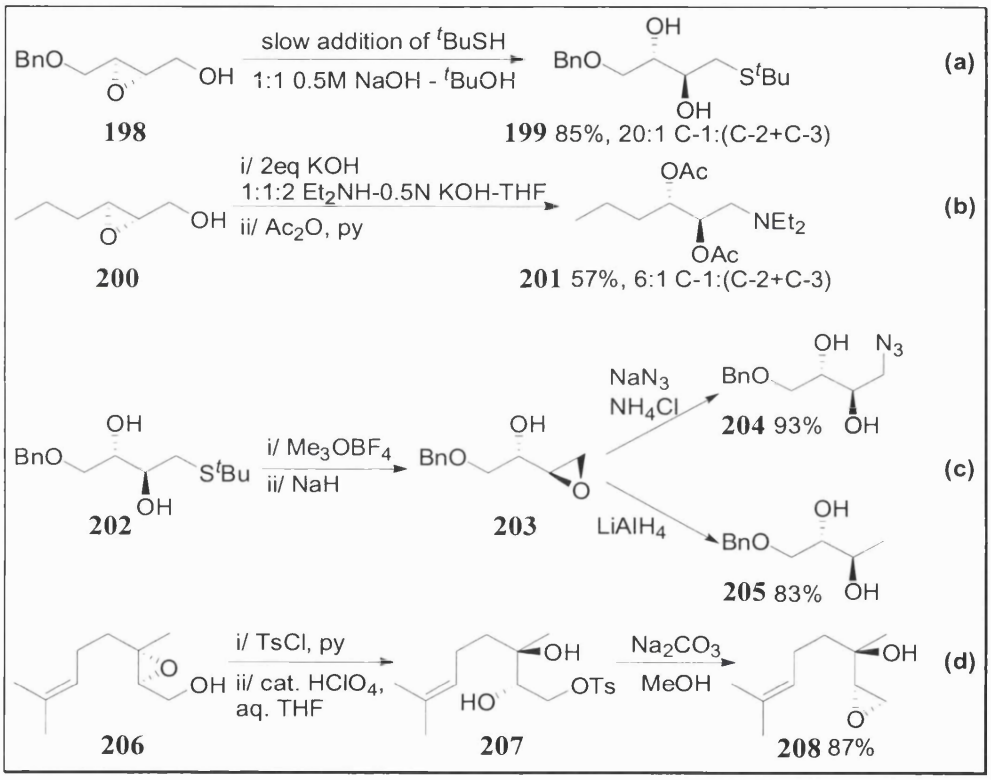


Scheme 79: Payne rearrangement – opening reaction

tert-Butylthiolate was found to capture the more reactive 1,2-epoxyalcohol selectively, driving the conversion of 2,3-epoxyalcohol **198** to 1-*tert*-butylthio-2,3-diol **199** (**Scheme 80, (a)**). Amines gave less selective results, with markedly lower isolated yields of the 1-amino-2,3-hydroxy product **201**, although the regioselectivity could be improved by the use of an excess of a sterically hindered amine and THF as a co-solvent (**Scheme 80, (b)**). The basic reaction conditions of this rearrangement-opening sequence however preclude the direct use of other nucleophiles. In an indirect approach, the 1-thio-2,3-diols **202** can be converted to 1,2-epoxyalcohols **203**[172] *via* S-alkylation followed by treatment with base. Reaction with nucleophiles such as sodium azide or lithium aluminium hydride provide the desired opening products **204** and **205** with excellent regioselectivity (**Scheme 80, (c)**). A similar indirect approach for the

[171] Behrens, C. H.; Soo, Y. K.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687, and references cited therein.
[172] The Payne rearrangement itself usually leads to a mixture of epoxyalcohols and is therefore of limited preparative use.

synthesis of 1,2-epoxyalcohols is known as the "diol sulfonate method" (**Scheme 80, (d)**). The C-1 hydroxyl group of epoxyalcohol **206** is converted into a sulfonate ester and the epoxide selectively opened at C-3 under acidic aqueous conditions with inversion of configuration. Base treatment of diol **207** affords the desired 1,2-epoxyalcohol **208**. It is noteworthy that the "diol sulfide method" proceeds with inversion of configuration at C-2, whereas the "diol sulfonate method" retains the stereochemistry at this centre.

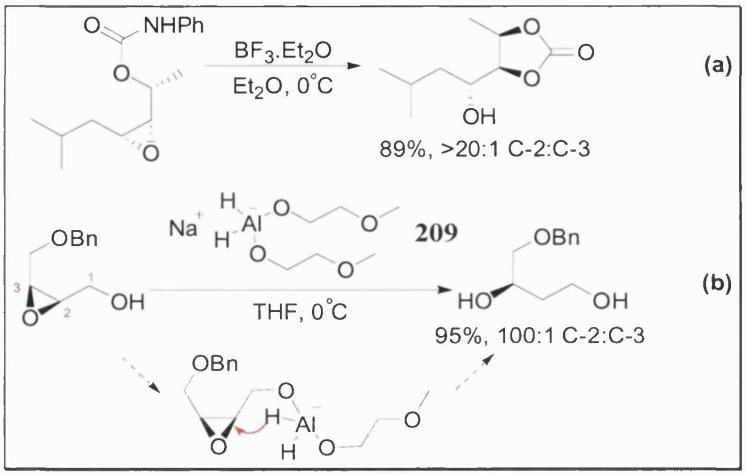


Scheme 80: Strategies for C-1 selective nucleophilic opening of 2,3 epoxyalcohols

Methods for C-2 selective nucleophilic substitution have been developed in both intramolecular and bimolecular fashion.

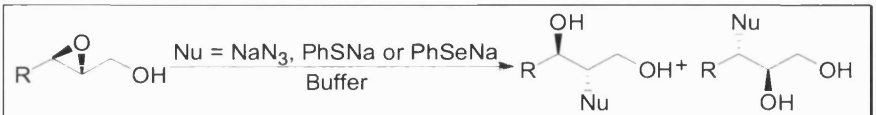
The intramolecular approaches make use of the C-1 hydroxyl to attach an internal nucleophile, such as a carboxylated reagent (carbonate or urethane) for O-attack of the

carbonyl and construction of a triol unit (**Scheme 81, (a)**), or Red-Al **209** for C-2 selective reduction (**Scheme 81, (b)**).

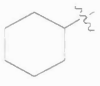
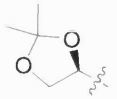


Scheme 81: Intramolecular C-2 selective nucleophilic opening of 2,3 epoxyalcohols

Bimolecular C-2 selective 2,3-epoxyalcohol opening requires increased steric hindrance at C-3 or the presence of an oxygenated substituent at C-4 to overcome the C-2 deactivation caused by the electron-withdrawing inductive effect of the primary hydroxyl (**Scheme 82**).[173] Azide, thiolate and selenide nucleophiles were used in C-2 selective reactions of 2,3-epoxyalcohols **195** and showed increased selectivity with sterically and electronically favoured systems.



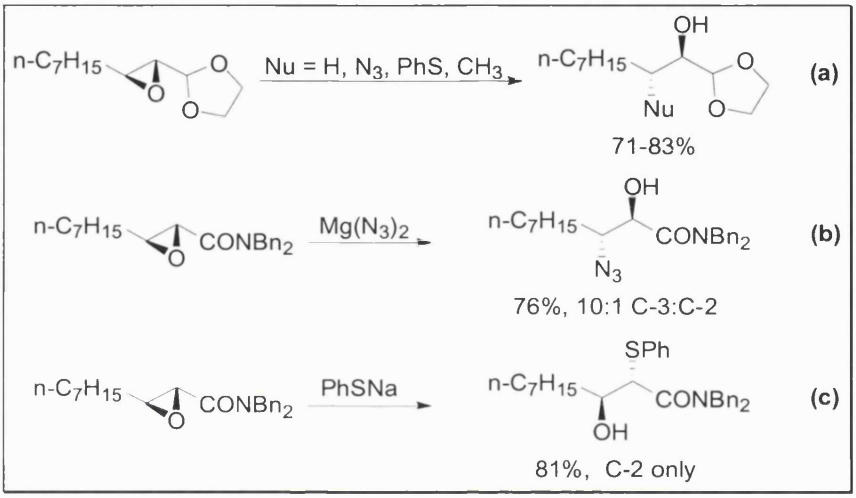
195

R		C-2:C-3	Yield
	Nu = NaN_3	1:1.7	93
	Nu = PhSNa	1:1	69
	Nu = NaN_3	C-2 only	47
	Nu = PhSNa	C-2 only	76
	Nu = NaN_3	10:1	90
	Nu = PhSNa	>10:1	76
	Nu = PhSeNa	10:1	90

Scheme 82: Bimolecular C-2 selective nucleophilic opening of 2,3 epoxyalcohols

[173] Behrens, C. H.; Sharpless, *J. Org. Chem.* **1985**, *50*, 5696, and references cited therein.

Although ring-opening of 2,3-epoxyalcohols at the C-3 position benefits from the C-2 deactivation in simple systems, this electronic bias is only moderate, and does not provide synthetically useful selectivities. Sharpless has developed conditions favouring the C-3 selective reaction, where the C-1 hydroxyl group is oxidised to the corresponding aldehyde acetal (thus providing steric bulk as well as higher electronegativity) (**Scheme 83, (a)**), or to the amide (**Scheme 83, (b)**).[174]



Scheme 83: C-3 selective nucleophilic opening of 2,3-epoxyacetals and 2,3-epoxyamides

However the scope of the reaction of 2,3-epoxyacetals is limited by the instability of epoxides to general acetalisation conditions, making the synthesis of the substrates difficult. The reaction with 2,3-epoxyamides itself is not well understood and gives the opposite regioselectivity with a thiolate nucleophile (**Scheme 83, (c)**).

A more versatile method for C-3 selective opening of 2,3-epoxyalcohols has been developed by Sharpless and co-workers, which uses bidentate coordination to a transition-metal alkoxide (**212**) to induce regioselectivity (**Figure 22, (a)**).[174] This is rendered possible by the substitution of an alkoxide by the primary hydroxyl of the substrate.

[174] Behrens, C. H.; Sharpless, *J. Org. Chem.* **1985**, *50*, 5696, and references cited therein.
[174] Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

The presence of stoichiometric amounts of titanium tetraisopropoxide was found to promote opening of *trans*-2,3-epoxyalcohols under mild conditions, using otherwise unreactive nucleophiles such as diethylamine, isopropanol, TMS-cyanide or ammonium chloride. The C-3 selectivity was moderate (cyanide, azide, thiolate) to excellent (amine, alkoxide, carboxylate). Similarly, 2,3-epoxyacids and amides underwent the desired C-3 selective opening with amine, phenol, azide and cyanide nucleophiles (**Figure 22, (b)**).[175]

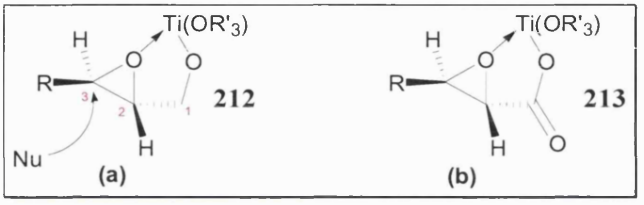


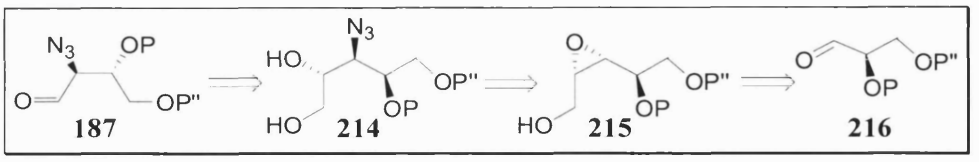
Figure 22: Bidentate titanium complexes of 2,3-epoxyalcohol derivatives

In view of these results for stereo- and regiospecific nucleophilic opening of 2,3-epoxyalcohols, three approaches were investigated for the synthesis of our target azidoaldehyde **187**, based on the chain extension-epoxidation-nucleophilic opening sequence of transformations described earlier.

II-3.2.1 D-Glyceraldehyde approach

In this first approach, we envisaged preparation of the target azidoaldehyde **187** by oxidative cleavage of the corresponding 1,2-diol **214** (**Scheme 84**). The 1,2-dihydroxy-3-azido sequence would be introduced by regioselective azide opening of epoxyalcohol **215**, which would be derived from aldehyde **216** by homologation to the allylic alcohol followed by asymmetric epoxidation.

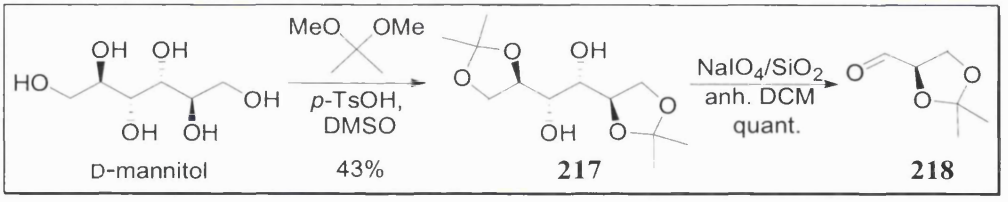
[175] Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560



Scheme 84: First approach to azidoaldehyde

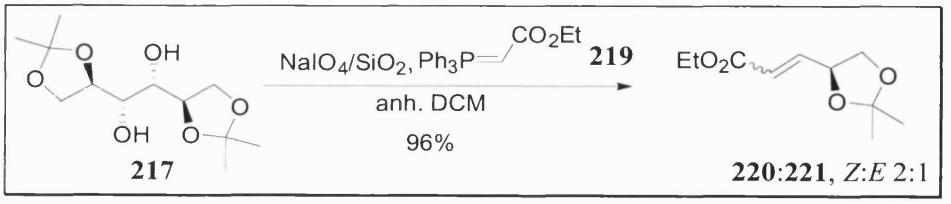
D-Glyceraldehyde acetonide **218**, which could easily be derived from D-mannitol, was chosen as the chiral building block for this approach.

1,2:5,6-Di-*O*-isopropylidene-D-mannitol **217** was prepared on a 50g scale by acid-catalysed transacetalisation of natural mannitol with 2,2-dimethoxypropane.[176] Subsequent oxidative cleavage was performed using silica-gel supported metaperiodate in anhydrous dichloromethane and afforded D-glyceraldehyde acetonide **218** quantitatively. This aldehyde could be used without further purification (**Scheme 85**).[177]



Scheme 85: Synthesis of glyceraldehyde acetonide

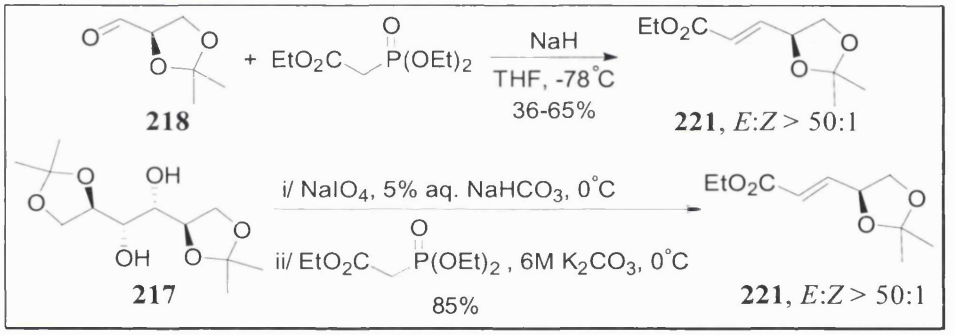
Wittig olefination of the crude glyceraldehyde acetonide was carried out in a one-pot process by addition of phosphorane **219** to the oxidation reaction mixture.[178] However a 2:1 mixture of the *Z*- and *E*-alkenes **220** and **221** was obtained (**Scheme 86**).[179]



Scheme 86: Wittig olefination of glyceraldehyde acetonide

[176] Kierstead, R. W.; Faraone, A.; Mennona, F. *J. Med. Chem.* **1983**, *26*, 1561.
[177] Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.
[178] Ray, P. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 149.
[179] Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373, and references cited therein.

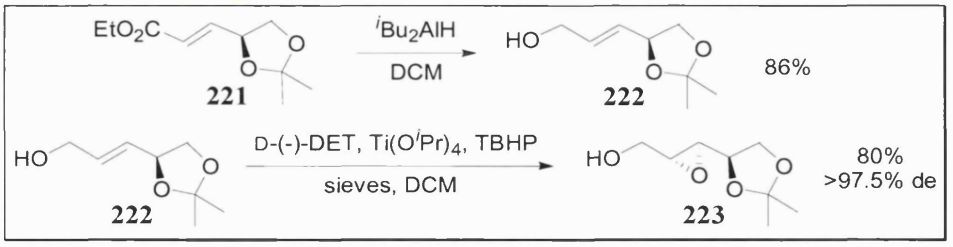
The desired *E*-alkene **221** could be formed selectively using Wadsworth-Emmons conditions: reaction of the crude glyceraldehyde acetonide with triethyl phosphonoacetate and sodium hydride at –78 °C afforded **221** as a single isomer. However we were aware of the sensitivity of the aldehyde to hydrolysis (particularly upon concentration and storage).[180] When the crude glyceraldehyde acetonide **218** was evaporated to dryness as opposed to being used as a solution in DCM, we observed a drop in the yield of olefination from 65% to 36%, and we later favoured procedures where **218** was reacted *in situ*. The best results were obtained under Marshall's aqueous conditions, which gave consistently high yield for the one-pot conversion of 1,2:5,6-di-*O*-isopropylidene-D-mannitol **217** to the desired olefin **221** (**Scheme 87**).[181]



Scheme 87: Wadsworth-Emmons olefination of glyceraldehyde acetonide

DIBAL-H reduction afforded chiral allylic alcohol **222** in 86% yield, which was the chosen substrate for Sharpless asymmetric epoxidation (**Scheme 88**). Treatment of **222** with unnatural D-(-)-diethyl tartrate, titanium(IV) isopropoxide and *tert*-butylhydroperoxide afforded the desired 2,3-epoxyalcohol **223** in 80% yield as a single isomer.

[180] Schmid, C. R.; Bryant, J. D. *Org. Syn. 75*, 139.
[181] Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.



Scheme 88: Matched case of SAE

The excellent diastereoselectivity of this reaction is explained by the diastereofacial preference of the titanium-unnatural tartrate complex for the α-face of the double bond matching the intrinsic preference of the chiral substrate (**Figure 23**).[182] However the reaction was slow and required stoichiometric quantities of tartrate and titanium(IV) isopropoxide, as well as molecular sieves to achieve complete conversion after 5 days.

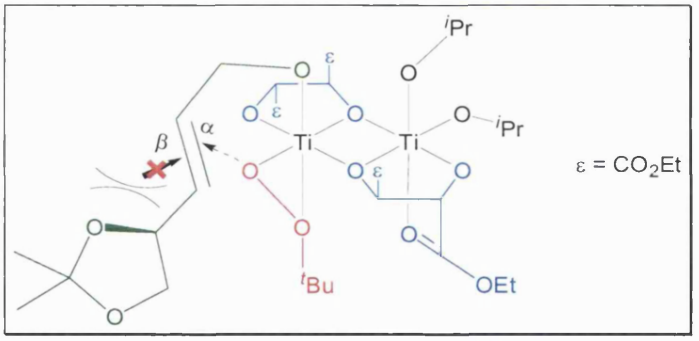
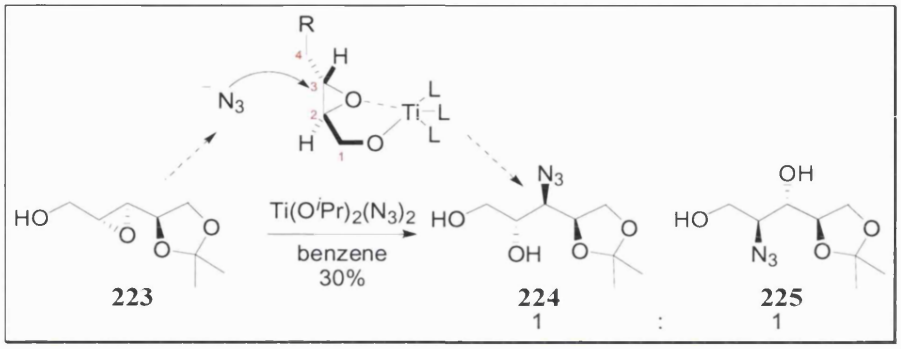


Figure 23: Reagent and substrate control in the SAE, a matched case

Having achieved the homologation of glyceraldehyde acetonide and the epoxidation, we needed to find suitable conditions for the C-3 selective azide opening of the 2,3-epoxyalcohol. Following Sharpless reports on transition-metal chelates, epoxyalcohol **223** was treated with a reagent prepared *in situ* from titanium isopropoxide and trimethylsilyl azide in order to favour C-3 substitution through the 5-membered Ti-chelate (**Scheme 89**).[183] However in this case the reaction was not selective and afforded a 1:1 inseparable mixture of the 1,2- and 1,3-diols **224** and **225** in low yield.

[182] (a) Sharpless, K. B. *Chem. Scr.* **1985**, *25*, 71. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.
[183] (a) Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800. (b) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.

This might be due to the presence of the acetal moiety at C-4 which can also chelate the titanium reagent and interfere with the desired pathway. Moreover the presence of oxygenated functional groups at C-4 had been shown to deactivate the C-3 position for nucleophilic attack, as had an increased steric bulk (here the acetonide). As a result the substrate and reagent control seem to be in opposition, accounting for a non-selective reaction.



Scheme 89: Attempted regioselective azide substitution

Treatment of the reaction mixture under with sodium periodate to separate the unwanted isomer from the azidoaldehyde was unsuccessful, and the approach using glyceraldehyde acetonide as a chiral building block was abandoned.

II-3.2.2 (Z) Butenediol approach: Kitawaga's synthesis of sphingosines

Kitagawa and co-workers utilised a very similar strategy to the one described previously in their synthesis of C_{18}-sphingosines (**Figure 24**).[184]

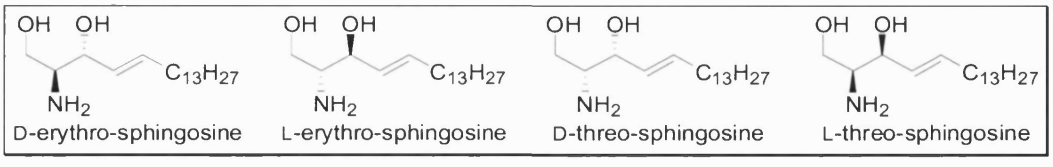


Figure 24: Two pairs of enantiomeric C_{18}-sphingosines

[184] (a) Shibuya, H.; Kawashima, K.; Ikeda, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 7205. (b) Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1154.

They accessed the *erythro* pair by a regioselective azide substitution of a *trans* epoxide followed by azide reduction and chain elongation, whereas the same sequence of steps using a *cis* epoxide afforded the *threo* isomers. Interestingly, they found that for the *cis* substrates the titanium-mediated epoxide opening was C-2 selective when the C-4 terminus was protected as a sterically hindered monomethoxytrityl- (MMTr-) ether (**Figure 25**).

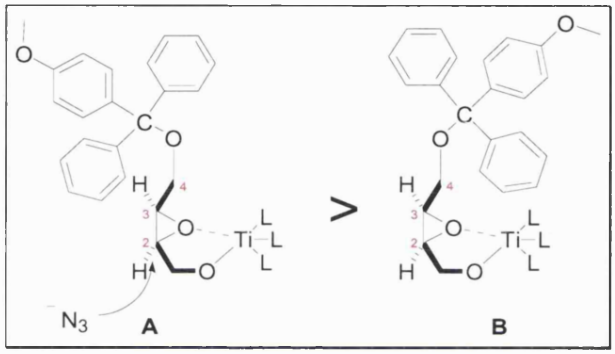
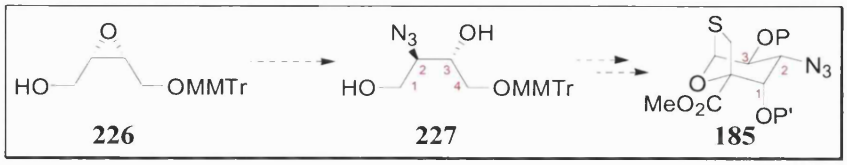


Figure 25: Steric factors in the regioselectivity of azide substitution

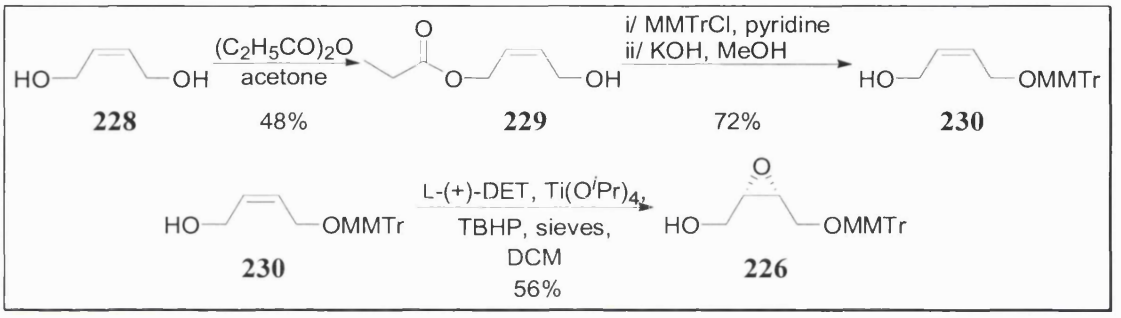
Although conformation **B** of the chelated reaction intermediate would lead to nucleophilic substitution at C-3 as previously shown in Scheme **83**, unfavourable steric interactions between the MMTr- moiety and the titanium ligands are expected to favour an alternative conformation **A**. In this conformation, nucleophilic attack at C-3 is believed to be shielded by the bulky protecting group and therefore occurs at C-2.

We decided to use Kitagawa's strategy to construct our target 2-azido-1,3-diol **227** with the desired *syn* configuration, which would then be used to synthesise the fully functionalised tagetitoxin precursor **185** (**Scheme 90**).



Scheme 90: Approach to 2-azido-1,3-diol *via cis*-epoxide

Symmetrical (*Z*) but-2-ene-1,4-diol **228** was protected as the 4-MMTr ether **230** *via* the monopropionate **229** in 35% yield over three steps. Stoichiometric Sharpless asymmetric epoxidation was carried out to give the desired (2*S*,3*R*)-epoxyalcohol **226**. Consistently with the known lower reactivity of *cis* alkenes, the reaction was sluggish and afforded only 56% of the desired product after 6 days (**Scheme 91**).[185]



Scheme 91: SAE of *cis*-allylic alcohol

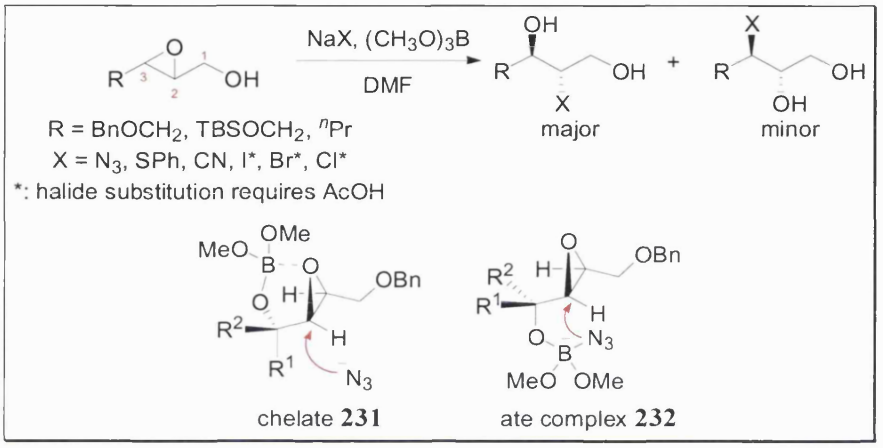
The epoxyalcohol **226** was then subjected to the azide substitution conditions described by Kitagawa using titanium isopropoxide and trimethylsilylazide, but this only resulted in recovered starting material after 6h. The apparent lack of reactivity of the substrate was in contradiction with the author's results, and could not be improved by the use of distilled titanium isopropoxide or new batches of reagents.

Our attention was drawn to a recent report of C-2 selective nucleophilic substitution of 2,3-epoxyalcohols.[186] Miyashita and co-workers showed that a variety of nucleophiles such as azides, halides, thiolates and cyanides reacted in a C-2 selective fashion with 2,3-epoxyalcohols when combined with trialkyl borates (**Scheme 92**). *trans*-Epoxyalcohols underwent the corresponding substitution with high regioselectivity (>92:8) and chemical yields, whereas *cis*-epoxyalcohols exhibited somewhat lower

[185] Ees were not determined at this stage due to the unpromising results and the approach was later abandoned.

[186] (a) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789. (b) Tomata, Y.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2003**, *44*, 8975.

yields and selectivity. Molecular calculations (Cartesian coordinates of transitions structures using the Gaussian 98 program) and mechanistic studies showed that the reaction proceeds *via* an intramolecular boron chelate **231**, rather than an ate complex **232**. The authors did not provide any rationale for the difference in selectivity observed for boron chelates compared to titanium chelates.



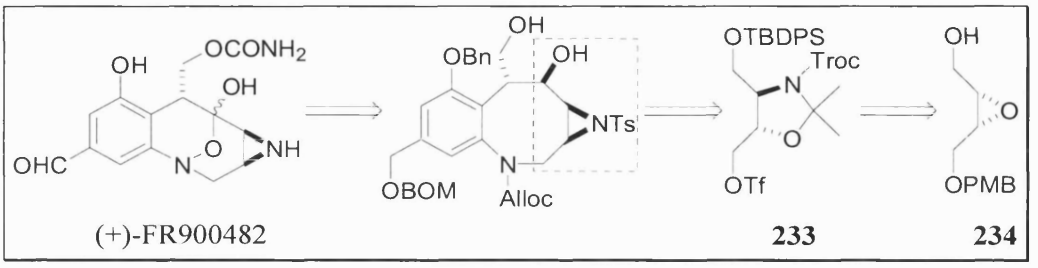
Scheme 92: *Endo*-mode epoxide opening through a boron chelate

However the epoxyalcohol **226** again proved unreactive under these conditions and only traces of the desired azido diol **227** could be isolated. It could be postulated that the bulk of the MMTr- protecting group which was supposed to result in a steric bias is too great and prevents the nucleophilic reaction altogether.

II-3.2.3 (Z) Butenediol approach: rapid entry

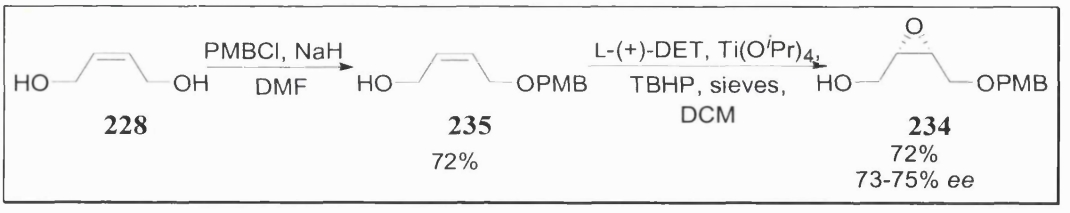
In a separate attempt to construct the azidoaldehyde which would be used in our aldol strategy, we decided to access the desired 1,3-diol **194** *via* an expeditious but unselective epoxide formation-azide substitution sequence, followed by separation of the desired isomer from the unwanted isomer. Terashima and Williams had

independently described a similar approach to the optically active *N*-protected oxazolidine **233** which provided the aliphatic segment of antitumor agent (+)-FR900482 (**Scheme 93**).[187] Terashima and co-workers' strategy is outlined below.



Scheme 93: Synthesis of (+)-FR900482 from a chiral epoxyalcohol

We expected this strategy to allow rapid entry to the target fragment, which would be used to test the aldol chemistry envisaged for the construction of a tagetitoxin precursor. The optically active epoxyalcohol **243** was obtained in two steps from (*Z*) but-2-ene-1,4-diol **228**. This was first mono-protected as a *p*-methoxybenzylether (PMB-) **235** in 72% yield. Catalytic SAE of the resulting *cis* allylic alcohol with L-(+)-diethyl tartrate afforded 72% of the desired epoxide product, albeit with moderate enantiomeric excess (**Scheme 94**).

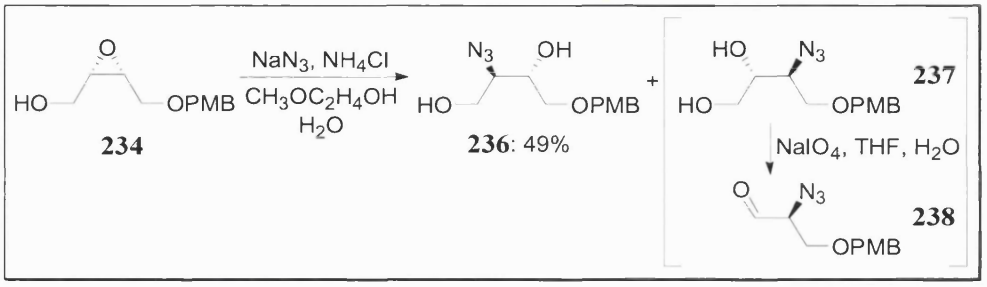


Scheme 94: Synthesis of optically active epoxyalcohol

Nucleophilic opening of epoxyalcohol **234** with sodium azide in the presence of ammonium chloride resulted in an inseparable equimolar mixture of azidodiols **236** and **237** (**Scheme 95**). The crude reaction mixture was then treated with sodium periodate

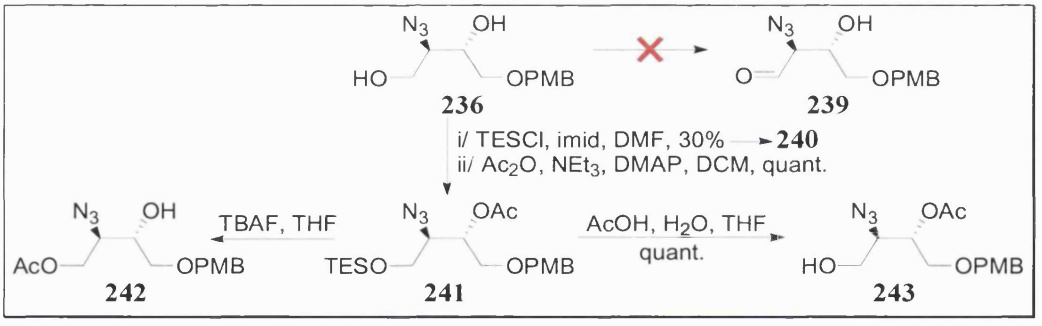
[187] (a) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239, and references cited therein. (b) Williams, R.M.; Rollins, S.B.; Judd, T.C. *Tetrahedron*, **2000**, *56*, 521.

in order to cleave the unwanted 1,2-diol **237**, after which the 1,3-diol **236** could be separated from the resulting aldehyde **238** in an overall 49% yield.



Scheme 95: Unselective epoxide opening and oxidative isolation of 1,3-diol

Attempts to oxidise the primary alcohol selectively using Dess-Martin oxidation[188] and several TEMPO-mediated processes[189] proved unsuccessful, the azidodiol either being left unchanged, or degraded into a mixture of unidentified products. It was therefore necessary to resort to an orthogonal protecting group strategy in order to obtain the target azidoaldehyde **239** (**Scheme 96**).



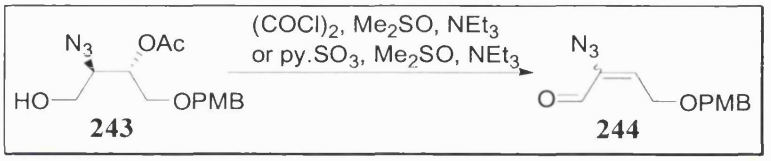
Scheme 96: Protecting group manipulation on azidodiol

The primary alcohol was first protected as a TES-ether **240**, then the secondary alcohol was esterified with acetic anhydride to give the fully protected intermediate **241**. Deprotection of the silyl ether had to be carried out under acidic conditions in order to avoid acetate migration on to the primary position and formation of the primary acetate

[188] Wender, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 2311.
[189] (a) TEMPO/sodium hypochlorite: Siedlecka, R.; Skarzewski, J.; Młochowski, J. *Tetrahedron Lett.* **1990**, *31*, 2177. (b) TEMPO/sodium bromite or calcium hypochlorite: Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org.Chem.* **1990**, *55*, 462. (c) TEMPO/trichloroisocyanuric acid: De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041.

242. Treatment with aqueous acetic acid in THF yielded the azidoalcohol **243** quantitatively.

Oxidation of this substrate under Swern conditions, or using pyridine-sulfur trioxide complex failed to give the desired aldehyde **239**, and the predominant product of these reactions was the α,β-unsaturated aldehyde **244** (**Scheme 97**). This stable conjugated system is expected to result from abstraction of the α-H under basic conditions, followed by elimination of the acetate protecting group.



Scheme 97: Formation of unsaturated aldehyde under basic conditions

The use of a less electron-withdrawing hydroxyl-protecting group might overcome this problem, and indeed different methods for the direct oxidation of primary silyl ethers in the presence of secondary silyl ethers had recently been reported, which used Swern conditions[190] or quinolinium fluorochromate.[191] However in view of the previous results, and the limitations in yields, selectivity and *ee*s of all three epoxide opening strategies presented so far, they were not taken any further.

[190] Rodríguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161.
[191] Chandrasekhar, S.; Pradyumna, K. M.; Takhi, M. *J. Org.Chem.* **1997**, *62*, 2628.

II-3.2.4 Conclusions on the attempted synthesis of the azidoaldehyde

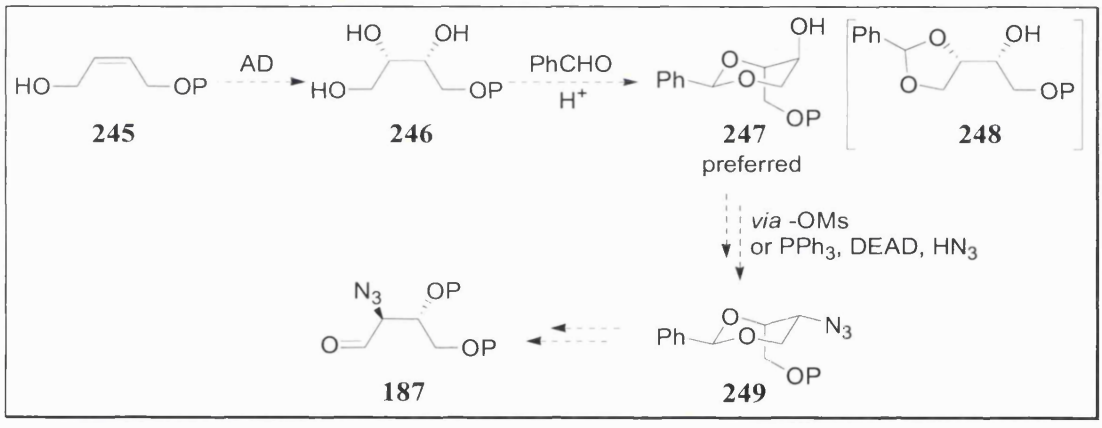
The strategies presented here for the synthesis of azidoaldehyde **187** relied on the success of a regioselective epoxide opening by an azide nucleophile. Despite the development of new reagents for such regioselective processes, it seems that azide nucleophiles show intrinsically moderate potential compared to bigger nucleophiles such as amines, alkoxides and esters.[175] The somewhat lower selectivities observed for *cis*-epoxyalcohols compared to *trans* epoxyalcohols had also been observed.[187] However the main detrimental factor in the three epoxyalcohol systems investigated is believed to be the presence of oxygenated functionalities at both termini of the substrates. Indeed the electronic factors known to activate or deactivate a particular position for nucleophilic opening are expected to be less efficient if the two ends of the epoxide are electronically very similar.[192]

In view of these observations, a different approach could be envisaged whereby the nucleophilic azide would be introduced by displacement of a leaving group rather than by nucleophilic opening of an epoxide, thereby eliminating the issue of regioselectivity. This could be achieved in a two-stage process *via* the formation of a sulfonate followed by treatment with an organic or inorganic azide source. Such chemistry is widely documented and has been developed to accommodate a range of substrates and reaction conditions.[193] Alternatively a modified Mitsunobu reaction with hydrazoic acid

[175] Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
[187] (a) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789. (b) Tomata, Y.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2003**, *44*, 8975.
[192] Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437, and references cited therein.
[193] Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297, and references cited therein.

converts alcohols to azides,[194] and could be applied to a polyhydroxylated system bearing suitable protecting groups.

Starting from the same mono-protected *cis* but-2-ene-1,4-diol **245** used previously, asymmetric dihydroxylation could be used to set up the *cis* vicinal diol **246** (**Scheme 98**).[195] Selective protection of the C-1 and C-3 hydroxyls to form dioxane **247** is expected to proceed preferentially upon acid-catalysed reaction with benzaldehyde. The C-2 hydroxyl would then be available for direct or indirect azide displacement with inversion of configuration to form the protected azido triol **249**. Selective cleavage of the benzylidene acetal resulting in the PMB ether of the more hindered hydroxyl[196] followed by oxidation would complete the synthesis of our target azidoaldehyde **187**.



Scheme 98: Revised strategy for the synthesis of azidoaldehyde fragment

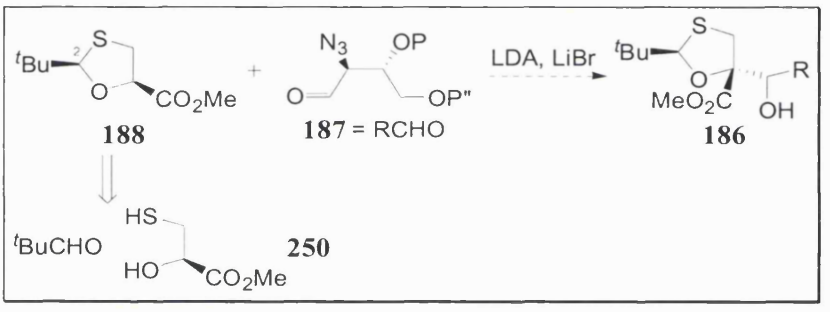
Although we can anticipate some issues, in particular with respect to the solubility of triol **246** and possible steric hindrance to the displacement of the alcohol in **247**, this proposed strategy builds on the learning from our previous attempts and should allow to access this key fragment in the synthesis of tagetitoxin.

[194] Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.
[195] van Nieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 843.
[196] Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, *10*, 2371.

II-3.3 Synthesis of the oxathiolane ester

II-3.3.1 Choice of a suitable chiral building block

The second target of our synthetic studies was the oxathiolane ester **188**, the enolate of which would be formed to react with azidoaldehyde **187**. As discussed previously, the stereochemistry at C-2 of the oxathiolane was crucial in order to induce approach of the aldehyde from the opposite face to the *tert*-butyl moiety and form the desired enantiomer **186** of the aldol adduct (**Scheme 99**). The stereochemistry at C-5 was less important *per se* since it would be lost during the generation of the ester enolate.



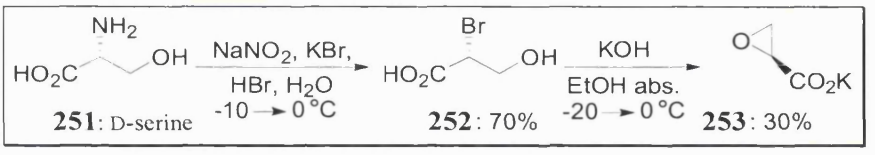
Scheme 99: Proposed stereoselective aldol reaction

Following our methodology work on the ring expansion of 1,3-oxathiolanes, we planned to use the same reaction to construct the oxathiolane ester **188**, namely by acid or Lewis acid-catalysed reaction of pivalaldehyde and the chiral mercapto alcohol **250**. To the best of our knowledge there are currently no reports specifically studying the diastereoselectivity of 1,3-oxathiolane formation. However it had been shown in our group[197,198] that the reaction of benzaldehyde and 1-phenyl-2-mercaptoethanol gave predominantly the *cis*-isomer of 2,5-diphenyl-1,3-oxathiolane. Diastereoisomeric control for the formation of related *N,N*- *N,O*- and *O,O*- acetals is known to be

[197] Dallimore, J. M. Sci. Thesis, **2002**, UCL.
[198] 2,5-Diphenyl-1,3-oxathiolane was obtained in a 3.5:1 *cis:trans* ratio.

dependent on the reaction conditions: acid catalysis favours the thermodynamic mixture[165,166,199,200] whereas rhodium catalysis allows kinetic control.[201] Therefore it was anticipated that the required mercapto alcohol methyl ester **250** for the oxathiolane condensation with pivaladehyde should have the *R* stereochemistry shown in **scheme 99**.

D-Serine **251** was chosen as the chiral starting material for the synthesis of mercapto-alcohol methyl ester **250** (**Scheme 100**). Substitution of the primary amine by a bromine with overall retention of configuration was achieved *via* diazotisation of the aminoacid in the presence of KBr, and the crude product **252** was used without further purification. Treatment with potassium hydroxide in absolute ethanol afforded (*S*)-(-)-potassium glycidate **253** in moderate yield.[202]



Scheme 100: (*S*)-(-)-potassium glycidate from unnatural serine

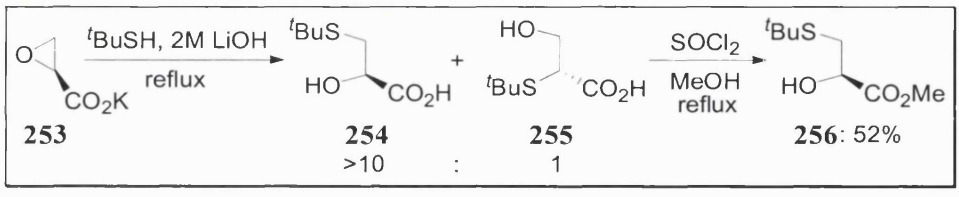
This synthesis posed some practical problems, in particular during the diazotisation where the control of the temperature at –10 °C was rendered difficult by the solidification of the aqueous medium. Moreover the recrystallisation of the glycidate was complicated by the stoichiometric amounts of potassium bromide generated during

[165] (a) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315. (b) Seebach, D.; Jeanguenat, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291.
[166] Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131.
[199] Seebach, D.; Lamatsch, B.; Amstutz, R.; Beck, A. K.; Dobler, M.; Egli, M.; Fitzi, R.; Gautschi, M.; Herradon, B.; Hibder, P. C.; Irwin, J. J.; Locher, R.; Maestro, M.; Maetzke, T.; Mourino, A.; Pfammatter, E.; Plattner, D. A.; Schikli, C.; Scweizer, W. B.; Seiler, P.; Stucky, G.; Petter, W.; Escalante, J.; Juaristi, E.; Quintana, D.; Miravitlles, C.; Molins, E. *Helv. Chim. Acta* **1992**, *75*, 913.
[200] (a) Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131. (b) Mulqueen, G. C.; Pattenden, G.; Whiting, D. A. *Tetrahedron* **1993**, *49*, 5359. (c) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 5705. (d) Boyce, R. J.; Pattenden, G. *Synlett* **1994**, 587.
[201] (a) Neveux, M.; Seiller, B.; Hagedorn, F.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1993**, *451*, 133. (b) Gorla, F.; Venanzi, L. M. *Helv. Chim. Acta* **1990**, *73*, 690. (c) Seebach, D.; Sommerfeld, T.; Jiang, Q.; Venanzi, L. M. *ibid.* **1994**, *77*, 1313.

the reaction and we were unable to titrate the inorganics present in the recrystallised material or prepare solutions of known concentrations for α_D determination.

The requirement for a regioselective glycidate opening at the methylene terminus in order to form mercapto alcohol methyl ester **250** precluded the use of hydrogen sulfide anion. Triphenylsilanethiol had been described as a practical solid equivalent of hydrogen sulfide, which would favour nucleophilic attack at the least hindered carbon and could be easily deprotected to give the corresponding hydroxymercaptan.[203] In our hands treatment of potassium glycidate **253** with triphenylsilanethiol and triethylamine failed to give the desired adduct and led to decomposition of the substrate.

Epoxide opening with a large excess of *tert*-butylmercaptan under aqueous basic conditions proceeded with a satisfactory 10:1 regioselectivity[204] in favour of thiolate attack at the less hindered carbon, and afforded 92% of an inseparable mixture of the *tert*-butyl-protected mercapto alcohol carboxylic acids **254** and **255** (**Scheme 101**). After conversion to the corresponding methyl ester using thionyl chloride and methanol, the major regioisomer **256** could be isolated in 52% yield.



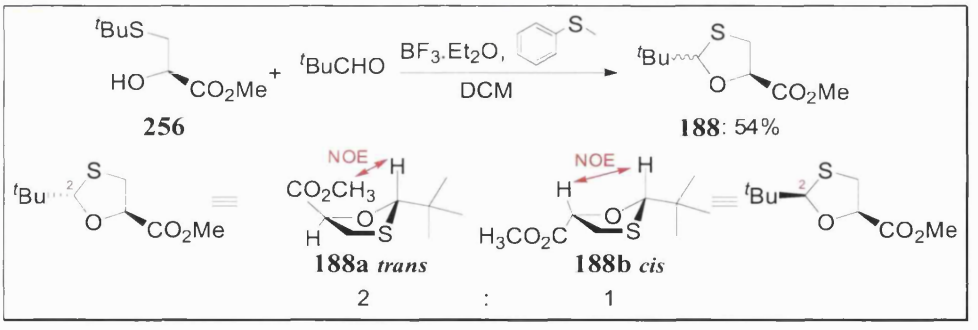
Scheme 101: (S)-*tert*-butyl-protected mercaptoethanol methyl ester

Removal of the *tert*-butyl moiety proved problematic and the protected mercapto-alcohol methyl ester **256** was not cleanly deprotected upon treatment with mercuric acetate/trifluoroacetic acid/hydrogen sulfide,[205] triethylsilane/trifluoroacetic acid[206] or

[202] Petit, Y.; Larchevêque, M. *Org. Syn. 75*, 37.
[203] Brittain, J.; Gareau, Y. *Tetrahedron Lett.* **1993**, *34*, 3363.
[204] Based on the integrations of the ^{1}H NMR spectrum of the crude reaction mixture.
[205] Nishimura, O.; Kitada, C.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576.
[206] Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 4625.

tetrafluoroboric acid/trifluoroacetic acid.[207] Attempts to form the disulfide under oxidative conditions using iodine or iodobenzene diacetate[208] were also unsuccessful. Indeed the stability of the *tert*-butyl protecting group for thiols is a known issue in peptide chemistry and has precluded its widespread use in favour of the more labile benzyl and acetamidomethyl groups.[209] An indirect de-*tert*-butylation process had been described, which involves (2-nitrophenyl)sulfenyl- (Nps-) cleavage of the *tert*-butyl thioether, followed by treatment with catalytic mercaptoethanol in mildly basic medium to form the cystine dimer and extrude the bis(2-nitrophenyl) disulfide. However we decided not to pursue this strategy since it would require further investigation into the reduction of the disulfide bond to generate the fully deprotected mercapto alcoholmethyl ester **230**.

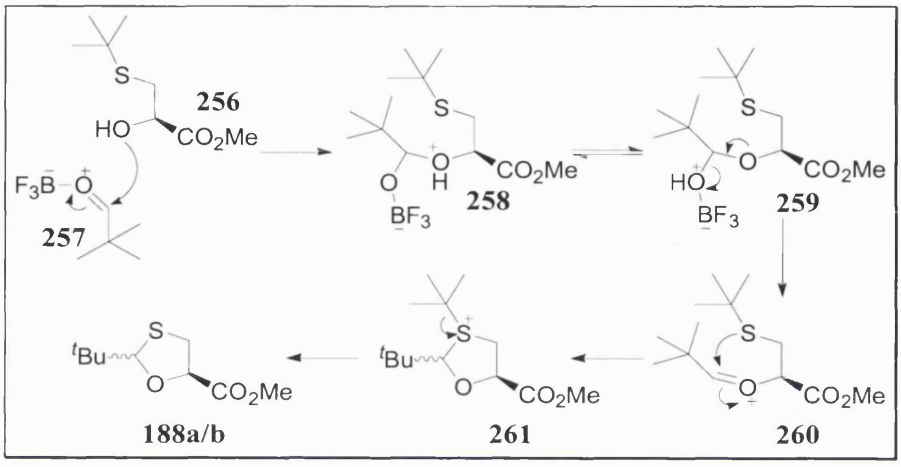
Instead the protected mercapto alcohol methyl ester **256** was treated directly with pivalaldehyde and boron trifluoride etherate complex, using thioanisole as a cation scavenger (**Scheme 102**). The desired oxathiolane ester **188** was thus obtained in a promising 54% yield of a 2:1 mixture of diastereoisomers. NOE experiments on the mixture involving irradiation of the C-2 proton allowed the assignment of the isomers as *trans* **188a** and *cis* **188b** respectively.



Scheme 102: One-pot ^{t}Bu- deprotection / oxathiolane formation

[207] Akaji, K.; Yoshida, M.; Tatsumi, T.; Kimura, T.; Fujiwara, Y.; Kiso Y. *J. Chem. Soc., Chem. Commun.* **1990**, 288.
[208] Kolovos, M. G.; Moutevelis-Minakakis, P. *Tetrahedron Lett.* **1992**, *33*, 5441.
[209] Pastuszak, J. J.; Chimiak, A. *J. Org.Chem.* **1981**, *46*, 1868, and references cited therein.

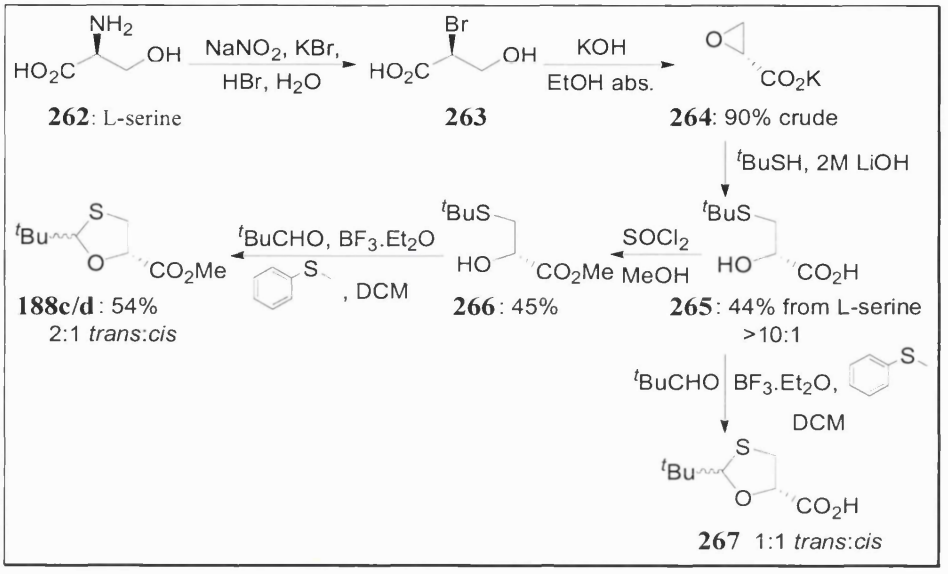
This novel cyclisation / deprotection is thought to proceed *via* hydroxyl attack of the activated aldehyde **257** to generate the acetal species **258** (**Scheme 103**). The pathway for the substitution at the acetal carbon is likely to involve sulfide attack at the oxonium ion **260**, leading to intermediate **261**, which would give the oxathiolane **188a/b** upon loss of a *tert*-butyl cation.



Scheme 103: Proposed mechanism for the novel ^{t}Bu- deprotection / oxathiolane formation

It appeared that contrary to the condensation of 2-phenyl-1,3-oxathiolane with benzaldehyde, our one-pot deprotection / oxathiolane formation led to the formation of the unwanted *trans*-diastereoisomer preferentially. The configuration at C-2 for this isomer was therefore opposite to the one required for the planned stereoselective aldol reaction.

In view of this result, the synthesis of the enantiomeric oxathiolane ester **188c** was achieved by repeating the same sequence of steps from natural L-serine **262**. The yields obtained were comparable, with an improvement on the overall yield when the glycidate was opened with *tert*-butylmercaptan without prior recrystallisation. The results are summarised in **scheme 104**.



Scheme 104: Oxathiolane ester from L-serine

Attempts to isolate the desired *trans* isomer **188c** by chromatography were unsuccessful. Similarly, the formation of oxathiolane acid **267** from crude **265** gave an inseparable 1:1 mixture of diastereoisomers and was not investigated any further.

The use of alternative acid catalysts was investigated in order to improve the yield of the deprotection/oxathiolane, but zinc chloride and *p*-toluenesulfonic acid failed to perform the desired condensation.

Since the investigation of this novel transformation is still at an early stage, we do not know if the reaction proceeds under kinetic or thermodynamic control. However the equilibration of the reaction mixture is plausible under Lewis-acidic conditions, *via* the oxonium **268** or sulfonium species **269** (**Figure 26**).

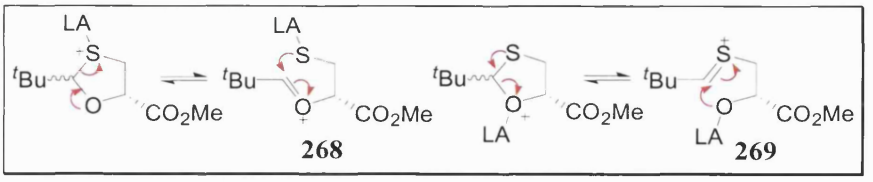


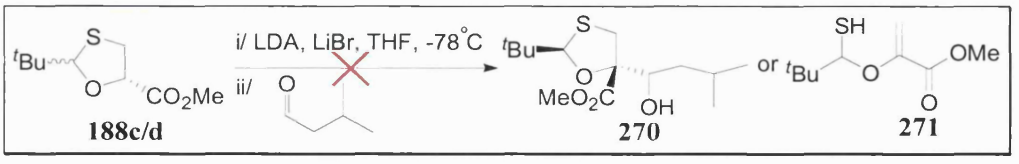
Figure 26: Possible Lewis-acid mediated equilibration of oxathiolanes

Further experiments on separate isomers would be necessary to assess whether this reaction proceeds under kinetic or thermodynamic control and if the diastereoisomeric ratio can be optimised to synthetically useful levels.

However given the time constraints on this project, it was decided to test the feasibility of the aldol reaction on the mixture of oxathiolane esters **188c/d**.

II-3.3.2 Attempted aldol reaction of oxathiolane ester

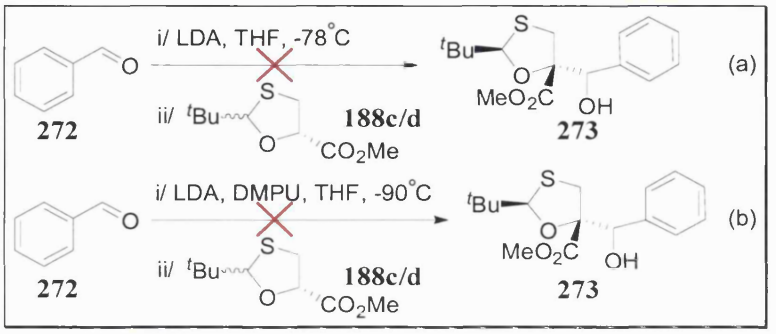
The mixed aldol reaction with isobutyraldehyde was attempted using Corey's conditions, where the oxathiolane ester **188c/d** was treated with lithium diisopropylamide in the presence of lithium bromide followed by addition of the electrophile (**Scheme 105**). However neither the desired aldol adduct **270** nor any products resulting from *β*-elimination (**271** or degradation products) could be identified upon work-up. The ^{1}H NMR spectrum of the crude reaction mixture showed no peak in the *tert*-butyl region or for the characteristic oxathiolane proton at C-2 (δ_{trans} 5.22 ppm, δ_{cis} 4.99 ppm). Similarly, the methyl ester singlet disappeared, suggesting decomposition of the substrate.



Scheme 105: Attempted aldol reaction on oxathiolane ester

In order to facilitate the trapping of the oxathiolane enolate, benzaldehyde **272** was added to the LDA solution prior to the oxathiolane ester. But in this case the aldehyde did not react and the oxathiolane decomposed as seen previously (**Scheme 106, (a)**).

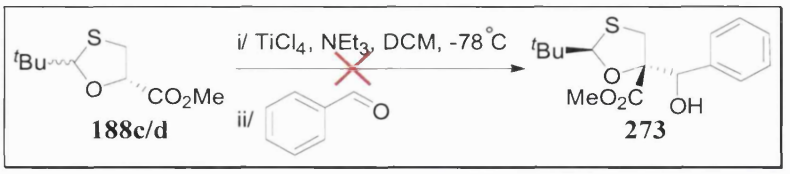
Even the use of lower temperature and strongly solvating conditions (LDA-DMPU)[166,210] for the aldol reaction with benzaldehyde failed to yield any desired adduct **273** (**Scheme 106, (b)**).



Scheme 106: Attempted aldol reactionwith a non-enolisable aldehyde

These results suggested that the oxathiolane lithium enolate, if indeed formed, decomposed too rapidly to react with the electrophile present in the reaction mixture. Titanium enolates of activated esters have been shown to create well-ordered transition states for aldol reactions, leading to useful levels of diastereoselectivity.[211] Stable enolates had been generated from activated thioesters and α-thio esters,[212] and it was hoped that the stronger titanium-oxygen bond would stabilise our oxathiolane enolate enough to undergo reaction with benzaldehyde. The oxathiolane ester **188c/d** was treated with titanium tetrachloride in dichloromethane at –78 °C, followed by triethylamine or DBU[213] to form the enolate, and benzaldehyde (**Scheme 107**). As for our previous efforts, these reaction conditions did not result in the formation of the desired aldol product **273**.

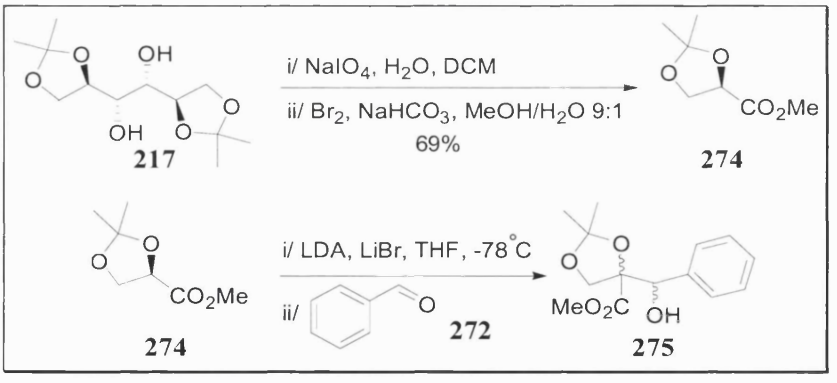
[166] Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131.
[210] Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.
[211] (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (b) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489. (c) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. (d) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613 and references cited therein. (e) Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S; Liu, W.-H. *J. Org. Chem.* **1995**, *60*, 3301.
[212] Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 7897, and references cited therein.
[213] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.



Scheme 107: Attempted titanium enolate formation / aldol reaction

Following these unsuccessful attempts to carry out the aldol reaction of oxathiolane ester **188c/d**, we suspected that the thioether moiety was the cause of the substrate decomposition, probably *via* the *β*-elimination pathway described by Seebach *et al.* in related thiazolidine ester systems.[165] We therefore decided to try the same chemistry on a closely related dioxolane ester system.

The dioxolane ester **274** was readily prepared by a two-step procedure from diisopropylidene-D-mannitol **217** in an overall 69% yield (**Scheme 108**).[214] The *O,O*-acetal substrate was then treated with LDA and benzaldehyde under standard conditions and small amounts of the aldol adduct **275** were isolated as a mixture of diastereoisomers (*ca.* 10% uncorrected on 200 mg scale).



Scheme 108: Aldol reaction of dioxolane ester and benzaldehyde

This unoptimised result suggests that the presence of the sulfur atom in the cyclic acetal system is the cause of the instability of the lithium enolate and the reason why the subsequent aldol chemistry fails to occur. This is in agreement with the results

[165] (a) Seebach, D.; Weber, T. *Tetrahedron Lett.* **1983**, *24*, 3315. (b) Seebach, D.; Jeanguenat, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2291.
[214] Ladame, S.; Bardet, M.; Perié, J.; Wilson, M. *Bioorg. Med. Chem.* **2001**, *9*, 773.

compiled by Seebach and co-workers, which show that enolates of sulfur-containing heterocycles (such as those derived from cysteine) cannot be trapped by electrophiles except under special *in situ* conditions.[164] Therefore it seems unlikely that our initial strategy involving the aldol reaction of an oxathiolane ester and an azidoaldehyde will be applicable for our synthesis of tagetitoxin

II-3.3.3 Conclusions on the synthesis of the oxathiolane ester

We have devised a synthesis of the oxathiolane ester fragment we intended to use for our aldol chemistry. This synthesis using serine as a chiral building block allowed access to both enantiomers of the desired *O,S*-acetal system. The diastereoselectivity of the acetal-forming reaction has not yet been optimised, but mechanistic studies and screening of catalysts may provide a better understanding of the parameters controlling the diastereoisomeric ratio.

We have also shown that the envisaged aldol reaction with the aldehyde fragment could not be achieved due to the intrinsic instability of sulfur-substituted esters under enolate-forming conditions.

[164] For a review, see Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708.

II-4 Conclusion

Tagetitoxin **2a** is a bacterial phytotoxin isolated in 1981 (**Figure 17**). Its unprecedented densely functionalised bridged bicyclic structure along with its unique biological activity as the only known specific inhibitor of RNA polymerase III make it a challenging target for the synthetic chemist. Previous unsuccessful approaches to the synthesis of tagetitoxin, or some sugar-derived analogues have highlighted the difficulties associated with the synthesis of such a structure.

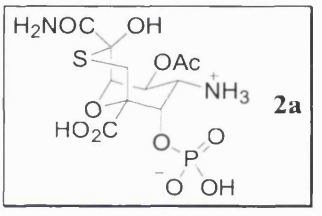
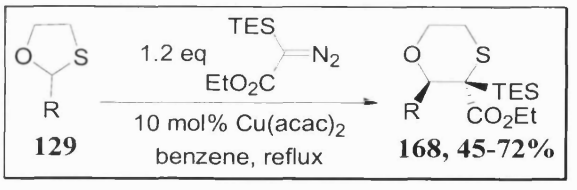


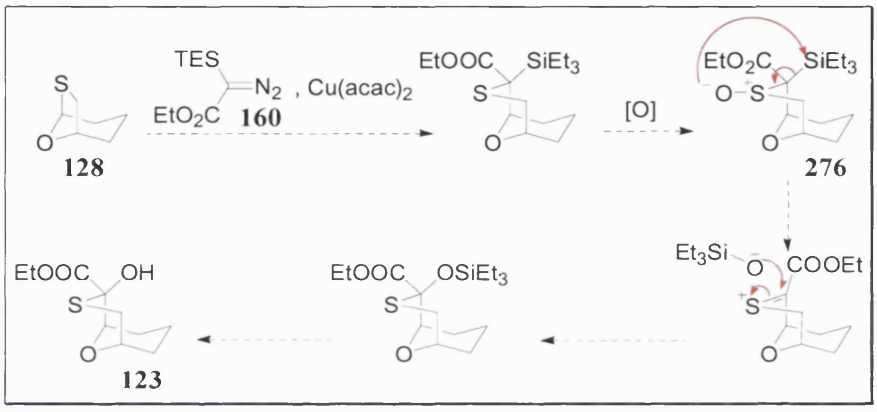
Figure 27: Tagetitoxin

Our approach to construct the core bridged bicyclic oxathiane involved the development of a new reaction: the copper(II)-catalysed ring expansion of 1,3-oxathiolanes, using a silylated diazoacetate. Model studies have shown that 2-aryl-1,3-oxathiolanes **129** were converted to the corresponding 2-aryl-3-carboxylate-3-TES-1,4-oxathianes **168** in good yields when treated with ethyl TES-diazoacetate and copper(II) acetylacetonate in refluxing benzene (**Scheme 109**). Alkyl substrates gave less reproducible results, but their reaction performed more reliably when a copper(I) catalyst ($Cu(MeCN)_4PF_6$) was used.



Scheme 109: Ring expansion of oxathiolanes

Introducing the silyl moiety on the diazocompound as a transient functionality in the ring expansion has proved a successful way to carry out the desired transformation. The desilylation of the products was quantitative, and improved yields were observed when the crude ring expansion reaction mixture was treated with TBAF in a one-pot fashion. However the silyl moiety could also prove convenient in the synthesis of the tagetitoxin core structure, allowing entry to the hydroxylated substrate **123** by a sila-Pummerer rearrangement of the sulfoxide **276** (**Scheme 110**).[215]

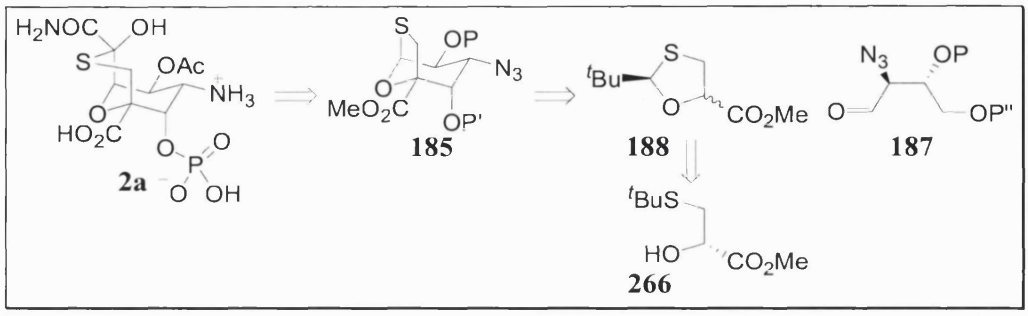


Scheme 110: Hydroxylation of ring expansion substrate by sila-Pummerer rearrangement

Preliminary studies in the group showed the feasibility of this reaction on 2-phenyl-1,4-oxathiane **147**.[198] The synthesis of bicyclic model substrates would be necessary in order to optimise the ring expansion conditions and possibly the sila-Pummerer rearrangement on systems more closely related to tagetitoxin.

We planned to synthesise tagetitoxin by ring expansion of a functionalised bridged bicyclic oxathiolane. The synthesis of this precursor was based on the aldol reaction of azidoaldehyde **187** and the enolate of oxathiolane ester **188** (**Scheme 111**).

[215] Oae, S.; Numata, T. *"The Pummerer type of reactions"* in Isotopes in Organic Synthesis; Buncel, E.; Lee, C.C. Eds.; Elsevier: New-York, **1980**; vol. 5, chap. 2.
[198] Dallimore, J. M. Sci. Thesis, **2002**, UCL.



Scheme 111: Aldol strategy for the synthesis of tagetitoxin precursor

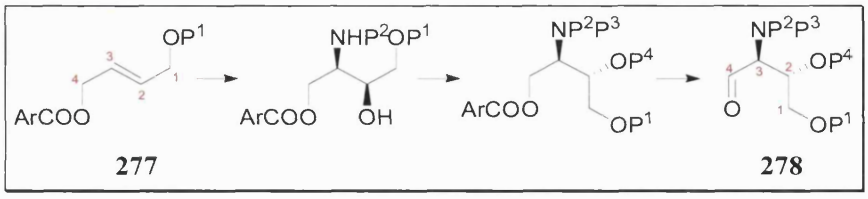
Three approaches to azidoaldehyde **187** were investigated, which involved regioselective opening of a chiral epoxide with an azide nucleophile. However the chosen epoxide substrates bore oxygenated substituents at both termini, which seemed to preclude electronic discrimination between the two possible sites of nucleophilic attack, and led to low regioselectivity.

The synthesis of oxathiolane ester **188** was achieved from natural serine, and included a novel one-pot cyclisation / sulfide deprotection of S-*tert*-butylmercaptoalcohol **266** in the presence of boron trifluoride etherate. Unfortunately, the sulfur atom proved incompatible with the planned aldol chemistry, due to competitive β-elimination.

Different approaches would therefore be required for the synthesis of the ring expansion precursor to tagetitoxin. In view of the difficulties associated with regioselective azide opening of oxygenated epoxides, nucleophilic displacement of a leaving group could be envisaged to introduce the azide moiety (*see II-3.2.4*).

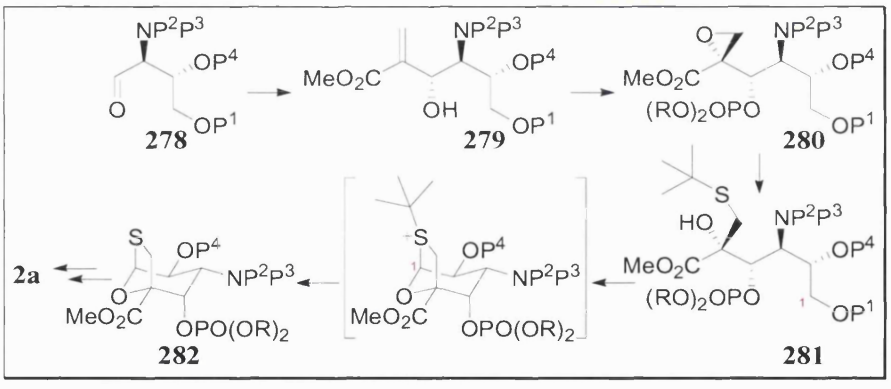
Alternatively, construction of the *syn* vicinal 3-amino-2-hydroxy functionalities could be achieved by asymmetric aminohydroxylation of *E* alkene **277** (**Scheme 112**).[216] Protecting-group manipulation and oxidation of the C-4 position would form aldehyde **278**.

[216] (a) Bodkin, J. A.; Mcleod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733. (b) Han, H.; Cho, C.-W.; Janda, K. D. *Chem. Eur. J.* **1999**, 1565. (c) Li, G. G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed Engl.* **1996**, *35*, 2813.



Scheme 112: Aminohydroxylation approach to aldehyde fragment

Conversion of aldehyde **278** *via* Baylis-Hillman reaction should provide allylic alcohol **279** with the desired *anti* diastereoselectivity (**Scheme 113**).[217] The stereochemistry at the free hydroxyl position should direct epoxidation from the *re* face to give epoxyalcohol **280**.[218] Phosphate formation followed by sulfide opening of the epoxide at the secondary carbon would afford intermediate **281**, which could be deprotected at the C-1 position and oxidised to give the corresponding hydroxyaldehyde. We hope to form the desired bridged bicyclic oxathiolane **282** under the conditions used for the cyclisation / deprotection of simple mercaptoalcohol **266** with pivalaldehyde.



Scheme 113: Proposed route for ring expansion substrate, precursor to tagetitoxin

The ring expansion of bicyclic oxathiolane **282** would achieve the construction of the tagetitoxin frame. Subsequent formation of the hemithioketal *via* sila-Pummerer

[217] (a) Manickum, T.; Roos, G. *Synth. Commun.* **1991**, *21*, 2269. (b) Drewes, S. E.; Khan, A. A.; Rowland, K. *Synth. Commun.* **1993**, *23*, 183.
[218] Bailey, M.; Markó, I. E.; Ollis, D. W. *Tetrahedron Lett.* **1991**, *32*, 2687.

rearrangement of the sulfoxide derivative and protecting-group manipulation would complete the first total synthesis of a tagetitoxin isomer **2a**.

III Experimental

III-1 General experimental procedures

Melting points were obtained using an Electrothermal 9100 apparatus and are uncorrected.

Proton NMR spectra were recorded at 300 MHz on a Bruker AMX-300 spectrometer, at 400 MHz on a Bruker AMX-400 spectrometer, or at 500 MHz on a Bruker DRX-500 spectrometer. Chemical shifts are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and app., approximate. Coupling constants are recorded in Hertz to the nearest 0.1Hz.

Carbon-13 NMR spectra were recorded at 75.4 MHz on a Bruker AMX-300 spectrometer, at 100.6 MHz on a Bruker AMX-400 spectrometer, or at 125.7 MHz on a Bruker DRX-500 spectrometer, using DEPT editing. Where necessary, carbon atoms were assigned using HMQC and HMBC experiments. Quaternary carbon atoms were assigned by the analysis of a decoupled spectrum used in conjunction with the DEPT program and the 2D experiments. Chemical shifts are quoted in parts per million and are referenced to the residual solvent peak, except for spectra in D_2O, which are referenced to internal 1,4-dioxan.

Steady state NOE difference experiments were recorded on a Bruker DRX-500 spectrometer. Quantification of the observed enhancements are given in %, relative to the inverted peak.

Infrared spectra were recorded as thin films or $CHCl_3$ casts on a Shimadzu FTIR-8700 Fourier transform spectrometer. Major features of each spectrum are reported. The following abbreviations are used: w, weak; m, medium; s, strong and br, broad.

Low resolution mass spectra were recorded on a Micromass 70-SE spectrometer using chemical ionisation (CI), electron impact (EI), fast atom bombardment (FAB) or electrospray (ESI). Mass spectra marked * were obtained using a Micromass ZAB-SE spectrometer at the University of London School of Pharmacy. Only molecular ions, fragments from molecular ions and major peaks are reported. High-resolution mass spectra were recorded on a Micromass 70-SE spectrometer, and the accurate mass quoted with an error (ΔM) in ppm.

Microanalyses were performed by Mrs J. Maxwell, Christopher Ingold Laboratories, University College London.

Optical rotations were measured with an Optical Activity AA-10 single-cell polarimeter at 20 °C with a pathlength of 1 dm.

Flash chromatography was carried out on BDH Silica 40-60 μm, Aldrich neutral alumina 50-200 micron deactivated with 6 wt% water or Acros Florisil® 100-200 mesh, using a modification of the method described by Still.[219] TLC was carried out on pre-coated, aluminium-backed normal phase Merck 60 F_{254} silica plates, and visualised by the quenching of u.v. fluorescence (λ_{max} 254nm) as well as staining with iodine, vanillin, phosphomolybdic acid, potassium permanganate, or anisaldehyde, all followed by heating.

All reactions in non-aqueous medium were performed under an inert atmosphere of nitrogen or argon, using anhydrous solvents.

[219] Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923.

All solvents were distilled before use. Anhydrous dichloromethane, toluene, pyridine and benzene were obtained by stirring over calcium hydride followed by distillation under nitrogen. Anhydrous diethyl ether and tetrahydrofuran were obtained by distillation from sodium/benzophenone ketyl under nitrogen and *N,N*-dimethyl formamide by distillation from calcium hydride under reduced pressure. Petrol 30-40 and 40-60 refer to the fraction of light petroleum ether boiling between 30-40 °C and 40-60 °C respectively. Solvents were evaporated at 30 °C or below on a Büchi R111 Rotavapor; high boiling solvents were evaporated at 50 °C on a Büchi R Rotavapor fitted with a Büchi Vac® V-500 pump.

All reagents were purified in accordance with the methods described in D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Pergamon Press, Third edition, 1988, or used as obtained from commercial sources.

Chemicals were purchased from Sigma-Aldrich Co. Ltd., Lancaster, Fluka, Acros, Alfa Aesar and Avocado.

III-2 Experimental procedures

III-2.1 Synthesis of silylated diazoacetates

Ethyl (trimethylsilanyl)diazoacetate **159**[147]

Ethyl diazoacetate (**147**, 1.14 g, 9.99 mmol) was dissolved in dry ether (100 mL) under nitrogen. Ethyldiisopropylamine (1.75 mL, 10.0 mmol) was added and the mixture was cooled to –78 °C. Trimethylsilyl triflate (1.8 mL, 9.9 mmol) was added dropwise over 10 min and the mixture was stirred for 20 min at –78 °C, then o/n at rt. The

trialkylammonium triflate precipitate was filtered and the filtrate was concentrated *in vacuo* to afford ethyl (trimethylsilanyl)diazoacetate (**159**, 1.64 g, 88%) as a clear yellow oil, containing less than 10% ethyl diazoacetate.

δ_H (300 MHz; $CDCl_3$):

0.26 (9H, s, $Si(C\underline{H}_3)_3$), 1.27 (3H, t, ^3J 7.1 Hz, $OCH_2C\underline{H}_3$), 4.19 (2H, q, ^3J 7.1 Hz, $OC\underline{H}_2CH_3$).

δ_C (75 MHz; $CDCl_3$):

0 ($Si(\underline{C}H_3)_3$), 15.9 ($OCH_2\underline{C}H_3$), 62.1 ($O\underline{C}H_2CH_3$), 97.0 ($\underline{C}N_2$), 170.8 ($\underline{C}$(O)OEt).

Ethyl (triethylsilanyl)diazoacetate **160**[147]

Ethyl diazoacetate (**147**, 3.48 g, 30.0 mmol) was dissolved in dry ether (100 mL) under nitrogen. Ethyldiisopropylamine (4.1 mL, 30 mmol) was added and the mixture was cooled to –78 °C. Triethylsilyl triflate (6.5 mL, 30 mmol) was added dropwise over 20 min and the mixture was stirred for 30 min at –78 °C, then o/n at rt. The trialkylammonium triflate precipitate was filtered, washed with ether (3 x 10 mL), and the filtrate was concentrated *in vacuo*. Flash chromatography (Al_2O_3; Petrol 40-60 / Ether 99:1) afforded ethyl (triethylsilanyl)diazoacetate (**160**, 5.29 g, 77%) as a clear yellow oil.

ν_{max}/cm^{-1} (neat):

2876 (s, C-H stretch), 2088 (s, diazo stretch), 1689 (s, C=N stretch), 1270.

δ_H (300 MHz; $CDCl_3$):

0.72 (6H, q, ^3J 8.8 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.93 (9H, t, ^3J 8.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.23 (3H, t, ^3J 7.1 Hz, $OCH_2C\underline{H}_3$), 4.15 (2H, q, ^3J 7.1 Hz, $OC\underline{H}_2CH_3$).

[147] (a) Emde, H.; Simchen, G. *Liebigs Ann. Chem.* **1983**, 816. (b) Allspach, T.; Gümbel, H.; Regitz, M. *J. Organomet. Chem.* **1985**, *290*, 33.

δ_C (75 MHz; $CDCl_3$):

3.5 ($Si(CH_2\underline{C}H_3)_3$), 6.8 ($Si(\underline{C}H_2CH_3)_3$), 14.7 ($OCH_2\underline{C}H_3$), 60.9 ($O\underline{C}H_2CH_3$), 96.7 ($\underline{C}N_2$), ($\underline{C}O_2Et$, not observed).

III-2.2 Synthesis of 1,3-oxathiolanes

2-Phenyl-1,3-oxathiolane **146**[131]

Benzaldehyde (10 mL, 0.1 mol), 2-mercaptoethanol (**162**, 7.6 mL, 0.1 mol) and *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol) were dissolved in toluene (100 mL and heated to reflux under Dean and Stark conditions for 16 h. The mixture was allowed to cool to room temperature, then washed with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with ether (2 x 100 mL) and the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was distilled under reduced pressure to give 2-phenyl-1,3-oxathiolane (**146**, 11.7 g, 72%) as a colourless oil.

b.p.: 90 °C / 1mmHg.

ν_{max}/cm^{-1}(neat):

3050 and 3000 (w, aromatic C-H stretch), 2872 (m, C-H stretch), 1699 (s, aromatic C=C), 1452, 1273.

δ_H (300 MHz; $CDCl_3$):

3.20 (1H, ddd, ^2J 9.8, ^3J 6.2, 3.2 Hz, 1 of $SC\underline{H}_2$), 3.28 (1H, ddd, ^2J 9.8, ^3J 8.7, 6.3 Hz, 1 of $SC\underline{H}_2$), 3.97 (1H, ddd, ^2J 9.2, ^3J 8.7, 6.2 Hz, 1 of $OC\underline{H}_2$), 4.54 (1H, ddd, ^2J 9.2, ^3J 6.3, 3.2 Hz, 1 of $OC\underline{H}_2$), 6.07 (1H, s, $OC\underline{H}S$), 7.31-7.39 (3H, m,) and 7.45-7.49 (2H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

34.0 (S<u>C</u>H_2), 71.9 (O<u>C</u>H_2), 87.1 (Ph<u>C</u>H), 126.7, 128.4, 128.6 and 139.3 (Ar-<u>C</u>).

<u>2-(4-Methoxyphenyl)-1,3-oxathiolane **152**</u>[220]

p-Anisaldehyde (5.0 mL, 41 mmol), 2-mercaptoethanol (**162**, 3.2 mL, 45 mmol) and *p*-toluenesulfonic acid monohydrate (75 mg, 0.4 mmol) were dissolved in toluene (50 mL) and heated to reflux under Dean and Stark conditions for 2 h. The mixture was allowed to cool to room temperature, then washed with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with ether (2 x 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ then concentrated *in vacuo*. Flash chromatography (SiO_2; Petrol 40-60 / ethyl acetate 85:15) afforded 2-(4-methoxyphenyl)-1,3-oxathiolane (**152**, 2.12 g, 27%) as a colourless oil.

ν_{max}/cm^{-1}(neat):

2962 (s, aromatic C-H stretch), 2870 (s, C-H stretch), 1069.

δ_H (300 MHz; $CDCl_3$):

3.19 (1H, ddd, ^2J 9.8, ^3J 6.2, 3.1 Hz, 1 of S<u>C</u>H_2), 3.28 (1H, ddd, ^2J 9.8, ^3J 8.8, 6.4 Hz, 1 of S<u>C</u>H_2), 3.81 (3H, s, O<u>C</u>H_3), 3.92 (1H, ddd, ^2J 9.1, ^3J 8.8, 6.3 Hz, 1 of O<u>C</u>H_2), 4.51 (1H, ddd, ^2J 9.1, ^3J 6.4, 3.1 Hz, 1 of O<u>C</u>H_2), 6.01 (1H, s, O<u>C</u>HS), 6.86-6.91 (2H,m) and 7.39-7.43 (2H, m, Ar-<u>H</u>).

δ_C (75 MHz; $CDCl_3$):

34.0 (S<u>C</u>H_2), 55.7 (O<u>C</u>H_3), 71.7 (O<u>C</u>H_2), 86.9 (Ar-<u>C</u>H), 113.7, 128.2, 130.9 and 159.8 (Ar-<u>C</u>).

[131] Kipnis, F.; Ornfelt, J. *J. Am. Chem. Soc.* **1949**, *79*, 3555.
[220] Cashman, J. R.; Proudfoot, J.; Ho, Y.-K.; Chin, M. S.; Olsen, L. D. *J. Am. Chem. Soc.* **1989**, *111*, 4844.

2-(4-Nitrophenyl)-1,3-oxathiolane **153**[220]

4-Nitrobenzaldehyde (6.23 g, 41.3 mmol), 2-mercaptoethanol (**162**, 3.3 mL, 46 mmol) and *p*-toluenesulfonic acid monohydrate (75 mg, 0.4 mmol) were dissolved in toluene (50 mL) and heated to reflux under Dean and Stark conditions for 2 h. The mixture was allowed to cool to room temperature, then washed with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with ether (2 x 100 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ then concentrated *in vacuo*. Flash chromatography (SiO_2; Petrol 40-60 / Ether 70:30) afforded 2-(4-nitrophenyl)-1,3-oxathiolane (**153**, 2.53 g, 29%) as a yellow solid, which was recrystallised from benzene.

m.p.: 73 °C (lit 73-75 °C).

ν_{max}/cm^{-1}($CHCl_3$ cast):

2923 (s, C-H stretch), 1606 (m, aromatic C=C stretch), 1519 and 1347.

δ_H (300 MHz; $CDCl_3$):

3.19-3.31 (2H, m, SC$\underline{H}_2$), 4.01 (1H, td, ^2J 9.1, ^3J 9.1, 6.4 Hz, 1 of OC$\underline{H}_2$), 4.55 (1H, ddd, ^2J 9.1, ^3J 6.0, 3.4 Hz, 1 of OC$\underline{H}_2$), 6.11 (1H, s, OC$\underline{H}$S), 7.57-7.60 (2H, m) and 8.18-8.22 (2H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

34.1 (S$\underline{C}H_2$), 72.4 (O$\underline{C}H_2$), 85.4 (O$\underline{C}$HS), 123.7, 127.2, 147.0 and 147.8 (Ar-$\underline{C}$).

2-Isobutyl-1,3-oxathiolane **154**[221]

Isovaleraldehyde (4.00 g, 46.4 mmol), 2-mercaptoethanol (**162**, 3.6 mL, 51 mmol) and *p*-toluenesulfonic acid monohydrate (75 mg, 0.4 mmol) were dissolved in toluene (50 mL) and heated at 85-90 °C for 1.5 h. The mixture was allowed to cool to room temperature, then washed with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was

extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Filtration on a short column (SiO_2; Petrol 40-60 / Ether 95:5) afforded 2-isobutyl-1,3-oxathiolane (**154**, 4.46 g, 66%) as a colourless oil.

ν_{max}/cm^{-1}(neat):

2957 (s, C-H stretch), 1368, 1163, 1114.

δ_H (300 MHz; $CDCl_3$):

0.96 (3H, d, ^3J 6.5 Hz) and 0.97 (3H, d, ^3J 6.5 Hz, $CH(C\underline{H}_3)_2$), 1.59-1.68 (1H, m, $C\underline{H}(CH_3)_2$), 1.71-1.90 (2H, m, $C\underline{H}_2CH(CH_3)_2$), 3.03 (2H, m, $SC\underline{H}_2$), 3.77 (1H, ddd, ^2J 9.1, ^3J 7.6, 7.2 Hz, 1 of $OC\underline{H}_2$), 4.33 (1H, dt, ^2J 9.1, ^3J 4.8 Hz, 1 of $OC\underline{H}_2$), 5.12 (1H, dd, ^3J 6.7, 6.2 Hz, $OC\underline{H}S$).

δ_C (75 MHz; $CDCl_3$):

22.6 and 22.7 ($CH(\underline{C}H_3)_2$), 26.4 ($\underline{C}H_2CH(CH_3)_2$), 32.5 ($\underline{C}H(CH_3)_2$, 45.3 ($S\underline{C}H_2$), 71.0 ($O\underline{C}H_2$), 85.7 ($O\underline{C}HS$).

1,3-Oxathiolane **174**[222]

Paraformaldehyde (5.00 g, 166 mmol), 2-mercaptoethanol (**162**, 11.6 mL, 166 mmol) and *p*-toluenesulfonic acid monohydrate (75 mg, 0.4 mmol) were dissolved in benzene (65 mL) and heated to reflux under Dean and Stark conditions o/n. The mixture was allowed to cool to room temperature, then benzene was distilled off using a 10 cm Vigreux column. Distillation under reduced pressure afforded 1,3-oxathiolane (**174**, 6.81 g, 45%) as a colourless oil.

b.p.: 62 °C / 1 mmHg

[221] Eliel, E. L.; Doyle, T. W. *J. Org. Chem.* **1970**, *35*, 2716.
[222] Bannister, B. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 540.

ν_{max}/cm^{-1}(neat):

2865 (s, C-H stretch), 1450, 1296, 1269,1233 and 1184.

δ_H (300 MHz; $CDCl_3$):

3.00 (2H, t, ^3J 6.0 Hz, $OCH_2C\underline{H}_2S$), 4.00 (2H, t, ^3J 6.0 Hz, $OC\underline{H}_2CH_2S$), 4.86 (2H, s, $OC\underline{H}_2S$).

δ_C (75 MHz; $CDCl_3$):

31.9 ($SC\underline{H}_2$), 71.5 ($OC\underline{H}_2$), 72.1 ($OC\underline{H}_2S$).

2-*tert*-Butyl-1,3-oxathiolane **175**[221]

Pivalaldehyde (3.96 g, 46.0 mmol), 2-mercaptoethanol (**162**, 3.6 mL, 51 mmol) and *p*-toluenesulfonic acid monohydrate (75 mg, 0.4 mmol) were dissolved in toluene (50 mL) and heated to reflux under Dean and Stark conditions for 4h. The mixture was allowed to cool to room temperature, then washed with sat. aq. $NaHCO_3$ (50 mL). The aqueous phase was extracted with ether (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give 2-*tert*-butyl-1,3-oxathiolane (**175**, 4.92 g, 73%) as a colourless oil. The crude product was used without further purification.

ν_{max}/cm^{-1}(neat):

2955 and 2865 (s, C-H stretch), 1480, 1393, 1363, 1183 and 1079.

δ_H (300 MHz; $CDCl_3$):

1.00 (9H, s, $C(C\underline{H}_3)_3$), 2.88 (1H, ddd, ^2J 10.0, ^3J 6.2, 5.7 Hz, 1 of $SC\underline{H}_2$), 2.98 (1H, ddd, ^2J 10.0, ^3J 5.3, 1.9 Hz, 1 of $SC\underline{H}_2$), 3.74 (1H, ddd, ^2J 8.6, ^3J 5.7, 5.3 Hz, 1 of $OC\underline{H}_2$), 4.39 (1H, ddd, ^2J 8.6, ^3J 6.2, 1.9 Hz, 1 of $OC\underline{H}_2$), 4.90 (1H, s, $OC\underline{H}S$).

δ_C (100 MHz; $CDCl_3$):

25.9 ($\underline{C}(CH_3)_3$), 32.2 ($C(\underline{C}H_3)_3$), 35.2 ($S\underline{C}H_2$), 72.2 ($O\underline{C}H_2$), 96.3 ($O\underline{C}HS$).

III-2.3 Synthesis of 1,4-oxathianes

Ethyl 2-phenyl-3-trimethylsilanyl-1,4-oxathiane-3-carboxylate **163**

2-Phenyl-1,3-oxathiolane (**146**, 260 mg, 1.6 mmol) and copper(II) acetylacetonate (41 mg, 0.16 mmol) were placed under nitrogen. A solution of ethyl (trimethylsilanyl)diazoacetate (**159**, 327 mg, 1.8 mmol) in dry benzene (2.5 mL) was added and the mixture was heated to reflux for 5h. The mixture was allowed to cool to room temperature and concentrated *in vacuo*. Filtration on a short column (alumina, Petrol 30-40 / Ether 1:1) afforded a mixture of diastereoisomers of ethyl 2-phenyl-3-trimethylsilanyl-1,4-oxathiane-3-carboxylate and 2-phenyl-1,3-oxathiolane in a *cis:trans:SM* ratio of 6:3:2, as assigned by integration of the PhC<u>H</u> protons at δ_H 5.53, δ_H 4.90 and δ_H 6.07 ppm respectively. Recrystallisation from ethanol afforded ethyl (*cis*) 2-phenyl-3-trimethylsilanyl-1,4-oxathiane-3-carboxylate (**163a**, 30 mg, 6%), as a white solid.

m.p.: 108-110 °C.

δ_H (500 MHz; $CDCl_3$):

-0.10 (9H, s, Si(C<u>H</u>$_3$)$_3$), 1.35 (3H, t, ^3J 7.1 Hz, OCH$_2$C<u>H</u>$_3$), 2.41 (1H, br d, ^2J 13.3 Hz, SCH<u>H</u>$_{eq}$), 3.24 (1H, ddd, ^2J 13.4, ^3J 11.3, 3.8 Hz, SCH<u>H</u>$_{ax}$), 3.69 (1H, dt, ^2J 12.0, ^3J 3.4 Hz, OCH<u>H</u>$_{eq}$), 4.12 (1H, td, ^2J 11.8, ^3J 11.8, 2.9 Hz, OCH<u>H</u>$_{ax}$), 4.26 (1H, dq, ^2J 10.8, ^3J 7.1 Hz) and 4.34 (1H, dq, ^2J 10.8, ^3J 7.1 Hz, OC<u>H</u>$_2$CH$_3$), 5.53 (1H, s, PhC<u>H</u>), 7.33-7.37 (3H, m) and 8.04-8.05 (2H, m, Ar-<u>H</u>).

δ_C (75 MHz; $CDCl_3$):

-2.3 (Si(<u>C</u>H$_3$)$_3$), 14.3 (OCH$_2$<u>C</u>H$_3$), 25.6 (S<u>C</u>H$_2$), 59.9 (O<u>C</u>H$_2$CH$_3$), 61.9 (O<u>C</u>H$_2$), 78.2 (Ph<u>C</u>H), 127.8, 128.7, 131.4 and 137.3 (Ar-<u>C</u>), 172.8 (<u>C</u>O$_2$Et), (<u>C</u>(SiMe$_3$)(CO$_2$Et), not observed).

m/z (FAB)*:

325 (100%), 247 (47), 235 (80), 226 (77), 218 (86).

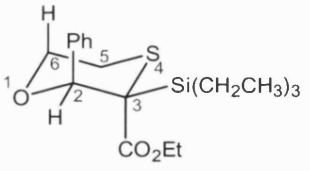
HRMS (FAB)*:

325.1306 (MH^+, $C_{16}H_{25}O_3SSi$ requires 325.1294, ΔM = 3.7 ppm).

Ethyl 2-phenyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate **164**

2-Phenyl-1,3-oxathiolane (**146**, 249 mg, 1.5 mmol) and copper(II) acetylacetonate (39.5 mg, 0.15 mmol) were dissolved in dry benzene (2 mL) under nitrogen. The mixture was heated to reflux and a solution of ethyl (triethylsilanyl)diazoacetate (**160**, 411 mg, 1.8 mmol) in dry benzene (2 mL) was added dropwise over 5 min. Reflux was continued o/n, then the reaction mixture was allowed to cool to rt and concentrated *in vacuo*. Purification by flash chromatography (Florisil®, Petrol 30-40 / Ether 90:10) afforded ethyl 2-phenyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate (**164a**, 369.6 mg, 67%) in a *cis:trans* diastereoisomeric ratio of 8:1, as assigned by integration of the PhC<u>H</u> protons at δ_H 5.57 and δ_H 5.01 ppm respectively.

Differential NOE experiments on the major isomer gave the following enhancements, consistent with a *cis* stereochemistry:



Irradiation / Response	$Si(C\underline{H}_2CH_3)_3$, 0.533 ppm	$Si(CH_2C\underline{H}_3)_3$, 0.867 ppm	6-$\underline{H}_{ax}$, 4.122 ppm	2-<u>H</u>, 5.597 ppm	Ar-<u>H</u>, 8.167 ppm
$Si(C\underline{H}_2CH_3)_3$	- 100 %	3 %	-	2 %	1 %
$Si(CH_2C\underline{H}_3)_3$	14 %	-100 %	-	-	-
5-$\underline{H}_{eq}$	-	-	2 %	-	-
6-$\underline{H}_{eq}$	-	-	14 %	0.2 %	-
6-$\underline{H}_{ax}$	-	-	-100 %	-	1 %
2-<u>H</u>	0.5 %	0.3 %	-	- 100 %	2 %
Ar-<u>H</u>	0.7 %	0.2 %	3 %	4 %	- 100 %

Ethyl (*cis*) 2-phenyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate **164a**:

ν_{max}/cm^{-1}:

2954 and 2877 (s, C-H stretch), 1726 (s, C=O stretch), 1631 (br, aromatic C=C stretch), 1193.

δ_H (500 MHz; $CDCl_3$):

0.47-0.58 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.85 (9H, t, ^3J 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.40 (3H, t, ^3J 7.2 Hz, $OCH_2C\underline{H}_3$), 2.31 (1H, br d, ^2J 13.4 Hz, $SCH\underline{H}_{eq}$), 3.30 (1H, ddd, ^2J 13.3, ^3J 12.3, 4.0 Hz, $SCH\underline{H}_{ax}$), 3.65 (1H, ddd, ^2J 12.3, ^3J 4.0, 2.2 Hz, $OCH\underline{H}_{eq}$), 4.10 (1H, td, ^2J 12.2, ^3J 12.2, 2.7 Hz, $OCH\underline{H}_{ax}$), 4.34 (2H, dq, ^2J 10.5, ^3J 7.2 Hz, $OC\underline{H}_2CH_3$), 5.57 (1H, s, PhC$\underline{H}$), 7.37-7.39 (3H, m) and 8.14-8.16 (2H, m, Ar-$\underline{H}$).

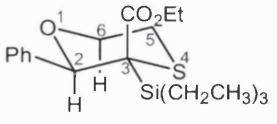
δ_C (125 MHz; $CDCl_3$):

2.8 ($Si(\underline{C}H_2CH_3)_3$), 7.5 ($Si(CH_2\underline{C}H_3)_3$), 14.1 ($OCH_2\underline{C}H_3$), 25.6 ($S\underline{C}H_2$), 59.1 ($O\underline{C}H_2CH_3$), 61.7 ($O\underline{C}H_2$), 77.9 (Ph$\underline{C}$H), 127.6, 128.4, 131.6 and 137.3 (Ar-$\underline{C}$), 172.6 ($\underline{C}O_2Et$), ($\underline{C}(SiEt_3)(CO_2Et)$, not observed).

m/z (FAB)*:

366 (M^+, 92%), 235 (87), 175 (100), 159 (91), 147 (82).

Differential NOE experiments on the minor isomer gave the following enhancements, consistent with a *trans* stereochemistry:



Irradiation / Response	$Si(C\underline{H}_2CH_3)_3$, 0.604 ppm	2-$\underline{H}$, 5.597 ppm	Ar-$\underline{H}$, 8.167 ppm
$Si(C\underline{H}_2CH_3)_3$	- 100 %	1.4 %	1 %
5-$\underline{H}_{eq}$	-	-	-
6-$\underline{H}_{ax}$	-	2 %	-
2-$\underline{H}$	0.6 %	- 100 %	1.5 %
Ar-$\underline{H}$	0.3 %	3 %	- 100 %

Ethyl (*trans*) 2-phenyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate 164b:

δ_H (500 MHz; $CDCl_3$):

0.54-0.64 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.93 (9H, t, ^3J 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.22 (3H, t, ^3J 7.3 Hz, $OCH_2C\underline{H}_3$), 2.33 (1H, app. dt, ^2J 13.2, ^3J 2.9 Hz, $SCH\underline{H}_{eq}$), 3.43 (1H, ddd, ^2J 13.2, ^3J 11.2, 3.8 Hz, $SCH\underline{H}_{ax}$), 3.92 (1H, ddd, ^2J 11.7, ^3J 11.2, 2.7 Hz, $OCH\underline{H}_{ax}$), 4.18 (2H, q, ^3J 7.3 Hz, $OC\underline{H}_2CH_3$), 4.31 (1H, app. dt, ^2J 11.7, ^3J 3.5 Hz, $OCH\underline{H}_{eq}$), 5.01 (1H, s, PhC<u>H</u>), 7.26-7.35 (3H, m) and 7.38-7.44 (2H, m, Ar-<u>H</u>).

Ethyl 2-(4-methoxyphenyl)-3-triethylsilanyl-1,4-oxathiane-3-carboxylate **165**

2-(4-Methoxyphenyl)-1,3-oxathiolane (**152**, 297 mg, 1.5 mmol) and copper(II) acetylacetonate (40 mg, 0.15 mmol) were dissolved in dry benzene (2 mL) under nitrogen. The mixture was heated to reflux and a solution of ethyl (triethylsilanyl)diazoacetate (**160**, 411 mg, 1.8 mmol) in benzene (1 mL) was added dropwise over 10 min. Reflux was continued o/n, then the reaction mixture was allowed to cool to rt and concentrated *in vacuo*. Purification by flash chromatography (Florisil®, Petrol 30-40 / Ether 70:30) afforded ethyl (*cis*) 2-(4-methoxyphenyl)-3-triethylsilanyl-1,4-oxathiane-3-carboxylate (**165a**, 369 mg, 62%) as a colourless oil.

ν_{max}/cm^{-1}(neat):

2953 and 2877 (s, C-H stretch), 1725 (s, C=O stretch), 1511 (s, aromatic C=C stretch), 1250 and 1180.

δ_H (300 MHz; $CDCl_3$):

0.48-0.58 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.85 (9H, t, ^3J 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.39 (3H, t, ^3J 7.2 Hz, $OCH_2C\underline{H}_3$), 2.28 (1H, br d, ^2J 13.2 Hz, $SCH\underline{H}_{eq}$), 3.30 (1H, ddd, ^2J 13.2, ^3J 12.5, 4.0 Hz, $SCH\underline{H}_{ax}$), 3.62 (1H, ddd, ^2J 12.1, ^3J 4.0, 2.0 Hz, $OCH\underline{H}_{eq}$), 3.85 (3H, s,

$OC\underline{H}_3$), 4.08 (1H, td, ^2J 12.1, ^3J 12.1, 2.4 Hz, $OCH\underline{H}_{ax}$), 4.34 (2H, dq, ^2J 10.9, ^3J 7.2 Hz, $OC\underline{H}_2CH_3$), 5.54 (1H, s, $OC\underline{H}Ar$), 6.89-6.92 (2H, m) and 8.08-8.11 (2H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

2.8, 7.7, 14.3, 25.7, 49.0, 55.2, 58.8, 61.8, 112.9, 129.5, 133.1, 159.7, 172.7, $\underline{C}_q$ not observed.

m/z (FAB)*:

397 (15%), 131 (82), 115 (100).

HRMS (FAB)*:

397.1883 (M^+, $C_{20}H_{32}O_4SSi$ requires: 397.1869, ΔM = 3.5 ppm).

Ethyl 2-(4-nitrophenyl)-3-triethylsilanyl-1,4-oxathiane-3-carboxylate **166**

2-(4-Nitrophenyl)-1,3-oxathiolane (**153**, 317 mg, 1.5 mmol) and copper(II) acetylacetonate (39.5 mg, 0.15 mmol) were dissolved in dry benzene (2 mL) under nitrogen. The mixture was heated to reflux and a solution of ethyl (triethylsilanyl)diazoacetate (**160**, 411 mg, 1.8 mmol) in benzene (1 mL) was added dropwise over 10 min. Reflux was continued o/n, then the reaction mixture was allowed to cool to rt and concentrated *in vacuo*. Purification by flash chromatography (Florisil®, Petrol 30-40 / Ether 80:20) afforded a *cis:trans* diastereoisomeric ratio of 4:1, as assigned by integration of the $Ar\underline{C}H$ protons at δ_H 5.64 and δ_H 5.13 ppm respectively. Recrystallisation from methanol afforded ethyl (*cis*) 2-(4-nitrophenyl)-3-triethylsilanyl-1,4-oxathiane-3-carboxylate (**166a**, 256 mg, 41%) as an orange solid.

m.p.: 62 °C.

ν_{max}/cm^{-1}($CHCl_3$ cast):

2955 and 2877 (s, C-H stretch), 1725 (s, C=O stretch), 1519,1347, 1193, 1016.

δ_H (300 MHz; $CDCl_3$):

0.44-0.61 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.87 (9H, t, ^3J 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 1.40 (3H, t, ^3J 7.3 Hz, $OCH_2C\underline{H}_3$), 2.39 (1H, dt, ^2J 13.4, ^3J 2.8 Hz, $SCH\underline{H}_{eq}$), 3.27 (1H, ddd, ^2J 13.3, ^3J 11.5, 4.0 Hz, $SCH\underline{H}_{ax}$), 3.69 (1H, ddd, ^2J 12.3, ^3J 4.0, 2.8 Hz, $OCH\underline{H}_{eq}$), 3.96 (1H, dt, ^2J 12.0, ^3J 2.8 Hz, $OCH\underline{H}_{ax}$), 4.35 (2H, dq, ^2J 10.7, ^3J 7.3 Hz,$OC\underline{H}_2CH_3$), 5.64 (1H, s, $OC\underline{H}(NO_2Ph)$), 8.14-8.37 (4H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

3.1, 7.7, 14.2, 25.6, 48.0, 59.9, 62.1, 122.1, 132.4, 144.6, 147.8, 172.3, $\underline{C}_q$ not observed.

m/z (FAB)*:

411 (M^+, 100%), 280 (74), 175 (55), 159 (61), 154 (76).

Elemental analysis:

$C_{19}H_{29}NO_5SSi$ requires: C, 55.45; H, 7.1; N, 3.4, S, 7.8%. Found C,55.4; H, 7.1; N, 3.5; S, 8.2.

Ethyl 2-isobutyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate **169**

Tetrakis(acetonitrile) copper(I) hexafluorophosphate (50 mg, 0.15 mmol) was suspended in dry benzene (2 mL) under nitrogen. 2-Isobutyl-1,3-oxathiolane (**154**, 219 mg, 1.5 mmol) and ethyl (triethylsilanyl)diazoacetate (**160**, 343 mg, 1.5 mmol), each in solution in dry benzene (1 mL) were added. The mixture was heated to reflux for 2.5 h, then allowed to cool to rt and concentrated *in vacuo*. Purification by flash chromatography (Florisil®, Petrol 30-40 / Ether 70:30) afforded ethyl (*trans*) 2-isobutyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate (**169a**, 160 mg, 30%) as a colourless oil.

δ_H (500 MHz; $CDCl_3$):

0.68-0-74 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.95-1.01 (15H, m, $CH(C\underline{H}_3)_2$ and $Si(CH_2C\underline{H}_3)_3$), 1.07 (1H, ddd, ^2J 14.5, ^3J 10.6, 2.9, 1 of $C\underline{H}_2(CHMe_2)$), 1.32 (3H, t, ^3J 7.2 Hz, $OCH_2C\underline{H}_3$),

1.72-1.78 (1H, m, C<u>H</u>Me$_2$), 2.06 (1H, ddd, ^2J 13.2, ^3J 2.8, 1.9 Hz, SCH<u>H</u>$_{eq}$), 2.73 (1H, ddd, ^2J 14.4, ^3J 12.2, 3.2 Hz, 1 of C<u>H</u>$_2$(CHMe$_2$)), 3.17 (1H, ddd, ^2J 13.2, ^3J 12.3, 4.0 Hz, SCH<u>H</u>$_{ax}$), 3.65 (1H, ddd, ^2J 12.1, ^3J 4.1, 1.9 Hz, OCH<u>H</u>$_{eq}$), 3.94 (1H, dt, ^2J 12.2, ^3J 2.7 Hz, OCH<u>H</u>$_{ax}$), 4.24 (2H, dq, ^2J 10.8, ^3J 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 4.54 (1H, ddd, ^3J 12.2, 2.9, ^4J 1.2 Hz, OC<u>H</u>(^{t}Bu)).

δ_C (75 MHz; $CDCl_3$):

2.9, 7.8, 14.2, 21.3, 24.1, 25.5, 30.8, 38.1, 49.9, 59.1, 61.4, 74.1, 172.6.

m/z (FAB)*:

346 (M^+, 42%), 317 (48), 289 (75), 215 (100), 175 (63), 159 (99).

<u>Ethyl 3-triethylsilanyl-1,4-oxathiane-3-carboxylate **176**</u>

Tetrakis(acetonitrile) copper(I) hexafluorophosphate (50 mg, 0.15 mmol) was suspended in dry benzene (2 mL) under nitrogen. 1,3-Oxathiolane (**174**, 135 mg, 1.5 mmol) and ethyl triethylsilanyldiazoacetate (**160**, 343 mg, 1.5 mmol), each in solution in dry benzene (1 mL) were added. The mixture was heated to reflux for 2.5h, then allowed to cool to rt and concentrated *in vacuo*. The mixture decomposed before purification. ^{1}H NMR of the crude reaction mixture:

δ_H (300 MHz; $CDCl_3$):

0.62 (6H, q, ^3J 7.6 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.90 (9H, t, ^3J 7.6 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 1.22 (3H, t, ^3J 7.2 Hz, OCH$_2$C<u>H</u>$_3$), 3.0 (1H, ddd, ^2J 11.0, ^3J 10.0, 7.6 Hz, SCH<u>H</u>$_{eq}$), 3.29 (1H, ddd, ^2J 11.0, ^3J 6.2, 1.4 Hz, SCH<u>H</u>$_{ax}$), 4.02 (2H, q, ^3J 7.2 Hz, OC<u>H</u>$_2$CH$_3$), 4.39 (1H, ddd, ^2J 10.5, ^3J 7.6, 1.4 Hz, OCH<u>H</u>$_{eq}$), 4.70 (1H, d, ^2J 5.7 Hz, 1 of OC<u>H</u>$_2$C(SiEt$_3$)(CO$_2$Et)), 4.85 (1H, td, ^2J 10.0, ^3J 10.0, 6.2 Hz, OCH<u>H</u>$_{ax}$), 4.91 (1H, d, ^2J 5.7 Hz, 1 of OC<u>H</u>$_2$C(SiEt$_3$)(CO$_2$Et)), contaminated with triethylsilyl residue at 0.52 (q, ^3J 8.1 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$) and 0.93 (t, ^3J 8.1 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$).

Ethyl 2-*tert*-butyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate **177**

Tetrakis(acetonitrile) copper(I) hexafluorophosphate (50 mg, 0.15 mmol) was suspended in dry benzene (2 mL) under nitrogen. 2-*tert*-Butyl-1,3-oxathiolane (**175**, 219 mg, 1.5 mmol) and ethyl (triethylsilanyl)diazoacetate (**160**, 343 mg, 1.5 mmol), each in solution in dry benzene (1 mL) were added. The mixture was heated to reflux for 4h, then allowed to cool to rt and concentrated *in vacuo*. Purification by flash chromatography (Florisil®, Petrol 30-40 / Ether 70:30) afforded ethyl (*trans*) 2-*tert*-butyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate (**177a**, 62.5 mg, 12%) as a colourless oil.

ν_{max}/cm^{-1} (neat):

2955 (s, C-H stretch), 1732 (s, C=O stretch), 1102.

δ_H (300 MHz; $CDCl_3$):

0.97 (9H, s, C($C\underline{H}_3$)$_3$), 1.03-1.06 (15H, m, Si($C\underline{H}_2CH_3$)$_3$), 1.29 (3H, t, ^3J 7.2 Hz, $OCH_2C\underline{H}_3$), 2.68 (1H, ddd, ^2J 13.7, ^3J 5.7, 5.4 Hz, SC$\underline{H}H_{eq}$), 3.04 (1H, ddd, ^2J 13.7, ^3J 7.8, 5.1 Hz, SC$\underline{H}H_{ax}$), 3.95 (1H, dt, ^2J 10.5, ^3J 5.1 Hz, OC$\underline{H}H_{eq}$), 4.09 (1H, s, OC$\underline{H}$'Bu), 4.11-4.20 (3H, m, OC$\underline{H}H_{ax}$ and $OC\underline{H}_2CH_3$).

δ_C (75 MHz; $CDCl_3$):

6.4, 9.0, 13.9, 23.8, 27.9, 37.4, 61.4, 68.7, 87.2, two $\underline{C}_q$ not observed.

m/z (FAB)*:

346 (M^+, 8%), 317 (30), 289 (75), 215 (24), 175 (30), 159 (38), 131 (90), 115 (100).

Elemental analysis:

$C_{17}H_{34}O_3SSi$ requires: C, 58.9; H, 9.9; S, 9.25%. Found C, 59.2; H, 9.8; S, 9.0.

Ethyl 2-phenyl-1,4-oxathiane-3-carboxylate **149**[223]

A solution of ethyl (*cis*) 2-phenyl-3-triethylsilanyl-1,4-oxathiane-3-carboxylate (**164a**, 0.35 g, 0.95 mmol) in THF (5 mL) was cooled to -78°C and treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.23 mL, 1.23 mmol). After 30 min the reaction mixture was poured into ice/water overlaid with diethyl ether (5 mL). The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give ethyl 2-phenyl-1,4-oxathiane-3-carboxylate (**149**, 0.24 g, 100%) as a *trans:cis* ratio of 2:1, as assigned by integration of the PhC<u>H</u> protons at δ_H 4.65 and δ_H 4.88 ppm respectively. Recrystallisation from methanol afforded pure ethyl (*trans*) 2-phenyl-1,4-oxathiane-3-carboxylate.

Ethyl (*trans*) 2-phenyl-1,4-oxathiane-3-carboxylate:

ν_{max}/cm^{-1}($CHCl_3$ cast):

1728 (s, C=O), 1307, 1159.

δ_H (300 MHz; $CDCl_3$):

0.87 (3H, t, ^3J 7.2 Hz, $OCH_2C\underline{H}_3$), 2.46 (1H, dt, ^2J 13.8, ^3J 2.4 Hz, $SCH\underline{H}_{eq}$), 3.07 (1H, ddd, ^2J 13.8, ^3J 11.9, 3.3 Hz, $SCH\underline{H}_{ax}$), 3.75 (1H, d, ^3J 9.5 Hz, $SC\underline{H}(CO_2Et)$), 3.85 (2H, q, ^3J 7.2 Hz, $OC\underline{H}_2CH_3$), 3.87-3.97 (1H, m, $OCH\underline{H}_{ax}$), 4.30 (1H, ddd, ^2J 11.9, ^3J 3.3, 2.4 Hz, $OCH\underline{H}_{eq}$), 4.65 (1H, d, ^3J 9.5 Hz, OC<u>H</u>Ph), 7.23-7.27 (5H, m, Ar-<u>H</u>).

δ_C (75 MHz; $CDCl_3$):

13.7 ($OCH_2\underline{C}H_3$), 27.1 ($S\underline{C}H_2$), 48.6 ($S\underline{C}H(CO_2Et)$), 61.2 ($O\underline{C}H_2CH_3$), 69.2 ($O\underline{C}H_2$), 82.3 (O<u>C</u>HPh), 125.4, 127.0, 128.3 and 139.0 (Ar-<u>C</u>), 168.9 ($\underline{C}O_2Et$).

[223] Kocienski, P.J.; Pelotier, B.; Pons, J.M.; Prideaux, H. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1378.

Ethyl (*cis*) 2-phenyl-1,4-oxathiane-3-carboxylate:

δ_H (300 MHz; $CDCl_3$):

0.87 (3H, t, ^3J 7.2 Hz, $OCH_2C\underline{H}_3$), 2.17 (1H, ddd, ^2J 13.4, ^3J 2.4, 2.1 Hz, $SCH\underline{H}_{eq}$), 3.29 (1H, d, ^3J 2.9 Hz, $SC\underline{H}(CO_2Et)$), 3.58 (1H, ddd, ^2J 13.4, ^3J 11.9, 3.3 Hz, $SCH\underline{H}_{ax}$), 3.85 (2H, q, ^3J 7.2 Hz, $OC\underline{H}_2CH_3$), 3.91 (1H, ddd, ^2J 11.9, ^3J 11.9, 2.1 Hz, $OCH\underline{H}_{ax}$), 4.47 (1H, dt, ^2J 11.9, ^3J 2.4 Hz, $OCH\underline{H}_{eq}$), 4.88 (1H, d, ^3J 2.9 Hz, $OC\underline{H}Ph$), 7.23-7.27 (5H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

13.7 ($OCH_2\underline{C}H_3$), 23.1 ($S\underline{C}H_2$), 42.1 ($S\underline{C}H(CO_2Et)$), 60.5 ($O\underline{C}H_2CH_3$), 69.6 ($O\underline{C}H_2$), 79.4 ($O\underline{C}HPh$), 127.7, 128.2, 128.6 and 139.6 (Ar-$\underline{C}$), 170.0 ($\underline{C}O_2Et$).

III-2.4 Synthesis of azidoaldehyde fragment: D-Mannitol approach

1,2:5,6-Di-*O*-isopropylidene-D-mannitol **217**[176]

A mixture of D-mannitol (91 g, 0.5 mol), *p*-toluenesulfonic acid (0.5 g, 2.5 mmol) and 2,2-dimethoxypropane (130 g, 1.25 mol) in dry Me_2SO (150 mL) was stirred at room temperature for 17h. The reaction mixture was poured into 3% aq. $NaHCO_3$ (500 mL), then extracted with ethyl acetate (1 x 600 mL, then 3 x 500 mL). The combined extracts were washed with water (3 x 250 mL), dried ($MgSO_4$) and concentrated *in vacuo*, affording a solid mass. The solid was recrystallised from hexane, washed with cold Et_2O / hexane 1:3 and dried to give 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**217**, 56 g, 43%) as a white solid.

[176] Kierstead, R. W.; Faraone, A.; Mennona, F. *J. Med. Chem.* **1983**, *26*, 1561.

δ_H (300 MHz; $CDCl_3$):

1.36 (6H, s) and 1.42 (6H, s, $C(C\underline{H}_3)_2$), 3.74-3.76 (2H, m, C<u>H</u>OH), 3.95-3.99 (2H, m, $C\underline{H}(O)CH_2$), 4.10-4.20 (4H, m, $C\underline{H}_2O$).

δ_C (75 MHz; $CDCl_3$):

24.7 and 26.2 ($C(\underline{C}H_3)_2$), 66.5 ($CH(O)\underline{C}H_2$), 70.6 (<u>C</u>HOH), 75.4 ($\underline{C}HOCH_2$), 110.2 ($\underline{C}(CH_3)_2$).

<u>(2*R*) 2,3-*O*-Isopropylidene glyceraldehyde **218**</u>[177]

Sodium periodate (2.57 g, 12 mmol) was dissolved in water (5 mL) at 70 °C and the solution was adsorbed onto silica (10 g), shaking vigorously to ensure a good homogeneity of the solid. 1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**217**, 5.00 g, 19 mmol) was dissolved in dry DCM (200 mL) under nitrogen. The silica-supported sodium periodate was added and the heterogeneous mixture was stirred vigorously at rt for 4h. The solids were filtered on a pad of Na_2SO_4 and washed with DCM (50 mL). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to afford crude (2*R*) 2,3-*O*-isopropylidene glyceraldehyde (**218**, 4.98 g, 100%) as a light yellow oil, which could be used without purification.

δ_H (300 MHz; $CDCl_3$):

1.42 (3H, s) and 1.49 (3H, s, $C(C\underline{H}_3)_2$), 4.10 (1H, dd, ^2J 8.8, ^3J 4.7 Hz, 1 of $CH(O)C\underline{H}_2$), 4.17 (1H, dd, ^2J 8.8, ^3J 7.5 Hz, 1 of $CH(O)C\underline{H}_2$), 4.37-4.39 (1H, m, $C\underline{H}(O)CH_2$), 9.72 (1H, d, ^3J 1.9 Hz, C<u>H</u>O).

[177] Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

(4S,E) Ethyl 4,5-O-(Isopropylidenedioxy)-pent-2-enoate **221**

Wittig procedure:[179]

1,2:5,6-Di-*O*-isopropylidene-D-mannitol (**217**, 500 mg, 1.9 mmol) was dissolved in dry DCM (20 mL) under nitrogen. Silica-supported sodium periodate (3.8 g, prepared as described previously) was added, followed by (ethoxycarbonylmethylene) triphenylphosphorane (**219**, 1.37 g, 3.8 mmol) and the heterogeneous mixture was stirred vigorously at rt for 2h. The solids were filtered on a pad of Na_2SO_4 and washed with DCM (20 mL). The filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 5:1) afforded a 2:1 mixture of *Z* and *E* ethyl 4,5-*O*-(isopropylidenedioxy)-pent-2-enoate **220** and **221** (730 mg, 96%), as assigned by integration of the alkene protons at δ_H 5.84 and δ_H 6.09 ppm respectively.

(4*S*,*Z*) ethyl 4,5-*O*-(isopropylidenedioxy)-pent-2-enoate **220**:

δ_H (400 MHz; $CDCl_3$):

1.29 (3H, t, ^3J 7.1Hz, $OCH_2C\underline{H}_3$), 1.41 (3H, s) and 1.45 (3H, s, $C(C\underline{H}_3)_2$), 3.62 (1H, dd, ^2J 8.3, ^3J 7.1 Hz, 1 of $CH(O)C\underline{H}_2$), 4.20 (2H, q, ^3J 7.1 Hz, $OC\underline{H}_2CH_3$), 4.38 (1H, dd, ^2J 8.3, ^3J 7.0 Hz, 1 of $CH(O)C\underline{H}_2$), 5.49 (1H, dddd, ^3J 7.1, 7.0, 6.8, ^4J 1.7 Hz, $C\underline{H}(O)CH=CH$), 5.84 (1H, dd, ^3J 11.6, ^4J 1.8 Hz, $CH=C\underline{H}CO_2Et$), 6.36 (1H, dd, ^3J 11.6, ^3J 6.6 Hz, $C\underline{H}=CHCO_2Et$).

See following experiment for the characterisation of (4*S*,*E*) ethyl 4,5-*O*-(isopropylidenedioxy)-pent-2-enoate **221.**

[179] Ray, P. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 149.

Wadsworth-Emmons procedure:[224]

A solution of sodium periodate (6.3 g, 29 mmol) in water (50 mL) was slowly added to a slurry of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**217**, 6.3 g, 24 mmol) in 5% aq. $NaHCO_3$ (50 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 1h. The reaction mixture was cooled to 0°C, then triethyl α-phosphonoacetate (22.6 g, 0.1 mol) and 6M aq. K_2CO_3 (150 mL) were added successively, maintaining the temperature at 0 °C. The resulting mixture was allowed to warm to rt and was stirred for 24h. The reaction mixture was extracted with DCM (4 x 50 mL) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (silica, hexane / ethyl acetate 5:1) afforded (4*S*,*E*) ethyl 4,5-*O*-(isopropylidenedioxy)-pent-2-enoate (**221**, 8.2 g, 85%) as a single isomer.

ν_{max}/cm^{-1} (neat):

2987 (s, C-H stretch), 1730 (s, C=O), 1662 (s, C=C), 1371, 1036.

δ_H (400 MHz; $CDCl_3$):

1.29 (3H, t, ^3J 7.1Hz, $OCH_2C\underline{H}_3$), 1.41 (3H, s) and 1.45 (3H, s, $C(C\underline{H}_3)_2$), 3.67 (1H, dd, ^2J 8.3, ^3J 7.1 Hz, 1 of $CH(O)C\underline{H}_2$), 4.18 (1H, dd, ^2J 8.3, ^3J 6.6 Hz, 1 of $CH(O)C\underline{H}_2$), 4.20 (2H, q, ^3J 7.1 Hz, $OC\underline{H}_2CH_3$), 4.66 (1H, dddd, ^3J 7.1, 6.6, 5.7, ^4J 1.4 Hz, $C\underline{H}(O)CH_2$), 6.09 (1H, dd, ^3J 15.6, ^4J 1.4 Hz, $CH=C\underline{H}CO_2Et$), 6.87 (1H, dd, ^3J 15.6, 5.7 Hz, $C\underline{H}=CHCO_2Et$).

δ_C (75 MHz; $CDCl_3$):

14.2 ($OCH_2\underline{C}H_3$), 25.7 and 26.4 ($C(\underline{C}H_3)_2$), 60.5 ($O\underline{C}H_2CH_3$), 68.8 ($CH(O)\underline{C}H_2$), 74.9 ($\underline{C}H(O)CH_2$), 110.1 ($\underline{C}(CH_3)_2$), 122.4 ($\underline{C}H=CHCO_2Et$), 144.6 ($CH=\underline{C}HCO2Et$), 166.0 ($\underline{C}O_2Et$).

[224] Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.

(4*S*,*E*) 4,5-*O*-(isopropylidenedioxy)-pent-2-enol **222**

DIBAL-H (20 wt% in toluene, 52 mL, 63 mmol) was added dropwise to a solution of (4*S*,*E*) ethyl 4,5-*O*-(isopropylidenedioxy)-2-pentenoate (**221**, 5.0 g, 25 mmol) in dry DCM (63 mL) at -78 °C and the mixture was stirred for 4h. The reaction was allowed to warm to rt and excess DIBAL-H was quenched with MeOH, then the mixture was diluted with diethyl ether (100 mL) and stirred with sat. aq. Rochelle's salt (50 mL) for 1h. The aqueous phase was diluted with water (100 mL) and extracted with ethyl acetate (4 x 100 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 1:1) afforded (4*S*,*E*) 4,5-*O*-(isopropylidenedioxy)-pent-2-enol (**222**, 3.4 g, 86%), as a colourless oil.

ν_{max}/cm^{-1} (neat):

3364 (br, O-H), 2878 (s, C-H stretch), 1699 (s, C=C), 1385, 1072.

δ_H (400 MHz; $CDCl_3$):

1.39 (3H, s) and 1.43 (3H, s, $C(C\underline{H}_3)_2$), 3.60 (1H, dd, ^2J 8.1, ^3J 7.7 Hz, 1 of $CH(O)C\underline{H}_2$), 4.10 (1H, dd, ^2J 8.1, ^3J 6.2 Hz, 1 of $CH(O)C\underline{H}_2$), 4.17 (2H, dd, ^3J 5.1, ^4J 1.5 Hz, $C\underline{H}_2OH$), 4.54 (1H, ddd, ^3J 7.6, 7.3, 6.4 Hz, $C\underline{H}(O)CH_2$), 5.72 (1H, ddt, ^3J 15.5, 7.4, ^4J 1.6 Hz, $C\underline{H}$=$CHCH_2OH$), 5.97 (1H, dt, ^3J 15.5, 5.1 Hz, CH=$C\underline{H}CH_2OH$).

δ_C (75 MHz; $CDCl_3$):

25.7 and 26.5 ($C(\underline{C}H_3)_2$), 62.1 ($\underline{C}H_2OH$), 69.2 ($CH(O)\underline{C}H_2$), 76.4 ($\underline{C}H(O)CH_2$), 109.2 ($\underline{C}(CH_3)_2$), 127.9 ($\underline{C}H$=$CHCH_2OH$), 133.6 (CH=$\underline{C}HCH_2OH$).

m/z (CI pos):

181 (M+Na, 5%), 59 (100), 173 (95).

HRMS (ESP pos):

$C_8H_{14}O_3Na$ (MNa^+) requires: 181.0835, Found: 181.0830, ΔM = 3 ppm.

(2*R*,3*S*,4*R*) 2,3-epoxy-4,5-*O*-(isopropylidenedioxy)-pentanol **223**

D-(-)-Diethyl tartrate (0.26 mL, 1.52 mmol) and titanium(IV) isopropoxide (0.37 mL, 1.26 mmol) were added dropwise to a slurry of dry DCM containing pre-dried 4Å molecular sieves at -20 °C and the mixture was stirred for 30 min under nitrogen. A solution of (4*S*,*E*) 4,5-*O*-(isopropylidenedioxy)-pent-2-enol (**222**, 200 mg, 1.26 mmol) in DCM (2 mL) was added dropwise and the mixture was stirred for a further 30 min at - 20 °C. *tert*-Butylhydroperoxide (5-6 M solution in decane, 0.75 mL, 3.78 mmol) was added and the reaction was stirred at -20 °C for 5 days. Aq. tartaric acid (10% solution, 3 mL) was added at -20 °C, then the mixture was allowed to warm to rt and stirred for 1h. The resulting emulsion was filtered on Celite and the solids washed with DCM and water. The filtrate was extracted with DCM (3 x 10 mL), then the combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 1:1) afforded a single isomer (2*R*,3*S*,4*R*) 2,3-epoxy-4,5-*O*-(isopropylidenedioxy)-pentanol (**223**, 0.18 g, 80%) as a colourless oil.

ν_{max}/cm^{-1}:

3418 (br, O-H), 2987 (s, C-H stretch), 1373, 1215, 1061.

δ_H (400 MHz; $CDCl_3$):

1.36 (3H, s) and 1.45 (3H, s, $C(C\underline{H}_3)_2$), 3.08-3.12 (2H, m, $\underline{H}C(O)C\underline{H}$), 3.69 (1H, dd, ^2J 12.9, ^3J 4.1 Hz, 1 of $C\underline{H}_2OH$), 3.91 (1H, dd, ^2J 8.0, ^3J 5.7 Hz, 1 of $CH(O)C\underline{H}_2$), 3.96 (1H, q, ^3J 5.7 Hz, $C\underline{H}(O)CH_2$), 3.97 (1H, dd, ^2J 12.9, ^3J 2.2 Hz, 1 of $C\underline{H}_2OH$), 4.13 (1H, dd, ^2J 8.0, ^3J 5.9 Hz, 1 of $CH(O)C\underline{H}_2$).

δ_C (125 MHz; $CDCl_3$):

25.2 and 26.5 ($C(\underline{C}H_3)_2$), 55.2 and 57.1 ($H\underline{C}(O)\underline{C}H$), 61.0 ($\underline{C}H_2OH$), 66.9 ($CH(O)\underline{C}H_2$), 75.3 ($\underline{C}H(O)CH_2$), 109.9 ($\underline{C}(CH_3)_2$).

m/z (ESP pos):

196.7 (M+Na, 100%), 55 (22), 173 (20).

$[\alpha]_D^{25}$ + 51.5 (c = 0.22, EtOH).

A side product of the epoxidation reaction was (4*S*,*E*) 4,5-*O*-(isopropylidenedioxy)-pent-2-enal[225] (*ca.* 10 mg, 5%), which was obtained as a colourless oil.

δ_H (400 MHz; $CDCl_3$):

1.42 (3H, s) and 1.46 (3H, s, $C(C\underline{H}_3)_2$), 3.73 (1H, dd, ^2J 8.3, ^3J 6.8 Hz, 1 of $CH(O)C\underline{H}_2$), 4.25 (1H, dd, ^2J 8.3, ^3J 6.7 Hz, 1 of $CH(O)C\underline{H}_2$), 4.79 (1H, td, ^3J 6.8, 6.7, 5.4 Hz, $C\underline{H}(O)CH_2$), 6.35 (1H, ddd, ^3J 15.6, 7.8, ^4J 0.6 Hz, CH=C<u>H</u>CHO), 6.77 (1H, dd, ^3J 15.6, 5.4 Hz, C<u>H</u>=CHCHO), 9.60 (1H, d, ^3J 7.8 Hz, C<u>H</u>O).

δ_C (75 MHz; $CDCl_3$):

25.6 and 26.4 ($C(\underline{C}H_3)_2$), 68.7 ($CH(O)\underline{C}H_2$), 74.9 ($\underline{C}H(O)CH_2$), 110.6 (($\underline{C}(CH_3)_2$), 132.4 (CH=<u>C</u>HCHO), 152.9 (<u>C</u>H=CHCHO), 192.9 (<u>C</u>HO).

<u>(2*S*,3*R*,4*S*) 3-Azido-4,5-*O*-(isopropylidenedioxy)-pentane-1,2-diol **224** and (2*S*,3*S*,4*R*) 2-azido-4,5-*O*-(isopropylidenedioxy)-pentane-1,3-diol **225**</u>

A solution of trimethylsilyl azide (0.23 mL, 1.72 mmol) and titanium(IV) isopropoxide (0.25 mL, 0.86 mmol) in dry benzene (5 mL) was heated to reflux under nitrogen for 6h. (2*R*,3*S*,4*R*) 2,3-Epoxy-4,5-*O*-(isopropylidenedioxy)-pentanol (**223**, 100 mg, 0.57mmol), in solution in dry benzene (1 mL), was added dropwise and the mixture was stirred at 70 °C for 30 min. The reaction mixture was allowed to cool to rt and concentrated *in vacuo* to give a mixture of regioisomers. Purification by flash chromatography (silica, toluene / ethyl acetate 1:1) afforded:

[225] Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1378.

(2*S*,3*R*,4*S*) 3-azido-4,5-*O*-(isopropylidenedioxy)-pentane-1,2-diol (**224**, 13 mg, 10%) as a light yellow oil;

ν_{max}/cm^{-1} (neat):

3394 (br, OH), 2987 (s, C-H stretch), 2112 (s, N_3), 1373, 1215, 1065.

δ_H (500 MHz; $CDCl_3$):

1.38 (3H, s) and 1.48 (3H, s, C(C$\underline{H}_3$)$_2$), 3.34 (1H, dd, ^3J 6.0, 4.0 Hz, C$\underline{H}$N$_3$), 3.75 (1H, dd, ^2J 8.7, ^3J 4.1 Hz, 1 of C$\underline{H}_2$OH), 3.78-3.82 (1H, m, C$\underline{H}$OH), 3.85 (1H, dd, ^2J 8.7, ^3J 2.6 Hz, 1 of C$\underline{H}_2$OH), 3.94 (1H, dd, ^2J 6.8, ^3J 5.4 Hz, 1 of CH(O)C$\underline{H}_2$), 4.12 (1H, dd, ^2J 6.9, ^3J 5.3 Hz, 1 of CH(O)C$\underline{H}_2$), 4.42 (1H, td, ^3J 5.3, 4.1 Hz, C$\underline{H}$(O)CH$_2$).

δ_C (75 MHz; $CDCl_3$):

25.2 and 26.1 (C($\underline{C}$H$_3$)$_2$), 63.1 ($\underline{C}$HN$_3$), 63.7 ($\underline{C}$H$_2$OH), 66.6 (CH(O)$\underline{C}$H$_2$), 71.3 ($\underline{C}$HOH), 76.0 ($\underline{C}$HOCH$_2$), 109.8 ($\underline{C}$(CH$_3$)$_2$).

(2*S*,3*S*,4*R*) 2-azido-4,5-*O*-(isopropylidenedioxy)-pentane-1,3-diol (**225**, 40 mg, 30%) as a light yellow oil;

ν_{max}/cm^{-1} (neat):

3418 (br, OH), 2987 (s, C-H stretch), 2104 (s, N_3), 1373, 1219, 1069.

δ_H (500 MHz; $CDCl_3$):

1.37 (3H, s) and 1.43 (3H, s, 1 of C(C$\underline{H}_3$)$_2$), 3.62 (1H, q, ^3J 5.0 Hz, C$\underline{H}$N$_3$), 3.85 (1H, dd, ^3J 6.2, 5.4 Hz, C$\underline{H}$OH), 3.93-4.00 (2H, m, C$\underline{H}_2$OH), 3.98 (1H, dd, ^2J 8.4, ^3J 6.1 Hz, 1 of CH(O)C$\underline{H}_2$), 4.11 (1H, dd, ^2J 8.4, ^3J 6.3 Hz, 1 of CH(O)C$\underline{H}_2$), 4.19 (1H, q, ^3J 6.2 Hz, C$\underline{H}$OCH$_2$).

δ_C (75 MHz; $CDCl_3$):

25.1 and 26.6 (C($\underline{C}$H$_3$)$_2$), 62.5 ($\underline{C}$H$_2$OH), 63.9 ($\underline{C}$HN$_3$), 66.0 (CH(O)$\underline{C}$H$_2$), 72.5 ($\underline{C}$HOH), 75.5 ($\underline{C}$HOCH$_2$), 114.0 ($\underline{C}$(CH$_3$)$_2$).

m/z (CI pos):

218 (M+H, 10%), 190 (100), 60 (60), 101 (58), 160 (45).

HRMS (ESP pos):

$C_8H_{15}N_3O_4Na$ (MNa^+) requires: 240.09602. Found: 240.09566. ΔM = 1.5 ppm.

$[\alpha]_D^{25}$ + 28.5 (c = 0.15, EtOH).

III-2.5 Synthesis of azidoaldehyde fragment: Kitagawa's approach

Note: Compounds **226**, **229**, **229a** and **230** were prepared following Kitagawa's approach.

(*Z*) 4-Hydroxybut-2-enyl propanoate **229**[184]

A solution of (*Z*) but-2-ene-1,4-diol (**228**, 26.7 g, 0.30 mol) in dry acetone (120 mL) was treated with propionic anhydride (39 mL, 0.30 mol), and the mixture was heated to reflux for 20h under nitrogen. After allowing the reaction mixture to cool to rt, the solvent was removed *in vacuo* and the residue was dissolved in ether (100 mL). The ether extract was washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 2:1) afforded (*Z*) 4-hydroxybut-2-enyl propanoate (**229**, 21.0 g, 48%) as a clear oil.

ν_{max}/cm^{-1}(neat):

3418 (br, O-H), 2982 (m, C-H stretch), 1732 (s, C=O), 1371, 1186, 1024.

[184] (a) Shibuya, H.; Kawashima, K.; Ikeda, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 7205. (b) Shibuya, H.; Kawashima, K.; Narita, N.; Ikeda, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1154.

δ_H (400 MHz; $CDCl_3$):

1.16 (3H, t, ^3J 7.6 Hz, C(O)$CH_2C\underline{H}_3$), 2.41 (2H, q, ^3J 7.6 Hz, C(O)$C\underline{H}_2CH_3$), 4.33 (2H, d, ^3J 7.1 Hz, $C\underline{H}_2OH$), 4.75 (2H, d, ^3J 7.1 Hz, $C\underline{H}_2OC(O)Et$), 5.68-5.73 (1H, m) and 5.89-5.94 (1H, m, C<u>H</u>=C<u>H</u>).

δ_C (75 MHz; $CDCl_3$):

9.0 ($CH_2\underline{C}H_3$), 27.6 ($\underline{C}H_2CH_3$), 58.4 ($\underline{C}H_2OH$), 60.0 ($\underline{C}H_2OC(O)Et$), 125.8 and 133.3 (<u>C</u>H=<u>C</u>H), 174.6 (<u>C</u>(O)Et).

<u>(*Z*) 4-[(4-Methoxyphenyl)diphenylmethoxy]but-2-enyl propanoate **229a**</u>[184]

Monomethoxytrityl chloride (3.2 g, 10.4 mmol) was added to a stirred solution of (*Z*) 4-hydroxy-but-2-enyl propionate (**229**, 1.00 g, 6.94 mmol) in dry pyridine (12 mL) and the mixture was stirred at rt for 5h under nitrogen. The reaction mixture was poured into an ice/water mixture (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with 5% HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$). Evaporation of the solvents *in vacuo* afforded *ca.* 4 g of (*Z*) 4-[(4-methoxyphenyl)diphenylmethoxy]but-2-enyl propanoate **229a** as a viscous yellow oil, contaminated with residual pyridine, which was used without further purification.

δ_H (400 MHz; $CDCl_3$):

1.06 (3H, t, ^3J 7.6 Hz, C(O)$CH_2C\underline{H}_3$), 2.24 (2H, q, ^3J 7.6 Hz, C(O)$C\underline{H}_2CH_3$), 3.67 (2H, d, ^3J 6.1 Hz, $C\underline{H}_2OCAr_3$), 3.76 (3H, s, $OC\underline{H}_3$), 4.44 (2H, d, ^3J 6.5 Hz, $C\underline{H}_2OC(O)Et$), 5.56-5.59 (1H, m) and 5.79-5.82 (1H, m, C<u>H</u>=C<u>H</u>), 6.78-6.81 (2H, m), 7.15-7.28 (10H, m) and 7.40-7.42 (2H, m, Ar-<u>H</u>).

(*Z*) 4-[(4-Methoxyphenyl)diphenylmethoxy]but-2-en-1-ol **230**[184]

Crude (*Z*) 4-[(4-methoxyphenyl)diphenylmethoxy]but-2-enyl propionate (**229a**, 2.00 g, 4.8 mmol) was diluted in toluene (50 mL) and concentrated to remove traces of pyridine. The remaining oil was diluted in MeOH (20 mL) and treated with 10% KOH/MeOH (20 mL) for 30 min at rt. The reaction mixture was poured into an ice/water mixture (20 mL), and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 4:1) afforded (*Z*) 4-[(4-methoxyphenyl)diphenylmethoxy]but-2-en-1-ol (**230**, 1.8 g, 72%) as a yellow oil.

ν_{max}/cm^{-1}(neat):

3444 (br, O-H), 1703, 1608 (m, C=C), 1510 (m, aromatic C=C), 1446, 1250.

δ_H (400 MHz; $CDCl_3$):

3.71 (2H, d, ^3J 5.5 Hz, $C\underline{H}_2OCAr_3$), 3.82 (3H, s, $OC\underline{H}_3$), 4.06 (2H, d, ^3J 5.7 Hz, $C\underline{H}_2OH$), 5.72-5.84 (2H, m, $\underline{H}C{=}C\underline{H}$), 6.86-6.88 (2H, m), 7.25-7.37 (6H, m) and 7.47-7.49 (4H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

55.3, 59.1, 82.0, 113.2, 127.2, 127.8, 127.9, 128.3, 129.2, 130.0, 131.2, 146.5, 158.7, $\underline{C}_q$ not observed.

(2*S*,3*R*) 2,3-Epoxy-4-[(4-methoxyphenyl)diphenylmethoxy]butan-1-ol **226**[184]

L-(+)-Diethyl tartrate (0.74 mL, 4.3 mmol) and titanium(IV) isopropoxide (1.15 mL, 3.91 mmol) were added to a slurry of dry DCM (30 mL) containing pre-dried 4Å molecular sieves at -20 °C and the mixture was stirred for 30 min under nitrogen. A solution of (*Z*) 4-[(4-methoxyphenyl)diphenylmethoxy]-but-2-en-1-ol (**230**, 1.41 g, 3.91

mmol) in DCM (10 mL) was added dropwise over 5 min and the mixture was stirred at -20 °C for 30 min. *tert*-Butylhydroperoxide (5-6 M solution in decane, 3.12 mL, 15.6 mmol) was added dropwise and the mixture was stirred at -20 °C for 6 days. The reaction mixture was treated with 10% aq. L-(+)-tartaric acid (40 mL) at -20 °C, and stirred for 1h at rt. The aqueous solution was extracted with DCM (5 x 20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in diethyl ether (50 mL), and treated with 1N aq. NaOH (12 mL) at 0 °C for 30 min. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 2:1) afforded (2*S*,3*R*) 2,3-epoxy-4-[(4-methoxyphenyl)diphenylmethoxy]butan-1-ol (**226**, 0.82 g, 56%) as a yellow oil.

δ_H (300 MHz; C_6D_6):

1.38 (1H, br s, $CH_2O\underline{H}$), 2.87 (1H, ddd, ^3J 9.8, 5.7, 4.7 Hz, $HOCH_2C\underline{H}(O)$), 3.06 (1H, ddd, ^3J 6.2, 4.7, 4.4 Hz, $(O)C\underline{H}CH_2OCAr_3$), 3.16 (1H, dd, ^2J 10.6, ^3J 4.4 Hz, 1 of $C\underline{H}_2OCAr_3$), 3.26 (3H, s, $OC\underline{H}_3$), 3.25-3.29 (2H, m, $C\underline{H}_2OH$), 3.44 (1H, dd, ^2J 10.6, ^3J 6.2 Hz, 1 of $C\underline{H}_2OCAr_3$), 6.69 (2H, d, ^3J 8.5 Hz, Ar-$\underline{H}$), 7.08-7.17 (6H, m, Ar-$\underline{H}$), 7.38 (2H, d, ^3J 8.5 Hz, Ar-$\underline{H}$), 7.51-7.60 (4H, m, Ar-$\underline{H}$).

δ_C (100 MHz; $CDCl_3$):

54.6 and 55.2 (($\underline{C}(O)\underline{C}$), 55.6 ($O\underline{C}H_3$), 60.8 and 62.2 ($O\underline{C}H_2$), 86.9 ($\underline{C}Ar_3$), 113.3, 127.1, 127.9, 128.3, 130.3, 135.1, 144.1 and 158.7 (Ar-$\underline{C}$).

(2*R*,3*S*) 2-Azido-4-[(4-methoxyphenyl)diphenylmethoxy]butane-1,3-diol **227**[226]

Trimethyl borate (0.42 mL, 3.72 mmol) and sodium azide (207 mg, 3.19 mmol) were added to a solution of (2*S*,3*R*) 2,3-epoxy-4-[(4-methoxyphenyl)diphenylmethoxy] butan-1-ol (**226**, 400 mg, 1.06 mmol) in dry DMF (28 mL) under nitrogen. After stirring at rt for 6h, the reaction mixture was cooled to 0 °C and treated with sat. aq. $NaHCO_3$ (20 mL) for 30 min. The solution was extracted with ethyl acetate (5 x 20 mL). The combined extracts were washed successively with water (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (silica, DCM / methanol 99:1) recovered (2*S*,3*R*) 2,3-epoxy-4-[(4-methoxyphenyl)diphenylmethoxy]butan-1-ol (**226**, 204 mg, 51%) predominantly, and allowed to isolate traces (<5 mg) of the desired diol (2*R*,3*S*) 2-azido-4-[(4-methoxyphenyl)diphenylmethoxy]butane-1,3-diol **227** as a light yellow oil.

δ_H (500 MHz; $CDCl_3$):

3.24 (1H, dd, ^2J 9.7, ^3J 5.7 Hz, 1 of $C\underline{H}_2OCAr_3$), 3.27 (1H, dd, ^2J 9.7, ^3J 6.0 Hz, 1 of $C\underline{H}_2OCAr_3$), 3.61 (1H, ddd, ^3J 6.2, 4.5, 4.0 Hz, $C\underline{H}N_3$), 3.73 (1H, dd, ^2J 11.6, ^3J 6.2 Hz, 1 of $C\underline{H}_2OH$), 3.78 (3H, s, $OC\underline{H}_3$), 3.79 (1H, dd, ^2J 11.6, ^3J 4.5 Hz, 1 of $C\underline{H}_2OH$), 3.85-3.87 (1H, m, C<u>H</u>OH), 6.83 (2H, dd, ^3J 9.0, 2.2 Hz, Ar-<u>H</u>), 7.20-7.32 (8H, m) and 7.39-7.44 (4H, m, Ar-<u>H</u>).

δ_C (125 MHz; $CDCl_3$):

55.2 ($O\underline{C}H_3$), 63.2 ($\underline{C}H_2OH$), 64.3($\underline{C}HN_3$), 64.4 ($\underline{C}H_2OCAr_3$), 71.4 (<u>C</u>HOH), 86.8 ($\underline{C}Ar_3$), 113.2, 127.1, 127.9, 128.2, 130.3, 135.1, 144.0 and 158.7 (Ar-<u>C</u>).

m/z (ESP pos):

442 (M+Na, 62%), 273 (100), 399 (20).

[226] Sasaki, M.; Taninno, K.; Hirai, A.; Miyashita, M. *Org. Lett.*, **2003**, *5*, 1789.

III-2.6 Synthesis of azidoaldehyde fragment: rapid entry

Note: Compounds **234**, **235** and **236** were prepared following Terashima's method.

(*Z*) 4-(4-Methoxybenzyloxy)but-2-en-1-ol **235**[187]

(*Z*) But-2-ene-1,4-diol (**228**, 1.75 mL, 0.018 mol) was added dropwise to a suspension of sodium hydride (60% dispersed in mineral oil, 630 mg, 0.016 mol) in anh. DMF (15 mL) at 0 °C and the reaction mixture was stirred for 30 min under nitrogen. 4-Methoxybenzyl chloride (2.12 mL, 0.016 mol) was then added at rt and the mixture was stirred for 3h. The reaction was quenched with sat. aq. NH_4Cl (2 mL). The mixture was diluted with ethyl acetate (40 mL), then the organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 1:1) afforded (*Z*) 4-(4-methoxybenzyloxy)but-2-en-1-ol (**235**, 2.7 g, 72%), as a light yellow oil.

ν_{max}/cm^{-1}(neat):

2859 and 2837 (s, C-H stretch), 1690 (w, C=C stretch), 1612 and 1515 (s, aromatic C=C stretch), 1250.

δ_H (500 MHz; $CDCl_3$):

3.81 (3H, s, $OC\underline{H}_3$), 4.07 (2H, d, ^3J 6.2 Hz) and 4.17 (2H, d, ^3J 6.2 Hz, $C\underline{H}_2CH=CHC\underline{H}_2$), 4.46 (2H, s, $OC\underline{H}_2PMB$), 5.72-5.76 (1H, m) and 5.79-5.83 (1H, m, $C\underline{H}=C\underline{H}$), 6.88 (2H, m) and 7.27 (2H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

55.3 ($OC\underline{H}_3$), 58.7 ($\underline{C}H_2OH$), 65.4 ($\underline{C}H_2OPMB$), 72.2 ($\underline{C}H_2C_6H_4OCH_3$), 128.3 and 132.4 ($H\underline{C}=\underline{C}H$), 113.9, 129.5, 129.9 and 159.3 (Ar-$\underline{C}$).

(2*S*,3*R*) 2,3-Epoxy-4-(4-methoxybenzyloxy)butan-1-ol **234**[187]

L-(+)-Diethyl tartrate (1.20 mL, 7 mmol), titanium(IV) isopropoxide (1.73 mL, 5.9 mmol) and *tert*-butylhydroperoxide (5-6 M solution in decane, 20 mL, 100 mmol) were added dropwise to a slurry of dry DCM (60 mL) containing pre-dried 4Å molecular sieves at -20 °C and the mixture was stirred for 30 min under nitrogen. A solution of (*Z*) 4-(4-methoxybenzyloxy)but-2-en-1-ol (**235**, 7.00 g, 34 mmol) in DCM (20 mL) was added dropwise over 1h and the mixture was allowed to warm to 0 °C and stirred for 3 days. The reaction mixture was diluted with ethyl acetate (250 mL), then *ca.* 100 mL of solvent was removed by evaporation *in vacuo* at rt. The residue was treated with an aqueous solution containing $Fe_2SO_4.7H_2O$ (10.4 g) and L-(+)-tartaric acid (4 g in 35 mL) at 0 °C, and the mixture was stirred for 1h. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and diethyl ether (2 x 50 mL). The combined extracts were treated with 30 wt% NaOH in brine (7 mL) at 0 °C for 1h. The aqueous layer was diluted with brine (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 2:1) afforded (2*S*,3*R*) 2,3-epoxy-4-(4-methoxybenzyloxy)butan-1-ol (**234**, 5.40 g, 72%) as a yellow oil.

ee: 73-75% (as determined by Chiral HPLC using CHIRALPAK® AD, ^{i}PrOH/hexane 15:85; retention times 20.2 min (minor), 21.9 min (major)).

ν_{max}/cm^{-1}(neat):

2934 (s, C-H stretch), 1612 and 1514 (s, aromatic C=C stretch), 1248, 810.

[187] (a) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239, and references cited therein. (b) Williams, R.M.; Rollins, S.B.; Judd, T.C. *Tetrahedron*, **2000**, *56*, 521.

δ_H (300 MHz; $CDCl_3$):

3.19-3.30 (2H, m, HC(O)CH), 3.61 (1H, dd, ^2J 11.2, ^3J 5.0 Hz, 1 of CH_2OPMB), 3.71 (1H, dd, ^2J 11.2, ^3J 6.2 Hz, 1 of CH_2OPMB), 3.68-3.78 (2H, m, CH_2OH), 3.81 (3H, s, OCH_3), 4.46 (1H, d, ^2J 11.4 Hz) and 4.55 (1H, d, ^2J 11.4 Hz, $OCH_2C_6H_4OCH_3$), 6.86-6.90 (2H, m) and 7.24-7.28 (2H, m, Ar-H).

δ_C (75 MHz; $CDCl_3$):

54.7 and 55.6 (HC(O)CH), 55.3 (OCH_3), 60.8 (CH_2OH), 67.8 (CH_2OPMB), 73.2 ($CH_2C_6H_4OCH_3$), 114.0, 129.4, 129.6 and 159.5 (Ar-C).

m/z (CI pos):

224 (M^+, 15%), 121 (100).

(2*R*,3*S*) 2-Azido-4-(4-methoxybenzylox)-butane-1,3-diol **236**[187]

(2*S*,3*R*) 2,3-Epoxy-4-(4-methoxybenzyloxy)butan-1-ol (**243**, 5.00 g, 22 mmol) was diluted in methoxyethanol (200 mL) and water (25 mL). Sodium azide (2.43 g, 44 mmol) and NH_4Cl (2.90 g, 44 mmol) were added and the mixture was heated to reflux for 4h. After cooling to rt, the reaction mixture was concentrated *in vacuo* and filtered through a silica plug, eluting with ethyl acetate. Concentration of the filtrate afforded a 1:1 regioisomeric mixture as an orange oil, which was diluted in 1:1 THF/water (30 mL). Sodium periodate (4.80 g, 24 mmol) was added and the mixture was stirred for 3h at rt. After dilution with ethyl acetate (100 mL) and brine (30 mL), the reaction mixture was washed with 20% aq. $Na_2S_2O_3$ (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude by flash chromatography (silica, hexane / ethyl acetate 2:1 → 1:1) afforded (2*R*,3*S*) 2-azido-4-(4-methoxybenzyloxy)butane-1,3-diol (**236**, 2.92 g, 49%) as a clear yellow oil.

ν_{max}/cm^{-1}(neat):

2934 (m, C-H stretch), 2106 (s, N_3), 1612 and 1514 (s, aromatic C=C stretch), 1250.

δ_H (300 MHz; $CDCl_3$):

3.54-3.65 (2H, m, $C\underline{H}_2OH$), 3.78-3.99 (4H, m, $C\underline{H}(N_3)C\underline{H}(OH)C\underline{H}_2O$), 3.81 (3H, s, $OC\underline{H}_3$), 4.50 (2H, s, $OC\underline{H}_2C_6H_4OCH_3$), 6.88-6.92 (2H, m) and 7.24-7.28 (2H, m, Ar-$\underline{H}$).

δ_C (75 MHz; $CDCl_3$):

55.3 ($OC\underline{H}_3$), 63.0 ($\underline{C}H_2OH$), 64.3 ($\underline{C}HN_3$), 70.6 ($\underline{C}H_2OPMB$), 71.1 ($\underline{C}HOH$), 73.3 ($\underline{C}H_2C_6H_4OCH_3$), 114.0, 129.5 and 160.0 (Ar-$\underline{C}$).

m/z (FAB pos):

290 (M+Na, 68%), 121 (100).

$[\alpha]_D^{25}$ - 16.7 (c = 1, EtOH).

(2*R*,3*S*) 2-Azido-1-triethylsilanyloxy-3-hydroxy-4-(4-methoxybenzyloxy)butane **236a**

A solution of triethylchlorosilane (0.75 g, 5.0 mmol) in anh. DMF (2 mL) was added dropwise to a solution of (2*R*,3*S*) 2-azido-4-(4-methoxybenzyloxy)butane-1,3-diol (**236**, 0.53 g, 2.0 mmol) and imidazole (0.34 g, 5.0 mmol) in anh. DMF (2 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 1h and overnight at rt. The reaction mixture was then diluted with ethyl acetate (10 mL) and water (10mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with sat. aq. NH_4Cl (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 4:1 → 1:1) afforded (2*R*,3*S*) 2-azido-1-triethylsilanyloxy-3-hydroxy-4-(4-methoxybenzyloxy) butane (236a, 0.23 g, 30%) as a light yellow oil and recovered (2*R*,3*S*) 2-azido-4-(4-methoxybenzyloxy)butane-1,3-diol (**236**, 0.12 g, 22%).

ν_{max}/cm^{-1}(neat):

2954 (s, C-H stretch), 2104 (s, N_3), 1612 and 1514 (s, aromatic C=C stretch), 1248.

δ_H (400 MHz; $CDCl_3$):

0.62 (6H, q, ^3J 8.0 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.96 (9H, t, ^3J 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 2.58 (1H, d, ^3J 4.8 Hz, CHO$\underline{H}$), 3.49-3.53 (3H, m, $C\underline{H}_2$OPMB and $C\underline{H}N_3$), 3.81 (3H, s, $OC\underline{H}_3$), 3.85 (1H, dd, ^2J 10.6, ^3J 6.4 Hz, 1 of $C\underline{H}_2OSiEt_3$), 3.91 (1H, dd, ^2J 10.6, ^3J 4.4 Hz, 1 of $C\underline{H}_2OSiEt)_3$), 3.90-3.95 (1H, m, C$\underline{H}$OH), 4.41 (2H, s, $OC\underline{H}_2C_6H_4OCH_3$), 6.88-6.90 (2H, m) and 7.24-7.27 (2H, m, Ar-$\underline{H}$).

δ_C (125 MHz; $CDCl_3$):

4.2 ($Si(\underline{C}H_2CH_3)_3$), 6.6 ($Si(CH_2\underline{C}H_3)_3$), 55.2 ($O\underline{C}H_3$), 63.7 ($\underline{C}H_2OSiEt_3$), 64.0 ($\underline{C}HN_3$), 70.4 ($\underline{C}H_2$OPMB), 70.8 ($\underline{C}$HOH), 73.2 ($\underline{C}H_2C_6H_4OCH_3$), 113.9, 129.8, 129.9 and 159.4 (Ar-$\underline{C}$).

m/z (FAB pos):

404 (M+Na, 45%), 121 (100).

HRMS (FAB pos):

$C_{18}H_{31}O_4N_3SiNa$ (MNa^+) requires: 404.1981. Found 404.1975. ΔM = 1.5 ppm.

$[\alpha]_D^{25}$ - 10.7 (c = 1, EtOH).

(2*R*,3*S*) 2-Azido-4-(4-methoxybenzyloxy)-3-acetoxy-1-triethylsilanylbutan-1-ol **241**

Acetic anhydride (37 μL, 0.4 mmol) and triethylamine (73 μL, 0.52 mmol) were added to a solution of (2*R*,3*S*) 2-azido-1-triethylsilanyloxy-3-hydroxy-4-(4-methoxybenzyloxy)butane (**236a**, 100 mg, 0.26 mmol) and DMAP (2.4 mg, 0.02 mmol) in dry DCM (2 mL) and the mixture was stirred at room temperature for 2h. The reaction was quenched with sat. aq. NH_4Cl (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried

($MgSO_4$) and concentrated *in vacuo* to give (2*R*,3*S*) 2-azido-4-(4-methoxybenzyloxy)-3-acetoxy-1-triethylsilanylbutan-1-ol (**241**, 0.11 g, 100%) as a yellow oil, which was used without further purification.

ν_{max}/cm^{-1}(neat):

2108 (m, N_3), 1741 (m, C=O stretch), 1614 (s) and 1514 (m, aromatic C=C stretch), 1247.

δ_H (400 MHz; $CDCl_3$):

0.59 (6H, q, ^3J 7.8 Hz, Si(C$\underline{H}_2$CH$_3$)$_3$), 0.94 (9H, t, ^3J 7.8 Hz, Si(CH$_2$C$\underline{H}_3$)$_3$), 2.09 (3H, s, OC(O)C$\underline{H}_3$), 3.55 (1H, dd, ^2J 10.3, ^3J 5.0 Hz, 1 of C$\underline{H}_2$OPMB), 3.59 (1H, dd, ^2J 10.3, ^3J 5.3 Hz, 1 of C$\underline{H}_2$OPMB), 3.62-3.69 (1H, m, C$\underline{H}$N$_3$), 3.72-3.80 (2H, m, C$\underline{H}_2$OSiEt$_3$), 3.81 (3H, s, OC$\underline{H}_3$), 4.42 (1H, d, ^2J 11.6 Hz) and 4.50 (1H, d, ^2J 11.6 Hz, OC$\underline{H}_2$C$_6$H$_4$OCH$_3$), 5.13 (1H, q, ^3J 5.3 Hz, C$\underline{H}$OC(O)CH$_3$), 6.87-6.89 (2H, m) and 7.24-7.26 (2H, m, Ar-$\underline{H}$).

δ_C (125 MHz; $CDCl_3$):

4.2 (Si(C$\underline{H}_2$CH$_3$)$_3$), 6.6 (Si(CH$_2$C$\underline{H}_3$)$_3$), 30.9 (OC(O)C$\underline{H}_3$), 55.3 (OC$\underline{H}_3$), 62.6 (C$\underline{H}_2$OSiEt$_3$), 62.9 (C$\underline{H}$N$_3$), 67.7 (C$\underline{H}_2$OPMB), 71.0 (C$\underline{H}$OC(O)CH$_3$), 73.0 (C$\underline{H}_2$C$_6$H$_4$OCH$_3$), 113.8, 129.5, 159.4 and 170.1 (Ar-C), 207.0 (OC(O)CH$_3$).

(2*R*,3*S*) 2-Azido-3-acetoxy-4-(4-methoxybenzyloxy)butan-1-ol **243**

Acetic acid (60 μL, 1.15 mmol) and H_2O (20 μL, 0.7 mmol) were added to a solution of (2*R*,3*S*) 2-azido-4-(4-methoxybenzyloxy)-3-acetoxy-1-triethylsilanylbutan-1-ol (**241**, 100 mg, 0.23 mmol) in THF (1 mL) and the mixture was stirred at 40 °C for 3h. After cooling to rt the reaction mixture was concentrated *in vacuo* and the residue was diluted with water (5 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 4:1) afforded (2*R*,3*S*) 2-azido-3-acetoxy-4-(4-methoxybenzyloxy)butan-1-ol (**243**, 73 mg, 100%) as a yellow oil.

δ_H (400 MHz; $CDCl_3$):

2.12 (3H, s, OC(O)C$\underline{H}_3$), 2.35 (1H, br t, ^3J 6.7 Hz, $CH_2O\underline{H}$), 3.60 (1H, dd, ^2J 10.6, ^3J 5.0 Hz, 1 of C$\underline{H}_2$OPMB), 3.62 (1H, dd, ^2J 10.6, ^3J 5.3 Hz, 1 of C$\underline{H}_2$OPMB), 3.66 (1H, br t, ^3J 6.0 Hz, C$\underline{H}N_3$), 3.76-3.81 (2H, m, C$\underline{H}_2$OH), 3.81 (3H, s, OC$\underline{H}_3$), 4.45 (1H, d, ^2J 11.6 Hz) and 4.50 (1H, d, ^2J 11.6 Hz, OC$\underline{H}_2C_6H_4OCH_3$), 5.17 (1H, q, ^3J 5.3 Hz, C$\underline{H}$OC(O)CH_3), 6.88-6.90 (2H, m) and 7.22-7.26 (2H, m, Ar-$\underline{H}$).

δ_C (100 MHz; $CDCl_3$):

20.9 (OC(O)$\underline{C}H_3$), 55.3 (O$\underline{C}H_3$), 61.4 ($\underline{C}H_2OH$), 62.8 ($\underline{C}HN_3$), 67.8 (O$\underline{C}H_2C_6H_4OCH_3$), 71.6 ($\underline{C}$HOC(O)$CH_3$), 73.2 ($\underline{C}H_2OCH_2C_6H_4OCH_3$), 113.9, 129.3, 129.5 and 159.5 (Ar-$\underline{C}$), 170.8 (O$\underline{C}$(O)CH_3).

(2*R*,3*S*) 2-Azido-3-hydroxy-4-(4-methoxybenzyloxy)butyl acetate **242**

A solution of (2*R*,3*S*) 2-azido-4-(4-methoxybenzyloxy)-3-acetoxy-1-triethylsilanyl butan-1-ol (**241**, 100 mg, 0.23 mmol) in THF (2 mL) was treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.30 mL, 0.30 mmol) at 0 °C over 5 min. After stirring at 0°C for 1.5 h, the mixture was allowed to warm to rt and water (5 mL) was added. The mixture was extracted with diethyl ether (4 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, hexane / ethyl acetate 2:1) afforded (2*R*,3*S*) 2-azido-3-hydroxy-4-(4-methoxybenzyloxy)butyl acetate (**242**, 59 mg. 81%) as a light yellow oil.

ν_{max}/cm^{-1}(neat):

2935 (s, C-H stretch), 2110 (s, N_3), 1745 (s, C=O strech), 1612 and 1514 (s, aromatic C=C stretch), 1250.

δ_H (400 MHz; $CDCl_3$):

2.10 (3H, s, OC(O)C$\underline{H}_3$), 2.39 (1H, d, ^3J 5.8 Hz, CH(O$\underline{H}$)), 3.51 (1H, dd, ^2J 9.7, ^3J 5.5 Hz, 1 of C$\underline{H}_2$OPMB), 3.62 (1H, dd, ^2J 9.7, ^3J 5.9 Hz, 1 of C$\underline{H}_2$OPMB), 3.73 (1H, ddd, ^3J 8.3, 4.5, 3.9 Hz, C$\underline{H}N_3$), 3.81 (3H, s, OC$\underline{H}_3$), 3.86 (1H, ddd, ^3J 5.9, 5.4, 4.0 Hz, C$\underline{H}$(OH)), 4.23 (1H, dd, ^2J 11.6, ^3J 8.2 Hz, 1 of C$\underline{H}_2$OAc), 4.33 (1H, dd, ^2J 11.6, ^3J 4.5 Hz, 1 of C$\underline{H}_2$OAc), 4.49 (2H, s OC$\underline{H}_2C_6H_4OCH_3$), 6.88-6.90 (2H, m) and 7.24-7.26 (2H, m, Ar-$\underline{H}$).

δ_C (125 MHz; $CDCl_3$):

20.8 (OC(O)$\underline{C}H_3$), 55.3 (O$\underline{C}H_3$), 61.6 ($\underline{C}HN_3$), 63.9 ($\underline{C}H_2$OAc), 69.8 ($\underline{C}$H(OH)), 70.5 ($\underline{C}H_2$OPMB), 73.2 (O$\underline{C}H_2C_6H_4OCH_3$), 113.9, 129.4, 129.5 and 159.5 (Ar-C), 170.6 (O$\underline{C}$(O)CH_3).

$[\alpha]_D^{25}$ - 13.2 (c = 0.3, EtOH).

2-Azido-4-(4-methoxybenzyloxy)-but-2-enal **244**

Note: The following procedure was carried out in view of obtaining (2R,3S) 2-azido-3-acetoxy-4-(4-methoxybenzyloxy)butan-1-al **239**, but was unsuccessful.[227]

Pyridine sulfur trioxide complex (216 mg, 0.68 mmol) was added to a solution of (2*R*,3*S*) 2-azido-3-acetoxy-4-(4-methoxybenzyloxy)butan-1-ol (**243**, 70 mg, 0.23 mmol) and triethylamine (0.2 mL, 1.4 mmol) in dry DMSO (1.2 mL), and the mixture was stirred at rt for 3h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between saturated aqueous NH_4Cl (5 mL) and ethyl acetate (5 mL). The

aqueous layer was extracted with ethyl acetate (3 x 2 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give crude 2-azido-4-(4-methoxybenzyloxy)-but-2-enal **244** (100 mg, uncorrected) as a brown oil.

δ_H (400 MHz; $CDCl_3$):

3.81 (3H, s, $OC\underline{H}_3$), 4.28 (2H, d, ^3J 5.9 Hz, $C\underline{H}_2OPMB$), 4.48 (2H, s, $OC\underline{H}_2C_6H_4OCH_3$), 5.97 (1H, t, ^3J 5.9 Hz, $N_3C{=}C\underline{H}$), 6.89-6.91 (2H, m) and 7.26-7.29 (2H, m, Ar-$\underline{H}$), 9.34 (1H, s, $C\underline{H}O$).

δ_C (125 MHz; $CDCl_3$):

55.3 ($O\underline{C}H_3$), 65.1 ($O\underline{C}H_2C_6H_4OCH_3$), 73.0 ($\underline{C}H_2OPMB$), 113.9, 114.3, 129.4, 129.6 and 159.5 (Ar-$\underline{C}$), 187.4 ($\underline{C}HO$).

III-2.7 Oxathiolane fragment

Note: Compounds **264**, and **265** were prepared following Cavelier's method.

Potassium (*R*) glycidate **264**[202,228]

L-Serine (**262**, 52.5 g, 0.5 mol) and KBr (200 g, 1.7 mol) were dissolved in 2M aq. HBr (520 mL, 1.1 mol) and the mixture was cooled to -10 °C with mechanical stirring. N_2 was bubbled through the mixture and sodium nitrite (42.8 g, 0.62 mol) was added in small portions so that the colour of the mixture faded between successive additions. The mixture was stirred at -10 °C for 1h then o/n at rt. Excess nitrous oxide was removed by vigorous N_2 bubbling for 1h. The reaction mixture was extracted with Et_2O (6 x 100 mL), the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to

[227] Mori, K.; Koseki, K. *Tetrahedron*, **1998**, *44*, 6013.
[202] Petit, Y.; Larchevêque, M. *Org. Syn. 75*, 37.
[228] (a) Cavelier, F. *Tetrahedron: Asymm.*, **1997**, *8*, 41. (b) Cavelier, F.; Yim, A-M. *OPPI*, **1998**, *30*, 103.

give (2*S*) 2-bromo-3-hydroxypropionic acid (**263**, 76.4 g, 90% crude yield) as a light green oil.

The crude substrate was diluted in anh. methanol and cooled to -40 °C. A solution of KOH in methanol (69 g in 400 mL) was added slowly and the mixture was stirred at -40 °C for 1h then o/n at rt. The solution was concentrated almost to dryness, then 1L diethyl ether was added and a white solid precipitated out of the solution. The precipitate was filtered, washed with cold diethyl ether and dried over P_2O_5 to afford 97 g of a mixture of potassium (*R*) glycidate **264** and KBr, which was used without purification.

Potassium (*R*) glycidate could be purified by recrystallisation from methanol/water, but the process was low yielding (20-25%).

δ_H (300 MHz; $CDCl_3$):

2.75 (1H, dd, ^2J 5.6, ^3J 2.8 Hz, 1 of C$\underline{H}_2$O), 2.89-2.92 (1H, m, 1 of C$\underline{H}_2$O), 3.33 (1H, dd, ^3J 4.4, 2.8 Hz, C$\underline{H}$O).

$[\alpha]_D^{25}$ + 33 (c = 20, H_2O). Lit.: + 32.1 (c = 20, H_2O).[202]

(2*S*) 3-(*tert*-Butylsulfanyl)-2-hydroxypropanoic acid **265**[228]

A mixture of crude potassium (*R*) glycidate (**264**, 1 g, *ca.* 4 mmol), *tert*-butylthiol (10.5 mL, 93 mmol) and 2M aq. LiOH (50 mL) was heated to reflux for 6h. The reaction mixture was allowed to cool to rt, then the excess *tert*-butylmercaptan was extracted with ethyl acetate (4 x 50 mL). The aqueous phase was acidified to pH 1 with 1N HCl and extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (silica, toluene / ethyl acetate 3:1) afforded (2*S*) 3-(*tert*-butylsulfanyl)-2-hydroxypropionic acid

[202] Petit, Y.; Larchevêque, M. *Org. Syn. 75*, 37.
[228] (a) Cavelier, F. *Tetrahedron: Asymm.*, **1997**, *8*, 41. (b) Cavelier, F.; Yim, A-M. *OPPI*, **1998**, *30*, 103.

(**265**) and the regioisomeric (2*S*) 2-(*tert*-butylsulfanyl)3-hydroxypropanoic acid as a 10:1 mixture (0.38 g, 54% from L-serine) as a light yellow oil.

(2*S*) 3-(*tert*-butylsylfanyl)-2-hydroxypropanoic acid **265**:

δ_H (300 MHz; $CDCl_3$):

1.33 (9H, s, $SC(C\underline{H}_3)_3$), 2.90 (1H, dd, ^2J 13.2, ^3J 6.4 Hz, 1 of $SC\underline{H}_2$), 3.06 (1H, dd, ^2J 13.2, ^3J 4.4 Hz, 1 of $SC\underline{H}_2$), 4.42 (1H, dd, ^3J 6.4, 4.3 Hz, C<u>H</u>OH).

δ_C (75 MHz; $CDCl_3$):

30.9 ($C(\underline{C}H_3)_3$), 32.8 ($\underline{C}H_2S$), 42.8 ($\underline{C}(CH_3)_3$), 69.7 (<u>C</u>HOH), 177.0 ($\underline{C}O_2H$).

(2*S*) 2-(*tert*-butylsulfanyl)3-hydroxypropanoic acid:

δ_H (300 MHz; $CDCl_3$):

1.37 (9H, s, $SC(C\underline{H}_3)_3$), 3.45 (1H, dd, ^3J 8.5, 6.1 Hz, $C\underline{H}SC(CH_3)_3$), 3.77 (1H, dd, ^2J 11.5, ^3J 6.1 Hz, 1 of $C\underline{H}_2OH$), 3.89 (1H, dd, ^2J 11.5, ^3J 8.4 Hz, 1 of $C\underline{H}_2OH$).

<u>(2*S*) Methyl 3-(*tert*-butylsulfanyl)-2-hydroxypropanoate **266**</u>

(2*S*) 3-(*tert*-Butylsulfanyl)-2-hydroxypropanoic acid (**265**, 2 g, *ca.* 11 mmol, contaminated with its regioisomer) was added to a solution of thionyl chloride (8.3 mL, 11.4 mmol) in dry methanol and the mixture was heated to reflux for 18h. The reaction mixture was allowed to cool to rt and concentrated to give a mixture of regioisomeric methyl esters. Purification by flash chromatography (silica, hexane / ethyl acetate 2:1) afforded (2*S*) methyl 3-(*tert*-butylsulfanyl)-2-hydroxypropanoate (**266**, 0.98 g, 45%) as a colourless oil.

ν_{max}/cm^{-1}:

3444 (br, O-H), 2960 (s, C-H stretch), 1743 (s, C=O), 1460, 1365, 1215, 1096.

δ_H (300 MHz; $CDCl_3$):

1.33 (9H, s, $SC(C\underline{H}_3)_3$), 2.87 (1H, dd, ^2J 13.1, ^3J 6.0 Hz, 1 of $SC\underline{H}_2$), 3.01 (1H, dd, ^2J 13.1, ^3J 4.3 Hz, 1 of $SC\underline{H}_2$), 3.81 (3H, s, $CO_2C\underline{H}_3$), 4.39 (1H, dd, ^3J 6.0, 4.4 Hz, 1 of $C\underline{H}OH$).

δ_C (75 MHz; $CDCl_3$):

31.0 ($C(\underline{C}H_3)_3$), 38.5 ($\underline{C}H_2S$), 44.6 ($\underline{C}(CH_3)_3$), 52.7 ($CO_2\underline{C}H3$), 70.3 ($\underline{C}HOH$), 173.7 ($\underline{C}O_2CH_3$).

m/z (CI pos):

137 (100%), 193 (MH^+, 35).

$[\alpha]_D^{25}$ + 28.3 (c = 0.92, EtOH).

(5*S*) Methyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate **188**

(2*S*) Methyl 3-(*tert*-butylsulfanyl)-2-hydroxypropanoate (**266**, 0.38 g, 2 mmol) was diluted in dry DCM (5 mL). Pivalaldehyde (0.22 mL, 2 mmol), boron trifluoride etherate complex (0.50 mL, 4 mmol) and thioanisole (0.24 mL, 2 mmol) were added and the mixture was stirred at rt for 3h. The excess boron trifluoride was quenched with aq. sat. $NaHCO_3$ (5 mL), then the aqueous phase was extracted with DCM (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture of diastereoisomers. Purification by flash chromatography (silica, hexane / ethyl acetate 9:1) afforded an inseparable mixture of diastereoisomers of (5*S*) methyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate (**188**, 0.22 g, 55%) in a *trans*:*cis* ratio of 2:1 as a colourless oil.

ν_{max}/cm^{-1} (neat):

2962 (s, C-H stretch), 1799 (m), 1743 (w, C=O), 1365, 1209, 1107.

δ_H (500 MHz; $CDCl_3$):

trans (2*R*,5*S*) methyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate **188c**: 0.98 (9H, s, $C(C\underline{H}_3)_3$), 3.12 (1H, dd, ^2J 10.8, ^3J 6.6 Hz, 1 of $SC\underline{H}_2$), 3.26 (1H, dd, ^2J 10.8, ^3J 2.5 Hz, 1 of $SC\underline{H}_2$), 3.77 (3H, s, $CO_2C\underline{H}_3$), 4.97 (1H, dd, ^3J 6.5, 2.5 Hz, $OC\underline{H}(CO_2CH_3)$), 5.22 (1H, s, $C\underline{H}C(CH_3)_3$).

cis (2*S*,5*S*) methyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate **188d**: 1.02 (9H, s, $C(C\underline{H}_3)_3$), 3.00 (1H, dd, ^2J 10.4, ^3J 9.1 Hz, 1 of $SC\underline{H}_2$), 3.23 (1H, dd, ^2J 10.4, ^3J 5.8 Hz, 1 of $SC\underline{H}_2$), 3.78 (3H, s, $CO_2C\underline{H}_3$), 4.49 (1H, dd, ^3J 9.1, 5.8 Hz, $OC\underline{H}(CO_2CH_3)$), 4.99 (1H, s, $C\underline{H}C(CH_3)_3$).

δ_C (125 MHz; $CDCl_3$):

(2*R*,5*S*) (*trans*) methyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate **188c**:

25.6 ($C(\underline{C}H_3)_3$), 34.3 ($S\underline{C}H_2$), 35.7 ($\underline{C}(CH_3)_3$), 52.3 ($O\underline{C}H_3$), 80.6 ($O\underline{C}HCO_2CH_3$), 95.9 ($O\underline{C}HS$), 171.3 ($\underline{C}O_2CH_3$).

(2*S*,5*S*) (*cis*) methyl 2-*tert*-butyl-1,3-oxathiolane-5-carboxylate **188d**:

25.8 ($C(\underline{C}H_3)_3$), 34.6 ($S\underline{C}H_2$), 35.3 ($\underline{C}(CH_3)_3$), 52.4 ($O\underline{C}H_3$), 80.8 ($O\underline{C}HCO_2CH_3$), 96.3 ($O\underline{C}HS$), 169.6 ($\underline{C}O_2CH_3$).

m/z (ESP pos):

227 (M+Na, 100%), 217 (30).

HRMS (ESP pos):

$C_9H_{16}O_3SNa$ (M+Na) requires: 227.0712. Found 227.0714. ΔM = 0.6 ppm.

(5*S*) 2-*tert*-Butyl-1,3-oxathiolane-5-carboxylic acid **267**

Crude (2*S*) 3-(*tert*-butylsulfanyl)-2-hydroxypropanoic acid (**265**, 0.35 g, 2 mmol) was diluted in dry DCM (5 mL). Pivalaldehyde (0.22 mL, 2 mmol), boron trifluoride etherate complex (0.50 mL, 4 mmol) and thioanisole (0.24 mL, 2 mmol) were added

and the mixture was stirred at rt for 3h. The excess boron trifluoride was quenched with aq. sat. $NaHCO_3$ (5 mL), then the aqueous phase was extracted with DCM (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford 0.30 g of a crude 1.1:1 mixture of diastereoisomers as a colourless oil.

δ_H (400 MHz; $CDCl_3$):

0.95 (9H, s, $C(C\underline{H}_3)_3$), 1.02 (9H, s, $C(C\underline{H}_3)_3$), 2.83 (1H, dd, ^2J 13.6, ^3J 7.3 Hz, 1 of $SC\underline{H}_2$), 2.88 (1H, dd, ^2J 13.4, ^3J 5.2 Hz, 1 of $SC\underline{H}_2$), 3.04-3.11 (2 x 1H, 2 m, 2 x 1 of $SC\underline{H}_2$), 4.42-4.45 (1H, m, $OC\underline{H}(CO_2H)$), 4.60-4.63 (1H, m, $OC\underline{H}(CO_2H)$), 5.15 (1H, s, $C\underline{H}C(CH_3)_3$), 5.39 (1H, s, $C\underline{H}C(CH_3)_3$).

m/z (CI pos):

191 (M+H, 65%), 173 (42).

HRMS (ESP pos):

$C_8H_{14}O_3SNa$ (M+Na) requires: 213.0561. Found 213.0570. ΔM = 4 ppm.

(2*R*) Methyl 2,3-*O*-isopropylidene glycerate **274**[214]

Compound **274** was prepared following Ladame's method.

Sodium periodate (8.1 g, 38 mmol) and water (2 mL) were slowly added to a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**217**, 5.00 g, 19 mmol) in DCM (50 mL) and the suspension was stirred vigorously for 4h. $MgSO_4$ (*ca.* 10 g) was added to the reaction mixture, which was then filtered and concentrated *in vacuo* to give D-glyceraldehyde acetonide **218**. A mixture of methanol / water (9:1, 50 mL), $NaHCO_3$ (12 g) and bromine (3.85 mL, 75 mmol) was then added slowly *via* a pressure-equalising dropping funnel, and the reaction mixture was stirred for 18h at rt. The excess bromine was reduced with $Na_2S_2O_3$, then the mixture was extracted with DCM

(2 x 75 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by a short flash chromatography (silica, hexane / ethyl acetate 1:1) afforded (2*R*) methyl 2,3-O-isopropylidene glycerate (**274**, 4.2 g, 69%) as a colourless oil.

ν_{max}/cm^{-1} (neat):

2990 (s, C-H stretch), 1737 (s, C=O), 1373, 1209, 1107.

δ_H (400 MHz; $CDCl_3$):

1.41 (3H, s) and 1.50 (3H, s, $C(C\underline{H}_3)_2$), 3.78 (3H, s, $CO_2C\underline{H}_3$), 4.11 (1H, dd, ^2J 8.6, ^3J 5.2 Hz, 1 of $OC\underline{H}_2$), 4.24 (1H, dd, ^2J 8.6, ^3J 7.2 Hz, 1 of $OC\underline{H}_2$), 4.60 (1H, dd, ^3J 7.2, 5.2 Hz, $OC\underline{H}(CO_2CH_3)$).

δ_C (75 MHz; $CDCl_3$):

25.5 and 25.8 ($C(\underline{C}H_3)_2$), 52.4 ($CO_2\underline{C}H_3$), 67.2 ($O\underline{C}H_2CHO$), 74.0 ($OCH_2\underline{C}HO$), 111.4 ($\underline{C}(CH_3)_2$), 171.6 ($\underline{C}O_2CH_3$).

m/z (ESP pos):

183 (M+Na, 100%), 184 (7).

Methyl 2,3-*O*-(isopropylidene)-2-(1-hydroxy-1-phenylmethyl) glycerate **275**

n-Butyllithium (1.6 M in THF, 0.78 mL, 1.25 mmol) was added dropwise at 0 °C to a solution of diisopropylamine (0.16 mL, 1.25 mmol) in THF (4 mL) and the mixture was stirred for 15 min. The reaction mixture was cooled to -78 °C, then a solution of (2*R*) methyl 2,3-O-isopropylidene glycerate (**274**, 200 mg, 1.25 mmol) in THF (2 mL) was added, followed by benzaldehyde (0.13 mL, 1.25 mmol). The reaction mixture was allowed to warm to rt over 3h, then was quenched with aq. sat. NH_4Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with brine (10mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a mixture of diastereoisomers (16.3 mg, 5%). Purification by preparative thin layer

chromatography (silica, hexane / ethyl acetate 2:1, 2 elutions) allowed separation of the two isomers of methyl 2,3-*O*-(isopropylidenedioxy)-2-(1-hydroxy-1-phenylmethyl) glycerate **275**, each being isolated as colourless oils in less than 10 mg.

First isomer:

δ_H (500 MHz; $CDCl_3$):

1.29 (3H, s) and 1.41 (3H, s, 1 of $C(C\underline{H}_3)_2$), 2.97 (1H, d, ^3J 6.0 Hz, CHO$\underline{H}$), 3.74 (3H, s, $CO_2C\underline{H}_3$), 4.14 (1H, d) and 4.24 (1H, d, ^2J 9.1 Hz, $OC\underline{H}_2$), 4.97 (1H, d, ^3J 6.0 Hz, C$\underline{H}$OH), 7.30-7.34 (5H, m, ar-$\underline{H}$).

δ_C (125 MHz; $CDCl_3$):

25.8 and 25.9 ($C(\underline{C}H_3)_2$), 52.6 ($O\underline{C}H_3$), 68.6 ($\underline{C}H_2O$), 75.6 ($\underline{C}$HOH), 86.9 ($\underline{C}(CH_3)_2$), 112.0 ($\underline{C}(O)CO_2CH_3$), 127.2, 128.2, 128.5, 137.8 (ar-$\underline{C}$), 173.0 ($\underline{C}O_2CH_3$).

Second isomer:

δ_H (500 MHz; $CDCl_3$):

1.33 (3H, s) and 1.45 (3H, s, 1 of $C(C\underline{H}_3)_2$), 2.81 (1H, d, ^3J 6.5 Hz, CHO$\underline{H}$), 3.63 (3H, s, $CO_2C\underline{H}_3$), 4.30 (1H, d) and 4.33 (1H, d, ^2J 9.1 Hz, $OC\underline{H}_2$), 4.96 (1H, d, ^3J 6.0 Hz, C$\underline{H}$OH), 7.28-7.32 (5H, m, ar-$\underline{H}$).

δ_C (125 MHz; $CDCl_3$):

25.7 and 25.9 ($C(\underline{C}H_3)_2$), 52.4 ($O\underline{C}H_3$), 69.2 ($\underline{C}H_2O$), 74.7 ($\underline{C}$HOH), 86.4 ($\underline{C}(CH_3)_2$), 112.3 ($\underline{C}(O)CO_2CH_3$), 127.4, 128.2, 128.4, 138.4 (ar-$\underline{C}$), 172.6 ($\underline{C}O_2CH_3$).

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