ASYMMETRIC SYNTHESIS OF β-LACTAMS

A thesis presented in part fulfilment of the requirements for the Degree of Doctor of Philosophy

by

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September 1990

To Mum, Dad and Anne

CONTENTS

Acknowledgements.

I would like to express my gratitude to Dr. E.W. Colvin for his helpful guidance and friendship throughout this work. I would also like to thank my fellow students for their help and friendship.

Thanks are also due to Dr. J. Cole (g.c.) and Dr. D. Rycroft (200 MHz ^{1}H and 50 MHz ^{13}C n.m.r). I would also like to acknowledge the valuable technical assistance of the Department, in particular that of Mrs. F. Lawrie (i.r.), Mr. J. Gall (n.m.r.), Mr. A. Ritchie (m.s.), Mrs. K. Wilson (microanalysis) and their respective staff.

ABBREVIATIONS

Ac	Acetyl
BBN	9-borabicyclo[3.3.1]nonane
Bu	n-Butyl
DCC	1,3-Dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DMAP	4-(N,N-dimethylamino)pyridine
Et	Ethyl
mCPBA	m-Chloroperbenzoic acid
Me	Methyl
Mn	Menthyl
NMR	Nuclear Magnetic Resonance
PNB	p-Nitrobenzoate
PG	Protecting group
TBDMS	tert-Butyldimethylsilyl
TBDPS	tert-Butyldiphenylsilyl
THF	Tetrah
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

SUMMARY

Several routes to optically enriched 2-azetidinones have been investigated. The most successful of these was that based on highly diastereoselective cycloaddition reactions between homochiral imines derived from (S)-methyl lactate and a range of achiral ketenes. The synthetic potential of the resulting azetidinones with respect to bicyclic β-lactam formation has also been investigated.

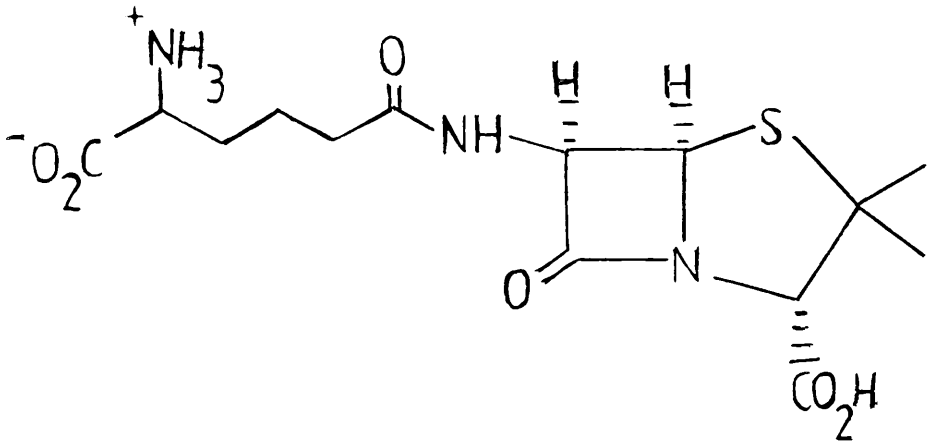
Introduction

Antibiotics can be defined as substances which, without possessing enzyme character, can, when present in low concentrations, inhibit the cell growth processes of bacteria.

To date, more than 4,000 antibiotics have been isolated from microbial sources and more than 30,000 synthetic or semisynthetic antibiotics have been prepared. The vast majority of these compounds contain a β-lactam ring. These compounds, the so-called β-lactam antibiotics, are amongst the most efficient weapons available to physicians in the fight against infectious diseases. As a result, the development of new β-lactam antibiotics remains one of the most active areas of pharmaceutical research.

The availability of a wide range of β-lactam antibiotics, suitable for the treatment or prevention of a broad spectrum of bacterial infections, is now taken for granted. However, the discovery and development of these drugs has been a slow and laborious process involving the contributions and co-operation of countless research workers over many decades.

The first step in the discovery of β-lactam antibiotics came in 1929 when Alexander Fleming reported[1] on the antibacterial activity of the mould *Penicillium*. Unfortunately, Fleming was not, apparently, of the opinion that the effects which he had



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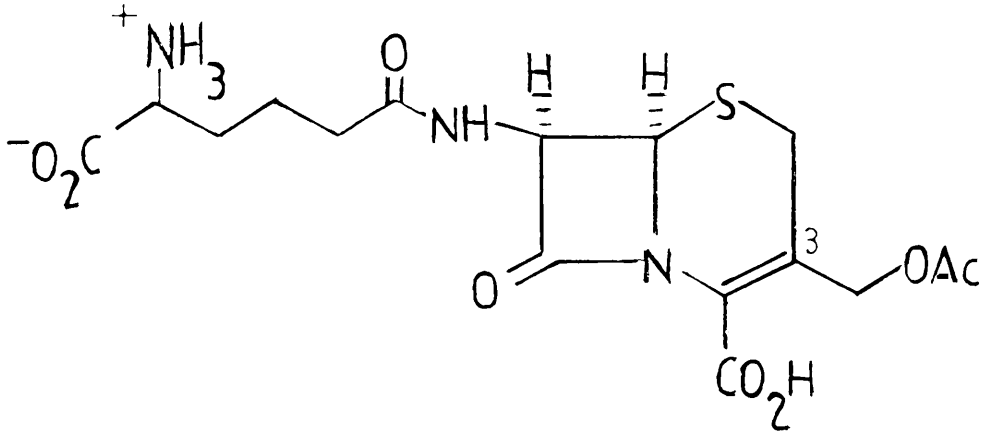


(2)

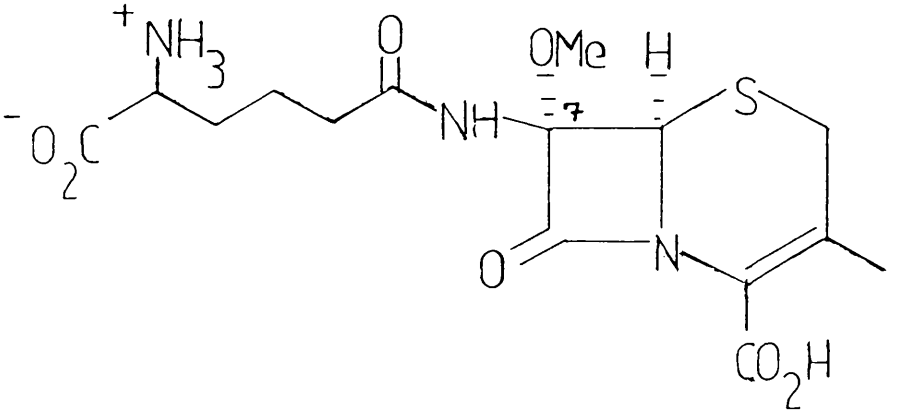
observed *in vitro* could be extended to living animals.

As a result, there was no further activity in the area until 1940, when Florey and Chain, at Oxford, successfully isolated[2] penicillin N (1), the compound responsible for the *Penicillium* mould's remarkable antibacterial activity. Shortly thereafter the actual structure of penicillin N was determined by X-ray crystallography.[3]

At about the same time Brotzu, working in Sardinia, observed a similar antibacterial effect in the mould *Cephalosporium acremonium*. This led eventually to the isolation[4] and structural elucidation[5] of cephalosporin C (2).

Using these structures as starting points, researchers successfully prepared, over many years, a vast range of both penicillins and cephalosporins by partial synthesis. These new compounds differed only in their acylamino substituents and, for cephalosporins, their C-3 substituents. As a result of such peripheral modifications a number of clinically useful and commercially viable β-lactam antibiotics were produced.[6]

Unfortunately, as a result of widespread and often careless overuse of these drugs, bacterial strains have emerged which produce enzymes, β-lactamases, capable of destroying many β-lactam antibiotics before they can reach the target site in the bacterium. Clearly there was a need to develop new β-lactam antibiotics, capable of resisting these enzymes. One such group of



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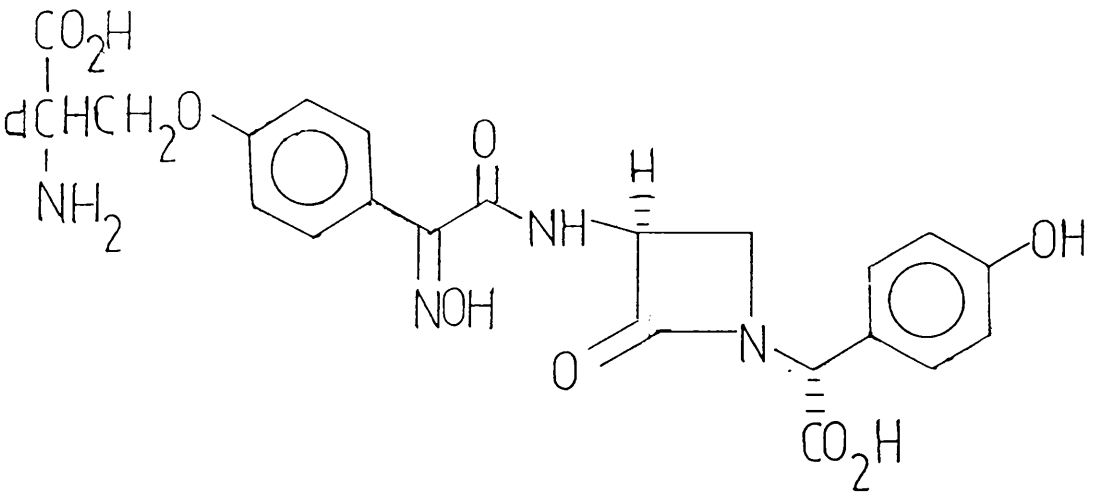

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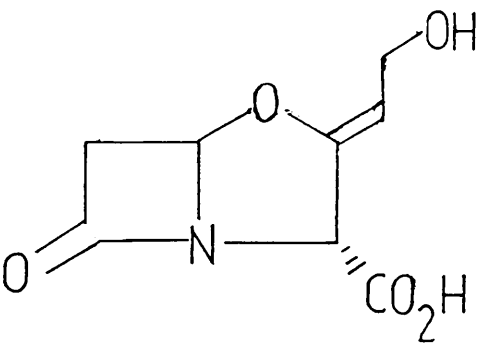

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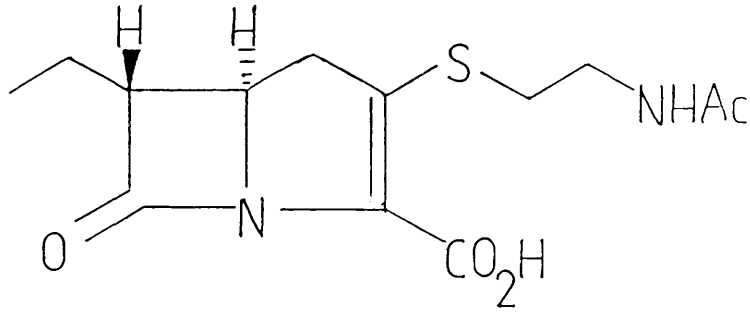
compounds emerged in 1971, with the isolation[7] from microbial systems of the cephalosporin analogue cephamycin (3). This compound has a very similar antibacterial profile to the cephalosporins. However, the presence of the 7-α-methoxy substituent imparts a far greater stability against β-lactamases.

More compounds with the highly desirable properties of cephamycin were clearly needed. In 1976 there was a considerable breakthrough which allowed fairly rapid movement towards this goal : three biogenetically novel β-lactam systems, all with very desirable biological properties were isolated from microbial systems.

Aoki et al., working at the Fujisawa Research Laboratories, isolated and characterised[8] nocardicin A (4). Although only moderately active against Gram-negative organisms, nocardicin A is particularly noteworthy as the first monocyclic β-lactam to be discovered with antibacterial activity. Several clinically useful monocyclic β-lactam antibiotics have subsequently been developed.

The isolation and structure determination of the oxapenam clavulanic acid (5) was carried out independently by workers at Beecham[9a] and at Glaxo.[9b] Since then it has become one of the most widely used β-lactam drugs. Its therapeutic value stems not from its antibacterial activity (which is, in itself very modest) but from its ability to irreversibly inhibit a wide range of β-lactamases. Thus clavulanic acid, when



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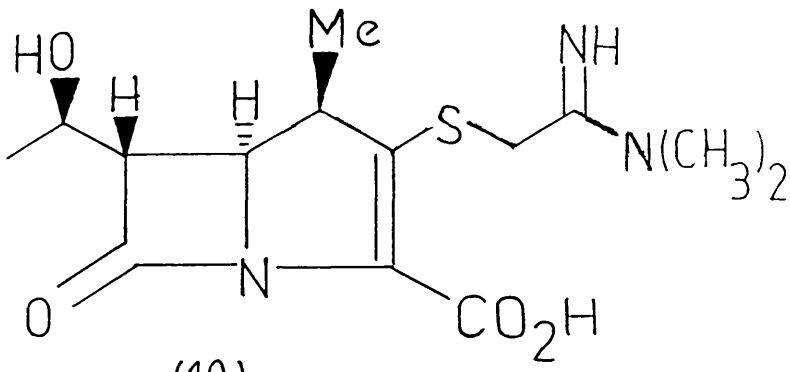

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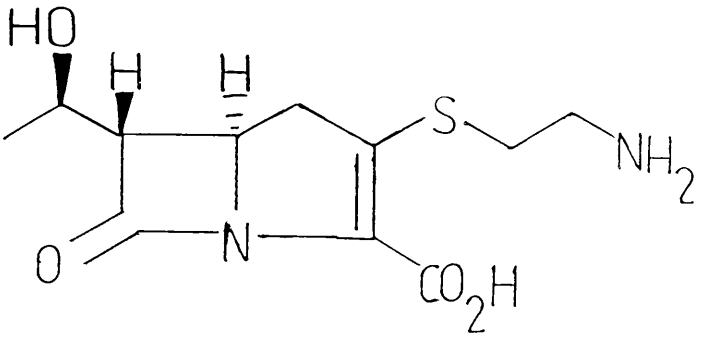

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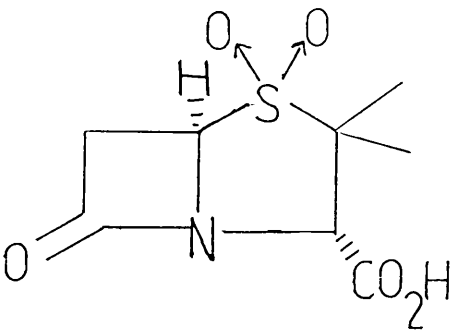

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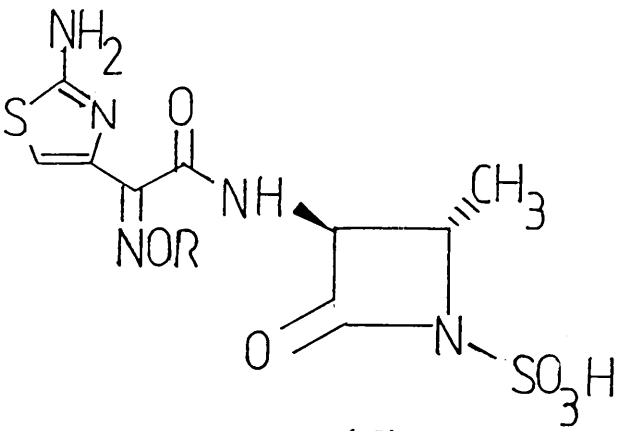


R = $-C(CH_3)_3$

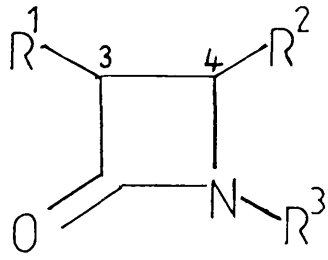
(8)

administered alongside a conventional β-lactam antibiotic, greatly increases the effective potency of the latter.

Kahan and co-workers isolated[10] and characterised thienamycin (6), a potent, broad spectrum antibiotic with notable natural stability against β-lactamases.

The discovery of these three novel systems led to an explosion of activity in the area. As a result, many unusual β-lactam systems with very desirable biological properties were found, not only by further screening of microbial systems but also by both partial and total synthesis. Examples of such compounds include: sulbactam (7), a potent β-lactamase inhibitor prepared semisynthetically;[11] azthreonam (8), a β-lactamase stable monocyclic β-lactam prepared by total synthesis and highly active against gram negative organisms;[12] PS-5 (9), a compound isolated in small amounts from fermentation systems but noteworthy for being a broad spectrum antibiotic with inhibitory activity against a range of β-lactamases[13] and 1-β-methylcarbapenem (10), a compound prepared by total synthesis and found to be highly resistant to β-lactamases while retaining the excellent antibacterial properties of thienamycin.[14]

Clearly, if many of these compounds are to be developed as viable drugs it is necessary to develop efficient total syntheses. However, as with most biologically active compounds, the activity of these molecules depends crucially on the absolute



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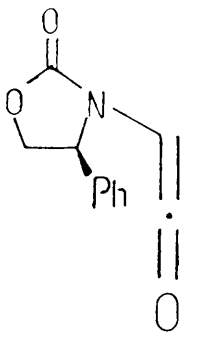
stereochemistry at each of the chiral centres present. Clearly, therefore, any acceptable total synthesis must yield the desired homochiral diastereoisomer as the major product.

Generally speaking, it is only the absolute configuration of the two chiral centres on the β-lactam ring which present a problem. If there are other chiral centres present they are usually relatively simple to introduce in a controlled fashion. Thus the main problem to be overcome to allow total synthesis of these target molecules is the production of azetidinones (11) with control of the absolute configuration at positions 3 and 4.

Several groups have successfully synthesised homochiral azetidinones by using the fixed chiral centres of homochiral starting materials as the new chiral centres in the β-lactam ring.[15] This approach, however, generally requires a large number of steps and is not flexible enough to allow synthesis of a significant range of useful precursors.

A much more flexible and direct approach involves the asymmetric synthesis of the β-lactam ring using the chiral centre of a homochiral starting material to influence the absolute configuration of the new chiral centres being formed at positions 3 and 4 in the azetidinone.

The following sections outline much of the work which has been carried out in this area. Particular attention has been paid to those approaches which give the best asymmetric induction and to those which yield synthetically useful products.



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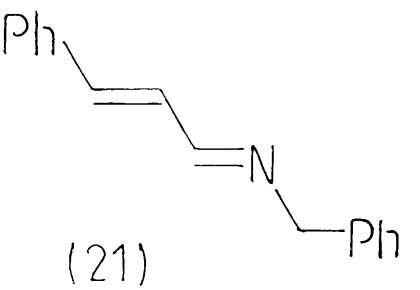

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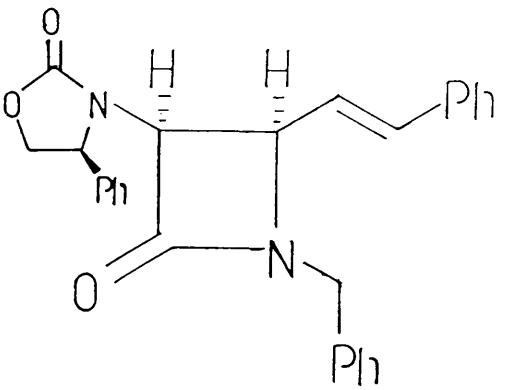

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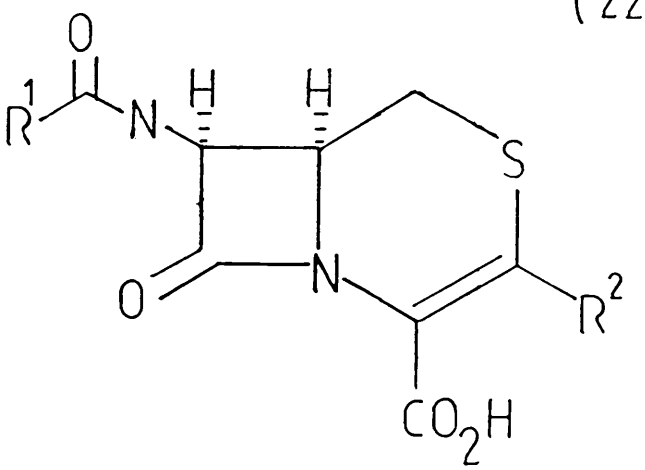

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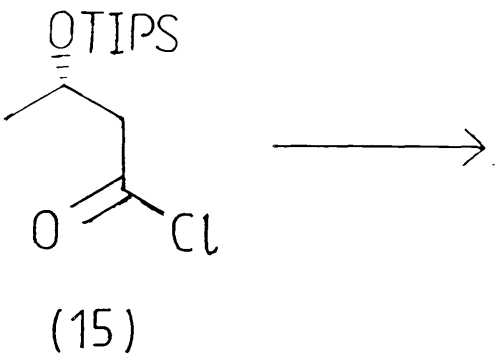

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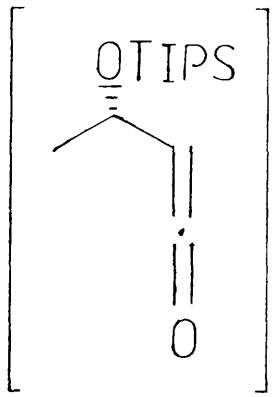

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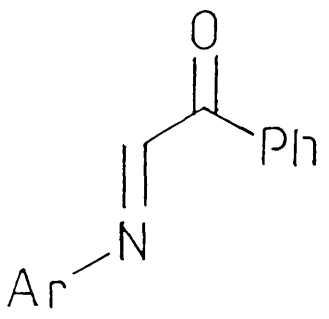

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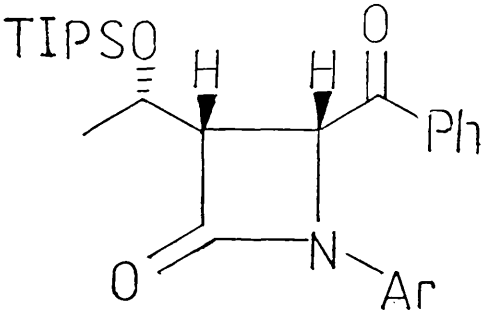

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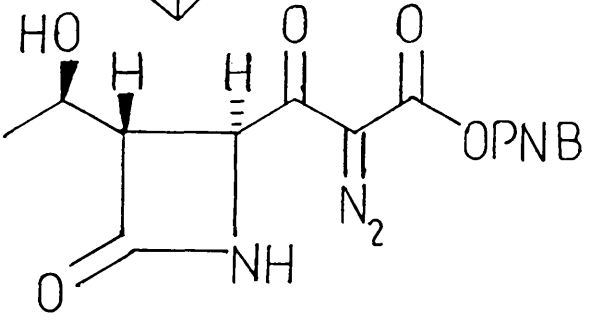

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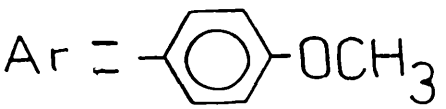
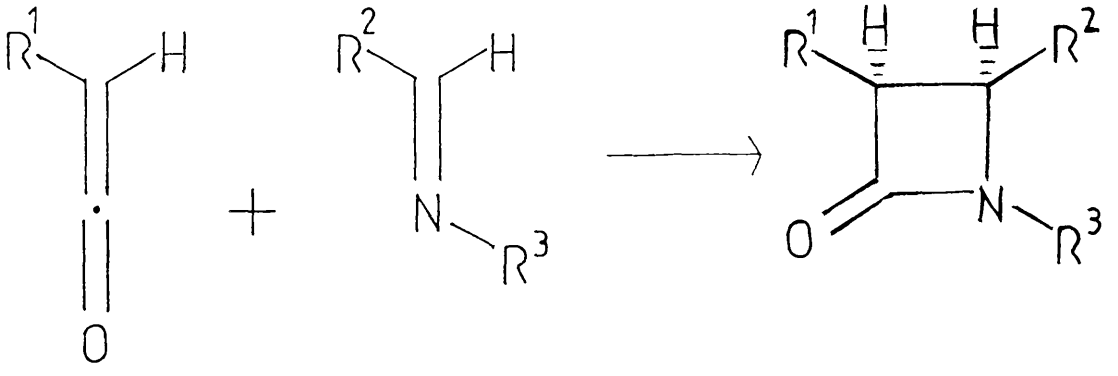
Ar = 



(12) (13) (14)

Ketene-Imine Cycloaddition

Ketenes (12) will react with imines (13) in a formal [2+2]-cycloaddition (the so-called Staudinger reaction), to give azetidinones (14).

Despite considerable attention, the mechanism of this reaction is still controversial (it is discussed in some detail on p. 19). However, it is generally found that, when (E)-imines are employed, this reaction will afford cis-disubstituted azetidinones with a very high degree of stereoselectivity.

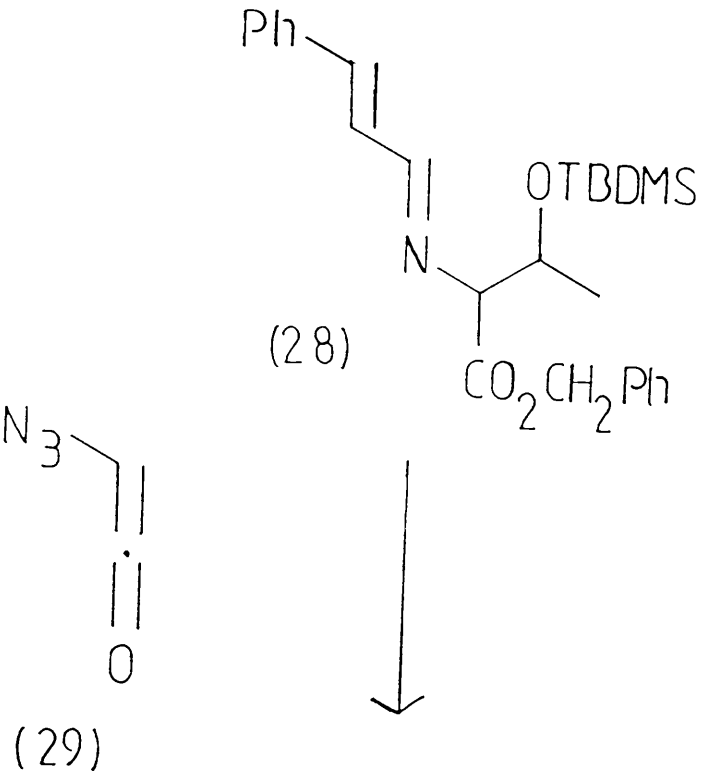
Clearly, if some control is to be exerted on the absolute stereochemistries at positions 3 and 4 in the β-lactam ring, a chiral auxiliary must be incorporated in one (or more) of R^1, R^2 and R^3.

Indeed, chirality has been incorporated in each of these three possible sites, with varying degrees of success in terms of chiral induction on cycloaddition.

(i) Chirality On R^1

Workers at Merck Sharp and Dohme used[16] homochiral acid chloride (15), derived from (+)-3-hydroxybutyric acid, to generate ketene (16), which was reacted in situ with imine (17). This gave the expected cis-azetidinone (18) in 90% yield, as a 7:1 mixture of diastereoisomers (77% d.e). β-Lactam (18) was converted to (19), a known precursor of carbapenems.

In an attempt to produce optically enriched 3-aminoazetidinones Evans and Sjorgen reacted[17] homochiral ketene (20), obtained from (+)-phenylglycine, with imine



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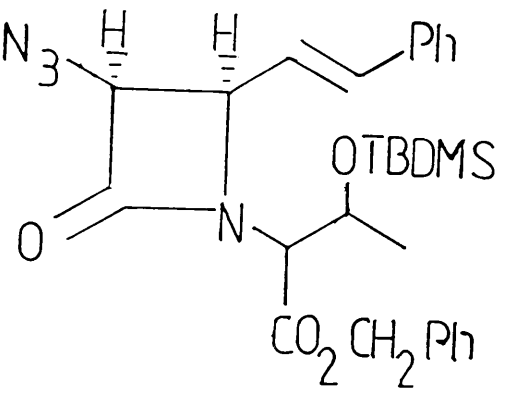

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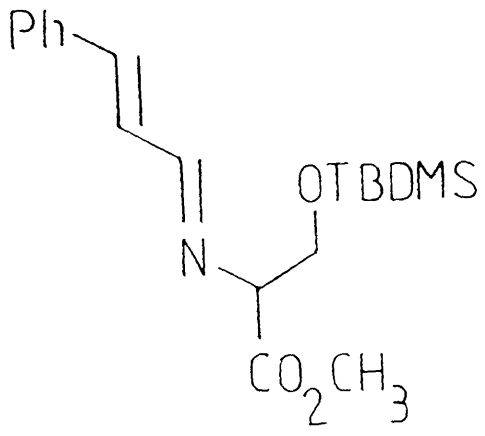

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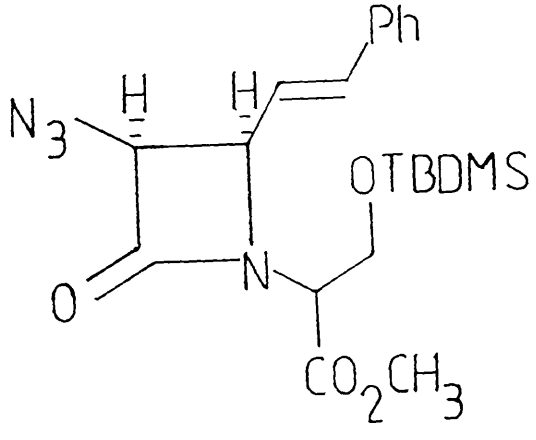

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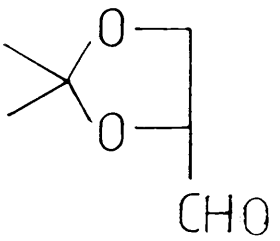

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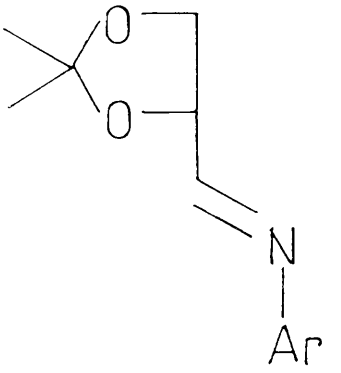

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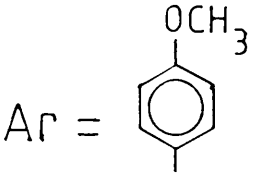

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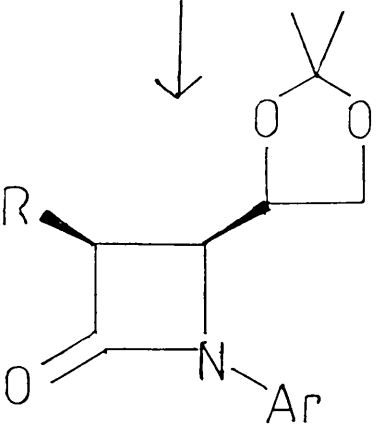


(21). This gave β-lactam (22) in 82% yield and with d.e. of 90%. The chiral amino protection was easily removed and the resulting β-lactam shown to be a precursor of isocephalosporins (23).

(ii) Chirality On R^2

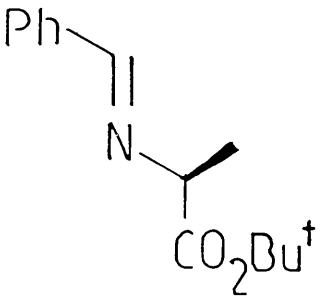
Hubschwerlen[18] and Bose[19] independently showed that readily available homochiral (+)- or (-)- glyceraldehyde acetonides (24) could be converted into chiral imines (25). These reacted in turn in a highly diastereoselective manner with the ketenes derived from azidoacetyl chloride or phthalimido acetyl chloride. The resulting β-lactams, which were essentially optically pure, have been converted into several synthetically useful systems.

(iii) Chirality On R^3

Clearly a large number of homochiral imines are readily available by condensation of aldehydes with suitably protected amino acids. Several such imines have indeed been prepared and reacted with various ketenes to produce azetidinones, with widely varying degrees of success in terms of asymmetric induction.

Just and Liak reacted[20] imine (26), derived from (-)-serine with the ketene from azido acetyl chloride to yield β-lactam (27). Unfortunately imine (26) was found to have epimerised either before or during reaction and lactam (27), although a single diastereoisomer, proved to be racemic.

However, when Tenneson and Belleau reacted[21] (+)-threonine-derived imine (28) with ketene (29) the product (30) had not suffered epimerisation; β-lactam



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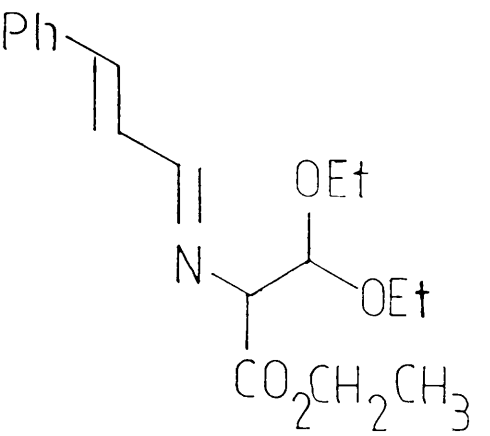

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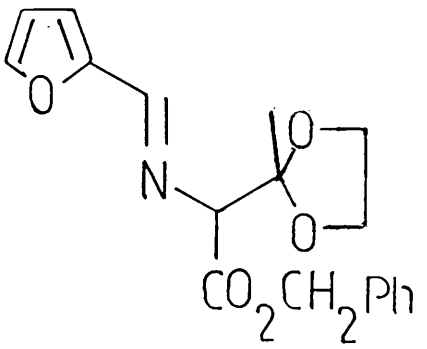

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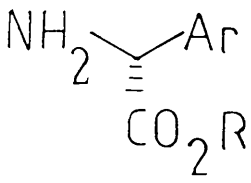

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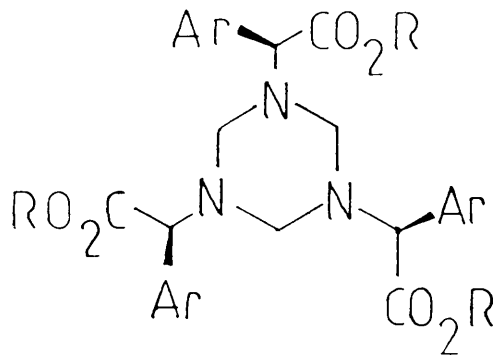

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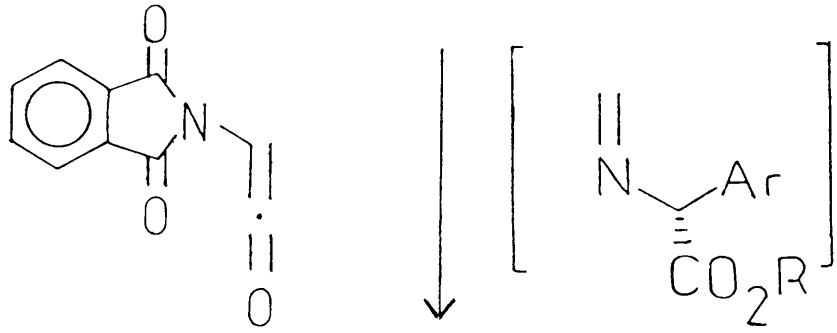

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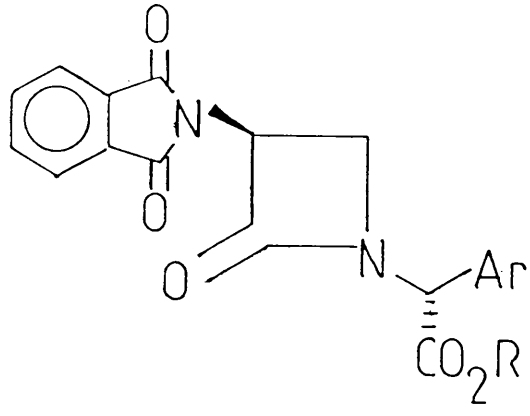

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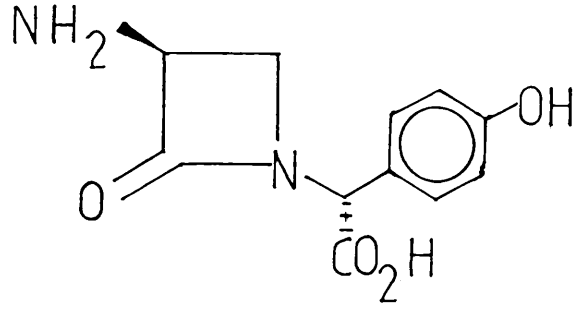


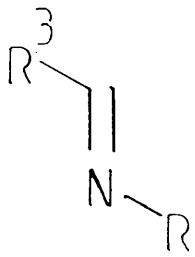
(36)

(30) was produced as a 9:1 (80% d.e) mixture of homochiral diastereoisomers; it can act as a precursor of O-2-isocephems.

In a variation on this approach workers at the Fujisawa Pharmaceutical company treated[22] arylglycines (31) with formaldehyde to produce homochiral trimer (32). This trimer acts as a source of unstable methylidene imines (33) when treated with boron trifluoride etherate. When generated in the presence of ketene (34), imines (33) yielded the 4-unsubstituted azetidinones (35) as 3:1 to 10:1 mixtures of diastereoisomers and in 39-87% yield, depending on the reaction conditions and on the arylglycine used.

Clearly this process has considerable value as a source of optically enriched 4-unsubstituted β-lactams, potential precursors of a number of biologically important monocyclic β-lactams. Indeed, lactam (35) has been shown to be a viable synthetic precursor of the nocardicins. The basic nocardicin nucleus, 3-amino-nocardicinic acid (36), has been synthesised using this route, as shown.

This amino acid based approach is, however, not of generally applicability in asymmetric β-lactam synthesis. A large number of amino acid derived imines, including (37)-(39), have been reacted[23] with ketenes such as (29) to produce the expected cis-β-lactams, but unfortunately the reactions have proceeded with little or no diastereoselectivity.



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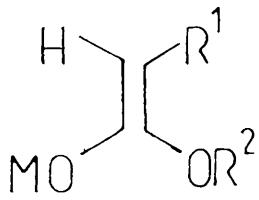

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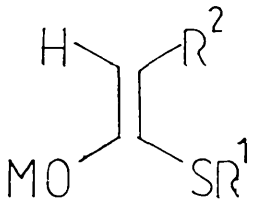

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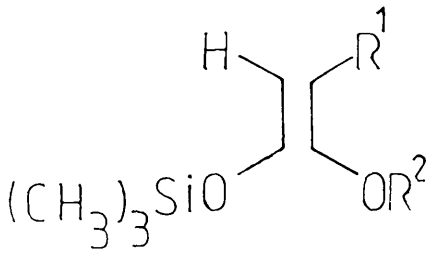

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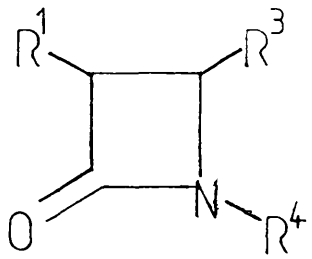

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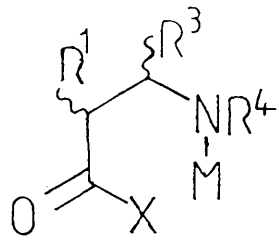

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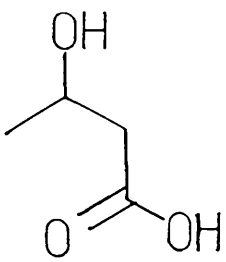


(46)

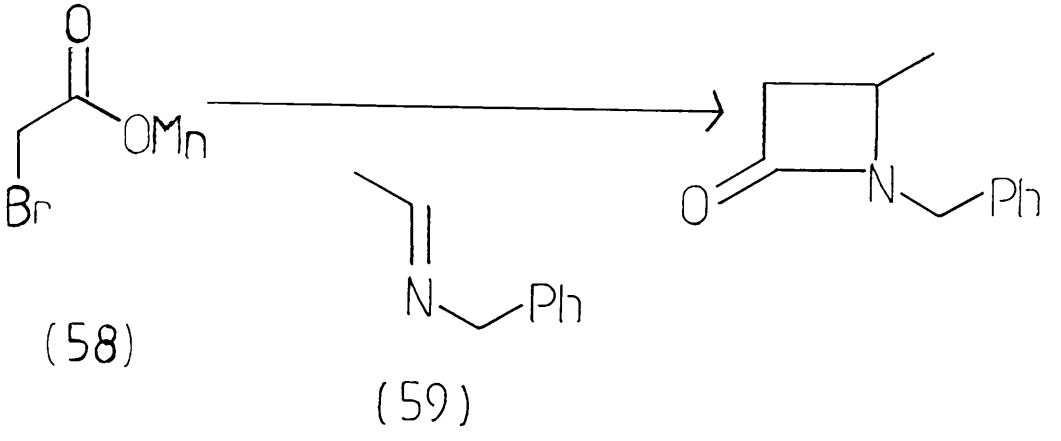
Ester Enolate - Imine Condensation

Imines (40) will undergo condensation with the enolates of alkyl esters (41), thioesters (42) or silyl ketene acetals (43) (the last in the presence of Lewis acids) to give β-lactams (44), *via* metalloamine β-amino esters (45).

Clearly, if any asymmetric induction is to be achieved in the formation of azetidinones (44) then a suitable chiral auxiliary must be incorporated into one of the four R groups, R^1 - R^4. Of these four possible approaches the use of chirality on R^1, R^2 and R^4 has been widely studied, generally with a fair degree of success. Imines with chirality on R^3, however, have attracted comparatively little attention. This is almost certainly because any synthetically useful imine with chirality on R^3 would be enolisable. Under the basic conditions of the condensation reaction the imine may therefore suffer proton abstraction. This would introduce the possibility of side reactions (for example self condensation of the imine) and of imine racemisation (if the chiral centre present was at the α-position).

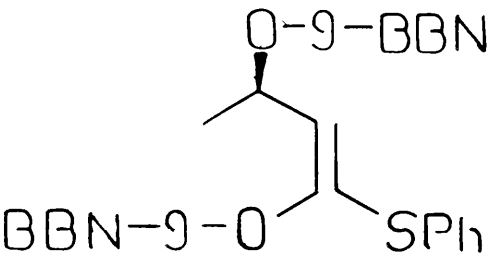
(i) Chirality On R^1

Several groups have successfully condensed enolates and thioenolates derived from readily available (+)- or (-)-3-hydroxybutyric acid (46) with various imines. The resulting 3-(hydroxyethyl)-substituted azetidinones were generally produced with very high

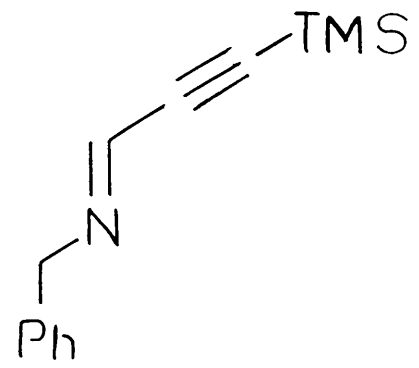


(58)

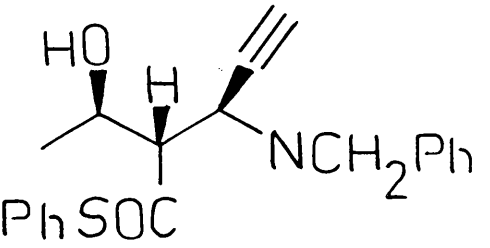
(59)


O-9-BBN
BBN-9-O
SPh

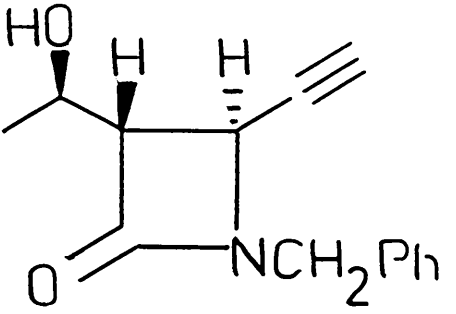
(53)


TMS
N
Ph

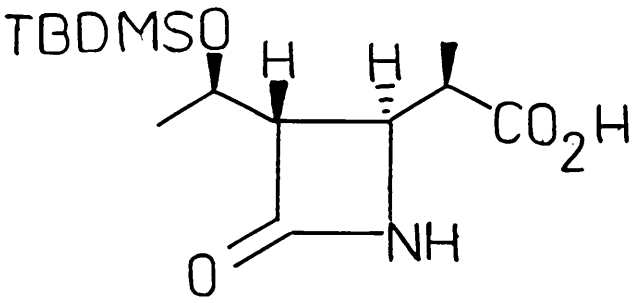
(54)


HO
H
NCH2Ph
PhSOC

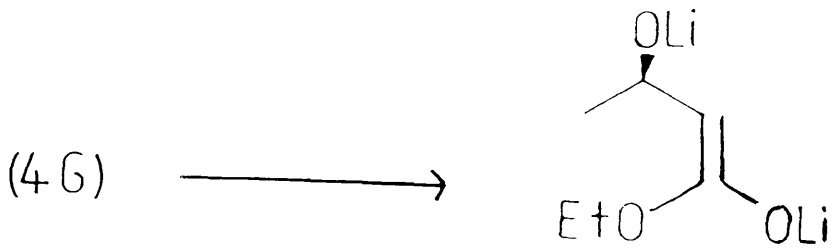
(55)

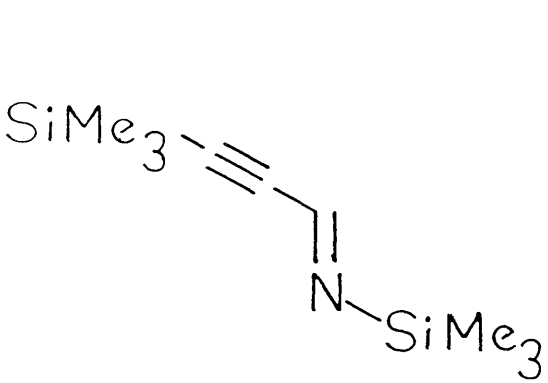

HO
H
H
O
NCH2Ph

(56)


TBDMSO
H
H
CO2H
O
NH

(57)





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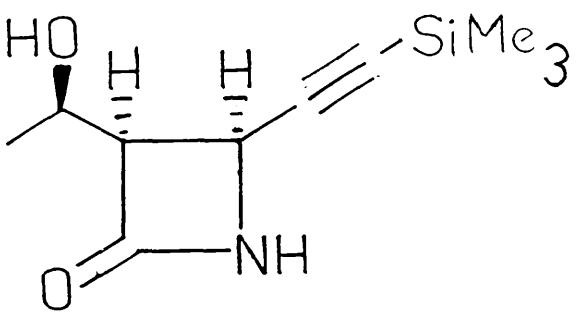

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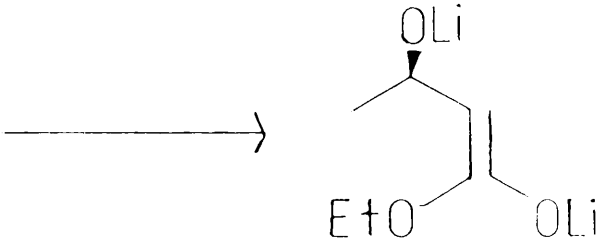
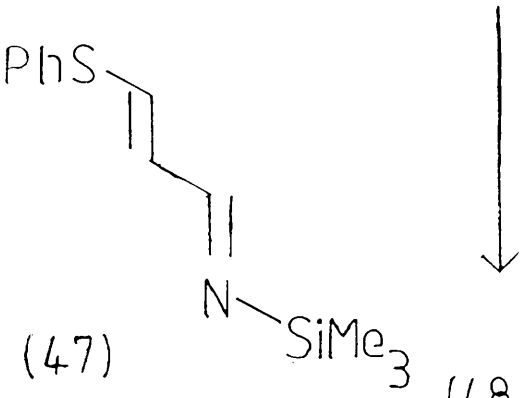
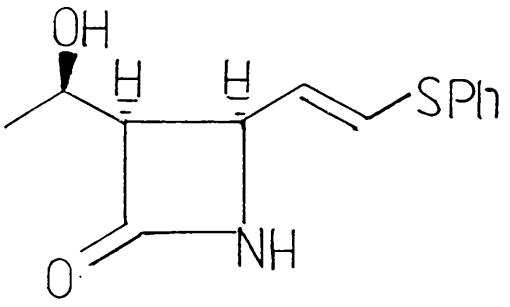
(46) 



(47)

(48) - (50)



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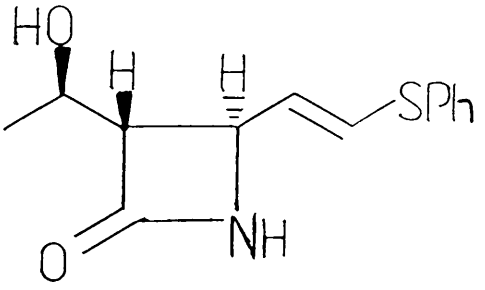

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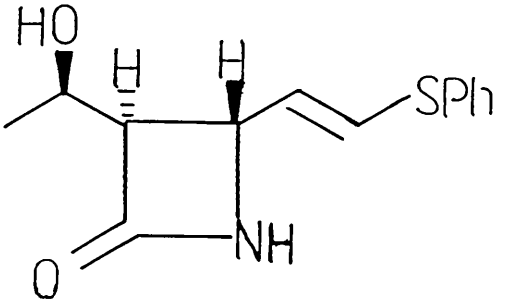


(49)

diastereoselectivity.

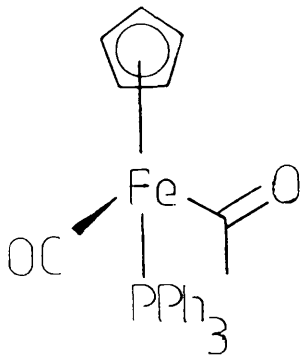
Hart and co-workers reacted[24] the lithium ester enolate of ethyl (-)-3-hydroxybutyrate with N-silylimine (47) to yield the three β-lactams (48), (49) and (50) in a ratio of 66:18:3.

Similarly, Chiba and Nakai combined[25] the lithium ester enolate derived from (46) with N-silylimine (51) to give β-lactam (52) in 79 % d.e. Lactam (52) was shown to be a precursor of thienamycin (6). Other groups have used this approach to synthesise various biologically active carbapenem systems such as PS-5[26] and epithienamycin[27] with high degrees of asymmetric induction.

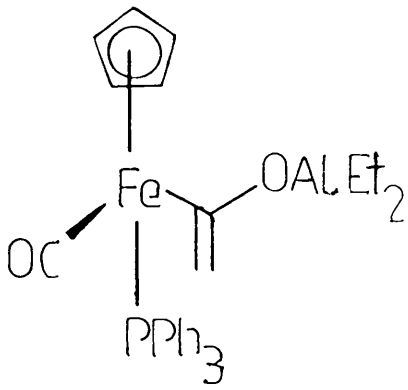
In a related approach homochiral vinyloxyborane (53), prepared from (-)-3-hydroxybutyric acid, was condensed[28] with imine (54) to give β-aminothiol (55) in 55% chemical yield and 90% d.e. Hydrolysis and cyclisation gave β-lactam (56), which was readily converted into the known 1-β-methylcarbapenem precursor (57). The same group showed that this approach could be extended more generally to asymmetric β-lactam synthesis[29] by condensing (53) with a wide range of imines to produce a number of potentially useful azetidinones with excellent asymmetric induction.

(ii) Chirality On R^2

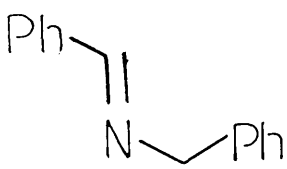
The first attempted asymmetric synthesis of this type involved the Reformatsky reaction of homochiral menthyl α-bromoester (58) with imines such as (59).[30]


Fe
O
OC
PPh3

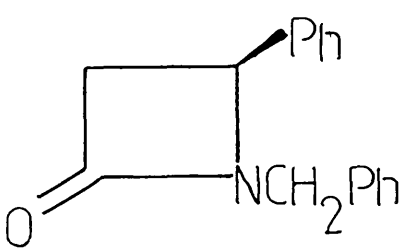
(71)


Fe
OAlEt2
OC
PPh3

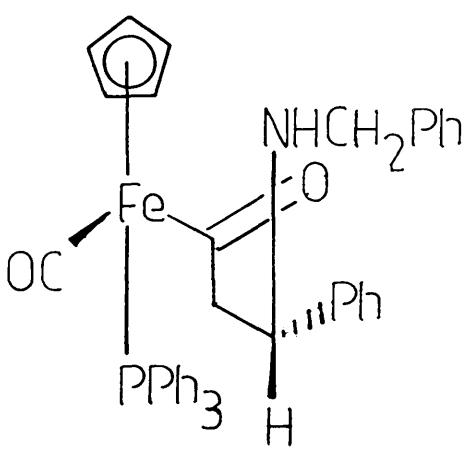
(72)


Ph
N
Ph

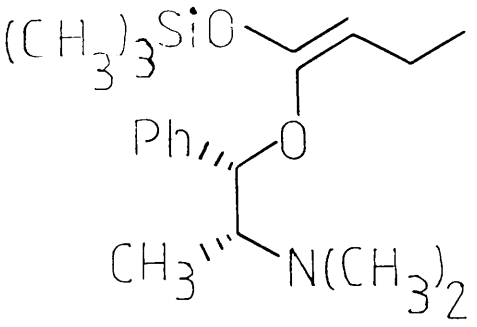
(73)


Ph
NCH2Ph
O

(75)


NHCH2Ph
O
Fe
OC
Ph
PPh3
H

(74)



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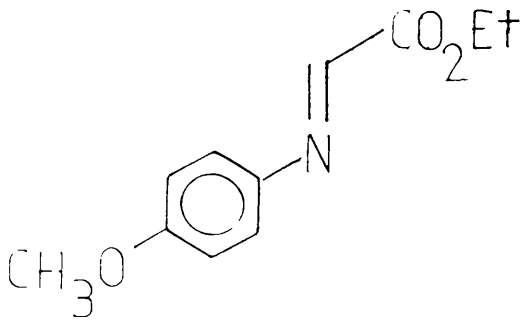

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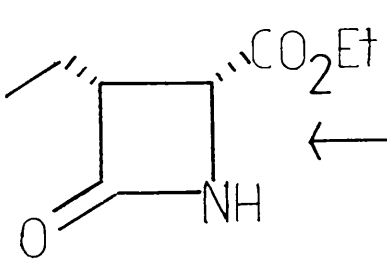

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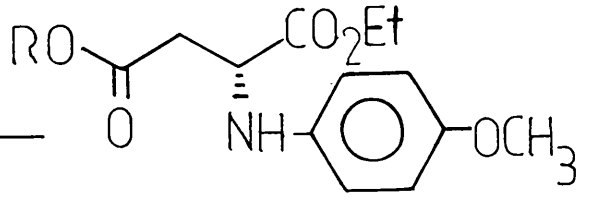

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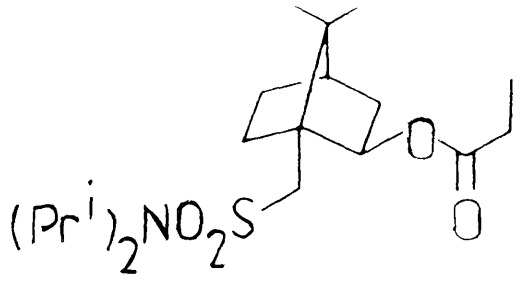

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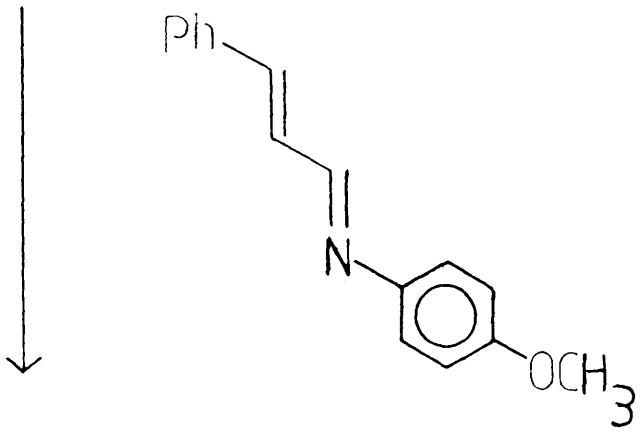

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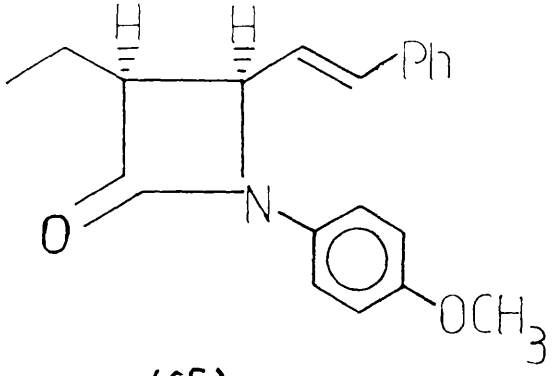

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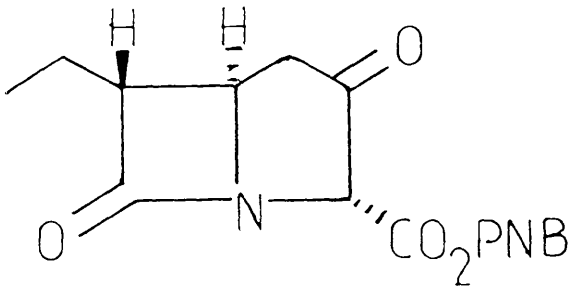

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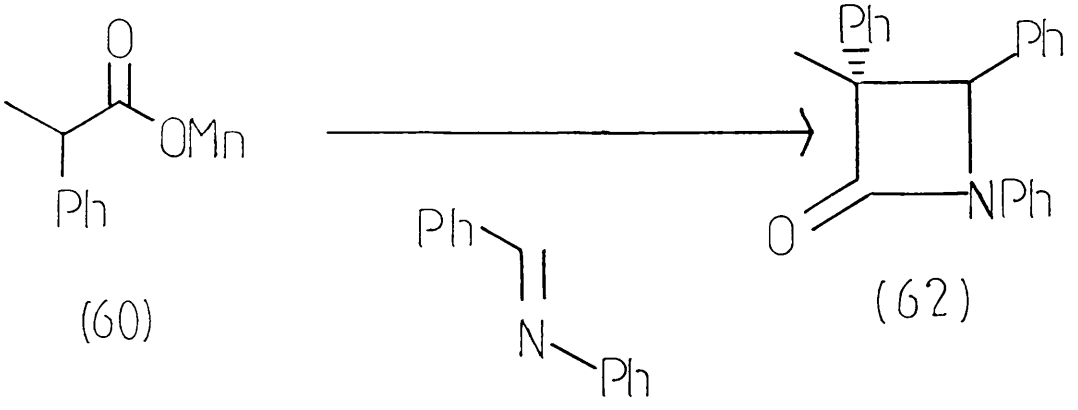


(60)

(61)

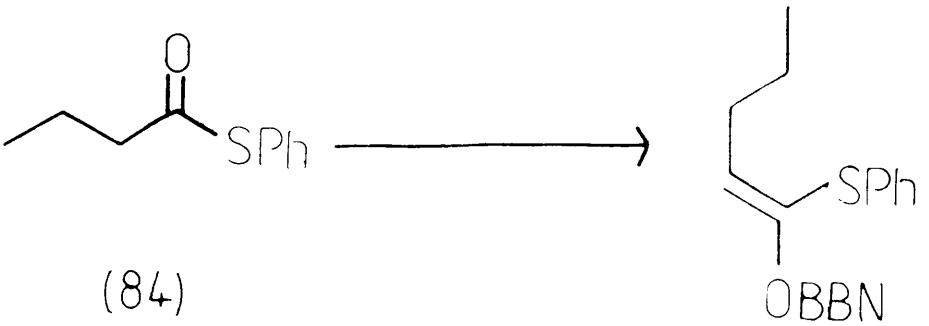
(62)

These reactions were found to proceed with modest diastereoselectivities, the resulting β-lactams being produced in 2-28% d.e. Later Gluchowski and co-workers showed[31] that the lithium enolate of ester (60), derived from (-)-menthol and 2-phenylpropionic acid reacted with imine (61) to give β-lactam (62) in 60% e.e.

A variation on this approach was used[32] by Hart et al in an asymmetric synthesis of PS-5 (9). The (+)-camphor derived ester (63) was converted into its lithium ester enolate and reacted with imine (64). This gave β-lactam (65) in 79% chemical yield and 91% e.e. Lactam (65) was then converted into the known PS-5 precursor (66).

Gennari et al showed[33] that homochiral silylketene acetal (67), readily prepared from N-methylephedrine, reacted with imine (68), in the presence of titanium tetrachloride, to give β-aminoester (69) in 70% overall yield and 75% d.e. Hydrogenolysis of the benzylic chiral auxiliary, followed by ring closure gave the PS-5 precursor (70), as shown.

In a synthetically related approach it has been shown that homochiral iron acyl compounds, with the chirality located on the iron, will form enolates capable of reacting in a highly diastereoselective manner with achiral imines. Oxidative cleavage of the resulting β-amino iron acyl compounds furnishes optically enriched β-lactams directly. For example, Liebeskind et al showed[34] that iron acyl (71), available in homochiral form could be converted into aluminium



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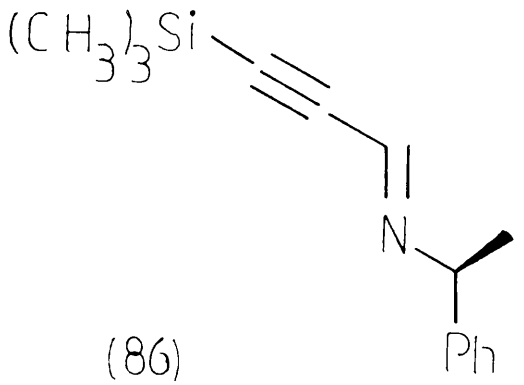

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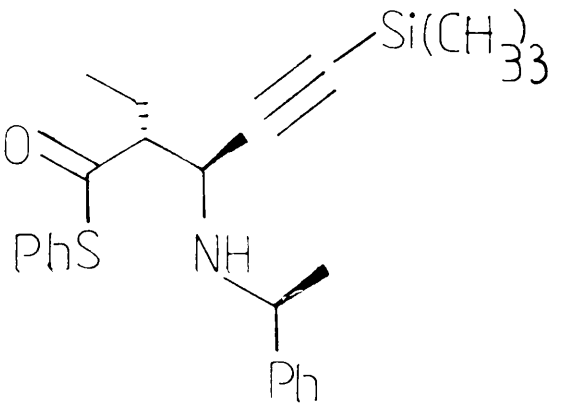

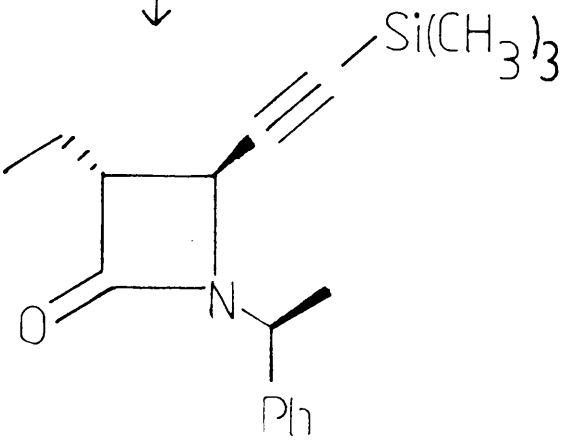

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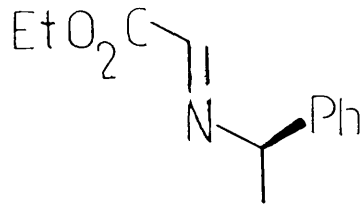

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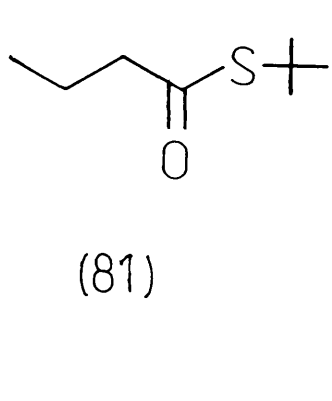

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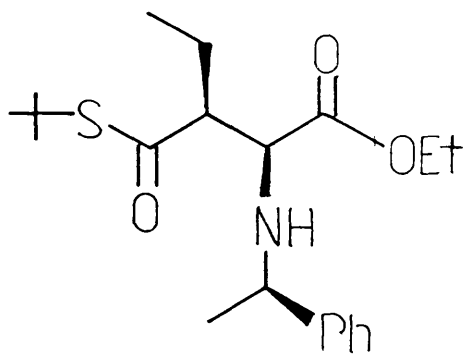

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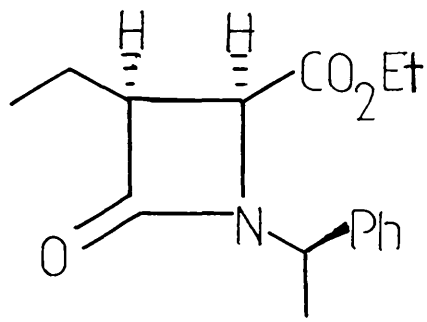

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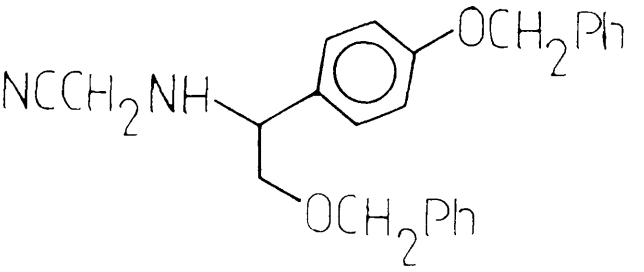

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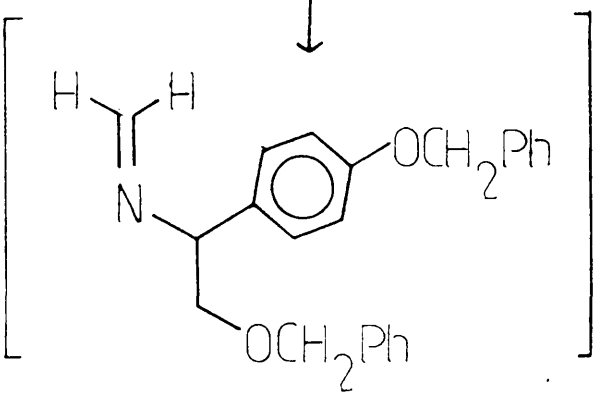

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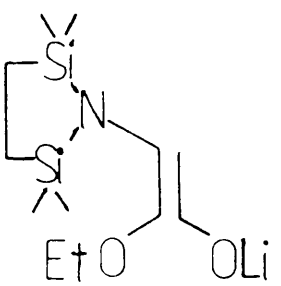

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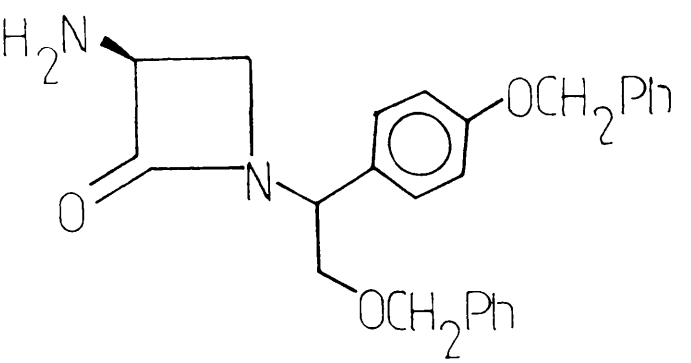


(79)

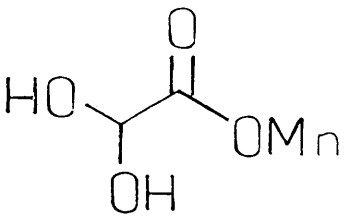
enolate (72), which reacted in turn with a range of imines with useful asymmetric induction. Thus, reaction of imine (73) with enolate (72) gave (74) which was oxidatively cleaved to β-lactam (75), in 75% overall yield and with 92% e.e.

(iii) Chirality On R^4

Overman and Osawa generated[35] homochiral methylidene imine (76) by in situ base treatment of the secondary N-(cyanomethyl)amine (77), derived from (-)-4-hydroxyphenylglycine. Imine (76) reacted with lithium ester enolate (78) to give the 3-amino β-lactam (79) in 72% chemical yield, as an 11:1 mixture of diastereoisomers (92% d.e). This route has obvious potential for the synthesis of novel 3-amino 4-unsubstituted azetidinones such as the nocardicins.

Chiral imine (80), prepared[36] by Mukaiyana et al from (+)-α-methylbenzylamine, was condensed with the tin(II) enolate of thioester (81). The resulting β-aminothioester (82) cyclised to give cis-azetidinone (83) with 70% d.e., as determined by chiral stationary phase chromatography.

In a complementary process, Shibasaki and co-workers transformed[37] thioester (84) into boron enolate (85). Reaction of (85) with (-)-α-methylbenzylamine derived imine (86) gave the trans-β-lactam (87) in 68% yield and with 95% d.e. Compounds (87) and (83) have both been shown to act as precursors of PS-5.



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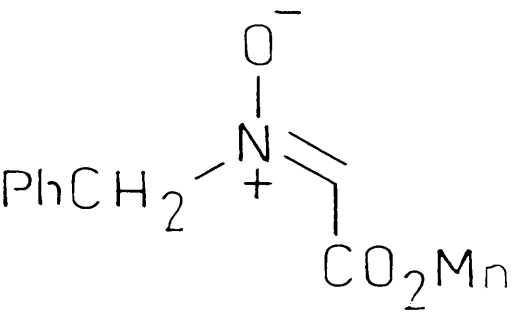

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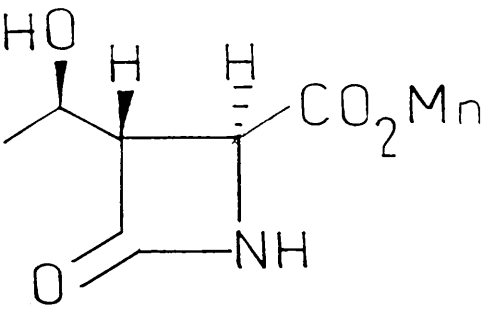

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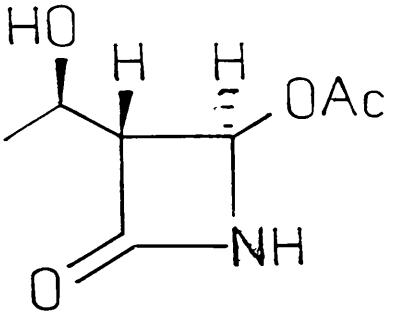

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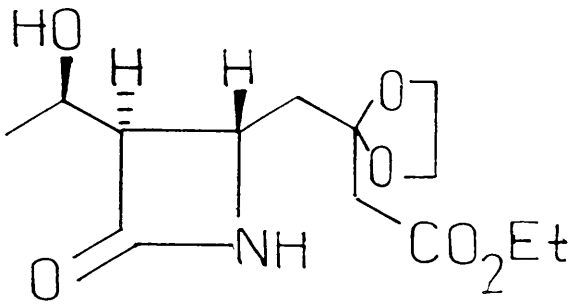

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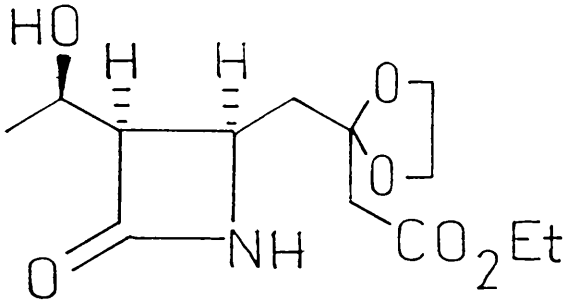

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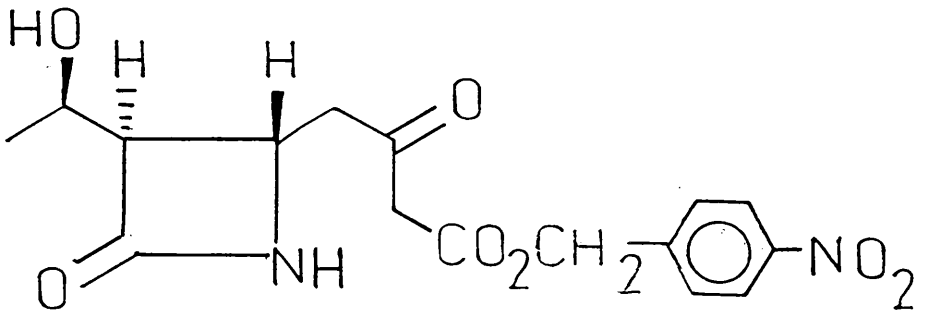

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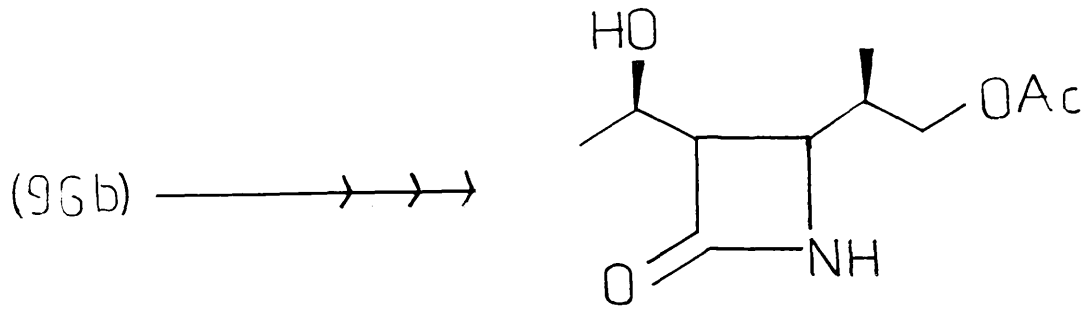

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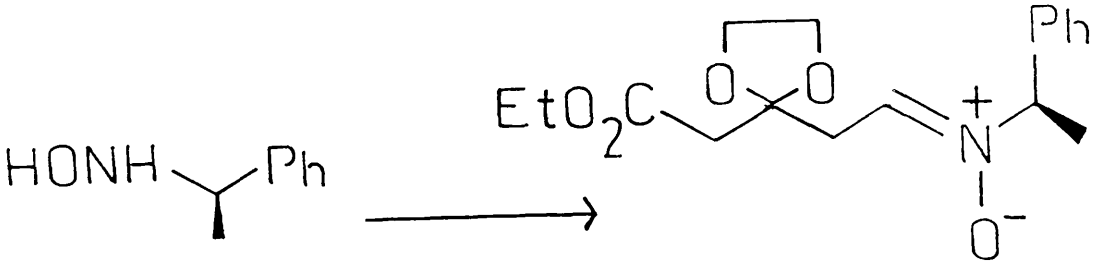

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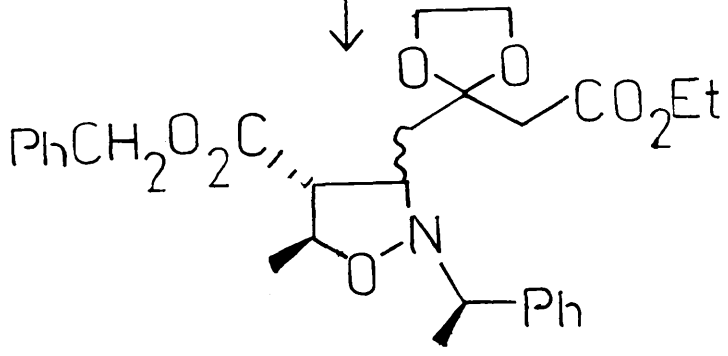

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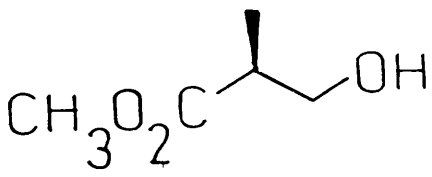

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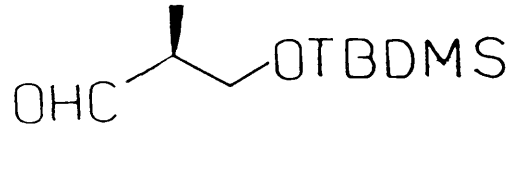

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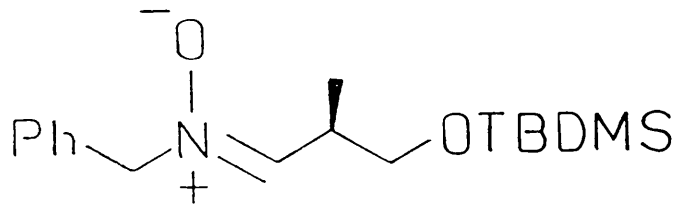

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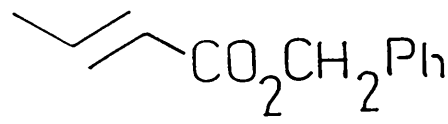

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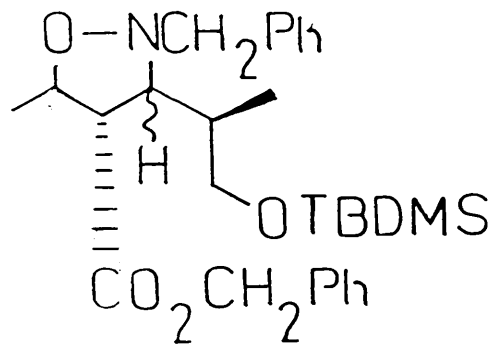
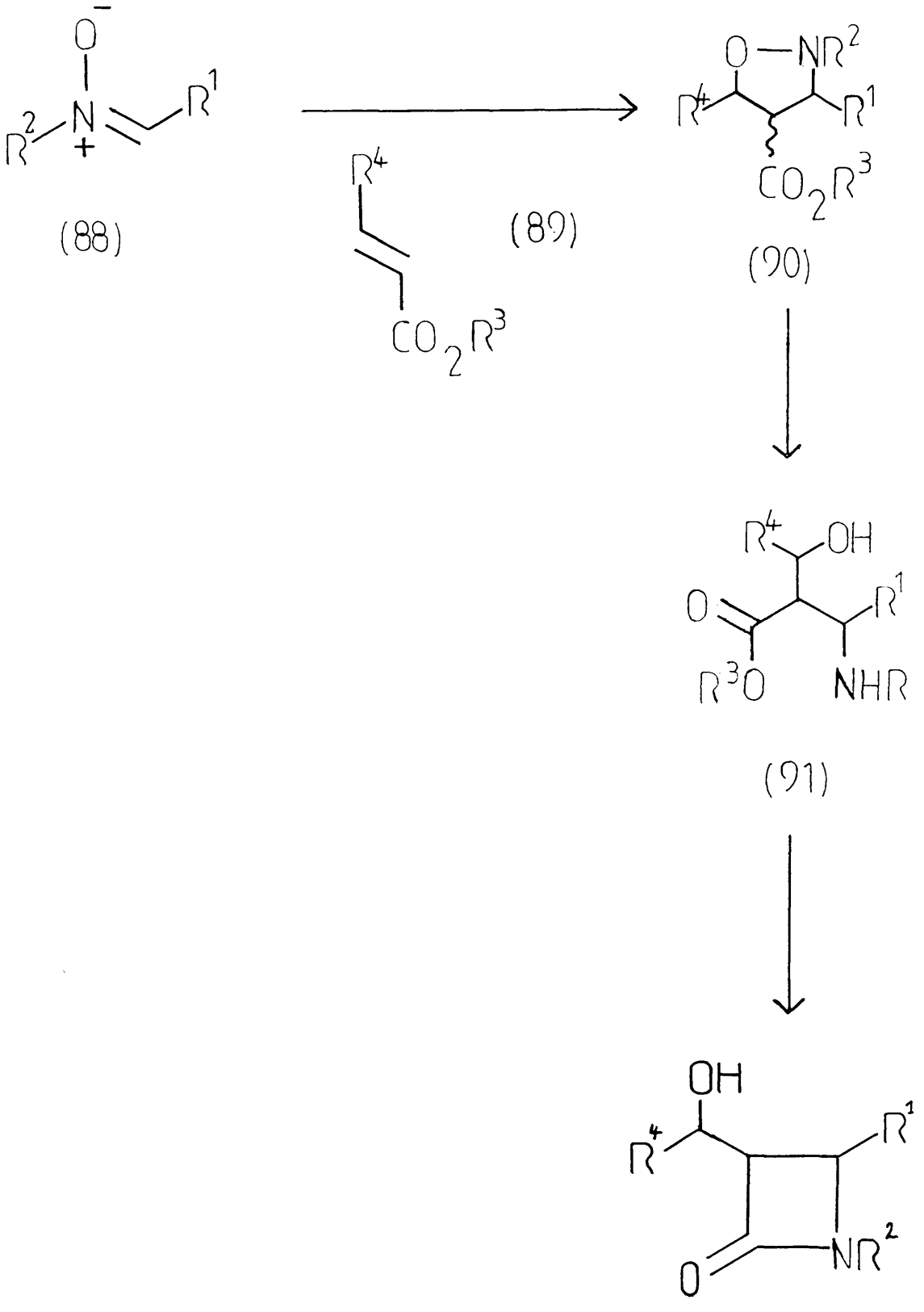


(96a): αH

(96b): βH


(88)
(89)
(90)
(91)

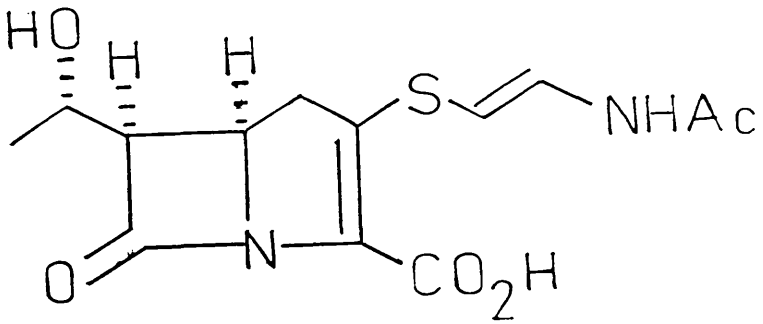
[3+2]-Dipolar Cycloadditons

Nitrones (88) react with αβ-unsaturated esters (89) to give isoxazolidines (90). These can be reduced to β-amino esters (91) which yield β-lactams on ring closure. Several asymmetric β-lactam syntheses based on this approach have been carried out.

Fukumoto and co-workers employed[38] chiral aldehyde (92), readily available from ester (93), to prepare homochiral nitrone (94). This reacted with benzyl crotonate (95) to give isoxazolidines (96a) and (96b) as the major products, in 23% combined yield from homochiral ester (93). Catalytic hydrogenation of (96b), followed by ring closure, gave β-lactam (97) in essentially optically pure form. Lactam (97) was shown to be a precursor of 1-β-methylcarbapenem (10).

Kametani used (R)-N-(methylbenzyl)hydroxylamine (98) to prepare[39] chiral nitrone (99). This nitrone reacted with benzyl crotonate (95) to give a mixture of isoxazolidines (100) which was converted into a mixture of cis and trans-β-lactams (101) and (102). Separation allowed the isolation of (102) in 24.5% overall chemical yield and in d.e. greater than 98%. Lactam (102) was converted into the thienamycin precursor (103), as shown.

Kametani and co-workers have additionally shown[40] that chiral nitrone (104), prepared from (-)-menthyl glyoxylate hydrate (105), will react with benzyl



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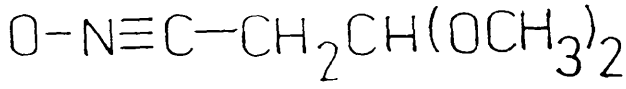

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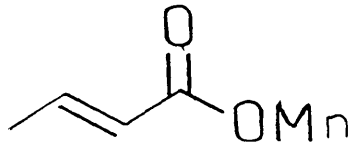

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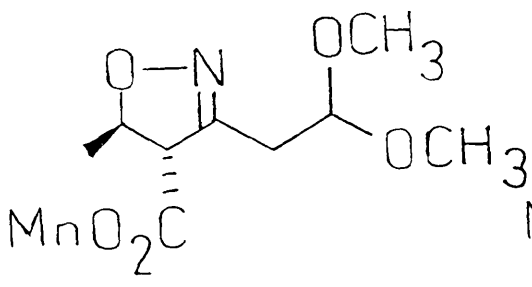

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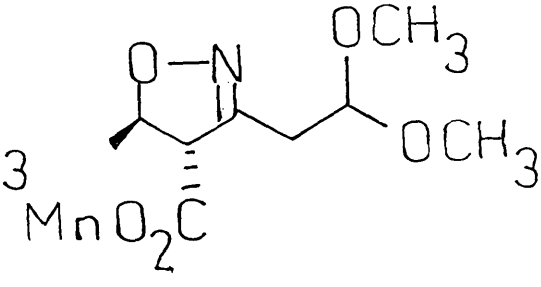

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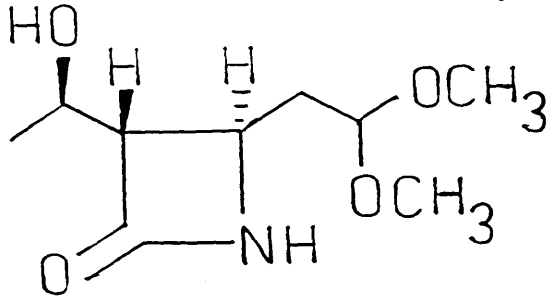

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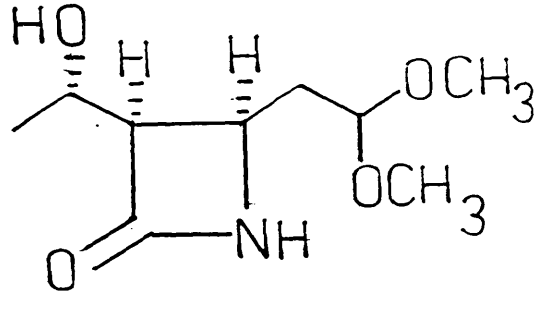

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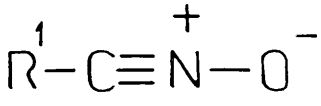

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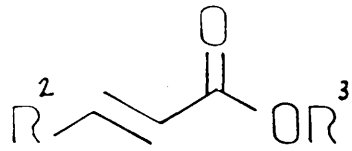

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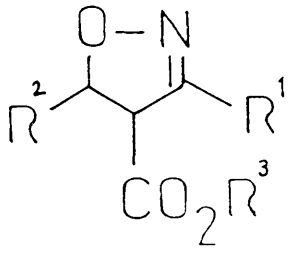

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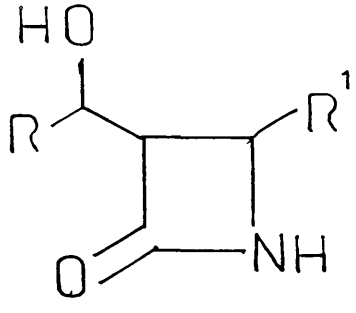
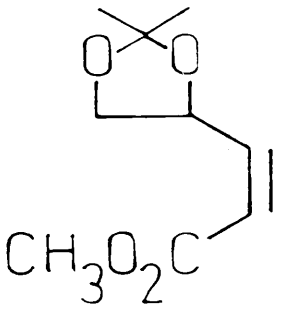


(111)

crotonate to furnish, after hydrogenation and ring closure, β-lactam (106) in essentially optically pure form, but in an overall yield of only 12%.

Lactam (106) was converted into the 4-acetoxy-azetidinone (107), a known precursor of penems and carbapenems.

In a closely related approach, nitrile oxides (108) react with αβ-unsaturated esters (109) to give isoxazolines (110). Once more catalytic hydrogenation followed by ring closure can furnish β-lactams (111). For example, Kametani reacted[41] nitrile oxide (112) with homochiral (-)-menthyl crotonate (113). This gave two diastereoisomeric isoxazolines (114) and (115). These were not separated but were converted into a mixture of the corresponding β-lactams (116) and (117). Lactam (116) was found to be produced with only 20% e.e.; isomer (117), however was found to possess 85% e.e. Lactam (117) has appropriate absolute configuration and functionality for conversion into epithienamycin A (118).



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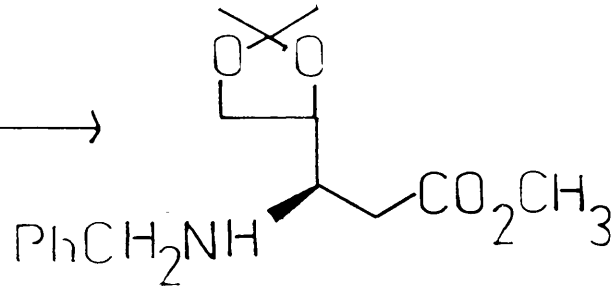

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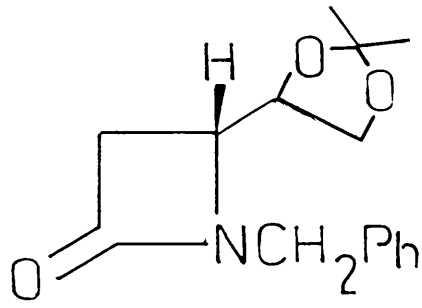

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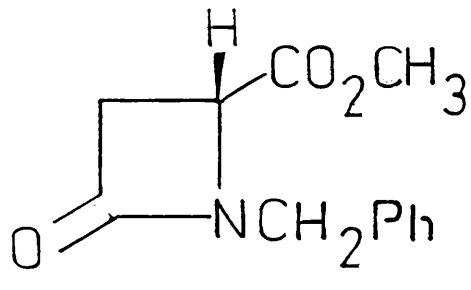

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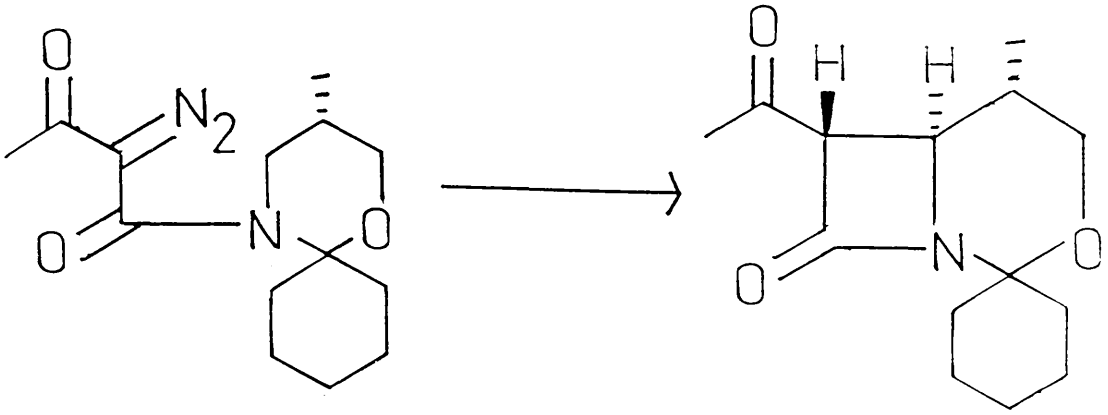

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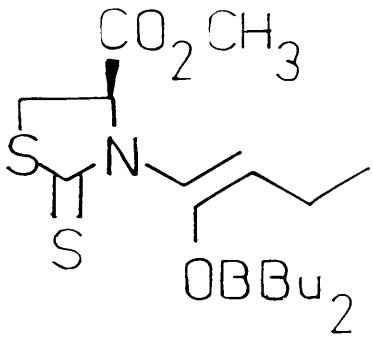

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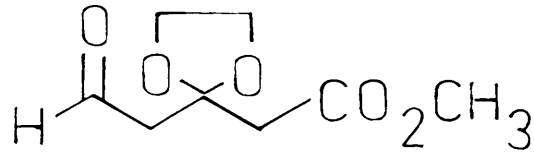

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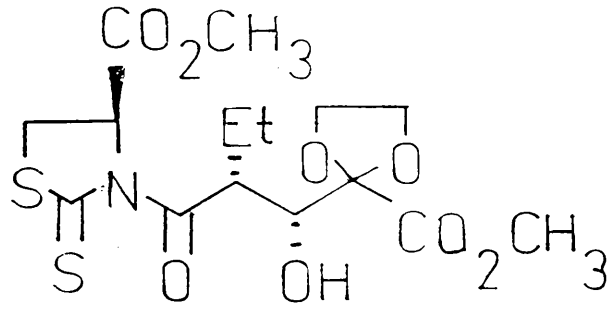

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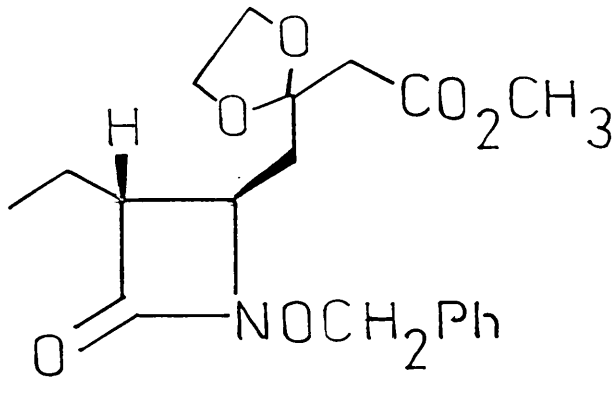

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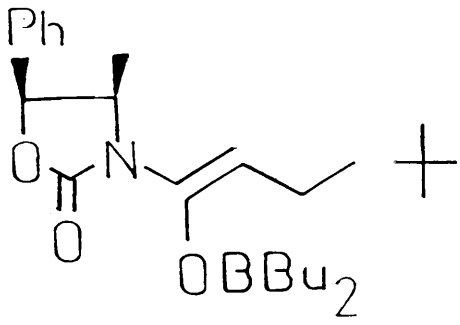
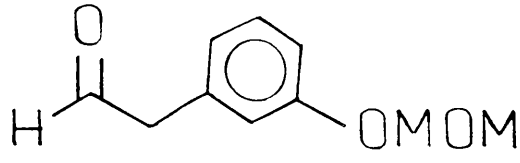


(119)



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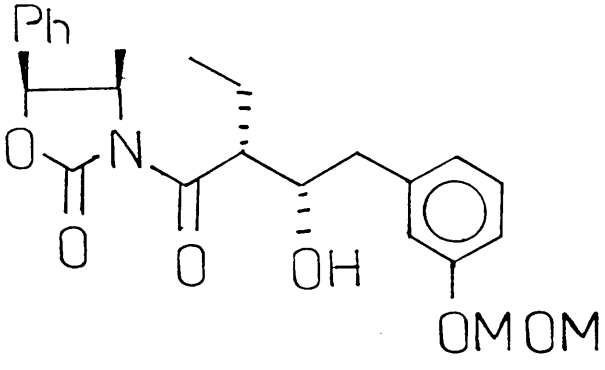


(121)

MOM = $-CH_2OCH_3$

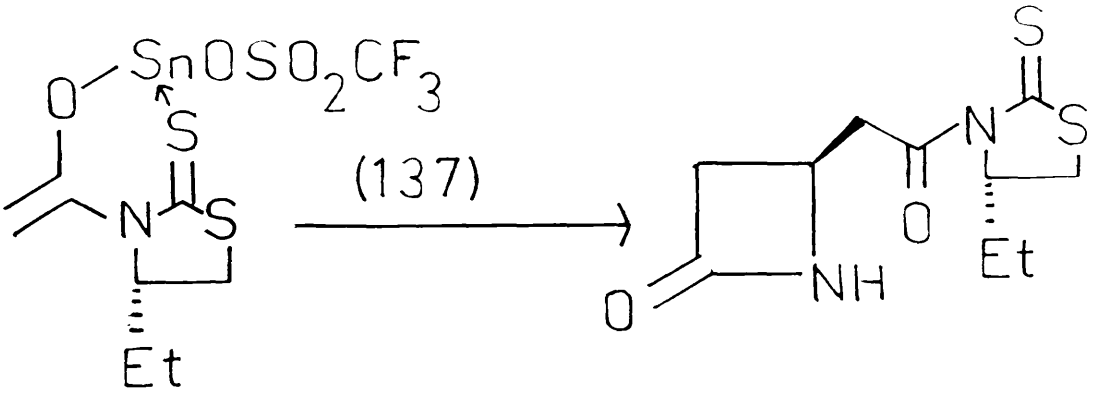
Miscellaneous

Various other approaches involving asymmetric induction have been used to produce optically enriched β-lactams.

Evans and Sjorgen reacted[42] homochiral boron enolate (119), derived from (+)-norephedrine, with aldehyde (120) in an asymmetric aldol reaction, to give β-hydroxyamide (121), apparently as a single diastereoisomer. Amide (121) was converted into enantiomerically pure PS-5 (9). The (-)-cysteine-derived boron enolate (122) underwent[43] a similar reaction with aldehyde (123) to give β-hydroxyamide (124), which in turn furnished the PS-5 precursor (125) with at least 93% e.e.

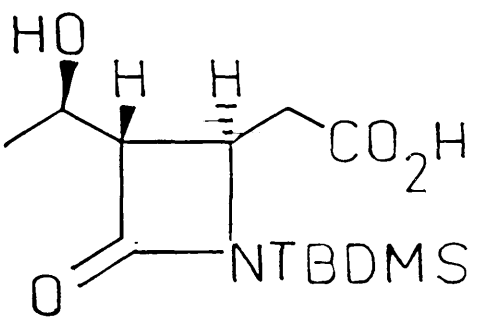
Brown and Southgate showed[44] that homochiral diazoalkane (126) (prepared from (-)-3-amino-2-methyl-propan-1-ol) underwent a rhodium(II)- catalysed insertion reaction to give trans β-lactam (127) as a 10:1 mixture of diastereoisomers. Lactam (127) can act as a versatile precursor of carbapenems.

Homochiral (Z)-αβ-unsaturated ester (128), readily available from (+)-glyceraldehyde acetonide, was shown[45] by Yamada et al to undergo a highly diastereoselective Michael addition reaction with benzylamine to yield β-amino ester (129) with 87.5% d.e. Ring closure of (129) yielded azetidinone (130) with high optical purity. The known thienamycin precursor (131) was

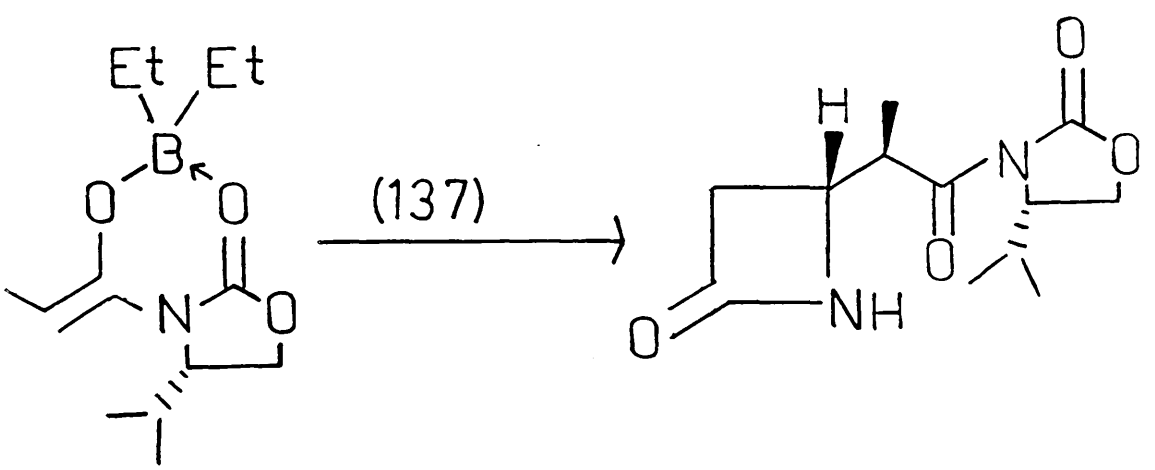


(140)

(141)

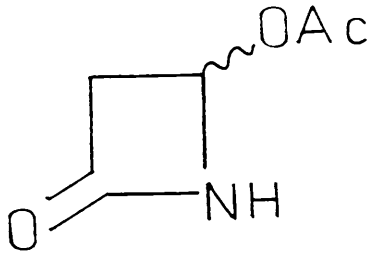


(142)



(143)

(144)



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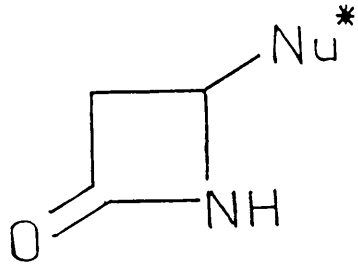

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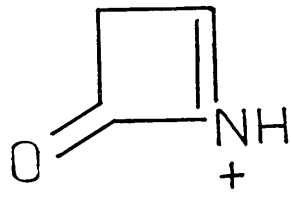
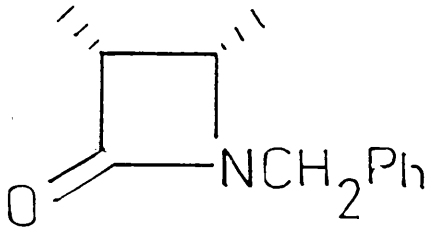


(139)

(133) ⟶



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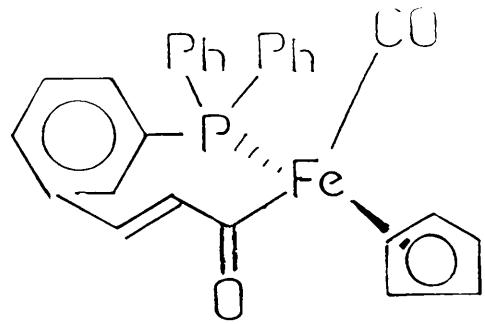

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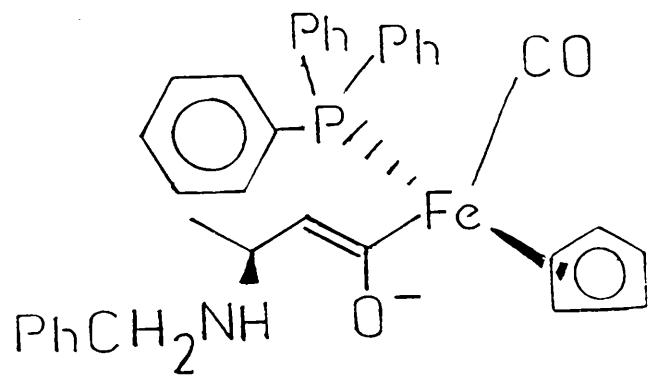

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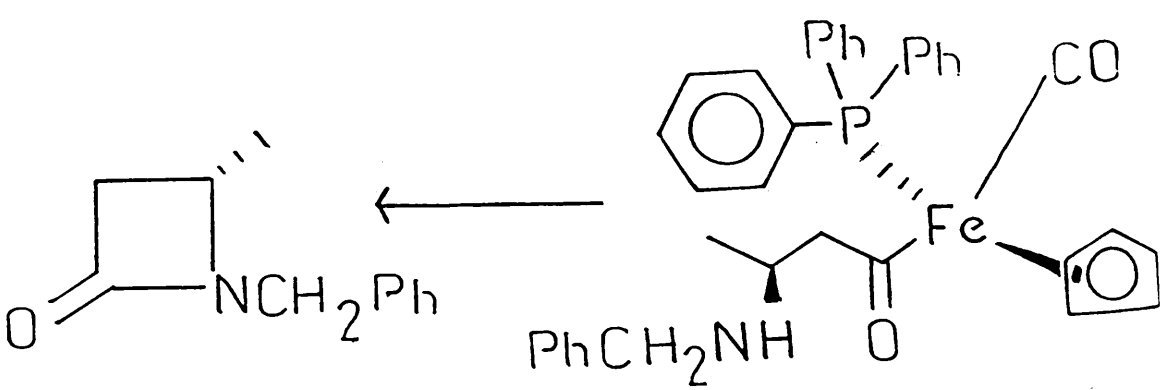


(135)

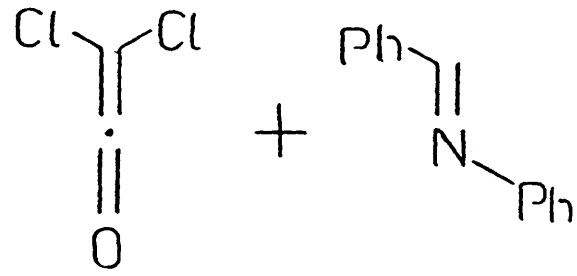
(134)

readily prepared from (130).

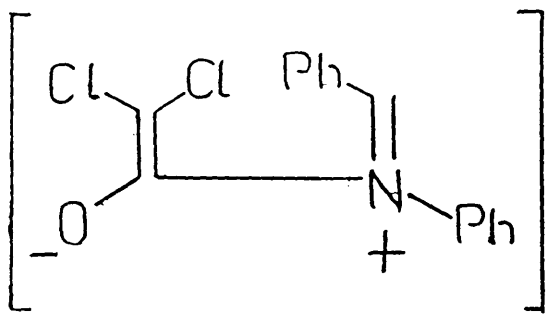
In a related approach, Davies showed[46] that homochiral (E)-crotonyl iron complex (132) reacted in a 1,4-fashion with lithium benzylamide to give enolate (133). This underwent protonation to provide the β-amino acyl complex (134) as a single diastereoisomer. Decomplexation gave β-lactam (135) with e.e. greater than 99%. Alternatively enolate (133) can be methylated and then decomplexed to yield β-lactam (136) with e.e. again greater than 99%.

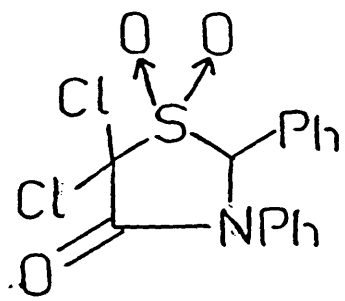
One other approach to azetidinones of high optical purity is well worthy of mention. Racemic 4-acetoxy azetidinone (137) has been reacted successfully with several homochiral nucleophiles to yield β-lactams (138) with very high diastereoselectivities. Such reactions have been postulated[47] to proceed via the prochiral planar intermediate (139).

For example, Fujita et al treated[48] the homochiral tin(II) enolate (140) with racemic 4-acetoxy azetidinone (137). This yielded β-lactam (141) in 82% yield and with 90% d.e. Further transformations provided the useful carbapenem precursor (142). Workers at Merck Sharp and Dohme have similarly shown[49] that the related valine-derived boron enolate (143) reacted with lactam (137), in the presence of zinc bromide, to give the analogous β-lactam (144) in 95% yield and with greater than 98% d.e.

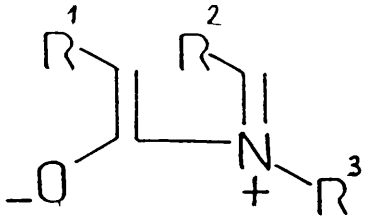


(151) (152)

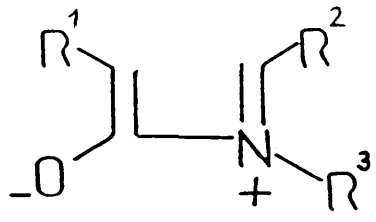




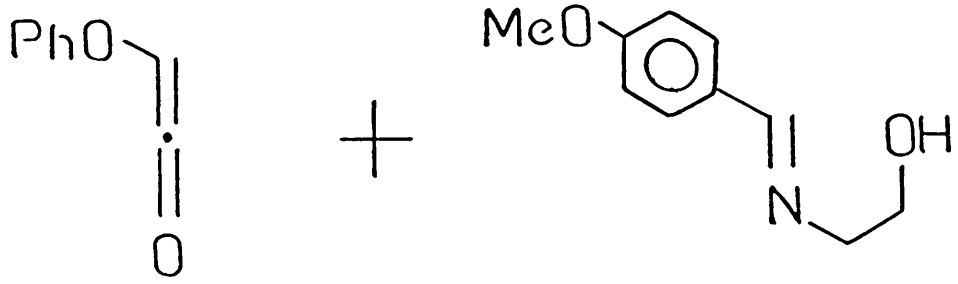
(153)



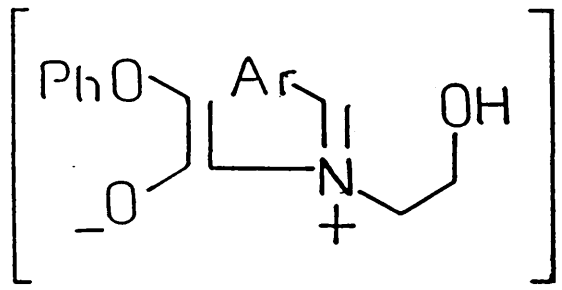
(145)



(146)



(147) (148)



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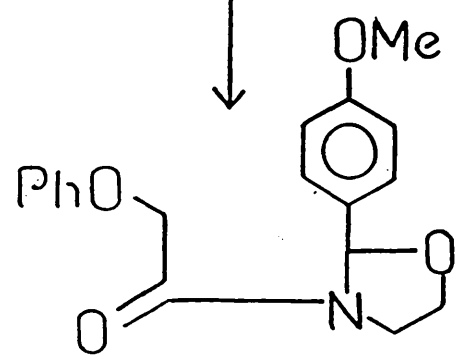
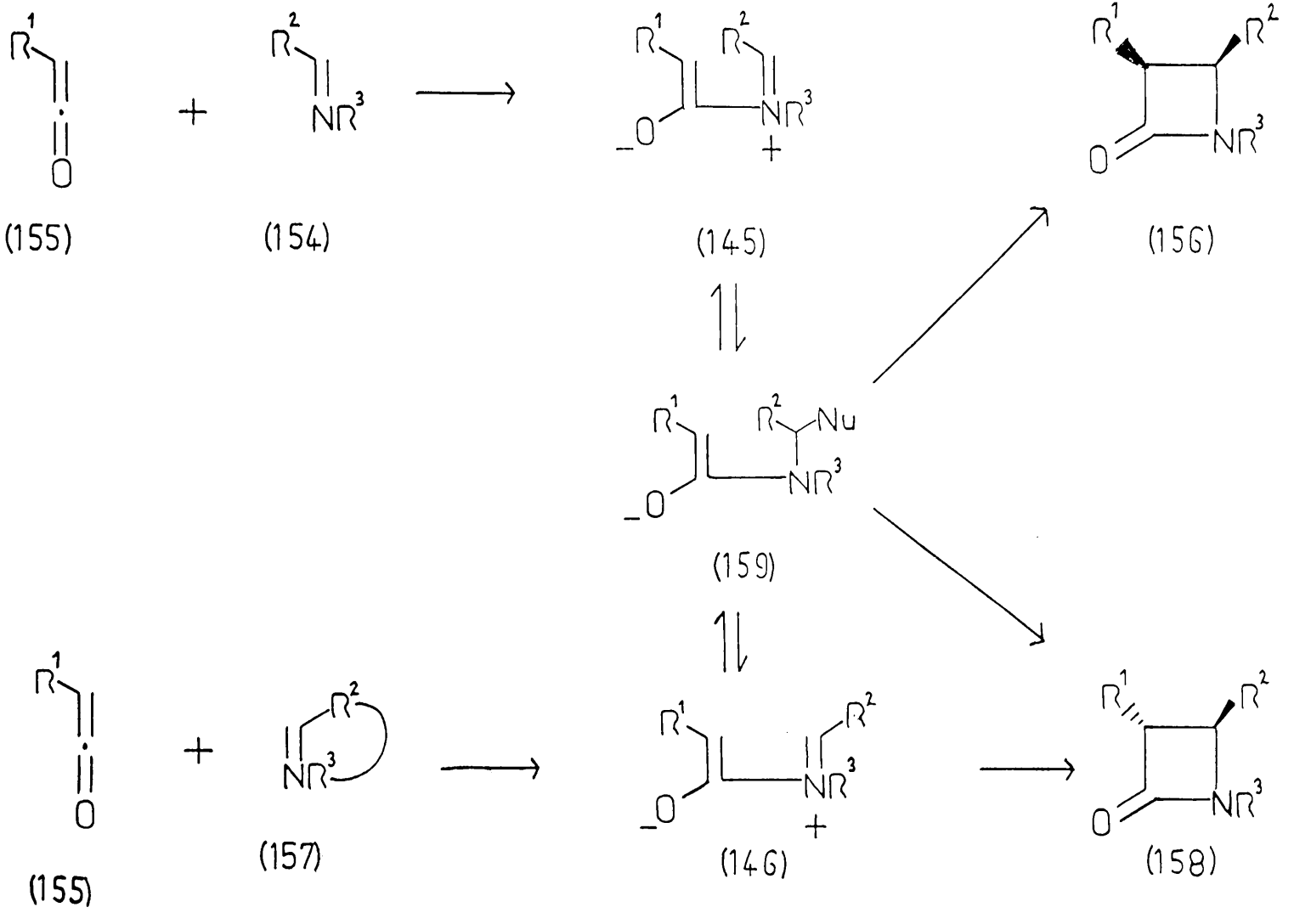


(149)

Discussion

The two approaches which have provided the most general and direct routes to a wide range of biologically active β-lactams involve the reaction of imines with either ketenes or lithium ester enolates. Clearly this is the area where asymmetric synthesis has the greatest potential. Accordingly, the research program described herein concentrated on efforts to obtain optically enriched β-lactams using asymmetric syntheses based on these two reactions.

Although the mechanism of the lithium ester enolate/imine condensation is apparently straightforward enough (a chair-like transition state involving lithium complexation has been proposed[24] for the initial bond formation) that of the ketene/imine cycloadditions remains, despite considerable investigation, a point of some contention. It is generally agreed that, with a few exceptions[16] the reaction proceeds *via* a zwitterionic intermediate such as (145) or (146). Indeed, several species of this type have been successfully trapped under the normal conditions of the reaction. For example, when Palomo and co-workers reacted[50] ketene (147), derived from phenoxyacetic acid, with hydroxyimine (148), oxazolidine (149) was isolated in 90% yield. Presumably compound (149) was formed by cyclisation of the proposed intermediate (150). Similarly, workers at Ciba-Geigy showed[51] that reaction of dichloroketene (151) with benzylideneaniline (152) using sulphur dioxide as a solvent, gave 5,5-dichloro-4-oxo-1,3-thiazolidine-1,1-dioxide (153) in 81% yield.

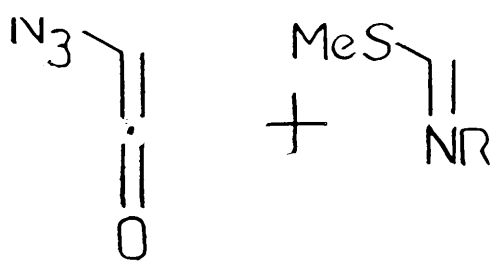

(155)
(154)
(145)
(156)
(159)
(155)
(157)
(146)
(158)

The observed product can be rationalised in terms of sulphur dioxide insertion into a zwitterionic intermediate analogous to (145).

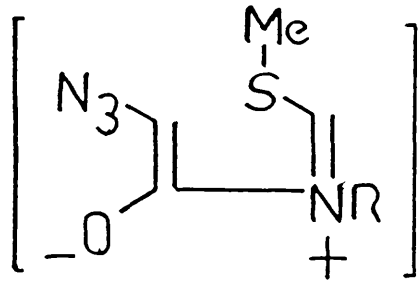
When the ketene component is generated in situ from the acid chloride (or some form of activated acid), the zwitterionic intermediate may result from direct acylation of the imine by the activated acid, followed by base induced proton abstraction.

The most puzzling aspect of the ketene/imine cycloaddition is its stereochemical outcome. Depending on the nature of the substituents on the ketene and the imine, the product may be entirely cis-3,4-disubstituted, entirely trans-3,4-disubstituted, or a mixture of the two.

The explanation which seems to fit all of the observed results most satisfactory is that offered[52] by Moore. It is assumed that dipolar intermediates (145) and (146) cyclise to azetidinones in a process which is strictly conrotatory (as predicted under Woodward-Hoffman rules, if the cyclisation is taken to involve 2 electron pairs). Thus acyclic E-imines (154) react with ketenes (155) to give intermediates to type (145); spontaneous cyclisation yields cis β-lactams (156) only. Conversely, cyclic Z imines (157) will yield trans β-lactams (158) by conrotatory closure of intermediates (146). If, however, the imine substituent R^3 is delocalising then the iminium carbon in (145) or (146) is particularly activated towards nucleophilic attack. Thus any nucleophilic species present in the system (for



(161) (160)



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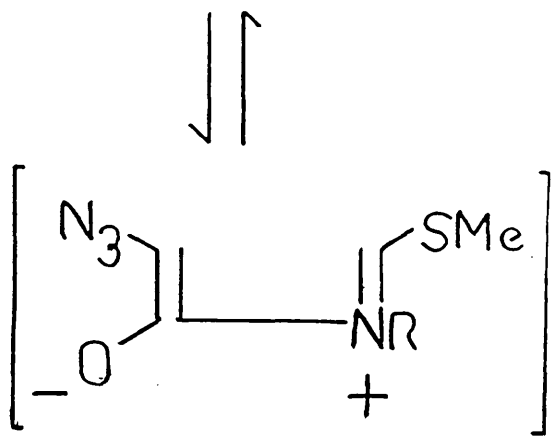

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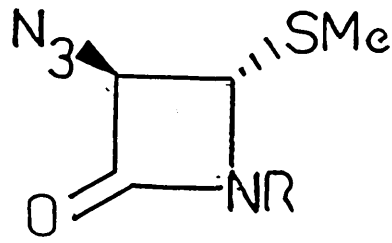
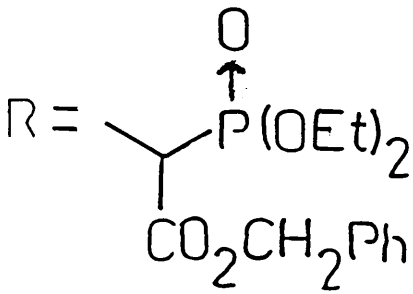


(162)

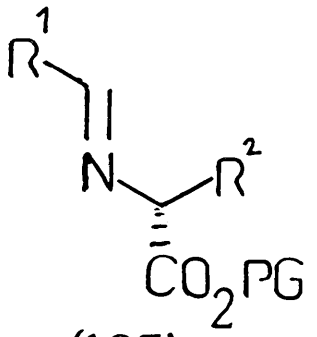


example chloride ions) can attack (145) or (146) to give a species of type (159). Intermediate (159) can allow either reversible interconversion of zwitterions (145) and (146) or it can close directly to the β-lactam. In either case a mixture of cis- and trans- β-lactams will result, normally with the thermodynamically more stable trans-isomer predominating. Thus, for example, imines with R^3=phenyl give [53] the more stable trans-product only or a mixture, with the trans-isomer predominating.

Similarly, if the imine R^2 substituent is capable of donating a lone pair to stabilise intermediate (145) or (146) then the barrier to bond rotation about the iminium bond is considerably reduced since it has diminished π-character, and interconversion of the two is possible. For example, imine (160) reacts[54] with ketene (161) to give only the more stable trans- β-lactam (162), presumably by interconversion of the two zwitterions (163) and (164) by simple bond rotation, as shown.

Moore's explanation may not be theoretically rigorous. It has, nevertheless, been remarkably successful in explaining the stereochemical outcome of ketene/imine cycloadditions.

As revealed in the introduction to this thesis, a considerable amount of work has already been carried out on asymmetric synthesis of β-lactams. Most emphasis has been placed on the reaction of homochiral lithium ester enolates and, to a lesser extent, of homochiral ketenes with achiral imines.



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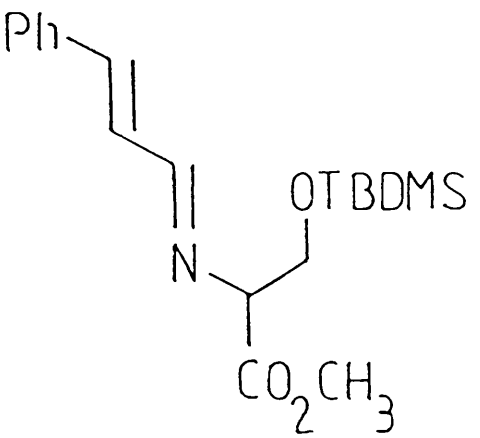

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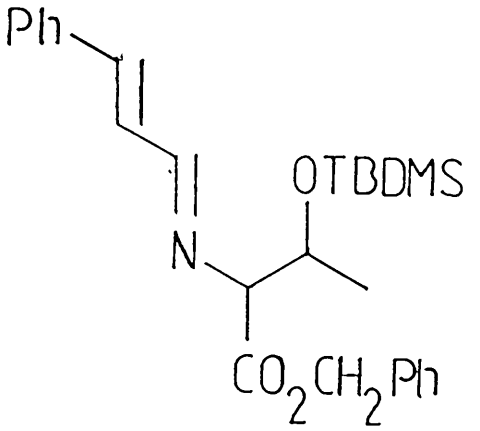

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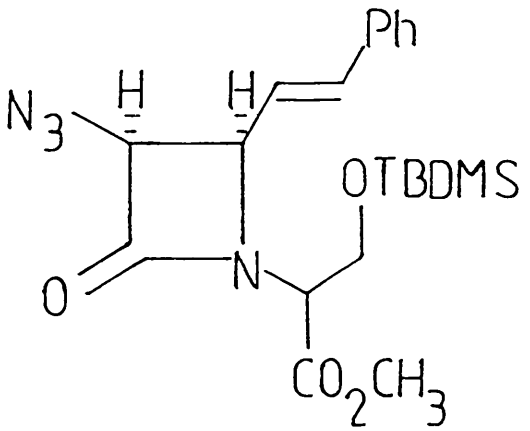

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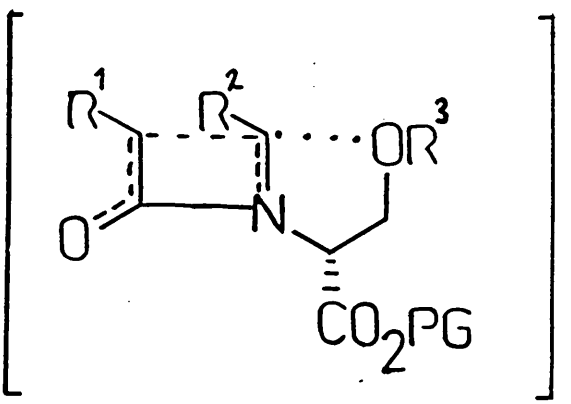
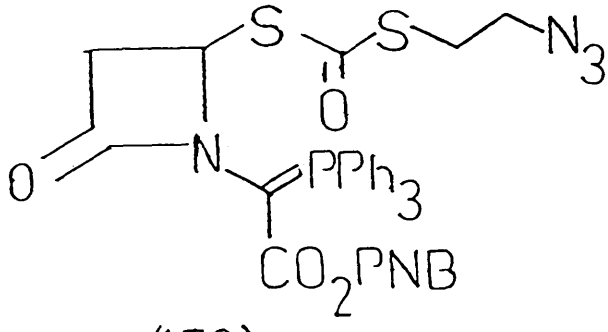


(169)

Any work which has been carried out using homochiral imines has relied heavily on the use of imines derived from suitably protected amino acids. As a consequence these imines (165) have had their chirality located on the tetrahedral carbon adjacent to the imine nitrogen. In general such imines have reacted[23] with little or no diastereoselectivity. Two notable exceptions to this generalisation involve the reaction of (-)-serine derived[20] imine (166) and of (+)-threonine derived[21] imine (167) with the ketene generated from azidoacetyl chloride. As described previously (p. 8), these two reactions proceed with d.e.s of 100% and 80% respectively. Why these two imines should react with ketenes in such a highly diastereoselective fashion whereas most other amino acid derived imines react with little or no selectivity is not obvious. One clear relationship between imines (166) and (167) is that both are derived from amines with a protected oxygen separated by two carbon atoms from the nitrogen. It is conceivable that the presence of a suitably protected oxygen in this position provides some interaction by which the energy difference between the two possible diastereoisomeric transition states leading for example, to β-lactam (168), is greatly increased. [One possible mechanism involves a pseudo bicyclic transition state such a (169). Evidence for the plausibility of such a transition state can be seen in the formation of oxazolidine (149), discussed on p(18)].

It may also be possible to obtain optically



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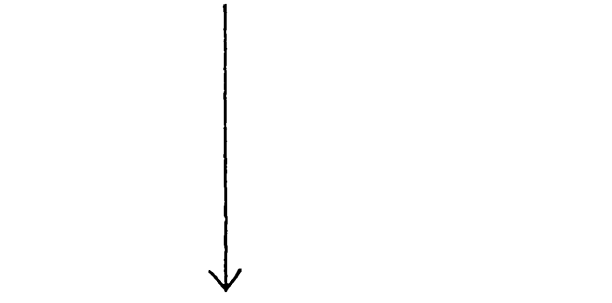

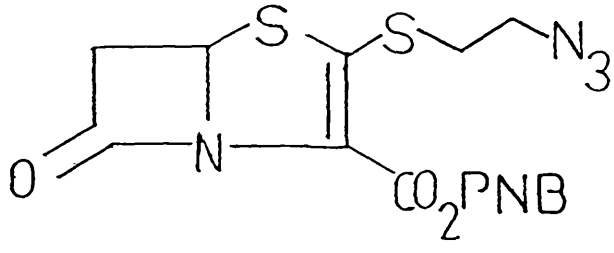

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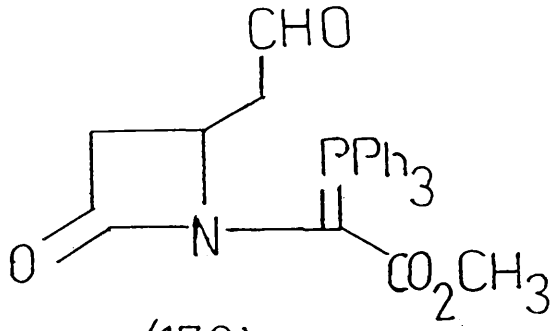

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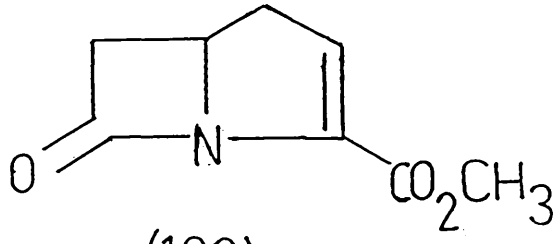

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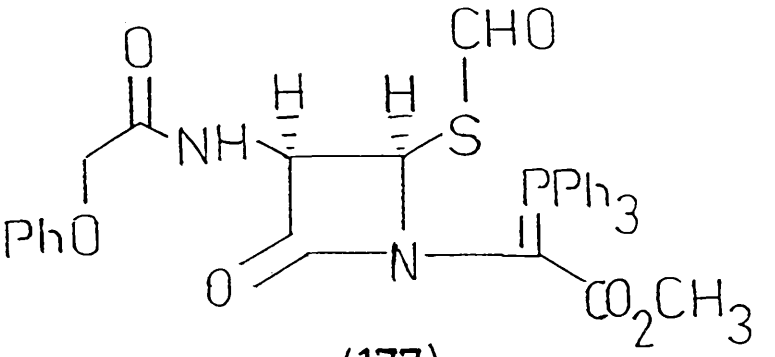

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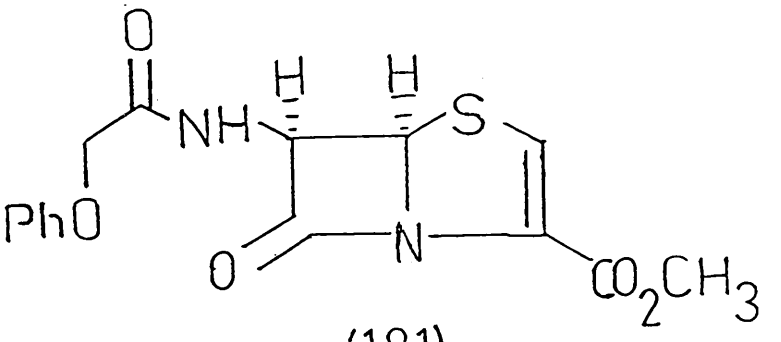

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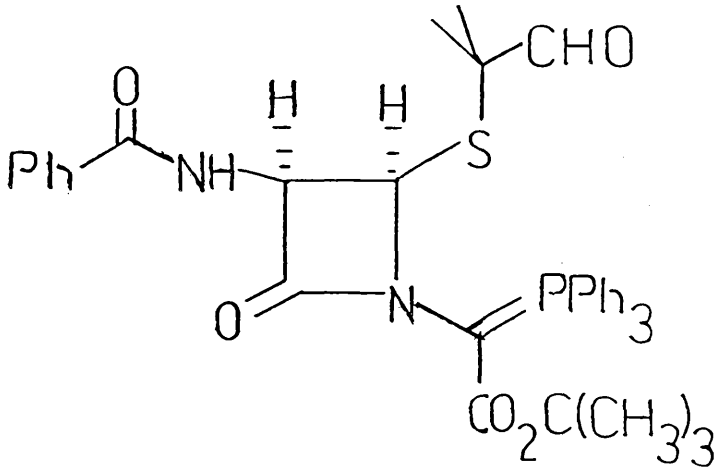

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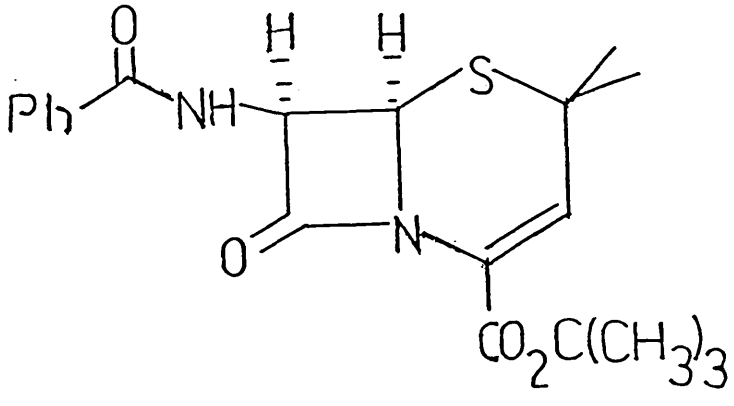
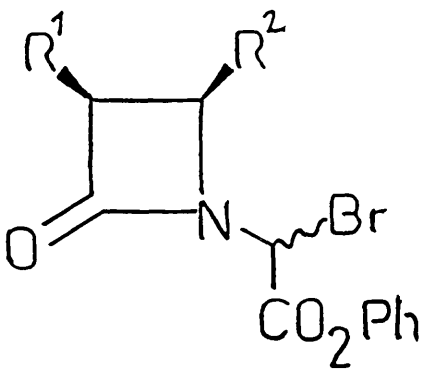


(180)

(173)



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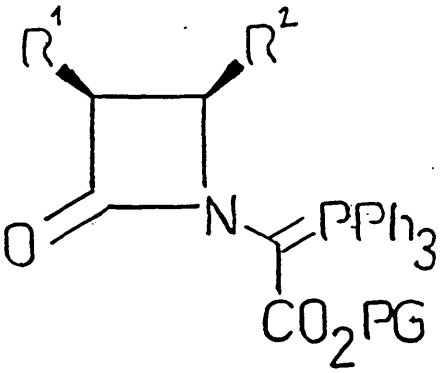

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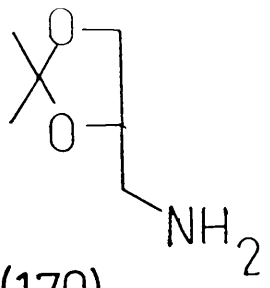

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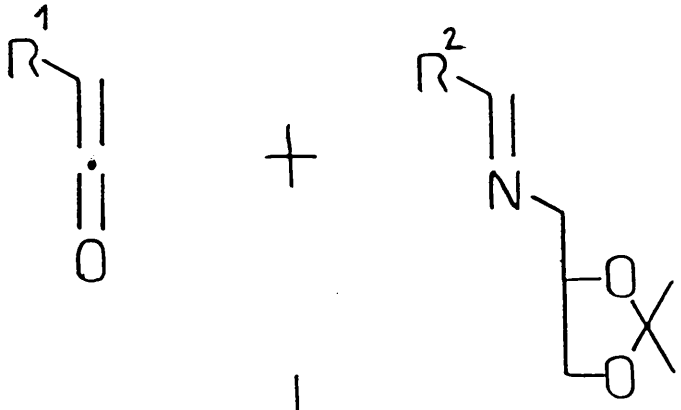
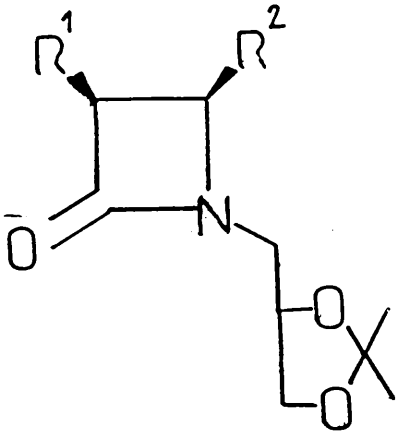
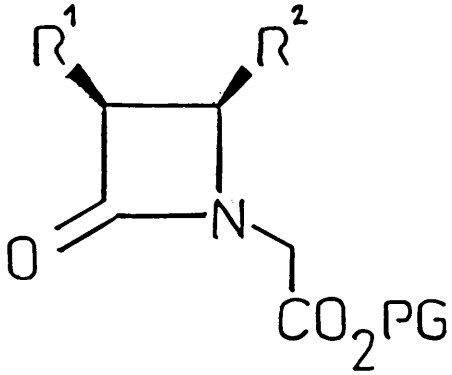


(171)



(172)



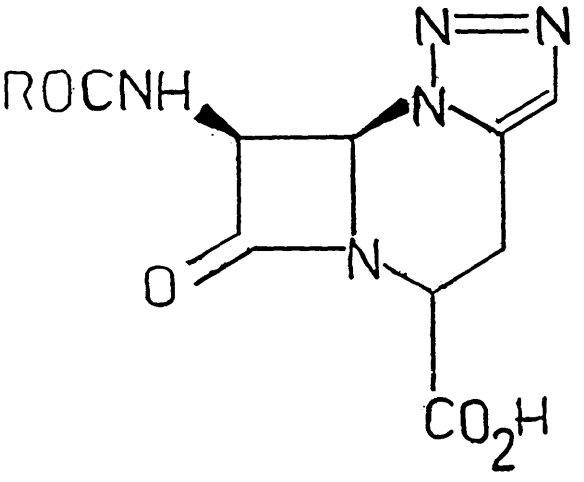
(173)

enriched β-lactams using a similar interaction but with the chiral centre located, for example, on the same carbon as the protected oxygen (i.e. on the second carbon atom from the nitrogen). To investigate this possibility, an amine was required which possessed a chiral centre and an oxygen in such a position. An amine which fulfils both requirements, and which is available[55] in homochiral form, is the acetonide amine (170).

Acetonide (170) should yield imines of type (171) and hence β-lactams (172). Such azetidinones have obvious synthetic potential : hydrolytic removal of the acetonide, followed by oxidative cleavage of the resulting diol would yield 2-oxo-1-azetidineacetic acid derivatives (173).

Such compounds are potential precursors of a wide range of useful bicyclic β-lactams. Photochemical treatment of compounds (173) with N-bromosuccinimide yields[56] the corresponding α-bromoesters (174). These, upon treatment with triphenylphosphine followed by base give[57] phosphonium ylids (175). These have been used extensively to synthesise bicyclic β-lactams, relying on an intramolecular Wittig reaction for the formation of the second ring. The cyclisation[58] of monocyclic β-lactams (176), (177), (178) and (179) to bicyclic compounds (180), (181), (182) and (183) respectively illustrate the versatility of this approach.

2-Oxo-1-azetidineacetic acid esters (173) have also been used directly in the synthesis of bicyclic β-



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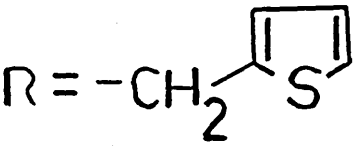

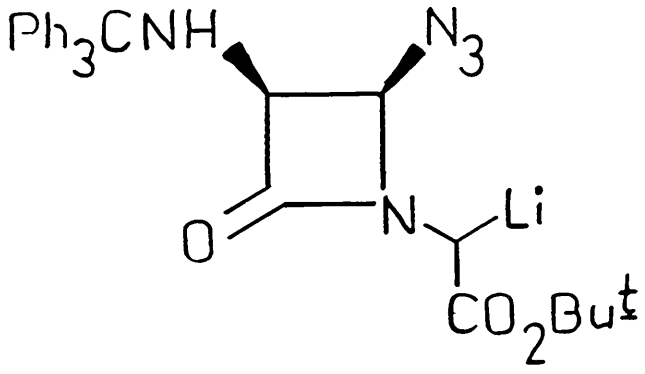

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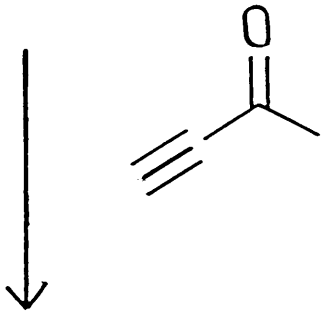

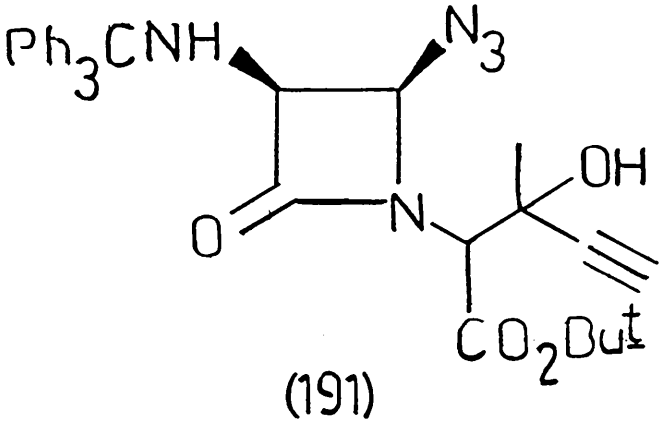

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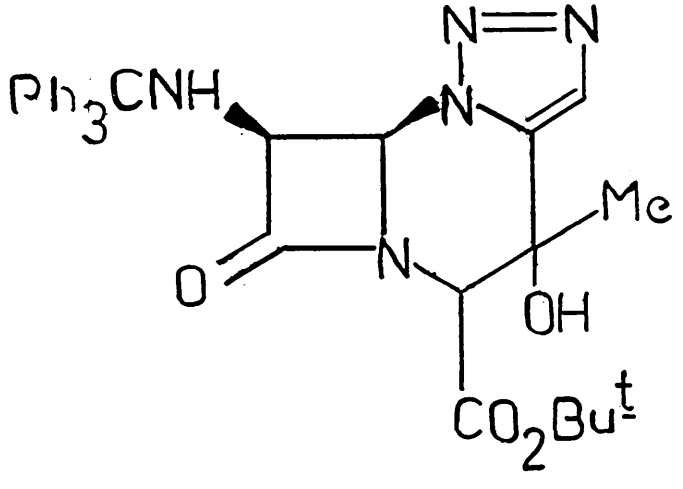

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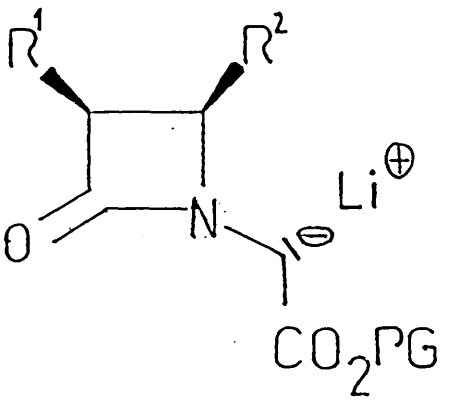

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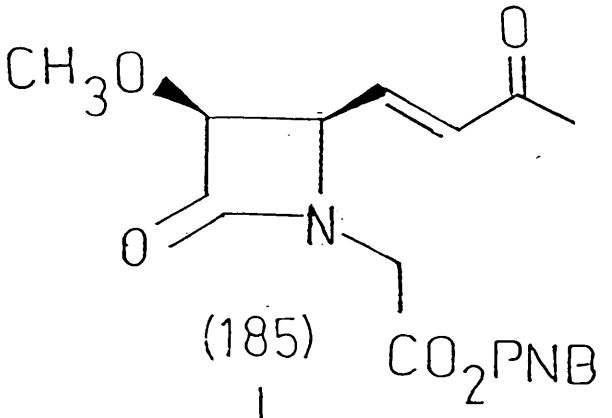

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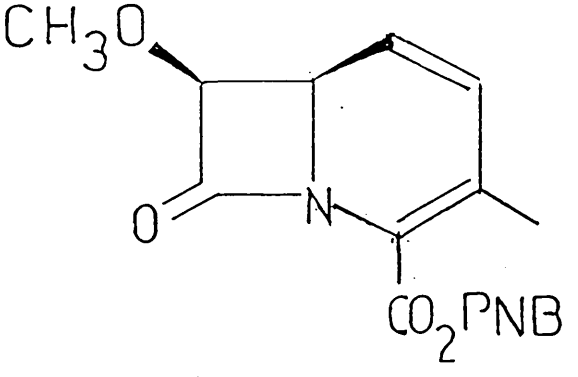

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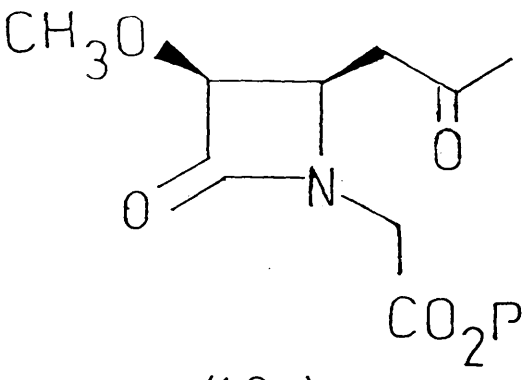
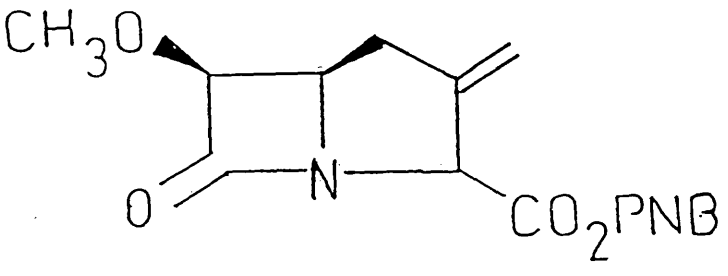


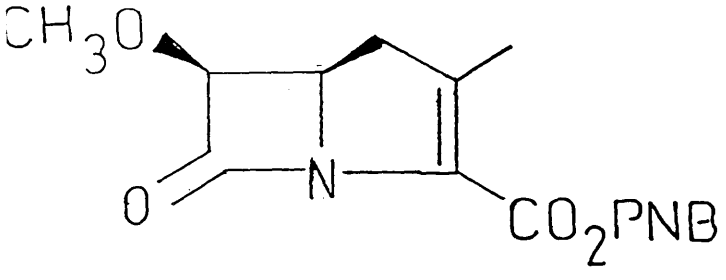
(184)

Base then B

Base then A



(186)



(187)

A: $MeSO_2Cl$ / Et_3N, 7h.

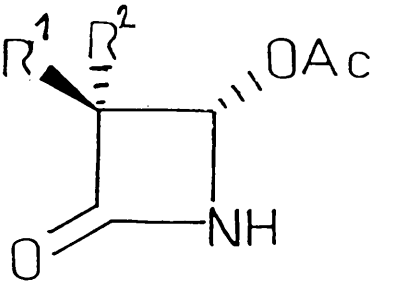
B: $SOCl_2$ / PYRIDINE, 0·5h.

lactams, utilising an aldol approach to establish the second ring. For example, monocyclic β-lactams (184) and (185) have been converted[59] into the bicyclic compounds (186), (187) and (188) respectively, using this methodology.

The ability of esters (173) to form ester enolates (189) on treatment with strong base has been further exploited in a number of syntheses of biologically active β-lactams. For example, lithium ester enolate (190) reacted[60] with but-3-yn-2-one to give lactam(191). This underwent a thermal, intramolecular [3+2] dipolar cycloaddition between the azido group and the alkyne to yield the novel triazolo-cephem (192). β-Lactam (192) was readily converted into the broad spectrum antibiotic (193).

The facile α-alkylation and acylation of acetate esters (173) has also been exploited in, for example, the synthesis of clavulanic acid analogues[61] and novel penem structures.[62]

It was thus decided to prepare amine (170), and from it a range of imines (171), to examine the behavior of the latter compounds in a range of established β-lactam ring-forming processes. Clearly, the motivation for such a study was twofold. Not only was there the possibility of preparing optically enriched β-lactams but there was also the prospect of the resulting azetidinones having significant potential as precursors of bicyclic β-lactams.



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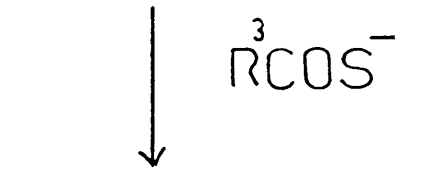

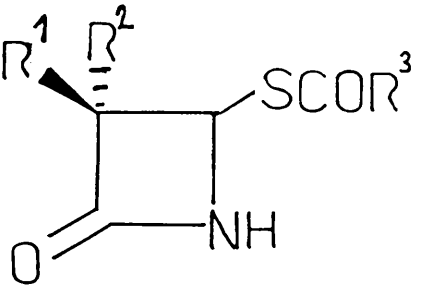

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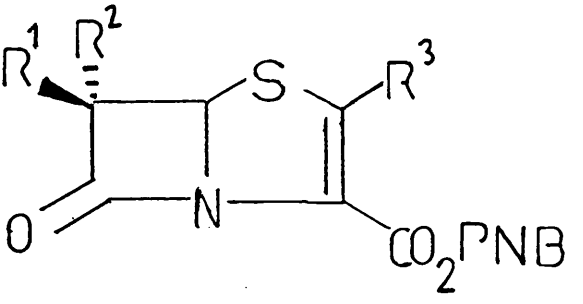
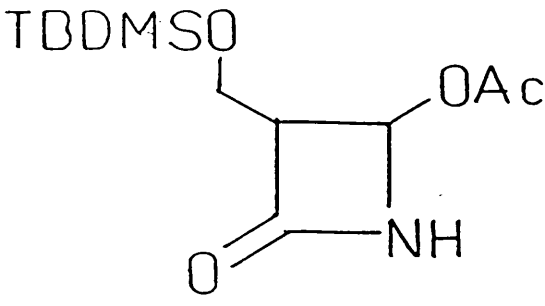


(207)

R^1, R^2, R^3 = ALKYL.



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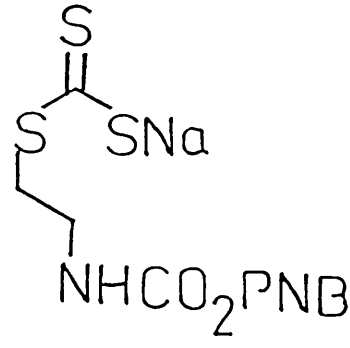

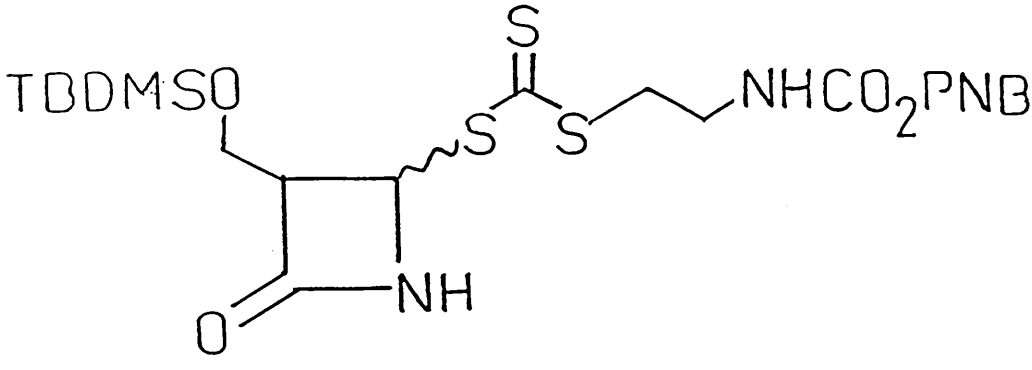

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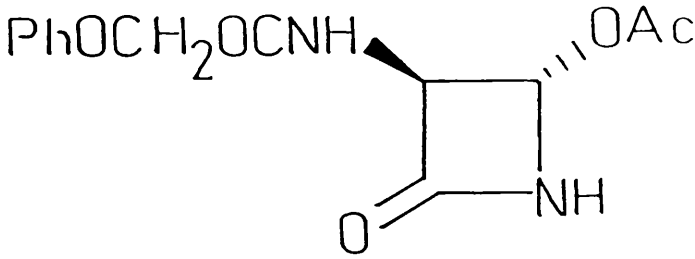
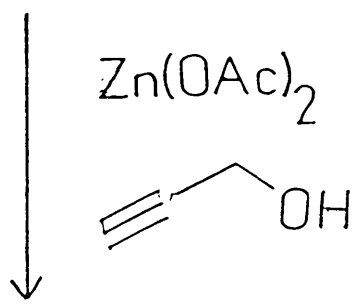
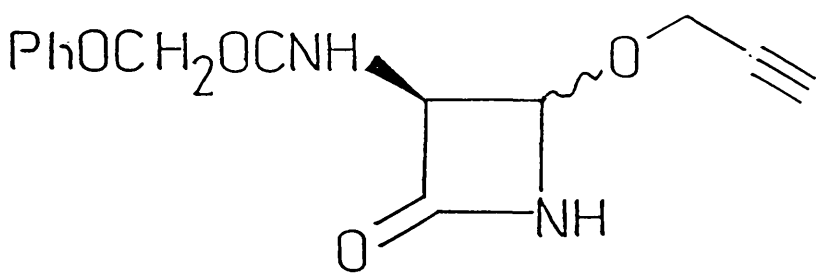
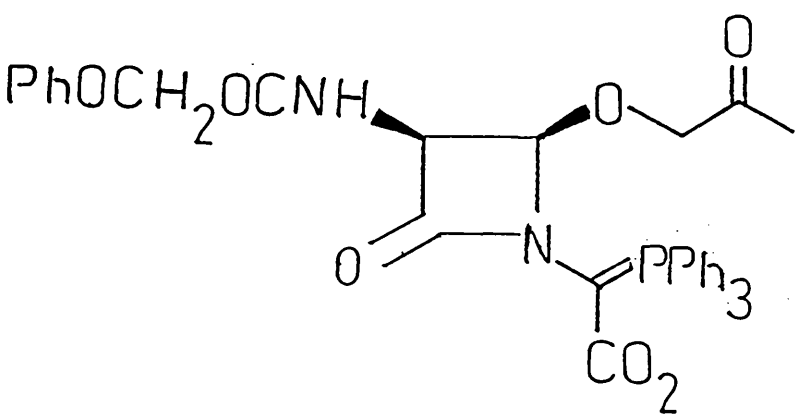

PhOCH2OCNH
OAc
NH
O

(199)

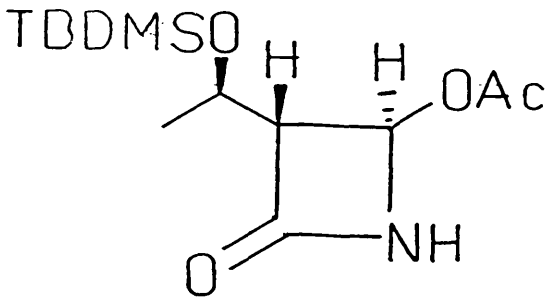

Zn(OAc)2
OH


PhOCH2OCNH
O
NH
O

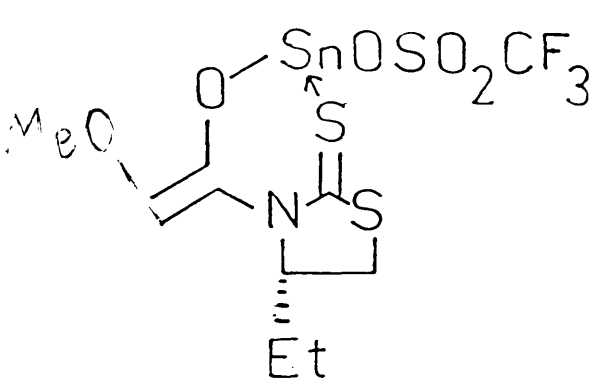
(203)

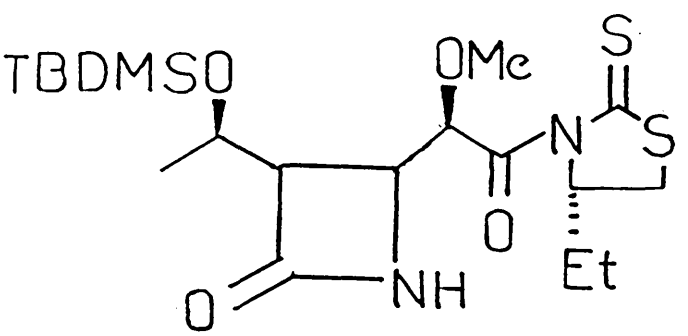

PhOCH2OCNH
O
O
O
N
PPh3
CO2

(206)

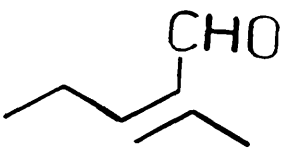

TBDMSO
H
H
OAc
NH
O

(198)

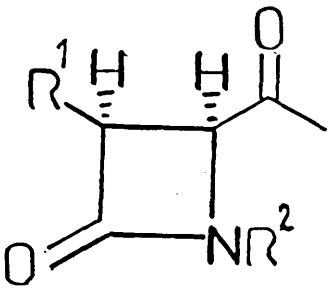

SnOSO2CF3
O
MeO
S
N
S
Et


TBDMSO
OMe
S
N
S
O
O
NH
Et

(202)



(194)



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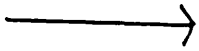

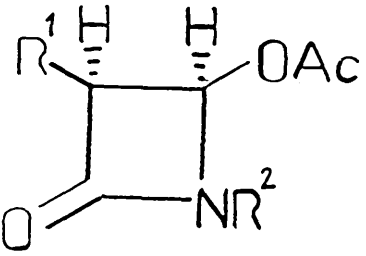

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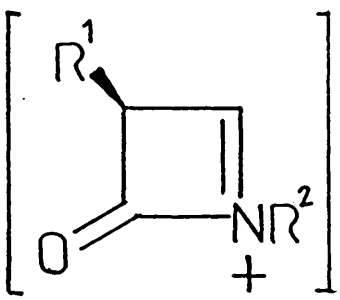


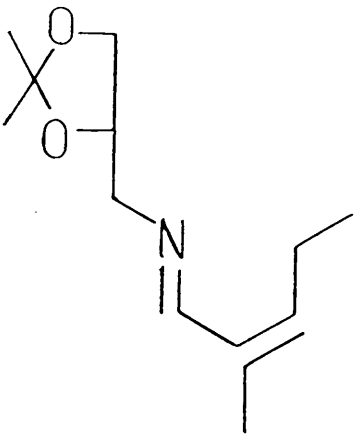
(197)

One point which required some consideration was selection of which aldehyde to use in the formation of imines (171). It was clearly desirable that the aldehyde chosen should give an azetidinone C-4 substituent which was compatible, in terms of bicyclic β-lactam formation, with the targeted N-acetic acid substituent.

One obvious choice was 2-methyl-αβ-unsaturated aldehydes such as 2-methylpent-2-enal (194) (readily available[63] from propanal by aldol condensation). These should furnish β-lactams which on ozonolysis should give 4-acetylazetidinones (195).

These species yield[64] after Baeyer Villiger oxidation, 4-acetoxy β-lactams (196). Such compounds have been shown to have considerable synthetic potential : in the presence of Lewis acids they react with a range of carbon, oxygen and sulphur nucleophiles, via the locally planar cation (197) (see also p.17). For example, 4-acetoxy β-lactams (198), (199), (200) and (201) reacted[65,58(b)] as shown to give azetidinones (202), (203), (204) and (205). A number of the nucleophiles introduced using this approach have been successfully converted into C-4 substituents compatible in terms of cyclisation, with an N-acetic acid substituent.

For example, the propargyl ether (203) has been converted[57] into a wide range of ketones (206), suitable for further cyclisation, either by an aldol or a Wittig approach. 4-Thioesters (205) have also been induced to



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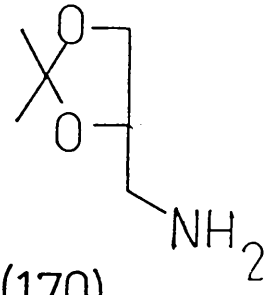
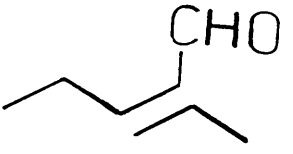


(170)



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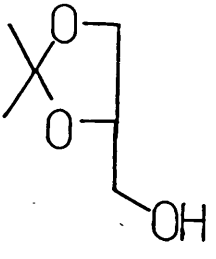

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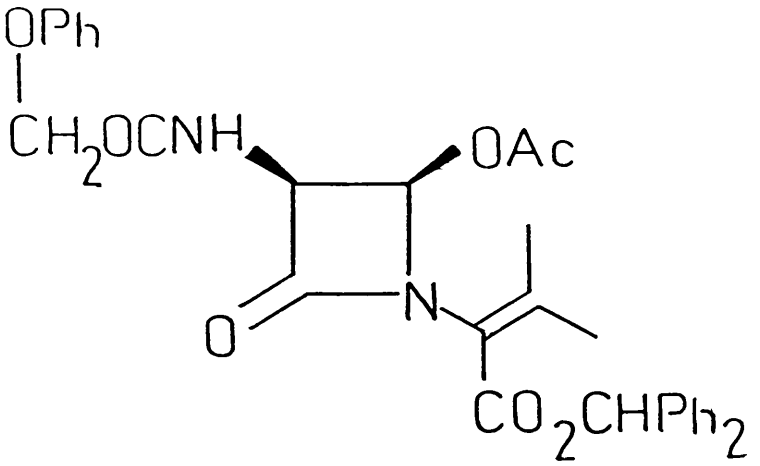
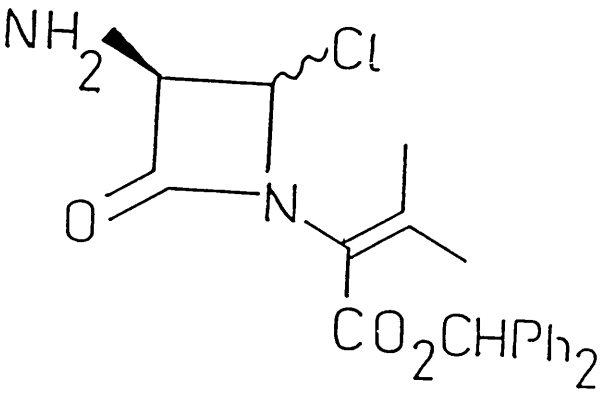
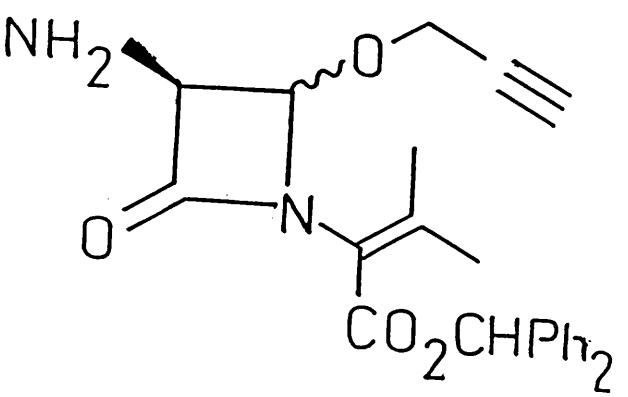


(208a)



(208b)



(209)

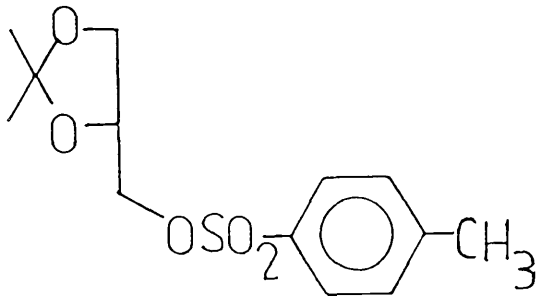
cyclise[58(b)] to a number of penems (207) as discussed on p(24).

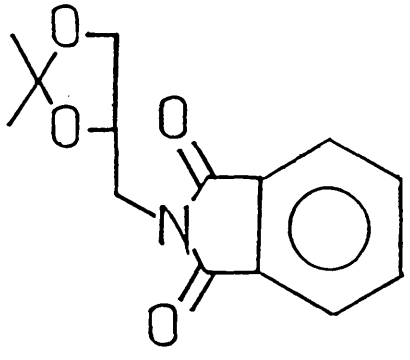
One weakness of this approach is that, because the displacement of acetate proceeds *via* a locally planar intermediate (197), the products are usually obtained as a mixture of *cis*- and *trans*-β-lactams with the thermodynamically more stable *trans*-isomer predominating. This is not usually a problem if the synthetic targets are carbapenems, such as thienamycin (6) since the *trans*-substituted lactam is indeed the desired isomer.

For the synthesis of *cis*-substituted β-lactams such as penicillins or cephalosporins and their analogues, on the other hand, the reaction conditions must be optimised to obtain the best yield of the desired *cis*-substituted lactam. Thus, for example conversion [66] of 4-acetoxy β-lactam (208a) to *cis*-propargylic ether (209) has been achieved *via* the 4-chloro compound (208b). When zinc chloride is used to catalyse the subsequent nucleophilic substitution on (208b) the *cis* : *trans* ratio is a fairly respectable 2:1. Stannous chloride and silver tetrafluoroborate give inferior ratios of 3:2 and 1:1 respectively.

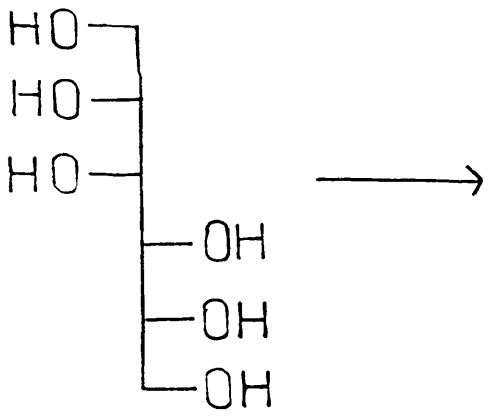
The initial target compound was thus imine (210), which should be available from amine (170) and aldehyde (194). The desired amine (170) was available[55] from 2,3-glycerol acetonide (211). Homochiral alcohol (211) was prepared from D-mannitol using the procedure of Baer.[67] This involved zinc chloride catalysed

(211)

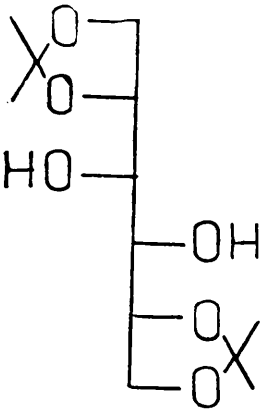




(212)



D-mannitol



(211)

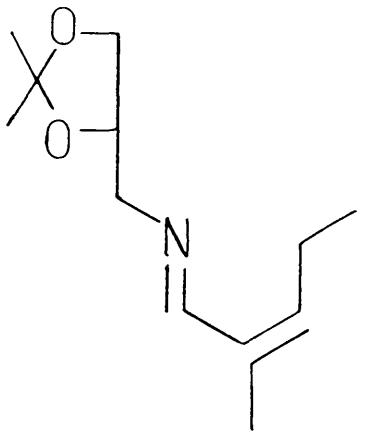
formation of the bisacetonide, followed by cleavage of this diol using aqueous sodium periodate, and finally *in situ* reduction with sodium borohydride of the (+)-glyceraldehyde acetonide thus generated. This gave (+)-2,3-glycerol acetonide in an overall yield of 79%.

Racemic alcohol (211) was also readily prepared[68] in multigram quantities by the *p*-toluenesulphonic acid catalysed reaction between glycerol and acetone, using a Dean and Stark apparatus. Since this reaction furnished large quantities of racemic alcohol (211) both cheaply and quickly all subsequent investigations into the β-lactam forming reactions of imines (171) were carried out using racemic material.

Racemic alcohol (211) was then converted[55] into its *p*-toluenesulphonate ester in good yield (89%). Reaction of this compound with liquid ammonia in a sealed tube for 96 hours gave the desired amine (170) in 53% yield.

In an attempt to find a higher yielding and less time consuming synthesis of amine (170), a Mitsunobu modified Gabriel synthesis[69] was attempted. Reaction of alcohol (211) with phthalimide, in the presence of triphenylphosphine and DEAD gave *N*-alkylphthalimide (212) in 91% yield.

Cleavage of compound (212) using hydrazine in refluxing methanol proved unsatisfactory, due to the volatility of the product amine (170). Even when the methanol was removed by careful distillation the desired



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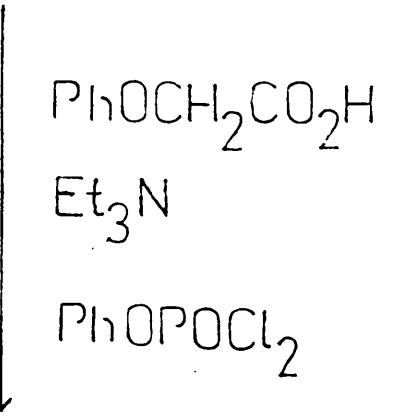
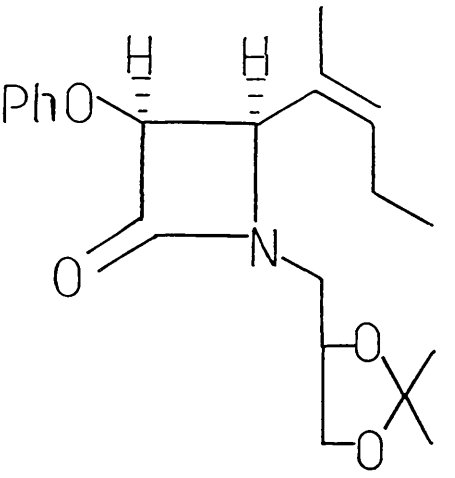




(213)

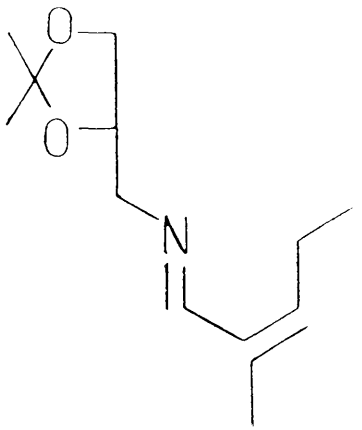
product (170) could be isolated in only 35% yield.

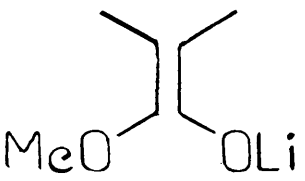
To overcome this problem, cleavage was carried out using methylhydrazine in dichloromethane. This allowed isolation of the desired amine (170) in 93% yield from phthalimide (212). The overall yield of 85% from alcohol (211) represents a considerable improvement on literature methods.

(E)-2-Methylpent-2-enal (194) was readily prepared[63] by aldol self-condensation of propanal. It was then condensed with amine (170) by stirring the two components in diethyl ether over potassium carbonate. Distillation of the crude product yielded imine (210) in good yield (91%).

Imine (210) thus prepared was then subjected to a series of β-lactam forming reactions to establish its potential in asymmetric β-lactam synthesis. Reaction with phenoxyacetic acid in the presence of phenyl dichlorophosphate and triethylamine[50] gave cis-azetidinone (213) in 83% yield. No trace of trans-lactam was detected. ^{1}H and ^{13}C NMR spectroscopy clearly showed that (213) was in fact a mixture of two diastereoisomers present in a ratio of approximately 1.45:1. Capillary G.C. successfully separated the two compounds and confirmed the above ratio, which corresponds to a d.e. of 18%.

This poor level of asymmetric induction was disappointing but it was hoped that imine (210) would react in a more selective fashion with a different





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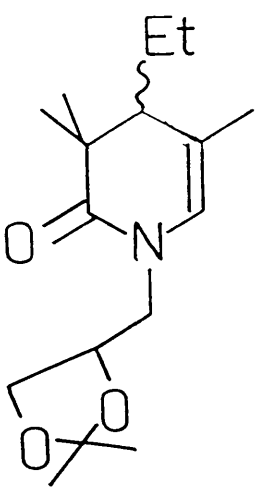

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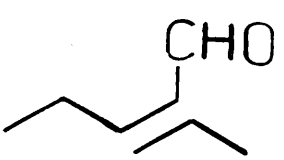

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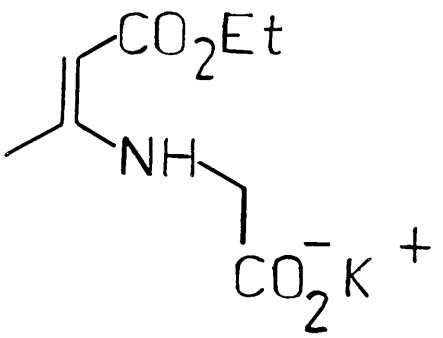

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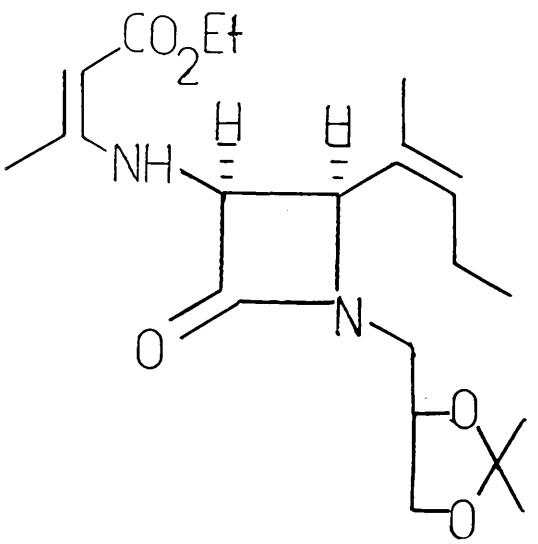


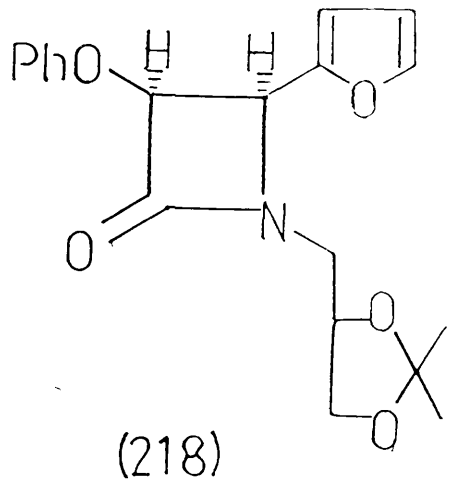
(215)

ketene.

Therefore, the Dane salt (214) derived from ethyl acetoacetate and glycine, was prepared[70] and reacted with imine (210), again using phenyl dichlorophosphate and triethylamine, to give the protected 3-aminoazetidinone (215) in excellent yield (87%); only the cis-isomer was observed.

Close inspection of lactam (215) by ^{1}H and ^{13}C NMR spectroscopy showed that it was a mixture of diastereoisomers. Capillary G.C. confirmed this and allowed separation of the two compounds showing them to be present in a ratio of 1.70:1 (d.e. 26%).

Once again the observed level of asymmetric induction was disappointing. In a final attempt to achieve some respectable degree of chiral induction using imine (210), the lithium ester enolate from methyl 2-methylpropionate was prepared and reacted with compound (210). Surprisingly, this yielded no β-lactam. Instead only aldehyde (194) (12%) and another compound (77%) were produced. Enal (194) was almost certainly generated by hydrolysis of unreacted starting material during the acidic work up. The second product was eventually characterised as dihydropyridone (216). This is clearly, in retrospect, the product of Michael addition of the ester enolate to imine (210), followed by lactamisation. Pyridone (216) was produced as a 2:1 mixture of diastereoisomers (by NMR spectroscopy and by capillary G.C).



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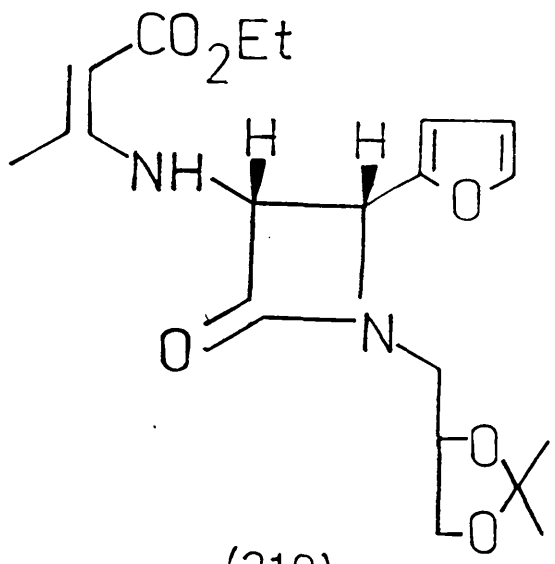

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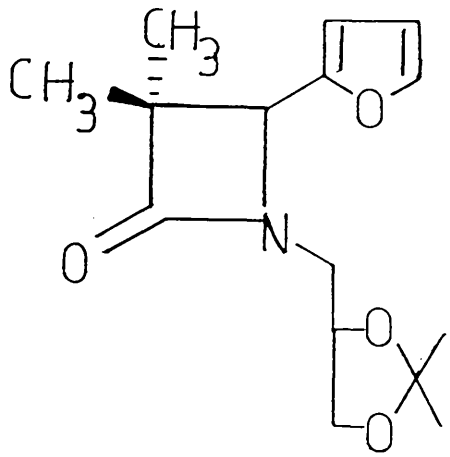

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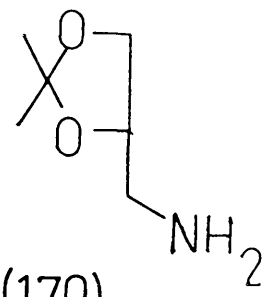

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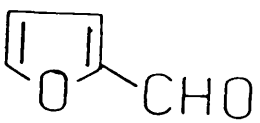
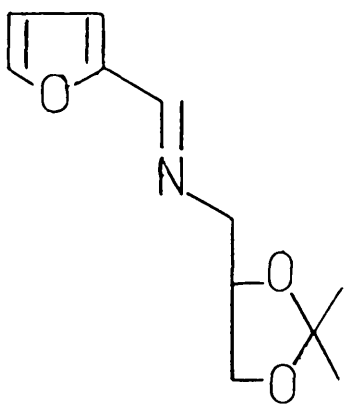


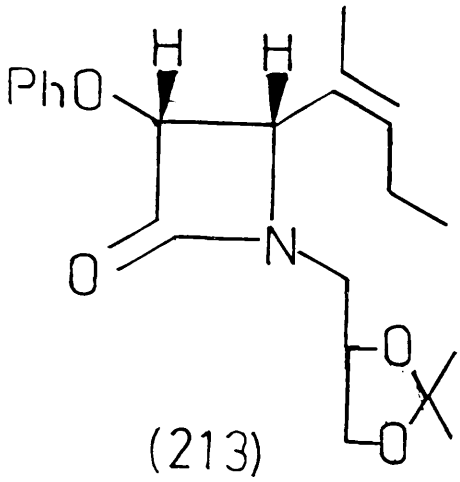


(217)

Although imine (210) had yielded several synthetically interesting azetidinones its peformance with respect to asymmetric β-lactam synthesis was rather disappointing. It was therefore decided to prepare a second imine from amine (170) to establish whether imines derived from this compound were generally ineffective in yielding optically enriched β-lactams or whether, by altering the aldehyde used to prepare the imine, it would be possible to improve significantly the disappointing levels of diastereoselectivity so far observed.

Thus amine (170) was condensed with freshly distilled furfuraldehyde, by stirring the two together in ether, over potassium carbonate, to give, after purification by distillation, compound (217) in 98% yield. This homochiral imine was subjected to the same three β-lactam forming reactions that had been carried out on imine (210). Thus reaction with the ketene from phenoxyacetic acid gave cis-β-lactam (218); reaction with the ketene derived from Dane salt (214) gave cis-3-amino β-lactam (219) and reaction the lithium ester enolate from methyl 2-methylpropionate gave a mixture of furfuraldehyde (14%) and 3,3-dimethyl β-lactam (220) (68%).

Lactams (218), (219) and (220) were shown by NMR spectroscopy and capillary G.C. to be mixtures of diastereoisomers with d.e's of 18%, 24% and 22% respectively.



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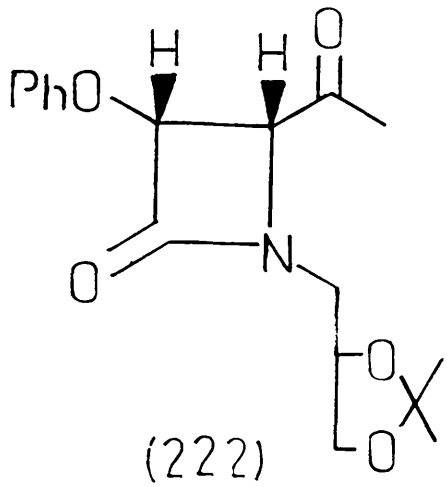

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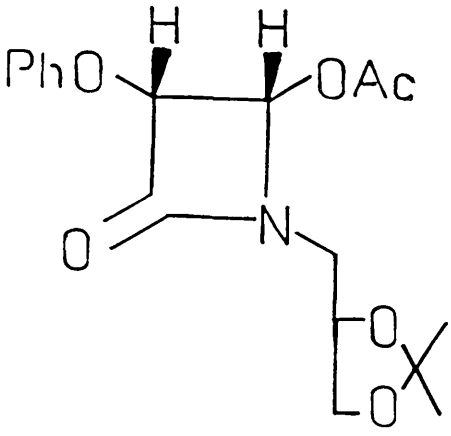

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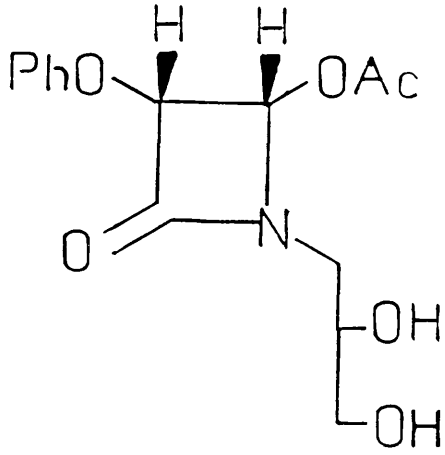

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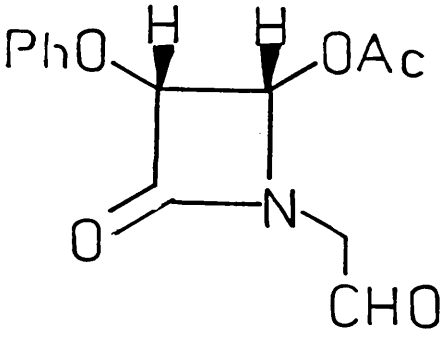

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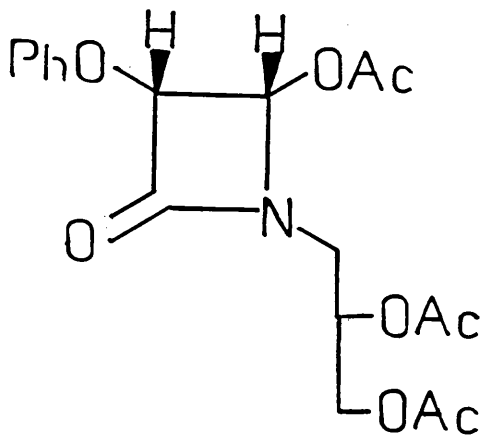
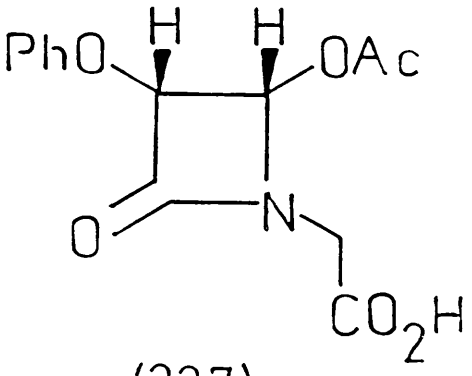


(225)

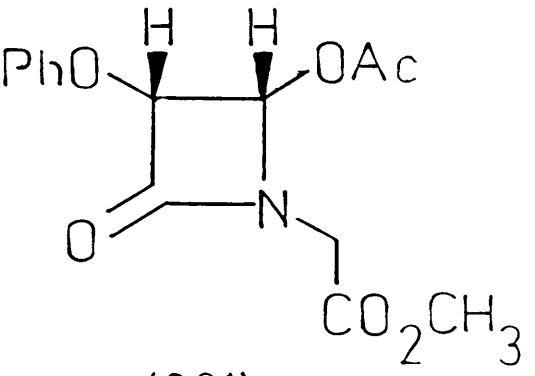
The poor levels of asymmetric induction observed in these reactions of imines (210) and (217) suggested that homochiral amine (170) was not a promising starting material for the asymmetric synthesis of β-lactams. However, imines (210) and (217) had clearly yielded a number of interesting azetidinones, with considerable potential as precursors of bicyclic β-lactams. As a result, some time was spent investigating the synthetic usefulness of some of these compounds.

Azetidinone (213) was converted into the potential bicyclic precursor (221) as follows: ozonolysis of lactam (213) gave methyl ketone (222) in good yield (91%). Baeyer Villiger oxidation of ketone (222) using mCPBA in refluxing benzene gave acetate (223) in a yield of 87%, with 9% recovery of starting material. As expected[64] this oxidative rearrangement proceeded with full retention of the cis-stereochemistry in the β-lactam ring. The acetonide protecting group in acetate (223) was successfully removed by treatment with 80% aqueous acetic acid. The crude product, diol (224), was fully characterised by conversion to its triacetate (225) by using pyridine/acetic anhydride. β-Lactam (225) was produced in an overall yield of 96% from acetonide (223). The cis-stereochemistry was retained throughout these transformations.

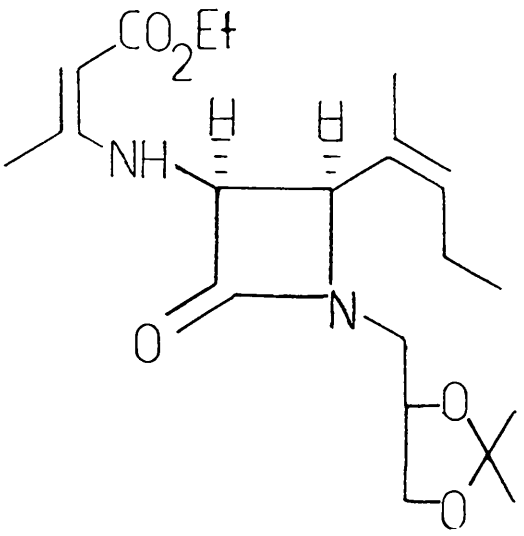
Crude diol (224), prepared as described, was then converted into aldehyde (226) by reaction with periodic acid in THF. Under this facile procedure filtration followed by solvent removal furnished the crude product



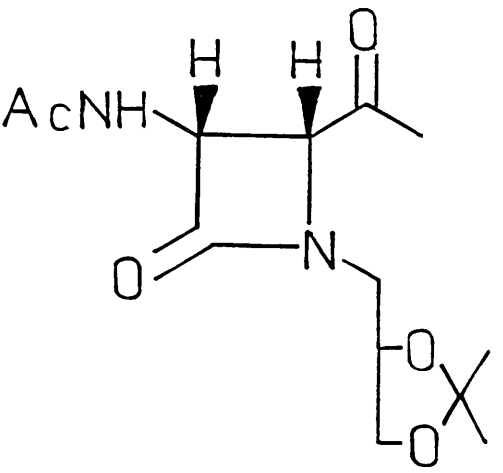
(227)



(221)



(215)

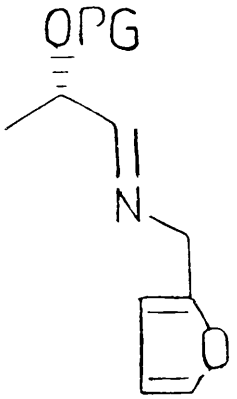


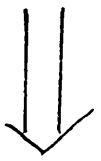
(228)

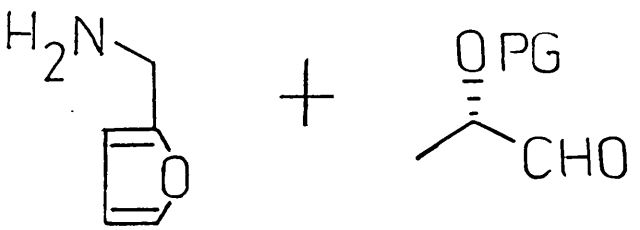
directly. Aldehyde (226) was found to be reasonably stable and could be readily purified by column chromatography. The overall yield for the two steps from acetonide (223) was excellent (96%).

Oxidation of aldehyde (226) was carried out using potassium permanganate in a two phase water/benzene system, in the presence of a phase transfer catalyst (benzyltriethylammonium bromide). No attempt was made to purify or charaterise acid (227). Instead immediate treatment with diazomethane in ether gave methyl ester (221) in a yield of 86% for the two steps.

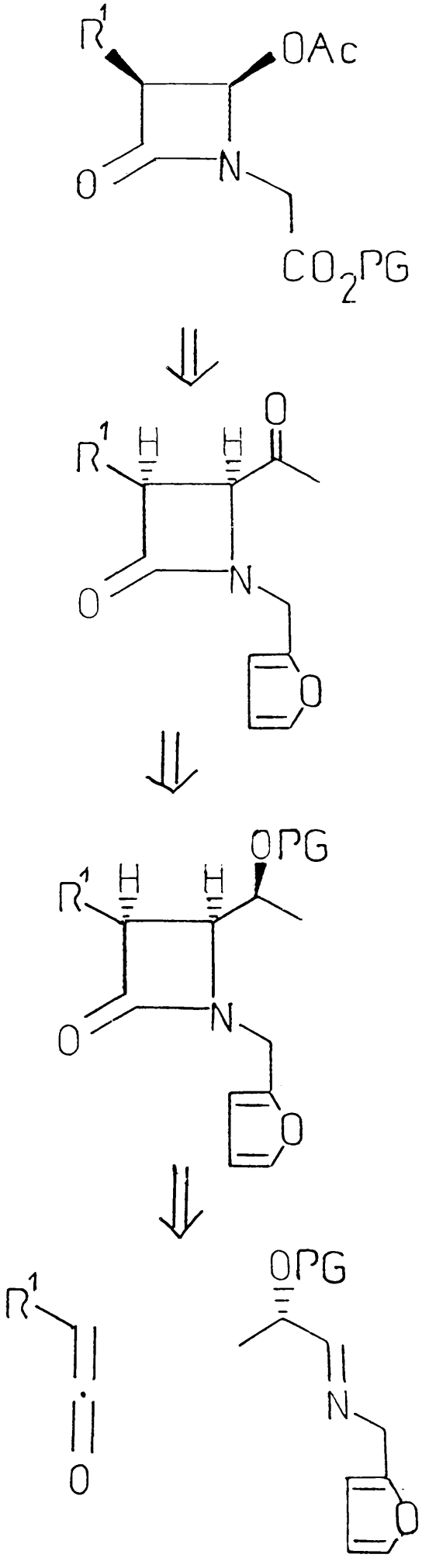
The overall yield from amine (170) to compound (221) was a very respectable 53%. Furthermore, it was also possible to demonstrate the synthetic potential of azetidinone (215) by ozonolysis of this compound to the methyl ketone/acetamide (228). Compound (228) was obtained as a white solid which, by ^{1}H spectroscopy was still a 1.7:1 mixture of diastereoisomers. However, recrystallisation yielded a white crystalline solid which by ^{1}H and ^{13}C NMR spectroscopy was considerably enriched in one diastereoisomer (d.e. greater than 90%). The yield of this material was 42% from lactam (215). Although this approach to optically enriched β-lactams is rather wasteful, the high yielding nature of the other steps involved and the synthetic utility of the C-1 and C-4 substituents on lactam (228) [as demonstrated by the conversion of lactam (213) into compound (221)] clearly show that this route has some potential for the synthesis of a range of bicyclic β-lactams of reasonable optical purity.





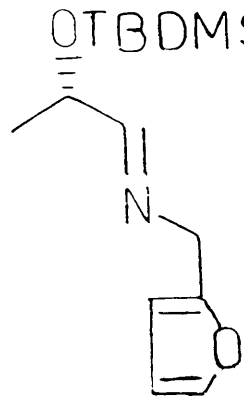


(229)

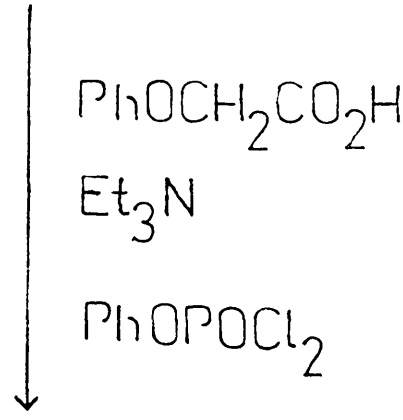

R1
OAc
O
N
CO2PG
R1
H
H
O
O
N
O
R1
H
H
OPG
O
N
O
R1
O
OPG
N
O

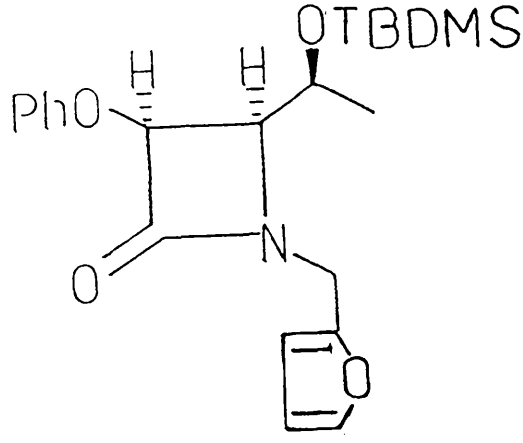
In conclusion these attempts to use imines derived from amine (170) in asymmetric β-lactam synthesis had been unsuccessful. This was almost certainly because the chiral centres in these imines were too many bonds away from the stereogenic centres as they formed. (There was clearly no suitable through space interaction to ovecome this problem).

As the considerable success of using ester enolates and ketenes derived from (3)-hydroxybutyric acid in asymmetric β-lactam synthesis demonstrates, the best way to promote diastereoselectivity in such reactions is to incorporate the chiral centre in one of the starting materials adjacent to the carbons where the new chiral centres will be formed. Thus it was decided to prepare an imine derived from a homochiral protected α-hydroxyaldehyde, since such a compound would certainly meet the above criterion. At the same time it was desirable that the resulting β-lactams could be converted with relative ease into compounds of significant synthetic utility. Again, taking 4-acetoxy-2-oxo-1-azetidineacetic acid esters as primary targets, it was fairly straightforward to work back retro-synthetically, as shown, to readily available furfurylamine (229) and protected α-hydroxypropanals. (Danishefsky has shown[71] that furans can be smoothly oxidised to the corresponding acids, using the ruthenium dioxide sodium periodate/water/carbon tetrachloride/acetonitrile system developed by Sharpless[72]). According to the literature[73] several of these aldehydes were indeed available, in homochiral

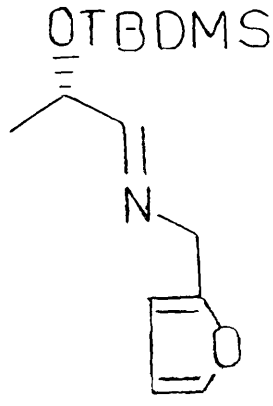


(230)

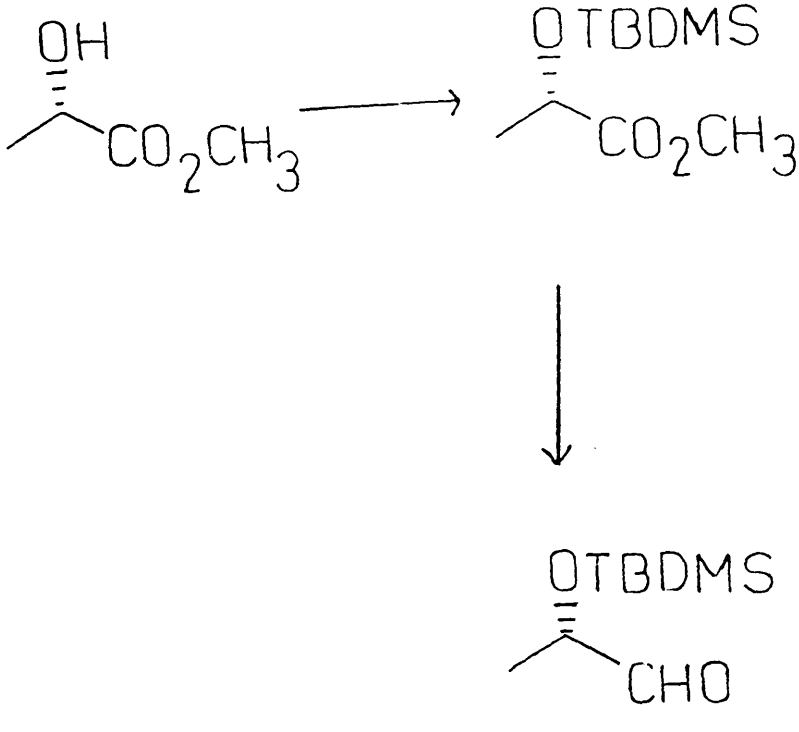




(232)



(230)



(231)

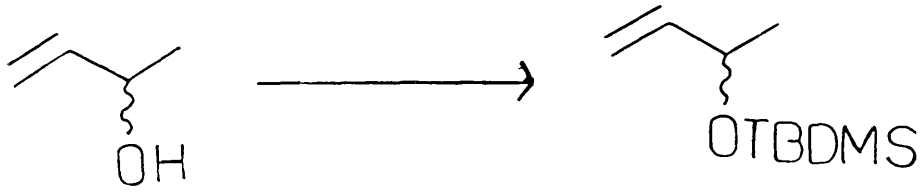
form, by DIBALH reduction of protected homochiral lactate esters.

Clearly it was desirable to opt for a protecting group which was both bulky (in the hope of optimising any asymmetric induction) and easily removed under mild conditions. It was therefore decided to prepare the O-TBDMS protected imine (230).

Homochiral aldehyde (231) was prepared by protecting (S)-(-)-methyl lactate as its TBDMS ether and then carefully reducing the resulting methyl ester with DIBALH at -78°C. Aldehyde (231) thus produced was purified by distillation and then condensed with freshly distilled furfurylamine (229). This gave imine (230) in 86% yield, after purification by distillation.

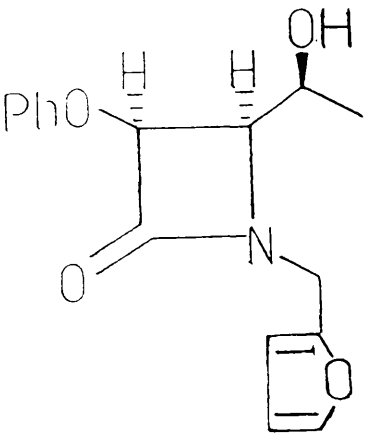
Imine (230) was successfully reacted with phenoxyacetic acid, in the presence of phenyl dichlorophosphate and triethylamine to give the cis-β-lactam (232) in 86% yield, after column chromatography. Again, no trace of the trans isomer was detected. ^{1}H and ^{13}C NMR spectroscopy both suggested that lactam (232) was a mixture of diastereoisomers, with one being present in large excess (d.e. about 80%). Capillary G.C. separated these two compounds and gave a d.e. value of 83%.

It was obviously necessary to establish that no epimerisation had occurred at the exocyclic chiral centre in lactam (232), either during the formation of imine (230) or during the conversion of this imine into

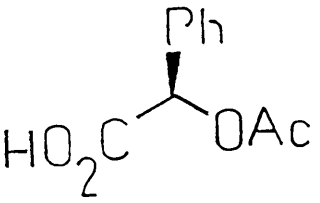


(236) (237)

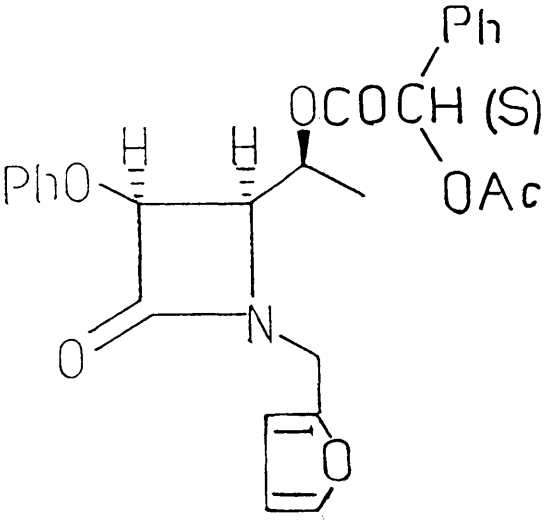
(±)–(231)



(233)



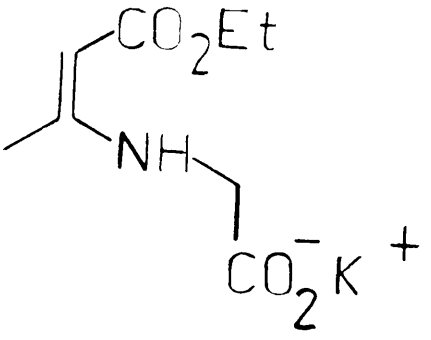
(234)



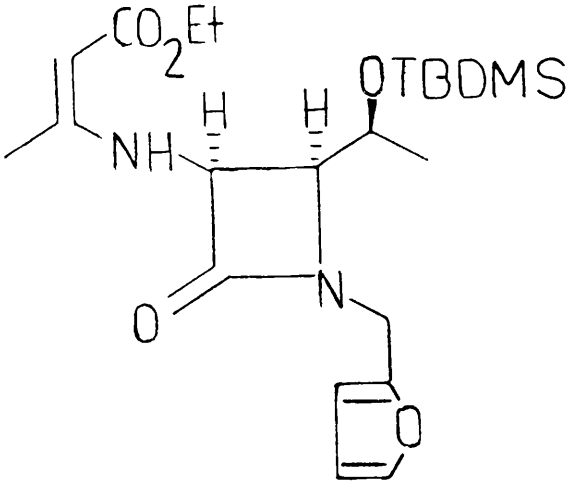
(235)

lactam (232). (Compound (232) had a measured $[\alpha]_D$ of -29^o. However, this did nothing to establish its chiral integrity. Partial racemisation could easily have occurred during the synthesis). This was achieved using the approach of inter alia, Whitesell.[74] Firstly lactam (232) was desilylated employing TBAF to give alcohol (233) in 87% yield. DCC/DMAP/Triethylamine mediated coupling of alcohol (233) to (S)-O-acetylmandelic acid (234) gave ester (235) in 91% yield. Ester (235) appeared as one compound, both by ^1H and ^{13}C NMR spectroscopy, suggesting very strongly that β-lactam (232) was indeed homochiral. (The fact that none of the minor diastereoisomer from lactam (232) was detected in ester (235) almost cetainly resulted from loss of material experienced as a result of sacrificial purification of alcohol (233) or ester (235) during the synthesis). This suggested very strongly that β-lactam (232) was indeed homochiral. As confirmation of this, racemic aldehyde (231) was deliberately prepared from (±)-3-hydroxybut-1-ene (236) by O-silylation to give TBDMS ether (237) followed by ozonolysis. When subjected to the same synthetic pathway, racemic aldehyde (231) yielded ester (235) as a 1:1 mixture of two diastereoisomers, one of which showed, within experimental error, identical spectroscopic behaviour to homochiral ester (235). This was taken as proof absolute of the fact that azetidinone (232) was homochiral.

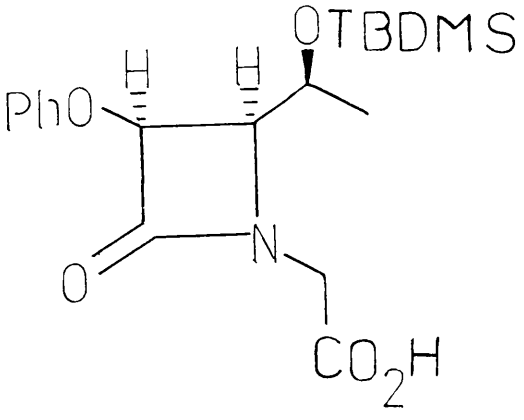
To establish the synthetic potential of N-[(furan-2-yl)methyl] substituted azetidinones like (232), ruthenium dioxide/sodium periodate oxidation[71] was

(230) + 

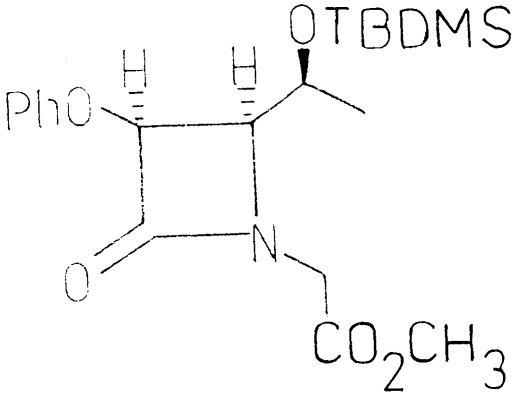
(214)



(240)



(238)

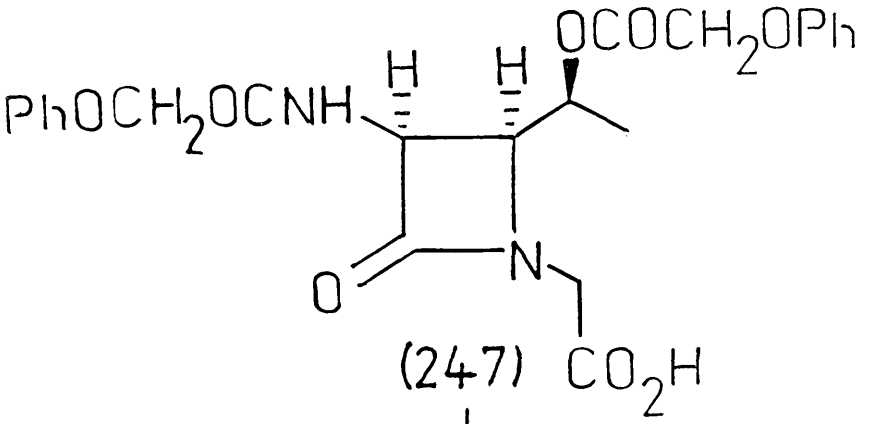


(239)

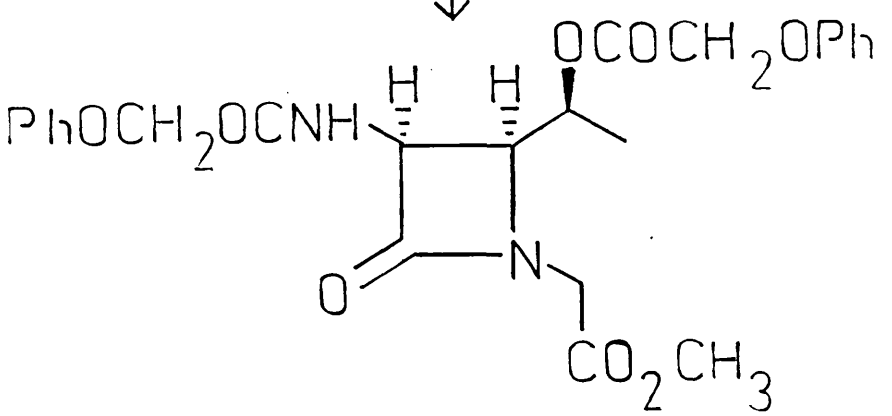
carried out. No attempt was made to purify or characterise the resulting acid (238) thus produced. Instead the crude acid was reacted immediately with diazomethane to give methyl ester (239). Lactam (239) could be purified by column chromatography and was produced in an overall yield of 83% from lactam (232).

Clearly, the next step was to extend this approach to the synthesis of β-lactams with more useful C-3 substituents while hopefully retaining the excellent d.e. observed in the production of azetidinone (232). Thus imine (230) was reacted with Dane salt (214) in the presence of phenyl dichlorophosphate and triethylamine to give cis β-lactam (240) in 86% yield. This product was shown (by NMR spectroscopy) to be greatly enriched in one diastereoisomer. Capillary G.C. showed the d.e. to be 91%. Azetidinone (240) had a measured $[\alpha]_D$ of $+26.5^o$. As before, the chiral integrity of lactam (240) was established by desilylation to alcohol (241) in 91% yield followed by coupling with (S)-O-acetyl-mandelic acid to give ester (242) in 89% yield. NMR spectroscopy indicated that lactam (242) was present as one diastereoisomer only. (Once more the minor diastereoisomer present in lactam (240) was presumably removed by sacrificial purification). This was confirmed by subjecting racemic aldehyde (231) to the above synthetic sequence, leading to the production of ester (242) as a 1:1 mixture of two diastereoisomers, by NMR spectroscopy. Azetidinone (240) was thus taken to be homochiral.

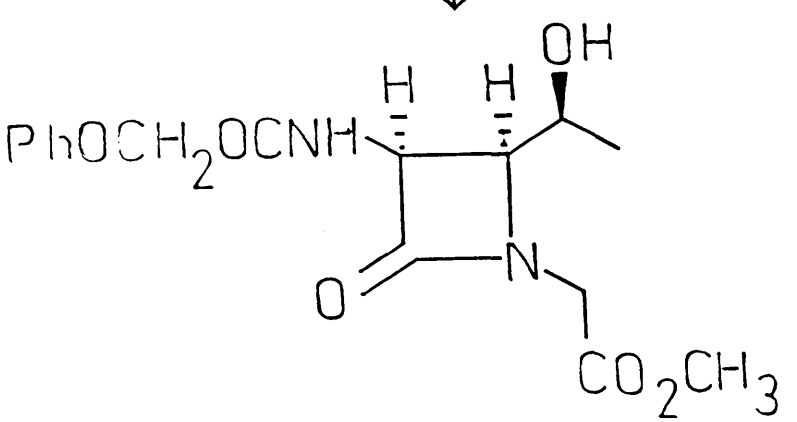
(246)



(247)



(248)



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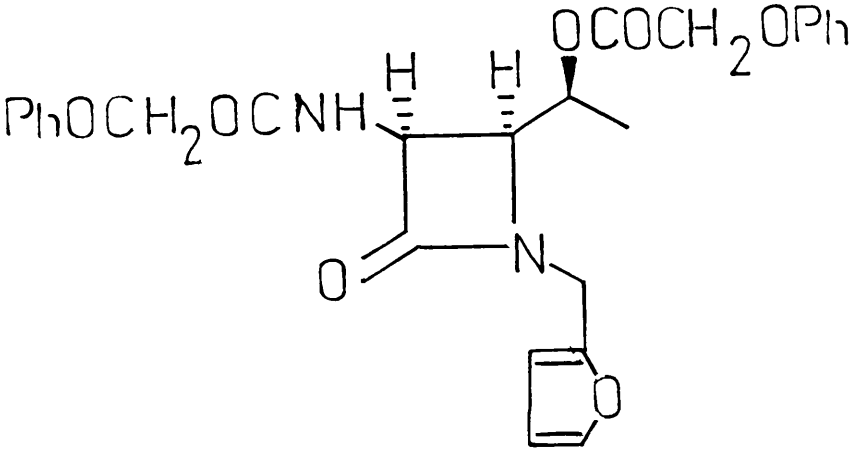

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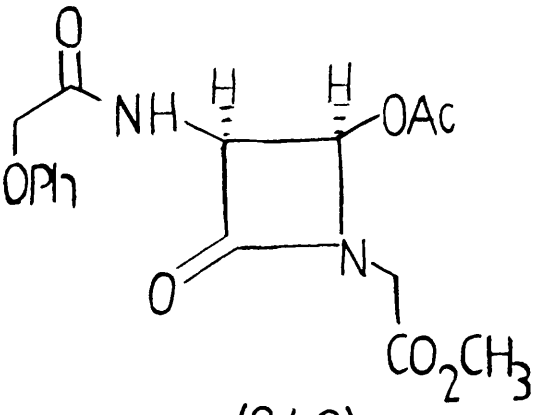
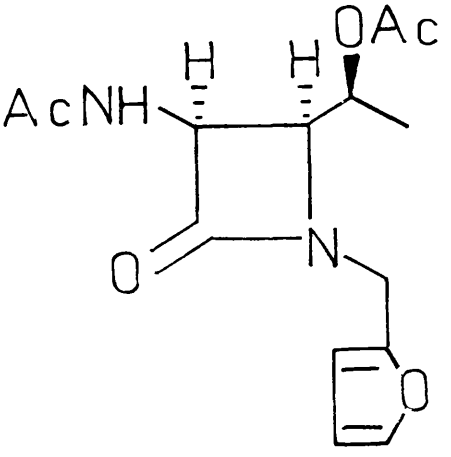


(243)



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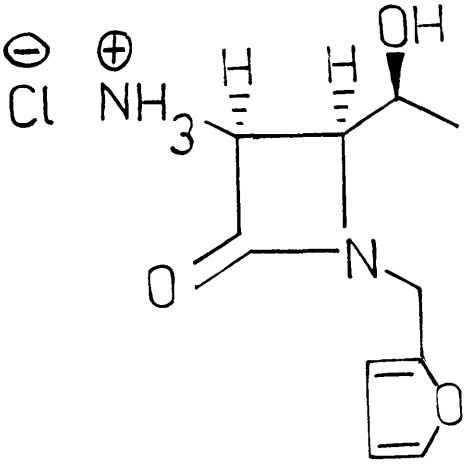

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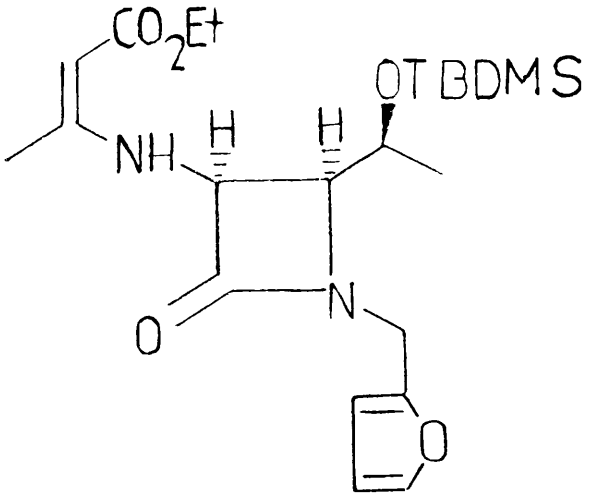
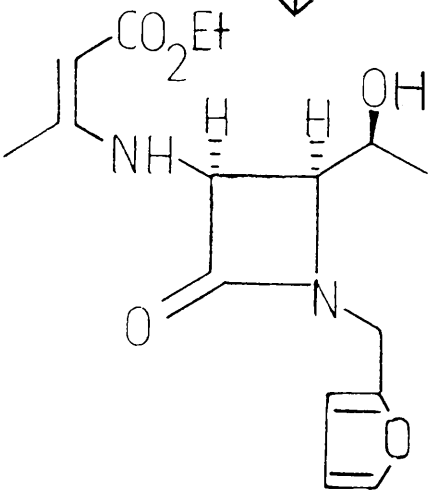
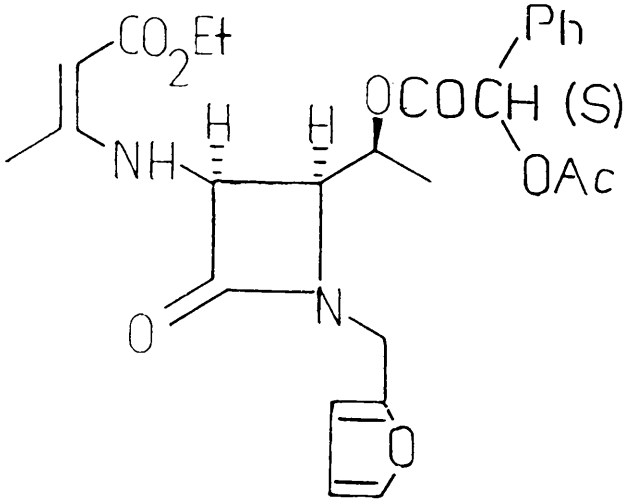

CO2Et
OTBDMS
NH
H
H
O
N
O

(240)


CO2Et
OH
NH
H
H
O
N
O

(241)


CO2Et
Ph
OCOCH (S)
OAc
NH
H
H
O
N
O

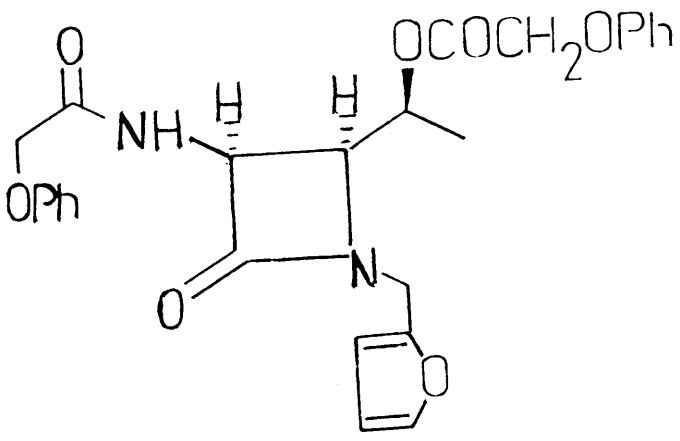
(242)

To demonstrate the synthetic potential of this route it was decided to attempt the conversion of lactam (240) into the potential bicyclic β-lactam precursor (243), which has the same C-3 side chain as penicillin V.

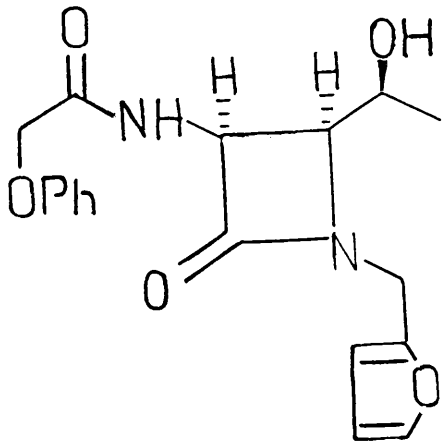
Selected hydrolytic cleavage of the vinylogous carbamate amino protecting group in the presence of the TBDMS ether was attempted by treating lactam (240) with 1M methanolic HCl for 10 min. Removal of the solvent gave a white, amorphous solid smelling strongly of ethyl acetoacetate. Washing this solid several times with pentane (whereupon this smell was effectively removed) was followed by immediate reaction of the crude product with excess triethylamine/acetic anhydride/DMAP. This gave acetate/acetamide (244) in 94% overall yield, from lactam (243). Clearly treatment of azetidinone (243) with methanolic HCl under these conditions had resulted in the non-selective cleavage of both the vinylogous carbamate and of the silyl ether to give the alcohol/amine hydrochloride salt (245).

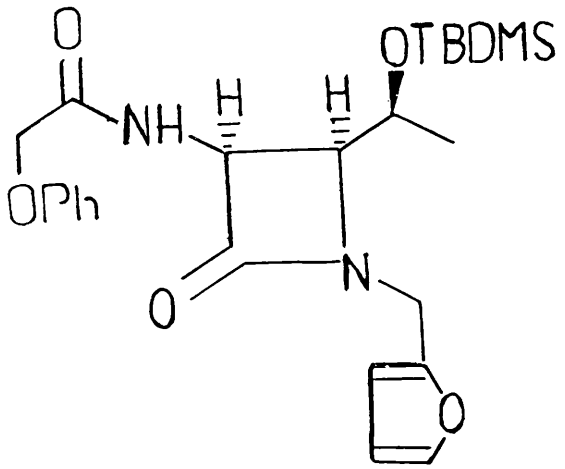
Alcohol (245) could also be converted, in 96% overall yield, into phenoxyacetamide/phenoxyacetate (246), by treatment with 2.1 equivalents of phenoxyacetyl chloride, in the presence of triethylamine and DMAP.

Compound (246) is an obvious potential precursor of the desired β-lactam (243). Thus azetidinone (246) was converted into acid (247) using Sharpless furan oxidation. Reaction of the crude product with


O
OCOCH2OPh
NH
H
H
OPh
O
N
O

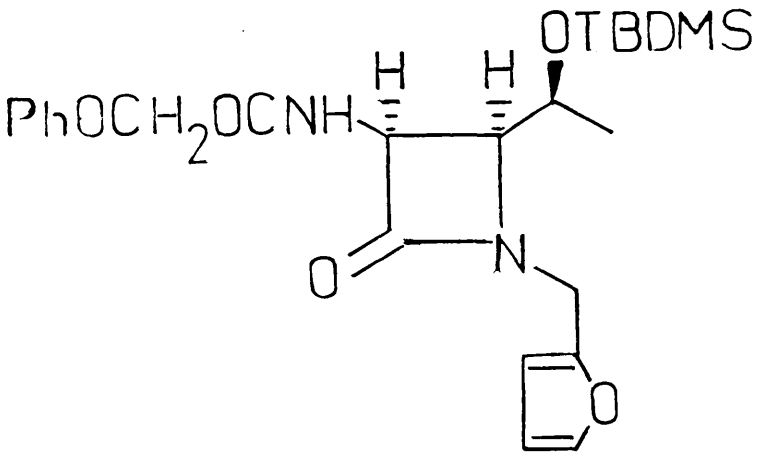
(246)


O
OH
NH
H
H
OPh
O
N
O

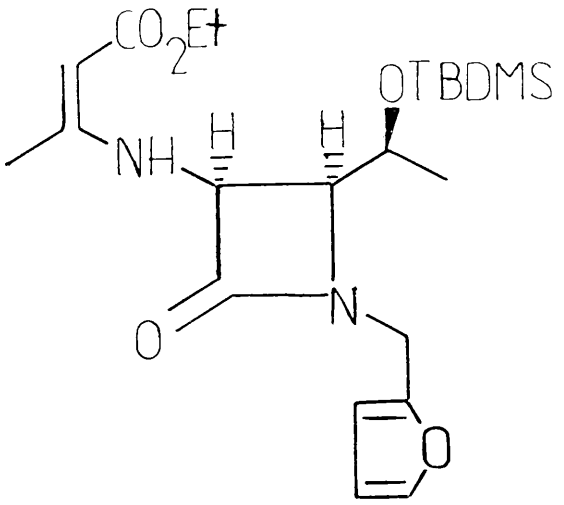

O
OTBDMS
NH
H
H
OPh
O
N
O

(251)

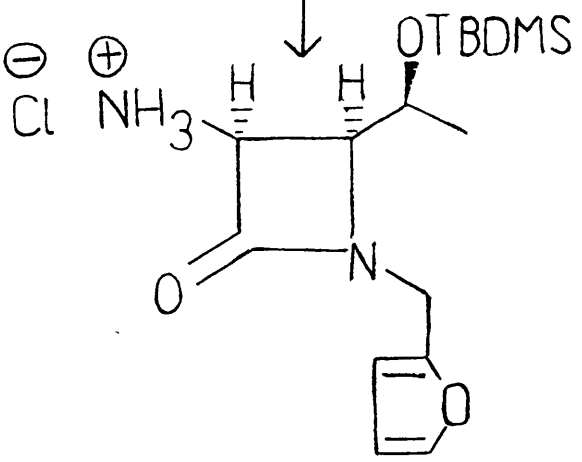
(250)



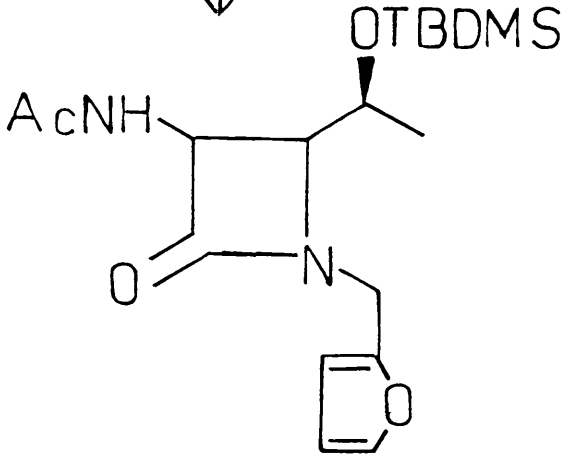
(251)



(240)



(250)

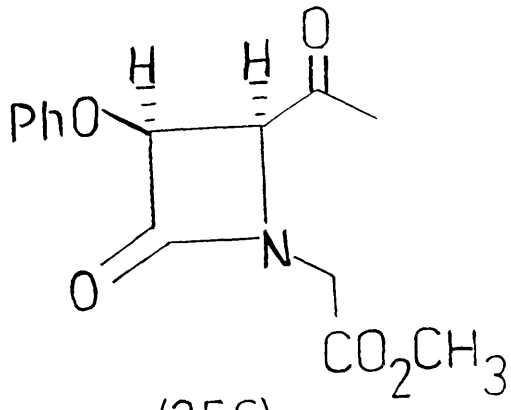


(249)

diazomethane furnished methyl ester (248) in 78% overall yield from furan (246).

Unfortunately, attempted cleavage of the phenoxyacetate ester in lactam (248) was unsuccessful, despite the use of a variety of known[75] ester cleavage systems, including potassium carbonate/methanol; potassium bicarbonate/methanol; potassium carbonate/THF; potassium bicarbonate/THF and ammonia/methanol. All of these procedures resulted in the production of very polar material, which could not be characterised.

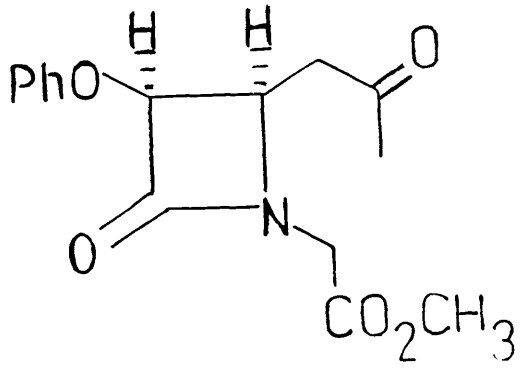
It was therefore decided to return to the initial concept of selective cleavage of the amino protecting group in the presence of the silyl ether. To make the cleavage conditions milder, the reaction of lactam (240) in 1M methanolic HCl was stopped after only 5 min by thoroughly purging the solution with nitrogen. Again solvent removal gave an amorphous white solid smelling strongly of ethyl acetoacetate. Washing with pentane, followed by acetylation using triethylamine, acetic amhydride and DMAP gave the desired acetate/silyl ether (249), in 89% overall yield from lactam (240). Selective cleavage to the desired amine hydrochloride salt (250) had thus been achieved. Reaction of this salt with phenoxyacetyl chloride in the presence of triethylamine and DMAP gave the target phenoxyacetamide (251) in an overall yield of 82% from lactam (240). Silyl ether (251) was also available in good yield from phenoxyacetate (246) in two steps, involving initial potassium carbonate/methanol mediated selective ester cleavage to the alcohol followed by treatment[76] with



(256)

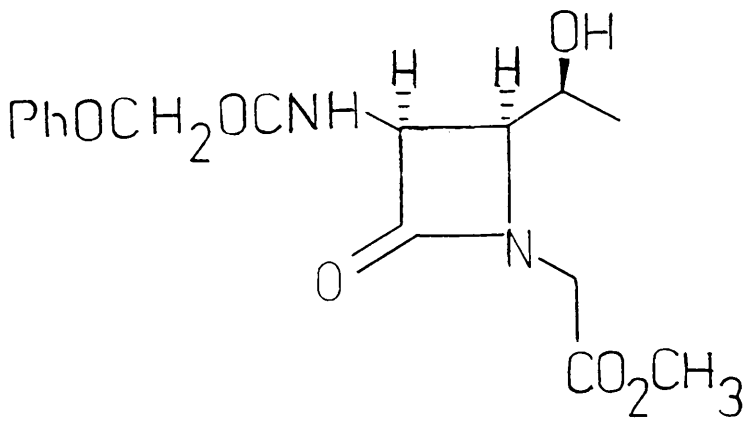
CH_2N_2

MeOH

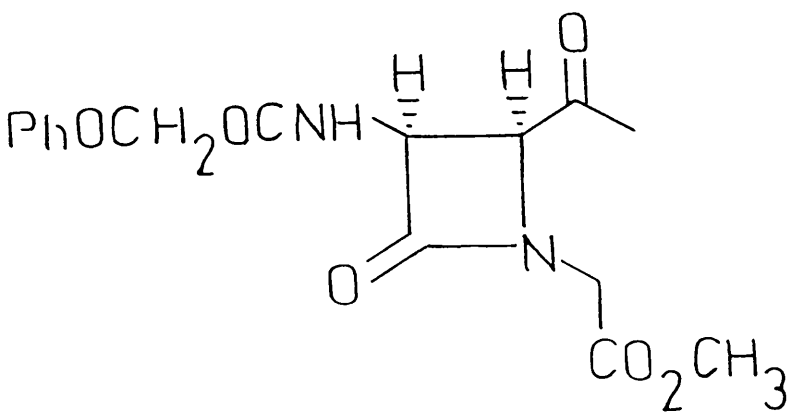


(257)

(253)

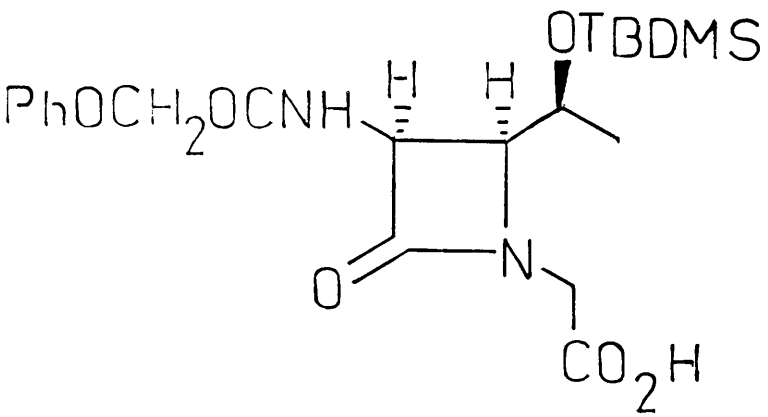


(254)

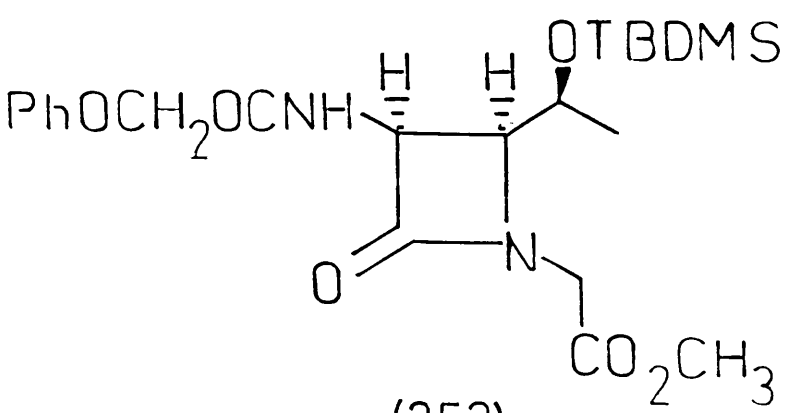


(255)

(251)


OTBDMS
PhOCH2OCNH
H
H
O
N
CO2H

(252)


OTBDMS
PhOCH2OCNH
H
H
O
N
CO2CH3

(253)

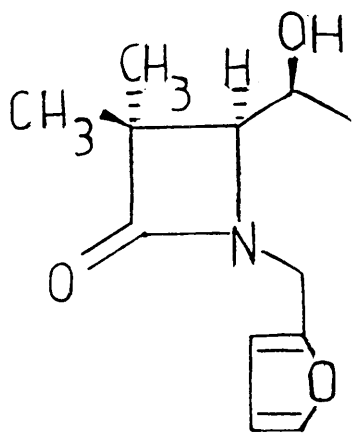
TBDMS triflate. This gave azetidinone (251) in an overall yield of 81% from phenoxyacetate (246). The facile selective phenoxyacetate hydrolysis of N-(furan-2-yl)methyl lactam (246) contrasts significantly with the difficulties experienced in attempted phenoxyacetate hydrolysis of methyl ester/lactam (248).

Lactam (251) was converted into acid (252) using Sharpless oxidation. Again, no attempt was made to purify or characterise this acid. Instead it was reacted directly with diazomethane to yield methyl ester (253) in 74% yield from furan (251).

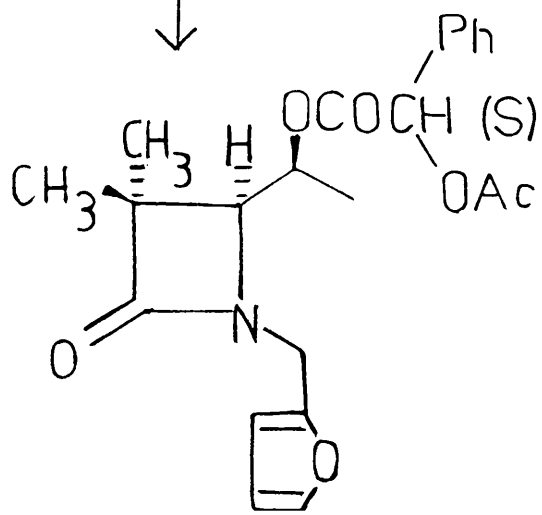
Cleavage of the silyl ether in compound (253) was achieved by treatment with TBAF in THF. This gave alcohol (254) in 92% yield. Oxidation to methyl ketone (255) was successfully carried out using the 3,5-dimethylpyrazole/chromium trioxide complex described[77] by Corey and Fleet. Ketone (255) was isolated in a yield of 83%, along with 9% of unreacted alcohol (254).

Methyl ketone (255) is, in fact a useful bicyclic β-lactam precursor in its own right. Palomo and co-workers have successfully homologated[78] several ketones of this type to 4-[(2-propanone)-1-yl] azetidinones using diazomethane. For example, azetidinone (256) has been converted into compound (257) in 43% yield. Base catalysed cyclisation of such compounds furnishes carbapenems. For example ketone (184) has been successfully cyclised[59(b)] selectively to bicyclic compound (186) or (187) as discussed previously (p 23).

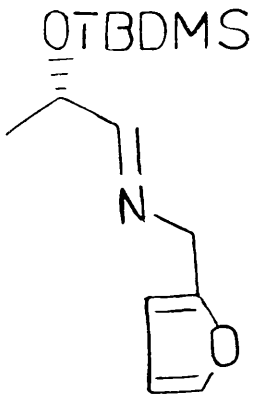
(258)



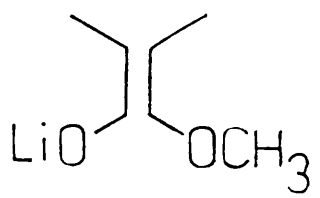
(259)

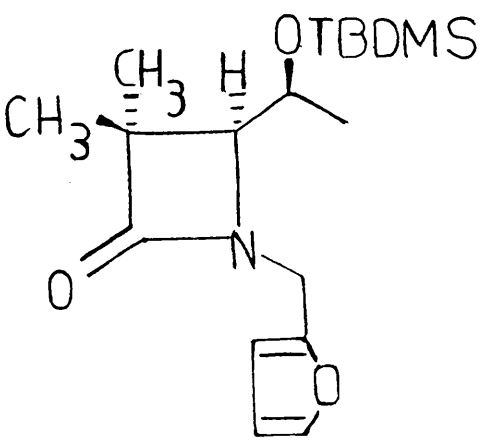


(260)

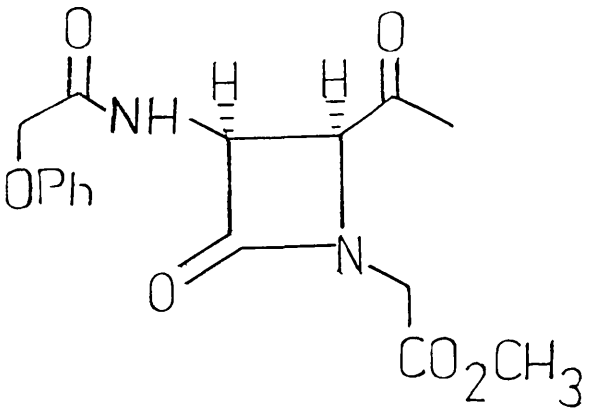


(230)

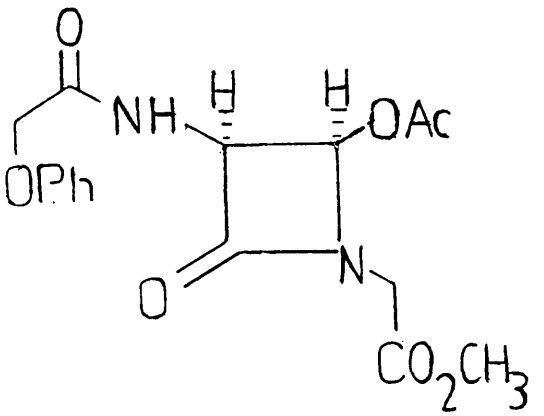




(258)



(255)



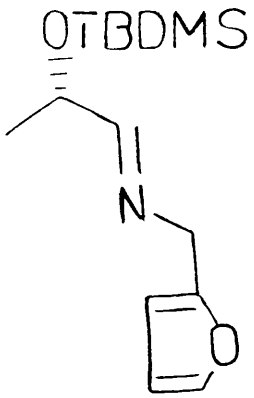
(243)

Conversion of methyl ketone (255) into the desired 4-acetoxy β-lactam (243) was easily carried out in excellent yield (93%) by reaction with mCPBA in reluxing benzene. The overall yield of compound (244) from homochiral imine (230) was 40%.

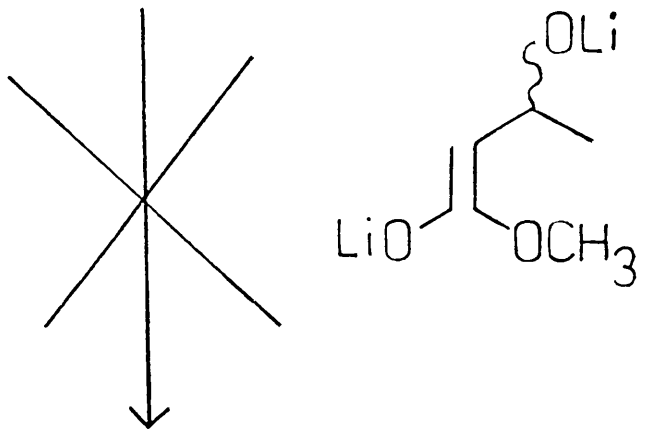
Clearly, therefore, this approach has been successful in achieving its goal of establishing a facile route to β-lactams of high optical purity and genuine synthetic potential.

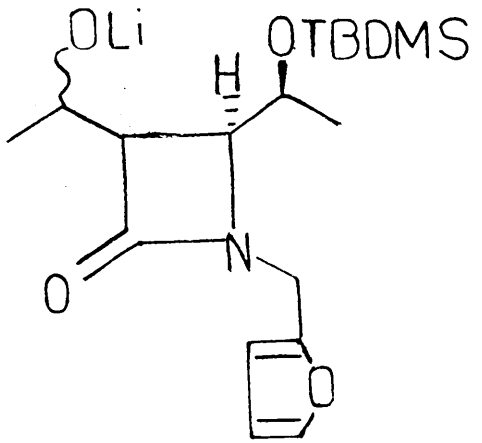
To extend further the applicability of this approach, a study was carried out on the feasibility of condensing imine (230) with lithium ester enolates. The fact that imine (230) had an α-proton and was therefore enolisable clearly represented a potential problem. However, when imine (230) was added at -78°C to the lithium ester enolate derived from methyl 2-methylpropionate and the reaction medium allowed to warm to room temperature over 12 hours, the 3,3-dimethyl β-lactam (258) was obtained in 58% yield, along with 29% of aldehyde (231) (presumably produced by hydrolysis of imine (230) during the acidic work up). Increasing the reaction time (either at -78°C or at room temperature) failed to improve the observed yield of β-lactam. NMR spectroscopy and capillary G.C. both showed that lactam (258) was produced with 89% d.e.

To establish the chiral integrity of lactam (258) it was desilylated to alcohol (259) and then coupled to (S)-O-acetylmandelic acid. This gave ester (260) in 84% overall yield. NMR spectroscopy indicated that

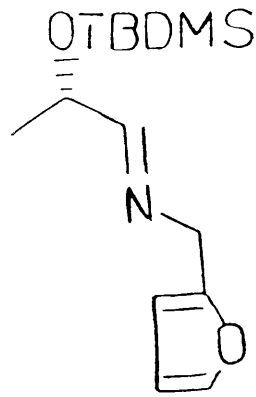


(230)





(262)



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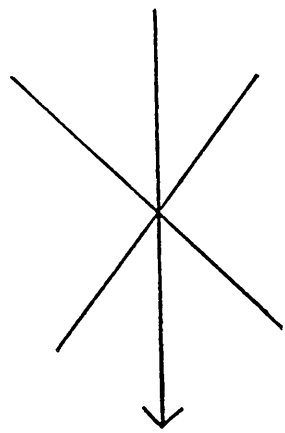
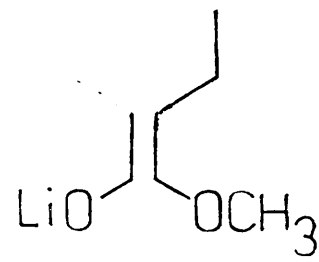
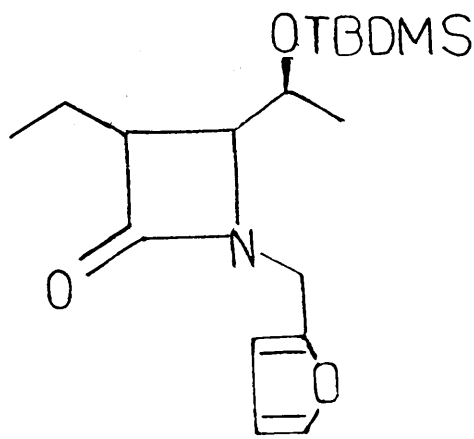




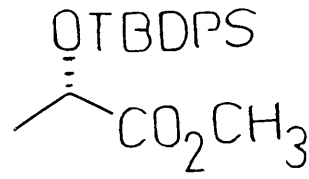


(261)

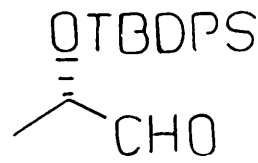
this compound was present as one diastereoisomer only. (Again it seems that the minor diastereoisomer present in lactam (258) was removed during sacrificial purification). When racemic aldehyde (231) was subjected to the same synthetic sequence ester (260) was produced as a 1:1 mixture of diastereoisomers. One of these corresponded (by NMR spectroscopy) to the single diastereoisomer produced when homochiral starting material was used. This established that 3,3-dimethyl lactam (258) was homochiral and therefore that imine (230) had not racemised under the reaction conditions.

Unfortunately, attempts to extend this reaction to the synthesis of azetidinones with more useful 3-alkyl substituents were unsuccessful. The lithium ester enolate from methyl propionate gave none of the desired 3-ethyl lactam (261) [a potential precursor of PS-5 (9)] when reacted with imine (230). Instead only aldehyde (231) was recovered, in 69% yield. Even the more reactive dianion from methyl 3-hydroxybutyrate yielded no trace of β-lactam; this was disappointing since the anticipated 3-[2-hydroxethyl] substituted lactam (262) would have been a possible precursor of thienamycin (6). As before, only aldehyde (231) was recovered after work up, this time in 73% yield.

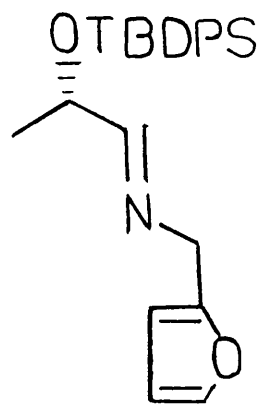
Both reactions were also carried out under a variety of conditions. However on no occasion was any detectable amount of β-lactam isolated. The failure of these two mono-substituted lithium ester enolates to react with imine (230) was not totally unexpected. Generally, the lithium ester enolate/imine condensation



(265)



(264)



(263)

has been successful only with N-silyl and N-phenyl imines, both of which are far more reactive electrophiles than N-alkyl imines such as (230).

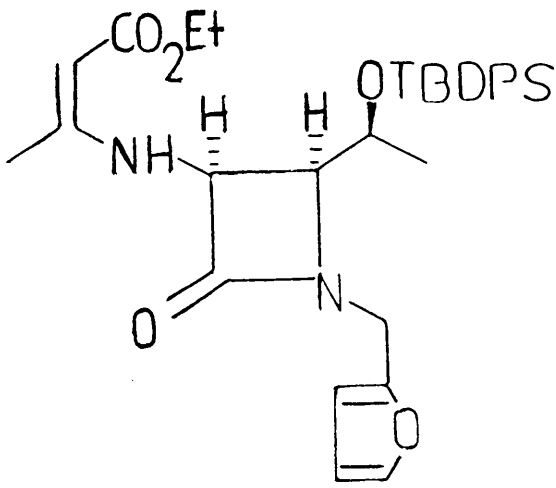
The fact that the lithium ester enolate derived from methyl 2-methylpropionate reacts with imine (230), albeit in a relatively modest yield, probably reflects the greater thermal stability of disubstituted ester enolates relative to monosubstituted species.

This failure of imine (230) to yield C-3 mono-alkylated azetidinones represents a significant limitation of its synthetic applicability. Overcoming this problem would therefore be a fruitful area for subsequent research.

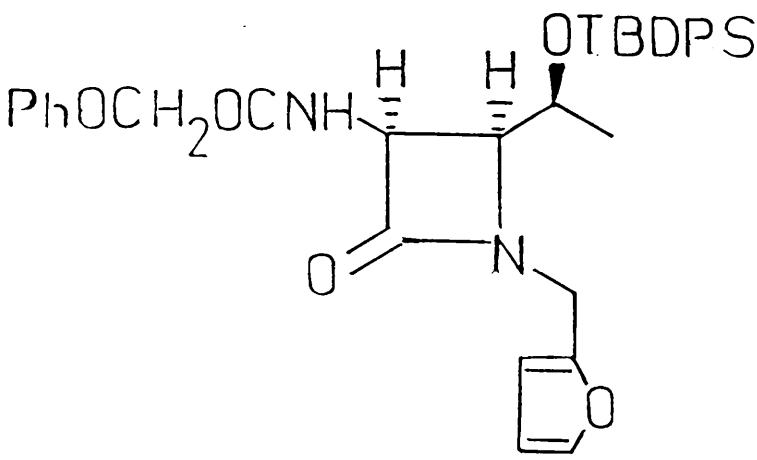
Finally, in an attempt to further improve the diastereoselectivities observed in this approach it was decided to prepare the homochiral O-TBDPS imine (263). It was hoped that the bulkier oxygen protecting group would increase the energy difference between the diastereoisomeric transition states leading to a particular β-lactam and hence increase the observed d.e's.

Thus O-TBDPS aldehyde (264) was prepared[73] by silylation of (S)-(-)-methyl lactate to give silyl ether (265) in 94% yield, followed by careful DIBALH reduction to the desired compound in 75% yield. Condensation of aldehyde (264) with freshly distilled furfurylamine (229) gave imine (263) in 91% yield, after purification by distillation.

(263)

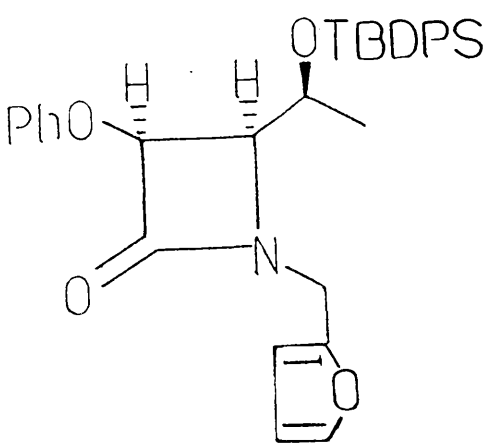


(267)



(268)

(263)



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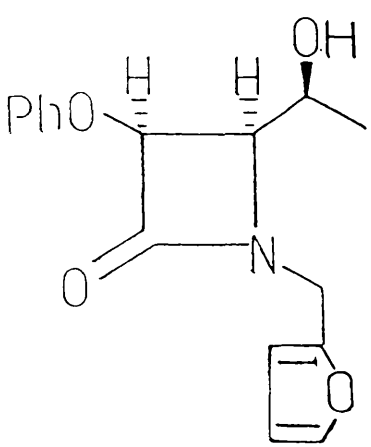
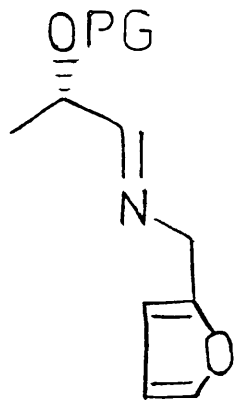


(233)

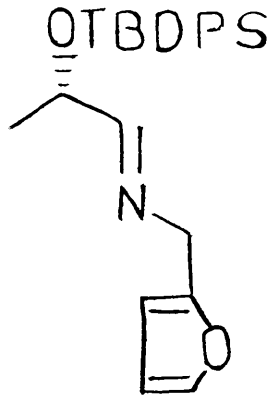
Imine (263) was then subjected to the same three β-lactam forming reactions as had been carried out on imine (230). Reaction with phenoxyacetic acid gave 3-phenoxy azetidinone (266) in 84% yield. ^{1}H NMR spectroscopy suggested that compound (266) was present as one diastereoisomer only. However, ^{13}C NMR spectroscopy showed that a trace of another compound (less than 5%) was in fact present. Unfortunately, at this time the capillary G.C. facility was unavailable. Packed column G.C. showed only one compound to be present. Desilylation of lactam (266) gave alcohol (233) with a measured $[\alpha]_D$ of -33.6^{o}. The corresponding O-TBDMS lactam yielded alcohol (233) with an $[\alpha]_D$ of -26.2^{o}. The relative values of these $[\alpha]_D$ measurements however, in reality gave no insight into the relative d.e's of β-lactams (232) and (266), since neither the sign not the magnitude of the optical rotation of any of the individual diastereoisomers present was known.

Next, imine (263) was reacted with Dane salt (214) to give the protected 3-amino lactam (267) in 85% yield. Both ^{1}H and ^{13}C NMR spectroscopy indicated that lactam (267) had been produced as one diastereoisomer only. Packed column G.C. also indicated that TBDPS ether (267) was present as a single compound.

Lactam (267) was readily converted into alcohol (254). Selective deprotection with 1M methanolic HCl followed by reaction with phenoxyacetyl chloride gave phenoxyacetamide (268) in good yield (96%). Sharpless



(272)



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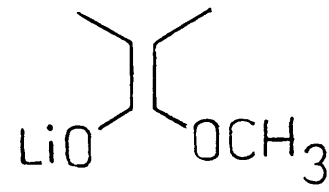
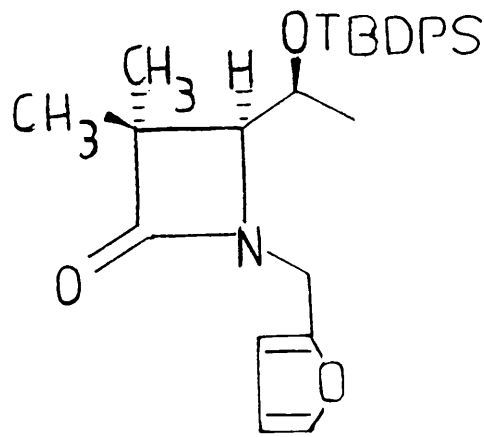
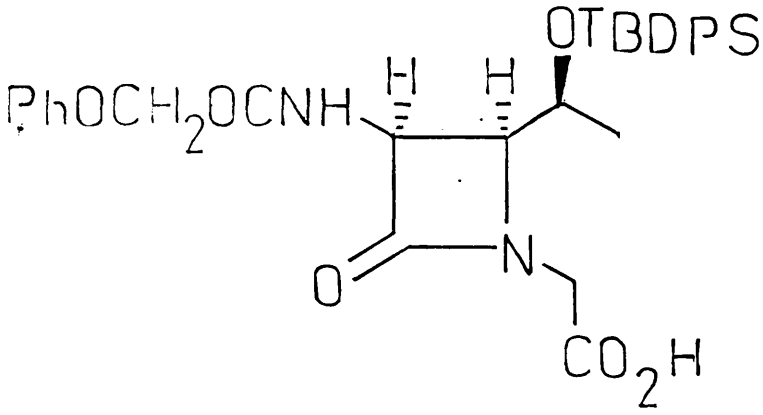


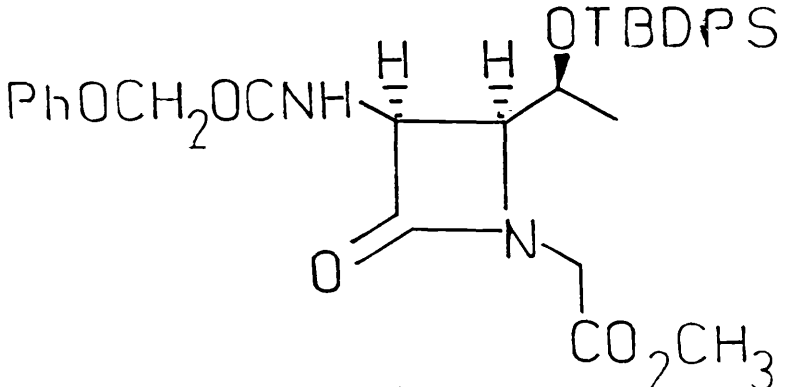


(271)

(268)


OTBDPS
PhOCH2OCNH
H
H
O
N
CO2H

(269)


OTBDPS
PhOCH2OCNH
H
H
O
N
CO2CH3

(270)

oxidation followed by diazomethane treatment of the resulting crude acid (269) gave methyl ester (270) in 82% yield for the two steps. Desilylation with TBAF gave alcohol (254) in 89% yield. The overall yield of 59% for these steps represents a significant improvement on the overall yield of 48% obtained for the conversion of O-TBDMS imine (230) into alcohol (254).

Finally imine (263) was reacted with the lithium ester enolate from methyl 2-methylpropionate. This gave 3,3-dimethyl β-lactam (271) in 63% yield, along with the recovery of 32% of aldehyde (264). Again, both ^{1}H and ^{13}C NMR spectroscopy indicated that lactam (271) had been produced as one diastereoisomer. Packed column G.C. also suggested that azetidinone (271) was present as a single compound.

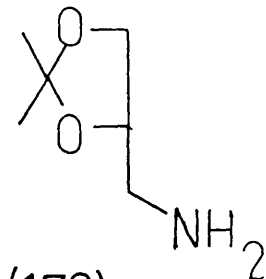
It can be concluded that O-TBDPS imine (263) may well allow the synthesis of synthetically useful β-lactams with even greater diastereoselectivities than those observed for the reactions of O-TBDMS imine (230). However, confirmation of the high D.E's apparently observed for the reactions of imine (263) is clearly needed. In the light of previous experience (with O-TBDMS compounds) this would be best achieved by using capillary G.C.

In conclusion O-protected imines (272) represent excellent starting materials for the synthesis of a range of useful azetidinones of high optical purity. Future work on extending this approach to allow the synthesis of C-3 mono-alkylated β-lactams could be particularly rewarding.

Experimental

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected. Bulb to bulb distillations were carried out on a Buchi GKR-50 Kugelrohr. Recorded boiling ranges refer to the indicated air-bath temperature. ^{1}H NMR spectra were recorded on a Bruker WP200 SY or AM 200 spectrometer, both operating at 200 MHz. ^{13}C NMR spectra were recorded on a Bruker WP 200 SY spectrometer or on a Bruker AM 200 spectrometer , both operating at 50MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.00 ppm), using Me_4Si or the 7.25 residual chloroform peak and the 77.0 ppm $CDCl_3$ peak as internal references for ^{1}H and ^{13}C NMR spectra respectively. ^{1}H NMR data are reported using the following convention: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The multiplicities of all the ^{13}C spectral resonances were determined by the use of DEPT spectra[79] with pulse angles, $\theta = 90^{o}$ and 135^{o}. Infra-red spectra were determined on a Perkin-Elmer 580 spectrometer. Low resolution mass spectra were determined on a VG upgraded MS12 instrument and high resolution mass spectra were determined on a MS 902S. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Capillary GC was carried out on a Hewlett-Packard 5880A G.C. fitted with a 25mxO-32mm I.D.CP Sil 5CB fused-silica capillary. Packed column G.C. was carried out on a Perkin-Elmer F33 G.C. fitted with a 6ft. 1% OV-1 GCQ 100/120 mesh packed column.

Reactions were normally carried out under an atmosphere of nitrogen. All solvents and reagents used were analytical grade where possible. THF and ether were distilled freshly from sodium/benzophenoneketyl. All of the following reagents/solvents were stored, after purification, over 4 Å molecular sieves, under nitrogen : dichloromethane (distilled fron CaH_2); benzene (distilled from P_2O_5 and filtered through Grade 1 basic alumina); phenoxyacetyl chloride; pyridine and diisopropylamine (both distilled from KOH). Triethylamine was distilled from and stored over KOH. All column chromatography was carried out using the dry column flash chromatography technique described by Harwood.[80] All organic solutions were dried over sodium sulphate. Light petrol refers to that fraction boiling between 40 and 60°C.



(170)

[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]amine (170).

(i) From Tosylate (273).[55]

Tosylate (273) (15.01g, 52.48mmol) and liquid ammonia (30ml) were placed in a sealed tube at -78°C and the reaction was stirred at room temperature for 98 h.

After evaporation of the ammonia anhydrous ether (100ml) was added and the ammonium p-toluenesulphonate removed by filtration. Careful concentration in vacuo gave the crude product.

Distillation gave amine (170) (3.64g, 27.8mmol, 53%) as a clear oil, b.p. 102°C/18mm Hg.

(ii) From Phthalimide (212)

(a) Hydrazine Cleavage

N-alkylphthalimide (212) (601mg, 2.30mmol) was dissolved in absolute ethanol (20.00ml) and hydrazine hydrate (0.14ml, 2.69mmol) was added, with stirring, at room temperature. The system was brought to reflux over 30 min, by which time copious amounts of a white precipitate had formed. The reaction was stirred at reflux for a further 8 h and then allowed to cool to room temperature. The reaction mixture was then added to ether (50ml) and the resulting slurry filtered through Celite. The ether was carefully removed in vacuo and then the ethanol was separated from the amine by distillation. This gave the desired amine (170) (107.4mg, 0.81mmol, 35%) as a clear oil, b.p. 82°C/20mm

Hg.

(b) Methyl Hydrazine Cleavage

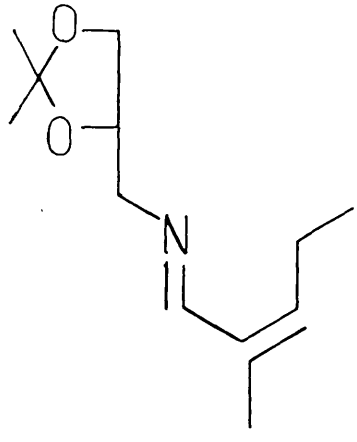
N-alkylphthalimide (212) (609mg, 2.33mmol) was dissolved in dichloromethane (25.0ml) and methylhydrazine (149μL, 2.80mmol) was added, with stirring at room temperature. The system was brought to reflux over 30 min, by which time copious amounts of a white precipitate had formed. The reaction was stirred at reflux for a further 8 h and then allowed to cool to room temperature. The reaction mixture was then filtered through Celite and the solvent carefully removed in vacuo. This gave the crude product. Purification by distillation gave pure amine (170) (287.7mg, 2.17mmol, 93%) as a clear oil, b.pt. 82°C/20mm Hg.

ν_{max} ($CHCl_3$) 3 670 cm^{-1}, 3 400 cm^{-1}

Found: M^+ 131.0958. $C_6H_{13}NO_2$ requires 131.09462.

C	(P.P.M)	Multiplicity
$C(CH_3)_2$	108.38	s
CHO	76.79	d
CH_2O	66.30	t
CH_2N	44.12	t
CH_3	26.24	q
CH_3	24.74	q

H	(P.P.M)	J(Hz)	Multiplicity
CHO	3.82	-	m
CH_2O	3.74 ↕ 2.49		m
CH_2N			
NH_2	1.17	-	s
CH_3	1.12	-	s
CH_3	1.06	-	s



(210)

N-[(Z-2-Pentene-2-yl)methylene]-(2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (210).

Oven dried potassium carbonate (2.50g) was placed in a dry, round bottomed flask and amine (170) (301mg, 2.29mmol) in ether (15.0ml) was added, followed by freshly distilled aldehyde (194)[62] (224mg, 2.29mmol) in ether (15.0ml).

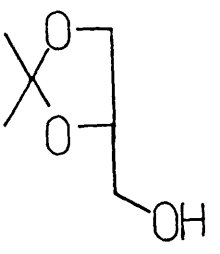
After stirring for 14 h, the reaction was halted and the potassium carbonate was removed by filtration. Concentration in vacuo followed by purification by bulb-to-bulb distillation gave imine (209) (441mg, 2.08mmol, 91%), as a clear oil, b.p. 100°C/2mm Hg.

ν_{max} ($CHCl_3$) 1 640 cm^{-1}, 1 630 cm^{-1}

Found : M^+, 211.1549. $C_{12}H_{21}NO_2$ requires 211.15722.

C	(P.P.M)	Multiplicity
HC=N	167.748	d
$CH_2CH=C$	144.282	d
$C(CH_3)=CH-$	135.098	s
$C(CH_3)_2$	109.10	s
CHO	75.56	d
CH_2O	67.69	t
CH_2N	63.52	t
$C(CH_3)_2$	26.72	q
$C(CH_3)_2$	25.65	q
CH_2CH_3	21.69	t
$CCH_3=CH-$	13.35	q
CH_2CH_3	11.25	q

H	(P.P.M)	J(Hz)	Multiplicity
CH=N	7.77	-	s
$CH_2CH=C$	5.83	7.00	t
	4.28		
CH_2O }	↕		m
CH_2N }			
	3.58		
CHO	3.50	-	m
CH_2CH_3	2.20	7.06, 7.51	d,q
$C(CH_3)=C$	1.86	-	s
$C(CH_3)_2$	1.36	-	s
$C(CH_3)_2$	1.31	-	s
CH_2CH_3	0.97	7.54	t



(211)

(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol (211)

(A) Homochiral[67B]

1,2,5,6-diacetonemannitol (1.90g, 7.30 mmol), prepared by the procedure of Baer[67A], was added over 5 min to an aqueous solution of sodium periodate (2.20g, 11.40 mmol, in 32.0ml of water) at $0^{o}C$ and with continuous stirring. After stirring for a further 5 min. sodium borohydride (0.64g, 16.8 mmol), was added slowly and in small portions (to avoid foaming) to the reaction. The reaction was allowed to stir at $0^{o}C$ for a further 3 h, whereupon the reaction mixture was neutralised with 10% acetic acid. The resulting aqueous solution was saturated with sodium chloride, filtered and then extracted with ethyl acetate (4 x 20ml). The combined organic extracts were dried and the solvent removed <u>in vacuo</u> to give the crude product.

Distillation furnished pure <u>alcohol</u> (211) (1.51g, 11.51 mmol, 79%) as a clear oil, b.p. $81^{o}C/10mm$ Hg.

$[\alpha]_D^{20}$ + 14.2^{o} (c.1.59, in EtOH)

{lit.[67B] $[\alpha]_D^{20}$ + 14.5)c.1.0, in EtOH)}

(A) Racemic[67]

Acetone (150.0ml, 118.6g, 2.04 moles) and glycerol (51.3g, 0.56 moles) were placed in a Dean and Stark apparatus, along with light petrol (150ml) and p-toluenesulphonic acid (1.49g, 8.5 mmoles). The system was heated under reflux until no more water collected (24h). It was then allowed to cool to room temperature whereupon oven-dried sodium acetate (3.08g, 51 mmoles) was added. After stirring for 1 h, the

reaction mixture was filtered with suction, through Celite and the solvents removed in vacuo.

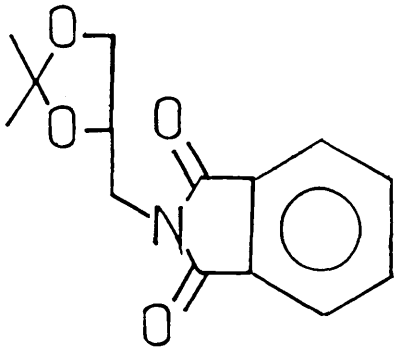
Purification by distillation gave alcohol (211) (58.63g, 0.45 mmol, 80%) as a clear oil, b.p. 60°C/6mm Hg.

ν_{max} ($CHCl_3$) 3 450 cm^{-1}.

Found : M^+ - Me, 117.0553. $C_6H_{12}O_3$ - Me requires 117.05517.

C	δ(P.P.M)	Multiplicity.
$C(CH_3)_2$	109.26	s
CHO	76.07	d
CH_2O	65.67	t
CH_2O	62.90	t
CH_3	26.58	q
CH_3	25.15	q

H	δ(P.P.M)	J (Hz)	Multiplicity
CHO	4.18	-	m
CH_2O	3.99 ↕ 3.54		m
CH_3	1.38	-	s
CH_3	1.32	-	s



(212)

N-(2,2-Dimethyl-1,3-dioxolan-4-yl)methylphthalimide (212)

To a stirred solution of alcohol (211) (2.00g, 15.15mmol) in THF (40ml) under N_2, was added sequentially Ph_3P (3.89g, 14.83mmol, in 40ml THF), phthalimide (2.23g, 15.15mmol in 40ml THF) and diethyl azodicarboxylate (2.90g, 2.63ml, 16.67 mmol). After stirring for 72 h, the solvent was removed in vacuo to yield a yellow, semisolid material. Ether/hexane (1:1, 50ml) was added and the resulting white solid was removed by filtration. This solid was washed with ether/hexane (1:1, 250ml). The combined filtrates were concentrated to give a yellow oil which solidified slowly on standing. Column chromatography followed by recrystallisation (ether/hexane) gave phthalimide (212) (3.65g, 14.83mmol, 91%) as a white solid, m.p. 105-106°C.

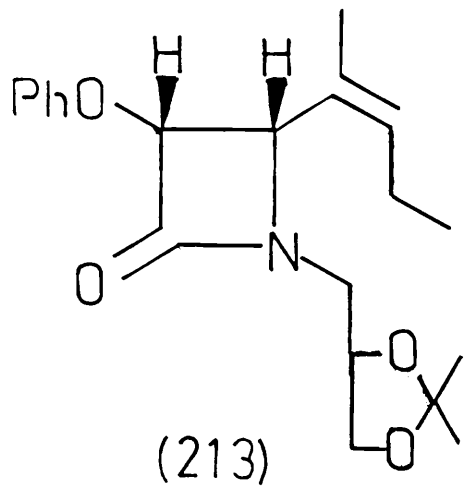
ν_{max} ($CHCl_3$) 1 740 cm^{-1}, 1 715 cm^{-1}.

Found : M-Me, 246.0764. $C_{14}H_{15}NO_4$-Me requires 246.07663.

Found : C 64.31; H 5.76; N 5.35%. $C_{14}H_{15}NO_4$ requires C 64.36, H 5.79; N. 5.36%.

C	(P.P.M)	Multiplicity
NCO	168.18	s
CH(Ar)	133.99	d
O=C-C(Ar)	131.91	s
CH(Ar)	123.32	d
$C(CH_3)_2$	109.78	s
CHO	73.24	d
CH_2O	67.27	t
CH_2N	40.89	t
CH_3	26.77	q
CH_3	25.30	q

H	(P.P.M)	J(Hz)	Multiplicity
α -C_6H_5	7.83	5.47, 3.10	d,d
β -C_6H_5	7.70	5.47, 3.09	d,d
CHO	4.42	-	m
CH_2O	4.05 ↕ 3.69		m
CH_2N			
CH_3	1.41	-	s
CH_3	1.28	-	s



(213)

cis-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-[1-methylpropen-1-yl]-3-phenoxy-2-azetidinone (213).

To a stirred solution of imine (210) (1.00g, 4.74mmol) in CH_2Cl_2 (5.5ml) under nitrogen were added sequentially triethylamine (2.00ml, 14.22mmol, 3 equivalents) and phenoxyacetic acid [0.72g, 4.74mmol, in CH_2Cl_2(5.5ml)]. Finally phenyl dichlorophosphate (0.71ml, 4.74mmol) was added dropwise over 5 min.

The reaction was stirred for 24 h whereupon it was washed with water (40ml) and dried. Concentration and purification by chromatography yielded cis-β-lactam (213) (1.36g, 3.94mmol, 83%) as a clear, viscous oil.

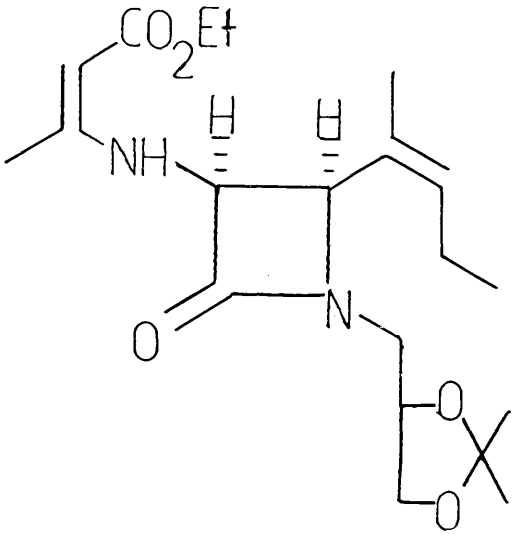
Capillary GC of compound (213) thus prepared showed it to be a 1.45:1 mixture of diastereoisomers.

ν_{max} ($CHCl_3$) 1 750 cm^{-1}

Found : M^+, 345.1934. $C_{20}H_{27}NO_4$ requires 345.194009.

C	(P.P.M)	Multiplicity
2	166.32	s
	165.73	s
O-C(Ar)	156.90	s
C=CH-CH_2	135.23	d
	135.11	d
m-C_6H_5	129.15	d
	129.02	d
C(CH_3)=CH	127.65	s
	127.60	s
p-C_6H_5	121.64	d
	121.60	d
o-C_6H_5	115.15	d
	115.11	d
C(CH_3)$_2$	109.51	s
	109.26	s
3	81.55	d
	81.42	d
CHO	74.11	d
	72.89	d
CH_2O	67.05	d
	66.84	d
4	66.43	d
	66.20	d
CH_2N	43.61	t
	42.54	t
	26.82	q
	26.56	q
C(CH_3)$_2$	25.00	q
	24.81	q
CH_2CH_3	20.79	t
C(CH_3)=CH	13.27	q
	13.24	q
CH_2CH_3	12.62	q
	12.53	q

H	(P.P.M)	J(Hz)	Multiplicity
m-C_6H_5	7.22-7.08	-	m
o-C_6H_5	6.96-6.78	-	m
p-C_6H_5			
$C(CH_3)=CH$	5.46	7.18	t
3	5.30	4.58	d
	5.29	4.53	d
	4.45	4.56	d
4			
	4.38	4.62	d
CHO	4.23	-	m
	4.02		
CH_2O			m
CH_2N			
	2.83		
CH_2CH_3	1.93	7.58, 7.23	d,q
$C(CH_3)=CH$	1.54	-	s
	1.39	-	s
$C(CH_3)_2$	1.35	-	s
	1.27	-	s
CH_2CH_3	0.76	7.58	t



(215)

cis-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-3-[(α-methyl-β-ethoxycarbonyl)vinylamine]-4-[(1-methylpropen-1-yl]-2-azetidinone (215).

To freshly prepared[70] Dane salt (214) (338mg, 1.502mmol) in CH_2Cl_2 (4ml) in a dry round bottomed flask with side arm, under nitrogen, was added, with stirring, triethylamine (0.59ml, 4.51mmol, 3 equivalents) followed by imine (210) (317.0mg, 1.502mmol) in CH_2Cl_2 (4ml).

The reaction mixture was cooled to 0^oC and phenyl dichlorophosphate (0.22ml, 1.50mmol) was added dropwise. This mixture was stirred for 14 h at room temperature whereupon it was washed sequentially with water (2 x 5ml) and 5% sodium bicarbonate solution (8ml). The organic extract was dried and concentrated in vacuo; purification of the crude product by chromatography gave lactam (215) (498.4mg, 1.310mmol, 87%) as a clear viscous oil.

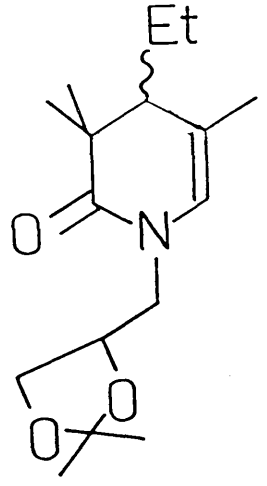
Capillary G.C. showed that compound (215) was a 1.7:1 mixture of diastereoisomers.

ν_{max} ($CHCl_3$) 3 230 cm^{-1}, 1 765 cm^{-1} 1 660 cm^{-1} 1 610 cm^{-1}.

Found: M^+, 380.2310. $C_{20}H_{32}N_2O_5$ requires 380.23112.

C	(P.P.M)	Multiplicity
	169.57	s
CO_2CH_2	167.41	s
2	166.81	s
NHC=C	159.02	s
CH_2-CH=C	133.07	d
	127.49	s
$C(CH_3)$=C	127.33	s
	109.64	s
$C(CH_3)_2$	109.38	s
NH-C=CH	85.44	d
	74.29	d
CHO	73.02	d
	67.15	t
CH_2O	66.61	t
4	64.95	d
	64.63	d
3	63.02	d
	62.89	d
CO_2CH_2	58.28	t
CH_2N	43.81	t
	42.61	t
	26.69	q
	26.64	q
$C(CH_3)_2$	25.13	q
	24.84	q
C=C-CH_2	21.11	t
	19.53	q
	14.35	q
CH_3	13.95	q
	13.91	q
	13.53	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	8.70	9.30	d
$C=CHCH_2$	5.42	7.03	t
	4.85	5.08, 9.31	d,d
3			
	4.85	5.02, 9.28	d,d
$C=CHCO_2$	4.45	-	s
	4.34	4.99	d
4	4.27	4.96	d
CHO	4.19	-	m
	3.98	7.16	q
$CO_2CH_2CH_3$	3.98	7.20	q
	3.65		
CH_2O			m
CH_2N			
	2.85		
$C=C-CH_2-CH_3$	2.08	7.08, 7.53	d,q
	1.86	-	s
$C=C-CH_3$	1.54	-	s
	1.37	-	s
	1.32	-	s
$C(CH_3)_2$	1.26	-	s
	1.25	-	s
	1.14	7.29	t
CH_2CH_3	0.94	7.50	t



(21G)

3,4-Dihydro-3,3-dimethyl-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-ethyl-5-methyl-2-pyridone (216)

To a dry round bottom flask with side arm, under nitrogen, was added THF (3ml) and diisopropylamine (0.186ml, 1.328 mmol). This solution was cooled to $O^{o}C$ and n-butyllithium (0.89ml of a 1.49M solution in hexanes, 1.33mmol) was added dropwise, over 5 min, with vigorous stirring. This solution was stirred for a further 15 min at $O^{o}C$, whereupon methyl 2-methylpropionate (0.132g, 0.136ml, 1.303mmol) was added over 5 min.

After stirring for a further 30 min at $O^{o}C$ the flask was cooled to $-78^{o}C$ and imine (210) (255.5mg, 1.207mmol) in THF (10ml) was added dropwise over 5 min.

The cooling bath was allowed to warm slowly to room temperature over 4-5h, and the reaction was then stirred for an additional 11 h at room temperature. It was then diluted with ether (25ml) and washed sequentially with 10% aqueous acetic acid (3 x 20ml), saturated sodium bicarbonate solution (2 x 25ml) and brine (25ml). The organic layer was dried and concentrated in vacuo.

Purification by column chromatography gave pure pyridone (216) (261.5 mg 0.929mmol, 77%) as a clear viscous oil, along with aldehyde (194) (14.5 mg 0.148 mmol, 12%).

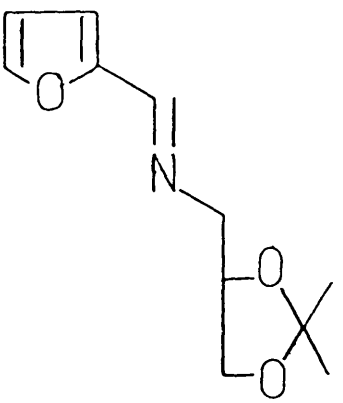
Capillary G.C. of pyridone (216) showed it to be a 2:1 mixture of diastereoisomers.

ν_{max} ($CHCl_3$) 3 300 cm^{-1} (broad), 1 655 cm^{-1}

Found: M^+, 281.1976. $C_{16}H_{27}NO_3$ requires 281.19909.

C	(P.P.M)	Multiplicity
NCO	175.29	s
N-CH=C	124.50	d
	124.26	d
C=C-CH_3	117.39	s
	116.97	s
$O_2C(CH_3)_2$	109.08	s
	108.95	s
CHO	74.81	d
	74.71	d
CH_2O	67.19	t
	67.08	t
CH-CH_2CH_3	49.71	d
	49.50	d
CH_2N	48.29	t
	47.82	t
CH-$C(CH_3)_2$	40.30	s
	40.02	s
CH_2CH_3	29.67	t
CH_3	26.68	q
CH_3	26.46	q
CH_3	26.11	q
CH_3	25.47	q
CH_3	25.30	q
CH_2-CH_3	21.57	t
CH_3	21.24	q
CH_3	21.37	q
CH_3	20.33	q
CH_3	19.88	q
CH_3	10.77	q
CH_3	9.68	q

H	(P.P.M)	J (Hz)	Multiplicity
NCH=C-	5.92	1.45	q
	5.89	1.50	q
CHO	4.20	-	m
CH_2O	3.97		
CH_2N			
	3.42	14.04, 5.02	d,d
$C=CCH_3$	1.74	1.50	d
	1.72	1.52	d
CHC=C	1.68	-	m
CH_2-CH_3	1.45	-	m
CH_3	1.40	-	s
CH_3	1.40	-	s
CH_3	1.39	-	s
CH_3	1.39	-	s
CH_3	1.30	-	s
CH_3	1.26	-	s
CH_3	1.16	-	s
CH_3	1.10	-	s



(217)

N-[(Furan-2-yl)methylene]-(2,2-dimethyl-1,3-dioxolan-4-yl)methanamine (217)

Oven dried potassium carbonate (2.00g, 14.5 mmol) was placed in a dry round bottomed flask and amine (170) (251mg, 1.91mmol) in ether (10ml) was added, followed by freshly distilled furfuraldehyde (182mg, 1.91 mmol) in ether (10ml).

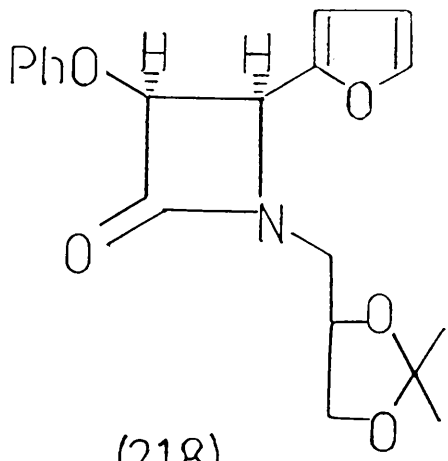
After stirring for 14 h, the potassium carbonate was removed by filtration. Concentration in vacuo followed by short-path distillation gave pure imine (217) (391 mg, 1.87 mmol, 98%) as a clear oil, b.p. 102°C/1mm Hg.

ν_{max} ($CHCl_3$) 1 640 cm^{-1}

Found: M^+, 209.1056. $C_{11}H_{15}NO_3$ requires 209.10156.

C	(P.P.M)	Multiplicity
CH=N	151.25	d
Furan-2-C	151.058	s
Furan-5-C	144.58	d
Furan-3-C	114.20	d
Furan-4-C	111.35	d
$C(CH_3)_2$	108.98	s
CHO	74.99	d
CH_2O	67.27	t
CH_2N	63.99	t
CH_3	26.57	q
CH_3	25.20	q

H	(P.P.M)	J (Hz)	Multiplicity
CH=N	8.00	-	s
Furan-5-H	7.39	1.71	d
Furan-3-H	6.65	3.42	d
Furan-4-H	6.35	3.43, 1.78	d,d
CHO	4.33	-	m
CH_2O	3.97		
CH_2N	3.60		
CH_3	1.24	-	s
CH_3	1.29	-	s



(218)

cis-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-(furan-2-yl)-3-phenoxy-2-azetidinone (218)

To a stirred solution of imine (217) (0.42g, 2.01mmol) in CH_2Cl_2 (2.5ml) under nitrogen was added sequentially triethylamine (0.85ml, 6.03mmol) and phenoxyacetic acid (0.30g, 2.01mmol) in CH_2Cl_2 (2.5ml). Finally phenyl dichlorophosphate (0.30ml, 2.01mmol) was added dropwise over 5 min.

The mixture was stirred for 24 h whereupon it was washed with water (18ml) and dried (Na_2SO_4). Removal of solvent gave a tarry solid.

Purification by chromatography gave cis-β-lactam (218) (0.599g, 1.75mmol, 87%) as a white, amorphous solid. Repeated attempts to crystallise this solid were unsuccessful.

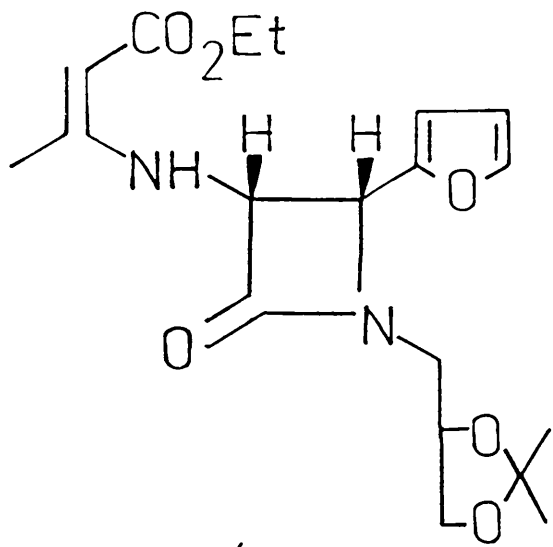
Capillary G.C. showed that β-lactam (218) was a 1.4:1 mixture of diastereoisomers.

ν_{max} ($CHCl_3$) 1 760 cm^{-1}

Found: M^+, 343.1400. $C_{19}H_{21}NO_5$ requires 343.14197.

C	(P.P.M)	Multiplicity
	166.00	s
2	165.42	s
-O-C(Ar)	156.90	s
	147.25	s
Furan-2-C	147.17	s
	143.19	d
Furan-5-C	143.13	d
m-C_6H_5	129.22	d
	122.10	d
p-C_6H_5	122.02	d
	115.39	d
o-C_6H_5	115.31	d
	110.77	d
Furan-4-C	110.66	d
Furan-3-C	110.59	d
	109.81	s
$C(CH_3)_2$	109.51	s
3	82.16	d
	82.09	d
	74.36	d
CHO	72.95	d
	67.07	t
CH_2O	66.95	t
4	57.25	d
	56.84	d
CH_2N	43.76	t
	42.65	t
CH_3	26.78	q
CH_3	26.70	q
CH_3	25.17	q
CH_3	24.89	q

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.30	0.78, 1.90	d,d
	7.29	0.81, 1.83	d,d
m-C_6H_5	7.12	7.18, 7.81	d,d
p-C_6H_5	6.86	7.15	t
o-C_6H_5	6.75	7.65	d
Furan-3-H	6.34	-	m
Furan-4-H	6.25	1.77, 3.33	d,d
	5.42	4.44	d
3	5.41	4.25	d
	5.16	4.27	d
4	5.07	4.36	d
CHO	4.26	-	m
	4.06		
CH_2O			
CH_2N			
	2.91		
	1.38	-	s
CH_3	1.25	-	s
	1.23	-	s



(219)

cis-1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-(furan-2-yl)-3-[(α-methyl-β-ethoxycarbonyl)vinylamino]-2-azetidinone (219).

To freshly prepared[70] Dane salt (214) (234mg, 1.039 mmol) in CH_2Cl_2 (2.5ml) in a dry round bottom flask with side arm, under nitrogen, was added with stirring, triethylamine (0.41ml, 3.12 mmol) followed by imine (217) [(217.1mg, 1.039mmol) in CH_2Cl_2 (2.5ml)].

The reaction mixture was cooled to 0^oC and phenyl dichlorophosphate (0.15ml, 1.039 mmol) was added dropwise. This mixture was stirred for 14 h at room temperature whereupon it was washed sequentially with water (2 x 3ml) and 5% sodium bicarbonate solution (5ml). The organic layer was dried and concentrated <u>in vacuo</u> to give the crude product as a viscous oil.

Purification by chromatography yielded <u>lactam</u> (219) (322mg, 0.852 mmol, 82%) as a white, amorphous solid which, despite repeated attempts, could not be crystallised.

Capillary G.C. showed β-lactam (219) to be a 1.6:1 mixture of diastereoisomers.

ν_{max} ($CHCl_3$) 1 765 cm^{-1}, 1 660 cm^{-1}, 1 615 cm^{-1}

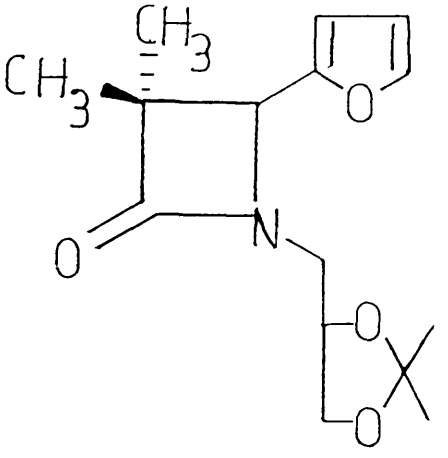
Found: M^+, 378.1773. $C_{19}H_{26}N_2O_6$ requires 378.17908.

C	(P.P.M)	Multiplicity
	169.95	s
CO_2CH_2	167.10	s
2	167.00	s
N-C=C	159.05	s
Furan-2-C	150.01	s
Furan-5-C	142.60	d
	142.58	d
Furan-4-C	110.40	d
Furan-3-C	110.36	d
$C(CH_3)_2$	109.53	s
	109.17	s
Furan-4-C	109.15	d
Furan-3-C	108.98	d
NH-C=CH	85.40	d
CHO	74.19	d
	73.01	d
CH_2O	67.18	t
	66.67	t
4	64.99	d
	64.68	d
CO_2CH_2	58.31	t
3	63.09	d
	62.85	d
CH_2N	43.81	t
	42.68	t
	26.73	q
$C(CH_3)$	26.64	q
	25.13	q
	25.01	q

C	(P.P.M)	Multiplicity
CH_2CH_3	19.56	q
	14.15	q
$C(CH_3)=CH$	13.99	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	8.75	9.80	d
Furan-5-H	7.35	0.85, 1.86	d,d
Furan-4-H	6.28	1.86, 3.25	d,d
Furan-3-H	6.24	0.88, 3.23	d,d
4	4.95	4.39	d
	4.93	4.28	d
3	4.80	4.25, 9.75	d,d
	4.78	4.41, 9.79	d,d
C=CH	4.58	-	s
	4.29	-	m
CHO	4.12	-	m
	4.01	7.14	q
$CO_2CH_2CH_3$	4.00	7.14	q
	3.98-3.70	-	m
CH_2O	3.58		
CH_2N			
	2.91	7.77, 14.27	d,d
$C(CH_3)=CH-$	1.85	-	s
	1.71	-	s

H	(P.P.M)	J (Hz)	Multiplicity
	1.31	-	s
	1.30	-	s
$C(CH_3)_2$	1.26	-	s
	1.24	-	s
CH_2CH_3	1.10	-	t
	0.99	-	t



(220)

3,3-Dimethyl-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(furan-2-yl)-2-azetidinone (220).

To a dry round bottom flask with side-arm, under nitrogen, was added THF (2ml) and diisopropylamine (0.143ml, 1.023 mmol). This solution was cooled to $0^{o}C$ and n-butyllithium (0.42ml of a 2.45M solution in hexanes, 1.02mmol) was added dropwise, over 5 min, with vigorous stirring. The solution was stirred for a further 15 min at $0^{o}C$ whereupon methyl 2-methylpropionate (0.102g, 0.105ml, 1.023 mmol) was added over 5 min.

After stirring for a further 30 min at $0^{o}C$ the flask was cooled to $-78^{o}C$ and imine (217) (194.3mg, 0.930mmol) in THF (10ml) was added dropwise over 5 min. The cooling bath was allowed to warm slowly to room temperature over 4-5 h and the reaction was then stirred for an additional 11 h at room temperature. It was then diluted with ether (20ml) and washed sequentially with 10% aqueous acetic acid (3 x 20ml), saturated sodium bicarbonate solution (2 x 20ml) and brine (20ml). The organic extract was dried (Na_2SO_4) and concentrated <u>in vacuo</u>.

The crude product thus obtained was purified by chromatography to give β-<u>lactam</u> (220) (178.0mg, 0.637 mmol, 69%) as a clear viscous oil. Also recovered was a small amount (12.6mg, 0.132 mmol, 14%) of furfuraldehyde.

Capillary G.C. showed that β-lactam (220) was a

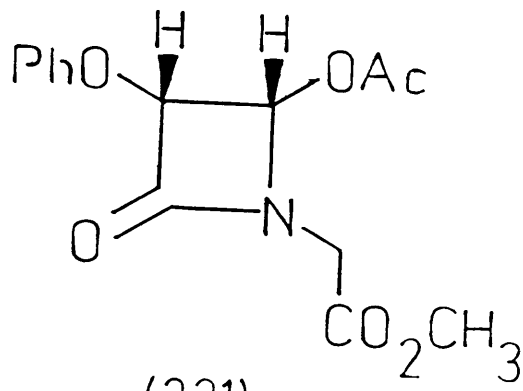
1.6:1 mixture of diastereoisomers.

ν_{max} ($CHCl_3$) 1 735 cm^{-1}

Found: M^+, 279.1467. $C_{15}H_{21}NO_4$ requires 279.14705.

C	(P.P.M)	Multiplicity
	174.27	s
2	173.70	s
Furan-2-C	150.12	s
Furan-5-C	142.75	d
	142.69	d
Furan-4-C	110.42	d
Furan-3-C	110.38	d
$\underline{c}(CH_3)_2$	109.60	s
	109.17	s
Furan-4-C	109.17	d
Furan-3-C	108.92	d
CHO	74.49	d
	73.55	d
CH_2O	67.20	t
	66.78	t
4	62.09	d
3	56.86	d
	56.72	d
CH_2N	43.36	t
	41.71	t
CH_3	26.74	q
	26.61	q
CH_3	25.21	q
	24.78	q
CH_3	22.39	q
	22.19	q
CH_3	17.54	q

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.37	0.81, 1.83	d,d
Furan-4-H	6.34	1.89, 3.25	d,d
Furan-3-H	6.24	0.85, 3.25	d,d
4	4.50	-	s
	4.47	-	s
CHO	4.25	-	m
	4.12	-	m
	4.05	6.27, 12.75	d,d
CH_2O	3.96		
			m
CH_2N			
	2.89		
$CC(CH_3)_2$	1.36	-	s
	1.36	-	s
	1.25	-	s
	1.25	-	s
$CHC(CH_3)_2$	1.21	-	s
	1.21	-	s
$CC(CH_3)_2$	0.96	-	s



(221)

cis-4-Acetoxy-2-oxo-3-phenoxy-1-azetidineacetic acid methyl ester (221).

Potassium permanganate (50mg, 0.32mmol) was added to water (2.5ml) and the solution stirred vigorously for 10 min. The solution was then cooled to $0^{o}C$ and benzyl-triethylammonium bromide (10mg, 0.04 mmol) was added, followed by a solution of aldehyde (226) (41mg, 0.156 mmol) in benzene (0.5ml).

After stirring overnight at room temperature, solid sodium bisulphite was added until the initially purple solution became colourless. Acidification with 1M HCl was followed by dilution with ethyl acetate (50ml). The organic layer was separated, dried and concentrated in vacuo to yield the crude acid (227). ^{1}H nmr spectroscopy showed that no aldehydic H was present.

No attempt was made to characterise or purify this acid. Instead it was converted into methyl ester (221).

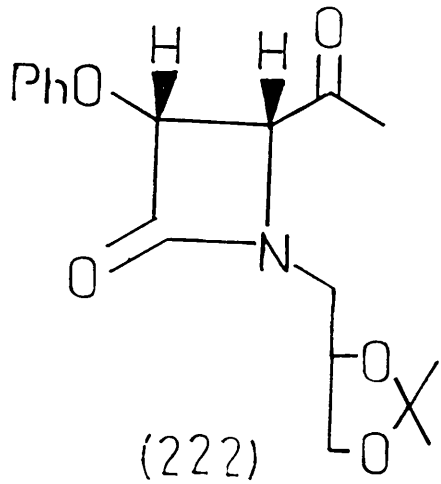
Acid (227) was dissolved in ether and diazomethane bubbled through the solution until a yellow colour persisted. The reaction was then stirred overnight, filtered through Celite and the ether removed in vacuo. The crude product was purified by chromatography to yield ester (221) [39.1mg, 0.133 mmol, 86% from diol (224)] as a clear viscous oil.

ν_{max} ($CHCl_3$) 1 790 cm^{-1}, 1 750 cm^{-1}

Found:M^{+},293.0893. $C_{14}H_{15}NO_6$ requires 293.08993.

C	(P.P,M)	Multiplicity
$CH_2CO_2CH_3$	171.18	s
$OCOCH_3$	167.97	s
2	165.58	s
O-C(Ar)	157.10	s
$\underline{m}$-C_6H_5	129.63	d
$\underline{p}$-C_6H_5	122.68	d
$\underline{o}$-C_6H_5	115.67	d
3	81.50	d
4	79.92	d
$CH_2CO_2CH_3$	52.69	q
CH_2N	42.06	t
$OCOCH_3$	20.70	q

H	(P.P.M)	J (Hz)	Multiplicity
$\underline{m}$-C_6H_5	7.30	7.59, 8.63	d,d
$\underline{p}$-C_6H_5	7.04	7.71	t
$\underline{o}$-C_6H_5	7.00	8.57	d
4	6.39	3.65	d
3	5.43	3.64	d
	4.34	17.98	d
CH_2N	3.88	18.00	d
$-CO_2CH_3$	3.77	-	s
$-OCOCH_3$	2.07	-	s



(222)

cis-4-Acetyl-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methyl]-3-phenoxy-2-azetidinone (222).

β-Lactam (213) (154mg, 0.446mmol) was dissolved in CH_2Cl_2 (60ml) and the solution cooled to -78°C. Ozone was bubbled through this solution until a blue colour persisted. The solution was then thoroughly purged with nitrogen until colourless.

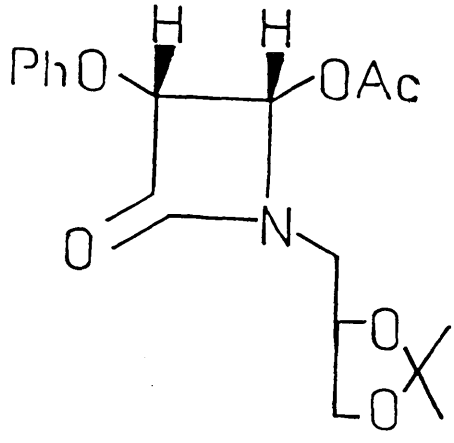
Dimethyl sulphide (0.11g, 0.13ml, 1.78mmol) was then added, and the solution stirred overnight. It was then washed sequentially with water (50ml) saturated brine (2 x 20ml) and water (20ml). The organic layer was then dried and concentrated in vacuo. Purification of the residue by chromatography furnished methyl ketone (222) (129mg, 0.404mmol, 91%) as a clear oil.

ν_{max} ($CHCl_3$) 1 770 cm^{-1}, 1 730 cm^{-1}.

Found: M-Me, 304.1181. $C_{17}H_{21}NO_5$-Me requires 304.11849.

C	(P.P.M)	Multiplicity
$COCH_3$	203.60	s
	202.78	s
2	165.67	s
	164.81	s
O-C(Ar)	157.13	s
	157.06	s
$\underline{m}$-C_6H_5	129.79	d
	129.64	d
$\underline{p}$-C_6H_5	122.86	d
	122.80	d
$\underline{o}$-C_6H_5	115.82	d
	115.78	d
$C(CH_3)_2$	110.04	s
	109.70	s
3	82.02	d
	81.85	d
CHO	74.89	d
	73.30	d
CH_2O	67.10	t
	66.79	t
4	65.85	d
	65.31	d
CH_2N	44.68	t
	43.64	t
$COCH_3$	28.09	q
	27.91	q
	26.87	q
$C(CH_3)_2$	26.80	q
	25.32	q
	24.89	q

H	(P.P.M)	J (Hz)	Multiplicity
m-C_6H_5	7.30	8.72, 8.90	d,d
o-C_6H_5	7.05	8.66	d
p-C_6H_5	6.94	8.95	t
3	5.50	5.28	d
	5.49	5.38	d
4	4.77	5.27	d
	4.65	5.39	d
CHO	4.28	-	m
CH_2O			m
	3.19	9.54, 14.24	dd
$COCH_3$	2.24	-	s
	2.22	-	s
	1.42	-	s
$C(CH_3)_2$	1.36	-	s
	1.31	-	s



(223)

cis-4-Acetoxy-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methyl-3-phenoxy-2-azetidinone (223).

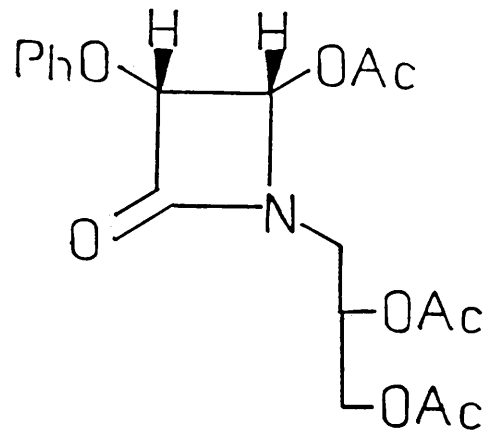
Methyl ketone (222) (102.5mg, 0.3209 mmol) was dissolved in dry benzene (15ml). To this solution was added, with stirring, a solution of m-chloroperbenzoic acid (0.22g, 1.28 mmol) in benzene (15ml). This solution was heated under gentle reflux for 28 h. The cooled reaction mixture was poured into saturated aqueous sodium bicarbonate (30ml). The organic phase was separated and washed with water (15ml) and then brine (2 x 15ml). Drying and concentration yielded a pale yellow oil. Purification by column chromatography yielded acetate (223) (94.0mg, 0.2801 mmol, 87%) as a clear, viscous oil. A small amount of unreacted starting material (8.1mg, 0.0253 mmol, 8%) was also isolated.

ν_{max} ($CHCl_3$) 1 780 cm^{-1}, 1 750 cm^{-1}.

Found: M^+, 335.1375. $C_{17}H_{21}NO_6$ requires 335.13689.

C	(P.P.M)	Multiplicity
O_2CCH_3	170.32	s
O_2CCH_3	170.22	s
2	165.83	s
	165.46	s
O-C(Ar)	157.02	s
$\underline{m}$-C_6H_5	129.86	d
	129.54	d
$\underline{p}$-C_6H_5	122.52	d
$\underline{o}$-C_6H_5	115.68	d
	115.57	d
$C(CH_3)_2$	109.99	s
	109.88	s
3	81.43	d
	81.35	d
4	80.47	d
	79.83	d
CH_2CHO	73.76	d
	73.18	d
CH_2O	67.06	t
	66.94	t
CH_2N	43.88	t
	43.58	t
CH_3	26.87	q
CH_3	26.75	q
CH_3	25.17	q
CH_3	25.11	q
CH_3	20.76	q
CH_3	20.65	q

H	(P.P.M)	J (Hz)	Multiplicity
$\underline{m}$-C_6H_5	7.34-7.18	-	m
$\underline{o}$-C_6H_5 $\underline{p}$-C_6H_5	7.08-6.87	-	m
4	6.49	3.29	d
	6.44	3.40	d
3	5.34	3.41	d
	5.32	3.34	d
CH_2CHO	4.31	-	m
	4.09		
CH_2O			
CH_2N			
	3.22	7.92, 14.33	d,d
O_2CCH_3	2.03	-	s
	2.02	-	s
	1.42	-	s
$C(CH_3)_2$	1.42	-	s
	1.32	-	s



(225)

cis-4-Acetoxy-1-[(2,3-diacetoxy)propan-1-yl]-3-phenoxy-2-azetidinone (225)

Acetonide (223) (231mg, 0.710 mmol) was dissolved in 80% aqueous acetic acid (5ml) and the solution was stirred for 24 h. It was then poured into ethyl acetate (50ml) and saturated sodium bicarbonate was added dropwise until no more carbon dioxide was evolved. The organic phase was then dried and concentrated in vacuo to give the crude diol (224).

For characterisation, crude diol (224) was converted into triacetate (225). A preformed pyridine/acetic anhydride mixture (1ml pyridine/2ml acetic anhydride) was added to the crude diol (224). The mixture was stirred for 48 h. Pyridine and acetic anhydride were removed by azeotropic distillation using toluene.

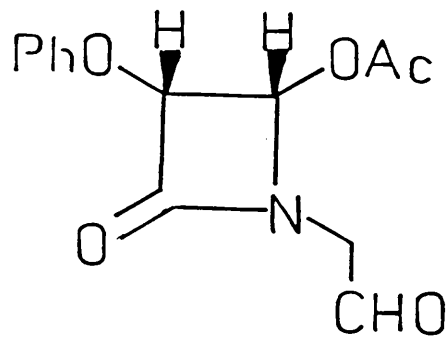
The crude product was purified by chromatography to give triacetate (225) [259mg, 0.683 mmol, 96% from acetonide (223)].

ν_{max} ($CHCl_3$) 1 785 cm^{-1}, 1 745 cm^{-1}.

Found: M^+, 379.1272. $C_{18}H_{21}NO_8$ requires 379.12671.

C	(P.P.M)	Multiplicity
	170.77	s
	170.60	s
$-OCOCH_3$	170.46	s
	170.42	s
	170.10	s
2	165.73	s
	165.67	s
O-C(Ar)	156.93	s
$\underline{m}-C_6H_5$	129.56	d
$\underline{p}-C_6H_5$	122.59	d
$\underline{o}-C_6H_5$	115.54	d
3	81.40	d
	81.16	d
4	80.04	d
	79.57	d
$-CH_2-CH-OCOCH_3$	69.00	d
	68.46	d
$-CH_2-OCOCH_3$	62.74	t
	62.66	t
$-CH_2N$	41.64	t
	41.41	t
	20.88	q
$OCOCH_3$	20.82	q
	20.64	q

H	(P.P.M)	J (Hz)	Multiplicity
m-C_6H_5	7.30	7.35, 8.12	d,d
o-C_6H_5	7.05	8.05	d
p-C_6H_5	7.00	7.30	t
4	6.39	3.49	d
	6.34	3.47	d
3	5.33	3.46	d
	5.26	3.45	d
CHO	4.21	-	m
CH_2O	3.71	7.54, 14.91	d,d
		-	m
CH_2N	3.25	3.45, 14.90	d,d
	2.10	-	s
	2.09	-	s
	2.05	-	s
CH_3	2.05	-	s
	2.04	-	s
	2.04	-	s



(226)

cis-4-Acetoxy-2-oxo-3-phenoxy-1-azetidineacetaldehyde (226).

Periodic acid dihydrate (42.6mg, 0.187 mmol) was added to THF (20ml). After stirring for 0.5 h the resulting homogeneous solution was added to a solution of crude diol (224) (47.7mg, 0.1697 mmmol) in THF (20ml) with stirring.

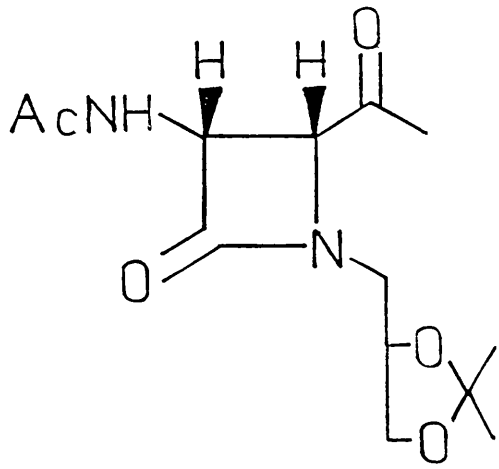
After stirring for a further 45 min a white precipitate of iodic acid had formed. This was removed by filtration and the filtrate concentrated in vacuo. Trituration with ethyl acetate followed by filtration and concentration of the filtrate gave a clear, viscous oil. Purification by column chromatography yielded aldehyde (226) (42.8mg, 0.1625 mmol, 96%), as a clear oil.

ν_{max} ($CHCl_3$) 1 785 cm^{-1}, 1 750 cm^{-1}, 1 720 cm^{-1}.

Found: M^+, 263.0799. $C_{13}H_{13}NO_5$ requires 263.07937.

C	(P.P.M)	Multiplicity
CHO	194.017	s
CO_2CH_3	171.254	s
2	165.900	s
O-C(Ar)	157.066	s
$\underline{m}$-C_6H_5	129.64	d
$\underline{p}$-C_6H_5	122.64	d
$\underline{o}$-C_6H_5	115.65	d
3	81.48	d
4	80.31	d
CH_2N	50.82	t
OCMe	20.692	q

H	(P.P.M)	J (Hz)	Multiplicity
CHO	9.59	-	s
$\underline{m}$-C_6H_5	7.31	7.42, 8.62	d,d
$\underline{p}$-C_6H_5	7.06	7.40	t
$\underline{o}$-C_6H_5	7.01	8.53	d
4	6.32	3.63	d
3	5.48	3.64	d
CH_2CHO	4.40	19.16	d
	4.13	19.16	d
$OCOCH_3$	2.07	-	s



(228)

cis-4-Acetyl-3-acetamido-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-azetidinone (228).

β-Lactam (215) (760.7mg, 1.999 mmol) in CH_2Cl_2 (40ml) was ozonolysed, using dimethyl sulphide (0.97g, 1.23ml, 16mmol) to reduce the ozonide, as described in the procedure for the preparation of β-lactam (222).

The crude methyl ketone/acetamide (228) thus produced was shown by ^1H nmr spectroscopy to be a mixture of diastereoisomers.

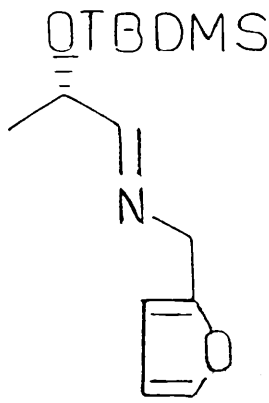
Recrystallisation (ethyl acetate/light petrol) gave a white crystalline solid (238.6mg, 839.6mmol, 42%) which was enriched in one diastereoisomer (d.e. greater than 90%).

ν_{max} ($CHCl_3$) 3 430 cm^{-1}, 3 340 cm^{-1}, 1 765 cm^{-1}, 1 720 cm^{-1}, 1 690 cm^{-1}, 1 510 cm^{-1}

Found: M^+, 284.1368. $C_{13}H_{20}N_2O_5$ requires 284.13722.

C	(P. P.M)	Multiplicity
$CHCOCH_3$	203.71	s
$NHCOCH_3$	170.53	s
2	165.07	s
$C(CH_3)_2$	108.97	s
CHO	73.72	d
CH_2O	66.58	t
4	64.81	d
3	59.01	d
CH_2N	43.82	t
$CHCOCH_3$	27.61	q
$C(CH_3)_2$	26.39	q
	24.87	q
$NHCOCH_3$	21.80	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	8.65	8.13	d
3	5.33	5.39, 8.14	d,d
4	4.66	5.42	d
CHO	4.16	-	m
CH_2O			
CH_2N	3.01	8.44, 13.98	d,d
$CHCOCH_3$	1.99	-	s
$NHCOCH_3$	1.83	-	s
$C(CH_3)_2$	1.24	-	s
	1.21	-	s



(230)

N-[2-(t-Butyldimethylsiloxy)-1-propylene]-(furan-2-yl) methanamine (230).

Aldehyde (231) (605mg, 3.212mmol) in ether (30ml) was treated with furfurylamine (0.34g, 3.21mmol), in the presence of oven-dried potassium carbonate (3.25g) using the procedure described for the preparation of imine (217).

Distillation yielded imine (230) (741mg, 2.775mmol, 86%) as a clear oil, b.p. 78°C/2mm Hg.

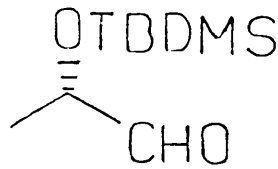
$[\alpha]_D^{20}$ -7.06 (c.0.66, CH_2Cl_2).

ν_{max} ($CHCl_3$) 1 670 cm^{-1}

Found: M^+, 267.1639. $C_{14}H_{25}NO_2Si$ requires 267.16545.

C	(P.P.M)	Multiplicity
CH=N	169.83	d
Furan-2-C	152.02	s
Furan-5-C	142.07	d
Furan-4-C	110.23	d
Furan-3-C	107.25	d
CHO	70.61	d
CH_2N	56.53	t
$C(CH_3)_3$	25.76	q
$CHCH_3$	21.56	q
$C(CH_3)_3$	18.13	s
$SiCH_3$	-4.69	q
	-4.77	q

H	(P.P.M)	J (Hz)	Multiplicity
CH=N	7.52	5.05, 0.41	d,t
Furan-5-H	7.34	0.87, 1.87	d,d
Furan-4-H	6.30	1.87, 3.18	d,d
Furan-3-H	6.18	0.79, 3.19	d,d
CH_2N	4.51	-	s
CHO	4.34	5.04, 6.45	d,q
$CHCH_3$	1.26	6.47	d
$C(CH_3)_3$	0.87	-	s
$SiCH_3$	0.04	-	s
	0.03	-	s



(231)

2-(t-Butyldimethylsiloxy)propanal (231)

(A)Homochiral (S)-enantiomer[73]

A solution of TBDMS ether (274) (2.00g, 9.16mmol) in CH_2Cl_2 (19.5ml) under nitrogen was cooled to -78°C. Diisobutylaluminium hydride (9.16 mmol, 1M in CH_2Cl_2, 9.16ml) was then added dropwise, with vigorous stirring, over 15 min. The reaction was stirred for a further 20 min at -78°C whereupon MeOH (13.60ml) was added rapidly to the solution and the cooling bath removed.

On warming to room temperature the reaction was diluted with ether (150ml) and the resultant white slurry was filtered off. The filtrate was concentrated in vacuo to yield the crude aldehyde.

Purification by either chromatography or distillation gave pure aldehyde (231) (1.28g, 6.82mmol, 75%) as a clear oil, b.p. 55°C/18mm Hg.

$[\alpha]_D^{20}$ -11.8° (c.0.89, $CHCl_3$)

{lit.[73] $[\alpha]_D^{19}$ -12.0 (c. 1.51, $CHCl_3$)}

(B) Racemic (231)

Racemic olefin (237) (1.29g, 6.93mmol) was dissolved in CH_2Cl_2 (60ml) and the solution cooled to -78°C. Ozone was then bubbled through this solution until a blue colour persisted. The system was then thoroughly purged with nitrogen until this blue colour

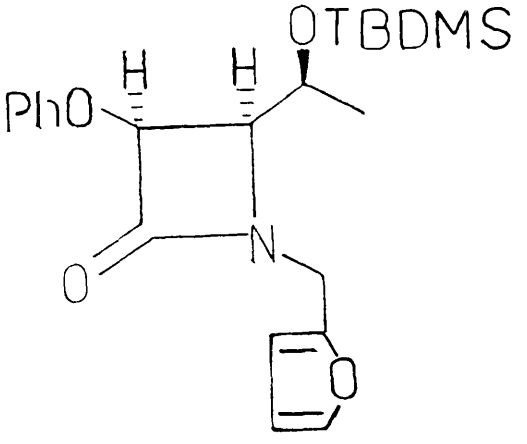
was removed. Triethylamine (0.82g, 1.13ml, 8.08 mmol) was then added and the cooling bath removed. The solution was stirred for 14 h whereupon the solvent was removed in vacuo and pentane (50ml) was added. Filtration through Celite and concentration gave the crude aldehyde. Purification by either chromatography or distillation gave pure, racemic aldehyde (231) (1.08g, 5.72mmol, 83%) as a clear oil, b.p. 55°C/18mm Hg.

ν_{max} ($CHCl_3$) 1 730 cm^{-1}

Found : M-C_4H_9, 131.0535. $C_9H_{20}O_2Si$-C_4H_9 requires 131.05283.

C	(P.P.M)	Multiplicity
CHO	204.26	d
$-CHCH_3$	73.80	d
$C(CH_3)_3$	25.70	q
$CHCH_3$	18.49	q
$C(CH_3)_3$	18.16	s
$SiCH_3$	-3.81	q
	-4.83	q

H	(P.P.M)	J (Hz)	Multiplicity
CHO	9.61	1.29	d
$CHCH_3$	4.08	1.29, 6.87	d,q
$CHCH_3$	1.26	6.86	d
$C(CH_3)_3$	0.90	-	s
$SiCH_3$	0.09	-	s
	0.08	-	s



(232)

cis-4-[1-(t-Butyldimethylsiloxy)ethyl]-1-[(furan-2-yl) methyl]-3-phenoxy-2-azetidinone (232)

Imine (230) (223mg, 0.833 mmol) in CH_2Cl_2 (1ml) was treated with phenoxy acetic acid (120mg, 0.83mmol in 1ml CH_2Cl_2) in the presence of triethylamine (0.35ml, 2.50mmol) and phenyl dichlorophosphate (0.12ml, 0.83mmol) using the procedure described for the preparation of β-lactam (218).

Purification by chromatography yielded cis β-lactam (232) (286mg, 0.713mmol, 86%) as a clear, viscous oil.

Capillary G.C. showed that lactam (232) was a 9.0:1 mixture of diastereoisomers.

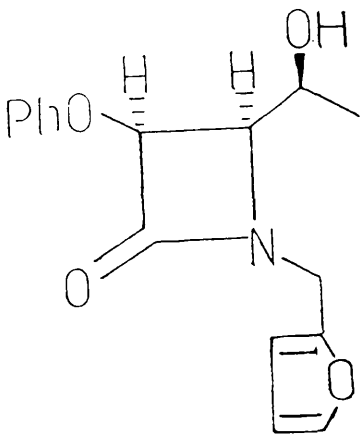
$[\alpha]_D^{20}$ -29.1^o (c 1.13, MeOH)

ν_{max} ($CHCl_3$) 1 760 cm^{-1}

Found: M-C_4H_9, 344.1294. $C_{22}H_{31}NO_4Si$-C_4H_9 requires 344.13181.

C	(P.P.M)	Multiplicity
2	166.73	s
O-C(Ar)	157.74	s
Furan-2-C	149.09	s
Furan-5-C	142.50	d
m-C_6H_5	129.50	d
p-C_6H_5	122.21	d
o-C_6H_5	115.91	d
Furan-4-C	110.34	d
Furan-3-C	108.46	d
3	79.89	d
$CHCH_3$	68.88	d
4	62.06	d
CH_2N	38.42	t
$C(CH_3)_3$	25.84	q
$CHCH_3$	21.50	q
$C(CH_3)_3$	17.91	s
$SiCH_3$	-4.14	s
	-4.43	s

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.37	0.81,1.82	d,d
m-C_6H_5	7.27	7.33,8.51	d,d
o-C_6H_5	7.09	8.51	d
p-C_6H_5	7.00	7.29	t
Furan-4-H	6.33	1.88,3.19	d,d
Furan-3-H	6.27	0.82,3.21	d,d
3	5.12	5.19	d
CH_2N	4.86	15.57	d
	4.29	15.40	d
$CHCH_3$	4.24	6.20,7.2	d,q
4	3.65	5.18,7.33	d,d
$CHCH_3$	1.22	6.14	d
$C(CH_3)_3$	0.92	-	s
$SiCH_3$	0.13	-	s
	0.12	-	s



(233)

cis-1-[(Furan-2-yl)methyl]-4-[1-(hydroxy)ethyl]-3-phenoxy-2-azetidinone (233).

(A) From TBDMS ether (232)

To silyl ether (232) (745.3mg, 1.8559mmol) in THF (40ml) was added tetrabutylammonium fluoride trihydrate (818mg, 2.56 mmol) and the resulting solution was stirred for 14 h. The solvent was then removed in vacuo. Ethyl acetate (40ml) was added to the resultant amorphous solid and, after filtration, the solvent was once more removed.

The crude alcohol thus produced was purified by chromatography to give β-lactam (233) (465.3mg, 1.619mmol, 87%) as a clear viscous oil.

$[\alpha]_D^{20}$ -26.2^o (c.0.89, CH_3OH).

(B) From TBDPS ether (262).

To silyl ether (262) (68.6mg, 0.1304mmol) in THF (30ml) was added TBAF (58mg, 0.182mmol, 1.40 equivalents) and the resulting solution was stirred for 14 h. The reaction was then worked up as in the desilylation of silyl ether (232). Purification of the resulting crude product by chromatography gave alcohol (233) (36.0mg, 0.1252mmol, 96%).

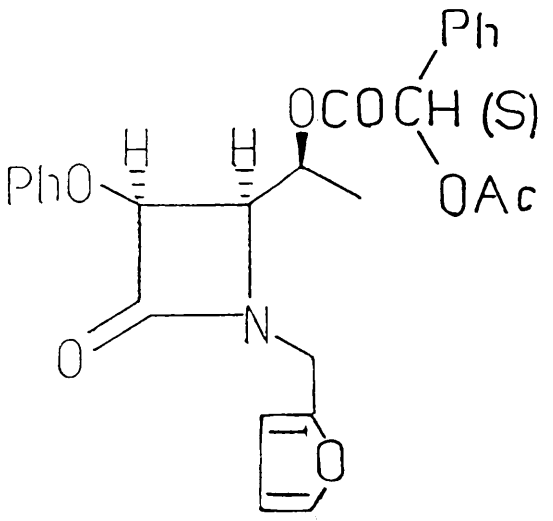
$[\alpha]_D$ -33.6^o (c. 0.98, CH_3OH).

ν_{max} ($CHCl_3$) 3 480 cm^{-1}, 1 760 cm^{-1}.

Found: M^+, 287.1145. $C_{16}H_{17}NO_4$ requires 287.11576.

C	(P.P.M)	Multiplicity
2	165.96	s
O-C(Ar)	157.37	s
Furan-2-C	148.98	s
Furan-5-C	142.70	d
m-C_6H_5	129.64	d
p-C_6H_5	122.82	d
o-C_6H_5	115.82	d
Furan-4-C	108.98	d
Furan-3-C	108.80	d
3	80.41	d
CHOH	67.24	d
4	62.37	d
CH_2N	38.59	t
CH_3	19.88	q

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.39	1.82,0.80	d,d
m-C_6H_5	7.30	7.21,8.97	d,d
o-C_6H_5	7.09	8.87	d
p-C_6H_5	7.02	7.26	t
Furan-4-H	6.35	1.86,3.23	d,d
Furan-3-H	6.31	0.63,3.19	d,d
3	5.21	5.17	d
CH_2N	4.80	5.17	d
	4.41	5.19	d
-CH(OH)	4.19	6.65,5.21	m
4	3.73	5.20,5.19	d,d
CH_3	1.30	6.51	d



(235)

cis-4-[1-(α-Acetoxy-α-phenyl)acetoxyethyl-1-[(furan-2-yl)methyl]-3-phenoxy-2-azetidinone (235).

To a solution of alcohol (233) (69.9mg, 0.2433 mmol) in CH_2Cl_2 (0.2ml) was added DMAP (3mg, 0.025mmol, 0.10 equivalents) in CH_2Cl_2 (0.2ml) and D-O-acetyl-mandelic acid[74] (234) (48mg, 0.250mmol, in 0.2ml CH_2Cl_2). The solution was cooled to 0^oC and DCC (50mg, 0.250mmol) in CH_2Cl_2 (0.2ml) was added, dropwise, over 8 min. The reaction was stirred for a further 48 h, whereupon it was filtered through Celite and washed sequentially with aqueous HCl (0.5M, 5ml), aqueous sodium carbonate (2M, 5ml) and brine (10ml). The organic layer was dried and concentrated in vacuo. Chromatography gave pure ester (235) (102.4mg, 0.2209mmol, 91%) as an amorphous solid.

$[\alpha]_D^{20}$ + 41.0 (c. 1.29, CH_3OH).

ν_{max} ($CHCl_3$) 1 760 cm^{-1}

Found: M^+, 463.1638. $C_{26}H_{25}NO_7$ requires 463.16310.

C	(P.P.M)	Multiplicity
2	170.42	s
O_2CCH_3	167.75	s
O_2CCH	165.74	s
O-C(Ar)	157.32	s
Furan-2-C	148.61	s
Furan-5-C	142.60	d
C-C(Ar)	133.00	s
$\underline{m}$-C_6H_5-O	129.54	d
	129.48	d
C-C_6H_5	129.24	d
	128.74	d
$\underline{p}$-C_6H_5-O	122.39	d
$\underline{o}$-C_6H_5-O	115.66	d
Furan-4-C	110.49	d
Furan-3-C	108.40	d
3	79.94	d
$CHCH_3$	74.67	d
O_2CCH	72.95	d
4	59.34	d
CH_2N	32.87	t
	20.60	q
CH_3	17.43	q

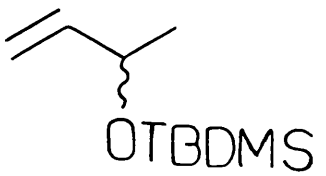
C	(P.P.M)	Multiplicity
2	170.42	s
	170.35	s
O_2CCH_3	167.75	s
O_2CCH	165.74	s
	165.65	s
-O-C(Ar)	157.32	s
	157.24	s
Furan-2-C	148.75	s
	148.61	s
Furan-5-C	142.60	d
	142.50	d
C-C(Ar)	133.05	s
	133.00	s
m-C_6H_5-O	129.54	d
	129.48	d
	129.42	d
C-C_6H_5	129.24	d
	129.13	d
	128.90	d
	128.74	d
p-C_6H_5-O	122.39	d
o-C_6H_5-O	115.66	d
Furan-4-C	110.49	d
	110.33	d
Furan-3-C	108.72	d
	108.40	d
3	79.94	d
	79.86	d
$CHCH_3$	74.67	d
	74.62	d
O_2CCH-	72.95	d
	72.71	d
4	59.34	d
	59.31	d

C	(P.P.M)	Multiplicity
CH_2N	37.87	t
	37.45	t
CH_3	20.60	q
	20.56	q
CH_3	17.43	q
	16.70	q

H	(P.P.M)	J (Hz)	Multiplicity
$C\text{-}C_6H_5$			
Furan-5-H	7.49-7.20	-	m
$\underline{m}\text{-}C_6H_5$			
$\underline{o}\text{-}C_6H_5\text{-}O$	7.08-6.92	-	m
$\underline{p}\text{-}C_6H_5\text{-}O$			
Furan-4-H	6.35	1.80,3.25	d,d
Furan-3-H	6.30	0.88,3.23	d,d
$CH\text{-}C_6H_5$	5.91	-	s
$CHCH_3$	5.32	6.24,8.35	d,q
3	5.22	5.18	d
	4.83	15.83	d
CH_2N	4.26	15.80	d
4	3.85	5.16,8.35	d,d
O_2CCH_3	2.20	-	s
$CHCH_3$	1.37	6.24	d

RACEMIC

H	(P.P.M)	J (Hz)	Multiplicity
C-C_6H_5			
Furan-5-H	7.53-7.17	-	m
m-C_6H_5-O			
o-C_6H_5-O	7.08-6.92	-	m
p-C_6H_5-O			
Furan-4-H	6.38-6.24	-	m
Furan-3-H			
	5.91	-	s
CH-C_6H_5	5.87	-	s
$CHCH_3$	5.42-5.23	-	m
	5.22	5.17	d
3	5.12	5.24	d
	4.83	15.82	d
CH_2N	4.29	15.85	d
	4.26	15.79	d
	3.85	5.16,8.33	d,d
4	3.81	5.21,7.94	d,d
CH_2N	3.20	15.79	d
	2.20	-	s
O_2CCH_3	2.17	-	s
	1.37	6.24	d
$CHCH_3$	1.13	7.38	d



(237)

3-(t-Butyldimethylsiloxy)-1-butene (237)

To a solution of TBDMSCl (1.50g, 9.92mmol) in CH_2Cl_2 (5ml) under N_2, was added with stirring imidazole (0.78g, 11.43mmol) in CH_2Cl_2 (5.25ml) followed by racemic 3-hydroxy-1-butene (0.59g, 8.20mmol) in CH_2Cl_2 (2ml).

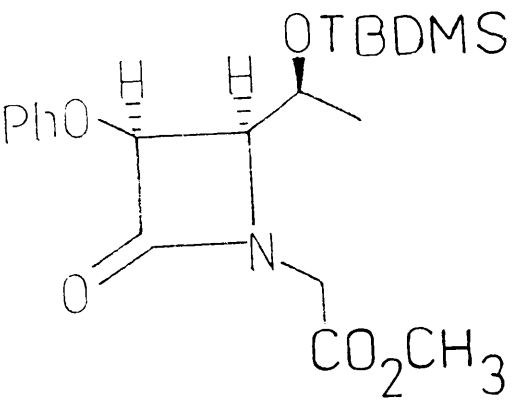
After stirring at room temperature overnight the reaction mixture was poured onto water (10ml) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (25ml) and the combined organic phases were washed sequentially with 5% HCl (aq) (15ml), water (15ml) and brine (15ml). The organic extract was then dried and concentrated in vacuo. This yielded an oil which was purified by distillation to yield pure alkene (232) (1.83g, 9.82mmol, 99%) as a clear oil, b.p. 52°C/18mm Hg.

ν_{max} ($CHCl_3$) 1 640 cm^{-1}

Found: M^+, 186.1457. $C_{10}H_{22}OSi$ requires 186.14399.

C	(P.P.M)	Multiplicity
$H_2C=CH$	142.81	d
$H_2C=CH$	112.38	t
$CHCH_3$	69.50	d
$C(CH_3)_3$	25.88	q
$CHCH_3$	24.22	q
$C(CH_3)_3$	18.31	s
$SiCH_3$	-4.70	q
	-4.86	q

H	(P.P.M)	J (Hz)	Multiplicity
$H_2C=C\underline{H}$	5.84	5.12,10.35,17.12	d,d,d
$\underline{H}\diagdown C=C\diagup H$	5.19	1.53,1.87,17.11	d,d,d
$\underline{H}\diagdown C=C\diagup H$	4.97	1.43,1.87,10.34	d,d,d
$CHCH_3$	4.27	-	m
$CHCH_3$	1.20	6.39	d
$C(CH_3)_3$	0.90	-	s
$SiCH_3$	0.05	-	s
	0.05	-	s



(239)

cis-4-[1-(t-Butyldimethylsiloxy)ethyl]-2-oxo-3-phenoxy-1-azetidineacetic acid methyl ester (239).

Water (3.1ml), CCl_4 (3.1ml), MeCN (4.6ml) and sodium periodate (0.81g, 3.76mmol) were all placed in a conical flask. The mixture was stirred vigorously for 30 min whereupon ruthenium dioxide (1mg, 0.068mmol) was added and vigorous stirring continued for a further 30 min.

To this mixture was added β-lactam (232) (101.5mg, 0.2528mmol) in MeCN (1ml). The reaction was stirred vigorously overnight. After dilution with water (10ml) the mixture was extracted with $CHCl_3$ (3 x 25ml). The combined organic extracts were dried and concentrated in vacuo to yield crude acid (238). ^1H nmr spectroscopy showed an absence of furan resonances.

No attempt was made to purify or characterise this acid. Instead the crude acid was converted directly into methyl ester (239).

Acid (238) was dissolved in ether:methanol (1:1) and diazomethane was bubbled through the solution until a yellow colour persisted. The reaction was then stirred for 14 h. After filtration through Celite the solvent was removed in vacuo to yield the crude ester. Purification by chromatography yielded ester (239) [82.3mg, 0.2093 mmol, 83% from furan (232)].

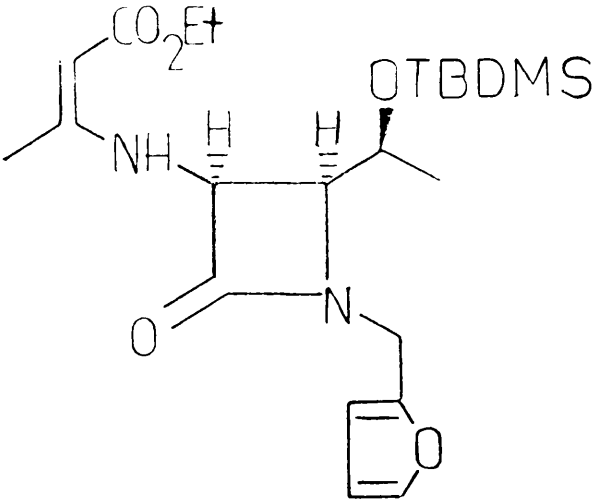
$[\alpha]_D^{20}$ -5.4^o (c. 0.56, MeOH)

ν_{max} ($CHCl_3$) 1 765 cm^{-1}, 1 725 cm^{-1}.

Found: M-Me, 378.1745. $C_{20}H_{31}NO_5Si$-Me requires 378.17367.

C	(P.P.M)	Multiplicity
CO_2CH_3	168.46	s
2	167.33	s
O-C(Ar)	157.70	s
$\underline{m}$-C_6H_5	129.63	d
$\underline{p}$-C_6H_5	122.31	d
$\underline{o}$-C_6H_5	115.89	d
3	80.18	d
$CHCH_3$	69.38	d
4	62.96	d
CO_2CH_3	52.31	q
CH_2N	42.80	t
$C(CH_3)_3$	25.76	q
$CHCH_3$	21.23	q
$C(CH_3)_3$	17.83	s
$SiCH_3$	-4.06	q
	-4.45	q

H	(P.P.M)	J (Hz)	Multiplicity
$\underline{m}$-C_6H_5	7.30	7.20,8.75	d,d
$\underline{o}$-C_6H_5	7.10	8.77	d
$\underline{p}$-C_6H_5	7.01	7.23	t
3	5.29	5.23	d
CH_2N	4.44	17.96	d
$CHCH_3$	4.24	6.02,8.35	d,q
CH_2N	3.96	17.96	d
4	3.94	5.10,8.33	d,d
CO_2CH_3	3.74	-	s
$CHCH_3$	1.21	6.03	d
$C(CH_3)_3$	0.88	-	s
$SiCH_3$	0.11	-	s
	0.08	-	s



(240)

cis-4-[1-(t-Butyldimethylsiloxy)ethyl]-1-[(furan-2-yl) methyl]-3-[(α-methyl-β-ethoxycarbonyl)vinylamino]-2-azetidinone (240)

Imine (230) (217.1mg, 1.039mmol) in CH_2Cl_2 (2.5ml) was reacted with freshly prepared Dane salt (214)[70] (234mg, 1.039mmol in 2.5ml CH_2Cl_2) in the presence of triethylamine (0.41ml, 3.12mmol) and phenyl dichlorophosphate (0.15ml, 1.04mmol) using the procedure described for the preparation of β-lactam (219).

Purification of the crude product by column chromatography yielded lactam (240) (335.2mg, 0.886 mmol 86%) as a clear viscous oil.

Capillary G.C of compound (240) showed that it was a 21:1 mixture of diastereoisomers.

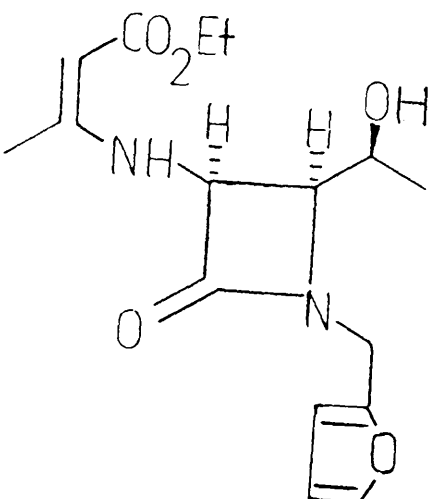
$[\alpha]_D^{20}$ $+26.5^o$ (c. 1.98, CH_3OH)

ν_{max} ($CHCl_3$) 1 760 cm^{-1}, 1 655 cm^{-1}, 1 620 cm^{-1}

Found: M^+, 436.2392. $C_{22}H_{36}N_2O_5Si$ requires 436.23934.

C	(P.P.M)	Multiplicity
CO_2CH	169.95	s
2	167.10	s
NC=C	159.07	s
Furan-2-C	149.06	s
Furan-5-C	142.40	d
Furan-4-C	110.28	d
Furan-3-C	108.38	d
N-C=CH	86.22	d
$CHCH_3$	69.68	q
3	62.43	d
4	60.34	d
CO_2-CH_2	58.57	t
CH_2N	38.40	t
$C(CH_3)_3$	25.77	q
CH_3	20.53	q
CH_3	19.42	q
$C(CH_3)_3$	17.84	s
CH_3	14.40	q
$SiCH_3$	-4.20	q
	-4.47	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	8.93	10.30	d
Furan-5-H	7.33	0.83,1.85	d,d
Furan-4-H	6.29	1.85,3.16	d,d
Furan-3-H	6.21	0.86,3.17	d,d
CH_2N	4.75	15.30	d
3	4.73	5.16,10.35	d,d
N-C=CH	4.55	-	s
CH_2N	4.21	15.45	d
CH_2CH_3	4.05	7.10	q
$CHCH_3$	4.05	-	m
4	3.48	5.16,8.21	d,d
$NC(CH_3)=C$	1.88	-	s
CH_2CH_3	1.20	7.11	t
$CHCH_3$	1.05	6.10	d
$C(CH_3)_3$	0.89	-	s
$SiCH_3$	0.10	-	s
	0.10	-	s



(241)

cis-1-[(Furan-2-yl)methyl]-4-[1-hydroxyethyl]-3-[(α-methyl-β-ethoxycarbonyl)vinylamino]-2-azetidinone (241)

Silyl ether (240) (201.8mg, 0.4621 mmol) in THF (40ml) was reacted with tetrabutylammonium fluoride (204mg, 0.647mmol) using the procedure described for the preparation of alcohol (233).

Purification by column chromatography yielded alcohol (241) (135.8mg, 0.4213mmol, 91%) as a clear viscous oil.

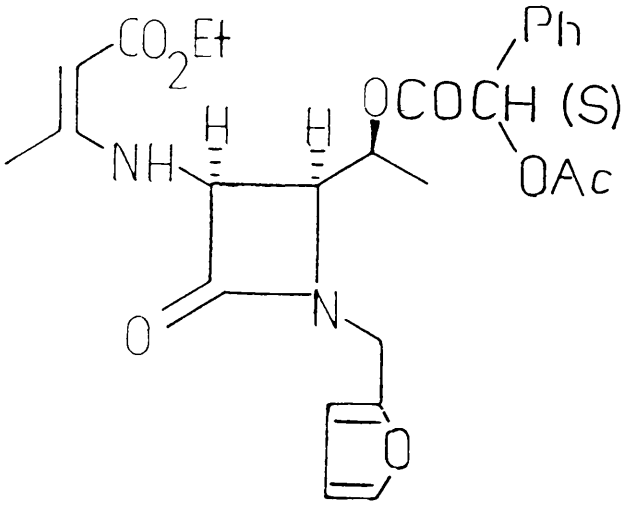
$[\alpha]_D^{20}$ -15.4^o (c. 1.52, CH_3OH).

ν_{max} ($CHCl_3$) 3 600 cm^{-1}, 3 280 cm^{-1}, 1 760 cm^{-1} 1 650 cm^{-1}, 1 610 cm^{-1}

Found: M^+, 322.1519. $C_{16}H_{22}N_2O_5$ requires 322.15287.

C	(P.P.M)	Multiplicity
CO_2CH_2	170.08	s
2	167.64	s
N-C=C	159.22	s
Furan-2-C	149.11	s
Furan-5-C	142.61	d
Furan-3-C	110.53	d
Furan-4-C	108.71	d
N-C=CH	86.11	d
$CH-CH_3$	66.46	d
3	62.83	d
4	60.82	d
CO_2-CH_2	58.66	t
CH_2N	38.72	t
CH_3	21.26	q
CH_3	19.82	q
CH_3	14.46	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	9.07	10.71	d
Furan-5-H	7.36	0.88,1.87	d,d
Furan-4-H	6.32	1.84,3.23	d,d
Furan-3-H	6.27	3.21,0.85	d,d
3	4.79	5.26,10.68	d,d
CH_2N	4.69	15.66	d
C=CH	4.55	-	s
CH_2N	4.39	15.72	d
$CH-CH_3$	4.20	-	m
CH_2-CH_3	4.04	6.45	q
4	3.63	4.65,5.19	d,d
OH	2.75	-	s
$C=C-CH_3$	1.91	-	s
CH_2-CH_3	1.21	6.43	q



(242)

cis-4-[1-(α-Acetoxy-α-phenyl)acetoxyethyl]-1-[(furan-2-yl)methyl]-3-[(α-methyl-β-ethoxycarbonyl)vinylamino]-2-azetidinone (242).

To a solution of alcohol (241) (79.2mg, 0.2456mmol) in CH_2Cl_2 (0.2ml) was added DMAP (3mg, 0.025mmol) in CH_2Cl_2 (0.2ml) and (S)-O-acetylmandelic acid[74] (234) (48mg, 0.25mmol, in 0.2ml CH_2Cl_2). The flask was cooled to 0^oC and DCC (50.1mg, 0.25mmol) in CH_2Cl_2 (0.2ml) was added, dropwise, over 8 min. The reaction was stirred for a further 48 h whereupon it was filtered through Celite and washed sequentially with aqueous HCl (0.5M, 5ml) aqueous sodium carbonate (2M, 5ml) and then brine (5ml). The organic layer was dried and concentrated in vacuo to give the crude ester. Chromatography gave pure ester (242) (108.9mg, 0.2186mmol, 89%) as an amorphous solid.

$[\alpha]_D^{20}$ $+48.3^o$ (c.0.86, CH_3OH)

ν_{max} ($CHCl_3$) 3 680 cm^{-1}, 1 760 cm^{-1}, 1 655 cm^{-1} 1 620 cm^{-1}

Found: M^+, 498.2006. $C_{26}H_{30}N_2O_8$ requires 498.20021.

HOMOCHIRAL

C	(P.P.M)	Multiplicity
CO_2CH	170.15	s
CO_2-CH	169.91	s
CO_2CH_2	167.65	s
2	166.30	s
NH-C=C	158.49	s
Furan-2-C	148.85	s
Furan-5-C	142.59	d
CH-C(Ar)	133.41	s
o-C_6H_5	129.21	d
m-C_6H_5	128.90	d
p-C_6H_5	127.45	d
Furan-3-C	110.48	d
Furan-4-C	108.68	d
NH-C=CH	87.03	d
$CHCH_3$	74.45	d
O_2CCH	72.54	d
4	60.82	d
3	60.29	d
CO_2CH_2	58.80	t
CH_2N	37.91	t
CH_3	20.62	q
	19.36	q
	16.46	q
	14.43	q

RACEMATE

C	(P.P.M)	Multiplicity
	170.88	s
CO_2CH	170.38	s
CO_2CH	170.15	s
CO_2CH_2	169.92	s
	167.65	s
2	166.30	s
	158.51	s
NH-C=C	158.41	s
Furan-2-C	148.75	s
	142.61	d
Furan-5-C	142.48	d
	133.41	s
-CH-C(Ar)	133.17	s
	129.03	d
o-C_6H_5	129.22	d
	129.03	d
m-C_6H_5	128.97	d
	127.97	d
p-C_6H_5	127.51	d
Furan-3-C	110.49	d
	110.32	d
Furan-4-C	108.69	d
	108.34	d
NH-C=CH	87.12	d
	87.02	d
$CHCH_3$	74.66	d
	74.45	d
O_2CCH	74.01	d
	72.56	d
4	60.80	d
4	60.74	d
3	60.28	d
3	60.23	d
CO_2CH_2	58.88	t
	58.82	t

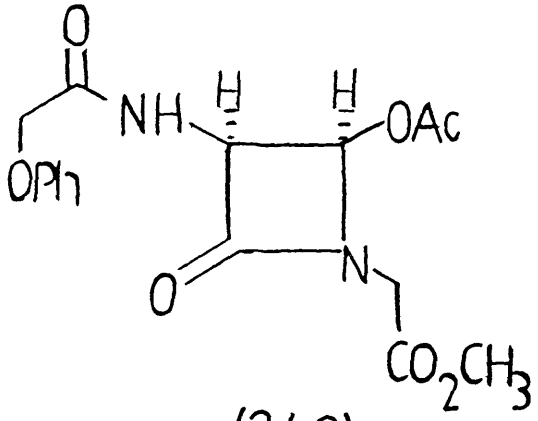
C	(P.P.M)	Multiplicity
CH_2N	37.90	t
	37.43	t
	20.68	q
	20.64	q
	19.38	q
CH_3	16.82	q
	16.46	q
	14.44	q
	14.05	q

HOMOCHIRAL

H	(P.P.M)	J (Hz)	Multiplicity
NH	9.02	10.60	d
Furan-5-H			
C_6H_5	7.45-7.34	-	m
Furan-4-H	6.33	1.83,3.25	d,d
Furan-3-H	6.27	0.80,3.24	d,d
CH-Ph	5.99	-	s
$CHCH_3$	5.08	6.33,7.87	d,q
3	4.84	5.14,10.55	d,d
CH_2N	4.73	16.14	d
N-C=CH	4.57	-	s
CH_2CH_3	4.19	7.14	q
CH_2N	4.05	16.09	d
4	3.70	5.12,7.88	d,d
O_2CCH_3	2.19	-	s
$C(CH_3)=CH$	1.86	-	s
CH_2CH_3	1.23	7.14	t
$CHCH_3$	1.01	6.32	d

RACEMATE

H	(P.P.M)	J (Hz)	Multiplicity
NH	9.02	10.60	d
	8.97	10.60	d
Furan-5-H C_6H_5	7.45-7.34	-	m
Furan-4-H	6.33	-	m
Furan-3-H	6.27	-	m
CH-Ph	5.99	-	s
	5.92	-	s
$CHCH_3$	5.07	-	m
3	4.85	5.13,10.62	d,d
	4.82	5.14,10.61	d,d
CH_2N	4.75	16.13	d
	4.72	16.05	d
N-C=CH	4.58	-	s
CH_2CH_3	4.19	7.15	q
CH_2N	4.05	16.11	d
	4.04	16.14	d
4	3.71	5.13,7.90	d,d
	3.69	5.13,7.91	d,d
O_2CCH_3	2.19	-	s
	2.16	-	s
$C(CH_3)=CH$	1.86	-	s
	1.84	-	s
CH_2CH_3	1.23	7.14	q
	1.23	7.14	q
$CHCH_3$	1.01	6.31	d



(243)

cis-4-Acetoxy-2-oxo-3-[(phenoxy)acetamido]-1-azetidineacetic acid, methyl ester (243).

β-Lactam (255) (21.5mg, 0.064mmol) was reacted with mCPBA (45mg, 0.257mmol) in refluxing benzene (10ml) using the procedure described for the preparation of 4-acetoxy β-lactam (223). Purification by column chromatography gave the desired lactam (243) (21.0mg, 0.0599mmol, 93%) as a clear oil.

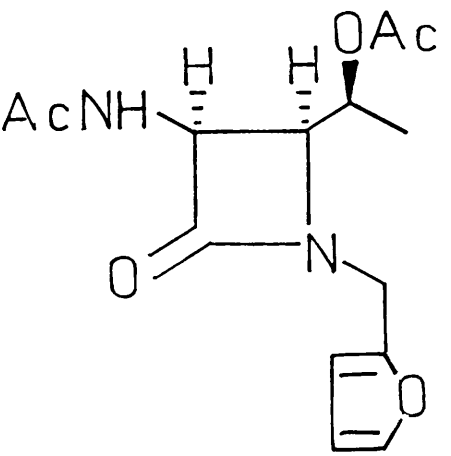
$[\alpha]_D^{20}$ $+16.0^o$ (c 0.89, CH_3OH)

ν_{max} ($CHCl_3$) 3 420cm^{-1}, 1 780cm^{-1}, 1 750cm^{-1}, 1 700cm^{-1}, 1 600cm^{-1}

Found: M^+, 350.1121. $C_{16}H_{18}N_2O_7$ requires 350.1114.

C	(P.P.M)	Multiplicity
NHCO	170.92	s
2	168.33	s
O_2CCH_3	168.05	s
CO_2-CH_3	166.40	s
O-C(Ar)	157.01	s
m-C_6H_5	129.86	d
p-C_6H_5	122.38	d
o-C_6H_5	114.64	d
4	79.57	d
CH_2O	67.22	t
3	58.43	d
CO_2CH_3	52.66	q
CH_2N	42.79	t
O_2C-CH_3	20.47	d

H	(P.P.M)	J (Hz)	Multiplicity
m-C_6H_5	7.35	7.53,7.69	d,d
NH	7.23	9.65	d
p-C_6H_5	7.02	7.50	d,d
o-C_6H_5	6.93	7.66	d
4	6.17	4.18	d
3	5.71	4.16,9.67	d,d
CH_2O	4.61	15.33	d
	4.52	15.41	d
	4.20	17.95	d
CH_2N	3.95	17.91	d
CO_2CH_3	3.75	-	s
O_2CCH_3	1.96	-	s



(244)

cis-3-acetamido-4-[1-(acetoxy)ethyl]-1-[(furan-2-yl)methyl]-2-azetidinone (244).

To a dry round bottom flask with side arm, under nitrogen, was added methanol (0.916ml). The flask was then cooled to $0^{o}C$ and acetyl chloride (144mg, 130µl, 1.832 mmol) was added dropwise.

After stirring for 5 min the ice-bath was removed and β-lactam (240) (200.3mg, 0.4581 mmol) in methanol (1ml) was added dropwise. After stirring for 10 min at room temperature the solvent was removed in vacuo, to yield a yellow, viscous oil, smelling strongly of ethyl acetoacetate. Washing with pentane (3 x 25ml) gave a white solid which was stirred overnight in 2:1 acetic anhydride:pyridine (15ml).

The solvent was removed by azeotropic distillation using toluene to give the crude product.

Purification by chromatography gave lactam (244) (127.1mg, 0.4320 mmol, 94%) as a clear viscous oil.

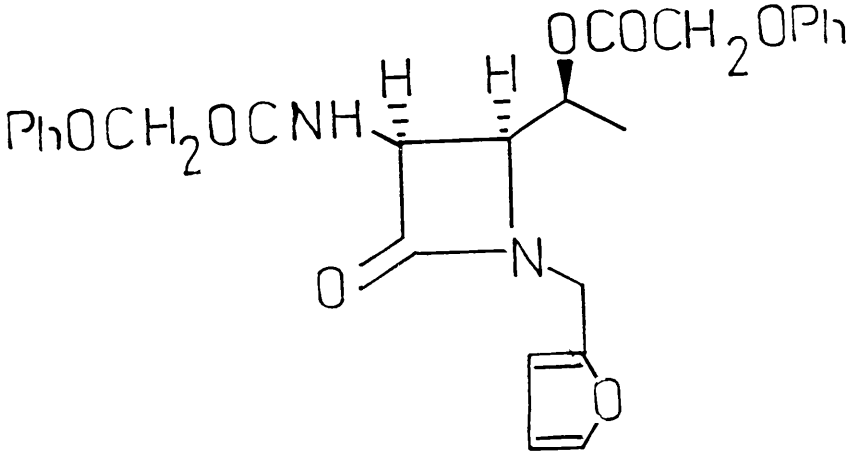
$[\alpha]_D^{20}$ $+28.2^{o}$ (c 1.31, CH_3OH).

ν_{max} ($CHCl_3$) 1 760 cm^{-1}, 1 740 cm^{-1}, 1 690 cm^{-1} 1 505 cm^{-1}.

Found: M^+, 294.1206. $C_{14}H_{18}N_2O_5$ requires 294.12072.

C	(P.P.M)	Multiplicity
$OCOCH_3$	170.81	s
NCO	170.25	s
2	167.11	s
Furan-2-C	148.53	s
Furan-5-C	142.51	d
Furan-3-C	110.49	d
Furan-4-C	108.29	d
$CH-CH_3$	71.24	d
3	60.44	d
4	56.96	d
CH_2N	38.86	t
CH_3	21.57	q
CH_3	21.14	q
CH_3	17.19	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	7.58	8.59	d
Furan-5-H	7.33	0.83,1.85	d,d
Furan-4-H	6.30	1.87,3.24	d,d
Furan-3-H	6.22	0.77,3.24	d,d
3	5.32	5.10,8.58	d,d
$CH-CH_3$	4.94	6.26,8.71	d,q
CH_2N	4.62	15.86	d
	4.13	15.70	d
	3.72	5.09,8.71	d,d
$COCH_3$	2.00	-	s
$COCH_3$	1.97	-	s
$CH-CH_3$	1.10	6.24	d



(246)

cis-1-[(Furan-2-yl)methyl]-3-phenoxyacetamido-4-[1-(phenoxyacetoxy)ethyl]-2-azetidinone (246)

β-Lactam (240) (205.3mg, 0.4695 mmol) in methanol (1ml) was treated with methanolic HCl [from 0.916ml methanol and acetyl chloride (130µl, 1.832 mmol)], as described in the preparation of β-lactam (244).

The resulting hydrochloride salt was dissolved in CH_2Cl_2 (20ml) and phenoxyacetyl chloride (0.169mg, 109µl 0.986 mmol) triethylamine (196µl, 1.408mmol) and DMAP (12mg, 0.1mmol, in 2ml CH_2Cl_2) were added to the solution.

After stirring for 2 h the solvent was removed <u>in vacuo</u>. Ethyl acetate (25ml) was added and the mixture was filtered through Celite. Concentration of the filtrate gave the crude product.

Purtification by column chromatography gave <u>lactam</u> (246) (216.6mg, 0.4531mmol, 96%), as a clear viscous oil.

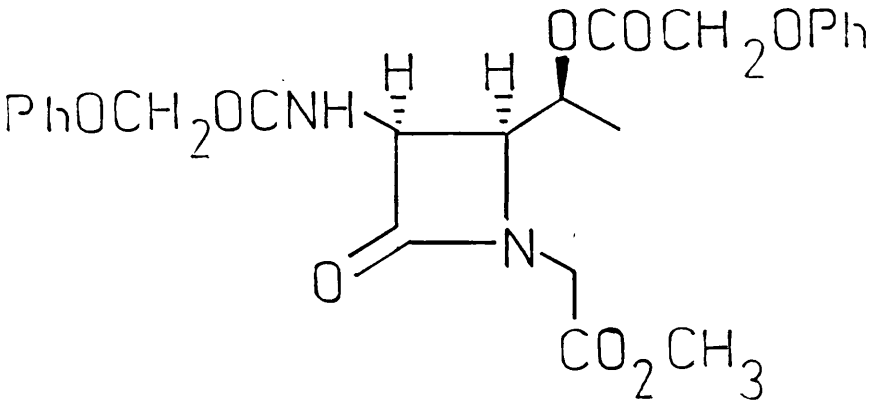
$[\alpha]_D^{20}$ $+39.3^o$ (c 0.81, CH_3OH)

ν_{max} ($CHCl_3$) 3 410 cm^{-1}, 1 765 cm^{-1}, 1 690 cm^{-1} 1 600 cm^{-1}

Found: M^+, 478.1748. $C_{26}H_{26}N_2O_7$ requires 478.17399.

C	(P.P.M)	Multiplicity
CH_2CO_2	169.04	s
NCO	167.96	s
2	166.01	s
O-C(Ar)	157.41	s
O-C(Ar)	156.86	s
Furan-2-C	148.40	s
Furan-5-C	142.55	d
m-C_6H_5	129.58	d
m-C_6H_5	129.45	d
p-C_6H_5	121.99	d
p-C_6H_5	121.67	d
o-C_6H_5	114.53	d
o-C_6H_5	114.35	d
Furan-3-C	110.46	d
Furan-2-C	108.55	d
$CHCH_3$	71.04	d
CH_2O	66.88	t
CH_2O	65.21	t
3	60.08	d
4	56.55	d
CH_2N	38.73	t
CH_3	17.46	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	8.07	8.47	d
Furan-5-H	7.34	0.85,1.84	d,d
m-C_6H_5	7.26-7.18	-	m
p-C_6H_5	6.96	7.28	t
o-C_6H_5	6.90-6.78	-	m
Furan-4-H	6.31	1.85,3.22	d,d
Furan-5-H	6.25	0.67,3.22	d,d
3	5.30	5.17,8.45	d,d
$CHCH_3$	5.07	6.34,6.55	d,q
CH_2N	4.61	15.85	d
CH_2O	4.55	-	s
CH_2O	4.45	-	s
CH_2N	4.10	15.89	d
4	3.79	6.60,5.18	d,d
CH_3	1.18	6.38	d



(248)

cis-2-Oxo-3-phenoxyacetamido-4- 1-(phenoxyacetoxy)ethyl - 1-azetidineacetic acid methyl ester (248).

β-Lactam (246) (232.1mg, 0.4851mmol) was oxidised using ruthenium dioxide (2mg, 0.131mmol) and sodium periodate (1.55g, 7.21mmol) in water (5.95ml), CCl_4 (5.95ml) and MeCN (8.83ml) using the procedure described for the preparation of acid (238). The crude acid thus produced was converted directly into methyl ester (248) using diazomethane, as described in the procedure for the preparation of methyl ester (239).

Chromatography gave ester (248) (178.5mg, 0.3793mmol, 78%), as a clear oil.

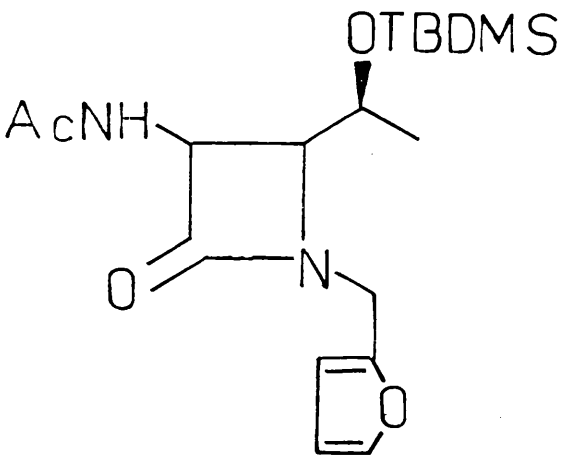
$[\alpha]_D^{20}$ +39.3° (c 0.81, CH_3OH).

ν_{max} ($CHCl_3$) 1 770 cm^{-1}, 1 750 cm^{-1}, 1 690 cm^{-1} 1 600 cm^{-1}

Found: M^+, 470.1695. $C_{24}H_{26}N_2O_8$ requires 470.16891.

C	(P.P.M)	Multiplicity
CO_2CH_3	169.07	s
NCO	168.42	s
2	167.94	s
CO_2CH	166.57	s
-O-C(Ar)	157.31	s
-O-C(Ar)	156.92	s
$\underline{m}$-C_6H_5	129.86	d
$\underline{m}$-C_6H_5	129.53	d
$\underline{p}$-C_6H_5	122.14	d
$\underline{p}$-C_6H_5	121.80	d
$\underline{o}$-C_6H_5	114.63	d
$\underline{o}$-C_6H_5	114.25	d
$CH-CH_3$	72.52	d
CH_2O	67.07	t
CH_2O	65.24	t
3	60.96	d
4	56.65	d
OCH_3	52.34	q
CH_2N	43.11	t
$CH-CH_3$	17.05	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	7.93	8.87	d
m-C_6H_5	7.26	7.71,8.11	d,d
p-C_6H_5	6.98	7.68	t
o-C_6H_5	6.87	8.15	d
3	5.52	5.22,8.86	d,d
$CHCH_3$	5.10	6.25,8.70	d,q
CH_2O	4.50	-	s
CH_2N	4.12	18.09	d
4	4.03	5.19,8.72	d,d
CH_2N	3.90	18.01	d
CO_2CH_3	3.63	-	s
$CHCH_3$	1.15	6.22	d



(249)

cis-3-Acetamido-4-[1-(t-butyldimethylsiloxy)ethyl]-1-[(furan-2-yl)methyl]-2-azetidinone (249).

To a dry round bottom flask with side arm, under nitrogen, was added MeOH (0.916ml). The flask was then cooled to $0^{o}C$ and acetyl chloride (144mg, 130µl, 1.832mmol) was added dropwise.

After stirring for 5 min the ice-bath was removed and β-lactam (240) (199.2mg, 0.4562mmol) in MeOH (1ml) was added dropwise. After stirring for 5 min at room temperature the solution was purged for 20 min with nitrogen. Concentration in vacuo yielded a yellow, viscous oil, smelling strongly of ethyl acetoacetate. Washing with pentane gave the crude silyl ether/hydrochloride salt (250) as a white solid.

This material was stirred overnight in a solution consisting of acetic anhydride (15.0ml), triethylamine (0.20ml, 1.44mmol) and DMAP (12mg, 0.1mmol).

The mixture was concentrated in vacuo and ethyl acetate (25ml) added. Filtration and solvent removal then gave the crude product.

Purification by chromatography gave silyl ether (249) (149.0mg, 0.4065mmol, 89%) as a viscous clear oil.

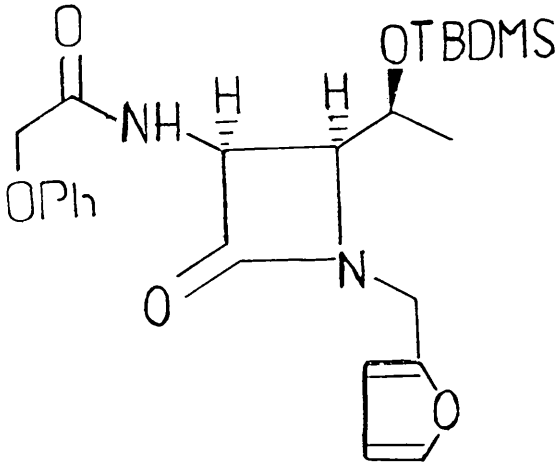
$[\alpha]_D^{20}$ $+12.1^{o}$ (c 1.82, CH_3OH)

ν_{max} ($CHCl_3$) 3 420 cm^{-1}, 1 760 cm^{-1}, 1 685 cm^{-1}, 1 505 cm^{-1}.

Found: M^+, 366.1979. $C_{18}H_{30}N_2O_4Si$ requires 366.19748.

C	(P.P.M)	Multiplicity
NCO	170.07	s
2	167.76	s
Furan-2-C	148.73	s
Furan-5-C	142.63	d
Furan-3-C	110.41	d
Furan-4-C	108.43	d
$CHCH_3$	68.09	d
3	62.10	d
4	56.58	d
CH_2N	38.68	t
$C(CH_3)_3$	25.84	q
$CHCH_3$	23.03	q
$COCH_3$	21.68	q
$C(CH_3)_3$	17.90	s
$SiCH_3$	-3.33	q
	-4.40	q

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.36	0.76,1.85	d,d
NH	6.56	9.20	d
Furan-4-H	6.32	1.87,3.22	d,d
Furan-3-H	6.22	0.69,3.22	d,d
3	5.31	9.19,5.19	d,d
CH_2N	4.81	15.90	d
	4.17	15.66	d
$CH\text{-}CH_3$	3.95	6.50,5.03	d,q
4	3.58	5.08,5.06	d,d
$COCH_3$	1.99	-	s
$CH\text{-}CH_3$	1.18	6.68	d
$C(CH_3)_3$	0.92	-	s
$SiCH_3$	0.13	-	s
	0.12	-	s



(251)

cis-1-[(Furan-2-yl)methyl]-3-[(phenoxy)acetamido]-4-[1-(t-butyldimethylsiloxy)ethyl]-2-azetidinone (251)

(A) From Silyl ether (240).

β-Lactam (240) (200.1mg, 0.4583 mmol) in methanol (1.0ml) was treated with methanolic HCl [from 0.916ml methanol and acetyl chloride (130µl, 1.832mmol)], as described in the preparation of β-lactam (249). The resulting hydrochloride salt (250) was dissolved in CH_2Cl_2 (20ml) and phenoxyacetyl chloride (117mg, 76µl, 0.687mmol) triethylamine (192µl, 1.375mmol) and DMAP (12mg, 0.1mmol, in 2.0ml CH_2Cl_2) were added to the solution.

After stirring for 2 h the solvent was removed in vacuo. Ethyl acetate (25.0ml) was added and the mixture was filtered through Celite. Concentration of the filtrate gave the crude product. Purification by chromatography gave β-lactam (251) (173.0mg, 0.3772 mmol, 82%), as a clear viscous oil.

$[\alpha]_D^{20}$ -13.8° (c 0.56, MeOH).

(B) From Alcohol (275)

To a solution of the alcohol (150.3mg, 0.4367 mmol) in CH_2Cl_2 (6.50ml) was added 2,6-lutidine (94mg, 102µl, 0.87mmol) and TBDMS triflate (172mg, 0.65mmol) in CH_2Cl_2 (1.72ml) with stirring, at room temperature. Stirring was continued for a further 30 min whereupon the reaction was poured into ether (20ml) and washed

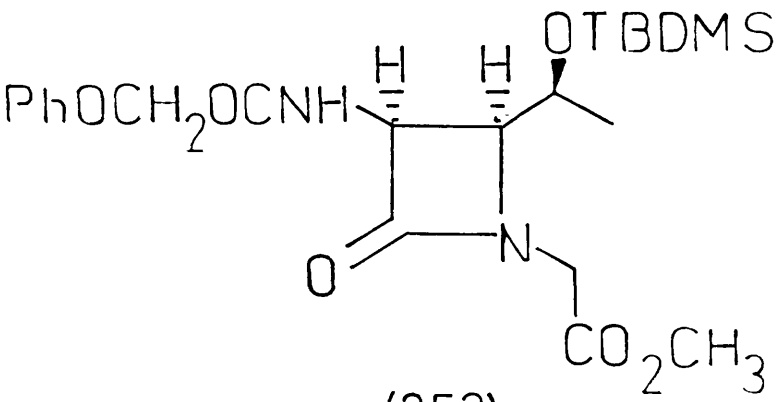
sequentially with water (15ml), saturated aqueous $CuSO_4$ solution (15ml) and brine (15ml). Drying, concentration and purification by chromatography gave silyl ether (251) (178.4mg, 0.3891 mmol, 89%), as a clear oil.

$[\alpha]_D^{20}$ -13.9^o 1 760 cm^{-1}, 1 690 cm^{-1}, 1 600 cm^{-1}

Found: M^+, 458.2230. $C_{24}H_{34}N_2O_5Si$ requires 458.22369.

C	(P.P.M)	Multiplicity
NHCO	168.72	s
2	166.65	s
O-C(Ar)	156.87	s
Furan-2-C	148.73	s
Furan-5-C	142.61	d
m-C_6H_5	129.80	d
p-C_6H_5	122.37	d
o-C_6H_5	114.69	d
Furan-3-C	110.39	d
Furan-4-C	108.46	d
CHOSi	68.16	d
CH_2O	67.20	t
3	61.89	d
4	56.06	d
CH_2N	38.72	t
$C(CH_3)_3$	25.83	q
$CHCH_3$	21.64	q
$C(CH_3)_3$	17.87	s
$Si(CH_3)_2$	-3.53	q
	-4.58	q

H	(P.P.M)	J (Hz)	Mutiplicity
Furan-5-H	7.37	0.82,1.87	d,d
m-C_6H_5	7.30	7.64,7.58	d,d
NH	7.16	9.00	d
p-C_6H_5	7.03	7.60	t
o-C_6H_5	6.90	7.62	d
Furan-4-H	6.32	1.85,3.00	d,d
Furan-3-H	6.23	3.00,0.90	d,d
3	5.31	5.14,9.01	d,d
CH_2N	4.83	15.78	d
CH_2O	4.52	-	s
CH_2N	4.18	15.74	d
$CH-CH_3$	3.81	6.20,6.00	m
4	3.60	5.21,5.85	d,d
$-CH-CH_3$	1.09	6.29	d
$-C(CH_3)_3$	0.89	-	s
$Si(CH_3)$	0.06	-	s
	0.05	-	s



(253)

cis-4-[1-(t-Butyldimethylsiloxy)ethyl]-2-oxo-3-(phenoxyacetamido]-1-azetidineacetic acid methyl ester (253)

β-Lactam (251) (78.0mg, 0.1701mmol) was oxidised using ruthenium dioxide (1mg, 0.06mmol) and sodium periodate (0.54g, 2.53mmol) in water (2.0ml), CCl_4 (2.0ml) and MeCN (8.83ml) using the procedure described for the preparation of acid (238).

The crude acid thus produced was converted directly into methyl ester (253) using diazomethane as described in the procedure for the preparation of methyl ester (239).

Chromatography gave methyl ester (253) (57.9 mg 0.1265mmol, 74%), as a clear oil.

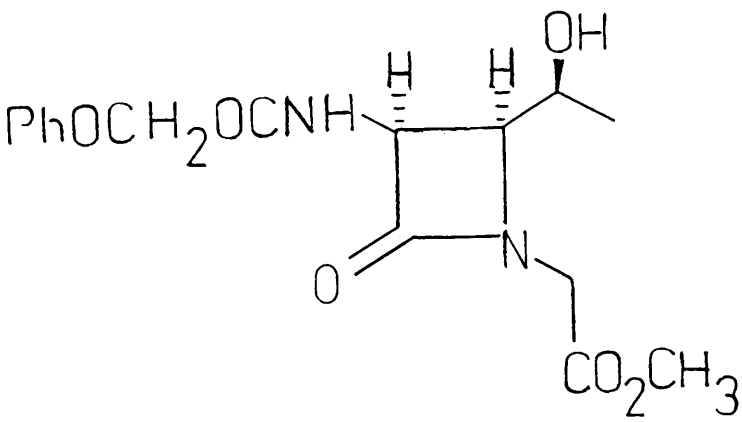
$[\alpha]_D^{20}$ $+15.3^o$ (c 2.02, CH_3OH)

ν_{max} ($CHCl_3$) 3 420 cm^{-1}, 1 770 cm^{-1}, 1 750 cm^{-1} 1 675 cm^{-1}, 1 520 cm^{-1}

Found: M^+, 450.2204. $C_{22}H_{34}N_2O_6Si$ requires 450.21862.

C	(P.P.M)	Multiplicity
CO_2CH_3	168.69	s
$NHCOCH_2$	168.22	s
2	167.20	s
O-C(Ar)	156.84	s
$\underline{m}$-C_6H_5	129.85	d
$\underline{p}$-C_6H_5	122.41	d
$\underline{o}$-C_6H_5	114.61	d
$CH-CH_3$	68.86	d
CH_2O	67.12	t
3	62.99	d
4	56.36	d
CO_2CH_3	52.41	q
CH_2N	43.16	t
$C(CH_3)_3$	25.76	q
$CH-CH_3$	21.26	q
$C(CH_3)_3$	17.82	s
$SiCH_3$	-3.70	q
	-4.58	q

H	(P.P.M)	J (Hz)	Multiplicity
m-C_6H_5	7.30	7.40,7.56	d,d
NH	7.15	9.00	d
p-C_6H_5	7.03	7.34	t
o-C_6H_5	6.91	7.64	d
3	5.43	4.99,8.99	d,d
CH_2O	4.53	-	s
	4.40	17.90	d
CH_2N	3.88	17.86	d
4	3.85	-	m
$CH-CH_3$	3.75	-	m
CO_2CH_3	3.73	-	s
$CH-CH_3$	1.03	5.92	d
$C(CH_3)_3$	0.85	-	s
	0.03	-	s
$SiCH_3$	0.01	-	s



(254)

cis-4-[1-(Hydroxy)ethyl]-2-oxo-3-[phenoxyacetamido]-1-azetidineacetic acid methyl ester (254)

(A) From TBDPS ether (270)

Silyl ether (270) (484.5mg, 0.8474mmol) in THF (35ml) was cleaved with tetrabutylammonium fluoride (373mg, 1.186mmol) using the procedure described for the perparation of alcohol (233).

Purification by chromatography gave alcohol (254) (263.1mg, 0.7822mmol, 92%), as a clear viscous oil.

$[\alpha]_D^{20}$ +33.6° (c 0.87, CH_3OH).

(B) From TBDMS ether (253)

Silyl ether (253) (185.1mg, 0.4108mmol) in THF (30ml) was cleaved with tetrabutylammonium fluoride (180.8mg, 0.5749mmol) using the procedure described for the preparation of alcohol (233).

Purification by chromatography gave alcohol (254) (132.0mg, 0.3657mmol, 89%) as a clear viscous oil.

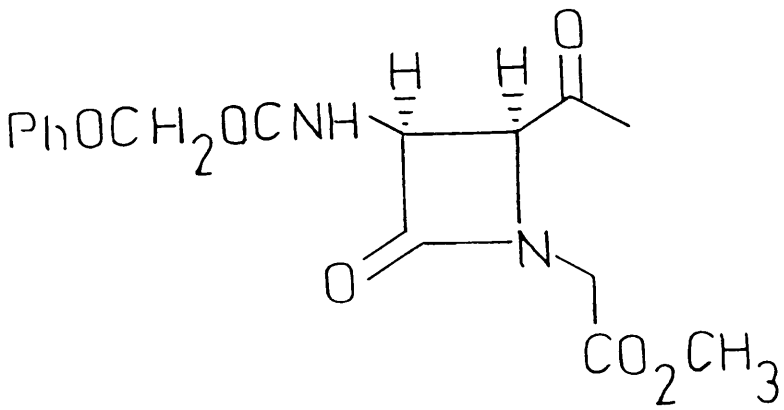
$[\alpha]_D^{20}$ +30.8° (c 1.41, CH_3OH)

ν_{max} ($CHCl_3$) 3 680 cm^{-1}, 3 400 cm^{-1}, 1 770 cm^{-1}, 1 745 cm^{-1}, 1 685 cm^{-1}, 1 600 cm^{-1}

Found: M^+, 336.1319. $C_{16}H_{20}N_2O_6$ requires 336.13214.

C	(P.P,M)	Multiplicity
CONH	170.94	s
CO_2CH_3	168.68	s
2	167.87	s
O-C(Ar)	157.02	s
m-C_6H_5	129.61	d
p-C_6H_5	122.01	d
o-C_6H_5	114.71	d
CH_2O	66.97	t
$CHCH_3$	64.95	d
3	63.88	d
4	56.45	d
CO_2CH_3	53.10	q
CH_2N	43.36	t
$CH-CH_3$	21.04	q

H	(P.P.M)	J (Hz)	Multiplicity
NH	8.08	10.34	d
m-C_6H_5	7.28	6.00,8.64	d,d
p-C_6H_5	7.00	5.88	t
o-C_6H_5	6.92	8.75	d
3	5.58	5.30,10.26	d,d
CH_2O	3.78	-	s
CH_2N	4.41	18.36	d
	3.80	18.31	d
4	3.79	5.28	d
$CHCH_3$	3.78-3.60	-	m
$CHCH_3$	1.18	6.78	d
OH	0.84	-	s



(255)

cis-4-Acetyl-2-oxo-3-[(phenoxyacetamido)-1-azetidineacetic acid, methyl ester (255).

3,5-Dimethylpyrazole (54mg, 0.56mmol) in CH_2Cl_2 (5ml) was added to a suspension of CrO_3 (56mg, 0.56mmol) in CH_2Cl_2 (5ml) and the mixture was stirred at room temperature under nitrogen for 15 min. Alcohol (254) (68.5mg, 0.2037mmol) in CH_2Cl_2 (10ml) was then added to the resulting solution and the stirring was continued overnight. The solvent was removed in vacuo and ethyl acetate (25ml) was added. Filtration, concentration of the filtrate and purification by chromatography gave methyl ketone (255) (56.5mg, 0.1691mmol, 83%) as a clear oil. A small amount of unreacted alcohol (254) (6.1mg, 0.0183 mmol, 8.9%) was also recovered.

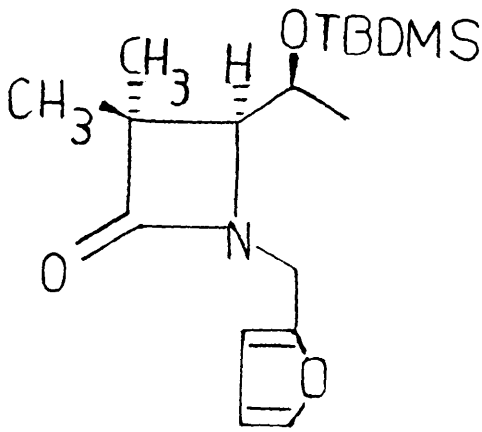
$[\alpha]_D^{20}$ -8.5^o (c 1.01, CH_3OH).

ν_{max} ($CHCl_3$) 3 400 cm^{-1}, 1 780 cm^{-1}, 1 750 cm^{-1}, 1 725 cm^{-1}, 1 695 cm^{-1}, 1 600 cm^{-1}

Found: M^+, 334.1153. $C_{16}H_{18}N_2O_6$ requires 334.11649.

C	(P.P.M)	Multiplicity
$CO-CH_3$	204.15	s
2	169.08	s
CONH	168.21	s
CO_2CH_3	164.75	s
O-C(Ar)	156.67	s
$\underline{m}\ C_6H_5$	129.80	d
$\underline{p}\text{-}C_6H_5$	122.42	d
$\underline{o}\text{-}C_6H_5$	114.61	d
CH_2O	66.85	t
3	64.38	d
4	58.86	d
CH_3O	52.51	q
CH_2N	42.10	t
CH_3CO	28.24	q

H	(P.P.M)	J (Hz)	Multiplicity
m-C_6H_5	7.30	7.35,8.34	d,d
NH	7.16	8.67	d
p-C_6H_5	7.02	7.38	t
o-C_6H_5	6.87	8.50	d
3	5.67	5.56,8.66	d,d
4	4.93	5.46	d
CH_2O	4.49	-	s
	4.48	18.20	d
CH_2N	3.84	18.27	d
CH_3O	3.73	-	s
CH_3CO	2.07	-	s



(258)

cis-4-[1-(t-Butyldimethylsiloxy)ethyl]-3,3-dimethyl-1-[(furan-2-yl)methyl]-2-azetidinone (258)

Imine (230) (465.2mg, 1.7394mmol) in THF (5ml) was reacted with the lithium ester enolate prepared by reaction of methyl 2-methylpropionate (0.190g, 0.201ml, 1.913mmol, 1.1 equivalents) with LDA [from diisopropylamine (0.271ml, 1.913mmol in 5ml THF) and n-butyllithium (0.80ml of a 2.5M solution in hexames, 1.91 mmol)] using the procedure described for the preparation of β-lactam (220). ^1H NMR spectroscopy showed the crude product to be a mixture of the desired β-lactam (256) and aldehyde (231).

Chromatography gave aldehyde (231) (95.65mg, 0.5079mmol, 29%) and the desired β-lactam (258) (341.8mg, 1.013mmol, 58%) as a clear viscous oil.

Capillary G.C. showed that the diastereoisomeric ratio was 17:1.

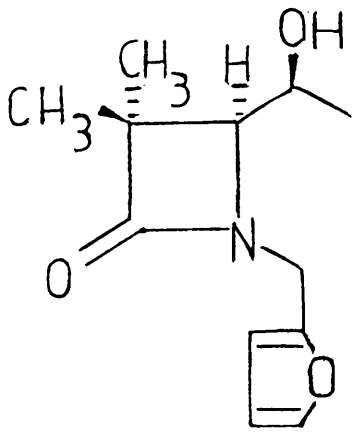
$[\alpha]_D^{20}$ -26.3^o (c 2.03, CH_3OH)

ν_{max} ($CHCl_3$) 1 760cm^{-1}

Found: M^+, 337.2070. $C_{18}H_{31}NO_3Si$ requires 337.20732.

C	(P, P.M)	Multiplicity
2	175.11	s
Furan-2-C	149.55	s
Furan-5-C	142.42	d
Furan-3-C	110.33	d
Furan-4-C	108.19	d
$CH-CH_3$	68.19	d
4	67.10	d
3	53.02	s
CH_2N	37.71	t
$C(CH_3)_3$	25.77	q
CH_3	23.28	q
CH_3	21.36	q
$C(CH_3)_3$	17.84	s
	17.34	q
$SiCH_3$	-3.36	q
	-4.81	q

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.34	0.82,1.85	d,d
Furan-4-H	6.24	1.87,3.22	d,d
Furan-3-H	6.19	0.84,3.22	d,d
CH_2N	4.75	15.88	d
$CHCH_3$	4.01	6.00,6.29	d,q
	3.92	15.85	d
4	2.95	6.02	d
CH_3	1.28	-	s
CH_3	1.22	-	s
$CHCH_3$	1.19	6.28	d
$C(CH_3)_3$	0.84	-	s
	0.05	-	s
$SiCH_3$			
	0.04	-	s



(259)

3,3-Dimethyl-1-[(furan-2-yl)methyl]-4-[1-(hydroxy) ethyl]-2-azetidinone (259)

TBDMS ether (258) (100.7mg, 0.2983 mmol) in THF (30ml) was cleaved with tetrabutylammonium fluoride (131mg, 0.418mmol) using the procedure described for the preparation of alcohol (233). Purification by chromatography yielded alcohol (259) (64.0mg, 0.2866 mmol, 96%) as a clear, viscous oil.

$[\alpha]_D^{20}$ $+12.3^o$ (c 1.32, CH_3OH)

Reaction of TBDPS ether (271) (330.5mg, 0.7158mmol) with TBAF (649mg, 2.00mmol) in THF (60ml) using an identical procedure gave alcohol (259) (135.0mg, 0.6044mmol, 84%).

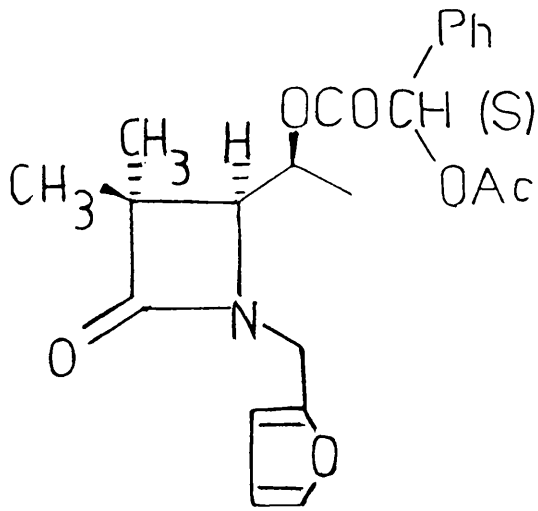
$[\alpha]_D^{20}$ $+13.2^o$ (c 0.86, CH_3OH)

ν_{max} ($CHCl_3$) 3 600cm^{-1}, 3 450cm^{-1}, 1 745cm^{-1}

Found: M^+, 223.1208. $C_{12}H_{17}NO_3$ requires 223.12084

C	(P.P.M)	Multiplicity
2	175.21	s
Furan-2-C	149.38	s
Furan-5-C	142.55	d
Furan-3-C	110.49	d
Furan-4-C	108.43	d
$CH-CH_3$	68.29	d
4	66.58	d
3	53.30	s
CH_2N	37.97	t
CH_3	23.10	q
CH_3	21.06	q
CH_3	17.15	q

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.35	0.84,1.86	d,d
Furan-4-H	6.31	1.86,3.23	d,d
Furan-3-H	6.22	0.65,3.23	d,d
CH_2N	4.58	15.83	d
	4.13	15.87	d
$CHCH_3$	3.91	6.45,6.85	d,q
4	2.98	6.94	d
OH	1.98	-	s
$C(CH_3)_3$	1.32	-	s
	1.25	-	s
$CHCH_3$	1.24	6.39	d



(260)

cis-4-[1-(α-Acetoxy-α-phenyl)acetoxyethyl]-3,3-dimethyl-1-[(furan-2-yl)methyl]-2-azetidinone (260).

Alcohol (259) (114.5mg, 0.5126mmol) in CH_2Cl_2 (1.50ml) was reacted with (S)-O-acetylmandelic acid (234)[74] (101mg, 0.53mmol) in the presence of DMAP (6mg, 0.05mmol) and DCC (104mg, 0.52mmol) in CH_2Cl_2 (0.45ml) using the procedure described for the preparation of ester (242).

Chromatography gave pure β-lactam (260) (179.6mg, 0.4496mmol, 88%) as a clear oil.

$[\alpha]_D^{20}$ $+42.1^o$ (c 1.28, CH_3OH)

ν_{max} ($CHCl_3$) 1 745cm^{-1}

Found: M^+, 399.1675. $C_{22}H_{25}NO_6$ requires 399.16819.

HOMOCHIRAL

C	(P.P.M)	Multiplicity
O_2CCH_3	174.17	s
O_2CCH	170.41	s
2	167.78	s
Furan-2-C	149.02	s
Furan-5-C	142.65	d
CH-C(Ar)	133.28	d
p-C_6H_5	129.51	d
o-C_6H_5	128.91	d
m-C_6H_5	127.53	d
Furan-3-C	110.39	d
Furan-4-C	108.58	d
$CHCH_3$	74.67	d
$CHCO_2$	69.82	d
4	65.24	d
3	53.69	d
CH_2N	37.69	t
CH_3	23.01	q
CH_3	20.60	q
CH_3	17.75	q
CH_3	16.85	q

RACEMATE

C	(P.P.M)	Multiplicity
CO_2	174.17	s
	174.04	s
CO_2	170.41	s
	170.25	s
2	167.80	s
	167.80	s
Furan-2-C	149.02	s
Furan-5-C	142.65	d
CH-C(Ar)	133.28	s
	133.23	s
$\underline{p}$-C_6H_5	129.51	d
	129.36	d
$\underline{o}$-C_6H_5	128.91	d
	128.84	d
$\underline{m}$-C_6H_5	127.53	d
	127.45	d
Furan-3-C	110.39	d
Furan-4-C	108.58	d
$CHCH_3$	74.67	d
	74.63	d
$CH\text{-}CO_2$	69.82	d
4	65.35	d
	65.24	d
3	53.69	s
	53.40	s
CH_2N	37.69	t
	37.56	t

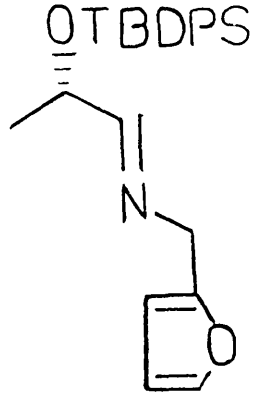
C	(P.P.M)	Multiplicity
	23.01	q
	22.61	q
	20.64	q
	20.60	q
CH_3		
	17.75	q
	17.28	q
	16.85	q
	16.37	q

HOMOCHIRAL

H	(P.P.M)	J (Hz)	Multiplicity
C_6H_5	7.41	-	m
Furan-5-H	7.34	0.86,1.85	d
Furan-4-H	6.29	1.86,3.28	d,d
Furan-3-H	6.17	0.78,3.30	d,d
$CHCO_2$	5.82	-	s
$CHCH_3$	5.10	6.43,6.41	d,q
	4.64	16.02	d
CH_2N			
	3.86	15.93	d
4	3.14	6.47	d
O_2CCH_3	2.17	-	s
$CHCH_3$	1.13	6.40	d
	1.00	-	s
$C(CH_3)_2$			
	0.80	-	s

RACEMATE

H	(P.P.M)	J (Hz)	Multiplicity
C_6H_5	7.41	-	m
Furan-5-H	7.34	-	m
Furan-4-H	6.30	-	m
Furan-3-H	6.17	-	m
CH-CO_2-	5.82	-	s
	5.80	-	s
$CHCH_3$	5.10	6.45,6.40	d,q
	5.02	6.46,6.81	d,
CH_2N	4.64	16.01	d
	4.57	15.83	d
	3.86	15.91	d
	3.76	15.90	d
4	3.14	6.46	d
	3.03	6.91	d
O_2CCH_3	2.17	-	s
	2.17	-	s
$CHCH_3$	1.30	6.40	d
$C(CH_3)_2$	1.24	-	s
	1.18	-	s
$CHCH_3$	1.13	6.40	d
$C(CH_3)_2$	1.00	-	s
	0.80	-	s



(263)

N-[2-(t-Butyldiphenylsiloxy)-1-propylene]-(furan-2-yl) methanamine (263)

Aldehyde (264) (2.33g, 7.46mmol) was treated with furfurylamine (0.72g, 7.46mmol) in ether (50.0ml) in the presence of potassium carbonate (2.00g) using the procedure described for the preparation of imine (217).

Purification by distillation gave imine (263) (2.67g, 6.82mmol, 91%) as a pale green oil, b.p. 124°C/0.1mm Hg.

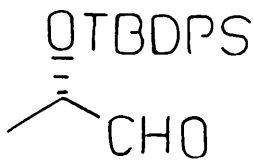
$[\alpha]_D^{20}$ -4.03 (c 1.84, CH_2Cl_2)

ν_{max} ($CHCl_3$) 1 670cm^{-1}

Found: M^+, 391.1959. $C_{24}H_{29}NO_2Si$ requires 391.19676.

C	(P.P.M)	Multiplicity
N=CH	169.45	d
Furan-2-C	151.94	s
Furan-5-C	142.00	d
m-C_6H_5	135.75	d
	135.68	d
Si-C(Ar)	133.77	s
	133.57	s
o-C_6H_5	129.62	d
	129.54	d
p-C_6H_5	127.61	d
	127.53	d
Furan-3-C	110.20	d
	110.11	d
Furan-4-C	107.25	d
$CHCH_3$	71.24	t
CH_2N	56.34	t
$C(CH_3)_3$	26.94	q
$CHCH_3$	21.42	q
$C(CH_3)_3$	19.13	s

H	(P.P.M)	J (Hz)	Multiplicity
N=CH			
m-C_6H_5	7.75-7.61	-	m
o-C_6H_5	7.49-7.29	-	m
p-C_6H_5			
Furan-5-H			
Furan-4-H	6.33	1.89,3.20	d,d
Furan-3-H	6.14	0.80,3.19	d,d
CH_2N	4.45	-	s
$CHCH_3$	4.53-4.30	-	m
$CHCH_3$	1.28	6.50	d
$C(CH_3)_3$	1.11	-	s



(264)

2-(t-Butyldiphenylsiloxy)propanal (264)

(S)-Ester (265) (6.00g, 17.52mmol) in CH_2Cl_2 (37.2ml) was reduced with diisobutylaluminium hydride (17.52ml, 1M solution in CH_2Cl_2) using the procedure described for the preparation of aldehyde (231).

Purification by either chromatography or distillation gave pure aldehyde (264) (4.10g, 13.21mmol, 75%) as a clear oil, b.p. 118°C/20mm Hg.

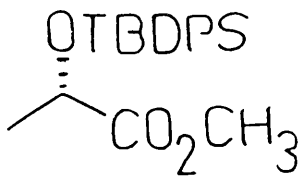
$[\alpha]_D^{20}$ -16.8° (c 1.05, CH_2Cl_2)

ν_{max} ($CHCl_3$) 1 735.

Found: M-C_4H_9, 255.0845. $C_{19}H_{24}O_2Si$-C_4H_9 requires 255.08413

C	(P,P,M)	Multiplicity
CHO	203.79	d
m-C_6H_5	135.69	d
	135.67	d
Si-C(Ar)	133.23	s
	132.88	s
p-C_6H_5	130.01	d
	129.94	d
o-C_6H_5	127.81	d
	127.73	d
$CHCH_3$	74.38	d
$-C(CH_3)_3$	26.83	q
$C(CH_3)_3$	19.18	s
$CHCH_3$	18.35	q

H	(P.P.M)	J (Hz)	Multiplicity
CHO	9.65	1.20	d
m-C_6H_5	7.77-7.62	-	m
o-C_6H_5	7.52-7.32	-	m
p-C_6H_5			
$CHCH_3$	4.11	1.18,6.87	d,q
$CHCH_3$	1.23	6.87	d
$C(CH_3)$	1.12	-	s



(265)

(S)-2-(t-Butyldiphenylsiloxy)propanoic acid methyl ester (265)[73]

(S)-Methyl lactate (3.00g, 2.75ml, 28.8mmol) in THF (12ml) was reacted with t-butyldiphenylsilyl chloride (10.29g, 9.74ml, 37.5mmol) in the presence of triethylamine (10.02ml, 72mmol) and DMAP (0.35g, 2.8mmol) using the procedure described for the preparation of t-butyldimethylsilyl ether (274). Purification by distillation or chromatography gave silyl ether (265) (9.32g, 27.2mmol, 95%) as a clear oil, b.p. 122°C/0.5mm Hg.

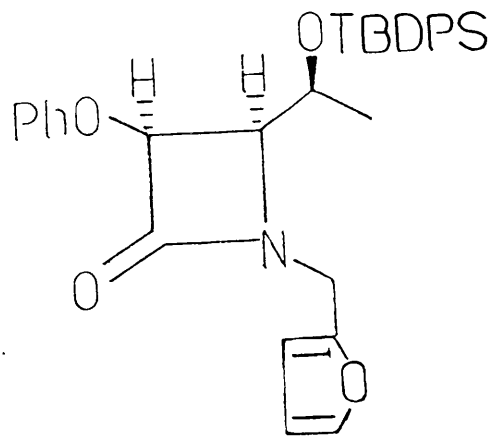
$[\alpha]_D^{20}$ -50.9° (c 1.29, EtOH)
[lit.[73] $[\alpha]_D^{20}$ -51.8° (c 0.78, EtOH)]

ν_{max} ($CHCl_3$) 1 750 cm^{-1}.

Found: M-C_4H_9, 285.0940. $C_{20}H_{26}O_3Si$-C_4H_9 requires 285.09470.

C	(P.P.M)	Multiplicity
CO_2CH_3	174.09	s
m-C_6H_5	135.81	d
m-C_6H_5	135.65	d
Si-C(Ar)	133.43	s
Si-C(Ar)	133.10	s
p-C_6H_5	129.72	d
o-C_6H_5	127.60	d
o-C_6H_5	127.51	d
$CHCH_3$	66.83	d
CO_2CH_3	51.50	q
$CHCH_3$	26.42	q
$C(CH_3)_3$	20.21	q
$C(CH_3)_3$	19.17	s

H	(P.P.M)	J (Hz)	Multiplicity
m-C_6H_5	7.75-7.70	-	m
o-C_6H_5 p-C_6H_5	7.45-7.39	-	m
$CHCH_3$	4.34	6.74	q
CO_2CH_3	3.58	-	s
$CHCH_3$	1.42	6.73	d
$C(CH_3)_3$	1.15	-	s



(266)

cis-4-[1-(t-Butyldiphenylsiloxy)ethyl]-1-[(furan-2-yl) methyl]-3-phenoxy-2-azetidinone (266).

Imine (259) (250.1mg, 0.6384 mmol) in CH_2Cl_2 (0.8ml) was treated with phenoxyacetic acid (90mg, 0.64mmol, in 0.8ml CH_2Cl_2) in the presence of triethylamine (0.27ml, 1.92mmol) and phenyl dichlorophosphate (0.092ml, 0.64mmol) using the procedure described for the preparation of β-lactam (213).

Purification by chromatography gave β-lactam (266) (282.6mg, 0.5375mmol, 84%), as a clear viscous oil. Packed column G.C. indicated that lactam (266) was present as one diastereoisomer only. ^{13}C NMR spectroscopy however, suggested that a trace of the other diastereoisomer (less than 5%) was present.

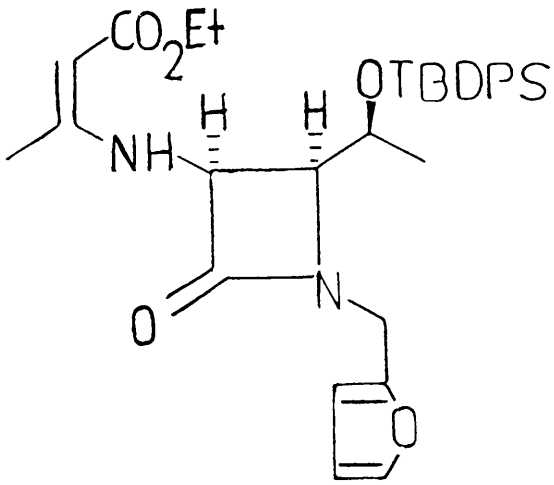
$[\alpha]_D^{20}$ -16.4 (c 0.89, CH_3OH).

ν_{max} ($CHCl_3$) 1 760cm^{-1}

Found: M-C_4H_9, 468.1628. $C_{32}H_{35}NO_4Si$-C_4H_9 requires 468.16311.

C	(P.P.M)	Multiplicity
2	166.71	s
O-C(Ar)	157.69	s
Furan-2-C	148.95	s
Furan-5-C	142.58	d
m-C_6H_5-Si-	135.81	d
m-C_6H_5-Si-	135.69	d
-Si-C(Ar)	134.47	s
-Si-C(Ar)	133.34	s
p-C_6H_5-Si	129.73	d
	129.62	d
m-C_6H_5-O	129.41	d
o-C_6H_5-Si	127.67	d
	127.49	d
p-C_6H_5-O	122.11	d
o-C_6H_5-O	115.87	d
Furan-3-C	110.38	d
Furan-4-C	108.57	d
3	80.17	d
$CHCH_3$	69.39	d
4	62.20	d
CH_2N	38.40	t
$C(CH_3)_3$	26.98	q
$CHCH_3$	20.97	q
$C(CH_3)_3$	19.17	s

H	(P,P,M)	J (Hz)	Multiplicity
m-C_6H_5-Si	7.79-7.60	-	m
o-C_6H_5-Si			
p-C_6H_5-Si	7.51-7.15	-	m
m-C_6H_5-O			
Furan-5-H			
o-C_6H_5-O	7.05-6.90	-	m
p-C_6H_5-O			
Furan-4-H	6.35	1.86,3.21	d,d
Furan-3-H	6.25	0.61,3.26	d,d
3	5.15	5.11	d
CH_2N	4.85	15.52	d
$CHCH_3$	4.40	-	m
CH_2N	4.39	15.60	d
4	3.80	5.12,6.09	d,d
$C(CH_3)_3$	1.08	-	s
$CHCH_3$	1.05	6.30	d



(267)

cis-4-[1-(t-Butyldiphenylsiloxy)ethyl]-1-[(furan-2-yl) methyl]-3-[(α-methyl-β-ethoxycarbonyl)vinylamino]-2-azetidinone (267).

Imine (263) (250.8mg, 0.6405mmol) in CH_2Cl_2 (1.8ml) was reacted with freshly prepared Dane salt (214)[70] (0.144g, 0.64mmol, in 1.8ml CH_2Cl_2) in the presence of triethylamine (0.27ml, 1.92mmol) and phenyl dichlorophosphate (0.092ml, 0.64mmol) using the procedure described for the preparation of β-lactam (219).

Purification of the crude product by chromatography yielded lactam (267) (303.8mg, 0.5422mmol, 85%) as a clear viscous oil. Packed column G.C. indicated that compound (267) was present as one diastereoisomer only. ^1H and ^{13}C NMR spectroscopy both agreed with this.

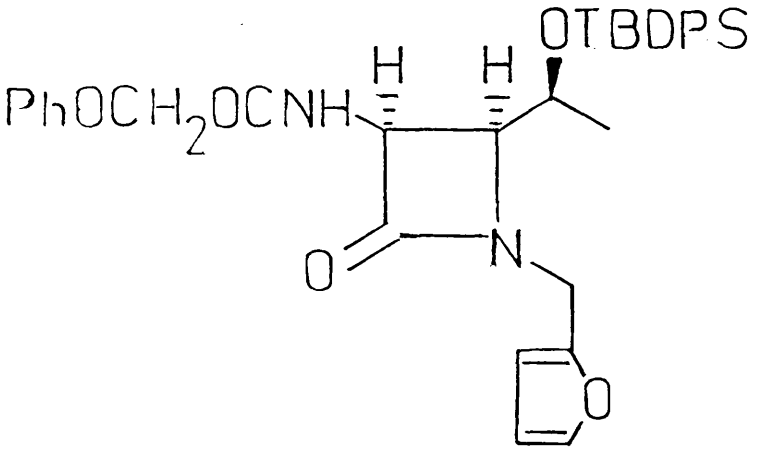
$[\alpha]_D^{20}$ $+18.6^o$ (c 1.32, CH_3OH)

ν_{max} ($CHCl_3$) 3 260cm^{-1}, 1 760cm^{-1}, 1 650cm^{-1} 1 615cm^{-1}

Found: M^+, 560.2702. $C_{32}H_{40}N_2O_5Si$ requires 560.2702

C	(P.P.M)	Multiplicity
CO_2CH_2	169.83	s
2	167.00	s
NH-C=C	159.01	s
Furan-2-C	148.79	s
Furan-5-C	142.53	d
m-C_6H_5	135.75	d
m-C_6H_5	135.54	d
Si-C(Ar)	134.15	s
Si-C(Ar)	133.34	s
o-C_6H_5	129.77	d
o-C_6H_5	129.69	d
p-C_6H_5	127.76	d
p-C_6H_5	127.54	d
Furan-3-C	110.417	d
Furan-4-C	108.627	d
NHC=CH	86.08	d
$CHCH_3$	70.17	d
3	62.21	d
4	60.83	d
CO_2CH_2	58.54	t
CH_2N	38.28	t
$C(CH_3)_3$	26.99	q
CH_3	19.51	q
$C(CH_3)_3$	19.23	s
CH_3	19.17	q
CH_3	14.48	q

H	(P,P,M)	J (Hz)	Multiplicity
NH	8.98	9.93	d
m-C_6H_5	7.73-7.65	-	m
o-C_6H_5			
p-C_6H_5	7.45-7.25	-	m
Furan-5-H			
Furan-4-H	6.28	1.90,3.21	d,d
Furan-3-H	6.28	0.80,3.20	d,d
3	4.79	5.07,9.95	d,d
CH_2N	4.62	15.57	d
C=CH	4.55	-	s
CH_2N	4.23	15.53	d
$CHCH_3$	4.15	6.37,7.12	d,q
CO_2CH_2	4.06	7.17	q
4	3.64	5.07,7.12	d,d
$C(CH_3)=C$	1.88	-	s
CH_2CH_3	1.21	7.12	t
$C(CH_3)_3$	1.05	-	s
$CHCH_3$	0.91	6.34	d



(2G8)

cis-4-[1-(t-Butyldiphenylsiloxy)ethyl]-1-[(furan-2-yl) methyl]-3-phenoxyacetamido-2-azetidinone (268).

Lactam (267) (262.1mg, 0.4673mmol) in MeOH (1.0ml) was treated with methanolic HCl [from methanol 0.93ml and acetyl chloride (132µl, 1.868mmol)] as described in the preparation of β-lactam (249). The resulting hydrochloride salt was dissolved in CH_2Cl_2 (20ml) and phenoxyacetyl chloride (88mg, 56µl, 0.51mmol) triethylamine (195µl, 1.402mmol) and DMAP (7mg, 0.04mmol in 2.0ml CH_2Cl_2) were added. After stirring for 2 h the solvent was removed in vacuo. Ethyl acetate (25.0ml) was added and the resulting slurry was filtered through Celite. Concentration of the filtrate followed by purification by chromatography gave β-lactam (268) (262.3mg, 0.4501mmol, 96%) as a clear oil.

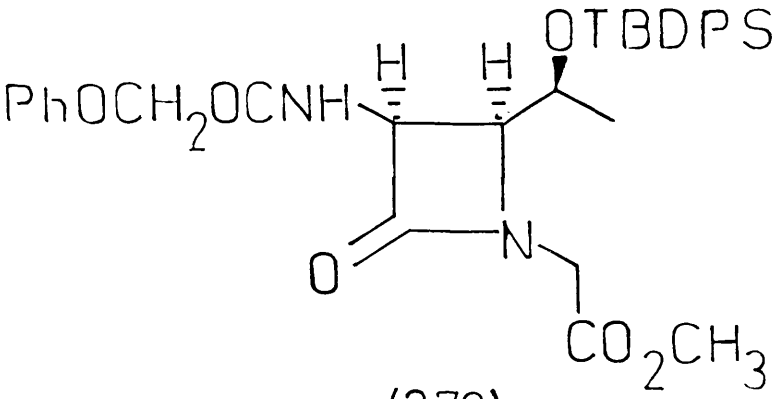
$[\alpha]_D^{20}$ -23.6° (c 0.58, CH_3OH)

ν_{max} ($CHCl_3$) 3 420 cm^{-1}, 1 760cm^{-1}, 1 690cm^{-1}, 1 600cm^{-1}.

Found: M^+, 582.2555. $C_{34}H_{38}N_2O_5Si$ requires 582.25499.

C	(P.P.M)	Multiplicity
NCO	168.53	s
2	166.63	s
O-C(Ar)	156.76	s
Furan-2-C	148.64	s
Furan-5-C	142.69	d
m-Si-C_6H_5	135.82	d
	135.50	d
Si-C-(Ar)	133.99	s
	133.33	s
	130.44	d
p-SiC_6H_5	129.90	d
m-O-C_6H_5	129.63	d
o-Si-C_6H_5	127.88	d
	127.63	d
p-O-C_6H_5	122.18	d
o-O-C_6H_5	114.68	d
Furan-3-C	110.41	d
Furan-4-C	108.55	d
CH-CH_3	68.46	d
CH_2O	66.95	t
3	61.67	d
4	56.30	d
CH_2N	38.73	t
$C(CH_3)_3$	27.09	q
$CHCH_3$	21.77	q
$C(CH_3)_3$	19.10	s

H	(P,P,M)	J (Hz)	Multiplicity
NH	7.84	8.90	d
m-Si-C_6H_5	7.69-7.58	-	m
o-Si-C_6H_5			
p-Si-C_6H_5			
m-O-C_6H_5	7.48-7.10	-	m
Furan-5-H			
o-O-C_6H_5	7.01	7.38	d
p-O-C_6H_5	6.93	6.82	t
Furan-4-H	6.32	1.88,3.20	d,d
Furan-3-H	6.20	3.10	d
3	5.34	5.31,8.88	d,d
CH_2O	4.85	15.68	d
	4.38	14.99	d
CH_2N	4.24	14.91	d
CH_2O	4.18	15.74	d
$CH-CH_3$	4.02	6.53,4.48	d,q
4	3.68	4.55,5.24	d,d
$C(CH_3)_3$	1.05	-	s
$CH-CH_3$	1.00	6.53	d



(270)

cis-4-[1-(t-Butyldiphenylsiloxy)ethyl]-2-oxo-3-phenoxyacetamido-1-azetidineacetic acid methyl ester (270)

β-Lactam (268) (720.1mg, 1.236 mmol) was oxidised using ruthenium dioxide (6mg, 0.34mmol) and sodium periodate (3.98g, 18.43mmol) in water (15.25ml), CCl_4 (15.25ml) and MeCN (22.48ml) using the procedure described for the preparation of acid (238). The crude acid thus produced was converted directly into methyl ester (266) using diazomethane, as described in the procedure for the preparation of β-lactam (248).

Chromatography gave ester (270) (578.9mg, 1.0125mmol, 82%) as an oil.

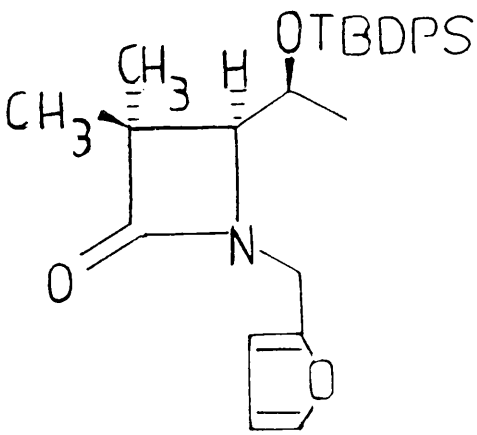
$[\alpha]_D^{20}$ $+21.3^o$ (c 1.62, CH_3OH)

ν_{max} ($CHCl_3$) 3 420 cm^{-1}, 1 770cm^{-1}, 1 750cm^{-1} 1 640cm^{-1}, 1 600cm^{-1}

Found: M^+, 574.2488. $C_{32}H_{38}N_2O_6Si$ requires 574.24992.

C	(P.P.M)	Multiplicity
2	168.56	s
NHCO	168.29	s
CO_2CH_3	167.23	s
O-C-(Ar)	156.73	s
m-Si-C_6H_5	135.78	d
	135.43	d
-Si-C-(Ar)	133.90	s
	133.23	s
m-O-C_6H_5	129.94	d
o-Si-C_6H_5	129.67	d
p-Si-C_6H_5	127.90	d
	127.65	d
p-O-C_6H_5	122.25	d
o-O-C_6H_5	114.62	d
$CHCH_2$	69.46	d
CH_2O	66.98	t
3	62.96	d
4	56.55	d
CO_2CH_3	52.43	q
CH_2N	43.23	t
$C(CH_3)_3$	27.00	q
$CHCH_3$	21.46	q
$C(CH_3)_3$	19.05	s

H	(P.P.M)	J (Hz)	Multiplicity
Furan-5-H	7.63	1.56,3.05	d,d
m-Si-C_6H_5	7.65-7.55	-	m
o-Si-C_6H_5			
p-Si-C_6H_5	7.48-7.15	-	m
m-O-C_6H_5			
o-O-C_6H_5	7.06	8.73	d
p-O-C_6H_5	6.97	7.41	t
Furan-4-H	6.75	2.10,3.05	d,d
Furan-3-H	6.21	1.50,2.12	d,d
3	5.45	4.83,8.95	d,d
NH	5.45	8.96	d
CH_2N	4.44	18.04	d
	4.40	15.19	d
CH_2O	4.28	15.18	d
$CHCH_3$	4.08-3.95	-	m
	4.00	2.71,4.86	d,d
CH_2N	3.89	18.06	d
$C(CH_3)_3$	1.01	-	s
$CHCH_3$	0.92	6.07	d



(271)

cis-4-[1-(t-^{B}utyldiphenylsiloxy)ethyl]-3,3-dimethyl-1-[(furan-2-yl)methyl]-2-azetidinone (271)

Imine (263) (415.1mg, 1.0600mmol) in THF (5ml) was reacted with the lithium ester enolate prepared by reaction of methyl 2-methylpropionate (120µl, 1.17mmol) with LDA [from diisopropylamine (163µl, 1.17mmol in 5ml THF) and n-butyllithium (0.47ml of a 2.5M solution in hexanes, 1.17mmol)] using the procedure described for the preparation of β-lactam (220). ^{1}H NMR spectroscopy showed the crude product to be a mixture of the desired β-lactam (271) and aldehyde (260). Chromatography gave pure aldehyde (264) (105.0mg, 0.3360mmol, 32%) and the desired β-lactam (271) (309.2mg, 0.6697mmol, 63%), the latter as a clear, viscous oil.

Packed column G.C. indicated that azetidinone (271) was present as one diastereoisomer only. ^{1}H and ^{13}C NMR spectroscopy agreed with this.

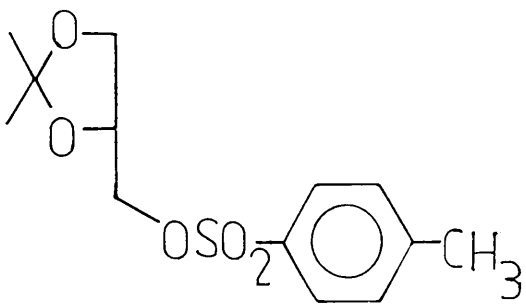
$[\alpha]_D^{20}$ -32.9 (c 0.63, CH_3OH)

ν_{max} ($CHCl_3$) 1 740 cm^{-1}

Found: M^+, 461.2350. $C_{28}H_{35}NO_3Si$ requires 461.23862

C	(P.P.M)	Multiplicity
2	174.58	s
Furan-2-C	149.17	s
Furan-5-C	142.33	d
m-C_6H_5	135.80	d
	135.75	d
Si-C(Ar)	133.88	s
	133.06	s
p-C_6H_5	129.80	d
	129.62	d
o-C_6H_5	127.65	d
	127.38	d
Furan-3-C	110.13	d
Furan-4-C	108.14	d
4	67.72	d
$CHCH_3$	67.66	d
3	52.96	s
CH_2N	37.46	t
$C(CH_3)_3$	26.63	q
CH_3	23.42	q
CH_3	20.66	q
$C(CH_3)_3$	18.92	s
CH_3	17.28	q

H	(P,P,M)	J (Hz)	Multiplicity
m-C_6H_5	7.73-7.58	-	m
o-C_6H_5	7.50-7.33	-	m
p-C_6H_5			
Furan-5-H	7.30	0.82,1.86	d,d
Furan-4-H	6.25	1.88,3.21	d,d
Furan-3-H	5.98	0.80,3.03	d,d
CH_2N	4.69	15.73	d
$CHCH_3$	3.97	4.80,6.42	d,q
CH_2N	3.67	15.78	d
4	2.98	4.78	d
$C(CH_3)_2$	1.33	-	s
	1.23	-	s
$CHCH_3$	1.13	6.43	d
$C(CH_3)_3$	1.05	-	s



(273)

(2,2-Dimethyl-1,3-dioxolan-4-yl)(p-toluenesulphonyloxy) methane (273).

To alcohol (211) (10.00g, 75.8 mmol) in pyridine (22.00ml, 272 mmol, 3.50 equivalents) was added p-toluenesulphonyl chloride (17.33g, 90.9mmol, 1.20 equivalents), in small portions over 2 min, by which time copious amounts of a white precipitate had formed. Stirring was continued for a further 2 h, whereupon the reaction mixture was diluted with ether (50ml) and then poured into water (150ml). The organic layer was separated and washed sequentially with 5% sodium hydroxide solution (3 x 50ml) and water (3 x 50ml). The resulting solution was dried (Na_2SO_4) and concentrated in vacuo to give crude tosylate (273).

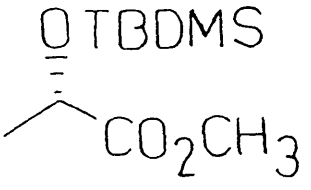
Purification by column chromatography gave the desired sulphonate ester (273) (19.41g, 67.6mmol or 89%) as a clear viscous oil.

ν_{max} ($CHCl_3$) 1 600 cm^{-1}.

Found : M-Me, 271.0640. $C_{13}H_{18}O_5S$-Me requires 271.06401

C	(P.P.M)	Multiplicity
$SO_2C(Ar)$	144.97	s
$CH_3C(Ar)$	132.29	s
C_6H_4	129.78	d
	127.79	d
$C(CH_3)_2$	109.85	s
CHO	72.73	d
CH_2O	69.41	t
CH_2O	65.89	t
$C(CH_3)_2$	26.43	q
	24.95	q
$ArCH_3$	21.47	q

H	(P.P.M)	J(Hz)	Multiplicity
C_6H_4	7.75	9.01	d
C_6H_4	7.31	9.02	d
CHO	4.23	-	m
	3.99	6.36, 8.77	d,d
CH_2O	3.96	9.16, 10.94	d,d
	3.93	11.01, 13.40	d,d
CH_2N	3.71	5.15, 8.77	d,d
$CH_3C(Ar)$	2.40	-	s
$C(CH_3)_2$	1.28	-	s
	1.26	-	s



(274)

(S)-2-(t-Butyldimethylsiloxy)propanoic acid methyl ester (274)[73]

To a stirred solution of (S)-methyl lactate (3.00g, 2.75ml, 28.8mmol) in THF (16ml) was added Et_3N (7.48g, 10.30ml, 73.8mmol) and DMAP (0.35g, 2.88mmol) in THF (3ml).

A solution of t-butyldimethylsilyl chloride (5.76g, 38.3mmol) in THF (10ml) was then added rapidly and with vigorous stirring to this system. An immediate white precipitate was observed.

After stirring for a further 16 h the solvent was removed in vacuo. The residue was triturated in ether (100ml) and the remaining salts removed by filtration. The filtrate thus obtained was washed sequentially with 15% acetic acid (50ml), water (50ml), saturated aqueous sodium sulphate (50ml) and finally water (50ml). The resulting ethereal solution was dried and concentrated in vacuo to give a pale yellow oil. Purification by either chromatography or distillation gave ester (268) (6.28g, 28.77 mmol, quantitative) as a clear oil, b.p. 84°C/18mm Hg.

ν_{max} ($CHCl_3$) 1 750 cm^{-1}

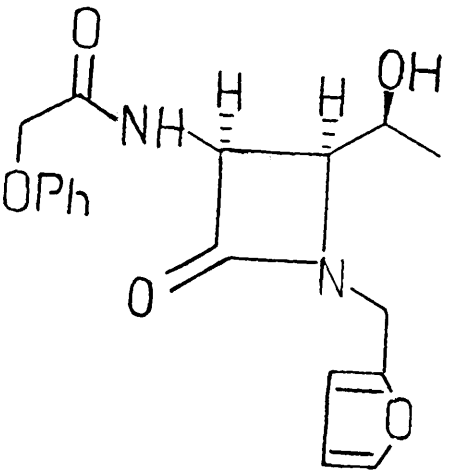
Found: M-Me, 203.1099. $C_{10}H_{22}O_3Si$-Me requires 203.11035.

$[\alpha]_D$ -31.0° (c.1.01, EtOH)

{lit.[73]. $[\alpha]_D^{20}$ -31.7° (c.0.66, EtOH)}

C	(P,P,M)	Multiplicity
CO_2CH_3	174.53	s
$CHCH_3$	68.34	d
CO_2CH_3	51.82	q
$C(CH_3)_3$	25.66	q
$CHCH_3$	21.31	q
$C(CH_3)_3$	18.26	s
$SiCH_3$	-5.04	q
	-5.33	q

H	(P.P.M)	J (Hz)	Multiplicity
$CHCH_3$	4.30	6.75	q
CO_2CH_3	3.69	-	s
$CHCH_3$	1.36	6.75	d
$C(CH_3)_3$	0.87	-	s
$SiCH_3$	0.064	-	s
	0.038	-	s



(275)

cis-1-[(Furan-2-yl)methyl]-4-[1-(hydroxy)ethyl]-3-(phenoxyacetamido]-2-azelidinone (275)

β-Lactam (246) (135.6mg, 0.2834mmol) was dissolved in 90% aqueous MeOH (10ml) and potassium carbonate (0.20g, 1.45mmol) was added. After stirring for 2.5 h the solvent was removed in vacuo. The resultant solid was partitioned between CH_2Cl_2 (50ml) and water (10ml). After separation the organic layer was dried. Concentration followed by purification by chromatography gave alcohol (275) (86.4mg, 0.2587mmol, 91%).

$[\alpha]_D^{20}$ +26.8° (c. 1.99, MeOH)

ν_{max} ($CHCl_3$) 3 600 cm^{-1}, 3 400 cm^{-1}, 1 760 cm^{-1}, 1 680 cm^{-1}, 1 600 cm^{-1}

Found: M^+, 344.1393. $C_{18}H_{20}N_2O_5$ requires 344.13722.

C	(P.P.M)	Multiplicity
NHCO	168.658	s
2	167.634	s
O-C(Ar)	157.022	s
Furan-2-C	148.760	s
Furan-5-C	142.746	d
m-C_6H_5	129.678	d
p-C_6H_5	122.077	d
o-C_6H_5	114.628	d
Furan-3-C	110.699	d
Furan-4-C	108.827	d
$COCH_2$	66.964	t
CHOH	65.649	d
3	62.183	d
4	56.192	d
CH_2N	39.099	t
CH_3	21.420	q

H	(P.P,M)	J (Hz)	Multiplicity
NH	7.84	9.90	d
Furan-5-H	7.38	1.86,0.84	d,d
m-C_6H_5	7.29	7.64,7.23	d,d
p-C_6H_5	7.00	7.36	t
o-C_6H_5	6.89	7.66	d
Furan-4-H	6.34	3.28,1.86	d,d
Furan-3-H	6.28	3.25,0.84	d,d
3	5.47	9.95,5.13	d,d
CH_2N	4.63	15.94	d
CH_2O	4.49	-	s
CH_2N	4.39	15.91	d
4	3.68	5.10,6.42	d,d
CH(OH)	3.68	-	m
CH_3	1.17	6.69	d

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