THE SYNTHESIS OF FUNCTIONALISED β-LACTAMS

by

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ABBREVIATIONS

Ac	Acetyl
AIBN	Azo-bis(isobutyronitrile)
4ÅMS	4 Å molecular sieves
CAN	Ceric (IV) ammonium nitrate
Cp	Cyclopentadienyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DHP	3,4-Dihydro-2H-pyran
DIBAH	Diisobutylaluminium hydride
DMAP	4-(N,N-dimethyl)aminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulphoxide
HMPA	Hexamethylphosphoramide
ImH	Imidazole
LDA	Lithium diisopropylamide
mcpba	m-Chloroperbenzoic acid
Ms	Methanesulphonate
NBS	N-Bromosuccinimide
PDC	Pyridinium dichromate
PNB	p-Nitrobenzyl
PPTS	Pyridinium p-toluenesulphonate
ptsa	p-Toluenesulphonic acid monohydrate
py	Pyridine
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulphonate
Ts	p-Toluenesulphonate

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SUMMARY

$\underline{N}$-t-Butyldimethylsilyl imines were prepared readily by oxidation of the corresponding primary amines. The application of $\underline{N}$-t-butyl-dimethylsilyl imines to the synthesis of monocyclic β-lactams was examined via the ester-imine condensation reaction with silyl ketene acetals.

Initial choice of ZnI_2 as Lewis acid for this reaction proved fruitful in certain instances. This reaction, performed in the presence of t-BuOH to suppress reaction of the initially formed $\underline{N}$-metallo β-amino ester with a further molecule of activated imine, followed by treatment with Grignard reagent, displays a modest <u>trans</u> selectivity in the product β-lactams. However, difficulties were encountered during utilization of more highly functionalised $\underline{N}$-t-butyldimethylsilyl imines. As a result, a second Lewis acid system was investigated.

Utilization of trimethylsilyl trifluoromethanesulphonate (TMSOTf) as the Lewis acid component produced, in a one-pot process, a range of β-lactams in a trans-selective manner. Chemical yields resulting from this approach were comparable to those achieved using ZnI_2 as Lewis acid and the diastereoselectivities found showed a modest increase over those induced in the earlier approach.

Low temperature quenching of the product derived from treatment of a non-enolisable aldehyde with lithium hexamethyldisilazide resulted in formation of the corresponding $\underline{N},\underline{N},\underline{O}$-tris(trimethylsilyl) amine acetal. Treatment of these compounds with TMSOTf provides access to the same reactive iminium species as found in the reaction between $\underline{N}$-silyl imines and TMSOTf and, as such, provides an alternative route to β-lactam synthesis.

Two functionalised silyl ketene acetals were prepared. Attempts to incorporate these substrates into the ester-imine condensation process met with only partial success. The cyclic silyl ketene acetal derived from δ-valerolactone was incorporated into a β-lactam nucleus, although some atypical characteristics were observed in this system.

As an alternative source of the electrophilic iminium species generated in the reaction between an imine or amine acetal with a Lewis acid, the reactivity of enamines was examined. Lewis acid catalysis did allow access to β-amino esters from enamines, although certain aspects of this process are, as yet, unexplained.
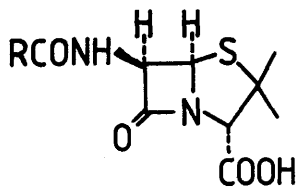
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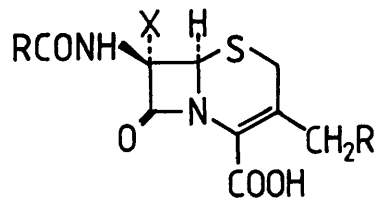
(2) X=H Cephalosporins
(3) X=OMe Cephamycins
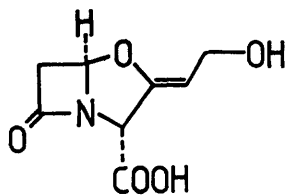
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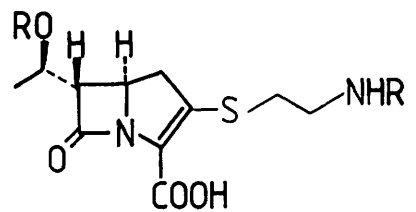
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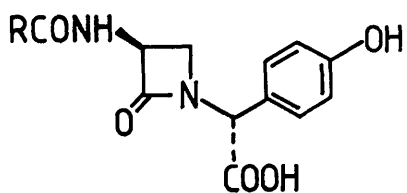
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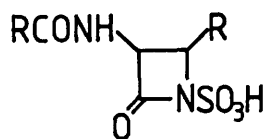
(7) Monobactams

Figure 1

INTRODUCTION

1. Background.

Since the discovery of penicillin (1) in 1929 by Sir Alexander Fleming,[1] compounds containing the β-lactam ring system have been the subject of intense chemical and biological investigation.[2] Several structurally related types of β-lactam antibiotic are known. Of those, two groups of therapeutic agents of great clinical importance are the penicillins (1) and cephalosporins (2). Recently, biological screening has revealed more structurally diverse compounds, such as the cephamycins (3), clavulanic acid (4) and the thienamycins (5), with the last having been the subject of tremendous synthetic effort over recent years due to their great potency and broad spectrum activity. Also of great utility are the monocyclic β-lactams comprising the nocardicins (6) and the monobactams (7). These structural units are depicted in Figure 1.

The β-lactam antibiotics inhibit bacteria by interfering with the synthesis of certain essential structural components of the bacterial cell wall. These components are not present in mammalian cells so that inhibition of growth of bacterial cell wall structures can occur with little or no adverse effect on mammalian cell metabolism. In practice, the β-lactam antibiotics are used widely for treating bacterial infections, being seen as highly effective bactericidal agents with very low toxicity.

The chemical synthesis of these compounds has played a crucial role in the discovery of more potent and broadly active drugs. These syntheses fall into two major tactical approaches, namely modification
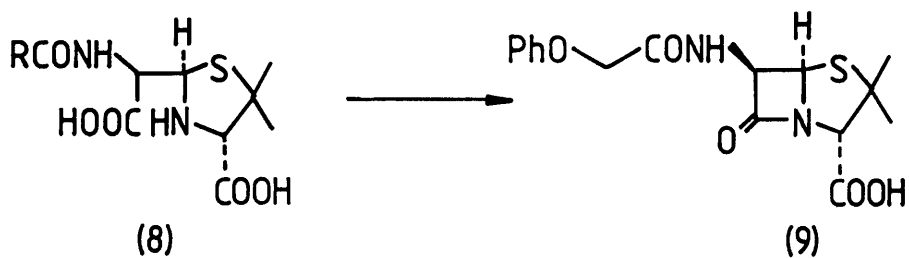
Scheme 1
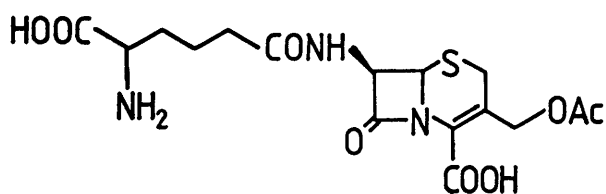
(10) Cephalosporin C
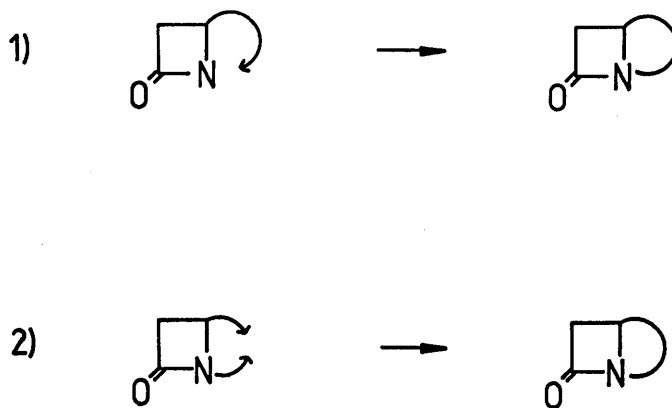
Scheme 2

of the side-chains of naturally occurring β-lactams to yield new,

semisynthetic species, and the total synthesis of target molecules.

It is more recent work in this latter area which will be reviewed

briefly here.

The first synthesis of a β-lactam antibiotic was successfully

completed by Sheehan[3] in 1959 (Scheme 1).   Realising that penicilloic

acid (8) was a degradation product of naturally occurring penicillin,

he completed the synthesis of penicillin V (9) from (8) by introduction

of the β-lactam ring at a late stage.

A conceptually different approach was utilized by Woodward[4] in

his renowned synthesis of cephalosporin C (10) in 1966.   Woodward chose

to create the β-lactam ring at an early stage and then proceed to

construct the second, thiazine ring.   This strategy has subsequently

dominated the total synthesis of β-lactam antibiotics for two reasons.

Firstly, as all members of this class of antibiotics possess, by

definition, a β-lactam unit, a single, suitably functionalised β-lactam

may have potential, after suitable elaboration, to furnish a range of

synthetic antibiotics.   Secondly, it has been found in practice to be

easier to form a fused bicyclic β-lactam by ring closure creating a five

or six membered ring, rather than a four membered ring.

2. Synthesis of Bicyclic β-Lactams from Monocyclic β-Lactams.

Over the last twenty years, the synthetic effort directed

towards the construction of fused bicyclic β-lactams from monocyclic

β-lactams has revealed two major approaches which are summarised in

(11) → (12)

(13) → (14) $\xrightarrow[\text{C}_6\text{H}_6]{\text{Rh}_2(\text{OAc})_4}$

(15) → (16) R = OTs

(17) R = S⌒⌒NHCOOPNB
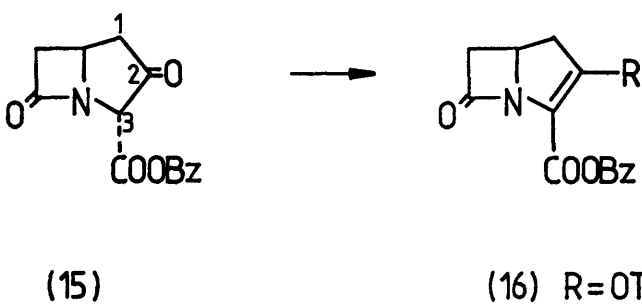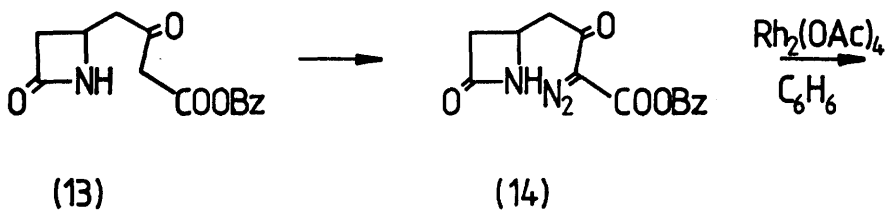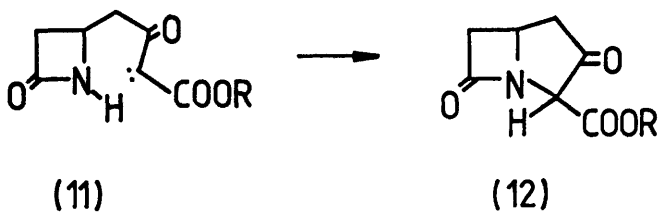
Bz = benzyl

Scheme 3

Scheme 2.   A fused bicyclic system can be prepared either by 1) chain extension at C-4 of the β-lactam ring and ring closure at nitrogen, or by 2) functionalisation at both C-4 and nitrogen of the β-lactam ring and ring closure at a non-β-lactam centre.

2.1 Ring Closure at Nitrogen.

Merck chemists[5] have developed a new synthesis of the carbapenem ring system.   The key step involves a highly efficient carbene insertion reaction which produces the bicyclic ring system in high yield, that is, carbene (11) yielding carbapenam (12) (Scheme 3).   The carbene precursor (14) was obtained from β-ketoester (13) by diazo exchange with p-carboxy-benzenesulphonyl azide; decomposition of diazo ketoester (14) was catalysed by $Rh_2(OAc)_4$ in benzene, effecting ring closure to carbapenam (15) in quantitative yield.   The 2-thia substitution pattern found in thie-namycin was readily introduced by formation of the vinyl tosylate (16) which underwent selective conjugate addition-elimination of N-(p-nitro-benzyloxycarbonyl) cysteamine, yielding the thienamycin related derivative (17).   This route to bicyclic systems has been used for the construction of a wide range of compounds and as such, represents an invaluable approach.

2.2 Ring Closure at a non-β-lactam centre.

The intramolecular process required to accomplish ring closure at a non-β-lactam centre requires elaboration at both C-4 and nitrogen of the β-lactam ring.   Once this has been achieved, intramolecular
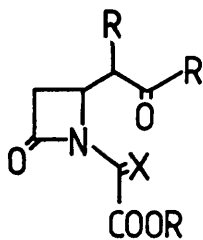
(18) X = PPh$_3$

(19) X = H, H
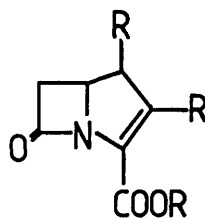
(20), from (18) via Wittig,

from (19) via aldol

Scheme 4

(21)

Scheme 5

(22)

1) Zn, AcOH

(23)

2) DMSO, DCC

(24)

Δ

(25) R = Buᵗ
(26) R = H
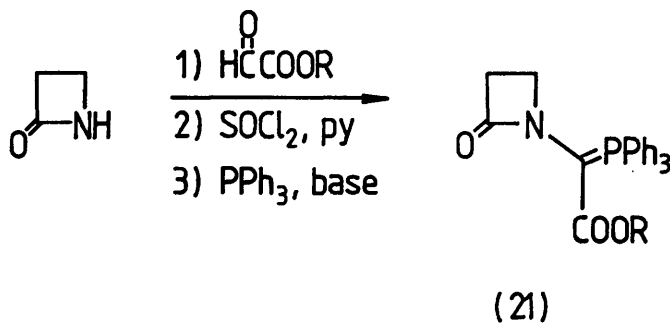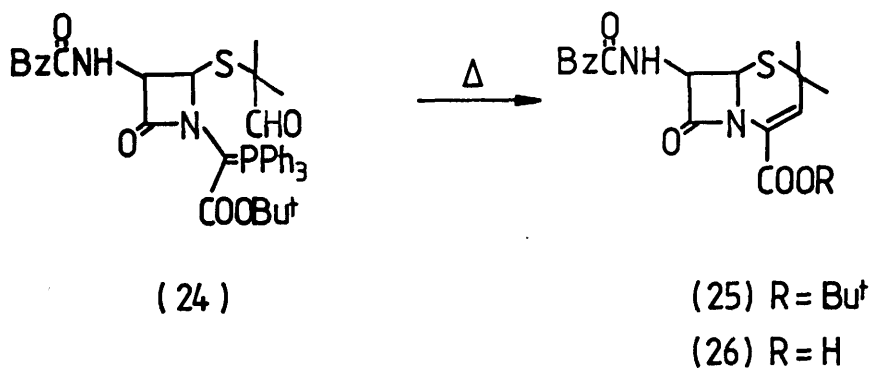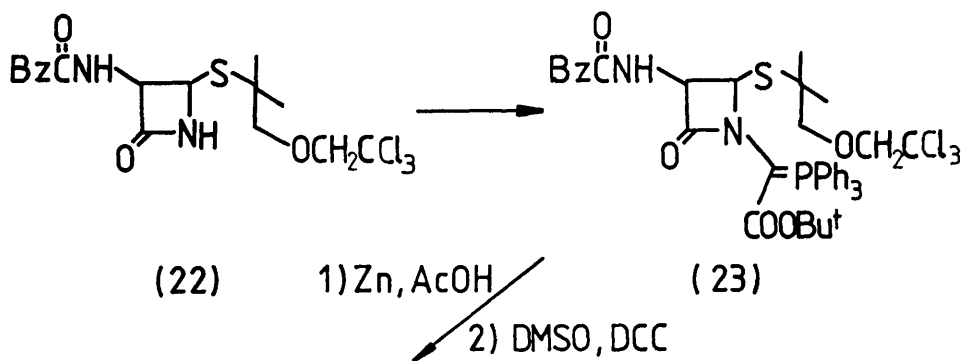
Scheme 6

ring closure can be accomplished either by a Wittig reaction or by an
aldol-type process (Scheme 4).

The Wittig approach was first employed by Woodward.[6]   Intro-
duction of the phosphorane unit proceeded readily via a three step
sequence which involved reaction of a glyoxylate ester with an N-
unsubstituted β-lactam (Scheme 5).   Conversion of the so formed
carbinolamine into the corresponding chloride followed by treatment with
PPh$_3$ and a base provided the desired phosphorane (21).   This type of
stabilised phosphorane proved hydrolytically stable and was tolerant of the
reaction conditions required to introduce the carbonyl containing moiety
at C-4 of the β-lactam ring.   Woodward[6] demonstrated the versatility of
this approach by synthesising the cephalosporin analogue (26) (Scheme 6).
Introduction of the phosphorane unit to N-unsubstituted β-lactam (22)
proceeded as outlined above to give (23).   Reductive removal of the
ether protecting group and Moffatt oxidation of the primary alcohol
yielded the desired aldehyde (24).   Ring closure was achieved by heating
(24) to give cephem (25), which in turn yielded the cephalosporin analogue
(26) after deprotection.   This reaction can accommodate a wide range
of glyoxylate esters and carbonyl containing moieties including ketones,
thiolesters, trithiocarbonates and certain anhydrides.

Ring closure at a non-β-lactam centre can also be achieved by
means of an intramolecular aldol-type reaction.   Glaxo chemists[7]
synthesised the β-lactam (27) containing suitable functionality at the
C-4 and nitrogen atoms.   Treatment of (27) with lithium hexamethyl-
disilazide at low temperature produced the carbapenam (28) in moderate

(27) →[LiN(SiMe₃)₂] (28) →[MsCl, Et₃N]

MeO ... (27)
COOPNB

(28)
COOPNB

(29)
COOPNB

Scheme 7

R^1 R^2
R^3O OM

(30) M=Metal, e.g. Li

+

R^4
N
R^5

(31)

→

R^1 R^4
R^2
O N R^5

(32)

Scheme 8

$$R = Ph, \quad \overset{\xi}{\diagdown}\diagup Ph$$

Scheme 9

$R^1 = R^2 = H$, alkyl, SAr, $\diagup\!\!\!\diagdown_\xi$

$R^3 = Ph$, 2 − furyl, $\overset{\xi}{\diagdown}\diagup Ph$,

$\overset{\xi}{\diagdown}\equiv\!\!-SiR_3$, $\overset{\xi}{\diagdown}\diagup SPh$
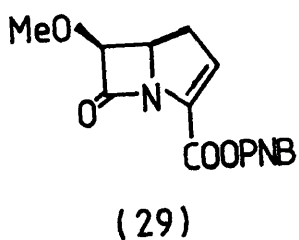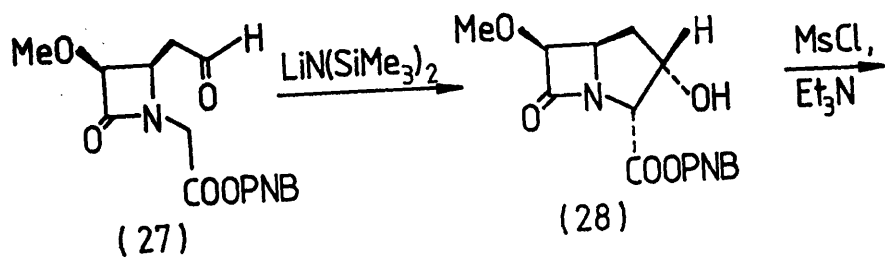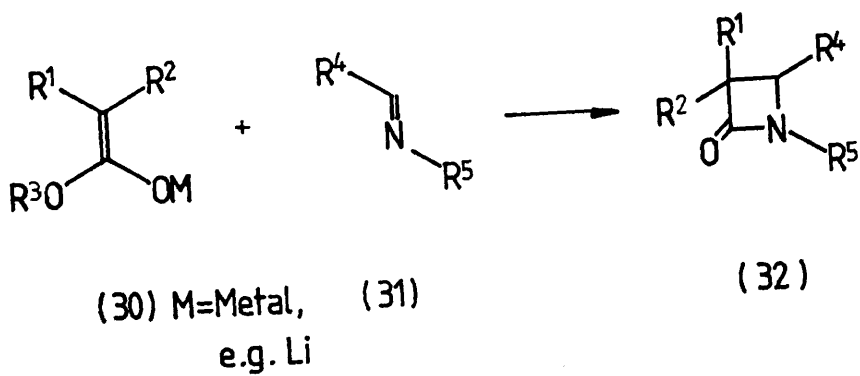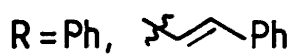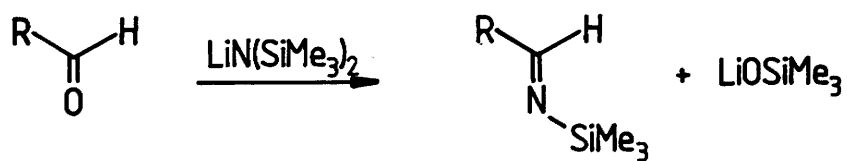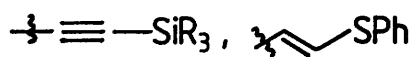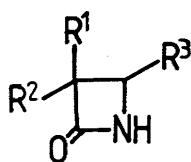
Figure 2

yield (Scheme 7).   Methanesulphonylation and elimination then allowed

ready access to the carbapenem system (29).

3. Synthesis of Monocyclic β-Lactams.

Monocyclic β-lactams have emerged as essential starting

materials for the construction of known and novel bicyclic systems.

Reviewed here are the principal ways in which the construction of these

strained rings has been successfully tackled.

There are many ways of synthesising the β-lactam ring.[8]

Most of these suffer from the disadvantage of producing β-lactams with

N-protective groups which are often not readily removed, as is mandatory

for subsequent elaboration to bicyclic systems.

3.1   Achiral Synthesis.

One of the most useful methods for β-lactam construction

involves an ester-imine cycloaddition route as depicted in Scheme 8.

Reaction of a lithium ester enolate (30) and an imine (31) results in

formation of an N-lithio β-amino ester which, under the reaction

conditions, cyclises spontaneously to form the β-lactam (32).   This

approach has been examined in some detail by Newcomb[9] and Hart[10].   The

problem of deblocking of the β-lactam nitrogen was overcome[10] by

utilization of N-trimethylsilyl aldimines (31, R^5 = trimethylsilyl),

prepared[11] by treatment of a range of non-enolisable aldehydes with a

slight excess of lithium hexamethyldisilazide in THF (Scheme 9).

Addition of a so formed solution of an N-trimethylsilyl imine to a

(33)　　　　(34) R² = Ar, SiMe₃　　　　(35)

(36)　　　　　　　　　　(37)

Scheme 10

(38)　　　(39) R = Ph　　　(40) R = Ph

Tr = trityl　　(41) R = Me　　(42) R = Me
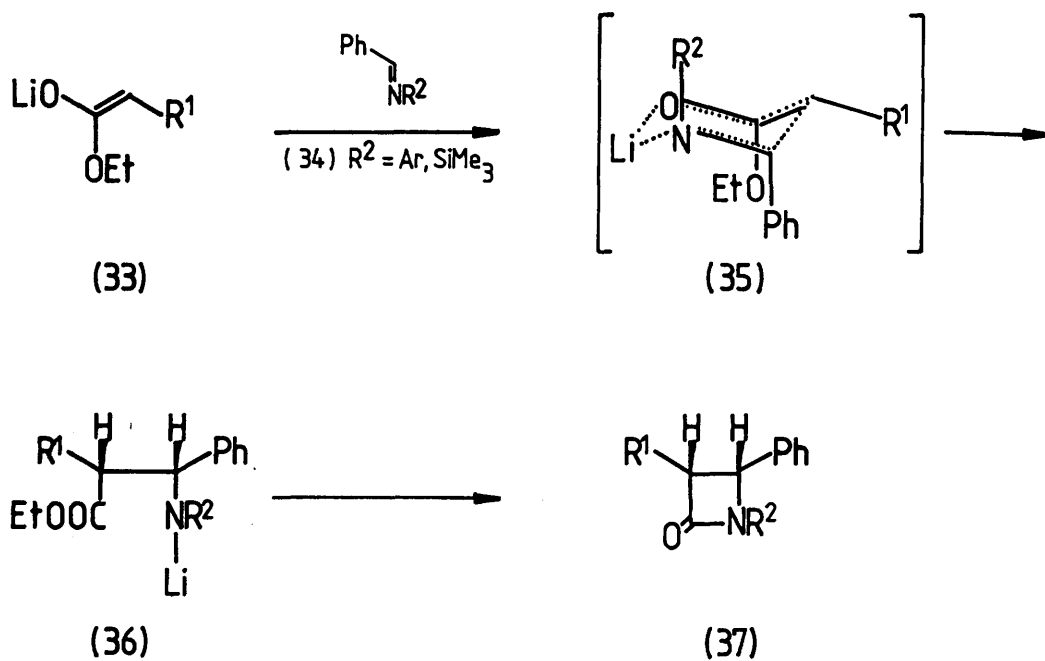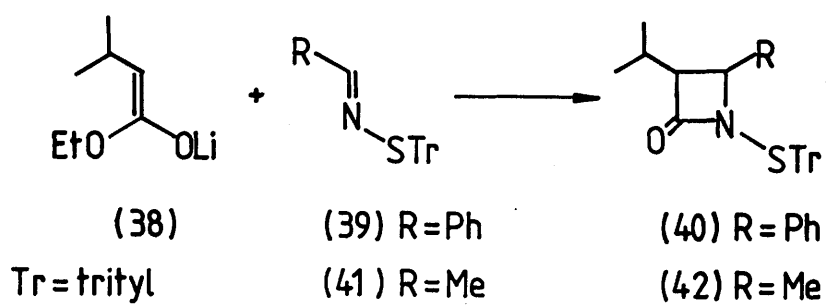
Scheme 11

solution of a pre-formed lithium ester enolate resulted in conversion
to the desired N-trimethylsilyl β-lactam in a one-pot process; the product
was isolated as the more useful N-unsubstituted β-lactam due to the
hydrolytic instability of the nitrogen-silicon bond.   β-Lactams formed
by this method are shown in Figure 2.   An interesting feature of this
reaction is (where applicable) an erythro diastereoselectivity exhibited
in the C-3/C-4 bond forming step and hence a selectivity for cis-β-
lactam formation.   This has been explained by invoking a six-membered
chair transition state similar to that frequently used to rationalise the
stereochemical course of aldol condensations[12] (Scheme 10).   Low
temperature kinetic deprotonation of esters with LDA selectively affords[13]
the (E)-enolate (33), which can add to imines (34) via a tightly co-
ordinated six-membered chair transition state (35), affording the erythro
adduct (36) which cyclises to the cis-β-lactam (37).   This model assumes
that the imine component exists predominantly as the (E) geometrical
isomer.

When treated with (Z)-enolates, generated using LDA in the
presence of HMPA,[13a] N-trimethylsilyl imines tended to give approximately
equal mixtures of diastereoisomers.   This may be because (Z)-enolates
do not react exclusively with N-trimethylsilyl imines via a co-ordinated
chair-like transition state similar to (35), but via a related boat-like
transition state or a combination of both.

Differences in diastereoselectivities were also noted when N-
aryl imines, such as benzylidene aniline (34, R^2 = Ph) were used.   This
may be due to interpretive problems caused by increased susceptibility
of the product N- aryl β-lactams to epimerise under the reaction

1) Bu$_3$P, EtOH, THF

2) TMSI, CH$_2$Cl$_2$

or 3) CuCl$_2$, THF, EtOH

Scheme 12

LiN(SiMe$_3$)$_2$

R^1 = H, alkyl,

R^2 = H, alkyl;
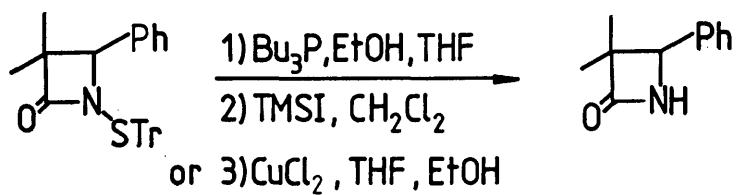
Me$_2$Si—N—SiMe$_2$
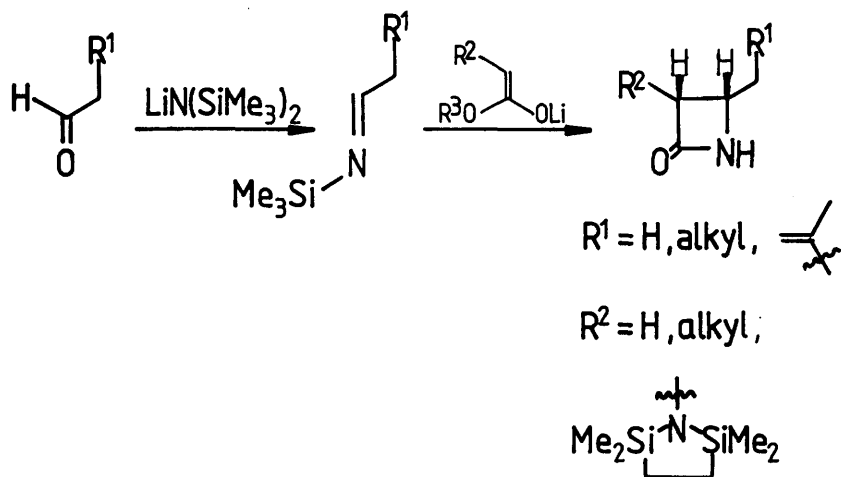
Scheme 13

conditions.[10b]

In a modification to this procedure, Hart[10c] has used N-trityl-sulphenyl imines as the electrophilic component in the ester-imine condensation route (Scheme 11).   Treatment of the N-tritylsulphenyl imine (39) with the lithium ester enolate (38) gave the N-trityl-sulphenyl β-lactam (40), showing a 4.5 : 1 diastereoselectivity in favour of the cis-β-lactam.   Utilization of enolisable N-trityl-sulphenyl imine (41) resulted in formation of β-lactam (42), again in a cis-selective manner.   This is noteworthy as it represents one of the few examples known of β-lactam formation in a reaction involving a lithium ester enolate and an enolisable imine although subsequent work by Cainelli[14] and co-workers has apparently shown that under the correct conditions, this type of reaction can readily be achieved, as will be discussed shortly.   Although this procedure does not result in immediate deblocking of the β-lactam nitrogen, this can be accomplished in excellent yield using a variety of reagents (Scheme 12).

N-trimethylsilyl imines have, as a drawback to their usage, the requirement that they be synthesised from non-enolisable aldehydes, thereby severely limiting the range of C-4 substituents that can be incorporated into the β-lactam ring.   This requirement for non-enolisable aldehydes has been claimed to be due to competitive enolisation of the aldehyde during the preparation of the imine,[10a] and/or to tautomerisation of the imine, to the corresponding enamine.[15]   Despite these reported limitations, it has been communicated[14] that treatment of an enolisable aldehyde at -30°C in THF with lithium hexamethyldisilazide

$$R^1CN + LiAl(OEt)_3H \longrightarrow \overset{R^1}{\underset{}{\diagdown}}=N-\overset{\ominus}{\underset{}{Al}}(OEt)_3 \quad Li^{\oplus}$$

$$(43) \hspace{5cm} (44)$$

$$\underline{TMSCl} \longrightarrow \overset{R^1}{\underset{}{\diagdown}}=N\diagdown_{SiMe_3} \quad \overset{R^2 \diagup R^3}{\underset{R^4O \diagdown OLi}{}} \longrightarrow \overset{R^2}{\underset{O}{\diagdown}}\overset{R^1}{\underset{NH}{}} \quad (45)$$

$$R^1 = Ph, 2-furyl, n-Pr$$

Scheme 14

$$[(\diagdown O \diagdown\diagup O \tfrac{1}{2}AlH_2]^{\ominus} \ Na^{\oplus} \hspace{3cm} \left[HAl \overset{}{\underset{}{\diagup}} \right]^{\ominus} Li^{\oplus}$$

$$(46) \hspace{5cm} (47)$$
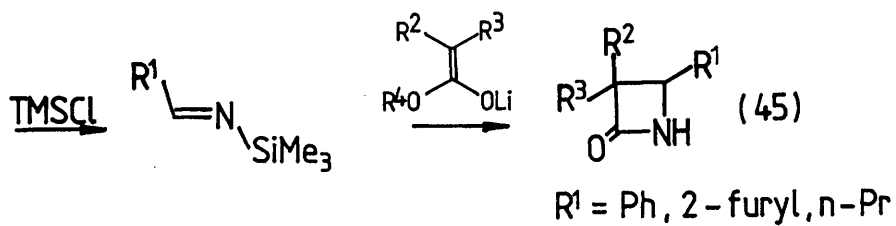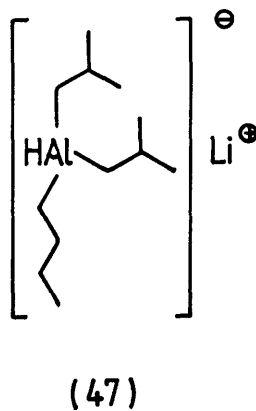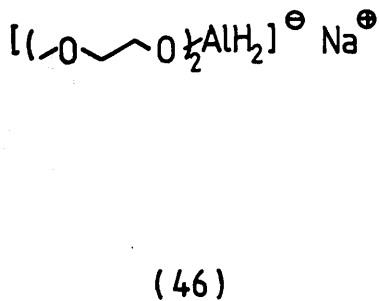
Figure 3
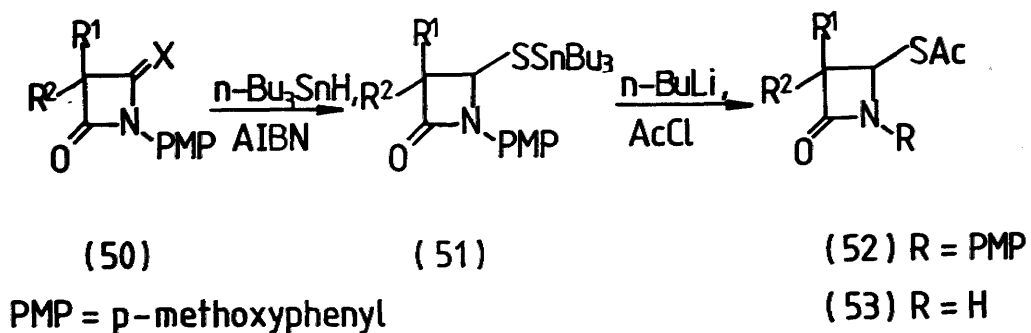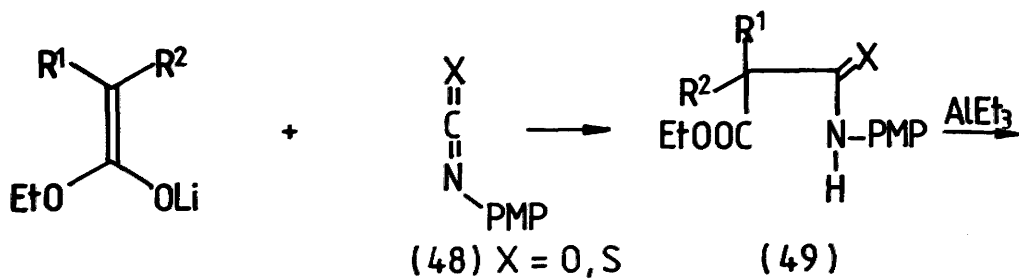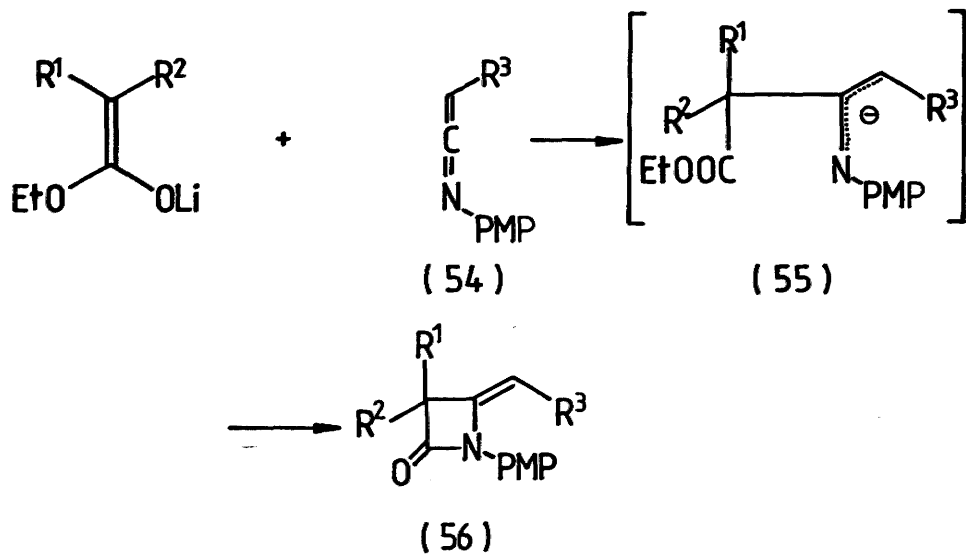
Scheme 15

Scheme 16

does in fact form the corresponding N-trimethylsilyl imine, although all
attempts to isolate pure imine failed.   In situ treatment of the N-
trimethylsilyl imine with a lithium ester enolate produced the desired
β-lactam, showing good cis diastereoselectivity in most cases (Scheme 13).

A less direct way of overcoming the problems associated with
non-enolisable aldehydes has been described[16] (Scheme 14).   Treatment
of either an aliphatic or aromatic nitrile with lithium triethoxy-
aluminium hydride (43) gave the addition product (44).   Trans-metallation
with trimethylchlorosilane resulted in in situ formation of the
corresponding N-trimethylsilyl imine, which could be treated with a
lithium ester enolate in the usual manner to yield the N-unsubstituted
β-lactam (45) with, in most cases, good cis diastereoselectivity.
Other aluminium reagents applicable to this route are sodium bis (2-methoxy-
ethoxy) aluminium hydride (46) and, in the case of aromatic nitriles,
the aluminate complex (47), generated in situ from DIBAH and n-BuLi
(Figure 3).

Heterocumulenes[17] have also found application to the synthesis
of interesting β-lactams (Scheme 15).   Treatment of isocyanate or
isothiocyanate (48) with a lithium ester enolate at -78°C led[17a] to the
malonamic or thiomalonamic ester (49) which furnished the β-lactam (50)
after treatment with $AlEt_3$ in refluxing toluene.   The utility of this
approach is illustrated in the preparation of 4-thioacetoxy β-lactam (53).
Reduction of thiomalonimide (50, X = S) using nBu_3SnH-AIBN gave the tin
mercaptide (51) which could be converted into the corresponding
thioacetoxy derivative (52) by treatment with nBuLi and acetyl chloride,

R^1

COLi

R^2

OEt

H

C=C=N

OMe

R^3

(54)

R

O

SBu^t

$\xrightarrow{\text{1) LDA}}$
$\text{2) Cp}_2\text{ZrCl}_2$

SBu^t

R

OZrCp$_2$Cl

SiMe$_3$

(59)

N   Ar

(57)

(58)

R

SiMe$_3$

But$S$

C=O

NH

Ar

+

R

SiMe$_3$

But$S$

C=O

NH

Ar

(60)

(61)

Scheme 17

(62)

(57)

1) LDA
2) Et$_2$AlCl
3) (59)

(63)   +   (64)

Scheme 18

1) LDA
2) Me$_2$AlCl
3)
(65)
R^4 = n-Pr, i-Pr
R^5 = CH$_2$Ph, CH$_2$CH$_2$Ph
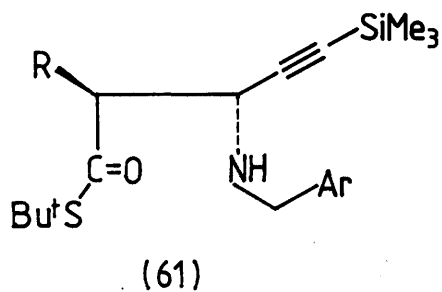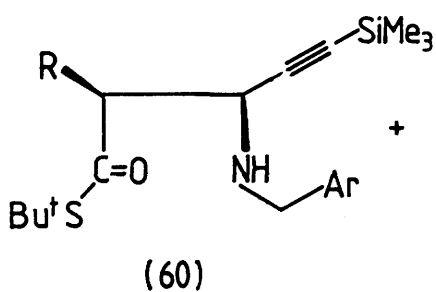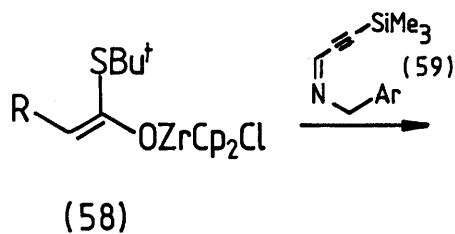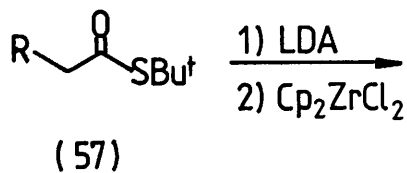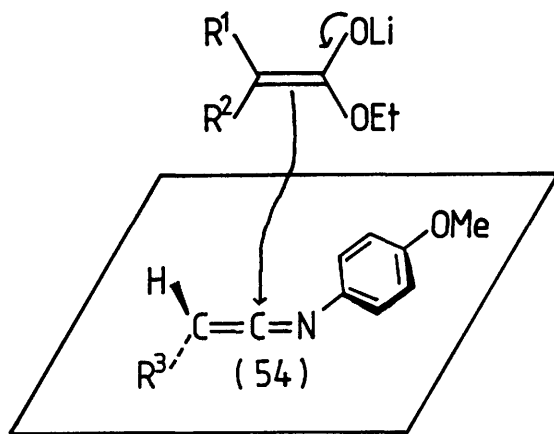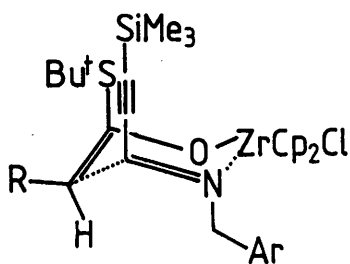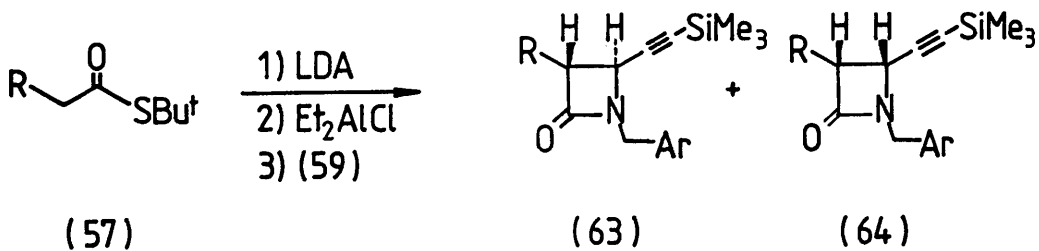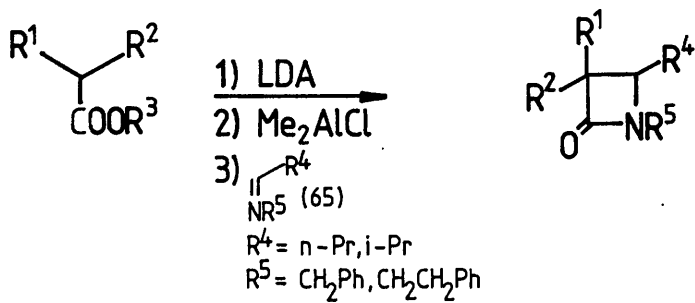
Scheme 19

N-unsubstituted β-lactam (53) was then revealed by oxidative deprotection.

In a similar approach,[17b] N-aryl ketenimine (54) was treated with a lithium ester enolate resulting in nucleophilic attack at the electrophilic sp carbon of the ketenimine. The acyclic intermediate (55) spontaneously cyclised to the 4-alkylidene β-lactam (56) (Scheme 16). In all but one example, the (Z) geometric isomer was the sole product, arising from attack by the nucleophilic enolate on the less hindered face of the imine component of the azomethine system of (54).

As has been shown, reactions involving lithium ester enolates normally show a marked erythro selectivity in their reactions with imines leading, on cyclisation, to cis-β-lactams. An interesting modification[18] of this procedure allows control of the stereochemistry of the C-3/C-4 bond forming step, permitting selection of either erythro or threo adduct formation, depending on the reaction conditions chosen. The zirconium enolate (58) was formed by sequential treatment of S-(t-butyl) propanethioate (57, R = Me) with LDA at -78°C and bis(cyclopentadienyl) dichlorozirconium. Addition of imine (59) resulted in preferential formation of the erythro β-amino ester (60), [diastereoisomeric ratio (60):(61), 4:1] (Scheme 17). This selectivity could be further enhanced by increasing the bulk of the R group of thioate (57). Utilization of (57, R = Pr^i) resulted in the ratio of products (60) and (61) improving to 21:1, respectively. The stereochemistry of zirconium enolates of this type has been shown[18,19] to be predominantly (E). As a result, it seems likely that the zirconium enolates react with the imine (59) preferentially via a pseudo-chair transition state (62), in analogy with the rationalisation offered by Hart[10b] to explain the stereoselectivities

observed in the reaction between (E)-lithium ester enolates and N-trimethylsilyl imines.

In contrast to these observed selectivities, the same authors[18] have shown that the diethylaluminium enolate derived from S-t-butyl-propanethioate (57, R = Me) reacted with the imine (59) in a threo-selective manner forming the trans-β-lactam (63) preferentially, [diastereoisomeric ratio (63):(64), 4:1] (Scheme 18). Utilization of (57, R = Et) also favoured formation of trans-β-lactam (63), [diastereoisomeric ratio (63):(64), 3:1]. Unfortunately, use of the bulkier thioester (57, R = Pr^i) saw a reversion to erythro selectivity, forming the cis-β-lactam (64) preferentially, [diastereoisomeric ratio (63):(64), 1 : 7]. It may be that the diethylaluminium enolates derived from (57, R = Me, Et) react with imine (59) via a pseudo-boat transition state, leading to selective formation of the corresponding threo adduct and, hence, trans-β-lactams (63, R = Me, Et), whereas the diethylaluminium enolate derived from (57, R = Pr^i) reacts via the same transition state depicted for the zirconium enolate case, although no convincing mechanistic rationale is available as yet.

In a similar study[20] utilizing enolisable imines (65), dimethyl-aluminium ester enolates were shown to lead selectively to cis-β-lactams (66) (1.5:1 to 9:1) under identical reaction conditions to the work[18] mentioned above. As this latter study surveys a much wider range of imines and esters, the two examples of trans selectivity cited may be uncharacteristic; the reaction of diethylaluminium enolates with imines may simply proceed via the pseudo-chair transition state already postulated.

$$R^1 = R^2 = H, \text{alkyl}$$
$$R^3 = \text{aryl}, \quad \overset{}{\diagup}\!\!=\!\!\diagdown\!\text{SiMe}_3, \quad \overset{}{\diagup}\!\!\equiv\!\!\text{SiMe}_3$$

Scheme 20

(73)　　　　　　　(74)　　　　　　　(75)

Scheme 21

(76)　　　　　　　(78)　　　　　　　(79)
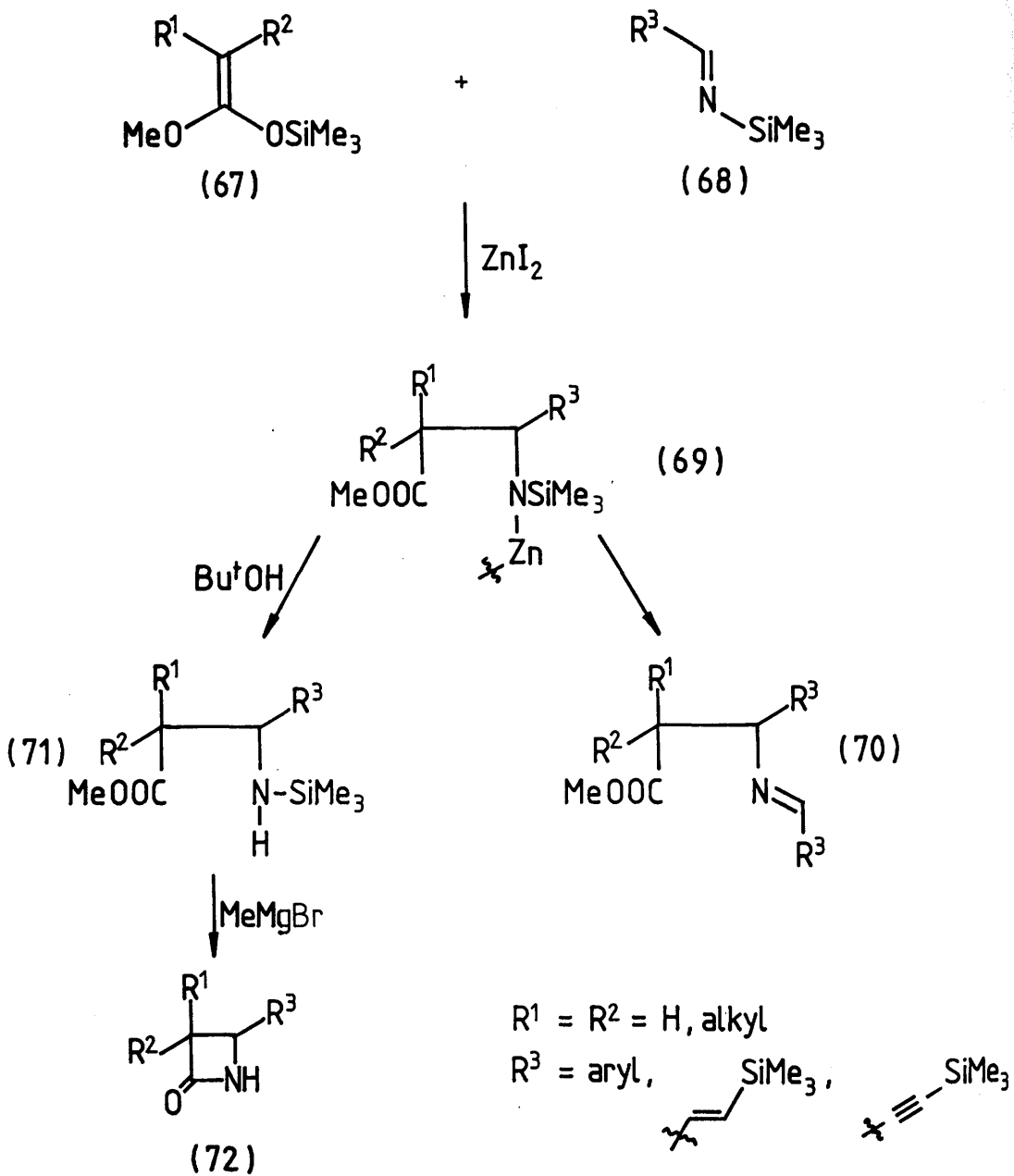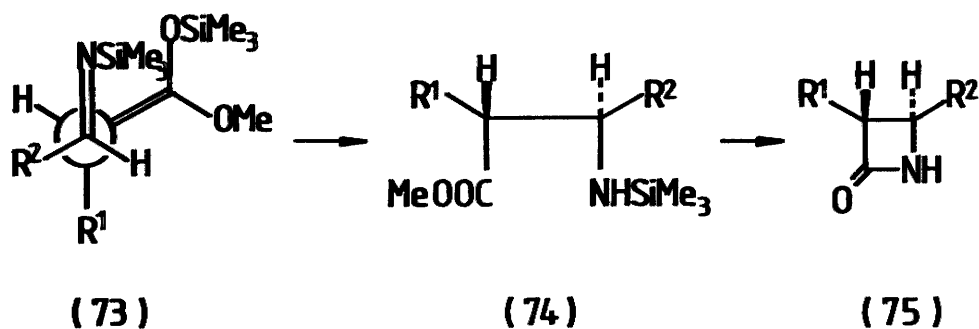
(80)　　　　　　　(81)
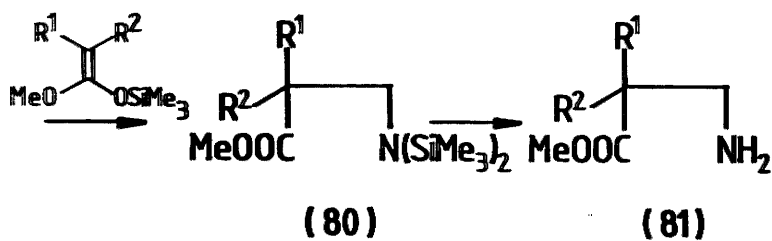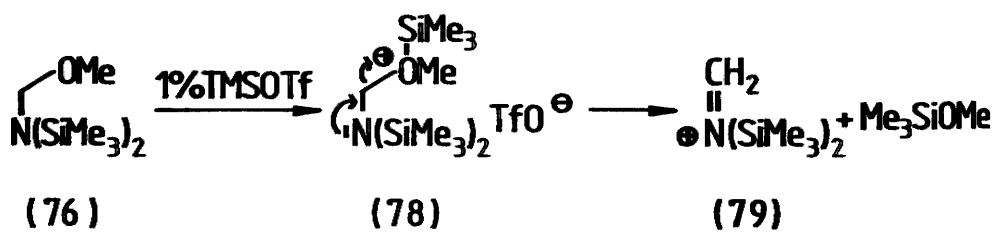
Scheme 22

The ester-imine condensation route to β-lactams has been approached in a conceptually different fashion. Lewis acid activation of an N̲-trimethylsilyl imine followed by nucleophilic attack by a ketene acetal has provided a useful additional entry into the β-lactam system.

Complexation of an N̲-trimethylsilyl imine (68) with ZnI$_2$[21] followed by treatment with a silyl ketene acetal (67), prepared from the corresponding ester by kinetic deprotonation, resulted in formation of the trans-aminated product (70), presumably via reaction of the N̲-metallo β-amino ester (69) with a further equivalent of activated N̲-trimethylsilyl imine (Scheme 20). Addition of t-BuOH to the reaction mixture provided, by cleavage of the nitrogen-zinc bond, the β-amino ester (71), which did not react further. Cyclisation of (71) was achieved by treatment with MeMgBr,[22] to produce a range of β-lactams (72). In situ treatment of the reaction mixture with MeMgBr led to β-lactams (72) directly. Where applicable, the β-lactams (72) were formed in a trans-selective manner, an observation explained by proposing (73) to be the preferred transition state; this leads to the trans-β-lactam (75) via the threo β-amino ester (74) (Scheme 21).

Electrophilic aminomethylation of carbon nucleophiles is an important area in synthetic organic chemistry and has indeed been useful[23] in the synthesis of β-amino esters, precursors of β-lactams (Scheme 22). Treatment of N̲,N-bis(trimethylsilyl)methoxymethylamine (76) with catalytic quantities of TMSOTf (77), furnished the highly reactive iminium species (79) via oxonium ion (78). Generation of (79) in the presence of a silyl ketene acetal led to formation of the N̲,N̲-bis(trimethylsilyl) β-amino ester (80) and thence (81) after desilylation.

$$3 \overset{CH_2}{\underset{NR}{\|}} \quad \longrightarrow \quad \text{(triazine ring)}$$

Scheme 23

(82)　　　(83)　　　(84)　　　(85)
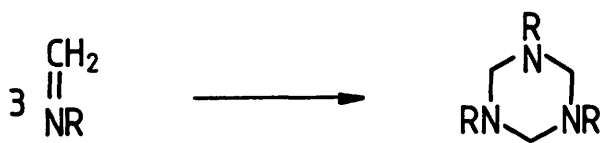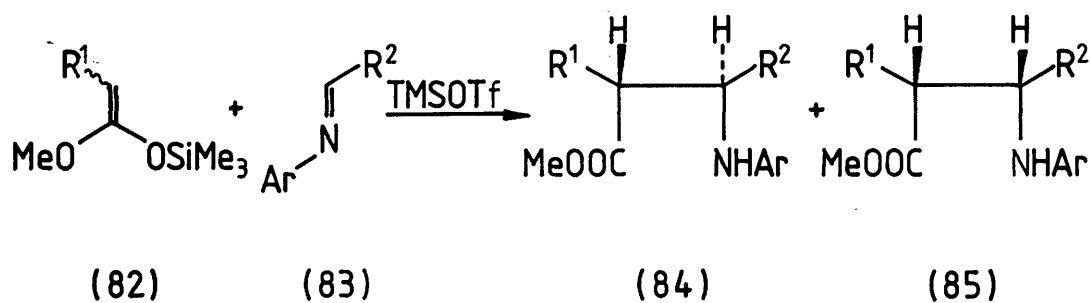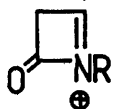
Scheme 24

Figure 4

This route, as well as being truly catalytic with respect to the Lewis acid component, overcomes the problem of triazine formation usually associated with formaldehyde derived imines (Scheme 23) and provides a potential route into the important nocardicin and monobactam families of β-lactam antibiotics.

The first indication of any stereoselectivity involved in the TMSOTf-catalysed reaction between silyl ketene acetals and imines was provided by Guanti[24] and co-workers (Scheme 24). Reaction of a range of non-enolisable N-aryl imines (83) with catalytic quantities of TMSOTf and substituted silyl ketene acetals (82) revealed the selective formation of the threo adduct (84) over the erythro adduct (85) and, in one case (R^1 = Me, R^2 = Ph, Ar = Ph), stereospecific formation of the threo adduct.

The Lewis acid approach using ZnI_2 or TMSOTf, showing diastereoselectivities favouring threo-β-amino ester formation and thence, trans-β-lactams, complements the lithium ester enolate approach, with its inherent selectivity towards erythro-β-amino ester and, thence, cis-β-lactam formation.

The usefulness of 4-acetoxy β-lactams[25] cannot be understated. Nucleophilic substitution reactions can take place at C-4 of the β-lactam ring, via the in situ generated azetidinium ion (Figure 4), allowing introduction of substituents necessary for bicyclic β-lactam formation. The desire to synthesise compounds of this type has uncovered some interesting chemistry. Direct access to N-unsubstituted 4-acetoxy β-lactams has been achieved[26] by treatment of vinyl acetates (86) with

(86)

+

(87)

R¹ = R² = H, Me

aq. NaHCO₃

(88)   (88)

Scheme 25

(90)   (91)   Et₃N   (92)

(90) + (91)

(93)   (95)

(94)   (96)

Scheme 26

R^1 H H Ph $\xrightarrow[\text{or 2) } O_3, Me_2S]{\text{1) KMnO}_4}$ (97) $\xrightarrow{\text{mcpba}}$ (98)

(96)

Scheme 27

R—N—allyl $\xrightarrow{\text{DBU}}$ R—N—

(99) (100)

PhO (101) $\xrightarrow{\text{KMnO}_4}$ PhO (102) $\xrightarrow{\text{mcpba}}$ PhO (103)
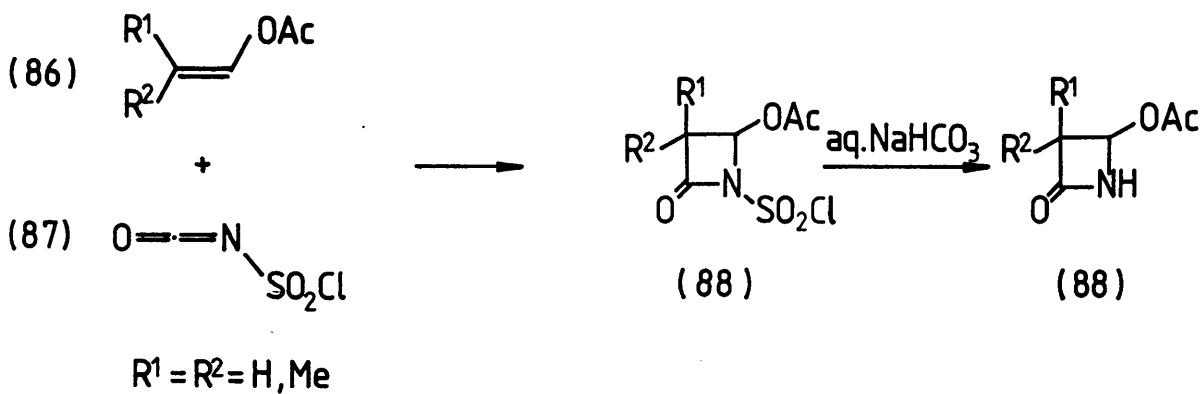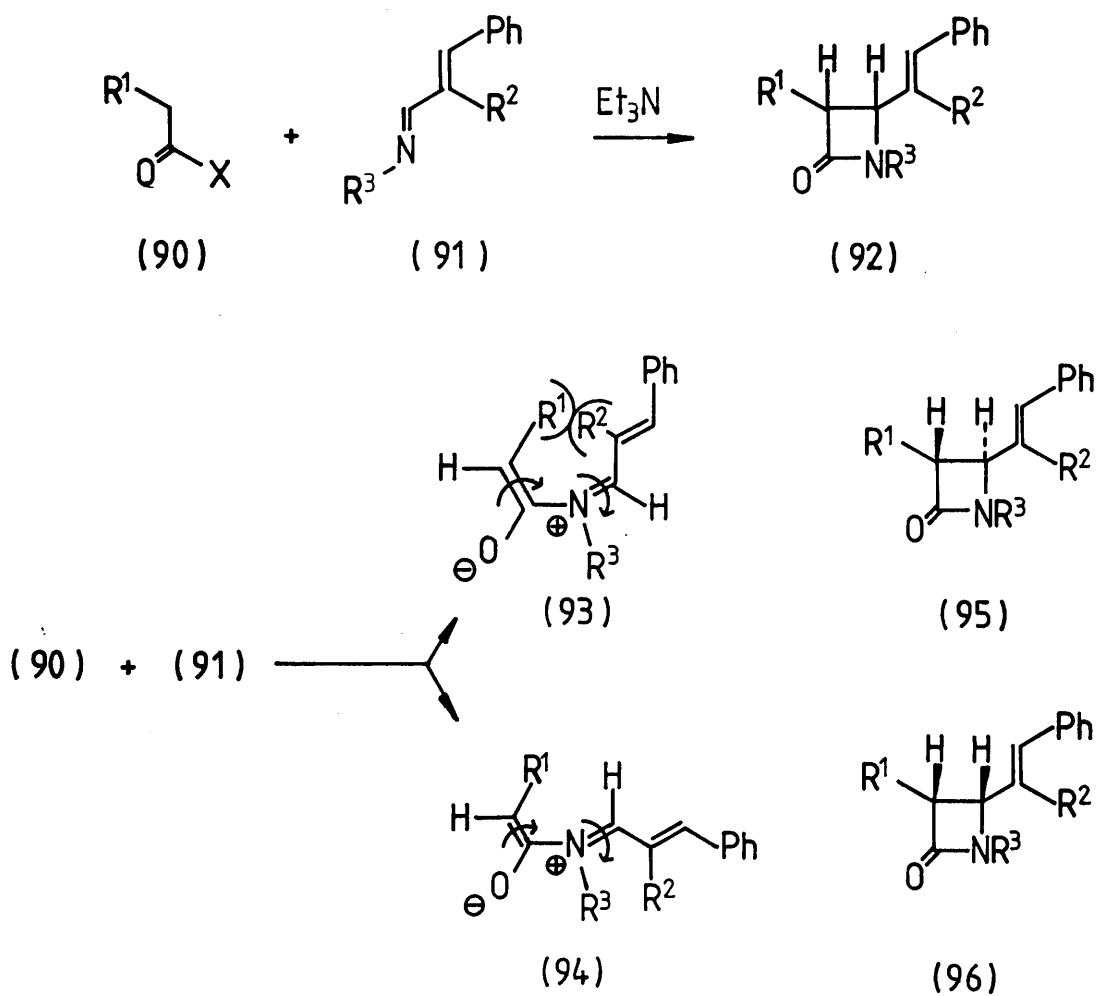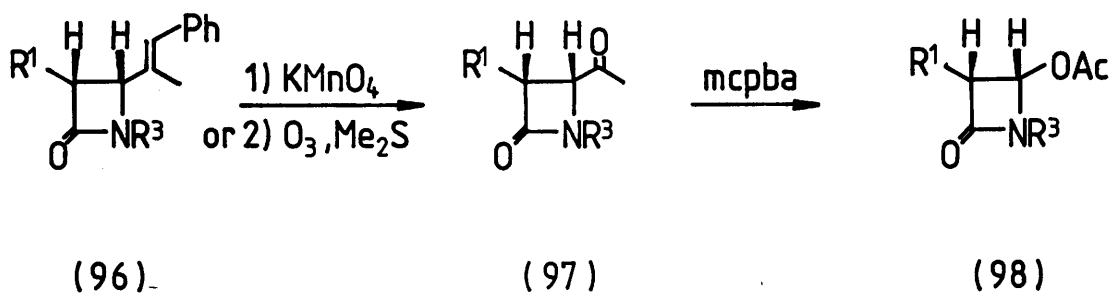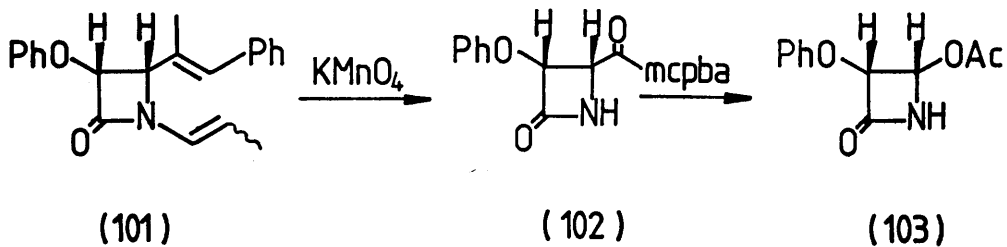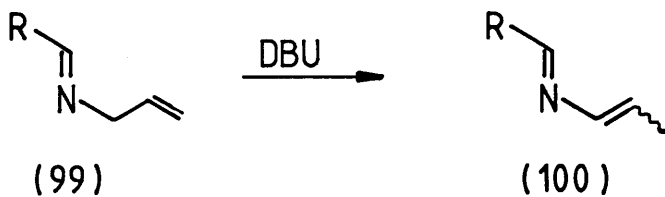
Scheme 28

chlorosulphonyl isocyanate (87), which yielded a range of N-chloro-
sulphonyl β-lactams (88) in good yield (Scheme 25).   Deblocking of the
β-lactam nitrogen was readily achieved, furnishing the N-unsubstituted 4-
acetoxy β-lactams (89).

Subsequent work[27] has involved reaction of an acid halide (90) with
a cinnamylideneamine (91) in the presence of Et_3N which yielded β-lactams
(92) (Scheme 26).   When R^2 = H, stereoselectivities of 1:1 up to 19:1
in favour of the cis-β-lactam (96) were observed.   However, increasing
the bulk of the aldehyde component of the imine, i.e., when R^2 = Me,
resulted in exclusive formation of the cis-β-lactam (96).   This result
can be explained by consideration of the possible mechanism of the
reaction.   It is generally accepted that the acid halide-imine reaction
proceeds through a dipolar intermediate[28] of type (93) and (94), rather than
by a concerted [2+2] addition.   The zwitterions (93) and (94), upon
conrotatory ring closure led to the corresponding trans- and cis-β-lactams
(95) and (96) respectively.   When R^2 = H, (93) and (94) may be formed,
leading to β-lactams (95) and (96), but when R^2 = Me, zwitterion (94)
is greatly favoured as the R^1/R^2 interaction is relieved and therefore
the cis-β-lactam (96) results as the exclusive reaction product.
Standard procedures then allowed access to the valuable 4-acetoxy β-
lactams (Scheme 27).   β-Lactam (96), upon oxidative cleavage using
either $KMnO_4$ or O_3, yielded the methyl ketone (97); Baeyer-Villiger
oxidation then furnished the 4-acetoxy β-lactam (98), with, as expected
retention of stereochemistry at C-4.

A related approach[29] involves 2-aza-1,3-dienes (100), synthesised

Scheme 29

Bz = benzyl
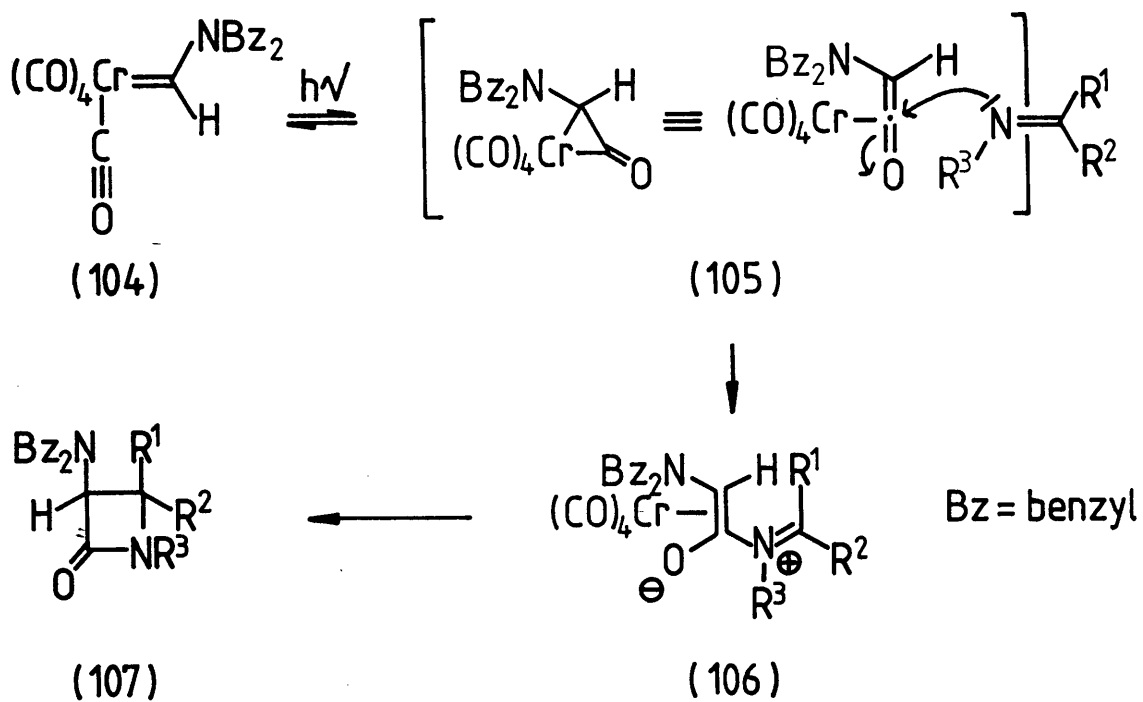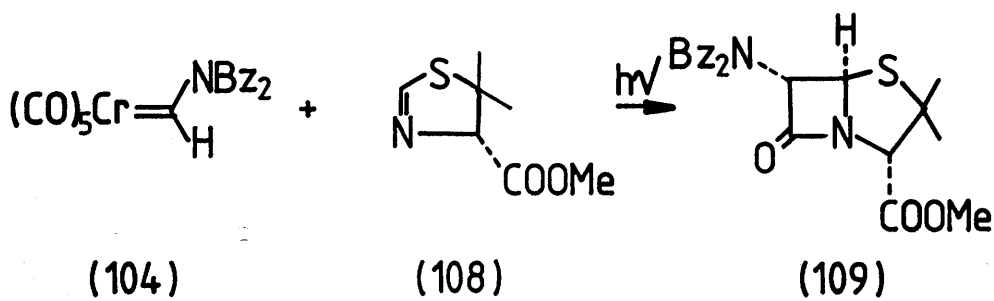
Scheme 30

via DBU-catalysed isomerisation of the N-allyl imines (99) obtained
in turn from the corresponding non-enolisable aldehydes and allyl
amine (Scheme 28).   Utilization of the acid halide-imine route
furnished a range of cis-β-lactams such as (101). $KMnO_4$ oxidation
resulted in a one-pot deprotection-oxidation, yielding methyl ketone
(102), again easily convertible into 4-acetoxy β-lactam (103).

Transition metal chemistry plays a very useful role in the
synthesis of β-lactams.   One approach[30] involves the photolysis of the
chromium(0) species (104)(Scheme 29).   The first step was a photo-
lytically induced insertion of carbon monoxide into the metal-carbon
double bond to produce ketene complex (105).   Nucleophilic attack
by an imine led to the metal-bound zwitterionic species (106), which
underwent a conrotatory ring closure to form the β-lactam (107).   The
stereochemical outcome of the photolytic reaction of imines with
chromium-aminocarbene complexes exactly parallels that found with free
ketenes, that is it is very highly cis-selective.   This is best
illustrated by the case of the chiral thiazoline (108) which reacted
with carbene complex (104) to form penam (109) in 93% chemical yield,
with an enantiomeric excess (ee) of greater than 98% (Scheme 30).   The
free-ketene approach yielded penam (109) with the same enantioselectivity,
but only in 6-13% chemical yield.[31]   The improved chemical yield is
due to the absence in the chromium-carbene approach of free ketenes, the
existence of which can lead to considerable by-product formation.

R = CH$_2$SO$_2$N(Pr^i)$_2$

(110)

1) LDA

2)

(112)

CAN →

(113) R = H
(114) R = SiMe$_2$Bu^t

(115) R = CHO
(116) R = COOH

(117)

(118) →

(119)

(120)

(118) = ![structure with OSiMe$_2$Bu^t, COOPNB, N$_2$]

(121)

Scheme 31

TiCl₄

Ph
NPh

(122)

(123)

(124)

Scheme 32

(125)

(126)

(127)

(128)

DIKETENE

DAM = di-p-anisylmethyl   (129)

(130)
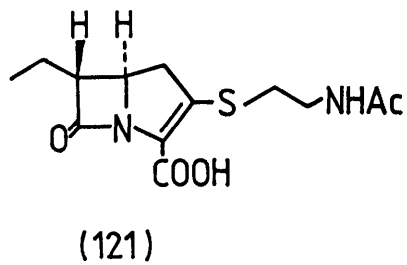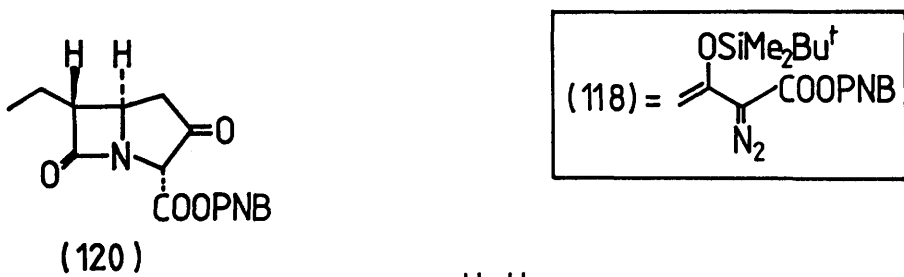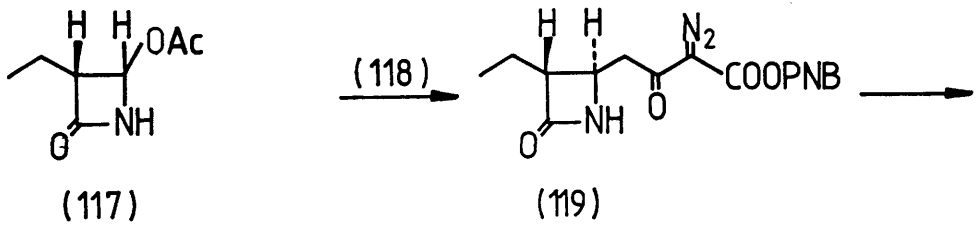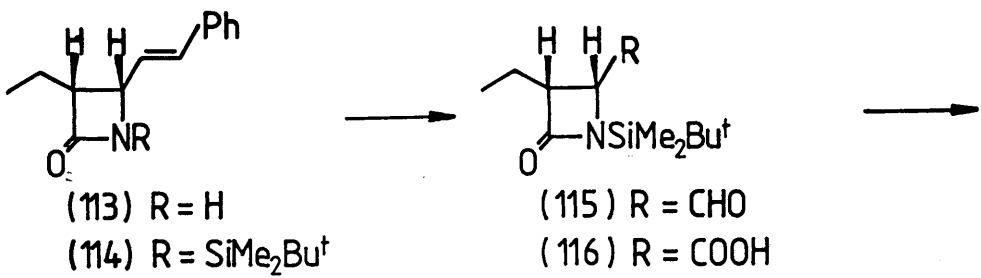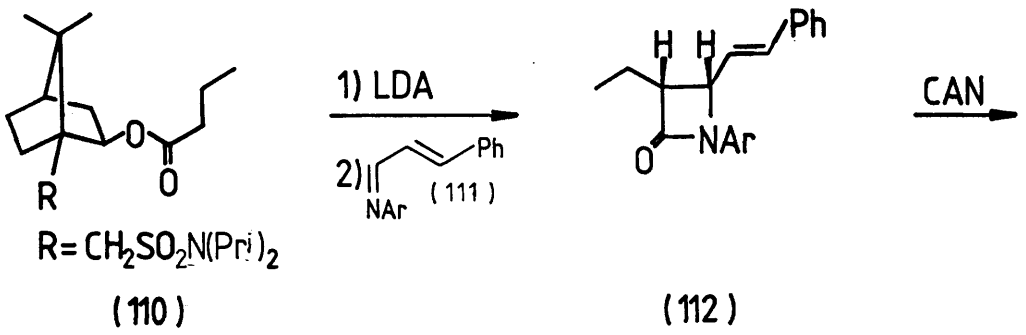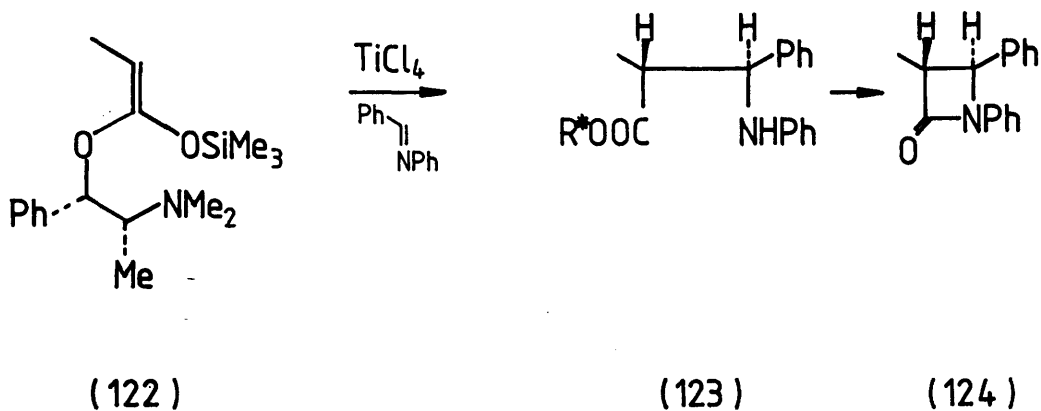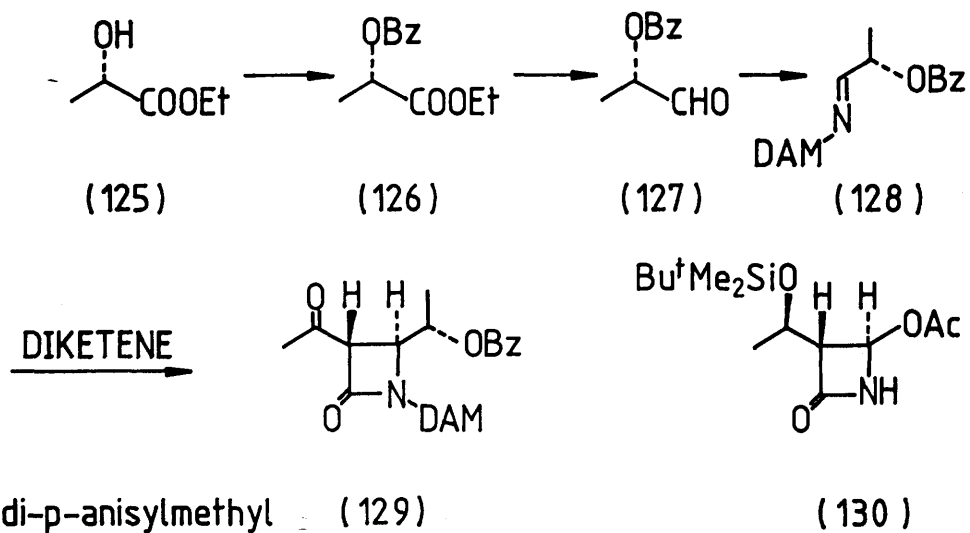
Scheme 33

3.2 Chiral Synthesis

The ester-imine condensation route has been shown to be an effective method for the preparation of β-lactams. Attempts to induce enantioselectivity during the C-3/C-4 bond formation step using menthyl esters[9,32] in this process have not been particularly successful. However, using the isoborneol derived butyrate (110), Hart[33] has achieved a high degree of asymmetric induction (Scheme 31). Thus, treatment of the lithium ester enolate of (110) with N-aryl cinnamaldimine (111) led to formation of cis-β-lactam (112) in 81% chemical yield and with 92%ee. A formal synthesis of carbapenem antibiotic (+)-PS-5 (121) resulted from this approach. Deprotection of N-aryl β-lactam (112), gave β-lactam (113), which was protected as the t-butyldimethylsilyl derivative (114). Ozonolysis of (114) gave the aldehyde (115), with Jones oxidation affording cis-β-lactam (116). Lead tetraacetate oxidative decarboxylation led to 4-acetoxy β-lactam (117) as a 2:1 mixture of trans and cis diastereoisomers. Treatment of this mixture with the silyl enol ether (118) furnished solely the trans-β-lactam (119), which was converted into the known[34] (+)-PS-5 precursor (120) by $Rh_2(OAc)_4$ catalysis, a protocol discussed earlier.

Asymmetric induction has also been achieved[35] in a similar manner by incorporation of chirality into the ester component of the ester-imine condensation route (Scheme 32). Treatment of the silyl ketene acetal (122) from (1S,2R)-N,N-dimethyl ephedrine-O-propanoate with benzylidene aniline in the presence of excess $TiCl_4$ yielded the threo-β-amino ester (123) as the major product, together with traces of two of the three other possible stereoisomers. Treatment of the crude reaction mixture

(131)   (132)   (133)
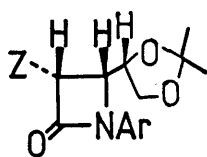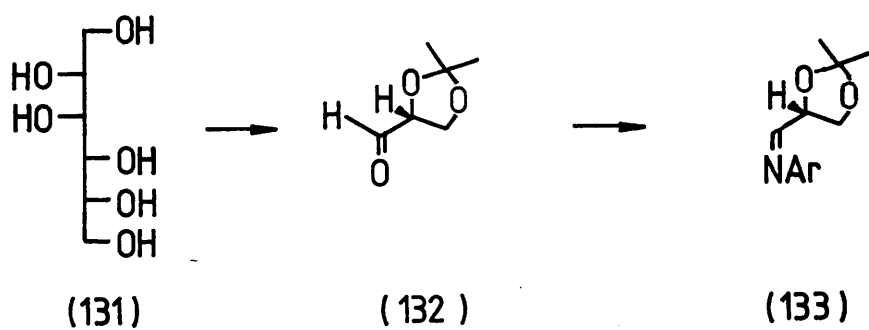
(134)

Z = N₃, OMe, OPh, OAc

Scheme 34

(135)   (136)   (137)

Bu^tMgCl

(138)   (139)
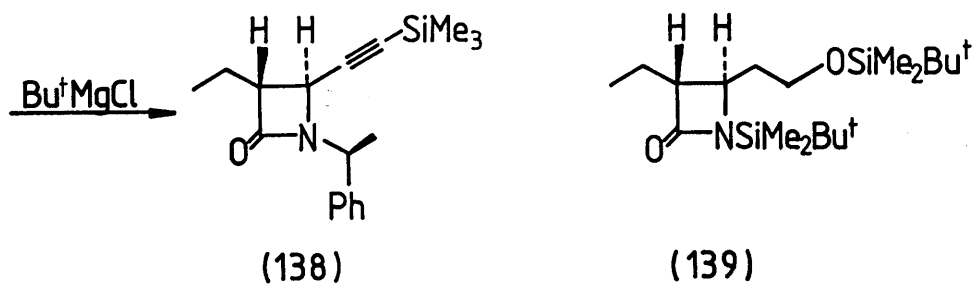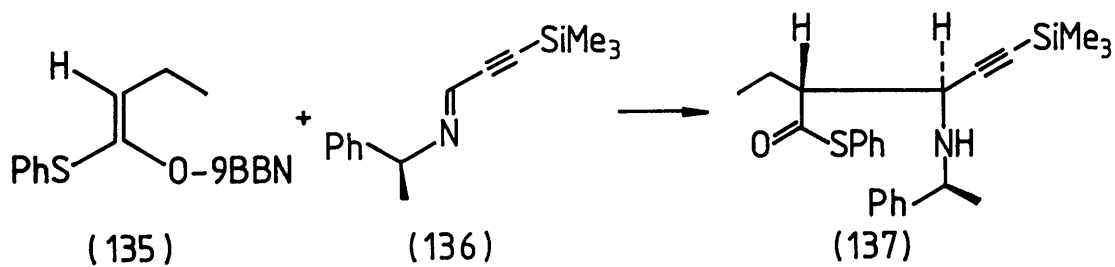
Scheme 35

with lithium hexamethyldisilazide in THF produced, after purification,
the trans-β-lactam (124) in 79% chemical yield and with 95%ee.

Asymmetric induction via chiral imine components has provided a
valuable source of chiral β-lactams of recognised utility in the field
of carbapenem synthesis.   Ethyl (S)-lactate (125) has been converted[36]
into the chiral imine (128)(Scheme 33).   Protection of (125) as the
benzyl ether (126), reduction to the aldehyde (127) and treatment with
di-p-anisylmethylamine yielded the chiral imine (128).   Treatment of
(128) with diketene in the presence of imidazole produced trans-β-lactam
(129) in high yield and with 96%ee.   Thienamycin precursor (130)[37] could
be readily synthesised from (129), firstly by stereoselective reduction
and protection of the C-3 methyl ketone substituent, secondly by deprotection
and oxidation of the C-4 hydroxyethyl substituent and finally by oxidative
deblocking of the β-lactam nitrogen atom.

Treatment of chiral aldehyde (132), derived from D-mannitol (131)
with an aromatic amine led[38] to chiral imine (133)(Scheme 34).   Utilization
of the acid halide-base procedure led to a range of β-lactams (134) as
the sole reaction products, with the requisite functionality present for
further synthetic elaboration.

In another approach[39] to the antibiotic (+)-PS-5 (121), the imine
(136), derived from 3-trimethylsilyl propynal and (S)-(α-methyl)benzyl-
amine, was added to the boron enolate (135), prepared from S-phenyl
butanethioate, which led to formation of the threo-β-amino ester (137),
which was cyclised using Bu^{t}MgCl to the trans-β-lactam (138), in 68%
overall yield and with 95%ee (Scheme 35).   β-Lactam (138) was then
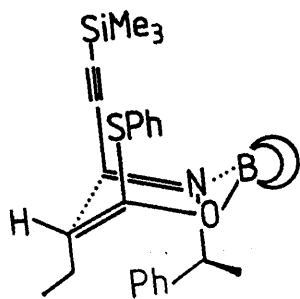
(140)
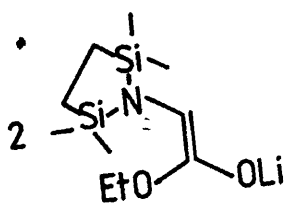
(141)
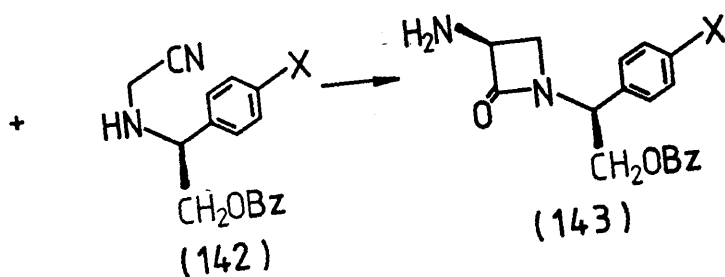
(142)

(143)
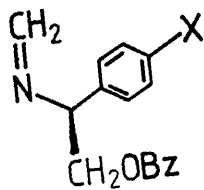
(144)

Scheme 36
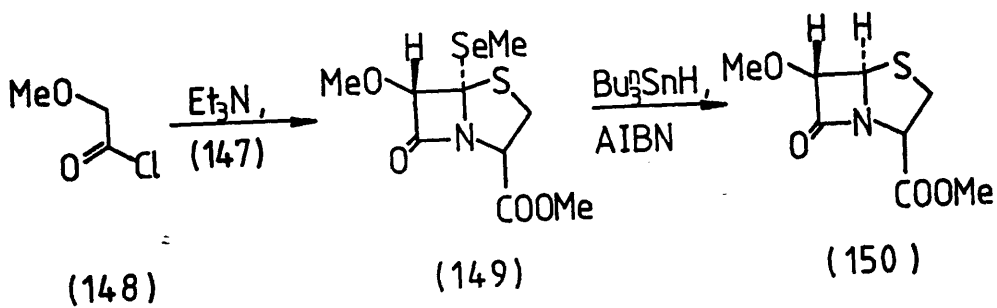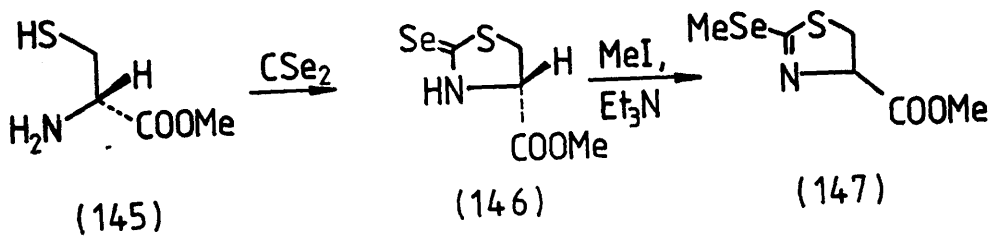
Scheme 37
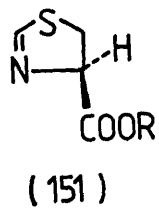
converted into the disilyl β-lactam (139), a known[34] intermediate in the

synthesis of (+)-PS-5 (121).   The extremely high level of asymmetric

induction in this reaction may be due to both the α-methyl benzyl moiety

and the ethynyl moiety assuming axial orientations in the preferred

cyclic chair-like transition state (140).

Synthesis of the monocyclic 4-unsubstituted β-lactams; the

nocardicins and the monobactams, has been hampered due to the inaccess-

ibility of monomeric formaldehyde imines.   An elegant approach that

both overcomes this problem and displays chiral induction has recently

been described[40] (Scheme 36).   Reaction of the chiral N-(cyanomethyl)

amine (142) with two equivalents of the lithium enolate of the silyl

protected glycine ester (141) yielded, by in situ formation of the

formaldehyde imine (144) the (S),(S)-β-lactam (143) in 65% yield and

with 95%ee, possessing the configuration at C-3 present in the nocardicin

and monobactam families of β-lactam antibiotics.

Although chiral acyclic imines may be used in the ester-imine

condensation route, yielding products with excellent enantiomeric excess,

chiral cyclic imines offer the possibility of asymmetric synthesis of

bicyclic β-lactams directly in a one-pot procedure.   Treatment[41] of

D-cysteine methyl ester (145) with carbon diselenide furnished (146) which,

upon reaction with MeI and Et_3N, yielded the 2-(methylseleno)thiazoline

(147) (Scheme 37).   Unfortunately, during the course of the methylation

reaction, considerable epimerisation took place, producing thiazoline

(147) with only 50%ee.   Reaction of thiazoline (147) with methoxy

acetyl chloride (148) in the presence of Et_3N resulted in formation of the

$$[\{(MeO)_3P\}(Cp)(OC)Fe=C=CMe_2]^{\oplus} \; TfO^{\ominus} \quad + \quad$$

(152)

(153)

(154)
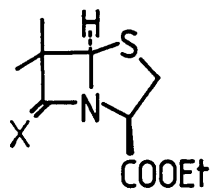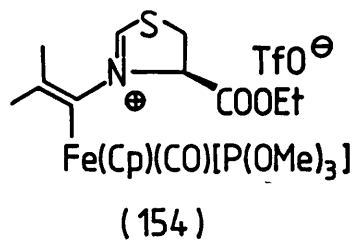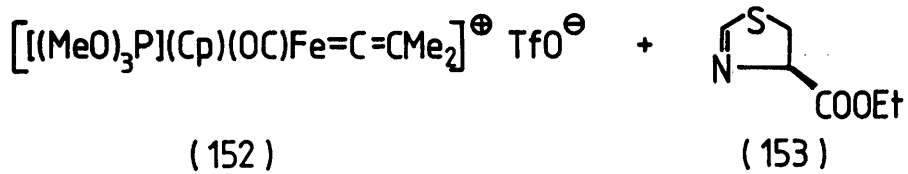
(155) X = Fe$^{\oplus}$(Cp)(CO)[P(OMe)$_3$] TfO$^{\ominus}$

(156) X = O

Scheme 38

1) nBuLi,

2) (acetaldehyde) O with H

3) NaH, MeI

(157)

2PhCH₂NHLi, MeI

(158)

Br₂
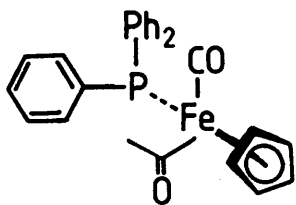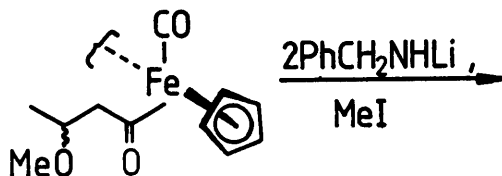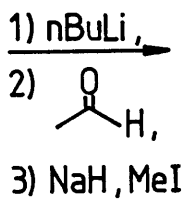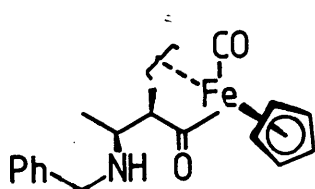
(159)
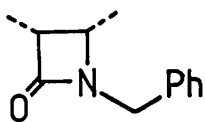
(160)
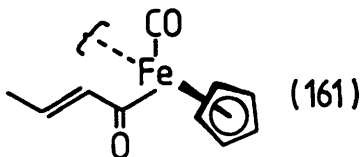
(161)

Scheme 39

penam (149) with the same enantiomeric excess as was present in the

starting imine.   Reductive deselenylation of (149) with nBu$_3$SnH in the

presence of AIBN proceeded in a highly stereoselective manner, furnishing

bicyclic β-lactam (150) in 83% yield.   Although this method does possess

drawbacks associated with loss of optical purity during the thiazoline

formation reaction, its major advantage is incorporation of the methylseleno

substituent into the imine moiety, greatly enhancing the efficiency of

the subsequent ketene-imine addition reaction.   2-Unsubstituted thiazolines

(151) have been known[42] for a considerable time, but their reactions under

the above conditions have been clouded by very poor chemical yields (<10%).

In a novel approach,[43] chiral thiazoline (153) has proved useful

for the construction of chiral bicyclic penams (Scheme 38).   Cationic

iron vinylidene (152), upon treatment with chiral imine (153) produced

the acyclic adduct (154) which cyclised upon standing or, more efficiently

by brief reflux in 1,2-dichloroethane, to give the azetidinylidene complex

(155) with reasonable (76%ee) selectivity.   Oxidation of (155) with

iodosobenzene in ethanol gave penam (156).

The highest reported[44] level of diastereoselection in the formation

of β-lactams arose from utilization of the optically pure (S)-(+)-acetyl

complex (157) (Scheme 39).   Treatment of (157) successively with nBuLi

and acetaldehyde, and then NaH and MeI, gave an essentially 1:1 diastereo-

isomeric mixture of the corresponding β-methoxy complexes (158).

Treatment of this mixture of complexes (158) with two equivalents of

lithium benzylamide and then MeI gave the 3-amino-2,3-dimethyl complex

(159) in a diastereoisomeric ratio of greater than 100:1:1:1.   The

formation of (159) is consistent with the tandem Michael addition –

(R)-(162)   (163)   (165)

(166)   (167)

(130)

(164) =

(168)
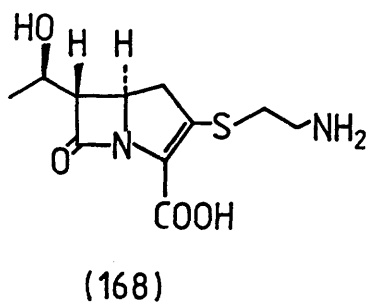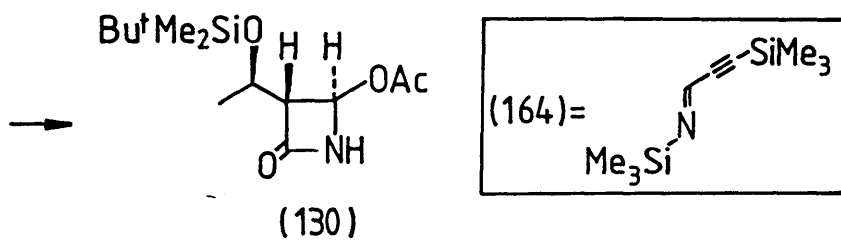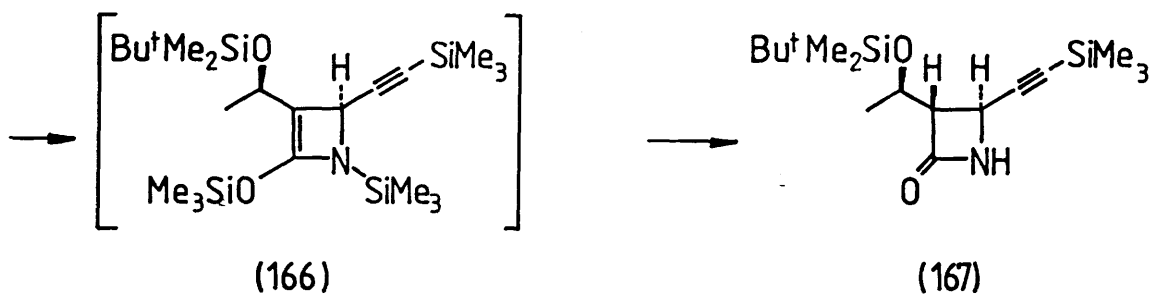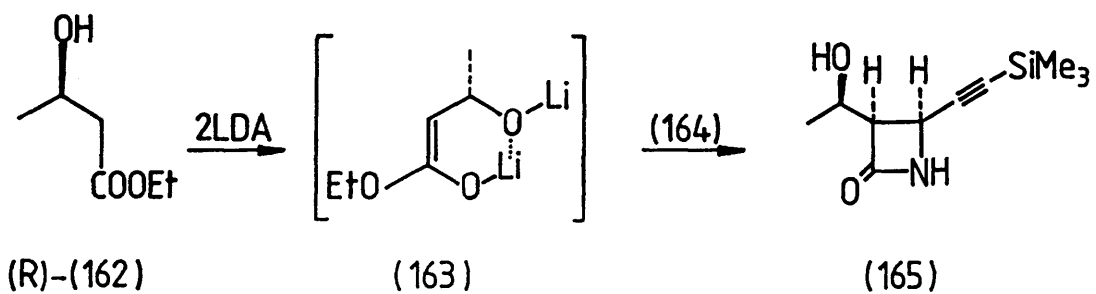
Scheme 40

methylation occurring on the (E)-crotonyl complex (161) from the unhindered face.   Complex (161) is presumably generated in situ by lithium benzylamide induced elimination of methanol.   Without purification, complex (159) was oxidatively decomplexed with bromine to give the cis-β-lactam (160).   As no trace of the thermodynamically more stable trans isomer could be detected, the β-lactam (160) has an optical purity of greater than 100:1.   The excellent stereocontrol exerted by the iron-acyl complex (157), coupled with the incorporation of substituents allowing further synthetic elaboration, make this approach possibly one of the most promising for future syntheses of useful chiral β-lactams.

Thienamycin (168), discovered in 1976, is a novel β-lactam antibiotic isolated from *Streptomyces cattleya*.[45]   It possesses exceptional potency and a wide spectrum of antibacterial activity, as well as good stability against β-lactamases.   Its synthesis has inspired, more than any other single compound, intense utilization of chiral variants of the ester-imine condensation route to β-lactam synthesis.[46]

Optically pure 3-hydroxy butyrates (162) are attractive ester components because of the potential of direct introduction of the 1-(hydroxy ethyl) substituent at C-3 of the β-lactam unit, necessary for thienamycin (168).   As shown by Chiba,[46a,46d] treatment of the di-lithium salt (163) of (R)-3-hydroxy butyrate (162) with the N-trimethyl-silyl propynaldimine (164) yielded the N-unsubstituted β-lactam (165) as the major product, possessing the incorrect configuration at C-3 required for thienamycin (168)(Scheme 40).   Selective O-silylation of β-lactam

OH
|
CH₃—CH—CH₂—COOEt

(S)-(162)

1) 2LDA

2)
NAr
(111)
with Ph

→

HO H   H
        Ph
      NAr
  O

(169)

→

RO H   H
        Ph
      NAr
  O

(170) R = H
(171) R = SiMe₂Buᵗ

→

Buᵗ Me₂SiO H   H
              R
            NAr
        O

(172) R = CHO
(173) R = COOH
(174) R = OAc

→

Buᵗ Me₂SiO H   H
              OAc
            NH
        O

(130)
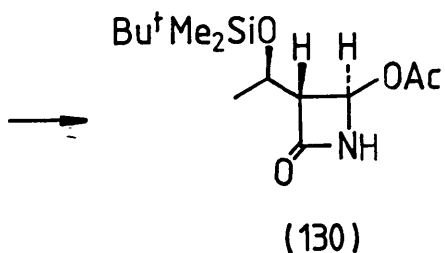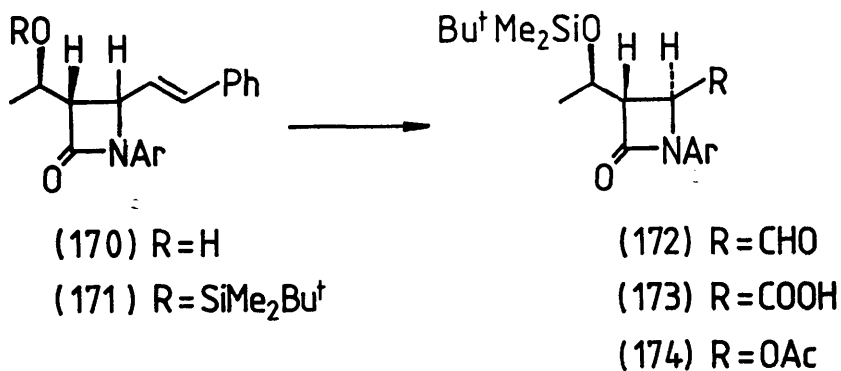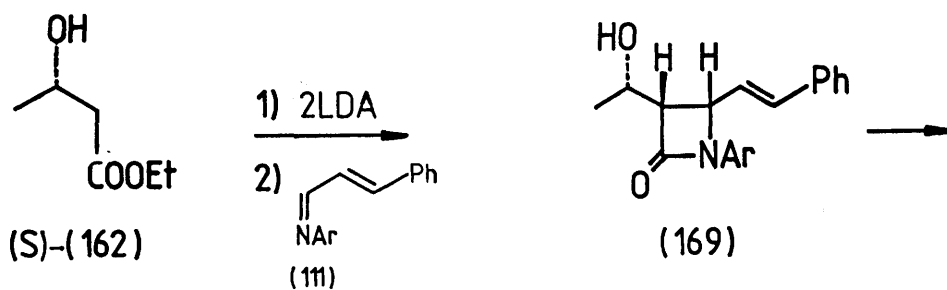
Scheme 41

(169) R = OH

(175) R =

(176)
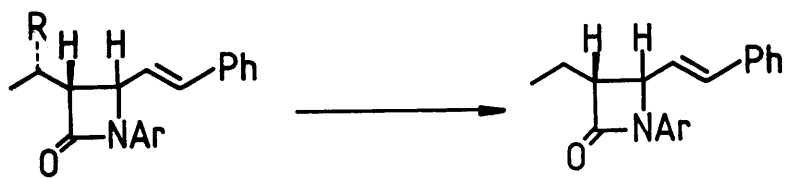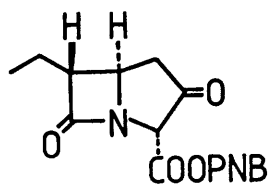
(120)
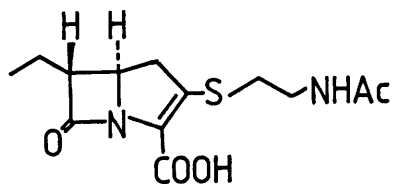
(121)

Scheme 42

(165) and further disilylation with two equivalents of TMSOTf in the

presence of Et$_3$N led, after hydrolysis, to the trans-β-lactam (167),

via the silyl enol ether (166).   Hydration of (167) followed by

Baeyer-Villiger oxidation furnished the 4-acetoxy β-lactam (130), a

known[36] precursor of thienamycin (168), in extremely high optical purity.

In a complementary fashion,[47] treatment of (S)-3-hydroxy butyrate

(162) with two equivalents of LDA followed by N-aryl imine (111) gave a

1:1 mixture of trans- and cis-β-lactam (169)(Scheme 41).   Mitsunobu

inversion cleanly gave the inverted (R)-(hydroxyethyl)β-lactam (170)

which was protected as the t-butyldimethylsilyl ether (171).   Treatment

of (171) with osmium tetraoxide in the presence of sodium periodate

yielded aldehyde (172) as a single trans isomer.   KMnO$_4$ oxidation to

the trans-acid (173), followed by oxidative decarboxylation produced the

trans-4-acetoxy β-lactam (174), leading to the known[37] precursor (130)

of thienamycin (168), after oxidative dearylation of (174).

The same authors[46e] have used the asymmetric induction induced by

(S)-(169) in a formal synthesis of β-lactam antibiotic (+)-PS-5 (121)

(Scheme 42).   Thioimidazolide (175) was prepared from a 1:1 cis and trans-

mixture of β-lactam (169) and thiocarbonyldiimidazole.   Reduction of

(175) with sodium borohydride in DMSO gave clean conversion to the

desired 3-ethyl β-lactam (176) which was readily converted into carbapenam

(120), a known[34] precursor of (+)-PS-5 (121).

Thus, optically pure 3-hydroxy butyrates have been shown to be of

great utility in the construction of important carbapenam precursors after

either, in the case of (R)-hydroxy butyrates, correction of the C-3

stereochemistry or, in the case of (S)-hydroxy butyrates, Mitsunobu
inversion of the hydroxyl stereochemistry.

Chiral 3-hydroxy butyrates have also been shown to be of use in
the synthesis of the valuable 1β-methyl carbapenems[48] which exhibit the
normal properties of this class of antibiotic, as well as high resistance
to renal dipeptidase-I,[49] enhancing their usefulness as therapeutic agents.

4. Conclusions.

Monocyclic β-lactams have proved to be essential structural
building blocks from which known and novel bicyclic β-lactam antibiotics
can be constructed. The wide range of approaches available, via the
formal [2+2] cycloaddition protocol, coupled with the opportunities for
incorporation of asymmetry, will ensure that the synthesis of monocyclic
β-lactams will continue to play a pivotal role in the synthesis of β-lactam
antibiotics.
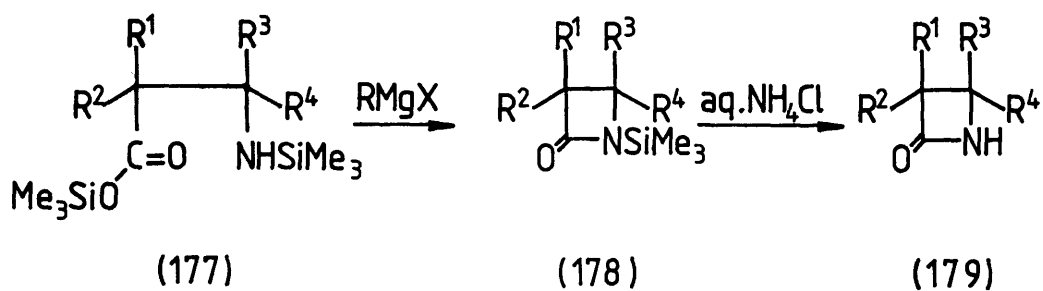
Scheme 43
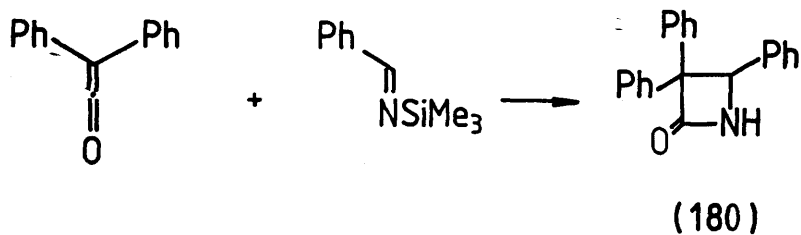
Scheme 44
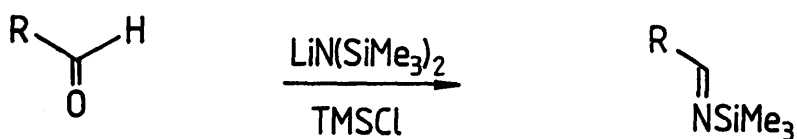
$R = Ph$
$= 2-furyl$
$= PhCH=CH$
$= PhC\equiv C$
$= Me_3SiC\equiv C$
$= Me_3SiCH=CH$

Scheme 45

DISCUSSION

Monocyclic β-lactams play a pivotal role in the synthesis of fused bicyclic β-lactam antibiotics. For this reason, synthetic routes towards monocyclic β-lactams that are both efficient and high yielding must be continually sought. These routes must also be able to facilitate the incorporation into the β-lactam ring of functionality suitable for further synthetic elaboration.

As has been discussed, the most efficient syntheses of bicyclic systems from monocyclic β-lactams requires either chain extension or ring closure at nitrogen. As a result, the synthesis of N-unsubstituted β-lactams becomes a desirable goal.

It has been reported[22] that the N-trimethylsilyl β-lactams (178), obtained by Grignard-induced cyclisation of N-trimethylsilyl esters (177), undergo extremely facile protio-desilylation to yield the corresponding N-unsubstituted β-lactams (179) (Scheme 43). As no formal deprotection step is required, development of a general route to N-trimethylsilyl β-lactams would constitute an essentially direct synthesis of N-unsubstituted β-lactams.

The most flexible routes to monocyclic β-lactams involve the formal [2+2] cycloaddition of a ketene or a ketene equivalent with an imine. In 1977, the first[50] instance of the use of an N-trimethylsilyl imine in this approach was reported (Scheme 44). Treatment of N-trimethylsilyl benzaldimine with diphenyl ketene at elevated temperature led, after work-up, to the N-unsubstituted β-lactam (180), albeit in only 12% yield.

R–CHO (R attached to CHO, with H below) $\xrightarrow{\text{LiN(SiMe}_3)_2}$ $\underset{H}{\overset{R}{\text{C}}}(\text{O}^{\ominus})-\text{N(SiMe}_3)_2 \longrightarrow$

$\underset{H}{\overset{R}{\text{C}}}(\text{OSiMe}_3)-\overset{\ominus}{\underset{\text{SiMe}_3}{N}}$ $\xrightarrow{0°C}$ $\underset{H}{\overset{R}{\text{C}}}=N-\text{SiMe}_3$

Scheme 46

$\underset{NH_2}{\overset{R}{\text{CH}_2}}$ $\xrightarrow[\text{Et}_3\text{N, DMAP}]{\text{Bu}^t\text{Me}_2\text{SiCl,}}$ $\underset{NHSiMe_2Bu^t}{\overset{R}{\text{CH}_2}}$ $\xrightarrow{\text{Bu}^t\text{OCl}}$ $\underset{\underset{\text{Cl}}{\overset{}{}}\text{N}\diagdown\text{SiMe}_2\text{Bu}^t}{\overset{R}{\text{CH}_2}}$

$\xrightarrow{\text{DBU}}$ $\underset{\underset{\text{SiMe}_2\text{Bu}^t}{N}}{\overset{R}{\text{CH}}}=$ (181a) R = Ph
         (182) R = 2 – furyl
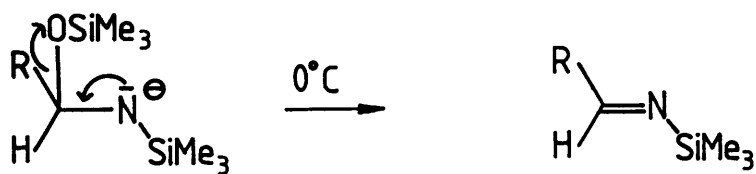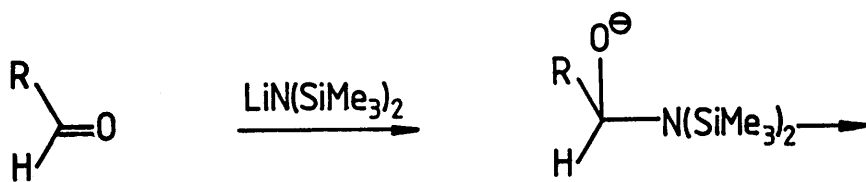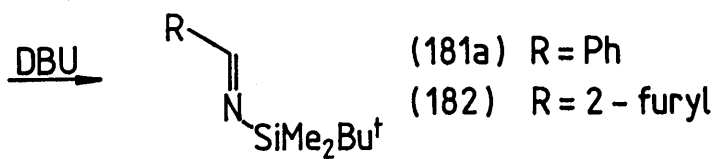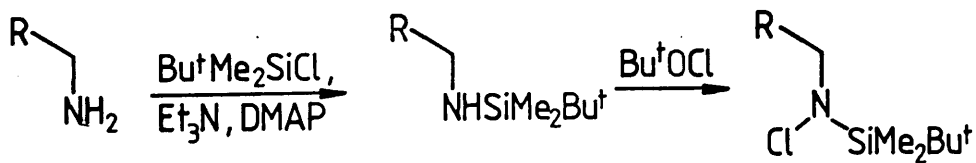
Scheme 47

A very limited number of N-trimethylsilyl imines, particularly

those derived from diaryl ketones,[51] has been known for some time.[52]

In a recent study[21] on the synthesis of N-unsubstituted β-lactams, a

range of N-trimethylsilyl imines was prepared by a modification of the

older procedures.   In detail, treatment of a solution of lithium

hexamethyldisilazide in THF at 0°C with one equivalent of a non-

enolisable aldehyde followed by one equivalent of chlorotrimethylsilane,

and non-aqueous isolation and distillation gave a range of N-trimethylsilyl

imines in good yield (Scheme 45).

The probable mechanism for this reaction involves a heteroatom variant

of Peterson Olefination[53] (Scheme 46).   N → O silyl migration followed

by elimination of trimethylsilanoxide ion at 0°C will yield the N-trimethyl-

silyl imine.

These N-trimethylsilyl imines were utilized[21] in a ZnI_2-mediated

reaction with O-trimethylsilyl ketene acetals, yielding, after treatment

in situ of the intermediate N-silyl β-amino esters with MeMgBr, a range

of N-unsubstituted β-lactams, as previously discussed (p.11).

It was against this background that a detailed study of the

preparation of functionalised monocyclic β-lactams was undertaken.

1. The ZnI_2-Mediated Reactions of N-t-Butyldimethylsilyl Imines and

   O-Trimethylsilyl Ketene Acetals.

The apparent[54] requirement that N-trimethylsilyl imines be

synthesised from non-enolisable aldehydes makes alternative routes to

N-silyl imines desirable.   One such route involves[55] the synthesis of

N-t-butyldimethylsilyl imines from the corresponding primary amines.

Ph
$\diagdown$
$\parallel$
N
$\diagdown$SiMe$_2$Bu^t

(181a)

+

MeO—C(=CH$_2$...)—OSiMe$_3$

(183)

$\xrightarrow{\text{ZnI}_2}$

MeOOC—CH(CH$_3$)—CH(Ph)—NHSiMe$_2$Bu^t

(184)

Scheme 48

furan—CH=N—SiMe$_2$Bu^t

(185a)

CH$_2$=CH—CH=N—SiMe$_2$Bu^t

(186)

MeO—C(=C(CH$_3$)$_2$)—OSiMe$_3$

(187)

MeO—C(=CHCH$_3$)—OSiMe$_3$

(183)
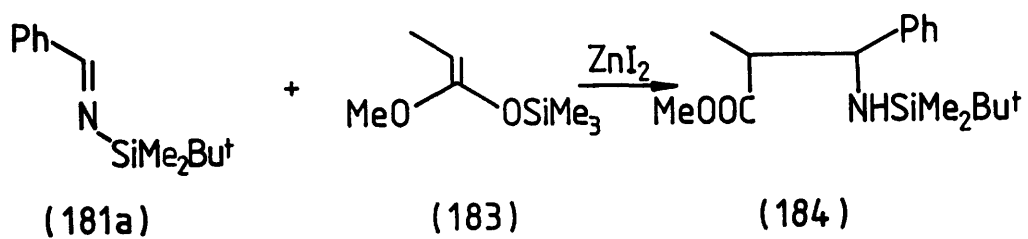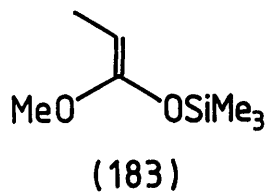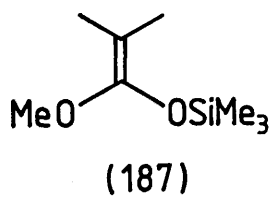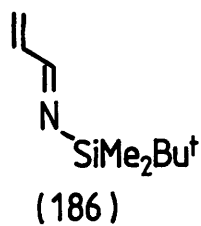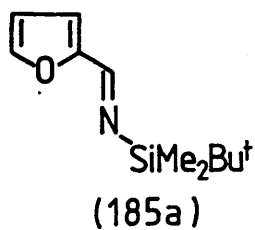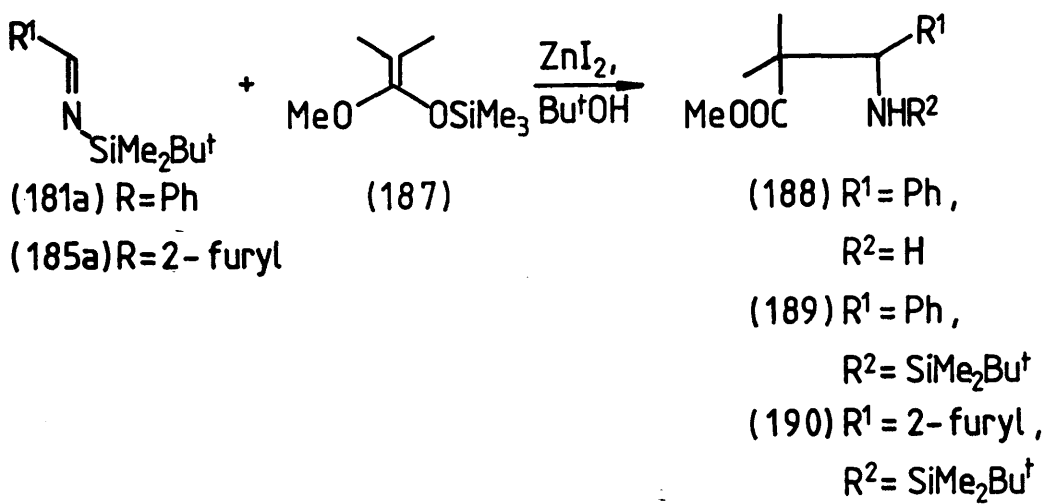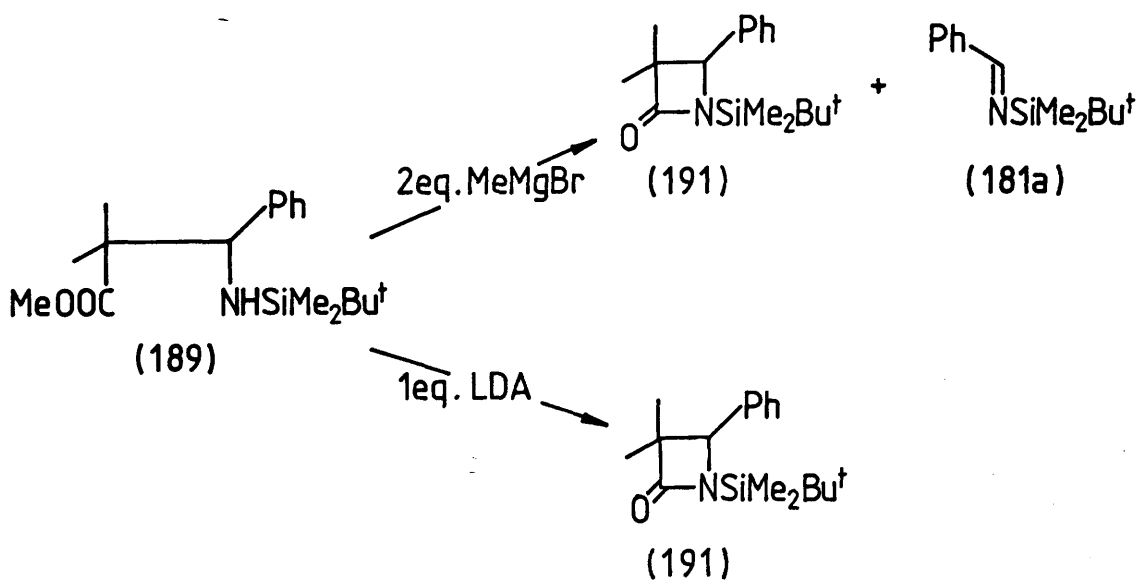
Scheme 49

Scheme 50

In practice (Scheme 47) the starting primary amine was converted into

its N-t-butyldimethylsilyl derivative, which on reaction with t-butyl

hypochlorite gave the N-chloro-N-silyl species.   This, on elimination

of HCl using DBU as base, produced the desired N-t-butyldimethylsilyl

imines (181a) and (182) in high yield.   At the commencement of this

study only one reaction of an N-t-butyldimethylsilyl imine had been

reported[55a] (Scheme 48).   Complexation of (181a) with ZnI_2 and addition

of silyl ketene acetal (183) yielded the N-t-butyldimethylsilyl β-amino

ester (184) in a threo selective manner (diastereoisomeric ratio threo :

erythro, 1.9 : 1).

N-t-butyldimethylsilyl imines are of greater potential value than

their N-trimethylsilyl analogues as the silyl group is much more

resistant to hydrolytic cleavage, and it should survive the conditions of

the ZnI_2 - mediated approach to monocyclic β-lactam synthesis.   In order

to ascertain the usefulness of N-t-butyldimethylsilyl imines, (185a) and

(186) were prepared, by the procedure discussed above, from furfurylamine

and allylamine, in 70% and 98% overall yield, respectively.

O-Trimethylsilyl ketene acetal (187) was prepared using a literature

procedure,[56] by deprotonation with LDA followed by O-silylation.   In a

similar manner,[13b,56] deprotonation of methyl propanoate at low temperature

led to selective formation of the (Z)-enolate [(Z):(E), 95:5] and thence

the (E)-ketene acetal (183).

As a measure of the usefulness of N-t-butyldimethylsilyl imines,

imines (181a) and (185a) were examined in the context of the ZnI_2-

mediated approach to β-lactam synthesis (Scheme 49).   Using a modification

of known procedures,[21,55] ZnI_2 was stirred in Et_2O at ambient temperature
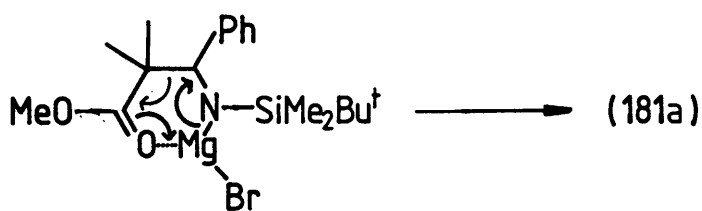
Scheme 51
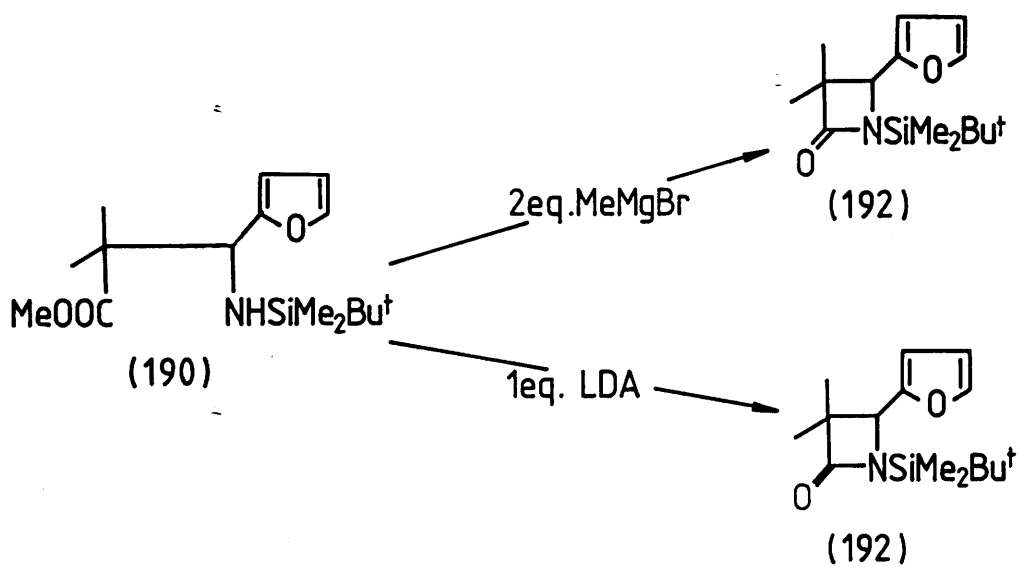
Scheme 52

until a homogeneous, pale-grey solution was formed. N-t-Butyldimethyl-

silyl benzaldimine (181a) was added, resulting in immediate formation

of a pale-green homogeneous solution of the ZnI_2-complexed imine.

Addition of silyl ketene acetal (187) followed immediately by t-BuOH

produced the crude N-t-butyldimethylsilyl β-amino ester (189) on

work-up.   Unfortunately, silica gel chromatography resulted in

desilylation, yielding the N-unsubstituted β-amino ester in 90% yield.

Repetition with subsequent purification on basic alumina furnished the N-

silyl β-amino ester (189) in 95% yield as a white crystalline solid.

In an analogous manner, N-t-butyldimethylsilyl furfuraldimine (185a) was

converted into the N-silyl β-amino ester (190) in 66% yield.

Having thus shown that the t-butyldimethylsilyl group could with-

stand the carbon-carbon bond forming conditions, conversion of N-silyl

β-amino esters (189) and (190) into the corresponding β-lactams was

then attempted.   Following the procedure developed by Birkofer,[22]

treatment of N-silyl β-amino ester (189) with one equivalent of MeMgBr

resulted in approximately 50% consumption of starting material.

Utilization of two equivalents of MeMgBr yielded the N-t-butyldimethyl-

silyl β-lactam (191) in 32% yield (Scheme 50).   Interestingly,

considerable quantities of imine (181a) were observed in the crude

reaction product, resulting from carbon-carbon bond cleavage, possibly

via the six-membered transition state, as shown in Scheme 51.

In the lithium ester enolate approach to β-lactam synthesis,[10]

in situ formation of N-lithio β-amino esters results in spontaneous

cyclisation to β-lactams under the reaction conditions.   In addition,

lithium dialkylamides have been shown[57] to induce β-amino esters to

(181a) R¹=Ph   (187) R²=CH₃

(185a) R¹=2-furyl (183) R²=H

(191) R²=CH₃ ,
        R¹=Ph

(192) R²=CH₃ ,
        R¹=2-furyl

(193) R²=H ,
        R¹=Ph

(194) R²=H ,
        R¹=2-furyl

Scheme 53
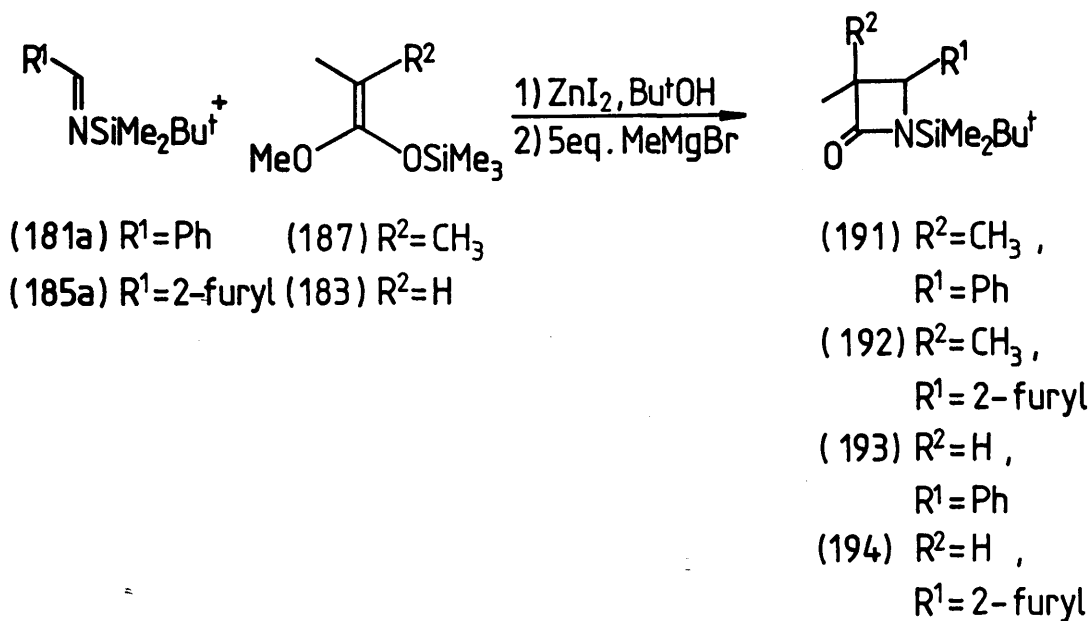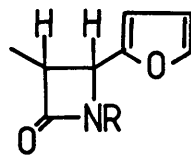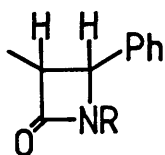
(195)[a]	R	trans:cis		(196)[a]	R	trans:cis	
(195)[a]	H	3:1	61%	(196)[a]	H	2:1	57%
(193)	SiMe₂Buᵗ	1·9:1	60%	(194)	SiMe₂Buᵗ	2:1	52%

a) see ref. 55a

(181b)

(185b)
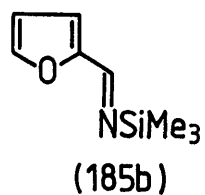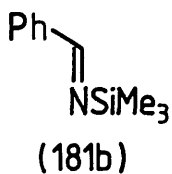
Table 1

cyclise to β-lactams. Based on these observations, $\underline{N}$-silyl β-amino ester (189) was treated with one equivalent of LDA, furnishing the $\underline{N}$-silyl β-lactam (191) in 72% as sole product.

The 2-furyl substituted $\underline{N}$-silyl β-amino ester (190), upon treatment with either two equivalents of MeMgBr or one equivalent of LDA, cyclised cleanly to give the $\underline{N}$-t-butyldimethylsilyl β-lactam (192) in 65% and 50% yield respectively (Scheme 52). No trace of the corresponding imine (185a) was observed under either set of conditions.

In a manner similar to the reported[21] process, $\underline{N}$-t-butyldimethyl-silyl β-lactams (191)-(194) were prepared by a one-pot procedure (Scheme 53). The preparation of $\underline{N}$-silyl β-amino esters proceeded as described above. Direct treatment of the reaction mixture with five equivalents of MeMgBr produced the corresponding $\underline{N}$-silyl β-lactams (191)-(194) in good yield. Interestingly, β-lactam (191) was produced in 72% yield with no observable trace of the corresponding imine (181a). This yield compares favourably with a combined yield of 68% obtained by cyclisation of the purified $\underline{N}$-silyl amino ester (189). β-Lactam (192) was produced in 52% yield, which again compares favourably with a combined yield of 43%.

Utilization of silyl ketene acetal (183) furnished β-lactam (193) in 60% yield as a 1.9:1 mixture of $\underline{trans}$ and $\underline{cis}$ diastereoisomers, the stereochemical assignments being based on H_3-H_4 coupling constants ($J_{\underline{trans}}$ = 2-3Hz and $J_{\underline{cis}}$ = 4-7Hz). Previous work[55a] involving $\underline{N}$-trimethylsilyl benzaldimine (181b) yielded $\underline{N}$-unsubstituted β-lactam (195) in 61% yield, as a 3:1 mixture of $\underline{trans}$ and $\underline{cis}$ diastereoisomers (Table 1).

MeO, OLi

(197)

\+

Ph
NSiMe₂Buᵗ

(181a)

→

Ph
NSiMe₂Buᵗ
O

(191)

Scheme 54

NSiMe₂Buᵗ

(186)

ZnI₂ ────────→ ⁻ polymer

SiMe₂Buᵗ
N

SiMe₂Buᵗ
N⊕ ZnI

────→

SiMe₂Buᵗ SiMe₂Buᵗ
N   N ₙ

(198)
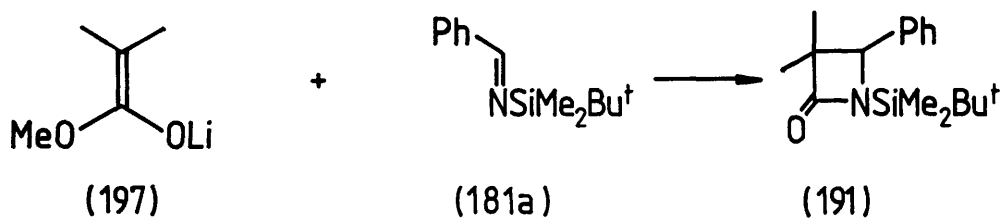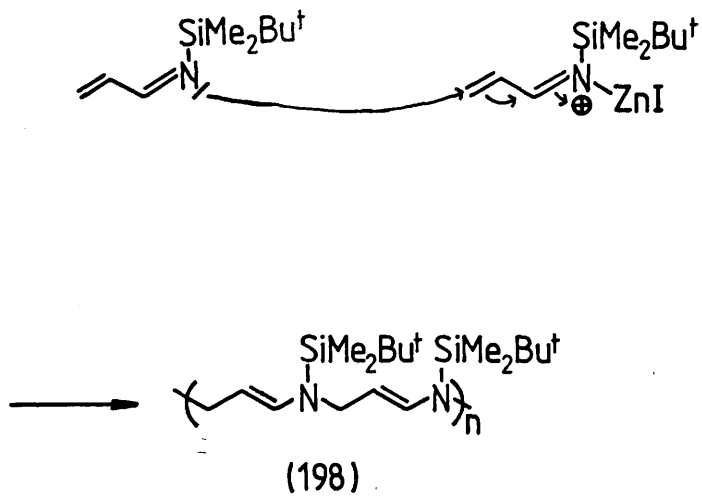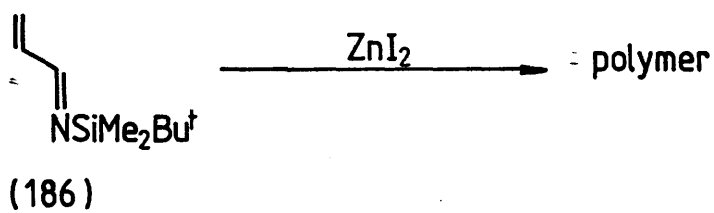
Scheme 55

$\underline{N}$-Silyl β-lactam (194) was produced from imine (185a) and silyl ketene acetal (183) in 52% yield as a 2:1 mixture of trans and cis diastereoisomers (Scheme 53). $\underline{N}$-Trimethylsilyl furfuraldimine (185b) yielded[55a] $\underline{N}$-unsubstituted β-lactam (196) in 57% yield, also as a 2:1 mixture of trans and cis diastereoisomers (Table 1). $\underline{N}$-t-Butyldimethyl-silyl imines (181a) and (185a) therefore proved applicable to the ZnI_2-mediated approach to β-lactam synthesis, yielding products in comparable yields and with approximately equal diastereoselectivities to those found in analogous cases involving $\underline{N}$-trimethylsilyl imines (181b) and (185b).

$\underline{N}$-t-Butyldimethylsilyl benzaldimine (181a) was also found to be of use in the lithium ester enolate approach to β-lactam synthesis (Scheme 54). Following the conditions described by Hart,[10] treatment of imine (181a) with lithium ester enolate (197), derived from methyl isobutyrate and LDA, produced the $\underline{N}$-t-butyldimethylsilyl β-lactam (191) cleanly and in 62% yield.

In an attempt to incorporate more useful functionality into the β-lactam ring, the allylamine derived $\underline{N}$-t-butyldimethylsilyl imine (186) was examined (Scheme 55). Addition of imine (186) to a solution of ZnI_2 in Et_2O resulted in immediate formation of a dark red gum. Subsequent addition of a silyl ketene acetal with or without t-BuOH did not result in the formation of recognisable products, large amounts of unreacted silyl ketene acetal being recovered. Work-up of the reaction mixture before addition of silyl ketene acetal yielded a viscous red oil which was sparingly soluble in chloroform. The [1]H n.m.r spectrum revealed many complex patterns at high-field and between δ5.0

(199)

(181b) + (187) → 10% / TMSOTf → MeOOC (188) + MeOOC (200)

Scheme 56

TfO–SiMe₃   (181b)   →   (201)   TfO⁻

(187)   +   (201)   →   (202)   →

(203)   + TMSOTf   (201)→   (200)
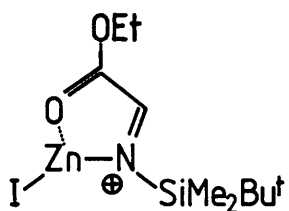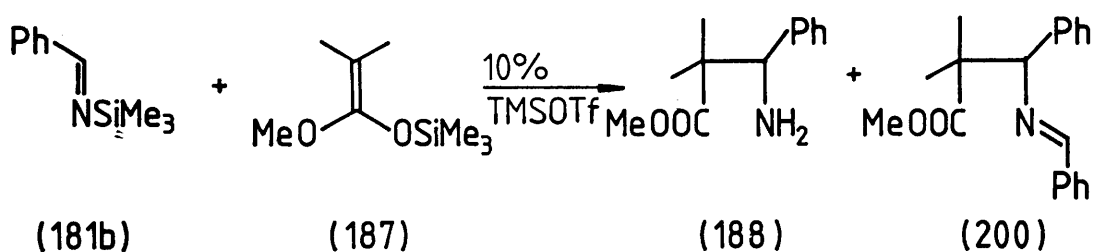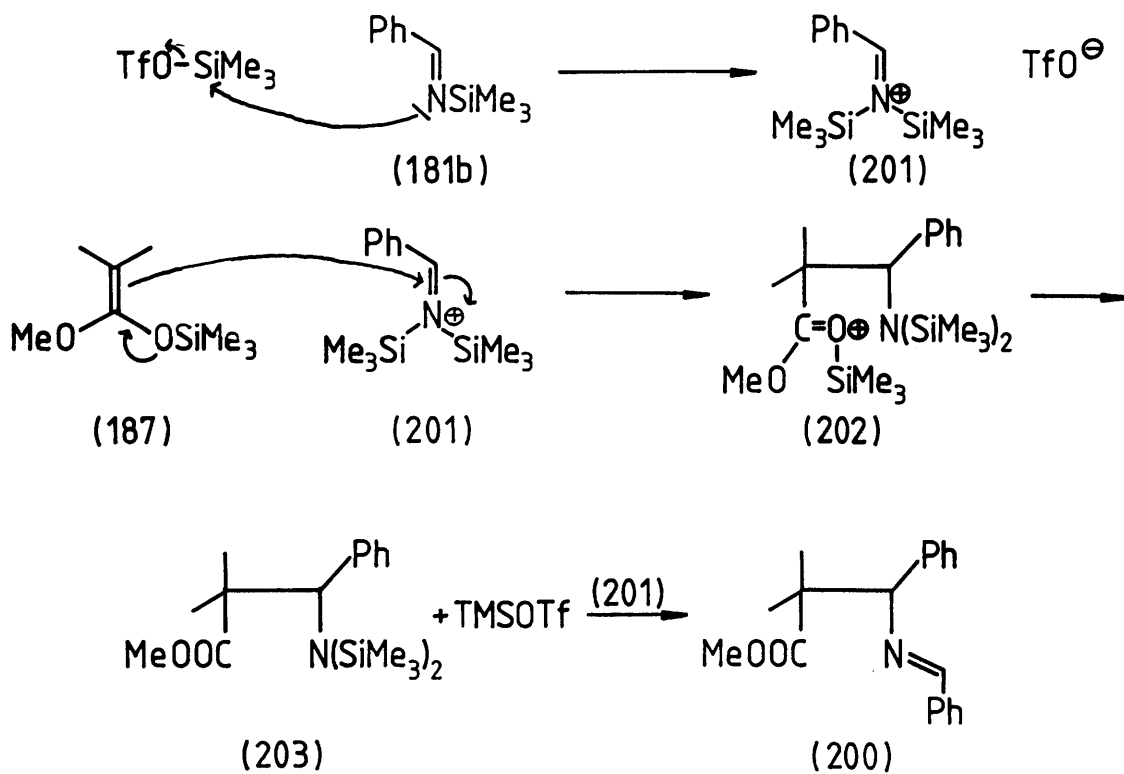
Scheme 57

and $\delta 6.0$.   These latter signals may be due to a ZnI_2-catalysed poly-

merisation of imine (186), leading to a silylated polymer of the form

(198).

Incorporation of the synthetically useful ethoxycarbonyl moiety

at C-4 of the β-lactam ring was attempted using N-t-butyldimethylsilyl

glyoxaldimine (182).   Addition of imine (182) to a solution of ZnI_2

in Et_2O resulted in formation of an orange solid.   No observable

change occurred upon addition of a silyl ketene acetal with or without

the presence of t-BuOH, and work-up yielded no recognisable products.

Zinc iodide, as well as co-ordinating to the imine nitrogen, may also

be co-ordinating to the ester carbonyl, forming the chelated iminium

species (199).   The imine bond of (199) would be polarised to a much

lesser degree than if ZnI_2 was bound solely to the imine nitrogen

resulting in an iminium species insufficiently electrophilic to react

with a silyl ketene acetal.

2. The TMSOTf-Mediated Reactions of N-Silyl Imines and O-Trimethylsilyl

Ketene Acetals.

These somewhat disappointing results prompted consideration of

alternative Lewis acid systems.   Trimethylsilyl trifluoromethane-

sulphonate[58] has been used successfully to mediate the addition of silyl

enol esters to carbonyl compounds[59] and N-aryl imines[60] and hence may be

of some use in mediating the reaction between silyl ketene acetals and

N-silyl imines.

Trimethylsilyl trifluoromethanesulphonate was first synthesised

by a modification of the method of Demuth.[61]   Addition of one

equivalent of tetramethylsilane to trifluoromethanesulphonic acid at ambient temperature resulted in vigorous evolution of methane gas. A very low yield of TMSOTf was obtained upon distillation of the reaction mixture, probably due to the evolution of methane driving off a large proportion of the tetramethylsilane. Quantitative yields of TMSOTf could be obtained by addition of 1.25 equivalents of tetramethylsilane to the acid at $0^{\circ}C$ and, after evolution of methane had ceased, addition of a further 0.25 equivalents of tetramethylsilane. Direct Kugelrohr distillation of the reaction mixture yielded the Lewis acid as a colourless oil which was made up as a standard solution in CH_2Cl_2.

Initially, addition of 0.1 equivalents of TMSOTf to an equimolar mixture of N-trimethylsilyl benzaldimine (181b) and silyl ketene acetal (187) in CH_2Cl_2 at $0^{\circ}C$ resulted in formation of a mixture of the desired β-amino ester (188) and the corresponding Schiff base (200) (Scheme 56). The mechanism of this reaction (Scheme 57) will involve attack upon TMSOTf by imine (181b) resulting in formation of the highly reactive N,N-bis(trimethylsilyl)iminium species (201). Subsequent attack by the nucleophilic silyl ketene acetal (187) on the electrophilic iminium carbon atom of (201) will yield the oxonium species (202). The catalytic cycle is completed by generation of N,N-bis(trimethylsilyl) β-amino ester (203) via either formation of TMSOTf or attack on (202) by imine (181b) yielding another molecule of the reactive iminium species (201). As the triflate anion is a very poor nucleophile, the latter course would seem the more probable. Formation of Schiff base (200) arises from reaction of β-amino ester (203) with a further molecule of iminium species (201). Schiff base formation was also noted in the

MeOOC / NSiMe₃ (with Zn, X crossed out) — Ph

(204)

+ Me₃SiI →

Ph
MeOOC N(SiMe₃)₂

(203)

Bu^tOH ↓

Ph
MeOOC NHSiMe₃

(205)

Scheme 58

(181b) + (187) →(100% TMSOTf, Bu^tOH)→
Ph
MeOOC NH₂

(188)

Scheme 59

Ph⟍
     ‖
     NR

(181b) R = SiMe₃
(181a) R = SiMe₂Bu^t

+

MeO⟍OSiMe₃

(183)

→(100% TMSOTf, Bu^tOH)→

H   H
| | Ph
MeOOC   NHR

(184) R = H
(206) R = SiMe₂Bu^t
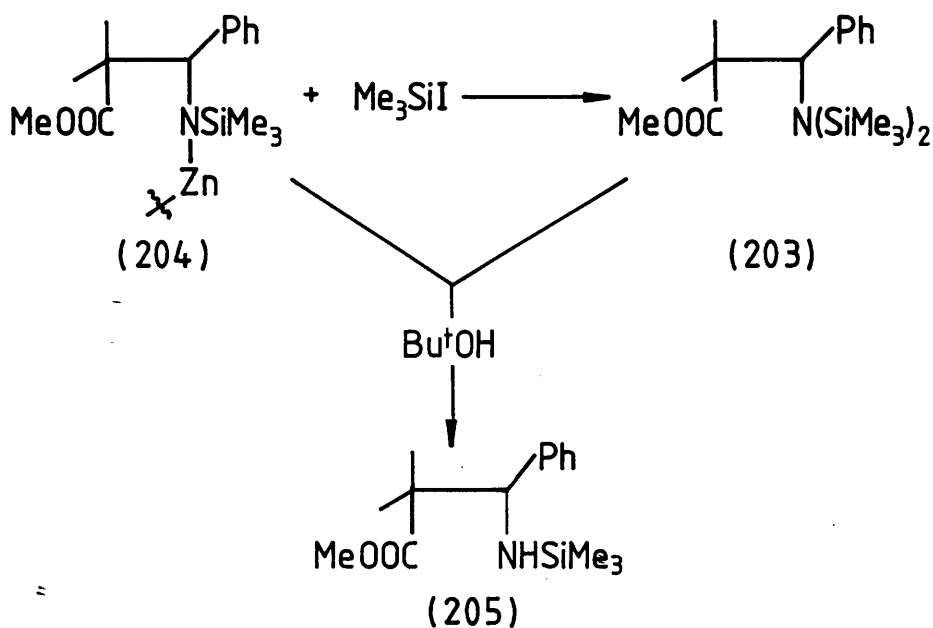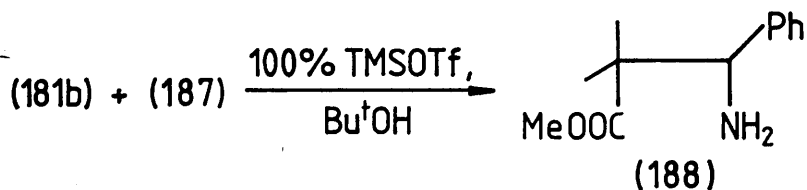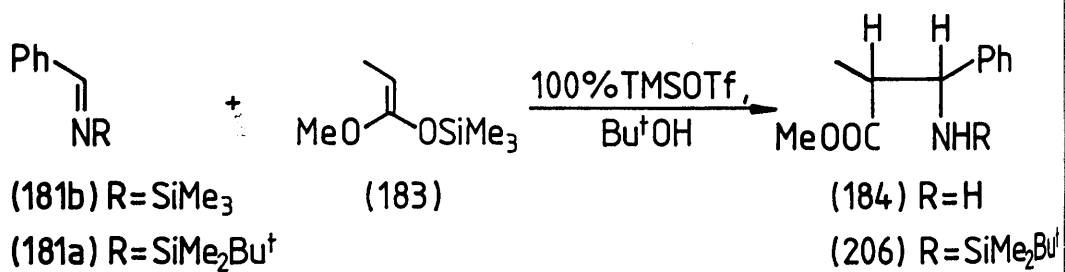
Scheme 60

ZnI_2-mediated reaction between N-silyl imines and O-silyl ketene acetals. Here, attack by a ketene acetal on a ZnI_2-complexed imine will lead to formation of the N-metallo β-amino ester (204) and iodotrimethylsilane (Scheme 58). Although (204) may react with a further molecule of activated imine to furnish Schiff base, it may also react with iodo-trimethylsilane, producing the same N,N-bis(trimethylsilyl) β-amino ester (203) as postulated in the TMSOTf-mediated reaction. Compound (203) may be the true Schiff base precursor and the suppression of Schiff base formation observed upon addition of t-BuOH may not be due to nitrogen-zinc bond cleavage, but to nitrogen-silicon bond cleavage of (203), leading to the less reactive N-trimethylsilyl β-amino ester (205). If the rates of reaction of N-metallo β-amino ester (204) with the activated imine and with iodotrimethylsilane are similar, then (204) will contribute to Schiff base formation along with (203).

The TMSOTf-mediated reaction between imine (181b) and ketene acetal (187) (Scheme 56) proved irreproducible, in that the relative proportion of products (188) and (200) varied from equimolar amounts of each to only trace amounts of Schiff base. If (203) is the Schiff base precursor common to both Lewis acid - mediated approaches, then suppression of this undesired reaction in the TMSOTf-mediated series may also be achieved by addition of t-BuOH.

Initial experiments utilizing catalytic quantities of TMSOTf and stoichiometric quantities of t-BuOH again proved irreproducible. However, complexation of imine (181b) with a full equivalent of TMSOTf, followed by addition of ketene acetal (187) and t-BuOH, gratifyingly yielded the N-unsubstituted β-amino ester (188) in 70% yield as the sole
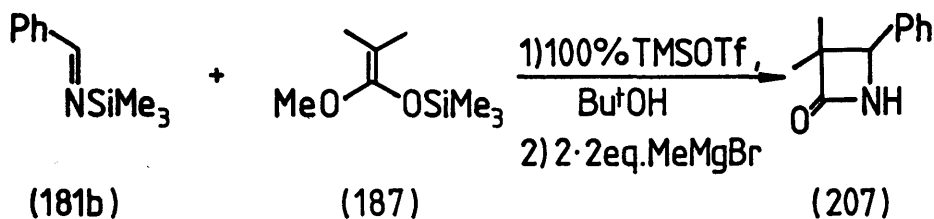
Scheme 61
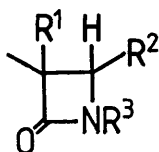
	R^1	R^2	R^3	%	trans:cis
1. (207)	Me	Ph	H	66	/
2. (208)	Me	2-furyl	H	69	/
3. (195)	H	Ph	H	62	3·9:1 (3:1)^a
4. (196)	H	2-furyl	H	65	2:1 (2:1)^a
5. (191)	Me	Ph	SiMe$_2$Bu^t	75	/
6. (192)	Me	2-furyl	SiMe$_2$Bu^t	71	/
7. (193)	H	Ph	SiMe$_2$Bu^t	43	5·6:1 (1·9:1)^a
8. (194)	H	2-furyl	SiMe$_2$Bu^t	71	3:1 (2:1)^a

a) using ZnI$_2$

Table 2

threo → trans

erythro → cis
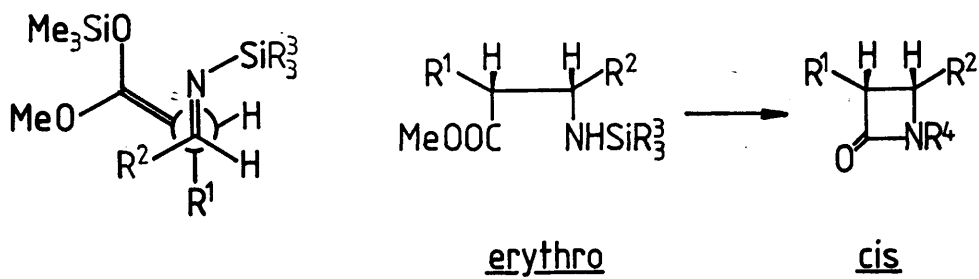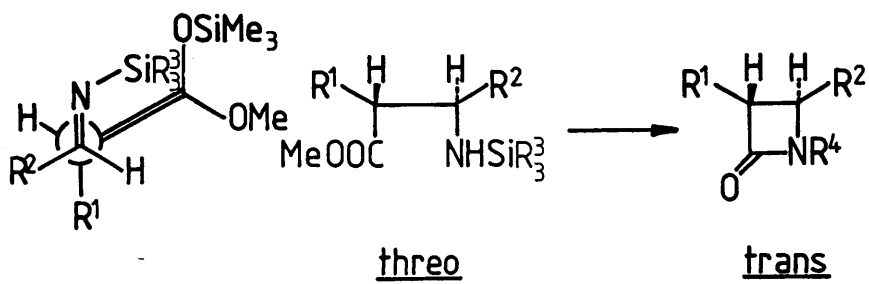
$R^4 = H, SiMe_2Bu^t$

Scheme 62

product (Scheme 59).

In order to investigate the possibility of inducing diastereo-selection in this approach, the reaction was repeated using silyl ketene acetal (183) (Scheme 60). The N-unsubstituted β-amino ester (184) was produced in 67% yield as a 3.9:1 mixture of threo and erythro diastereoisomers, based on the observation that $J_{2,3}$ (threo)>$J_{2,3}$(erythro). This ratio could be improved to 7.8:1 by carrying out the reaction at -78°C. N-t-Butyldimethylsilyl imine (181a) reacted in a similar manner yielding the N-silyl β-amino ester (206) in 60% yield as a 5.6:1 mixture of threo and erythro diastereoisomers.

If the postulated mechanism has substance, treatment of the in situ generated N-trimethylsilyl β-amino ester (205) with MeMgBr may allow direct access to β-lactams. Indeed, treatment of the reaction mixture obtained from the TMSOTf-induced reaction between imine (181b) and ketene acetal (187) with MeMgBr yielded the N-unsubstituted β-lactam (207) directly and in 66% yield (Scheme 61).

Utilization of this general procedure furnished a range of N-unsubstituted and N-t-butyldimethylsilyl β-lactams (Table 2). The threo selectivity observed in the initial bond forming step can be explained by invoking transition states such as those shown (Scheme 62). In this interpretation, the reaction course would seem to exhibit a preference to follow a syn-clinal lk approach, leading to the threo-β-amino ester and thence the trans-β-lactam. In the ZnI$_{2}$-mediated case, it seems unlikely that chelation between the nitrogen-bound zinc and the silyloxy oxygen atom of the ketene acetal is playing a major role, as the stereochemical outcome noted under either Lewis acid-

EtOOC
$\diagdown$

NSiMe$_2$Bu^t

(182)

$+$

MeO $\diagup$ OSiMe$_3$

(187)

$\xrightarrow{\text{10\% TMSOTf}}$

COOEt

MeOOC $\diagdown$ NHR

(209) R=H

(210) R=SiMe$_2$Bu^t

(209) $\xrightarrow[\text{2) MeMgBr}]{\text{1) Me}_3\text{SiCl , Et}_3\text{N}}$

COOEt

NH

O

(211)

(210) $\xrightarrow[\text{or LiNR}_2]{\text{RMgX}}$

COOEt

NSiMe$_2$Bu^t

O

(212)
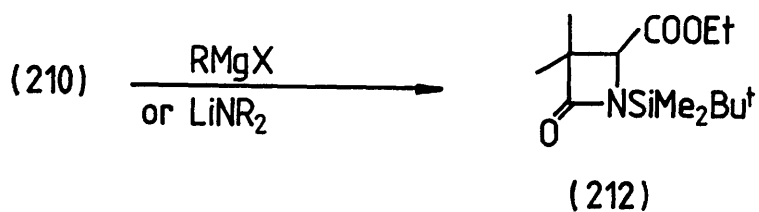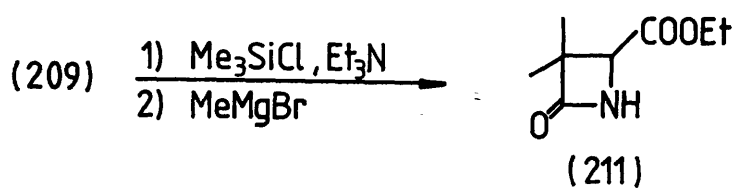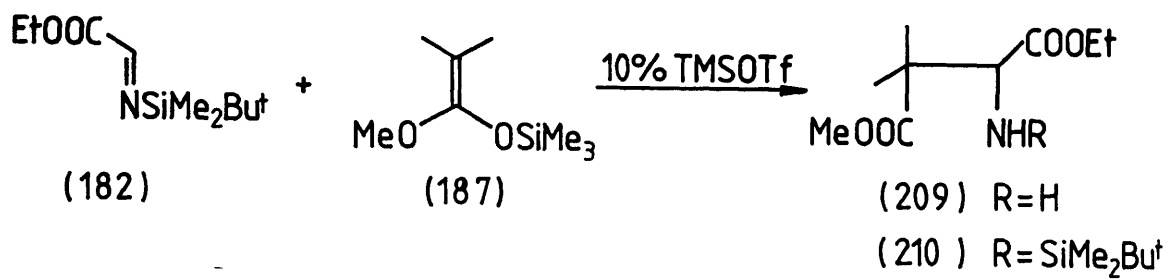
Scheme 63

mediated approaches is similar.   However, the lower degree of

selectivity obtained using ZnI$_2$ as Lewis acid may be explained by noting

that if any chelation does occur, it is more likely to be found in the

transition state leading to erythro-β-amino ester formation, therefore

lowering the energy difference between the two transition states.

This rationale assumes that the imine component is predominantly

the (E) geometrical isomer.   Indeed,the imine is produced in a

geometrically pure form.

As mentioned earlier, N-t-butyldimethylsilyl glyoxaldimine (182)

would not react with ZnI$_2$ in the desired manner.   Treatment of an equi-

molar mixture of this imine and silyl ketene acetal (187) with 0.1

equivalents of TMSOTf resulted, after work-up, in formation of the N-t-

butyldimethylsilyl β-amino ester (210) (Scheme 63).   Compound (210)

arose via selective mono-desilylation of the corresponding in situ

formed N-t-butyldimethylsilyl-N-trimethylsilyl β-amino ester by sodium

hydrogen orthophosphate.   Column chromatography on silica gel of (210)

resulted in desilylation, yielding N-unsubstituted β-amino ester (209)

in 63% yield.   Alternatively, purification on basic alumina or base-

washed silica gel prevented desilylation, yielding (210) in 88% yield.

No trace of the corresponding Schiff base could be detected, a result of

the lower reactivity of imine (182) compared to aromatic imine (181b).

The yields of β-amino esters (209) and (210) were prone to large

fluctuations with, in some instances, no β-amino ester being formed at

all.   This was easily rectified by carrying out the reaction in the

presence of crushed 4 Å molecular sieves, absorbing any residual water

that may be present due to the aqueous work-up used in isolating imine

1. + $\xrightarrow{\text{CH}_3\text{CN}, \Delta}$

NSiMe$_2$Bu^t

(186) (213)

2. " + " $\xrightarrow{\text{Toluene}, \Delta}$

3. " + " $\xrightarrow{\text{C}_6\text{H}_6, \Delta}$

4. " + " $\xrightarrow{\text{C}_6\text{H}_6, \text{DBU}, \Delta}$

5. " + $\xrightarrow{\text{C}_6\text{H}_6, \Delta}$

(214)

6. " + PhCHO $\xrightarrow{\text{10\% BF}_3.\text{OEt}_2, \atop \text{C}_6\text{H}_6, \Delta}$

(215)

7. " + $\xrightarrow{\text{C}_6\text{H}_6, \Delta, \atop \text{sealed tube}}$

(216)

8. " + " $\xrightarrow{\text{1.6\% ptsa}, \Delta \atop \text{C}_6\text{H}_6, \text{sealed tube}}$
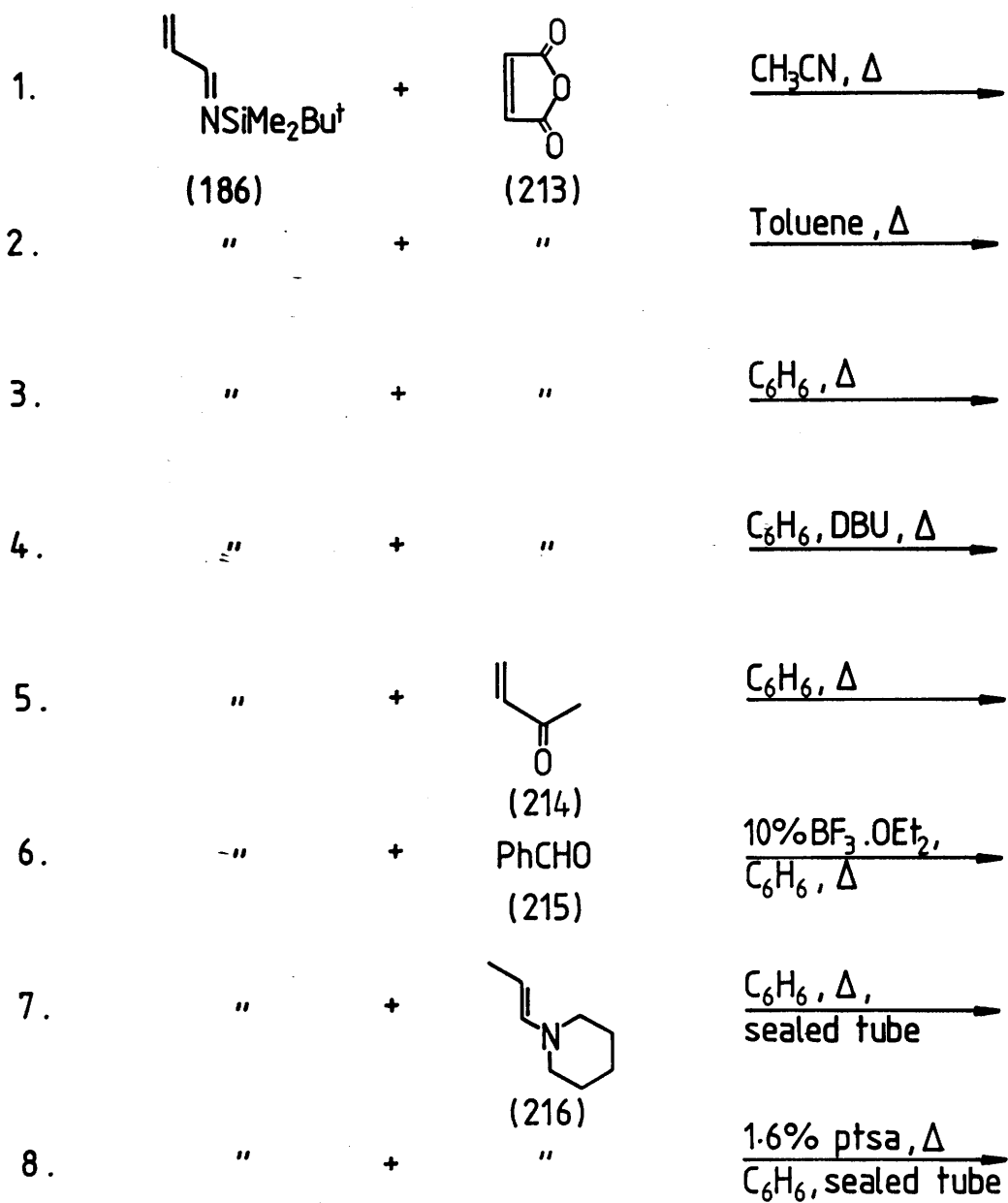
Scheme 64

(182).   This consisted simply of washing an n-pentane solution of

the crude imine with water, drying and evaporating the organic extract.

Imine (182) was used without distillation, as this resulted in decompos-

ition.

The N-unsubstituted β-amino ester (209) was silylated with

chlorotrimethylsilane in the presence of triethylamine and the reaction

mixture treated with MeMgBr to yield the N-unsubstituted β-lactam (211)

in 50% yield (Scheme 63).   N-Silyl β-amino ester (210) behaved similarly,

yielding N-silyl β-lactam (212) in 85% yield.   Unfortunately, subsequent

runs of those MeMgBr-mediated cyclisations yielded varying amounts

of by-products resulting from attack on the ethoxycarbonyl substituent

by MeMgBr, either before or after β-lactam formation.   However,

utilization of the bulkier Grignard reagent t-BuMgCl furnished N-silyl

β-lactam (212) in 79% yield.   Lithium hexamethyldisilazide and LDA also

induced cyclisation, forming N-silyl β-lactam (212) in 69% and 65%

yield respectively.

Disappointingly, the allylamine-derived imine (186) would not

react with TMSOTf under a variety of conditions to yield anything other

than complex mixtures.   As imine (186) is also a 1-aza diene, attempts

were made to utilize this compound in a Diels-Alder reaction (Scheme 64).

Reaction of imine (186) with maleic anhydride (213) under a variety of

conditions yielded no recognisable products (entries 1-4).   Utilization

of methyl vinyl ketone (214) gave no improvement (entry 5).   2-Aza dienes

have been shown[62] to react with aromatic aldehydes in the presence of a

Lewis acid to yield 1,3-oxazines.   Following this procedure (entry 6)

imine (186) did not yield any recognisable products.   1-Aza dienes

$$\underset{H}{\overset{R}{\diagdown}} C=O \xrightarrow[\text{TMSCl, -78°C}]{\text{LiN(SiMe}_3)_2,} \underset{H}{\overset{R}{\diagdown}} \underset{OSiMe_3}{\overset{|}{C}} - N \overset{SiMe_3}{\underset{SiMe_3}{\diagup}}$$

(217) R = Ph

(218) R = 2 – furyl

Scheme 65

$$\underset{H}{\overset{R}{\diagdown}} \underset{O^{\ominus}}{C} - N \overset{SiMe_3}{\underset{SiMe_3}{\diagup}}$$

(219)

$$\underset{N(SiMe_3)_2}{\overset{R}{\diagdown}} C{\overset{OSiMe_3}{\diagup}} \xrightarrow{\text{TMSOTf}} \underset{N(SiMe_3)_2}{\overset{R}{\diagdown}} C{\overset{\overset{SiMe_3}{|}}{\overset{\oplus}{O}SiMe_3}} \ TfO^{\ominus}$$

(220)

$$\longrightarrow \underset{\oplus N(SiMe_3)_2}{\overset{R}{\diagdown}} C \ TfO^{\ominus} \ + \ Me_3SiOSiMe_3$$

(221)   (222)
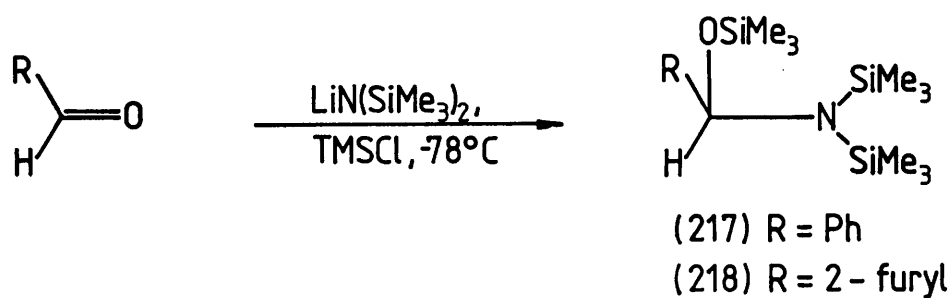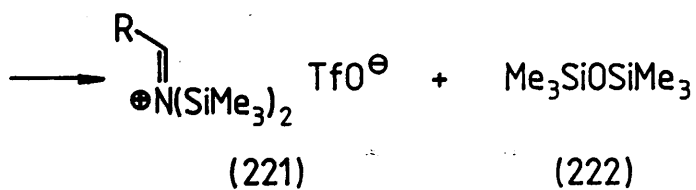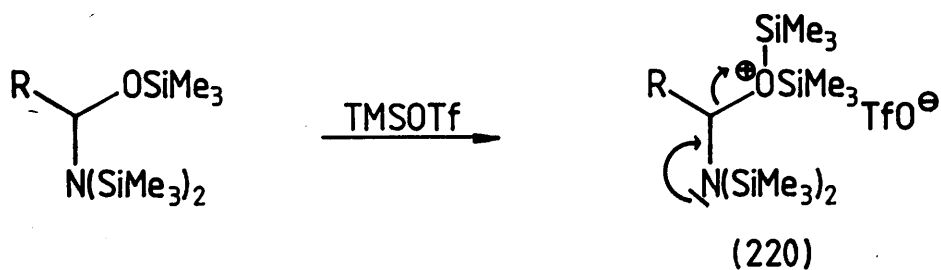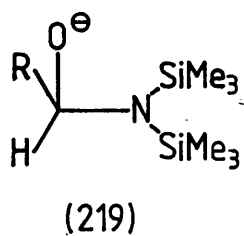
Scheme 66

have been utilized[63] in inverse electron demand Diels-Alder reactions[64] with enamines.   Reaction of (186) with N-(1-propenyl)piperidine (216) (entries 7 and 8) again produced no recognisable products.   The bulky t-butyldimethylsilyl group of (186) may prevent attainment of the cisoid conformation and hence explain the absence of Diels-Alder adduct formation.

As this work was nearing completion, Guanti[24] and co-workers published their account of diastereoselection in the TMSOTf-mediated reaction of silyl ketene acetals with N-aryl imines, as previously discussed (p.12).

3. The Synthesis and Reactions of N,N,O-Tris(Trimethylsilyl)Amine Acetals.

With regard to the mechanism of N-trimethylsilyl imine synthesis, N → O silyl migration does not, in general, appear to proceed at a significant rate at -78°C; under these conditions, the amine acetal adduct (219) can be trapped as its tris(trimethylsilyl) derivative (Scheme 65).   For example, treatment of benzaldehyde in THF at -78°C with lithium hexamethyldisilazide followed by chlorotrimethylsilane, also at -78°C, produced, after non-aqueous work-up and distillation, the amine acetal (217), contaminated to a slight extent with the corresponding N-trimethylsilyl imine (181b).   As adduct (219, R = Ph) seemed to be undergoing N → O silyl migration followed by elimination of trimethylsilyloxide ion to yield (181b) at an observable rate at -78°C, an alternative preparation of amine acetal (217) was sought.

Treatment of a mixture of benzaldehyde and chlorotrimethylsilane at -78°C with lithium hexamethyldisilazide allowed immediate trapping

Scheme 67

$$\underset{(223)}{\overset{\displaystyle\overset{\displaystyle OR^2}{\underset{\displaystyle NR^1_2}{}}}{}} \quad \xrightarrow{\text{TMSOTf}} \quad \underset{(224)}{\overset{\displaystyle\overset{\displaystyle CH_2}{\underset{\displaystyle \oplus NR^1_2}{\parallel}}}{}} \quad TfO^{\ominus} + Me_3SiOR^2$$

Scheme 67

Scheme 68

Ph—(OSiMe₃)—N(SiMe₃)₂ (217) + MeO—C=C(OSiMe₃) (187) $\xrightarrow{\text{5% TMSOTf}}$ no reaction

Scheme 68

Scheme 69

(202) $\underset{MeO}{}$ C=O⊕ ... Ph, N(SiMe₃)₂, SiMe₃

(202)   +   Ph—(OSiMe₃)—N(SiMe₃)₂ (217)   ⇌

MeOOC—...—Ph, N(SiMe₃)₂ (203)   +   Ph—⊕OSiMe₃ (SiMe₃)—N(SiMe₃)₂ (220)

Scheme 69

(217) + (187) $\xrightarrow{\text{50\% TMSOTf}}$ (217) +

(188)   (200)

Scheme 70

(217) + (187) $\xrightarrow{\text{100\% TMSOTf}}$ (188) + (200)

1:1

Scheme 71

(217) + (187) $\xrightarrow[\text{Bu}^t\text{OH}]{\text{100\% TMSOTf}}$

(188)
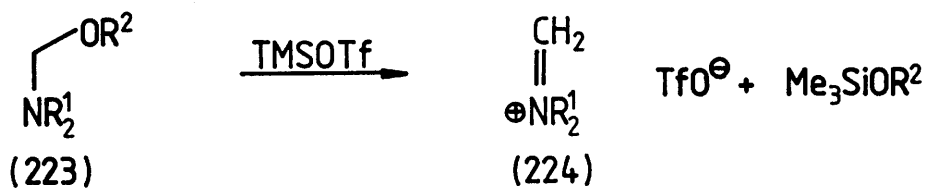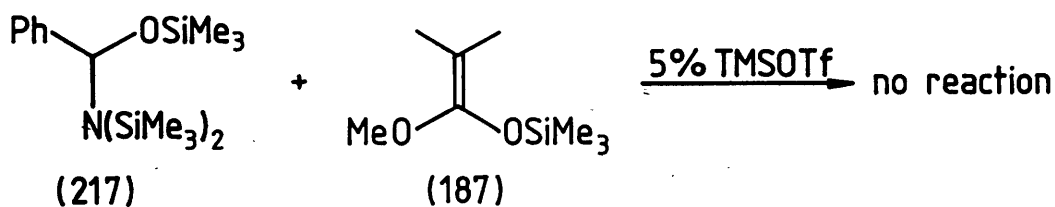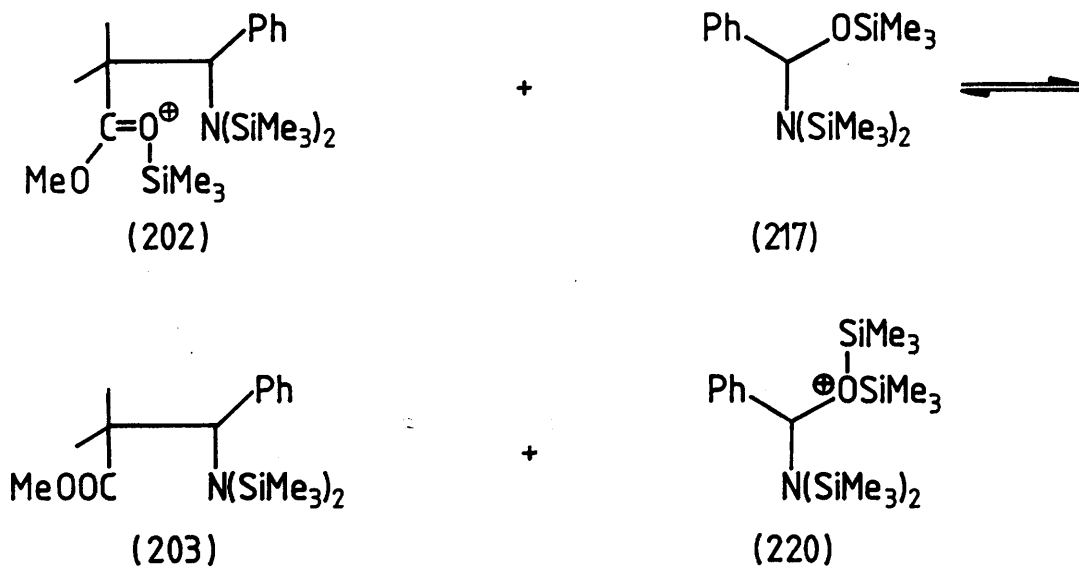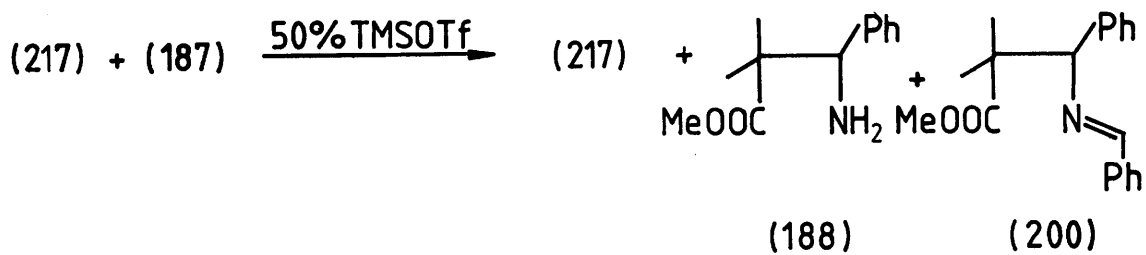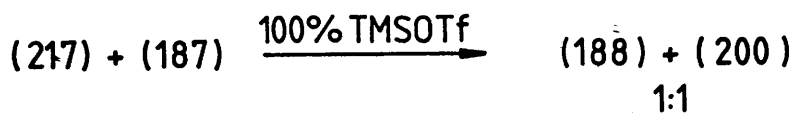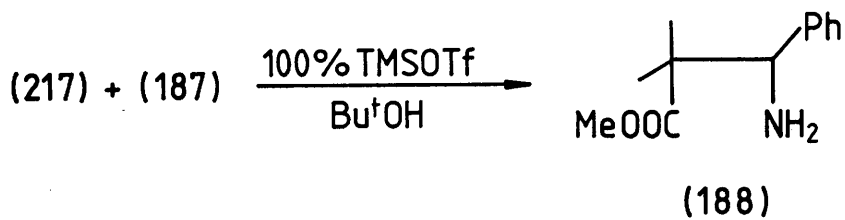
Scheme 72

of the adduct (219), furnishing the amine acetal (217) in 54% yield

as a colourless oil.   In an analogous manner, the furfural-derived

amine acetal was produced in 87% yield.

It is conceivable that amine acetals can be utilized as a source

of the highly reactive iminium species (221) (Scheme 66).   Selective

O-silylation of an amine acetal with TMSOTf should produce, via elimination

of hexamethyldisiloxane (222), the N,N-bis(trimethylsilyl)iminium ion (221),

the same species as that postulated in the TMSOTf-mediated reaction of

N-trimethylsilyl imines.   Additionally, alkoxy methyl amines (223)

have been used, via TMSOTf-catalysed generation of formaldehyde-derived

iminium species (224), for the α-amino methylation of carbonyl

compounds[23,65] (Scheme 67).

Addition of 0.05 equivalents of TMSOTf to an equimolar mixture

of amine acetal (217) and silyl ketene acetal (187) resulted in

essentially no reaction, even after prolonged reaction times (Scheme 68).

The refusal of TMSOTf to function in a catalytic manner under those

conditions may be due to the amine acetal (217) being insufficiently

nucleophilic to displace the trimethylsilyl group from the stabilised

oxonium species (202) (Scheme 69).

Utilization of 0.5 equivalents of TMSOTf resulted in 50%

consumption of starting amine acetal (217) (Scheme 70) to produce a 1:1

mixture of the desired N-unsubstituted β-amino ester (188) and the

corresponding Schiff base (200).   Addition of catalytic quantities

of 2,6-lutidine or 4-(N,N-dimethyl)aminopyridine did not result in full

consumption of amine acetal (217).   Indeed, utilization of equimolar

quantities, with respect to TMSOTf, of those bases resulted in no
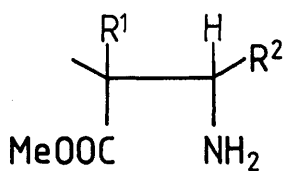
		R^1	R^2	%	threo:erythro
1.	(188)	Me	Ph	69	/
2.	(225)	Me	2-furyl	74	/
3.	(184)	H	Ph	69	3.9:1
4.	(226)	H	2-furyl	64	2:1

Table 3
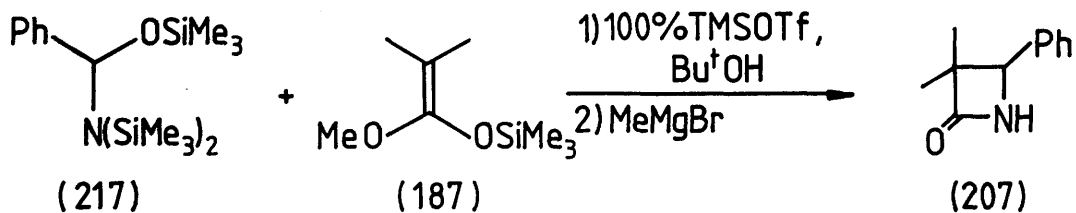
Scheme 73

reaction whatsoever.

In an attempt to induce complete conversion of amine acetal (217) into the iminium ion (221,R = Ph), one equivalent of TMSOTf was utilized.   Subsequent addition of silyl ketene acetal (187) furnished a 1:1 mixture of β-amino ester (188) and Schiff base (200) with no starting material being detectable (Scheme 71).

Following the protocol devised to suppress trans-amination in both the earlier ZnI$_2$ and TMSOTf-mediated processes, addition of one equivalent of t-BuOH directly after ketene acetal addition gave the N-unsubstituted β-amino ester (188) cleanly and in 69% yield (Scheme 72).

A range of β-amino esters was produced by this sequence (Table 3). Entries 3 and 4 show diastereoselectivities exactly paralleling those found in the TMSOTf-mediated reaction of N-trimethylsilyl imines (181b) and (185b).   This result is not unexpected due to the participation in both reactions of the iminium species (221).

This process can also be developed into a one-pot synthesis of β-lactams (Scheme 73).   Treatment of the in situ generated β-amino ester (205) with MeMgBr allowed direct access to the N-unsubstituted β-lactam (207) in 40% yield.

4. The Synthesis and Reactions of Polyfunctionalised O-Trimethylsilyl
   Ketene Acetals.

Syntheses directed towards the incorporation of functionality suitable for further synthetic elaboration into the β-lactam ring have tended to concentrate predominantly on the imine component of the ester-imine condensation approach.   Attempts to introduce functionality

Me₃Si—C≡C—CH=C(OMe)(OSiMe₃)

(227)

⇒

Me₃Si—C≡C—CH₂—COOR

(228)

⇒

Me₃Si—C≡C—CH₂—OH

(229)

Scheme 74

HC≡C—CH₂—OH

(230)

$\xrightarrow{\text{DHP,PPTS}}$

HC≡C—CH₂—OTHP

(231)

$\xrightarrow[\substack{2)\text{TMSCl} \\ 3)\text{H}_3\overset{\oplus}{\text{O}}}]{1)\text{EtMgBr}}$

Me₃Si—C≡C—CH₂—OH

(229)

Scheme 75

Me₃Si—C≡C—CH₂—OH

(229)

$\xrightarrow{\text{Ph}_3\text{P, CCl}_4}$

Me₃Si—C≡C—CH₂—Cl

(232)

Scheme 76

Me₃Si───────SiMe₃ $\xrightarrow[\text{2)}\ \triangle^O]{\text{1)MeLi ,LiBr}}$ Me₃Si───── OH

(233)   (234)

Scheme 77

Me₃Si─────
         OH
(234)

$\xrightarrow{\text{RuO}_2, \text{IO}_4^\ominus}$ no reaction

$\xrightarrow{\text{PDC ,DMF}}$ no reaction

$\xrightarrow{\text{JONES, } \overset{O}{\triangle}}$ Me₃Si─────
                             COOR

(235) R = H
(236) R = Me
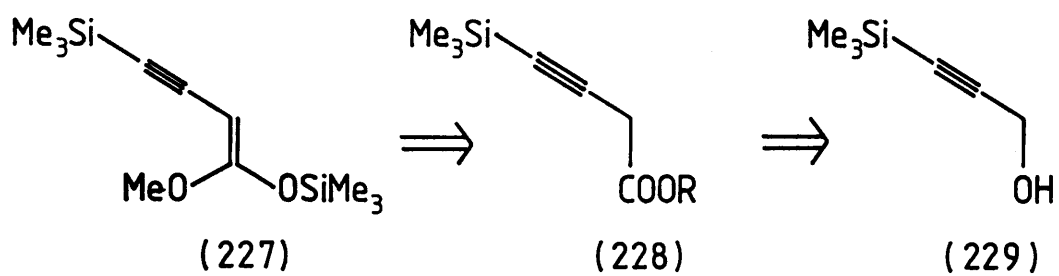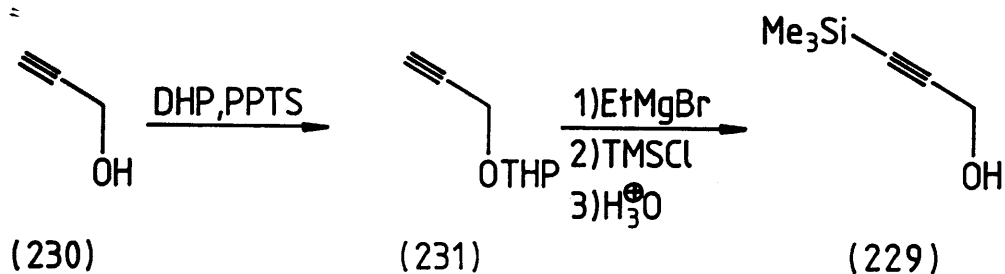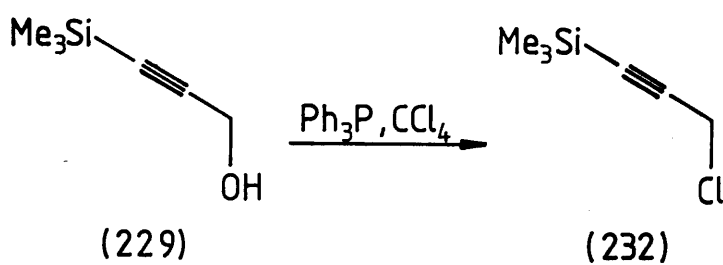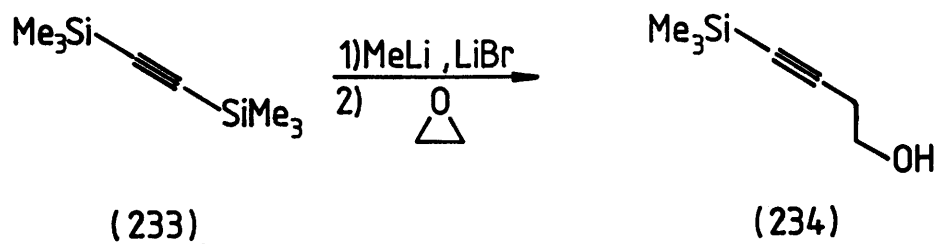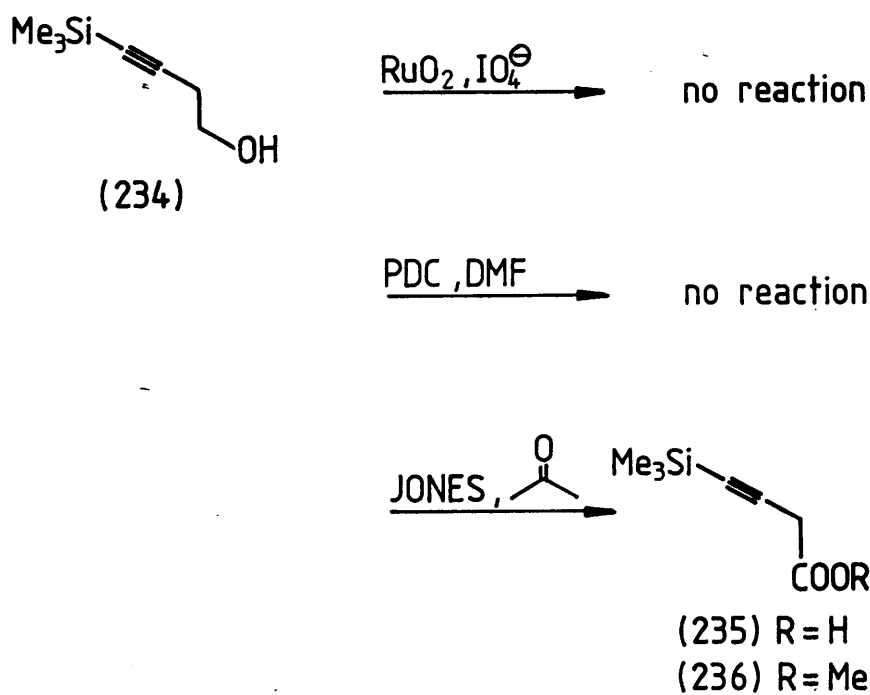
Scheme 78

by way of the ester component have been confined thus far to the derivatives of 3-hydroxy butyrates[46-48] and 2-heteroatom-substituted carboxylic acids.[14,16,66]

The synthetic utility of alkynes makes incorporation of an alkyne into a β-lactam unit an attractive proposition. It is conceivable that silyl ketene acetal (227) can be prepared from the known[67] propynol (229), _via_ the carboxy compound (228) (Scheme 74). Alcohol (229) has been synthesised in moderate yield by silylation of the dianion of propargyl alcohol, followed by selective _O_-desilylation with aqueous acid. In an attempt to improve on this procedure, propargyl alcohol (230) was protected as the corresponding THP-ether (231) in quantitative yield (Scheme 75). Deprotonation of (231) with EtMgBr, silylation and aqueous acid-catalysed deprotection revealed the silyl propynol (229) in 75% yield.

Homologation of propynol (229) was then envisaged as proceeding _via_ the corresponding Grignard reagent, derived from the chloride (232) (Scheme 76). Treatment of propynol (229) with triphenylphosphine and CCl_4 yielded the chloride (232) in 48% yield. Although reaction of chloride (232) with magnesium appeared to form the desired Grignard reagent, quenching the reaction mixture with either solid or gaseous carbon dioxide gave no trace of the required acid.

Treatment of propynol (229) with either Ph_3PBr_2[68] or Ph_3P/NBS did not allow access to the more reactive bromide.

In an alternative approach, direct synthesis of the silyl butynol (234) was then attempted (Scheme 77). It has been reported[69] that
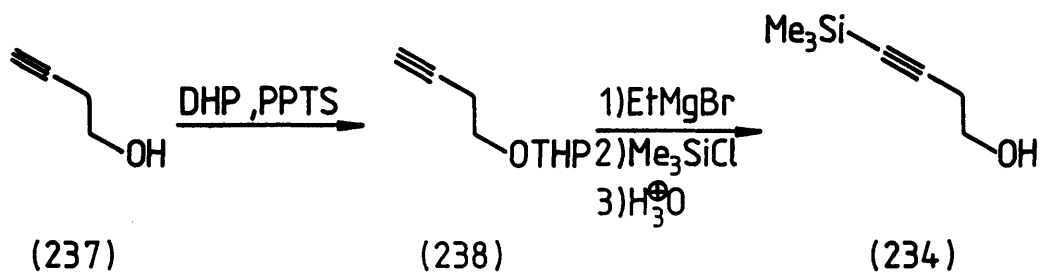
Scheme 79
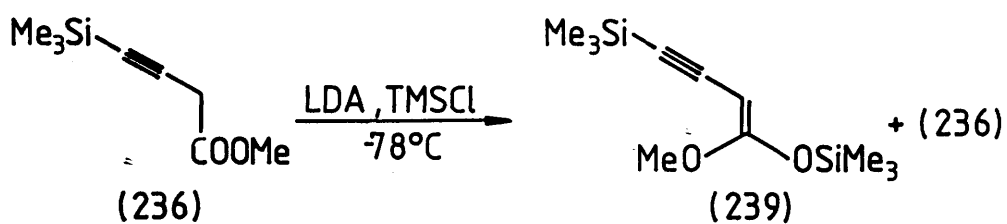
Scheme 80

(240)
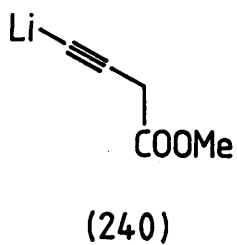
treatment of bis(trimethylsilyl)acetylene (233) with one equivalent of MeLi-LiBr results in mono-desilylation. Reaction of (233) with MeLi-LiBr and subsequent addition of an excess of ethylene oxide yielded the desired butynol (234) in 94% yield. Attempts to oxidise butynol (234) to the corresponding carboxylic acid (235) using either RuO_2 in the presence of periodate[70] or PDC in DMF[71] resulted in recovery of starting material (Scheme 78). However, Jones oxidation afforded acid (235) in 83% yield (based on consumed starting material). Esterification to (236) was readily achieved by treatment of the crude acid (235) with either ethereal diazomethane (65%) or, more conveniently, methanol in the presence of a catalytic quantity of concentrated sulphuric acid (68%).

Subsequent synthesis of butynol (234) followed an analogous route to that of propynol (229) (Scheme 79). Tetrahydropyranylation of 3-butyn-1-ol (237) yielded (238) in quantitative yield. Deprotonation, silylation and deprotection then furnished the silyl butynol (234) in 82% yield.

Treatment of methyl ester (236) with one equivalent of LDA at low temperature, followed by addition of chlorotrimethylsilane, resulted in the formation of a 2:1 mixture of the desired silyl ketene acetal (239) and the starting ester (236) (Scheme 80). Careful and repeated Kugelrohr distillation gave essentially pure silyl ketene acetal (239), albeit in moderate yield. Distillation of the ester from calcium hydride prior to use offered no improvement. Utilization of 1.1 equivalents of LDA did not increase the relative proportion of silyl ketene acetal (239), whereas utilization of two equivalents gave a very complex mixture. No advantage was gained from carrying out the reaction
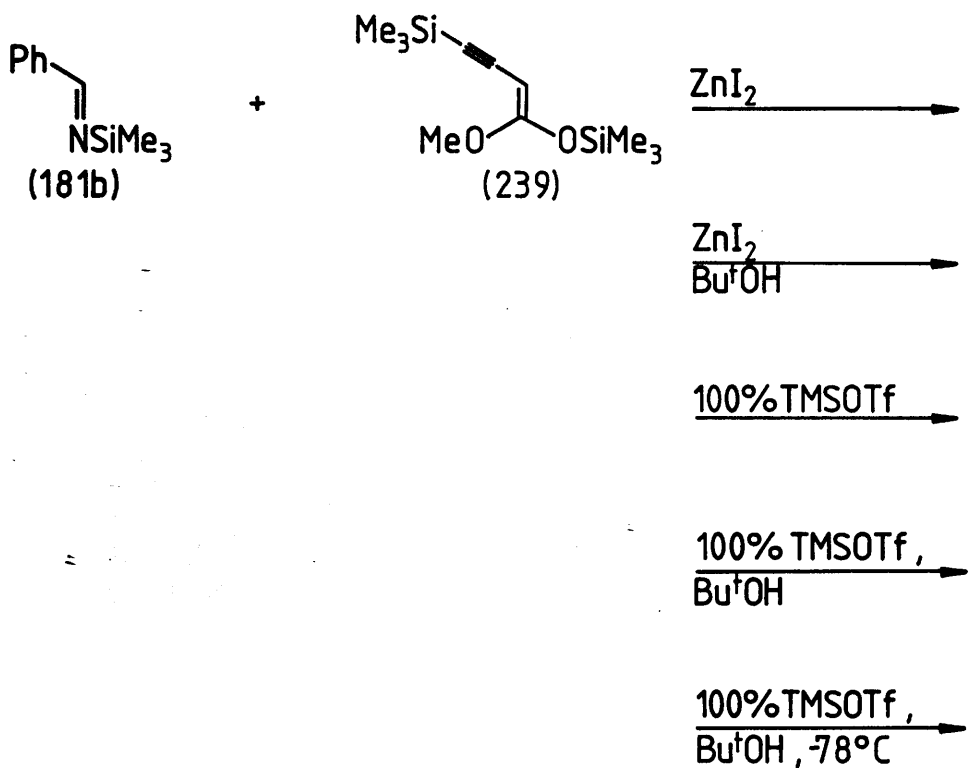
Scheme 81
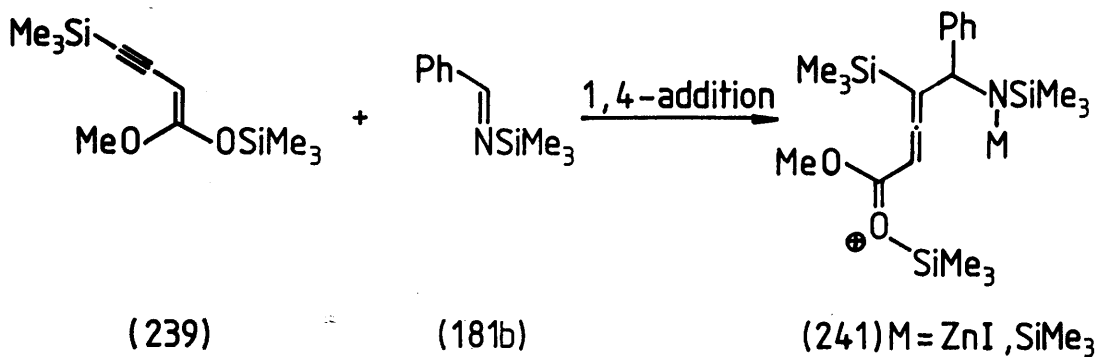
Scheme 82

under conditions of internal quench, whereby LDA was added to a mixture of the ester (236) and chlorotrimethylsilane at low temperature. The presence of starting ester (236) in the reaction product may arise from LDA-induced desilylation of (236), yielding anion (240) which, upon addition of chlorotrimethylsilane, would regenerate ester (236).

Disappointingly, reaction of silyl ketene acetal (239) with N-trimethylsilyl benzaldimine (181b) under the ZnI_2 or TMSOTf-mediated reaction conditions shown in Scheme 81 resulted in either return of starting material or the production of complex mixtures from which no recognisable products could be obtained.

Silyloxydienes and silyl ketene acetals derived from α,β-unsaturated esters generally undergo selective attack by electrophiles at the γ-position.[72] It is entirely possible that γ-attack does take place in the reaction between silyl ketene acetal (239) and imine (181b), but that the primary allenic reaction product (241) undergoes further complex transformations under the reaction conditions (Scheme 82).

Following the procedure of Hart,[10] reaction of the lithium ester enolate (242) with imine (181b) merely returned both starting materials.

The ester-imine condensation route to β-lactams has proven very useful for the construction of the three contiguous chiral centres found in the potent antibiotic thienamycin (168). Many excellent achiral and chiral syntheses of β-lactams containing the 1'-hydroxyethyl substituent at C-3 have been described.[46-48] A recent report[73] outlined the use of silyl ketene acetal (245) in a TMSOTf-promoted reaction with an N-aryl imine. Although this was the first report of compound (245) no experimental detail for its preparation was provided.

Me₃Si–C≡C–C(OMe)=C(OLi)

$$Me_3Si-C\equiv C-\underset{\underset{MeO}{|}}{C}=\underset{\underset{OLi}{|}}{C}$$

(242)

(168) Thienamycin
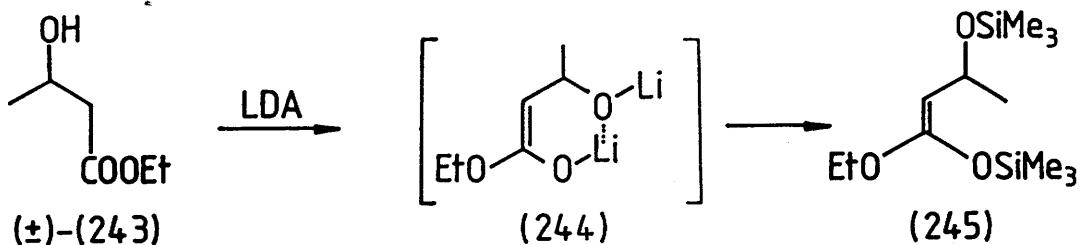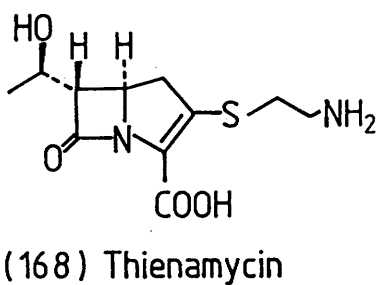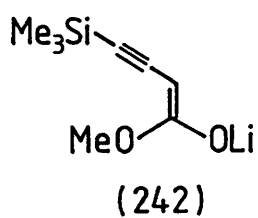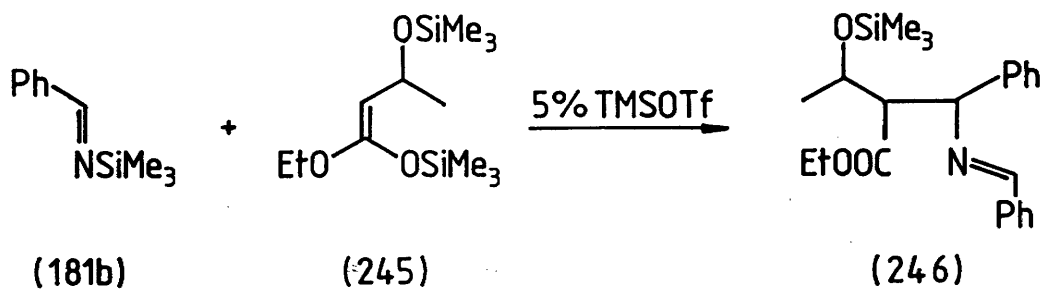
Scheme 83

Scheme 84

In our hands, treatment of racemic ethyl 3-hydroxy butyrate (243) with two equivalents of LDA at low temperature, followed by chlorotrimethylsilane, yielded the silyl ketene acetal (245) as a single geometrical isomer in 97% yield (Scheme 83). It is probable that the ketene acetal (245) is produced in the (Z) configuration, via the chelated six-membered transition state (244).[46a,74]

Treatment of a mixture of silyl ketene acetal (245) and imine (181b) in CH_2Cl_2 with 0.05 equivalents of TMSOTf resulted in formation of the Schiff base (246) in 81% yield as sole product (Scheme 84). Schiff base (246) existed as a 4:1 mixture of threo and erythro diastereoisomers. It has been shown[46-48] that the stereochemistry at C-2 (C-3) of β-amino esters (β-lactams) formed from optically pure 3-hydroxy butyrates is dictated in a stereospecific manner by the stereochemistry of the hydroxyl group. If (S)-3-hydroxy butyrate is utilized, the carbon atom α to the hydroxyl-bearing carbon will have the (S) configuration, and conversely when (R)-3-hydroxy butyrates are used.

For this reason, of the eight stereoisomers of Schiff base (246) which are possible, only four were found. The threo diastereoisomer of (246) is comprised of enantiomers (246a) and (246b), and the erythro diastereoisomer (246) of enantiomers (246c) and (246d).

Attainment of the stereochemistry required for thienamycin (168) could then be achieved by inversion of the hydroxyl stereochemistry of (246a) via the Mitsunobu reaction.

Interestingly, precomplexation of imine (181b) with a full equivalent of TMSOTf and subsequent addition of silyl ketene acetal (245),

RO H H
\ | | Ph
_s_/\s/\|
/ \ / \ /
EtOOC N
‖
Ph

(246a)

RO H H
\ | | Ph
_s_/\s/\|
/ \ / \ /
EtOOC N
‖
Ph

(246c)

RO H H
\ | | Ph
_R_/\R/\|
/ \ / \ /
EtOOC N
‖
Ph

(246b)

RO H H
\ | | Ph
_R_/\R/\|
/ \ / \ /
EtOOC N
‖
Ph

(246d)

R = SiMe$_3$

$$(181b) + (245) \xrightarrow[\text{Bu}^t\text{OH}]{100\%\,\text{TMSOTf}}$$

Ph
|
O NH
\ / \
/ \ / Ph
| |
COOEt

(247)

Scheme 85

OSiMe₃ structure (246)

$$OSiMe_3$$

(246)

TMSOTf →

(248)

‖

(248)

(247) ←

Scheme 86

(247)

Bu^t Me₂SiCl, ImH, DMF →

(249)

Scheme 87

(250)   +   (247)   ⟶   (249)

Scheme 88

threo

erythro
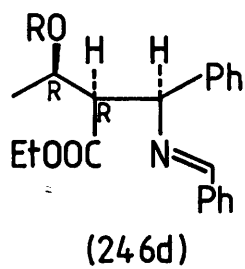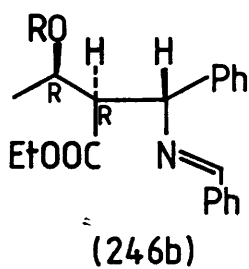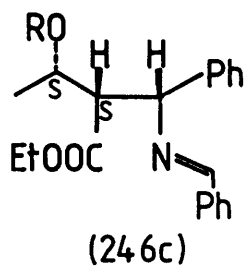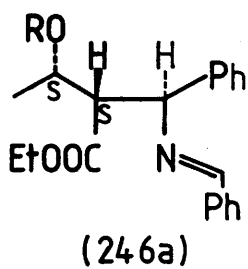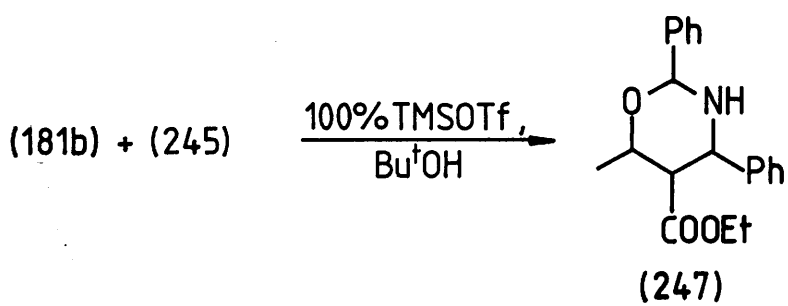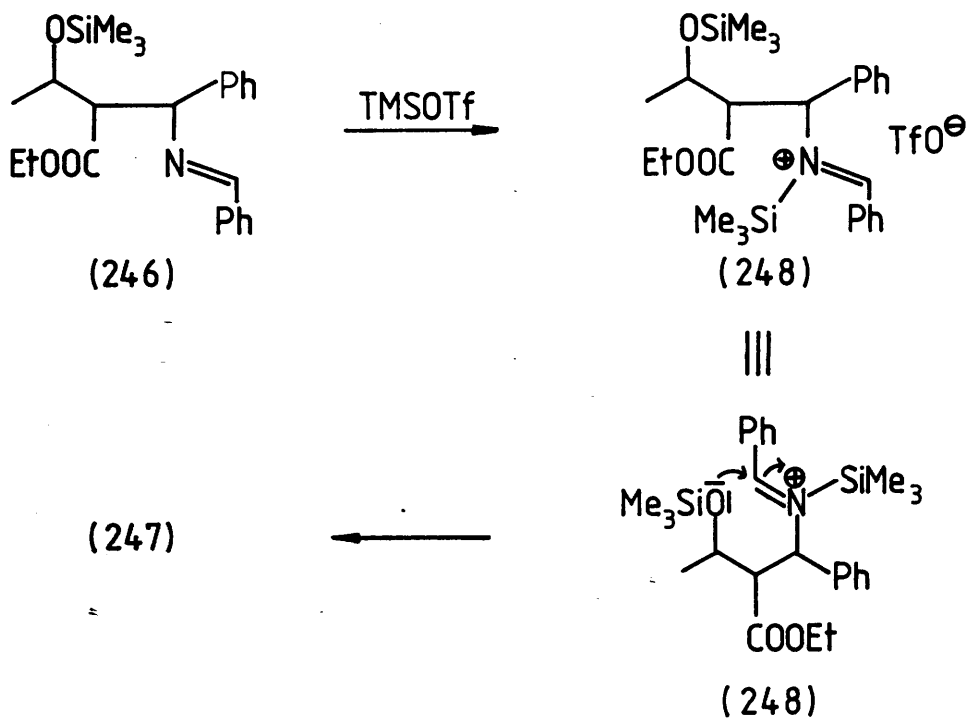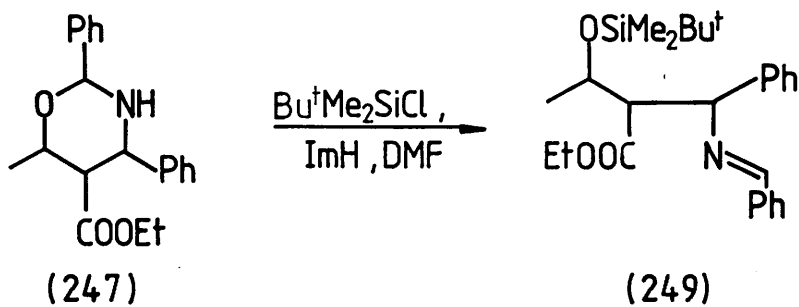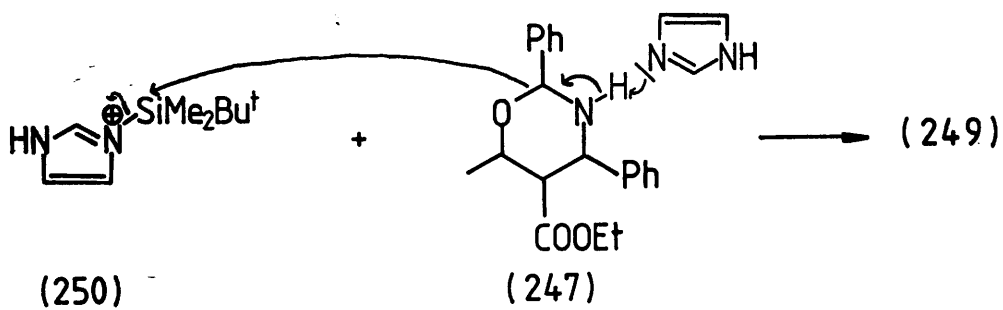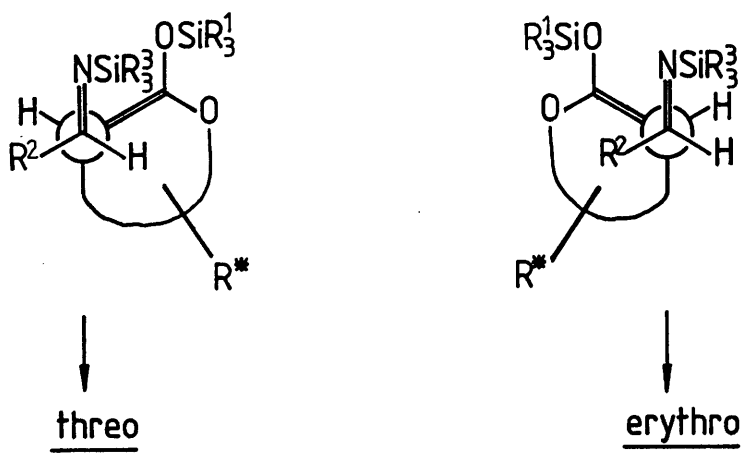
Scheme 89

and t-BuOH to suppress trans-amination, yielded the oxazine (247) in
75% yield (Scheme 85).   The mechanism of this transformation may involve
complexation of TMSOTf to the Schiff base (246), to yield the iminium
species (248) (Scheme 86).   Having attained the correct conformation,
intramolecular nucleophilic attack on the iminium moiety of (248) by the
silyloxy   oxygen atom would then lead to oxazine (247) after aqueous
work-up.

Utilization of five equivalents of t-BuOH gave no improvement.
Carrying out the reaction in the presence of two equivalents of TMSOTf
with no t-BuOH resulted in the expected increase in yield of (247) to
84%.   Zinc iodide offered no advantage over TMSOTf.

Ring opening of oxazine (247) was achieved readily (Scheme 87).
Addition of t-butylchlorodimethylsilane and excess imidazole to a
solution of (247) in DMF resulted in clean formation of the silyloxy
Schiff base (249) in 81% yield.   Deprotonation of oxazine (247) by
imidazole and attack on the highly reactive silylating agent (250) by
the liberated oxygen anion will yield the Schiff base (249) (Scheme 88).

Cyclic ketene acetals derived from lactones have not yet been
the subject of much attention with regard to β-lactam synthesis.   The
availability of chiral substituted lactones makes their application to
the ester-imine condensation route very attractive.   Consideration
of the postulated transition states leading to both threo and erythro
β-amino esters reveals the potential for asymmetric induction, using
correctly configured silyl ketene acetals (Scheme 89).

Silyl ketene acetal (252) has been known[75] for some time, although
its preparation has never been detailed.   Kinetic deprotonation of

(251)   (252)

Scheme 90

(181b)   (252)   (253)   (254)

Scheme 91

(255)

(253)

nBu₄NF →

$(Me_2N)_3\overset{\oplus}{S}\ Me_3\overset{\ominus}{Si}F_2$ →

MeLi , LiBr →

aq.HF , CH₃CN →

(256)
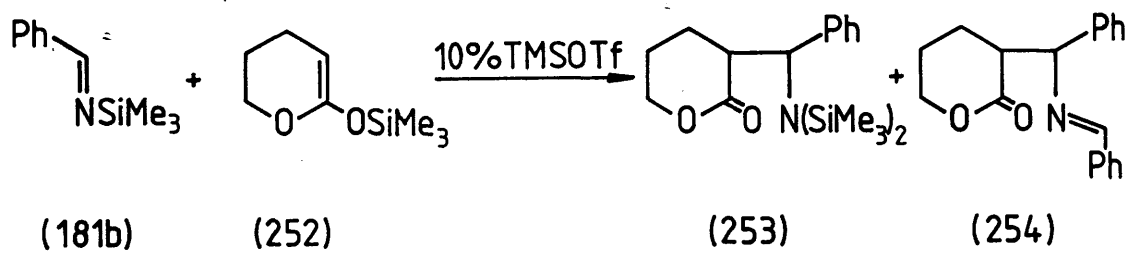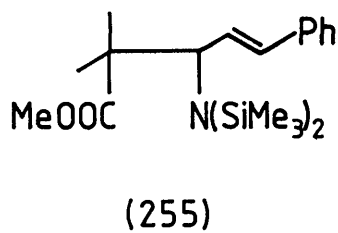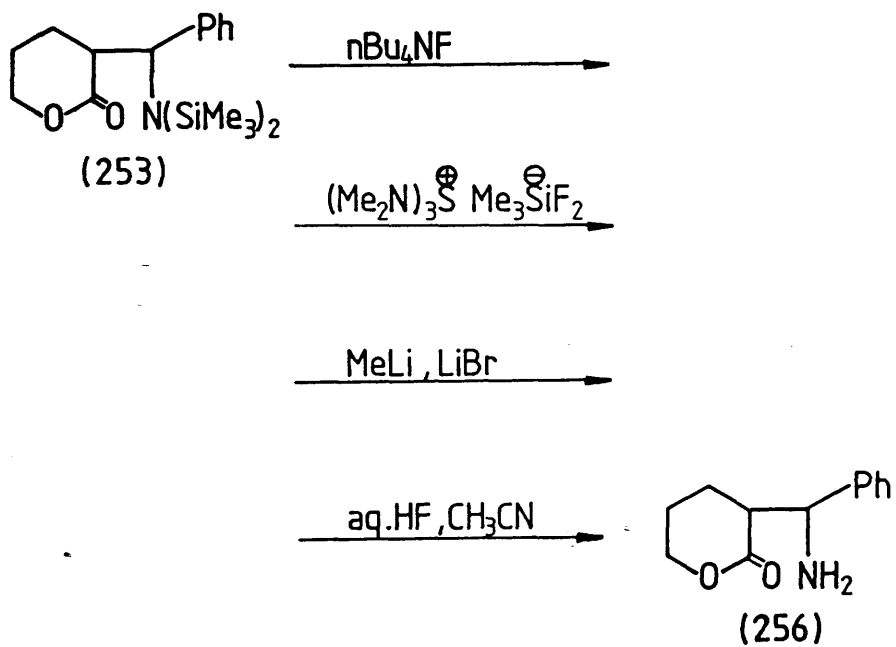
Scheme 92

δ-valerolactone (251) yielded, upon addition of chlorotrimethylsilane,
the cyclic ketene acetal (252) in 83% yield (Scheme 90).   To a mixture
of imine (181b) and ketene acetal (252) was added 0.05 equivalents of
TMSOTf, resulting in formation of a 3:1 mixture of the N,N-bis(trimethyl-
silyl) β-amino ester (253) and the corresponding Schiff base (254), both
as a 3:1 mixture of threo and erythro diastereoisomers (Scheme 91).
The isolation of the N-silylated β-amino ester (253) instead of the
expected N-unsubstituted variant is atypical,   although one other such
example is known.[55a]   Treatment of a mixture of silyl ketene acetal
(187) and N-trimethylsilyl cinnamaldimine with 0.1 equivalents of nBu$_4$NF
yielded the N,N-bis(trimethylsilyl)β-amino ester (255) in low yield.

Cleavage of both silicon-oxygen and silicon-carbon bonds has been
achieved by use of 'naked' fluoride ion.[76]   The most accessible
source of 'anhydrous' fluoride ion is nBu$_4$NF.3H$_2$O.   Careful oven-drying
under high vacuum is required to obtain the reactive fluoride species
and many uncertainties are associated with its preparation.[77]   For
this work, 'anhydrous' nBu$_4$NF was prepared by heating the trihydrate
in a Kugelrohr apparatus at 70°C/0.001mm Hg for 5h prior to use.
Treatment of N,N-bis(trimethylsilyl) β-amino ester (253) with 0.2
equivalents of nBu$_4$NF prepared in this way resulted in recovery of
starting material (Scheme 92).   Utilization of tris(dimethylamino)
sulphur trimethylsilyldifluoride[78] also returned starting material.

Lithium enolates can be liberated from the corresponding silyl
enol ethers by the action of MeLi-LiBr.[79]   It was envisaged that
treatment of (253) with this reagent should furnish the corresponding
N-lithio-N-silyl β-amino ester, which could spontaneously cyclise to yield

(256)

1) Me_3SiCl, Et_3N
2) $MeMgBr$
3) Ac_2O, py

$\underset{Cl}{\overset{O}{\parallel}}$, MeOH

COOH
|
COOH

TsCl, NaOH

Ac_2O, py

Scheme 93

(254)

MeOH, Δ

NH₄Cl, THF–H₂O

1N HCl

ptsa

TMSOTf

Scheme 94

(201)

TfO⁻
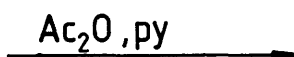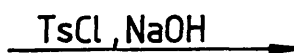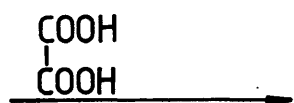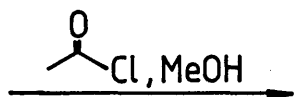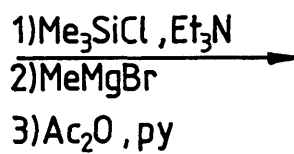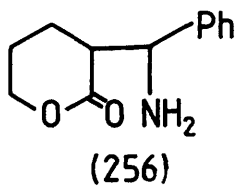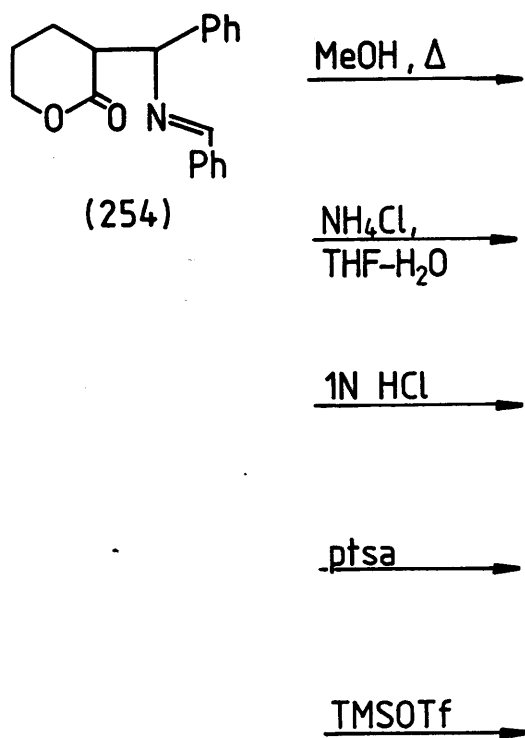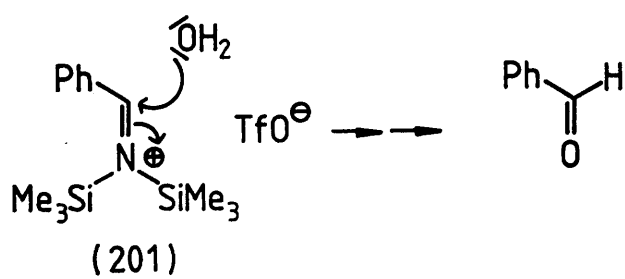
Scheme 95

the desired β-lactam.   However, compound (253) merely decomposed on reaction with MeLi-LiBr.

Turning to aqueous conditions, utilization of aqueous hydrogen fluoride appeared to yield the desired N-unsubstituted β-amino ester (256).   The ^{1}H n.m.r spectrum of (256) was essentially the same as that of (253), apart from the absence of high-field silicon-methyl signals.   At a practical level, β-amino ester (256) was a very viscous oil that could not be purified by conventional column chromatography. Attempts to derivatise (256) in order to aid characterisation are outlined in Scheme 93.   Treatment of the β-amino ester (256) with chlorotrimethylsilane in the presence of triethylamine, followed by MeMgBr and attempted derivatisation of the crude reaction product with acetic anhydride in the presence of pyridine furnished no β-lactam containing products.   Reactions aimed at forming the corresponding hydrochloride and oxalate salts, as well as the p-toluene sulphonamide and acetamide derivatives all failed.

Deblocking of the Schiff base (254) nitrogen atom could not be achieved under acidic conditions (Scheme 94).   Disappointingly, treatment of (254) with excess TMSOTf, followed by an aqueous work-up, yielding starting material.   This result is surprising since the reactive iminium species (201), derived from N-trimethylsilyl benzaldimine (181b) and TMSOTf, undergoes hydrolysis when treated with water, yielding benzaldehyde and, presumably, bis(trimethylsilyl) amine (Scheme 95).

No advantage was gained by catalysing the reaction between ketene acetal (252) and imine (181b) with a full equivalent of TMSOTf or by utilization of the ZnI$_2$ approach.   The lithium ester enolate of δ-

Ph－
‖
NSiMe$_2$Bu^t

(181a)

→

(Ph)
O O N–SiMe$_2$Bu^t
|
M

(257) M = ZnI , SiMe$_3$

Ph
O O NHSiMe$_2$Bu^t

(258)

Scheme 96

Ph－
‖
NSiMe$_3$

(181b)

+

OSiMe$_3$

(252)

$\xrightarrow{nBu_4NF}$

Scheme 97

Ph
NPh
(259)

+

(252) OSiMe₃

10%TMSOTf →

100%TMSOTf →

ZnI_2,Bu^{t}OH →

Ph
O NHPh
(260)

Scheme 98

Ph
O NHPh
(260)

LiN(SiMe₃)₂ →

Ph
O
(261)

+ PhNH₂
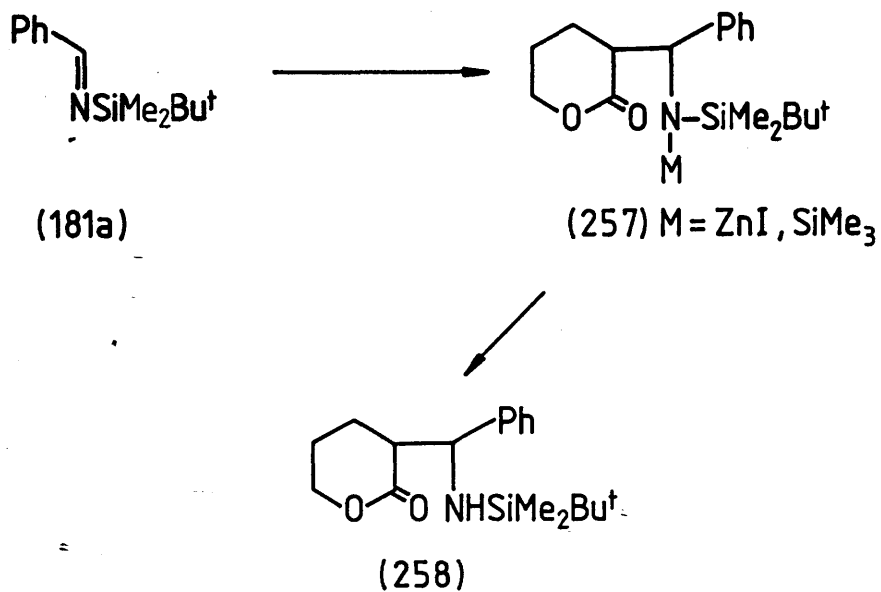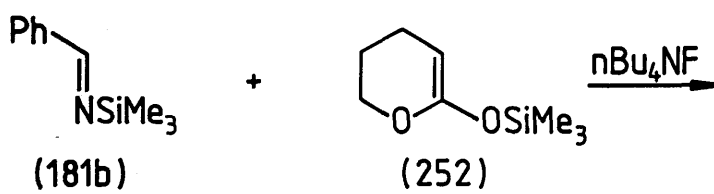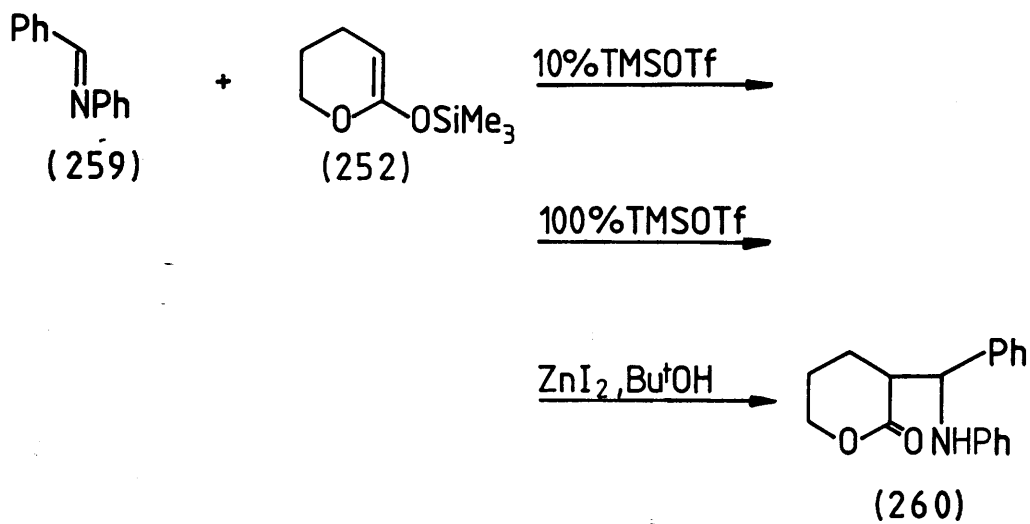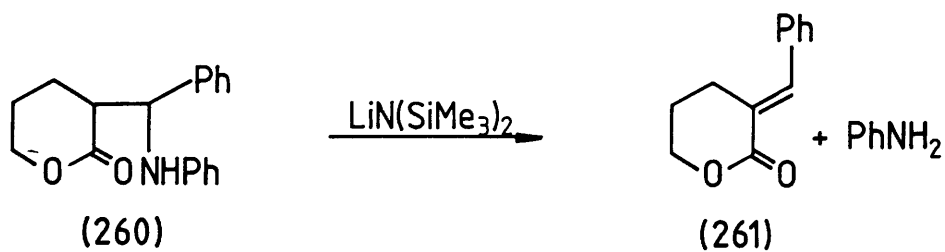
Scheme 99

valerolactone (251) gave, upon reaction with imine (181b), a complex mixture of products.

Utilization of N-t-butyldimethylsilyl benzaldimine (181a) would hopefully allow access to the mono-silyl β-amino ester (258) by way of the differentially substituted β-amino ester (257), but both ZnI_2 and TMSOTf failed to induce this reaction in a satisfactory manner (Scheme 96). Reaction of imine (181b) and ketene acetal (252) with 0.1 equivalents of nBu_4NF yielded starting material only (Scheme 97).

As β-amino esters derived from δ-valerolactone (251) appear to exhibit unusual behaviour, a more stable system was sought. Reaction of benzylidene aniline (259) with ketene acetal (252) using both catalytic and stoichiometric quantities of TMSOTf resulted in essentially no reaction. However, ZnI_2 mediation produced the desired N-phenyl β-amino ester (260) in 75% yield as a 2:1 mixture of threo and erythro diastereosiomers (Scheme 98). Attempted cyclisation of (260) using lithium hexamethyldisilazide produced the known[80] α,β-unsaturated lactone (261), via elimination of aniline (Scheme 99). Treatment of (260) with both MeMgBr and t-BuMgCl resulted in substantial C-2/C-3 bond cleavage, yielding benzylidene aniline (259) and polymerised δ-valerolactone.

In order to obtain the more familiar β-amino ester skeleton prior to cyclisation, N-phenyl β-amino ester (260) was treated with sodium methoxide in methanol (Scheme 100). Surprisingly, hydroxy β-amino ester (262) was produced quantitatively, re-cyclising to (260) over 12h upon storage at $-10^{o}C$. The ring-opened β-amino ester (202) was treated immediately after chromatographic purification with acetic anhydride and pyridine to yield the corresponding acetate (263) in 82%

(260)

NaOMe, MeOH →

(262) R = H
(263)   = Ac
(264)   = SiMe$_2$Bu^t

Bu^{t}MgBr →

(265)
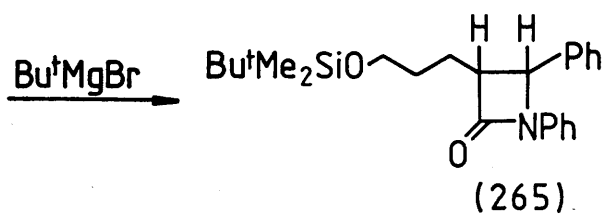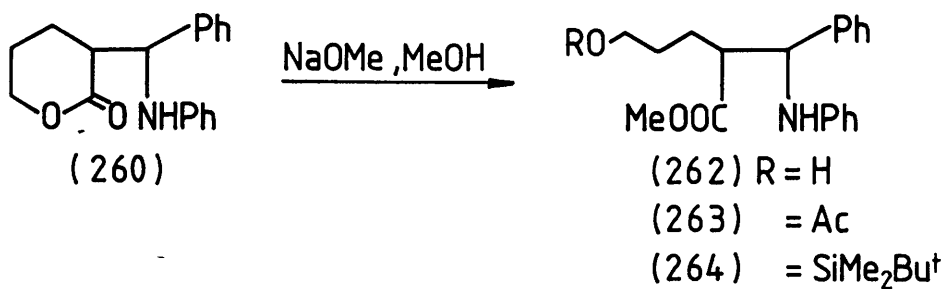
Scheme 100

(181a) R = Ph
(185a)   = 2-furyl
(182)   = COOEt
(186)   = ⋋⟍

yield.   Alternatively, treatment of (262) with t-butylchlorodimethyl-
silane and imidazole furnished the corresponding silyl ether (264) in
78% yield.   Treatment of (264) with t-BuMgCl cleanly produced the
N-phenyl β-lactam (265) in 90% yield as a 2:1 mixture of trans and cis
diastereoisomers.

5. The Synthesis and Reactions of Polyfunctionalised Imines.

In the previously discussed synthesis of N-t-butyldimethylsilyl
imines (181a), (185a), (182) and (186), the ease with which dehydrochloro-
ination of the corresponding N-chloro-N-silyl amines takes place can be
explained by noting that introduction of the imine moiety produces a
conjugated π-system.   To test the general applicability of this
silylation-halogenation-elimination approach to imine synthesis from
primary amines, a simple saturated system was examined.

Silylation of n-butyl amine proceeded readily, yielding the N-t-
butyldimethylsilyl amine (267) in 98% yield (Scheme 101).   N-chlorination
with t-butyl hypochlorite gave the desired N-chloro-N-silyl amine (268)
in quantitative yield.   Unfortunately, dehydrochlorination could not
be induced by treatment with DBU, even after prolonged reaction times
at elevated temperature.   Utilization of potassium carbonate, triethyl-
amine or 4-(N,N-dimethyl)aminopyridine under a variety of conditions resulted
in recovery of starting material.

Addition of lithium hexamethyldisilazide to the N-chloro-N-silyl
amine produced a complex mixture of products, containing a large
proportion of the N-silyl amine (267).   Dechlorination probably resulted
from metal-halogen exchange, yielding the N-lithio-N-silyl amine (269).

$$\text{(266)} \quad \text{NH}_2 \quad \xrightarrow[\text{Et}_3\text{N, DMAP}]{\text{Bu}^t\text{Me}_2\text{SiCl,}} \quad \text{Bu}^t\text{Me}_2\text{SiNH} \quad \text{(267)} \quad \xrightarrow{\text{Bu}^t\text{OCl}} \quad \text{Bu}^t\text{Me}_2\text{Si} \overset{\text{N}}{\underset{\text{Cl}}{}} \quad \text{(268)}$$

Scheme 101

$$\text{Bu}^t\text{Me}_2\text{SiN} \overset{}{\underset{\text{Li}}{}}$$

(269)

$$\text{Bu}^t\text{Me}_2\text{SiNH} \quad \xrightarrow{n\text{BuLi}} \quad \text{Bu}^t\text{Me}_2\text{SiN} \overset{}{\underset{\text{Li}}{}} \quad \xrightarrow{\text{Bu}^t\text{OCl}}$$

(267)   (269)

$$\text{Bu}^t\text{Me}_2\text{SiNCl} \quad + \; \text{LiOBu}^t \quad \longrightarrow \quad \text{Bu}^t\text{Me}_2\text{SiN} \quad + \; \text{LiCl} + \text{Bu}^t\text{OH}$$

(268)   (270)

Scheme 102

$$H_2N \quad OH \xrightarrow[\text{Et}_3\text{N, DMAP}]{\text{Bu}^t\text{Me}_2\text{SiCl,}} \text{Bu}^t\text{Me}_2\text{SiNH OSiMe}_2\text{Bu}^t$$

(270) (272)

Scheme 103

$$H_2N \quad OH \xrightarrow[\text{2)NaOEt}]{\text{1)HCl, AcOH}} H_2N \quad OAc \xrightarrow[\text{Et}_3\text{N, DMAP}]{\text{Bu}^t\text{Me}_2\text{SiCl,}} \text{AcNH OR}$$

(271) (273) (274) R = H

(275) R = SiMe$_2$Bu^t

Scheme 104

(276) xylene, Δ (277)
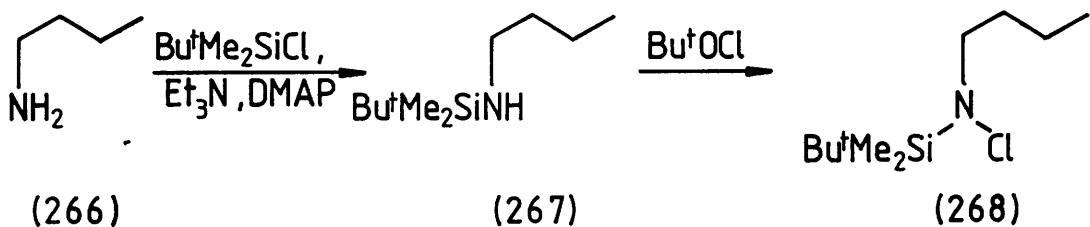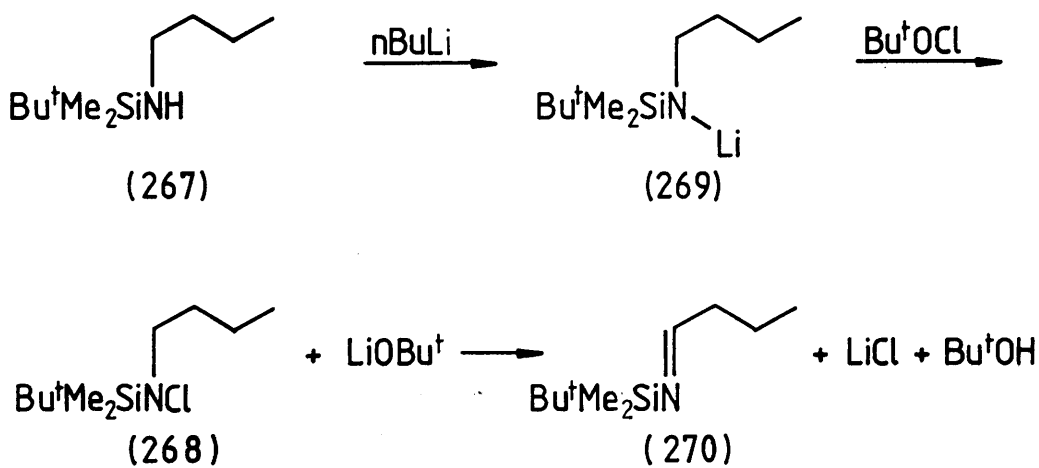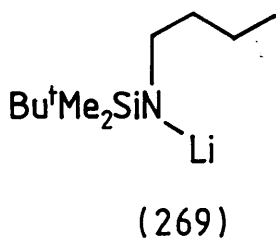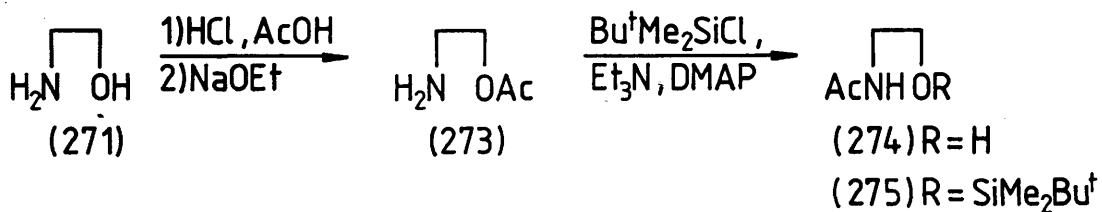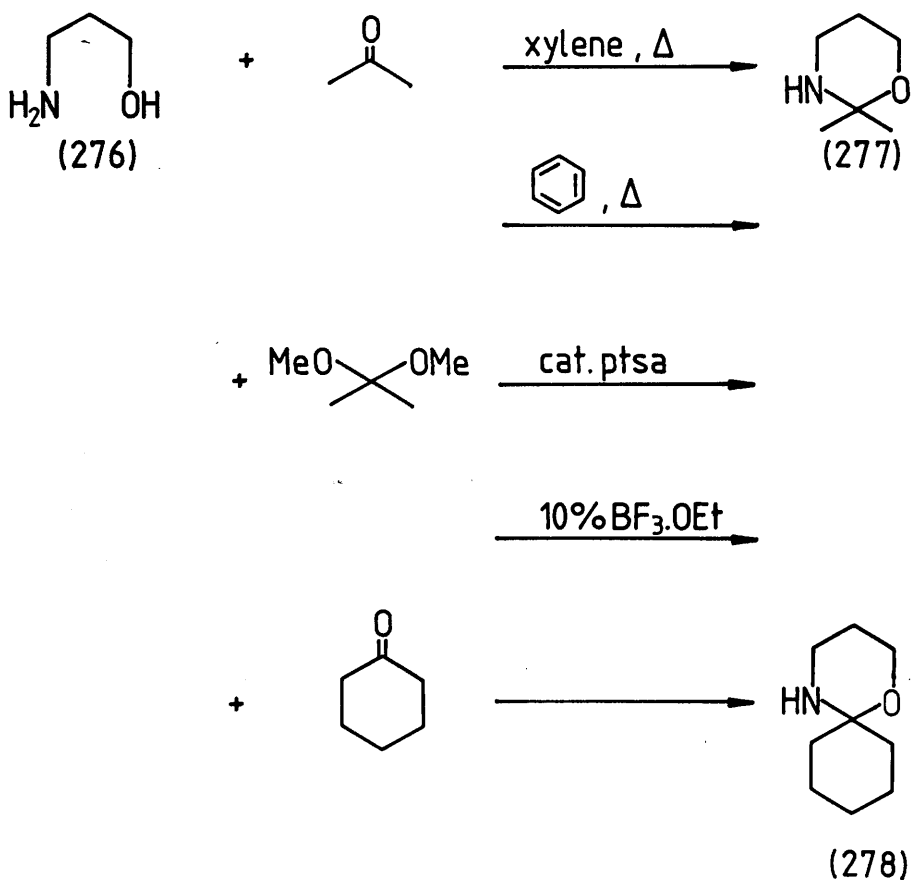
Scheme 105

This reactive species would protonate upon work-up, yielding N-silyl
amine (267).

As this undesired process would probably occur with all lithium
dialkylamide bases, utilization of a strong thermodynamic base was then
investigated.   It was envisaged (Scheme 102) that treatment of the
nitrogen anion (269), obtained from reaction between the N-silyl amine
(267) and nBuLi would, upon addition of t-butyl hypochlorite, produce the
N-chloro-N-silyl amine (268) in the presence of lithium t-butoxide.
Loss of HCl could then proceed to yield the desired N-t-butyldimethylsilyl
imine (270).   In practice, addition of nBuLi to a solution of N-silyl
amine (267) in THF, followed by addition of t-butyl hypochlorite, produced
a complex mixture of products with no trace of a low field signal
corresponding to an imine proton being detected in the ^{1}H n.m.r spectrum
of the crude mixture.

Attempts were then made to synthesise the N-t-butyldimethylsilyl
imine derived from ethanolamine (271) (Scheme 103).   Silylation of
both heteroatoms of (271) proceeded only to a slight degree, yielding the
desired N,O-bis(silyl)compound (272) in low yield, together with impurities
which made the isolation of (272) impossible.

A search of the literature revealed very few instances of selective
protection of one of the heteroatoms of (271).   However, O-acetyl
ethanolamine (273) was prepared according to a literature method[81]
(Scheme 104).   Unfortunately, attempted silylation of (273) resulted
in acyl-transfer, producing an inseparable mixture of alcohol (274) and
silyl ether (275).   This was confirmed by analysis of the i.r. spectrum
of the mixture of (274) and (275), which revealed the presence of the

(278)

Bu^tOCl

(279)

+ (278)

Scheme 106

H_2N OH

(276)

Me_2SiCl_2, py

(280)

Scheme 107

(281)

(282)

(283)

(284)
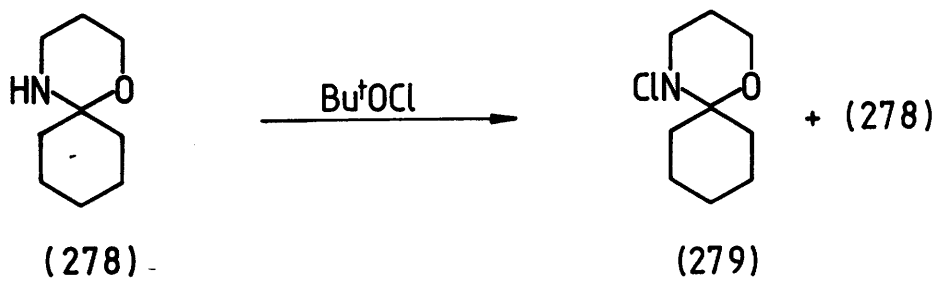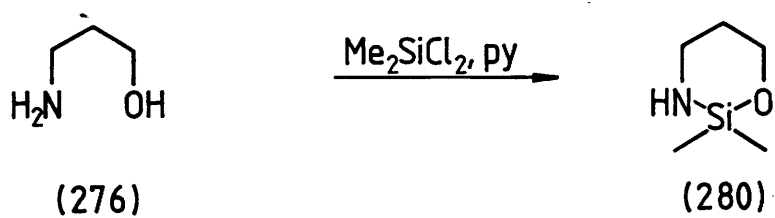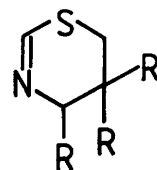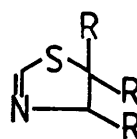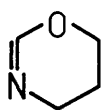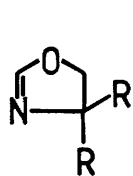
amide I and II absorptions at 1650 cm^{-1} and 1550 cm^{-1} respectively, as expected for a secondary amide.

The problems associated with attempted differential protection of ethanolamine (271) could potentially be overcome by amine acetal formation. Synthesis of oxazines (277) and (278) have been reported by condensation of 3-amino propanol (276) with acetone[82] and cyclohexanone[83] respectively (Scheme 105). Difficulty was encountered when attempting to construct the oxazine (277); considerable by-product formation prevented isolation of the pure compound. Utilization of 2,2-dimethoxy propane in conjunction with acid catalysis resulted in recovery of starting material. However, spiro-oxazine (278) was readily prepared in 60% yield.

Initial reaction of (278) with t-butyl hypochlorite in a manner analogous to that discussed previously resulted in incomplete reaction, forming a 2:1 mixture of the desired N-chloro oxazine (279) and unreacted (278) (Scheme 106). Utilization of excess t-butyl hypochlorite merely resulted in decomposition.

Turning to the succinimide halogenation reagents, N-chloro- and N-bromosuccinimide, oxazine (278) succumbed to partial halogenation as indicated by the appearance of a low field triplet in the ^{1}H n.m.r spectrum of the crude product. This multiplicity is due to the methylene protons α to the nitrogen centre. Disappointingly, and before complete conversion of oxazine (278) into the corresponding N-halo compound, substantial decomposition occurred, yielding polymeric materials. Addition of catalytic quantities of dibenzoyl peroxide offered no advantage. Attempts to protect both heteroatoms of (276)

HS
CLH₃N— ̈ —H
COOEt
(285)

1) NH₃(g)
2) HC(OEt)₃ ,ptsa, Δ
3) Δ

$\xrightarrow{\hspace{3cm}}$

N≡ / S
COOEt
(153)

Scheme 108

MeO OSiMe₃
(187)

+

N≡ / S
COOEt
(153)

$\xrightarrow[\text{10\% TMSOTf}]{\text{4ÅMS}}$

MeOOC HN— S
COOEt
(286)

Scheme 109

O= N— S
COOEt
(287)

MeOOC HN—⟨structure⟩ S —RMgX or LiN(SiMe₃)₂→ MeOOC MN—⟨structure⟩ S

MeOOC HN—structure, COOEt

(286)

RMgX or LiN(SiMe$_3$)$_2$ →

MeOOC MN—structure, COOEt

(288) M = MgX , Li

⇅

MeOOC N—structure, SM, COOEt

(289)

Scheme 110

MeO—⟨structure⟩—OLi
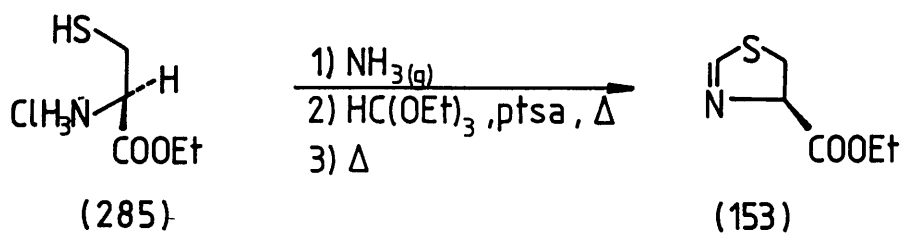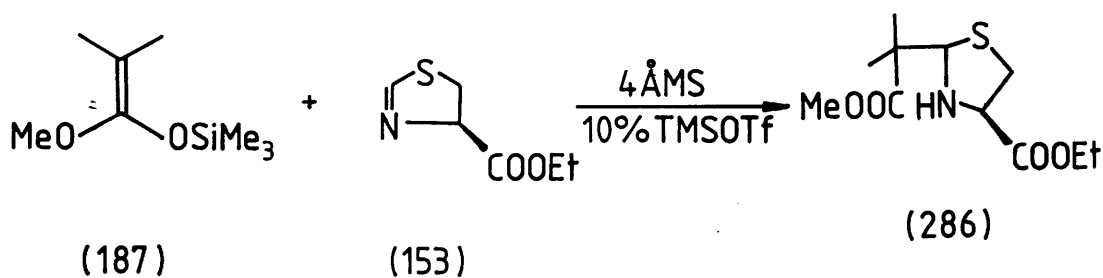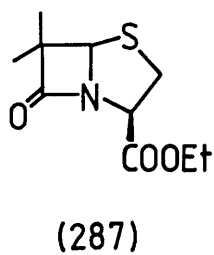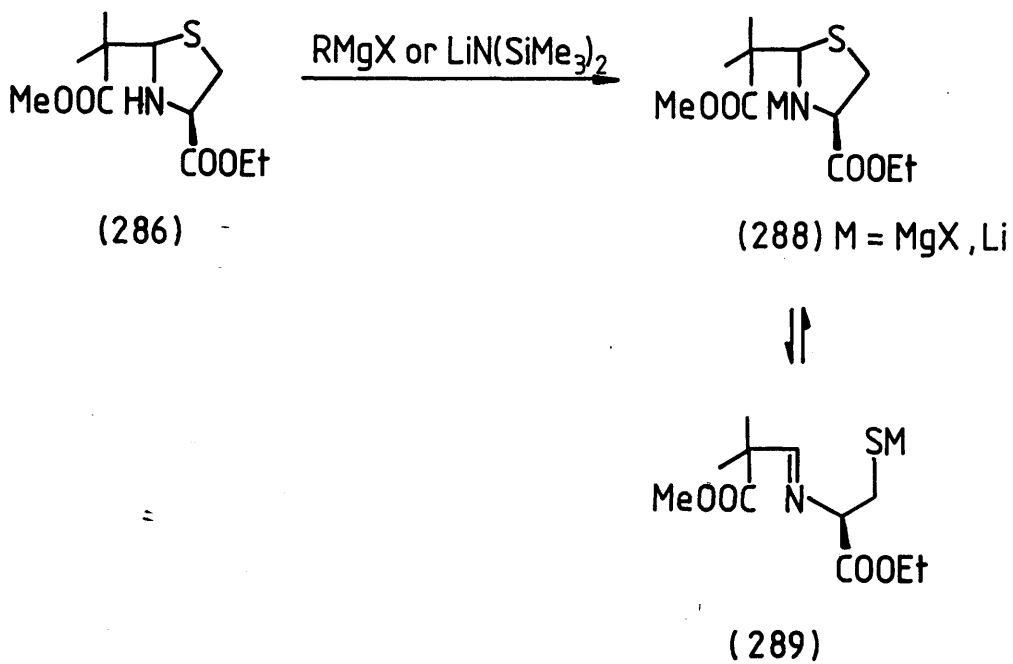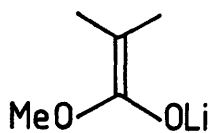
(197)

via silylation using dichlorodimethylsilane,[84] succeeded to a limited

extent (Scheme 107).   Again, by-product formation prevented isolation

of the desired product (280).

The ready availability of oxazolines (281),[30] oxazines (282),[85]

thiazolines (283)[42] and thiazines (284)[42] make these compounds attractive

imine components for the direct synthesis of bicyclic β-lactams.

Application of these compounds to the ketene-imine approach to β-lactam

synthesis has allowed access to the important cepham frameworks,[30,42,43]

as well as to nuclear analogues, the oxapenams and oxacephams.[30]

Chiral thiazoline (153) was prepared according to the method of

Manhas (Scheme 108).[42]   Gaseous ammonia was passed through a solution of

L-cysteine ethyl ester hydrochloride (285) in methanol.   Removal of

solvent yielded L-cysteine ethyl ester, which was dissolved in ethanol

and heated to reflux in the presence of triethyl orthoformate and a

catalytic quantity of p-toluenesulphonic acid.   Extractive work-up

yielded N-formylcysteine ethyl ester which upon distillation yielded

the chiral thiazoline (153).

To a mixture of (153), silyl ketene acetal (187) and crushed 4Å

molecular sieves in CH_2Cl_2 at $-78°C$ was added 0.1 equivalents of TMSOTf

(Scheme 109).   Work-up afforded the β-amino ester (286) in 98% yield,

apparently as a single diastereoisomer.

Cyclisation of β-amino ester (286) into the penam (287) was then

attempted (Scheme 110).   Treatment of (286) with MeMgBr or t-BuMgCl

resulted in partial recovery of starting material along with materials

obtained from attack on the ester substituents by the Grignard reagents.

Utilization of lithium hexamethyldisilazide gave a complex mixture of

products.

PhO

COOH

(290)

$\xrightarrow{\text{PhOPOCl}_2, \\ \text{Et}_3\text{N}}$

PhO

O=C—O—P—Cl

OPh

(291)

$\downarrow$ Et₃N

PhO

O

(292)

Scheme 111

PhO

O

(290)

$+$

thiazoline—COOEt

(153)

$\longrightarrow$

PhO

⊖O

⊕N—S

COOEt

(293)

$\updownarrow$

PhO

⊖O

N⊕—S

COOEt
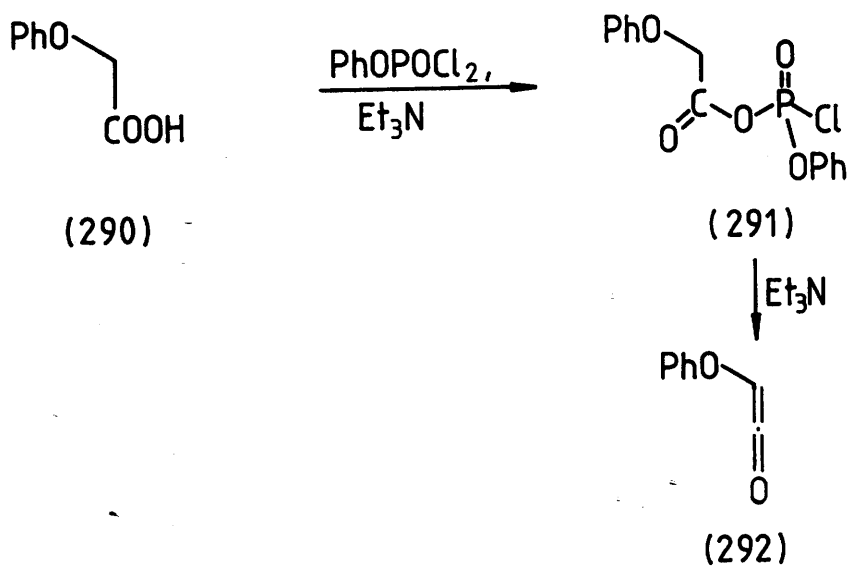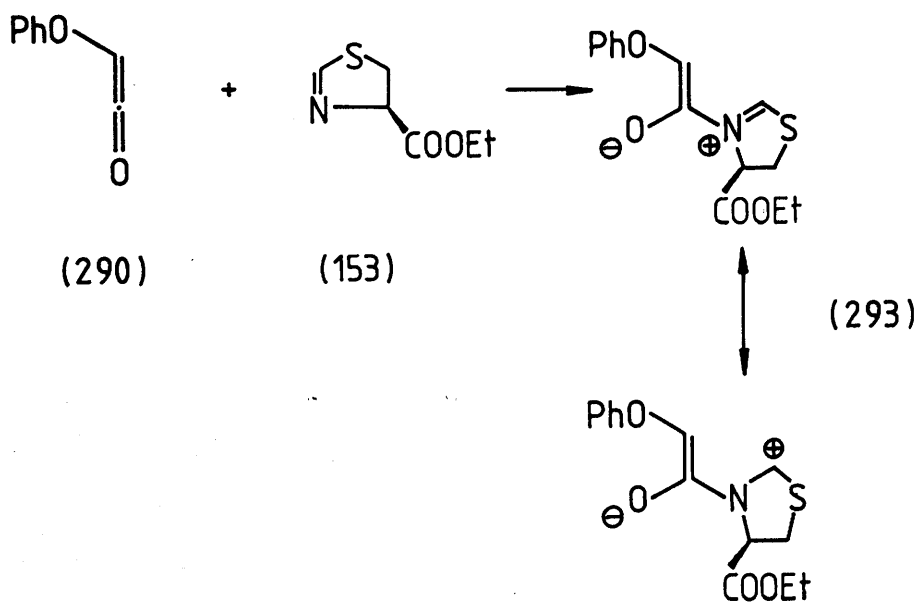
Scheme 112

The mechanism of these attempted transformations involves generation of a formal nitrogen anion (288), which can conceivably equilibrate with the thiolate ion (289). Even if this general approach to cyclisation of (286) could be made to furnish the desired bicyclic species (287), there is the danger that, due to the equilibrium between (288) and (289), any stereoselectivity exhibited in the initial bond-forming process would be lost.

Two attempts were made to construct the penam directly. Firstly, addition of lithium ester enolate (197) to the chiral thiazoline yielded no recognisable products. Secondly, a variant of the acid halide-imine approach to β-lactam construction was investigated (Scheme 111).[66] Addition of phenoxyacetic acid (290) to phenyl dichlorophosphate in the presence of triethylamine results in formation of the phosphate ester (291). It is not clear whether phosphate ester (291) or the in situ generated ketene (292) is the reactive species. Addition of an imine then produces the corresponding β-lactam, with a reported selectivity for cis-β-lactam formation. Utilization of chiral thiazoline (153) as the imine component in this approach did not yield any β-lactam containing material. This may be due in part to the proposed intermediate (293), derived from attack on the ketene (290), or an equivalent, by the chiral imine (153) (Scheme 112). There is no additional functionality present in (293) than can suitably stabilise the developing positive charge. Indeed, utilization of thiazolines of the form (294, X = H) in the acid halide-imine approach to β-lactam synthesis invariably resulted in a very low yield of the desired penam being observed.[42] However, when X = aryl, thiazolines (294) were of great utility, yielding the corresponding penams in excellent yield, presumably a result of the aryl substituent

(294)

(295) → TMSOTf → (296) TfO⊖

(297)

Scheme 113

(298)   (299)

(300) R = COOMe

Scheme 114

(301) R = CH₃   (303)   (216) R = CH₃
(302) R = nPr   (304) R = nPr
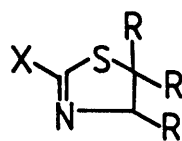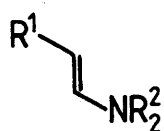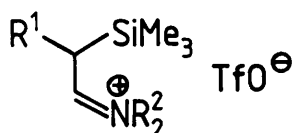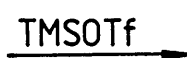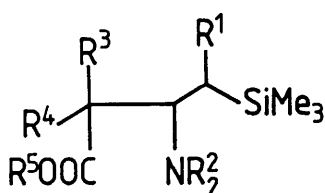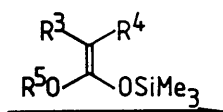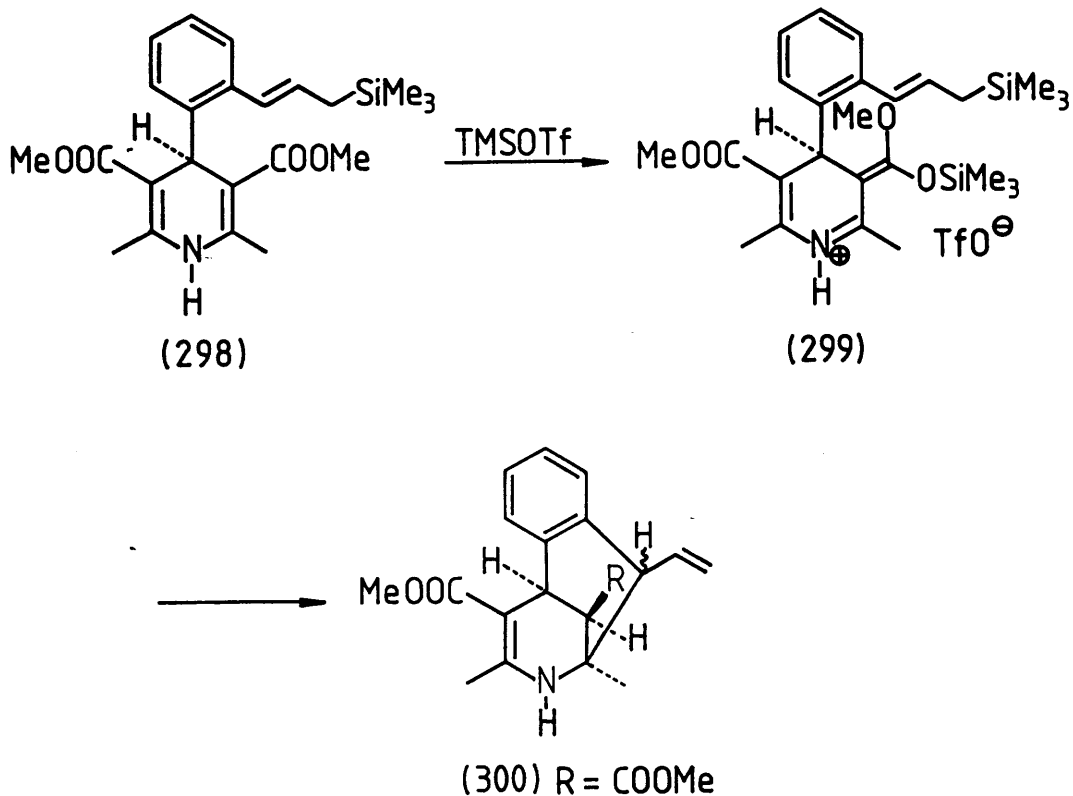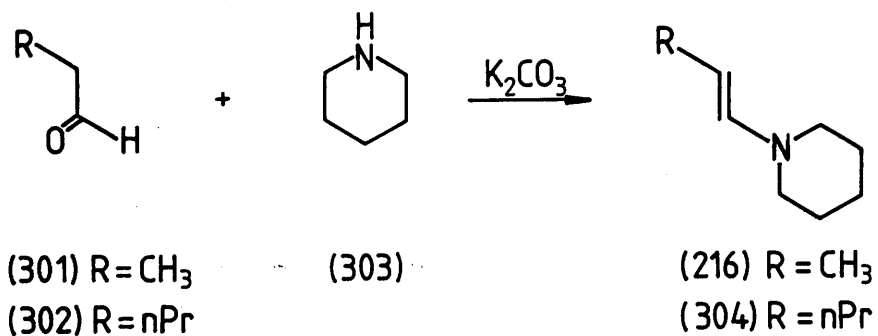
Scheme 115

effectively stabilising the developing positive charge.

6.   The Synthesis of β-Amino Esters From Enamines.

In a conceptually different approach it was envisaged that, under carefully controlled conditions, simple imine-enamine tautomerism might provide the highly reactive iminium species required for reaction with a silyl ketene acetal (Scheme 113).   Enamine (295) could react with TMSOTf to furnish the α-silyl iminium species (296).   Attack by a silyl ketene acetal would then provide the β-amino ester (297).

Inspection of the literature revealed that an enamine can indeed be made to react in this general manner (Scheme 114).[86]   Treatment of dihydropyridine (298) with excess TMSOTf resulted in formation of terminal alkene (300).   This reaction probably proceeds via complexation of (298) with TMSOTf, yielding the iminium species (299).   Subsequent intramolecular attack on the iminium moiety of (299) by the allyltri-methylsilane unit yielded the alkene (300), upon hydrolytic work-up. Encouraged by this observation, a TMSOTf-mediated reaction between enamines and silyl ketene acetals was explored.

Enamines (216)[87] and (304) were prepared by addition of excess piperidine (303) to either propanal (301) or pentanal (302) in the presence of potassium carbonate (Scheme 115).   Distillation yielded enamine (216) as a 1:1 mixture with piperidine, and enamine (304), free of starting material.   Due to the similarity in boiling point of enamine (216) and piperidine, enamine (216) was utilized in this impure form.

Reaction of enamine (216) with a full equivalent of TMSOTf in the

MeO‾ ‾OSiMe₃ rendered as chemical structures.

(187)   +   (216) R = CH₃
            (304) R = nPr

4ÅMS,
100% TMSOTf

(305) R = CH₃
(306) R = nPr

Scheme 116

(303)   TMSOTf →   (307)   (216) →   (308) R = CH₃
                                      (309) R = nPr

(187) →   (305) R = CH₃
          (306) R = nPr
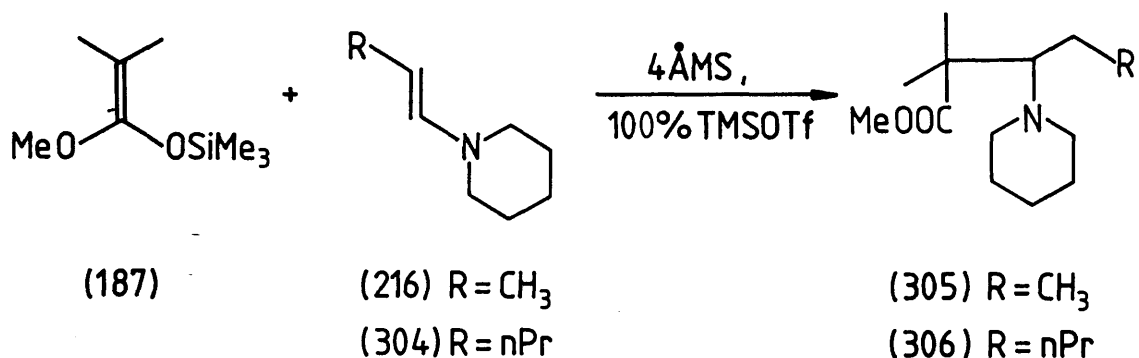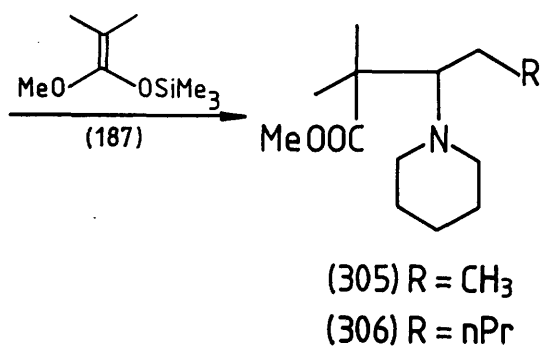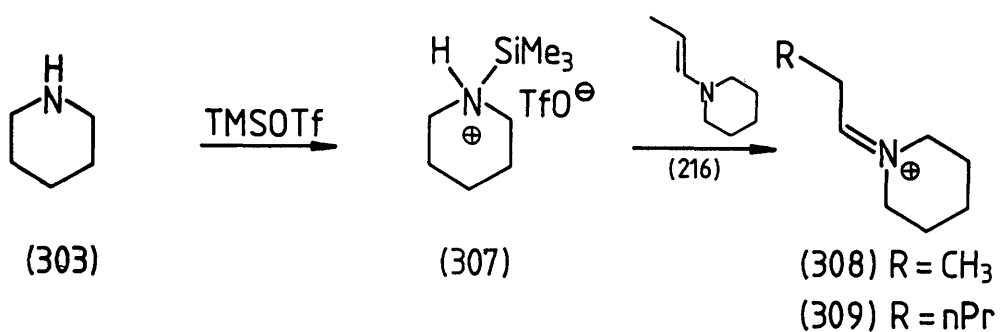
Scheme 117

presence of crushed 4 Å molecular sieves, produced a vivid red solution.

Addition of silyl ketene acetal (187) did not result in any observable

change.   Aqueous work-up and chromatographic purification yielded the

non-silicon containing β-amino ester (305) in 48% yield (Scheme 116).

This yield may be put into perspective when it is noted that the

starting enamine (216) was only 50% pure.   It is perhaps not surprising

that no silicon substituent was found in the reaction product.   The

piperidine (303) may, upon addition of TMSOTf, furnish the ammonium

species (307) (Scheme 117).   In the presence of enamine (216), cation

(307) could act as a proton source, providing the iminium ion (308) via

simple imine-enamine tautomerism.   Subsequent reaction of (308) with

silyl ketene acetal (187) would then yield the observed β-amino ester

(305).

However, utilization of pure enamine (304) in this approach also

furnished a non-silicon containing β-amino ester, that is, compound

(306) in 85% yield (Scheme 116).   Unintentional hydrolysis of TMSOTf

prior to reaction would produce trifluoromethanesulphonic acid and,

thence, β-amino ester (306) via the iminium ion (309).   Repeating this

reaction many times with freshly prepared Lewis acid never gave any trace

of the expected silylated reaction product.   Use of catalytic quantities

of TMSOTf resulted in essentially no reaction.

This reaction proceeded smoothly with or without the use of 4 Å

molecular sieves and was also catalysed efficiently by trifluoromethane-

sulphonic acid.   Utilization of chlorotrimethylsilane in place of

TMSOTf allowed non-aqueous isolation of the reaction products, as its

volatility permitted simple evaporation of the reaction mixture.   In

practice, the chlorotrimethylsilane-mediated reaction furnished β-amino ester (306) in low yield, along with considerable quantities of unrecognisable materials. Repetition of this reaction, but with an aqueous work-up, gave the β-amino ester in a yield comparable to that found in the TMSOTf-mediated example.

A brief ^{1}H n.m.r study of this process was carried out. To the enamine (304) in CD_2Cl_2 was added one equivalent of TMSOTf. The spectrum of this mixture was completely unresolved apart from a high-field singlet, presumably due to a trimethylsilyl moiety. Addition of approximately 0.2 equivalents of silyl ketene acetal (187) produced signals corresponding to the β-amino ester (306). As time progressed these signals increased in intensity as the signals corresponding to silyl ketene acetal (187) decreased. Once (187) had been totally consumed, the spectrum consisted of signals associated with the β-amino ester (306) and the species formed from reaction of enamine (216) with TMSOTf. Addition of a further 0.8 equivalents of silyl ketene acetal (187) resulted in complete disappearance of the unresolved signals, leaving only signals due to β-amino ester (306) and TMSOTf. In the early stages of reaction, the high-field portion of the ^{1}H n.m.r spectra was complex due to various trimethylsilyl moieties. However, towards the end of the reaction it did not appear that the expected silicon-containing β-amino ester was present.

There is, as yet, no convincing mechanistic rationale to explain the non-appearance of a trimethylsilyl moiety in the product β-amino ester (306).

R——\
‖
NSiMe₃
$\xrightarrow{\text{TMSOTf}}$
R——\
‖
⊕N(SiMe₃)₂

(221)
$\xrightarrow{\text{TfO}^{\ominus}\ \text{Nu}}$
R——CH(Nu)
|
N(SiMe₃)₂

(310)

Scheme 118

Ph——\
‖
NSiMe₃

(181b)
+
══\
SiMe₃

(311)
$\xrightarrow{\text{10\% TMSOTf}}$ no reaction

$\xrightarrow{\text{ZnI}_2}$ "

$\xrightarrow{\text{SnCl}_4}$ "

$\xrightarrow{\text{BF}_3.\text{OEt}_2}$ "

Scheme 119

Ph
$\parallel$
NSiMe$_3$

(181b)

+

SiMe$_3$

(312)

10% TMSOTf $\longrightarrow$ no reaction

ZnI$_2$ $\longrightarrow$ "

SnCl$_4$ $\longrightarrow$ "

BF$_3$.OEt$_2$ $\longrightarrow$ "

ZnCl$_2$ $\longrightarrow$ "

TiCl$_4$ $\longrightarrow$

Ph
$|$
N
$\parallel$
Ph

(313)
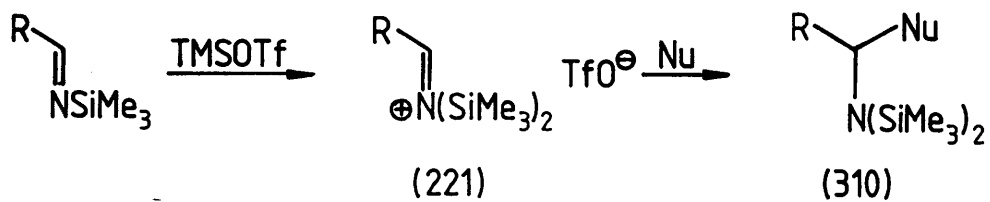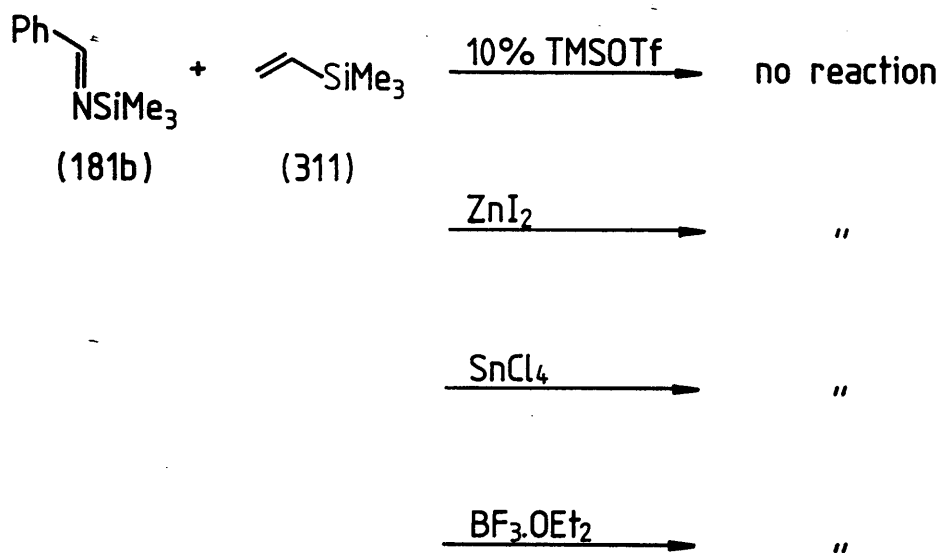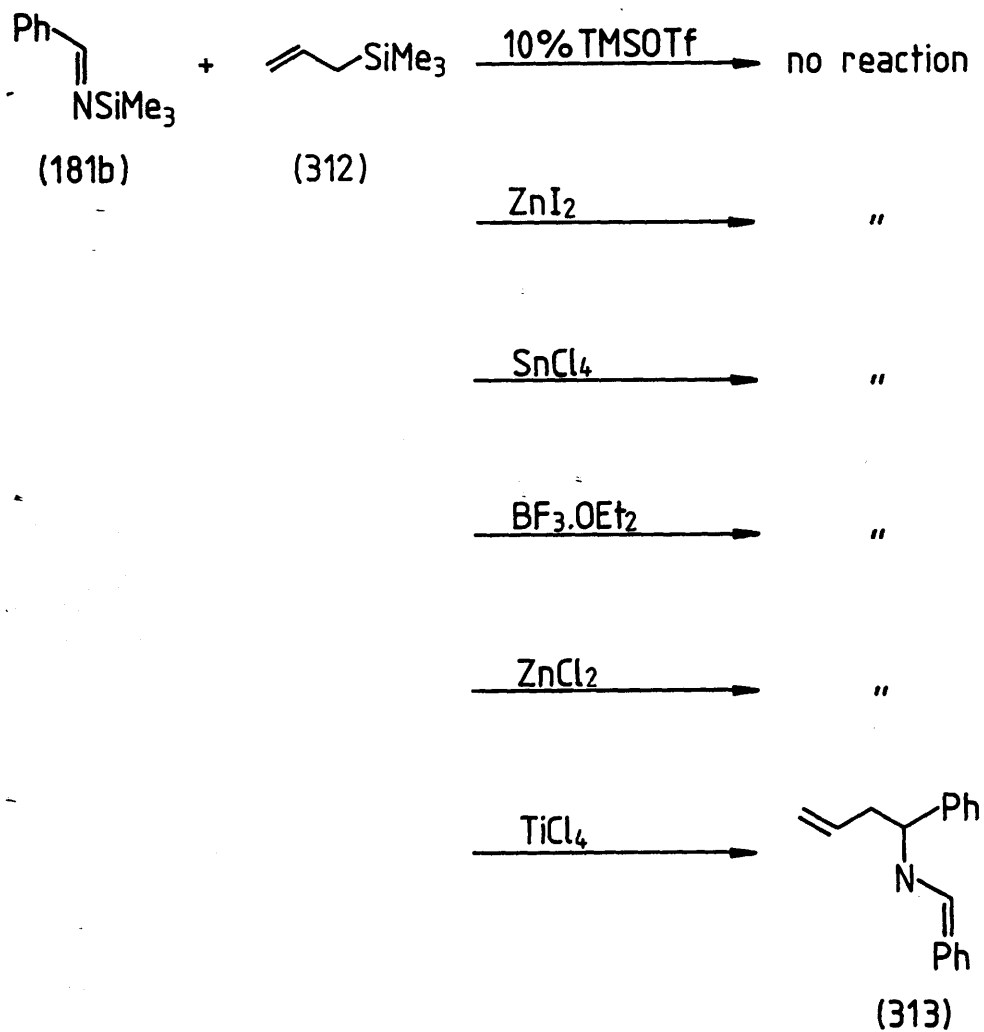
Scheme 120

7. **The Reactions of N-Trimethylsilyl Benzaldimine with Vinyl and Allyltrimethylsilane.**

In order to ascertain the reactivity of iminium ions (221) towards nucleophiles other than silyl ketene acetals, attempts were made to synthesise functionalised amines of the form (310) (Scheme 118). These amines, once synthesised, could be useful precursors of interesting 4,4-disubstituted β-lactams via the corresponding N-t-butyldimethylsilyl imines.

Initially, to a mixture of N-trimethylsilyl benzaldimine (181b) and the reactive nucleophile vinyltrimethylsilane (311) was added 0.1 equivalents of TMSOTf (Scheme 119). Disappointingly, only products arising from hydrolysis of imine (181b) were isolated. All attempts to induce reaction of vinyltrimethylsilane with the iminium species derived from reaction between imine (181b) and ZnI_2, $SnCl_4$ and $BF_3.OEt_2$ failed.

As was discussed earlier (p 50), TMSOTf has been used[86] to induce the intramolecular reaction of an allyltrimethylsilane unit with an electrophilic iminium moiety. In a similar system,[88] $TiCl_4$ has been effective in mediating the intermolecular reaction of allyltrimethylsilane with an iminium ion.

Various Lewis acids were employed in an attempt to induce the reaction between imine (181b) and allyltrimethylsilane (312) (Scheme 120). Only by utilization of $TiCl_4$ at low temperature could the desired reaction be achieved, yielding a 2:1 mixture of the Schiff base (313) and benzaldehyde. The Schiff base (313) was isolated in 62% yield. Attempts to suppress the trans-amination process by utilization of three equivalents of allyltrimethylsilane and two equivalents of t-BuOH merely

resulted in a lower yield of the Schiff base (313), probably due to

consumption of allyltrimethylsilane via reaction with the alcohol.

Attempts to liberate the free base corresponding to (313) were

inefficient.

8. Conclusions and Outlook.

N-Trimethylsilyl and N-t-butyldimethylsilyl imines can be utilized

to good effect in the ester-imine condensation approach to β-lactam

synthesis.   As mediators for this process, both ZnI_2 and TMSOTf have

been shown to be effective.   Although the yields of products from both

Lewis-acid mediated approaches are comparable,   TMSOTf induces a slightly

greater threo diastereoselectivity in the initial bond-forming step.

Both processes can be developed into direct, one-pot syntheses of

β-lactams; N-trimethylsilyl imines yield the corresponding N-unsubstituted

β-lactams, and N-t-butyldimethylsilyl imines the corresponding N-silyl

β-lactams.

A disadvantage found when using ZnI_2 as Lewis acid, that of

complexation with other functionality present in the imine in addition

to the nitrogen atom, has been overcome by the utilization of TMSOTf,

producing, for example, the synthetically useful 4-ethoxycarbonyl

β-lactam (212).

Although both Lewis acid-mediated approaches are plagued by over-

reaction, producing the corresponding Schiff base, this can be suppressed

by addition of t-BuOH.   Protiodesilylation of the in situ generated

N,N-bis(silyl) β-amino esters common to both approaches prevents reaction

with a further molecule of activated imine.

Low temperature quenching of the enolate derived from attack upon

a non-enolisable aldehyde by lithium hexamethyldisilazide results in

formation of the corresponding amine acetal.   These amine acetals have

been shown to be useful precursors of β-amino esters, and can also be

used to synthesise β-lactams directly, in a one-pot process.

Cyclic ketene acetal (252) has been used in the ester-imine

approach, although certain compounds derived from (252) exhibited unusual

behaviour.   Incorporation of this ketene acetal bodes well for the

future use of ketene acetals derived from chiral lactones.

The synthesis of a wide range of β-lactams is dependent on the

availability of requisite starting materials.   The synthesis of

β-amino esters (305) and (306) from enamines opens up a whole class of

compounds as potential β-lactam precursors.   Incorporation of removable

N-substituents into the enamine component should allow access to β-amino

esters which may be converted into the corresponding β-lactams.

What remains to be investigated is, with due regard to the mechanistic

rationale governing diastereoselection, the utilization of chiral starting

materials, to yield enantiomerically pure β-lactams.   When predictable

asymmetric induction can be readily and efficiently achieved, the

ketene acetal-imine approach will become a truly effective protocol for

the construction of chiral β-lactams and, after suitable synthetic

elaboration, clinically important bicyclic β-lactam antibiotics.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Bulb-to-bulb distillations were carried out on a Buchi GKR-50 Kugelrohr; recorded boiling ranges refer to the indicated air bath temperatures. [1]H n.m.r Spectra were recorded on a Perkin-Elmer R32 spectrometer operating at 90MHz and a Bruker WP200 SY spectrometer operating at 200MHz. [1]H n.m.r chemical shifts are reported in parts per million (δ) relative to Me$_4$Si (0.00ppm). Infrared spectra were determined on a Perkin-Elmer 580 spectrometer. Low resolution mass spectra were determined on a VG uprated MS12 instrument and high resolution mass spectra were determined on an MS 902S. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Optical rotations were measured on an Optical Activity AA100 polarimeter.

Reactions were carried out under an atmosphere of either nitrogen or argon. All reactions involving organo-lithium reagents or trimethylsilyl trifluoromethanesulphonate were carried out under an atmosphere of argon exclusively. Tetrahydrofuran and Et$_2$O were distilled freshly from sodium benzophenone ketyl radical. Dichloromethane was distilled from P$_2$O$_5$, then filtered through basic alumina and stored over 4 Å molecular sieves. N,N-dimethylformamide was distilled from blue silica gel and stored over 4 Å molecular sieves. t-Butanol was distilled from sodium. Triethylamine, DBU and all primary amines were distilled from CaH$_2$. Molecular sieves (4Å) were pulverised and activated at 120°C prior to use in reactions.

The term 'non-aqueous work-up' refers to the process whereby the crude reaction mixture was diluted with either Et$_2$O or n-pentane, filtered through Celite 535 and concentrated in vacuo. This process

was repeated until a homogeneous crude product remained.   Organic

extracts were dried with Na_2SO_4 exclusively and concentrated on a Buchi

rotary evaporator in vacuo.   Dry column flash chromatography[89] refers

to a technique already described.

t-Butyl hypochlorite.[90]

A 1ℓ, 3-necked round-bottomed flask fitted with a mechanical

stirrer was charged with 15% NaOCl solution (200ml, 0.40mol) and water

(300ml).   The solution was cooled to 0°C and light was excluded before

a mixture of t-BuOH (37ml, 0.39mol) and AcOH (24.5ml, 0.43mol) was

added in one portion.   The solution was stirred vigorously for 3 min.,

then transferred to a 1ℓ separating flask.   The aqueous layer was

removed and the yellow organic layer was washed with saturated sodium

hydrogen carbonate (50ml) and water (50ml) and dried over $CaCl_2$ for 3h.

Filtration yielded t-butyl hypochlorite (37.2g, 88%) as a yellow liquid

that was stored in amber bottles in a desiccator over $CaCl_2$ in the dark.

The t-butyl hypochlorite so-formed was sufficiently pure for subsequent

use without further purification.

Synthesis of N-t-Butyldimethylsilyl Amines - General Procedure.

To the appropriate freshly distilled/recrystallised amine (20mmol)

in Et_2O (10ml) was added triethylamine (2.78ml,22mmol) and 4-(N,N-dimethyl)

aminopyridine (49mg, 0.40mmol) in Et_2O (2ml).   The solution was cooled

to 0°C and t-butylchlorodimethylsilane (3.01g, 20mmol) in Et_2O (10ml) was

added over 3 min.   The resulting heterogeneous solution was warmed to

ambient temperature and stirred for at least a further 12h.   Non-aqueous

work-up and Kugelrohr distillation yielded the pure N-t-butyldimethylsilyl

amine.

Utilization of this general procedure yielded the following

N-t-butyldimethylsilyl amines.

<u>N-t-Butyldimethylsilyl benzylamine</u>: 3.98g (90%), b.p. 110°C/1.5mmHg (lit.[55] b.p. 100-105°C/1.0mmHg); ν_{max}(CHCl$_3$) 3400, 2940, 2845, 1595, 1445, 1390 and 1110 cm^{-1}: δ0.15 (6H,s,SiCH$_3$), 1.05 (9H,s,SiBu^t), 4.12 (2H,d,J 7Hz, CH$_2$N) and 7.40 (5H,m,ArH);(Found:M$^+$, 221.1601.C$_{13}$H$_{23}$NSi requires 221.1600).

<u>N-t-Butyldimethylsilyl-2-furfurylamine</u>: 3.97g (94%), b.p. 115-123°C/ 20mmHg; ν_{max} (CCl$_4$) 3420, 2940, 1600, 1470, 1460, 1250, 1150 and 840 cm^{-1}; δ 0.05 (6H,s,SiCH$_3$), 0.87 (9H,s,SiBu^t), 3.86 (2H,d,J 9Hz, CH$_2$N), 6.10 (1H,m,H$_4$), 6.28 (1H,m,H$_3$) and 7.30 (1H,m,H$_5$):(Found:M$^+$-CH$_3$, 196.1153. C$_{11}$H$_{21}$NOSi requires M-CH$_3$, 196.1153).

<u>Ethyl N-t-butyldimethylsilyl glycinate</u> : from the hydrochloride as general procedure except utilizing 44mmol triethylamine: 4.30g (99%), b.p. 105-110°C/0.84mmHg (lit.[55] b.p. 100°C/0.8mmHg); ν_{max} (CHCl$_3$) 3400, 2950, 2850, 1730, 1595 and 1140 cm^{-1}; δ 0.17 (6H,s,SiCH$_3$), 1.00 (9H,s, SiBu^t), 1.38 (3H,t,J 7.5Hz,CH$_3$), 3.69 (2H,d,J 8Hz, CH$_2$N) and 4.30 (2H,q,J 7.5Hz, CH$_2$); (Found: M$^+$-C$_4$H$_9$, 160.0795.C$_{10}$H$_{23}$NO$_2$Si requires M-C$_4$H$_9$, 160.0794).

<u>N-t-Butyldimethylsilyl allylamine</u> : 2.70g, (99%), b.p. 100°C/0.8mmHg; ν_{max} (CCl$_4$) 3420, 2960, 2940, 2860, 1640, 1470, 1460, 1260 and 840 cm^{-1}; δ 0.02 (6H,s,SiCH$_3$), 0.88 (9H,s,SiBu^t), 3.40 (2H,m,CH$_2$N), 5.08 (2H,m, CH=CH$_2$) and 5.92 (1H,m,CH=CH$_2$); (Found: M$^+$, 171.1482.C$_9$H$_{21}$NSi requires M, 171.1438).

<u>N-t-Butyldimethylsilyl n-butylamine (267)</u>: 3.67g, (98%), b.p. 100-110°C/ 20mmHg; ν_{max} (CCl$_4$) 2960, 2930, 2860, 1475, 1465, 1260, 1120 and 830 cm^{-1}; δ 0.02 (6H,s,SiCH$_3$), 0.90 (9H,s,SiBu^t), 1.38 (7H,m,NCH$_2$CH$_2$CH$_2$CH$_3$) and 2.75 (2H,m,CH$_2$N); (Found: M$^+$,187.1778.C$_{10}$H$_{25}$NSi requires M, 187.1750).

Synthesis of N-t-Butyldimethylsilyl Imines - Procedure A.

To the appropriate N-t-butyldimethylsilyl amine (20mmol) in THF (30ml) at $0^{\circ}C$ was added t-butyl hypochlorite (20mmol) in THF (5ml) via pipette through a side-arm. The reaction mixture was stirred at $0^{\circ}C$ for 2h before non-aqueous work-up. The crude N-chloro-N-t-butyldimethylsilyl amine was weighed and dissolved in Et_2O (30ml), cooled to $0^{\circ}C$, and freshly distilled DBU (20mmol) in Et_2O (5ml) was added over 2 min. The resulting heterogeneous reaction mixture was warmed to ambient temperature and stirred for at least a further 12h. Non-aqueous work-up and Kugelrohr distillation yielded the pure N-t-butyldimethylsilyl imine.

Procedure B.

As procedure A, except DBU (22mmol) was utilized and the work-up consisted of the reaction mixture being taken up in n-pentane (10ml), filtered through Celite 535 and concentrated. The residue was taken up in n-pentane (50ml), washed with water (2x50ml) and brine (50ml). The organic layer was dried and concentrated to yield the N-t-butyldimethyl-silyl imine in a form sufficiently pure for subsequent use.

Utilization of these general procedures yielded the following N-t-butyldimethylsilyl imines.

N-t-Butyldimethylsilyl benzaldimine (181a) : Procedure A, 3.31g, (84%), b.p. $100-105^{\circ}C/0.76mmHg$ (lit.[55] b.p. $110-120^{\circ}C/0.9mmHg$); ν_{max} (CHCl$_3$) 3060, 2950, 2860, 2720, 1645, 1580 and 1250 cm^{-1}; δ 0.20 (6H,s,SiCH$_3$), 0.97 (9H,s,SiBu^t), 7.40 (3H,m,ArH), 7.70 (2H,m,ArH) and 8.94 (1H,s,CH=N); (Found: M$^+$, 219.1445. C$_{13}$H$_{21}$NSi requires M, 219.1443).

N-t-Butyldimethylsilyl-2-furfuraldimine (185a): Procedure A, 2.90g (74%), b.p. $146-162^{\circ}C/20mmHg$; ν_{max} (CCl$_4$) 2960, 2940, 2900, 2860, 1650 and 840cm^{-1};

δ 0.20 (6H,s,SiCH$_3$), 0.93 (9H,s,SiBu^t), 6.48 (1H,dd, J 2 and 4Hz, H$_4$),

6.83 (1H,d,J 4Hz, H$_3$), 7.52 (1H,d,J 2Hz, H$_5$) and 8.70 (1H,s,CH=N);

(Found: M$^+$, 209.1210. C$_{11}$H$_{19}$NOSi requires M, 209.1231).

N-t-Butyldimethylsilyl glyoxaldimine (182) : Procedure B, 4.26g (100%);

ν_{max} 2960, 2930, 2860, 1740, 1715, 1665, 1580 and 1250 cm^{-1}; δ 0.27

(6H,s,SiCH$_3$), 1.00 (9H,s,SiBu^t), 1.42 (3H,t,J 7Hz,CH$_3$), 4.39 (2H,q,J 7Hz,

CH$_2$) and 8.26 (1H,s,CH=N).

N-t-Butyldimethylsilyl-1-azabuta-1,3-diene (186) : Procedure B, 2.64g

(99%); ν_{max} (CCl$_4$) 2950, 2920, 2880, 2860, 1650, 1470, 1460, 1250 and

840 cm^{-1}; δ 0.15 (6H,s,SiCH$_3$), 0.84 (9H,s,SiBu^t), 6.11 (2H,m,CH=CH$_2$),

6.40 (1H,m,CH=CH$_2$) and 8.47 (1H,d,J 8Hz, CH=N); (Found: M$^+$, 169.1274.

C$_9$H$_{19}$NSi requires M, 169.1282).

Zinc Iodide.[91]

A 250ml round bottomed flask was charged with zinc dust (20g,

0.306mol), iodine (43g, 0.169mol) and Et$_2$O (100ml). The mixture was

heated at reflux until the solution became colourless, then it was

filtered through Celite 535. The filtrate was concentrated in vacuo and

the residual solid was flame dried under high vacuum, to yield ZnI$_2$ (51.54g,

96%) which was rapidly pulverised and stored in a desiccator in the dark

over P$_2$O$_5$.

Synthesis of N-t-Butyldimethylsilyl β-Amino Esters from the ZnI$_2$-Mediated

Reaction Between N-t-Butyldimethylsilyl Imines and O-Trimethylsilyl Ketene

Acetals - General Procedure.

Zinc iodide (1.053g, 3.3mmol) in Et$_2$O (50ml) was stirred at ambient

temperature for 30 min. To the resulting solution was added sequentially,

the appropriate N-t-butyldimethylsilyl imine (3.0mmol) in Et$_2$O (3ml), the

appropriate $\underline{O}$-trimethylsilyl ketene acetal (3.0mmol) in Et_2O (3ml) and

t-BuOH (3.0mmol) in Et_2O (3ml).   The resulting solution was stirred for

1h before it was diluted with Et_2O (50ml), washed with 5% aqueous NH_3

(50ml), dried, concentrated and the residual oil was purified by dry column

flash chromatography.

        Utilization of this general procedure yielded the following

$\underline{N}$-t-butyldimethylsilyl β-amino esters.

Methyl 3-(N-t-butyldimethylsilyl)amino-2,2-dimethyl-3-phenyl propanoate(189):

(914mg, 95%), as a white crystalline solid, m.p. 46-47°C (from n-pentane);

ν_{max} (CCl_4) 3420, 2960, 2940, 2860, 1740, 1475, 1250, 1130, 830 and

705 cm^{-1}; δ -0.25 (3H,s,$SiCH_3$), -0.12 (3H,s,$SiCH_3$), 0.75 (9H,s,SiBu^t),

1.06 [6H,s,$(CH_3)_2CCOOCH_3$], 3.63 (3H,s,$COOCH_3$), 3.70 (1H,s,NCH), and 7.22

(5H,m,ArH); (Found: C, 67.30; H, 9.73; N, 4.49%; M^+-C_4H_9, 264.1417.

$C_{18}H_{31}NO_3Si$ requires C, 67.24; H, 9.72; N, 4.36%; M-C_4H_9, 264.1414).

Methyl 3-(N-t-butyldimethylsilyl)amino-3-(2-furyl)-2,2-dimethyl-

propanoate (190): (606mg, 65%), as a pale green oil, b.p. 110-120°C/

0.75mmHg; ν_{max} (CCl_4) 3400, 2960, 2940, 2860, 1740, 1470, 1260, 1150,

1110, 1010, 870 and 840 cm^{-1}; δ -0.17 (3H,s,$SiCH_3$), 0.09 (3H,s,$SiCH_3$),

0.75 (9H,s,SiBu^t), 1.04 (3H,s,$CH_3CCOOCH_3$), 1.11 (3H,s,$CH_3CCOOCH_3$), 3.63

(3H,s,$COOCH_3$), 4.12 (1H,d,J 12Hz,NCH), 6.00 (1H,d,J 3Hz,H_3), 6.21 (1H,q,

J 1 and 2Hz,H_4), 7.22 (1H,bs,H_5); (Found : C, 61.74; H, 9.30; N, 4.69%;

M^+-C_4H_9, 254.1216.$C_{16}H_{29}NO_3Si$ requires C, 61.69; H, 9.38; N, 4.50%;

M-C_4H_9, 254.1207).

Synthesis of <u>N</u>-t-Butyldimethylsilyl-2-Azetidinones from the ZnI$_2$-Mediated Reaction Between <u>N</u>-t-Butyldimethylsilyl Imines and O-Trimethylsilyl Ketene Acetals - General Procedure.

Zinc iodide (1.053g, 3.3mmol) in Et$_2$O (50ml) was stirred at ambient temperature for 30 min. To this solution was added sequentially the appropriate <u>N</u>-t-butyldimethylsilyl imine (3.0mmol) in Et$_2$O (3ml), the appropriate <u>O</u>-trimethylsilyl ketene acetal (3.0mmol) in Et$_2$O (3ml) and t-BuOH (3.0mmol) in Et$_2$O (3ml). The resulting solution was stirred for 1h before being cooled to 0°C and MeMgBr in Et$_2$O (5.0ml, 3M, 15.0mmol) added over 1 min. The reaction mixture was then warmed to ambient temperature and stirred for at least a further 12h before being diluted with Et$_2$O (50ml), washed with saturated aqueous ammonium chloride, dried, concentrated and the residue was purified by dry column flash chromatography.

Utilization of this general prcedure yielded the following <u>N</u>-t-butyldimethylsilyl-2-azetidinones.

<u>N</u>-t-butyldimethylsilyl-3,3-dimethyl-4-phenyl-2-azetidinone (191) : (624mg, 72%), as a colourless oil, b.p. 108°C/0.55mmHg; ν_{max} (CHCl$_3$) 3010, 2960, 2940, 2860, 1730 and 1260 cm^{-1}; δ -0.15 (3H,s,SiCH$_3$), 0.32 (3H,s,SiCH$_3$), 0.72 (3H,s,CH$_3$CCO), 0.99 (9H,s,SiBu^t), 1.44 (3H,s,CH$_3$CCO), 4.34 (1H,s,NCH) and 7.31 (5H,s,ArH); (Found :M$^+$-CH$_3$ 274.1631.C$_{17}$H$_{27}$NOSi requires M-CH$_3$, 274.1621).

<u>N</u>-t-Butyldimethylsilyl-4-(2-furyl)-3,3-dimethyl-2-azetidinone (192): (435mg, 52%) as a white crystalline solid, m.p. 38.5 - 40.5°C(from light petroleum); ν_{max} 2960, 2930, 2860, 1750, 1290 and 1255 cm^{-1}; δ -0.12 (3H,s,SiCH$_3$), 0.25 (3H,s,SiCH$_3$), 0.91 (9H,s,SiBu^t), 0.97 (3H,s,CH$_3$CCO), 1.37 (3H,s,CH$_3$-CCO), 4.27 (1H,s,NCH), 6.27 (2H,m,H$_3$ and H$_4$) and 7.35 (1H,bs,H$_5$); (Found: C, 64.46; H, 9.23; N, 5.04%; M$^+$-C$_4$H$_9$, 222.0949. C$_{15}$H$_{25}$NO$_2$Si requires

C, 64.36; H,9.00; N, 5.00%; M-C$_4$H$_9$, 222.0946).

N-t-Butyldimethylsilyl-3-methyl-4-phenyl-2-azetidinone (193) : (495mg, 60%) as an inseparable mixture of <u>trans</u> and <u>cis</u> diastereoisomers, in a ratio of 1.9:1.

<u>Trans</u> - (193): δ -0.20 (3H,s,SiCH$_3$), 0.22 (3H,s,SiCH$_3$), 0.93 (9H,s,SiBu^t), 1.37 (3H,d,J 8Hz,CH$_3$), 3.07 (1H,dq, J 2 and 8Hz, CH$_3$CH), 4.10 (1H,d,J 2Hz, CHN) and 7.32 (5H,bs,ArH).

<u>Cis</u> - (193) : δ -0.20 (3H,s,SiCH$_3$), 0.22 (3H,s,SiCH$_3$), 0.62 (3H,d,J 7Hz,CH$_3$), 0.93 (9H,s,SiBu^t), 3.57 (1H,m,CH$_3$CH), 4.70 (1H,d,J 5Hz,CHN) and 7.32 (5H,bs,ArH).

N-t-Butyldimethylsilyl-4-(2-furyl)-3-methyl-2-azetidinone (194): (413mg, 52%) as an inseparable mixture of <u>trans</u> and <u>cis</u> diastereoisomers, in a ratio of 2:1.

<u>Trans</u> - (194) : δ -0.07 (3H,s,SiCH$_3$), 0.10 (3H,s,SiCH$_3$), 0.80 (9H,s,SiBu^t), 1.30 (3H,d,J 8Hz,CH$_3$), 3.30 (1H,dq, J 2 and 8Hz, CH$_3$CH), 4.03 (1H,d,J 2Hz, CHN), 6.22 (2H,m,H$_3$ and H$_4$) and 7.25 (1H,m,H$_5$).

<u>Cis</u>- (194): δ -0.07 (3H,s,SiCH$_3$), 0.10 (3H,s,SiCH$_3$), 0.80 (9H,s,SiBu^t), 0.98 (3H,d,J 7Hz,CH$_3$), 3.65 (1H,m,CH$_3$CH), 4.66 (1H,d,J 4Hz,CHN), 6.22 (2H,m,H$_3$ and H$_4$) and 7.25 (1H,m,H$_5$).

Trimethylsilyl Trifluoromethanesulphonate.

A 25ml, B14 neck round bottomed flask equipped with a 3-way tap was attached to an argon line and charged with trifluoromethane sulphonic acid (0.88ml, 10mmol) via the 3-way tap, and then cooled to 0°C. Tetramethylsilane (1.70ml, 12.5mmol) was added via the 3-way tap and the mixture stirred for 15 min. A further portion of tetramethylsilane (0.34ml, 2.5mmol) was added via the 3-way tap and the mixture was allowed

to warm to ambient temperature and stirred for a further 15 min.   Direct

Kugelrohr distillation yielded trimethylsilyl trifluoromethansulphonate

(2.21g, 100%) as a colourless oil, b.p. 78°C/20mmHg (Lit.[61] b.p. 40°C/11mmHg)

which was made up to 10ml with CH_2Cl_2 and used as a 1.0M solution.

Synthesis of N-Unsubstituted and N-t-Butyldimethylsilyl β-Amino Esters

from the TMSOTf-Mediated Reaction Between N-Trialkylsilyl Imines and

O-Trimethylsilyl Ketene Acetals - Procedure A.

        To a solution (0.1M) of the appropriate N-trimethylsilyl imine

(2.00mmol) in CH_2Cl_2 was added the appropriate O-trimethylsilyl ketene

acetal (2.00mmol) in CH_2Cl_2 (2ml).   The reaction mixture was cooled to

0°C and a solution of trimethylsilyl trifluoromethanesulphonate (0.20ml,

1.0M, 0.20mmol) in CH_2Cl_2 was added over 30 sec.   The reaction mixture

was warmed to ambient temperature and stirred for at least a further 16h

before being diluted with Et_2O (50ml) and washed with saturated disodium

hydrogen orthophosphate (50ml).   The aqueous wash was extracted with

Et_2O (50ml) and the combined organic extracts were dried, concentrated and

the residue was purified by dry column flash chromatography.

Procedure B.

        To a solution (0.1M) of the appropriate N-trimethylsilyl imine

(2.00mmol) in CH_2Cl_2 at 0°C was added a solution of trimethylsilyl

trifluoromethanesulphonate (2.00ml, 1.0M, 2.00mmol) in CH_2Cl_2 over 30 sec.

and the resulting solution was stirred for 10 min.   A solution of the

appropriate O-trimethylsilyl ketene acetal (2.00mmol) in CH_2Cl_2 (2ml) was

added, followed immediately by t-BuOH (2.00mmol) in CH_2Cl_2 (2ml).   The

reaction mixture was warmed to ambient temperature and stirred for at

least a further 16h and then worked-up as in procedure A.

Procedure C.

To a solution (0.1M) of the appropriate N-trimethylsilyl imine (2.00mmol) in CH_2Cl_2 at $0^{\circ}C$ was added a solution of trimethylsilyl trifluoromethanesulphonate (2.00ml, 1.0M, 2.00mmol) in CH_2Cl_2 over 30 sec. and the resulting solution was stirred for 10 min. before being cooled to $-78^{\circ}C$. A solution of the appropriate O-trimethylsilyl ketene acetal (2.00mmol) in CH_2Cl_2 (2ml), was added followed immediately by t-BuOH (2.00mmol) in CH_2Cl_2 (2ml). The reaction mixture was warmed to ambient temperature and stirred for at least a further 16h and then worked-up as in procedure A.

Procedure D.

All operations were identical to procedure A except that the appropriate N-t-butyldimethylsilyl imine (2.00mmol) was used.

Procedure E.

All operations were identical to procedure. B except that the appropriate N-t-butyldimethylsilyl imine (2.00mmol) was used.

Utilization of these general procedures yielded the following β-amino esters.

α-[Bis(trimethylsilyl)aminobenzyl]-δ-valerolactone (253) : Procedure A on a 3.503mmol scale, (550mg, 45%) and the corresponding Schiff base (254), (77mg, 15%), both as inseparable mixtures of threo and erythro diastereo- isomers, in the ratio of 3:1, respectively. (253): b.p. $220^{\circ}C/0.9$mmHg; ν_{max} ($CHCl_3$) 3020,2950, 1730, 1250, 930 and 830 cm^{-1}; δ(threo) 0.10 [18H,s,N$(SiMe_3)_2$], 1.70 (4H,m,$OCH_2\underline{CH}_2\underline{CH}_2$), 3.32 (1H,m,CHCOO), 4.32 (2H,m, OCH_2), 4.75 (1H,d,J 10Hz, NCH), and 7.21 (5H,s,ArH), (erythro) 0.10

[18H,s,N(SiMe$_3$)$_2$], 1.70 (4H,m,OCH$_2$CH$_2$CH$_2$), 3.32 (1H,m,CHCOO), 4.32 (2H,

m,OCH$_2$), 4.80 (1H,d, J 9Hz,NCH) and 7.21 (5H,s,ArH); (Found : M$^+$,

349.1864.C$_{18}$H$_{31}$NO$_2$Si$_2$ requires M, 349.1885).

(254):b.p. 205°C/0.7mmHg; ν_{max} (CCl$_4$) 3060, 3030, 2975, 2860, 1730, 1640,

1450 and 1150 cm^{-1}; δ (threo) 1.80 (4H,m,OCH$_2$CH$_2$CH$_2$), 3.05 (1H,m,CHCOO),

4.25 (2H,m,OCH$_2$), 5.28 (1H,d,J 4Hz,NCH), 7.35 (8H,m,ArH), 7.80 (2H,m,ArH),

and 8.40 (1H,s,N=CH), (erythro) 1.80 (4H,m,OCH$_2$CH$_2$CH$_2$), 3.05 (1H,m,CHCOO),

4.25 (2H,m,OCH$_2$), 5.06 (1H,d,J 8Hz,NCH), 7.35 (8H,m,ArH), 7.80 (2H,m,ArH)

and 8.48 (1H,s,N=CH); (Found: M$^+$, 293.1411.C$_{19}$H$_{19}$NO$_2$ requires M,293.1411).

Ethyl-3-benzylideneamino-3-phenyl-2-(1'-trimethylsilyloxy)-

ethyl propanoate (246):

Procedure A on a 2.130mmol scale, (180mg, 43%) as an inseparable mixture

of threo and erythro diastereoisomers, in the ratio of 4:1, b.p. 130°C/

0.42mmHg; ν_{max} (CHCl$_3$) 3040, 3020, 2980, 2960, 1720, 1640, 1150, 840

and 705 cm^{-1}; δ (threo) 0.12 (9H,s,SiCH$_3$), 0.97 (3H,t,J 7Hz,COOCH$_2$CH$_3$),

1.30 (3H,m,CH$_3$CHO), 3.40 (1H,dd, J 5 and 11Hz,CHCOOEt), 3.93 (3H,m,COOCH$_2$-

CH$_3$ and CHOSi), 4.60 (1H,d,J 11Hz,NCH), 7.35 (8H,m,ArH), 7.73 (2H,m,ArH)

and 8.27 (1H,s,N=CH), (erythro) 0.12 (9H,s,SiCH$_3$), 0.97 (3H,t,J 7Hz,COOCH$_2$-

CH$_3$), 1.30 (3H,m,CH$_3$CHO), 2.55 (1H,dd, J 10 and 10Hz, CHCOOEt), 3.93 (4H,m,

COOCH$_2$CH$_3$, CHOSi and NCH), 7.35 (8H,m,ArH), 7.73 (2H,m,ArH), and 8.24

(1H,s,N=CH); (Found: M$^+$, 397.2087. C$_{23}$H$_{31}$NO$_3$Si requires M, 397.2065).

Methyl 3-amino-2,2-dimethyl-3-phenyl propanoate (188): Procedure B on a

2.306mmol scale, (334mg, 70%), b.p. 150°C/0.3mmHg; ν_{max} (CCl$_4$) 2980, 2950,

1730, 1265, 1140 and 700 cm^{-1}; δ 1.07 (3H,s,CH$_3$), 1.12 (3H,s,CH$_3$), 1.72

(2H,s,NH$_2$), 3.68 (3H,s,COOCH$_3$), 4.22 (1H,s,NCH) and 7.26 (5H,s,ArH);

(Found: M+H$^+$, 208.1338. C$_{12}$H$_{17}$NO$_2$ requires M+H, 208.1333).

Methyl 3-amino-2-methyl-3-phenyl propanoate (225) : Procedure B on a

2.512 mmol scale, (325mg, 67%), as an inseparable mixture of <u>threo</u> and

<u>erythro</u> diastereoisomers, in a ratio of 3.9:1, respectively, b.p. 140°C/

0.5mmHg; δ (<u>threo</u>) 0.85 (3H,d,J 8Hz,CH$_3$CH), 1.80 (2H,bs,NH$_2$), 2.65 (1H,m,

CH$_3$CH), 3.66 (3H,s,COOCH$_3$), 3.95 (1H,d,J 9Hz,CHN) and 7.25 (5H,s,ArH),

(<u>erythro</u>) 1.10 (3H,d,J 8Hz,CH$_3$CH), 1.80 (2H,bs,NH$_2$), 2.65 (1H,m,CH$_3$CH),

3.50 (3H,s,COOCH$_3$), 4.25 (1H,d,J 5Hz,CHN) and 7.25 (5H,s,ArH).

Procedure C on a 2.436 mmol scale, (287mg, 61%) as an inseparable mixture

of <u>threo</u> and <u>erythro</u> diastereoisomers, in a ratio of 7.8:1.

Methyl 3-(N-t-butyldimethylsilyl)amino-2,2-dimethyl-3-ethoxycarbonyl

propanoate (210) : Procedure D on a 5.210mmol scale, in the presence of

4 Å molecular sieves, (1.45g, 88%), b.p. 85-94°C/0.1mmHg; ν_{max} (CCl$_4$)

3380, 2950, 2930, 2860, 1740, 1260, 1180, 1140, 1125 and 830 cm^{-1};

δ 0.02 (6H,s,SiCH$_3$), 0.88 (9H,s,SiBu^t), 1.14 (3H,s,CH$_3$CCOOCH$_3$), 1.21

(3H,s,CH$_3$CCOOCH$_3$), 1.28 (3H,t, J 6Hz, COOCH$_2$CH$_3$), 3.66 (1H,d,J 14Hz,NCH),

3.72 (3H,s,COOCH$_3$) and 4.16 (2H,q,J 6Hz,COOCH$_2$CH$_3$); (Found: C, 56.68;

H, 10.03; N, 4.88%; M$^+$-C$_4$H$_9$ 260.1325. C$_{15}$H$_{31}$NO$_4$Si requires C, 56.74;

H, 9.84; N, 4.41%; M-C$_4$H$_9$, 260.1312).

Methyl 3-(N-t-butyldimethylsilyl)amino-2-methyl-3-phenyl propanoate (206):

Procedure E on a 3.307mmol scale, (609mg, 60%) as an inseparable mixture

of <u>threo</u> and <u>erythro</u> diastereoisomers, in a ratio of 5.6:1; δ (<u>threo</u>)

0.10 (6H,s,SiCH$_3$), 0.85 (3H,d,J 8Hz,CH$_3$CH), 0.92 (9H,s,SiBu^t), 2.65(1H,m,

CH$_3$CH), 3.66 (3H,s,COOCH$_3$), 3.95 (1H,d,J 9Hz,CHN) and 7.25 (5H,s,ArH),

(<u>erythro</u>) 0.09 (6H,s,SiCH$_3$), 0.90 (9H,s,SiBu^t), 1.10 (3H,d,J 8Hz,CH$_3$CH)

2.65 (1H,m,CH$_3$CH), 3.50 (3H,s,COOCH$_3$), 4.25 (1H,d,J 5Hz,CHN), 7.25 (5H,s,

ArH).

Direct Synthesis of N-Unsubstituted and N-t-Butyldimethylsilyl 2-
Azetidinones from the TMSOTf-Mediated Reaction Between N-Trimethylsilyl
Imines and O-Trimethylsilyl Ketene Acetals - Procedure A.

To a solution (0.1M) of the appropriate N-trimethylsilyl imine
(2.00mmol) in CH_2Cl_2 at $0^{\circ}C$ was added a solution of trimethylsilyl
trifluoromethanesulphonate (2.00ml, 1.0M, 2.00mmol) in CH_2Cl_2 over 30 sec.
and the solution was stirred for 10 min. A solution of the appropriate
O-trimethylsilylketene acetal (2.00mmol) in CH_2Cl_2 (2ml) was added
followed immediately by t-BuOH (2.00mmol) in CH_2Cl_2 (2ml). The reaction
mixture was warmed to ambient temperature and stirred for 2.5h before
being recooled to $0^{\circ}C$. A solution of MeMgBr in Et_2O (1.47ml, 3M, 4.40mmol)
was added over 1 min. The reaction mixture was warmed to ambient
temperature and stirred for at least a further 16h before being diluted
with Et_2O and washed with 1N HCl. The aqueous wash was extracted with
Et_2O and the combined organic extracts were dried, concentrated and the
residue was purified by dry column flash chromatography.

Procedure B.

As procedure A except that the appropriate N-t-butyldimethyl-
silyl imine (2.00mmol) was used, MeMgBr (2.13ml, 3M, 6.40mmol) was
added at the appropriate time and saturated aqueous ammonium chloride
was used in place of 1N HCl.

Utilization of these general procedures yielded the following
2-azetidinones.

3,3-Dimethyl-4-phenyl-2-azetidinone (207): Procedure A, on a 0.968mmol
scale (112mg, 66%) as a white crystalline solid, m.p. 105.5-106°C (from
n-pentane) (lit.[10a] m.p. 103-104.5°C and [92] m.p. 104-105°C); ν_{max} (CCl_4)

3420 and 1780 cm^{-1}; δ 0.74 (3H,s,CH$_3$), 1.44 (3H,s,CH$_3$), 4.50 (1H,s,NCH),

6.68 (1H,bs,NH) and 7.30 (5H,bs,ArH); (Found : C, 75.32; H, 7.58;

N, 7.94%; M$^+$, 175.0998. C$_{11}$H$_{13}$NO requires C, 75.39; H, 7.48; N, 7.99%;

M, 175.0994).

<u>4-(2-Furyl)-3,3-dimethyl-2-azetidinone (208)</u> : Procedure A, on a 1.012mmol

scale (115mg, 69%) as a white crystalline solid, m.p. 106-108°C(from

n-pentane), ν_{max} (CCl$_4$) 3420 and 1775 cm^{-1}; δ 0.96 (3H,s,CH$_3$), 1.40 (3H,

s,CH$_3$), 4.41 (1H,s,NCH), 6.30 (2H,m,H$_3$ and H$_4$), 6.55 (1H,bs,NH) and

7.38 (1H,bs,H$_5$); (Found : M$^+$, 165.0791. C$_9$H$_{11}$NO$_2$ requires M, 165.0787).

<u>3-Methyl-4-phenyl-2-azetidinone (195)</u>: Procedure A, on a 1.113mmol scale,

the <u>trans</u>-β-lactam (77mg, 43%), the <u>cis</u>-β-lactam (19mg,11%) and an

inseparable mixture of <u>trans</u>- and <u>cis</u>- β-lactam (14mg, 8%) in a ratio

of 7:1.

<u>Trans</u> - (195): m.p. 101-103°C (from n-pentane)(Lit.[93] m.p. 99-100°C);

ν_{max} (CCl$_4$) 3420 and 1760 cm^{-1}; δ 1.38 (3H,d,J 8Hz,CH$_3$), 3.02 (1H,dq,J 2 and

8Hz,CH$_3$C$\underline{H}$), 4.28 (1H,d,J 2Hz,NCH) and 7.33 (5H,s,ArH); (Found: C, 74.32;

H, 6.90; N, 8.59%; M$^+$, 161.0848. C$_{10}$H$_{11}$NO requires C, 74.51; H, 6.88;

N, 8.69% ; M, 161.0838).

<u>Cis</u> - (195): m.p. 105-106°C (from n-pentane)(lit.[93]m.p. 105-106°C);

ν_{max} (CCl$_4$) 3420 and 1775 cm^{-1}; δ 0.78 (3H,d,J 7.5Hz,CH$_3$), 3.57 (1H,m,

CH$_3$C$\underline{H}$), 4.88 (1H,d,J 5.5Hz,NCH), 6.50 (1H,bs,NH) and 7.30 (5H,m,ArH);

(Found : M$^+$, 161.0842.C$_{10}$H$_{11}$NO requires M, 161.0838).

<u>4-(2-Furyl)-3-methyl-2-azetidinone (196)</u> : Procedure A, on a 2.102mmol

scale, the <u>trans</u>-β-lactam (140mg,44%) and the <u>cis</u>-β-lactam (66mg,21%).

<u>Trans</u> - (196) : m.p. 113-114°C (from n-pentane) (lit.[55] m.p. 113-114°C);

ν_{max} (CHCl$_3$) 3418, 3120, 2880, 1770, 1670, 1600 and 1350 cm^{-1}; δ 1.33

(3H,d, J 7Hz,CH$_3$), 3.32 (1H,dq, J 2 and 7Hz, C$\underline{H}$CH$_3$), 4.27 (1H,d,J 2Hz,CHN),

6.30 (2H,m, H$_3$ and H$_4$), 5.53 (1H,bs,NH) and 7.36 (1H,m,H$_5$); (Found :

C, 63.63; H, 5.90; N, 9.30%; M$^+$, 151.0628.C$_8$H$_9$NO$_2$ requires C, 63.56;

H, 6.00; N, 9.27%; M$^+$, 151.0634).

$\underline{Cis}$ - (196) : m.p. 81-82°C (from n-pentane)(lit.[55] m.p. 82-83.5°C);

ν_{max} (CHCl$_3$) 3420, 3020, 2980, 2940, 1765 and 1340 cm^{-1}; δ 0.95 (3H,d, J

8Hz,CH$_3$), 3.50 (1H,m,C$\underline{H}$CH$_3$), 4.77 (1H,d,J 5Hz,CHN), 6.28 (2H,m,H$_3$ and H$_4$),

5.54 (1H,bs,NH) and 7.35 (1H,m,H$_5$).

N-t-Butyldimethylsilyl-3,3-dimethyl-4-phenyl-2-azetidinone (191):

Procedure B, on a 2.169mmol scale (470mg,75%) all properties being

identical to those reported earlier.

N-t-Butyldimethylsilyl-4-(2-furyl)-3,3-dimethyl-2-azetidinone (192):

Procedure B, on a 3.624 mmol scale (718mg, 71%) all properties being

identical to those reported earlier.

N-t-Butyldimethylsilyl-3-methyl-4-phenyl-2-azetidinone (193) :

Procedure B, on a 2.573mmol scale (304mg,43%) as an inseparable mixture

of $\underline{trans}$ and $\underline{cis}$ diastereoisomers, in a ratio of 5.6:1.   All properties

were identical to those reported earlier.

N-t-Butyldimethylsilyl-4-(2-furyl)-3-methyl-2-azetidinone (194) :

Procedure B, on a 2.998mmol scale (564mg,71%) as an inseparable mixture

of $\underline{trans}$ and $\underline{cis}$ diastereoisomers, in a ratio of 3:1.   All properties

were identical to those reported earlier.

Synthesis of 2-Azetidinones from β-Amino Esters.

N-(t-Butyldimethylsilyl)-4-ethoxycarbonyl-3,3-dimethyl-2-azetidinone (212).

To the β-amino ester (210)(330mg, 1.041mmol) in Et$_2$O (10.4ml) at 0°C was added Bu^{t}MgCl in Et$_2$O (1.04ml, 2M, 2.082mmol) over 1 min. The reaction mixture was warmed to ambient temperature and stirred for 3.5h before being diluted with Et$_2$O (50ml) and washed once with saturated aqueous ammonium chloride (50ml) and brine (50ml). The organic layer was dried, concentrated and the residue was purified by dry column flash chromatography to yield the 2-azetidinone (212) (233mg, 79%) as a colourless oil, b.p. 130°C/1.0mmHg; ν_{max} (CHCl$_3$) 3010, 2950, 2920, 2850, 1735 and 1250 cm^{-1}; δ 0.11 (3H,s,SiCH$_3$), 0.36 (3H,s,SiCH$_3$), 1.00 (9H,s, SiBu^t), 1.20 (3H,s,CH$_3$CCO), 1.36 (3H,t,J 5Hz,COOCH$_2$CH$_3$), 1.48 (3H,s, CH$_3$CCO), 3.88 (1H,s,NCH) and 4.29 (2H,q,J 5Hz,COOCH$_2$CH$_3$); (Found: M$^+$-C$_4$H$_9$, 228.1054. C$_{14}$H$_{27}$NO$_3$Si requires M-C$_4$H$_9$, 228.1051).

N-(t-Butyldimethylsilyl)-3,3-dimethyl-4-phenyl-2-azetidinone (191).

To diisopropylamine (154μl, 1.1mmol) in THF (2ml) at 0°C was added nBuLi in hexane (0.38ml, 2.6M, 1.0mmol) and the reaction mixture stirred for 10 min. The β-amino ester (189) (321mg, 1.0mmol) in THF (1ml) was added over 30 sec. at 0°C. The reaction mixture was warmed to ambient temperature and stirred for 2.5h before being diluted with Et$_2$O (50ml) and washed with saturated aqueous ammonium chloride (20ml). The aqueous wash was extracted with Et$_2$O (3 x 20ml) and the combined organic extracts were dried, concentrated and the residue was purified by dry column flash chromatography to yield the β-lactam (191) (207mg,72%), all properties being identical to those reported earlier.

4-(2-Furyl)-3-methyl-2-azetidinone (196).

To a 2:1 mixture of the threo and erythro diastereoisomers of

β-amino ester (226) (117mg, 0.64mmol) in Et$_2$O (4ml) was added triethyl-

amine (94μl, 0.671mmol).   The reaction mixture was cooled to 0°C and

chlorotrimethylsilane (85μl, 0.671mmol) was added.   The reaction mixture

was warmed to ambient temperature and stirred for 24h before being re-cooled

to 0°C.   MeMgBr in Et$_2$O (0.54ml, 3M, 1.630mmol) was added over 1 min, and

the reaction mixture was allowed to warm to ambient temperature and then

stirred for 15h before being diluted with Et$_2$O (30ml) and washed with 1N

HCl (30ml).   The aqueous wash was extracted with Et$_2$O (30ml) and the

combined organic extracts were dried, concentrated and the residue was

purified by dry column flash chromatography to yield the β-lactam (196)

(61mg, 63%) as an inseparable mixture of trans and cis diastereoisomers,

in a ratio of 2:1.   All properties were identical to those reported

earlier.

Attempted Diels-Alder Reactions of N-t-Butyldimethylsilyl-1-azabuta-1, 3-diene (186).

Procedure A. To a solution of maleic anhydride (213) (537mg, 5.48mmol)

in acetonitrile (20ml) was added a solution of the imine (186) (463mg,

2.74mmol) in acetonitrile (10ml).   The mixture was heated to reflux for

5h and then cooled to ambient temperature.   The solvent was removed in

vacuo to reveal what appeared to be polymeric material.   Repetition of

this reaction using toluene, benzene or benzene and a catalytic quantity

of DBU, offered no advantage.

Procedure B.   To a solution of the imine (186) (36mg, 0.213mmol) in

benzene was added methylvinylketone (214) (15mg, 0.213mmol) in benzene

(0.2ml).   The mixture was heated to 50°C for 1hr.   After cooling to

ambient temperature, the solvent was removed in vacuo to reveal what

appeared to be polymeric material.

Procedure C.[62]   To a solution of the imine (186) in benzene (2.5ml)
was added a solution of benzaldehyde (215) (280mg, 2.64mmol) in benzene
(2.8ml) and a solution of $BF_3.OEt_2$ (34mg, 0.24mmol) in benzene (0.7ml).
The mixture was heated to reflux for 8h.   The mixture was allowed to cool
to ambient temperature and diluted with Et_2O (50ml) and washed with 3N KOH
(50ml).   The aqueous wash was extracted with Et_2O (3 x 50ml) and the
combined organic extracts were washed with brine (50ml), dried and
concentrated to yield polymeric materials.

Procedure D.   To a solution of the imine (186) (238mg, 1.408mmol)
in benzene (5ml) was added a solution of N-(1-propenyl)-piperidine (216)
(176mg, 1.408mmol) in benzene (1.8ml).   This mixture was placed in a tube
and the tube was sealed before being heated to between $142^{o}C$ and $144^{o}C$ for
16h.   The mixture was allowed to cool to ambient temperature and the
solvent was removed in vacuo to yield polymeric materials.   Repetition
of this reaction in the presence of a catalytic quantity of p-toluenesulphonic
acid monohydrate offered no improvement.

Synthesis of N,N,O-Tris(Trimethylsilyl)Amine Acetals.

Benzaldehyde N,N,O-tris(trimethylsilyl)amine acetal (217).

        To hexamethyldisilazane (2.32ml, 11mmol) was added nBuLi in
hexane (4.00ml, 2.5M, 10mmol) over 5 min.   The solution was stirred for
15 min., THF (18ml) was added and the mixture cooled to $-78^{o}C$.
Chlorotrimethylsilane (1.27ml, 10mmol) was added over 2 min., and stirring
continued for a further 10 min.   Freshly distilled benzaldehyde (1.06g,
10mmol) in THF (10ml) was added over 7 min., and the reaction mixture was
stirred at $-78^{o}C$ for a further 30 min before being warmed to ambient

temperature over 30 min. Non-aqueous work-up and Kugelrohr distillation

yielded the amine acetal (217) (1.82g, 54%) as a colourless oil, b.p.

100-110°C/0.04mmHg; ν_{max} (CCl$_4$) 2960, 2900, 1265, 1255 and 920 cm^{-1};

δ 0.10 [18H,s,N(SiMe$_3$)$_2$], 0.22 (9H,s,OSiCH$_3$), 5.85 (1H,s,C$\underline{H}$Ph) and

7.30 (5H,m,ArH); (Found : M^{+}, 339.1848.C$_{16}$H$_{33}$NOSi$_3$ requires M, 339.1861).

Furfural N,N,O-tris(trimethylsilyl) amine acetal (218).

All operations were identical with the procedure described

above for benzaldehyde $\underline{N}$,$\underline{N}$,$\underline{O}$-tris(trimethylsilyl) amine acetal (217)

except that freshly distilled furfural (0.96g, 10mmol) in THF (10ml) was

employed. Kugelrohr distillation of the crude product afforded the amine

acetal (218) (2.86g, 87%) as a colourless oil, b.p. 90-110°C/0.3mmHg;

ν_{max} (CCl$_4$) 2960, 2900, 1260, 870 and 850 cm^{-1}; δ 0.11 [18H,s,N(SiMe$_3$)$_2$],

0.26 (9H,s,OSiCH$_3$), 5.75 (1H,s,C$\underline{H}$NSi$_2$), 6.10 (1H,m,H$_4$), 6.25 (1H,m,H$_3$),

and 7.28 (1H,s,H-5); (Found : M^{+}, 329.1661.C$_{14}$H$_{31}$NO$_2$Si$_3$ requires M,

329.1654).

Synthesis of β-Amino Esters from the TMSOTf-Mediated Reaction Between

N,N,O-Tris(Trimethylsilyl)Amine Acetals and O-Trimethylsilyl Ketene

Acetals - General Procedure.

To a solution (0.1M) of the appropriate amine acetal (2.00mmol)

in CH$_2$Cl$_2$ at 0°C was added a solution of trimethylsilyl trifluoromethane-

sulphonate (2.00ml, 1.0M, 2.00mmol) in CH$_2$Cl$_2$ and the reaction mixture

was stirred for 10 min. A solution of the appropriate $\underline{O}$-trimethylsilyl

ketene acetal (2.00mmol) in CH$_2$Cl$_2$ (2ml) was added, followed immediately

by t-BuOH (2.00mmol) in CH$_2$Cl$_2$ (2ml). The reaction mixture was warmed

to ambient temperature and stirred for at least a further 16h before

being diluted with Et$_2$O (50ml) and washed with saturated aqueous disodium

hydrogen orthophosphate. The aqueous wash was extracted once with Et$_2$O

(50ml) and the combined organic extracts were dried, concentrated and the residue was purified by dry column flash chromatography.

Utilization of this general procedure yielded the following β-amino esters.

Methyl 3-amino-2,2-dimethyl-3-phenyl propanoate(188): on a 2.302mmol scale (329mg,69%), all properties being identical to those reported earlier.

Methyl 3-amino-3-(2-furyl)-2,2-dimethyl propanoate(225): on a 3.016mmol scale (439mg,74%); δ 0.95 (3H,s,$\underline{CH}_3$CCOOCH$_3$), 1.03 (3H,s,$\underline{CH}_3$CCOOCH$_3$), 1.62 (2H, bs,NH$_2$), 3.52 (3H,s,COOCH$_3$), 4.05 (1H,s,CHN), 6.00 (1H,m,H$_3$), 6.12 (1H, m,H$_4$) and 7.13 (1H,m,H$_5$).

Methyl 3-amino-2-methyl-3-phenyl propanoate(184):on a 2.467mmol scale (329mg, 69%) as an inseparable mixture of threo and erythro diastereoisomers, in a ratio of 3.9:1.   All properties were identical to those reported earlier.

Methyl-3-amino-3-(2-furyl)-2-methyl propanoate(226):on a 2.601 mmol scale (305mg, 64%) as an inseparable mixture of threo and erythro diastereo-isomers, in a ratio of 2:1, δ(threo) 0.80 (3H,d,J 8Hz,$\underline{CH}_3$CH), 1.60 (2H,bs, NH$_2$), 2.65 (1H,dq,J 7 and 8Hz,CH$_3$$\underline{CH}$), 3.50 (3H,s,COOCH$_3$), 3.86 (1H,d,J 7Hz, CHN), 6.00 (1H,m,H$_3$), 6.11 (1H,m,H$_4$) and 7.13 (1H,m,H$_5$), (erythro) 0.95 (3H,d,J 8Hz,$\underline{CH}_3$CH), 1.60 (2H,bs,NH$_2$), 2.30 (1H,m,CH$_3$$\underline{CH}$), 3.45 (3H,s, COOCH$_3$), 4.02 (1H,d,J 5Hz,CHN), 6.00 (1H,m,H$_3$), 6.11 (1H,m,H$_4$) and 7.13 (1H,m,H$_5$).

Synthesis of 2-Azetidinone (207) from the TMSOTf-Mediated Reaction of

Amine Acetal (217) and Silyl Ketene Acetal (187).

To the amine acetal (217) (324mg, 0.956mmol) in CH_2Cl_2 (10ml)

at $0^\circ C$ was added a solution of trimethylsilyl trifluoromethanesulphonate

(1.21ml, 0.79M, 0.956mmol) in CH_2Cl_2 over 30 sec., and the resulting

reaction mixture was stirred for 10 min. Ketene acetal (187) (166mg,

0.956mmol) in CH_2Cl_2 (0.5ml) was added followed immediately by t-BuOH

(71mg, 0.956 mmol) in CH_2Cl_2 (0.5ml). The reaction mixture was warmed

to ambient temperature and stirred for 8.5h before being re-cooled to $0^\circ C$.

MeMgBr in Et_2O (0.80ml, 3M, 2.390mmol) was added over 30 sec. The

reaction mixture was warmed to ambient temperature and stirred for 12.5h

before being diluted with Et_2O (50ml) and washed with 1N HCl (50ml). The

aqueous layer was extracted with Et_2O (3 x 50ml) and the combined organic

extracts were dried, concentrated and the residue was purified by dry

column flash chromatography to yield the β-lactam (207) (67mg, 40%), all

properties being identical to those reported earlier.

2-Propyn-1-ol tetrahydropyranyl ether (231)

To a solution of 2-propyn-1-ol (230) (22.5g, 0.4mol) in CH_2Cl_2

(350ml) was added DHP (100ml, 1.1mol) and pyridinium p-toluenesulphonate

(5.03g, 0.020mol). The mixture was stirred for 4h at ambient temperature

before being diluted with Et_2O (400ml) and washed with saturated sodium

hydrogen carbonate (2 x 100ml) and brine (100ml). The organic extract

was dried, concentrated and the residue distilled to yield the THP-ether

(231) (43.6g, 78%) as a colourless oil, b.p. 74-76$^\circ C$/7mmHg.

3-Trimethylsilyl prop-2-yn-1-ol (229).

To magnesium (4.25g, 0.175mol) in Et_2O (75ml) was added ethyl bromide (13.1ml, 0.175mol) in Et_2O (15ml) at such a rate as to maintain a gentle reflux. The mixture was stirred for 0.5h before 2-propyn-1-ol THP-ether (231) (24.5g, 0.175mol) in Et_2O (50ml) was added over 20 min. The solid that formed was broken up by spatula and the mixture stirred at ambient temperature for 12h. Chlorotrimethylsilane (22.2ml, 0.175mol) was added over 30 min, and the mixture heated to reflux for 8h before being cooled to ambient temperature. A further portion of chlorotrimethyl-silane (11.2ml, 0.088mol) was added over 5 min., and the mixture stirred for a further 12h before being cooled to $0^{o}C$. 1N HCl (80ml, 0.080mol) was added over 30 min, with vigorous stirring and the mixture stirred for a further 30 min before being warmed to ambient temperature. The mixture was diluted with Et_2O (100ml) and brine (100ml). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 100ml). The combined organic extracts were washed with water (2 x 100ml) and brine (100ml) dried, concentrated and the residue was distilled to yield the alcohol (229) (19.04g, 85%) as a colourless oil, b.p. $73-75^{o}C/11mmHg$ (lit.[67] b.p. $56^{o}C/7mmHg$); δ 0.25 (9H,s,$SiCH_3$), 2.28 (1H,bs,OH) and 4.30 (2H,s,CH_2).

3-Chloro-1-trimethylsilyl-1-propyne (232).

To 3-trimethylsilyl-3-propyn-1-ol (229) (6.40g, 50mmol) in CCl_4 (5.80ml, 60mmol) was added triphenylphosphine (13.1g, 50mmol) and the mixture heated to $85^{o}C$. A vigorous exothermic reaction occurred. When this had subsided, the mixture was heated to $100^{o}C$ for 3h, and then cooled to ambient temperature. The reaction mixture was diluted with n-pentane, filtered through a column of silica (40g) and the column eluted with n-pentane (200ml). The eluent was concentrated and distilled to yield

the chloride (232) (3.53g, 48%) as a colourless oil, b.p. 98°C/20mmHg,

ν_{max} (CHCl$_3$) 2960, 2180, 1260, 1030 and 850 cm^{-1}; δ 0.10 (9H,s,SiCH$_3$)

and 4.05 (2H,s,CH$_2$); (Found : M$^+$, 146.0342 and 148.0292.C$_6$H$_{11}$SiCl requires

146.0316 and 148.0286).

Attempted Grignard Reagent Formation from 3-Chloro-1-Trimethylsilyl-1-

Propyne (232) and Magnesium.

To magnesium (0.08g, 3.23mmol) and Et$_2$O (10ml) at ambient

temperature was added a solution of the chloride (232) (0.47g, 3.23mmol)

in Et$_2$O (5ml) over 10 min.   As no reaction appeared to be occurring, a

trace amount of I$_2$ was added.   After 10 min, the reaction mixture became

cloudy and it appeared as if a large proportion of the magnesium had been

consumed.   However, quenching this reaction with either gaseous or solid

carbon dioxide did not furnish any trace of the desired acid (235).

4-Trimethylsilyl-3-butyn-1-ol (234).

To a solution of bis-(trimethylsilyl)acetylene (233) (1.70g,

10mmol) in THF (10ml) at 0°C was added a solution of MeLi-LiBr (6.45ml,

1.55M, 10mmol) in Et$_2$O over 2 min.   The mixture was stirred at 0°C for

1h.   Ethylene oxide (0.98ml, 20mmol) was added and the mixture warmed

to ambient temperature and stirred for a further 16h.   The mixture was

diluted with saturated aqueous ammonium chloride (50ml) and extracted

with Et$_2$O (3 x 100ml).   The combined organic extracts were dried,

concentrated and the residue distilled to yield the alcohol (234) (1.33g,

94%) as a colourless oil, b.p. 110°C/20mmHg (lit.[94] b.p. 70°C/6mmHg);

ν_{max} (CHCl$_3$) 3620, 3020, 2960, 2170, 1250 and 850 cm^{-1}; δ 0.15 (9H,s,SiCH$_3$),

1.93 (1H,bs,OH), 2.30 (2H,t,J 7Hz,C≡CCH$_2$) and 3.52 (2H,t,J 7Hz,CH$_2$O);

(Found : M$^+$-CH$_3$, 127.0585.C$_7$H$_{14}$OSi requires M-CH$_3$, 127.0576).

Attempted oxidation of 4-Trimethylsilyl-3-Butyn-1-ol (234)-Procedure A.[70]

To CCl_4 (6.4ml), acetonitrile (6.4ml) and water (9.5ml) was added the alcohol (234) (452mg, 3.18mmol) and sodium periodate (2.781g, 13.0mmol). To this heterogeneous solution was added RuO_2 (9.3mg, 0.070mmol) and the mixture was stirred vigorously for 16h. The mixture was diluted with CH_2Cl_2 (32ml) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20ml) and the combined organic extracts were dried and concentrated to yield starting material only.

Procedure B.[71]

To a solution of the alcohol (234) (1.00g, 7.0mmol) in DMF (20ml) at ambient temperature was added PDC (9.27gm 24.6mmol) and the mixture was stirred for 16h. The mixture was diluted with water (200ml) and extracted with Et_2O (5 x 100ml). The combined organic extracts were washed with brine (100ml), dried and concentrated to yield starting alcohol only.

4-trimethylsilyl-3-butyn-1-oic acid (235).

To 4-trimethylsilyl-3-butyn-1-ol (234) (9.93g, 70mmol) in acetone (70ml) was added Jones reagent[95] (2.42M in CrO_3)(57.9ml, 140mmol) dropwise over 15 min., the temperature being kept below 15°C by means of an ice-water bath. The reaction mixture was allowed to warm to ambient temperature and stirred vigorously for 3h before being diluted with EtOAc (50ml) and a saturated aqueous solution of sodium chloride (50ml). The aqueous layer was extracted with EtOAc (3 x 50ml) and the combined organic extracts were dried and concentrated. The residue was taken up in EtOAc (100ml) and extracted with a saturated aqueous solution of sodium hydrogen carbonate (3 x 100ml). The aqueous extracts were extracted with Et_2O (3 x 100ml) and the combined organic extracts were dried and concentrated to yield the starting alcohol (234) (4.26g, 43%). The aqueous extracts

were acidified to pH2 with concentrated hydrochloric acid, then saturated

with solid sodium chloride and extracted with EtOAc (3 x 100ml).   The

combined organic extracts were dried and concentrated to yield the acid

(235) (5.21g, 48%, yield based on starting material consumed : 83%) as a

crystalline solid which was used without further purification.   A small

portion was recrystallised for analysis, m.p. 53-55°C (from light

petroleum); ν_{max} (CCl$_4$) 3000, 2180, 1720, 1250, 840 cm^{-1}; δ 0.15 (9H,s,

-SiMe$_3$), 3.36 (2H,s,C≡CCH$_2$), 11.60 (1H,bs,-COOH);

(Found : M$^+$, 141.0379.C$_7$H$_{12}$O$_2$Si requires M, 141.0369). (Found : C,53.68;

H, 7.63%. C$_7$H$_{12}$O$_2$Si requires C,53.81; H, 7.74%).

Methyl-4-trimethylsilyl-3-butyn-1-oate (236) - Procedure A.

To crude 4-trimethylsilyl-3-butyn-1-oic acid (235) (1.56g, 10mmol)

in Et$_2$O (10ml) at 0°C was added ethereal diazomethane until t.l.c analysis

showed complete consumption of starting material.   The mixture was warmed

to ambient temperature and washed with both saturated aqueous sodium

hydrogen carbonate (50ml) and sodium chloride (50ml), dried, concentrated

and the residue was distilled to yield the ester (236) (1.11g, 65%) as a

colourless oil, b.p. 140-150°C/20mmHg; ν_{max} (CHCl$_3$) 3040, 2960, 2180,

1740, 1440, 1250 and 850 cm^{-1}; δ 0.18 (9H,s,SiCH$_3$), 3.35 (2H,s,CH$_2$C≡C)

and 3.78 (3H,s,COOCH$_3$); (Found : M$^+$-CH$_3$, 155.0527. C$_8$H$_{14}$O$_2$Si requires

M-CH$_3$, 155.0525).

Procedure B.

To crude 4-trimethylsilyl-3-butyn-1-oic acid (235) (1.56g, 10mmol)

in methanol (2.35ml, 58mmol) was added concentrated sulphuric acid

(0.08ml, 1.50mmol) and the mixture heated at reflux for 2h.   After cooling

to ambient temperature, the mixture was diluted with Et$_2$O (100ml) and

washed with saturated sodium hydrogen carbonate (50ml) and brine (50ml),

dried, and concentrated and the residue was distilled to yield the ester (236) (1.16g, 68%). All properties were identical to those reported earlier.

3.Butyn-1-ol tetrahydropyranyl ether (238).

To 3-butyn-1-ol (10g, 143mmol) in DHP (19.5ml, 214mmol) was added freshly recrystallised pyridinium tosylate (3.52g, 14mmol). The mixture was stirred at ambient temperature for 2h before being diluted with Et_2O (100ml) and washed with saturated aqueous sodium hydrogen carbonate (3 x 50ml) and brine (50ml). The organic layer was dried, concentrated and the residue was distilled to yield the THP-ether (238) (22.02g, 100%) as a colourless oil, b.p. 95-100°C/20mmHg (lit.[96] b.p. 92-95°C/18mmHg); ν_{max} (CHCl$_3$) 3310, 3010, 2950, 2880, 2850, and 1035 cm^{-1}; δ 1.60 (6H,m, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$CHOO), 1.97 (1H,t,J 2Hz,HC≡C), 2.48 (2H,dt, J 2 and 7Hz,C≡CC$\underline{H}_2$), 3.75 (4H,m,C$\underline{H}_2$OTHP and C$\underline{H}_2$OCHO) and 4.66 (1H,m,OCHO); (Found : M$^+$-H, 153.0915. C$_9$H$_{14}$O$_2$ requires M-H, 153.0912).

4-Trimethylsilyl-3-butyn-1-ol (234).

To magnesium (3.77g, 155mmol) in Et_2O (100ml) was added ethyl bromide (12.8ml, 171mmol) in Et_2O (20ml) at such a rate as to maintain a gentle reflux. The mixture was stirred for 0.5h before 3-butyn-1-ol tetrahydropyranyl ether (238) (18.34g, 119mmol) in Et_2O (50ml) was added over 20 min. The solid that formed was broken up by spatula and the mixture stirred at ambient temperature for 12h. Chlorotrimethylsilane (25.6ml, 202mmol) was added over 30 min, and the mixture was heated to reflux for 8h before being cooled to ambient temperature. A further portion of chlorotrimethylsilane (15.1ml, 119mmol) was added over 5 min., and the mixture stirred for a further 12h before being cooled to 0°C. 1N HCl (54ml, 54mmol) was added over 30 min, with vigorous stirring and the mixture stirred for a further 30 min before being warmed to ambient

temperature.   The mixture was diluted with Et$_2$O (200ml) and brine (100ml)

The layers were separated and the aqueous layer was extracted with Et$_2$O

(3 x 200ml).   The combined organic extracts were washed with water

(3 x 100ml), brine (100ml), dried, concentrated and the residue was

distilled to yield the alcohol (234) (13.86g, 82%), all properties being

identical to those reported earlier.

(E)-1-Methoxy-4-trimethylsilyl-1-trimethylsilyloxy-2-buten-3-yne (239)

        To diisopropylamine (0.41ml, 2.94mmol) in THF (2.25ml) at 0°C

was added nBuLi (1.13ml, 2.6M, 2.94mmol) in hexane, over 2 min.   The

reaction mixture was stirred for a further 10 min, before being cooled

to -78°C.   Freshly distilled methyl 4-trimethylsilyl-3-butyn-1-oate

(236) (0.50g, 2.94mmol) in THF (1.5ml) was added over 3 min, and the

reaction mixture was stirred for 1h at -78°C.   Chlorotrimethylsilane

(0.37ml, 2.94mmol) was added over 2 min at -78°C and the reaction mixture

was stirred for 1h before being warmed to ambient temperature over 30 min.

Non-aqueous work-up and Kugelrohr distillation yielded a 4:1 mixture of

ketene acetal (239) and starting ester (236), (0.61g, 86%).

(239) : δ 0.16 (9H,s,C≡CSiCH$_3$), 0.27 (9H,s,OSiCH$_3$), 3.58 (3H,s,OCH$_3$) and

3.92 (1H,s,CH=C).

        Utilization of 1.1 equivalents of LDA resulted in no change to

the product distribution.   Utilization of 2.0 equivalents of LDA resulted

in formation of no identifiable materials.   The 'internal quench' method

of Corey[97] offered no advantage over the method stated above.

(Z)-1-Ethoxy-1,3-bis(trimethylsilyl)-1-butene (245).

To diisopropylamine (3.24ml, 23.1mmol) in THF (8ml) at 0°C was added nBuLi (8.86ml, 2.37M, 21.0mmol) in hexane, over 5 min.   The reaction mixture was stirred for a further 10 min., before being cooled to -78°C.   Freshly distilled ethyl 3-hydroxy butanoate (1.32g, 10.0mmol) in THF (4ml) was added over 3 min and the reaction mixture was stirred for 1h at -78°C.   Chlorotrimethylsilane (2.54ml, 20.0mmol) was added over 5 min and the reaction mixture was stirred for 1h at -78°C before being warmed to ambient temperature over 30 min.   Non-aqueous work-up and Kugelrohr distillation yielded the ketene acetal (245) (2.68g, 97%) as a colourless oil, b.p. 140°C/20mmHg; ν_{max} (CHCl$_3$) 2980, 1670, 1250, and 850 cm^{-1}; δ (CCl$_4$) 0.10 (9H,s,CH$_3$CHOSiCH$_3$), 0.29 (9H,s,C=COSiCH$_3$), 1.16 (3H,d,J 5Hz,CH$_3$CHOSi), 1.32 (3H,t,J 7Hz,COOCH$_2$CH$_3$), 3.16 (1H,d,J 9Hz, CH=C), 3.72 (2H,q,J 7Hz,COOCH$_2$CH$_3$) and 4.52 (1H,m,CH$_3$CHOSi); (Found : C, 51.92; H, 10.38%; M$^+$-CH$_3$, 261.1357. C$_{12}$H$_{28}$O$_3$Si$_2$ requires C, 52.12; H, 10.21%; M-CH$_3$, 261.1335.

5-Ethoxycarbonyl-6-methyl-2,4-diphenyl tetrahydrooxazine (247).

To N-trimethylsilyl benzaldimine (181b) (334mg, 1.887mmol) in CH$_2$Cl$_2$ (1.9ml) was added TMSOTf (0.59M) in CH$_2$Cl$_2$ (3.20ml, 1.887mmol) in one portion.   After 5 min, ketene acetal (245)(261mg, 0.944mmol) in CH$_2$Cl$_2$ (1.5ml) was added.   The mixture was warmed to ambient temperature and stirred for 19h before being diluted with Et$_2$O (50ml) and washed with saturated aqueous disodium hydrogen orthophosphate (50ml).   The organic layer was dried, concentrated and the residue purified by dry column flash chromatography to yield the oxazine (247) (229mg, 75%) as what appeared to be a single diastereoisomer, b.p. 168°C/0.9mmHg; ν_{max} (CHCl$_3$) 3040, 3020, 2980, 2940, 2880, 1720, 1460, 1375, 1310, 1135 and 700cm^{-1}; δ 0.98 (3H,t,J 7Hz,COOCH$_2$CH$_3$), 1.33 (3H,d,J 6Hz,CH$_3$CHO), 1.78 (1H,bs,NH),

2.52 (1H,dd,J 1 and 9Hz, CHCOOEt), 3.95 (2H,q,J 7Hz,COOCH$_2$CH$_3$), 4.10 (1H,

m,CH$_3$CHO), 4.34 (1H,d,J 9Hz,NCHPh), 5.41 (1H,s,OCHN) and 7.48 (10H,m,ArH);

(Found : M$^+$, 325.1678. C$_{20}$H$_{23}$NO$_3$ requires M, 325.1672).

Ethyl-3-benzylideneamino-2-(1'-t-butyldimethylsilyloxy)-

ethyl-3-phenyl propanoate (249):

To 5-ethoxycarbonyl-6-methyl-2,4-diphenyl oxazine (247) (124mg,

0.382mmol) in DMF (0.25ml) was added t-butylchlorodimethylsilane (173mg,

1.151mmol) and imidazole (178mg, 2.616mmol) and the mixture was stirred

at ambient temperature for 21h.   It was then diluted with EtOAc (200ml)

and washed with brine (50ml).   The organic extract was dried, concentrated

and the residue purified by dry column flash chromatography to yield the

silyloxy Schiff base (249) (143mg, 81%) as what appeared to be a single

stereoisomer, b.p. 140°C/0.45mmHg; δ 0.44 (6H,s,SiCH$_3$), 1.22 (9H,s,SiBu^t),

1.26 (3H,m,COOCH$_2$CH$_3$), 1.61 (3H,m,CH$_3$CHO), 3.79 (1H,dd,J 5 and 10Hz,

CHCOOEt), 4.24 (2H,q,J 7Hz,COOCH$_2$CH$_3$), 4.44 (1H,m,CH$_3$CHO), 4.92 (1H,d,J

10Hz, NCHPh), 7.69 (8H,m,ArH), 8.08 (2H,m,ArH) and 8.62 (1H,s,N=CH);

(Found : M$^+$.C$_4$H$_9$, 382.1832. C$_{26}$H$_{37}$NO$_3$Si requires M-C$_4$H$_9$, 382.1831).

2-Trimethylsilyloxy-4,5-dihydropyran (252).

To diisopropylamine (6.17ml, 44mmol) in THF (30ml) at 0°C was

added a solution of nBuLi (16.88ml, 2.37M, 40mmol) in hexane, over 5 min.

The reaction mixture was stirred for a further 10 min, before being

cooled to -78°C.   A solution of freshly distilled δ-valerolactone

(4.00g, 40mmol) in THF (10ml) was added over 5 min, and the reaction

mixture was stirred for 1h at -78°C.   Chlorotrimethylsilane (5.08ml,

40mmol) was added over 5 min, and the reaction mixture was stirred for

1h before being warmed to ambient temperature over 30 min.   Non-aqueous

work-up and Kugelrohr distillation yielded the ketene acetal (252)

(5.72g, 83%) as a colourless oil, b.p. 140-150°C/20mmHg; ν_{max} (CHCl$_3$)

3010, 2960, 2850, 1680, 1250, 910 and 845 cm^{-1}; δ 0.10 (9H,s,SiCH$_3$),

1.65 (2H,m,OCH$_2$CH$_2$CH$_2$), 1.96 (2H,m,OCH$_2$CH$_2$CH$_2$), 3.72 (1H,m,CH=C) and

3.94 (2H,m,OCH$_2$CH$_2$CH$_2$); (Found : M$^+$, 172.0920. C$_8$H$_{16}$O$_2$Si requires

M, 172.0915).

<u>Attempted Desilylation of α-[Bis(trimethylsilylamino)benzyl]-δ-</u>

<u>valerolactone (253)</u>.

<u>Procedure A</u>. To a solution of the β-amino ester (253) (71mg, 0.203mmol)

in THF (0.4ml) at ambient temperature was added a solution of oven-dried

(70°C/0.001mmHg,5h) nBu$_4$NF (11mg,0.041mmol) in THF (0.5ml). The mixture

was stirred at ambient temperature for 16h. The solvent was removed in

vacuo to yield starting material (63mg, 89%) as sole product. Utilization

of catalytic quantities of tris(dimethylamino) sulphur trimethylsilyl-

difluoride offered no improvement.

<u>Procedure B</u>. To a solution of the β-amino ester (253) (179mg, 0.513mmol)

in Et$_2$O (1ml) at 0°C was added a solution of MeLi-LiBr (0.34ml, 1.5M, 0.513

mmol) in Et$_2$O over 1 min. The mixture was warmed to ambient temperature

and stirred for 15h, before being diluted with Et$_2$O (50ml) and washed with

saturated aqueous ammonium chloride (50ml). The organic extract was

dried and concentrated to furnish products that had arose from decomposition

of β-amino ester (253).

<u>α-(1-Benzylamino-δ-valerolactone (256)</u>.

To α-[Bis(trimethylsilylamino)benzyl]-δ-valerolactone (253)

(153mg, 0.438mmol) in acetonitrile (1ml) at 0°C was added HF (20M) in

water (11μl, 0.220mmol) and the reaction mixture was stirred for 1h by

which time t.l.c showed total consumption of starting material. The

mixture was diluted with brine (50ml) and potassium carbonate was added

to pH11.   The mixture was saturated with sodium chloride, filtered

through Celite 535 and extracted with EtOAc (3 x 100ml).   The combined

organic extracts were dried and concentrated to yield the β-amino ester

(256) (70mg, 78%) as a very viscous colourless oil which was utilised

without further purification; ν_{max} (KBr) 3350, 2950, 1730, 1160 and 700cm^{-1}.

Attempted Derivatisation of α-(1-Benzylamino)-δ-valerolactone (256)

As the corresponding hydrochloride salt:

To methanol (1.5ml) at 0°C was added acetyl chloride (47μl, 0.663

mmol) over 30 sec, and the mixture stirred for 10 min.   α-(1-Benzylamino)-

δ-valerolactone (256) (136mg, 0.663mmol) in methanol (1ml) was added

over 30 sec, and the mixture stirred for 10 min.   Concentration yielded

a thick orange paste.   All attempts to crystallise this paste failed.

As the corresponding oxalate salt:

To α-(1-benzylamino)-δ-valerolactone (256) (65mg, 0.317mmol),

partially dissolved in Et$_2$O (1.5ml) was added oxalic acid (29mg, 0.317mmol)

in Et$_2$O (0.5ml) resulting in the formation of copious amounts of white

crystals.   Filtration yielded a sticky gum.

As the corresponding p-toluenesulphonamide.

To α-(1-benzylamino)-δ-valerolactone (256) (122mg, 0.595mmol) was

added sodium hydroxide (10%) in water (0.95ml, 2.380mmol) and p-toluene-

sulphonyl chloride (170mg, 0.893mmol).   Acetone (2ml) was added and the

resulting homogeneous solution was shaken for 2 min.   The mixture was

concentrated and the residue heated to boiling and then allowed to cool.

Addition of 1N HCl resulted in formation of a milky solution.   The

solution was extracted with EtOAc (2 x 50ml) and the combined organic

extracts were dried and concentrated to yield a gum.   No trace of the desired sulphonate could be detected.

As the corresponding acetamide:

α-(1-Benzylamino)-δ-valerolactone (256) (93mg, 0.454mmol) was dissolved in acetic anhydride (1.0ml, 10.599mmol) and the mixture was heated to 100°C for 30 min.   The excess acetic anhydride was removed by azeotropic distillation using toluene (3 x 15ml).   The residual oil was taken up in Et_2O (50ml) and washed with brine (25ml).   The organic layer was dried, concentrated and the residue was purified by dry column flash chromatography.   No trace of the desired acetamide could be found.

As the corresponding 2-azetidinone:

To α-(1-benzylamino)-δ-valerolactone (256) (49mg, 0.239mmol) in CH_2Cl_2 (1.2ml) was added triethylamine (37μl, 0.263 mmol) and chlorotrimethylsilane (30μl, 0.239 mmol).   The resulting heterogeneous reaction mixture was stirred for 15.5h before being cooled to 0°C. MeMgBr in Et_2O (0.24ml, 3M, 0.717mmol) was added over 1 min, and the reaction mixture was warmed to ambient temperature and stirred for a further 7.5h.   The reaction mixture was diluted with Et_2O (50ml) and washed with saturated aqueous ammonium chloride (30ml).   The aqueous wash was extracted with Et_2O (30ml) and the combined organic extracts were dried and concentrated.   The residual oil was taken up in Et_2O (4ml) and to this solution was added acetic anhydride (4ml,42.4mmol) and pyridine (2ml,24.7mmol) and the mixture was stirred for 21h.   The Et_2O was removed in vacuo and the excess acetic anhydride and pyridine were removed azeotropically in vacuo with toluene (3 x 30ml) and CCl_4 (30ml) to yield 42mg of a brown oil.   No trace of the desired 2-azetidinone could be found.

Attempted Deblocking of α-(N-Benzylideneaminobenzyl)-δ-valerolactone (254).

Procedure A.

A solution of the Schiff base (254) (62mg, 0.212mmol) in methanol (2ml) was heated to reflux for 12h. The mixture was allowed to cool to ambient temperature. Removal of solvent in vacuo resulted in recovery of starting materials.

Procedure B.

To a solution of the Schiff base (254)(75mg, 0.256mmol) in THF (2ml) and water (2ml) at ambient temperature was added saturated aqueous ammonium chloride (30ml). The homogeneous solution was stirred for 16h. Extractive work-up did not yield any recognisable products. Repetition of this process using 1N HCl offered no advantage.

Procedure C.

To a solution of the Schiff base (254) (224mg, 0.765mmol) in Et_2O (5ml) was added a homogeneous solution of p-toluenesulphonic acid monohydrate (145mg, 0.765mmol) in Et_2O (5ml). A white solid formed immediately. However, filtration yielded a thick paste, the result of decomposition of the in situ formed p-toluenesulphonate salt.

Procedure D.

To a solution of the Schiff base (254) (71mg, 0.242mmol) in CH_2Cl_2 (2.4ml) was added a solution of TMSOTf (0.25ml, 0.95M, 0.242mmol). The solution was stirred for 10 min. Aqueous work-up yielded starting material only. Utilization of two equivalents of TMSOTf offered no advantage.

Benzylidene Aniline.[98]

To benzaldehyde (106g, 1mol) was added aniline (93g, 1mol) over 3 min, and the mixture stirred for 15 min., before being added to 95% EtOH (300ml) and stirred vigorously for 10 min. The mixture was cooled to $0°C$ and filtered to yield a solid which was recrystallised from 95% EtOH to yield the imine (170.38g, 94%) as a pale green solid, m.p. 47.5-51°C (lit.[98] m.p. 52°C); ν_{max} (CCl_4) 3060, 3030, 2880, 1630, 1590, 1580, 1480, 1445, 1190, 1165 and 695 cm^{-1}; δ 7.35 (8H,m,ArH), 7.87 (2H,m,ArH) and 8.40 (1H,s,N=CH); (Found : M^+, 181.0889. $C_{13}H_{11}N$ requires 181.0887).

α-[1-(N-phenyl)benzylamino]-δ-valerolactone (260).

Zinc iodide (742mg, 2.325mmol) in Et_2O (23ml) was stirred at ambient temperature for 30 min. To this solution was added benzylidene aniline (421mg, 2.325mmol) in Et_2O (3ml), ketene acetal (252) (400mg, 2.325mmol) in Et_2O (1ml), and t-BuOH (172mg, 2.325mmol) in Et_2O (1ml). The resulting solution was stirred at ambient temperature for 20h before being diluted with Et_2O (100ml), washed with 5% aqueous NH_3 (50ml), dried, and concentrated. The residue was purified by dry column flash chromatography to yield the β-amino ester (260) (490mg, 75%) as an inseparable mixture of threo and erythro diastereoisomers, in a ratio of 2:1, respectively, m.p. 134-139°C (from EtOAc/light petroleum); ν_{max} $(CHCl_3)$ 3380, 3000, 1710, 1595, 1490, 1245, 1150, 1075 and 700 cm^{-1}; δ (threo) 1.76 (4H,m,OCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 3.04 (1H,m,CHCOO), 4.14 (2H,m,OC$\underline{H}_2$CH$_2$CH$_2$), 4.83 (1H,d,J 5Hz,NCH), 5.12 (1H,bs,NH), 6.58 (3H,m,ArH), 7.10 (2H,m,ArH) and 7.32 (5H,m,ArH), (erythro) 1.76 (4H,m,OCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 3.04 (1H,m,CHCOO), 4.14 (2H,m,OC$\underline{H}_2$CH$_2$CH$_2$), 4.79 (1H,d,J 3Hz,NCH), 5.12 (1H,bs,NH), 6.58 (3H, m,ArH), 7.10 (2H,m,ArH) and 7.32 (5H,m,ArH); (Found : C, 76.82; H, 6.80; N, 5.01%; M^+, 281.1410. $C_{18}H_{19}NO_2$ requires C, 76.84; H, 6.81; N, 5.00%; M, 281.1411).

α-Benzylidene-δ-valerolactone (261)

To hexamethyldisilazane (0.93ml, 4.40mmol) in THF (8ml) at 0°C was added nBuLi in hexane (1.69ml, 2.37M, 4.00mmol) over 2 min and the solution stirred for 10 min before being cooled to -78°C. Chlorotrimethylsilane (0.51ml, 4.00mmol) was added over 2 min., and the solution stirred for a further 10 min. α-[1-(N-phenyl)benzylamino]-δ-valerolactone (260) (1.124g, 4.00mmol) in THF (10ml) was added over 4 min. The solution was warmed to ambient temperature and stirred for 20h before being diluted with Et_2O (100ml) and washed with saturated ammonium chloride (50ml). The aqueous wash was extracted with Et_2O (50ml) and the combined organic extracts were dried and concentrated. The residual oil was purified by dry column flash chromatography to yield the lactone (261) (446mg, 59%) as a white crystalline solid, m.p. 62°C(from light petroleum) (lit.[80] m.p. 63°C); ν_{max} (CHCl$_3$) 3020, 1705, 1610, 1265, 1170, and 1125 cm^{-1}; δ 1.94 (2H,m, CH$_2$CH$_2$CH$_2$), 2.86 (2H,dt, J 2 and 7Hz,CH$_2$C=C), 4.37 (2H,m,OCH$_2$), 7.35 (5H,bs, ArH) and 7.86 (1H,t,J 2Hz, C=CH); (Found : C, 76.41; H, 6.19%; M$^+$, 188.0829 C$_{12}$H$_{12}$O$_2$ requires C, 76.57; H, 6.42%; M, 188.0834).

Methyl 2-(3-hydroxypropyl)-3-phenyl-3-(N-phenyl)amino Propanoate (262).

Sodium (45mg, 1.943mmol) in methanol (39ml) was swirled at ambient temperature until all the sodium had been consumed. To this solution was added α-[1-(N-phenyl)benzylamino]-δ-valerolactone (260) (546mg, 1.943mmol) in methanol (30ml) and the mixture heated to reflux for 15h. The mixture was cooled to ambient temperature and diluted with saturated aqueous ammonium chloride (50ml) and the methanol was removed in vacuo. The aqueous solution was extracted with EtOAc (3 x 50ml) and the combined organic extracts were washed with brine (50ml), dried and concentrated. The residue was purified by dry column flash chromatography to yield the hydroxy β-amino ester (262) (608mg, 100%) as an inseparable mixture of

threo and erythro diastereoisomers, in a ratio of 2:1, b.p. 230°C/

0.04mmHg; ν_{max} (CHCl$_3$) 3630, 3420, 3030, 3020, 2960, 1725, 1600 and

1500 cm^{-1}; δ (threo) 1.62 (4H,m,HOCH$_2$CH$_2$CH$_2$), 2.80 (1H,m,CHCOOCH$_3$),

3.50 (3H,s,COOCH$_3$), 3.85 (2H,t, J 6Hz, HOCH$_2$), 4.57 (1H,d,J 6Hz,NCH),

6.48 (3H,m,ArH), 7.00 (2H,m,ArH), and 7.20 (5H,m,ArH), (erythro) 1.62

(4H,m,HOCH$_2$CH$_2$CH$_2$), 3.12 (1H,m,CHCOOCH$_3$), 3.47 (3H,s,COOCH$_3$), 4.62 (1H,

d, J 5Hz, NCH), 6.48 (3H,m,ArH), 7.00 (2H,m,ArH) and 7.20 (5H,m,ArH).

Methyl 2-(3'-acetoxypropyl)-3-phenyl-3-(N-phenyl)aminopropanoate (263)

Methyl 2-(3'-hydroxypropyl)-3-phenyl-3-(N-phenyl)amino propanoate

(262) (313mg, 1.00mmol) was dissolved in acetic anhydride (5ml) and

pyridine (2.5ml) and stirred at ambient temperature for 24h.   The excess

acetic anhydride and pyridine were removed azeotropically in vacuo with

toluene (3 x 15ml) and the residue was purified by dry column flash

chromatography to yield the acetoxy β-amino ester (263) (291mg, 82%)

as an inseparable mixture of threo and erythro diastereoisomers, in the

ratio of 2:1, b.p. 245°C/0.09mmHg; ν_{max} (CHCl$_3$), 3420, 3020, 2960, 1760,

1600, 1500, 1250 and 705 cm^{-1}; δ (threo) 1.72 (4H,m,AcOCH$_2$CH$_2$CH$_2$), 1.97

(3H,s,CH$_3$COO), 2.78 (1H,m,CHCOOCH$_3$), 3.55 (3H,s,COOCH$_3$), 3.98 (2H,t,J 6Hz,

AcOCH$_2$), 4.53 (1H,d,J 7Hz, NCH), 6.53 (3H,m,ArH), 7.08 (2H,m,ArH) and

7.25 (5H,m,ArH), (erythro) 1.72 (4H,m,AcOCH$_2$CH$_2$CH$_2$), 1.97 (3H,s,CH$_3$COO),

2.78 (1H,m,CHCOOCH$_3$), 3.53 (3H,s,COOCH$_3$), 3.98 (2H,t,J 6Hz,AcOCH$_2$), 4.61

(1H,d,J 6Hz,NCH), 6.53 (3H,m,ArH), 7.08 (2H,m,ArH) and 7.25 (5H,m,ArH);

(Found : M$^+$, 355.1778. C$_{21}$H$_{25}$NO$_4$ requires 355.1777).

Methyl 2-(3'-t-butyldimethylsilyloxypropyl)-3-phenyl-3-(N-phenyl)amino-propanoate (264).

To methyl 2-(3-hydroxypropyl)-3-phenyl-3-(N-phenyl)amino propanoate (262) (924mg, 2.952mmol) was added t-butylchlorodimethyl-silane (489mg, 3.247mmol), imidazole (502mg, 7.380mmol) and DMF (2ml). The mixtured was stirred at ambient temperature for 61h. It was then diluted with EtOAc (200ml) and washed with brine (50ml). The organic extract was dried, concentrated and the residue purified by dry column flash chromatography to yield the silyloxy β-amino ester (264) (981mg, 78%) as an inseparable mixture of <u>threo</u> and <u>erythro</u> diastereoisomers, in the ratio 2:1 b.p. 200°C/0.5mmHg; ν_{max} (CHCl$_3$) 3420, 3040, 3020, 2980, 2930, 2860, 1760, 1600, 1500, 1350, 1100, 880, and 700 cm^{-1}; δ (<u>threo</u>) 0.04 (6H,s,SiCH$_3$), 0.83 (9H,s,SiBu^t), 1.55 (4H,m,SiOCH$_2$C̲H̲$_2$C̲H̲$_2$), 2.83 (1H,m,C̲HCOOCH$_3$), 3.52 (2H,t,J 5Hz, SiOCH$_2$), 3.58 (3H,s,COOCH$_3$), 4.54 (1H,d,j 7Hz,NCH), 6.56 (3H,m,ArH), 7.14 (2H,m,ArH) and 7.28 (5H,m,ArH), (<u>erythro</u>) -0,08 (6H,s,SiCH$_3$), 0.82 (9H,s,SiBu^t), 1.55 (4H,m,SiOCH$_2$C̲H̲$_2$C̲H̲$_2$), 2.62 (1H,m,C̲HCOOCH$_3$), 3.56 (3H,s,COOCH$_3$), 3.68 (2H,t,J 5Hz,SiOCH$_2$), 4.62 (1H,d,J 6Hz,NCH), 6.56 (3H,m,ArH), 7.14 (2H,m,ArH) and 7.28 (5H,m,ArH); (Found : M$^+$, 427.2540. C$_{25}$H$_{37}$NO$_3$Si requires M, 427.2533).

N-Phenyl-3-(3'-t-butyldimethylsilyloxypropyl)-4-phenyl-2-azetidinone (265).

To methyl 2-(3-t-butyldimethylsilyloxypropyl)-3-phenyl-3-(N-phenyl) amino propanoate (264) (266mg, 0.623mmol) in Et$_2$O (6.2ml) at 0°C was added Bu^{t}MgCl (0.62ml,2M,1.246mmol) in Et$_2$O over 1 min. The mixture was warmed to ambient temperature and stirred for 28h before being diluted with Et$_2$O (100ml) and washed with saturated aqueous ammonium chloride (50ml). The aqueous wash was extracted with Et$_2$O (50ml) and the combined organic extracts were washed with brine (50ml), dried, concentrated and the residue was purified by dry column flash chromatography to yield the

2-azetidinone (265) (222mg, 90%) as an inseparable mixture of <u>trans</u> and <u>cis</u> diastereoisomers, in the ratio of 2:1, b.p. 160°C/0.04mmHg; ν_{max} (CHCl$_3$) 3020, 2960, 2930, 2860, 1740, 1600, 1500 and 1390 cm^{-1}; δ (<u>trans</u>) 0.02 (6H,s,SiCH$_3$), 0.87 (9H,s,SiBu^t), 1.87 (4H,m,SiOCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 3.09 (1H,m,CHCO), 3.63 (2H,t,J 5Hz,SiOCH$_2$), 4.63 (1H,d,J 2Hz,NCH) and 7.29 (10H,m,ArH), (<u>cis</u>) -0.07 (6H,s,SiCH$_3$), 0.80 (9H,s,SiBu^t), 1.87 (4H,m, SiOCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 3.44 (1H,d,J 5Hz,COCH), 3.63 (2H,t,J 5Hz,SiOCH$_2$), 5.14 (1H,d,J 5Hz,NCH) and 7.29 (10H,m,ArH); (Found : M$^+$, 395.2274. C$_{24}$H$_{33}$NO$_2$Si requires M, 395.2272).

<u>Attempted Formation of N-t-Butyldimethylsilyl Butanaldimine (270)</u>.

To a solution of <u>N</u>-t-butyldimethylsilyl butylamine (267) (664mg, 3.551mmol) in THF (7ml) at 0°C was added a solution of nBuLi (1.50ml, 2.6M, 3.906mmol) in hexane over 1 min. The solution was stirred at 0°C for 10 min, before a solution of t-butyl hypochlorite (0.43g, 3.906mmol) in THF (2ml) was added over 1 min. The solution was warmed to ambient temperature and stirred for 17h. Non-aqueous work-up did not yield any recognisable products.

<u>1-Oxa-5-azaspiro[5,5]undecane (278)</u>.[83]

To 3-amino-1-propanol (15.3ml, 200mmol) in benzene (100ml) was added cyclohexanone (27.9ml, 270mmol) and the mixture heated at reflux for 18h over a water-trap. Concentration and distillation of the residue yielded the oxazine (278) (18.75g, 60%), b.p. 110°C/20mmHg (lit.[83] b.p. 119-120°C/29mmHg) which crystallised upon standing, yielding white crystals, m.p. 42-46°C (lit.[83] m.p. 44-45°C).

Attempted N-Halogenation of 1-Oxa-5-azaspiro[5,5]undecane (278).

Procedure A. To a solution of (278) (775mg, 5mmol) in THF (10ml) at

0°C was added a solution of t-butyl hypochlorite (0.54g, 5mmol) in

THF (10ml). The reaction mixture was warmed to ambient temperature and

stirred for 16.5h. Non-aqueous work-up yielded an inseparable mixture

of the desired N-chloro oxazine (279), and (278), in a ratio of 2:1.

Procedure B. To a solution of (278) (1.55g, 10mmol) in CCl_4 (100ml) at

ambient temperature was added N-bromosuccinimide (1.78g, 10mmol).

Evaporation of a portion of this reaction revealed partial conversion of

(278) into the desired N-bromo compound. However, before complete

consumption of (278), extensive decomposition took place, producing no

pure materials. Utilization of N-chlorosuccinimide offered no

advantage.

(4R)-Ethoxycarbonyl-Δ^2-thiazoline (153).[42]

Through a solution of L-cysteine ethyl ester hydrochloride (50g,

269mmol) in methanol (500ml) was passed ammonia gas at ambient temperature

for 15 min. The precipitated ammonium chloride was filtered off.

Concentration yielded L-cysteine ethyl ester which was dissolved in

absolute ethanol (200ml) containing p-toluenesulphonic acid (50mg, 0.263

mmol) and the solution was heated to reflux. To this solution was added

triethyl orthoformate (150ml, 902mmol) over 0.5h and the mixture maintained

at reflux for 3h. The mixture was allowed to cool to ambient temperature

and concentrated. The residue was dissolved in CH_2Cl_2 (200ml) and

washed with water (3 x 75ml). The organic layer was dried and concentrated

to yield N-formyl-L-cysteine ethyl ester as a viscous oil (24.07g), which

was not purified further. Distillation of N-formyl-L-cysteine ethyl ester

yielded the thiazoline (153) (5.83g, 14%) as a colourless oil, b.p. 84°C/

1.0mmHg (lit.[42] b.p. 120°C/0.3mmHg); $[\alpha]_D^{20}$ + 100.5° (c = 1, CHCl$_3$);

ν_{max} (CCl$_4$) 2990, 1740 and 1570 cm^{-1}; δ 1.35 (3H,t,j 7Hz,COOCH$_2$CH$_3$),

3.53 (1H,m,SCH$_2$CH), 4.32 (2H,q,J 7Hz,COOCH$_2$CH$_3$), 5.14 (2H,m,SCH$_2$) and

8.06 (1H,m,N=CH); (Found : C,45.46; H, 5.85; N, 8.89; S,20.14%; M$^+$,

159.0348. C$_6$H$_9$NO$_2$S requires C, 45.26; H, 5.70; N,8.80; S, 20.15%;

M, 159.0352).

Methyl 2,2-dimethyl-2-[2'-(4'R)-ethoxycarbonyl-Δ^2-thiazoline] (286).

     To a mixture of (4R)-ethoxycarbonyl-Δ^2-thiazoline (153) (424g,

2.665mmol), ketene acetal (187)(464mg, 2.665mmol) and 4 Å molecular

sieves (1.0g) in CH$_2$Cl$_2$ (26.6ml) at -78°C was added TMSOTf in CH$_2$Cl$_2$

(0.52ml, 0.51M, 0.266mmol). The mixture was stirred for 6h, warmed to

ambient temperature and stirred for a further 9h before being diluted

with Et$_2$O (50ml) and filtered through Celite 535. The organic extract

was washed with water (50ml) dried, concentrated and the residue purified

by dry column flash chromatography to yield the β-amino ester (286)

(679mg, 98%) as a colourless oil, b.p. 185°C/0.005mmHg; ν_{max} (CCl$_4$) 3300,

2980, 2960 and 1740 cm^{-1}; δ 1.32 (9H,m,Me$_2$CCOOCH$_3$ and COOCH$_2$CH$_3$),

2.70 (1H,dd,J 10 and 10Hz,SCH$_2$CH), 3.22 (2H,m,SCH$_2$), 3.75 (3H,s,COOCH$_3$),

4.21 (2H,m,COOCH$_2$CH$_3$), 4.70 (1H,m,NH) and 5.00 (1H,s,NCHS); (Found :

M$^+$, 261.1035. C$_{11}$H$_{19}$NO$_4$S requires M, 261.1030).

Reaction of Thiazoline (153) and Phenoxyacetic acid (290).

     To a solution of phenoxyacetic acid (290) (484mg, 3.180mmol) in

CH$_2$Cl$_2$ (6ml) was added triethylamine (1.33ml, 9.541mmol) and the thiazoline

(153) (506mg, 3.180mmol) at ambient temperature. Phenyl dichlorophosphate

(0.48ml, 3.180mmol) was added over 30 sec, and the solution was stirred

for 19h at ambient temperature. The mixture was diluted with CH$_2$Cl$_2$

(20ml) and washed with water (20ml). The organic extract was diluted

with Et_2O (50ml), washed with brine (20ml), dried and concentrated.
No β-lactam-containing species could be detected.

N-(1-Propenyl)-piperidine (216).[87]

To piperidine (148ml, 1.50 mol) in Et_2O (150ml) was added
potassium carbonate (105g) and the mixture was cooled to -5°C.   Propanal
(54ml, 0.75mol) was added with the temperature being maintained below
5°C.   The mixture was then warmed to ambient temperature and stirred
for 0.5h, before being filtered through Celite 535.   Concentration at
atmospheric pressure and careful distillation of the residue yielded
the enamine (216) (67.36g, 72%) as a colourless oil, b.p. 65°C/20mmHg
(lit.[87] b.p. 61-63°C/15mmHg) which was contaminated with ~50% piperidine.
This mixture was used without further purification.

N-(1-Pentenyl)-piperidine (304)

All operations were identical with the procedure described above
for N-(1-propenyl)-piperidine (216), except that pentanal (79.6ml, 0.75mol)
was employed.   Concentration at atmospheric pressure and careful
distillation of the residue yielded the enamine (304) as a colourless
oil, b.p. 89-94°C/8mmHg.

Synthesis of β-Amino Esters from the TMSOTf-Mediated Reaction Between Enamines and O-Trimethylsilyl Ketene Acetals.

Methyl 2,2-dimethyl-3-piperidinopentanoate (305).

To the enamine (216) (125mg, 1.00mmol) and 4 $\overset{o}{A}$ molecular
sieves (0.5g) in CH_2Cl_2 (10ml) at 0°C was added a solution of trimethyl-
silyl trifluoromethanesulphonate (1.07ml, 0.94M, 1.00mmol) in CH_2Cl_2 and
the reaction mixture was stirred for 0.5h at 0°C.   Ketene acetal (187)
(174mg, 1.00mmol) in CH_2Cl_2 (0.5ml) was then added.   The reaction

mixture was warmed to ambient temperature and stirred for 17h before being diluted with Et_2O (50ml), filtered through Celite 535 and washed with saturated aqueous disodium hydrogen orthophosphate (20ml). The aqueous wash was extracted with Et_2O (3 x 50ml) and the combined organic extracts were dried, concentrated and the residue was purified by dry column flash chromatography to yield the β-amino ester (305) (108mg, 48%), as a colourless oil, b.p. 100-110°C/0.5mmHg; ν_{max} (CCl_4) 2980, 2940, 1730 and 1140 cm^{-1}; δ 1.05 (3H,s,CH_3), 1.10 (3H,s,CH_3), 1.38 (11H,m,$N\overline{CH_2CH_2CH_2CH_2CH_2}$ and CH_2CH_3), 2.65 (5H,m,$N\overline{CH_2}CH_2CH_2CH_2\overline{CH_2}$ and CHN) and 3.63 (3H,s,$COOCH_3$), (Found : M$^+$, 227.1899. $C_{13}H_{25}NO_2$ requires M, 227.1879).

Methyl 2,2-dimethyl-3-piperidinoheptanoate (306).

All operations were identical with the procedure described above for methyl 2,2-dimethyl-3-piperidinopentanoate (305) except that enamine (304) (153mg, 1.00mmol) was employed. Dry column flash chromatographic purification of the residue yielded the β-amino ester (306) (217mg, 85%), as a colourless oil, b.p. 90-100°C/0.07mmHg; ν_{max} (CCl_4) 2940 and 1730 cm^{-1}; δ 0.05 (3H,s,CH_3), 1.12 (3H,s,CH_3), 1.35 (15H,m, $N\overline{CH_2CH_2CH_2CH_2CH_2}$ and $CH_2CH_2CH_2CH_3$), 2.70 (5H,m, $N\overline{CH_2}CH_2CH_2CH_2\overline{CH_2}$ and CHN) and 3.65 (3H,s,$COOCH_3$); (Found : M$^+$, 255.2204. $C_{15}H_{29}NO_2$ requires M, 255.2191).

The Lewis Acid - Mediated Reaction Between N-Trimethylsilyl Benzaldimine (181b) and Vinyltrimethylsilane (311).

To a solution of the imine (181b) (177mg, 1mmol) in CH_2Cl_2 (0.96ml) at 0°C was added a solution of TMSOTf (0.12ml, 0.86M, 0.10mmol) over 1 min. The mixture was stirred for 30 min, before a solution of vinyltrimethylsilane (311) (100mg, 1mmol) in CH_2Cl_2 (1ml) was added over 1 min, at 0°C. The mixture was allowed to warm to ambient temperature

and stirred for 23h.   Aqueous work-up yielded products resulting from

hydrolysis of (181b).   Utilization of one equivalent of TMSOTf,ZnI_2,

$SnCl_4$ or $BF_3.OEt_2$ offered no advantage.

The Lewis Acid - Mediated Reaction Between N-Trimethylsilyl

Benzaldimine (181b) and Allyltrimethylsilane (312).

        To a solution of the imine (181b) (177mg, 1mmol) in CH_2Cl_2 (1ml)

at 0°C was added a solution of TMSOTf (0.13ml, 0.79M, 0.10mmol) in CH_2Cl_2

over 1 min.   The mixture was stirred for 30 min, before a solution of

allyltrimethylsilane (312) (114mg, 1mmol) in CH_2Cl_2 (1ml) was added over

1 min at 0°C.   The mixture was allowed to warm to ambient temperature

and stirred for 21h.   Aqueous work-up yielded products resulting from

the hydrolysis of (181b).   Utilization of one equivalent of TMSOTf,

ZnI_2, $ZnCl_2$, $SnCl_4$ or $BF_3.OEt_2$ offered no advantage.

N-Benzylidene-1-phenyl-3-butene amine (313).

        To N-trimethylsilyl benzaldimine (181b) (177mg, 1.0mmol) in

CH_2Cl_2 (2ml) at -78°C was added a solution of $TiCl_4$ (1.90ml,0.53M,1.0mmol)

in CH_2Cl_2 over 1 min.   The mixture was stirred for 0.5h and allyltrimethyl-

silane (114mg, 1.0mmol) in CH_2Cl_2 (1ml) was added over 1 min.   The reaction

mixture was stirred for 1h, warmed to ambient temperature and stirred for

a further 18h before being diluted with Et_2O (50ml) and washed with

saturated aqueous sodium hydrogen carbonate (50ml).   The aqueous wash was

extracted with Et_2O (50ml) and the combined organic extracts were washed

with water (2 x 30ml) and brine, dried, concentrated and the residue was

purified by dry column flash chromatography to yield the Schiff base

(313) (118mg, 62%); δ 3.11 (2H,m,C$\underline{H}_2$CHN), 4.82 (1H,m,CHN), 5.42 (2H,m,C$\underline{H}_2$=

CH), 6.18 (1H,m,CH_2=C$\underline{H}$), 7.82 (8H,m,ArH), 8.13 (2H,m,ArH) and 8.61 (1H,

s,N=CH).

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