Studies Towards the Synthesis of Thienamycin.

by

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of Ph.D.

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Summary

Almost all successful syntheses of bicyclic β-lactams involve the early synthesis of the monocyclic azetidin-2-one ring. Of the numerous methods developed to achieve this, the [2+2] cycloaddition of chlorosulphonyl isocyanate (CSI) to functionalised alkenes has proven to be particularly useful. In general, addition is performed on alkenyl acetates providing C-4 acetoxyazetidinones, which have found widespread use since the 4-acetoxy substituent can be replaced with various nucleophiles in an elimination/addition sequence. However, there are few functionalised alkenes which directly introduce the C-4 carbon substitution required for carbapenem synthesis upon cycloaddition with CSI.

Earlier investigations within this group have shown that allylsilanes undergo regioselective cycloaddition with CSI to yield C-4 silylmethyl substituted β-lactams.[133,137] 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. Use of phenyldimethylsilyl substitution allows access, albeit in low yield, to the corresponding hydroxymethyl azetidinones, *via* oxidative cleavage of the C-Si bond.

We were intrigued by reports from Fleming[142] and Taddei[141] that allylsilanes bearing a chiral centre directly adjacent to the double bond undergo reaction with various electrophiles, including CSI, with remarkably high stereoselectivity. The initial aim of this project was to prepare an δ-oxa-allylsilane, with such a chiral centre, which would undergo regio- and stereoselective cycloaddition with CSI to yield a C-3 hydroxyethyl substituted β-lactam. Subsequent oxidative cleavage of the silylmethyl group would led to a useful precursor for the powerful carbapenem antibiotic Thienamycin. Unfortunately, all attempts to carry out cycloaddition with these substrates resulted in a rapid 1,4 silyl elimination to penta-1,3-diene. In an attempt to overcome this problem, an alternative allylsilane was designed and prepared. Disappointingly, however, this compound did not react with CSI.

The second aim of this project was to improve the efficiency of the key oxidative cleavage step. Our interest was awakened by a report from Ito[191] which briefly mentioned the use of iodine monochloride (ICl) for the iododesilylation of phenyldimethylsilyl moieties prior to oxidative cleavage. In order to study the applicability of this method to C-4 silylmethyl β-lactams simple *N*-protected precursors were prepared. Gratifyingly, treatment with ICl resulted in cleavage of the Si-Ph bond and formation of the chlorodimethylsilyl β-lactams which were hydrolysed to the corresponding silanols in high yield. Oxidation of these compounds using a modification of Tamao's[191] procedure gave the potentially useful C-4 hydroxymethyl β-lactams in good to moderate yield. Alternatively, one of the intermediate chlorosilanes could be directly oxidised using AcOOH/KF.

Acknowledgements

I would like to thank sincerely Dr. E.W. Colvin for his help, support and friendship throughout the course of this project. Thanks also to my fellow Loudon Laboratory students for their friendship and advice over the last three years.

Thanks are also due to the technical staff of the department, namely Mr. J. Gall, Dr D.S. Rycroft, Mr. T. Ritchie, Mr. J. McIver and Mr. G. MacCulloch for their assistance with spectroscopic analyses. Financial support for the project from S.E.R.C. is gratefully acknowledged.

Finally, thanks to my parents, Ailsa and Peter, for their help and encouragement and to Jacq for her patience and understanding.

Abbreviations

AcOOH	Peracetic acid
AIBN	Azobisisobutyronitrile
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
Boc	t-Butyloxycarbonyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cbz	Carbobenzyloxy (benzyloxycarbonyl)
CSI	Chlorosulphonyl isocyanate
DAM	Di-*p*-anisylmethyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
HMPA	Hexamethylphosphoramide
LHMDS	Lithium hexamethyldisilazide
LDA	Lithium diisopropylamide
MEM	Methoxyethoxymethyl
NBS	*N*-Bromosuccinamide
ONB	*o*-Nitrobenzyl
OTf	Trifluoromethanesulphonate
PMB	*p*-Methoxybenzyl
PNB	*p*-Nitrobenzyl
PNZ	*p*-Nitrobenzyl carbonate
Selectride®	Tri-sec-butylborohydride
TBAF	Tetrabutylammonium fluoride

TBDMS	t-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl

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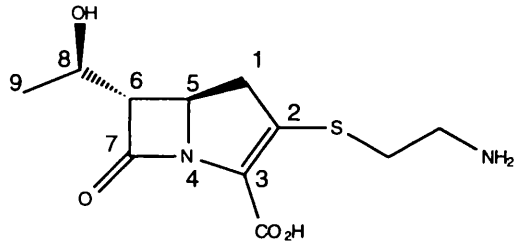
Numbering Systems

Carbapenems:



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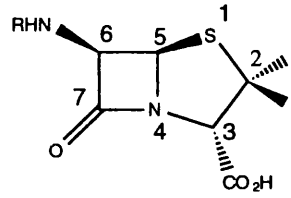

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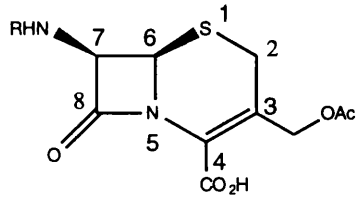

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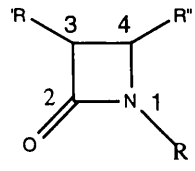


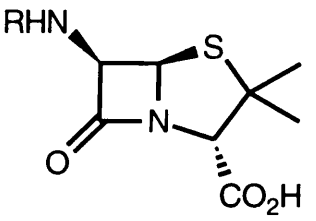
To Mum and Dad

1.1 History and Development

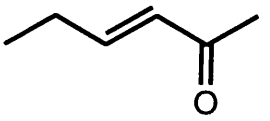
As early as 1877, Pasteur and Joubert reported that bacterial cultures were often ruined by the overgrowth of the mould *Penicillium notatum*, and it soon became generally recognised by microbiologists that one organism could inhibit the growth of another by secretion of toxic substances. Most of these secretions, however, were toxic to test animals and aroused little interest.

In 1928, at St. Mary's Hospital, London, Fleming noted that one of his cultures of staphylococci had become infected with colonies of the mould *Penicillium notatum* and that bacteria in the vicinity of these spots had lysed. Fleming subcultured this mould and found that the broth in which it had grown had a lethal effect on a number of species of Gram-negative bacteria.[1] He named the active ingredient **penicillin.** Although Fleming went on to show that the filtered broth was non-toxic to both animals and man, clinical use and attempted isolation were not successful - "penicillin is easily destroyed, and to all intents and purposes we failed. We were bacteriologists - not chemists - our relatively simple procedures were unavailing."

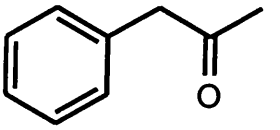
In 1940, in Oxford, Chain and Florey managed to extract a crude sample of penicillin which they demonstrated could cure systemic infections of streptococci and staphylococci in mice. The following year, after strenuous efforts, enough penicillin had been obtained for a modest clinical trial; the results were remarkably impressive. The recognition of its therapeutic potential led to massive Anglo-American efforts to produce penicillin by industrial fermentation for the war effort. Despite these efforts the structure of penicillin was not elucidated until 1945, when X-ray crystallography, microanalysis and chemical degradation showed the structure to be penicillin F (1).[2]



R =



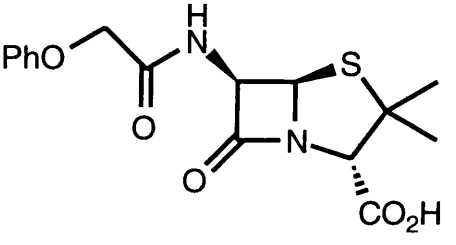
(1)



(2)

The difficulty in assigning the structure of (1) was due primarily to its instability in both acidic and alkaline media. Ironically the reactivity of the β-lactam ring towards nucleophiles, which is the source of this instability, is central to the biological mode of action. R.B.Woodward[3] gave an elegant explanation of this reactivity in terms of the fused five membered ring inhibiting nitrogen lone pair delocalisation and thus preventing amide resonance stability.

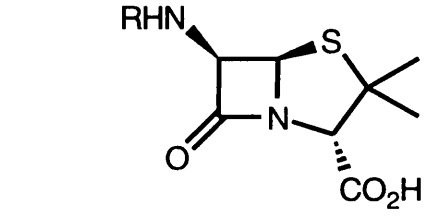
It was soon realised that the quantity and type of penicillin produced during fermentation depended upon the strain used and the composition of the growth medium. In 1948 workers at Beechams found that the aminoacyl group of penicillin could be altered by the addition of certain monosubstituted acetic acids to the fermentation broth. In this way penicillin V (3), the first acid stable penicillin, was produced. This technique is limited, however, and modern production is almost solely concerned with the production of penicillins V (3) and G (2) using high yielding strains of *Penicillium chrysogenum.*



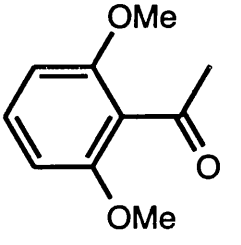
(3)

This limitation was to change dramatically in 1958 when, again at Beechams, it was found that the omission of acetic acids from the fermentation process yielded

the penicillin nucleus 6-aminopenicillanic acid (6APA) (4). This discovery opened a new era in β-lactam chemistry. The ability to produced thousands of semi-synthetic derivatives (mainly by reacylation of the β-6 amino group with various aryl and heteroaryl substituted acetic acids) led to drugs with improved therapeutic range and acid stability, exemplified by methicillin (5). As a result of low fermentation yields 6-APA is now produced by bacterial amidase hydrolysis of penicillin G (2).

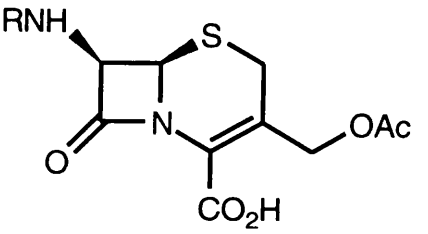


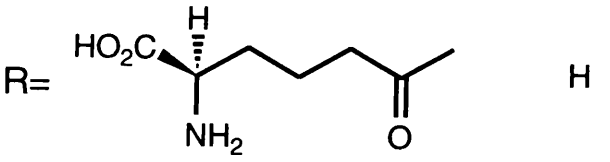
R = H



(4) (5)

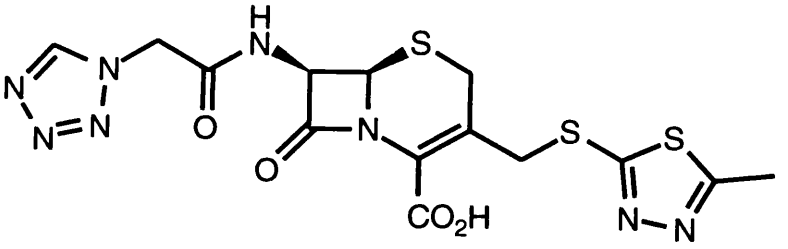
During the late 1940s physicians began to notice that certain strains of *Staphylococcus aureus* were producing an enzyme called β-lactamase which hydrolysed penicillin thus rendering it inactive.[4] Strains of bacteria which produce this type of enzyme are resistant to treatment. The discovery of a new mould, *Cephalosporium acremonium*, in Sardinia was, however, to partially overcome this problem. Investigation by Abrahams and co-workers in Oxford[5] revealed that its antibiotic activity was in part due to the novel antibiotic cephalosporin C (6). The antibacterial activity of cephalosporin C was low, but the apparent relationship to the penicillin family, coupled with its resistance to staphylococcal β-lactamases, made it of immediate interest. Unlike penicillin, however, the nucleus 7-aminocephalosporinic acid, 7-ACA (7) could not be produced efficiently by fermentation and had to be manufactured by hydrolysis of cephalosporin C.





(6) (7)

This precursor, like 6-APA, allowed a great number of semisynthetic cephalosporins to be produced (mainly by C7 and C3' alterations), *e.g.*, cefaxolin (8).

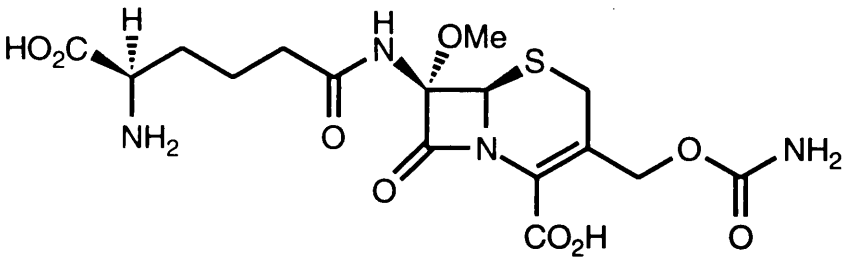


(8)

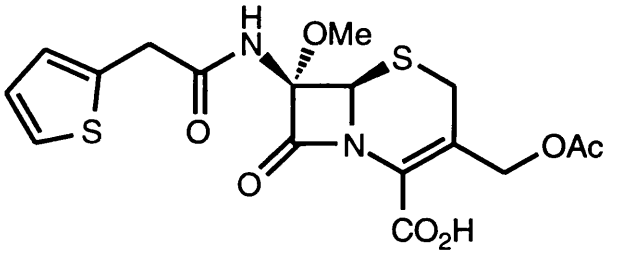
Cefaxolin is a member of the first generation of semi-synthetic cephalosporins and is effective against organisms resistant to penicillin G and methicillin. The drug is administered as its sodium salt and marketed by Lilly under the trade name Kefzol.

By the late 1960s the use of such broad spectrum antibiotics caused an alarming rise in the number of bacterial strains resistant to both penicillins and cephalosporins. This applied more pressure on research groups to find new, and hopefully more resistant, antibiotic families.

In 1971, 17 years after the discovery of cephalosporin C, an essential structural variant, cephamycin A (9)[6] was discovered by Nagarajan and co-workers from the yeast *Streptomyces*. Cephamycins are 7α-methoxy cephalosporins with exceptional stability against β-lactamase producing bacteria. Their discovery gave birth to a second generation of cephalosporins exemplified by cefoxitin (10) which is active against Gram-negative bacteria.

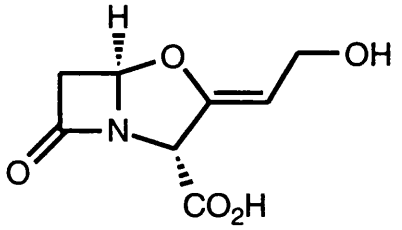


(9)



(10)

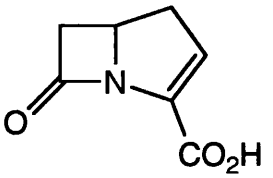
In 1976, during the course of screening for natural inhibitors of β-lactamases, workers at Beechams isolated the β-lactam clavulanic acid (11)[7] from *Streptomyces clavuligerus*. Although it does not possess significant antibacterial activity, clavulanic acid (11) is a powerful and irreversible inhibitor ("suicide substrate") of many β-lactamases from both Gram positive and negative bacteria.[8] Co-administration of (11) with amoxycillin was found to be effective against many previously resistant infections. This synergistic combination was launched as Augmentin® in 1981.



(11)

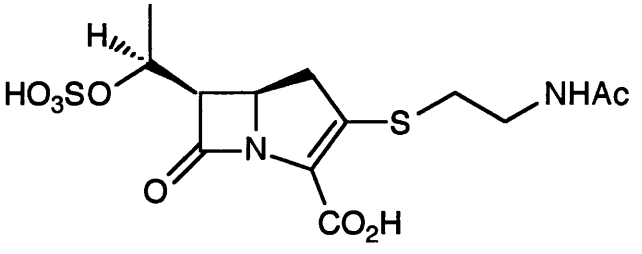
The second class of novel β-lactams antibiotics to be discovered in 1976 was the carbapenems. This family of about 50 metabolites (within seven sub-groups), from *Streptomyces* spp. is characterised by the highly reactive 1-carbathiapen-2-em ring system (12). Most of this group are either highly active against bacteria or β-

lactamase inhibitors. Indeed, it is interesting to note that this activity even extends to the parent nucleus which has a potency equivalent to clinical penicillins.[9]



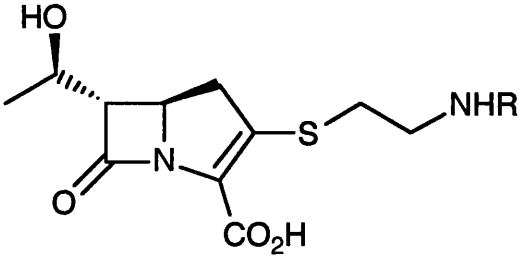
(12)

The first members of this class to be isolated were the olivanic acids,[10] *e.g.*, (13). These compounds are potent inhibitors of β-lactamases but for various reasons, including metabolic instability, they have not been developed clinically.



(13)

A few months later a research group at Merck announced the isolation of thienamycin (14) from *Streptomyces catttleya*.[11]

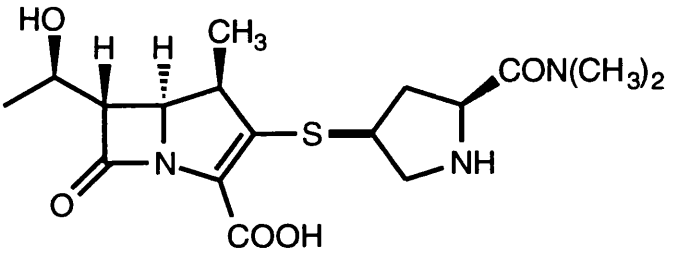


(14) R=H (15) R= $CONH_2$

Thienamycin not only has extremely broad antibacterial activity, but is both an effective inhibitor of, and stable to, β-lactamases. The natural product, however, is unstable in aqueous solution: the amino group of the C-2 side chain cleaves the β-lactam ring intramolecularly.[12] This initial problem was overcome by producing the N-formimidoyl derivative (imipenem) (15). Unfortunately, it was found that this

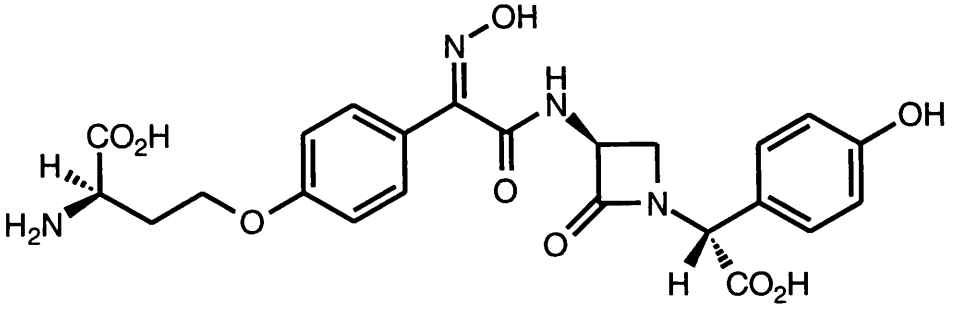
compound is inactivated *in vivo* by renal dehydropeptidase I (DHP-I) and so has unfavourable pharmacokinetics.[13] A combination of (15) and a DHP-I inhibitor (Cilastatin®), which suppresses imipenem metabolism within the kidney, is now marketed very successfully by Merck as Primaxin®.[14] Due to very low fermentation titres Merck has found it necessary to produce imipenem by total synthesis.

The necessity for the administration of two drugs is obviously economically undesirable. More recently the synthesis of synthetic analogues by several groups has shown that a C1 β-methyl confers considerable DHP-1 stability to thienamycin. Compound SM-7338 (16), developed by workers at Sumitomo, exhibits a well balanced antibacterial spectrum including antipseudomonal activity and high stability to DHP-1.[15]



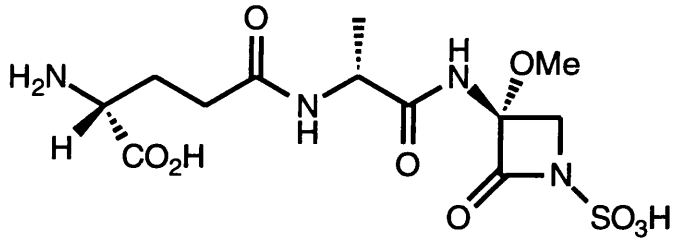
(16)

The first natural monocyclic β-lactam, nocardicin A (17), was also isolated in 1976.[16] It has only modest antimicrobial properties and has never been developed for clinical use. The discovery of the nocardicin class was made possible by the use of ultrasensitive screening techniques.



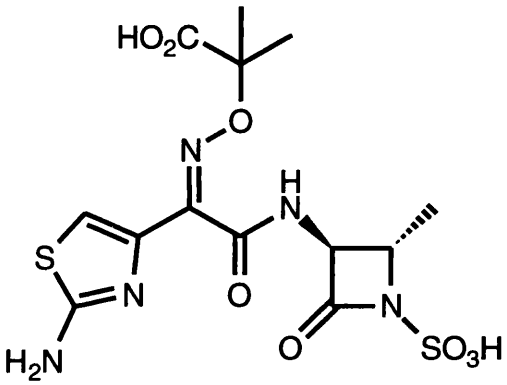
(17)

A second and clinically more useful class of monocyclic β-lactams, the monobactams, were isolated from soil bacteria in 1981 by teams at Takeda[17] and Squibb.[18] The first member of this class was sulfazecin (18). The presence of the unusual *N*-sulphonic acid group is thought to activate the β-lactam ring towards nucleophilic attack.



(18)

From this family has emerged aztreonam (19). Marketed by Squibb for the treatment of serious pseudomonal infections, aztreonam, like imipenem, has to be produced by total synthesis.

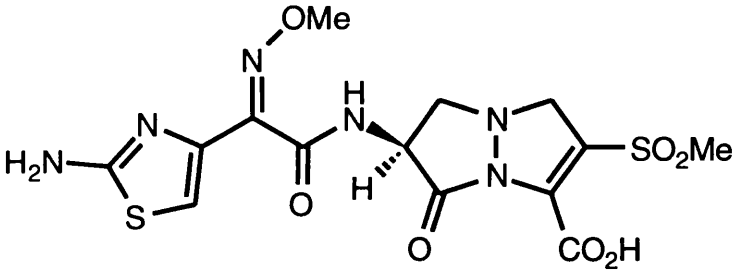


(19)

Despite continued efforts with very sensitive screening techniques, no further new β-lactam families have been found to date and it seems unlikely that many more will be uncovered. The continued evolution of β-lactamases and resistant bacteria, however, demand that new clinical antibiotics be developed. This demand is being met in two ways :

- Variation of existing families, *e.g.*, by combining the most potent features of existing penicillins and cephalosporins.
- Design and synthesis of molecules which, although not β-lactams, mimic their pharmacophore.[19]

The most successful attempt to produce such β-lactam surrogates was achieved by chemists at Lilly. These antibiotics, based upon [3.3.0] fused pyrazolidinones, *e.g.* , LY193239 (20),[20] show very promising antibacterial activity and are currently being investigated further by several groups.



(20)

1.2 Biological Activity

Central to the activity of all β-lactams is their ability to inhibit selectively enzymes essential for the biosynthesis of bacterial cell walls and more precisely peptidoglycan biosynthesis.[21] Mammalian cells have no comparable structure, which explains the selective toxicity of β-lactams towards bacteria.

Bacteria have a high internal osmotic pressure and require a structure external to the cell to prevent rupture of the relatively fragile cytoplasmic membrane. This protection is afforded by the cell wall, a mesh-like polymer, peptidoglycan, which encapsulates the bacterial cell. Peptidoglycan is composed of linear chains of glycan consisting of alternating N-acetylglucosamine (NAG) and N-muramic acid (NAM) residues, linked β-[1,4] [Fig. (1)]. Each NAM residue is linked (via a lactate bridge) to a pentapeptide which in turn is linked to pentaglycyl chain at the lysine residue. The final stage in the biosynthesis of peptidoglycan is carried out by the enzyme glycopeptidase transferase and involves the cross linking of these peptide chains. The enzyme forms an acyl intermediate with the penultimate D-alanine residue of the five amino acid sequence which then reacts with the amino group of the terminal glycine of an adjacent peptide, expelling D-alanine (hatched line indicates the point of peptide cleavage) and forming the cross link.[22]

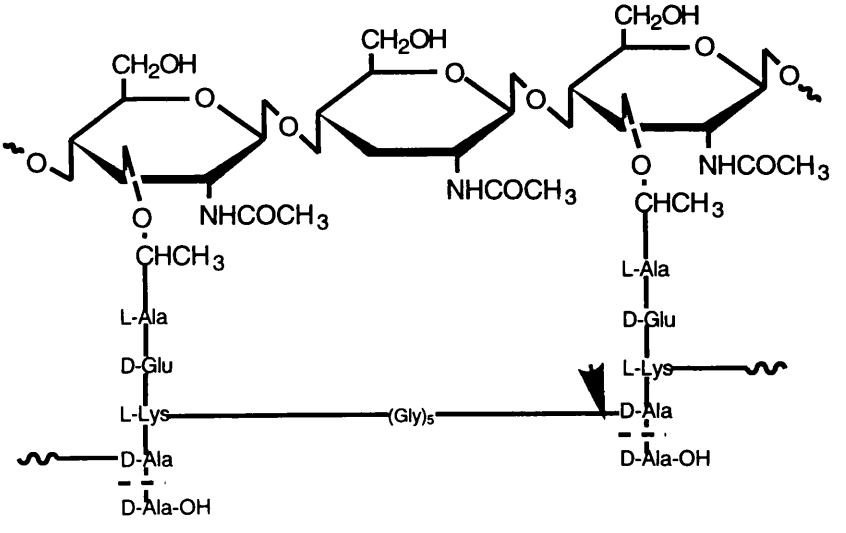
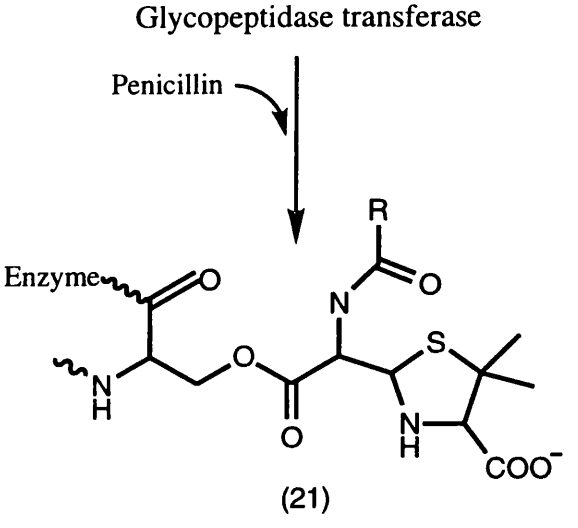


Figure 1. Structure of peptidoglycan. The heavy arrow indicates the site of action of transpeptidase.

It was proposed by Tipper and Strominger that penicillin mimics the R-alanyl-R-alanine C terminus of the natural substrate.[23] Preferential binding of the β-lactam to the enzyme's active site results in azetidinone ring opening by a serine residue. Although the resultant penicilloyl/enzyme ester (21) is stable, it is not fully known whether its resistance to hydrolysis and subsequent lack of enzyme regeneration account for the observed inhibition [Fig. 2].



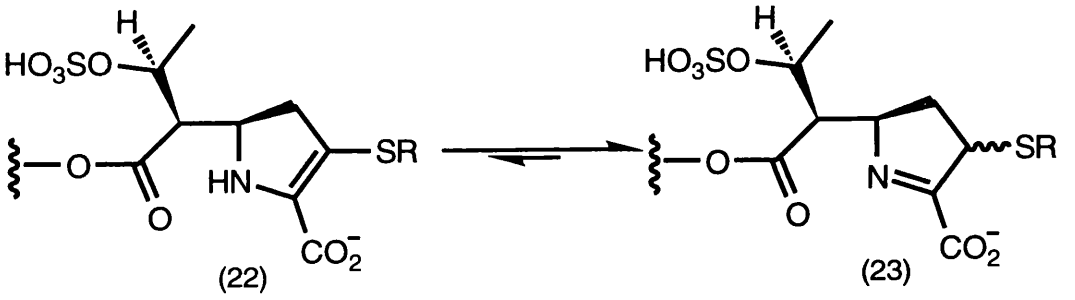
(21)

Figure 2. Structure of the penicilloyl-enzyme complex.

Prevention of this final step causes defective formation of peptidoglycan and eventual cell lysis by osmotic pressure, resulting in cell death.[24]

In recent years this has been a very active field of research and it has become apparent that the interaction of bacteria with β-lactams is much more complex than originally thought. Although it is believed that this general mechanism applies for all β-lactam antibiotics the details change from bacterial species to species. It is now known that β-lactams have several possible enzyme targets, the penicillin binding proteins (PBP). To date, seven have been found ; however, only binding to numbers 1, 2 and 3 cause cell death. Other members of this group are β-lactamases which, as mentioned before, hydrolyse β-lactams to inactive products.[25] The main difference between β-lactamases and transpeptidases is that the former do not form stable

enzyme-substrate intermediates, *i.e.*, they have a high catalytic turn-over. The spread of bacterial resistance is mainly due to the evolution of this class of enzyme. The success of β-lactamases inhibitors such as clavulanic acid (11) and the carbapenems relies on their ability to form very stable acyl-enzyme intermediates which inactivate the enzyme. This stability is due to rearrangement of the enzyme bound inhibitor as is the case with olivanic acids. Knowles and co-workers have demonstrated that olivanic acids progressively inhibit β-lactamases by tautomerism of the initial product of azetidinone ring opening, Δ^2-pyrroline (22), to the apparently more stable Δ^1-intermediate (23).[26] Again, this may not be the complete picture and indeed there is evidence that the enzyme released after interaction with this compound is conformationally altered and unable to recognise natural substrates.[27,28]



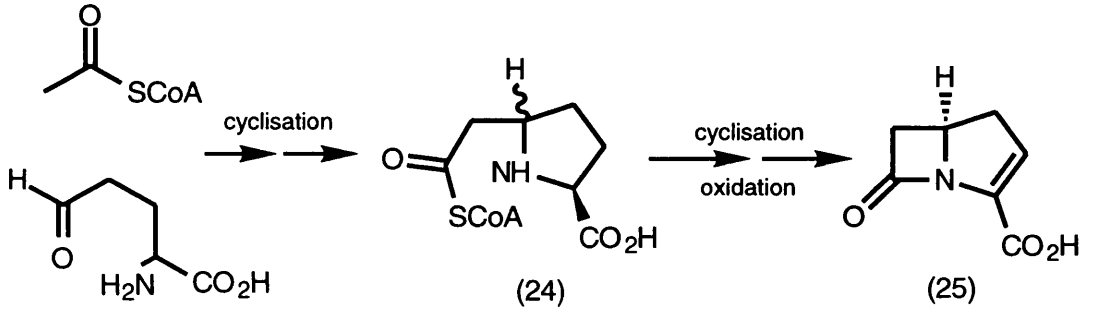
From the extensive studies in this area what does appear to be clear is that to be antibacterially active β-lactams must have the following fundamental properties:

- good bacterial cell wall permeability, *i.e.*, the drug must be able to get to the the target enzymes (PBPs)
- high stability to deactivating enzymes such as β-lactamases
- high affinity for the enzymes essential for bacterial cell growth.

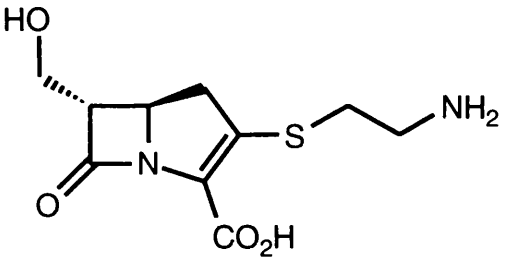
1.3 Biosynthesis

The obvious importance of penicillin and cephalosporins has spawned much research into their biosynthesis. As a result, there is now a relatively clear and detailed picture of the events during their biosynthesis.[29] This is not the case with the carbapenem family. Although studies are still in an initial phase, it has been found that the biosynthetic pathways to carbapenems are markedly different from that of their predecessors.

Some of the earliest studies were carried out by workers at Merck who, using labelling experiments, established that the pyrrolidine ring of thienamycin is derived from glutamic acid.[30] Further investigation by this group revealed acetate to be the source of C-7 and C-6 of the β-lactam ring.[31] Baldwin and Schofield have suggested that acetyl coenzyme-A may condense with glutamate semi-aldehyde to give intermediate (24) which can be cyclized and oxidised to give the carbapenem nucleus (25) which is thought to be a biosynthetic intermediate.[29] Isolation of (25) from the species *Erwina* and *Serratia*, as it *p*-nitrobenzyl ester, has supported this assumption.[32]



The isolation of northienamycin (26)[33] prompted the Merck group to examine the possibility that the hydroxyethyl side-chain of thienamycin was formed by two single methyl transfers to the carbapenem nucleus. They showed that this is indeed the case and that the methyl source is methionine or its activated form, S-adenosyl methionine (SAM).



(26)

Floss and co-workers[34] have shown by feeding experiments that chirally labelled methyls (^{1}H, ^{2}H, ^{3}H) from methionine are transferred with near retention of configuration (at C-9) in contradiction to the expected inversion associated with S-adenosylmethionine transferases.[35] This surprising discovery has been explained as possibly arising from an initial methyl transfer from SAM to cobalamin, followed by a second transfer, with net retention, to the carbapenem skeleton. It is of note that carbapenem biosynthesis is enhanced by the addition of cobalt or vitamin B_{12}. [Figure (3)] shows a hypothetical biosynthetic pathway postulated, by the Merck group, for the introduction of the 2C sidechain to C-6 of carbapenems.

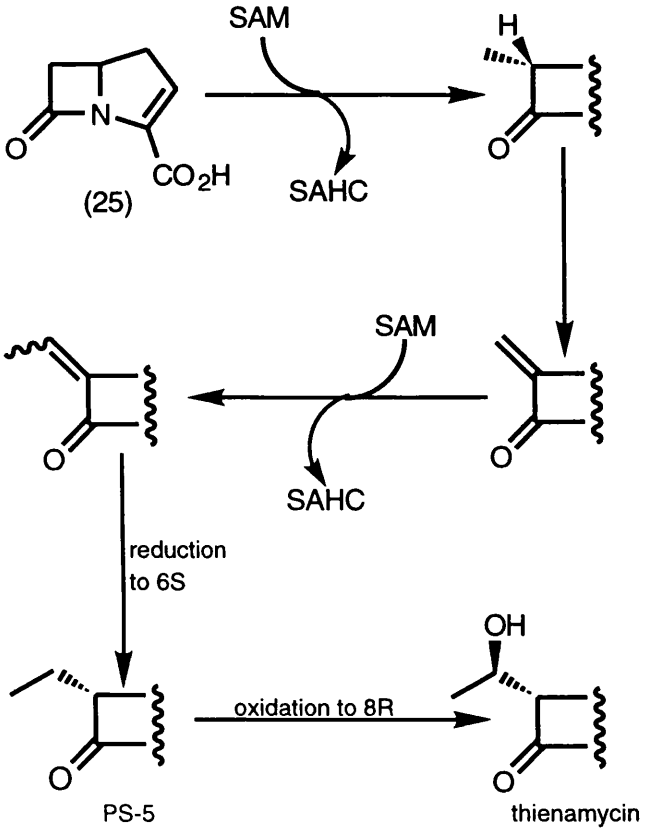
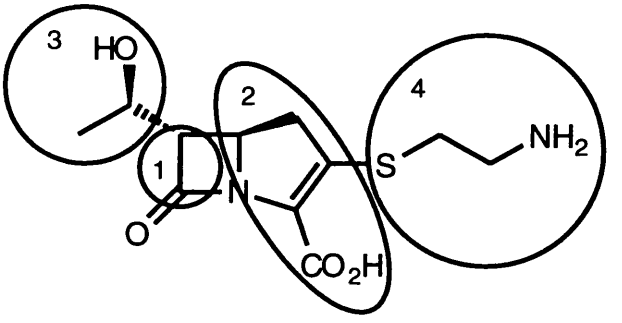


Figure 3.

Labelling has also shown that the C-2 sidechain in thienamycin originates from cystine.[29] It has been suggested that the final stages of biosynthesis may involve the [1,4] addition of cystine (or a related metabolite) to the intermediate (25) followed by decarboxylation and oxidation. A recent biomimetic synthesis by a group at Beechams follows a very similar route.[36]

A summary of the biosynthetic origins of thienamycin is shown in [Figure 4.].



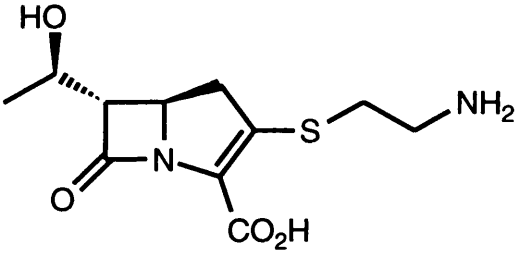
1. Acetate (Acetyl CoA)
2. Glutamate or Glutamate semi-aldehyde
3. Methionine (S-Adenosylmethionine)
4. Cystine

Figure 4.

1.4 Synthesis of carbapenems

1.4.1 Introduction.

The discovery of thienamycin and the other carbapenem antibiotics was a highly significant event in several ways. Thienamycin not only possesses an unrivalled antimicrobial potency but its unique structure has radically altered the understanding of β-lactam structure activity relationships. This combination of features together with its unavailability from fermentation has aroused a great deal of interest in the synthesis of thienamycin, carbapenems and their analogues. The objectives of total synthesis are multipurpose; synthesis directed at natural products have been used as demonstrations of methodology for the construction of the bicyclic nucleus while, more importantly, the evolution of synthetic strategy has allowed rapid analogue synthesis and thus development of more potent antibiotics.



(14)

Research groups at Merck played a key role in the development and synthesis of (14), the first racemic synthesis was published in 1978[37] and that of (+)-thienamycin being completed shortly thereafter in 1980.[38] This second synthesis was subsequently modified by Melillio and co-workers to allow industrial production of the *N*-formimidoyl analogue, imipenem (15) (see Section **1.4.3.3.2**).[39] Although subsequent literature coverage has been extensive, few papers other than those from Merck have dealt with the total synthesis of the natural isomer. In contrast, there have been numerous formal syntheses published and it is testament to the success and efficiency of the Merck synthesis that many of these routes are aimed at its intermediates.

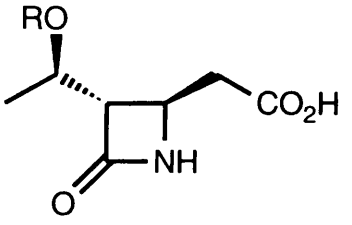
Examination of thienamycin's structure reveals two major obstacles to be overcome:

- Elaboration of the three contiguous chiral centres, at C-5, C-6 and C-8, in a stereocontrolled manner thus avoiding troublesome separations and the need to 'carry' unwanted diastereomers during further elaboration
- Construction of the highly unstable carbapenem ring system

Prior to 1980 most synthetic studies concentrated on the construction of the then novel carbapenem nucleus with little attention being paid to the incorporation of the hydroxyethyl side-chain or to absolute stereocontrol.[40] The lability of the carbapenems has dictated that in most synthetic studies the β-lactam ring and all chiral centres are constructed first, followed by formation of the second ring in conjunction with, or followed by, C-2 sidechain incorporation. This general strategy, first adopted by R.B. Woodward[41] in his synthesis of cephalosporin C, has two advantages over the alternative approach adopted by Sheehan[42] in his synthesis of penicillin:

- The problems of molecular strain are minimised by leaving formation of the destabilising second ring for as long as possible, *i.e.*, usually the penultimate step (to be followed by mild functional group deprotection)
- Sequential ring formation allows greater scope for the synthesis of analogues.

While there are relatively few methods for the closure of the second ring, usually based on intramolecular Wittig or diazo insertion reactions the literature is replete with methods for the synthesis of 4 substituted α-[(*R*)-1-hydroxyethyl]-2-azetidinones. Two such pivotal intermediates are (27) and (28).



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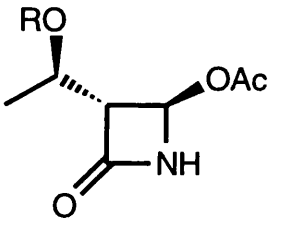
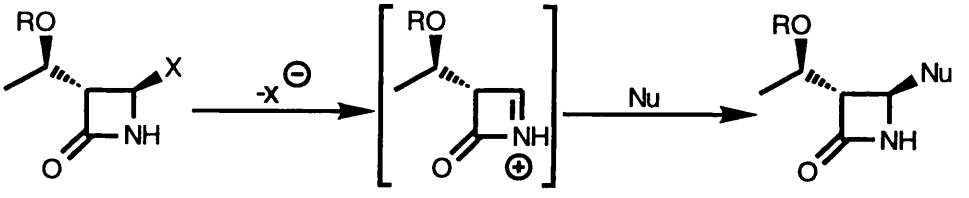


(28)

The former is a Merck intermediate and as such has been the target of many formal syntheses. However, it has been (28) which has proved to be the most versatile carbapenem intermediate since a variety of C-4 sidechains required for elaboration of the second ring can be incorporated by substitution of the acetoxy group with a range of nucleophiles (Scheme 1). These C-4 alkylations are regarded as a type of aldol reaction between enolates or their equivalents (in the presence of a Lewis acid) and the *N*-acyliminium ion (29) [1,4 dehydro β-lactam].



(29)

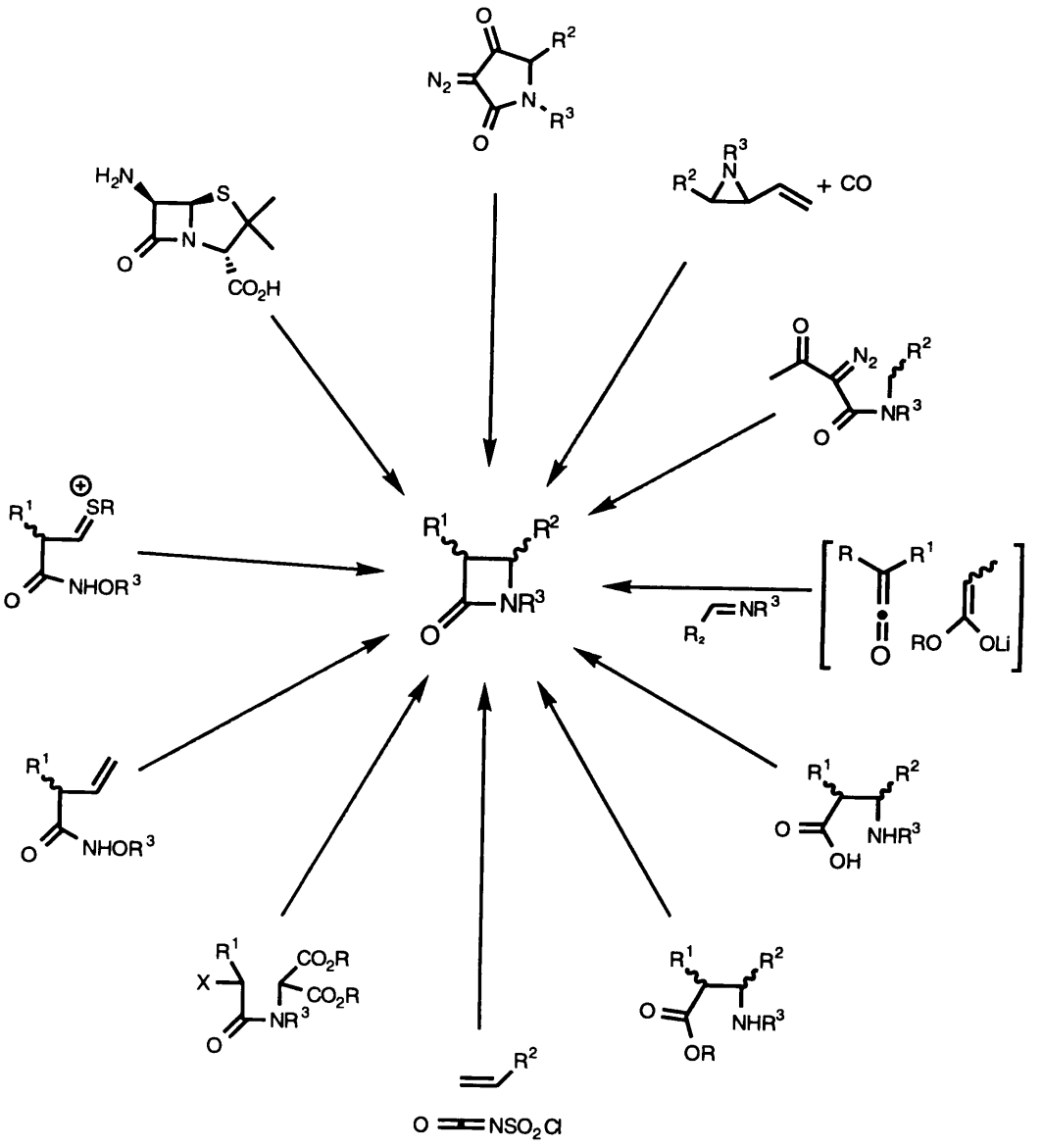
Scheme 1.

The mechanism of this reaction has two important consequences: (i) only *trans* substituted products are obtained and (ii) the stereoselective synthesis of (28) is considerably simplified as the relative stereochemistry at C-4 is not important. It has been found that this type of C-4 alkylation can also be achieved with 4-halo and 4-thio substituted β-lactams.

In the following review I shall first consider some of the more important routes to monocyclic azetidinones then discuss methods for ring closure to the carbapenem together with methods of controlling the stereochemistry of the hydroxyethyl sidechain. Finally I shall highlight some of the stereocontrolled syntheses. While it is not possible to give a complete account of this area I wish to convey some of the more significant results.

1.4.1 Formation of monocycles

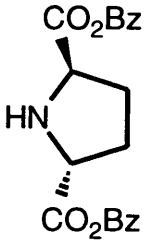
Scheme (2), illustrates most of the general routes encountered in the synthesis of thienamycin and the other carbapenems.



Scheme 2.

1.4.1.1 Photochemical Ring Contraction.

The earliest synthesis of a carbapenem ring system was achieved by Lowe who carried out the photolytic Wolff rearrangement of diazodione (32).[43] This intermediate was prepared by the coupling of amine (30) with *t*-butyl hydrogen malonate yielding an amide intermediate which underwent diastereoselective cyclization and decarboxylation to afford (31) when treated with NaH. Diazo transfer with MsN_3 and Et_3N gave (32) which when photolysed at -70°C in the presence of β-methylphenethyl carbazate gave carbapenem (33). This compound was very unstable and could not be isolated. Despite these isolation problems, Lowe's protocol has been successfully used by a group at Merck for the synthesis of northienamycin.[44]



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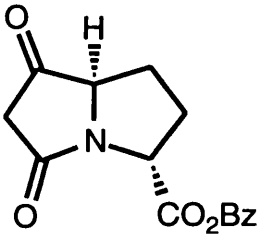

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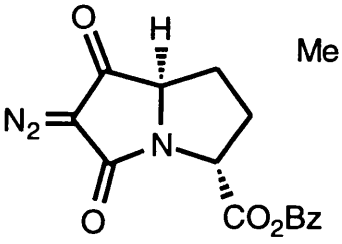

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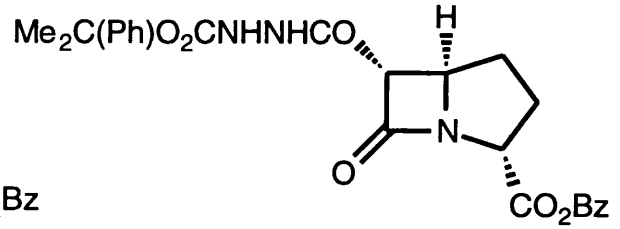
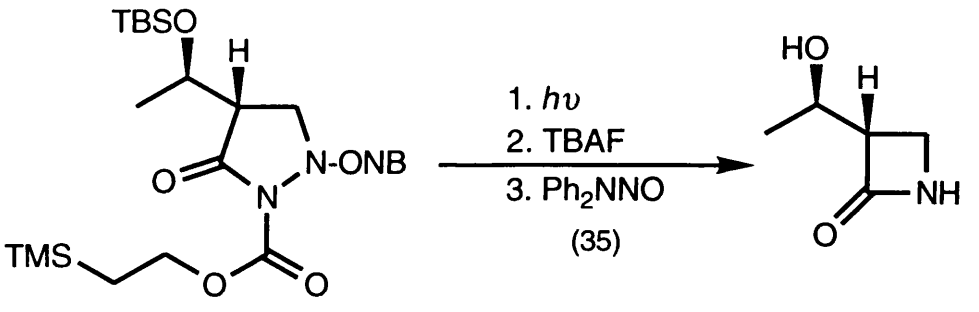


(33)

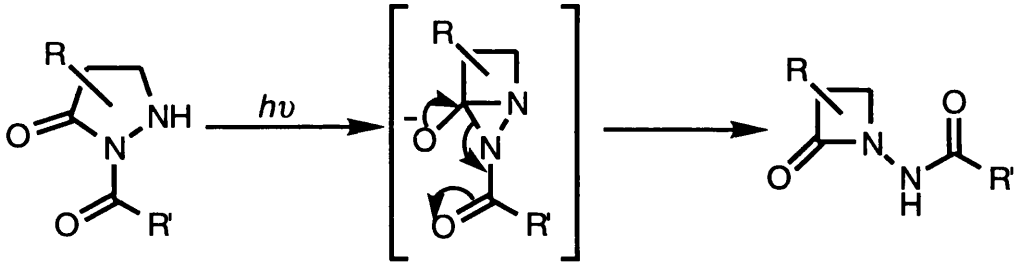
Unlike more conventional methods, photochemical ring contraction has received little attention in the synthesis of carbapenems. There are, however, two notable exceptions: photoisomerisation of 4-pyrimidones[45] and the ring contraction of pyrazolidinones. In a recent reinvestigation of the latter by White and co-workers it was found that photolysis of (34) first removes the *o*-nitrobenzyl group and then

effects ring contraction.[46] Deprotection and mild nitrosative deamination with (35) give the thienamycin precursor (36) in good yield.



(34) (36)

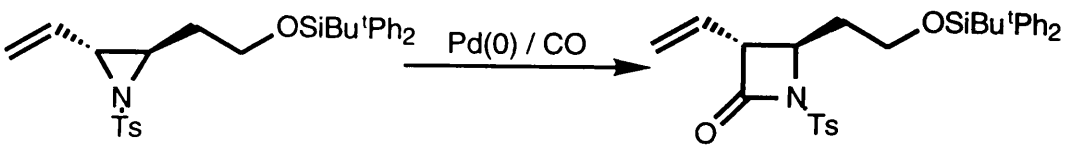
It has been suggested that this ring contraction proceeds *via* the highly reactive bicyclic diazirine (37) which collapses to the azetidinone by a retro-aldol type fragmentation.



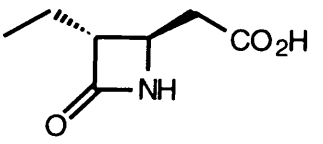
(37)

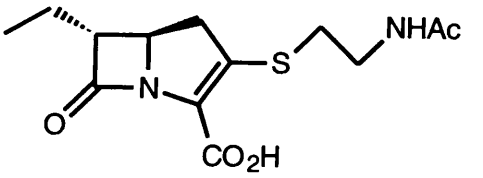
1.4.1.2 Ring Expansion: Carbonylation of Aziridines.

This approach, first studied by Alper [47] in 1983, has recently been used by Tanner in a formal synthesis of PS-5 (41).[48] Optically pure aziridine (38) underwent regio- and stereoselective carbon monoxide insertion in the presence of a catalytic amount of a Pd(0) complex to give β-lactam (39) in moderate yield. A sequence of de-protection, double bond reduction and oxidation of the alcohol gave (40), a known intermediate in the total synthesis of PS-5 (41).



(38) (39)



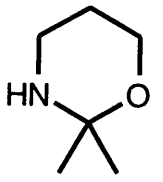


(40) (41)

The application of organometallic chemistry in the synthesis of β-lactams has been reviewed by Barrett and Sturgess.[49]

1.4.1.3 α-Diazoamides.

In an extension of earlier work by Corey[50] and Lowe,[51] workers at Beechams utilised the intramolecular insertion of a carbene/carbenoid into a C-H bond to achieve β-lactam ring closure.[52] Treatment of tetrahydrooxazine (42) with diketene, followed by diazo exchange of the resultant acetoacetamide (43) gave intermediate (44). Subsequent decomposition with a catalytic amount of $Rh_2(OAc)_4$ yielded (45), a key intermediate in the first Merck thienamycin synthesis.[37]



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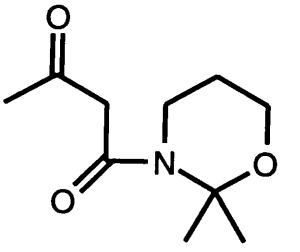

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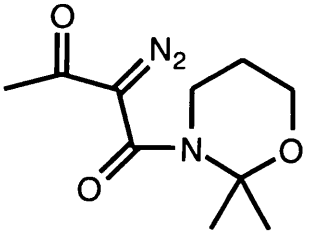
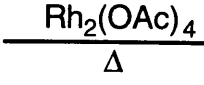
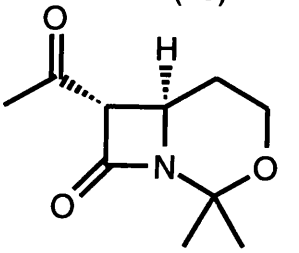
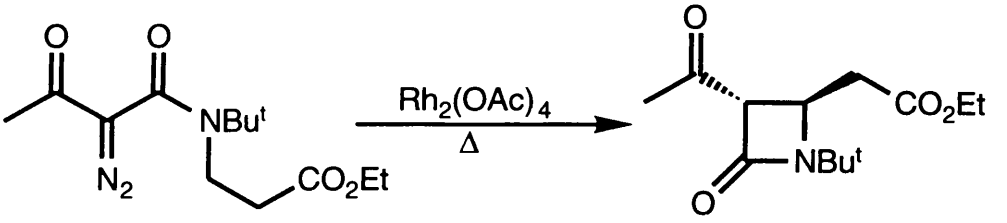






(44) (45)

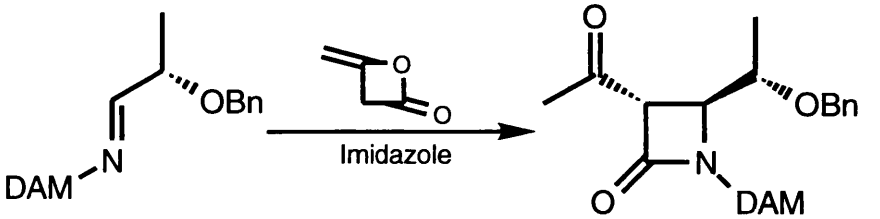
In a further extension to this strategy Doyle has shown that diazoamide (46) undergoes exclusive β-lactam formation to provide (47) in very high yield and with excellent stereocontrol.[53] The use of chiral rhodium catalysts in this reaction is currently under investigation.



(46) (47)

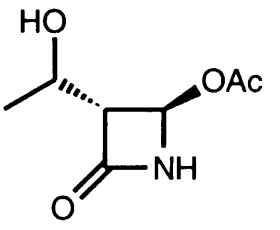
1.4.1.4 Ketene /Imine Cycloaddition.

This reaction, first investigated by Staudinger[54] in 1907, involves the *in situ* formation of a ketene (from the corresponding acid chloride) and its condensation with an imine to give predominantly the *cis* C-3/C-4 disubstituted azetidinone. Although widely used in the synthesis of classical β-lactams, few reports of C-3 alkyl, acetyl or alkylidene sidechain incorporation existed until recently. Terashima has utilised the chirality of ethyl lactate to produce optically pure thienamycin precursors.[55] Condensation of chiral imine (48) with diketene, in the presence of imidazole, furnished the *trans* 3-acetyl-β-lactam (49) as the major product.



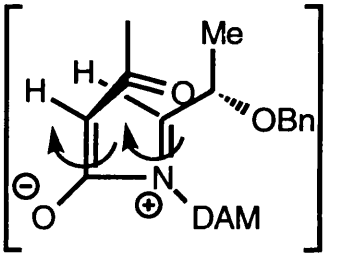
(48) (49)

This compound was elaborated in six steps to the previously mentioned intermediate (28).



(28)

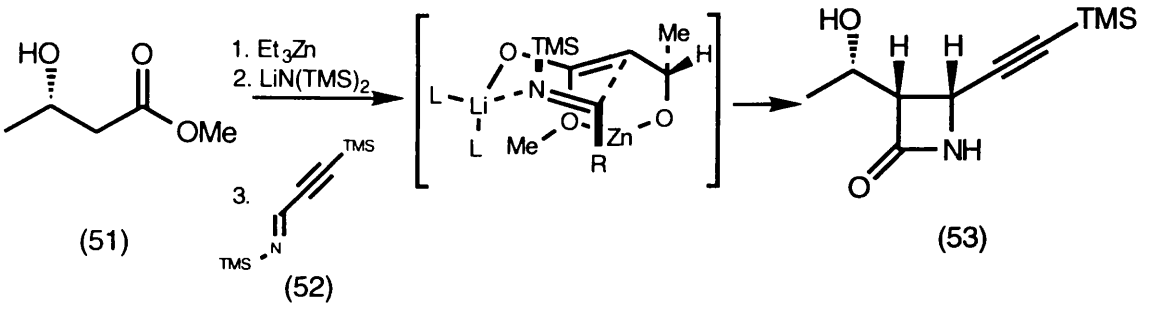
The mechanism of the [2+2] cycloaddition is not clearly understood; however, the initial formation of the zwitterionic species (50) followed by a conrotatory ring closure, governed by the chiral centre, explains the formation of the *cis* product which then undergoes imidazole catalysed epimerisation to (49).



(50)

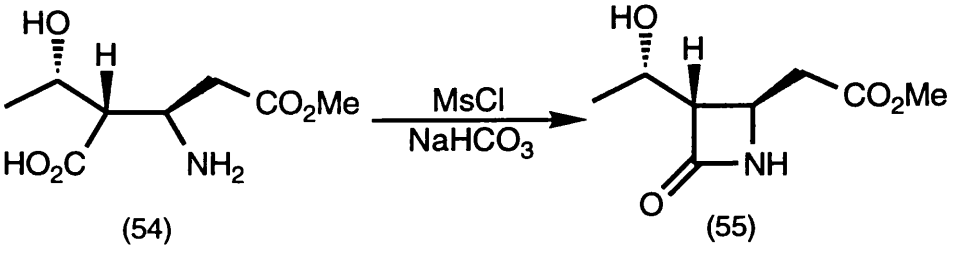
1.4.1.5 Ester enolate/Imine Cycloaddition.

This route involves the reaction of an ester enolate, or equivalent, with an imine followed by cyclization of the resultant metallated amine (*cf.* Section **1.4.1.7**). Originally investigated by Gilman in 1943,[56] the increase in the scope of this reaction coincided with the development of the aldol reaction with which it has many similarities. Use of 3-hydroxybutyrates as the ester components leads to β-lactams with the α-hydroxyethyl sidechain of thienamycin. The obvious potential of this strategy attracted investigation by a number of groups.[57] A recent example comes from Oguni who achieved good yields and excellent diastereoselectivity.[58] Thus, treatment of (*S*)-ethyl β-hydroxybutyrate (51) with diethylzinc followed by lithium hexamethyldisilazide [$LiN(TMS)_2$] and imine (52) furnished *cis* β-lactam (53) as a single diastereomer.



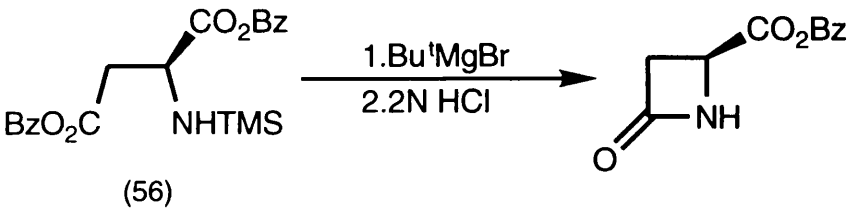
1.4.1.6 Cyclization of β-Amino Acids.

One of the most fundamental approaches to the synthesis of azetidinones is the dehydration of β-amino acids. However, the hydroxyl function is not a sufficiently good leaving group to allow cyclization under mild conditions; direct transformation requires harsh conditions and is often accompanied by β-elimination. Consequently, numerous coupling reagents, such as dicyclohexylcarbodimide (DCC)[59] or Mukiyama's[60] reagent have been employed to facilitate ring closure. A simple and highly efficient methodology was recently developed by a group at Merck for the cyclization of (54), an intermediate in the industrial production of imipenem.[61] Thus, treatment of (54) with MsCl and $NaHCO_3$ yielded β-lactam (55) in 97% yield.



1.4.1.7 Cyclization of β-Amino Esters.

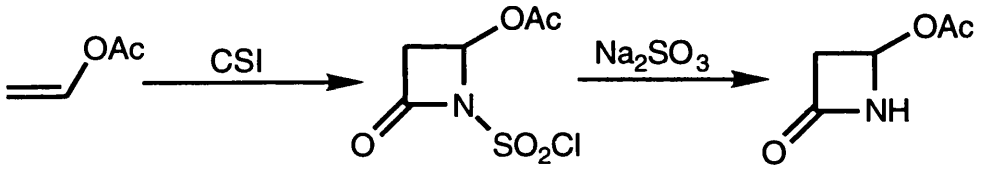
This procedure is somewhat easier to achieve than the above method. Normally, treatment of the mono-protected β-amino ester with a Grignard reagent effects ring closure; for example, in the first Merck synthesis of (+) thienamycin the protected aspartic acid derivative (56) underwent cyclization upon treatment with Bu^tMgBr.[38]



(56)

1.4.1.8 Alkenes and Chlorosulphonyl Isocyanate.

The [2+2] cycloaddition reaction between olefins and chlorosulphonyl isocyanate (CSI), followed by *in situ* reductive workup is a versatile methodology for the production of functionalised azetidinones. For example, vinyl acetate (57) reacts with CSI to give *N*-chlorosulphonyl β-lactam (58) which can be reduced in situ with aqueous Na_2SO_3 to give C-4 acetoxy β-lactam (59) in modest yield.[62]

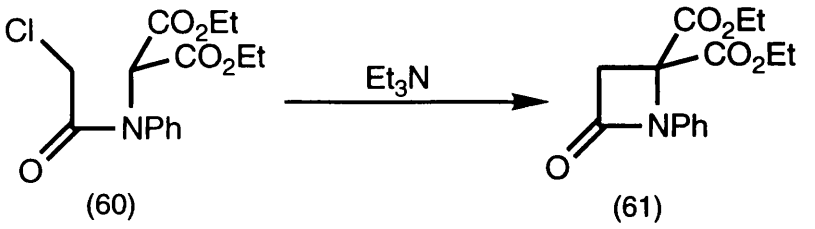


(57) (58) (59)

As mentioned previously, such C-4 substituted β-lactams are important precursors in the synthesis of carbapenems and have found widespread use. Examples of this strategy and the reaction of CSI with other olefins will be discussed later.

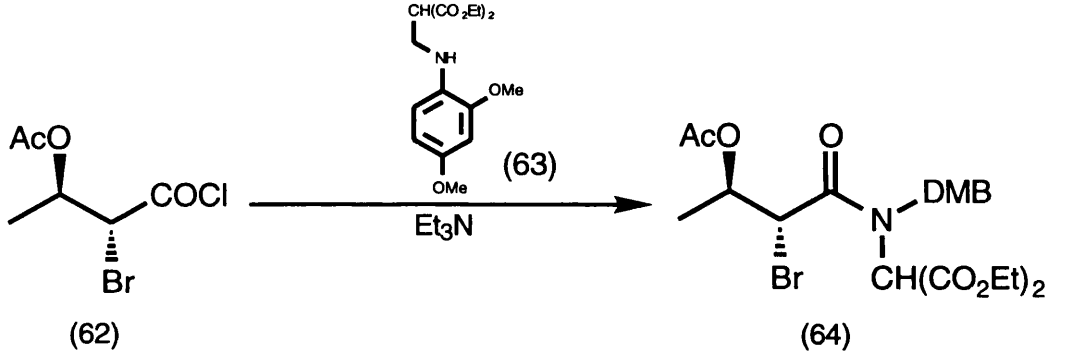
1.4.1.9 Intramolecular S_N2.

Sheehan and Bose first demonstrated that azetidinones could be constructed through the formation of the C-3-C-4 bond; *e.g.*, (60) cyclized smoothly in the presence of triethylamine to yield β-lactam (61).[63]

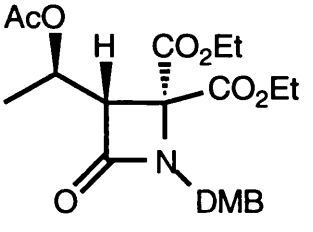


(60) (61)

Shiozaki and Hiraoka utilised this construction in the stereocontrolled synthesis of the thienamycin precursor (65).[64] The acid chloride (62) was condensed with 2,4-dimethoxybenzylamine derivative (62) to provide amide (64). When treated with DBU this amide underwent an intramolecular S_N2 to yield azetidinone (65) with complete stereochemical inversion.



(62) (64)

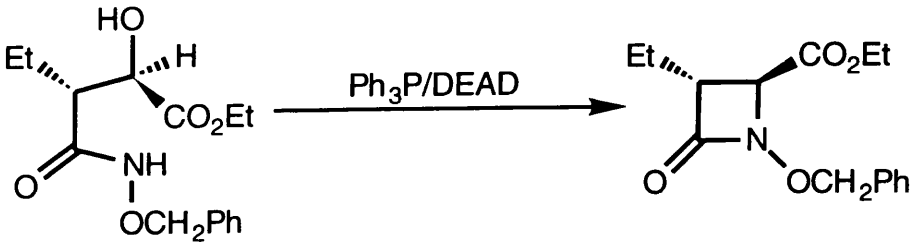


(65)

1.4.1.10 Cyclization of β-Functionalised-Hydroxamates.

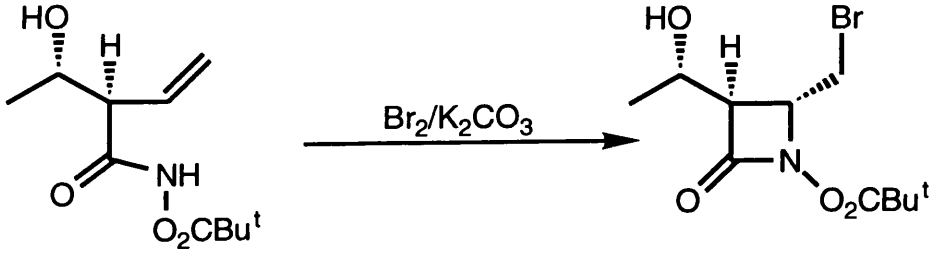
Early attempts to synthesize β-lactams by N/C-4 formation were hampered by side reactions, such as elimination. These problems arose because of the inability to deprotonate the amide while simultaneously activating the C-4 carbon. Miller and co-workers made the important discovery that hydroxamates are acidic enough to be deprotonated under very mild conditions (Cs_2CO_3) and that the resultant anion is sufficiently nucleophilic to displace halides from the β position thus providing a

facile route to azetidinones.[65] More conveniently, a hydroxyl group can also be displaced under Mitsunobu conditions; for example, β-hydroxy-hydroxamate (66) undergoes ring closure to give the PS-5 precursor (67).[66]



(66) (67)

This approach was recently extended by Miller to the oxidative cyclization of β,γ-unsaturated hydroxamates.[67] Thus, treatment of hydroxamate (68) with Br_2/K_2CO_3 furnished the β-lactam (69) in 89% yield, with complete stereocontrol.

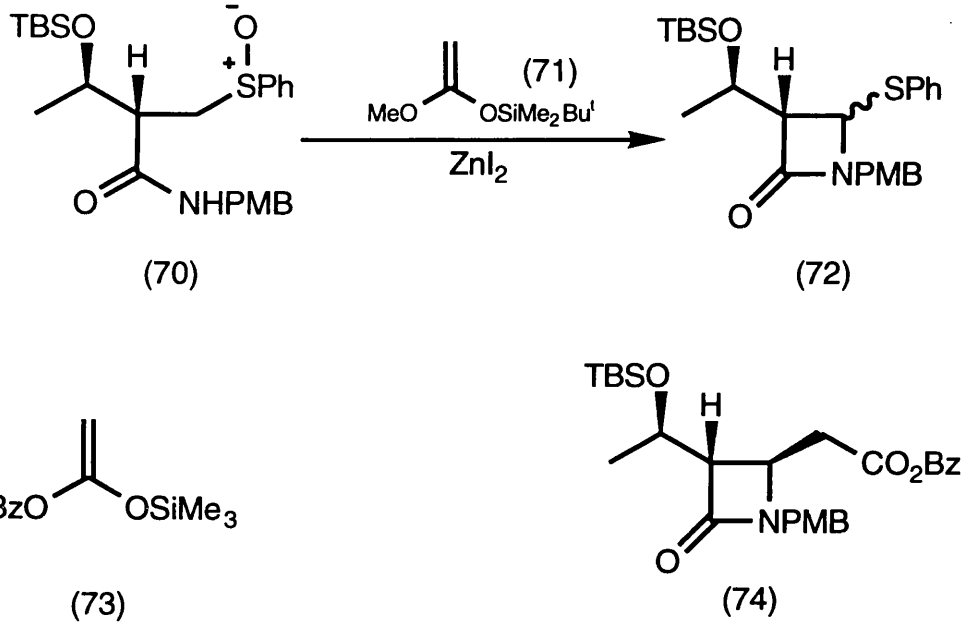


(68) (69)

1.4.1.11 Cyclization of β-Amido Sulphoxides.

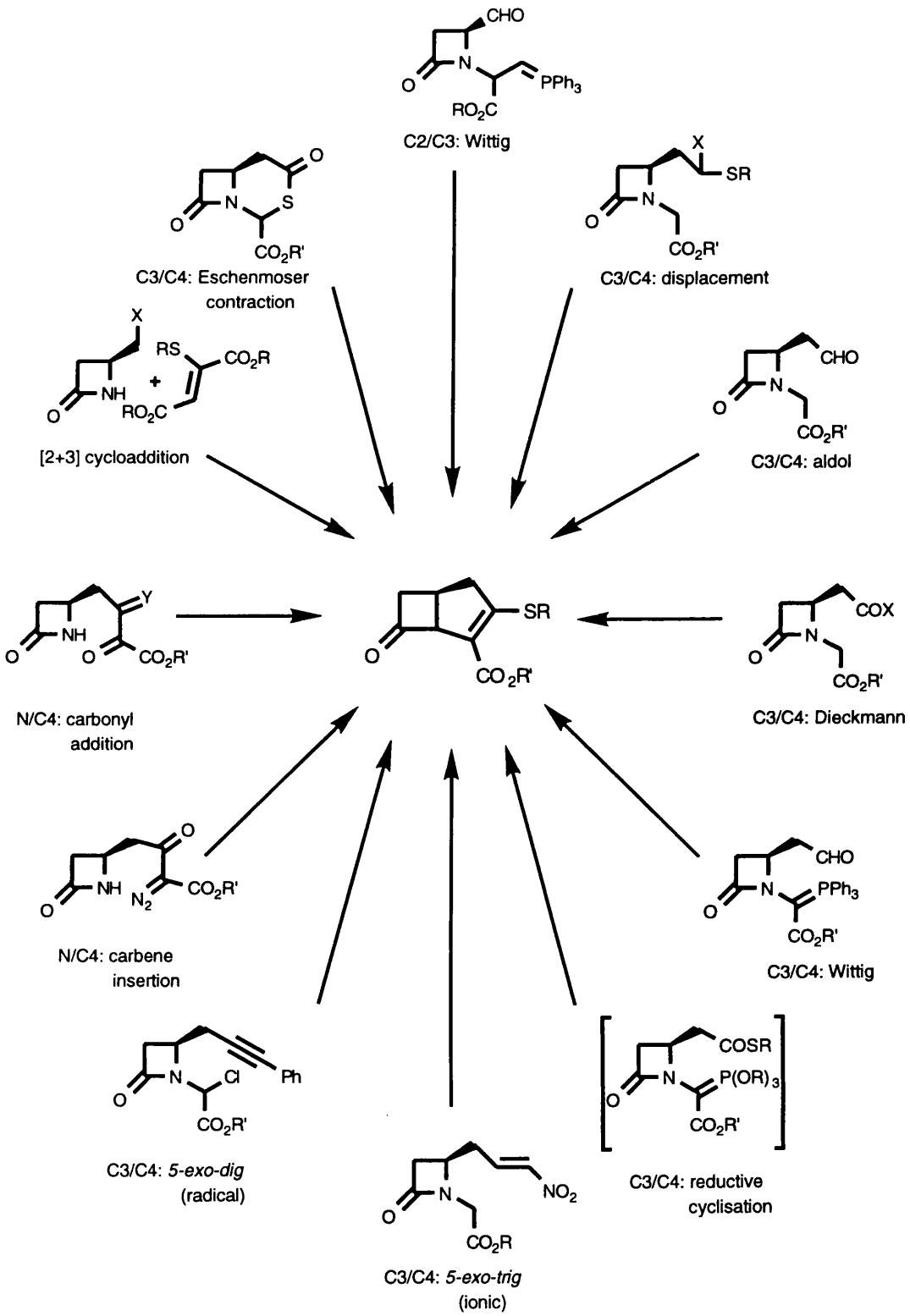
This procedure relies on formation of the N/C-4 bond and has some similarities to the previous example. A silicon-induced Pummerer rearrangement is used to generate a thioacetal at the C-4 position which upon treatment with ZnI_2 forms a suphonium cation. Intramolecular trapping of this cation by the amide results in ring closure to give synthetically useful C-4 sulphenyl β-lactams. Kita used this methodology in a recent formal synthesis of thienamycin; treatment of readily available sulphoxide (70) with *O*-methyl-*O*-*tert*-butyldimethylsilyl keteneacetal (71) in the presence of ZnI_2 provided the 4-phenylthioazetidinone (72) in good yield.[68] This intermediate was subsequently oxidised to the corresponding sulphoxide which upon treatment with (73) gave the *trans* azetidinone (74).

in good yield.[68] This intermediate was subsequently oxidised to the corresponding sulphoxide which upon treatment with (73) gave the *trans* azetidinone (74).



1.1.4.12 Degradation of Penicillin.

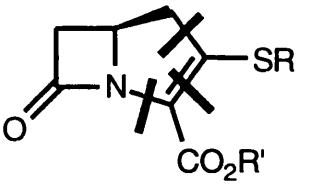
The use of 6-APA, which is cheap and readily available, to control the absolute stereochemistry of thienamycin is appealing, but it is necessary to first convert the C-5 thio and C-6 amino groups into the appropriately functionalised alkyl chains. Although a number of groups have adopted this approach most rely on the same degradation strategy, which will be discussed in Section (**1.4.3.1.1**).


C2/C3: Wittig
C3/C4: Eschenmoser contraction
C3/C4: displacement
[2+3] cycloaddition
C3/C4: aldol
N/C4: carbonyl addition
C3/C4: Dieckmann
N/C4: carbene insertion
C3/C4: Wittig
C3/C4: 5-exo-dig (radical)
C3/C4: reductive cyclisation
C3/C4: 5-exo-trig (ionic)

Scheme 4.

1.4.2 Sidechain Elaboration and Pyrrolidine Ring Closure

Scheme (3) shows the possible points of bond disconnection/formation for the synthesis of the carbapenem nucleus from monocyclic β-lactams.

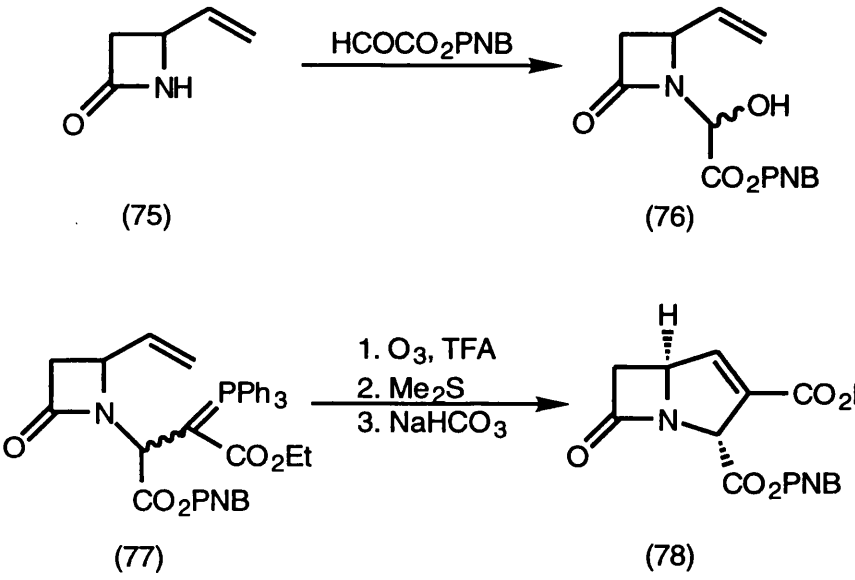


Scheme 3.

All of these disconnections have been realised with varying degrees of efficiency. Scheme (4) (opposite) illustrates some of the general approaches adopted for pyrrolidine ring closure in the synthesis of both natural products and their analogues.

1.4.2.1 C-1/C-2 Closure.

Pyrrolidine ring closure by formation of the C-1/C-2 bond has been achieved by using intramolecular aldol[69] and Wittig reactions. For example, Sharma and Stoodley prepared carbinol (76) by the condensation of vinyl azetidinone (75) with *p*-nitrobenzyl glyoxylate.[70] Further manipulation *via* the corresponding chloride gave phosphorane (77). Ozonolysis in the presence of trifluoroacetic acid revealed the required aldehyde, without affecting the phosphorane. Neutralisation of the reaction resulted in spontaneous cyclization to afford the carbapen-1-em (78) in high yield.

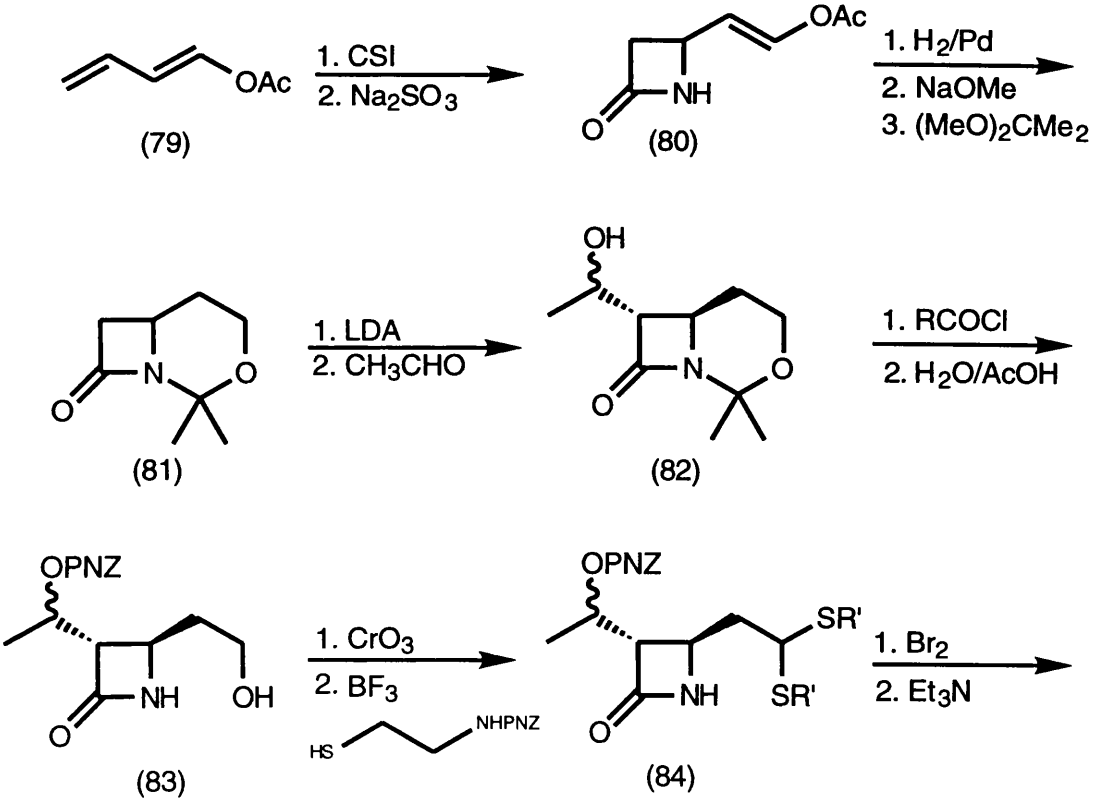


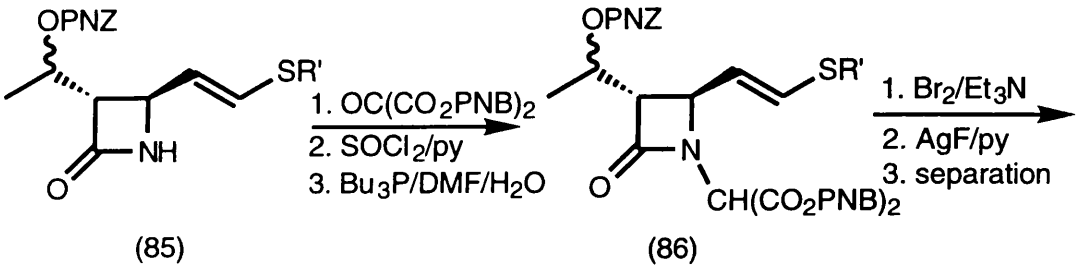
Rather surprisingly the double bond in (78) could not be isomerised to the carbapen-2-em which is after all a conjugated ester. This major shortcoming has been encountered with almost all other routes using this disconnection and consequently, little attention has been paid since the initial studies, particularly as the Δ^2 isomer seems to be essential for biological activity.

1.4.2.2 C-2/C-3 Closure.

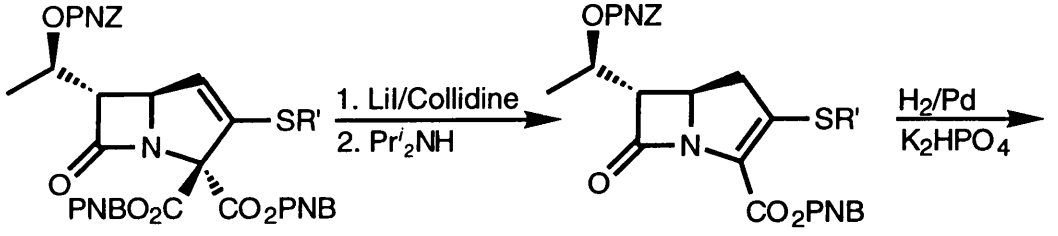
1.4.2.2.1 Substitution.

Investigators at Merck completed the first total synthesis of thienamycin by an intramolecular substitution reaction.[37] The starting point of this synthesis, monocyclic β-lactam (80), was conveniently prepared by the regioselective cycloaddition of CSI with 1-acetoxybutadiene (79), followed by *in situ* reductive hydrolysis. Efficient elaboration gave acetonide (81) which upon hydroxyethylation (LDA/CH_3CHO) furnished the *trans* β -lactam (82) as a mixture of epimers. Protection of this alcohol as a *p*-nitrobenzyl (PNZ) carbonate and removal of the acetonide gave (83) which was converted (85) *via* thioacetal (84). Condensation of (85) with *bis-p*-nitrobenzyl ketomalonate followed by chlorination and subsequent reduction gave (86) which underwent intramolecular alkylation to (87) upon exposure to Br_2/Et_3N. Dehydrobromination with AgF/pyridine introduced the required unsaturation and allowed the C-8 epimers to be separated by chromatography. Lithium iodide mediated monodecarboxylation, partial Δ^2-Δ^3 isomerisation and hydrogenolytic deprotection of (82) then gave racemic thienamycin (89).

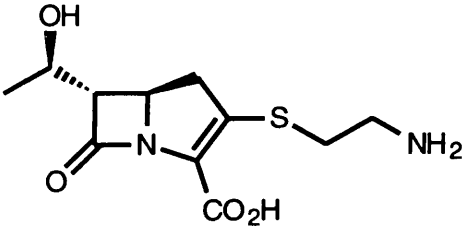




(85) (86)

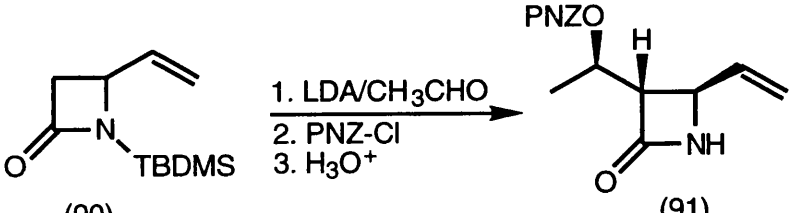


(87) (88)



(89)

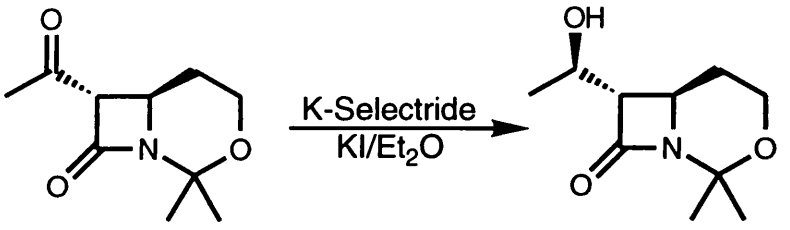
A more practical route to intermediate (85) has also been reported.[71] Vinyl azetidinone (90) was elaborated to (91) which upon successive treatment with *N*-(*p*-nitrobenzyloxycarbonyl)ethanesulfenyl bromide and DBU provided (85).



(90) (91)

The major shortcoming of the Merck synthesis was the lack of selectivity during the aldol condensation. This drawback, however, was to be overcome by the selective reduction of the C-8 ketone (92) introduced either by direct *trans* acylation of (81) or oxidation of the aldol mixture (82).[72] The reagent of choice for the

reduction was found to be a mixture of K-Selectride and KI in ether, which gave the desired alcohol (93) with high selectivity.

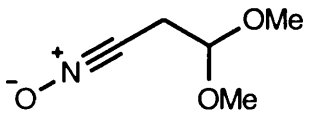


(92) (93)

Stereoselection in favour of the *trans*-(*R*) isomer has been explained by selective hydride delivery from the less sterically hindered β-face of potassium chelated structure (94).

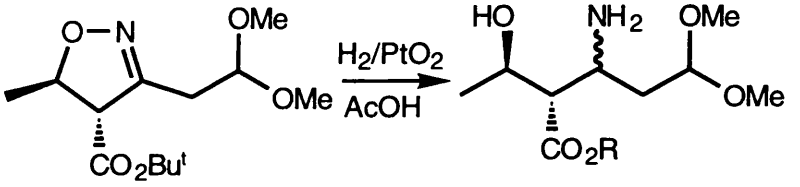
(94) *trans-R*

As mentioned in Section (**1.4.1**), the publication of the Merck route spawned a considerable amount of interest, and several routes to monocyclic intermediates have emerged. One such formal synthesis, by Kametani, utilised the stereoselective [2+3] cycloaddition between nitrile oxide (95) and methyl crotonate (96) to establish the correct relative stereochemistry of the hydroxyethyl sidechain prior to β-lactam formation.[73] Isoxaline (97), the major product of the cycloaddition, was reduced to amino ester (98) which, although a mixture of C-3 epimers, possessed the same stereochemistry at C-4 and C-5 as thienamycin. Selective cyclization of this epimeric mixture and subsequent elaboration gave the Merck intermediate (99).

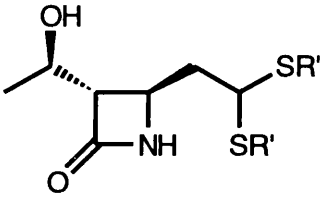


(95)

(96)



(97) (98)

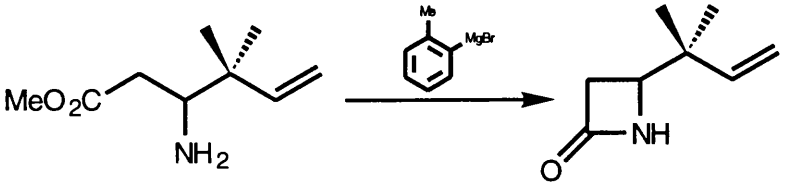


(99)

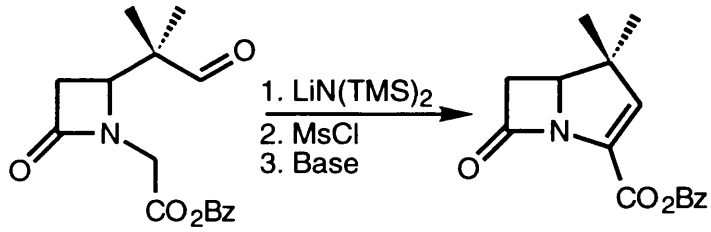
Kametani subsequently used optically pure nitrones in this protocol in order to control both absolute and relative stereochemistry.[74]

1.4.2.2.2 Aldol/Dieckmann Condensation.

Shibaya and Kubota prepared β-lactam (101) by cyclization of β-amino-ester (100) using *o*-tolyl magnesium bromide.[75] Condensation of (101) with benzyl bromoacetate, ozonolysis and reductive work-up gave the non-enolisable aldehyde (102) which underwent aldol cyclization upon treatment with $LiN(TMS)_2$. Trapping of the resultant alkoxide anion with mesyl chloride (MsCl) and subsequent base induced elimination gave carbapenem (103). Later attempts by Glaxo chemists to use this strategy with enolisable aldehydes were considerably less successful.[76]

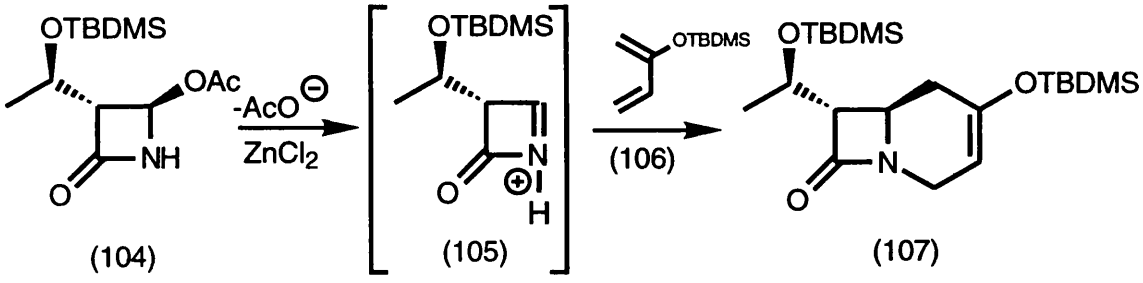


(100) (101)

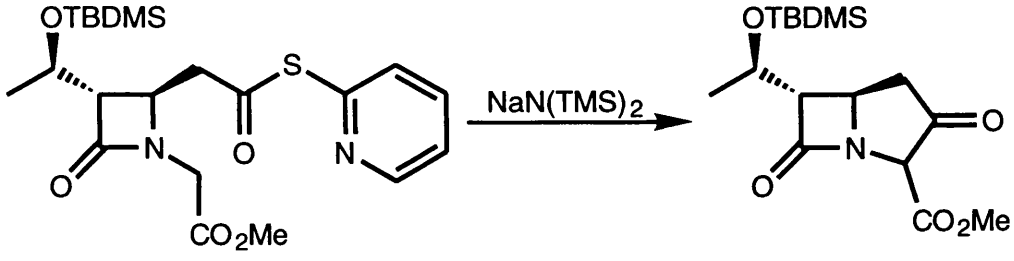


(102) (103)

A more successful and, consequently, widely used variant of the aldol reaction is the Dieckmann cyclization. Meyers and co-workers used this reaction in a highly efficient and novel synthesis of the carbapen-2-one system (109) from commercially available azetidinone (104).[77] The proposed iminium ion (105), produced *in situ* by the action of $ZnCl_2$ upon (104) reacted with silyloxydiene (106) to afford *trans*-carbacephem (107) in 65% yield. Ozonolysis of the cephem ring, oxidative work-up using Schrieber's modification[78] and treatment with $Ph_3P/(PyS)_2$ gave the thiopyridyl ester (108). Dieckmann cyclization was achieved using $NaN(TMS)_2$ and afforded carbapenan-2-one (109) in 30% overall yield from (104).



(104) (105) (106) (107)

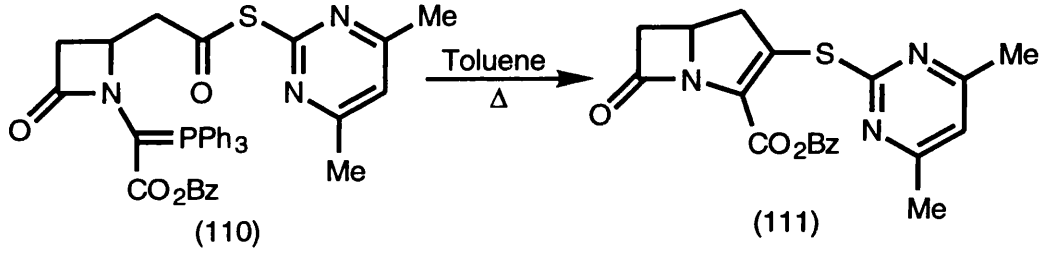


(108) (109)

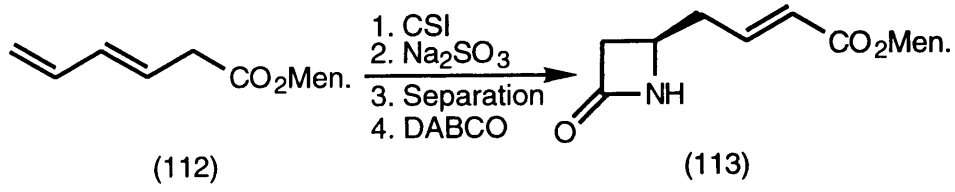
1.4.2.2.3 Wittig Condensation.

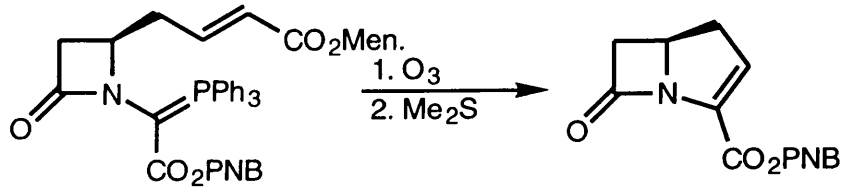
This procedure has been widely used for the production of both thienamycin and carbapen-2-em derivatives. Three types of condensation have been developed: phosphorane/aldehyde; phosphorane/ketone and phosphorane/thioester.

Unfortunately, the obvious potential of this method for the direct formation of Δ^2 pyrrolidines incorporating a C-2 thioalkyl sidechain has not been realised due to the insufficient reactivity of triphenylphosphoranes with alkyl thioesters. However, investigators at Beechams found that certain electron deficient aryl thioesters accelerate the rate of condensation and ring closure occurs in high yield, *e.g.*, carbapenem (111) is obtained in 80% yield by heating (110) at reflux in toluene for 3 hours.[79]



Although a few exceptions exist,[80] ketones are generally unreactive to this type of phosphorane condensation and consequently yields are low. On the other hand, the use of aldehydes has been met with considerable success. For example, a group at Bristol obtained optically pure azetidinone (113) by the recrystallisation of a mixture of diastereomers gained by CSI cycloaddition with (112).[81] Standard elaboration gave phosphorane (114), which upon treatment with ozone and neutral work-up, underwent ring closure to furnish (115) in good yield.



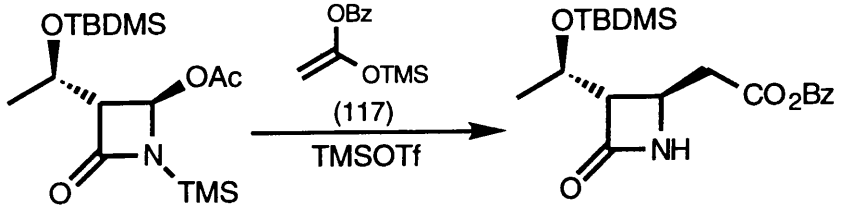


(114) (115)

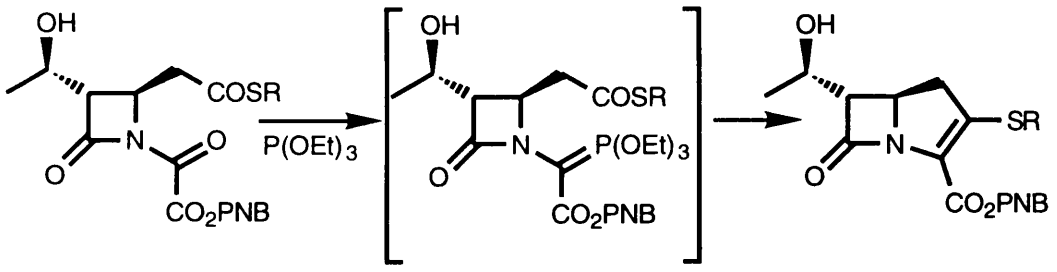
This strategy of *in situ* aldehyde generation by double bond ozonolysis,[82] or alcohol oxidation[83] followed by spontaneous cyclization to the carbapenem has been used by a number of groups.

1.4.2.2.4 Reductive cyclization.

Originally developed by a group at Schering[84] for penem synthesis, this method has proven to be of great utility in the synthesis of both C-2 unsubstituted and C-2 thiosubstituted carbapenems. Starting from azetidinone (116) chemists at Sankyo[85] used methodology previously developed by Barrett and Quayle[86] to stereospecifically introduce a 2C ester side-chain at C-4. Thus, treatment of (116) with keteneacetal (117) in the presence of trimethylsilyl triflate (TMSOTf) yielded (118). *N*-Acylation then gave oxalamide (119) which upon treatment with $P(OEt)_3$ provided trialkoxyphosphorane (120) *via* a postulated carbene intermediate.[87] The crude phosphorane, which could not be isolated, was then heated to furnish carbapenem (121) in good yield.



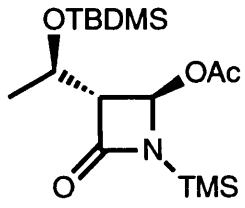
(116) (118)



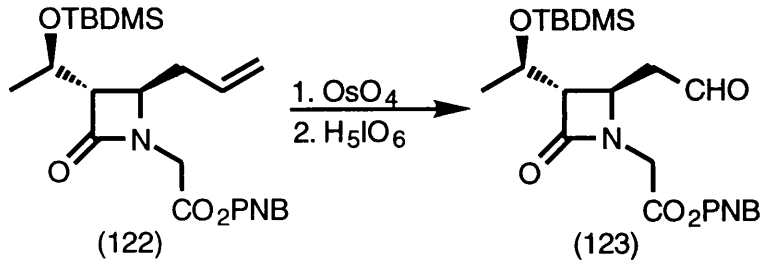
(119) (120) (121)

1.4.2.2.5 Conjugate Addition to a Nitroalkene.

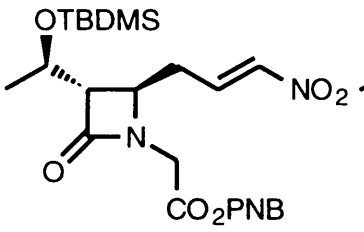
Hanessian has recently extended his novel *5-exo-trig* cyclization approach to the synthesis of penems[88] to carbapenems.[89] Azetidinone (116) was transformed into the allyl derivative (122) which was dihydroxylated and oxidatively cleaved to (123). Reaction with nitromethane, followed by sequential mesylation and base induced elimination furnished the nitroalkene required for Michael-type addition. Selective deprotonation of (124) with $LiN(TMS)_2$ resulted in exclusively *5-exo-trig* cyclization, the α-nitro anion being trapped *in situ* with PhSeCl. Subsequent oxidation of (125) to the corresponding selenoxide and thermal elimination gave carbapenem (126). Cleavage of the exocyclic nitroalkene gave the advanced intermediate (127) which was converted in to thienamycin using the 1,4 addition-elimination procedure previously developed at Merck.[90]



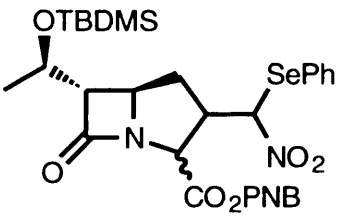
(116)



(122) (123)



(124)



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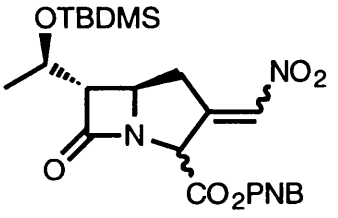

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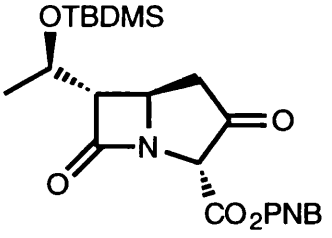
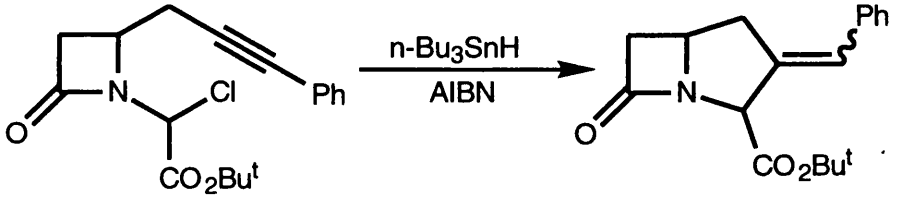


(127)

In a conceptually similar approach Bachi and co-workers have formed the pyrrolidine ring using a *5-exo-dig* radical cyclization.[91] Thus, treatment of chloro-β-lactam (128) with Bu_3SnH/AIBN afforded azetidinone (129) as a mixture of geometrical isomers in nearly quantitative yield.

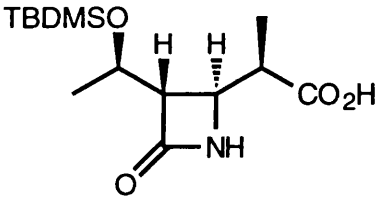


(128) (129)

1.4.2.2.6 Thiazoline Ring Contraction.

The most recently developed procedure for the construction of the carbapenem nucleus comes from Horikawa[92] and co-workers and is based on the ring contraction of a bicyclic thiazoline utilising the Eschenmoser sulphide contraction.[93] Azetidinone (130) was elaborated to alcohol (131) which was converted to the corresponding chloride. Without isolation, the crude chloride was treated with Pr^i_2NEt to afford thiazolinone (132) as one diastereomer; base induced retro-Michael addition generates the thiocarboxylate anion which displaces the adjacent chloride. Ring contraction proceeds smoothly upon successive treatment with NaH/Ph_3P/DMF then $(PhO)_2POCl$. Without isolation, (133) is treated with

mercaptan (134) to afford 1β-methylcarbapenem (135), a precursor of the potent Sankyo antibiotic SM-7338 (16).



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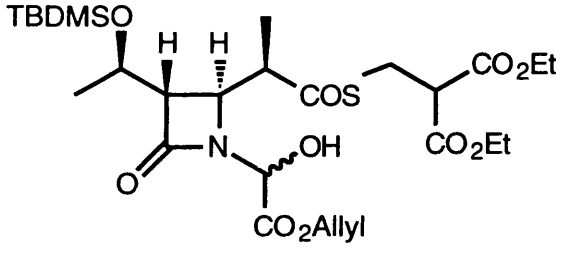

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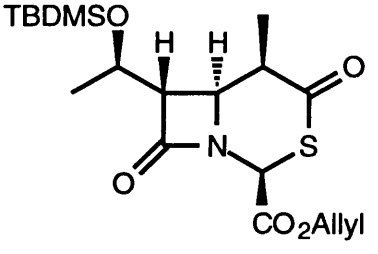

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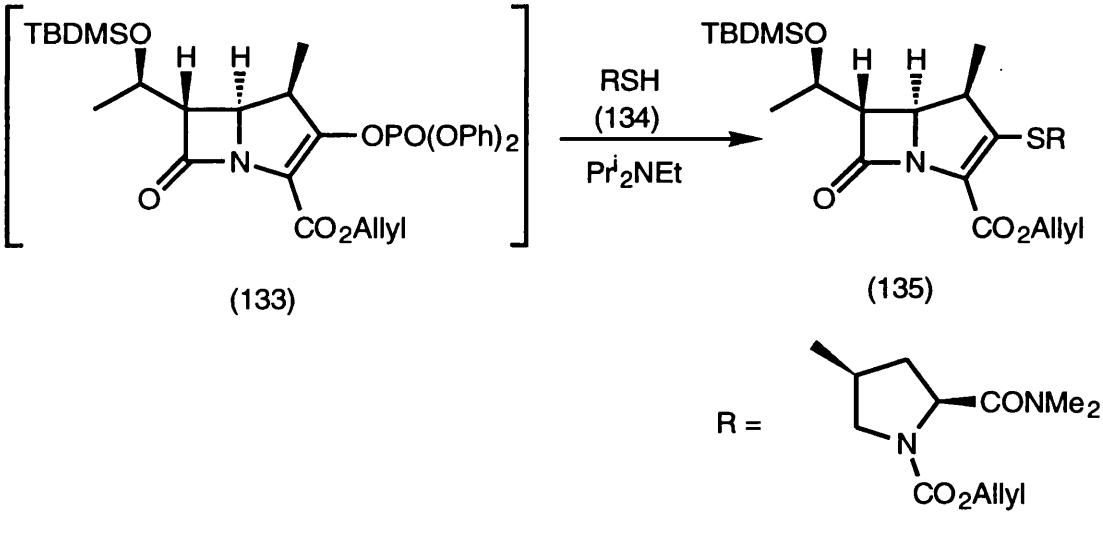
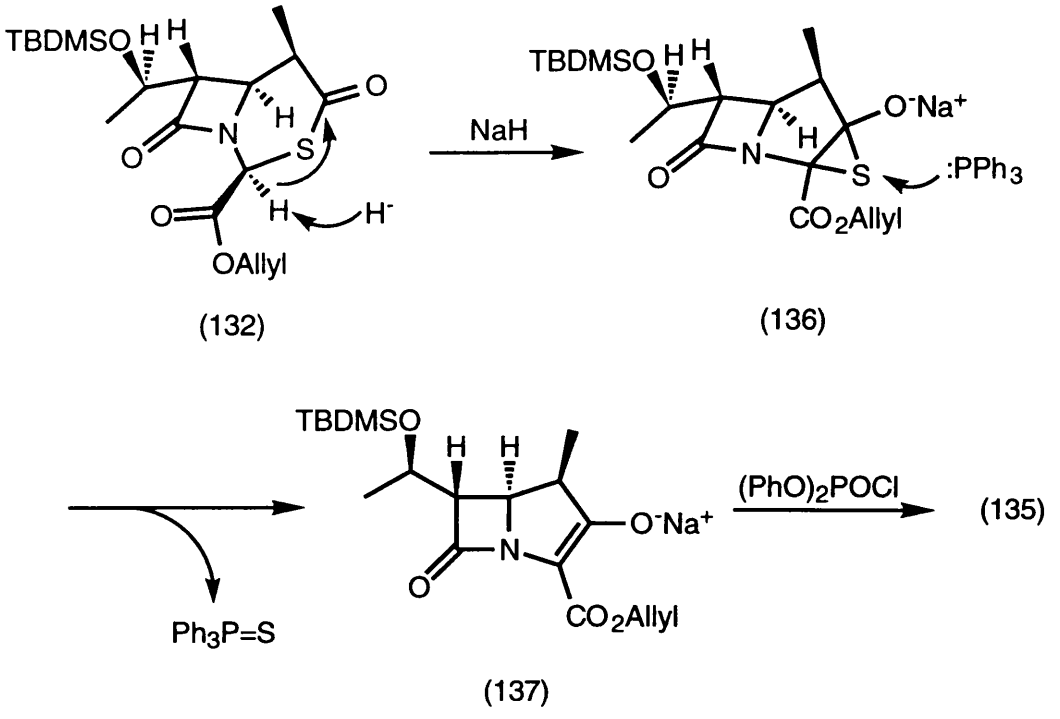


(133)

(135)

The mechanism for this contraction probably involves the initial abstraction of the proton on the 4-position of (132) and attack of the resultant stabilised anion upon the neighbouring carbonyl to form thiirane (136). Sulphur extrusion by Ph_3P then leads to sodium salt (137) which is trapped *in situ* by $(PhO)_2POCl$ to give (135).



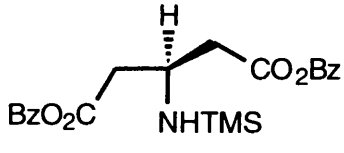
1.4.2.3 C-3/N-4 Closure

1.4.2.3.1 Carbene/Carbenoid Insertion.

This method of ring closure, developed by a group at Merck, involves the intramolecular insertion of a C-3 carbene/carbenoid into the neighbouring amide N-H bond.[94] It was this method coupled with a novel addition/elimination sequence for efficient C-2 sidechain incorporation that Salzmann and co-workers at Merck used in the first stereocontrolled synthesis of (+) thienamycin.[38]

Benzyl-protected L-aspartate (56) was cyclized to β-lactam (138) and the ester reduced. Subsequent *N*-silylation, mesylation and displacement with iodide gave azetidinone (139). One carbon homologation to (140) was achieved by displacement of the iodide with 2-lithio-2-trimethylsilyl dithiane. Acylation of the enolate of (140) with acetyl imidazole gave unstable ketone (141) which was stereoselectively reduced to (142) using K-Selectride®/KI. Dithiane hydrolysis provided a trimethylsilyl ketone intermediate which underwent a facile Baeyer-Villiger rearrangement with hydrogen peroxide. The resultant acid (143) was then homologated to (144) using Masamune's[95] method, *i.e.*, conversion to the acyl

imidazolide and condensation with the magnesium salt of mono-*p*-nitrobenzyl malonate. Deprotection and diazo transfer afforded (145) which underwent cyclization to (146) upon thermolysis with rhodium tetraacetate $Rh_2(OAc)_4$. The synthesis was then completed by *in situ* formation of vinyl phosphate (147) with $(PhO)_2POCl$ and addition/elimination of cysteaminyl derivative (148) to give (149) which afforded (+) thienamycin (14) upon hydrogenolytic deprotection.



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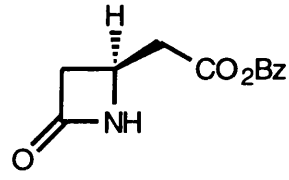

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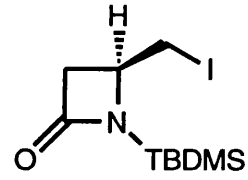

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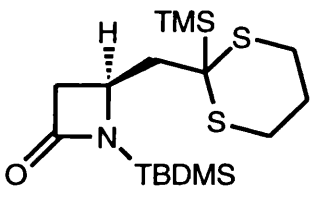

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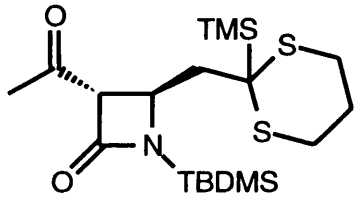

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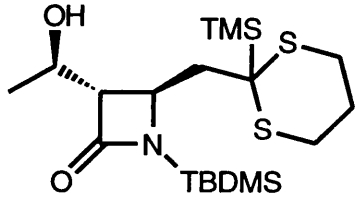

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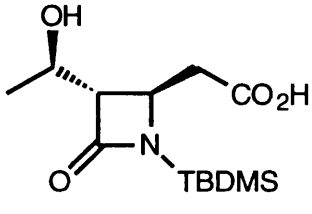

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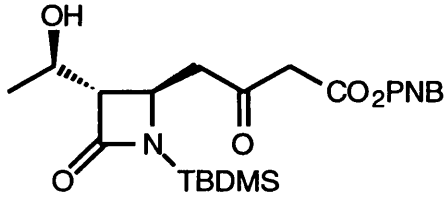

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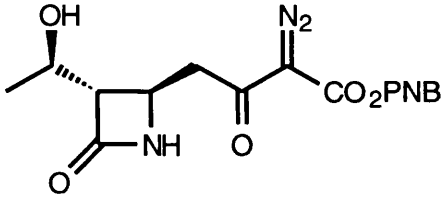

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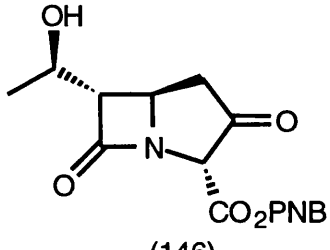

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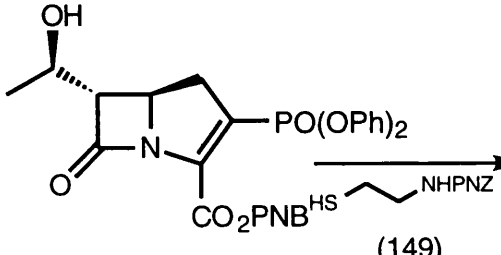
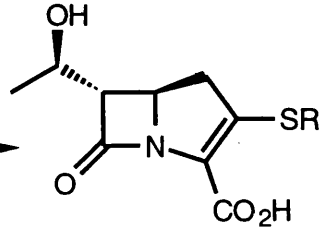


(147)

(149)



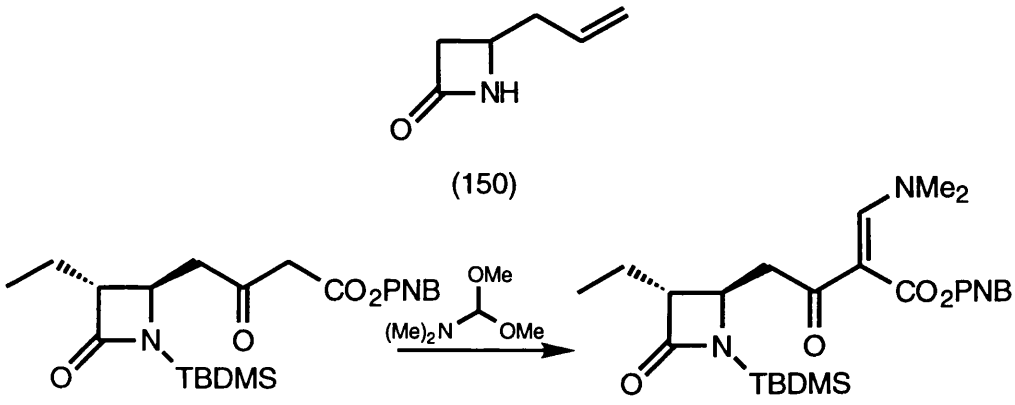
(150)

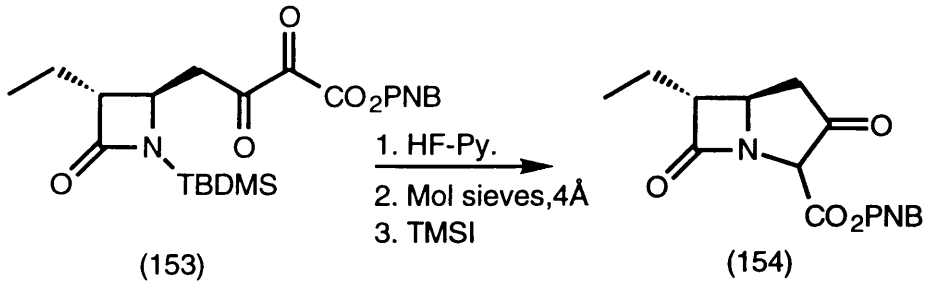
The key cyclization reaction is noteworthy on three counts. Firstly, the reaction was quantitative which was unprecedented in the synthesis of carbapenems. Secondly, only one diastereomer of (146) was formed, presumably due to facile epimerisation at acidic C-2, and thirdly no costly hydroxyl protection was required.

The efficiency of the diazo ring closure allowed not only the rapid production of numerous analogues but eventually formed the cornerstone of the commercial synthesis of imipenem (15) (see Section **1.4.3.3.2**).

1.4.2.3.2 Amide to Carbonyl Addition.

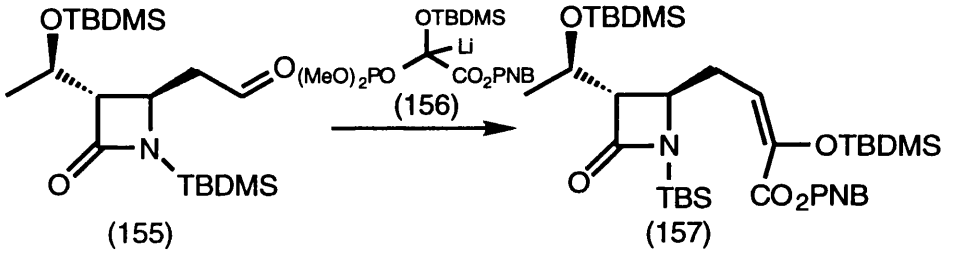
Wasserman has shown that the carbapenem ring can be constructed by the condensation between the β-lactam nitrogen and a suitably functionalised vicinal tricarbonyl C-4 residue.[96] Allylazetidinone (150) was elaborated to β-ketoester (151) in 4 steps. Condensation of (151) with DMF dimethylacetal gave enamine (152) which was photolytically cleaved with singlet oxygen furnishing α,β–diketoester (153). Annelation was achieved by *N*-silyl deprotection. Deoxygenation with TMSI then yielded the known PS-5 precursor (154),[97] albeit in disappointing yield (30%).





(153) (154)

More recently, Fiegelson has also used a N-4/C-3 keto condensation in an interesting and efficient synthesis of thienamycin which simultaneously forms the pyrroline ring and incorporates the C-2 sidechain.[98] Azetidinone (155) was treated with Horner-Emmons reagent (156) to afford (157) as a mixture of geometric isomers. Treatment with Br_2 unveiled bromo-α-ketoester (158) which reacted with protected thiol (159) to give the corresponding displacement product in quantitative yield. *N*-Deprotection then provided key intermediate (160) which upon treatment with $TiCl_4$ underwent ring closure and dehydration to furnish (161) in 54% yield.



(155) (157)

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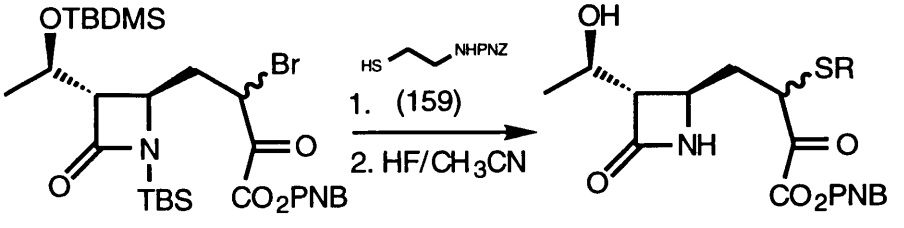
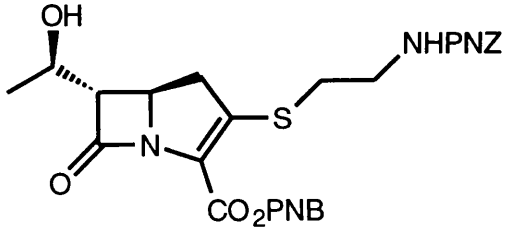


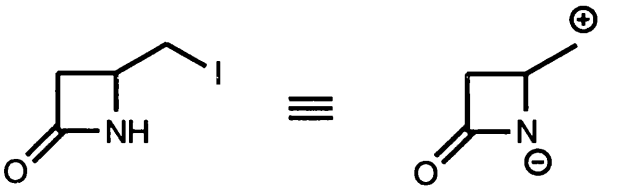
(158) (160)



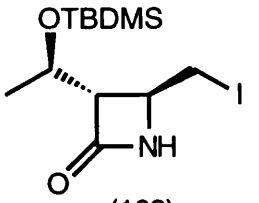
(161)

1.4.2.4 Novel [3+2] Cycloaddition.

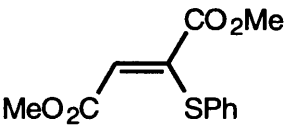
Examination of 4-iodomethylazetidin-2-one (162) reveals that this compound has both nucleophilic and electrophilic centres, *i.e.*, the amide and iodomethyl groups respectively. Chemists at Sankyo have used this dual reactivity in a novel type of [3+2] cycloaddition.[99] Reaction of (163) with fumarate derivative (164) in the presence of KH/18-crown-6 gave azetidinones (165) and (166) which could be elaborated to a useful 2-ketocarbapenam using Trost's oxidative decarboxylation methodology.[100]



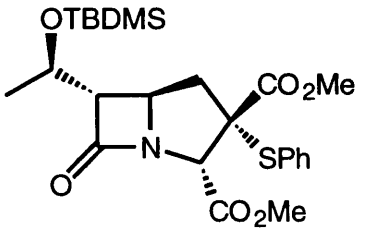
(162)



(163)



(164)



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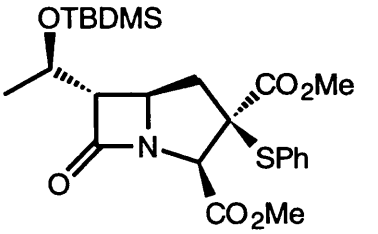


(166)

This reaction seems to proceed by initial Michael addition of the amide anion to (164) followed by trapping of the resultant anion by the C-4 iodomethyl group.

1.4.3 Stereocontrolled Synthesis

The first stereocontrolled synthesis of (+)-thienamycin, by a group at Merck in 1980,[38] underlined the need for efficient control of absolute rather than just relative stereochemistry in the synthesis of carbapenems. As a result there was a significant change in the synthetic strategies employed towards this family of natural products.

To date, three main approaches have been used to control the absolute stereochemistry in the synthesis of carbapenems:

1.4.3.1 Chiral Pool.

1) 6-Aminopenicillanic Acid (6APA)

2) Amino Acids

3) 3-Hydroxybutyrates

4) Sugars

1.4.3.2 Optical Resolution.

1.4.3.3 Prochiral Precursors.

1) Chemoenzymic Hydrolysis

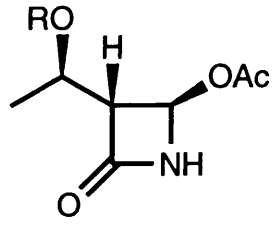
2) Chiral Auxiliaries

1.4.3.1 Chiral Pool.

This approach to stereocontrolled synthesis uses the pre-existing chirality present in natural products to determine that of the target. It should be noted, however, that not all the asymmetrical centres in the starting material need necessarily appear in the target (see Section **1.4.3.1.4**); the structure of the starting material acts as a template which can be manipulated/degraded to fit the particular target molecule.

1.4.3.1.1 6-Aminopenicillanic Acid.

A number of groups have utilised 6-APA, the most frequently used approach being its conversion into the versatile 4-acetoxy β-lactam (28) or related compounds.



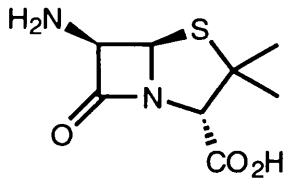
(28)

Although the use of readily available 6-APA to control the absolute stereochemistry of carbapenems is attractive, two major synthetic tasks must be undertaken in order to transform the stereochemistry of penicillin (5*R*, 6*S*) to that of thienamycin (5*R*, 6*S*, 8*R*):

- (i) removal of the C-6 amino group followed by stereospecific introduction of the α-(*R*)-hydroxy-ethyl sidechain
- (ii) removal of the thiazolidine ring followed by *trans* substitution at C-5.

A representative example comes from chemists at Sankyo whose procedure involved initial conversion of 6-APA (4) into the 6,6-dibromo derivative (167).[101] Generation of the bromoenolate, by treatment with methylmagnesium bromide, and quenching with acetaldehyde furnished 6α -bromo-6β–[(*R*)-hydroxyethyl]penicillanate (168) in excellent yield. Subsequent silylation and reductive debromination with Zn/AcOH afforded predominantly 6α–[(*R*)-hydroxyethyl]penicillinate (169). Thiazolidine ring opening was achieved by heating (169) with mercuric acetate in acetic acid to give exclusively the 3,4-*trans*-azetidinone (170). Oxidative removal of the *N*-substituent then provided (28). A

similar approach to the synthesis of (28) from 6-APA has also been published by a group at Merck.[102]



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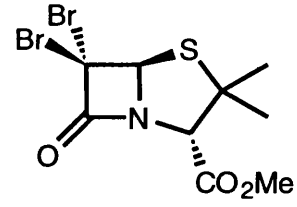

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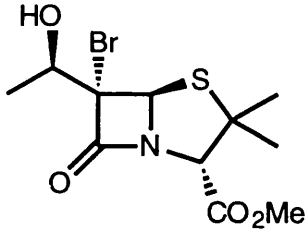
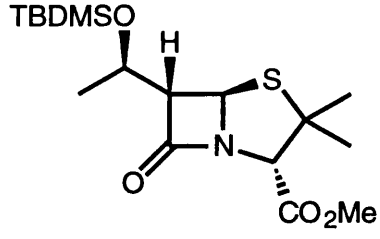


(168)



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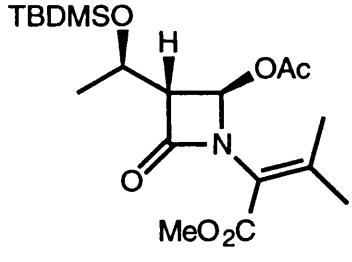


(170)

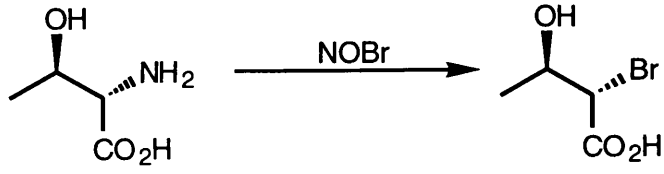
1.4.3.1.2 <u>Amino Acids.</u>

Aspartic acid and its derivatives seem ideal starting materials for the synthesis of optically pure azetidinones since they have the requisite β-amino acid unit for cyclization and both enantiomers are readily available. The first two chiral syntheses of thienamycin, by groups at Merck, used (*R*)-dibenzyl aspartate as starting material and source of chirality. However, although undoubtedly successful, these routes relied on the inefficient, and not to mention expensive, introduction of a *trans*-3-acetyl sidechain *via* enolate/electrophile methodology <u>after</u> formation of the β-lactam. Reduction of the resultant ketone then gave the required *trans*-(*R*)-hydroxyethyl sidechain.

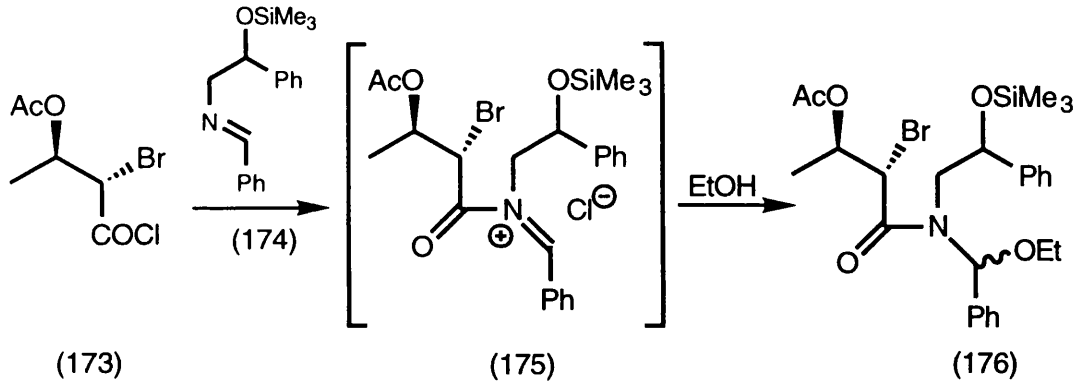
A popular, and highly efficient, strategy for the synthesis of thienamycin has been to utilise the chiral α-amino acid L-threonine (171) and thus circumvent this problem by introducing and predetermining the stereochemistry of the hydroxyethyl sidechain prior to β-lactam ring closure. Most investigators have achieved β-lactam formation using the C-3/C-4 intramolecular displacement protocol discussed in Section (**1.4.1.9**). A recent example from a group at Schering serves to illustrate the general strategy.[103]

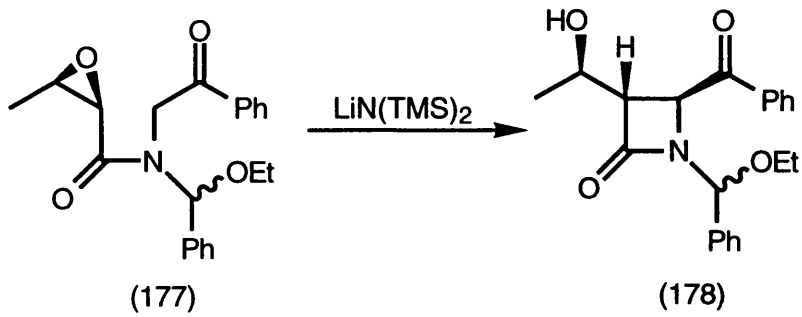
In previous examples of this protocol it was found that the presence of a bulky *N*-protecting group, usually anisyl, was mandatory for efficient cyclization. However this constituted a major disadvantage as *N*-deprotection of the resultant azetidinone required quantitative amounts of ceric ammonium nitrate (CAN), an expensive reagent. Chackalamannil and co-workers[103] have overcome this drawback by protecting the nitrogen with a hydrolytically labile α-alkoxymethyl group.

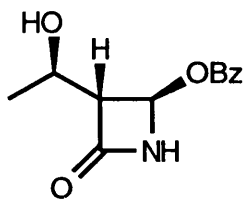
The action of nitrosyl bromide (NOBr) on L-threonine (171) produced bromo-butanoic acid (172) which, after acetylation, was converted to the acid chloride (173). Sequential treatment of (173) with unstable imine (174) and capture of the resultant iminium ion (175) with anhydrous ethanol yielded (176) as a mixture of diastereomers. Treatment with potassium carbonate and oxidation of the resultant epoxy alcohol gave cyclization precursor (177) in high yield. Ring closure was accomplished by treatment with $LiN(TMS)_2$; this reaction proceeds with complete inversion to yield (178). Deprotection under mild hydrolytic conditions (1N H_2SO_4/THF) and Baeyer-Villiger oxidation then gave thienamycin precursor (179).



(171) (172)



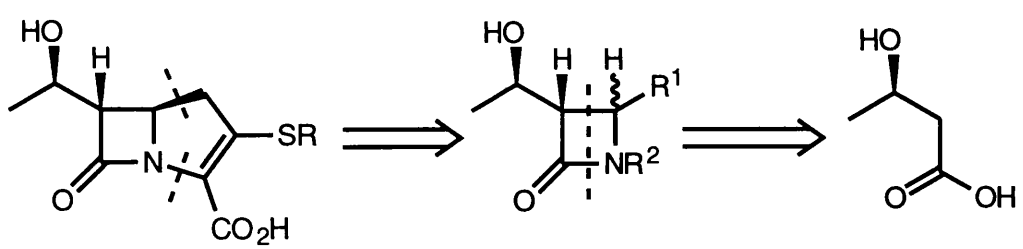




(179)

1.4.3.1.3 <u>**3-Hydroxybutyrates**</u>.

Retrosynthetic analysis of thienamycin, as shown in Scheme (5), suggests the use of (*R*)-3-hydroxybutyric acid (180) as a potential chiral starting material. Its appeal is also enhanced by the ready availability of both enantiomers from a number of sources; including baker's yeast reduction[104] or rhodium catalysed asymmetric hydrogenation[105] of the corresponding β-ketoester.

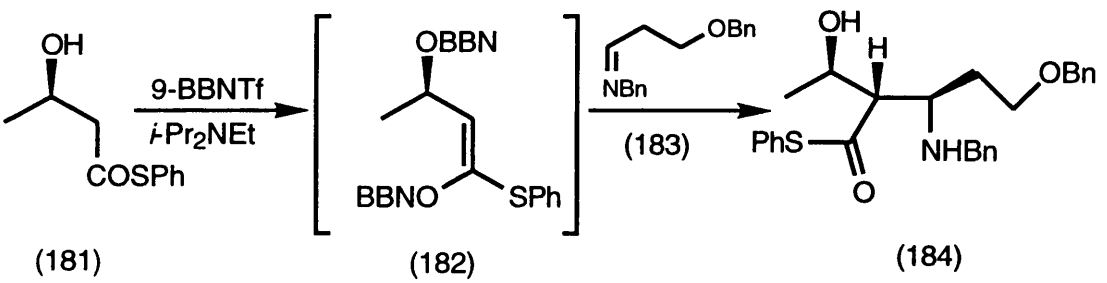


(180)

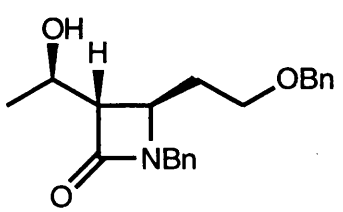
Scheme 5.

The potential of this starting material was first realised by Hart who found that its lithium dianion underwent stereoselective reaction with non-enolisable imines to give *cis*-hydroxyethyl β-lactams.[106] Hart's initial investigation has stimulated a considerable amount of interest in this strategy. The most successful example to date has been achieved by Shibasaki who utilised boron (vinyloxyboranates) rather than lithium enolates to prepare optically pure thienamycin precursor (186).[107]

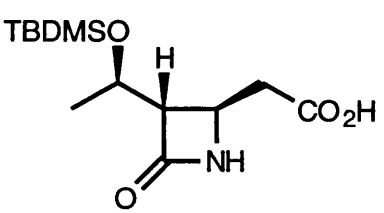
Thus, (*R*)-phenylthioester (181) was converted to *Z-(O)*-vinyloxyborane (182) by treatment with 9-borabicyclo[3.3.1]nonyl triflate (9-BBN-Tf) and Hünig's base. Reaction of this enolate with imine (183) furnished β-amino ester (184) in 37% yield. Subsequent cyclization and silylation gave intermediate (185) accompanied by two isomers in a yield of 90% (ratio 9:1:0.2). This compound could then be transformed to acid (186), an intermediate in the Merck thienamycin synthesis.[38]



(181) (182) (184)



(185)



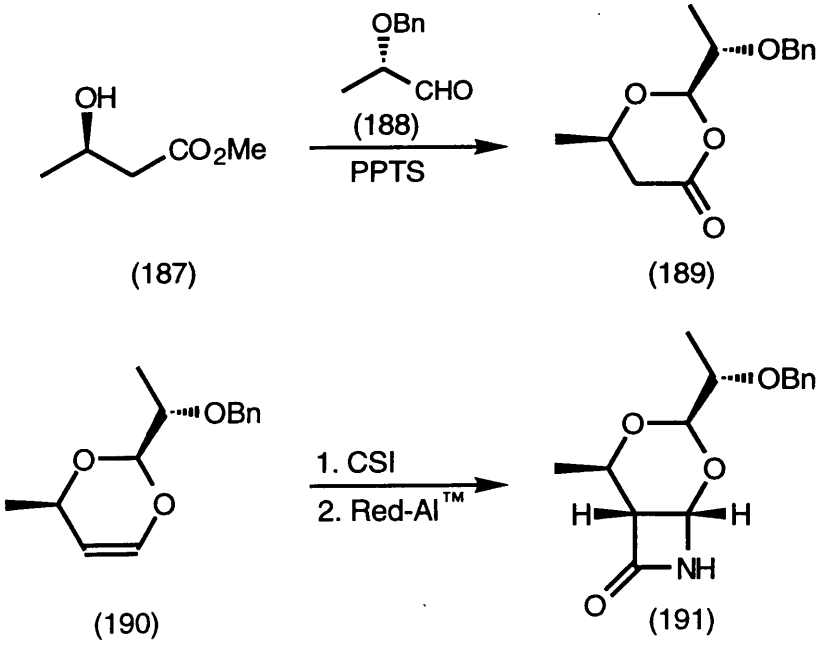
(186)

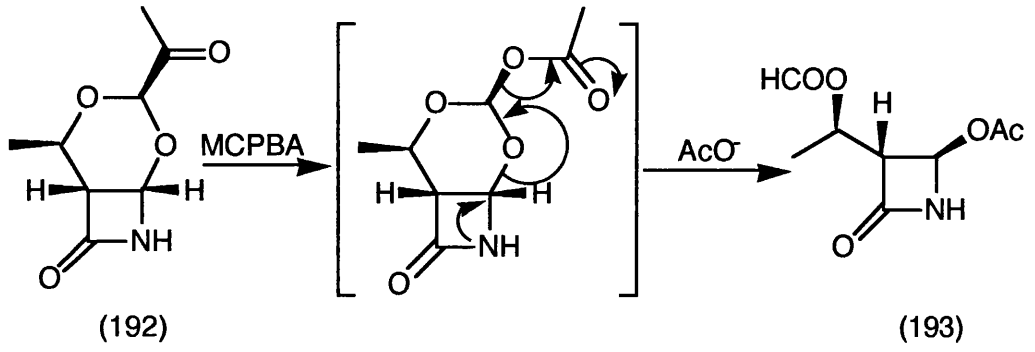
The remarkable features of this approach are that (i) the correct absolute stereochemistry at all three centres is obtained with high diastereoselectivity in one step and (ii) imines derived from aliphatic aldehydes can be used. This second point represents an important development as the use of non-enolisable imines such as *N*-

trimethylsilylcinnamylidene imines demands multiple step manipulation to synthetically more useful C-4 substitution.

In an alternative, but equally effective approach, Terashima has employed the stereoselective [2+2] cycloaddition of CSI with 2H,4H-1,3-dioxin-4-one (190), derived from (*R*)-hydroxybutyrate, to prepare key intermediate (193).[108]

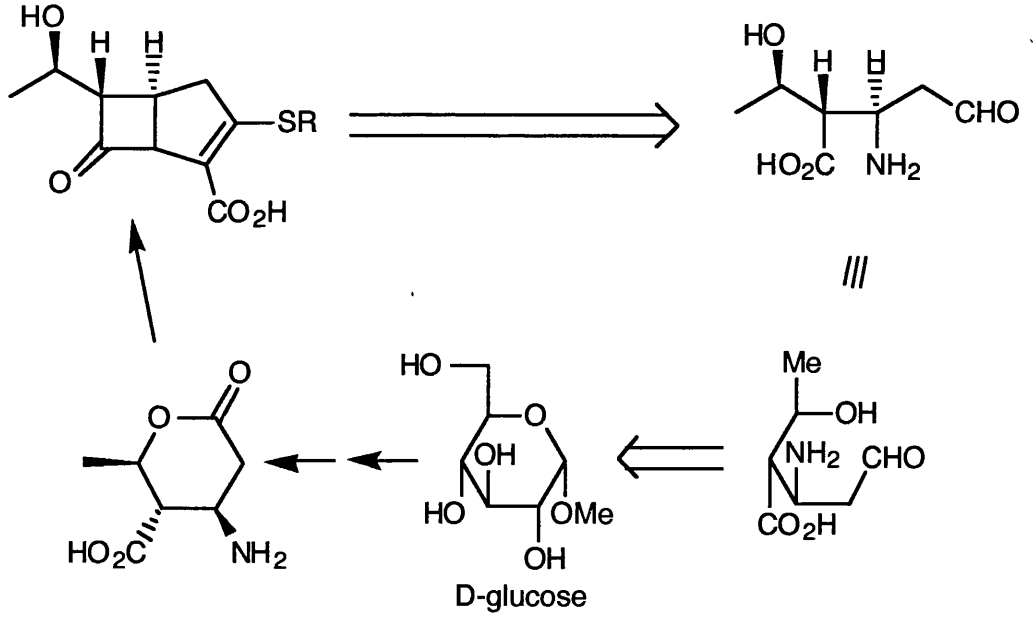
Acid catalysed condensation of methyl-(*R*)-hydroxybutyrate (187) with (*S*)-2-benzyloxypropanal (188) gave (189) as the only product. Reduction to the corresponding hemi-acetal and dehydration with $SOCl_2$ gave enol ether (190) which underwent stereo- and regioselective cycloaddition with CSI to furnish (191) in good yield. Hydrogenolytic deprotection and oxidation then gave ketone (192) which underwent an unprecedented Baeyer-Villiger oxidation and rearrangement to (193). Conveniently, this intermediate can be subjected to C-4 acetoxy displacement with Reformatsky reagents (to produce β C-1 methyl analogues) without the need for prior hydroxyl protection with expensive TBDMSCl.





1.4.3.1.4 Carbohydrates.

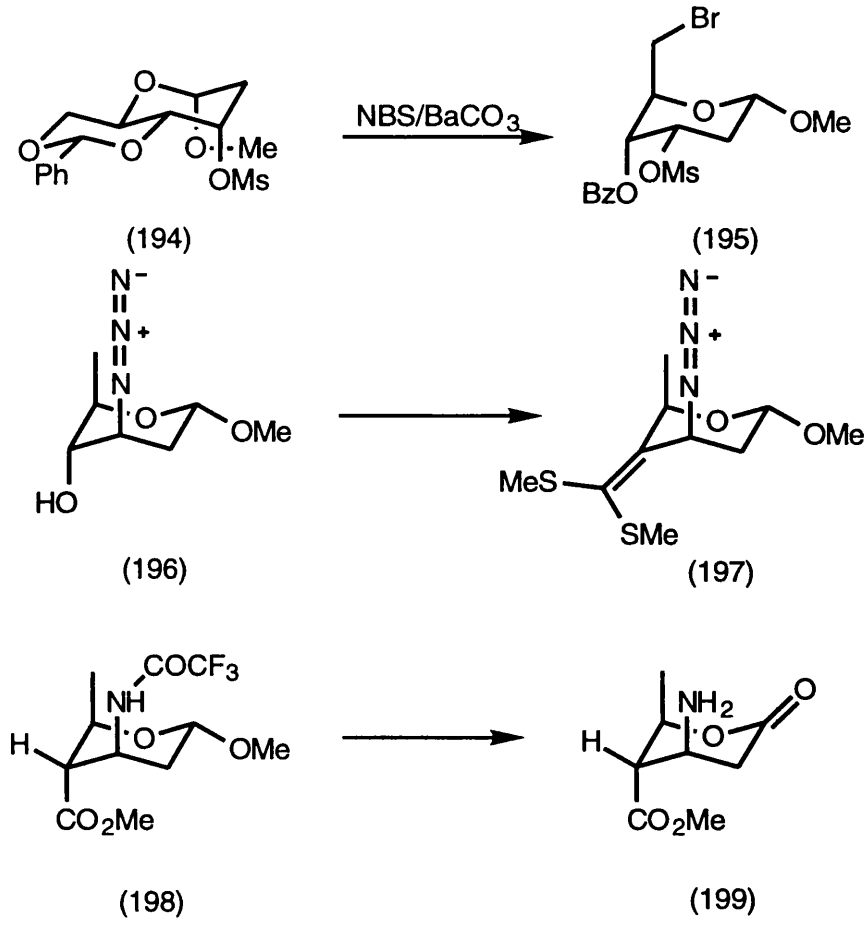
The 'symmetry' relationship between thienamycin and D-glucose illustrated in Scheme (6), has been exploited by Hanessian and co-workers in a formal synthesis of thienamycin. [109]



Scheme 6.

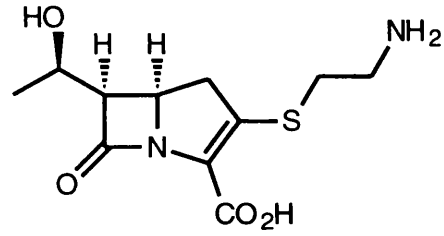
D-Glucose was elaborated to intermediate (195) *via* the acetal ring opening of benzylidene hexapyranoside (194) using Hanessian's NBS/$BaCO_3$ reagent system.[110] This precursor was then debrominated and the required C-3 amino group introduced by azide displacement of the C-3 mesylate ester. Subsequent manipulation of (196) gave the dithioketeneacetal (197) which, together with the azide, was reduced with $LiAlH_4$. Prior co-ordination of this reagent with the initially formed axial C-3 amine

ensured exclusive β-face hydride delivery to the adjacent dithioketeneacetal. Routine manipulation then gave ester (198) which was subjected to hydrolysis, oxidation and deprotection to provide Melillo's lactone[119] (199), a pivotal intermediate in the commercial synthesis of imipenem (15) (see Section **1.4.3.2**).



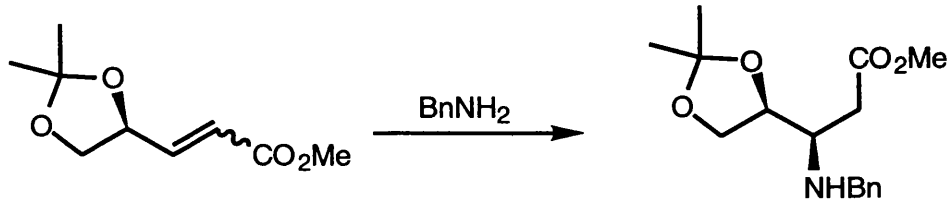
(194) (195) (196) (197) (198) (199)

Koga[111] and Durette[112] have both published syntheses of thienamycin using a very similar approach to that of Hanessian while Vasella, in a demonstration of the versatility of this approach, has prepared unnatural carbapenem epithienamycin (200) from D-glucose.[113]

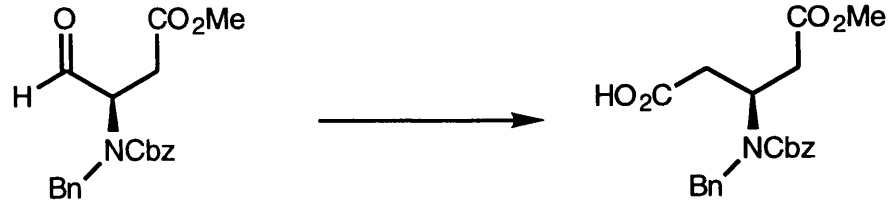


(200)

Yamada and co-workers, starting from the simplest carbohydrate D-glyceraldehyde, have reported the enantioselective synthesis of azetidinones (205) and (206).[114] Stereoselective Michael addition of benzylamine to the chiral α,β unsaturated ester (201), which is derived from D-glyceraldehyde acetonide, afforded amine (202), regardless of double bond geometry. Protection of the amine, hydrolysis of the acetonide and diol cleavage furnished aldehyde (203) which was homologated to acid (204). Deprotection of the amine and cyclization gave (*S*)-β-lactam (205). This protocol can also be used to prepare the 'unnatural' (*R*)-β-lactam (206), by cyclization of intermediate (202) followed by hydrolysis of the acetonide and oxidative diol cleavage.



(201) (202)

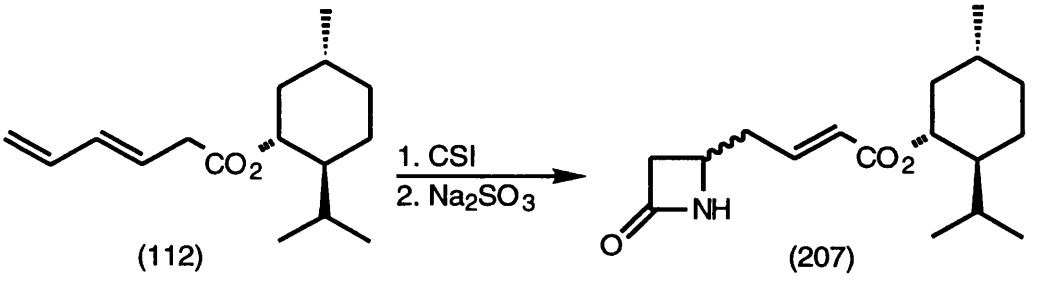


(203) (204)

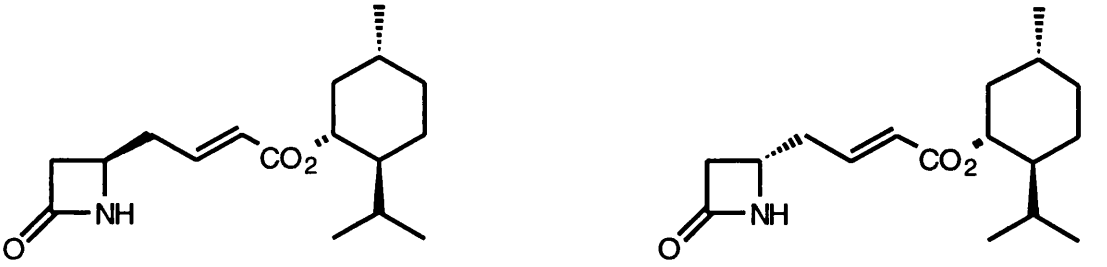
(205) (206)

1.4.3.2 Optical Resolution.

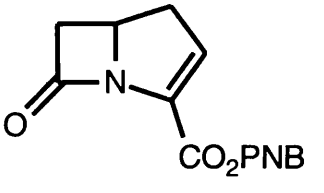
Although rather inefficient this technique has found some applications in the synthesis of carbapenems where both 'natural' and 'unnatural' enantiomers are required for clinical evaluation. For example, Ueda and co-workers at Bristol, prepared both enantiomers of the parent carbapenem (115).[81] Cycloaddition between L-menthyl ester (112) and CSI proceeded with little chiral induction furnishing near equal amounts of both diastereomers (207) in a total yield of 54%. These diastereomers, however, were readily separated by crystallisation to give (113) and (208) in 28 and 21% yield respectively. Removal of the menthyl auxiliaries during the subsequent manipulations (see Section **1.4.2.2.3**) gave both enantiomers of (115) in good optical yield.



(112) (207)



(113) (208)



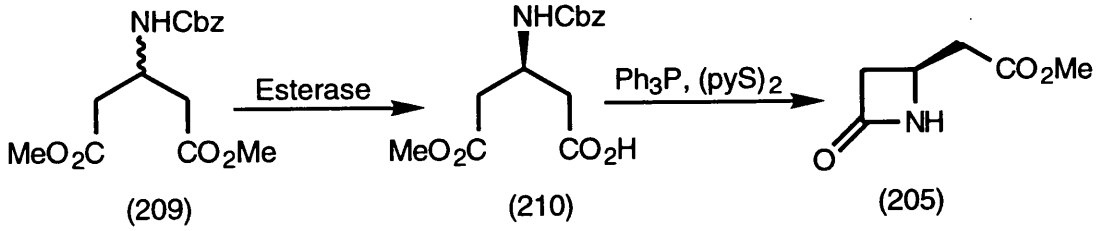
(115)

1.4.3.3 Prochiral Precursors.

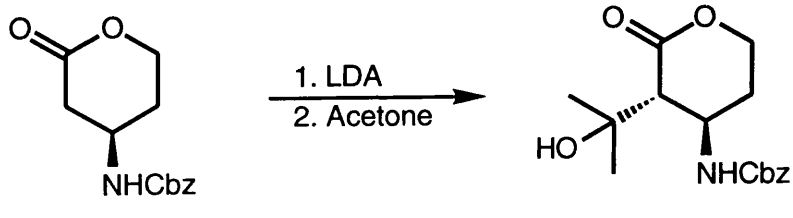
1.4.3.3.1 Chemoenzymic Hydrolysis.

A viable alternative to tapping the chiral pool for optically pure starting materials is the enantioselective generation of chiral centres by the enzymatic hydrolysis of prochiral esters. Ohno obtained chiral half-ester (210), in very high optical yield, by pig liver esterase (PLE) mediated hydrolysis of dimethyl *N*-benzyloxycarbonyl-β–aminoglutamate (209).[115] This useful precursor has been converted into azetidinone (205) which in turn has been elaborated to key intermediates in the synthesis of (+) PS-5 and -6[116] and (-)-asparenomycin C.[117] Ohno has also used ester (210) in the stereoselective synthesis of *cis* fused (-)-carpetimycin A (215).[118]

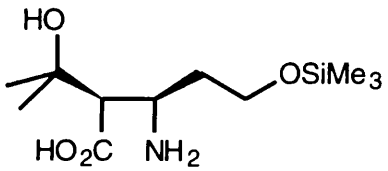
Reduction of (210) followed by cyclization gave δ-lactone (211) which underwent a stereoselective hydroxyisopropylation upon reaction of its enolate with acetone. Acid catalysed lactone opening of (212) gave β–amino ester (213) which after protecting group manipulation, Grignard mediated cyclization and oxidation gave (214). This acid was then homologated using Masamune's[95] method and ring closure accomplished *via* the Merck carbene insertion methodology.



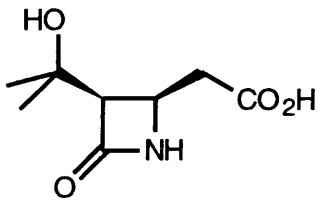
(209) (210) (205)



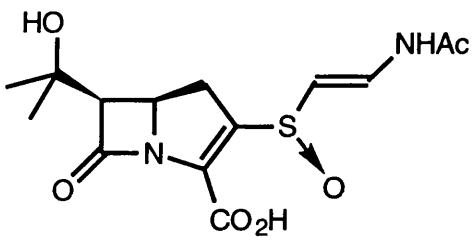
(211) (212)



(213)



(214)



(215)

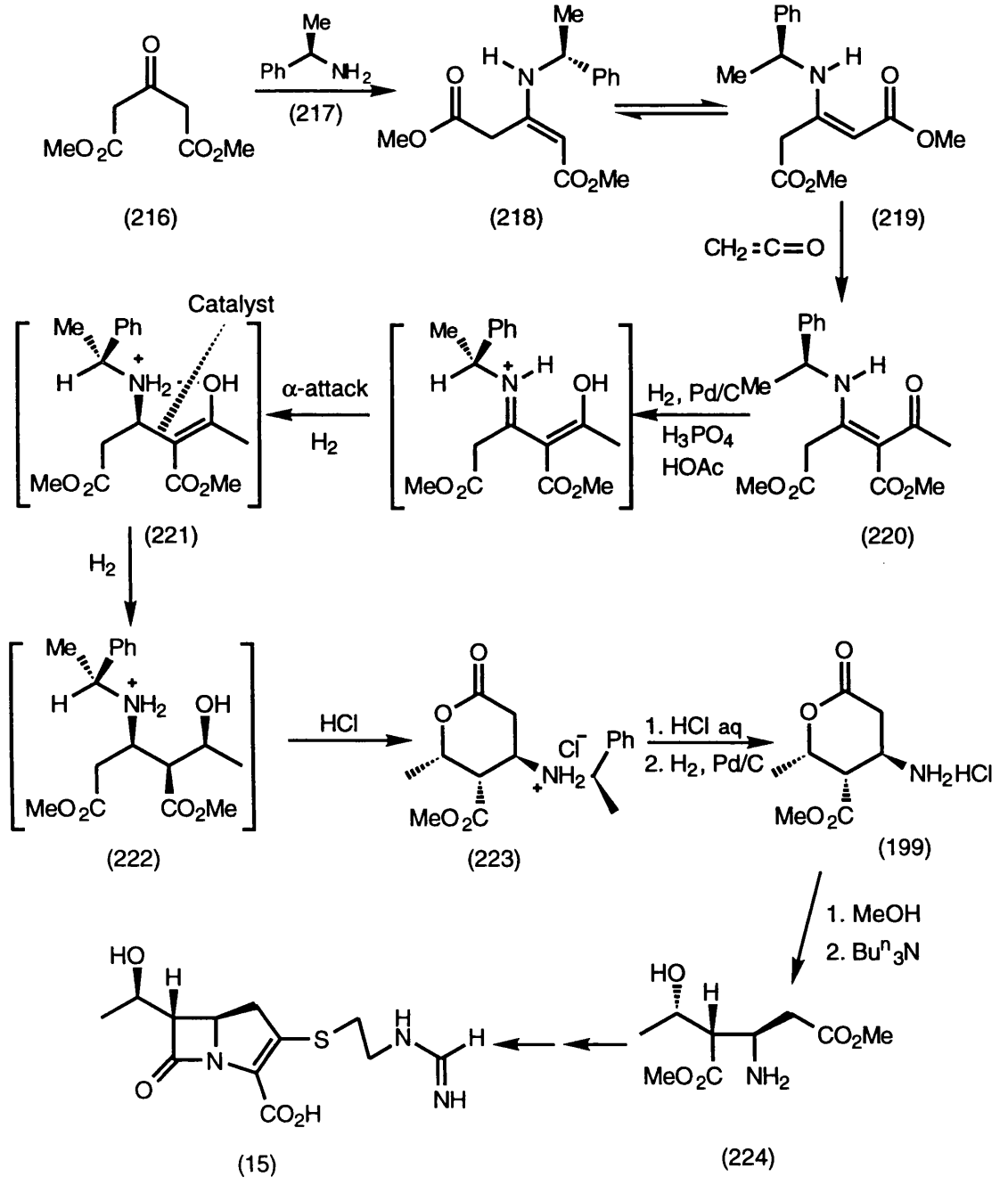
1.4.3.3.2 <u>Chiral Auxiliaries.</u>

In the preceding examples, the source of chirality in the target molecules has been pre-existing asymmetry, whether from the chiral pool or by enzymatic hydrolysis of prochiral material. In these cases the chiral centres have influenced the generation of new asymmetrical centres while also being fully or partially retained in the final product. Chiral auxiliaries, on the other hand, are used as a temporary source of asymmetry which induce chirality at newly forming centres before being removed.

The importance of chiral auxiliaries in the synthesis of carbapenems is illustrated in the final example in this review. It is this procedure, developed by Melillo and co-workers at Merck, that is used in the commercial production of imipenem (15).[119] The key element of this synthesis is the highly stereoselective reduction of chiral enamino ketone (220), establishing the three contiguous chiral centres of imipenem (15).

The starting point of this synthesis is dimethyl acetonedicarboxylate (216), which is condensed with (*R*)-(+)-α-methylbenzylamine (217), the chiral auxiliary, yielding an equilibrium mixture of enamine isomers (218) and (219). Direct acylation of this mixture with ketene gas, or less conveniently with Ac_2O, gave enamino ketone (220) in 96% yield from (*R*)-α-methylbenzylamine. Unfortunately, this compound was found to be inert to hydrogenation in neutral or basic media and

with a wide range of catalysts. However, use of a platinum catalyst with phosphoric acid provided the desired (*SSR-R*) alcohol (222) *via* enol (221), with the chiral amine residue controlling the stereochemistry of hydrogenation. Alcohol (222) was then cyclized to lactone (223) by treatment with HCl. Ester hydrolysis, hydrogenolysis of the chiral auxiliary and treatment with methanol then furnished (199) (Melillo's lactone). The free base was then liberated with $Bu^n{}_3N$ to give β-amino acid (224) which was converted to imipenem (15) by carbene insertion methodology and a Mitsunobu inversion to correct the stereochemistry of the sidechain.



Conclusion.

In contrast to the penicillins where the large quantities required for clinical use are available via fermentation, the carbapenems are only accessible by total synthesis. The unprecedented biological activity displayed by this class of antibiotics has ensured that synthetic routes to carbapenems have been avidly pursued in order to facilitate access and improve resistance to bacteria.

While many the majority of earlier studies involved the formation of the azetidinone ring and subsequent sidechain manipulation, much emphasis is now placed in determining the absolute stereochemistry of all chiral centres prior to β-lactam ring closure.

2 CSI Cycloaddition

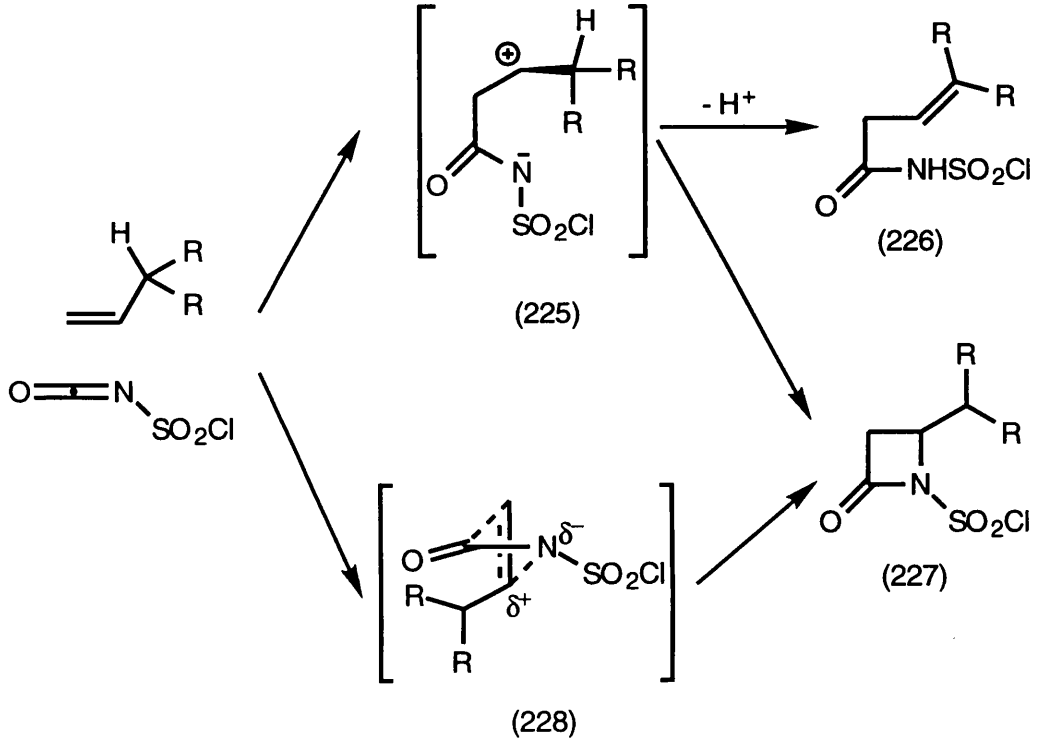
2.1 Introduction.

The cycloaddition of CSI with olefins, first studied by Graf[120] at Hoechst, has proven to be a most convenient method for the synthesis of azetidin-2-ones. The scope of this reaction has been investigated with a wide range of olefins including alkenes, dienes,[121] allenes,[122] enol esters,[62] vinyl sulphides,[123] vinyl silanes[124] and allyl halides.[125] These cycloadditions are highly stereo- and regiospecific; *cis* olefins give *cis* fused products, and addition takes place in such a way that the more stable formal carbonium ion is generated.

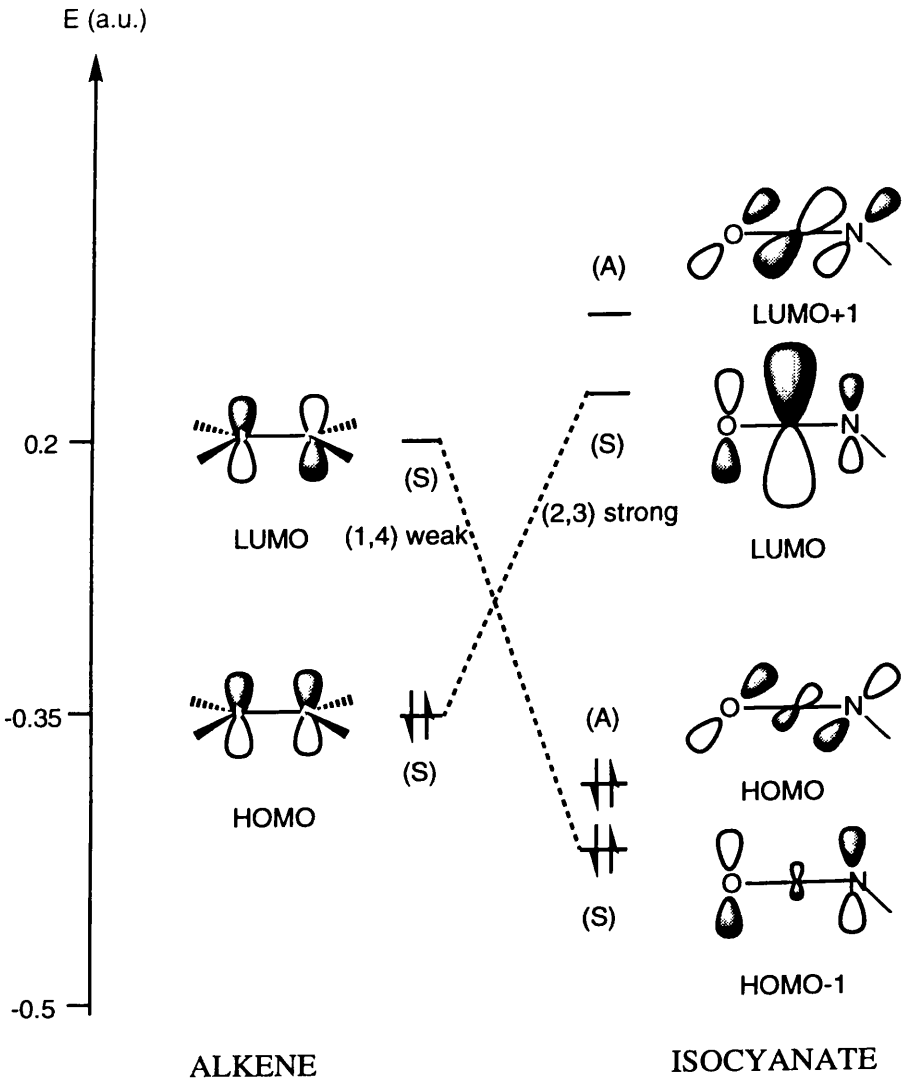
2.2 Mechanism of CSI/Alkene Cycloaddition.

In spite of the synthetic importance of this reaction, there remains ambiguity as to its precise mechanism. Graf originally proposed the two-step process shown in Scheme (7).[126] Initial formation of a 1,4 zwitterionic intermediate (225) is followed by either closure to β-lactam (226), or proton abstraction to form a β,γ–unsaturated imidate ester (227). This mechanism accounts for both the simultaneous formation of β-lactams and amides in ratios largely unaffected by reaction conditions, and the very high solvent rate dependency.[127]

Moriconi on the other hand, has proposed a near concerted, thermally allowed [π2s+π2a] cycloaddition, which proceeds through transition state (228). Moriconi has cited the preference for CSI to undergo [2+2] cycloaddition with dienes in support of this mechanism.[121]

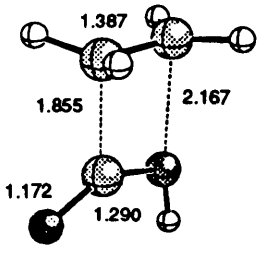


Scheme 7.



Scheme 8. Orbital interaction diagram for the *suprafacial suprafacial* reaction between an isocyanate and an olefin. The (S) and (A) labels refer to the symmetric and antisymmetric character of the orbitals with respect to the plane of β-lactam ring.

A recent theoretical study by Cossio,[128] however, has shown that the reaction may actually proceed *via* a concerted, although asynchronous, *suprafacial-suprafacial* mechanism. The transition state (229) associated with such a mechanism is predicted to be highly distorted; the calculated bond orders corresponding to the C-2/C-3 and N/C-4 bonds are 0.6 and 0.3 respectively. As a consequence, (229) has a large charge separation (an excess charge of 0.3 on both N and C sites) which is compatible with the reaction rate acceleration associated with the use of polar solvents.



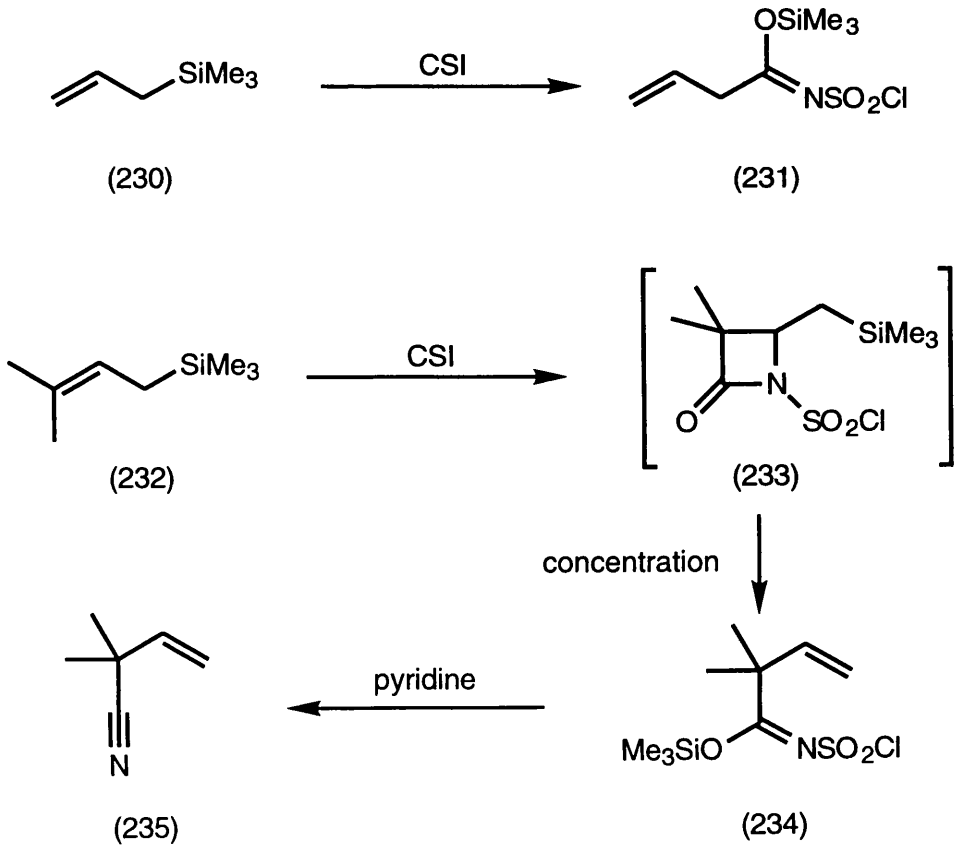
(229)

The *suprafacial-suprafacial* geometry predicted can be rationalised by analysis of molecular orbital interaction diagrams. Inspection of Scheme (8) (opposite) shows that the highest occupied molecular orbital (HOMO) of the alkene can efficiently interact with the lowest unoccupied molecular orbital (LUMO) of the isocyanate to form the C-2/C-3 bond, *i.e.*, nucleophilic addition of the alkene to the carbonyl of the isocyanate. In turn, the HOMO-1 of the isocyanate can interact with the LUMO of the olefin, to form the N/C-4 bond. The energy gap between these two orbitals is greater than that between the former pair and accounts for the lower N/C-4 bond order and thus the asynchronicity of the mechanism. Finally, the antisymmetric HOMO of the isocyanate unable to interact with the symmetric π orbitals of the alkene remains unchanged during the reaction to become the amide lone-pair.

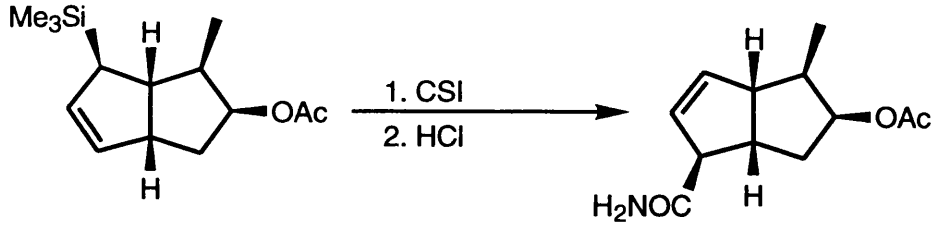
2.3 Allylsilanes and Chlorosulphonyl Isocyanate.

Only a few of the olefins mentioned on page 62 are suitable for the synthesis of carbapenem precursors and most of those which are have severe limitations. For example, the reaction of allyl iodide with CSI requires a large excess of the olefin and a reaction time of 7 days to yield 4-iodomethylazetidin-2-one (162) in low yield.[129]

Investigations within this group were originally prompted by reports from Dunoguès[130,131] on the potentially useful reaction of CSI with simple allylsilanes. Allyltrimethylsilane (230) underwent reaction with CSI to give silyl imidate (231) while dimethylallylsilane (232) gave unstable *N*-chlorosulphonyl β-lactam (233) which, although detected by IR and ^{1}H NMR spectroscopy, could not be isolated. Concentration of the reaction mixture caused a suspected silatropic shift giving imidate ester (234) which was subsequently converted into the corresponding nitrile (235) by treatment with pyridine.

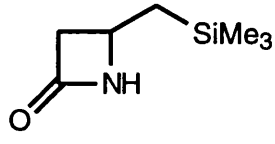


Fleming[132] subsequently used this observation as a key step in a synthesis of loganin aglycone. Thus, β,γ-unsaturated amide (237) was prepared by the regio- and stereoselective addition of CSI to allylsilane (236) followed by acid hydrolysis of the resultant silyl imidate.



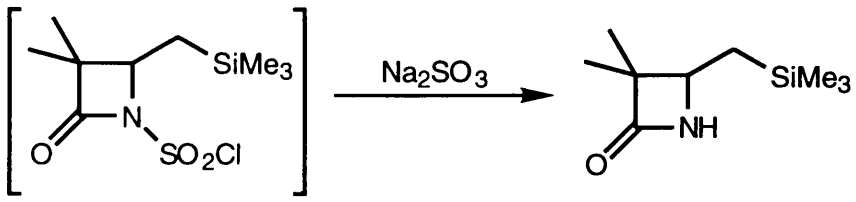
(236) (237)

A re-investigation of the Dunoguès communication, within this group, has found that when allyltrimethylsilane (230) is treated with CSI a clean reaction to the silyl imidate (231) occurs, with no intermediate *N*-chlorosulphonyl β-lactam being detected by ^{1}H NMR spectroscopy.[133] Ricci[134] has subsequently managed to isolate 4-(trimethylsilylmethyl)azetidinone (238), albeit in low yield, by carrying out this reaction at low temperature.



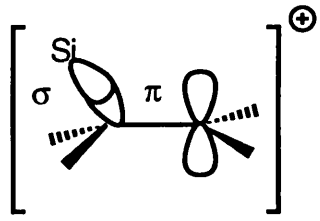
(238)

On the other hand, this group has found that *N*-chlorosulphonyl β lactam (233) can be readily intercepted by *in situ* reduction with aqueous Na_2SO_3[135] to furnish (239) in 60% yield.[133] It has also been found that, in general, these reactions must be carried out at a relatively low concentration (0.2M) in order to prevent silatropic rearrangement.



(233) (239)

The anti-Markovnikov regioselectivity of these cycloadditions must be under the control of the β-effect,[136] silicon encouraging the development of positive charge, partial or otherwise, β to itself by $(\sigma\text{–p})_\pi$ overlap between the bonding σ-level of the C-Si bond and the adjacent empty p-orbital of the carbonium ion (Scheme 9).



$(\sigma\text{–p})_\pi$
β-effect

Scheme 9.

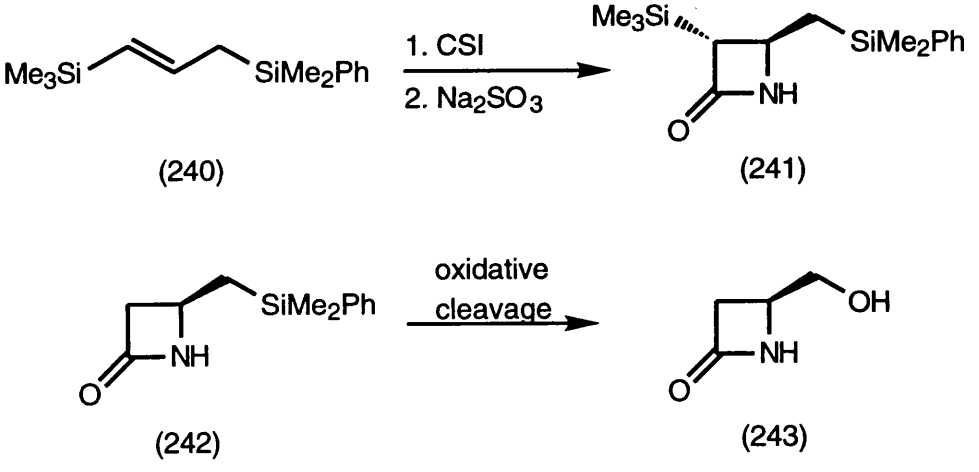
It is interesting to note that while *N*-chlorosulphonyl β-lactams derived from allylsilanes are unstable, those derived from simple olefins decompose to the corresponding β,γ–unsaturated *N*-chlorosulphonyl amides very slowly.

Work within this group[137,138] has been aimed at establishing the scope and utility of this reaction. Unfortunately, azetidinone (239) is not usefully functionalised at C-3 and trimethylsilyl groups are highly resistant to functionalisation. Consequently, the study was extended in two complementary directions.

1) Alteration of the olefinic substitution to allow direct access to C-3 substituted carbapenems such as thienamycin, the asparenomycins, or PS-5.

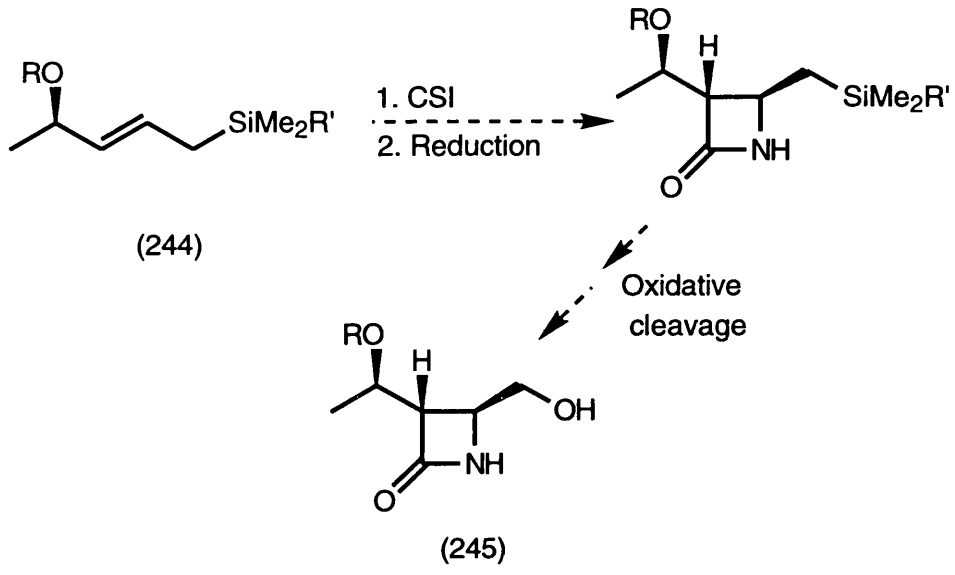
2) Alteration of the silyl substituents to allow oxidative cleavage of the C-Si bond and thus introduction of a hydroxymethyl, or oxidatively related, group at C-4.

Much of the work in this current project stemmed from the following sequence of reactions carried out by M. Monteith.[139] Allylsilane (240) reacted smoothly with CSI to give *trans* β-lactam (241) after reductive hydrolysis. The C-3 trimethylsilyl group was then removed to give (242). Since phenyldimethylsilyl groups can be cleaved[140] to hydroxyl groups by a sequence of protiodesilylation and oxidation this compound is a masked form of 4-hydroxymethylazetidinone (243). Accordingly, the silyl group was oxidatively cleaved, albeit in poor yield, to provide (243) which, once suitably protected, was further elaborated at C-3 using standard enolate/electrophile methodology.



As mentioned in Chapter 1, incorporation of C-3 substituents after β-lactam formation is inefficient and the first aim of this project was to produce an allylsilane (244) which would stereoselectively incorporate a thienamycin like C-3 *trans*-hydroxyethyl sidechain upon regiocontrolled cycloaddition with CSI (Scheme 10).

The second aim was to improve the efficiency of the oxidative cleavage step by exploring alternative silyl substitution (R') and/or oxidising conditions. In this way, it was hoped that the potentially useful thienamycin precursor (245) might be produced efficiently and with a high degree of stereocontrol.

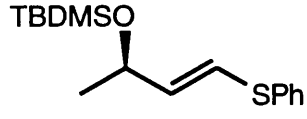


Scheme 10.

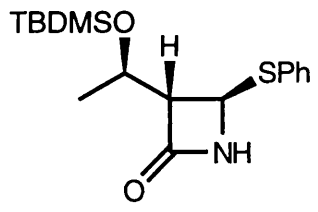
Literature precedent for the stereoselective cycloaddition of allylsilane (244) came from two sources:

1) CSI /Vinylsulphides.

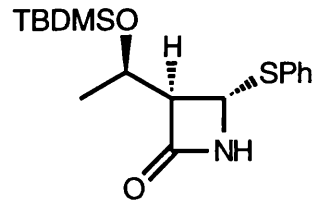
Ishiguro[123] found that (*E*)-vinyl sulphide (246) underwent reaction with CSI to give a 2.5 : 1 mixture of 4-phenylthioazetidinones (247) and (248).



(246)

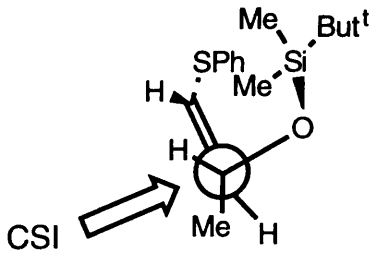


(247)



(248)

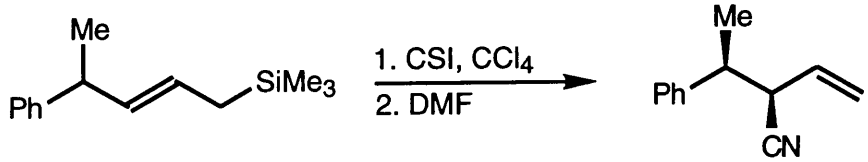
The selectivity for (247) can be rationalised using the staggered transition state conformation, shown in Scheme (11). Attack of CSI from the less hindered face of this conformer leads to the major diastereomer (247), while attack from the opposite face leads to the minor product (248).



Scheme 11.

2) CSI /Chiral Allylsilanes.

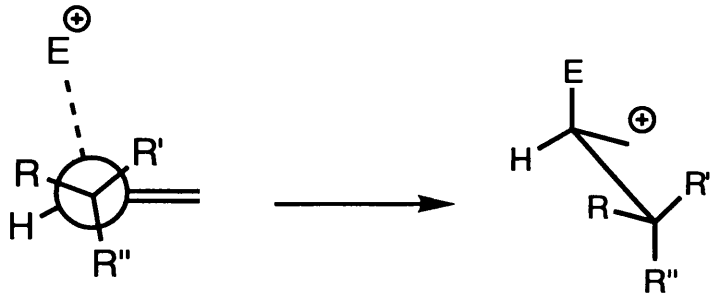
The presence of a stereocentre directly attached to the double bond of an allylsilane has an influence on the stereochemistry of its reaction with electrophiles. Taddei[141] and Fleming[142] have demonstrated that allylsilane (249) underwent reaction with CSI with a diastereomeric excess (d.e.) of 90%. This level of 1,2-diastereomeric induction is quite remarkable considering that (249) is an acyclic system with no obvious nucleophilic co-ordination sites to direct the approaching electrophile. As both groups carried out this reaction at a relatively high concentration the intermediate β-lactam (251) rearranged *in situ* to the corresponding silyl imidate ester which, when treated with DMF, furnished the unsaturated nitrile (250).



(249) (250)

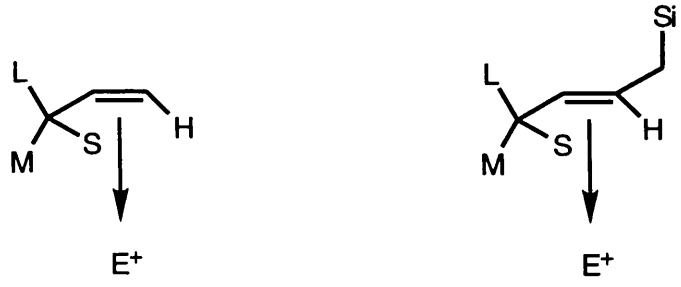
The origin of this diastereoselectivity has been rationalised using a transition state model for the attack of electrophiles and nucleophiles upon allylic systems

developed by Houk.[143] Briefly, when an electrophile attacks a double bond adjacent to a chiral centre, the substituents on the allylic sp^3 centre will be staggered with respect to both the bond being formed and the partially pyramidalised sp^2 carbon undergoing attack as shown in Scheme 12.



Scheme 12.

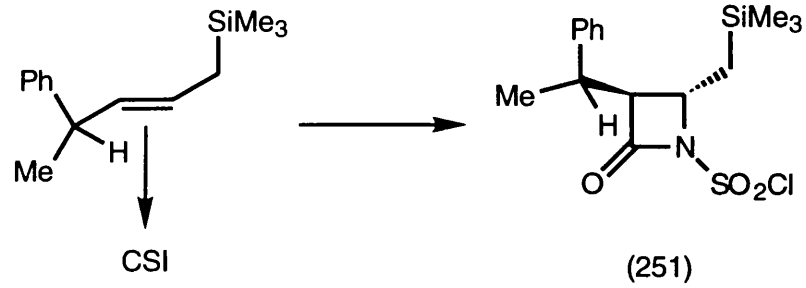
When the substituents (R, R' and R") on the allylic centre are of sufficiently varying size, $A_{1,3}$ strain ensures that the largest substituent is antiperiplanar to the incoming electrophile while the hydrogen partially eclipses the double bond. In the case of allylsilanes, the Si-CH_2 will align itself parallel to the adjacent π system in order to allow maximum stabilisation of any developing positive charge *via* the β-effect (Scheme 13).[144]



Scheme 13

The highest stereoselectivity in such systems seems to be achieved when the allylic centre is attached to hydrogen, methyl and a much larger group. Following from this, allylsilane (249) will adopt the conformation shown in Scheme (14).

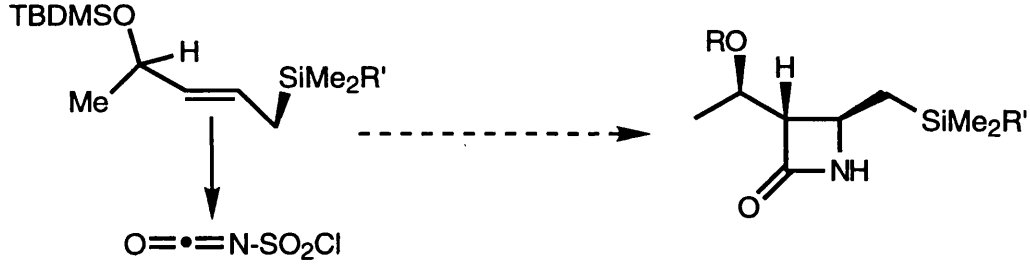
Attacked by CSI from the less hindered of its diastereotopic faces gives azetidinone (251) which has the same stereochemistry as unsaturated nitrile (250).



(251)

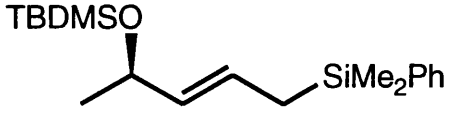
Scheme 14.

The obvious structural similarities between the olefins in examples 1) and 2) and allylsilane (244) were very encouraging. Houk's model suggests (252) as the reacting conformer. Approach of CSI from the less hindered face of this conformer leads to azetidinone (253) which possesses all three of thienamycin's chiral centres with the correct relative stereochemistry.



(252) (253)

It was decided to attempt this cycloaddition initially on the *O*-TBDMS protected allylsilane (254). This protecting group was known to be stable to both CSI and the reductive hydrolysis conditions.

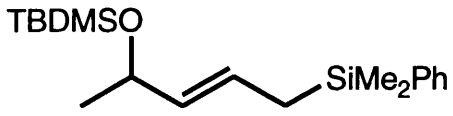


(254)

3 Synthesis of δ-Oxa-Allylsilanes

3.1 Introduction

Although the structure of (254) is relatively simple we desired its synthesis to be flexible enough to achieve the following:



(254)

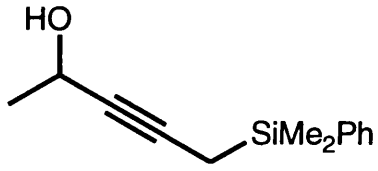
1) Stereoselective production of the (*E*)-isomer only and thus the *trans* azetidinone.

2) Incorporation of the range of silyl substitution needed to investigate the oxidative cleavage step. While phenyldimethylsilyl is relatively stable, other oxidatively cleavably groups such as $Si(Me)_2OPr^i$ and $Si(Me)(OPr^i)_2$ are not. It would therefore be advantageous if the silyl group was incorporated in the final synthetic step.

3) Production of (254) in enantiomerically pure form when required.

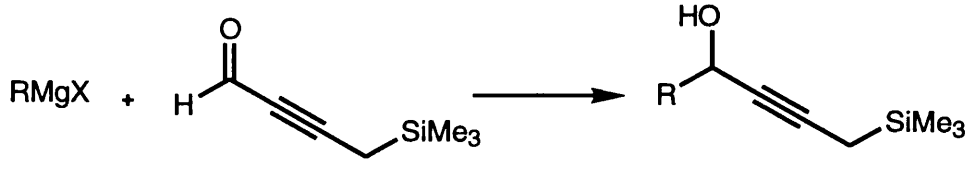
3.2 Attempted Synthesis *via* a Propargylsilane.

For initial studies it was decided to attempt the synthesis of (254) *via* the stereoselective reduction of the corresponding 1-alkynol (255). Hydroalumination of 1-alkynols with $LiAlH_4$ and hydrolysis of the resultant vinyl alanate is a well established and efficient method for the synthesis of (*E*)-allylic alcohols.[145]



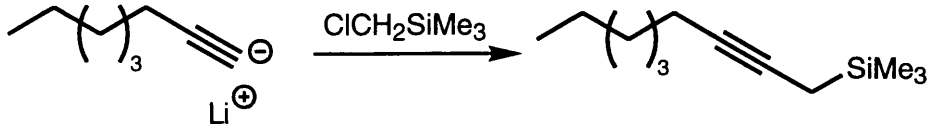
(255)

At the outset of this work there appeared to be two routes in the literature to such propargylsilanes. Clive and Angoh[146] prepared (257) by treating aldehyde (256) with a range of Grignard reagents. This route was, however, rejected because the multistep procedure required to produce (256) would exclude the use of labile silanes.



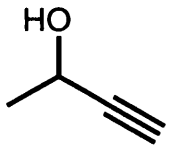
(256) (257)

The route eventually chosen followed a protocol developed by Peterson for the synthesis of propargyltrimethylsilanes.[147] Alkylation of lithiated 1-alkynes with trimethylsilylmethyl halides gave the corresponding propargylsilanes in reasonable yield, *e.g.*, 1-octyne (258) was successively treated with Bu^nLi and Me_3SiCH_2Cl to yield (259) in 60%.



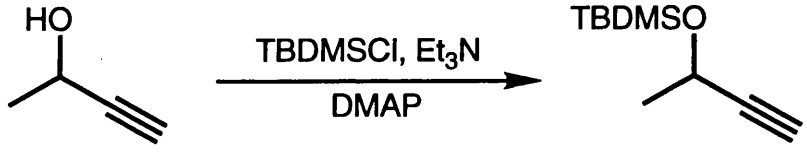
(258) (259)

Application of this disconnection to (255) gave but-1-yn-3-ol (260) and chloromethyldimethylphenylsilane which are both commercially available.



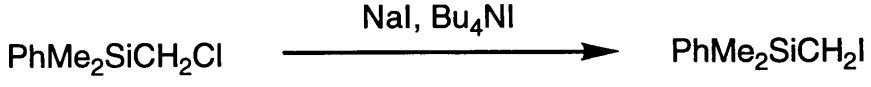
(260)

TBDMS Protection of the hydroxyl group seemed appropriate to the alkylation conditions and accordingly, (261) was prepared in good yield, using standard DMAP/Et_3N catalysed methodology.[148]



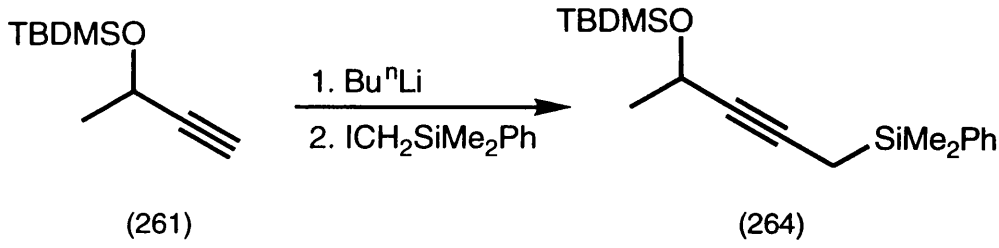
(260) (261)

Successive treatment of (261) with Bu^nLi and $PhMe_2SiCH_2Cl$, at -15°C, followed by overnight heating at 55°C gave only starting materials. Reasoning that the alkylation might proceed more successfully with a better leaving group, iodomethylsilane (263) was prepared by carrying out a Finkelstein reaction on chloromethylsilane (262). Following the method of Peterson,[149] (262) was heated with NaI, in the presence of tetra-butylammonium iodide to give (263) in good yield.

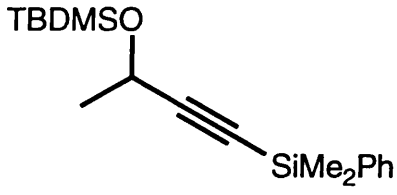


(262) (263)

Repetition of the alkylation reaction using (263) gave propargylsilane (264) accompanied by *ca.* 20% of the terminally 1-silylated alkyne (265). Unfortunately, all attempts to separate these compounds by distillation and chromatography failed.

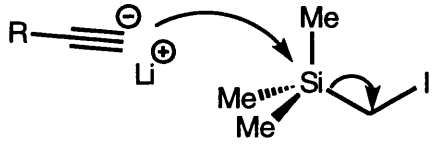


(261) (264)



(265)

This rather surprising type of by-product has also been observed by Peterson who suggested the mechanism shown in Scheme (15).[149] Ho[150] has subsequently rationalised this unusual regioselectivity using the concept of hard and soft, acids and bases (H.S.A.B.). Lithiated 1-alkynes are hard bases and attack the silicon centre, a hard acid, in preference to the CH_2I group, a soft acid.

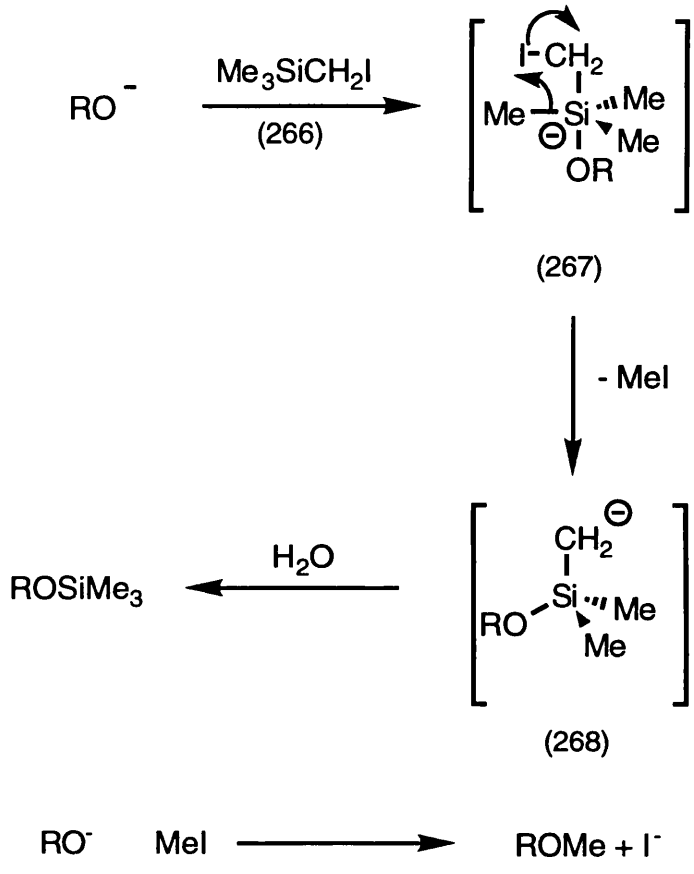


Scheme 15.

Although iodomethide (CH_2I^-) seems an unlikely leaving group, other reports of anomalous alkylation have appeared in the literature. Chakraborty and Reddy[151] have reported that when iodomethyltrimethylsilane (266) is treated with a range of alkoxides only the corresponding trimethylsilyl- and methyl ethers are isolated.

It has been suggested that Si-C bond heterolysis may result from the initial nucleophilic attack of the alkoxide upon silicon to form the penta-co-ordinated species (267). Methyl iodide is then eliminated generating the stabilised anion (268)

which, when protonated, gives the trimethylsilyl ether. The methyl ethers arise from the alkylation of any remaining alkoxide with methyl iodide (Scheme 16). Although this mechanism may account for formation of (265) no product of methylation was isolated.



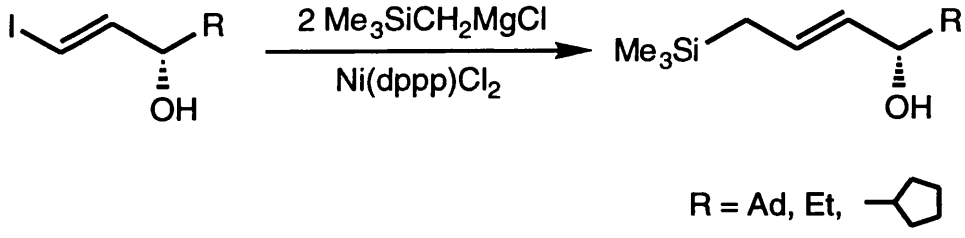
Scheme 16.

Peterson found that the formation of 1-silyl alkynes could be prevented by using Me_3SiCH_2OTf and HMPA as a co-solvent. In view of the lengthy and relatively harsh conditions required to produce the appropriate triflate and the known toxicity of HMPA, an alternative route to allylsilane (254) was sought.

3.3 Synthesis *via* a Vinyl Iodide.

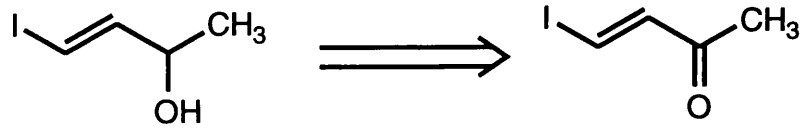
The transition metal catalysed coupling of alkenyl halides with trimethylsilylmethyl Grignard reagents provides an excellent method for the regio- and stereoselective synthesis of allylsilanes.[152]

Our interest in this method was stimulated by a communication from Sato and co-workers,[153] who employed it in the synthesis of a range of chiral δ–hydroxy-allylsilanes with a similar structure to that of (254) (Scheme 17). Characteristically, the coupling proceeds in very high yield and with complete retention of olefinic stereochemistry. In the example shown, two equivalents of Grignard reagent are used in place of hydroxyl protection.



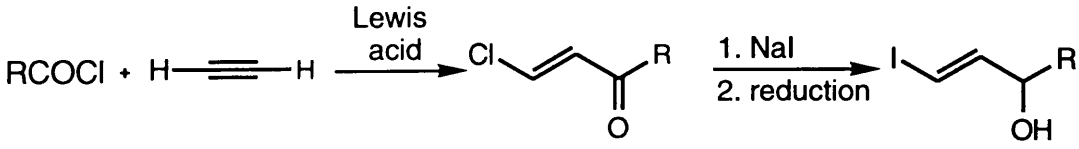
Scheme 17.

For our purposes we required allylic alcohol (269) which was obtained by the reduction of β-iodovinyl ketone (270).



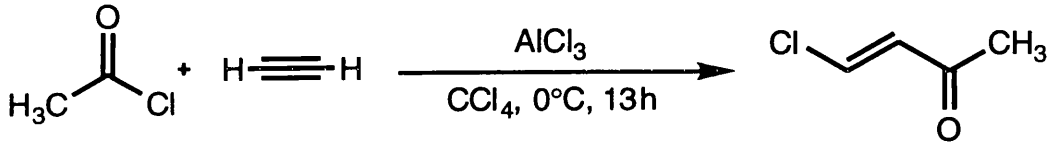
(269) (270)

Although a number of possible routes to *trans*-β-iodovinyl ketones exist, the most convenient one involves the Lewis acid catalysed addition of acid chlorides to acetylene. Halogen exchange then provides the β-iodovinyl ketones which are reduced to give the allylic alcohols (Scheme 18).



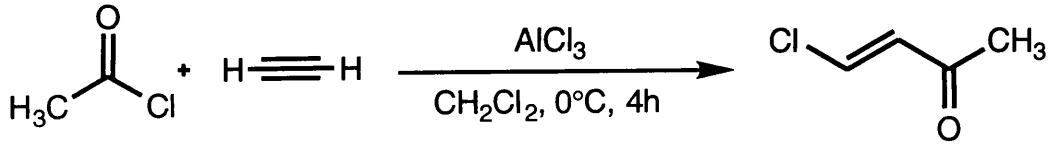
Scheme 18.

Benson and Pohland[154] prepared (272) by passing acetylene through a carbon tetrachloride solution of aluminium trichloride and acetyl chloride (271). The reaction proceeded in high yield and gave only the *trans* product.



(271) (272)

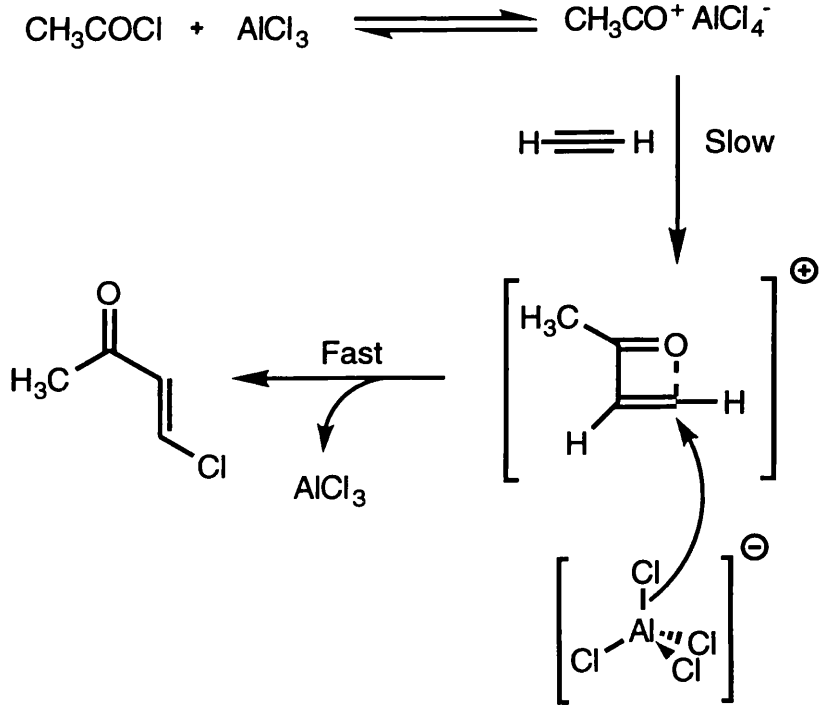
Attempts to produce (272) following Benson's[154] original procedure gave disappointingly low yields. Extensive product breakdown during distillation was evident from the formation of large quantities of a black polymer. The instability of (272) was probably due to traces of HCl, which are known to catalyse the rapid breakdown of these compounds. Lohringer and Sixt[155] have noted that β-chlorovinyl ketones can be stabilised by the addition of phenol or hydroquinone (0.5% by weight). By repeating the reaction in dichloromethane and distilling the crude product from and on to hydroquinone the yield was greatly improved. The *trans* geometry of (272) was confirmed by an olefinic coupling of 15.1 Hz in the ^{1}H NMR spectrum.



(271) (272)

Despite reports[156] that the use of dichloromethane can result in the production of both (*E*) and (*Z*) products, no signals corresponding to the (*Z*) isomer could be seen in the 200MHz ^1H NMR spectrum of (272). Changing the reaction solvent from CCl_4 to CH_2Cl_2 had an additional advantage in that the time required for the reaction to go to completion was reduced from 13 to 4 hours.

Martens[156] has suggested that this reaction proceeds *via* attack of the acylium cation on acetylene leading to the formation of a high energy[157] vinyl cation which is partially stabilised by interaction with the adjacent carbonyl in an oxetene like intermediate (Scheme 19). Rapid attack of the tetrachloroaluminate anion upon the empty p-orbital of this intermediate then occurs from the less hindered side to give the product of *trans* addition.

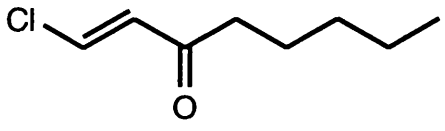


Scheme 19.

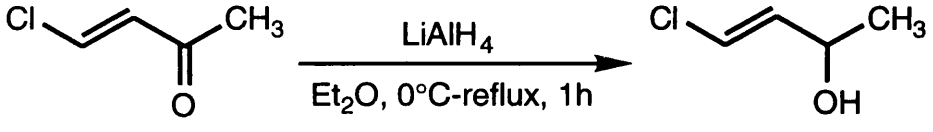
It is interesting to note that when acetylene was passed through a suspension of $AlCl_3$ in CH_2Cl_2 a deep purple colour rapidly appeared. This may be due to the formation of an donor/acceptor complex between acetylene and aluminium chloride.

Rather than produce the vinyl iodide we decided to attempt the coupling on the vinyl chloride and, in doing so, remove a step from the synthetic route. Consequently, our attention turned to the reduction of (272).

Treatment with $NaBH_4$ in ethanol gave poor yields despite having been used successfully by Corey and Beames[158] for the reduction of (273). Reduction with $LiAlH_4$, on the other hand, gave (274) in excellent yield.

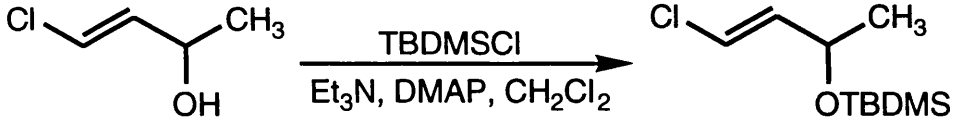


(273)



(272) (274)

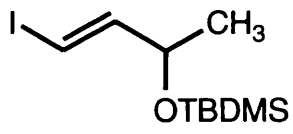
Rather than use (274) directly in the coupling reaction, it was first protected as its TBDMS ether. Thus, treatment of (274) with TBDMSCl under DMAP/Et_3N catalysed conditions furnished silyl ether (275).



(274) (275)

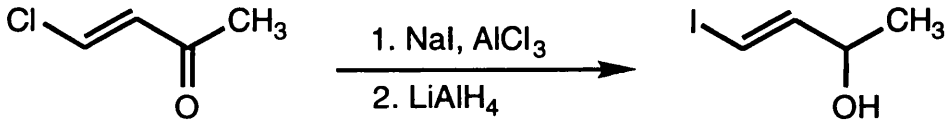
Following the procedure of Sato,[153] this vinyl chloride was treated with a solution of $PhMe_2SiCH_2MgCl$ in ether, in the presence of a catalytic amount of $Ni(dppp)Cl_2$. After stirring overnight at room temperature, ^1H NMR spectroscopy showed that the reaction had only gone to 30% completion. Disappointingly, prolonged reaction times did not improve the situation.

While there are numerous reports of the Ni (II) catalysed coupling of Me_3SiCH_2MgCl and alkenyl iodides and bromides, there are only a few involving alkenyl chlorides. In view of this it was decided to prepare vinyl iodide (276) and hopefully overcome this problem.



(276)

β-Iodovinyl ketone (270) was prepared using Corey's[158] modification of Pohland and Benson's[154] original procedure. Thus, (272) was treated with NaI in the presence of a catalytic amount of $AlCl_3$ to give (270) in excellent yield. Reduction with $LiAlH_4$ furnished allylic alcohol (269) which was then protected as its TBDMS ether (276) using standard conditions.



(272) (269)

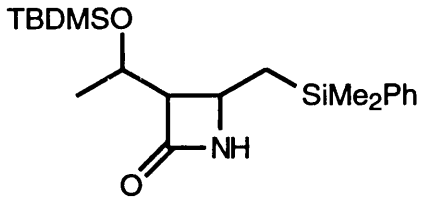
Repetition of the coupling procedure using (276) gratifyingly gave the desired allylsilane (254) in a yield of 98%. The *trans* stereochemistry this compound was confirmed by an olefinic coupling of 15.2 Hz in the ^1H NMR spectrum.

(276) (254)

4. Reaction of CSI with δ-Oxa-allylsilanes

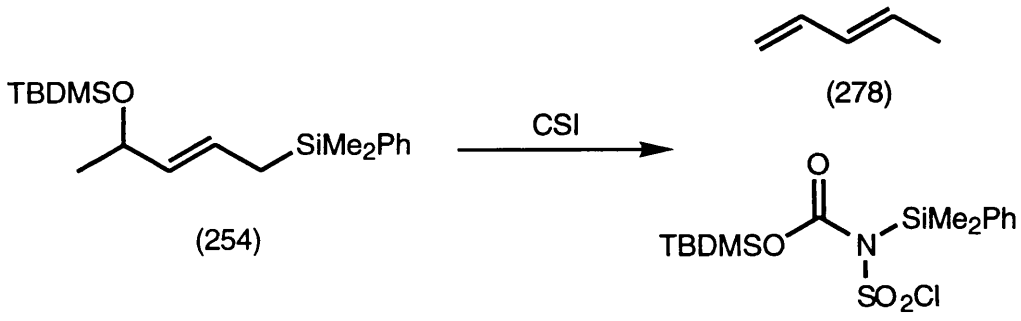
4.1 Reaction of CSI with allylsilane (254).

With the synthesis of (254) now in hand, it was submitted to the usual cycloaddition conditions, *i.e.*, a 0.2M carbon tetrachloride solution of (254) was treated with 1.1 equivalents of CSI. After stirring for two hours, the reaction was quenched with an aqueous solution of sodium sulphite. Disappointingly, however, no trace of either starting material, or the expected product (277) was found. Only a small amount of an uncharacterised mixture of silyl residues was recovered.



(277)

In order to investigate this reaction further, the experiment was repeated, and its progress followed by ^1H NMR spectroscopy. Addition of 1.5 equivalents of CSI to a solution of (254) resulted in immediate loss of the starting material and the appearance of a complex group of signals in the ^1H olefinic region. ^1H NMR Decoupling experiments suggested that *trans*-1-penta-1,3-diene (278) was present. This was subsequently confirmed by comparison with the ^1H NMR spectrum of an authentic sample. A second product was also formed at this stage and was tentatively assigned the *N*-silylated carbamate structure (279).

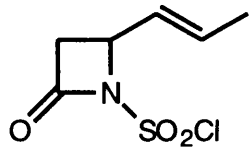


(254)

(278)

(279)

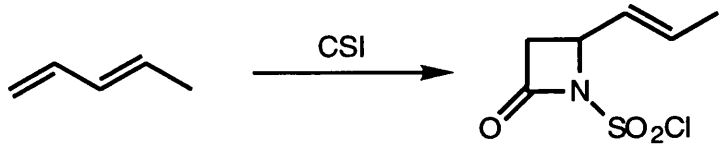
After a further 2.5 h, the signals corresponding to (279) remained unchanged, while (278) was partially replaced by a new product. After 20h, (278) had been completely replaced by the new product, which ^{1}H NMR decoupling experiments and ^{13}C NMR spectroscopy revealed to be C-4 vinylazetidinone (280).



(280)

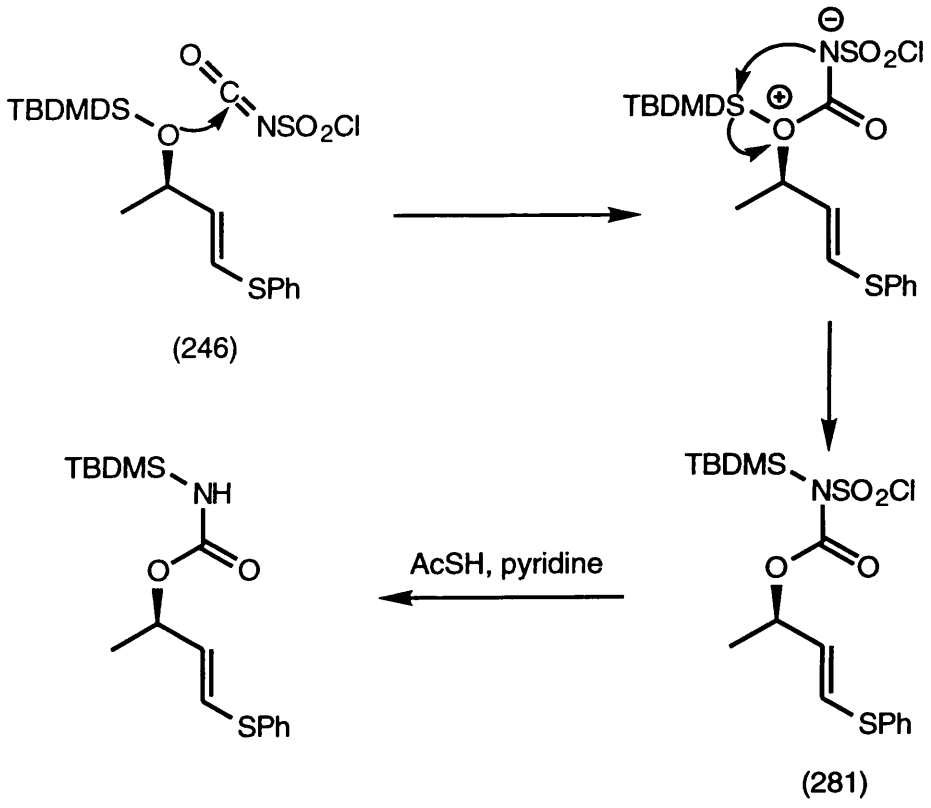
At this stage, a sample of the reaction mixture was removed and analysed by IR spectroscopy. A strong carbonyl absorption at 1826cm^{-1} confirmed the presence of an *N*-chlorosulphonyl β-lactam while an absorption at 1750 cm^{-1} was in accord with carbamate (279). Mass spectrometry showed a large peak at 209 amu which corresponds to the molecular ion (M^{+}) of (280).

The formation of (280) presumably results from the regioselective cycloaddition of (278) with excess CSI.



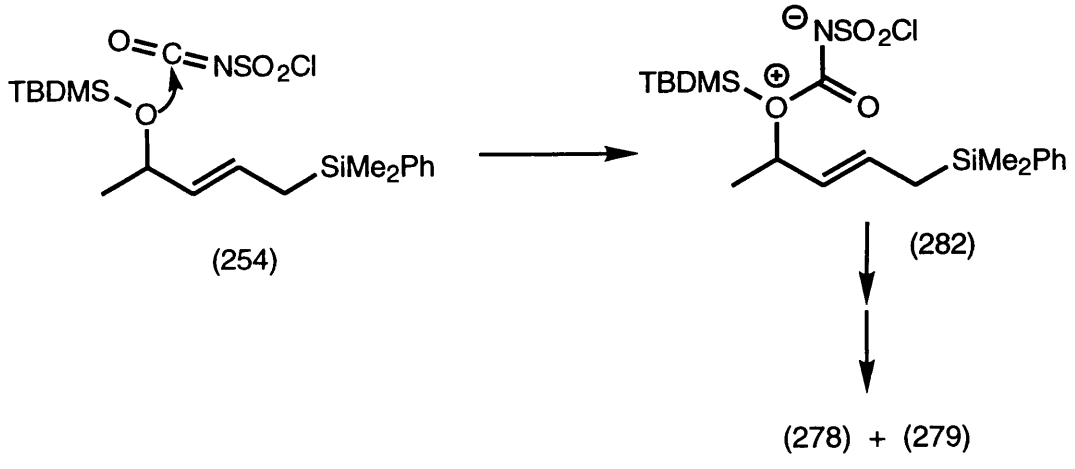
(278) (280)

From these observations it was clear that CSI acts as a Lewis acid upon (254) causing a vinylogous Peterson elimination (1,4 elimination) more rapidly that cycloaddition. Ishiguro[123] has found that the reaction between CSI and allylic ether (246) in chloroform gives *N*-silylated carbamate (281) possibly *via* the mechanism shown in Scheme 20.



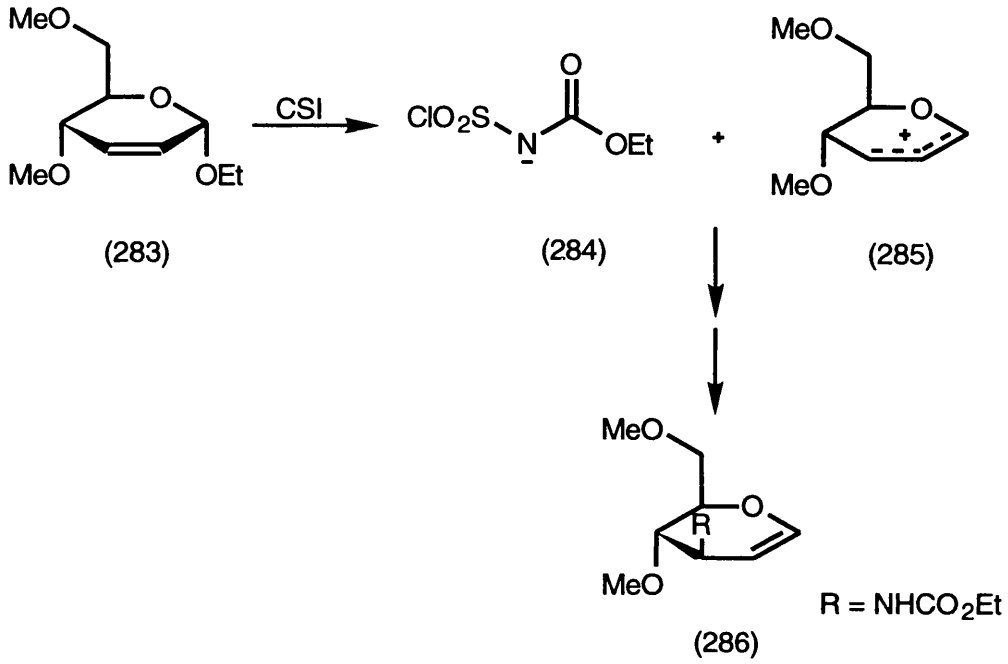
Scheme 20.

The formation of (278) and (279) can also be rationalised using this mechanism. Interaction of an allylic oxygen lone pair with the highly electrophilic sp centre of the isocyanate leads to zwitterion (282) (Scheme 21). This species is capable of undergoing a 1,4 elimination (vinylogous Peterson) to the observed products by a stepwise (E1-like) Peterson elimination, or possibly *via* a more concerted process (E2-like).



Scheme 21.

Interestingly, Joordan[159] has reported that CSI, acting as a Lewis acid, abstracts the anomeric ethoxy group of (283) to generate carbamate anion (284) and the stable allylic oxo-carbonium ion (285) (Scheme 22). Unable to undergo fragmentation, (285) recombines with (284) at C-3 to give carbamate (286) after hydrolysis.



Scheme 22.

In an attempt to prevent elimination we began to explore alternative reaction conditions and protecting groups which would favour cycloaddition.

4.2 Alternative solvents.

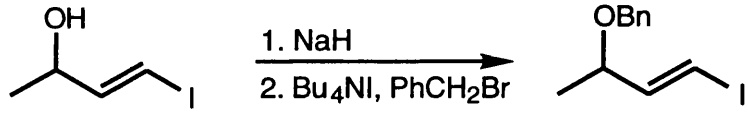
Ishiguro[123] found that formation of carbamate (281) could be prevented by performing the cycloaddition in iso-propyl ether. However, when allylsilane (254) was treated with CSI in this solvent, no β-lactam product could be isolated.

Disappointingly, use of hexane, ether and dichloromethane also resulted in rapid elimination.

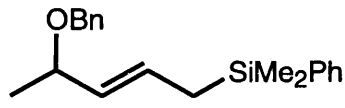
Bearing in mind that the rate of cycloaddition between CSI and alkenes is markedly increased in polar solvents,[127] the reaction was repeated in a 1:1 mixture of nitromethane and dichloromethane. Again, no products of cycloaddition were isolated.

4.3 Alternative protecting groups.

Benzyl protection was selected for initial investigation in view of its compatibility with azetidinones. Treatment of (269) with NaH and then benzyl bromide, under phase transfer conditions,[160] gave benzyl ether (287). Coupling of (287) with $PhMe_2SiCH_2MgCl$, under the same conditions as before, gave (288) in excellent yield.

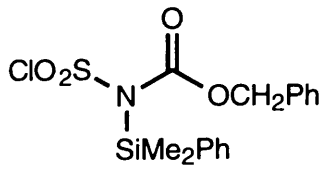


(269) (287)



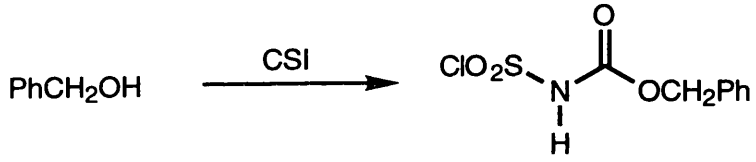
(288)

The reaction between (288) and CSI was followed by ^1H and ^{13}C NMR spectroscopy. Unfortunately, addition of 1.5 equivalents of CSI resulted in immediate loss of starting material and formation of *trans* 1-penta-1,3-diene (278) and carbamate (289). IR Spectroscopic analysis of the reaction mixture showed a strong carbonyl absorption at 1727 cm^{-1}. As before, (278) underwent cycloaddition with excess CSI to give vinyl azetidinone (280).



(289)

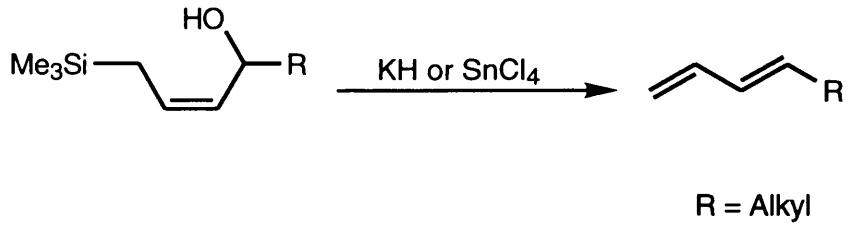
In order to confirm the presence of (289) we decided to prepare carbamate (291). The reaction between CSI and alcohols is known to produces *N*-sulphonyl carbamates, *via* nucleophilic attack of the hydroxyl upon the sp carbon of the isocyanate. Gratifyingly, the spectral data obtained from the reaction between benzyl alcohol (290) and CSI closely matched that of (289) (apart from having an NH rather than $NSiMe_2Ph$ group), *e.g.*, both compounds have a strong carbonyl absorption at $1727cm^{-1}$.



(290) (291)

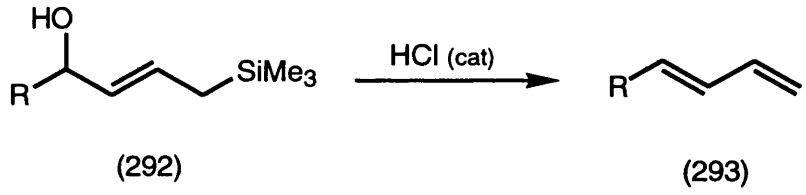
All subsequent attempts to achieve cycloaddition with (254) unfortunately failed despite investigating a range of solvents.

At the outset of this investigation we were aware that *cis* allylsilanes of the type shown in Scheme (22) were known to undergo facile vinylogous Peterson olefination, upon treatment with KH or $SnCl_4$.[146,161] Despite this reactivity, we were encouraged by the fact that *trans*-δ-hydroxy-allylsilanes undergo diastereoselective epoxidation with a range of electrophilic reagents, including Sharpless epoxidation conditions.[153] The yields of these reactions are high, with no elimination, despite the presence of $Ti(OPr^i)_4$.



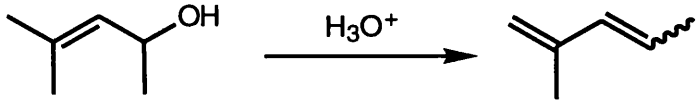
Scheme 22.

However, during our investigations Parsons[162] demonstrated that (292) underwent acid catalysed elimination to furnish the *trans* 1,3-dienes (293) in excellent yield. Only a catalytic amount of HCl was required to effect complete elimination.



(292) (293)

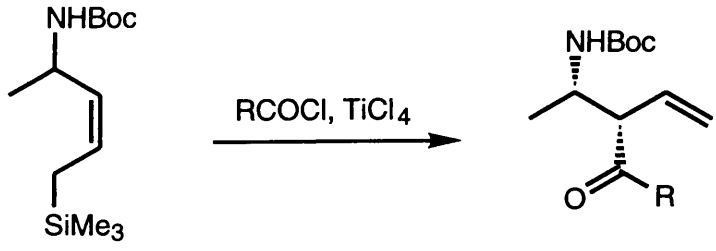
Interestingly, allylic alcohol (294) displays similar instability under acidic conditions. Farmer[163] has found that catalytic amounts of acid cause the dehydration of both (294) and its ester derivatives to give butadiene (295).



(294) (295)

Bearing in mind that CSI is often contaminated by traces of sulphur trioxide and hydrogen chloride we wondered whether the breakdown of the allylsilanes may be due to traces of these impurities rather than CSI itself, a point also noted by Joordan.[159] Addition of Hünig's base, as an acid scavenger, to the system did not prevent elimination.

Suprisingly, Taddei and co-workers[164] have found that Boc-protected δ-amino-allylsilane (296) undergoes electrophilic substitution with $RCOCl/TiCl_4$ to yield (297) as one diastereomer.

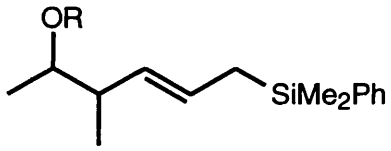


(296) (297)

5. Design and Synthesis of ε-Oxa-Allylsilanes

5.1 Design of an ε-Oxa-Allylsilane.

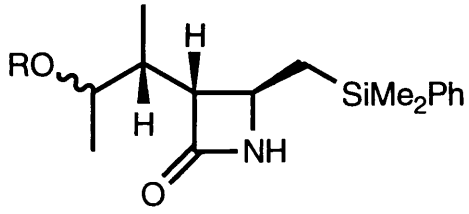
The initial aim of this project was to introduce a C-3 hydroxyethyl sidechain directly upon cycloaddition. However, the ease with which δ-oxa-allylsilanes undergo elimination prevented us from achieving this. Our attention therefore turned to the design and synthesis of an alternative allylsilane, which could stereoselectively introduce a masked hydroxyethyl group. In order to control the stereochemistry of the cycloaddition the allylsilane chosen would require a stereocentre directly attached to the olefin. As discussed in Chapter 2, maximum stereoselectivity is attained when this chiral centre was attached to hydrogen, methyl and a larger group. Accordingly, allylsilane (298) was chosen for investigation.



(298)

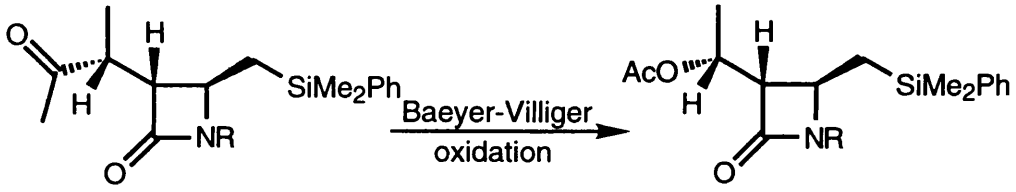
By moving the hydroxyl group one position away from the silyl group, the problem of elimination is prevented; ε-hydroxy-allylsilanes, such as (298), are known to undergo 'normal' nucleophilic addition to electrophiles.[165]

It was envisaged that regiocontrolled cycloaddition of (298) with CSI, followed by reductive hydrolysis, would give the *trans* substituted azetidinone (299) with the chiral centre adjacent to the olefin controlling the stereoselectively of the reaction.



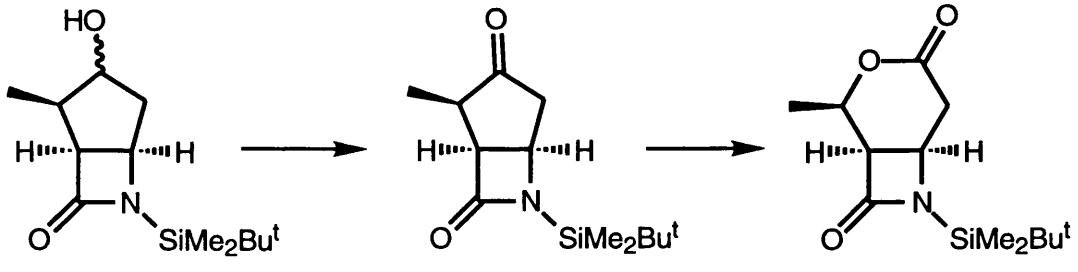
(299)

The required C-3 hydroxyethyl sidechain could then be unmasked by a sequence of alcohol deprotection and oxidation giving ketone (300). Regioselective Baeyer-Villiger oxidation of this unsymmetrically substituted ketone would then furnish acetate (301).



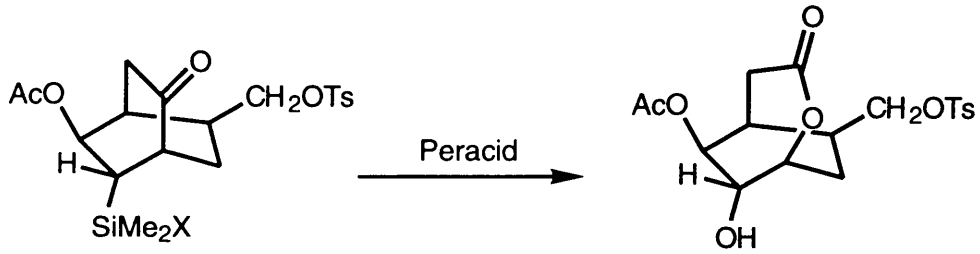
(300) (301)

Precedence for this strategy came from Ohno's[166] synthesis of thienamycin. Alcohol (302) was oxidised to methylcyclopentanone (303) which, when treated with MCPBA, underwent regioselective Baeyer-Villiger oxidation unmasking the hydroxyethyl sidechain as δ-lactone (304).



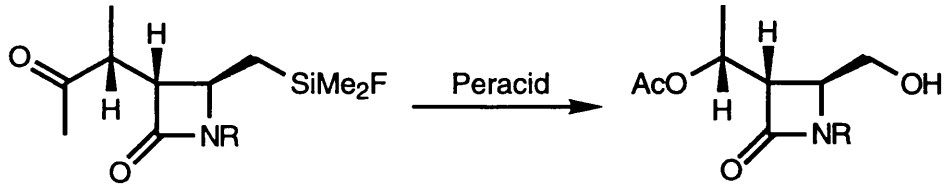
(302) (303) (304)

In view of the fact that peracids, such as MCPBA, are known to cleave the Si-C bonds of fluorosilanes[167] we were excited by the possibility of exploiting the dual functionalisation strategy recently employed by Stork[168] in a synthesis of reserpine. This synthetic route is cleverly designed such that peracid treatment, which converts the *endo*-fluorodimethylsilyl group of (305) to a hydroxyl group, simultaneously converts the ketone into lactone (306).



(305) (306)

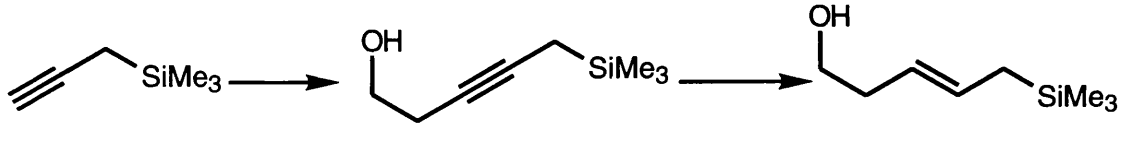
Applying this strategy to azetidinone (300), we planned to convert the phenyldimethylsilyl group into the corresponding halodimethylsilane (307) by protio- or bromodesilylation. Treatment with peracid would then simultaneously unmask the C-3 sidechain and oxidatively cleave the silyl group to yield the useful carbapenem precursor (308).



(307) (308)

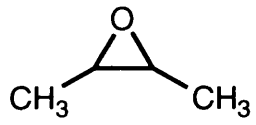
5.2 Synthesis of δ-Oxa-Allylsilanes

Speckamp[169] had previously developed a simple two step synthesis of ε-hydroxy-allylsilane (311) which involved the ring opening of oxirane with the diethylalkynyl alane[170] of propargyltrimethylsilane (309) to give homopropargylic alcohol (310). Stereospecific reduction with lithium aluminium hydride then gave (311).

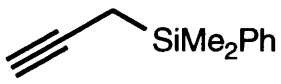


(309) (310) (311)

Disconnection of target allylsilane (298), following Speckamp's protocol, led to epoxide (312) and propargylsilane (313)

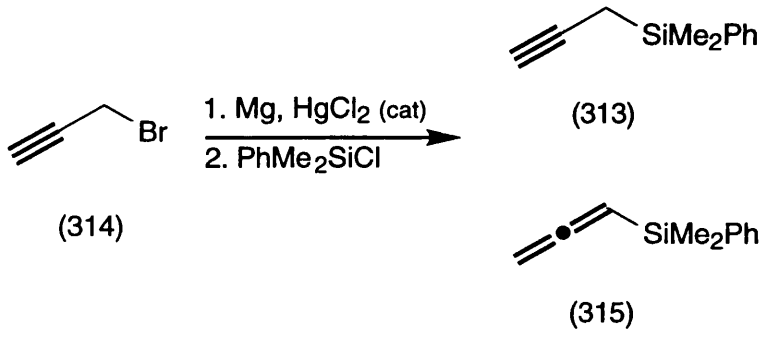


(312)



(313)

While both diastereomers of (312) were commercially available, (313) on the other hand, had to be prepared using a modification of Miginiac's[171] procedure for propargyltrimethylsilane (309). Thus, an ethereal solution of propargyl magnesium bromide (314) was prepared by the mercuric chloride catalysed Grignard reaction of propargyl bromide. Treatment of the Grignard reagent with $PhMe_2SiCl$ then gave propargylsilane (313). ^1H NMR Spectroscopy revealed the presence of the allenic isomer (315) (*ca.* 15%). Neither fractional distillation or column chromatography, however, could separate these isomers.

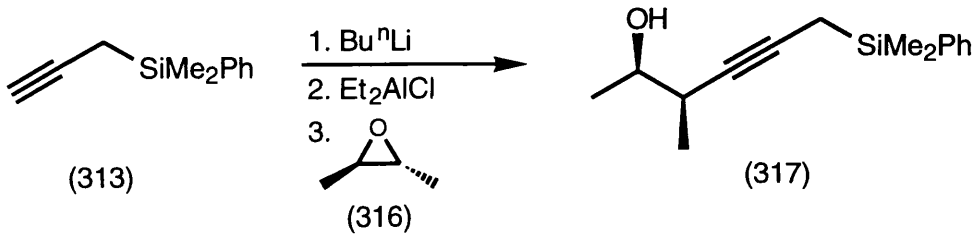


(314)

(313)

(315)

The diethylalkynyl alane of (313), prepared by successive treatment with Bu^nLi and diethylaluminium chloride, was quenched with *trans* epoxide (316) to yield (317) in a disappointingly low yield. This may be due to the presence of the allenyl silane in the starting material.

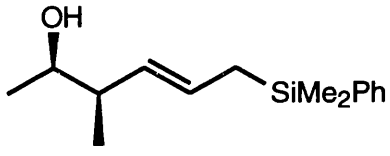


(313)

(316)

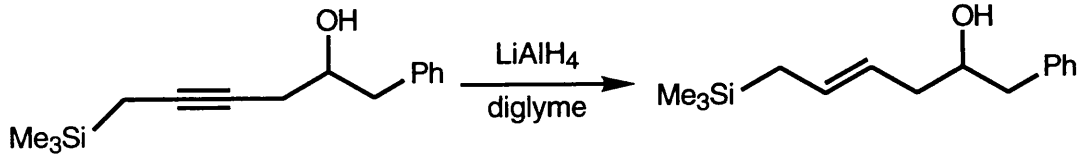
(317)

In an attempt to increase the efficiency of this step the reaction was repeated under Yamaguchi's[172] conditions. Successive treatment of (313) with Bu^nLi, $BF_3{\cdot}Et_2O$ and (316), gave a slightly more acceptable yield of (317). Ganem[173] has shown that this reaction may not proceed *via* the difluoroalkynyl borane species originally proposed by Yamaguchi,[172] but rather involve the lithium acetylide and $BF_3{\cdot}Et_2O$ reacting independently as nucleophile and strong Lewis acid. With propargyl silane (317) now in hand we were ready to proceed with reduction to (318).



(318)

Following Speckamp's[169] procedure, (317) was heated in DME, at reflux, with lithium aluminium hydride for 48 hours. However, after this time, only starting material was recovered. The resistance of certain ε-hydroxy-propargylsilanes to hydride reduction has also been noted by Mohr[165] who was unable to reduce propargyl silane (319) under these conditions. Reduction using the more forcing conditions developed by Rossi[174] ($LiAlH_4$/diglyme/140 C) gave (320) but only in poor yield.



(319) (320)

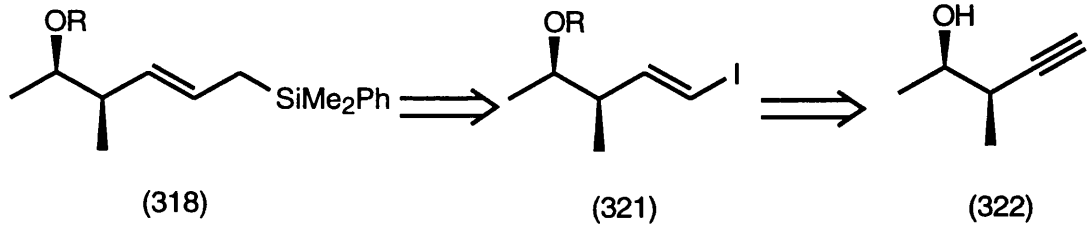
Disappointingly, when (317) was exposed to these conditions, extensive breakdown of the starting material occurred and no allylsilane could be separated from the complex mixture.

Unfortunately, few other methods for the stereoselective reduction of disubstituted 3-alkynols are known; most are based on metal/ammonia reductions. A recent procedure involves the treatment of the *O*-TBDMS derivatives with sodium/ammonia in the presence of butanol, the corresponding (*E*-)-homoallylic alcohols being obtained in excellent yield.[175] However, it seemed unlikely that (317) would survive these conditions in view of the fact that Jackson and co-workers[176] have shown that both aryl and allylsilanes readily undergo Birch reduction.

Despite being unable to prepare (298) we were sufficiently encouraged by the potential of the dual functionalisation strategy to investigate an alternative synthetic route.

5.2.1 Synthesis of Allylsilane (298)

In view of the earlier success with the vinyl halide/Grignard coupling method we adopted this strategy again for the synthesis of (318). This entailed the synthesis of vinyl iodide (321) which, in turn, was prepared from (322) (Scheme 23).

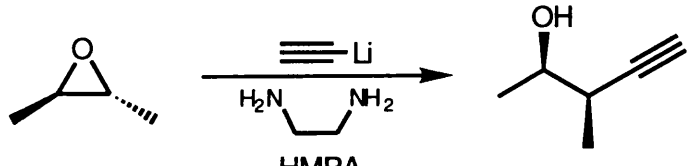


(318) (321) (322)

Scheme 23.

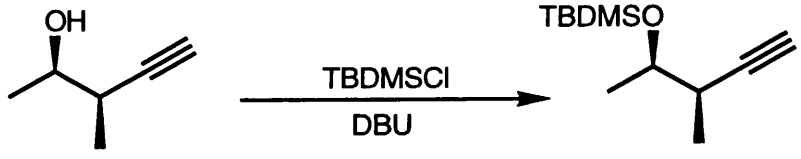
Alcohol (322) is available by the ring opening of epoxide (316) with the ethylenediamine complex of lithium acetylide. Adams's[177] original preparation of this compound used DMSO as the reaction solvent, and as a consequence, work-up and isolation were rather tedious. Kocienski,[178] on the other hand, has found that by using HMPA, work-up is simplified and yields of (322) are improved. However, despite the use of such a polar solvent, the reaction is sluggish and takes several days

to reach completion. Treatment of (316) with the lithium acetylide complex in HMPA gave (322) in an acceptable yield after stirring at room temperature for 6 days.



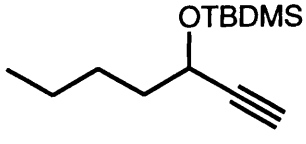
(316) (322)

Attempts to protect this alcohol as its TBDMS ether using the TBDMSCl/Et_3N/DMAP reagent system proceeded very slowly. Silylation using Palomo[179] conditions (TBDMSCl/DBU) was more successful and (323) was produced in good yield.



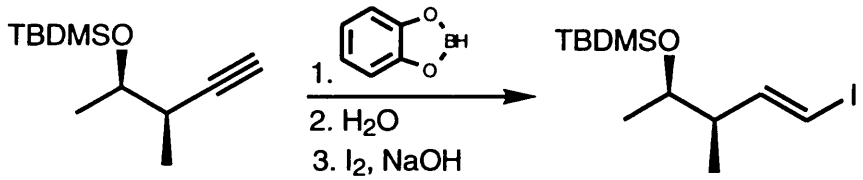
(322) (323)

Numerous methods exist for the conversion of terminal alkynes to the corresponding *E*-vinyl iodides. One of the most common methods involves regioselective hydroalumination with DIBAL-H followed by iodinolysis of the resultant alkenyl alane.[180] Pappo,[181] however, found that this procedure was unsuccessful with *O*-TBDMS protected alkyne (324). An alternative method[182] involving hydroboration and iodinolysis of the alkenyl boronic acid, was more successful.



(324)

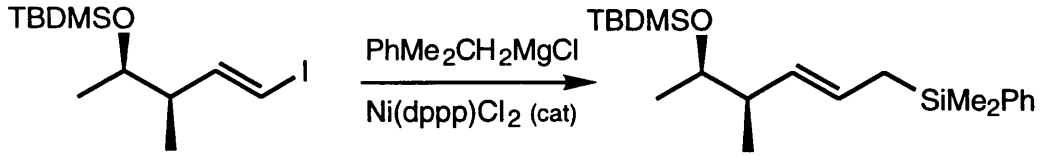
Hydroboration of (323) with catechol borane and hydrolysis gave the corresponding alkenyl boronic acid which was immediately treated with iodine in the presence of sodium hydroxide to yield (*E*)-vinyl iodide (325) in rather low yield.



(323) (325)

Suspecting that this poor yield may have been due to reaction between residual catechol and iodine, the crude boronic acid was taken up in ether and washed several times with water. Resubmission of this ethereal solution to the same iodinolysis conditions disappointingly did not give any improvement in yield. Although Kabalka[183] has demonstrated that yields of iodinolysis can be improved by using iodine monochloride and sodium acetate, we felt that the *O*-TBDMS protection of (323) would not be stable to such conditions.

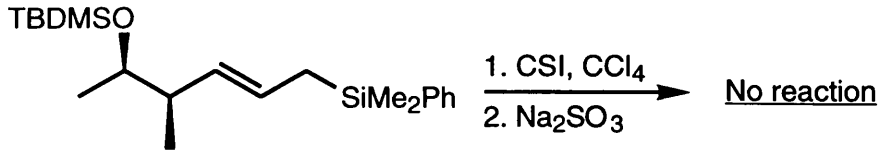
Nickel catalysed coupling of (325) with $PhMe_2SiCH_2MgCl$ gave allylsilane (326) in very high yield. The (*E*) olefinic stereochemistry was confirmed by ^1H NMR spectroscopy decoupling experiments.



(325) (326)

Treatment of (326) with CSI, under standard conditions, was followed by ^1H NMR spectroscopy. After 19 hours at room temperature no reaction had occurred

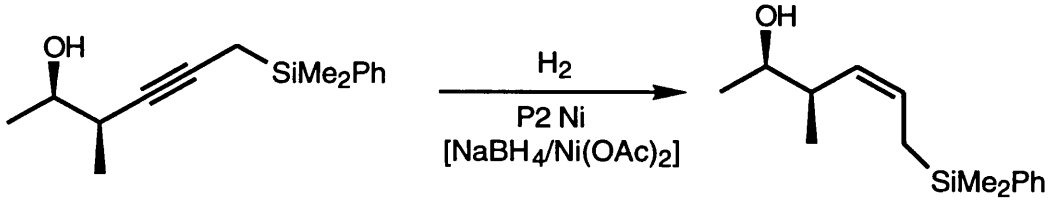
and subsequent work up and purification gave a near quantitative return of starting material.



(326)

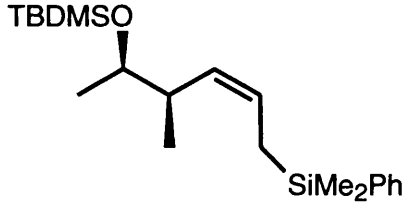
Despite repeating this procedure in a range of solvents, including 1/1 dichloromethane/nitromethane no products of cycloaddition were isolated and only starting material recovered.

Hoping that the (*Z*) isomer (328) might prove more reactive towards CSI, (327) was prepared by partial hydrogenation of propargylsilane (317), following the method of Brown.[184]



(317) (327)

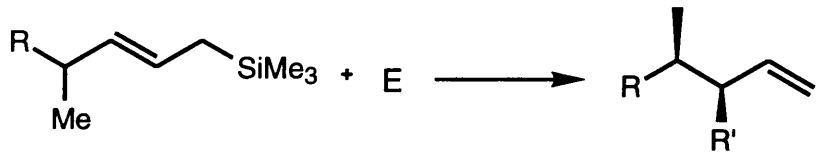
Silylation of the hydroxyl group with DBU/TBDMSCl then gave (328). Unfortunately, this compound also failed to react with CSI under a similar range of conditions.



(328)

The lack of reactivity towards CSI shown by both (326) and (328) has been somewhat difficult to rationalise because of the general lack of information about the

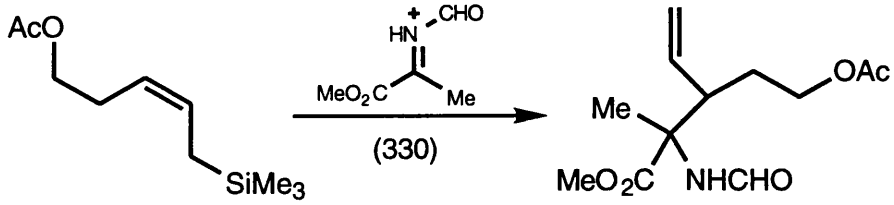
reactivity of ε-oxa-allylsilanes with electrophiles. Steric repulsion between the allylsilane and approaching electrophile seems an unlikely reason, however, given that hindered allylsilanes of the type shown in Scheme (24) readily undergo substitution with various electrophiles, including CSI.[141]



R = Ph, Et, Bu^t E = PhSCl, CSI, RCHO/$TiCl_4$

Scheme 24.

Caution must be used, however, in drawing too close a comparison between these unfunctionalised silanes and our own substrates as heteroatoms attached to allylsilanes can effect their reactivity. Hiemstra and co-workers[185] have found that the reaction between ε-acetoxy-allylsilane (329) and the iminium species (330) is slow and gives (331) only in very low yield. It seems unlikely that this is simply due to steric hindrance and may point to some unfavourable electronic interaction between the substrate and electrophile.



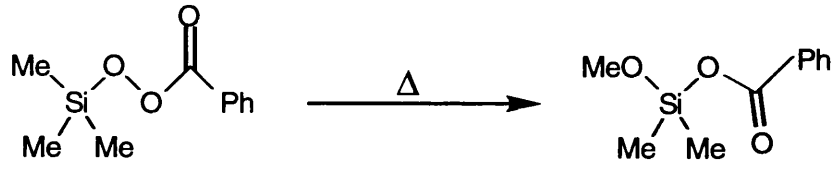
(329) (331)

6 Oxidative Cleavage

6.1 Introduction

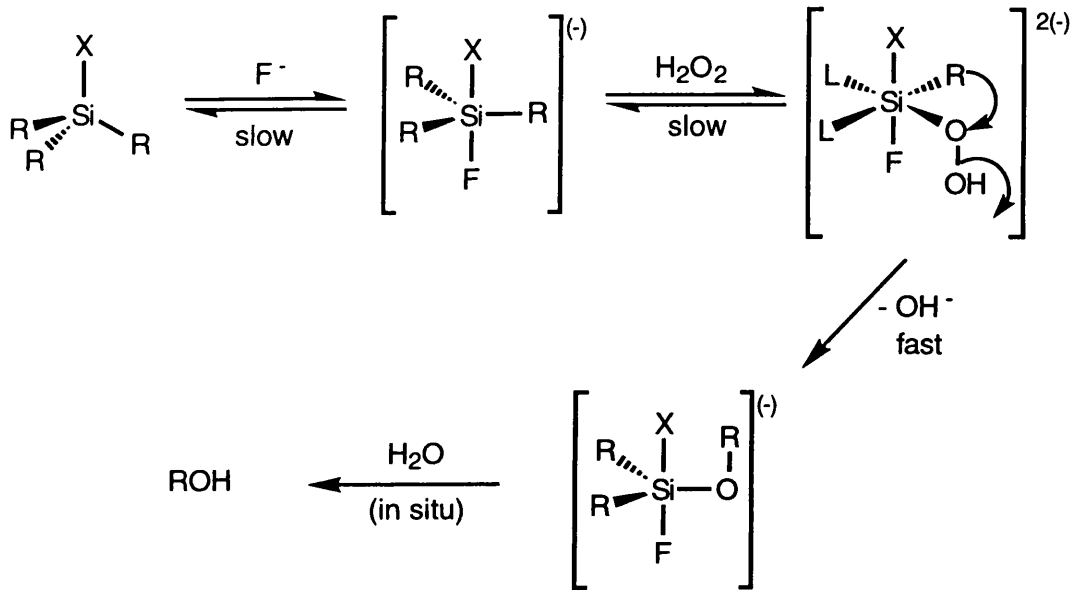
The addition of CSI to allylsilanes is only practical if further synthetic manipulations can be performed on the silyl residue after it has controlled the regiochemistry of cycloaddition. The oxidative cleavage of the carbon-silicon bond to yield the corresponding alcohol allows further functionalisation.

The first example of such a cleavage was noted by Buncel and Davies[186] in 1958 during a study of triorgano perbenzoates, *e.g.*, (332) underwent facile rearrangement to give the aryloxysilane (333). This reaction lay dormant until its synthetic potential was realised through the independent studies of Tamao[187] and Fleming.[140]



(332) (333)

In general, successful cleavage of Si-C bonds requires the presence of at least one electron withdrawing group on the silicon centre. Thus the Si-C bonds of fluoro-, alkoxy- and dialkylaminosilanes are readily cleaved to the corresponding hydroxyl. Hydrogen peroxide and peracids are the most commonly used oxidants, although the use of triethylamine-*N*-oxide as an extremely mild oxidant for ethoxysilanes has recently been reported.[188] A source of fluoride is normally a mandatory additive in what is believed to be an assisted rearrangement of the silyl peroxide. The oxidation (with H_2O_2), has been considered to proceed through intramolecular migration of an organic group from silicon to the adjacent oxygen atom in penta- or hexacoordinate hydroperoxysilicon intermediates as shown in Scheme (25). Eventual hydrolysis of the rearranged species releases the alcohol. Oxidation proceeds with complete retention of configuration at sp^3 carbons.



Scheme 25.

The requirement for the silyl group to carry an electron withdrawing group can be fulfilled in one of two ways.

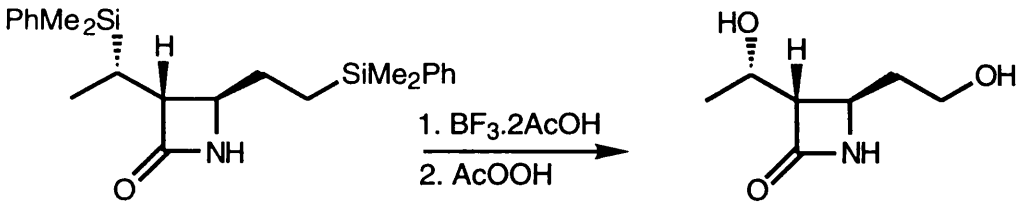
a) Alkoxy and Dialkylaminosilanes

Prepared by the base mediated displacement of the corresponding chlorosilane, these silanes have the advantage that they can be directly oxidised with hydrogen peroxide, under mild conditions. Unfortunately, alkoxysilanes were not suitable for our purposes as they are known to hydrolyse during sodium sulphite reduction of *N*-chlorosulphonyl β-lactams.[189]

b) Masked Fluorosilanes

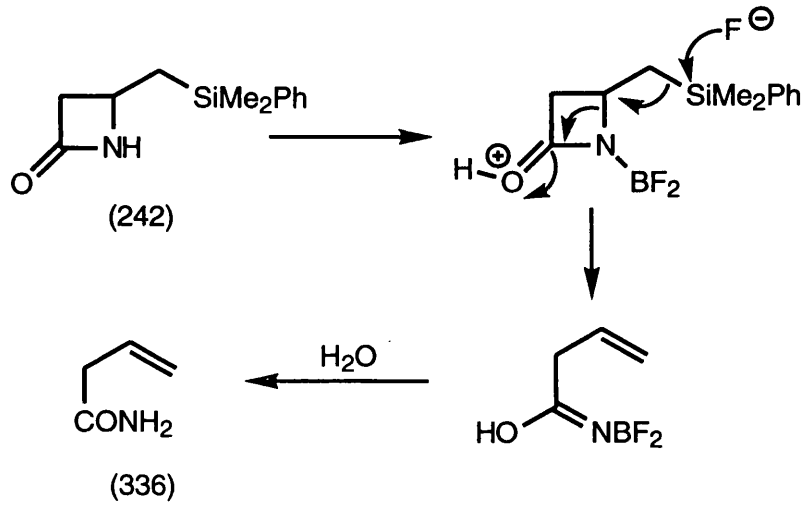
While fluorosilanes are generally too reactive to withstand multistep manipulations, they can be conveniently generated by late stage electrophilic desilylation of the more stable phenyl- or allyldimethylsilyl groups in the presence of a source of fluoride. Fleming,[190] in his synthesis of thienamycin, has shown that the cleavage of phenyldimethylsilyl groups is compatible with β-lactam functionality.

Protiodesilylation of (334) with $BF_3 \cdot 2AcOH$ and peracid oxidation of the resultant fluorosilane gave diol (335) with retention of configuration.



(334) (335)

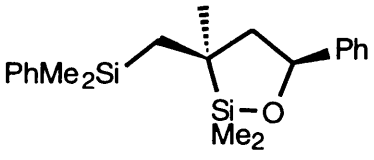
Previous attempts to apply this protocol to azetidinone (242) resulted in rapid rearrangement to β,γ-unsaturated amide (336).[139] This is thought to occur by initial protonation of the β-lactam carbonyl, and possibly boron co-ordination to nitrogen, followed by nucleophilic attack at silicon allowing the molecule to unzip, in a Peterson-like elimination (Scheme 26).



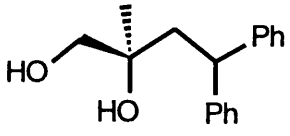
Scheme 26.

We were therefore understandably intrigued by a recent report from Ito and co-workers[191] which briefly mentioned the use of iodine monochloride (ICl) to cleave a Si-Ph bond prior to oxidative cleavage. It was found that treatment of 1,2-oxasilolane (337) with trifluoroacetic acid did not cleave the Si-Ph bond, but caused an intramolecular migration of phenyl from silicon to the benzylic carbon to give

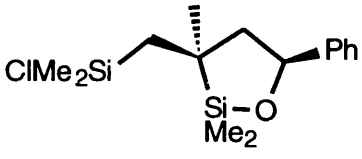
(338) after oxidation. Treatment with ICl, on the other hand, gave chlorosilane (339) which, after conversion to the corresponding isopropoxysilane, was oxidised then acetylated to yield (340). The selectivity shown by ICl for the cleavage of the Si-Ph bond only was very encouraging.



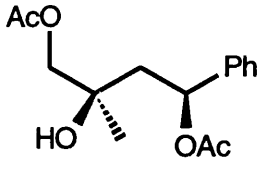
(337)



(338)

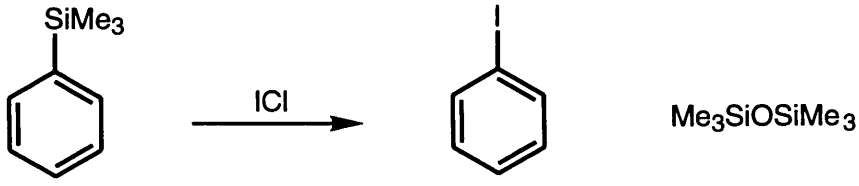


(339)



(340)

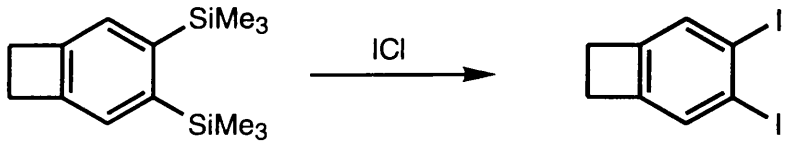
Iodine monochloride is a particularly effective reagent for the *ipso* desilylation of aryltrimethylsilanes. Iododesilylation was first studied by Stock and Spector[192] who found that treatment of phenyltrimethylsilane (341) with ICl, in acetic acid, gave iodobenzene (342) and hexamethyldisiloxane (343) in a yield exceeding 90%.



(343)

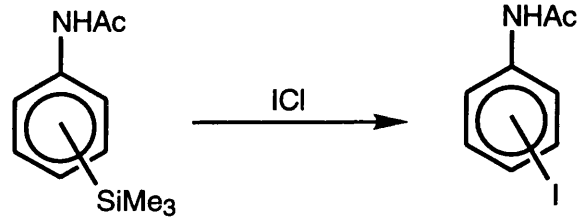
(341) (342)

This reaction has been successfully employed for the highly regioselective synthesis of a range of aryl iodides, *e.g.*, Vollhardt[193] converted bis-(trimethylsilyl)benzocyclobutene (344) to (345) by treatment with two equivalents of iodine monochloride, the reaction proceeding in very high yield.



(344) (345)

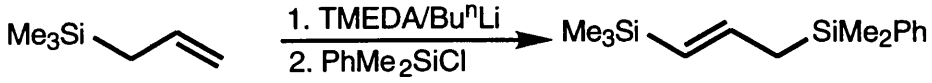
Because of the general lack of information about ICl we were not sure if this highly reactive interhalogen would interact unfavourably with a β-lactam. However, we were encouraged to find, form the work of Calas,[194] that acetanilides are compatible with aromatic iododesilylation conditions, *e.g.*, (346) undergoes iodination in excellent yield when exposed to one equivalent of ICl.



(346) (347)

6.2.1 Preparation of (Phenyldimethylsilyl)methyl β-Lactams.

The allyl/vinyldisilane (240) previously reported by Fleming and Langley,[195] was prepared by deprotonation of allyltrimethylsilane (230), in the presence of TMEDA, followed by quenching of the resultant allylic anion with phenyldimethylsilyl chloride.



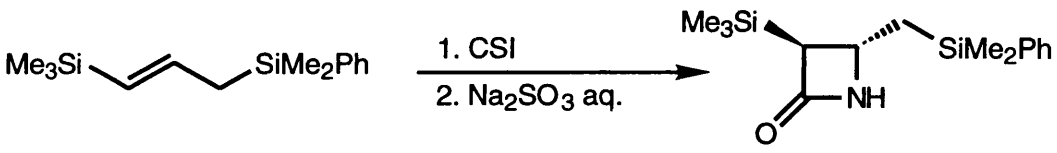
(230) (240)

Fleming used a slight excess of base and a 1h quench at -5 C. In order to prevent the production of the unwanted regioisomer (348) it was critical to maintain this quench temperature and work up the reaction immediately after the one hour

quench. If the reaction was allowed to stir overnight before work-up, an inseparable 1:1 mixture of both isomers was formed.

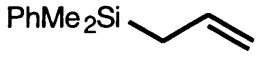
(348)

Disilane (240) has the β-effect of both silicons acting to stabilise the same carbonium ion and reacts smoothly with CSI to furnish (241) after sulphite quench. As expected, the *trans* geometry of the alkene is transferred to the β-lactam. This reaction can be carried out on a multigram scale providing that the concentration is kept at 0.2M.

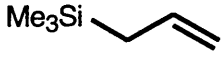


(240) (241)

While the reaction between allyltrimethylsilanes and CSI is complete within 2 to 3 hours, the corresponding phenyldimethyl substrates take considerably longer to react. This decreased nucleophilicity in going from trimethyl- to phenyldimethylsilyl groups has been documented by Mayr and Hagen[196] who found that allylsilane (349) was five times less reactive towards a diphenylmethyl cation than allyltrimethylsilane (230). The electron withdrawing properties of the phenyl ring presumably reduces the overlap between the Si-CH_2 bond with the adjacent π system.

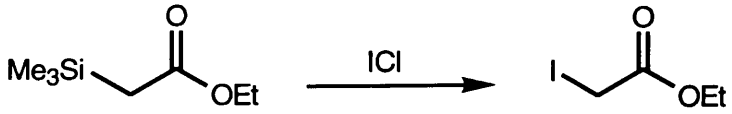


(349)



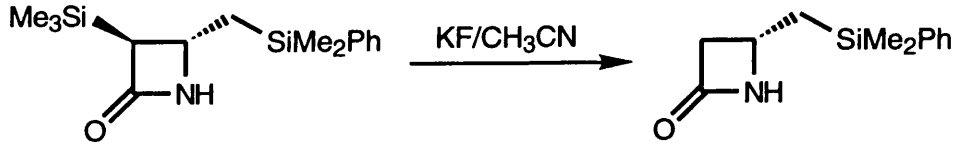
(230)

While C-3 trimethylsilylazetidinones have proven to be synthetically useful they also undergo electrophilic substitution with bromine.[139] With regards to iodine monochloride, ethyl trimethylsilylacetate (350) is rapidly converted to ethyl iodoacetate (351).[197] With this reactivity in mind we felt it would be prudent to remove the C-3 trimethylsilyl group of (241) before embarking on our investigation.



(350) (351)

Desilylation of 3-(trimethylsilyl)-azetidinones has been described by Weis and co-workers[198] and treatment of (241) with their KF/CH_3CN reagent system over 4 days furnished β-lactam (242) in excellent yield. Use of NaF/CH_3CN gave an almost quantitative return of starting material.

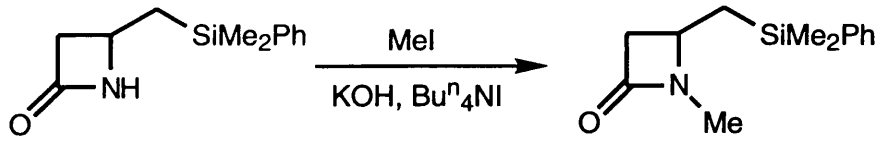


(241) (242)

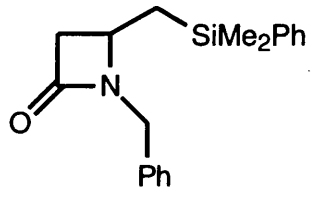
6.2.2 Protection of (Phenyldimethylsilyl)methyl β-Lactams.

Although it appeared that (242) might be stable to iodinolysis, previous investigations have shown that when oxidative cleavage is performed on *N*-protio β-lactams, the polar nature of both the product and reaction conditions (AcOOH/AcOH) cause severe isolation problems. Indeed, both Monteith[139] and Fleming[190] found that non-aqueous workup and hydroxyl protection is necessary for successful product isolation. Accordingly, *N*-methyl derivative (352) was prepared by treatment of (242) with MeI/KOH, under phase transfer catalysis.[199] The

potentially more useful *N*-benzyl derivative (353) was also prepared under similar conditions.



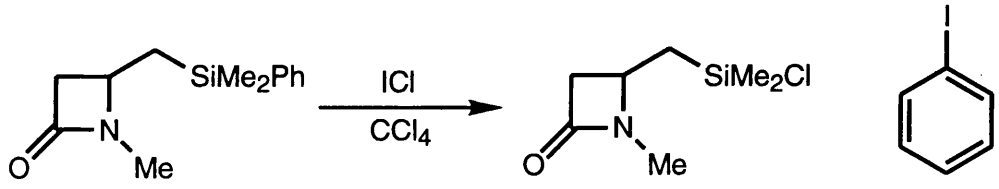
(242) (352)



(353)

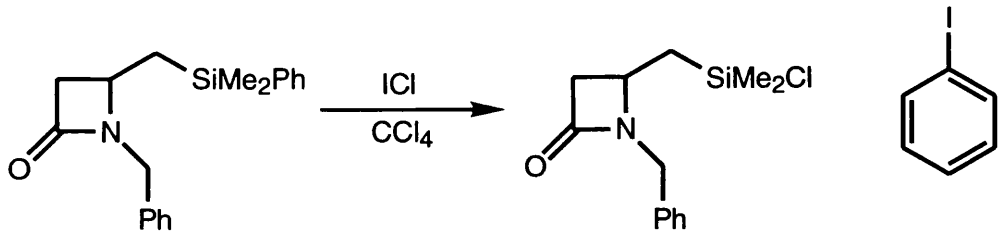
6.3.1 Iododesilylation of (Phenyldimethylsilyl)methyl β-Lactams.

Although a standard solution of iodine monochloride in dichloromethane is commercially available we opted to use the neat reagent in conjunction with carbon tetrachloride and, in doing so, allow the reaction to be followed directly by ^{1}H and ^{13}C NMR spectroscopy. To our delight when (352) was treated with one equivalent of ICl, chlorosilane (354) and iodobenzene (347), the products of iododesilylation, were formed almost immediately. After stirring overnight, at room temperature, the reaction had gone to approximately 70% completion. Prolonged reaction times under these reaction conditions made little improvement.



(352) (354) (347)

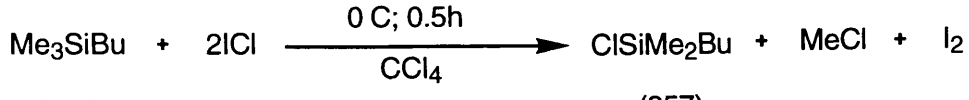
Gratifyingly, (353) also underwent iododesilylation, under similar conditions, to yield (355) and iodobenzene (347).



(353) (355) (347)

In both cases use of one equivalent of ICl resulted in only 70% conversion. In contrast, the reaction between ICl and aryltrimethylsilanes, under similar conditions, is characterised by very high yields. The addition of an electron withdrawing CH_2 group may retard the rate of electrophilic substitution of (phenyldimethylsilylmethyl)-β-lactams by reducing the ability of the Si-Ph bond to stabilise developing positive charge. Attempts to drive this process to completion by heating did not give any marked improvement. Complete conversion to chlorosilane was, however, achieved by heating the β-lactams with 1.4 equivalents of iodine monochloride, at reflux, for 12h. Unfortunately, time considerations did not allow us to explore the use of more polar solvents which might obviate the need to heat this reaction.

Examination of the spectroscopic data for (354) and (355) revealed that, in addition to iodobenzene, methyl iodide was also present. Formation of this unexpected product may result from the electrophilic cleavage of a Si-Me bond by iodine monochloride. Dunoguès[197] has shown that ICl selectively cleaves one of the Si-Me bonds of (356) to give a quantitative yield of chlorosilane (357) and methyl chloride. Unfortunately the other product/s of this cleavage could not be identified.

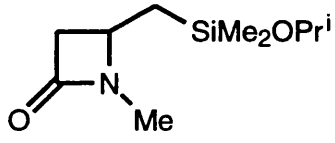


(356) (357)

Because of the highly unpleasant nature of ICl we attempted *in situ* generation by the action of $CuCl_2$ upon iodine.[200] However, when (352) was exposed to this reagent combination in acetonitrile only starting material was recovered.

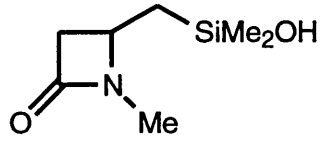
6.3.2 Attempted Preparation of an (Isopropoxydimethylsilyl)methyl β-lactam.

Encouraged by the relative ease with which the Si-Ph bond could be cleaved we now tried to prepare isopropoxysilane (358) by treating chlorosilane (354), *in situ*, with Pr^iOH/Et_3N. Although a small amount of (358) was produced, this compound was highly unstable to column chromatography and could not be separated from the complex mixture of products.



(358)

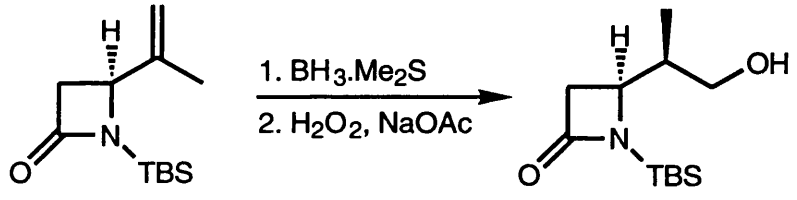
More encouragingly, direct hydrolysis of (354) with 'wet' THF gave a high yield of silanol (359) which, due to its unexpected polarity, proved difficult to purify.



(359)

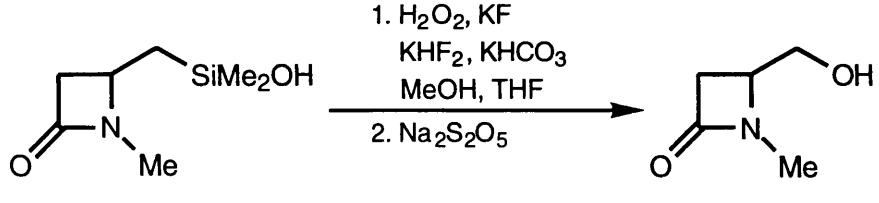
6.4 Oxidative Cleavage of (Hydroxydimethylsilyl)methyl β-lactams.

Dimethylsilanols are known to undergo oxidative cleavage when treated with Tamao's mixture of hydrogen peroxide, potassium fluoride and sodium bicarbonate.[201] However, we were somewhat apprehensive about exposing (359) to alkaline hydrogen peroxide which in view of its nucleophilic nature might attack the azetidinone ring. Accordingly, our initial attempt to oxidise (359) involved peracetic acid which we knew to be compatible with azetidinones. After stirring (359) for 1 day in a solution of peracetic acid in acetic acid buffered with sodium acetate only starting material was returned. It was at this stage that a report from Gurjar and co-workers[202] was found which documented the conversion of C-4 vinylazetidinone (360) to (361). Hydroboration and subsequent oxidative cleavage with hydrogen peroxide and sodium acetate proceeded with no ring opening.



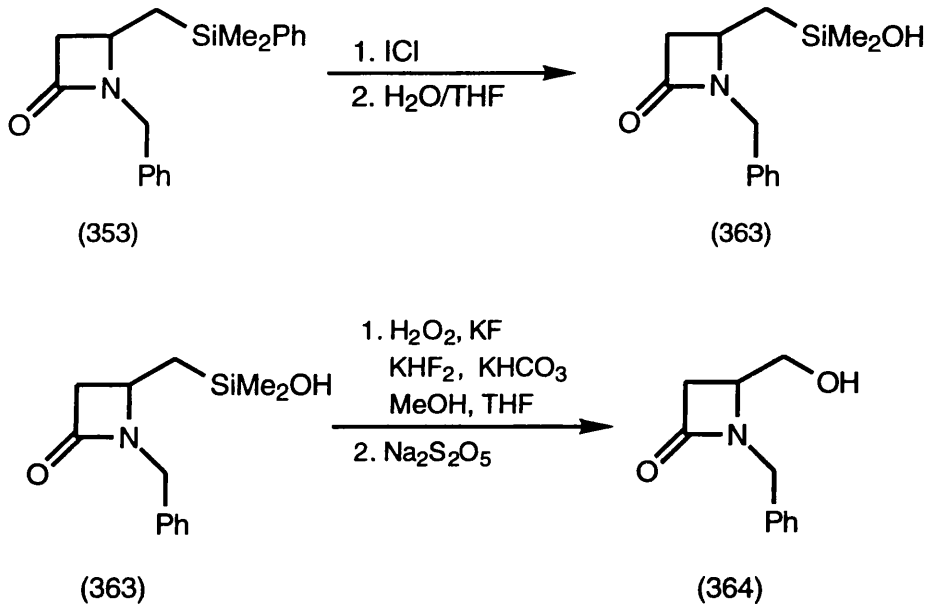
(360) (361)

With our fears of azetidinone ring opening partially allayed we proceeded with the oxidation of (359) using hydrogen peroxide. However, rather than using the more usual mixture of hydrogen peroxide, potassium fluoride and sodium carbonate we opted for the method described by Ito.[191] We were delighted to find that after stirring for 3 days alcohol (362) was isolated in 74% yield.



(359) (362)

This sequence of iododesilylation and oxidation were also successfully applied to (353). Thus, hydrolysis of chlorosilane (355) gave silanol (363) in 82% yield. Oxidation of this compound under similar conditions as before then gave potentially useful *N*-benzyl alcohol (364) in 46% yield.



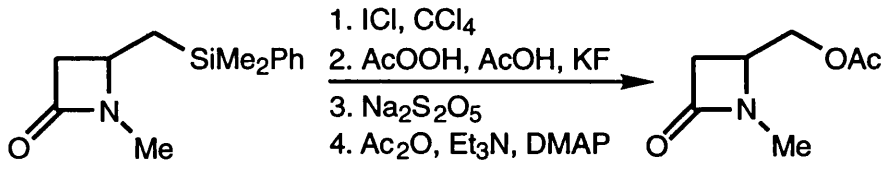
6.5 Oxidation of (Chlorodimethylsilyl)methyl β-lactams.

Rather than isolate the dimethylsilanol intermediates we felt that it might be more efficient and certainly more convenient to directly oxidise the (chlorodimethylsilyl)methyl β-lactams *in situ*. In doing so, however, we would be presented by a problem. Iodobenzene is oxidised by peroxides, and in particular, reaction with peracetic acid generates phenyliodine(III) diacetate, a known oxidant.[203] In order to prevent possible side reactions all volatiles, including iodobenzene, were removed prior to oxidation by placing the reaction flask under vacuum for several hours.

Kumada[187] has noted that chlorosilanes do not readily undergo oxidative cleavage with MCPBA. On the other hand, Fleming's[140] one pot bromodesilylation/oxidation method generates a bromosilane *in situ* which is

hydrolysed before undergoing oxidative cleavage with peracetic acid. It occurred to us that (chlorodimethylsilyl)methyl β-lactams might undergo oxidative cleavage when treated with this oxidant.

Chlorosilane (355) was generated, as before, and the volatiles removed under vacuum to give a thick black oil which fumed when exposed to air. Initial attempts to oxidise this compound with peracetic acid alone or MCPBA in DMF returned only starting material. However, the addition of a 15% solution of peracetic acid in acetic acid and an excess of potassium fluoride to (355) was accompanied by a substantial exotherm. After stirring, at room temperature for 3 days the reaction was diluted with ether and the excess peracid destroyed with powdered sodium thiosulphate. Care was taken to cool the reaction at this stage in order to moderate the vigour of the reduction. After filtration of the solids, acetic acid was removed under vacuum. Rather than attempt isolation at this stage the crude product was acetylated with $Ac_2O/Et_3N/DMAP$. Gratifyingly, workup then gave acetate (365) in 56% yield. Despite having protected the hydroxyl group, this compound was found to be extremely polar and consequently difficult to purify by column chromatography.



(353) (365)

Disappointingly, subsequent attempts to extend this protocol to the more useful *N*-benzyl derivative failed, with no recognisable products being isolated. This was not altogether unexpected, however, as *N*-benzyl protecting groups are known to be unstable to peracids.[204]

6.5 Conclusions

While the initial aim of this project was to use a suitability functionalised allylsilane to produce stereoselectively a 3-(hydroxyethyl)azetidinone *via* [2+2] cycloaddition with CSI, δ-oxa-allylsilanes were found to undergo rapid 1,4-silyl elimination upon exposure to this reagent. All attempts to prevent this unwanted reaction met with failure. Ironically, Asaoka[205] has recently utilised this type of elimination in an efficient synthesis of optically active 1,3-cyclohexadienes.

Whether the elimination, in our case, is due to CSI itself, or catalytic amounts of SO_3 and HCl present in the commercial reagent, remains unknown. Recently, Chmielewski[206] has made the intriguing discovery that, by storing CSI over anhydrous potassium or sodium carbonate, and addition of these bases to the reaction mixture, a number of sugar vinyl ethers, which had previously decomposed upon exposure to CSI, underwent [2+2] cycloaddition. In view of the compatibility of this method with highly acid sensitive substrates, such as dihydropyran, its use with δ-oxa-allylsilanes may prevent 1,4-silyl elimination allow cycloaddition to occur. Unfortunately, the late appearance of this report and time considerations have not allowed an investigation of this promising modification.

Sufficiently encouraged by reports from Fleming[142] and Taddei[141] on the highly diastereoselective reaction of chiral allylsilanes with CSI, an alternative ε-oxa-allylsilane was devised, which would undergo cycloaddition, rather than elimination, and could subsequently be transformed to a C-3 hydroxyethyl carbapenem precursor using a dual functionalisation strategy. Unfortunately, these allylsilanes did not react with CSI. The reason for this lack of reactivity is not fully understood. However, while there are several examples of the reaction of ε-oxa-allylsilanes with electrophiles most involve intramolecular addition to *O*-oxocarbenium ions.

The second aim of the project was to develop an efficient method for the oxidative cleavage of 4-(phenyldimethylsilyl)methyl β-lactams. Prompted by a report from Ito,[191] two *N*-protected (phenyldimethylsilyl)methyl β-lactams were prepared and their reaction with iodine monochloride studied. Treatment with this reactive interhalogen, under relatively mild conditions, resulted in complete iododesilylation to yield the corresponding (chlorodimethylsilyl)methyl β-latcams and iodobenzene. While only carbon tetrachloride was used for these studies, future investigations may wish to explore the use of other, more polar solvents, which might allow efficient iododesilylation to be achieved at ambient temperatures. The apparent cleavage of a Si-CH_3 bond in this reaction raises the intriguing possibility that a method for the oxidative cleavage of trimethylsilyl groups might be developed.

Gratifyingly, hydrolysis of the 4-(chlorodimethylsilyl)methyl β-lactams gave the corresponding silanols in high yield. Oxidation of these compounds using a modification of Tamao's procedure gave the desired 4-(hydroxymethyl)azetidinones in good yield.[191] While initial studies involved simple *N*-methyl protection, this sequence of iododesilylation, hydrolysis and oxidation was also successfully carried out with synthetically more useful *N*-benzyl protection, to yield a potential carbapenem precursor. A procedure for the direct oxidation of one of the intermediate (chlorodimethylsilyl)methyl β-lactams, using AcOOH/KF, was also developed. Unfortunately, this method was incompatible with *N*-benzyl protection. A possible alternative might be to protect the 4-(phenyldimethylsilyl)methyl β-lactams as their glycine derivatives (*N*-CH_2CO_2R), which would also serve as a handle for subsequent carbapenem ring closure, *e.g.*, *via* Dieckmann cyclization (Section **1.4.2.2.2**).

Although the initial aim of the project has not been achieved, a relatively efficient method for the key oxidative step has been developed and should allow further developments in this area.

7 Experimental Section.

General Methods.

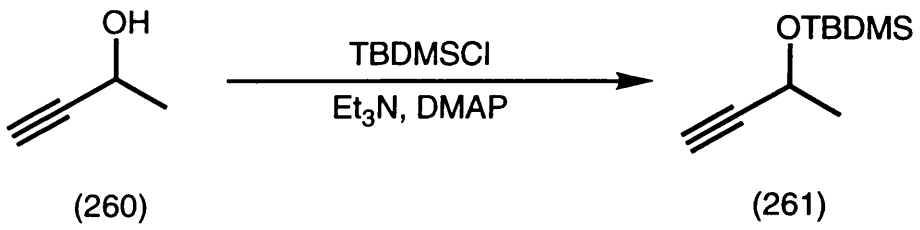
Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Short path distillations were carried out using a Büchi GKR-50 Kugelrohr. Recorded boiling ranges refer only to the indicated air bath temperature. ^1H NMR spectra were recorded on a Bruker AM200SY or a 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. 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 at 77.0 ppm in the ^{13}C NMR spectrum. Coupling constants (*J*) are quoted in Hertz. The multiplicities stated in the ^{13}C NMR spectra were determined by the use of DEPT spectra with the pulse angles, ϕ= 90 and 135 . Data are reported using the following convention: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broadened. Infrared spectra were recorded on a Perkin-Elmer 983 or a Perkin-Elmer P-1000 spectrometer. Mass spectra were obtained using a VG/Kratos MS12 spectrometer or a VG/Kratos MS90S spectrometer for high resolution work.

Separation of compounds was carried out by dry flash chromatography,[207] under reduced pressure, on Merck Kieselgel 60H. Alternatively, separations were performed by positive pressure flash chromatography[208] using Merck Kieselgel 60.

Unless otherwise stated, reactions were carried out under nitrogen. THF, Et_2O, DME and Pr^i_2O were distilled immediately prior to use from sodium/benzophenone. CH_2Cl_2 and CH_3CN were distilled from CaH_2, CCl_4 was distilled from P_2O_5 and CH_3NO_2 was dried over, and distilled from $CaCl_2$. All other solvents were dried by storing over activated 4 Å molecular sieves.

Unless otherwise stated, organic solutions were dried over magnesium sulphate and evaporated on a rotary evaporator under reduced pressure.

2-(t-Butyldimethylsilyloxy)but-3-yne. (261)



(260) (261)

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

A flame dried 50ml round bottomed flask, under N_2, was charged with Et_3N (3.29g, 4.5ml, 32.6mmol), DMAP (200mg, 1.64mmol) and 3-butyn-2-ol (260) (1.85g, 26.4mmol) in dry CH_2Cl_2 (20ml). A solution of TBDMSCl (4.5g, 29.9mmol) in CH_2Cl_2 (10ml) was added *via* syringe and the mixture stirred at room temperature overnight. The reaction mixture was then transferred to a separating funnel and washed with water (3x20ml) and brine (20ml). The organic layer was dried, concentrated and the residue purified by dry flash column chromatography to yield the title compound as a clear oil (4.05g, 22mmol, 83%).

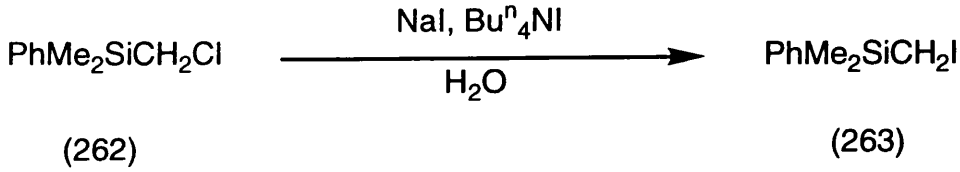
$\nu_{max.}$(film) 3307 and 1250 cm^{-1}.

δ_H(200 MHz) 4.38 (1H, qd, *J* 6.5 and 2.1, C<u>H</u>Me), 2.24 (1H, d, *J* 2.1, CCH), 1.29 (3H, d, *J* 6.5, CH<u>Me</u>), 0.77 (9H, s, Bu^t), 0.00 (3H, s, Si<u>Me</u>Me), -0.01 (3H, s, SiMe<u>Me</u>).

δ_C(50 MHz) 86.37 (d, C<u>C</u>H), 71.14 (s, <u>C</u>CH), 58.77 (d, <u>C</u>HMe), 25.75 (q, Bu^t), 25.31 (q, CH<u>Me</u>), 18.20 (s, Bu^t), -4.69 (q, Si<u>Me</u>Me), -5.04 (q, SiMe<u>Me</u>).

Found: M^+, 184.1288, $C_{10}H_{20}OSi$ requires M, 184.1283.

(Phenyldimethylsilyl)methyl iodide. (263)



(262) (263)

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

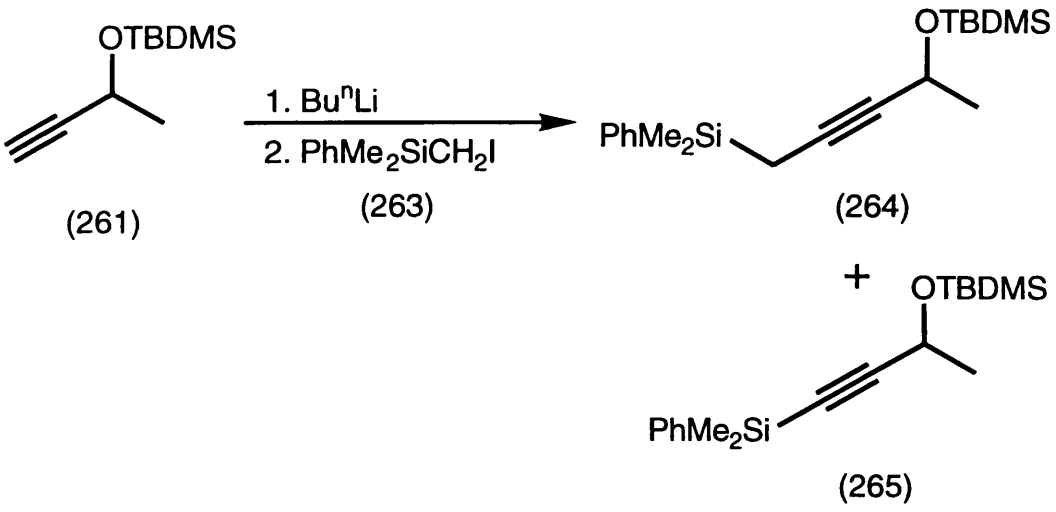
A 20ml round bottomed flask fitted with a condenser was charged with (phenyldimethylsilyl)methyl chloride (4g, 21.7mmol), NaI (6.52g, 43.5mmol), tetrabutylammonium iodide (2.07g, 4.3mmol) and water (5.5ml). The mixture was heated at reflux for 4h then cooled to room temperature. The liquid phase was decanted into a separating funnel and the solid residue washed with water (3x10ml) and pentane (3x10ml). All the liquids were combined and shaken. The organic layer was removed and the aqueous layer re-extracted with pentane (2x10ml). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by distillation at reduced pressure to yield the iodomethylsilane as a clear oil (4.46g, 16.2mmol,75%), b.p. 126 C/25mmHg.

δ_H(200 MHz) 7.59-7.34 (5H, m, Ph), 2.20 (2H, s, CH_2I), 0.46 (6H, s, $SiMe_2$).

δ_C(50 MHz) 136.73, 133.63, 129.58, 127.94, -2.93, -7.21.

Found: M^+, 275.9828, $C_9H_{13}ISi$ requires M, 275.9833.

Attempted Preparation of 5-Phenyldimethylsilyl-2-(t-butyldimethylsilyloxy)pent-3-yne. (264)



(261) (263) (264) (265)

Procedure: S.K. Chiu and P.E. Peterson, *Tetrahedron Lett.*, 1980, **21**, 4047.

A flame dried 20ml round bottomed flask fitted with a condenser, under N_2, was charged with a solution of (261) (867.1mg, 4.71mmol) in dry THF (4.7ml) and placed in a cooling bath at -30 C. Bu^{n}Li (2.87M in hexanes) (1.64ml, 4.71mmol) was then added dropwise and the reaction mixture stirred at -30 C for 15min and then a further 15min at 0 C. (Phenyldimethylsilyl)methyl iodide (263) (1.302g, 4.71mmol) was then added and the reaction stirred at 55-58 C for 21h. At this stage, the reaction was quenched with saturated aqueous NH_4Cl solution (10ml) and extracted with ether (3x15ml). The organic extracts were dried, concentrated and the residue subjected to dry flash column chromatography yielding a clear oil (874mg) which contained the title compound (264) together with (265), in a ratio of 4:1.

5-Phenyldimethylsilyl-2-(t-butyldimethylsilyloxy)pent-3-yne. (264)

δ_H(200 MHz) 7.60-7.35 (5H, m, Ph), 4.57-4.46 (1H, m, CHMe), 1.74 (2H, d, *J* 2.1, $SiCH_2$), 1.38 (3H, d, *J* 2.6, CHMe), 0.92 (9H, s, Bu^t), 0.40 (6H, s, $SiMe_2Ph$), 0.12 (3H, s, SiMeMeBu^t), 0.11 (3H, s, SiMeMeBu^t).

δ_C(50 MHz) 137.67 (s), 133.55 (d), 129.27 (d), 127.77 (d), 82.20 (s), 80.66 (s), 59.38 (d), 25.81 (q), 25.83 (q), 18.27 (s), 6.37 (t), -3.44 (q), -4.70 (q), -5.03 (q).

Found: M^+, 332.2009, $C_{19}H_{32}OSi_2$ requires M, 332.1992.

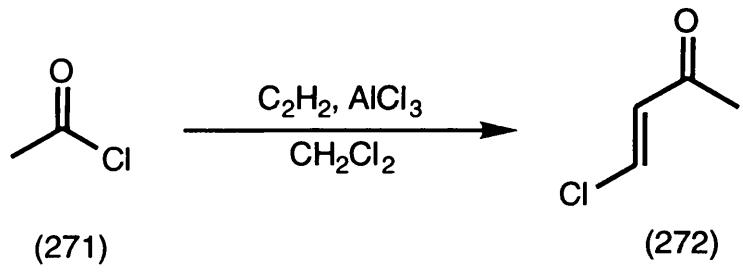
4-Phenyldimethylsilyl-2-(t-butyldimethylsilyloxy)but-3-yne. (265)

δ_H(200 MHz) 7.54-7.29 (5H, m, Ph), 4.49 (1H, q, *J* 6.6, CHMe), 1.38 (3H, d, *J* 6.6), 0.90 (9H, s, Bu^t), 0.40 (6H, s, $SiMe_2Ph$), 0.11 (3H, s, SiMeMeBu^t), 0.09 (3H, s, SiMeMeBu^t).

δ_C(50 MHz) 139.50 (s), 133.61 (d), 128.73 (d), 127.66, 109.17(s), 85.55 (s), 59.38 (s), 25.70 (q), 25.34 (q), 18.23 (s), -2.96 (q), -4.61 (q), -4.71 (q).

Found: *m/z* 317.1772, $C_{18}H_{30}OSi_2$-H requires 317.1757.

(*E*)-1-Chlorobuten-3-one. (272)



(271) (272)

Caution: Great care must be exercised when handling the title compound which is a powerful vesicant.

A 2l three-necked flask fitted with a gas inlet tube, Trubore stirrer and condenser protected with a $CaCl_2$ drying tube was charged with dry CH_2Cl_2 (400ml) and cooled to 0 C in a ice bath. After passing acetylene through the solvent for 5 min the gas inlet tube was removed and $AlCl_3$ (98g, 0.74mol) added. Acetylene was then passed through the stirred mixture for a further 15 min during which the reaction mixture turned a deep purple colour. The gas inlet tube was then replaced by a rubber septum and acetyl chloride (271) (49.5g, 45ml, 0.63mol) added dropwise over 5 min *via* syringe. The gas inlet tube was replaced and a steady stream of acetylene was passed through the stirred suspension for 4h. After this time the black reaction mixture was cautiously poured into a slurry of crushed ice (500g) and brine (300ml). The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (3x100ml). The combined organic extracts were then dried over $CaCl_2$ and hydroquinone (4g, 29mmol) added to the dry filtrate. Concentration and purification of the residue by distillation at reduced pressure gave the title compound as a clear oil (39g, 0.37mol, 58%). (b.p. 50 C/25mmHg) [lit.[154] 55 C/30mmHg].

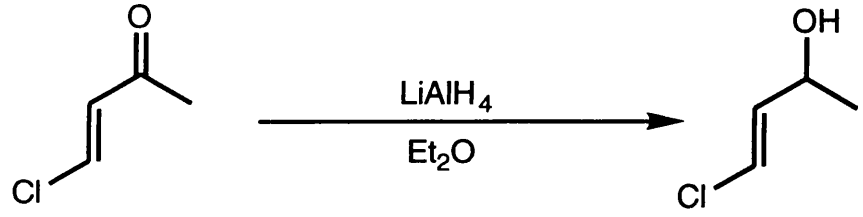
$\nu_{max.}(CHCl_3)$ 1679, 1592 and 1583 cm^{-1}.

δ_H(200MHz) 7.3 (1H, d, *J*, 13.7, CHC<u>H</u>Cl), 6.5 (1H, d, *J* 13.7, C<u>H</u>CHCl), 2.3 (3H, s, Me).

δ_C(50MHz) 195.50 (s, CO), 137.42 (d, CH<u>C</u>HCl), 133.37 (d, <u>C</u>HCHCl), 27.92 (q, Me).

Found: M^+, 104.0026, $C_4H_5ClO(^{35}Cl)$ requires $M(^{35}Cl)$, 104.0029.

(*E*)-1-Chlorobuten-3-ol. (274)



(272) (274)

A flame dried 500ml round bottomed flask fitted with a condenser, under N_2, was charged with $LiAlH_4$ (1.814g, 47.8mmol) and dry ether (100ml). The flask was then placed in a cooling bath at 0 C. A solution of *(E)* -1-chlorobuten-3-one (272) (10g, 95.8mmol) in ether (50ml) was then added over 10 min *via* syringe to the stirred suspension. After the initial exotherm had subsided the reaction mixture was heated at reflux for 1h, allowed to cool to room temperature and cautiously quenched with water (25ml). The reaction mixture was then washed with H_2SO_4 (1M, 50ml) and water (2x25ml). The organic layer was removed and the aqueous washings re-extracted with ether (2x25ml). After drying and concentrating the combined organic extracts, purification of the residue by short path distillation, at reduced pressure, gave the alcohol as a clear oil (9.83g, 92.2mmol, 96%). b.p. 105 C/27mmHg. [lit. b.p.[209] 107-109/201mmHg].

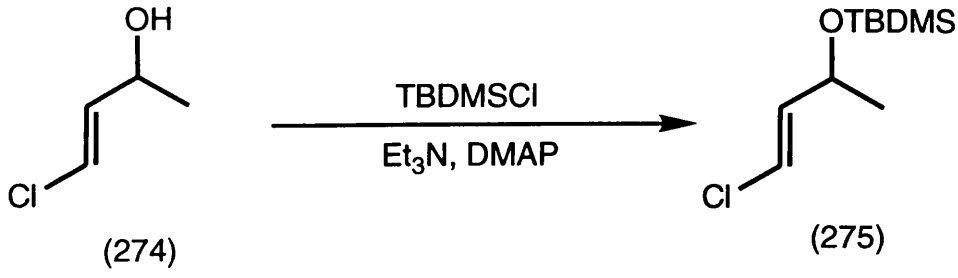
$\nu_{max.}$(film) 3332 and 1636 cm^{-1}.

δ_H(200 MHz) 6.19 (1H, dd, *J* 13.3 and 1.0, ClHCCH), 5.95 (1H, dd, *J* 13.3 and 6.4, ClHCCH), 4.37-4.23 (1H, m, CHOH), 1.26 (3H, d, *J* 6.4, Me).

δ_C(50 MHz) 137.15 (d), 119.04 (d), 67.00 (d), 23.06 (q).

Found: *m/z* 107.0076 (^{37}Cl), C_4H_7ClO-H requires 107.0078 (^{37}Cl).

(E)-3-t-Butyldimethylsilyloxy-1-chlorobut-1-ene. (275)



(274) (275)

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

A flame dried 200ml round bottomed flask, under N_2, was charged with Et_3N (12.12g, 16.7ml, 120mmol), DMAP (563mg, 4.6mmol) and *(E)*-1-chlorobuten-3-ol (274) (9.80g, 92.2mmol) in dry CH_2Cl_2 (40ml). TBDMSCl (16.68g, 110.7mmol) in CH_2Cl_2 (50ml) was then added *via* syringe and the reaction stirred at room temperature for 23h. The reaction mixture was then diluted with CH_2Cl_2 (50ml) and washed with water (3x50ml) and brine (50ml). The organic layer was dried, concentrated and the residue purified by distillation at reduced pressure to yield the title compound as a colourless oil (16.09g, 72.8mmol, 79%). b.p. 65-70 C/30mmHg.

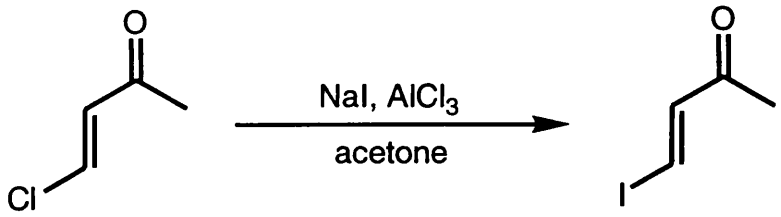
$\nu_{max.}(CHCl_3)$ 1628, 1254 and 836 cm^{-1}.

δ_H(200 MHz) 6.17 (1h, dd, *J* 13.1 and 1.1, ClHCCH), 5.93 (1H, dd, *J* 13.1 and 5.2, ClHCCH), 4.33 (1H, m, CHMe), 1.23 (3H, d, *J* 6.4, CHMe), 0.89 (9H, s, Bu^t), 0.06 (3H, s, SiMeMe), 0.05 (3H, s, SiMeMe).

δ_C(50 MHz) 137.85 (d, ClHCCH), 117.67 (d, ClHCCH), 67.67 (d, CO), 25.80 (q, Bu^t), 24.30 (d, CHMe), 18.19 (s, Bu^t), -4.78 (q, SiMeMe), -4.82 (q, SiMeMe).

Found: M^+, 220.1049 (^{35}Cl), $C_{10}H_{21}ClOSi$ requires M, 220.1050 (^{35}Cl).

(*E*)-1-Iodobuten-3-one. (270)



(272) (270)

Procedure: W.R. Benson and A.E. Pohland, *J. Org. Chem.*, 1964, **29**, 385.

To a 50 ml single-necked round bottomed flask, fitted with a condenser protected by a $CaCl_2$ drying tube, was added NaI (5.35g, 35.7 mmol) and dry acetone (22ml). *(E)*-1-Chlorobuten-3-one (272) (2.05g, 19.14 mmol) and $AlCl_3$ (6mg, 0.05mmol, 0.26mol%) were then added and the mixture heated at reflux for 1h. Concentration of the reaction mixture gave a brown residue which was partitioned between pentane (30ml) and water (30ml). The aqueous layer was re-extracted with pentane (2x50ml) and the combined organics washed with aqueous $Na_2S_2O_5$ (1M, 50ml) and brine (2x20ml). Drying and concentration gave the title compound as pale yellow crystals (3.66g, 18.7 mmol, 95%) which was found to be pure by ^1H NMR spectroscopy. Subsequent re-crystallisation from pentane, at -20 C, gave white crystals which decolourised rapidly (m.p. 54-55 C). [lit.[154] 55-56 C].

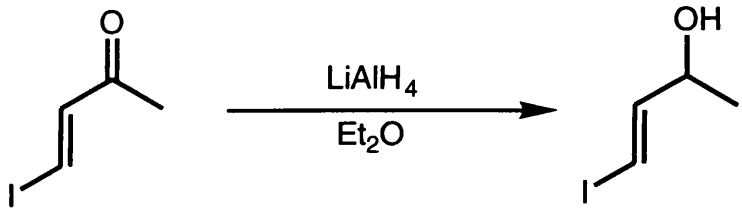
$\nu_{max.}(CHCl_3)$ 1734 and 1635 cm^{-1}.

δ_H(200 MHz) 7.8 (1H, d, *J* 15.1, CHC<u>H</u>I), 7.1 (1H, d, *J* 15.1, C<u>H</u>CHI), 2.2 (3H, s, COMe).

δ_C(50 MHz) 195.50 (s, CO), 145.37 (d, CH<u>C</u>HI), 99.69 (d, <u>C</u>HCHI), 27.01 (q, CO<u>Me</u>).

Found: M^+, 195.9386, C_4H_5IO requires M, 195.9387.

(*E*)-1-Iodobuten-3-ol. (269)



(270) (269)

To a flame dried flask fitted with a condenser, under N_2, was added $LiAlH_4$ (167mg, 12.57mmol) and dry ether (10ml). The flask was then placed in a bath at 0 C and a solution of *(E)* -1-iodobuten-3-one (270) (1.72g, 8.79mmol) in ether (5ml) added dropwise *via* syringe. After the initial exotherm subsided the mixture was heated at reflux for 1h. On cooling to room temperature, the reaction was quenched with water (10ml) then aqueous NaOH (3M, 5ml). The reaction mixture was then washed with H_2SO_4 (1M, 10ml) and water (2x10ml) and the organic residues dried over Na_2SO_4. Concentration *in vacuo* and purification of the residue by short-path distillation at reduced pressure gave the title compound as a clear oil (1.46g, 7.39 mmol, 84%) (b.p. 155 C/29 mmHg).

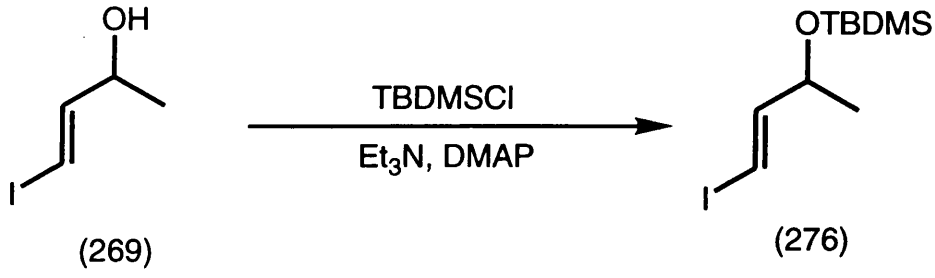
$\nu_{max.}$(film) 3336, 1606 and 934 cm^{-1}.

δ_H(200 MHz) 6.58 (1H, dd, *J* 14.5 and 5.9, IHCC<u>H</u>), 6.30 (1H, dd, *J* 14.5 and 1.0, I<u>H</u>CCH), 4.24 (1H, m, C<u>H</u>Me), 2.60 (1H, bs, OH), 1.20 (3H, d, *J* 6.4, CH<u>Me</u>).

δ_C(50 MHz) 149.40 (d, IHC<u>C</u>H), 76.73 (d, IH<u>C</u>CH), 70.42 (d, COH, 22.54 (q, CH<u>Me</u>).

Found: M^+, 197.9547, C_4H_7IO requires M, 197.9543.

(E)-3-(t-Butyldimethylsilyloxy)-1-iodobut-3-ene. (276)



(269) (276)

A flame dried 100ml round bottomed flask, under N_2, was charged with Et_3N (3.5g, 2.54ml 25mmol), DMAP (178mg, 1.5mmol) and a solution of *(E)*-1-iodobuten-3-ol (269) (4.13g, 20.8mmol) in dry CH_2Cl_2 (20ml). TBDMSCl (3.45g, 22.9mmol) in CH_2Cl_2 (30ml) was added and the reaction stirred at room temperature for 21h. The reaction mixture was then diluted with CH_2Cl_2 (25ml) and washed with water (3x25ml) and brine (25ml). The organic layer was dried, concentrated and the pale yellow residue purified by dry flash column chromatography to yield the title compound as a clear oil (5.72g, 18.3mmol, 88%).

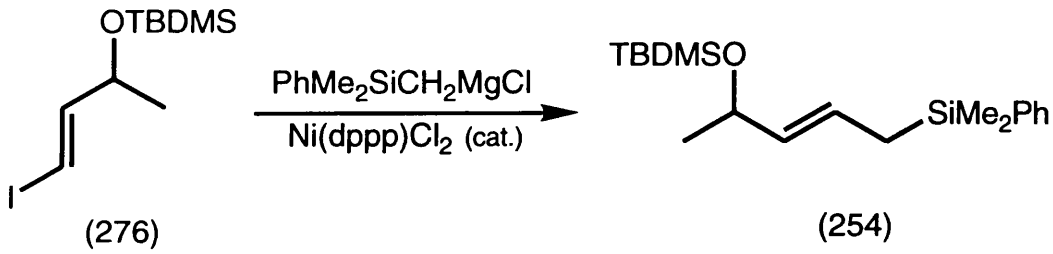
$\nu_{max.}(CHCl_3)$ 1607, 1257 and 836 cm^{-1}.

δ_H(200 MHz) 6.50 (1H, dd, *J* 14.3 and 5.0, IHCC<u>H</u>), 6.17 (1H, dd, *J* 14.3 and 1.3, I<u>H</u>CCH), 4.19 (1H, m, C<u>H</u>Me), 1.15 (3H, d, *J* 6.4, CH<u>Me</u>), 0.85 (9H, s, Bu^t), 0.01 (3H, s, Si<u>Me</u>MeBu^t), 0.00 (3H, s, SiMe<u>Me</u>Bu^t).

δ_C(50 MHz) 150.04 (d, IHC<u>C</u>H), 75.02 (d, IH<u>C</u>CH), 71.03 (d, <u>C</u>HMe), 25.77 (q, Bu^t), 23.73 (q, CH<u>Me</u>), 18.16 (s, Bu^t), -4.82 (q, Si<u>Me</u>MeBu^t), -4.89 (q, SiMe<u>Me</u>Bu^t).

Found: M^+, 313.0427, $C_{10}H_{21}IOSi$ requires M, 313.0408.

(E)-1-Phenyldimethylsilyl-4-(t-butyldimethylsilyloxy)pent-2-ene. (254)



(276) (254)

Coupling procedure: Y. Kitano, T. Matasumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi and F. Sato, *Tetrahedron Lett.*, 1987, **23**, 6351.

Preparation of Grignard solution:

Mg turnings (421mg, 17.3mmol) were placed in a 25ml round bottomed flask fitted with a condenser. The flask was then flame dried, under vacuum, and purged with N_2. On cooling to room temperature, the flask was charged with dry ether (11ml) and the magnesium activated with 1,2-dibromoethane (2 drops). A solution of $PhMe_2SiCH_2Cl$ (2.99g, 10.8mmol) in ether (11ml) was added over 15min and the reaction then heated at reflux for 1h.

Coupling:

A flame dried 50ml round bottomed flask, under N_2, was charged with [$Ni(dppp)Cl_2$] (64.5mg, 0.11mmol) and a solution of vinyl iodide (276) (2.25g, 7.2mmol) in dry ether (20ml). The Grignard solution was then added to the stirred suspension *via* syringe. At this point, the reaction mixture turned brown and a crystalline solid precipitated. After stirring for 18h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl solution (25ml) and the organic layer separated. The aqueous layer was re-extracted with ether (25ml) and the combined organics dried over Na_2SO_4. Concentration and purification of the residue by dry flash column chromatography gave the allylsilane as a clear, colourless oil (2.21g, 6.6mmol, 92%).

$\nu_{max.}$(film) 1662, 1502 and 1250 cm^{-1}.

δ_H(200 MHz) 7.55-7.30 (5H, m, Ph), 5.57-5.42 (1H, m, C<u>H</u>CH_2), 5.28 (1H, dd, *J* 15.2 and 5.9, C<u>H</u>CHCH_2), 4.25-4.13 (1H, m, C<u>H</u>Me), 1.64 (2H, d, *J* 7.7, CHC<u>H_2</u>Si), 1.13 (3H, d, *J* 6.3, CH<u>Me</u>), 0.85 (9H, s, Bu^t), 0.24 (6H, s, Si<u>Me</u>$_2$Ph), 0.00 (3H, s, Si<u>Me</u>MeBu^t), -0.01 (3h, s, SiMe<u>Me</u>Bu^t).

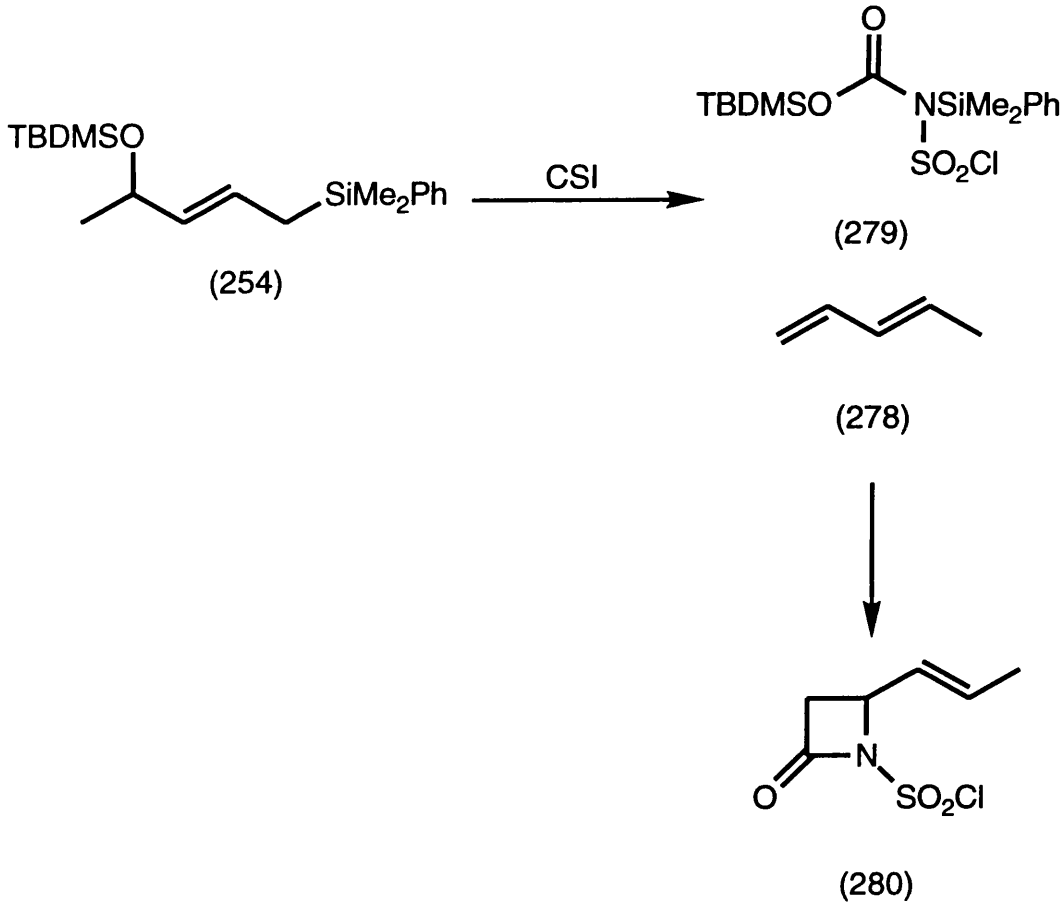
^{1}H NMR Decoupling Experiments:

1) Irradiation at 1.64 ppm causes the collapse of the multiplet at 5.57-5.42 ppm to the A of an ABX system (dd, *J* 15.2 and 0.8).
2) Irradiation at 1.13 ppm causes the collapse of the multiplet at 4.25-4.13 to the A of an AB system (d, *J* 5.9).

δ_C(50 MHz) 139.73 (s), 134.19 (d), 133.59 (d), 128.94 (d), 127.71 (d), 124.50 (d), 69.59 (d), 25.90 (q), 21.35 (t), 18.29 (s), 14.14 (q), -3.37 (q), -3.61 (q), -4.59 (q), -4.79 (q).

Found: M^+ 334.2143, $C_{19}H_{34}OSi_2$ requires M, 334.2148.

Reaction of CSI with *(E)*-1-phenyldimethylsilyl-4-(t-butyldimethylsilyloxy)pent-2-ene. (254)



A flame dried 10ml round bottomed flask, under N_2, was charged with a solution of allylsilane (254) (152mg, 0.52mmol) in dry CCl_4 (2.5ml) and cooled to 0 C. CSI (52μl, 0.60 mmol) was then carefully added to the stirred solution *via* syringe and after 2min, an aliquot of the reaction mixture was placed in an oven dried NMR tube fitted with a rubber septum. This NMR tube was immediately transferred to a 200MHz NMR spectrometer and spectra recorded over 20h. After this time, aliquots were removed from the tube and analysed by IR spectroscopy and mass spectrometry.

Reaction after 5min:

Diene (278) and carbamate (279) were found to be present. No starting material could be detected.

(E)-Penta-1,3-diene (278)

δ_H(200 MHz) 6.34-5.96 (2H, m), 5.66 (1H, dq, *J* 14.9 and 6.7), 5.03 (1H, bd, *J* 16.1), 4.92 (1H, bd, *J* 9.9), 1.79 (3H, bd, *J* 6.7).

^{1}H NMR Decoupling Experiments:

1) Irradiation at 5.03 ppm/4.92 ppm caused the collapse of the multiplet at 6.34-5.96 to two signals at 6.25 ppm (1H, m) and 6.05 ppm (1H, ddq, *J* 14.9, 10.3 and 1.4).
2) Irradiation at 1.79 ppm causes the broad doublets at 5.03 and 4.92 ppm to sharpen 5.03 (1H, dd, *J* 16.1 and 1.8) and 4.92 (1H, dd, *J* 9.9 and 1.4).
3) Irradiation at 1.79 ppm also causes the collapse of the multiplet at 6.34-5.96ppm to two signals at 6.25ppm (1H, m) and 6.05ppm (1H, dd, *J* 14.9 and 10.3).

Carbamate (279)

δ_H(200 MHz) 7.52-7.29 (5H, m), 0.94 (9H, s), 0.36 (6H, s), 0.05 (6H, s).

δ_C(50 MHz) 150.00 (s), 140.00 (s), 132.86 (d), 129.06 (d), 127.55 (d), 25.76 (q), 17.78 (s), 0.91 (q), -2.81 (q).

$\nu_{max.}$(CCl_4) 1750 cm^{-1}.

Found: *m/z* 340 (M^+-^{35}Cl).

Reaction after 2.5, 4.5 and 8h:

The ^{1}H NMR signals corresponding to carbamate (279) remained unchanged while those corresponding to *(E)*-penta-1,3-diene (278) were gradually replaced by signals from β-lactam (280). After 20h, no signals in the ^{1}H NMR spectrum corresponding to (278) remained.

(E)-1-(Chlorosulphonyl)-propenyl-4-azetidin-2-one (280)

δ_H(200 MHz) 6.05 (1H, dq, *J* 15.0 and 6.5, CHC<u>H</u>Me), 5.57 (1H, ddq, *J* 15.0, 6.5 and 1.6, C<u>H</u>CHMe), 4.70 (1H, m, C<u>H</u>N), 3.44 (1H, dd, *J* 16.4 and 6.7, C<u>H</u>HCO), 3.02 (1H, dd, *J* 16.4 and 4.0, CH<u>H</u>CO), 1.86 (3H, dd, *J* 6.5 and 1.6, Me).

^{1}H NMR Decoupling Experiment:

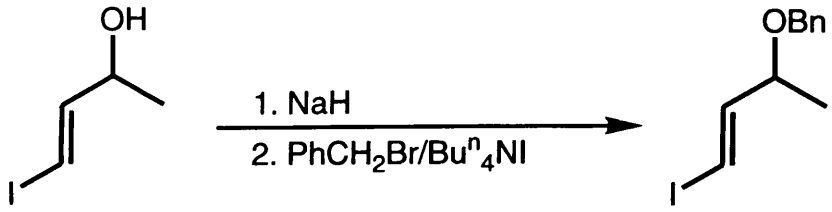
1) Irradiation at 4.70 ppm caused a collapse of the doublet of doublets at 3.44 ppm to the A of an AB spin system (d, *J* 16.4), a collapse of the doublet of doublet at 3.02 ppm to the B of an AB spin system (d, *J* 16.4) and a collapse of the doublet of doublet of quartets at 5.57 ppm to the A an ABX spin system (dq, *J* 15 and 1.6).

δ_C(50 MHz) 160.49 (s, C=O), 125.72 (d), 120.26 (d), 58.32 (d, CHN), 44.19 (t, <u>C</u>H$_2$CO), 25.00 (q).

$\nu_{max.}$(CCl_4) 1825 and 1415 cm^{-1}.

Found: *m/z* 209 [M$^+$(^{37}Cl)].

(*E*)-3-Benzyloxy-1-iodobut-1-ene. (287)



(269) (287)

Procedure: S. Czernecki, C. Georgoulis and C. Provelenghiou, *Tetrahedron Lett.*, 1976, **36**, 3535.

A flame dried 50ml round bottomed flask, under N_2, was charged with NaH (95%) (351mg, 13.9mmol) and dry THF (5ml) then placed in a cooling bath at 0 C. A solution of *(E)*-1-iodobuten-3-ol (269) in ether (15ml) was then added dropwise *via* syringe and the reaction heated at reflux for 15min. After allowing the flask to cool, Bu^n_4NI (230mg, 0.62mmol) and $PhCH_2Br$ (2.38g, 1.65ml, 13.9mmol) were added and the reaction stirred at room temperature for 24h. Concentration of the reaction mixture gave a residue which was partitioned between pentane (25ml) and water (25ml). The organic layer was removed and the aqueous layer re-extracted with pentane (15ml). The combined organic extracts were then washed with saturated sodium thiosulphate solution (25ml) and dried. Concentration and purification of the yellow residue by dry flash column chromatography gave the title benzyl ether as a clear oil (3.52g, 12.25mmol, 97%).

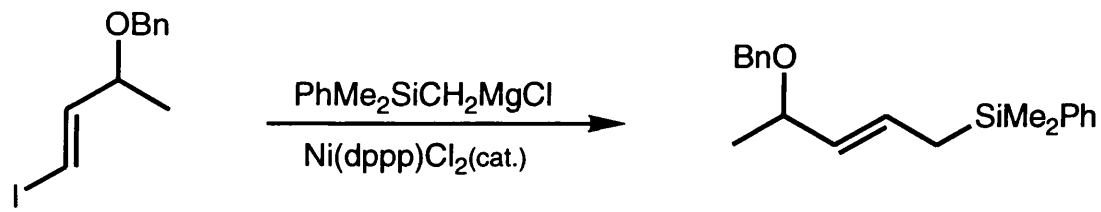
$\nu_{max.}(CHCl_3)$ 1657, 1600 and 950 cm^{-1}.

δ_H(200 MHz) 7.25 (5H, s, Ph), 6.45 (1H, dd, *J* 14.5 and 7.2, IHCC<u>H</u>), 6.25 (1H, d, *J* 14.5, I<u>H</u>CCH), 4.50 (1H, d, *J* 11.9, C<u>H</u>HPh), 4.31, (1H, d, *J* 11.9, CH<u>H</u>Ph), 3.85 (1H, m, C<u>H</u>Me), 1.21 (3H, d, *J* 6.4, Me).

δ_C(50 MHz) 147.88 (d), 138.18 (s), 128.42 (d), 127.62 (d), 77.76 (d), 77.17 (d), 70.28 (t), 20.80 (q).

Found: M^+, 288.0019, $C_{11}H_{13}IO$ requires M, 288.0013.

(*E*)-1-Phenyldimethylsilyl-4-(benzyloxy)pent-2-ene. (288)



(287) (288)

Coupling procedure: Y. Kitano, T. Matasumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi and F. Sato, *Tetrahedron Lett.*, 1987, **23**, 6351.

Preparation of Grignard Solution:

A solution of $PhMe_2SiCH_2MgCl$ in ether (10ml) was prepared from $PhMe_2SiCH_2Cl$ (2.30g, 8.3mmol) and Mg turnings (232mg, 9.6mmol) following the procedure described earlier (page 135).

Coupling:

A flame dried 50ml round bottomed flask, under N_2, was charged with $[Ni(dppp)Cl_2]$ (81mg, 0.14mmol) and a solution of vinyl iodide (287) (2.0g, 6.9mmol) in dry ether (15ml). The Grignard solution was then transferred to the stirred suspension *via* syringe. After stirring at room temperature for 21h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20ml) and the organic layer separated. The aqueous layer was re-extracted with ether (20ml) and the combined organics dried over Na_2SO_4. Concentration and purification of the residue by dry flash column chromatography gave the allylsilane as a clear, colourless oil (2.02g, 6.5mmol, 94%).

$\nu_{max.}(CHCl_3)$ 1656, 1494 and 1250 cm^{-1}.

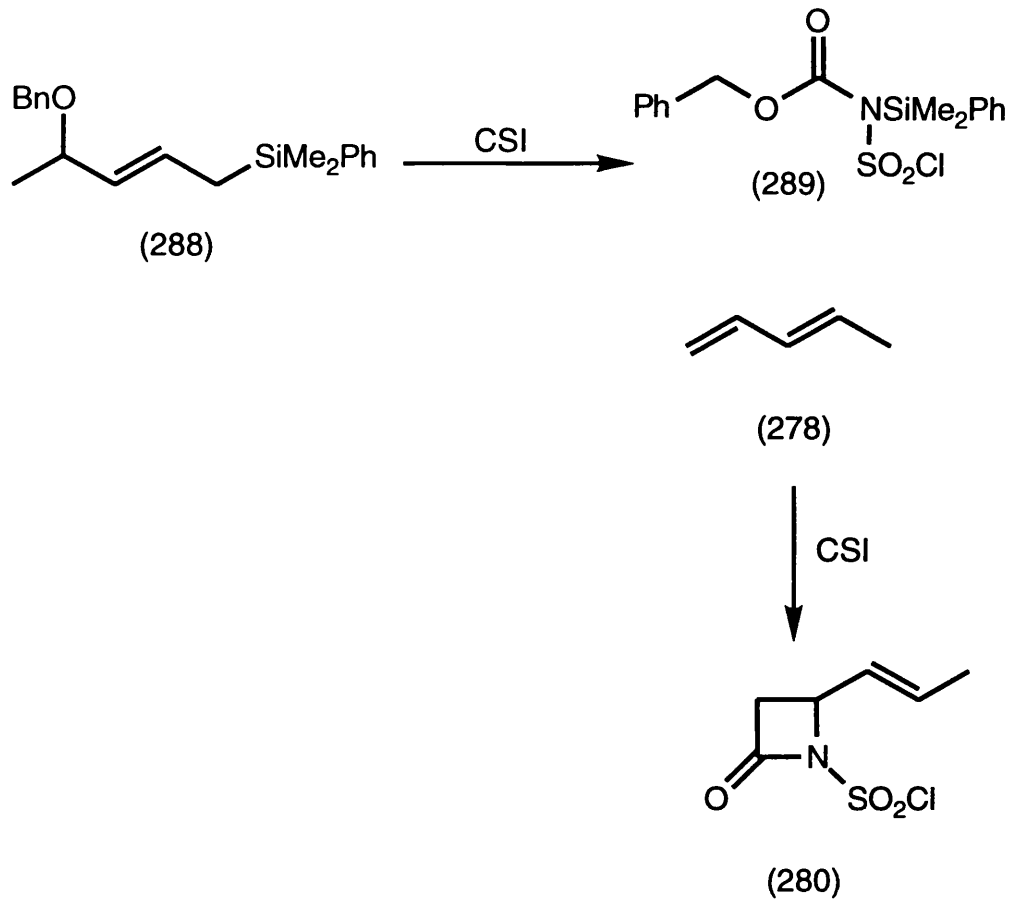
δ_H(200 MHz) 7.55-7.20 (10H, m, Ph), 5.57 (1H, dt, *J* 15.3 and 8.0, C<u>H</u>CH_2), 5.23 (1H, ddt, *J* 15.3, 8.0 and 1.1, C<u>H</u>CH), 4.48 (1H, d, *J* 12.0, C<u>H</u>HPh), 4.26 (1H, d, *J* 12.0, CH<u>H</u>Ph), 3.87-3.74 (1H, m, C<u>H</u>Me), 1.75 (2H, bd, *J* 8.0, C<u>H_2</u>Si), 1.23 (3H, d, *J* 6.3, CH<u>Me</u>), 0.30 (6H, s, Si<u>Me_2</u>Ph).

δ_C(50 MHz) 139.05 (s), 138.39 (s), 133.60 (d), 131.29 (d), 129.07 (d), 128.28 (d), 127.81 (d), 127.72 (d), 127.66 (d), 127.26 (d), 75.97 (d), 69.38 (t), 22.11 (q), 21.74 (t), -3.27 (q), -3.31 (q).

Found: *m/z*, 295.1517, $C_{20}H_{26}OSi\text{-}CH_3$ requires 295.1518.

Reaction of CSI with *(E)*-1-phenyldimethylsilyl-4-(benzyloxy)pent-2-ene.

(288)



A flame dried 10ml round bottomed flask, under N_2, was charged with a solution of allylsilane (288) (169mg, 0.55mmol) in dry CCl_4 (2.5ml) and cooled to 0 C. CSI (72μ l, 0.83mmol) was then carefully added to the stirred solution *via* syringe and after 2min an aliquot of the reaction mixture was placed in an oven dried NMR tube fitted with a rubber septum. This NMR tube was transferred to a 200MHz NMR spectrometer and spectra recorded after 15min and 10h. An aliquot of the reaction mixture was then removed and analysed by IR spectroscopy.

Reaction after 15min:

No starting material was present at this stage, only diene (278) and carbamate (289) were found to be present.

(E)-Penta-1,3-diene (278)

Data as before

Carbamate (289)

δ_H(200 MHz) 7.74-7.32 (10H, m, Ph), 5.36 (2H, s), 0.83 (6H, s).

δ_C(50 MHz) 158.27 (s), 136.19 (s), 136.19 (s), 134.74 (d), 133.67 (d), 132.96 (d), 131.22 (d), 129.38 (d), 128.86 (d), 128.47 (d), 78.27 (t), -3.71 (s).

$\nu_{max.}$(CCl_4) 1727 cm^{-1}.

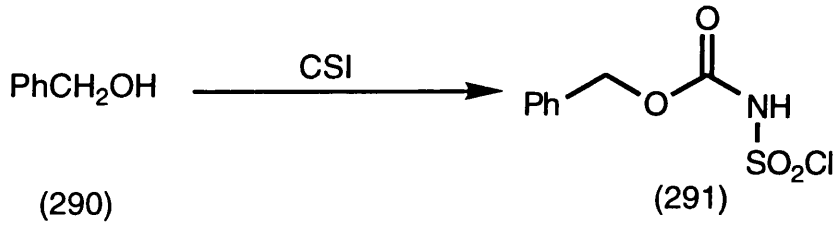
Reaction after 10h:

The ^1H NMR signals corresponding to carbamate (289) remained unchanged while (278) had undergone cycloaddition with CSI to give azetidinone (280).

(E)-1-Chlorosulphonyl-propenyl-4-azetidinone (280)

Data as before.

Benzyl *N*-chlorosulphonylcarbamate. (291)



(290) (291)

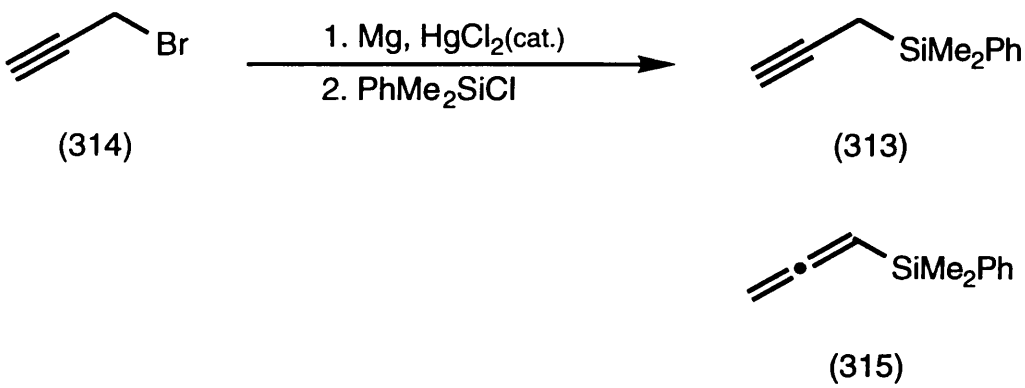
An oven dried NMR tube fitted with a rubber septum was charged with a solution of benzyl alcohol (290) (110mg, 1.02mmol) in $CDCl_3$ (1ml). CSI (89µl, 1.02mmol) was then added slowly *via* syringe. The NMR tube was transferred to a 200MHz NMR spectromer and the ^1H and ^{13}C NMR spectra recorded. An aliquot of the reaction mixture was then removed and analysed by IR spectroscopy.

$\nu_{max.}(CHCl_3)$ 3357, 1773 and 1439 cm^{-1}.

δ_H(200 MHz) 9.20-8.40 (1H, bs, NH), 7.31 (5H, s, Ph), 5.22 (2H, s, $C\underline{H}_2Ph$).

δ_C(50 MHz) 148.93 (s), 133.55 (s), 129.17 (d), 128.31 (d), 128.61 (d), 70.15 (d).

3-(Phenyldimethylsilyl)prop-1-yne. (313)



(314) (313) (315)

Procedure: J. Pornet, N. Kolani, D. Mesnard, L. Miginiac and K. Jaworski, *J. Organomet. Chem.*, 1985, **236**, 4014.

A 100ml round bottomed flask was charged with magnesium turnings (1.69g, 70mmol) and two crystals of $HgCl_2$, flame dried under vacuum and then purged with N_2. The flask was then cooled to 0°C and a solution of propargyl bromide (314) (80% in toluene, 8.71g, 59mmol) added dropwise *via* syringe. After stirring at 0°C for 1.5h, the flask was cooled to -20°C and a solution of phenyldimethylsilyl chloride (5g, 29.3mmol) in dry ether (60ml) added over 15min. The reaction was then allowed to warm to room temperature and stirred overnight before being quenched with saturated aqueous NH_4Cl solution (20ml). The organic layer was separated and washed with water (2x15ml) and the combined aqueous phases re-extracted with ether (2x15ml). The combined organic extracts were then washed with brine (20ml) and dried over Na_2SO_4. Concentration *in vacuo* and purification of the residue by flash column chromatography gave a mixture of alkynylsilane (313) and allenylsilane (315) (8g, 46mmol, 79%) as a clear oil, in a ratio of 7:1.

3-(Phenyldimethylsilyl)prop-1-yne. (313):

$\nu_{max.}(CHCl_3)$ 3300 and 2125 cm^{-1}.

δ_H(200 MHz) 7.65-7.34 (5H, m), 1.88 (1H, d, *J* 2.9), 1.74 (2H, t, *J* 2.9), 0.43 (6H, s).

δ_C(50 MHz) 137.50 (s), 133.55 (d), 129.46 (d), 127.87 (d), 82.01 (d), 67.50 (s), 6.20 (t), -3.59 (s).

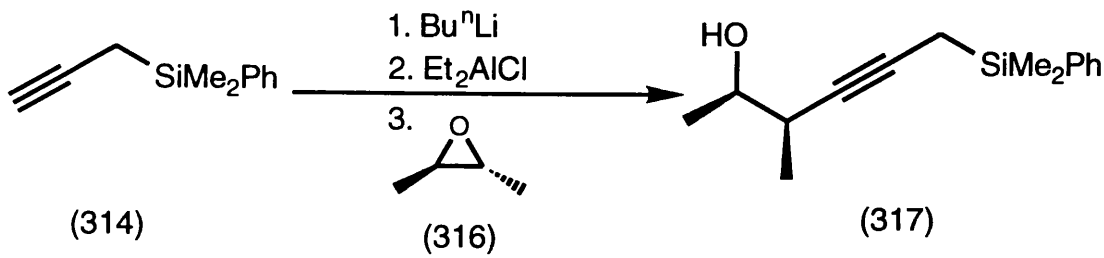
Found: M^+ 174.0866, $C_{11}H_{14}Si$ requires M, 174.0865.

1-(Phenyldimethylsilyl)-1,2-propadiene. (315):

$\nu_{max.}(CHCl_3)$ 1931 cm^{-1}.

δ_H(200 MHz) 7.65-7.34 (m), 5.05 (1H, t, *J* 7.2), 4.38 (2H, d, *J* 7.2), 0.39 (6H, s).

(2*R**, 3*R**)-3-Methyl-6-(phenyldimethylsilyl)-hex-4-yn-2-ol. (317)



(314) (316) (317)

Procedure: H. Hiemstra, M.H.A.M. Sno, R.J. Vijn and W.N. Speckamp, *J. Org. Chem.*, 1985, **50**, 4014.

A flame dried 50ml flask, under N_2, was charged with a solution of crude propargylsilane (313) (2g, 11.48mmol) in dry toluene (17ml). The flask was cooled to -78°C and Bu^{n}Li (1.44M in hexanes, 8.2ml, 11.8mmol) added dropwise to the stirred mixture. After stirring at -78°C for 20min, Et_2AlCl (1M in toluene, 11.5ml, 11.5mmol) was added dropwise, *via* syringe, and the mixture stirred for 25min. A solution of *trans*-2,3-epoxybutane (316) (Lancaster) (829mg, 11.5mmol) in toluene (5ml) was then added over 5min and the reaction allowed to warm to -40°C and stirred for 1h. The flask was then allowed to warm to room temperature overnight before being quenched with saturated aqueous NH_4Cl solution (20ml). The organic layer was separated, washed with water (2x20ml) and brine (20ml) then dried. Concentration *in vacuo* and purification of the residue by dry flash column chromatography yielded the title compound (317) as a clear oil (923mg, 3.75mmol, 33%).

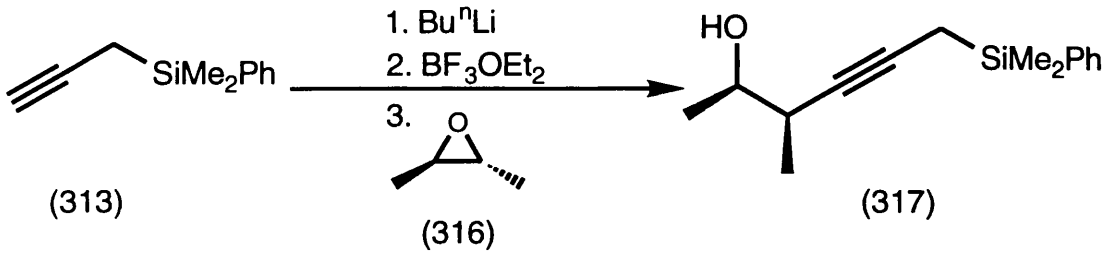
$\nu_{max.}(CHCl_3)$ 3620, 3430 and 1250 cm^{-1}.

δ_H(200 MHz) 7.54-7.27 (5H, m, Ph), 3.65-3.45 (1H, m, C<u>H</u>OH), 2.40-2.55 (1H, m, C<u>H</u>Me), 1.62 (2H, d, *J* 2.5, C<u>H</u>$_2$Si), 1.55 (1H, bs, OH), 1.05 (3H, d, *J* 6.3, Me), 1.0 (3H, d, *J* 7.0, Me), 0.30 (6H, s, Si<u>Me</u>$_2$Ph).

δ_C(50 MHz) 137.54 (s), 133.52 (d), 129.36 (d), 127.82 (d), 79.87 (s), 80.50 (s), 70.47 (d), 34.29 (d), 19.11 (q), 16.56 (q), 6.32 (t), -0.05 (q), -3.47 (q).

Found: M^+ 246.1425, $C_{15}H_{22}OSi$ requires , M 246.1439.

(2*R**, 3*R**)-3-Methyl-6-(phenyldimethylsilyl)hex-4-yn-2-ol. (317)



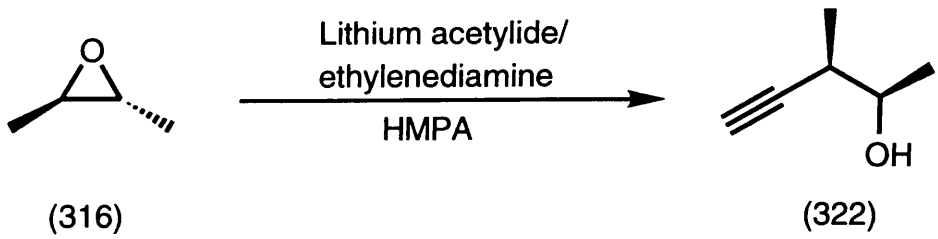
(313) (316) (317)

Procedure: M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **24**, 391.

A flame dried 50ml round bottomed flask, under N_2, was charged with a solution of crude propargylsilane (313) (2.08g, 11.95mmol) in dry THF (15ml) and cooled to -78°C. Bu^nLi (1.55M in hexanes, 7.7ml, 11.9mmol) was then added dropwise. After stirring for 15min, boron trifluoride etherate (1.6ml, 12.9mmol) was added *via* syringe and stirring continued for a further 15min. A solution of *trans*-2,3-epoxybutane (316) (Lancaster) (660mg, 9.2mmol) in THF (5ml) was then added and the reaction stirred for 1h before being quenched with saturated aqueous NH_4Cl solution (10ml). The reaction mixture was extracted with AcOEt (3x15ml) and the combined organic phases dried over Na_2SO_4. Concentration *in vacuo* and purification of the residue by dry flash column chromatography gave the title compound (317) as a clear oil (1.12g, 4.6mmol, 44%).

Spectral data as before.

(2*R**,3*R**)-3-Methyl-4-pentyn-2-ol. (322)



(316) (322)

Procedure: T.M. Willson, P. Kocienski, K. Jarowicki, K. Isaac, A. Faller, S.F. Campbell and J. Bordner, *Tetrahedron,* 1990, **46**, 1757.

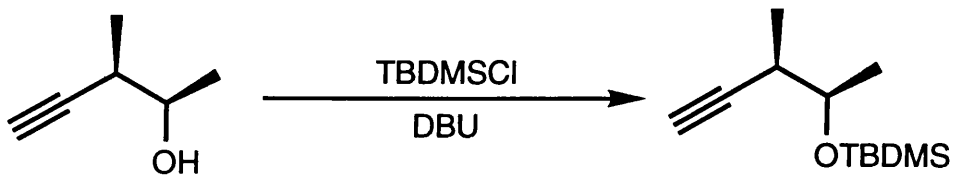
A flame dried 200ml flask, under N_2, was charged with lithium acetylide ethylenediamine complex (90%, 50g, 0.543mol) and dry HMPA (50ml) then cooled to 0°C. Epoxide (316) (10.8g, 0.15mol) was added in one portion and the flask immediately sealed. The reaction was warmed to room temperature and stirred for 7 days, then cautiously poured into dilute aqueous HCl (1M, 300ml). This mixture was extracted with ether (6x150ml) and the combined organic extracts dried over Na_2SO_4. Careful concentration *in vacuo* and purification of the residue by distillation gave (322) as a clear oil (7.4g, 0.09mol, 60%), b.p. 75-78°C/24mmHg. [lit.[178] 69-73°C/22mmHg].

$\nu_{max.}$(film) 3375, 3301 and 2112 cm^{-1}.

δ_H(200 MHz) 3.62-3.47 (1H, m), 2.47-2.36 (1H, m), 2.15 (1H, bs), 2.08 (1H, d, *J* 2.4), 1.21 (3H, d, *J* 6.2), 1.13 (3H, d, *J* 7.1).

δ_C(50 MHz) 85.71 (s), 70.42 (d), 70.14 (d), 33.81 (d), 19.38 (q), 16.15 (q).

(2*R**, 3*R**)-2-(t-Butyldimethylsilyloxy)-3-methylpen-4-yne. (323)



(322) (323)

Procedure: J.M. Aizpurua and C. Palomo, *Tetrahedron Lett.*, 1985, **26**, 475.

A flame dried 100ml flask, under N_2, was charged with DBU (5.60g, 36.7mmol), TBDMSCl (5.1g, 33.9mmol) and dry CH_2Cl_2 (40ml). A solution of alcohol (322) (3g, 30.6mmol) in CH_2Cl_2 (10ml) was added and the mixture stirred for at room temperature for 48h. The reaction was then diluted with CH_2Cl_2 (20ml), the organic layer separated and washed with cold water (3x20ml), dilute aqueous HCl (0.05M, 20ml) and saturated $NaHCO_3$ solution (20ml). After drying and concentration of the organic phase, purification of the residue by flash column chromatography gave the title compound as a clear oil (5.45g, 26.1mmol, 85%).

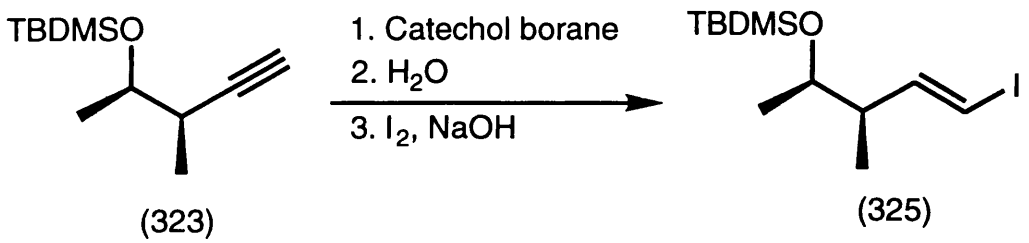
$\nu_{max.}$(film) 3314, 2361, 2115 and 1257 cm^{-1}.

δ_H(200 MHz) 3.67-3.54 (1H, m), 2.36-2.28 (1H, m), 2.04 (1H, d, *J* 2.4), 1.25 (3H, d, *J* 2.0), 1.16 (3H, d, *J* 7.0), 0.83 (9H, s), 0.00 (6H, s).

δ_C(50 MHz) 87.00 (s), 71.60 (d), 69.44 (d), 34.55 (d), 25.76 (q), 21.71 (q), 18.00 (s), 17.26 (q), -4.43 (q), -4.86 (q).

Found: *m/z* 197 (M^+-Me), 155 (M^+-Bu^t) and 131 ($Bu^tMe_2SiO^+$).

(2*R**, 3*R**)-(*E*)-2-(t-Butyldimethylsilyloxy)-3-methyl-5-iodopent-4-ene. (325)



(323) (325)

A flame dried 20ml round bottomed flask, under N_2, was charged with (323) (1g, 4.7mmol) and catechol borane (679mg, 5.7mmol) (Aldrich) then stirred at room temperature for 22h. At this stage, water (20ml) was cautiously added and the reaction stirred for 24h. The white solid produced was filtered off, dissolved in ether (20ml) and this ethereal solution washed with ice water (2x20ml) then placed in a 100ml round bottomed flask which was cooled to 0°C. Aqueous NaOH (3M, 5ml, 15mmol) then a solution of I_2 (1.22g, 9.5mmol) in ether (15ml) were added. After vigorous stirring for 30min, the reaction was quenched with powdered $Na_2S_2O_5$ (5g, 26mmol) and stirred for a further 10min. The reaction was then washed with ether (3x25ml) and then the combined organic phases washed with water (2x25ml) and dried. Concentration and purification of the residue by dry flash chromatography gave vinyl iodide (325) as a clear oil (475mg, 1.4mmol, 30%).

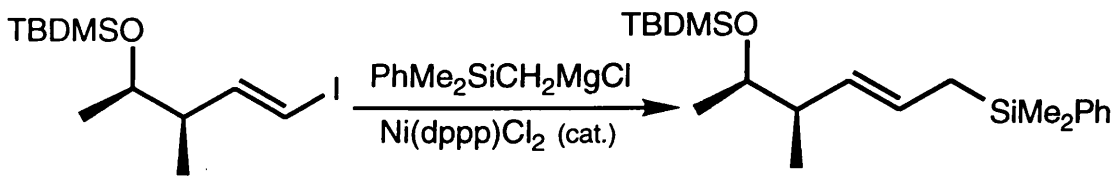
$\nu_{max.}(CHCl_3)$ 1605 and 1257 cm^{-1}.

δ_H(200 MHz) 6.63 (1H, dd, *J* 14.5 and 7.9, IHCC<u>H</u>), 5.95 (1H, dd, *J* 14.5 and 1.0, I<u>H</u>CCH), 3.68-3.56 (1H, m, C<u>H</u>OSi), 2.21-2.11 (1H, m), 1.04 (3H, d, *J* 6.2), 0.98 (3H, d, *J* 6.8), 0.85 (9H, s, Bu^t), 0.00 (6H, s, $SiMe_2$).

δ_C(50 MHz) 149.36 (d), 74.68 (d), 71.04 (d), 48.01 (d), 25.82 (q), 20.89 (q), 18.01 (s), 14.30 (q), -4.41 (q), -4.85 (q).

Found: M^+, 340.0714, $C_{12}H_{25}IOSi$ requires M, 340.0721.

(2*R**,3*R**)-(*E*)-2-(t-Butyldimethylsilyloxy)-3-methyl-6-(dimethylphenylsilyl)hex-4-ene. (326)



(325) (326)

Coupling procedure: Y. Kitano, T. Matasumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi and F. Sato, *Tetrahedron Lett.*, 1987, **23**, 6351.

Preparation of the Grignard solution:

Mg turnings (71mg, 2.9mmol) were placed in a 10ml round bottomed flask fitted with a condenser which was then flame dried under vacuum and purged with N_2. On cooling to room temperature, dry ether (2.5ml) was added and the magnesium activated by addition of 1,2-dibromoethane (1 drop). A solution of $PhMe_2SiCH_2Cl$ (412mg, 2.2mmol) in ether (3.5ml) was then added over 5min and the reaction heated at reflux for 1h.

Coupling:

A flame dried 50ml round bottomed flask, under N_2, was charged with [Ni(dppp)Cl_2] (50mg, 0.1mmol) and a solution of vinyl iodide (325) (632mg, 1.9mmol) in ether (10ml). The Grignard solution was then added to the stirred suspension *via* syringe. After stirring at room temperature for 18h, the mixture was quenched with saturated aqueous NH_4Cl solution (10ml) and the organic layer separated. The aqueous layer was extracted with ether (25ml) and the combined organics dried over Na_2SO_4. Concentration and purification of the residue by dry

flash column chromatography gave the allylsilane (326) as a clear, colourless oil (627mg, 1.74mmol, 92%).

$\nu_{max.}$(film) 1469 and 1250 cm^{-1}.

δ_H(200 MHz) 7.59-7.34 (5H, m, Ph), 5.49-5.34 (1H, m, CHC<u>H</u>CH_2), 5.23 (1H, ddt, *J* 15.3, 7.7 and 1.0, C<u>H</u>$CHCH_2$), 3.62-3.49 (1H, m, C<u>H</u>OSi), 2.50-2.10 (1H, m), 1.63 (2H, dd, *J* 7.5 and 1.0, C<u>H</u>$_2$Si), 1.06 (3H, d, *J* 6.0), 0.97 (3H, d, *J* 6.8), 0.85 (9H, s, Bu^t), 0.23 (6H, s, Si<u>Me</u>$_2$Ph), 0.00 (6H, s, Si<u>Me</u>$_2$$Bu^t$).

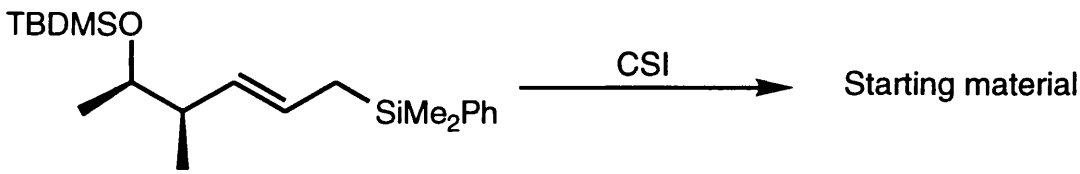
^{1}H NMR Decoupling Experiment:

1) Irradiation at 1.63 ppm caused the collapse of the multiplet at 5.49-5.34 ppm to the A of an ABX system (1H, dd, *J* 15.3 and 0.5).

δ_C(50 MHz) 138.96 (s), 133.61 (d), 132.45 (d), 128.86 (d), 127.67 (d), 125.16 (d), 72.55 (d), 45.14 (d), 25.91 (q), 21.83 (t), 21.27 (q), 18.11 (s), 17.00 (q), -3.34 (q), -4.31 (q), -4.78 (q).

Found: *m/z* 347.2227, $C_{20}H_{35}OSi_2$-Me requires 347.2226.

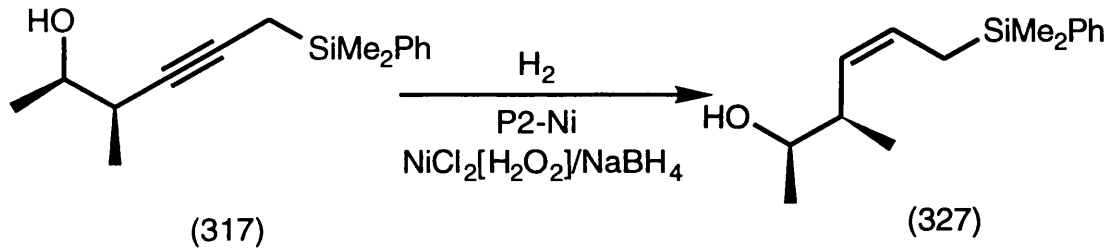
Attempted cycloaddition of ($2R^*, 3R^*$)-*(E)*-2-(t-Butyldimethylsilyloxy)-3-methyl-6-(dimethylphenylsilyl)hex-4-ene (326) with CSI (typical procedure).



(326)

A flame dried 10ml round bottomed, under N_2, was charged with a solution of allylsilane (326) (259mg, 0.72mmol) in dry CCl_4 (3.6ml) and cooled to 0°C. CSI (66µl, 0.76mmol) was carefully added to the stirred solution *via* syringe over 1min. The flask was allowed to warm to room temperature and stirred for 19h. Aqueous Na_2SO_3 (25%, 2ml) was then added and the mixture stirred for 1h before being diluted with CCl_4 (15ml) and washed with water (2x15ml). The organic phase was then dried and concentrated *in vacuo*. Purification of the residue by dry flash column chromatography gave only starting material (326) (243mg, 94%).

(2*R**, 3*R**)-3-Methyl-6-(phenyldimethylsilyl)-hex-4-en-2-ol. (327)



(317) (327)

Procedure: C.A. Brown and V.K. Ahuja, *J. Org. Chem.*, 1973, **38**, 2226.

To a stirred solution of $[NiCl_2(OAc)_2]$ (172mg, 0.69mmol) in ethanol (95%, 5ml), under *ca.* 1 atmosphere of H_2, was added a solution of $NaBH_4$ in ethanol (1M, 0.67ml, 0.67mmol). After 1min, the catalyst was poisoned with 1,2-diaminoethane (4 drops) then stirred for 10min before a solution of propargylsilane (317) (3.33g, 13.5mmol) in ethanol (5ml) was added. The mixture was then stirred for 21h under *ca.* 1 atmosphere of H_2. Workup involved the addition of activated charcoal to the reaction mixture and filtration through a pad of Celite. Concentration and purification of the residue by flash chromatography gave allylsilane (327) as a clear oil (2.96g, 11.9mmol, 88%).

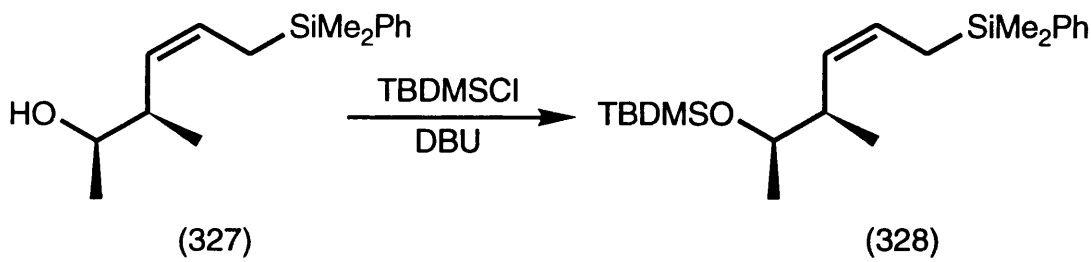
$\nu_{max.}$(film) 3337, 1554 and 1250 cm^{-1}.

δ_H(200 MHz) 7.58-7.29 (5H, m, Ph), 5.37-5.21 (1H, m, CHC<u>H</u>CH_2), 5.10 (1H, dd, *J* 9.8 and 9.4, C<u>H</u>$CHCH_2$), 3.50-3.38 (1H, m, C<u>H</u>OH), 2.36-2.24 (1H, m), 1.80 (1H, bs, OH), 1.65 (1H, ddd, *J* 1.1, 9.3 and 13.8, C<u>H</u>HSi), 1.10 (1H, ddd, *J* 1.5, 5.4 and 13.8, CH<u>H</u>Si), 1.04 (3H, d, *J* 6.1, Me), 0.85 (3H, d, *J* 7.4, Me), -0.06 (6H, s, Si<u>Me</u>$_2$Ph).

δ_C(50 MHz) 138.58 (s), 133.14 (d), 131.66 (d), 128.79 (d), 127.21 (d), 124.40 (d), 78.83 (d), 40.86 (d), 21.25 (q), 17.81 (t), 17.05 (q), -4.30 (q), -4.76 (q).

Found: M^+ 248.1594, $C_{15}H_{24}OSi$ requires M, 248.1596.

(2*R**, 3*R**)-(*Z*)-2-t-Butyldimethylsilyloxy-3-methyl-6-(phenyldimethylsilyl)-hex-4-en-2-ol. (328)



(327) (328)

Procedure: J.M. Aizpurua and C. Palomo, *Tetrahedron Lett.*, 1985, **26**, 475.

A flame dried 50ml round bottomed flask, under N_2, was charged with DBU (1.92g, 12.6mmol), TBDMSCl (1.74g, 11.5mmol) and dry CH_2Cl_2 (20ml). A solution of alcohol (327) (2.62g, 10.5mmol) in CH_2Cl_2 (5ml) was then added and the mixture stirred at room temperature for 48h. The reaction was then diluted with CH_2Cl_2 (25ml), the organic layer separated and washed with water (2x25ml), cold aqueous HCl (0.05M, 25ml) and saturated Na_2CO_3 solution (25ml). After drying and concentration of the organic phase, purification of the residue by flash column chromatography gave the title compound (328) as a clear oil (3.59g, 51.5mmol, 94%).

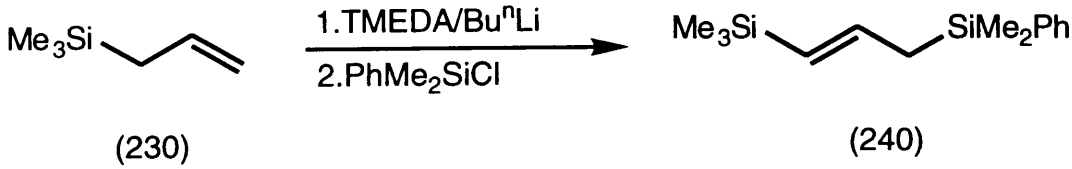
$\nu_{max.}$(film) 1572 and 1253 cm^{-1}.

δ_H(200 MHz) 7.54-7.28 (5H, m, Ph), 5.39-5.24 (1H, m, CHC<u>H</u>CH_2), 5.08 (1H, dd, *J* 9.8 and 9.2, C<u>H</u>$CHCH_2$), 3.48-3.35 (1H, m, C<u>H</u>OSi), 2.33-2.22 (1H, m), 1.77 (1H, ddd, *J* 1.2, 9.1 and 13.8, C<u>H</u>HSi), 1.61 (1H, ddd, *J* 1.5, 5.7 and 13.8, CH<u>H</u>Si), 1.02 (3H, d, *J* 6.1, Me), 0.88 (9H, s, Bu^t), 0.81 (3H, d, *J* 7.5, Me), 0.25 (6H, s, Si<u>Me</u>$_2$Ph), -0.03 (6H, s, Si<u>Me</u>$_2Bu^t$).

δ_C(50 MHz) 138.79 (s), 133.56 (d), 131.96 (d), 128.93 (d), 127.69 (d), 124.04 (d), 72.62 (d), 39.52 (d), 25.91 (q), 22.00 (q), 18.13 (s), 17.78 (t), 16.74 (q), -3.20 (q), -3.30 (q), -4.26 (q), -4.77 (q).

Found: *m/z* 347.2223, $C_{21}H_{38}OSi_2$-Me requires 347.2226.

(E)-3-Phenyldimethylsilyl-1-(trimethylsilyl)prop-1-ene. (240)



(230) (240)

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

To a flame dried flask, under N_2, at -5°C was added TMEDA (6.81g, 8.82ml, 58.6mmol) and Bu^nLi (1.57M in hexanes, 37.3ml, 58.6mmol) then allyltrimethylsilane (230) (5.82g, 50.9mmol). After stirring for 3.25h, $PhMe_2SiCl$ (8.71g, 51.0mmol) was added dropwise and the reaction stirred for 1h at -5°C, then quenched with aqueous HCl (1M, 25ml). The organic layer was removed and the aqueous layer re-extracted with hexane (2x25ml). The combined organic extracts were washed with HCl (1M, 25ml) then water (2x25ml) and the aqueous phases re-extracted with hexane (25ml). Following drying and concentration of the combined organic extracts, distillation of the residue gave the title compound as a clear colourless oil (9.85g, 78%), b.p. 70-75°C/0.3mmHg. (lit.[195] b.p. 76-80/0.4 mmHg).

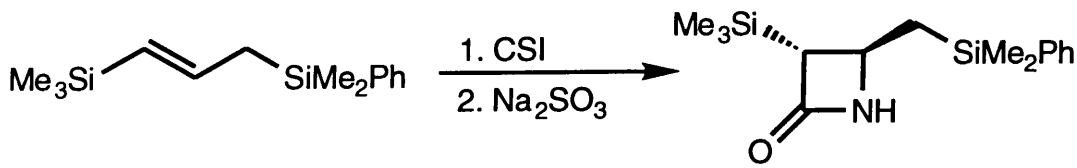
$\nu_{max.}$(film) 1604 and 1250 cm^{-1}.

δ_H(200 MHz) 7.57-7.35 (5H, m), 6.02 (1H, dt, *J* 18.4 and 7.7), 5.47 (1H, dt, *J* 18.4 and 1.1), 1.88 (2H, dd, *J* 7.7 and 1.1), 0.30 (6H, s), 0.00 (9H, s).

δ_C(50 MHz) 140.00 (d), 142.93 (d), 138.50 (s), 133.64 (d), 128.96 (d), 127.67 (d), 27.38 (t), -1.05 (q), -3.53 (q).

Found: M^+ 248.1425, $C_{14}H_{24}Si_2$ requires M, 248.1416.

Trans-3-trimethylsilyl-4-(phenyldimethylsilylmethyl)azetidin-2-one. (241)



(240) (241)

A flame dried flask, under N_2, at 0°C was charged with the allyl/vinyldisilane (240) (3.0g, 12.1mmol) in dry CCl_4 (60ml). CSI (1.80g, 1.11ml, 12.7mmol) was then added dropwise *via* syringe and the reaction mixture stirred for 4h, at which stage 25% aqueous Na_2SO_3 solution (100ml) and CCl_4 (25ml) were added. After stirring overnight, the CCl_4 layer was removed and the aqueous layer re-extracted with CH_2Cl_2 (3x20ml). The combined organic extracts were then dried and concentrated. Purification of the residue by flash column chromatography gave the β-lactam as a white crystalline solid (1.59g, 5.45mmol, 45%), m.p. 117-119°C (sublimed).

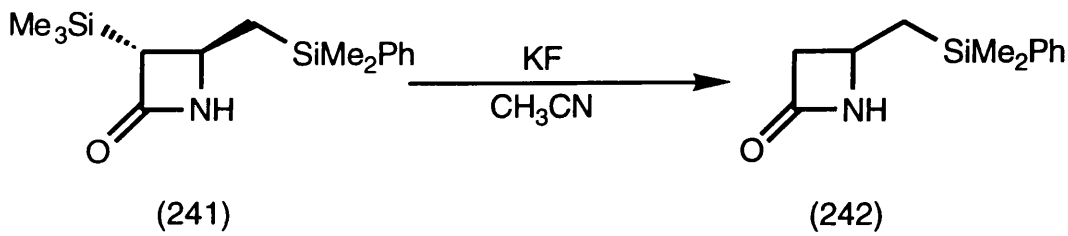
$\nu_{max.}(CHCl_3)$ 3402, 1735 and 1251 cm^{-1}.

δ_H(200 MHz) 7.61-7.37 (5H, m, Ph), 5.45 (1H, br s, NH), 3.50 (1H, ddd, *J* 7.6, 6.4 and 2.2), 2.36 (1H, d, *J* 2.2, CHCO), 1.30 (1H, dd, *J* 14.6 and 6.4, C<u>H</u>H), 1.20 (1H, dd, *J* 14.6 and 7.6, CH<u>H</u>), 0.33 (3H, s, Si<u>Me</u>MePh), 0.32 (3H, s, SiMe<u>Me</u>Ph), 0.06 (9H, s, $SiMe_3$).

δ_C(50 MHz) 170.33 (s), 137.66 (s), 133.41 (d), 133.00 (d), 129.44 (d), 128.05 (d), 52.06 (d), 47.29 (d), 24.71 (t), -2.51 (q), -2.84 (q).

Found: M^+ 291.1483, $C_{19}H_{19}NOSi_2$ requires M, 291.1475.

4-(Phenyldimethylsilylmethyl)azetidin-2-one. (242)



(241) (242)

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

A 250ml round bottomed flask was charged with β-lactam (241) (2.56g, 8.8mmol) in CH_3CN (100ml) along with KF (2.60g, 44.8mmol). The reaction mixture was stirred at room temperature for 4 days then concentrated *in vacuo*. The residue was then taken up in AcOEt (50ml) and washed with water (20ml) and brine (2x20ml). After drying over $MgSO_4$ the solution was concentrated; purification of the residue by flash chromatography yielded the β-lactam (242) as a clear viscous oil. (1.81g, 94%).

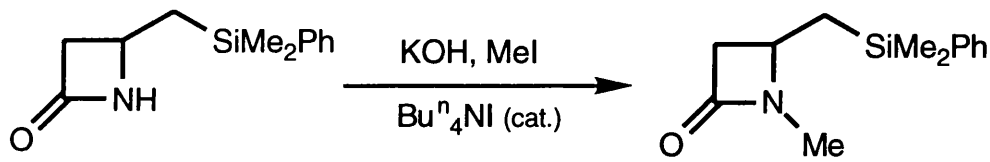
$\nu_{max.}(CHCl_3)$ 3414 and 1750 cm^{-1}.

δ_H(200 MHz) 7.50-7.29 (5H, m, Ph), 6.14 (1H, br s, NH), 3.70 (1H, d d d d, *J* 8.0, 6.6, 4.9 and 2.4, CHN), 2.93 (1H, d d d, *J* 14.8, 4.9 and 2.1, C<u>H</u>HCO), 2.38 (1H, d d d, *J* 14.8, 2.4 and 1.3, CH<u>H</u>CO), 1.28 (1H, d d, *J* 14.4 and 6.6, C<u>H</u>HSi), 1.13 (1H, d d, *J* 14.4 and 8.0, CH<u>H</u>Si), 0.32 (3H, s, Si<u>Me</u>MePh), 0.31 (3H, s, SiMe<u>Me</u>Ph).

δ_C(50 MHz) 168.00 (s), 137.50 (s), 133.38 (d), 129.43 (d), 128.02 (d), 45.74 (t), 45.68 (d), 23.36 (t), -2.57 (q), -2.74 (q).

Found: *m/z* 218.0998, $C_{12}H_{17}NOSi$-H requires 218.1001.

1-Methyl-4-(phenyldimethylsilylmethyl)azetidin-2-one. (352)



(242) (352)

Procedure: D. Reuschling, H. Pietsch and A. Linkies, *Tetrahedron Lett.*, 1978, **19**, 615.

A flame dried 50ml round bottomed flask, under N_2, was charged with freshly powdered KOH (377mg, 6.7mmol), Bu^n_4NI (197mg, 0.6mmol) and dry THF (10ml). The flask was cooled to 0°C and a solution of MeI (2.6g, 18.3mmol) and β-lactam (242) (1.34g, 6.1mmol) in THF (5ml) was added dropwise to the stirred suspension. The reaction was then allowed to warm to room temperature and stirred for 24h before being diluted with ether (30ml) and filtered through a pad of Celite. The filtrate was washed with water (20ml) and brine (20ml) and the organic phase then dried and concentrated. Purification of the residue by flash column chromatography gave β-lactam (352) as viscous oil (1.36g, 96%).

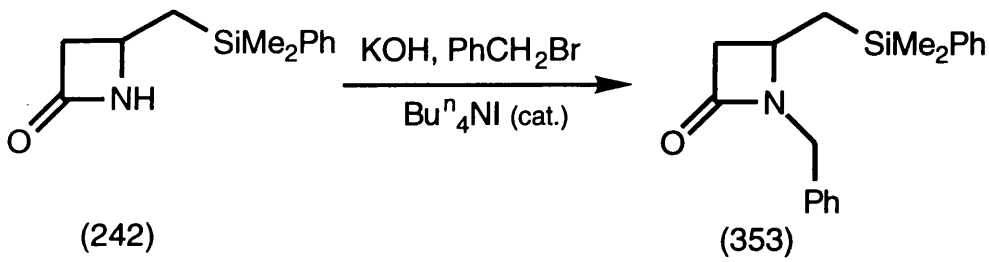
$\nu_{max.}(CHCl_3)$ 1735 cm^{-1}.

δ_H(200 MHz) 7.46-7.28 (5H, m, Ph), 3.53-3.42 (1H, m, C<u>H</u>N), 2.82 (1H, dd, *J* 14.4 and 4.8, C<u>H</u>HCO), 2.64 (3H, s, N<u>Me</u>), 2.27 (1H, dd, *J* 14.4 and 0.9, CH<u>H</u>CO), 1.40 (1H, dd, *J* 14.0 and 3.0, C<u>H</u>HSi), 0.79 (1H, dd, *J* 14.0 and 12.0, CH<u>H</u>Si), 0.28 (6H, s, Si<u>Me</u>$_2$Ph).

δ_C(50 MHz) 166.76 (s), 137.50 (s), 133.34 (d), 129.38 (d), 127.98 (d), 50.26 (d), 44.23 (t), 25.71 (q), 19.84 (t), -2.66 (q), -2.76 (q).

Found: *m/z* 232.1156, $C_{13}H_{19}NOSi$-H requires 232.1157.

1-Benzyl-4-(phenyldimethylsilylmethyl)azetidin-2-one. (353)



(242) (353)

Procedure: D. Reuschling, H. Pietsch and A. Linkies, *Tetrahedron Lett.*, 1978, **19**, 615.

A flame dried 50ml round bottomed flask, under N_2, was charged with freshly powdered KOH (282mg, 5.0mmol), Bu^n_4NI (135mg, 0.4mmol) and dry THF (8ml). The flask was cooled to 0°C and a solution of benzyl bromide (1.8g, 10.5mmol) and β-lactam (242) (916mg, 4.2mmol) in THF (4ml) was added dropwise to the stirred suspension. The reaction was then allowed to warm to room temperature and stirred for 17h before being diluted with ether (30ml) and filtered through a pad of Celite. The filtrate was washed with water (20ml) and brine (20ml) and the organic phase dried and concentrated. Purification of the residue by flash column chromatography gave β-lactam (353) as viscous oil (940mg, 73%).

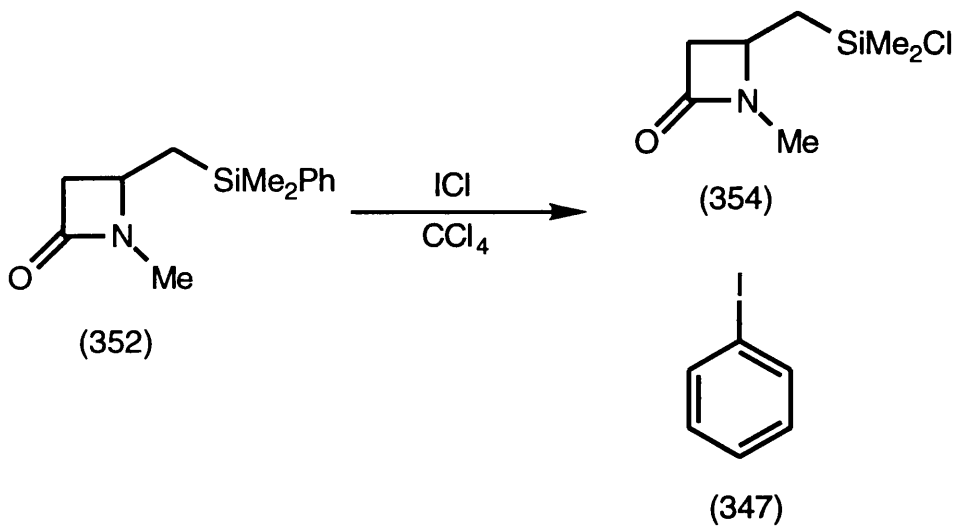
$\nu_{max.}(CHCl_3)$ 1736 cm^{-1}.

δ_H(200 MHz) 7.44-7.22 (10H, m, Ph), 4.62 (1H, d, *J* 15.3, C<u>H</u>HPh), 4.03 (1H, d, *J* 15.3, CH<u>H</u>Ph), 3.58-3.49 (1H, m, C<u>H</u>N), 2.89 (1H, dd, *J* 14.4 and 4.8, C<u>H</u>HCO), 2.38, (1H, dd, *J* 14.4 and 2.2, CH<u>H</u>CO), 1.38 (1H, dd, *J* 14.1 and 2.8, C<u>H</u>HSi), 0.89 (1H, dd, *J* 14.1 and 1.8, CH<u>H</u>Si), 0.28 (6H, s, Si<u>Me</u>$_2$Ph).

δ_C(50 MHz) 166.66 (s), 137.52 (s), 136.00 (s), 133.31 (d), 129.36 (d), 128.71 (d), 128.13 (d), 127.97 (d), 127.54 (d), 48.78 (d), 44.01 (t), 43.70 (t), 20.11 (t), -2.61 (q), -2.80 (q).

Found: *m/z* 232.1469, $C_{19}H_{23}NOSi$-H requires 232.1470.

1-Methyl-4-(chlorodimethylsilylmethyl)azetidin-2-one. (354)



A flame dried 20ml round bottomed flask fitted with a condenser, under N_2, was charged with iodine monochloride (215mg, 1.32mmol) (Aldrich) and dry CCl_4 (4ml). A solution of β-lactam (352) (220mg, 0.94mmol) in CCl_4 (2.5ml) was added dropwise to the stirred solution and the reaction heated at reflux for 10h. After allowing the reaction to cool to room temperature, an aliquot of the mixture (1ml) was removed *via* syringe and placed in an oven dried NMR tube which was then transferred to a 200MHz NMR spectrometer.

Note: chemical shifts in the ^1H NMR spectra are relative to iodobenzene.

1-Methyl-4-(chlorodimethylsilylmethyl)azetidin-2-one. (354)

$\nu_{max.}(CCl_4)$ 1758 cm^{-1}.

δ_H(200 MHz) 3.70-3.53 (1H, m, CHN), 3.01 (1H, dd, *J* 14.1 and 4.8, CHHCO), 2.71 (3H, s, NMe), 2.50 (1H, d, *J* 14.1, CHHCO), 1.48 (1H, dd, 14.3 and 3.0, CHHSi), 0.97 (1H, dd, 14.2 and 11.5, CHHSi), 0.45 (3H, s, SiMeMeCl), 0.44 (3H, s, SiMeMeCl).

δ_C(50 MHz) 164.72 (s, CO), 49.18 (d, CHN), 44.79 (t, CH_2CO), 26.19 (q, NMe), 23.21 (t, $SiCH_2$), 2.64 (q, $SiMe_2Cl$).

Iodobenzene. (347)

$\nu_{max.}(CCl_4)$ 1574, 1472 and 1440 cm^{-1}.

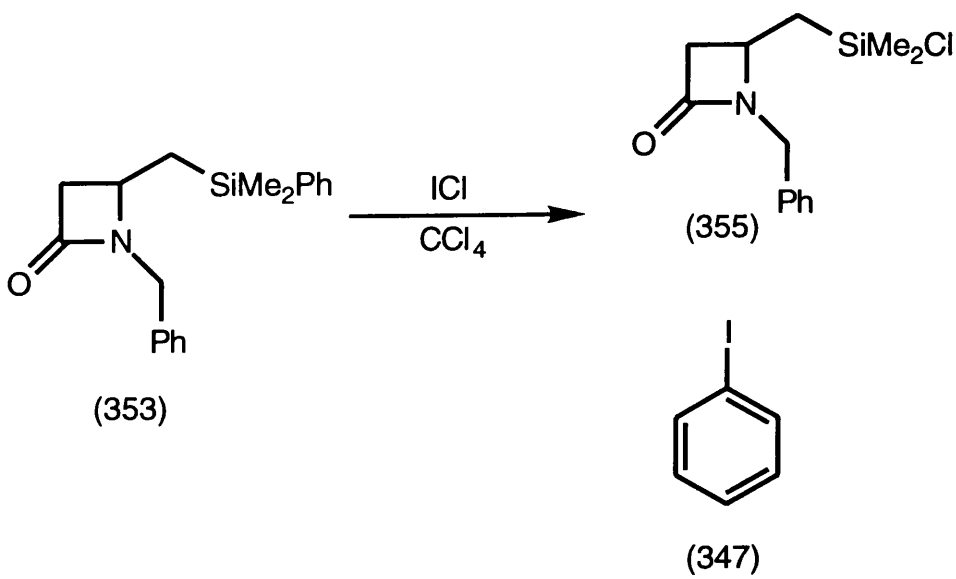
δ_H(200 MHz) 7.63 (2H, dd, *J* 8.1 and 1), 7.29-7.17 (1H, m), 7.10-7.00 (2H, m).

δ_C(50 MHz) 137.56 (d), 130.20 (d), 127.33 (d), 94.63 (s).

Methyl iodide (trace).

δ_H(200 MHz) 2 ppm (s)

1-Benzyl-4-(chlorodimethylsilylmethyl)azetidin-2-one. (355)



A flame dried 10ml round bottomed flask fitted with a condensor, under N_2, was charged iodine monochloride (Aldrich) (112mg, 0.47mmol) and dry CCl_4 (2.5ml). A solution of β-lactam (353) (99 mg, 0.61mmol) in CCl_4 (2.5ml) was added dropwise to the stirred solution and the reaction heated at reflux for 12h. After allowing the reaction to cool to room temperature, an aliquot of the mixture (1ml) was removed *via* syringe and placed in an oven dried NMR tube which was then transferred to a 200MHz NMR spectrometer and the ^1H and ^{13}C spectra recorded. β-Lactam (355) and iodobenzene (347) were found to be present in *ca.* a 1:1 ratio. No starting material could be detected, although a small amount of methyl iodide was present (ratio of (355):MeI was *ca.* 8:1).

1-Benzyl-4-(chlorodimethylsilylmethyl)azetidin-2-one. (355)

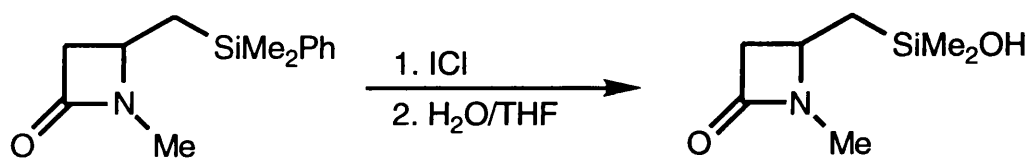
δ_H(200 MHz) 7.59-7.44 (5H, m, Ph), 4.81 (1H, d, *J* 15.4, C<u>H</u>HPh), 4.27 (1H, d, *J* 15.4, CH<u>H</u>Ph), 3.88 (1H, m, C<u>H</u>N), 3.26 (1H, dd, *J* 14.5 and 4.9, C<u>H</u>HCO), 2.83 (1H, dd, *J* 14.5 and 2.2, CH<u>H</u>CO), 1.43 (1H, dd, *J* 11.0 and 3.3, C<u>H</u>HSi), 0.94 (1H, dd, *J* 14.0 and 11.0, CH<u>H</u>Si), 0.32 (6H, s, $SiMe_2Cl$).

δ_C(50 MHz) 167.14 (s), 135.98 (s), 128.59 (d), 127.91 (d), 127.41 (d), 48.57 (d), 43.87 (t), 43.64 (t), 22.02 (t), 0.43 (q), 0.26 (q).

<u>Iodobenzene/Methyl iodide</u>

Data as before.

1-Methyl-4-(dimethylhydroxysilylmethyl)azetidin-2-one. (359)



(352) (359)

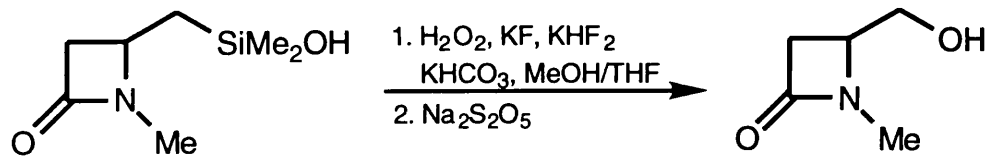
A flame dried 50ml round bottomed flask fitted with a condenser, under N_2, was charged with iodine monochloride (Aldrich) (279mg, 1.7mmol) and dry CCl_4 (8ml). A solution of β-lactam (352) (287mg, 1.23mmol) in CCl_4 (2ml) was added dropwise to the stirred solution and the reaction heated at reflux for 10h. A mixture of THF (10ml) and water (2ml) was then cautiously added and the reaction stirred for 3h. The mixture was then concentrated *in vacuo*, the residue dissolved in CH_2Cl_2 (20ml) and washed with water (10ml) and brine (10ml). The organic phase was then dried and concentrated. Purification of the residue by dry column chromatography gave β-lactam (359) as a viscous brown oil (187mg, 1.1mmol, 88%).

$\nu_{max.}(CHCl_3)$ 3675, 3400, 1736 and 1261cm^{-1}.

δ_H(200 MHz) 3.57-3.46 (1H, m, C<u>H</u>N), 2.98 (1H, dd, *J* 14.3 and 4.8, C<u>H</u>HCO), 2.68 (3H, s, NMe), 2.46 (1H, dd, *J* 14.3 and 0.9, CH<u>H</u>CO), 1.80 (bs, OH), 1.17 (1H, dd, 14.1 and 2.8, C<u>H</u>HSi), 0.62 (1H, dd, 14.1 and 11.9, CH<u>H</u>Si), 0.07 (6H, s, $SiMe_2$).

δ_C(50 MHz) 166.71 (s), 49.65 (d), 44.22 (t), 25.81 (q), 21.92 (t), 1.10 (q).

1-Methyl-4-(hydroxymethyl)azetidin-2-one. (362)



(259) (362)

Procedure: M. Murakami, M. Suginome, K. Fujimoto, H. Nakamura, P.G. Andersson and Y. Ito, *J. Am. Chem. Soc.*, 1993, **115**, 6487.

A 20ml round bottomed flask was charged with β-lactam (359) (180mg, 1.04mmol), KHF_2 (325mg, 4.2mmol), KF (121mg, 2.1mmol), $KHCO_3$ (1.04g, 10.4mmol), THF (1.8ml) and methanol (1.8ml). Hydrogen peroxide (30% in water, 0.53ml) was then added to the mixture and stirred at room temperature for 60h. At this stage, the reaction was diluted with Et_2O (10ml), the flask was placed in a cold water bath (10°C) and freshly powdered $Na_2S_2O_5$ (1g, 5.2mmol) added. After stirring for 1h, the volatiles were removed and the solid residue slurried with AcOEt (10ml), filtered through Celite and concentrated *in vacuo*. This process was repeated and purification of the residue by dry flash column chromatography gave the title compound as a viscous oil (76.8mg, 0.77mmol, 74%).

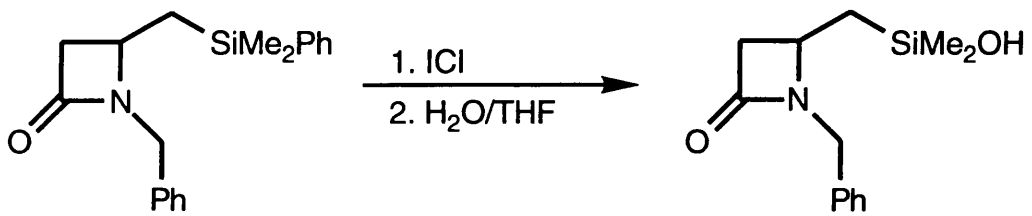
$\nu_{max.}(CHCl_3)$ 3626, 3404 and 1740 cm^{-1}.

δ_H(200 MHz) 3.83 (1H, dd, *J* 13.5 and 2.6, C<u>H</u>HOH), 3.63 (1H, dd, *J* 13.5 and 4.5, CH<u>H</u>OH), 3.63-3.55 (1H, m, C<u>H</u>N), 3.55-3.45 (1H, bs, OH), 2.87 (1H, dd, *J* 14.3 and 4.7, C<u>H</u>HCO), 2.79 (3H, s, NMe), 2.71 (1H, bd, *J* 14.3).

δ_C(50 MHz) 166.09 (s), 61.42 (t), 53.60 (d), 38.40 (t), 27.34 (q).

Found: M^+, 155.0631, $C_5H_9NO_2$ requires M, 115.0633.

1-Benzyl-4-(dimethylhydroxysilylmethyl)azetidin-2-one. (363)



(353) (363)

A flame dried 50ml round bottomed flask fitted with a condenser, under N_2, was charged with iodine monochloride (Aldrich) (114mg, 0.7mmol) and dry CCl_4 (6ml). A solution of β-lactam (353) (168mg, 0.54mmol) in CCl_4 (2ml) was added dropwise to the stirred solution and the reaction heated at reflux for 14h. A mixture of THF (10ml) and water (2ml) was then cautiously added and the reaction stirred for 3h. The mixture was then concentrated *in vacuo*, the residue dissolved in CH_2Cl_2 (15ml) and washed with water (5ml) and brine (5ml). The organic phase was then dried and concentrated. Purification of the residue by dry flash column chromatography gave β-lactam (363) as a colourless, oily solid (109mg, 0.44mmol, 82%).

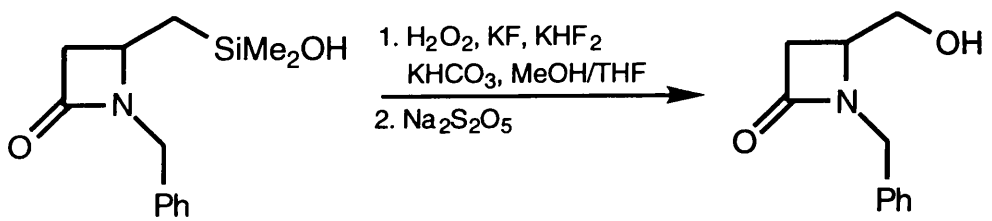
$\nu_{max.}(CHCl_3)$ 3684, 3400, 1736 and 1211 cm^{-1}.

δ_H(200 MHz) 7.39-7.23 (5H, m, Ph), 4.64 (1H, d, *J* 15.3, C<u>H</u>HPh), 4.03 (1H, d, *J* 15.3, CH<u>H</u>Ph), 3.55 (1H, m, C<u>H</u>N), 2.99 (1H, dd, *J* 14.3 and 4.9, C<u>H</u>HCO), 2.50 (1H, dd, *J* 14.3 and 2.1, CH<u>H</u>CO), 1.72 (bs, OH), 4.31 (1H, dd, *J* 13.5 and 3.0, C<u>H</u>HSi), 0.61 (1H, dd, *J* 13.5 and 13.0, CH<u>H</u>Si), 0.00 (6H, s, $SiMe_2$).

δ_C(50 MHz) 166.50(s), 135.73 (s), 128.73 (d), 128.07 (d), 127.62 (d), 48.09 (d), 44.06 (t), 43.71 (t), 22.41 (t), 0.97 (q), 0.94 (q).

Found: M^+, 249.1171, $C_{13}H_{19}NO_2Si$ requires M, 249.1184.

1-Benzyl-4-(hydroxymethyl)azetidin-2-one. (364)



(363) (364)

Procedure: M. Murakami, M. Suginome, K. Fujimoto, H. Nakamura, P.G. Andersson and Y. Ito, *J. Am. Chem. Soc.*, 1993, **115**, 6487.

A 20ml round bottomed flask was charged with β-lactam (363) (176mg, 0.72mmol), KHF_2 (238mg, 3.1mmol), KF (106mg, 1.8mmol), $KHCO_3$ (610mg, 6.1mmol), THF (1.5ml) and methanol (1.5ml). Hydrogen peroxide (30% in water, 0.5ml) was then added to the mixture which was stirred at room temperature for 60h. At this stage, the reaction was diluted with Et_2O (10ml), the flask placed in a cold water bath (10°C) and freshly powdered $Na_2S_2O_5$ (1g) was then added. After stirring for 1h, the volatiles were removed *in vacuo*. The solid residue was then slurried with AcOEt (6ml), filtered through Celite and concentrated *in vacuo*. This process was repeated and purification of the residue by dry flash column chromatography gave the title compound as a viscous oil (82mg, 46%).

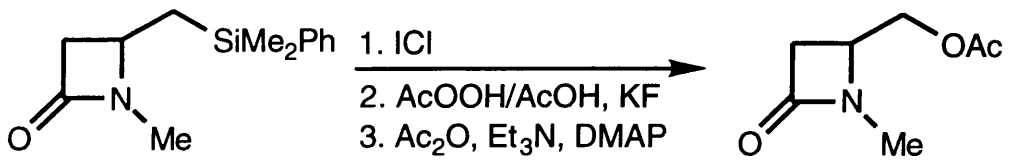
$\nu_{max.}(CHCl_3)$ 3684, 3415 and 1743 cm^{-1}.

δ_H(200 MHz) 7.38-7.23 (10H, m, Ph), 4.49 (1H, d, *J* 15.1, C<u>H</u>HPh), 4.34 (1H, d, *J* 15.1, CH<u>H</u>Ph), 3.72-3.51 (1H, m, C<u>H</u>N), 2.92 (1H, dd, *J* 14.6 and 4.6, C<u>H</u>HCO), 4.17 (1H, dd, *J* 14.6 and 2.1, CH<u>H</u>CO), 2.60-2.30 (1H, bs, OH).

δ_C(50 MHz) 167.55, 136.13, 128.91, 128.20, 127.84, 61.99, 52.42, 45.24, 38.56.

Found: M^+, 191.0944, $C_{11}H_{13}NO_2$ requires M, 191.0946.

1-Methyl-4-(acetoxymethyl)azetidin-2-one. (365)



(353) (365)

A flame dried 25ml round bottomed flask fitted with a condenser, under N_2, was charged with iodine monochloride (201mg, 1.24mmol) and dry CCl_4 (6ml). A solution of β-lactam (353) (206mg, 0.88mmol) in CCl_4 (4ml) was added dropwise to the stirred solution and the reaction heated at reflux for 16.5h. After cooling to room temperature, the volatiles were carefully removed under vacuum (0.5mmHg for 7h) leaving a viscous black oil. To this residue was added AcOOH (40% in AcOH, 5g), AcOH (3ml) and KF (205mg, 3.54mmol) and the mixture left to stir for 3 days. At this stage, the reaction was diluted with Et_2O (50ml), the flask placed in a cold water bath (10°C) and freshly powdered $Na_2S_2O_5$ (6g, 32mmol) added. After stirring for 30min, the ethereal solution was filtered through Celite and concentrated *in vacuo*. The solid residue was slurried with AcOEt (10ml) and filtered through Celite, concentrated *in vacuo* then taken up in THF (5ml). This solution was then treated with Ac_2O (835μl, 8.8mmol), Et_3N (1.8ml, 13.3mmol) and DMAP (5mg, 0.04mmol) and left to stir overnight. Concentration *in vacuo* and purification of the residue by dry flash column chromatography gave acetate (365) as a viscous oil (84mg, 55%).

$\nu_{max.}(CHCl_3)$ 1748 (broad) cm^{-1}.

δ_H(200 MHz) 4.41 (1H, dd, *J* 12.0 and 3.5, C<u>H</u>HOAc), 4.05 (1H, dd, *J* 12.0 and 5.7, CH<u>H</u>OAc), 3.74-3.66 (1H, m, C<u>H</u>N), 2.98 (1H, dd, *J* 14.5 and 5.1, C<u>H</u>HCO), 2.77 (3H, s, NMe), 2.59 (1H, bd, *J* 14.5, CH<u>H</u>CO), 2.06 (3H, s, CO<u>Me</u>).

δ_C(50 MHz) 170.48 (s), 166.50 (s), 63.68 (t), 50.72 (d), 39.56 (t), 27.44 (q), 20.64 (q).

Found: *m/z* 97.0527, $C_7H_{11}NO_3$-AcOH requires, 97.0528.

8 References

1. A. Fleming, *Brit. J. Exptl. Pathol.*, **10**, 226 (1929).
2. *'The Chemistry of Penicillin'*, ed. H.T. Clarke, J.R. Johnson and R. Robertson, Princeton University Press, 1949.
3. I. Ernst, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, *J. Am. Chem. Soc.*, 1979, **100**, 8214-8222.
4. E.P. Abrahams and E. Chain, *Nature* (London), 1940, **146**, 837.
5. E.P. Abrahams and G.G.F. Newton, *J. Biochem.*, 1961, **79**, 377.
6. R. Nagarajan and D.O. Spry, J. *Am. Chem. Soc.*, 1971, **93,** 2310 and E.M. Gordon and R.B. Sykes, in *'Chemistry and Biology of β-Lactam Antibiotics'*, ed. R.B. Morin and M. Gorman, Academic Press, New York, Vol. 1, 1982, page 199.
7. T.T. Howarth, A.G. Brown and T.J. King, *J. Chem. Soc., Chem. Commun.*, 1976, 266.
8. C. Reading and M. Cole, *Antimicrob. Agents Chemother.*, 1977, **11**, 852.
9. L.D. Cama and B.G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 8006.
10. A.G. Brown, D.F. Corbett, A.J. Eglington and T.T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 523.
11. J.S. Kahan, F.M. Kahan, R. Gogelman, S.A. Currie, M. Jackson, E.O. Stapley, T.W. Miller, D. Hendlin, S. Mochales, S. Herdandez, H.B. Woodruf and J. Birnbaum, *J. Antibiotics,* 1979, **32**, 1.
12 W.J. Leanza, K.J. Wilonger, T.W. Miller and B.G. Christensen, *J. Med. Chem.*, 1979, **22**, 1435.
13. R. Hajdu, F.M. Kahan, H. Kropp and J.G. Sundelof, *Antimicrob. Agents Chemother.*, 1982, **22**, 62.
14. A.G. Brown, *Pure Appl. Chem.*,1987, **24,** 180.

15. M. Fukasawa, T. Inoue, M. Kato, H. Matsumura and M. Sunagawa, *J. Antibiotics*, 1990, **18,** 519.

16. M. Hashimoto, T. Kamiya and T. Komori, *J. Am. Chem. Soc.*, 1976, **98**, 3023.

17. A. Imada, K. Kitano, K. Kintaka, M. Muroi, M. Asai, *Nature* (London), 1981, **289**, 590.

18. R.B. Sykes, C.M. Cimarusti, D.P. Bonner, K. Bush, D.M. Floyd, N.H. Georgopapadakou, W.H. Koster, W.C. Liu, W.L. Parker, P.A. Principe, M.L. Rathnum, W.A. Slusarchyk, W.H. Trejo and J.S. Wells, *Nature* (London), 1981, **291**, 489.

19. L.N. Jungheim and R.J. Ternansky, in '*The Chemistry of β-Lactams*', ed. M.I. Page, Blackie, 1992, page 306.

20. R.J. Ternansky and S.E. Draheim, *Tetrahedron Lett.*, 1990, **31**, 2805.

21. C.J. Coulson, '*Molecular Mechanisms of Drug Action*', Taylor and Francis, London, 1980, p. 60.

22 J.M. Frère, M. Nguyen-Distèche, J. Coyette and B. Joris, in '*The Chemistry of β-Lactams*, ed. M.I. Page, Blackie, 1992, p. 148.

23. D.J. Tipper and J.L. Stominger, *Proc. Natl. Acad. Sci. (U.S.A.)*, 1965, **54,** 1133.

24. G.B. Shockman, L.Danoe-Moore, T.D. McDowell and W. Wong, in '*Chemistry and Biology of β-Lactam Antibiotics*', ed. R.B. Morin and M. Gorman, Academic Press, New York, Vol. 3, 1982, p. 210.

25. S.G. Walley, in '*The Chemistry of the β-Lactams*', ed. M.I. Page, Blackie, 1992, p. 198.

26. C.J. Easton and J.R. Knowles, *Biochemistry,* 1982, **21**, 2857.

27. T. Hashizume, A. Yamaguchi and T. Sawai, *Chem. Pharm. Bull.,* 1988, **36**, 676.

28. J. Monk and S.G. Waley, *Biochem. J.*, 1988, **253,** 323.

29. J.E. Baldwin and C. Schofield, in '*The Chemistry of ß-Lactams*', ed. M.I Page, Blackie, 1992, p. 1.

30. W.L. Parker, M.L. Rathnum, J.S. Wells, W.H. Trejo, P.A. Principe and R.B. Sykes, *J. Antibiotics,* 1982 **35**, 653; M. Miyashita, N. Chida and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.,* 1984, 195.

31. J.M. Williamsom, E. Inamine, K.E. Wilson, A.W. Douglas, J.M. Liesch and G.A. Albers-Schönberg, *J. Biol. Chem.,* 1985, **260**, 4637.

32. B.W. Bycroft, C. Maslen, S.J. Box, A. Brown and J.W. Tyler, *J. Antibiotics,* 1988, **41**, 1231.

33. K.E. Wilson, A.J. Kempf, L.M. Liesch and B.H. Arison, *J. Antibiotics,* 1983, **36**, 1109.

34. D.R. Houck, K. Kobayashi, J.M. Williamson and H.G. Floss, *J. Am. Chem. Soc.,* 1986, **108**, 5365.

35. R.W. Woodard, M.D. Tasi, H.G. Floss, P.A. Crooks and J.K. Coward, *J. Biol. Chem.,* 1980, **255**, 9124.

36. J.H. Bateson, R.I. Hickling, T.C. Smale and R. Southgate, *J. Chem. Soc., Perkin Trans. 1,* 1990, 1793.

37. D.B.R. Johnston, S.M. Schmitt, F.A. Bouffard and B.G. Christensen, *J. Am. Chem. Soc.,* 1978, **100**, 313.

38. T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen and F.A. Bouffard, *J. Am. Chem. Soc.,* 1980, **102**, 6161.

39. D.G. Mellilo, R.J. Cvetovich, K.M. Ryan and M. Sletzinger, *J. Org. Chem.,* 1986, **51**, 1498.

40. T. Kametani, *Heterocycles,* 1982, **17**, 463.

41. R.B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan and H. Vorbrüggen, *J. Am. Chem. Soc.,* 1966, **88**, 852.

42. J.C. Sheehan and K.R. Henery-Logan, *J. Am. Chem. Soc.,* 1957, **79**, 1262.

43. G. Lowe and D.D. Ridley, *J. Chem. Soc., Perkin Trans. 1,* 1973, 2024.

44. European Patent Application 10,312. Merck and Co., Inc.

45. J. Brennan, in *Recent Advances in β-lactam Antibiotics,* eds. A.G. Brown and S.M. Roberts. The Royal Society of Chemistry, London, 1988, p.23.

46. J.D. White and S.G. Toske, *Bioorganic and Medicinal Chemistry Letters*, 1993, **3**, 2383.

47. H. Alper, F. Urso and D.J.H. Smith, *J. Am. Chem. Soc.,* 1983, **105**, 6737.

48. D. Tanner and P. Somfai, *Biorganic and Medicinal Chemistry Letters*, 1993, **3**, 2415.

49. A.G.M. Barrett and M.A. Sturgess, *Tetrahedron,* 1988, **44**, 5615.

50. E.J. Corey and A.M.J. Felix, *J. Am. Chem. Soc.,* 1965, **87**, 2518.

51. D.M. Brunwin, G. Lowe and J. Parker, *J. Chem. Soc., Perkin Trans. 1,* 1973, 479.

52. R.J. Ponsford and R. Southgate, *J. Chem. Soc., Chem. Commun.,* 1979, 846.

53. M.P. Doyle, S. Oon, F.R. van der Heide and C.B. Brown, *Biorganic and Medicinal Chemistry Letters*, 1993, **3**, 2409.

54. H. Staudinger, *Liebigs Ann. Chem.,* 1907, **356**, 51.

55. Y. Ito, Y. Kobayashi, T. Kababata, M. Takase, S. Terashima, *Tetrahedron,* 1989, **45**, 5767.

56. H. Gilman and M. Speeter, *J. Am. Chem. Soc.,* 1943, **44**, 5615.

57. G.I. Georg, in '*Studies in Natural Products Chemistry*', ed. A.-ur-Rahman, Elsevier, Oxford, Vol. 4, 1989, page 431.

58. N. Oguni and Y. Ohkawa, *J. Chem. Soc., Chem. Commun.,* 1988, 1376.

59. D.G. Mellilo, I. Shinkai, T. Kiu, K. Ryan and M. Sleztinger, *Tetrahedron Lett.,* 1980, 2783.

60. Y. Yamamoto, N. Asao and T. Uyehara, *J. Am. Chem. Soc.,* 1992, **114**, 5427.

61. M.F. Loewe, R.J. Cvetovich and G.G. Hazen, *Tetrahedron Lett.,* 1991, **32**, 2299.

62. K. Clauss, D. Grimm and G. Prossel, *Liebigs Ann. Chem.,* 1974, 539.

63. J.C. Sheehan and A.K. Bose, *J. Am. Chem. Soc.,* 1950, **72**, 5158.

64. M. Shiozaki and T. Hiraoka, *Tetrahedron Lett.,* 1980, **21**, 4473.

65. M.J. Miller, *Accts. Chem. Res.* , 1986, **19**, 49.

66. M.J. Miller, J.S. Bajwa, P.G. Mattingly and K. Peterson, *J. Org. Chem.*, 1982, **47**, 4928.

67. C. Ma and M.J. Miller, *Tetrahedron Lett.*, 1991, **32**, 2577.

68. Y. Kita, N. Shibata, T. Miki, Y. Takemura and O. Tamura, *Chem. Pharm. Bull.*, 1992, **40**, 12.

69. K. Hirai, K. Fujimoto, Y. Iwano, T. Hiraoka, T. Hata and C. Tamura, *Tetrahedron Lett.*, 1981, **22**, 1021.

70. R. Sharma and R.J. Stoodley, *Tetrahedron Lett.*, 1981, **22**, 2025.

71. German Offenlegungsschrift 2,751,597. Merck and Co., Inc.

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

73. T. Kametani, S. Huang, S. Yokohama, Y. Suzuki and M. Ihara, *J. Am. Chem. Soc.*, 1980, **102**, 2060.

74. T. Kametani, T. Nagahara and T. Honda, *J. Org. Chem.*, 1985, **51**, 1498.

75. M. Shibuya and S. Kubota, *Tetrahedron Lett.*, 1980, **21**, 4009.

76. M.W. Foxton, R.C. Mearman, C.E. Newall and P. Ward, *Tetrahedron Lett.*, 1981, **22**, 2497.

77. A.I. Meyers, T.J. Thomas, S. Scholz and Y. Ueda, *Tetrahedron Lett.*, 1987, **28**, 5103.

78. S.L. Schreiber, R.E. Claus and J. Reagan, *Tetrahedron Lett.*, 1982, **23**, 3867; *Organic Synthesis*, 1985, **64**, 150.

79. A.J.G. Baxter, P. Davis, R.J. Ponsford and R. Southgate, *Tetrahedron Lett.*, 1980, **21**, 5071.

80. A.J.G. Baxter, K.H. Dickenson, P.M. Roberts, T.C. Smale and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1973, 236.

81 Y. Ueda, C.E. Damas and V. Vinet, *Can. J. Chem.*, 1983, **61**, 2257.

82. J.H. Bateson, R.I. Hickling, P.M. Roberts, T.C. Smale and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1980, 1084.

83. L.D. Cama and B.G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 8006.

84. A. Afonso, F. Hon, J. Weinstein and A.K. Ganguly, *J. Am. Chem. Soc.*, 1982, **104**, 6138.

85. A. Yoshida, Y. Tajima, N. Takeda and S. Oida, *Tetrahedron Lett.*, 1984, **25**, 2793.

86. A.G.M. Barrett and P. Quayle, *J. Chem. Soc., Chem. Commun.*, 1981, 1076.

87. A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, *Chem. Pharm. Bull.*, 1983, **31**, 768.

88. S. Hanessian, A. Bedeschi, C. Bannani and N. Mongelli, *J. Am. Chem. Soc.*, 1985, **107**, 1438.

89. S. Hanessian, D. Desilets and Y.L. Bennani, *J. Org. Chem.*, 1990, **55**, 3038.

90. I. Shinaki, R.A. Reamer, F.W. Hartner, T. Liu and M. Sletzinger, *Tetrahedron Lett.*, 1982, **23**, 4903.

91. M.D. Bachi, A. De Mesmaeker and N.S. De Mesmaeker, *Tetrahedron Lett.*, 1987, **28**, 2887.

92. O. Sakurai, T. Ogiku, M. Takahashi, H. Horikawa and T. Iwasaki, *Tetrahedron Lett.*, 1994, **35**, 2187.

93. M. Roth, P. Dubs, E. Götschi and A. Eschenmoser, *Helv. Chim. Acta.*, 1971, **54**, 710.

94. L.D. Cama and B.G. Christensen, *Tetrahedron Lett.*, 1978, **19**, 4233.

95. D.W. Brooks, L.D.L. Lu and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 72.

96. H.H. Wasserman and W.T. Han, *Tetrahedron Lett.*, 1984, **25**, 3747.

97. D. Favara, A. Omedi-Salè, P. Consonni and A. Depoli, *Tetrahedron Lett.*, 1982, **23**, 3105.

98. G.B. Feigelson, *Tetrahedron Lett.*, 1993, **34**, 4747.

99. K. Fujimoto, Y. Iwano and K. Hirai, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1887.

100. B.M. Trost and Y. Tamuru, *J. Am. Chem. Soc.*, 1977, **99**, 3101.

101. K. Hirai, Y. Iwano and K. Fujimoto, *Heterocycles*, 1982, **17**, 201.

102. F. DiNinno, T.R. Beattie and B.G. Christensen, *J. Org. Chem.*, 1977, **42**, 2960.

103. A. Alfonso, S. Chackalamannil, N. Fett, A.K. Ganguly and M. Kirkup, in *'Recent Advances in the Chemistry of β-Lactams'*, eds. P.H. Bentley and R. Southgate. The Royal Society of Chemistry, London, 1988, page 295.

104. D. Seebach, M.A. Sutter, S. Roggo and J. Zimmerman, *Org. Synth.*, 1983, **66**, 485.

105. T. Iimori and M. Shibasaki, *Tetrahedron Lett.*, 1985, **26,** 1523.

106. D.C. Ha, D.J. Hart and T.K. Yang, *J. Am. Chem. Soc.*, 1984, **106**, 4819.

107. T. Imori, and M. Shibasaki, *Tetrahedron Lett.*, 1985, **26**, 1523.

108. Y. Ito, Y. Kobayashi and S. Terashima, *Tetrahedron Lett.*, 1989, **30**, 5631.

109. S. Hanessian, D. Desilets, G. Rancourt and R. Fortin, *Can. J. Chem.*, 1982, **60**, 2292.

110. S. Hanessian and N.R. Plessas, *J. Org. Chem.*, 1969, **34**, 1035.

111. N. Ikota, O. Yoshino and K. Koga, *Chem. Pharm. Bull.*, 1982, **30,** 1929.

112. P.L. Durette, *Carbohyd. Res.*, 1982, **100,** C27.

113. A. Knierzinger and A. Vasella, *J. Chem. Soc., Chem. Commun.*, 1984, 9.

114. H. Matsunaga, T. Sakamaki, H. Nagaoka and Y. Yamada, *Tetrahedron Lett.*, 1983, **24**, 3009.

115. M. Ohno, S. Kobayashi, T. Imori, Y.F. Wang and T. Izawa, *J. Am. Chem. Soc.*, 1981, **102,** 2405.

116. T. Kametani, T. Honda, A. Nakayama, Y. Sasaki, T. Mochizuki and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2228.

117. K. Ohano, Y. Kyotani, H. Ishihama, S. Kobayashi and M. Ohno, *J. Am. Chem. Soc.*, 1985, **105**, 7186.

118. T. Iimoroi, Y. Takahashi, T. Izawa, K. Kobayashi and M. Ohno, J. *Am. Chem. Soc.*, 1983, **105**, 1659.

119. D.G. Melillo, R.J. Cvetovich, K.M. Ryan, M. Sletzinger, *J. Org. Chem.*, 1986, **51**, 1498.

120. R. Graf, *Chem. Ber.*, 1956, **89**, 1071.

121. E.J. Moriconi and W.C. Meyer, *J. Org. Chem.*, 1971, **36**, 2841.

122. E.J. Moriconi and J.F. Kelly, *J. Am. Chem. Soc.*, 1966, **88**, 3657.

123. T. Nakatsuka, H. Iwata, R. Tanaka, S. Imajo and M. Ishiguro, *J. Chem. Soc., Chem. Commun.*, 1991, 662.

124. T.J. Barton and R.J. Rodigo, *J. Org. Chem.*, 1975, **40**, 582.

125. K. Clauβ, *Tetrahedron Lett.*, 1974, **15**, 1271.

126. R. Graf, *Liebigs Ann. Chem.*, 1963, **661**, 111.

127. J.K. Rasmussen and A. Hassner, *Chem. Rev.*, 1976, **76**, 389.

128. F.P. Cossio, B. Lecea, X. Lopez, G. Roa, A. Arrieta and J.M. Ugalde, *J. Chem. Soc., Chem. Commun.*, 1993, 1450.

129. T. Tanaka and T. Miyadera, *Heterocycles,* 1982, **19**, 1497.

130. G. Déléris, J. Dunoguès and R. Calas, *J. Organometal. Chem.*, 1976, **116**, C 45.

131. G. Déléris, J.P. Pillot and J.C. Rayez, *Tetrahedron,* 1980, **36**, 2215.

132. I. Fleming and B. Au-Yeung, *Tetrahedron,* 1980, **37**, Supplement No. 1, 13.

133. E.W. Colvin and M. Monteith, *J. Chem. Soc., Chem. Commun.*, 1990, 1230.

134. C. Nativi, E. Perrotta, A. Ricci and M. Taddei, *Tetrahedron Lett.*, 1991, **32**, 2265.

135. T. Durst and M.J. O'Sullivan, *J. Org. Chem.*, 1970, **35**, 2043.

136. E.W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, p.15.

137. E.W. Colvin, M.A. Loreto, M. Monteith and I. Tommasini, in *Frontiers in Organosilicon Chemistry*, eds A.R. Bassindale and P.P. Gasper, The Royal Society of Chemistry, Cambridge, 1991, p. 356.

138. E.W. Colvin, W.A. König, M.A. Loreto, J.Y. Rowden and I. Tommasini, *Biorganic and Medicinal Chemistry Letters*, 1993, **3**, 2405.

139. M. Monteith, Ph.D. Thesis, Glasgow University, 1991.

140. I. Fleming, R. Henning and H. Plaut, *J. Chem. Soc., Chem. Commun.*, 1984, 29.

141. C. Nativi, G. Palio and M. Taddei, *Tetrahedron Lett.*, 1991, **32**, 1583.

142. I. Fleming and J.J. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3267.

143. M.N. Paddon-Row, N.G. Rondan and K.N. Houk, *J. Am. Chem. Soc.*, 1982, **104**, 7162.

144. I. Fleming, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3363.

145. P.F. Hudrlik and A.M. Hudrlik in, *'The Chemistry of the Carbon-Carbon Triple Bond,* ed. S. Patai, Wiley, New York, 1978, page 199.

146. A.G. Angoh and D.L.J. Clive, *J. Chem. Soc., Chem. Commun.*, 1984, 534.

147. S.K. Chiu and P.E. Peterson, *Tetrahedron Lett.*, 1980, **21**, 4047.

148. S.K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, **20**, 99.

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

150. T. Ho, *Tetrahedron,* 1985, **41**, 1.

151. T.K. Chakraborty and G.V. Reddy, *J. Chem. Soc., Chem. Commun.*, 1989, 251.

152. K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato and M. Kumada, *Bull. Chem. Soc. Japan*, 1976, **49**, 1958.

153. Y. Kitano, T. Matsumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi and F. Sato, *Tetrahedron Lett.*, 1987, **28**, 6351.

154. W.R. Benson and A.E. Pohland, *J. Org. Chem.*, 1964, **29**, 385.

155. W. Lohringer and J. Sixt, *C.A.*, 1959, **53**, 19882g.

156. H. Martens, F. Janssens and G. Hoornaert, *Tetrahedron,* 1975, **31**, 177.

157. M. Hanck, *Acc.Chem. Res,* 1970, **3**, 209.

158. E.J. Corey and D.J. Beames, *J. Am. Chem. Soc.*, 1972, **94**, 7210.

159. R.H. Hall, A. Joordan and G.J. Lourens, *J. Chem. Soc., Perkin Trans. 1*, 1973, 38.

160. S. Czernecki, C. Georgoulis and C. Provelenghiou, *Tetrahedron Lett.*, 1976, **36**, 3535.

161. I. Fleming, I.T. Morgan and A.K. Sarkar, *J. Chem. Soc., Chem. Commun.*, 1990, 1575.

162. R. Angell, P.J. Parsons, A. Naylor and E. Tyrrell, *Synlett*, 1992, 599.

163. Bacon and Farmer, *J. Chem. Soc.*, 1937, 1065.

164. M. Franciotti, A. Mordini and M. Taddei, *Synlett*, 1992, 137.

165. P. Mohr, *Tetrahedron Lett.*, 1993, **34**, 6251.

166. H. Kaga, S. Kobayashi and M. Ohno, *Tetrahedron Lett.*, 1988, **29**, 1057.

167. E.W. Colvin, in *Comprehensive Organic Synthesis*, eds. B.M. Trost and I. Fleming, Pergamon, Oxford, 1991, **7**, 641.

168. G. Stork, *Pure Appl. Chem.*, 1989, **61**, 439.

169. H. Hiemstra, M.H.A.M. Sno, R.J. Vijn and W.N. Speckamp, *J. Org. Chem.*, 1985, **50**, 4014.

170. J. Fried, C.H. Lin and S.H. Ford, *Tetrahedron Lett.*, 1969, **10**, 1379.

171. J. Pornet, N.B. Kolani, D. Mesnard, L. Miginiac and K. Jaworski, *J. Organomet. Chem.*, 1982, **236**, 177.

172. M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 1983, **23**, 391.

173. M.J. Eis, J.E. Wrobel and B. Ganem, *J. Am. Chem. Soc.*, 1984, **106**, 3693.

174. R. Rossi and A. Carpita, *Synthesis*, 1977, 561.

175. R.E. Doolittle, D.G. Patrick and R.H. Heath, *J. Org. Chem.*, 1993, **58**, 5063.

176. C. Eaborn, R.A. Jackson and R. Pearce, *J. Chem. Soc., Perkin Trans. 1*, 1975, 470.

177. M.A. Adams, A.J. Duggan, J. Smolanoff and J. Meinwald, *J. Am. Chem. Soc.*, 1979, **101**, 5364.

178. T.M. Wilson, P. Kocienski, K. Jarowicki, K. Isaac, A. Faller, S.F. Campbell and J. Bordner, *Tetrahedron*, 1990, **46**, 1757.

179. J.M. Aizpurua and C. Palomo, *Tetrahedron Lett.*, 1985, **26**, 475.

180. G. Zweifel and R.B. Steeke, *J. Am. Chem. Soc.*, 1967, **89**, 2754.

181. P.W. Collins, E.Z. Dajani, M.S. Bruhn, C.H. Brown, J.R. Palmer and R. Pappo, *Tetrahedron Lett.*, 1975, 4217.

182. H.C. Brown and S.K. Gupta, *J. Am. Chem. Soc.*, 1972, **94**, 4370.

183. G.W. Kabalka, E.E. Gooch and H.C. Hsu, *Synthetic Commun.*, 1981, **11**, 247.

184. C.A. Brown and V.K. Ahuja, *J. Org. Chem.*, 1973, **38**, 2226.

185. E.C. Roos, H. Hiemstra, W.N. Speckamp, B. Kapstein, J. Kamphuis and H.E. Schoemaker, *Synlett*, 1992, 451.

186. E. Buncel and A.G. Davies, *J. Chem. Soc.*, 1958, 1550.

187. K. Tamao, T. Kakui, M. Akita, T. Iwahara, R. Kanatani, J. Yoshida and M. Kumada, *Tetrahedron*, 1983, **39**, 983.

188. H. Sakurai, M. Ando and N. Kawada, *Tetrahedron Lett.*, 1986, **27**, 75.

189. J. Rowden, Ph.D. Thesis, Glasgow University, 1994.

190. I. Fleming and J.D. Kilburn, *J. Chem. Soc., Chem. Commun.*, 1986, 1198.

191. M. Mukakami, M. Suginome, K. Fujimoto, H. Nakamura, P.G. Andersson and Y. Ito, *J. Am. Chem. Soc.*, 1993, **115**, 6487.

192. L.M. Stock and A.R. Spector, *J. Org. Chem.*, 1963, **28**, 3272.

193. R.L. Hillard and K.P.C. Vollhardt, *J. Am. Chem. Soc.*, 1977, **99**, 4058.

194. G. Félix, J. Dunoguès and R. Calas, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 402.

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

196. G. Hagen and H. Mayr, *J. Am. Chem. Soc.*, 1991, **113**, 4954.

197. M. Bordeau, S.M. Djamei and J. Dunogues, *Bull. Soc. Chim. France*, 1986, 413.

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

199. D. Reuschling, H. Pietsch and A. Linkies, *Tetrahedron Lett.*, 1978, **19**, 615.

200. W.C. Baird, J.H. Surridge and M. Buza, *J. Org. Chem.*, 1971, **36**, 3324.

201. I. Fleming and S.B.D. Winter, *Tetrahedron Lett.*, 1993, **34**, 7287.

202. M.K. Gurjar, M.N. Bhanu, V.B. Khane, A. Bandani, M.N. Deshmukh and A.V. Rama Rao, *Tetrahedron*, 1991, **47**, 7117.

203. A. Varvoglis, *Synthesis*, 1984, 709.

204. T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd Ed., Wiley, New York, 1991.

205. M. Asaoka, K. Kobayashi and H. Takei, *Bull. Soc. Chem. Jpn.*, 1994, **67**, 1141.

206. Z. Kaluza, W. Abramski, C. Belzecki, J. Grodner, D. Mostowicz, R. Urbanski and M. Chmielewski, *Synlett*, 1994, 539.

207. L.M. Harwood, *Aldrichimica Acta*, 1985, **18**, 25.

208. W.G. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

209. L.J. Andrews, *J. Am. Chem. Soc.*, 1949, **68**, 2854.