Approaches to the synthesis of phosphorus analogues of the beta-lactam antibiotics.

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APPROACHES TO THE SYNTHESIS OF PHOSPHORUS ANALOGUES OF THE β-LACTAM ANTIBIOTICS

Submitted by STUART J. MICKEL, B.Sc.

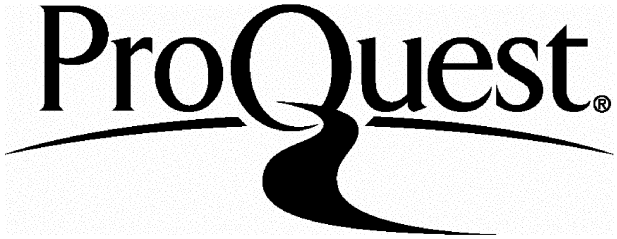
for the degree of Ph.D.

of the University of Bath

1982

Stuart J. Mickel

September, 1982



To my parents.

ACKNOWLEDGEMENTS

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I wish to express my sincere gratitude to Professor Malcolm Campbell for his guidance and encouragement throughout this research. I also wish to thank my colleagues and friends at Pfizer Central Research, in particular Drs. J.E. Kemp, C.W. Greengrass, S.J. Ray, J.E. Arrowsmith and K. Richardson, for many helpful discussions.

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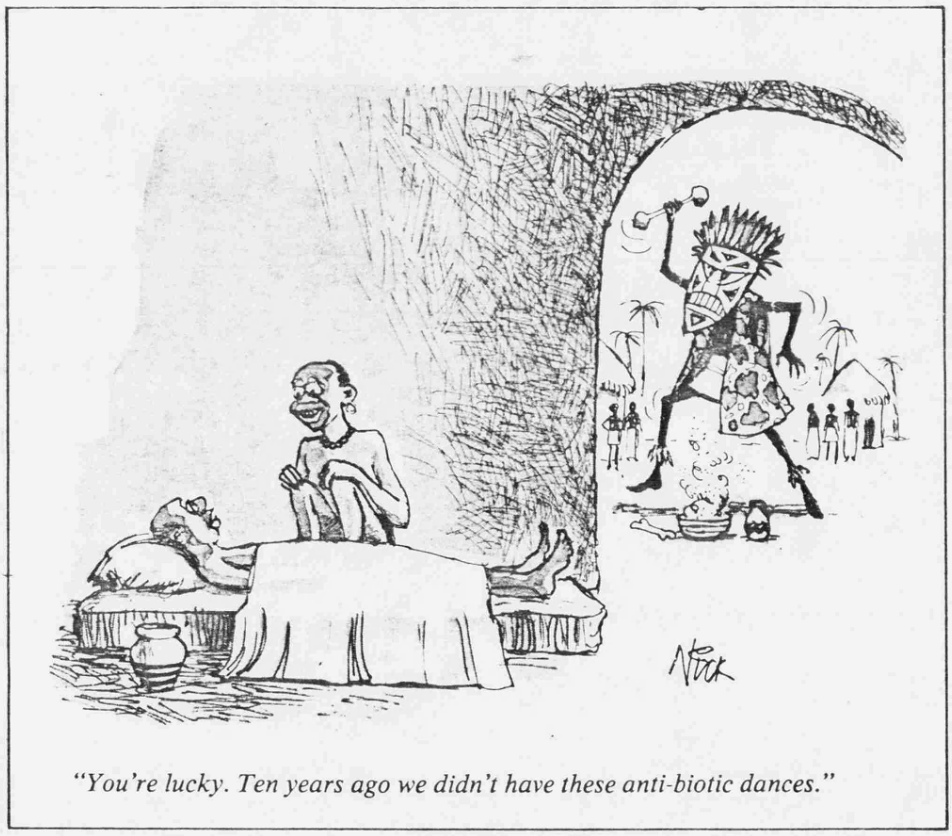


"You're lucky. Ten years ago we didn't have these anti-biotic dances."

ABSTRACT

In pursuit of routes to phosphorus containing analogues of the β-lactam antibiotics, a range of organophosphorus and azetidin-2-one chemistry has emerged. New reactions, synthetic methods and intermediates of potential use in analogue synthesis have been defined.

The organophosphorus systems, phosphonoformaldehyde (I) and 2-oxophosphonomalonate (II), were synthesised and their reactions with substituted azetidin-2-ones investigated.

Azetidin-2-ones (III), (IV) and (V) were prepared by a new route in good overall yield (35-40%) from 4-acetoxyazetidin-2-one.

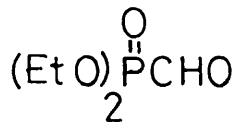
A literature method for bis-deprotection of phosphonate methyl esters was extended and monophosphonic acids (VI) and (VII) were prepared. Intermolecular coupling of (VII) with 4-acetoxy-azetidin-2-one afforded the novel β-lactam (VIII) in low yield.

Application of the deprotection methodology to azetidin-2-ones (III) and (V) afforded silyl oxyphosphonates (IX) and (X), aqueous hydrolysis of which gave the unstable phosphonic acids (XI) and (XII) which could not be isolated. Model studies on a monophosphonic acid led to phosphonochloridate (XIII) and mixed O,S-alkylphosphonoacetates (XIV).

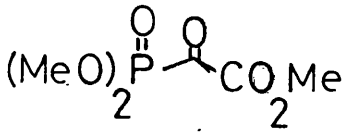
The interesting synthetic intermediate, 4-chloroazetidin-2-one (XV), was prepared by chlorinolysis of azetidin-2-ones (XVI). The potential of (XV) in β-lactam synthesis was shown by its conversion to (XVII) and (XVIII) on treatment with silver acetate or silver isothiocyanate.

Mono deprotection at phosphorus in azetidin-2-ones (XIX) and (XX) led to the novel phosphonic acids (XXI) and (XXII) which were found to be unstable.

Rhodium acetate catalysed intermolecular insertion of the carbene derived from 2-diazomethylacetoacetate into the NH bond of 4-dimethylphosphonoazetidin-2-one afforded the new β-keto ester (XXIII) in good yield (35-50%). Conversion of (XXIII) to the enamines (XXV) and (XXVI) proceeded in high overall yield (80%) via the enol mesylate (XXIV).



(I)



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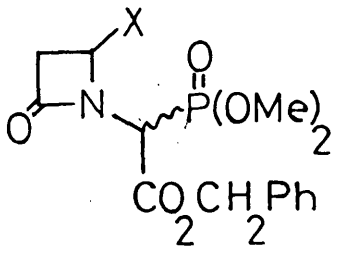
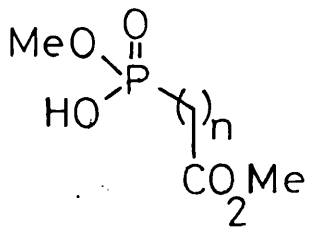
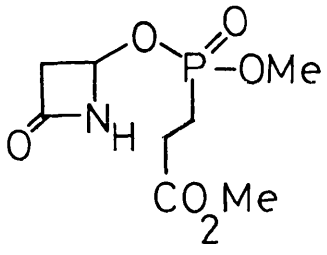


(III) X=OAc
(IV) X=SPh
(V) X=Cl



(VI) n=1
(VII) n=2



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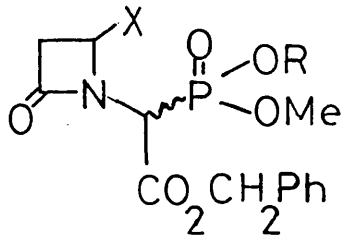
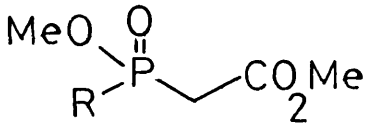
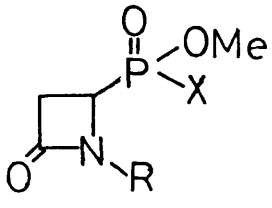


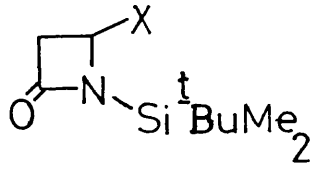
(IX) X=OAc, R=$SiMe_3$
(X) X=Cl, R=$SiMe_3$
(XI) X=OAc, R=H
(XII) X=Cl, R=H



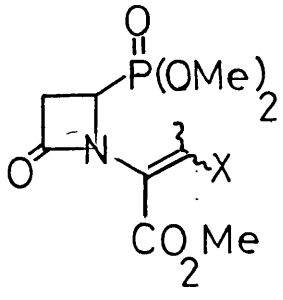
(XIII) R=Cl
(XIV) R=SPh or SCH_2Ph



(XIX) X=OMe, R=$SiMe_2$-^{t}Bu
(XX) X=OMe, R=$CH_2CO_2CH_2Ph$
(XXI) X=OH, R=$SiMe_2$-^{t}Bu or H
(XXII) X=OH, R=$CH_2CO_2CH_2Ph$



(XV) X=Cl
(XVI) X=SPh or SMe
(XVII) X=OAc
(XVIII) X=SCN



(XXIII) X=OH
(XXIV) X=OSO_2Me
(XXV) X=NHMe
(XXVI) NH^{t}Bu

CONTENTS

* * *

ABBREVIATIONS

The following abbreviations are used in the text:

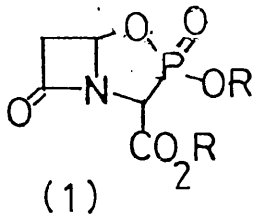
Ac	Acetyl (CH_3CO)
Acac	Acetoacetate
AIBN	Azo-bis-isobutyronitrile
atm	Atmosphere
Bzl	Benzyl ($C_6H_5CH_2$)
^{t}Bu	tert-Butyl ($-CMe_3$)
cat	Catalytic
C.I.	Chemical ionisation
CSA	Camphor sulphonic acid
DBU	1,5-Diazabicyclo[5.4.0]undec-5-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMAP	4-N,N-Dimethylaminopyridine
DME	Dimethoxyethane
DMS	N,N-Dimethylformamide
DMSO	Dimethylsulphoxide
E.I.	Electron impact
Et	Ethyl (CH_3CH_2)
HMPA	Hexamethylphosphoric triamide
HMPT	Hexamethylphosphorus triamide
HOAc	Acetic acid
HPLC	High performance liquid chromatography
Hz	Hertz

i.r.	Infra-red
J	Coupling constant
LDA, LDPA	Lithium N,N-Diisopropylamide
m-CPBA	meta-Chloroperbenzoic acid
Me	Methyl (CH_3)
m.Mol	milli moles
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
n.m.r.	Nuclear magnetic resonance
NUC	Nucleophile
OAc	Acetate ($CH_3CO_2^-$)
Ph	Phenyl (C_6H_5)
ppm	Parts per million
PheOMe	Phenylalanine methyl ester
p-TSA	para-Toluenesulphonic acid
Py	Pyridine
^{i}Pr	iso-Propyl [$CH(CH_3)_2$]
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMGA	Tetramethylguanadinium azide
TMS	Trimethylsilyl
Ts	Tosyl (ρ-toluenesulphonyl)
u.v.	Ultra violet

INTRODUCTION

INTRODUCTION

The objective of this research programme was to investigate synthetic routes leading to the novel heterocyclic β-lactams (1) - (4).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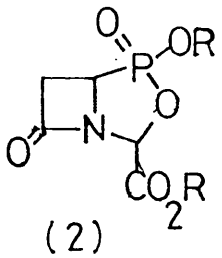
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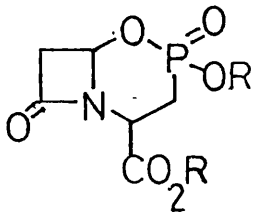
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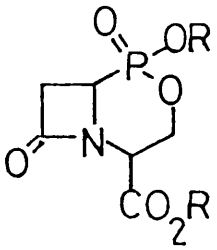

(3)

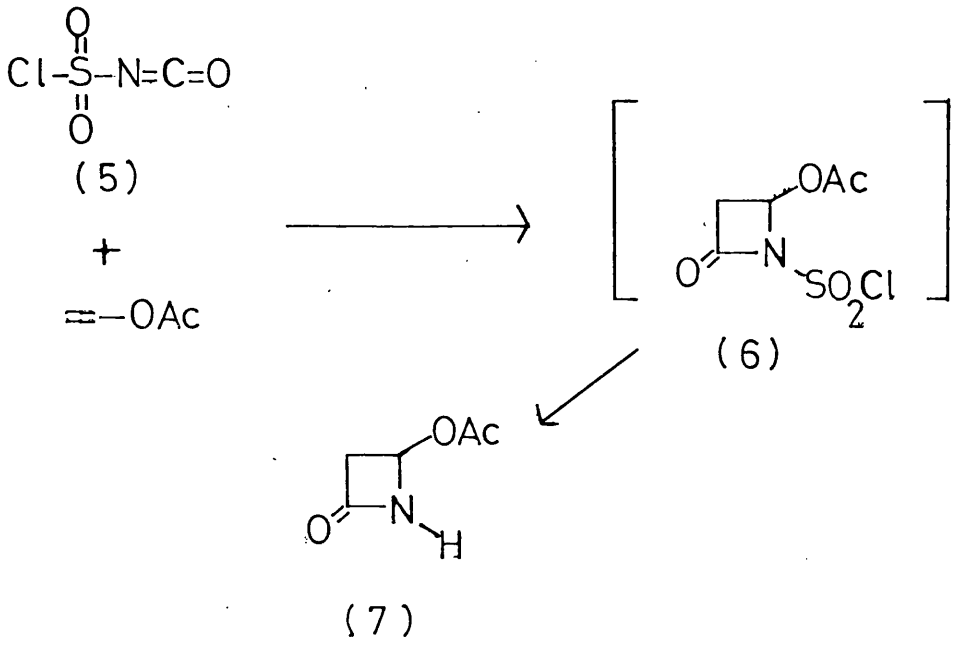
As one of the main precursors for such systems is 4-acetoxy-azetidin-2-one (7) it is pertinent to review the uses of substituted azetidin-2-ones as synthons.

1.0.0 PREPARATION OF SUBSTITUTED AZETIDIN-2-ONES

The chemical degradation of penicillins, leading to substituted azetidin-2-ones, is a well-documented process[1] and examples of this will be discussed. Some other methods involve (a) 2+2 cycloaddition, (b) ring closure of β-amino acids, and (c) cyclisation of propion-amides.

1.0.1 2+2 Cycloadditions

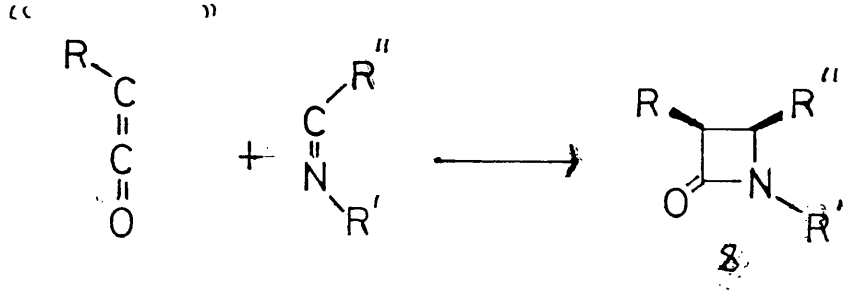
The use of chlorosulphonyl isocyanate (5)[2] in β-lactam synthesis,[3,4] by reaction with activated olefins, has been intensively studied. The most important reaction[5,6] is shown below:



(5) + ≡—OAc → [(6)] → (7)

N-Chlorosulphonylazetidin-2-one (6) was reduced *in situ* to afford 4-acetoxyazetidin-2-one (7) in moderate yield (40%). Displacement of the acyloxy group from (7) has been investigated[5] and a wide range of 4-substituted derivatives are known.

Ketene-imine cycloadditions have also been extensively studied.[7] The general scheme, leading to *cis*-substituted β-lactams (8), is as follows:



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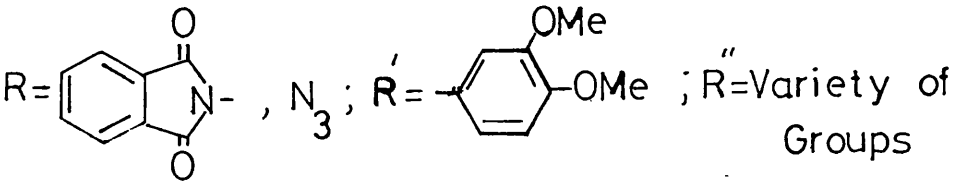
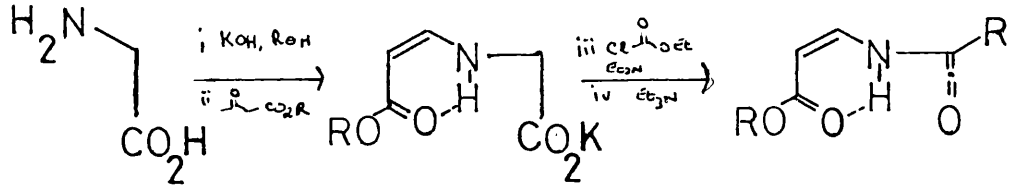


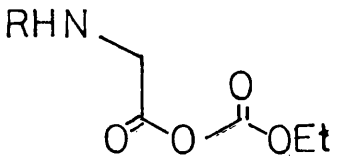
R = phthalimido, N_3; R′ = 2,3-dimethoxyphenyl; R″ = Variety of Groups

Substituted acyl halides, upon treatment with a mild base, e.g. triethylamine, serve as ketene precursors. A safer method (in the case of azidoacetyl chloride), is the use of Dane's salt[8] as follows:



Dane's Salt

Formation of ketene proceeds from the mixed anhydride (9) of the protected glycine (Dane's salt) followed by base-induced elimination.



(9)

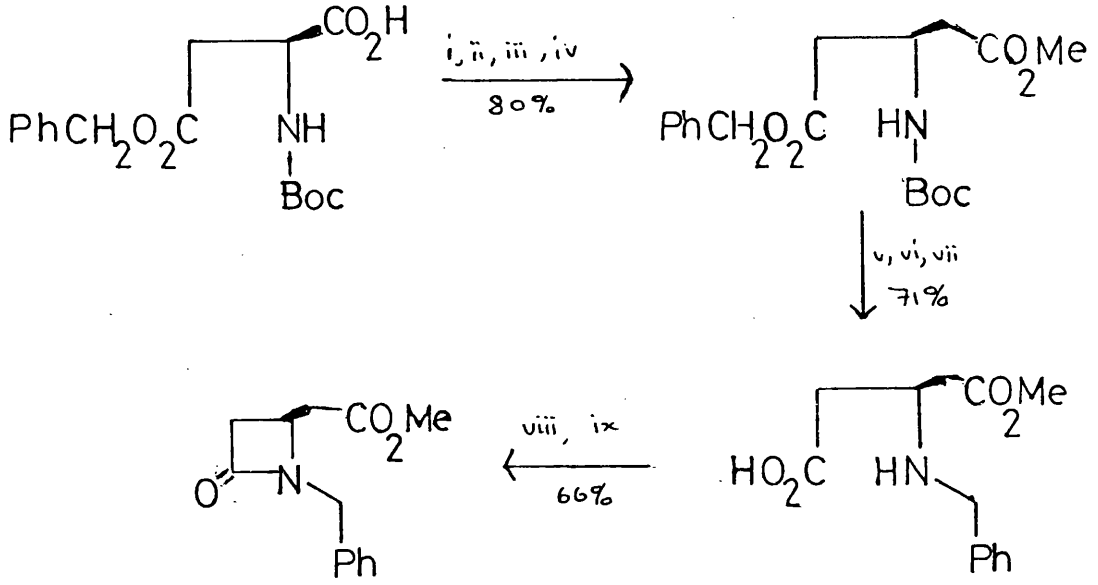
Trapping of the ketene with an imine followed by treatment of the β-lactam with p-toluenesulphonic acid afforded the 3-aminoazetidin-2-ones.

1.0.2 Ring Closure of β-Amino Acids

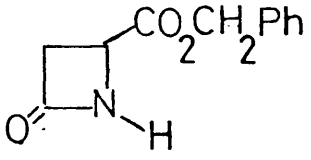
A typical example, developed by Koga,[9] en route to a carbapenam is outlined in Scheme 1.

Merck researchers[10] also used a similar approach, based on Schramm's method[11] for the cyclisation of amino acids to β-lactams, leading to the azetidin-2-one (10). This involved treatment of N-trimethylsilyl dibenzylaspartate with ethylmagnesium bromide to afford (10) in ca. 20% yield.

Scheme 1

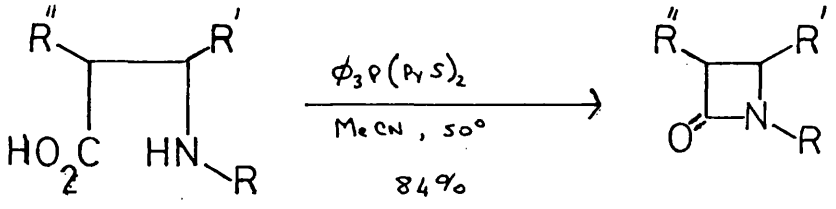


Reagents: (i) $ClCO_2Et$, Et_2O; (ii) CH_2N_2, Et_2O; (iii) Et_3N; (iv) $PhCO_2Ag$, MeOH; (v) HCl, EtOAc; (vi) PhCHO; (vii) H_2, Pd/C. MeOH; (viii) $SOCl_2$; (ix) Et_3N, C_6H_6.



(10)

Another method of aspartic acid ring closure utilised Mukaiyama's reagent[12] $[Ph_3P(PyS)_2]$.[13]

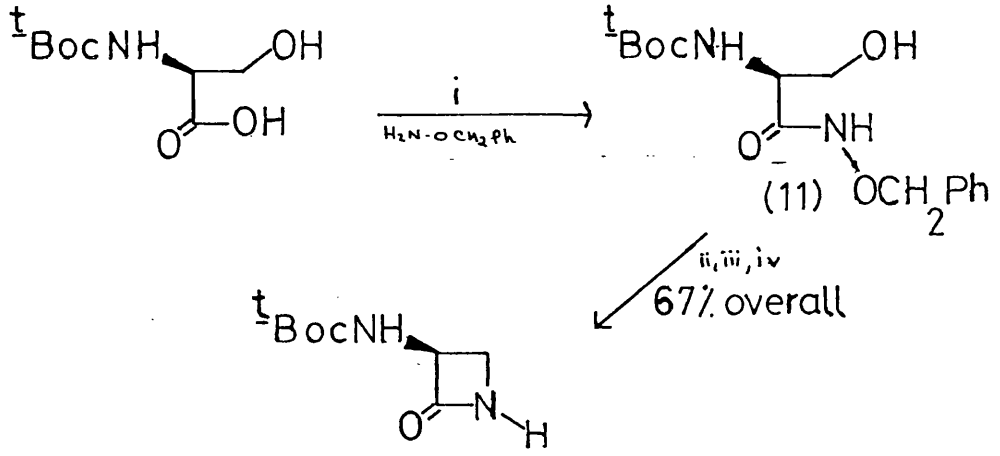


The method is very mild and high yielding and is readily applicable to a large number of β-amino acids.[12]

1.0.3 Cyclisation of Propionamides

One of the most viable routes to 3-aminonorcardicinic acid was recently developed by Miller *et al.*,[14] starting from serine (Scheme 2).

Scheme 2



Reagents: (i) carbodimide; (ii) Ph_3P, CCl_4, Et_3N; (iii) H_2, Pd/C; (iv) $TiCl_3$.

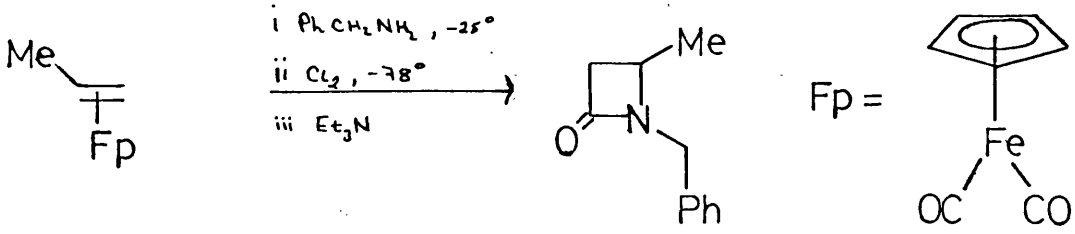
Cyclisation of the serine-O-benzylhydroxamate (11) proceeded in high yield via the alkyl halide. Other methods of cyclisation involve (a) diethylazidodicarboxylate/triphenylphosphine,[15] (b) phase transfer catalysis,[16] and (c) sodium hydride in DMF/DCM.[17]

Some more recent developments in azetidin-2-one synthesis should also be recounted here.

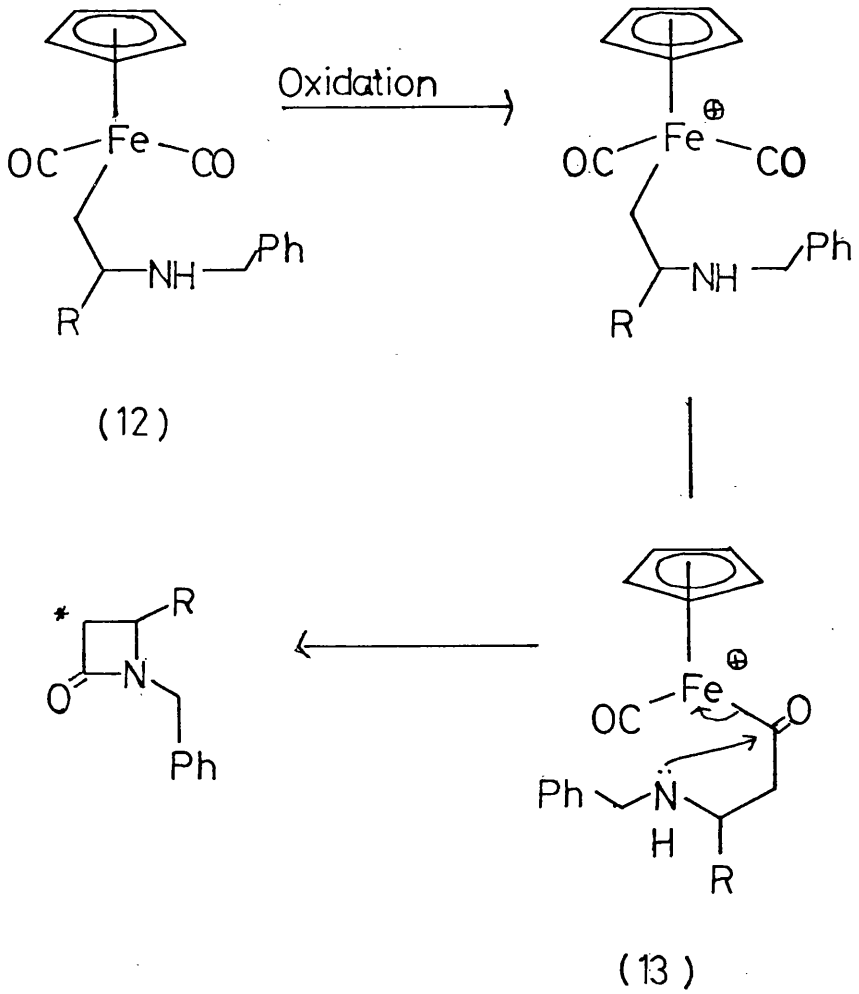
1.0.4 Organometallic Compounds in Azetidin-2-one Synthesis

Carbon monoxide insertion into transition metal-carbon bonds is a synthetic method well established in organometallic chemistry

and this approach has recently been applied to β-lactam synthesis by Wong and his co-workers[18], thus:

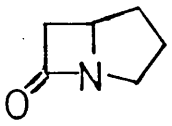


This reaction proceeds as follows:

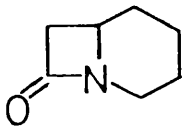


The oxidative ligand transfer (12) → (13) occurred with retention of configuration at the migrating carbon atom.

This process has been extended to produce the bicyclic β-lactams (14) and (15).

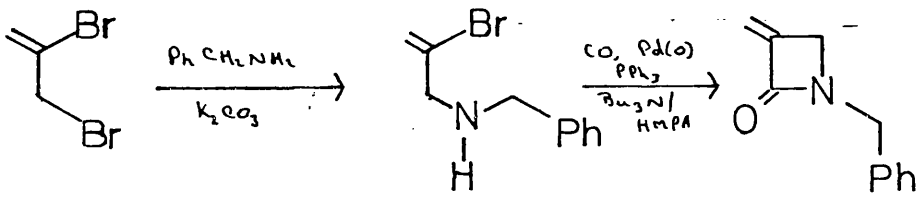


(14)

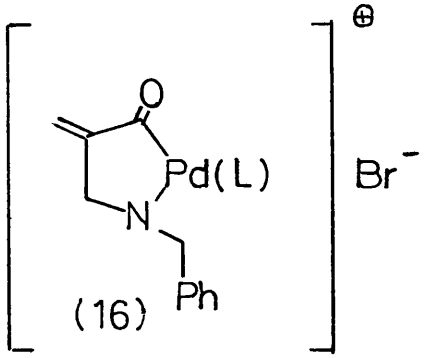


(15)

Ban *et al.*[19] have utilised the palladium catalysed insertion of carbon monoxide into 2-amino-3-bromopropenes shown below.



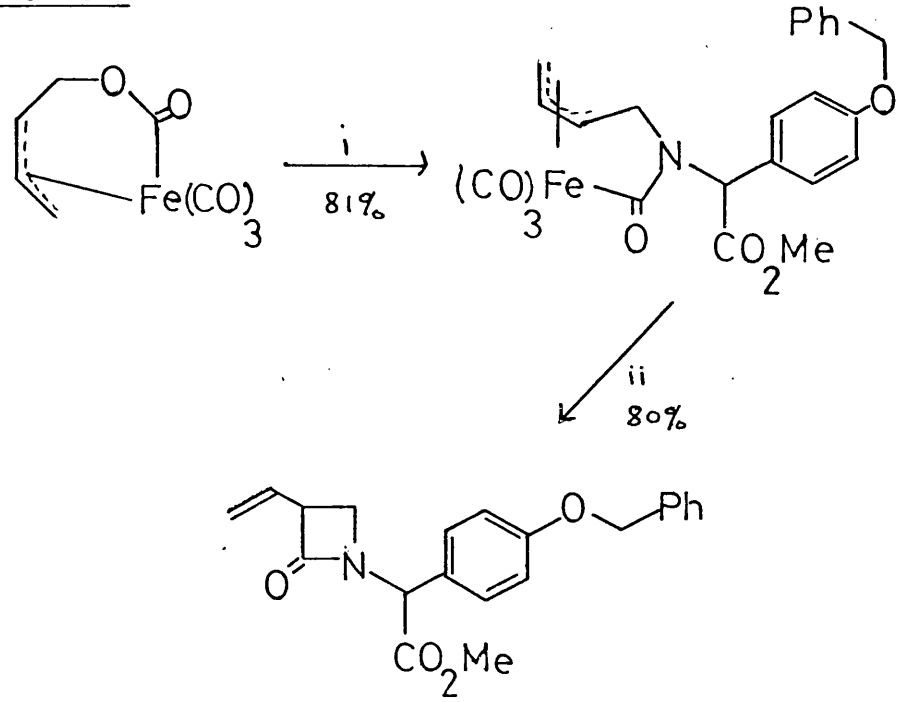
Use of palladium acetate (0.5 mol %) afforded the β-lactam in 53% yield. The key intermediate was assumed to be the acyl palladium species (16) which collapsed to give the β-lactam and regenerating the palladium (0) moiety.

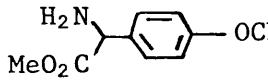


(16)

Ley[20] has employed a similar approach utilising tricarbonyl iron lactam complexes in a route to norcardicin analogues (Scheme 3).

Scheme 3

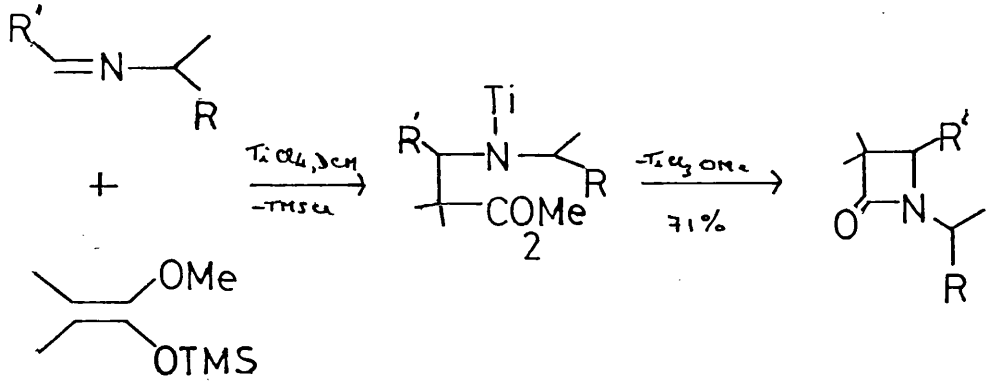


Reagents: (i) 

, $ZnCl_2$; (ii) Ce^{4+}

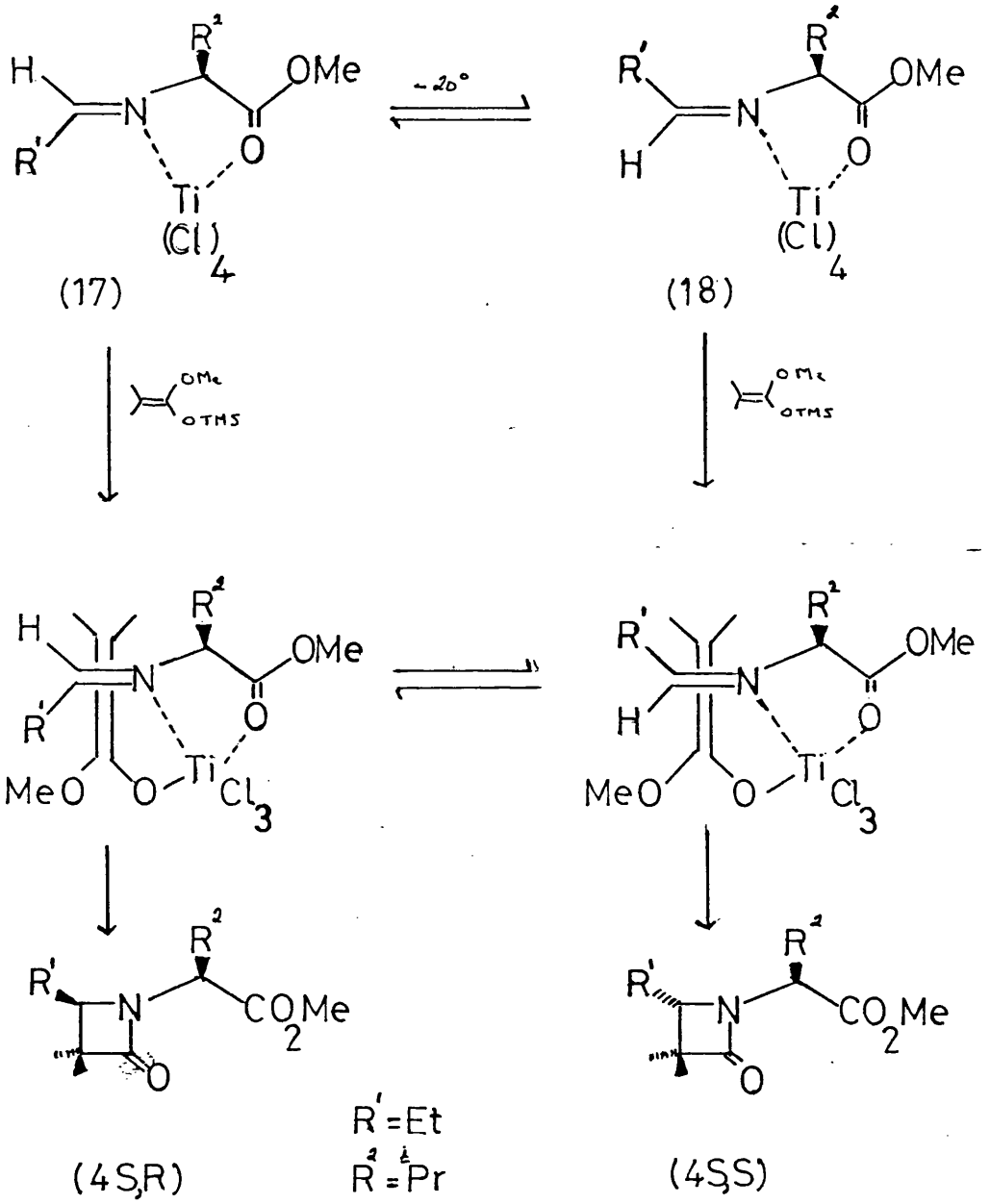
Both methods outlined above offer the potential for highly stereospecific syntheses of β-lactams.

An asymmetric synthesis of azetidin-2-one derivatives has been reported by Ojima *et al.*;[21]



The method was highly enantioselective with asymmetric induction between 44-98% for the (S) configuration at C4. This was explained by the formation of a rigid bicyclic transition state

where two possibilities exist (17) and (18).

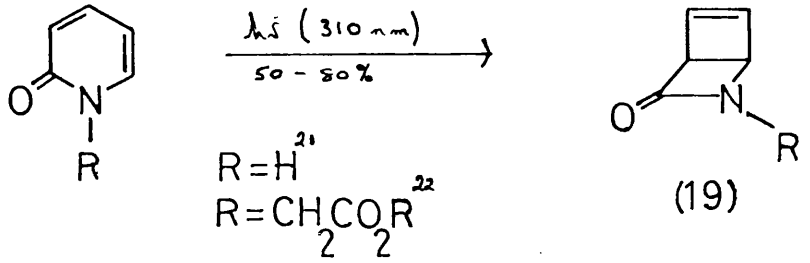


At -78°C (17) is the exclusive kinetic product. Above -20°C this was converted into an equilibrium mixture of (17) and (18). The latter being more thermodynamically stable than the former (1:4 at 30°C). The resulting stereoselectivity (SR) to (SS) is 3:97.

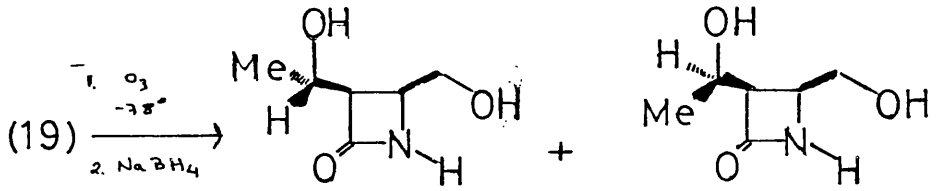
1.0.5 Photochemical Routes to Azetidin-2-ones

Lowe[22] and Brennan[23] have recently described an azetidin-2-one synthesis employing a photochemically-induced cyclisation of

pyridone derivatives, as follows:



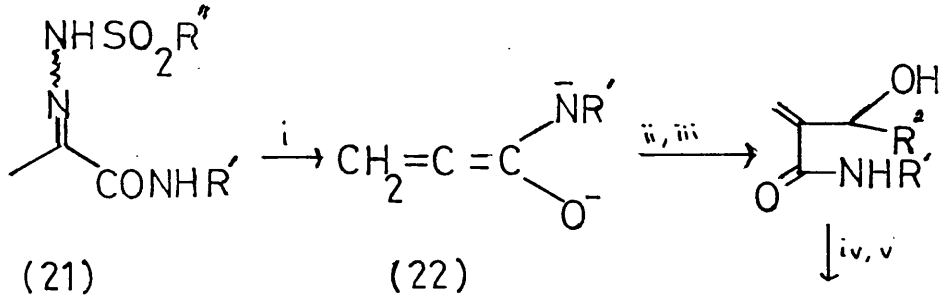
The bicyclo[2.2.0]hexane (19) has been elaborated (R=H) to a thienamycin precursor (19 → 20 below).



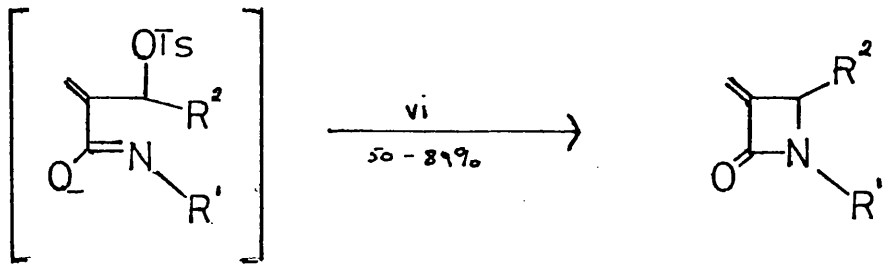
1.0.6 Other Routes to Azetidin-2-ones

Barrett *et al.*[24] developed a novel route to 3-methylidene azetidin-2-ones from N-benzenesulphonylhydrazones of type (21) (Scheme 4), which allowed access to more highly functionalised systems.

Scheme 4

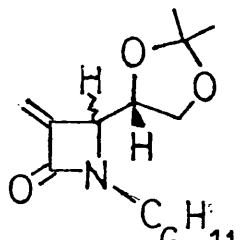


Scheme 4 continued



Reagents: (i) ^{n}BuLi (3.2-3.4 equiv.), -78°C : 25°C in DME; (ii) R^2CHO, -78°C : 25°C; (iii) H_2O; (iv) ^{n}BuLi (2 equiv.), THF, -78°C; (v) TsCl, -78°C; (vi) 25°C, 10 min.

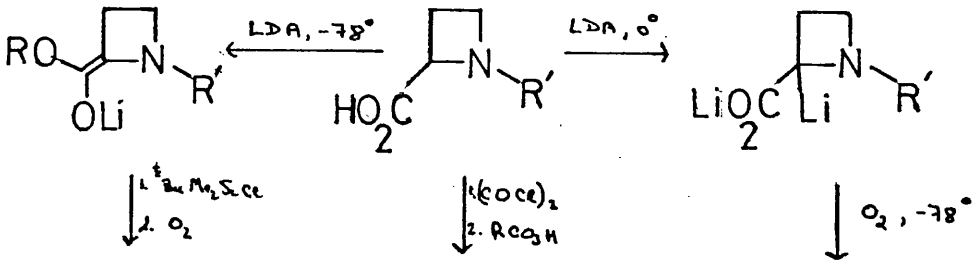
Structural variants of (22) offered potential routes to more highly derivatised systems, for example (23);



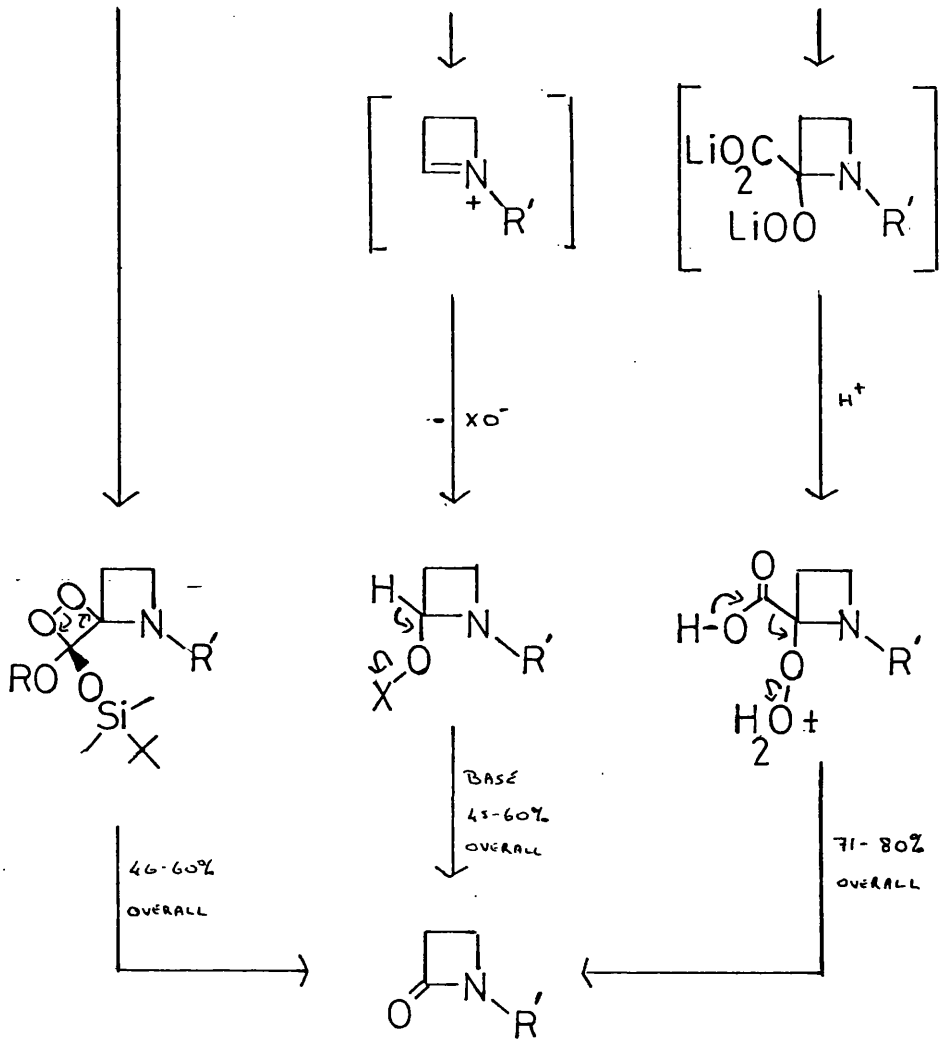
(23)

Finally, Wasserman[25] has developed several novel approaches to azetidin-2-one syntheses from azetidine-2-carboxylic acids (Scheme 5). This stratagem has been developed for the synthesis of 3-aminonorcardicinic acid.

Scheme 5



Scheme 5 continued



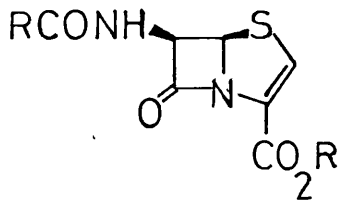
R^1 = Alkyl, x = $PhCO_2^-$

2.0.0 USE OF AZETIDIN-2-ONES AS PRECURSORS IN THE SYNTHESIS OF PENCILLIN ANALOGUES

In this section several selected syntheses of penicillin analogues are presented. These demonstrate the usefulness of azetidin-2-one derivatives for this purpose.

2.0.1 Synthesis of Penems

Recently Woodward *et al.*[26] reported the synthesis of a novel type of β-lactam, the penem, whose basic ring system is shown below,

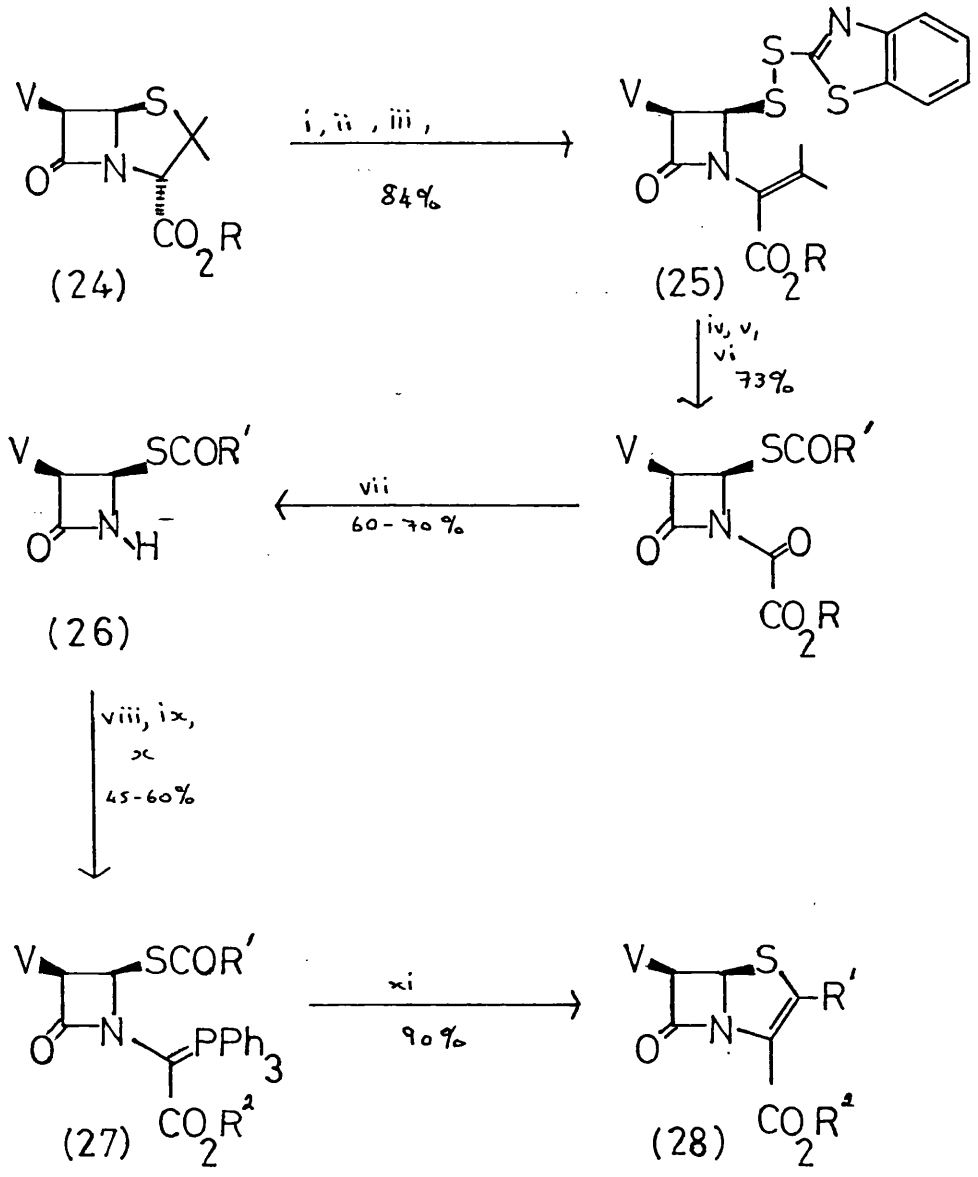


incorporating, in one ring system, the structural features most commonly regarded as necessary for biological activity in penicillins and cephalosporins. The synthesis employed penicillin V as a chiral precursor. Thus, conversion of penicillin V (24) to the sulphoxide (Scheme 6) followed by treatment with mercaptobenzthiazole/triethylamine[27] gave the benzthiazolyl disulphide (25) in high yield. Reductive acylation of (25) with triphenyl phosphine/acetic anhydride and subsequent removal of the seco-penicillin side chain afforded the key azetidin-2-one intermediate (26) in 60-70% overall yield. Conversion of (26) to the azetidin-2-one phosphorane (27) was accomplished by reaction with a glyoxylate ester then thionyl chloride followed by triphenyl phosphine and Hünig's base. Intramolecular Wittig olefination proceeded on warming (27), giving the penem (28) in quantitative yield when R^1=Me, R^2=^{t}Bu. The course of the Wittig reaction was found to be dependent on the nature of R^1 and R^2 [e.g. R^1=^{i}Pr, R^2=^{t}Bu gave only 10% conversion to (28)].

The synthesis shown below demonstrated the viability of synthetic strategies proceeding via azetidin-2-one intermediates of type (26).

A related route to substituted penems has been developed by McCombie *et al.*,[28] part of which is shown in Scheme 7.

Scheme 6 Woodward's Penem Synthesis

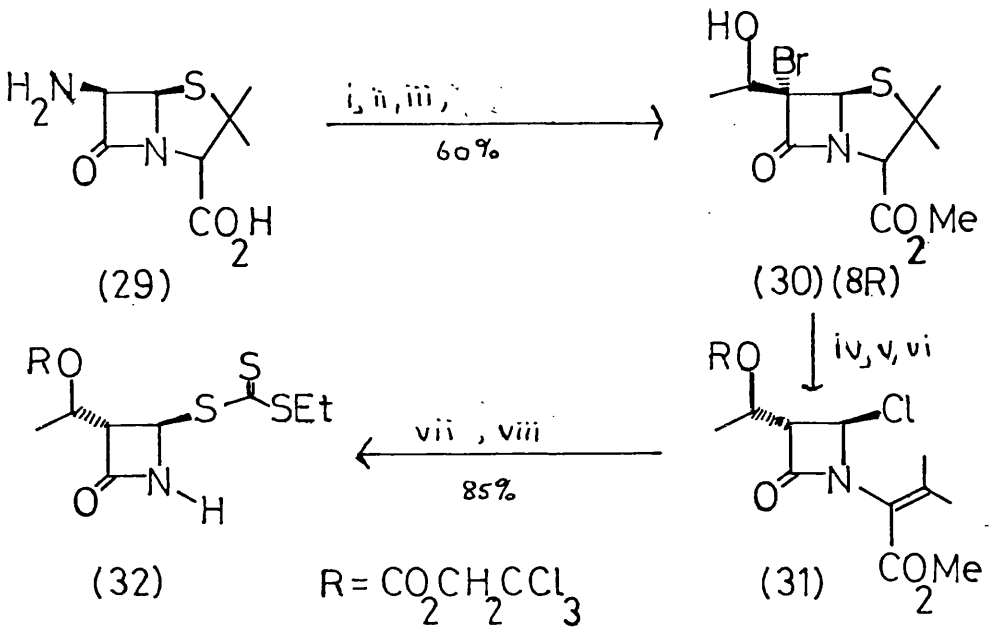


Reagents: (i) $NaIO_4$; (ii) HS-(benzothiazole) ; (iii) Et_3N, DCM; (iv) Ph_3P, Ac_2O, HOAc; (v) Py; (vi) O_3, MeOH, -20°C; (vii) MeOH, H_2O; (viii) $(HO)_2CO_2R^1$, sieve; (ix) $SOCl_2$, Hünig's base, dioxane; (x) Ph_3P, Hünig's base, toluene, Δ; (xi) toluene, Δ.

Diazotisation of 6-aminopenicillanic acid (29) followed by bromination, then introduction of the hydroxyethyl side chain and esterification afforded the (8R) isomer (30) after crystallisation. Further elaboration of (30) proceeded via hydrogenation, hydroxyl group

protection and chlorinolysis resulted in the seco-penicillin (31) (100%).

Scheme 7

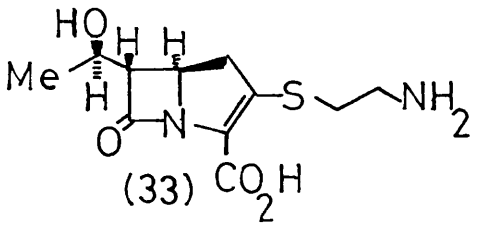


Reagents: (i) $NaNO_2$, H_2SO_4, Br_2, 0°C; (ii) MeI, K_2CO_3, DMF; (iii) MeMgBr, THF, -78°C, CH_3CHO then H^+; (iv) H_2, $Pd/CaCO_3$; (v) CCl_3CH_2OCOCl, Py, DCM; (vi) Cl_2 (2.5 equiv.), CCl_4, -20°C; (vii) O_3, DCM, -70°C; (viii) EtSK, CS_2, EtOH.

Reaction of azetidin-2-one (31) with ozone followed by potassium ethyltrithiocarbonate gave the key β-lactam trithiocarbonate (32) in 85% yield. Further elaboration of (32) was accomplished via the Woodward methodology (see Scheme 6).

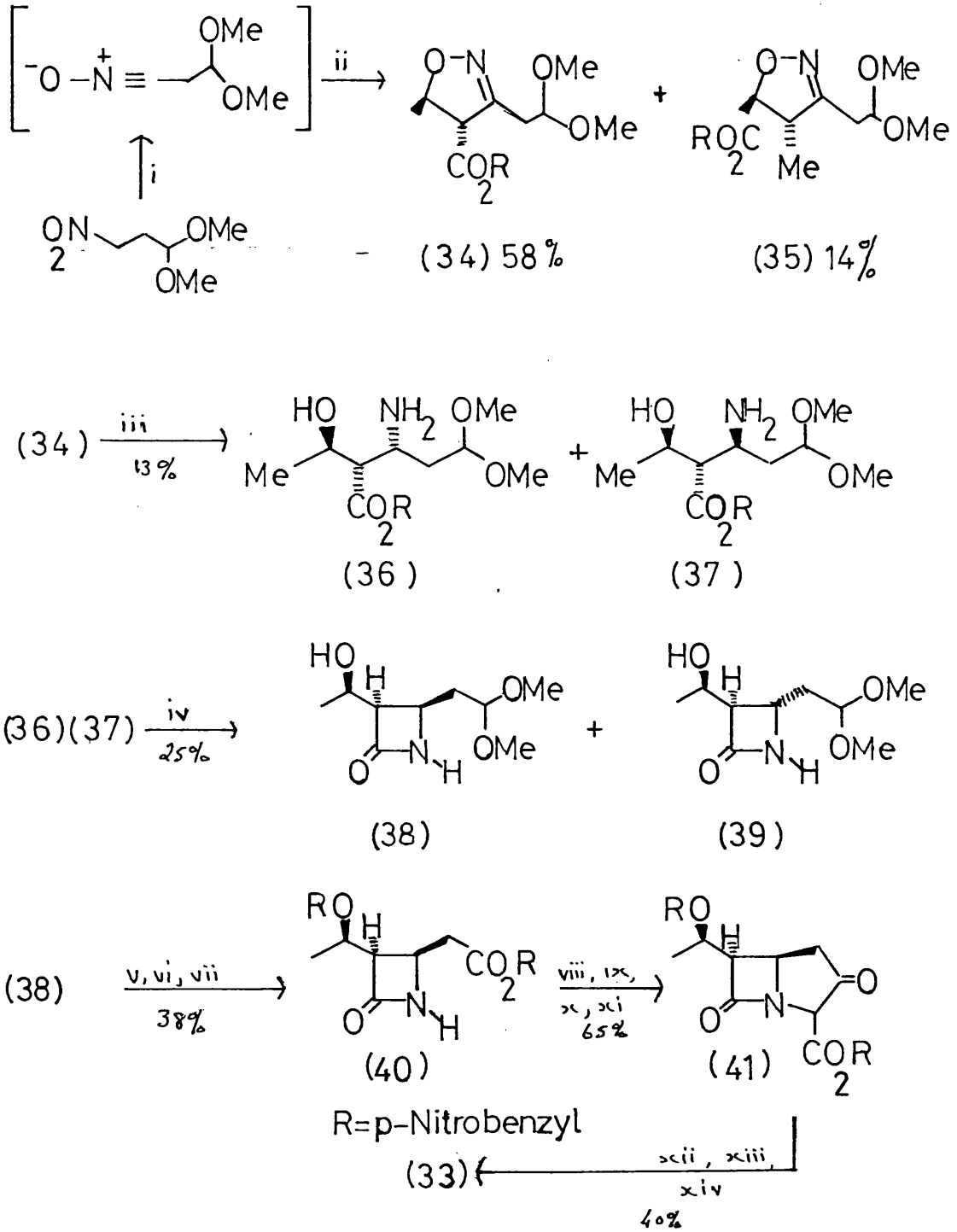
2.0.2 Synthesis of Thienamycins

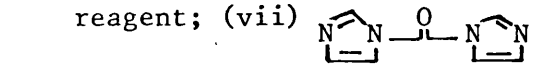
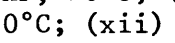
Thienamycin (33) is a highly potent, broad spectrum antibiotic and apart from having a carbapenem bicyclic ring the molecule contains a C-6 hydroxyethyl substituent.



Several groups have devised synthetic routes to the basic ring system of (33). One of the more notable approaches was by Kametani *et al.*[29] This route proceeded via the isoxazoline derivative (34), obtained by a 1,3-dipolar cycloaddition of a nitrile oxide and ^{t}butyl crotonate (Scheme 8).

Scheme 8 Kametani's Thienamycin Synthesis

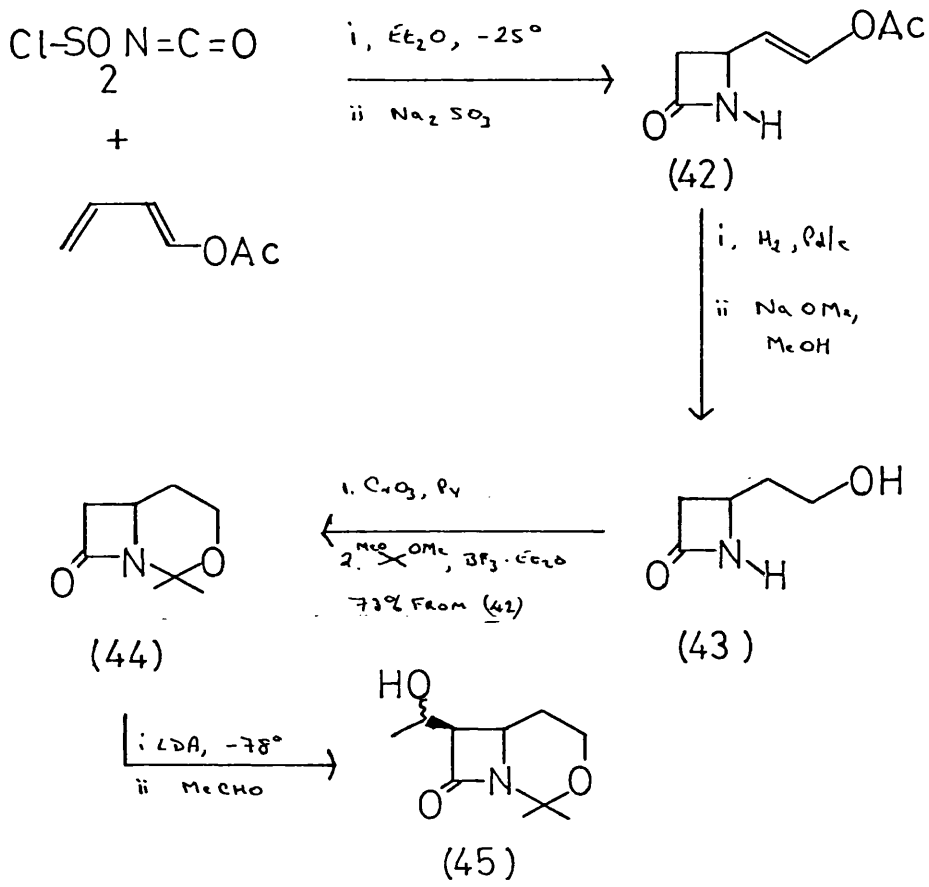


Reagents: (i) PhNCHO, Et_3N; (ii) *trans* MeCH=CHCO$_2$^{t}Bu, C_6H_6; (iii) $NaBH_4$, MeOH, 20°C, $NiCl_2$;(iv) NaOH, MeOH then DCC, dioxane 60°C; (v) p-NBOCOCl, Py; (vi) HOAc, H_2O, 55°C; (vii) Jones' reagent; (vii)  , THF; (ix) $MgO_2CCH_2CO_2$p-NB, THF, 20°C; (x) TsN_3, Et_3N, MeCN, 20°C; (xi) $Rh_2(OAc)_4$, C_6H_6, 80°C; (xii) ( )$_2$NH, DMAP,  ; (xiii) ( )$_2$NH, $HSCH_2CH_2NHAc$; (xiv) H_2, Adam's catalyst, THF, 32 mMol $NaHCO_3$, H_2O, 20°C.

Reduction of the isoxazoline (34) under a variety of conditions, gave the amino esters (36) and (37) in 25% yield. Saponification and ring closure of this mixture with carbodiimide afforded the azetidin-2-ones (38) and (39) in a ratio of 1:2.5. This ratio was obtained even if pure (36) was used, suggesting that epimerisation occurred under the cyclisation conditions. Use of O,N-trimethylsilyl protected (36) followed by treatment with ethylmagnesium bromide[11] did not improve the isomer ratio. After separation of azetidin-2-one (38) the synthesis was completed by protection of the hydroxyethyl group and conversion of the acetal to the bicyclic keto acid (41) by treatment of the acid (40) with the magnesium salt of a mono-malonic ester. Diazo-exchange with subsequent carbene insertion followed by displacement of the enol phosphate by N-acetyl cysteamine, and deprotection, afford thienamycin (33).

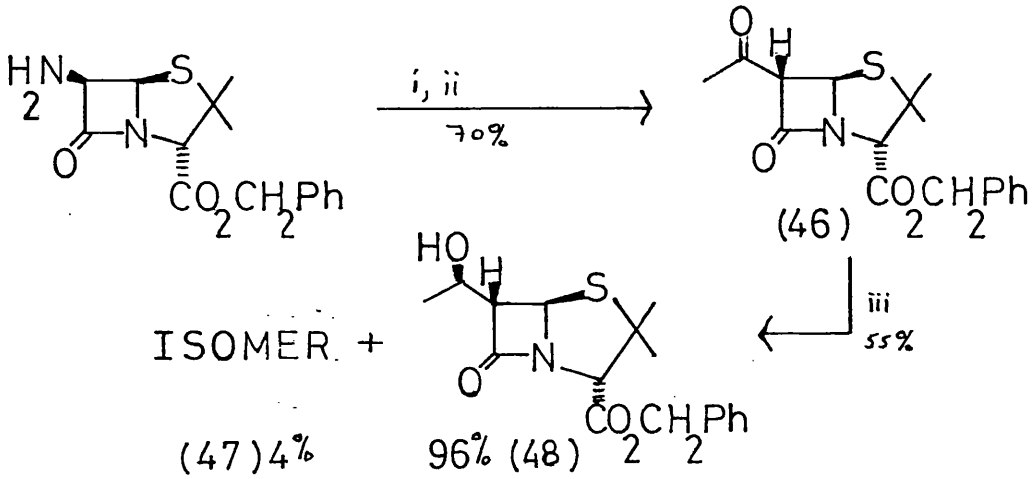
Merck[38] have also achieved a total synthesis of thienamycin from 4-acetoxyvinylazetidin-2-one (42) (obtained from a [2+2] cyclo-addition of CSI and 1-acetoxy-1,3-butadiene). Part of this synthesis is outline below.

Reduction of the vinyl acetate followed by hydrolysis gave the alcohol (43). Conversion to the aldehyde and protection afforded the acetonide (44). Quenching of the C-7 enolate anion of (44) with acetaldehyde resulted in the introduction of the required hydroxyethyl side chain. Further elaboration of this system yielded the thienamycin ring system (33).[30]

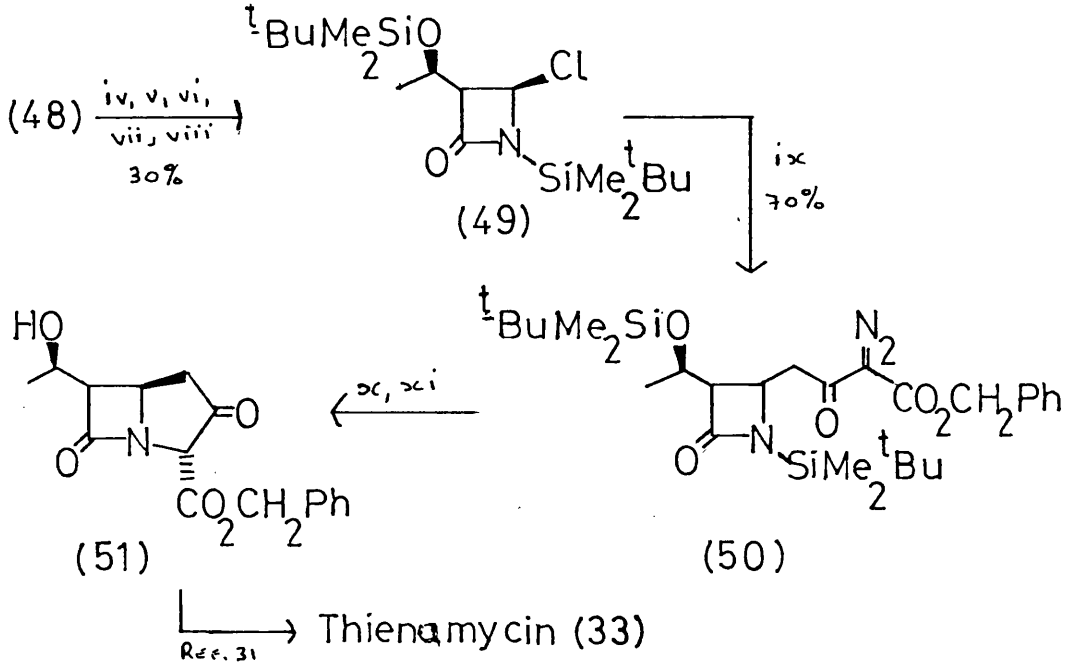


Merck have also developed a stereospecific synthesis of thienamycin starting from 6-aminopenicillanic acid.[31] This synthesis (Scheme 9) is noteworthy for a stereospecific amine-borane reduction of the ketone (46) and the use of a novel carbene equivalent.

Scheme 9 Merck Thienamycin Synthesis



Scheme 9 continued



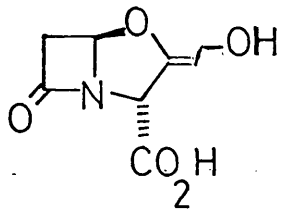
Reagents: (i) $NaNO_2$, HCl, 0°C; (ii) CH_3CHO, $ZnCl_2$, 10°C; (iii) $MgOCOCF_3$ (5 equiv.) then BH_3-N(Et)$_3$ (2 equiv.), 0°C; (iv) ^{t}BuMe$_2$SiCl; (v) $BrCH_2CO_2Me$, KO^{t}Bu, THF, 20°C; (vi) $KMnO_4$, Py, H_2O; (vii) ^{t}BuMe$_2$SiCl, Et_3N, DMF, 20°C; (viii) Cl_2, CCl_4; (ix) TMSO, CO_2CH_2Ph, N_2 $AgBF_4$, MeCN; (x) MeOH, H_2O, HCl; (xi) $Rh_2(OAc)_4$, C_6H_6, O.

Thus, treatment of 6-diazopenicillanate with acetaldehyde in the presence of a Lewis acid led to the unstable ketone (46) which was stereospecifically reduced with an amine-borane complex to (47) and (48) [4:96 respectively]. Degradation of (48) by standard methods[32,33,34] led to the key intermediate 4-chloroazetidin-2-one (49). The complete side chain, necessary for formation of the thienamycin ring system, was inserted in one step by Lewis acid catalysed desilylation of the silyl enol ether (from reagent (ix), Scheme 9) resulting in formation of the diazo ketone (50) in high yield (70%). Desilylation and carbene insertion afforded a bicyclic precursor (51) previously converted to thienamycin,[31] thus 6-amino-penicillanic acid has been shown to be a valuable precursor to azetidin-2-one intermediates for the synthesis of β-lactam analogues.

Finally in this section some approaches to clavulanic acid will be discussed.

2.0.3 Clavulanic Acid Synthesis

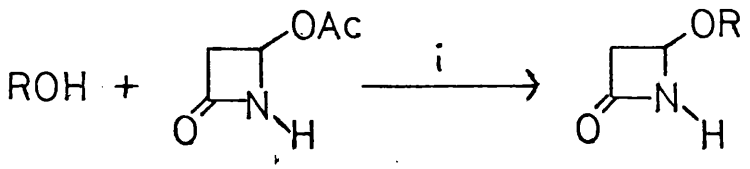
Clavulanic acid (52) is a potent β-lactamase inhibitor and therefore has great value as a synergist in the treatment of β-lactam resistant bacterial infections.



(52)

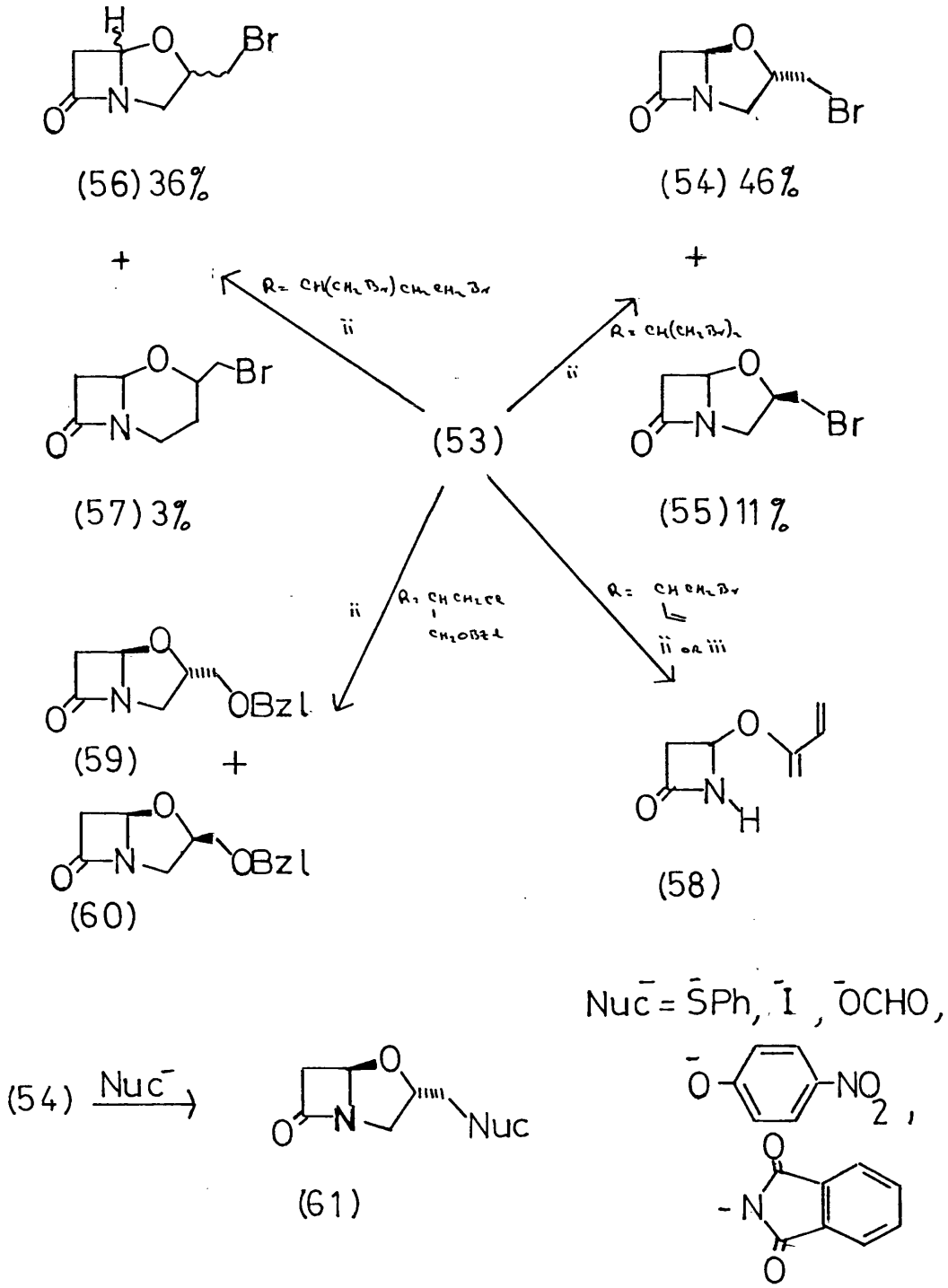
Notable syntheses in this area have been achieved from Beechams[35] via 4-methylthioazetidin-2-one. More recently the same group has described a general synthesis of the 1-aza-4-oxabicyclo-[3.2.0]heptan-7-one ring system[36,37,38] leading to a number of clavam derivatives, some of which were found to be β-lactamase inhibitors (Scheme 10).

Scheme 10 Synthesis of Clavam Derivatives



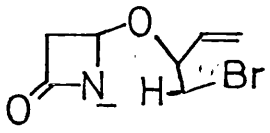
(3) (53)

Scheme 10 continued



Reagents: (i) $Zn(OAc)_2$, $2H_2O$, C_6H_6, 80°C; (ii) K_3CO_4, DMF; (iii) DBU, THF.

Lewis acid catalysed displacement of the 4-acetoxy group from (3) with alcohols proceeded in good yield resulting in the 4-alkyloxyazetidin-2-ones (53). Treatment with base afforded the bicyclic systems (Scheme 10). The 4-alkoxyazetidin-2-one diene (58) was produced by transfer of the acidic allylic proton in the intermediate (62).

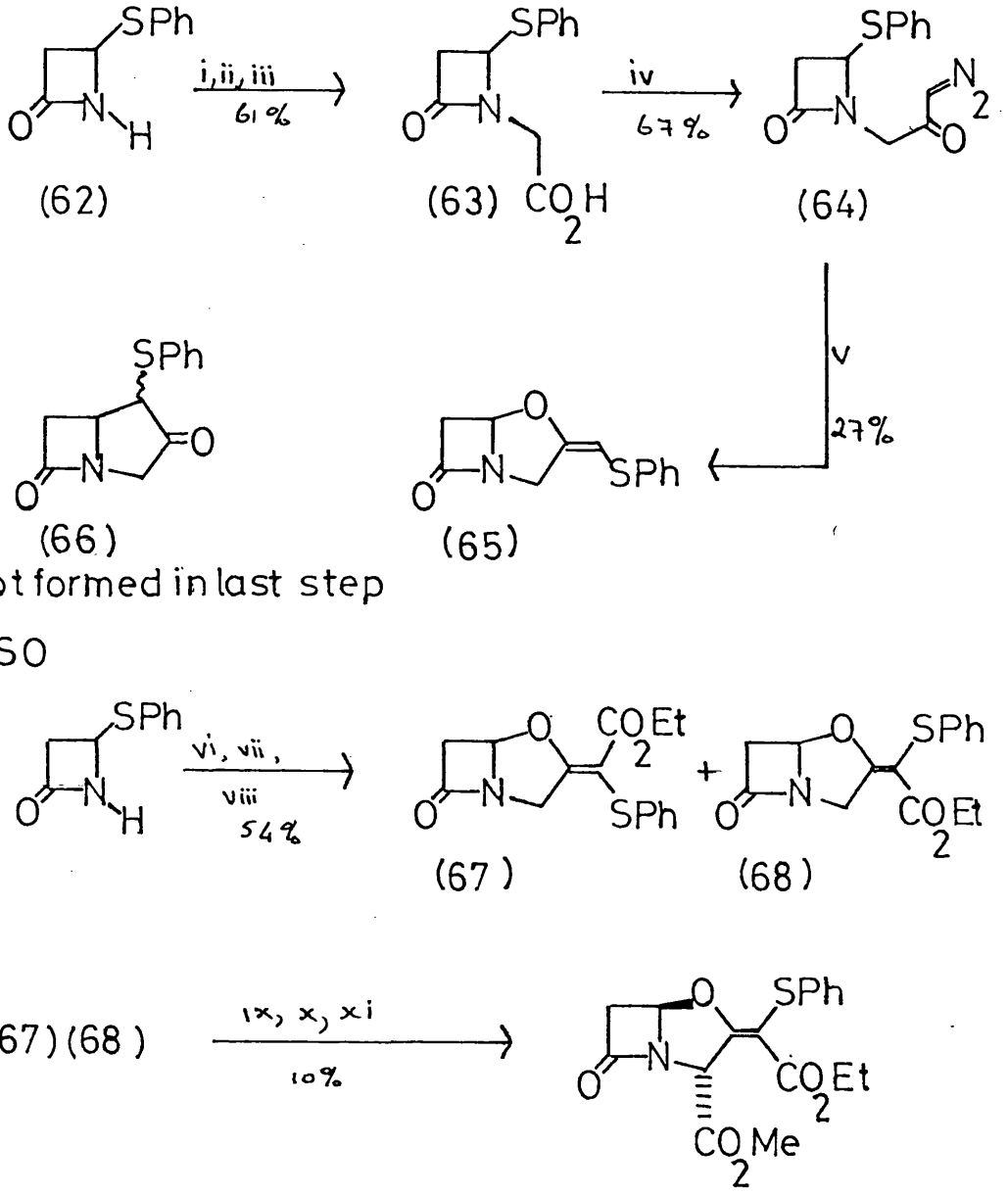


(62)

Azetidin-2-one (53) (R=CH(CH_2Br)CH_2CH_2Br) can in theory form the five- or six-membered ring. In practice the five-membered ring was preferentially formed and is an example of a 5-exo-tet process which, according to the Baldwin guidelines,[39] is favoured over the 6-endo-tet route. Displacement of bromine from (54) with nucleophiles was also a facile process (Scheme 10).

The Sankyo group synthesised a clavulanic acid derivative[40] by copper catalysed decomposition of azetidin-2-one diazoketones (Scheme 11). This was originally intended as a synthetic route to carbapenem systems via a Stevens arrangement of a carbene derived sulphur ylid but oxapenams resulted.

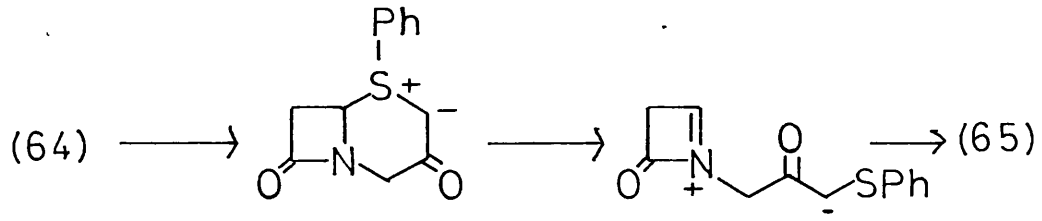
Scheme 11 Sankyo Clavam Synthesis



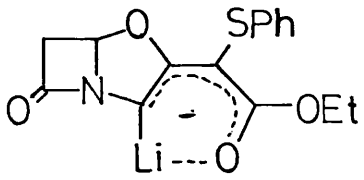
ALSO

Reagents: (i) NaH; (ii) $BrCH_2CO_2Me$, THF/DMF; (iii) LiI, Py; (iv) $ClCO_2{}^{i}Bu$, Et_3N then CH_2N_2, Et_2O, -20°C; (v) Cu (powder), C_6H_6, 80°C; (vi) $^{n}BuLi$, THF then $BrCH_2CH(OMe)CHCO_2Et$, H^+; (vii) TsN_3, Et_3N; (viii) Cu (II) $(Acac)_2$; (ix) $LiN(TMS)_2$, THF, -110°C; (x) CO_2; (xi) CH_2N_2, Et_2O.

This was explained by initial insertion of the carbene into the carbon sulphur bond followed by cleavage and subsequent ring closure via the carbonyl oxygen as shown below:



As noted in Scheme 11, reaction of the isomer mixture (67) and (68) with lithium hexamethyldisilazide followed by carbon dioxide resulted in the formation of a single product (69). This indicated that the reaction proceeded via the same intermediate anion (70) and that the vinyl sulphide existed in the Z-configuration. None of the above compounds showed any antibacterial or β-lactamase activity.



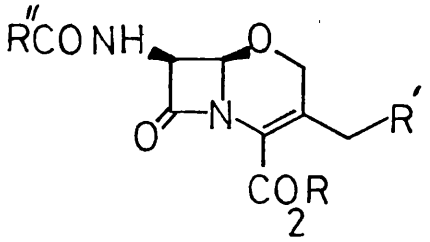
(70)

2.0.4 Summary

The above examples have been selected from a vast array of β-lactam syntheses appearing in the recent chemical literature. They have been chosen to demonstrate important strategies.

3.0.0 AZETIDIN-2-ONES IN THE SYNTHESIS OF HETERO-CEPHALOSPORINS

As for penicillins, hetero-analogues of the cephalosporin group of β-lactams have been synthesised.[1] One of the most important of these is the oxacephem system with the general structure (71).



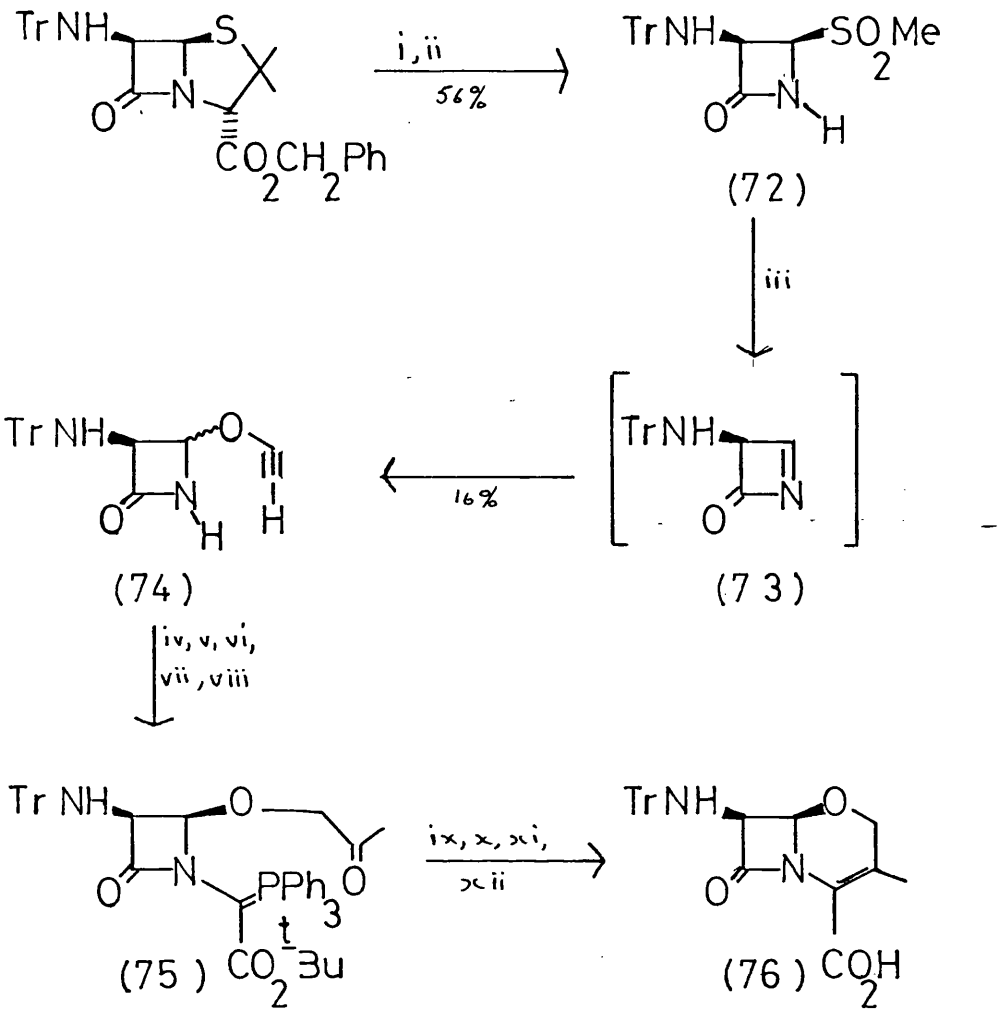
(71)

3.0.1 Oxacephem Synthesis

A semi-synthetic approach to compounds (71) has been developed by the Beecham group[41] starting from 3-tritylamino-4-methylsulphonyl-azetidin-2-one (72) itself available from 6-aminopenicillanic acid. This route is outlined in Scheme 12.

Displacement of the methane sulphonyl group with propargyl alcohol in the presence of a Lewis acid led to the masked hydroxy-acetone (74). Preparation of the phosphorane by standard procedures[26] followed by Hg(II) catalysed addition of piperidine with resultant enamine hydrolysis afforded the Wittig precursor (75). Thermolysis initiated intramolecular ring closure gave the oxacephem carboxylic acid (76) after deprotection.

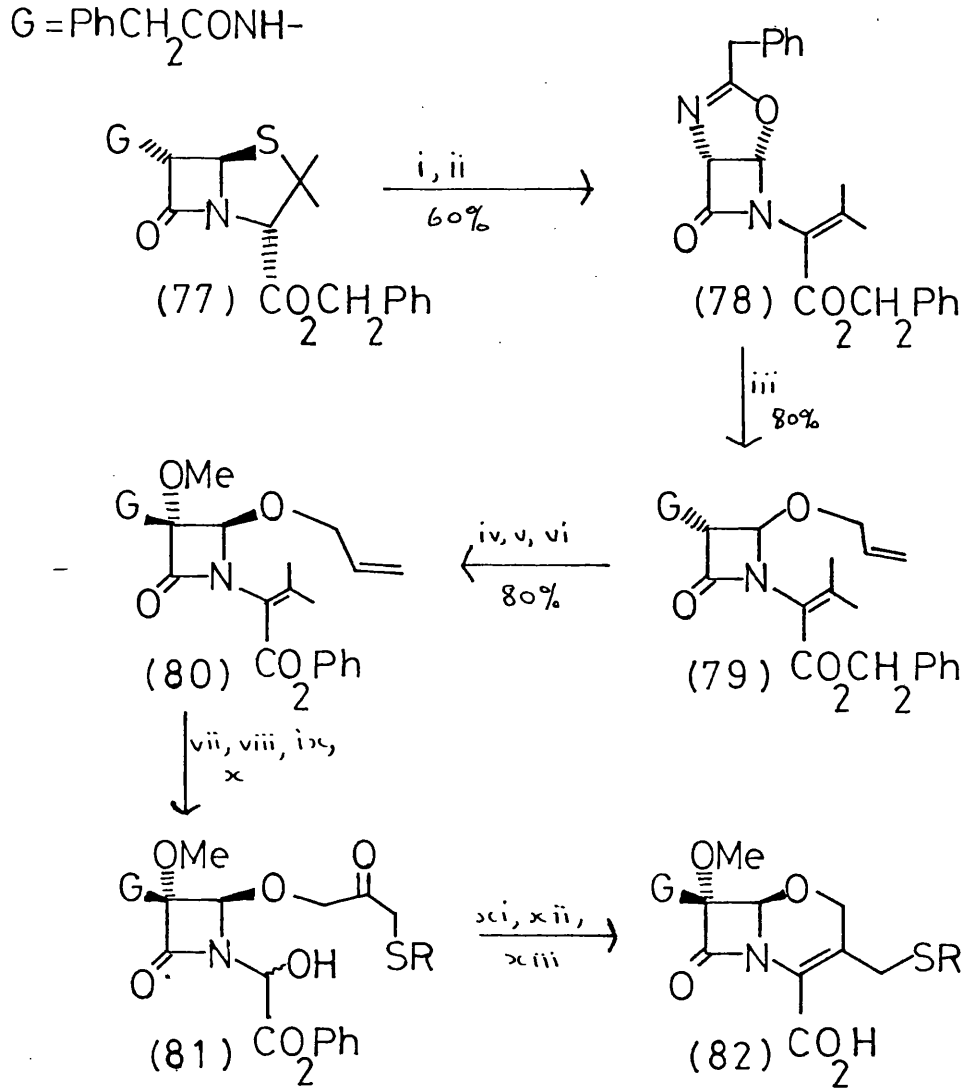
Scheme 12 Beecham's Oxacephem Synthesis



Reagents: (i) MeI, NaH, THF, 20°C; (ii) $KMnO_4$, HOAc, 0°C, DMF; (iii) $HOCH_2C{\equiv}CH$, $Zn(OAc)_2$, toluene, Δ; (iv) separate; (v) $^tBuO_2CCHO$; (vi) $SOCl_2$, Py; (vii) PPh_3; (viii) piperidine, $HgCl_2$, H_2O, 20°C; (ix) dioxane, Δ; (x) PTSA; (xi) ROCl, base; (xii) TFA.

A different approach to the key azetidin-2-one intermediate (81) was employed by Shionogi[42] from epi-penicillin G (77) (Scheme 13) in a stereocontrolled synthesis of 7α-methoxy-1-oxacephems.

Scheme 13 Shionogi Oxacephem Synthesis



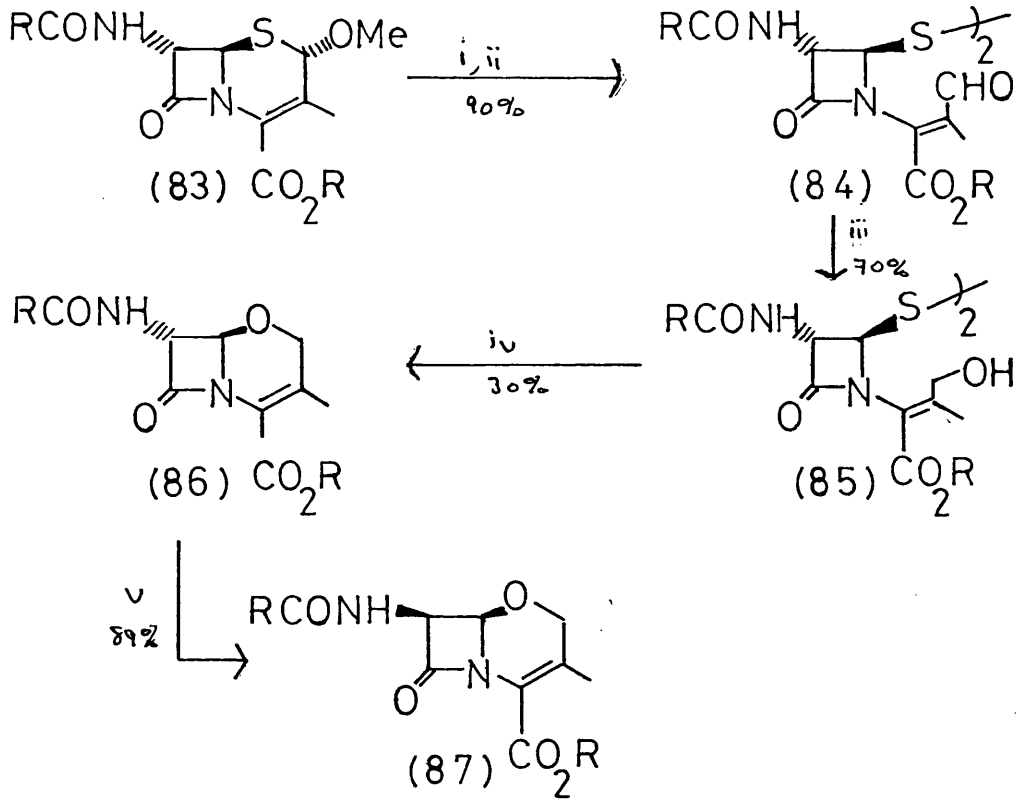
Reagents: (i) Cl_2, DCM, -20°C; (ii) NaOH, $^{n}Bu_4^{+}Cl^{-}$, H_2O; (iii) $HOCH_2CHCH_2$, CF_3SO_3H (cat.); (iv) ^{t}BuOCl (1.5 equiv.); (v) LiOMe, MeOH; (vi) Zn, HOAc; (vii), NBS, DMSO, H_2O then KO^{t}Bu; (viii) 1-methyl-1H-tetrazole-5-thiol, ^{n}BuLi (cat.), 20°C; (ix) CrO_3, Py; (x) O_3, -15°C then Zn, HOAc; (xi) $SOCl_2$, Py, DCM, -18°C; (xii) PPh_3, CH_2Cl_2, 40°C; (xiii) dioxane reflux.

Reaction of epi-oxazoline (78) with allyl alcohol in the presence of a catalytic amount of triflic acid resulted in the stereospecific introduction of the allyloxy side chain producing the azetidin-2-one (79). Stereospecific introduction of the 3-methoxy group was achieved by N-chlorination with ^{t}butylhypochlorite

followed by elimination and trapping of the resultant imine with lithium methoxide giving (80) in 80% yield. Further elaboration of the allyl side chain, via the epoxide, afforded the methoxylated Beecham intermediate (81) which was cyclised to (82) by standard methods.

Eli. Lilly have developed a synthesis of the 3-methyl analogue of (82) from 2α-methoxyceph-3-em[43] (83). As detailed in Scheme 14, β-lactam (83) was chosen for two reasons, (a) the methoxy group at C-2 facilitates the opening of the dihydrothiazine ring,[44] and (b) the 7α-amido group directs subsequent oxygen centered cyclisation from the azetidin-2-one β-face.

Scheme 14 Eli Lilly Oxacephem Synthesis

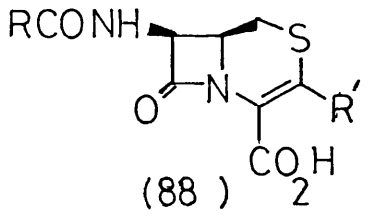


Reagents: (i) NCS, MeOH, DCM, 0°C; (ii) $HgCl_2$, $CdCO_3$, 20°C; (iii) $NaBH_3CN$, THF, H_2O, pH 3.2; (iv) $Mg(OCOCF_3)$, MeCN, 25°C; (v) ^tBuOCl, THF, -70°C then LiOMe, MeOH.

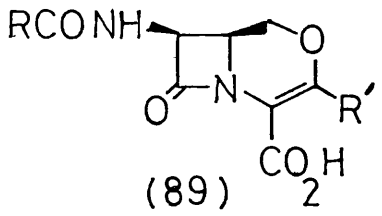
Intermediate (85) was obtained by reaction of cephem (83) with N-chlorosucinimide and mercuric chloride. Cyclisation proceeded as expected affording the oxacephem epimer (86). Epimerisation of the 7α-amido group was achieved by the method of Baldwin[45] and Kopper,[46] and introduction of the 7α-methoxy group was accomplished by utilising the imine-lithium methoxide route[42] giving the oxacephem (87) in high overall yield (89%).

3.0.2 Isocephems and Iso-oxacephems

Another interesting group of cephalosporin analogues are the 2-isocephems (88) and 2-iso-oxacephems (89). Their general structure is indicated below:



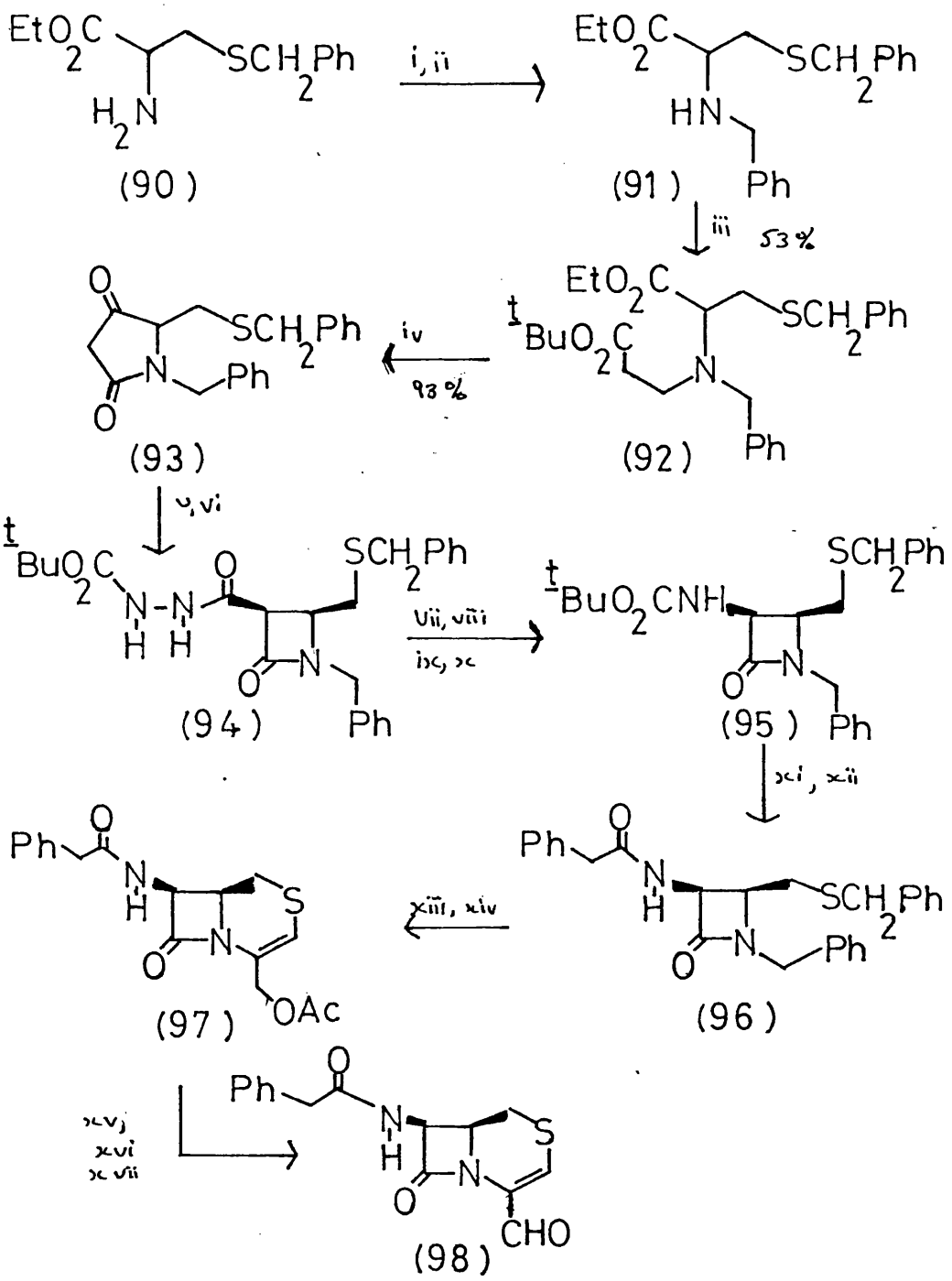
(88)



(89)

A synthesis of (88) (R=H)[47] utilised a photolytic Wolf rearrangement of a 3-diazopyrrolidin-2,4-dione (Scheme 15). Reduction of the Schiff base (obtained from condensation of S-benzyl-L-cysteine ethylester (90) with benzaldehyde, by treatment with dimethylamine-borane-acetic acid led to the N-benzyl derivative (91). Carbodiimide coupling of (91) with ^{t}butyl hydrogen malonate followed by potassium ^{t}butoxide treatment gave the pyrrolidine-2,4-dione (93). Diazo exchange and photolytic ring contraction in the presence of ^{t}butylcarbazate afforded the azetidin-2-ones (94) in a 1:1 ratio. Conversion to the carbamates (95) followed by deprotection and phenylacylation led to the key azetidin-2-one (96),

Scheme 15 2-Isocephem Synthesis

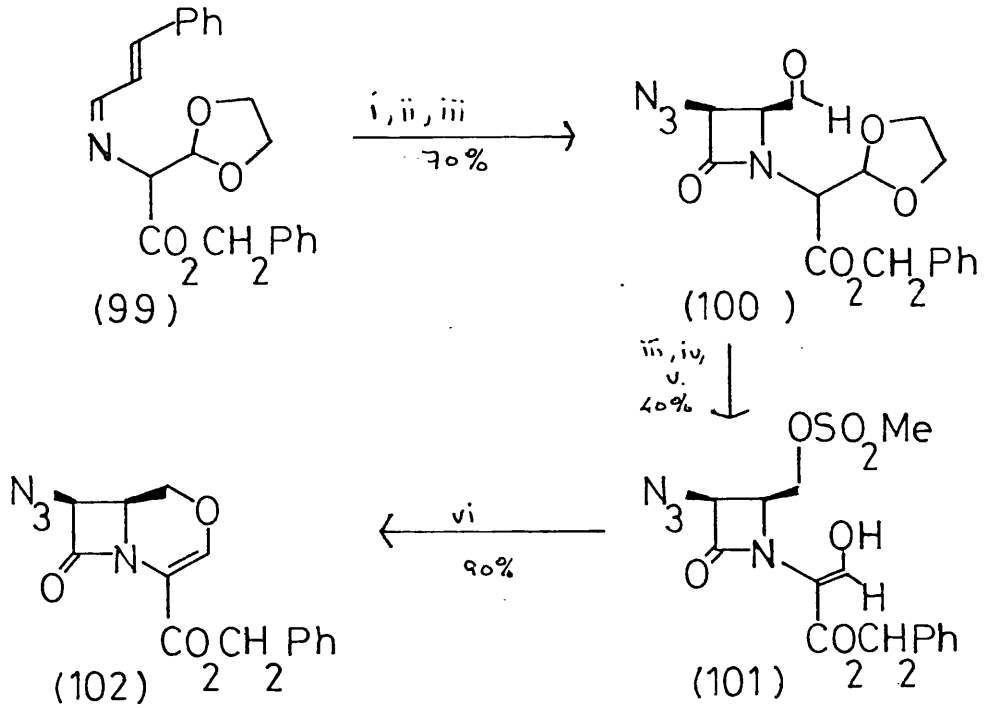


Reagents: (i) PhCHO; (ii) Me_2NH-BH_3, HOAc; (iii) ^{t}-$BuO_2CCH_2CO_2H$, DCC; (iv) KO^t-Bu; (v) $MeSO_2N_3$, Et_3N; (vi) hv, ^{t}-BuO_2CNHNH_2; (vii) CF_3CO_2H; (viii) HCl, $NaNO_2$; (ix) Δ; (x) ^{t}-BuOH; (xi) CF_3CO_2H; (xii) $PhCH_2COCl$, Et_3N; (xiii) Na-NH_3; (xiv) $AcOCH_2COCHCl$, DMF; (xv) $SOCl_2$, Py; (xvi) citrus acetyl esterase; (xvii) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

separated from its isomer by crystallisation. Formation of the bicyclic system (97) was achieved by reaction of (96) with 1-acetoxy-3-chloroacetone, where the more nucleophilic thiolate anion displaced chlorine. Chlorination and enzymatic hydrolysis of the allylic acetate with subsequent reduction led to the biologically active 2-isocephem aldehyde (98).

A classical ketene-imine cycloaddition route has been employed by the Bristol group[47] in a recent synthesis of the 2-iso-oxacephems (Scheme 15a). The cycloaddition step is interesting as it gave the *cis* product exclusively. This is in contrast to the findings of Bose[49] who showed that *trans* stereochemistry predominated in other examples.

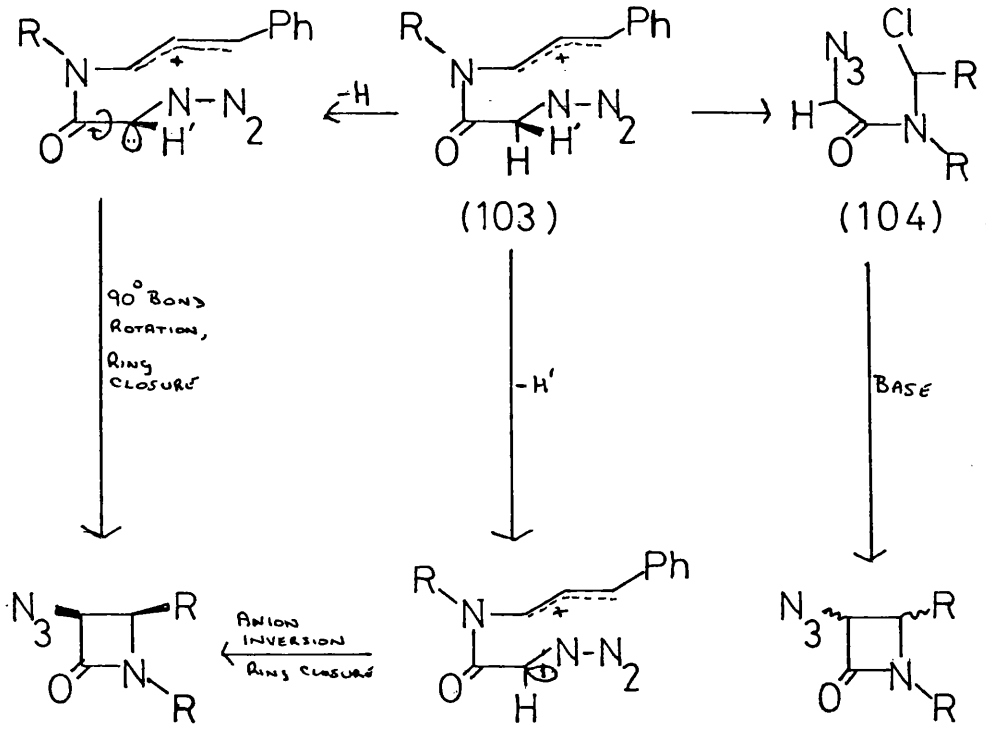
Scheme 15a Bristol 2-Isooxacephem Synthesis



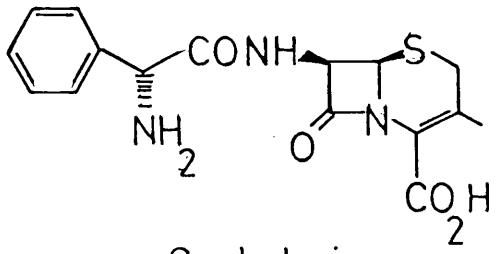
Reagents: (i) N_3CH_2COCl, Et_3N; (ii) O_3, DCM, -78°C; (iii) $NaBH_4$, THF, -10°C; (iv) $MeSO_2Cl$, Et_3N, DCM; (v) CF_3CO_3H; (vi) Et_3N, DCM.

As mentioned above, the cycloaddition step is unusual in providing *cis* stereochemistry only. This was rationalised as

follows; upon addition of the acid chloride to the imine an acyliminium ion (103) was rapidly and reversibly formed, with stabilisation of the positive charge by the azido group. In the absence of a base (103) formed the alkyl halide (104), proton abstraction then led to the *cis-trans* mixture. In the presence of a base deprotonation of the imminium ion occurred leading to the *cis*-β-lactam. This sequence is summarised below:



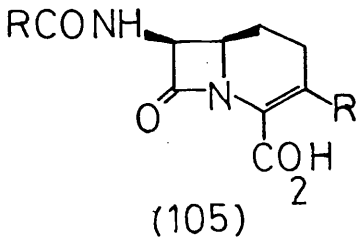
The other key step in the synthesis was the intramolecular displacement of mesylate (101) → (102). This was accomplished by hydrolysis of the acetal (100) followed by generation of the enol anion. Ring closure proceeded in high yield (90%) giving the 2-iso-oxacephem (102). This racemic compound (after azido to phenoxyacetamido side chain) had biological activity comparable to that of cephalexin.



Cephalexin

3.0.3. Carbacephems

Carbacephems have also been the subject of intensive study and a number of routes to the ring system (105) have been devised.

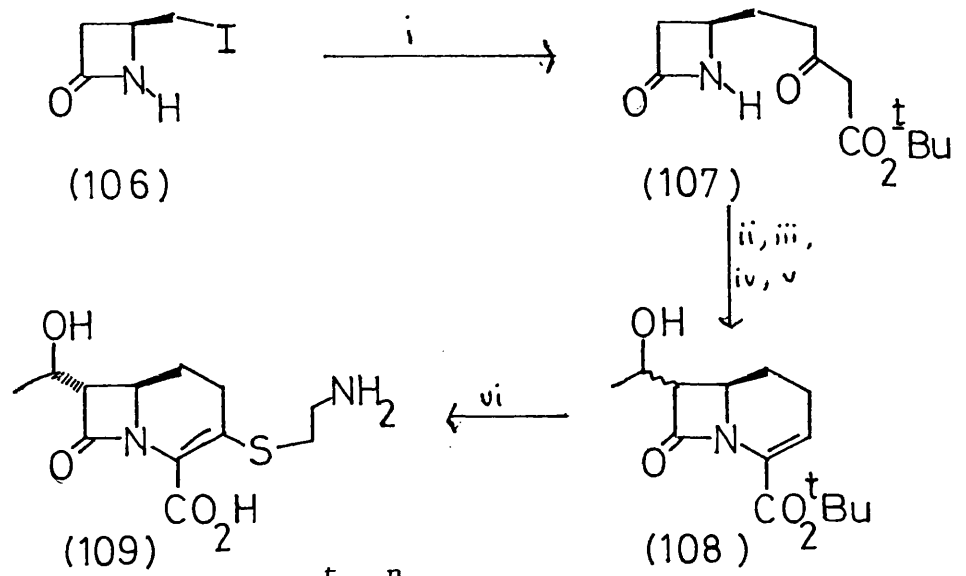


(105)

Utilising an approach devised for a thienamycin synthesis[51] the Merck group have synthesised homothienamycin (109)[50] starting from aspartic acid. This synthesis (Scheme 16) started from the 4-iodomethylazetidin-2-one (106)[10] obtained by the TMS-Grignard[11] initiated ring closure of dibenzylaspartic acid.

A point of note was the conversion (106) → (107). If the β-lactam was N-silylated no reaction occurred with the dianion. In contrast to thienamycin the bicyclic system (109) was more stable and showed markedly reduced biological activity.

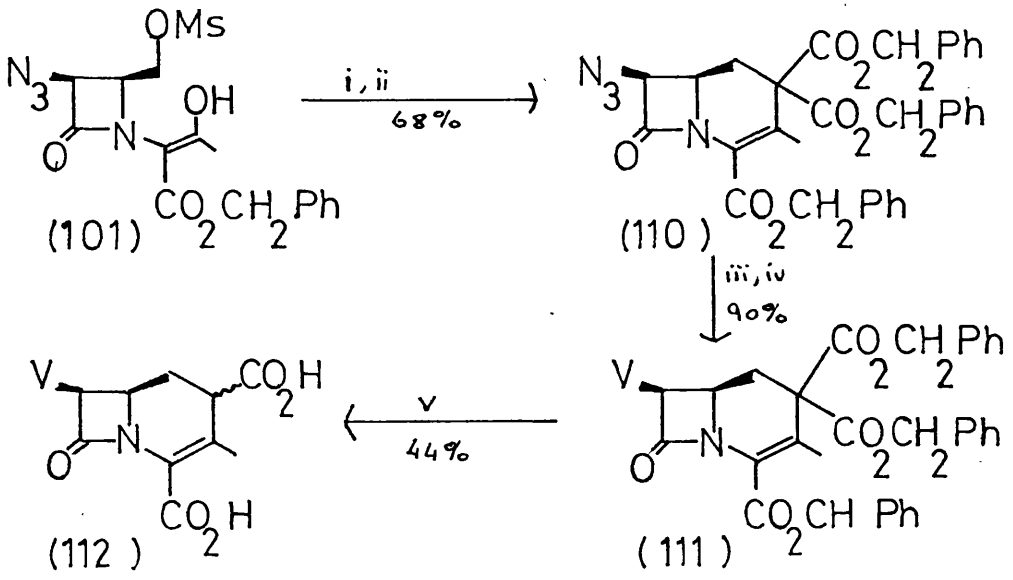
Scheme 16 Merck Synthesis of Homothienamycin



Reagents: (i) $CH_3COCH_2CO_2{}^{t}Bu$, ${}^{n}BuLi$ (2equiv.); (ii) TsN_3, Et_3N; (iii) $Rh_2(OAc)_4$, C_6H_6; (iv) Ts_2O, Et_3N; (v) LDA, CH_3CHO; (vi) $HS\sim NH_2$, Et_3N; (viii) CF_3CO_2H, PhOMe, DCM then anisole, Dowex, SO.

The Bristol group have also been interested in this area and have modified[52,53] their 1-iso-oxacephem synthesis from the azetidin-2-one (101) (Scheme 17).

Scheme 17 Bristol's Carbacephem Synthesis

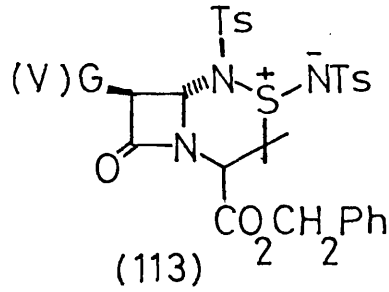


Reagents: (i) $(CF_3SO_2)O$, Et_3N, 0°C; (ii) $NaCH(CO_2CH_2Ph)_2$, THF, 25°C; (iii) H_2S, Et_3N; (iv) $PhOCH_2CO_2H$, EEDQ; (v) H_2, Pd/c.

Thus reaction of the enol triflate of (101) with the sodium salt of dibenzylmalonate afforded the bicyclic system (110) in 66% yield. Reduction of the 7-azido group followed by amide formation resulted in the introduction of the V-side chain, hydrogenolysis and decarboxylation gave the cephem (112). The biological activity of this compound was very low.

3.0.4 Azacephems

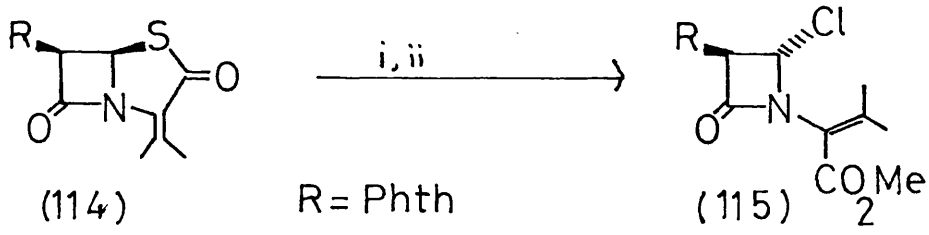
1-Azacephems have also attracted interest from a number of groups. Campbell *et al.*[54,55] have found that reaction of penicillin G or V with two equivalents of chloramine-T afforded the 6-epi-1-azacepham derivative (113).



(113)

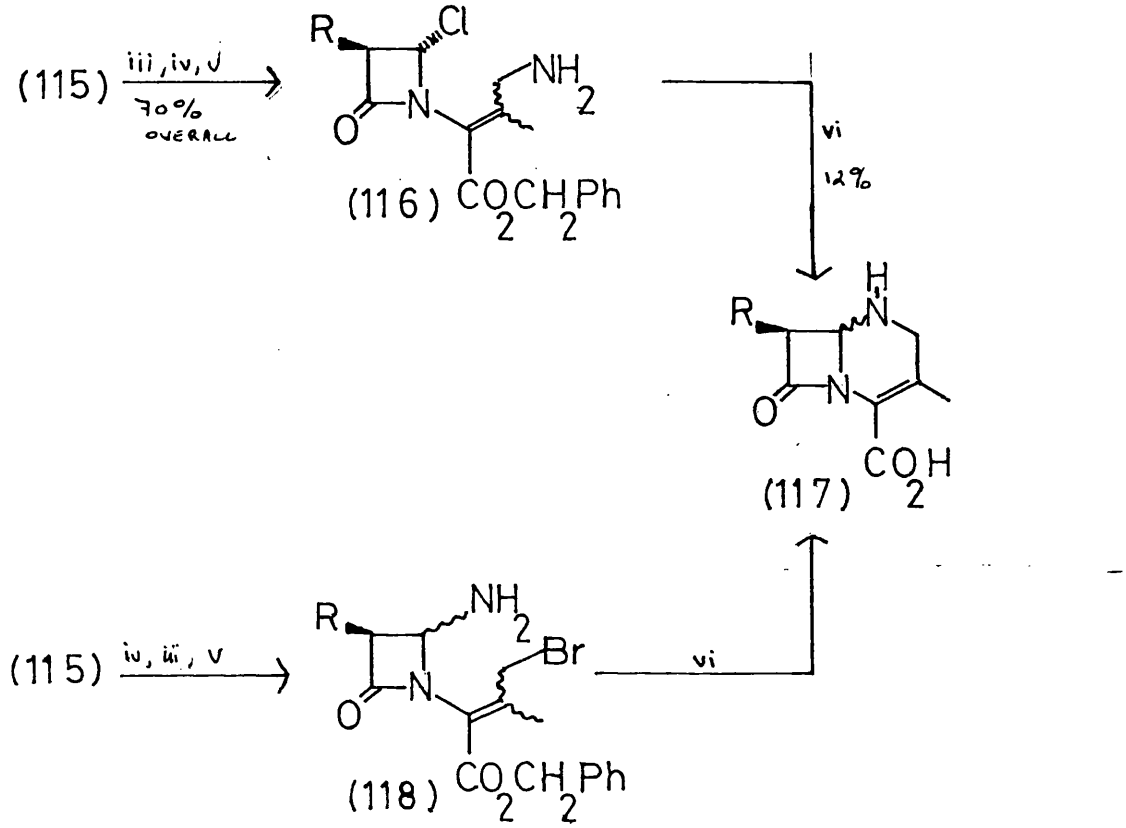
A partial total synthesis of 1-azacephems, from anhydropenicillins (114), has been described by Wolfe *et al.*[56,57] (Scheme 18).

Scheme 18 Wolf's 1-Azacephem Synthesis



(114) R = Phth (115)

Scheme 18 continued



Reagents: (i) Cl_2, CCl_4; (ii) HBO_3 then CH_2N_2; (iii) NBS; (iv) TMGA; (v) PtO_2, C_6H_6, H_2, 45 PSI; (vi) ^{t}-BuOK, ^{t}-BuOH.

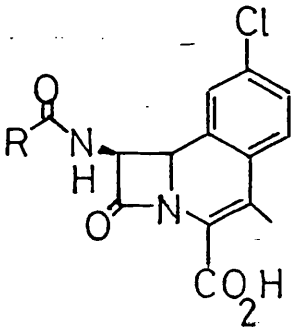
Reaction of 6-phthalimidoanhydropenicillin (114) with chlorine followed by hydrolysis and diazomethane treatment afforded the 4-chloroazetidin-2-one (115) in quantitative yield. Allylic bromination with one equivalent of N-bromosuccinimide, treatment with tetramethylguanidinium azide and hydrogenation gave the isomeric mixture of allylic amines (116). Base initiated cyclisation of (116) resulted in the formation of the 1-azacephem (117) in low yield (12%). Reaction of (115) with tetramethyl guanidinium azide followed by hydrogenation and allylic bromination gave azetidin-2-one (118), cyclisation of which afforded (117).

3.0.5 Summary

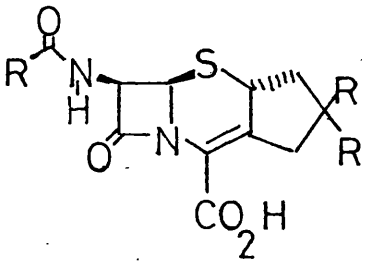
Again azetidin-2-ones have been shown to be key intermediates in a variety of routes leading to novel cephem derivatives, some of which have been shown to be biologically active.

4.0.0 AZETIDIN-2-ONES AS INTERMEDIATES IN THE SYNTHESIS OF OTHER NOVEL β-LACTAMS

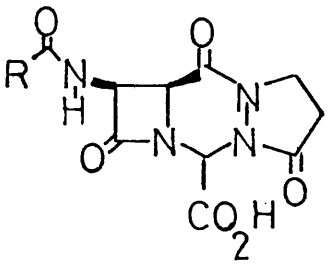
Many novel β-lactams, apart from those described above, have been reported. These include benzo-fused carbacephems (119),[58] cyclopentanocephems (120)[59] and tricyclic diazacephems (121).[60]



(119)



(120)

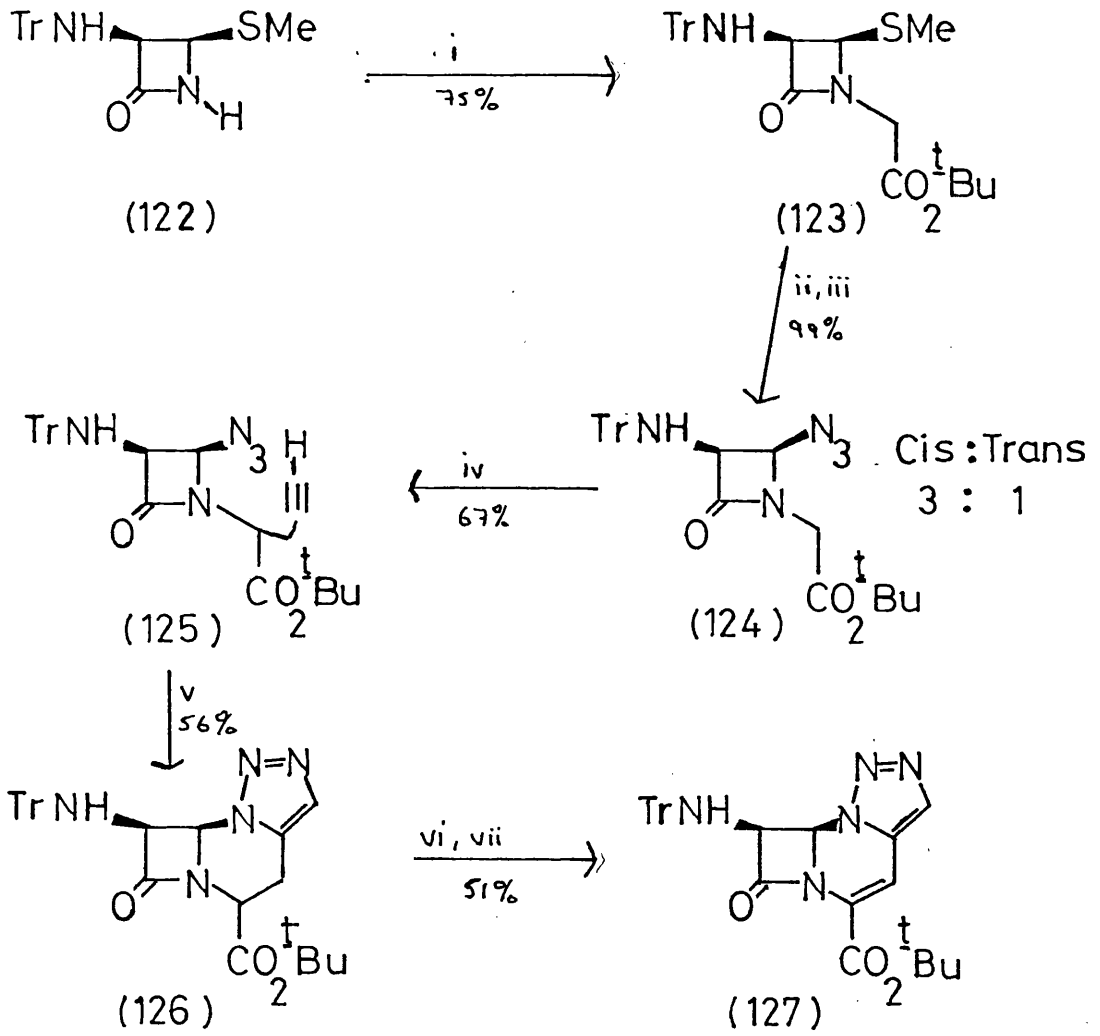


(121)

4.0.1 Triazolocephem Synthesis

One recent synthesis by Beechams described[61] a 4-azidoazetidin-2-one in the synthesis of a novel triazole fused β-lactam (127) (Scheme 19). Alkylation of 4-methylthio-3-tritylaminoazetidin-2-one (122), readily available from benzyl-6β-tritylaminopenicillanate,[62] followed by chlorinolysis and treatment with sodium azide, afforded the 4-azidoazetidin-2-one (124) in 75% overall yield. Introduction of the prop-2-ynyl side chain was accomplished by alkylation of the ester enolate of (124) with propargyl bromide. Thermolysis of (125) initiated 1,3-dipolar cycloaddition resulting in formation of the triazolocepham (126) in high yield (80%). Introduction of the Δ^4 double bond was achieved by phenylselenation followed by oxidation and *syn*

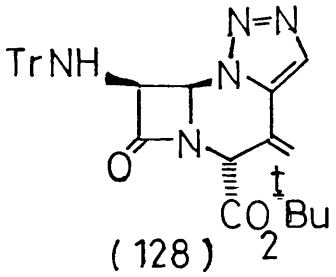
Scheme 19 Beecham's Triazolocephem Synthesis



Reagents: (i) $BrCH_2CO^tBu$, K_2CO_3, DMF; (ii) Cl_2, CCl_4, -20°C; (iii) NaN_3, DMF, 25°C; (iv) $LiN(TMS)_2$, -78°C then $BrCH_2GCH$; (v) toluene, Δ; (vi) $LiN(TMS)_2$, -78°C then PhSeBr; (viii) m-CPBA, 0°C.

elimination. The β-lactam carbonyl in (129) occurred at ca. 1805cm^{-1} in the i.r. spectrum, higher than most penicillins and cephalosporins, indicative of a highly strained and more reactive carbonyl system. However, conversion of the tritylamino group to the V-side chain and de-esterification led to a system with only moderate biological activity.

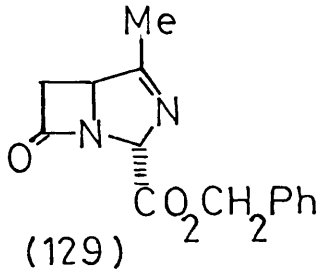
This synthesis has considerable generality and has been used to prepare analogues including those with substituents at what would be cephalosporin 3-position. For example, the 4-methylidene β-lactam (128) has been prepared.



(128)

4.0.2 2-Azapenem Derivatives

The Beecham group have also described[63] an interesting route to the diazabicyclo[3.2.0]heptane ring system (129) from 4-vinyl-azetidin-2-one (130).

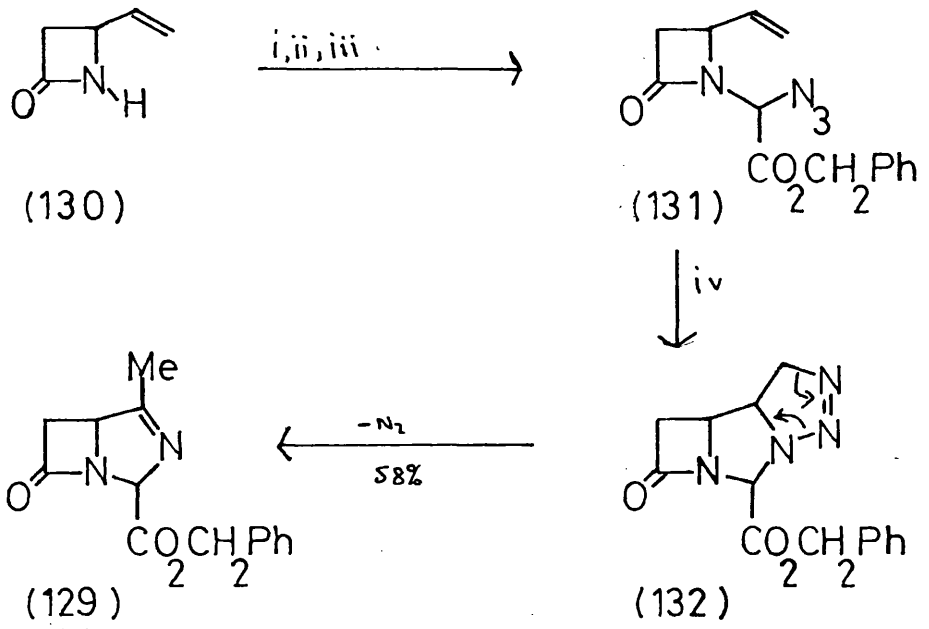


(129)

The key intermediate, a tricyclic β-lactam containing the triazoline ring, lost nitrogen on heating to give (129) (Scheme 20).

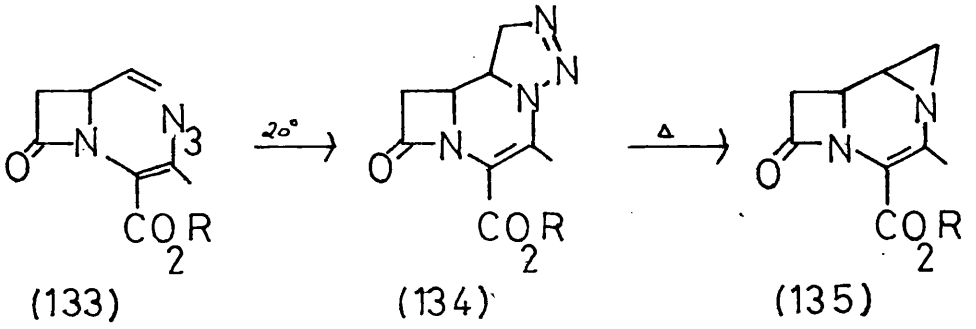
Conversion of (130) to the azidomethyl β-lactam (131) was achieved by utilising normal β-lactam methodology. Azide (131) afforded the triazolino compound (132) upon heating in toluene. This compound lost nitrogen giving the target system as a mixture of diastereoisomers.

Scheme 20 7-oxo-1,3-Diazabicyclo[3.2.0]Heptane Synthesis



Reagents: (i) $HOCCO_2CH_2Ph$, C_6H_6, Δ; (ii) $SOCl_2$, 2,6-lutidine, -15°C, THF; (iii) TMGA, $CHCl_3$, 20°C; (iv) heat.

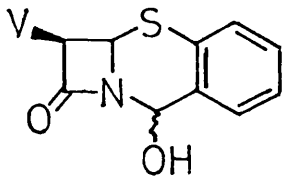
The same group also synthesised the diazatricyclo[5.2.0.$0^{4,6}$]-none-2-ene ring system (135) employing a similar approach to that shown in Scheme 20, the key intermediate triazoline (134) being obtained from vinyl azide (133) as outlined below:



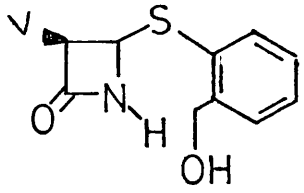
Neither (129) nor (135) showed any significant biological activity.

4.0.3 2,3-Benzo Fused Cephem Synthesis

Japanese chemists have synthesised[64] the 2,3-benzocephems (136) from 4-acetoxyazetidin-2-one (7).



(136)



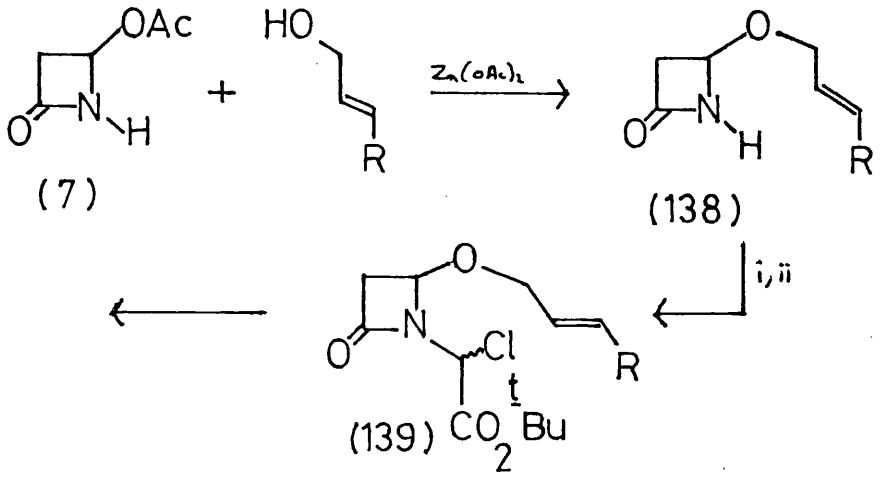
(137)

Displacement of the 4-acetate group from 4-acetoxyazetidin-2-one with o-mercaptobenzyl alcohol afforded the 4-(2-hydroxymethylphenylthio)azetidin-2-one (137) in 70% yield. Oxidation of (137) with PCC resulted in formation of the tricyclic β-lactam (136) in 62% yield. This compound was bioloigcally inactive. However, oxidation of (136) to the sulphoxide, with m-CPBA, afforded a mildly active compound.

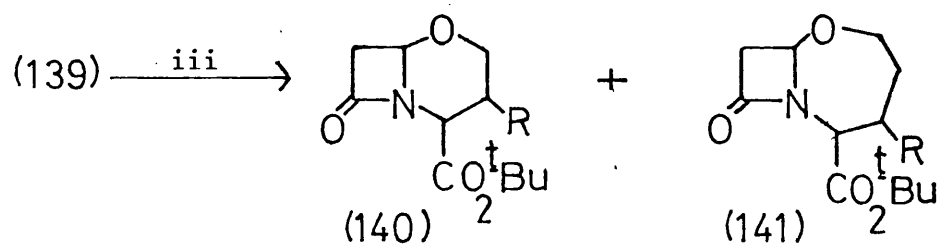
4.0.4 Diazobicyclo[4.2.0]octane and [5.2.0]nonane Synthesis

Bachi *et al.* have devised a novel cyclisation process based on a free radical reaction pathway,[65,66] starting from 4-substituted azetidin-2-ones. This sequence, leading to 4,6- and 4,7-fused systems is shown in Scheme 21.

Scheme 21

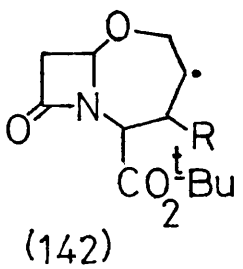


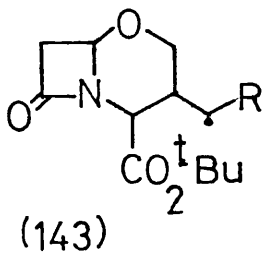
Scheme 21 contined.



Reagents: (i) $(HO)_2CCO_2{}^{t}Bu$; (ii) $SOCl_2$, 2,6-lutidine; (iii) $^{n}Bu_3SnH$, 2-4 mole % AIBN, C_6H_6, Δ.

The course of these radical reactions was highly dependent on the nature of the substituent R on the vinyl side chain. Thus a terminal olefin afforded the bicyclo[5.2.0]nonane only, the endo addition mode. If R=carboxymethyl, the exo mode was favoured leading to the bicyclo[4.2.0]octane system. Thus the stability of the radical produced from (139) is an important factor in determining the endo *vs.* exo mode. When R=H the secondary radical (142) is more stable than the primary radical (143) and the bicyclononane results. If R=Ph or CO_2Me radical (143) becomes more favoured and the bicyclooctane results. Phenylseleno- and phenylmethylthioazetidin-2-ones may also be used as free radical precursors. The main disadvantage of this process is the relatively low yield (10-50%).


(142)


(143)

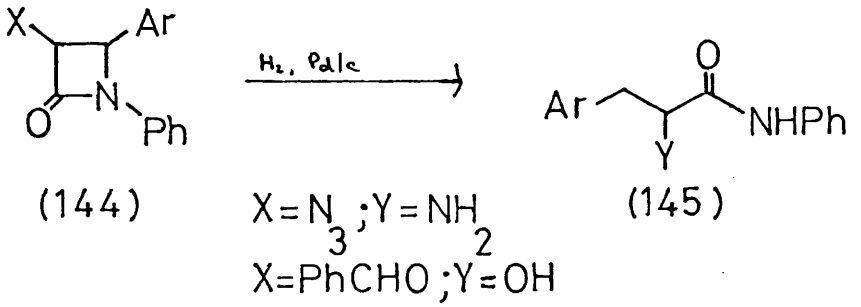
4.0.5 Summary

A selection of recent syntheses of novel bicyclic β-lactams has been presented, once again demonstrating the usefulness of azetidin-2-ones as synthetic intermediates.

5.0.0 AZETIDIN-2-ONES AS SYNTHONS FOR BIOLOGICALLY ACTIVE MOLECULES OTHER THAN BICYCLIC β-LACTAMS

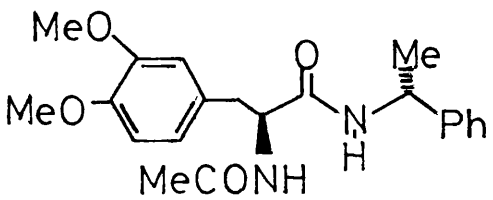
Although the use of azetidin-2-ones in β-lactam synthesis is well documented, little attention has been focused on their use as synthetic intermediates for non β-lactam targets.

It is well known that cleavage of the β-lactam ring usually occurs at the N-C=O bond. One other mode of cleavage, namely N-C4, has recently been exploited by Ojima *et al.*[67] This group noted that 3-substituted-4-arylazetidin-2-ones (114) were selectively cleaved at the N-C4 bond by hydrogenolysis over a palladium catalyst to give the corresponding amides of α-amino acids (145) in good yield:

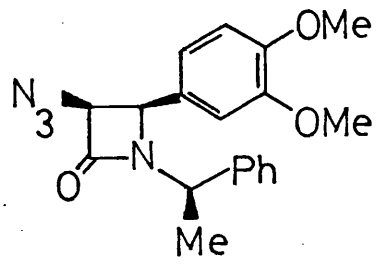


(144) X=N$_3$;Y=NH$_2$ X=PhCHO ;Y=OH (145)

Ojima also carried out[67] an asymmetric synthesis of the propionamide (146) from azetidin-2-one (147) noting a 40% chirality transfer.



(146)



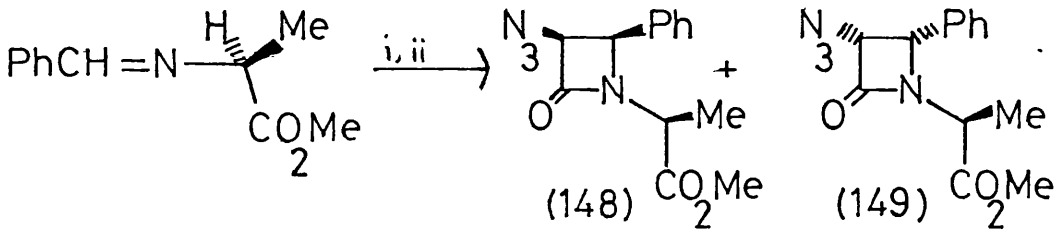
(147)(1R,3R,4S)

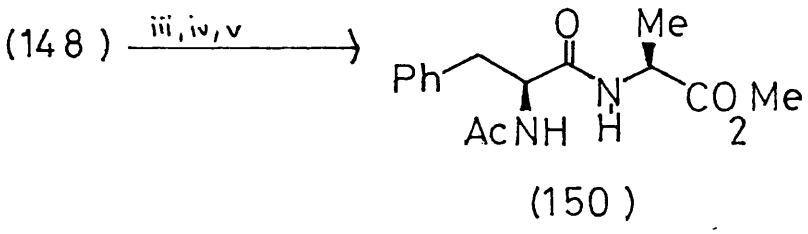
This route provided an effective and convienent route to the amides of α-amino acids such as dopa, ρ-fluorophenylalanine and tryptophan.

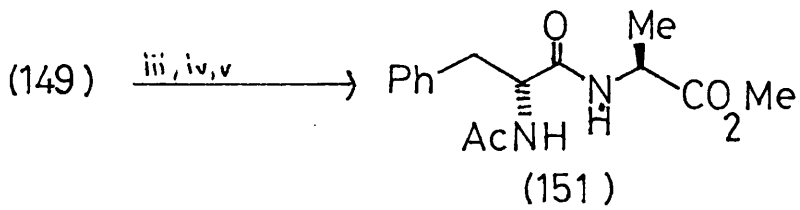
5.0.1 Dipeptide Synthesis via Azetidin-2-ones

Following on from the above work, Ojima *et al.*[68] extended their methodology to a dipeptide synthesis not involving any of the conventional dehydrating agents such as carbodiimides. The key step was the facile and selective cleavage of the β-lactam ring (Scheme 22).

Scheme 22 Dipeptide Synthesis



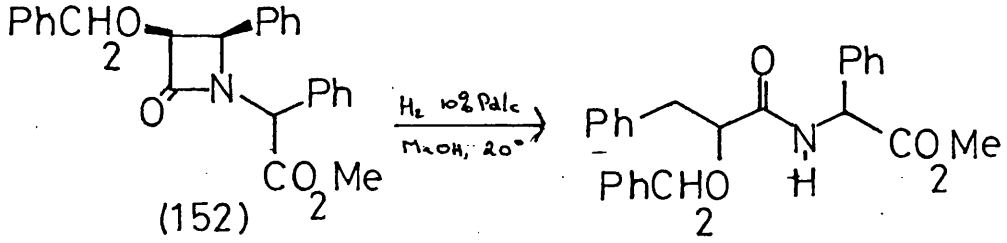




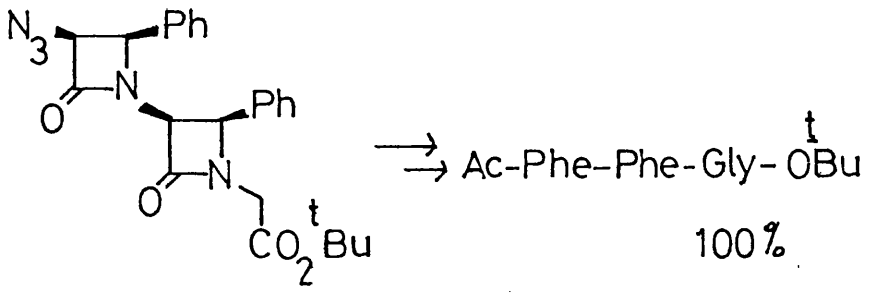
Reagents: (i) N_3CH_2COCl, Et_3N; (ii) HPLC; (iii) H_2, Pd/C; (iv) AcCl, Me-N⌒O; (v) H_2, Pd/C, 50°C.

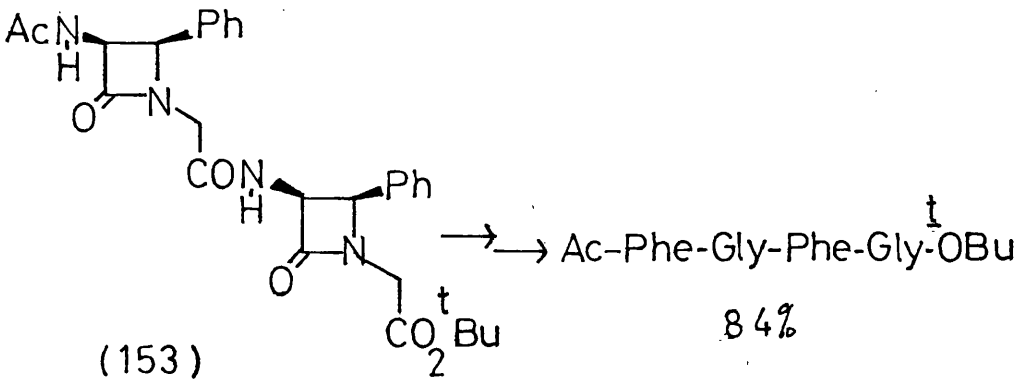
Standard ketene-imine cycloaddition followed by HPLC separation afforded the azetidin-2-ones (148) and (149). Hydrogenation of the 3-azido group at room temperature followed by N-acylation gave the 3-acylamino azetidin-2-one. Hydrogenation of which at 50°C yielded

the dipeptides (150) and (151). Ojima also noted that hydrogenolysis of the 3-benzyloxyazetidin-2-one (152) resulted in cleavage of the β-lactam ring prior to loss of the benzyl group, thus indicating the accelerating effect of the β-lactam ring strain, as benzyl-oxygen bond cleavage is normally faster than benzyl-nitrogen bond breaking.[69] However, in the case of the 3-azido group the amine was always produced as the only product.



The above route has been further extended to provide tri- and tetrapeptides from bis-β-lactams (153). By cleavage at the C4-N and C4^1-N bonds:-





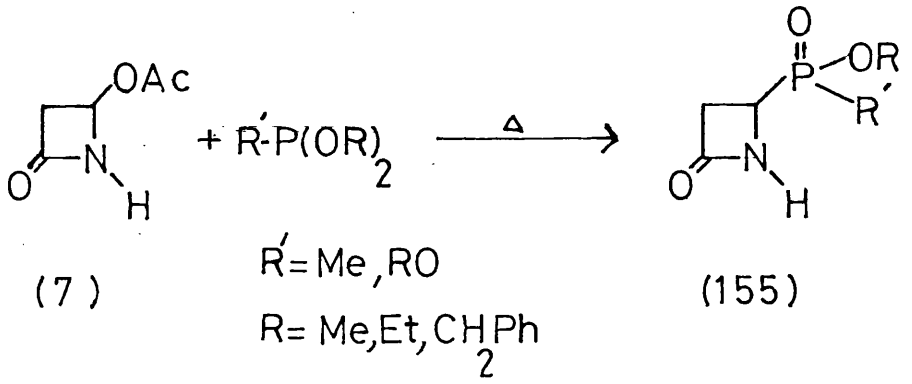
5.0.2 Aminophosphonic Acid Synthesis

Aminophosphonic acids, as analogues of natural amino acids, are of increasing interest as biologically active compounds. One recent example being alaphosphin (154) which inhibits alanine racemase.[70]

$H_2NCH(Me)CONHCH(Me)PO_3H_2$

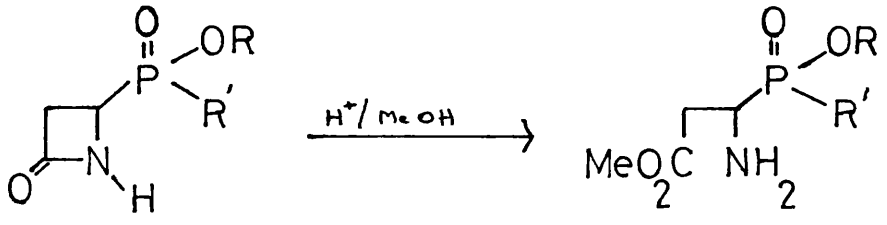
(154)

In an extension of a brief study by Hoechst,[5] Campbell *et al.* have synthesised[71] a variety of 4-phosphono- and -phosphino-azetidin-2-ones from 4-acetoxyazetidin-2-one, via an Arbusov reaction, in high yield (7) → (155).



(7) (155)

Acid hydrolysis[71] of β-lactams (155) provided a new route to α-aminophosphonic and -phosphinic analogues of aspartic acid (155) → (156).

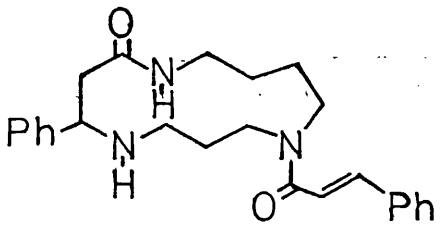


(155) (156)

Also N-acylation of (155) with N-protected amino acids or peptides, followed by acid hydrolysis, led to a variety of phosphono and phosphino oligopeptides.[71]

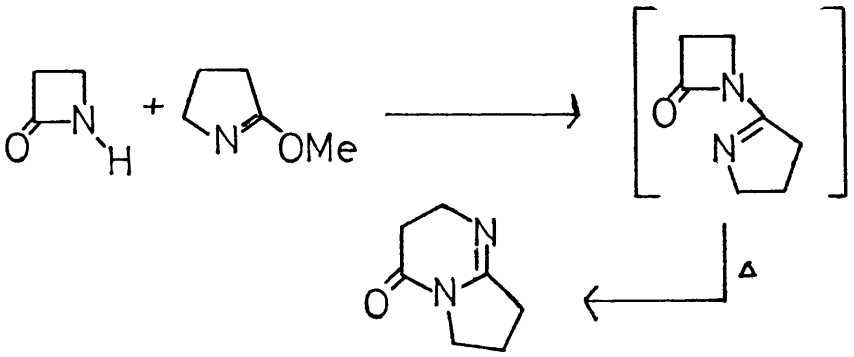
5.0.3 Azetidin-2-ones as Synthons for Ring Expansion Processes

Recently Wasserman *et al.*[72] described a synthesis of dihydroperiphylline (157), a polyamine alkaloid with notable biological activity, utilising an azetidin-2-one in an addition-ring expansion process.



(157)

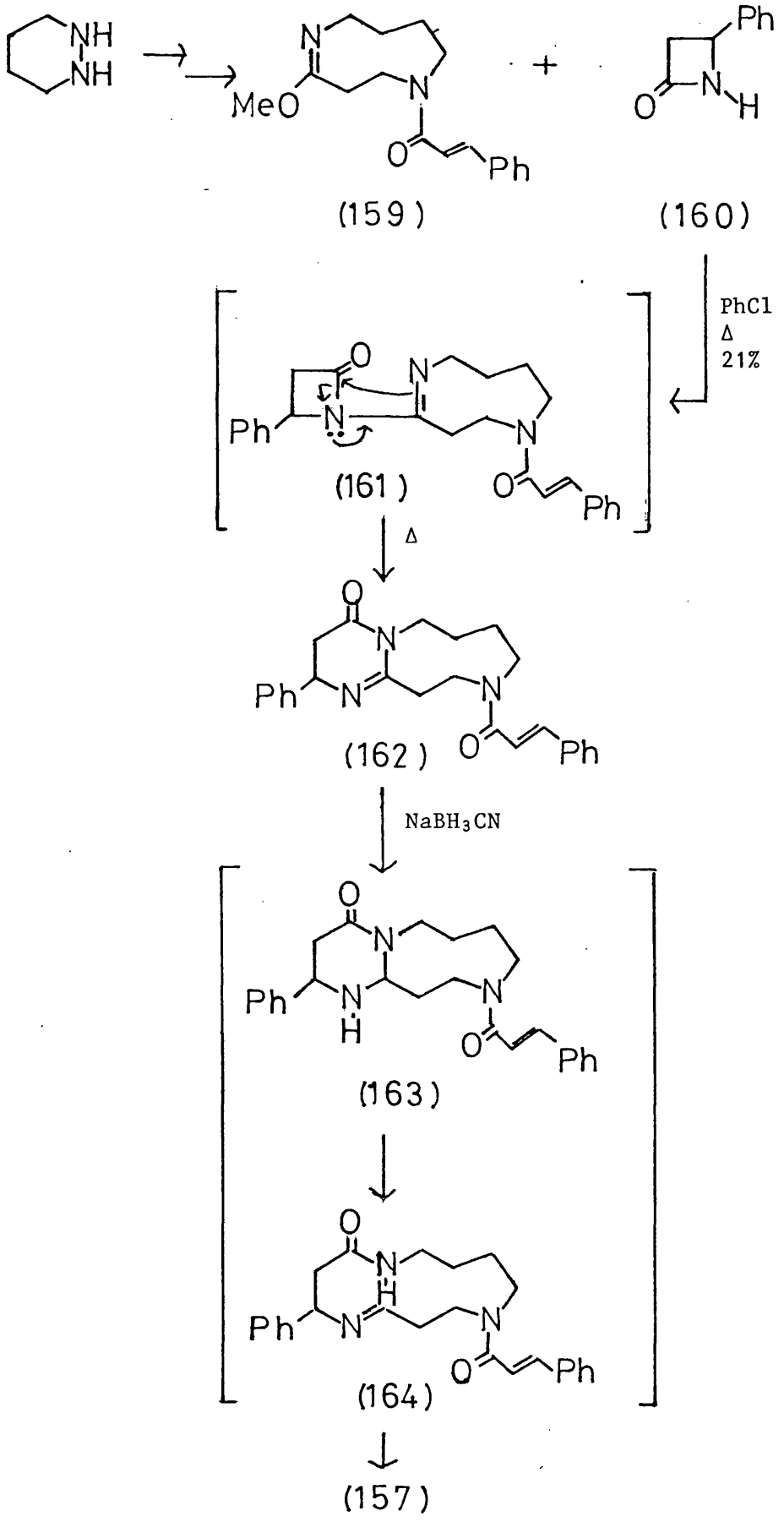
The ring expansion reaction, discovered by Bormann,[73] involved the addition of azetidin-2-ones to lactim ethers leading to tetrahydropyrimidines (158) in good yield:



(158)

Wasserman's route to dihydroperiphylline (157) is summarised in Scheme 23.

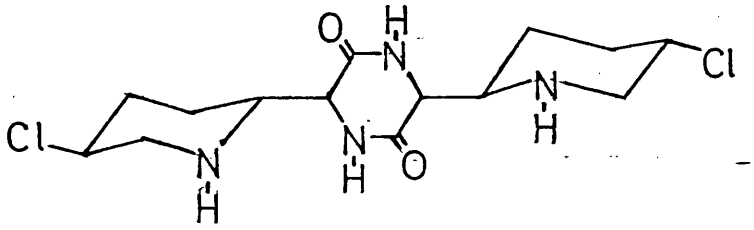
Scheme 23 Dihydroperiphylline Synthesis



Simple heating of the lactim ether (159) with 4-phenyl-azetidin-2-one (160) afforded the tetrahydropyrimidine (161) in 67% yield. Reduction with sodium cyanoborohydride resulted in formation of (157) presumably via the intermediates (163) and (164).

5.0.4 Synthesis of Anti-Tumour Agent 593A

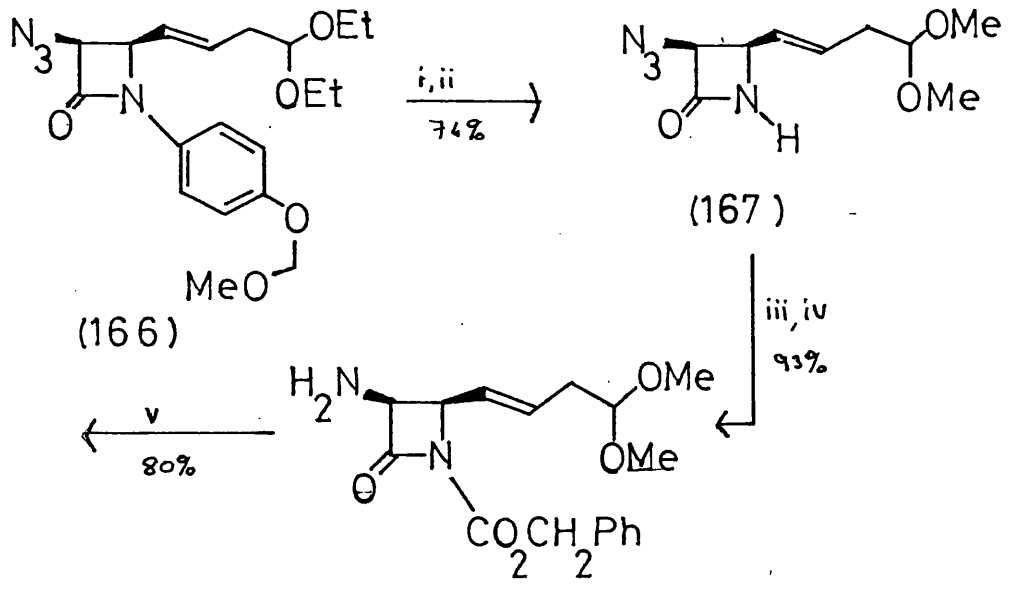
Fukuyama *et al.* utilised[74] a β-lactam ring cleavage in their total synthesis of piperazine dione anti-tumour drug 593A (165).



(165)

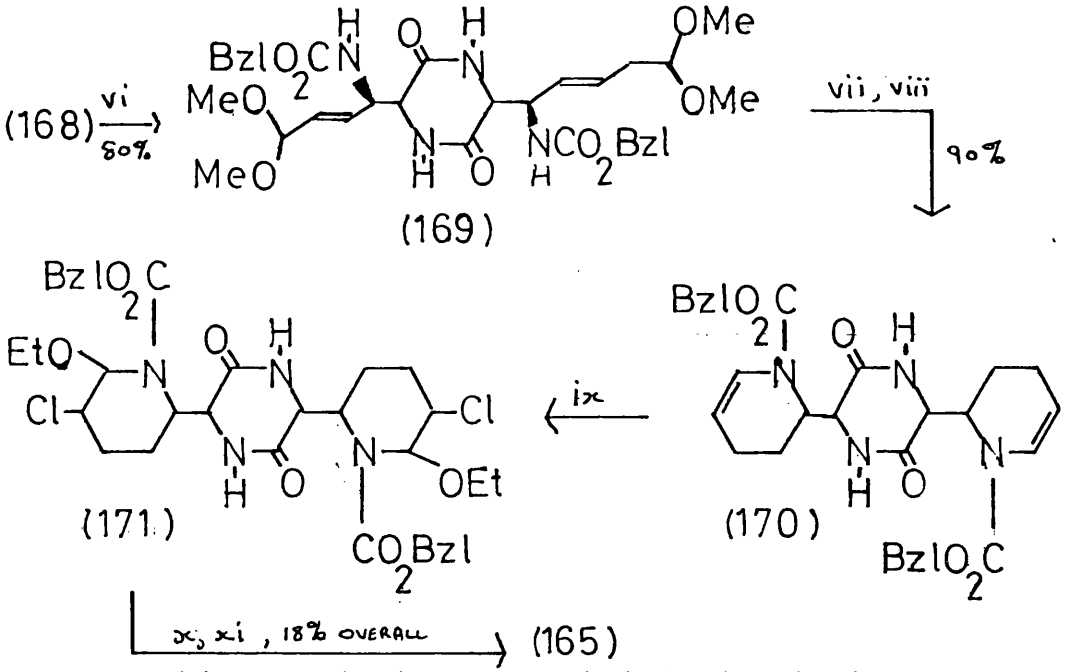
The use of a β-lactam overcame the difficulties of (a) controlling the stereochemistry of α,β-diamino acids, and (b) the dimerisation of amino acids in forming the piperazine dione ring (Scheme 24).

Scheme 24 Agent 593A Synthesis



(166) (167) (168)

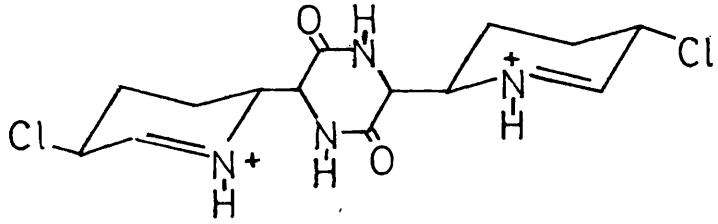
Scheme 24 continued.



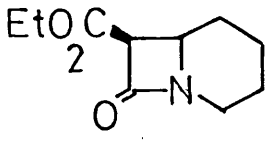
Reagents: (i) HCl,$CH(OMe)_3$,MeOH,Δ; (ii) $(NH_4)_2Ce(NO_3)_6$,THF,H_2O,0°C; (iii) $PhCH_2OCOCl$,Et_3N,-30°C; (iv) Zn,HOAc/Et_2O,20°C; (v) 20°C; (vi) H_2,PtO_2,MeOH; (vii) CSA,quinoline; (viii) Cl_2,EtOH,DCM,0°C; (ix) BCl_3; (x) $NaBH_3CN$,HOAc,MeOH,20°C.

Azetidin-2-one (166) was prepared by ketene-imine cycloaddition in the usual manner,[7] oxidative removal of the N-phenylmethylether protecting group, accomplished by treatment with ceric ammonium nitrate,[75] afforded azetidin-2-one (167) in high yield (74%). Reaction of (167) with benzyl oxycarbonyl chloride and reduction of the 3-azido group gave the unstable azetidin-2-one (168) which dimerised on standing to the piperazine diones (169) (60:40), the unwanted isomer of which was separated by chromotography.

Noteworthy in this reaction sequence was the stereoselective reduction of chloroether (171) which resulted in formation of the target (165). This was explained by preferential formation of the thermodynamically favoured tetra quasi-equatorial iminium ion (172) under acidic conditions.

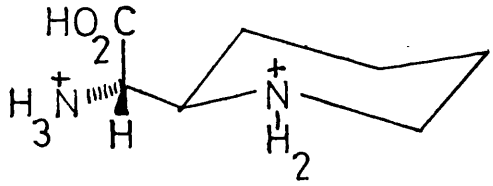


(172)



(173)

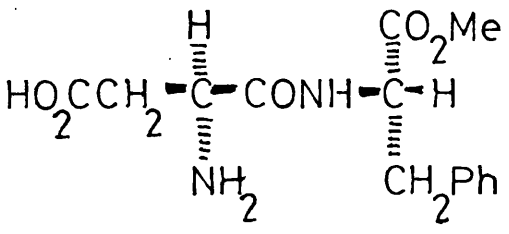
Golding *et al.*[76] also reported a route to (165), again based on a β-lactam precursor (173). Introduction of an amino group at C7 was accomplished by quenching of the C7 enolate anion with tosyl azide and hydrogenolysis. Acidic hydrolysis afforded the piperidine (174), a useful intermediate in the synthesis of (165).



(174)

5.0.5 β-Lactams in the Synthesis of Sweeteners

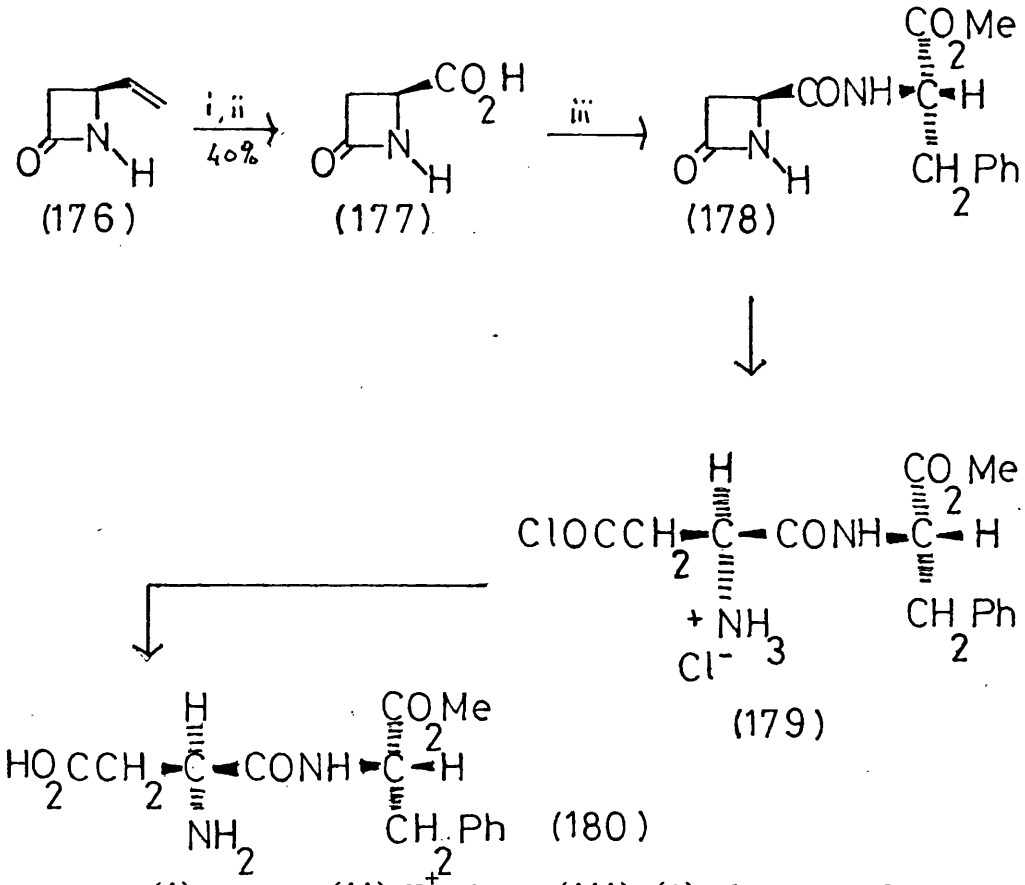
Aspartame (175) is an amino acid with sweetness 150 times greater than sugar. Only the (S,S) isomer has this property, the other optical isomer being bitter.



(175)(S,S)

This substance should therefore lend itself to an asymmetric synthesis starting from a chiral azetidin-2-one. Such a route (Scheme 25) was devised by the Hoechst group.[77]

Scheme 25 Aspartame Synthesis



Reagents: (i) $KMnO_4$; (ii) H^+, H_2O; (iii) (S)-PheOMe, DCC, MeCN, H_2O; (iv) HCl, DCM; (v) $NaHCO_3$, H_2O.

5.0.6 Summary

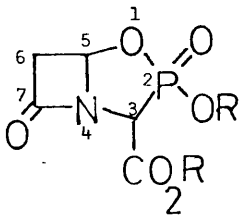
In this section a variety of syntheses of biologically active molecules has been presented illustrating the wider synthetic utility of azetidin-2-ones.

RESULTS AND DISCUSSION

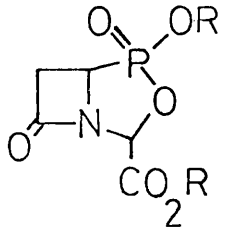
RESULTS AND DISCUSSION

6.0.0 INTRODUCTION

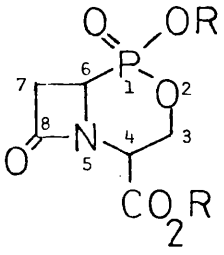
This thesis presents results of our attempts to synthesise the bicyclic β-lactams (1) → (3) of which (1) and (2) contain the 1,4,2-oxazaphospholidine ring system, with (3) containing the 1,4,2-oxazaphosphorinane ring.



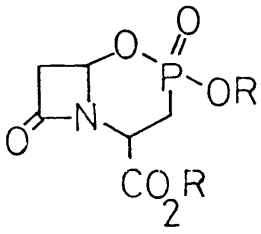
(1)



(2)



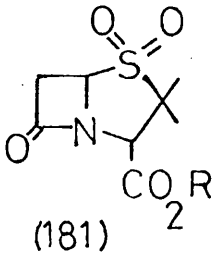
(3)



(4)

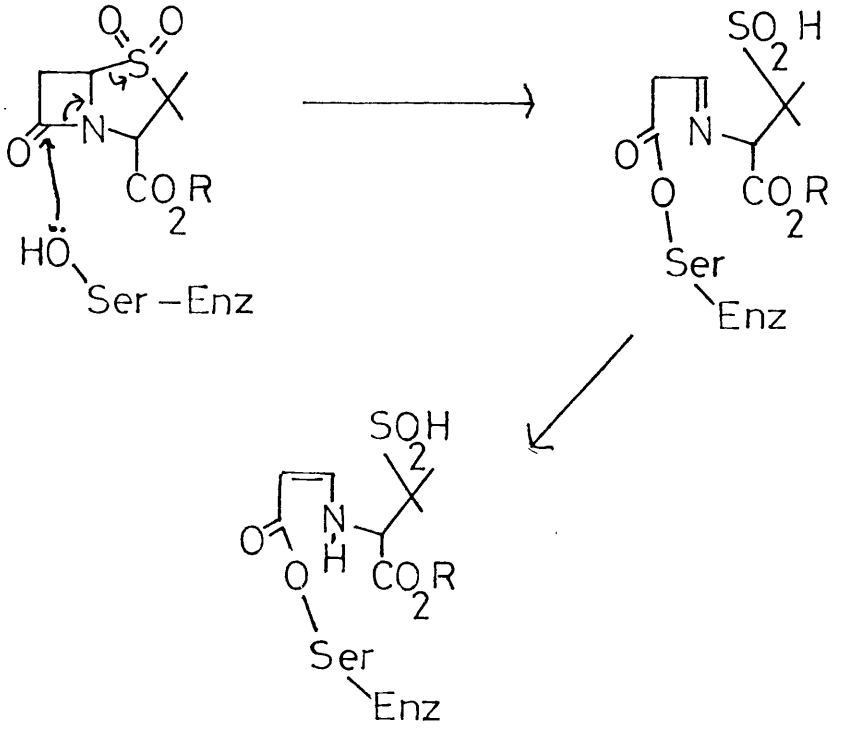
The results obtained will be related to each of these target molecules with respect to formation of the 1-5 bond in (1), 1-5 and 2-3 bonds in (2) [penicillin numbering] and the 1-2 bond in (3). Approaches to the alternative bicyclic system (4) were not investigated.

The rationale behind selection of these target systems was based on the discovery of the potent β-lactamase inhibitor CP 45899 (181),[78] a penicillin sulphone.

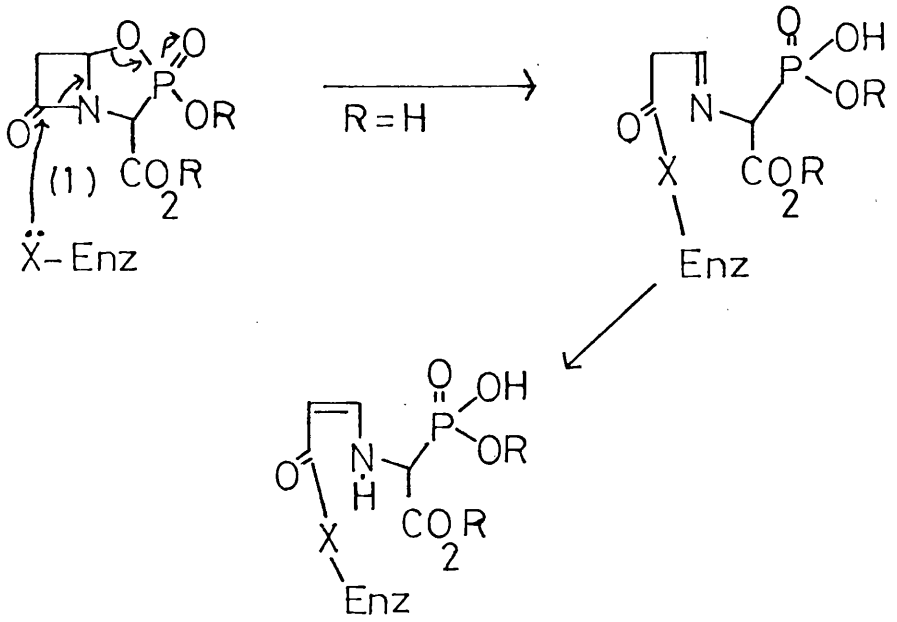


(181)

The mode of action of this compound is thought to proceed via the following[78] pathway:

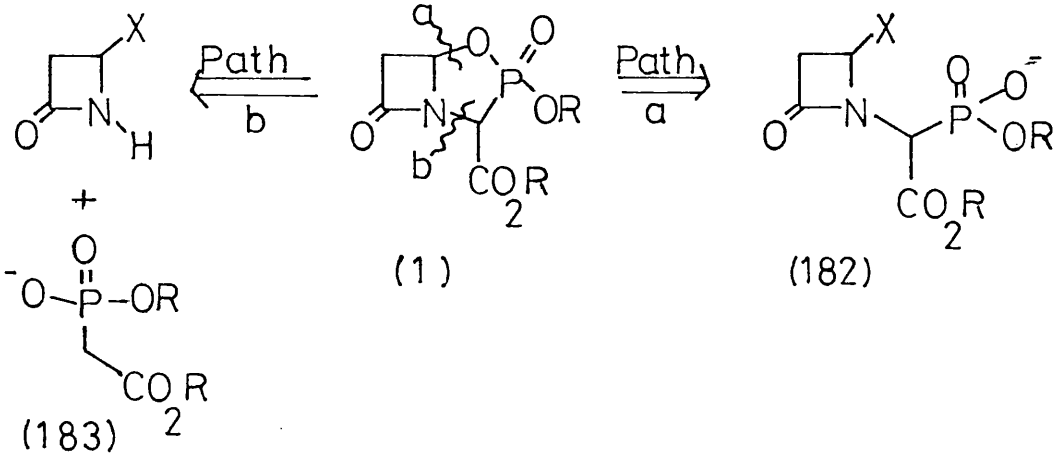


The P(V) [phosphonyl] group is isosteric with the sulphone functionality. Therefore it was thought that if the target systems, represented by structures (1) → (3), could be synthesised then they may have a similar mode of action to CP 45899 (181), for example (1).



6.0.1. Formation of the 1-5 Bond in Compound (1)

A reterosynthetic scheme is outlined below.

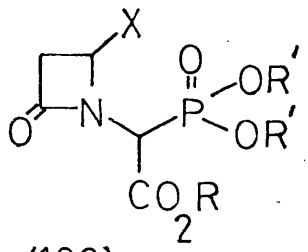


Two routes to the target (1) may be envisaged (i) Path a, intramolecular displacement of a suitable leaving group from the 4-position of the azetidin-2-one ring, and (ii) Path b, intermolecular

displacement of the 4-X group followed by formation of the 3-4 carbon-nitrogen bond. Each of these pathways will be discussed in turn.

6.0.2 Path a : Intramolecular Displacement

The monocyclic β-lactam (182), in the reterosynthetic scheme, is potentially an important precursor to the target system (1).

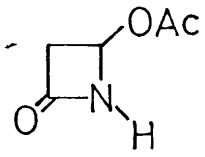


(182)

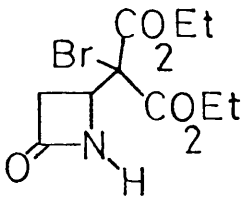
Where X is a suitable leaving group, e.g. acetate or chloro, and R' is an easily removed protecting group, e.g. methyl or benzyl. Compounds of this type have already been synthesised by Christensen *et al.*[80,81] in their route to Δ^3-cephalosporin derivatives. However, this method is lengthy and does not lend itself to large scale application, as the overall yield is low (ca. 9%). We have investigated several routes to compounds of type (182) and our results are presented below.

6.0.3 N-Alkylation of Azetidin-2-ones

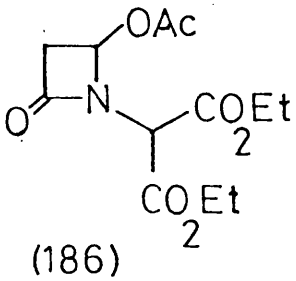
N-Alkylation of 4-acetoxyazetidin-2-one (184)[5] is a reaction well documented in the chemical literature. For example, Kametani *et al.*[82] have reported that N-alkylation occurred with 2-bromodiethylmalonate resulting in the formation of azetidin-2-ones (185) and (186) in 35% and 23% yield respectively.



(184)

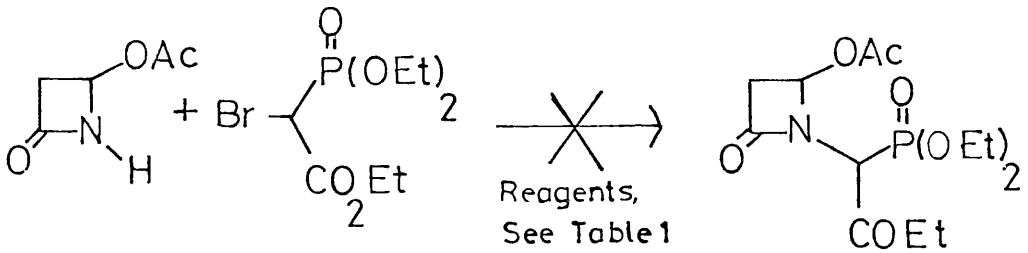


(185)



(186)

Accordingly we prepared 2-bromotriethylphosphonoacetate (187), by N-bromosuccinimide bromination of triethylphosphonoacetate, in 95% yield. However, intermolecular coupling with 4-acetoxy-azetidin-2-one (184), according to the reaction scheme below, failed to produce any β-lactam products (188) corresponding to those found by Kametani.[82]



(184) (187) Reagents, See Table 1 (188)

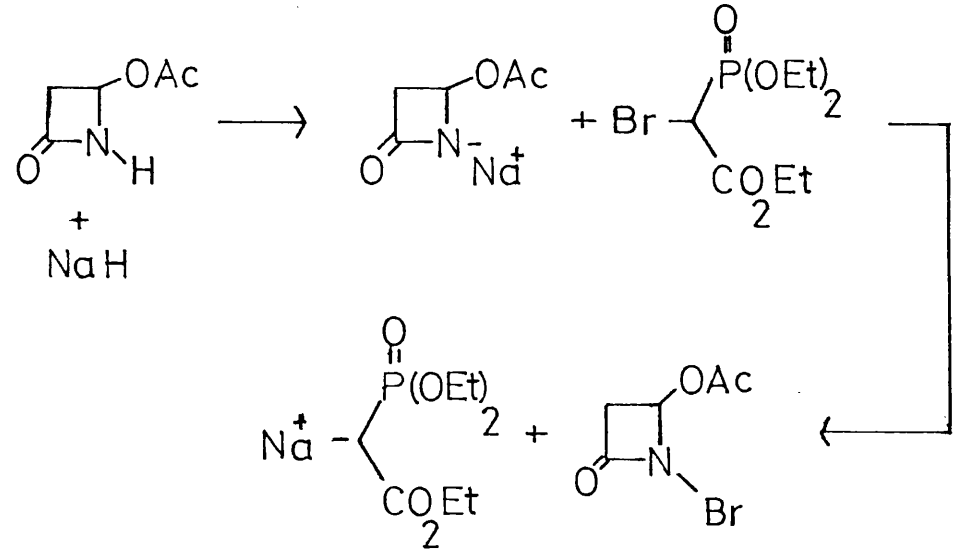
The only β-lactam isolated was from the reaction with sodium hydride at 50°C which gave 1-bromo-4-acetoxyazetidin-2-one (189), identical with an authentic sample. A possible mechanism for the formation of this compound is based upon the known ability of α-bromodiketones to act as 'positive bromine' donors. Apart from the tendency of (187) to behave as a 'bromium' source, because of the stabilisation of the resultant carbanion, we also suggest that steric hinderance, due to the bulky phosphono group, will tend to disfavour S_N2 displacement of bromine.

TABLE 1

Reaction of 4-Acetoxyazetidin-2-one with 2-Bromotriethylphosphono Acetate

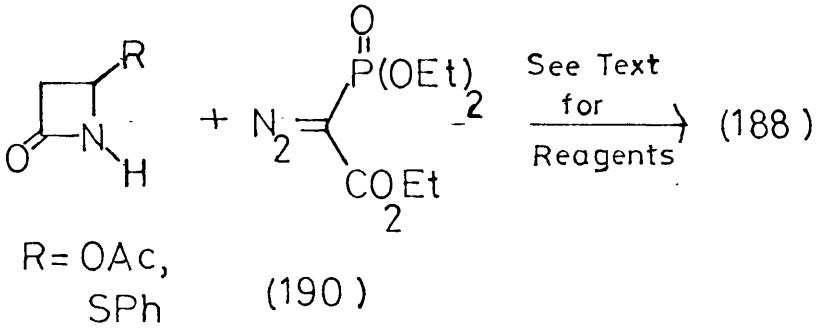
Reagent	Solvent	Temperature °C	Time (hs)	Products
Et_3N	DMF	25	24	β-lactam cleavage
NaH[82]	THF	-70-25	1	starting materials
NaH	THF	50	24	N-bromo-4-acetoxy-azetidin-2-one
$KOH/Bu_4N^+Br^-$ [83]	THF	4	2	starting materials
K_2CO_3	DMF	20	48	β-lactam cleavage
pyridine	pyridine	20	24	" "
LDPA	THF	-70-20	24	" "

Mechanism of 1-Bromo-4-Acetoxyazetidin-2-one formation

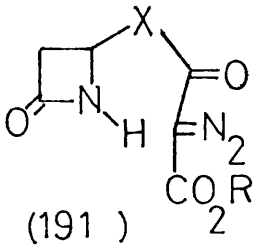


(189)

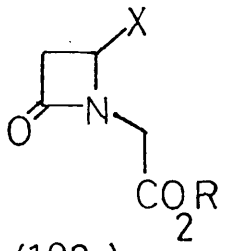
Carbene insertion into the N-H bond of amines and amides is a useful mild way to prepare sterically hindered derivatives[84] and may also provide a means to obtain β-lactams of type (188). Thus treatment of triethylphosphonoacetate with sodium hydride followed by tosyl azide[85] afforded the phosphono-carbene precursor, 2-diazo-triethylphosphonoacetate (190)[86] in 90% yield. The reaction, outlined below, was therefore examined under a variety of conditions.



Reaction of 4-acetoxy- or 4-phenylthioazetidin-2-one with (190) in the presence of copper(I) cyanide at 60°C in THF, rhodium(II) acetate in refluxing benzene,[87] or photolysis in benzene at 20°C failed to produce the desired product (188). This is in contrast to the successful intramolecular carbene insertion in compounds of type (191).[87]



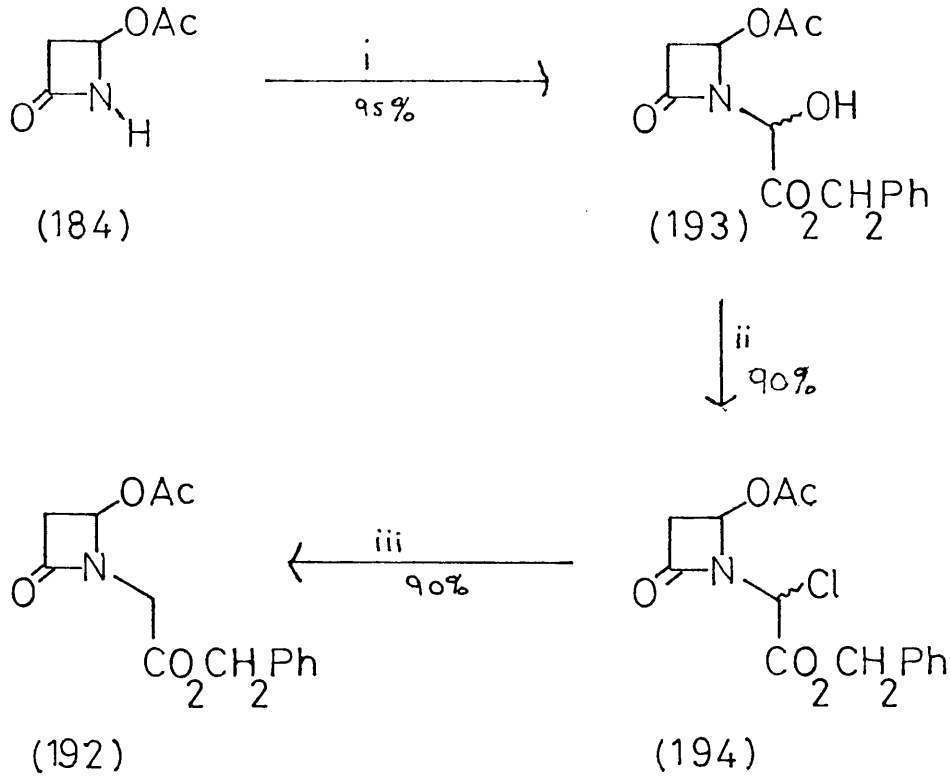
Another potential route to compounds of type (188) is via C-phosphorylation of the N-methylene group in N-(alkoxycarbonyl)methyl-azetidin-2-ones of general structure (192).



(192)

All our attempts to prepare (192) (X=OAc) by direct N-alkylation with bromoacetates failed. However, β-lactam (192) (X=OAc) was obtained via the novel route shown in Scheme 26.

Scheme 26 Preparation of Benzyl-2-[(4RS)4-Acetoxy-2-Oxoazetidin-1-yl] Acetate (192)

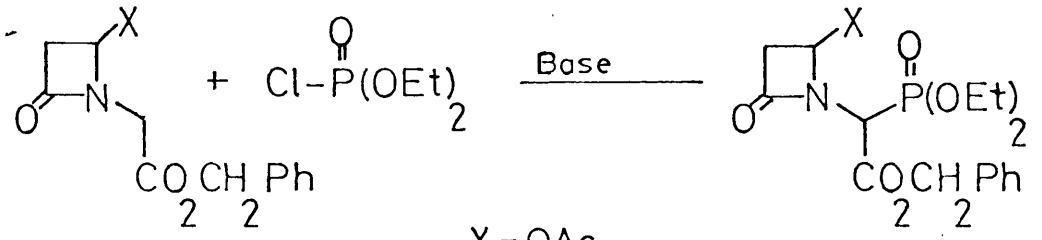


Reagents: (i) $(HO)_2CCO_2CH_2Ph$ (184a), Et_3N (catalytic), THF 20°C, 18 hours; (ii) $SOCl_2$, 2,6-lutidine, THF, -25-0°C, 18 hours; (iii) $^{n}Bu_3SnH$, C_6H_4, AIBN (1 mole %), 80°C, 3 hours.

Thus coupling of 4-acetoxyazetidin-2-one (184) with benzyl glyoxylate afforded the adduct (193) as an oily mixture of diastereoisomers (i.r.: 3600-3100, OH, 1790 and 1780; β-lactam and ester carbonyls: H^1-n.m.r. showed signals at δ=6.10 and 5.95 for H4) in 95% yield. Treatment of alcohol (193) with thionyl chloride at -25°C gave, after flash chromatography on silica, a quantitative yield of the chloride (194). H^1-n.m.r. showed a marked downfield shift in the signal for H4, δ=6.3 in (194), 6.10 and 5.95 in (193), also a shift of 0.6 ppm was observed for the methine proton [δ=6.10 in (194) *vs.* 5.5 and 5.4 in (193)], indicating the incorporation of a strongly electron withdrawing functionality. Dehalogenation of (194) was accomplished by reaction with tri-n-butyltin hydride in refluxing benzene giving (192) as an oil in nearly quantitative yield after chromatography. The H^1-n.m.r. of (192) showed the N-methylene protons as an AB quartet centered on δ=4.0 with J=16.2 Hz. The 4-phenylthio derivative (192) [X=SPh] was prepared, by N-alkylation with benzylbromoacetate, in 80% yield by a literature procedure.[88]

Functionalisation of the N-methylene group in compounds of type (192) is a well documented process and has been achieved by a variety of reagents, for example, carbon dioxide,[89] acyl halides[90] and alkyl chloroformates.[91] Therefore it seemed reasonable to attempt a C-phosphorylation. Accordingly we investigated the following reaction.

Quenching of the anion of (192), formed by treatment with the strong base lithium hexamethyldisilazide, with phosphorochloridate (195) failed to give β-lactam products corresponding to (188), β-lactam cleavage being the only reaction as judged by spectroscopic methods.

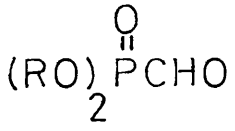


(192) (195) (188)

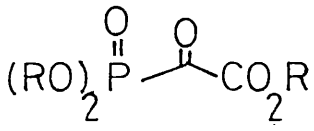
The failure of N-alkylation methods to give the acyclic β-lactam (188) led us to consider the viability of N-acylation as a potential route to the required reterosynthetic intermediate (188) and its derivatives.

6.0.4 N-Acylation of Azetidin-2-ones

The acylating systems required for reaction with 4-acetoxy-azetidin-2-one, to give analogues of β-lactam (188), were the phosphonoformate (196) and the 2-oxophosphonomalonate (197).



(196)

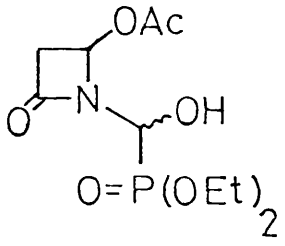


(197)

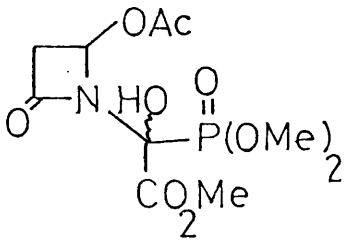
The novel phosphonoformate (196) was obtained by ozonolysis of diethylvinylphosphonate after a reductive work up (sodium metabisulphite). This substance was extremely air sensitive and consequently analytical data was not obtained, but H^1-n.m.r. showed a signal at δ=9.25 attributable to the aldehyde proton and i.r. showed an absorption at 1740 cm^{-1} corresponding to the carbonyl stretch of aldehydes.

Oxophosphonomalonate (197), a new reagent, was prepared utilising a procedure devised by Merck chemists for 2-oxodiethylmalonate.[92] Thus treatment of trimethylphosphonoacetate with powdered selenium dioxide in refluxing xylene afforded oxophosphonomalonate (197) in 98% yield after re-esterification with diazomethane. H^1-n.m.r. of (197) showed only signals corresponding $\overset{O}{\overset{\|}{P}}(OMe)_2$ and CO_2Me groups. I.r. had absorptions at 3600-3100 and 1750 cm^{-1}, the former indicating that (197) was partially hydrated. This compound is an interesting new reagent, the potential of which is being investigated in these laboratories.

Reaction of (196) and (197) with 4-acetoxyazetidin-2-one under the conditions shown in Scheme 26 failed to produce the required β-lactams (198) and (199).



(198)

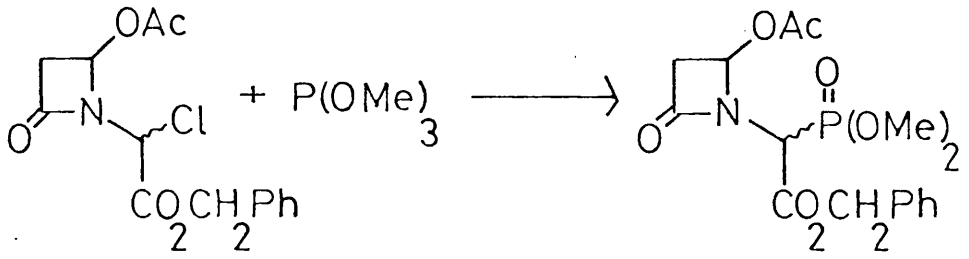


(199)

Also, refluxing (196) or (197) with the β-lactam in benzene, under Dean-Stark conditions, did not lead to the required reactions, starting materials being recovered.

We were successful, however, in carrying out an Arbusov reaction of (194) with refluxing trimethylphosphite, isolating benzyl-(2RS)-2-[(4RS)-4-acetoxy-2-oxazetidin-1-yl]-2-dimethylphosphonoacetate (200) in 35-40% yield after chromatography on silica.

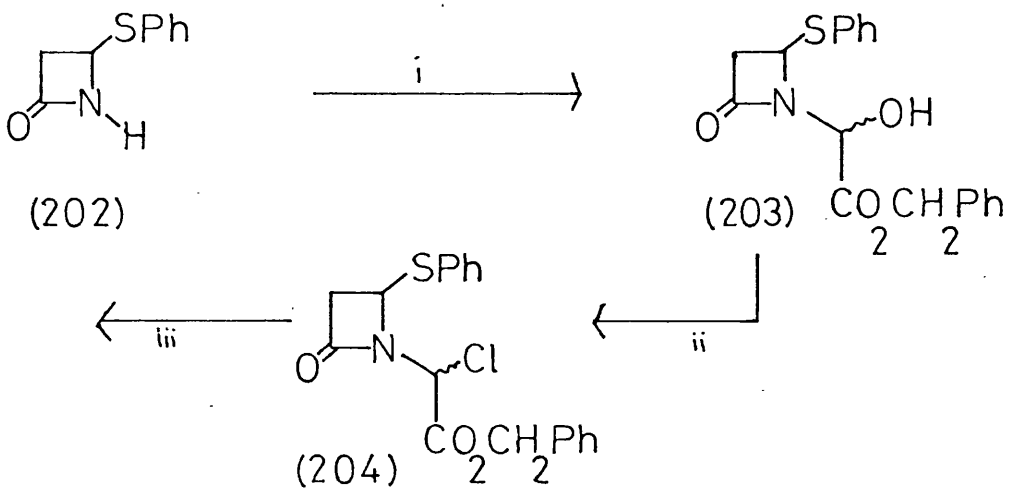
This compound gave the correct elemental analysis and had a β-lactam stretching frequency of 1780 cm^{-1} in the i.r. Also, strong



(194) (200)

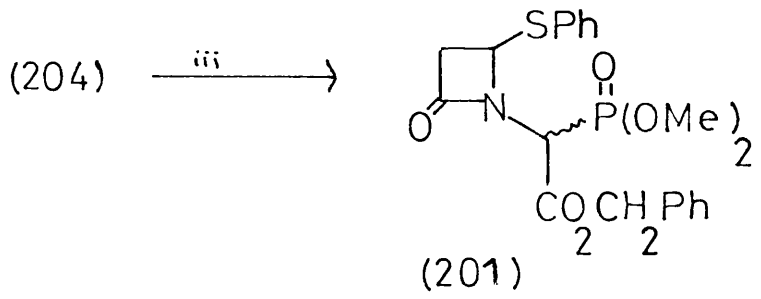
absorptions at 1260 and 1060 cm^{-1} for the P=O and POMe groups respectively were noted. H^1-n.m.r. indicated the diastereoisomeric nature of this compound, with signals corresponding to H4 at δ=6.45 and 6.22 [cf. 6.3 for (194)] and the CHP=O signal at δ=5.98 which appears as a doublet with J=24.6 Hz collapsing to a broad singlet on P^{31}-decoupling. The 4-phenylthio analogue (201) was prepared (Scheme 27) from 4-phenylthioazetidin-2-one (202). This compound showed a β-lactam carbonyl absorption at 1785 cm^{-1} in the i.r. The H^1-n.m.r. spectrum had the H4-signal and the methine proton at δ=5.1 and 4.8 respectively.

Scheme 27 Preparation of Benzyl-(2RS)-2-[(4RS)-4-Phenylthio-2-Oxoazetidin-1-yl]-2-Dimethyl-phosphonoacetate (201)



(202) (203) (204)

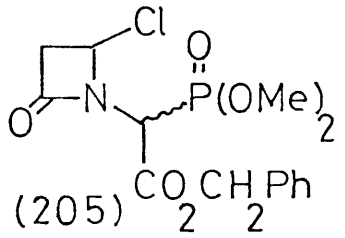
Scheme 27 continued.



Reagents: (i) $(HO)_2CCO_2CH_2Ph$, Et_3N (catalytic), THF, 20°C, 18 hours; (ii) $SOCl_2$, 2,6-lutidine, THF, -25-0°C, 18 hours; (iii) $P(OMe)_3$, Δ, 4 hours.

The latter signal occurred as two sets of doublets (diastereoisomers) with J=13.3 Hz, collapsing to two singlets on P^{31}-decoupling. Elemental analysis was commensurate with the molecular formula.

Also prepared in this series was the 4-chloro derivative (205) by reaction of (201) with chlorine at -70°C.



Although this derivative was unstable to chromatography on silica or neutral alumina, spectroscopic data indicated its formation. This is summarised below for the main spectral features.

Chemical ionisation mass spectroscopy (ammonia) showed molecular ions at m/e 361 and 363 with the required ratio of 3:1 for Cl^{35} and Cl^{37}. This data, therefore, seems to support the formation of a chloro derivative of probable structure (205).

H^1-n.m.r.

Compound	H4	H3	NCHR
201	5.1	3,20	4.78
205	6.0 5.85	3.46	4.84

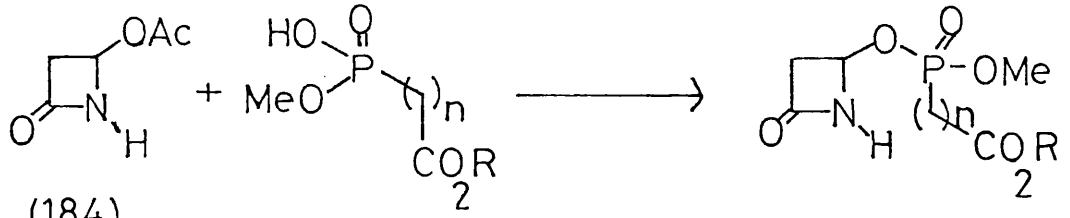
i.r. β-lactam C=O

Compound	cm^{-1}
201	1785
205	1795

The stage was now apparently set for mono-deprotection of the phosphorus esters followed by ring closure to give the target β-lactam (1). This is discussed in section 6.1.0 below.

6.0.5 Path b : Intermolecular Displacement at the 4-Position of an Appropriately Substituted Azetidin-2-one

Displacement of the acetate functionality from 4-acetoxyazetidin-2-one (184) is a well established reaction in β-lactam chemistry for the synthesis of penicillin and cephalosporin analogues.[93,94] Therefore we decided to investigate nucleophilic displacement of acetate with phosphonic acid nucleophiles according to the general scheme below.



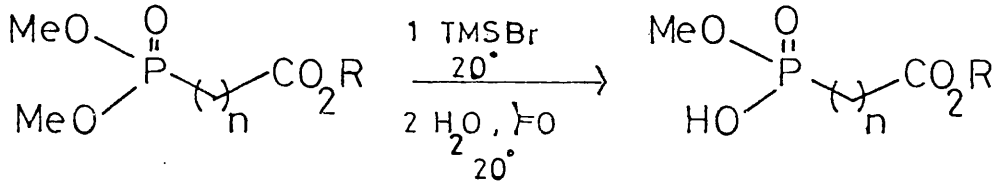
(184) (206) n=1 (207) n=2 (208) n=1 (209) n=2

Ring closure of (208) and (209) would then be accomplished by standard methods, e.g. diazo exchange[86] (tosyl azide, followed by carbene insertion[87]), giving the target (1). In order to achieve this objective monoalkylphosphonic acids were required [e.g. (206)

and (207)] and consequently an investigation into the feasibility of their preparation was undertaken.

6.0.6 Monodeprotection of Phosphorus

The problem of suitable deprotection of phosphorus esters in the presence of carboxylic esters has been addressed by a number of groups.[95,96] One approach[96] involved reaction of the phosphonate ester with two equivalents of trimethylsilyl bromide followed by aqueous hydrolysis to give the bis-phosphonic acid in good yield. Reaction conditions were mild and other functional groups were reported to be relatively inert. We have established that this methodology is appropriate for the monodeprotection at phosphorus, using one equivalent of trimethylsilyl bromide followed by aqueous hydrolysis. Thus:-

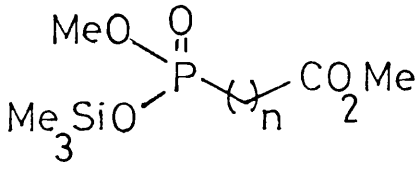


(210) n = 1
(211) n = 2[93]

(206) n = 1
(207) n = 2

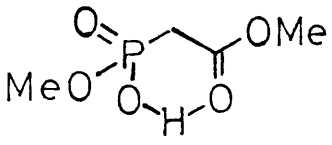
Formation of the intermediate monotrimethylsilyloxyphosphonate (212) is best achieved in four hours using dichloromethane or chloroform as solvent with one equivalent of trimethylsilyl bromide under an inert atmosphere.

This reaction was conveniently monitored by H^1-n.m.r. spectroscopy, the formation of methyl bromide (δ 2.68) being complete after 3-4 hours at room temperature, the only other notable changes in the spectrum being a decrease in intensity of the $\overset{O}{\overset{\|}{P}}(OMe)_2$ signal



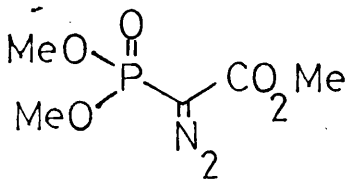
(212) n = 1 or 2

(δ 3.80) and the appearance of $SiOMe_3$ at δ 0.2. Aqueous hydrolysis of the silyloxy esters (212) afforded the phosphonic acids (206) and (207) as extremely hydroscopic oils which have limited stability. The i.r. spectrum of these compounds showed a broad intramolecular POH stretch from 3650 to 2500 cm^{-1} with the ester carbonyl at 1740 cm^{-1}. H^1-n.m.r. of these monophosphonic acids showed a broad, D_2O exchangable, signal at ca. δ 8.20. This value is variable, presumably depending on the water content of the sample. A molecular ion was not detected. Interestingly, the methylene protons of (206) appear as two sets of doublets centered on δ 3.05. This may be due to the formation of a strong intramolecular hydrogen bond causing the methylene protons to become non-equivalent.

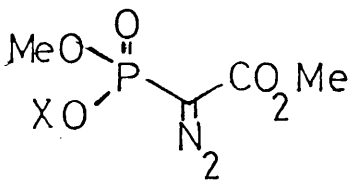


The spectrum does not change on recording in d^6-DMSO, and heating the sample initiates decomposition as judged by the increase in the number of signals observed.

This methodology was also applied to the diazophosphoacetate (213).



(213)



(214) X = H

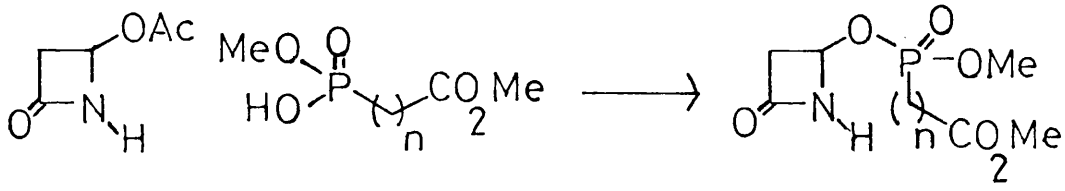
(215) X = K^+

The diazophosphonic acid (214) obtained in 90% yield after aqueous hydrolysis. I.r. spectroscopy showed that the diazo group had survived the reaction conditions (2140 cm^{-1}) indicating that acid catalysed decomposition of the diazo functionality had not taken place. This result is interesting, as the phosphonic acids are relatively strong (pKa 2.4) and one might expect decomposition. The H^1-n.m.r. showed a broad exchangable (D_2O) signal at δ 8.5 possibly due to the POH group. Treatment of (214) with aqueous potassium hydroxide, until the resulting pH of the aqueous solution was 7, followed by freeze drying afforded the potassium salt (215). The spectral data for this compound showed little change from that recorded for (214) except the loss of the broad POH signals in the i.r. and H^1-n.m.r.

Having successfully achieved a route to monophosphonic acids their intermolecular displacement of acetate from 4-acetoxy-azetidin-2-one (184) was studied.

6.0.7 Reaction of Phosphonic Acids (206) and (207) with 4-Acetoxyazetidin-2-one (184)

We have examined the displacement of the 4-acetate with (206) and (207) under a variety of conditions (Table 2). The general reaction is as follows:



(184) (206)n=1 (207)n=2 (216)n=1 (217)n=2

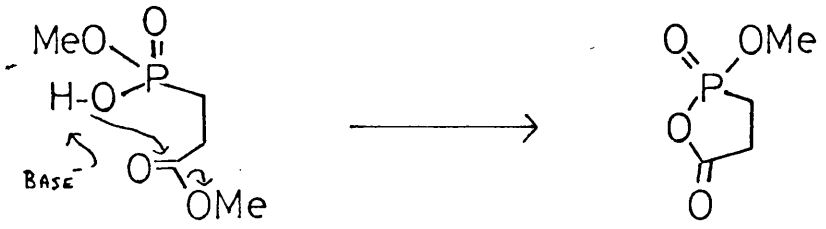
TABLE 2

Reaction of Phosphonic Acids (206) and (207 with 4-Acetoxyazetidin-2-one (184)

Reagent	Solvent	Temperature °C	Time (hs)	Products
KH, 18-c-6	THF	25	16	β-lactam cleavage
$NaHCO_3$, 15-c-5	THF	25	16	" "
DBU	THF/H_2O	25	16	starting materials
Ag_2CO_3	H_2O	25	16	" "
Cu_2CO_3[98]	H_2O	25	16	" "
K_2CO_3	H_2O	25	16	" "
K_2CO_3	DMF	25 then 80	16	β-lactam cleavage
KOH, $^nBu_4N^-Br^+$ [83]	THF	25	16	β-lactam (217)
$Zn(OAc)_2H_2O$[99]	THF	60	16	starting materials
Et_3N	DCM	25 then 40	16	" "

As may be seen from Table 2 the phosphonic acid (206) failed to react in the desired manner, this possibly being due to the equilibrium established in this reaction lying far over to the side of the starting materials. The β-lactam (217) was formed in small amounts using phase transfer conditions.[83] The presence of this compound was indicated by spectroscopic measurements. I.r. spectroscopy showed the β-lactam carbonyl at 1770 [cf. 1790 in (184)], H^1-n.m.r. had a broad signal at δ 7.3 attributable to the NH proton and a doublet of doublets at δ 5.06, this being in the range observed for the H5 proton of oxapenams.[100] Also observed in this spectrum were a doublet at δ 3.76 [$\overset{O}{\overset{\|}{P}}(OMe)_2$] and a singlet at δ 3.72 [CO_2Me] together with a complex group of signals from δ 3.1-1.2 corresponding to H3 and $\overset{O}{\overset{\|}{P}}(\underline{CH_2})_2CO_2R$. The most conclusive evidence for the formation of (217) was the mass spectrum of the compound isolated after chromatography on silica. This showed a peak at m/e 251 corresponding to the molecular ion for (217). Accurate mass determination on this peak gave a value of 251.0670, required 251.0559 (instrument had a resolution of 300 ppm with 10% error in manual peak matching). The base peak was at m/e 209 corresponding to loss of ketone. The above evidence pointed to the formation of the novel β-lactam (217) in very low yield (< 5%). However, this reaction was not reproducible and (217) was never obtained in adequate quantity for further studies. This may be due, in part, to the phosphonic acid (207), as under certain of the reaction conditions employed (207) may lactonise although the lactone (218) was never isolated.

Some evidence was obtained for the formation of (218); H^1-n.m.r. indicated the presence of methanol (δ 3.48) and a corresponding decrease in intensity of the methoxycarbonyl signal; i.r. analysis



(207) (218)

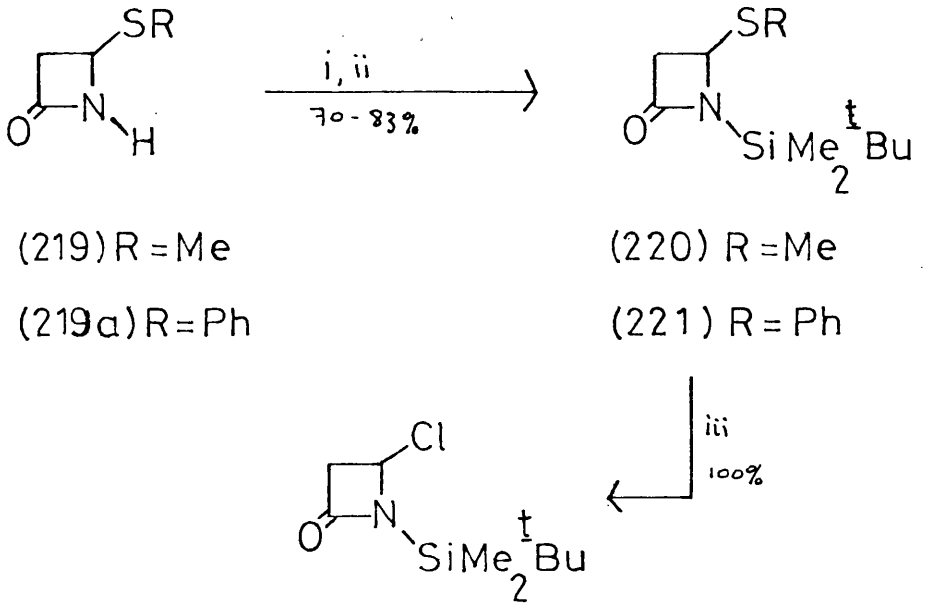
of the reaction mixture showed a new carbonyl at 1740 cm^{-1}, indicative of an anhydride type of structure. Russian workers have synthesised similar compounds but no spectral data were reported.[101] It is also of interest that the phosphonic acid (206) slowly de-esterified on standing at room temperature. This was conveniently monitored by n.m.r. Alternative routes to β-lactams of type (216) and (217) were therefore investigated and are discussed below.

6.0.8 Preparation of (1RS) 1-^{t}Butyldimethylsilyl-(4RS)-4-chloroazetidin-2-one and Reaction with Silver Salts

Suitably substituted 4-chloroazetidin-2-ones are valuable reactive intermediates and have found many applications in β-lactam chemistry.[93,94] The parent 4-chloroazetidin-2-one itself has not been isolated but chlorinolysis of 1 - or 3-substituted-4-alkyl- or -arylthioazetidin-2-ones provides a mild convenient route to these derivatives.[31, 102] Utilising this approach we have synthesised the novel 1-^{t}butyldimethylsilyl-4-methylthio (220) or phenylthio-azetidin-2-one (221) according to Scheme 28.

This treatment of 4-methylthio- or 4-phenylthioazetidin-2-one[5] with ^{n}butyllithium followed by quenching of the lithium salt with ^{t}butyldimethylsilylchloride afforded the N-silylazetidin-2-ones (220) and (221) in 70% and 84% yield after chromatography on silica.

Scheme 28 Preparation of (1RS)-1-^{t}Butyldimethyl-silyl-(4RS)4-Chloroazetidin-2-one (222)



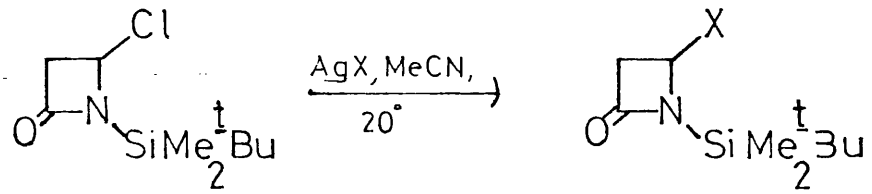
(222)

Reagents: (i) ^{n}BuLi, THF, -78°C, 1 hour; (ii) ^{t}BuMe$_2$SiCl, THF, -78-0°C, 18 hours; (iii) Cl_2, DCM, -78-0°C.

Spectroscopic data, elemental analysis and high resolution mass measurement were in accord with the structures shown. Chlorinolysis of (220) and (221) in dichloromethane produced, after work up, a yellow oil whose i.r. spectrum showed a carbonyl at 1780 cm^{-1} [β-lactam C=O in (221) 1730 cm^{-1}]. H^1-n.m.r. of this substnace showed a doublet of doublets at δ 5.60 due to H4 [H4 in (221) δ 4.85]. In the C^{13} n.m.r. spectrum a doublet at 64.51 ppm corresponded to C4 [C4 in (221) 54.75 ppm]. The mass spectrum has $M^{+}-1$ peaks at m/e 318 and 320 in a ratio of 3:1 indicating the presence of chlorine. The compound was not stable over an extended period of time, hence neither accurate mass measurement nor elemental analysis were obtained.

The data presented above strongly suggests the formation of the 4-chloroazetidin-2-one (222).

In order to demonstrate the utility of (222) we treated this compound with silver acetate and silver isothiocyanate to displace chloride by acetate or isothiocyanate. Reaction of (222) with suspensions of silver acetate or silver isothiocyanate in dry acetonitrile at room temperature afforded β-lactams (223) and (224) in 30% yield after chromatography on silica.



(222)

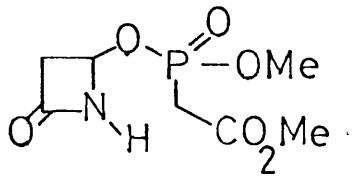
(223) X=OAc

(224) X=SCN

The acetate methyl group of (223) appeared at δ 2.08 [cf. 2.10 in (184)], H4 in (223) came at δ 6.0 [H4 in (184) δ 5.81]. The mass spectrum of (223) showed an M^++1 ion at m/e 244.

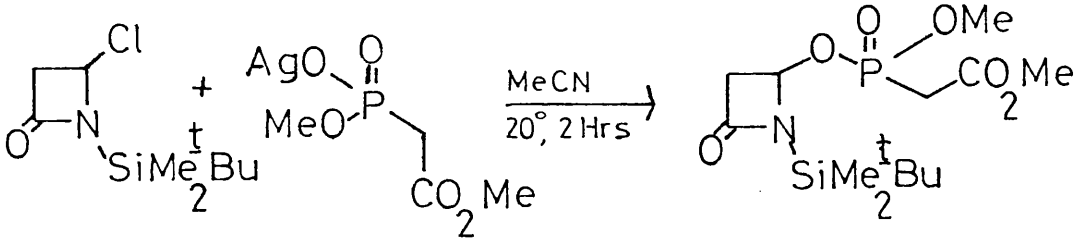
Due to the ambident nature of the isothiocyanate nucleophile one could expect, in theory, attack by either sulphur or nitrogen. However, in this case spectroscopic data (i.r.) showed the presence of an isothiocyanate group (2080 cm^{-1}). With the β-lactam carbonyl at 1770 cm^{-1}, the H4 signal in the H^1-n.m.r. spectrum appeared at δ 5.15 [cf. H4 in (46) δ 5.60]. High resolution mass measurement was in agreement with the proposed structure (224). This reaction indicated that heteronucleophilic displacement of chloride is possible when the azetidin-2-one is N-protected. The product (224) offered interesting possibilities for further elaboration to cephalosporin analogues but was not further explored in the programme.

We now went on to examine this approach as a method of synthesising β-lactams of type (216).



(216)

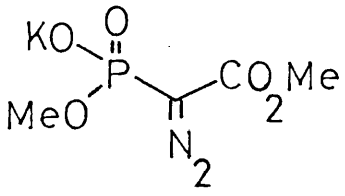
The silver salt of the monophosphonic acid (206) was prepared by adding a chloroform solution of (206) to a suspension of silver oxide in chloroform at room temperature in the dark. This silver salt was isolated, after filtration of the suspension through celite, as a light sensitive oil. The H^1-n.m.r. spectrum of this oil did not change on deuteration, also the signal at δ 3.05 was a simple doublet as compared with (206). I.r. spectroscopy did not show the broad signal from 3600-2300 cm^{-1} [cf. (206)] and the ester carbonyl was at 1740 cm^{-1}, unfortunately the mass spectrum (e.i.) did not show a mass ion. Proceeding on the assumption that the silver salt had been formed we treated the 4-chloroazetidin-2-one (222) with this oil (225) as follows:-



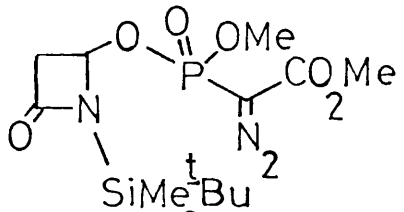
(222) (225) (226)

Removal of the solvent after 2 hours at 20°C afforded a yellow oil. An i.r. spectrum of this crude reaction mixture indicated that the required reaction had occurred [1770 cm^{-1} β-lactam cf. 1730 cm^{-1} and 1740 cm^{-1} in (222)]. However, all attempts at isolation of a

pure sample of (226) failed due to the apparent instability of the substance on a variety of chromatographic media (SiO_2, Al_2O_3). Use of the potassium salt of 2-diazodimethylphosphonoacetate (215), prepared as previously described (section 6.0.6), also failed to give the desired product (227).



(215)



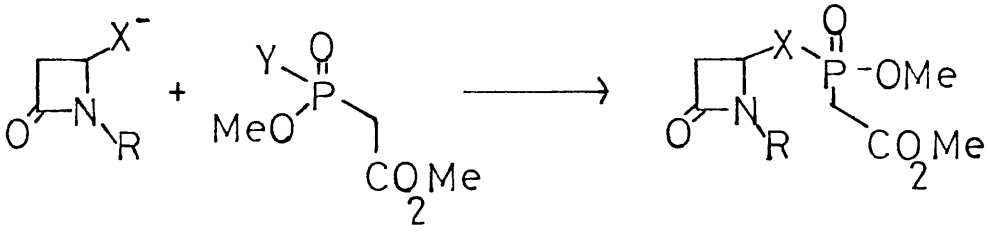
(227)

In spite of the lack of success in our systems β-lactam (222) has significance as a precursor for other analogues (see references 31 and 102).

One final approach to β-lactams (216) and (217) was investigated.

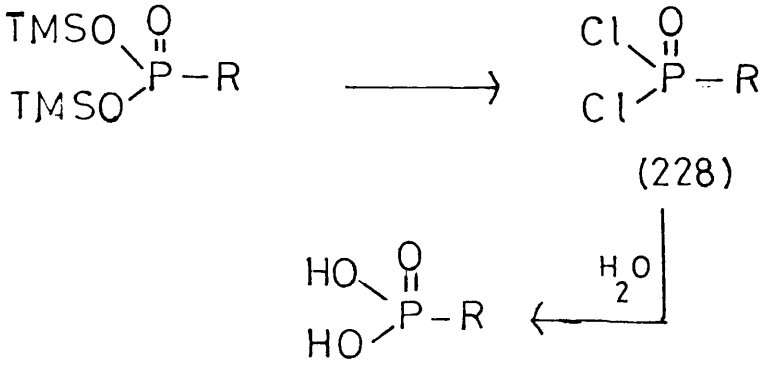
6.0.9 Preparation and Reactions of Thiolate Anions Derived from 4-Benzylthioazetidin-2-ones with Phosphonochloridates

Use of the substituted azetidin-2-one moiety as a nucleophile rather than an electrophile also offers some potential for obtaining analogues of (216) and (217). This statagem is outlined in the general reaction scheme below:



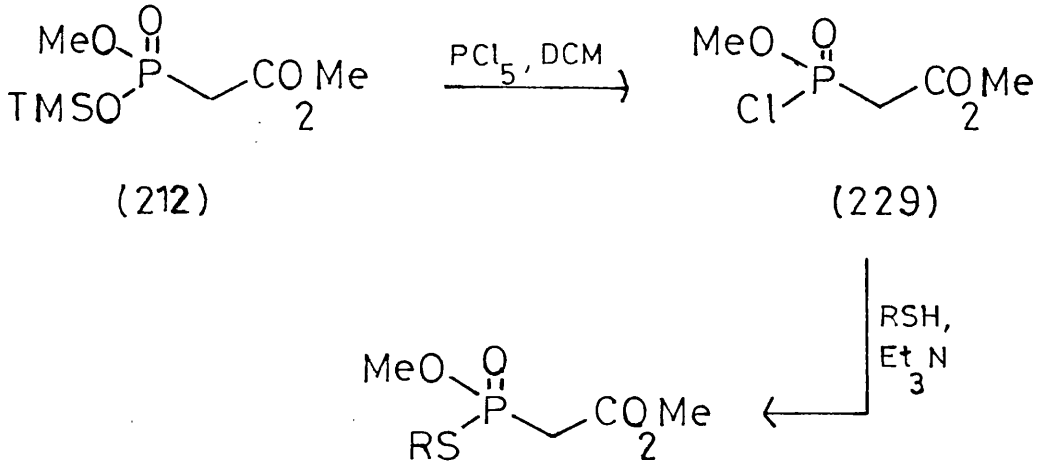
Where X^- and Y are thiolate anions and chlorine or other leaving groups respectively.

Morita *et al.*[103] have recently reported a synthesis of bis-phosphonic acids by treatment of the bis-trimethylsilyloxy esters (formed by reaction of the bis-alkyl phosphonate with two equivalents of trimethylsilyl bromide) with phosphorus pentachloride followed by aqueous hydrolysis.



Morita also notes that the chlorine atoms in (228) may be replaced by nucleophiles but no further comment was made.

We have extended this work.

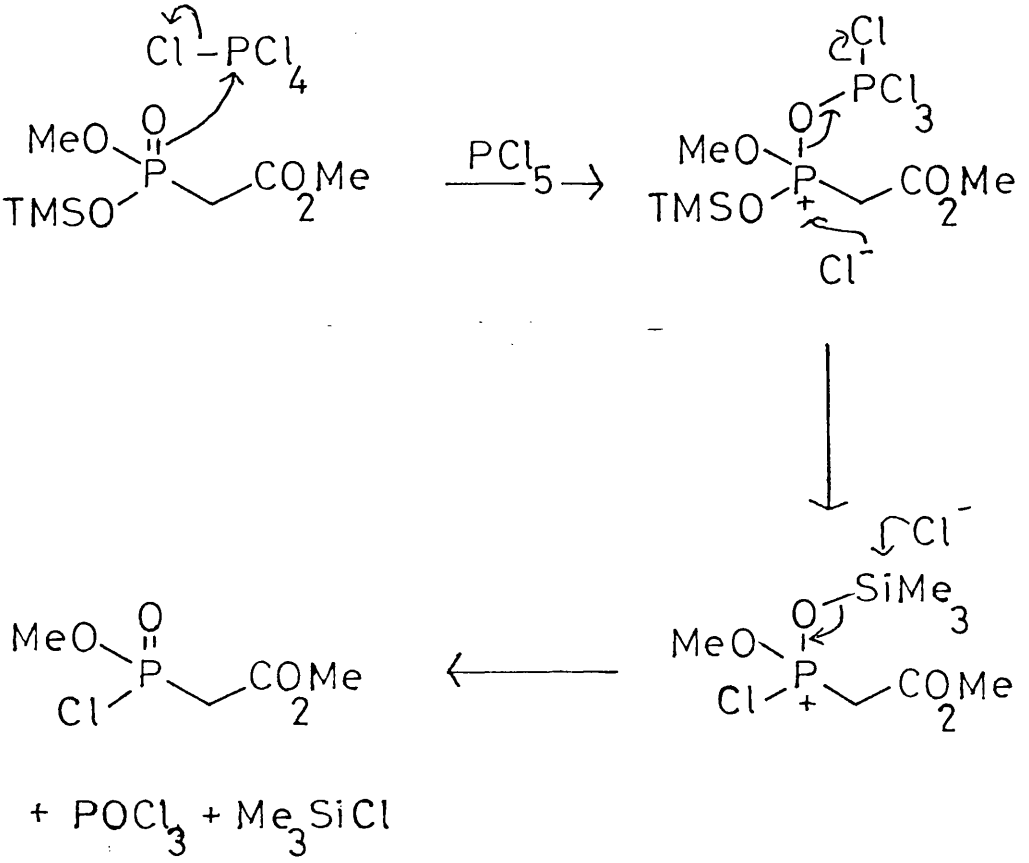


(230) R = Ph

(231) R = CH_2Ph

Treatment of the trimethylsilyloxyphosphonate (212) with one equivalent of phosphorus pentachloride at room temperature resulted in formation of the phosphonochloridate (229). We propose a possible mechanism for this transformation (Scheme 29).

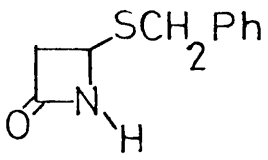
Scheme 29



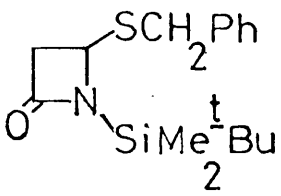
This is presumably analogous to attack of phosphorus pentachloride at a carbonyl group leading to gem dihalides.[104]

Reaction of (229) with thiophenol or benzyl mercaptan in dichloromethane containing triethylamine led to quantitative formation of the thiol esters (230) and (231). These compounds had the required signals in the H^1-n.m.r. spectrum [e.g. (230) δ 7.4 (5H,Ph), 3.88 (3H, POMe), 3.7 (3H,CO_2Me), 3.3 (2H,$\underline{CH_2}CO_2R$)] and gave a high resolution mass measurement in agreement with the proposed structures.

The success of this model study led us to examine the reaction of phosphonochloridate (229) with a 4-thiolate anion derived from 4-benzylthioazetidin-2-one (232).[5]

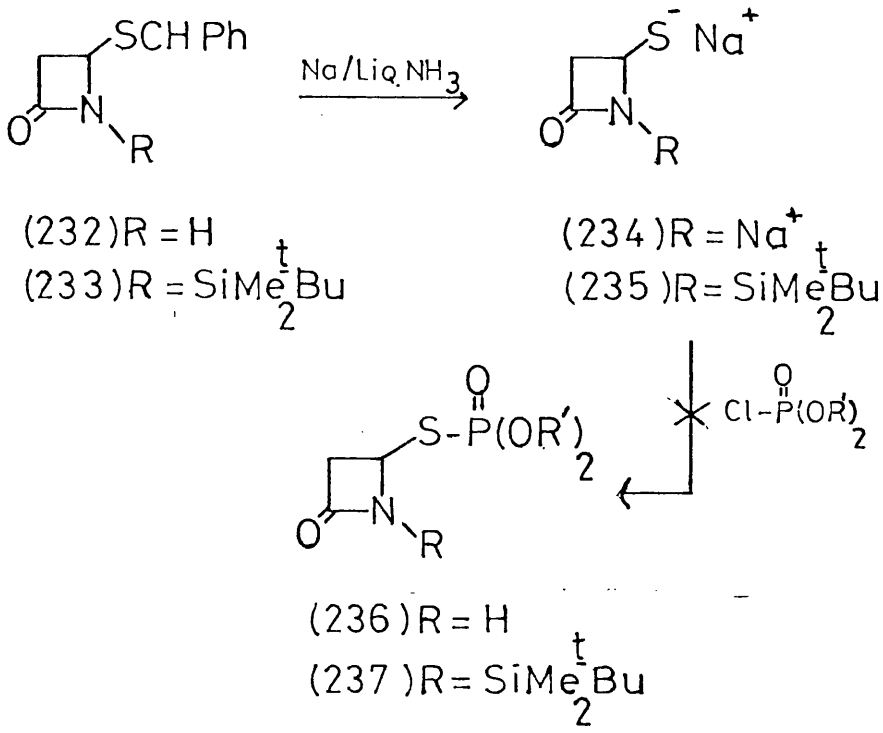


(232)



(233)

Azetidin-2-one (233) was prepared, by treatment of (232) with one equivalent of ^{n}butyllithium followed by ^{t}butyldimethylsilyl chloride, in 83% yield after chromatography on silica. Elemental analysis of (233) was in agreement with the proposed structure. Generation of the 4-thiolate anions of (232) and (233) was carried out according to Claus *et al.*[5] Treatment of β-lactams (232) and (233) with sodium/liquid ammonia followed by removal of the excess ammonia at -20°C under a dry nitrogen stream resulted in isolation of a white powder, presumably the di- and mono-sodium salts (234) and (235). Reaction of (234) and (235) with a dialkylphosphorochloridate did not result in the formation of the desired products (236) and (237). Lactam ring cleavage was noted in the case of (232) and treatment of (233) under these conditions led to a mixture of starting material and β-lactam cleaved products which were not isolated.

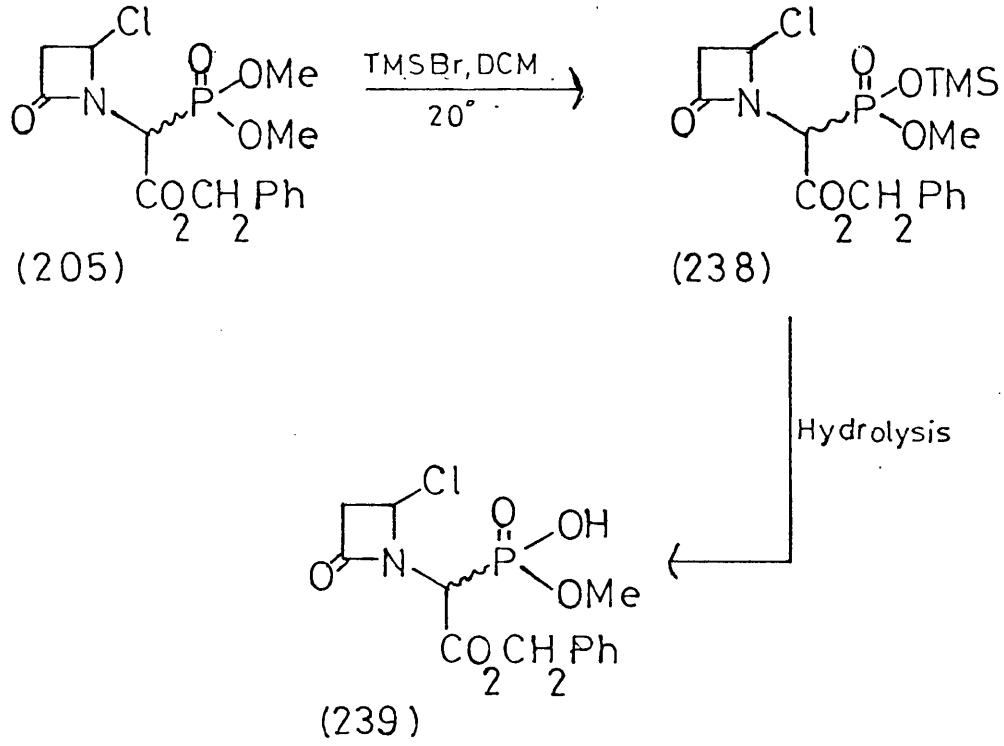


Having successfully achieved monodeprotection at phosphorus we now turned our attention to monodeprotection in the presence of a β-lactam and our results are presented below.

6.1.0 Attempted Monodeprotection of Phosphorus in Benzyl-(2RS)-2-[(4RS)-4-Acetoxy-2-Oxoazetidin-1-yl]-2-Dimethylphosphonoacetate (200) and Benzyl-(2RS)-2-[(4RS)-4-Chloro-2-Oxoaxetidin-1-yl]-2-Dimethyl-phosphonoacetate (205)

As was shown in section 6.0.6, monodeprotection of phosphono-acetates occurred readily under mild conditions. However, it remained to be seen whether or not the β-lactam ring could survive such a procedure. Accordingly the reaction sequence from (205), (Scheme 30), was investigated.

Scheme 30



(205) (238) (239)

This reaction was initially carried out as an n.m.r. experiment in order to observe the formation of the silyloxyphosphonate (238). Addition of one equivalent of trimethylsilyl bromide to a deuteriochloroform solution of (205) under argon in an n.m.r. tube, resulted in a rapid reduction in intensity of the $\overset{O}{\overset{\|}{P}}(OMe)_2$ signals at δ 3.80 and the appearance of a singlet at δ 2.68 due to methyl bromide, also observed were two trimethylsilyl signals, δ 0.45 (Me_3SiBr) and δ 0.40 ($\overset{O}{\overset{\|}{P}}$-$OSiMe_3$). After 60 minutes at 20°C H^1-n.m.r. showed the reaction to be 80% complete with 100% completion after 3-4 hours. I.r. showed the β-lactam carbonyl at 1770, ester at 1730 cm^{-1}, together with P=O and POMe at 1220 and 1160 cm^{-1} respectively. Removal of the solvent *in vacuo* afforded the monosilyloxyphosphonate (238) in quantitative yield. Neither mass ion nor elemental analysis were obtained for this unstable material. The hydrolysis of (238)

to the monophosphonic acid (239) was attempted under a variety of conditions (Table 3).

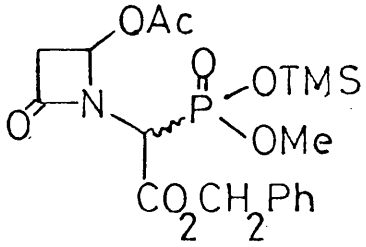
TABLE 3

Attempted Hydrolysis of Silyloxyphosphonate (238) to Monophosphonic Acid (239)

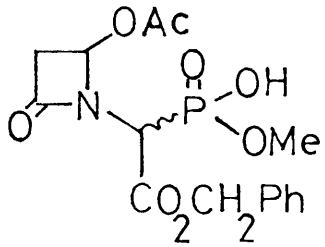
Reagent	Solvent	Temperature °C	Time (hs)	Result
KH, 18-crown-6	DMF/DCM 1:6	25	16	β-lactam cleavage
AgF, $AgBF_4$ 1:1	MeCN	25	2	" "
$^nBu_4N^+F^-$	$CHCl_3$	25	16	" "
$AgBF_4$	MeCN	25	16	" "
$C_6H_{11}NH_2$	H_2O, ⊱O	25	16	" "
$C_6H_5NH_2$	H_2O, ⊱O	25	16	" "

As may be seen from Table 3 we were unsuccessful in our attempts to isolate the phosphonic acid (239) either as the free acid or as cyclohexylamine, monoanilinium or tetra-^{n}butylammonium salts.

The above sequence of reactions was also carried on the 4-acetoxy derivative (200) affording, in the first instance, the monosilyloxyphosphonate (240). However, hydrolysis of (240) under the conditions listed in Table 3 failed to afford β-lactam products corresponding to either (241) or the target compound (1). The exact reason for the failure of the above sequence is not clear, but it may lie in the poor nucleophilicity and high acidity of the phosphonic acids.

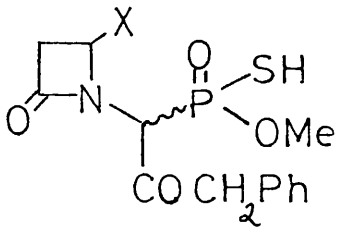


(240)

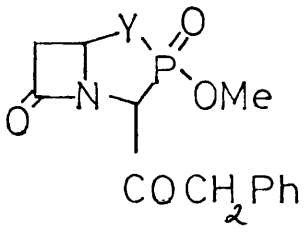


(241)

As sulphur is known[105] to be superior to oxygen in soft-soft nucleophilic displacements our basic stratagem was extended in an attempt to prepare thiophosphonic acids of type (242) ultimately leading to sulphur analogues of the target (1).

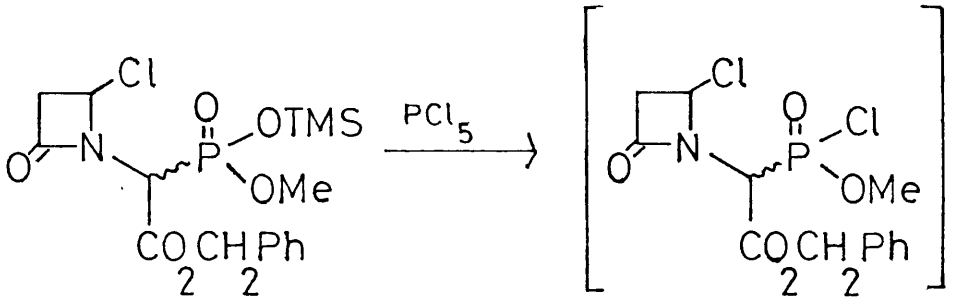


(242) X= OAc or Cl



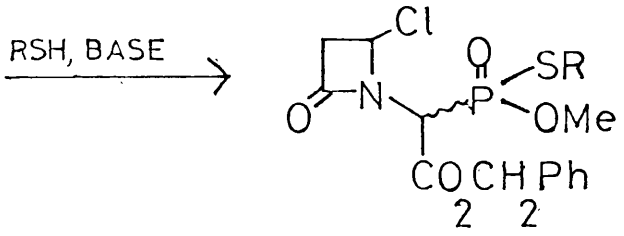
(1) Y = S

The reaction sequence leading to phosphonochloridates, discussed in section 6.0.9, was applied to the β-lactam systems as follows:



(238)

(243)



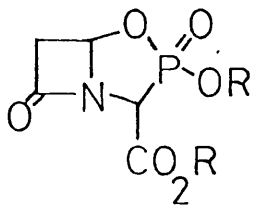
(244) R = CH_2Ph

(245) R = H

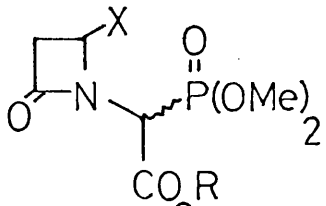
Reaction of silyloxyphosphonate (238) with one equivalent of phosphorus pentachloride under argon at 20°C for one hour led, after removal of the volatile material *in vacuo*, to isolation of an unstable compound which was treated immediately with benzyl mercaptan followed by triethylamine. Spectroscopic examination (i.r.) after 16 hours at 20°C showed β-lactam cleavage, a similar result was obtained with sodium hydrosulphide (NaSH). If the phosphonochloridate (238) has indeed been formed then the resulting molecule (243) has three reasonable sites for nucleophilic attack by sulphur; the β-lactam, 4-chloro substituent and the phosphonochloridate. The possibility, in the case of NaSH, of initial formation of a thiophosphonate followed by β-lactam cleavage also cannot be precluded. The use of hydrogen sulphide gas and hexamethyldisilazane at -25°C was also unsuccessful in producing the desired β-lactam (245).

6.1.1 Summary

This section has been concerned with methods of forming the 1,5-bond in the bicyclic β-lactam (1). Various routes to the immediate monocyclic precursor (182) have been investigated with this compound (188) (X=OAc) being obtained in 40% overall yield.



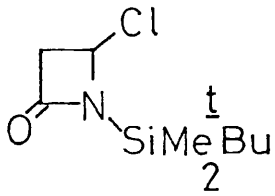
(1)



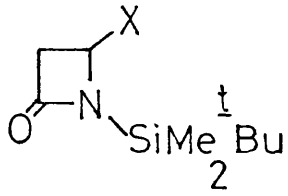
(188) X=OAc,Cl
R=CH_2Ph

Monodeprotection of phosphorus methyl esters was accomplished with trimethylsilyl bromide followed by aqueous hydrolysis. However, the monophosphonic acids were unstable and could not be induced to undergo base or acid catalysed cyclisation to the target (1). Attempts to convert phosphonic acids to monothiophosphonic acids were inconclusive.

A more promising route appeared to be via the novel 4-chloro-azetidin-2-one (222). Model studies with this compound indicated that the 4-chloro substituent was readily replaced by nucleophiles (silver salts) affording the novel azetidin-2-ones (223) and (224).



(222)



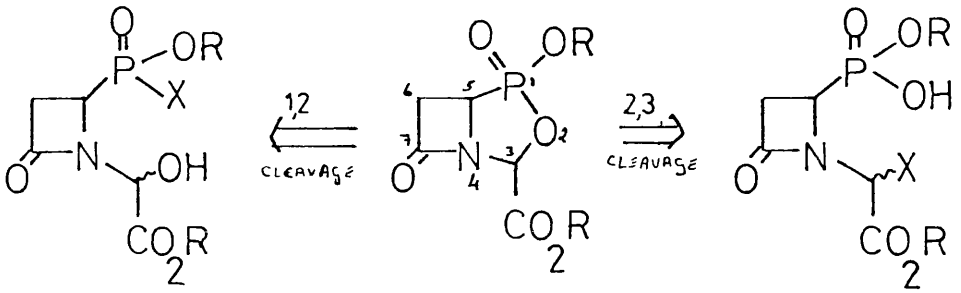
(223) X= OAc
(224) X=SCN

However, after treatment of (222) with silver salts of monophosphonic acids (225) spectroscopic data gave some indication that the required compounds had been formed (226) but the compounds were unstable to chromatography.

Throughout this investigation no evidence what so ever was observed that the target system (1) had been formed.

7.0.0 FORMATION OF THE 2-3 BOND IN β-LACTAM (2)

A possible reterosynthetic pathway involving P(1)-O(2) and O(2)-C(3) bond cleavage is outlined below.

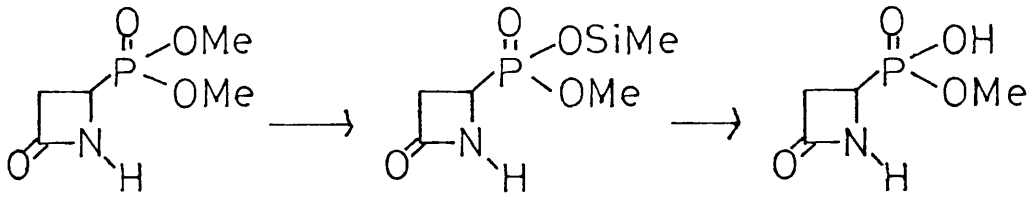


(246) (2) (247)

Therefore we attempted to synthesise compounds of type (246) and (247) where X is a good leaving group, for example, chlorine. As both of these targets required functional group manipulation at phosphorus an investigation of the reactivity of phosphorus at this position in the β-lactam ring was undertaken.

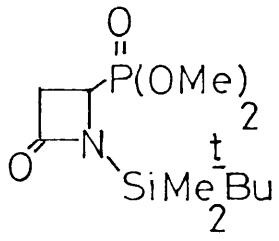
7.0.1 Monodeprotection of Phosphorus

For this study we employed 4-dimethylphosphonoazetidin-2-one (248), a compound first prepared by Claus *et al.*,[5] by an Arbusov reaction of 4-acetoxyazetidin-2-one with trimethylphosphite, subsequently examined in detail by Campbell *et al.*[71] Monodeprotection of phosphorus in azetidin-2-one (248) was attempted via the route previously described (section 6.0.6).



(248) (249) (250)

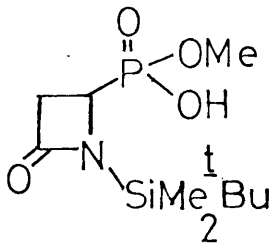
However, treatment of (248) with one equivalent of trimethylsilyl-bromide followed by aqueous hydrolysis resulted in β-lactam cleavage as judged by spectroscopic data. Presumably, this arose because N-silyation is a more facile process in this system than attack at the P-O bond. Thus, hydrogen bromide is produced which, under the hydrolysis conditions, initiates β-lactam cleavage. However, the possibility of the phosphonic acid being formed followed by auto catalytic β-lactam cleavage by this acidic group cannot be precluded. Therefore we prepared the N-^{t}butyldimethylsilyl azetidin-2-one (251), by reaction of (248) with ^{n}butyllithium followed by ^{t}butyldimethyl-silylchloride, in 35% yield after chromatography on silica.



(251)

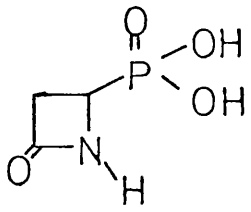
After treatment of (251) with trimethylsilyl bromide followed by hydrolysis an oil was isolated which had the following main spectroscopic features. i.r.: 3600-2400 (broad), 3400, 1770, 1740, 1240 and 1040 cm^{-1}; H^1-n.m.r. (δ values) 3.85 (multiplet, 4H), 3.25 (multiplet, 3H), 0.95, 0.30. The broad peak in the i.r. from 3600-2400 cm^{-1} may be due to an intermolecular OH bond, with the adsorption at 3400 cm^{-1} attributable to NH. The carbonyl peaks at 1770 and 1740 cm^{-1} respectively corresponding to the β-lactam carbonyl in azetidin-2-ones (248) and (251), with P=O and POR being responsible for the bands at 1240 and 1040 cm^{-1}. The H^1-n.m.r. indicated a mixture of β-lactams (250) and (252), as shown by the

integral ratio of the signals at δ 3.85 and δ 3.25 (2:1). Absorptions at 0.95 and 0.30 corresponding to ^{t}BuSi and Me_2Si with markedly reduced intensity. The mass spectrum of this oil showed molecular ions at m/e 279 and 166 for (252) and (250) respectively.



(252)

The conclusion must therefore be that the formation of the mono-phosphonic acid (252) was successful and lactam (250) was presumably formed by auto catalytic removal of the acid labile ^{t}butyldimethyl-silyl group by the phosphonic acid. As judged by H^1-n.m.r. this N-desilylation was ca. 40% complete after 16 hours at room temperature and nearly quantitative after 3 days. Further proof of the formation of (250) and (252) was obtained by treating the mixture with ethereal diazomethane. T.l.c. showed a mixture of fully protected dimethylphosphonates (248) and (251), this being supported by H^1-n.m.r. which showed an N-H signal at δ 7.2 together with an increase in signal intensity of the multiplet at δ 3.8 [$P(OMe)_2$ and H4]. Thus, the above data points strongly to the formation of β-lactam (252) together with variable amounts of (250). It should be noted that the monophosphonic acid (250) appeared to be unstable as only 80% by weight of the material recovered after diazomethane treatment was β-lactam, thus indicating the acid lability of this system. Attempts to prepare the di-acid (253) by treatment of (248) with two equivalents of trimethylsilyl bromide, followed by aqueous hydrolysis, were unsuccessful.



(253)

Having demonstrated that monodeprotection of phosphorus at the 4-position of an azetidin-2-one ring could be achieved we now went on to investigate further functional group manipulation at phosphorus.

7.0.2 Reaction of Silyloxyphosphonate (255) with Phosphorus Pentachloride

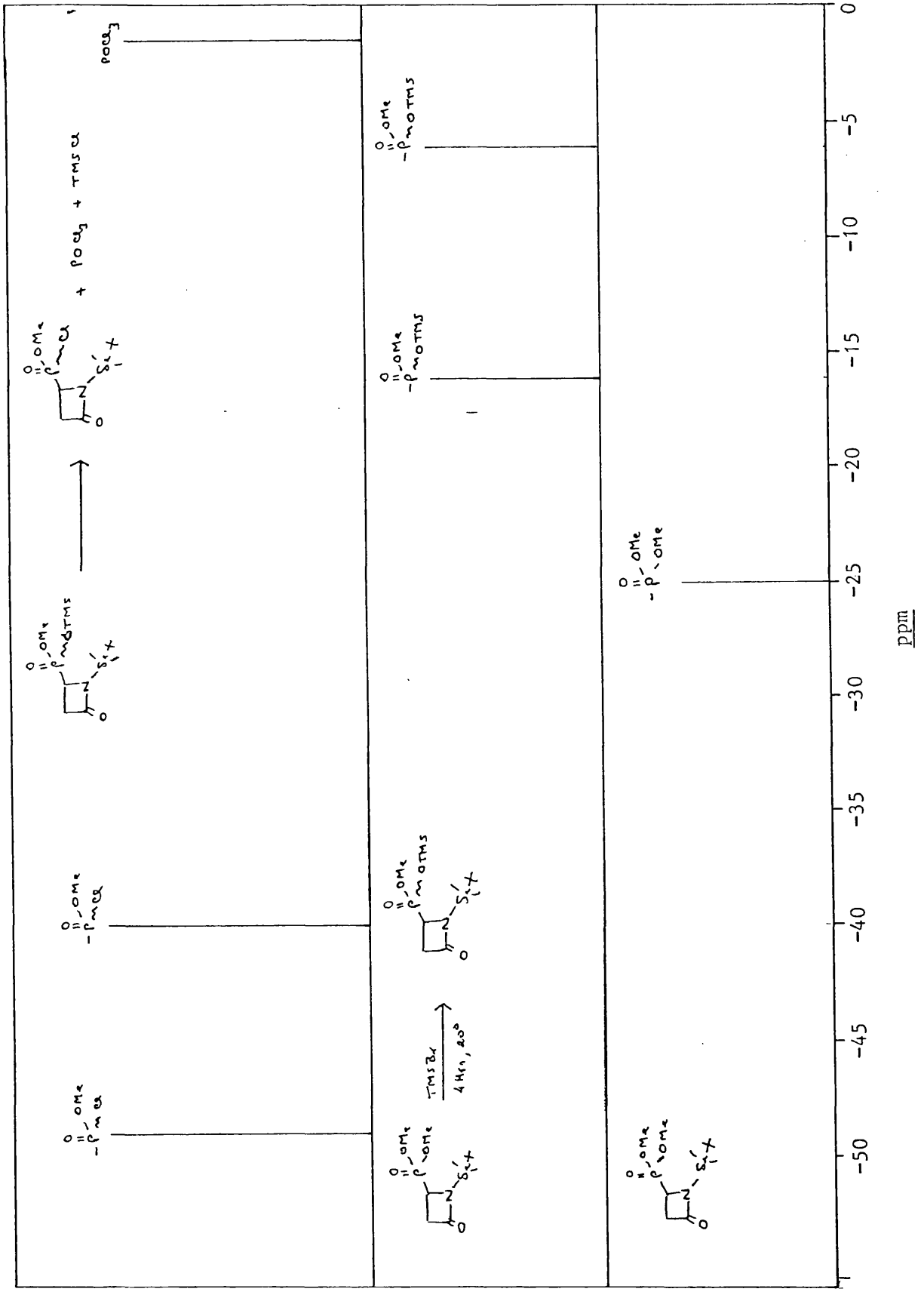
As was shown in section 6.0.9 the reaction of phosphonochloridates with sulphur nucleophiles is relatively facile. We therefore applied this reaction sequence to the β-lactam case shown below:

(251) (254)

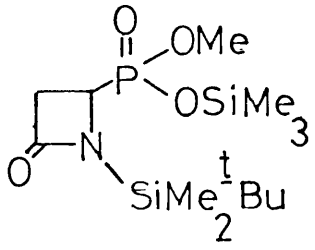
Treatment of (251) with one equivalent of trimethylsilyl bromide for four hours followed by reaction of the silyloxyphosphonate with phosphorus pentachloride led to formation of the phosphonochloridate (254). The course of this reaction may be conveniently monitored by P^{31}-n.m.r. (see spectra on page 90), by observing the formation

P^{31}-N.m.r. Spectra Recorded During Formation of Phosphonochloridate (254)

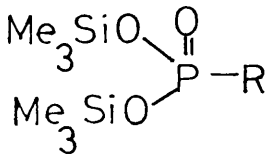
Schematic Representation Only



of phosphorus oxychloride, which is a by-product from this reaction. As may be seen from these spectra two new P^{31} signals at -15.6 and -5.5 ppm (downfield from 88% phosphoric acid) appear after four hours with trimethylsilyl bromide [cf. -25 ppm in (251)]. These signals are presumably due to the intermediate silyloxyphosphonate (255) which is diastereoisomeric in nature, accounting for the two signals observed.



(255)

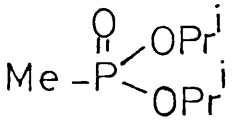
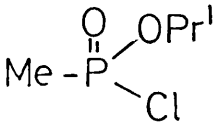
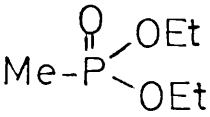
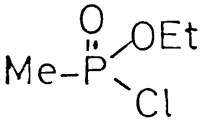
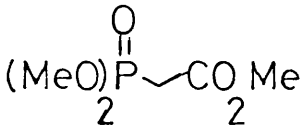
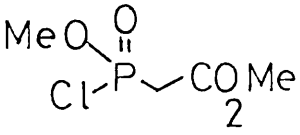


(256)

These figues are in good agreement with those observed by McKenna *et al.*[96] for bis-trimethylsilyloxyphosphonates of type (256). On addition of one equivalent of phosphorus pentachloride new signals were immediately observed, in the P^{31}-n.m.r., at -2.9 ppm, -40 and -48 ppm, these were assigned as follows: -2.9 ppm due to phosphorus oxychloride (lit., -2.8 ppm[106]), -40 and -48 ppm attributable to the diastereoisomeric phosphonochloridate (254). This downfield shift was in agreement with those reported for other alkyl phosphonochloridates (Table 4). I.r. showed that the β-lactam ring had remained intact during this process with absorptions at 1780 (β-lactam C=O), 1300 (P=O) and 1040 cm^{-1} (POMe). P^{31} and H^1-n.m.r. indicated that (254) had been formed in almost quantitative yield.

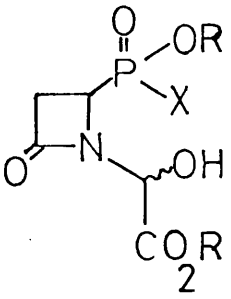
TABLE 4

P^{31} - Chemical Shift in Some Phosphonates and Phosphonochlorides

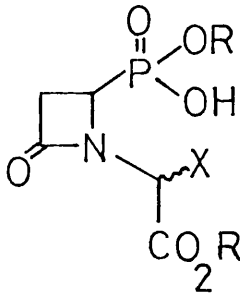
Compound	P^{31}-n.m.r. Chemical Shift (ppm downfield from 88% H_3PO_4)	Reference
	-27.3	107
	-40.1	108
	-30.0	109
	-39.5	109
	-23.0	Section 6.0.9
	-32.9	" "

7.0.3 Synthesis of Monocyclic Precursors to Target (2)

As was mentioned in section 7.0.0, monocyclic β-lactams of general structures (246) and (247) would be desirable as potentially important precursors to target (2).

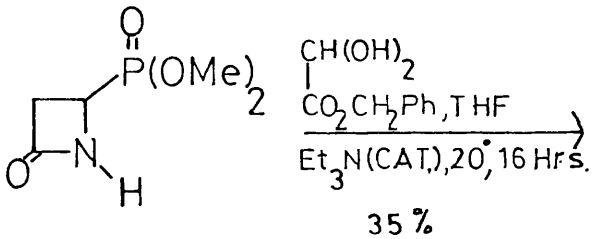


(246)

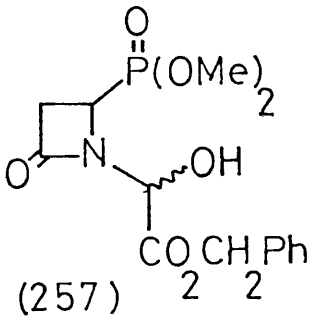


(247)

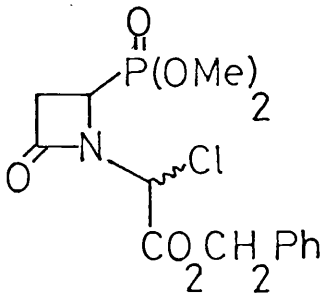
We therefore made recourse to the glyoxylate strategy and prepared the novel β-lactams benzyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-2-hydroxyacetate (257) and benzyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-2-chloroacetate (258) from 4-dimethylphosphonoazetidin-2-one (248) as follows:



(248)

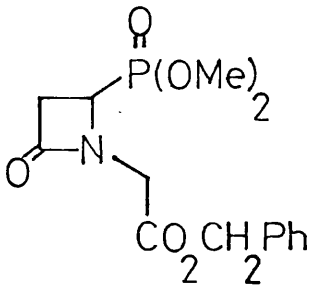


(257)



(258)

Treatment of 4-dimethylphosphonoazetidin-2-one (248) with hydrated benzyl glyoxylate, in the manner previously described (section 6.0.3), afforded the glyoxylate adduct (257) in 35% yield. The formation of this compound was demonstrated by the P^{31}-n.m.r. spectrum which showed signals at -23.4 and -22.6 ppm (downfield from 89% H_3PO_4), indicating its diastereoisomeric nature. The H^1-n.m.r. had peaks at δ 5.84 (broad dd, lost on D_2O exchange) due to the hydroxyl group, δ 5.5 for the methine proton, H4 occurred as a multiplet at δ 4.0 [cf. H4 in (248) δ 3.75]. Mass spectroscopy showed a molecular ion at m/e 344. Elemental analysis was correct for the proposed molecular formula. This strongly suggested the formation of glyoxylate adduct (257). After reaction of (257) with thionyl chloride the signal attributable to the methine proton in the H^1-n.m.r. had moved downfield to δ 6.10 [cf. δ 5.5 in (257)]. The mass spectrum showed molecular ions at m/e 363 and 361 in the ratio 1:3. This evidence suggests the formation of the chloride (258). Unlike the previous examples of these compounds, (258) was not amenable to purification by chromatography on silica. Also prepared, by tin hydride reduction of (258), was the novel β-lactam benzyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]acetate (259).

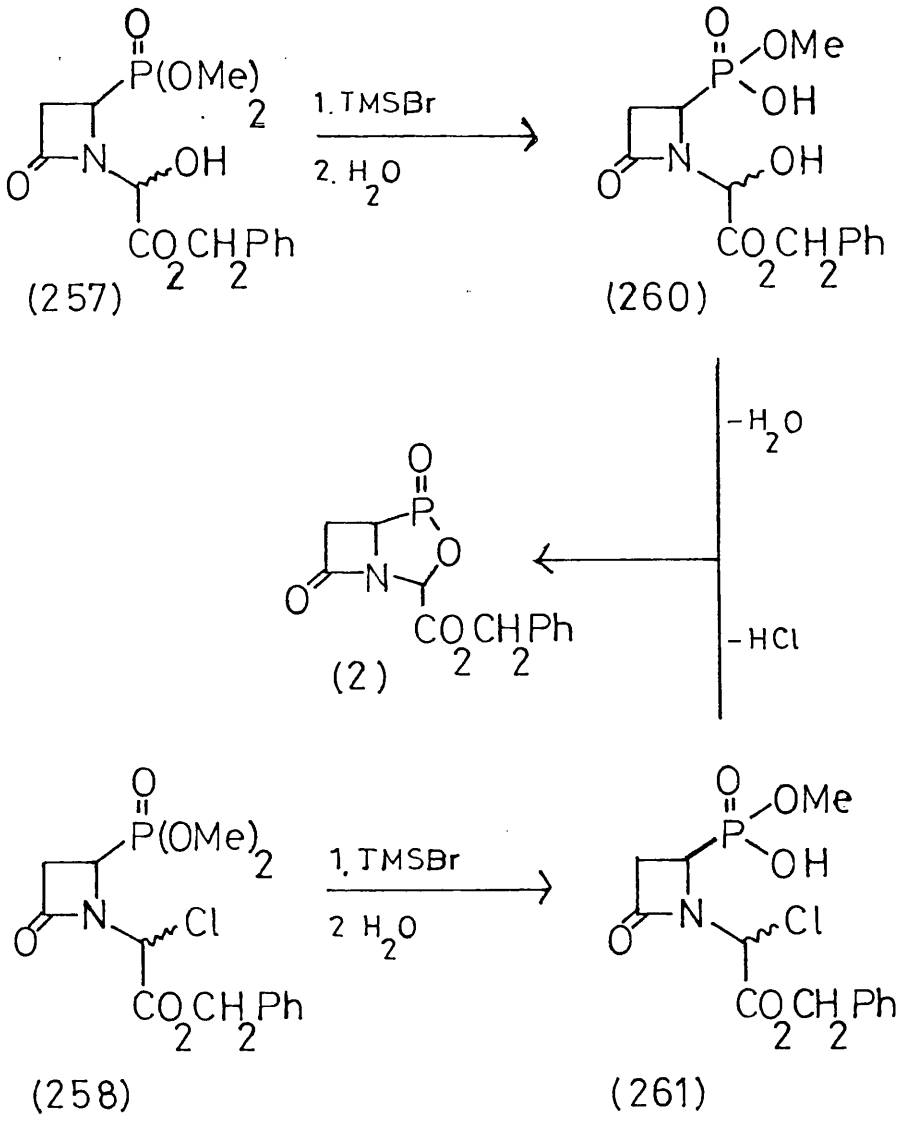


(259)

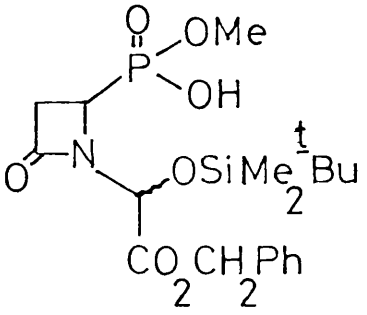
The mass spectrum of (259) showed an M^+-1 ion at m/e 326 and elemental analysis was commensurate with the molecular formula. The H^1-n.m.r. spectrum of this compound had several interesting features and these will be discussed in Appendix I.

With the precursors (257) and (258) to the bicyclic system (2) in hand we now proceeded to investigate their potential in the synthetic routes below (Scheme 31).

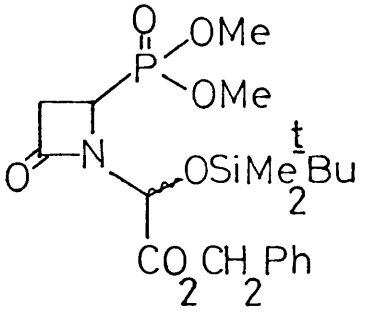
Scheme 31



Reaction of glyoxylate adduct (257) with two equivalents of trimethylsilyl bromide followed by aqueous hydrolysis (pH 7 buffer) was unsuccessful in yielding monophosphonic acid (260), β-lactam cleavage being the only result, as judged by i.r. spectrosocpy. This was presumably due to the formation of hydrogen bromide in the initial silylation step which, under the hydrolysis conditions initiated β-lactam cleavage. Accordingly hydroxyl group protection was necessary. We chose the ^{t}butyldimethylsilyl ether for this purpose as it was anticipated that formation of the monophosphonic acid (262) would initiate acid catalysed decomposition of the silyl ether affording the required β-lactam (260).



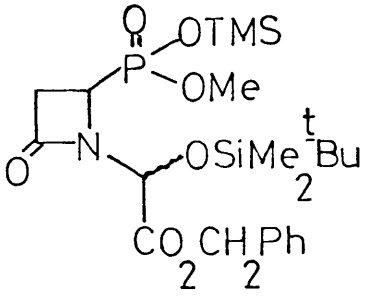
(262)



(263)

Thus treatment of glyoxylate adduct (257) with ^{t}butyldimethylsilyl chloride in the presence of diphenylamine and 4-N,N-diethylamino-pyridine (4-DMAP) gave the silyl ether (263) in almost quantitative yield. The H^1-n.m.r. spectrum of (263) showed no signals at δ 5.84 (due to OH) and the incorporation of $Si^{t}Bu$ (δ 0.98 and 0.95, diastereoisomers) and $SiMe_2$ (δ 0.38 and 0.10, diastereoisomers); i.r. did not show any significant change in β-lactam carbonyl stretching frequency [1770 cm^{-1} in (257) and (263)]. However, the broad band at 3700-2800 cm^{-1} (due to OH) in the spectrum of (257) was not present in the i.r. of (263). No mass ion was observed.

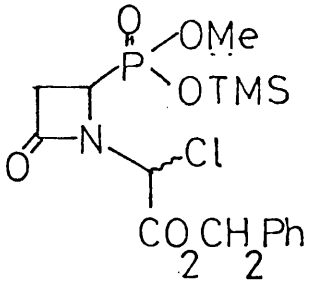
Proceeding on the assumption that ^{t}-butyldimethylsilyl ether (263) had been formed it was treated with one equivalent of trimethylsilyl bromide. The H^1-n.m.r. spectra of the reaction mixture, after 4 hours, indicated that complete reaction had occurred; namely new signals were observed at δ 2.64 (methyl bromide) and δ 0.40 ($POSiMe_3$). A corresponding decrease in intensity of the multiplets at δ 3.80 ($\overset{O}{\overset{\|}{P}}(OMe)_2$ and H4) to 4H was also noted. I.r. showed no appreciable change in the β-lactam carbonyl stretching frequency (1770 cm^{-1}). Again no mass ion was observed with chemical ionisation (NH_3 or isobutene). However, from the available data and previous results it was concluded that the mono-silyloxyphosphonate (264) had been formed in essentially quantitative yield.



(264)

Hydrolysis of (264) to the desired monophosphonic acid (262) under all conditions investigated resulted in β-lactam cleavage (i.r. spectrum), leading to a mixture of polar products which were not separated. The cause is unclear but the high acidity of the phosphonic acid (pKa ∿2) may be the decisive factor in promoting β-lactam cleavage via a retro-glyoxylate reaction followed by acid catalysed decomposition of the resulting azetidin-2-one-4-monophosphonic acid (250), the instability of which has already been demonstrated (section 7.0.1).

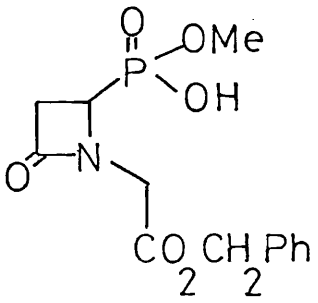
Recourse was therefore made to β-lactam (258), reaction of which with one equivalent of trimethylsilyl bromide followed by treatment with silver carbonate in 10% aqueous acetone led to β-lactam cleavage as judged by i.r. Use of silver tetrafluoroborate on the intermediate silyloxyphosphonate (265) also gave the same result.



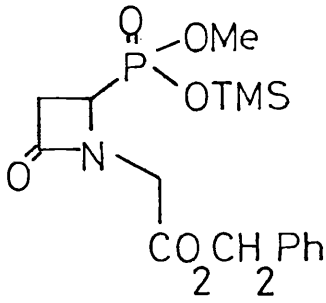
(265)

These reaction sequences were not further investigated.

We also briefly investigated the potential of β-lactam (259) in a route to the target bicyclic β-lactam (3) and this will be treated in more detail in section 8.0.1. This compound was also subjected to our deprotection methodology in order to obtain the monophosphonic acid (266).



(266)



(267)

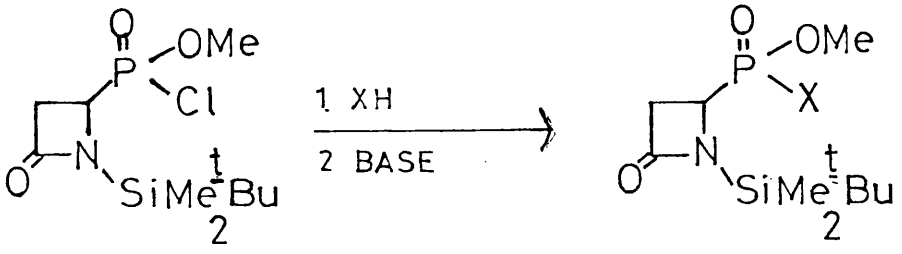
Examination of the H^1-n.m.r. spectrum of the reaction mixture after addition of one equivalent of trimethylsilyl bromide to (259) indicated that formation of the silyloxyphosphonate (267) was complete after ca. 4 hours. Removal of the volatile material

in vacuo followed by dissolution of the residue in D_2O/d^6 acetone afforded monophosphonic acid (266). H^1-n.m.r. spectroscopy pointed to the survival of the β-lactam ring, i.e. the AB system at δ 4.38 and 3.5, due to the N methylene group, was present as was the H4 and $\overset{O}{\overset{\|}{P}}(OMe)_2$ multiplet at δ 4.1-3.7 which simplified on P^{31}-decoupling, H3 appears at δ 3.0 as a complex multiplet. Further proof of this structure was obtained from chemical ionisation mass spectrosocpy (NH_3) which showed m/e 313 (M^+) for monodeuterophosphonic acid (266). The above data therefore strongly suggested the formation of monophosphonic acid (266), thus demonstrating the mildness and chemoselectivity of the deprotection technique.

Some other approaches to the target system (2) were also investigated and are discussed below.

7.0.4 Intermolecular Nucleophilic Displacement at Phosphorus

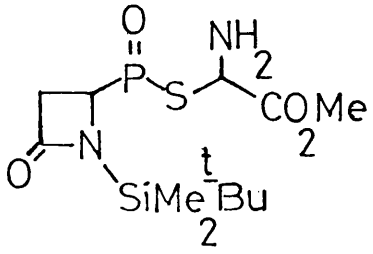
The reaction of phosphonochloridate (254) with nucleophiles was investigated as follows:-



(254) (268)

X=$PhCH_2SH$; $HNSO_2PhMe$; $HSCH(NH_2)CO_2Me$

Cysteine was of interest in this context because if azetidin-2-one (269) could be prepared diazotisation, silyl removal and carbene insertion would lead to the sulphur analogue of (2).

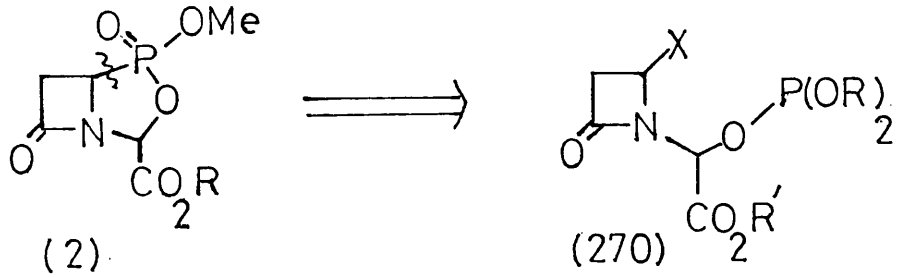


(269)

However, treatment of (254) with either benzylmercaptan or cysteine in the presence of triethylamine failed to produce the monothio esters (268) [X=SCH_2Ph or X=S-$CH(NH_2)CO_2Me$] β-lactam cleavage being the only reaction. The use of sodium ρ-toluenesulphonamide also resulted in β-lactam cleavage. The reason for this lack of reactivity at phosphorus is unclear but the β-lactam ring is obviously the most reactive site in this molecule towards nucleophilic attack. This reaction sequence was not investigated further.

7.0.5 Intramolecular Nucleophilic Displacement of a Leaving Group from the 4-Position of the Azetidin-2-one Ring

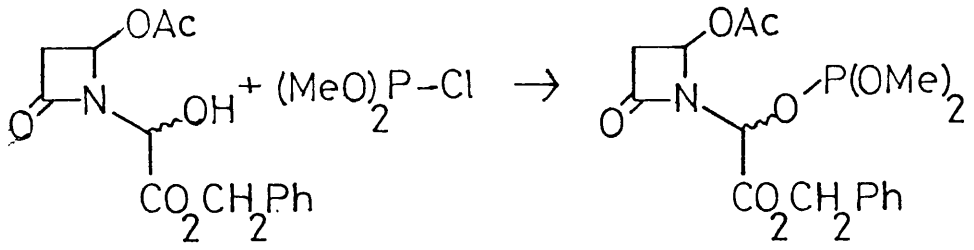
The basic stratagem is outlined in the following retrosynthetic sequence.



(2) (270)

Therefore we undertook a synthesis of β-lactam phosphite (270) [X=OAc, R=Me] as it was anticipated that an intramolecular Arbusov reaction would occur resulting in the target system (2).

One of the standard methods[110] for the preparation of trialkylphosphites is to react phosphorus trichloride with three equivalents of an alcohol in the presence of a suitable base. A variation of this approach was chosen as the synthetic route to (270) [X=OAc, R=Me].

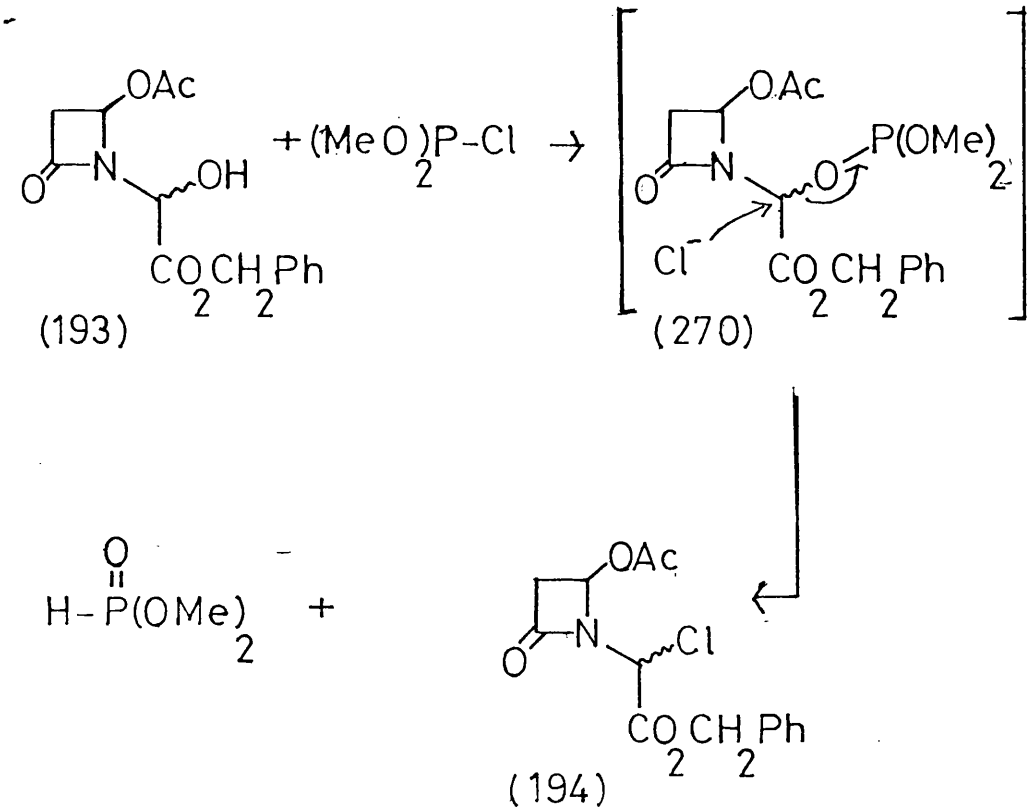


(193) (271) (270)

Dimethylchlorophosphite (271) was synthesised by a literature procedure[111] which involved reaction of trimethylphosphite with phosphorus trichloride in the presence of tetraethylammonium bromide in 70% yield (it should be noted that the distillation temperature should be kept below 40°C as the pot residue may detonate - see Jones *et al.*, Inorg. Chem., 1971, *10*, 1576). Reaction of the glyoxylate adduct (193) with the phosphite (271) in the presence of N,N-diethylaniline in refluxing tetrahydrofuran led, after chromatography on silica, to the isolation of a new β-lactam product. This was shown to be benzyl-(2RS)-2-[(4RS)-4-acetoxy-2-oxoazetidin-2-yl]-2-chloroacetate (194). We propose that the formation of this compound by the above series of reactions is as shown in Scheme 32.

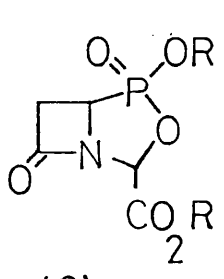
All attempts to intercept the phosphite (270), for example, by carrying out the reaction in the presence of HCl scavengers such as cyclohexene or barium carbonate failed and β-lactam (194) was the only product isolated. No further studies were undertaken with this system. This reaction is therefore the chlorophosphite equivalent of the thionyl chloride transformation of alcohols to chlorides.

Scheme 32

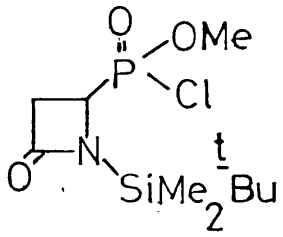


7.0.6 Summary

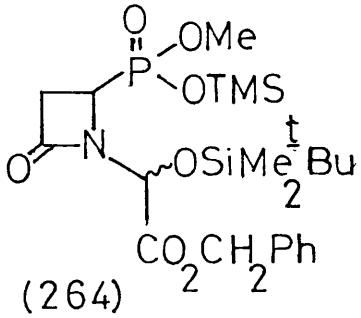
This section has been concerned with methods of forming the 1,5 and 2,3 bonds in the target system (2). Various precursors have been obtained, (254) and (264). However, cyclisation to (2) was not achieved.



(2)

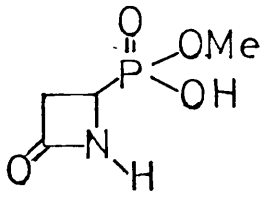


(254)

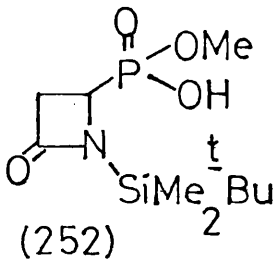


(264)

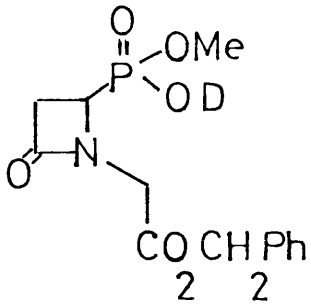
Successful monodeprotection of phosphorus led to the novel systems (250), (252) and (266).



(250)



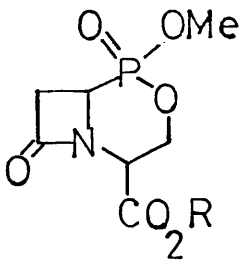
(252)



(266)

These monophosphonic acids were found to be unstable, β-lactam cleavage occurring within a few hours at room temperature. During this series of investigations no indication was found to support the formation of the target system (2).

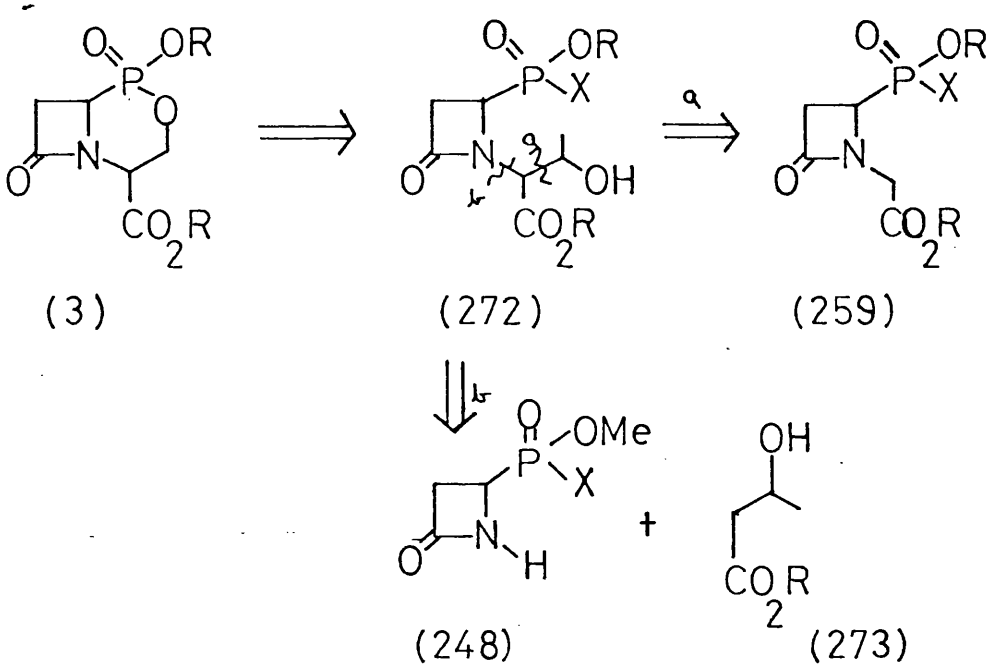
Approaches to the target (3) will now be discussed.



(3)

8.0.0 FORMATION OF THE 1,2-BOND IN TARGET (3)

A possible reterosynthetic pathway is as follows:

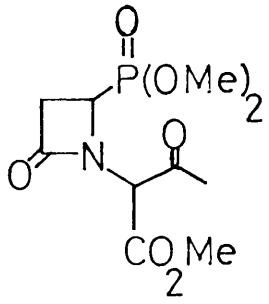


(3) (272) (259)

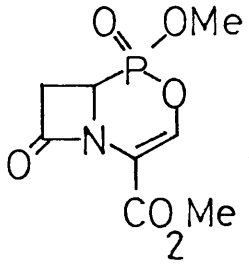
(248) (273)

The key intermediate in the above sequence is azetidin-2-one (272), which may be further disconnected, as shown, to the N-methylene β-lactam (259) (path a) [described in Section 7.0.3] or azetidin-2-one (248) (path b).

As a β-hydroxy ester of structure (272) may be liable to elimination of water under any basic or acidic cyclisation attempts we decided to synthesis the β-lactam β-keto ester (274), enolisation and cyclisation of which could lead to the bicyclic enol phosphonate (275).



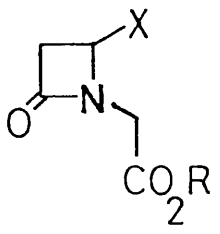
(274)



(275)

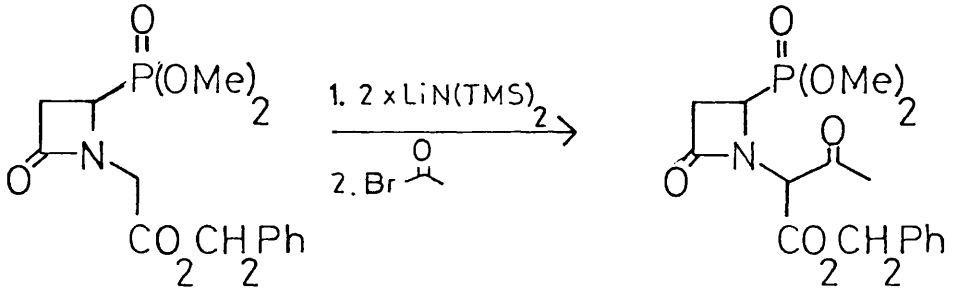
8.0.1 Synthesis of methyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-3-oxobutanoate (274)

As previously mentioned (Section 6.0.3) functionalisation of the N-methylene group in compounds of type (192) is well documented.[89,90,91]



(192)

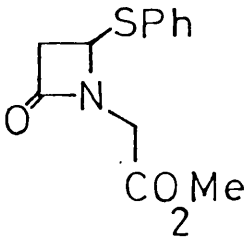
We therefore attempted to acylate the ester enolate anion of (259) with acetyl bromide:



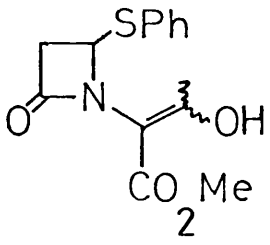
(259) (276)

Treatment of (259) with two equivalents of lithium hexamethyldisilazide followed by addition of acetyl bromide and acetic acid work up[113] was unsuccessful and (276) was not isolated. Quenching of the ester enolate anion with carbon disulphide also failed and starting material (259) was recovered.

The exact reason for this lack of reaction is unclear but may be due in part to the sterically bulky dimethylphosphono group. This is in contrast to β-lactams (277) which are readily acylated[113] affording β-keto esters (278) in high yield.

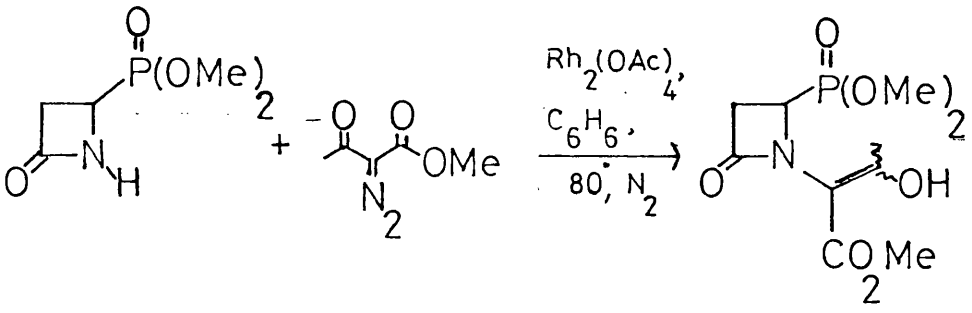


(277)



(278)

We were successful in obtaining the novel β-keto ester (274) by the following route:



(248) (279) (274)

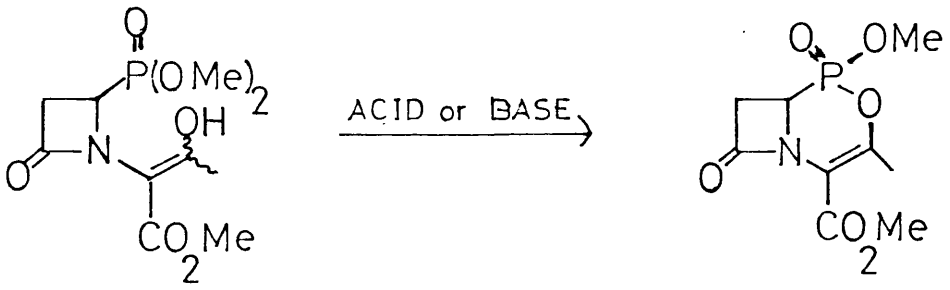
Diazoacetoacetate (279) was prepared in quantitative yield by reaction of methylacetoacetate with tosyl azide in acetonitrile containing one equivalent of triethylamine. Slow addition of (279) to a dilute refluxing benzene solution of 4-dimethylphosphonoazetidin-2-one (248) in the presence of a catalytic amount of rhodium(II) acetate led to isolation of methyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxo-azetidin-1-yl]-3-oxobutanoate (274) in 35% yield after chromatography on silica. The use of freshly prepared 2-diazomethylacetoacetate led to an improved yield of 50% which was not bettered. The i.r. of this compound showed bands at 1770 (β-lactam C=O), 1750 (ester), 1660 (C=O) and 1610 cm^{-1} (enol), in addition to the P=O and POMe absorptions at 1250 and 1040 cm^{-1} respectively. H^1-n.m.r. showed the enolic OH signal at δ 12.0 with H4 of the β-lactam ring at

δ 4.1, the $\overset{O}{\overset{\|}{P}}(OMe)_2$ and CO_2Me at δ 3.80 (d,P^{31} irradiation, collapses to singlet) and 3.86 respectively. The enolic methyl group appeared at δ 2.20 which, on recording the spectrum in d^5-pyridine, underwent an aromatic induced solvent shift to δ 2.40. The ultraviolet spectrum supported the enolic structure for (274) [λ_{max}, 250 nmε19,531]. The existance of analogous compounds in the enol form has also been documented.[120] High resolution mass measurement and elemental analysis were in accordance with the molecular formulae.

With the key intermediate to the target system (275) in hand we now proceeded to investigate intramolecular cyclisation of (274) under acidic and basic conditions.

8.0.2. Attempted cyclisation of methyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-3-oxobutanoate (274) to target (275)

The general reaction under investigation is as shown.



(274) (275)

This reaction was investigated under a variety of conditions ranging from strong Lewis acids to strong bases (Table 5). None of the conditions investigated led to the required reaction, starting material (274) being recovered, almost quantitatively, in the majority of cases.

The reason for this lack of reactivity, even under quite vigorous conditions (KH, 18-crown-6- 60°C, 16 hours) is unclear,

but it may be due to (a) steric hinderance by the 4-dimethyl-phosphono group, or (b) attack by methanol (formed in the reaction), with reversion to (274).

TABLE 5

Conditions used for Cyclisation Attempts of (274)

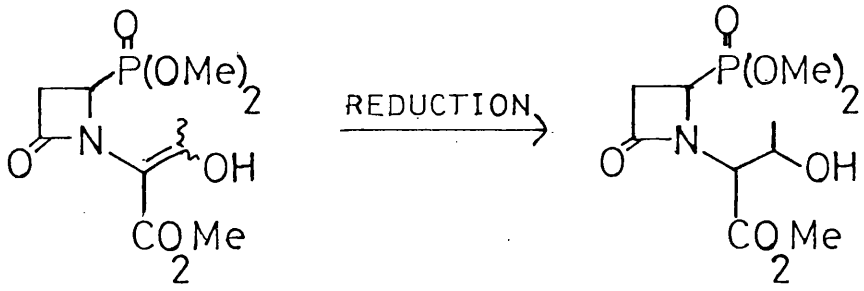
Reagents	Solvent	Temperature °C	Time (hs)	Products
d^5-pyridine	d^5-pyridine	20	20	Enol form of (274)
toluene	toluene	100	20	Starting material
$AlCl_3$	CD_2Cl_2	20	16	" "
$TiCl_4$	CD_2Cl_2	20	16	" "
$Ph_3C^+BF_4^-$	CD_3CN	20	16	" "
Hünig's base	DCM	20	20	" "
KH	THF	40	2	" "
KH, HMPT	THF	66	2	" "
KH, 18-C-16	THF	66	16	" "
DBU	THF	20° than 60°	16	" "
DBU, $CaCl_2$	THF	20	72	" "

However, the cyclisation attempt in the presence of anhydrous calcium chloride, as a methanol trap, was unsuccessful.

This is also in contrast to the findings of the Bristol group who successfully utilised β-lactam β-keto esters in their synthesis of 2-isooxacephems[48] and carbacephems[52,53].

8.0.3 Attempted reduction of β-keto ester (274) to β-hydroxy ester (280)

It was anticipated that if the β-keto ester group in (274) would be reduced to the corresponding β-hydroxy ester (280) then the hydroxy group may be more nucleophilic in the intended cyclisation. Therefore we attempted to prepare β-hydroxy ester (280) by direct reduction of β-keto ester (274).



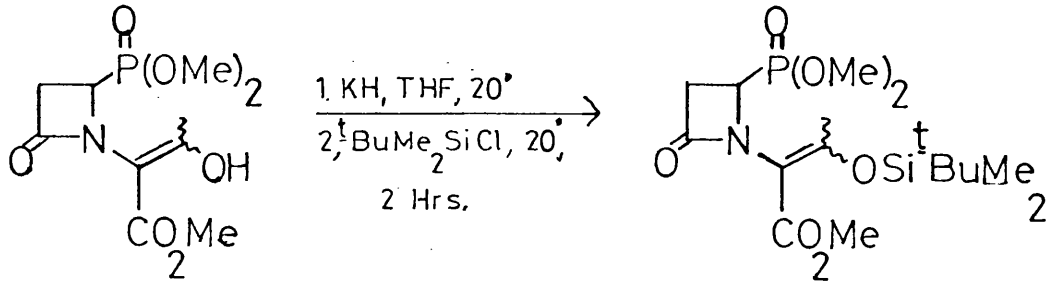
(274) (280)

Reaction of (274) with sodium borohydride in dry THF at 0°C resulted in the isolation of starting material only. This may be due to the basicity of the borohydride promoting enolisation and inhibiting the reduction process. Borohydride reduction in methanol buffered with sodium acetate led to β-lactam cleavage. Use of diborane in THF at 20°C then 60°C gave no reaction. Hydrogenation of (274) over 5% palladium on charcoal in ethyl acetate at 20°C/1 atm. or in the presence of a catalytic amount of hydrochloric acid at 1 atm. failed to give (280), β-keto ester (274) being isolated quantitatively. Hydrogenation under more vigorous conditions were also investigated. Thus, treatment of (274) with hydrogen over a rhodium/alumina catalyst at 50 atm. for 16 hours at 20°C gave no reaction. Use of a literature method,[114] for the asymmetric reduction of β-keto esters, involving the use of Raney Nickel modified with sodium bromide/tartaric acid at 100°C/80 atm. resulted in β-lactam cleavage.

In view of the above lack of success several indirect cyclisation attempts were investigated.

8.0.4 Preparation and reactions of silyl enol ether (281)

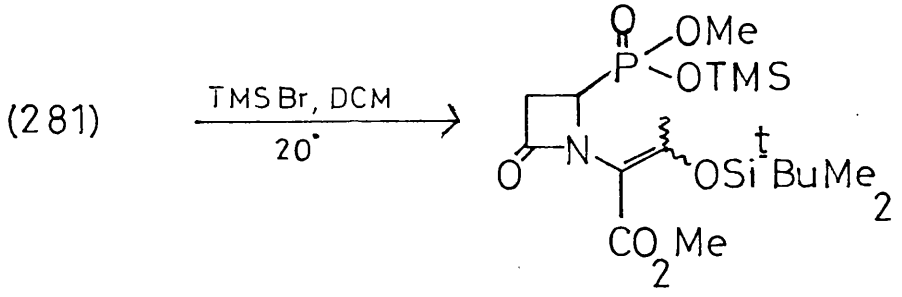
^{t}Butyldimethylsilyl enol ether (281) was prepared by reaction of β-keto ester (274) with potassium hydride followed by ^{t}butyldimethylsilyl chloride.



(274) (281)

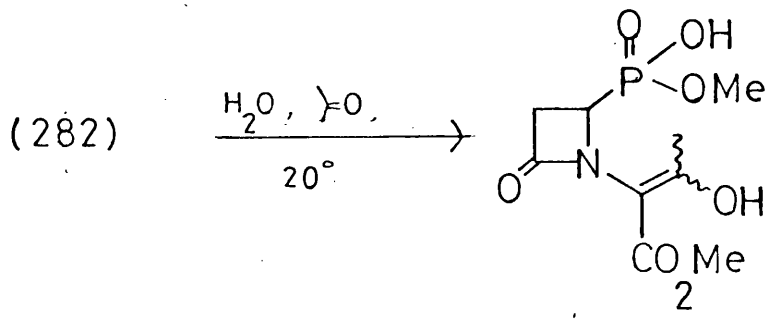
^{t}Butyldimethylsilyl enol ether (281) was not stable to chromatographic media (silica, alumina), however, spectroscopic examination indicated the complete formation of (281) after 2 hours at 20°C [i.r. 1770 (β-lactam C=O), 1720 (α,β-unsaturated ester), 1610 cm^{-1} (C=C), δ ($CDCl_3$), no enolic OH signal, 2.40 (enolic methyl, cf. spectrum of (274) in d^5-pyridine, enolic methyl δ 2.40), 0.95 and 0.90 (*cis* and *trans* ^{t}Bu), 0.3 and 0.1 (*cis* and *trans* $SiMe_2$)]. No mass ion was observed. Proceeding on the assumption that ^{t}butyldimethylsilyl enol ether had been formed we investigated the reaction sequence shown in Scheme 33, the objective being to obtained monophosphonic acid (283), dehydration of which should lead to the bicyclic enol phosphonate (3).

Scheme 33



(282)

Scheme 33 continued



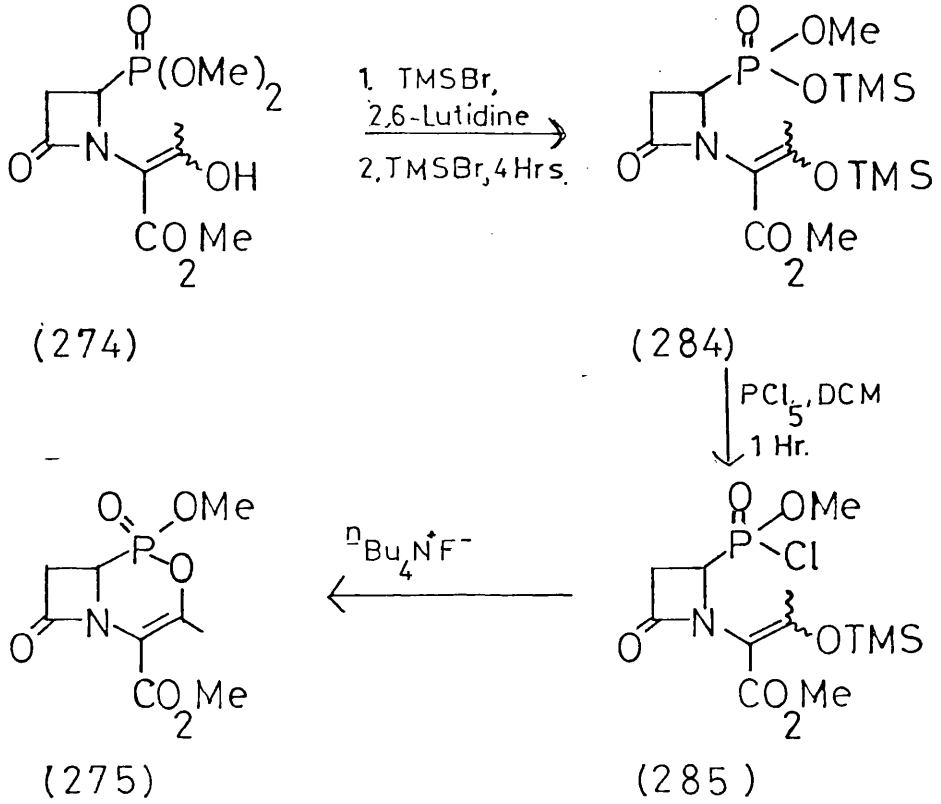
(283)

After treatment of ^{t}-butyldimethylsilyl enol ether (281) with one equivalent of trimethylsilyl bromide (4 hours at 20°C), i.r. showed that the β-lactam ring was intact [1780 cm^{-1} cf. 1770 cm^{-1} in (281)]. Hydrolysis of (282) was carried out in 10% aqueous acetone. After 16 hours at 20°C i.r. indicated β-lactam cleavage. This may again be due to the high acidity of the monophosphonic acid (283). Treatment of the mixed silyl azetidin-2-one (282) with trimethylsilyl triflate also failed to produce the target system (3). A modification of the route shown in Scheme 33 is outlined in Scheme 34.

Treatment of β-keto ester (274) with trimethylsilyl bromide (1 equiv.) and 2,6-lutidine afforded the trimethylsilyl enol ether [analogous to (281)]. Addition of a further equivalent of trimethylsilyl bromide resulted in the formation of (284) which was identified spectroscopically [i.r., 1780 (β-lactam), 1730 (ester), 1610 (C=C), 1220 (P=O), 1040 cm^{-1} (POMe), δ 4.3-3.2 (9H,m,POMe, H4 and H3), 2.35 (3H,s,Me), 0.5-0.1 (m,$SiMe_3$)]. Reaction of impure (284) with phosphorus pentachloride in dry DCM for 1 hour at 20°C followed by removal of the solvent afforded the labile phosphonochloridate (285) [i.r., 1780 (β-lactam C=O), 1735 (ester), 1610 (C=C), 1240 (P=O) and 1040 cm^{-1} (POMe)]. Treatment of (285)

with anhydrous tetra-n-butylammonium fluoride failed to give the target system (275). The reason for this is not clear and in such a complex reaction sequence many factors could contribute.

Scheme 34

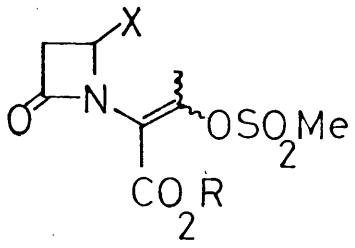


We therefore sought alternative routes to the target system (3) and its analogues.

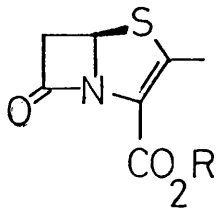
8.0.5 Preparation of methyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-3-methanesulphonylbut-2-enoate (288)

Monocyclic β-lactam enol mesylates of general structure (286) have played an important part in the synthesis of novel bicyclic β-lactam systems.

For example, the Glaxo group[115] have utilised mesylates of type (286) (x = Cl) in a chiral synthesis of the penem system (287). We therefore sought to apply this type of intermediate to our synthetic problem

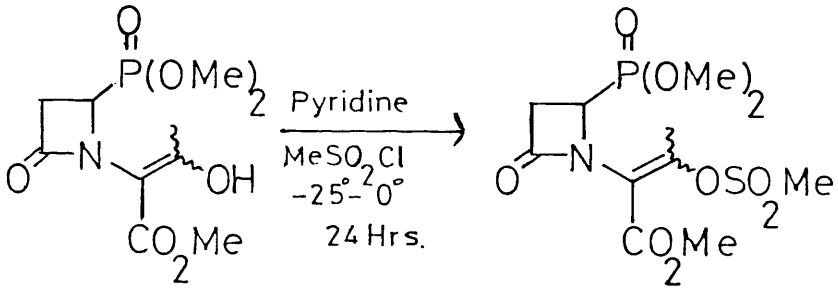


(286)



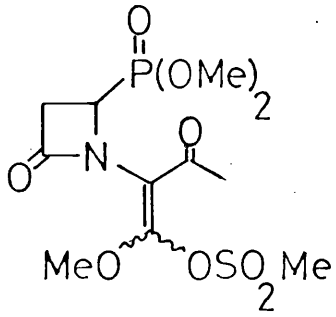
(287)

Reaction of β-keto ester (274) with a ten-fold excess of methanesulphonyl chloride in pyridine at 0°C led, after flash chromatography on silica, to the isolation of enol mesylate (288) in 75% yield.



(274) (288)

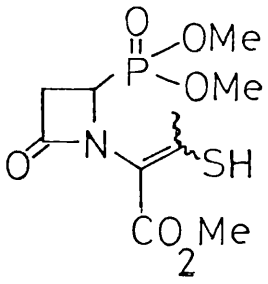
The i.r. of (288) showed bands at 1780 (β-lactam C=O), 1730 (ester), 1620 (C=C), 1370 (sulphonate S=O), 1230 (P=O) and 1040 cm^{-1} (POMe). In the H^1-n.m.r. H4 appeared at δ 4.22, H3 and the methyl group of the methanesulphonyl unit at δ 3.35 with the enolic methyl signal at δ 2.68. High resolution mass measurement gave M^+ at 371.0447 (required 371.0440), in agreement with the molecular formula $C_{11}H_{18}NO_9PS$. This data supported the formation of the enol mesylate with probable structure (288). However, the alternative structure (289) could not be rigorously precluded. With the probable β-lactam enol mesylate (288) available we now proceeded to investigate its synthetic utility in approaches to the target (3).



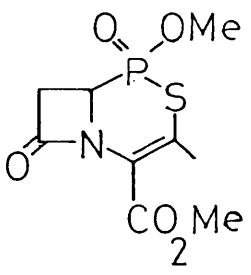
(289)

8.0.6 Attempted conversion of enol mesylate (288) to β-lactam thioenols (290)

As sulphur should have been a better nucleophile than oxygen in the type of cyclisation process envisaged, we attempted to convert enol mesylate (288) to thioenol (290), in order to investigate the cyclisation of (290) to the thio analogue of target (275) bicyclic system (291).



(290)



(291)

This conversion [(288) → (290)] was examined under a variety of conditions (Table 6).

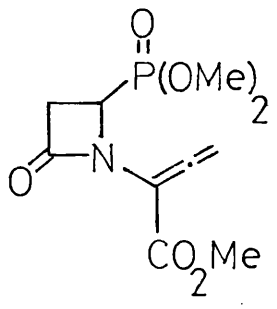
As indicated in Table 6 we failed to prepare thioenol (289). This is in contrast to the findings of the Glaxo group[115] who successfully applied this strategy in a synthesis of penem (287). The reactions examined attempted to cover both possible modes of thiol addition, namely conjugate addition to the α,β-unsaturated ester followed by elimination of methane sulphonic acid or formation of a reactive allene intermediate (292) which would be

trapped by the thiolate anion.[116] The reason for lack of reaction, in our case, is not clear and is in contrast to the findings of the Glaxo group.[115]

TABLE 6

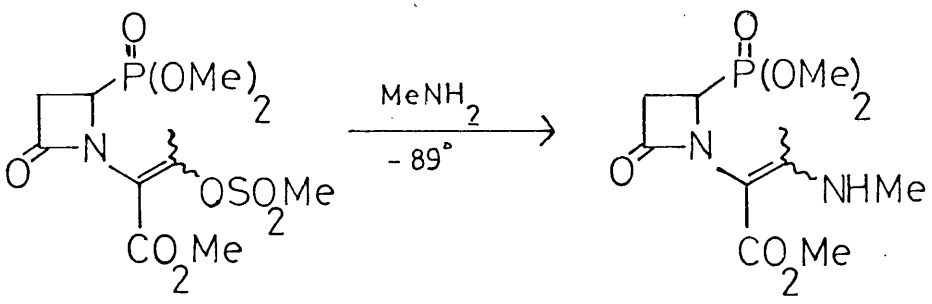
Conditions Investigated for the Attempted Conversion of Mesylate (289) to Thioenol (289)

Reagent	Solvent	Temperature (°C)	Time (hs)	Products
H_2S, Et_3N, DMAP	DCM	20	3	Starting material
H_2S, Et_3N	DCM	20	20	" "
NaSH, $(\text{)}_2NEt$, $Bu_4N^+Br^-$	EtOAc, H_2O	20	1	β-Lactam cleavage
NaSH	H_2O, O	20	16	" "
$Bu_4N^+HS^-$	MeCN	20° then reflux	2½ then 16	Starting material
$Bu_4N^+HS^-$, DBU	THF	20	16	" "
$LiN(TMS)_2$ $Bu_4N^+HS^-$	THF	-78 → 20	2	" "



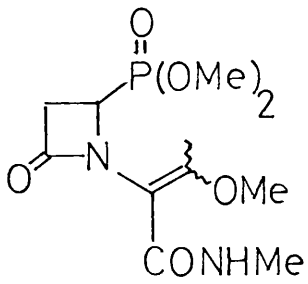
(292)

We were, however, successful in preparing the novel enamine, methyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-aminomethylbut-2-enoate (293) in 88% yield be treatment of enol mesylate (289) with excess methylamine at -89°C.



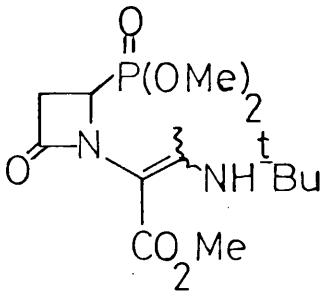
(288) (293)

The H^1-n.m.r. of enamine (293) showed the expected doublet at δ 2.98 assigned to the N-methyl group. The β-lactam protons appeared at very similar chemical shifts to those in β-keto ester (274) [e.g. H4 in (274) δ 4.1, 4.12 in (293)]. The i.r. had an NH stretch at 3460 cm^{-1} with the β-lactam and ester carbonyl at 1770 and 1750 cm^{-1} respectively. Also observed in the i.r. were bands at 1660 (enamine), 1605 (C=C), 1240 (P=O) and 1040 cm^{-1} (POMe). High resolution mass measurement gave M^+ 306.0976 ($C_{11}H_{19}N_2O_6P$ requires 306.0980). Once again the above data suggested the formation of a β-lactam enamine (293)[116]. However, the alternative structure (294) cannot be ruled out.

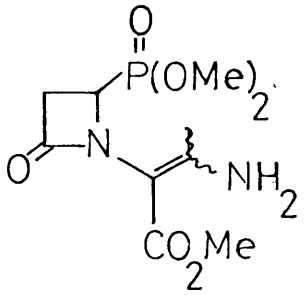


(294)

The reaction was reproducible and ^{t}-butylenamine (295) was also prepared by a similar sequence of reactions. High resolution mass measurement showed M^{+} 348.1453 [(295) requires 348.1450].

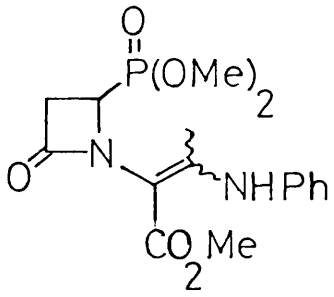


(295)



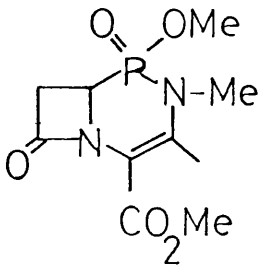
(296)

Interestingly the reaction of enol mesylate (288) with liquid ammonia failed to produce primary enamine (296) and starting material (288) was isolated. The explanation may lie in the difference in nucleophilicity between ammonia and methylamine or ^{t}-butylamine. Also treatment of enol mesylate (288) with one equivalent of N,N-diisopropylethylamine and one equivalent of aniline failed to give the aromatic enamine (297), starting material (288) being isolated.



(297)

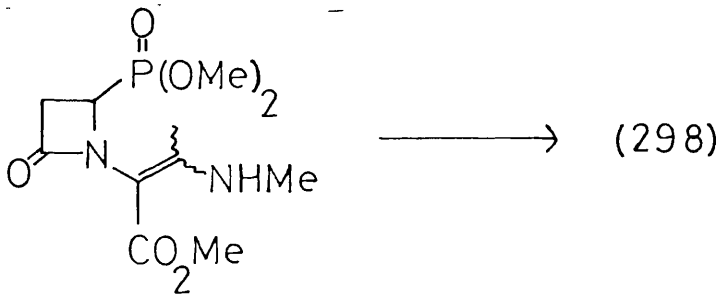
The above series of conversions indicate the capricious nature of this type of compound (288) and it remained to be seen if the enamine (293) would afford the nitrogen analogue of the target (298).



(298)

8.0.7 Reactions of methyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-3-aminomethylbut-2-enoate (293)

The general reaction attempted was as follows:

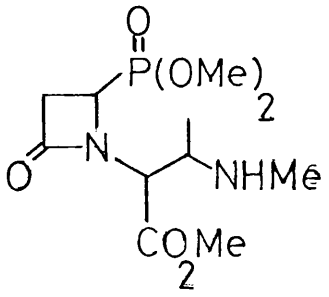


(293)

Several attempts at cyclisation were investigated, for example, treatment of enamine (293) with potassium hydride in THF at 20°C led to complete recovery of starting material after work-up. Photolysis of (293) at low or medium pressure in benzene or THF also failed to afford the required bicyclic system (298), enamine (293) being recovered. Thermolysis of (293) in benzene did not initiate cyclisation, starting material being recovered. Reaction of (293) with sodium hexamethyldisilazide led, after work-up, to the isolation of a non-β-lactam product. The structure of this compound has not been established, however, i.r. and H^1-n.m.r. indicated that the $P(OMe)_2$ group was not present. Two carbonyl stretching frequencies were noted in the i.r. at 1720 and 1690 cm^{-1} together with a band at 1640 cm^{-1}, these may be due to an α,β-unsaturated ester system, an amide and an enamine respectively.

H^1-n.m.r. showed signals attributable to a methoxy group at δ 3.87, N-methyl, δ 2.96 and a methyl signal at δ 2.58. A group of signals at δ 7.3 was also observed. High resolution mass measurement gave $C_9H_{12}N_2O_3$ (299) as a molecular formula (M^+, 196.0845).

In anticipation that a secondary amine of structure (300) would be more nucleophilic than the enamine (293), we attempted to reduce the double bond in (293) in order to obtain amine (300).

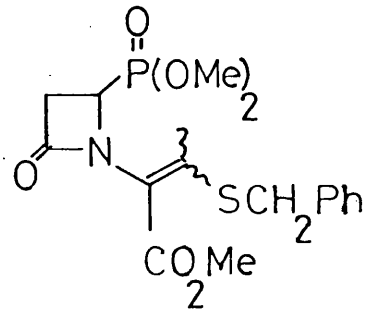


(300)

Hydrogenation of (293) over rhodium/alumina or platinium oxide in methanol at 1 atm. did not affect the desired transformation, enamine (293) being recovered. Sodium cyanoborohydride in acidic methanol[117] (pH 4.5) caused β-lactam cleavage.

Conversion of enamine (293) to the thioenol (290) was also examined, utilising conditions described by Di Ninno *et al.*[118] for the transformation of β-enamino esters to β-thioxo esters (TFA, H_2S, DMF). We have been unable to obtain the thioenol (290).

Treatment of (293) with benzyl mercaptan in refluxing chloroform, containing one equivalent of trifluoroacetic acid, for 16 hours failed to produce the S-benzylthioenol ether (301), starting materials being recovered.

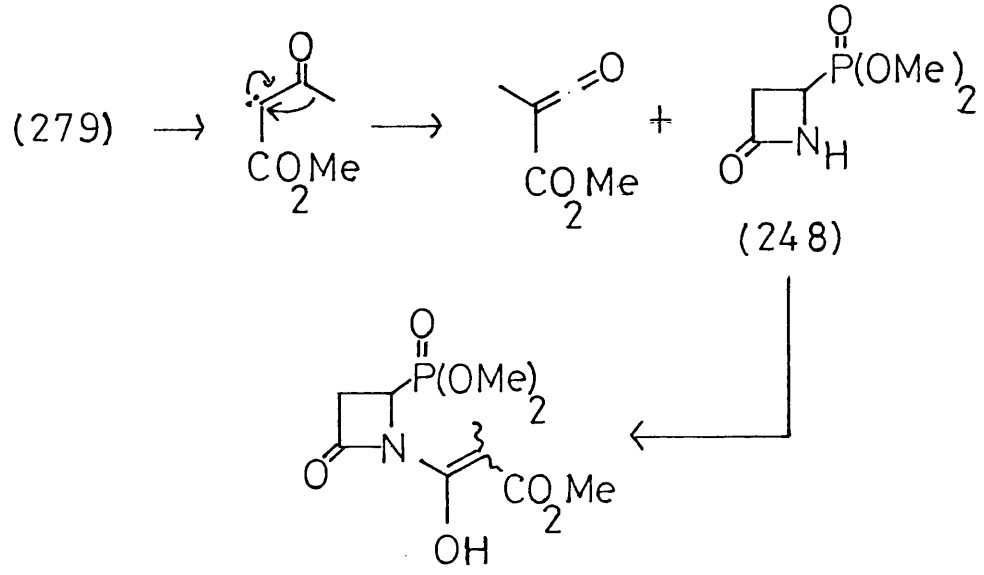


(301)

8.0.8 Structure of β-Keto Ester (274)

The surprising failure of these compounds [β-keto ester (274) and enamine (293)] to undergo the required cyclisation raised some doubts as to their actual structure and consequently we re-examined the available data on the β-keto ester (274).

A possible alternative structure for (274) is the amide (302) which could be produced by azetidin-2-one (248) trapping the ketene derivated from a Wolff rearrangement of the carbonoid species obtained from 2-diazomethylacetoacetate (279). This process is outlined below.

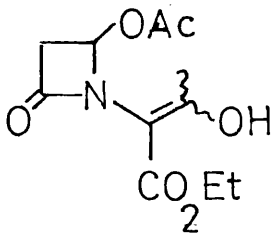


(302)

The high resolution mass spectrum contained fragment ions at m/e 265, 251, 250 and 234 corresponding to loss of CO, ketene, CH_3CO and CO_2Me from the parent system. The first two fragments in this series arise from cleavage of the β-lactam ring and would be present in the mass spectrum of both proposed structures (274) and (302), as would the m/e 234. However, the fragment at m/e 250, probably corresponding to loss of the acetyl (CH_3CO) unit, could only arise from structure (274). The related fragment expected from structure (302) was m/e 206 (loss of the CH_3CHCO_2Me unit), and was not observed in the mass spectrum.

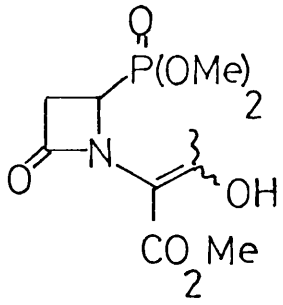
The literature[91,120] describing β-lactam β-keto esters analogous to (274) indicates that they exist completely in the enol form, thus structure (302) would be expected to be enolised as shown. The u.v. spectra for (274) [or alternative structure (302)] exhibited λ_{max} (MeOH) 250 nm, ε 19,500, indicating the enolic nature of this compound.

The use of ethyl-α-diazoacetoacetate in this type of reaction was studied by Porter *et al.*[121] and subsequently reinvestigated by the Beecham group.[91] The latter workers did not record the isolation of any β-lactam products resulting from a Wolff rearrangement of the carbene precursor, and β-keto ester (303) was produced in 7.5% yield.



(303)

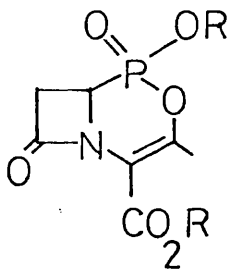
The isolation of (303) by the carbene insertion route and the data available in our case point to the β-lactam β-keto ester structure (274).



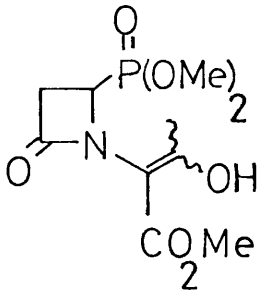
(274)

8.0.9 Summary

In this section various approaches to the target system (275) were investigated. A key intermediate, β-keto ester (274), was synthesised in 35% yield from 4-dimethylphosphonoazetidin-2-one.



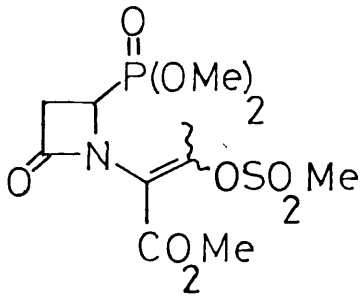
(275)



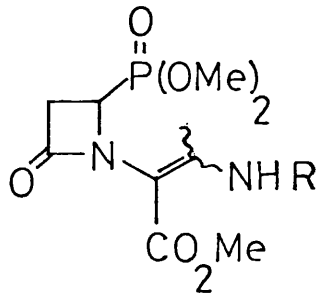
(274)

All attemptes to cyclise (274) to bicyclic/β-lactam (275) failed.

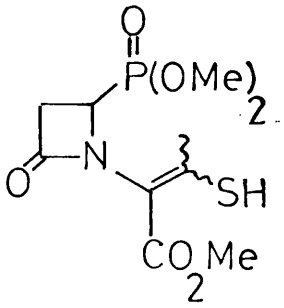
Monocyclic β-lactam (274) was converted to the enol mesylate (288) and enamines (293) and (295).



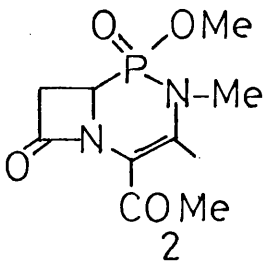
(288)



(293) R = Me
(295) R = ^{t}Bu



(290)



(298)

Attempts to prepare thioenol (290) from either (288) or (293) were not successful. Attempted cyclisation of (293) to the nitrogen analogue of the target system (298) also failed under basic conditions, photolysis or thermolysis.

EXPERIMENTAL

9.0.0 EXPERIMENTAL

I.r. spectra were recorded with Perkin Elmer 257 and 197 spectrometers. H^1-n.m.r. spectra were recorded at 60 MHz with Perkin Elmer R12, R12B or Varian T-60 spectrometers and at 100 MHz with a Jeol JNM-PS-100 instrument. C^{13}-n.m.r. spectra were recorded with a Jeol FX90Q spectrometer at 25.2 MHz. P^{31}-n.m.r. spectra were recorded with a Jeol JNM-PS-100 spectrometer at 40.5 MHZ. U.v. spectra were recorded on a Perkin-Elmer 402 ultraviolet-visible spectrophotometer. Mass spectra were obtained with A.E.I. M.S. 12 and U.G. 7070 E and F machines.

Reactions were monitored by t.l.c. on Merck DC-alufolien Kieselgel 60 F254 or Merck DC-alufolien aluminium oxide 60 F254 using an appropriate solvent system. Column chromatography was carried out using short path pressurised columns packed with Merck silica gel PF254. Visualisation of reaction components was achieved by ultraviolet light and spraying with a 5% ethanolic solution of anisaldehyde containing traces of acetic acid and concentrated sulphuric acid, followed by heating. The spray was useful as components with similar or identical Rf developed at different rates to afford different colours.

Petroleum ether refers to the fraction of B.P. 40-60°. All solvents used for chromatography were distilled before use. Reaction solvents were dried and distilled before use. Tetrahydrofuran was pre-dried over sodium wire then refluxed over sodium benzophenone ketyl until dry and re-distilled immediately prior to use.

Nitrogen and argon refer to the dried gases. Glassware used for alkyllithium reactions was flame dried under dry argon.

(4RS)-4-ACETOXYAZETIDIN-2-ONE (184)

Freshly distilled vinyl acetate (500 ml, 467 g, 5.43 mol) was added to a three-necked round-bottomed flask under nitrogen and cooled to 15°C. Chlorosulphonylisocyanate (87.0 ml, 141.5 g, 1.0 mol) was added with stirring in 15 seconds. The mixture was stirred at 20-25°C for 20 minutes [reaction temperature must not exceed 25°C]. During this period the reaction mixture became dark red in colour. After 20 minutes the mixture was cooled to -20°C and added slowly to a mixture of sodium bicarbonate (235 g, 2.79 mol), sodium bisulphite (82.5 g, 0.654 mol), water (200 ml) and ice (500 g) with stirring at a rate such that the temperature did not rise above 10°C. After addition was complete the mixture was stirred for 20 minutes, the final pH of the solution being 7. The sodium sulphate was filtered off and the excess vinyl acetate separated. The aqueous layer was extracted with dichloromethane (4 x 500 ml) and the extracts combined with the vinyl acetate layer, the combined organic phase was dried ($MgSO_4$) and refluxed with activated charcoal. Filtration and evaporation of the filtrate gave a yellow oil which slowly solidified. Chromatography on silica afforded 4-acetoxyazetidin-2-one (184) as a pale yellow solid (56.0 g, 43%). M.pt. 34°C, ν_{max} ($CHCl_3$), 3350 (NH), 1790 (β-lactam C=O) and 1730 cm^{-1} (acetate C=O).

(2RS)-2-BROMOTRIETHYLPHOSPHONOACETATE (187)

Triethylphosphonoacetate (2.24 g, 10 mMol) was dissolved in dry carbon tetrachloride (20 ml) under nitrogen and treated with N-bromo-succinimide (1.78 g, 10 mMol). The stirred suspension was brought to reflux and reaction initiated with benzoyl peroxide (30 mg). After

refluxing for 45 minutes, cooled and filtered, evaporation of the filtrate *in vacuo* gave (2RS)-2-bromotriethylphosphonoacetate (187) as a colourless oil (2.89 g, 95%). ν_{max} (thin film), 1750 (ester), 1390 (P=O) and 1340 cm^{-1} (POEt), δ ($CDCl_3$), 4.5 (1H,d,J=20Hz,CHBr), 4.20 (6H,m, $P(O\underline{CH_2}CH_3)_2$ and $CO_2\underline{CH_2}CH_3$), 1.29 (9H,m, $P(OCH_2\underline{CH_3})_2$ and $CO_2CH_2\underline{CH_3}$), $\underline{M}^+$, 304 (Br^{79}).

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH (2RS)-2-BROMOTRIETHYLPHOSPHONOACETATE (187)

(a) Anhydrous triethylamine (1.01 g, 10 mMol) was added to a solution of (4RS)-4-acetoxyazetidin-2-one (184) (1.29 g, 10 mMol) in dry DMF (10 ml) under nitrogen and treated with (2RS)-2-bromotriethylphosphonoacetate (187) (3.04 g, 10 mMol) and the resulting solution stirred at 20°C for 16 hours poured into ethyl acetate/water and extracted. The organic phase was washed with water (2 x 100 ml), dried ($MgSO_4$). Evaporation *in vacuo* afforded a dark red oil. T.l.c., i.r. and H^1-n.m.r. showed that no β-lactam material was present.

(b) Sodium hydride[82] (240 mg, 10 mMol) was suspended in dry THF under nitrogen and cooled to -78°C. (4RS)-4-Acetoxyazetidin-2-one (184) (1.29 g, 10 mMol) was added and the suspension stirred for 30 minutes after which time (2RS)-2-bromotriethylphosphonoacetate (187) (3.04 g, 10 mMol) was added. The mixture was stirred at -78°C for 1 hour then warmed to 20°C. After this time the suspension was filtered and the filtrate evaporated *in vacuo* affording a yellow oil. I.r. and H^1-n.m.r. indicated the presence of starting materials only.

(c) Conditions as for (b) except for 16 hour reflux. Work-up as described for (b), no reaction observed.

(d) (4RS)-4-Acetoxyazetidin-2-one (184)[83] (1.29 g, 10 mMol) and (2RS)-2-bromotriethylphosphonoacetate (187) (3.04 g, 10 mMol) were

dissolved in dry THF under nitrogen and treated with tetra-n-butylammonium bromide (330 mg, 1 mMol) and powdered potassium hydroxide (620 mg, 11 mMol). The resulting brown solution was stirred at 20°C for 2 hours, work-up as described in (a) above gave a yellow oil. H^1-N.m.r. and i.r. indicated a mixture of starting materials only.

(e) Potassium carbonate (1 equiv.) under the conditions described in (a) resulted in β-lactam cleavage.

(f) Use of pyridine as solvent afforded β-lactam cleavage.

(g) LDA under conditions (b) followed by aqueous ammonium chloride work-up gave only a mixture of starting materials.

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH BROMOMETHYLACETATE

Conditions used were identical to those described above for the attempted reaction of (4RS)-4-acetoxyazetidin-2-one (184) with (2RS)-2-bromotriethylphosphonoacetate (187). Similar negative results were obtained.

2-DIAZOTRIETHYLPHOSPHONOACETATE (190)[86]

Sodium hydride (240 mg, 10 mMol) was suspended in dry THF under nitrogen and cooled to -78°C and treated with triethylphosphonoacetate (2.24 g, 10 mMol) and stirred at -78°C for 1 hour. Tosyl azide[85] (1.97 g, 10 mMol) was added and the mixture warmed to 20°C and the resulting turbid solution poured into water and extracted with benzene (2 x 100 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give 2-diazotriethylphosphonoacetate (190) as a yellow oil (2.30 g, 92%). ν_{max} (thin film), 2140 (diazo), 1710 (ester), 1280 (P=O) and 1120 cm^{-1} (POEt), δ ($CDCl_3$), 4.2 (6H,m, $\overset{O}{\overset{\|}{P}}(O\underline{CH_2}CH_3)_2$ and $CO_2\underline{CH_2}CH_3$), 1.9 (9H,m, $\overset{O}{\overset{\|}{P}}(OCH_2\underline{CH_3})_2$ and $CO_2CH_2\underline{CH_3}$).

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH 2-DIAZO-TRIETHYLPHOSPHONOACETATE (190)

(a) (4RS)-4-Acetoxyazetidin-2-one (184) (258 mg, 2 mMol) was dissolved in dry THF and added to a suspension of copper (I) cyanide (180 mg, 2 mMol) in dry THF under nitrogen. The brown suspension was treated with 2-diazotriethylphosphonoacetate (190) (500 mg, 2 mMol) and the mixture refluxed for 7 days. T.l.c., i.r. and H^1-n.m.r. after this time indicated only a mixture of starting materials to be present.

(b) Rhodium acetate (5 mg) and (4RS)-4-acetoxyazetidin-2-one (184) (258 mg, 2 mMol) were heated to reflux in dry degassed benzene under nitrogen, then 2-diazotriethylphosphonoacetate (190) (500 mg, 2 mMol) was added dropwise over 30 minutes. After 16 hours at reflux i.r. indicated only starting materials to be present.

(c) (4RS)-4-Acetoxyazetidin-2-one (184) (323 mg, 2.5 mMol) and 2-diazotriethylphosphonoacetate (190) (625 mg, 2.5 mMol) were dissolved in dry degassed benzene under nitrogen and irradiated with a low pressure Hanovia u.v. lamp for 24 hours at 20°C. T.l.c., i.r. and H^1-n.m.r. indicated that (4RS)-4-acetoxyazetidin-2-one (184) was the only β-lactam present.

(d) The above conditions were repeated with 4-phenylthio-azetidin-2-one (202), the same results were obtained.

ATTEMPTED PREPARATION OF METHYL-2-[(4RS)-4-ACETOXY-2-OXO-AZETIDIN-1-YL]-ACETATE (192) BY DIRECT N-ALKYLATION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184)

(a) (4RS)-2-Acetoxyazetidin-2-one (184) (0.38 g, 3 mMol) was dissolved in dry THF under nitrogen and added to a suspension of sodium hydride (142 mg, 50% suspension, 3 mMol) and the mixture heated

to 50°C. Methyl bromoacetate (459 mg, 3 mMol) was added dropwise and the mixture heated at 50°C for 16 hours. After this time the reaction was diluted with ethyl acetate and washed with water. The organic phase was dried ($MgSO_4$) and removed to give a yellow oil. I.r. and H^1-n.m.r. showed β-lactam cleavage to have taken place.

(b) The above was repeated with anhydrous potassium carbonate (1 equiv.) in acetone at 20°C. I.r. and H^1-n.m.r. after 16 hours showed no reaction to have occurred.

(c) Potassium carbonate in dry DMF resulted in isolation of starting materials after work-up.

(d) Use of sodium hydride at -10-20°C under conditions (a); no reaction.

(e) Potassium ^{t}-butoxide in dry DMF; no reaction after work-up described in (a).

BENZYL GLYOXYLATE (184a)

Tartaric acid (15 g, 100 mMol) and triethylamine (20.4 g, 200 mMol) were dissolved in dry DMF (200 ml) and cooled to 10°C. Freshly distilled benzyl bromide (35 g, 200 mMol) was added and the mixture stirred at 10°C for 16 hours. After this time the mixture was filtered and the filtrate evaporated *in vacuo* to give an oily residue which was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate (2 x 50 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. Crystallisation of the residue from ether/petroleum ether (1:2) gave dibenzyl tartrate as a white powder (32.5 g, 95%). ν_{max} (KBr), 3500 (OH), 1750 cm^{-1} (ester), δ ($CDCl_3$), 7.3 (10H,s, Ph), 5.41 (4H,s,CH_2Ph), 4.6(2H,Br,s,OH exchange with D_2O), 3.3 (2H,s,CH). Dibenzyl tartrate (6.6 g, 20 mMol), suspended in water/acetic acid (100:40) (200 ml), was treated with sodium metaperiodate (4.2 g, 20 mMol)

and stirred at 20°C until all the solid had dissolved (ca. 4 hours). The mixture was evaporated to dryness *in vacuo* and the residue partitioned between water and ethyl acetate. After thorough washing of the ethyl acetate layer with aqueous sodium bicarbonate it was dried ($MgSO_4$) and removed *in vacuo* to give benzyl glyoxylate (184a) as a yellow oil (8.16 g, 100%). ν_{max} (thin film), 3440 (OH), 1750 cm^{-1} (ester), δ ($CDCl_3$), 7.25 (5H,s,Ph), 5.4 (3H,Br.s becomes 1H on exchange with D_2O, CH and OH), 5.1 (2H,s,CH_2Ph).

BENZYL-(2RS)-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]-2-HYDROXY ACETATE (193)

Benzyl glyoxylate (184a) (2.00 g, 11 mMol) was added to a solution of (4RS)-4-acetoxyazetidin-2-one (184) (1.29 g, 10 mMol) in dry THF (7 ml) at 20°C. One drop of triethylamine was added and the mixture stirred for 16 hours at 20°C. After this time ethyl acetate was added and the organic phase washed with water (6 x 50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give benzyl-(2RS)-2-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]-2-hydroxy acetate (193) as a pale yellow oil (2.64 g, 90%). ν_{max} (thin film), 3600-3100 (OH), 1790 (β-lactam CO), 1775 cm^{-1} (acetate CO), δ ($CDCl_3$), 7.32 (5H,s,Ph), 6.10 and 5.95 (1H,dd,J=5.69 and 1.85Hz,H4,diastereoisomers), 5.48 and 5.40 (1H,s,NCH_2CO_2R,diastereoisomers), 5.28 and 5.19 (2H,s,CH_2Ph,diastereoisomers), 4.5 (1H,Br.s, exchange with D_2O, OH), 3.14 (2H,m,H3), 2.02 and 1.90 (3H,s,OCOMe, diastereoisomers). (Found: C, 57.1; H, 5.35; N, 4.73. $C_{14}H_{15}NO_6$ requires C, 57.43; H, 5.12; N, 4.78%).

BENZYL-(2RS)-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]-2-CHLORO ACETATE (194)

Hydroxy acetate (193) (2.93g, 10 mMol) was dissolved in dry THF under nitrogen and cooled to -25°C. At this temperature 2,6-lutidine

(1.07 g, 10 mMol) was added followed by freshly distilled thionyl chloride (1.19 g, 10 mMol) over 30 minutes. The mixture was warmed to 0°C (1 hour) and stirred at this temperature for 16 hours. The mixture was filtered and the filtrate evaporated *in vacuo* to give an oil. Flash chromatography on silica afforded benzyl-(2RS)-2-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]-2-chloro acetate (194) as a pale yellow oil (3.0 g, 96%), ν_{max} (thin film), 1795 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 7.30 (5H,s,Ph), 6.3 (1H,dd,J=4.03 and 1.61Hz,H4), 6.09 (1H,s,NCHCl), 5.20 and 5.18 (2H,s,CH_2Ph,diastereoisomers), 3.20 (2H,m,H3,diastereoisomers), 2.05 (3H,s,OCOCH_3). (Found: C, 53.95; H, 5.19; Cl, 11.28; N, 4.19. $C_{14}H_{14}Cl^{35}NO_5$ requires C, 53.93; H, 4.49; Cl, 11.40; N, 4.49%).

BENZYL-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]ACETATE (192)

Chloroacetate (194) (779 mg, 2.5 mMol) was dissolved in dry degassed benzene under nitrogen and treated with tri-n-butyltin hydride (773 mg, 2.65 mMol) and benzoyl peroxide (5 mg) and the solution refluxed for 3 hours. After cooling the solvent was removed and the residue partitioned between acetonitrile and hexane. The acetonitrile was washed with hexane (6 x 20 ml) and removed *in vacuo* to give benzyl-2-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]acetate (192) as a yellow oil (678 mg, 98%), ν_{max} (thin film), 1795 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 7.29 (5H,s,Ph), 5.95 (1H,dd,J=2.08 and 0.83Hz,H4), 5.08(2H,s,CH_2Ph), 4.03 (2H,d,J=16.2Hz,NCH_2CO_2R), 3.1 (2H,m,H3), 2.08 (3H,s,OCOMe), $\delta_{C^{13}}$ ($CDCl_3$), 170.54 (s,OCOMe), 167.18 (s,β-lactam,C=O), 164.69(s,CO_2R), 134.54-127.36 (m,Ph), 75.68 (d,C4), 66.26 (t,NCH_2CO_2R), 43.61 (t, CO_2CH_2Ph), 42.04 (t,C3), 19.61 (q,OCOCH_3). (Found: C, 60.39; H, 5.57; N, 4.86. $C_{14}H_{15}NO_5$ requires C, 60.64; H, 5.42; N, 5.05%).

^{t}BUTYL-2-[(4RS)-4-PHENYLTHIO-2-OXOAZETIDIN-1-YL]ACETATE (192)

(4RS)-4-Phenylthioazetidin-2-one (202) (895 mg, 5 mMol) was dissolved in dry THF under argon and cooled to -78°C, n-butyllithium (5 mMol) was added and the yellow solution stirred for 1 hour at this temperature. After addition of ^{t}butylbromoacetate (975 mg, 5 mMol) the reaction was warmed slowly to room temperature and stirred for 3 hours, then quenched by pouring into an ice ether mixture. The organic layer was washed with water, dried ($MgSO_4$) and removed *in vacuo*. Chromatography of the residue on silica gave ^{t}butyl-2-[(4RS)-4-phenylthio-2-oxoazetidin-1-yl]acetate (192) as a pale yellow oil (916 mg, 63%). ν_{max} (thin film), 1765 (β-lactam C=O), 1730 cm^{-1} (ester), δ ($CDCl_3$), 7.35 (5H,s,Ph), 5.25 (1H,dd,J=5.0 and 2.0Hz,H4), 4.2 (1H,d,J=18Hz,NCH_2CO_2R,ABq), 3.50 (1H,d,J=18Hz,NCH_2CO_2R,ABq), 3.45-2.65 (2H,m,H3), 1.30 (9H,s,^{t}Bu); M^+, 293.

ATTEMPTED REACTION OF BENZYL-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]-ACETATE (192) WITH DIETHYLPHOSPHOROCHLORIDATE (195)

Hexamethyldisilazane (178 mg, 1.1 mMol) was added at -78°C to a dry THF solution of ^{t}butyllithium (1.1 mMol) under argon and stirred for 30 minutes at -78°C before addition of benzyl-2-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]acetate (192) (277 mg, 1 mMol). The yellow solution was stirred for a further 30 minutes at -78°C and diethylphosphorochloridate (195) (133 mg, 0.86 mMol) was added. After warming to 20°C the mixture was poured into a mixture of saturated aqueous ammonium chloride and ethyl acetate. Separation of the organic phase, drying ($MgSO_4$) and evaporation *in vacuo* gave a yellow oil. T.l.c., i.r. and H^1-n.m.r. indicated β-lactam cleavage.

ATTEMPTED REACTION OF ^{t}BUTYL-2-[(4RS)-4-PHENYLTHIO-2-OXOAZETIDIN-1-YL]ACETATE (192) WITH DIETHYLPHOSPHOROCHLORIDATE (195)

^{t}Butyl-2-[(4RS)-4-phenylthio-2-oxoazetidin-1-yl]acetate (192) (293 mg, 1 mMol) was added to a solution of lithium hexamethyl disilazide in dry THF/HMPT (1:1) at -50°C under argon and the mixture was stirred at this temperature for 1 hour before addition of diethylphosphorochloridate (195) (173 mg, 1 mMol) and slow warming to 0°C (2 hours). The reaction was poured into ice/ethyl acetate and extracted, the organic layer was removed, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. T.l.c., i.r. and H^1-n.m.r. indicated no reaction.

DIETHYLPHOSPHONOFORMALDEHYDE (196)

Diethylvinylphosphonate (1.64 g, 10 mMol) was dissolved in dry DCM and cooled to -78°C. Ozone was passed into the solution until the colour of the solution was just pale blue. The ozonide was then treated with saturated aqueous sodium metabisulphite and the mixture extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and evaporated *in vacuo* to afford diethylphosphonoformaldehyde (196) as a clear oil (1.66 g, 100%). ν_{max} $CHCl_3$), 1730 (aldehyde C=O), 1220 (P=O) and 1050 cm^{-1} (POEt), δ ($CDCl_3$), 9.25 (1H,s,CHO), 4.20 (4H,m,$\overset{O}{\overset{\|}{P}}(OCH_2CH_3)_2$) and 1.35 (6H,m, $\overset{O}{\overset{\|}{P}}(OCH_2CH_3)$).

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH DIETHYLPHOSPHONOFORMALDEHYDE (196)

(4RS)-4-Acetoxyazetidin-2-one (184) (129 mg, 1 mMol) was dissolved in dry THF and treated with diethylphosphonoformaldehyde (196) (166 mg, 1 mMol). One drop of triethylamine was added and the mixture

left at 20°C for 16 hours. T.l.c., H^1-n.m.r. and i.r. after this time showed only starting materials to be present. Similar result obtained with (4RS)-4-phenylthioazetidin-2-one (202).

METHYL-2-DIMETHYLPHOSPHONO-2-OXOACETATE (197)

Trimethylphosphonoacetate (1.82 g, 10 mMol) was dissolved in xylene (100 ml) and powdered selenium dioxide was added (1.11 g, 10 mMol). The suspension was heated at 150°C for 5 hours, cooled and filtered through celite. Removal of the solvent *in vacuo* gave a yellow oil. This was dissolved in ether and treated with diazomethane. Evaporation of the ether afforded methyl-2-dimethylphosphono-1-oxoacetate (197) as a pale yellow oil (1.92 g, 98%). ν_{max} ($CHCl_3$), 1770 (C=O), 1745 (ester), 1270 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 3.90 (3H,s,$\overset{O}{\overset{\|}{P}}(OMe)_2$), 3.80 (6H,d,J=15.0Hz,$\overset{O}{\overset{\|}{P}}(OMe)_2$).

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH METHYL-2-DIMETHYLPHOSPHONO-2-OXOACETATE (197)

(a) Methyl-2-dimethylphosphono-2-oxoacetate (197) (196 mg, 1 mMol) and triethylamine (1 drop) were added, at 20°C, to a dry THF solution of (4RS)-4-acetoxyazetidin-2-one (184) (129 mg, 1 mMol) and the mixture stirred for 16 hours at 20°C. Dilution with ethyl acetate, washing with water, drying ($MgSO_4$) and evaporation *in vacuo* gave a dark yellow oil. T.l.c., i.r. and H^1-n.m.r. data indicated no reaction had taken place.

(b) (4RS)-4-Acetoxyazetidin-2-one (184) (129 mg, 1 mMol) was added to a solution of methyl-2-dimethylphosphono-2-oxoacetate (197) (196 mg, 1 mMol) in dry toluene and the mixture refluxed for 4 hours with azeotropic removal of water. Removal of the solvent and chromatography of the residue on silica produced starting materials as judged by t.l.c. and H^1-n.m.r.

BENZYL-(2RS)-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]-2-DIMETHYL-PHOSPHONOACETATE (200)

Benzyl-(2RS)-2-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]-2-chloro acetate (194) (1.45 g, 4.6 mMol) was dissolved in freshly distilled trimethylphosphite (25 ml) and heated to reflux, under nitrogen, for 3 hours. The excess trimethylphosphite was removed *in vacuo* and the residue chromatographed on silica to give benzyl-(2RS)-2-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]-2-dimethylphosphonoacetate (200) as a pale yellow oil (625 mg, 35%). ν_{max} ($CHCl_3$), 1780 (β-lactam C=O), 1750 (ester), 1230 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.34 (5H,s,Ph), 6.50 and 6.30 (1H,dd,J=4.9 and 1.6Hz,H4,diastereoisomers), 5.24 (2H,s, CH_2Ph), 5.0 (1H,d,J=24.6Hz,$H^1\{P^{31}\}$ collapses to singlet, $CH\overset{O}{\overset{\|}{P}}$), 3.80 (6H, d,J=10.8Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}(OMe)_2$), 3.2 (2H,m,H3) and 2.1, 2.04 (3H,s,OCOMe,diastereoisomers), M^++1, 386, M^++1-42, 344 (C.I. CH_4 carrier gas). (Found: C, 49.94; H, 5.33; N, 3.77. $C_{16}H_{20}NO_8P$ requires C, 49.84; H, 5.19; N,3.64%).

(4RS)-4-PHENYLTHIOAZETIDIN-2-ONE (202)[5]

Sodium borohydride (1.44 g, 37.5 mMol) was added portionwise to a cooled solution of thiophenol (2.75 g, 25 mMol) in absolute ethanol under nitrogen. When evolution of hydrogen had ceased a solution of (4RS)-4-acetoxyazetidin-2-one (184) (3.23 g, 25 mMol) was added in one portion and the mixture stirred for 20 minutes at 20°C. The reaction was diluted with dichloromethane and washed with brine. The organic phase was dried ($MgSO_4$) and removed *in vacuo* to give a white solid. Recrystallisation from ether/petroleum ether (1:2) afforded (4RS)-4-phenylthioazetidin-2-one (202) as colourless plates (2.57 g, 88%). ν_{max} ($CHCl_3$), 3200 (NH) and 1730 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 7.1 (6H,s, becomes 5H on D_2O exchange, Ph and NH), 4.9 (1H,dd,J=8.0 and 2.0Hz,H4), 3.65 (2H,m,H3), M^+, 179.

BENZYL-(2RS)-2-HYDROXY-2-[2-OXO-(4RS)-4-PHENYLTHIOAZETIDIN-1-YL]-ACETATE (203)

(4RS)-4-Phenylthioazetidin-2-one (202) (1.79 g, 10 mMol) was dissolved in dry THF at 20°C and treated with benzyl glyoxylate (1.82 g, 10 mMol) and triethylamine (1 drop) and stirred at 20°C for 16 hours. The mixture was poured into ethyl acetate/water and extracted. Washing of the organic layer with water (4 x 20 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave benzyl-(2RS)-2-hydroxy-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]acetate (203) as a pale yellow oil (3.3 g, 96%). ν_{max} ($CDCl_3$), 3500 (OH), 1780 (β-lactam C=O) and 1725 cm^{-1} (ester C=O), δ ($CDCl_3$), 7.38 (10H,s,Ph), 5.51, 5.45 (1H,s,CHOH,diastereoisomers), 5.20 (2H,s,CH_2CO_2R), 5.05 (1H,dd,J=6.0 and 2.0Hz,H4), 4.7-4.3 (1H,Br.s,lost on D_2O exchange,OH) and 3.0 (2H,m,H3).

BENZYL-(2RS)-2-CHLORO-2-[2-OXO-(4RS)-4-PHENYLTHIOAZETIDIN-1-YL]-ACETATE (204)

Benzyl-(2RS)-2-hydroxy-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]-acetate (203) (3.43 g, 10 mMol) was dissolved in dry THF under nitrogen and cooled to -25°C. 2,6-Lutidine (1.07 g, 10 mMol) was added followed by dropwise addition of freshly distilled thionyl chloride (1.19 g, 10 mMol) over 30 minutes. The reaction was warmed to 0°C and stirred for 16 hours. The mixture was then filtered and the filtrate evaporated *in vacuo*. Flash chromatography of the residue on silica afforded benzyl-(2RS)-2-chloro-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]-acetate (204) as a yellow oil (3.59 g, 99%). ν_{max} ($CHCl_3$), 1780 (β-lactam C=O) and 1760 cm^{-1} (ester C=O), δ ($CDCl_3$), 7.35 (10H,s,Ph), 6.1, 5.95 (1H,s,CHCl, diastereoisomers), 5.25, 5.18 (2H,s,CH_2CO_2R, diastereoisomers), 4.3-3.5 (1H,m,H4,diastereoisomers), 3.3-2.7 (2H,m,H3,diastereoisomers).

BENZYL-(2RS)-2-DIMETHYLPHOSPHONO-2-[2-OXO-(4RS)-4-PHENYLTHIOAZETIDIN-1-YL]ACETATE (201)

Benzyl-(2RS)-2-chloro-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl] acetate (204) (3.61 g, 10 mMol) was dissolved in freshly distilled trimethyl phosphite (30 ml) and heated to reflux, under nitrogen, for 6 hours. After this time the excess trimethyl phosphite was evaporated *in vacuo* and the residue chromatographed on silica to give benzyl-(2RS)-2-dimethylphosphono-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]acetate (201) as a pale yellow oil (1.50 g, 37%). ν_{max} (CH_2Cl_2), 1780 (β-lactam C=O), 1740 (ester C=O), 1190 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.36 (10H,s,Ph), 5.24 (2H,s,$\underline{CH_2}CO_2R$), 5.14 (1H,dd,J=6.0 and 2.0Hz,$H^1\{P^{31}\}$ simplifies signal,H4), 4.90, 4.64 (1H,d,J=13.3Hz,$H^1\{P^{31}\}$ gives two singlets,$\underline{CH}\overset{O}{\overset{\|}{P}}$, diastereoisomers), 3.90 (6H,d,J=13.0Hz,$\overset{O}{\overset{\|}{P}}(O\underline{Me})_2$), 3.40 (1H,dd,J=16.6 and 6.0Hz,H3 *cis*) and 2.94 (1H,dd,J=16.6 and 6.0Hz, H3 *trans*), M^+, 435 (C.I., isobutene and ammonia carrier gas). (Found: C, 55.5; H, 5.15; N, 3.07. $C_{20}H_{22}NO_6PS$ requires C, 55.17; H, 5.06; N, 3.22%).

BENZYL-(2RS)-2-[(4RS)-4-CHLORO-2-OXOAZETIDIN-1-YL]-2-DIMETHYLPHOSPHONO-ACETATE (205)

Benzyl-(2RS)-2-dimethylphosphono-2-[(2-oxo-(4RS)-4-phenylthio-azetidin-1-yl]acetate (201) (100 mg, 0.23 mMol) was dissolved in dry dichloromethane and cooled to -78°C. The solution was treated with excess chlorine and warmed to 0°C and the volatile material removed *in vacuo* to give benzyl-(2RS)-2-[(4RS)-4-chloro-2-oxoazetidin-1-yl]2-dimethylphosphonoacetate (205) as a yellow oil (82 mg, 99%). ν_{max} ($CHCl_3$), 1790 (β-lactam C=O), 1750 (ester C=O), 1270 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.36 (5H,s,Ph), 6.0, 5.84 (1H,dd,J=4.0 and <1.0Hz,H4,diastereoisomers), 5.24 (2H,s,$\underline{CH_2}CO_2R$), 4.82 (1H,d,

J=25Hz,$H^1\{P^{31}\}$ collapses to singlet,$\underset{\underset{O}{\|}}{CHP}$), 3.78 (6H,d,J=15Hz,$H^1\{P^{31}\}$ collapses to singlet $\underset{\underset{O}{\|}}{P}(OMe)_2$) and 3.36 (2H,m,H3), M^+ 361,363 (Cl^{35}:Cl^{37}, 3:1, C.I. NH_3 carrier gas).

GENERAL METHOD FOR PREPARATION OF PHOSPHONIC ACID MONO METHYL ESTERS (206) AND (207)

A solution of the phosphono acetate (1 equiv.) in dry DCM was treated with trimethylsilyl bromide (1 equiv.) under nitrogen. The resulting yellow solution was stirred for 4 hours at 20°C and the volatile material removed *in vacuo* to give the monotrimethylsilyloxy-phosphono acetates (212, n=1 or 2) as pale yellow oils (100%). ν_{max} ($CHCl_3$) for methyl-2-(methyltrimethylsilyloxyphosphono)acetate (212, n=1), 1740 (ester C=O), 1260 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$) for (212, s=1), 3.90 (3H,d,J=15.9Hz,$\underset{\underset{O}{\|}}{P}(OMe)$), 3.85 (3H,s,$CO_2Me$), 3.10 (2H, d,J=18.0Hz,$\underline{CH_2}CO_2R$) and 0.40 (9H,s,$SiMe_3$). ν_{max} ($CDCl_3$) for methyl-3-(methyltrimethylsilyloxyphosphono)propionate (212, n=2), 1740 (ester C=O), 1250 (P=O) and 1180 cm^{-1} (POMe). The monotrimethylsilyloxy-phosphonates were dissolved in chloroform and stirred with aqueous acetone (10%) for 16 hours at 20°C. Removal of the solvent *in vacuo* gave the monophosphonic acids as pale red oils (100%). ν_{max} ($CHCl_3$) for monophosphonic acid acetate (206), 3500-2000 (POH), 1740 (ester C=O), 1250 (P=O) and 1040 (POMe), δ ($CDCl_3$) for (206), 10.4 (1H,Brs, lost on D_2O exchange,POH), 3.90 (3H,d,J=15.0Hz,$\underset{\underset{O}{\|}}{P}(OMe)$), 3.74 (3H, s,$CO_2\underline{Me}$) and 3.04 (2H,d,J=18.9Hz,$\underset{\underset{O}{\|}}{P}\underline{CH_2}CO_2R$), δ ($CHCl_3$) for mono-phosphonic acid propionate (207), 8.5 (1H, brs,$\underline{POH}$ exchange with D_2O), 3.70 (d,3H,J=12.0Hz,$\underset{\underset{O}{\|}}{P}OMe$), 3.66 (3H,s,$CO_2Me$) and 2.9-1.5 (4H, multiplet, $\underset{\underset{O}{\|}}{P}\underline{CH_2}\underline{CH_2}$-).

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH MONOPHOSPHONOIC ACID ACETATE (206)

(a) Phosphonic acid acetate (206) (168 mg, 1 mMol) was dissolved in dry THF under argon and treated with potassium hydride (40 mg, 1 mMol) at 20°C. After stirring for 10 minutes a solution of (4RS)-4-acetoxyazetidin-2-one (184) (129 mg, 1 mMol) and dibenzo-18-crown-6 (36 mg, 0.1 mMol) in dry THF was added and the mixture stirred for 16 hours at 20°C. The solvent was then removed to give a yellow oil. T.l.c. and i.r. indicated β-lactam cleavage to have occurred.

(b) Use of sodium bicarbonate and 15-crown-5 (0.1 equiv.) following method (a) gave the same result.

(c) Monophosphonic acid (206) (168 mg, 1 mMol) was dissolved in aqueous THF at 20°C and DBU (142 mg, 1 mMol) added. The turbid solution was treated with (4RS)-4-acetoxyazetidin-2-one (184) (129 mg, 1 mMol) and the reaction left at 20°C for 16 hours. The solvent was removed *in vacuo* to give a yellow oil. H^1-n.m.r. and i.r. indicated the presence of starting materials only.

(d) A suspension of silver carbonate (276 mg, 1 mMol) in water was treated with the monophosphonic acid (206) (168 mg, 1 mMol) and stirred at 20°C until evolution of CO_2 had ceased. An aqueous solution of (4RS)-4-acetoxyazetidin-2-one (184) (129 mg, 1 mMol) was added and the suspension stirred for 16 hours at 20°C. The mixture was filtered through celite and the filtrate evaporated *in vacuo*. Chromatography of the residue on silica afforded only starting materials.

(e) Conditions (d) were used with copper carbonate, the same result being obtained.

(f) Potassium carbonate with conditions (d) gave no reaction.

(g) (4RS)-4-Acetoxyazetidin-2-one (184) (128 mg, 1 mMol) was dissolved in dry THF and treated with powered potassium hydroxide (56 mg, 1 mMol) and monophosphonic acid (206) (168 mg, 1 mMol) followed by tetra-n-butylammonium bromide (32.2 mg, 0.1 mMol) and the suspension stirred at 20°C for 20 hours. Removal of the solvent *in vacuo* afforded starting material only.

ATTEMPTED REACTION OF (4RS)-4-ACETOXYAZETIDIN-2-ONE (184) WITH MONOPHOSPHONIC ACID PROPIONATE (207)

(a) Phosphonic acid (207) (455 mg, 2.5 mMol) was dissolved in dry DMF and treated with anhydrous potassium carbonate (345 mg, 2.5 mMol) and stirred for 15 minutes before addition of (4RS)-4-acetoxyazetidin-2-one (184) (323 mg, 2.5 mMol). The reaction was stirred at 20°C for 3 hours followed by 80°C for 2 hours, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a pale yellow oil. I.r. and H^1-n.m.r. indicated β-lactam cleavage.

(b) (4RS)-4-Acetoxyazetidin-2-one (184) (323 mg, 2.5 mMol) was dissolved in dry DCM at 20°C and treated with the phosphonic acid (207) (455 mg, 2.5 mMol) and triethylamine (277 mg, 2.5 mMol). The mixture was stirred at 20°C for 5 hours followed by refluxing for 16 hours. Removal of the solvent and chromatography of the residue on silica gave starting materials only.

(c) DBU in DCM following method (b) gave the same result.

(d) (4RS)-4-Acetoxyazetidin-2-one (184) (129 mg, 1 mMol) was dissolved in dry THF under nitrogen and phosphonic acid (207) (182 mg, 1 mMol) and zinc acetate[99] dihydrate (22 mg, 0.1 mMol) were added. The mixture was refluxed for 20 hours, poured into water and extracted

with ethyl acetate. The organic layer was dried ($MgSO_4$) and removed *in vacuo* and the residue chromatographed on silica to give starting materials only.

(e) Powered potassium hydroxide (112 mg, 2 mMol)[83] was added to a dry THF solution of (4RS)-4-acetoxyazetidin-2-one (184) (258 mg, 2 mMol) in THF under nitrogen and the phosphonic acid (207) (364 mg, 2 mMol) was added followed by tetra-n-butylammonium bromide (66 mg, 0.2 mMol). The mixture was stirred for 20 hours at 20°C and the solvent evaporated *in vacuo*. Chromatography of the residue on silica gave methyl-O-methyl-O-[(4RS)-2-oxoazetidin-4-]-3(RS)-phosphonopropanoate (217) as a yellow oil (3 mg, 0.6%). ν_{max} ($CHCl_3$) 1770 (β-lactam C=O), 1740 (ester C=O), 1230 (P=O) and 1035 cm^{-1} (POMe), δ ($CDCl_3$), 5.06 (1H,dd,J=5.0 and 2.0Hz,H4), 3.76 (3H,d,J=12.0Hz, $\overset{O}{\overset{\|}{P}}(OMe)$), 3.72 (3H,m,$CO_2Me$), 3.0 (2H,m,H3) and 2.7-1.0 (4H,m,$CH_2CH_2CO_2R$). M^+. (Found: 251.0670. $C_8H_{14}NO_6P$ requires 251.0559 [determined manually at Pfizer Central Research, Kent]).

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-PHENYLTHIOAZETIDIN-2-ONE (221)

^{t}Butyllithium (2.5 mMol) in dry THF under argon at -78°C was treated with a dry THF solution of (4RS)-4-phenylthioazetidin-2-one (219a) (448 mg, 2.5 mMol). The yellow solution was stirred for 1 hour at -78°C. ^{t}Butyldimethylsilyl chloride (377 mg, 2.5 mMol) was added and the solution warmed to 20°C and stirred overnight. Quenching of the reaction with ice/water and extraction with ethyl acetate gave, after drying of the solvent ($MgSO_4$) and removal *in vacuo*, (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-phenylthioazetidin-2-one (221) as a yellow oil (0.615 g, 84%). ν_{max} ($CHCl_3$), 1730 cm^{-1} (βlactam C=O), δ ($CDCl_3$), 7.25 (5H,s,Ph), 4.8 (1H,dd,J=6.0 and 3.0Hz, H4), 3.36 (1H,dd,J=18.0 and 6.0Hz,H3,*cis*), 2.82 (1H,dd,J=18.0 and

3.0Hz,H3,*trans*), 0.9 (9H,s,^{t}Bu) and 0.2 (6H,s,Me_2), $\delta_{C^{13}}$ ($CDCl_3$), 169.01 (s,β-lactam C=O), 131.19-126.59 (m,Ph), 55.52 (d,C4), 46.96 (t,C3), 24.85 (q,$\underline{C}Me_3$), 16.84 (s,$\underline{C}Me_3$) and 5.53 (q,Si$\underline{Me}_2$). (Found: C, 61.53; H, 7.79; N, 4.88; $\underline{M}^+$, 293.1224. $C_{15}H_{23}NOSSi$ requires C, 61.43; H, 7.85; N, 4.78%; $\underline{M}^+$, 293.1274).

(4RS)-4-METHYLTHIOAZETIDIN-2-ONE (219)

Methane thiol (4.12 g, 87.6 mMol) condensed in a dry ice trap was added over 3 minutes to a stirred solution of sodium hydroxide (3.60 g, 0.09 mol) in water/acetone (43:16) at 0°C. A solution of (4RS)-4-acetoxyazetidin-2-one (184) (10.56 g, 82 mMol) in acetone (26 ml) was added over 15 minutes at 0°C and stirred for 3 hours. The acetone was removed *in vacuo* and the residue extracted with ethyl acetate. The organic phase was extracted with brine, dried ($MgSO_4$) and concentrated to ca. 15 ml. Petroleum ether (40-60) was added (10 ml) and the turbid solution left at 0°C overnight. Filtration of the suspension and washing of the solid with petroleum ether (40-60)/ether (1:4) gave (4RS)-4-methylthioazetidin-2-one (219) as white flakes (6.0 g, 63%). δ ($CDCl_3$), 7.15 (1H,Brs,NH), 4.80 (1H,dd,J=6.0 and 2.5Hz,H4), 3.20 (2H,m,H3) and 2.2 (3H,s,SMe).

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-METHYLTHIOAZETIDIN-2-ONE (220)

(4RS)-4-Methylthioazetidin-2-one (219) (1.18 g, 10 mMol) was dissolved in dry THF under nitrogen and cooled to -78°C. ^{n}Butyllithium (10 mMol) was added slowly and the mixture stirred for 1 hour at -78°C before addition of ^{t}butyldimethylsilyl chloride (1.50 g, 10 mMol). The yellow solution warmed to 20°C (2 hours) and stirred for 18 hours. The mixture was poured into ethyl acetate/ice and extracted.

The organic phase was washed with water, dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. Chromatography on silica afforded (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-methylthioazetidin-2-one (220) as a pale yellow oil (1.71 g, 74%). ν_{max} ($CHCl_3$), 1740 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 4.65 (1H,dd,J=5.5 and 2.0Hz,H4), 3.48 (1H,dd,J=18.0 and 7.0Hz,H3,*cis*), 2.10 (1H,dd,J=18.0 and 3.0Hz,H3,*trans*), 2.08 (3H,s,SMe), 0.95 (9H,s,^{t}Bu) and 0.30 (6H,s,Me_2). (Found: $\underline{M}^+$, 231.1112, $C_{10}H_{21}NOSSi$ requires M^+, 231.1113).

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-CHLOROAZETIDIN-2-ONE (222)

A solution of (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-methyl- or -phenylthioazetidin-2-one (219) or (219a) in DCM was treated with a DCM solution of chlorine (excess) at -78°C for 1 hour and warmed to room temperature. Removal of the volatile material *in vacuo* gave (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-chloroazetidin-2-one (222) as a pale yellow oil (186 mg, 100%) [no further purification was attempted]. ν_{max} ($CHCl_3$), 1780 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 5.60 (1H,m,H4), 3.35 (2H,m,H3), 0.93 (9H,s,^{t}Bu) and 0.30 (6H,s,Me_2), δ_{C13} ($CDCl_3$), 168.04 (s,$\underline{C}$=O), 64.51 (d,C4), 50.91 (t,C3), 25.28 (q,$\underline{C}Me_3$), 17.05 (s,$\underline{C}Me_3$) and 6.10 (q,$SiMe_2$).

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-ACETOXYAZETIDIN-2-ONE (223)

Silver acetate (137 mg, 0.82 mMol) was suspended in dry acetonitrile at 20°C under argon, in the dark, and treated with an acetonitrile solution of (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-chloroazetidin-2-one (222) (181 mg, 0.82 mMol). Stirring was contined for 2 hours at room temperature and filtered through celite. The filtrate was evaporated *in vacuo* and the residue chromatographed on silica to give (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-acetoxyazetidin-2-one (223) as a pale yellow oil (56.8 mg, 30%). ν_{max} ($CHCl_3$), 1760

(β-lactam C=O) and 1720 cm^{-1} (acetate C=O), δ ($CDCl_3$), 6.01 (1H,dd, J=5.0 and 1.5Hz,H4), 3.4 (1H,dd,J=18.0 and 6.0Hz,H3,*cis*), 2.85 (1H, dd,J=18.0 and 2.0Hz,H3,*trans*), 2.03 (3H,s,OCOMe), 0.95 (9H,s,^{t}Bu) and 0.21 (6H,s,Me_2). M^+, 243.

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-ISOTHIOCYANATOAZETIDIN-2-ONE (224)

Silver isothiocyanate (165 mg, 1 mMol) was suspended in dry acetonitrile under argon at 20°C and treated with (1RS)-1-^{t}butyl-dimethylsilyl-(4RS)-4-chloroazetidin-2-one (222) (220 mg, 1 mMol). The suspension was stirred for 2 hours, in the absence of light, then filtered through celite and the filtrate evaporated *in vacuo* to give a yellow oil. Chromatography on silica afforded (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-isothiocyanatoazetidin-2-one (224) as a pale yellow oil (97 mg, 29%). ν_{max} ($CHCl_3$), 2160 (CN) and 1770 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 5.18 (1H,dd,J=10.0 and 5.0Hz,H4), 3.5 (1H,dd,J=16.0 and 6.0Hz,H3,*cis*), 3.20 (1H,dd,J=16.0 and 3.0Hz,H3, *trans*), 1.0 (9H,s,^{t}Bu) and 0.3 (6H,s,Me_2). (Found: M^+, 242.0909. $C_{10}H_{18}N_2SSi$ requires 242.0900).

METHYL-2-(SILVERMONOMETHYLPHOSPHONO)ACETATE (225)

Monomethylphosphono acetate (206) (168 mg, 1 mMol) was dissolved in dry chloroform and treated with silver oxide (116 mg, 0.5 mMol) and anhydrous magnesium sulphate (0.5 g) and the suspension stirred for 48 hours at 20°C in the absence of light. Filtration through celite followed by removal of the solvent afforded the silver salt (225) as a pale yellow oil which slowly darkened on exposure to light (274 mg, 100%). ν_{max} ($CHCl_3$), 1740 (ester C=O), 1250 (P=O) and 1060 cm^{-1} (POMe), δ ($CDCl_3$), 3.85 (3H,d,J=15Hz,$\overset{O}{\overset{\|}{P}}$(OMe)), 3.80 (3H,s, CO_2Me) and 3.0 (2H,d,J=24Hz,$\overset{O}{\overset{\|}{P}}CH_2CO_2Me$).

ATTEMPTED REACTION OF (1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-CHLORO-AZETIDIN-2-ONE (222) WITH THE SILVER SALT (225)

A suspension of the silver salt (225) (100 mg, 0.36 mMol) in dry acetonitrile under nitrogen was treated with an acetonitrile solution of (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-chloroazetidin-2-one (222) (98.6 mg, 0.36 mMol) at 20°C and stirred for 3 hours. The mixture was filtered through celite and the filtrate evaporated *in vacuo* to give a yellow oil (120mg). ν_{max} ($CHCl_3$), (crude reaction mixture), 1780 (β-lactam C=O), 1740 (ester C=O), 1250 (P=O) and 1060 cm^{-1} (POMe). Chromatography on silica or neutral alumina gave a non β-lactam containing material which was not further examined.

METHYL-2-DIAZO-2-(MONOMETHYLPOTASSIUMPHOSPHONO)ACETATE (215)

Trimethylsilyl bromide (153 mg, 1 mMol) was added to a solution of 2-diazotrimethylphosphono acetate (213) (208 mg, 1 mMol) in dry chloroform under argon at 20°C and the resulting yellow solution stirred for 4 hours. The volatile material was removed *in vacuo* to give a pale yellow solid which was dissolved in 10% aqueous acetone and left at room temperature for 24 hours. Removal of the solvent *in vacuo* afforded the monomethylphosphonic acid (214) as a pale yellow oily solid (194 mg, 100%). ν_{max} ($CHCl_3$), 3000-2400 (POH), 2150 (diazo), 1710 (ester C=O), 1300 (P=O) and 1060 cm^{-1} (POMe). The phosphonic acid was dissolved in water and treated with aqueous potassium hydroxide until the pH was 7.0. Freeze drying of this solution gave the potassium salt (215) as a pale yellow solid (232 mg, 100%).

REACTION OF (1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-CHLOROAZETIDIN-2-ONE (222) WITH METHYL-2-DIAZO-2-(MONOMETHYLPOTASSIUMPHOSPHONO)-ACETATE (215)

A suspension of methyl-2-diazo-2-(monomethylpotassiumphosphono)-acetate (215) (232 mg, 1 mMol) in dry acetonitrile at 20°C under nitrogen was treated with an acetonitrile solution of (1RS)-1-^{t}butyl-dimethylsilyl-(4RS)-4-chloroazetidin-2-one (222) (220 mg, 1 mMol). The suspension was stirred for 1.5 hours and filtered through celite. Evaporation of the filtrate *in vacuo* gave a yellow oil (300 mg). ν_{max} ($CHCl_3$), 2150 (diazo), 1760 (β-lactam C=O), 1705 (ester C=O), 1260 (P=O) and 1060 cm^{-1} (POMe), δ ($CDCl_3$), 5.65 (1H,m,H4), 4.0-3.2 (8H,m,$\overset{O}{\overset{\|}{P}}$(OMe),$CO_2Me$ and H3), 1.0 (9H,s,Si^{t}Bu) and 0.3 (6H,s,Si$\underline{Me}_2$). Chromatography of this material on silica or neutral alumina failed to give any β-lactam containing material with spectral data corresponding to that above. Nothing further was undertaken with this system.

REACTION OF MONOTRIMETHYLSILYLOXYPHOSPHONATE (212) WITH PHOSPHORUS PENTACHLORIDE

Trimethylphosphono acetate (10 g, 55 mMol) was dissolved in dry chloroform and treated with trimethylsilyl bromide (8.42 g, 55 mMol) at 20°C under an inert atmosphere. After stirring for 4 hours the volatile material was removed *in vacuo* to give a yellow oil. This oil was dissolved in dry DCM and added to a suspension of phosphorus pentachloride (11.33 g, 55 mMol) in dry DCM (exothermic). The suspension was stirred for 1 hour at 20°C after which time all the solid had dissolved. Removal of the volatile material *in vacuo* gave the phosphonochloridate (229) as a pale yellow oil (9.58 g, 94%). ν_{max} ($CHCl_3$), 1740 (ester C=O), 1280 (P=O) and 1040 cm^{-1} (POMe),

δ ($CDCl_3$), 4.0 (3H,d,J=15Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}$-OMe), 3.80 (3H,s,$CO_2Me$) and 3.54 (2H,d,J=20Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}\underline{CH_2}CO_2R$). No mass ion obtained.

REACTION OF PHOSPHOROCHLORIDATE (229) WITH BENZYL MERCAPTAN

Phosphorochloridate (229) (1.78 g, 9.5 mMol) was dissolved in dry ether under argon at 20°C and added to an ethereal solution of benzyl mercaptan (1.24 g, 10 mMol) and triethylamine (1.01 g, 10 mMol) and the suspension stirred at 20°C for 18 hours. Removal of the volatile material *in vacuo* gave methyl-(S-benzyl-O-methylphosphono)-acetate (231) as a pale yellow oil (2.60, 95%). ν_{max} ($CHCl_3$), 1750 (ester), 1260 (P=O) and 1050 cm^{-1} (POMe).
δ ($CDCl_3$), 4.18 (3H,d,J=15.0Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}$-OMe), 3.64 (5H,m,$H^1\{P^{31}\}$ collapses to singlet, $CO_2\underline{Me}$ and $Ph\underline{CH_2}S$) and 3.14 (2H,d,J=18.9Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}\underline{CH_2}CO_2R$). (Found: $\underline{M}^+$, 274.0428. $C_{11}H_{15}O_4PS$ requires $\underline{M}^+$, 260.0272).

REACTION OF PHOSPHONOCHLORIDATE (229) WITH THIOPHENOL

Thiophenol (1.10 g, 10 mMol) and triethylamine were dissolved in dry ether under argon at 20°C. Phosphonochloridate (229) (1.86 g, 10 mMol) was added (care, extremely exothermic) and the suspension stirred for 1 hour at room temperature. The mixture was poured into ethyl acetate/water and extracted. The organic layer was washed with water, dried ($MgSO_4$) and removed *in vacuo* to give methyl-(O-methyl-S-phenylphosphono)acetate (230) as a pale yellow oil (2.60 g, 100%).
δ ($CDCl_3$), 7.38 (5H,s,Ph), 3.90 (3H,d,J=15.0Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}$-OMe), 3.70 (3H,s,$CO_2Me$) and 3.30 (2H,d,J=18.0Hz,$H^1\{P^{31}\}$ collapses to singlet,$\overset{O}{\overset{\|}{P}}\text{-}\underline{CH_2}CO_2R$). (Found: 260.0232. $C_{10}H_{13}O_4PS$ requires 260.0272).

(4RS)-4-BENZYLTHIOAZETIDIN-2-ONE (232)[5]

Sodium borohydride (0.22 g, 5.8 mMol) was added in portions to a cooled solution (0°C) of benzyl mercaptan (0.48 g, 3.9 mMol) in absolute ethanol (15 ml). When the initial reaction had subsided a solution of (4RS)-4-acetoxyazetidin-2-one (184) (0.5 g, 3.9 mMol) in absolute ethanol (3 ml) was added in one portion. After 1.5 hours the reaction was diluted with DCM and washed with brine, dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. Chromatography on silica afforded (4RS)-4-benzylthioazetidin-2-one (232) as a yellow oil which crystallised on cooling (474 mg, 63%). ν_{max} (CH_2Cl_2), 3400 (NH), 1760 (β-lactam C=O) and 900 cm^{-1} (Ph), δ ($CDCl_3$), 7.30 (6H,s,Ph and NH), 4.60 (1H,dd,J=5.0 and 2.0Hz,H4), 3.80 (2H,s,$\underline{CH_2}$Ph), 3.25 (1H,ddd,J=16.0, 5.0 and 2.0Hz,H3,*cis*) and 2.70 (1H,dd,J=16.0 and 2.0Hz,H3,*trans*).

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-BENZYLTHIOAZETIDIN-2-ONE (233)

(4RS)-4-Benzylthioazetidin-2-one (232) (237 mg, 1 mMol) was dissolved in dry THF under nitrogen at -50°C. ^{n}Butyllithium (1 mMol) was added and the mixture stirred for 1 hour at -50°C before addition of ^{t}butyldimethylsilylchloride (188 mg, 1.3 mMol). The mixture was warmed to 20°C and stirred for 4 hours and poured into iced water/ethyl acetate and extracted. The organic phase was washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil. Chromatography on silica afforded (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-benzylthioazetidin-2-one (233) as a yellow oil (327 mg, 83%). ν_{max} ($CHCl_3$), 1750 cm^{-1} (β-lactam C=O), δ ($CDCl_3$), 7.25 (5H,s, Ph), 4.52 (1H,dd,J=6.5 and 1.6Hz,H4), 3.78 (2H,s,$\underline{CH_2}$Ph), 3.38 (1H,dd,J=18.0 and 7.0Hz,H3,*cis*) and 2.95 (1H,dd,J=18.0 and 3.0Hz,H3,*trans*), $\delta_{C^{13}}$ ($CDCl_3$), 170.59 (s,$\underline{C}$=O), 137.55 (s,Ph), 128.77-127.36 (m,Ph),

54.55 (d,C4), 48.32 (t,C3)*, 34.08 (t,$\underline{CH_2}$Ph)*, 26.33 (q,$\underline{CMe_3}$), 18.31 (s,$\underline{CMe_3}$), 5.60 (q,Si$\underline{Me_2}$). (Found: C, 62.63; H, 8.11; N, 4.39. $C_{16}H_{25}NOSSi$ requires C, 62.54; H, 8.14; N, 4.56%).

*Assignment may be reversed.

REACTION OF (4RS)-4-BENZYLTHIOAZETIDIN-2-ONE (232) WITH SODIUM/LIQUID AMMONIA[5] FOLLOWED BY DIETHYLPHOSPHOROCHLORIDATE

Sodium (53.3 mg, 2.3 mMol) was dissolved in liquid ammonia and treated with (4RS)-4-benzylthioazetidin-2-one (232) (224 mg, 1.16 mMol). The mixture was stirred for 6 hours at -78°C after which time the solution became yellow and the ammonia was removed. After warming the solution to -30°C, with a stream of nitrogen, diethylphosphorochloridate (200 mg, 1.16 mMol) in dry THF was added to the white residue and the mixture warmed slowly to 20°C, poured into saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. H^1-n.m.r. showed the presence of starting material only.

Use of DMF as a solvent after removal of the excess ammonia resulted in β-lactam cleavage.

REACTION OF (1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-BENZYLTHIOAZETIDIN-2-ONE (233) WITH SODIUM/LIQUID AMMONIA FOLLOWED BY DIETHYLPHOSPHOROCHLORIDATE

Sodium (25 mg, 1.09 mMol) was dissolved in liquid ammonia and treated with (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-benzylthioazetidin-2-one (233) (333 mg, 1.09 mMol). The mixture was stirred until the blue colour had vanished, then warmed to -30°C and the excess ammonia removed in a stream of nitrogen. The white residue was suspended in dry ether and treated with an ethereal solution of diethylphosphoro-

chloridate (187 mg, 1.09 mMol) and warmed to 20°C. The reaction was poured into water and extracted with ethyl acetate. Drying of the organic phase ($MgSO_4$) and removal *in vacuo* gave a yellow oil, spectroscopic examination of which indicated only starting material to be present.

REACTION OF BENZYL-(2RS)-2-[(4RS)-4-CHLORO-2-OXOAZETIDIN-1-YL]-2-DIMETHYLPHOSPHONOACETATE (205) WITH TRIMETHYLSILYL BROMIDE

Benzyl-(2RS)-2-[(4RS)-4-chloro-2-oxoazetidin-1-yl]-2-dimethylphosphonoacetate (205) (36.1 mg, 0.1 mMol) was dissolved in dry $CDCl_3$ (200 µl) under argon at 20°C and treated with trimethylsilyl bromide (15.3 mg, 0.1 mMol in 100 µl). The reaction volume was adjusted to 700 µl with $CDCl_3$ and monitored by H^1-n.m.r. (observe increase in δ = 2.68 [MeBr] and decrease in δ = 3.80 [$\overset{O}{\overset{\|}{P}}(OMe)_2$]). After 4 hours at 20°C the solvent was removed *in vacuo* to give benzyl-(2RS)-2-[(4RS)-4-chloro-2-oxoazetidin-1-yl]-(2RS)-2-methyltrimethylsilyloxyphosphonoacetate (238) as a pale yellow oil (42 mg, 100%). ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1730 (ester C=O), 1220 (P=O) and 1070 cm^{-1} (POMe and POTMS), δ ($CDCl_3$), 7.40 (5H,s,Ph), 6.05 and 5.85 (1H,m,H4,diastereoisomers), 5.30 (2H,s,$\underline{CH_2}$Ph), 4.0-3.2 (5H,m, $\overset{O}{\overset{\|}{P}}$(OMe) and H3) and 0.40 (9H,s,Si$\underline{Me_3}$).

ATTEMPTED HYDROLYSIS OF BENZYL-(2RS)-2-[(4RS)-4-CHLORO-2-OXOAZETIDIN-1-YL]-(2RS)-2-O-METHYL-O-TRIMETHYLSILYLPHOSPHONOACETATE (238)

(a) Silyloxyphosphonate (238) (42 mg, 0.1 mMol) was dissolved in dry DMF/DCM (1:4) under argon and treated with anhydrous potassium fluoride (5.9 mg, 0.1 mMol) and dicyclohexano-18-crown-6 (3.73 g, 0.01 mMol) and the mixture stirred at 20°C for 16 hours. The solvent was then removed *in vacuo* to give a yellow oil. I.r. showed that β-lactam cleavage had occurred.

(b) Silyloxyphosphonate (238) (113 mg, 0.27 mMol) was dissolved in dry acetonitrile under nitrogen and added to a suspension of silver fluoride (113 mg, 0.27 mMol) and silver tetrafluoroborate (72 mg, 0.27 mMol) under argon. The mixture was stirred for 2 hours at 20°C, then filtered through celite and the filtrate evaporated *in vacuo* to give a pale yellow oily solid. I.r. showed β-lactam cleavage.

(c) Anhydrous tetra-n-butylammonium fluoride (35.2 mg, 0.14 mMol) was dissolved in dry $CDCl_3$ and added to a $CDCl_3$ solution of silyloxyphosphonate (238) (50 mg, 0.14 mMol). The mixture was monitored by H^1-n.m.r. which showed no reaction to be taking place. After 48 hours at 20°C i.r. showed β-lactam cleavage to have occurred.

(d) Silver tetrafluoroborate (1 eqiv.) under conditions (b) resulted in β-lactam cleavage.

(e) Silyloxyphosphonate (238) (50 mg, 0.14 mMol) was dissolved in 10% aqueous acetone containing cyclohexylamine (14 mg, 0.14 mMol) and the solution left at 20°C for 20 hours. Removal of the solvent *in vacuo* gave a yellow residue. I.r. showed no β-lactam to be present.

(f) Use of aniline (1 equiv.) in 10% aqueous acetone gave the same result as in (e).

REACTION OF BENZYL-(2RS)-2-[(4RS)-4-ACETOXYAZETIDIN-1-YL]-2-DIMETHYL-PHOSPHONOACETATE (200) WITH TRIMETHYLSILYL BROMIDE

Conditions were as described for benzyl-(2RS)-2-[(4RS)-4-chloro-2-oxoazetidin-1-yl]-2-dimethylphosphonoacetate (205). Impure mono-trimethylsilyloxyphosphonate (240). ν_{max} ($CDCl_3$), 1780 (β-lactam C=O), 1740 (ester), 1230 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.36 (5H,s, Ph), 6.4-6.0 (1H,m,diastereoisomers), 5.21 (2H,s,$\underline{CH_2}$Ph), 3.9-3.6 (3H,m, POMe), 3.5-2.9 (2H,m,H3), 2.06 and 2.03 (3H,s,OCO$\underline{Me}$,diastereoisomers).

ATTEMPTED HYDROLYSIS OF BENZYL-(2RS)-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]-2-O-METHYL-O-TRIMETHYLSILYLPHOSPHONOACETATE (240)

Conditions as for hydrolysis of 4-chloroazetidin-2-one (238) led to similar results. No monophosphonic acid (241) or its amine salts were isolated.

REACTION OF BENZYL-(2RS)-2-[(4RS)-4-CHLORO-2-OXOAZETIDIN-1-YL]-2-O-METHYL-O-TRIMETHYLSILYLPHOSPHONOACETATE (238) WITH PHOSPHORUS PENTACHLORIDE

Silyloxyphosphonate (238) (105 mg, 0.25 mMol) was dissolved in dry DCM under argon and added to a suspension of phosphorus pentachloride (51.50 mg, 0.25 mMol) in dry DCM and the suspension stirred for 1 hour at 20°C, after which time all the solid had dissolved. Removal of the solvent *in vacuo* gave a yellow oil, presumably benzyl-(2RS)-2-[(4RS)-4-chloro-2-oxoazetidin-1-yl]-2-chloro-O-methylphosphonoacetate (243) (91 mg, 100%), no further purification was attempted. ν_{max} ($CHCl_3$), 1790 (β-lactam C=O), 1745 (ester C=O), 1260 (P=O) and 1050 cm^{-1} (P-OMe).

REACTION OF β-LACTAM PHOSPHONOCHLORIDATE (243) WITH THIOLS

(a) β-Lactam phosphonochloridate (243) (38.7 mg, 0.11 mMol) was dissolved in dry THF/DMF (10:1) under nitrogen at 20°C and treated with anhydrous sodium hydrosulphide (6 mg, 0.11 mMol). The mixture was stirred for 2 hours at 20°C, poured into water and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and removed *in vacuo* to give a pale yellow oil. I.r. examination showed β-lactam cleavage to have taken place.

(b) Repetition of (a) using wet THF caused β-lactam cleavage.

(c) Phosphonochloridate (243) (102 mg, 0.28 mMol) was dissolved in dry DCM under nitrogen and treated with benzyl mercaptan (34.72 mg, 0.28 mMol) and triethylamine (28.3 mg, 0.28 mMol). The mixture was stirred at 20°C for 18 hours, poured into water and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. I.r. shows β-lactam cleavage to have occurred.

(d) A dry DCM of H_2S was treated with the β-lactam phosphonochloridate (242) (102 mg, 0.28 mMol) and stirred at 20°C for 5 minutes before addition of N,N-diisopropylethylamine (26 mg, 0.28 mMol). The resulting solution was left under a positive pressure of H_2S for 15 hours and the solvent was removed to give a yellow oil. I.r. examination showed β-lactam cleavage.

(e) Using hexamethyldisilazide (1 equiv.) as the base under conditions (d) also produced cleaved β-lactam.

REACTION OF 4-DIMETHYLPHOSPHONOAZETIDIN-2-ONE (248) WITH TRIMETHYLSILYL BROMIDE

4-Dimethylphosphonoazetidin-2-one (248) (100 mg, 0.56 mMol) was dissolved in dry DCM under argon and treated with trimethylsilyl bromide (85.4 mg, 0.56 mMol) and stirred for 4 hours at 20°C. H^1-n.m.r. and i.r. indicated β-lactam cleavage.

(1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-DIMETHYLPHOSPHONOAZETIDIN-2-ONE (251)

^{n}Butyllithium (10 mMol) was added to a stirred suspension of 4-dimethylphosphonoazetidin-2-one (248) (1.79 g, 10 mMol) in dry THF under argon at -50°C and the mixture stirred for 1 hour before addition

of ^{t}butyldimethylsilyl chloride (1.50 g, 10 mMol). The reaction was warmed to 20°C (2 hours) and stirred for 20 hours, poured into ethyl acetate/water and extracted. Drying of the organic phase ($MgSO_4$), removal of the solvent *in vacuo* and chromatography of the residue on silica afforded (1RS)-1-^{t}butyldimethylsilyl-(4RS)-4-dimethylphosphonoazetidin-2-one (251) as a pale yellow oil (1.03 g, 35%). ν_{max} ($CHCl_3$) 1740 (β-lactam C=O), 1250 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 3.80 (7H,m,$\overset{O}{\overset{\|}{P}}(OMe)_2$ and H4), 3.30 (2H,m,H3), 0.99 (9H,s,Si^{t}Bu) and 0.28 (6H, s,$SiMe_2$), $\delta_{C^{13}}$ ($CDCl_3$), 171.61 (s,β-lactam C=O), 53.36 (m,$\overset{O}{\overset{\|}{P}}(OMe)_2$), 44.46 (dd,$J_{C^{13}-P^{31}}$=130Hz,C4), 39.75 (t,C3), 26.42 (q,CMe_3), 18.73 (s, CMe_3) and 5.58 (q,$SiMe_3$), $\delta_{P^{31}}$ ($CDCl_3$), -25. M^+, 293. (Found: C, 45.11; H, 8.12; N, 4.82. $C_{11}H_{24}NO_4PSi$ requires C, 45.05; H, 8.19; N, 4.78%).

REACTION OF (1RS)-1-^{t}BUTYLDIMETHYLSILYL-(4RS)-4-DIMETHYLPHOSPHONOAZETIDIN-2-ONE (251) WITH TRIMETHYLSILYL BROMIDE

N-Silylazetidin-2-one (251) (50 mg, 1.7 mMol) was dissolved in dry $CDCl_3$ under argon and treated with trimethylsilyl bromide (26 mg, 0.17 mMol). H^1-n.m.r. indicated formation of the trimethylsilyloxyphosphonate (255) to be complete after 2 hours. ν_{max} ($CDCl_3$), 1760 (β-lactam C=O), 1220 (P=O) and 1040 cm^{-1} (P-OMe). The volatile material was removed *in vacuo* and the residue dissolved in DCM and treated with 10% aqueous acetone and the two phase system stirred at 20°C for 16 hours. Evaporation *in vacuo* gave a yellow oil consisting of the N-silylphosphonic acid (252) and the monophosphonic acid (250), M^+, 279 and 165 respectively. Treatment of this mixture with diazomethane afforded a mixture of 4-dimethylphosphonoazetidin-2-one (248) and the N-^{t}butyldimethylsilyl derivative (251), spectroscopically identical to authentic samples. Over 3 days at 0°C N-silyl derivative

(252) autocatalytically deprotected to give (25) but monophosphonic acid (250) was unstable and purification was not successful. Impure monophosphonic acid (250), ν_{max} ($CDCl_3$), 1740 (β-lactam C=O), 1240 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.38 (1H,Brs,NH), 3.70 (4H,d, J=12Hz,$\overset{O}{\overset{\|}{P}}$(OMe) and H4), 3.20 (2H,m,H3).

REACTION OF SILYLOXYPHOSPHONATE (251) WITH PHOSPHORUS PENTACHLORIDE

(P^{31}-n.m.r. experiment). β-Lactam silyloxyphosphonate (251) (965 mg, 2.75 mMol) (prepared as described above) was dissolved in deuteriochloroform (800 μ) and added to freshly sublimed phosphorus pentachloride (573 mg, 2.75 mMol) in an n.m.r. tube. Monitoring of the reaction showed that formation of phosphorus oxychloride was complete after one hour at 20°C. ν_{max} ($CDCl_3$), (254) 1780 (β-lactam C=O), 1280 (P=O) and 1040 cm^{-1} (POMe).

BENZYL-(2RS)-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-2-HYDROXY ACETATE (257)

4-Dimethylphosphonoazetidin-2-one (248) (3.58 g, 20 mMol) was dissolved in the minimum of dry THF and treated with a THF solution of benzyl glyoxylate (184a) (4.00 g, 22 mMol) and one drop of triethylamine. The solution was left for 20 hours at 20°C, diluted with ethyl acetate and washed with water (6 x 20 ml). Drying of the organic phase and removal *in vacuo* afforded benzyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-2-hydroxy acetate (257) as a pale yellow oil (2.49 g, 36.4%). ν_{max}, 3600-3100 (OH), 1770 (β-lactam C=O), 1740 (ester C=O), 1220(P=O), 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.30 (5H,s,Ph), 5.83 (1H,br,dd,exchange D_2O), 5.58 and 5.50 (1H,s,CHOH, diastereoisomers), 5.19 (2H,s,CH_2Ph), 4.0 (1H,m,{P^{31}} simplifies

signal,{H^1} at 3.15 and {P^{31}} two singlets,H4), 3.70 (6H,d,J=10Hz, {P^{31}} two singlets,$P(OMe)_2$), 3.15 (2H,m,H3), $\delta_{p^{31}}$ ($CDCl_3$), -23.35 and -22.55 (downfield from 88% H_3PO_4), M^+,343. (Found: C, 49.14; H, 5.38; N, 3.78; P, 8.84. $C_{14}H_{18}NO_7P$ requires C, 48.99; H, 5.25; N, 4.08; P, 9.04%).

BENZYL-(2RS)-2-CHLORO-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (258)

Benzyl (2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-2-hydroxy acetate (257) (1.72 g, 5 mMol) was dissolved in dry THF under nitrogen and cooled to -25°C. 2,6-Lutidine (0.54 g, 5 mMol) was added followed by dropwise addition of freshly distilled thionyl chloride (0.59 g, 5 mMol). After addition was complete the suspension was stirred at -25°C for 1 hour, warmed to 0°C and left for 16 hours. After this time the suspension was filtered under argon and the filtrate evaporated to dryness affording benzyl-(2RS)-2-chloro-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]acetate (258) as a yellow oil (1.62 g, 90%). ν_{max} ($CHCl_3$), 1790 (β-lactam C=O), 1750 (ester), 1230 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.38 (5H,s,Ph), 6.10 and 6.08 (1H,s,CHCl, diastereoisomers), 5.20 (2H,s,CH_2Ph), 4.15 (1H,m,H4), 3.70 (6H,d,J=10.2Hz,$\overset{O}{\overset{\|}{P}}(OMe)_2$), 3.25 (2H, m,H3), M^+, 363 (Cl^{37}) and 361 (Cl^{35}) (1:3).

BENZYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (259)

Benzyl-(2RS)-2-chloro-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]acetate (258) (1.69 g, 5 mMol) was dissolved in dry degassed benzene under nitrogen and treated with tri-^{n}butyltin hydride (1.59 g, 5.5 mMol) and benzoyl peroxide (10 mg) and the resulting solution

refluxed for 3 hours. After this time the solvent was removed *in vacuo* to give a yellow oil. This oil was dissolved in acetonitrile and extracted with hexane (8 x 20 ml). Removal of the acetonitrile afforded benzyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-acetate (259) as a pale yellow oil (813 mg, 50%). ν_{max} ($CHCl_3$), 1780 (β-lactam), 1740 (ester), 1220 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.31 (5H,s,Ph), 5.1 (2H,s,$\underline{CH_2}Ph$), 4.4 (1H,d,J=18Hz, N-$\underline{CH_2}$ a part of AB system), 4.0 (1H,m,H4), 3.75 (7H,m,$P(OMe)_2$ and $N\underline{CH_2}$,B part of AB system), 3.18 (2H,m,H3), $\delta_{C^{13}}$ ($CDCl_3$), 166.93 (s,β-lactam C=O), 165.58 (s,ester C=O), 134.59 (s,Ph), 127.60-127.22 (m,Ph), 66.11 (t,$N\underline{CH_2}$), 52.51 (m,$\overset{O}{\overset{\|}{P}}(OMe)_2$), 51.92 (d,J=160Hz,$J_{C^{13}-P^{31}}$,C4), 42.06 (t,C3), 25.08 (t,$\underline{CH_2}Ph$), $\delta_{P^{31}}$ -23.1 ppm (downfield from 88% H_3PO_4). M^+, 327. (Found: C, 50.90; H, 5.58; N, 4.16; P, 9.15. $C_{14}H_{18}NO_6P$ requires C, 51.38; H, 5.50; N, 4.28; P, 9.48%).

ATTEMPTED PREPARATION OF MONOMETHYLPHOSPHONIC ACID (260)

Benzyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-2-hydroxy acetate (257) (100 mg, 0.30 mMol) was dissolved in dry dichloromethane at 20°C under nitrogen and treated with trimethylsilyl bromide (88.74 mg, 0.6 mMol). The yellow solution was stirred for 3 hours at 20°C. After this time aqueous potassium dihydrogen phosphate was added (1 ml, 0.1 M, pH 6.5) and the mixture stirred for 1 hour at 20°C. Removal of the solvent *in vacuo* gave a yellow solid which was suspended in methanol. Filtration of this suspension and removal of the methanol afforded a pale yellow solid. Spectroscopic data indicated β-lactam cleavage.

The above method was repeated in the presence of one equivalent of triethylamine followed by aqueous hydrolysis over an acid ion

exchange resin. Removal of the solvent gave a yellow/white solid. I.r. indicated β-lactam cleavage.

The above methods were not further examined.

BENZYL-(2RS)-2-^{t}BUTYLDIMETHYLSILYLOXY-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (263)

Benzyl-(2RS)-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-2-hydroxy acetate (257) (35.3 mg, 0.1 mMol) was dissolved in dry $CDCl_3$ and treated with diphenylamine (16.92 mg, 0.1 mMol), DMAP (1.22 mg, 0.01 mMol) and ^{t}butyldimethylsilyl chloride (15.07 mg, 0.1 mMol) under argon at 20°C in a total volume of 0.7 ml. After stirring for 16 hours examination of the H^1-n.m.r. spectrum showed the reaction to be complete. Impure (263) ν_{max} ($CDCl_3$), 2800-2300 (amine hydrochloride), 1770 (β-lactam C=O), 1740 (ester),1240 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 5.54 and 5.44 (1H,s,CHOSi, diastereoisomers), 5.20 (2H,br.s,CH_2Ph), 4.0 (1H,Br,m,H4), 3.78 and 3.72 (6H, d,J=10.4Hz,$\overset{O}{\overset{\|}{P}}(OMe)_2$, diastereoisomers), 3.16 (2H,m,H3), 0.98 and 0.92 (9H,s,Si^{t}Bu,diastereoisomers), 0.38 and 0.12 (6H,s,$SiMe_2$,diastereoisomers). (No M^+ under E.I. on C.I. conditions). H^1-n.m.r. indicates quantitative conversion of (257) to (263).

REACTION OF ^{t}BUTYLDIMETHYLSILYL ETHER (263) WITH TRIMETHYLSILYL BROMIDE

^{t}Butyldimethylsilyl ether (263) (prepared as above) was treated with one equivalent of trimethylsilyl bromide in deuteriochloroform at 20°C under argon. H^1-n.m.r. showed the formation of methyl bromide (δ = 2.64) to be complete after 16 hours at 20°C. Impure monotrimethylsilyloxyphosphonate (264) ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1740 (ester), 1250 (P=O), 1040 cm^{-1} (POMe), δ ($CDCl_3$)

5.56 and 5.48 (1H,s,CHOSi,diastereoisomers), 5.24 (2H,br.s,CH_2Ph), 4.20-3.60 (4H,P(OMe) and H4), 3.20 (2H,m,H3), 0.96 and 0.84 (9H,s, $SiBu^t$,diastereoisomers), 0.44 and 0.38 (6H,s,$SiMe_2$,diastereoisomers), 0.08 (9H,s,$SiMe_3$).

ATTEMPTED PREPARATION OF MONOMETHYLPHOSPHONIC ACID (262)

Impure monotrimethylsilyloxyphosphonate (264) was treated with D_2O and stirred for 20 hours at 20°C. Spectroscopic analysis after this time indicated β-lactam cleavage.

Hydrolysis of (264) in the presence of cyclohexylamine (one equivalent) also resulted in β-lactam cleavage.

Reaction of (264) with 10% aqueous acetone at 20°C for 16 hours gave no isolable β-lactam.

REACTION OF BENZYL-(2RS)-2-CHLORO-2-[(4RS-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (258) WITH TRIMETHYLSILYL BROMIDE

Chloro acetate (258) (105 mg, 0.29 mMol) was dissolved in dry $CDCl_3$ and trimethylsilyl bromide (44 mg, 0.29 mMol) added at 20°C under argon and the solution left for 16 hours. Impure monotrimethylsilyloxyphosphonate (265) ν_{max} ($CDCl_3$), 1780 (β-lactam C=O), 1750 (ester), 1250 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.35 (5H,s,Ph), 6.40 and 6.35 (1H,s,CHCl,diastereoisomers), 5.30 and 5.25 (2H,s,CH_2Ph,diastereoisomers), 4.2-2.9 (6H,m,P-OMe,H3,H4), 0.09 (s,$SiMe_3$).

Removal of the volatiles *in vacuo* afforded (265) as a dark yellow oil

REACTION OF MONO-TRIMETHYLSILYOXYPHOSPHONATE (265) WITH SILVER TETRAFLUOROBORATE

Mono trimethylsilyloxyphosphonate (265) (122 mg, 0.29 mMol) was dissolved in dry acetonitrile under nitrogen at 20°C and added to a suspension of silver tetrafluoroborate (59 mg, 0.30 mMol) in dry acetonitrile at 20°C. The mixture was left for 16 hours, filtered and the filtrate evaporated to dryness *in vacuo* to give a dark yellow solid. Spectroscopic examination indicated β-lactam cleavage.

Use of silver carbonate in 10% aqueous acetone gave the same result.

REACTION OF BENZYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (259) WITH TRIMETHYLSILYL BROMIDE

β-Lactam benzyl acetate (259) (32.7 mg, 0.1 mMol) was dissolved in dry $CDCl_3$ and added to a solution of trimethylsilyl bromide (15.3 mg, 0.1 mMol) under argon at 20°C. After 3 hours at 20°C, H^1-n.m.r. showed the formation of methyl bromide (δ 2.64) to be complete. Impure (267) ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1740 (ester), 1250 (P=O), 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.32 (5H,s, Ph), 5.14 (2H,s,$\underline{CH_2}$Ph), 4.44-3.64 (6H,m,$\underline{NCH_2}$,P-OMe,H4), 3.24 (2H, m,H3), 0.4 (9H,s,$SiMe_3$). Removal of the solvent *in vacuo* afforded mono trimethylsilyloxyphosphonate (267) as a pale yellow oil.

PREPARATION OF MONO-METHYLPHOSPHONIC ACID (266)

Mono trimethylsilyloxyphosphonate (267) (38.5 mg, 0.1 mMol) was dissolved in chloroform and treated with 10% aqueous acetone for 16 hours at 20°C. After this time removal of the solvent *in*

vacuo gave (266) as a yellow oil. δ (D_2O), 7.32 (5H,s,Ph), 5.14 (2H,s,$\underline{CH_2}$Ph), 4.18-3.44 (6H,m,$\underline{NCH_2}$,POMe,H4), 3.04 (2H,m,H3). M^+, 313 (C.I., NH_3 carrier gas).

REACTION OF PHOSPHONOCHLORIDATE (254) WITH CYSTEINE

A suspension of cysteine (172 mg, 10 mMol) in chloroform under argon at -25°C was treated with a dry chloroform solution of the phosphonochloridate (254) (269 mg, 1 mMol) and the mixture treated with N,N-diisopropylamine (1.0 g, 10 mMol) and warmed to 20°C (2 hours). After this time the reaction was diluted with ethyl acetate and washed with water (2 x 10 ml), dried ($MgSO_4$) and the solvent evaporated to give a yellow oil. Spectroscopic examination showed that β-lactam cleavage had occurred.

REACTION OF PHOSPHONOCHLORIDATE (254) WITH BENZYL MERCAPTAN

Phosphonochloridate (254) (92 mg, 0,34 mMol) was dissolved in dry DCM under argon and cooled to -25°C and treated with benzyl mercaptan (42.16 mg, 0.34 mMol) and triethylamine (34.34 mg, 0.34 mMol). The mixture was warmed to 20°C and stirred for 16 hours. Spectroscopic examination of the reaction mixture showed β-lactam cleavage and was not further examined.

REACTION OF PHOSPHONOCHLORIDATE (254) WITH SODIUM ρ-TOLUENE SULPHONAMIDE

ρ-Toluene sulphonamide (684 mg, 4.0 mMol) was dissolved in dry THF under argon and added to a suspension of sodium hydride (96 mg, 4.0 mMol) and the mixture stirred for 1 hour at 20°C. Phosphonochloridate (254) (270mg, 1 mMol) in dry THF was added and the suspension stirred for 16 hours at 20°C. The reaction was

poured into saturated aqueous ammonium chloride/ethyl acetate and extracted. After drying ($MgSO_4$) and removal of the solvent *in vacuo* gave a white solid which was shown to be p-toluene sulphonamide. No β-lactam containing compound was isolated. Nothing further was undertaken with this system.

DIMETHYLCHLOROPHOSPHITE (271)

Tetraethylammonium bromide (109) was suspended in freshly distilled trimethylphosphite (62.04 g, 0.5 mMol) under nitrogen and cooled to 0°, phsophorus trichloride (32.5 g, 0.24 mMol) was added dropwise over 1 hour, and the resulting mixture stirred for 16 hours at 20°C. Filtration of the reaction undernitrogen and distillation of the filtrate *in vacuo*[1] afforded dimethylchlorophosphite[2] (271) (44.81 g, 70%). B.pt. 35-36°C/30 mm Hg., ν_{max} (thin film), 2980, 1450, 1180, 1020 and 760 cm^{-1}, δ ($CDCl_3$), 3.62 (6H,d,J=11.0Hz).

(i) Low temperature distillation is crutial so as to avoid explosive decomposition of the pot residue, see Jones *et al.* Inorg. Chem., 1971, 10, 1536.

(ii) Dimethylchlorophosphite (271) has an obnoxious odour, is a severe irritant and is extremely toxic. It reacts violently with water,

REACTION OF BENZYL-(2RS)-2-[(4RS)-4-ACETOXY-2-OXOAZETIDIN-1-YL]-2-HYDROXYACETATE (193) WITH DIMETHYLCHLOROPHOSPHITE (271)

Glyoxylate adduct (193) (1.46 g, 5 mMol) was dissolved in dry THF under nitrogen and treated with N,N-diethylaniline (0.75 g, 5 mMol) and the mixture heated to reflux. Dimethylchlorophosphite (271) (0.65 g, 5 mMol) was added dropsise over 1 hour and reflux continued for 4 hours. The suspension was filtered under nitrogen

and the filtrate evaporated to dryness to give a yellow oil. Chromatography on silica afforded benzyl-(2RS)-2-chloro-[(4RS)-4-acetoxy-2-oxoazetidin-1-yl]acetate (194) (622 mg, 40%) identical with the compound prepared by thionyl chloride treatment of (193).

Repetition of the above at a lower temperature or in the presence of cyclohexene or barium carbonate failed to give β-lactam phosphite (270). Lower yields of (194) being the only result.

ATTEMPTED ACYLATION OF BENZYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (259)

β-Lactam (259) (100 mg, 0.31 mMol) was dissolved in dry THF under argon and added to a solution of lithium hexamethyldisilazide (0.33 mMol) in dry THF at -50°C and the mixture stirred for 1 hour before dropwise addition of freshly distilled acetyl bromide (41 mg, 0.33 mMol). After warming to 20°C (1 hour) the reaction was stirred for 16 hours, cooled to 0°C and treated with glacial acetic acid. The mixture was diluted with ethyl acetate and extracted with water. Drying of the organic phase ($MgSO_4$) and evaporation to dryness afforded a yellow oil. I.r. and H^1-n.m.r. indicated β-lactam cleavage.

REACTION OF BENZYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]ACETATE (259) WITH CARBON DISULPHIDE

β-Lactam (259) (26 mg, 0.06 mMol) was dissolved in dry THF under argon and cooled to -78°C. Lithium hexamethyldisilazide (0.16 mMol) was added and the mixture stirred for 5 minutes before addition of dry carbon disulphide (6.04 mg, 0.08 mMol). Stirring was continuted for 2 hours and the reaction was quenched by the

addition of glacial acetic acid (0.5 ml). Dilution with ethyl acetate and washing with brine gave a yellow oil after drying ($MgSO_4$) and removal of the solvent. Spectroscopic examination showed this to be starting material (259) (weight recovered, 23 mg, 88%).

METHYL-2-[2-OXO-(4RS)-4-PHENYLTHIOAZETIDIN-1-YL]ACETATE (277)

A solution of ^{n}-butyllithium (10 mMol) in THF under argon at -78°C was treated with a dry THF solution of (4RS)-4-phenylthioazetidin-2-one (202) (1.79 g, 10 mMol) and stirred for 1 hour at -78°C. After this time freshly distilled bromomethylacetate (1.53 g, 10 mMol) was added and the reaction warmed to 20°C (1 hour), stirred for 1 hour and poured into ethyl acetate, ice/water and extracted. The organic phase was dried ($MgSO_4$) and removed *in vacuo* to afford a yellow oil. Chromatography on silica gave methyl-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]acetate (277) as a pale yellow oil (1.52 g, 61%). ν_{max} ($CHCl_3$), 1780 (β-lactam C=O), 1740 cm^{-1}(ester), δ ($CDCl_3$), 7.30 (5H,s,Ph), 5.15 (1H,m,H4), 4.20 (1H,d,J=18Hz,N-CH_2,A part of AB_q), 3.65 (1H,d,J=18.0Hz,N$\underline{CH_2}$,B part of AB_q), 3.50 (3H,s,CO_2Me), 3.30-2.55 (2H,m,H3). This data is in agreement with the published spectral data.[113]

METHYL-(2RS)-2-[2-OXO-(4RS)-4-PHENYLTHIOAZETIDIN-1-YL]-3-OXO-BUTANOATE (278)

Methyl-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]acetate (277) (251 mg 1 mMol) was dissolved in dry THF under argon and added to a THF solution of lithium hexamethyldisilazide (2 mMol) at - 78°C and stirred for 5 minutes before addition of freshly distilled acetyl bromide (123 mg, 1 mMol). Stirring was continued for

90 minutes at -78°C followed by neutralisation of the mixture with glacial acetic acid (0.2 ml). The resulting suspension was poured into ethyl acetate/brine and extracted. Drying ($MgSO_4$) and removal of the solvent gave a yellow oil. Chromatography on silica afforded methyl-(2RS)-2-[2-oxo-(4RS)-4-phenylthioazetidin-1-yl]-3-oxobutanoate (278) as a pale yellow oil (226 mg, 77%), ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1720 (ester), 1660 (C=O), 1610 cm^{-1} (C=C), δ ($CDCl_3$), 12.58 (½H,s,enolic OH), 7.24 (5H,s,Ph), 5.22 (1H,m,H4), 4.4 (½H,m.NCH), 3.60 (3½H,m,CO_2Me and H3), 3.60-2.99 (2H,m,H3), 2.30 and 2.15 (3H,s,CH_3). Latter signals indicated ∿40% enolisation. Spectral details are in agreement with those published.[113]

2-DIAZOMETHYLACETOACETATE (279)

Methylacetoacetate (1.16 g, 10 mMol) and triethylamine (1.01 g, 10 mMol) were dissolved in acetonitrile at 20°C and treated with tosyl azide (1.97 g, 10 mMol). The yellow solution was stirred for 3 days at 20°C and the solvent removed *in vacuo*. Flash chromatography of the residue on silica [elution with petroleum ether (40/60) : chloroform (6:1)] afforded 2-diazomethyl-acetoacetate (279) as a yellow oil (1.53 g, 93%). ν_{max} (CH_2Cl_2), 2140 (diazo), 1710 (ester) and 1660 cm^{-1} (α,β-unsaturated C=O), δ ($CDCl_3$), 3.90 (3H,s,CO_2Me), 2.48)3H,s,COMe).

METHYL-(2RS)-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-3-OXOBUTANOATE (274)

4-Dimethylphosphonoazetidin-2-one (248) (358 mg, 2 mMol) was dissolved in dry degassed benzene (40 ml) and rhodium (II) acetate (5 mg) was added. The solution was heated to reflux under

nitrogen and 2-diazomethylacetoacetate (279) (284 mg, 2 mMol) was added dropwise over 30 minutes, reflux was continued for 8 hours. After this time the solvent was removed *in vacuo* and the residue chromatographed on silica. Elution with ethyl acetate/acetone (5:1 initially to 1:2 finally) afforded methyl-(2RS)-2-[(4RS)-4-dimethyl-phosphono-2-oxoazetidin-1-yl]-3-oxobutanoate (274) as a pale yellow oil (203 mg, 35%). λ_{max} 250 nm, (ε) 19500, ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1740 (ester), 1660 (C=O), 1615 (enol C=C) 1250 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 11.95 (enolic OH), 4.10 (2H,m,H4 and N-CH), 3.94-3.70 (9H,m,$P(OMe)_2$ and CO_2Me,{P^{31}} simplifies signal), 3.30 (2H,m,H3), 2.40 and 2.20 (3H,s,COMe,enolic and ketolic forms, ca. 90% enolic). [Found: C, 41.06; H, 5.54; N, 4.60; M^+, 293.0664. $C_{10}H_{16}NO_7P$ requires C, 40.96; H, 5.46; N, 4.78%; M^+, 293.0664].

Refluxing the H^1-n.m.r. in d^5-pyridine produced the following spectrum, δ (d^5-pyridine), 4.20 (1H,m,H4,{P^{31}} simplifies to dd), 3.95-3.60 (9H,m,$P(OMe)_2$ and CO_2Me,{P^{31}} simplifies signal), 3.40 (2H,m,H3), 2.38 (3H,s,C(OH)Me).

ATTEMPTED CYCLISATION OF METHYL-(2RS)-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]3-OXOBUTANOATE (274) TO BICYCLIC β-LACTAM (275)

(a) Oxobutanoate (274) (150 mg, 0.51 mMol) was dissolved in dry toluene under nitrogen and heated to reflux for 16 hours. T.l.c. analysis after this time showed no reaction.

(b) β-Keto ester (274) (50 mg, 0.17 mMol) was dissolved in dry CD_2Cl_2 (0.5 ml) under argon and treated with resublimed aluminium trichloride (2.8 mg, 0.017 mMol) and the reaction monitored by H^1-n.m.r. After 16 hours at 20°C the spectrum recorded was identical to that of β-keto ester (274) in $CDCl_3$.

(c) Conditions (b) with titanium tetrachloride (3.22 mg, 0.017 mMol), identical result.

(d) Conditions (b) with trityl tetrafluoroborate (1 equiv.) in CD_3CN, identical result.

(e) β-Lactam (274) (129 mg, 0.44 mMol) was dissolved in dry dichloromethane and stirred with Hûnig's base (2 g) for 16 hours at 20°C. I.r. and t.l.c. indicated no reaction.

(f) β-Lactam (274) (100 mg, 0.34 mMol) was dissolved in dry THF under argon and added to a suspension of potassium hydride (13.7 mg, 0.34 mMol, oil free) in dry THF under argon at 20°C. T.l.c. after 1 hour showed no reaction and the mixture was heated to 40°C, t.l.c. after 1 hour showed no reaction. 18-Crown-6 (0.1 equiv.) was added and the reaction refluxed for 18 hours, t.l.c. showed no reaction. HMPT (2 ml) was added and reflux continued, t.l.c. after 16 hours showed no reaction and work-up with 5% citric acid and extraction with ethyl acetate, drying of the solvent ($MgSO_4$) and evaporation *in vacuo* afforded (274) (93 mg), i.r. identical to untreated sample.

(g) β-Keto ester (274) (100 mg, 0.34 mMol) was dissolved in dry THF under argon and treated with DBU (52.02, 0.34 mMol) and the solution stirred at 20°C for 16 hours, t.l.c. after this time indicated no reaction.

ATTEMPTED REDUCTION OF METHYL-(2RS)-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-3-OXOBUTANOATE (274) TO β-HYDROXY ESTER (280)

(a) Sodium borohydride (95. mg, 0.25 mMol) was suspended in dry THF under nitrogen and cooled to 0°C. The β-lactam (274) (293 mg, 1 mMol) in THF was added dropwise over 15 minutes and the reaction

warmed to 20°C after addition was complete. T.l.c. indicated no reaction, therefore an additional quantity of sodium borohydride (9.5 mg, 0.25 mMol) was added and stirring continued. T.l.c. after a further 90 minutes at 20°C indicated no reaction and β-keto ester (274) was recovered (285 mg, 97%).

(b) A solution of sodium borohydride (38 mg, 1 mMol) in dry methanol solution of β-lactam (274) (293 mg, 10 mMol) at 0°C under nitrogen. The mixture was warmed to 20°C and stirred for 90 minutes, diluted with ethyl acetate and washed with water (2 x 10 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. I.r. and H^1-n.m.r. indicated β-lactam cleavage.

(c) β-Keto ester (274) (100 mg, 0.34 mMol) was dissolved in dry THF under argon at 0°C and treated with a THF solution of diborane (0.34 ml, 0.25 Mol solution, 0.34 mMol) and stirred for 90 minutes at 0°C. T.l.c. indicated no reaction and the reaction was warmed to 20°C. After 1 hour t.l.c. showed no reaction. Refluxing of the mixture for 3 hours led, after aqueous work-up, to recovery of (274) (90 mg, 90%).

(d) β-Lactam (274) (104 mg, 0.36 mMol) was dissolved in ethyl acetate at 20°C. Palladium on charcoal (5%, 5 mg) was added followed by 1 drop of dilute hydrochloric acid and the suspension left under a hydrogen atmosphere for 18 hours. T.l.c. indicated no reaction and after filtration through celite and removal of the solvent, 75 mg of (274) was recovered.

(e) Conditions (d) with 5 mg, 5%, rhodium on alumina at 50 PSI hydrogen for 18 hours in ethyl acetate gave an identical result, 155 mg, 100% recovery of (274).

(f) β-Lactam (274) (100 mg, 0.34 mMol) was dissolved in

ethyl acetate and Raney nickel (prepared as described in reference 114) was added. The suspension was placed under an atmosphere of hydrogen and left at 80 ATM. and 100°C for 16 hours. The mixture was cooled and filtered though celite and the filtrate evaporated to give a yellow oil (70 mg). I.r. indicated complete β-lactam cleavage.

METHYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-3-^{t}BUTYL-DIMETHYLSILYLOXYBUT-2-ENOATE (281)

Potassium hydride (40 mg, 1 mMol) was suspended in dry THF at 20°C under argon and treated with a THF solution of β-keto ester (274) (293 mg, 1 mMol). After evolution of hydrogen had ceased the yellow solution was stirred for 15 minutes before addition of ^{t}butyldimethylsilyl chloride (153 mg, 1 mMol). The resulting suspension was stirred for 16 hours at 20°C and the solvent removed *in vacuo* to give ^{t}butyldimethylsilyl enol ether (281) as a pale yellow oil (400mg, 99%). No further purification was attempted, impure (281) ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1720 (ester), 1610 (enol C=C), 1250 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 4.02 (1H,m, H4), 3.80 - 3.40 (9H,m,$P(OMe)_2$ and CO_2Me), 3.25 - 2.95 (2H,m,H3), 2.35 (3H,s,MeCOSi), 0.90 and 0.82 (9H,s,Si^{t}Bu,isomers) and 0.20 (6H,s,$SiMe_2$).

REACTION OF ^{t}BUTYLDIMETHYLSILYL ENOL ETHER (281) WITH TRIMETHYLSILYL BROMIDE FOLLOWED BY AQUEOUS HYDROLYSIS

^{t}Butyldimethylsilyl enol ether (281) (210mg, 0.52 mMol) was dissolved in dry chloroform under argon and treated with trimethylsilyl bromide (80 mg, 0.52 mMol) at 20°C. After 4 hours the solvent

was removed to give the mixed silyl derivative (282) as a pale yellow oil, impure (282) ν_{max} ($CDCl_3$), 1770 (β-lactam C=O), 1730 (ester), 1260 (P=O) and 1050 cm^{-1} (POMe). No further purification was attempted. This oil was dissolved in chloroform and stirred with 10% aqueous acetone (10 ml) for 16 hours at 20°C. Removal of the solvent *in vacuo* gave a yellow semi-solid oil. I.r. indicated β-lactam cleavage. The reaction was not examined further.

REACTION OF MIXED SILYL ENOL ESTER (282) WITH TRIMETHYLSILYL TRIFLATE

The mixed silyl β-lactam (282) (157 mg, 0.34 mMol) (prepared as previously described) was dissolved in dry chloroform and treated with trimethylsilyl triflate (70 mg, 0.34 mMol) under argon. The mixture was stirred for 16 hours at 20°C. I.r. analysis indicated β-lactam cleavage. The reaction was not further investigated.

ATTEMPTED PREPARATION OF PHOSPHONOCHLORIDATE (285) AND ATTEMPTED CYCLISATION TO (275)

β-Lactam (274) (105 mg, 0.36 mMol) was dissolved in dry dichloromethane under argon at 20°C and stirred with 2,6-lutidine (38.5 g, 0.36 mMol) for 1 hour, trimethylsilyl bromide (55 mg, 0.34 mMol) was added and the reaction stirred for 18 hours. After this time a further equivalent of trimethylsilyl bromide (55 mg, 0.34 mMol) and the solution left for 4 hours. Impure (284) ν_{max} (CH_2Cl_2), 1770 (β-lactam C=O), 1730 (ester), 1610 (enol C=C), 1260 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 4.15 (1H,m,H4), 3.9 - 3.65 (6H,m,P-OMe and CO_2Me), 3.35 (2H,m,H3), 2.30 (3H,C(OTMS)Me), 0.25 (9H,s,$OSiMe_3$) and 0.10 (9H,s,POTMS). This mixture was dissolved

in dry chloroform and treated with phosphorus pentachloride (75 mg, 0.36 mMol) for 1 hour at 20°C. Impure (285), ν_{max} ($CHCl_3$), 1780 (β-lactam C=O), 1740 (ester), 1610 (enol C=C), 1250 (P=O) and 1040 cm^{-1} (POMe). After treatment of impure (185) with anhydrous tetra-n-butylammonium fluoride spectroscopic data indicated β-lactam cleavage. The reaction was not further examined.

METHYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-3-METHANE SULPHONYLBUT-2-ENOATE (288)

β-Keto ester (274) (100 mg, 0.34 mMol) was dissolved in dry pyridine (15 ml) under argon and cooled to -25°C. Methane sulphonyl chloride (389 mg, 3.4 mMol) was added over 15 minutes and the suspension warmed to 0°C and stirred for 18 hours. After this time the solvent was removed *in vacuo* and the dark red residue flash chromatographed on silica to give methyl-2-[(4RS)-4-dimethyl-phosphono-2-oxoazetidin-1-yl]-3-methane sulphonylbut-2-enoate (288) as a pale yellow oil (83 mg, 66%). ν_{max} ($CHCl_3$), 1775 (β-lactam C=O), 1730 (ester), 1640 (C=C), 1370 (S=O), 1240 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 4.22 (1H,m,H4,{P^{31}} simplifies signal), 3.95 - 3.64 (9H,m,$P(OMe)_2$ and CO_2Me,{P^{31}} simplifies to two singlets), 3.40 - 3.20 (5H,m,H3 and $SO_2\underline{Me}$), 2.68 (3H,s,C=C-$\underline{Me}$). [Found, M^+, 371.0447, $C_{11}H_{18}NO_9PS$ requires M^+, 371.0440].

ATTEMPTED PREPARATION OF THIO ENOL (290)

(a) Enol mesylate (288) (126mg, 0.34 mMol) was dissolved in dry dichloromethane under argon and treated with triethylamine (34.3 mg, 0.34 mMol) and 4-N,N-dimethylamino pyridine (4.1 mg, 0.034 mMol). Dry hydrogen sulphide gas was then passed through the solution for 10 minutes and the mixture stirred at 20°C for 3 hours.

The solvent was removed *in vacuo* and the residue chromatographed on silica. This resulted in recovery of 65 mg of enol mesylate (288).

(b) The above conditions were repeated in the absence of DMAP for 6 hours at 20°C with an identical result [quantitative recovery of (288)].

(c) Treatment of enol mesylate (288) with one equivalent of sodium hydrogen sulphide in ethyl acetate / water in the presence of N,N-diisopropylethylamine (1 equiv.) and tetra-n-butylammonium bromide (0.1 equiv.) resulted in β-lactam cleavage (i.r.).

(d) Conditions as for (c) except water/acetone used, resulted in β-lactam cleavage.

(e) Enol mesylate (288) (160 mg, 0.43 mMol) was dissolved in dry acetonitrile under argon and cooled to 0°C. Tetra-n-butylammonium hydrogen sulphide (119 mg, 0.43 mMol) was added and the mixture stirred at 0°C. After 2½ hours t.l.c. indicated no reaction, heating of the solution did not produce the required reaction [t.l.c. showed (288) only].

(f) Mesylate (288) (147 mg, 0.40 mMol) was dissolved in dry THF under nitrogen and treated with DBU (60 mg, 0.40 mMol) and the resulting solution stirred for 15 minutes before addition of tetra-n-butylammonium hydrogen sulphide (109 mg, 0.40 mMol). T.l.c. after 2½ hours indicated no reaction.

(g) Conditions (f) with lithium hexamethyldisilazide (1 equiv.) in THF at -78°C followed by aqueous work-up gave 50% recovery of mesylate (288) as the only β-lactam present.

METHYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-3-AMINO-METHYLBUT-2-ENOATE (293)

Enol mesylate (288) (124 mg, 0.33 mMol) was dissolved in dry dichloromethane (0.5 ml) and added to methylamine (10 ml) at liquid nitrogen temperature. The solution was warmed rapidly to 0°C (5 minutes) and the solvent removed *in vacuo* to give a yellow oil. Flash chromatography on silica gave methyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-3-aminomethylbut-2-enoate (293) as a yellow oil (88 mg, 88%). λ_{max} 288 nm, ε 18300, ν_{max} ($CHCl_3$), 3460 (NH), 1770 (β-lactam C=O), 1750 (ester), 1660 (enamine), 1600 (C=C), 1250 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 9.0 (1H,Br,s,NH), 4.10 (1H,m,H4,$\{P^{31}\}$ simplifies signal), 3.95 - 3.5 (9H,m,$P(OMe)_2$ and CO_2Me,$\{P^{31}\}$simplifies signal), 3.3 - 2.6 (5H,m,H3 and NHMe,d), 2.04 (3H,s,C=C-Me). [Found: M^+, 306.0970. $C_{11}H_{19}N_2O_6P$ requires M^+, 306,0956].

METHYL-2-[(4RS)-4-DIMETHYLPHOSPHONO-2-OXOAZETIDIN-1-YL]-3-^{t}BUTYL-AMINOBUT-2-ENOLATE (295)

Procedure as for methylamino enamine (293) gave methyl-2-[(4RS)-4-dimethylphosphono-2-oxoazetidin-1-yl]-3-^{t}butylaminobut-2-enolate (295) as a yellow oil after flash chromatography on silica (220 mg, 100%). ν_{max} ($CHCl_3$), 3400 (NH), 1780 (β-lactam C=O), 1750 (ester), 1670 (enamine), 1610 (C=C), 1250 (P=O) and 1050 cm^{-1} (POMe), δ ($CDCl_3$), 7.1 (1H,Br,s,NH), 4.20 (1H,m,H4), 3.90 - 3.50 (9H,m,$P(OMe)_2$ and CO_2Me), 3.2 - 2.7 (2H,m,H3), 2.3 (3H,s,Me) and 1.30 (9H,s,N-^{t}Bu). [Found: M^+, 348.1450. $C_{14}H_{25}N_2O_6P$ requires M^+, 348.1453].

REACTION OF ENOL MESYLATE (288) WITH LIQUID AMMONIA

Conditions described for preparation of (293) were followed using liquid ammonia. After removal of solvent 174 mg, 98% mesylate (288) was recovered.

ATTEMPTED REACTION OF MESYLATE (288) WITH ANILINE

Enol mesylate (283) (152 mg, 0.41 mMol) was dissolved in dry DCM under argon and treated with freshly distilled aniline (76 mg, 0.82 mMol) at 0°C followed by freshly distilled N,N-diisopropyl-ethylamine (83 mg, 0.82 mMol) and the mixture warmed to 20°C. T.l.c. indicated no reaction and the mixture was refluxed. T.l.c. showed no reaction and nothing further was attempted with this system.

ATTEMPTS TO CYCLISE METHYLAMINOENAMINE (293) TO BICYCLIC ENAMINE (298)

(a) Enamine (293) (10 mg, 0.03 mMol) was dissolved in dry THF under argon and added to a suspension of oil free potassium hydride (2 mg, 0.03 mMol) in dry THF at 20°C. T.l.c. after 18 hours indicated no reaction. Aqueous work-up led to 80% recovery of (293).

(b) Reaction of (293) with sodium hexamethyldisilazide (1 equiv.) at -78°C → 20°C for 3 hours resulted in the isolation of an unknown compound (5 mg) with the following spectroscopic features: ν_{max} ($CHCl_3$), 3450 (NH), 1710 (ester), 1690 (amide) and 1650 cm^{-1} (enamine), δ ($CDCl_3$), 7.30, 3.87 (CO_2Me), 2.95, 2.58. λ_{max} ($CHCl_3$), 246.261 nm, ε 20100. [Found: M^+, 196.0848. $C_9H_{12}N_2O_3$ requires M^+, 196.0845].

(c) Enamine (293) (20 mg, 0.06 mMol) was dissolved in dry degassed benzene under nitrogen and irradiated with a medium pressure Hanovia u.v. lamp, after 4 hours t.l.c. indicated no reaction. Irradiation with a low pressure u.v. lamp also gave no reaction.

Change of solvent from benzene to THF also gave no reaction.

(d) Thermolysis of (293) in benzene gave no reaction (t.l.c.).

ATTEMPTED REDUCTION OF ENAMINE (293) TO AMINE (300)

(a) Enamine (293) (50 mg, 0.16 mMol) wad dissolved in absolute methanol (3 ml) and treated with platinium oxide (5 mg). The suspension was stirred at 20°C under a hydrogen atmosphere for 16 hours. Filtration through celite and evaporation of the filtrate led to 95% recovery of (293).

(b) Conditions as for (a) with 1 drop of glacial acetic acid - 90% recovery of (293).

(c) β-Lactam (293) (50 mg, 0.16 mMol) was dissolved in methanol and the pH adjusted to 4.5 with glacial acetic acid. Sodium cyano borohydride (10 mg, 0.16 mMol) was added and the suspension stirred for 18 hours at 20°C. After this time the solvent was removed *in vacuo* to give a pale yellow oil. I.r. analysis indicated β-lactam cleavage.

ATTEMPTED CONVERSION OF ENAMINE (293) TO THIO ENOL (290)

The enamine (293) (50 mg, 0.16 mMol) was dissolved in dry DMF (1 ml) under nitrogen and cooled to 0°C. TFA (20 mg, 0.176 mMol) was added and dry hydrogen sulphide passed through the solution for 10 minutes. After 30 minutes at 0°C the mixture was poured into ethyl acetate/water and extracted. The organic phase was dried ($MgSO_4$) and removed *in vacuo* to give a yellow oil. I.r. showed this to be enamine (293) [recovery 45 mg].

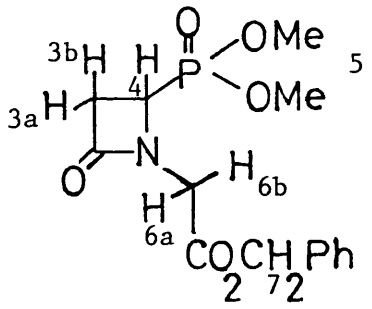
ATTEMPTED CONVERSION OF ENAMINE (293) TO 3-BENZYLTHIO ENOL (301)

Enamine (293) (50 mg, 0.16 mMol) was dissolved in dry chloroform (1 ml) and treated with TFA (20.5 mg, 0.176 mMol) and benzyl mercaptan (20.3 mg, 0.16 mMol). The mixture was stirred at 20°C for 4½ hours, t.l.c. indicated no reaction, therefore the mixture was refluxed for a further 18 hours. T.l.c. again indicated no reaction. No further investigation of this system was attempted.

APPENDICES

APPENDIX 1

Lanthanide Shift Study of Benzyl-2-[(4RS)-4-dimethylphosphono-2-oxo azetidin-1-yl]acetate (259)



(259)

The lanthanide shift study was carried out with $Eu(fod)_3$ and the results are tabulated below.

[$Eu(fod)_3$]:[substrate]	Chemical Shift (δ value)						
	H3a	H3b	H4	H5*	H6a	H6b	H7
0	3.26	3.12	4.08	3.76	4.42	3.80	5.12
6.74×10^{-3}	3.28	3.20	4.12	3.80	4.46	3.85	5.16
3.57×10^{-2}	3.44	3.36	4.36	3.97	4.52	4.00	5.20
1.11×10^{-1}	3.68	4.40	5.16	4.58	4.90	4.48	5.30
1.74×10^{-1}	4.10	4.67	5.93	5.14	5.28	4.98	5.45
2.89×10^{-1}	4.62	5.64	7.12	5.96	6.04	5.76	5.84
Correlation coefficient	0.997	0.991	0.999	0.999	0.995	0.999	0.981
Slope (ppm)	4.72	8.83	10.61	7.75	5.59	6.81	2.34
Intercept (ppm)	3.25	3.16	4.03	3.74	4.36	3.78	5.11

* Taken from mid-point of doublet.

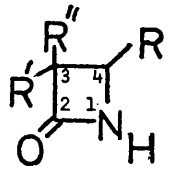
As may be seen from the table, a high degree of linearity was obtained throughout the concentration range of $Eu(fod)_3$ employed. From the calculated slopes of the responses obtained it may be deduced that H3a, H4, H5 and H6b were influenced strongly by the lanthanide shift reagent, inferring that they exist in a configuration on the same face of the molecule as the binding site of the shift reagent. The coordination point of the shift reagent in the molecule was the phosphoryl oxygen $(P=O)^{125}$ confirmed by the magnitude of the slope of H4 (10.6 ppm). One of the N-methylene protons (6a and 6b) appeared as a (dd) with $J_{H^1-H^1}=18Hz$ and $J_{H^1-P^{31}}=2.2Hz$, the latter removed by P^{31} decoupling.

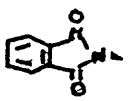
APPENDIX 2

Compilation of n.m.r. Date for Substituted Azetidin-2-ones

TABLE 1

C^{13}-N.m.r. Chemical Shifts in 4-Substituted Azetidin-2-ones



Substituent			Chemical Shift [ppm* (multiplicity)]		
R	R'	R''	C2	C3	C4†
OAc	H	H	166.4(s)	45.0(t)	73.2(d)
SO_2-C_6H_4Me	H	H	166.6(s)	41.4(t)	65.2(d)
N_3	H	H	166.4(s)	45.7(t)	63.2(d)
SPh	H	H	166.6(s)	45.3(t)	54.1(d)
SMe	H	H	166.9(s)	44.7(t)	52.5(d)
$\overset{O}{\overset{\|\|}{P}}(OMe)_2$ ††			166.5(s)	57.1(ddd) $J_{C^{13}-P^{31}} < 7.4Hz$	47.9(dd) $J_{C^{13}-P^{31}} = 170Hz$
$\overset{O}{\overset{\|\|}{P}}(OCH_2Ph)_2$ ††	H	H	167.0(s)	41.1(td) $J_{C^{13}-P^{31}} < 7.4Hz$	42.2(dd) $J_{C^{13}-P^{31}} = 171Hz$
$\overset{O}{\overset{\|\|}{P}}(OEt)_2$ ††	H	H	167.0(s)	41.1(td) $J_{C^{13}-P^{31}} < 7.4Hz$	41.9(dd) $J_{C^{13}-P^{31}} = 171Hz$
$\overset{O}{\overset{\|\|}{P}}(OMe)_2$ ††	H	H	166.9(s)	41.1(td) $J_{C^{13}-P^{31}} < 7.4Hz$	41.5(dd) $J_{C^{13}-P^{31}} = 171Hz$

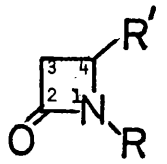
* Downfield from TMS.

† J. value measured from mid-point of doublet.

†† Synthesised by Dr. N.I. Carruthers, Ph.D. Thesis, Heriot-Watt University, Edinburgh, 1980.

TABLE 2

C^{13}-N.m.r. Chemical Shifts in 1,4-Disubstituted Azetidin-2-ones



Substituent		Chemical Shift [ppm* (multiplicity)]		
R	R'	C2	C3	C4
[1]$CH(OH)CO_2CH_2Ph$	OAc	168.3(s)	44.8(t)	75.6(d)
[2]$CH_2\ CO_2CH_2Ph$	OAc	167.1(s)	44.0(t)	75.7(d)
[3]$CH_2\ CO_2CH_2Ph$	$\overset{O}{\overset{\|\|}{P}}(OMe)_2$	166.9(s)	51.9(td) $J_{C^{13}-P^{31}} < 7.4Hz$	47.1(dd) $J_{C^{13}-P^{31}} = 171Hz$
$Si\overset{t}{-}BuMe_2$	$\overset{O}{\overset{\|\|}{P}}(OMe)_2$	171.6(s)	41.6(td)	43.5(dd) $J_{C^{13}-P^{31}} = 130Hz$
$Si\overset{t}{-}BuMe_2$	SPh	170.3(s)	48.2(t)	54.8(d)
$Si\overset{t}{-}BuMe_2$	Cl	168.0(s)	50.9(t)	64.5(d)
$Si\overset{t}{-}BuMe_2$	[4]SCH_2Ph	170.6(s)	48.3(t)	54.6(d)

* Downfield from TMS.

1 C^{13}-Shift of methine carbon in $CH(OH)CO_2CH_2Ph$ 73.2(d)

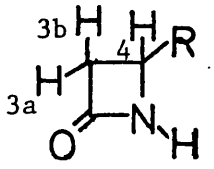
2 C^{13}-Shift of methylene carbon in $CH_2CO_2CH_2Ph$ 66.3(t)

3 " " " " " " " 66.1(t)

4 " " " " " " SCH_2Ph 34.1(t)

TABLE 3

H^1-N.m.r. Chemical Shifts in 4-Substituted Azetidin-2-ones



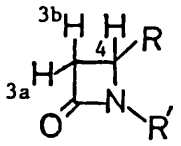
Substituent	Chemical Shift (δ values downfield from TMS)		
R	H3a	H3b	H4
OAc	3.28 (dd,J=15.0 and 4.6Hz)	3.00 (dd,J=15.0 and 1.5Hz)	5.81 (dd,J=4.6 and 1.6Hz)
N_3	3.10 (ddd,J=16.0, 3.0 and <1.0Hz)	2.70 (dd,J=16.0 and <1.0Hz)	4.80 (d,J=3.0Hz)
SMe[1]	3.20		4.80 (dd,J=6.0 and 2.5Hz)
SPh	3.65		4.90 (dd,J=8.0 and 2.0Hz)
[1]SCH_2Ph	3.25 (ddd,J=16.0, and 2.0Hz)	2.70 (dd,J=16.0 and 2.0Hz)	4.60 (dd,J=5.0 and 2.0Hz)
$\overset{O}{\overset{\|\|}{P}}(OMe)_2$*	3.06 unresolved multiplet		Lies under $P(OMe)_2$ signal
$\overset{O}{\overset{\|\|}{P}}(OEt)_2$*	3.08 unresolved multiplet		3.66 (ddd,J=9.0, 5.0 and 3.0Hz)
$\overset{O}{\overset{\|\|}{P}}(OCH_2Ph)_2$*	3.06 unresolved multiplet		3.65 (ddd,J=9.0, 4.2 and 4.1Hz)
SePh	3.40 (ddd,J=16.0, 6.0 and 1.0Hz)	2.90 (dd,J=16.0 and 1.5Hz)	5.20 (dd,J=4.0 and 2.0Hz)

* Synthesised by Dr. N.I. Carruthers, Ph.D. Thesis, Heriot-Watt University, Edinburgh, 1980.

[1] H^1-N.m.r. shift of methylene protons ($S\underline{CH_2}Ph$) - 3.80 (s).
H^1-N.m.r. shift of thiomethyl group - 2.2 (s).

TABLE 4

H^1-N.m.r. Chemical Shifts in 1,4-Disubstituted Azetidin-2-ones



Substituent		Chemical Shifts (δ values downfield from TMS)		
R^1	R^2	H3a	H3b	H4
OAc [1a]	Si^tBuMe_2	3.4 (dd,J=18.0 and 6.0)	2.85 (dd,J=18.0 and 2.0Hz)	6.01 (dd,J=5.0 and 1.5Hz)
OAc [1b]	$CH(OH)CO_2CH_2Ph$ [2a]	3.14 [multiplet]		6.10 and 5.95 (dd, J=5.69 and 1.85Hz) [diastereoisomers]
OAc [1c]	$CH(Cl)CO_2CHPh$ [2b]	3.20 [multiplet]		6.3 (dd,J=4.3 and 1.61Hz)
OAc [1d]	$CH_2CO_2CH_2Ph$ [2c]	3.14 (dd,J=16.0 and 4.0Hz)	2.96 (dd,J=16.0 and 2.08Hz)	5.95 (dd,J=2.08 and 0.83Hz)
OAc [1e]	$CH(\overset{O}{\overset{\|}{P}}(OMe)_2]CO_2CH_2Ph$ [2d]	3.20 [multiplet]		6.5 and 6.3 (dd, J=4.9 and 1.6Hz) [diastereoisomers]
SPh	$CH(OH)CO_2CH_2Ph$ [2e]	3.0 [multiplet]		5.05 (dd,J=6.0 and 2.0Hz)
SPh	$CH[\overset{O}{\overset{\|}{P}}(OMe)_2]CO_2CH_2Ph$ [2f]	3.40 (dd,J=16.0 and 6.0Hz)	2.94 (dd,J=16.0 and 4.0Hz)	5.14 (dd,J=6.0 and 2.0Hz)
Cl	$CH[\overset{O}{\overset{\|}{P}}(OMe)_2]CO_2CH_2Ph$ [2g]	3.36 [multiplet]		6.0 and 5.84 (J=4.0 and <1.0Hz)
SCN	Si^tBuMe_2	3.5 (dd,J=16.0 and 6.0Hz)	3.20 (dd,J=16.0 and 3.0Hz)	5.18 (dd,J=10.0 and 5.0Hz)
SCH_2Ph [3]	Si^tBuMe_2	3.38 (dd,J=18.0 and 7.0Hz)	2.95 (dd,J=18.0 and 3.0Hz)	4.52 (dd,J=6.6 and 1.6Hz)
$\overset{O}{\overset{\|}{P}}(OMe)_2$	$CH(OH)CO_2CH_2Ph$ [4a]	3.15 [multiplet]		4.0 [multiplet]
$\overset{O}{\overset{\|}{P}}(OMe)_2$	$CH(Cl)CO_2CH_2Ph$ [4b]	3.25 [multiplet]		4.15 [multiplet]
$\overset{O}{\overset{\|}{P}}(OMe)_2$	$CH_2CO_2CH_2Ph$ [4c]	3.18 [multiplet]		4.10 [multiplet]
$\overset{O}{\overset{\|}{P}}(OMe)_2$	Si^tBuMe_2	3.30 [multiplet]		Lies under $\overset{O}{\overset{\|}{P}}(OMe)_2$ signal
$\overset{O}{\overset{\|}{P}}(OMe)_2$	$C{=}C(Me(a))(OH)CO_2Me$ 5a	3.30 [multiplet]		4.10 [multiplet]
$\overset{O}{\overset{\|}{P}}(OMe)_2$	$C{=}C(Me(a))(OSO_2Me)CO_2Me$ 5b	3.30 [multiplet]		4.22 [multiplet]
$\overset{O}{\overset{\|}{P}}(OMe)_2$	$C{=}C(Me(a))(NHMe)CO_2Me$ 5c	3.3 - 2.6 [multiplet]		4.10 [multiplet]

Table 4 continued

1a - H^1-N.m.r. chemical shift of methyl in OCOMe - δ 2.03 (s)

1b - " " " " " " " - δ 1.90 (s)

1c - " " " " " " " - δ 2.05 (s)

1d - " " " " " " " - δ 2.08 (s)

1e - " " " " " " " - δ 2.10 and 2.04 (s)(diastereoisomers)

2a - " " " " methine protons - δ 5.48 and 5.40 (s)(diastereoisomers)

2b - " " " " " " - δ 6.09 (s)

2c - " " " " methylene protons - δ 4.03 (ABq,J=16.2Hz)

2d - " " " " methine protons - δ 5.00 (d,J=25Hz,{P^{31}} collapses to singlet)

2e - " " " " " " - δ 5.51 and 5.45 (s)(diastereoisomers)

2f - " " " " " " - δ 4.90 and 4.04 (d,J=13Hz)

2g - " " " " " " - δ 4.82 (d,J=25Hz)

3 - " " " " SCH Ph protons - δ 3.78 (s)

4a - " " " " methine protons - δ 5.58 and 5.50 (s)(diastereoisomers)

4b - " " " " " " - δ 6.10 and 6.08 (s)(diastereoisomers)

4c - " " " " methylene protons - δ 4.40 and 3.75 (ABq,J=18Hz)

One of the methylene protons coupled to P^{31}, J=2.2Hz.

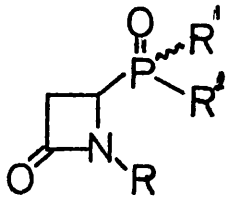
5a - H^1-N.m.r. chemical shift of methyl (a) - δ 2.40 and 2.20 (s)

5b - " " " " " " - δ 2.68 (s)

5c - " " " " " " - δ 2.04 (s)

TABLE 5

P^{31}-N.m.r. Chemical Shifts in 4-Phosphono and -Phosphino Azetidin-2-ones



Substituent			Chemical Shift (ppm)*
R	R^1	R^2	
H	OMe	OMe[1]	-20.5
H	OEt	OEt[1]	-18.1
H	OCH_2Ph	OCH_2Ph[1]	-19.4
H	Me	OEt[1]	-16.0, -17.2 (diastereoisomers)
H	Me	OCH_2Ph[1]	-14.4, -15.7 (")
H	Me	OCH_2CCl_3[1]	-50.2, -50.1 (")
$CH(OH)CO_2CH_2Ph$	OMe	OMe	-23.4, -22.6 (")
$CH_2CO_2CH_2Ph$	OMe	OMe	-23.1
Si^tBuMe_2	OMe	OMe	-25.0
Si^tBuMe_2	$OSiMe_3$	OMe	-15.6, -5.5 (")
Si^tBuMe_2	Cl	OMe	-48.0, -40.0 (")

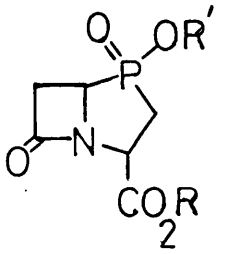
* Downfield from 88% phosphoric acid, H^1-decoupled.

[1] Synthesised by Dr. N.I. Carruthers, Ph.D. Thesis, Heriot-Watt University, Edinburgh, 1980.

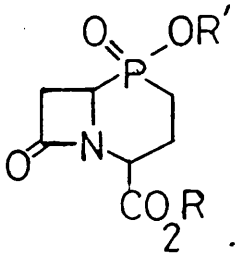
APPENDIX 3

Synthesis of Precursors for the 1-Phosphapenicillins and 1-phosphacephalosporins

This section will be concerned with the synthesis of possible precursors to the 1-phosphapenicillins (304) and 1-phosphacephalosporins (305).

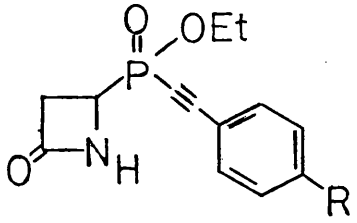


(304)



(305)

The key intermediates for this investigation were the azetidin-2-one phosphono acetylenes (306) and (307), the former reported by Carruthers,[119] and the latter synthesised by Dr. Winton in these laboratories.



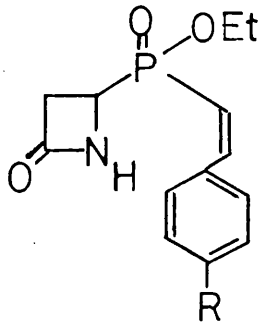
(306) R = H

(307) R = OMe

It was anticipated that if the acetylenic group could be elaborated, e.g. to keto or alkene, then a cyclisation could be achieved by application of the Woodward methodology.[26]

We have prepared the novel vinyl phosphino azetidin-2-ones

(308) and (309) by a Lindlar hydrogenation of acetylenes (306) and (307) [$Pd/BaSO_4$, pyridine, H_2, 20°, 4 hours] in 77% and 85% yield respectively.

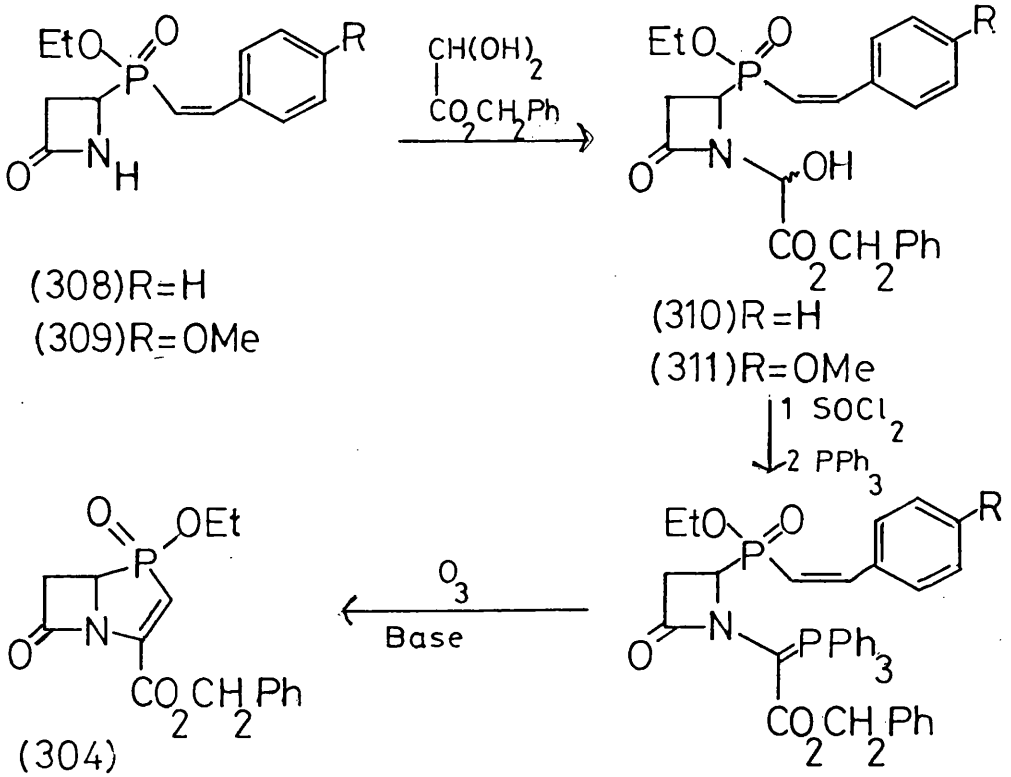


(308) R=H
(309) R=OMe

The vinylic proton α to phosphorus appeared at δ 5.84 in (308) and δ 5.62 in (309) which simplified on P^{31}-decoupling. High resolution mass measurement on (308) and (309) was in agreement with the proposed molecular formula.

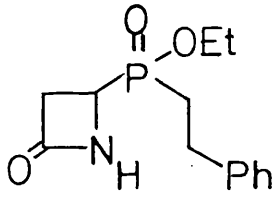
A possible route to the target 1-phosphapenicillin (304) from (308) or (309) is outlined in Scheme 35.

Scheme 35

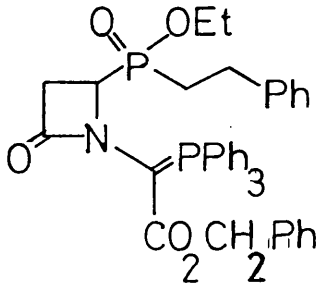


In preparation for the route shown we have synthesised the novel glyoxylate adducts (310) and (311) by the method previously described (section 6.0.3). The i.r. of these adducts showed a broad absorption at 3550 - 3150 cm^{-1} (OH), with the β-lactam carbonyl at 1780 cm^{-1} (310) and (311). H^1-n.m.r. showed incorporation of a D_2O exchangable signal at δ 5.7 - 5.4 in (310) and δ 5.6 - 5.3 in (311) (OH) and a singlet at δ 5.20 in (310) and δ 5.1 in (311) ($C\underline{H}_2Ph$). Elemental analysis was correct for the proposed structure of adduct (310).

In one instance, over-reduction of the triple bond in (306) occurred on hydrogenation leading to the fully saturated system (314) and this compound was converted to the phosphorane (315) in order to test the methodology.



(314)

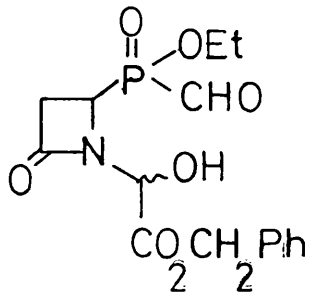


(315)

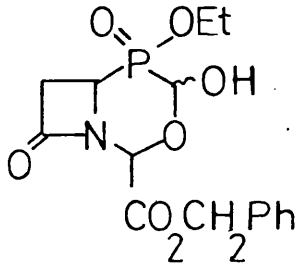
Phosphorane (315) had the β-lactam carbonyl in the i.r. at 1760 cm^{-1} [cf. 1780 cm^{-1} in (310)]. H^1-n.m.r. showed the absence of the N$C\underline{H}$ proton at circa δ 5.3 [cf. N-$C\underline{H}$- in (310) δ 5.6]. High resolution mass measurement was in agreement with the proposed molecular formula. Further investigation of this synthetic strategem is underway in these laboratories.

The interemdiates shown in Scheme 35 could also lead to bicyclic structures, for example, ozonolysis of (310) or (311) should lead to the phosphino formate (316) which could ring close

affording the bicyclic system (317).

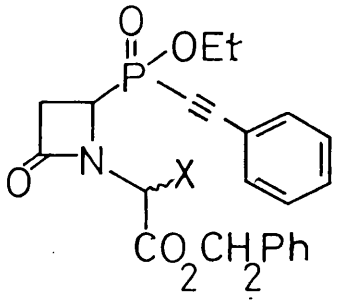


(316)



(317)

Phosphino acetylenes (306) and (307) have further potential, for example, we have synthesised the glyoxylate adduct (318) by the usual methodology.

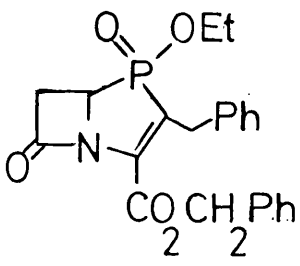


(318) X = OH

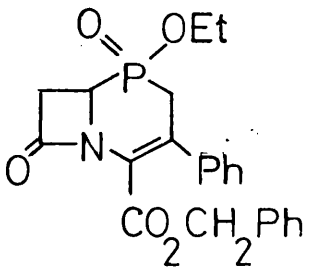
(319) X = Cl

This compound had the appropriate spectral properties (H^1-n.m.r. and i.r.) and gave elemental analyses in accordance with the proposed structure.

Further elaboration of (318) could be envisaged as proceeding via the chloromethyl derivative (319) followed by a tin hydride initiated radical ring closure, as described by Bachi *et al.*,[65,66,122] leading to either phosphapenicillin (320) or phosphacephalosporin (321).



(320)

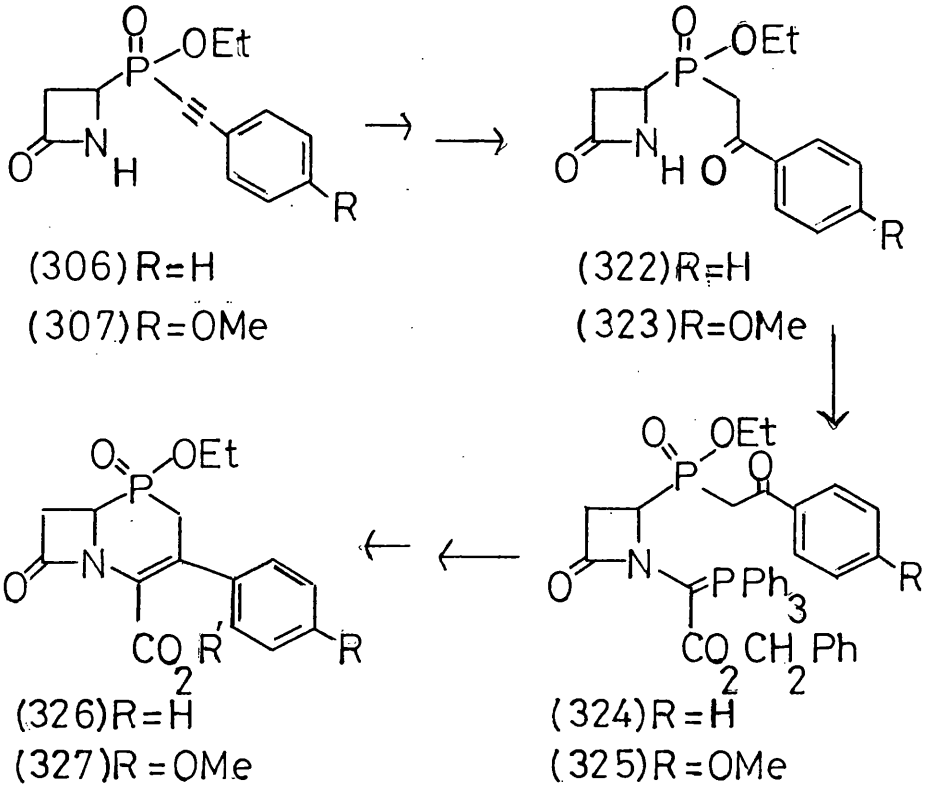


(321)

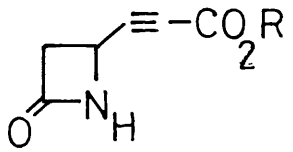
The Bachi cyclisation methodology could, of course, also be applied to the vinylic phosphino azetidin-2-ones (310) and (311) leading ultimately to the fully saturated analogues of (320) and (321).

Conversion of the acetylenes (306) or (307) to the ketones (322) or (323) followed by the Woodward strategy should lead to the $\Delta^{3,4}$-1-phosphacephem (326) (327). This is summarised in Scheme 36.

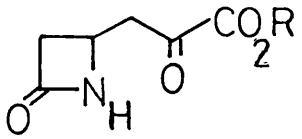
Scheme 36



Acetylene to ketone conversions are well recorded. However, some of the conditions employed may cause β-lactam cleavage. Recently Ikegami *et al.*[123] have reported this conversion with the β-lactam acetylenes (328) affording ketone (329).



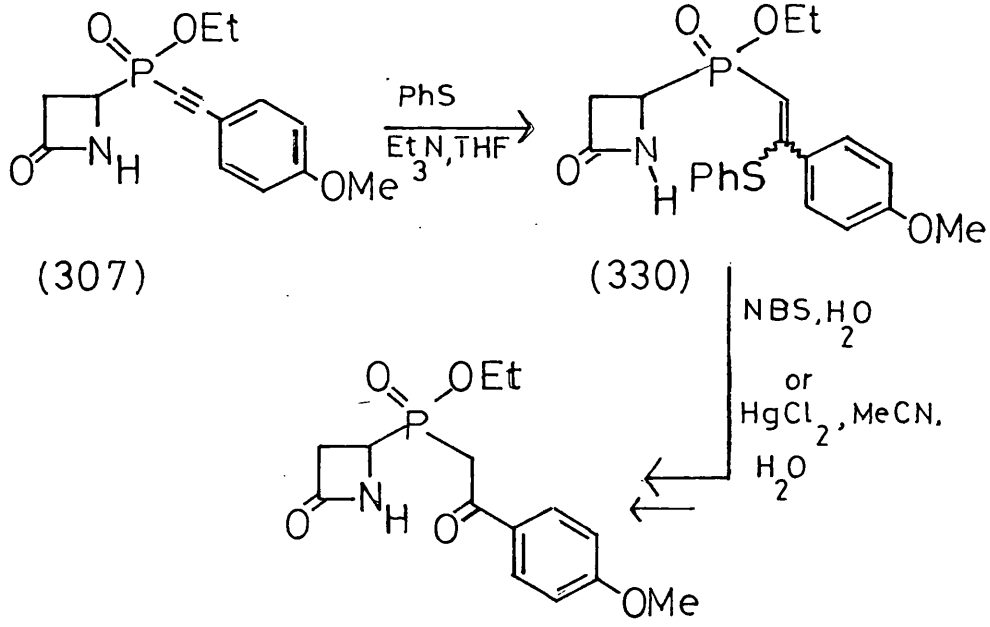
(328)



(329)

This sequence of reactions proceeded via Michael addition of thio phenol to the triple bond followed by aqueous NBS treatment of the intermediate vinyl sulphide. We have applied this route to β-lactam phosphinoacetylene (307) (Scheme 37).

Scheme 37



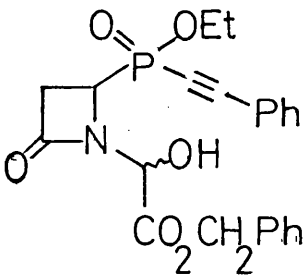
(307) (330) (331)

Thus treatment of acetylene (307) with excess thio phenol and excess triethylamine in refluxing THF afforded vinyl sulphide (330) after chromatography on silica. I.r. showed the β-lactam carbonyl (1780 cm^{-1}) and the double bond at 1590 cm^{-1}. H^1-n.m.r. indicated the presence of a vinylic proton at δ 6.1 (d,J=16Hz) which collapsed to a singlet on P^{31}-decoupling. High resolution mass measurement was in agreement with the proposed structure (330).

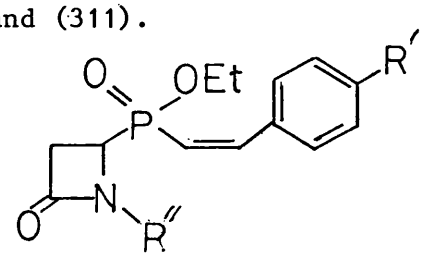
With the vinyl sulphide (330) available, several routes leading to ketone (331) become accessible, for example, reaction of (330) with mercuric chloride in wet acetonitrile[124] could lead to the required ketone (331) or further NBS treatment followed by reduction[123] could also produce ketone (331).

Summary

Several potentially important precursors to the 1-phospha-penicillins (304) and -cephalosporins (305) have been synthesised, for example, glyoxylate adducts (318), olefins (308) and (309), together with glyoxylate adducts (310) and (311).

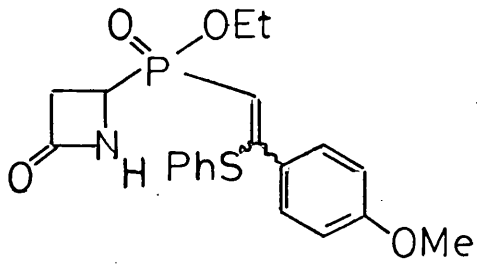


(318)



(308) R′=R″=H
(309) R′=OMe, R″=H
(310) R′=H, R″= -CH(OH)CO_2CH_2Ph
(311) R′=OMe, R″= -CH(OH)CO_2CH_2Ph

An intermediate in the conversion of acetylene (307) to ketone (331), namely vinyl sulphide (330), has been prepared.



(330)

The precursors synthesised have important implications for the synthesis of target systems (304) and (305) and they are at present under more detailed study in these laboratories.

4-(O-Ethylphenylvinylphosphino)azetidin-2-one (308)

4-(O-Ethylphenylethylnyl)phosphinoazetidin-2-one (306) (0.4 g, 1.52 mMol) was dissolved in dry pyridine at 20°C and treated with 5% palladium/barium sulphate (5 mg). The mixture was stirred under a hydrogen atmosphere for 4½ hours. After removal of the solvent chromatography of the residue on silica afforded 4-(O-ethylphenylvinylphosphino)azetidin-2-one (308) as a yellow oil (0.31 g, 77%). ν_{max} ($CHCl_3$), 3420 (NH), 1780 (β-lactam C=O), 1600 (aromatic (C=C), 1240 (P=O) and 1040 cm^{-1} (POMe), δ ($CDCl_3$), 7.9 - 7.1 (7H,m,Ph,NH and $\overset{O}{\overset{\|}{P}}-C=CH-$), 5.8 (1H,dd,J=17.10 and 4.0Hz, $\overset{O}{\overset{\|}{P}}CH=C--$), 4.10 (2H,m,$\overset{O}{\overset{\|}{P}}-OCH_2CH_3$), 3.30 (1H,m,H4), 3.10 (2H,m,H3) and 1.30 (3H,m,$\overset{O}{\overset{\|}{P}}-OCH_2CH_3$). [Found: M^+, 265.0887. $C_{13}H_{16}NO_3P$ requires M^+, 265.0884].

4-(O-Ethylparamethoxyphenylvinylphosphino)azetidin-2-one (309)

4-(O-Ethylparamethoxyphenylethylnylphosphino)azetidin-2-one (307) (423 mg, 1.44 mMol) was dissolved in dry ethyl acetate/pyridine (1:1)

and treated with 5% palladium/barium sulphate (5 mg). The suspension was stirred for 18 hours at 20°C under an atmosphere of hydrogen. After removal of the solvent chromatography of the residue gave 4-(O-ethyl-paramethoxyphenylvinylphosphino)azetidin-2-one (309) as a yellow oil (360 mg, 85%). ν_{max} ($CHCl_3$), 3430 (NH), 1770 (β-lactam C=O), 1260 (P=O) and 1040 cm^{-1} (POEt), δ ($CDCl_3$), 7.80 (1H,dd, J=8.0 and 2.0Hz, $\overset{O}{\overset{\|}{P}}CH=\underline{CH}$-Ph), 7.64 - 6.60 (5H,m,Ph and NH), 5.64 (1H,dd,J=16.0 and 2.0Hz, $\overset{O}{\overset{\|}{P}}\underline{CH}$=CH-Ph), 4.18 (2H,m, $\overset{O}{\overset{\|}{P}}O\underline{CH_2}CH_3$), 3.80 4H,m,OMe and H4), 3.10 (2H,m,H3) and 1.30 (3H,m, $\overset{O}{\overset{\|}{P}}OCH_2\underline{CH_3}$). [Found: M^+, 295.0961. $C_{14}H_{18}NO_4P$ requires M^+, 295.0974).

Benzyl-(2RS)-2-[(4RS)-4-O-ethylphenylvinylphosphino-2-oxoazetidin-1-yl]-2-hydroxy acetate (310)

4-(O-Ethylphenylvinylphosphino)azetidin-2-one (308) (311 mg, 1.17 mMol) was dissolved in dry THF (5 ml) and treated with hydrated benzyl glyoxylate (214 mg, 1.17 mMol) and 1 drop of triethylamine. The clear solution was stirred for 18 hours at 20°C diluted with ethyl acetate and extracted with warm (6 x 50 ml). Drying of the solvent ($MgSO_4$) and removal afforded benzyl-(2RS)-2-[(4RS)-4-O-ethylphenylvinylphosphino-2-oxoazetidin-1-yl]-2-hydroxy acetate (310) as a pale yellow oil (368 mg, 77%). ν_{max} ($CHCl_3$), 3550 - 3200 (OH), 1780 (β-lactam C=O), 1760 (ester), 1600 (C=C), 1250 (P=O) and 1040 cm^{-1} (POEt), δ ($CDCl_3$), 7.80 - 7.0 (11H,Ph and $\overset{O}{\overset{\|}{P}}CH=\underline{CH}$), 6.0 - 5.3 (3H,m, $\overset{O}{\overset{\|}{P}}CH=\underline{CH}$,Ph and $\underline{CH}$OH becomes 2H on deuteration), 5.20 (2H,s, $\underline{CH_2}$Ph), 4.3 - 3.6 (3H,m, $\overset{O}{\overset{\|}{P}}$-$O\underline{CH_2}CH_3$ and H4), 3.0 (2H,m,H3) and 1.20 (3H,m, $\overset{O}{\overset{\|}{P}}$-$OCH_2\underline{CH_3}$). [Found: C, 56.58; H, 5.68; N, 3.16. $C_{22}H_{24}NO_6P$-$2H_2O$ requires C, 56.77; H, 5.59; N, 3.01%].

Benzyl-(2RS)-2-[(4RS)-4-O-ethyl-paramethoxyphenylvinylphosphino-2-oxoazetidin-1-yl]-2-hydroxy acetate (311)

Method as for adduct (310), (311) obtained in 66% yield as a pale yellow oil. ν_{max} ($CHCl_3$), 3550 - 3100 (OH), 1785 (β-lactam C=O), 1740 (ester), 1250 (P=O) and 1040 cm^{-1} (POEt), δ ($CDCl_3$), 7.9 - 6.6 (10H,m,Ph and $\overset{O}{\overset{\|}{P}}CH=\underline{CH}$), 6.3 - 5.3 (3H,m,$\overset{O}{\overset{\|}{P}}\underline{CH}=CH$,OH and $\underline{CH}OH$ becomes 2H on deuteration), 5.25 (2H,s,$\underline{CH_2}Ph$), 4.3 - 3.6 (6H, m,$\overset{O}{\overset{\|}{P}}O\underline{CH_2}CH_3$,H4 and OMe), 2.95 (2H,m,H3) and 1.2 (3H,m,$P\text{-}O\underline{CH_2}\underline{CH_3}$).

4-O-Ethyl-2-phenylethylphosphinoazetidin-2-one (314)

4-O-Ethylphenylethynylazetidin-2-one (306) (0.6 g, 2.28 mMol) was dissolved in dry pyridine and treated with 5% palladium/barium sulphate (5 mg). The suspension was stirred under a hydrogen atmosphere for 48 hours at 20°C. After this time the solvent was removed *in vacuo* to give 4-O-ethyl-2-phenylethylphosphinoazetidin-2-one (314) as a yellow oil (0.6 g, 98%). ν_{max} ($CHCl_3$), 3500 (NH), 1770 (β-lactam C=O), 1280 (P=O) and 1040 cm^{-1} (POEt), δ ($CDCl_3$), 7.20 (5H,s,Ph), 4.10 (2H,m,$\overset{O}{\overset{\|}{P}}\text{-}O\underline{CH_2}CH_3$), 3.9 - 3.5 (1H,m, H4), 3.25 - 2.7 (4H,m,H3 and $\overset{O}{\overset{\|}{P}}\text{-}\underline{CH_2}CH_2$), 2.4 - 1.8 (2H,m,$\overset{O}{\overset{\|}{P}}CH_2\underline{CH_2}$) and 1.30 (3H,m,$\overset{O}{\overset{\|}{P}}\text{-}O\underline{CH_2}\underline{CH_3}$).

Preparation of phosphorane (315)

Azetidin-2-one (314) (290 mg, 1.09 mMol) was dissolved in dry THF and treated with hydrated benzyl glyoxylate (199 mg, 1.09 mMol) and 1 drop of triethylamine at 20°C. The solution was stirred for 18 hours, diluted with ethyl acetate and extracted with water (6 x 50 ml). The solvent was dried ($MgSO_4$) and removed to give the glyoxylate adduct. ν_{max} ($CHCl_3$), 3600 - 2900 (OH), 1780 (β-lactam C=O) and 1740 cm^{-1} (ester). The impure glyoxylate adduct (177 mg,

0.41 mMol) was dissolved in dry THF/dioxane (1:1) (10 ml) under argon and cooled to -25°C and 2,6-lutidine (44.2 mg, 0.41 mMol) and was added followed by thionyl chloride (42.2 mg, 0.41 mMol). The suspension was warmed to 0°C and stirred for 5 hours. After this time the mixture was filtered under argon and the filtrate evaporated to dryness (cold finger). The crude chloro derivative was re-dissolved in dry dioxane under argon and treated with triphenylphosphine (162 mg, 0.62 mMol) and 2,6-lutidine (44.2 mg, 0.41 mMol) and the solution stirred at 50-55°C for 18 hours. Filtration of the mixture and evaporation of the filtrate *in vacuo* gave phosphorane (315) as a yellow oil (305 mg). ν_{max} ($CHCl_3$), 3060 (CH), 1770 (β-lactam C=O), 1760 (ester), 1660 (phosphorane), 1200 (P=O) and 1040 cm^{-1} (POEt), δ ($CDCl_3$), 7.8 - 7.0 (25H,m,Ph), 5.25 (2H,s,$\underline{CH_2}Ph$), 4.3 - 3.8 (3H,m,$P(=O)-O\underline{CH_2}CH_3$ and H4), 3.2 - 2.0 (6H, m,$P(=O)\underline{CH_2}\underline{CH_2}$ and H3) and 1.30 (3H,m,$P(=O)-OCH_2\underline{CH_3}$). M^+,675 [Found: M^+, $C_{40}H_{39}NO_5P_2$ requires M^+, 675.2310; $C_{40}H_{39}NO_5P_2$ requires M^+, 675.2303].

Benzyl-(2RS)-2-[(4RS)-4-O-ethylphenylethynylphosphino-2-oxoazetidin 1-yl]-2-hydroxy acetate (318)

4-O-Ethylphenylethynylphosphinoazetidin-2-one (306) (26.3 mg, 1 mMol) was dissolved in dry THF at 20°C and treated with hydrated benzyl glyoxylate (182 mg, 1 mMol) and 1 drop of triethylamine. The solution was stirred for 18 hours at 20°C, diluted with ethyl acetate and washed with water (6 x 50 ml). The organic phase was dried ($MgSO_4$) and removed to afford benzyl-(2RS)-2-[(4RS)-4-O-ethylphenyl-ethynylphosphino-2-oxoazetidin-1-yl]-2-hydroxy acetate (318) as a pale yellow oil (312 mg, 73%). ν_{max} ($CHCl_3$), 3550 - 3100 (OH), 2200 (C≡C), 1780 (β-lactam C=O), 1760 (ester), 1220 (P=O) and 1040 cm^{-1} (POEt), δ ($CDCl_3$), 7.6 - 7.2 (10H,m,Ph), 5.7 - 5.4 (2H,m,OH and

CHOH, becomes 2H on deuteration), 5.22 (2H,s,CH_2Ph), 4.4 - 3.9 (3H,m,$\overset{O}{\overset{\|}{P}}$-O$CH_2CH_3$ and H4), 3.30 (2H,m,H3) and 1.40 (3H,m,$\overset{O}{\overset{\|}{P}}$-O$CH_2CH_3$). [Found: C, 62.08; H, 5.25; N, 3.39. $C_{22}H_{22}NO_6P$ requires C, 61.83; H, 5.15; N, 3.28%].

Reaction of 4-O-ethyl-paramethoxyphenylethynylphosphinoazetidin-2-oen (307) with thiophenol

Azetidin-2-one (307) (465 mg, 1.59 mMol) was dissolved in dry THF (10 ml) under argon and treated with thiophenol (1.74 g, 15.8 mMol) and triethylamine (1.60 g, 15.8 mMol). The mixture was refluxed for 30 minutes and the solvent removed *in vacuo*. Chromatography of the residue on silica afforded vinyl sulphide (330) as a yellow oil (215 mg, 34%). λ_{max} ($CHCl_3$), 290 nm, ε 15700, ν_{max} ($CDCl_3$), 3430 (NH), 1780 (β-lactam C=O), 1590 (C=C), 1190 (P=O) and 1050 cm^{-1} (POEt), δ ($CDCl_3$), 7.6 - 6.4 (10H,m,Ph and NH), 6.10 (1H,d,J=16.0Hz,$\overset{O}{\overset{\|}{P}}$-CH=$CR_2$,{$P^{31}$} decoupling simplifies to singlet), 4.20 (2H,m,$\overset{O}{\overset{\|}{P}}$-O$CH_2CH_3$), 3.9 - 3.8 (4H,m,OMe and H4), 3.25 (2H,m,H3) and 1.35 (3H,m,$\overset{O}{\overset{\|}{P}}$-$CH_2CH_3$). M^+, 403 [Found: M^+, 403.1008. $C_{20}H_{22}NO_4PS$ requires M^+, 403.1007].

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