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Carbapenem Precursors from Allyl and (Allenylmethyl)silanes.

by

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Thesis presented in part fulfilment for the degree
of Ph.D.

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Summary

Most successful syntheses of β -lactam antibiotics involve the early generation of a monocyclic β -lactam ring. The addition of CSI to functionalised alkenes has proven to be of great synthetic utility in this step. Generally the addition is performed on enol acetate type alkenes, the product 4-acetoxyazetidiones finding widespread use since the 4-acetoxy substituent can be replaced by a variety of nucleophiles in an elimination/addition sequence. Unfortunately none of the additions of CSI to functionalised alkenes is generally applicable to the formation of 4-carbon substituted azetidiones, which could then serve as carbapenem precursors.

Earlier reports by Dunoguès⁽¹⁾ and Fleming⁽²⁾ intrigued us since the addition of CSI to allylsilanes produced N-chlorosulphonyl-O-silyl imidates via the corresponding N-chlorosulphonyl β -lactams arising from formal [2+2] cycloaddition between the allylsilane and CSI. These intermediate β -lactams possessed a 4-carbon substituent as found in the carbapenem series and we have been able to repeat the work of Dunoguès and intercept the intermediate β -lactams with Na_2SO_3 to furnish the corresponding N-protio β -lactams⁽³⁾ in yields generally superior to those of other CSI/alkene addition/reduction sequences.⁽⁴⁾

The regiochemistry of cycloaddition is controlled by the β -effect of silicon, i.e., silicon's ability to stabilise the development of partial positive charge β to itself. This is well demonstrated by the regiochemistry of addition of CSI to 1-trimethylsilyl-4-methylpenta-2,3-diene, which will be described, when contrasted with the addition of CSI to 2-methylpenta-2,3-diene, which has previously been described by Moriconi.⁽⁵⁾ Generally, yields in the addition of CSI to (allenylmethyl)silanes were low, but the 3-alkylidene-4-(silylmethyl)azetidiones produced are advanced carbapenem precursors difficult to access by other methodologies.

Initial studies by Dunoguès, Fleming and ourselves made use of trimethyl substituted silyl moieties which served to demonstrate the scope and utility of the method, but rendered the product azetidiones of little utility. Extending the cycloaddition to oxidatively cleavable silyl residues, namely phenyldimethyl substituted silicon moieties, furnished high yields in the cycloaddition, although a slightly lower

allylsilane reactivity was observed as the trimethylsilyl substituent was replaced by a phenyldimethylsilyl moiety. Unfortunately the fluoroborane⁽⁶⁾ and KBr/AcOOH⁽⁷⁾ mediated procedures developed by Fleming to accomplish oxidative cleavage of the phenyldimethylsilyl species did not furnish any of the target 4-(hydroxymethyl)-azetidinone but the mercuridesilylation/oxidative rearrangement protocol, also developed by Fleming⁽⁷⁾, accomplished the required transformation, albeit in low yield.

Further synthetic manipulations were then carried out on this oxidatively cleaved 3-unsubstituted-azetidinone, namely Peterson olefination, which was found to be impossible with the corresponding 4-(phenyldimethylsilylmethyl)azetidinone, and conversion into a thienamycin precursor possessing the correct relative configuration at all three chiral centres.

Acknowledgements

I would like to sincerely thank Dr.E.W.Colvin for his help, encouragement and friendship throughout the course of this project. I would also like to thank my fellow Henderson laboratory students and Tricia for their friendship and advice over the last few years.

Thanks are also due to the technical staff of the department, namely Mrs.F.Lawrie, Mr.G.MacCulloch, Dr.D.S.Rycroft, Mr.J.Gall, Mr.J.McIver, Mrs.K.Wilson, Mr.T.Ritchie and Dr.W.J.Cole for their assistance with spectroscopic and elemental analyses.

Abbreviations

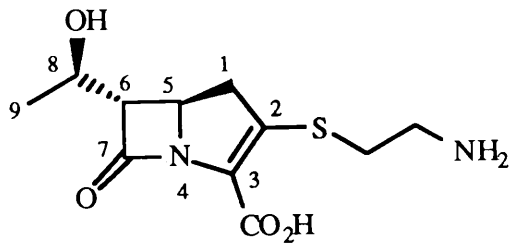
AcOOH	Peracetic acid
9-BBN	9-Borabicyclo[3.3.1]nonane
BSTFA	Bis(trimethylsilyl)trifluoroacetamide
Bz	Benzyl
Cbz	Benzyloxycarbonyl
CSI	Chlorosulphonyl isocyanate
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMS	Dimethyl sulphide
DMSO	Dimethyl sulphoxide
LHMDS/KHMDS	Lithium/Potassium hexamethyldisilazide.
LDA	Lithium diisopropylamide
MEM	Methoxyethoxymethyl
NBS	<u>N</u> -Bromosuccinimide
OMs	Methanesulphonate
OTf	Trifluoromethanesulphonate
OTs	<i>p</i> -Toluenesulphonate
PNB	<i>p</i> -Nitrobenzyl
Selectride	Tri- <i>sec</i> -butylborohydride
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>t</i> -Butyldimethylsilyl
TBDPS	<i>t</i> -Butyldiphenylsilyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl

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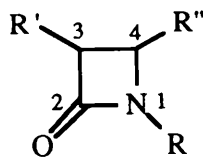
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Numbering System

Bicyclic β -lactams are numbered in the fashion:

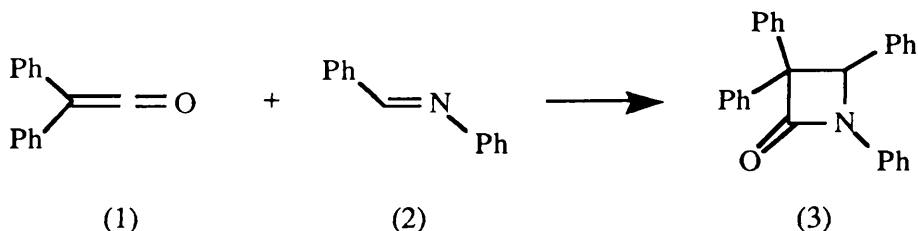


and monocyclic β -lactams in the fashion:

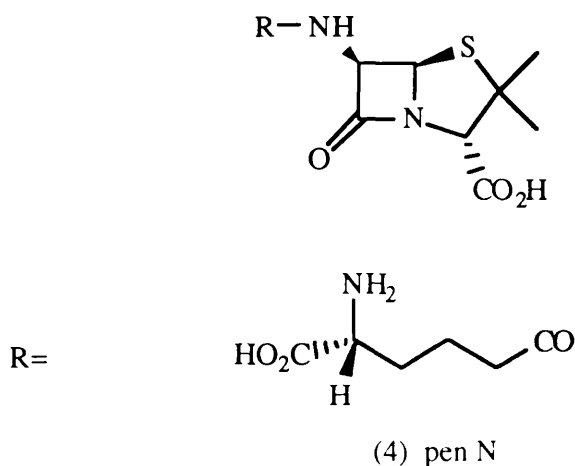


To Mum and Dad

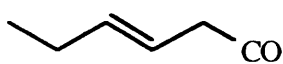
The four membered monocyclic azetid-2-one or β -lactam was first synthesised by Staudinger in 1907 by condensation of diphenylketene (1) with imine (2) to form the monocyclic β -lactam (3). (8)



In 1929 Fleming, whilst working with an agar plate inoculated with a *Staphylococcus* sp. observed retardation of the *Staphylococcus* sp. growth due to contamination and release of a substance by *Penicillium notatum*. Fleming was able to show that a filtrate of the culture possessed significant activity against Gram-positive bacteria but not against Gram-negative bacteria. Twelve years later, in Oxford, Florey and Chain isolated and purified a penicillin from the crude mould extracts. They also demonstrated the *in vivo* potential of penicillin as a chemotherapeutic agent by the successful treatment of experimentally infected animals. Five years later the combined results of chemical degradation and X-ray crystallography established the structure of penicillin N (4). This delay, from isolation to structure determination, was due largely to the extreme lability of the molecule, in contrast to the stable monocyclic β -lactam synthesised by Staudinger. The instability of the antibiotic has been attributed to the steric strain imposed by the presence of the second sulphur-containing ring.



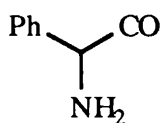
R=



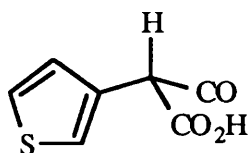
(5) pen F

H

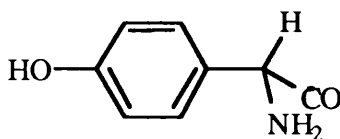
(6) 6-APA



(7) ampicillin



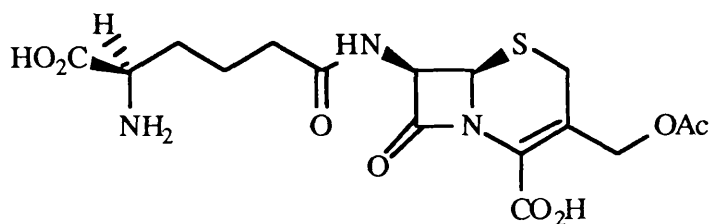
(8) ticarcillin



(14) amoxicillin

Left to its own devices the Penicillin fungus will produce mainly penicillin N (4) and penicillin F (5). In the mid-1950's Beecham scientists, whilst working with Penicillin chrysogenum, noticed that a variety of penicillins were produced whose different amide side chains were derived from monosubstituted acetic acids and varied with the nature of the side chain precursors in the fermentation medium. The absence of an added side chain precursor acid led to the identification of 6-aminopenicillanic acid (6-APA) (6) as a penicillin precursor. Slightly later 6-APA became available in bulk quantities by enzymatic or chemical hydrolysis of natural penicillins. This in turn, after acylation of the 6-amino substituent, led to the evaluation of a vast array of synthetic penicillins, some of which have found clinical application, e.g., ampicillin (7) and ticarcillin (8).

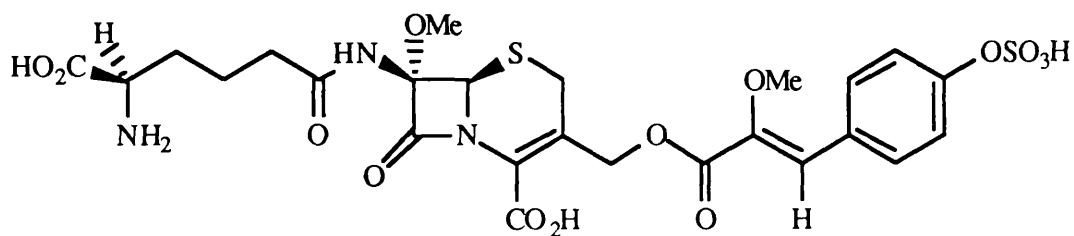
In the early 1950's a strain of Cephalosporium acremonium isolated by Brotzu in Sardinia was re-examined at Oxford⁽⁹⁾ and shown to exhibit antibiotic activity. This antibiotic activity was mainly due to the presence of penicillin N (4) but also from a new material cephalosporin C. (9)



(9)

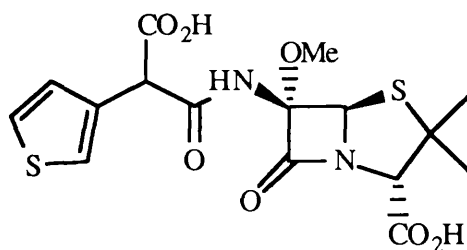
Cephalosporin C was isolated and its structure determined by a combination of chemical degradation and X-ray crystallography. Compared to the penicillins, cephalosporin C has higher acid stability and better resistance to β -lactamase enzymes.

By the mid 1960's the use of penicillins and cephalosporins resulted in the widespread emergence of β -lactamase enzymes which could hydrolyse the β -lactam antibiotics thus rendering them inactive. Therefore the preparation of penicillins and cephalosporins with high stability to β -lactamases became a priority. A major advance came from Lilly and Merck screening programmes with the discovery of the cephamycins⁽¹⁰⁾, such as cephamycin A (10) around this time.



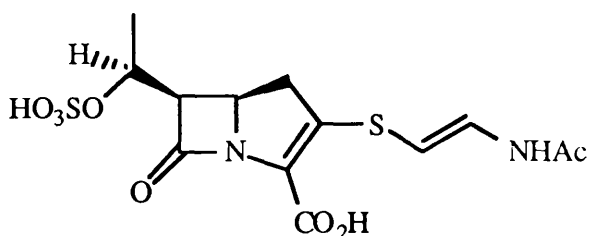
(10)

These compounds, possessing a 7- α -methoxy substituent, showed some degree of β -lactamase stability and this modification was then carried over to the penicillins where a 6- α -methoxy substituent has also resulted in enhanced stability toward β -lactamases, e.g., with temocillin (11).

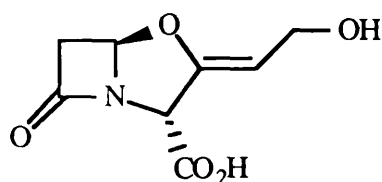


(11)

The next major advance came in the late 1960's with the isolation of two new types of β -lactamase inhibitor, namely the olivanic acids, e.g. (12) (11), and clavulanic acid (13). (12)



(12)



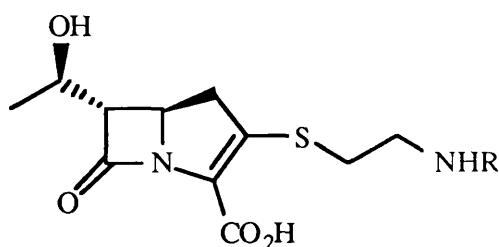
(13)

Unfortunately although the olivanic acid family, the first of the non-classical antibiotics, are potent β -lactamase inhibitors they have never made it to the market place on account of their low fermentation titres and poor stability to renal dehydropeptidase (DHP-I). Clavulanic acid, on the other hand, whilst not as potent a β -lactamase inhibitor and being only weakly active as an antibiotic in its own right, is readily available from fermentation and shows good synergy with penicillins. Today it is marketed as a blend with amoxicillin (14) and sold as augmentin by SmithKline Beecham. This blend finds a wide variety of uses, combining a good antibiotic agent

and a β -lactamase inhibitor.

The carbapenems (such as the olivanic acids) and the clavams (such as clavulanic acid), being the first 1-deithia- β -lactams, drastically altered traditional thoughts on structure/activity relationships. This area even today is still not fully understood and is still a subject of very active research.

Around the same time as the discovery of the olivanic acids and clavulanic acid, Merck workers discovered the carbapenem thienamycin (15) when screening the soil microorganism Streptomyces cattleya.⁽¹³⁾

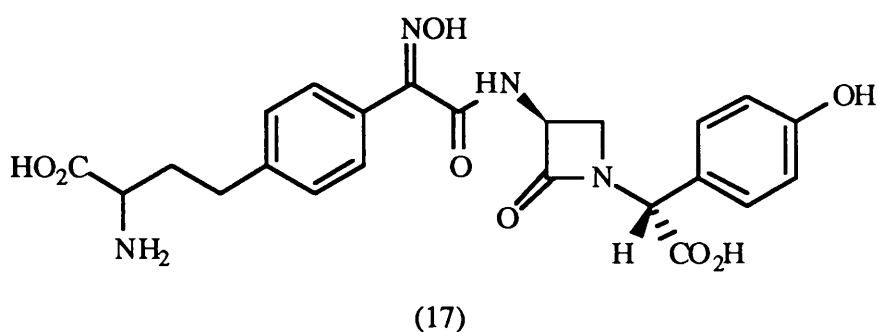


(15) R=H

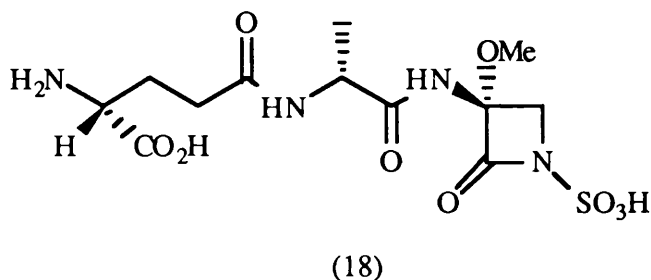
(16) R=CHNH₂

This compound is not nearly as good a β -lactamase inhibitor as the olivanic acids, but shows more stability to DHP-I. Unfortunately in concentrated solution it tends to dimerise and so is generally administered as the N-formimidoyl derivative (imipenem) (16). Generally imipenem is administered with a DHP-I inhibitor (see later). To date the natural carbapenems number over forty, these belonging to seven subgroups, although total synthesis has yielded a variety of carbapenems not found in nature. The naturally occurring compounds are not readily available by fermentation and thienamycin, administered as imipenem, made via total synthesis is the only one which has been developed to the clinic.

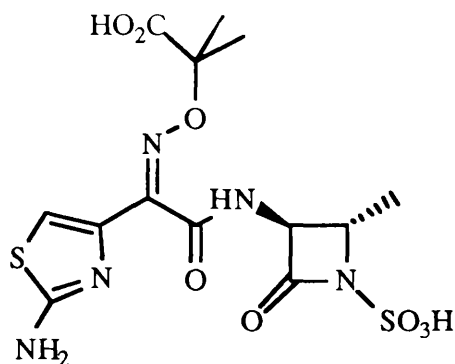
Simultaneous with the discovery of the carbapenems and clavulanic acid, the nocardicins, e.g., nocardicin A (17), were isolated. These compounds, possessing only a monocyclic ring, were shown to be antibiologically active and exhibited some β -lactamase stability.⁽¹⁴⁾ Unfortunately they have never been developed to the clinic but again were significant in terms of previous thoughts on structure/activity relationships.



The final structural variant, again a non-classical β -lactam antibiotic, came from screening programmes by the Takeda company when the monobactams, such as sulfazecin (18), were isolated.⁽¹⁵⁾

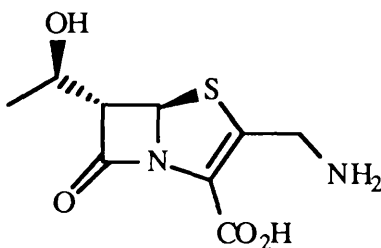


Currently, a synthetic analogue, aztreonam (19), is marketed for use against certain Gram-negative bacteria.



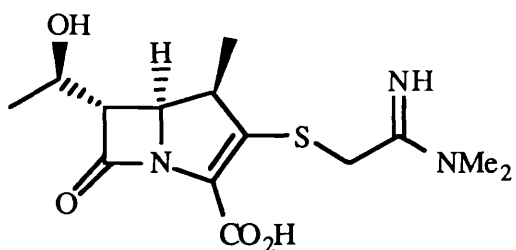
(19)

Given the variety of β -lactam structural types now known and the vast screening programmes which have occurred since the 1960's, it is unlikely that any new type of β -lactam will be discovered and new clinical antibiotics will be variants of the types surveyed. An interesting example of this has been the clinical development of the 6-hydroxyethyl penems, e.g., (20). The penems, which are not found in nature, combine features common to the penicillins and carbapenems in an effort to discover new or improved activity.



(20)

The addition of substituents to elucidate different or improved activity is very common in the search for biologically active compounds; for example, in the carbapenem series, the addition of a 1- β -methyl group greatly increases stability towards DHP-I, e.g., (21). Here the basic bicyclic core has an added structural feature not found in nature which markedly improves its antibiotic function, as will be detailed later.

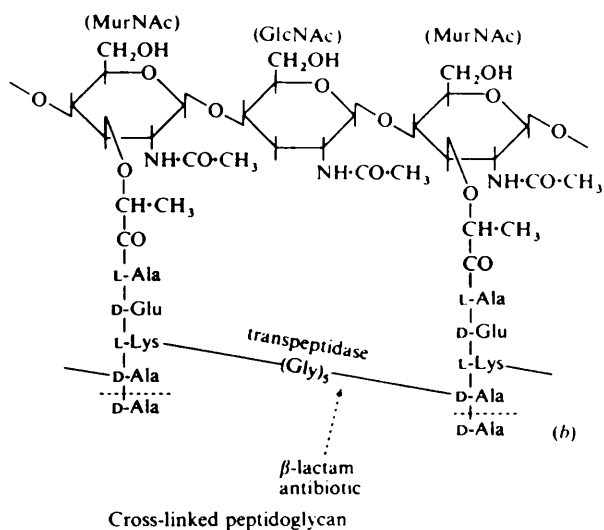


(21)

The mode of action of β -lactam antibiotics has been most widely studied with the penicillins and it is assumed that the cephalosporins and the carbapenems function analogously.

Treatment of a bacterial infection depends on the exploitation of metabolic differences between the bacterium and host. β -Lactam antibiotics are thought to interfere with bacterial cell wall biosynthesis thus rendering the walls prone to rupture.

The main component of the bacterial cell wall is peptidoglycan which in essence is a polymer surrounding the cell providing rigidity and support.(16)



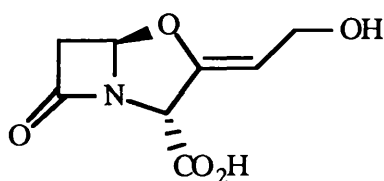
The final biosynthetic step in formation of the peptidoglycan is cross-linking, whereby the terminal glycine of the cross-link is attached to the D-ala portion of the four amino acid sequence with expulsion of another D-ala.(17) It was originally thought that this step was inhibited by penicillin due to its structural similarity to the D-ala-D-ala portion of the amino acid chain.(18)

Unfortunately this may be an over simplification of the inhibition of a very complex process and indeed a D-alanine carboxypeptidase and a peptidoglycan endopeptidase which are sensitive to penicillin have been identified. (19),(20),(21),(22)

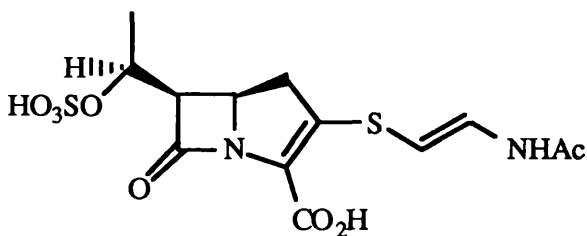
More recent approaches to elucidate the mode of action have involved identifying penicillin binding proteins with the aid of radiolabelled penicillins. Studies such as these however are still at an early stage.

As has been mentioned earlier, bacterial resistance to β -lactams has become a widespread problem. This resistance is associated with β -lactamase enzymes which destroy the azetidinone ring. Indeed almost as soon as the utility of penicillins was discovered, the β -lactamase enzyme was observed.⁽²³⁾

The nature of these β -lactamase enzymes is unclear but it is known that they can be inhibited in two ways; namely by irreversible inhibitors, such as clavulanic acid (13), and by reversible inhibitors, such as the carbapenems, e.g., the olivanic acid (12).

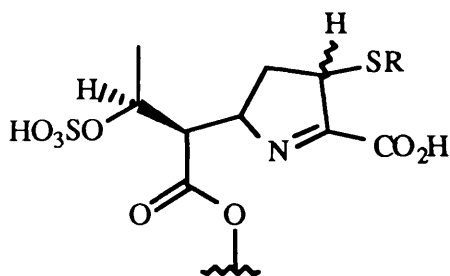


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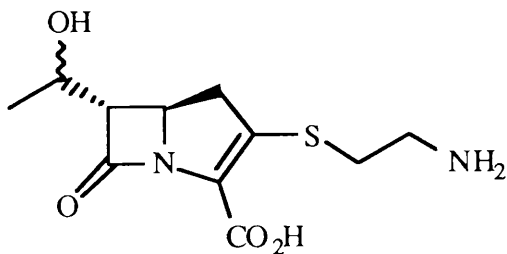


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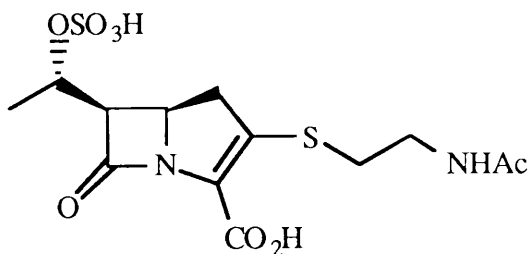
The carbapenems are thought to function as β -lactamase inhibitors by tautomerism to the Δ^1 pyrroline (22) after ring opening of the azetidinone by a serine residue on the β -lactamase.⁽²⁴⁾



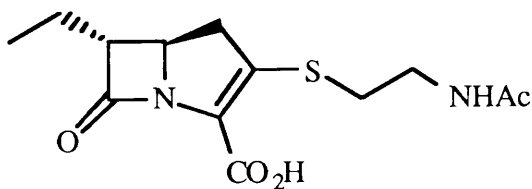
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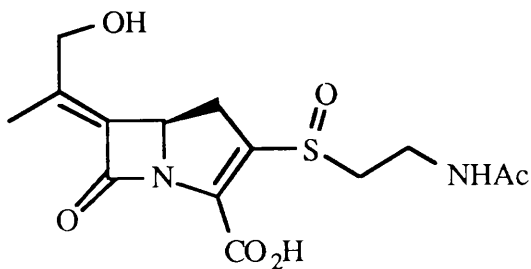
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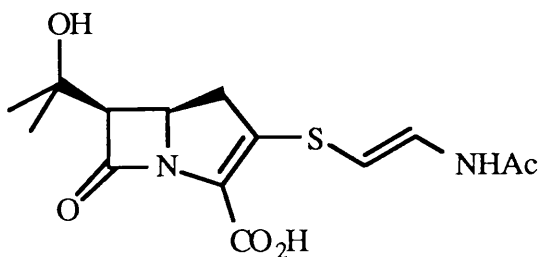
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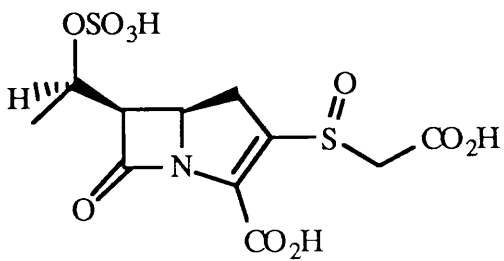
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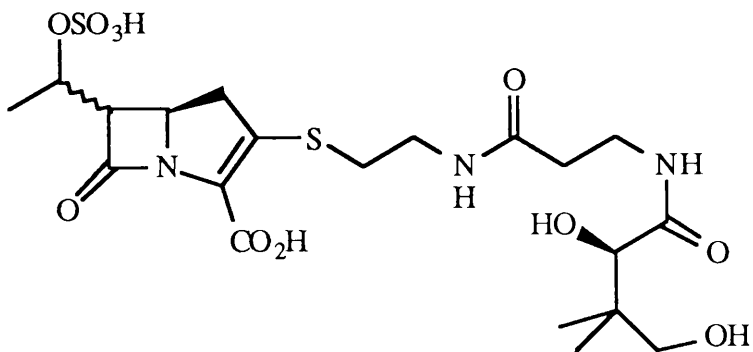
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(27)



(28)



(29)

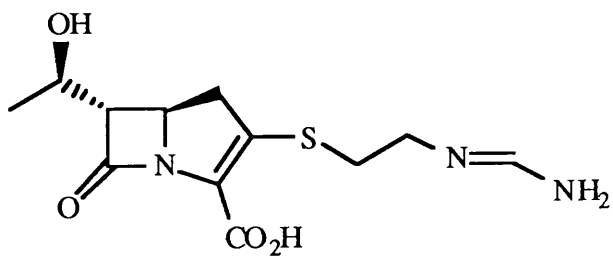
To date over forty carbapenems have been isolated from various Streptomyces species.⁽²⁵⁾ Immense structural variations exist within the group which includes the thienamycins (23), the olivanic acids (24), the PS-series (25), the asprenomycins (26), the carpetimycins (27), the pluradomycins (28) and the OA series (29). However unlike the penicillins and cephalosporins, where alterations in stereochemistry result in virtually complete loss of antibiotic activity, the majority of carbapenems are highly active broad spectrum antibiotics.⁽²⁶⁾

The only criterion for antibiotic activity seems to be that the configuration at C-5 is (R). Generally high antibiotic activity is linked to the combination of 8-(S) and cis C-5/C-6 configuration or of 8-(R) and trans C-5/C-6 configuration at the β -lactam.⁽²⁶⁾

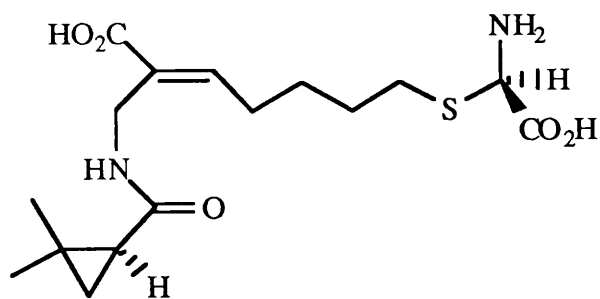
β -Lactamase stability appears to follow even less of a structural activity relationship than does antibiotic activity and no hard and fast rules are available.

Thienamycin (15), the only carbapenem to be developed to the clinic, has a free amine group and as already mentioned tends to dimerise in concentrated solutions.⁽²⁷⁾ This has been overcome by the formation of imipenem (16), the formimido derivative. Unfortunately imipenem, like thienamycin, suffers from problems of hydrolysis by renal dehydropeptidase (DHP-I)⁽²⁸⁾ and is therefore administered with cilistatin (30), a DHP-I inhibitor developed by Merck, and sold as primaxin, the most potent broad spectrum antibiotic available.⁽²⁵⁾

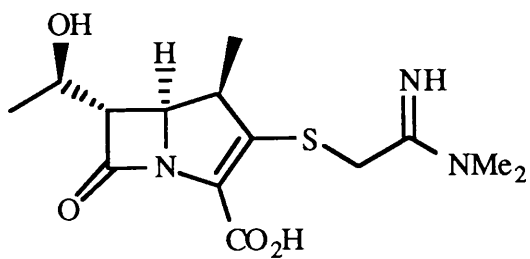
Obviously antibiotic administration with a DHP-I inhibitor is costly and synthetic carbapenems, such as (21), have been developed by the Merck group⁽²⁹⁾ where the 1- β -methyl substituent greatly enhances stability to DHP-I, unlike the 1- α -methyl compound which shows no enhanced DHP-I stability relative to thienamycin.⁽³⁰⁾



(16)



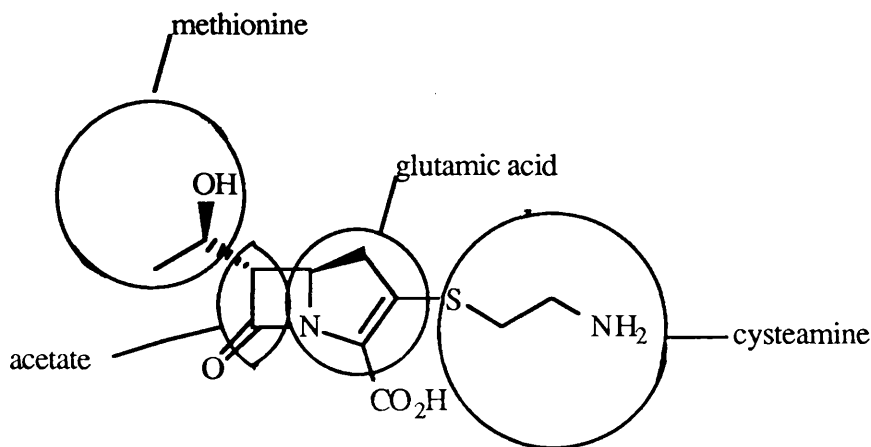
(30)



(21)

The biosynthetic route to the carbapenem antibiotics is markedly different, with respect to precursors, to that found in the penicillins and cephalosporins. Radioactive and stable isotope studies with *Streptomyces cattleya* have demonstrated that in thienamycin (15) the C-6 and C-7 carbon atoms of the β -lactam ring are acetate derived, the cysteamine side chain from cysteamine and the pyrroline moiety originates from glutamate.(31),(32),(33)

Rather surprisingly, both carbon atoms of the hydroxyethyl side chain are derived from the methyl of methionine, with C-9 being incorporated with retention of configuration via a double inversion process.(34)

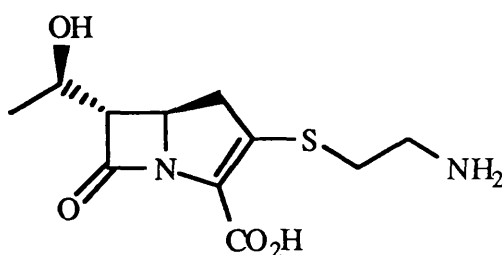


(15)

Chemical synthesis of the penicillins and cephalosporins has played a key role in highlighting new structures and activities. With the discovery of the carbapenems in the late 1960's two new fields of β -lactam synthesis were born. Firstly a range of penicillins containing the C-2/C-3 double bond, as found in the carbapenems, were synthesised, namely the penems.⁽³⁵⁾ More importantly, since the carbapenems are not available via fermentation and show very good antibacterial properties, significant quantities of these compounds were required for clinical evaluation.

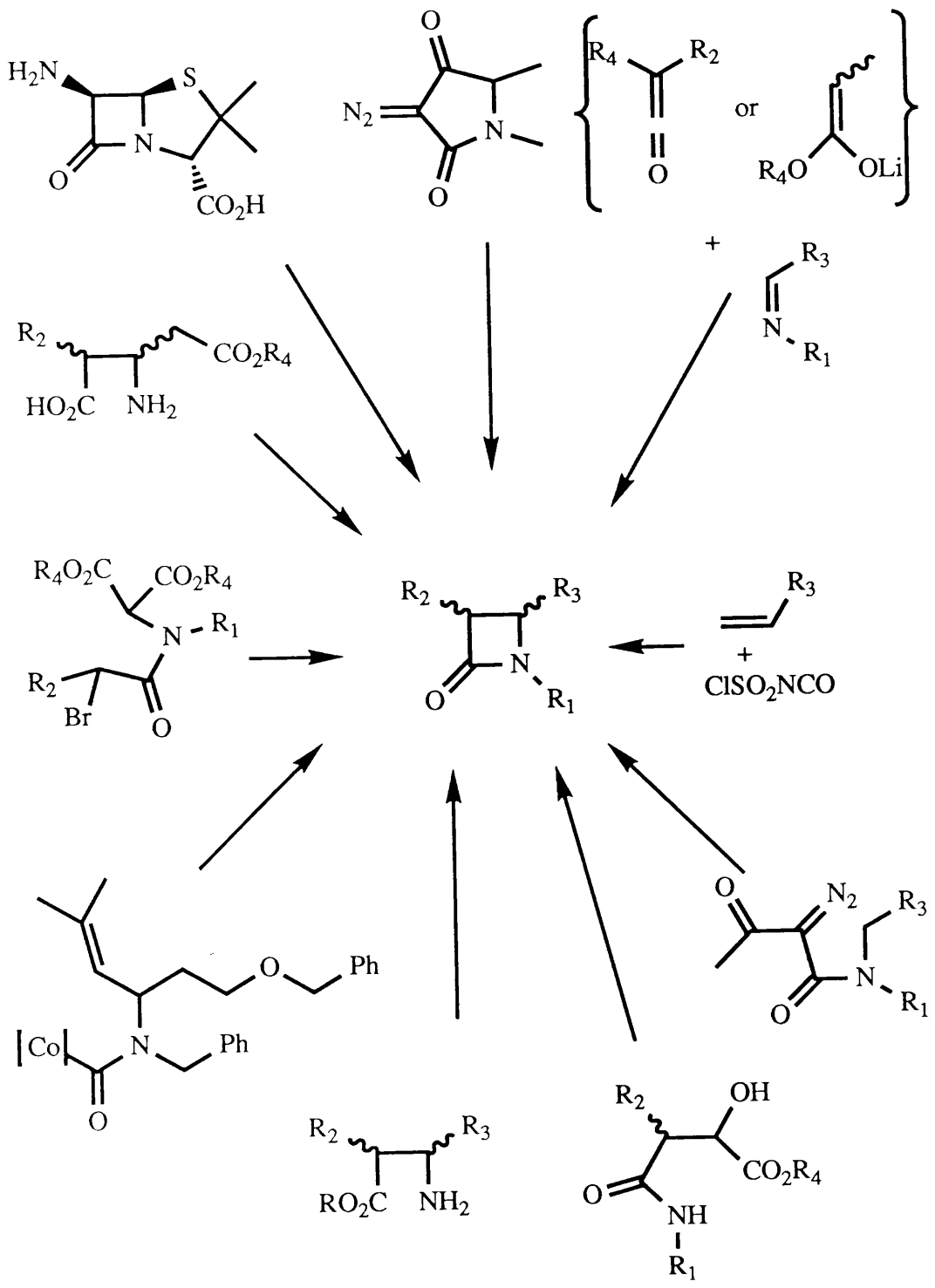
Although Sheehan⁽³⁶⁾, in the first synthesis of penicillin, had formed the β -lactam ring late on in his synthetic scheme, most successful syntheses begin with the early generation of the monocyclic ring followed by substituent elaboration and eventual closure of the second ring. Two main reasons lie behind this strategy; firstly, azetidinone rings are not as easily formed as the five membered ring of the pyrroline and secondly, since all β -lactam antibiotics contain the azetidinone ring, an efficient route to this moiety would then allow entry to various types of β -lactam antibiotic.

Carbapenem synthesis has been the subject of some very elegant chemistry⁽³⁷⁾ and is covered by excellent reviews.^{(38),(39)} Most synthetic routes in fact have been towards thienamycin (15).



(15)

From its isolation in 1976⁽¹³⁾ till 1980 synthetic routes only concerned themselves with relative and not absolute stereochemistry. The first total synthesis of racemic thienamycin was achieved by the Merck group in 1978⁽⁴⁰⁾ and this instigated a number of synthetic schemes to intermediates on this route (see later). In 1980⁽⁴¹⁾, the same group of Merck chemists published a stereocontrolled route to (+)-thienamycin



Scheme 1

which proved to be a turning point in carbapenem synthesis, in that most subsequent literature has focused on the synthesis of carbapenems in homochiral form. Obviously the chirality in thienamycin is centred around the azetidinone ring, and synthetic efforts since 1980 have been directed toward the generation of this moiety in chiral form, with very few advances in the chemistry associated with closure of the pyrroline ring.

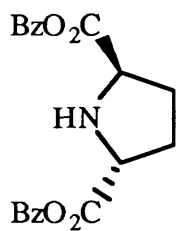
Bearing these points in mind, this review will consider general routes to N-substituted and N-unsubstituted azetidinones, followed by methods to control the stereochemistry of the hydroxyethyl side chain in conjunction with ring closure to form the bicycle, and then move on to highlight some of the more recent stereocontrolled synthetic pathways.

1.5.1 Monocyclic Formation.

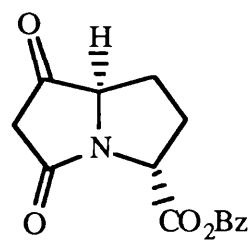
The majority of routes to the β -lactam ring commonly encountered in carbapenem synthesis are outlined in Scheme 1. These result in either N-unsubstituted β -lactams which are ready for further elaboration, or in N-substituted β -lactams which, after removal of the nitrogen substituent, are ready for further transformations.

1.5.1.1 Ring Contraction

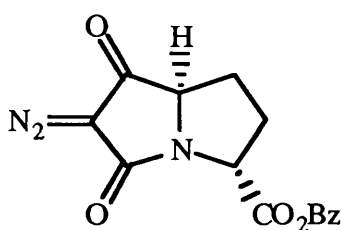
This method, although not general, deserves mention in that the first synthesis of the carbapenem ring system was accomplished via photolytic Wolff rearrangement of the diazodione (33).⁽⁴²⁾ Amine (31) was coupled with t-butyl hydrogen malonate to afford an intermediate amide which upon treatment with NaH and removal of the t-butoxycarbonyl group by heating in toluene furnished dione (32). Diazo transfer with MsN_3 and Et_3N gave the diazodione (33), which upon photolysis in the presence of β -methylphenethyl carbazate gave the corresponding ring contraction product (34).



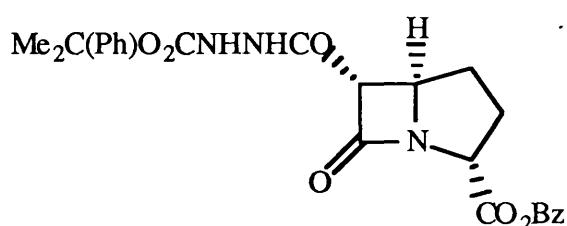
(31)



(32)



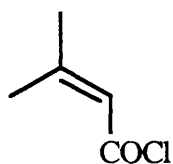
(33)



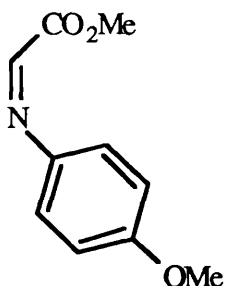
(34)

1.5.1.2 Ketene and Imine Cycloaddition.

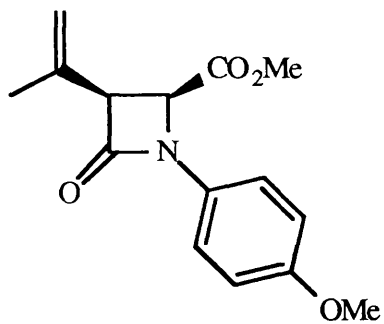
This procedure originated in the field of penicillins and cephalosporins.⁽⁴³⁾ It has also found widespread application in the synthesis of carbapenems.⁽⁴⁴⁾ Generally a ketene is generated from an activated acid derivative and added to an imine to produce β -lactams which normally have C-3/C-4 cis substitution. This has been detailed recently in an excellent paper by Hegedus and co-workers.⁽⁴⁵⁾ An interesting example comes from Manhas and co-workers⁽⁴⁶⁾ where an α,β -unsaturated acid chloride (35) was treated with Et_3N in the presence of imine (36) to furnish the 3-isopropenyl β -lactam (37).



(35)



(36)



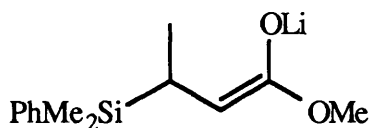
(37)

1.5.1.3 Li Ester Enolate and Imine Cycloaddition.

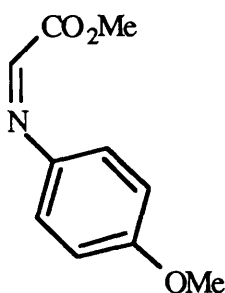
Deprotonation of an ester with a lithium base, such as LDA, results in the formation of a lithium ester enolate which can be condensed with imines to form β -lactams. A novel example comes from Palomo and co-workers⁽⁴⁷⁾ who prepared intermediate (39) from α,β -unsaturated ester (38), not via conventional LDA treatment of an ester, but using the conjugate addition of a PhMe_2Si anion according to the method of Fleming and Kilburn.⁽⁴⁸⁾ After reaction with imine (36) an 80% yield of β -lactam (40) was obtained as a single diastereomer.



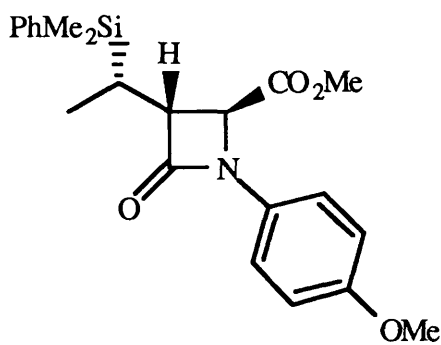
(38)



(39)



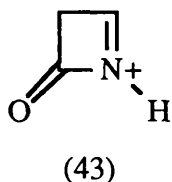
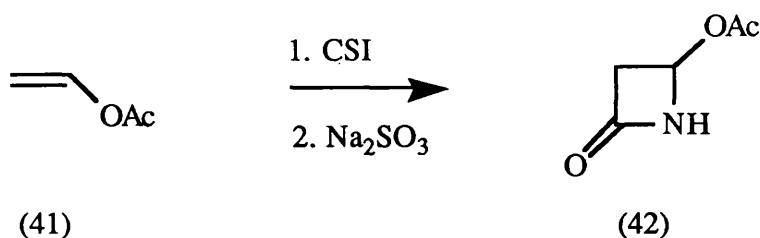
(36)



(40)

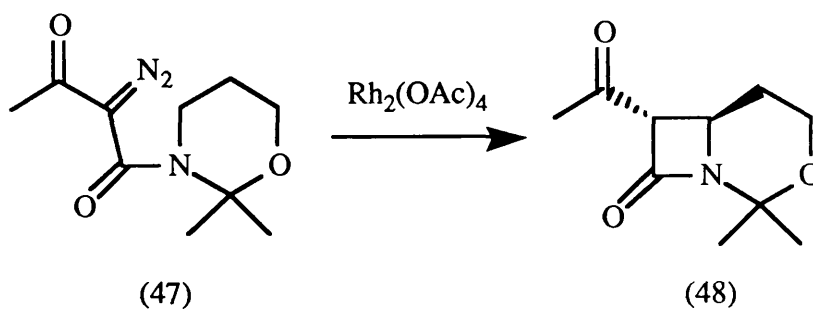
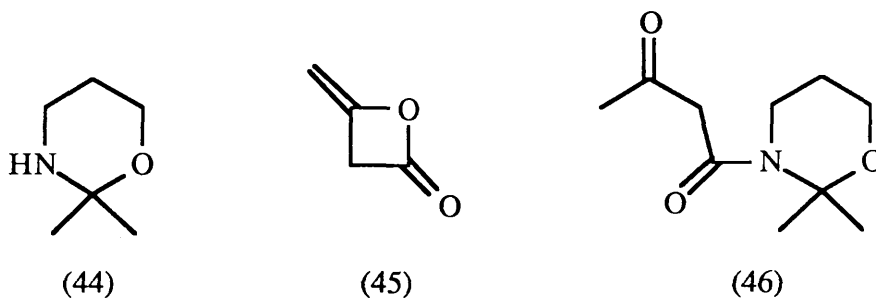
Reaction of functionalised alkenes, such as vinyl acetate (41), with CSI provides an N-chlorosulphonyl β -lactam which can be reduced with aqueous Na_2SO_3 to afford the 4-acetoxiazetidione (42).⁽⁴⁾ Displacement of an electronegative substituent, such as acetoxy from the 4-position of a β -lactam, via the intermediate azetidinium ion (43), has proven to be of great synthetic value and finds widespread use in the carbapenem series^{(49),(50)} as will be seen later.

The addition of CSI to a variety of functionalised alkenes has been well documented and will be discussed later.



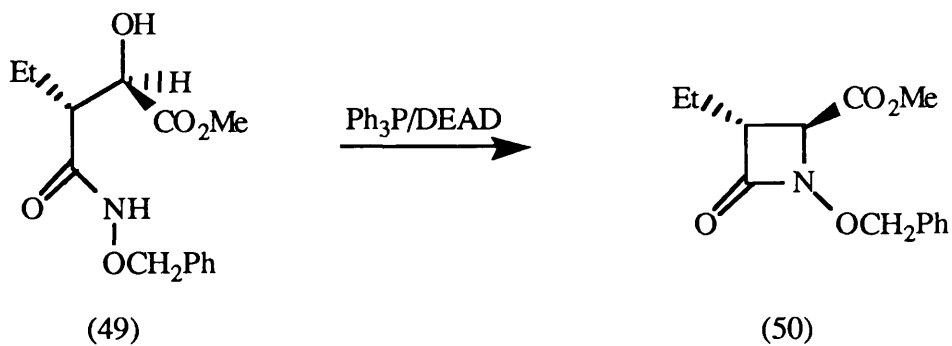
1.5.1.5 α -Diazoamides.

In methodology developed by Brunwin, Lowe and Parker⁽⁵¹⁾ for penicillin synthesis, a carbene is inserted into a CH bond to close the four membered ring. Beecham chemists⁽⁵²⁾ have taken this method and formed intermediate (46) from the addition of diketene (45) to tetrahydrooxazine (44). Diazo transfer led to intermediate (47) which upon treatment with $\text{Rh}_2(\text{OAc})_4$ furnished carbapenem precursor (48).

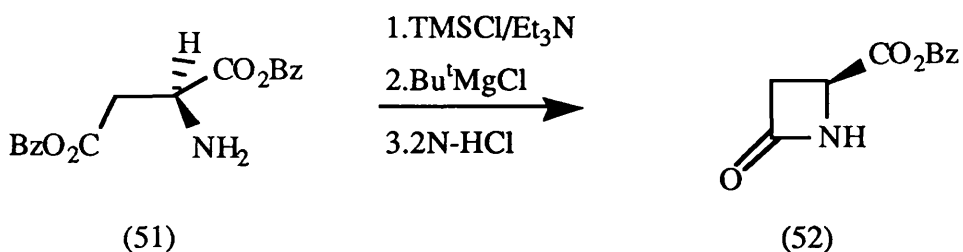


1.5.1.6 β -Hydroxy Hydroxamates.

The nucleophilicity of an amide nitrogen can be used to displace a leaving group from the β -position to itself to form an azetidinone ring. β -Hydroxy hydroxamates, such as (49), upon activation of the hydroxy function, under Mitsunobu⁽⁵³⁾ conditions, ring close to afford β -lactams, such as (50).⁽⁵⁴⁾

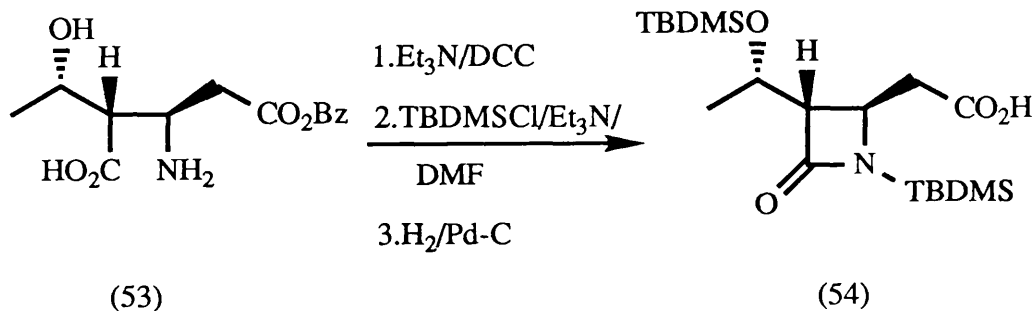


Ring closure of primary or secondary β -amino esters provides a facile entry to the azetidinone ring system. Following deprotonation of the amine with a Grignard reagent⁽⁵⁵⁾, ring closure occurs; for example, in the Merck synthesis of (+)-thienamycin⁽⁴¹⁾ (see later) the aspartic acid derivative (51) was N-silylated then ring closed with Grignard reagent and finally the silyl group removed by acid treatment to furnish azetidinone (52).



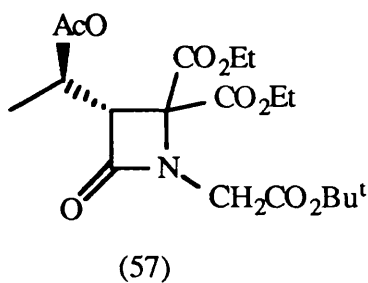
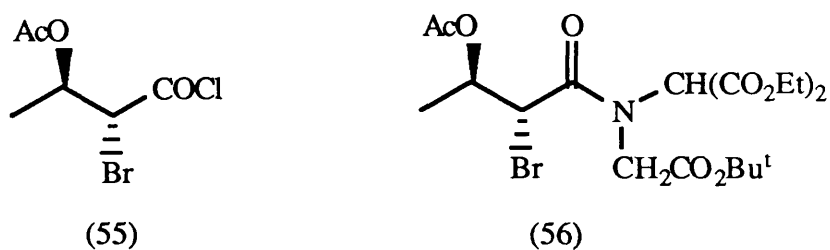
1.5.1.8 β -Amino Acids.

Ring closure of a β -amino acid has been used widely in the synthesis of carbapenems to provide facile access to N-unsubstituted azetidinones. Unfortunately the hydroxyl function is not able to act as a leaving group unless activated. This can be facilitated by the use of a variety of coupling reagents, such as $Ph_3P.PyS-SPy$ ⁽⁵⁶⁾, DCC⁽⁵⁷⁾ or more recently $PhOPOCl_2$.⁽⁵⁸⁾ For example, in a production scale version of the Merck synthetic route to racemic thienamycin⁽⁵⁷⁾, the β -amino acid (53) was treated with DCC/ Et_3N , silylated and catalytically hydrogenolysed to form β -lactam (54), the hydroxyl stereochemistry being inverted at a later stage.



1.5.1.9 Intramolecular S_N.

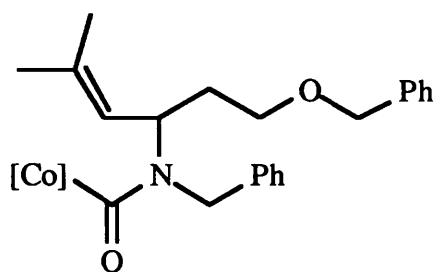
This type of procedure is most usually employed to facilitate ring closure between C-3 and C-4 of the azetidinone ring. The precursors to this process are generally activated α -bromo acids.⁽⁵⁹⁾ For example, the Sankyo group elaborated bromo acid chloride (55) into amide (56). This amide carries a doubly activated proton, and after removal of this proton by DBN the system undergoes an intramolecular displacement to furnish azetidinone (57).



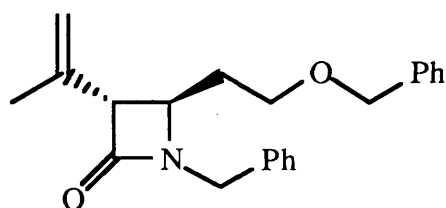
Synthetic routes to penems benefited greatly from the availability of chiral azetidiones by degradation of penicillin. Carbapenem precursors are similarly available, but unfortunately after degradation the 4-thio substituent must be replaced by a carbon unit which lengthens the synthetic sequence. An example of this will be dealt with later.

1.5.1.11 Carbamoyl Cobalt Cyclisations.

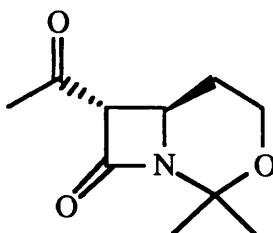
A route recently reported by Pattenden and Reynolds⁽⁶⁰⁾ in which 4 exo trigonal cyclisation of carbamoyl cobalt derivative (58), derived from the corresponding carbamoyl chloride, results in the formation of bicyclic (59). This compound has subsequently been converted into (48), an intermediate in the synthesis of thienamycin.



(58)



(59)



(48)

Figure 1 shows the possible modes of bicyclic formation from the pre-formed monocyclic.

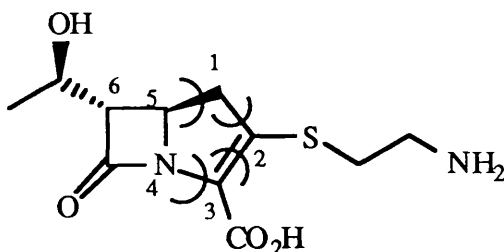


Figure 1

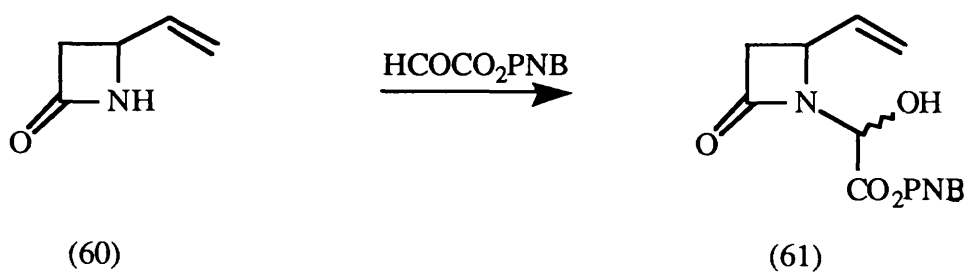
All the possible disconnections shown have been attempted with varying degrees of success.

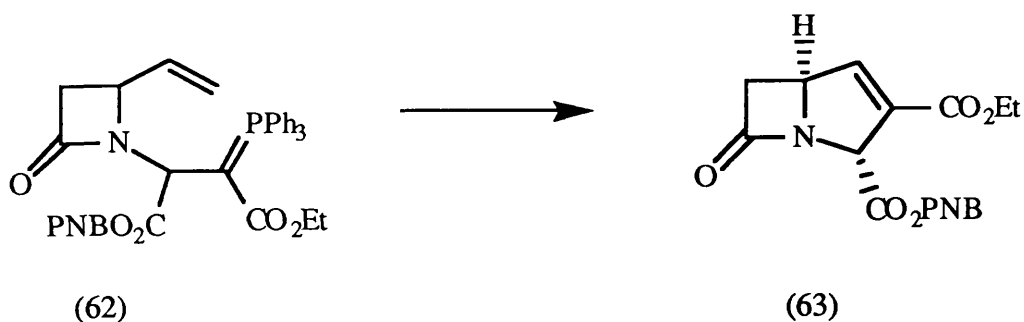
1.5.2.1 C-1/C-2 Closure

Wittig reaction.

Notable contributions in this area have come from Sharma and Stoodley⁽⁶¹⁾ amongst others (Scheme 2). 4-Vinylazetidinone (60) in condensation with PNB-glyoxalate gave the diastereomeric carbinols (61). The carbinol mixture was converted via the chloride into phosphorane (62). Ozonolysis in the presence of trifluoroacetic acid, to protonate and thus protect the phosphorane, reduction of the ozonide and neutralisation afforded carbapen-1-em (63) in a yield of 50% from carbinol (61). Unfortunately no isomerisation, by base treatment, to carbapen-2-em could be achieved.

Scheme 2



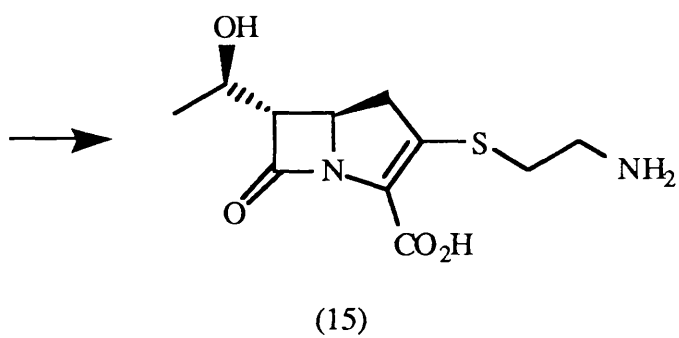
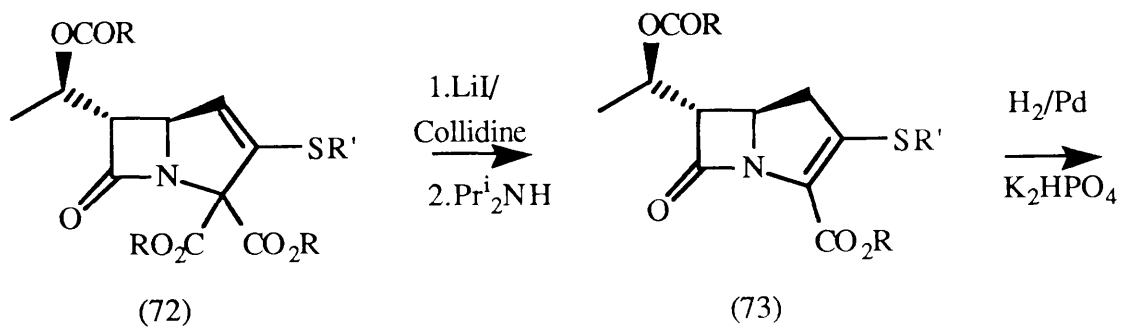


1.5.2.2 C-2/C-3 Closure.

Five methods have been described to effect ring closure between C-2 and C-3; namely substitution, aldol condensation, Wittig condensation, conjugate addition to an unsaturated nitro compound and reductive cyclisation between two carbonyls.

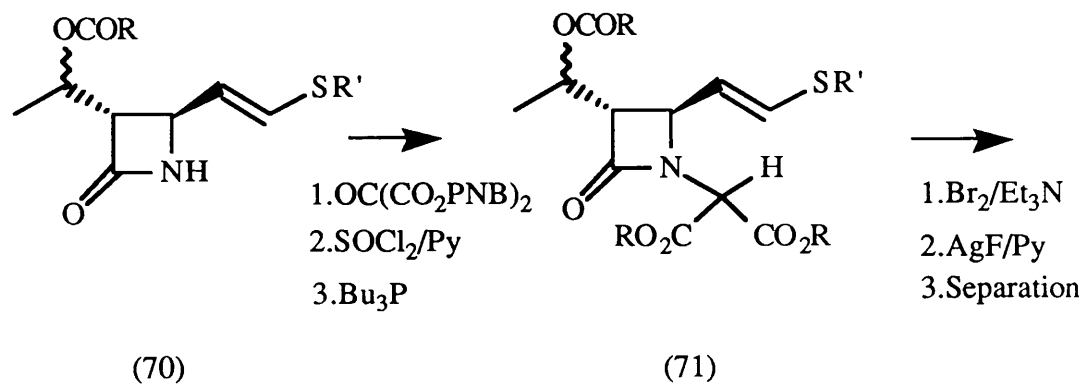
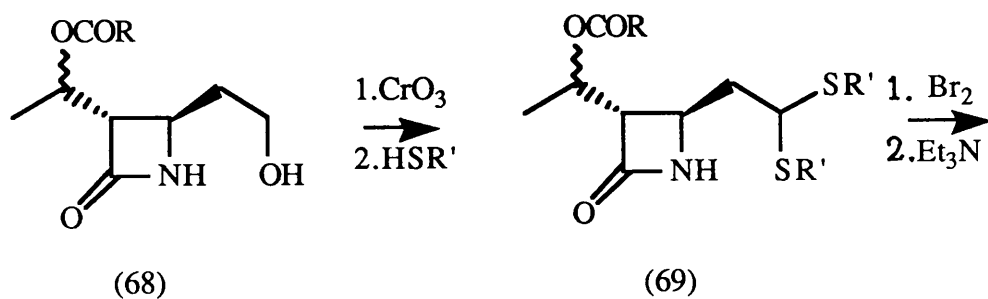
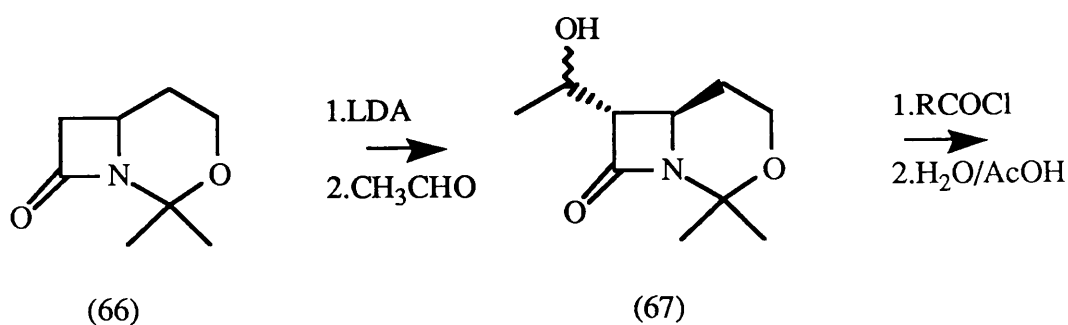
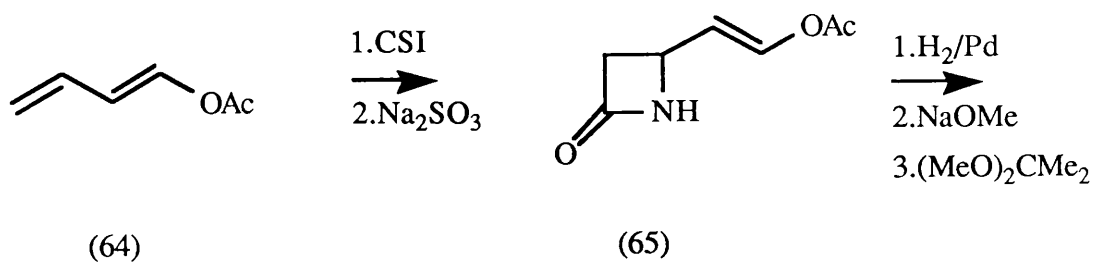
1.5.2.2.1 Substitution

The first total synthesis of racemic thienamycin⁽⁴⁰⁾ (Scheme 3), by the Merck group, involved a closure of the pyrroline ring by intramolecular substitution. Reaction of CSI and 1-acetoxybutadiene (64) yielded the starting β -lactam (65) which was subsequently elaborated to tetrahydrooxazine (66). Hydroxyethylation produced the trans- β -lactam (67) as an epimeric mixture. Protection of the free hydroxyl and cleavage of the acetonide furnished (68) which was converted into thioacetal β -lactam (69). Treatment with Br_2 then triethylamine furnished the mixture of thioenol ethers (70) as mainly the (E)-isomer. Condensation of (70) with bis(p-nitrobenzyl) ketomalonate, chlorination and reduction afforded intermediate (71), which underwent cyclisation upon treatment with Br_2 and triethylamine. The intermediate was then de-brominated with AgF and the 8(R) and 8(S)-epimers separated by chromatography to yield carbapenem (72). Iodide induced decarboxylation followed by isomerisation produced carbapenem (73) which, on hydrogenolysis gave racemic thienamycin (15).

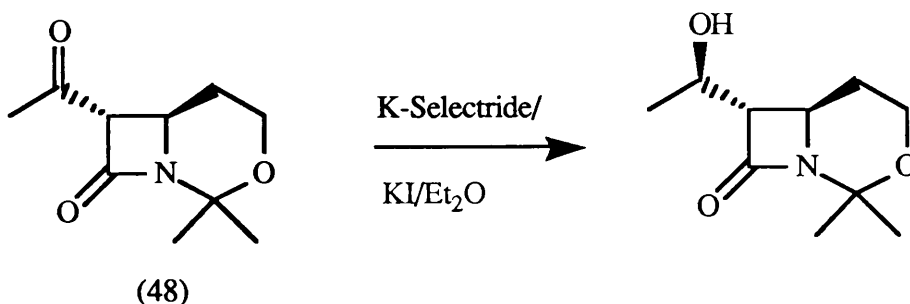


$\text{R}=\text{PNB}$

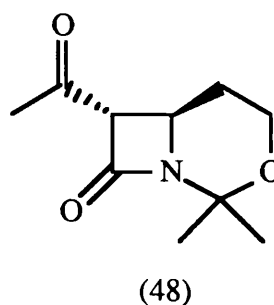
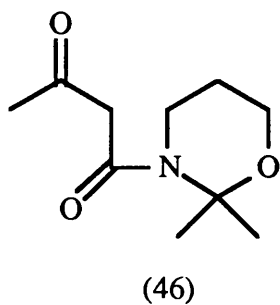
$\text{R}'=(\text{CH})_2\text{NHCOPNB}$

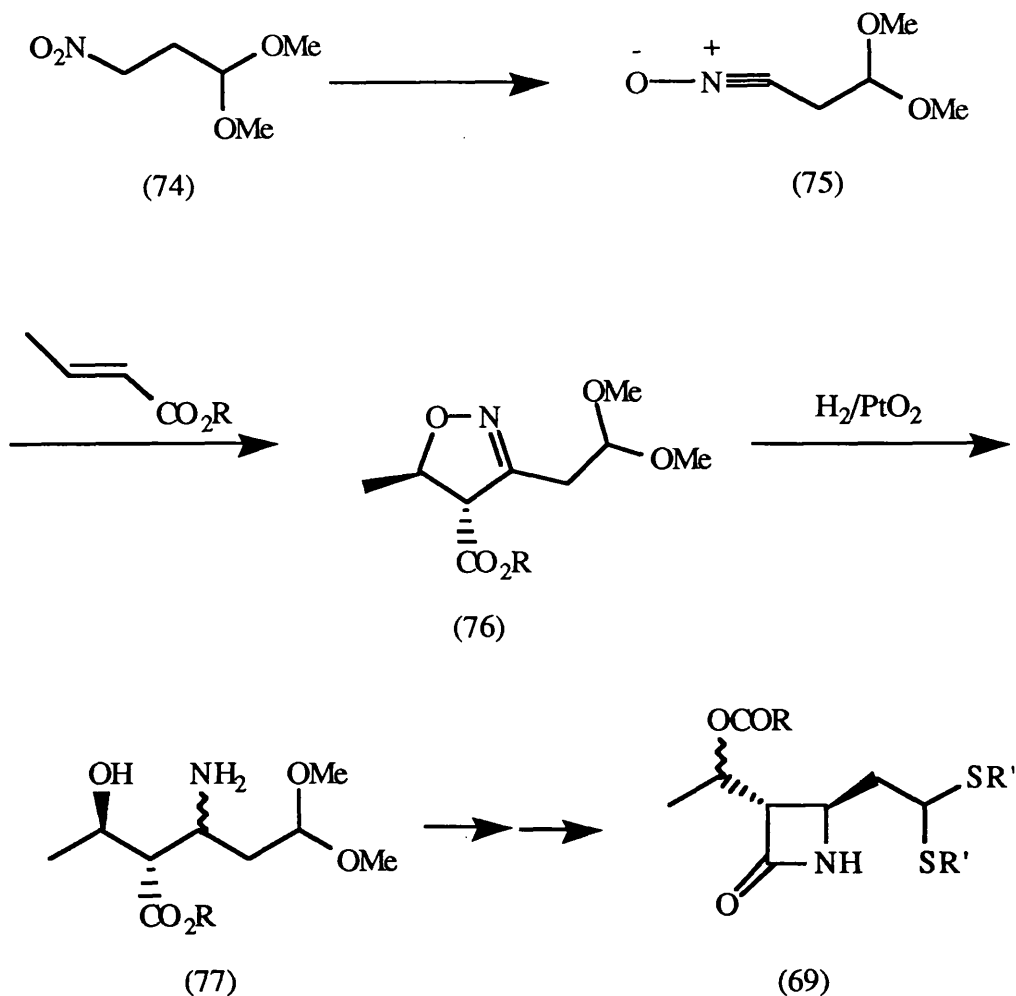


Non-stereoselectivity in the production of hydroxyethyl compound (67) was a drawback with this synthetic scheme; this was overcome by stereoselective reduction of the corresponding ketone (48) with K-Selectride in the presence of KI in Et₂O⁽⁶²⁾ to form the required (R)-alcohol.



As mentioned earlier, there then followed a flood of papers on routes to intermediates in the Merck scheme, thereby constituting formal syntheses of racemic thienamycin. For example, Beecham chemists⁽⁵²⁾ published a route to (48) involving β -ketoamide (46) whereas Kametani and co-workers⁽⁶³⁾ converted nitro acetal (74) into nitrile oxide (75) which underwent 1,3-dipolar cycloaddition with a crotonic ester to form isoxazoline (76); this was reduced to β -amino acid (77) and subsequently cyclised and elaborated to intermediate (69).

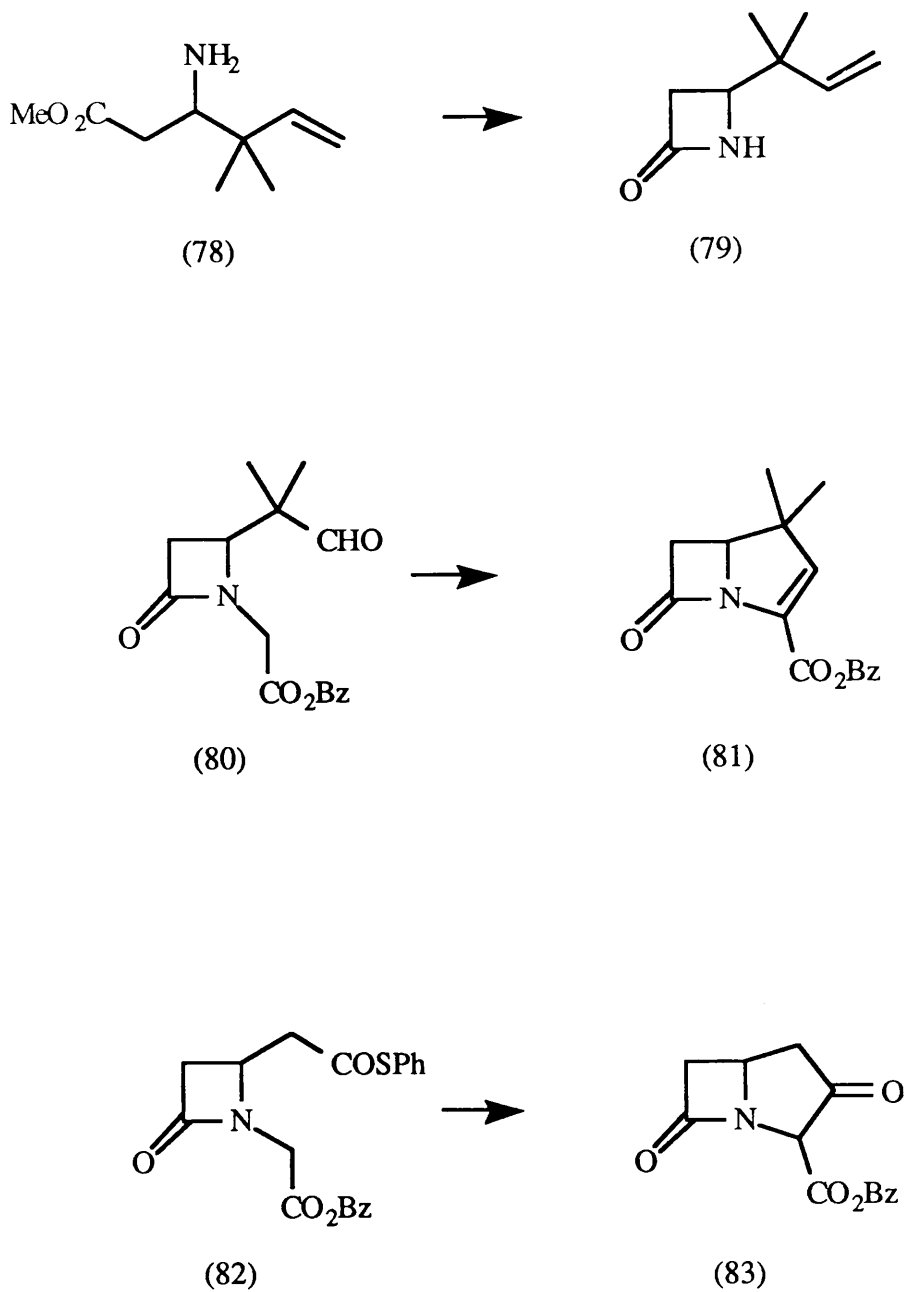




1.5.2.2.2 Aldol Condensation.

Shibuya and Kubota⁽⁶⁴⁾ prepared β -lactam (79) (Scheme 4) from the corresponding β -amino ester (78) with *o*-tolylmagnesium bromide being used to close the azetidinone ring. *N*-alkylation, then ozonolysis and reductive work-up gave β -lactam (80), which was cyclised by LHMDS mediated aldol reaction. The resulting β -hydroxy ester was mesylated and eliminated with 3,3,6,9,9-pentamethyl-2,10-diaza-bicyclo-[4.4.0]-1-decene to furnish carbapen-2-em (81). It is perhaps worth noting that Glaxo chemists, on a similar system using an enolisable aldehyde as the aldol acceptor, obtained a significantly lower yield.⁽⁶⁵⁾

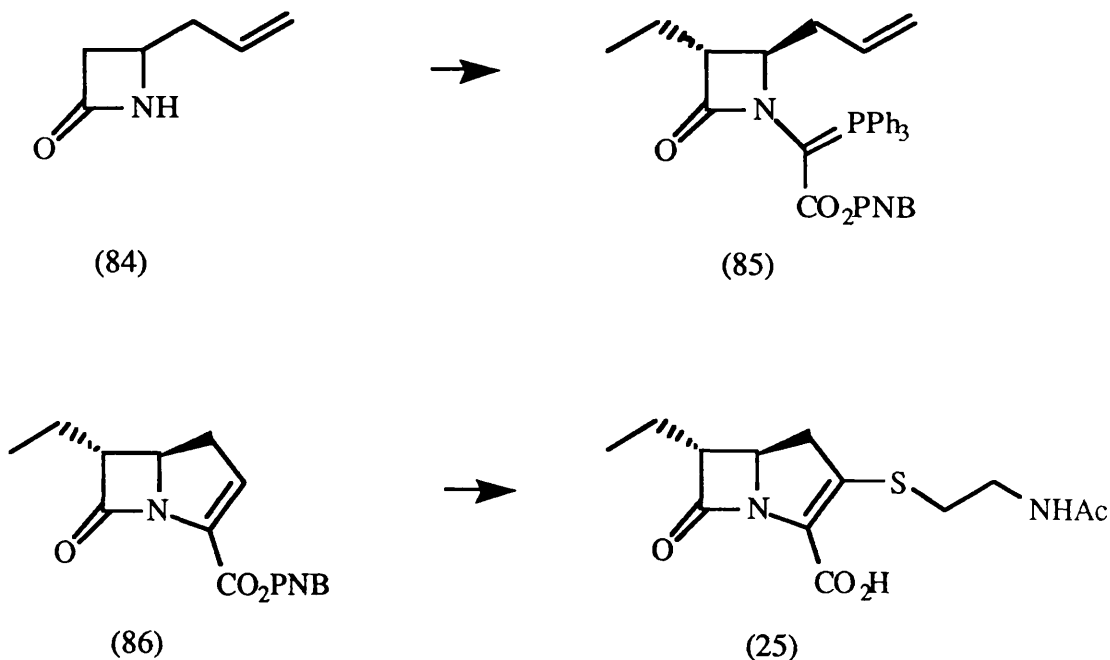
The closely related Dieckmann condensation has also been used very successfully in carbapenem synthesis.⁽⁶⁶⁾ For example, thiolester (82) on treatment with LHMDS formed the 2-keto carbapenem (83) in high yield with no sign of any other product.

Scheme 4

Three types of Wittig condensation have been described, these being between a phosphorane and an aldehyde, a phosphorane and a ketone, and finally between a phosphorane and a thiolester.

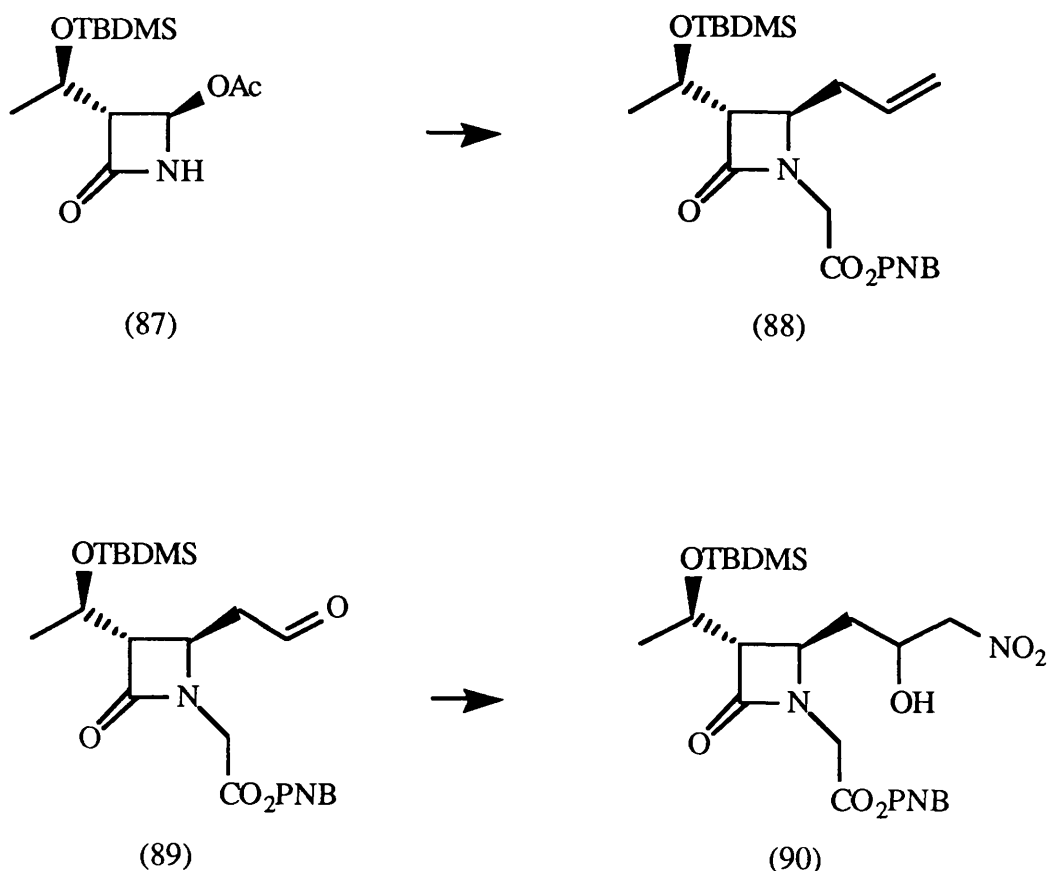
Although Wittig reaction between a phosphorane and a thiolester would seem ideal, in that a C-2 thio substituted carbapenem would result, the reaction is sluggish and yields are moderate to low.⁽⁶⁷⁾ Unfortunately the same is true of Wittig reactions with ketones, but the reaction works well with aldehydes. For example, the Beecham group⁽⁶⁸⁾ (Scheme 5) elaborated 4-allylazetidinone (84) by standard methods to phosphorane (85). This was then ozonolysed in the presence of strong acid, the ozonide reduced and the ylide re-formed. Spontaneous cyclisation followed to yield carbapenem (86) which was converted into racemic PS-5 (25).

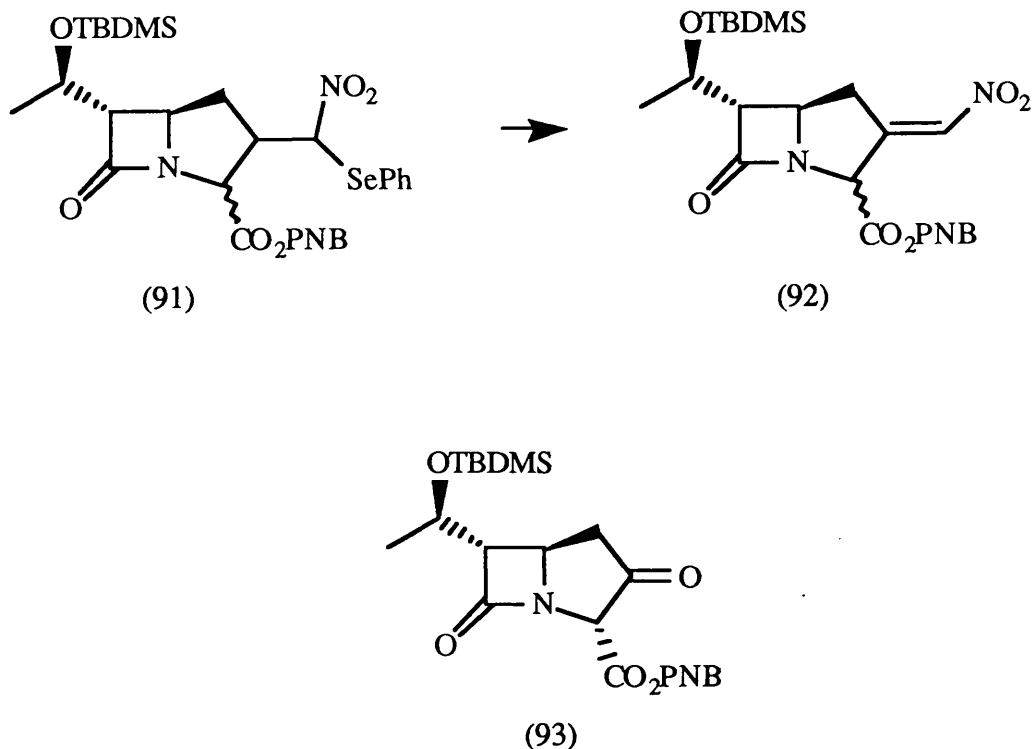
Scheme 5



Hanessian and co-workers (Scheme 6) have extended their Michael cyclisation methodology from the penem series⁽⁶⁹⁾ to the carbapenems.⁽⁷⁰⁾ Azetidinone (87) was allylated at C-4 and the nitrogen alkylated to form (88). This was then converted into the diol, oxidatively cleaved to the aldehyde (89) and alkylated with nitromethane to furnish (90). After mesylation and base induced elimination the intermediate was treated with LHMDs and PhSeCl to afford the bicyclic (91) which was subsequently oxidised to the selenoxide and warmed to afford unsaturated nitro olefin (92). Ozonolysis with concomitant epimerisation gave the 2-keto carbapenem (93), which was then converted, via the Merck methodology (see later), into thienamycin.

Scheme 6



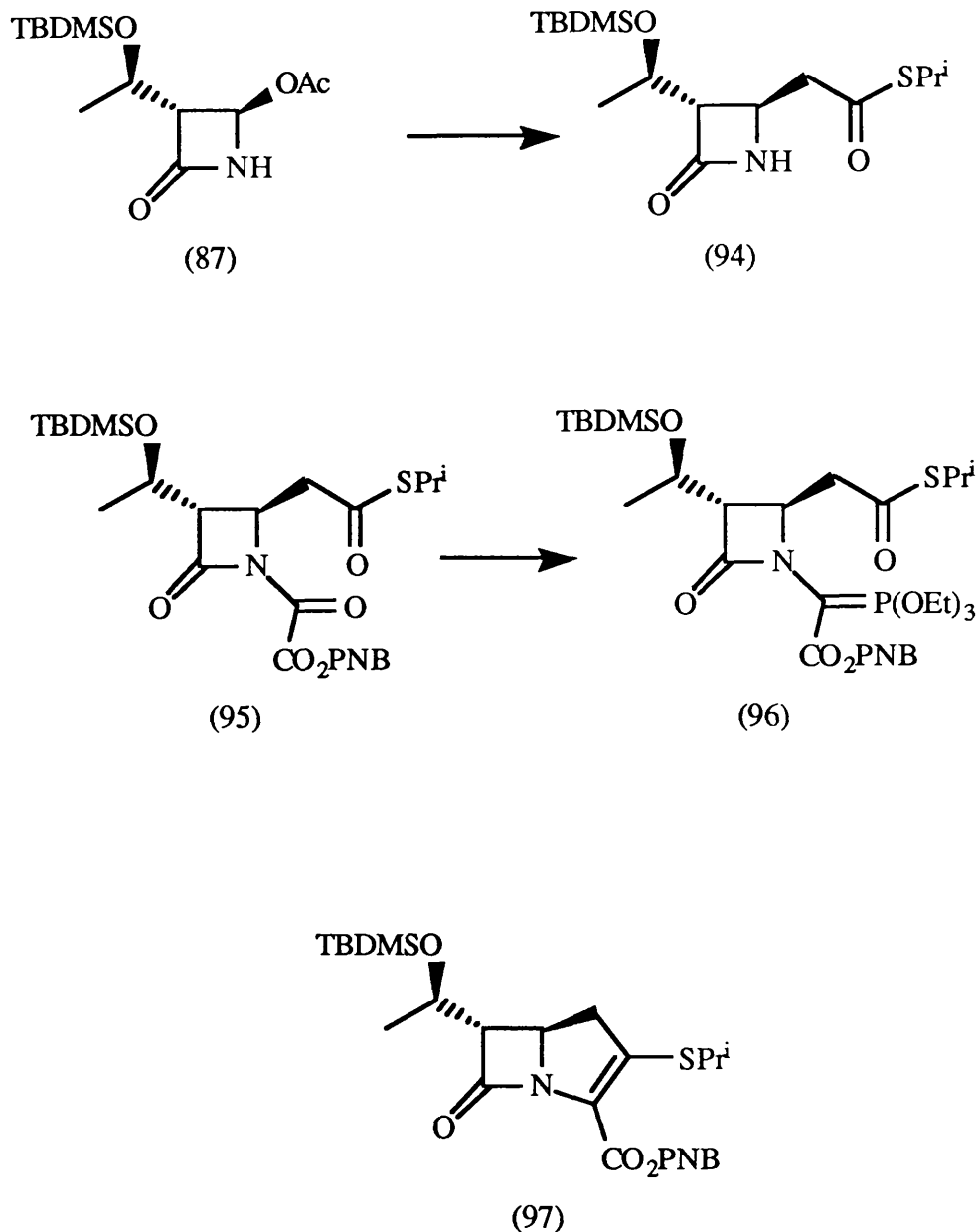


1.5.2.2.5 Reductive Cyclisation

Reductive cyclisation to form the C-2/C-3 bond in the final carbapenam, with trialkyl phosphites, has proven to be of great synthetic utility in the synthesis of C-2 unsubstituted⁽⁷¹⁾ and C-2 thio-substituted carbapenems.⁽⁷²⁾ For example, utilising methodology developed by Barrett and Quayle⁽⁵⁰⁾, the azetidinone (87) was *N*-silylated and the 4-acetoxy substituent displaced with a silyl ketene acetal. After *N*-desilylation and thiolester formation the β-lactam (94) was formed. Treatment with *p*-nitrobenzyloxyoxalyl chloride and Et₃N resulted in the formation of the corresponding oxalimide (95) which was treated with five equivalents of triethyl phosphite to form the intermediate trialkoxyphosphorane (96), possibly *via* a carbene intermediate.⁽⁷³⁾ The phosphorane was not purified but heated at reflux in the presence of hydroquinone to furnish the desired carbapenam (97) in good yield (Scheme 7).

This route provides an alternative ring closure to the Wittig route, requiring fewer steps and possibly milder conditions.

Scheme 7

1.5.2.3 C-1/C-5 Closure.

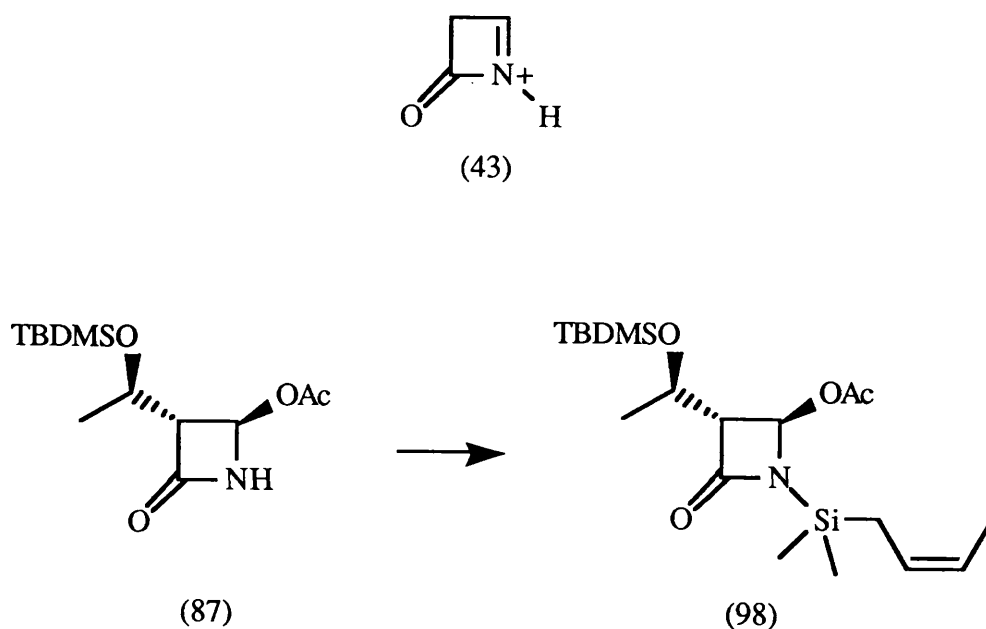
Displacement of an electronegative substituent from the 4-position of an azetidinone ring, as above, leads into the next bond forming reaction. Formation of the C-1/C-5 bond is extremely common in carbapenem synthesis, not so much to close the pyrroline ring as to furnish advanced precursors, which after further manipulation can be elaborated to a bicycle.

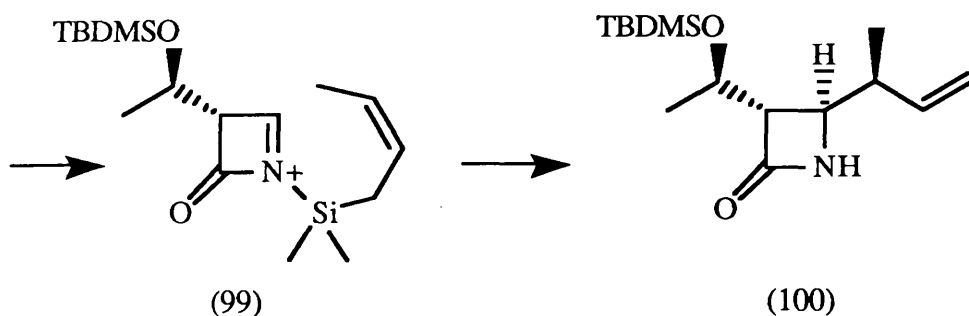
The postulated intermediate in the displacement is the azetidinium ion (43), the process not being a straightforward S_N2 displacement. A variety of electronegative substituents can be used as a leaving group, such as chloro, phenylsulphonyl or acetoxy, and these can be displaced by a variety of nucleophiles, including silyl enol ethers, allylsilanes, organometallic reagents, thioesters and sulphides.

An excellent example occurs in the recent work of Uyeo and Itani⁽⁷⁴⁾ in the stereocontrolled synthesis of a 1 β -methyl carbapenem precursor (100). (Synthetic routes to these 1 β -methyl carbapenems are being reported more and more as their superior *in vivo* stability is recognised).

The work of Uyeo and Itani, (Scheme 8), combines the inherent nucleophilicity of an allylsilane and the leaving group ability of a 4-acetoxy substituent to deliver a nucleophile intramolecularly. The 4-acetoxy β -lactam (87) was treated with (Z)-but-2-enylchlorodimethylsilane in the presence of Et_3N to afford the N-silyl β -lactam (98). Upon treatment with TMSOTf then MeOH/ Et_3N the precursor (100) was obtained. The authors have postulated that the reaction proceeds *via* intermediate (99) to afford precursor (100) in excellent yield (84% from acetate).

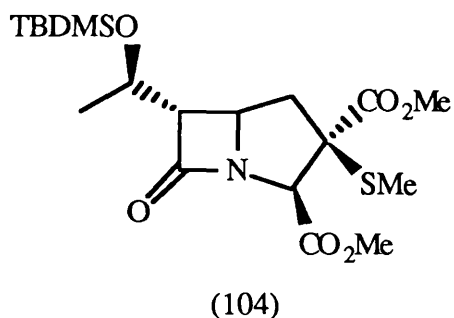
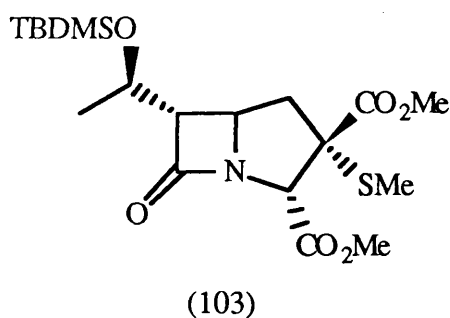
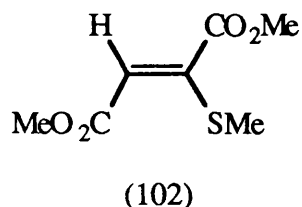
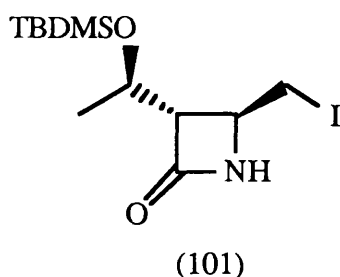
Scheme 8





1.5.2.4 Cyclisation by a New Type of [3+2] Cycloaddition.

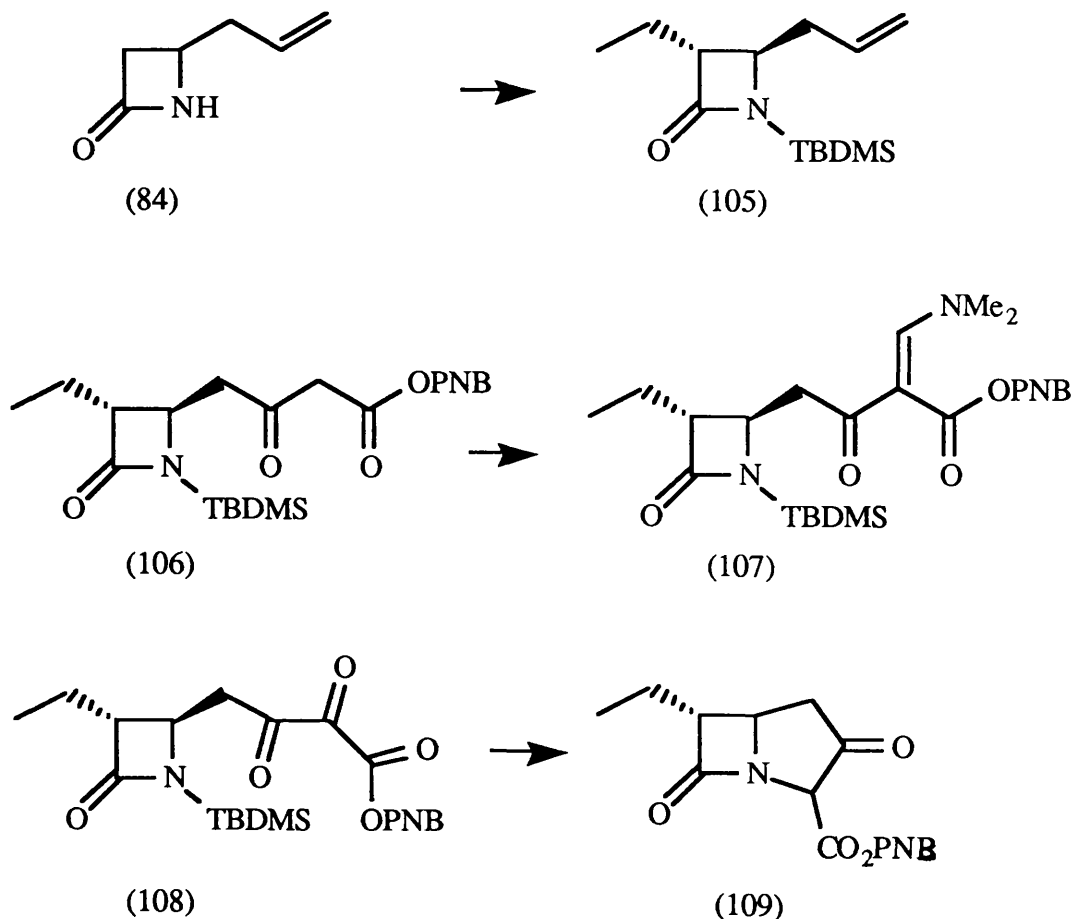
A novel mode of cyclisation has been reported by the Sankyo group⁽⁷⁵⁾, wherein 4-(iodomethyl)azetidinone (101) was reacted with alkene (102) in the presence of KH and 18-crown-6 to furnish the carbapenems (103) and (104) in low yield, via a conjugate addition to the alkene followed by an intramolecular displacement of the iodide. These compounds could possibly be converted into a synthetically useful 2-keto carbapenem, utilising the oxidative decarboxylation method of Trost.⁽⁷⁶⁾



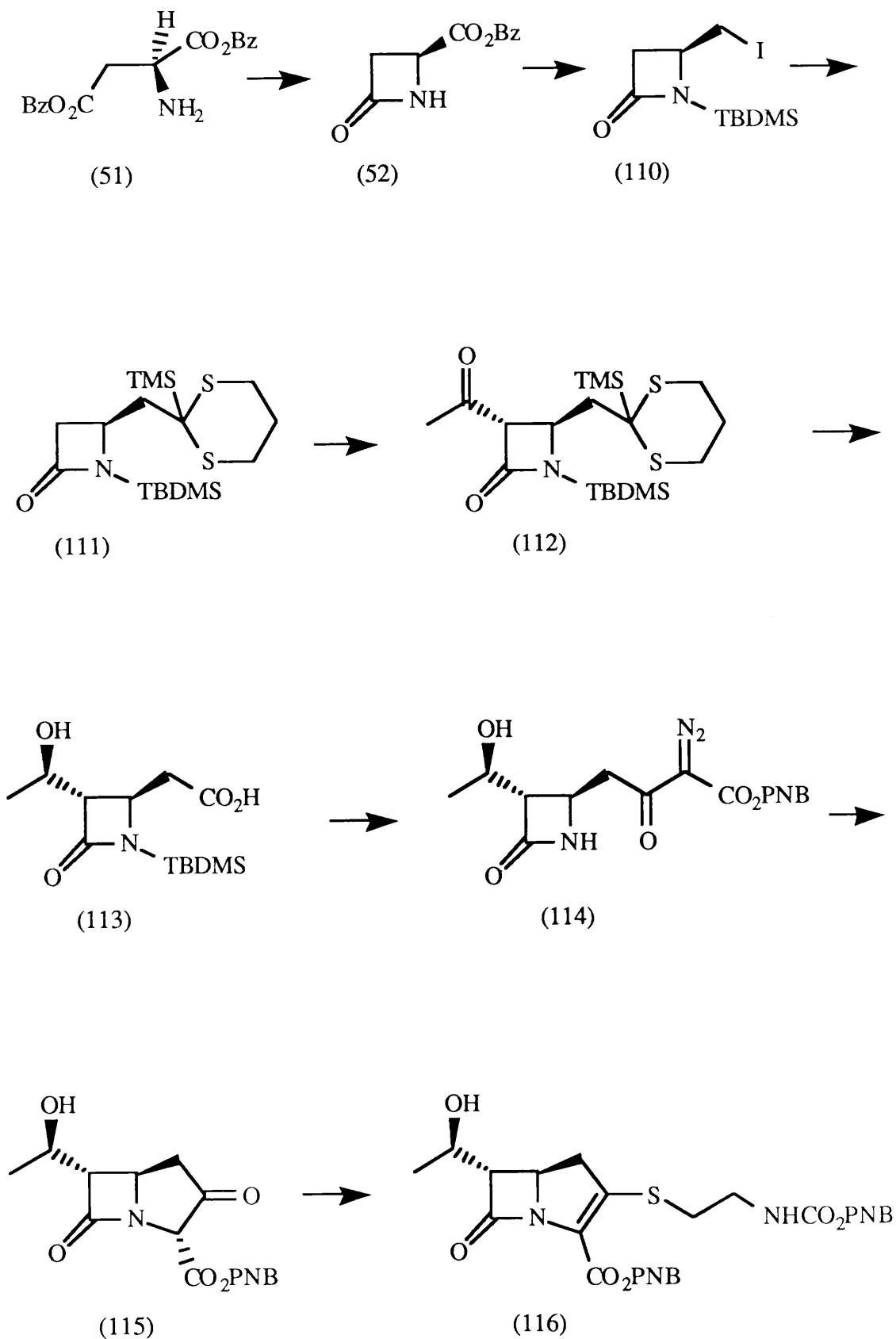
1.5.2.5.1 Amide Nucleophilicity

This ring closure is perhaps the most widely used method of ring closure due to the versatility of the amide nitrogen. Indeed the nucleophilicity of this nitrogen has often been used to close the pyrrolidine ring. Wasserman and Han⁽⁷⁷⁾, (Scheme 9), elaborated 4-allylazetidione (84) to (105) via N-silylation and alkylation at the C-3 position. Following oxidative cleavage of the olefin side chain to the nor-carboxylic acid, Masamune⁽⁷⁸⁾ chain extension via treatment with carbonyldiimidazole and the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid furnished β -lactam (106). The enamino ketone (107), formed by treatment of (106) with dimethylformamide dimethyl acetal, was converted into the vicinal tricarbonyl species (108) by the action of singlet oxygen. Upon desilylation, cyclisation was followed by TMSI mediated de-oxygenation to furnish (109), a known precursor to PS-5.⁽⁷⁹⁾

Scheme 9



Scheme 10



The Merck⁽⁴¹⁾ synthesis of (+)-thienamycin (Scheme 10) was a milestone, not only in terms of being the first enantiospecific carbapenem synthesis, but also because it illustrated a method of C-3/N-4 ring closure which has subsequently become very widely used. Namely, the C-3/N-4 bond was closed by carbene generation followed by insertion into the NH bond of the azetidinone ring to form the bicyclic structure (115). This bicyclic β -keto ester, was elaborated via an addition/elimination sequence to generate (+)-thienamycin.

Dibenzyl aspartate (51) was cyclised to β -lactam (52). Reduction to the (hydroxymethyl)azetidinone, mesylation, iodide displacement and N-silylation furnished azetidinone (110) in good yield. The Iodide was displaced with 2-lithio-2-(trimethylsilyl)-1,3-dithiane to give (111), which was acylated with LDA and acetylimidazole to furnish (112). Stereospecific reduction, with K-Selectride, to the 8(R)-alcohol and mercuric chloride mediated hydrolysis of the thioacetal followed by hydrogen peroxide treatment of the product gave β -lactam (113). Masamune chain extension followed by removal of the silyl group and diazo transfer afforded azetidinone (114) which underwent cyclisation on treatment with $\text{Rh}_2(\text{OAc})_4$ to give 2-keto carbapenem (115). Conversion into the vinyl phosphate with $(\text{PhO})_2\text{POCl}$ and displacement with the *p*-nitrobenzyl carbamate of cysteamine furnished (116), which upon hydrogenolysis gave natural (+)-thienamycin (15).

This type of ring closure has found widespread use in the total synthesis of carbapenems and has recently been extended by Miller and co-workers⁽⁸⁰⁾ to allow insertion into N-O-alkyl bonds in addition to N-H bonds.

(+)-Thienamycin, synthesised by the Merck group⁽⁴¹⁾ in 1980, prompted a vast change in synthetic strategies toward carbapenems, highlighting the need for absolute and not just relative stereocontrol.

Over the last decade or so this problem has been addressed by many chemists, utilising three main approaches:

1.5.3.1) Chiral Pool.

- .1) Amino acids
- .2) Sugars
- .3) 6-Aminopenicillanic acid (6APA)
- .4) 3-Hydroxybutyrates

1.5.3.2) Optical Resolution.

1.5.3.3) Achiral Precursors.

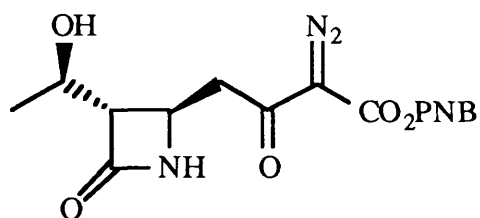
- .1) Chemoenzymatic Hydrolysis
- .2) Chiral Auxiliary

1.5.3.1 Chiral pool

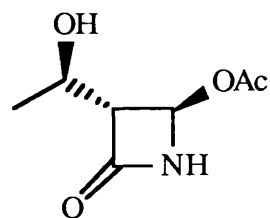
Most synthetic schemes have concentrated on routes from pre-existing chirality in the form of readily available chiral starting materials.

1.5.3.1.1 Amino acids

The Merck synthesis⁽⁴¹⁾ of (+)-thienamycin, outlined in Scheme 10, utilised aspartic acid in a scheme which involved sixteen steps to synthesise intermediate (114). A different group within the Merck laboratories subsequently published a route to (114) from aspartic acid in ten steps via the 4-acetoxiazetidione (117).⁽⁸¹⁾



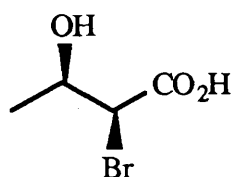
(114)



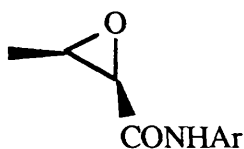
(117)

Both of these Merck syntheses relied on the generation of a trans substituted 3-acetyl β -lactam *via* enolate/electrophile chemistry. This was then followed by stereoselective reduction of the 3-acetyl substituent which gave the required (R) stereochemistry in the hydroxyethyl side chain.

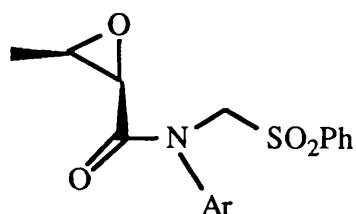
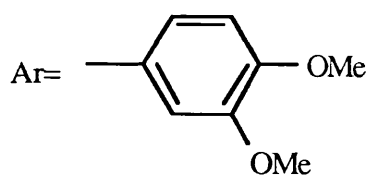
Other groups have approached the problem from a different perspective in that they have started with a chiral α -hydroxyamino acid, such as L-threonine, thereby obviating the need for a chiral reduction.⁽⁸²⁾ In this case, L-threonine was converted into bromide (118) and on to epoxide (119) then to sulphone (120). Intramolecular ring opening of the epoxide followed by protection of the free hydroxyl group and ozonolysis, to remove the amide protecting group, gave β -lactam (121) in high yield. This scheme therefore furnishes an homochiral azetidinone which, due to the leaving group ability of the phenylsulphonyl group, can be used as a carbapenem precursor.



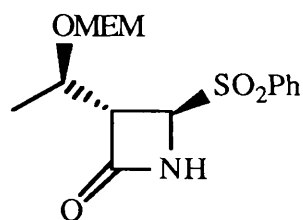
(118)



(119)



(120)

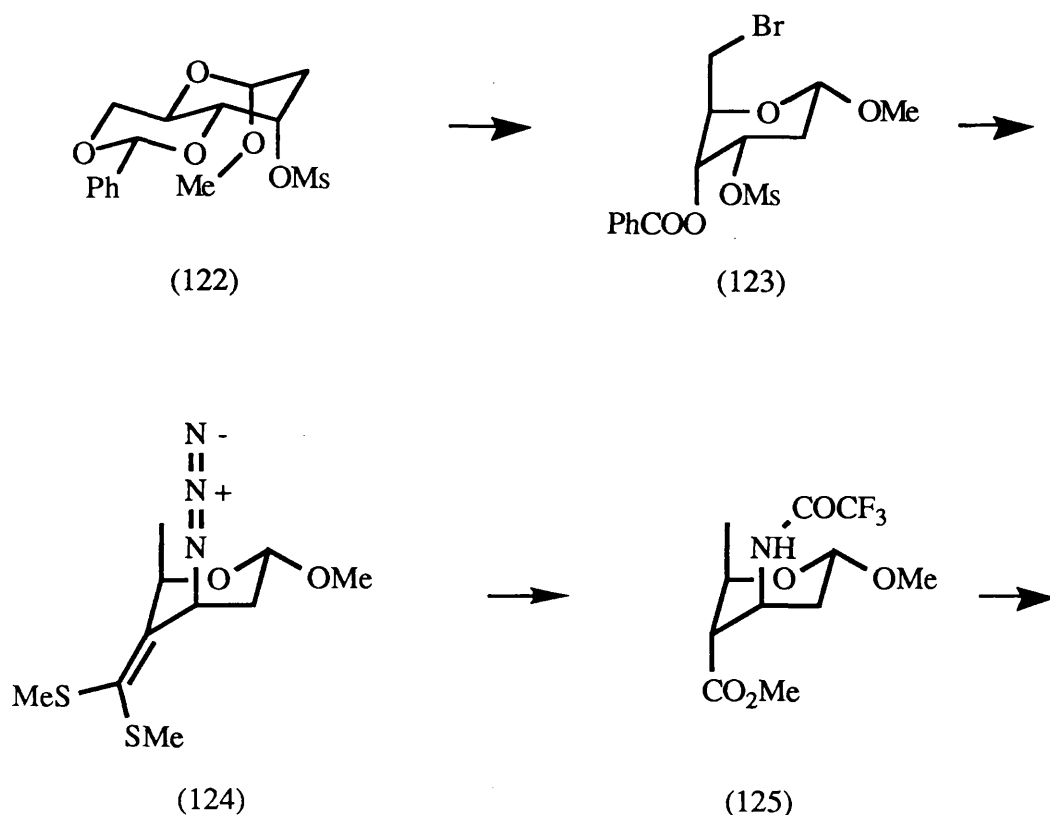


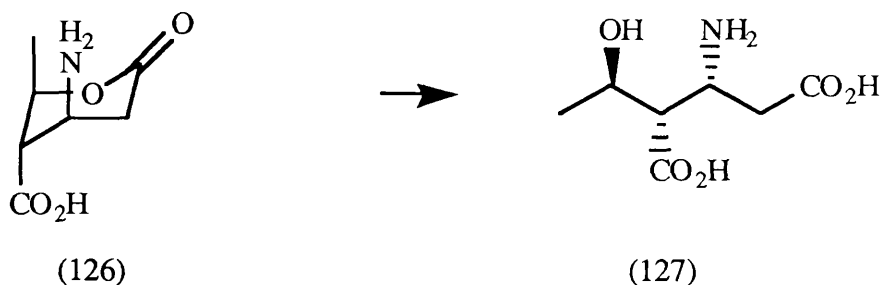
(121)

D-glucose is a readily available, inexpensive chiral starting material for the synthesis of carbapenems as well as for a number of other enantiospecific syntheses. The inherent chirality of the system can be fine-tuned to suit the synthetic target as illustrated by the synthesis of (+)-thienamycin⁽⁸³⁾ and the enantiomerically pure epithienamycin (136)⁽⁸⁴⁾ from the same starting material.

Hanessian and co-workers⁽⁸³⁾ (Scheme 11) elaborated D-glucose to intermediate (123) by making use of the NBS/CCl₄/BaCO₃⁽⁸⁵⁾ reagent system to open a methyl-4,6-O-(benzylidene)hexapyranoside (122). This precursor was converted, in high yield, into the ketene dithioacetal (124) and on to lactone (126) via acetal (125). This lactone (126) was found to open in aqueous solution to β-amino acid (127) which, in racemic form, had previously been used in the synthesis of thienamycin.⁽⁸⁶⁾ This therefore constitutes a formal synthesis of (+)-thienamycin.

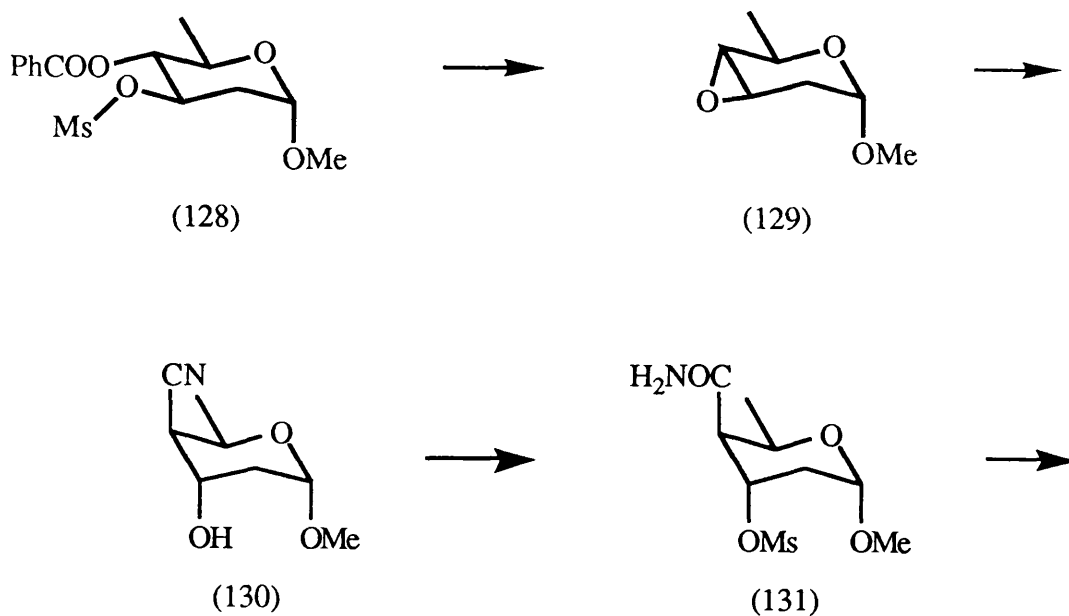
Scheme 11

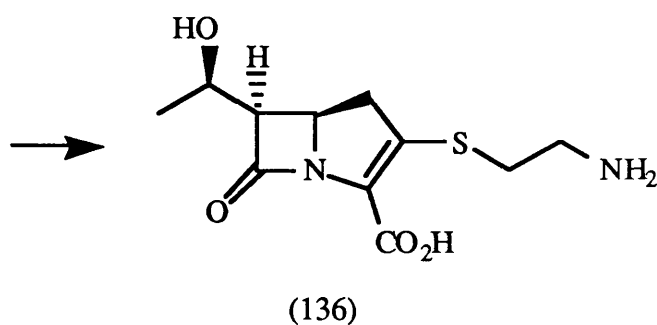
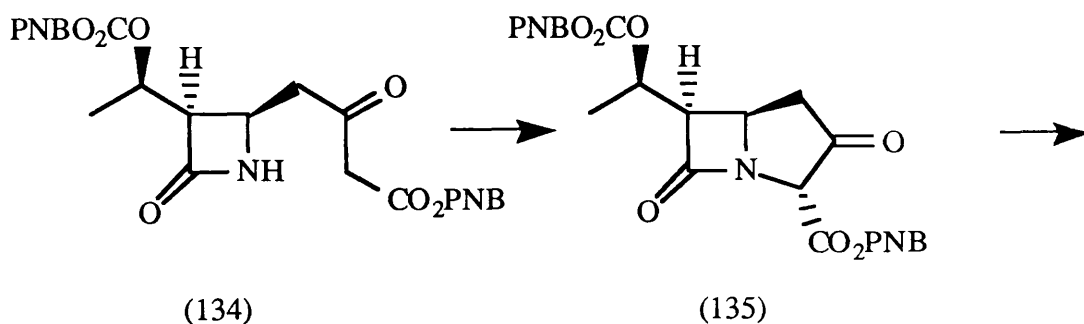
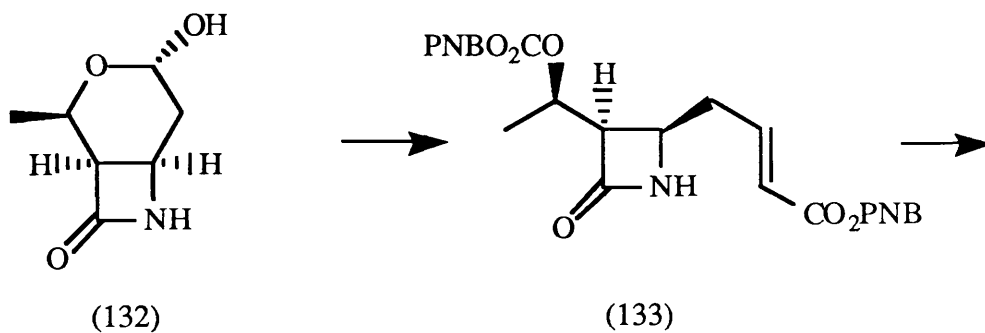




On the other hand Vasella and Knierzinger⁽⁸⁴⁾ (Scheme 12) elaborated D-glucose to intermediate (128) which underwent methanolysis followed by mesylate displacement to furnish epoxide (129). Ring opening with diethylaluminium cyanide gave the hydroxynitrile (130) which was elaborated to the amide then mesylated to furnish (131). Ring closure and acetal cleavage produced precursor (132). Wittig olefination and hydroxyl protection furnished carbonate (133), which was oxidised to ketone (134). This ketone, after diazo exchange, and carbene generation was cyclised to carbapenem (135). This was subsequently converted into an epimeric form of thienamycin (136), a compound not found in nature, which was shown to have less antibiotic activity but more β -lactamase stability than thienamycin.

Scheme 12



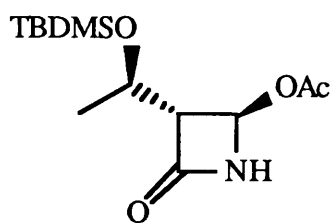


1.5.3.1.3 6-Aminopenicillanic acid (6APA).

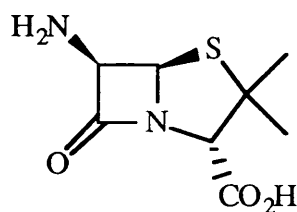
Although 6-APA is a readily available, optically active precursor for carbapenem synthesis, it is necessary to convert the thio and C-6 amino groups into properly functionalised alkyl groups with correct stereochemistry.

Perhaps one of the most frequent uses of 6-APA, which has been independently reported by several groups, is conversion into the useful 4-acetoxy β -lactam (87). The method employed by the Sankyo group⁽⁸⁷⁾ involved conversion of 6-APA (6) into the 6,6-dibromo derivative, esterification of the 3-carboxylic acid function, treatment with

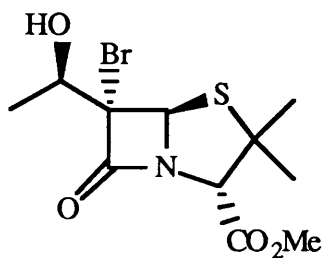
methylmagnesium bromide to generate the monobromo enolate and quenching with acetaldehyde to furnish the 6-hydroxyethyl β -lactam (137). After silylation this β -lactam was reductively debrominated to generate β -lactam (138). Treatment of this bicycle with $\text{Hg}(\text{OAc})_2$ in acetic acid, afforded the trans- β -lactam (139) whose nitrogen substituent was oxidatively removed with KMnO_4 in aqueous acetone to yield (87).



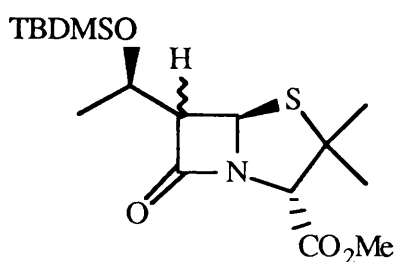
(87)



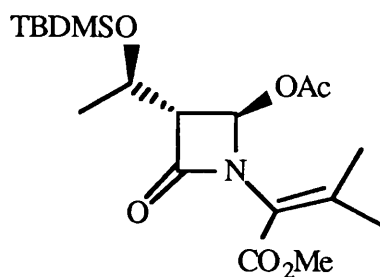
(6)



(137)

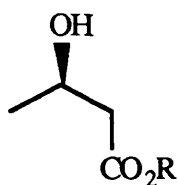


(138)

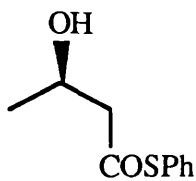


(139)

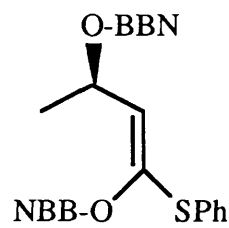
Perhaps one of the most obvious retrosynthetic disconnections of thienamycin suggests the use of a 3-(R)-hydroxybutyrate (140) as a chiral building block. Indeed, lithium ester enolates of these compounds, in condensation with imine species, have proven to be of great synthetic value. The reaction is not limited to the use of traditional Li ester enolates and an interesting example occurs in the use of boron enolates. Shibasaki and Iimori⁽⁸⁸⁾ converted butyrate (140, R=Me) into thiolester (141), which upon treatment with 9-BBN triflate in the presence of Hunig's base afforded vinyloxyborane (142). This was condensed with imine (143) to afford β -amino ester (144) which was subsequently cyclised and silylated to give the enantiomerically pure β -lactam (145) along with the two diastereomeric β -lactams (146) and (147) in a yield of 90% (ratio 9:1:0.2).



(140)



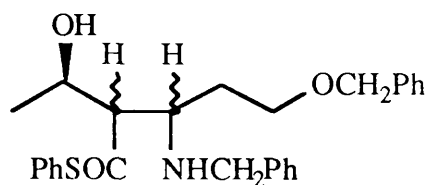
(141)



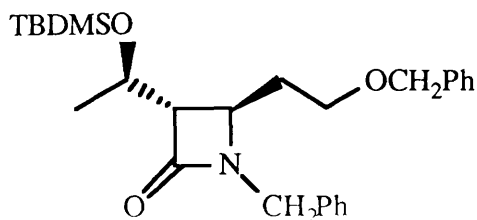
(142)



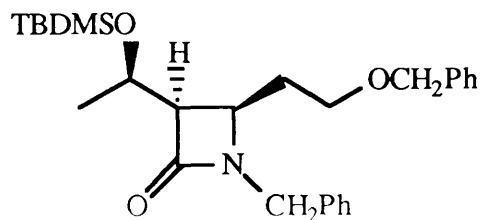
(143)



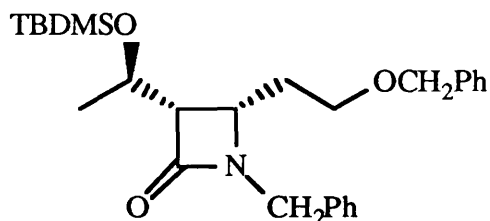
(144)



(145)



(146)



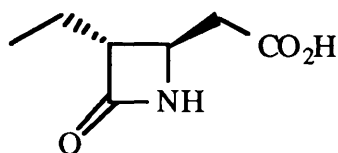
(147)

1.5.3.2 Optical Resolution.

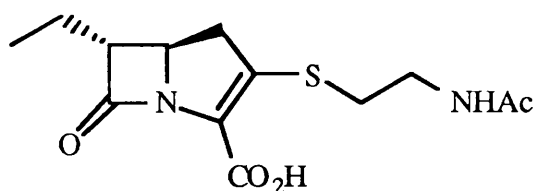
Although optical resolution may be considered wasteful, it has found many applications in carbapenem synthesis. For example, Favara and co-workers accomplished the synthesis of enantiomerically pure PS-5⁽⁷⁹⁾ via the addition of CSI to a mixture of acetoxyhexadienes (148). The mixture of four β -lactams was hydrogenated, deacetylated and oxidised with KMnO_4 to produce selectively the racemic trans acid (149) after crystallisation from ethyl acetate. Optical resolution of this racemate was accomplished by treatment with α -1,4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol and the (+)-enantiomer converted into (+)-PS-5 (25).



(148)



(149)



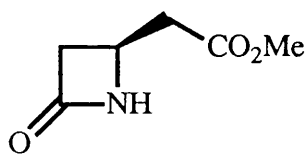
(25)

1.5.3.3 Achiral Precursors.

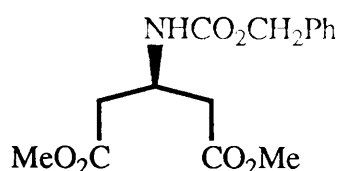
1.5.3.3.1 Chemoenzymatic Hydrolysis.

The synthetically useful (+)-4-(carbomethoxymethyl)azetidinone (150) has been prepared by pig liver esterase mediated hydrolysis of prochiral dimethyl *N*-benzyloxycarbonyl- β -aminoglutarate (151). After hydrogenolysis to remove the benzyloxycarbonyl protecting group, the chiral halfester (152) was cyclised with $\text{PPh}_3/\text{PyS.SPy}$ to yield (150) in high optical purity.⁽⁸⁹⁾

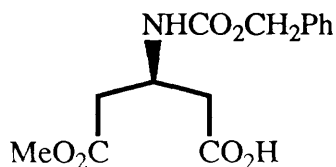
This (+)-4-(carbomethoxymethyl)azetidinone has been converted into key intermediates for the synthesis of (+)-PS-5 and (+)-PS-6⁽⁹⁰⁾ as well as (+)-thienamycin⁽⁹¹⁾ and perhaps most interestingly (-)-asprenomycin C (153)⁽⁹²⁾, where the elaborated azetidinone (154) underwent a stereoselective Peterson olefination via the postulated chelation controlled intermediate (155).



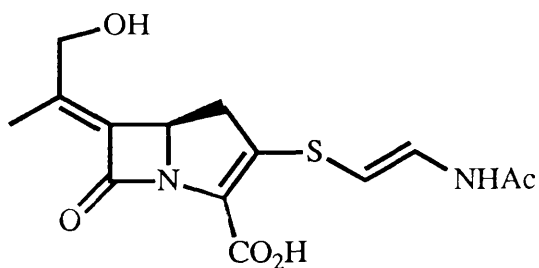
(150)



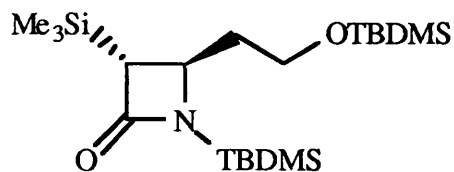
(151)



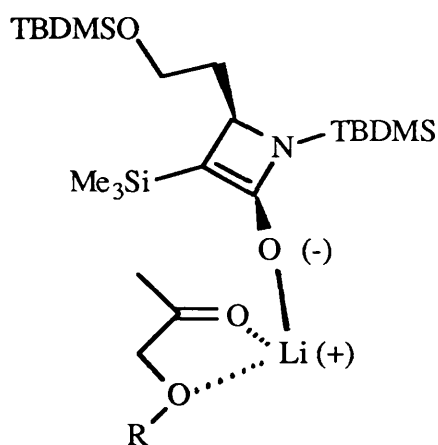
(152)



(153)



(154)



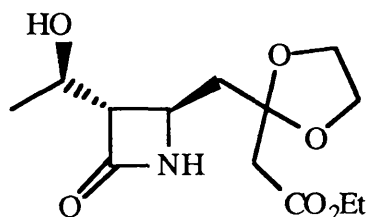
(155)

1.5.3.3.2 Chiral Auxiliary.

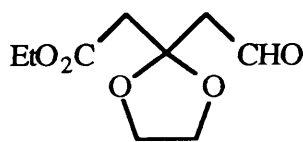
The examples mentioned thus far have taken pre-existing chiral centres or have enzymatically generated them from a prochiral material and used them to influence chirality generation at a new centre with the original chiral moiety still being retained in the final product. This section will deal with the temporary introduction of a chiral centre which will induce chirality at a newly forming centre before being removed and therefore not appearing in the final product.

Kametani and co-workers⁽⁹³⁾ have used this method in the preparation of intermediate (156) used in the synthesis of (+)-thienamycin. The achiral aldehyde (157) was condensed with (S)-*N*-(α -phenethyl)hydroxylamine to yield nitron (158). 1,3-Dipolar cycloaddition with benzyl crotonate gave adduct (159) in 23% yield along with a diastereomer whose *relative* configuration was not determined.

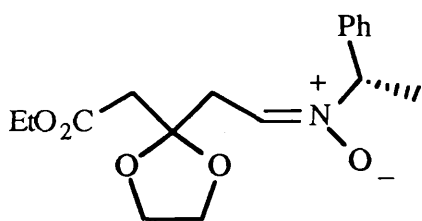
Catalytic hydrogenolysis followed by coupling of the resulting β -amino acid (160) resulted in formation of β -lactam (156). This was subsequently converted into the known (161) whereupon comparison of rotations indicated that intermediate (159) had at least a 98% *diastereomeric* excess.



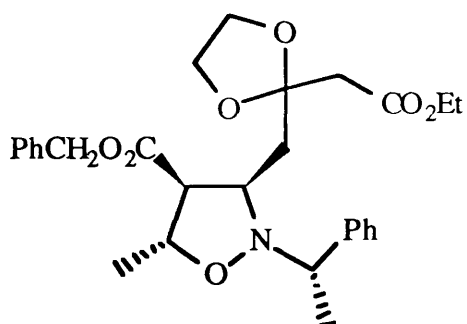
(156)



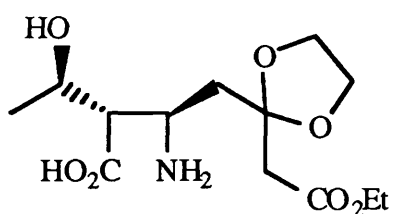
(157)



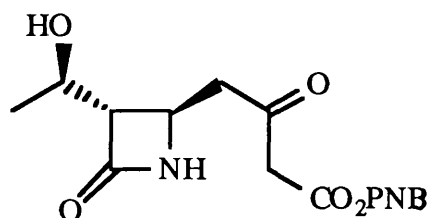
(158)



(159)

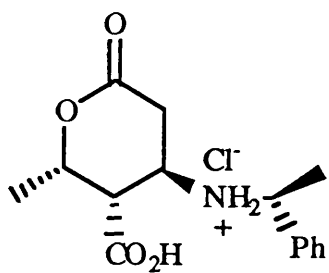


(160)

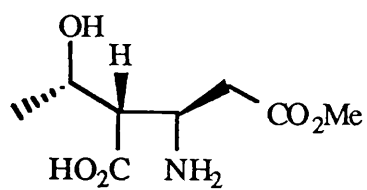


(161)

The final example in this review also features chiral induction by a removable moiety. Rather fittingly this procedure is the large scale Merck synthetic route to (+)-thienamycin.⁽⁹⁴⁾ The achiral starting material, dimethyl acetonedicarboxylate (162) is condensed with (R)-(+)- α -methylbenzylamine to furnish the equilibrium mixture of enamines (163) and (164). Acylation of this mixture with acetic anhydride or diketene leads to the enamino ketone (165) in high yield. This ketone is then subjected

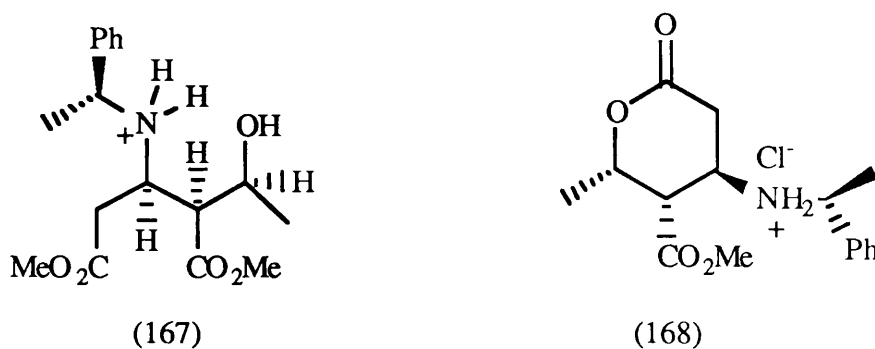
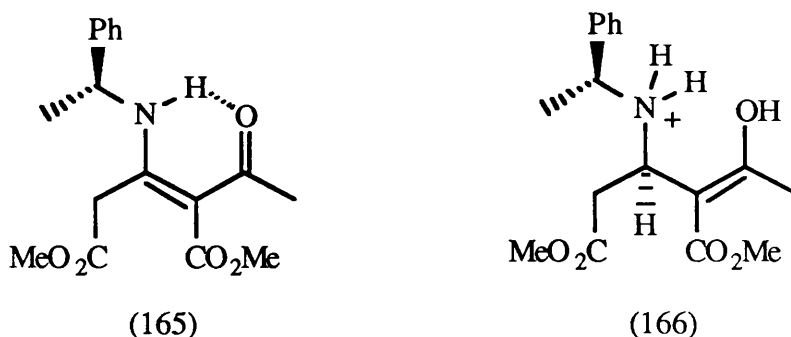
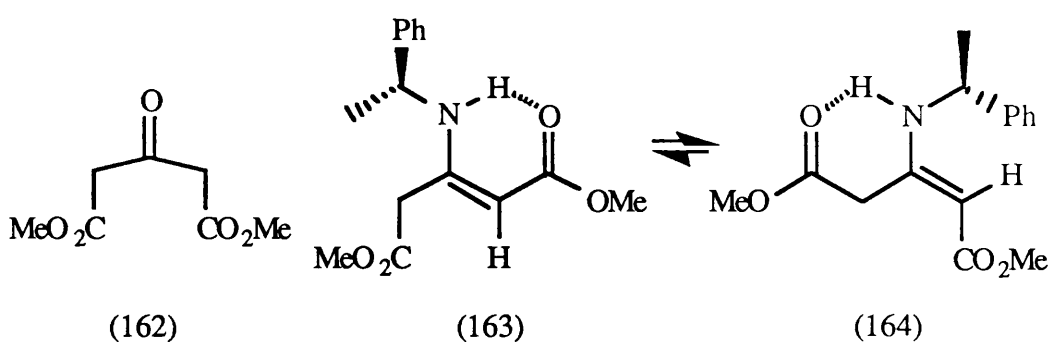


(169)



(170)

to hydrogenation over Pt in the presence of H_3PO_4 to form alcohol (167) via the enol (166), with the chiral amine residue controlling the stereochemistry of hydrogenation. This alcohol is then cyclised to lactone (168) by HCl treatment and hydrolysed to the acid (169). Following hydrogenolysis of the chiral auxiliary, and methanolysis of the lactone, the free base is liberated with Bu^n_3N to furnish β -amino acid (170), which is converted into (+)-thienamycin by standard methodology with a Mitsunobu inversion of the (S)-stereochemistry in the hydroxyethyl side chain.



Conclusion.

Unlike the penicillins where sufficient quantities for clinical use are available via fermentation and the cephalosporins where sufficient quantities are available from the ring expansion of 6-APA, the carbapenems are only available via total synthesis. Therefore synthetic routes toward carbapenems have been pursued avidly both to facilitate access and to improve biological function.

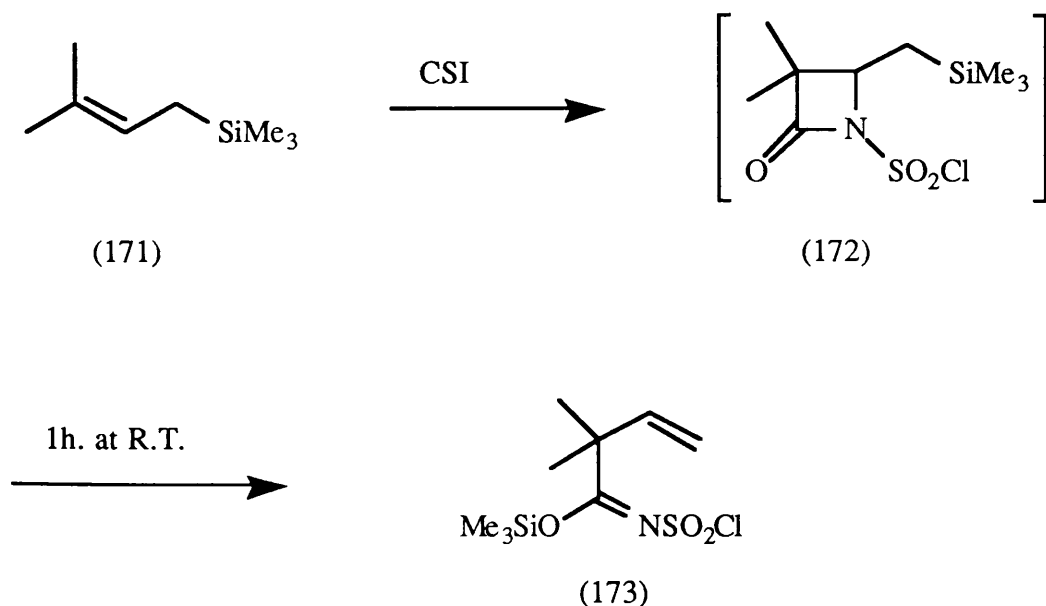
Currently, most research efforts are directed toward the control of absolute stereochemistry of the carbapenem. This is generally accomplished by the stereocontrolled generation of the azetidinone ring which is then used to induce chirality at centres generated later on in the synthetic scheme.

The addition of CSI to an sp^2 hybridised system has proven to be a versatile route to the four membered azetidinone ring. For example, addition to alkenes⁽⁹⁵⁾, enol esters⁽⁴⁾, dienes⁽⁹⁶⁾, allenes⁽⁵⁾, vinylsilanes⁽⁹⁷⁾, allyl iodides⁽⁹⁸⁾, allenyl sulphides⁽⁹⁹⁾ and vinyl sulphides⁽¹⁰⁰⁾ to form β -lactams have all been documented.

Unfortunately very few of the above methods are suitable to generate the carbapenem nucleus directly, and those which do suffer from severe limitations. For example, the addition of CSI to allyl iodide occurs over seven days in the dark and although displacement of an electronegative substituent from C-4 of an azetidinone ring is facile, this route does not allow direct access to the required moiety.

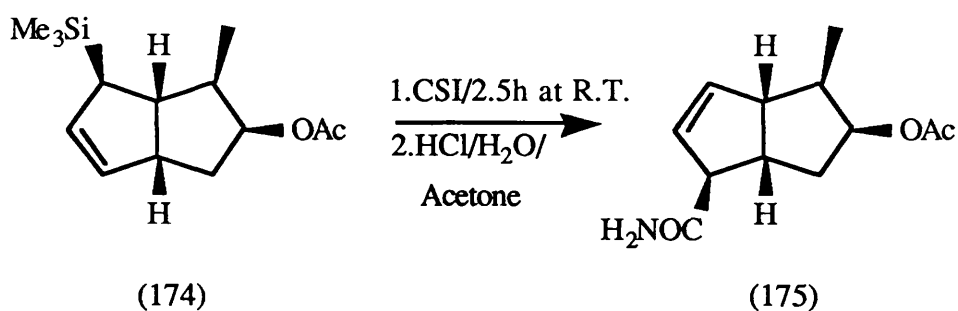
Bearing this in mind, we were intrigued by an earlier report of Dunoguès and co-workers⁽¹⁾ where the addition of CSI to allylsilanes, such as (171), resulted in the formation of N-chlorosulphonyl-O-silyl imidates (173), via in some cases at least an N-chlorosulphonyl β -lactam (172). This intermediate β -lactam had been observed by infra-red and ^1H NMR spectroscopy but no attempt had been made to intercept it (Scheme 13).

Scheme 13



This experimental observation of Dunoguès had been utilised by Fleming and Au-Yeung⁽²⁾ in a synthesis of loganin aglucone acetate (Scheme 14). This involved generation of β,γ -unsaturated amide (175) via the addition of CSI to allylsilane (174) at 0°C followed by stirring for 2.5h at ambient temperature, then an HCl/H₂O/acetone hydrolysis to furnish the amide.

Scheme 14

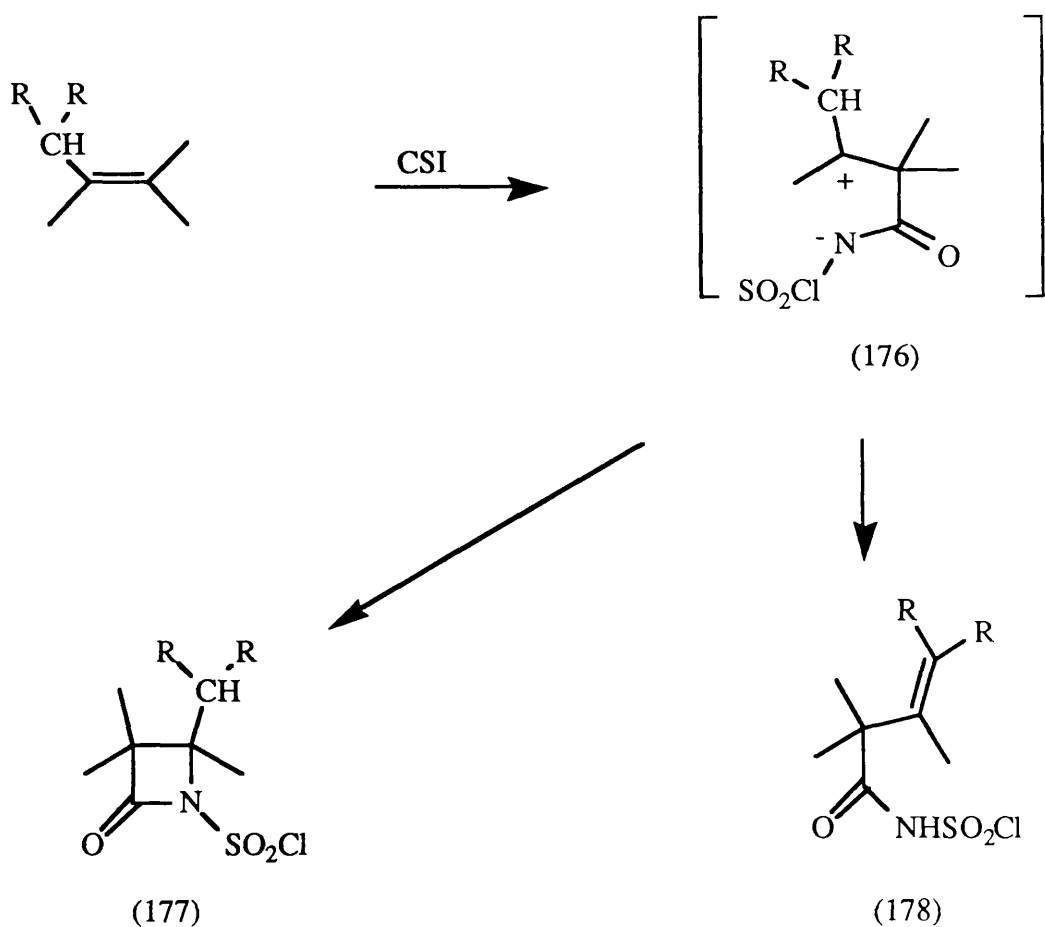


Our investigation commenced with the repetition of Dunoguès experiments in an attempt to intercept and reduce the intermediate N-chlorosulphonyl β -lactam and thereby furnish a C-4 carbon substituted azetidinone suitable for elaboration into the carbapenem series.

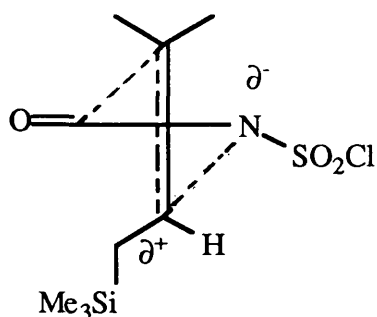
Useful precursors for elaboration to the carbapenem series will only result from the cycloaddition of CSI to allylsilanes if the regiochemistry of addition can be controlled.

In 1963 Graf⁽¹⁰¹⁾ proposed a two step mechanism (Scheme 15) for alkenes, where the initially formed zwitterionic species (176) can ring close to form β -lactam (177) or form the unsaturated amide (178) via proton loss.

Scheme 15



On the other hand Moriconi and Meyer⁽⁹⁶⁾ have proposed a near concerted, thermally allowed $[\pi 2_s + \pi 2_a]$ cycloaddition, probably initiated by π -complex formation and proceeding through the polar transition state (179).

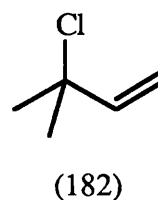
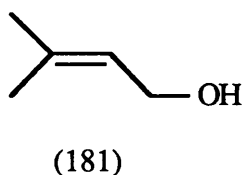
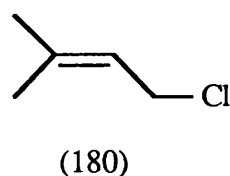
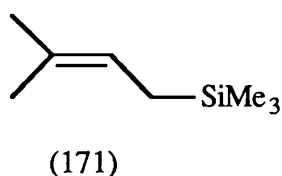


(179)

Regardless of which mechanism is actually operating a degree of positive charge is developed either in the intermediate (176) or in the transition state (179). We hoped therefore to be able to control the regiochemistry of addition using the ability of silicon to stabilise developing positive charges β to itself.⁽¹⁰²⁾

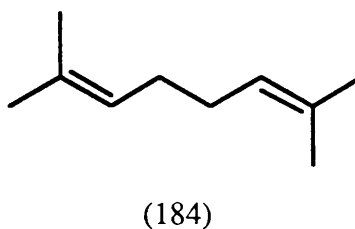
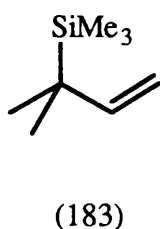
Indeed in the earlier work of Dunoguès and Fleming the cycloaddition had proceeded with its regiochemistry controlled by silicon. If we could intercept and reduce the intermediate N-chlorosulphonyl β -lactams then addition of CSI to allylsilanes would provide a regiocontrolled route to 4-(silylmethyl)azetidinones, which are potentially useful carbapenem precursors.

Dunoguès and co-workers⁽¹⁰³⁾ made use of (dimethylallyl)trimethylsilane (171), prepared from the corresponding allyl chloride (180) via a Grignard reaction. Initial attempts to obtain this chloride from dimethylallyl alcohol (181) with the $\text{PPh}_3/\text{CCl}_4$ reagent system were successful. However, material derived from this route was found to be unreactive in the Grignard reaction, presumably due to the presence of CCl_4 which could not be separated from the allyl chloride (180) on account of their similar boiling points.



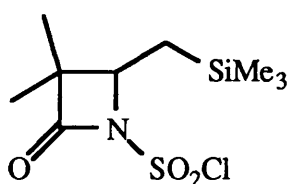
Treatment of the allyl alcohol (181) with PCl_3 in pentane produced the regio-isomeric allyl chlorides (180) and (182) in a ratio of 2.3:1. These regio-isomers could be separated by careful distillation at atmospheric pressure to furnish the desired chloride in a yield of 42% from the alcohol.

Unfortunately, although this chloride reacted vigorously in the Grignard reaction, the conditions used by Dunoguès with Et_2O as solvent gave the desired allylsilane contaminated by allylsilane (183) and Wurtz coupling product (184).

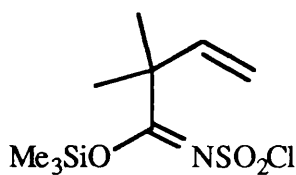


Later, Dunoguès (104) proposed the use of THF as solvent in the Grignard reaction with slow addition of allyl chloride at 0°C to furnish the allylsilane. Gratifyingly allyl chloride (180), derived via the PCl₃ route from alcohol (181), underwent Grignard reaction smoothly in THF to give allylsilane (171) in a yield of 50% after distillation.

The addition of CSI to allylsilane (171) was carried out by Déléris⁽¹⁰⁵⁾ with an allylsilane concentration of 3.5M in CCl₄. Fleming⁽²⁾, in the synthesis of loganin aglucone acetate had used a concentration of 1.9M allylsilane in CCl₄. For the purpose of re-investigation, the reaction was carried out in approximately 0.2M solution. The reaction was monitored by ¹H NMR spectroscopy and it was observed that all the allylsilane had disappeared after two hours. In marked contrast to the work of Dunoguès, the N-chlorosulphonyl β-lactam product (172) was stable for up to forty eight hours at room temperature with no visible signs of rearrangement to imidate (by ¹H NMR spectroscopy), whereas at a concentration of 3.5M Dunoguès observed rearrangement to imidate (173) in one hour at room temperature. However upon concentration, even in the cold, we did observe rearrangement to imidate.

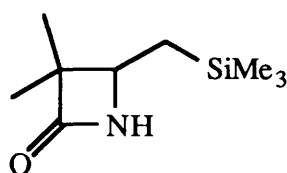


(172)



(173)

These limited experimental observations suggest some form of intermolecular rearrangement to form the imidate species. Most pleasingly, interception of the N-chlorosulphonyl β-lactam with 25% Na₂SO₃ solution⁽¹⁰⁶⁾ and stirring overnight accomplished reduction of the N-chlorosulphonyl β-lactam to the N-protio β-lactam thereby furnishing 3,3-dimethyl-4-(trimethylsilylmethyl)azetidinone (185) in a yield of 62%. This was a most encouraging result since the addition of CSI to vinyl acetate only proceeds in a yield of 40%.⁽⁴⁾

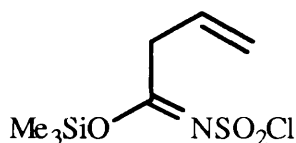


(185)

The cycloaddition of CSI with allyltrimethylsilane (186) to produce imidate (187) has also been investigated by Dunoguès, with no intermediate β -lactam having been described. In order to ascertain whether or not rearrangement to imidate proceeds via an intermediate N-chlorosulphonyl β -lactam, and if so could it be reduced to furnish an N-protio β -lactam, CSI was added to allyltrimethylsilane (186) in CCl_4 (again using a 0.2M solution).



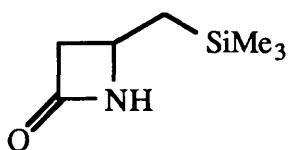
(186)



(187)

When the reaction was performed at 0°C , ^1H NMR spectroscopic monitoring indicated clean rearrangement to imidate with no intermediate β -lactam being observed. The reaction was repeated with the NMR sample being cooled to -40°C at which point only allyltrimethylsilane and a trace of imidate were observed before the CCl_4 solidified. Gradually the sample temperature was raised through -30°C , -20°C , -10°C to 0°C with a steady increase in imidate being observed accompanied by a corresponding decrease in allyltrimethylsilane and no detectable intermediate N-chlorosulphonyl β -lactam.

Ricci and co-workers⁽¹⁰⁷⁾ utilising CH_2Cl_2 , rather than CCl_4 , as solvent and a temperature of -78°C rather than 0°C again with an allylsilane concentration of 0.2M have managed to perform the cycloaddition of CSI and allyltrimethylsilane to furnish 4-(trimethylsilylmethyl)azetidinone (188) in reasonable yield, following a carbonate/bicarbonate mediated reduction.



(188)

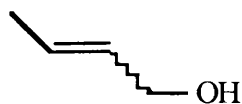
Crotylsilanes

Having repeated and confirmed Dunoguès' results with allyltrimethylsilane as well as having intercepted and reduced the intermediate *N*-chlorosulphonyl β -lactam from the addition of CSI to (dimethylallyl)trimethylsilane, the most logical step then seemed to be the addition with crotylsilane (189).



(189)

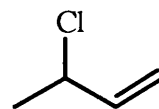
Preparation of the necessary crotylsilanes ((*E*)&(*Z*)) more or less followed the procedure adopted for (dimethylallyl)trimethylsilane (171). Namely PCl_3 /pyridine treatment of alcohol (190) furnished a mixture of allyl chlorides (191) and (192). (Note that in the previous case the PCl_3 mediated conversion of alcohol into chloride was performed in pentane. This time however no low boiling solvent was used due to the high volatility of the product chlorides.)



(190)

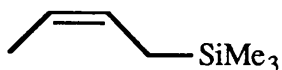


(191)

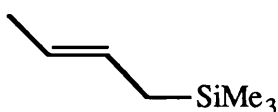


(192)

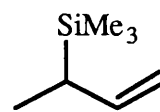
Careful distillation at atmospheric pressure separated the required primary chlorides (191) from the contaminating secondary chloride (192) to afford the desired compounds in a yield of 54%. Slutsky and Kwart⁽¹⁰⁸⁾ have shown that Grignard reaction with this allyl chloride (191) ((E)&(Z)) resulted in the production of (Z) and (E)-crotylsilanes (193) and (194) along with the rearranged secondary silane (195). Unfortunately the major product, in their study, was the rearranged allylsilane (75%). We adapted their procedure slightly to include an internal TMSCl quench, i.e., the Grignard reaction was performed in the presence of TMSCl. This minor modification did in fact reduce the quantity of secondary silane to ca. 40% but the rearranged silane was still the major product. However since the desired isomers are the thermodynamically favoured ones, fluoride ion promoted isomerisation of (195) to (193) and (194) by the method of Hosomi et al.⁽¹⁰⁹⁾ should have been possible.



(193)



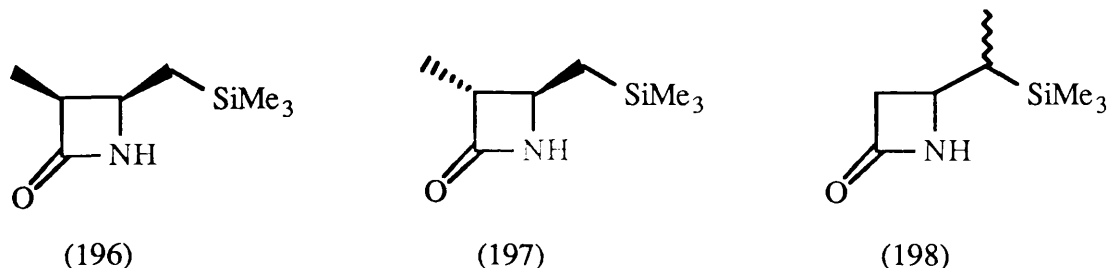
(194)



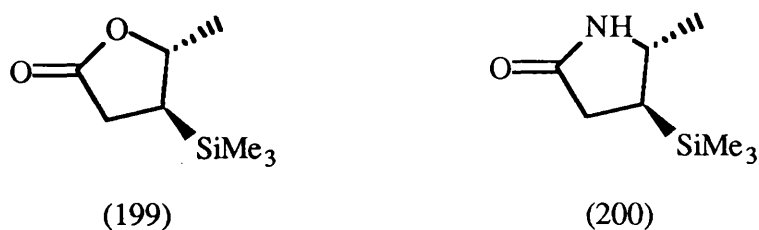
(195)

Isomerisation of the allylsilanes mixture did proceed according to the method of Hosomi et al., albeit in a disappointing yield of ca. 10%. This low yield can most probably be accounted for by the isomerisation process being carried out at 100°C, very close to the boiling point of the allylsilanes. Unfortunately allylsilanes (193) and (194) derived from this route did not react at all with CSI for some unknown reason. In view of the low yield and unreactivity toward CSI of material derived from the TBAF catalysed rearrangement it was decided to react the mixture of allylsilanes (193), (194) and (195), from the Grignard reaction directly with CSI. It was envisaged that this would produce β-lactams (196) and (197) from the primary silanes as well as (198)

from the secondary silane and these would hopefully be separable by chromatography.



The reaction, followed by ^1H NMR spectroscopy, had reached completion in 1.5h and was then quenched with aqueous Na_2SO_3 . After work-up, TLC analysis of the crude reaction product showed only one component, but capillary GC analysis indicated the presence of four compounds. Dry column flash chromatography on silica was found to be an unsuitable purification procedure due to degradation of the mixture. However chromatography on neutral alumina separated the four compounds which were then characterised as the expected cis and trans- β -lactams (196) and (197) along with the rather surprising γ -lactone (199) and γ -lactam (200). In each case only one diastereomer was produced and this was assumed to be trans.

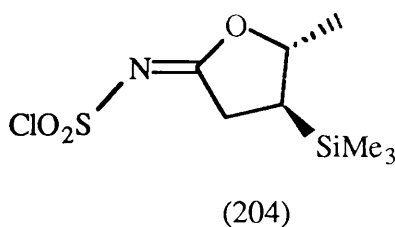
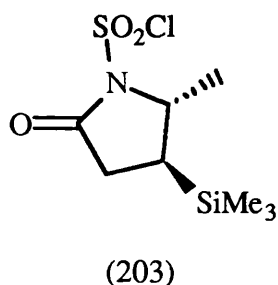
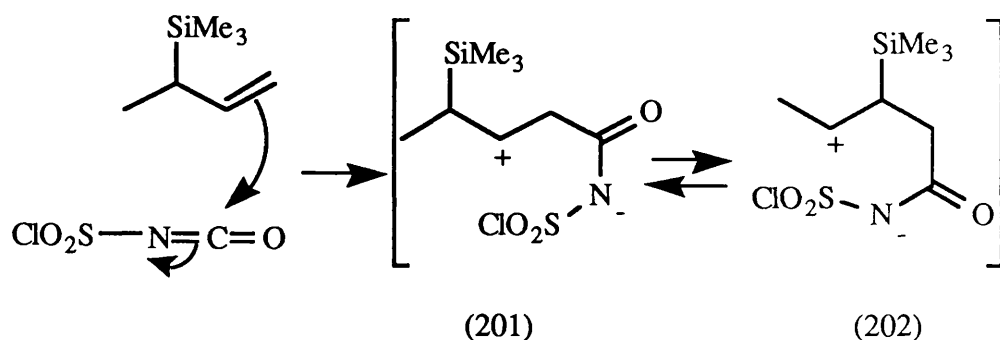


The β -lactams arise in a straight forward fashion from allylsilanes (193) and (194). Unfortunately no assignment of the cis/trans ratio was possible in the allylsilanes mixture and so we are uncertain as to whether or not the geometric ratio of the allylsilanes is preserved in the product β -lactams. Chromatographic separation of the diastereomeric β -lactams was not fully complete on neutral alumina but enough pure

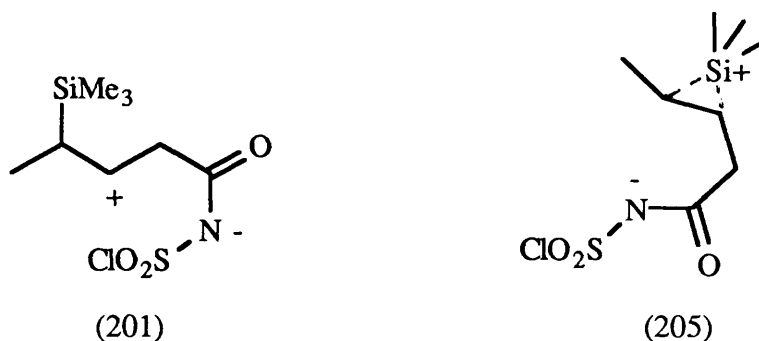
material of each was isolated to allow characterisation. Yields quoted in the experimental section refer to a total β -lactam weight obtained by flash chromatography divided into cis and trans components according to the GC ratios of the two β -lactams.

Some form of rearrangement has occurred to produce the γ -lactone and γ -lactam from allylsilane (195). Their production can be rationalised by proposing initial electrophilic attack by CSI on the allylsilane to form the zwitterionic species (201), as proposed by Graf.⁽¹⁰¹⁾ Rearrangement of this intermediate produces (202) which closes through nitrogen to form *N*-chlorosulphonyl lactam (203), which after reduction furnishes lactam (200) or closes via oxygen to furnish imidate (204) and this hydrolyses during sulphite reduction to lactone (199).

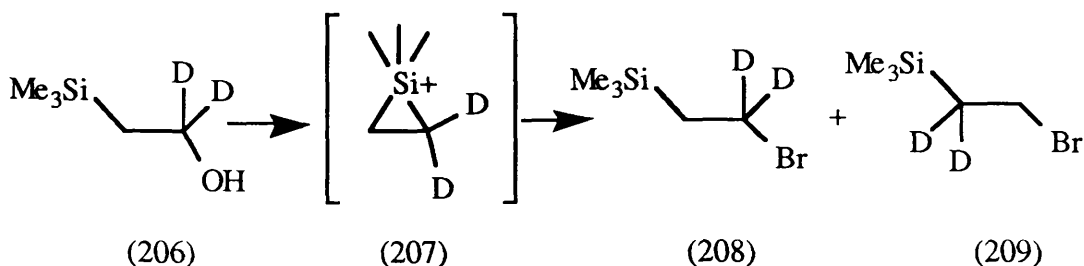
Note that in each of the intermediates proposed below the cation is both secondary and β to silicon, i.e., of approximately equal energies and five membered ring closure is chosen with no sign of the four membered ring closure occurring (see later).



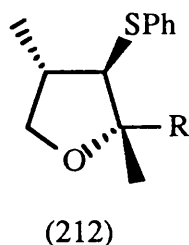
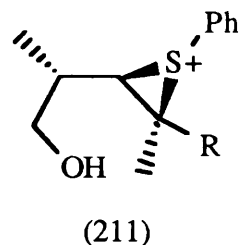
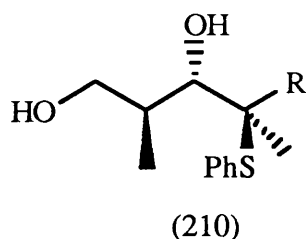
The actual nature of the intermediates (201) and (202) is not known but for each ring closure only one diastereomeric product is observed. This control may simply be due to the fact that in the postulated intermediates there exists a chiral centre and since ring closure generates a second chiral centre diastereomeric transition states, with differing activation energies, would be possible. However perhaps more likely is that intermediate (201) rearranges to a silicon bridged intermediate (205) which then has the choice of a 5 endo tet ring closure or the less favoured 4 exo tet closure to furnish the γ -lactone/lactam or the β -lactam respectively. Stereocontrolled opening of this siliconium intermediate would lead to single diastereomeric products.



Siliconium intermediates have previously been postulated by Jarvie and co-workers⁽¹¹⁰⁾ in the halogenation of deuteriated alcohol (206) which upon treatment with PBr_3 afforded bromides (208) and (209), possibly via intermediate (207).



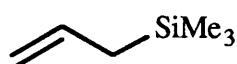
5 endo tet ring closure rather than 4 exo tet has also been observed by Warren and McIntyre in the synthesis of tetrahydrofurans.⁽¹¹¹⁾ Phenylthio alcohols (210) were converted into the corresponding episulphonium ions (211) which then exhibited 5 endo tet ring closure to afford tetrahydrofurans (212) in preference to 4 exo tet ring closure to afford oxetanes, which were never observed.



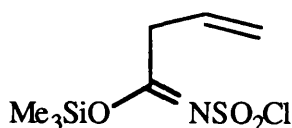
Ring closure via oxygen from intermediate (202) or (205) affords imidate (204). This mode of ring closure, although unusual, has previously been described by Malpass and Tweddle.⁽¹¹²⁾

The combined yield of γ -lactone and γ -lactam is around 18%, which is comparable to the yield of major β -lactam, i.e., the trans compound (197). When one considers that the corresponding allylsilanes ratio, i.e., the ratio of (195) to the major primary allylsilane was approximately 1:1 it is obvious that this rearrangement, after addition of CSI to allylsilane (195) must be fairly favourable. In the allylsilane mixture the ratio of primary silanes was approximately 3:2 which is in fairly close correspondence with the ratio of trans- β -lactam (197) (18.6%) to cis- β -lactam (196) (15%).

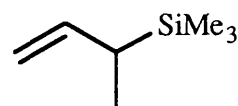
Another intriguing facet of this rearrangement is that allyltrimethylsilane (186) rearranges after CSI addition to imidate (187), whereas a totally different reactivity is exhibited by allylsilane (195).



(186)



(187)



(195)

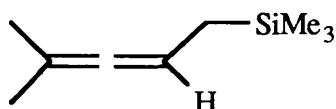
Repetition and extension of Dunoguès earlier work has shown that the intermediate N-chlorosulphonyl β -lactams could be intercepted and reduced by aqueous Na_2SO_3 treatment to furnish N-unsubstituted azetidinones suitable for elaboration into the carbapenem series.

Unfortunately, since neither allylsilanes (186) nor (195) produced the expected C-3 unsubstituted azetidinones and usefully functionalised allylsilanes are relatively uncommon, it was decided to extend this study in two complementary directions.

1). Alter the allylsilane substitution pattern to allow direct access to carbapenem precursors, such as the asparenomycons.

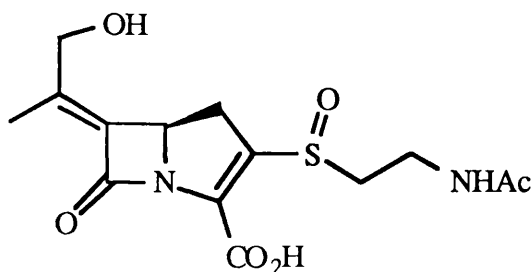
2). Alter the silicon substituents so that whilst silicon would still control the regiochemistry of addition it would carry more useful functionality for further manipulation.

Usefully substituted allylsilanes which, after cycloaddition with CSI, could be converted into carbapenem precursors are relatively uncommon. One possible exception to this is (allenylmethyl)silanes, e.g., (213), which have previously been described by Goré(113) and Vermeer.(114)

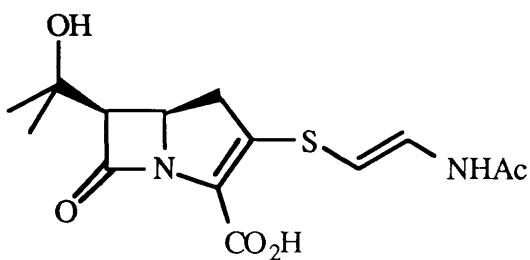


(213)

It was hoped that since the reaction between allenes and CSI had been well studied and the regiochemistry of cycloaddition documented(115) it would be possible to extend our study and add CSI to (allenylmethyl)silanes. If, as previously encountered, the β -effect of silicon controlled the regiochemistry of addition then this would allow access to the C-6 alkylidene functionality as found in the asparenomycons (26) and the carpetimycins (27), the latter formally derivable from a C-6 isopropylidene moiety by treatment with aqueous NBS in DMSO, followed by Bu^n_3SnH reduction.(116)



(26)



(27)

As already mentioned, Moriconi and Kelly⁽⁵⁾ investigated the reaction of CSI with allenes and found that addition generally occurred to the central carbon of the allene to generate the more stable carbonium ion. The intermediate then closed to furnish β -lactams in disappointingly low yields of ca. 20%. Buynak and co-workers investigated the cycloaddition of allenyl acetates^{(117),(118)} and allenyl sulphides^{(99),(116),(119)} with CSI and found that the regiochemistry of electrophile addition was controlled by the mesomeric effect of the heteroatom. Again low yields, similar to those of Moriconi and Kelly, were reported.

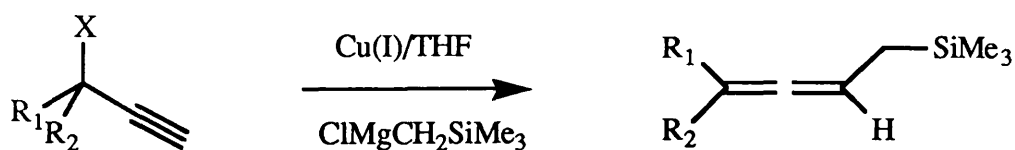
Since the reaction of CSI with allylsilanes had proven to be substantially higher yielding than the corresponding addition to vinyl acetate it was thought that CSI addition to (allenylmethyl)silanes may be higher yielding than the addition to other allenyl species.

In addition if the reaction were successful, with the β -effect of silicon controlling the regiochemistry of cycloaddition, we would have rapid access to a highly functionalised system suitable for further transformation.

3.1 3-Alkylidene β -Lactams.

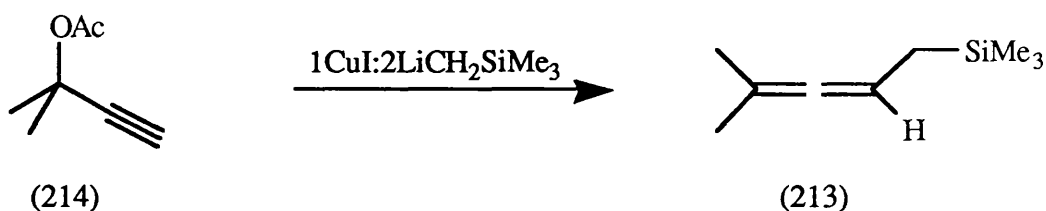
Generation of (allenylmethyl)silanes by the method of Goré and co-workers (experimental detail kindly supplied by Professor Goré) involved the Cu(I) catalysed S_N2' displacement of a leaving group, X, from terminal alkynes with (trimethylsilylmethyl)magnesium chloride. (Scheme 16)

Scheme 16

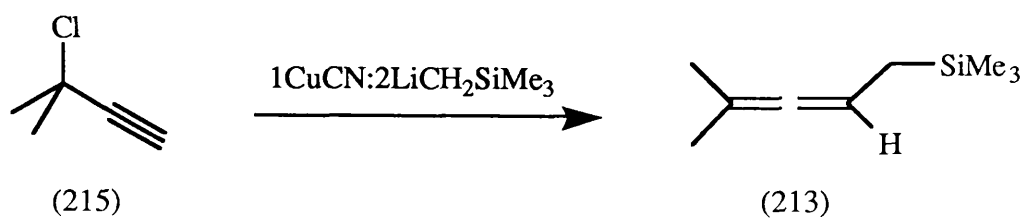


The actual displacement is dependent on the Cu(I) species being soluble in THF. Goré had achieved this by means of a 1:1 complex of CuBr:LiBr in THF. However repetition of this procedure did not produce a THF soluble complex even after repeated reagent drying procedures.

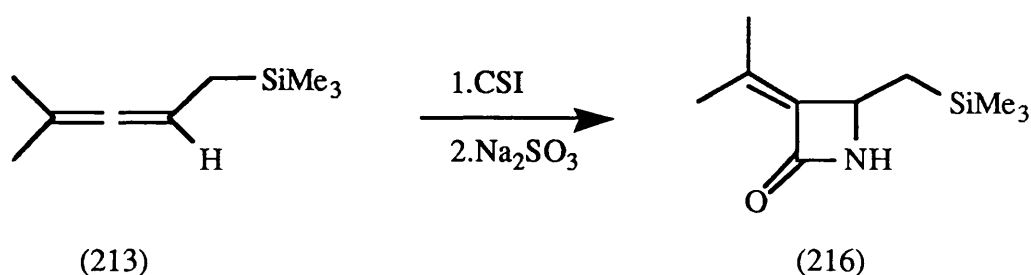
Lithium dialkyl cuprates (LiCuR_2) were then investigated as a source of the CH_2SiMe_3 anion. Preparation from CuI and (trimethylsilylmethyl)lithium proceeded smoothly at 0°C and the organocuprate reacted well with acetate (214), prepared in good yield from the corresponding alcohol by the method of Goré and Psaume, to furnish the (allenylmethyl)silane (213) in quantitative yield.



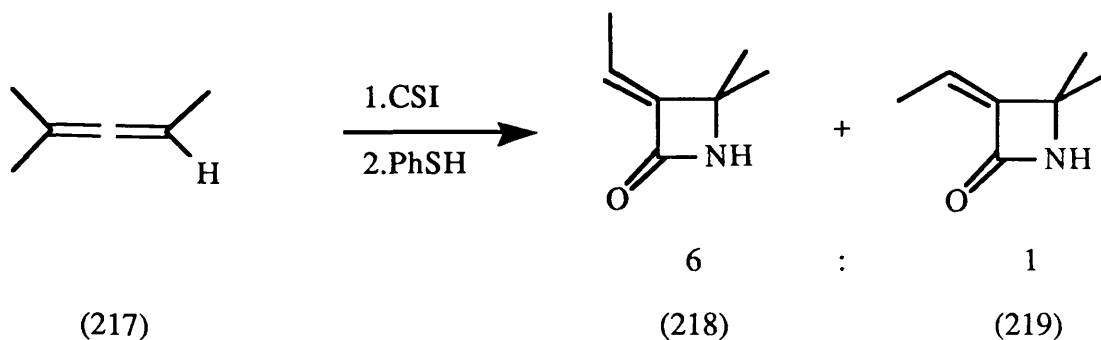
Although the superior qualities of higher order, mixed organocuprates⁽¹²⁰⁾ were not required, the ready availability and low cost of CuCN led us to adopt this as the method of choice, in conjunction with (trimethylsilylmethyl)lithium, to deliver the CH_2SiMe_3 anion. Unfortunately it was found that, although (allenylmethyl)silane (213) was stable to chromatographic silica, it had such a low residence time on the column that no purification was effected. Likewise distillation as a method of purification proved fruitless. However use of the corresponding alkynyl chloride (215), prepared by the method of Raphael *et al.*⁽¹²¹⁾, in conjunction with the higher order organocuprate resulted in the production of a much cleaner sample of (allenylmethyl)silane which could be used without further purification.



With an excellent method in hand to prepare the (allenylmethyl)silanes attention was turned to the cycloaddition with CSI. Gratifyingly when (allenylmethyl)silane (213) was reacted with CSI the 3-(isopropylidene)azetidinone (216) was obtained, albeit in a disappointing yield of 23%.

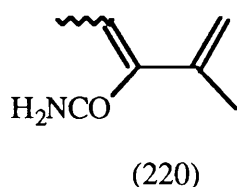


As a corollary Moriconi and Kelly⁽⁵⁾ have reported the addition of allene (217) with CSI, followed by PhSH reduction, to give β -lactams (218) and (219) in yields very similar to those encountered in the addition of CSI to (allenylmethyl)silane (213).



In this example the regiochemistry of cycloaddition is controlled by carbocation stability, i.e., tertiary v. secondary. However, with the very similar (allenylmethyl)silane (213), the regiochemistry is reversed, giving clear confirmation that the β -effect of silicon is indeed controlling the cycloaddition in this case.

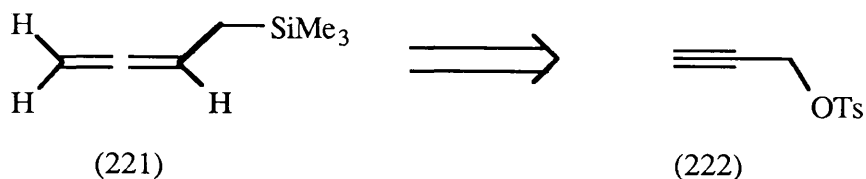
Moriconi and Kelly were able to account for loss of some of their material in the form of the very polar amide (220) which was recovered by CHCl_3 extraction of the aqueous phase following reduction. However, in our case, extraction of the aqueous phase after reduction did not furnish any material.



Since (trimethylsilylmethyl)lithium is readily available this procedure is ideal to generate (allenylmethyl)trimethylsilanes. However the generation of (allenylmethyl)silanes with more usefully substituted silyl residues is more of a problem since the required lithio species are difficult to access. On the other hand (chloromethyl)silanes having more synthetically useful silyl moieties are readily available. Therefore it was decided to re-examine the Grignard procedure. Rather than re-attempt the $\text{CuBr}:\text{LiBr}$ methodology, it was decided to examine the possibility of using a $\text{CuBr}:\text{SMe}_2$ complex commercially available from Aldrich.⁽¹²²⁾ This complex was also found to be insoluble in THF unless SMe_2 was added as co-solvent.

Subsequent studies were carried out with (trimethylsilylmethyl)magnesium chloride, since this was readily available, although the use of a Grignard reagent should allow us to extend the methodology to prepare (allenylmethyl)silanes with alternate silyl substitution. Gratifyingly, with this modification, the procedure worked well with (trimethylsilylmethyl)magnesium chloride and alkynyl chloride (215) to furnish (allenylmethyl)silane (213) in good yield.

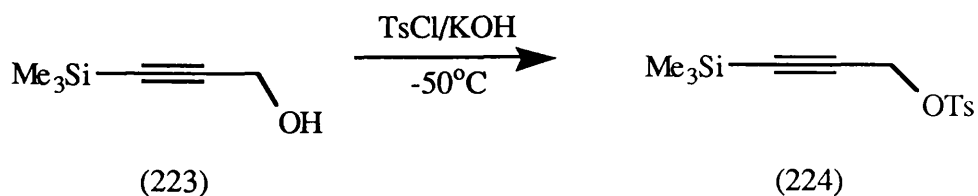
The next required (allenylmethyl)silane was (221) which should be available from tosylate (222).

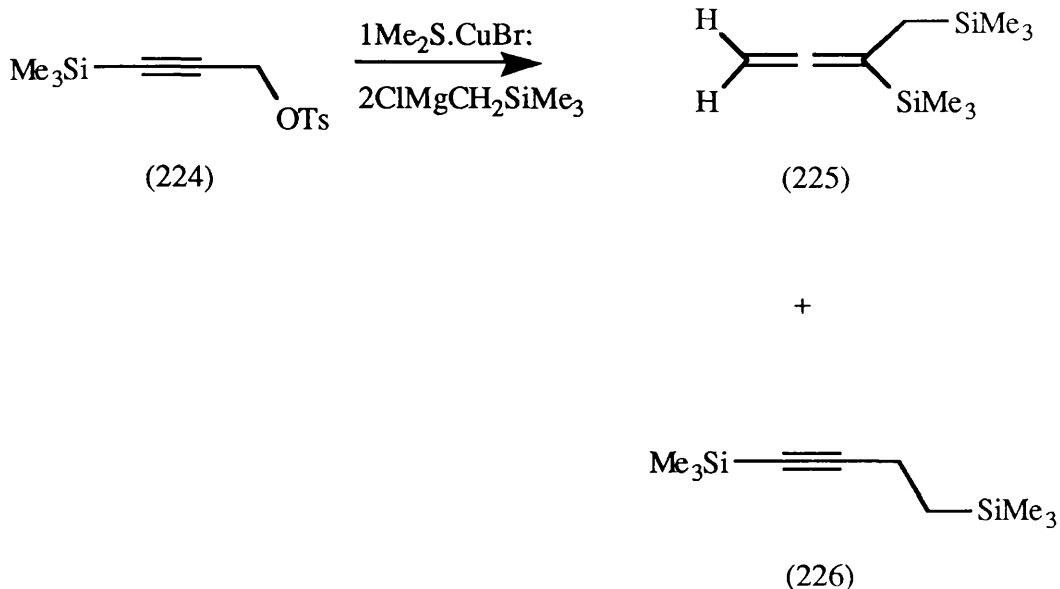


Propargyl alcohol was converted into its tosylate in quantitative yield, according to the procedure of Westmijze and Vermeer.⁽¹²³⁾ Treatment with $\text{CuBr} \cdot \text{SMe}_2 / \text{ClMgCH}_2\text{SiMe}_3$ provided the required (allenylmethyl)silane in high yield, although as previously encountered purification was impossible.

Unfortunately reaction of (allenylmethyl)silane (221) with CSI did not return detectable amounts of β -lactam although starting material was consumed. The products from this reaction were never characterised.

Similarly 3-(trimethylsilyl)prop-2-yn-1-ol (223) suggested itself as a precursor to (allenylmethyl)silane (225). It was hoped that this disilane would allow us to investigate the competitive reactivity, toward CSI, of allyl and vinylsilanes. Accordingly tosylate (224) was prepared in high yield and converted into (allenylmethyl)silane using our previous methodology.

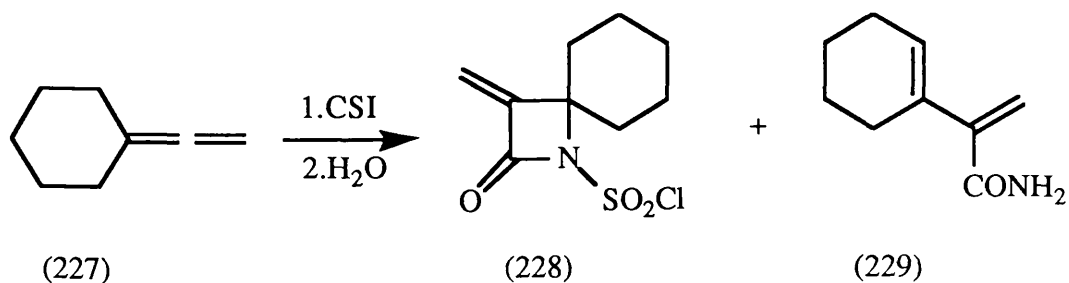




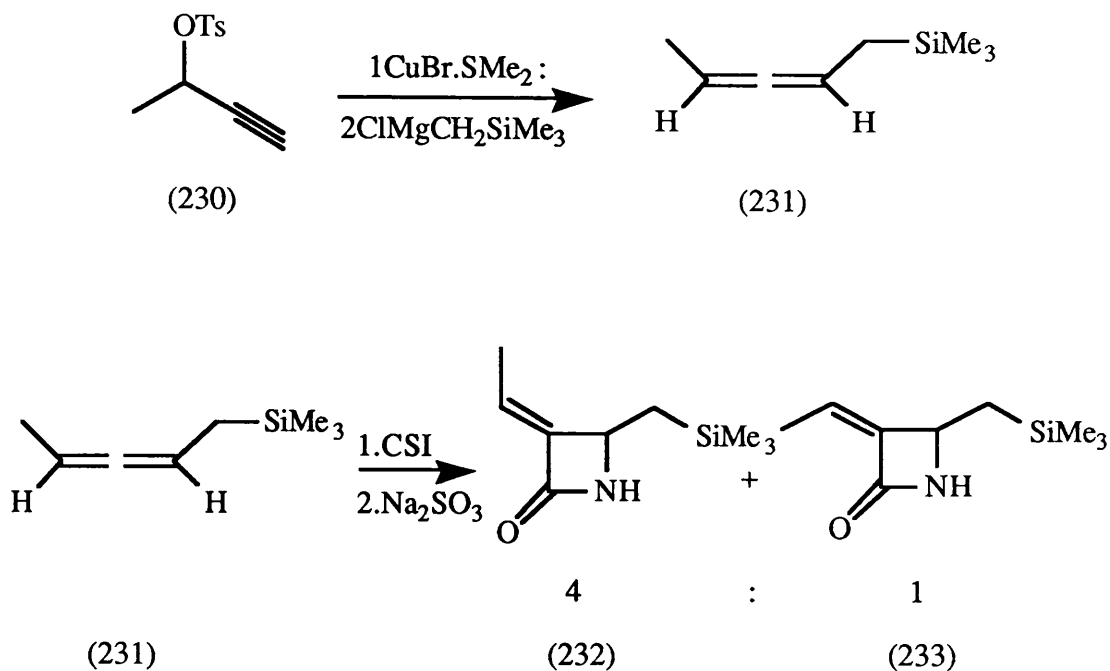
In this case however steric crowding at the silyl substituted terminus of alkyne (224) allowed the $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}2'$ processes to become competitive and the major product from the $\text{CuBr.SMe}_2/\text{ClMgCH}_2\text{SiMe}_3$ reaction was indeed alkyne (226) (37%) along with the minor product (allenylnethyl)silane (225) (31%). These two compounds were readily separable by dry column flash chromatography.

Again, as with 1-trimethylsilylbuta-2,3-diene (221), (allenylnethyl)silane (225) reacted with CSI to return no recognisable material.

In both cases above, reaction of CSI with a terminal allene did not return any β -lactam nor indeed any recognisable material. This was most disappointing since Moriconi and Kelly had reacted terminal allenes, such as (227) with CSI to obtain β -lactam (228), (40%) and amide (229), (32%).



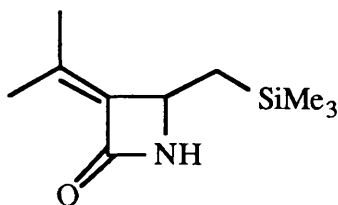
More pleasingly, (allenylmethyl)silane (231) prepared in high yield via similar methodology from tosylate (230), reacted smoothly with CSI to furnish β -lactams (232) and (233), albeit in low yield (6.5%), in a ratio of 4:1 (E):(Z).



The (E):(Z) ratio can be easily explained by consideration of the allene geometry in (231). With two orthogonal π systems, the π system of the allylsilane moiety is co-planar with the methyl and hydrogen groups of the ethylidene portion. Consequently attack, by CSI, on the π system of the allylsilane residue necessitates approach along the plane of substituents on the ethylidene portion of (allenylmethyl)silane (231). Therefore, since the hydrogen substituent is much smaller than the methyl group, electrophile approach occurs preferentially from this face to give mainly (E)-(ethylidene)azetidinone (232).

Although the cycloadditions of (allenylmethyl)silanes were only partially successful they did illustrate that facile access could be gained, via CSI addition, to a series of advanced precursors, such as (216), which otherwise would require fairly involved substituent elaboration to generate the 3-alkylidene moiety. Generation of this moiety has been carried out by a variety of other methods, e.g., mesylation of a

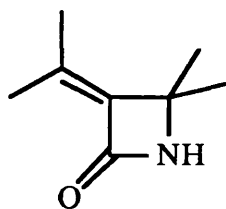
hydroxyl followed by DBU mediated elimination⁽¹²⁴⁾, Wittig olefination of 6-keto penicillins⁽¹²⁵⁾ and Peterson olefination of 3-trimethylsilyl β -lactams.⁽⁹²⁾



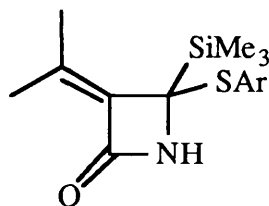
(216)

3.2 Attempted Preparation of Tetrasubstituted (Allenylmethyl)silanes.

Moriconi and Buynak independently observed that, whilst the addition of CSI to trisubstituted or less substituted allenes proceeded in low yield, the addition to tetrasubstituted allenes produced excellent yields of material. Neither author attempted to explain this experimental observation. For example, the β -lactam (234) was produced in 72% yield and (235) was prepared in 87% yield by the addition of CSI to tetramethylallene or an allenyl sulphide respectively.



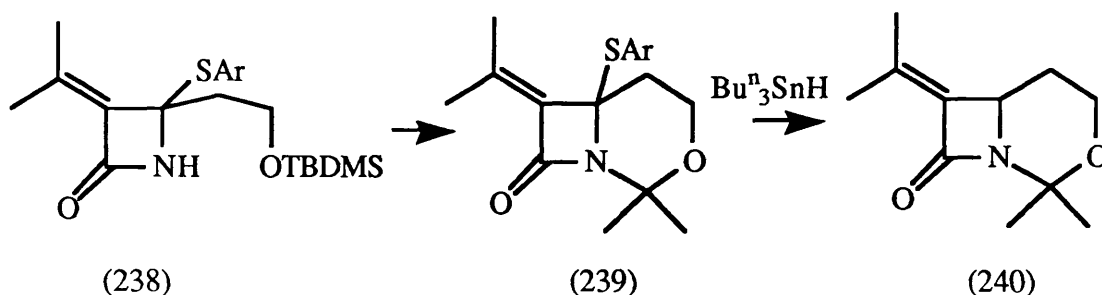
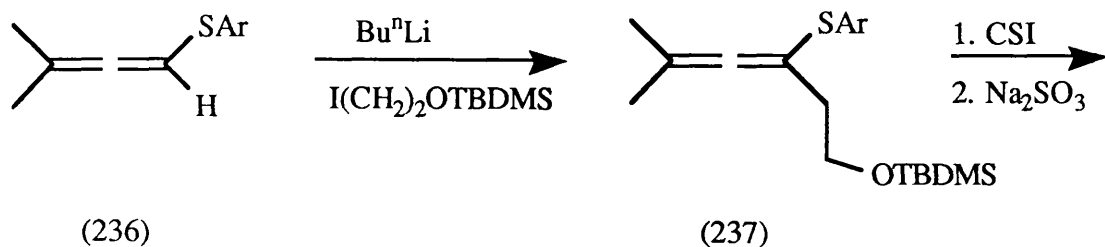
(234)



(235)

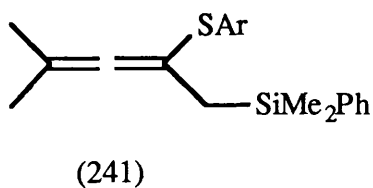
The production of allene and alkyne in the preparation of (allenylmethyl)silane (225) indicated that the $\text{CuBr}\cdot\text{SMe}_2/\text{ClMgCH}_2\text{SiMe}_3$ methodology would not be an ideal method to access tetrasubstituted (allenylmethyl)silanes. Buynak⁽¹¹⁶⁾ however had demonstrated that allenyl sulphide (236) could be metallated α to sulphur and

quenched with an electrophile to generate tetrasubstituted allene (237). This allene reacted with CSI to furnish β -lactam (238) which was converted into the tetrahydrooxazine (239). Reduction with Bu^n_3SnH then afforded (240).

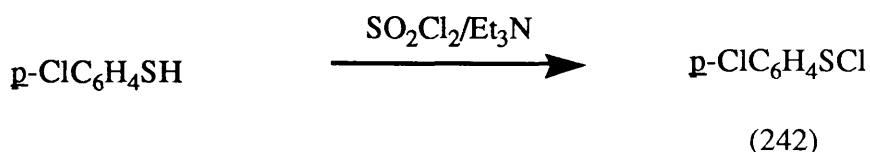


Ar = *p*-ClC₆H₄

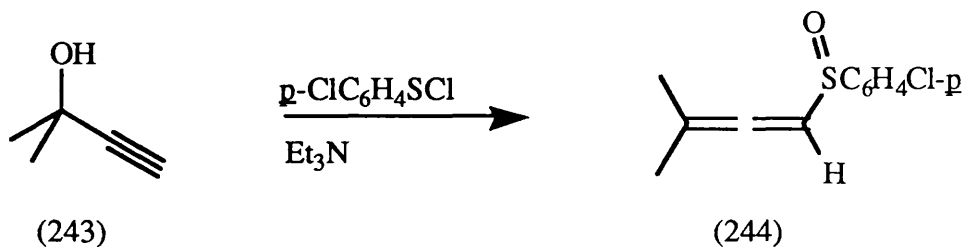
We intended to repeat the work of Buynak to prepare allene (236), then to deprotonate and quench with an alternate electrophile to produce (allenylmethyl)silane (241). Note that, in this instance we have altered the silyl substitution pattern from trimethyl to phenyldimethyl which should allow oxidative cleavage following β -lactam formation. (see later)



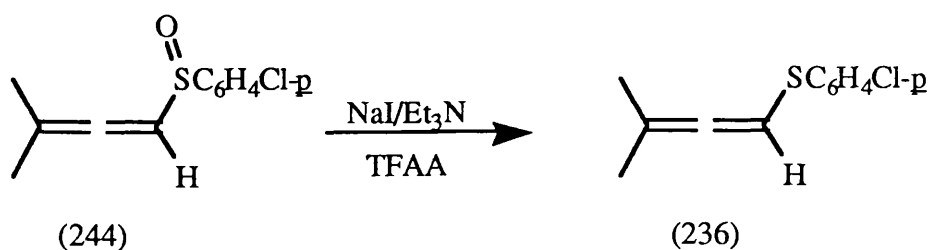
The starting material in Buynak's synthetic scheme, *p*-chlorophenylsulphenyl chloride (242) was prepared in reasonable yield from *p*-chlorothiophenol by treatment with sulphuryl chloride.

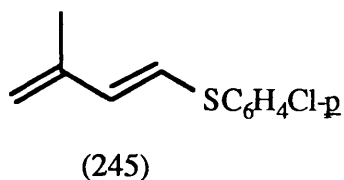


Conversion of (242) into sulphinyllallene (244) with alcohol (243) proceeded in low yield (15%) in contrast to the literature yield of 75%.



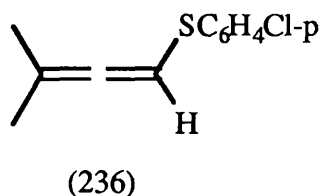
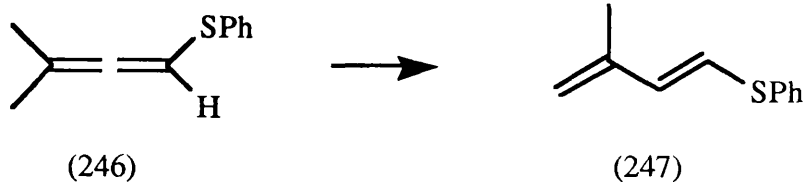
Reduction of sulphoxide (244) to allenyl sulphide (236) with NaI/Et₃N/TFAA proceeded smoothly to furnish the sulphide contaminated by diene (245).





We found that production of this diene could be minimised, but not eliminated, by careful handling and refrigeration of the reaction product.

Pasto and co-workers⁽¹²⁶⁾ have previously documented the rearrangement of alkylallenes to conjugated dienes at elevated temperatures. Allenyl sulphides have also been reported to rearrange to butadienes, e.g., the thioallene (246) rearranges to diene (247) in quantitative yield over two hours at 65°C.⁽¹²⁷⁾



Allenyl sulphide (236), contaminated by a trace of butadiene (245), was metallated at -78°C with BuⁿLi over 30min then (phenyldimethylsilyl)methyl chloride in THF was added along with 10mol% of NaI. The products from this attempted alkylation appeared to be mainly butadiene (245). Buynak's alkylation procedure utilised an alkyl iodide rather than a chloride and so we decided to convert the (phenyldimethylsilyl)methyl chloride into the corresponding iodide prior to the attempted

displacement rather than by catalytic methods during the displacement. This was accomplished by the phase transfer method of Peterson⁽¹²⁸⁾ in 70% yield. Unfortunately repetition of the above metallation and electrophile quench, this time with (phenyldimethylsilyl)methyl iodide, gave a complex mixture in which no discrete materials were observed.

From this work it appeared that although access to a tetrasubstituted allene, via this methodology, was possible the reaction conditions would require a degree of fine-tuning; due to time constraints this was not possible.

In spite of this failure to produce a tetrasubstituted allene our initial studies have shown that addition of CSI to (allenylmethyl)silanes, whilst not high yielding, does provide rapid access to highly functionalised 3-alkylidene β -lactams.

So far these studies have utilised trimethyl substituted silyl moieties. Although these have been useful to demonstrate the scope and utility as well as illustrating the regiocontrol exerted by silicon, the trimethylsilyl substituent is not synthetically useful.

Therefore the next extension to the method was the retention of the silyl substituent, to control the regiochemistry of cycloaddition, but carrying different functionality which would allow the silyl residue, after cycloaddition, to participate in further synthetic manipulations.

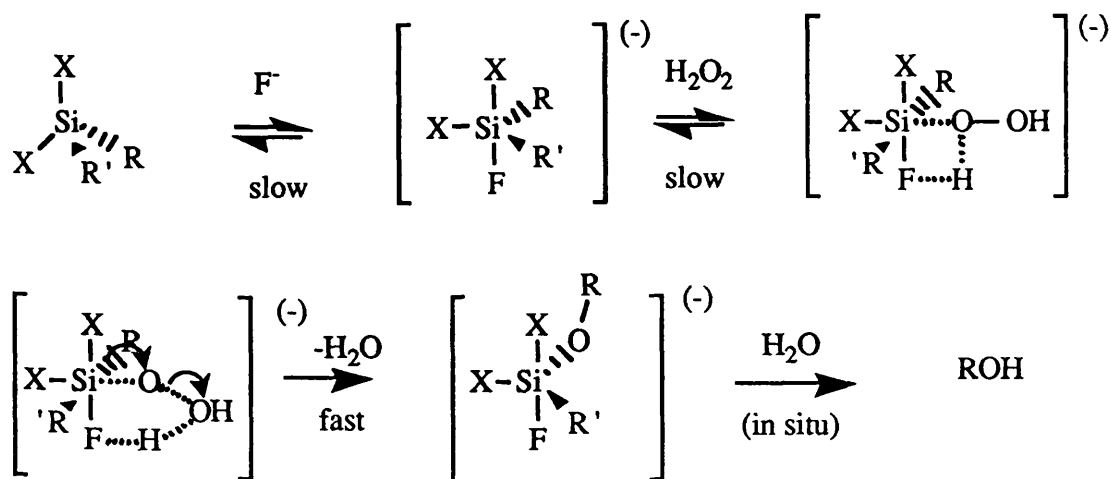
4.1 Introduction.

The addition of CSI to allyl or (allenylmethyl)silanes discussed previously is only of practical use if further synthetic manipulations can be performed on the silyl residue after it has controlled the regiochemistry of cycloaddition.

Perhaps one of the most useful functionalities for further elaboration is the alcohol group which can in theory be derived by the oxidative cleavage of a carbon-silicon bond. The first example of such cleavage was reported by Buncl and Davies in 1958(129) during their study of triorganosilyl perbenzoate rearrangement to alkoxy or aryloxysilanes.

Little attention was paid to the possible uses of this oxidative cleavage until recently with the independent studies of Tamao(130) and Fleming(6) with their respective co-workers. These elegant studies have resulted in the widespread use of silyl moieties as masked hydroxyls.

For successful cleavage the silane must carry at least one electronegative substituent, such as alkoxy or fluorine. The oxidant is generally hydrogen peroxide or a peracid although recently an amine oxide(131) which mediates rearrangement of trifluorosilanes has been described as an alternative oxidant for sensitive systems. Generally fluoride ion is a mandatory additive in what is believed to be an assisted rearrangement of a silyl peroxide, via an hexacoordinate silicon species as shown in Scheme 17.

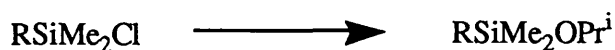
Scheme 17

Alkoxy or Fluorosilanes

The heteroatom substituent requirement for oxidative cleavage can be fulfilled in one of two ways.

a) Alkoxysilanes

Alcohol displacement of a chlorosilane results in the formation of an alkoxysilane, suitable for oxidative cleavage.⁽¹³²⁾



Unfortunately the alkoxysilane may not be compatible with sodium sulphite reduction of the N-chlorosulphonyl moiety.

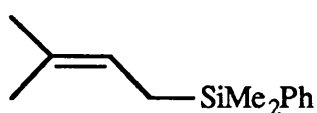
b) Masked Fluorosilanes

Late electrophilic desilylation of phenyldimethylsilyl residues, in the presence of fluoride ion, or the fluoride ion displacement of allyldimethylsilyl and furyldimethylsilyl moieties generates reactive fluorosilanes from the easy to handle organosilyl species.

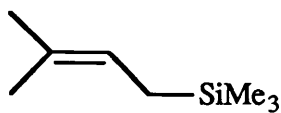
The ready availability combined with the latent synthetic potential and compatibility with CSI and aqueous reduction made the phenyldimethylsilyl moiety the obvious choice as an oxidatively cleavable silyl species.

4.2 Preparation of (Phenyldimethylsilyl)methyl β -Lactams.

The allylsilane (248) was prepared in similar fashion to allylsilane (171) from allyl chloride (180) via a Grignard reaction. This time however the electrophilic quench was phenyldimethylsilyl chloride rather than trimethylsilyl chloride, to furnish allylsilane (248) in 81% yield.



(248)

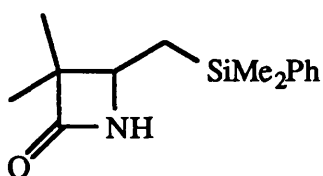


(171)

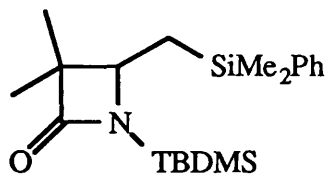


(180)

Preparation of the corresponding β -lactam (249) from allylsilane (248) and CSI proceeded smoothly to yield the azetidinone in 44% yield after sulphite reduction. Unfortunately this material did not exhibit a molecular ion in its high resolution mass spectrum and so the β -lactam was *N*-silylated to furnish azetidinone (250) in high yield. Gratifyingly this material gave a satisfactory mass spectrum.

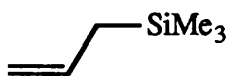


(249)

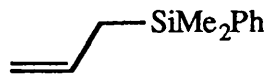


(250)

Cycloaddition of allylsilane (171) was found to be complete after 2h, although it was generally left on overnight before the sulphite quench was applied. However allylsilane (248) was found to take 6.5h to react with CSI. This decreased nucleophilicity of the phenyldimethylsilyl species relative to trimethylsilyl has been documented by Mayr and Hagen⁽¹³³⁾, who found that allyltrimethylsilane (186) was five times more reactive toward a diphenylmethyl cation than was allylsilane (251).

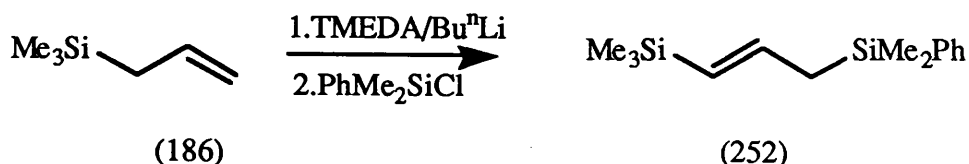


(186)

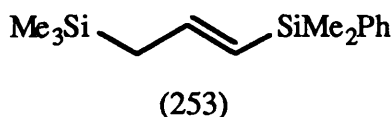


(251)

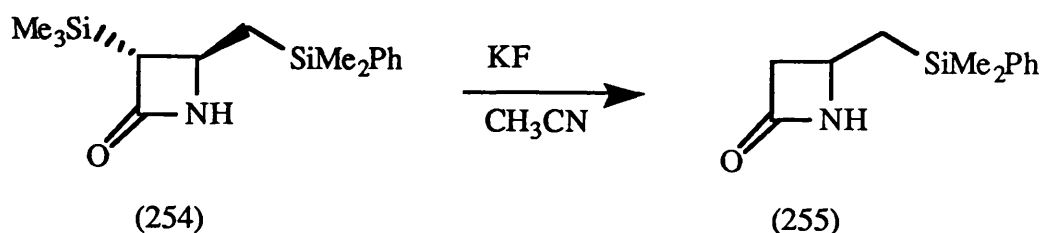
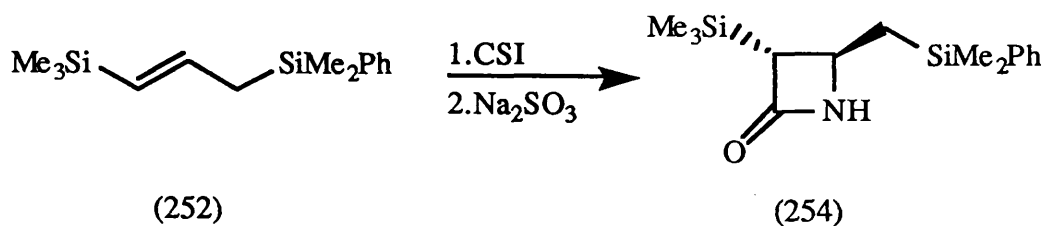
The allyl/vinyldisilane (252) previously described by Fleming and Langley⁽¹³⁴⁾ was prepared in good yield from allyltrimethylsilane (186) by deprotonation in the presence of TMEDA followed by quenching of the resulting anion with phenyldimethylsilyl chloride.



The literature conditions involve use of a slight excess of base at -5°C and a 1h phenyldimethylsilyl chloride quench again at -5°C . It was found that using this slight excess of base the silyl chloride quench time could not be extended nor the quench performed at higher temperature without the undesired regioisomer (253) being produced along with desired isomer (252).



The disilane (252) has the β -effect of both silicones acting to stabilise the same carbonium ion and the silane was found to react smoothly with CSI to furnish β -lactam (254), after sulphite quench, in a yield of 55%, the trans geometry of the alkene being retained in the β -lactam. The generation of this β -lactam was most pleasing, since as well as being suitable for oxidative cleavage, the 3-trimethylsilyl substituent should allow further synthetic manipulations. In addition, as discussed earlier, 3-unsubstituted β -lactams are not available via this methodology, but desilylation of 3-(trimethylsilyl)-azetidinones has been described by Fritz, Sutter and Weis⁽¹³⁵⁾ in 1986 and stirring with their KF/CH₃CN reagent system over 3 days furnished the otherwise inaccessible β -lactam (255).

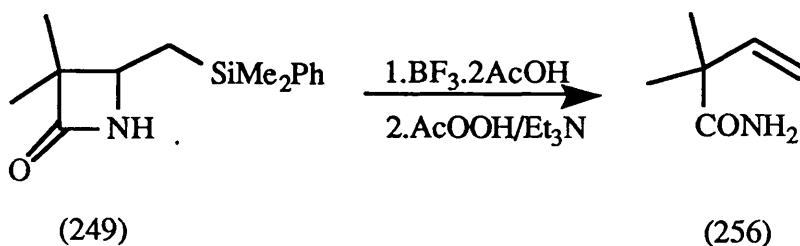


4.3 Fluoroborane Mediated Oxidative Cleavage

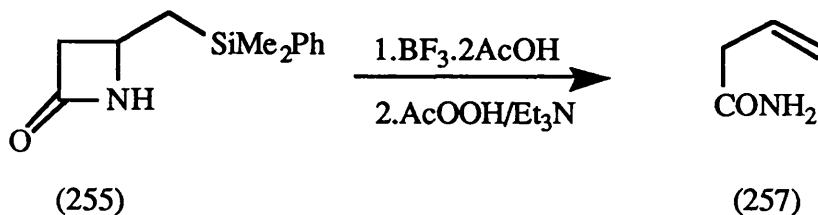
Protodesilylation of the benzene ring of a phenyldimethylsilyl residue proceeds by protonation of the aromatic ring followed by fluoride ion displacement of benzene to furnish a fluorosilane. Two reagents are generally available to effect this transformation, namely HBF_4 and $\text{BF}_3 \cdot 2\text{AcOH}$.

Unsuccessful studies were performed on each of the β -lactams (249), (254), and (255) although with an overview of all three separate cases a rational explanation of their individual behaviour can be postulated.

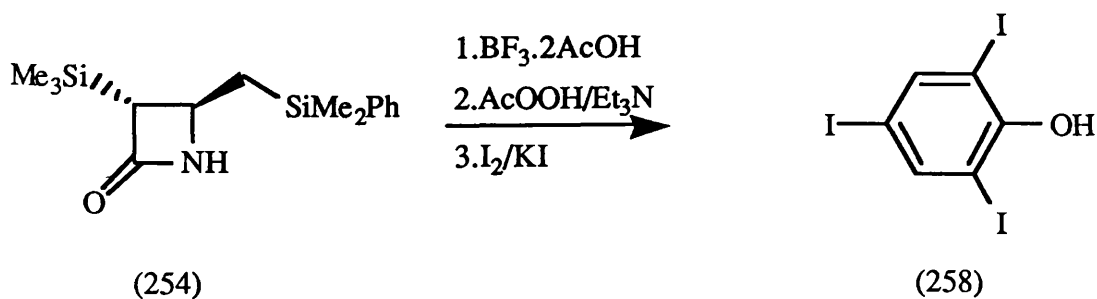
β -Lactam (249) was treated with $\text{BF}_3 \cdot 2\text{AcOH}$ in CH_2Cl_2 for two hours then $\text{THF}/\text{Et}_3\text{N}$ and peracetic acid were added. Following work-up, starting material (39%) and unsaturated amide (256) (48%) were obtained.



Similarly the 3-unsubstituted β -lactam (255) yielded β,γ -unsaturated amide (257) in a yield of 70%.

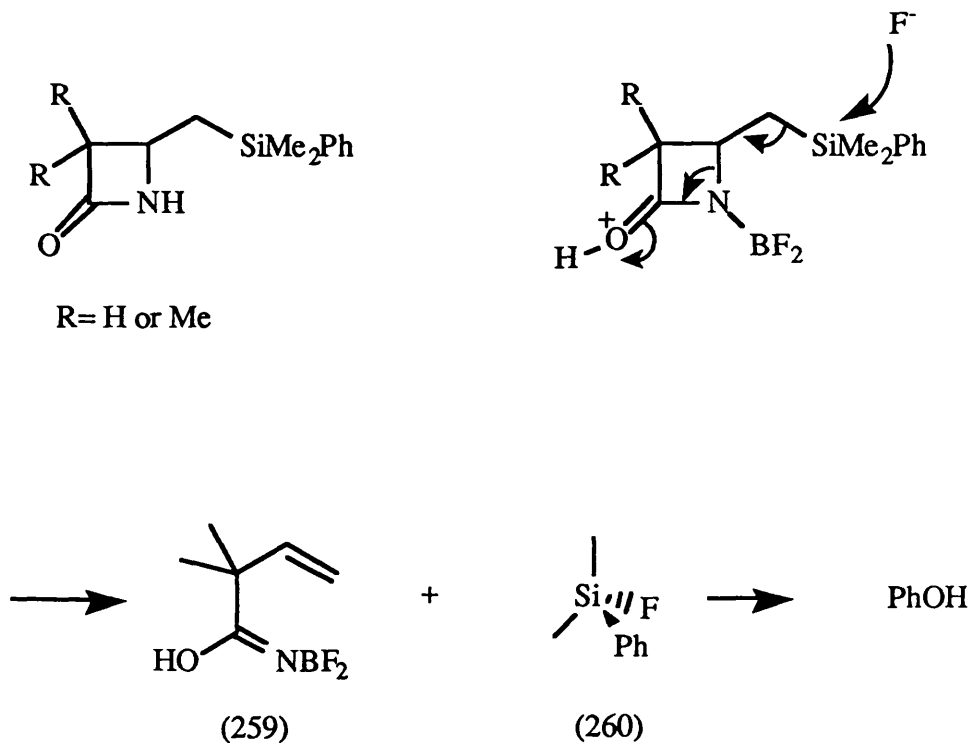


The *trans*-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)azetidinone (254) under analogous reaction conditions did not afford any unsaturated amide, only starting material and an aromatic species. This aromatic species was obviously not starting material on account of the downfield ^1H NMR shifts of some of the aromatic protons and indeed was identified as phenol, which due to volatility was derivatised and characterised as 2,4,6-triiodophenol (258). The overall yield of (258) was 45% along with 27% of the starting β -lactam (254).



Reactions of β -lactams (249) and (255) to produce amides appeared markedly different to that of β -lactam (254) which produced phenol. However closer examination of the ^1H NMR spectra of the crude reaction products from β -lactams (249) and (255) did in fact show the presence of phenol; in fact in all three cases the same reaction is occurring in that phenol and an unsaturated amide are being produced. Unfortunately in the case of the 3-trimethylsilyl β -lactam (254) the unsaturated amide was not observed. This may be due to the presence of the 3-trimethylsilyl group which, as will be shown later, causes complications in the presence of peracid.

The rearrangement to unsaturated amide and phenol can be rationalised as follows: initial protonation of the β -lactam ring rather than the phenyl group, along with possible boron co-ordination to nitrogen is followed by nucleophilic attack at silicon allowing the whole molecule to unzip to intermediate (259). Solvolysis of this intermediate furnishes the β,γ -unsaturated amide, whilst the remaining silyl residue (260) now carries an electronegative substituent and undergoes oxidative rearrangement with peracid to furnish, after solvolysis, phenol.

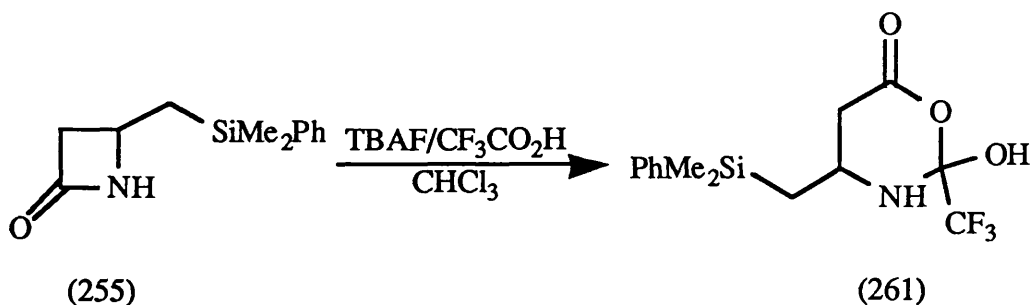


At this point it was concluded that, with our systems, the use of acid to protidesilylate in the presence of a Lewis acid was not feasible. As postulated earlier the Lewis acid may complex to nitrogen which facilitates rearrangement to imidate in exactly the same way as the sulphonyl chloride moiety had behaved. Note however that in the sulphonyl chloride case at ca. 0.2M no rearrangement occurred until concentration in vacuo but here at ca. 0.3M rearrangement to imidate occurs either with or without concentration.

4.4 Other Studies.

The studies of Tamao and Ishida⁽¹³⁶⁾ on the displacement of an allyl moiety from allyldimethylsilyl species involved the use of $\text{CF}_3\text{CO}_2\text{H}$ and displacement with F^- in the absence of a Lewis acid catalyst. Consequently we decided to try the protidesilylation of (phenyldimethylsilylmethyl)- β -lactams with $\text{CF}_3\text{CO}_2\text{H}$ and TBAF as the source of fluoride ion with no Lewis acid present, in an effort to avoid rearrangement to imidate.

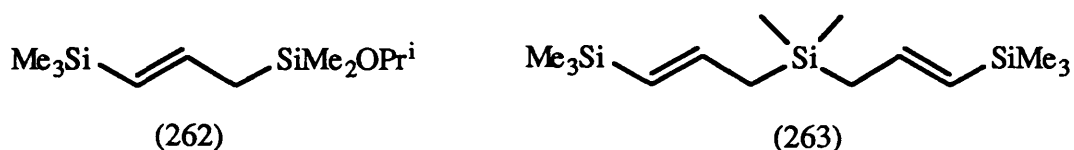
Use of azetidinone (255) under these conditions resulted in formation of the ring expanded ketopiperidine (261) in 60% yield. The appearance of this product can be rationalised as follows: initial $\text{CF}_3\text{CO}_2\text{H}$ opening of the azetidinone is followed by ring closure of the intermediate to furnish the ketopiperidine.



No fluorosilane was observed in this study and the ketopiperidine appeared to be a single diastereomer.

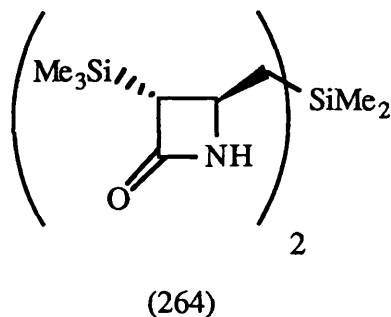
At this point it seemed that protodesilylation of the benzene ring would not be feasible, using H^+/F^- methodology on our 4-(phenyldimethylsilylmethyl) β -lactams. Consequently alternative ways to achieve oxidative cleavage were examined.

Initial studies in an attempt to prepare the isopropoxysilane (262) from allyltrimethylsilane (186), dimethyldichlorosilane and isopropanol resulted in the formation of bisallylsilane (263).



Time considerations and the distinct possibility that the pH of sodium sulphite reduction would result in hydrolysis of the silyl ether anyway meant that no other routes to allylsilane (262) were investigated.

CSI addition to allylsilane (263) did furnish the unusual β -lactam (264) which has also been reported recently by Nativi, Perrota, Ricci and Taddei.⁽¹⁰⁷⁾

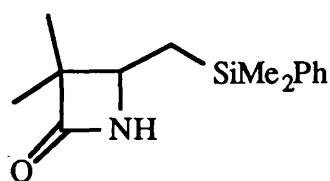


A more promising solution was the bromodesilylation and mercuridesilylation methods employed by Fleming and Sanderson⁽⁷⁾, where the benzene ring of a phenyldimethylsilyl residue was brominated or mercurated then displaced with acetate to furnish an electronegatively substituted silyl moiety which could then undergo the oxidative rearrangement process. This procedure does not require the addition of a fluoride ion to achieve oxidative rearrangement. These electrophiles are well known to be effective in aromatic desilylations. Bromodesilylation has been studied by Eaborn and Webster⁽¹³⁷⁾ and mercuridesilylation by Benkeser, Hoke and Hickner.⁽¹³⁸⁾ Fortunately both electrophiles are compatible with peracid and so the two step sequence can be carried out in one pot.

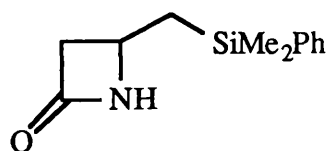
Unfortunately neither of the electrophiles are very pleasant to handle but Br₂ can be generated *in situ* by the action of peracid on a bromide salt. If oxidative cleavage can be performed successfully the 4-(hydroxymethyl)azetidinone products will be very polar, and since the mercuridesilylation involves an aqueous work-up this will not be compatible with our 4-(phenyldimethylsilylmethyl) β-lactams.

With regard to the two above points it was decided to employ the bromodesilylation procedure generating Br₂ from KBr in the presence of NaOAc to buffer the sulphuric acid present in commercial peracetic acid. Following reaction the mixture was diluted with Et₂O and stirred with freshly powdered Na₂S₂O₅.

Azetidinones (249) and (255) under Fleming and Sanderson's bromodesilylation conditions returned approximately 40% starting material, with no (hydroxymethyl)-azetidinones and in fact no other recognisable material being observed.

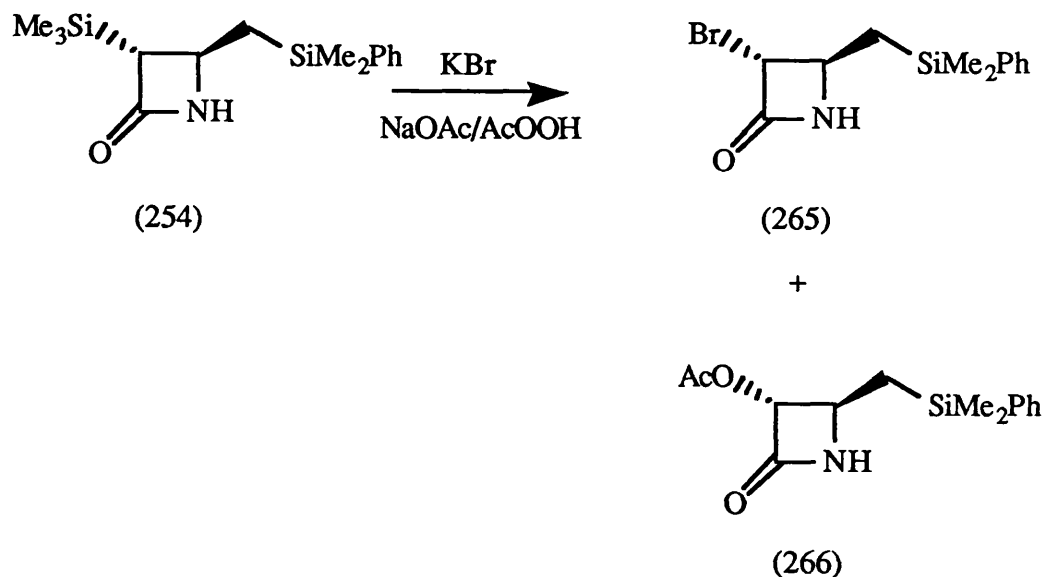


(249)

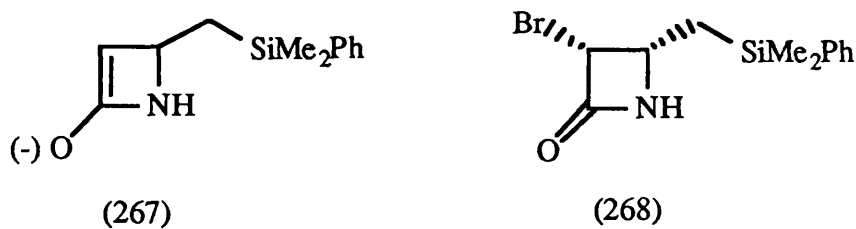


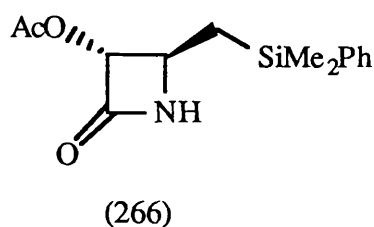
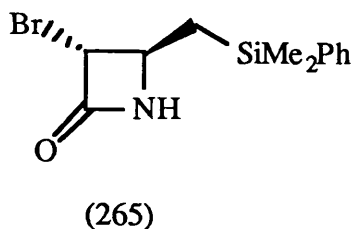
(255)

Analogous reaction with β -lactam (254) did not return starting material, nor (hydroxymethyl)azetidinone but rather surprisingly the trans-3-bromo (265) and trans-3-acetoxy-4-(phenyldimethylsilylmethyl)azetidinone (266) in yields of 32% and 21% respectively.

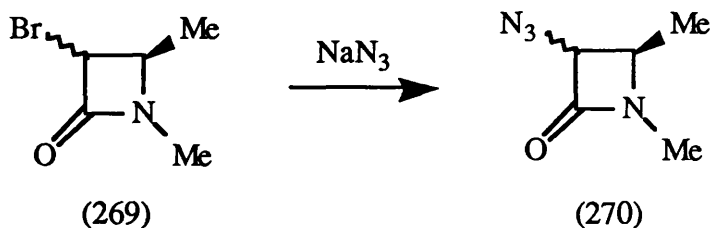


Mechanistically this reaction may be rationalised as a nucleophilic attack on the 3-trimethylsilyl substituent, analogous to the KF/CH₃CN desilylation of (254), to generate the enolate (267), which then reacts with bromine to generate the cis-3-bromo β -lactam (268) and the trans-3-bromo β -lactam (265). S_N2 displacement of bromine from the cis- β -lactam by solvent or buffer then furnishes the trans-3-acetoxy β -lactam (266) along with the non solvolysed trans-3-bromo β -lactam.



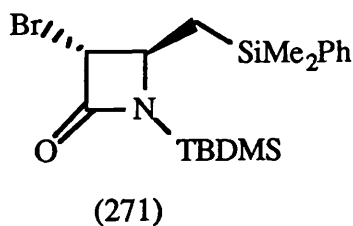


Nucleophilic displacement of bromine from the 3-position of an azetidinone has previously been reported by Kühlein and Jensen⁽¹³⁹⁾ when a mixture of *cis* and *trans*- β -lactam (269) was converted into *cis* and *trans*- β -lactam (270) with inversion of the *cis/trans* ratio.



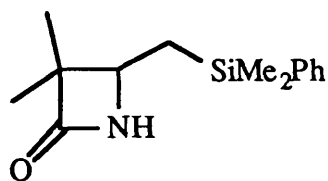
In our case only the *cis*-3-bromo β -lactam (268) undergoes solvolysis with acetate due to the bulky C-4 substituent interfering with nucleophile approach in the *trans*-3-bromo β -lactam (265).

Note: β -lactam (265) did not exhibit a molecular ion for the ^{81}Br isotope in its high resolution mass spectrum. In an effort to circumvent this problem β -lactam (265) was converted into its *N*-TBDMS derivative (271), but unfortunately neither did the silylated β -lactam give a satisfactory molecular ion for the ^{81}Br isotope in its high resolution mass spectrum.



Bromodesilylation with β -lactams (249), (254) and (255) did not afford any oxidatively cleaved material. In no case was there any evidence that bromination of the phenyl ring did occur, although Br_2 generated by the addition of peracetic acid to KBr did appear to be consumed. Of the two methods described by Fleming and Sanderson the bromodesilylation procedure appeared more attractive than mercuridesilylation for a number of reasons: the toxicity of the mercury salt is not ideal and in addition no NaOAc buffer can be used in the mercuridesilylation procedure since acid is needed to catalyse mercuration of the benzene ring, therefore the Hg^{2+} procedure is not applicable to substrates with acid sensitive groups. Finally and most importantly the aqueous wash involved in the Hg^{2+} process would not be compatible with the products of oxidative cleavage, the 4-(hydroxymethyl)azetidinones. Unfortunately our 4-(phenyldimethylsilylmethyl)azetidinones did not succumb to the bromodesilylation/oxidative rearrangement process and so an investigation of the mercuridesilylation process had to be made.

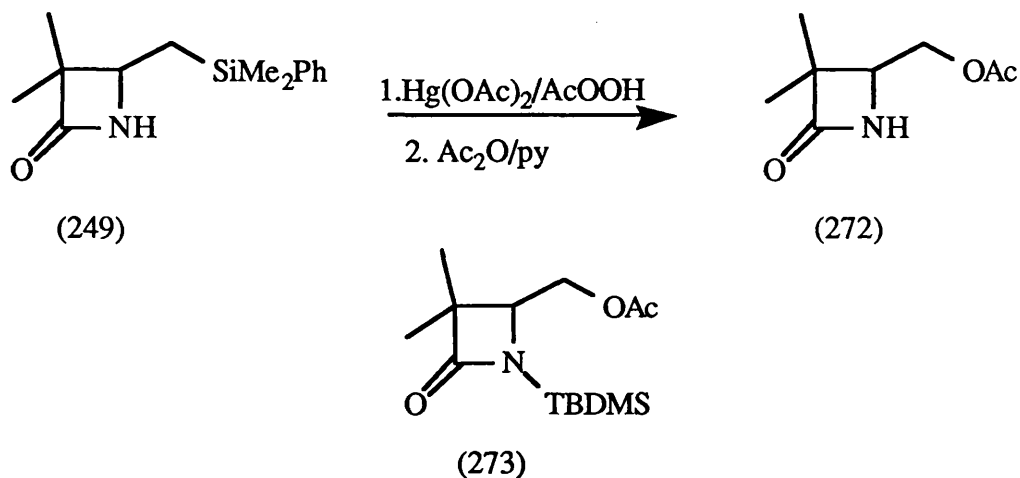
It appeared that the aqueous wash, after mercuridesilylation/oxidative rearrangement, could be avoided if the bromodesilylation work-up were utilised, i.e., treatment with freshly powdered thiosulphate in ether, filtration and finally evaporation in vacuo. An initial experiment utilising the conditions of Fleming and Sanderson with β -lactam (249) and one hour to desilylate and oxidatively rearrange, followed by aqueous isolation, returned only 30% starting material.



(249)

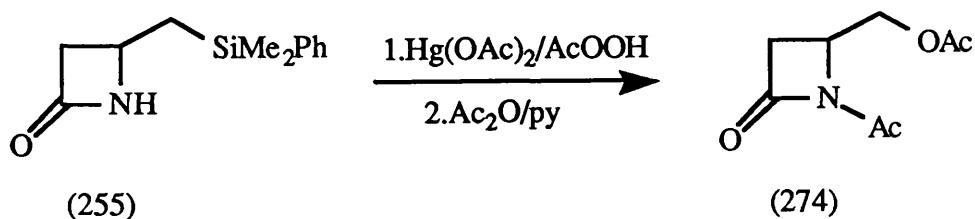
Following on from this exciting observation the experiment was repeated, this time over the suggested three hour period. At this point it should be noted that the commercially available peracetic acid used in our study was 32% by weight in acetic acid whereas Fleming and Sanderson had used 15% by weight in acetic acid. To overcome this difference all our reactions were performed in equal volumes of glacial acetic acid and 32% peracetic acid. After the three hour reaction of β -lactam (249) the

non-aqueous work-up of the bromodesilylation procedure was carried out on this reaction mixture and the crude residue, after evaporation, acetylated. Following concentration and purification the 4-(acetoxymethyl)azetidione (272) was isolated in a 15% yield. This compound was still found to be extremely polar and to facilitate purification was converted, by the action of TBDMSOTf/2,6-lutidine, into the *N*-TBDMS derivative (273), which was then readily purifiable by dry column flash chromatography.



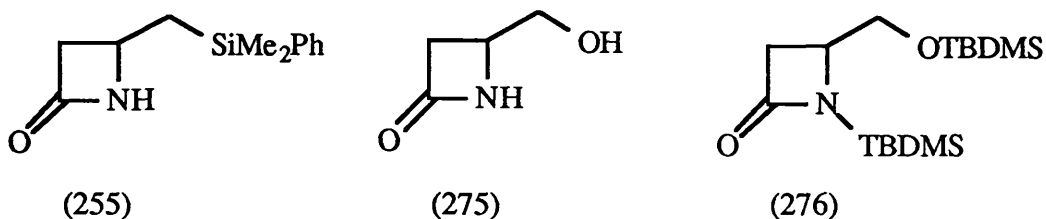
Production of the oxidatively cleaved 3,3-dimethyl β -lactam (272) served to establish conditions and procedures to accomplish the oxidative cleavage but in terms of further transformations the 3,3-dimethyl β -lactam was of no further synthetic use.

Oxidative cleavage of β -lactam (255) on the other hand, would furnish a synthetically useful, unsubstituted carbapenem precursor. Mercuridesilylation and oxidative rearrangement followed by thiosulphate reduction and concentration of β -lactam (255) gave a crude residue, which unlike the 3,3-dimethyl β -lactam (249) had to be chromatographed before derivatisation. Overnight acetylation, of this chromatographed residue, rather surprisingly furnished the acetamido acetate (274) in a yield of 29%.



At the outset of the oxidative cleavage study it was envisaged that a 3-methylene compound, such as (274), would be further elaborated via enolate/electrophile chemistry, at C-3. Unfortunately the acetate protecting groups are not compatible with this type of chemistry and so would have to be removed and replaced by, for example, silyl protecting groups. The ester should be removable but the imide function would almost certainly hydrolyse via opening of the β -lactam ring.

Rather than trying to establish conditions to achieve hydrolysis of the acetate functions whilst still retaining the β -lactam ring it was decided to repeat the oxidative cleavage of azetidinone (255) and bis-silylate the product 4-(hydroxymethyl)azetidinone (275) to furnish the synthetically useful (276) which could be elaborated via the planned enolate/electrophile chemistry.



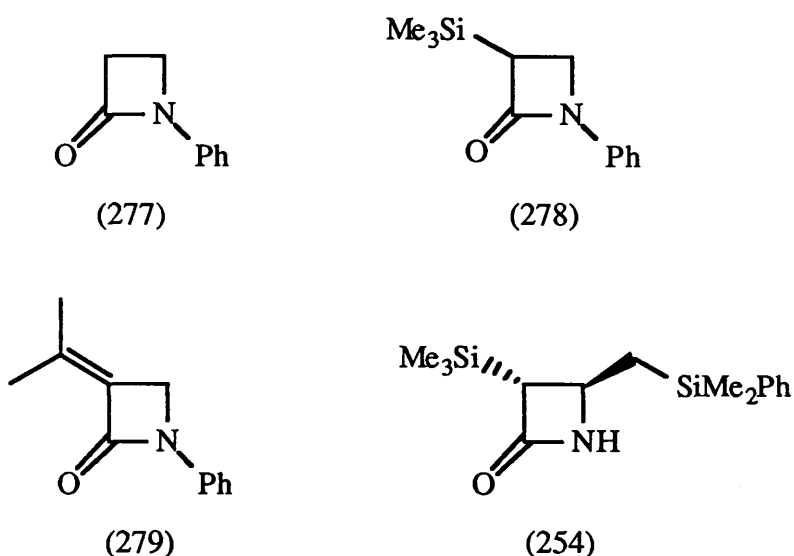
Gratifyingly after oxidative cleavage of the mercurated azetidinone, reduction of the excess peracid, concentration and chromatographic purification, the β -lactam (275) was silylated (TBDMSCl/Et₃N/DMAP) and purified to furnish the bis-TBDMS derivative (276) in 20% yield. It is perhaps worth noting that in the parent 4-(phenyldimethylsilylmethyl)azetidinones, N-silylation was not possible under these conditions and recourse to the TBDMSOTf/2,6-lutidine reagent system had to be made.

Practically it was found that after the mercuridesilylation and oxidative rearrangement sequence the ether/thiosulphate reduction had to be carried out in a cooling bath at ca. 15°C to compensate for the heat produced during reduction.

With this oxidatively cleaved and protected azetidinone (276) in hand further synthetic manipulations were now possible and these will be detailed in subsequent chapters.

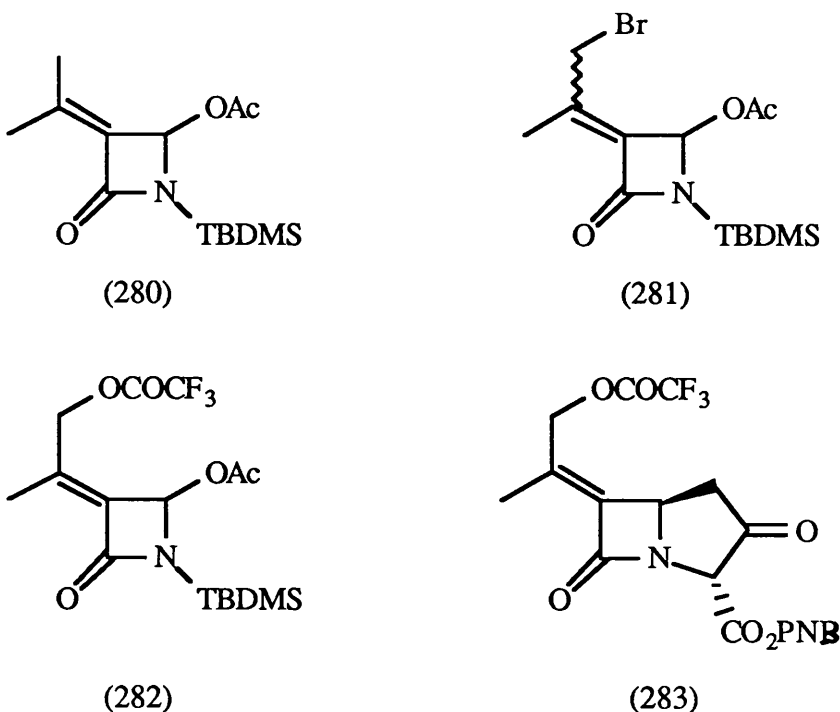
Note: at no stage was a mercuridesilylation/oxidative rearrangement procedure ever attempted on 3-trimethylsilyl β -lactam (254) due to the problems encountered with the bromodesilylation/oxidative rearrangement procedure.

Shibuya and co-workers⁽¹⁴⁰⁾ reported the formation of *N*-phenyl-3-(trimethylsilyl)azetidinone (278) in 95% yield from *N*-phenylazetidinone (277) via LDA induced deprotonation and reaction of the resulting enolate with TMSCl. Peterson olefination⁽¹⁴¹⁾ of β -lactam (278) then afforded a range of 3-(alkylidene)azetidinones, such as (279), in moderate to good yield.



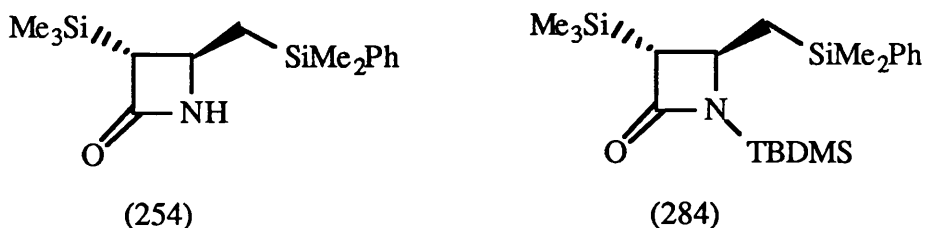
As already mentioned, our *trans*-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)-azetidinone (254) is suitable for oxidative cleavage, as discussed in Chapter 4, and the 3-trimethylsilyl substituent should hopefully lend itself to Peterson olefination as demonstrated by Shibuya and co-workers.

Successful Peterson olefination on our system would then allow entry into the asparenomicin and carpetimycin series of carbapenems.⁽¹¹⁶⁾ Buynak and co-workers have also explored a variety of other synthetic transformations on the 3-alkylidene β -lactam system, e.g., conversion of azetidinone (280) via bromide (281) and trifluoroacetate (282) into the asparenomicin precursor (283). Therefore, following Peterson olefination, our system can be converted in a variety of ways into carbapenem precursors.



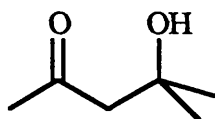
5.1 Attempted Peterson Olefination With 4-(Phenyldimethylsilylmethyl) β -Lactams.

Protection of the amide function of β -lactam (254) was necessary before any attempt was made to perform the Peterson olefination. Conversion into the *N*-TBDMS derivative (284) proceeded in 94% yield with the TBDMSOTf/2,6-lutidine reagent system.



Shibuya's procedure to form 3-alkylidene β -lactams from 3-(trimethylsilyl)-azetidinones involved treatment of the precursor β -lactams with LDA at -78°C and then quenching of the resultant enolate with a carbonyl acceptor. Elimination of TMSOH from the resulting β -hydroxysilane was instantaneous or occurred during work-up to furnish the 3-alkylidene products.

Rather mysteriously LDA treatment of β -lactam (284) at -78°C followed by acetone addition and work-up returned only starting material (over 90%). Shibuya's reaction conditions of three minutes to deprotonate the β -lactam and ten minutes to quench the enolate before work-up were extended to thirty minutes and two hours respectively with no reaction being observed apart from the formation of aldol adduct (285).

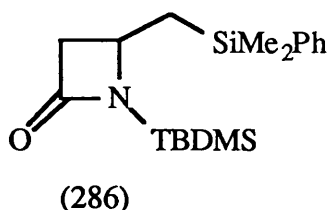


(285)

Our initial observations led us to the conclusion that perhaps the β -lactam enolate, generated in the first step could extract a proton from acetone, thereby leading to no apparent reaction. Consequently it was decided to change the electrophile from acetone to a non-enolisable species, such as, methyl iodide. Attempted LDA deprotonation of azetidinone (284) over thirty minutes followed by a methyl iodide quench and one hour stirring followed by work-up afforded only starting material. A similar apparent lack of reaction was observed when the electrophile quench was deuterium chloride in D_2O .

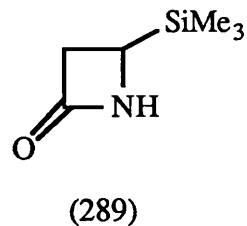
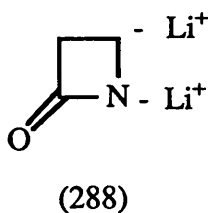
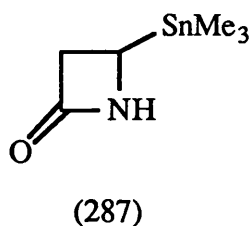
Generation of the allyl/vinylidisilane (252) had been aided by sequestration of the Li^+ cation by TMEDA thereby increasing the basicity of the Bu^- anion. Treatment of N -TBDMS β -lactam (284) with LDA/TMEDA and acetone again returned starting material.

So far all the deprotonation attempts had been with LDA; it was therefore decided to alter the base to KHMDS in an effort to effect deprotonation then carbon-carbon bond formation. Treatment of β -lactam (284) with KHMDS in THF at -78°C for thirty minutes followed by an acetone quench and warming over 3.5h, with TLC monitoring, produced a material of lower R_f than the starting material. However the lower R_f material was in fact the 3-desilylated β -lactam (286), isolated in a yield of 43%. No other recognisable product was observed in this reaction.

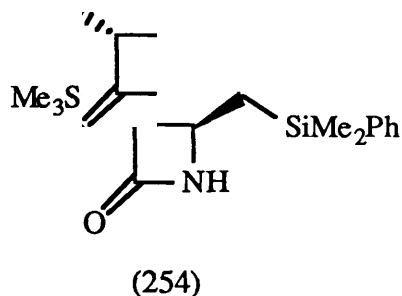


Repetition of this KHMDS mediated deprotonation using $p\text{NO}_2\text{C}_6\text{H}_4\text{CHO}$, a non-enolisable aldehyde, as the electrophile again over prolonged reaction times, afforded only desilylated starting material (286) in 42% yield. Close TLC monitoring of this reaction indicated that starting material only began to disappear after two and a half hours and since the corresponding LDA reactions were only left on for two hours to quench it is uncertain whether or not prolonged reaction times with LDA would effect this desilylation to form (286).

A recent report by Quayle and co-workers⁽¹⁴²⁾ outlined the preparation of 4-(trimethylsilyl)azetidinone (289) from the 4-(trimethylstannyl)azetidinone (287) via the postulated di-anion (288), after transmetalation with MeLi.

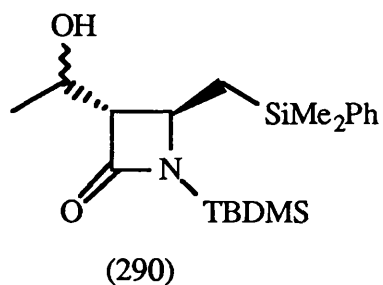
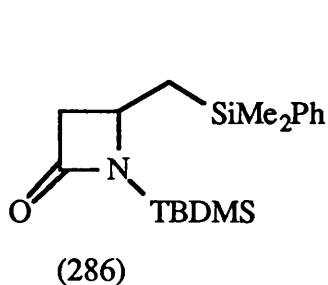


It was therefore decided to attempt the Peterson olefination sequence on the unprotected N-protio β -lactam thereby generating a di-anion of the type postulated by Quayle and co-workers. Treatment of (254), with LDA, and ten minutes stirring at -78°C then quenching with acetone and further stirring over one hour followed by aqueous NH_4Cl quench and work-up returned starting material (82%). A similar sequence with MeLi as base again returned starting material (78%).

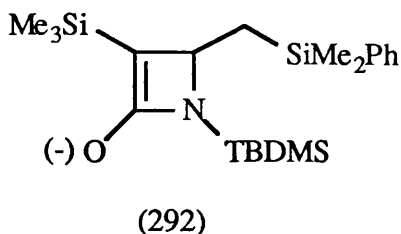
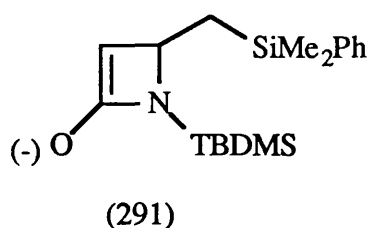


5.2 Aldol Manipulations on 4-(Phenyldimethylsilylmethyl)azetidinone (286).

By this stage our total failure to induce reaction at the 3-position of β -lactams (254) and (284) had become very time consuming. In an effort to check that the system was compatible with such chemistry the β -lactam (286) was prepared by KF/CH₃CN treatment, and *N*-silylation of β -lactam (254). Treatment of this azetidinone, with LDA, at -78°C and quenching of the resultant enolate with acetaldehyde furnished the 3-(hydroxyethyl)azetidinone (290) as mainly the trans compound, epimeric at the hydroxy carbon in a moderate yield of 61%.

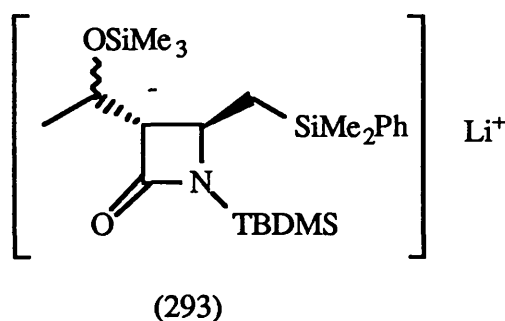


From this study it appeared that approach of an electrophile to the locally planar enolate (291) was fairly facile and by corollary should also be possible to the planar enolate (292).

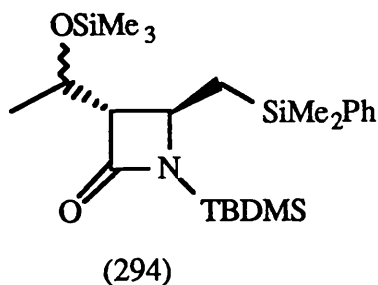


Therefore it would appear that hindrance of approach of the electrophile to enolate (292) is not the reason for lack of Peterson olefination.

Intermediate (290) was an interesting compound since it appeared that following Q-silylation and C-3 deprotonation the anion (293), which is a postulated Peterson intermediate, would be obtained. It was envisaged that instantaneous collapse of this system would then ensue to furnish a 3-alkylidene β -lactam.

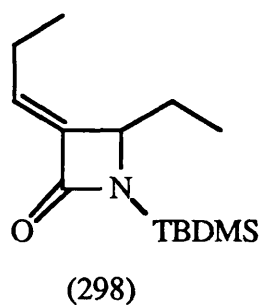
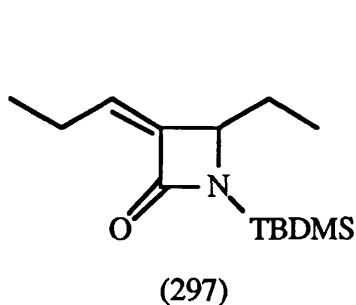
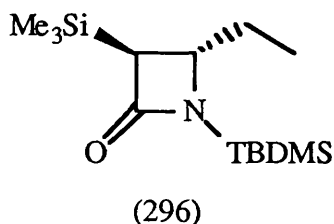
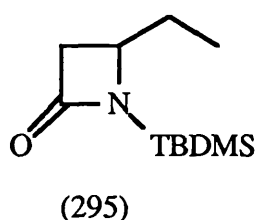


Q-Silylation of β -lactam (290) with TMSCl/Et₃N/DMAP furnished the azetidinone (294) in high yield. KHMDS treatment of (294), at -78°C, and warming to 0°C returned starting material (ca. 100%), whereas NaH treatment at 0°C over an extended reaction time effected Q-desilylation to reform the hydroxyethyl β -lactam (290). In neither case was any 3-alkylidene β -lactam observed.



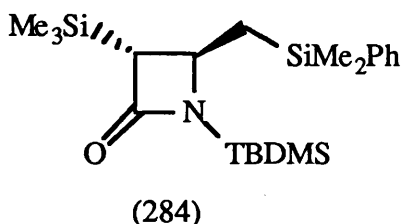
Again there seems to be some problem in either generating or quenching an enolate when the β -lactam carries a C-3 substituent other than hydrogen. The fact that the 4-phenyldimethylsilylmethyl substituent does not interfere with electrophile approach to the enolate (291) would seem to indicate that if a C-3 substituted-4-(phenyldimethylsilylmethyl)azetidinone can generate an enolate then electrophile quench should indeed be possible.

The earlier studies of Shibuya and co-workers only concerned Peterson olefination with C-4 unsubstituted β -lactams. However the work of Ogilvie and Durst⁽¹⁴³⁾ on a very similar system to β -lactam (284) may provide a better analogy. β -Lactam (295) was deprotonated and quenched with TMSCl to furnish the trans-azetidinone (296) ($J_{3,4}=2.6\text{Hz}$) in good yield. Treatment of β -lactam (296), with LDA at -78°C , for ten minutes and then addition of propionaldehyde furnished the 3-(alkylidene)azetidinones (297) and (298) in an approximately 1:1 ratio (yield 67%).



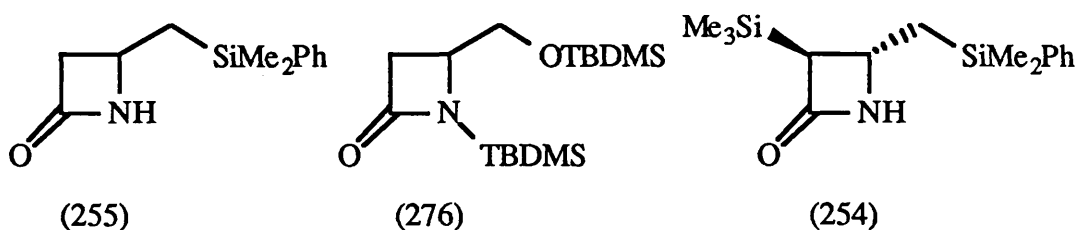
These studies by Ogilvie and Durst, demonstrate that a 3-trimethylsilyl-4-alkylazetidinone will take part in Peterson olefination and our studies indicate that the 4-phenyldimethylsilylmethyl substituent is not incompatible with electrophilic approach to an enolate generated from this system. In addition the very presence of the 3-trimethylsilyl substituent should increase the acidity of the C-3 methine proton

relative to the methylene protons in the C-3 unsubstituted case. Therefore the failure of β -lactam (284) to undergo Peterson olefination is most peculiar; whether it is due to a failure to deprotonate or a failure to quench the resulting enolate is not certain since the evidence cited above seems to indicate that both steps should be possible.



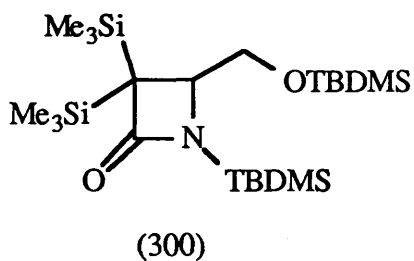
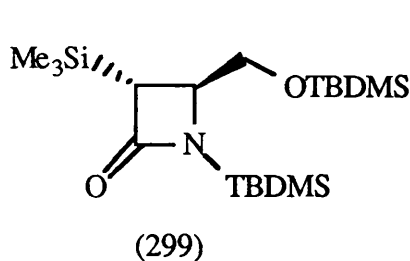
5.3 Peterson Olefination with 4-(t-Butyldimethylsiloxymethyl)azetidinone.

With the successful mercuridesilylation and oxidative rearrangement of β -lactam (255) having been accomplished to furnish the bis-TBDMS derivative (276), as discussed in the preceding chapter, it was decided to investigate the Peterson type chemistry, so unsuccessful on the 4-phenyldimethylsilylmethyl β -lactams, on this system which now had a 4-t-butyldimethylsiloxymethyl substituent.

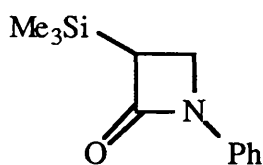


Compound (276) had to be re-silylated at the C-3 position prior to base/carbonyl treatment. This may seem wasteful in that β -lactam (255) was derived from 3-trimethylsilyl β -lactam (254). However it was felt that removal of the C-3 trimethylsilyl substituent from β -lactam (254) prior to peracetic acid treatment would be wise in view of the previously described bromination/acetolysis of this compound on exposure to $\text{Br}_2/\text{AcOH}/\text{AcOOH}$.

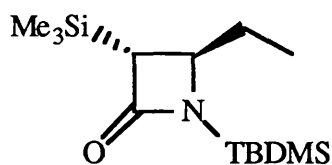
Treatment of (276), with LDA (1.1equiv) at -78°C , followed by a TMSCl quench (excess) and warming to room temperature, furnished a yellow oil, consisting of two components by TLC analysis. Neither of these two compounds was starting material, since this could not be visualised by I_2 staining. They were very close in R_f and dry column flash chromatography was found to be unsuitable to effect separation of these two compounds. Gratifyingly positive pressure chromatography did separate them. The lower R_f component of the mixture was in fact the desired *trans*-3-trimethylsilyl β -lactam (299), obtained in a yield of 67%. The presence of the higher R_f component and the modest yield of desired material caused some concern until spectroscopic analysis confirmed that the higher R_f component of the mixture was the 3,3-bistrimethylsilyl β -lactam (300), which was produced in 24% yield. It is perhaps worth noting that even although only a 10% excess of LDA was used, β -lactams (299) and (300) were produced in a ratio of ca. 3:1, highlighting the increased acidity of the 3-trimethylsilyl compound relative to the 3-unsubstituted compound.



Our observation of significant quantities of 3,3-(bistrimethylsilyl)azetidinone (300) is in contrast to the work of Shibuya who reported the preparation of β -lactam (278) in 95% yield. However the studies of Ogilvie and Durst who prepared β -lactam (296) in a yield of 83% are more in agreement with our own findings although the authors do not comment on their material balance.



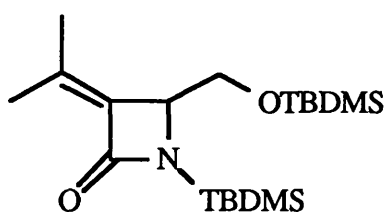
(278)



(296)

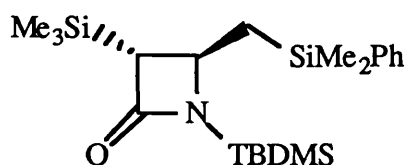
Production of this 3,3-bistrimethylsilyl derivative although not ideal could be minimised by control of the β -lactam:LDA ratio. The appearance of this product indicated that whatever the origin of the problem in the trans-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)azetidinone was, i.e., either a failure to deprotonate or a failure to quench the resulting enolate, the replacement of the 4-phenyldimethylsilylmethyl substituent by a 4-t-butyldimethylsilyloxymethyl substituent has circumvented the problem.

Most pleasingly, when β -lactam (299) was treated, with LDA at -78°C , then quenched with acetone the 3-alkylidene β -lactam (301) was produced in quantitative yield.

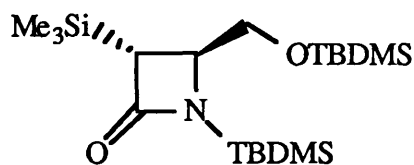


(301)

After the 4-phenyldimethylsilylmethyl substituent has been replaced by a 4-t-butyldimethylsilyloxymethyl substituent, deprotonation and electrophile quench with acetone or TMSCl becomes fairly facile. This changeover in behaviour between β -lactams (284) and (299) is not understood.

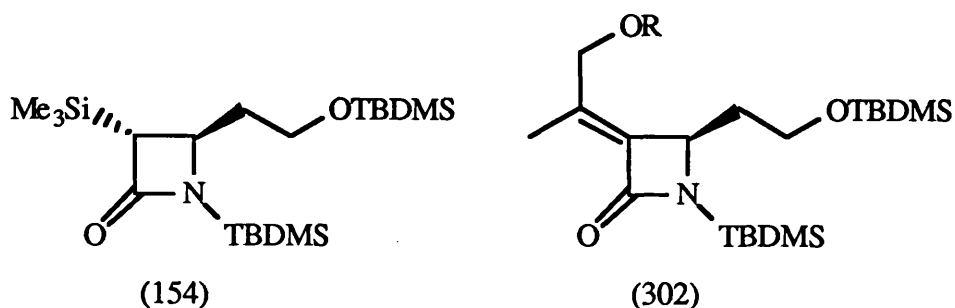


(284)

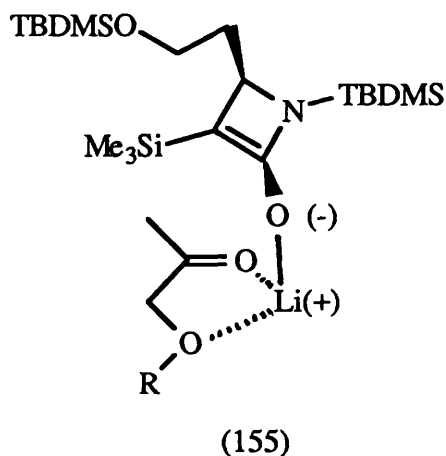


(299)

An interesting Peterson olefination with the C-4 homologue of β -lactam (299) was reported by Ohno and co-workers in 1983⁽⁹²⁾ The azetidinone (154), in homochiral form, was converted into a C-3 alkylidene β -lactam (302) which has the correct substitution pattern for elaboration to the asparenomycin series.

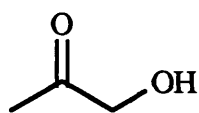


The C-3-alkylidene side chain was derived from hydroxyacetone, the protecting group R taking a variety of forms including the benzyloxycarbonyl function. The interesting feature of this Peterson olefination was that regardless of the protecting group R, exclusive generation of the (E)-alkylidene β -lactam was observed via the postulated transition state (155) which upon carbon-carbon bond formation and syn elimination of TMSOH would afford the (E)-alkylidene β -lactam (302).

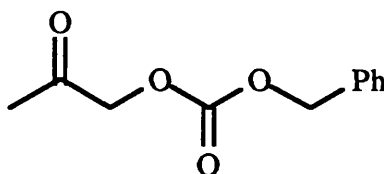


As shown in the above transition state, the C-4 siloxyethyl substituent plays no part in the postulated mechanism to control alkene geometry. Therefore it was envisaged that a C-4 siloxymethyl substituent would be entirely compatible with exclusive (E)-alkene generation and thereby furnish a fairly advanced asparenomycin precursor with the correct olefin geometry.

Protection of hydroxyacetone (303) as its benzyloxycarbonyl derivative proved to be far from trivial. Preparation by the method of Losse and Bachmann⁽¹⁴⁴⁾ resulted in the production of benzyloxycarbonyl protected hydroxyacetone (304) as well as the chromatographically inseparable benzyl alcohol. Repeated purification by dry column flash chromatography and positive pressure chromatography failed to separate these two compounds. Finally, the rather wasteful procedure of silylating the benzyl alcohol in the presence of benzyloxycarbonyl protected hydroxyacetone to allow chromatographic separation, had to be adopted. Column chromatography was now found to separate these two compounds to yield the pure protected hydroxyacetone (304) in 63% yield from hydroxyacetone (303).

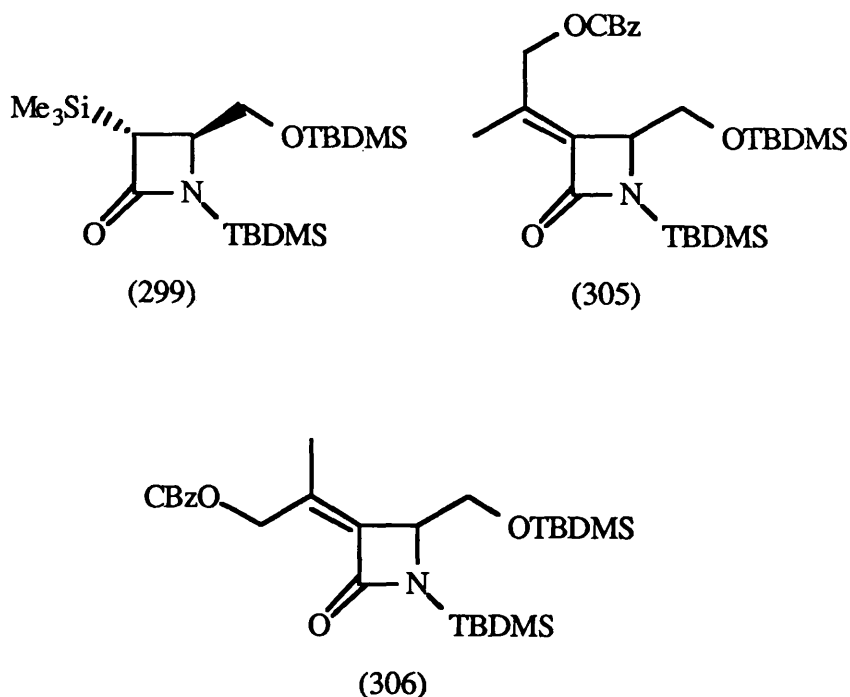


(303)



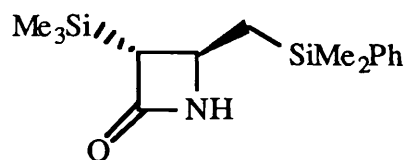
(304)

With the benzyloxycarbonyl protected hydroxyacetone in hand all that remained was the actual Peterson olefination, using the conditions already established with acetone. Treatment of racemic β -lactam (299) with LDA at -78°C and quenching with ketone (304), resulted in the production of Peterson product in 40% yield with recovery of 23% starting material. Surprisingly the Peterson product was a 2:1 mixture of geometric isomers at the C-3 double bond, the major product being the (E)-alkene (305) along with the contaminating (Z)-alkene (306). (These ratios are easily decided by comparison of the methyl signals in the ^1H NMR spectra, where the (E)-alkene methyl signal is moved downfield by the anisotropy of the β -lactam carbonyl).

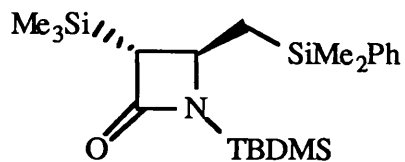


Since, in the transition state postulated by Ohno and co-workers the C-4 siloxyethyl substituent is well removed from the region associated with stereocontrol and therefore should play no part, it is difficult to envisage why employment of a C-4 siloxymethyl substituent should cause this stereocontrol to virtually collapse.

Whilst β -lactam (254) appeared ideal for oxidative cleavage and Peterson olefination, both synthetic manipulations caused a variety of problems. In terms of the Peterson olefination, no reaction was ever observed with the N-TBDMS derivative of (254), i.e. (284), apart from C-3 desilylation upon extended reaction times. Fortunately once oxidative cleavage had occurred thus converting the C-4 side chain into a siloxymethyl substituent, Peterson olefination, after re-silylation at the C-3 position, proceeded smoothly to furnish the alkylidene side chain found in a variety of β -lactam structures. The total failure to deprotonate and/or quench the resulting enolate from β -lactam (284) is not at all understood and we have no idea which of the two operations is causing the problem.



(254)

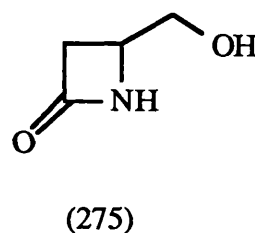
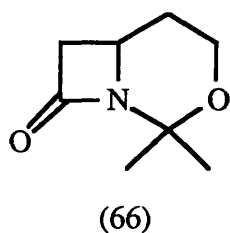


(284)

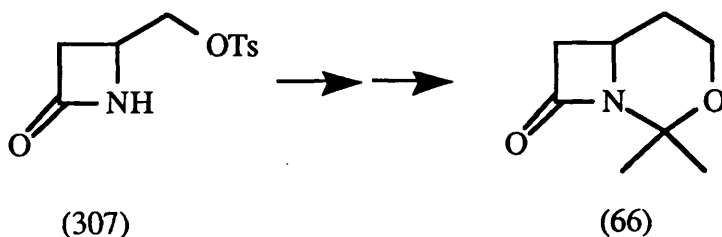
Having circumvented the problems associated with the oxidative cleavage and Peterson olefination of β -lactam (254) further synthetic manipulations were now possible and will be detailed in the following chapter.

6.1 C-4 Substituent Manipulation.

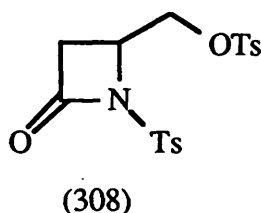
β -Lactam (66) has been used extensively in the synthesis of carbapenems, for example, in the Merck synthesis of racemic thienamycin,⁽⁴⁰⁾ where (66) was treated with LDA/acetaldehyde to furnish a 3-hydroxyethyl side chain. Consequently it was decided that this bicyclic compound would be an ideal carbapenem precursor which should be accessed easily from our 4-(hydroxymethyl)azetidinone (275) by homologation of the C-4 hydroxymethyl side chain followed by tetrahydrooxazine formation.



It was envisaged that the C-4 hydroxymethyl homologation could be performed by initially converting the β -lactam (275) into (tosyloxymethyl)azetidinone (307). Displacement of the tosyloxy function with a vinyl anion, ozonolysis and reduction followed by acetonide formation should furnish the tetrahydrooxazine (66).



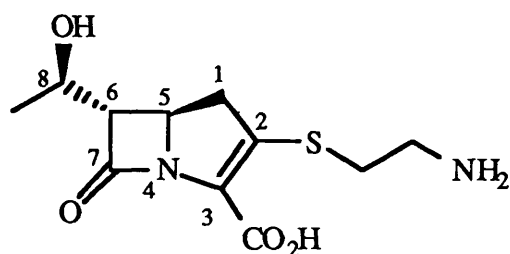
Conversion of 4-(hydroxymethyl)azetidinone (275) into the 4-(tosyloxymethyl)-azetidinone (307) had previously been described by Stoodley and co-workers.⁽¹⁴⁵⁾ After oxidative cleavage of β -lactam (255), tosylation of the product azetidinone (275) should furnish the desired compound. Having carried out the mercuridesilylation and oxidative rearrangement sequence, tosylation at -30°C , under the conditions described by Stoodley, furnished the tosylate (307), but in a disappointing yield of 5%. In an effort to augment this yield the tosylation procedure of Vermeer and Westmijze⁽¹²³⁾ ($\text{TsCl/KOH}/-50^{\circ}\text{C}$) was applied to the crude residue from oxidative cleavage. The original procedure utilised Et_2O as solvent but 4-(hydroxymethyl)azetidinone (275) is not soluble in Et_2O and so the solvent was changed to EtOAc . With this modification the N, Q bis-tosylate (308) rather than the Q-tosylate (307) was recovered, again in a low yield of 3%.



Stoodley converted alcohol (275) into tosylate (307) in a moderate yield of 50%. Therefore our disappointing yield should be improvable but perhaps not by enough to make any more synthetic transformations worthwhile. Due to this and time considerations the study on C-4 homologation was taken no further.

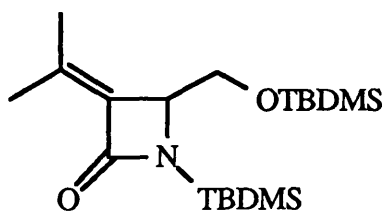
Generation of the (R)-Hydroxyethyl Side Chain of Thienamycin.

Thienamycin (15) contains a C-6 hydroxyethyl substituent with the (R) configuration at C-8. Three methods are commonly employed to generate this side chain with the correct configuration, namely acylation and stereospecific reduction of a C-3 unsubstituted azetidinone, utilising pre-existing chirality from an α -hydroxy amino acid, and finally from a β -hydroxybutyric acid derivative which has the correct (R) configuration at the asymmetric carbon.



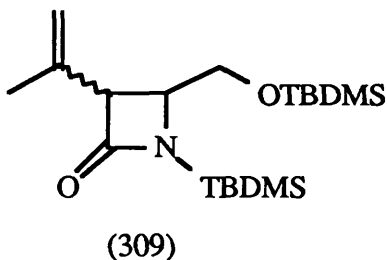
(15)

Whilst all of these methods work very well, it was felt that the alkylidene β -lactam (301), resulting from oxidative cleavage and Peterson olefination, could readily be converted into a potential precursor of racemic thienamycin with the correct relative configuration at all three chiral centres.

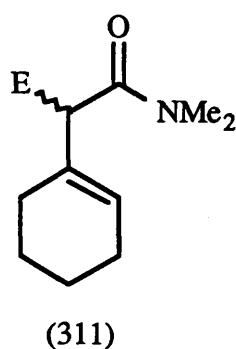
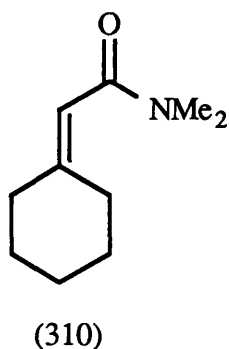


(301)

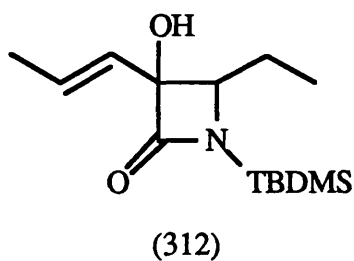
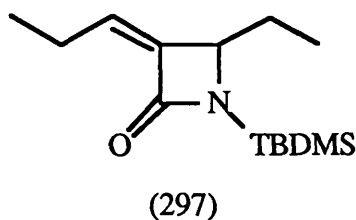
Delocalised anions formed by deprotonating α,β -unsaturated carbonyl systems are known to add hard electrophiles preferentially at the α -position, resulting in deconjugation. Deconjugation of β -lactam (301) to β,γ -unsaturated amide (309) would therefore be possible.



Snieckus and co-workers⁽¹⁴⁶⁾ deprotonated a range of conjugated amides, such as (310), then added an electrophile to the α -carbon to form β,γ -unsaturated amides, such as (311), in good yield.



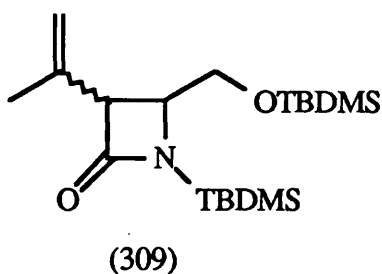
Ogilvie and Durst⁽¹⁴³⁾ extended this study to α,β -unsaturated azetidinones, e.g., (297), to form α -hydroxy- β,γ -unsaturated azetidinones, such as (312), in moderate yield.



Unfortunately no assignment of the relative C-3/C-4 stereochemistry was possible in the study by Ogilvie and Durst, but it was assumed that the C-3 hydroxyl group entered trans to the C-4 substituent.

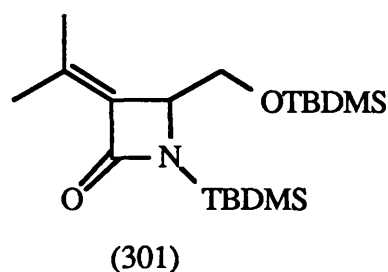
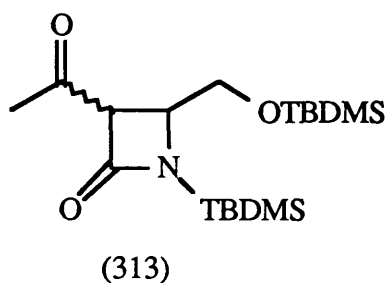
Our idea was to deprotonate the 3-isopropylidene β -lactam (301) then kinetically protonate the delocalised anion to generate 3-isopropenyl β -lactam (309). At the outset it was hoped that selective reprotonation in the α -position would produce either C-3/C-4 cis substitution or C-3/C-4 trans substitution by judicious choice of the H^+ source.

Initial experiments with HCl quenching of the enolate generated from β -lactam (301) produced a mixture of C-3/C-4 cis and C-3/C-4 trans diastereomeric β -lactams. In the 1H NMR spectrum two separate olefin multiplets could be observed quite clearly around 5ppm and these were used to judge the cis/trans ratio of diastereomers. The 1H NMR spectrum was not first order and resonances could not be assigned to the cis/trans mixture of β -lactams. Therefore no comment can be made, at this stage, as to which diastereomer was in excess. Similar results were encountered when glacial acetic acid was used to quench the generated enolate. In this case the deprotonation/acetic acid quench gave a quantitative yield of isopropenyl β -lactam (309) as a mixture of two diastereomers in ratios ranging from 5:1 to 2:1.



It had been hoped that stereoselective α -protonation of the generated enolate would be possible to furnish a C-3/C-4 cis or trans- β -lactam, depending on the choice of H^+ source. The use of glacial acetic acid, as already mentioned, furnished a mixture of cis and trans products with the trans- β -lactam always the major product (see later). The use of a more bulky proton source, such as t-butanol, to achieve stereoselective α -protonation was not attempted due to time considerations.

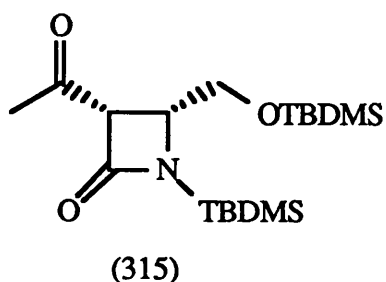
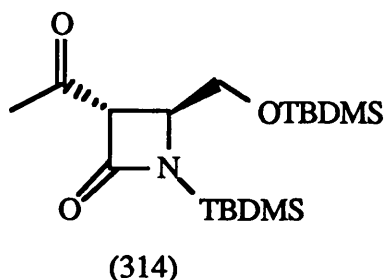
It was envisaged that ozonolysis of the isopropenyl β -lactam (309) would furnish a β -ketoamide in which the C-3 methine would resonate further downfield in the ^1H NMR spectrum than would the C-3 methine in the 3-isopropenyl β -lactam, with all other shifts remaining approximately constant. Therefore conversion into the 3-acetyl β -lactam (313) would hopefully allow assignment of the cis/trans ratio from the deprotonation/kinetic quench sequence with β -lactam (301).



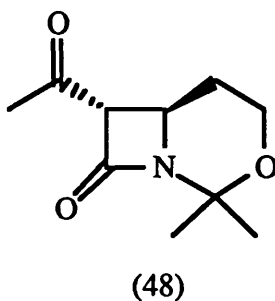
The 3-acetyl β -lactam (313) is in essence a β -ketoamide in which the C-3 proton will be fairly acidic. Therefore the reductive work-up after ozonolysis cannot be basic, if we wish to retain a genuine cis/trans ratio from the kinetic quench. With this in mind the reducing agent chosen was DMS and gratifyingly ozonolysis of β -lactam (309) followed by DMS reduction, washing and concentration afforded a mixture of cis and trans-3-acetyl β -lactams (313). The major component of this mixture had a C-3 methine resonance at 4.1 ppm in the ^1H NMR spectrum. This resonance occurred as a doublet with a coupling constant of 2.7 Hz, indicative of C-3/C-4 trans fusion. Assignment of signals to the minor cis isomer proved impossible.

The predominantly trans mixture of 3-acetyl β -lactams should be convertible into the thermodynamically favoured trans isomer by mildly basic treatment. Most pleasingly an overnight stir with 0.6 equivalents of Et_3N furnished the trans-3-acetyl β -lactam (314) as the sole product, with a C-3 methine doublet identical to that on which the cis/trans determination was made in the 3-acetyl β -lactam mixture.

By ^1H NMR and ^{13}C NMR spectroscopy this material appeared to be a single diastereomer; the absence of the *cis*-3-acetyl β -lactam (315) was confirmed by capillary GC analysis.



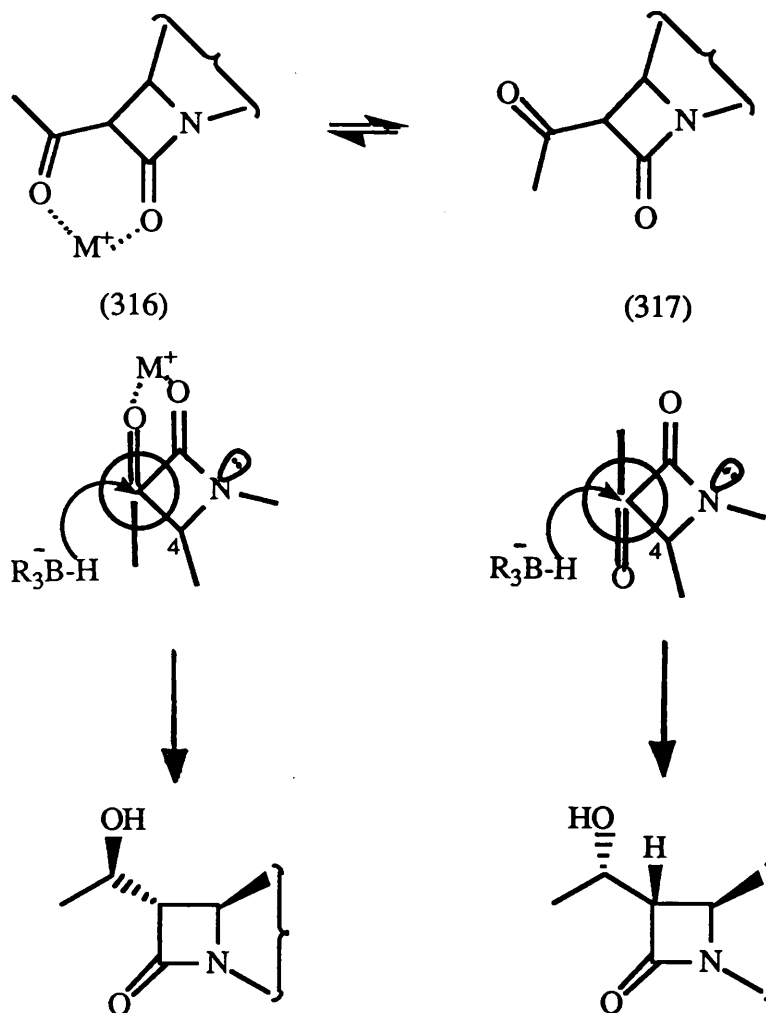
With a pure sample of *trans*- β -lactam in hand it was hoped that a stereoselective reduction to a thienamycin precursor with the correct relative configuration would be possible using the K-Selectride/KI/Et₂O procedure developed by the Merck group. This reduction had been investigated extensively by Bouffard and Christensen⁽⁶²⁾ on the bicyclic β -lactam (48).



To obtain stereoselective reduction some constraint has to be introduced to the conformationally mobile side chain via metal ion complexation of the 1,3-dicarbonyl functionality.

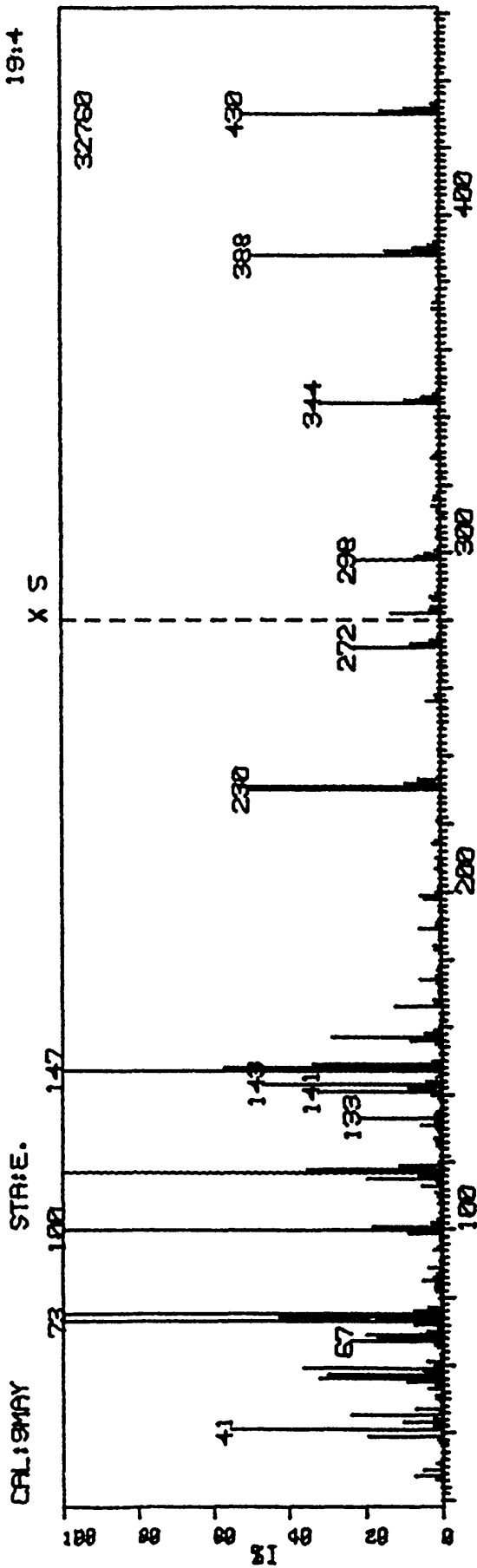
Unfortunately simple reducing agents, such as NaBH₄ and LiBH₄, provided ca. 50/50 mixtures of desired (R) and undesired (S)-carbinols. However reduction with the

bulky tri-sec-butylborohydrides, L-Selectride and K-Selectride, resulted in high but opposite (R)/(S) selectivities being observed.

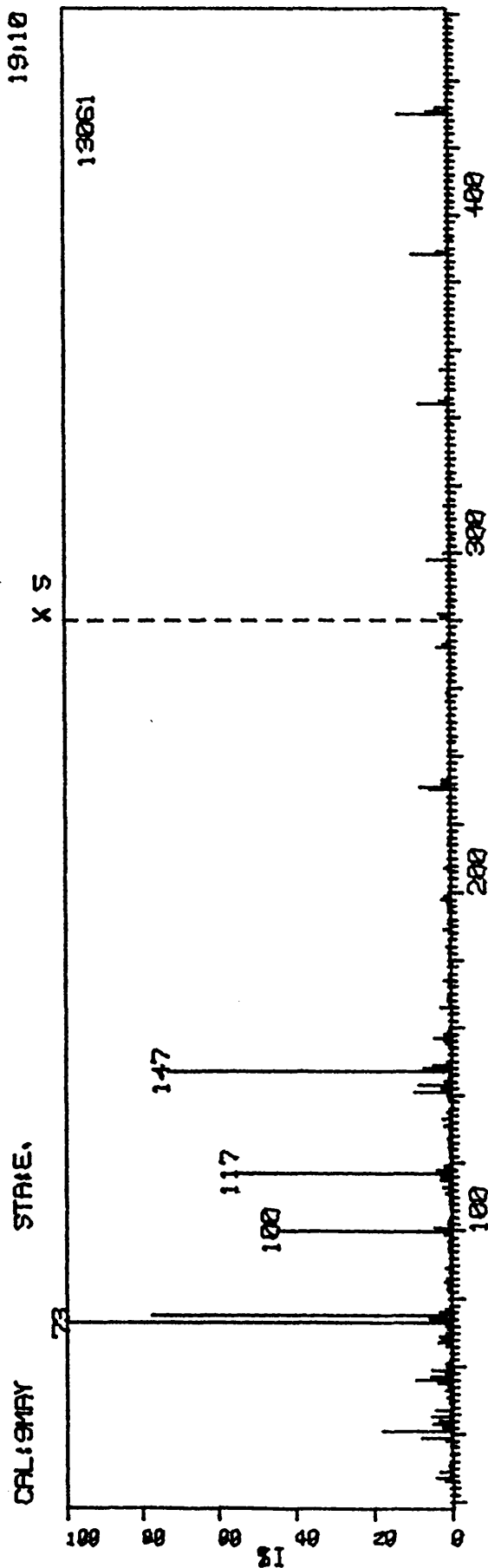


The Selectride always attacks from the face shown since attack on the face of the ketone carbonyl opposite to that indicated is disfavoured due to steric repulsions resulting from the C-4 proton on the azetidinone and also due to electrostatic interactions between the negatively charged borohydride anion and the lone pair of electrons on the β -lactam nitrogen.

19:4



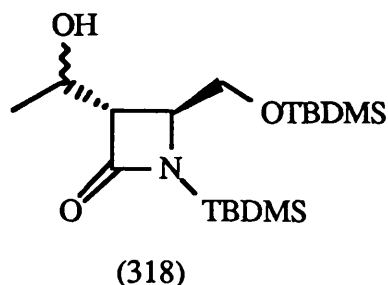
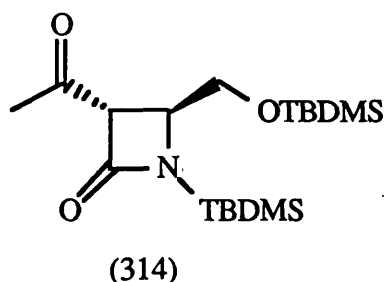
19:10



The Merck workers found that K-Selectride furnished the desired (R)-carbinol via the chelated intermediate (316) whereas L-Selectride furnished the (S)-carbinol via the non-chelated (317). The preferred cation complexation ($K^+ > Li^+$) is consistent with the reported chelation effectiveness of alkali metal ions with neutral imides ($K^+ > Li^+$) unlike enolate ions where Li^+ has been shown to be a better chelating cation than K^+ .(147)

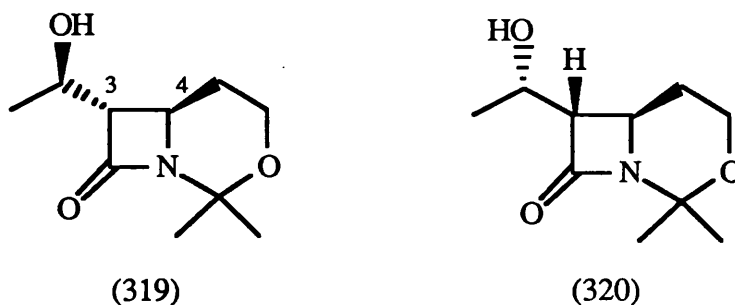
The reduction was carried out, rather strangely, in the presence of KI, an additive which did not affect the selectivity in the K-Selectride reduction but which did improve the yield. Unfortunately the Merck workers do not give an indication of how much KI was added, but Ley and co-workers⁽¹⁴⁸⁾ in a similar reduction utilised 1.2 equivalents of KI:1 equivalent of 3-acetyl β -lactam.

Gratifyingly the K-Selectride/KI/Et₂O reduction of β -lactam (314), using the conditions of Ley, proceeded smoothly to furnish (hydroxyethyl)azetidinone (318) in high yield.



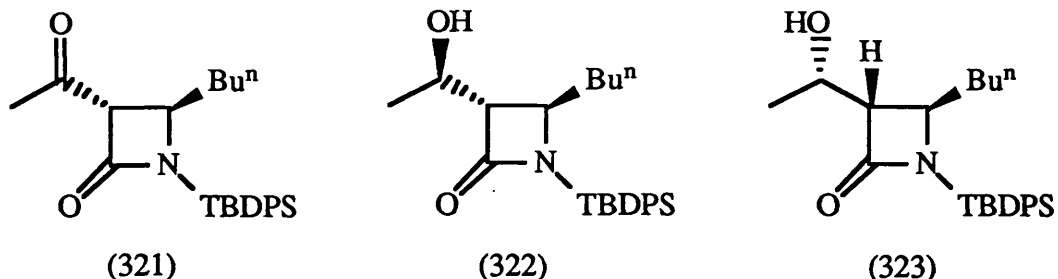
This compound by ¹H NMR analysis appeared to be one isomer but capillary GC analysis of its silyl ether afforded excellent separation into the two diastereomeric carbinols in a ratio of 12:1. Most pleasingly GC-MS experiments confirmed the authenticity of our peak assignments, see Figure 2, in that both diastereomeric components, resolved on GC, exhibited identical molecular ions and fragmentation patterns in their respective mass spectra.

The assignment of (R) or (S)-stereochemistry at the carbinol centre is fairly routine in bicyclic β -lactams on account of the rigidity imposed by the second ring. For example, the earlier work of the Merck group⁽⁴⁰⁾, whilst investigating the suitability of aldol chemistry to introduce the hydroxyethyl side chain, had assigned the ^1H NMR signals and coupling constants of the epimeric β -lactams (319) and (320).

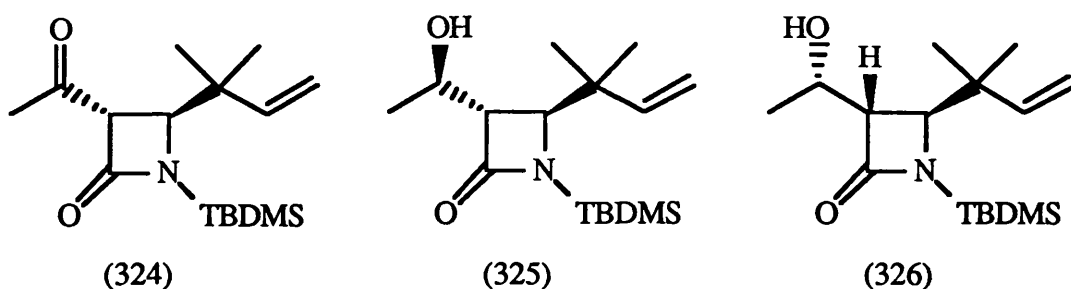


In the (R)-compound (319) the C-3 methine resonates as a doublet of doublets with a characteristic C-3/C-4 trans coupling constant of 1.5 Hz and a coupling constant of 7 Hz to the proton on the hydroxyl carbon. In the (S)-compound (320) coupling constants of 1.5 Hz and 4.5 Hz are observed. Therefore in the bicyclic series, after reduction of the 3-acetyl substituent, examination of the ^1H NMR coupling constants will determine which isomer is produced by the reduction, since the (R)-epimer always exhibits a larger coupling constant between the borohydride derived proton and the C-3 methine proton.

Unfortunately the situation is not nearly as simple in the monocyclic series; removal of the second ring allows the substituents much more conformational freedom, resulting in very little difference in the magnitude of the coupling constants so diagnostic in the bicyclic β -lactams. For example, in the work of Pecquet and d'Angelo⁽¹⁴⁹⁾, reduction of β -lactam (321) produced carbinols (322) and (323) where the configuration was determined by mesylation followed by base induced elimination of the mesylate group to furnish 3-alkylidene β -lactams. In these compounds the allylic methyl group orientation was taken as indicative of (R) or (S)-stereochemistry in the starting carbinol.

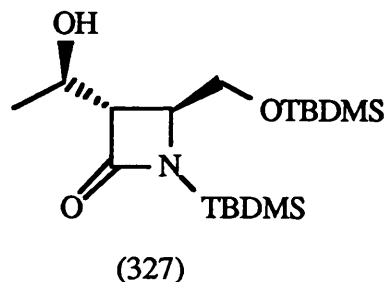
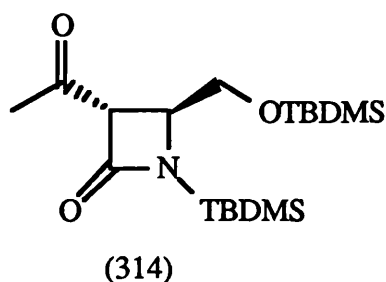
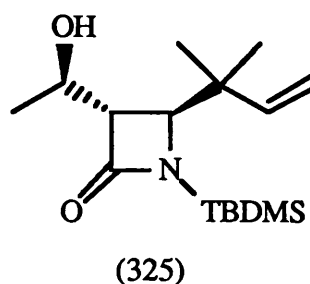
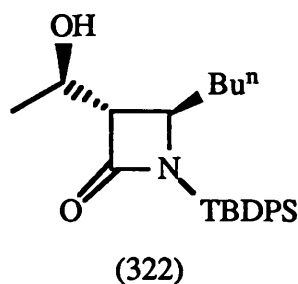


The (R)-hydroxy compound (322) exhibited a J of 5.5 Hz between C-3 and the borohydride derived proton, whereas its epimer had a J of 7 Hz with only 0.04ppm difference in the position of the C-3 methine resonances in the respective ^1H NMR spectra. Note that the coupling constants are perhaps too close to allow unambiguous assignment from the ^1H NMR spectrum and that the relative magnitudes of the epimeric coupling constants are opposite to those in the bicyclic case. Similarly Shibuya and co-workers⁽¹⁵⁰⁾ prepared carbinols (325) and (326) by aldol methodology or reduction of β -lactam (324).



The epimeric carbinols (325) and (326) exhibited very little difference in C-3 chemical shift in their ^1H NMR spectra and the coupling constants of 5.5 Hz for the (R)-carbinol and 6.5 Hz for the (S)-epimer were very similar to those observed by Pecquet and d'Angelo.

K-Selectride mediated reduction of β -lactam (314) produced a 12:1 ratio of epimers (as racemates) in which the minor component was not detectable by ^1H NMR spectroscopy. The major diastereomer had a C-3 methine resonance at 2.98 ppm, as a doublet of doublets $J=5.8$ and 2.4 Hz. Although 5.8 Hz, for the coupling constant in question, is extremely close to the value exhibited by the (R)-alcohols (322) and (325) of Pecquet and Shibuya the configuration after reduction of (314) can only be assigned tentatively as (R), i.e., structure (327).



The chelation controlled intermediate (316) along with the steric and electronic factors postulated by Bouffard and Christensen should still be valid for the K-Selectride mediated reduction of β -lactam (314) to furnish carbinol (327). Also the ^1H NMR spectroscopic evidence, although not conclusive, is certainly consistent with the production of the (R)-hydroxyethyl substituent and so the product resulting from reduction has been assigned as (327), a thienamycin precursor possessing the correct relative configuration at all three chiral centres.

This method is more elaborate than the Merck method to generate a 3-acetyl β -lactam, but it does offer an alternative strategy utilising intermediates which could possibly serve as precursors to carbapenems other than thienamycin.

Conclusions

The repetition and extension of Dunoguès' 1976 study has provided a versatile, facile route to monocyclic β -lactams carrying suitable carbon substitution at C-4 for elaboration into carbapenem precursors, by affording a functionality not readily accessible via CSI addition to other alkenes. The addition of CSI to allylsilanes followed by an aqueous reduction furnishes azetidinones in yields generally superior to those of other CSI cycloadditions. The addition to (allenylmethyl)silanes results in the formation of β -lactams in yields which are comparable to those encountered in the addition of CSI to simple allenes. Although the yields encountered with CSI and (allenylmethyl)silanes are modest the products are highly functionalised azetidinones otherwise difficult to access requiring fairly elaborate synthetic manipulations.

The regiochemistry of cycloaddition is controlled by the β -effect of silicon, as illustrated by the reaction of CSI with 1-trimethylsilyl-4-methylpenta-2,3-diene when contrasted with its reaction with 2-methylpenta-2,3-diene.

Our initial feasibility studies concentrated on the use of a trimethylsilyl moiety; the β -lactams generated were of little use for further synthetic manipulation. The study was extended by altering the silyl substitution pattern so that, whilst silicon would still control the regiochemistry of cycloaddition, the silyl moiety in the corresponding β -lactam product would have further synthetic potential. Conversion of carbon-silicon bonds into carbon-oxygen bonds is well documented; to effect this transformation the silyl residue must carry an electronegative substituent. Toward this end we concentrated our efforts on the generation of fluorosilanes from phenyldimethylsilyl moieties, as described by Fleming. A range of 4-(phenyldimethylsilylmethyl)azetidinones were prepared and subjected to the conventional fluoroborane mediated protodesilylation conditions, only to undergo rearrangement to form β,γ -unsaturated amides accompanied by phenol as the product of oxidative cleavage. Recent studies by Ricci and co-workers⁽¹⁵¹⁾ have shown that a phenyldimethylsilyl moiety can be converted, in good yield, into the corresponding chlorosilane by treatment with gaseous HCl. The absence of an added Lewis acid in this procedure may well mean that our 4-(phenyldimethylsilyl)azetidinones would be compatible with this protocol.

The more recent bromodesilylation and oxidative rearrangement procedure of Fleming did not yield any 4-(hydroxymethyl)azetidiones from the precursor 4-(phenyldimethylsilylmethyl)azetidiones although a strange bromination/acetolysis sequence was encountered with 3-trimethylsilyl-4-(phenyldimethylsilylmethyl)-azetidione. Gratifyingly, Fleming's mercuridesilylation/oxidative rearrangement procedure did furnish the desired 4-(hydroxymethyl)azetidiones, albeit in low yield from the starting 4-(phenyldimethylsilylmethyl)azetidiones.

Conversion into the corresponding chlorosilane, by the method of Ricci *et al.*, followed by oxidative rearrangement may well provide an alternative means to access the required 4-(hydroxymethyl) β -lactams in more acceptable yield but it should be noted that chlorosilanes have been found to react sluggishly in the oxidation procedure.⁽¹⁵²⁾

Peterson olefination on N-TBDMS or unprotected trans-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)azetidione returned only starting material. Peterson reaction however on the oxidatively cleaved trans-N-t-butylsilyl-3-trimethylsilyl-4-(t-butylsilyloxymethyl)azetidione, with acetone as the carbonyl acceptor, proceeded in quantitative yield. Most surprisingly, the same β -lactam underwent Peterson olefination with benzyloxycarbonyl protected hydroxyacetone to provide a 2:1 mixture of (E):(Z)-alkenes, in contrast to the work of Ohno on the C-4 homologue where Peterson olefination with the same carbonyl acceptor reportedly produced only the (E)-alkene.

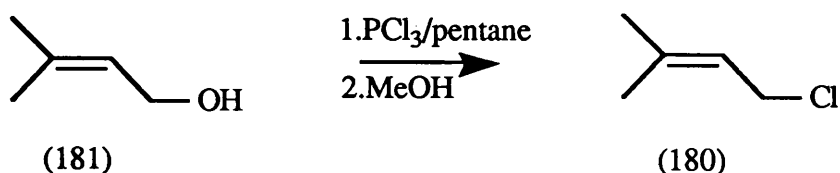
The oxidatively cleaved 4-(hydroxymethyl)azetidione has potential as an intermediate to bicyclic carbapenem precursors but unfortunately, due to time constraints this potential was not fully explored. Most pleasingly this oxidatively cleaved β -lactam could be converted into a thienamycin precursor with the correct relative configuration at all three chiral centres, in a fashion which may allow diversion into synthetic routes to other carbapenems.

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Bulb to bulb distillations were carried out using a Büchi GKR-50 Kugelrohr. Recorded boiling ranges refer to the indicated air bath temperature. ^1H NMR spectra were recorded on a Bruker AM200SY or a Bruker WP200SY spectrometer both operating at 200MHz or on a Perkin Elmer R32 spectrometer operating at 90MHz. ^{13}C NMR spectra were recorded on the Bruker spectrometers operating at 50MHz and ^{19}F NMR spectra on the AM200SY spectrometer operating at 188.3MHz. Chemical shifts in the ^1H 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 ^1H NMR spectrum and the central signal of the triplet at 77.0 ppm in the ^{13}C NMR spectrum. The multiplicities, where stated, in the ^{13}C spectra were determined by the use of DEPT spectra with pulse angles, $\theta=90^\circ$ and 135° .⁽¹⁵³⁾ The chemical shifts in the ^{19}F NMR spectra are reported in parts per million relative to CFCl_3 at 0.0ppm. Data are reported using the following convention: (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). Infrared 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. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

Separation of compounds was carried out by dry column flash chromatography, under reduced pressure, on Merck Kieselgel 60H or on Riedel-de-Haën aluminium oxide D. Alternatively separations were performed by positive pressure chromatography under nitrogen using Merck Kieselgel 60.

All reactions were carried out under a blanket of nitrogen. THF and Et_2O were distilled prior to use from sodium/benzophenone ketyl. CH_2Cl_2 and CH_3CN were distilled from CaH_2 , CCl_4 was distilled from P_2O_5 , then passed through a basic alumina column and CHCl_3 was washed with water, dried over K_2CO_3 and distilled from P_2O_5 , all solvents were stored over 4Å molecular sieves, after distillation.

Organic solutions were dried over magnesium sulphate and evaporated on a rotary evaporator under reduced pressure.

1-Chloro-3-methylbut-2-ene. (180)

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

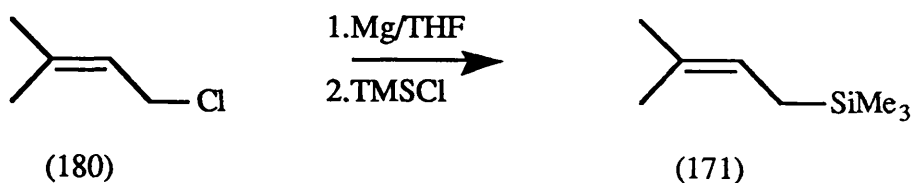
To a flame dried round bottomed flask, under N_2 , at 0°C was added pentane (50ml) and the allylic alcohol (181) (7.9g, 9.32ml, 91.2mmol). To this was added PCl_3 (7.56g, 4.80ml, 55mmol) dropwise over 2min. After stirring for 20min, MeOH (4.2g, 5.3ml, 131mmol) was added. At this stage, the biphasic reaction mixture was washed with water (20ml), 10 % aqueous NaHCO_3 solution (20ml), and finally brine (20ml). After drying of the organic layer, pentane was removed by careful distillation at atmospheric pressure. Careful distillation of the residue separated the desired allylic chloride from the isomeric 3-chloro-3-methylbut-1-ene to yield the title compound (4.03g, 42.3 %) as a clear oil, b.p. $90^\circ\text{C}/760\text{mmHg}$.

ν_{max} (CCl_4) 3090-3030, 1668, and 1450 cm^{-1} .

δ_{H} (200MHz) 5.43 (1H, t septet, J 8.0 and 1.4, CH), 4.08 (2H, d, J 8.0, CH_2), 1.76 (3H, br s, CH_3), 1.72 (3H, br s, CH_3).

δ_{C} (50MHz) 139.39($\text{C}(\text{CH}_3)_2$), 120.51(CH), 41.22(CH_2), 25.67(CH_3), 17.65(CH_3).

Found: M^+ , 104.0401 (^{35}Cl), $\text{C}_5\text{H}_9\text{Cl}$ requires M , 104.0393 (^{35}Cl).

1-Trimethylsilyl-3-methylbut-2-ene. (171)

Procedure: J.Dubac, A.Laporterie, H.Iloughmane, J.P.Pillot, G.Délérís and J. Donoguès, *J. Organomet. Chem.*, 1985, **281**, 149.

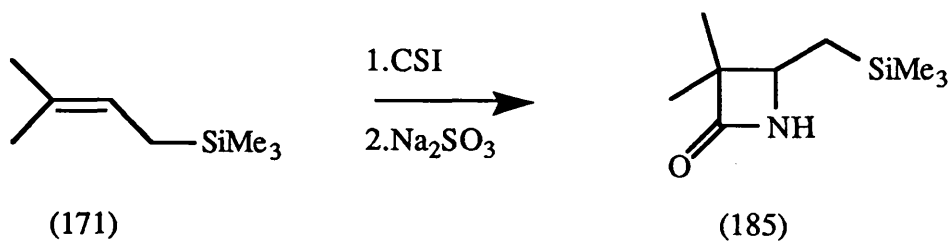
A round bottomed flask, equipped with a condenser, containing Mg (2.78g, 114.6 mmol) and a stirrer bar was flame dried and placed under N₂. THF (12ml) and ca. 1ml of neat allylic chloride (180) were added. Once the Grignard reaction had commenced the flask was placed in an ice bath and more THF (19ml) added. The rest of the allylic chloride (4.0g, 38.2mmol) was dissolved in THF (23ml) and added over 2h. The reaction mixture was then allowed to warm to room temperature, TMSCl (4.15g, 4.84ml, 38.2mmol) added dropwise and the mixture stirred overnight at ambient temperature. The mixture was concentrated to approximately half volume in vacuo, the organic supernatant decanted off and the inorganic residue washed with THF (10ml) then pentane (10ml). The combined organic extracts were diluted with pentane (50ml), washed with aqueous NH₄Cl solution (100ml) and water (100ml). After drying, the organic layer was concentrated in vacuo. Distillation of the residue yielded the title compound as a clear oil (2.69g, 50 %) b.p. 120°C/760 mmHg.

ν_{\max} (thin film) 1452, 1383, 1378, and 1250 cm^{-1} .

δ_{H} (200MHz) 5.14 (1H, t sept, J 8.5 and 1.4, CH), 1.69 (3H, br s, CH_3), 1.55 (3H, br s, CH_3), 1.38 (2H, d, J 8.5, CH_2), -0.03 (9H, s, SiMe_3).

δ_{C} (50MHz) 128.64(s), 120.00(d), 25.77(q), 18.60(t), 17.54(q), -1.76(q).

Found: M^+ , 142.1170. $\text{C}_8\text{H}_{18}\text{Si}$ requires M , 142.1178.

3,3-Dimethyl-4-(trimethylsilylmethyl)azetidin-2-one. (185)

To a flame dried flask, under N₂, at 0°C was added the allylsilane (171) (300mg, 2.11mmol) in CCl₄ (10ml). CSI (298mg, 184μl, 2.11mmol) was then added dropwise and the reaction mixture left to stir overnight, at ambient temperature, after which time 25% aqueous Na₂SO₃ solution (10ml) and CCl₄ (5ml) were added. After stirring overnight the CCl₄ layer was removed and the aqueous phase extracted with CH₂Cl₂ (2x10ml). The combined organic extracts were dried and concentrated in vacuo. The title compound was isolated, after positive pressure chromatography of the residue, as a white crystalline solid (240mg, 61.4%), m.p. 87-88 °C (pentane).

ν_{\max} (CHCl₃) 3420, 3110, 3085, 1771, and 1751 cm⁻¹.

(after dilution) 3420, 1771 cm⁻¹.

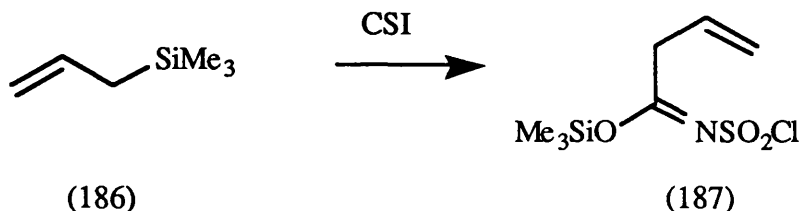
δ_{H} (200MHz) 5.85 (1H, br s, NH), 3.44 (1H, d d, *J* 9.2 and 5.4, CH), 1.26 (3H, s, CH₃), 1.11 (3H, s, CH₃), 0.86 (1H, d d, *J* 14.5 and 5.4, CHH), 0.76 (1H, d d, *J* 14.5 and 9.2, CHH), 0.04 (9H, s, SiMe₃).

δ_{C} (50MHz) 175.16(s), 58.03(d), 54.46(s, C(CH₃)₂), 22.19(q), 18.80(t), 17.15(q), -1.05(q).

Found: M^+ , 185.1215. C₉H₁₉NOSi requires M , 185.1236.

Found C 58.20%, H 10.23%, N 7.50%

C₉H₁₉NOSi requires C 58.32%, H 10.33%, N 7.56%

Addition of CSI to Allyltrimethylsilane (186)

A flame dried flask under N_2 was charged with allyltrimethylsilane (186) (236mg, 2.07mmol) in CCl_4 (10ml) and the flask cooled to $0^\circ C$. CSI (298mg, 184 μ l, 2.11mmol) was then added dropwise and an aliquot of the mixture removed and placed in an NMR tube. This NMR tube was transferred to a 90MHz 1H NMR spectrometer at $-40^\circ C$, and spectra were recorded over the next 15min. During this time virtually no reaction occurred and eventually the solution solidified. The spectrometer temperature was then raised to $-30^\circ C$, $-20^\circ C$ and finally to $-10^\circ C$ with spectra being recorded constantly.

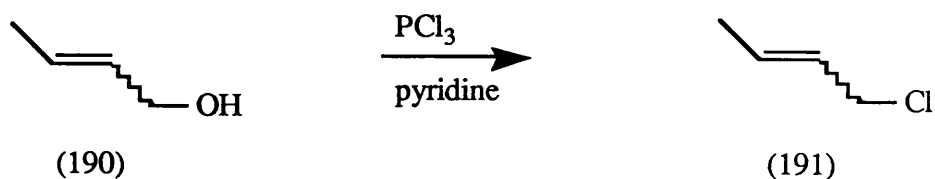
Note: 1H NMR spectra ran in CCl_4 (ref. $SiMe_3$ of allyltrimethylsilane (186) at 0.0ppm).

allyltrimethylsilane (186)

δ_H (90MHz) 6.0-5.3 (1H, m, =CH), 4.9-4.5 (2H, m, =CH₂), 1.6-1.3 (2H, br d, CH₂Si), 0.0 (9H, s, SiMe₃).

imidate (187)

δ_H (90MHz) 6.1-5.6 (1H, m, =CH), 5.4-5.1 (2H, m, =CH₂), 3.4 (2H, br d, CH₂), 0.42 (9H, s, SiMe₃).

(Z) and (E)-1-Chlorobut-2-ene. (191)

Procedure: L.F.Hatch and S.S.Nesbitt, *J. Am. Chem. Soc.*, 1950, 72, 727.

To a flame dried flask, under N_2 , at 0°C containing PCl_3 (3.05g, 1.94ml, 22.2mmol) was added, with stirring, the allylic alcohol (190) (4.01g, 4.74ml, 55.6mmol) in pyridine (1.23g, 1.26ml, 15.6mmol) dropwise. At this stage the biphasic mixture was set up for short path distillation, placed under vacuum (20mmHg) and the receiver flask chilled to -78°C . Final traces of volatiles were distilled with the aid of an hairdryer. The distillate was dried over Na_2SO_4 then distilled via a 10cm Vigreux column to yield the allylic chloride (191) as a clear oil (2.75g, 54.7%). b.p. $60-70^\circ\text{C}/760$ mmHg.

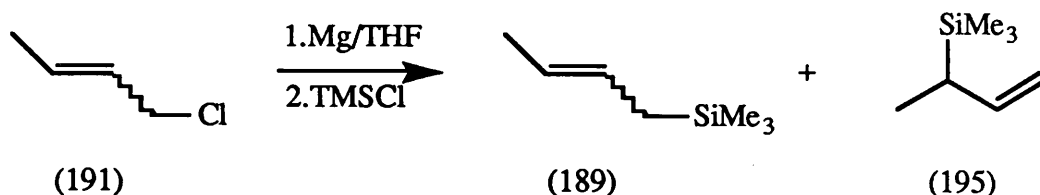
Mainly one isomer produced and spectroscopic data refer to this.

ν_{max} (thin film); 3035, 2950, and 1669 cm^{-1} .

δ_{H} (200MHz) 5.85-5.52 (2H, m, CHCH_3 and CHCH_2), 4.01 (2H, d, J 6.9, CH_2), 1.72 (3H, d, J 5.1, CH_3).

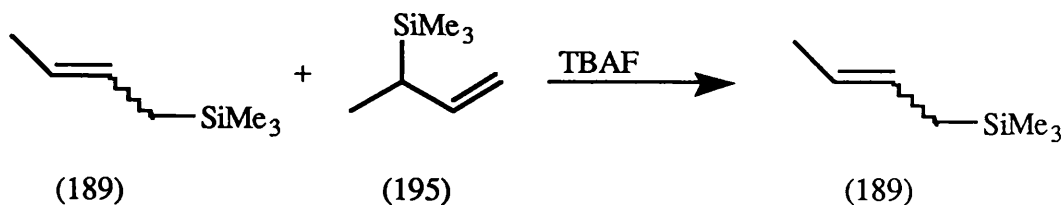
δ_{C} (50MHz) 130.95(d), 127.11(d), 45.41(t), 17.58(q).

Found: M^+ , 92.0207 (^{37}Cl), 90.0235 (^{35}Cl); $\text{C}_4\text{H}_7\text{Cl}$ requires 92.0207 (^{37}Cl), 90.0236 (^{35}Cl).

(Z) and (E)-1-Trimethylsilylbut-2-ene and 3-Trimethylsilylbut-1-ene. (189) & (195)

Procedure: J.Slutsky and H.Kwart, *J. Am. Chem. Soc.*, 1973, **95**, 8678.

A 100ml round bottomed flask equipped with a condenser and containing Mg (1.56g, 64.2mmol) was flame dried and placed under N₂. THF (6ml) and TMSCl (2.32g, 2.71ml, 21.4mmol) were added via syringe followed by ca. 0.3ml of the allylic chloride (191). After the Grignard reaction had commenced, the flask was placed in ice and further THF (10ml) added. The rest of the allylic chloride (1.94g, 21.4mmol) in THF (14.5ml) was then added over the next 2.5h and the reaction mixture left to stir overnight at room temperature. Work-up consisted of filtration through Celite, dilution with pentane (50ml) and washing with aqueous NH₄Cl solution (50ml) then water (50ml). The organic extract was dried and concentrated in vacuo to give the three title compounds (2.04g, 75%) in a ratio of 1:1.5:1.7. The major isomer being the 3-trimethylsilylbut-1-ene.

(Z) and (E)-1-Trimethylsilylbut-2-ene. (189)

Procedure: A.Hosomi, A.Shirahata and H.Sakurai, *Chem. Lett.*, 1978, 901

TBAF.3H₂O (98mg, 0.31mmol) was dried in a 10ml round bottomed flask at 70°C/0.2 mmHg for 3h (Büchi Kugelrohr) and the mixture of allylsilanes (189) and (195) (2.93g, 22.9mmol) added. The flask was then equipped with a condenser and heated at 100°C for 20h. The volatiles were removed by distillation (96°C/760 mmHg). ¹H NMR analysis indicated however that the conversion into primary allylsilane was not complete and so the process was repeated; TBAF.3H₂O (19.9mg, 0.06mmol) and the allylsilane mixture (0.5g, 3.9mmol) were heated at 100°C overnight. Similar purification yielded the title compounds as a clear oil. (246mg, 8.4%).

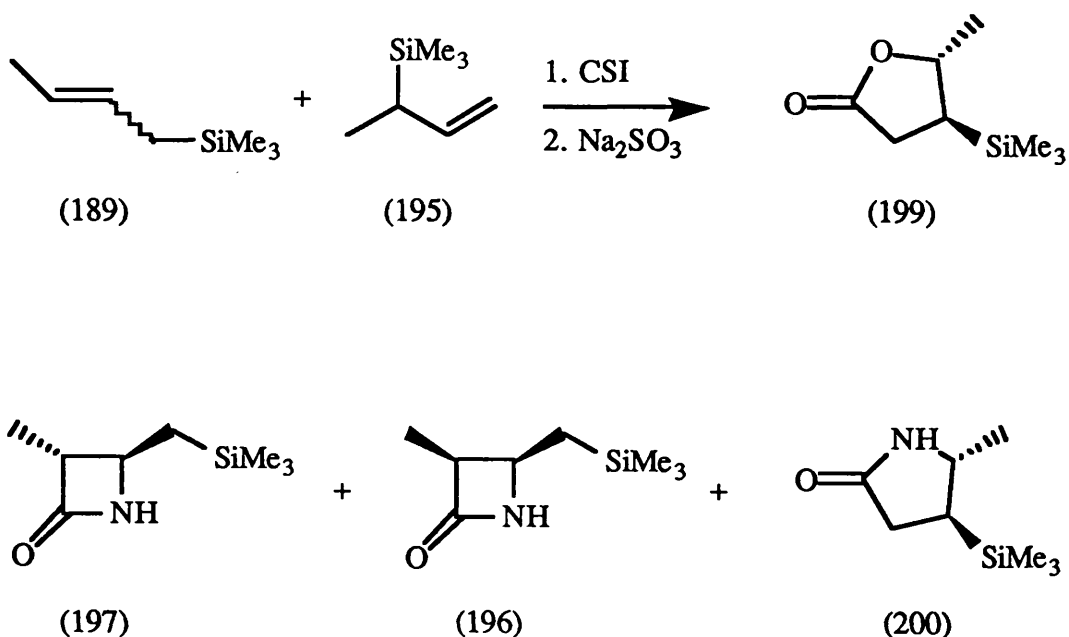
ν_{\max} (CHCl₃) 3000, 2960 and 1252 cm⁻¹

δ_{H} (200MHz) 5.45-5.25 (2H, m, CHCH₃ and CHCH₂), 1.56 (3H, m, CH₃), 1.5 (2H, m, CH₂), 0.06 (9H, s, SiMe₃).

δ_{C} (50MHz) 126.45(d), 121.17(d), 18.03(t), 12.58(q), -1.80(q). and 130.13(d), 123.07(d), 17.93(t), 12.86(q), 1.93(q).

Found: M^+ 128.1040, C₇H₁₆Si requires M , 128.1017

Addition of CSI to the Allylsilanes (189) and (195) Mixture.



To a flame dried flask under N₂ at 0°C was added a mixture of the allylsilanes (189) and (195) (201.5mg, 1.57mmol) in CCl₄ (6.4ml). CSI (222.2mg, 137.1μl, 1.57mmol) was added dropwise and the mixture stirred for 1.5h, at 0°C, then quenched by the addition of 25% aqueous Na₂SO₃ solution (12ml) and CCl₄ (6ml). After stirring overnight the organic layer was removed and the aqueous layer re-extracted with Et₂O (2x10ml). The organic extracts were combined, dried and concentrated. The residue was purified by dry column flash chromatography on neutral alumina to give the tetrahydrofuran-2-one (199) (16.2mg, 6.0%), trans-β-lactam (197) (50mg, 18.6%), and the cis-β-lactam (196) (39.2mg, 15.0%) as clear oils along with the pyrrolidin-2-one (200) (31.3mg, 11.6%) as a white solid.

Trans-5-methyl-4-(trimethylsilyl)tetrahydrofuran-2-one.(199)

ν max. 1770, 1750 and 1255 cm^{-1} .

δ_{H} (200MHz) 4.45 (1H, d q, J 10.4 and 6.1, CHO), 2.55 (1H, d d, J 17.6 and 9.2, CHH), 2.35 (1H, d d, J 17.6 and 12.8, CHH), 1.40 (1H, d d d, J 12.8, 10.4 and 9.2, CHSi), 1.40 (3H, d, J 6.1, CH_3), 0.07 (9H, s, SiMe_3).

δ_{C} (50MHz) 177.43(s), 80.12(d, CHO), 32.36(t), 31.93(d), 21.74(q), -2.90(q).

Found: M^+ , 172.0922, $\text{C}_8\text{H}_{16}\text{O}_2\text{Si}$ requires M , 172.0920.

GC Analysis: Column: 25mx0.32mm I.D. fused silica capillary CP Sil 19CB.

Temp.Program: 80°C for 2mins.

up to 115°C over 1min.

up to 190°C over 5mins.

up to 250°C over 5mins.

Retention time 7.85mins.

Trans-3-methyl-4-(trimethylsilylmethyl)azetidin-2-one. (197)

ν_{\max} . 3415 and 1750 cm^{-1} .

δ_{H} (200MHz) 5.85 (1H, br s, NH), 3.35 (1H, d d d, J 8.7, 6.0 and 2.1, CHN), 2.69 (1H, q d d, J 7.4, 2.1 and 1.1, CHCO), 1.29 (3H, d, J 7.4, CH_3), 1.05 (1H, d d, J 14.3 and 6.0, CHH), 0.94 (1H, d d, J 14.3 and 8.7, CHH), 0.04 (9H, s, SiMe_3).

δ_{C} (50MHz) 171.43(s), 54.69(d, CHN), 53.41(d, CHCO), 23.88(t), 12.99(q), -1.19(q).

Found: M^+ 171.1077, $\text{C}_8\text{H}_{17}\text{NOSi}$ requires M , 171.1079

G C Analysis: Conditions as previous

Retention time 9.94 mins.

Cis-3-methyl-4(trimethylsilylmethyl)azetidin-2-one.(196)

ν_{\max} (CHCl₃): 3420, 1755 and 1252cm⁻¹.

δ_{H} (200MHz) 5.95 (1H, br s, NH), 3.85 (1H, d d d, *J* 8.3, 6.2 and 5.2, CHN), 3.25 (1H, q d, *J* 7.6 and 5.2, CHCO), 1.16 (3H, d, *J* 7.6, CH₃), 0.80 (1H, d, *J* 8.3, CHH), 0.80 (1H, d, *J* 6.2, CHH), 0.04 (9H, s, SiMe₃).

δ_{C} (50MHz) 172.34(s), 49.65(d, CHN), 48.92(d, CHCO), 18.02(t), 9.16(q), -1.09(q).

Found: M^+ , 171.1067, C₈H₁₇NOSi requires M , 171.1079.

G C Analysis: Conditions as previous

Retention time: 11.34mins.

Trans-4-trimethylsilyl-5-methylpyrrolidin-2-one. (200)

ν_{\max} . (CHCl₃) 3431 and 1689 cm⁻¹.

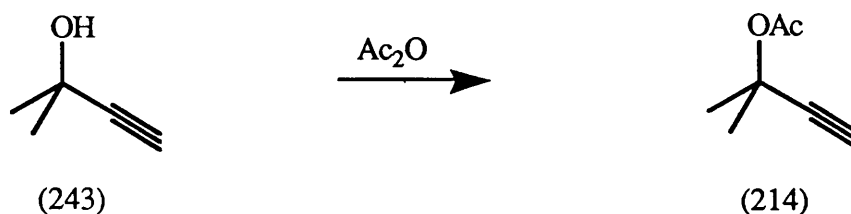
δ_{H} (200MHz) 6.25 (1H, br s, NH), 3.65 (1H, d q, *J* 8.1 and 6.1, CHN), 2.41 (1H, d d, *J* 17.1 and 10.1, CHH), 2.16 (1H, d d, *J* 17.1 and 10.8, CHH), 1.22 (1H, m, CHSi), 1.22 (3H, d, *J* 6.1, CH₃), 0.03 (9H, s, SiMe₃).

δ_{C} (50MHz) 178.33(s), 52.02(d, CHN), 33.19(t), 30.16(d, CHSi), 23.36(q), -3.00(q).

Found: *m/z*, 156.0858, C₈H₁₇NOSi-CH₃ requires 156.0845.

GC Analysis: Conditions as previous

Retention time 14.08min.

3-Acetoxy-3-methylbut-1-yne. (214)

Procedure: B.Psaume, Ph.D. Thesis, Université Claude Bernard-Lyon, 1981, p. 51.

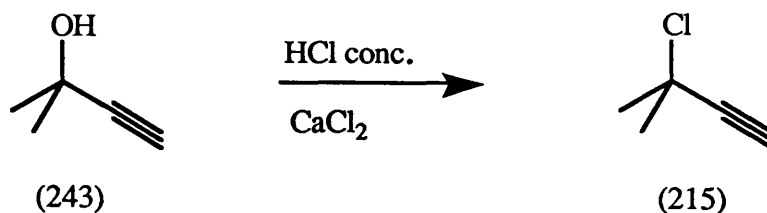
To a flame dried flask, under N₂, was added the alcohol (243) (10g, 11.52ml, 118.8mmol), and acetic anhydride (36.38g, 33.62ml, 356.4mmol). The mixture was heated under reflux for 3h then left to cool overnight. The mixture was then partitioned between aqueous NaOH solution (5N, 20ml) and Et₂O (20ml). After shaking, the aqueous layer was removed and the organic phase washed with aqueous NaOH solution (5N, 20ml). The combined aqueous phases were re-extracted with Et₂O (20ml) and the combined organic extracts dried and concentrated. At this stage ¹H NMR analysis indicated a 1:1 ratio of starting material to product (8.94g). The alcohol/acetate mixture was taken up in acetic anhydride (32.55g, 30.1ml, 319mmol) and refluxed overnight. After cooling and work-up as described above, distillation yielded the title compound as a colourless oil (8.06g, 54%) b.p. 60°C/20mmHg.

ν_{max} . (CHCl₃) 3305, 2120 and 1740 cm⁻¹.

δ_{H} (90MHz) 2.50 (1H, s, CH), 2.02 (3H, s, COCH₃), 1.68 (6H, s, CH₃).

δ_{C} (50MHz) 169.32(s), 84.63(d), 72.17(s), 71.46(s), 28.79(q), 21.83(q).

Found: M^+ 126.0683, C₇H₁₀O₂ requires M , 126.0681

3-Chloro-3-methylbut-1-yne.(215)

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

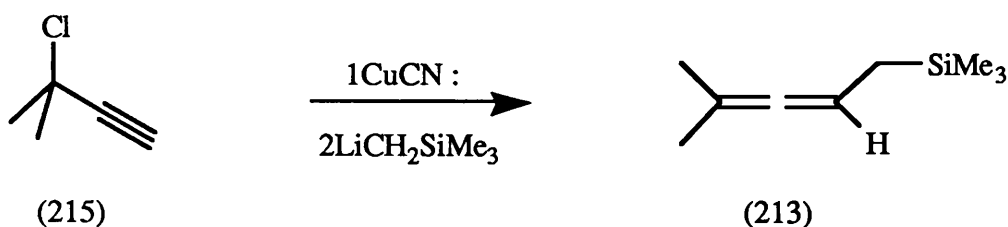
A 50ml round bottomed flask under N_2 was charged with oven dried CaCl_2 (3.96g, 35.66mmol) and conc. HCl (15.5ml, 140mmol). The reaction mixture was chilled to 0°C and the alcohol (243) (3g, 3.46ml, 35.66mmol) added. After stirring for 30min the flask contents were transferred to another 50ml round bottomed flask containing excess, oven dried, K_2CO_3 . Distillation via a 10cm Vigreux column yielded the title compound as a clear oil (1.4g, 38%) b.p. $58^\circ\text{C}/760$ mmHg.

ν_{max} . (CHCl_3) 3305 and 2120 cm^{-1} .

δ_{H} (200MHz) 2.61 (1H, s, CH), 1.85 (6H, s, CH_3).

δ_{C} (50MHz) 86.52(ClCC), 71.88(CH), 56.95(ClC), 34.53(CH_3).

Found: M^+ , 102.0223, $\text{C}_5\text{H}_7\text{Cl}$ (^{35}Cl) requires M , 102.0236 (^{35}Cl).

1-Trimethylsilyl-4-methylpenta-2,3-diene. (213)

Cuprate Procedure: J.A.Soderquist and B.Santiago, *Tetrahedron Lett.*, 1989, **30**, 5693.

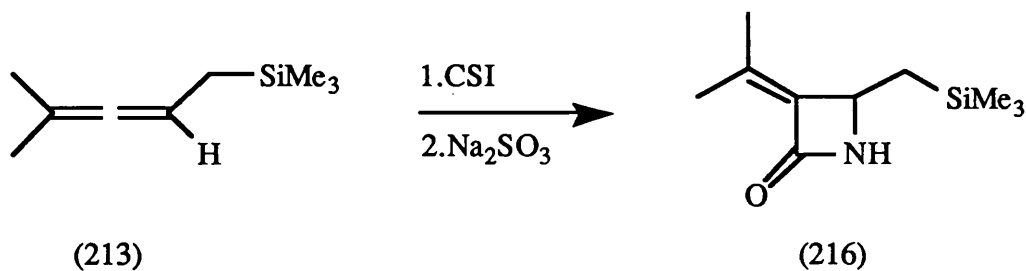
CuCN (295.5mg, 3.30mmol) and a stirrer bar were placed in a 50ml round bottomed flask which was then flame dried under vacuum and purged with N₂. On cooling the flask was placed in a bath at -78°C and THF (8.25ml) added. (Trimethylsilylmethyl)lithium (1M in pentane) (6.60ml, 6.60mmol) was added dropwise. Upon completion of the addition the flask was removed from the cooling bath and stirring continued at room temperature for 15min. The flask was again cooled to -78°C and the chloride (215) (338.4mg, 3.30mmol) in THF (5ml) added dropwise. The mixture was allowed to stir for 1h at -78°C then for 1h at 0°C. After quenching with a 9:1 aqueous NH₄Cl solution:33% aqueous NH₄OH solution (15ml) the mixture was diluted with Et₂O (20ml). The organic layer was separated and the aqueous layer was re-extracted with Et₂O (20ml). After drying and concentration in vacuo, of the combined organic extracts, the allene was isolated as a yellow oil (499.4mg).

ν_{\max} . (CHCl₃) 1960 and 1250cm⁻¹.

δ_{H} (200MHz) 4.92 (1H, m, CH), 1.65 (6H, d, *J* 2.7, CH₃), 1.24 (2H, d, *J* 8.2, CH₂), 0.01 (9H, s, SiMe₃).

δ_{C} (50MHz) 202.10(s, =C=), 94.04(s), 84.97(d), 20.98(q), 18.22(t), -2.00(q).

Found: M^+ , 154.1181. C₉H₁₈Si requires M , 154.1179.

3-Isopropylidene-4-(trimethylsilylmethyl)azetidin-2-one. (216)

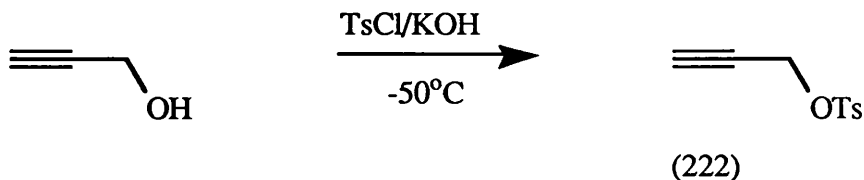
A 25ml round bottomed flask which had been flame dried and purged with N₂ was charged with (allenylmethyl)silane (213) (93.1mg, 0.60mmol) in CCl₄ (6ml) and chilled to 0°C. CSI (90.7mg, 56μl, 0.64mmol) was then added dropwise and the reaction mixture left to stir for 1h at 0°C. At this stage a 25% aqueous Na₂SO₃ solution (12ml) and CCl₄ (6ml) quench was applied. After stirring overnight, at room temperature, the organic layer was removed and the aqueous phase re-extracted with Et₂O (2x10ml). The combined organic extracts were dried and concentrated. Purification of the residue by dry column flash chromatography gave the title alkylidene β-lactam as a white solid (27.2mg, 23%). m.p. 103-105°C.

ν_{\max} (CHCl₃) 3435 and 1737 cm⁻¹.

δ_{H} (200MHz) 6.05 (1H, br s, NH), 4.18 (1H, d d, *J* 10.4 and 3.0, CHN), 2.02 (3H, s, CH₃), 1.72 (3H, s, CH₃), 1.16 (1H, d d, *J* 14.8 and 3.0, CHH), 0.89 (1H, d d, *J* 14.8 and 10.4, CHH), 0.05 (9H, s, SiMe₃).

δ_{C} (50MHz) 165.32(s), 138.47(s, C(CH₃)₂), 135.71(s, CCO), 53.43(d, CHN), 22.02(t), 19.94(q), 19.77(q), -0.82(q).

Found: M^+ , 197.1234, C₁₀H₁₉NOSi requires M , 197.1236.

Toluenesulphonyloxyprop-2-yne. (222)

Procedure: H. Westmijze and P. Vermeer, *Synthesis*, 1979, 390

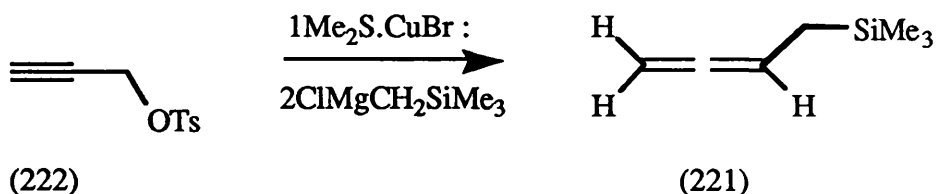
To a 25ml round bottomed flask, under N_2 , was added TsCl (953mg, 5mmol) in Et_2O (6ml) and propargyl alcohol (224mg, 233 μl , 4mmol). The reaction mixture was chilled to -50°C and freshly powdered KOH (1.50g, 26.7mmol) added. After warming to 0°C over 20 min, the flask was transferred to a cooling bath at 0°C and stirred for 30min. Water (20ml) was then added and the organic layer was separated. The aqueous layer was re-extracted with Et_2O (2x10ml). After drying and concentration of the combined organics purification of the residue by dry column flash chromatography gave the tosylate as a clear oil (831mg, 99%).

ν_{max} . (CHCl_3) 3308, 2135 and 1600 cm^{-1} .

δ_{H} (200MHz) 7.75 (2H, d, J 8.4, ArH), 7.31 (2H, d, J 8.4, ArH), 4.63 (2H, d, J 2.5, CH_2), 2.47 (1H, t, J 2.5, CH), 2.40 (3H, s, CH_3).

δ_{C} (50MHz) 145.40(s, ArC $\underline{\text{S}}$), 132.50(s, ArC $\underline{\text{C}}$ H CH_3), 129.76(d), 127.68(d), 77.32(s), 75.15(d), 57.28(t), 21.47(q).

Found: M^+ , 210.0341, $\text{C}_{10}\text{H}_{10}\text{SO}_3$ requires M , 210.0351.

1-Trimethylsilylbuta-2,3-diene. (221)

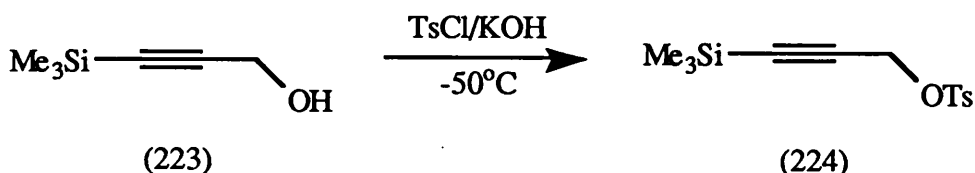
A 50ml round bottomed flask containing $\text{Me}_2\text{S}\cdot\text{CuBr}$ (1.03g, 5mmol) and a magnetic stirrer bar was flame dried and purged with N_2 . The flask was cooled to -78°C then THF (15ml) and Me_2S (6.34g, 7.5ml, 102mmol) were added. The flask was then allowed to warm to room temperature until all the complex solubilised at which point it was re-cooled to -78°C . The Grignard reagent (1M in Et_2O) (10ml, 10mmol) was then added dropwise and the flask warmed to room temperature over 10min. The reaction mixture was again re-cooled to -78°C and the tosylate (222) (1.050g, 5mmol) in THF (12ml) added dropwise. After stirring at -78°C for 1.5h the mixture was stirred at 0°C for a further 1h then quenched with a 9:1 aqueous NH_4Cl solution: 33% aqueous NH_4OH solution (20ml). The organic phase was removed and the aqueous phase extracted with Et_2O (2x30ml). The combined organic extracts were dried and concentrated in vacuo to give the crude allenylmethylsilane (221) as a yellow oil. (515mg, 82%).

ν_{\max} (CHCl₃) 1950 and 1250 cm⁻¹.

δ_{H} (200MHz) 5.06 (1H, t t, *J* 8.6 and 6.6, CH), 4.61 (2H, d t, *J* 6.6 and 2.8, =CH₂), 1.29 (2H, d t, *J* 8.6 and 2.8, CH₂Si), 0.00 (9H, s, SiMe₃).

δ_{C} (50MHz) 209.00(s, =C=), 86.50(d), 74.00(t), 8.80(t), -1.75(q).

Found: *m/z* 126(*M*⁺), 111(*M*⁺-*Me*), 73(SiMe₃).

1-Toluenesulphonyloxy-3-(trimethylsilyl)prop-2-yne. (224)

Procedure : H. Westmijze and P. Vermeer, *Synthesis*, 1979, 390.

Alcohol preparation: M. Nugent, Ph.D. Thesis, University of Glasgow, 1988, p.

81

A flame dried flask under N₂ was charged with the alcohol (223) (1.924g, 2.22ml, 15mmol) in Et₂O (22.5ml), followed by TsCl (2.86g, 15mmol) in Et₂O (8ml). The flask was cooled to -50°C then freshly powdered KOH (5.61g, 100mmol) added with vigorous stirring. The reaction mixture was allowed to warm to 10°C over 1.25h then diluted with water (50ml). The organic layer was removed and the aqueous layer re-extracted with Et₂O (2x20ml). After drying and concentration of the combined organic extracts, purification of the residual oil by dry column flash chromatography gave the title compound (3.583g, 85%) as a white crystalline solid m.p. 51-53°C (pentane).

ν_{\max} (CHCl₃) 3305, 2195, 1598 and 1250 cm⁻¹.

δ_{H} (200MHz) 7.79 (2H, d, *J* 8.1, ArH), 7.32 (2H, d, *J* 8.1, ArH), 4.69 (2H, s, CH₂), 2.43 (3H, s, ArCH₃), 0.05 (9H, s, SiMe₃).

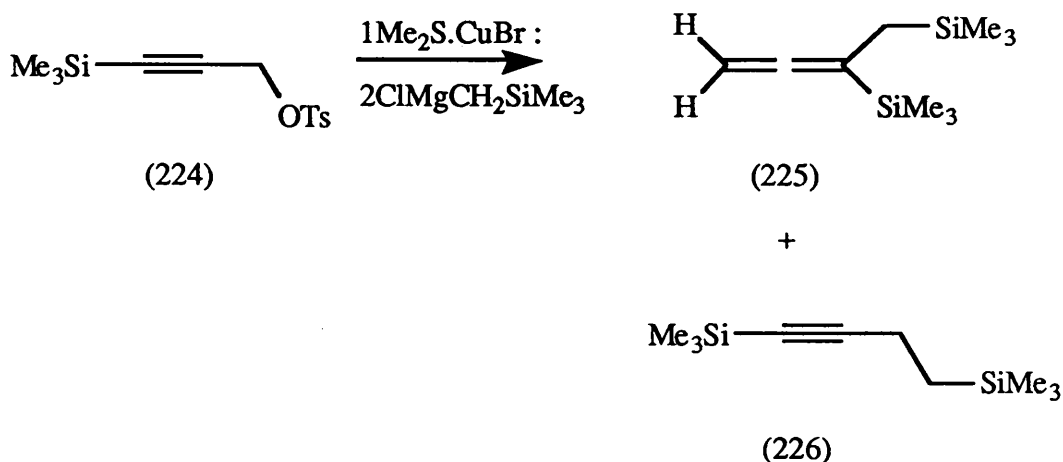
δ_{C} (50MHz) 144.98(s, ArCS), 133.09(s), 129.75(d), 128.05(d), 96.10(s), 94.93(s), 58.33(t), 21.61(q), -0.66(q).

Found: M^+ , 282.0764, C₁₃H₁₈SO₃Si requires M , 282.0746.

Microanalysis: Found C 55.21% H 6.47%.

C₁₃H₁₈SO₃Si requires C 55.28% H 6.42%.

Addition of (Trimethylsilylmethyl)magnesium Chloride to
1-Toluenesulphonyloxy-3-(trimethylsilyl)prop-2-yne. (224)



A 25ml round bottomed flask, with stirrer bar, containing $\text{Me}_2\text{S} \cdot \text{CuBr}$ (412mg, 2mmol) was flame dried and purged with N_2 . The flask was cooled to -78°C then THF (6ml) and Me_2S (2.54g, 3ml, 41mmol) were added. The cooling bath was removed until all the complex had solubilised and then the -78°C bath was replaced. The Grignard reagent (1M in Et_2O) (4ml, 4mmol) was added dropwise and the cooling bath removed, the reaction mixture stirred at room temperature for 10min and the bath replaced. Then the tosylate (224) (547mg, 2mmol) in THF (4ml) was added dropwise over ca. 2min and the reaction mixture left to stir at -78°C for 1.5h then at 0°C for 1h. The mixture was quenched with 9:1 aqueous NH_4Cl solution:33% aqueous NH_4OH solution (20ml) and the organic layer removed. After re-extraction of the aqueous phases with Et_2O (3x20ml) the combined organic extracts were dried and concentrated in vacuo. Purification of the residue by dry column flash chromatography gave the allene (225) (122mg, 31%), and the alkyne (226) (148.5mg, 37%) as clear oils.

1,2-Bis(trimethylsilyl)buta-2,3-diene.(225)

$\nu_{\max}(\text{CHCl}_3)$ 1920 and 1250 cm^{-1} .

$\delta_{\text{H}}(200\text{MHz})$ 4.27 (2H, t, J 2.9, =CH₂), 1.24 (2H, t, J 2.9, CH₂Si), 0.07 (9H, s, SiMe₃), 0.05 (9H, s, SiMe₃).

$\delta_{\text{C}}(50\text{MHz})$ 208.65(s,=C=), 90.51(s), 68.43(t), 15.95(t), -0.85(q), -1.69(q).

Found: M^+ , 198.1256, C₁₀H₂₂Si₂ requires M , 198.1260.

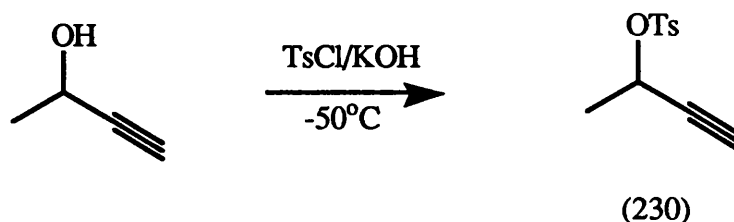
1,4-Bis(trimethylsilyl)but-1-yne.(226)

$\nu_{\max}(\text{CHCl}_3)$ 2172 and 1251 cm^{-1} .

$\delta_{\text{H}}(200\text{MHz})$ 2.24 (2H, t, J 7.9, CH₂C), 0.77 (2H, t, J 7.9, CH₂Si), 0.11 (9H, s, SiMe₃), 0.00 (9H, s, SiMe₃).

$\delta_{\text{C}}(50\text{MHz})$ 109.68(s, CCH₂), 83.54(s, CSi), 15.92(t, CH₂C), 14.43(t, CH₂Si), 0.11(q), -1.61(q).

Found: M^+ , 198.1253, C₁₀H₂₂Si₂ requires M 198.1260.

3-Toluenesulphonyloxybut-1-yne. (230)

Procedure: H.Westmijze and P.Vermeer, *Synthesis*, 1979, 390.

A flame dried flask under N₂ at -50°C was charged with TsCl (2.00g, 10.5mmol) in Et₂O (14ml) and 3-hydroxybut-1-yne (700mg, 10mmol) in Et₂O (3ml). Freshly powdered KOH (3.78g, 67.5mmol) was added and the reaction mixture stirred for 1h at -50°C then at 0°C for 1h. The ethereal suspension was then partitioned between water (20ml) and Et₂O (20ml). The organic layer was removed and the aqueous layer re-extracted with Et₂O (2x15ml). After drying, the combined organic extracts were concentrated in vacuo. Purification of the residue by dry column flash chromatography gave the tosylate as a white crystalline solid (1.95g, 87%), m.p. 52-53°C (pentane).

ν_{\max} (CHCl_3) 3315, 2130 and 1600 cm^{-1} .

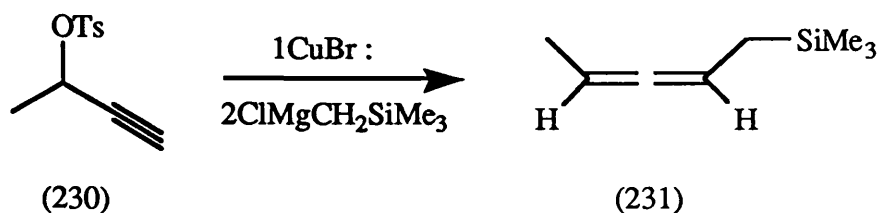
δ_{H} (200MHz) 7.71 (2H, d, J 8.3, ArH), 7.25 (2H, d, J 8.3, ArH), 5.06 (1H, q, J 6.8 and 2.2, CHCH_3), 2.40 (1H, d, J 2.2, CH), 2.35 (3H, s, ArCH₃), 1.45 (3H, d, J 6.8, CH₃).

δ_{C} (50MHz) 144.77(s, ArCS), 133.37(s, ArCCH₃), 129.53(d), 127.67(d), 79.56(d, OCHCH₃), 75.57(s), 67.21(d), 22.25(q), 21.35(q).

Found: M^+ , 224.0508, $\text{C}_{11}\text{H}_{12}\text{SO}_3$ requires M , 224.0507.

Microanalysis: found C 58.90% H 5.26%

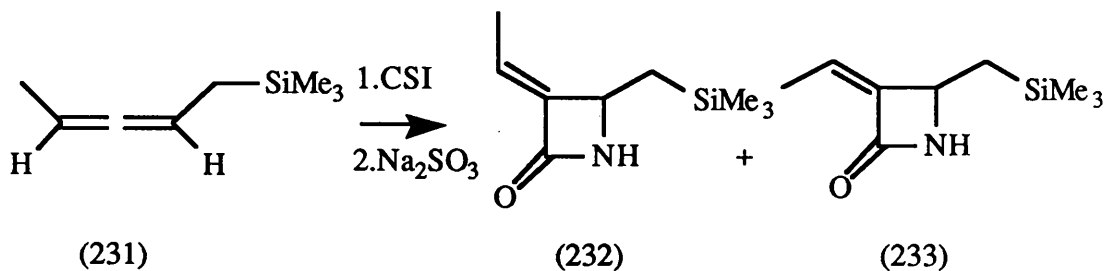
$\text{C}_{11}\text{H}_{12}\text{SO}_3$ requires C 58.91% H 5.39%

1-Trimethylsilylpenta-2,3-diene. (231)

A 25ml round bottomed flask containing a stirrer bar and $\text{Me}_2\text{S}\cdot\text{CuBr}$ (308.4mg, 1.5mmol) was flame dried and purged with N_2 . The flask was cooled to -78°C then THF (4.5ml) and Me_2S (1.90g, 2.25ml, 31mmol) were added. At this point the cooling bath was removed and the mixture left at room temperature until all the complex had dissolved, then re-cooled to -78°C . The Grignard reagent (1M in Et_2O) (3ml, 3mmol) was added and the reaction flask brought to room temperature, stirred for 10min, then re-cooled to -78°C . The tosylate (230) (336.4mg, 1.5mmol) in THF (4ml) was added dropwise and stirring continued for 1h at -78°C followed by 1h at 0°C . The reaction was quenched by the addition of a 9:1 aqueous NH_4Cl solution:33% aqueous NH_4OH solution (10ml), the organic layer was removed and the aqueous layer extracted with Et_2O (2x20ml). The combined organic extracts were dried and concentrated to yield the title compound as a yellow oil. (191.5mg, 91%)

δ_{H} (200MHz) 5.07-4.95 (2H, m, CHCH_3 and CHCH_2), 1.61 (3H, d, J 10.0, CH_3), 1.26 (2H, d, J 10.9, CH_2), 0.01 (9H, s, SiMe_3).

δ_{C} (50MHz) 205.01(s, $=\text{C}=\text{C}$), 86.36(d), 84.65(d), 14.79(q), 8.59(t), -2.11(q).

(E) and (Z)-3-Ethylidene-4-(trimethylsilylmethyl)azetidin-2-one. (232) & (233)

To a flame dried flask, under N₂, at 0°C was added the unpurified (allenylmethyl)silane (231) (191.3mg, 1.36mmol) in CCl₄ (6.8ml). CSI (192.5mg, 118.8μl, 1.36mmol) was then added dropwise. After stirring at 0°C for 1.5h the reaction was quenched by the addition of 25% aqueous Na₂SO₃ (7.5ml) and CCl₄ (7.5ml). The mixture was left to stir overnight, then the CCl₄ layer removed and the aqueous layer re-extracted with CH₂Cl₂ (2x10ml). The organic extracts were combined, dried and concentrated. Purification of the residue by dry column flash chromatography, on neutral alumina yielded the (E) and (Z)-ethylidene β-lactams as a white crystalline solid (16.1mg, 6.5%) in an (E):(Z) ratio of 4:1 m.p. 119-122°C.

ν_{\max} (CHCl_3) 3425 and 1745 cm^{-1} .

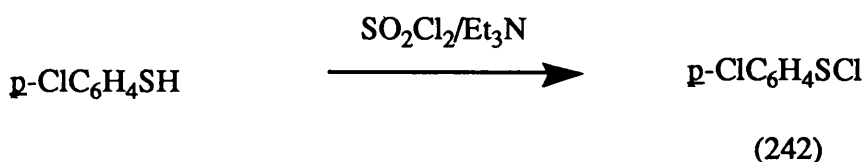
^1H and ^{13}C NMR characterisation refer to the major (E) isomer.

δ_{H} (200MHz) 6.52 (1H, br s, NH), 6.07 (1H, q d, J 7.2 and 1.5, CH), 4.26 (1H, d m, J 10.4, CHN), 1.73 (3H, d d, J 7.2 and 0.6, CH_3), 1.17 (1H, d d, J 14.8 and 3.0, CHHSi), 0.94 (1H, d d, J 14.8 and 10.4, CHHSi), 0.04 (9H, s, SiMe_3).

δ_{C} (50MHz) 164.56(s), 145.58(s), 121.67(d), 53.80(d), 22.10(t), 13.35(q), -0.88(q).

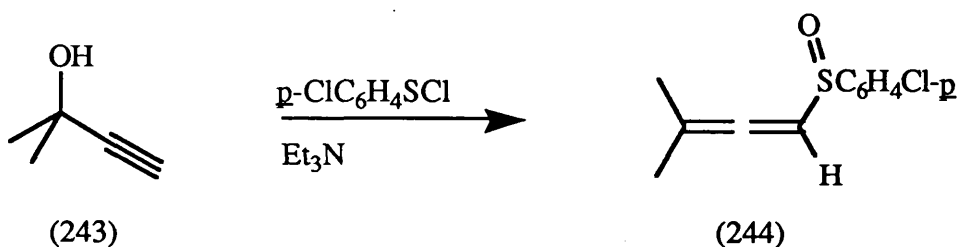
Found: M^+ , 183.1064, $\text{C}_9\text{H}_{17}\text{NOSi}$ requires M , 183.1079.

p-Chlorophenylsulphenyl chloride. (242)



Procedure: D.N.Harpp, B.T.Friedlander and R.A.Smith, *Synthesis*, 1979, 181.

A flame dried flask under N_2 was charged with 4-chlorothiophenol (1.45g, 10mmol) in CCl_4 (18ml). To this was added triethylamine (2 drops) and the flask cooled to 0°C . Sulphuryl chloride (1.48g, 0.88ml, 11mmol) was then added dropwise and the mixture stirred at 0°C for 30min. Solvent was removed in vacuo and the sulphenyl chloride distilled as an orange oil. (1.2g, 66%) b.p. $115^\circ\text{C}/7\text{mmHg}$. (b.p. $85-90^\circ\text{C}/5\text{mmHg}$).

1-(4-Chlorophenylsulphinyl)-3-methylbuta-1,2-diene. (244)

Procedure: L.Horner and V.Binder, *Liebigs Ann. Chem.*, 1972, **757**, 33.

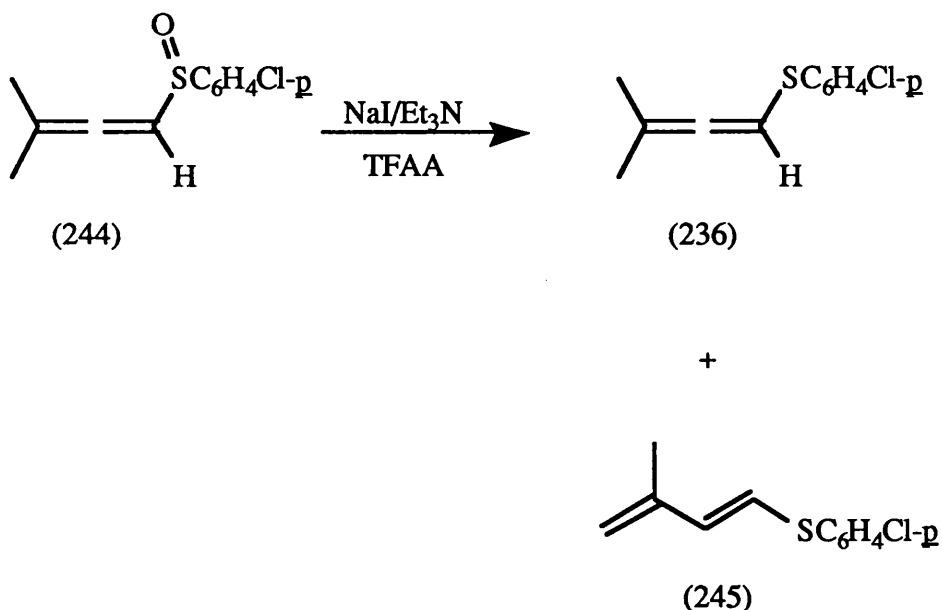
A flame dried flask under N_2 was charged with alcohol (243) (564mg, 0.79ml, 6.71mmol) in Et_2O (10ml) along with triethylamine (764mg, 1.03ml, 7.56mmol) and the flask cooled to $-78^\circ C$. Sulphenyl chloride (242) (1.2g, 6.71mmol) in Et_2O (5ml) was added dropwise, the reaction mixture left to stir, at $-78^\circ C$, for 2h and then allowed to warm to room temperature. At this stage the reaction mixture was washed with water (20ml) the organic layer removed and the aqueous phase extracted with Et_2O (2x15ml). The combined organic extracts were washed with HCl (1M, 30ml), aqueous Na_2CO_3 solution (10ml) and dried. After concentration and purification of the residual oil by dry column flash chromatography, the allene was isolated as a white solid. (222mg, 15%).

ν_{max} ($CHCl_3$) 1955 cm^{-1} .

δ_H (200MHz) 7.55-7.30 (4H, m, Ar), 5.81 (1H, septet, J 2.7, CH), 1.73 (3H, d, J 2.7, CH_3), 1.70 (3H, d, J 2.7, CH_3).

δ_C (50MHz) 201.66(s, =C=), 143.39(s), 136.67(s), 129.12(d), 125.41(d), 104.95(s, $C(CH_3)_2$), 100.25(d), 19.82(q), 19.66(q).

Found: M^+ , 226.0220 (^{35}Cl), $C_{11}H_{11}SOCl$ requires M , 226.0219 (^{35}Cl).

Reduction of 1-(4-Chlorophenylsulphinyl)-3-methylbuta-1,2-diene (244).

Procedure: J.D.Buynak and M.Narayana Rao, *J. Org. Chem.*, 1986, **51**, 1571.

A 15ml round bottomed flask containing NaI (339mg, 2.27mmol) was flame dried and purged with N₂. To this was added allene (244) (200mg, 0.88mmol) in acetone (5ml) and the flask cooled to -55°C. Triethylamine (405mg, 0.56ml, 4mmol) was added followed by the dropwise addition of TFAA (515mg, 0.35ml, 2.45mmol). After vigorous stirring and warming to -30°C over 15min the reaction mixture was transferred to a separating funnel containing pentane (10ml), aqueous 5% Na₂SO₃ solution (8ml) and aqueous 5% NaHCO₃ solution (5ml). This mixture was shaken for one minute, the organic layer removed and the aqueous phase re-extracted with pentane (2x10ml). The combined organic extracts were dried and concentrated and the residue purified by dry column flash chromatography to yield the thioallene as a clear oil. (143mg, 77%).

Note: This product upon closer examination, contained diene in addition to allene.

1-(4-Chlorophenylthio)-3-methylbuta-1,2-diene. (236)

ν_{\max} (CHCl₃) 1950 cm⁻¹.

δ_{H} (200MHz) 7.35-7.25 (4H, m, Ar), 5.78 (1H, septet, *J* 2.6, CH), 1.76 (6H, d, *J* 2.6, CH₃)

δ_{C} (50MHz) 203.27(s, =C=), 134.78(s), 132.01(s), 130.29(d), 128.86(d), 101.01(s, C(CH₃)₂), 83.57(d), 20.30(q).

Found: M^+ , 210.0244 (³⁵Cl), C₁₁H₁₁SCl requires M , 210.0270 (³⁵Cl).

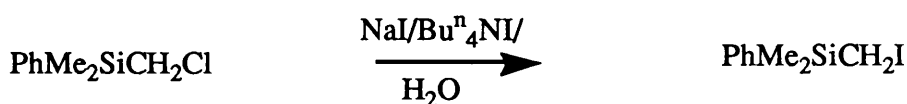
1-(4-Chlorophenylthio)-3-methylbuta-1,3-diene. (245)

ν_{\max} (CHCl₃) 3030, 1680 and 1478 cm⁻¹.

δ_{H} (200MHz) 7.29 (4H, s, ArH), 6.48 (1H, d, *J* 15.5, CHS), 6.27 (1H, d, *J* 15.5, CHC), 5.00-4.91 (2H, m, CH₂), 1.87 (3H, br s, CH₃).

δ_{C} (50MHz) 140.72(s), 135.52(d), 134.60(s), 133.82(s), 130.98(d), 129.25(d), 122.44(d), 116.71(t), 18.50(q).

Found: M^+ , 210.0252 (³⁵Cl), C₁₁H₁₁SCl requires M , 210.0270 (³⁵Cl).

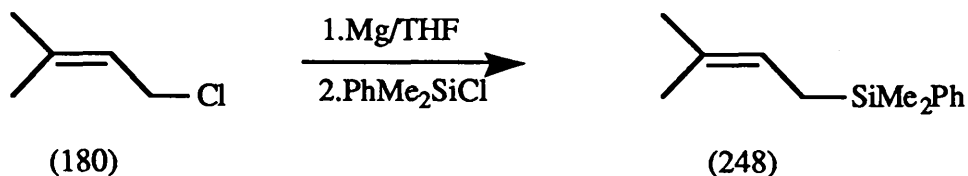
(Phenyldimethylsilyl)methyl iodide.

Procedure: S.Ambasht, S.K.Chiu, P.E.Peterson and J.Queen, *Synthesis*, 1980, 318.

A 10ml round bottomed flask was charged with (phenyldimethylsilyl)methyl chloride (1g, 5.4mmol), NaI (1.613g, 10.8mmol), tetrabutylammonium iodide (399mg, 1.08mmol) and water (2ml). The mixture was heated at reflux for 2.5h then cooled to room temperature. The liquid phase was decanted into a separating funnel and the solid residue washed with water (3x3ml) and pentane (3x3ml). All the liquids were combined and shaken. The organic layer was removed and the aqueous phase re-extracted with pentane (2x5ml). The combined organic extracts were dried and concentrated in vacuo. The residue was purified by distillation to yield the iodosilane as a clear oil (1.03g, 69%), b.p. 100°C/20mmHg. (b.p. 139.5°C/760mmHg).

δ_{H} (200MHz) 7.58-7.53 (2H, m, ArH), 7.42-7.38 (3H, m, ArH), 2.20 (2H, s, CH₂I), 0.46 (6H,s, SiMe₂).

δ_{C} (50MHz) 136.73, 133.62, 129.57, 127.93, -2.93, -7.20.

1-Phenyldimethylsilyl-3-methylbut-2-ene.(248)

Procedure: J.Dubac, A.Laporterie, H.Illoughmane, J.P.Pillot, G.Déléris, and J. Dunoguès. (adapted), *J. Organomet. Chem.*, 1985, **281**, 149.

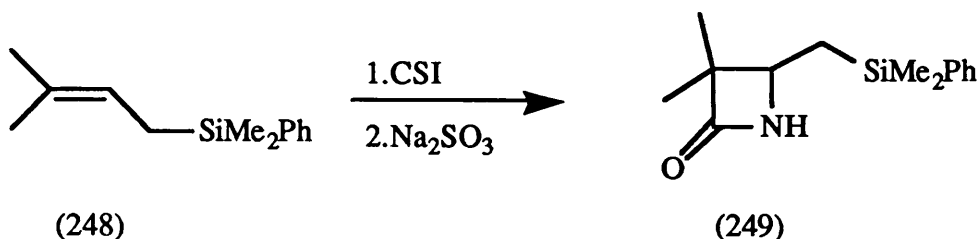
A 50ml round bottomed flask equipped with a condenser and stirrer bar containing Mg (1.24g, 51mmol) was flame dried and purged with N₂. To this was added THF (5ml) followed by 6 drops of the neat allyl chloride (180). The Grignard reaction commenced immediately and the reaction flask was plunged into ice. THF (9ml) was added followed by the rest of the allyl chloride (1.78g, 17.0mmol) in THF (10.5ml) over 2h. The reaction mixture was allowed to warm to room temperature over 1h, then re-cooled to 0°C and PhMe₂SiCl (2.90g, 17.0mmol) added dropwise. After stirring overnight at ambient temperature the reaction mixture was concentrated to half volume in vacuo and the organic supernatant transferred to a separating funnel. This was diluted with pentane (30ml) and washed with aqueous NH₄Cl solution (30ml) then water (2x30ml). The organic solution was dried, concentrated and the residue distilled to yield the allylsilane as a clear oil (2.83g, 81.4%), b.p. 58°C/0.15mmHg. (115°C/15mmHg).

ν_{\max} 3080, 3020 and 1250 cm^{-1} .

δ_{H} (200MHz) 7.65-7.30 (5H, m, Ph), 5.19 (1H, t sep, J 8.4 and 1.5, CH),
1.71 (3H, br s, CH_3), 1.65 (2H, d m, J 8.4 and unassigned, CH_2), 1.52 (3H,
br s, CH_3), 0.29 (6H, s, SiMe_2Ph).

δ_{C} (50MHz) 139.30(s, ArC), 133.55(d), 129.52(s, $\text{C}(\text{CH}_3)_2$), 128.82(d),
127.64 (d), 119.29(d, =CH), 25.77(q), 17.66(t), 17.57(q), -3.25(q).

Found: M^+ , 204.1340, $\text{C}_{13}\text{H}_{20}\text{Si}$ requires M , 204.1334

3,3-Dimethyl-4-(phenyldimethylsilylmethyl)azetidin-2-one. (249)

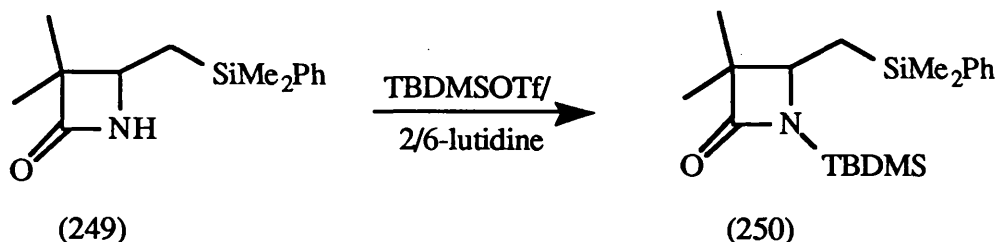
A flame dried flask under N₂ was charged with allylsilane (248) (388.7mg, 1.90mmol) in CCl₄ (9.1ml) and the flask cooled to 0°C. CSI (269mg, 166 μ l, 1.90mmol) was added dropwise and the reaction mixture left to stir at 0°C for 2h then at room temperature for 4.5h. The reaction was quenched by the addition of 25% aqueous Na₂SO₃ solution (18ml) and CCl₄ (9ml). After stirring overnight the CCl₄ layer was removed and the aqueous phase re-extracted with CH₂Cl₂ (2x10ml). The combined organic extracts were dried, concentrated and the residue purified by dry column flash chromatography to yield the β -lactam as a yellow oil. (208.5mg, 44%).

ν_{\max} (CHCl₃) 3401 and 1749 cm⁻¹.

δ_{H} (200MHz) 7.55-7.47 and 7.38-7.32 (5H, m, Ph), 5.53 (1H, br s, NH), 3.39 (1H, d d, *J* 9.6 and 4.8, CHN), 1.20 (3H, s, CH₃), 1.08 (3H, s, CH₃) 1.00 (2H, m, CH₂), 0.35 (3H, s, SiMeMePh), 0.33 (3H, s, SiMeMePh).

δ_{C} (50MHz) 174.79(s), 137.75(s), 133.36(d), 129.48(d), 128.12(d), 57.58(d, CHN), 54.47(s, CCO), 22.04(q), 18.39(t), 17.03(q), -2.51(q), -3.20(q).

N-t-Butyldimethylsilyl-3,3-dimethyl-4-(phenyldimethylsilylmethyl)-azetidin-2-one. (250)



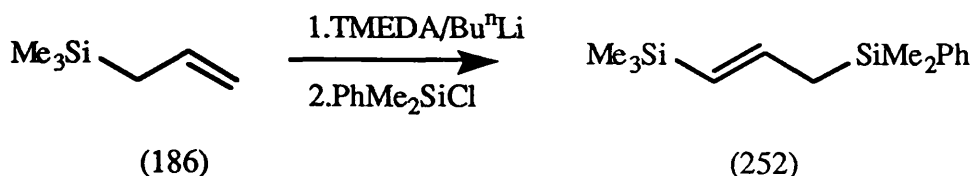
To a flame dried flask, under N_2 , was added β -lactam (249) (31.9mg, 0.13mmol) in CH_2Cl_2 (2.2ml), the 2,6-lutidine (28mg, 30 μ l, 0.26mmol) and finally TBDMSOTf (0.22M in CH_2Cl_2) (0.70ml, 0.15mmol). The reaction mixture was stirred overnight, then diluted with Et_2O (20ml) and washed with saturated aqueous $CuSO_4$ solution (20ml), water (20ml) and finally brine (20ml). The organic solution was dried, concentrated and the residue purified by dry column flash chromatography to yield the protected β -lactam as a clear oil. (38mg, 81.5%).

ν_{max} ($CHCl_3$) 1721 cm^{-1} .

δ_H (200MHz) 7.51-7.46 and 7.38-7.25 (5H, m, Ph), 3.42 (1H, d d, J 7.5 and 6.9, CHN), 1.20 (2H, m, CH_2), 1.08 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.91 (9H, s, Bu^t), 0.34 (3H, s, $SiMe_2Ph$), 0.33 (3H, s, $SiMe_2Ph$), 0.17 (6H, s, $SiMe_2Bu^t$).

δ_C (50MHz) 179.77(s), 137.91(s), 133.53(d), 129.37(d), 127.95(d), 59.73(d, CHN), 53.15(s), 26.28(q, Bu^t), 22.86(q, CH_3), 19.79(t), 18.24(s, Bu^t), 17.53(q, CH_3), -2.29(q, $SiMe_2Ph$), -2.51(q, $SiMe_2Ph$), -5.12(q, $SiMe_2Bu^t$), -5.52(q, $SiMe_2Bu^t$).

Found: M^+ , 361.2248, $C_{20}H_{35}NOSi_2$ requires M , 361.2257.

Trans-3-phenyldimethylsilyl-1-(trimethylsilyl)prop-1-ene. (252)

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

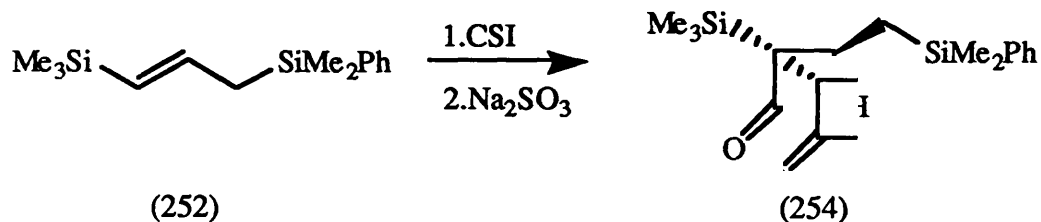
To a flame dried flask, under N₂, at -5°C was added TMEDA (2.70g, 3.5ml, 23mmol) and BuⁿLi (1.93M in hexanes) (11.9ml, 23mmol) then allyltrimethylsilane (186) (2.29g, 3.18ml, 20mmol). After stirring for 3.5h PhMe₂SiCl (3.584g, 21mmol) was added dropwise and the mixture stirred for a further 1h at -5°C, then quenched with aqueous HCl (1M, 20ml) and hexane (20ml). The organic layer was removed and the aqueous layer re-extracted with hexane (20ml). The combined organic extracts were washed with HCl (1M, 20ml) then water (20ml) and the aqueous phases re-extracted with hexane (20ml). Following drying and concentration of the combined organic extracts, distillation of the residue gave the title compound as a clear oil (3.57g, 72%), b.p. 70°C/0.35mmHg. (b.p. 76-80°C/0.4mmHg).

ν_{\max} (CHCl₃) 1602 and 1250 cm⁻¹.

δ_{H} (200MHz) 7.3-7.6 (5H, m, Ph), 6.02 (1H, d t, *J* 18.4 and 7.7, CHCH₂),
5.48 (1H, d t, *J* 18.4 and 1.0, CHSi), 1.89 (2H, d d, *J* 7.7 and 1.0, CH₂), 0.32
(6H, s, SiMe₂Ph), 0.06 (9H, s, SiMe₃).

δ_{C} (50MHz) 146.00(d, CHCH₂), 142.94(d, CHSi), 138.61(s), 133.65(d),
128.97(d), 127.67(d), 27.39(t), -1.04(q, SiMe₂Ph), -3.51(q, SiMe₃).

Found: M^+ , 248.1412, C₁₄H₂₄Si₂ requires M , 248.1416

Trans-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)azetid-2-one. (254)

A flame dried flask under N_2 at 0°C was charged with the allyl/vinyldisilane (252) (652.6mg, 2.63mmol) in CCl_4 (12ml). CSI (372mg, 229 μl , 2.63mmol) was then added dropwise via syringe and the reaction mixture stirred for 2.5h, at which stage 25% aqueous Na_2SO_3 solution (24ml) and CCl_4 (12ml) were added. After stirring overnight the CCl_4 layer was removed and the aqueous layer re-extracted with CH_2Cl_2 (2x20ml). After drying the combined organic extracts were concentrated. Purification of the residue by dry column flash chromatography gave the β -lactam as a white crystalline solid (422.8mg, 55%), m.p. $118\text{-}120^\circ\text{C}$ (sublimed).

ν_{\max} (CHCl_3) 3402, 1735 and 1251 cm^{-1} .

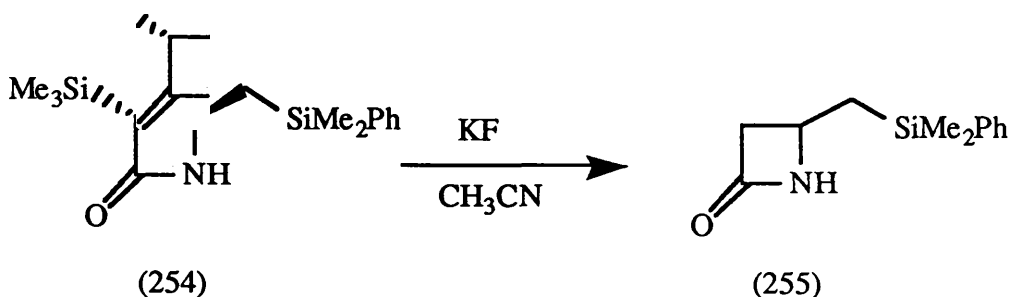
δ_{H} (200MHz) 7.51-7.30 (5H, m, Ph), 5.60 (1H, br s, NH), 3.50 (1H, d d d, J 7.6, 6.4 and 2.2, CHN), 2.37 (1H, d, J 2.2, CHCO), 1.28 (1H, d d, J 14.6 and 7.6, CHH), 1.20 (1H, d d, J 14.6 and 6.4, CHH), 0.32 (3H, s, SiMeMePh), 0.31 (3H, s, SiMeMePh), 0.05 (9H, s, SiMe_3).

δ_{C} (50MHz) 170.33(s), 137.66(s), 133.38(d), 129.39(d), 128.05(d), 51.99(d, CHN), 47.22(d, CHCO), 24.70(t), -2.54(q, SiMe_2Ph), -2.85(q, SiMe_3).

Found: M^+ , 291.1459, $\text{C}_{15}\text{H}_{25}\text{NOSi}_2$ requires M , 291.1475

Microanalysis: Found C 61.74% H 8.53% N 4.71%

$\text{C}_{15}\text{H}_{25}\text{NOSi}_2$ requires C 61.79% H 8.64% N 4.80%

4-(Phenyldimethylsilylmethyl)azetidin-2-one. (255)

Procedure: H.Fritz, P.Sutter and C.D.Weis, *J. Org. Chem.*, 1986, **51**, 558.

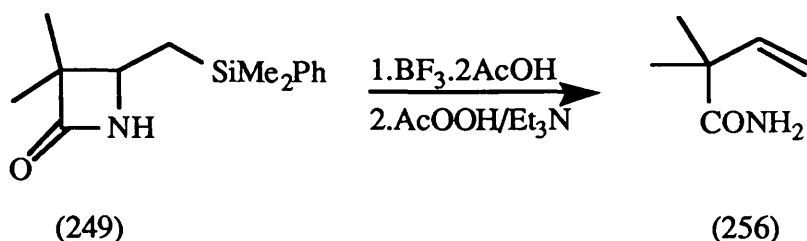
A 50ml round bottomed flask was charged with β -lactam (254) (147.8mg, 0.51mmol) in CH_3CN (15ml) along with KF (140mg, 2.40mmol). The reaction mixture was stirred at room temperature for 3 days then filtered through Celite. Concentration and purification of the residue by dry column flash chromatography yielded the β -lactam as a clear oil. (112mg, 100%).

ν_{max} (CHCl_3) 3415 and 1750 cm^{-1} .

δ_{H} (200MHz) 7.51-7.30 (5H, m, Ph), 5.74 (1H, br s, NH), 3.72 (1H, d d d d, J 8.0, 6.6, 4.9 and 2.4, CHN), 2.98 (1H, d d d, J 14.8, 4.9 and 2.1, CHHCO), 2.42 (1H, d d d, J 14.8, 2.4 and 1.3, CHHCO), 1.30 (1H, d d, J 14.4 and 6.6, CHHSi), 1.15(1H, d d, J 14.4 and 8.0, CHHSi), 0.33 (3H, s, SiMeMePh), 0.32 (3H, s, SiMeMePh).

δ_{C} (50MHz) 167.70(s), 137.50(s), 133.38(d), 129.47(d), 128.09(d), 45.89(t, CH_2CO), 45.69(d), 23.74(t), -2.71(q), -3.05(q).

Found: M^+ , 219.1078, $\text{C}_{12}\text{H}_{17}\text{NOSi}$ requires M , 219.1079.

Attempted Oxidative Cleavage of β -Lactam (249)

A flame dried flask under N_2 was charged with β -lactam (249) (85.2mg, 0.344mmol) in CH_2Cl_2 (1ml). To this was added $\text{BF}_3 \cdot 2\text{AcOH}$ (64.6mg, 48 μl , 0.344mmol) and the reaction mixture stirred at room temperature for 2h. THF (1ml), triethylamine (175mg, 240 μl , 1.72mmol) and peracetic acid (802mg, 0.71ml, 3.38mmol) were then added dropwise. After stirring at room temperature for 2h the solution was diluted with Et_2O (25ml) and freshly powdered $\text{Na}_2\text{S}_2\text{O}_5$ (2.2g, 11.58mmol) added. The mixture was stirred for 30min, filtered through Celite and concentrated in vacuo. The unsaturated amide was purified by dry column flash chromatography and isolated as a white solid. (18.7mg, 48%). m.p. 86-88 $^\circ\text{C}$. (m.p. 93 $^\circ\text{C}$). Note:- starting material (33.2mg, 39%) was also recovered.

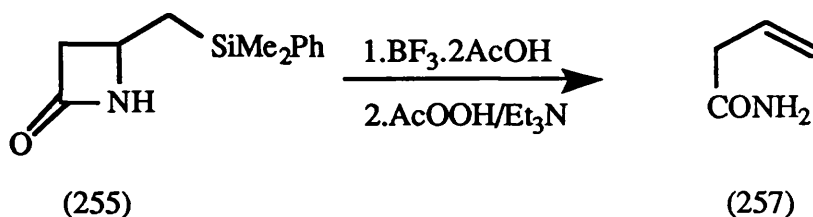
2,2-Dimethylbut-3-enamide. (256)

ν_{max} (CHCl_3) 3522, 3410, 1750(w), 1679, 1635 and 1575 cm^{-1} .

δ_{H} (200MHz) 6.30-5.50 (2H, br s, NH_2), 6.02 (1H, d d, J 17.5 and 10.6, CH), 5.22 (1H, d d, J 17.5 and 1.0, CHH), 5.19 (1H, d d, J 10.6 and 1.0, CHH), 1.29 (6H, s, CH_3).

δ_{C} (50MHz) 179.37(s), 143.10(d), 111.43(t), 45.09(s), 24.62(q).

Found: M^+ , 113.0842, $\text{C}_6\text{H}_{11}\text{NO}$ requires M , 113.0841.

Attempted Oxidative Cleavage Of β -Lactam (255).

To a flame dried flask, under N₂, was added β -lactam (255) (134.7mg, 0.61mmol) in CH₂Cl₂ (1.4ml). BF₃·2AcOH (115mg, 85 μ l, 0.61mmol) was then added dropwise. After stirring for 2h at room temperature the flask contents were diluted with CH₂Cl₂ (5ml) and concentrated in vacuo.

To a separate flame dried flask, under N₂, was added the product from the first stage in THF (0.75ml) and MeOH (0.75ml) followed by triethylamine (309mg, 425 μ l, 3.05mmol) and peracetic acid (473mg, 419 μ l, 1.99mmol). After stirring at room temperature for 2h the reaction mixture was diluted with Et₂O (20ml) and freshly powdered Na₂S₂O₅ (2g, 10.5mmol) added. After stirring for 30min the mixture was filtered through Celite and concentrated in vacuo. The amide was isolated after dry column flash chromatography of the residue as a white solid (36.5mg, 70%). m.p. 65-67°C. (m.p. 72-73°C).

↑
Literature

But-3-enamide. (257)

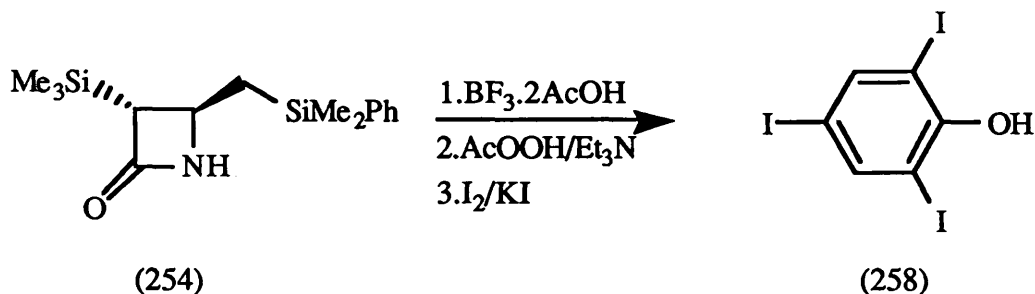
ν_{\max} (CHCl₃) 3235, 3410, 1681, 1640 and 1587 cm⁻¹.

δ_{H} (200MHz) 6.30-5.60 (2H, 2x br s, NH₂), 5.91 (1H, d d t, *J* 17.9, 9.4 and 7.1, =CH), 5.20 (2H, m, =CH₂), 2.99 (2H, d t, *J* 7.1 and 1.2, CH₂CO).

δ_{C} (50MHz) 173.67(s), 131.07(d), 119.71(t), 40.91(t).

Found: *M*⁺, 85.0526, C₄H₇NO requires *M*, 85.0528

Attempted Oxidative Cleavage of Trans-3-trimethylsilyl-4-(phenyldimethylsilyl-methyl)azetidinone (254).



Iodination procedure: J.Wilkie, *J. Chem. Ind. (Chem. Ind. (London))*, 1911, 30, 398.

To a flame dried flask, under N_2 , was added the β -lactam (254) (117.9mg, 0.404mmol) in CH_2Cl_2 (1.05ml) and $\text{BF}_3 \cdot 2\text{AcOH}$ (76mg, 56 μl , 0.404mmol). After stirring at room temperature for 2h, THF (1ml), triethylamine (204mg, 281 μl , 2.02mmol) and peracetic acid (949mg, 0.84ml, 4.0mmol) were added. The reaction mixture was stirred at room temperature for 2h, then diluted with Et_2O (25ml) and freshly powdered $\text{Na}_2\text{S}_2\text{O}_5$ (2.2g, 11.58mmol) added. The mixture was stirred for 30min then filtered through Celite and concentrated in vacuo. At this point the residual solid was taken up in water (19ml) and mixed with aqueous 0.27M Na_2CO_3 solution (19ml). This was then added to an aqueous I_2 (0.48g, 1.9mmol) solution in water (19ml). (The I_2 had been solubilised by the addition of KI, 5mol%). After 5min sulphuric acid (1M) was added until the solution became acidic. The excess iodine was removed by the addition of aqueous Na_2SO_3 (1M, 5ml):HCl (1M, 5ml) solution. After extraction with Et_2O (2x40ml) the organic extract was washed with water (40ml), dried and concentrated then the residue purified by dry column flash chromatography to furnish iodophenol as a yellow solid. (84.7mg, 45%), m.p. 158 $^\circ\text{C}$. (m.p. 156 $^\circ\text{C}$).
 Note:- starting material was also recovered (30mg, 27%).

Literature

2,4,6-Triiodophenol. (258)

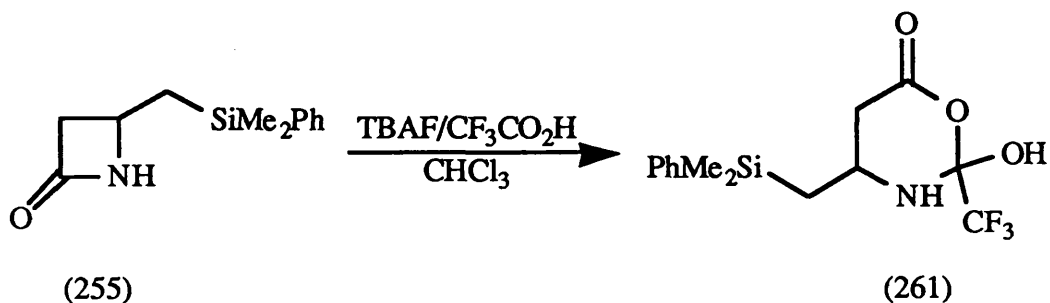
ν_{\max} (CHCl₃) 3480(br), 3020(br) and 1440 cm⁻¹.

δ_{H} (200MHz) 7.92 (2H, s, ArCH), 5.78 (1H, br s, OH).

δ_{C} (50MHz) 153.76(s), 146.39(d), 83.39(s), 83.35(s).

Found: M^+ , 471.7311, C₆H₃I₃O requires M , 471.7314.

2-Trifluoromethyl-2-hydroxy-3-oxa-4-keto-6(phenyldimethylsilyl-
methyl)piperidine. (261)



To a flame dried flask, under N_2 , equipped with a condenser was added β -lactam (255) (48.6mg, 0.22mmol) in CHCl_3 (3ml) along with TBAF.3 H_2O (139mg, 0.44mmol). To this was added $\text{CF}_3\text{CO}_2\text{H}$ (76.5mg, 51 μl , 0.66mmol) and the reaction flask placed in an oil bath at 55 $^\circ\text{C}$ for 32h. At this point more $\text{CF}_3\text{CO}_2\text{H}$ (151.2mg, 102 μl , 1.32mmol) was added and the reaction mixture heated at 55 $^\circ\text{C}$ for a further 20h. The solution was then concentrated in vacuo and the residue purified by dry column flash chromatography to yield the piperidine (43.6mg, 60.0%) as a clear oil.

ν_{\max} (CHCl₃) 3680, 3500, 3420 and 1720 cm⁻¹.

δ_{H} (200MHz) 8.20 (1H, br s, OH), 7.50-7.30 (5H, m, Ph), 6.79 (1H, br d, NH), 4.40 (1H, m, CHN), 2.65 (1H, d d, *J* 16.7 and 5.0, CH₂HCO), 2.52 (1H, d d, *J* 16.7 and 4.8, CH₂HCO), 1.32 (1H, d d, *J* 14.9 and 8.9, CH₂HSi), 1.19 (1H, d d, *J* 14.9 and 6.4, CH₂HSi), 0.35 (3H, s, SiMeMePh), 0.34 (3H, s, SiMeMePh).

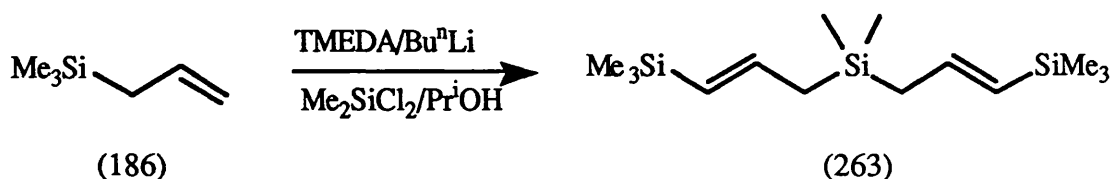
¹H NMR Decoupling Experiments

- 1) Irradiation at 1.32 ppm causes collapse to an ABX system at 4.40 ppm.
- 2) Irradiation at 2.52 ppm causes collapse to an ABX system at 4.40 ppm.
- 3) Irradiation at 4.40 ppm causes ABX system at 2.52 ppm to collapse to an AB system.
- 4) Irradiation at 4.40 ppm causes ABX system at 1.32 ppm to collapse to an AB system.
- 5) Irradiation at 4.40 ppm causes NH doublet to collapse to br singlet.

δ_{C} (50MHz) 176.47(s), 156.05(q, ²*J*_{CF} 37.1, CCF₃), 137.30(s), 133.34(d), 129.54 (d), 128.19(d), 115.50(q, ¹*J*_{CF} 287.9, CF₃), 44.24(d), 40.13(t, CH₂CO), 21.66(t, CH₂Si), -2.78(q, SiMeMePh), -3.17(q, SiMeMePh).

δ_{F} (188.3MHz) -76.75 (s), ref. CFCl₃ at 0.0ppm.

Found: *m/z* 318.0777, C₁₄H₁₈NO₃SiF₃-CH₃ requires 318.0773.

Bis(3-(trimethylsilyl)prop-2-enyl)dimethylsilane. (263)

A flame dried flask under N_2 at -5°C was charged with TMEDA (1.35g, 1.75ml, 11.6mmol), Bu^nLi (2.4M in hexanes) (4.68ml, 11.25mmol) and finally allyltrimethylsilane (186) (1.14g, 1.59ml, 10mmol) and the mixture stirred for 3.25h. A separate flame dried flask under N_2 at -5°C was charged with TMEDA (1.35g, 1.75ml, 11.6mmol) and Me_2SiCl_2 (1.355g, 1.27ml, 10.5mmol). To this was added, dropwise, the organometallic generated earlier and the mixture left to stir at -5°C for 1h. Isopropanol (661mg, 0.85ml, 11mmol) was added and the reaction left to stir overnight. Work-up consisted of dilution with pentane (20ml) and washing with saturated aqueous CuSO_4 solution (20ml) then water (20ml). The aqueous layer was re-extracted with pentane (2x10ml) and the combined organic extracts dried and concentrated in vacuo to yield 2.42g of crude material. ^1H NMR analysis indicated that a 1:1 mixture of the title compound and (diisopropoxy)dimethylsilane had been obtained. A small sample of the title compound was purified, for characterisation, by dry column flash chromatography.

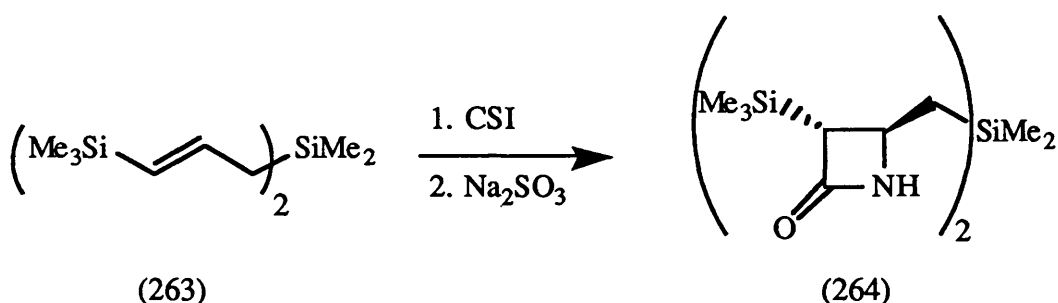
ν_{\max} (CHCl₃) 3020, 1604 and 1250 cm⁻¹.

δ_{H} (200MHz) 6.01 (2H, d t, J 18.4 and 7.8, $\underline{\text{C}}\text{HCH}_2$), 5.44 (2H, d t, J 18.4 and 1.2, CHSi), 1.64 (4H, d d, J 7.8 and 1.2, CH₂), 0.38 (18H, s, 2xSiMe₃), -0.19 (6H, s, SiMe₂).

δ_{C} (50MHz) 143.07(d, $\underline{\text{C}}\text{HCH}_2$), 128.66(d, CHSi), 26.46(t), -0.98(q, SiMe₃), -4.00 (q, SiMe₂).

Found: M^+ , 284.1815, C₁₄H₃₂Si₃ requires M , 284.1812.

Addition of CSI to Bis(3-(trimethylsilyl)prop-2-enyl)dimethylsilane. (263)



A flame dried flask under N_2 was charged with allylsilane (263) (225mg, 0.79mmol) in CCl_4 (4ml) and cooled to 0°C . CSI (225mg, 139 μl , 1.59mmol) was then added dropwise and the mixture stirred for 1h. The reaction was then quenched by the addition of 25% aqueous Na_2SO_3 solution (8ml) and CCl_4 (8ml). After stirring for 1h and standing for a further 3h the organic layer was removed and the aqueous layer re-extracted with CH_2Cl_2 (2x20ml). The combined organic extracts were dried, concentrated and the residue purified by dry column flash chromatography to yield the bis- β -lactam (264) (59mg, 21%) as a clear oil.

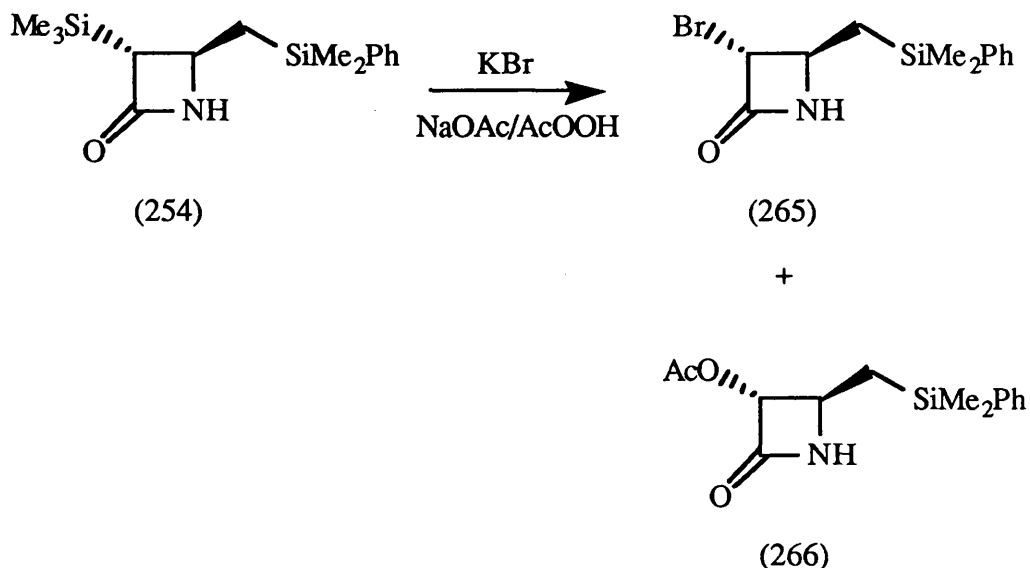
ν_{max} (CHCl_3) 3410, 1736 and 1255 cm^{-1} .

δ_{H} (200MHz) 6.65 (1H, br s, NH), 6.46 (1H, br s, NH), 3.50 (2H, m, CHN), 2.38 (2H, m, CHSi), 1.2-0.9 (4H, m, CH_2), 0.98 (9H, s, SiMe_3), 0.10 (9H, s, SiMe_3), 0.08 (3H, s, SiMe_2), 0.07 (3H, s, SiMe_2).

δ_{C} (50MHz) 170.54(s), 170.42(s), 52.10(d, CHN), 47.24(d, CHSi), 24.58(t), 24.37(t), -2.34(q, SiMe_2), -2.68(q, SiMe_3).

Found: m/z 355.1682, $\text{C}_{16}\text{H}_{34}\text{N}_2\text{O}_2\text{Si}_3-\text{CH}_3$ requires 355.1693.

Attempted Oxidative Cleavage of Trans-3-trimethylsilyl-4-(phenyldimethylsilyl)-methyl)azetidin-2-one (254)



Oxidative Procedure: I.Fleming and P.E.J.Sanderson, *Tetrahedron Lett.*, 1987, 28, 4229.

To a flame dried flask, under N₂, was added β-lactam (254) (219.2mg, 0.75mmol) in glacial acetic acid (1.90ml) along with KBr (107mg, 0.90ml) and NaOAc (191mg, 2.33mmol). Peracetic acid (1.096g, 0.97ml, 4.59mmol) was then added dropwise with the reaction flask being cooled, intermittently, to 0°C. More NaOAc (574mg, 7.0mmol) and peracetic acid (3.288g, 2.91ml, 13.77mol) were then added and the reaction mixture left to stir overnight at room temperature. After stirring at 35°C for 1h the flask contents were diluted with Et₂O (76ml), freshly powdered Na₂S₂O₅ (7.6g, 40mmol) was added and the mixture stirred vigorously for 30min. The ethereal suspension was then filtered through Celite and the filtrate concentrated *in vacuo*. The solid residue was taken up in CHCl₃ (10ml) and washed with water (10ml). After re-extraction of the aqueous phase with CHCl₃ (10ml) the combined organic extracts were dried and concentrated. Purification of the residue by dry column flash chromatography yielded the 3-bromo β-lactam (265) (70.4mg, 32%) and the 3-acetoxy β-lactam (266) (42.6mg, 21%) as clear oils.

Trans-3-bromo-4-(phenyldimethylsilylmethyl)azetidin-2-one.(265)

ν_{\max} (CHCl₃) 3410 and 1773 cm⁻¹.

δ_{H} (200MHz) 7.53-7.35 (5H, m, Ph), 6.13 (1H, br s, NH), 4.18 (1H, d d, *J* 2.4 and 1.8, CHCO), 3.81 (1H, d d d, *J* 7.9, 7.2 and 1.8, CHN), 1.29 (1H, d d, *J* 14.4 and 7.2, CHHSi), 1.22 (1H, d d, *J* 14.4 and 7.9, CHHSi), 0.40 (3H, s, SiMeMePh), 0.39 (3H, s, SiMeMePh).

δ_{C} (50MHz) 163.71(s), 136.81(s), 133.42(d), 129.72(d), 128.22(d), 58.21(d, CHCO), 49.67(d, CHN), 22.95(t), -2.85(q), -3.09(q).

Found: M^+ , 297.0201 (⁷⁹Br), C₁₂H₁₆NOSiBr requires M , 297.0185 (⁷⁹Br).

Trans-3-acetoxy-4-(phenyldimethylsilylmethyl)azetidin-2-one.(266)

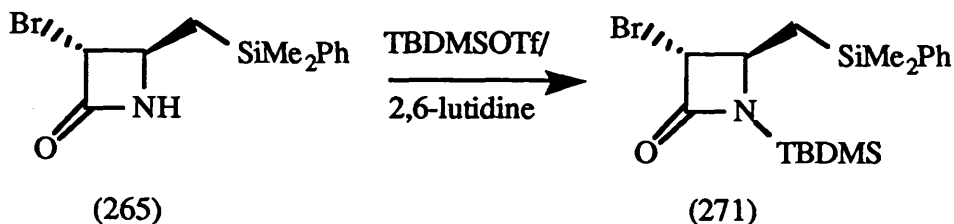
ν_{\max} (CHCl₃) 3405, 1775 and 1750 cm⁻¹.

δ_{H} (200MHz) 7.40-7.36 (5H, m, Ph), 5.66 (1H, br s, NH), 5.07 (1H, t, *J* 1.7, CHOAc), 3.64 (1H, d d d, *J* 9.5, 5.0 and 1.7, CHN), 2.09 (3H, s, CH₃CO), 1.45 (1H, d d, *J* 14.6 and 5.0, CHHSi), 1.18 (1H, d d, *J* 14.6 and 9.5, CHHSi), 0.35 (3H, s, SiMeMePh), 0.33 (3H, s, SiMeMePh).

δ_{C} (50MHz) 169.74(s), 164.56(s), 137.14(s), 133.37(d), 129.70(d), 128.26(d), 82.68(d, CHO), 55.21(d, CHN), 21.42(t), 20.44(q), -2.64(q, SiMeMePh), -3.47(q, SiMeMePh).

Found: M^+ , 277.1120, C₁₄H₁₉NO₃Si requires M , 277.1134

Trans-N-t-butyltrimethylsilyl-3-bromo-4-(phenyldimethylsilyl
methyl)azetidin-2-one.(271)



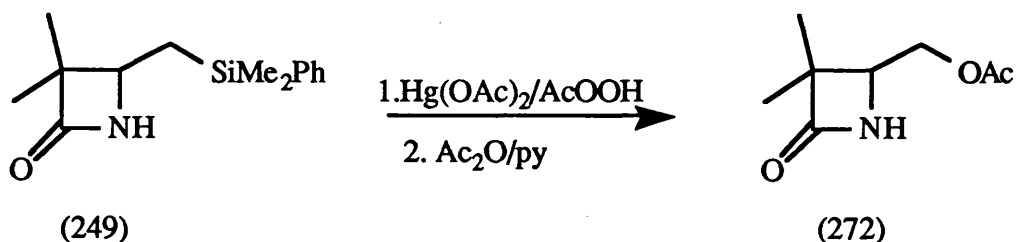
A flame dried flask under N_2 was charged with β -lactam (265) (67.5mg, 0.23mmol) in CH_2Cl_2 (3.8ml) followed by 2,6-lutidine (48.4mg, 53 μ l, 0.45mmol). Then TBDMSOTf (0.22M in CH_2Cl_2) (1.22ml, 0.27mmol) was added dropwise and the reaction mixture left to stir overnight at room temperature. Work-up consisted of diluting with Et_2O (20ml) and washing with saturated aqueous $CuSO_4$ solution (20ml), water (20ml) and brine (20ml). After drying and concentration of the organic extract, the residue was purified by dry column flash chromatography to give the title compound as a clear oil. (81.5mg, 87%)

ν_{max} ($CHCl_3$) 3030 and 1748 cm^{-1} .

δ_H (200MHz) 7.60-7.35 (5H, m, Ph), 4.10 (1H, d, J 2.2, CHCO), 3.74 (1H, d d, J 12.6, 3.1 and 2.2, CHN), 1.42 (1H, d d, J 14.2 and 3.1, CHHSi), 1.20 (1H, m, CHHSi), 0.94 (9H, s, Bu^t), 0.41 (3H, s, SiMeMePh), 0.40 (3H, s, SiMeMePh), 0.23 (3H, s, SiMeMe Bu^t), 0.21 (3H, s, SiMeMe Bu^t).

δ_C (50MHz) 168.30(s), 136.98(s), 133.41(d), 129.55(d), 128.06(d), 59.81(d, CHCO), 48.94(d, CHN), 26.12(q, Bu^t), 24.56(t), 18.38(s, Bu^t), -2.71 (q, SiMeMePh), -2.85(q, SiMeMePh), -5.46(q, SiMeMe Bu^t), -5.78(q, SiMeMe Bu^t).

Found: m/z 354.0322 (^{79}Br), $C_{18}H_{30}NOSi_2Br-Bu^t$ requires 354.0345 (^{79}Br).

3,3-Dimethyl-4-(acetoxymethyl)azetidin-2-one. (272)

Oxidative Procedure: I.Fleming and P.E.J.Sanderson (adapted), *Tetrahedron Lett.*, 1987, 28, 4229.

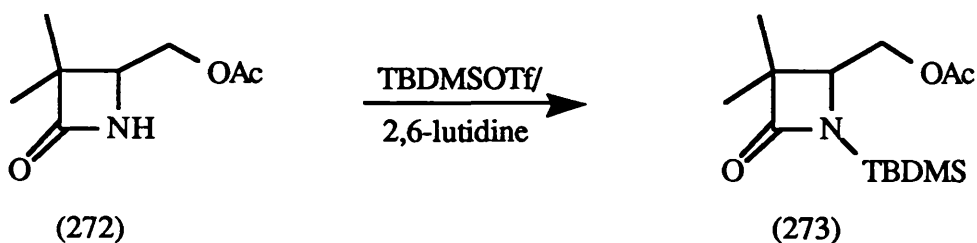
A flame dried flask under N_2 was charged with β -lactam (249) (149.5mg, 0.60mmol) in glacial acetic acid (4ml). To this was added peracetic acid (4.52g, 4ml, 19mmol) and $\text{Hg}(\text{OAc})_2$ (289mg, 0.91mmol). The reaction mixture was stirred at room temperature for 3h then diluted with Et_2O (80ml) and freshly powdered $\text{Na}_2\text{S}_2\text{O}_5$ (12g, 63mmol) added. After stirring for 30min the ethereal solution was filtered through Celite and concentrated in vacuo. The solid residue was re-slurried with Et_2O (10ml), filtered through Celite and again concentrated in vacuo. At this stage the mixture was taken up in pyridine (3ml) and acetic anhydride (1.5ml) along with DMAP (2mg, 0.02mmol). The mixture was stirred overnight then concentrated in vacuo and the residue purified by dry column flash chromatography to give the acetate as a clear oil. (15mg, 15%).

ν_{\max} (CHCl₃) 3415, 1762 and 1742 cm⁻¹.

δ_{H} (200MHz) 5.90 (1H, br s, NH), 4.28 (1H, d d, *J* 11.6 and 4.5, CHHO),
4.08 (1H, d d, *J* 11.6 and 7.8, CHHO), 3.52 (1H, d d, *J* 7.8 and 4.5, CHN),
2.08 (3H, s, CH₃CO), 1.35 (3H, s, CH₃), 1.21 (3H, s, CH₃).

δ_{C} (50MHz) 174.24(s), 170.79(s), 64.55(t), 57.67(d), 53.87(s), 22.61(q),
20.77(q), 16.48(q).

Found: *m/z* 156.0674, C₈H₁₃NO₃-CH₃ requires 156.0661.

N-t-Butyldimethylsilyl-3,3-dimethyl-4-(acetoxymethyl)azetidin-2-one. (273)

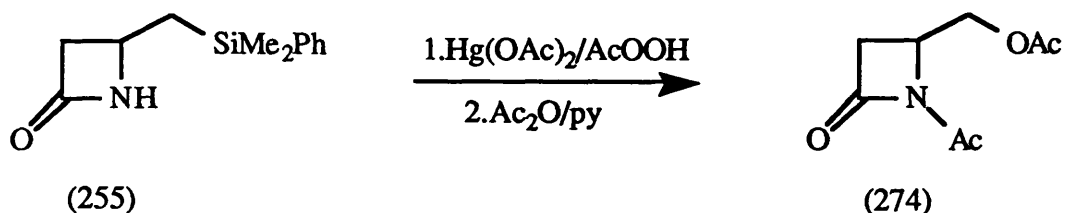
A flame dried flask under N_2 was charged with β -lactam (272) (18.8mg, 0.11mmol) in CH_2Cl_2 (3ml), followed by 2,6-lutidine (24mg, 26 μ l, 0.22mmol) and finally TBDMSOTf (0.13M in CH_2Cl_2) (1.60ml, 0.20mmol). After stirring overnight, at room temperature, the mixture was diluted with Et_2O (20ml) and washed with aqueous $CuSO_4$ solution (20ml), water (20ml) and finally brine (20ml). The organic extract was dried, concentrated and finally the residue purified by dry column flash chromatography to yield the N-silyl β -lactam as a clear oil. (28.7mg, 91%)

ν_{max} ($CHCl_3$) 1739 cm^{-1} (br).

δ_H (200MHz) 4.16 (2H, d, J 6.3, CH_2), 3.43 (1H, t, J 6.3, CHN), 2.06 (3H, s, CH_3COO), 1.31 (3H, s, CH_3), 1.15 (3H, s, CH_3), 0.94 (9H, s, Bu^t), 0.25 (3H, s, $SiMeMeBu^t$), 0.20 (3H, s, $SiMeMeBu^t$).

δ_C (50MHz) 179.30(s), 170.44(s), 64.64(t), 59.15(d), 53.88(s), 26.17(q, Bu^t), 23.64(q, CH_3COO), 20.78(q), 18.41(s, Bu^t), 16.46(q), -5.36 (q, $SiMeMeBu^t$), -5.56(q, $SiMeMeBu^t$).

Found: m/z 228.1063, $C_{14}H_{27}NO_3Si-Bu^t$ requires 228.1056.

N-Acyl-4-(acetoxymethyl)azetidin-2-one. (274)

Oxidative Procedure: I.Fleming and P.E.J.Sanderson (adapted), *Tetrahedron Lett.*, 1987, 28, 4229.

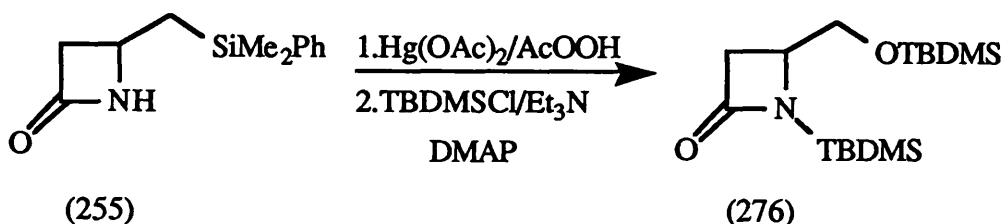
To a flame dried flask under N₂ was added β-lactam **(255)** (189.6mg, 0.86mmol) in glacial acetic acid (5.8ml), followed by peracetic acid (6.55g, 5.8ml, 27.6mmol). Hg(OAc)₂ (416mg, 1.31mmol) was added and the mixture then left to stir at room temperature for 3.5h. At this point the reaction was diluted with Et₂O (80ml), the flask placed in a cold water bath (15°C) and freshly powdered Na₂S₂O₅ (12g, 63mmol) added. After stirring for 30min the ethereal solution was filtered through Celite and concentrated in vacuo. The solid residue was slurried in EtOAc (3ml) and filtered through a small pad of silica, concentrated in vacuo then taken up in pyridine (3ml) and acetic anhydride (1.5ml) along with DMAP (5mg, 0.04mmol). The mixture was left to stir overnight, concentrated in vacuo and purified by dry column flash chromatography to yield the acetamido acetate as a clear oil (46.4 mg, 29%).

ν_{\max} (CHCl₃) 1792, 1745 and 1708 cm⁻¹.

δ_{H} (200MHz) 4.47 (1H, d d, *J* 12.0 and 4.2, CHHOAc), 4.35 (1H, d d, *J* 12.0 and 3.3, CHHOAc), 4.23 (1H, m, CHN), 3.12 (1H, d d, *J* 16.3 and 6.2, CHHCO), 2.89 (1H, d d, *J* 16.3 and 3.5, CHHCO), 2.33 (3H, s, CH₃), 2.05 (3H, s, CH₃).

δ_{C} (50MHz) 170.49(s), 167.94(s), 164.27(s), 61.62(t, CH₂O), 48.38(d), 39.09(t), 23.69(q), 20.58(q).

Found: M^+ , 185.0710, C₈H₁₁NO₄ requires M , 185.0688.

N-t-Butyldimethylsilyl-4-(t-butyldimethylsiloxymethyl)azetidin-2-one. (276)

A flame dried flask under N₂ was charged with β-lactam (255) (190mg, 0.87mmol) in glacial acetic acid (5.8ml). Peracetic acid (6.55g, 5.8ml, 27.6mmol) and Hg(OAc)₂ (416mg, 1.31mmol) were then added and the reaction mixture stirred at room temperature for 3h. The reaction was quenched by the addition of Et₂O (80ml), the flask cooled in a water bath, at 15°C, and freshly powdered Na₂S₂O₅ (12g, 63mmol) added. After stirring vigorously for 30min the mixture was filtered through Celite and concentrated *in vacuo*. The solid residue was taken up in EtOAc (5ml), re-filtered through Celite, concentrated *in vacuo* and the residue purified by dry column flash chromatography, the highly polar 4-(hydroxymethyl)azetidinone being eluted with EtOAc. The β-lactam (29mg, 0.29mmol) eluted from silica was then taken up in CH₂Cl₂ (4ml) and added to a flame dried flask, under N₂, containing TBDMSCl (128.5mg, 0.85mmol) and DMAP (5mg, 0.04mmol). To this was added triethylamine (152mg, 209μl, 1.50mmol) and the mixture left to stir overnight. Work-up consisted of diluting with CH₂Cl₂ (5ml) and washing with water (10ml). The organic layer was removed and the aqueous phase re-extracted with CH₂Cl₂ (10ml). The combined organic extracts were dried, concentrated and the residue purified by dry column flash chromatography to yield the title compound as a clear oil. (57mg, 20%)

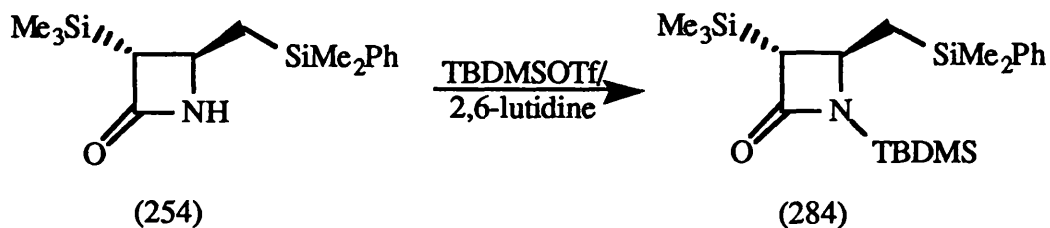
ν_{\max} (CHCl₃) 1727 cm⁻¹.

δ_{H} (200MHz) 3.76-3.59 (3H, m, CH₂O and CHN), 3.05 (1H, d d, *J* 15.2 and 5.1, CHHCO), 2.75 (1H, d d, *J* 15.2 and 2.4, CHHCO), 0.94 (9H, s, Bu^t), 0.88 (9H, s, Bu^t), 0.22 (3H, s, SiMeMeBu^t), 0.21 (3H, s, SiMeMeBu^t), 0.05 (6H, s, SiMe₂Bu^t)

δ_{C} (50MHz) 172.79(s), 65.27(t, CH₂O), 50.19(d), 41.21(t, CH₂CO), 26.17(q), 25.86(q), 18.39(s), 18.31(s), -5.41(q), -5.73(q).

Found: *m/z* 314.1970, C₁₆H₃₅NO₂Si₂-CH₃ requires 314.1972.

Trans-N-t-butyltrimethylsilyl-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)-azetidin-2-one. (284)



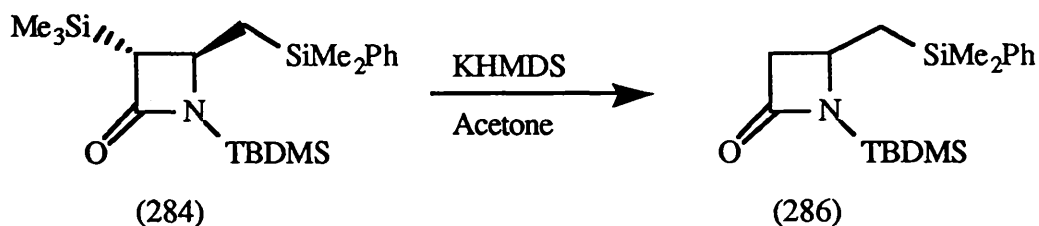
To a flame dried flask under N_2 was added β -lactam (254) (89.3mg, 0.31mmol) in CH_2Cl_2 (5ml) followed by 2,6-lutidine (64.5mg, 70 μ l, 0.60mmol). The reaction mixture was stirred at room temperature and TBDMSOTf (0.30M in CH_2Cl_2) (1.98ml, 0.60mmol) added dropwise. After stirring overnight the reaction mixture was diluted with Et_2O (20ml), and washed with saturated aqueous CuSO_4 solution (20ml), water (20ml) and finally brine (20ml). The organic extract was dried, concentrated and the residue purified by dry column flash chromatography to yield the title compound as a clear oil (116.8mg, 94%).

ν_{\max} (CHCl_3) 1715 and 1705 cm^{-1} .

δ_{H} (200MHz) 7.51-7.30 (5H, m, Ph), 3.43 (1H, d t, J 11.4 and 2.6, CHN), 2.36 (1H, d, J 2.4, CHCO), 1.52 (1H, d d, J 14.2 and 2.8, CHHSi), 1.17 (1H, d d, J 14.2 and 11.4, CHHSi), 0.95 (9H, s, Bu^t), 0.29 (6H, s, SiMe_2Ph), 0.17 (3H, s, SiMeMeBu^t), 0.16 (3H, s, SiMeMeBu^t), -0.02 (9H, s, SiMe_3).

δ_{C} (50MHz) 174.68(s), 137.78(s), 133.47(d), 129.28(d), 127.93(d), 49.88, (d, CHN), 48.72(d, CHCO), 26.28(q, Bu^t), 26.23(t), 17.92(s, Bu^t), -2.32(q, SiMeMePh), -2.49 (q, SiMeMePh), -5.11 (q, SiMe_2Bu^t), -5.76 (q, SiMe_3).

Found: M^+ , 405.2325, $\text{C}_{21}\text{H}_{39}\text{NOSi}_3$ requires M , 405.2340.

Attempted Peterson Olefination (KHMDS).

A flame dried flask under N₂ at -78°C was charged with KHMDS (0.5M in toluene) (0.58ml, 0.29mmol) and then the β -lactam (284) (99.3mg, 0.24mmol) in THF (0.8ml). The reaction mixture was stirred, at -78°C, for 30min then acetone (21mg, 25.5 μ l, 0.36mmol) was added. The bath was allowed to warm over 3.5h and then quenched with aqueous NH₄Cl solution (3ml) and Et₂O (3ml). The organic layer was removed and the aqueous layer re-extracted with Et₂O (2x5ml). After drying and concentration of the combined organic extracts, purification of the residue by dry column flash chromatography gave only de-silylated starting material as a clear oil (27.5mg, 43%).

N-t-Butyldimethylsilyl-4-(phenyldimethylsilylmethyl)azetidin-2-one.(286)

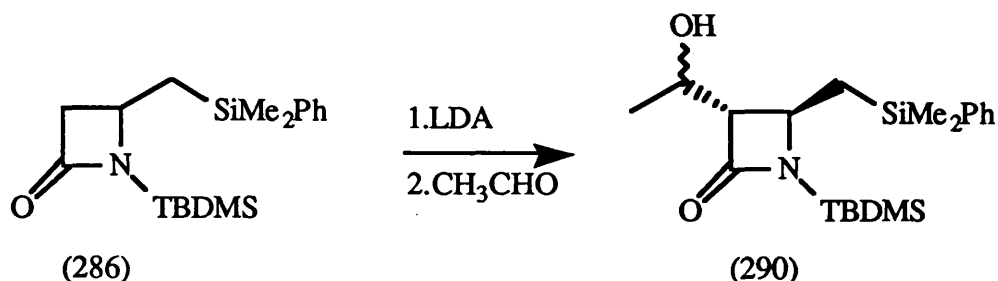
ν_{\max} (CHCl₃) 1721 and 1255 cm⁻¹.

δ_{H} (200MHz) 7.50-7.30 (5H, m, ArH), 3.61 (1H, d m, *J* 12.4 and unassigned, CHN), 2.95 (1H, d d, *J* 15.2 and 5.3, CHHCO), 2.38 (1H, d d, *J* 15.2 and 2.9, CHHCO), 1.42 (1H, d d, *J* 14.0 and 2.7, CHHSi), 1.04 (1H, d d, *J* 14.0 and 12.4, CHHSi), 0.93 (9H, s, Bu^t), 0.31 (3H, s, SiMeMePh), 0.30 (3H, s, SiMeMePh), 0.19 (3H, s, SiMeMeBu^t), 0.18 (3H, s, SiMeMeBu^t).

δ_{C} (50MHz) 172.33(s), 137.58(s), 133.26(d), 129.76(d), 127.90(d), 47.19(d), 45.45(t), 26.15(q, Bu^t), 24.84(t), 18.05(s, Bu^t), -2.72(q, SiMeMePh), -2.91(q, SiMeMePh), -5.40(q, SiMeMeBu^t), -5.91(q, SiMeMeBu^t).

Found: M^+ , 333.1952, C₁₈H₃₁NOSi₂ requires M , 333.1944.

Trans-N-t-butyl dimethylsilyl-3-(1-hydroxyethyl)-4-(phenyldimethylsilylmethyl)-azetidin-2-one. (290)



A flame dried flask under N_2 was charged with LDA solution (0.41M, 0.94ml, 0.38 mmol) at $-78^\circ C$. To this was added β -lactam (286) (128.5mg, 0.38mmol) in THF (2ml) over 1min. After stirring at $-78^\circ C$ for 10min, acetaldehyde (52mg, 65 μ l, 1.18mmol) was added. The reaction mixture was allowed to warm to $0^\circ C$ and then stirred at $0^\circ C$ for 1h. The reaction was quenched by the addition of water (20ml) and Et_2O (20ml). The organic layer was removed and the aqueous layer re-extracted with CH_2Cl_2 (2x15ml). After drying the combined organic extracts were concentrated and the residue purified by dry column flash chromatography to furnish the title compound as a clear oil (89.2mg, 61.0%). Note: mainly the trans diastereomers, epimeric at the alcohol carbon, were produced.

ν_{max} (CHCl₃) 3680, 3610, 3015 and 1720 cm⁻¹.

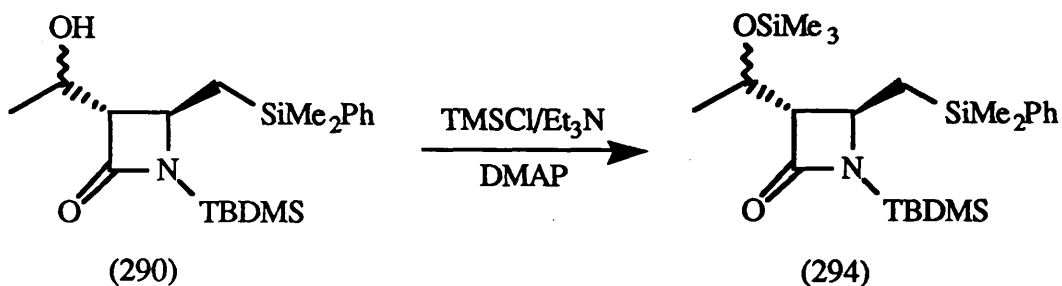
NMR data refer to major diastereomer.

δ_{H} (200MHz) 7.55-7.30 (5H, m, Ph), 3.75 (1H, d q, *J* 7.3 and 6.3, CHOH), 3.50 (1H, d d d, *J* 11.9, 3.1 and 2.4, CHN), 2.65 (1H, d d, *J* 7.3 and 2.4, CHCO), 1.70 (1H, br s, OH), 1.20 (2H, m, CH₂), 1.08 (3H, d, *J* 6.3, CH₃), 0.92 (9H, s, Bu^t), 0.35 (3H, s, SiMeMePh), 0.34 (3H, s, SiMeMePh), 0.20 (3H, s, SiMeMeBu^t), 0.17 (3H, s, SiMeMeBu^t).

δ_{C} (50MHz) 173.52(s), 137.88(s), 133.51(d), 129.42(d), 128.07(d), 66.66(d, CHOH), 64.38(d, CHN), 51.72(d, CHCO), 26.21(q, Bu^t), 24.74(t, CH₂Si), 21.13(q), 18.11(s, Bu^t), -2.33(q, SiMeMePh), -2.76(q, SiMeMePh), -5.14(q, SiMeMeBu^t), -5.67(q, SiMeMeBu^t).

Found: M^+ , 377.2191, C₂₀H₃₅NO₂Si₂ requires M , 377.2206.

Trans-N-t-butyl(dimethylsilyl)-3-(1-trimethylsiloxyethyl)-4-(phenyl dimethylsilylmethyl)azetidin-2-one. (294)



A 10ml round bottomed flask containing DMAP (5mg, 0.04mmol) was flame dried and purged with N_2 . To this was added β -lactam (290) (89.2mg, 0.24mmol) in Et_2O (4ml) and TMSCl (29.3mg, 34.2 μl , 0.27mmol) followed by triethylamine (27.1mg, 37.2 μl , 0.27mmol). After stirring overnight at room temperature the reaction mixture was diluted with water (10ml) and Et_2O (10ml). The organic layer was removed and the aqueous phase re-extracted with Et_2O (2x10ml). The combined organic extracts were dried, concentrated and the residual oil purified by dry column flash chromatography to yield the silyl ether as a colourless oil. (98.9mg, 93%)

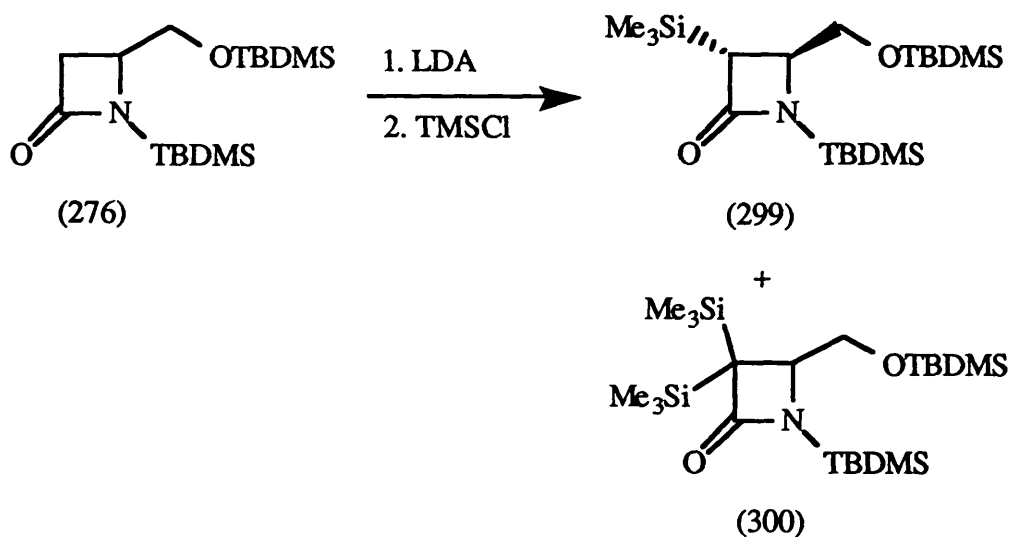
ν_{\max} (CHCl₃) 3018, 1727, 1720 and 1255 cm⁻¹.

δ_{H} (200MHz) 7.50-7.30 (5H, m, Ph), 3.92 (1H, m, CHOSi), 3.61 (1H, m, CHN), 2.64 (1H, d d, *J* 7.1 and 2.1, CHCO), 1.20 (2H, m, CH₂), 1.06 (3H, d, *J* 6.1, CH₃), 0.95 (9H, s, Bu^t), 0.37 (3H, s, SiMeMePh), 0.35 (3H, s, SiMeMePh), 0.24 (3H, s, SiMeMeBu^t), 0.20 (3H, s, SiMeMeBu^t), 0.06 (9H, s, SiMe₃).

δ_{C} (50MHz) 173.60(s), 138.48(s), 133.45(d), 129.13(d), 127.88(d), 67.27(d, CHOSi), 65.25(d, CHN), 51.13(d, CHCO), 26.30(q, Bu^t), 25.03(t, CH₂Si), 21.18(q), 18.20(s, Bu^t), 0.33(q, SiMe₃), -2.32(q, SiMeMePh), -2.89(q, SiMeMePh), -5.25(q, SiMeMeBu^t), -5.58(q, SiMeMeBu^t).

Found: *m/z* 434.2363, C₂₃H₄₃NO₂Si₃-CH₃ requires 434.2367.

Trans-N-t-butyltrimethylsilyl-3-trimethylsilyl-4-(t-butyltrimethylsilyloxy-
methyl)azetidin-2-one. (299)



To a flame dried flask, under N_2 , at $-78^\circ C$ was added LDA (0.41M, 0.25ml, 0.10mmol) followed by the dropwise addition of β -lactam (276) (29.2mg, 0.089mmol) in THF (5ml). After stirring at $-78^\circ C$ for 10min, TMSCl (10.3mg, 12 μ l, 0.095mmol) was added and the reaction mixture left to warm to room temperature. Then Et_2O (15ml) and water (15ml) were added to quench the reaction. After shaking, the organic layer was removed and the aqueous phase re-extracted with Et_2O (2x15ml). The combined organic extracts were then dried, concentrated and the residue purified by positive pressure chromatography to separate the 3,3-bistrimethylsilyl compound (300) (9.9mg, 24%) and furnish the 3-trimethylsilyl β -lactam (299) (24mg, 67%) as a clear oil.

Trans-N-t-butyltrimethylsilyl-3-trimethylsilyl-4-(t-butyltrimethylsilyloxy)methyl)azetidinone. (299)

ν_{\max} (CHCl₃) 1723, 1710 and 1251 cm⁻¹.

δ_{H} (200MHz) 3.79 (1H, d d, *J* 10.1 and 4.7, CHHO), 3.51 (1H, d d, *J* 10.1 and 6.4, CHHO), 3.32 (1H, d d d, *J* 6.4, 4.7 and 2.6, CHN), 2.54 (1H, d, *J* 2.6, CHCO), 0.94 (9H, s, Bu^t), 0.88 (9H, s, Bu^t), 0.20 (3H, s, SiMeMeBu^t), 0.19 (3H, s, SiMeMeBu^t), 0.12 (9H, s, SiMe₃), 0.04 (6H, s, SiMe₂Bu^t).

δ_{C} (50MHz) 174.80(s), 67.05(t), 51.73(d, CHN), 47.01(d, CHCO), 26.14(q, Bu^t), 25.92(q, Bu^t), 18.39(s, Bu^t), 18.08(s, Bu^t), -2.82(q, SiMe₃), -5.28(q, SiMeMeBu^t), -5.42(q, SiMeMeBu^t), -5.48(q, SiMeMeBu^t), -5.69(q, SiMeMeBu^t).

Found: M^+ , 401.2582, C₁₉H₄₃NO₂Si₃ requires M , 401.2602.

N-t-Butyldimethylsilyl-3,3-bistrimethylsilyl-4-(t-butyldimethylsiloxy-methyl)azetidin-2-one. (300)

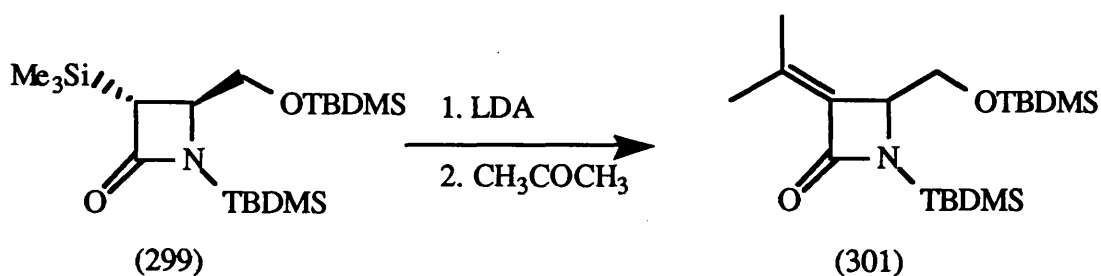
ν_{\max} (CHCl₃) 1707 and 1254 cm⁻¹.

δ_{H} (200MHz) 3.84 (2H, m, CH₂O), 3.45 (1H, m, CHN), 0.93 (9H, s, Bu^t), 0.90 (9H, s, Bu^t), 0.25 (3H, s, SiMeMeBu^t), 0.19 (9H, s, SiMe₃), 0.15 (3H, s, SiMeMeBu^t), 0.13 (9H, s, SiMe₃), 0.06 (3H, s, SiMe₂Bu^t), 0.06 (3H, s, SiMe₂Bu^t).

δ_{C} (50MHz) 176.06(s), 64.98(t), 56.61(d), 49.23(s, C(SiMe₃)₂), 26.14(q, Bu^t), 25.97(q, Bu^t), 18.45(s, Bu^t), 17.98(s, Bu^t), 1.19(q, SiMe₃), -1.15(q, SiMe₃), -5.30(q, SiMe₂Bu^t), -5.42(q, SiMe₂Bu^t).

Found: *m/z* 458.2755, C₂₂H₅₁NO₂Si₄-CH₃ requires 458.2762

N-t-Butyldimethylsilyl-3-isopropylidene-4-(t-butyldimethylsiloxy-
methyl)azetidin-2-one. (301)



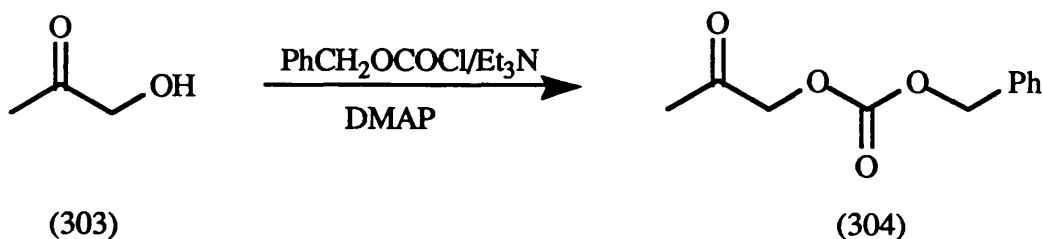
A flame dried flask under N_2 , at -78°C , was charged with LDA (0.41M, 0.15ml, 0.06mmol) and to this was added β -lactam (299) (23.8mg, 0.06mmol) in THF (2ml). After stirring at -78°C for 10min acetone (6mg, $8\mu\text{l}$, 0.1mmol) was added and the reaction mixture allowed to warm to room temperature. The reaction was then quenched by the addition of water (15ml) and Et_2O (15ml). The organic layer was removed and the aqueous phase re-extracted with Et_2O (15ml). The combined organic extracts were dried, concentrated and the residue purified by dry column flash chromatography to yield the 3-alkylidene β -lactam as a clear oil. (21.5mg, 98%).

ν_{\max} (CHCl₃) 1714 cm⁻¹.

δ_{H} (200MHz) 4.04 (1H, t m, *J* unassignable CHN) 3.79 (1H, d d, *J* 10.7 and 4.6, CHHO), 3.71 (1H, d d, *J* 10.7 and 5.4, CHHO), 2.02 (3H, s, CCH₃CH₃), 1.75 (3H, s, CCH₃CH₃), 0.95 (9H, s, Bu^t), 0.88 (9H, s, Bu^t), 0.23 (6H, s, SiMe₂Bu^t), 0.04 (6H, s, SiMe₂Bu^t).

δ_{C} (50MHz) 169.48(s), 136.25(s), 134.97(s), 65.41(t), 59.61(d), 26.27(q, Bu^t), 25.87(q, Bu^t), 21.07(q), 19.84(q), 18.47(s, Bu^t), 18.35(s, Bu^t), -5.22(q), -5.47(q), -5.52(q), -5.57(q).

Found: *m/z* 354.2284, C₁₉H₃₉NO₂Si₂-CH₃ requires 354.2285.

Benzyloxycarbonyl Protected Hydroxyacetone. (304)

Procedure: G.Losse and G.Bachmann, *Chem.Ber.*, 1964, **97**, 2671.

A flame dried flask under N_2 was charged with hydroxyacetone (303) (74.1mg, 69 μl , 1mmol) in CHCl_3 (2ml) followed by triethylamine (121.4mg, 167 μl , 1.2mmol) and DMAP (10mg, 0.08mmol). To this mixture was added benzyl chloroformate (102mg, 86 μl , 0.6mmol) and the reaction stirred overnight, at room temperature. The solvent was removed in vacuo and the residue taken up in Et_2O (15ml) and water (15ml). After removal of the organic layer the aqueous phase was re-extracted with Et_2O (2x15ml). The combined organic extracts were dried, concentrated and the residue purified by dry column flash chromatography. Unfortunately the title compound was found to be inseparable from benzyl alcohol, produced by degradation of benzyl chloroformate. Consequently the mixture (135.1mg) was taken up in CH_2Cl_2 (6ml) along with DMAP (10mg, 0.08mmol) and TBDMSCl (61mg, 0.4mmol) then added to a flame dried flask under N_2 . To this was added triethylamine (102mg, 140 μl , 1mmol) and the reaction left to stir overnight at room temperature. At this point water (15ml) and Et_2O (15ml) were added. After removal of the organic layer the aqueous phase was re-extracted with Et_2O (15ml). The combined organic extracts were dried, concentrated and the residue purified by dry column flash chromatography to yield the carbonate as a yellow oil. (79mg, 63%)

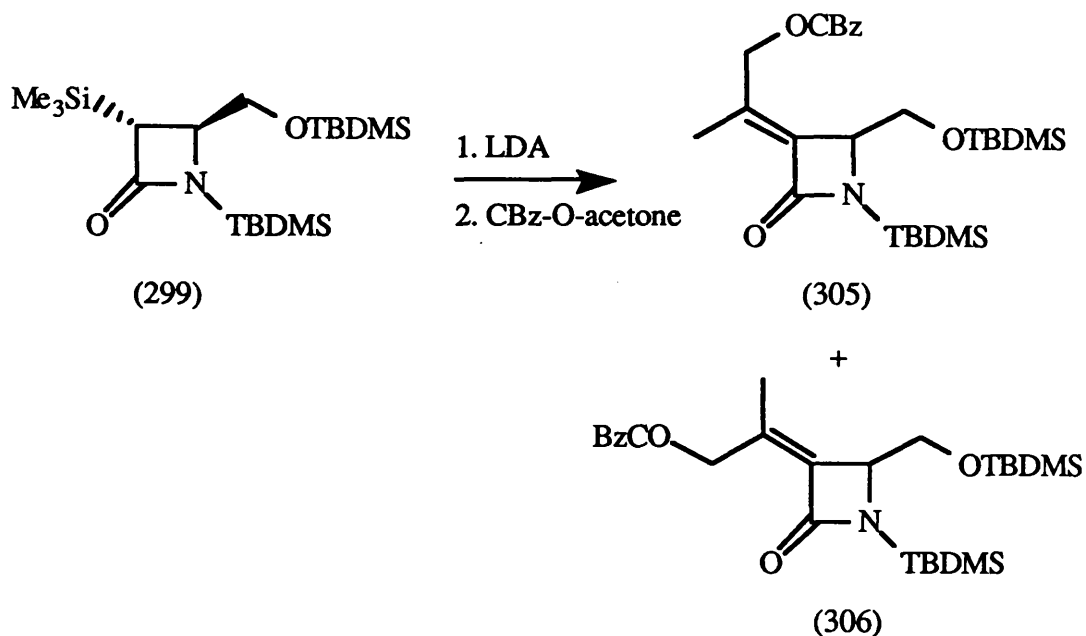
ν_{\max} (CHCl_3) 3110, 1840, 1790, 1780 and 1540 cm^{-1} .

δ_{H} (200MHz) 7.37-7.35 (5H, m, Ph), 5.19 (2H, s, CH_2Ph), 4.65 (2H, s, CH_2O), 2.14 (3H, s, CH_3CO).

δ_{C} (50MHz) 201.22(s), 154.59(s), 134.76(s), 128.53(d), 128.20(d), 128.13(d), 70.61(t), 70.10(t), 25.83(q).

Found: M^+ , 208.0732, $\text{C}_{11}\text{H}_{12}\text{O}_4$ requires M , 208.0736.

Reaction Of 3-Trimethylsilyl β -Lactam (299) With
Benzyloxycarbonyl Protected Hydroxyacetone (304).



A flame dried flask under N_2 at -78°C was charged with LDA (0.41M, 0.23ml, 0.09mmol) followed by the β -lactam (299) (33mg, 0.082mmol) in THF (3ml). After stirring at -78°C for 15min the carbonate (304) (18.7mg, 0.09mmol) in THF (2.2ml) was added. The reaction mixture was left to warm to room temperature, then diluted with water (15ml) and Et_2O (15ml). The organic layer was removed and the aqueous phase re-extracted with Et_2O (15ml). After drying and concentration of the combined organic extracts the residue was purified by positive pressure chromatography to give both geometric isomers of the alkylidene β -lactam as a clear oil (16.5mg, 40%), in a ratio of 2:1 (E):(Z). (^1H NMR integrals on CH_3).

Note:- starting material (7.7mg, 24%) was also recovered.

ν_{max} (CHCl₃) 1735 cm⁻¹ (br).

NMR data for major isomer

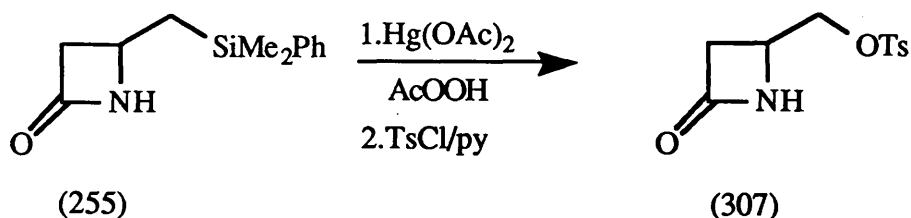
δ_{H} (200MHz) 7.37-7.35 (5H, m, Ph), 5.16 (2H, s, CH₂Ph), 4.75 (1H, d, *J* 13.2, CCHHO), 4.59 (1H, d, *J* 13.2, CCHHO), 4.10 (1H, br q, CHN), 3.84 (1H, d d, *J* 10.6 and 4.1, CHHOSi), 3.65 (1H, d d, *J* 10.6 and 5.9, CHHOSi), 2.04 (3H, d, *J* 0.4, CH₃), 0.95 (9H, s, Bu^t), 0.86 (9H, s, Bu^t), 0.22 (6H, s, SiMe₂Bu^t), 0.02 (6H, s, SiMe₂Bu^t).

δ_{C} (50MHz) 168.65(s, CON), 154.81(s, OCOO), 138.26(s, =C), 134.97(s, =C), 131.78(s), 128.61(d), 128.56(d), 128.36(d), 69.83(t), 68.15(t), 65.04(t, CH₂Si), 59.57(d), 26.17(q, Bu^t), 25.82(q, Bu^t), 18.43(s, Bu^t), 18.30(s, Bu^t), 14.99(q, CH₃), -5.32(q, SiMeMeBu^t), -5.52(q, SiMeMeBu^t), -5.66(q, SiMe₂Bu^t).

Minor isomer only resonances which were assignable:-

δ_{H} (200MHz) 5.15 (1H, d, *J* 12.1, CHHO), 5.00 (1H, d, *J* 12.1, CHHO), 1.81 (3H, br s, CH₃).

Found: *M*⁺, 519.2831, C₂₇H₄₅NO₅Si₂ requires *M*, 519.2836.

4-(Toluenesulphonyloxymethyl)azetidin-2-one. (307)

Oxidative procedure: I.Fleming and P.E.J.Sanderson (adapted), *Tetrahedron Lett.*, 1987, 28, 4229

Tosylation procedure: J. Brennan, G.Richardson and R.J.Stoodley, *J. Chem. Soc., Perkin Trans 1.*, 1983, 649.

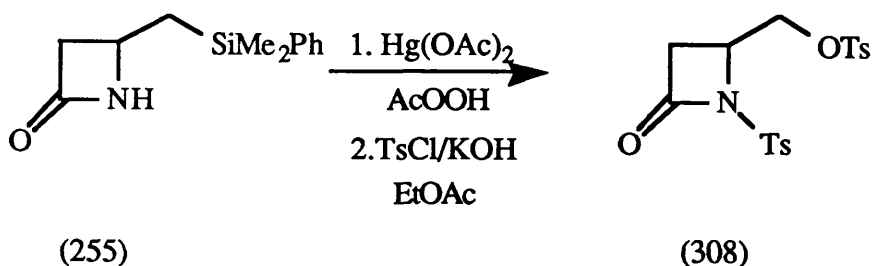
A flame dried flask under N_2 was charged with β -lactam (255) (269.9mg, 1.23mmol) in peracetic acid (9.13g, 8.08ml, 38mmol) followed by $Hg(OAc)_2$ (582mg, 1.83mmol) in glacial acetic acid (8.08ml). After stirring, at room temperature, for 3h the reaction mixture was diluted with Et_2O (80ml) and chilled in a water bath at $15^\circ C$. To this mixture was added freshly powdered $Na_2S_2O_5$ (12g, 63mmol) and the whole stirred vigorously for 30min. After filtration through Celite and concentration in vacuo the solid residue was taken up in $EtOAc$ (5ml) and re-filtered through Celite. Following concentration in vacuo the material was purified by dry column flash chromatography, the highly polar 4-(hydroxymethyl)azetidinone being eluted with $EtOAc$. The purified β -lactam (26.3mg, 0.26mmol) was taken up in pyridine (2ml) and cooled to $-30^\circ C$. To this mixture was added $TsCl$ (57.5mg, 0.3mmol) and the mixture stirred, at $-30^\circ C$, for 1h. The mixture was warmed to $0^\circ C$ then stirred for 1h at $0^\circ C$, filtered through Celite and concentrated in vacuo. The title compound was isolated after dry column flash chromatography of the residue as a yellow oil (14.4mg, 5%).

ν_{\max} (CHCl₃) 3421, 1778, 1616 and 1368 cm⁻¹.

δ_{H} (200MHz) 7.78 (2H, d, J 8.5, ArH), 7.35 (2H, d, J 8.5, ArH), 5.93 (1H, br s, NH), 4.22 (1H, d d, J 10.2 and 3.5, CHHO), 4.00 (1H, d d, J 10.2 and 7.4, CHHO), 3.91 (1H, m, CHN), 3.08 (1H, d d d, J 15.0, 5.2 and 2.2, CHHCO), 2.63 (1H, d d d, J 15.0, 2.5 and 1.3, CHHCO), 2.46 (3H, s, ArCH₃).

δ_{C} (50MHz) 166.05, 145.44, 132.24, 130.08, 127.93, 71.34, 45.69, 40.62, 21.68.

Found: M^+ , 255.0558, C₁₁H₁₃NO₄S requires M , 255.0565.

N-Toluenesulphonyl-4-(toluenesulphonyloxymethyl)azetidin-2-one. (308)

Oxidative procedure: I.Fleming and P.E.J.Sanderson (adapted), *Tetrahedron Lett.*, 1987, 28, 4229.

Tosylation procedure: H.Westmijze and P.Vermeer (adapted), *Synthesis*, 1979, 390.

To a flame dried flask, under N_2 , was added β -lactam (255) (207.5mg, 0.95mmol) in peracetic acid (7g, 6.2ml, 29.5mmol) followed by $\text{Hg}(\text{OAc})_2$ (448mg, 1.41mmol) in glacial acetic acid (6.2ml). After stirring at room temperature for 3h the mixture was diluted with Et_2O (80ml) and cooled in a water bath at 15°C . To this was added freshly powdered $\text{Na}_2\text{S}_2\text{O}_5$ (12g, 63mmol) and the reaction mixture stirred vigorously for 30min then filtered through Celite. After concentration in vacuo, the solid residue was taken up in EtOAc (5ml), re-filtered through Celite, concentrated and purified by dry column flash chromatography, the highly polar 4-(hydroxymethyl)-azetidinone (37.3mg, 0.37mmol) being eluted with EtOAc . This clear oil was taken up in EtOAc (1.5ml) and added to a flame dried flask under N_2 at -30°C containing TsCl (70mg, 0.37mmol). Freshly powdered KOH (121mg, 2.15mmol) was added to this mixture and the cooling bath warmed to 0°C over 20min then maintained at 0°C for 30min. The reaction mixture was filtered through Celite, concentrated and the residue purified by dry column flash chromatography to yield the title compound as a white solid, (11.7mg, 3%), m.p. $126\text{--}128^\circ\text{C}$.

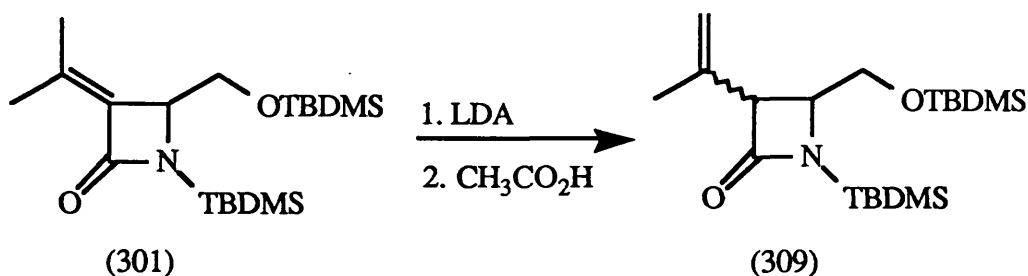
ν_{\max} (CHCl₃) 3040, 1810(w), 1738 and 1382 cm⁻¹.

δ_{H} (200MHz) 7.84-7.72 (4H, m, Ar), 7.38-7.31 (4H, m, Ar), 4.40-4.00 (3H, m, CH₂O and CHN), 3.06 (1H, d d, *J* 16.1 and 5.6, CHHCO), 2.95 (1H, d d, *J* 16.1 and 3.8, CHHCO), 2.46 (3H, s, ArCH₃), 2.44 (3H, s, ArCH₃).

δ_{C} (50MHz) 162.20(s), 145.67(s, ArCS), 145.55(s, ArCS), 135.02(s, ArCH₃), 131.98(s, ArCH₃), 130.10(d), 130.10(d), 127.98(d), 127.47(d), 67.12(t), 51.52(d), 39.98(t), 21.72(q).

Found: M^+ , 409.0639, C₁₈H₁₉NO₆S₂ requires M , 409.0654.

Cis and Trans N-t-butyldimethylsilyl-3-isopropenyl-4-(t-butyldimethyl
siloxymethyl)azetidin-2-one. (309)



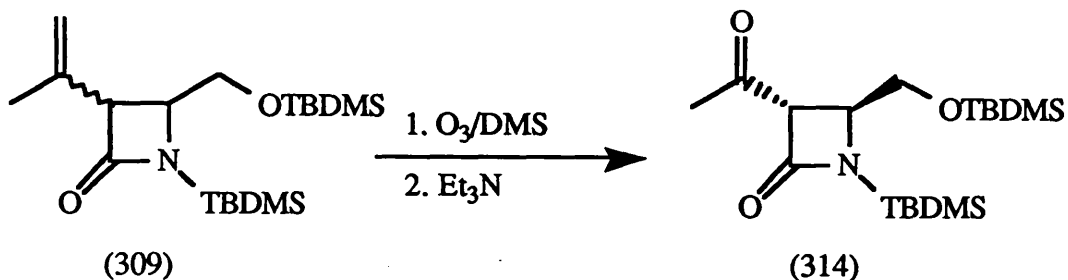
To a flame dried flask, under N_2 , at -78°C was added LDA (0.41M, 0.5ml, 0.2mmol) followed by the dropwise addition of β -lactam (301) (32.3mg, 0.87mmol), in THF (5ml). After stirring for 15min the reaction was quenched by the addition of glacial acetic acid (41.2mg, 40.4ml, 0.70mmol) and the mixture allowed to warm to 0°C then stirred at 0°C for 1h. At this stage the mixture was diluted with Et_2O (10ml) and water (10ml). The organic layer was removed and the aqueous phase re-extracted with Et_2O (10ml). The combined organic extracts were dried and concentrated in vacuo. Purification of the residue by dry column flash chromatography yielded the title compounds (31.3mg, 97%) as a clear oil.

Note: variable ratios of cis and trans product were obtained, these typically ranged from 5:1 to 2:1 (trans:cis).

δ_{H} (200MHz) major 4.95-4.80 (2H, br d, CH_2), 3.70-3.40 (4H, m, CHCO , CHN and CH_2O), 1.77 (3H, br s, CH_3), 0.94 (9H, s, Bu^t), 0.88 (9H, s, Bu^t), 0.21 (3H, s, SiMeMeBu^t), 0.19 (3H, s, SiMeMeBu^t), 0.10 (6H, s, SiMe_2Bu^t).

δ_{H} (200MHz) minor 5.10-5.00 (2H, br d, CH_2), 3.70-3.50 (4H, m, CHCO , CHN and CH_2O), 1.85 (3H, br s, CH_3), 0.95 (9H, s, Bu^t), 0.87 (9H, s, Bu^t), 0.28 (3H, s, SiMeMeBu^t), 0.25 (3H, s, SiMeMeBu^t), 0.04 (3H, s, SiMeMeBu^t), 0.03 (3H, s, SiMeMeBu^t).

Trans-N-t-butyltrimethylsilyl-3-acetyl-4-(t-butyltrimethylsilyloxy
methyl)azetidin-2-one. (314)



A solution of β -lactams (309) (31.3mg, 0.085mmol) in CH_2Cl_2 (20ml) was chilled to $-78^\circ C$ and purged with ozone, until a blue colouration persisted. The reaction mixture was then quenched with dimethyl sulphide (125mg, 147 μ l, 2.0mmol) at $-78^\circ C$ and left to stir overnight at room temperature. After washing with water (20ml) followed by drying and concentration of the organic layer, 1H NMR analysis indicated the presence of cis and trans-3-acetyl β -lactams. The mixture of β -lactams was taken up in CH_2Cl_2 (2ml) and transferred to a pre-dried 10ml round bottomed flask. To this mixture was added triethylamine (5.2mg, 7 μ l, 0.051mmol). After stirring overnight at room temperature the solvent was removed in vacuo and the residue purified by dry column flash chromatography to yield N-silyl β -lactam (314) (20.9mg, 66%) as a clear oil.

ν_{\max} (CHCl₃) 1746 and 1716 cm⁻¹.

δ_{H} (200MHz) 4.10 (1H, d, *J* 2.7, CHCO), 4.02 (1H, d d d, *J* 4.2, 3.6 and 2.7, CHN), 3.75 (1H, d d, *J* 11.2 and 3.6, CHHO), 3.68 (1H, d d, *J* 11.2 and 4.2, CHHO), 2.30 (3H, s, CH₃CO), 0.93 (9H, s, Bu^t), 0.88 (9H, s, Bu^t), 0.24 (3H, s, SiMeMeBu^t), 0.19 (3H, s, SiMeMeBu^t), 0.05 (6H, s, SiMe₂Bu^t).

δ_{C} (50MHz) 200.34(s), 167.84(s), 66.31(d, CHCO), 63.24(t), 52.11(d, CHN), 29.80(q, CH₃CO), 26.04(q, Bu^t), 25.81(q, Bu^t), 18.46(s, Bu^t), 18.22(s, Bu^t), -5.43(q, SiMeMeBu^t), -5.52(q, SiMeMeBu^t), -5.58(q, SiMeMeBu^t), -5.80(q, SiMeMeBu^t).

Found: *m/z* 314.1596, C₁₈H₃₇NO₃Si₂-Bu^t requires 314.1608.

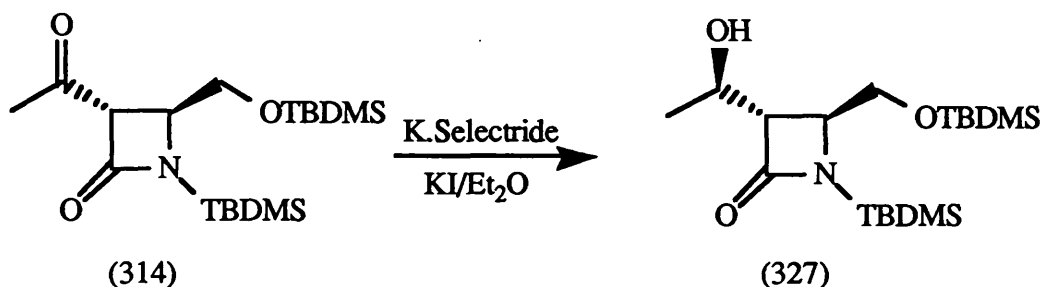
GC Analysis: Column: 25mx0.32mm I.D. fused silica capillary CP sil 5CB, 0.12 μ m.

Temp. Gradient. initial 90°C

final 180°C

retention time 9.26mins.

Trans-N-t-butyltrimethylsilyl-3-(1-hydroxyethyl)-4-
(t-butyltrimethylsilyloxymethyl)azetidin-2-one. (327)



Procedure: F.A.Bouffard and B.G.Christensen, *J. Org. Chem.*, 1981, **46**, 2208.

A 10ml round bottomed flask containing KI (11mg, 0.068mmol) and a magnetic stirrer bar was flame dried and purged with N_2 . To this was added β -lactam (314) (18.3mg, 0.049mmol) in Et_2O (1ml). The reaction mixture was cooled to 0°C and K-Selectride (1M in THF, 123 μ l, 0.123mmol) added dropwise. After stirring at 0°C for 1.25h, glacial acetic acid (12mg, 11 μ l, 0.2mmol) was added. The reaction mixture was immediately diluted with EtOAc (5ml), filtered through Celite and concentrated in vacuo. After purification of the residue by dry column flash chromatography the alcohol was isolated as a white solid, (13.8mg, 75%), m.p. $66-68^\circ\text{C}$ along with starting material (4.4mg, 24%).

$\nu_{\text{max}}(\text{CHCl}_3)$ 3500-3300 (br), 1730 cm^{-1} .

$\delta_{\text{H}}(200\text{MHz})$ 4.15 (1H, m, CH_3CHOH), 3.80 (1H, m, CHN), 3.59 (2H, m, CH_2O), 2.98 (1H, d d, J 5.8 and 2.4, CHCO), 1.35 (1H, br s, OH), 1.25 (3H, d, J 6.4, CH_3), 0.94 (9H, s, Bu^t), 0.88 (9H, s, Bu^t), 0.23 (3H, s, SiMeMeBu^t), 0.19 (3H, s, SiMeMeBu^t), 0.06 (6H, s, SiMe_2Bu^t).

$\delta_{\text{C}}(50\text{MHz})$ 173.41(s), 65.21(d, CH_3CHOH), 64.93(t), 62.29(d, CHN), 53.35(d, CHCO), 26.11(q, Bu^t), 25.86(q, Bu^t), 21.17(q, CH_3), 18.34(s, Bu^t), 18.30(s, Bu^t), -5.30(q, SiMeMeBu^t), -5.46(q, SiMeMeBu^t), -5.53(q, SiMeMeBu^t), -5.72(q, SiMeMeBu^t).

Found: m/z 316.1755, $\text{C}_{18}\text{H}_{39}\text{NO}_3\text{Si}_2\text{-Bu}^t$ requires 316.1764.

GC Analysis:

Column 25mx0.32mm I.D. fused silica capillary CP Sil 19CB, 0.18 μ m.

Temp. gradient 80°C for 2min

then 30°C min⁻¹ for 1min

then 20°C min⁻¹ till end.

Starting ketone - retention time 12.71min

Alcohol " " 14.96min (broad)

Silyl ether " " 14.23min and 14.58min

Ratio 12 : 1

Trimethylsilyl ether preparation

A solution of the crude reaction product in EtOAc (2mg in 1ml) was prepared. From this stock solution a 100 μ l aliquot was removed and evaporated to dryness, with N₂, in a microbiological test-tube. Pyridine (10 μ l) and BSTFA (20 μ l) were added and the tube tightly closed. After heating at 80°C for 30min the reagents were evaporated in an N₂ stream and the whole diluted with EtOAc (100 μ l).

AppendixTBDMSOTf.

A flame dried Kügelrohr flask equipped with a condenser was charged with TBDMSCl (1.125g, 7.46mmol) and then triflic acid (1.19g, 0.66ml, 7.46mmol) was added via the condenser top. The reaction mixture was heated at 60°C for 18h and the triflate removed by bulb to bulb distillation, to yield 1.86g (94%) (b.p. 130°C/20mmHg), the vacuum being released under N₂. The TBDMSOTf was then diluted to 25ml with dry CH₂Cl₂ to furnish a 0.28M solution.

LDA in THF (0.41M).

To a flame dried flask, under N₂, at -78°C was added diisopropylamine (253mg, 0.32ml, 2.5mmol) and THF (5ml). To this was added dropwise BuⁿLi (2.3M in hexanes) (1.1ml, 2.5mmol) and the reaction mixture stirred for 15min. The LDA (0.4M) was then ready for use and the required quantity removed by syringe.

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