β-Lactams From Unsaturated Organosilanes

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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December 1992

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SUMMARY

The synthesis of β-lactams from allyl- and (allenylmethyl)silanes, such as (167) and (256), was achieved by a combination of the olefin/CSI approach to β-lactams, developed by Graf, [58,59] and the Na_2SO_3 reduction system used by Durst and O'Sullivan.

The Asparenomycin precursor (259) was synthesised from the TBDMS-protected allene (256) and CSI, with the regiochemistry of the process controlled by the β-effect of silicon. [117] Attempts were made to incorporate the oxidatively cleavable $-SiMe_2O^iPr$ moiety in the synthesis of the Asparenomycin precursor (259), some success being achieved with the synthesis of the allene (270). Cycloaddition of this allene (270) failed to yield the corresponding β-lactam (271).

Allyl/vinyldisilanes, such as (315), were transformed into the corresponding β-lactams, (318), by treatment with CSI, followed by reductive work-up with Na_2SO_3. Incorporation of the oxidatively cleavable $-SiMe_2O^iPr$ moiety into β-lactam (321), followed by oxidation with H_2O_2 and bis-silylation, yielded the silylated 4-hydroxymethyl- β-lactam (332) in 75% yield, a useful carbapenem precusor.

Peterson olefination of β-lactam (349), using LDA and the hypernucleophilic agent DMEU, resulted in production of the C-3 alkylidene β-lactam (357) in 30% isolated yield. With the furylsilyl

β-lactam (342) a similar result was obtained, but separation of product and starting material proved impossible. The phenylsilyl β-lactam (355) showed no C-3 alkylidene product under the optimised conditions developed during these investigations.

ACKNOWLEDGEMENTS

I would like to thank my Supervisor, Dr. E. W. Colvin for his help, encouragement and patience during the course of my studies. Thanks also are extended to Dr. D. Rycroft, Mr. J. Gall and Mr J. McIver for NMR spectra, and Mr. A. Ritchie for mass spectral analysis. Thanks to Mr. J. Tweedie for assistance in the large scale preparation of certain compounds. Thanks also to Mr. Stuart Travers for the NMR spectra of several compounds.

I would like to thank my fellow labmates, especially Mr. G. Thomas, Mr. S. Barr, Mr. J. Strachan, Mr. D. Calderwood and Mr. D. Tudor for making my time there so enjoyable. Thanks are also due to Dr. M. A. Loreto and Dr. M. J. Monteith for help and advice during the early part of my project. Thanks also to Miss J. Rowden for help in the laboratory towards the end of my project.

Finally, many, many thanks are due to Mrs. L. Tommasini for her skill and patience in the typing of this thesis.

DEDICATION

To my parents, Athos and Lucy, for their constant love and encouragement.

ABBREVIATIONS

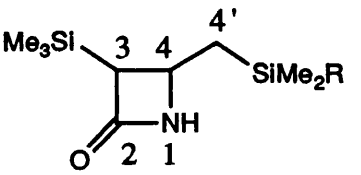
The following abbreviations are used during the course of this thesis :

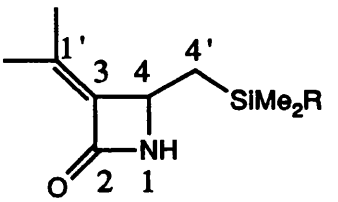
BuLi	n-Butyllithium
CBZ	Carboxybenzyl
CPase	Carboxypeptidase
CSI	Chlorosulphonylisocyanate
DBU	1,5-Diazabicyclo[4.5.0]undec-5-ene
de	Diastereomeric excess
DMF	Dimethylformamide
DMAP	4,4-Dimethylaminopyridine
DMEU	N,N'-Dimethylethylene urea
E (E^+)	Electrophile
HOMO	Highest occupied molecular orbital
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
M	Molar
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
Nu (Nu^-)	Nucleophile
PBP	Penicillin binding protein
PNB	*p*-Nitrobenzoyl
PTase	Peptidoglycan transpeptidase
TBAF	Tetrabutylammoniumfluoride
TBDMS-	*tert*-Butyldimethylsilyl
TBDMSCl	*tert*-Butyldimethylsilylchloride

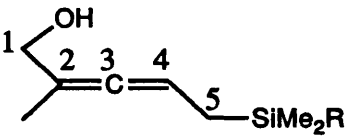
TBDMSOTf	*tert*-Butyldimethylsilyl trifluoromethylsulphonate
TFA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMEDA	NNN'N'-Tetramethylethylenediamine
TMSCl	Trimethylsilylchloride

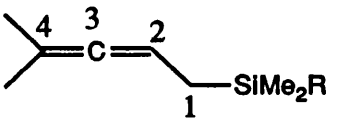
CONTENTS

The following numbering convention was used throughout the course of the discussion and experimental sections









Chapter 1

Structure and Biology of β-Lactam Antibiotics

1.1 Discovery

> *"There are thousands of different moulds and thousands of different bacteria, and that chance put the mould in the right spot at the right time was like winning the Irish sweep"*
>
> *Fleming*

The serendipitous discovery by Fleming[1] of a substance produced by a Penicillium mould, *Penicillium notatum*, that caused lysis of Staphylococcus colonies, was one of the most important discoveries in medicinal chemistry. It resulted in an intensive research effort across the disciplines of chemistry, biochemistry, bacteriology and medicine. Early on, Fleming himself was aware of the potential that his simple observation had in saying that "someday it would come into its own as a therapeutic agent". He found that administration to both animal and human patients gave favourable results, with no apparent signs of toxicity, but he could not concentrate the active component, finding the substance to be readily destroyed.

Using sophisticated methods of chemical isolation and purification not known to Fleming, Florey and Chain were able to isolate and purify Penicillin to such an extent that they could readily show its therapeutic value and subsequently elucidate the nature of the

active antibacterial factor.[2,5] The structure of benzylpenicillin was confirmed in 1945 by Crowfoot and co-workers.[6]

An intensive trans-Atlantic collaborative research programme launched during World War II resulted in a large body of information being assimilated about the Penicillins, as well as great advances being made in the large scale production by fermentation techniques. Indeed, the fermentation method developed by Beechams during the same period resulted in a lack of interest in the production of these compounds by total synthesis, this not being achieved until long after the War.

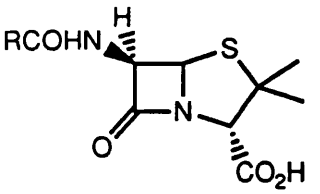
A further significant step forward in the fight against bacterial infection came with the discovery of the closely related family of β-lactams, the Cephalosporins. In 1948 an antibiotic substance was isolated by Giuseppe Brotzu, an Italian Professor of Bacteriology, from the fungus *Cephalosporium acremonium*, found in the sea near a sewage outlet for the Sardinian city of Cagliari. He found the isolated substance to be an effective antibiotic when administered directly to human patients. When his findings were brought to the attention of Sir Edward Abraham at the Oxford School of Pathology, an intensive research effort was initiated, culminating in the isolation and structural elucidation of Cephalosporin C,[3] independently confirmed by the X-ray studies of Hodgkin and Maslen.[4] The structure was found to be closely related to the Penicillins, possessing instead a fused 6-membered thiazine ring and an endocyclic double bond.

Since these early pioneering discoveries, many different types of

β-lactam have been discovered, each with its own spectrum of biological activity. This constant discovery of new β-lactams must be maintained if this class of antibiotic is to keep pace with ever changing bacterial resistance.

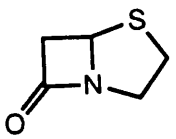
1.2 Structure of Penicillins and Cephalosporins

The penicillins are based on the fused bicyclic penam system, (1) consisting of a β-lactam fused with a thiazoline ring. During the 1940s, the structure of the Penicillins was examined by both IR and degradative techniques,[7] but it was left to X-ray studies[6] to unambiguously assign the structure.

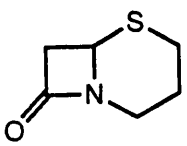


The nature of the amide group in a fused penam system is markedly different from that of the normal acyclic amide, [8(a)] and, as discussed later, this is of crucial importance in the mode of biological action of these compounds. In a normal amide, the lone pair of the nitrogen can delocalise into the adjacent π-system of the carbonyl group, resulting in a co-planar arrangement of the substituents around

nitrogen. In the penam system, due to the nature of the fused rings, the nitrogen substituents cannot attain a co-planar arrangement and effective lone pair overlap is not possible. This results in the penam lactam carbonyl carbon being more electrophilic and thus a more effective biological acylating agent.



(1)



(2)

For the Cephalosporins, based on the cepham system (2), the same general structural features appear. The nitrogen of the Cephalosporins is slightly less above the plane defined by its substituents, as evidenced by the sum of the angles around nitrogen (345-351°) compared to that of the Penicillins (337-351°).

1.3 Mechanism of Antibacterial Action

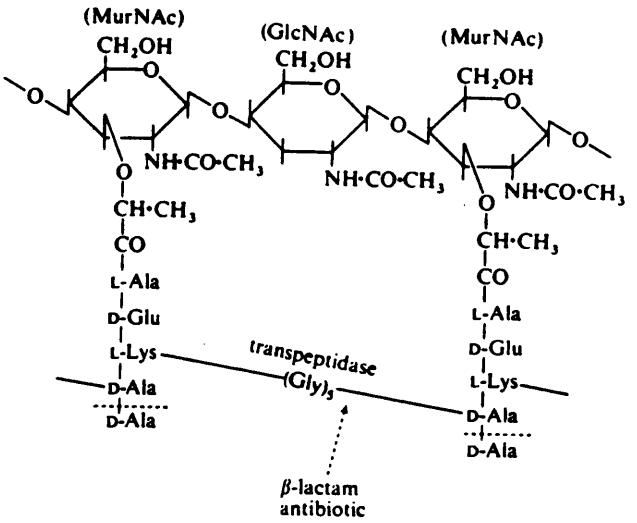
Initial studies on the mode of action of β-lactam antibiotics concluded that they selectively inhibit bacterial cell biosynthesis. Fleming noted that Penicillin was not a cytostatic agent, but that it actually caused lysis of the cell walls of susceptible bacteria. The first biochemical clue to the site of action was provided by Park et al[9(a,b)] who noted the accumulation of novel uridine nucleotides in the cytoplasm of penicillin treated *Staphylococcus aureus,* similar in composition[10] to those of the recently discovered cell wall. This gave support to the theory that they were cell wall precursors accumulating due to Penicillin interference.

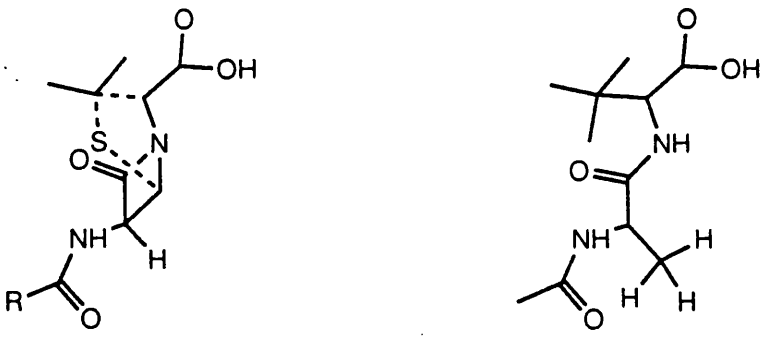
The period between 1956 and 1966 revealed much about the complex nature of bacterial cell wall biosynthesis,[11] and this led to the discovery that one of the final steps in the process, catalysed by an enzyme called peptidoglycan transpeptidase (PTase), was the penicillin-sensitive step.[12,13,14]

Early studies,[15] and subsequent research [16,17] have found the existence of several penicillin-binding proteins (PBPs) in the cell walls of all bacteria studied thus far. For example, in *E. coli*, six PBPs have been isolated, two of which are PTase and a closely related enzyme carboxypeptidase (CPase), the others being responsible for cell division and shape. Since penicillins can bind to more than one of the PBPs, it seems that the mechanism of Penicillin inhibition is more complex than simple inhibition of PTase.

Of the cell wall constituents, it is largely the peptidoglycan that is responsible for cell shape and prevention of osmotic rupture. Apart from small variations, all bacterial peptidoglycans are similar in that they are composed of long linear chains of alternating N-acetylglucosamine and N-acetylmuramic acid. These chains are cross-linked by short peptides, amide-linked to the D-lactyl group of N-acetyl muramic acid, with the last two residues usually consisting of alanine-alanine. The peptidoglycan strands can be cross-linked in a variety of ways,[18] and the extent of this cross-linking can vary from 25% in *E.coli*, to 90% in *S.aureus*.

As mentioned previously, the final stage in bacterial cell wall biosynthesis is the cross-linking of the peptidoglycan side-chains. A free amino group on the third residue of an N-acetylmuramyl pentapeptide of one glycan strand displaces the terminal D-alanine from a pentapeptide of a second glycan strand in the transpeptidation reaction. This final step is the one that is sensitive to Penicillin, since the biosynthetic steps leading to the construction of the linear, uncross-linked strands have been shown to be insensitive to Penicillin.[19,20]



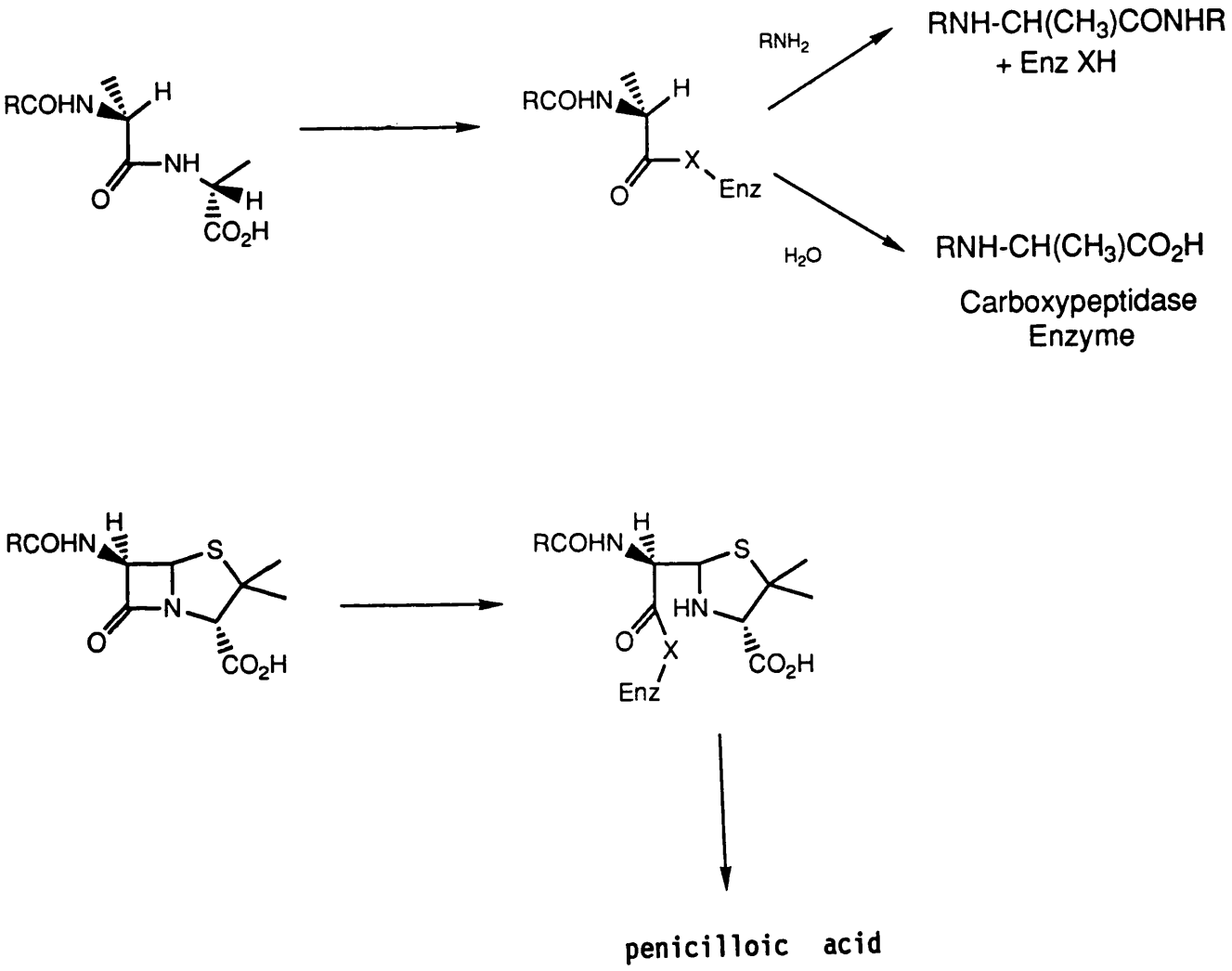


Scheme (1.1)

The proposed explanation for the specific nature of Penicillin's interference in bacterial cell wall biosynthesis is that it acts as a structural analogue of the dipeptide terminus of unlinked peptidoglycan strands. (Scheme 1.1). It has been proposed[21] that one of the possible conformations of the acyl-D-alanyl-D-alanine terminus of the peptidoglycan is very similar to the fixed conformation of Penicillin.

It is significant that the reactive amide linkage in both substrates is in the same relative position. The PTase reacts with the peptide substrate to form a reactive acyl-enzyme complex, with the cross-linking occurring on reaction of this complex with a free amino group of another peptide side-chain. Penicillin reacts with the PTase to form a stable penicilloyl-enzyme complex which stops PTase taking any further part in catalysing the cross-linking process. This penicilloyl-enzyme complex is disrupted by the action of β-lactamase

enzymes that some bacteria possess, resulting in the regeneration of the active PTase and an inactive penicilloic acid, with no antibacterial activity. (Scheme 1.2)



(Scheme 1.2)

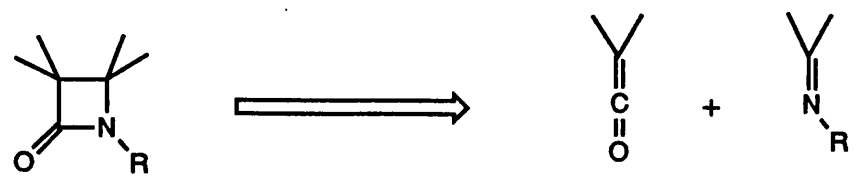
Chapter 2

Azetidin-2-one Synthesis From Ketene/Imine [2+2] Formal Cycloaddition

2.1 Introduction

The first synthetic route to the β-lactam functionality involved the simultaneous formation of the C-2/N-1 and C-3/C-4 bonds via the reaction of a ketene (or ketene equivalent) with an imine (Scheme 2.1). The regiochemistry of the addition is such that the sole product is an azetidin-2-one, with no regioisomeric azetidin-3-one being formed. It is clear that the nucleophilic nitrogen attacks the highly electrophilic central ketene carbon.

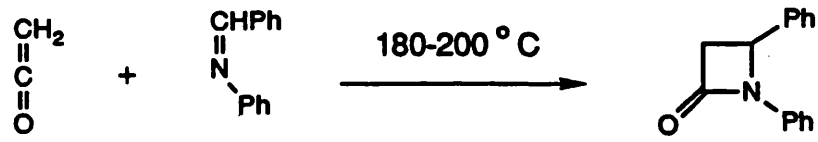
This approach has received much attention over the years, having been extensively applied to the synthesis of both natural and unnatural β-lactam antibiotics, as well as having been adapted to enable asymmetric synthesis to be achieved.



(Scheme 2.1)

2.2 Synthetic Development

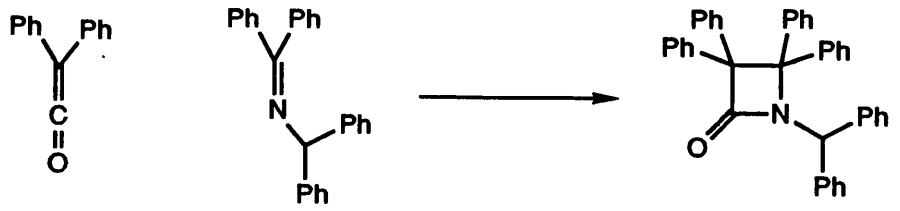
The first synthesis of a β-lactam was reported in 1907 by Staudinger,[22] in an investigation into the reaction of ketenes with imines. Although a convenient route to the β-lactam, (5) the reaction between ketene (3) and N-phenylimine (4) proceeded under very harsh (180-200°C) conditions (Scheme 2.2).



(3) (4) (5)

(Scheme 2.2)

In contrast to the extremes of temperature reported by Staudinger,[22] Rachman[23] et al reported a room temperature example of ketene/imine cycloaddition. They found that diphenylketene (6) and benzophenone imine (7) reacted at ambient temperature to give the β-lactam (8) in 80% yield (Scheme 2.3).

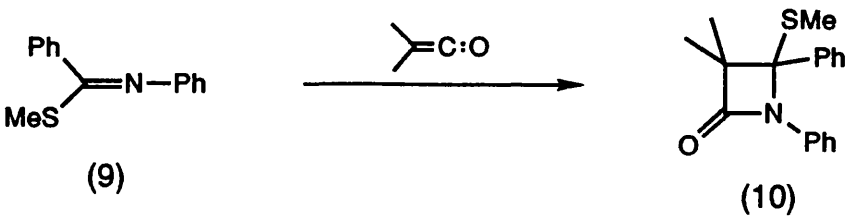


(6) (7) (8)

(Scheme 2.3)

The majority of β-lactams prepared by this early ketene/imine method were derived from dimethyl[25] or diphenylketene,[22,24] reacting with the Schiff base of an aromatic aldehyde or ketone. Other ketenes, including diethylketene,[26] ethylcarbethoxyketene[27] and methylphenylketene[28] have also been used to prepare monocyclic β-lactams. However, it can be seen that the synthetic scope of the methodology was severely limited by the lack of functional group diversity that could be successfully applied to the procedure; all the ketenes bore alkyl or aryl substituents and both the C and N atoms of the imine usually bore alkyl groups.

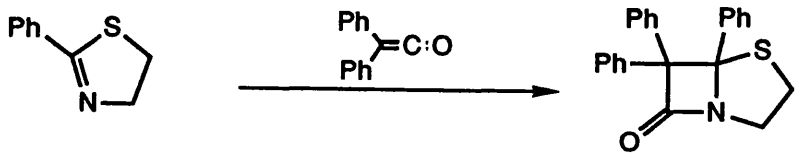
With all the recently acquired knowledge about the structure and reactivity of the Penicillins, [2,5,6] Holley and Holley[29] synthesised β-lactam (10) from the thioimidate (9) and dimethylketene, as part of an investigation into the structural features present in the Penicillins that made them so reactive to a wide variety of reactions, (Scheme 2.4).



(9) (10)

(Scheme 2.4)

Sheehan and Corey[30] reported the synthesis of the fused β-lactam (12) from diphenylketene and 2-phenyl-2-thiazoline[7,30] (11) (Scheme 2.5). This clearly showed that the methodology could be successfully applied to the rapid synthesis of fused β-lactam systems, analogous to the naturally occurring systems.



(11) (12)

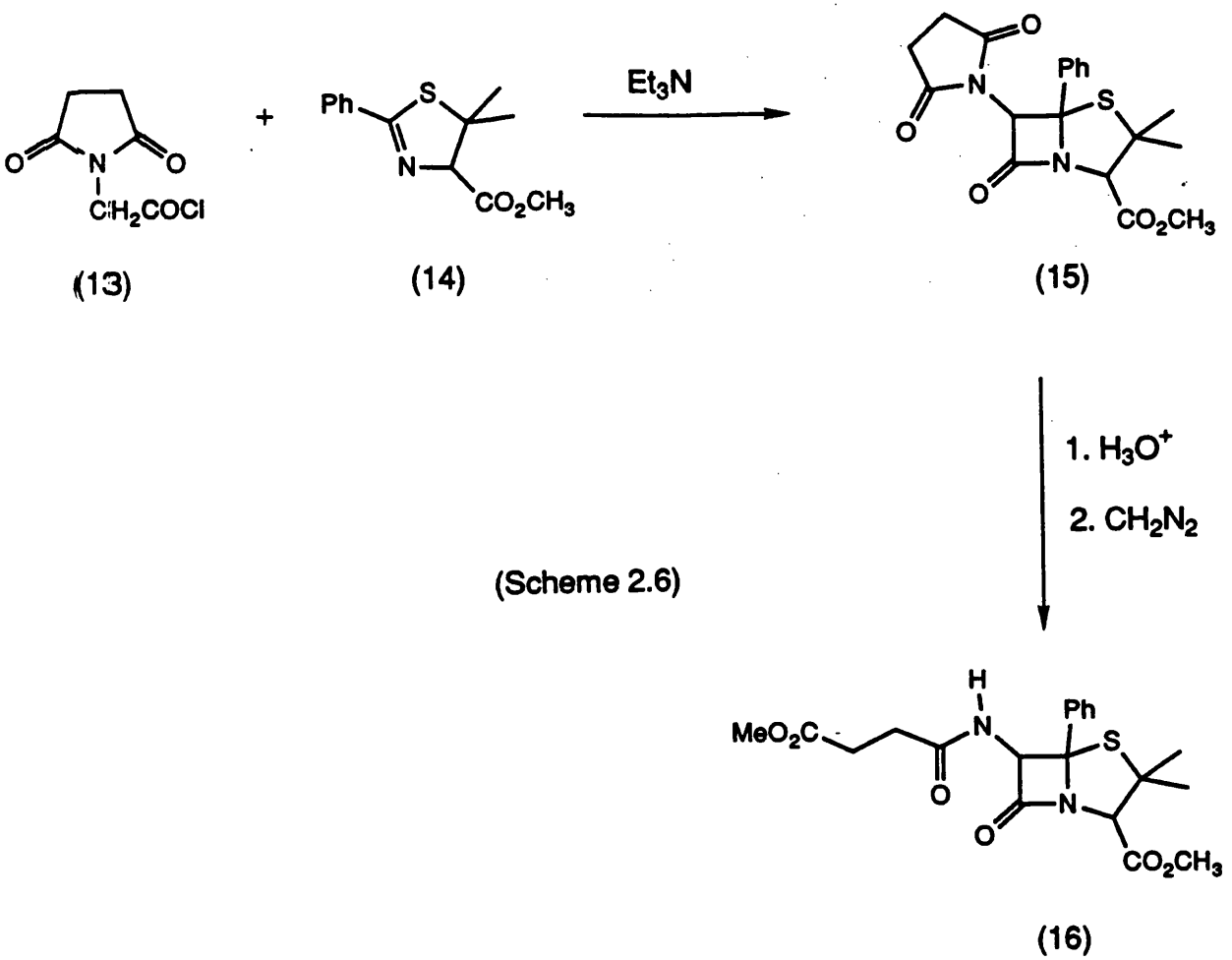
(Scheme 2.5)

2.3 Synthesis of Fused β-lactams

2.3.1 Penicillins

Clearly, the reaction between a ketene, or ketene equivalent, and a functionalised thiazoline or thiazine, would lead, in a single step, to the generation of the penem and cephem nuclei respectively. This approach has been extensively studied and successfully applied to the synthesis of both the Penicillins and Cephalosporins.

In 1950, Sheehan and Buhle[31] synthesised a 5-phenylpenicillin (15) containing all the elements of the natural penicillins, namely the fused thiazoline ring, the gem-dimethyl groups and the carboxylate group, via the reaction between succinimidoacetylchloride (13) and the thiazoline (14). Hydrolysis and treatment with diazomethane gave the β-lactam (16) with the acylamino side-chain (Scheme 2.6).

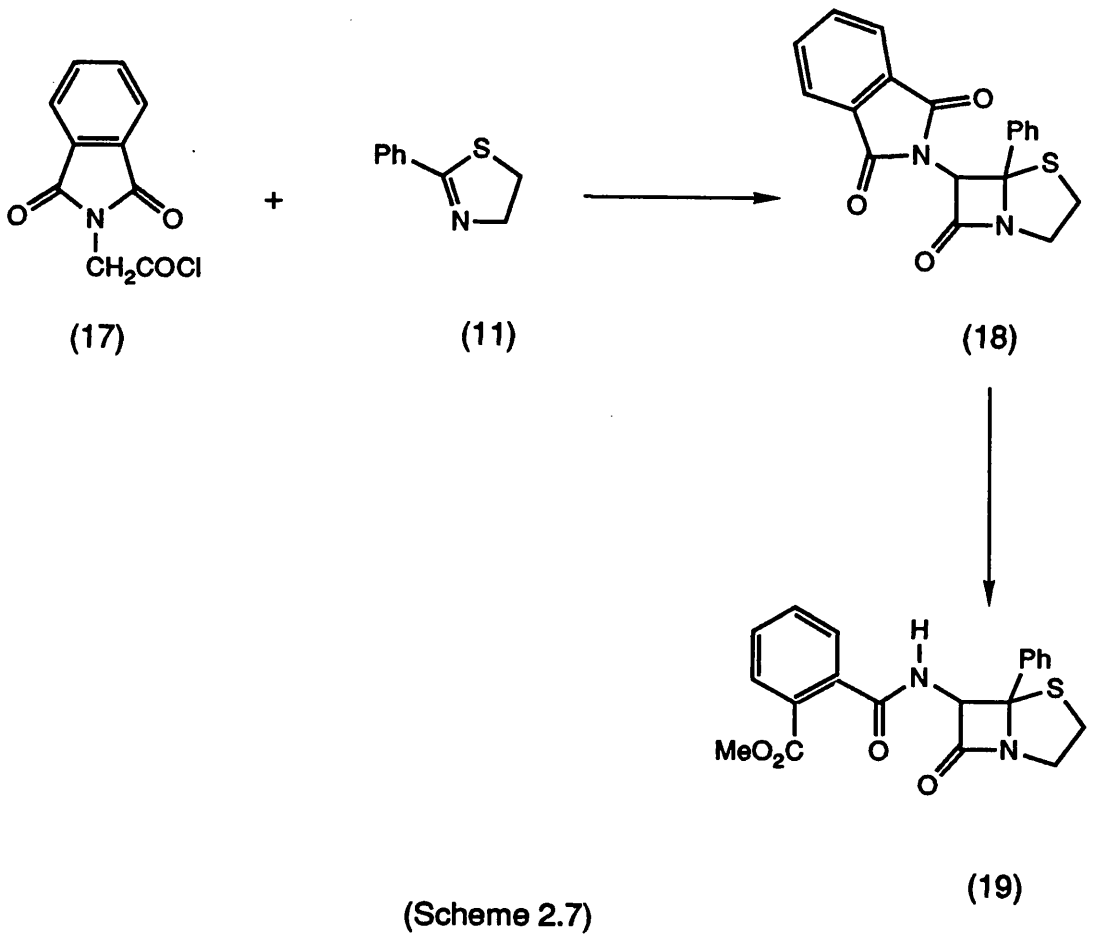


(13) (14) (15)

(Scheme 2.6)

(16)

In a similar manner, β-lactam (18) was produced from 2-phenyl-2-thiazoline (11) and phthaloylglycl chloride (17) (Scheme 2.7).

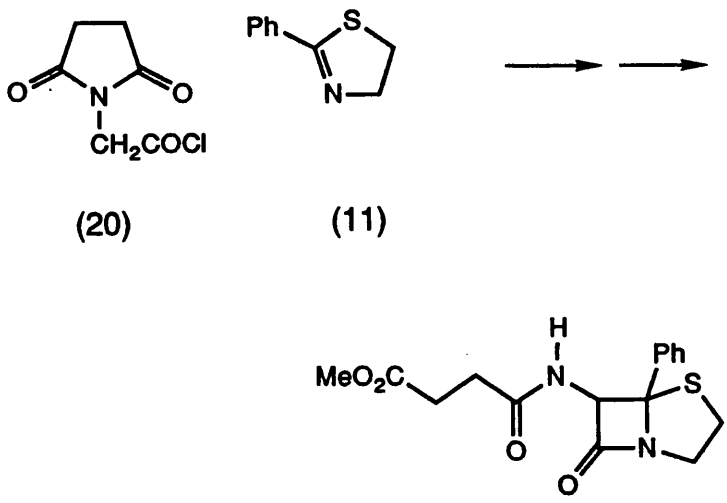


(17) (11) (18)

(19)

(Scheme 2.7)

Hydrolysis of this β-lactam produced a β-lactam (19) containing both the acylamino side chain and the fused thiazoline ring found in the naturally occurring series.[32(b)] The best form of masked nitrogen used was the succinimido acetylchloride (13), used in the synthesis of β-lactam (21).[33] The advantage of the succinimido over the phthalimido substituent was that hydrolysis of the succinimido gave an alkylacylamido side chain, more closely related to that found in the natural series. (Scheme 2.8).



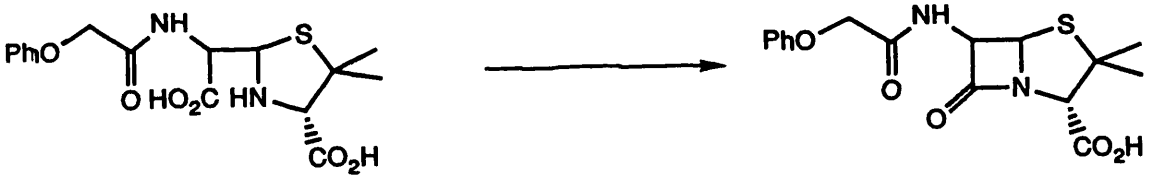
(20) (11) (21)

(Scheme 2.8)

In connection with studies relating to the total synthesis of Penicillin, Sheehan and Ryan[32(a)] reacted phthaloylglycylchloride with a range of Schiff bases, and obtained 1,4-disubstituted-3-phthalimido-2-azetidinones in which the free amino substituent was obtained by hydrazinolysis. This conversion with hydrazine, while convenient for use in the monocyclic system, was found not to be of use in the fused systems, due to the Penicillins' instability to hydrazine.[7]

The scission-prone nature of the β-lactam ring of these bicyclic compounds meant that the first successful attempt at total synthesis

had to involve the late construction of the β-lactam, since it was not robust enough to withstand many steps of chemical elaboration. Thus, in the first synthesis of the antibiotic Penicillin (22), Sheehan and Henery-Logan[34] constructed this sensitive molecule by forming the amide β-lactam bond in the very last step, via activation by an aliphatic carbodiimide. It was known that aliphatic carbodiimides could form amide bonds in aqueous solution, directly from the amine and carboxyl components, under very mild conditions (Scheme 2.9).[35]

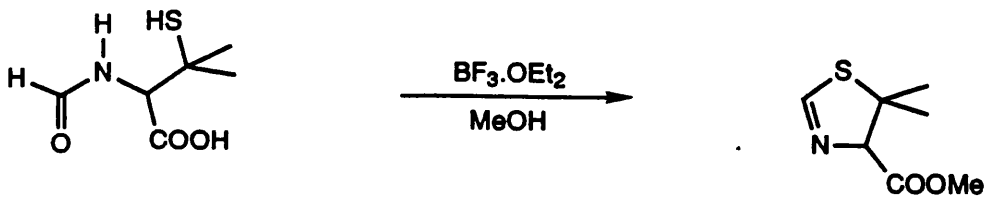


(22)

(Scheme 2.9)

With the chemical lability of the penicillins very much in mind, Bose and co-workers utilised their newly developed azidoketene/imine methodology[36] to the total synthesis of 5,6-trans-Penicillin V methyl ester.[37] Thiazoline (24), bearing all the correct substituents found

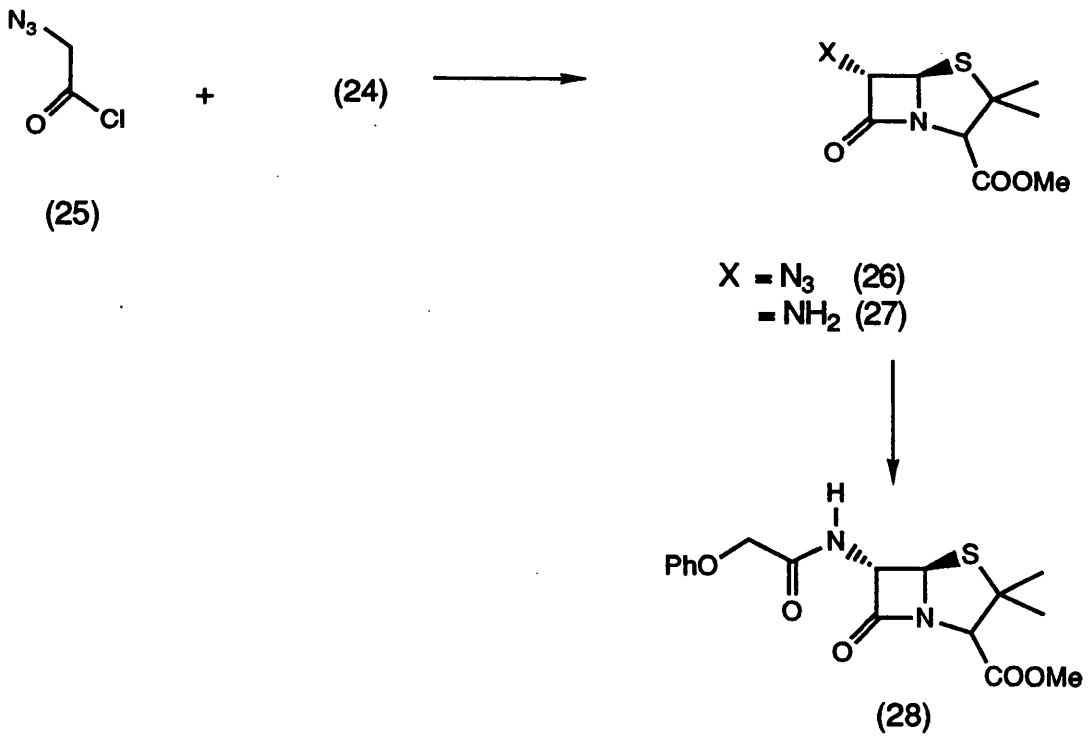
in penicillin, was prepared by heating (±)-N-formylpenicillamine[7] (23) with $BF_3 \cdot OEt_2$ in MeOH (Scheme 2.10).



(23) (24)

(Scheme 2.10)

The reaction between thiazoline (24) and azidoacetylchloride (25) was found to be extremely sensitive to moisture, and careful exclusion of water led to reproducible yields of 5-8% of the β-lactam (26). The stereochemistry of the β-lactam (26) was shown by NMR spectroscopy[38] to be trans with respect to H-5/H-6 of the β-lactam ring. Careful catalytic reduction of the β-lactam with Adams catalyst afforded the 6-aminopenicillanic ester (27) in moderate yield. This impure β-lactam was then directly acylated with phenoxyacetylchloride, giving the amido ester (28) in ca. 17% yield from the azido β-lactam (26) (Scheme 2.11). The overall low yield of the process in no way detracted from the importance of this methodology, since it represented a real advance in the rational construction of these compounds.

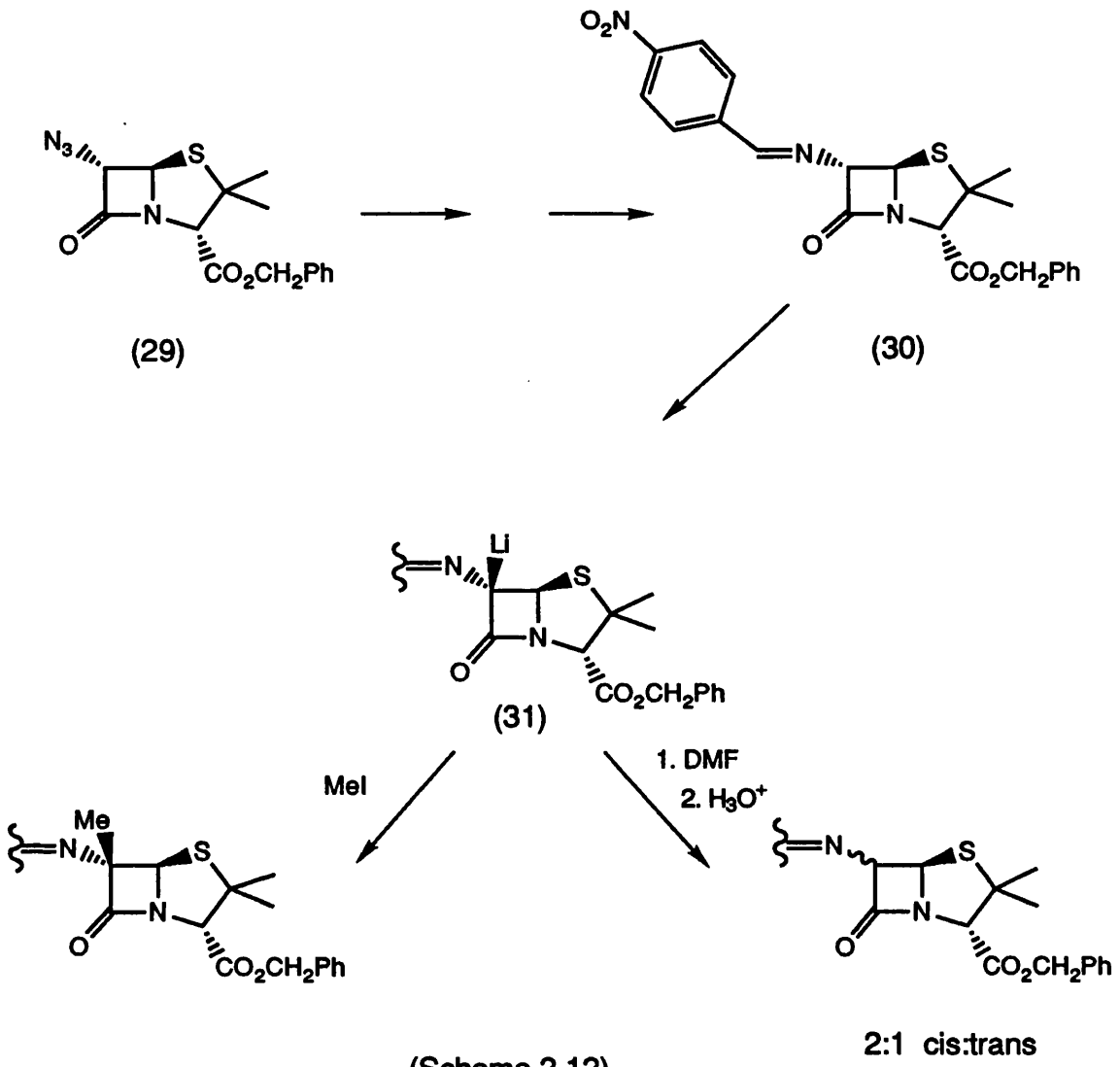


(Scheme 2.11)

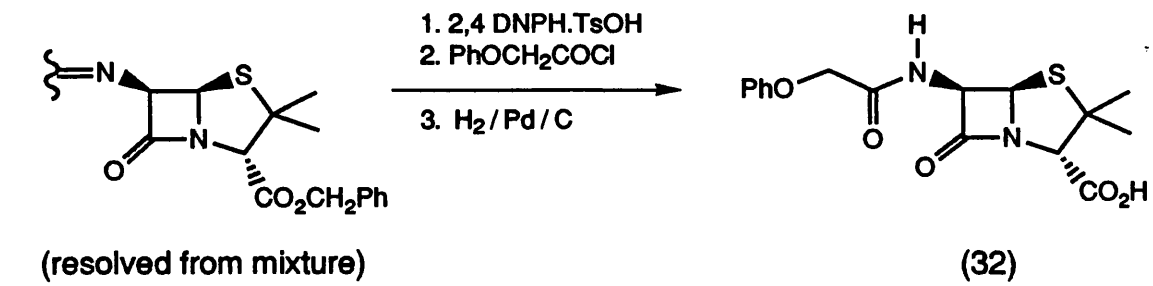
Although the thiazoline/azidoacetylchloride method is the most direct and convenient approach to these compounds, it suffers from the major disadvantage that the stereochemistry of the newly created β-lactam chiral centres (C-5 and C-6) is trans, instead of the cis arrangement found in the naturally occurring compounds. The trans product is the thermodynamic product and so cannot be isomerised to the natural cis arrangement via a simple enolate species.

This problem was tackled by Firestone and co-workers.[39] Their synthesis[39] involved construction of the azido-penicillin, by the same approach as Bose and co-workers,[37] but involved an epimerisation step, under kinetic control, to achieve the desired β-lactam stereochemistry. They found that conversion of (29) into its p-nitrobenzaldehyde Schiff base (30) followed by treatment with phenyllithium, gave a stereochemically defined 6-lithio-6-imino-β-lactam (31), as evidenced by the retention of stereochemistry at C-6 when (31) was reacted with methyliodide. When DMF was added to the 6-lithio-β-lactam (31), the

free anion was formed with loss of configurational memory, since protonation of this gave a 2:1 mixture of kinetic (cis) to thermodynamic (trans) products (Scheme 2.12). Removal of the Schiff base and acetylation was achieved by standard procedures,[40] with hydrogenolysis affording penicillin G (32). (Scheme 2.13). Thus, a total synthesis of a penicillin with the correct stereochemistry had been achieved by means of a simple link between the work of two research groups.



(Scheme 2.12)



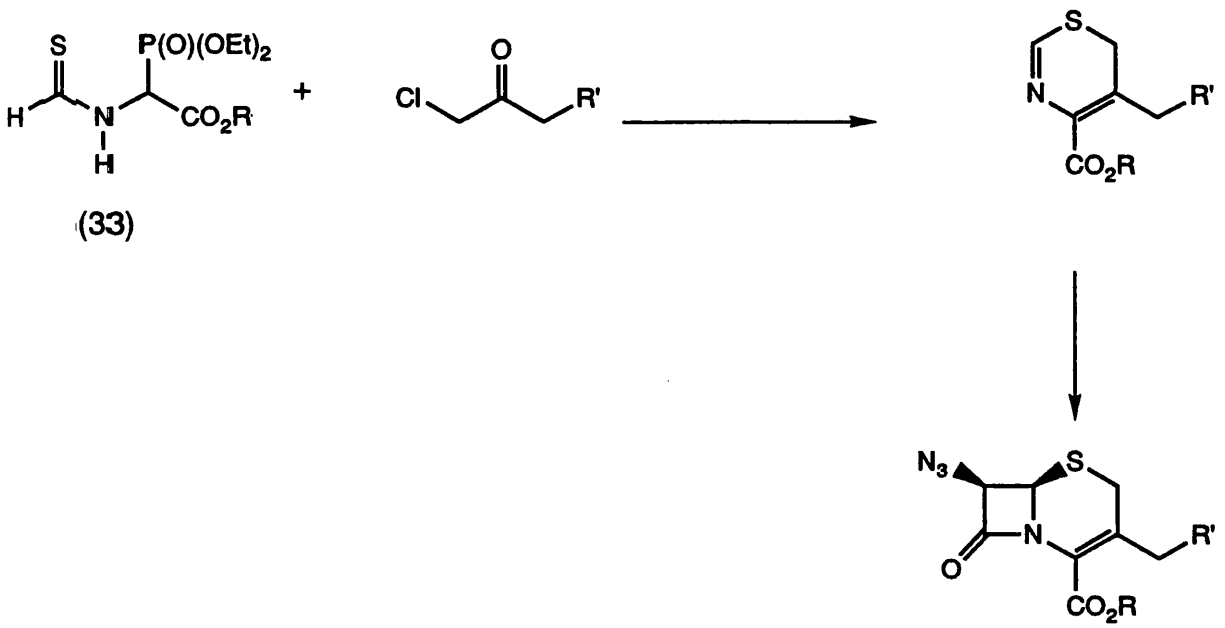
(Scheme 2.13)

2.3.2 Cephalosporins

Since the first reported synthesis of Cephalosporin C by Woodward and co-workers,[41] there has been a great deal of research into efficient syntheses of these antibiotics, and the ketene/imine approach has been of major significance to this end. The first synthesis,[41] although not employing the ketene/imine approach, used L-(+)-cysteine as the initial chiral building block, followed by an elegant series of chemical modifications to introduce the β-lactam nitrogen, construct the thiazoline ring and functionalise the amide side-chain.

The first syntheses to utilise the highly convergent azidoacetylchloride/thiazine route were reported in a series of papers by Ratcliffe and Christensen.[42] The synthesis of a range of semi-synthetic 7α-methoxy substituted cephalosporins that had desirable antimicrobial properties prompted these workers to devise a simple and unique route for the preparation of both natural and synthetic cephalosporins.

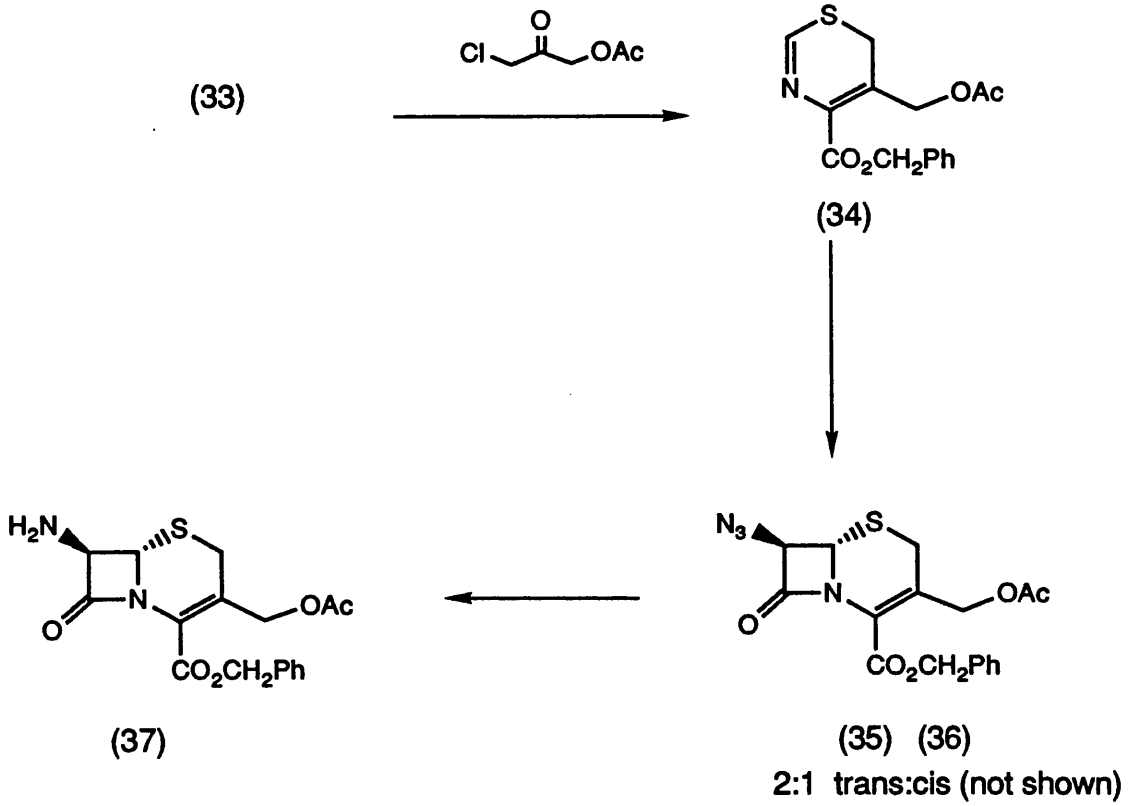
The preparation of the cephalosporins was achieved by reaction of the thioformamide (33)[42(a)] with a series of 1-chloro-2-propanones [42(b)] followed by reaction with azidoacetylchloride (Scheme 2.14).



(33)

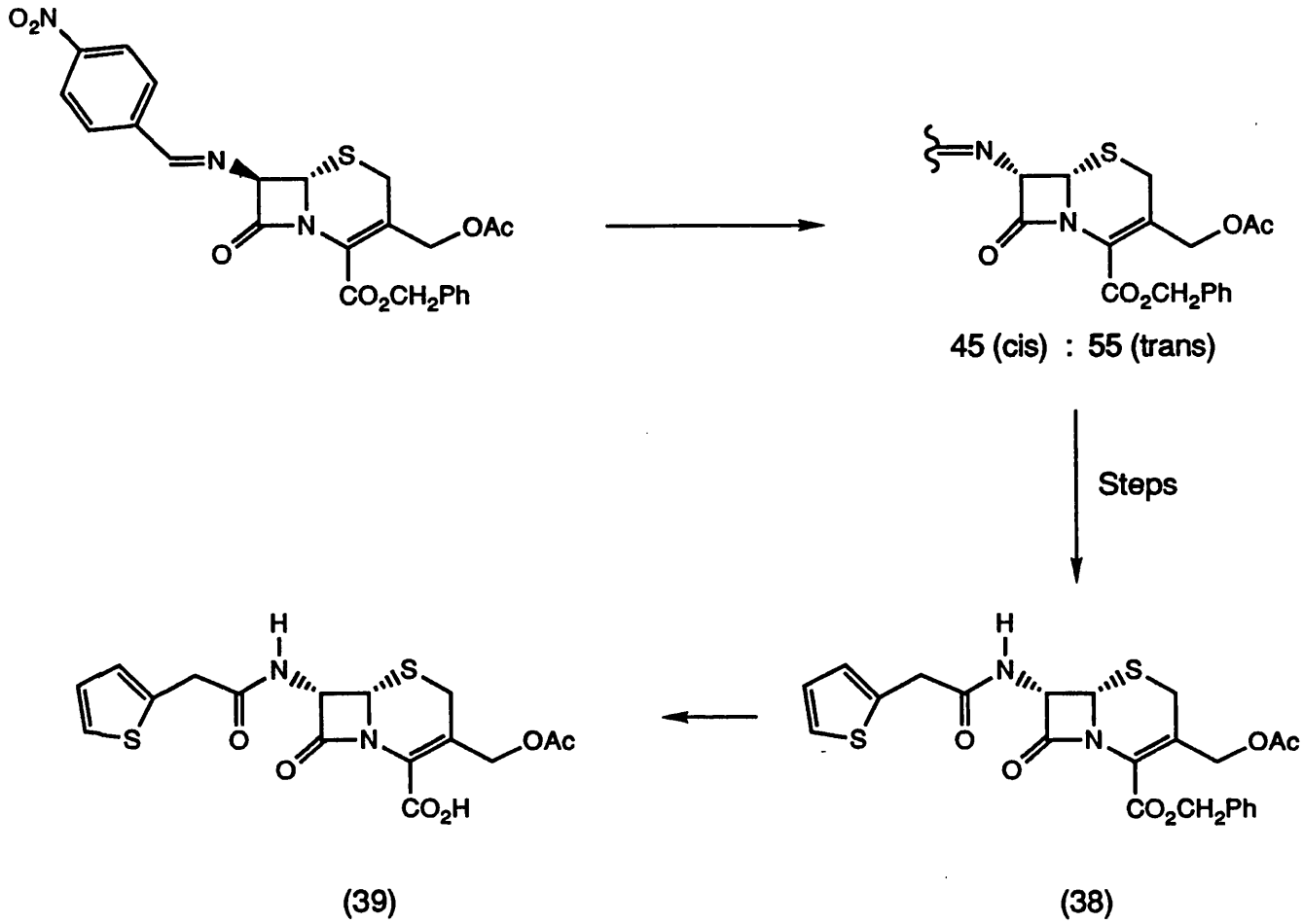
(Scheme 2.14)

This general scheme was successfully applied to the synthesis of some cephalosporin antibiotics.[42(b,c)] Treatment of thioformamide (33) with 1-chloro-3-acetoxy-2-propanone gave thiazine (34) which afforded a 2:1 mixture of cephems (35) and (36) on reaction with azidoacetylchloride (Scheme 2.15).



(Scheme 2.15)

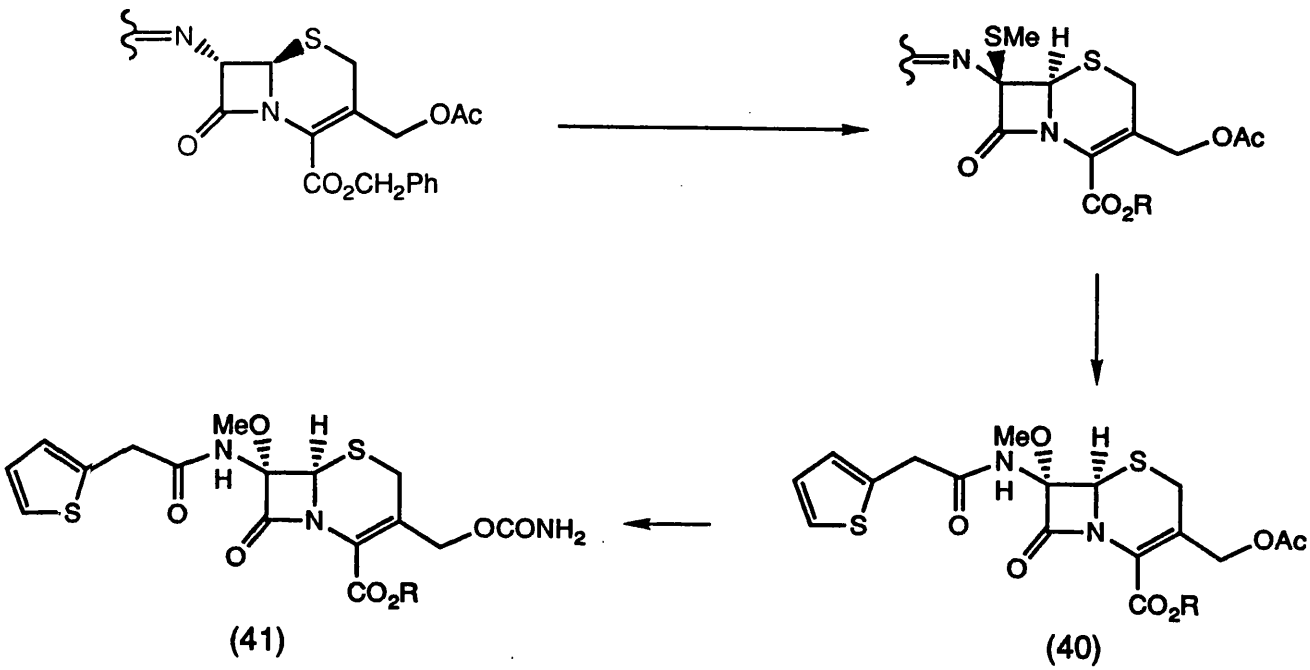
Attempts to convert the obtained trans- cephem (37) into the naturally occurring cis- cephems via the Schiff base anion methodology of Firestone and co-workers[40] resulted in only a 55:45 mixture of epi (trans) to normal (cis) cephems. The Schiff base mixture gave, on deprotection, the corresponding amino cephem mixture, which was acylated with thienylacetylchloride. The resulting amides were readily separated by column chromatography. The racemic cis-isomer (38) was converted to *rac*-cephalothin (39) in 95% yield by hydrolysis of the ester (Scheme 2.16).



(Scheme 2.16)

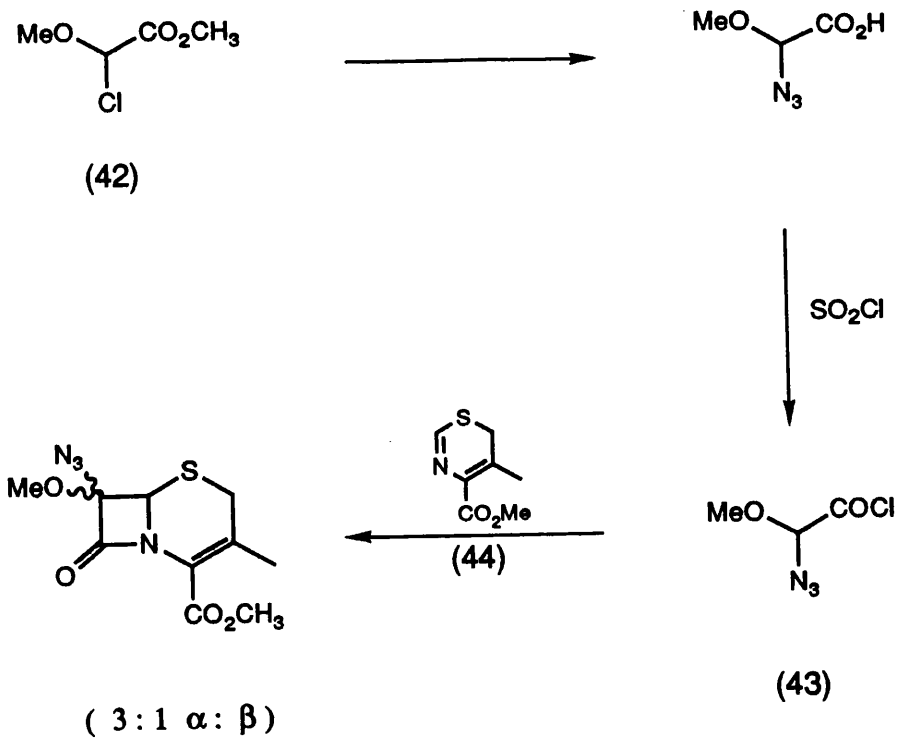
Also synthesised by this general methodology was the semi-synthetic, broad spectrum antibiotic Cefoxitin (41),[42(c)] which exhibits high stability toward β-lactamases as well as good activity against Gram-positive and Gram-negative bacteria. Two approaches to this antibiotic were investigated by these workers.[42(c)] The first route involved synthesis from the previously prepared Schiff base,[42(b)] by formation of the anion and reaction with MeSI, removal of the Schiff base, acylation with thienylacetylchloride and finally methanolysis to give the 7-α methoxy ester (40). It is important to note that none of the epimeric 7-β methoxy β-lactam was detected in the

reaction mixture. The 7-α methoxy ester (40) was then converted to Cefoxitin as shown in Scheme 2.17.



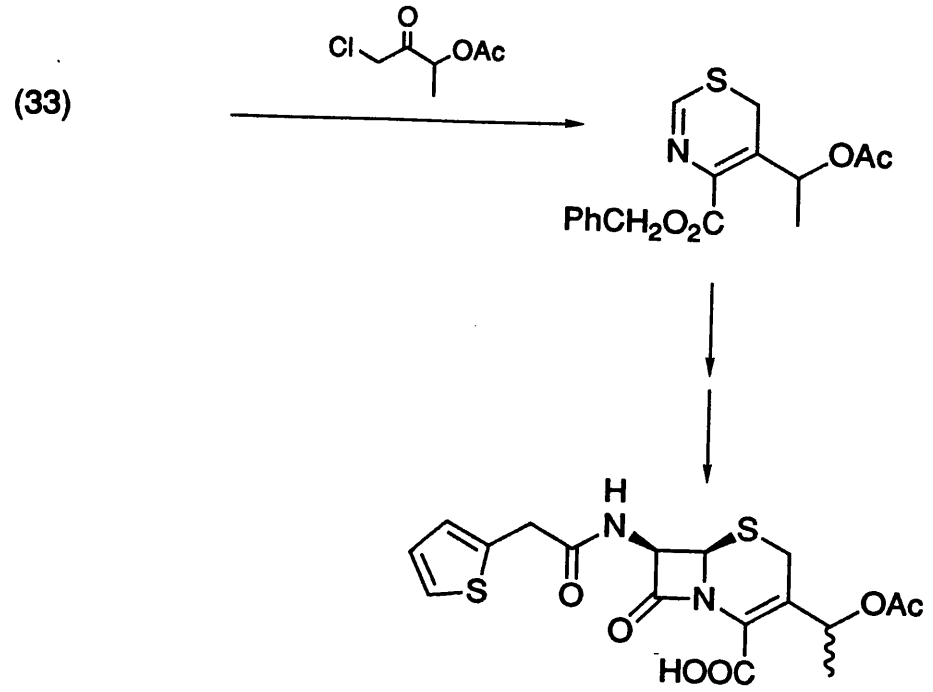
(Scheme 2.17)

A second, more direct approach, was used to obtain Cefoxitin, by incorporation of a methoxyl moiety into an azido acetyl chloride, so that the target could be obtained directly on reaction with a thiazine ring system. The methoxyazidoacetylchloride (43) was synthesised from methyl-2-chloro-2-methoxyacetate (42), addition to thiazine (44)[42(b)] yielding a 3:1 (α:β) mixture of epimeric cephems, although only in low yield (Scheme 2.18). 7-Methoxy-7-azidocephems have been previously shown to be useful precursors to medicinally active antibiotics.[43]



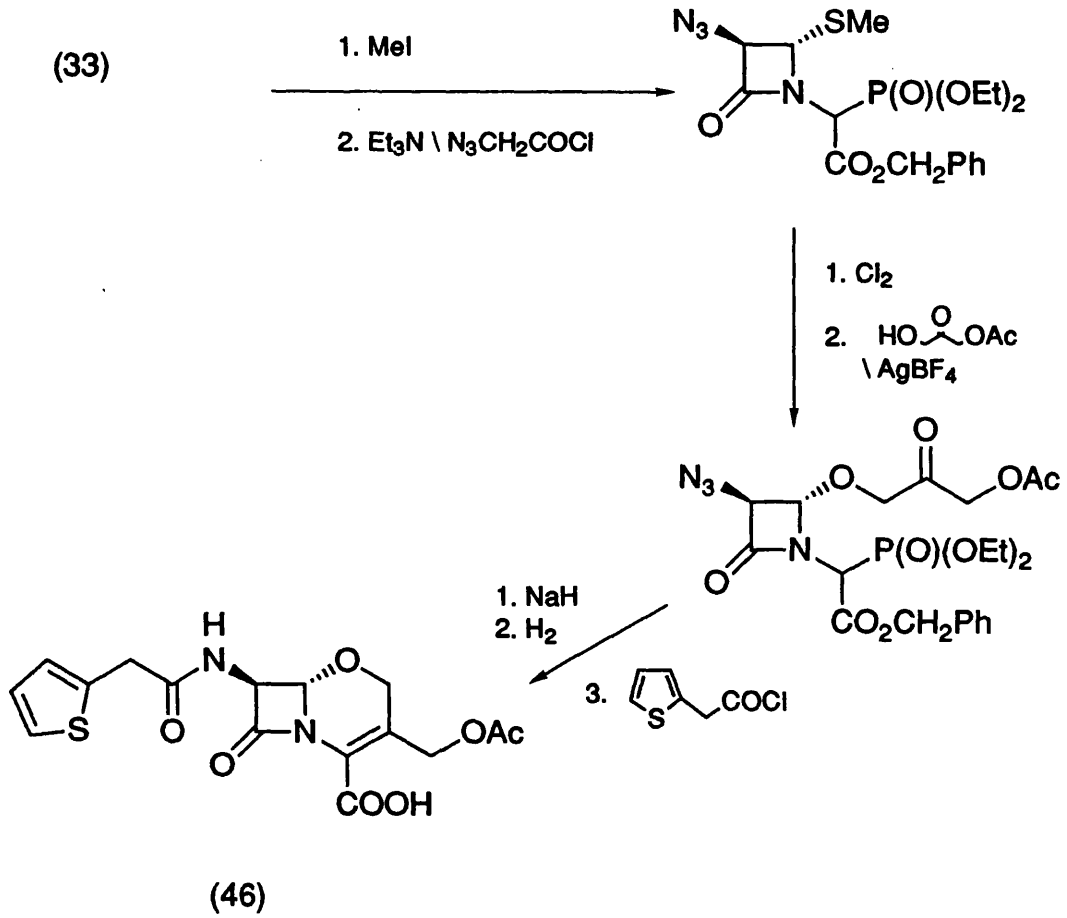
(Scheme 2.18)

Using a similar synthesis, Ratcliffe and co-workers[44] synthesised 3′-methylcephalothin (45) from 1-chloro-3-acetoxy-2-butanone and thioformamide (33) (Scheme 2.19), again demonstrating the versatility of this process.



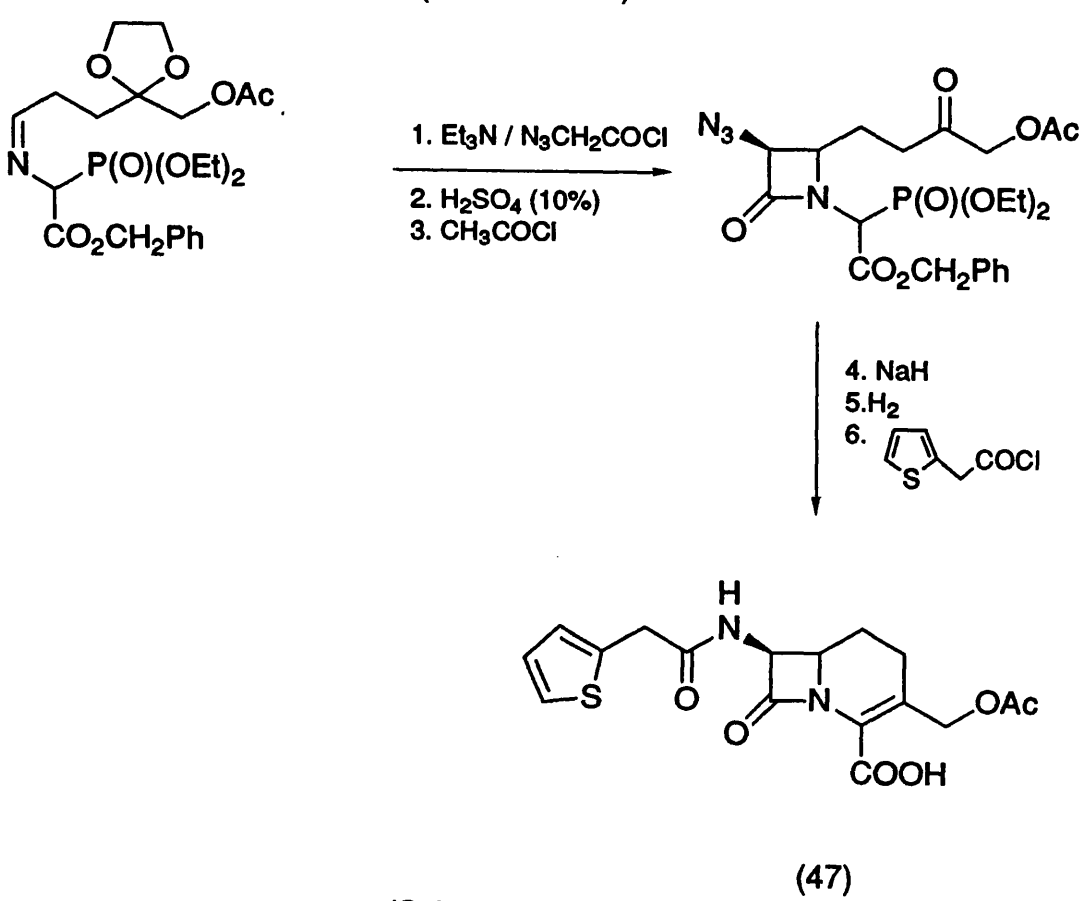
(Scheme 2.19) (45)

The methodology developed by Ratcliffe[39] was utilised by Christensen and co-workers, [45,46] in the synthesis of the unnatural 1-oxa (46) and 1-carba (47) analogues of cephalothin (Scheme 2.20, 2.21).



(46)

(Scheme 2.20)



(47)

(Scheme 2.21)

2.4 Asymmetric Applications of the Ketene/Imine Route

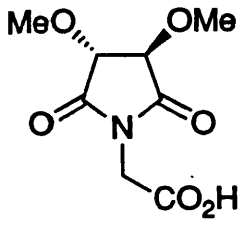
The development of asymmetric variations of the ketene/imine route has centred on two general approaches;

1. Use of a chiral auxiliary on the ketene (equivalent) moiety.
2. Use of a chiral auxiliary on the imine moiety.

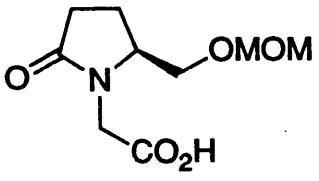
2.4.1 Chiral Ketene Equivalents

Perhaps the most successful approach to asymmetric induction has come from the use of chiral auxiliaries to ketene precursors. The auxiliaries are generally homochiral nitrogen heterocycles, since partial removal of the auxiliary should leave the nitrogen atom in the final β-lactam.

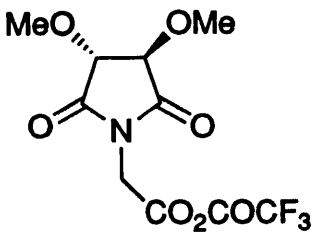
Ikota and Hanaki[47] reported successful asymmetric induction using the tartrimide (48) and pyrrolidone (49) derivatives (Scheme 2.22). These auxiliaries were obtained from (+)-tartaric acid and (S)-glutamic acid respectively. Each acid was converted to the mixed anhydride with TFA and reacted with N-substituted benzaldehydeimines (50) (Scheme 2.22).

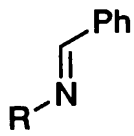


(48)

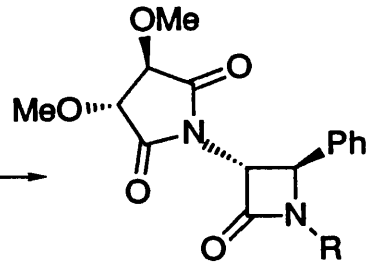


(49)



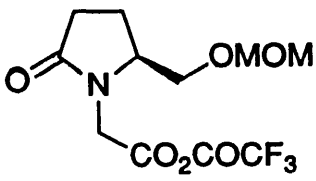


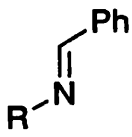
(50)



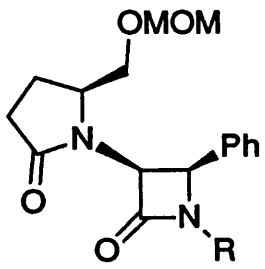
(51)

74% d,e





(50)



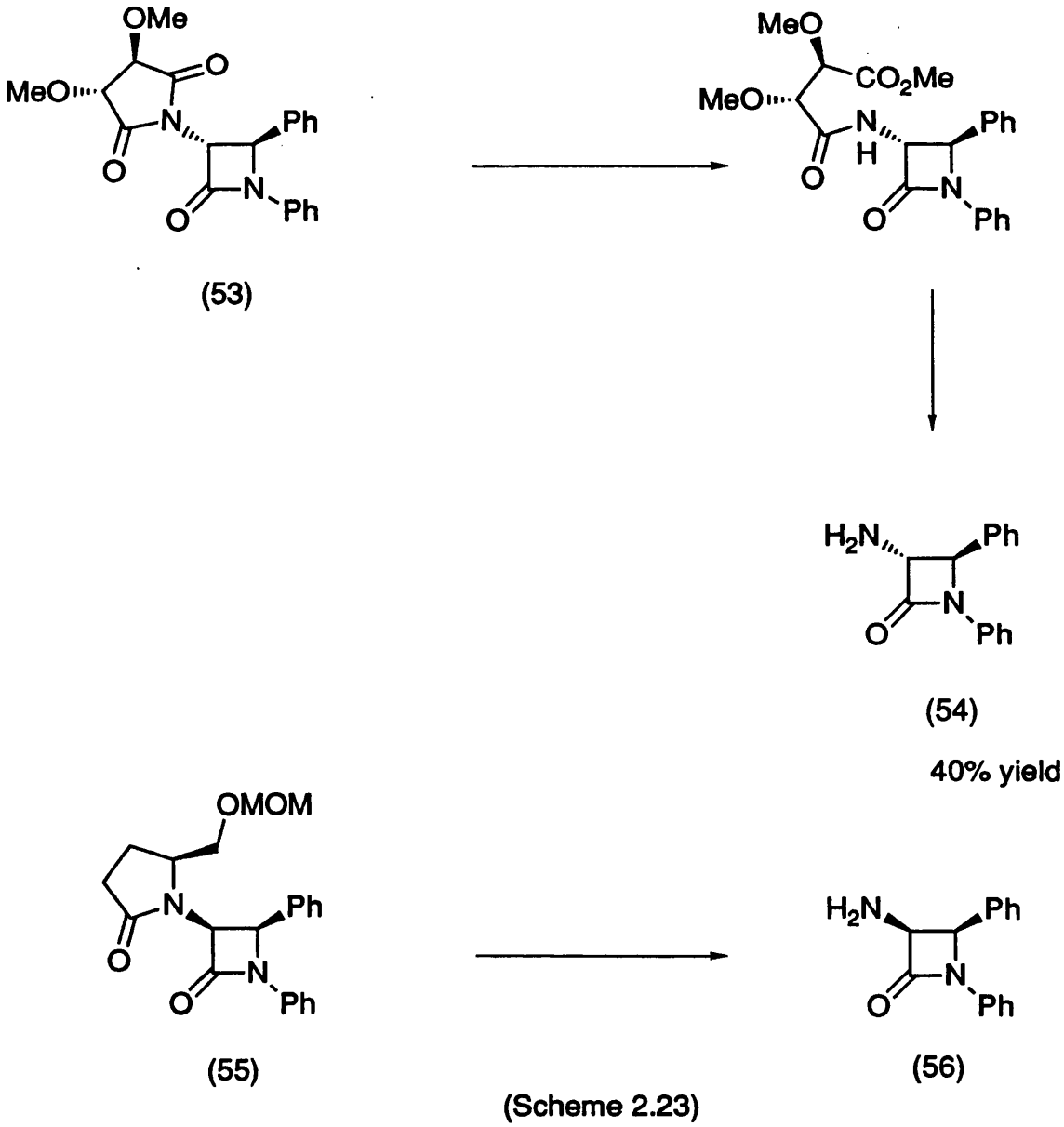
(52)

94% d,e

(Scheme 2.22)

The two auxiliaries gave opposite stereochemical outcomes when reacted with the imine (50) : the tartrimide auxiliary resulted in a 74% de of trans β-lactam (51), whereas the pyrrolidone auxiliary resulted in a 94% de of the cis product (52). This was an important result in terms of the general applicability of the methodology, since it meant that the desired stereochemistry of the β-lactam could be determined simply by choosing the correct chiral handle.

It is important that any auxiliary used should be easily removed, the number of chemical steps involved in this removal should be kept to a minimum, and the yields of these steps should be high. Unfortunately, the generally excellent inductions observed by Ikota and Hanaki[47] are offset somewhat by the relative difficulty of removal of the chiral auxiliaries; the tartrimide derivative (53) was removed in three steps, yielding the free amino β-lactam (54) in a modest 40% overall yield. The pyrrolidine (55) necessitated eight chemical steps for transformation into the free amino function (56), a clearly unacceptable situation (Scheme 2.23).



(53)

(54)

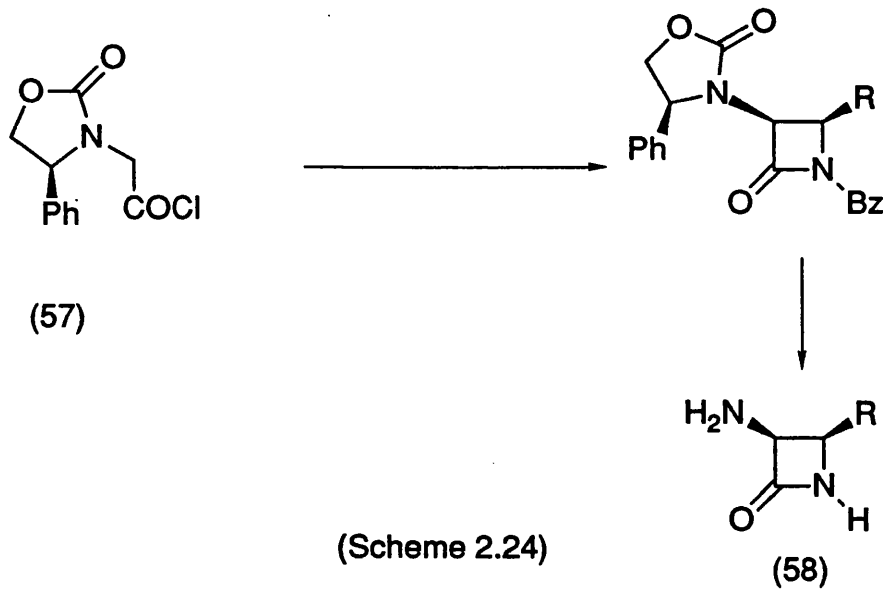
40% yield

(55)

(56)

(Scheme 2.23)

On a similar theme, Evans and Sjorgren[48] reported excellent (92-97%) asymmetric induction within the cis azetidinone (58), with no detection of a trans product. Their methodology involved the use of the homochiral oxazolidinone derivative (57) as the chiral ketene equivalent ; this chiral auxiliary was readily removed in one step. Also of note is the use of benzyl protection of the imine nitrogen, since this is simply removed, thus allowing for the convenient production of N-protio β-lactams (58) by the ketene/imine route (Scheme 2.24).

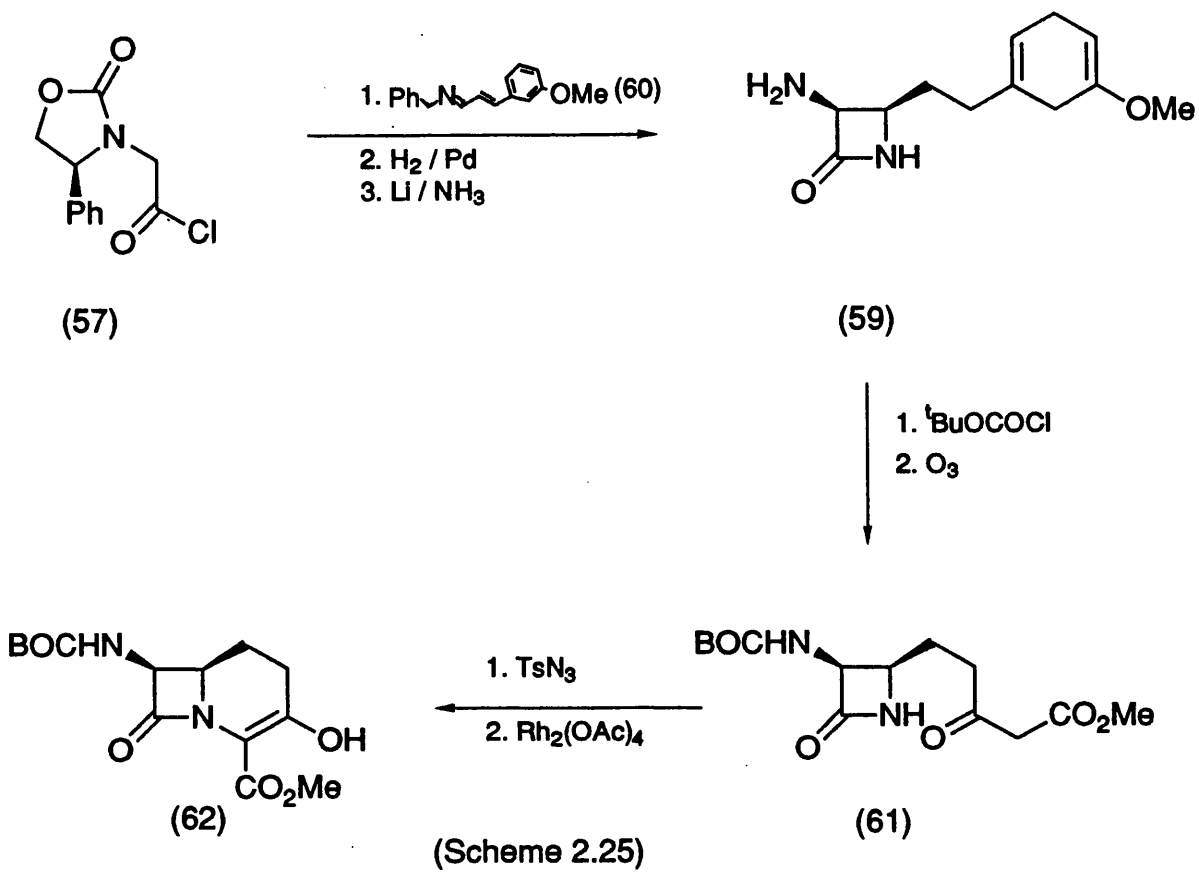


(57)

(Scheme 2.24)

(58)

Evans and Sjorgren applied this methodology[48] to a synthesis of carbacephem derivatives.[49] Synthesis of the β-lactam (59) was achieved by cycloaddition of homochiral ketene equivalent (57) with the conjugated imine (60), removal of the chiral auxiliary, β-lactam nitrogen deprotection and reduction of the aromatic ring. Protection of the amino nitrogen and ozonolysis afforded the β-keto ester (61), which was cyclised to the carbacephem (62) by a Rh-mediated carbene insertion (Scheme 2.25).

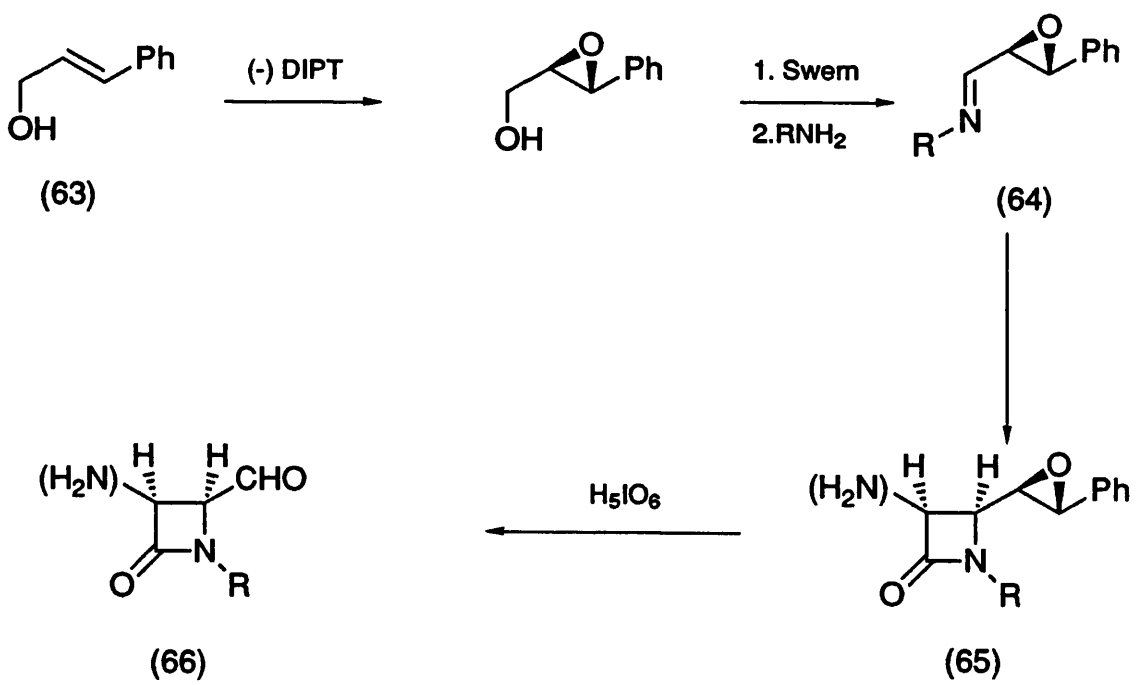


(57) (59) (61) (62)

(Scheme 2.25)

2.4.2 Chiral Imines

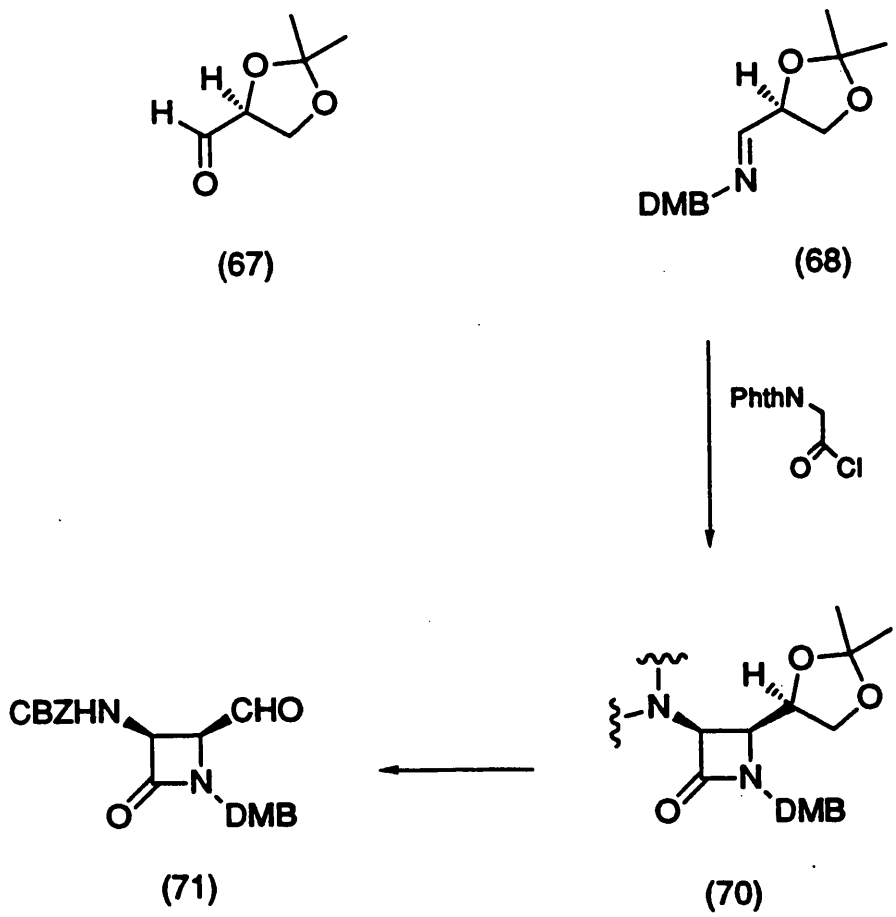
This possibility was explored by Evans and Williams,[50] with the use of a homochiral epoxyimine species. The homochiral epoxyimines (64) were obtained by Sharpless asymmetric epoxidation of a suitable allylic alcohol (63). The diastereomeric excess was generally excellent (80-94%) with only the major diastereomer shown for clarity. Periodic acid cleavage of the epoxide (65) led to the 4-formyl β-lactam (66) in excellent (73-78%) yields (Scheme 2.26). Such 4-formyl β-lactams have proven to be useful intermediates in the synthesis of both monobactams and isocepham antibiotics.[51]



(Scheme 2.26)

Prior to this work, Hubschwerlen and Schmid[52] reported the asymmetric synthesis of monocyclic β-lactams employing chiral imines (68) derived from (S)-glyceraldehyde acetonide (67).

Cyclocondensation with activated phthalimidoglycine derivatives (69) gave the β-lactam (70) as the sole product. The azetidinone (70) was easily converted into the CBZ-protected-4-formyl β-lactam (71), thus achieving a simple, enantiospecific synthesis of a synthetically useful monocyclic β-lactam (Scheme 2.27).

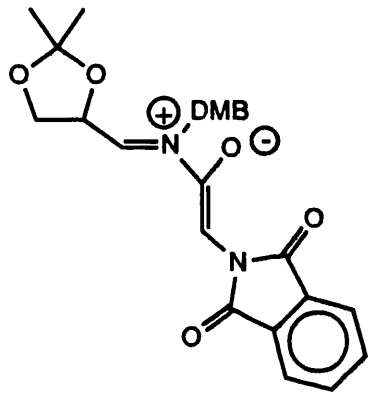


(67) (68) (71) (70)

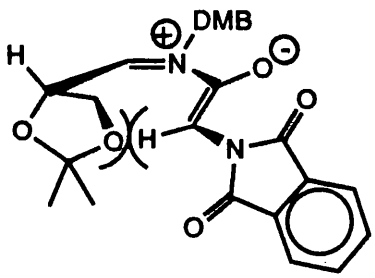
(Scheme 2.27)

The mechanism of β-lactam formation from imines and activated glycine derivatives is believed to proceed via a two step process. The first step is acylation of the imine nitrogen leading to a zwitterionic intermediate (72). The imine is present only as the trans geometric isomer, and the enolate C=C is also assumed to be

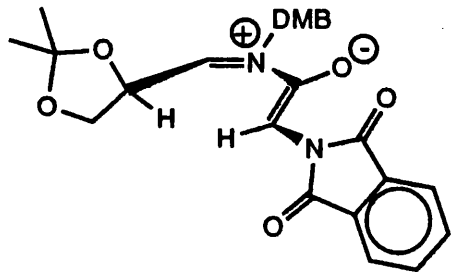
trans. The second step involves conrotatory ring closure, and since rotation is not possible around either the imine C=N or the enolate C=C, there are only two possible rotamers (73) and (74). Only these two are possible because a lone pair of the acetonide oxygen nearest to the C=N bond interacts with the electron deficient iminium π-system, and, for this interaction to be maximised, the C-O bond must be syn-periplanar to the π-orbitals of the C=N bond. Of these two rotamers, (74) suffers from unacceptable steric congestion, and so only (73) is seen, leading to the sole observed product (Scheme 2.28).



(72)



(74)



(73)

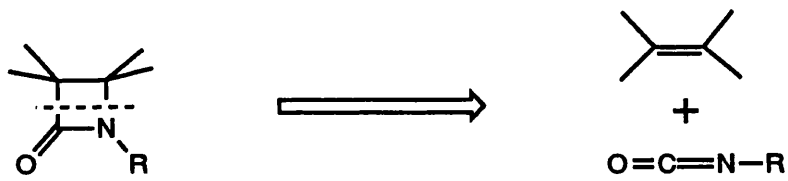
(Scheme 2.28)

Chapter 3

Azetidin-2-one synthesis from olefin/isocyanate [2+2] formal cycloaddition

3.1 Introduction

The formal [2+2] cycloadditive route to the β-lactam functionality could also be envisaged as a process involving the simultaneous formation of the C-2/C-3 and N-1/C-4 bonds of the ring. With the β-lactam drawn as shown in figure (75), this "horizontal" approach would lead, retrosynthetically, to the addition of a functionalised olefin to an isocyanate (Scheme 3.1).



(75)

(Scheme 3.1)

This route enjoys several advantages over the much used predecessor, the ketene/imine route, namely:-

1. the functionality that appears at C-3 and C-4 of the β-lactam ring is incorporated in the olefin precursor.

Usefully functionalised olefins are more readily constructed than the highly reactive ketene intermediates of the ketene/imine route.

2. the reaction conditions, on the whole, tend to be milder, and as a result, this route can be used for the incorporation of sensitive functionality.

3. production of N-protio β-lactams is facile. In the ketene/imine route, the nitrogen atom often carries an alkyl or aryl substituent.

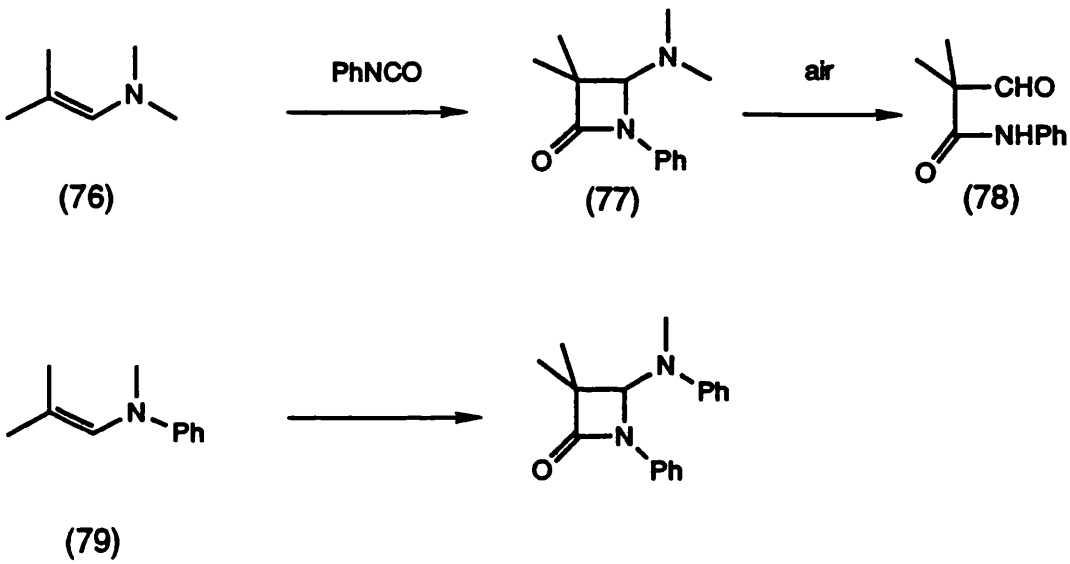
4. the stereochemistry of the olefin is transferred to the β-lactam in a predictable manner; thus cis- olefins produce cis- β-lactams, and trans- olefins trans- β-lactams.

It is this final point that is perhaps the most important aspect of the process, and one which has undoubtedly raised it above being more than an interesting β-lactam synthesis and placed it alongside the ketene/imine route in terms of importance to β-lactam chemistry.

3.2 Historical development

The first true application of this approach was reported by Perelman and Misak.[53] Prior to this, and with the notable exception of Sheehan,[54] "all the known syntheses of β-lactams that create two bonds entail simultaneous formation of the same two bonds, i.e.

carbonyl to nitrogen and C-3 to C-4".[55] They found that N,N-dimethylisobutyleneamine (76) reacted exothermically with phenylisocyanate to form an oil whose IR spectrum was devoid of any isocyanate bands, but which did contain the diagnostic band of the β-lactam carbonyl stretch (Scheme 3.2).

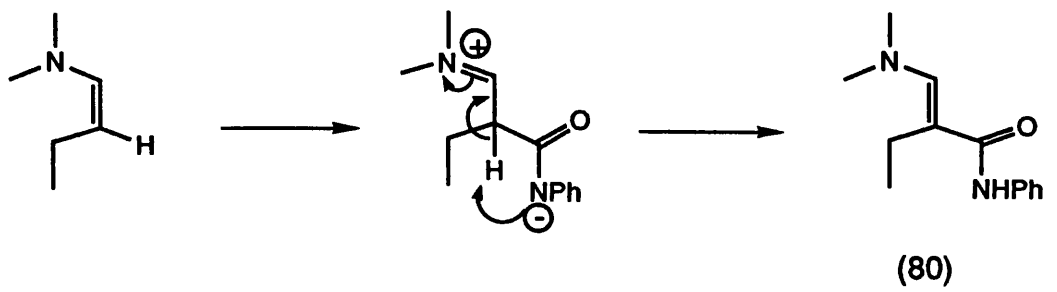


(Scheme 3.2)

This unstable β-lactam (77) decomposed rapidly on exposure to the air the α-formylisobutyranilide (78). In contrast, the N-methyl-N-phenyl compound (79) was found to be far more stable, being resistant not only to water washings, but also to IM acid and base. It too decomposed on several days exposure to the atmosphere.

Previous work[56,57] on the reactions of enamines and isocyanates had found β-carbonylcarboxamides as the products, and it is possible that β-lactam intermediates were present but never observed.

The enamines used in previous investigations[56,57] into isocyanate additions all had one feature in common, the presence of a β-hydrogen. As an alternative to the initial adduct being stabilised by β-lactam formation, it is possible that proton transfer occurs, resulting in the formation of the αβ-unsaturated amide, (80) which is in turn hydrolysed to the observed products (Scheme 3.3).

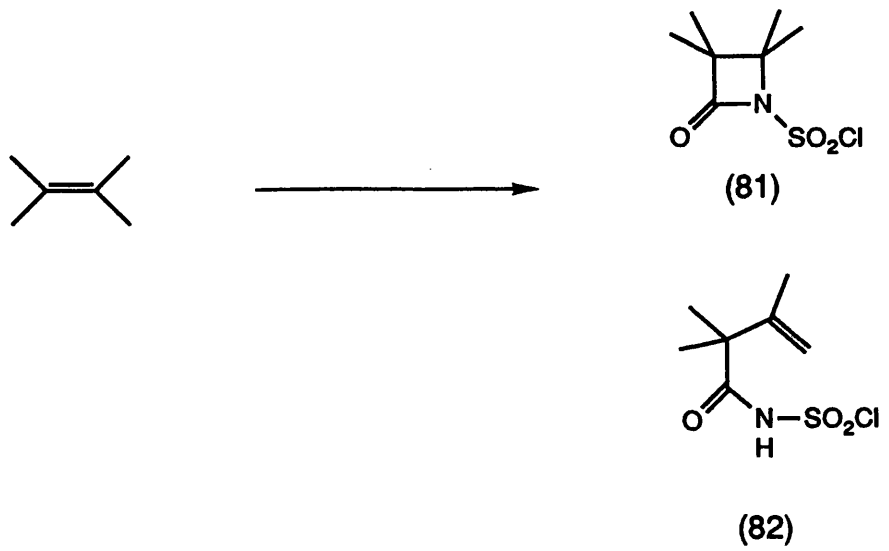


(80)

(Scheme 3.3)

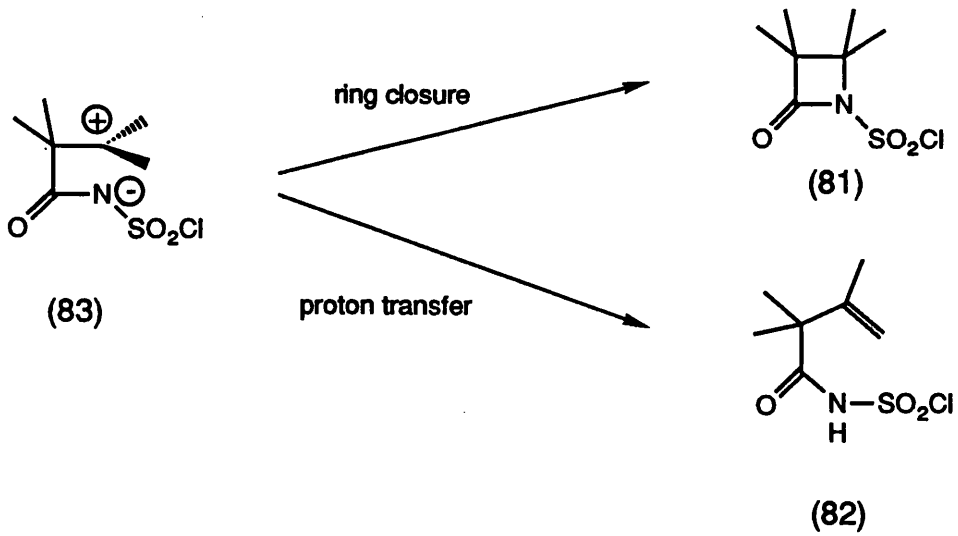
The early pioneering work in this field was carried out by Graf.[58] He was the discoverer of chlorosulphonylisocyanate (CSI), the most reactive isocyanate known, and the first to report full experimental details for the reaction between CSI and a variety of hydrocarbon olefins. In this initial publication[58] it was observed

that, in addition to the formation of a β-lactam (81) a small, but always relatively constant, proportion of an unsaturated N-chlorosulphonamide (82) was produced (Scheme 3.4).



(Scheme 3.4)

To explain this finding, Graf proposed[58] a mechanism that involved the initial formation of a 1,4-dipolar (zwitterionic) intermediate (83), which could then be stabilised by either ring-closure to give the β-lactam (81) or by proton transfer to give the unsaturated amide (82) (Scheme 3.5).

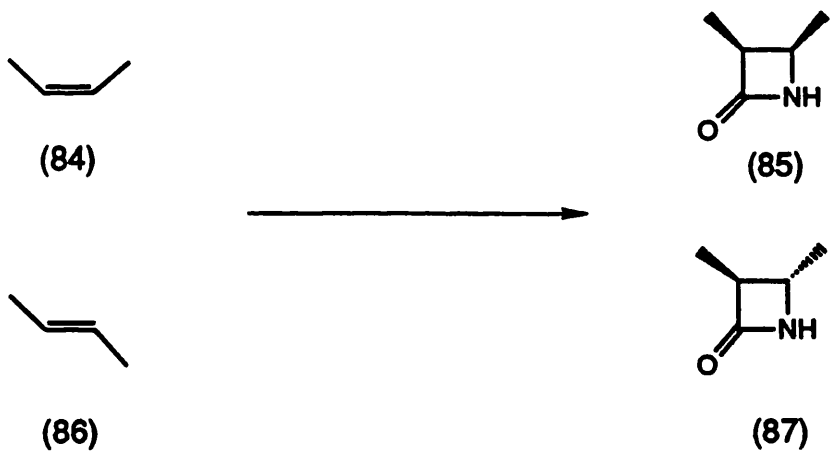


(Scheme 3.5)

In nearly all cases, the β-lactam to amide ratio was ca. 2/2.5 : 1 over all the olefins used. The reaction between isobutylene and CSI led to a 70% yield of azetidinone and a 30% yield of unsaturated sulphonamide.

As well as describing the reactions of many olefins with CSI, Graf also reported on the reactions of acids,[58,59(a)] aldehydes,[58,59(a)] aromatic "olefins" such as thiophene and furan,[58,59(a)] and the reduction of the intermediate N-chlorosulphonyl β-lactams to the N-protio β-lactams, using thiophenol /pyridine,[58,59(a)] and potassium iodide/NaOH.[59(b)] The production of N-protio β-lactams was of great utility, since the variety of compounds that could be made from a common N-protio precursor was greater. The imine nitrogen was usually protected with an alkyl or aryl group due to its basicity.

As mentioned previously, one of the most important aspects of this route to β-lactams was the fact that the geometry of the olefin double bond was transferred, in a likewise sense, to the corresponding relative stereochemistry across C-3 and C-4 of the azetidin-2-one ring. The generality of this was first set out in the work of Bestian[60] and co-workers in some elegantly simple experiments with a range of cis- and trans- olefins and CSI. They found that cis-2-butene (84) afforded the cis-azetidinone (85), and, likewise, trans-2-butene (86) the trans-azetidinone (87) in excellent yields (85%) (Scheme 3.6). Across a wide range of olefin types, the chemical yields ranged from fair (55%) to good (85%), highlighting also the methods' potential as a preparative route to β-lactams.

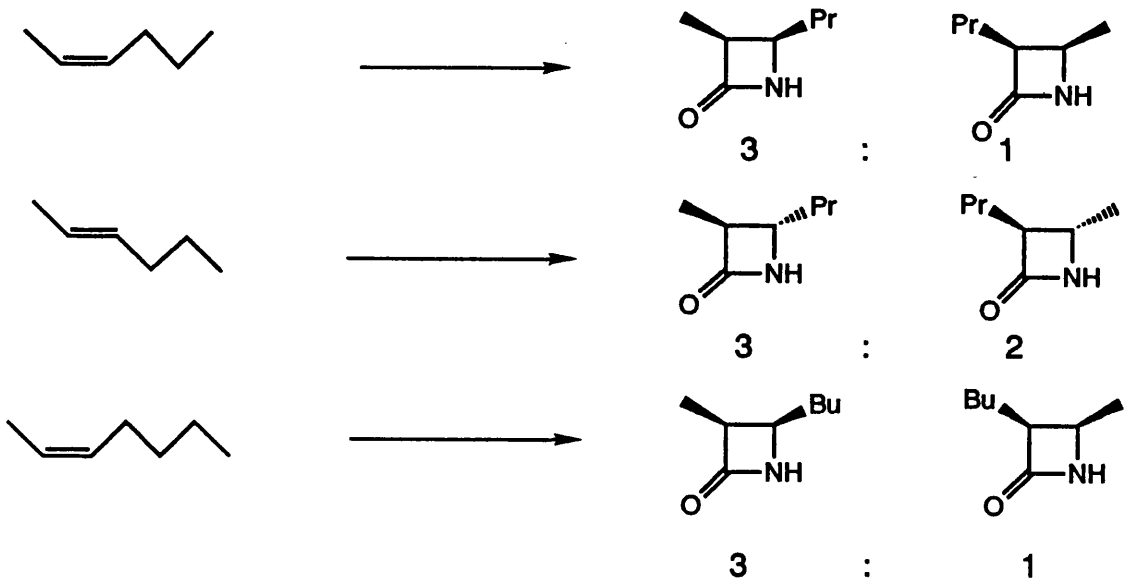


(84) (85)

(86) (87)

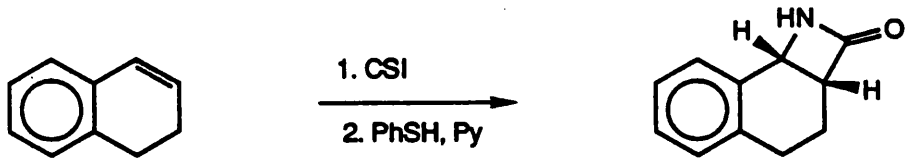
(Scheme 3.6)

With unsymmetrical olefins,[60] the problem of regiochemistry of addition arises, since the olefin now has two possible orientations of addition. Bestian[60] found that the ratio of the regioisomeric β-lactams was dependent on the nature of the olefin (Scheme 3.7).



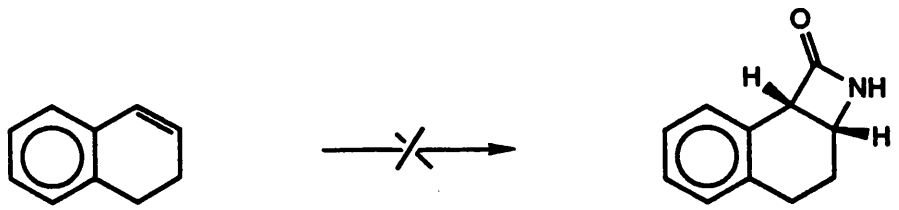
(Scheme 3.7)

Work with other types of unsaturated systems have also been widely reported in the literature. In a continuation of their work on azacyclobutanes, Moriconi and Mazzochi[61] reported on the addition of CSI to dihydronapthalene (88) to give, after pyridine/thiophenol reduction, the bicyclic β-lactam (89) (Scheme 3.8). This was found to be the only β-lactam produced, with none of the regioisomeric β-lactam detected (Scheme 3.9).



(88) (89)

(Scheme 3.8)

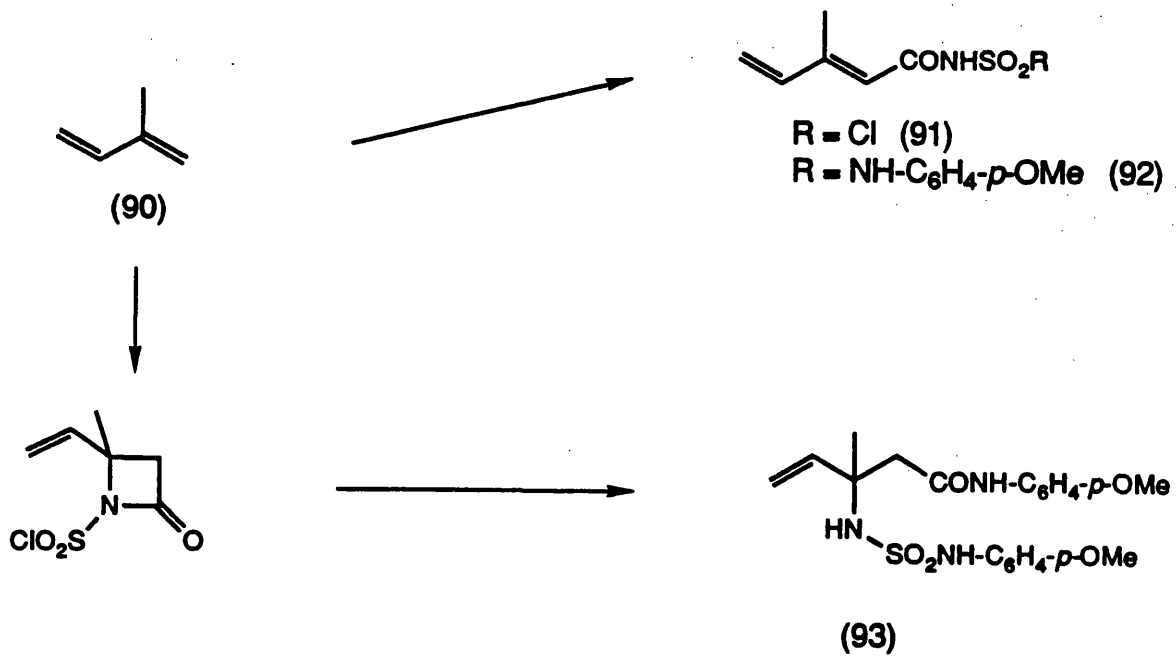


(Scheme 3.9)

Continuing their work with CSI and olefinic subtrates, Moriconi and Kelly[62] reported the synthesis of β-lactams containing an exocyclic double bond via the use of allenes as subtrates. After reduction with thiophenol/pyridine, a range of C-3 alkylidene β-lactams were obtained, along with ca. 30% of the 2-carboxamido-1,3-butadiene derivative. The addition was found to proceed by addition of CSI to the central carbon of the allene, the β-lactam products originating from the most stable preceding cation (see later).

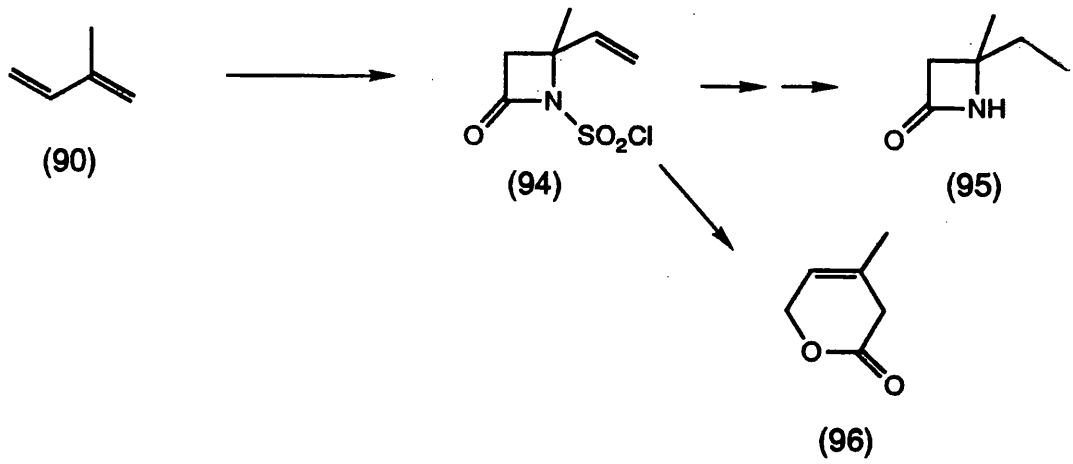
Prior to the work of Moriconi et. al.,[61,62] Hoffmann and Diehr[63] made important observations in the area of conjugated dienes and their reaction with CSI. They found that reaction of, for example, isoprene, (90) with CSI at ambient temperature led to the N-

chlorosulphonyl carboxamide (91), isolated as the p-methoxyanilide(92). At lower temperatures, usually 0°C, they isolated the dianilide (93) (Scheme 3.10). They inferred the structure and presence of the β-lactam intermediates from the nature of their isolated products.



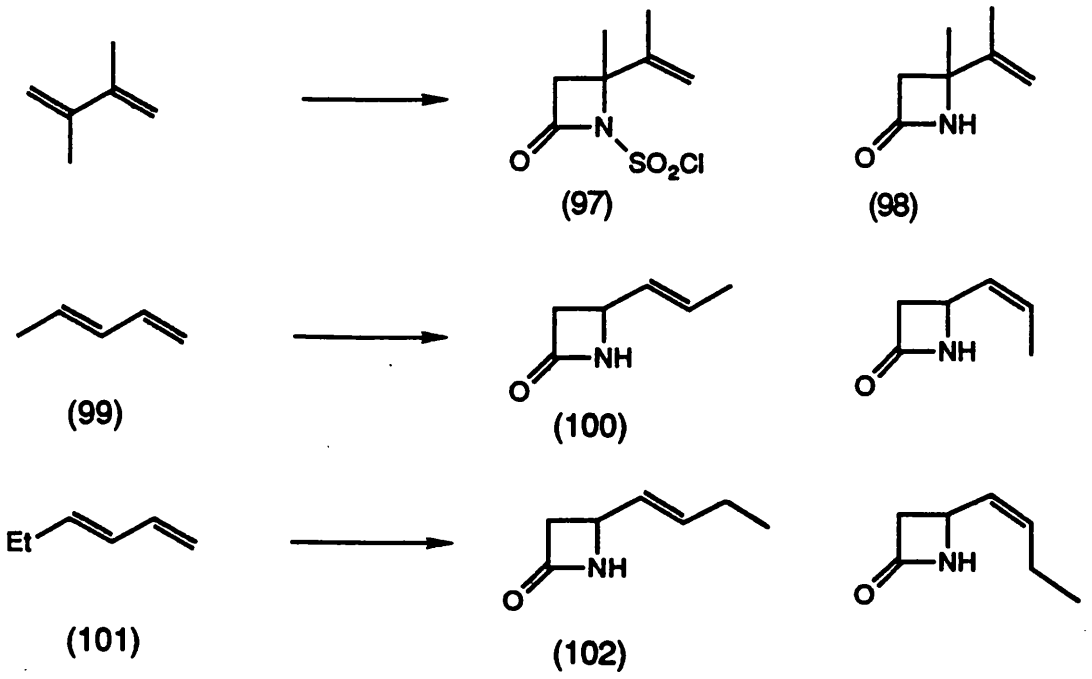
(Scheme 3.10)

Moriconi and Meyer[64] were able to isolate β-lactams with vinylidene substituents at C-3 of the azetidnone ring via the diene/CSI approach. Again, using isoprene (90) as the diene component, they found that careful low temperature addition of CSI in ether led to the N-chlorosulphonyl β-lactam (94). This product, after careful conversion to the N-protio and reduction of the vinyl C-3 side chain with H_2/Pd, was identical with the β-lactam (95), obtained by the reaction of 2-methylbutene and CSI. The C-3 vinyl-N-chlorosulphonyl β-lactam (94) was unstable to warming, upon which it ring-opened to give, after careful hydrolysis, the lactone (96) (Scheme 3.11).



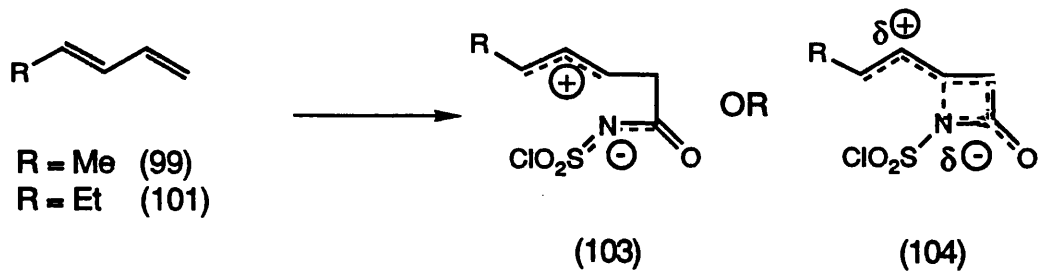
(Scheme 3.11)

The reactions of a variety of conjugated dienes was discussed by Moriconi and Meyer[65] in a continuation of their earlier work[64] on such systems. Representative dienes and their products are shown (Scheme 3.12). Contrary to the findings of Goebel and Clauss,[66] they[65] report the synthesis of the 4-methyl-4-isopropenyl β-lactam (97), and its conversion into the N-protio β-lactam (98) in 57% yield.



(Scheme 3.12)

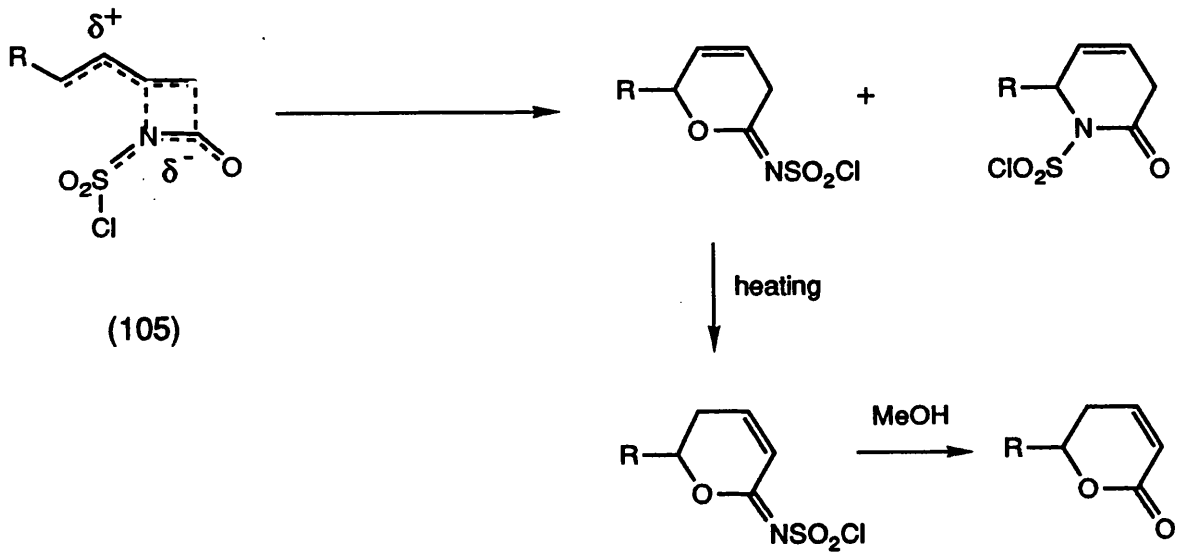
With unsymmetrical conjugated dienes, such as (99) and (101), CSI could, in theory, add to either the terminal or the internal double bond, to give two possible regioisomeric products. It was found, however, that in each case the CSI added only to the terminal double bond in a Markovnikov fashion. The vinyl side chains of the β-lactam products, (100) and (102), were found to have a mixture of geometric isomers at C-4. This clearly lends credence to the postulated allylically stabilised cations (103) or (104) proposed by Moriconi[64] (Scheme 3.13).



(103) (104)

(Scheme 3.13)

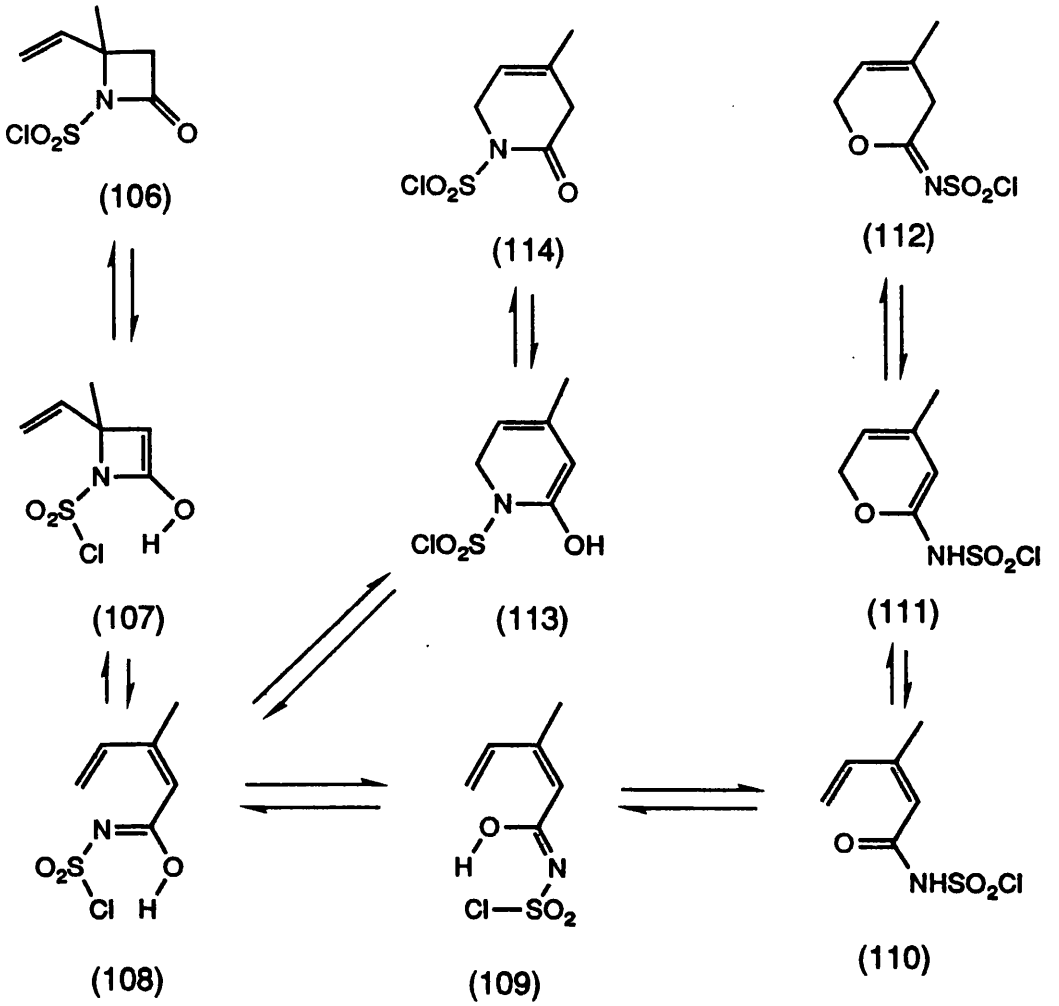
Such vinylic β-lactams were found to rearrange to N- and O- 1,4-cycloadducts, the expected products of the symmetry-allowed $\pi 4_s + \pi 2_s$ process between dienes and CSI. Moriconi[65] and others[66,67] postulated that the rearrangement could proceed in a stepwise fashion via the ring opened dipolar intermediate (105) (Scheme 3.14).



(105)

(Scheme 3.14)

Also tentatively suggested is the sequence of symmetry-allowed events that could occur from the enol form (107) of the azetidinone (106) (Scheme 3.15).

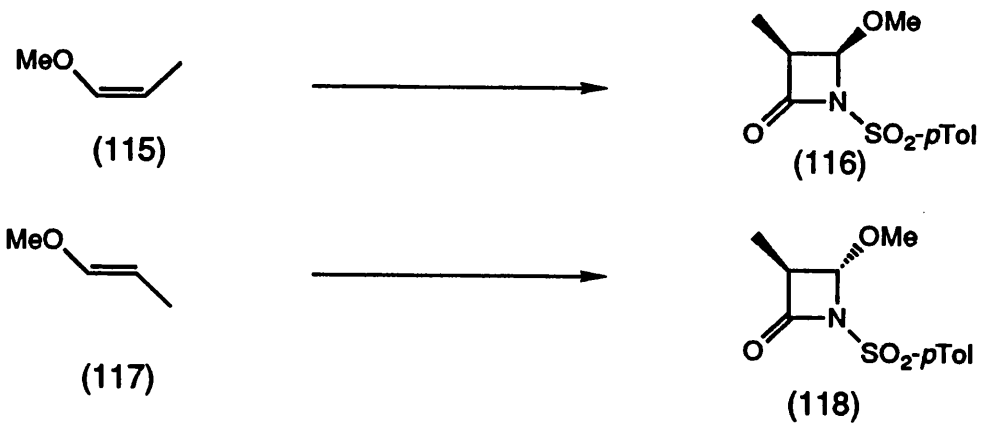


(Scheme 3.15)

The authors[65] suggest that the enol form (107) is made possible by an intermolecular hydrogen bond between the enol hydroxyl and the chlorine of the chlorosulphonyl group. This hydrogen-bonded enolic species (107) then undergoes 4-electron conrotary electrocyclic ring opening to (108). Conformational freedom around C-C allows for the existence of the conformer (109), which can undergo a 1,3 sigmatropic hydrogen shift to the butadienoic N-chlorosulphonamide (110).

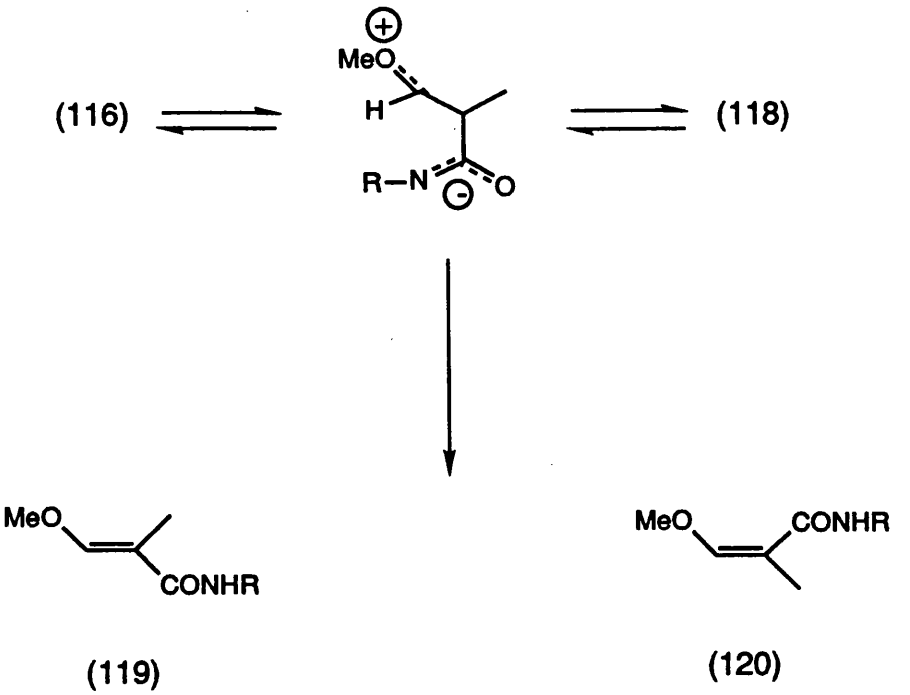
Symmetry-allowed 6-electron electrocyclisation gives the 6-membered azalactone (111), which is simply a tautomeric form of the observed product (112). Electrocyclisation of (108) leads to (113), the enol tautomer of the γ-lactam product (114).

The kinetics and stereochemistry of additions between p-tolylsulphonylisocyanate and enol ethers were reported by Effenberger and co-workers.[68] In agreement with others[60] they too found that the stereochemistry of the enol ethers (115) and (117) were transferred predictably to give the β-lactams (116) and (118). This statement was qualified somewhat with the finding that the stereospecific nature of the addition was only found in the temperature range -20°C to +20°C (Scheme 3.16).



(Scheme 3.16)

Slow isomerisation took place on extended stirring at room temperature. Upon heating to 80°C, it was found that the azetidinones (116) and (118) rearranged to the trans- and cis- acrylamides (119) and (120) (Scheme 3.17).

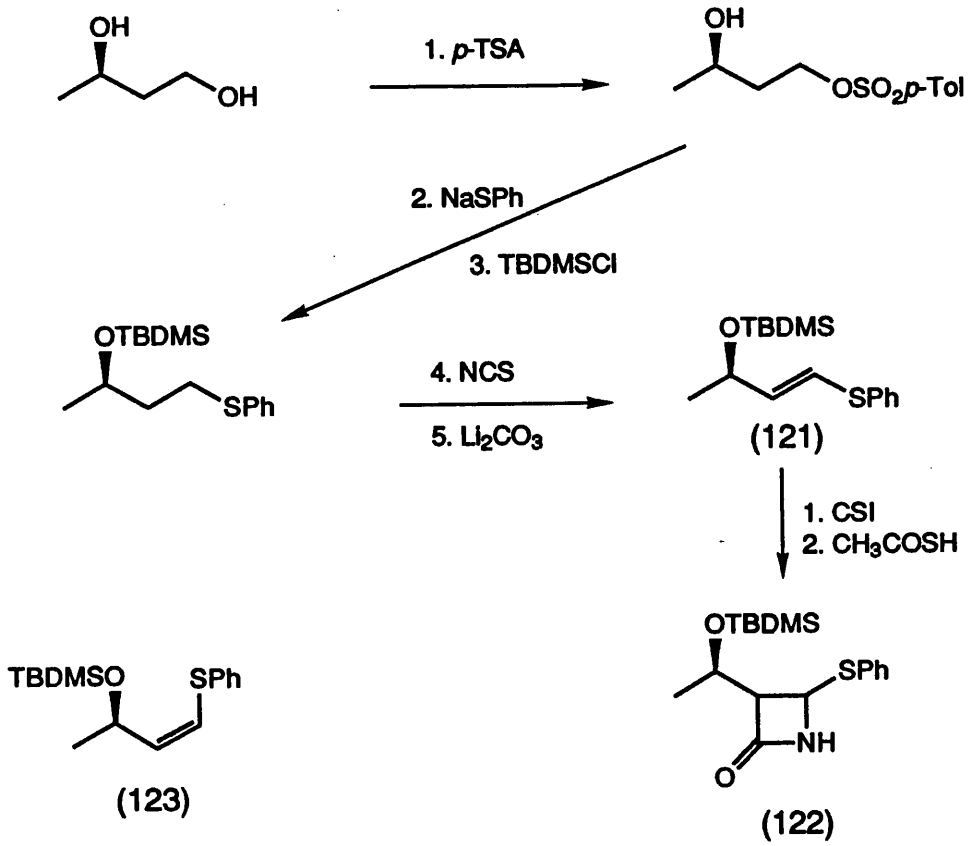


(119) (120)

(Scheme 3.17)

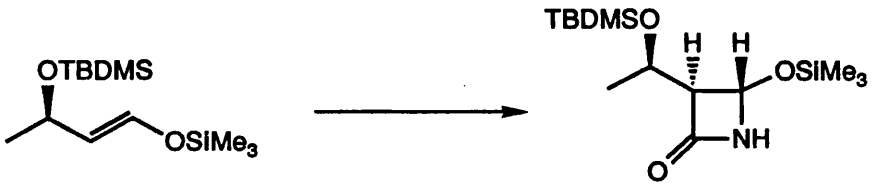
Recently, Ishiguro[69] et. al. have published their findings on the reaction between cis- and trans- vinyl sulphide and CSI. Reaction between the vinyl sulphide (121), obtained in 6 steps from the microbially produced (R)-butane-1,3-diol, and CSI results in formation of the 4-thio azetidin-2-one, (122) which is a useful precursor to the important carbapenem family of β-lactams (Scheme 3.18). Transformation of the 4-thiophenyl substituent into a 4-acetoxy azetidinone, via a copper mediated reaction, allows for many and varied

nucleophilic substitutions to occur at this position.



(Scheme 3.18)

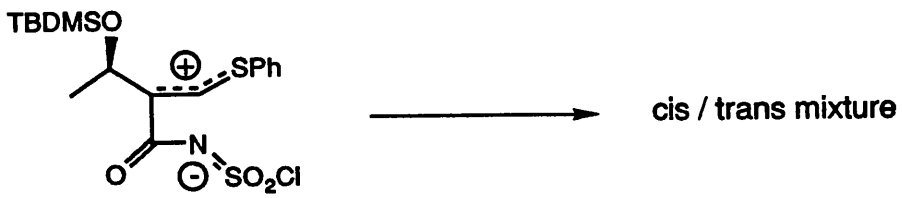
These workers [69] found that the cis vinyl sulphide (123) did not give only the cis β-lactam, but rather a mixture of diastereoisomers, although high stereoselection had been observed in the addition of the E-vinyl silylenol ether (124) to CSI (Scheme 3.19).[70]



(124)

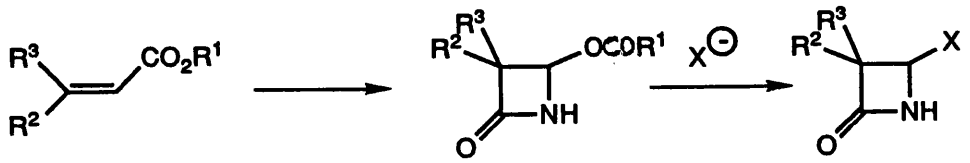
(Scheme 3.19)

This lack of stereochemical transfer indicates a stepwise mechanism in operation, with the lifetime of any dipolar intermediate (125) being sufficiently long-lived to allow for rotation around the C-C single bond (Scheme 3.20). These findings are in sharp contrast to all other research [60,68,70] into the stereochemical outcomes of olefin/CSI cycloadditions.



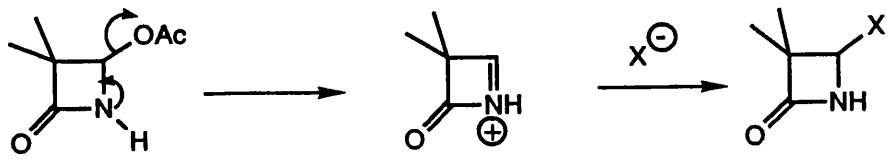
(Scheme 3.20)

The work of Clauss et al.[71] on the synthesis of 4-acetoxy-azetidin-2-ones from vinyl acetates was of great importance to this methodology. Such 4-acetoxy-azetidinones are very useful intermediates in the synthesis of functionalised β-lactams, due to the fact that the 4-acetoxy moiety is readily replaced by a variety of nucleophiles (Scheme 3.21).



(Scheme 3.21)

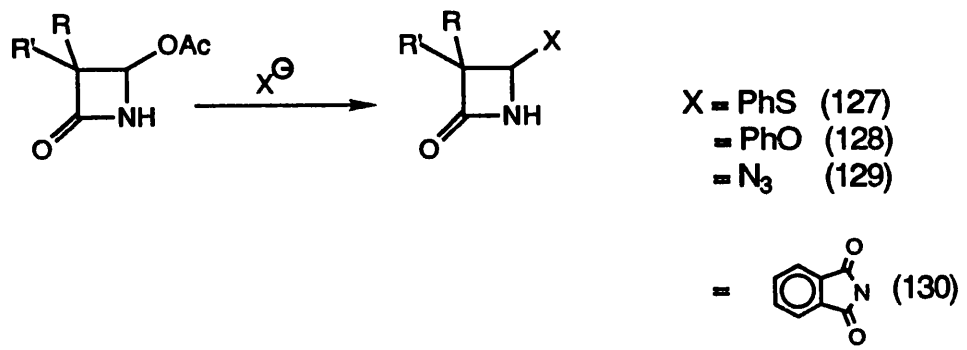
The displacement occurs readily, forming an iminium ion (126), which is a good acceptor of nucleophiles (Scheme 3.22).



(126)

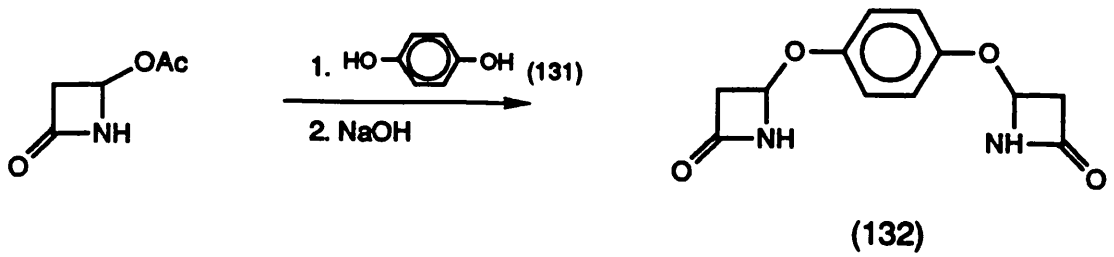
(Scheme 3.22)

Among the nucleophiles used were thiolates, phenoxides, azides and phthalimides, giving rise to 4-thiophenyl (127), 4-phenoxy (128), 4-azido- (129) and 4-phthalimido (130) azetidinones (Scheme 3.23).



(Scheme 3.23)

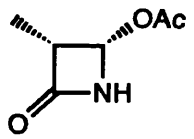
One interesting example was the use of p-hydroquinone (131) to form the bridged bis-β-lactam (132) (Scheme 3.24).



(132)

(Scheme 3.24)

Also investigated by these workers[71] were some stereochemical aspects of this synthetically useful acetoxy displacement. They found that with a variety of nucleophiles, the cis-3-methyl-4-acetoxy β-lactam (133) reacted to give predominantly the trans- stereoisomer, but with a small quantity of cis product also forming. Since the addition of a nucleophile to the iminium species can occur reversibly, the trans (thermodynamic) product is favoured. It was found that larger nucleophiles gave a greater proportion of the trans product (Table 3.1).



(133)

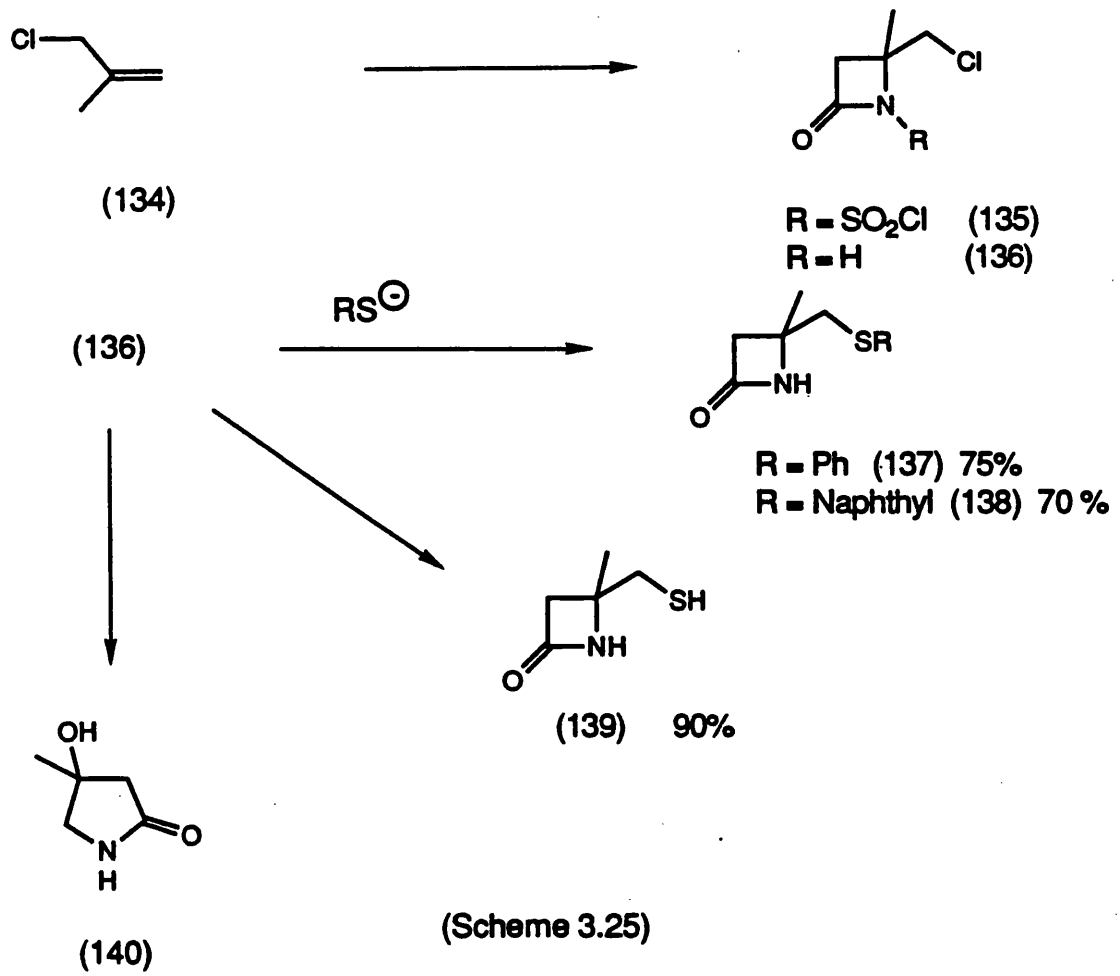
Nucleophile (X^-)	% yield	% cis
PhO	100	0
PhS	100	7
Et S	69	17
$PhSO_2$	88	5
MeO	90	20
N_3	87	35

Table 3.1

In an interesting insight into the mechanism of this displacement reaction, these workers[71] used a 4-(camphorsulphonyl)-β-lactam, with a variety of nucleophiles, in the hope that some asymmetric induction could be achieved. They found, however, virtually zero induction in all cases and this can be rationalised in terms of the reaction proceeding via a true S_N1-type intermediate, with the chiral auxiliary having already departed before the nucleophile has arrived, and therefore unable to influence the nucleophiles orientation of attack.

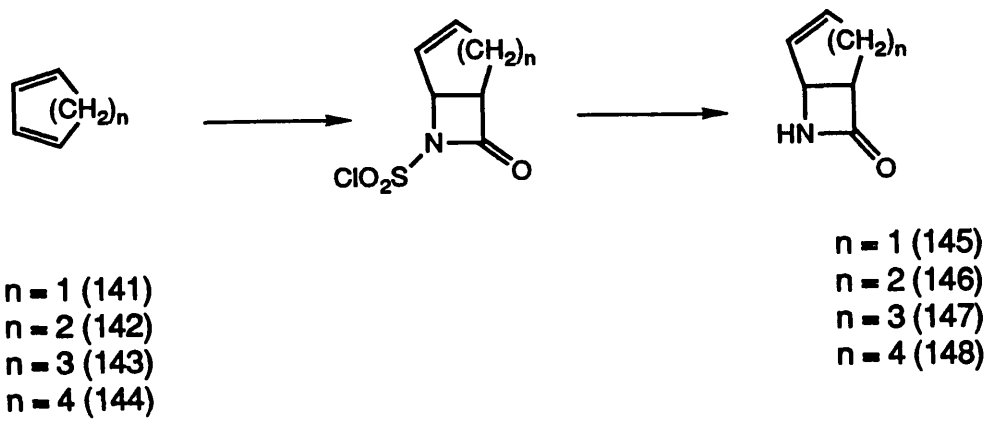
Clauss[72] continued his interest in the synthesis of usefully functionalised monocyclic β-lactams with the synthesis of 4-(chloromethyl)-4-methyl β-lactam (135) from methallylchloride (134) and

CSI. This β-lactam was then converted to the stable N-protio β-lactam (136) by reductive cleavage of the N-chlorosulphonyl group. The 4-(chloromethyl) substituent was particularly useful since the chlorine atom could be displaced by an external nucleophile to generate new and useful functionality at C-4. To this end, Clauss reacted the 4-(chloromethyl) β-lactam (136) with the thiophenyl and thionaphthyl anions to produce the β-lactams (137) and (138) in 75% and 70% yields respectively. To produce a 4-thio-β-lactam, Clauss reacted β-lactam (136) with NaSH in methanol at 65°C and produced the β-lactam (139) in 90% yield. Attempts to synthesise a 4-(hydroxymethyl) β-lactam by an analogous reaction with KOH succeeded only in yielding the γ-lactam (140) (Scheme 3.25).



(Scheme 3.25)

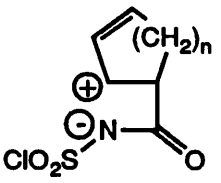
The reaction between CSI and a number of acyclic dienes had received attention in the literature,[63,66,65] but little work was reported with cyclic dienes. Malpass and Tweedle[73] studied the reaction between cyclopent-(141), hex-(142), hept-(143) and octadiene (144) with CSI, and found that these compounds reacted rapidly with CSI to afford the fused β-lactams (145), (146), (147) and (148) in good yields (Scheme 3.26).



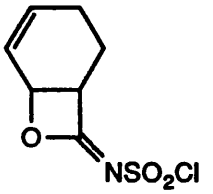
(Scheme 3.26)

They had expected to see the formation of 1,4 adducts, since the cyclic dienes are naturally held in a cisoid conformation by the constraints of the ring. The acyclic dienes will adopt a transoid conformation and so have been found to give, as the primary product, the 1,2 (β-lactam) product, followed by thermal rearrangement to the 1,4 species. However, they found that the initially formed β-lactams were reasonably stable and required thermal energy to effect rearrangement. Also, the ease of this thermal rearrangement decreased

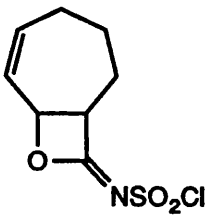
with the size of the ring, suggesting that the mechanism proceeds through a ring-cleaved zwitterion (149), the allylic cation being less easily stabilised by π-bond resonance as the geometry of the larger rings lessens the overlap necessary for effective stabilisation (Scheme 3.27). For the bicyclic β-lactams where n=2,3 the rearrangement products were the imino lactones (150) and (151); for n=1, the only product was the γ-lactam (152).



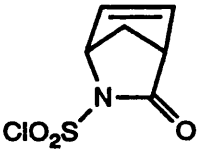
(149)



(150)



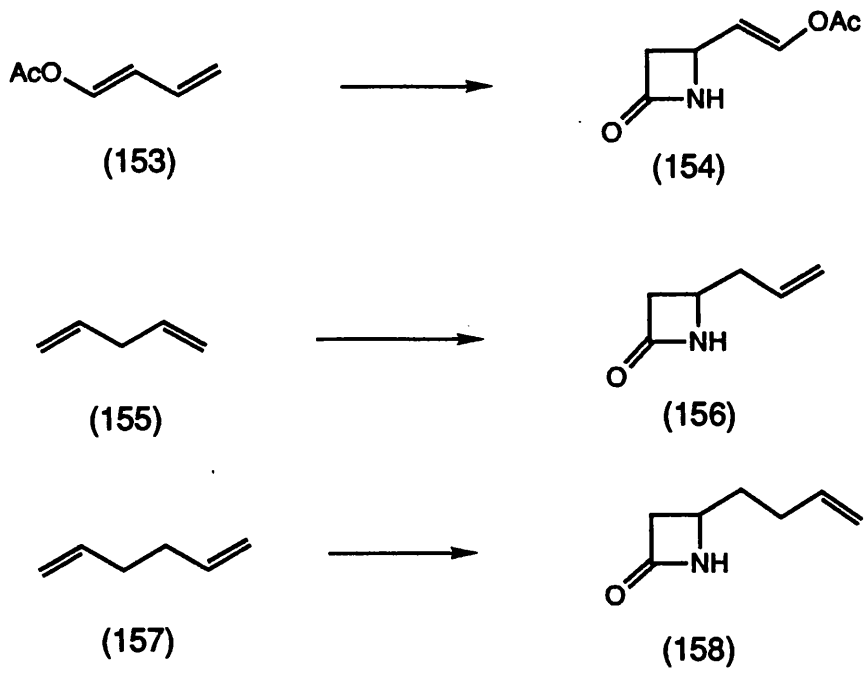
(151)



(152)

(Scheme 3.27)

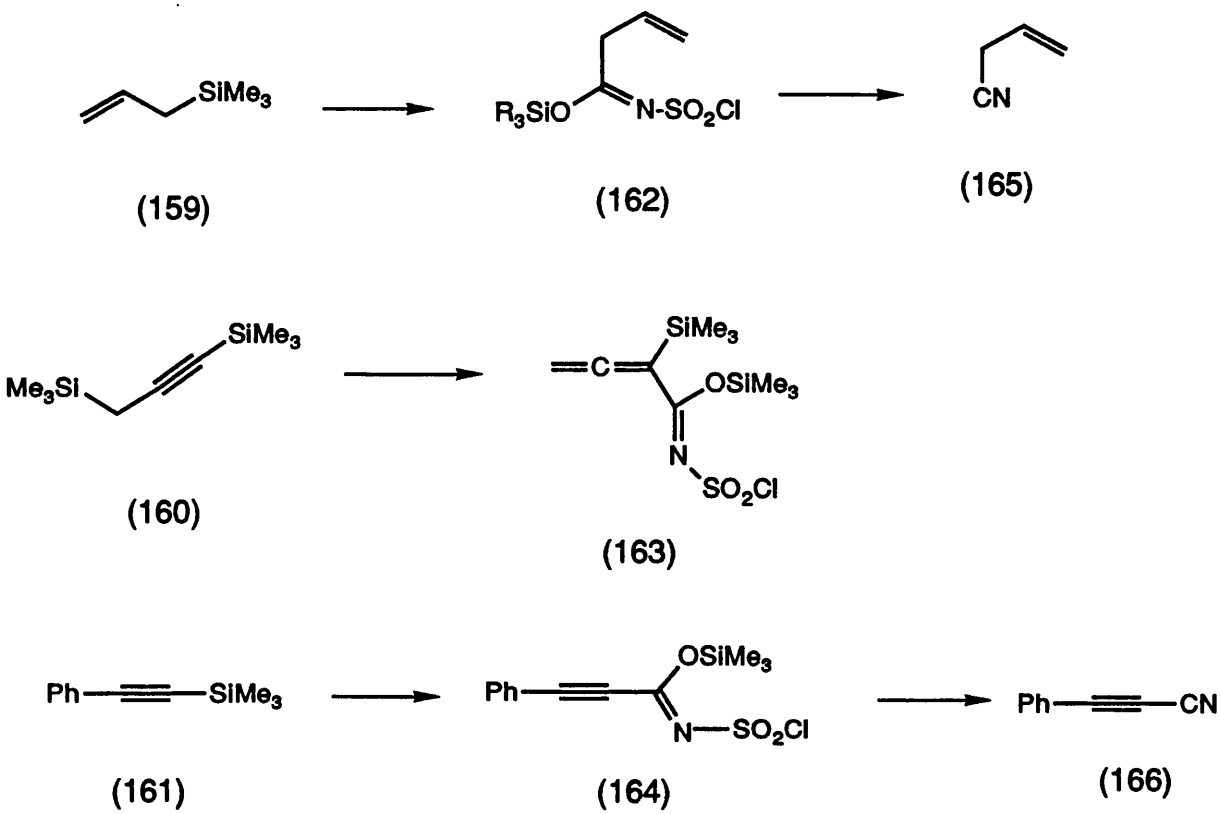
Southgate and co-workers[74] utilised the reaction between dienes and CSI in the preparation of cephalosporin precursors. They reacted the conjugated 1-acetoxy-1,3-butadiene (153) with CSI to furnish the β-lactam (154). With the non-conjugated penta-1,4- and hexa-1,5-dienes (155) and (157) the β-lactams (156) and (158) were obtained. With the unsaturated substituent at the 4-position of the azetidinone ring, many possible synthetic strategies were available to synthesise the cephalosporin nucleus. (Scheme 3.28)



(Scheme 3.28)

The use of unsaturated silanes with CSI was first reported by Dunoguès and co-workers,[75] and this served to open the methodology to include a much wider, and synthetically more useful, range of elements. The reactions of a number of unsaturated silanes, such as allylic, (159) propargylic (160) and acetylenic (161) were studied. These substrates were found to react with CSI to produce O-silyl-N-chlorosulphonyl imino ethers (162), (163) and (164) which were then transformed into unsaturated nitriles (165) and (166) by treatment with pyridine. The nitriles produced were always regiochemically predictable, that is, there were no mixtures of regioisomeric nitriles

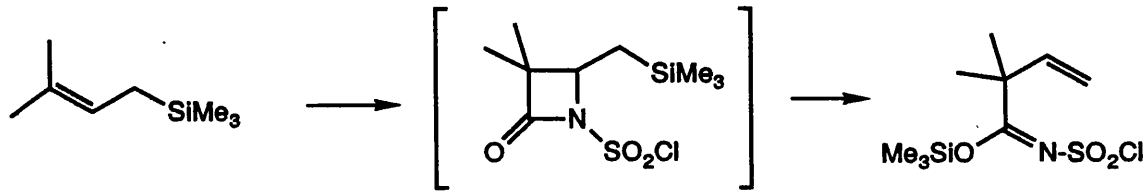
obtained (Scheme 3.29).



(Scheme 3.29)

The most interesting result from the point of view of β-lactam chemistry was the detection of an N-chlorosulphonyl β-lactam intermediate (168) in the reaction between the dimethylallylsilane (167) and CSI in CCl_4 at 0°C. The intermediate was detected by the distinctive β-lactam C=O stretch* at 1812 cm^{-1} in the IR. On warming to room temperature, this β-lactam was found to rearrange to the imino ether (169) (Scheme 3.30).

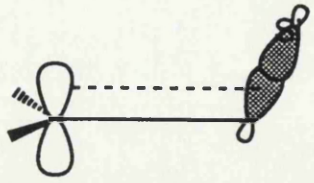
* for N-SO_2Cl β-lactams



(167) (168) (169)

(Scheme 3.30)

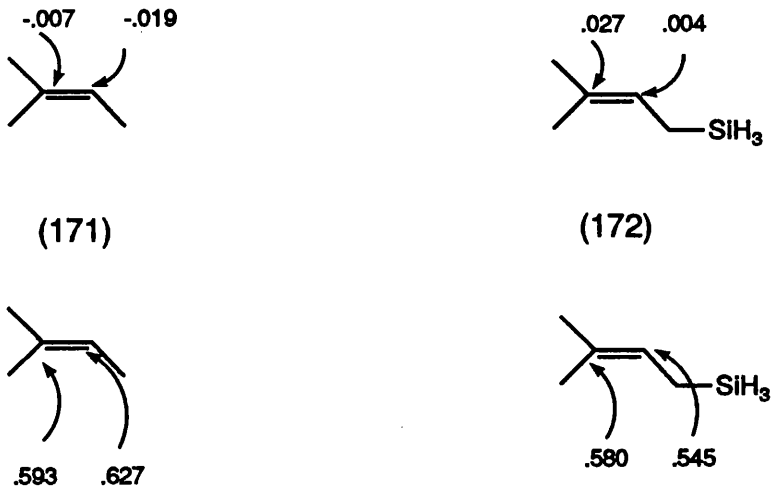
The regiochemistry of the final nitrile, and hence the β-lactam precursor, was controlled by the β-effect,[117] the stabilisation of any developing cationic centre β-disposed to silicon over any other cationic intermediate. The stabilisation arises from the overlap of the Si-C bond with the developing p-orbital at the beta- position (170). For efficient overlap, and hence stabilisation, the Si-C bond and the lobe of the developing p-orbital must be syn-periplanar (Scheme 3.31).



(170)

(Scheme 3.31)

A theoretical approach was adopted by Déléris et al.[76] to ascertain the effect silicon has on the chemistry of the olefinic double bond, compared to the hydrocarbon analogue, in the cycloaddition with CSI. Using the MINDO/3 method of Dewar[77] they calculated both the net atomic charges and the HOMO coefficients of the olefin (171) and allylsilane (172). The results indicated a reversal of reactivity as shown by the differences in both the net atomic charges and the HOMO coefficients (Scheme 3.32).

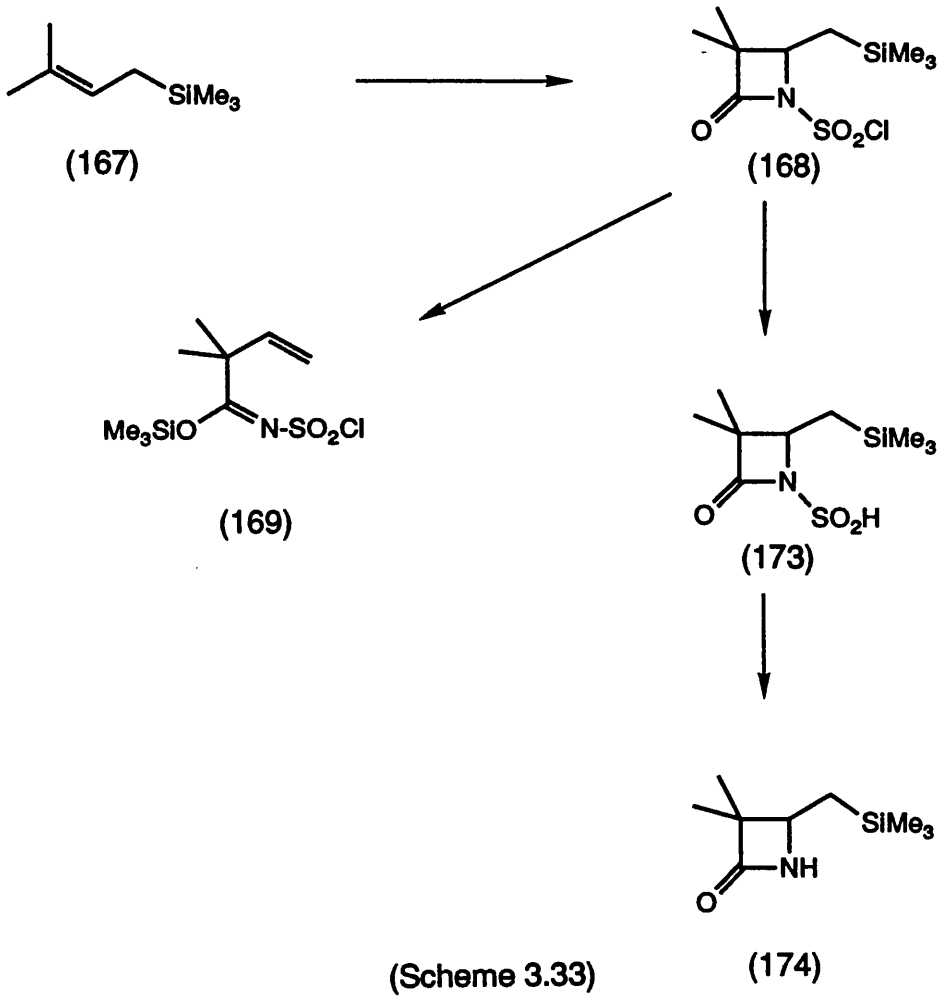


(Scheme 3.32)

The opposite nature of the HOMO coefficients explains the regiochemical preference; the largest coefficient of the allylsilane (and the olefin) will interact most favourably with the atom of the CSI moiety that has the largest coefficient, normally assumed to be the central carbon atom. Since the larger coefficient is on a different carbon atom in the olefins (171) and (172) the regiochemical differences are explained, although no conclusions as to the precise mechanism were drawn. Also in these studies, it was found that the optimised angles and bond distances for the allylsilane (172) meant that the Si-C bond was nearly parallel to the ethylenic π-cloud, ideal for overlap.[78,117].

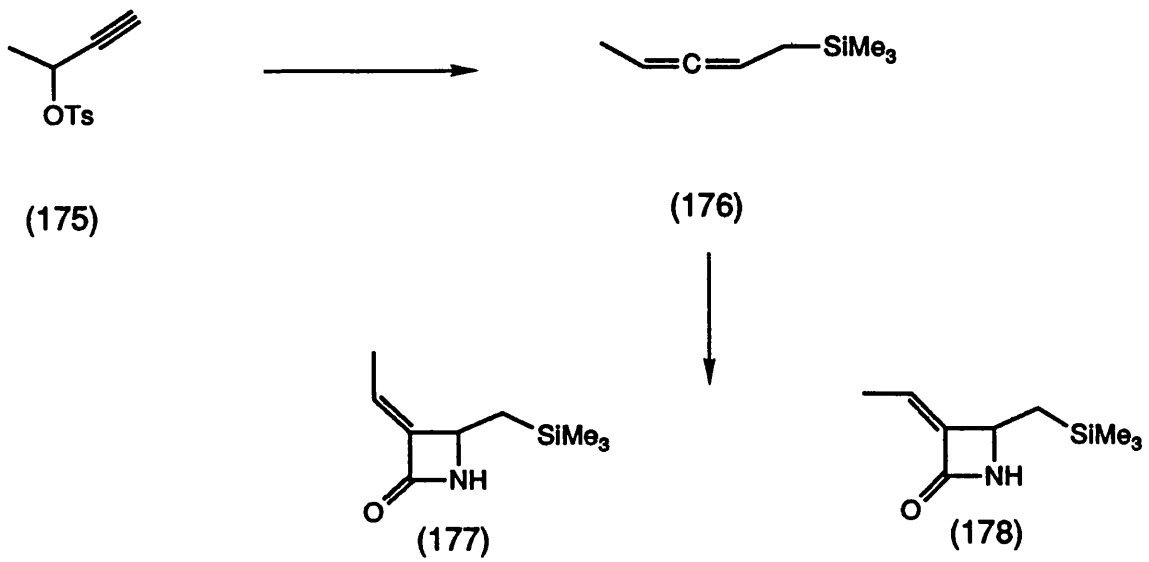
Recently, Colvin and Monteith[79(a)] reported a very useful procedure for the synthesis of monocyclic β-lactams from allylsilanes and CSI. They found that the intermediate β-lactams reported by Dunoguès and co-workers[75,76] could be intercepted and reduced to the

stable N-protio β-lactams utilising a method reported by Durst and O'Sullivan[80]. The inorganic reducing agent sodium sulphite was known to reduce alkylsulphonylchlorides to alkylsulphinic acids. In the case of the N-sulphonylchloride β-lactam (168), the N-sulphinic acid (173) spontaneously loses SO_2 to form the N-protio azetidinone (174). The intermediate β-lactams were found to be stable at room temperature for 24h at ambient temperature, although the concentration used was ca. 0.2M compared to that of Dunoguès at 3.5M. Concentration in the cold afforded the imino ether (169), suggesting a bimolecular process and supporting the reported greater lability of these intermediates in the higher concentrations used by Dunoguès[75] (Scheme 3.33).



(Scheme 3.33)

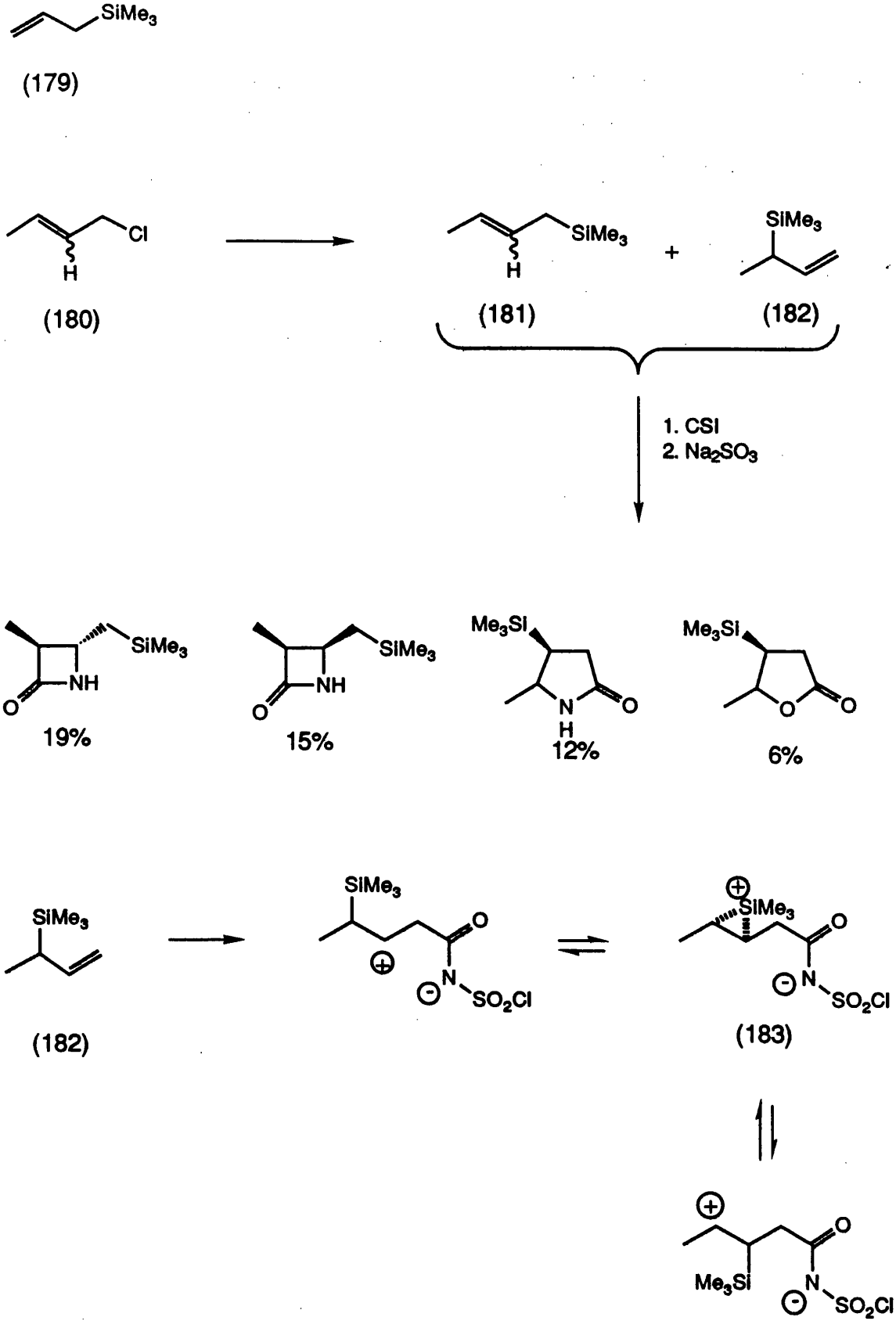
The use of other unsaturated silanes was also reported in this preliminary communication.[79(a)] Allenylmethylsilanes (176), prepared from propargylic tosylates (175) and organocuprates, were reacted with CSI then reduced with Na_2SO_3 to afford the mixture of isomeric C-3-alkylidene β-lactams (177) and (178) (Scheme 3.34).



(175) (176) (177) (178)

(Scheme 3.34)

Colvin and Monteith confirmed the observation by Dunoguès and co-workers that allyltrimethylsilane (179) did not form a β-lactam intermediate with CSI. Colvin et. al. also reported interesting reactivity shown by allylsilane (182) towards CSI. [79(b)] The allylsilane mixture (181) and (182), obtained from the cis/trans mixture of allylchloride (180), gave the four products shown (Scheme 3.35). The cis and trans β-lactams arose from the cis/trans mixture of terminal silane (181); the lactam and lactone have come from the internal silane (182), possibly via the bridged intermediate (183).


SiMe3
(179)
Cl
H
(180)
SiMe3
H
(181)
SiMe3
(182)
+
1. CSI
2. Na2SO3
SiMe3
NH
O
19%
SiMe3
NH
O
15%
Me3Si
N
H
O
12%
Me3Si
O
O
6%
SiMe3
(182)
SiMe3
O
N
SO2Cl
SiMe3
O
N
SO2Cl
(183)
Me3Si
O
N
SO2Cl

(Scheme 3.35)

3.3 Synthetic Applications

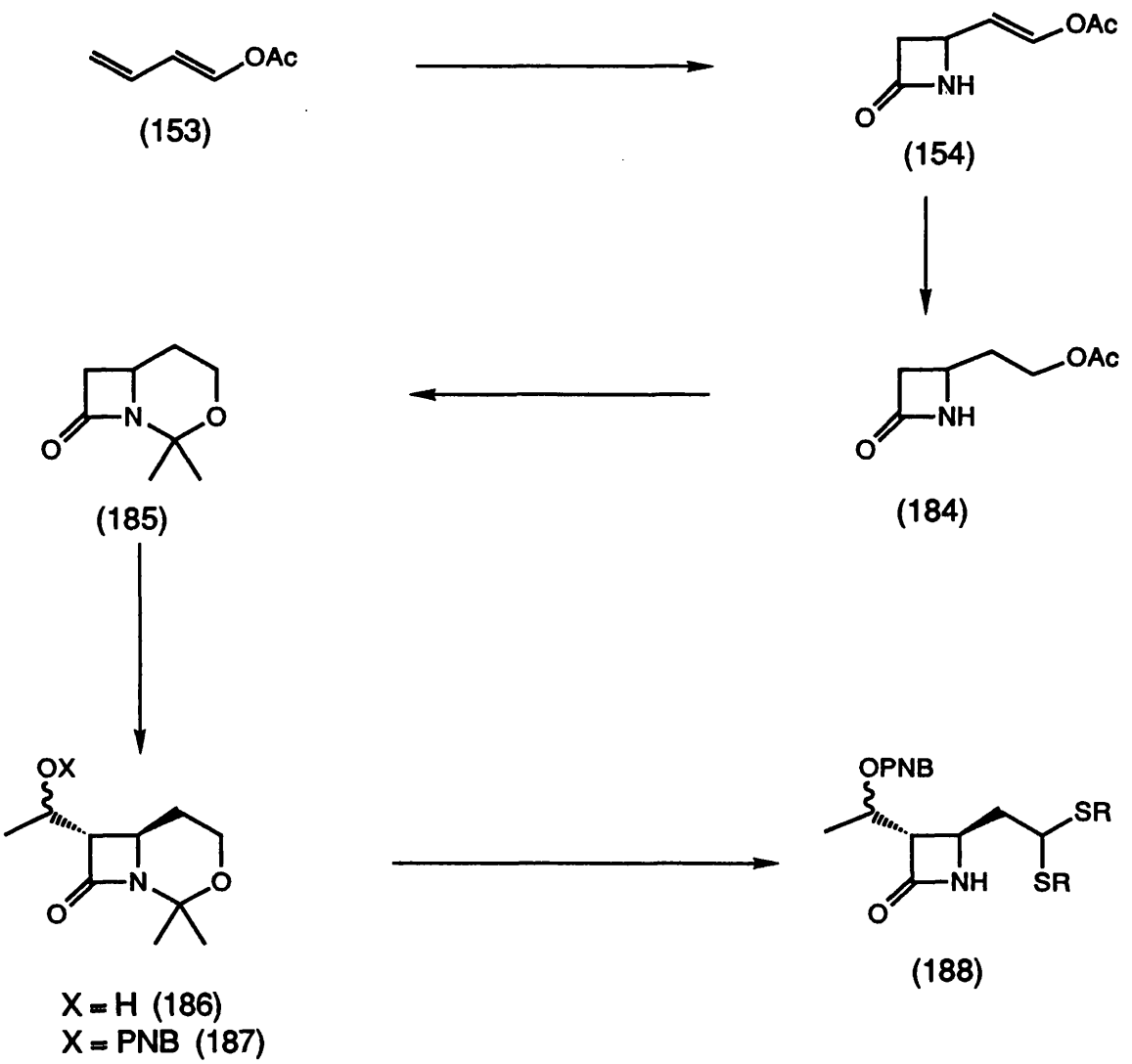
The utility of any methodology can be measured in terms of its application to the synthesis of new compounds, and the generality of its use. An important application of the CSI/olefin [2+2] cycloaddition was reported by Johnston[81] and co-workers in the first total synthesis of Thienamycin. (Scheme 3.36)

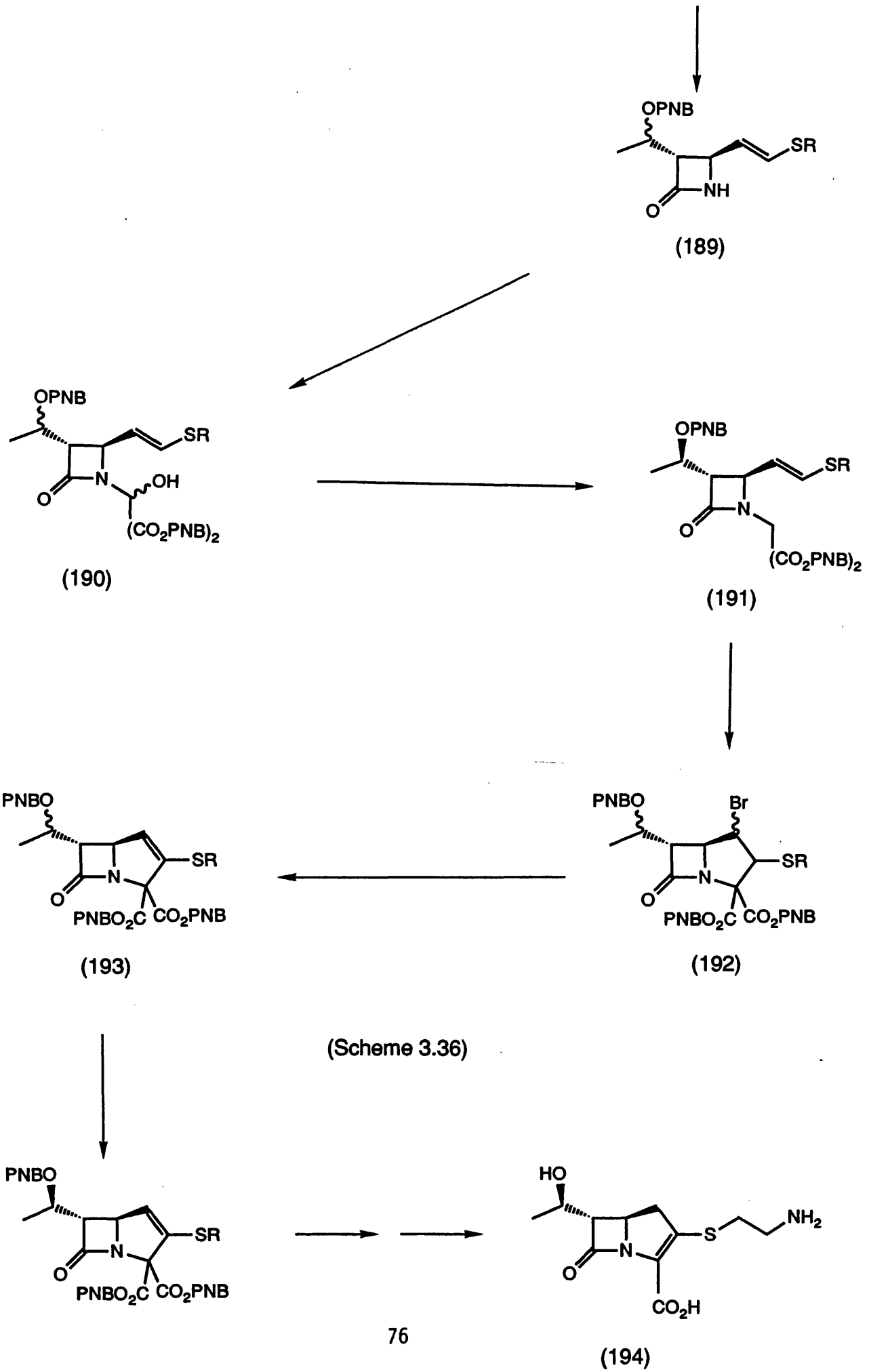
This was an important target for several reasons; biologically, the molecule has a high antibacterial activity and high potency against both Gram-positive and negative bacteria and synthetically the substituent on the 6-position is present as the alpha-epimer. Also, the molecule lacks the usual 6-amido substituent normally associated with biological activity.

The early construction of the azetidin-2-one ring system was achieved in the first step of the synthesis, through the reaction of 1-acetoxybuta-1,3-diene (153) with CSI, followed by reductive cleavage[80] to form the monocyclic β-lactam (154) in 42% yield. Hydrogenation and deacetylation gave the 4-(hydroxyethyl) β-lactam (184), subsequently protected as the acetonide (185). Treatment of the acetonide with LDA and acetaldehyde gave the trans-hydroxyethyl β-lactam (186), protected as the PNB ester (187). Removal of the acetonide protection, and subsequent oxidation to the aldehyde was immediately followed by formation of the thioacetonide (188), in 46% yield. Treatment of the thioacetonide with bromine followed by Et_3N gave mainly the trans-thioenol ether (189). Condensation of the thioenol ether with p-nitrobenzylketomalonate gave the hydroxymalonate (190), converted into

the fully reduced compound (191), in 60% yield, by a two step process involving conversion to the chloride with $SOCl_2$ and immediate reaction with $P(n\text{-}Bu)_3$.

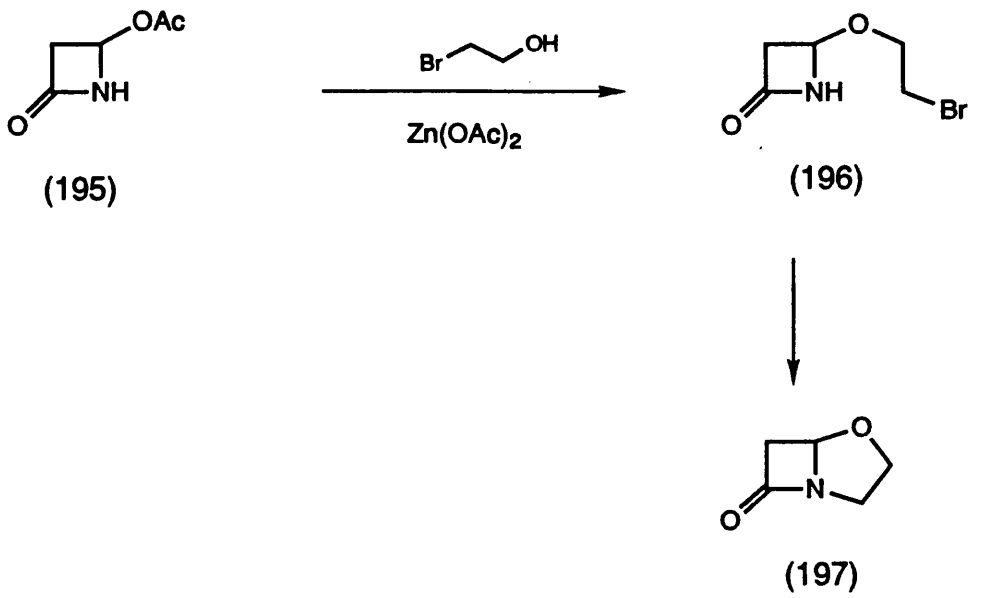
The bicyclic system was constructed by bromo-cyclisation, followed by Et_3N affording (192) in 58% yield. Dehydrobromination with AgF and pyridine produced (193) as a 1:1 mixture of 8-PNBoxy epimers, carried through from the introduction of the 6-hydroxyethyl side chain. After chromatographic separation of the diastereomers, conversion to the final product was effected by decarbalkoxylation, double bond isomerisation with diisopropylamine, and hydrogenolysis to produce (±) thienamycin, (194) showing half the antibacterial potency of the naturally occurring material (Scheme 3.36).


OAc
(153)
OAc
NH
O
(154)
OAc
NH
O
(184)
N
O
O
(185)
OX
N
O
O
X = H (186)
X = PNB (187)
OPNB
SR
NH
SR
O
(188)


OPNB
SR
NH
O
(189)
OPNB
SR
N
OH
O
(CO2PNB)2
(190)
OPNB
SR
N
O
(CO2PNB)2
(191)
PNBO
Br
SR
N
O
PNBO2C CO2PNB
(192)
PNBO
SR
N
O
PNBO2C CO2PNB
(193)
PNBO
SR
N
O
PNBO2C CO2PNB
HO
S
NH2
N
O
CO2H
(194)

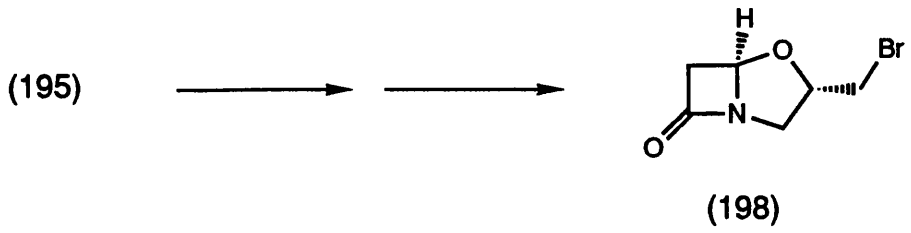
(Scheme 3.36)

Bentley and Hunt[82] made the simplest member of the clavam (4-oxa-1-azabicyclo[3.2.0]heptane) ring system (197) by cyclisation of the alkoxyazetidinone (196) with DBU. This alkoxyazetidinone was itself made by the zinc acetate-mediated coupling of 2-bromoethanol to 4-(acetoxy)-azetidinone (195) (Scheme 3.37).



(Scheme 3.37)

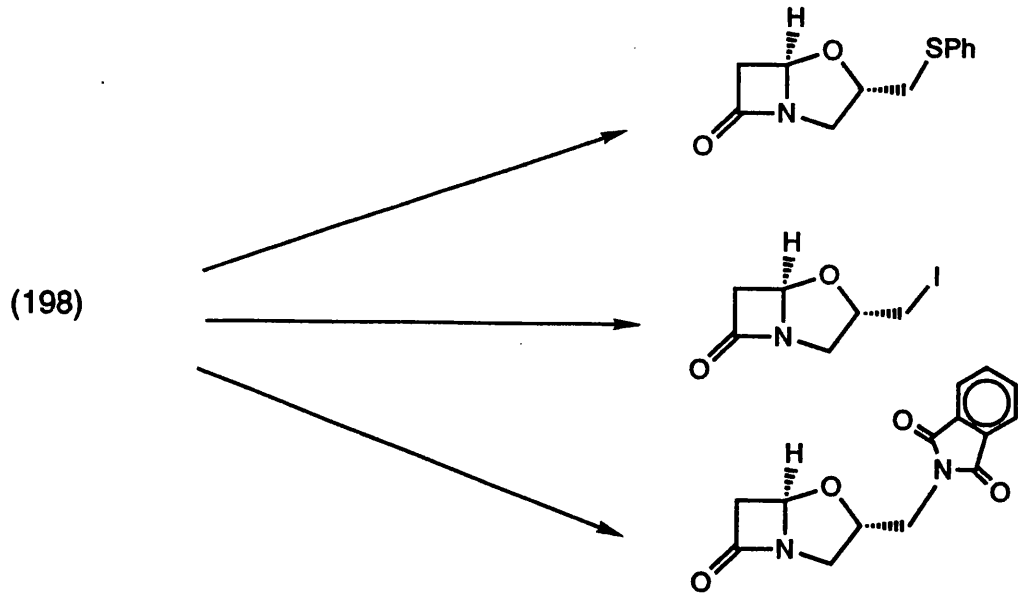
Other representatives of the family were made from β-lactam (195) and the appropriate alcohol by the same method. (Scheme 3.38)



(198)

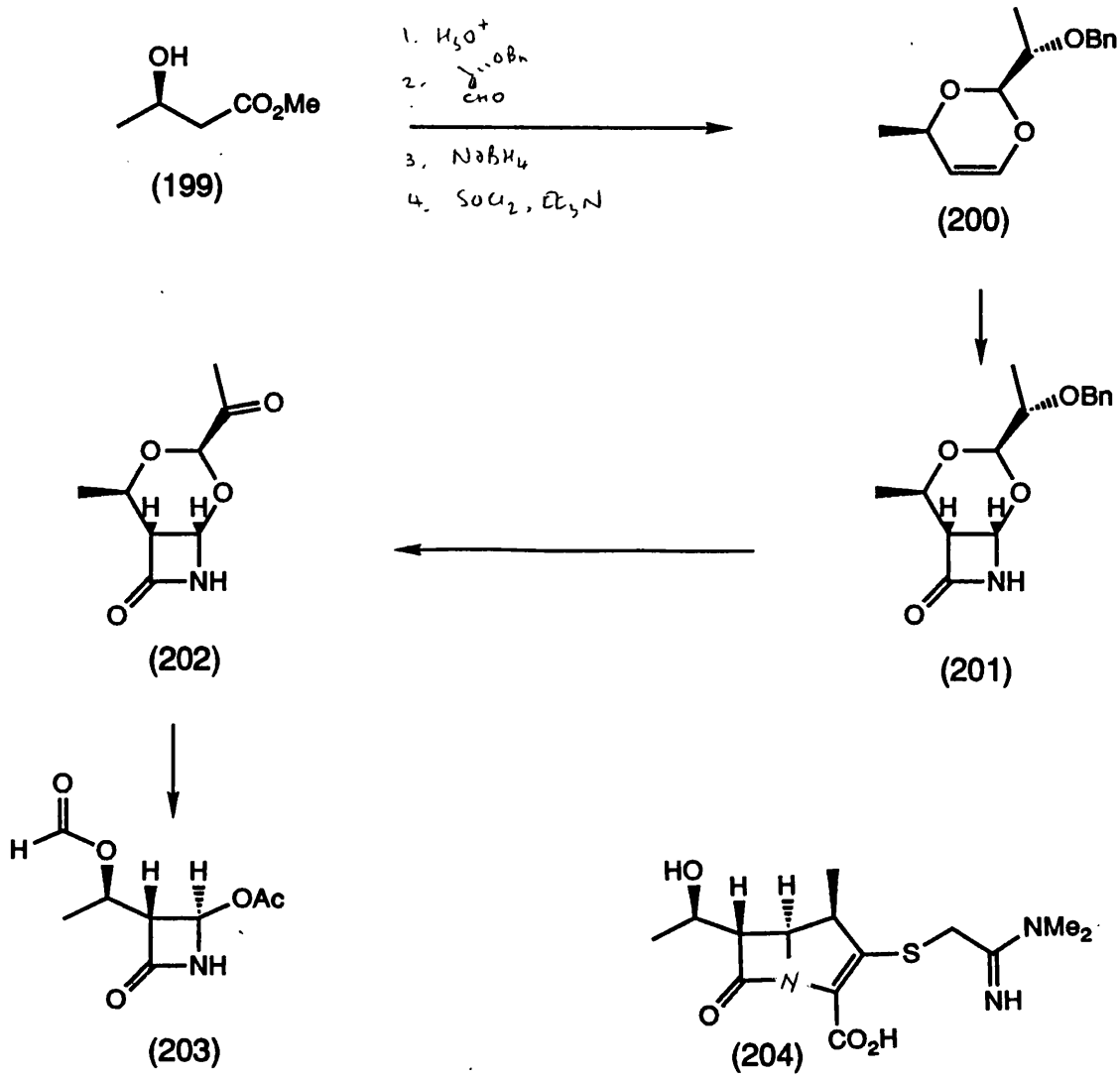
(Scheme 3.38)

Of these clavams (198) was used to prepare other members of the family by displacement of the halogen by a variety of nucleophiles (Scheme 3.39).



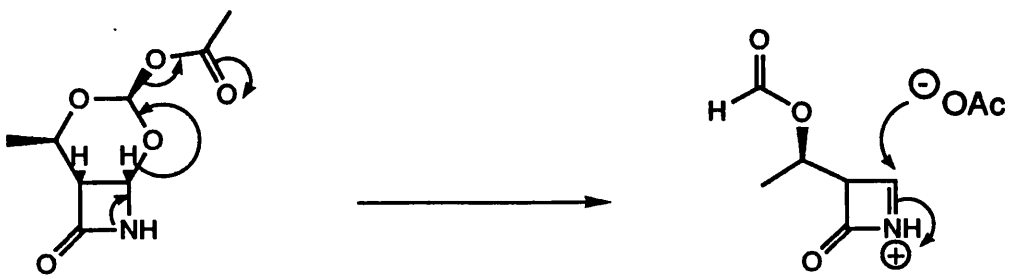
(Scheme 3.39)

The synthesis of a key intermediate of the 1-β-methylcarbapenem (204) was carried out by Terashima et al.,[83] successfully utilising the olefin/isocyanate method. This synthetic antibiotic shows excellent chemical and metabolic stability as well as a broad spectrum of activity[84] and so was an important synthetic target. The 2,4-cis-disubstituted 4H-1,3-dioxin derivative (200), stereoselectively obtained from (R)-3-hydroxybutyrate (199), reacted with CSI to afford, after reduction, the β-lactam (201) as a 98:2 mixture of two diastereoisomers, one recrystallisation giving pure product. After debenzylation and oxidation to the ketone (202), Baeyer-Villiger oxidation produced the 4-(acetoxy)-β-lactam (203) as a 10:1 mixture of the desired product and the C-4 epimer. (Scheme 3.40)



(Scheme 3.40)

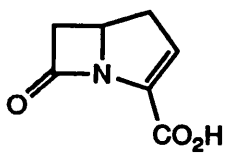
The mechanism of this unusual rearrangement involves cleavage of the acetyl moiety, giving the acyl-iminium cation, (205) which was converted to the 4-(acetoxy)-β-lactam by in situ trapping with acetic acid, resulting in predominantly the trans isomer (Scheme 3.41).



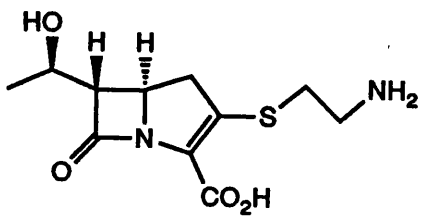
(205)

(Scheme 3.41)

Southgate et al.[74] used the CSI/diene approach in the synthesis of biologically active olivanic acid (206) analogues, a carbapenem Streptomycete family of which Thienamycin (194) is a member (Scheme 3.42).



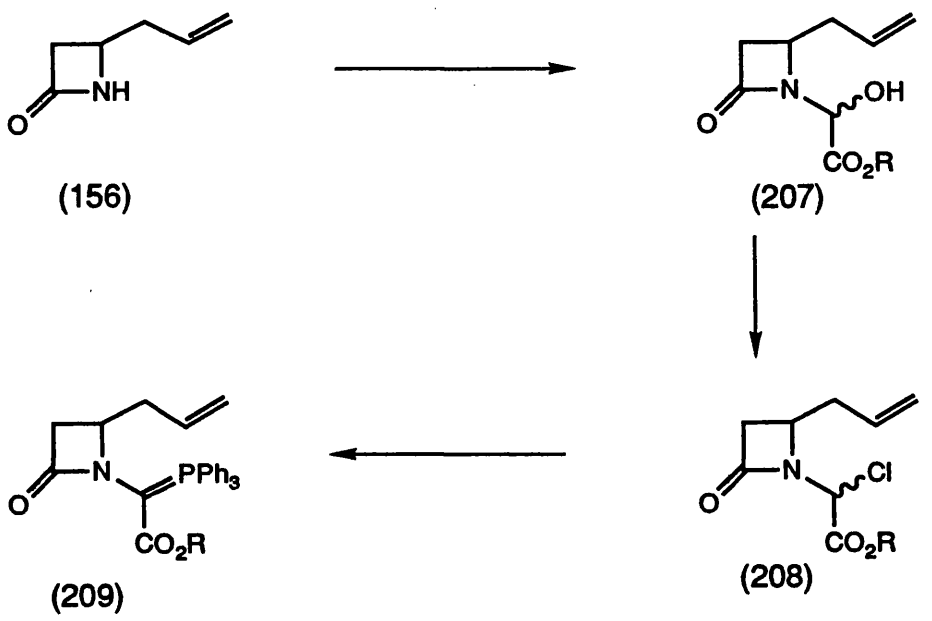
(206)



(194)

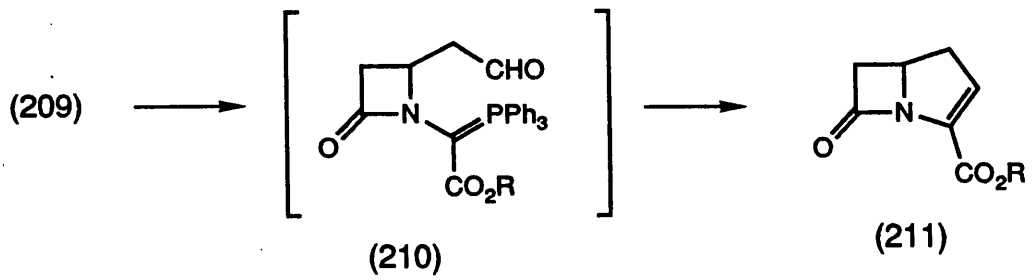
(Scheme 3.42)

The 4-homo allyl-azetidinone (156) was prepared from penta-1,4-diene and CSI and transformed into the phosphorane (209) by conversion of the hydroxy-ester diastereomeric mixture (207), into the corresponding chlorides (208), and then treatment with triphenylphosphine (Scheme 3.43).



(Scheme 3.43)

Selective ozonolysis of the terminal double bond was achieved in the presence of trifluoroacetic acid. The resultant salt decomposed to the desired phosphorane (210) on partitioning between ethylacetate and aqueous $NaHCO_3$, and spontaneously cyclised to give the ester of olivanic acid (211) (Scheme 3.44).



(Scheme 3.44)

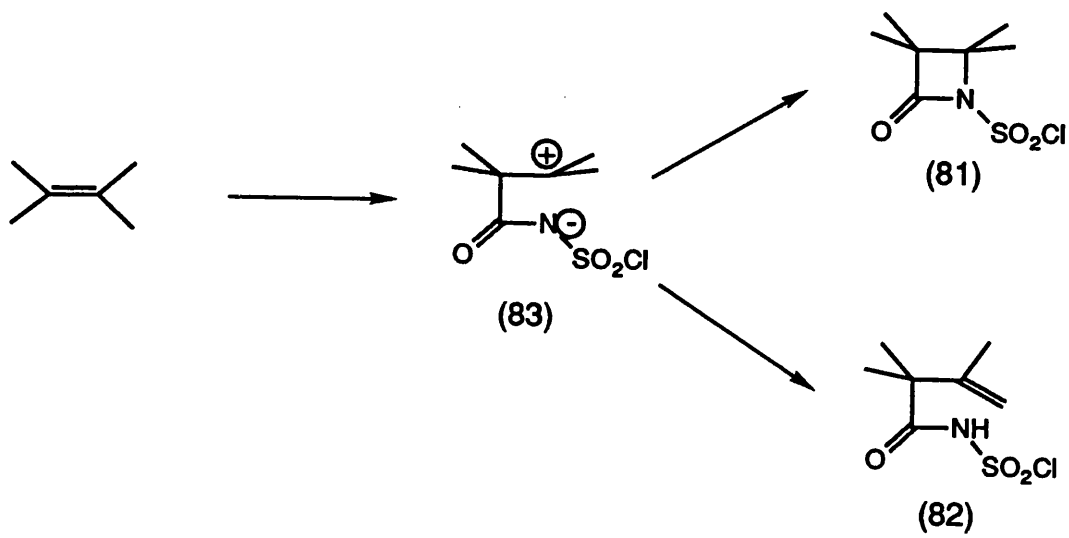
The deprotection of the esters to the acid, needed for biological evaluation, was achieved using an electrochemical procedure[85] developed specifically for the deprotection of the carboxylate group in the naturally occurring series.

3.4 Mechanism of Olefin/Isocyanate [2+2] Cycloaddition

Two differing mechanistic interpretations have been offered to explain the kinetics, stereochemical course and products of the reaction between functionalised olefins and isocyanates.

3.4.1 The Zwitterionic Pathway

This was proposed by Graf[7] and involves the initial formation of a 1,4-dipolar (zwitterionic) intermediate (83). This intermediate can stabilise itself in one of two ways - ring closure to form the β-lactam (81) or proton shift, giving the unsaturated amide (82) (Scheme 3.45). It is also possible that the amide could be formed directly in an 'ene' type reaction, and if this were true then this implies that the zwitterionic intermediate selectively collapses to the β-lactam, with the complete exclusion of any amide formation.



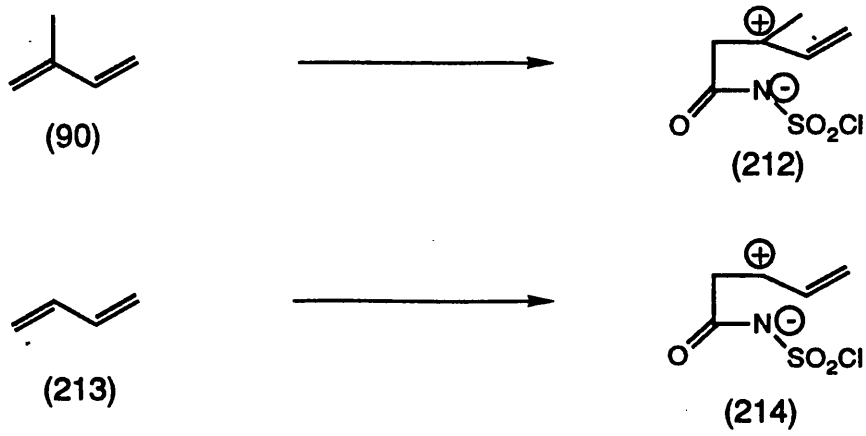
(Scheme 3.45)

Graf has reported IR studies indicating that during the course of the olefin/isocyanate cycloaddition the relative proportions of amide to β-lactam remains essentially constant.[8(a)] This is consistent with a mechanism in which the amide and the β-lactam are formed independently and simultaneously from a common intermediate, and not by rearrangement of an initially formed β-lactam. This, however, does not rule out the possibility of two different mechanisms occurring simultaneously, and leading to two different products.

One of the most significant pieces of evidence in favour of the dipolar intermediate is the enhancement in the rate of the reaction as the polarity of the solvent increases. Clauss[86] has studied the effects of solvent polarity in this reaction and found that the rate in the polar nitromethane (0.5-1.0 $1.mol^{-1}.sec^{-1}$) was markedly faster than the rate in the non-polar n-hexane (3-5 x 10^{-5} $1.mol^{-1}.sec^{-1}$). It is clear that a polar intermediate will be stabilised by a polar solvent, and the result of this solvation will be a lowering of the activation energy, and hence an increase in the rate. No such stabilisation is possible in a non-polar solvent, and so the rate in this case is ca. 100,000 times slower.

The structure of the olefin also determines the rate of the reaction,[86] and this is directly related to the ability of the olefin to stabilise a positive charge in the Graf[7]-type zwitterionic intermediate. Clauss[86] found that isoprene (90) reacted much faster (1.2-1.5 x 10^{-2} $1.mol.sec^{-1}$) than butadiene (213) (2-2.5 x 10^{-5} $1.mol^{-1}.sec^{-1}$) due to the greater stability of the carbenium ion in the isoprene adduct (212) compared to that of the butadiene adduct (214)

(Scheme 3.46).

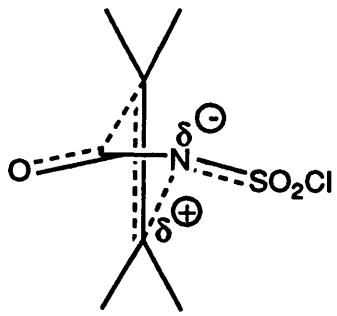


(Scheme 3.46)

Graf[7,8(a)] too has reported qualitative observations on the relationship between olefin structure and reaction rates. It was found that olefins having at least one of the doubly bonded carbons attached to two substituents reacted very rapidly with CSI, the reactions being strongly exothermic and virtually complete within seconds to several minutes. In contrast, α-olefins, $RCH=CH_2$, and olefins having a non-terminal double bond, R'CH=CHR reacted much more slowly with CSI.[7,8(a)]

Electron-withdrawing substituents on the olefin were found to reduce the rate of the reaction, due simply to the reduced nucleophilicity of the double bond. This is in keeping with a reaction which involves initial nucleophilic attack on an electrophilic species.

For the Graf postulate to be true, it is essential that the lifetime of the zwitterionic intermediate is significantly less than the rotational lifetime around the newly formed C-C, since studies[9,17] have shown that the geometry of the olefin is predictably transferred to the β-lactam. It may well be that the lifetime of the intermediate dipolar species is longer-lived than the rotational time around C-C, but the rotational freedom is hindered by strong ion-ion interactions, due to the proximity of the anionic and cationic centres to each other (83) (Scheme 3.47).

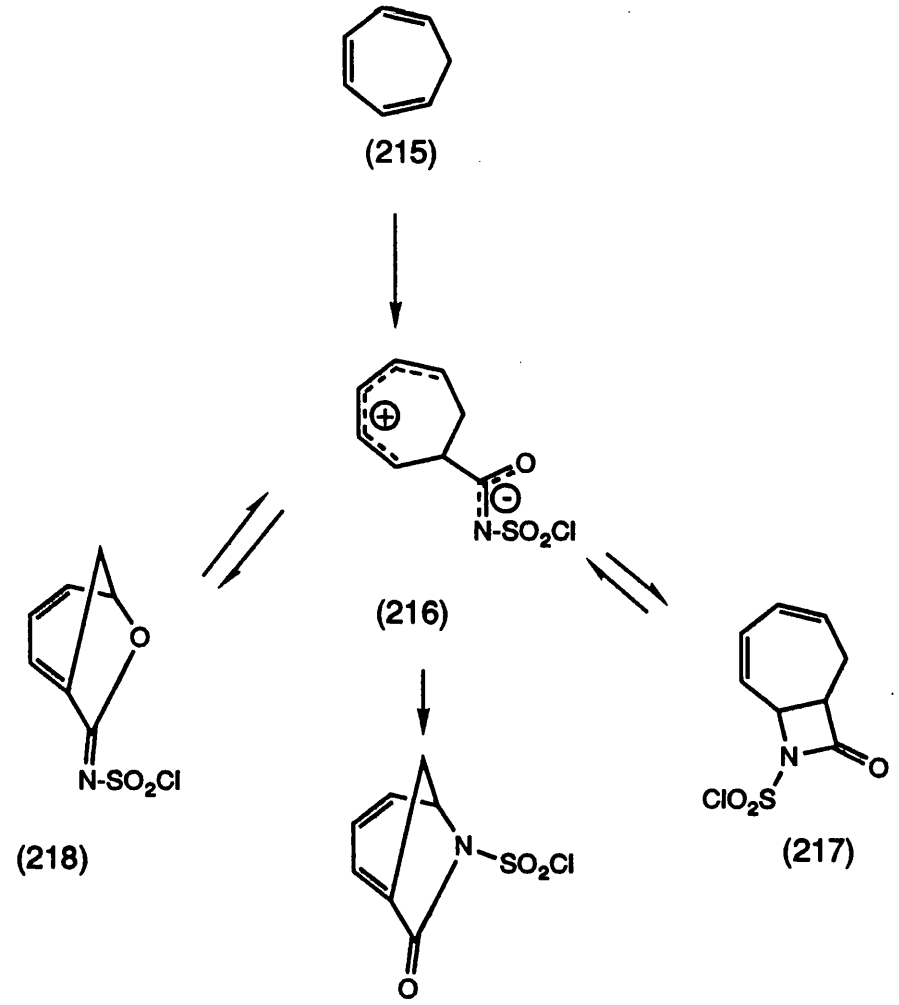


(83)

(Scheme 3.47)

Malpass[87,88] has reported evidence for a stepwise, dipolar mechanism in operation during the olefin/CSI addition. Equimolar quantities of cycloheptatriene (215) and CSI reacted together very slowly in CCl_4 over several days, the first formed product being the imino lactone (218) and, over a period of a further few days, the N-chlorosulphonyl lactam (219). This suggested initial formation of the

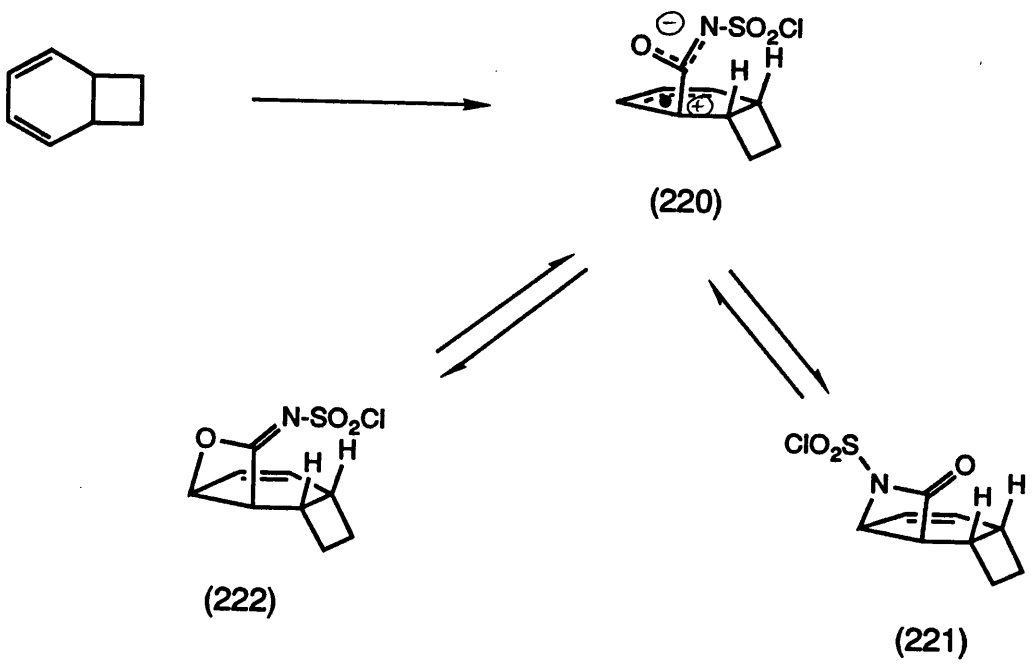
kinetic iminolactone (218), followed by ring cleavage to the dipolar intermediate (216), which then undergoes irreversible ring closure to the thermodynamic lactam (219) (Scheme 3.48).



(Scheme 3.48)

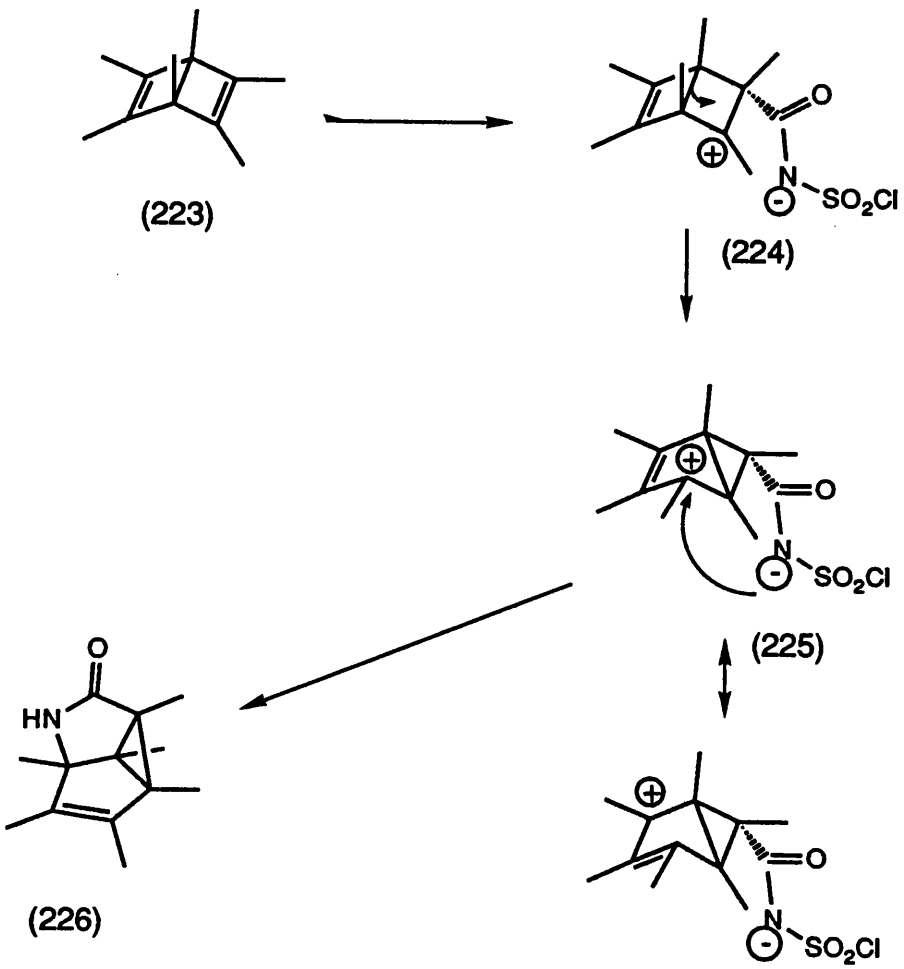
Also, Malpass and Tweedle[88] have reported direct evidence for the involvement of a dipolar intermediate in the olefin/CSI reaction. The products obtained clearly arose by a similar sequence of events previously described for other diene systems,[87] but in this case they were able to demonstrate the intermediacy of a dipolar species (220) by converting a sample of isolated iminolactone (222) into the β-lactam (221), clearly showing that these two products were derived from a

common intermediate (Scheme 3.49).



(Scheme 3.49)

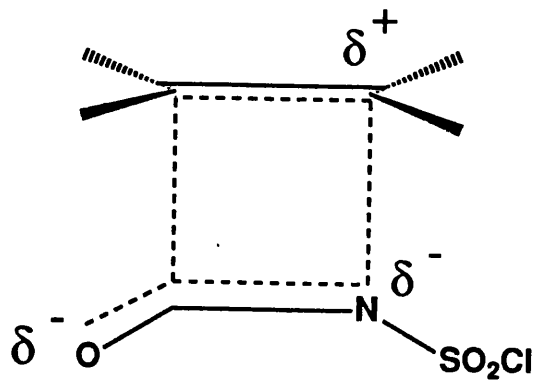
In an investigation into the addition of electrophiles to hexamethyldewarbenzene (223), Paquette and Krow[89] found that addition of CSI resulted in the isolation of, after hydrolysis, the tricyclic lactam (226), clearly originating from the dipolar species (224) via the skeletally rearranged species (225) (Scheme 3.50).



(Scheme 3.50)

3.4.2 The Concerted Pathway

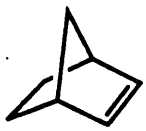
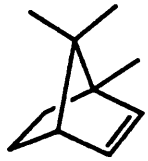
The alternative to the zwitterionic mechanism is the near concerted [2+2] cycloadditive mechanism favoured by Moriconi.[15,91] In this mechanism, the olefin and CSI form the β-lactam via the transition state (227) (Scheme 3.51).

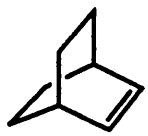


(227)

(Scheme 3.51)

Moriconi and Crawford[92] reacted CSI with a range of rearrangement-prone olefins, reasoning that the existence of a true dipolar species would result in the formation of olefins that had undergone skeletal rearrangement.



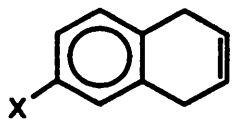
(Scheme 3.52)

With all of the norbornyl systems investigated (Scheme 3.52), a single exo-adduct was obtained, with no evidence of skeletal rearrangement. From this result, they postulated that a true dipolar species could not be present. Since a totally concerted pathway was disallowed by the Woodward Hoffmann rules[90] they postulated a near concerted mechanism, proceeding via a π-complex between the olefin and CSI. This then collapses to give a closely associated dipolar species, in which the extent of C-N bond formation is greater than in the Graf intermediate. That skeletal rearrangement is not observed means that collapse of this dipolar species is faster than skeletal rearrangement.

A near concerted mechanism is a convenient explanation for the

stereochemical fidelity of the process: the geometry of the olefin, be it cis or trans, is never lost, since there is never a true C-C bond round which bond rotation can occur.

In an interesting study, Mazzochi and Harrison[93] chose to look at the reaction between CSI and the 6-substituted dihydronaphthalene system (228), since extensive molecular orbital calculations[94] had indicated that, for a given substituent, the orbital coefficients on the alkene carbons were essentially identical (Scheme 3.53).



(228)

(Scheme 3.53)

If the reaction is under the control of a HOMO-LUMO interaction, as would be the case in a near concerted mechanism, then an equal distribution of the two possible regioisomeric addition products would be expected. If, on the other hand, the mechanism proceeds via a dipolar transition state, then the ratio of regioisomers formed should parallel the relative stabilities of the preceding carbenium ions.

The systems investigated were those with X = H, CH_3, OCH_3, Cl and NO_2, for a comparison of any possible substituent effects. For these compounds, the syn : anti ratio varied from 77:23 to 45:55, this latter figure being the closest to the expected 1:1 ratio of a near concerted mechanism. Neither did the evidence point to a dipolar mechanism. It was known that homopara carbenium ions (resulting from syn addition) show a rate enhancement of ca. 230 over homometa carbenium ions, but the largest k_{syn} to k_{anti} was found to be only 3.3 : 1. This result showed that the mechanism could not be interpreted simply in terms of a dipolar species.

Thus it seems likely that neither a near concerted or stepwise process is in operation, and indeed Mazzochi and Harrison[93] propose the initial formation of a π-complex, similar to that proposed by Moriconi.[92] The reactivity of this complex is determined by the olefin HOMO energy, followed by collapse to σ-complex in a product distribution step.

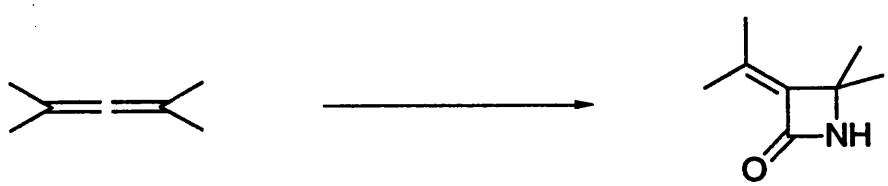
There is a vast amount of evidence that points to the existence of both mechanistic pathways, and, as suggested by Rassmussen and Hassner,[95] it seems likely that the particular mechanistic pathway followed depends on the nature of the olefin, with a spectrum of mechanisms possible, from the stepwise to the near concerted. Thus, polarisable alkenes, able to stabilise a positive charge, will tend to react via a stepwise mechanism, whereas olefins able to offer only poor stabilisation to carbenium ions will tend to go through a more concerted pathway.

Chapter 4

β-Lactams From (Allenylmethyl)silanes

4.1 Synthesis of Asparenomycin Precursors

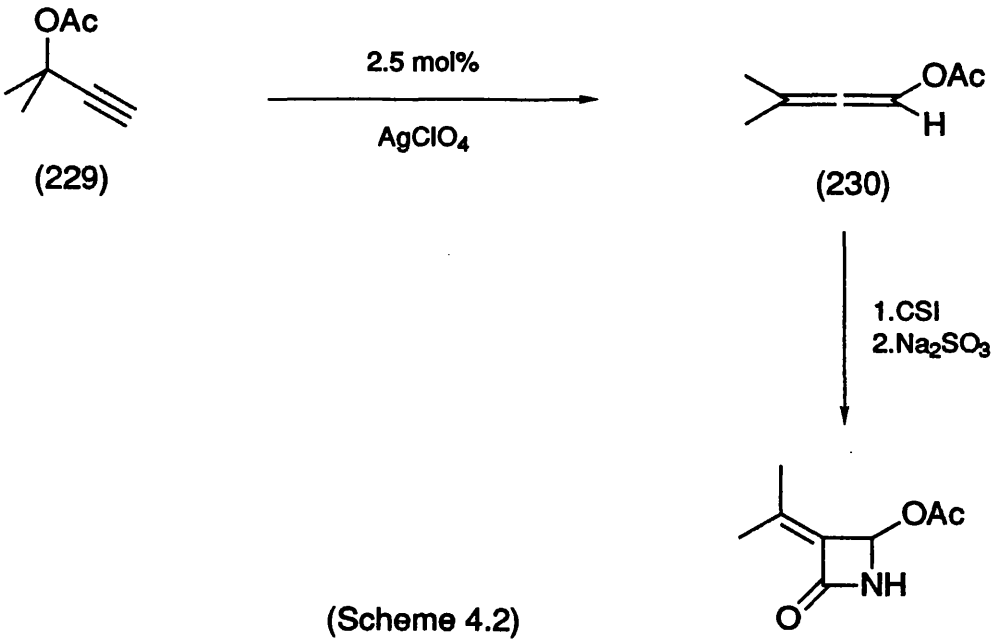
The reaction between an allene and CSI generates a β-lactam with a C-3 alkylidene side chain (Scheme 4.1). The medicinal value of such β-lactams is well established, [96] many of them possessing β-lactamase activity *in vivo*. The biological activity of such β-lactams, coupled with the recent surge in the number of papers published on this subject[97] establishes them as important synthetic targets.



(Scheme 4.1)

The synthesis of highly functionalised β-lactams from allenes and CSI has been investigated by Buynak and co-workers. [98,101,102, 103] They were able to construct versatile intermediates suitable for further synthetic elaboration, by an extension of the approach initially utilised by Morriconi and Kelly. [62] Use of allenyl acetate

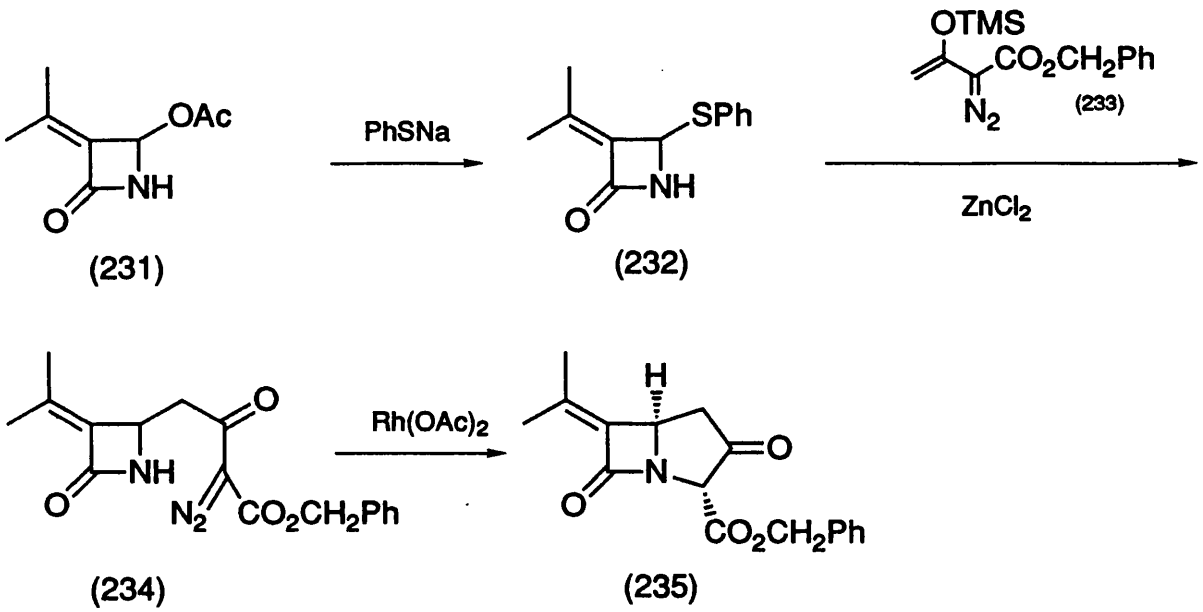
(230), obtained by a silver-catalysed rearrangement of propargylic acetates (229), [99] led directly to the 4-acetoxy-β-lactam (231) (Scheme 4.2).



(229) (230) (231)

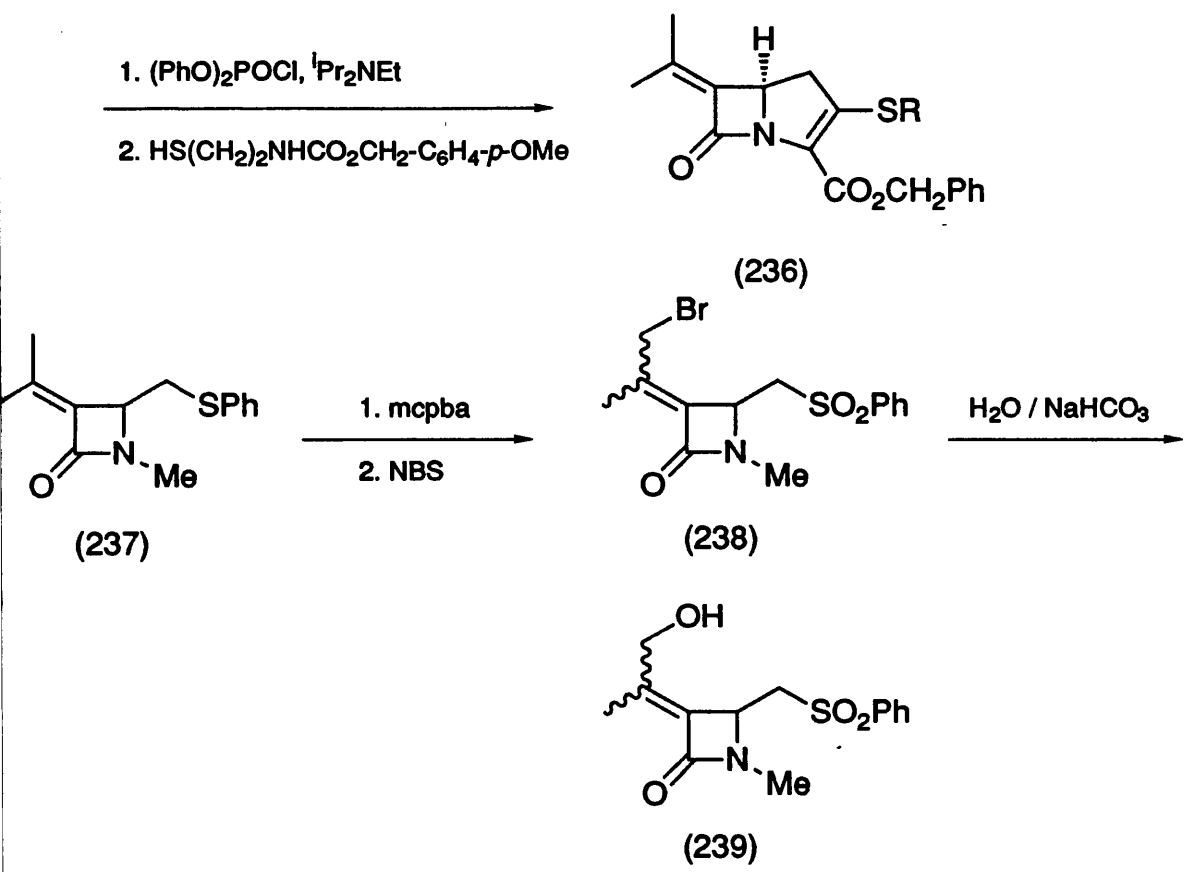
(Scheme 4.2)

Such 4-acetoxy-β-lactams are well known for their ability to undergo substitution reactions at C-4, the acetoxy group being readily replaced by a variety of nucleophiles. [71] Treatment of the β-lactam (232), obtained from (231) by treatment with NaSPh, with the trimethylsilyl enol ether[100] (233), resulted in the formation of the useful carbapenem precursor (234). Rhodium acetate-mediated cyclisation of (234) furnished the bicyclic carbapenem (235), which was further elaborated to the advanced bicyclic β-lactam (236). Oxidation of the N-methyl sulphide (237) was followed by allylic bromination with NBS, producing the (E) and (Z) allylic bromides (238) as a 3:1 mixture. The bromides were hydrolysed to the alcohols (239), which possess the side chain functionality of the naturally occurring carbapenem β-lactamase inhibitors, the Asparenomycins (Scheme 4.3).



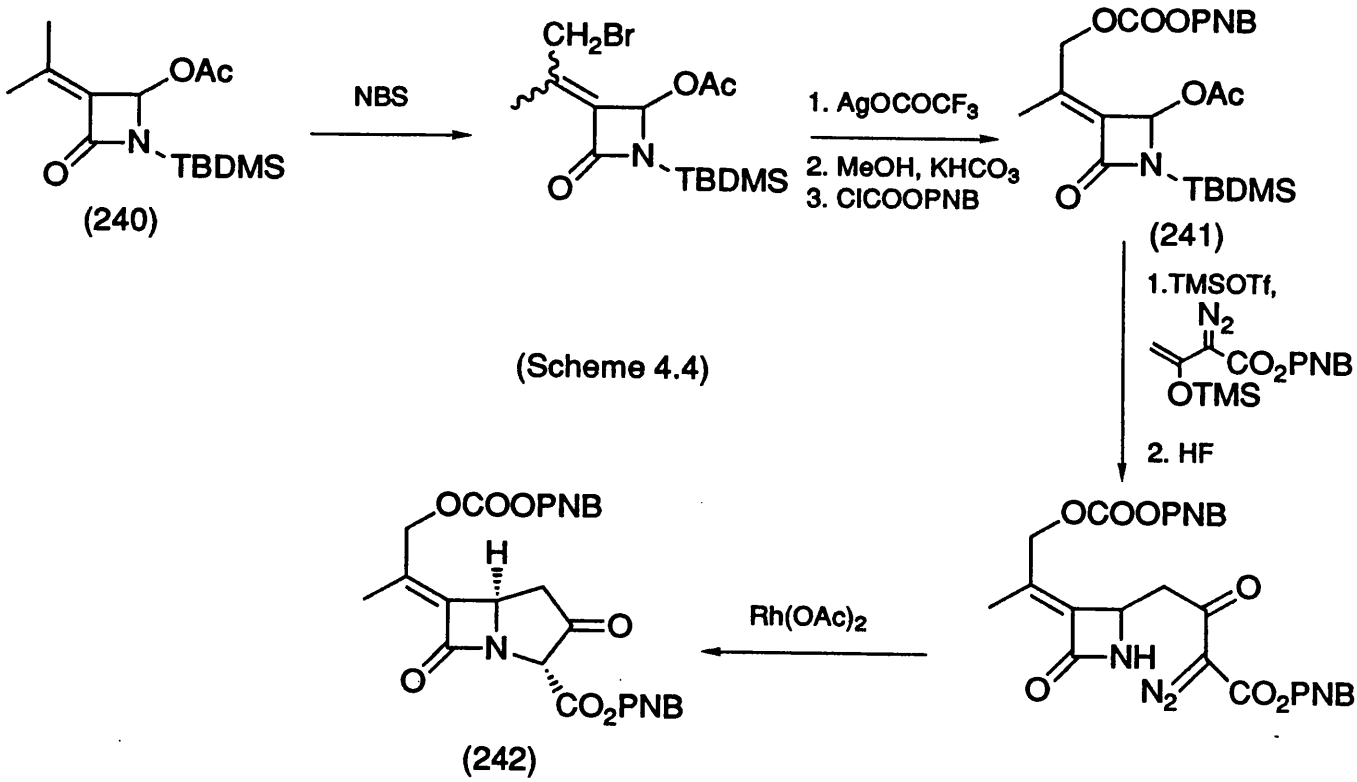
(231) (232) (234) (235)

(Scheme 4.3)


1. (PhO)2POCl, iPr2NEt
2. HS(CH2)2NHCO2CH2-C6H4-p-OMe
H
SR
N
O
CO2CH2Ph
(236)
SPh
N
Me
O
(237)
1. mcpba
2. NBS
Br
SO2Ph
N
Me
O
(238)
H2O / NaHCO3
OH
SO2Ph
N
Me
O
(239)

(Scheme 4.3)

Buynak and co-workers have applied their functionalised allene methodology to the formal synthesis of a wide range of functionalised β-lactams, including Carpetimycin A, [101] Thienamycin [102] and Asparenomycin C. [103] In the last example, the synthesis was along the lines of their earlier communication, that is allylic functionalisation of β-lactam (240), displacement of the 4-acetoxy substituent in (241) with a carbon nucleophile, and Rh-mediated cyclisation to (242) (Scheme 4.4).



(Scheme 4.4)

The complexity of the β-lactams that can be readily constructed by the use of functionalised allenes, as shown through the work of Buynak, led us to consider the application of (allenylmethyl)silanes to the synthesis of carbapenem precursors. There were several reasons for this approach:

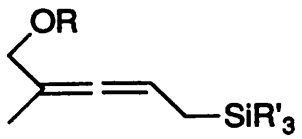
(i) (allenylmethyl)silanes are readily constructed from suitable propargylic compounds.

(ii) the silicon atom is suitably positioned to control the regiochemistry of the cycloaddition process through the β-effect.[117]

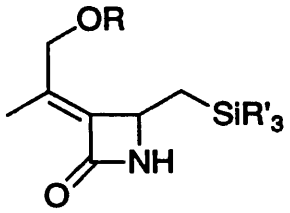
(iii) with the regiochemistry thus controlled, the resulting β-lactam will possess the correct substitution for elaboration to carbapenem antibiotics.

(iv) finally, the substitution on the silicon atom can be varied to allow the possibility of oxidative cleavage to a 4-(hydroxymethyl) β-lactam.

Since work on side-chain functionalisation of C_3-alkylidene β-lactams had been investigated,[98] it was decided to construct an (allenylmethyl)silane that would lead directly to a β-lactam with the desired side-chain functionality already established. To this end we decided to synthesise allene (243), since cycloaddition of this would yield the β-lactam (244), already possessing the C-3 side chain of the Asparenomycins.



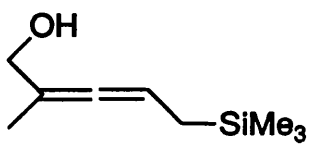
(243)



(244)

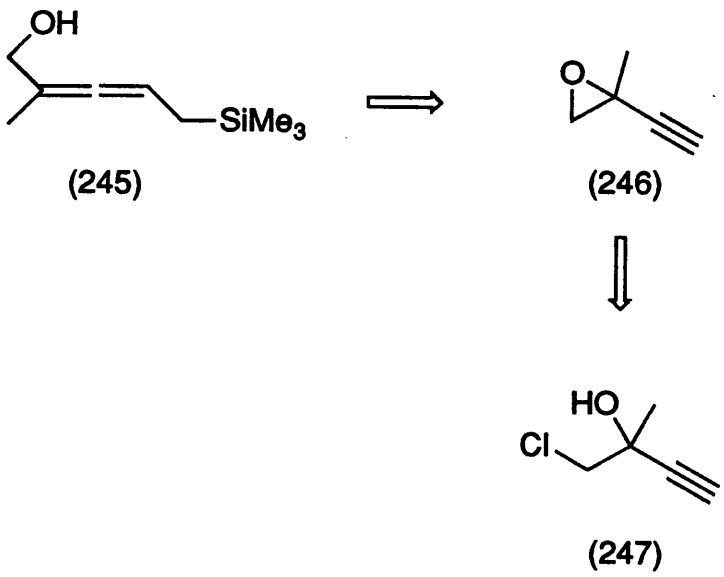
We were confident that silicon would indeed be able to control the regiochemistry of the cycloaddition. The work of Dunoguès and co-workers [75] on the synthesis of nitriles from allylsilanes and CSI had revealed regio-predictable products, explained by intermediates stabilised by the β-effect.[117]

Initially, efforts were concentrated on the construction of an allene that would yield the requisite side-chain functionality. It was decided that attempts to perform oxidative cleavage on a suitably substituted silyl moiety would best be addressed after the construction of the allene, and its cycloaddition to form a β-lactam, had been achieved. Thus, the trimethylsilyl allene (245) was seen as the initial target for synthesis.



(245)

Retrosynthetically, it can be seen that allene (245) can be constructed from the propargylic epoxide (246), itself the result of cyclisation of the chlorohydrin (247) (Scheme 4.5).



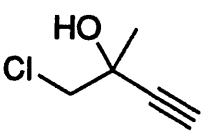
(245) (246) (247)

(Scheme 4.5)

Synthesis of the halohydrin [104] (247) was achieved by initial formation of ethylmagnesium bromide, followed by a Grignard exchange process, achieved by adding the pre-formed EtMgBr/THF solution to THF saturated with acetylene gas. It was found that the addition of the EtMgBr must be over 1h, due to the fact that rapid addition results in the formation of the bis-Grignard species (248), which is shown by the presence of a white gelatinous material deposited on the bottom of the flask. The formation of ethynylmagnesium bromide is indicated by the presence of a deep red colouration.

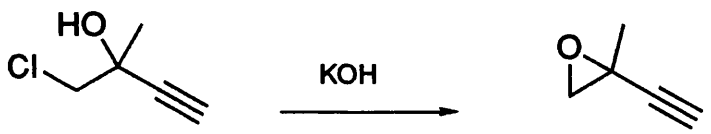
(248)

The yield of the process is maximised by the allocation of a further 1h after addition of EtMgBr, to allow the acetylenic Grignard species time to form, since an accurate stoichiometry of acetylene was not possible. It was essential that the reaction was maintained at low temperature during this time, due to the instability of the acetylenic Grignard reagent. To this solution was added chloroacetone, forming the magnesium salt of the required halohydrin .Only the reactive, highly electrophilic carbonyl carbon was attacked by the acetylenic anion, with no indication of attack at the chlorine bearing carbon. Careful addition of NH_4Cl produces the free alcohol (247), which is distilled to purity in an excellent overall yield of 64% for the three steps.



(247)

Epoxide (246), the required precursor to the allene (245) was obtained by base-mediated cyclisation.[104]



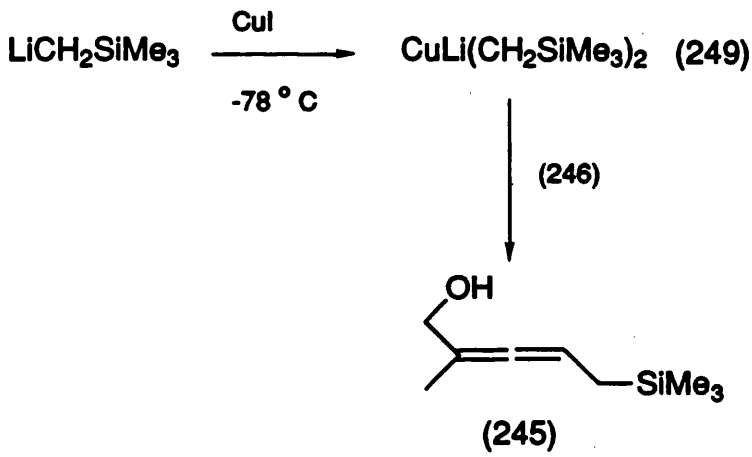
(247) (246)

The choice of base used to effect this cyclisation was not as simple as it first appeared. The problem lies not in finding a base strong enough to remove the alcohol proton, but in finding one which will not cause problems in the subsequent purification stage of the process. The epoxide (246) was known to be highly volatile, and so the choice of solvent in which to carry out the reaction was ether, since it is the lowest boiling of the commonly used organic solvents. The problem with most organic bases is the fact that the by products formed after deprotonation would be very difficult to separate from the reaction mixture. It was necessary to use an inorganic base that was insoluble in ether, and used in vast excess as a suspension. The excess base could then be simply removed in an aqueous washing stage during the work-up procedure. Such a base was KOH, and it did indeed furnish the epoxide (246) in acceptable yield (51%) from the chlorohydrin (247).

A further problem in the cyclisation of the epoxide was the question of intermolecular reaction. This possibility was kept to a

minimum by using fairly dilute (1M) conditions. This route to the epoxide, although subject to the constraints detailed above, is probably the most convenient route for the preparation of this compound when questions of cost of reagents and synthesis length are addressed.

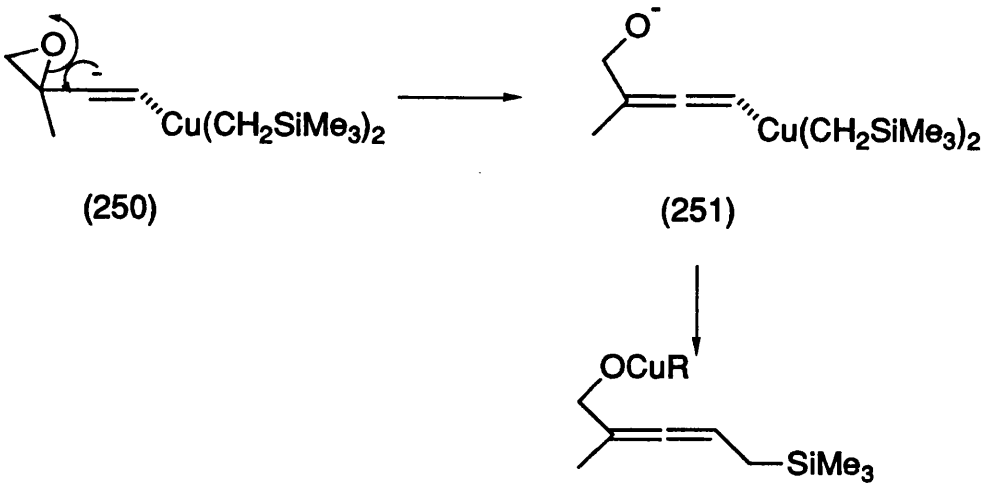
The epoxide (246) undergoes an S_N2' reaction to form the hydroxy(allenylmethyl)silane (245). Formation of the organocuprate (249) from lithio(methyltrimethylsilane) and CuI at -78°C, followed by addition of the epoxide (246), furnished the allene[105] (245) in 51% yield (Scheme 4.6).



(Scheme 4.6)

The mechanism of such organocuprate additions to propargylic substrates is still the subject of much discussion, but it has been suggested [106] that the first step involves electron transfer from the organocuprate (249) to the acetylenic moiety, forming the anionic intermediate (250). Elimination of the leaving group, in this case the opening of the epoxide ring, would generate a new organocuprate species, tentatively assigned the structure (251). The final step is

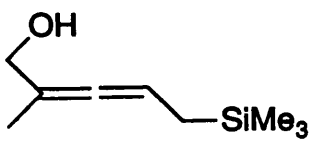
the transfer of the alkylsilyl moiety, as a radical, to the copper-bearing carbon of intermediate (251) (Scheme 4.7).



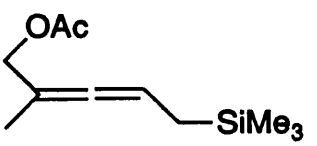
(250) (251)

(Scheme 4.7)

Treatment of the reaction mixture with NH_4Cl generates the free hydroxyallene (245), thus completing the synthesis of the functionalised allene. However, before the cycloaddition step can be carried out, the hydroxyl group must be protected to avoid reaction with the electrophilic CSI.[59] The first choice for protection of the hydroxyl group was as the acetate (252).

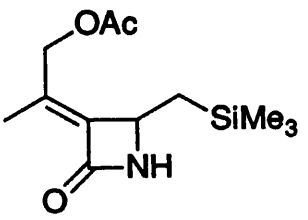


(245)



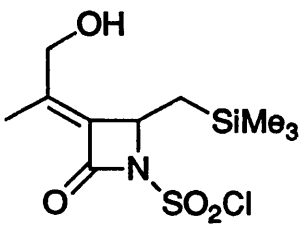
(252)

Protection proceeded well using $Ac_2O/DMAP/Et_3N$, [107] but subsequent reaction with CSI showed this to be an unsuitable means of protection, since hydrolysis of the protecting group *in situ* resulted in no isolation of the desired β-lactam (253). Subsequently, conditions were found (see Chapter 7) for the isolation of (253), although in low yield.

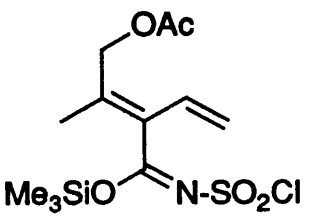


(253)

At first it was thought that the basic nature of the Na_2SO_3 reduction process (pH 11) was responsible for the hydrolysis, but this did not explain the total lack of β-lactam product, since hydrolysis of β-lactam (253) should have furnished the unprotected β-lactam (254), but this was found not to be the case. Also, no recovery of the imidate (255) was seen.

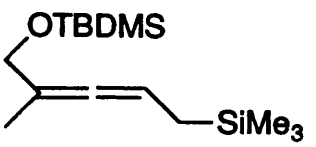


(254)



(255)

Protection as the TBDMS ether was thought to be a better solution, since this would be a more robust form of protection and subsequent removal would proceed readily with no rupture of the β-lactam ring. Using TBDMSCl/DMAP/Et_3N, [108] the allene (256) was obtained in a modest 61 % yield.

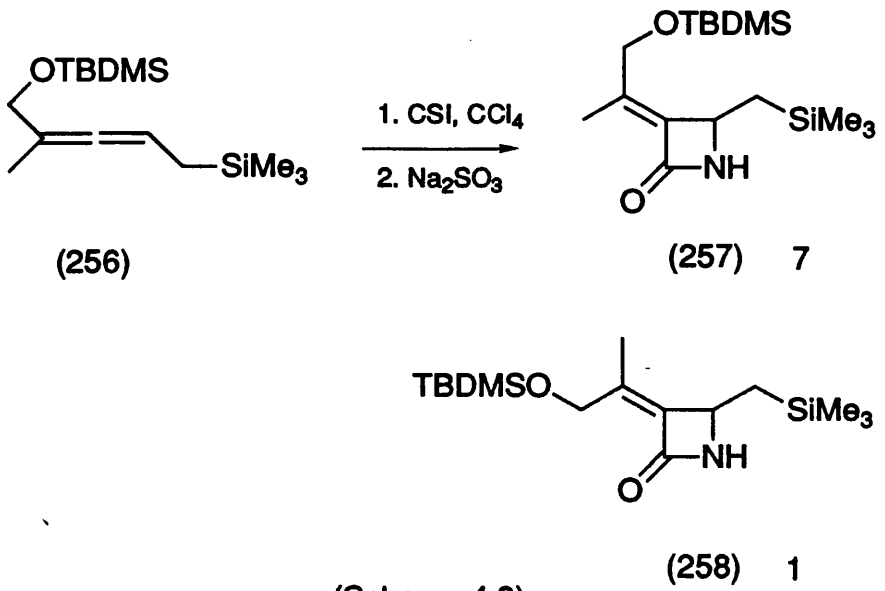


(256)

It was later found that use of the highly electrophilic silylating agent TBDMSOTf [109] gave yields of allene (256) in excess of 90 %.

With a suitably protected allene precursor in hand, the next step involved the cycloaddition reaction with CSI to furnish the desired Asparenomycin precursor. Due to the extreme reactivity of CSI, reactions of this type are traditionally carried out in inert solvents, and in this case the conditions of Graf,[58] using CCl_4, were followed. The course of the reaction is conveniently monitored by ^1H NMR spectroscopy, by observing the disappearance of the allene proton multiplet at δ 5.0 ppm, and the appearance of the C-4 proton of the

product β-lactam at δ 4.1 ppm. On complete disappearance of the allene proton, the reaction was quenched with Na_2SO_3 to effect reduction of the N-chlorosulphonyl group to the N-protio. Using the TBDMS-protected allene (256), a β-lactam was obtained as a mixture of geometric isomers (257) and (258), in 31% yield (Scheme 4.8).



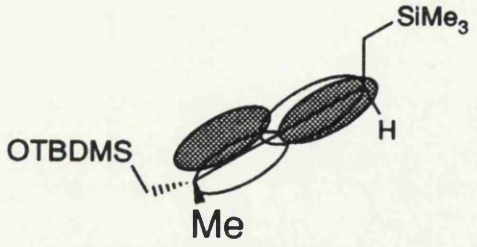
(256)

(257) 7

(258) 1

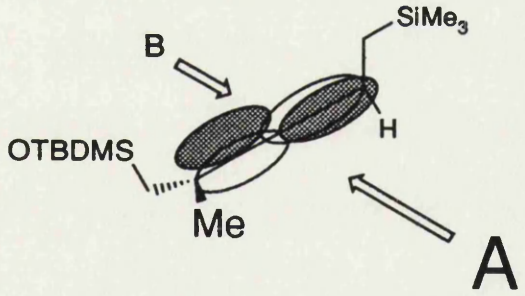
(Scheme 4.8)

The β-lactam with the correct side chain geometry was found to be the major isomer in the 7:1 mixture obtained. The selectivity of the cycloaddition process can be explained when the nature of the allene cumulene double bond system is considered. The diene component of an allene has the π-orbitals in an orthogonal arrangement to each other (256).



(256)

As shown below, the π-orbitals of the allylsilane moiety of allene (256) are peri-planar with the substituents at the terminus of the adjacent double bond. This means that the approach geometry of CSI is also along the plane of those substituents (Scheme 4.9).

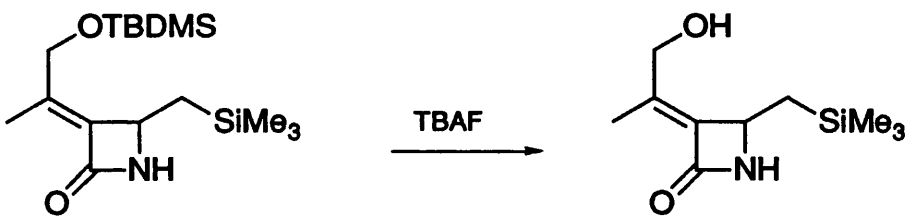


(Scheme 4.9)

Approach along pathway A will be the less sterically hindered, this being the side of the smaller sustituent, and so will be favoured over the other trajectory, B, leading to the products (257) and (258) in the observed ratios. The two isomeric β-lactams were found to be

separable by flash column chromatography, although some material was lost due to incomplete separation in some of the fractions.

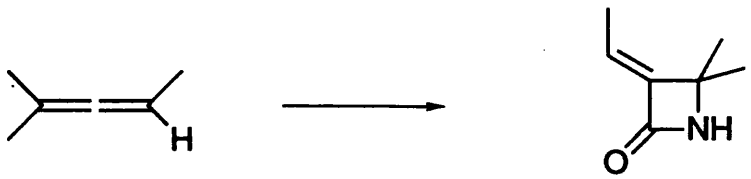
The final stage in the formal production of the Asparenomycin side chain functionality was the deprotection of the hydroxyl group. The first attempt was with KF/CH_3CN, but this returned only starting material. Success was achieved using a 1M solution of TBAF[110] in THF, furnishing the β-lactam (259) in 90% yield (Scheme 4.10).



(257) (259)

(Scheme 4.10)

Thus, construction of a useful carbapenem precursor had been achieved between the reaction of a functionalised allene and CSI. Silicon, as expected, controlled the regiochemistry of the cycloaddition process. This contrasts with the regiochemistry shown for the allene (260), used by Moriconi[62(b)], the product (261) being determined by the selection of a tertiary carbonium ion over a secondary carbonium ion.

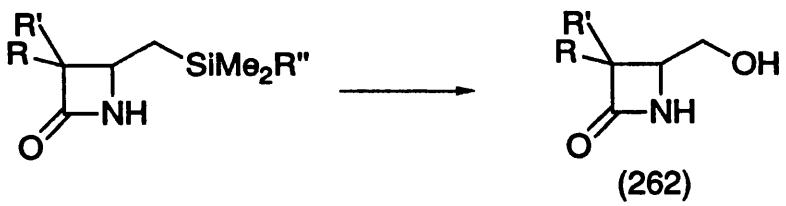


(260) (261)

In addition, the desired geometrical isomer (257) of β-lactam was obtained as the major product through control imposed by the allene structure.

4.2 Oxidative cleavage studies

A logical synthetic extension of this route was to incorporate a silyl moiety that would permit oxidative cleavage of the C-Si bond to the synthetically useful C-O bond (Scheme 4.11).



(262)

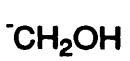
(Scheme 4.11)

Such a 4-hydroxymethyl-β-lactam (262) would be capable of elaboration to bicyclic structures by a variety of methods. It was decided to establish a method for the incorporation of such a silyl

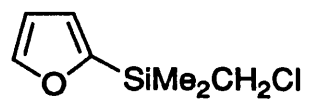
moiety, and then apply it to our synthesis of Asparenomycin precursors. The $SiMe_2O^iPr$ system, successfully utilised by Tamao and co-workers, was chosen. [111] Work in the group, by M. Monteith, [112] had already investigated the use of $SiMe_2Ph$ as a masked hydroxyl group, but overall yields were found to be low for this process. Since the yield of the CSI cycloaddition was quite low, it was important that the yields from oxidative cleavage should be as high as possible.

The chloride (263) was readily obtained from isopropanol and (chloromethyl)dimethylchlorosilane in 69% yield. This reagent would serve as the synthetic equivalent for the synthon (264). Initially, it had been intended to use the furylchloromethylsilane (265) as the masked hydroxyl equivalent, but problems of reaction in the presence of CSI (see later) prevented its use.

(263)

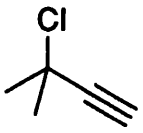


(264)

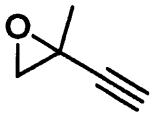


(265)

Propargylic chloride (266) was used in this model system as the allene precursor, so that one could rapidly establish the viability of the process. It was anticipated that chloride (266) would exhibit similar reactivity to epoxide (246).

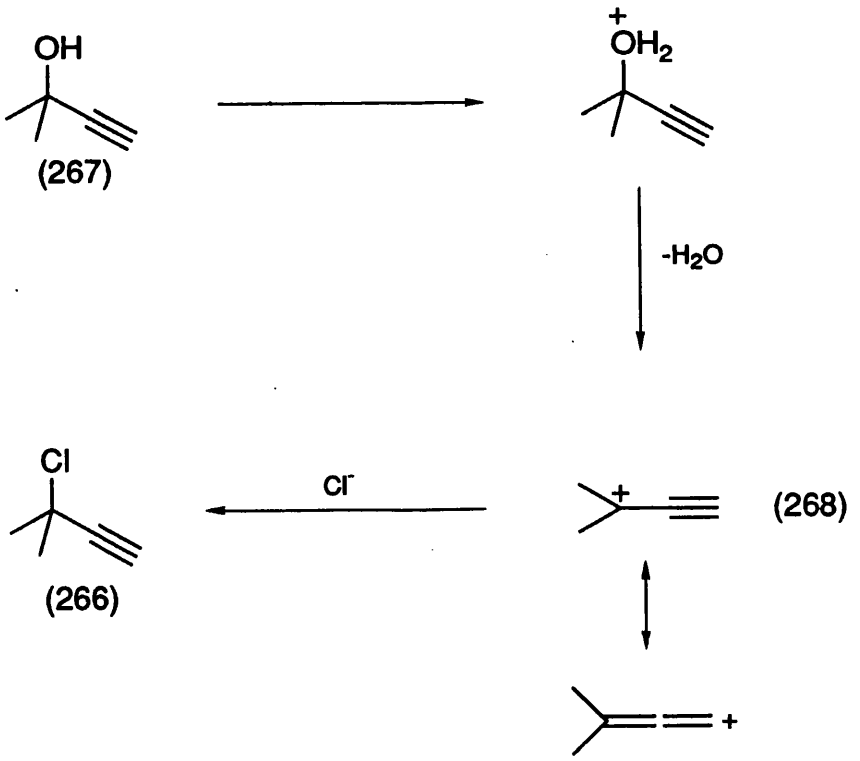


(266)



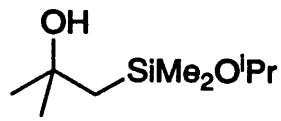
(246)

The chloride was obtained by treatment of 1,1-dimethyl propargylic alcohol (267) with conc. HCl.[113] The mechanism for the formation of (266) is thought to involve protonation of the alcohol, followed by ionisation to the stabilised cation (268) in an S_N1 process. This species is subsequently attacked by chloride ion to form the product (266) in modest yield (Scheme 4.12).

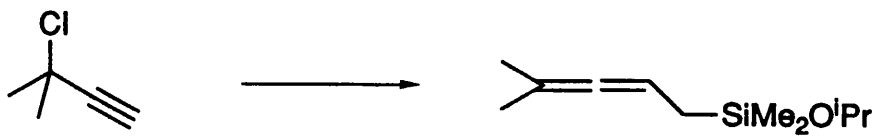


(Scheme 4.12)

The stability of chloride (263) to the conditions of the reaction, was investigated by formation of the Grignard reagent, and reaction of this with acetone, to form the alcohol (269) in 78% yield. Using the method of Itoh, Sasaki and Nishiyama [114] conjugate addition of the chloride (263), as the magnesiocuprate, to the propargylic chloride (266) was achieved, furnishing the allene (270) in 61% yield (Scheme 4.13).



(269)



(266) (270)

(Scheme 4.13)

The allene (270) could not be purified further, due to the instability of the $SiMe_2O^iPr$ moiety on silica (Kieselgel 60H) or neutral alumina. The production of allene (270) was gratifying, since doubts had been raised earlier, by Tamao and Ishida, about the difficulty of achieving such conjugate addition in enone systems.[115]

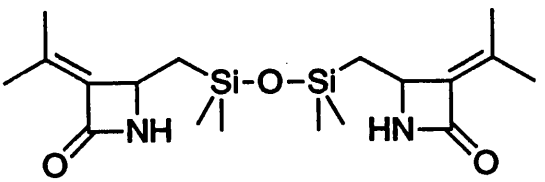
The next step was the reaction of the allene (270) with CSI to afford the β-lactam (271), possessing both C_3 alkylidene functionality and a silyl moiety ready for oxidative cleavage (Scheme 4.14).

(270) (271)

(Scheme 4.14)

Although unable to be purified further, allene (270) was pure enough to be used in the cycloaddition step with CSI. This reaction was carried out in CCl_4 at 0°C . After 6h, reduction of the N-chlorosulphonyl β-lactam was achieved using a Na_2SO_3/NH_4Cl solution buffered to pH 7.7 - 8.2 (see later). The result was a compound that was certainly a β-lactam, but one in which the ^iOPr moiety had been lost from the molecule. The IR spectrum clearly showed the presence of the β-lactam carbonyl group at 1740 cm^{-1}, as well as bands suggestive of silyl methyl groups, at 800 - 850 cm^{-1}. Examination

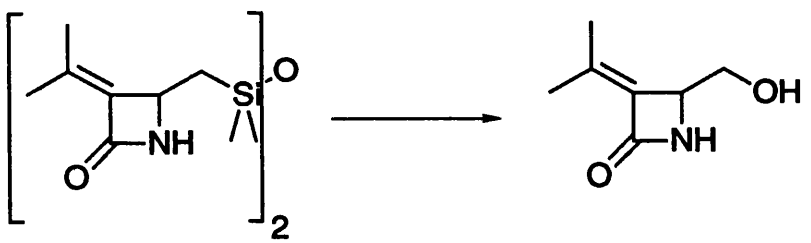
of the ^{1}H NMR spectrum (200 MHz) confirmed the loss of the ^{i}OPr group, the presence of the silyl methyls and the other proton resonances expected , δ 1.1-1.3 (2H, m, CH_2Si), δ 1.63 (3H, s, CH_3), δ 1.93 (3H, s, CH_3), δ 4.12 (1H, dd, C_4-H). This data suggested the structure (272).



(272)

The mass spectrum proved to be very complex, and it proved difficult to determine the existence of particular species. It did show that many compounds were present, possibly resulting from the formation of dimeric species such as (272) and ions produced from them.

Since a β-lactam had been produced that appeared to have silicon still bonded to an electronegative element, in this case oxygen, it was decided to attempt oxidative cleavage on this material, in the hope that the β-lactam (273) would be formed (Scheme 4.15).

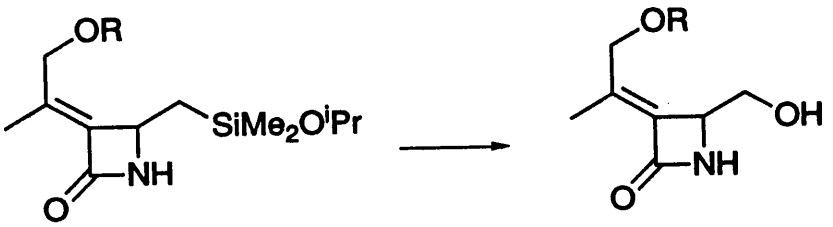


(272) (273)

(Scheme 4.15)

Oxidative cleavage, using the conditions of Tamao [116] was attempted on the β-lactam material (272) arising from the reaction of allene (270) with CSI. Examination of the product isolated revealed loss of the CH_2Si resonance at δ 1.1-1.3, appearance of signals at δ 3.6-3.8, indicative of CH_2OH, and the presence of a large broad singlet at δ 1.9-2.2, suggestive of a hydroxyl group. The signals for the cis and trans methyl groups, δ 1.93 and δ 1.63, were still present, as was the signal for the C-4 proton at δ 4.1. This was clear indication that the β-lactam ring was intact after the attempted cleavage procedure.

With the successful conjugate addition of organocuprate, containing an isopropoxysilylmoiety, to form the functionalised allene (270), and its apparent transformation into a β-lactam, the signs were encouraging for the application of this methodology to the synthesis of Asparenomycin precursor (275) by oxidative cleavage of the β-lactam (274) (Scheme 4.16).



(274) (275)

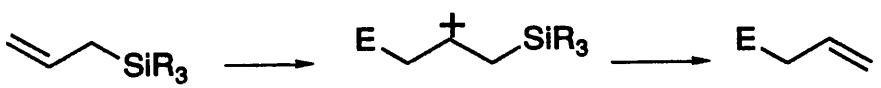
(Scheme 4.16)

Chapter 5

Synthesis of β-Lactams from Allylsilanes

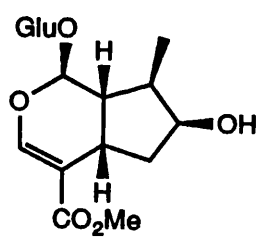
5.1 Allylsilanes

Allylsilanes (276) exhibit useful reactivity that has resulted in their widespread application in organic synthesis. [117] They undergo regiocontrolled electrophilic attack at the γ-carbon, allowing the favourable development of a β-cationic centre, made possible by the β-effect of silicon (Scheme 5.1). [117]



(276) (277)

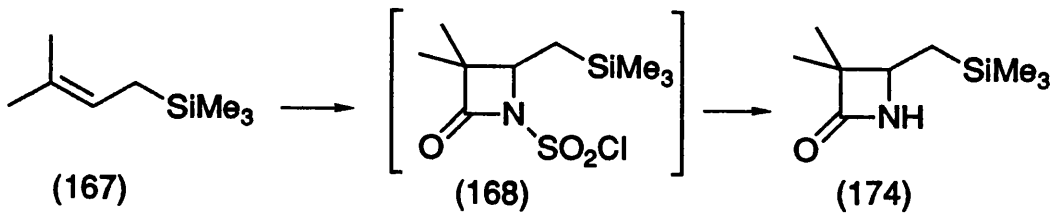
(Scheme 5.1)



(278)

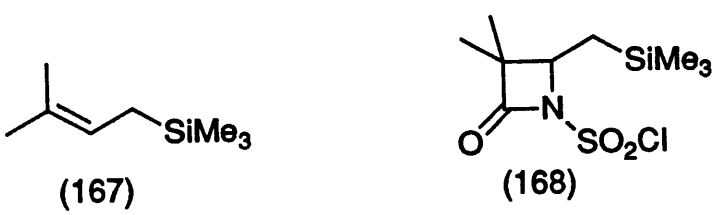
Such silyl-stabilised intermediates (277) normally undergo loss of the silyl moiety, with overall net double bond shift. Fleming has made good use of this reactivity in the synthesis of loganin (278). [118]

The use of allylsilanes as precursors of β-lactams has been investigated recently by Colvin and Monteith. [79] *In situ* reduction of the intermediate N-chlorosulphony-β-lactam (168) resulted in the facile production of N-protio-β-lactams, potential precursors to a range of carbapenem structures (Scheme 5.2).

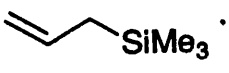


(Scheme 5.2)

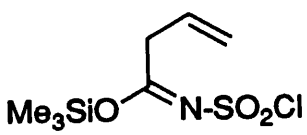
Dunoguès and co-workers[75] first observed the formation of the intermediate β-lactam (168) during the course of the reaction between allylsilane (167) and CSI.



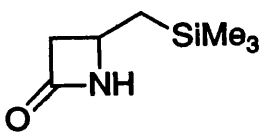
Colvin and Monteith[79] found that intermediate (168) could be intercepted *in situ* using the aqueous sodium sulphite reduction conditions employed by Durst and O'Sullivan.[80] Reduction of alkylsulphonyl chlorides to the corressponding sulphinic acids using Na_2SO_3 had long been known. In the β-lactam systems, the N-sulphinic acids spontaneously lose SO_2, forming the stable N-protio β-lactams. Dunoguès reported that the allylsilane (159) reacted with CSI to yield only the imidate (162), although recently Ricci and co-workers have managed to obtain the β-lactam (279) by a variation of this methodology. [119]



(159)

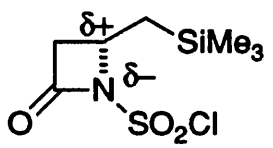


(162)

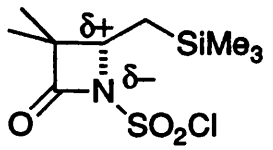


(279)

Using low temperature ^1H NMR spectroscopy, Colvin and Monteith established that allylsilane (159) proceeded directly to imidate (162) without the detection of any β-lactam intermediate. [79] The difference in the observed reactivity of allylsilanes (159) and (167) cannot be attributed to any difference in the stability of the intermediate carbo cations (280) and (281), since both are secondary and β- to silicon.



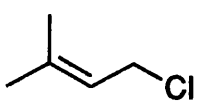
(280)



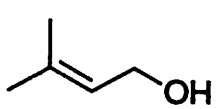
(281)

Graf[59(a)] has reported that the stability of N-chlorosulphonyl-β-lactams increases with increasing substitution at C3 and C4. However, since the allylsilane (159) appears not to proceed via a β-lactam intermediate, this is clearly an unsuitable explanation.

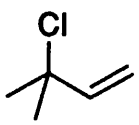
The dimethylallylsilane [120] (167) was obtained from the chloride (283), itself obtained from the alcohol (282) by treatment with PCl_3. [121] ^1H NMR spectroscopy showed there to be a mixture of isomeric chlorides (283) and (284).



(283)

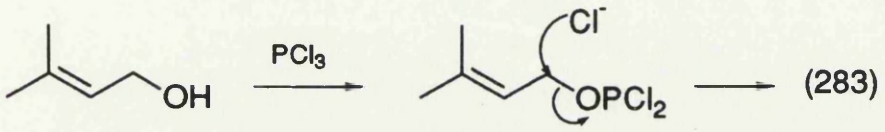


(282)



(284)

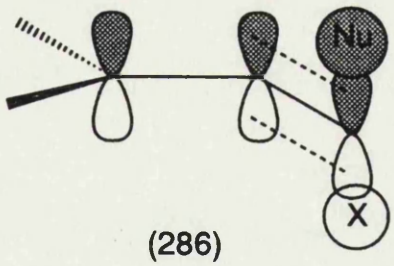
These chlorides were present in a ratio of ca. 3:1 in favour of the required material. The chloride (283) arises through S_N2 attack of chloride ion at the allylic carbon of intermediate (285) (Scheme 5.3)



(285)

(Scheme 5.3)

The S_N2 reaction is encouraged by the stabilisation imparted on the transition-state (286) due to interaction with the p-orbitals of the adjacent π-system (Scheme 5.4).

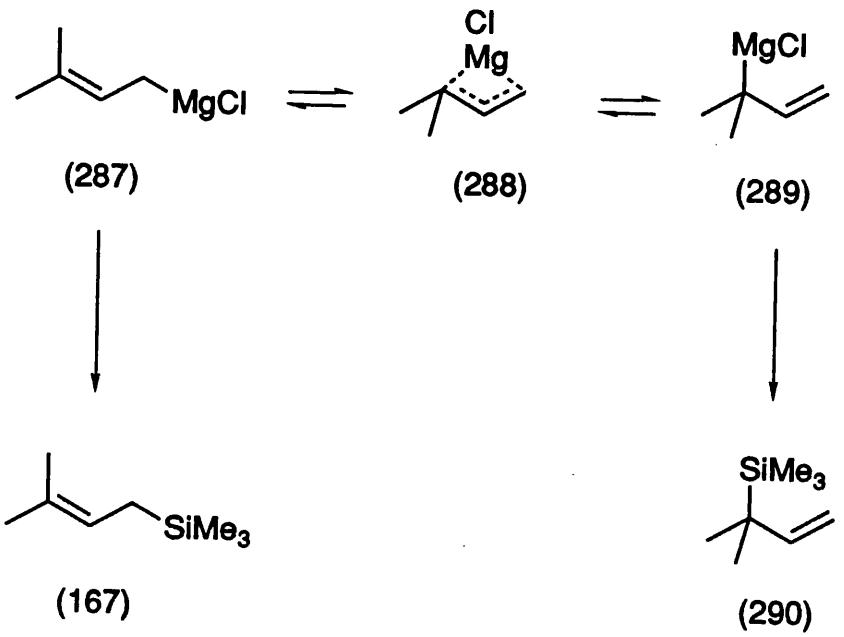


(286)

(Scheme 5.4)

This favours the S_N2 pathway over the alternative mechanism, the S_N2' route, which is responsible for the minor product (284). The S_N2' pathway has no similar stabilisation possible, and indeed the chloride anion is attacking a carbon of high electron density. Attack at the γ-carbon atom also results in an increase in steric congestion at this centre, due to the resultant change in the hybridisation (sp^2 to sp^3).

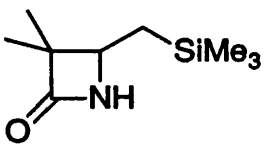
The mixture of isomeric chlorides can readily be distilled apart, purification being aided by the desired product (283) having the higher boiling point. Chloride (283) was transformed into the dimethylallyl silane (167) via Grignard reaction. [120] The allylic Grignard reagent (287) is not regiostable, since the isomeric silane (290) is also formed, from the Grignard species (289),presumably through an intermediate/transtition state like (288) (Scheme 5.5).



(Scheme 5.5)

The desired allylsilane (167) was found to be the major product, and could readily be separated from the isomeric silane (290). The yield of the desired silane (167) was improved by having TMSCl present in the reaction mixture from the start, the rationale being that the Grignard reagent (287) will react to form the silane before significant rearrangement can occur.

The dimethylallyl silane (167) was found to react smoothly with CSI to furnish the β-lactam (174), after Na_2SO_3 reduction. This welcome result clearly showed that such allyl silanes could be used to prepare β-lactams, via cycloaddition with CSI, with complete control over the regiochemistry of the process. This question of regio-control is an important one, since product mixtures would detract from the applicability of the methodology.



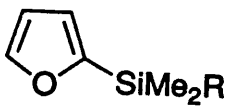
(174)

Although the use of such allylsilanes was an important step in the synthetic development of the olefin/CSI route, it clearly suffered from several disadvantages. The allylsilanes, such as (167), carry functionality of limited usefulness in terms of further synthetic elaboration. Secondly, the trimethylsilyl moiety is a synthetic dead end, and further chemistry is not possible on these systems. We decided to extend this potentially useful chemistry in two complementary directions :

(i) incorporation of synthetically more useful functionality at the γ-carbon of the allylsilane, leading to incorporation of a synthetic handle at C-3 of the monocyclic β-lactam system.

(ii) variation of the silyl substitution so that oxidative can be achieved, thus allowing more complex molecules to be constructed.

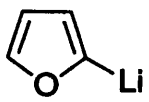
Since the application of the $SiMe_2Ph$ system had been investigated within the group, [112] it was decided to investigate the potential of another system. The (furyl)dimethylsilyl system (291)



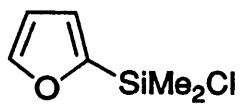
(291)

had been reported as a good masked hydroxyl system by Stork. [122] In the stereospecific synthesis of reserpine, Stork required a mild procedure for the synthesis of the -$SiMe_2F$ moiety, the precursor to oxidative cleavage. The furylsilyl system developed by Stork was converted to the fluorosilane by mild reflux in the presence of TBAF. Also, the choice of oxidant, a peracid, converted a ketone to a lactone, and effected oxidative cleavage, in a single step. It was decided to investigate the applicability of this system to our methodology.

The furylchlorosilane (293) was readily synthesised by first performing an α-metallation on furan, by refluxing with BuLi in ether for 4h, forming 2-lithiofuran (292).

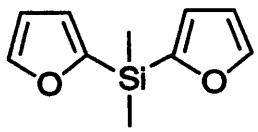


(292)



(293)

The pre-formed 2-lithiofuran (292) was added to 2 equivalents of Me_2SiCl_2, forming the chlorosilane (293) in 50% yield after distillation. A previous attempt at the synthesis of (293) had involved addition of a stoichiometric quantity of Me_2SiCl_2 to a solution of 2-lithiofuran, resulting in a low yield of (293), the major product (294) being that of double displacement.



(294)

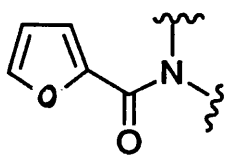
The problem associated with the synthesis of (293) is that the product initially formed, (293) itself, is certainly as reactive as the starting dichlorosilane. This means that (293) can compete with the dichlorosilane for 2-lithiofuran. As the reaction proceeds, more and more of the product of double-displacement, (294), is formed. To overcome this problem, we decided to add the 2-lithiofuran gradually to the Me_2SiCl_2 so that the 2-lithiofuran was completely consumed, its concentration never allowed to rise to the point where double displacement starts to become a problem. This, coupled with the relatively dilute conditions employed, was successful in keeping the quantity of (294) to a minimum, thus maximising the yield of product.

With the furylchlorosilane (293) in hand, production of the dimethylallylsilane (295) proceed well, using *in situ* trapping of the Grignard (287) with the chlorosilane. This allylsilane (295) was the logical extension from the trimethylsilyl analogue (167), since the inclusion of the furyl moiety meant that oxidative cleavage was now a possibility. It was expected that the allylsilane (295) would react with CSI to furnish the β-lactam (296) (Scheme 5.6).

(295) (296)

(297) Actual product

(Scheme 5.6)



However, a ^1H NMR spectrum of the product obtained showed that this was not the case. After Na_2SO_3 reductive quench and product isolation, it was found that the olefinic proton of (295) was still present (δ 5.1), integrating as 1 proton, showing that addition of CSI to the double bond had not occurred, even though the allylsilane had been allowed 3h to react.

It was also found that the isolated organic material did not contain any signals that corresponded to furyl ring protons, although the silyl methyl groups were still present. This result indicated cleavage of the Si-C bond that connected the furyl ring to the silyl moiety.

It was decided to monitor the course of the CSI/allylsilane reaction by ^1H NMR spectroscopy to ascertain the nature of this reaction. Since the reaction was carried out in CCl_4, a small quantity of the reaction mixture was removed just after complete addition of CSI, and placed in an NMR tube for examination at regular intervals.

Spectra obtained at 45 mins, 1.5h and 3h confirmed that the olefinic double bond in (295) was unreactive towards CSI, since at all times up to 3h the olefinic proton resonance could be clearly seen and always integrated as 1 proton. No noticeable change in the chemical shift of the olefinic proton was observed, indicating that reaction had occurred some distance from the double bond.

This, however was not true of the furyl ring protons, which could clearly be seen to have different chemical shifts (Table 5.1).

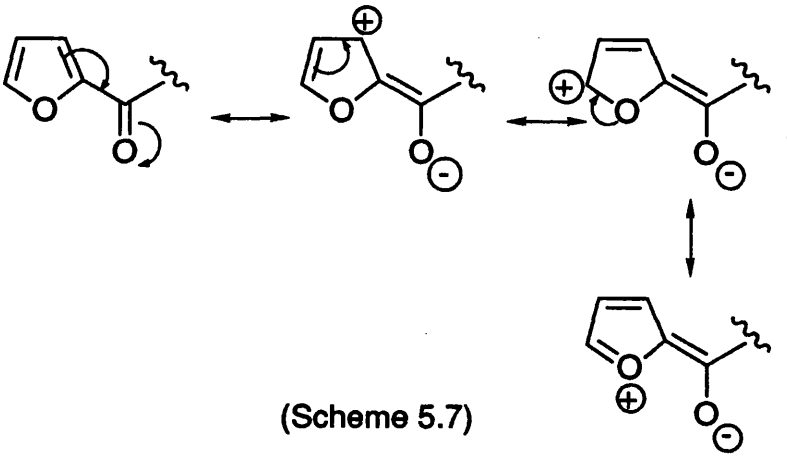
Allylsilane (295)	Product (297)
C_3 δ 6.6	δ 7.7
C_4 δ 6.37	δ 6.7
C_5 δ 7.64	δ 7.85

(Table 5.1)

These assignments are based on the magnitude of the coupling constants for the furan ring, *J* 3.6 Hz (H3-H4), *J* 1.65 Hz (H4-H5) and *J* 0.56 Hz (H1-H5).

Since the furyl protons present in product (297) were still clearly aromatic in nature, it was evident that addition of CSI across one of the double bonds of the furan moiety of (295) had not occurred. It was necessary to postulate a mechanism that left the furyl ring intact, but which explained the chemical shift changes observed.

Such chemical shift changes in the furyl ring proton resonances are indicative of a strong electron-withdrawing at C-2 of the furan ring, such as a carbonyl group (Scheme 5.7).



(298)

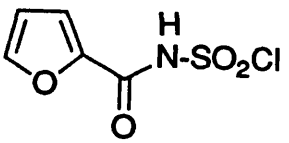
(Scheme 5.7)

This explains the finding that the proton at C-3 is the most strongly deshielded (δ 6.6 to δ 7.7), due to its proximity to the electron sink. The proton on C-5 suffers only small deshielding because the adjacent oxygen can act to stabilise the positive charge by interaction of its lone pair (298).

The contribution of canonical form (298) to the overall resonance hybrid is small due to the extent of charge separation, thus meaning that the proton on C-5 will experience little deshielding. The remaining proton on C-4 suffers slightly more deshielding because it is adjacent to the most deshielded proton in the molecule.

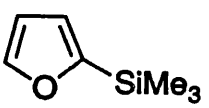
The evidence collected at that point in time suggested that the electron-withdrawing substituent was a carbonyl group, supported by the similarity to proton signals in furyl compounds that possess such a structural feature. Graf[58] had reported that CSI reacted with furan to form the amide (299), and with this in mind the process of elucidating

the mechanism was initiated.



(299)

It was decided that the best way to determine the nature of this allylsilane/CSI interaction was to use a simple model compound that would exhibit similar reactivity to (295), but the interpretation of spectral data would be simpler, thus facilitating mechanistic determination. Such a compound was 2-trimethylsilylfuran (300).

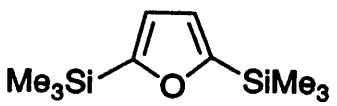


(300)

This has a correctly located silyl moiety, so should show similar reactivity to allylsilane (295) with CSI. The interpretation of the ^{1}H

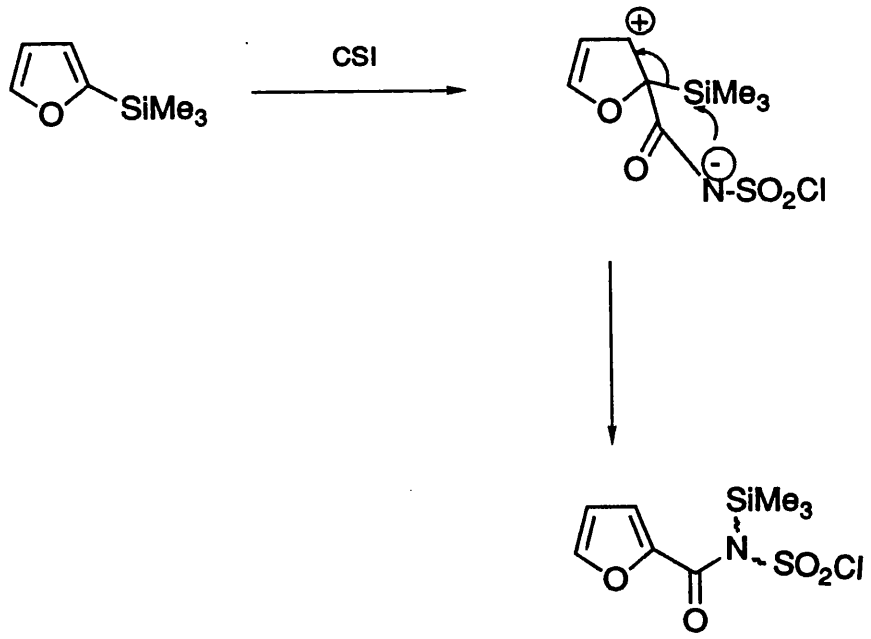
NMR data will be simplified, since the only protons present are those of the furyl ring and the silyl methyl groups.

Synthesis of (300) was achieved, from the previously described 2-lithiofuran and TMSCl, in good (78%) yield, with the remainder of the material balance attributable, presumably, to the bis-trimethylsilyl furan (301).



(301)

The reaction between 2-trimethylsilylfuran (300) and CSI was monitored by ^{1}H NMR spectroscopy over the course of the 3h reaction time. Spectra taken at 1h, 2h and 3h showed the gradual replacement of the signals attributed to the starting material (δ 6.37, δ 6.61, δ 7.64 and δ 0.24) by those of the product (δ 6.7, δ 7.7, δ 7.8 and δ 0.60). The chemical shifts of the product silyl methyl groups suggested that silicon was attached to a more electronegative element than in (300). After 3h, it was found that all the starting material (300) had been consumed. The facts presented thus far are all in support of the mechanism (Scheme 5.8).

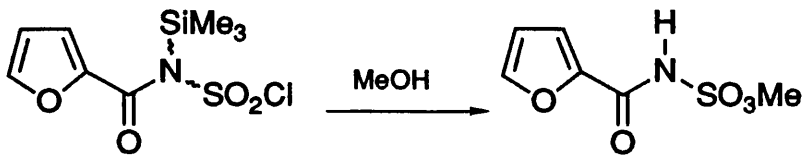


(Scheme 5.8) (302)

Furan exhibits the least aromatic "character" of similar heterocycles, such as thiophene and pyrrole. It behaves like an enol ether towards electrophiles, and requires milder reaction conditions if electrophilic substitution is to occur. With the 2-trimethylsilyl moiety, (300) behaves like an activated vinyl silane, the reactivity displayed above in Scheme 5.8, being consistent with the sequence of events during electrophilic attack, namely β-cation development, desilylation and double bond regeneration. [117]

Attack of the CSI on (300) occurs only at the double bond bearing the silyl moiety, since only on this side can the development of a stabilised β-cation occur. The furan ring is then regenerated by an intra molecular silyl shift from C to N, thus explaining the observed difference in the chemical shift value of the silyl methyl groups.

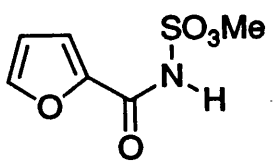
Attempts were made to isolate the product amide (302) in order to confirm the postulated mechanism. Several unsuccessful methods were tried, but the most fruitful was found to be treatment of crude (302) with excess methanol, to produce the N-(methylsulphonate)-2-furfurylamide (303) (Scheme 5.9).



(302) (303)

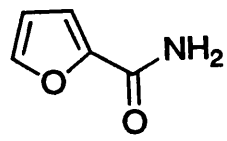
(Scheme 5.9)

The product (303) was found to be completely desilylated, and also showed the presence of the amide (E) and (Z) isomers (303) and (304) in approximately equal amounts.



(304)

The chemical shifts observed were consistent with the furyl protons of similar compounds. The reason that no furyl-containing product was isolated from the post Na_2SO_3 quench of allylsilane (295) \ CSI reaction was presumably due to formation of (305), which could not be recovered from the aqueous phase by either "salting out" or polar back-extraction techniques.



(305)

5.2 Allyl/vinyl disilanes *

As part of the investigation into extending the methodology to allow further synthetic elaboration at C-3 of the monocyclic β-lactam, it was envisaged that the use of allyl/vinyl disilanes, (306), could furnish β-lactams of the type (307) (Scheme 5.10)

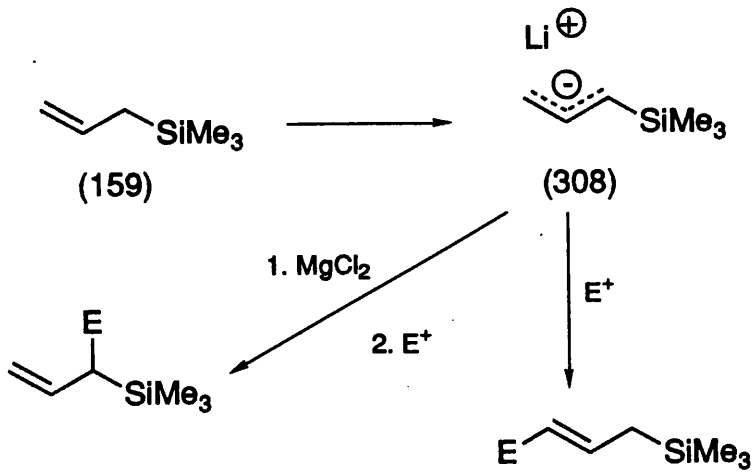
(306) (307)

(Scheme 5.10)

Such β-lactams could participate in a number of further possible transformations, such as Peterson olefination (Chapter 6) or oxidative cleavage (see later).

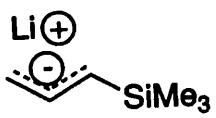
Compounds of the general type (306) were obtained by the method of Fleming and Langley. [123] Allyltrimethylsilane (159) was deprotonated α to silicon by the use of the BuLi/TMEDA base system. TMEDA acts by complexing with the Li^+ ions, thus rendering the butyl anion more basic, and able to deprotonate allyltrimethylsilane. The resultant lithio-anion (308) is known to favour products resulting from γ-attack. The attack selectivity can be reversed by use of a magnesium counterion, leading to products of α attack (Scheme 5.11).

* 1,3 disilyl-1-propenes



(Scheme 5.11)

The lithio-anion (308) is held in the trans-conformation, this being the thermodynamically more stable of the two possibilities (308) and (309).

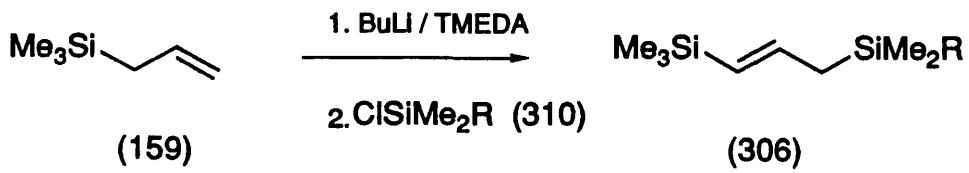


(308)

(309)

Steric considerations are important in this trans selectivity : (309) would suffer from unacceptable interaction between the CH_2 and $SiMe_3$ groups. In addition, the complexing of the Li^+ would be impaired in the congested cis form (309).

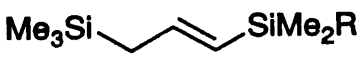
With the trans selectivity and the preference for γ-attack, reaction of this anion with an electrophilic chlorosilane of the general type (310) results in the production of the trans disilane (306) (Scheme 5.12).



(159) (306)

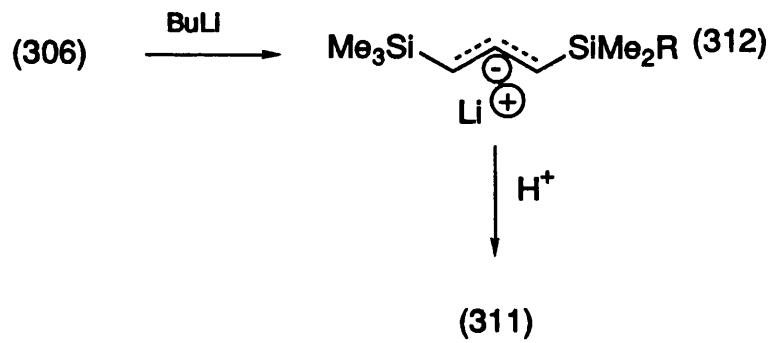
(Scheme 5.12)

The chlorosilane (310) was left to react with the pre-formed lithio-anion (308) for 1h at -5°C. It was found that if the reaction was allowed to proceed for periods greater than 1h, or if the temperature was allowed to rise substantially above 0°C, isomerisation of the first formed olefinic product (306) to the double bond-shifted product (311) occurred.



(311)

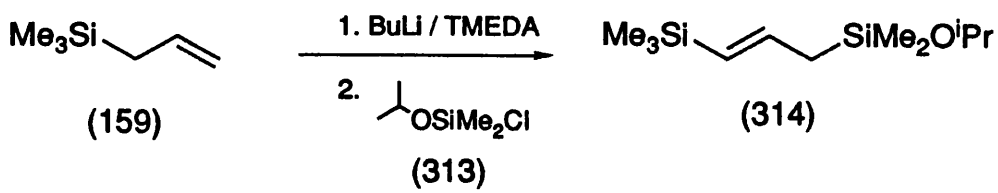
This isomerisation is the result of unreacted BuLi abstracting a proton from (306), forming a new anionic species (312), which is subsequently re-protonated, forming (311) (Scheme 5.13).



(Scheme 5.13)

Formation of this isomeric olefin must be avoided, since separation of it from the desired product (306) would be very difficult. The trans nature of the disilanes was confirmed by the magnitude of the coupling constant between the olefinic protons, J = 17 - 18 Hz. In the usual work-up procedure, aqueous HCl is used to remove the TMEDA into the aqueous layer.

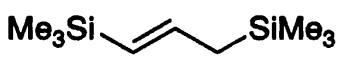
However, when R = O^iPr, the use of HCl was found to be incompatible, and the conditions were modified, with $CuSO_4$ being used to remove the TMEDA. Disilane (314) was obtained by reacting the lithio anion (308) with (isopropoxy)dimethylchlorosilane (313) (Scheme 5.14). The requisite chlorosilane (313) was readily accessed by adding isopropanol to 2 equivalents of Me_2SiCl_2, in an analogous manner to the synthesis of (furyl)chlorosilane (293).



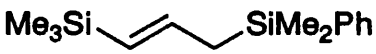
(159) (313) (314)

(Scheme 5.14)

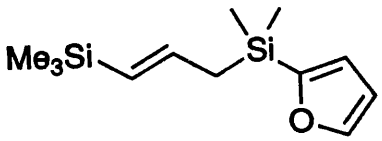
The allyl/vinyldisilanes produced by this methodology were R = Me (315), Ph (316), Furyl (317) and O^iPr (314).



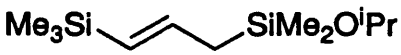
(315)



(316)



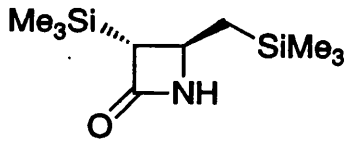
(317)



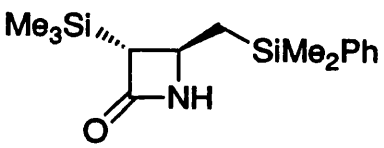
(314)

Silanes (315), (316) and (317) formed part of a study into Peterson olefination (Chapter 6), and (314) was investigated for its potential as a masked hydroxyl equivalent.

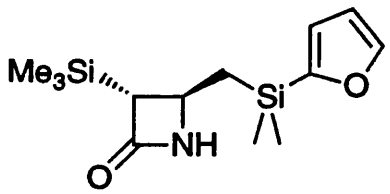
The allyl/vinyldisilanes obtained reacted smoothly with CSI to afford the β-lactams (318), (319), (320) and (321) in 26 - 45% yield.



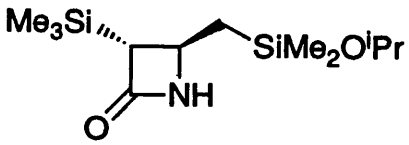
(318)



(319)



(320)

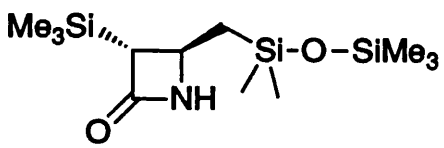


(321)

For disilane (314), it was found that the $-SiMe_2O^iPr$ moiety was not robust enough to survive the usual Na_2SO_3 reductive quench, since this generates a pH of between 10 and 11, basic enough to effect hydrolysis. A milder reductive quench was required that would leave the $-SiMe_2O^iPr$ species intact, but still be effective in the reduction of $N-SO_2Cl$ to N-H.

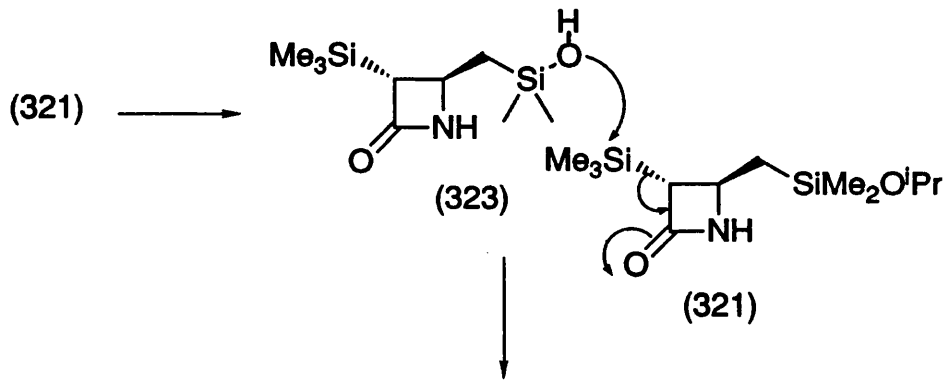
Using the allyl/vinyl disilane (315) as a model to ascertain the reductive effectiveness, it was found that a Na_2SO_3/NH_4Cl system, buffered at a pH between 7.7 and 8.2, gave isolated yields of the β-lactam (318) comparable to the usual Na_2SO_3 system, thus demonstrating an equal capacity to effect reduction. When applied to the synthesis of β-lactam (321), it was found that this compound could be obtained with the $-SiMe_2O^iPr$ unit intact, with an overall crude yield of 45%. The β-

lactam (321) could not be further purified since it was found to be unstable on silica (Kieselgel 60H) and neutral alumina. The product isolated from the attempted purification by flash column chromatography appeared to be in agreement with the structure (322).



(322)

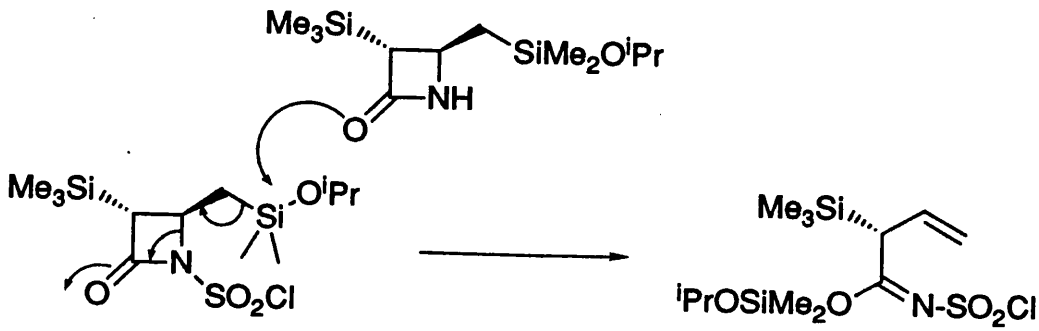
This β-lactam (322) could result from the hydrolysis of (321) on the silica, as for the allene (270), to form (323), which then gives the observed bis-silyl ether (322) by attack at the relatively labile C-3 trimethylsilyl moiety (Scheme 5.15).



(Scheme 5.15)

It was also found that the formation of β-lactam (321) from disilane (314) did not occur in the usual solvent, CCl_4, the only detectable product being the imidate (324). When the more polar solvent CH_2Cl_2 was used, again imidate (324) was the only product.

The ^{i}OPr substituent makes the already electropositive silicon even more so, and this encourages nucleophilic attack, presumably by the amide carbonyl oxygen of another β-lactam molecule, leading to the formation of the O-silyl imino ether (324) (Scheme 5.16)

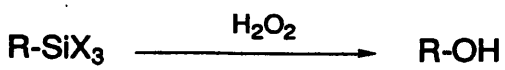


(325) (Scheme 5.16) (324)

Switching from the polar CH_2Cl_2 to the non-polar pentane resulted in the clean reaction of disilane (314) with CSI, forming the β-lactam (321) in good yield for this process. It is unclear why the reaction did not proceed in CCl_4, since this is itself a non-polar solvent. In CH_2Cl_2, due to its polarity, it could be reasoned that dipole-dipole interactions could stabilise, and thus encourage, the development of intermediate (325).

5.3 Oxidative Cleavage

In 1983, Tamao and co-workers found that the silicon-carbon bonds in the fluoro-, chloro-, alkoxy-, and amino-silanes could be readily cleaved by 30 % hydrogen peroxide, resulting in the formation of alcohols (Scheme 5.17). [124]

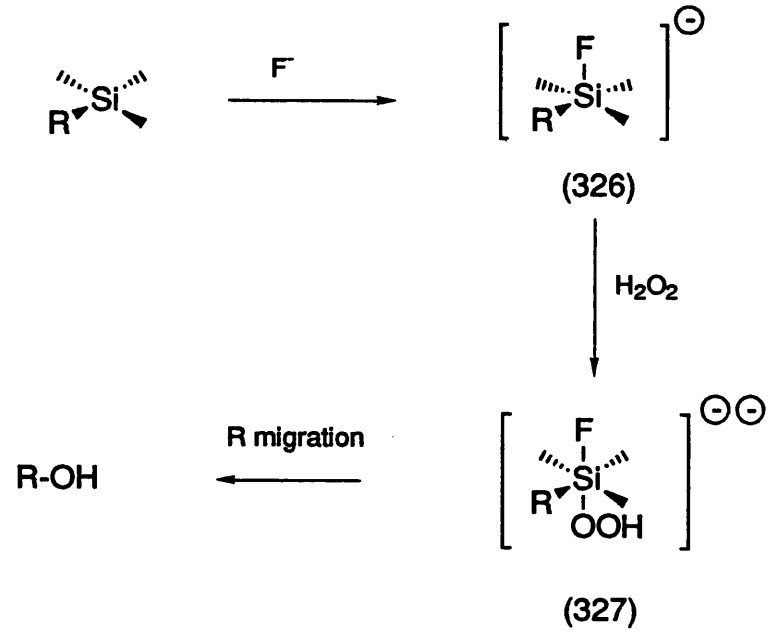


SiX_3 = $SiMe_2F$, SiF_3, $SiMe_2Cl$
$SiCl_3$, $SiMe_2OR$, $SiMe(OR)_2$,
$Si(OR)_3$, $SiMe_2(NR_2)$.

(Scheme 5.17)

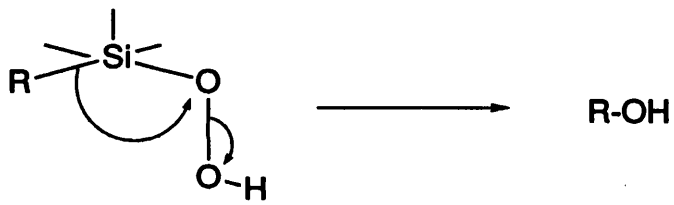
The common feature in all of these oxidatively cleavable silanes is the presence of at least one electronegative atom directly bonded to silicon. The utility of such a process has been demonstrated numerous times, with examples of both regio- and stereo- control in the transformation of organosilicon compounds into oxygenated organic molecules.

In the presence of fluoride ion, the reaction is thought to proceed via a 5-coordinate initial intermediate [125] (326), followed by a 6-coordinate transition-state complex (327) (Scheme 5.18)



(Scheme 5.18)

In the absence of catalytic fluoride ion, the reaction is thought to proceed via the 5-coordinate intermediate (328), followed by Si-to-C migration, and hydrolysis to the alcohol (Scheme 5.19).



(328)

(Scheme 5.19)

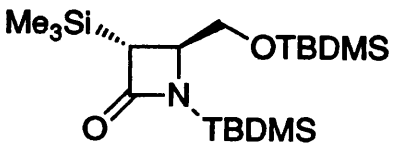
Although initially it had been the intention to investigate the usefulness of the furylsilanes, such as (295) and (317), the unwelcome addition of CSI to some members of the series detracted somewhat from the potential applicability of the process. It was decided, therefore, to concentrate on the isopropoxysilyl methodology of Tamao, [111] since it was assumed that this moiety could not suffer deleterious interaction with CSI.

The required β-lactam (321) was accessed by the chemistry previously described in this chapter. It was envisaged that oxidative cleavage of β-lactam (321) would lead to the 4-(hydroxymethyl)-β-lactam (329), which, after suitable protection of the hydroxyl group, could then participate in Peterson olefination, furnishing the usefully functionalised β-lactam (330) (Scheme 5.20).

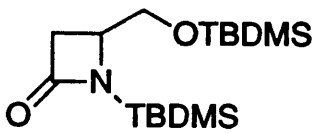
(329) (330)

(Scheme 5.20)

The β-lactam (321) was subjected to the conditions of Tamao [111] to effect the oxidative cleavage, that is using H_2O_2 as the oxidant and $NaHCO_3$ as the base. Due to the expected high polarity of the newly formed hydroxymethyl β-lactam, it was decided to silylate both the amide nitrogen and the hydroxyl group by treatment with two equivalents of TBDMSOTf. The product, although oxidatively cleaved, was the C-3 desilylated β-lactam (332), and not (331) as had been hoped.



(331)



(332)

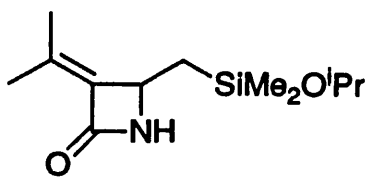
These initial conditions used H_2O_2 in ca. tenfold excess, and so it was perhaps not surprising that the C-3 trimethylsilyl moiety was lost.

In an attempt to retain the C-3 trimethylsilyl group, the amount of peroxide used was reduced from ca. 10 equivalents to 4.5, then to 2.1, but in all cases β-lactam (332) was the sole product after TBDMS protection. The oxidative cleavage was attempted in the absence of methanol, since refluxing in methanol would itself be sufficient to remove the C-3 trimethylsilyl moiety. It was found that only starting material was returned in near quantitative yield.

Although we were disappointed at the loss of the useful C-3

trimethylsilyl group, we were pleased to see that the overall yield for the two step process of oxidative cleavage and silylation was ca. 75%, a clear improvement on the $SiMe_2Ph$ system. Indeed, the overall yield for the production of (321) from the allyl/vinyldisilane (314) is a healthy 34%. The major problem with the use of $-SiMe_2O^iPr$ is that this unit is not very robust, and so cannot be carried through many chemical steps, whereas $-SiMe_2Ph$ can.

In order to overcome this problem of C-3 trimethylsilyl loss, it was decided to try to perform Peterson olefination first, hopefully forming the β-lactam (271), which could then be oxidatively cleaved.

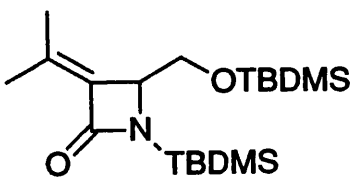


(271)

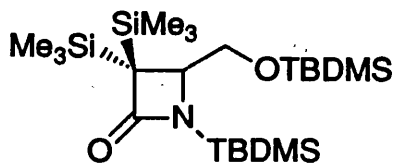
The investigation into the attempted Peterson olefination of β-lactam (321) is discussed more fully in chapter 6.

The problem of C-3 trimethylsilyl loss is not as bad as it seems at first, as β-lactam (331) has been produced from (332) in good yield. This chemistry was carried out by group colleague, M. Monteith, [112] on the same β-lactam (332), the product of the fluoride mediated oxidative

cleavage of β-lactam (319). The re-silylated material (331) was required for further chemical elaboration to the C-3 alkylidene product (333), through Peterson olefination. M. Monteith found that along with the re-silylated material, a small quantity (ca. 25%) of the di-silylated β-lactam (334) was formed, although these compounds were readily separable by flash column chromatography.



(333)



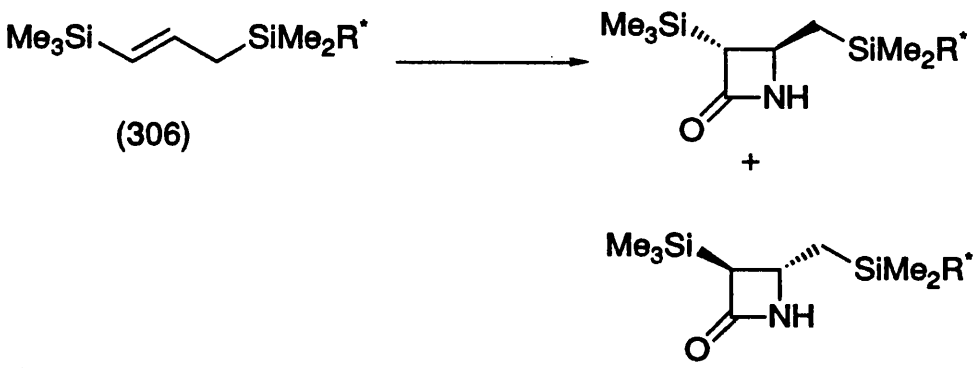
(334)

In conclusion, a range of allyl/vinyl disilanes can be accessed by this methodology, and subsequently transformed into the corresponding β-lactams. Use of the $-SiMe_2O^iPr$ as a masked hydroxyl afforded a useful carbapenem precursor (332) in greater yields than for other investigated systems. The C-3 desilylation problem can be overcome by conversion of (332) into the re-silylated β-lactam (331), which is then capable of further synthetic elaboration.

5.4 Chiral Allyl\vinyldisilanes

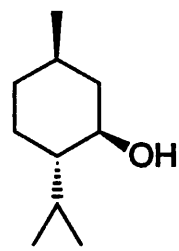
The importance of asymmetric induction is well recognised in the field of organic synthesis, especially so when constructing

biologically active molecules. In an attempt to try to exert some degree of stereocontrol on the disilane\CSI cycloaddition process, the use of a chiral alkoxysilyl moiety incorporated into the disilane seemed a promising approach. The presence of pre-existing chirality in the disilane (306) would lead to diastereomeric transition states, with possibly enough energetic differentiation to afford an excess of one over the other (Scheme 5.21).

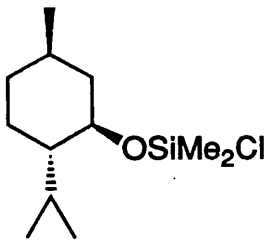


(Scheme 5.21)

The use of a bulky, homochiral alcohol in the synthesis would lead to its incorporation in the disilane. Due to its ready availability and steric bulk, (-) menthol (335) was chosen as the chiral handle.

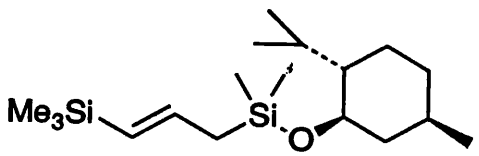


(335)



(336)

The menthoxysilane (336) had already been synthesised, and had found use as a chiral silating agent. [126] This compound was then transformed into the disilane (337), $[\alpha]_D$ = -28.62°, by the now standard method,in 65% yield (180°C/0.1 mmHg).

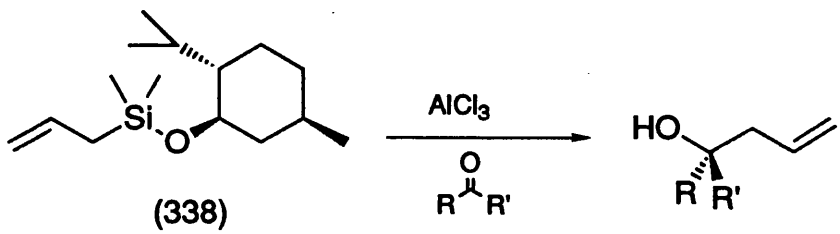


(337)

The disilane was reacted with CSI (5h, 0°C, pentane) and then quenched with the Na_2SO_3/NH_4Cl buffered system developed for use with sensitive alkoxysilyl moieties. The extent of induction could be seen by comparing the integral areas of the two diastereomeric C-4 protons in the reaction mixture. The C-4 proton is closest to the chiral handle, and so the difference in chemical shift of these protons is greatest. These diastereomeric protons showed multiplets at δ 3.35 and δ 3.55 and were baseline resolved, thus allowing for accurate estimation of the chiral induction.

Unfortunately, the diastereomeric C-4 proton signals were found

to be present in a 1:1 ratio, showing that no induction had occurred. Construction of molecular models showed the chiral handle to be too distant from the double bond to exert any diastereofacial selection. Work had previously been carried out on the addition of electrophiles to allylsilanes of the type (338), (Scheme 5.22).[126]



(338)

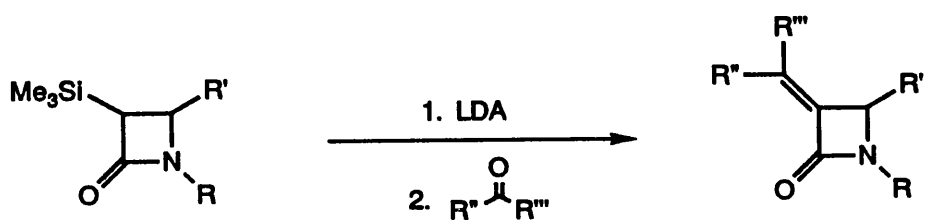
(Scheme 5.22)

Although the nature of the chemistry detailed in Scheme 5.22 is different from cycloadditions with CSI, the distance of the chiral handle from the double bond in both molecules is the same, yet these workers saw modest inductions of 18-20%, whereas we saw none.

Chapter 6

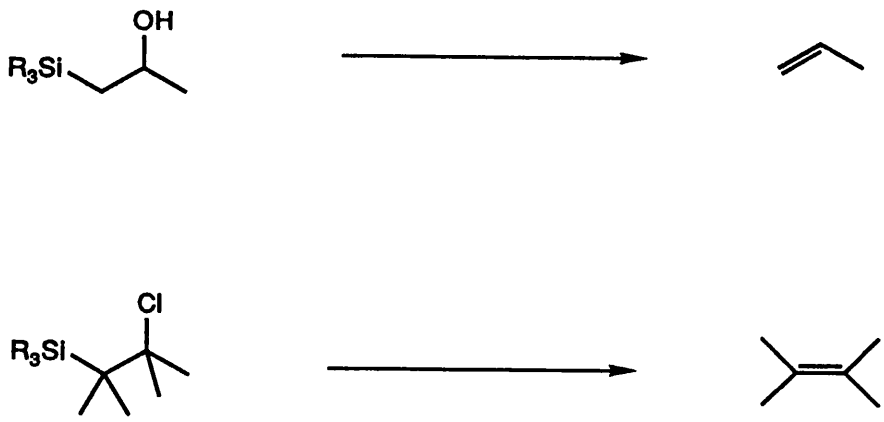
Peterson Olefination

The use of (allenylmethyl)silanes, such as (245), to furnish α-alkylidene β-lactams, has been discussed already (Chapter 4). As an alternative to the construction of a functionalised allene, as a precursor to a functionalised β-lactam, the use of a common C-3 silylated β-lactam gives the methodology more general application. Such a β-lactam should participate in Peterson olefination, potentially leading to a range of C-3 alkylidene β-lactams (Scheme 6.1).



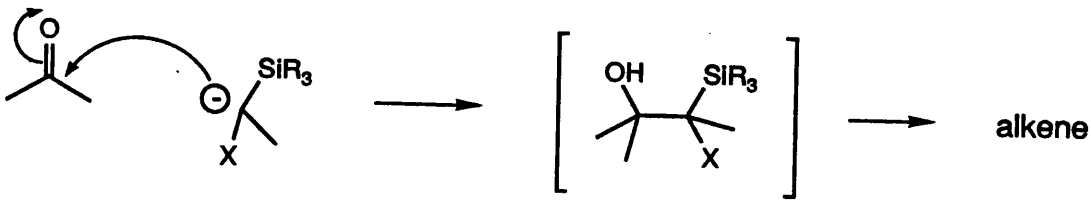
(Scheme 6.1)

In 1947, Sommer and Whitmore reported that 2-hydroxypropyltrialkylsilanes underwent elimination, in the presence of dilute HCl, to form propene. [127] They also found that β-chloroalkylsilanes could be made to eliminate similarly, again yielding alkenes (Scheme 6.2). [127]



(Scheme 6.2)

The generation of an alkene via the attack of an α-silyl carbanionoid (339), on a carbonyl species, is commonly referred to as the Peterson olefination. [128] If X is electron-withdrawing and capable of anion stabilisation, then the alkene is obtained directly. On the other hand, if X cannot stabilise an adjacent carbanion, then the β-hydroxysilane intermediate (340) is often isolable, and can be transformed subsequently into the alkene by treatment with acidic or basic reagents (Scheme 6.3).

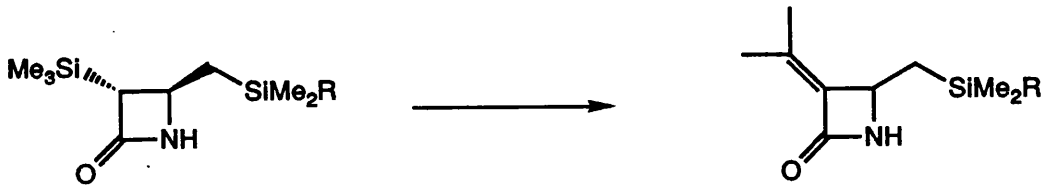


(339) (340)

(Scheme 6.3)

Typically, the alkenes formed during the Peterson olefination will display (where applicable) geometrical isomerism. For the purposes of our investigation into this process, it was decided to use acetone as the carbonyl component, since the problem of geometrical isomerism in the product could not arise.

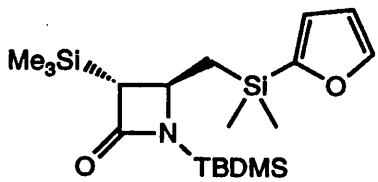
The β-lactams that were used in this study were of the general structure (307), and since X in this case is the amide carbonyl group, it was expected that the C-3 alkylidene β-lactams (341) would be formed directly, with no isolation of β-hydroxysilane (Scheme 6.4).



(307) (341)

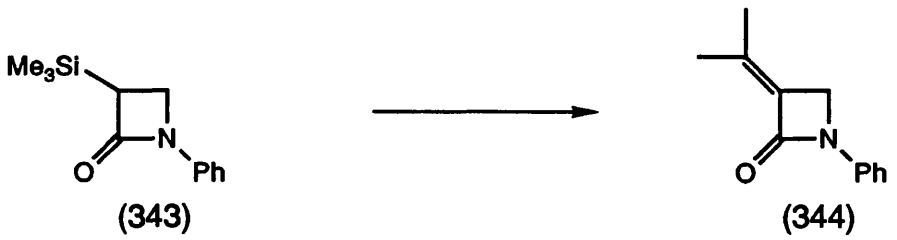
(Scheme 6.4)

As mentioned previously, the furyl-containing β-lactam (320) was of interest because of its potential for oxidative cleavage. The utility of this moiety as a masked hydroxyl group was not further explored, due to the fact that (dimethylsilylfuryl)allyl silanes, containing only one Si atom, undergo reaction at the furan ring with CSI (see Chapter 4), making the method not applicable. The β-lactam (320) was readily obtained from allyl/vinyl disilane (317) (due to the activating effects of both Si atoms), and presented itself as a very useful compound. Although oxidative cleavage studies (Chapter 5) were concentrated on the $-SiMe_2O^iPr$ moiety, β-lactam (320) was the initial starting point for these Peterson olefination studies. The amide nitrogen must be protected prior to the deprotonation step, and so the N-TBDMS β-lactam (342) was prepared.



(342)

It was decided to start with conditions that had been previously employed in similar systems. Shibuya and co-workers [129] had been able to synthesise the C-3 alkylidene β-lactam (344) from the C-3 silyl β-lactam (343) by using the kinetic base LDA at -78°C, with the carbonyl component added at this temperature (Scheme 6.5).



(343) (344)

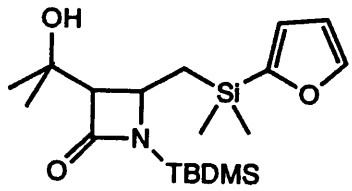
(Scheme 6.5)

When these conditions were applied to the furyl β-lactam (342), it was found that only starting material was returned, with no indication of olefination having occurred. The detection of C-3 alkylidene β-lactam product would be clear to see by ^{1}H NMR spectroscopy, since the C_3-H would be lost, and the C_4-H proton resonance would be shifted downfield (from δ 2.36 to δ 4.15), due to its proximity to the C=C bond.

It was thought that the lack of reaction was due to insufficient time allowed for LDA to deprotonate β-lactam (342). Consequently, the deprotonation time was increased from 15 mins to 30 mins. Thin layer chromatography (pentane/ethylacetate, 80:20) of the product now revealed there to be two components present, one a non-polar fraction

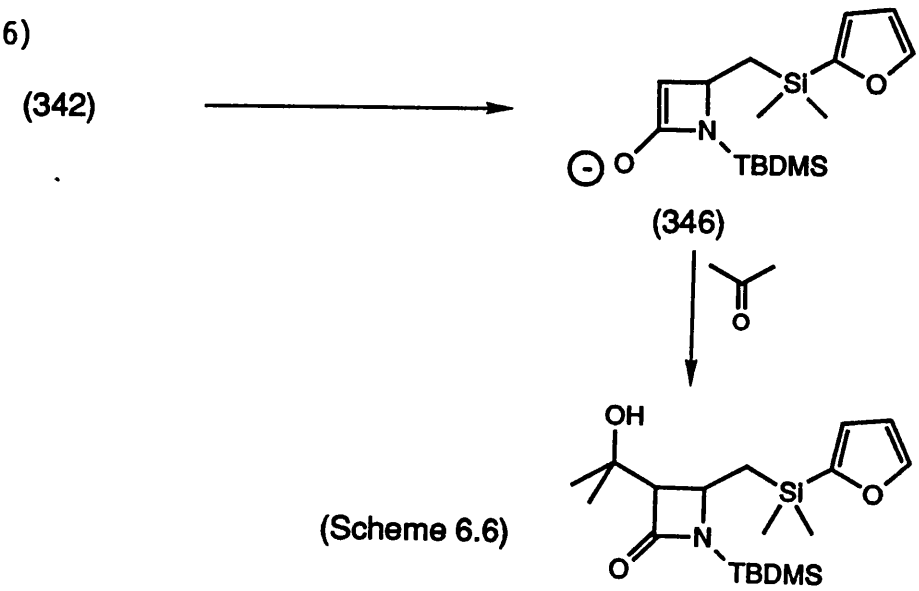
with an R_f of 0.9 corresponding to that of the starting β-lactam (342), and the other being much more polar, with an R_f of 0.26. Column chromatography separated these two components.

The more polar fraction (R_f 0.26) was found to be β-lactam (345). The H3 and H4 ring protons (δ 2.7 and δ 3.6) can be seen, as can the two diastereotopic methyl groups at δ 1.2-1.3.



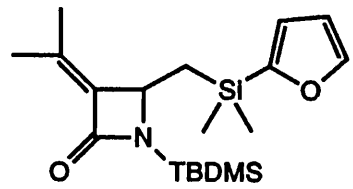
(345)

This product had clearly arisen from the desilylation of β-lactam (342), and reaction of the β-lactam enolate species (346) with acetone (Scheme 6.6)



(Scheme 6.6)

Inspection of the ^1H NMR spectrum of the non-polar fraction showed it to be composed of starting material (342), and alkylidene product (347), in an approximate 1:1 ratio. The proportion of the Peterson product is easily ascertained by direct comparison of the integral heights of the H-3 proton of the β-lactam with the H-4 proton of the product olefin (347). As well as the signals of the starting material (see experimental section), the cis and trans methyl groups of the olefinic β-lactam could be seen (δ 1.96 and δ 1.53) as could the H-4 proton multiplet (δ 4.4).

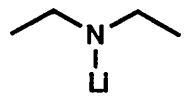


(347)

An attempt was made to separate these two compounds by flash column chromatography, using a gradient system that became progressively more polar in 5% increments. This proved to be unsuccessful due to the closeness of their respective polarities. Since the product mixtures from these reactions could not be separated, complete conversion to product became highly important.

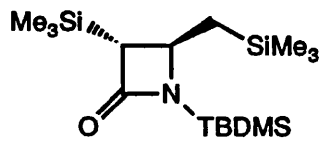
It was thought that use of the slightly smaller kinetic base N-lithiodiethylamine (348), might improve the deprotonation step, if

steric factors were at play. Strangely, under the same conditions that furnished the 1:1 mixture just described, the result here was the return of starting material.



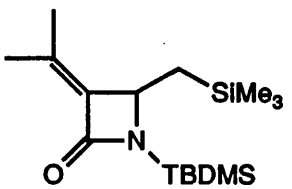
(348)

At this stage, it was decided to concentrate efforts on a model system, to optimise conditions for this, and then apply those conditions to the desired material. The β-lactam (349) was chosen for this purpose, since it was readily accessed and would (hopefully) exhibit similar reactivity to (342).



(349)

Treatment of the β-lactam (349) with LDA at -78°C, followed by acetone at -78°C returned only starting material, whereas use of N-lithiodiethylamine under identical conditions furnished a 2:1 mixture of starting material and olefin product (350).



(350)

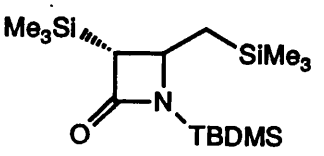
This was a clear indication that steric factors were in operation, since only the smaller base gave alkylidene product. Although the trimethylsilyl species is far bulkier than the furyl ring, it was thought that the silyl moieties in both β-lactams were too distant to interfere with access to the C_3 proton. A conformation can be drawn in which the (trimethylsilyl)methyl group, due to its trans disposition to the C_3 trimethylsilyl group, is blocking the face from which the base must approach the proton. However, due to conformational freedom around the C_4-C_4' bond, permanent obstruction of that face is not possible. The table below shows that under a variety of conditions, the β-lactam (349) failed to yield a C-3 alkylidene product with LDA.

CONDITIONS	RESULT
-78°C, 30 mins; acetone, -78°C, 30 mins	S.M.
- 78°C → 0°C, 20 mins; acetone, -78°C, 20 mins	S.M.
0°C, 30 mins; acetone, -78°C, 30 mins	S.M.
-78°C, 10 mins; acetone, -78°C → 0°C, 30 mins	S.M.

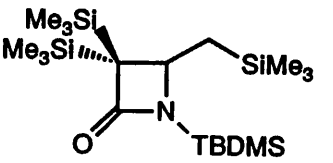
It was then decided to increase the basicity of the LDA by adding TMEDA. Under the conditions of Shibuya, [129] this base system returned only starting material. When BuLi/TMEDA at 0°C for 30 mins was used, starting material was again returned.

It was therefore decided to discover if the problem was of a steric nature, or one of incomplete deprotonation. It seemed possible that any enolate species formed *in situ* could be quenched by abstraction of a proton from acetone, thus reducing the yield of alkylidene product.

To this end, it was decided to form the enolate under the standard -78°C conditions, react it with TMSCl, and look for the proportion of starting material (349) to bis-silylated product (351).

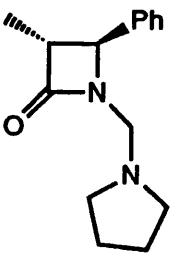


(349)



(351)

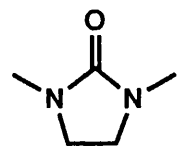
It was found that the bis-silylated product (351) was formed, again as the minor component of a 2:1 mixture with returned starting β-lactam (349). This was suggestive of incomplete deprotonation, and not enolate quenching by acetone. This was a somewhat surprising result, since the acidity of the C-3 proton in systems such as (343) is not in doubt, and indeed similar deprotonations have been carried out by others such as Shibuya. [129] Even in the absence of a C-3 silyl group, which increases acidity, deprotonations using LDA have been performed on β-lactams such as (352). [130]



(352)

Also, work performed in the group [112] on the Peterson olefin of β-lactams such as (331) has revealed near quantitative yield of product.

To increase the basicity of the LDA base system, the complexing agent DMEU (353), which has found successful application as a hypernucleophilic agent, was used.

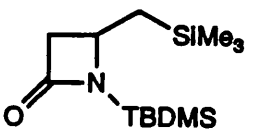


(353)

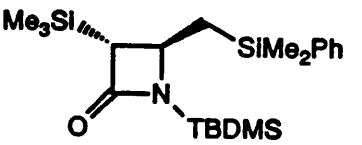
Using DMEU as a co-solvent with THF, it was found that the proportion of alkylidene product could be raised to 50%, as calculated from the ^{1}H NMR spectrum of the product mixture. Isolation of the alkylidene product from the reaction mixture, by column chromatography, was difficult, and resulted in a 30% isolated yield.

The optimal conditions for this reaction was found when THF and DMEU were in the ratio 1:1, and the base used was LDA. Use of N-lithiodiethylamine (348) gave the same result. The temperature could not fall below -30°C, since the DMEU was found to freeze. Also obtained from this reaction mixture was a more polar component, which

corresponded to the de-silylated product (354). When the THF to DMEU ratio was 2:1, the proportion of alkylidene product was only 30%, but purification by column chromatography was more efficient, presumably due to the smaller proportion of DMEU contaminant. As detailed in the experimental section, purification of the product mixture was achieved by reaction with KF in CH_3CN to effect total desilylation, and increase the polarity difference between the product and starting material.



(354)



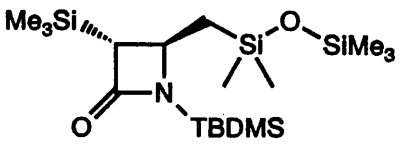
(355)

Increasing the proportion of DMEU to THF beyond this value resulted in a reversal of this trend, with the return of only starting material obtained.

Attempted Peterson olefination on the phenylsilyl β-lactam (355) using these optimised conditions gave only starting material; the explanation of this result is not clear.

Peterson olefination was also attempted on the O^iPr β-lactam (321), since, as mentioned in Chapter 5, carrying out oxidative cleavage first resulted in the loss of the C-3 silyl group. Protection

of the amide nitrogen with TBDMSOTf resulted in the isolation of a compound whose ^{1}H NMR spectrum was in accord with the structure (356).



(356)

When this compound was subjected to the optimised conditions (see earlier) a mixture composed of starting material (356) and alkylidene product in a 2:1 ratio was obtained. This however proved to be inseparable on column chromatography.

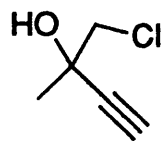
The constraints of time did not allow for further investigation into the application of the Peterson olefination to such C-3 silyl β-lactams. The observation of alkylidene products during the course of this study suggests that conditions can be found for quantitative conversion to C-3 alkylidene β-lactams, useful intermediates in the synthesis of more complex carbapenems.

Bulb to bulb distillation was carried out on a Buchi GKR-50 Kugelrohr, the quoted boiling points refering to the indicated air bath temperature. ^{1}H NMR spectra were recorded on a Bruker AM200SY or a Bruker WP200SY, both operating at 200 MHz. ^{13}C spectra were recorded on the same Bruker spectrometers operating at 50 MHz. Chemical shifts in the ^{1}H and ^{13}C NMR spectra are reported in parts per million (δ) relative to the residual proton shift in deuteriochloroform, at 7.25 ppm for the ^{1}H NMR spectrum, and the central signal of the triplet at 77.0 in the carbon spectrum. Multiplicities, where quoted, are reported using the following convention s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. IR spectra were recorded on a Perkin Elmer 983 spectrometer. Mass spectra were obtained using a VG/Kratos MS12 spectrometer or a VG/Kratos MS90S spectrometer for high resolution work.

Separation of compounds was carried out by flash column chromatography, under reduced pressure, on Merck Kieselgel 60H. Column solvents, pentane and ethylacetate, were used, unpurified or dried.

All reactions were carried out under a nitrogen atmosphere. THF and Et_2O were distilled prior to use from sodium/benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2, and CCl_4 distilled from P_2O_5. All distilled solvents were stored over 4Å molecular sieves.

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



(247)

Ref: N. M. Klyvera and I. A. Rubstov, *Chem. Abstr.* **63**, 17875c

To a flame-dried 100 ml round bottomed flask containing oven-dried magnesium turnings (2 g, 0.08 mol) under nitrogen, and fitted with an efficient reflux condenser was added THF (20 ml). To this was added Ethylbromide (10.01 g, 0.09 mol) in THF (40 ml) over 1h. The reaction was maintained at reflux during the course of the addition. After this period, the Grignard formed was transferred, under positive nitrogen pressure via a Teflon tube, and needle, to a pressure equilibrating dropping funnel, which was placed in the middle neck of a 500 ml three-necked round bottomed flask. The outer two necks form the inlet and outlet of acetylene gas, which was bubbled through THF (50 ml), after first passing through an acetone/solid carbon dioxide trap at -78°C. The THF was left to saturate with acetylene gas for 10-15 mins, after which time the ethylmagnesiumbromide in THF was added at 0°C over 1½ h to form a deep red solution. After the addition was complete, the acetylene flow was stopped, and chloroacetone (5.55 g, 0.06 mol) in THF (20 ml) was added over 45 mins at 0°C and left to stir for a further 30 mins. After this time, saturated ammonium chloride

(30 ml) was cautiously added and the resultant solution vigorously stirred for a further 30 mins. The solution was then transferred to a separating funnel, and the aqueous lower layer extracted with ether (3 x 15 ml). The ethereal and THF fractions were combined and dried. Most of the solvent was removed by distillation at atmospheric pressure to produce a dark brown liquid, which was fractionally distilled at reduced pressure to afford the **title compound** as a clear liquid (4.5 g, 64%) 50°C/20mmHg.

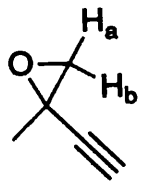
ν_{max} 3300, 3200-3600, 1240, 675 cm^{-1}

δ_H 1.62 (3H, s, CH_3), 2.52 (1H, s, CH), 2.7 (1H, bs, OH), 3.65-3.66 (2H, s, s, CH_2Cl).

δ_C 25.37 (CH_3), 53.46 (C_4), 67.71 (C_3), 72.3 (C_1), 84.5 (C_2).

Found: M^+ - Cl 83.0497. C_5H_7O requires 83.0495.

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



(246)

Ref: N. M. Klyvera and I. A. Rubstov, *Chem. Abstr.*, 1965, **63**, 17875c

To a flame-dried 3-neck 200 ml round bottomed flask under N_2 was added halohydrin (247) (2.3 g, 20 mmol) and THF (20 ml). The flask was then cooled to 0°C and powdered potassium hydroxide (15 g, 0.2 mol) was added via a powder tube fitted to the middle neck of the flask, over 20-25 mins. After complete addition, the reaction mixture was stirred for a further 1h at 10-15°C, after which time iced NH_4Cl (20 ml) was cautiously added. The mixture was then transferred to a separating funnel, and the aqueous layer extracted with ether (3 x 15 ml). The ethereal extracts were combined, dried, filtered and concentrated by distillation at atmospheric pressure. The resultant yellow liquid was fractionally distilled at atmospheric pressure to afford the title compound as a clear liquid (0.7 g, 51%), b.p. 90°C/760mmHg.

ν_{max} 2000, 1450 cm^{-1}

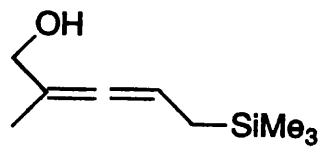
δ_H 1.55 (3H, s, CH_3), 2.27 (1H, s, CH), 2.72 (1H, d, *J*

4.95, H_a), 3.01 (1H, d, *J* 4.95, H_b).

δ_C 22.62 (CH_3), 66 (C_4), 68.1 (C_3), 70.24 (C_1), 83.1 (C_2)

Found: M^+ 82.0408. C_5H_6O requires M 82.0418.

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



(245)

Ref: H. Kleijn and P. Vermeer, *J. Org. Chem.*, 1985, **50**, 5143

Pre-dried CuI (0.419 g, 2.2 mmol) was placed in a 50 ml flame-dried round bottomed flask under N_2. Dry ether (4 ml) was added and the flask chilled to 0°C using an ice/water bath. Lithium(methyltrimethylsilane, 1M solution in pentanes) (4.4 ml, 4.4 mmol) was added in 2 equivalent portions to produce a clear brown solution. The flask was then cooled to -78°C with an acetone/dry ice bath, and a precipitate was observed to form. Epoxide (246) (180.4 mg, 2.2 mmol) in dry ether (8 ml) was added dropwise to the pre-formed cuprate over 10-15 mins. The reaction mixture was left stirring at -78°C for a further 2h. After this period, the reaction mixture was diluted with dry ether (40 ml), and quenched with NH_4Cl solution (25 ml). The contents of the flask were then transferred to a separating funnel, and the aqueous layer extracted with ether (3 x 15 ml). The ethereal fractions were combined, dried and concentrated under reduced pressure rotary evaporation. The resultant crude oil was purified by flash column chromatography using a pentane/ethyl acetate gradient (10% increments) to afford the **title compound** as a clear oil (0.109 g, 51%).

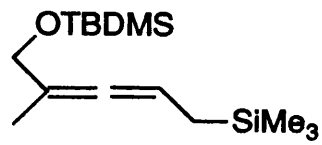
ν_{max} 3200-3600, 1950, 860 cm^{-1}

δ_H 0.2-0.3 (9H, s, $SiMe_3$), 1.31 (2H, d, *J* 8, CH_2Si), 1.7 (3H, d, *J* 2.86, CH_3), 3.95 (2H, d, *J* 2, CH_2O), 5.1 (1H, m, CH)

δ_C 0 ($SiCH_3$), 16.1 (CH_3), 17.9 (C_5), 65.2 (C_1), 87.2 (C_4), 98.6 (C_2), 199 (C_3)

Found: M^+ 170.1107. $C_9H_{18}OSi$ requires M 170.1126.

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



(256)

Ref: S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99

To a flame-dried flask under N_2 was added the allenylmethylsilane (245) (0.3 g, 1.76 mmol) in dry dichloromethane (2 ml). To this was added *tert*-butyldimethylsilylchloride (0.292 g, 1.94 mmol), triethylamine (0.350 g, 3.52 mmol) and a catalytic quantity of 4,4-dimethylamino pyridine (5mg). The reaction mixture was stirred overnight at room temperature. After this period it was diluted with ether (5 ml) and washed with $NaHCO_3$ (5 ml) and water (5 ml). The organic fraction was dried and concentrated by reduced pressure rotary evaporation, to yield a crude yellow oil, which was purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments), yielding the **title compound** as a clear oil (0.305 g, 61%).

ν_{max} 1945, 860 cm^{-1}

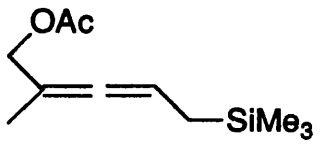
δ_H 0.1-0.3 (15H, s, SiMe), 0.9 (9H, s, ^tBu), 1.34 (2H, d, *J* 8, CH_2Si), 1.73 (3H, d, *J* 3, CH_3), 4.07 (2H, d, *J* 2,

CH_2O), 5.1 (1H, m, CH)

δ_C -1.96, -1.75 ($SiCH_3$), 16.02 (CH_3), 18.44 (C_5), 26.4 (^tBu), 64.05 (C_1), 90.81 (C_4), 98.3 (C_2), 199.39 (C_3)

Found: $M^+ - CH_3$ 269.1703. $C_{14}H_{29}OSi_2$ requires 269.1756.

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



(252)

To a flame-dried flask under N_2 was added the allenylmethylsilane (245) (0.246 g, 1.76 mmol) in dry dichloromethane (2 ml). To this was added acetic anhydride (0.5 g, 1.72 mmol), triethylamine (0.725g, 7.2 mmol) and a catalytic quantity of 4,4-dimethylamino pyridine (5mg). The reaction mixture was stirred at room temperature overnight. After this period it was diluted with ether (5 ml) and washed with $NaHCO_3$ (5 ml) and water (5 ml). The organic fraction was dried and then concentrated by reduced pressure rotary evaporation, to yield a crude yellow oil, which was purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). The title compound was obtained as a clear oil (0.233 g, 76%).

ν_{max} 1730, 1950, 1250, 860 cm^{-1}

δ_H 0.1 (9H, s, $SiCH_3$), 1.28 (2H, d, J 8, CH_2Si), 1.76 (3H, d, J 3, CH_3), 2.04 (3H, s, $COCH_3$), 4.43 (2H, d, J 2,

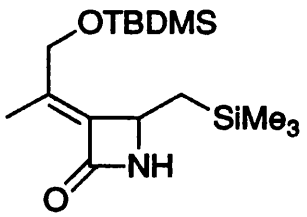
CH_2O), 5.08 (1H, m, CH).

δ_C 0 ($SiCH_3$), 16.52 (C_5), 17.8 (CH_3), 20.7 (CH_3CO), 66.5 (C_1), 88.1 (C_4), 94.3 (C_2), 170.9 $CH_3\underline{C}O$), 202.7 (C_3).

Found: M^+ 212.1221. $C_{11}H_{20}O_2Si$ requires M 212.1227.

3-[2'-(O-*tert*-butyldimethylsilyl)methylethylidene]

-4-(trimethylsilylmethyl)-2-azetidinone



(257)

To a flame-dried round bottomed flask under N_2 was added TBDMS-protected allenylmethylsilane (256) (0.293 g, 1.03 mmol) in CCl_4 (10.15 ml). The flask was chilled to 0°C and CSI (0.0901 ml, 1.23 mmol) was added dropwise over 2 mins. The reaction mixture was stirred at 0°C for 4.5h, then 25% Na_2SO_3(aq)(10.5 ml) was added, and the mixture left to stir overnight at room temperature. The resultant biphasic reaction mixture was then transferred to a separating funnel and the organic (lower) layer was retained, dried, and concentrated *in vacuo* to give a crude solid, which was subsequently purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). This yielded the **title compound** as a crystalline solid (0.104 g, 31%) m.p. 109-111°C.

ν_{max} 2860-2960, 1740, 1470, 1260, 840, 1070-1110 cm^{-1}

δ_H 0.2 (9H, s, $SiMe_3$), 0.6 (6H, s, $SiMe_2$), 0.9 (9H, s, ^tBu), 0.92 (1H, dd, *J* 14.77, 10.22, C<u>H</u>HSi), 1.23 (1H,

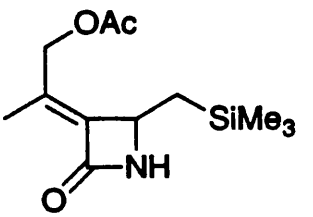
dd, J 14.77 2.91, CH<u>H</u>Si), 1.97 (3H, s, CH_3), 4.11 (2H, s, CH_2OSi), 4.25-4.35 (1H, dd, J 10.22 2.91, CH), 6.15 (1H, bs, NH).

δ_C 0-0.06 ($SiCH_3$), 14.8 (CH_3), 20.61 (<u>C</u>Me_3) 22.64 (CH_2Si), 25 (C<u>Me</u>$_3$), 54.34 (C_4), 64.11 (CH_2OSi), 137.33 (C_3) 138.48 (C_1'), 165 (C_2).

Found: M^+ 327.2041. $C_{16}H_{33}NO_2Si_2$ requires M 327.2040.

3-[(2'-Acetoxy)methylethylidene]-4-(trimethylsilylmethyl)-

-2-azetidinone



(253)

To a flame-dried round bottomed flask under N_2 was added O-acetyl allenylmethylsilane (252) (0.297 g, 1.4 mmol) in CCl_4 (14 ml). The flask was then chilled to 0°C and CSI (0.126 ml, 1.45 mmol) was added dropwise over 2 mins. The mixture was stirred at 0°C for 18h, then quenched with a water (1.8 ml), ice (8 g), $NaHCO_3$ (4.27g), Na_2SO_3 (3 g) mixture for 10-15 mins. When the CCl_4 layer was of neutral pH the reaction mixture was transferred to a separating funnel and the organic (lower) layer retained, dried and concentrated *in vacuo* to give a crude solid, which was subsequently purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). This yielded the title compound as a crystalline solid (4.2 mg, 1.17%) m.p. 121-123°C.

ν_{max} 3300-3600, 2850-2950, 1740, 1720 cm^{-1}

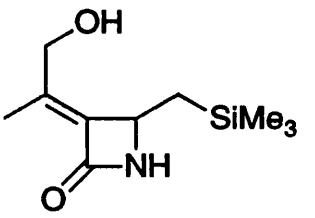
δ_H 0 (9H, s, $SiMe_3$), 0.94 (1H, dd, *J* 14.63 2.76, CHHSi), 1.2 (1H, dd, *J* 14.63 10.58, CHHSi), 2.03 (3H, s,

$\underline{C}H_3C{=}C$), 2.09 (3H, s, $\underline{C}H_3CO$), 4.3 (1H, dd, J 10.58 2.76, CH), 4.54 (2H, s, CH_2OAc), 6.1-6.2 (1H, bs, N$\underline{H}$).

δ_C 0 ($SiCH_3$), 15.2 ($\underline{C}H_3C{=}C$), 20.78 ($\underline{C}H_3CO$), 22.46 (C_4'), 54 (C_4), 63.82 (C_2'), 132.08 (C_3), 141.53 (C_1'), 164.31 (C_2), 170.46 ($O\underline{C}OCH_3$).

Found: $M^+ - CH_3$ 240.1043. $C_{11}H_{18}NO_3Si$ requires 240.1050.

3-[(2'-hydroxy)methylethylidene]-4-(trimethylsilylmethyl)-2-azetidinone



(259)

To a flame-dried 50 ml round-bottomed flask under N_2 was added TBDMS-protected β-lactam (257) (49.1 mg, 0.15 mmol) and THF (5.0 ml). To this was added TBAF (1 M in THF) (0.195 ml, 0.195 mmol) dropwise, and then left to stir overnight at room temperature. After this time the reaction mixture was diluted with ether (5 ml), washed with brine (5 ml) and dried. Purification by flash column chromatography using a pentane/ethylacetate gradient (10% increments) yielded the title compound as a white solid (28.4 mg, 86%) m.p. 139-141°C.

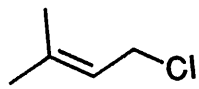
ν_{max} 3200-3600, 1740, 1200, 700-800 cm^{-1}

δ_H 0.1 (9H, s, $SiMe_3$), 1.1-1.3 (2H, m, CH_2Si), 1.97 (3H, s, CH_3), 4.02-4.08 (1H, dd, *J* 15.63 8.75, C_4-H), 4.1 (2H, s, CH_2O), 6.15 (1H, bs, NH), 6.36 (1H, bs, OH).

δ_C 0 (Si-C), 14.66 (CH_3), 22.74 (CH_2Si), 54.03 (C_4), 65.64 (CH_2O), 137.41 (C_3), 139.43 (C_1'), 165 (C_2).

Found: M^+ 213.1226. $C_{10}H_{19}O_2NSi$ requires M 213.1220

1-Chloro-3-methyl-2-butene



(283)

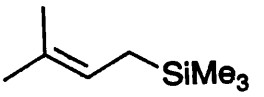
Ref: R. M. Coates, D. A. Ley and P. L. Cavender, *J. Org. Chem.*, 1978, **43**, 4915.

A flame-dried flask under N_2 was charged with 1-hydroxy-3-methyl-2-butene (5 g, 58 mmol) and pentane (30 ml) and then chilled to 0°C using an ice/water bath. Phosphorus (III) chloride (2.53 ml, 28.91 mmol) was added dropwise and the reaction allowed to stir at 0°C for a further 30 mins after which time methanol (2.5 ml) was cautiously added. The reaction was then washed with saturated $NaHCO_3$ (4 ml), water (4 ml) and brine (4 ml), concentrated *in vacuo* (no heating) and then distilled to yield the **title compound** as a clear liquid (2.71 g, 44%) 90°C/760mmHg.

ν_{max} 2850-2980, 1670, 740-800 cm^{-1}

Found: M^+ 104.0381 (^{35}Cl) 106.0347 (^{37}Cl). C_5H_9Cl requires M 104.0392 (^{35}Cl) 106.0363 (^{37}Cl).

1-Trimethylsilyl-3-methyl-2-butene



(167)

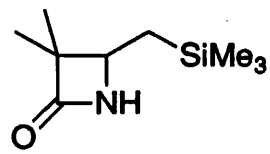
Ref: J. Dubac, A. Laporterie, H. Iloughmane, J. P. Pillot, G. Déléris and J. Dunoguès, *J. Organomet. Chem.*, 1985, **281**, 149 (Adapted)

To a flame-dried flask containing oven-dried Mg (0.316 g, 13 mmol) and fitted with a reflux condenser, was added THF (2 ml) and TMSCl (0.7 g, 6.45 mmol). To initiate the Grignard reaction, 2-3 drops of allylic chloride (283) were added at 0°C. Once initiated (warming of flask), the remainder of allylic chloride (0.482 g, 4.61 mmol) in the THF (3 ml) was added dropwise over 2h. After this period, the reaction was allowed to stir overnight at room temperature, diluted with pentane (5 ml), filtered through Celite 535, washed with water (5 ml) and brine (5 ml), then distilled to yield the **title compound** as a clear liquid (0.388 g, 59.23 %) 87°C/760mmHg.

ν_{max} 2850-2990, 1610, 845 cm^{-1}

Found: M^+ 142.1184. $C_8H_{18}Si$ requires M 142.1178

3,3-Dimethyl-4-trimethylsilylmethyl-2-azetidinone



(174)

To a flame-dried round bottomed flask under N_2 was added allylsilane (167) (0.331 g, 2.33 mmol) in CCl_4 (13 ml). The flask was then chilled to 0°C and CSI (0.202 ml, 2.32 mmol) was added dropwise over 2 mins. The mixture was stirred at 0°C for 2h, then quenched with Na_2SO_3 (aq) (25%) (13 ml) solution overnight. The reaction mixture was then transferred to a separating funnel and the organic (lower) layer retained, dried and concentrated *in vacuo* to give a crude solid, which was subsequently purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). This yielded the **title compound** as a crystalline solid (0.22 g, 52 %) m.p 87-89°C.

ν_{max} 2900-2990, 1750, 850 cm^{-1}

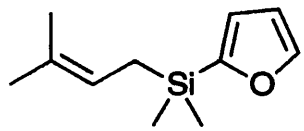
δ_H 0 (9H, s, $SiMe_3$), 0.7-0.83 (2H, m, CH_2), 1.07 (3H, s, CH_3), 1.22 (3H, s, CH_3), 3.38 (1H, dd, *J* 10.31 5.06).

δ_C -1.4 (SiMe), 17.01 (CH_3), 18.68 (CH_2), 22.25 (CH_3),

54.53 (C_3), 58.1 (C_4), 175.2 (C_2).

Found: M^+ 185.1221. $C_9H_{19}ONSi$ requires M 185.1230.

1-[(Furyl)dimethylsilyl]-3-methyl-2-butene



(295)

Ref: J. Dubac, A. Laporterie, H. Iloughmane, J. P. Pillot, G. Déléris and J. Dunoguès, *J. Organomet. Chem.*, 1985, 281, 149 (Adapted)

To a flame-dried flask containing oven-dried Mg (0.35 g, 14.4 mmol) and fitted with a reflux condenser, was added THF (4.35 ml) and furyldimethylchlorosilane (293) (0.760 g, 5.25 mmol). To initiate the Grignard reaction, 2-3 drops of allylic chloride (283) were added at 0°C. Once initiated (warming of flask), the remainder of the allylic chloride (0.491 g, 4.7 mmol) in THF (2.7 ml) was added dropwise over 2h. After this period, the reaction was allowed to stir overnight at room temperature, diluted with pentane, filtered through Celite 535, washed with water (4 ml) and brine (4 ml) then distilled to yield the **title compound** as a clear liquid (0.477 g, 52%) 150°C/22mmHg.

ν_{max} 2850-2950, 1580, 845 cm^{-1}

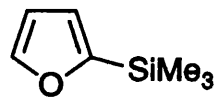
δ_H 0.23 (6H, s, $SiMe_2$), 1.3 (2H, d, *J* 7.61, CH_2Si), 1.5 (3H, s, CH_3), 1.68 (3H, s, CH_3), 5.14 (1H, tq, *J* 7.61

1.4, CH), 6.37 (1H, dd, *J* 3.23 1.64), 6.6 (1H, dd, *J* 3.23 0.55), 7.64 (1H, dd, *J* 1.64 0.55).

δ_C -3.58 (SiMe), 17.01 (CH_2), 17.5 (CH_3), 25.76 (CH_3), 109.32 (CH), 118.59 (C_2), 119.69 (CH), 129.98 (C_3), 146.55 (CH), 159.23 (CH).

Found: M^+ 194.1133. $C_{11}H_{18}OSi$ requires M 194.1140

2-Trimethylsilylfuran



(300)

A flame-dried flask under N_2 was charged with n-Buli (2.3M solution in pentanes) (6 ml, 13.8 mmol) and dry ether (15 ml). The reaction was then cooled to -20°C using an ice/methanol bath, then furan (1 ml, 13.76 mmol) was added dropwise at -20°C. After the addition was complete, the reaction was allowed to warm to room temperature and then refluxed gently for 4h. After cooling to 0°C, TMSCl (1.74 ml, 13.76 mmol) was added dropwise and the reaction allowed to stir overnight at room temperature. The reaction was then concentrated *in vacuo* (no heating) and the resultant yellow liquid distilled under reduced pressure to yield the title compound as a clear liquid.
(1.523 g, 76%) 120°C/20mmHg.

ν_{max} 2850-2980, 830 cm^{-1}

δ_H 0.24 (9H, s, $SiMe_3$), 6.37 (1H, dd, *J* 3.20 1.64), 6.61 (1H, dd, *J* 3.20 0.56), 7.64 (1H, dd, *J* 1.64 0.56 Hz)

δ_C -1.7 (SiMe), 109.27, 119.38, 146.51, 155.18

Found: M^+ 140.0648. $C_7H_{12}OSi$ requires M 140.0657

2-[(Chloromethyl)dimethylsilyl]furan

(265)

A flame-dried round bottomed flask fitted with an efficient condenser and under N_2 was charged with n-Buli (2.3M solution in pentanes) (6 ml, 13.8 mmol) and ether (35 ml). The flask was then chilled to -20°C using an ice/methanol/salt bath. Furan (1 ml, 13.76 mmol) was added dropwise at -20°C over 2 mins and the flask allowed to warm to room temperature and then gently refluxed for 4h to produce a bright orange solution of 2-lithiofuran. After this time, the reaction was allowed to cool to room temperature, then further chilled to 0°C using an ice bath. (Chloromethyl)dimethylchlorosilane (1.81 ml, 13.76 mmol) in ether (3 ml) was added dropwise, and the reaction left to stir for 18h at room temperature. The reaction mixture was then filtered through Celite 535, washed with pentane (2 x 10 ml), concentrated *in vacuo* and distilled at reduced pressure to yield the title compound as a clear liquid (1.21 g, 51%) 160°C/20mmHg.

ν_{max} 2850-2950, 1550, 1230-1260, 810-840 cm^{-1}

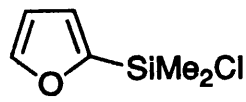
δ_H 0.4 (6H, s, $SiMe_2$), 2.94 (2H, s, CH_2Cl), 6.41 (1H, dd,

J 3.26, 1.65), 6.74 (1H dd, J 3.26, 0.54) 7.67 (1H, dd, J 1.65 0.54).

δ_C -4.91 (Si-C), 29.48 ($\underline{C}H_2Cl$), 109.56 (CH) 121.36 (CH), 147.27 (CH), 156.12 (CH).

Found: M^+ 174.0262 (^{35}Cl) 176.0243 (^{37}Cl). $C_7H_{11}OSiCl$ requires M 174.0267 (^{35}Cl) 176.0238 (^{37}Cl)

2-Dimethylsilylchlorofuran



(293)

A flame-dried round bottomed flask fitted with an efficient condenser and under N_2 was charged with n-butyllithium (2.3M solution in pentanes) (6 ml, 13.8 mmol) and ether (35 ml). The flask was then chilled to -20°C using an ice/methanol/salt bath. Furan (1 ml, 13.76 mmol) was added dropwise at -20°C over 2 mins and the flask allowed to warm to room temperature and then gently refluxed for 4h to produce a bright orange solution of 2-lithiofuran. A second flame-dried flask with side arm was charged with dimethyldichlorosilane (3.54 g, 27.44 mmol) and ether (20 ml) and then chilled to 0°C using an ice/water bath. To this was added the pre-formed 2-lithiofuran solution over 50 mins. After complete addition, the reaction was allowed to stir for a further 18h at room temperature, then filtered through a pad of Celite 535 and washed with pentane (2 x 10 ml). Concentration by reduced pressure rotary evaporation gave a dark brown liquid which was distilled at reduced pressure to yield the **title compound** as a clear liquid (1.1 g, 50%), 50°C/20mmHg.

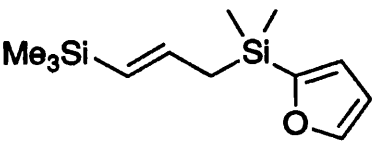
ν_{max} 2830-2980, 850 cm^{-1}

δ_H 0.68 (6H, s, $SiMe_2$), 6.43 (1H, dd, *J* 3.3 1.65), 6.85 (1H, dd, *J* 3.3 0.54), 7.69 (1H, dd, *J* 1.65 0.54)

δ_C 1.56 (SiMe), 109.73, 121.80, 147.68, 155.36

Found: M^+ 160.0108 (^{35}Cl) 162.0093 (^{37}Cl) C_6H_9OSiCl requires M^+ 160.0111 (^{35}Cl) 162.0081 (^{37}Cl)

trans-1-(Trimethylsilyl)-3-[(furyl)dimethylsilyl]-1-propene



(317)

Ref: I. Fleming and J. A. Langley, *J. Chem. Soc. Perkin Trans. 1*, 1981, 1421

A flame-dried round bottomed flask under N_2 was charged with N,N tetramethylethylene diamine (0.822 ml, 5.4 mmol) and n-Buli (2.3M solution in pentanes) (2.05 ml, 4.7 mmol) and then chilled to -5°C using an ice/salt/water bath. Allyltrimethylsilane (0.537 g, 4.7 mmol) was added dropwise over 2-3 mins and the reaction allowed to stir at -5°C for a further 3.25h. After this period 2-dimethylsilylchlorofuran (293) (0.764 g, 4.7 mmol) was added dropwise and the solution stirred for a further 1h at -5°C. The contents of the flask were then poured into aqueous HCl (1M, 4 ml) and then transferred to a separating funnel. The reaction mixture was then extracted with pentane (2 x 10 ml), and the organic extracts washed with HCl (4 ml) and water (4 ml), dried and concentrated by reduced pressure rotary evaporation. The resultant residue was distilled at reduced pressure to yield the **title compound** as a clear liquid (0.679 g, 54%) 200°C/20mmHg.

ν_{max} 2820-2990, 1600, 1250, 840, 855 cm^{-1}

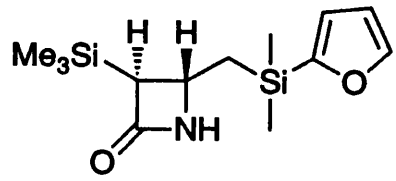
δ_H 0 (9H, s, $SiMe_3$), 0.22 (6H, s, $SiMe_2$), 1.83 (2H, dd, *J* 7.81 1.24, CH_2Si), 5.4-5.5 (1H, dt, J 16.88, 1.24 $CHSiMe_3$), 5.9-6.1 (1H, dt, *J* 16.88 7.81), 6.36 (1H, dd, *J* 3.18 1.64), 6.61 (1H, dd, *J* 3.18 0.55), 7.65 (1H, dd, *J* 1.64 0.55).

δ_C -3.78 ($SiMe_3$), -1.04 ($SiMe_2$), 26.44 (CH_2), 109.35 (CH), 120 (CH), 129.23 (CH), 142.43 (CH), 146.71 (CH), 158.71 (CH)

Found: M^+ 238.1215. $C_{12}H_{22}OSi_2$ requires M 238.1209

trans-3-(Trimethylsilyl)-4-[(dimethylfurylsilyl)methyl]

-2-azetidinone



(320)

A flame-dried flask under N_2 was charged with allyl/vinyldisilane (317) (0.174 g, 0.73 mmol) and CCl_4 (7.4 ml). The flask was chilled to 0°C and CSI (0.0833 ml, 9.62 mmol) was added dropwise over 2 mins. The reaction was allowed to stir for a further 45 mins at 0°C then 25% Na_2SO_3(aq)(8 ml) was added, and the resultant biphasic mixture left to stir overnight at room temperature. After this time, the contents of the flask were transferred to a separating funnel and the organic (lower) layer retained, dried and concentrated *in vacuo* to give a crude oil which was subsequently purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). This yielded the **title compound** as a clear oil (0.055 g, 27%).

ν_{max} 3220, 1740, 855 cm^{-1}

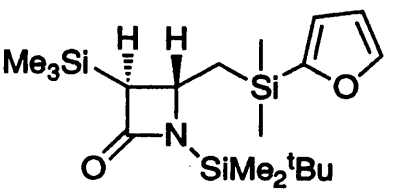
δ_H 0.07 (9H, s, $SiMe_3$), 0.28 (6H, s, $SiMe_2$), 1.1-1.3 (2H, m, CH_2Si), 2.36 (1H, d, *J* 2.22, C_3-H), 3.45-3.6 (1H, m, C_4-H), 5.75 (1H, bs, NH), 6.39 (1H, dd, *J* 3.24 1.65), 6.65 (1H, dd, 3.24 0.5), 7.65 (1H, dd, *J* 1.65 0.5)

δ_C -2.81, 24.25 (CH_2), 47.01 (C_3), 51.87 (C_4), 109.68, 120.86, 147.07, 157.62, 170.52 (C_2).

Found: M^+ 281.1272. $C_{13}H_{23}NO_2Si_2$ requires M 281.1260

trans-3-(Trimethylsilyl)-4-[(dimethylfurylsilyl)methyl]

N-*tert*-butyldimethylsilyl-2-azetidinone



(342)

Ref: E. J. Corey, H. Cho, Ch. Rücker and D. H. Hua,

Tetrahedron Lett., 1981, **22**, 3455.

A flame-dried flask under N_2 was charged with azetidinone (320) (0.144 g, 0.512 mmol) and dichloromethane (2 ml). To this was added 2,6 lutidine (0.109 g, 1.02 mmol) and TBDMSOTf (0.163M in CH_2Cl_2) (3.45 ml, 0.562 mmol). The reaction was allowed to stir overnight at room temperature then diluted with ether (5 ml), washed with saturated $CuSO_4$ (5 ml), water (5 ml) and brine (5 ml) and dried to afford a crude oil which was purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments) to give the title compound as a clear oil (0.177 g, 91%).

ν_{max} 2850-2990, 1735, 800-900 cm^{-1}

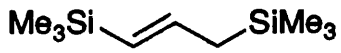
δ_H 0.02 (9H, s, $SiMe_3$), 0.17-0.19 (6H, s, $SiMe_2$), 0.26-0.29 (6H, s, CH_2SiMe_2), 0.95 (9H, s, ^tBu), 1.05-1.3 (1H, dd, *J*

14.21 11.37), 1.45-1.55 (1H, dd, *J* 14.21 2.84), 2.35 (1H, d, *J* 2.48), 3.45 (1H, dt, *J* 11.31 2.48), 6.38 (1H, dd, *J* 3.24 1.65), 6.63 (1H, dd, *J* 3.24 0.49), 7.55 (1H, dd, *J* 1.65 0.49).

δ_C -5.79, -5.12, -2.47, 17.92 (CH_2Si), 48.50 (C_3), 49.86 (C_4), 109.55 (CH), 120.72 (CH), 146.83 (CH), 157.69 (CH), 174.73 (C=O).

Found : M^+ 380.1885. $C_{18}H_{34}NO_2Si_3$ requires M 380.1887.

trans-1-(Trimethylsilyl)-3-(trimethylsilyl)-1-propene



(315)

Ref: I. Fleming and J. A. Langley, *J. Chem. Soc. Perkin Trans. 1*, 1981, 1421

A flame-dried round bottomed flask under N_2 was charged with N,N tetramethylethylene diamine (2.06 ml, 13.53 mmol) and n-Buli (2.3M solution in pentanes) (5.12 ml, 11.77 mmol) and then chilled to -5°C using an ice/salt/water bath. Allyltrimethylsilane (1.87 ml, 11.8 mmol) was added dropwise over 2-3 mins, and the reaction allowed to stir at -5°C for a further 3.25h. After this period trimethylchlorosilane (1.5 ml, 11.8 mmol) was added dropwise, and the solution stirred for a further 1h at -5°C. The contents of the flask were then poured into aqueous HCl (1M, 6 ml) and then transferred to a separating funnel. The reaction mixture was then extracted with pentane (2 x 6 ml), and the organic extracts washed with HCl (1M) (6 ml) and water (6 ml), dried and concentrated by reduced pressure rotary evaporation. The resultant residue was distilled at reduced pressure to yield the title compound as a clear liquid (1.71 g, 78%) 145°C/22mmHg.

ν_{max} 960, 850 cm^{-1}

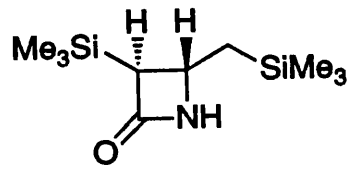
δ_H -0.18 (9H, s, $SiMe_3$), 0.25 (9H, s, $SiMe_3$), 1.62 (2H, dd, *J* 7.77 1.25), 5.53-5.5 (1H, dt, *J* 18.41 1.25), 5.9-6.11 (1H, dt, *J* 18.41 7.77)

δ_C -2.03, -1.0 (Si-C), 28.33 (CH_2), 128.01 (C_2), 143.67 (C_1)

Found: M^+ 186.1256. $C_9H_{22}Si_2$ requires M 186.1254

trans-3-Trimethylsilyl-4-trimethylsilylmethyl

-2-azetidinone



(318)

A flame-dried flask under N_2 was charged with allyl/vinyldisilane (315) (1.42 g, 7.62 mmol) and CCl_4 (38 ml). The flask was then chilled to 0°C and CSI (0.731 ml, 8.39 mmol) was added dropwise over 2 mins. The reaction was allowed to stir for a further 3h at 0°C then 25% Na_2SO_3(aq) (35 ml) was added, and then left to stir overnight at room temperature with efficient mixing of the two layers. After this time, the biphasic reaction mixture was transferred to a separating funnel and the organic (lower) layer retained, dried and concentrated *in vacuo* to give a crude solid which was subsequently purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). This yielded the **title compound** as a white, crystalline solid (0.454 g, 26%) m.p. 94-96°C.

ν_{max} 3250,1745, 860 cm^{-1}

δ_H -0.1 (9H, s, $SiMe_3$), 0 (9H, s, $SiMe_3$), 0.88-0.98 (2H, m, CH_2Si), 2.24 (1H, d, *J* 4.36), 3.37-3.45 (1H, dt, *J* 8.44

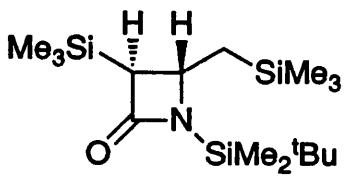
4.36), 5.62 (1H, bs, NH)

δ_C -2.65 ($SiMe_3$), -1.08 ($CH_2Si\underline{Me}_3$), 25.71 (C_4'), 47.65 (C_3), 51.90 (C_4), 170.56 (C_2)

Found: M^+ 229.1312 $C_{10}H_{23}NOSi_2$ requires M 229.1311

trans-3-Trimethylsilyl-4-trimethylsilylmethyl

N-*tert*-butyldimethylsilyl-2-azetidinone



(349)

Ref: E. J. Corey, H. Cho, Ch. Rücker and D. Hua, *Tetrahedron Lett.*, 1981, 22, 3455

A flame-dried flask under N_2 was charged with azetidinone (318) (0.343 g, 1.01 mmol) and dichloromethane (2 ml). To this was added 2,6 lutidine (0.23 ml, 2.02 mmol) and TBDMSOTf (0.39M in CH_2CH_2) (6.13 ml, 2.42 mmol). The reaction was allowed to stir overnight at room temperature then diluted with ether (5 ml), washed with saturated $CuSO_4$ (5 ml), water (5 ml) and brine (5 ml), dried to afford a crude oil which was purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments) to give the **title compound** as a clear oil (0.483 g, 85%).

ν_{max} 1720, 1260, 800-900 cm^{-1}

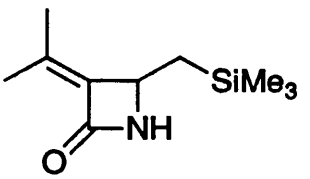
δ_H 0.02 (9H, s, CH_2SiMe_3), 0.1 (9H, s, $SiMe_3$), 0.15-0.17 (6H, s, $SiMe_2$), 0.93 (9H, s, ^tBu), 1.2-1.35 (2H, m, CH_2Si), 2.41 (1H, d, *J* 3.75 C_3-H), 3.45 (1H, dt, *J* 12.5 3.75 C_4-H).

δ_C -5.8, -5.13, -2.33, -1.06 ($SiCH_3$), 25.62 (CH_2Si), 26.25 ($C\underline{Me}_3$), 48.90 (C_3), 49.90 (C_4), 174.31 (C_2)

Found: M^+ 343.2196. $C_{16}H_{37}NOSi_3$ requires M 343.2172

3-Isopropylidene-4-(methyltrimethylsilyl)

-2-azetidinone



(357)

A flame-dried flask under N_2 was charged, in the following order, with THF (5.55 ml), DMEU (2.78 ml), diisopropylamine (0.5 ml, 3.47 mmol) and n-Buli (1.93M solution in pentanes) (1.798 ml, 3.47mmol). The flask was then cooled to -25°C to -30°C, allowing the LDA approximately 30 minutes to form. After this time, a portion of this pre-formed LDA/DMEU stock solution (1 ml, 3.27×10^{-4}mol) was quickly transferred to a second flame-dried flask at -30°C. To this second flask was added azetidinone (349) (0.112 g, 3.27×10^{-4}mol) in THF (2 ml), and the reaction allowed to stir at -30°C for a further 30 mins. After this time acetone (30 l, 4.08×10^{-4}mol) was added and the reaction allowed to warm to room temperature. The reaction was then diluted with ether (15 ml) and washed with water (10 ml). The aqueous layer was extracted with ether, and the ethereal extracts combined, dried and concentrated *in vacuo* to yield a crude oil. This was taken up in acetonitrile (6.75 ml) transferred to a round bottomed flask, to which was added potassium fluoride (0.126 g, 2.16 mmol), and the reaction allowed to stir at room temperature for 48h. After this time, the

solvent was removed *in vacuo* and the resultant oil purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments) to yield the **title compound** as a crystalline solid (0.019 g, 30%) m.p. 98-99°C.

ν_{max} 3250, 1740, 840 cm^{-1}

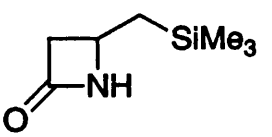
δ_H 0.43 (9H, s, $SiMe_3$), 0.85-1.1 (2H, m, CH_2), 1.71 (3H, s, CH_3), 2.01 (3H, s, CH_3), 4.21 (1H, dd, *J* 10.18 2.28), 6.08 (1H, bs, NH)

δ_C -1.12 ($SiCH_3$), 15.25 (CH_3), 19.76 (CH_3), 22.03 (CH_2), 51.77 (CH), 135.72 (C_3), 138.46 (C_3'), 165.31 (C_2)

Found: M^+ 197.1235. $C_{10}H_{19}NOSi$ requires M 197.1230

Also isolated by flash column chromatography;

4-(Methyltrimethylsilyl)-2-azetidinone



(279)

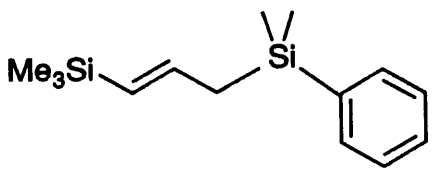
ν_{max} 1745, 1050 cm^{-1}

δ_H 0.04 (9H, s, $SiMe_3$), 0.85-1.00 (1H, dd, *J* 14.25 9.05, C<u>H</u>HSi), 1.04-1.09 (1H, dd, *J* 14.25 5.67, CH<u>H</u>Si), 2.51 (1H, dd, *J* 14.67 2.42 C3-H,) 3.08 (1H, dd, *J* 14.67 4.88), 3.77 (1H, m, C4-H)

δ_C -1.23 ($SiMe_3$), 24.32 (C_4'), 45.75 (C_3), 47.42 (C_4), 167.94 (C_2)

Found: M^+ 157.0922. $C_7H_{15}NOSi$ requires 157.0923

trans-1-(Trimethylsilyl)-3-[(phenyl)dimethylsilyl]-1-propene



(316)

Ref: I. Fleming and J. A. Langley *J. Chem. Soc. Perkin Trans. 1* 1981, 1421

A flame-dried round bottomed flask under N_2 was charged with N,N tetramethylethylene diamine (0.53 ml, 3.48 mmol) and n-Buli (1.93M solution in pentanes) (1.6 ml, 3.11 mmol) and then chilled to -5°C using an ice/salt/water bath. Allytrimethylsilane (0.49 ml, 3.11 mmol) was added dropwise over 2-3 mins and the reaction allowed to stir at -5°C for a further 3.25h. After this period phenyldimethylchlorosilane (0.531 g, 3.11 mmol) was added dropwise, and the solution stirred for a further 1h at -5°C. The contents of the flask were then poured into aqueous HCl (1M, 4 ml) and then transferred to a separating funnel. The reaction mixture was then extracted with pentane (2 x 5 ml), and the organic extracts washed with HCl (5 ml) and water (5 ml), dried and concentrated by reduced pressure rotary evaporation. The resultant residue was distilled at reduced pressure to yield the title compound as a clear liquid (0.431 g, 56%)70°C/0.15mmHg

ν_{max} 1610, 955, 800-850 cm^{-1}

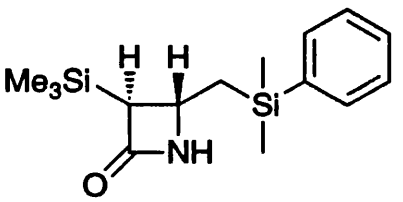
δ_H 0 (9H, s, $SiMe_3$), 0.25 (6H, s, $SiMe_2$), 1.86 (2H, dd, J 7.5 1.25, CH_2Si), 5.37-5.47 (1H, dt, *J* 16.87 1.25), 5.9-6.16 (1H, dt, *J* 16.87 7.5), 7.3-7.6 (5H, m, Ar).

δ_C -3.49, -1.04 (SiMe), 27.40 (CH_2), 127.67, 128.96, 129.65, 133.03, 133.65, 142.95

Found: M^+ 248.1426. $C_{14}H_{24}Si_2$ requires M 248.1410

trans-3-(Trimethylsilyl)-4-[(dimethylphenylsilyl)methyl]

-2-azetidinone



(319)

A flame-dried flask under N_2 was charged with allylvinyldisilane (316) (0.37 g, 1.49 mmol) and CCl_4 (7.5 ml). The flask was then chilled to 0°C and CSI (0.155 ml, 1.79 mmol) was added dropwise over 2 mins. The reaction was allowed to stir for a further 3h at 0°C then 25% Na_2SO_3(aq) (7.5 ml) was added, and then left to stir overnight at room temperature with efficient mixing of the two layers. After this time, the biphasic reaction mixture was transferred to a separating funnel and the organic (lower) layer retained, dried and concentrated *in vacuo* to give a crude solid which was subsequently purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments). This yielded the **title compound** as a white, crystalline solid (0.145 g, 33.4%) m.p. 105-107°C.

ν_{max} 3000-3040, 1740, 770 cm^{-1}

δ_H 0.05 (9H, s, $SiMe_3$), 0.31 (6H, s, s, $SiMe_2Ph$), 1.1-1.3 (2H, m, CH_2Si), 2.35 (1H, d, *J* 2.21, C_3-H), 3.4-3.55 (1H,

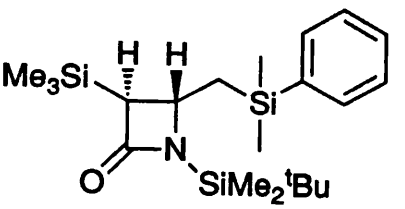
m, C_4-H), 5.5 (1H, bs, NH), 7.25-7.49 (5H, m, Ar).

δ_C -2.8, -2.3 (SiMe), 24.73 (CH_2), 47.27 (C_3), 52.07 (C_4), 128.10, 129.45, 133.42, 137.64 (Ar-C), 170.31 (C_2)

Found: M^+ 291.1456. $C_{15}H_{25}NOSi_2$ requires M 291.1467

trans-3-(Trimethylsilyl)-4-[(dimethylphenylsilyl)methyl]

N-*tert*-butyldimethylsilyl-2-azetidinone



(355)

Ref: E. J. Corey, M. Cho, Ch. Rücker and D. H. Hua, *Tetrahedron Lett.*, 1981, 22, 3455

A flame-dried flask under N_2 was charged with azetidinone (319) (0.125 g, 0.43 mmol) and dichloromethane (2 ml). To this was added 2,6 lutidine (0.1 ml, 0.88 mmol) and TBDMSOTf (0.22M in CH_2Cl_2) (2.3 ml, 0.51 mmol). The reaction was allowed to stir overnight at room temperature then diluted with ether (5 ml), washed with saturated $CuSO_4$ (5 ml), water (5 ml) and brine (5 ml), dried to afford a crude oil which was purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments) to give the **title compound** as a clear oil (0.146 g, 84%).

ν_{max} 3010-3040, 1740 cm^{-1}

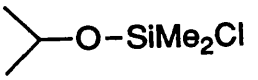
δ_H 0.01 (9H, s, $SiMe_3$), 0.19-0.22 (6H, s, $SiMe_2{}^tBu$), 0.29-0.32 (6H, s, s, $Si\underline{Me}_2Ph$), 0.98 (9H, s, ^tBu), 1.1-1.3 (2H, m, CH_2Si), 2.39 (2H, d, *J* 2.39, C3-H), 3.42-3.53 (1H, m,

C4-H), 7.27-7.51 (5H, m, Ar).

δ_C -5.12, -2.5, -2.3 (SiMe), 26.21 (CH_2), 48.69 (C_3), 49.85 (C_4), 127.92, 129.27, 133.47, 137.75 (Ar-C), 174.68 (C_2).

Found: M^+ 405.2298. $C_{21}H_{39}ONSi_3$ requires M 405.2338

Dimethylisopropoxychlorosilane



(313)

A 100 ml round-bottomed flask under N_2 was charged with dimethyldichlorosilane (15.75ml, 0.13 mol) and ether (100 ml) and then chilled to 0°C using an ice bath. To this was added isopropanol (5ml, 0.065mol) in ether (175ml) over 30 mins. The reaction was allowed to stir overnight at room temperature then concentrated *in vacuo* and fractionally distilled at atmospheric pressure to yield the title compound as a colourless liquid (7.50 g, 78%) 110°C/760mmHg.

ν_{max} 1125, 1090, 830 cm^{-1}

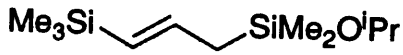
δ_H 0.44 (6H, s, $SiMe_2$), 1.18 (6H, d, *J* 6.08), 4.15 (1H, septet, *J* 6.08)

δ_C 0.73 ($SiMe_2$), 25.22 (CH_3), 66.39 (CH)

Found: M^+ 117.0733. $C_5H_{13}OSi$ requires M 117.0735

trans-1-(Trimethylsilyl)-3-[(isopropoxy)dimethylsilyl)]

-1-propene



(314)

Ref: I. Fleming and J. A. Langley, *J. Chem. Soc. Perkin Trans.1,* 1981, 1421 (Adapted)

A flame-dried round bottomed flask under N_2 was charged with N,N tetramethylethylene diamine (4.55 ml, 29.88 mmol) and n-Buli (2.3M solution in pentanes) (11.36 ml, 26.12 mmol) and then chilled to -5°C using an ice/salt/water bath. Allyltrimethylsilane (4.15 ml, 26.18 mmol) was added dropwise over 2-3 mins and the reaction allowed to stir at -5°C for a further 3.25h. After this period dimethylisopropoxychlorosilane (313) (4 g, 26.22 mmol) was added dropwise, and the solution stirred for a further 1h at -5°C. The contents of the flask were then poured into aqueous $CuSO_4$ (10 ml) and then transferred to a separating funnel. The reaction mixture was then extracted with pentane (2 x 10 ml), and the organic extracts washed with $CuSO_4$ (10 ml) and water (10 ml), dried and concentrated by reduced pressure rotary evaporation. The resultant residue was distilled at reduced pressure to yield the **title compound** as a clear liquid (2.67 g, 44%) 110°C/22mmHg.

ν_{max} 1605, 990, 810-900

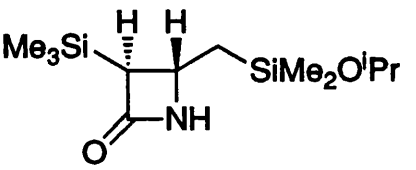
δ_H 0.007 (9H, s, $SiMe_3$), 0.08 (6H, s, $Si\underline{Me}_2O$), 1.12 (6H, d, *J* 6.08), 1.72 (2H, dd, *J* 7.71 1.25), 4.0 (1H, septet, *J* 6.08), 5.4-5.55 (1H, dt, *J* 18.42 1.25), 5.9-6.1 (1H, dt, *J* 18.42 7.71)

δ_C -1.88, ($Si\underline{Me}_3$), -1.01 ($Si\underline{Me}_2$), 25.72 (CH_3), 28.68 (C_3), 64.99 (CH), 129.01 (C_1), 142.58 (C_2).

Found: M^+ 230.1521. $C_{11}H_{26}OSi_2$ requires M 230.1515

trans-3-(Trimethylsilyl)-4-[(dimethylisopropoxysilyl)methyl]

-2-azetidinone



(321)

A flame-dried flask under N_2 was charged with allyl/vinyldisilane (314) (0.95 g, 4.12 mmol) and pentane (41 ml). The flask was then chilled to 0°C and CSI (0.43 ml, 4.94 mmol) was added dropwise over 2 mins. The reaction was allowed to stir for a further 6h at 0°C then a Na_2SO_3/NH_4Cl solution buffered at pH 7.9 (41 ml) was added, and then left to stir overnight at room temperature with efficient mixing of the two layers. After this time, the biphasic reaction mixture was transferred to a separating funnel and the organic (upper) layer retained, dried and concentrated *in vacuo* to give the **title compound** as a clear oil (0.5 g, 45.2%).

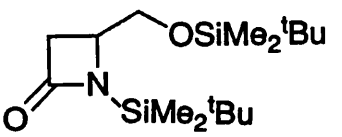
ν_{max} 3220-3400, 1740, 1260 cm^{-1}

δ_H 0-0.02 (15H, s, s, SiMe), 0.8-0.95 (2H, m, CH_2Si), 1.08-1.13 (6H, d, *J* 6.1), 2.45-2.4 (1H, d, *J* 2.03), 3.4-3.51 (1H, m, C4-H), 4.01 (1H, septet, *J* 6.1), 6.1 (1H, bs, NH).

δ_C -2.85, -1.13 (Si-C), 25.13 (CH_3), 25.53 (CH_2), 46.97 (C_3), 51.91 (C_4), 65.18 (CH), 170.97 (C_2).

Found: $M^+ - CH_3$ 258.1351. $C_{11}H_{24}NO_2Si_2$ requires M 258.1345

4-[O-*tert*-butyldimethylsilyl)methyl]-N-*tert*-butyl dimethylsilyl-2-azetidinone



(332)

A 25 ml round bottomed flask under N_2 was charged with azetidin-2-one (321) (0.252 g, 0.92 mmol), THF (2.28 ml), MeOH (2.28 ml) and $NaHCO_3$ (0.38 g, 4.58 mmol). To this was added H_2O_2 (30% solution) (0.415 ml, 4.15 mmol) and the reaction refluxed gently at 80-90°C for 5h. The reaction was then allowed to cool to room temperature and left to stir overnight. After this time well-ground $Na_2S_2O_8.5H_2O$ (9.84 g, 30 mmol) was added and reaction stirred for 30 mins to quench the excess peroxide present. The reaction mixture was subsequently diluted with ether (10 ml) and filtered through a pad of Celite 535. After concentration *in vacuo* (protective shield), the reaction mixture was diluted with ether (10 ml), dried (Na_2SO_4) filtered through Celite and concentrated *in vacuo* to yield a crude oil, (0.163 g) which was taken up in CH_2Cl_2 (4 ml) and placed in a flame-dried 25 ml round bottomed flask under N_2. To this was added 2,6 lutidine (0.9 ml, 7.72 mmol) and TBDMSOTf (0.27M solution in CH_2Cl_2 (7.16 ml, 1.94 mmol) and the reaction was left to stir at room temperature overnight, diluted with ether (5 ml), washed with saturated $CuSO_4$ (5 ml), water (5 ml) and brine (5 ml), dried to

afford a crude oil which was purified by flash column chromatography using a pentane/ethylacetate gradient (10% increments) to give the **title compound** as a clear oil (0.23 g, 76.3%).

ν_{max} 1755, 1000-1110, 760-850 cm^{-1}

δ_H 0.21 (6H, s, $SiMe_2$), 0.87 and 0.93 (18H, s, ^tBu), 2.69-3.10 (2H, ddd, *J* 15.18 5.15 2.47 Hz), 3.53-3.79 (3H, m, C_4-H and $C\underline{H}_2OSi$).

δ_C -5.76, -5.52, -5.44 ($SiCH_3$), 18.34 ($\underline{C}Me_3$), 25.73, 25.81 ($C\underline{Me}_3$), 41.15 (C_3), 50.14 (C_4), 65.20 ($\underline{C}H_2O$), 172.7 (C_2)

Found: $M^+ - CH_3$ 314.1951. $C_{15}H_{32}NO_2Si_2$ requires 314.1962

(Chloromethyl)dimethylisopropoxysilane

(263)

A flame-dried flask under N_2 was charged with (chloromethyl)dimethylchlorosilane (5.16 ml, 39.1 mmol) and ether (45 ml). The flask was then chilled to 0°C and isopropanol (3 ml, 1 mmol) in ether (25 ml) added dropwise over 20 mins. The reaction mixture was then allowed to stir overnight at room temperature, concentrated *in vacuo* and then fractionally distilled at reduced pressure to yield the **title compound** as a clear liquid (4.52 g, 69%) 114°C/22mmHg.

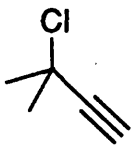
ν_{max} 1000-1050, 710 cm^{-1}

δ_H 0.24 (6H, s, $SiMe_2$), 1.15 (6H, d, *J* 6.07, 2 x CH_3), 2.75 (2H, s, CH_2Cl), 4.05 (1H, septet, *J* 6.07, CH)

δ_C -3.04 (SiMe), 25.65 (CH_3), 29.92 (CH_2), 65.69 (CH)

Found: M^+ 166.0520 (^{35}Cl) 168.0530 (^{37}Cl). $C_6H_{15}SiOCl$ requires M 166.0580 (^{35}Cl) 168.0551 (^{37}Cl)

3-Chloro-3-methyl-1-butyne



(266)

Ref: R. W. Mills, R. D. H. Murray and R. A. Raphael, *J. Chem. Soc. Perkin Trans. 1*, 1973, 133

A flame-dried round bottomed flask under N_2 was charged with pre-dried $CaCl_2$ (3.96 g, 35.66 mmol) and conc. HCl (36% w/w) (15.5 ml, 140 mmol) and then chilled to 0°C using an ice/water bath. To this was added 1,1-dimethylpropargyl alcohol (3.46 ml, 35.66 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 prior to disposal. The organic layer was retained, neutralised with K_2CO_3 and then carefully distilled at atmospheric pressure using a 10cm Vigreaux column to yield the **title compound** as a clear liquid (1.53 g, 42%) 76°C/760mmHg.

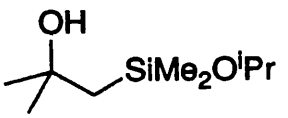
ν_{max} 3300, 660 cm^{-1}

δ_H 1.58 (6H, s, CH_3), 2.36 (1H, s, CH)

δ_C 34.54 (CH_3), 56.76 (C-Cl), 71.91 (CH), 86.38 ($Me_2C\underline{C}$)

Found: M^+ 102.0243 (^{35}Cl) 104.0180 (^{37}Cl). C_5H_7Cl requires M 102 0236 (^{35}Cl) 104.0206 (^{37}Cl)

1-(dimethylisopropoxysilyl)-2-hydroxy-2-methyl-propane



(269)

A flame-dried flask under N_2, fitted with an efficient reflux condenser and containing oven-dried Mg turnings (0.875 g, 3.6 mmol) was charged with dry THF (1 ml). To this was added a small quantity of neat chloromethylsilane (263) (ca.5-10 drops) and the flask heated with a hot air gun. To aid the Grignard initiation, a small quantity of iodine/THF solution was added (1-2 drops) and the flask heated until the brown colouration disappeared. The remainder of the chloromethylsilane (263) (0.5 g, 3.6 mmol) in the THF (2 ml) was added dropwise over 5 mins, maintaining the reaction at reflux throughout the addition period. The reaction was allowed to stir for a further 35/40 mins then acetone (0.231 ml, 3.78 mmol) was added dropwise at 0°C and the reaction allowed to stir for a further 1h at 0°C. After this time saturated NH_4Cl (3 ml) was added and the reaction filtered through a pad of Celite 535 and washed with ether (3 x 3 ml). The organic washings were washed with H_2O (3 ml), dried and concentrated *in vacuo* to yield the **title compound** as a crude oil that could not withstand further purification (0.445 g, 78%).

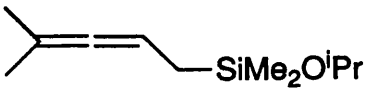
ν_{max} 3200-3600, 2840-2980, 1250, 840 cm^{-1}

δ_H -0.06 (6H, s, $SiMe_2$), 0.85 (2H, s, CH_2), 1.11 (6H, d, *J* 6.05, $OCHC\underline{Me}_2$), 1.21 (6H, s, 2 x CH_3), 3.45 (1H, bs, OH), 4.1 (1H, septet, *J* 6.05, CH)

δ_C 0.532 (Si-C), 25.51 ($CH\underline{Me}_2$), 32.77 (CH_2), 65.38 ($O\underline{C}HMe_2$), 70.81 ($Me_2\underline{C}$)

Found: M^+ 190.0810. $C_9H_{22}O_2Si$ requires M 190.1383

1-(Dimethylisopropoxysilyl)-4-methyl-penta-2,3-diene



(270)

Ref: K. Itoh, M. Sasaki and H. Nishiyama, *Chem. Lett.*, 1981, 905

A 50ml round bottomed flask and condenser containing pre-dried Mg turnings (65 g, 2.67 mmol) was flame-dried and placed under N_2. To this was added THF (0.75 ml) and a small quantity of neat chloromethylsilane (263) (ca. 0.2 ml). The Grignard was initiated by adding 1-2 drops of an iodine/THF solution and heating 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 (0.371 g, 2.23 mmol) in the THF (1.48 ml) over 5 mins. The reaction was allowed to react until the Grignard was complete, signified by the flask returning to room temperature. To a second flame-dried round bottomed flask containing pre-dried CuI (0.424 g, 2.23 mmol) and the THF (2.23 ml) was added, via syringe, the pre-formed Grignard reagent dropwise at 0°C over 5 mins. After complete addition, the reaction flask was cooled to -40°C and allowed to stir at this temperature for a further 40 mins. After this time, the flask was further cooled to -78°C and the propargylic chloride (266) (0.228 g, 2.23 mmol) in the THF (4.46 ml) added dropwise. The reaction was allowed to stir for a

further 40 mins at this temperature then quenched with saturated NH_4Cl solution (5 ml). The resultant mixture was then transferred to a separating funnel and extracted with ether (3 x 6 ml), dried and concentrated *in vacuo* to yield the **title compound** as a crude oil that would not withstand chromatographic purification (0.27 g, 61%).

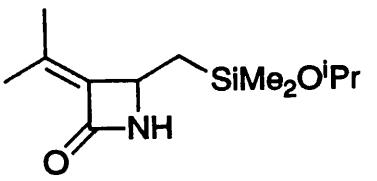
ν_{max} 1945, 1250, 910 cm^{-1}

δ_H 0.1 (6H, s, $SiMe_2$), 1.03 (6H, d, *J* 6.08), 1.24 (2H, d, *J* 8.17), 1.52 (6H, d, *J* 2.87), 3.75-3.95 (1H, septet, *J* 6.08), 4.72-4.90 (1H, m, C2-H).

δ_C -1.96 (Si-C), 18.31 (CH_2), 20.73 (CH_3), 25.69, ($OCH\underline{M}e_2$), 64.9 ($O\underline{C}HMe_2$), 83.95 (C_2), 94.18 (C_4), 199 (C_3)

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

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



(271)

A flame-dried flask under N_2 was charged with dimethylallene (270) (0.214 g, 1.08 mmol) and CCl_4 (11 ml). The flask was then chilled to 0°C and CSI (0.11 ml, 1.3 mmol) was added dropwise over 2 mins. The reaction was allowed to stir for a further 4.5h at 0°C then a Na_2SO_3/NH_4Cl solution buffered at pH 7.9 (11 ml) was added, and left to stir overnight at room temperature with efficient mixing of the two layers. After this time, the biphasic reaction mixture was transferred to a separating funnel and the organic (lower) layer retained, dried and concentrated *in vacuo* to give not the title compound, but rather compound (272) (see Chapter 4.2), in agreement with the following data (0.125 g, 48%).

ν_{max} 3200-3650, 1740, 1250, 845 cm^{-1}

δ_H 0.01-0.2 (6H, s, SiMe), 1.1-1.3 (2H, m, CH_2Si), 1.63 (3H, s, CH_3), 1.93 (3H, s, CH_3), 4.12 (1H, m, C4-H).

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