β-Lactams from Functionalised (Allenylmethyl)silanes

by

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A thesis presented in part fulfilment of the requirement for the degree of Doctor of Philosophy.

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University of Glasgow
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Abbreviations

The following abbreviations have been used throughout the course of this thesis:

D-ala	D-alanine
6-APA	6-aminopenicillanic acid
BuLi	*n*-butyl lithium
CSI	chlorosulfonyl isocyanate
CTA	cellulose triacetate
DCC	dicyclohexylcarbodiimide
DET	diethyl tartrate
DIPT	diisopropyl tartrate
DMAP	dimethylaminopyridine
DMF	dimethylformamide
Eu(hfc)3	tris[3-(heptafluoropropylhydroxymethylene)camphorato] europium (III)
LDA	lithium diisopropylamide
M	molar
NAG	*N*-acetyl-D-glucosamine
NAM	*N*-acetylmuramic acid
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
PNB	*p*-nitrobenzoyl
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDMSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TMSCl	trimethylsilyl chloride

Contents

Dedicated to mum and dad, Murray, Phyllis and Brett
for their continual faith and encouragement.

Section 1.1 Discovery

It is well over sixty years since Sir Alexander Fleming first observed antibiosis between a *Penicillium* mould and staphlococcal bacterial cultures.[1] Penicillin, the inhibitory substance, proved difficult to isolate and it was only when Florey and Chain [2] reinvestigated the bacteriocidal properties of *Penicillium notatum* at Oxford in 1938 that the active component Penicillin N (Fig. 1) was isolated from cultures of the mould. These historical developments culminated in the discovery of one of the most remarkable therapeutic agents this century and this antibiotic substance has preoccupied scientists for more than four decades.

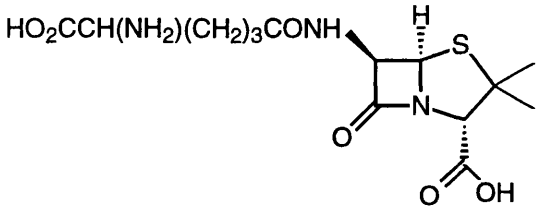


Figure 1

As the potential therapeutic value of penicillin was recognised, a worldwide search for other antibacterial substances from microorganisms was undertaken. This revealed a second class of β–lactam antibiotics, namely the cephalosporins, following detailed examination of the antibacterial substance isolated from a strain of *Cephalosporium acremonium* [3] provided by Professor Brotzu from a sample taken near a sewage outlet in Sardinia. One of these substances, cephalosporin C (Fig. 2), showed activity against gram-negative and penicillin-resistant bacteria. Development of this discovery of cephalosporin C led to the clinical use of cephalothin, cephalexin etc. - the so called first generation cephalosporins.

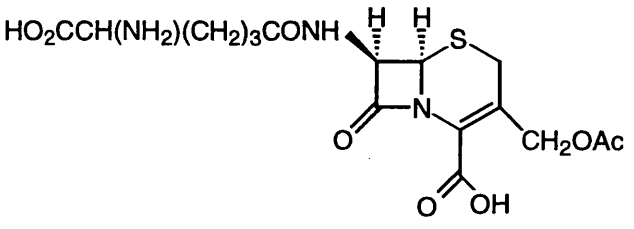
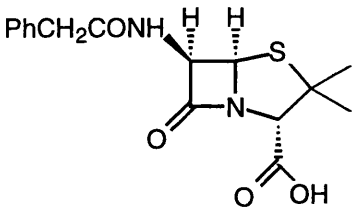
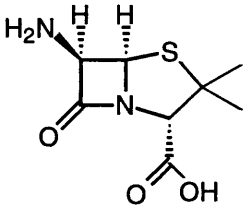


Figure 2

During World War II a monumental Anglo-American research programme was set up, aimed at producing penicillin in sufficient quantities for widespread use. This collaboration led to the manufacture of penicillin G (Fig. 3) using *Penicillium chrysogenum.* Other penicillin derivatives could then be prepared by feeding certain precursors to the fermentation broth. Rapid developments in fermentation technology, particularly by Beecham chemists, resulted in large-scale production of 6-aminopenicillanic acid, 6-APA (Fig. 3) and until recently, most clinically used β–lactams were acyl derivatives of this penicillin nucleus e.g. methicillin, ampicillin. It is only since the discovery of new, naturally occurring β–lactams possessing both good antibacterial properties and resistance to enzymatic cleavage that a renewed interest in the chemical synthesis of these compounds has been stimulated.



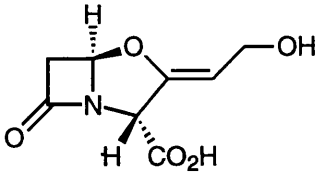
penicillin G



6-aminopenicillanic acid
(6-APA)

Figure 3

A particularly important breakthrough was the identification of clavulanic acid (Fig. 4), a potent β-lactamase inhibitor, following a biological screen devised by Beecham in 1967 designed to detect potential β-lactamase inhibitors.

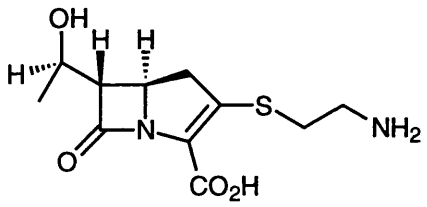


clavulanic acid

Figure 4

This assay also highlighted a number of other β-lactamase inhibitory substances, most notably the family of carbapenem β-lactam antibiotics which inhibit both β-lactamase activity and cell wall synthesis. To date over forty

carbapenem β-lactam antibiotics have been reported and include the thienamycins, carpetimycins and asparenomycins although so far, thienamycin (Fig. 5), since it demonstrates the greatest antibacterial activity, is the only carbapenem to be developed clinically.



thienamycin

Figure 5

Section 1.2 Structure and Biological Activity of the β-Lactam Ring

Elucidation of the penicillin structure indicated that these systems consisted of a fused β–lactam and thiazolidine ring. In penicillins this β-lactam ring is *cis* substituted and the substituents on the bicyclic system are then usually described by the prefix α or β rather than the equivalent *exo* or *endo* description. 6-β-Side chains have been shown to confer acid stability and have allowed the development of orally administered penicillins. Cephalosporins consist of a β-lactam ring fused to a dihydrothiazine, however, in these systems 7-β-side chains do not increase acid stability to such a great extent as in the penicillin series, and it is the substituent at position 3 which is most important for biological activity.

In contrast, the carbapenem antibiotics have no heteroatom in the ring fused to the β-lactam and, as such, were a milestone in affecting the traditional thoughts associated with structure/activity relationships prevailing in the penicillin and cephalosporin areas. In addition, these systems have a *trans*-substituted β-lactam ring and a *R* configuration at C-8 and have been found to be the most stable compounds to β-lactamase enzymes.

Although it was proposed as early as 1943 that penicillin contained a β–lactam ring,[4] this was not generally accepted until an X-ray crystallographic determination of the structure had been completed.[5] This β–lactam subunit is an essential feature of the molecule and its biological activity can be attributed to it, since shortly after penicillin was introduced for use as a therapeutic agent, it was suggested that the antibiotic's activity was due either to the inherent strain of the four-membered ring[6] or to reduced amide resonance.[7]

The nature of the amide group in the fused bicyclic penam system is considerably different to that in a normal acyclic amide accounting for the increase in biological activity. In a normal amide the nitrogen atom and the three atoms connected to it are coplanar, due to the lone pair of electrons on nitrogen being delocalised into the π-orbital system of the adjacent carbonyl. Increased bond angle strain within the penam system prevents this planar arrangement, decreasing the likelihood of effective amide delocalisation. This renders the β–lactam carbonyl carbon more susceptible to nucleophilic attack, making the penicillin molecule a very effective biological acylating agent.

The biological activity of the cephalosporins has also been related to the chemistry of the β–lactam amide bond. Here the nitrogen atom lies slightly less above the plane (0.24 Å) [8] than is observed in penicillins (0.40 Å).[9] However, in this case there is an additional decrease in amide resonance due to the

presence of unsaturation in the dihydrothiazine ring α,β to the lactam nitrogen atom.

This increase in biological activity caused by loss of amide resonance and inherent ring strain has led synthetic chemists to attempt the development of more effective antibiotics by making the β–lactam system more strained or non-planar. However, the evidence to support these two proposals is still very ambiguous as in some 1-carbo-1-penems the nitrogen atom can lie as much as 0.54 Å above the plane and yet still be biologically inactive. Loss of amide resonance should also result in an increase in basicity of the nitrogen.on the β-lactam ring as a consequence of increased localisation of the lone pair on the nitrogen atom, but the β-lactam nitrogen shows no enhanced electron pair donating ability. There is very little evidence, therefore, of inhibited amide resonance in both penicillins and cephalosporins and we can only conclude that it must be the nature of the substituents on the ring which are important for biological activity.

Section 1.3 The Mode of Action of β–Lactam Antibiotics

Penicillins and cephalosporins appear to have the same mode of action. They interfere with the biosynthesis of rigid bacterial cell walls, which have no mammalian counterpart, resulting in lysis and cell death. A considerable amount of work has been done to elucidate the structure and synthesis of bacterial cell walls and to propose the mechanism by which antibiotics inhibit this synthesis.

Of the cell wall constituents, it is largely the peptidoglycan which is responsible for cell shape and prevention of osmotic rupture. The glycan strands are composed of alternating residues (Fig. 6) of *N*-acetyl-D-glucosamine (NAG) and *N*-acetylmuramic acid (NAM) with short peptide crosslinks. Transpeptidation occurs when the terminal D-alanine residue from a short peptide chain which terminates with D-ala-D-ala is displaced by a free amino group on an adjacent peptide and it is this process which is penicillin sensitive. Earlier stages in the biosynthesis, where the glycan polymer is not crosslinked, are not sensitive to penicillin.

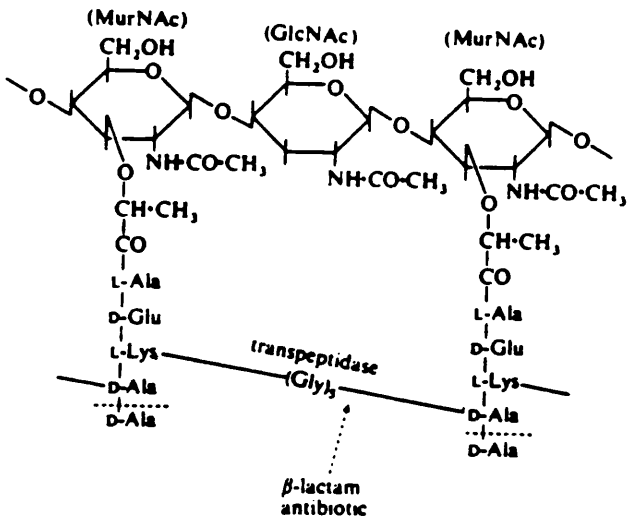


Figure 6

Tipper and Strominger [6] have proposed a plausible model for the molecular basis of the selectivity of β–lactam action. They demonstrated that D-alanine is released during the normal transpeptidation process along with an insoluble product, whereas in the presence of penicillin or cephalosporin no such release is observed. This provided compelling evidence of the inhibiting effects of penicillin antibiotics.

These experimental results reinforced an earlier suggestion [7] that penicillin may be a structural analogue of a conformational isomer of D-ala-D-ala and is recognised by the transpeptidase as a substrate, irreversibly acylating the enzyme by cleavage of the weak amide bond in the β–lactam ring. Thus, further crosslinking by that particular enzyme is prevented (Fig. 7).

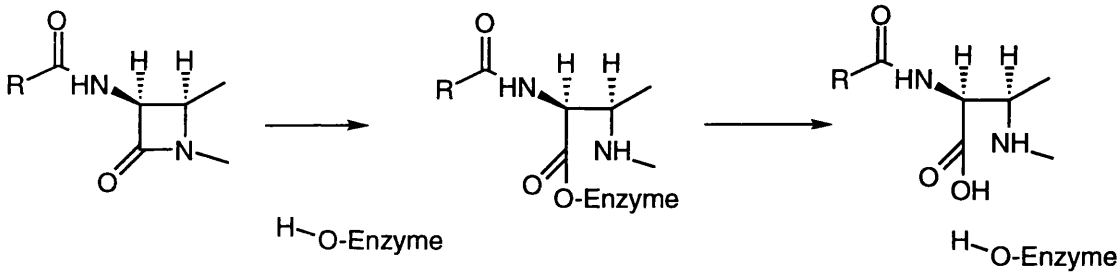


Figure 7 Irreversible Bacterial Enzyme Inhibition by a β–Lactam

β–Lactam antibiotics exert their lethal action only on growing bacterial cells. A few penicillin-tolerant bacteria have been observed to stop dividing in the presence of the antibiotic, but resume growth as soon as the penicillin is removed from the medium. By the mid 1960s, with the widespread use of penicillins and cephalosporins, problems of resistance associated with bacteria capable of producing a variety of β–lactamases became a major concern in β–lactam therapy.

There are several different classes of β–lactamases, however, these can be divided into two main sections; those enzymes incorporating serine and those enzymes incorporating zinc. The former have an active site serine and function by an acyl-enzyme mechanism, whereas the latter are metalloenzymes and appear to involve only noncovalent intermediates.

β–Lactamase mechanisms have been studied extensively [10] showing that the overall reaction is cleavage of the β–lactam ring. There is a close similarity between the serine β–lactamases and the penicillin-binding enzymes which are the targets for antibiotics. As a result the enzyme recognises the penicillin

antibiotic as a substrate and binds reversibly, generating inactive penicilloic acid and leaving the peptidoglycan transferase enzyme free (Fig. 8).

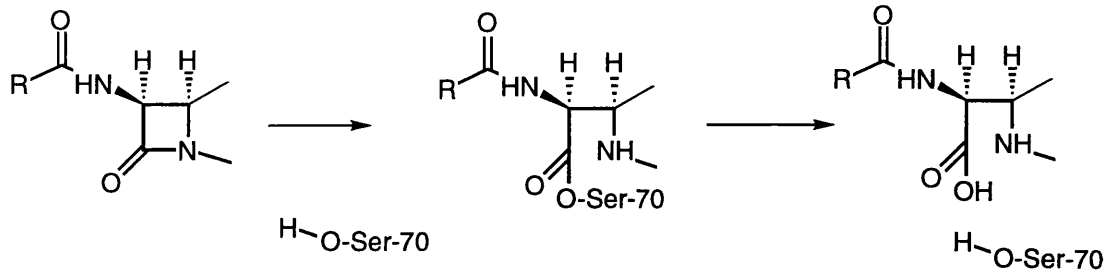
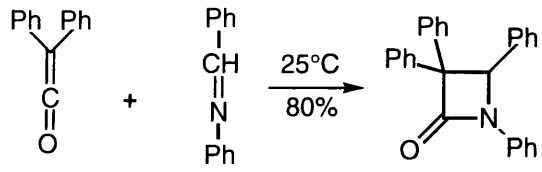


Figure 8 Mechanism of Action of Serine β-Lactamases

The main characteristic of metalloenzymes is that they catalyse the hydrolysis of nearly all β-lactams and, unlike the serine β-lactamases, are not inhibited by the usual β-lactamase inactivators, such as clavulanic acid. There are relatively few zinc β-lactamases known and the mechanism by which they act is still comparatively obscure, although it is believed that it differs very little from that of the serine β-lactamases only requiring zinc ions for activation. However, it is interesting to note the incredible selectivity that these two classes of enzymes exhibit, being able to differentiate between hydrolysis of the nonpolar amide bond in β-lactams and yet remain inert to the ordinary planar amide bond in peptides. This insight into the mechanism of action of these highly developed enzymes has stimulated a great deal of research into the synthesis of compounds designed to exhibit both potent antibacterial activity and strong β-lactamase inhibition.

Section 2.1 Synthesis of the β-Lactam Ring

In the first known synthesis of a β-lactam, Staudinger[11] reacted diphenylketene (**1**) with benzylideneaniline (**2**) at room temperature to give a crystalline β-lactam product (**3**) in good yield (Scheme 2.1).

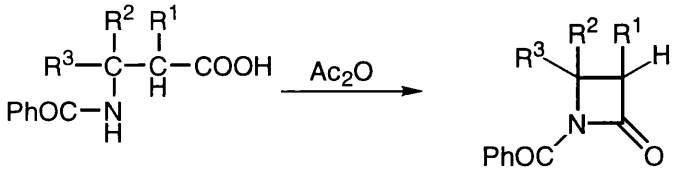


(1) **(2)** **(3)**

Scheme 2.1

Until this time, no authentic β-lactams were known as it had not yet been realised that the method used for the synthesis of γ-lactams i.e. thermal dehydration of the appropriate amino acids could also be applied to the formation of these four-membered ring systems. However, once the β-lactam or thiazolidine structure was accepted, it was realised that known routes to β-lactams were inadequate for a practical synthesis of penicillin.

There is no single general method for the preparation of β-lactams and, in principle, the ring can be generated by the simultaneous formation of either one, two, three or all four bonds. The formation of the N-1 to C-2 bond is brought about by cyclisation of β-amino acid derivatives. Simple heating of β-amino acids, although originally thought to afford β-lactams, fails to do so as a result of deamination through β-elimination and cyclisation usually only occurs with the aid of reagents, such as acetic anhydride, acetyl chloride, phosphorus trichloride and thionyl chloride.



R^1= alkyl, R^2= R^3= aryl

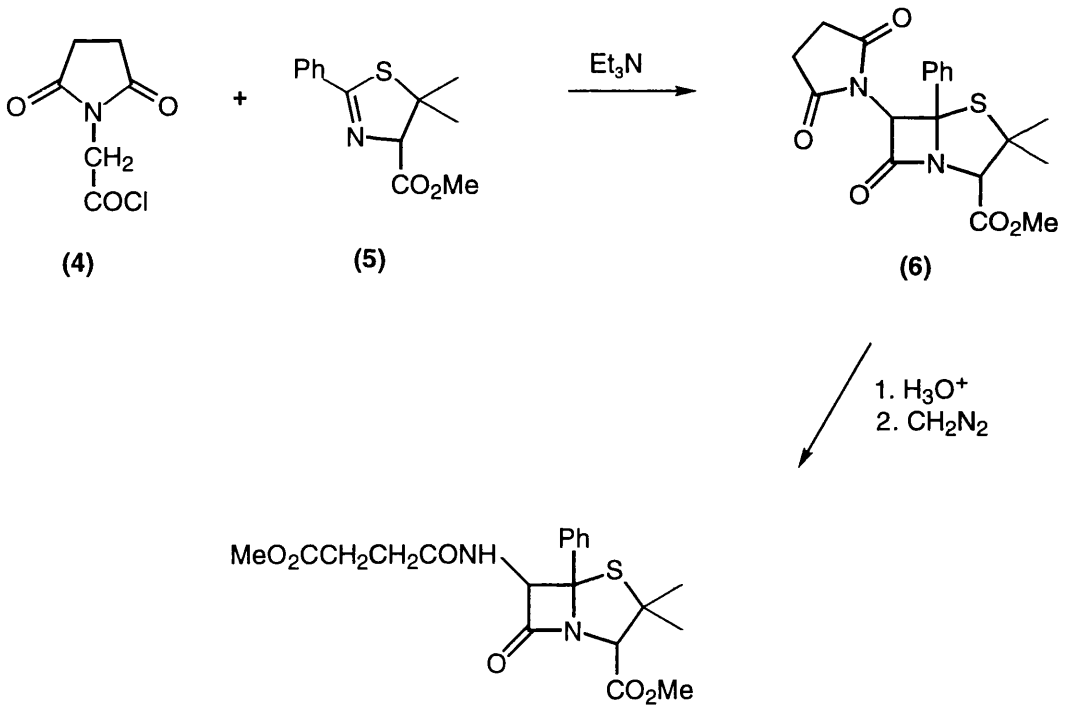
Simultaneous formation of two bonds, either N-1 and C-2 to C-3 and C-4, the so called 'ketene-imine' method, or N-1 and C-4 to C-2 and C-3 by cycloaddition of isocyanates to reactive alkenes, have been studied extensively and are discussed in greater detail in the following sections.

Generally, the preparation of highly substituted β-lactams is more readily accomplished, since these compounds are usually more stable to ring cleavage. Thus, the outstanding problem in β-lactam synthesis was the development of new and efficient routes to the less stable β-lactams.

Section 2.2 Synthesis of Fused β-Lactams

A considerable study has been made of the preparation of fused β-lactams by the combination of ketenes with suitably functionalised thiazolines or thiazines, since these would lead to the generation of the penem and cepham nuclei, respectively.

In 1950 Sheehan [12] *et al* successfully synthesised a 5-phenylpenicillin (**6**), which had the complete structure of the natural penicillins, by the interaction of succinimidoacetyl chloride (**4**) and thiazoline (**5**) in the presence of triethylamine (Scheme 2.2). Base hydrolysis and esterification with diazomethane gave the β-lactam with an acylamino side chain.



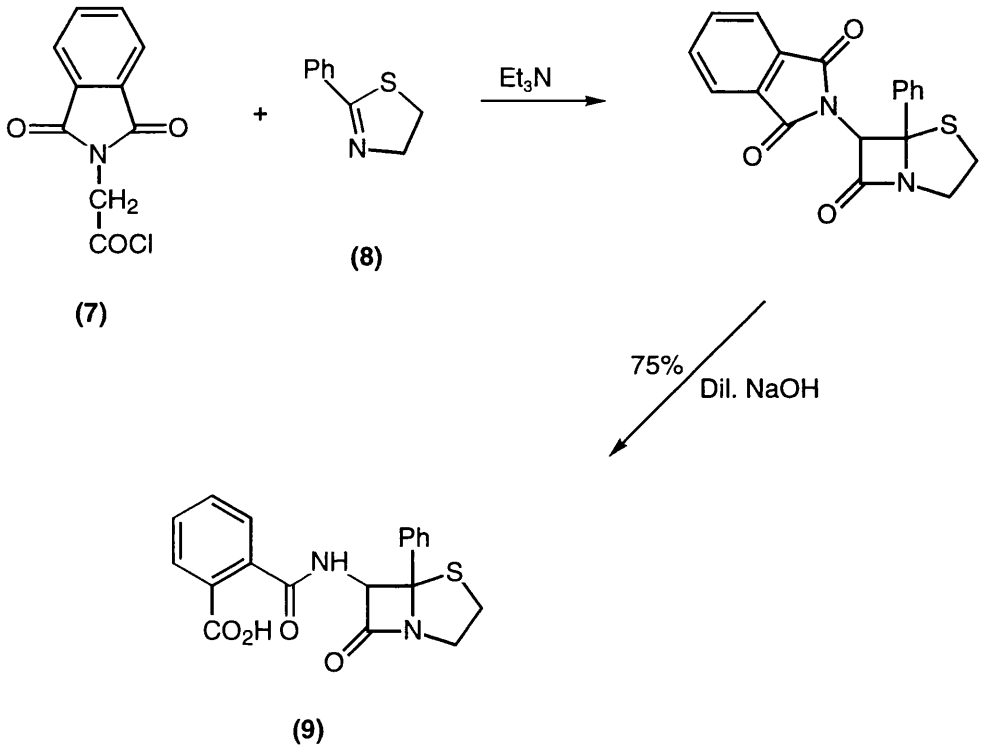
(4) (5) (6)

Scheme 2.2

This work was part of a substantial programme directed towards the total synthesis of penicillins and simpler analogues with similar structural features. Using these conditions a variety of imines and thiazolines formed the β-lactam adducts in every case. The reaction is apparently very sensitive to the nature of the thiazoline ring substituents. A phenyl group in the 2-position of the thiazoline gave higher yields than a methyl, whereas the presence of

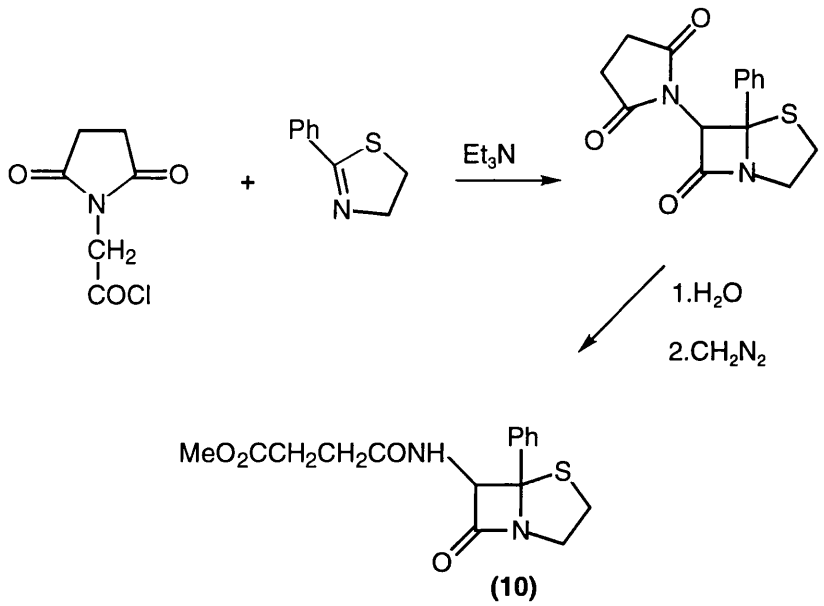
hydrogen, chlorine or sulfhydryl in this position resulted in no isolation of β-lactam product.

An extension of this synthesis was used to prepare β-lactam (**9**) by reacting 2-phenyl-2-thiazoline (**8**) with phthaloylglycyl chloride (**7**) [13] (Scheme 2.3). Sheehan and Ryan [14] had previously reacted phthaloylglycyl chloride with a range of Schiff bases obtaining 1,4-disubstituted 3-phthalimido-2-azetidinones. The phthaloyl protecting group is easily removed, under mild conditions, using hydrazine [15] to liberate the free amino compound without cleaving the β-lactam amide bond. However, although this procedure was convenient for the monocyclic system it cannot be translated to fused systems due to penicillin's instability towards hydrazine. [16]



Scheme 2.3

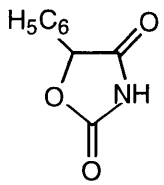
Using a similar method β-lactam (**10**) was formed employing succinimido protection (Scheme 2.4). [17]



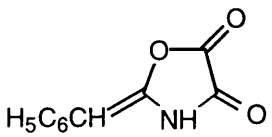
(10)

Scheme 2.4

The succinimido group has advantages over the phthalimido group, since hydrolysis leads to the substituted acetamino functionality characteristic of biologically active natural and biosynthetic penicillins. The heterocyclic compounds (**11**) and (**12**) were also successfully employed as protecting groups[18, 19] since they can be degraded to the phenylacetamido substitution characteristic of benzylpenicillin.



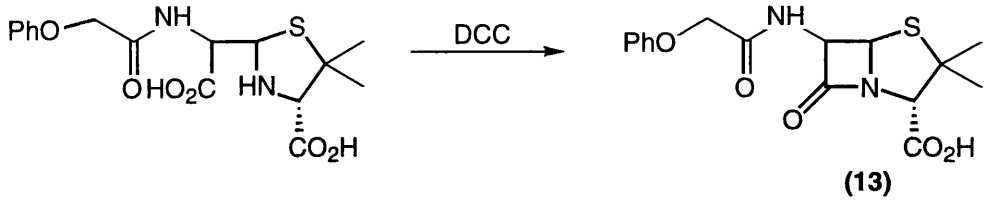
(**11**)



(**12**)

Sheehan and Henery-Logan [20, 21] reported the first rational synthesis of a natural penicillin, Penicillin V (**13**) (Scheme 2.5). As it was generally believed at this time that the instability of penicillin was due to inherent strain in the 4-membered lactam ring, construction of the reactive bicyclic structure was usually left until late in the synthetic sequence. Ring closure was effected using *N,N*-dicyclohexylcarbodiimide, a reagent introduced by Sheehan and Hess [22] for the formation of amides from amine and carboxyl components under very mild conditions. It is interesting to note that carbodiimides and other peptide-

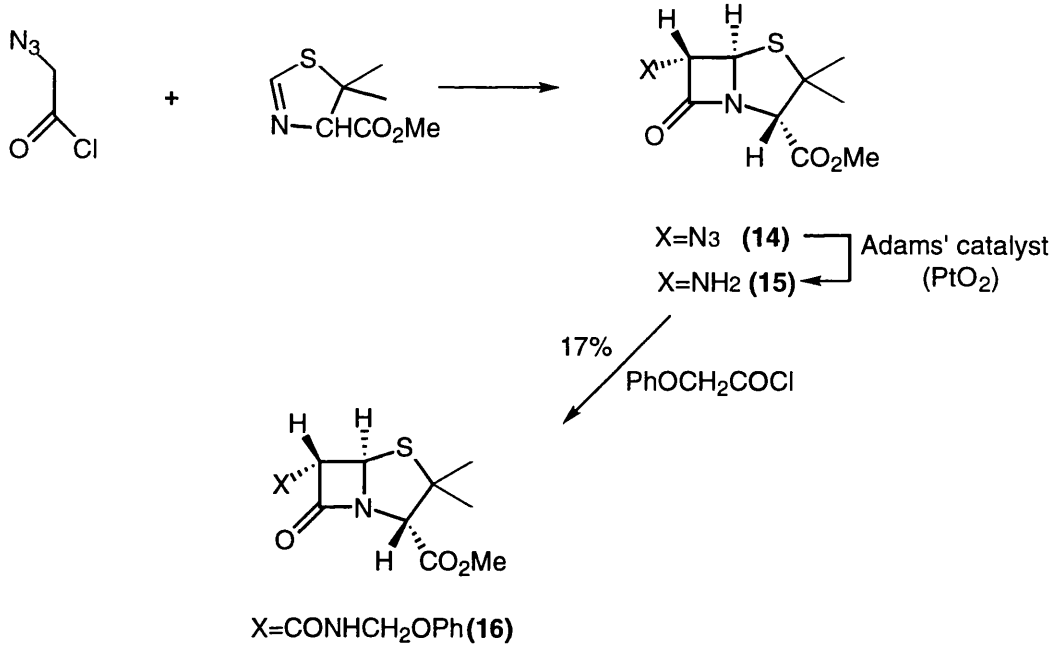
forming reagents have not been explored for the construction of monocyclic β-lactam rings.



(13)

Scheme 2.5

The scission-prone nature of the β-lactam ring prompted Bose[23] and co-workers to introduce azidoacetyl chloride as a valuable reagent for β-lactam synthesis by the 'acid chloride-imine' method.[24] Extension of this newly developed method led to the synthesis of 5,6-*trans*-penicillin V methyl ester (Scheme 2.6). [25] The use of the azido group as a precursor of the amide side chain in penicillin was expected to permit the construction of the β-lactam ring at an early stage of the synthesis since subsequent steps were not detrimental to the ring system.

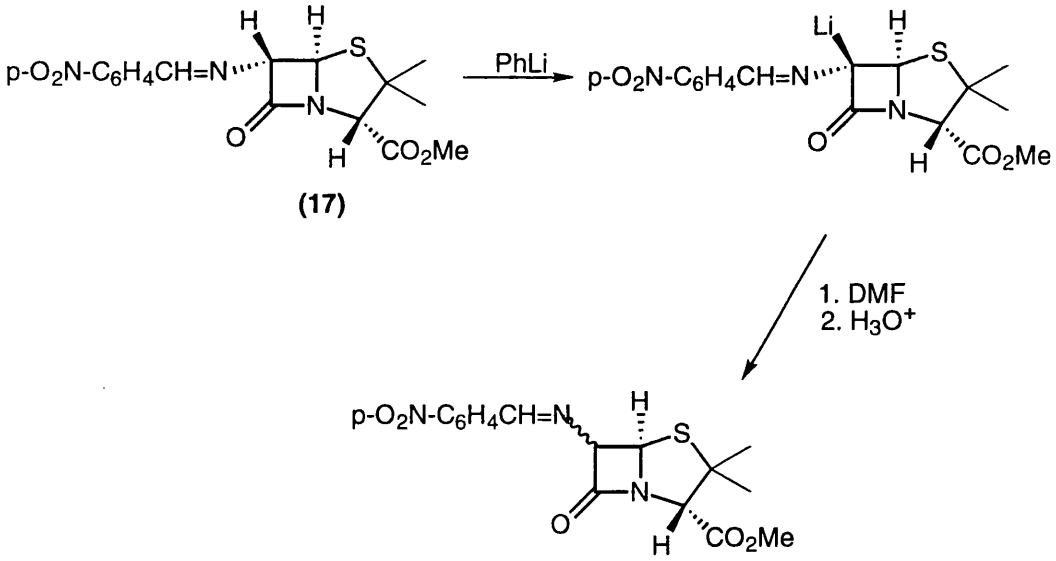


X=CONHCH2OPh **(16)**

Scheme 2.6

The reaction was found to be extremely moisture sensitive and only gave reproducible yields (5-8%) of β-lactam (**14**) after rigorous exclusion of moisture. ^{1}H-NMR studies [26] indicated a 5,6-*trans* stereochemistry. Catalytic reduction using Adams' catalyst gave the impure 6-aminopenicillanic acid ester (**15**) in moderate yield which was directly acylated to form the product 6-*epi*-penicillin V methyl ester (**16**).

A major drawback of most total syntheses of penicillins and cephalosporins is that the newly created stereochemistry of the lactam hydrogen atoms is *trans* rather than *cis*, as it is in the biologically active natural substances. This problem has been overcome by Firestone [27] and co-workers who reported that 6α-aminopenicillins and 7α-aminocephalosporins can be epimerised largely to their β-epimers. The *trans*-form is thermodynamically more stable, probably due to steric factors, and therefore epimerisation is not possible by simple equilibration. However, treatment of the *p*-nitrobenzaldehyde Schiff bases (**17**) with phenyllithium followed by irreversible kinetically controlled protonation afforded predominantly the β-orientated epimer.

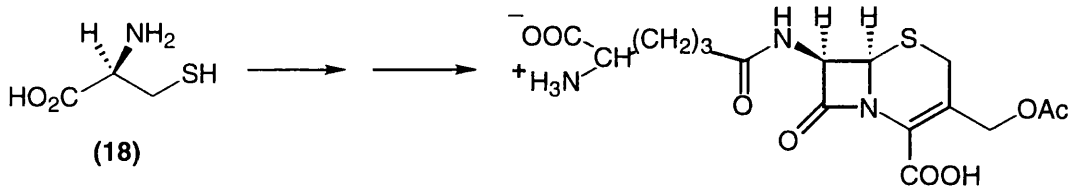


(17)

Thus, an important link between Bose's synthesis of *epi*-penicillins and the total synthesis of naturally occurring penicillins was established.

Section 2.3 Synthesis of Cephalosporins

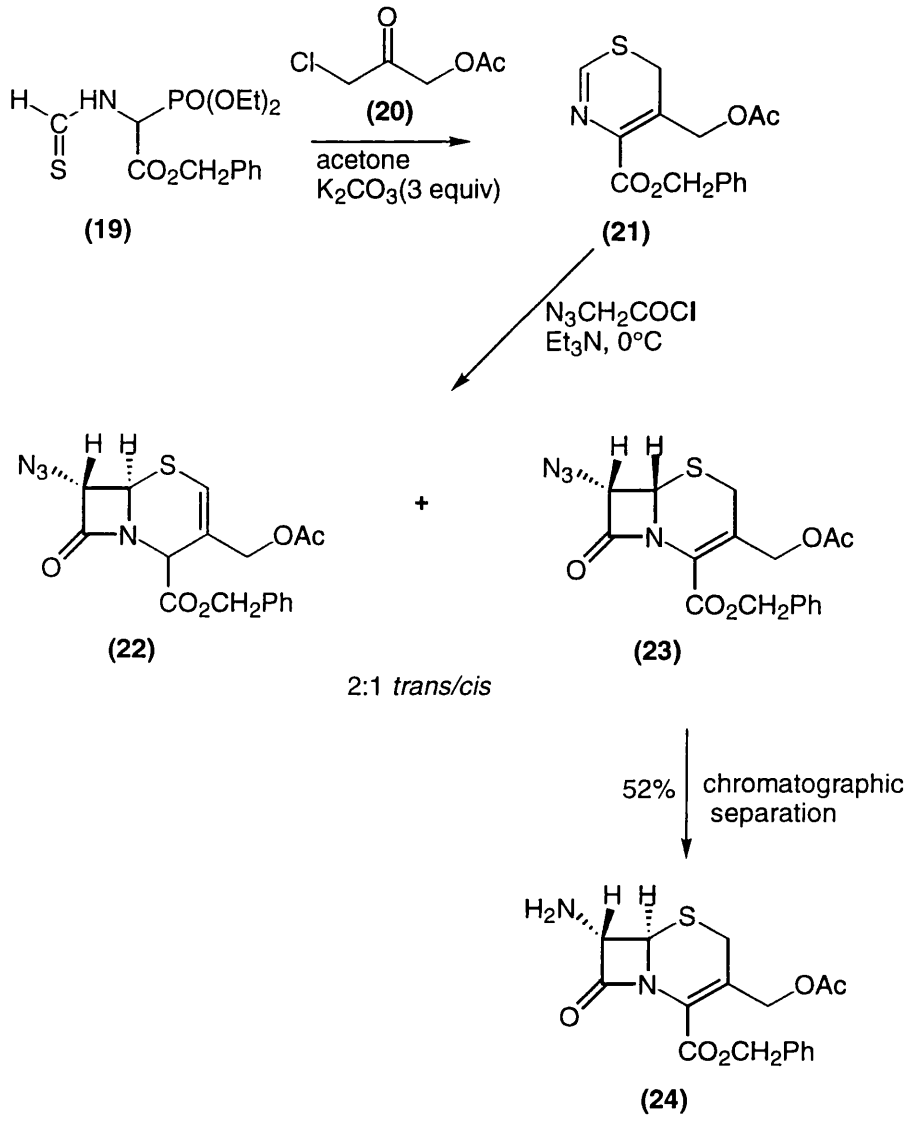
Woodward's synthesis of cephalosporin C [28] shows an elegant approach to complete stereocontrol by employing L-cysteine (**18**) as the chiral building block. A series of chemical transformations delaying construction of the second ring resulted in the first synthesis of this natural antibiotic (Scheme 2.7).



Scheme 2.7

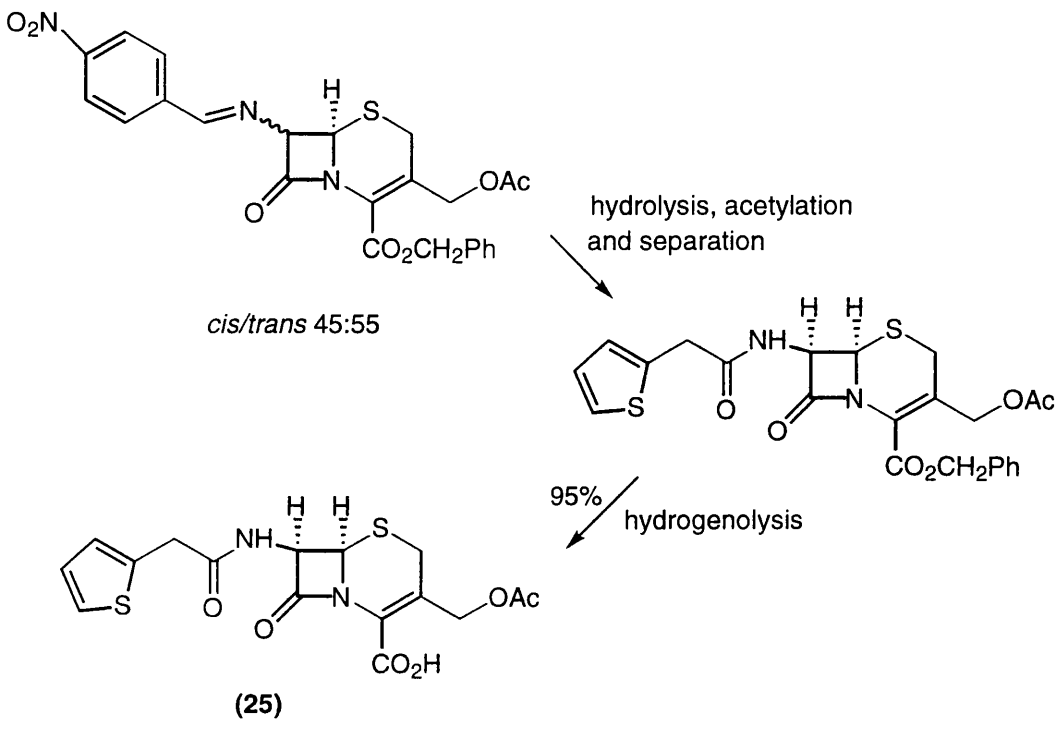
The first syntheses to utilise the highly convergent azidoacetyl chloride/thiazine route were reported in a series of papers by Ratcliffe and Christensen [29-31] following the preparation of a series of semi-synthetic 7α-methoxy-substituted cephalosporins [31] possessing desirable antimicrobial properties.

Thiazinecarboxylates (**21**) were initially prepared by the condensation of thiophosphonoacetates with a range of chloro-2-propanones. Thioformamide (**19**) was treated with 3-acetoxy-1-chloro-2-propanone (**20**) to give a crude thiazine which reacted smoothly with azidoacetyl chloride to give a mixture of azidocephems (**22**) and (**23**) which were separable by chromatography (Scheme 2.8).



Scheme 2.8

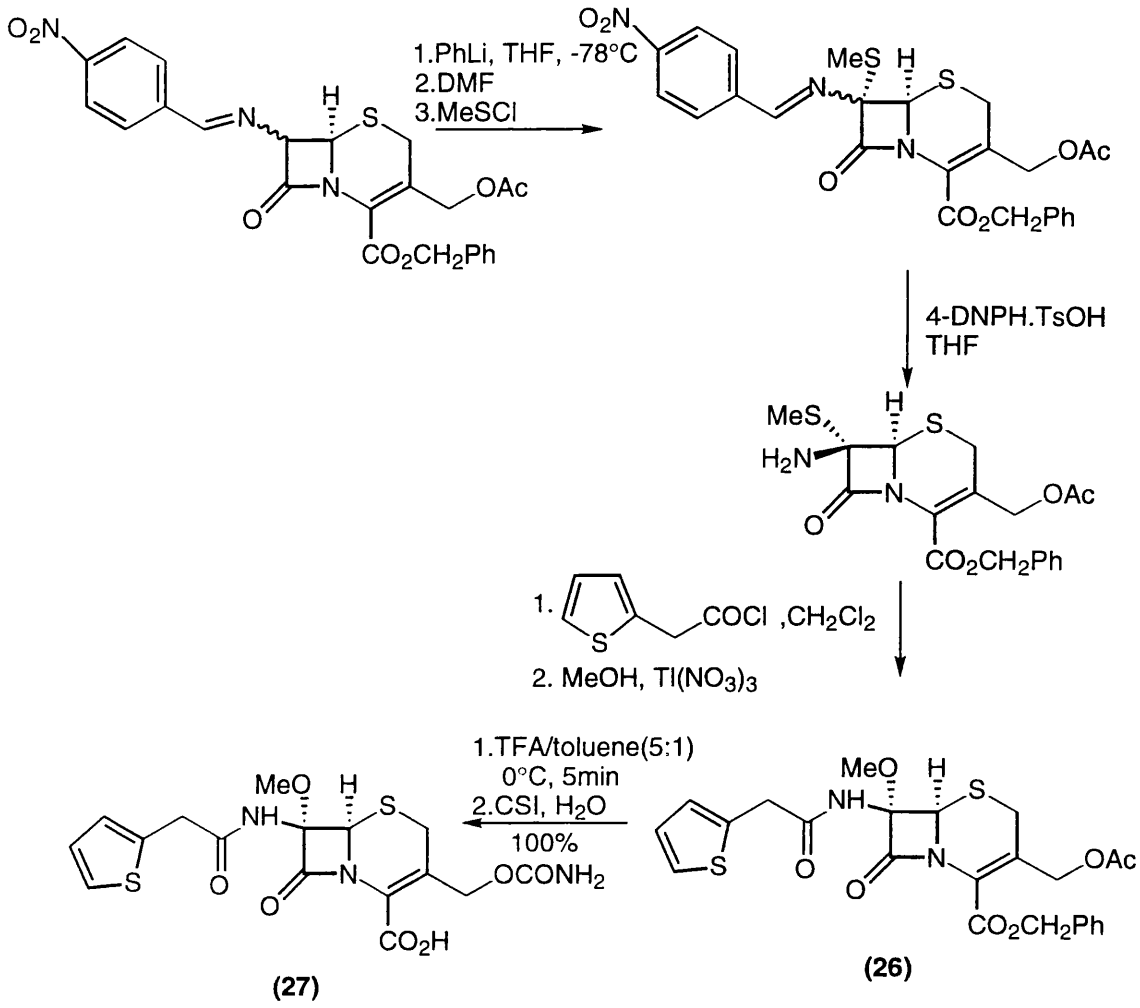
Epimerisation of the obtained *trans*-cephem (**24**) using the Schiff base anion methodology [27] resulted in a 55:45 *trans/cis* mixture. Deprotection followed by acylation with 2-thienylacetyl chloride allowed chromatographic separation of the resulting amides; subsequent hydrogenolysis of the *cis*-isomer gave racemic cephalothin (**25**) in 95% yield (Scheme 2.9)



Scheme 2.9

Ratcliffe and Christensen also applied this general methodology to the synthesis of Cefoxitin, [31] a broad spectrum, semi-synthetic cephalosporin showing good activity against gram-positive and gram-negative bacteria as well as exhibiting a high stability towards β-lactamases.

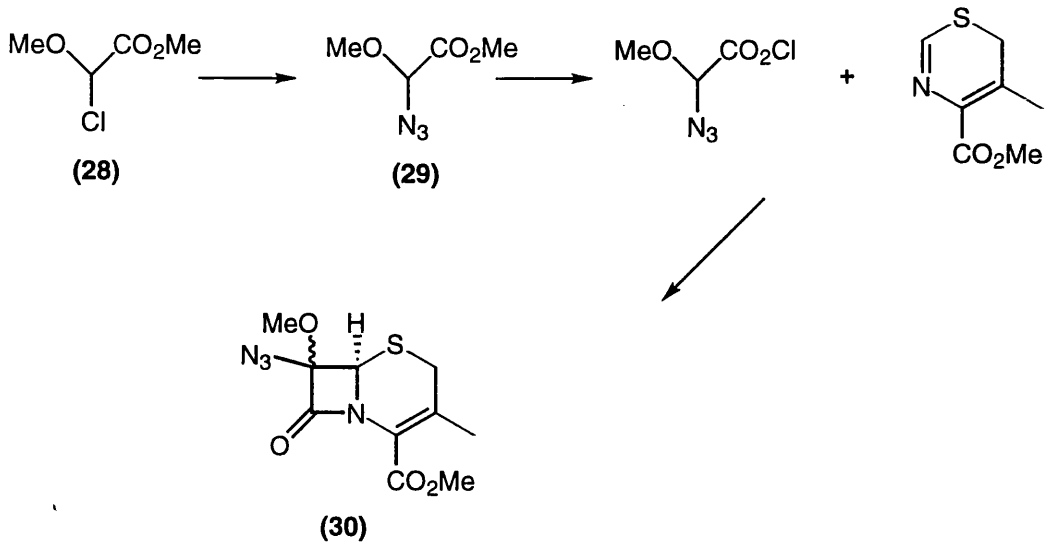
Cefoxitin had been prepared previously from cephamycin C [33] *via* a novel acyl exchange reaction. In this case the synthesis was approached by two different routes, the first following much the same pathway as in the preparation of Cephalothin. It is important to note, however, that in this case no 7β-methoxy-β-lactam was detected in the crude reaction mixture (Scheme 2.10).



Scheme 2.10

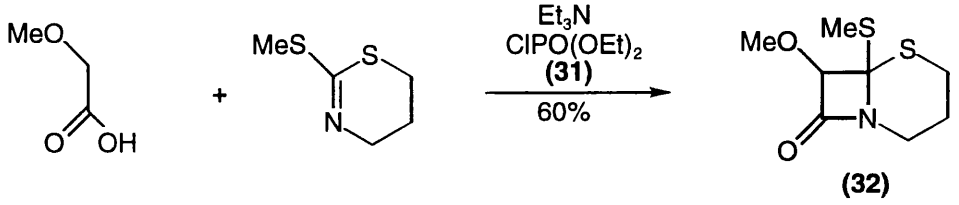
The 7α-methoxy ester (**26**) was converted to the corresponding free acid by subsequent treatment with chlorosulfonyl isocyanate and hydrolysis to give racemic Cefoxitin (**27**) in good overall yield.

A more direct route was also investigated (Scheme 2.11) by converting a methoxy acetate (**28**) into an azido derivative (**29**) which was then be reacted *via* the corresponding acid chloride with a thiazine ring system to give the desired product. A 3:1 mixture of epimeric cephems (**30**) were isolated in low yield. 7-Azido-7α-methoxycephems have previously been shown to be convenient precursors to clinically useful antibiotics. [32]



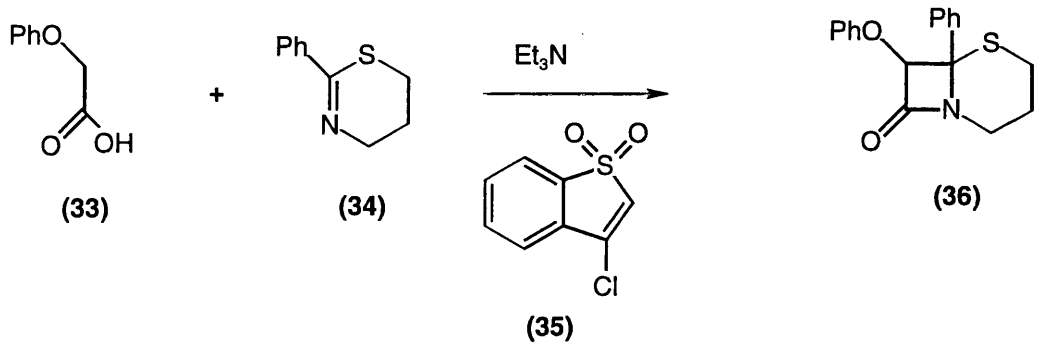
Scheme 2.11

Following the observation that azidoacetyl chloride was prone to explosive decomposition, Bose[34] and co-workers investigated alternative syntheses of α-amido-β-lactams circumventing the use of an azido acid chloride. Taking note of the amide bond formation during annelation to a β-lactam, they examined the possibility of using peptide reagents for β-lactam synthesis. By employing various phosphorylating agents [35] these authors discovered that cyclisation of an imine and an acid in the presence of triethylamine and diethylphosphorochloridate (**31**) results in formation of a β-lactam (**32**) (Scheme 2.12). Other phosphorylating agents proved less successful.



Scheme 2.12

Interaction of thiazine (**34**) and phenoxyacetic acid (**33**) using saccharyl chloride (**35**) afforded the cephem derivative (**36**) in 60% yield (Scheme 2.13). [36]

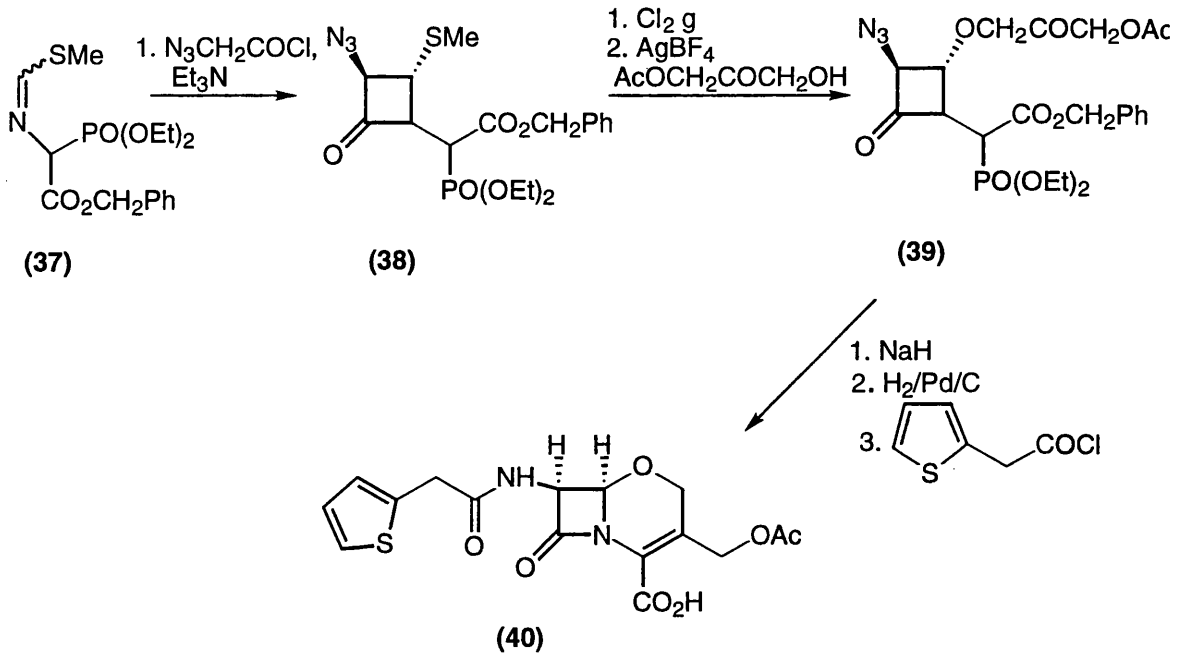


Scheme 2.12

Synthesis of nuclear analogues of the parent cephalosporins, in which the sulfur atom is substituted by equivalent groups, is of interest since it is thought that the sulfur atom could bind to an electrophilic site on the enzyme and hence be responsible for its biological activity. Replacement of sulfur in the bicyclic system by a smaller atom would, therefore, determine whether sulfur is necessary for activity as well as introducing increased ring strain, resulting in a more active β-lactam moiety.

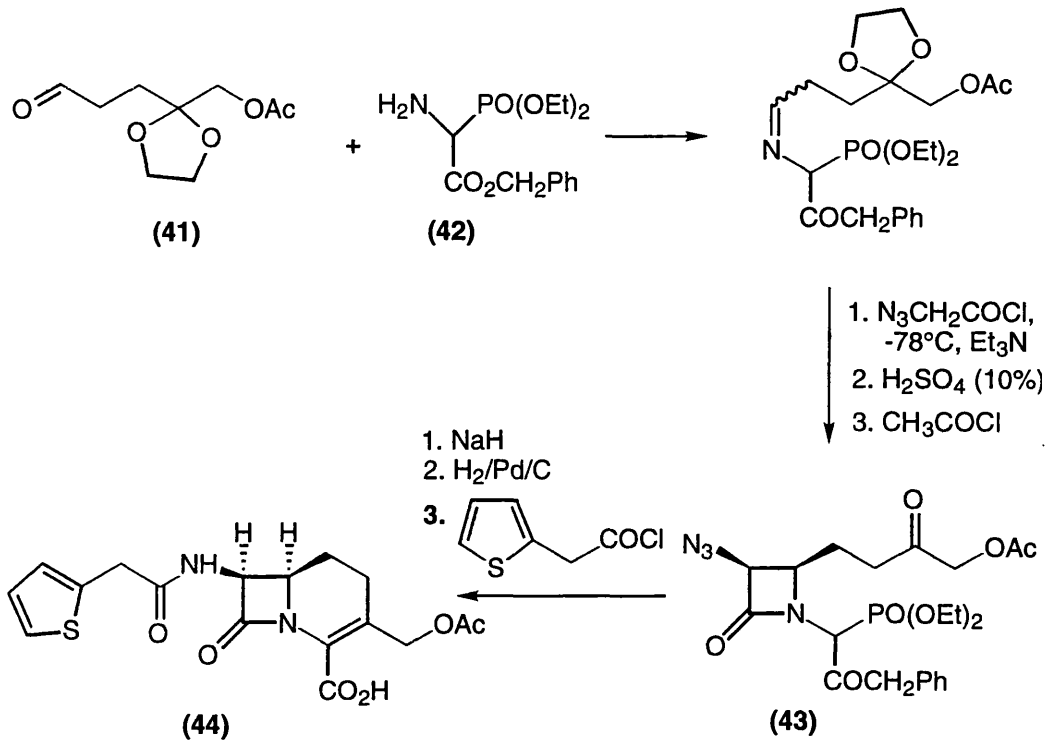
Christensen and co-workers investigated these proposals by synthesising molecules retaining all the features of Cephalothin but replacing the sulfur with either an oxygen [37] or a methylene [38] group.

Benzyl α-(*S*-methylthioimidato)diethylphosphonoacetate (**37**) was formed in a series of steps from benzyl α-aminodiethylphosphonoacetate. Treatment with azidoacetyl chloride afforded the *trans* β-lactam (**38**) although subsequent synthetic manipulations resulted in a mixture of *cis/trans* isomers (1:1) of azetidinone (**39**) since thiol displacement is believed to go through an intermediate iminium ion. Horner-Emmons ring closure of (**39**) followed by separation, hydrogenolysis and acylation, gave racemic 1-oxacephalothin (**40**) (Scheme 2.14). This oxygen analogue proved to be biologically more effective the Cephalothin, showing particularly good antibacterial activity against a strain of *E. coli.* However, it is conceivable that the oxygen replaces the sulfur and binds similarly to an electrophilic site on the enzyme with which these molecules interact. In order to rule out this possibility the heteroatom would, therefore, have to be replaced by a functionality incapable of binding to the enzyme site.



Scheme 2.14

The incorporation of a methylene group provides such a functionality and thus, 1-carbacephalothin (**44**) [37] was synthesised, in a similar manner, from the crucial synthon (**41**). Condensation with the aminophosphonate amine (**42**) gave an unstable Schiff base which underwent a stereospecifically *cis* cycloaddition to (**43**) when reacted with azidoacetyl chloride at -78 °C (Scheme 2.15). Compound (**44**) also exhibited comparable biological activity to the parent Cephalothin, consequently proving the hypothesis that sulfur is not a prerequisite for antibiotic activity.

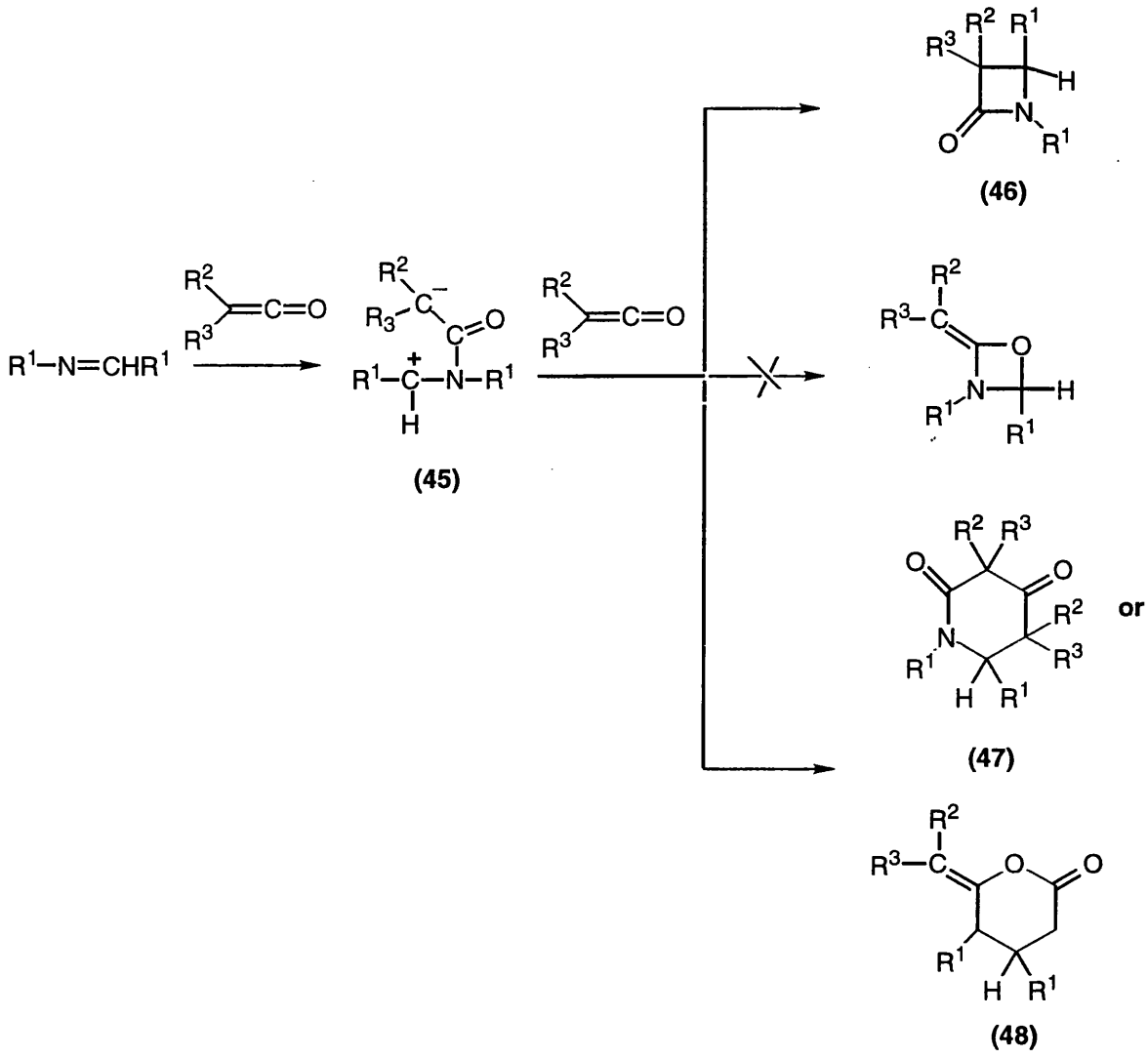

OAc
O
O
(41)
+
H2N
PO(OEt)2
CO2CH2Ph
(42)
N
PO(OEt)2
COCH2Ph
1. N3CH2COCl, -78°C, Et3N
2. H2SO4 (10%)
3. CH3COCl
1. NaH
2. H2/Pd/C
3.
COCl
S
N3
(43)
NH
H
H
CO2H
(44)

Scheme 2.15

Section 2.4 2-Azetidinone Synthesis from Ketene/Imine [2+2] Formal Cycloaddition

The first synthetic route to the β-lactam functionality by Staudinger [11] and co-workers in 1907 involved the reaction of a ketene (or ketene equivalent) with an imine. The reaction of ketenes, in particular disubstituted ketenes, provides a good route to a number of mono- and bicyclic β-lactams.

The choice of ketene precursor is important, because it gives β-lactams with a suitable group at C-3. The structural requirements of the imine are less easy to define due to the inconsistency in the results obtained from different procedures. β-Lactam formation by the ketene-imine interaction may occur by a concerted 1,2-cycloaddition, or by a stepwise process and involves reaction of one molecule of ketene with the imine to generate a zwitterionic species (**45**). The zwitterionic compound can stabilise itself either through ring closure to the β-lactam (**46**) or can further react with a second molecule of ketene in a 1,4-dipolar fashion to afford the six-membered ring adduct (**47**) or (**48**). The course of the reaction is determined by the substituent groups in the reacting species (Scheme 2.16).



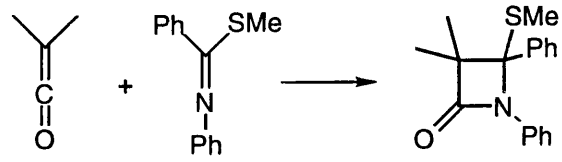
Scheme 2.16

Most of the β-lactams prepared by the early ketene-imine method were derived from dimethyl- [11] or diphenylketene [11,39] and with the Schiff base of an aromatic aldehyde or ketone. A range of other disubstituted ketenes such as phenylmethoxycarbonylketene [40] and diethylketene [41] has also been used, although the successful use of monosubstituted ketenes in the synthesis of β-lactams has yet to be reported. Monosubstituted ketenes react with imines extremely slowly and have been shown to polymerise even under very mild conditions.[11]

The scope of the ketene-imine procedure is limited by the lack of functional group diversity on both ketenes and imines. The ketenes are generally prepared *in situ* by dehydrohalogenation of substituted acyl chlorides

in the presence of a base, usually triethylamine. All of the β-lactams prepared by this method have been obtained from ketenes bearing aryl or alkyl substituents and imines in which both the carbon and nitrogen atoms are substituted by alkyl groups.

As a result of the interest in the relationship between structural features and the reactivity of the penicillin molecule, Holley and Holley [42] synthesised 3,3-dimethyl-4-methylthio-1,4-diphenyl-2-azetidinone (**49**) from a thioimidate and dimethylketene (Scheme 2.17) in order to determine whether the sulfur substituent or fusion of the β-lactam to a five-membered ring was responsible for increased biological activity in benzylpenicillin.

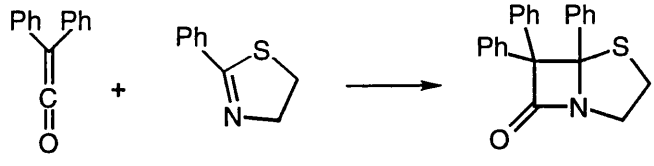


(49)

Scheme 2.17

In agreement with the views expressed by Woodward [7] they concluded that it is in fact fusion of the β-lactam to a five-membered ring which greatly increases the reactivity of benzylpenicillin. However, this reaction was important because it demonstrated the use of thioimidates in the construction of penicillin β-lactam models and could be extended to the synthesis of bicyclic β-lactams closely related to penicillin.

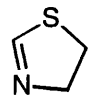
Sheehan and Corey [43] reported the synthesis of the fused β-lactam (**52**) from diphenylketene (**50**) and 2-phenyl-2-thiazoline (**51**) (Scheme 2.18) clearly indicating that this methodology could be applied to the synthesis of structural analogues of the naturally occurring compounds.



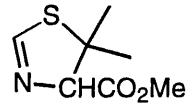
(50) **(51)** **(52)**

Scheme 2.18

2-Thiazoline (**53**) and methyl 5,5-dimethyl-2-thiazoline-4-carboxylate (**54**) were also apparently suitable precursors although no successful results were reported for these compounds.



(53)



(54)

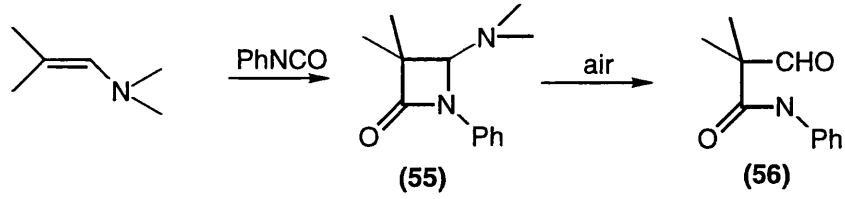
Section 2.5 Azetidinone Synthesis from Alkene/Isocyanate [2+2] Formal Cycloaddition

From a preparative point of view, the cycloaddition reaction of chlorosulfonyl isocyanate (CSI) with a great number of alkenes and dienes is of special interest because it represents a simple method of preparing the β-lactam ring system in a single step.

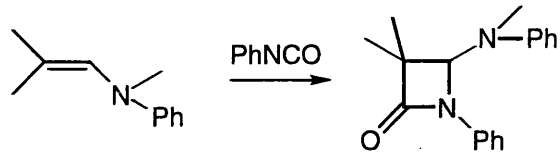
This alternative route to β-lactams has several advantages over the ketene-imine approach, the most important being that usefully functionalised alkenes can be easily constructed and incorporated into the β-lactam ring system. Most of the ketene intermediates are highly reactive and reaction conditions are harsh, preventing incorporation of a sensitive functionality. Isocyanate cycloadditions tend to occur under milder conditions and *N*-protio-β-lactams can be easily isolated, unlike those obtained by the ketene-imine route where the nitrogen atom often carries an alkyl or aryl substituent. However, by far the most important aspect of this procedure is that the stereochemical outcome of the reaction can be predicted, since *cis*-alkenes produce *cis*-β-lactams and *trans*-alkenes produce *trans*-β-lactams.

The first true synthesis of a β-lactam involving simultaneous formation of the C-2/C-3 and N-1/C-4 bonds of the ring was reported by Perelman and Mizsak.[44] Prior to this the only other β-lactam synthesis known which utilised an isocyanate was the phenylisocyanate-diazomethane synthesis of Sheehan.[45,46] Until that time all other known syntheses of β-lactams that created two new bonds entailed simultaneous formation of the same two bonds, i.e., carbonyl to nitrogen and C-3 to C-4. [43]

Perelman and Mizsak found that *N,N*-dimethylisobutenylamine reacted with phenyl isocyanate exothermically to give an oil which had the characteristic β-lactam carbonyl stretch in its IR spectrum (Scheme 2.19).



(55) (56)



(57)

Scheme 2.19

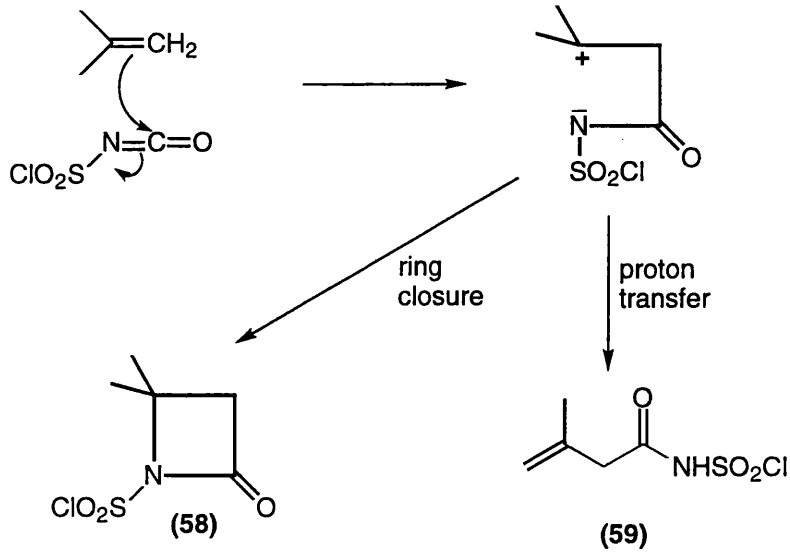
The β-lactam formed (**55**) was unstable and decomposed rapidly on exposure to moist air to the α-formylisobutyranilide (**56**). It was suggested that replacement of one of the *N*-methyl groups by a phenyl substituent would allow delocalisation of the lone pair on nitrogen, stabilising the ring system. Although this β-lactam (**57**) was resistant to both water and acid/base treatment, it also decomposed on several days exposure to the atmosphere.

Previous work [47-49] on the reactions of enamines and isocyanates reported β-carbonylcarboxamides as products, and it is possible that the labile β-lactam intermediates were present but had been overlooked.

The first synthesis of a β-lactam by the cycloaddition of CSI to an alkene was reported by Graf in 1966 [50] (Scheme 2.20). Whereas unactivated alkenes do not normally react with isocyanates, the structural elements in CSI, particularly the polar chlorosulfonyl group; enhance its reactivity such that [2+2] cycloadditions to simple alkenes occur readily.

CSI is probably the most reactive isocyanate known and was discovered by Graf in 1952. [51,52] If CSI is considered as an electrophile then there are two possible points of attack by nucleophilic reagents, either at the sulfonyl group or at the carbonyl function. In addition, the polarisation of the C=N double bond is sufficiently influenced by the sulfonyl group to change the usual mode of reaction observed in isocyanates, enabling cycloadditions to the C=N of the cumulative function to occur.

Unfortunately, the high reactivity of CSI precludes the use of protic solvents. Solvents which are generally inert to CSI include aliphatic, aromatic and chlorinated hydrocarbons, diethyl ether and acetonitrile. The speed of the cycloaddition reaction depends on the polarity of the solvent [53] as well as on the electrophilicity of the isocyanate moiety of the sulfonyl isocyanates and on the nucleophilicity of the C=C double bond.

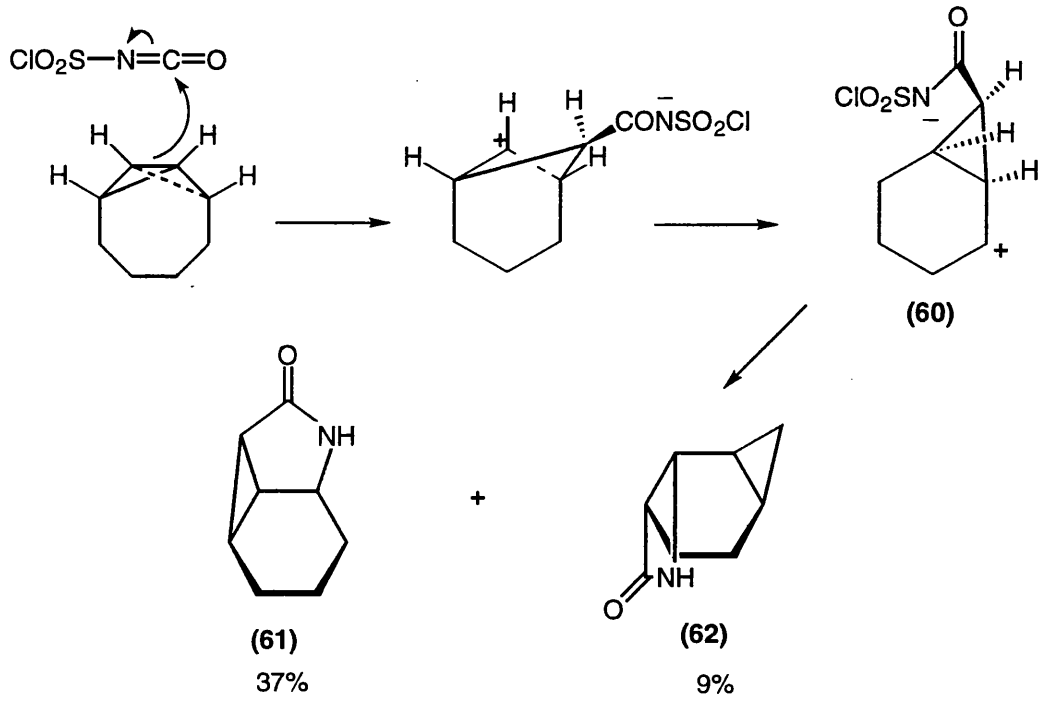


Scheme 2.20

In this first synthesis of a β-lactam using CSI as the electrophilic moiety, the major byproduct of the cycloaddition step was found to be the β-γ-unsaturated carboxamide-*N*-sulfonyl chloride (**59**). Moreover, the 2-azetidinone (**58**) formed was only substituted in the 4-position indicating that the nitrogen of the CSI attached to the more highly substituted carbon atom in Markovnikoff fashion. These observations led Graf to propose a two-step mechanism for the reaction involving the initial formation of a zwitterionic adduct which could stabilise itself through ring closure to the β-lactam or by proton loss to the unsaturated amide (**59**).

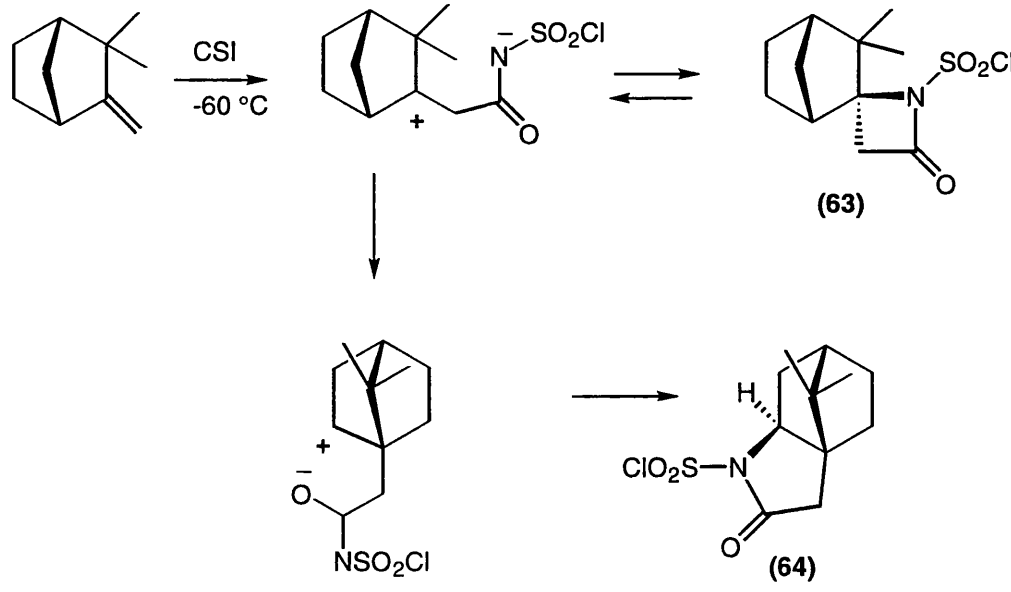
Evidence in support of the proposal was given in an early review [54] which showed that increasing the nucleophilicity of the alkene had a pronounced effect on increasing the rate of reaction. An additional influence was the polarity of the solvent used, the reaction showing a 4×10^4 increase in rate on changing from hexane to the more polar nitromethane. Also, the relative amounts of β-lactam (**58**) and unsaturated amide (**59**) produced in most cases were not influenced by changing reaction conditions.

Paquette[55] and co-workers investigated the addition of CSI to a variety of bicyclo[1.1.0]alkanes and by varying the substituents on the bicyclo system they proposed a mechanism, in agreement with experimental observations, whereby CSI attacks initially at the less hindered bridgehead carbon atom. Subsequent carbonium rearrangement and collapse of the resulting zwitterion (**60**) gave the γ-lactam (**61**) in 37% yield and the β-lactam (**62**) in 9% yield after alkaline hydrolysis (Scheme 2.21).



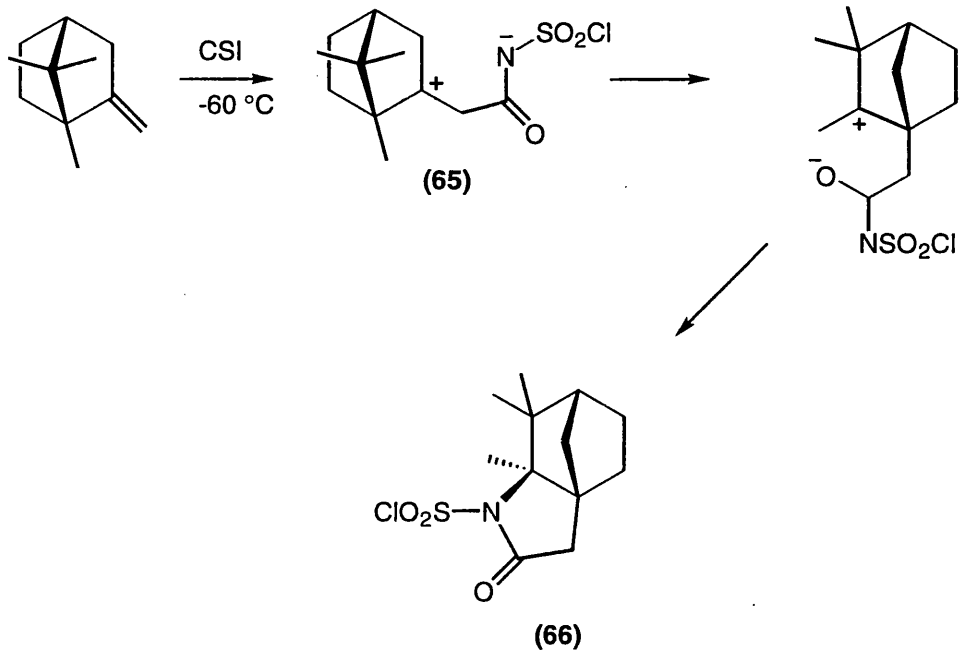
Scheme 2.21

Further support for Graf's proposal was provided by Malpass and Tweddle[56] who investigated the reaction of CSI with camphene and α-fenchene. Interaction of CSI and camphene at low temperatures gave the thermally labile *N*-chlorosulfonyl-β-lactam (**63**) as well as the γ-lactam (**64**) *via* Wagner-Meerwein rearrangement (Scheme 2.22).



Scheme 2.22

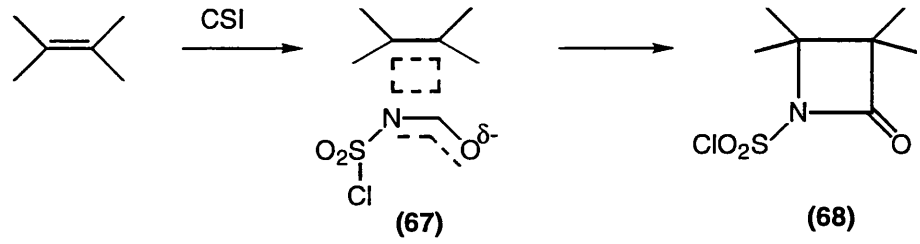
In the logical extension to α-fenchene, CSI was rapidly consumed at -60°C but attempts to observe or isolate a β-lactam intermediate failed (Scheme 2.23).



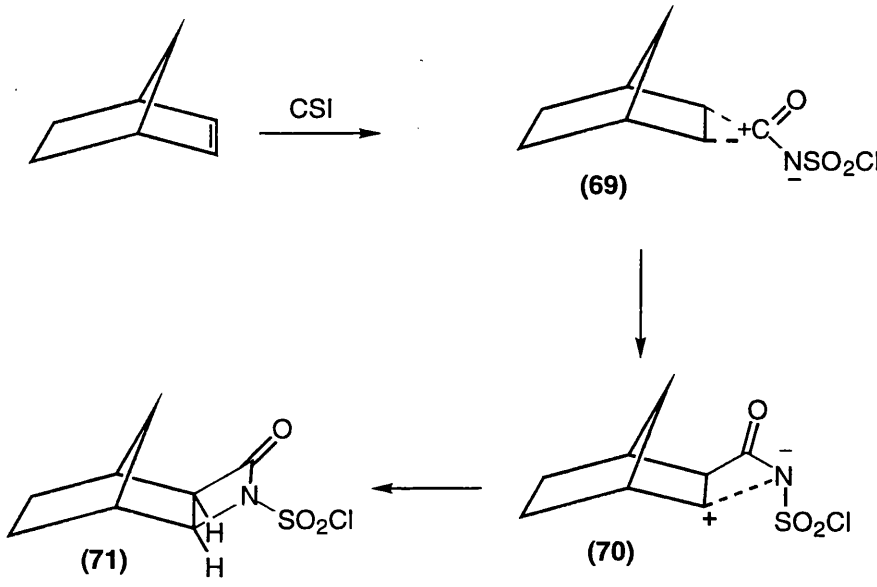
Scheme 2.23

The 7-methyl group in (**65**) evidently inhibits the approach of the bulky *N*-chorosulfonyl group and a Wagner-Meerwein shift occurs to produce ultimately (**66**). This observation of ready rearrangement in the α-fenchene reaction clearly implicates the presence of a dipolar intermediate with ring closure to the γ-lactam (**66**) giving the more thermodynamically stable product. Since camphene reacts with CSI under the same conditions the formation of β-lactam (**63**) must be the product of kinetically controlled cyclisation.

Moriconi, on the other hand, envisaged a (near) concerted, thermally allowed [π2s+π2a] cycloaddition suggesting that this is probably initiated by π-complex formation (**67**), proceeding through a polar transition state (**68**), to the β-lactam. To account for this, CSI, accordingly, acts as the antarafacial component on cycloaddition.



Moriconi cites evidence in favour of this proposal in an early paper[57] by the apparent lack of rearrangement in the reaction of CSI with rearrangement-prone bridged bi- and tricyclic olefins. Addition of CSI to norbornene leads to a single product, the *N*-chlorosulfonyl-*exo*-β-lactam (**71**) (Scheme 2.24). The *exo* stereochemistry of the adduct was determined by NMR and based on the precedented, preferred pathway for additions with similar electrophiles such as benzenesulfonyl azides. [58]

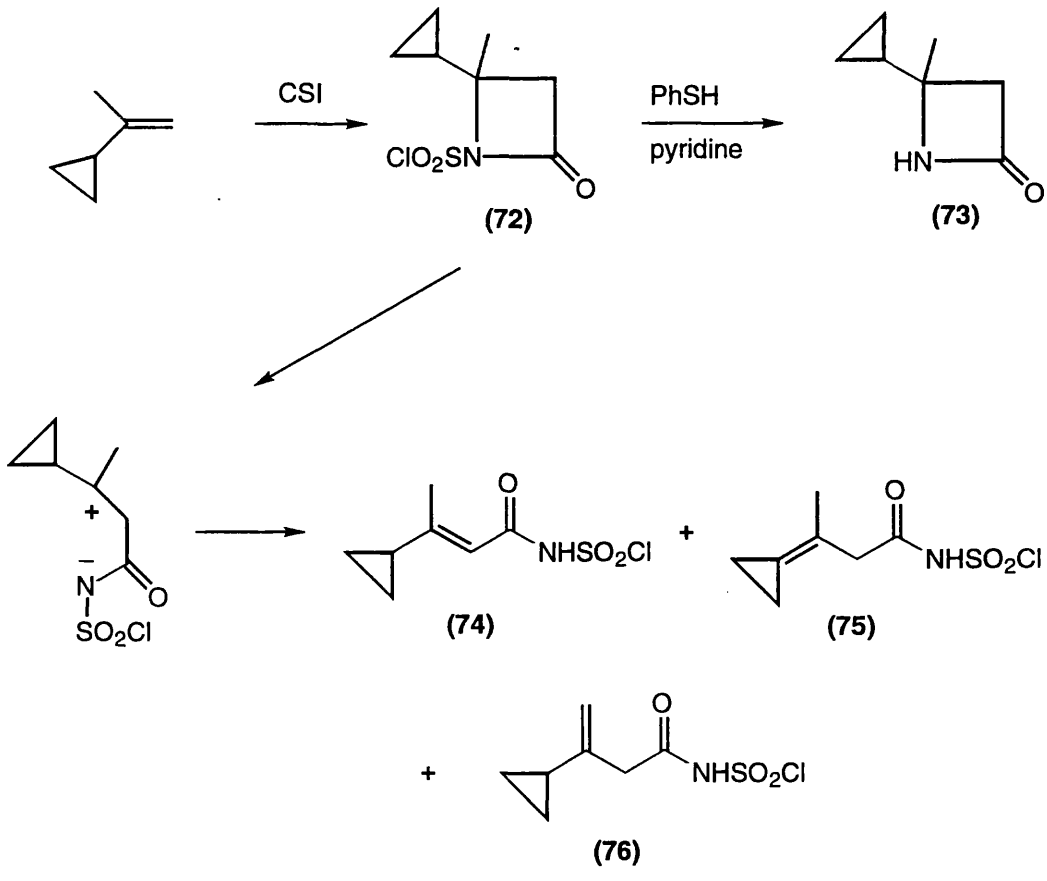


Scheme 2.24

Since the Woodward-Hoffman rules [59] do not allow a simple [π2+π2] concerted cycloaddition, Moriconi's rationale was based on the premise that the two new σ-bonds are not necessarily formed at the same rate. He proposed that initial attack at the preferred *exo* face by the electrophilic CSI resulted in the equilibrium formation of a bicyclic π-complex (**69**), which rearranges to the 1,4-dipole (**70**) where the charged species are in correct alignment for bonding.

That no rearrangement is observed implies that collapse of (**70**) to the β-lactam (**71**) occurs very rapidly.

Barton and Rogido supported Moriconi's view reporting the initial formation of β-lactam (**72**) from 2-cyclopropyl-1-propene and CSI [60] (Scheme 2.25). Immediate quench with thiophenol-pyridine afforded the *N*-protio-β-lactam (**73**). However, in the absence of this quench the intermediate *N*-chlorosulfonyl-β-lactam (**72**) was observed to undergo heterocyclic ring opening to the more stable carbonium ion resulting in the formation of isomeric unsaturated amides (**74-76**).

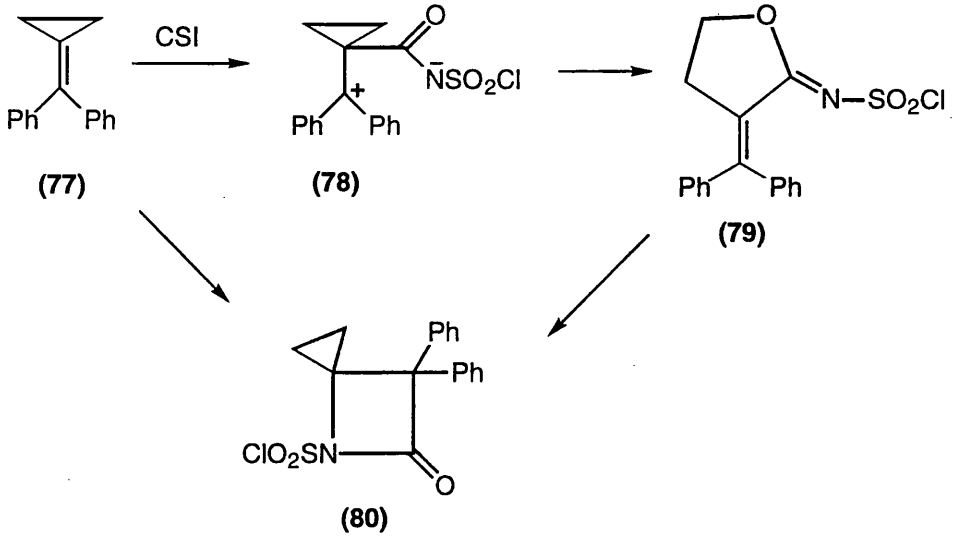


Scheme 2.25

Thus, the addition of CSI to 2-cyclopropyl-1-propene appears initially to involve a concerted cycoaddition affording a β-lactam which rearranges through carbon-nitrogen heterolytic cleavage and prototropic shift.

Barton and Rogido were interested to note a proposal by Dunkelblum [61] who suggested that the reaction of diphenylmethylene-cyclopropane (**77**) with

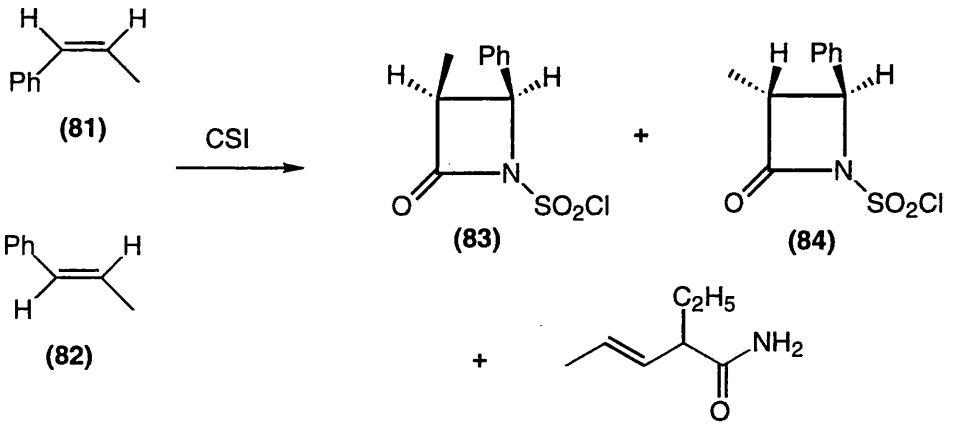
CSI afforded a ring-opened iminolactone (**79**) *via* the initial formation of a dipolar intermediate (**78**) (Scheme 2.26).



Scheme 2.26

This report disagreed with their earlier observations and so a reinvestigation of the reaction was undertaken. [62] In their hands reaction of CSI with (77) afforded a compound whose IR and NMR data strongly suggested the formation of a β-lactam (**80**). After 24 hours at room temperature, the NMR spectrum exhibited the peaks reported for (**79**). This implies a mechanism involving the initial formation of a highly strained β-lactam which suffers heterolysis to the dipolar intermediate (**78**) and then ring closure to the iminolactone supplying further evidence for a concerted pathway in the CSI addition to alkenes.

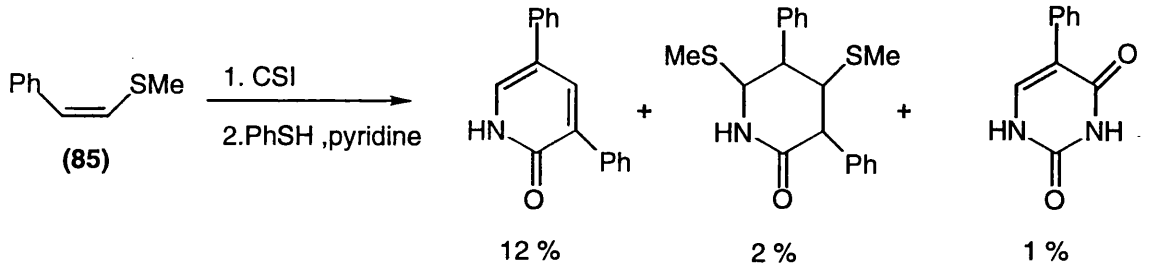
CSI adds stereospecifically *cis* to both *cis*- and *trans*-alkenes yielding [2+2] cycloadducts. *cis* -(**81**) and *trans*-β-Methylstyrene (**82**) were reacted with CSI [63] to give *N*-chlorosulfonyl-*cis* - (**83**) and *N*-chlorosulfonyl-*trans*-3-methyl-4-phenyl-2-azetidinone (**84**), respectively (Scheme 2.27).



Scheme 2.27

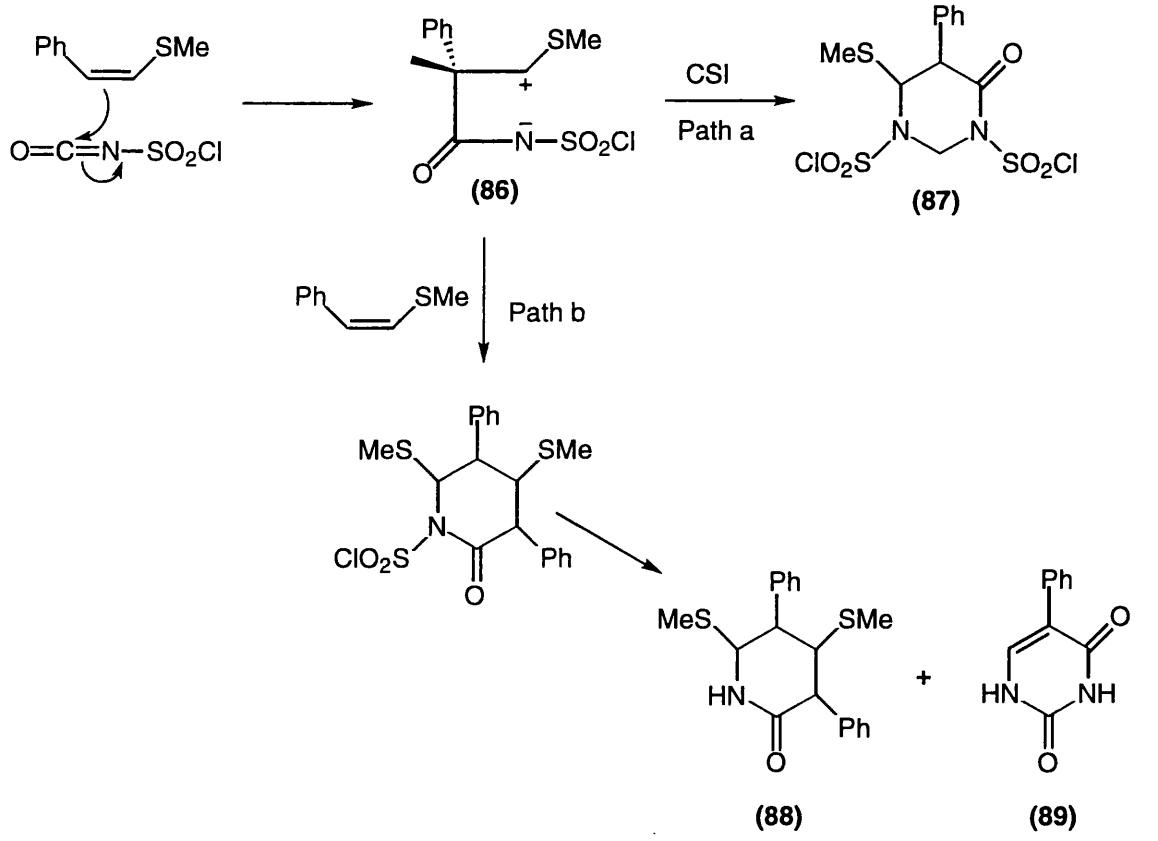
This stereoselective *cis* addition of CSI eliminates the presence of a dipolar intermediate since rotational isomerism would result in a *cis/trans* mixture unless such rotation is hindered, either by dipolar interaction or by steric factors. Concerted cycloaddition, on the other hand, could only occur if the Woodward-Hoffman rules were modified allowing participation of electrons from the sulfur d-orbital or from the lone pair on the nitrogen atom in CSI. Taking into account all the arguments for and against concerted cycladdition, it seems likely that either or both mechanisms may be operative. Substitution on the alkene and hence charge stabilisation determines the extent of C-N bond formation in relation to C-C bond formation in the transition state (or intermediate as the case may be) hence, influencing the mechanism by which the reaction occurs.

The preparation of heterosubstituted β-lactams bearing the fundamental nucleus of the penicillin and cephalosporin antibiotics was attempted by the reaction of CSI with sulfur-substituted alkenes. In connection with previous observations by Graf [65], who found that thiophene reacted with CSI to give the thiophene-carboxamide-*N*-sulfonyl chloride, and not the β-lactam, Hirai *et al* discovered that the addition of CSI to *cis*-β-methylthiostyrene (**85**) gave a mixture of products in low yield upon hydrolysis (Scheme 2.28).[64]



Scheme 2.28

The formation of these products could be explained by the mechanistic pathway shown (Scheme 2.29).

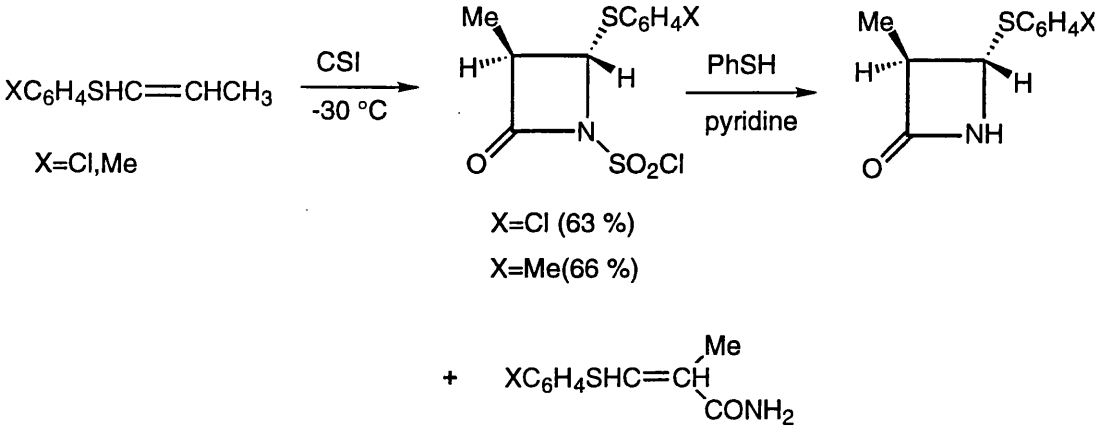


Scheme 2.29

CSI reacts with the alkene (**85**) in the normal manner to give a dipolar intermediate (**86**) which reacts further, either with another molecule of CSI (path a) to give the uracil derivative (**87**) or with the alkene (path b) to produce the pyridone derivatives (**88**) and (**89**) instead of collapsing to the desired β-lactam.

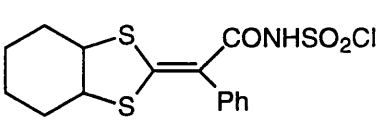
Use of 3-phenylthio-2-propenes also failed to give the product β-lactam and it was only when the benzene ring was substituted in the *para* position with

either a chlorine or methyl group, thus stabilising the 1,4-dipolar intermediate, that the 2-azetidinone rings were isolated (Scheme 2.30).

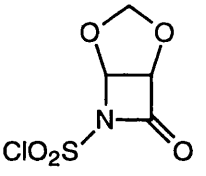


Scheme 2.30

Disappointingly, other heterosubstituted alkenes were reported to produce only the open-chain unsaturated amides (**90**) [66] or gave unstable β-lactams (**91**) [67] which decomposed on attempted purification.

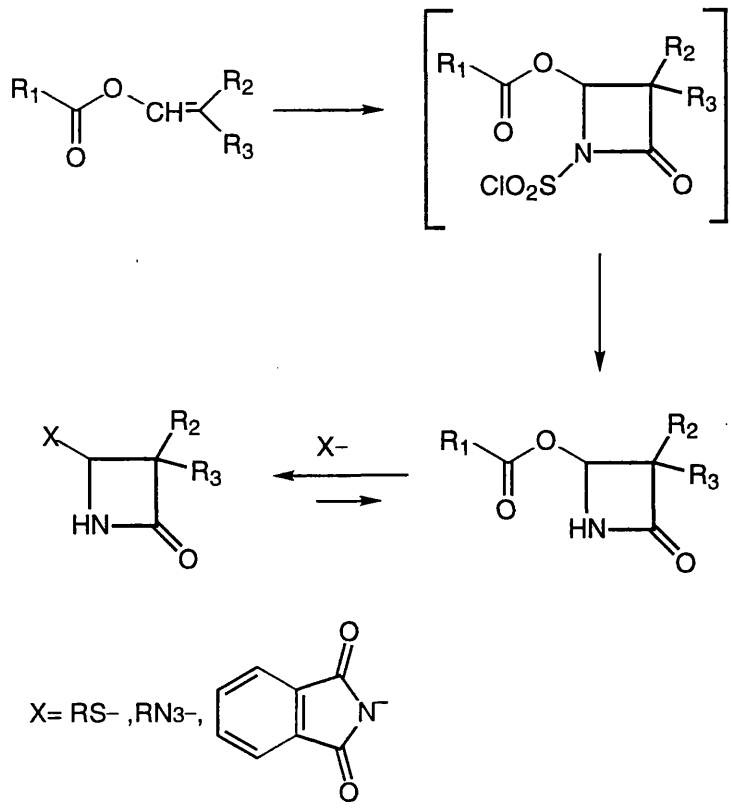


(90)



(91)

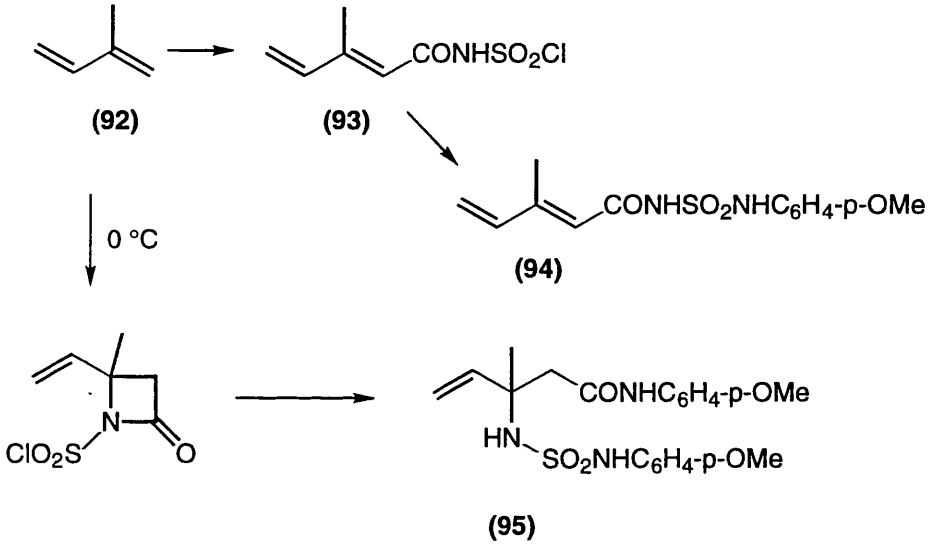
The difficulties associated with the attempted synthesis of heterosubstituted β-lactams was elegantly overcome by the use of vinyl esters as the alkene components.[68] Unfortunately, the azetidinones formed were sensitive to acid, base and heat and, therefore, had to be prepared under carefully controlled conditions at low temperatures. However, this reaction is synthetically very important for the preparation of penicillin-related compounds since the acyloxy group can be readily exchanged with a variety of nucleophiles. For example, 4-thio-, 4-azido- and 4-phalimido-β-lactams have all been prepared in good yield in this manner (Scheme 2.31).


R1
O
CH
R2
R3
O
R1
O
R2
R3
O
N
ClO2S
O
X
R2
R3
HN
O
X-
R1
O
R2
R3
O
HN
O
X= RS- ,RN3-,
O
N
O

Scheme 2.31

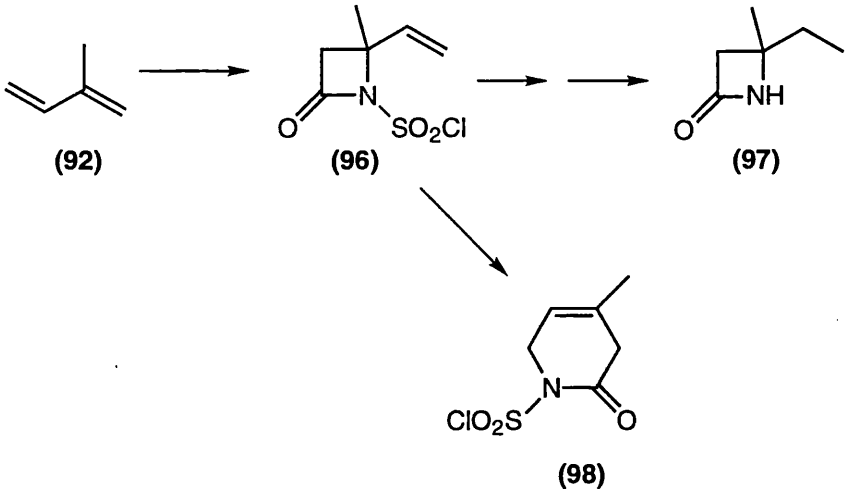
Section 2.6 2-Azetidinone Synthesis from Diene/Isocyanate [2+2] Formal Cycloaddition

Work with other types of unsaturated systems has also been reported in the literature. In particular, Hoffman and Diehr [69] made important observations in the area of conjugated dienes and their reaction with CSI to give β-lactams with vinylic side chains. They discovered that isoprene (**92**) reacts with CSI at room temperature to give the *N*-chlorosulfonyl carboxamide (**93**) which was isolated as the *p*-methoxyanilide (**94**). In contrast, the dianilide (**95**) was isolated when the reaction was repeated at 0 °C. The presence of a β-lactam intermediate was deduced from the nature of the isolated products (Scheme 2.32).



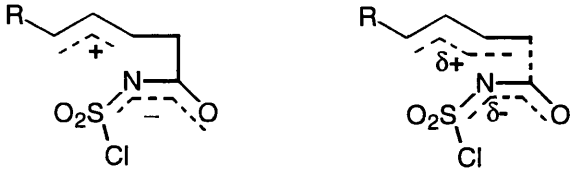
Scheme 2.32

Since Hoffman and Diehr failed to assign a specific structure to their cycloadduct, Moriconi and Meyer [70] re-examined the reaction of CSI with a variety of conjugated dienes at lower temperatures. Again, using isoprene (**92**) as the diene substrate, they isolated the *N*-chlorosulfonyl-β-lactam (**96**). After careful hydrolysis and reduction (Pd-C) of the vinyl side chain, the same 3-ethyl-3-methyl-2-azetidinone (**97**) was obtained *via* CSI addition to 2-methylbutene. The 1,2-cycloadduct (**96**) ring opened on warming and recyclised to afford a lactone (**98**) after hydrolysis (Scheme 2.33).

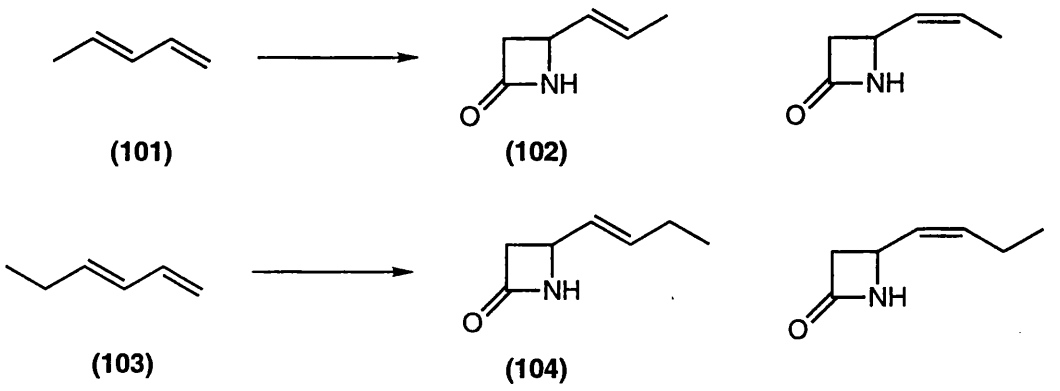


Scheme 2.33

Other conjugated dienes were also discussed in a continuation of Moriconi and Meyer's earlier work on such systems. [71] In theory, unsymmetrical conjugated dienes such as (**101**), (**103**) could react with CSI either at the terminal or internal double bond to give two similarly stabilised secondary allylic carbocations. These appear as a dipolar intermediate (**99**) in a stepwise addition or as a polar transition state (**100**) in a near-concerted process.



Ring closure to the β-lactams would therefore result in formation of two possible regioisomers, however, in practice the CSI is seen to add in a Markovnikoff orientation to the terminal double bond. The product β-lactams obtained (**102**) and (**104**) were found to be a mixture of geometric isomers at C-4 (Scheme 2.34) further implicating the presence of Moriconi's proposed allylically stabilised carbocation intermediates.

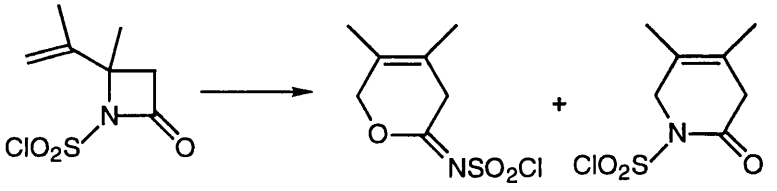


(101) (102)

(103) (104)

Scheme 2.34

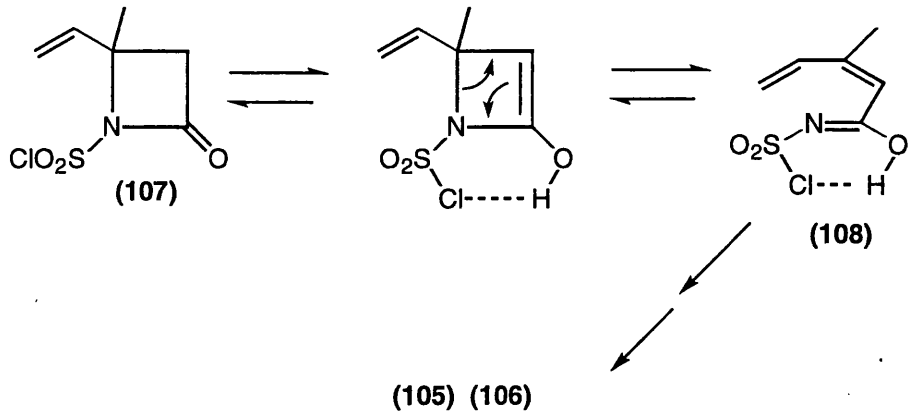
In no instance was the symmetry-allowed [π4s+π2s] reaction observed since the participation of CSI as a π2s component is severely hindered, in molecular orbital terms, by the orthogonal $\pi_{C=O}$ system on one side and the tetrahedral d-p π_{SO2Cl} on the other. However, the *N*-chlorosulfonyl-β-lactam products were observed to thermally rearrange to *N*-(**105**) and *O*-1,4-cycloadducts (**106**) in the presence of polar solvents probably in a stepwise fashion [72-74] *via* the ring-opened dipolar intermediate (**99**) (Scheme 2.35).



(105) (106)

Scheme 2.35

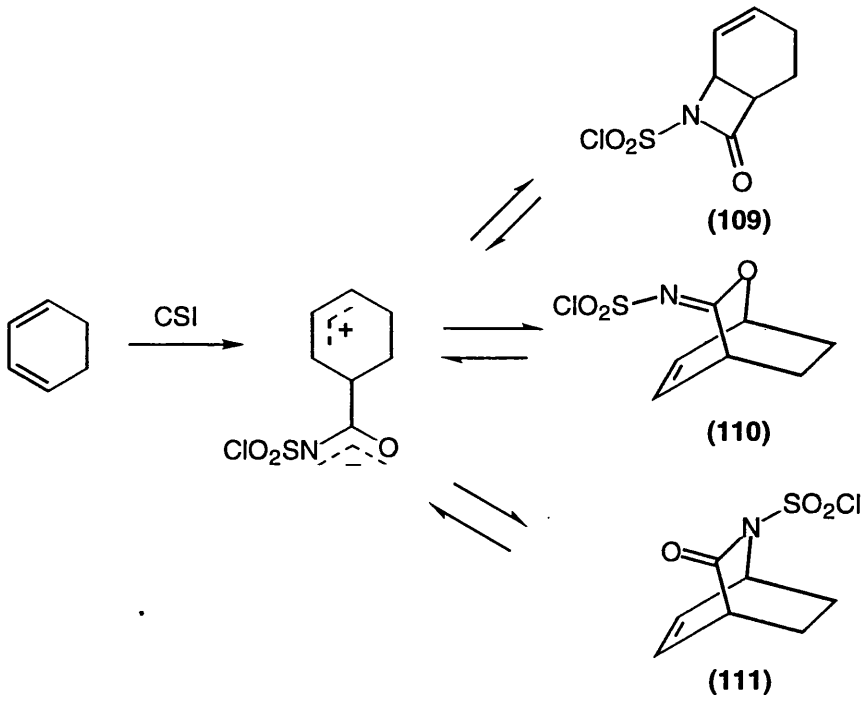
A second postulated pathway involves a sequence of symmetry-allowed transformations which could occur after enolisation of the initially formed β-lactam (**107**) to the azetine (**108**). The formation of the azetine is enhanced by the intramolecular H-bond to the chlorine atom. However, this alternative is much less probable (Scheme 2.36).



Scheme 2.36

The cycloaddition reactions of CSI to cyclic 1,3-dienes is of interest for a number of reasons. It has already been observed [70] that acyclic dienes undergo 1,4-addition even though the diene unit adopts a *transoid* configuration. Cyclic 1,3-dienes naturally adopt a *cisoid* conformation and hence we would expect these compounds to behave similarly. If this is so, then 1,4-addition to cyclic dienes would provide a simple route to aza- and oxabicyclic systems (*via* 1,4-cyclisation through nitrogen and oxygen, respectively).

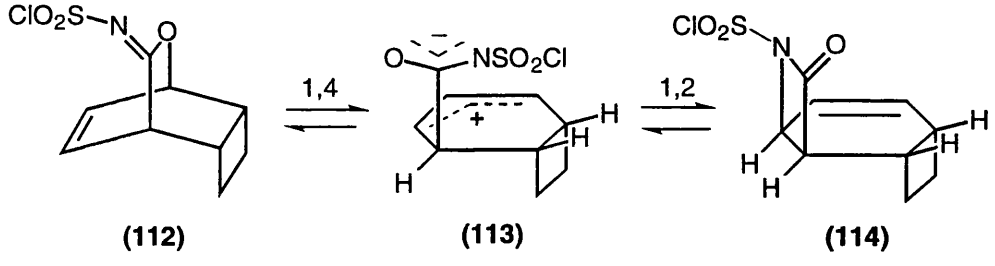
The first reported addition to a cyclic diene was by Durst and O'Sullivan[75] who formed a stable *N*-chlorosulfonyl-β-lactam from 1,3-cyclooctadiene. Malpass and Tweddle investigated the reaction of 1,3-cyclohexadiene with CSI at room temperature producing the bicyclo-β-lactam shown (**109**). It is interesting to note that the initial β-lactam formed rearranged on standing to give the 1,4-cyclisation product (**110**), which underwent further heterolytic cleavage under reflux, finally cyclising through nitrogen to the azabicyclo-adduct (**111**) (Scheme 2.37).



Scheme 2.37

Malpass and Tweddle proposed a mechanism involving a dipolar intermediate (**113**) in order to explain the products obtained, giving evidence for a true dipole in the [2+2] cycloaddition step.

The IR spectrum of a solution of the unstable iminolactone (**112**) showed the presence of a β-lactam (**114**) after one hour, clearly demonstrating that these two products were derived from a common dipolar intermediate (**113**), which cyclises to give 1,2-addition products under kinetic control and 1,4-adducts under thermodynamic control (Scheme 2.38).

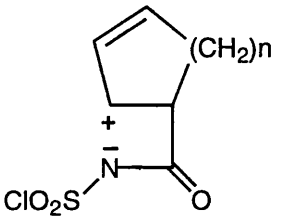


(112) **(113)** **(114)**

Scheme 2.38

Their initial studies were extended to include a wider range of ring sizes, and it was found that both 1,2- and 1,4-addition of CSI to a number of cyclic dienes could be achieved.[76] The initially formed β-lactams were reasonably stable but the ease of thermal rearrangment to the 1,4-cycloadduct decreased

with increasing ring size. This suggests that the mechanism proceeds through a ring-cleaved zwitterion (**115**), where the allylic cation is less easily stabilised by π-bond resonance as the larger ring geometry lessens the overlap necessary for effective stabilisation.

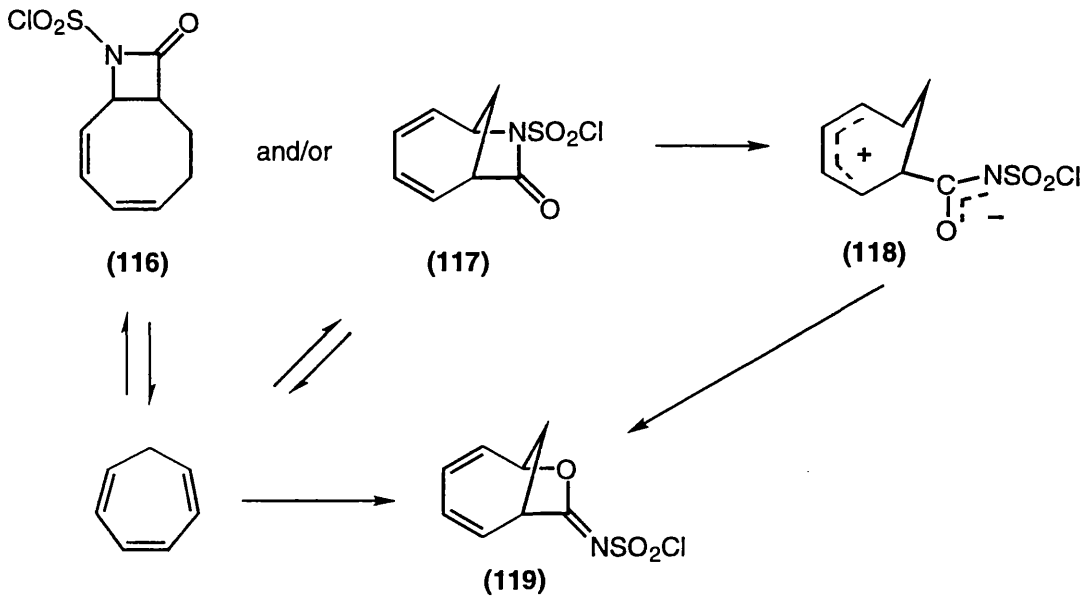


(115)

This reaction is important since the experimental conditions can be manipulated in order to gain a high degree of control over which isomer is produced. There is precedent that changing the polarity of solvent [56] affects the degree of cyclisation through oxygen (to give iminolactones) or through nitrogen (to give lactams) and research carried out by Speckamp *et al* [77] on the 1,4-addition of CSI to a vinyldihydronaphthalene has shown that control may also be achieved through choice of reaction time and temperature.

The formation of such [2+2] cycloadducts from the reaction between CSI and acyclic and cyclic conjugated dienes suggested the possibility of similar reactivity between CSI and conjugated trienes. Moriconi *et al* [78] reported the first such case in the reaction between CSI and cycloheptatriene.

On stirring equimolar amounts of cycloheptatriene and CSI at room temperature they reported a single *N*-chlorosulfonyl iminoether (**119**) arising from 1,6-cycloaddition, with trace amounts of a second *N*-cyclised product (**116**) or (**117**) which could not be isolated (Scheme 2.39).



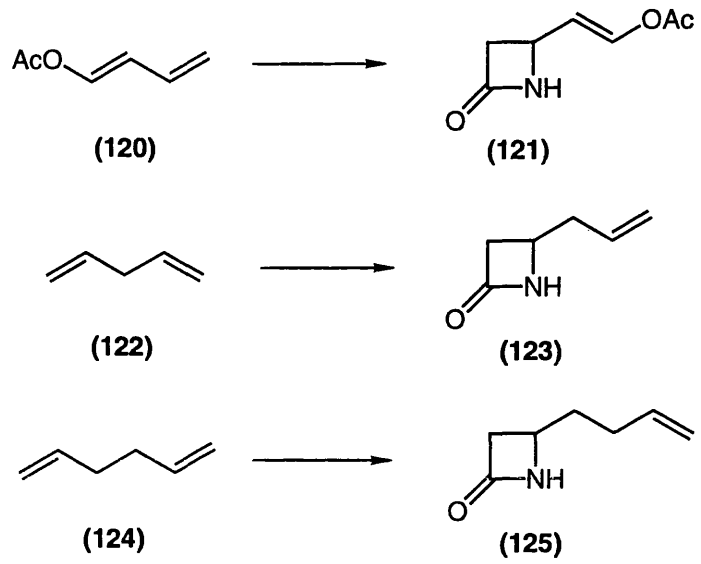
Scheme 2.39

In view of their theory postulating that β-lactam formation precedes, rather than follows, the generation of Graf's open 1,4-dipole [79] the authors suggested an electrophilic, near-synchronous process [80] leading to 1,2- (**116**) and/or 1,6-cycloaddition (**117**) products. Thermal and irreversible ring opening of either affords the dipolar intermediate (**118**) which stabilises itself by cyclisation to the thermodynamically more stable iminoether (**119**).

Malpass [81] reinvestigated the reaction of CSI with cycloheptatriene choosing a less polar solvent, CCl_4. The reaction in CCl_4 was much slower and initially, formation of the *N*-chlorosulfonyl-β-lactam (**116**) was observed. However, after refluxing the crude mixture for 7 days gradual rearrangement to (**117**), followed by ring opening and subsequent recyclisation occurred giving the product cycloadduct (**119**). A dipolar addition of CSI seems reasonable in view of the considerable stabilisation available to the cationic centre in (**118**). Thus, in contrast to Moriconi's postulate, Malpass implied that (**117**) was clearly the ultimate product of thermodynamic control and not an unstable precursor of (**119**) formed *via* a concerted [π6s+π2a] cycloaddition. Furthermore, in accord with a dipolar mechanism, the reaction of CSI with cyclooctane did not occur to a measurable degree in nonpolar solvents.

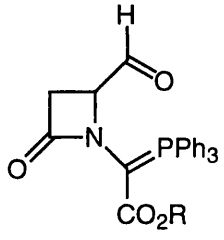
Southgate and co-workers [82] undertook an examination of the cycloaddition reactions of CSI with a number of dienes, utilising this reaction in the preparation of cephalosporin precursors. Thus, from 1-acetoxy-1,3-butadiene (**120**) they obtained β-lactam (**121**), whereas the nonconjugated 1,4-penta-

(**122**) and 1,5-hexadienes (**124**) furnished β-lactams (**123**) and (**125**), respectively, on reaction with CSI (Scheme 2.40).



Scheme 2.40

The unsaturated vinyl substituent at the 4-position of the azetidinone served as a useful precursor to the appropriately functionalised phosphorane (**126**). The intramolecular Wittig reaction of such an azetidinylphosphorane grouping with an aldehyde or ketone has been widely used for the preparation of novel cephalosporins. [83, 84]

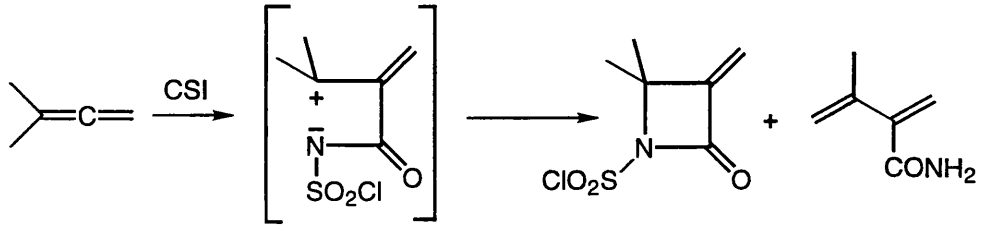


(**126**)

Section 2.7 2-Azetidinone Synthesis from Allene/Isocyanate [2+2] Formal Cycloaddition

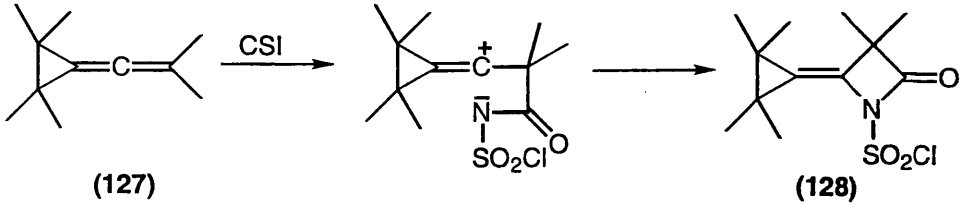
The reaction between an allene and CSI generates a β-lactam with an exocyclic double bond. A class of extremely active compounds called the ' ene-type ' β-lactam antibiotics has been shown to possess such a C-3 alkylidene side chain and exhibit strong antibacterial properties, in addition to possessing good β-lactamase activity. The medicinal importance of such compounds, [85-87] coupled with the recent surge in the number of papers published on this subject, has meant they have become valuable synthetic targets.

Symmetrically and unsymmetrically substituted allenes [88] react with CSI in a two-step, 1,2-dipolar cycloaddition mechanism consistent with the mechanism proposed by Graf.[65] CSI adds predominantly to the central carbon of the allenic system generating the more stable, tertiary carbonium ion which can rotate to gain additional stabilisation as an allylic cation. The two electron-withdrawing groups adjacent to the N-atom serve to stabilise the developing negative charge (Scheme 2.41).



Scheme 2.41

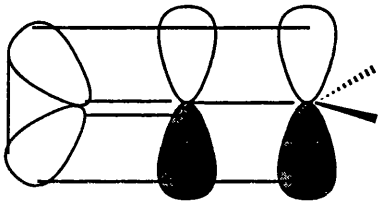
Alkylidenecyclopropanes, however, exhibit a more complicated behaviour toward CSI. 2-Methyl-1-(tetramethylcyclopropylidene)-2-propene (**127**) reacts with CSI to form lactam (**128**) exclusively, as a result of electrophilic attack at the terminal allenic carbon (Scheme 2.42) [89]



(127) **(128)**

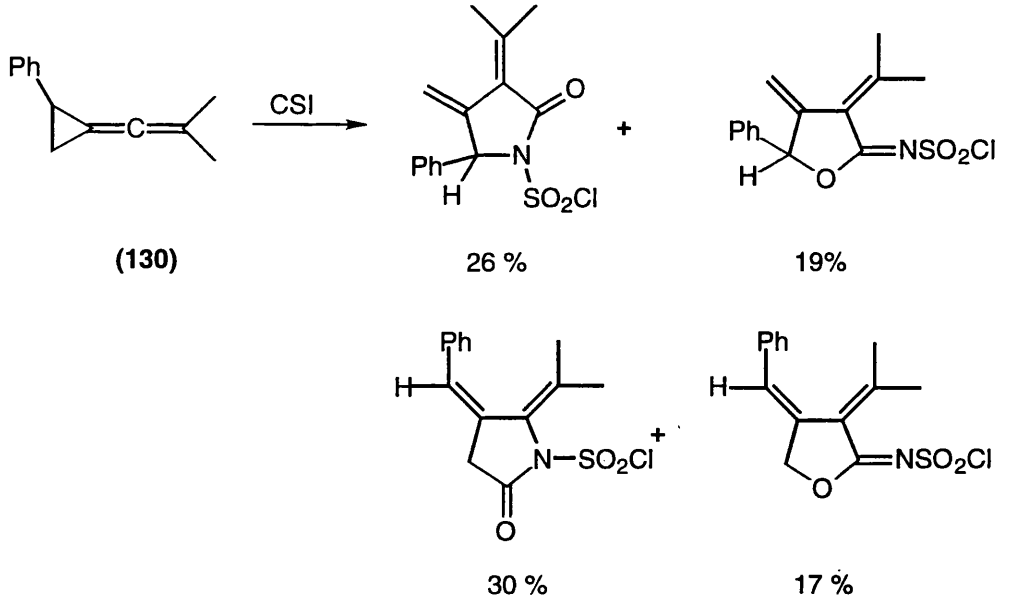
Scheme 2.42

Crandall and co-workers [90] attribute this reversal in normal orientation of addition to the unique overlap of the cyclopropyl σ-bonds with the π-orbital of the reactive olefinic unit which is rigidly enforced by the allenic geometry (**129**). As a consequence, the cyclopropyl system, with its well-known propensity for stabilising cationic centres,[91] is able to participate favourably in the transition state for electrophilic attack at this double bond without appreciable change of molecular geometry.



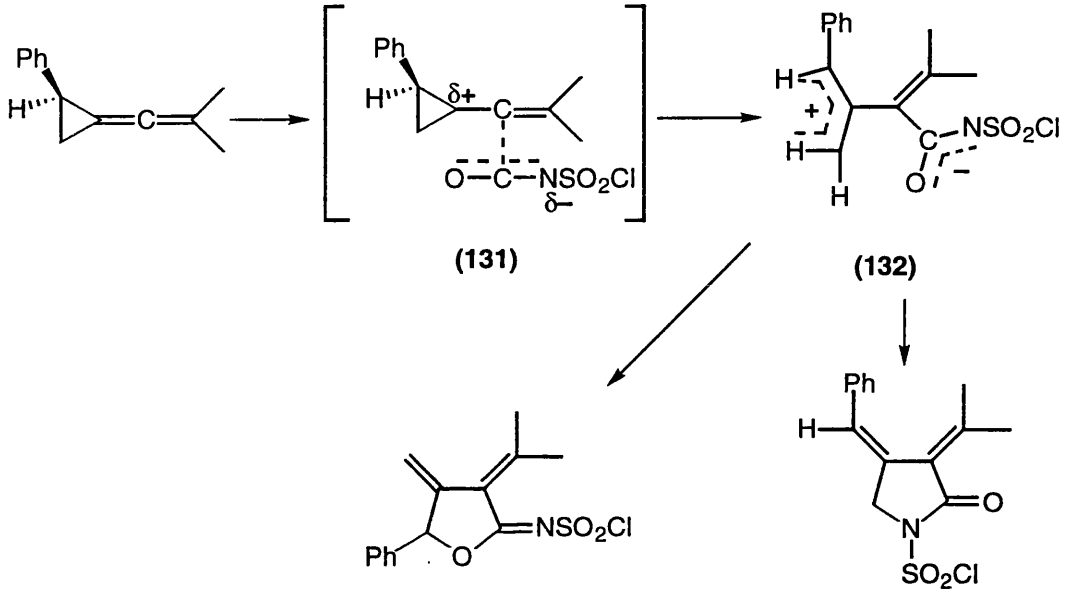
(129)

An independent study by Pasto and co-workers [92] reported that the reaction of 2-phenylisobutenylidenecyclopropane (**130**) with CSI produced a mixture of adducts resulting from electrophilic attack at C-4 (Scheme 2.43).



Scheme 2.43

This leads to the development of either a cyclopropyl cation (**131**) which ring opens to produce a resonance stabilised cation (**132**) or a nonresonance stabilised tertiary cation at C-5. The former mode of reaction is quite favourable owing to the release in strain energy of the 3-membered ring and the stabilisation of the incipient allylic cation. Collapse of the dipolar intermediate to products occurs to an essentially equal extent at both ends of the allylic cation, C-N bond formation being slightly favoured over C-O bond formation (Scheme 2.44).



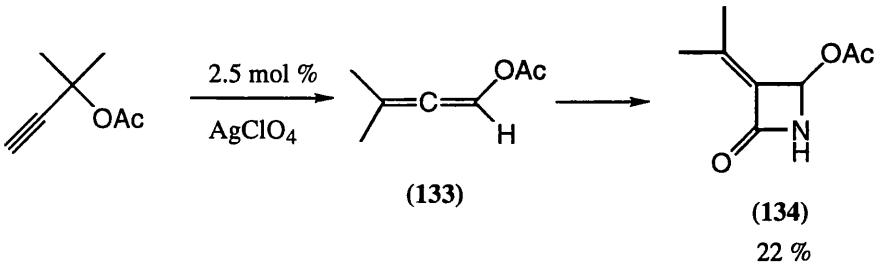
Scheme 2.44

The results of this study reveals that the mode of reaction producing either cyclopropane-retained or -opened products appears to be a function of the number and type of substituents attached to the cyclopropane ring.

Chiral 2-phenylisobutenylidenecyclopropane gave optically active ring-opened products on addition to CSI. A detailed study of the stereochemical aspects of this reaction led Pasto [93,94] to explain the results in terms of the relative rates of bond rotation versus collapse of the dipolar intermediate formed in the reaction but this will be discussed in depth in a later chapter.

Buynak and co-workers [96,97] have published a series of papers as part of a study to explore the cycloaddition of CSI to functionalised allenes with the aim of preparing useful intermediates for the synthesis of carbapenem and other antibiotics. Utilising the approach adopted by Moriconi and Kelly,[88] allenyl acetate (**133**) was obtained *via* the silver-catalysed rearrangement of the

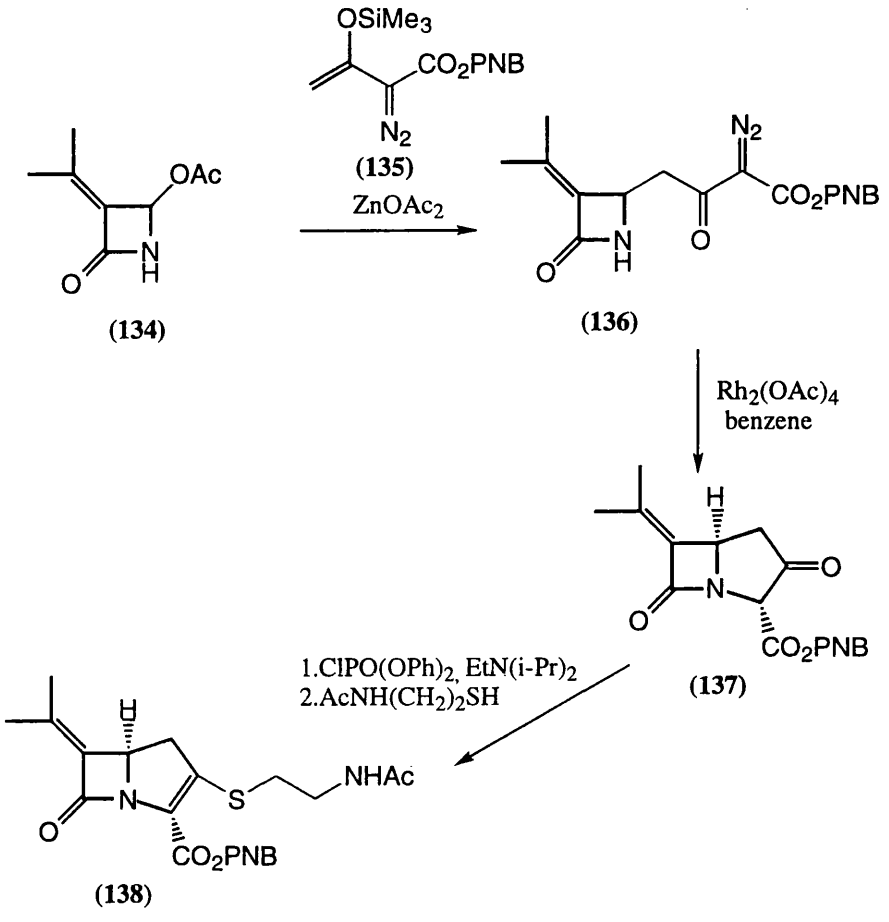
corresponding propargyl acetate.[95] It is well known that the 4-acetoxy-β-lactam (**134**) formed undergoes substitution at C-4 with a variety of nucleophiles (Scheme 2.45).[68]



(133) **(134)** 22 %

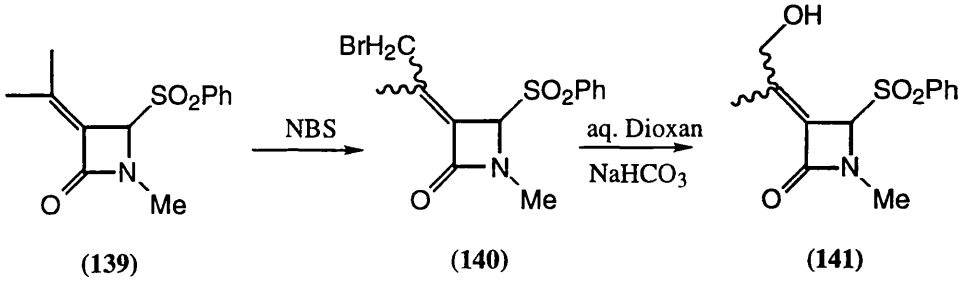
Scheme 2.45

The β-lactam formed is unusually stable to resonance interaction of the carbonyl carbon with both the nitrogen lone pair and the exocyclic double bond. Treatment of (**134**) with the trimethylsilyl enol ether of *p*-nitrobenzyl α-diazoacetate (**135**) in the presence of zinc acetate produced the useful carbapenem precursor (**136**). Cyclisation to the keto ester (**137**) was effected with rhodium acetate and subsequent manipulation afforded the bicyclic β-lactam (**138**) (Scheme 2.46).



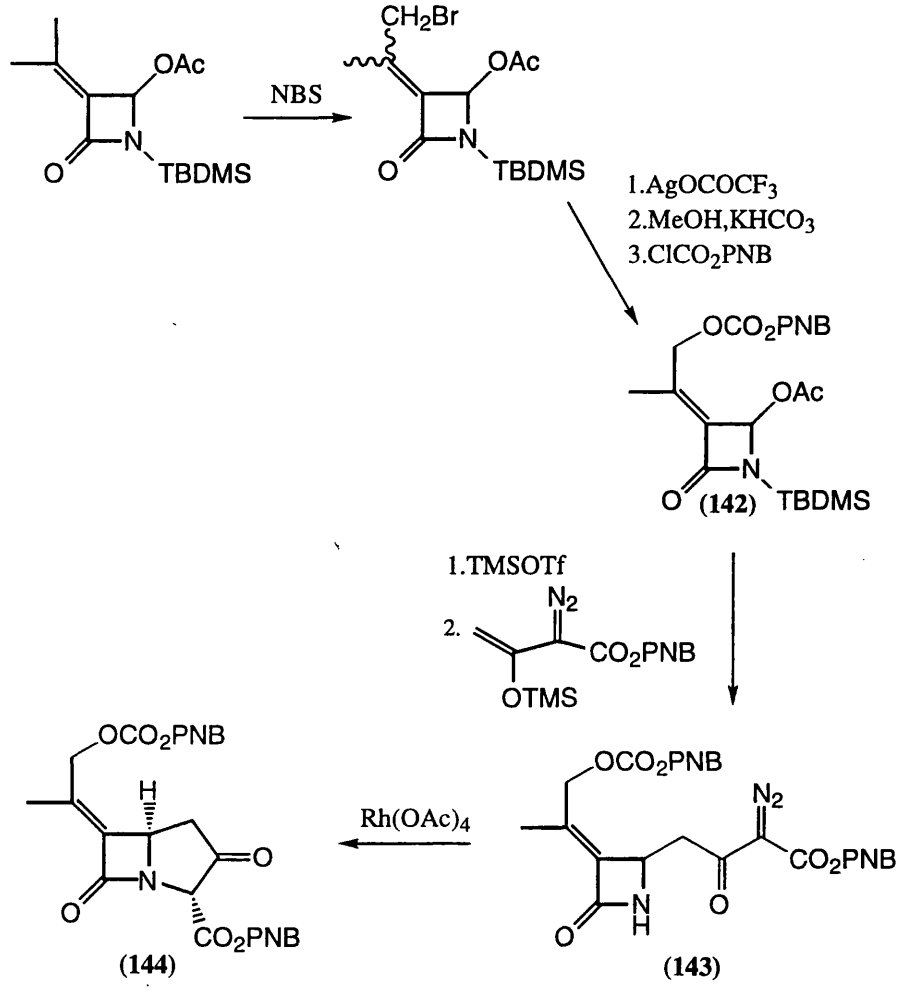
Scheme 2.46

The bicyclic β-lactam (**138**) is a useful synthetic precursor to the asparenomycin antibiotics which possess an α-(hydroxymethyl)ethylidene side chain since Buynak had earlier demonstrated [96] that the sulfone (**139**) produces a mixture of (*Z*)- and (*E*)-allylic bromides (**140**) on treatment with *N*-bromosuccinimide. These materials could then be transformed into the allylic alcohols (**141**) by heating in aqueous dioxane in the presence of $NaHCO_3$ (Scheme 2.47).



Scheme 2.47

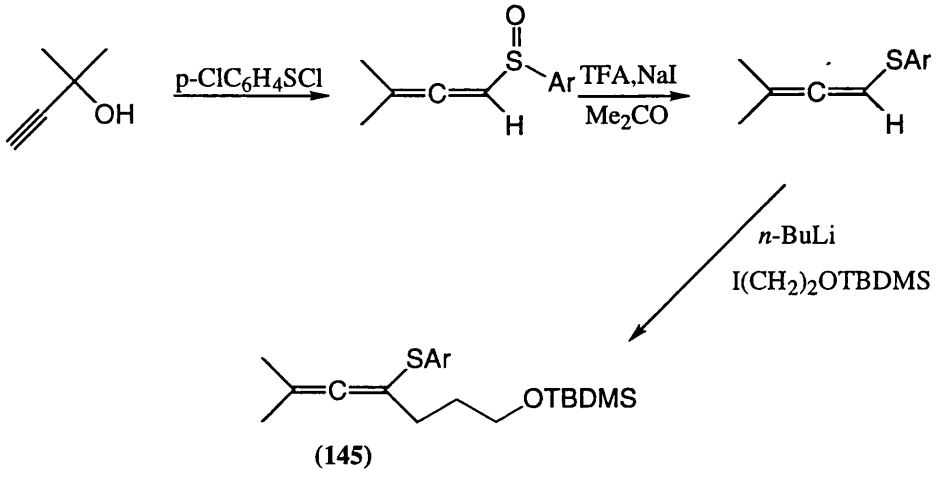
Application of this methodology allowed the preparation of the β-lactamase inhibitor asparenomycin C.[97] Again allylic functionalisation of the β-lactam (**142**) followed by nucleophilic displacement of the 4-acetoxy substituent provided the β-keto ester (**143**). Rhodium-mediated cyclisation afforded the bicyclic keto ester (**144**) which had previously been transformed into asparenomycin C by Ohno and co-workers (Scheme 2.48).[98]



Scheme 2.48

Allenyl sulfides are useful substitutes for allenyl acetates in the production of α-alkylidene-β-lactams *via* CSI addition, both in terms of their increased stability and the ease with which additional substituents can be introduced at either terminal carbon. They are readily prepared by the reduction of allenyl sulfoxides, and substitution to give the tetraalkylated allene (**145**) is easily effected by treatment with *n*-butyllithium (Scheme 2.49).

Buynak utilised this methodology in the formal synthesis of thienamycin [99] and carpetimycin A [100] complementing existing methodology by providing an additional route to the introduction of the α-hydroxyalkyl side chain.



(145)

Scheme 2.49

The arylthio group is important for several reasons. It has already been shown [88] that tetraalkylated allenes give the best yields of addition products and the sulfur moiety facilitates in the preparation of highly substituted compounds by activating the allene towards lithiation. Furthermore, the CSI addition proceeds regiospecifically and under mild conditions as a result of both the activating and directing effects of sulfur. Combined with its ease of removal, this procedure, therefore, provides easy access to these biologically important ring systems.

Thus, Buynak has clearly demonstrated that a wide range of α-alkylidene β-lactams can be readily constructed from functionalised allenes giving access to synthetically versatile precursors to the carbapenem antibiotics. Moreover, the α-alkylidene substituent does not appear to introduce unusual instability into the ring and is a convenient handle for the introduction of hydroxyalkyl side chains common to the carbapenems.

Taking these considerations into account, we decided to attempt the synthesis of useful carbapenem precursors from (allenymethyl)silanes where the incorporation of silicon serves two functions, firstly, as a means of controlling the regiochemistry during the [2+2] cycloaddition reaction with CSI and secondly, by acting as a potentially oxidatively cleavable group. Concentrating solely on the importance of the silicon substituent, it was decided to construct an (allenymethyl)silane that would lead directly to a β-

lactam with the desired side-chain functionality and hence, the (hydroxymethyl)allene (**165**) was chosen as a suitable synthon since cycloaddition with CSI would then yield the β-lactam (**169**), already possessing the C-3 side chain typical of the asparenomycin antibiotics.

Section 3.1 Chiral Allene Synthesis

Functionalised allenes are a convenient choice of precursor for the formation of β-lactams, not only because they are readily constructed from suitable propargylic substrates but also because they have the ability to exhibit chirality and, therefore, enable the synthesis of enantiomerically enriched compounds.

A molecular orbital treatment of the allene molecule correctly predicts that the most stable bonding rearrangement involves two mutually perpendicular π-bonds with the central C-atom (sp hybridised) joined in a straight line to the two terminal carbon atoms (sp^2 hybridised). As a result, only the two hydrogen atoms at one end project above and below the plane containing the rest of the molecule, and the two π-bonds are not conjugated with each other because they are not coplanar (Fig. 9).

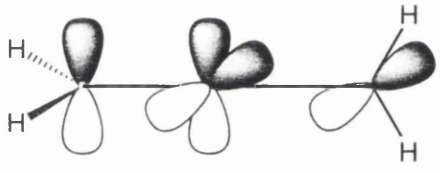
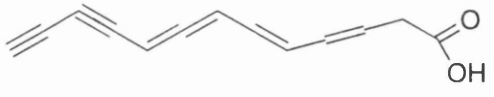


Figure 9 Arrangement of Allenic π-Bonds

The stereochemical consequences of the bonding in allenes was predicted by van't Hoff, [101] who foresaw that optical isomerism due to a lack of molecular symmetry is possible if the terminal carbon atoms bear two different substituents.

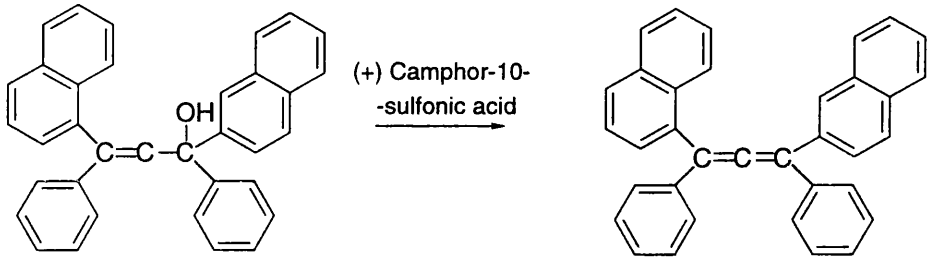
The first naturally occurring optically active allene was Mycomycin (**146**), isolated from elaboration products of *Norcardia acidophilus* in 1952. [102] It was later recognised that many other optically active allenes occur in natural products, principally amongst fungal metabolites, brown algae and sea urchins.



(**146**)

The high degree of reactivity of the allene function in a variety of reactions has led to the use of substituted allenes as intermediates in a number

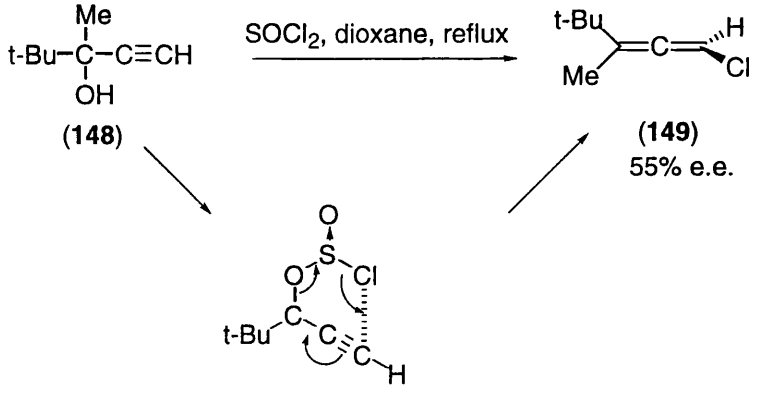
of synthetic pathways leading to highly complex structures. In 1953, Maitland and Mills [103] obtained the first chiral allene by dehydrating racemic (**147**) with (+)-camphor-10-sulfonic acid (Scheme 3.1), thus confirming van't Hoff's predictions that an unsymmetrically substituted allene could exist in two enantiomeric forms. However, recrystallisation of the product led to a large increase in the optical rotation, demonstrating that the product obtained directly from the dehydration process was predominantly a racemic mixture, only partially enriched in one enantiomer.



(**147**)

Scheme 3.1

The first stereospecific synthesis of a chiral allene from an optically active tetrahedral carbon compound was described by Landor *et al.*[104] Landor demonstrated that resolved 3,4,4-trimethylpent-1-yn-3-ol (**148**) and its enantiomer react with thionyl chloride in boiling dioxane to give 1-chloro-3,4,4-trimethyl-1,2-pentadiene (**149**) with an optical purity of about 55%. The reaction proceeds through a cyclic S_Ni mechanism with the chlorine atom approaching stereoselectively from the side on which the hydroxyl group is situated (Scheme 3.2).



(**148**)

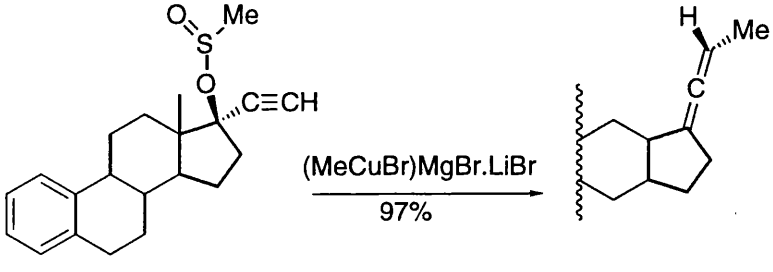
(**149**)
55% e.e.

Scheme 3.2

During the last decade a revival in the synthesis of optically active allenes has been noted, particularly those syntheses involving the reaction of organocuprates with propargyl derivatives. This is principally a chirality transfer reaction involving a highly stereoselective, mechanism-controlled, metal-mediated propynyl/allenyl rearrangement and the general procedure has proved to be exceptionally useful for the synthesis of complex structures which have been used as intermediates in the vitamin D series.[105] However, it is interesting to note that, although substituted allenes can be prepared by the reactions of alkyl cuprates with propargyl derivatives, they cannot be prepared by the reaction of allenyl cuprates with alkyl derivatives. The reason for this is that when the allenyl group is bonded to copper it behaves similarly to an alkynyl group, being nonreactive in the transfer reaction.

The stereochemistry of the organocuprate reactions of propargylic derivatives appears more complex than for simple alkyl and allyl compounds, since a greater number of possible mechanistic pathways can be discerned. Furthermore, experimental studies are impeded by racemisation of the allenic products under the reaction conditions, since it has been shown previously [106] that chiral allenes are readily racemised by various organocuprates.

Until recently, it has been proposed that displacement occurs in a predominantly *anti* manner [107-109] for acyclic systems, while in steroidal cases *syn* -products are preferred,[110] although this could alternatively be explained by the structural constraints placed on the acetylenic moiety present in the steroidal systems. This theory has since been revised on the basis of an X-ray analysis [108] of the allene (**151**) obtained by the reaction of mestranol methanesulfinate (**150**) with methylcopper, indicating that the 1,3-substitution proceeds in an overall *anti* fashion both in steroidal and nonsteroidal cases (Scheme 3.3).

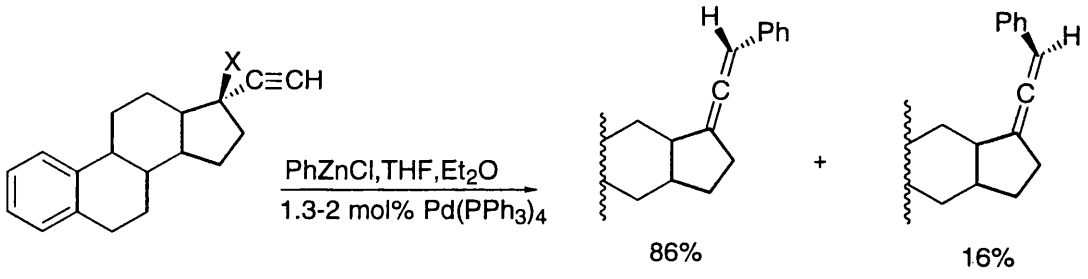


(150) **(151)**
100% e.e.

Scheme 3.3

The continuing confusion over the proposed mechanism in steroidal systems prompted Okamura *et al* [109] to publish their results on the lithium dimethylcuprate induced conversion of propargylic esters into allenes using a steroidal C/D fragment derived from vitamin D3 as a stereochemical probe. They treated a number of C/D ring propargyl esters with one equivalent of dimethylcuprate in diethyl ether at 0°C and found that in all cases the predominant product originated from an *anti* mode of displacement of the leaving group. Of further interest was the observation that the nature of the leaving group did not affect the stereoselectivity of the reaction.

Pd(0)-catalysed displacement with organozinc compounds also occurs in an *anti* manner.[111] Again this reaction has been examined both in steroidal and nonsteroidal systems. In the steroidal series esters derived from mestranol were subjected to reaction with phenylzinc chloride using $Pd(PPh_3)_4$ as the catalyst producing diastereoselectivities of over 84 % in all cases (Scheme 3.4).

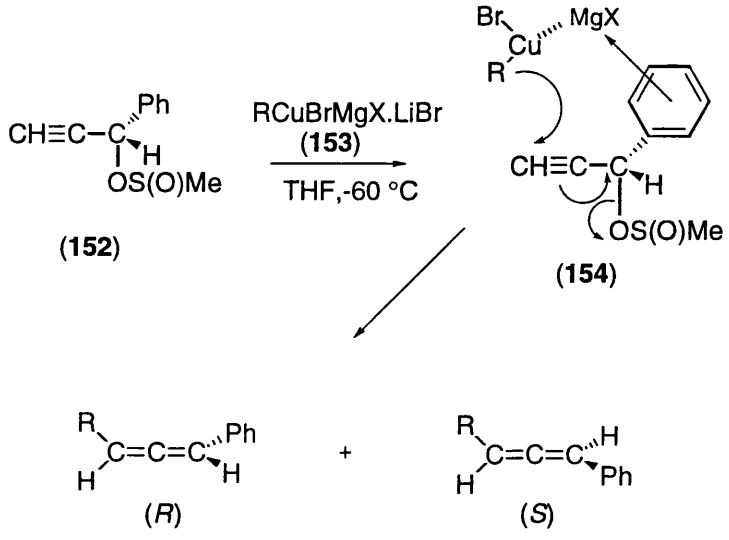


Scheme 3.4

Identical reaction conditions in the acyclic systems, again demonstrated that the induced 1,3-substitution proceeded with *anti* diastereoselectivites of over 80 %. However, conversion of a sulfinate ester proceeded with a much greater stereoselectivity, although the reason for this was unknown. The use of sulfinate esters as acetylenic moieties has since been examined by a number of groups.

As early as 1978, Tadema *et al* [112] reported on the efficient synthesis of chiral phenylallenes from 1-phenyl-2-propen-1-yl esters by applying organocopper(I) reagents. At that time nothing was known about the stereochemical pattern of organocuprate-induced 1,3-substitutions in nonsteroidal propargylic sulfinates. The methanesulfinate (**152**) was treated with the organocuprate (**153**) at -60 °C to afford the (*R*)- and (*S*)-allenes in high yield. The stereochemistry at sulfur in the allenic sulfoxides is not important for further synthetic purposes and racemisation at sulfur is often observed

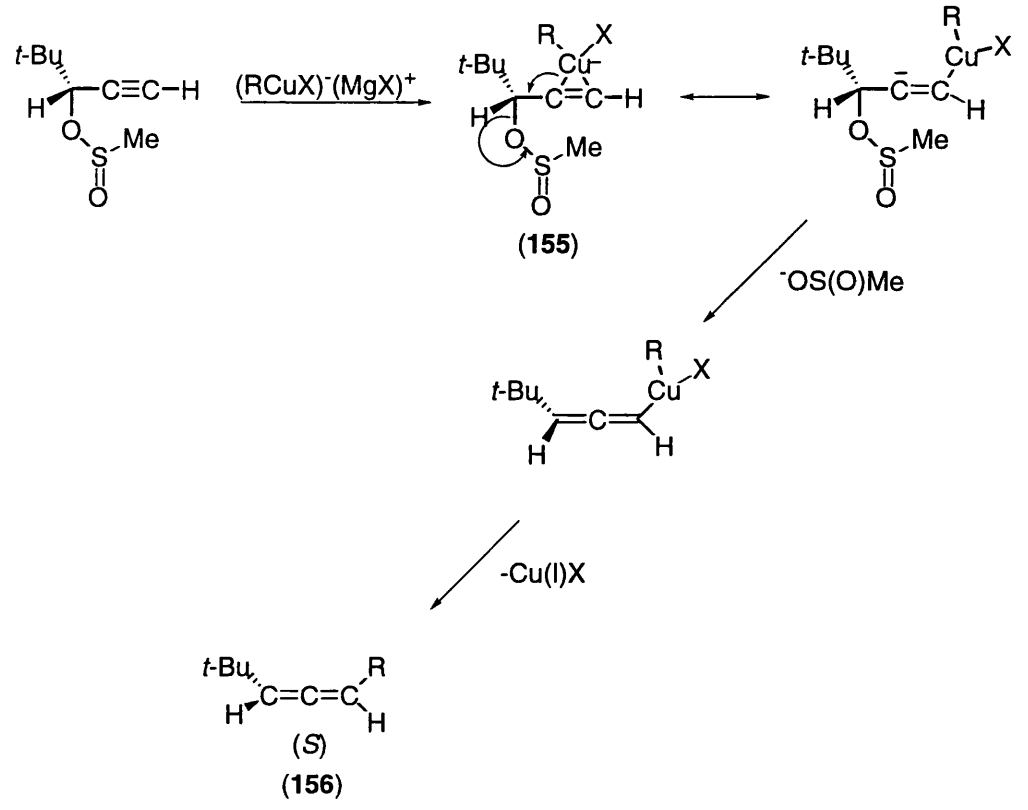
without affecting the allenic axial dissymmetry. Results showed an enantiomeric excess of 88 % of *R* over *S* implying that *anti* 1,3-substitution had occurred and was therefore the normal stereochemical pathway in esters derived from secondary propargylic alcohols (Scheme 3.5).



Scheme 3.5

The stereochemistry of the 1,3-substitution involved was disputed at first, but it was unambiguously shown by X-ray crystallography that methylcopper(I) induces stereospecific *anti* 1,3-substitution in steroidal substrates. This was in agreement with an earlier proposal by Crabbe *et al,* [113] nevertheless, Tadema also felt that this reaction merited more study, since he proposed that the preferred *anti*-1,3-substitution could equally be explained by the formation of a cuprate-arene π-complex (**154**) between (**152**) and (**153**). Therefore, a study of sulfinic esters bearing no aryl group on the chiral centre is necessary in order to justify this statement.

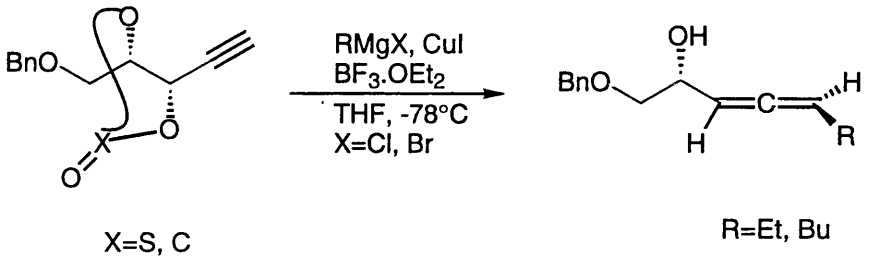
In accordance with the observations made by Tadema, Elsevier and Vermeer examined the reaction of methanesulfonate and sulfinate esters of several optically pure (or enriched) prop-2-yn-1-ols bearing alkyl substituents instead of the aryl group moiety above.[114] These authors also reported an S_N2' reaction proceeding with a high *anti* stereoselectivity and proposed a plausible mechanism (Scheme 3.6).



Scheme 3.6

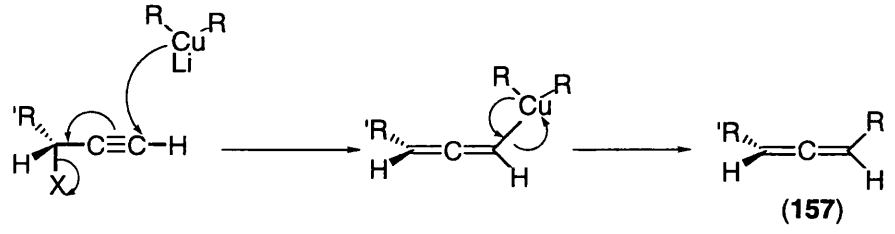
In order to rationalize the observed stereochemical outcome, they envisaged the formation of a π-complex (**155**) between the organocopper(I) fragment and the acetylenic moiety. Subsequent elimination of the leaving group only occurs when the copper and sulfonate groups are mutually periplanar since this geometry favours orbital overlap between the relevant copper(I) p- and d-orbitals with the acetylenic π and π* systems, respectively. The resulting σ-allenyl copper(III) species is unstable and collapses readily to give the (*S*)-allene (**156**). This last step occurs *via* a reductive elimination of CuX and proceeds with retention of configuration, as is usually observed for such alkyl shifts on transition metal centres.[115] The presence of a Cu(III) intermediate as a transient species has also been suggested by other groups,[116-119] therefore, its occurrence is quite possible.

Further *anti* diastereoselectivites of > 99 % have recently been achieved by the reaction of cyclic carbonates or sulfites of acyclic alkynyl diols with organocopper reagents,[120] and again the reaction is thought to proceed*via* an overall S_N2' mechanism (Scheme 3.7).

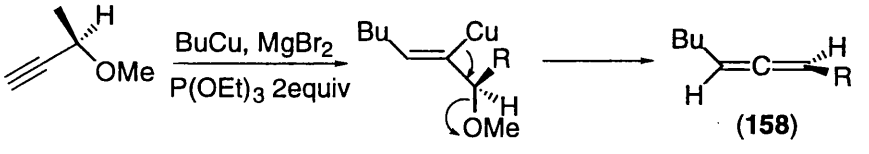


Scheme 3.7

All the observations to date on the mechanistic aspects of the formation of chiral allenes from propargylic ethers and organocopper reagents have been encompassed in a comprehensive study by Alexakis and co-workers.[121] Although it was generally believed that the reaction of propargylic derivatives with organocopper reagents proceeds *via* a copper(III) intermediate resulting from an *anti* S_N2' nucleophilic attack of the Cu(I) atom to give an allene (**157**), with retention of configuration (Scheme 3.8), these authors have shown that with some ethers *syn* addition to the triple bond takes place first, followed by a β–elimination of the resulting alkenylcopper species. With the use of chiral propargylic ethers and a stoichiometric amount of the organocopper reagent, this β–elimination step is purely *anti*, resulting in the formation of a chiral allene (**158**) with 98 % optical purity (Scheme 3.9).



Scheme 3.8



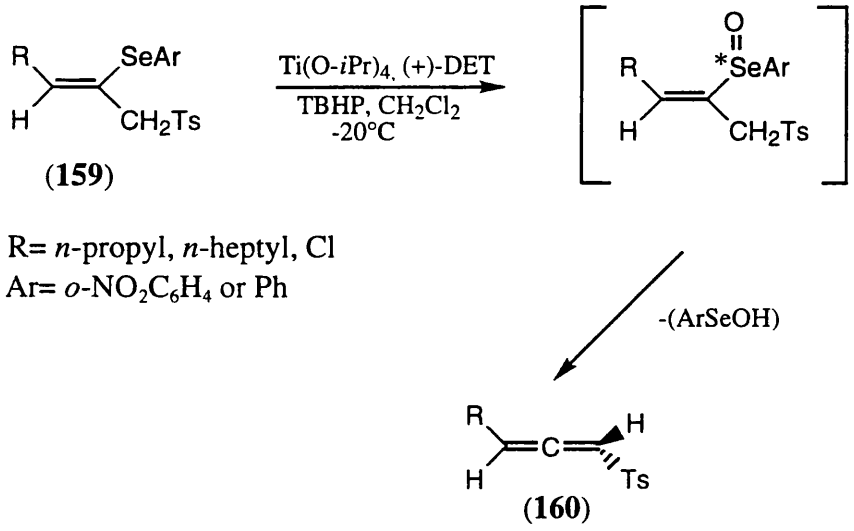
Scheme 3.9

Since it had been reported [122] that allenes can also be obtained by the reaction of Grignard reagents and catalytic amounts of Cu(I), Alexakis and co-

workers repeated the same reaction using a Grignard reagent and 5 mol. % of a Cu(I) salt with quite unexpected results. Using a variety of Grignard reagents, RMgX, where X= Cl, Br and I, it appeared that the nature of X played a crucial role in the reaction, not only affecting the optical purity, but also the sense of the overall process *syn* or *anti*. As a general rule, with RMgCl, a *syn* overall process is always obtained, whereas with RMgI an *anti* process invariably occurs.

These results had been corroborated in an earlier paper [123] where the diastereoselectivity of a copper-catalysed reaction of a Grignard reagent with propargylic epoxides could be controlled by changing the reaction conditions, particularly the halogen atom of RMgX. In this case, optimised *anti* conditions involved a Grignard reagent derived from an alkyl bromide and a copper salt complexed with a strong ligand, whereas *syn* conditions involved the use of RMgCl. It is important to note that the use of the strong ligand to complex the copper prevents the formation of Cu(0) by decomposition, thus reducing the likelihood of racemisation of the final allene by this copper species.[124]

Recent studies describe a new methodology for chiral allene synthesis *via* double asymmetric induction. [125] This reaction differs from the conventional chiral allene syntheses previously discussed where the chirality is already built into the molecule and is situated on the carbon adjacent to an acetylene functionality. As shown in the previous examples, chirality is then induced into the allenic skeleton through propynyl rearrangement. This second alternative procedure involves asymmetric oxidation of the selenide (**159**) employing the Sharpless reagent, which is followed by subsequent asymmetric selenoxide elimination (Scheme 3.10).



(**159**)

R= *n*-propyl, *n*-heptyl, Cl
Ar= *o*-$NO_2C_6H_4$ or Ph

(**160**)

Scheme 3.10

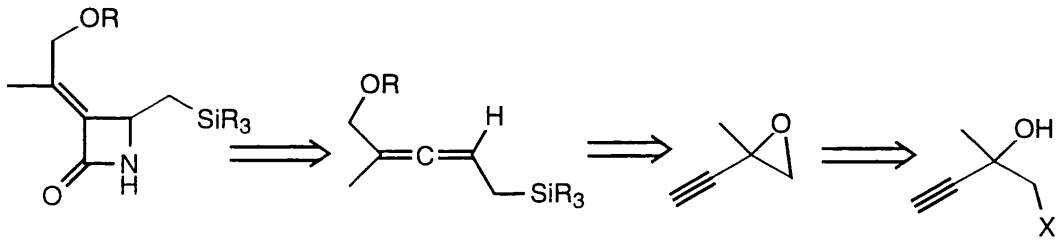
The allenes (**160**) were obtained in good chemical yield and in modest enantiomeric excess (10-20%). The authors found that varying the R group did not significantly affect the enantioselectivity of the reaction, however, introduction of an *o*-nitro substituent into the phenyl moiety of the selenide resulted in improved enantiomeric excesses. The effect of the *o*-nitro group is not obvious although two possible explanations have been proposed for this enhancement, either through stabilisation of the chiral selenoxide by steric interaction or alternatively, by acceleration of the elimination step caused by an electronic effect. Although these enantiomeric excesses have not been optimised, this procedure, nevertheless, reports the first case of asymmetric selenoxide elimination and provides an additional route to the asymmetric synthesis of usefully functionalised allenes.

It can be concluded, therefore, that allenes are useful synthons in organic synthesis, maintaining their stereochemical integrity under a variety of chemical conditions. The syntheses of chiral allenes of high enantiomeric purity from chiral precursors, notably propargyl compounds, have been shown to occur by a mechanism-controlled reaction with the central chiralty of the substrate being converted into allene axial chirality in the product. This observation is vitally important for the synthesis of enantiomerically pure compounds, and in view of the fact that we aimed to synthesise functionalised β-lactams from suitable chiral allene precursors, was certainly very promising.

Discussion
Section 4.1

The preparation of highly functionalised allenes by Buynak and co-workers [96] has led to the production of versatile intermediates for the synthesis of ene-type β-lactam antibiotics, such as the asparenomycins. Introduction of additional functionality at C-3 of the azetidinone could, in theory, be achieved by the use of highly substituted alkenes. However, CSI is particularly reactive towards a wide variety of functional groups [126] and such a process is not usually feasible.

This facile access to substituted allenes prompted us to consider the application of (allenylmethyl)silanes to the synthesis of asparenomycin precursors. The use of (allenylmethyl)silanes as synthetic precursors is favourable since it allows the easy construction of the azetidinone ring system incorporating the C-3 exocyclic double bond functionality common to the asparenomycin antibiotics. Retrosynthetic analysis of the desired β-lactam leads to the allene shown which, in turn, can be formed from a suitable propargyl precursor.



Silicon controls the regiochemistry of the cycloaddition process, being suitably positioned to stabilise the development of a carbonium ion β to the silicon atom through the silicon β-effect.[127] This electron-donating effect is believed to occur by π-σ-π conjugation between the silicon-carbon bond and the developing positive charge in the transition state (Fig. 10).

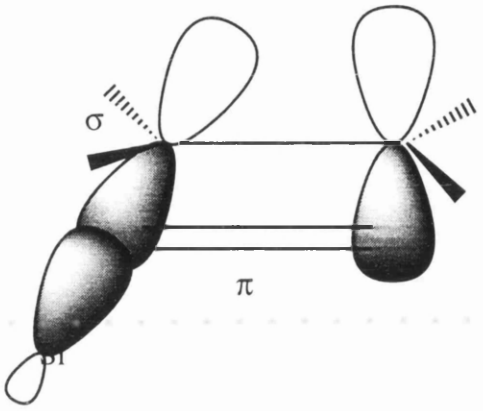
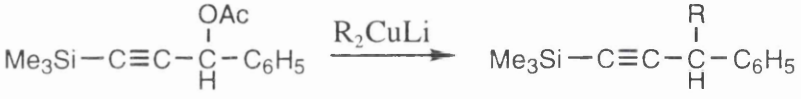


Figure 10

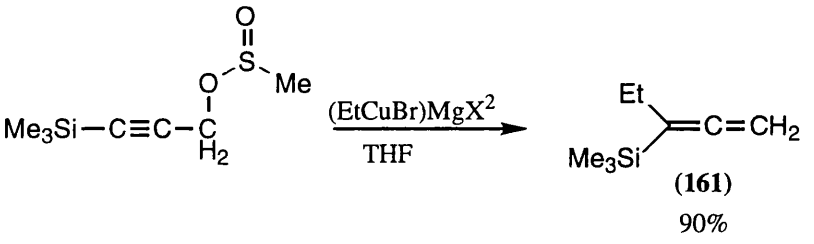
In addition, the substitution on the silicon atom can be varied to incorporate potentially oxidatively cleavable groups, thereby enabling the preparation of the synthetically useful 4-(hydroxymethyl)-β-lactams which can undergo subsequent chemical transformation to afford the bicyclic systems.

During the past twenty years, numerous new and highly useful methods have been developed for the synthesis of substituted allenes. Lithium and magnesium organocuprates react with propargyl acetates [128] to give both alkylated and nonalkylated allenes. However, it has been shown[129] that treatment of γ-(acetoxyalkynyl)silanes with dialkylcuprates results in direct replacement of the acetoxy group (Scheme 4.1).



Scheme 4.1

In contrast, Vermeer *et al* [119] have formed an attractive route to a large variety of silylated allenes by the use of a complex organometallic reagent with trimethylsilyl-protected propynyl sulfinates and sulfenates. In this case α-attack occurs and the allenylsilanes (**161**) are produced in good yield (Scheme 4.2).

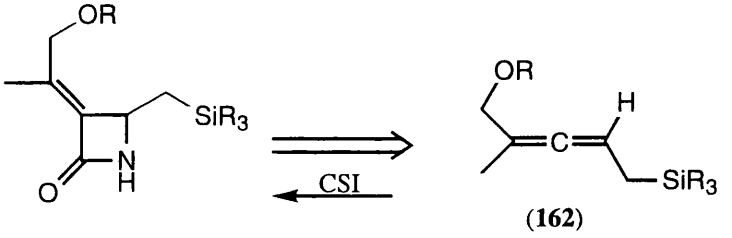


(161)

90%

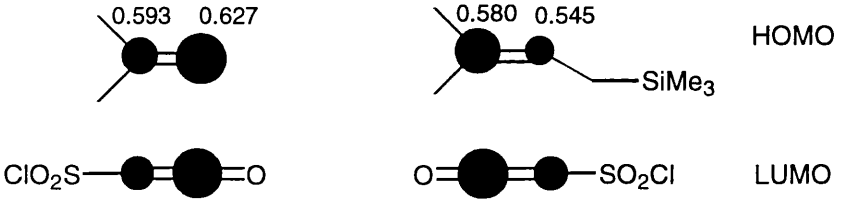
Scheme 4.2

As we wished to prepare a β-lactam already possessing the asparenomycin C-3 sidechain then an obvious synthetic precursor is the (hydroxymethyl)allene (**162**), since cycloaddition of this precursor with CSI should yield the desired β-lactam product.



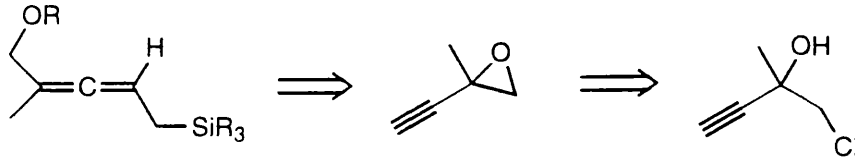
(162)

An early report by Dunogues [130] had shown that CSI reacts with allylsilanes to give an intermediate β-lactam product with the regiochemistry opposite to that observed in the hydrocarbon series. This can be easily explained in terms of the electron densities at C-1 and C-2 which reveal the existence of inverse polarity along the double bonds of the alkene and the allylsilane, therefore, reversing the regiochemistry of the cycloaddition process. Molecular orbital calculations also reinforce this theory, showing that the major interaction will occur between the sp^2 carbon bearing the largest coefficient in the alkene HOMO and the atom which bears the largest coefficient in the CSI LUMO.



Unusually, the silyl group is not lost in this reaction; electrophilic attack on allylsilanes normally leads to silyl loss with the formation of substituted products with a net double bond shift. Thus, the silyl group exerts a strong influence on the ease and regiochemistry of these reactions which can be explained by the β-effect. [127] As a result, we were confident that silicon would indeed control the regiochemistry of the cycloaddition process.

Since most successful syntheses of allenes involve rearrangement of propargyl derivatives, specifically through 1,4-conjugate addition of an organocuprate complex, then retrosynthetic analysis of allene (**162**) would lead to the propargyl epoxide (**163**) as the desired synthon. Epoxides may be prepared in a number of ways, however, the dehydrohalogenation of β-halogeno alcohols with aqueous alkali has been widely used [131] and hence the chlorohydrin (**164**) lends itself as a useful starting material.



(**162**) (**163**) (**164**)

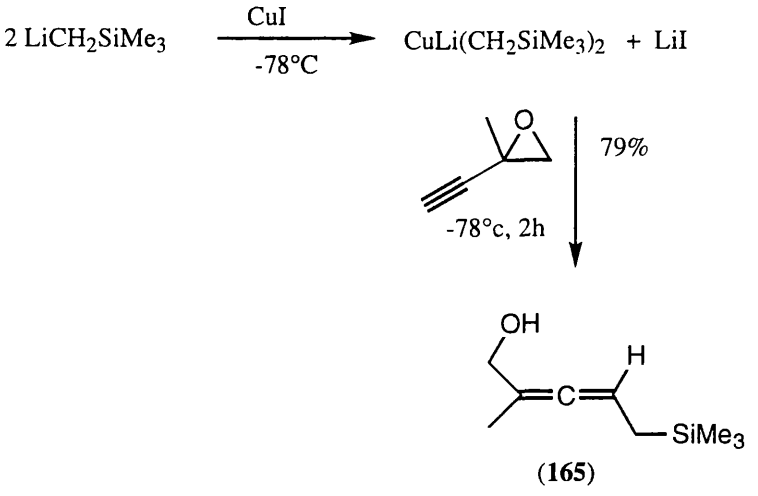
Synthesis of the halohydrin (**164**) [132] was achieved by initial formation of ethylmagnesium bromide, followed by Grignard exchange to form the more acidic acetylenic Grignard reagent. This was obtained by adding the EtBr/THF mixture carefully over a period of one hour to a THF solution saturated with acetylene gas. The actual time period over which addition takes place is crucial, since slow addition results in decomposition of the preformed Grignard, whereas formation of the bis-Grignard species was observed as a white precipitate at the bottom of the flask on rapid addition of the ethylmagnesium bromide.

After complete addition the reaction mixture was maintained under an acetylenic atmosphere for a further hour in order to maximise the yield. Low temperatures (0°C) are required throughout, due to the unstable nature of the acetylenic Grignard. In the next stage chloroacetone was added slowly to the Grignard mixture at low temperature affording the magnesium salt of the halohydrin. Attack by the organometallic reagent occurred only at the highly electrophilic carbonyl carbon with no indication of attack at the chlorine bearing carbon. Final quenching with NH_4Cl liberated the free alcohol from

the magnesium salt and the chlorohydrin product was easily isolated in 79% yield by fractional distillation under reduced pressure.

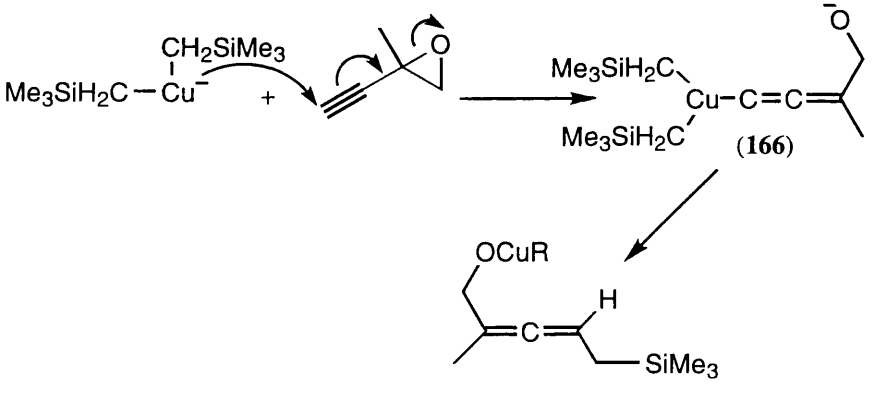
Epoxide (**163**) was formed readily by alkali-mediated cyclisation using potassium hydroxide as base. This strong base was chosen over other weaker bases purely for ease of isolation since the epoxide is known to be very volatile. The solvent chosen for the reaction was diethyl ether, again mainly for convenience so that the product could be easily separated by distillation. Hence, this precludes the use of usual organic and amine bases such as butoxide or LDA which, although strong enough to remove the hydroxyl proton, will dissolve in the solvent and hinder purification. In addition, the normal workup procedures for these reactions involve the use of acid which will ring open the epoxide product. For this reason it was necessary to use an inorganic base which was insoluble in diethyl ether and could be used in vast excess as a suspension. The excess base was then simply removed during the workup by washing with aqueous NaCl. The final problem in this synthesis was the possibility of intermolecular reaction during cyclisation of the epoxide, however, this side reaction was minimised by working under very dilute reaction conditions (*ca.* 1M) and by adding the chlorohydrin to the suspension *via* syringe so that there was always an excess of base.

Propargyl epoxides undergo allylic rearrangement during ring opening by organocuprates in what amounts to a S_N2' reaction. Typically, organocuprates are formed by the addition of either an organolithium or an organomagnesium reagent to a copper(I) salt under an inert atmosphere. In this case the diorganocuprate was formed from lithium methyltrimethylsilane (1M solution in pentanes) and purified CuI at -78 °C under nitrogen. Slow addition of the epoxide to the preformed cuprate at -78°C gave the (hydroxymethylallenyl)silane (**165**) in good yield (Scheme 4.3).



Scheme 4.3

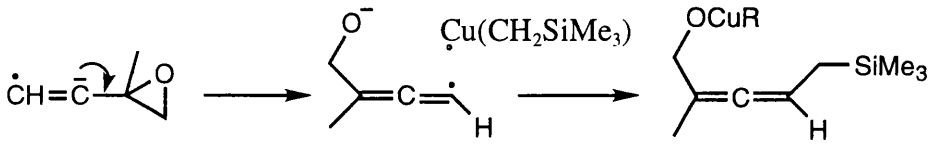
Two general mechanisms have been proposed for the conjugate addition of organocuprates. The first suggests a direct nucleophilic attack by copper on the propargyl epoxide with elimination of the leaving group, [133] in this instance ring opening of the epoxide, to form the anionic intermediate (**166**) (Scheme 4.4).



Scheme 4.4

This mechanism differentiates organocuprates from the more typical organometallics such as Grignard reagents or organolithiums where the carbon atom assumes the role of the attacking nucleophile. The final step is the transfer of the alkylsilyl moiety to the copper-bearing carbon of intermediate (**166**).

An alternative mechanism proposed by Crabbe *et al* [134] implies that an electron transfer from the reagent to the acetylene molecule occurs, followed by ring opening of the epoxide and transfer of an alkylsilyl radical (Scheme 4.5).

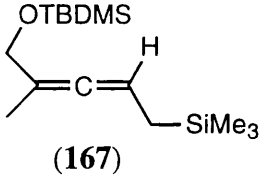


Scheme 4.5

Both mechanisms are believed to proceed through an oxidation-addition reaction to give a copper(III) species,[135] followed by reductive elimination, although there is no evidence for this. The free hydroxyallene is generated from the anionic intermediate by reductive treatment with NH_4Cl.

The next stage in the synthesis is the cycloaddition step with CSI, however, before this step can be carried out the hydroxyl group must be protected in order to avoid reaction with the electrophilic CSI which reacts with alcohols to form the esters of *N*-chlorosulfonyl carbamic acid.[79]

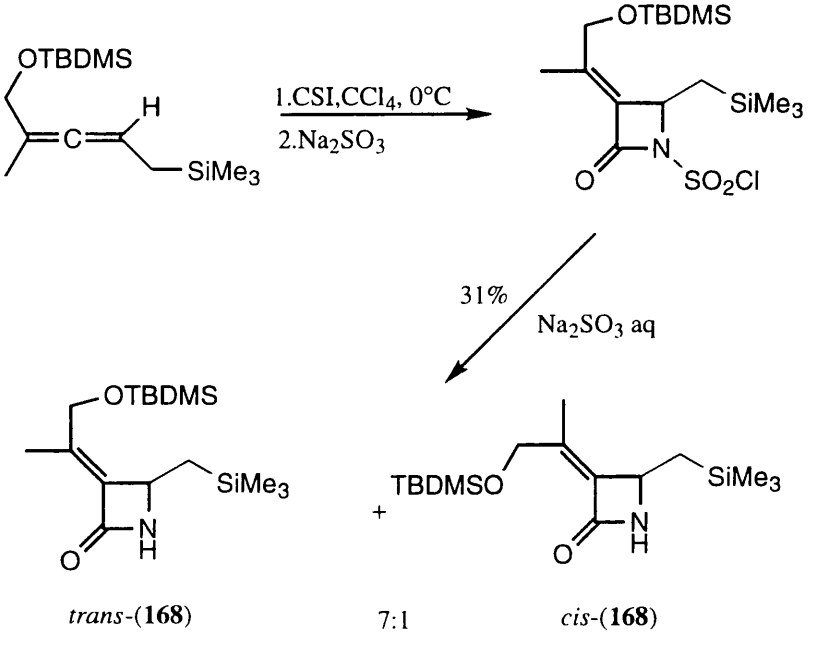
The TBDMS ether was chosen as the protecting group, since it is particularly stable under a wide range of reaction conditions, being 10^4 times more stable than the TMS ether. It has been much used for hydroxyl protection[136] partly because of its susceptibility to specific and facile removal by either fluoride ion or aqueous acid. Protection was readily accomplished using TBDMS chloride as reagent employing 4-dimethylaminopyridine [137] as catalyst to give allene (**167**) in 88% yield. The yield was improved by the use of the highly electrophilic silylating agent TBDMS triflate [138] which is effective for the silylation of sterically hindered alcohols. Practically, the use of this silylating agent is also preferable since, being a liquid rather than a solid reagent, it allows the reaction to be carried out homogeneously where an inert atmosphere can be maintained and, in this case, gave the desired TBDMS-protected allene in 98% yield.



(**167**)

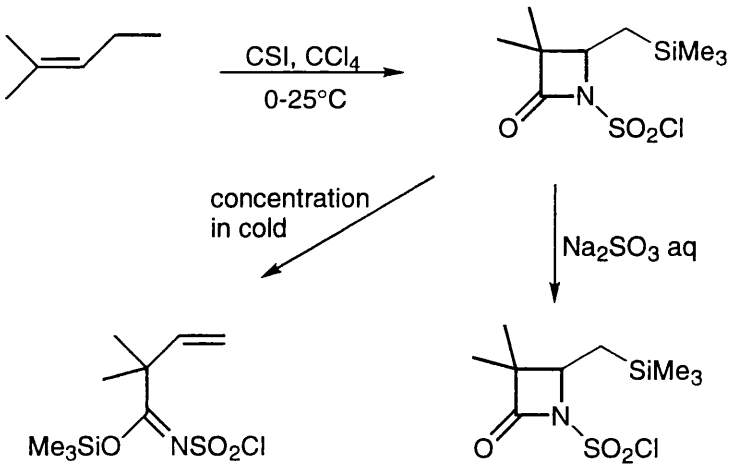
Having obtained this suitably protected allene precursor we now wished to synthesise the desired asparenomycin progenitor *via* a cycloaddition reaction with CSI. The conditions previously employed by Graf [65] were chosen, using CCl_4 as solvent since it is known [53] that CSI is inert to chlorinated

hydrocarbons. The reaction was carried out at 0°C and the course of the reaction conveniently monitored by ^{1}H-NMR spectroscopy. Disappearance of the allenic proton at 5.0 ppm and the appearance of a signal at 4.1 ppm due to the C-4 proton in the ring system indicated the formation of the product β-lactam. Once the starting material had been completely consumed, as shown by the absence of the allenic proton in the NMR spectrum, then the *N*-chlorosulfonyl β-lactam formed could be intercepted by *in situ* treatment with aqueous sodium sulfite.[75] *N*-Chlorosulfonyl β-lactams have been reduced by a variety of methods, however, sodium sulfite as the inorganic reducing reagent is a good choice since the *N*-sulfinic acid formed readily loses sulfur dioxide to afford the *N*-protio β-lactam (**168**) in good yield (Scheme 4.6).



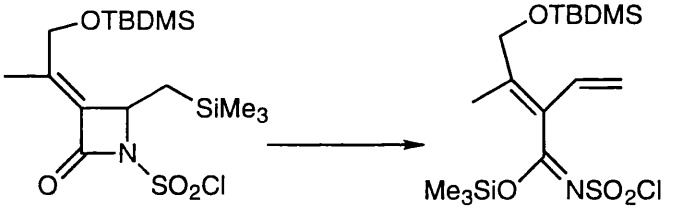
Scheme 4.6

It has previously been shown within our research group[198] that, in the absence of a sodium sulfite quench, dimethylallylsilane was observed to undergo rearrangement on concentration to form the imidate ester (Scheme 4.7).



Scheme 4.7

In theory, the intermediate *N*-sulfonyl-β-lactam formed during our reaction could also rearrange to the imidate ester, however, this can be prevented by working under dilute reaction conditions as the rearrangement is thought to occur by a bimolecular pathway (Scheme 4.8).



Scheme 4.8

The β-lactams were formed as a 7:1 (*E* /*Z*) mixture of isomers, the major isomer possessing the precise C-3 alkylidene functionality of the asparenomycins. This isomeric ratio was readily determined from the ^{1}H NMR where the signal arising from the methyl at C-1' is clearly separated into two peaks corresponding to the major and minor at 1.72 and 1.80 ppm, respectively. Integration of these two signals revealed the 7:1 (*E*/*Z*) β-lactam ratio shown.

The stereoselectivity of the cycloaddition process, leading to the observed product ratio, can be explained if the geometry of the cumulene double bond is taken into consideration. In allenes the central carbon aton is sp-bonded with the two remaining p-orbitals perpendicular to each other, each one overlapping with the p-orbital of an adjacent carbon atom. As a consequence, the two remaining bonds of each carbon atom are forced into perpendicular planes (Fig. 11).

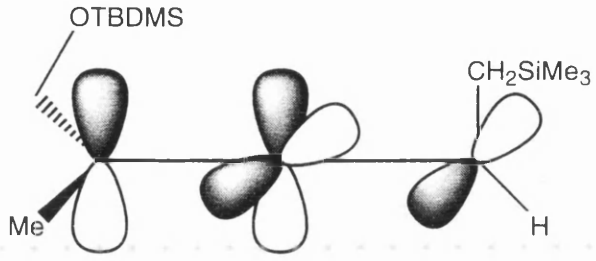
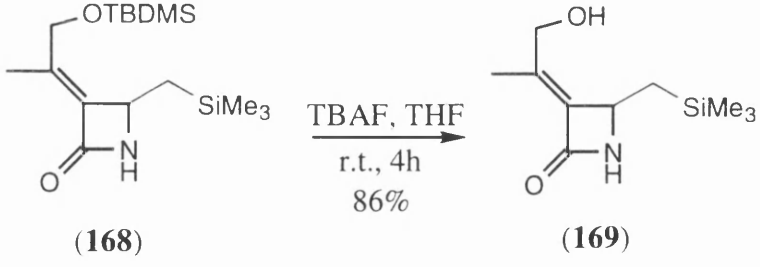


Figure 11

Thus, the approach geometry of CSI towards the π-bond of the allylsilane moiety is along the same plane as the substituents at the terminus of the adjacent double bond. Obviously, CSI will approach from the side bearing the smaller methyl substituent since this face is less sterically congested and hence results in the observed 7:1 product ratio. These isomeric β-lactams were conveniently separated by flash column chromatography, with careful elution, using a gradient solvent system.

The final stage in the synthesis was the simple removal of the protective TBDMS ether without harming the sensitive β-lactam functionality. This was readily accomplished by treatment with 2-3 equivalents of *tetra-N*-butylammonium fluoride in THF at ambient temperature, the fluoride ion in an aprotic medium being a powerful agent for the cleavage of silyl ethers in general. Once again the reaction could be conveniently by TLC and cleavage to the alcohol occurred rapidly at room temperature to furnish the β-lactam (**169**) in 86% yield (Scheme 4.9).



(**168**) (**169**)

Scheme 4.9

The successful synthesis of a useful carbapenem precursor was, therefore, completed starting from chloroacetone in six steps in 7.5% overall yield by S_N2 addition of an acetylenic Grignard reagent to chloroacetone

followed by simple dehydrohalogenation, in the presence of base, to furnish the epoxide (**163**). Conjugate addition of lithiummethyl(trimethyl)silane at -78°C afforded the (hydroxymethyl)allene (**165**) which was protected as its TBDMS ether before cycloaddition with CSI to yield the desired β-lactam (**168**). Simple TBAF deprotection at ambient temperature furnished β-lactam (**169**) possessing the precise C-3 alkylidene functionality of the asparenomycin antibiotics. The key step in this synthesis is the regioselective silicon-controlled [2+2] cycloaddition process which has proved to be of great utility in the preparation of monocyclic β-lactams.

Section 5.1 Chromatographic Separation of Diastereomers

Allene (**167**) is of course racemic, and reaction of CSI with a homochiral allene to form the β-lactam would enable the stereochemical features of the [2+2] cycloaddition reaction to be investigated. Asymmetric synthesis to produce an optically pure allene was disregarded due to the ambiguity in the mechanism of organocuprate conjugate addition reactions to propargyl derivatives which, coupled with the intermediate copper species ability to racemise the final product, led to varying degrees of enantioselectivity. Therefore, our only other alternative was to attempt the resolution of the (allenylmethyl)silanes.

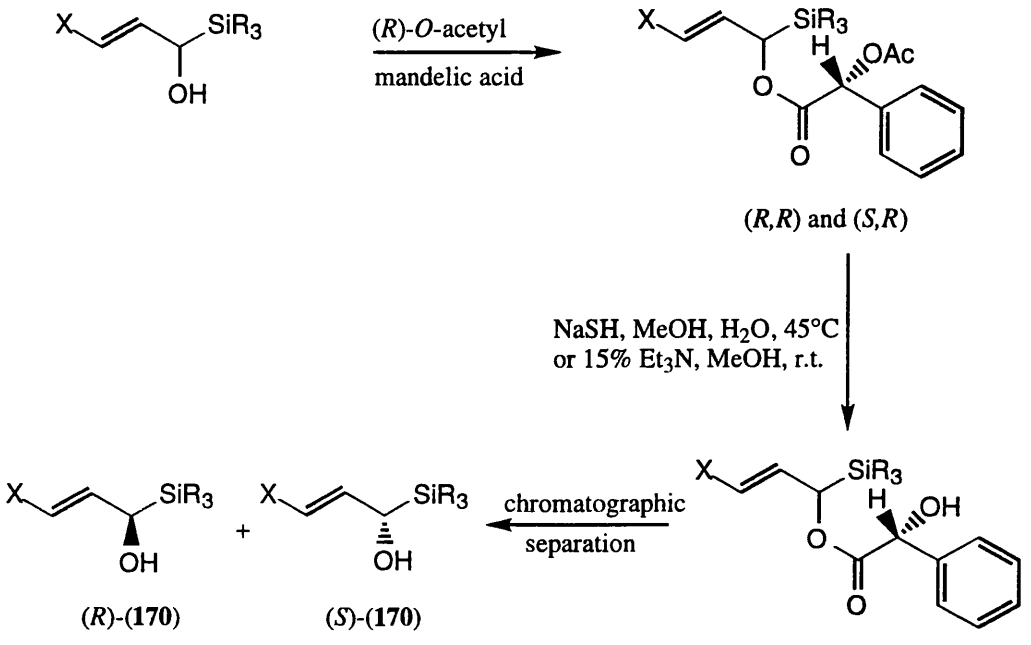
The basic principle of resolution is that enantiomeric discrimination has to be effected by the use of chiral reagents or a chiral medium through the formation of diastereomeric relationships. Unlike racemisation, resolution is not a thermodynamically favourable process and is not expected to occur spontaneously under ordinary circumstances.

Section 5.2 Formation of Diastereomers

Current methods for the resolution of chiral alcohols concentrate on the formation of diastereomeric esters through reaction with optically pure acids but this method suffers from the potential of the acid to racemise or self-condense during esterification. The number of enantiomerically pure, naturally occurring acids are few, but those that are generally effective for this technique are represented by camphanic acid [139] and α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's reagent).[140] Unfortunately, the use of these, as well as other acids, is hampered by inaccessability and/or high cost.

The use of mandelic acid as resolving reagent appeared to be a good option since it is relatively cheap and the mandelate esters of racemic alcohols have been prepared previously. The diastereomers formed have been shown to be easily separable by gas chromatography.[141] Furthermore, Panek and Sparks [142] have performed a classical resolution utilising (*R*)-*O*-acetylmandelic acid as the chiral handle for the development of a procedure for resolution and absolute stereochemical assignment of oxygenated allyl- and vinylsilanes.

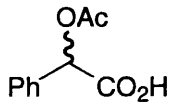
They found that the existing procedures of enzymic[143] and Sharpless kinetic resolution [144] for allylic alcohols were unsuccessful in these types of systems giving low ee's (Scheme 5.1).



Scheme 5.1

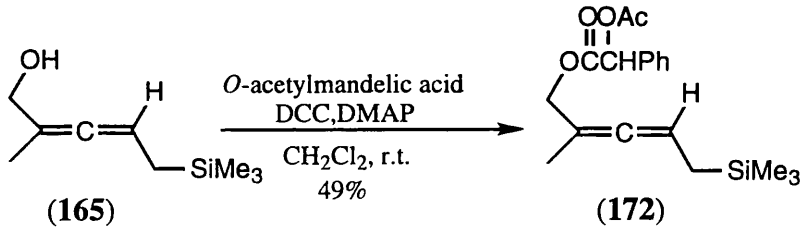
Resolution of the mandelate esters was accomplished by medium pressure chromatography eluting with a gradient solvent system affording 34% and 40 % of the (*S,R*)- and (*R,R*)-diastereomers, respectively. The two diastereomers eluted extremely closely and arbitrary fractions had to be checked by ^{1}H NMR for purity as TLC or UV detection did not show the separation. Lithium aluminium hydride reduction of the mandelate esters provided the desired alcohols (**170**) in optically pure form.

Adopting the procedure described by Panek and Sparks, we attempted the resolution of (hydroxymethylallenyl)silane (**165**). *O*-Acetylmandelic acid (**171**) was synthesised, albeit in poor yield, following the method outlined by Breitholle and Stammer.[145] The use of *O*-acetylmandelic acid provides an alternative procedure for the acid-sensitive allene since esterification then occurs under essentially neutral conditions. In this paper, treatment of racemic mandelic acid with neat acetyl chloride at 60 °C for 2 hours afforded crystalline *O*-acetylmandelic acid. However, in our hands a yellow oil was obtained from the reaction mixture which, even following acid/base extraction, required two days standing at 0 °C before crystallisation of the product occurred.



(**171**)

The (hydroxymethylallenyl)silane (**165**) was readily converted into the corresponding methylmandelate ester (**172**) by reaction with the semi-crystalline *O*-acetylmandelic acid using dicyclohexylcarbodiimide for carboxylate activation (Scheme 5.2). Chromatographic separation of the diastereomeric esters by medium pressure chromatography on silica gel was attempted but proved difficult at this stage due to the nonpolar nature of the esters. Various solvent systems were employed, with limited success, and further attempts at resolution using a gravity column with 100 % hexane as eluant yielded only small quantities of diastereomerically enriched material. NMR analysis of the recovered methylmandelate ester revealed a diastereomeric ratio of 9:1.5 but in quantities insufficient for use as a practicable method.

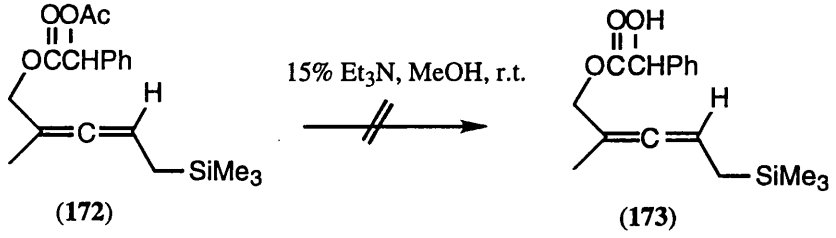


(**165**) (**172**)

Scheme 5.2

In an effort to impart more polarity to the esters, we attempted the selective hydrolysis of the acetate ester, in the presence of the mandelate, without damage to the sensitive allenylsilane. Whitesell and Reynolds [146] had previously reported the selective thiolysis of an acetylmandelate ester on a chiral secondary alcohol although this procedure only appeared to be successful when working in small quantities. On the other hand, Panek[142] conveniently overcame this problem by using a tertiary amine in anhydrous methanol. Under these conditions the rate of acetate cleavage is faster and he proposed that hydrolysis of the mandelate ester is not a factor. Thus, the mandelate ester (**172**) was treated with 15 % triethylamine in absolute methanol for 18 hours at room temperature. Unfortunately, in contrast to Panek's

observations, we were disappointed to observe complete hydrolysis of the mandelate ester, resulting in recovery of the (hydroxymethylallenyl)silane in almost quantitative yield, with none of the desired hydroxy ester (**173**) being isolated whatsoever.



(**172**) (**173**)

Gas chromatographic resolution of the diastereomeric *O*-acetylmandelate esters was seen as a more promising alternative, even though it is known that certain diastereomeric pairs can be separated only with great difficulty. A number of alkyl esters of mandelic acid have been successfully resolved by means of preparative gas chromatography [147] although their ease of separation has been explained by a *cis/trans* model, creating a structural difference in the diastereomeric pair. This *cis /trans* relationship occurs as a result of hydrogen bonding between the hydroxy group and the carbonyl oxygen causing restricted rotation and thus, fixing the molecule in one position. These *cis /trans* -isomers can therefore be considered as diastereomers and separation is easily effected.

In our system no such hydrogen bonding existed, since we employed the acetyl derivative of mandelic acid as the chiral handle in order to prepare the acid-sensitive allene ester. Thus, any structural difference in the axially disymmetric diastereomeric pair is minimal and resolution by gas chromatography again proved unsuccessful, even with the use of longer columns and increased retention times.

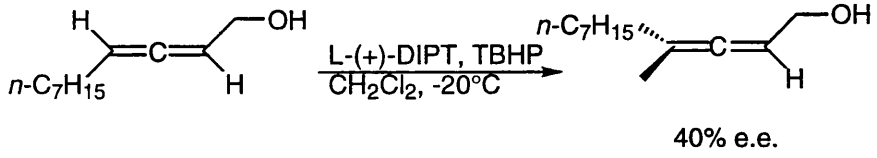
On the presumption that these structural differences were insufficiently different for separation of the two diastereomers by any form of chromatography employing an achiral stationary phase, we endeavoured to find a means of resolution relying on different properties of the allenic system.

Section 6.1 Kinetic Resolution

The enantioselective preparation of asymmetric compounds is an important and rapidly expanding area of chemistry. As an alternative to diastereomeric formation a pair of enantiomers can also be separated *via* kinetic resolution, whereby one of the enantiomers reacts faster with a chiral substrate than the other. Thus, there is an energy difference between the two diastereomeric transition states, which is manifested as a relative rate difference and, theoretically, the reaction should continue until the last molecule of the more reactive enantiomer is consumed, leaving a substance possessing absolute enantiomeric purity. However, kinetic resolution suffers from the disadvantage that at least half of the starting material is lost and is generally seen as a poor alternative to asymmetric synthesis.

By far the most efficient kinetic resolution in recent years has been Sharpless asymmetric epoxidation, [144] which has provided a convenient and widely applicable method for the preparation of a large number of chirally enriched compounds with enantiomeric excesses of >99 %. Epoxidation is a popular reaction in organic synthesis because the epoxide is readily opened to produce 1,2 functionality in a stereospecific manner and gives rise to the possibility of the simultaneous creation of two contiguous chiral centres in one reaction.

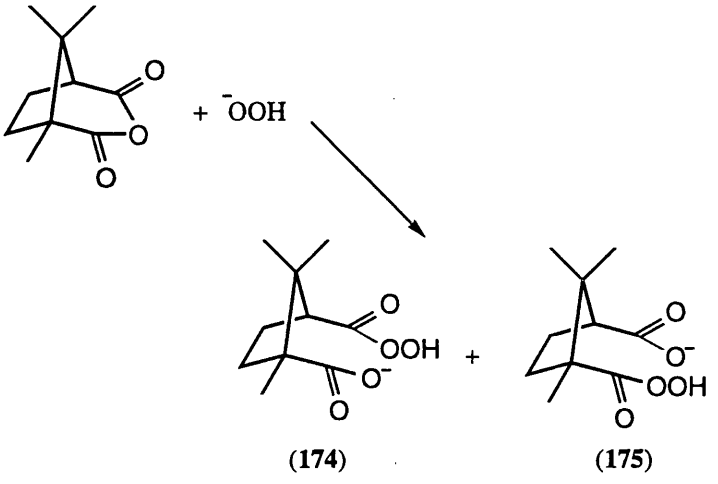
In particular, we were encouraged by the report[144] that allenyl alcohols had previously been successfully resolved by Sharpless asymmetric epoxidation with the recovered substrate possessing an enantiomeric excess of 40% (Scheme 6.1). This demonstrated that the same conditions could be applied to our system, hopefully resulting in the isolation of an enantiomerically enriched allenylsilane.



Scheme 6.1

The first reported asymmetric epoxidation was performed in 1965 by Henbest [147] who used (+)-peroxycamphoric acid to produce alkenes with disappointing enantiomeric excesses (ee's) of <5 %. In fact, most of the early attempts utilising chiral epoxy acids resulted in ee's approaching only 10 %. In

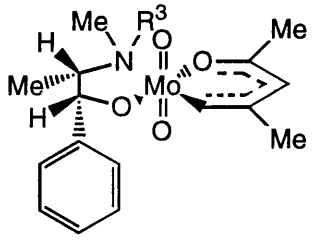
1977, Pirkle re-evaluated the use of peroxycamphoric acid as an asymmetric oxidising agent [148] and found that the peroxy acid used by previous investigators was not pure. He claimed that the unpurified extract contained a mixture of isomers (**174**) and (**175**) which led to decreased optical purity in the final products (Scheme 6.2). With purified oxidants he obtained increases in optical yield of 50-100 % to those previously reported for isolated alkenes.



(**174**) (**175**)

Scheme 6.2

The first reported cases of metal-catalysed asymmetric epoxidation involved allylic alcohols and a high-valent metal. Reactions with allylic alcohols proceed more rapidly and under milder conditions than the epoxidation of alkenes lacking a nearby hydroxyl group [149] due to the propensity of high-valent transition metals to form covalent metal-oxygen bonds quickly. The use of a high-valent metal is quite understandable when one realises that high levels of asymmetric induction must necessitate a transition state with restricted degrees of freedom. Application of an asymmetric metal catalyst is considered the most efficient way to minimise loss of a precious chiral source and in 1977 Yamada *et al* [150] employed a molybdenum complex (**176**) with *N*-alkylephedrine as the chiral ligand, successfully effecting asymmetric epoxidations with ee's of up to 33 %.



(176)

Yamada maintained that catalysts for asymmetric epoxidation must fulfill two requirements, namely that the catalyst should contain the chiral ligand which is fixed and does not dissociate from the central metal atom during the reaction, and secondly that the catalyst should also contain two labile ligands, both of which can be replaced by reactants under the influence of the fixed chiral ligand. This theory has been emphasised by Sharpless who reports [151] that a threefold excess of the transition metal catalyst is necessary in order to obtain high enantiomeric excesses.

Asymmetric epoxidation of allylic alcohols by hydroperoxides and titanium tartrates was discovered in 1980.[144] Sharpless had invested several years of effort in designing and screening numerous chiral ligands to modify vanadium- and titanium-catalysed epoxidations before settling on the dialkyl esters of tartaric acid as the ligands providing optimum stereoselectivities. The reaction was performed in a nonpolar organic solvent using an alkyl hydroperoxide (usually *tert*-butyl hydroperoxide, TBHP) as oxidant.

The beauty of the Sharpless epoxidation is that experimentally the epoxidations are quite straightforward and the reaction conditions can be manipulated in order to tailor them to a particular substrate. Furthermore, the stereochemical outcome of these kinetic resolutions is highly predictable. If the allylic alcohol is drawn as shown (Fig. 12) then the enantioface selection rule is that the L-tartrates mediate delivery of the oxygen atom to the bottom face of the alkene and correspondingly D-tartrates to the top face. In the majority of cases the reactions occur in yields ranging from 70-90% and with ee's of greater than 90 %.

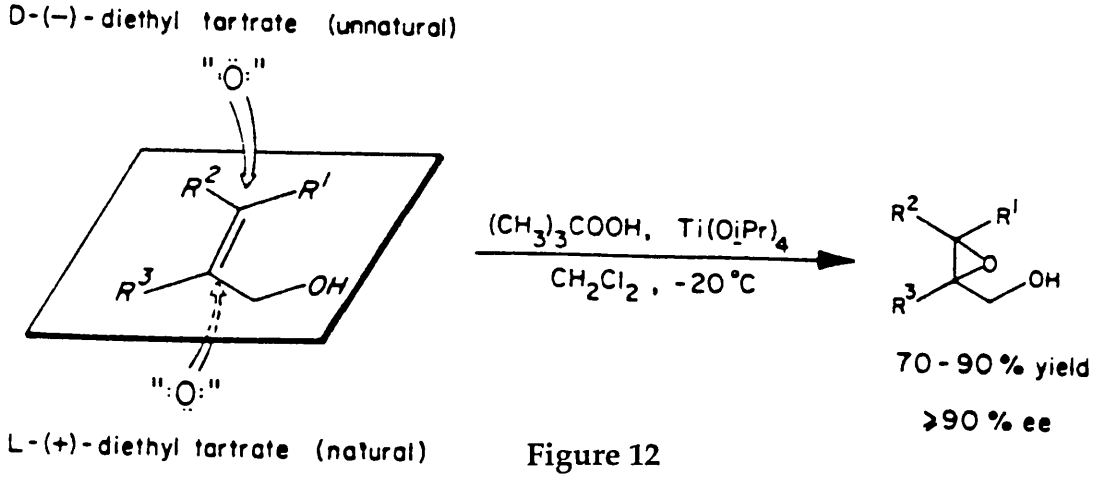


Figure 12

Asymmetric Epoxidation of Prostereogenic Allylic Alcohols

The titanium-catalysed epoxidation is favoured over other d^0 metal-catalysed epoxidations because of the ability to use a number of dialkyl tartrates as ligands as a means of inducing asymmetry into the reaction. According to the mechanism proposed by Sharpless and co-workers, the metal catalyst is a dimer consisting of two dialkyl tartrates covalently bound to two titaniums (Fig. 13). This structure has been proved both by NMR studies and mass spectral measurements performed on a mixture of equivalent molar amounts of $Ti(OR)_4$ and chiral dialkyl tartrate ligand in solution. This means that the allylic alcohol and alkyl hydroperoxide can then bind to either one of two of the equivalent metal centres.

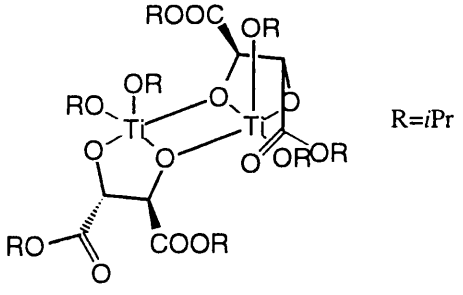


Figure 13 Catalyst Dimer

The first kinetic resolution of racemic secondary allylic alcohols by the titanium-tartrate-TBHP complex was reported in 1981.[152] The parameter of interest is the ratio of the rates of epoxidation of the fast (k_{fast}) and slow reacting (k_{slow}) enantiomers, termed as the " relative rate " ($k_{rel}=k_{fast}/k_{slow}$) because the efficiency of the resolution is closely related to the magnitude of k_{rel}.

Another possible explanation is that kinetic resolution could instead be due to different affinities of the enantiomeric substrates for the chiral metal centre. If both enantiomers were epoxidised at the same rate but one enantiomer was a substantially better ligand than the other then again, kinetic resolution would occur.

For efficient resolution of allylic alcohols Sharpless has stipulated a particular set of reaction conditions. In the original report [144] on the titanium-catalysed epoxidation the general procedure called for a stoichiometric amount of the " titanium-tartrate " catalyst, however, a later modification allowed the asymmetric epoxidation to be carried out with just 5-10 mol. % of the catalyst.[153]

The key feature of the catalytic modification was the use of molecular sieves (zeolites) whose role is vital to the success of the reaction increasing both rate and selectivity. The molecular sieves are used not only during the course of the reaction but also as a desiccant for the allylic alcohol and TBHP solution. The main function, however, is the protection of the catalyst from adventitious water present in the reaction medium (3Å, 4Å and 5Å sieves are equally effective). Water reacts rapidly with titanium alkoxides to give titanium hydroxides and oxo-bridged units (Ti-O-Ti) [154] consuming available co-ordination sites and thus poisoning the catalyst. In the absence of molecular sieves one equivalent of water is sufficient to destroy the catalyst system.

The interaction of water with the catalyst is initially reversible, molecular sieves being capable of shifting this equilibrium toward the water-free state, however, eventually the molecular sieves become saturated and are not capable of fully regenerating the active system.

Applying these new conditions, we attempted kinetic resolution of the allenyl alcohol (**165**) *via* Sharpless asymmetric epoxidation using 5 mol. % of the catalyst system as recommended. Reactions were performed employing the natural (+)-diisopropyl tartrate (DIPT) and (-)-diethyl tartrate (DET) as chiral ligands in dichloromethane at -20 °C (Drikold/acetone bath). Cooling serves two purposes, the obvious one of optimising enantioselectivity and the less obvious one of minimising transesterification processes, since it is well known that titanium alkoxides are excellent transesterification catalysts.

The nature of the oxidant is also important and from a study investigating various oxidants and oxidation solvents, Sharpless now stipulates the use of *tert*-butyl hydroperoxide in isooctane, since this appears to be the most stable system showing very little difference in selectivity either in the presence or absence of molecular sieves.

In our system no epoxide was isolated from the reaction medium since the vinyl epoxide formed is a highly unstable, water-soluble oxirane which ionises readily and is lost in the workup (Fig. 14).

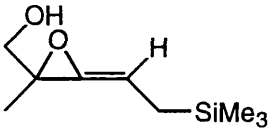


Figure 14

However, the starting allenyl alcohol was recovered in the expected yield and optical purity measurements indicated that there had indeed been some enantioselectivity during the course of the reaction. Synthesis of the β-lactams was completed using these chirally enriched alcohols and the yields and optical rotations of the enantiomeric allenes and product β-lactams using each chiral ligand are shown in the following table.

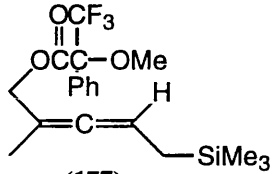
	OH		OTBDMS		β-lactam	
Chiral Ligand	Yield (%)	Optical Rotation	Yield (%)	Optical Rotation	Yield (%)	Optical Rotation
(+)-DIPT	37	+2.89	53	+2.38	10	+0.61
(-)-DET	32	-2.94	54	-4.40	28	-0.42

Variation of the tartrate ester is a useful parameter to examine when seeking optimal conditions for a specific reaction and Sharpless had found that increasing the size of the alkyl group in the tartrate ester significantly increases the rate difference for epoxidation of both the (*R*) - and (*S*)-enantiomers. This effect appears to arise principally from a further retardation in the rate of the slow-reacting enantiomer. For this reason DIPT is regarded as the best tartrate for kinetic resolutions although we did not observe improved enantioselectivities when using this ligand indicating that the structure of the tartrate ester had little, if no effect, on enantioselection and, therefore, did not consider this to be an important reaction variable.

Also, the use of excess tartrate is very important in these reactions. Under the reaction conditions titanium alkoxides undergo rapid ligand

exchange processes which are essential for the catalysis but can also give rise to significant concentrations of achiral titanium alkoxide catalysts resulting in the incursion of epoxidation pathways involving titanium alkoxide species which are not ligated to tartrate, thus, lower enantioselectivities are observed. As a consequence, Sharpless recommends a titanium-tartrate ratio of 1:>1.2 in order to overcome this problem.

Synthesis of the Mosher's ester (**177**) of the kinetically resolved alcohol enabled the determination of the enantiomeric excess by analysis of the ^{19}F NMR (^{1}H NMR exhibited no diastereoselection), however, a poor enantiomeric excess of only 9 % was observed.



(**177**)

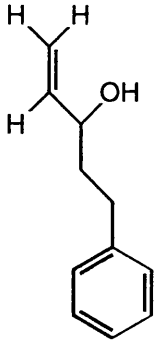
There are several possible reasons for this poor enantioselectivity in the Sharpless epoxidation reaction but the principal inhibiting factors are water from incompletely dried reagents, solvents or equipment, and also from small amounts generated during the reaction from side reactions such as oxidation to the aldehyde or slow titanium-catalysed decomposition of the hydroperoxide. However, the presence of water was not thought to be a major cause, in our case, as both the experimental glassware and the molecular sieves were scrupulously dried beforehand by standing in an 150°C oven for several days and the solvents were distilled immediately prior to use. Diol ethers generated by *in situ* opening of the epoxy alcohol products can also cause lower selectivity. By virtue of their chelating ability they bind well enough to the remaining two ligand sites of a titanium centre to prevent TBHP and allylic alcohol from gaining access to the metal. It is our belief that the poor enantioselectivity observed in our reaction was caused principally by formation of the water-soluble oxirane side product whose high instability and propensity for ring opening significantly decreases the efficiency of the kinetic resolution.

A major cause of poor enantioselectivities is improper preparation of the catalyst. Correct preparation of the catalyst is crucial for optimal rates and selectivity. In general, the catalyst is prepared *in situ* by mixing the tartrate and $Ti(O\text{-}iPr)_4$ at -20 °C, whereupon TBHP is added. The three components are

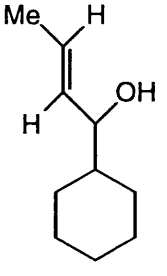
stirred together at -20 °C for 30 minutes prior to the addition of the allylic alcohol, which is added last to minimise transesterification processes. This "ageing" process is critical to the success of the reaction.

The nature of the allylic alcohol seems to have little effect on stereoselectivity. Placing alkyl groups at four of the five possible positions of the allylic alcohol results in little or no loss of enantioselectivity suggesting that the alcohol is subject to a set of enantioselective interactions that are not substantially disturbed by substitution on the carbon skeleton. Therefore, the interactions responsible for kinetic resolution cannot be wholly steric in nature. The expected dependence of rate on alkene substitution is observed though, with the more highly substituted double bond giving a greater epoxidation rate.

However, investigations on a variety of substituted allylic alcohols have shown that *trans* substitution at C-3 leads to high enantioselectivities since this position is the least sterically encumbered. It takes the substitution of a very large, branched structure at the (*E*)-C-3 position of the allylic alcohol to perturb the asymmetric epoxidation to a significant extent. On the other hand, the C-2 and (*Z*)-C-3 positions are more sensitive to steric hindrance and substitution of bulky groups in these positions leads to greatly diminished stereoselectivity in the epoxidation reaction. In our system there is a methyl substituent at C-2 but this group is presumed not to be bulky enough to merit the low optical purities observed. Similarly, the methylene group at C-1 does not affect the epoxidation because while it has been shown that aryl (**178**) and secondary alkyl groups (**179**) at C-1 give excellent kinetic resolution, substitution of a large *tert*-butyl group here resulted in complete loss of enantioselectivity.

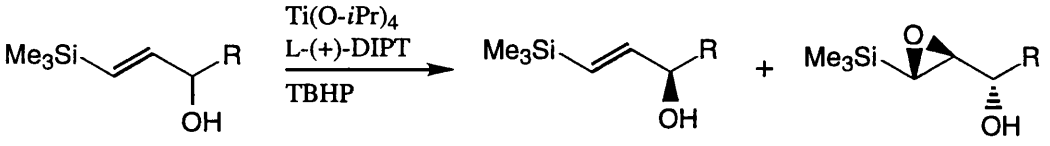


(178)
99% e.e.



(179)
97% e.e.

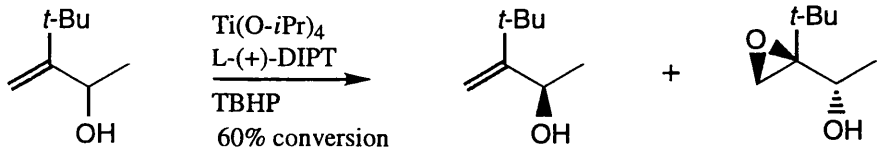
There is evidence in the literature for a very highly efficient kinetic resolution of secondary allylic alcohols bearing a trimethylsilyl group by the Sharpless asymmetric epoxidation. Kitano *et al* [155] have demonstrated that the presence of a trimethylsilyl group in the C-3 position of allylic alcohols results in the increase of both the rate of epoxidation and also the magnitude of k_{rel} (Scheme 6.3).



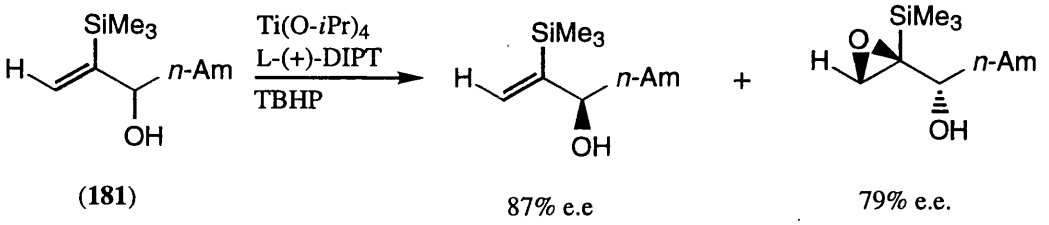
Scheme 6.3

In all cases both the allylic and epoxy alcohols were obtained with enantiomeric excesses of >99 % with the exception of the sterically demanding *tert*-butyl group which gave an enantiomeric excess of only 13 %. The β-trimethylsilyl secondary allylic alcohols also gave exceedingly high optical purities, which is surprising in view of the fact that it is reported that secondary allylic alcohols with bulky tertiary groups in the β-position are not good kinetic resolution substrates. In the reaction of (**180**) the enantiomeric excess of the recovered starting alcohol was only 30 % at 60 % conversion, whereas, substitution of the *tert*-butyl group with a trimethylsilyl to give compound (**181**) pushed the enantiomeric excess up to 87 %.

The high efficiency of the kinetic resolution observed here may be attributed to two factors concerning the trimethylsilyl group i.e. the steric effect and the electronic effect. The electronic effect, however, seems to be more important since there is a significant difference in the efficiency of the kinetic resolution of (**180**) and (**181**) which must be accounted for by more than just a simple decrease in the steric bulk (Scheme 6.4).



(**180**) 30% e.e



(**181**) 87% e.e 79% e.e.

Scheme 6.4

Thus, although high ee's have been observed from the kinetic resolution of both allenic[144] and silyl-substituted [155] allylic alcohols in the literature, the ee obtained from the kinetic resolution of allenyl alcohol (**165**) was disappointingly low and, once again, an alternative resolution procedure was required.

Section 7.1 Chromatographic Resolution Employing Cellulose Triacetate

Over the past few years, with the expanding interest in biological processes, which are often highly stereoselective, the chromatographic resolution of chromatographic compounds on chiral stationary phases has developed in parallel to asymmetric synthesis.

Different types of sorbents have been used for this purpose, although the main drawback appears to be the solubility of the sorbent in organic solvents. One of the main approaches to overcoming this problem has been the use of naturally occurring, optically active polymers as the chiral stationary phase. These substances are preferred because of their insolubility in most of the commonly used eluant mixtures. Similar to the 'lock and key' interaction between an enzyme and its substrate, the polymer can lock onto the different stereochemistries of each enantiomer and thus provide chiral recognition.

In order for a polymer to be suitable as a chiral stationary phase it must possess certain characteristics. Obviously, the polymer must be chemically stable and, in particular, stable to the organic solvents which are going to be encountered during the resolution process. If HPLC is to be used , then the polymer must possess sufficient mechanical strength to withstand the pressures applied. The degree of rigidity within the structure is dependent on the extent of crosslinking. Most importantly, they need to have a highly ordered structure so that there is only one type of chiral absorbing site, thus maximising the resolving ability of the polymer.

Cellulose is an obvious choice as a potential chiral stationary phase as it fulfills all of these criteria, being inherently optically active with a highly ordered structure capable of stereoselectivity. Native cellulose, referred to as cellulose I, exists as a highly crystalline, unbranched polymer consisting of repeating D-(+)-glucose residues joined together by α-1,4-linkages (Fig. 15).

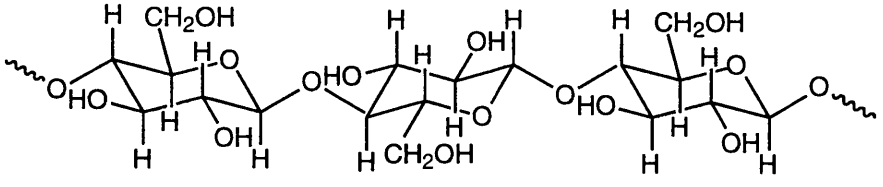


Figure 15 Structure of Cellulose

X-ray analysis and electron microscopy of cellulose taken from the sea algae *Valonia venticosa* [156] has established that hydrogen bonding between the numerous neighbouring hydroxyl groups results in these chains being aligned side by side in bundles which twist further to form helical structures. It is these rope-like helical structures with which the enantiomer of interest stereospecifically interacts and resolution of the racemic mixture consequently occurs. However, although cellulose has been used for many years as a resolving agent, its resolving power is poor and it is inclined to swell in many solvents and may start to collapse under pressure.

Hesse and Hagel [157] were the first to note that derivatisation of the hydroxyl groups in cellulose did not destroy its helical structure. In fact, much to the contrary, this gave rise to a whole new group of cellulose derivatives which had a greater resolving power than native cellulose itself. Many different types of cellulose derivatives have been prepared although the esters, in particular, have proved to be extremely useful chiral phases. Resolutions performed on the tribenzoate, trisphenylcarbamate, tricinnamate, as well as on the triacetate derivatives, have all proved successful, usually in different areas of application. In general, cellulose triacetate is suitable for many racemates, especially those containing a phosphorus atom at the asymmetric centre.

Cellulose triacetate is obtained by heterogeneous acetylation of native cellulose or microcrystalline cellulose and is believed to maintain the cellulose I structure. The relationships between cellulose and its triacetate were studied in detail by Sprague *et al*[158] who confirmed that the crystallographic structure is dependent on the crystallographic form of the original cellulose and also on the experimental conditions used for the acetylation process. They found that there were two types of cellulose triacetate (CTA), namely CTA I which was obtained by heterogeneous acetylation of cellulose I (i.e. no dissolution), whereas CTA II, with a different crystal structure, is formed if dissolution of the acetate occurs during the acetylation process.

The premise for the chromatographic separation of enantiomers is retention and subsequent chiral discrimination. Once again it was Hesse and Hagel [159] who first demonstrated that the morphology of cellulose plays an important role in the chiral recognition process. During the recognition mechanism the enantiomers intrude into certain kinds of chiral cavities between the laminae in the crystalline regions of cellulose. This type of chromatography has been termed 'inclusion chromatography', where the guest molecules are jammed in the crystalline sections of a swollen macromolecular gel.

The role of crystallinity of cellulose triacetate and its influence on chiral recognition mechanisms has been investigated by Francotte *et al.* [160] They found that an increase in the crystallinity of cellulose triacetate resulted in a material with a lower loading capacity and a reduced ability to discriminate between enantiomers. From these observations they rationalised that inclusion of the molecules in the chiral cavities had diminished, probably as a consequence of reduced mobility of the glucose units in the polymeric chains. Obviously, the space between polyglucoside chains constitutes a highly ordered chiral environment, with each glucose unit having five chiral carbon atoms. Since the interaction energies are very sensitive to the spacial arrangement of all molecules in the chiral cavities, then even moderate alterations in the crystal structure may strongly influence the chiral recognition process. In the extreme case, a perfect crystallite will be too tightly packed to allow the inclusion of a molecule into the lattice. These findings are in agreement with an earlier proposal [159] which stated that amorphous cellulose is not useful as a stationary phase owing to a supposed loss of these chiral cavities.

The main influencing factor for chiral recognition with cellulose triacetate as a stationary phase is the choice of mobile phase. Thus the nature of the solvent employed during the chromatographic separation is critical to the degree of enantioseparation obtained. The solvent generally acts first as a swelling agent and then as a dispersing agent. In most cases ethanol or ethanol/water mixtures have been used since ethanol has a high dielectric constant and interacts strongly with the acetoxy groups of the cellulose triacetate, probably through H-bonding, affording the greatest resolution. However, it should be noted that chlorinated solvents, such as dichloromethane or chloroform, are unsuitable as they remove the derivatised cellulose from its silica support.

It has been proposed by Scallan [161] that swelling causes some cleavage in the radial planes of cellulose and an intrusion of solvent between the fibrils is thus possible giving the swollen cellulose the appearance of a 'honeycomb' (Fig. 16).

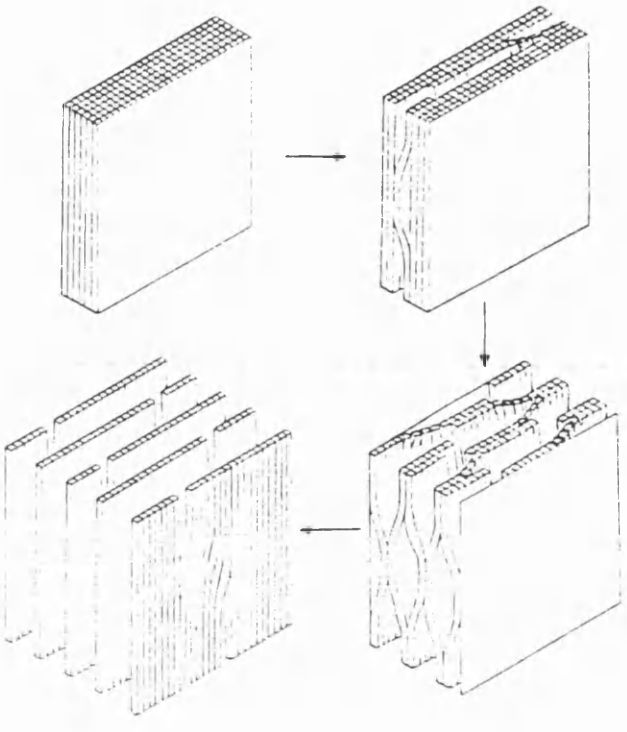


Figure 16

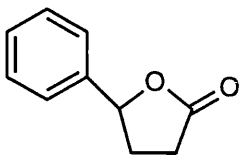
Scallan's Modification of the Lammellar Structure of a Delignified Cell Wall

Little is known about the role of the swelling agent in the chiral recognition process, although it has been shown that nonswollen cellulose triacetate only displays a weak chiral recognition ability. However, it is thought that ethanol probably adopts the same role as the water layers in normal-phase silica.[162] Nevertheless, what has become apparent is that the chiral cavities in the sorbent are situated between the elementary fibrils of the swollen material (see Fig. 16) and not between the individual cellulose molecules or indeed within the actual crystals themselves.

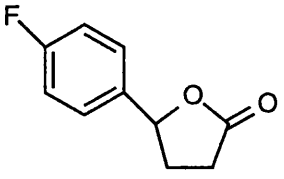
The presence of such a clearly defined chiral cavity has led to a better understanding of the mechanistic aspects of molecular interactions between cellulose triacetate and different types of enantiomers. Hesse and Hagel [159] concluded that inclusion between the laminae is governed mainly by the shape of the included molecules and only to a minor extent, if at all, by other factors such as electrostatic interactions involving the functional groups of the molecules. They proposed that in such an asymmetric environment the conditions for inclusion of the two mirror image isomers of a chiral molecule are significantly different so that one of the enantiomers is preferentially bonded and retained. This bonding becomes reversible when a suitable solvent is chosen, whereby a sorption equilibrium is established and the two enantiomers can be chromatographically resolved.

It has been shown[160] that separation is even more effective if one of the substituents at the asymmetric centre is an aromatic nucleus. It is this portion of the molecule which will enter the cavity because then the aromatic ring is jammed in the niches between every two acetylated glucose units in a defined position.

Francotte *et al* [163] have demonstrated this in their enantioseparation of five- and six-membered ring lactones. They showed that lactones bearing an aryl substituent interact more strongly with the cellulose triacetate support than the analogous alkyl lactones. In addition, the substituent on the aryl moiety can have a dramatic effect on the chiral discrimination. Accordingly, lactone (**182**) exhibited a much greater enantioseparation than the *para*-substituted fluoro derivative (**183**).



(182)

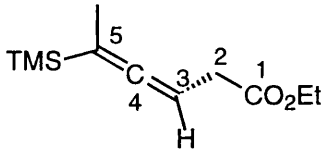


(183)

In a continuation of this study the authors also noted that compounds bearing a hydroxyl functionality (alcohols, acids etc.) are not resolved under the usual chromatographic conditions. This is thought to arise because these types of substrate are strongly solvated by the eluant which disfavours interaction with the solid phase and so very short retention times are observed.

All of the above resolutions have been performed using chiral HPLC, however, as a result of its outstanding properties, cellulose triacetate is also extremely efficient for normal chromatographic separations.

Recently, a chromatographic method for the enantioseparation of allenes was described employing cellulose triacetate as the chiral support in reverse phase chromatography.[164] In this paper a number of allenyl esters were successfully resolved with high yields and enantioselectivities. During the course of their studies Krause and Handke discovered that the separation factor and enantiomeric excess showed a strong dependence on the size of the substituents attached to C-5 of the allene. However, in contrast to this statement, the number of substituents attached to the allene moiety appeared to bear no relation to the efficiency of the enantioseparation. For a series of ethyl esters the trimethylsilyl substituted allene (**184**) displayed the greatest degree of enantioselectivity.

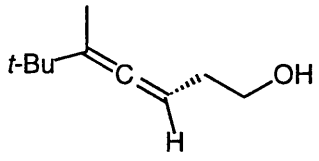


(184)

e.e.>98%

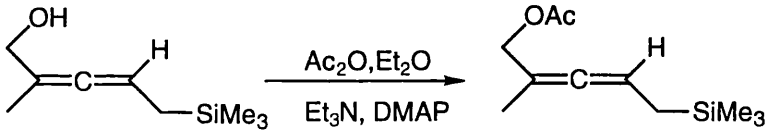
In accordance with the results obtained by Francotte and co-workers[163] no enantioseparation by preparative column chromatography was observed for

the allenyl alcohol (**185**) despite the existence of a large *tert*-butyl group at the C-5 position.



(**185**)

As a consequence, Krause and Handke[164] concluded that the presence of a carbonyl function in the allene is essential. Enantioseparation was achieved for allenes bearing ester, thioester and keto groups, whereas the alcohol showed no separation whatsoever. Thus, with so many precendented examples of successful enantioseparations of chiral allenes in the literature, we attempted the resolution of the hydroxyallene (**165**) by reverse phase chromatography using commercially available cellulose triacetate (Merck, 16363, 25-40 micron) as stationary phase and ethanol as eluant. Taking into account the observations made by Handke, allene (**165**) was converted into its acetate (**186**) by simple reflux with acetic anhydride in the presence of triethylamine (Scheme 7.1).



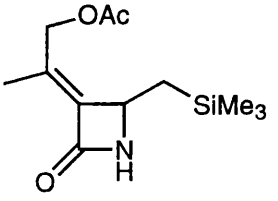
(**165**) (**186**)

Scheme 7.1

Prior to column packing the cellulose triacetate was refluxed in absolute ethanol for half an hour to induce swelling and packed as a slurry. Reverse phase chromatography using ethanol as eluant resulted in the partial resolution of the allene (**186**). Fractions were taken at regular intervals and the solvent removed from each separate fraction before optical rotation measurements were obtained. The results from a typical resolution are shown in the table below.

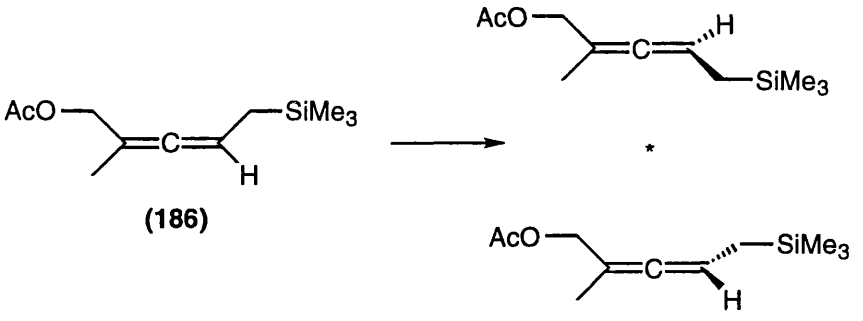
Fraction	$[\alpha]_D$ (EtOH)
12	-34.38
13	-13.25
14	-8.37
15	+1.94
17	+25.34

The combination of suitable fractions (as determined by optical rotation measurements) provided two samples of resolved acetate with $[a]_D^{22}$ +35° and -29°, corresponding to enantiomeric excesses of 82.4% and 67%, respectively. It had been shown previously within the research group[165] that (acetoxymethyl)allenes are unsuitable substrates for reaction with CSI. The acetoxy group was seen to be an unsatisfactory means of protection, since hydrolysis of the protecting group occurred under the reaction conditions and none of the desired β-lactam product (**187**) could be isolated. Thus, a more stable form of protection was required, and as in the racemic synthesis described earlier, the TBDMS ether was considered to be the best choice.



(**187**)

Ester cleavage was readily affected in 84% yield by alkaline hydrolysis employing weak conditions (K_2CO_3/MeOH) in order to keep the sensitive allene functionality intact. Monitoring of the reaction by TLC indicated that removal of the acetyl group occurred fairly readily and, in fact, the starting material was completely consumed after stirring for two hours at ambient temperature. Subsequent formation of the TBDMS ether and separate cycloaddition of these allenes with CSI as before afforded, after reductive cleavage, the TBDMS protected β-lactams with enantiomeric excesses of 48.5% and 42%, respectively (see Fig. 17).



500 mg, column 230 x 25 mm cellulose triacetate (25-40μ), EtOH

Combined Fractions	OH		OSiMeBu-*t*	β-lactam
	ca. 85% →	quant. →	ca. 30% →	
12-13 159 mg	-29.5° e.e. 67.0%	-32°	-31.8°	-17.6° e.e.42.1%
17-28 252 mg	+34.9° e.e. 82.4%	+33.1°	+36.2°	+16.9° e.e.48.4%

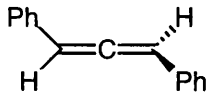
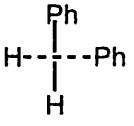
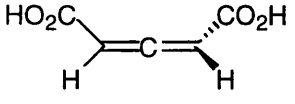
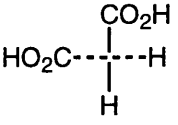
Figure 17
Chromatographic Separation by Cellulose Triacetate

Thus, a partial resolution of the acetoxyallene (**186**) was successfully accomplished using cellulose triacetate as stationary phase and, furthermore, cycloaddition of the allene with CSI demonstrated that there had indeed been transfer of the axial chirality of the allene to the C-4 carbon-centred chirality of the product β-lactams with approximately 60% efficiency (for a discussion of this observation see Section 9.1).

Resolution of the allenes should also enable us to determine the absolute configuration of the two separate enantiomers by the application of Brewster's rules. [166] According to Brewster " a center of optical activity can be described as an asymmetric screw pattern of polarizability". This hypothesis encompasses a set of empirical rules relating the sign of the optical rotation to structure, conformation and absolute configuration.

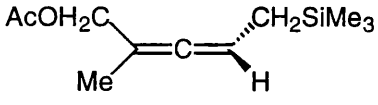
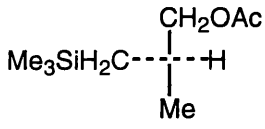
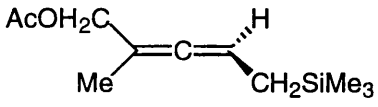
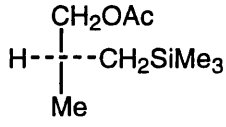
The high degree of success in predicting the absolute configuration of molecules containing asymmetric carbon atoms using the relative polarisabilites of the substituents prompted Lowe [167] to suggest that the same principal might apply to disymmetric allenes. By correlating the structure with

the absolute configurations of allenes whose absolute configuration had previously been established he was then able to predict their sign of rotation.

Absolute Config. of Allene	View Along Orthogonal Axis	Screw Pattern of Polarisability	$[\alpha]_D$	Config.
		clockwise	+	*S*
		anticlockwise	–	*R*

Lowe claimed that if the allenes are viewed along their orthogonal axes with the more polarisable substituent being placed at the top of the vertical axis, then if the more polarisable substituent in the horizontal axis lies to the right then a clockwise (or left-handed) screw pattern of polarisability will be obtained and the enantiomer should be dextrorotatory. On the other hand, if the more polarisable substituent in the horizontal axis lies to the left, then an anticlockwise (right-handed) screw pattern of ploarisability is obtained and the enantiomer is laevorotatory.

If we consider the allenylacetate (**186**) in a similar manner, then the order of polarisability of the four substituents will be $CH_2OAc>CH_2SiMe_3>Me>H$ and placing the most polarisable group at the top of the vertical axis will give the two enantiomeric structures (**186**)-A and (**186**)-B shown. By comparing these structures with the table above we can, therefore, deduce that the allene (**186**)-A will have a -ve optical rotation with a *R* configuration.

Absolute Config. of Allene	View Along Orthogonal Axis	Screw Pattern of Polarisability	$[\alpha]_D$	Config.
 (**186**)-A		anticlockwise	–	*R*
 (**186**)-B		clockwise	+	*S*

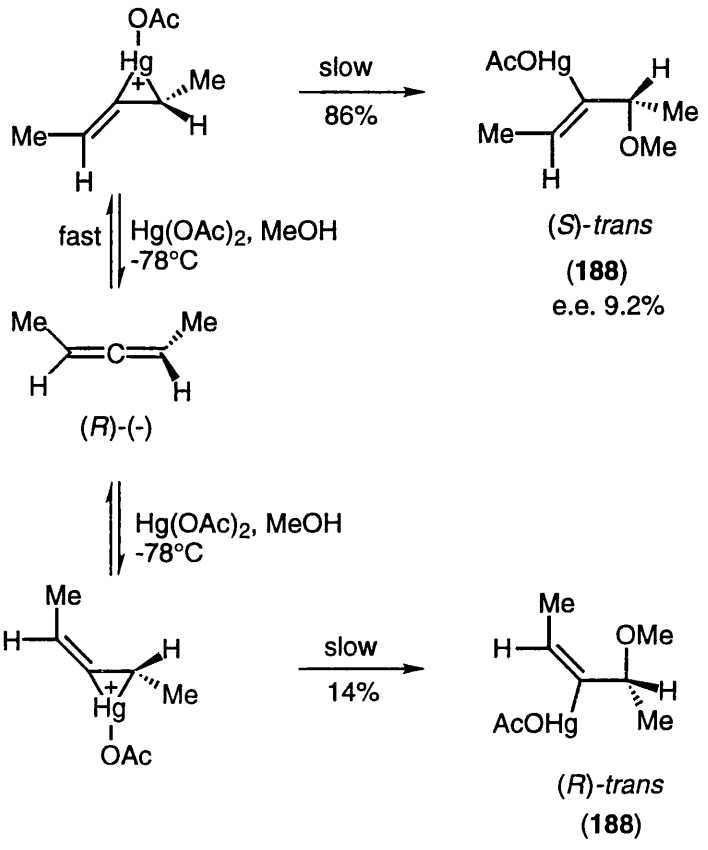
In conclusion then, the partial resolution of the allenylacetate (**186**) by reverse phase chromatography using cellulose triacetate as the chiral stationary phase afforded the (*R*)-(-)- and the (*S*)-(+)-allenes displaying enantiomeric excesses of 67% and 82.4%, respectively; the absolute configuration of the allenes being determined by Brewster's rules.

Section 8 .1 Determination of Enantiomeric Excess

Once the allenes had been resolved, one of the major problems we encountered was determination of the enantiomeric excess. Obviously, since the allenes display axial asymmetry rather than chirality at a tetrahedral sp^3 carbon centre, then any difference between the diastereomers of such compounds will be minimal and as a result the complete resolution of such axially chiral compounds proved to be no easy task.

Despite considerable interest in the chemistry of chiral allenes, there is a scarcity of absolute methods for determining the enantiomeric purity. Most of the published examples deal with determination by correlation to a given reference substance and absolute methods have not been employed. In some of the recent papers describing the synthesis of optically active allenes and vinyl allenes,[128] the specific rotations of the pure enantiomers have even been omitted altogether. Chemical transformation of the chiral allene to a known reference compound is also seldom observed as most reactions that might be used to modify the allene functionality do not proceed stereospecifically.

NMR methods are generally of more fundamental applicability but again, reports of the application of chiral shift reagents in allenic chemistry are rare. Pirkle and Boeder[168] applied an indirect approach by analysing the chiral ethers (**188**) obtained *via* methoxymercuration of chiral allenes by using ^1H NMR in the presence of (*R*)-1-(9-anthryl)-2,2,2 trifluoroethanol as chiral solvating agent and thus were able to estimate the enantiomeric purity of the starting allenic hydrocarbon (Scheme 8.1).



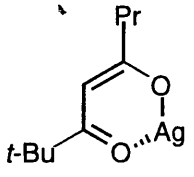
Scheme 8.1

Earlier work had shown that the use of chiral fluoro alcohols as chiral solvating agents in NMR had been successful. The spectra of enantiomeric benzylic, allylic, or propargylic alcohols and their ethers had been rendered nonequivalent by the use of these reagents.

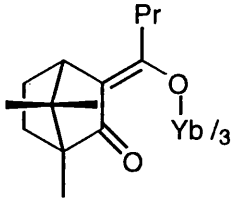
Pirkle favoured the methoxymercuration transformation of the chiral allenes to form the corresponding mercury-containing methyl ethers as this reaction was believed to be highly stereospecific and, furthermore, the methoxy groups give rise to sharp singlets in the NMR spectrum making determination of the enantiomeric purity relatively staightforward. However, this procedure may not be completely accurate as it relies on complete stereospecificity during the methoxymercuration reaction. A second hindering factor is that this method is more or less limited to equally 1,3-disubstituted allenes, otherwise too many stereo- and regioisomers are formed which further complicate the NMR spectrum.

Mannschreck and co-workers [169] describe the first absolute method for the determination of the optical purity of allenic hydrocarbons. This procedure is particularly useful as it does not rely on the enantiomeric purity of the chiral auxiliary or on the stereospecificity of a reaction. These authors adopted a

method which had previously been developed for the direct chiral recognition of monoethylenic hydrocarbons. The procedure relies on a mixture of the achiral salt (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)silver [Ag(fod)] (**189**) and the addition of an optically active lanthanide complex tris[3-(heptafluoropropylhydroxymethylene)camphorato]ytterbium(III) derivative [(+)-Yb(hfc)$_3$] (**190**) with one equivalent of each being added to one equivalent of the allene in a NMR sample tube.



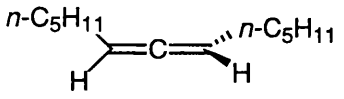
(189)



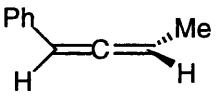
(190)

The lanthanide metals are paramagnetic and in NMR have a pronounced anisotropic effect on the local field experienced by a nearby magnetic nuclei, thus, inducing shifts in the NMR spectrum. They are usually only effective with certain classes of compounds such as alcohols, esters, amines, ketones and epoxides since these chemical shift reagents operate by associating with nonbonding electrons in the substrate through the metal orbitals. In an incompletely resolved enantiomeric mixture the two enantiomers under investigation may have different binding constants and when bound to the metal complex can even adopt different conformations with the result that their signals are shifted to different extents. This provides a good means of determining the proportion of *R* and *S* forms present. By mixing these lanthanide shift reagents with a silver analogue, spectral shifts can also be induced in alkenes and aromatic compounds since silver (I) has a high affinity for π-electrons.

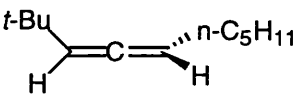
In Mannschreck's paper[169] the observed shifts of the allenes were comparable to the induced shifts of heterofunctional organic compounds in the presence of lanthanide complexes alone. In this manner, the enantiomeric excesses of 1,3-disubstituted allenes (**191-193**) were successfully determined and led to the optical purities shown (Scheme 8.2).



(*R*)-(-)-(**191**)
o.p. 49%



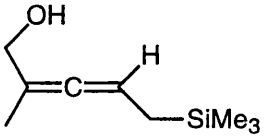
(*R*)-(-)-(**192**)
o.p. 15%



(*R*)-(-)-(**193**)
o.p. 11%

Scheme 8.2

Although not following this procedure exactly, we did attempt the absolute determination of the enantiomeric excess of the allenyl alcohol (**165**) by employing chiral lanthanide shift reagents and analysing the NMR spectra obtained.

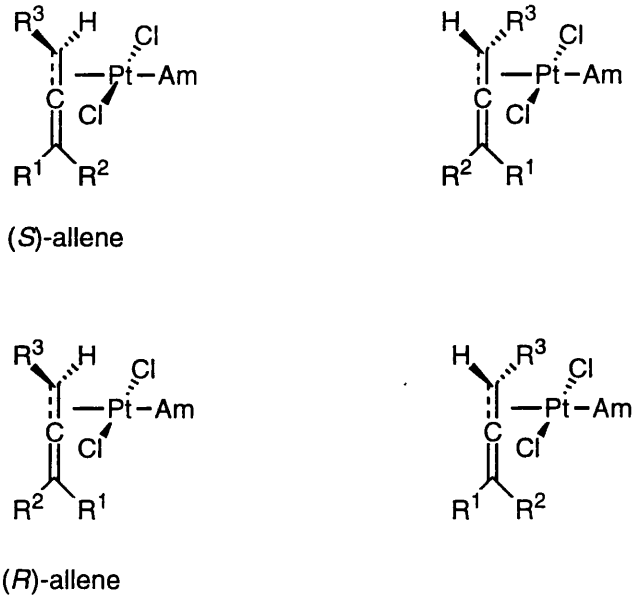


(**165**)

Chiral lanthanide shift reagents represent a useful combination of a chiral solvating agent and an achiral lanthanide shift reagent. However, compared to chiral solvating agents, chiral lanthanide shift reagents can be employed to a greater variety of organic and organometallic compounds. In addition, the magnitude of the spectral nonequivalence is far greater leading to more accurate enantiomeric excess determinations.

In our case the tris[3-(heptafluoropropylhydroxymethylene) camphorato]europium (III) derivative [Eu(hfc)$_3$] was employed, adding 0.1 equivalents to a sample of the trisubstituted (hydroxymethyl)allene (**165**) dissolved in deuterochloroform in a NMR tube and gradually increasing the amount of shift reagent added in order to detect any change in chemical shift of either the allenic proton or the methyl signal at C-2, since in the study by Mannschreck these were the the two proton signals in the allenic hydrocarbon most noticeably shifted. However, the results were disappointing and even with 2 equivalents of the shift reagent added to the sample no movement of signals were detected either in the 200 MHz ^{1}H- or ^{13}C-NMR spectra. From these observations we can only conclude that either the chiral auxiliary was not enantiomerically pure or, which is more likely, the chemical nonequivalence of the diastereomeric pair formed was not sufficient enough to be detected by 200 MHz NMR.

The enantiomeric determination of trisubstituted chiral allenes has been described by Salvatori *et al.* [170] In this paper the diastereomeric complexes of *trans*-dichloro[(*S*)-α-methylbenzylamine](allene)platinum (II) were prepared by treating the allene with *trans*-dichloro[(*S*)-α-methylbenzylamine](ethylene) platinum(II) in deuterochloroform at 30-40 °C for a few minutes. The allene replaces the co-ordinated ethylene and the concentration of the complex formed can be detected by their ^{195}Pt resonances in NMR. Four diastereomers were formed arising from the binding to platinum of the two prostereogenic faces of the two enantiomeric allenes (Scheme 8.3). However, the enantiomeric composition of the allene can be readily obtained by comparing the sum of the two peaks assigned to the (*R*)-enantiomer with those assigned to the (*S*)-antipode.



Scheme 8.3

Although a relatively expensive method, this procedure has several advantages in that only small amounts of the allene (50-100 mg) are required for the NMR, which are run very quickly and, more importantly, the co-ordinated allene can be quantitatively replaced by treating the solution with an excess of allene.

As discussed previously, (see Section 6.1) the enantiomeric excess of the chirally enriched allenyl alcohol, obtained *via* kinetic resolution by Sharpless epoxidation, was determined by ^{19}F-NMR analysis of the Mosher's ester derivative. However, even this method was inaccurate because of the reliance on complete chirality transfer on formation of the diastereomers and, in fact,

the ^{19}F NMR only spectrum showed a broad 'double-hump' representing the CF_3 group on the Mosher's ester and not two distinct signals corresponding to each member of the diastereomeric pair. Thus, as a result of our limited success, the inaccuracy and the relative expense of enantiomeric excess determination by NMR methods it was decided to adopt an alternative technique.Once again, enantioselective chromatography was considered to be a promising option. Although there was evidence that unsaturated compounds with axial and planar chirality could be separated by liquid chromatography, very few papers existed reporting the resolution of functionalised allenes. As shown previously, [165] (see Section 7.1) some functionalised allenes have been resolved by liquid chromatography with cellulose triacetate as stationary phase but on a preparative scale this technique is not satisfactory for determination of enantiomeric excess, especially as we had achieved only partial resolution of the (hydroxymethyl)allene (**165**).

Pietruszka and co-workers [171] have employed enantioselective gas chromatography using modified cyclodextrins as stationary phases in order to separate chiral allenic hydrocarbons. Cyclodextrins were isolated as degradation products of starch by Villiers as early as 1891 [172] but it was not until 1948 that their ability to form molecular inclusion complexes was recognised.[173] The structure of these complexes consists of a series of nonreducing oligosaccharides which are made up of six or more (α)-D-glucopyranose units joined together by α-1,4-glycoside bonds (Fig. 17). Only the dextrorotatory enantiomers of cyclodextrins are known; the racemic forms and the levorotatory forms are not available.

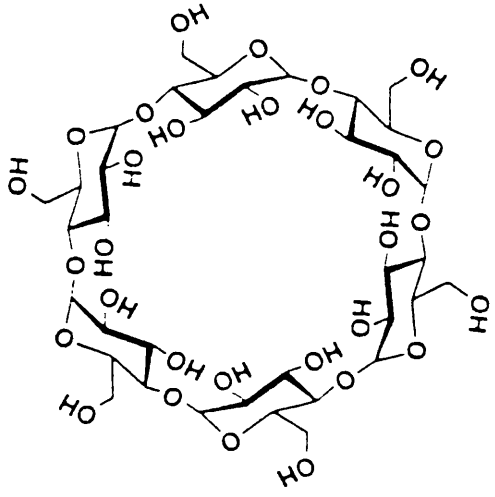


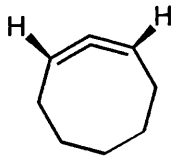
Figure 17

The chiral cavities within the cyclodextrins have a high electron density because of the lone pairs on the oxygen atoms and are both hydrophobic and nonpolar since none of the hydroxyl groups on the glycoside units point inwards. As with cellulose triacetate, which was discussed in the previous chapter, the separation mechanism is dependent on the molecular geometry of the substrate, rather than on any chemical interactions between the substrate and the alkylated cyclodextrin.

The main application of chiral cyclodextrin phases at present is in enantiomer analysis by gas chromatography of chiral compounds that can be vapourised without decomposition. An important aspect for practical applications with the use of alkylated cyclodextrins as chiral stationary phases in high resolution gas chromatography is that, in many cases, the enantiomers can be separated without previous derivatization. Prior to carrying out the separation process, the alkylated cyclodextrins are first diluted with polysiloxanes and then coated onto glass or fused silica capillary columns. This technique has then permitted the enantiomeric separation of, not only polar diols and alcohols, sugars, alkyl halides etc., but also the separation of nonpolar alkenes and cyclic saturated hydrocarbons.

The first gas chromatographic enantiomeric separation using a cyclodextrin derivative was achieved in 1983 by Koscielski *et al* [174]. He successfully separated the apolar, racemic hydrocarbons α- and β-pinene and *cis*- and *trans*-pinene using a packed column in which the supporting material was coated with a solution of native α-cyclodextrin in formamide. Since then König *et al* [175] have found that by introducing *n*-alkyl groups with longer chains onto the cyclodextrins it is possible to obtain liquid cyclodextrin derivatives which are better suited for gas chromatographic separation as these new compounds are thermally stable and can be coated onto appropriately deactivated glass surfaces. This new technique enabled the separation of a large number of compounds and, in particular, the enantioseparation of allenes was then readily achieved. [176]

Using this procedure even resolution of the kinetically labile 1,2-cyclooctadiene (**194**) and 1-halo-1,2-butadienes (**195**) were successfully achieved on a 25-m fused silica capillary column coated with heptakis(6-*O*-methyl-2,3-di-*O*-*n*-pentyl)-β-cyclodextrin (6-me-2,3-pe-β-CD).



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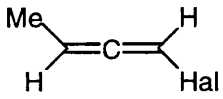
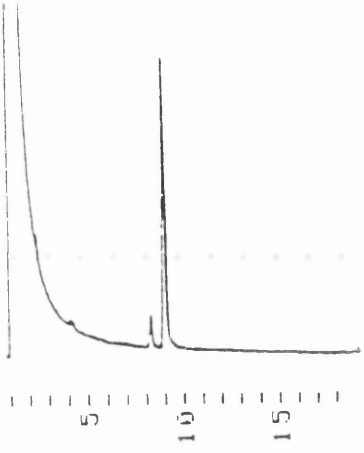


(195)

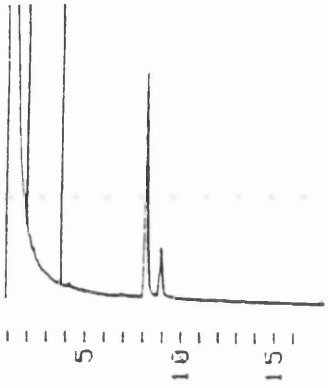
More importantly, however, these authors were also able to resolve a series of homologous unfunctionalised chiral allenic hydrocarbons, in particular, 1-*tert*-butyl-3-alkylallenes, where alkyl is ethyl, *n*-propyl, isopropyl, *n*-butyl etc., using different stationary phases.[177] This was a significant breakthrough due to the current interest in the stereochemical formation of the allenic moiety and in the reactions that these molecules undergo. Moreover, intensive investigations of the stereochemical features of the [2+2] cycloaddition reactions of optically active and racemic allenes have been reported [178] and, therefore, this procedure provides a useful analytical tool for these mechanistic studies where determination of the enantiomeric excess of the chiral allenes is absolutely essential.

The success that these authors had in resolving a wide range of functionalised allenes, which had hitherto proved to be unresolvable, was very promising in view of the extreme difficulties that we experienced in determination of the enantiomeric excess of the (hydroxymethyl)allene (**165**). Correspondence with Professor König enabled us to send him samples of both the resolved allenyl acetate (**186**) and the subsequently formed β-lactam (**168**) for attempted resolution using his modified cyclodextrin phases. Separation factors α for enantiomers are generally low using these cyclodextrin derivatives but this is usually compensated for by the high efficiency of capillary columns and ordinarily, analysis times are very short. The results from the capillary GC analysis carried out by Prof. König are shown below.

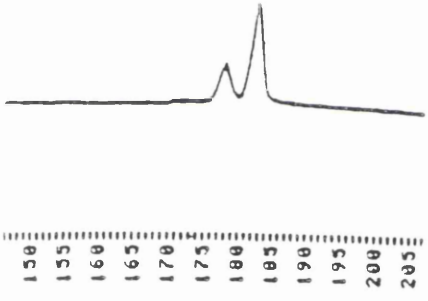
(+)-Acetoxyallene, e.e. 82.4%



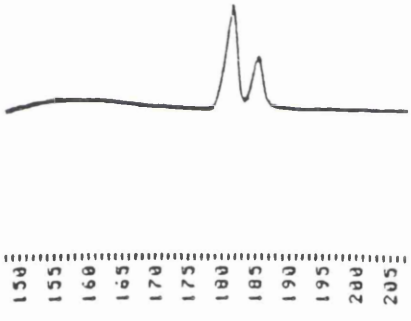
(-)-Acetoxyallene, e.e. 67.0%



(+)-β-Lactam, e.e. 58.5%



(-)-β-Lactam, e.e. 42.0%

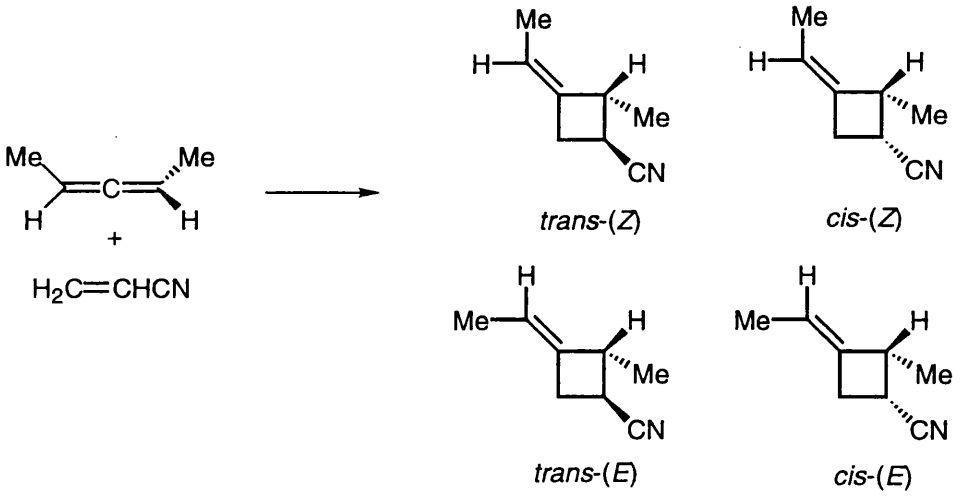


The allenes were resolved on a 8-m column using heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin at 80°C displaying relatively high enantiomeric excesses. Separation of the β-lactam products proved to be more difficult and it was only after 3 hours using a 15m column with octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin as the chiral support that resolution was achieved giving the enantiomeric excesses shown.

Section 9.1 Stereochemical Features of [2+2] Cycloaddition

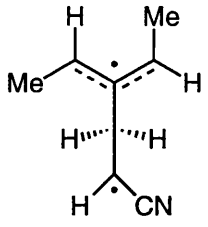
Determination of the enantiomeric excesses of both the resolved allene and its cyclised products in this way demonstrates that in the [2+2] cycloaddition reaction of the enantiomerically enriched TBDMS-protected allenes with CSI an axis-centre chirality transfer has occurred and, thus, provokes further discussion on the actual mechanism of the reaction. The stereochemical features of the [2+2] cycloaddition reactions of chiral allenes has been the subject of a major study by Pasto and co-workers over the past decade.[178]

These studies were initiated by an interesting paper by Baldwin and Roy,[179] which showed that the cycloaddition of optically active 1,3-dimethylallene with acrylonitrile produced four cycloadducts, all of which were optically active (Scheme 9.1).

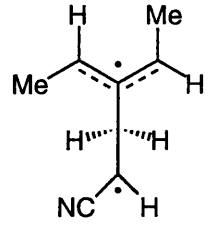


Scheme 9.1

This observation led the authors to postulate the existence of two chiral diradical intermediates (**196**) and (**197**) which are formed by the least hindered approach of the acetonitrile molecule to the allene and lead to the two pairs of (*E*)- and (*Z*)-cycloadducts shown above on ring closure.

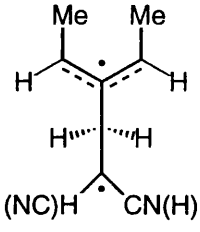


(196)

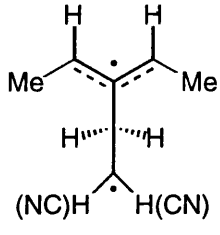


(197)

However, Pasto envisaged that another two diradical intermediates were possible (**198**) and (**199**), although (**199**) would not be formed to any great extent as this intermediate arises from a more sterically congested approach of the reactant.

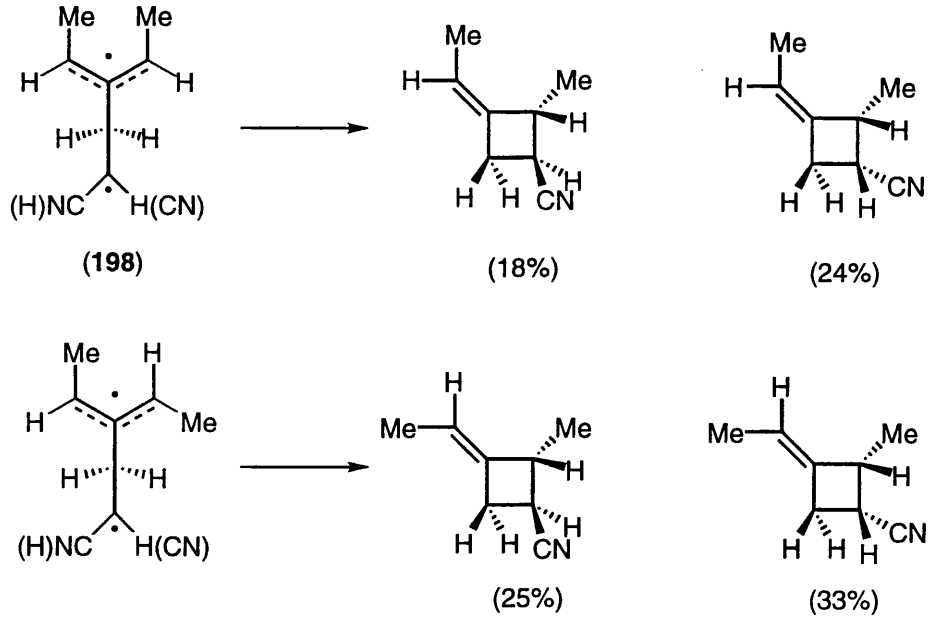


(198)



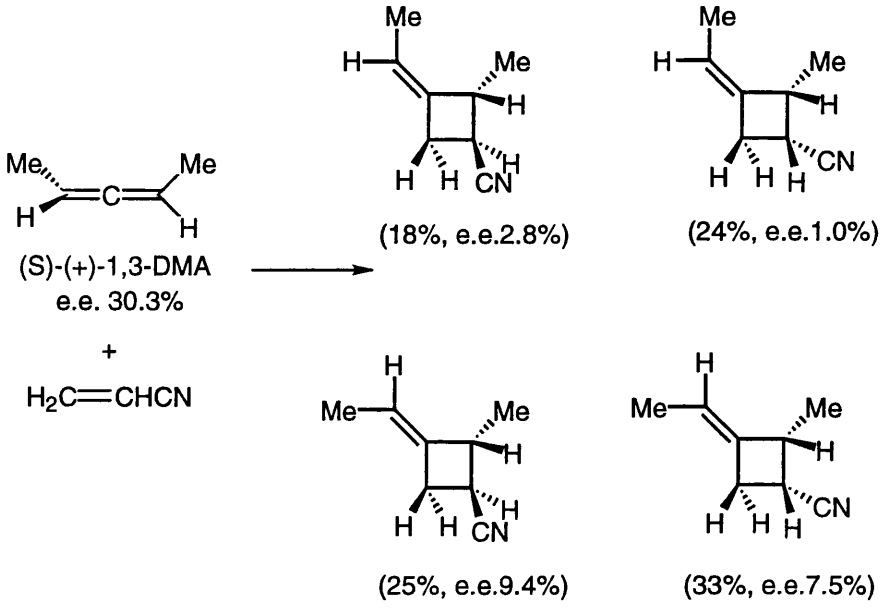
(199)

Results from his laboratory showed that on cycloaddition a mixture of the four cycloadducts was isolated with the yields given in brackets, being formed from the intermediates shown (Scheme 9.2). Thus, from analysis of the percentage of each cycloadduct formed it was obvious that the *anti, syn* intermediate (**198**) must be present in greatest amounts. Pasto proposed that this intermediate could be the more thermodynamically favoured, presupposing that formation of these diradical intermediates is reversible.



Scheme 9.2

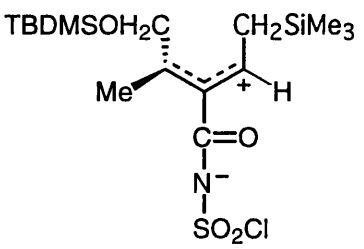
In order to test this theory, one must obviously repeat the same reaction but using a chiral starting material. If formation of the diradical intermediates is reversible then chirality will be lost during the reaction and any recovered, unreacted allene will show a loss in enantiomeric excess. Furthermore, if the reaction is truly reversible, the enantiomeric excesses of the cycloadducts should be seen to decrease with increased reaction time. However, once the diradical intermediates are formed there is no mechanism for their racemisation i.e., the enantiomeric excess is "locked in " and so the extent of the transfer of the enantiomeric excess of the allene to the diradical intermediates is directly indicated by the enantiomeric excesses of the final cycloadducts. The results from the reaction of chirally enriched 1,3-dimethylallene and acrylonitrile[180] (Scheme 9.3) showed that 37% of the enantiomeric excess of the starting allene had been transferred to the cycloadduct while, allowing for experimental error, virtually no chirality loss was observed on measuring the optical rotation of the unreacted 1,3-dimethylallene. This evidence tends to suggest that, in this case, formation of the diradical intermediates is irreversible.



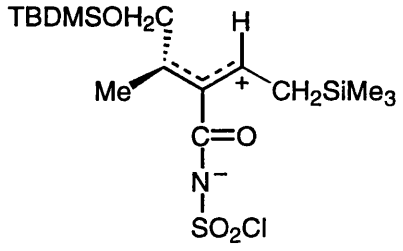
Scheme 9.3

Pasto repeated this [2+2] cycloaddition reaction using chirally enriched 1,3-dimethylallene and several different types of substituted allenes, in some cases showing >96% transfer of enantiomeric excess.[181] By analysis of these results using both molecular modelling calculations and NMR shift studies to determine the enantiomeric excesses, he concluded that formation of a reversible intermediate usually occurs as a result of steric congestion and causes racemisation[182], whereas, in most cases, the energy barrier for racemisation of the intermediate is higher than that for ring closure. He suggests that in the diradical mechanism a single minimum energy conformation appears to exist in which the alkene moiety of the radical intermediate is perpendicular to the allyl radical.

If we expand this information to include our system then the ionic intermediates formed on reaction of the chirally enriched TBDMS allene with CSI will be those shown (**200-203**). Obviously, intermediates (**202**) and (**203**) will be disfavoured as these correspond to approach of the electrophile from the most hindered side of the allene. This statement is reinforced by the fact that we do indeed observe a 7:1 ratio of the two β-lactam products with the major isomer possessing the (*E*)-alkylidene side chain.



(200)



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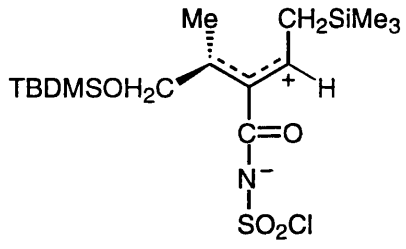
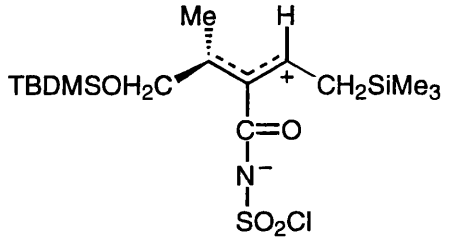
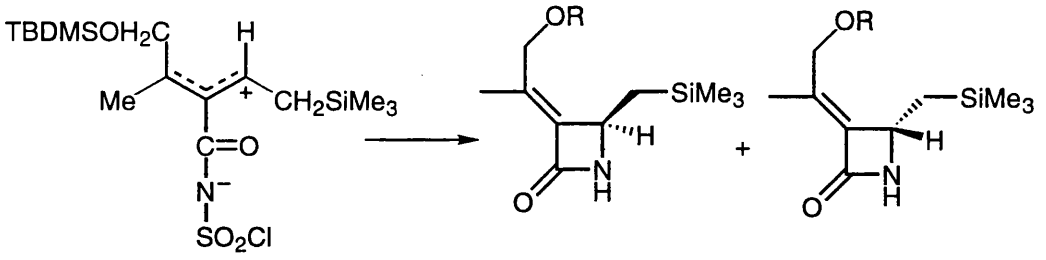


(202)



(203)

Intermediate (**200**) is also extremely sterically congested because of the *syn* relationship between the two bulky silyl groups and, therefore, is not likely to exist in large amounts. Thus, the anionic intermediate (**201**) will be the major isomer and will ring close to form the cycloadducts shown, after reductive cleavage of the chlorosulfonyl moiety (Scheme 9.3). The absolute configuration at C-4 of the β-lactam ring was not obtained.



(201)

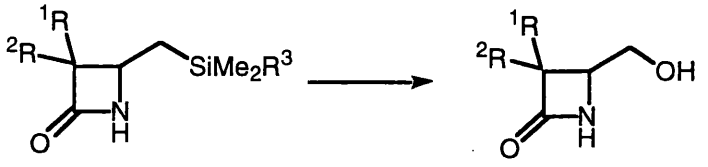
Scheme 9.3

Taking into account all of the above observations the fact that we did see a high degree of transfer of enantiomeric excess (approximately 60%) from the starting allene to the cycloadduct does not disprove or prove either of the two

mechanisms proposed by Graf and Moriconi for the [2+2] reactions of CSI since Pasto has clearly demonstrated that as long as a mechanism for the chiral intermediate to racemise does not exist then ring closure occurs with retention of configuration. Thus, Moriconi's suggestion of a stepwise process via a dipolar intermediate is still viable on the condition that the energy barrier to rotation is higher than that of ring closure to the final product. Even so, it is interesting to note that the axial symmetry of the allenyl alcohol can be transferred to the C-4-carbon-centred chirality of the product β-lactams. This phenomenon has recently been termed "memory of chirality".

Oxidative Cleavage Studies
Section 10.1
Isopropoxy(dimethyl)silyl as a Masked Hydroxy Equivalent

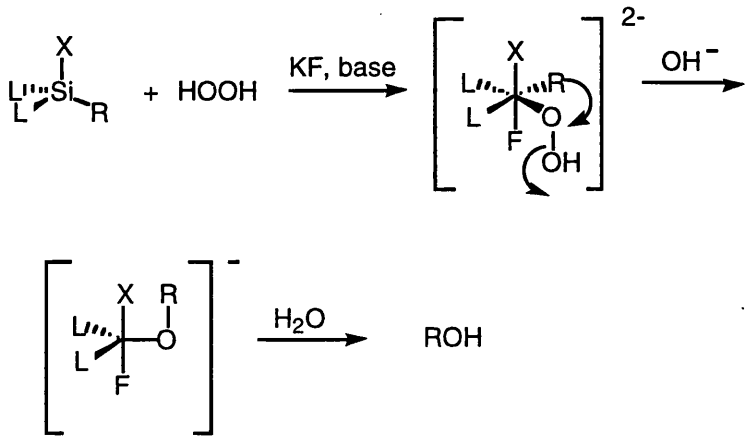
Although a satisfactory resolution of the product β-lactams had been achieved, enabling us to access both enantiomers in good yield, synthetically the β-lactam (**168**) is a dead end since the trimethylsilyl group at C-4 does not allow for further functionalisation. A logical extension thus involves modifying the silyl substituent in order to permit oxidative cleavage of the carbon-silicon bond, resulting in the overall introduction of a hydroxymethyl group or oxidatively related group at C-4. The hydroxymethyl-β-lactam obtained would then be much more synthetically useful and could be elaborated by numerous methods to form a bicyclic β-lactam.



Silicon-carbon bonds are fairly resistant to oxidative cleavage but in some selected cases, silyl groups have been proposed as synthetic equivalents to alcohols. The first report of such cleavage was by Buncel and Davies in 1958[183] during an investigation into the rearrangement reactions of triorganosilyl perbenzoates to produce alkoxy- or aryloxysilanes *via* an intramolecular migration of either a methyl or a phenyl group.

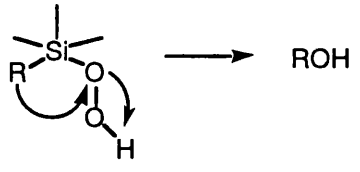
Until now, the synthetic utility of this oxidative cleavage has not been exploited but recently, extensive studies by Tamao and Kumada,[186] and independently by Fleming[193] have demonstrated how potentially useful this synthetic manipulation can be.

The successful cleavage of silyl groups requires the presence of electron-withdrawing substituents, such as alkoxy or fluorine, on the silicon centre. Fluorosilanes are readily oxidised, using hydrogen peroxide or MCPBA as oxidant, to give the corresponding alcohol with retention of configuration. A mechanism has been proposed [184] involving a hexaco-ordinate silicon species (Scheme 10.1) where the presence of a fluoride ion is essential, in what is believed to be an assisted rearrangement of a silyl peroxide to form an alkoxysilane which undergoes facile hydrolysis to give the alcohol.



Scheme 10.1

In the absence of catalytic fluoride ion, the reaction is thought to proceed through a five co-ordinate intermediate. Silicon to carbon migration, followed by hydrolysis, leads to the alcohol (Scheme 10.2).



Scheme 10.2

A number of functional groups have been utilised as masked forms of the hydroxy group although the greatest success seems to have been achieved with the use of the isopropoxy- and dimethylphenylsilyl groups, where the reactions are stereospecific and high yielding. The furyl(dimethyl)silyl moiety has also been used as a silyl group, synthetically equivalent to the hydroxy group, by Stork in a synthesis of (-)-reserpine [185] after failing to effect selective protiodesilylation of the dimethyl(phenyl)silyl functionality. This type of functionality was believed to be a better alternative due to the enhanced reactivity of the furan ring towards fluoride displacement, however, previous studies within our research group[165] had shown that, in our system, this was not the case as the addition of CSI to the furyl system detracted somewhat from the potential applicability of this procedure.

Tamao and co-workers discovered that the silicon-carbon bond in organoalkoxysilanes is readily cleaved by 30% hydrogen peroxide, as well as MCPBA under mild conditions to give the corresponding alcohols with retention of configuration.[186] They initially used the (diisopropoxysilyl)-methyl Grignard reagent as the nucleophilic hydroxymethylating agent for

aldehydes and ketones [187], but further studies showed that the presence of only one isopropoxy group on silicon is sufficient for the oxidative cleavage of the carbon-silicon bond and, since the monoisopropoxysilyl counterpart was more readily available, this reagent was preferred.

This new methodology provided a convenient procedure for the cleavage of unactivated ordinary alkylsilicon bonds. Several types of oxidant were used under various conditions but it was found that neutral conditions gave optimal yields and the oxidation proceeded smoothly if the substrate carried at least one alkoxy group on silicon.

Thus, on account of the success of the oxidative cleavage achieved by Tamao and co-workers on a wide range of substrates using this alkoxysilyl moiety, we also decided to opt for the isopropoxy(dimethyl)silyl group, incorporating it into the β-lactam system which, we envisaged, would eventually lead us to useful potential asparenomycin precursors.

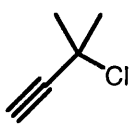
The actual hydroxymethylating agent used is an isopropoxy(dimethylsilyl)methyl Grignard reagent which, although commercially available, can be readily prepared from relatively cheap starting materials. Hence, the chloromethylsilane was easily obtained by simply stirring a mixture of isopropanol and (chloromethyl)dimethylchlorosilane in diethyl ether overnight at room temperature (Scheme10.3).

Scheme 10.3

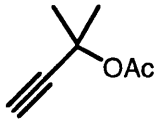
The corresponding Grignard reagent can then be formed in the normal manner from reaction between the chlorosilane and magnesium in THF. Formation of the Grignard reagent is fairly slow and the reaction needed to be initiated by the addition of a few drops of 1,2-dibromoethane and subsequent heating with a hairdryer until reaction proceeded. However, once the Grignard is formed, it is surprisingly stable, despite the co-existence of the reactive primary Grignard reagent and a labile alkoxy group on silicon. This then serves as the hydroxymethyl anion equivalent.

$$(i\text{-PrO})Me_2SiCH_2MgCl = HOCH_2^-$$

We decided to attempt the oxidative cleavage reaction on a model compound initially in order to study the actual viability of the process. Thus, a propargyl system was chosen which would imitate the conjugate addition of the propargyl epoxide, showing the same reactivity, but avoiding any complicating functionality which might interfere with the course of the oxidation. Two such systems were proposed, namely the propargyl chloride (**194**) and the acetate (**195**), however, the chloride was finally chosen in preference, as it was thought that the chloride ion , being a better leaving group would provide a cleaner reaction under the conditions used.



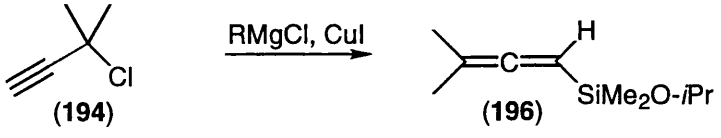
(194)



(195)

The propargyl chloride was prepared, in modest yield, by the reaction of dimethylpropargyl alcohol in the presence of a vast excess of concentrated HCl. The reaction is thought to proceed by an S_N1 mechanism *via* a stabilised cationic intermediate. Isolation of the chloride proved difficult on the scale selected because of the presence of solid $CaCl_2$ which acts as a dehydrating reagent, however, careful distillation using a Vigreux column gave the desired product in 38% yield.

This chloride could then be further reacted, employing the conditions of Itoh *et al*,[188] in a 1,4-conjugate addition reaction following attack by the organocuprate species formed from the (isopropoxydimethylsilyl)methyl Grignard reagent, to furnish the allene (**196**) (Scheme 10.4).



(194) **(196)**

R=-CH_2SiMe_2O-*i*Pr

Scheme 10.4

The yield of the allene was disappointing but this was attributed to poor solubility of the cuprate in diethyl ether rather than to low reactivity of the propargyl chloride. The most common procedure for the preparation of metal

dialkyl cuprates consists of addition of two molar equivalents of an alkyl lithium or alkylmagnesium solution to an ethereal slurry of one of the commercially available copper(I) salts, CuI, CuBr or CuCl. A major drawback to this procedure is that the presence of transition metal impurities in the copper(I) salts may cause decomposition of the formed cuprate lowering the yield of the final product.

Several other solvents have been used in an attempt to increase the solubility of the cuprate, particularly, THF, pyridine, dimethylformamide and dimethylsulfoxide. These can all be classed as donor solvents and may increase solubility by complexing to the lithium/magnesium ion or to the cuprate itself, however, while increased reaction rates were observed in 1,2-additions of cuprates to alkyl halides, the 1,4-addition reactions of cuprates to α,β-unsaturated systems[189] were inhibited under these conditions.

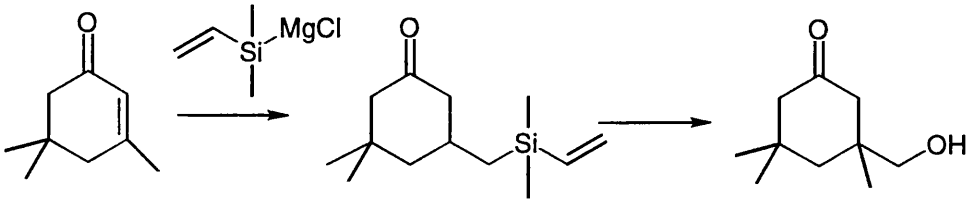
The use of additives, such as hexamethylphosphoramide and dimethyl sulfide, is also common, and it was incorporation of the latter which successfully increased the solubility of the cuprate resulting in much higher yields (91%) of the desired allene (**196**). Heathcock [190] had previously shown that complexes of certain copper(I) salts with the dimethyl sulfide ligand were both soluble in diethyl ether and could even be obtained as crystalline solids.

The actual $Me_2S{\cdot}CuI$ complex formed , in our case, was not soluble in diethyl ether, forming a suspension, but did dissolve on further addition of dimethyl sulfide to form a pale brown, colourless solution. This observation had previously been reported, whereby CuBr and CuCl complexes were immediately soluble in diethyl ether but CuI requires the presence of additional dimethyl sulfide to act as a solvating agent. However, the major advantage of this procedure is that the highly volatile dimethyl sulfide ligand can then be easily removed from the reaction product on workup by simple evaporation.

Tamao[186] states that the reaction products, $(i\text{-PrO})Me_2SiCH_2E$, from reaction of the monoisopropoxy Grignard reagent, are stable, being robust to both weakly acidic and basic conditions as well as to silical gel chromatography but we found that this was not the case. The allene formed proved to be very unstable and could not be purified using either conventional silica or neutral alumina columns, although it was discovered later that passing the crude reaction mixture down a column of Florisil did not result in concomitant decomposition of the allene product and hence this procedure was adopted for purification of all additional compounds containing the labile isopropoxy(dimethyl)silyl moiety.

Formation of the allene was encouraging as earlier workers had expressed some uncertainty as to the possibility of effecting such a 1,4-

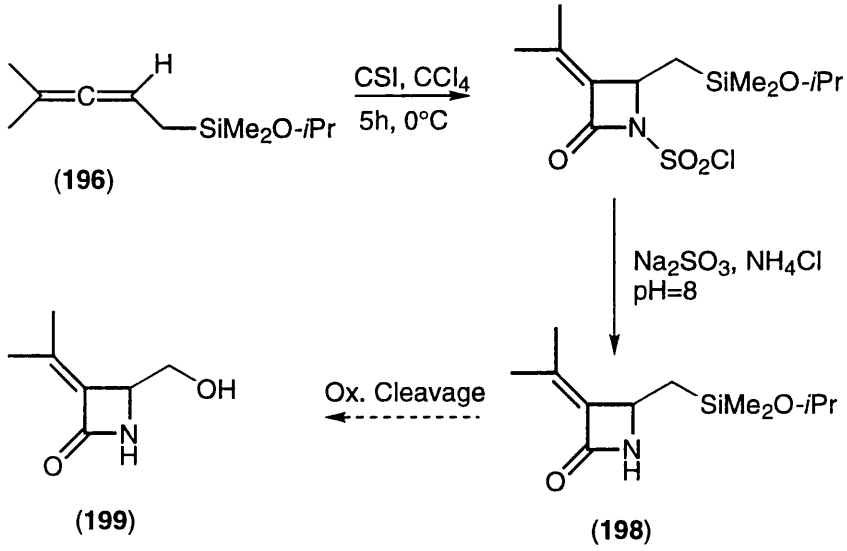
conjugate addition in these types of systems. Tamao [191] had encountered extreme difficulty when attempting the conjugate addition of isopropoxy(dimethyl)silyl cuprates to enones achieving only limited success with the simple cyclohexenone substrate (**197**) and instead had to resort to the use of an allylsilyl reagent in order to accomplish the desired transformations (Scheme 10.5).



(**197**)

Scheme 10.5

The next stage in the synthesis was to determine whether this unstable isopropoxy(dimethyl)silyl moiety would withstand addition of the highly reactive CSI. Purified allene was used in the cycloaddition step employing the same conditions as before [65] and once again the course of the reaction was monitored by NMR. In this case the reaction was quenched after 5 hours at 0°C to yield the desired *N*-protio-β-lactam (**198**) after purification on Florisil (Scheme 10.6).



(**196**)

(**199**)

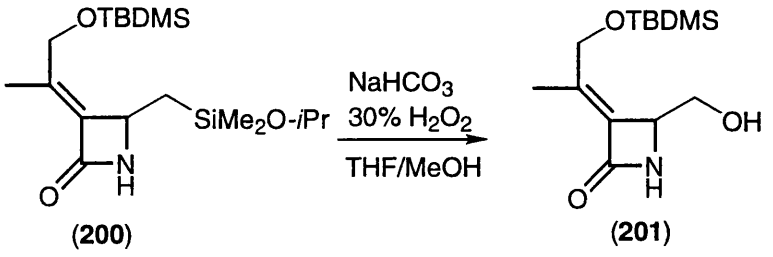
(**198**)

Scheme 10.6

In the first attempted reaction reduction of the *N*-chlorosulfonyl-β-lactam to the *N*-protio derivative was performed using a buffered Na_2SO_3/NH_4Cl solution (pH=8.0) in order to protect the sensitive silyl functionality. However, subsequent reactions showed that this precaution was unnecessary as no decrease in yield was observed when buffering of the Na_2SO_3 solution was omitted.

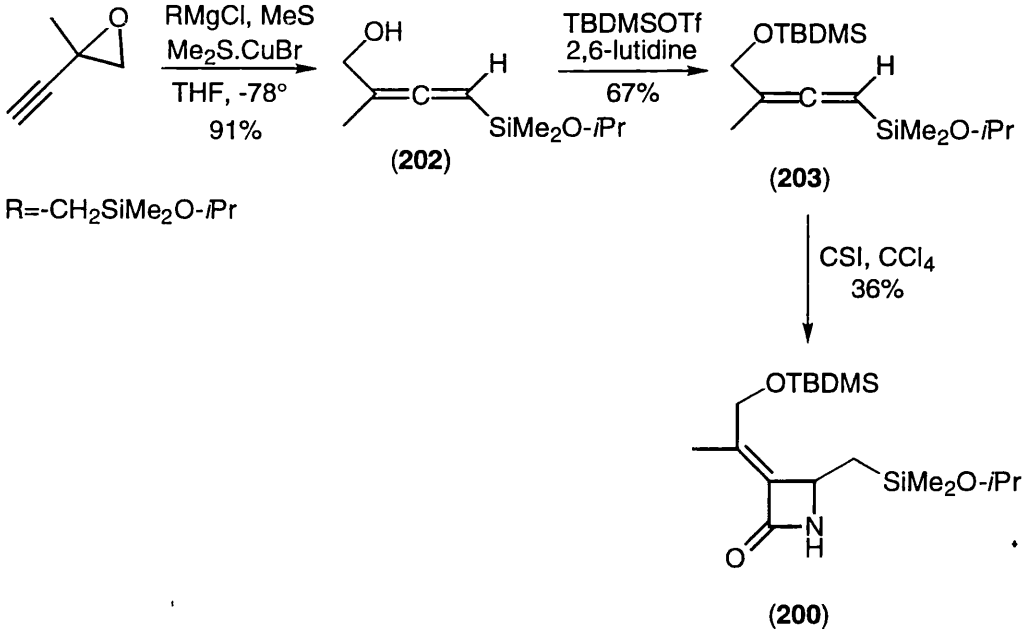
The β-lactam formed possesses both the C-3 alkylidene functionality present in the asparenomycins and a potentially oxidatively cleavable silyl moiety at C-4. Thus, oxidative cleavage was attempted on this simple model substrate applying the same conditions as those employed by Tamao *et al.*[191] Since the product β-lactam (**199**) is inherently water soluble, a suitable nonaqueous workup was chosen, whereby, finely ground $Na_2S_2O_3.5H_2O$ was added to the reaction mixture, replacing the dilute $NaHSO_3$ normally used as a means of eliminating any superfluous peroxide. Isolation of the product obtained from the organic layer and examination of the ^{1}H-NMR spectrum revealed loss of the -$SiMe_2$ resonance at 0.12ppm and of the CH_2Si resonance at 0.9-1.1ppm, but, otherwise, the large series of proton signals meant that no identifiable product could be distinguished. Mass spectral analysis was also disappointing giving very few peaks indicative of the presence of a β-lactam.

Nevertheless, studies on this model system have demonstrated that conjugate addition of an organocuprate bearing an isopropoxysilyl moiety can be successfully accomplished and subsequent reaction with CSI does indeed form the functionalised β-lactam (**198**). The incorporated silyl functionality at C-4 on the β-lactam ring is then capable of being oxidatively cleaved to the corresponding hydroxymethyl substituent. Although results from the oxidative cleavage reaction on the model system were not conclusive, it was encouraging to note that the β-lactam ring was still intact following the attempted cleavage. Accordingly, this methodology can then be applied to the propargyl epoxide derivative eventually forming the hydroxymethyl-β-lactam (**201**), which is a useful precursor leading to the synthesis of asparenomycin analogues (Scheme 10.7).



Scheme 10.7

Conjugate addition of the organocuprate, formed *via* the $Me_2S.CuI$ complex, produced the (hydromethylallenyl)silane (**202**) in good yield (Scheme 10.8).



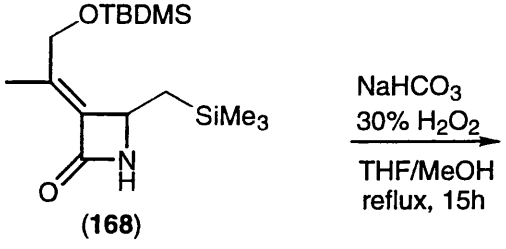
Scheme 10.8

Once again the hydroxyl group on C-1 must be protected before the cycloaddition step is attempted and this was realised, as in the previous case, by silyl protection using TBDMSOTf as the silylating reagent. The [2+2] cycloaddition with CSI proceeded smoothly giving the desired β-lactam (**200**) in 36% yield (Scheme 10.8). This β-lactam was subjected to the conditions employed by Tamao [191] in order to effect oxidative cleavage. In this case 30% hydrogen peroxide was used as oxidant and $NaHCO_3$ as a mild base. Results from the ^1H NMR were very poor because although the isopropoxy group had clearly been removed it appeared that the β-lactam ring has also been cleaved under these severe conditions as no β-lactam proton signals were visible. A

forest of peaks around the methylene alkyl region and the reemergence of an allenyl proton at 5.5 ppm indicated that decomposition of the β-lactam ring and a series of intervening side reactions had obviously occurred. Mass spectral analysis also proved difficult as a series of peaks were observed, none of which seemed to correspond to the required atomic weights for either the unreacted β-lactam, or the oxidatively cleaved product.

Since we were encountering so many problems with the attempted oxidative cleavage of the isopropoxy(dimethyl)silyl side chain on the β-lactam ring it was decided to extend our studies in two complementary directions.

Firstly, in order to ensure that the Tamao conditions were not too harsh for the sensitive β-lactam structure, a simple β-lactam (**168**), not containing an oxidatively cleavable group, was subjected to identical reaction conditions (Scheme 10.9)



(**168**)

Scheme 10.9

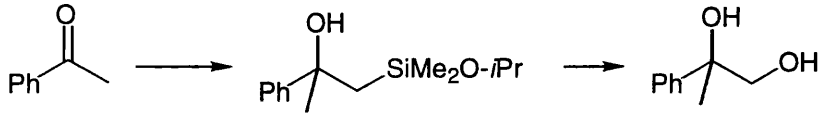
After refluxing in THF/methanol for 15 hours, as outlined in Tamao's paper,[191] and nonaqueous workup the starting β-lactam was recovered in 67% yield. This result verifies that the experimental conditions employed for the cleavage are not detrimental to the β-lactam ring which remains intact even after such a severe reflux.

Breakup of the lactam ring, therefore, cannot be blamed for the failure of the reaction and so the next logical extension was to take a compound which Tamao had shown could be successfully oxidatively cleaved and see if we could repeat this result in our laboratory.

Acetophenone was chosen as the starting ketone mainly because it was readily available and has a relatively simple NMR spectrum enabling us to detect any new proton signals without complication.

Addition of the isopropoxysilyl Grignard reagent proceeded smoothly furnishing the silane (**204**) as expected, and oxidative cleavage of this compound formed the desired dihydroxy product in a similar yield to that obtained by Tamao (Scheme 10.10). The success of this reaction in our hands, coupled with the fact the β-lactam ring was able to withstand these conditions, was indeed encouraging, indicating that careful manipulation of the

experimental parameters should allow us to overcome our previous problems and successfully perform this transformation.



(204)

Scheme 10.10

Therefore, taking the above considerations into account, the experiment was attempted again on the model system. Presuming that the hydroxymethyl β-lactam is being formed and is subsequently lost in the workup, it was decided to silylate the hydroxyl group by treatment with 1.2 equivalents of TBDMSOTf *in situ* in an endeavour to lower the polarity and, hence, facilitate isolation of the final product.

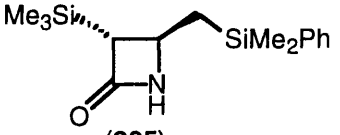
The period of reflux was also decreased from 15 hours to 5 hours to ascertain whether this had any effect on minimising possible side reactions. ^{1}H-NMR analysis of the purified reaction mixture, in this case, looked more promising as loss of the isopropoxy moiety had definitely occurred showing an absence of the -CH proton of the isopropoxy group at 3.85-4.04 ppm and of the two methyl signals from the same group at 1.09 ppm. Also encouraging was the appearance of two new signals at 0.7 ppm and 1.13 ppm which could correspond to to the *t*-BuSi and SiMe signals of the desired β-lactam, respectively. Unfortunately, since very little material was recovered (approximately 6mg), the ^{13}C NMR was not conclusive although the emergence of a new carbon peak at 60.8 ppm did provide further evidence of a CH_2OSi moiety within the molecule.

Hence, although the yields were still impractically low, the indications that we had indeed effected the oxidative cleavage reaction were reassuring and so the same reaction conditions were applied to the TBDMS-protected (hydroxymethyl)β-lactam. The ^{1}H-NMR spectrum obtained of the product isolated from this reaction again showed loss of the isopropoxy group from the C-4 side chain and, more interestingly, a new series of peaks around 3.6ppm whose coupling constants and relative position in the NMR spectrum suggested the presence of a CH_2O- group adjacent to the proton at C-4 of the β-lactam ring. Analysis of the ^{13}C-NMR spectrum reinforced this observation as two CH_2O- peaks could clearly be seen at 64 and 65 ppm intimating that

successful conversion of the isopropoxy(dimethyl)silyl to hydroxyl group (in this case protected hydroxyl group) had been achieved. Unfortunately, time constraints meant that we were unable to repeat this reaction in order to verify this statement.

Section 10.2
(Dimethyl)phenylsilyl as a Masked Hydroxy Equivalent

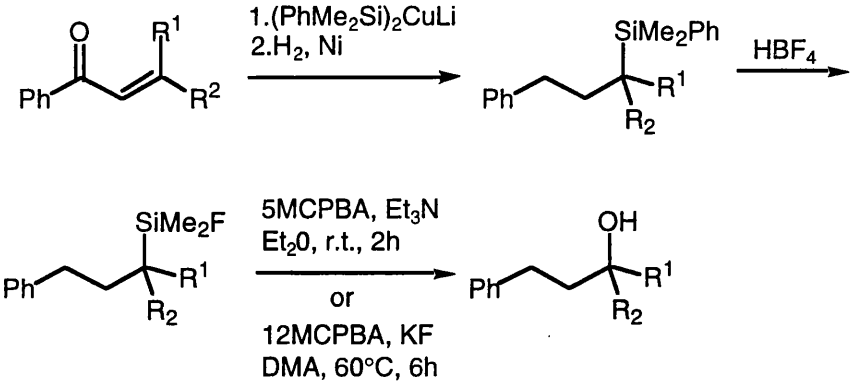
On account of the limited success that was achieved with the attempted oxidative cleavage of the isopropoxy(dimethyl)silyl side chain, it was decided to investigate the use of the (dimethyl)phenylsilyl moiety as an alternative. It was reasoned that the (dimethyl)phenylsilyl unit, being chemically more robust, would withstand further transformations and, furthermore, oxidative cleavage of this group had been successfully accomplished, albeit in low yield, by a previous co-worker [192] on the β-lactam (**205**).



(**205**)

It was Fleming[193] who first discovered the potential of (dimethyl)phenylsilyl groups to behave as a masked hydroxy group. He realised the advantages that this group has over a simple protected hydroxyl group in that it is electronically quite dissimilar and, therefore, will affect the chemistry of the molecule into which it is substituted in an entirely different way.

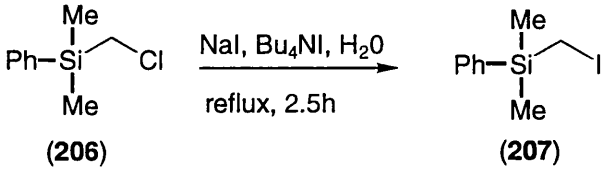
In his initial communication,[193] the (dimethyl)phenylsilyl group was converted into a hydroxy group in a facile two-step reaction involving conversion of the silane into a fluorosilane and subsequent peracid-mediated rearrangement, as reported by Buncel and Davies,[183] to form the corresponding alcohols (Scheme 10.11). Actual transformation of the (dimethyl)phenylsilyl group into a hydroxyl requires an electrophilic attack on the aryl group attached to silicon in the first step.



Scheme 10.11

However, since this preliminary paper further studies have led to the development of a simple one-pot procedure[194] with no observed decrease in yields. This second method uses either bromine or mercuric ion in an acetic acid solution of peracetic acid as the electrophile to effect the desilylation. The rearrangement once again occurs with retention of configuration, and has been found to be compatible with both ketone and ester functionalities.

As before, it is the (dimethyl)phenylsilyl Grignard reagent which is the actual hydroxymethylating agent, thus, this Grignard reagent was prepared from (chloromethyl)dimethylphenylsilane using the normal conditions. It was anticipated that formation of the Grignard reagent from the chloride (**206**) might be quite slow and so the more reactive iodide (**207**) was prepared in good yield using a standard halogen exchange reaction (Scheme 10.12).

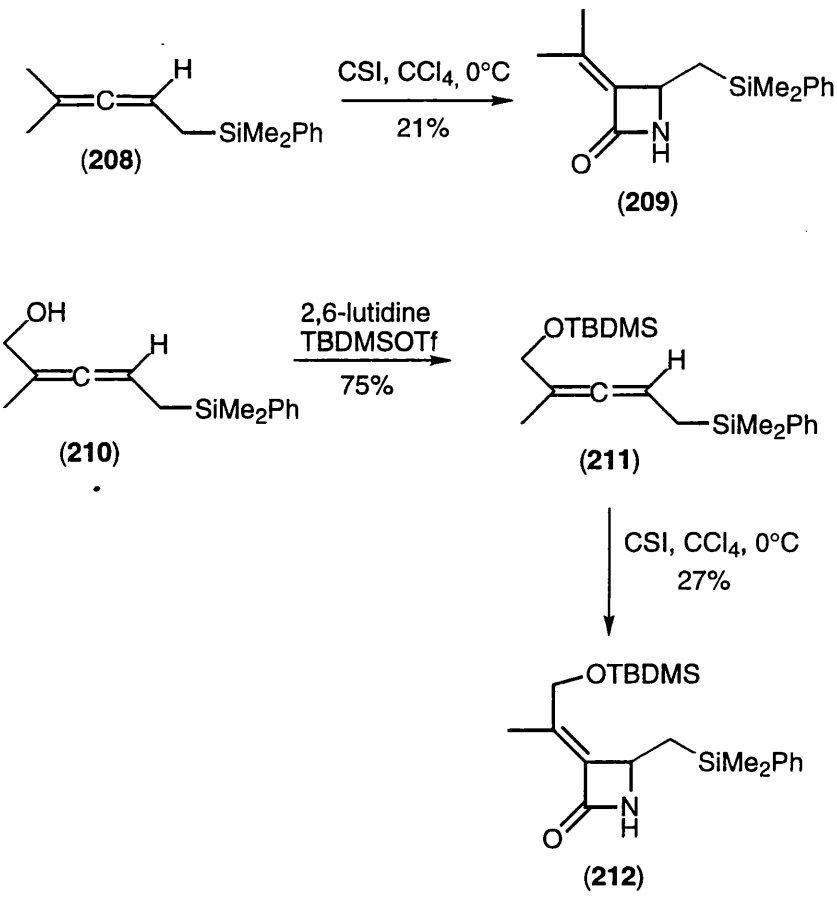


(206) **(207)**

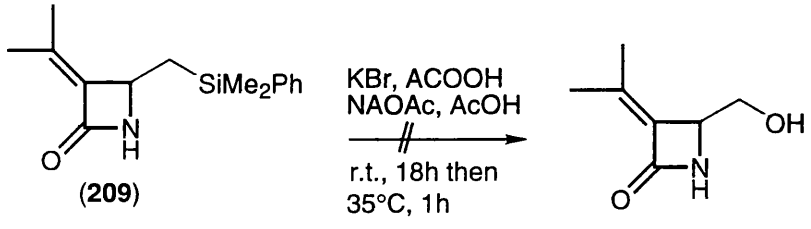
Scheme 10.12

Comparison of the rates of formation of the corresponding Grignards from these two halosilanes revealed that there was negligible difference in reactivity and so the chlorosilane (**206**) was used as the starting material.

Cuprate addition afforded the (dimethyl)phenylsilyl-substituted allenes (**208**) and (**209**) using the same conditions as previously, and the β-lactams (**210**) and (**211**) were formed in moderate yield following addition to CSI.



The oxidative cleavage reaction was attempted on these two β-lactam systems employing both sets of conditions suggested by Fleming.[193] In the first instance bromine was used as the electrophile and β-lactam (**210**) as the substrate (Scheme 10.13). It was thought that the absence of an electron-withdrawing group attached to the exocyclic double bond would minimise any deleterious side reactions caused, either by attack of the electrophile here, or just simple epoxidation by the peracetic acid which is used in excess. The bromine was generated *in situ* by adding the peracid solution to potassium bromide which avoided the dangers and unpleasantness of handling bromine itself.

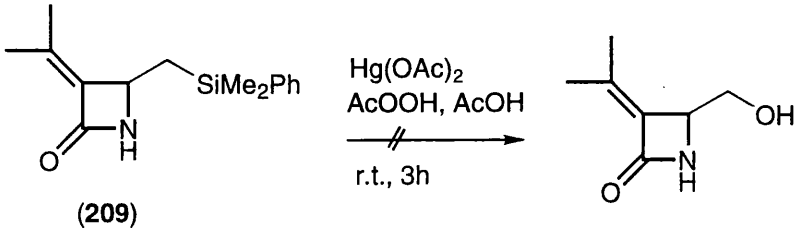


Scheme 10.13

The sodium acetate present acts as a buffer and is particularly useful when working with acid-sensitive groups as it helps to compensate for the effect of any sulfuric acid which is usually found in commercially available supplies of peracetic acid. Examination of the material isolated from the above reaction proved to be extremely disappointing as the yield was low and TLC showed a mixture of products. ^{1}H-NMR analysis of the separated fractions revealed no recognisable product giving very poor resolution and a series of unidentifiable peaks, although in the last fraction signals corresponding to the aromatic region at 7.5 ppm and the C-4 proton at 4.1 ppm of the starting β-lactam (**210**) were observed. Results from the attempted cleavage of β-lactam (**211**), even when we strived to improve product isolation by *in situ* quenching with TBDMS triflate, were no better, affording an even lower yield of a mixture of products whose structure could not be determined.

The use of mercuric ion as an electrophile in aromatic desilylations is well known [195] and was thought to be an ideal choice in our system since it has been shown to be compatible with ester, amide and ketone functional groups. Mercuric ion is, relatively speaking, a better electrophile for the π-system of the benzene ring than it is for the carbonyl group and hence, theoretically, there should also be less inclination for attack at the exocyclic double bond of the β-lactam ring. In this case the use of sodium acetate as a buffer is not possible as the acid present in the reaction medium is necessary to catalyse the mercuration of the benzene ring.

Fleming[194] had considered the use of catalytic quantities of mercuric ion in the oxidation process but the phenylmercuric acetate formed during the reaction did not appear to be oxidised under the peracetic acid conditions and so molar quantities of mercuric acetate were required (Scheme 10.14).



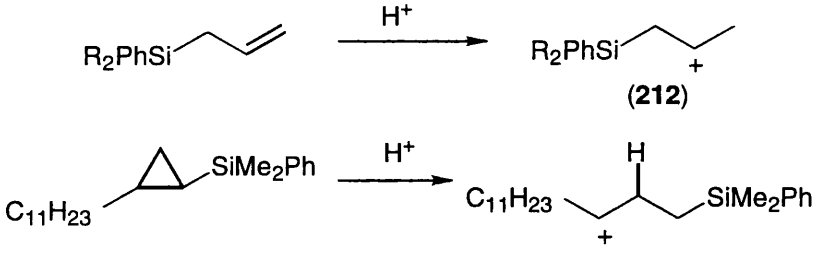
(**209**)

Scheme 10.14

We were frustrated to find, once again, that no recognisable oxidatively cleaved products could be detected from the reaction mixture of both β-lactam

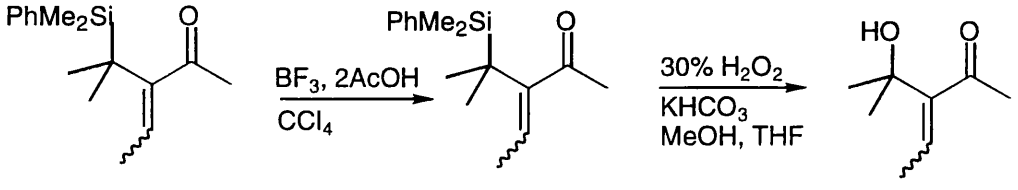
systems. Unfortunately, due to lack of time, these reactions were unable to be repeated under different conditions in an endeavour to resolve the problems associated with this reaction. Hence, it can only be concluded that these conditions for the silyl-to-hydroxy group conversion are not compatible with the β-lactam ring since both the carbonyl group at C-2, which in the β-lactam system is more reactive anyway, being less resonance-stabilised than in a normal amide bond, and the alkylidene group at C-3 are susceptible to electrophilic attack.

It is worth commenting that Fleming also failed to effect oxidative cleavage in small ring systems, notably in cyclopropane rings. His reasoning for this was that although cyclopropanes are generally less reactive than alkenes they display the same type of behaviour towards electrophiles. It had previously been shown that the carbon-carbon double bond in allylsilanes is protonated under oxidative cleavage conditions[196] and Fleming envisaged that the same thing was happening in this case forming the stable cationic intermediate shown (**212**) (Scheme 10.15).



Scheme 10.15

However, he managed to overcome this problem by substituting an electron-withdrawing group in the β-position to the silyl group which should both destabilise the intermediate cation formed and also encourage preferential attack on the phenyl ring (Scheme 10.16).[197]



Scheme 10.16

This strategy did indeed prove successful furnishing the hydroxy product without disturbing the enone carbon-carbon double bond, but in low yield and only after manipulation of the reaction conditions employing Fleming's original two-step procedure. These results indicate that the (dimethyl)phenylsilyl-to-hydroxyl group conversion is not an easy feat and that not only the functional groups present in the molecule, but also the effect that the silyl functionality has on stabilising any intermediates during the reaction, has to be given careful consideration. Since the (dimethyl)phenysilyl group appears to be problematic, affording only very low yields of oxidatively cleaved products, then had time permitted, an investigation of alternative silyl groups acting as masked hydroxyl equivalents would have been undertaken, giving more thought to possible stabilisation of intermediates formed during the oxidative cleavage process.

Experimental

Unless stated otherwise, all commercial reagents were purchased and used without further purification. The reactions were all carried out under a nitrogen atmosphere. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl under nitrogen prior to use. Methylene chloride (CH_2Cl_2) was distilled from CaH_2, carbon tetrachloride (CCl_4) distilled from phosphorus pentoxide (P_2O_5) and methanol (MeOH) distilled from magnesium turnings/iodine (I_2) prior to use. All distilled solvents were stored over 4Å molecular sieves.

Flash column chromatography was performed on Merck Kieselgel 60H and Sorbsil C60 under reduced pressure, and on Florisil where specifically mentioned. All extraction and chromatographic solvents: pentane, hexane, ethyl acetate and diethyl ether were used unpurified and undried.

Enantiomeric excesses were determined by capillary G.C. analysis using modified cyclodextrin stationary phases. The allenes were resolved on an 8-m column using heptakis (2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin at 80 °C and the β-lactams were resolved on a 15-m column using octakis (2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin at 135 °C.

Bulb-to-bulb distillation was carried out on a Büchi GKR-50 Kugelrohr, the quoted boiling points referring to the indicated air bath temperature.

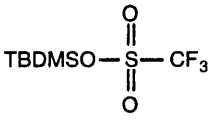
^1H (200 MHz) and ^{13}C (50 MHz) NMR were recorded on a Bruker AM200SY or a Bruker WP200SY at ambient temperature. Chemical shifts are reported in parts per million (δ) relative to the residual proton shift in deuterochloroform at 7.25ppm (^1H NMR) and the central signal of the triplet at 77.0ppm (^{13}C NMR). Infra red spectra (IR) were obtained on a Perkin-Elmer 983 spectrometer. Mass spectra were obtained using a VG/Kratos MS12 spectrometer (low resolution/chemical ionisation) and a VG/Kratos MS90S spectrometer (high resolution/chemical ionisation). Optical rotations were determined on an AA/100 Polarimeter (Optical Activity Ltd.).

Purification of Copper Iodide

To a suspension of potassium iodide (260g; 1.57 mol) in water (200ml) was added impure copper iodide (26g; 0.21 mol). The resulting solution turned yellow-orange in colour. To this was added partially ground animal charcoal (2g) and the mixture filtered through a 2-cm thick pad of Celite. The aqueous orange solution was collected and added to a vast excess of water, precipitating the copper iodide as very fine, off-white particles. The solid particles were removed by filtration and washed with water, MeOH and pentane and dried in a desiccator; yield: 20.23g (78%).

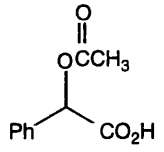
N.B. The purified copper iodide should be stored in a brown glass container to prevent UV decomposition.

tert-Butyldimethylsilyl Trifluoromethanesulfonate



A flame-dried Kugelrohr bulb, fitted with a condenser and under N_2, was charged with TBDMSCl (1.125g; 7.46mmol) and trifluoromethanesulfonic acid (1.19g; 0.66ml; 7.46mmol). The reaction mixture was allowed to stir at 60°C for 18 hours after which time the triflate was isolated by bulb-to-bulb distillation, the vacuum being released under N_2, to give a clear liquid; yield: 1.86g (94%); 130°C/20mm Hg. The TBDMSOTf was then diluted to 25ml with dry CH_2Cl_2 furnishing a 0.28M solution.

2-Acetoxyphenylacetic Acid

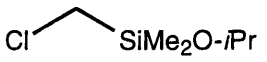


(171)

A mixture of L-mandelic acid (3.52g; 23mmol) and acetyl chloride (10.0ml; 0.14mol) was warmed together (water bath 40°C) in a round-bottomed flask fitted with condenser, with stirring for 2 hours. The excess acetyl chloride was removed in vacuo leaving a colourless oil which was taken up in EtOAc (10.0ml) and purified by acid/base extraction. The organic layer was dried (Na_2SO_4) and evaporated to give a yellow oil which crystallised after 48 hours at 5°C. Recrystallisation from benzene/*n*-hexane gave a white semi-crystalline solid; yield: 2.23g (50%); m.p. 94-95°C (Lit.98°C).[145]

ν_{max}	1745, 1700 cm^{-1}
δH	2.10 (3H, s, CH_3), 5.95 (1H, s, CH), 7.18-7.48 (5H, m, Ar-H), 11.70 (1H, s, CO_2H)

(Chloromethyl)dimethylisopropoxysilane



A flame-dried flask, under N_2, was charged with (chloromethyl)dimethylsilane (5.16ml; 39.1mmol) and Et_2O (45ml). The flask was then cooled to 0°C and isopropanol (3ml; 39.1mmol) in Et_2O (25ml) added, dropwise, over 20 minutes. The reaction mixture was allowed to stir overnight at room temperature, concentrated *in vacuo* and then fractionally distilled to afford the title compound as a clear liquid; yield: 4.0g (66%); 114°C/22mm Hg.

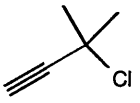
ν_{max} 1000-1077, 759 cm^{-1}

δH 0.22 (6H, s, $SiMe_2$), 1.6 (6H, d, *J*=6.1, CH_3),
2.77 (2H, s, CH_2Cl), 4.06 (1H, septet, *J*=6.1, CH)

δC -3.05 ($SiMe_2$), 25.65 (CH_3), 29.94 (CH_2Cl), 65.70 (CH)

Mass Spec: *m/z* (%)=153 (21), 75 (17), 45 (13), 38 (12), 36 (27), 28 (39),
18 (100), 17 (29)
Found M^+ 166.0524 $C_6H_{15}ClOSi$ requires M^+ 166.0581

3-Chloro-3-methyl-1-butyne



(194)

A flame-dried, round-bottomed flask, under N_2, was charged with pre-dried $CaCl_2$ (3.96g; 35.7 mmol) and conc. HCl (15.5 ml; 140 mmol; 36 % w/w) and then chilled to 0 °C using an ice/water bath. To this was added 3,3-dimethylpropargyl alcohol (3.46 ml; 35.7 mmol) and the reaction allowed to stir for 30 mins at 0 °C. After this time the reaction mixture was transferred to a separating funnel (fume-cupboard) and the aqueous layer separated and carefully neutralised with K_2CO_3 for disposal. The organic layer was retained, neutralised with K_2CO_3 and then carefully distilled at atmospheric pressure using a 10 cm Vigreux column to give the title compound as a clear liquid; yield: 3.17g (38 %); 74 °C/760 mm Hg.

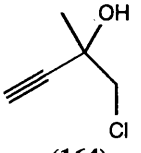
ν_{max} 3300, 652 cm^{-1}

δH 1.85 (6H, s, CH_3), 2.41 (1H, s, CH)

δC 34.48 (CH_3), 56.89 (C-Cl), 71.80 (CH), 86.46 ($Me_2C\underline{C}$)

Mass Spec: *m/z* (%)=87 (20), 67 (M^+-^{35}Cl, 100), 65 (M^+-^{37}Cl, 17), 51 (33), 41 (33), 39 (29), 28 (23)
Found M+ 102.0232 (^{35}Cl) 104.0203 (^{37}Cl)
C_5H_7Cl requires 102.0236 (^{35}Cl) 104.0206 (^{37}Cl)

4-Chloro-3-hydroxy-3-methyl-1-butyne



(164)

To a flame-dried flask containing oven-dried Mg turnings (2g; 83 mmol), fitted with condenser, was added THF (20.0 ml) under a N_2 atmosphere. Ethyl bromide (6.86 ml; 92 mmol) in THF (40.0 ml) was added over one hour maintaining the reaction at reflux during the course of addition. The pre-formed Grignard was then transferred to a pressure-regulated dropping funnel, under positive N_2 pressure *via* a flexi needle. The funnel was then placed in the middle neck of a 500 ml three-necked round-bottomed flask containing anhydrous THF (50.0 ml) saturated with acetylene gas. (Prior to saturation the acetylene gas is passed through an acetone/Drikold trap at -78 °C). The THF was left to saturate with acetylene gas for 10-15 mins, after which time the ethylmagnesium bromide in THF was added at 0 °C over 1-1.5 hours forming a deep red solution. Once addition was complete, the acetylene flow was stopped and chloroacetone (4.86 ml; 61 mmol) in THF (25.0 ml) was added at 0°C over 45 mins and then left to stir for a further 30 mins. The reaction mixture was quenched with saturated ammonium chloride (30.0 ml) and the aqueous layer extracted with Et_2O (3x 20.0 ml). The combined extracts were dried ($MgSO_4$) and the solvent removed by distillation at atmospheric pressure to yield a dark brown liquid. Fractional distillation afforded the title compound as a colourless liquid; yield: 5.89g (79 %); 48 °C/19 mm Hg.

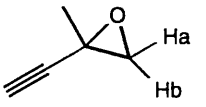
ν max 3316, 3000-3555, 1127, 679 cm^{-1}

δH 1.55 (3H, s, CH_3), 2.49 (1H, s, CH), 2.94 (1H, bs, OH), 3.55 (1H, s, C<u>H</u>HCl), 3.64 (1H, s, CH<u>H</u>Cl)

δC 26.76 (CH_3), 53.61 (C-4), 67.71 (C-3), 72.6 (C-1), 84.4 (C-2)

Mass Spec: *m/z* (%)=103 (8), 69 (M^+-CH_2Cl, 100), 53 (11), 43 (69), 39 (38), 28 (18)
Found M^+-H 117.0103 C_5H_6OCl requires 117.0107

3,4-Epoxy-3-methyl-1-butyne



(163)

To a flame-dried, three-necked flask, equipped with stirrer bar, under N_2 was added anhydrous Et_2O (30.0ml) and powdered potassium hydroxide (27.5g; 0.49 mmol) *via* a powder tube. The flask was cooled to 0°C and the halohydrin (4.21g; 0.04mol) in anhydrous Et_2O (28.5ml) added dropwise over 20 minutes. The reaction mixture was stirred for a further 1 hour at 10-15 °C and then quenched carefully with a saturated NaCl solution (27.5ml). The aqueous layer was extracted with Et_2O (3 x 20.0ml), dried (K_2CO_3) and concentrated. Fractional distillation of the resultant yellow liquid at atmospheric pressure afforded the title compound as a clear liquid; yield: 1.54g (46%); b.p. 92°C/760mm Hg.

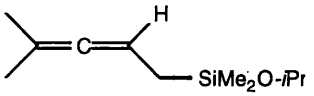
ν_{max} 3300, 2950, 2140-2100, 1250, 840 cm^{-1}

δH 1.51 (3H, s, CH_3), 2.26 (1H, s, CH), 2.69 (1H, d, *J*=5.5, H_a), 2.98 (1H, d, *J*=5.5, H_b)

δC 22.54 (CH_3), 65.77 (C-4), 67.86 (C-3), 70.27 (C-1), 83.00 (C-2)

Mass Spec: *m/z* (%)=82 (M^+, 5), 54 (24), 52 (M^+-CH_2O, 100), 51 (86), 50 (69), 43 (36), 39 (65), 28 (26), 27 (29)
Found M^+ 82.0422 C_5H_6O requires M^+ 82.0419

1-(Dimethylisopropoxysilyl)-4-methyl-2,3-pentadiene



(196)

A 25 ml round-bottomed flask, with stirrer bar, containing pre-dried Mg (204mg; 8.5 mmol) was flame dried and purged with N_2. To this was added THF (2.0 ml) and a small quantity of neat chloromethylsilane (ca. 0.2 ml). The Grignard was initiated by adding 1-2 drops of dibromoethane and heated with a hot gun. Once the reaction had commenced the Grignard formation was kept at the point of reflux by adding the remainder of the chloromethylsilane (1.33g, 8mmol) in THF (2.0 ml) over 5 mins. Grignard completion was signified by the flask returning to room temperature.

A second flame-dried, round-bottomed flask containing $Me_2S.CuBr$ (824mg, 4 mmol) was cooled to -78 °C and then THF (10.0 ml) and Me_2S (5.08g; 6 ml; 82 mmol) were added. The cooling bath was removed until all the complex had solubilised and then the cooling (-78 °C) bath was replaced. The pre-formed Grignard reagent was added, dropwise, and the cooling bath removed, the reaction mixture stirred at room temperature for 10 mins and the bath replaced. Then the propargyl chloride (410mg; 4 mmol) in THF (9.2 ml) was added, dropwise, over ca. 2 mins and the reaction mixture left to stir at -78 °C for 1.5 hours, then at 0 °C for 1 hour. The mixture was quenched with aqueous NH_4Cl/ 33 % aqueous NH_4OH solution (9:1) (26.0 ml) and the organic layer removed. The aqueous phase was extracted with Et_2O (3x 20.0 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by dry column chromatography (Florisil; pentane/EtOAc; 5% increments) gave the title compound as a colourless oil; yield: 717mg (91 %).

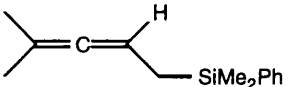
ν_{max}	1257, 1043, 843 cm-1
δH	0.13 (6H, s, $SiMe_2$), 1.14 (6H, d, *J*=6.1, $OCH\underline{Me}_2$), 1.37 (2H, d, *J*=8.2, CH_2Si), 1.65 (6H, d, *J*=2.9, CMe_2), 4.01 (1H, septet, *J*=6.1, $OC\underline{H}Me_2$), 4.92 (1H, m, C-2-H)

δC -2.00 (SiMe), 18.25 (CH_2), 20.71 (CH_3), 25.65 (OCH$\underline{Me_2}$), 64.85 (OC$\underline{H}Me_2$), 83.90 (C-2), 94.18 (C-4), 202.14 (C-3)

Mass Spec: *m/z* (%)=198 (M+, 1.4), 117 (22), 75 (100), 59 (12), 45 (14), 43 (13), 28 (41)

Found M+ 198.1439 $C_{11}H_{22}OSi$ requires 198.1440

1-(Dimethylphenylsilyl)-4-methyl-2,3-pentadiene



(208)

A 25 ml round-bottomed flask, with stirrer bar, containing pre-dried Mg (204mg; 8.5 mmol) was flame dried and purged with N_2. To this was added THF (2.0 ml) and a small quantity of neat (chloromethyl)dimethylphenylsilane (ca. 0.2 ml). The Grignard was initiated by adding 1-2 drops of dibromoethane and heated with a hot gun. Once the reaction had commenced the Grignard formation was kept at the point of reflux by adding the remainder of the (chloromethyl)dimethylphenylsilane (1.48g; 8mmol) in THF (2.0 ml) over 5 mins. Grignard completion was signified by the flask returning to room temperature.

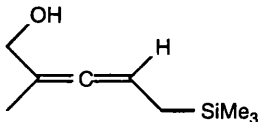
A second flame-dried, round-bottomed flask containing $Me_2S.CuBr$ (824mg, 4 mmol) was cooled to -78 °C and then THF (10.0 ml) and Me_2S (5.08g; 6 ml; 82 mmol) were added. The cooling bath was removed until all the complex had solubilised and then the -78 °C bath was replaced. The pre-formed Grignard reagent was added dropwise and the cooling bath removed, the reaction mixture stirred at room temperature for 10 mins and the bath replaced. Then the propargyl chloride (410mg; 4 mmol) in THF (9.2 ml) was added dropwise over ca. 2 mins and the reaction mixture left to stir at -78 °C for 1.5 hours, then at 0 °C for 1 hour. The mixture was quenched with aqueous NH_4Cl/ 33 % aqueous NH_4OH solution (9:1) (26.0 ml) and the organic layer removed. The aqueous phase was extracted with Et_2O (3x 20.0 ml), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by dry column chromatography (Florisil; pentane/EtOAc; 5% increments) gave the title compound as a colourless oil; yield: 578mg (67 %).

ν_{max}	3000-2900, 1930, 1257, 843, 700-710 cm^{-1}
δH	0.35 (6H, s, $SiMe_2$), 1.51 (2H, d, *J*=8.6, CH_2Si), 1.63 (6H, d, *J*=2.9, CMe_2), 4.96 (1H, m, CH), 7.46 (5H, m, ArH)

δC -3.35 ($SiMe_2$), 17.34 (C-1), 20.83 (CH_3), 84.42 (C-2), 94.37 (C-4), 127.68 (*o*-Ph), 128.88 (*m*-Ph), 133.64 (*p*-Ph), 138.90 (*i*-Ph), 202.29 (C-3)

Mass Spec: *m/z* (%)=135 (100), 120 (11), 107 (12), 105 (19), 43 (20)
Found M^+ 216.1330 $C_{14}H_{20}Si$ requires M^+ 216.1334

1-Hydroxy-2-methyl-5-trimethylsilyl-2,3-pentadiene



(165)

To a flame-dried flask, containing pre-dried copper iodide (2.38g; 12.5mmol), under N_2, was added anhydrous Et_2O (30.0ml) and the flask cooled to 0°C (ice/water bath). Lithium methyltrimethylsilane (1M solution in pentanes) (25.0ml; 25.0mmol) was added in two equivalent portions affording a clear brown solution. The flask was then further cooled to -78°C (acetone/Drikold) forming a light brown precipitate. To the pre-formed cuprate was added epoxide (1.03g, 12.5mmol) in anhydrous Et_2O (35.0ml) over 20 minutes. After addition the reaction mixture was left stirring at -78°C for a further 2 hours and then carefully quenched with saturated NH_4Cl solution (25.0ml) and allowed to warm to ambient temperature. The aqueous layer was extracted with Et_20 (3 x 20.0ml) and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) afforded the title compound as a colourless oil; yield: 1.69g (79%).

ν_{max} 3200-3600, 1970, 863 cm-1

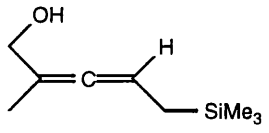
δH 0.01 (9H, s, $SiMe_3$), 1.35 (2H, d, *J*=8.0, CH_2Si), 1.67 (3H, d, *J*=2.9, CH_3), 3.95 (2H, d, *J*=2.8, CH_2O), 5.22 (1H, m, CH)

δC 0.0 ($SiMe_3$), 15.94 (CH_3), 18.33 (C-5), 63.98 (C-1), 90.66 (C-4), 99.71 (C-2), 199.30 (C-3)

Mass Spec: *m/z* (%)=79 (35), 75 (46), 73 (100), 59 (21), 45 (43), 44 (34), 43 (41), 41 (29), 40 (20)

Found M^+ 170.1113 $C_9H_{18}OSi$ requires M^+ 170.1126

1-Hydroxy-2-methyl-5-trimethylsilyl-2,3-pentadiene



To a flame-dried flask, with stirrer bar, under N_2, was added the acetoxy allene (53mg; 0.25mmol) in anhydrous MeOH (2.0ml) and potassium carbonate (250mg; 1.8mmol). The reaction mixture was stirred for 2 hours at room temperature and then filtered, washed with MeOH and concentrated *in vacuo* to yield a yellow, oily solid. This solid was dissolved in the minimum amount of water, extracted with EtOAc (3 x 5.0ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) gave the title compound as a colourless oil; yield: 29mg (84%).

ν_{max} 3200-3600, 1970, 863 cm^{-1}

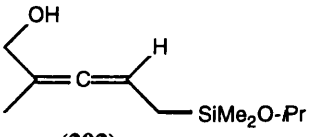
δH 0.01 (9H, s, $SiMe_3$), 1.35 (2H, d, *J*=8.0, CH_2Si),
1.67 (3H, d, *J*=2.9, CH_3), 3.95 (2H, d, *J*=2.8, CH_2O),
5.22 (1H, m, CH)

δC 0.0 ($SiMe_3$), 15.94 (CH_3), 18.33 (C-5), 63.98 (C-1),
90.66 (C-4), 99.71 (C-2), 199.30 (C-3)

Mass Spec: *m/z* (%)=170 (M+, 0.6), 75 (53), 73 (90), 45 (57), 43 (100),
39 (24), 29 (44), 28 (81), 27 (25)
Found M^+ 170.1113 $C_9H_{18}OSi$ requires M^+ 170.1126

Optical Rotation: $[\alpha]^{20}_D$-32.0° (*c*=2, EtOH)
$[\alpha]^{21}_D$+33.1° (*c*=2, EtOH)

1-Hydroxy-2-methyl-5-(dimethylisopropoxysilyl)-2,3-pentadiene



(202)

A 25 ml round-bottomed flask, with stirrer bar, containing pre-dried Mg (204mg; 8.5 mmol) was flame dried and purged with N_2. To this was added THF (2.0 ml) and a small quantity of neat (chloromethyl)isopropoxysilane (ca. 0.2 ml). The Grignard was initiated by adding 1-2 drops of dibromoethane and heated with a hot gun. Once the reaction had commenced the Grignard formation was kept at the point of reflux by adding the remainder of the (chloromethyl)dimethylisopropoxysilane (0.72ml; 4mmol) in THF (2.0 ml) over 5 mins. Grignard completion was signified by the flask returning to room temperature.

A second, flame-dried round-bottomed flask containing $Me_2S.CuBr$ (824mg, 4 mmol) was cooled to -78 °C and then THF (10.0 ml) and Me_2S (5.08g; 6 ml; 82 mmol) were added. The cooling bath was removed until all the complex had solubilised and then the -78 °C bath was replaced. The pre-formed Grignard reagent was added dropwise and the cooling bath was then removed, the reaction mixture stirred at room temperature for 10 mins and the bath replaced. The propargyl chloride (410mg; 4 mmol) in THF (9.2 ml) was added, dropwise, over ca. 2 mins and the reaction mixture left to stir at -78 °C for 1.5 hours, then at 0 °C for 1 hour. The mixture was quenched with aqueous NH_4Cl/ 33 % aqueous NH_4OH solution (9:1) (26.0 ml) and the organic layer removed. The aqueous phase was extracted with ether (3x 20.0 ml), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by dry column chromatography (Florisil; pentane/EtOAc; 5% increments) gave the title compound as a colourless oil; yield: 775mg (91%).

ν_{max} 3300-3690, 1960, 1000-1077, 860 cm^{-1}

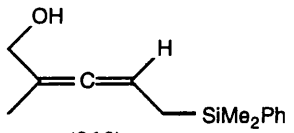
δH 0.13 (6H, s, $SiMe_2$), 1.14 (6H, d, *J*=6.1, $CH\underline{Me_2}$),
1.35 (2H, t, *J*=8.6, CH_2Si), 1.64 (3H, d, *J*=2.9, CH_3),
3.92 (2H, d, *J*=2.5, CH_2O),

3.88 (1H, septet, J=6.1, C<u>H</u>Me$_2$), 4.9 (1H, m, CH)

δC -1.80 (SiMe$_2$), 15.61 (CH$_3$), 18.37 (CH$_2$Si), 25.54 (CH<u>Me$_2$</u>), 63.54 (CH$_2$OH), 65.25 (C<u>H</u>Me$_2$), 89.73 (C-4), 100.27 (C-2), 199.49 (C-3)

Mass Spec: m/z (%)=147 (39), 117 (22), 79 (42), 75 (100)
Found M^+-OCHMe$_2$ 155.0877 $C_8H_{15}OSi$ requires 155.0892

1-Hydroxy-2-methyl-5-(dimethylphenylsilyl)-2,3-pentadiene



(210)

A 25-ml round-bottomed flask, with stirrer bar, containing pre-dried Mg (204mg; 8.5 mmol) was flame dried and purged with N_2. To this was added THF (2.0 ml) and a small quantity of neat (chloromethyl)dimethylphenylsilane (ca. 0.2 ml). The Grignard was initiated by adding 1-2 drops of dibromoethane and heated with a hot gun. Once the reaction had commenced the Grignard formation was kept at the point of reflux by adding the remainder of the (chloromethyl)dimethylphenylsilane (1.48g; 8mmol) in THF (2.0 ml) over 5 mins. Grignard completion was signified by the flask returning to room temperature.

A second, flame-dried round-bottomed flask containing $Me_2S.CuBr$ (824mg, 4 mmol) was cooled to -78 °C and then THF (10.0 ml) and Me_2S (5.08g; 6 ml; 82 mmol) were added. The cooling bath was removed until all the complex had solubilised and then the -78 °C bath was replaced. The pre-formed Grignard reagent was added dropwise and the cooling bath removed, the reaction mixture stirred at room temperature for 10 mins and the bath replaced. Then the epoxide (328mg; 4 mmol) in THF (9.2 ml) was added dropwise over ca. 2 mins and the reaction mixture left to stir at -78 °C for 1.5 hours, then at 0 °C for 1 hour. The mixture was quenched with aqueous NH_4Cl/ 33 % aqueous NH_4OH solution (9:1) (26.0 ml) and the organic layer removed. The aqueous phase was extracted with ether (3x 20.0 ml), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by dry column chromatography (silica gel; pentane/EtOAc; 5% increments) gave the title compound as a colourless oil; yield: 914mg (98%).

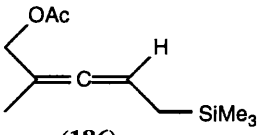
ν_{max}	3365, 1262, 853, 709 cm^{-1}
δH	0.32 (6H, s, $SiMe_2$), 1.26 (2H, s, CH_2Si), 1.60 (3H, d, *J*=3.3, CH_3), 3.84 (2H, d, *J*=2.5, CH_2O), 5.23 (1H, m, CH), 7.49-7.60 (5H, m, ArH)

δC -4.71 ($SiMe_2$), 15.75 (CH_3), 17.84 (CH_2Si), 63.98 (CH_2OH), 90.66 (C-4), 99.71 (C-2), 199.34 (C-3), 127.67 (*o*-Ph), 129.43 (*m*-Ph), 132.81 (*p*-Ph), 137.69 (*i*-Ph)

Mass Spec: *m/z* (%)=135 (100), 105 (24), 79 (55), 75 (73), 43 (46), 28 (23), 18 (54)

Found M^+ 232.1274 $C_{14}H_{20}OSi$ requires M^+ 232.1283

1-Acetoxy-2-methyl-5-trimethylsilyl-2,3-pentadiene



(186)

A flame-dried flask, equipped with stirrer bar, under N_2 was charged with the allenylmethylsilane (1.06g; 6.2mmol) in anhydrous CH_2Cl_2 (15.0ml). To this was added acetic anhydride (3.16g; 31.2mmol), triethylamine (3.14g; 31.2mmol) and a catalytic quantity of 4,4-dimethylaminopyridine (5mg). The reaction mixture was stirred at room temperature overnight, then diluted with Et_2O (20ml) and washed with $NaHCO_3$ (20.0ml), concentrated *in vacuo* and purification by dry column flash chromatography (silica gel; pentane/EtOAc; 5% increments) afforded the title compound as a colourless oil; yield: 1.19g (90%).

ν_{max} 1950, 1728, 1250, 855 cm^{-1}

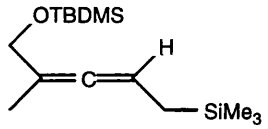
δH 0.0 (9H, s, $SiMe_3$), 1.30 (2H, d, *J*=8.5, CH_2Si), 1.67 (3H, d, *J*=2.9, CH_3), 2.06 (3H, s, $COCH_3$), 4.47 (2H, d, *J*=2.2, CH_2O), 5.1 (1H, m, CH)

δC -2.04 (SiMe), 16.52 (CH_3), 17.81 (C-5), 20.96 ($CO\underline{C}H_3$), 66.61 (C-1), 88.15 (C-4), 94.34 (C-2), 170.90 ($C^{=}O$), 202.69 (C-3)

Mass Spec: *m/z* (%)=212 (M+, 0.3), 79 (35), 75 (42), 73 (100), 45 (30), 43 (98)
Found M^+ 212.1223 $C_{11}H_{20}O_2Si$ requires M^+ 212.1227

Optical Rotation: $[\alpha]_D$-29.5° (*c*=2, EtOH) (67.0 % e.e.)
$[\alpha]_D$+34.9° (*c*=2, EtOH) (82.4 % e.e.)

1-(*O-tert*-Butyldimethylsilyl)-2-methyl-5-trimethylsilyl-2,3-pentadiene



(167)

To a flame-dried flask, equipped with stirrer bar, under N_2 was added the (allenylmethyl)silane (240mg; 1.41mmol) in dry CH_2Cl_2 (2.0ml). To this was added *tert*-butyldimethylsilyl chloride (230mg; 1.55mmol), triethylamine (280mg; 2.82mmol) and a catalytic quantity of 4,4-dimethylaminopyridine (5mg). The reaction mixture was stirred overnight at room temperature, diluted with Et_2O (5.0ml) and washed once with $NaHCO_3$ (5.0ml) and water (5.0ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude oil. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 2% increments) afforded the title compound as a colourless oil; yield: 345mg (86%).

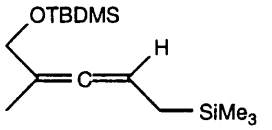
ν_{max} 1942, 855 cm^{-1}

δH 0.02 (15H, s, $SiMe_3$), 0.90 (9H, s, *t*-Bu),
1.28 (2H, d, *J*=8.4, CH_2Si), 1.67 (3H, d, *J*=2.9, CH_3),
4.07 (2H, d, *J*=2.2, CH_2O), 5.04 (1H, m, CH)

δC -5.22, -5.18 ($SiMe_3$), 16.01 (CH_3), 17.99 (C-5), 25.94 (*t*-Bu),
65.98 (C-1), 87.03 (C-4), 98.57 (C-2), 201.34 (C-3)

Mass Spec: *m/z* (%)=284 (M+, 0.1), 147 (58), 139 (30), 75 (41), 73 (100),
59 (21), 45 (28)
Found M^+ 284.1998 $C_{15}H_{32}OSi_2$ requires M^+ 284.1992

1-(*O-tert*-Butyldimethylsilyl)-2-methyl-5-trimethylsilyl-2,3-pentadiene

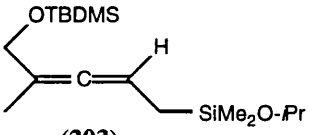


(167)

To a flame-dried flask, with stirrer bar, under N_2, was added the (allenylmethyl)silane (227mg; 1.06mmol) in anhydrous CH_2Cl_2 (2.5ml). To this was added 2,6-lutidine (247µl; 2.12mmol) and TBDMS triflate (336mg; 1.27mmol) and the reaction mixture stirred overnight at room temperature. After this time the reaction mixture was diluted with Et_2O (5.0ml), washed with $CuSO_4$ (5.0ml), water (5.0ml) and brine (5.0ml) and the organic fraction dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 2% increments) afforded the title compound as a colourless oil; yield: 1.26g (98%).

(For experimental data, see previous page)

1-(*O-tert*-Butyldimethylsilyl)-2-methyl-5-(dimethylisopropoxysilyl) -2,3-pentadiene



(**203**)

To a flame-dried flask, with stirrer bar, under N_2, was added the (allenylmethyl)silane (227mg; 1.06mmol) in anhydrous CH_2Cl_2 (2.5ml). To this was added 2,6-lutidine (247µl; 2.12mmol) and TBDMS triflate (336mg; 1.27mmol) and the reaction mixture stirred overnight at room temperature. After this time the reaction mixture was diluted with Et_2O (5.0ml), washed with $CuSO_4$ (5.0ml), water (5.0ml) and brine (5.0ml) and the organic fraction dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil. Purification by dry column flash chromatography (Florisil; pentane/EtOAc; 2% increments) afforded the title compound as a colourless oil; yield: 233mg (67%).

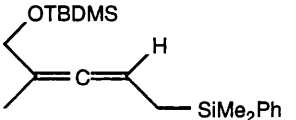
ν_{max} 2750-2950, 1500, 1250, 860 cm^{-1}

δH 0.06 (12H, s, SiMe), 0.88 (9H, s, *t*-Bu),
1.13 (6H, d, *J*=6.1, $CH\underline{Me_2}$),
1.39 (2H, d, *J*=8.4, CH_2Si), 1.65 (3H, d, *J*=2.9, CH_3),
3.95 (1H, septet, *J*=6.1, $C\underline{H}Me_2$),
4.05 (2H, d, *J*=2.2, CH_2O), 4.99 (1H, m, CH)

δC -5.27, -2.31 (SiMe), 15.95 (CH_3), 18.12 (C-5),
25.62 ($CH\underline{Me_2}$), 25.71 (*t*-Bu), 64.95 ($C\underline{H}Me_2$), 65.94 (C-1),
86.13 (C-4), 98.74 (C-2), 200.34 (C-3)

Mass Spec: *m/z* (%)=271 (M^+-*t*-Bu, 2.1), 149 (35), 147 (25), 133 (26),
117 (60), 75 (100), 73 (44)
Found M^+ -*t*-Bu 271.1566 $C_{13}H_{27}O_2Si_2$ requires 271.1549

1-(*O-tert*-Butyldimethylsilyl)-2-methyl-5-(dimethylphenylsilyl)-2,3-pentadiene



(**211**)

To a flame-dried flask, with stirrer bar, under N_2, was added the (allenylmethyl)silane (227mg; 1.06mmol) in anhydrous CH_2Cl_2 (2.5ml). To this was added 2,6-lutidine (247µl; 2.12mmol) and TBDMS triflate (336mg; 1.27mmol) and the reaction mixture stirred overnight at room temperature. After this time the reaction mixture was diluted with Et_2O (5.0ml), washed with $CuSO_4$ (5.0ml), water (5.0ml) and brine (5.0ml) and the organic fraction dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 2% increments) afforded the title compound as a colourless oil; yield: 965mg (75%).

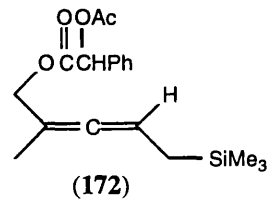
ν_{max} 3050, 2856-2955, 1115, 800 cm^{-1}

δH 0.03 (6H, s, Si<u>Me</u>$_2$Ph), 0.30 (6H, s, Si<u>Me</u>$_2$*t*-Bu), 0.89 (9H, s, *t*-Bu), 1.52 (2H, d, *J*=8.3, CH_2Si), 1.60 (3H, d, *J*=2.8, CH_3), 3.99 (2H, *J*=2.1, CH_2O), 5.05 (1H, m, CH), 7.36 (5H, ArH)

δC -5.23, -3.40 (SiMe), 15.80 (CH_3), 17.09 (C-5), 25.89 (*t*-Bu), 65.78 (C-1), 86.51 (C-4), 98.80 (C-2), 127.67 (*o*-Ph), 128.93 (*m*-Ph), 133.62 (*p*-Ph), 138.63 (*i*-Ph), 201.52 (C-3)

Mass Spec: *m/z* (%)=346 (M^+, 1.4), 209 (22), 147 (41), 135 (100), 73 (35)
Found M+ 346.2152 $C_{20}H_{34}OSi_2$ requires M^+ 346.2148

2-Methyl-5-trimethylsilyl-2,3-pentadienyl 2-Acetoxy-2-phenylacetate



(172)

To a solution of the allenylmethyl alcohol (44mg; 3.64mmol) in CH_2Cl_2 (4.0ml) was added 4,4-dimethylaminopyridine (44mg; 0.36mmol) and *O*-acetylmandelic acid (722mg; 4mmol) in CH_2Cl_2 (4.0ml) under a N_2 atmosphere. The flask was cooled to 0°C (ice/water bath) and dicyclohexylcarbodiimide (802mg; 4mmol) in CH_2Cl_2 (4.0ml) added, dropwise, over 8 minutes. This gave an immediate white precipitate of urea. The reaction mixture was stirred overnight at room temperature whereupon it was filtered through a pad of Celite and washed with 2M Na_2CO_3 (5.0ml) and then saturated brine (5.0ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude ester. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 5% increments) furnished the title compound as a colourless oil; yield: 620mg (49%).

νmax 1755, 1248, 840-955 cm^{-1}

δH 0.0 (9H, s, $SiMe_3$), 0.01 (9H, s, $SiMe_3$),
1.22 (2H, d, *J*=8.6, CH_2Si), 1.54 (3H, d, *J*=2.8, CH_3),
2.20 (3H, s, $COCH_3$), 4.49 (2H, d, *J*=2.1, CH_2O, minor),
4.55 (2H, d, *J*=2.1, CH_2O, major), 5.05 (1H, m, CH),
5.95 (1H, s, C<u>H</u>OAc), 7.44 (5H, m, ArH)

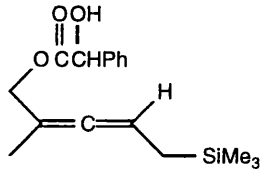
δC -2.07 ($SiMe_3$), 16.21 (CH_3, major), 16.50 (CH_3, minor),
17.65 (CH_2Si), 20.70 (CO<u>C</u>H_3), 66.60 (C-1, minor)
67.71 (C-1, major), 74.47 (C<u>H</u>OAc), 88.13 (C-4), 93.86 (C-2),
127.61 (*o*-Ph), 128.67 (*m*-Ph), 129.12 (*p*-Ph), 133.84 (*i*-Ph),
168.63 (C=O), 170.23 (C=O), 203.05 (C-3)

Mass Spec: *m/z* (%)=197 (32), 149 (21), 118 (27), 107 (43), 79 (36),

73 (100), 43 (71)

Found M^+ 346.1585 $C_{19}H_{26}O_4Si$ requires M^+ 346.1600

2-Methyl-5-trimethylsilyl-2,3-pentadienyl 2-Hydroxy-2-phenylacetate



(173)

To a round-bottomed flask, equipped with stirring bar, under N_2, was added the mandelate ester (390mg; 1.13mmol) in a solution of triethylamine in MeOH (10.0ml; 15% v/v). The reaction mixture was stirred at room temperature for 18 hours and concentrated *in vacuo.* Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10 % increments) gave a hydrolysis product which was shown by NMR to be the (hydroxymethyl)allene; recovered yield: 185mg (96%).

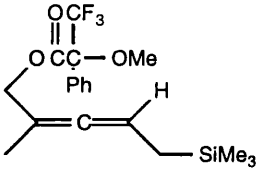
ν_{max} 3200-3600, 1970, 863 cm^{-1}

δH 0.01 (9H, s, $SiMe_3$), 1.35 (2H, d, *J*=8.0, CH_2Si), 1.67 (3H, d, *J*=2.9, CH_3), 3.95 (2H, d, *J*=2.8, CH_2O), 5.22 (1H, m, CH)

δC 0.00 ($SiMe_3$), 15.94 (CH_3), 18.33 (C-5), 63.98 (C-1), 90.66 (C-4), 99.71 (C-2), 199.30 (C-3)

Mass Spec: *m/z* (%)=170 (M^+, 0.6), 75 (53), 73 (90), 45 (57), 43 (100), 39 (24), 29 (44), 28 (81), 27 (25)
Found M^+ 170.1113 $C_9H_{18}OSi$ requires M^+ 170.1126

1-[Methoxy-(trifluoromethly)phenylacetoxy]-2-methyl-5-trimethylsilyl-2,3-pentadiene



(177)

To a suspension of 1-methyl-2-chloropyridinium iodide (90mg; 0.3mmol) in CH_2Cl_2 (0.5ml) was added a mixture of allenyl alcohol (42.5mg; 0.25mmol), Mosher's acid (58.5mg; 0.25mmol) and triethylamine (84ml; 0.6mmol) under a N_2 atmosphere and the resulting mixture refluxed for 3 hours (CH_2Cl_2 insoluble salt progressively dissolved as the reaction proceeded). The solvent was removed *in vacuo* and the resulting crude residue purified by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) to afford the title compound as a yellow oil; yield: 38.4mg (40%).

ν_{max} 2850, 1960, 1740, 1450, 100-1300, 850 cm^{-1}

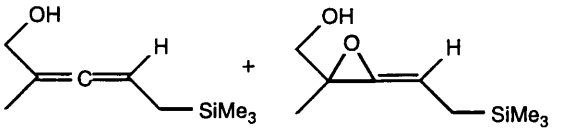
δH 0.01 (9H, s, $SiMe_3$), 1.27 (2H, *J*=8.6, CH_2Si), 1.65 (3H, d, *J*=2.9, CH_3), 3.41 (3H, q, *J*=1.1, OCH_3), 3.56 (3H, q, *J*=1.1, OCH_3), 4.73 (2H, d, *J*=1.9, CH_2O), 5.14 (1H, m, CH), 7.40 (5H, m, Ar-H)

δC -2.05 ($SiMe_3$), 16.58 (CH_3), 17.67 (C-5), 55.45 (OCH_3), 68.89 (C-1), 88.40 (C-4), 88.48 ($\underline{C}CF_3$), 93.39 (C-2), 114.67, 120.40, 126.14, 131.88 (CF_3), 127.36 (*o*-Ph), 128.35 (*m*-Ph), 129.55 (*p*-Ph), 132.29 (*i*-Ph), 166.37 (C=O), 203.65 (C-3)

Mass Spec: *m/z* (%)=386 (M^+, 0.1), 197 (20), 189 (58), 105 (34), 79 (47), 77 (35), 73 (100), 45 (20)
Found M^+ 386.1519 $C_{19}H_{25}F_3O_3Si$ requires M^+ 386.1525

Optical Rotation: $[\alpha]^{13}_D$+1.78 (*c*=2, EtOH)
$[\alpha]^{14}_D$+31.09 (*c*=2, EtOH)

Kinetic Resolution of 1-Hydroxy-2-methyl-5-trimethylsilyl-2,3-pentadiene



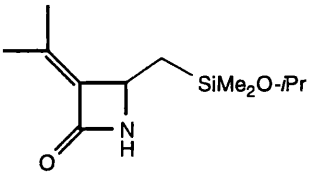
A 25-ml, round-bottomed flask, equipped with stirrer bar, containing 4Å powdered, activated molecular sieves (0.12g) was flame-dried and purged with N_2. CH_2Cl_2 (6.0ml) was added and the flask cooled to -20°C (acetone/Drikold) with stirring. L-(+)-diisopropyltartrate (56.2mg; 0.24mmol) or D-(-)-diethyl tartrate (49.5mg; 0.24mmol) and Ti(O-*i*Pr)$_4$ (56.8mg; 0.06ml; 0.20mmol) were added sequentially. The reaction mixture was stirred at -20°C as *tert*-butyl hydroperoxide (0.48ml; 2.40mmol) was added *via* syringe over 5 minutes. The resulting mixture was stirred at -20°C for 30 minutes.

Allenylmethyl alcohol (0.68g; 4.0mmol) in CH_2Cl_2 (2.0ml) and stored for 10-15 minutes over 4Å sieves was added, dropwise, over 20 minutes, maintaining the temperature at -20 to -15°C. The cooling bath was then firmly packed with Drikold and left stirring overnight.

After this time the reaction mixture was quenched with saturated Na_2SO_4 (0.2ml) immediately after addition of Et_2O (1.0ml). The resulting homogeneous mixture was stirred vigorously for 2 hours at room temperature, filltered through a Celite pad and the resulting orange-yellow paste washed with several portions of anhydrous Et_2O until the paste became somewhat granular. The orange-yellow layer was scraped off the Celite pad into an Erlenmeyer flask fitted with a condenser. EtOAc (4.0ml) was added along with a stirring bar and the resulting suspension stirred vigorously for 5 minutes in boiling EtOAc. The slurry was then filtered through the same Celite pad and the orange-yellow solid washed once with hot EtOAc (2.0ml). The combined filtrates were concentrated to afford crude product along with the tartrate diester. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 5% increments) afforded the resolved alcohol; yield: 258 mg (38%).

νmax	3200-3600, 1970, 863 cm^{-1}
δH	0.01 (9H, s, $SiMe_3$), 1.35 (2H, d, *J*=8.0, CH_2Si), 1.67 (3H, d, *J*=2.9, CH_3), 3.95 (2H, d, *J*=2.8, CH_2O), 5.22 (1H, m, CH)
δC	0.0 ($SiMe_3$), 15.94 (CH_3), 18.33 (C-5), 63.98 (C-1), 90.66 (C-4), 99.71 (C-2), 199.30 (C-3)
Mass Spec:	*m/z* (%)=170 (M+, 0.6), 75 (53), 73 (90), 45 (57), 43 (100), 39 (24), 29 (44), 28 (81), 27 (25) Found M^+ 170.1113 $C_9H_{18}OSi$ requires M^+ 170.1126
Optical Rotation:	$[\alpha]^{16}_D$ +2.89° (*c*=2, EtOH) $[\alpha]^{10}_D$ -2.94° (*c*=2, EtOH)

3-Isopropylidene-4-[(dimethylisopropoxysilyl)methyl]-2-azetidinone



(198)

To a flame-dried, round-bottomed flask, under N_2, was added the dimethylallene (245mg; 1.24mmol) and CCl_4 (12.6ml). The flask was cooled to 0°C and CSI (109µl; 1.24mmol) added dropwise over 2 minutes. The reaction was stirred at 0°C for a further 4.5 hours, quenched with a 25% aqueous Na_2SO_3 solution (12.6ml) and stirred vigorously at room temperature overnight. The organic layer was retained, dried (Na_2SO_4) and concentrated *in vacuo* to give a white oily solid. Purification by dry column flash chromatography (Florisil; pentane/EtOAc; 5% increments) furnished the title compound as a white crystalline solid; yield: 75mg (25%).

ν_{max} 1740, 1250, 840 cm^{-1}

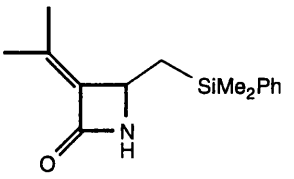
δH 0.11 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.78 (1H, dd, *J*=14.0, *J*=11.1, C<u>H</u>HSi), 1.02 (1H, dd, *J*=14.0, *J*=2.9, CH<u>H</u>Si), 1.09 (6H, d, *J*=6.1, CH<u>Me</u>$_2$), 1.66 (3H, s, CH_3), 1.96 (3H, s, CH_3), 3.94 (1H, septet, *J*=6.1, C<u>H</u>Me$_2$), 4.12 (1H, dd, *J*=11.1, *J*=2.9, C-4-H), 6.39 (1H, bs, NH)

δC -1.08, -0.52 (SiMe$_2$), 19.63 (CH_3), 19.89 (CH_3), 22.07 (CH_2Si), 25.75 (CH<u>Me</u>$_2$), 52.41 (C-4), 65.20 (C<u>H</u>Me$_2$), 135.15 (C-3), 138.65 (C'-1), 165.14 (C-2)

Mass Spec: *m/z* (%)=241 (M^+, 0.6), 117 (19), 91 (18), 77 (21), 75 (100), 28 (26)

Found M^+ 241.1498 $C_{12}H_{23}NO_2Si$ requires 241.1498

3-Isopropylidene-4-[(dimethylphenylsilyl)methyl]-2-azetidinone



(209)

To a flame-dried, round-bottomed flask , under N_2, was added the dimethylallene (245mg; 1.24mmol) and CCl_4 (12.6ml). The flask was cooled to 0°C and CSI (109µl; 1.24mmol) added, dropwise, over 2 mins. The reaction was stirred at 0°C for a further 4.5 hours, quenched with a 25% solution of aqueous Na_2SO_3 solution (12.6ml) and stirred vigorously at room temperature overnight. The organic layer was retained, dried (Na_2SO_4) and concentrated *in vacuo* to give a white oily solid. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 10% increments) furnished the title compound as a white crystalline solid; yield: 135mg (21%).

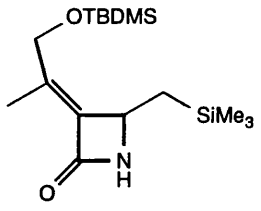
ν_{max} 2859-2950, 1728, 1464, 1377, 837 cm^{-1}

δH 0.32 (3H, s, SiMePh), 0.35 (3H, s, SiMePh),
1.05 (1H, dd, *J*=14.8, *J*=10.5, CHHSi),
1.32 (1H, dd, *J*=14.8, *J*=2.7, CHHSi),
1.66 (3H, s, CH_3), 1.96 (3H, s, CH_3),
4.07 (1H, dd, *J*=10.5, *J*=2.7, C-4-H), 5.70 (1H, bs, NH),
7.38 (5H, m, Ar-H)

δC -2.78, -2.28 (SiMe), 19.68 (CH_3), 19.92 (CH_3),
21.54 (CH_2Si), 53.07 (C-4), 128.12 (*o*-Ph), 129.41 (*m*-Ph),
133.41 (*p*-Ph), 135.57 (*i*-Ph), 138.07 (C-3), 138.13 (C'-1),
164.94 (C-2)

Mass Spec: *m/z* (%)=259 (M^+, 8), 244 (29), 137 (40), 135 (100), 107 (20),
105 (23), 67 (21), 43 (43), 28 (34)
Found M^+ 259.1406 $C_{15}H_{21}NOSi$ requires 259.1392

3-[2'-(*O-tert*-Butyldimethylsilyl)methylethylidene]
-4-(trimethylsilylmethyl)-2-azetidinone



(168)

A flame-dried flask under N_2 was charged with TBDMS-protected (allenylmethyl)silane (293 mg; 1.03 mmol) in dry, distilled CCl_4 (10.5 ml) and then chilled to 0 °C. CSI (90.1 µl; 1.03 mmol) was added, dropwise, over 2-5 mins. The reaction mixture was stirred at 0 °C for 4.5 hours and then quenched with a 25 % aqueous Na_2SO_3 solution (10.5 ml) and left to stir overnight at room temperature. After this period the biphasic reaction mixture was placed in a separating funnel and the organic layer retained, dried ($MgSO_4$) and concentrated to yield a crude crystalline product. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10 % increments) gave the title compound as a white crystalline solid; yield: 105 mg (31%).

ν_{max} 2855-2924, 1743, 1155, 839 cm^{-1}

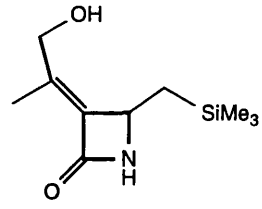
δH 0.0 (15H, s, $SiMe_3$), 0.88 (9H, s, *t*-Bu), 1.23 (1H, dd, *J*=14.7, *J*=10.5, C<u>H</u>HSi), 1.27 (1H, dd, *J*=14.7, *J*=2.8, CH<u>H</u>Si), 1.96 (3H, s, CH_3) 4.10 (2H, d, *J*=3.6, CH_2O), 4.28 (1H, dd, *J*=10.5, *J*=2.8, C-4-H), 6.41 (1H, bs, NH)

δC -5.39 (SiMe), -0.74 (*t*-BuSi), 22.69 (CH_2Si), 25.92 (C<u>Me</u>$_3$), 54.32 (C-4), 64.14 (CH_2OSi), 137.39 (C-3), 138.54 (C-1), 165.38 (C-2)

Mass Spec: *m/z* (%)=327 (M+, 0.1), 270 (54), 180 (23), 147 (36), 79 (48), 75 (38), 73 (100), 45 (22)
Found M+ 327.2046 $C_{16}H_{33}NO_2Si_2$ requires 327.2049

Optical Rotation: $[\alpha]_D$= -17.6 ° (*c*=2, EtOH) (42.1 % e.e.)
$[\alpha]_D$= +16.9 (*c*=2, EtOH) (48.4 % e.e.)

3-[2'-(Hydroxymethyl)ethylidene]
-4-(trimethylsilylmethyl)-2-azetidinone



(169)

To a round-bottomed flask, equipped with stirrer bar, under N_2, was added a solution of the β-lactam in anhydrous THF (5.0ml). To this was added *tert*-butylammonium fluoride, dropwise, *via* syringe over 5 minutes and then the reaction mixture was stirred at room temperature for 4 hours. After this period the reaction mixture was diluted with Et_2O (5.0ml), washed with brine (5.0ml) and dried ($MgSO_4$). Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 10% increments) afforded the title compound as a white, crystalline solid; yield: 28.4mg (86%).

ν_{max} 3233-3609, 1743, 1192, 700-800 cm^{-1}

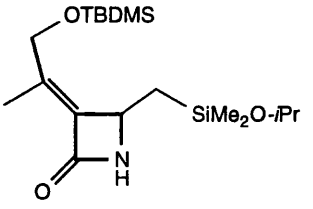
δH 0.04 (9H, s, $SiMe_3$), 0.91 (1H, dd, *J*=14.7, *J*=10.5, C<u>H</u>HSi), 1.24 (1H, dd, *J*=14.7, *J*=2.7, C<u>H</u>HSi), 2.02 (3H, s, CH_3), 4.30 (1H, dd, *J*=10.5, *J*=2.7, C-4-H), 4.14 (2H, s, CH_2O), 6.21 (1H, bs, NH), 6.42 (1H, bs, OH)

δC -0.88 ($SiMe_3$), 14.84 (CH_3), 22.75 (CH_2Si), 54.18 (C-4), 63.53 (CH_2O), 136.97 (C-3), 139.51 (C-1'), 165.21 (C=O).

Mass Spec: *m/z* (%)=100 (25), 79 (23), 75 (62), 74 (28), 73 (100), 67 (41), 59 (40), 45 (78), 44 (28), 43 (60), 42 (20), 41 (30), 39 (23), 28 (95), 18 (56)

Found M+ 213.1193 $C_{10}H_{19}NO_2Si$ requires 213.1185

3-[2'-(*O-tert*-Butyldimethylsilyl)methylethylidene]-4-(dimethylisopropoxysilylmethyl)-2-azetidinone



(200)

To a flame-dried, round-bottomed flask, under N_2, was added the protected allenylmethyl alcohol (398mg; 1.21mmol) and CCl_4 (12.4ml). The flask was cooled to 0°C and CSI (106.2µl; 1.21mmol) added, dropwise, over 2 mins. The reaction was stirred at 0°C for a further 4.5 hours, quenched with a 25% aqueous Na_2SO_3 solution (12.4ml) and stirred vigorously at room temperature overnight. The organic layer was retained, dried (Na_2SO_4) and concentrated *in vacuo* to give a white, oily solid. Purification by dry column flash chromatography (Florisil; pentane/EtOAc; 10% increments) furnished the title compound as a white crystalline solid; yield: 162mg (36%).

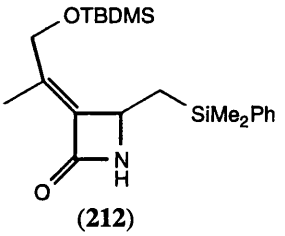
ν_{max} 3020, 1740, 1240, 840 cm^{-1}

δH 0.07 (12H, s, SiMe), 0.89 (9H, s, *t*-Bu),
1.18 (6H, d, *J*=6.1, CH<u>Me</u>$_2$), 1.66 (2H, d, *J*=2.9, CH_2Si),
1.98 (3H, s, CH_3), 4.01 (1H, septet, *J*=6.12, C<u>H</u>Me$_2$),
4.11 (1H, dd, *J*=10.9, *J*=2.9, C-4-H),
4.20 (2H, d, *J*=3.2, CH_2O), 5.95 (1H, bs, NH)

δC -5.26 (SiMe$_2$*t*-Bu), -0.45 (Si<u>Me</u>$_2$O-*i*Pr), 22.77 (CH_2Si),
25.78 (CH<u>Me</u>$_2$), 25.83 (CH_3), 25.94 (*t*-Bu), 53.25 (C-4),
64.25 (CH_2O), 64.96 (C<u>H</u>Me$_2$), 136.79 (C-3), 138.72 (C-1'),
165.22 (C=O)

Mass Spec: *m/z* (%)=117 (64), 107 (19), 93 (33), 81 (24), 79 (30),
75 (100), 45 (27), 43 (23), 28 (24)
Found M^+-*t*-Bu 314.1606 $C_{14}H_{28}NO_3Si_2$ requires 314.1608

3-[2'-(*O-tert*-Butyldimethylsilyl)methylethylidene]-4-(dimethylphenylsilylmethyl)-2-azetidinone



(212)

To a flame-dried, round bottom flask, under N_2, was added the dimethylallene (245mg; 1.24mmol) and CCl_4 (12.6ml). The flask was cooled to 0°C and CSI (109µl; 1.24mmol) added, dropwise, over 2 mins. The reaction was stirred at 0°C for a further 4.5 hours, quenched with a 25% solution of aqueous Na_2SO_3 solution (12.6ml) and stirred vigorously at room temperature overnight. The organic layer was retained, dried (Na_2SO_4) and concentrated *in vacuo* to give a white oily solid. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 10% increments) furnished the title compound as a white crystalline solid; yield: 162mg (27%).

ν_{max} 3024, 2840-2932, 1732, 1460, 1240, 837 cm^{-1}

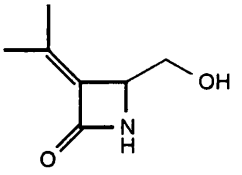
δH 0.06 (6H, s, $SiMe_2$), 0.32 (3H, s, $SiMe_2Ph$), 0.36 (3H, s, $SiMe_2Ph$), 0.88 (9H, s, *t*-Bu), 1.10 (1H, dd, *J*=14.8, *J*=10.5, C<u>H</u>HSi), 1.42 (1H, dd, *J*=14.8, *J*=2.7, CH<u>H</u>Si), 1.93 (3H, s, CH_3), 3.99 (2H, d, *J*=3.9, CH_2O), 4.25 (1H, dd, *J*=10.5, *J*=2.7, C-4-H), 5.53 (1H, bs, NH), 7.42 (5H, m, ArH)

δC -5.40, -2.90, -2.13 (SiMe), 14.77 (CH_3), 22.19 (CH_2Si), 25.90 (*t*-Bu), 53.93 (C-4), 64.13 (CH_2O), 128.16 (*o*-Ph), 129.45 (*m*-Ph), 133.41 (*p*-Ph), 137.34 (*i*-Ph), 138.13 (C-3), 138.36 (C'-1), 164.88 (C-2)

Mass Spec: *m/z* (%)=389 (M^+, 9), 332 (21), 254 (20), 135 (100), 127 (21), 43 (22)

Found M^+ 389.2191 $C_{21}H_{35}NO_2Si_2$ requires 389.2206

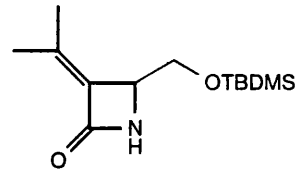
3-Isopropylidene 4-[(*O*-*tert*-butyldimethylsilyl)methyl]-2-azetidinone



(199)

Potassium bromide (39mg; 0.33mmol) and anhydrous sodium acetate (69mg; 0.84mmol) were added to a stirred solution of the (dimethylphenylsilyl)β-lactam (70mg; 0.27mmol) in glacial acetic acid (0.70ml). Peracetic acid (0.70ml of a 15% solution in acetic acid; 1.68mmol) was added, dropwise, cooling with ice. More sodium acetate (207mg; 2.52mmol) and peracetic acid (2.1ml; 5.04mmol) were added and the resulting turbid mixture stirred at room temperature for 18 hours and at 35°C for 1 hour. Et_2O (27.0ml) and finely ground sodium thiosulphate (2.76g) were added, resulting in an exothermic reaction, and the resulting suspension was stirred vigorously for 0.5 hours, filtered through Celite and evaporated *in vacuo* to give a yellow oily residue; crude yield: 16.8mg. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) gave a mixture of fractions, none of which were recognisable by ^1H NMR.

3-Isopropylidene 4-[(*O*-trimethylsilyl)methyl]-2-azetidinone



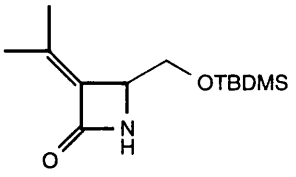
To a flame-dried flask, fitted with condenser, were added the (dimethylisopropoxysilyl)β-lactam (66.4mg; 0.27mmol), MeOH (0.8ml), THF (0.8ml), $NaHCO_3$ (22mg; 0.26mmol) and 30% H_2O_2 solution (0.24; 2.4mmol) and the reaction mixture refluxed for 7 hours and then stirred overnight at room temperature. To the mixture was added TBDMS triflate (75µl; 0.32mmol) and 2,6-lutidine (63µl; 0.54mmol) *in situ* and the resulting solution stirred for a further 2 hours at room temperature. Finely ground sodium thiosulphate (202mg; 0.81mmol) was added and the resulting suspension stirred vigorously for 0.5 hour to eliminate any peroxides. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to afford a crude yellow oil. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 10% increments) gave a colourless oil; yield: 19.2mg (28%).

δH 0.08 (12H, m, SiMe), 1.55 (3H, s, CH_3), 1.87 (3H, s, CH_3),
3.89 (1H, dd, *J*=14.1, *J*=7.8, C<u>H</u>HO),
3.92 (1H, dd, *J*=14.1, *J*=2.5, CH<u>H</u>O),
4.06 (1H, dd, *J*=7.8, *J*=2.46, C-4-H), 6.73 (1H, bs, NH)

δC 0.01 (SiMe), 14.49 (CH_3), 23.05 (t-Bu), 52.94 (C-4),
61.23 (CH_2O), 135.85 (C-3), 138.98 (C-1'), 165.46 (C=O)

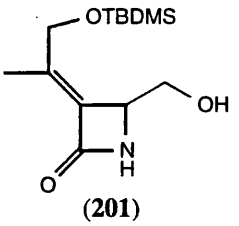
Mass Spec: *m/z* (%)=255 (15), 160 (13), 128 (22), 96 (17), 64 (100), 32 (23), 28 (18), 18 (20)

3-Isopropylidene 4-[(*O*-*tert*-butyldimethylsilyl)methyl]-2-azetidinone



Mercuric acetate (234mg; 0.74mmol) was added to a stirred solution of the (dimethylisopropoxysilyl)β-lactam (127mg; 0.49mmol) in peracetic acid (5.4ml of a 15% solution in acetic acid; 12.96mmol) and the mixture stirred at room temperature for 3 hours. After this time TBDMS triflate (249µl; 1.07mmol) and 2,6-lutidine (210µl; 2.15mmol) were added and the reaction mixture stirred overnight at room temperature. The mixture was quenched with Et_2O (15.0ml) and finely ground sodium thiosulphate (0.9g; 5.89mmol) resulting in an exothermic reaction and the resulting suspension was stirred vigorously for 0.5 hour. The brown-green precipitate was filtered, washed with $CuSO_4$ (10.0ml), H_2O (10.0ml), $NaHCO_3$ (10.0ml) and brine (10.0ml) and the organic extract dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oily solid; crude yield: 72mg. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) gave a mixture of fractions, none of which were recognisable by NMR.

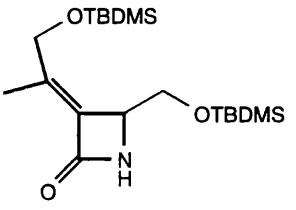
3-Isopropylidene 4-[(*O*-*tert*-butyldimethylsilyl)methyl]-2-azetidinone



(201)

Potassium bromide (37mg; 0.31mmol) and anhydrous sodium acetate (65mg; 0.79mmol) were added to a stirred solution of the (dimethylphenylsilyl)β-lactam (99mg; 0.25mmol) in glacial acetic acid (0.64ml). Peracetic acid (0.62ml of a 15% solution in acetic acid 1.49mmol) was added dropwise, cooling with ice. More sodium acetate (193mg; 2.34mmol) and peracetic acid (1.93ml; 4.63mmol) were added and the resulting turbid mixture stirred at room temperature for 18 hours and at 35°C for 1 hour. Et_2O (25.0ml) and finely ground sodium thiosulphate (2.55g) were added, resulting in an exothermic reaction, and the resulting suspension was stirred vigorously for 0.5 hours, filtered through Celite and evaporated *in vacuo* to give a yellow oily residue; crude yield: 16.8mg. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) gave a mixture of fractions, none of which were recognisable by ^1H NMR.

3-[2'-(O-*tert*-Butyldimethylsilyl)methylethylidene]-4-[(*O*-*tert*-butyldimethylsilylmethyl)]-2-azetidinone



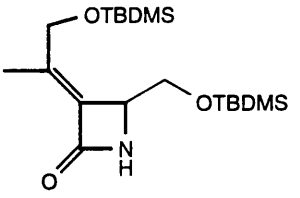
To a flame-dried, round-bottomed flask, fitted with condenser, were added the (dimethylisopropoxysilyl)β-lactam (98.5mg; 0.27mmol), MeOH (0.8ml); THF (0.8ml); $NaHCO_3$ (22mg; 0.26mmol) and 30% H_2O_2 (0.24ml; 2.4mmol). The mixture was refluxed with stirring for 5 hours and then stirred overnight at room temperature. Finely ground sodium thiosulphate (202mg; 0.81mmol) was added and the resulting suspension stirred vigorously for 0.5 hour to eliminate any peroxides. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo* to afford a crude oil which was subsequently taken up in CH_2Cl_2 (1.0ml) and transferred to a flame-dried flask under N_2 . To this were added 2,6-lutidine (63µl; 0.54mmol) and TBDMS triflate (75µl; 0.32mmol) in CH_2Cl_2 and the reaction mixture stirred overnight at room temperature. The reaction mixture was then diluted with Et_2O (2.0ml), washed with $CuSO_4$ (2.0ml), water (2.0ml) and brine (2.0ml), dried (Na_2SO_4) and concentrated *in vacuo* to afford a crude oil. Purification by dry column flash chromatography (silica gel; pentane/EtOAc; 10% increments) afforded a white semi-crystalline solid; yield: 25mg (24%).

δH -0.02 (9H, s, SiMe), 0.81 (12H, s, *t*-Bu), 1.89 (3H, s, CH_3),
3.79 (1H, dd; *J*=11.4, *J*=4.2, C-4 -H),
4.04 (2H, d, *J*=5.4, CH_2O), 6.73 (1H, bs, NH)

δC -5.56 (SiMe), 15.25 (CH_3), 18.44 (*t*-Bu),
57.79 (C-4), 64.52 (CH_2O), 65.13 (CH_2O-2'),
132.78 (C-3), 139.41 (C-1'), 165.88 (C=O)

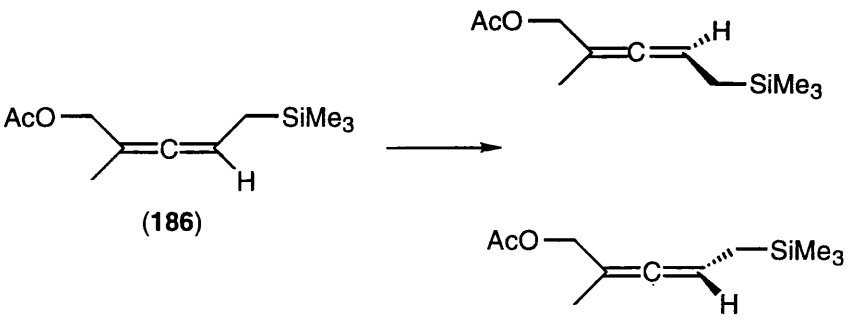
Mass Spec: *m/z* (%)=261 (13), 205 (14), 147 (44), 145 (16), 75 (18), 73 (100), 28 (40), 18 (30)

3-Isopropylidene 4-[(*O*-*tert*-butyldimethylsilyl)methyl]-2-azetidinone



Mercuric acetate (178mg; 0.56mmol) was added to a stirred solution of the (dimethylphenylsilyl)β-lactam (145mg; 0.37mmol) in peracetic acid (4.1ml of a 15% solution in acetic acid; 9.84mmol) and the mixture stirred at room temperature for 3 hours. After this time TBDMS triflate (188µl; 0.81mmol) and 2,6-lutidine (159µl; 1.63mmol) were added and the reaction mixture stirred overnight at room temperature. The mixture was quenched with Et_2O (10.0ml) and finely ground sodium thiosulphate (0.7g; 4.44mmol), resulting in an exothermic reaction, and the resulting suspension was stirred vigorously for 0.5 hour. The brown-green precipitate was filtered, washed with $CuSO_4$ (10.0ml), H_2O (10.0ml), $NaHCO_3$ (10.0ml) and brine (10.0ml) and the organic extract dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oily solid; crude yield: 32mg. Purification by dry column flash chromatography (silica gel; hexane/EtOAc; 10% increments) gave a mixture of fractions, none of which were recognisable by ^1H NMR.

Chromatographic Resolution Employing Cellulose Triacetate



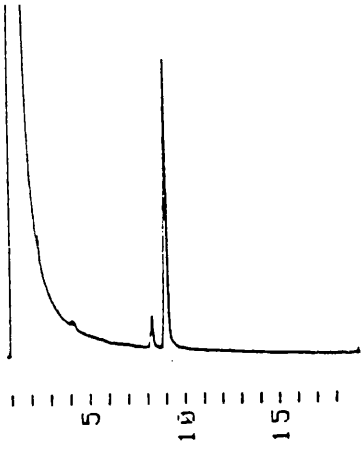
Enantioseparation of the acetyl-protected allene (**186**) was attempted by positive pressure, reverse phase preparative column chromatography employing commercially available cellulose triacetate (Merck, 16363, 25-40μ) as the chiral stationary phase using the following procedure. Cellulose triacetate (25g) was placed in a 250ml round-bottomed flask fitted with condenser. 100ml of analar EtOH was added and the mixture was refluxed for 30 mins to induce swelling. After sufficient cooling (10 mins) the mixture was packed, as a slurry, into a normal preparative column (25 x 230 mm) removing all bubbles and ensuring that the tightly packed cellulose triacetate phase does not crack. The acetoxyallene (500mg, 2.36 mmol) in analar EtOH(1-2ml) was carefully loaded onto the column and the column run under a positive pressure (air pump) using analar EtOH as eluant. Elution of the compound was monitored by TLC, the individual acetoxyallene containing fractions were evaporated to dryness and optical rotation measurements made on each separate fraction. The results obtained from a typical column are shown in the table below. Fractions 12-13 were combined; yield: 159mg (32%); $[\alpha]^{11}_D$ -29.5 (*c*=2, EtOH) and fractions 17-28; yield: 252mg (50%); $[\alpha]^{11}_D$ +34.9 (*c*=2, EtOH).

Column Fraction	12	13	14	15	17
Optical Rotation $[\alpha]_D$	-34.38	-13.25	-8.37	+1.94	+25.34

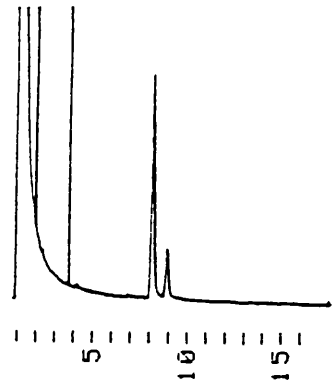
DETERMINATION OF ENANTIOMERIC EXCESS

Enantiomeric excesses were determined by capillary GC analysis using modified cyclodextrin phases. The allenes were resolved on a 8-m capillary with heptakis(2,6-di-O-methyl-3-O-pentyl)-β-cyclodextrin at 80°C.

(+)-Acetoxyallene, e.e. 82.4%

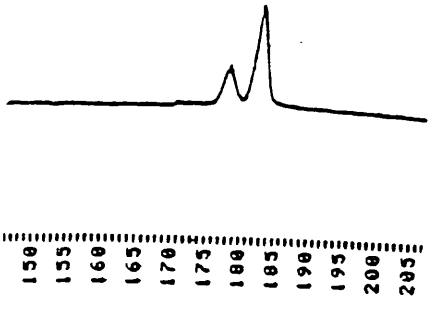


(-)-Acetoxyallene, e.e. 67.0%

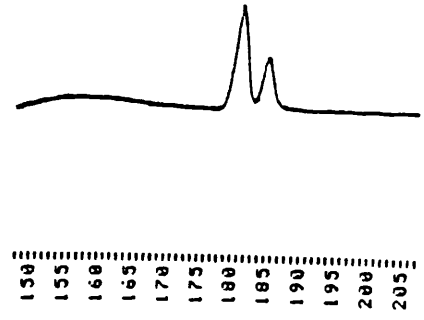


The β-lactams were resolved on a 15-m capillary with octakis(2,6-di-O-methyl-3-O-pentyl)-γ-cyclodextrin at 135°C.

(+)-β-lactam, e.e. 48.5%



(-)-β-lactam, e.e. 42.0%



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