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Synthesis of intermediates for carbapenem antibiotics and synthetic analogues of dehydroepiandrosterone (DHEA)

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A thesis presented to the University of Dublin
for the degree of
Doctor of Philosophy in Pharmaceutical Chemistry.

Based on research carried out under the supervision of
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Trinity College Dublin.

September, 1999

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This thesis has not been presented as an exercise
for a degree at any other university.
The work described, except where duly acknowledged,
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Summary

The work presented in this thesis is divided into two parts.

Part one consists of the synthesis and chemical modification of β-lactams as potential intermediates for carbapenem antibiotics.

Part two describes the synthesis of analogues of 3β-androst-5-ene-17-one (DHEA) and 3β-hydroxyandrost-5-ene-7,17-dione (7-oxo-DHEA) as potential therapeutic agents.

The carbapenems are a group of non-classical β-lactam compounds containing a bicyclic carbapen-2-em-3-carboxylic acid nucleus. They possess potent antibacterial activity together with an unprecendented level of stability to a wide variety of β-lactamases. Thienamycin, the first known carbapenem was isolated from *Streptomyces cattleya* in 1976. The C-2 aminoethylthio substituent or a derivative thereof is accredited with the antipseudomonal activity demonstrated, while the hydroxyethyl or substituted alkyl C-6 substituent is thought to be responsible for the high degree of β-lactamase stability observed for these structures. Research to date involving the development of synthetic carbapenems has concentrated on the modification of the C-2 side chain. In this work the synthesis of monocyclic β-lactams containing a reactive C-3 vinyl side chain, which are suitably substituted to facilitate conversion to novel carbapenem compounds is presented.

Chapter 1 consists of a literature survey. The synthesis of a series of 1,4-diaryl-3-vinylazetidin-2-ones is reported in Chapter 2. Epoxidation of the vinyl group of these compounds is examined, providing opportunities for further chemical transformation. It is envisaged that the introduction of such side chains to the carbapenem skeleton would result in the development of novel carbapenems. In Chapter 3 the stereocontrolled synthesis of a series of 3-vinyl β-lactams and 3-isopropenylazetidin-2-ones via two alternative synthetic routes is reported. The vinylic side chain at the C-3 position of the β-lactam provides scope for chemical transformations. The isomerisation of the double bond at C-3 with base provides the alkylidene side chain which is present in the asparenomycin series of carbapenems, whose members are regarded as the ene-carbapenems. The reduction of these 3-alkylidene-4-formylazetidin-2-ones to the corresponding 4-hydroxymethyl β-lactams is examined. Conversion of the alcohol to the corresponding mesylate facilates a series of nucleophilic substitution reactions to provide carbapenem intermediates such as the 4-iodomethyl β-lactams.

The introduction of an α,β-unsaturated ketone substituent at C-3 to yield a series of azetidin-2-ones is outlined in Chapter 4. The addition of α,β-unsaturated aldehydes to readily available C-3 unsubstituted β-lactams in the presence of LDA, followed by oxidation of the resulting alcohol, allows the formation of these products. The synthetic potential of these products is investigated further via epoxidation of the double bond affording appropriate oxiranes. Radical oxidation of 4-unsubstituted β-lactams resulted in the unexpected isolation of 3,3-disubstituted azetidin-2-ones, containing C-3 acyl and C-3 benzyl groups.

In Chapter 5, the stereocontrolled synthesis of a series of 3-alkyl-4-formylazetidin-2-ones is reported. The formyl side chain at C-4 position of the β-lactam ring provides various opportunities for further chemical transformations. Oxidation of the 4-formyl group to epoxides affords highly reactive oxiranes which are themselves suited to further chemical manipulation. An unexpected novel ring enlargement of 4-formyl-3-vinylazetidin-2-one to 4-methyl-1-(4-methoxyphenyl)-2-pyrrolidinone is described. A reaction mechanism for this novel transformation is proposed in Chapter 5. Extension of the research conducted in this part of the thesis would be expected to contribute to the total synthesis of novel carbapenems.

In the past fifteen years, research on the biological role of DHEA has shown that DHEA also has a number of diverse physiological roles in diseases such as diabetes and cancer and plays a role in many conditions, for example obesity and the process of ageing. However DHEA is not useful as a therapeutic agent because the high dose rate necessary to achieve these desired characteristics may also stimulate the production of sex hormones, which is associated with various undesired side effects. 7-Oxo-DHEA is reported to have therapeutic properties but without the undesired side effects associated with DHEA. Because of the functionality of DHEA at C-3, C-5, C-6 and C-17, a number of chemical modifications can be carried out. The principle objective of this part of the thesis is the preparation of a number of analogues of DHEA containing a ketone at C-7 and possessing the thermogenic properties of DHEA but without the undesired side effects.

Chapter 6 consists of a literature survey. In Chapter 7 the halogenation and tosylation of DHEA are examined. Synthesis of 7-oxo-DHEA via several alternative synthetic routes is described. Epoxidation of $\Delta^{3,5}$-androstadiene-7,17-dione, followed by regioselective ring opening of the epoxide with alcohols catalysed with cerium ammonium nitrate is investigated. Hydroxylation at C-4 of 7-oxo-DHEA is also examined providing further functionality to the DHEA structure.

Abbreviations

Ac	Acetyl
Ar	Aryl
Ax	Axial
Bn	Benzoyl
b.p.	Boiling point
Bu	Butyl
^{t}Bu	*tert*-Butyl
Bzl	Benzyl
CAN	Cerium(IV) ammonium nitrate
Cfu	Colony forming units
^{13}C-NMR	Carbon-13-nuclear magnetic resonance
COSY	Correlated spectroscopy
CSI	Chlorosulfonyl isocyanate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DEPT	Distortion enhancement by polarisation transfer
DIBALH	Diisobutylaluminum hydride
DHP-1	Dehydropeptidase-1
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
ED_{50}	The effective dose at which 50% curative result is observed
EDAX	X-ray fluoroscence analysis
EI	Electron impact
Et	Ethyl
EtOAc	Ethyl acetate
Eq	Equatorial
FAB	Fast atom bombardment
G3PDH	Glycerol-3-phosphate dehydrogenase
^{1}H-NMR	Proton nuclear magnetic resonance
^{i}Pr	Iso-propyl
IR	Infrared
LDA	Lithium diisopropylamide

Me	Methyl
*m*CPBA	*meta*-Chloroperbenzoic acid
MIC	Minimal concentration needed to completely inhibit the growth of a given bacterial strain
MMPP	Magnesium monoperphthalate
m.p.	Melting point
MRSA	Methicillin resistant *Staphylococcus aureus*
NADPH	Nicotinamide adenine dinucleotide phosphate
OAc	Acetoxy
PAE	Postantibiotic effect
PBP	Penicillin binding protein
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMP	*p*-Methoxyphenyl
PNB	*p*-Nitrobenzyl
Py	Pyridine
RT	Room temperature
t-	*Tert*
Ts	Tosylate
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TMCS	Trimethylchlorosilane
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilyl
U.V	Ultraviolet spectroscopy

Chapter 1

Carbapenems: Structure, Synthesis and Antibacterial Activity

1.1 General Introduction

Throughout recorded history, bacterial infections have periodically extended heavy tolls on the human population; for example the black death (bubonic plague) episode of 1347-1351, when *Yersinia pestis* killed an estimated 25 million people in Asia and Europe[1]. The discovery of penicillin in 1929 by Sir Alexander Fleming[2,3] led to one of the most successful endeavours in all infectious chemotherapy[3]. Since the discovery of penicillin, pharmaceutical companies have produced more than one hundred clinical antibacterial agents and antibiotics to combat a wide variety of bacterial infections and many thousands of antibacterial compounds have been produced for experimental evaluation. The major class of clincial antibacterial agents are β-lactams (including penicillins, cephalosporins, monobactams and carbapenems)[2]. However in the past several years, the rapid emergence of bacterial resistance to antibiotics has been observed.

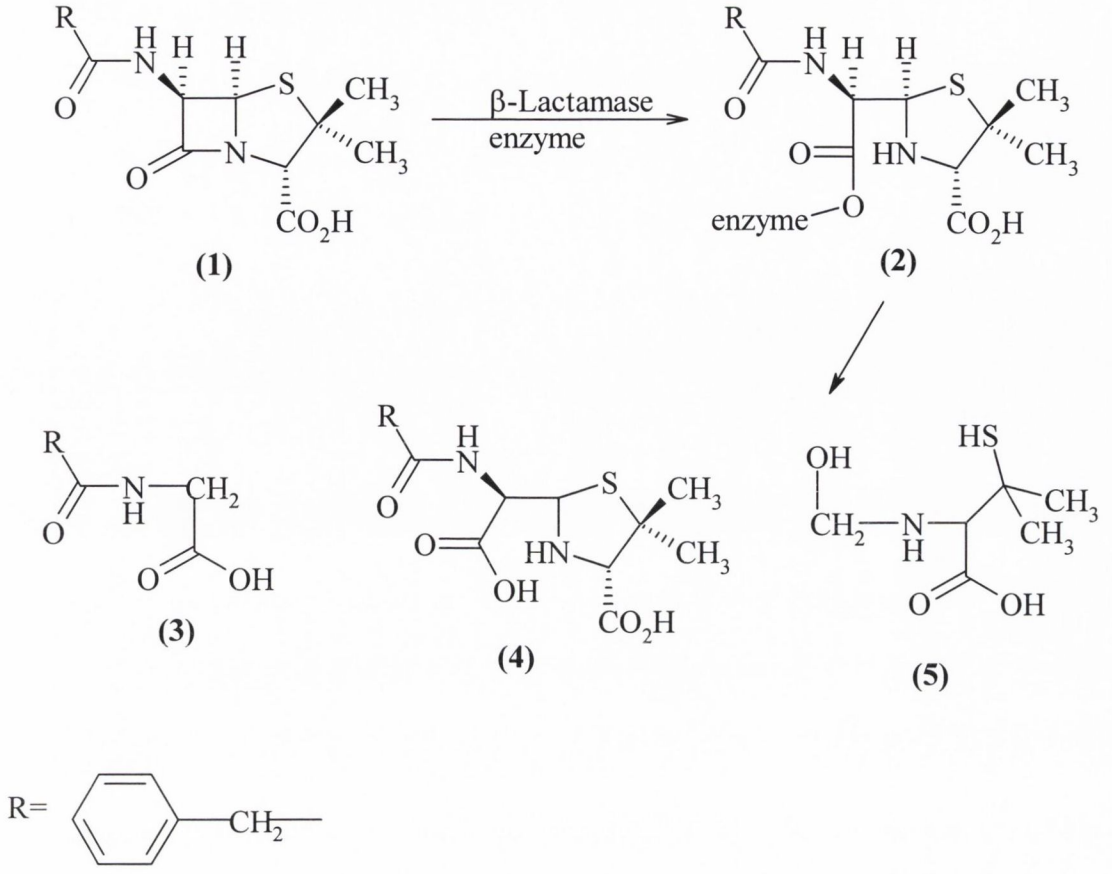
β-Lactam antibiotics are characterised structurally by the presence in the molecule of a β-lactam, a cyclic amide forming a four atom ring. The integrity of this ring is essential for activity. All β-lactam antibiotics have a common mechanism of action: inhibition of bacterial cell wall synthesis by interacting in different ways with the penicillin binding proteins (PBP), enzymes involved in the synthesis of peptidoglycan. The β-lactam group includes two of the most important families of clinical antibiotics; the penicillins, in which the β-lactam ring is fused with a thiazolidine (a five-atom ring), and the cephalosporins, which are characterised by fusion with a dihydrothiazine (a six-atom ring). In addition to these ``classical`` β-lactam antibiotics, several new and interesting β-lactam structures have been isolated from microorganisms or obtained by semisynthesis. Collectively referred to as the "non-classical" β-lactams, they include the cephamycins or 7-methoxycephalosporins, the carbapenems, and the oxapenems, in which the five-atom ring contains a carbon or an oxygen atom instead of sulphur. In the recently discovered monobactams, the β-lactam ring is not fused to the second ring system[3].

1.2 Natural Penicillins and Cephalosporins

The era of extensive use of antibiotics in medicine began in 1942 when penicillin G (**1**) was introduced into clinical practice. Penicillin G (benzyl penicillin) (**1**)[3] is active against gram positive bacteria including *Nesseria spp.*, *Treponema pallidum, Streptococcus pyogenes, Enterococcus faecalis*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *Enterococcus faecalis*. Its great efficacy *in vivo* and lack of toxicity made it, for half a century, the antibiotic of choice in the treatment of several infectious diseases. The pharmacokinetic properties of Penicillin G (**1**), however were not satisfactory. It is absorbed only partially when adminstered orally and most of it is inactivated by the acidic pH in the stomach. When injected, e.g. as the soluble potassium salt, it is rapidly absorbed but also rapidly excreted in the urine with a serum half-life of only 30 minutes. Penicillin G (**1**) was chosen for commercial production among the natural penicillins produced by *Penicillin notatum* because its fermentation yield could be substantially increased by the addition of the lateral chain precursor phenylacetic acid. This revealed an important aspect of structure-activity relationship in penicillins: when the lipophilicity of the side chain is increased, the binding to serum proteins is also increased, normally resulting in lower therapeutic efficacy. The following areas of modification of Penicillin G (**1**) were soon identified from which useful clinically compounds were developed:

(a) Improvement of absorption after oral adminstration.
(b) Enlargement of the spectrum of activity to gram negative bacteria.
(c) Reduction of incidence of allergic reactions.
(d) Acquisition of activity against resistant *Staphylococcal* strains.

With the extensive use of penicillin G (**1**), *Staphylococcus aureus* resistant strains soon emerged. This was the result of ability of these strains to produce enzymes called β-lactamases or penicillinases that inactivate penicillin G (**1**) (**Scheme 1**).



Scheme 1

The β-lactamase enzyme hydrolyses the cyclic amide of the β-lactam molecule (penicillin G (**1**)) resulting in the product (**2**) in which the ring opened penicillin is linked covalently to the enzyme. Loss of the enzyme results in the formation of the three products (**3**), (**4**) and (**5**). In gram negative bacteria these enzymes are localized in the periplasmic region and inactivate the antibiotic as soon as it penetrates the outer membrane. In gram positive bacteria they are excreted mainly in the culture medium. The bacterial β-lactamases are extremely heterogenous, both in structure and in substrate specificity.

The synthesis of a number of penicillins with structural variations in the side chain revealed that when the carbon atom α to the amide is included in an aromatic ring carrying substituents in the *ortho* position, the resulting steric hindrance protects the nearby β-lactam ring from the enzymatic attack[3]. Activity against penicillinase producing *Staphylococci* and insensitivity to acids (and thus absorbtion after oral adminstration) are two properties combined in isoxazolylpenicillins e. g. flucloxacillin (**6**).

By comparing the activities of the many derivatives prepared it has been possible to establish a correlation between some structural features and the property of inhibiting the growth of gram negative strains:

(a) A moderate enhancement of activity is obtained by substitution of the phenyl group of penicillin G (**1**) with certain heterocyclic rings.

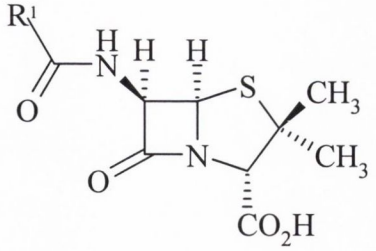
(b) The effect of polar substituents on the C-6 amide chain in positions far from the amide bond is positive but small. When the substituent is an amino group this effect is more pronounced.

(c) The activity decreases when the carbon atom α to the amide is fully substituted.

(d) The activity decreases when the lipophilic character of the chain is increased.

Among many derivatives prepared ampicillin (**7**) showed superior therapeutic efficacy (**Figure 1**). It inhibits all bacteria susceptibile to Penicillin G (**1**) and most strains of *Escherichia coli, Proteus mirabilis* and *Haemophilus influenzae*. However it is inactive against most strains of *Klebsiella, Enterobacter, Proteus* and totally inactive against *Pseudomonas*. The lack of activity against these strains is related to the presence of inducible β-lactamases. Ampicillin (**7**) is also sensitive to the action of *Staphylococcal* penicillinase and thus inactive against *Staphyloccus aureus* strains that produce this enzyme.

Because ampicillin (**7**) is fairly resistant to acid degradation, it is used orally. However, its oral absorption is not entirely satisfactory and many derivatives have been prepared to improve this aspect, e.g amoxycillin (**8**). A different approach towards the improvement of oral absorption involves the preparation of lipophilic derivatives inactive *in vitro* but easily hydrolysed in the body to give the active free antibiotic. As simple esters are not easily hydrolysed by the serum esterases because of the proximity of the bulky thiazole ring, double esters of the type -CO-O-CH_2-O-COR have been developed. The enzymatic hydrolysis of the second ester group unmasks a hemiacetal group, which spontaneously hydrolyzes. Among these, the most widely used is pivampicillin (**9**).



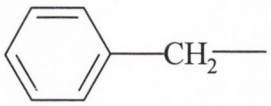
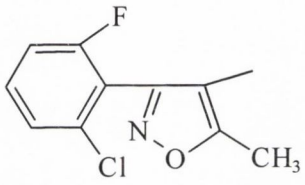
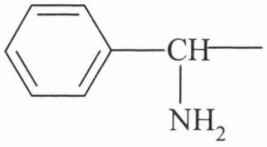
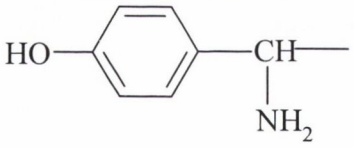
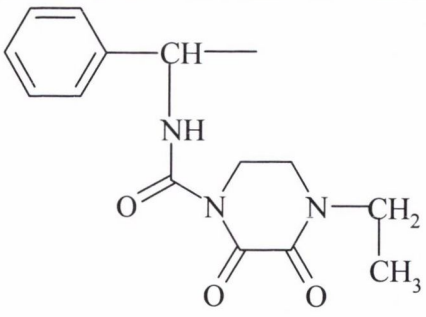
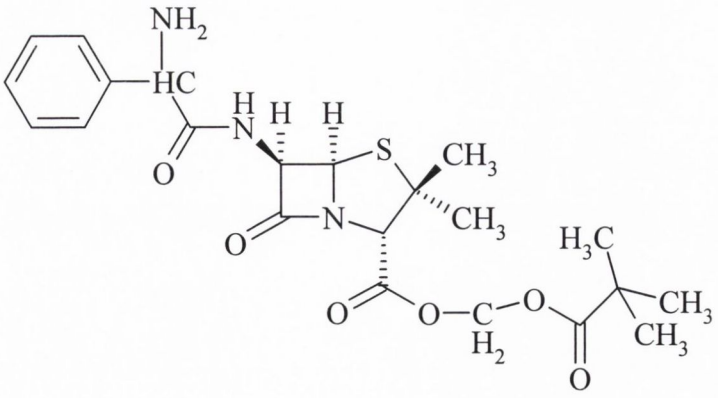
Compound	**R^1**	**Compound No.**
Penicillin G		**(1)**
Flucloxacillin		**(6)**
Ampicillin		**(7)**
Amoxycillin		**(8)**
Piperacillin		**(10)**

Figure 1: *Structural development of penicillins*



(9)

Amoxycillin (**8**) is almost completely orally absorbed and therefore, besides showing higher efficacy, is responsible for a lower incidence of intestinal disorders. The increased activity against *E. coli* obtained by introducing polar groups in the position α to the amide chain led to the preparation of molecules with stronger polar groups in this position for their potential activity against *Pseudomonas* or *Proteus* strains. A ureido derivative of ampicillin e.g. piperacillin (**10**) proved to be active against *Pseudomonas* and *Proteus spp* .

The discovery and development of the cephalosporins began with the observation by Brotzu that a cephalosporium species produced antibiotic material that was active against gram negative as well as gram positive organisms. This fungus was later found by Oxford workers to produce at least six antibiotic substances. A major hydrophilic component was identified as Penicillin N^4 whereas a minor component was identified as Cephalosporin C (**11**)[5, 6, 7]. Cephalosporin C (**11**) was active against penicillinase-producing *Staphylococcus aureus*. A feature shared by penicillins and cephalosporins is the functionalised amino group on the C-3 opposite the nitrogen of the β-lactam.

The first cephalosporin introduced into medical pratice was cephalothin (**12**). Cephalothin (**12**) is active against *Staphylococci* which is both susceptible and resistant to penicillin and against *Neisseria spp.* and most *E. coli, Salmonella spp.* and *Proteus mirabilis* strains. The limitations to its clinical use, which have promoted further research in the cephalosporin field, may be summarized as follows:

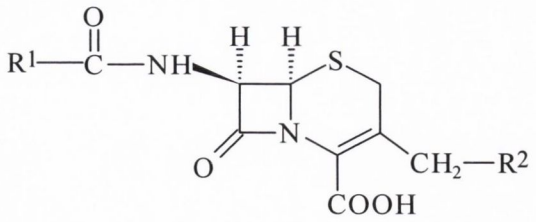
(a) It is not absorbed orally.

(b) It is inactive against *Pseudomonas aeruginosa*, *Serratia marcescens*, *Enterobacter* and *Bacteroides fragilis* strains.

The phenylglycine side chain of ampicillin (**7**) was shown to be an excellent moiety for cephalosporins also. The first orally active cephalosporin, cephaloglycine (**13**) has the natural substituent acetoxymethyl at position 3. Its spectrum of antibacterial activity is similar to that of cephalothin (**12**) which includes most gram positive bacteria (with the exceptions common to most cephalosporins, of *Enterococcus faecalis* and *Neisseria spp., E. coli*, and *Proteus mirabilis*).

Second and third generation cephalosporins are characterized by their enhanced activity, obtained mainly by the choice of suitable substituents at the amide chain combined with a substituent in position 3. The antibacterial spectra of cefamandole (**14**) and cefuroxime (**15**) (second generation) include indole positive *Proteus* and *Enterobacter spp.* and *Haemophilus influenzae*. Cefamandole (**14**) maintains good activity against gram positive species, and is more active than first generation cephalosporins against *E. coli*, and *P. mirabilis*.

The prototype of third generation cephalosporins is cefotaxime (**16**), characterized by an acyl chain, which bears in an α-position a methoxyimino group (the syn isomer) and in the β-position an aminothiazole. The presence of the substituent in an α-position protects the molecule from attack of β-lactamases and thus cefotaxime (16) combines an excellent activity against *Enterobacteria* with an acceptable activity against gram positives (with the exception of *Enterococci*) and a fair activity against *Pseudomonas spp.* [8,9].



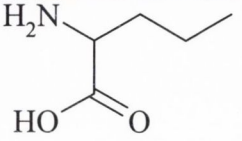
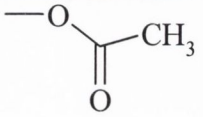
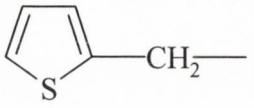
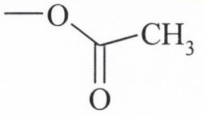
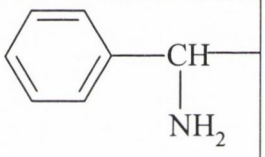
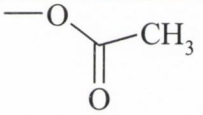
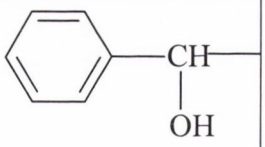
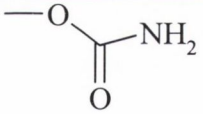
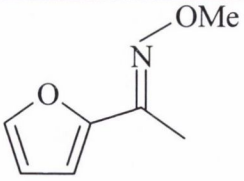
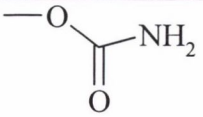
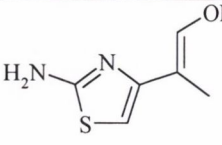
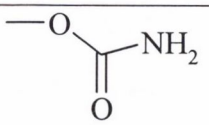
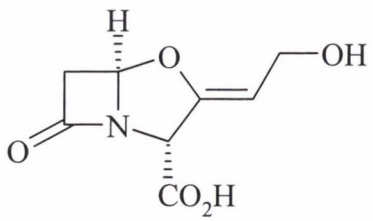
Compound	R^1	R^2	Compound No.
Cephlosporin C			**(11)**
Cephalothin			**(12)**
Cephaloglycine			**(13)**
Cefamandole			**(14)**
Cefuroxime			**(15)**
Cefotaxime			**(16)**

Figure 2: *Structural development of cephalosporins*

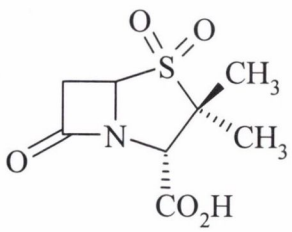
1.3 β-Lactamase Inhibitors and Monobactams

The emergence of resistant strains of pathogenic microorganisms has hindered advances in chemotherapy of bacterial infections[10]. The major causes of resistance to antibiotic therapy is the production of β-lactamase enzymes by pathogenic bacteria. Their hydrolytic destruction of the β-lactam amide unit can however be overcome by structured alteration of the β-lactam rendering it insensitive to hydrolysis of the β-lactamases or by the use of β-lactamase inhibitors, such as clavulanic acid (**17**)[11], isolated from *Streptomyces clavuligerus*. This oxapenam molecule consists of a β-lactam ring condensed with an oxazoline giving rise to a penicillin type nucleus with an oxygen substituting for the sulphur atom. It combines covalently with various β-lactamases inactivating them. Clavulanic acid (**17**) has an antibacterial spectrum which is quite broad but with marginal activity. It can be considered an inhibitor of β-lactamases of *Staphylococci spp.* and of several gram negative β-lactamases such as those produced by *Proteus, Escherichia* and *Haemophilus spp.*, but not of *Pseudomonas* or *Enterobacter*. It is used in combination with amoxycillin (**8**) (the combination is marketed as ``Augmentin``) to treat infections from bacteria resistant to amoxycillin (**8**).

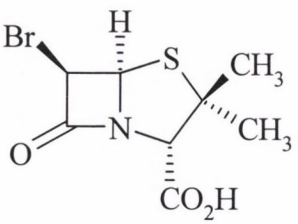
Another inhibitor of β-lactamases is sulbactam (**18**)[3]. It shows an activity similar to that of clavulanic acid (**17**) but is used in combination with ampicillin (**7**). 6β-Bromopenicillanic acid[12] (**19**) is an inhibitor of β-lactamases of *Staphylococcus aureus, Escherichia coli* (strain 3310), *Bacillus licheniformis* and *Pseudomonas aeruginosa.*



(17)

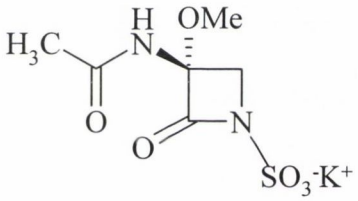


(18)

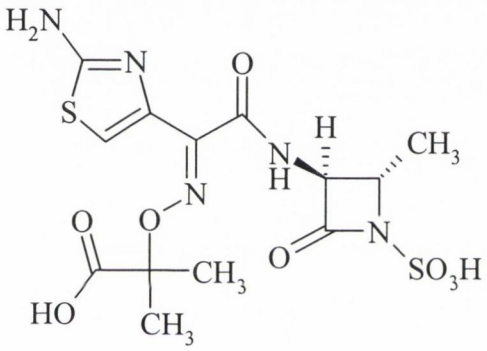


(19)

In 1978 a soil sample collected in the Pine Barrens of southern New Jersey was screened for the presence of β-lactam producing bacteria by the Squibb Institute[13]. A novel product identified as SQ26180 (**20**) was produced by strains of a gram negative bacterium *Chromobacterium violaceum* and classified as a monobactam. All monobactams are characterised by the 3-acylamino-2-oxoazetidine-1-sulphonic acid moiety. This unique structural feature is the sulphonic acid moiety directly attached to the β-lactam nitrogen atom. Among the numerous products synthesized, aztreonam[3] (**21**) has found clinical use. It is insensitive to β–lactamases and is particularly active against gram negative aerobes, including some strains of *Pseudomonas aeruginosa.* Its use is mainly justified by its lower toxicity with respect to other antibiotics possessing the same spectrum of action.



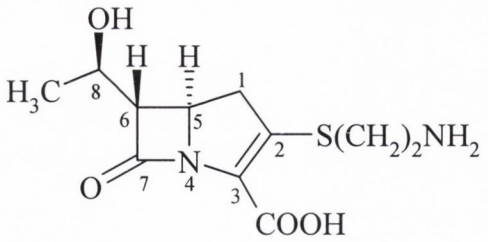
(20)



(21)

1.4 Carbapenems

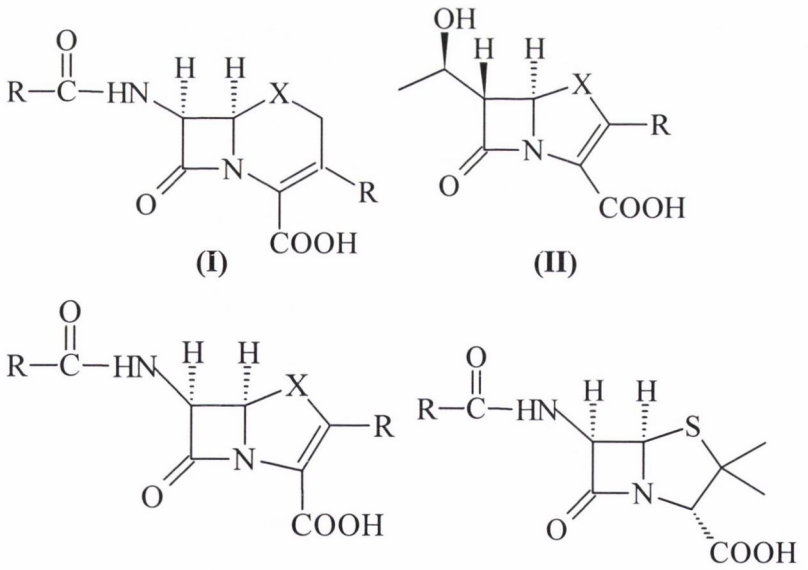
The carbapenems are a naturally occuring family of broad spectrum β-lactam antibiotics which possess β-lactamase properties. In 1976, almost five decades after the discovery of penicillin and two decades after cephalosporins were reported, Kahan *et al* at the Merck, Sharp and Dohme Research Laboratories isolated the β-lactam thienamycin (**22**) from *Streptomyces cattleya*[14, 15]. Other naturally occuring members of the carbapenem group include the olivanic acids, epithienamycins, carpetimycins, asparenomycins, pluracidomycins and the PS group.



(22)

The non-classical β-lactams differ structurally from the classical β-lactams e.g. penicillins and cephalosporins in a number of features[25] **(Table 1)**. The most obvious structural difference between the classical β-lactam antibiotics and the carbapenem products is the absence of a ring sulphur atom and a more strained pyrroline-azetidinone ring system. The amide bond of the ring system is highly reactive. The side chain at C-6 can be either *cis* or *trans* orientated with respect to the substituents about the azetidin-2-one ring. The configuration of the hydroxy bearing C-8 can be either *R* or *S*.

Table 1:General structural features of β–lactam type antibiotics.



(I) **(II)**

(III) **(IV)**

Cephalosporins and Oxapenems

(I): X=S: cephem; X=O: oxacephem
(II): X=S: penem; X=O: oxapenem

Carbapenems and Penams

(III): X=CH_2: carbapenems
(IV): Penam

The carbapenems are named as 7-oxo-1-azabicyclo[3.2.0.]hept-2-ene-2-carboxylic acids in the Chemical Abstracts. The penems are structurally related analogues that possess a sulphur atom at the position adjacent to the ring fusion (**Table 1**). They offer good potency against *Pseudomonas aeruginosa*. They are not accesible from natural sources unlike the carbapenems. They have an important stereocenter adjacent to the C-6 center which is usually a hydroxyalkyl substituent bearing the *R* designation.

A wide variety of structurally varied carbapenems have been isolated from *Streptomyces* species. A general outline of the structural types of carbapenems isolated to date follows in **Table 2**. In general the C-2 group is a cysteamine or a derivative thereof. The amino group may be acylated, the sulphur can be present as a sulphoxide or the ethylene functional group may be unsaturated. *Streptomyces cattleya* produces four carbapenems, e.g. thienamycin (**22**), 9-northienamycin (**23**), *N*-acetylthienamycin (**24**), *N*-acetyldehydrothienamycin (**25**). *Streptomyces olivaceus* produces the olivanic acids e.g. MM17780 (**26**), MM13902 (**27**), MM22380 (**28**), MM2382 (**29**), MM22381 (**30**) and MM 22383 (**31**). *Streptomyces cremus subsp. auratilis* produces the PS compounds e.g. PS5 (**32**) and PS6 (**33**).

The carpetimycins are obtained from *Streptomyces griseus* e.g. carpetimycin A (**34**), carpetimycin B (**35**). *Streptomyces pluracidomyceticus* produces the pluracidomycins e.g. pluracidomycin B (**36**), pluracidomycin C1 (**37**), pluracidomycin C2 (**38**), pluracidomycin C3 (**39**), pluracidomycin D (**40**), pluracidomycin A2 (**42**) and *Streptomyces sulfonfaciens* produces pluracidomycin A1 (**41**). The epithiemamycins e.g. epithienamycin B sulfoxide (**43**) is produced by *Streptomyces pluracidomyceticus* while epithienamycin F (**26**), epithienamycin E (**27**), epithienamycin A (**28**), epithienamycin B (**29**), epithienamycin C (**30**) and epithienamycin D (**31**) are produced by *Streptomyces olivaceus*. Asparenomycin A (**44**), asparenomycin B (**45**), asparenomycin C (**46**) and 6643-X (**47**) are all produced by *Streptomyces tokunonensis* and *Streptomyces argenteolus*.

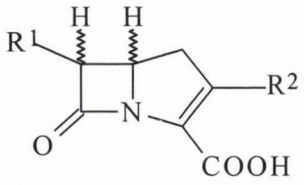
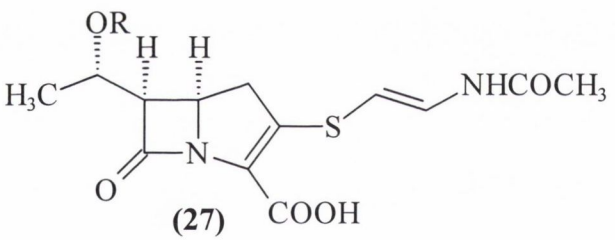


Table 2:Naturally occuring Carbapenems

No	Name	Producing Organism	R^1	R^2	C-8	C5,6
22	Thienamycin	*S. cattleya*	$CH(CH_3)OH$	$SCH_2CH_2NH_2$	*R*	*trans*
23	9-Nor-thienamycin	*S. cattleya*	CH_2OH	$SCH_2CH_2NH_2$	-	*trans*
24	*N*-Acetylthienamycin	*S. cattleya*	$CH(CH_3)OH$	$SCH_2CH_2NHCOCH_3$	*R*	*trans*
25	*N*-Acetyldehydrothienamycin	*S. cattleya*	$CH(CH_3)OH$	$SCH{=}CHNHCHCH_3$	*R*	*trans*
26	MM 17880/ Epithienamycin F 1	*S.olivaceus*	$CH(CH_3)OSO_3Na$	$SCH_2CH_2NHCOCH_3$	*S*	*cis*
27	MM 13902/ Epithienamycin E	*S.olivaceus*	$CH(CH_3)OSO_3H$	$SCH{=}CHNHCOCH_3$	*S*	*cis*
28	MM 22380/ Epithienamycin A 1	*S.olivaceus*	$CH(CH_3)OH$	$SCH_2CH_2NHCOCH_3$	*S*	*cis*
29	MM 22382/ Epithienamycin B	*S.olivaceus*	$CH(CH_3)OH$	$SCH{=}CHNHCOCH_3$	*S*	*cis*
30	MM 22381/ Epithienamycin C	*S.olivaceus*	$CH(CH_3)OH$	$SCH_2CH_2NHCOCH_3$	*S*	*trans*
31	MM 22383/ Epithienamycin D	*S.olivaceus*	$CH(CH_3)OH$	$SCH{=}CHNHCOCH_3$	*S*	*trans*
32	PS-5	*S. cremus sub sp. auratilis*	CH_2CH_3	$SCH_2CH_2NHCOCH_3$	-	*trans*
33	PS-6	*S. cremus sub sp. auratilis*	$CH(CH_3)CH_3$	$SCH_2CH_2NHCOCH_3$	-	*trans*
34	Carpetimycin A	*S. griseus (cryophilus)*	$C(CH_3)CH_3OH$	$SOCH{=}CHNHCOCH_3$	-	*cis*
35	Carpetimycin B	*S. griseus (cryophilus)*	$C(CH_3)CH_3SO_3H$	$SOCH{=}CHNHCOCH_3$	-	*cis*
36	Pluracidomycin B	*S. pluracidomyceticus*	$CH(CH_3)OSO_3H$	$SOCH_2COOH$	*S*	*cis*
37	Pluracidomycin C1	*S. pluracidomyceticus*	$CH(CH_3)OSO_3H$	$SOCH(OH)_2$	*S*	*cis*
38	Pluracidomycin C2	*S. pluracidomyceticus*	$CH(CH_3)OSO_3H$	$S(O)CH_2CH_2OH$	*S*	*cis*
39	Pluracidomycin C3	*S. pluracidomyceticus*	$CH(CH_3)OSO_3H$	$S(O)CH_2CH_2NHAc$	*S*	*cis*
40	Pluracidomycin D	*S. pluracidomyceticus*	$CH(OH)CH_3$	SO_3H	*R*	*cis*
41	Pluracidomycin A1	*S. sulfonofaciens*	$CH(CH_3)OSO_3H$	SO_3H	*S*	*cis*
42	Pluracidomycin A2	*S. pluracidomyceticus*	$CH(CH_3)OSO_3H$	SO_2H	*S*	*cis*
43	Epithienamycin-B sulfoxide	*S. pluracidomyceticus*	$CH(OH)CH_3$	$SOCH{=}CHNHCOCH_3$	*R*	*trans*
44	Asparenomycin A	*S.tokunonensis* and *S.argenteolus*	CH_3CCH_2OH	$SOCH{=}CHNHCOCH_3$	-	-
45	Asparenomycin B	*S.tokunonensis* and *S.argenteolus*	CH_3CCH_2OH	$SOCH_2CH_2NHCOCH_3$	-	-
46	Asparenomycin C	*S.tokunonensis* and *S.argenteolus.*	CH_3CCH_2OH	$SCH_2CH_2NHCOCH_3$	-	-
47	6643-X	*S.tokunonensis* and *S.argenteolus.*	CH_3CCH_2OH	$SCH{=}CHNHCOCH_3$	-	-

1.4.1 Olivanic acids

Streptomyces olivaceus has been found to produce a class of compounds structurally related to thienamycin (**22**) which exhibits broad spectrum antibacterial activity and posess β-lactamase inhibitory properties. The Beecham group has termed these compounds olivanic acids[22]. All the olivanic acids have two common structural features that set them apart from thienamycin. The aminoethylthio side chain, whether saturated or unsaturated, is invariably *N*-acetylated, and the chiral centre of the hydroxy ethyl side-chain always has the *S*-configuration[16] whereas C-6 is in the *R*-configuration. Whereas thienamycin (**22**) is *trans* substituted about the azetidinone ring, olivanic acids MM17880 (**26**), MM13902 (**27**), MM22380 (**28**), and MM22382 (**29**) are *cis* substituted. Olivanic acids MM22381 (**30**) and MM22383 (**31**) are differentiated from the other members of the olivanic acids by their *trans* stereochemistry. Olivanic acids MM17880 (**26**) and MM13902 (**27**) are sulphate esters of MM22380 (**28**) and MM22382 (**29**). Their longwave uv absorption near 300nm is useful for their identification.



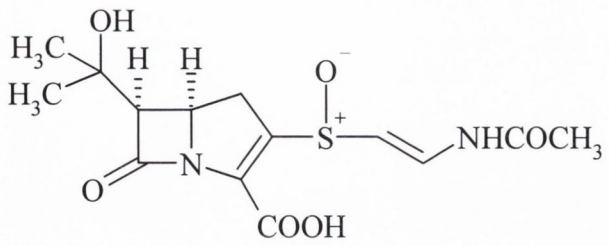
(27)

MM 13902
R= -SO_3H

1.4.2 Carpetimycins

Since the discovery of the thienamycin (**22**) and olivanic acid families of carbapenems in the mid 1970`s a number of other carbapenem families have emerged. The carpetimycins were isolated from *Streptomyces* species KC-6643. They display similar β-lactamase inhibitory properties to those of the olivanic acids[17]. These compounds provide examples of the C-6-isopropyl substituent, but now also include the C-8 hydroxy group. The configuration at the C-5 and C-6 of the carpetimycins are the same as those of the sulphated olivanic acids. Carpetimycin B (**35**) is 8-methyl-

MM 4550 if one assumes the same *R*-sulphoxide chirality for both compounds, Carpetimycin A (**34**) is the corresponding C-8 alcohol[16].



(34)

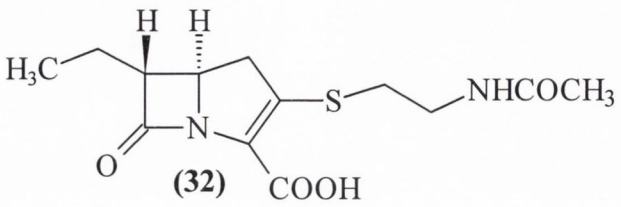
1.4.3 Asparenomycins

Asparenomycins containing a characteristic 1-(hydroxymethyl)ethylidene side chain at C-6 have been isolated from both *Streptomyces tokunonesis* and *Streptomyces argenteolus* and are known as the *ene* carbapenems[18-20]. They are structurally unique because the common side chain at C-6 is a 1-(hydroxymethyl)ethylidene group in the *E*-form and they have only one asymmetric carbon which is at the C-5 with *R* configuration. Asparenomycin A (**44**) is ring substituted at the 2-position by an aminoethenylthio group and the sulphur is oxidised to the corresponding sulphoxide[21]. It exhibits potent broad spectrum antibacterial activity and β-lactamase inhibitory activity. Asparenomycin A (**44**) was obtained as the major isolated product while asparenomycins B (**45**) and C (**46**) were obtained in minute quantites. Isolation of 6643-X (**47**) added a fourth member to the class. They are effective against the group 1a, 1b, and 1c β-lactamase enzymes (Richmond and Sykes classification). However they appear to be chemically unstable and thus far have not been developed for clinical use.

1.4.4 PS-Series

Other natural carbapenems include the PS series. These *N*-protected cysteamine type side chain compounds show a decrease in antipseudomonal activity. At high concentrations in aqueous solution, the amino group of the cysteaminyl side chain is cleaved[16]. PS-5 (**32**), a carbapenem antibiotic isolated from fermentations of *S. cremus subsp. auratilis* is active against a variety of gram positive and gram negative bacteria and shows inhibitory activity against β-lactamases produced by

various bacteria. The structure of PS-5 differs most noticibly from that of thienamycin (**22**) and the olivanic acids by the lack of an oxygen functionality in the 6-ethyl side chain. Derivatisation of the PS-5 is therefore limited to modification of the carboxy group and the acetamidoethyl thio side chain. Esters of PS-5 were prepared by reacting the parent antibiotic as its sodium salt, with an alkyl halide in DMF.



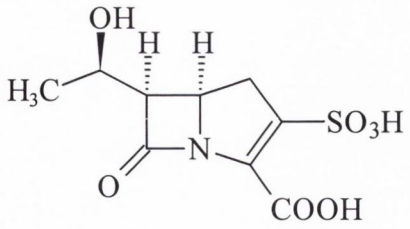
(32)

1.4.5 Epithienamycins

The epithienamycins have been isolated from *Streptomyces flavogriseus*[22] and are variants of the olivanic acids while the unsubstituted carbapenem structure i.e. SQ27860 (**43**) has been obtained from *Erwinna spp.* and *Serratia spp.*[23]. The epithienamycins consist of the sulphated β-lactamase inhibitors e.g. epithienamycin F (**26**), epithienamycin E (**27**), and the non-sulphated antibiotics epithienamycin A (**28**), epithienamycin B (**29**), epithienamycin C (**30**) epithienamycin D (**31**). The β-lactamase inhibitors epithienamycin E (**27**) and epithienamycin F (**26**) are sulphate esters of the C-8 hydroxy group and have 5*R*, 6*R*, and 8*S* configurations. The non-sulphated epithienamycins, epithienamycin A (**28**), epithienamycin B (**29**), epithienamycin C (**30**) and epithienamycin D (**31**) have, 5*R*, 6*S* and 8*S* configuration respectively[16].

1.4.6 Pluracidomycins

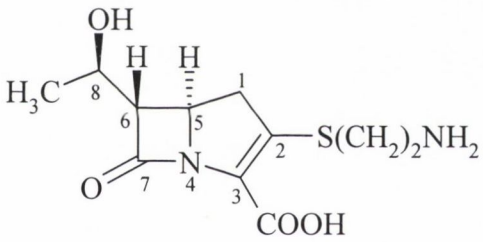
The pluracidomycins exhibit both β-lactamase inhibitory properties and are active against both gram negative and gram positive bacteria. The pluracidomycins are isolated from *Streptomyces sulfonofaciens* and *Streptomyces pluracidomyceticus*[24a]. Compounds with residues R^2 of the type $-SO_3H$, $-SOCH_2CO_2H$, $-SOCH(OH)_2$ on C-2 have been isolated in this series of compounds e.g. pluracidomycin D (**40**). All compounds within this group are *cis* substituted[24b].



(40)

1.5. Thienamycin

Thienamycin **(22)** was the first member of the carbapenem class to be isolated. It is a zwitterionic compound carrying an aminoethylthio substituent in the 2-position and a 1-hydroxyethyl substituent in the 6-position of the carbapenem nucleus. The absolute stereochemistry at the three chiral centres and has been determined as 5*R*, 6*S* and 8*R*[16].



(22)

Only carbapenem compounds with the absolute configuration *R* at C-5 have been reported to occur naturally and are likely to have biological activity[26]. Thienamycin possess a *trans* orientated *R*-1-hydroxyethyl side chain. Thienamycin (**22**) and northienamycin (**23**) remain the only two natural products bearing a non-acylated aminoethylthio side chain. This C-2 side chain is known to play a significant role in extending antibacterial activity, especially antipseudomonal activity[27].

Comparison of thienamycin (**22**) with other natural carbapenem products have revealed that this configuration of the C-6 side chain provides β-lactamase stability and antibacterial potency. The aminoethylthio group has been implicated in the high concentration instability of thienamycin presumably caused by the intramolecular aminolysis of the β-lactam amide. Derivatisation of this amino group to impart chemical stability and also with an aim to increasing resistance to β-lactamase has become an objective. The biological activity shown by this β-lactam structure was

unique, being active against both gram positive and gram negative bacteria, even against *Pseudomonas aeruginosa*, which is resistant to the majority of clinically used antibiotics. The carbapenems offer several novel functional group targets for chemical manipulation. The most obvious of these are at the C-6 hydroxyethyl and C-2 aminoethyl thio group.

The carbapenems are sufficiently stable only in a limited pH range around neutrality[16]. Thus, in addition to the difficulty experienced in increasing fermentation yields e.g. by strain optimization, this instability has made their isolation in large quantities from culture filtrates difficult. Therefore, derivatisation of naturally occuring carbapenems, e.g. thienamycin (**22**) and synthetic investigation of novel carbapenem structures are aimed at increasing the chemical stability of these compounds while retaining the β-lactamase inhibitory properties and the broad spectrum activity associated with carbapenems.

1.6 Structure Determinations

The structural eludication of thienamycin (**22**) which is well documented in the literature, was first disclosed in detail by Albers-Schönberg and co-workers in 1976 and 1978[6,28]. Quantitative energy-dispersive X-ray fluorescence analysis (EDAX) confirmed one sulphur atom per molecule, and the ultra-violet absorption maximum was found at 297nm. Infra-red absorption at ν1765cm^{-1} similar to that of cephalosporin C (**11**) was regarded as strong evidence in favour of the presence of a β-lactam ring system despite the much higher inherent ring strain. Field-desorption mass spectrum of pure thienamycin (**22**), showed a molecular ion peak at m/z 273. The ^{13}C-NMR spectrum showed a total of 11 carbon atoms and the ^{1}H-NMR spectrum showed 12 non-exchangeable protons and confirmed that H-5 and H-6 are *trans* to each other. The absolute configuration was confirmed by chemical transformations and X-ray crystallographic analysis[29,6,28].

1.7 Synthesis of Thienamycin

The low yields of thienamycin (**22**) obtained from the fermentation broth of *Streptomyces cattleya*, prompted researchers to develop synthetic routes to it. The first total synthesis of (±)-thienamycin was communciated by Johnston and co-workers in

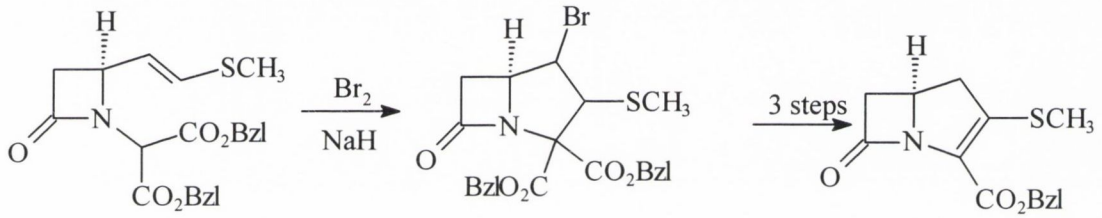
1978 using a C_2-C_3 bond formation[30]. The basic scheme followed three major strategic elements:

(i) Elaboration of a monocyclic β-lactam into an intermediate containing the peripheral functionality of thienamycin (**22**).

(ii) Cyclization to a carbapenem ring system by forming the C_2-C_3 bond.

(iii) Final transformation into the fully functionalized carbapenem system.

Schmitt *et al*[32] had shown that the azetidinone (**48**) could be cyclized to the carbapenem (**49**) by succesive bromination and base induced malonic ester type alkylation (**Scheme 2**). Subsequent decarboalkoxylation and double bond isomerization yielded the prototype carbapen-2-em (**50**).

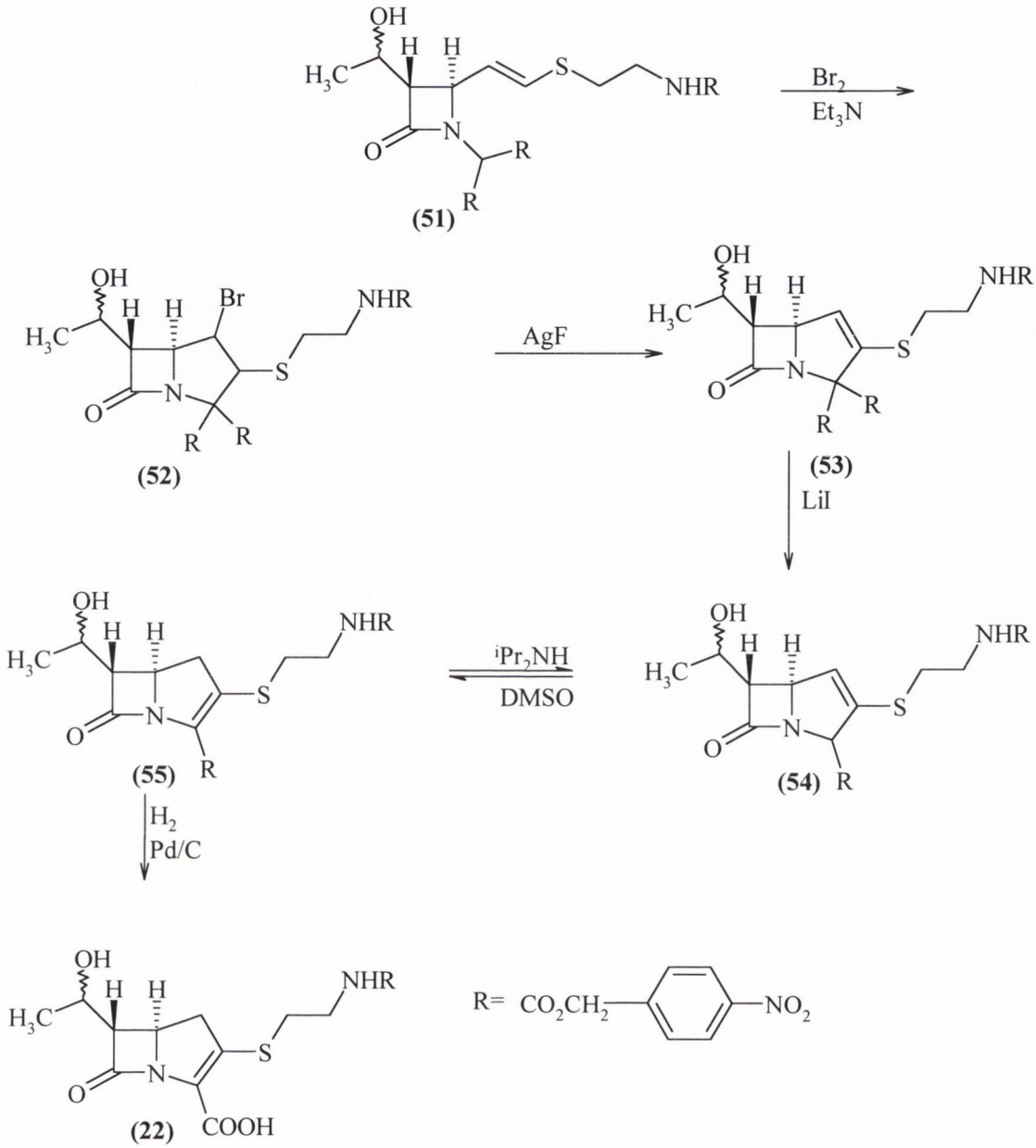


(48) **(49)** **(50)**

Bzl=benzyl

Scheme 2

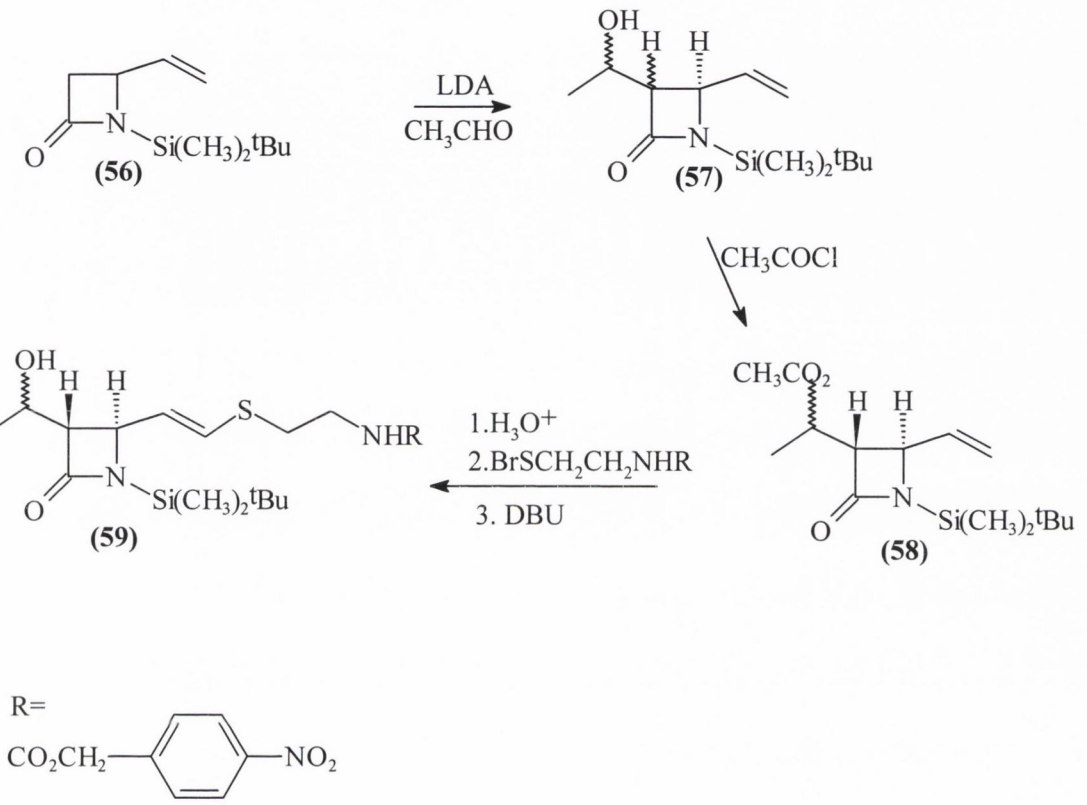
This method of ring closure became a key feature in the synthesis of (±)-thienamycin and was utilised by Johnston *et al* in his reported synthesis of compound (**52**) (**Scheme 3**)[30,32]. Compound (**51**) was ring cyclised to (**52**) with bromine and base. The bromine of compound (**52**) was displaced with silver flouride yielding the alkene product (**53**). Compound (**53**) was monodecarboxylated to carbapen-1-em (**54**) with lithium iodide in collidine at 120°C. Exposure of (**54**) with base in DMSO gave (**55**). Final removal of the *p*-nitrobenzyl protecting groups gave (±)-thienamycin.



Scheme 3

The most practical route to the synthesis of the azetidin-2-one (**59**)[33] (a key intermediate in the synthesis of (±)-thienamycin), involved silylation of the readily available 4-vinylazetidinone to give the *N*-protected derivative (**56**) (**Scheme 4**). Hydroxyethylation of (**56**) via the aldol procedure provided a mixture of diastereomers (**57**) which could be seperated into *trans* and *cis* forms.

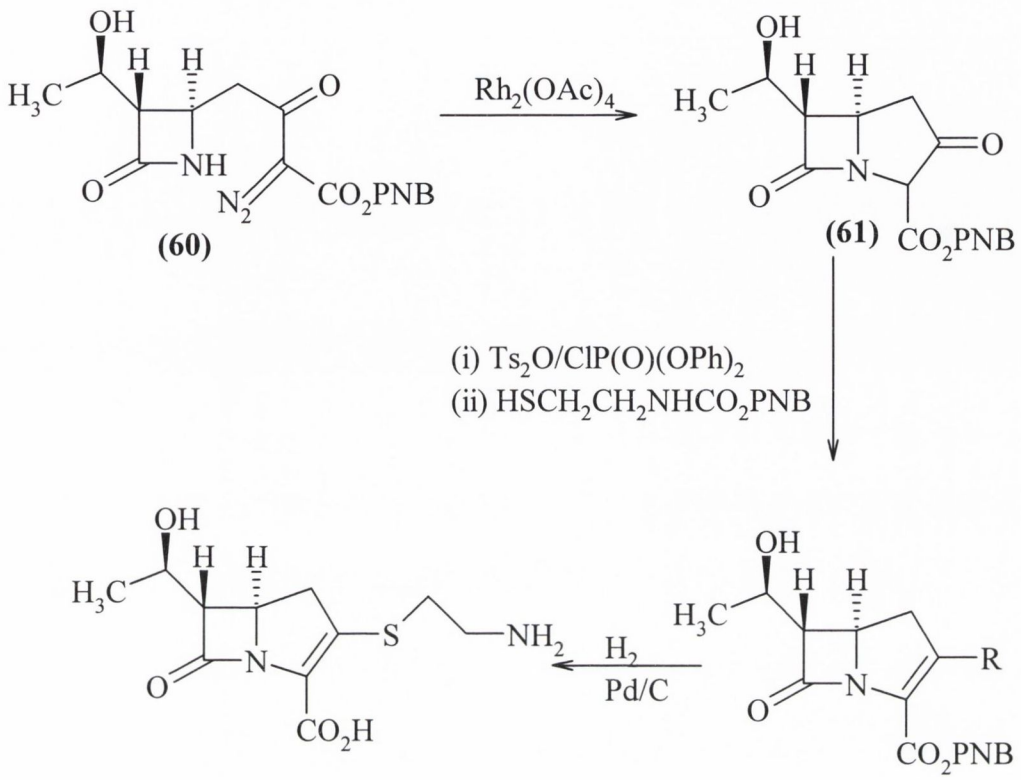
Acylation of the *trans* mixture gave the desired isomer (**58**). Compound (**58**) was converted to the intermediate (**59**) by the reaction of the double bond with *N*-(*p*-nitrobenzyloxycarbonyl)ethanesulfenyl bromide and base.



Scheme 4

(±)-Thienamycin was found to have only half the potency of natural (+)-thienamycin (**22**). Merck chemists[31] developed a stereospecific synthesis of (+)-thienamycin. The pivotal reaction in this sequence involves a novel and highly efficient carbene insertion reaction which produces the bicyclic nucleus by forming the C_3-N_4 bond (**Scheme 5**). This involved the carbene insertion of a diazo-β-ketoester (**60**) in the presence of a catalytic amount of rhodium (II) acetate to produce the bicyclic keto ester (**61**) by C_3-N_4 bond formation. Introduction of the protected cysteamine side chain was performed via the addition of *N*-(*p*-nitrobenzylcarbonyl)cysteamine to the vinyl tosylate (**62**) or the enol phosphate to give (**63**). Removal of the protecting group by hydrogenation afforded (+)-thienamycin (**22**)[31,34,35]. The early introduction of the hydroxyethyl side chain in the synthetic route with the correct relative configurations at C-5 and C-6, paved the way for the key step to the reaction. From a strategic viewpoint, the carbene insertion reaction allows the

construction of most of the structure and all of the stereochemistry prior to the formation of the strained and reactive bicyclic ring system.



(22)

(62) R=OTs

(63) R=$OPO(OPh)_2$

(64) R=$SCH_2CH_2NHCO_2PNB$

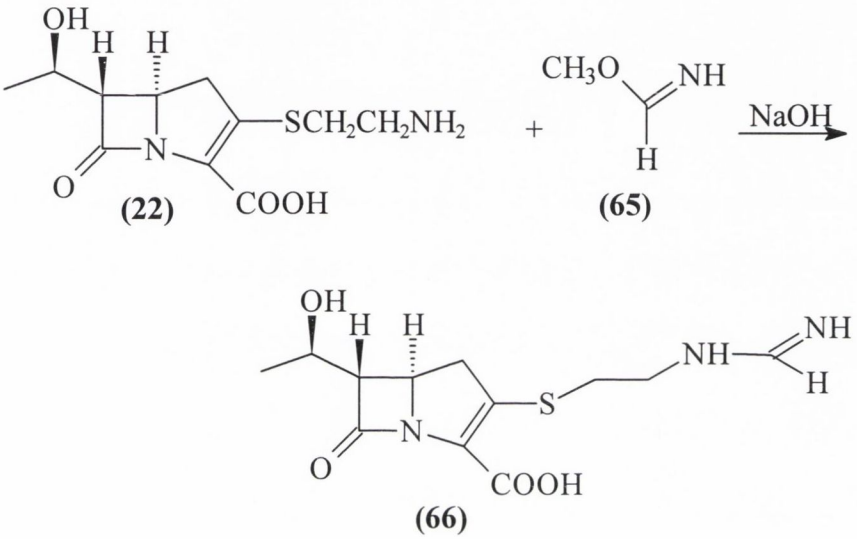
PNB=4-$CH_2C_6H_4NO_2$

Scheme 5

1.8 Biological Activity of Chemical Derivatives of Thienamycin

Biological comparsion of thienamycin (**22**) with other carbapenem natural products has revealed that this configuration of the 6-side chain, *trans-R*, provides maximum β-lactamase stability and antibacterial potency[36]. To improve the chemical stability of the basic amine further modification was necessary. In 1979 Leanza *et al* noted the presence of the basic cysteamine side chain of thienamycin (**22**) appeared to extend its bioactivity to include the *Pseudomonas* strains[27]. Hence the substitution of the amino group to render it more basic, with for example an *N*-imidoyl derivative which would result in a compound retaining its antipseudomonal activity but with increased high concentration stability. The most successful derivative of thienamycin

(**22**) is prepared by the coupling reaction of thienamycin (**22**) and the methyl imidate (**65**) to give the corresponding *N*-formimidoyl derivative (**66**)[16] (**Scheme 6**). This *N*-formimidoylthienamycin (**66**) was sufficiently stable chemically yet its antimicrobial spectrum is equivalent to thienamycin (**22**). Indeed, it`s potency against pseudomonal strains is greater[37]. This derivative was selected for clinical trials and has the generic name imipenem (MK0787) (**66**).



Scheme 6

1.8.1 Mode of action of imipenem (66)

As do other β-lactam antibiotics, imipenem (**66**) inhibits bacterial cell wall synthesis. However, its morphological effects are different, in that it induces conversion of gram negative rods directly to small spheres without the formation of the elongated filaments commonly seen with penicillins and cephalosporins. This suggests that imipenem (**66**) acts at a different site in the biosynthetic pathway of bacterial cell wall synthesis compared with existing β-lactam antibiotics[38].

1.8.2 Antibacterial spectrum

Imipenem (**66**) possesses high activity against staphylococci and shows no trace of cross-resistance with penicillins against penicillin resistant strains. It shows good affinity for penicillin binding protein 2 in *E. coli* and *P. aeruginosa* and binds well to PBP`s 1 4, 5 and 6[38,39].

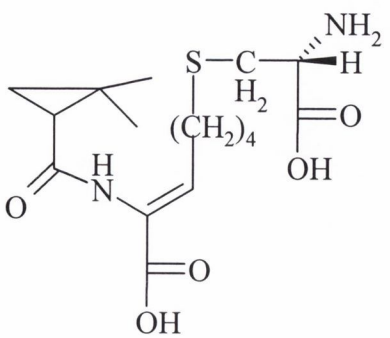
1.8.3 Stability of imipenem

From an early stage in the development process it was observed that very low levels of thienamycin (**22**) and imipenem (**66**) were recovered from the urine of several animal species when given the drug, as it was being degraded *in vivo*. Because of the fear of rapid resistance developing, a programme to investigate and prevent this *in vivo* degradation was initated. Incubation of thienamycin (**22**) with a variety of rat tissue homogenate readily identified the kidney as the primary site of antibiotic destruction. It was inactivated by the known enzyme renal dipeptidase (dehydropeptidase-1, DHP-1). Two strategies to prevent this enzymatic destruction were apparent:

(i) To design an inhibitor of the enzyme and use the concomitant adminstration of the inhibitor to prevent breakdown of the antibiotic.

(ii) To devise an analogue that was both active as an antibacterial and stable to the enzyme.

Both strategies have been investigated. Directed screening of a series of compounds containing the dehydropeptide structure against the kidney enzyme identified *Z*-2-benzamido-2-butenoic acid as a moderately effective inhibitor. By noting the structural similarity of thienamycin (**22**) and this inhibitor and by using the general inhibitory ability of this class of compounds, the series was optimised for both potency and pharmacological properties. The sodium salt of cilastatin (**67**) was chosen for combination with imipenem (**66**) in the commercial product[40].



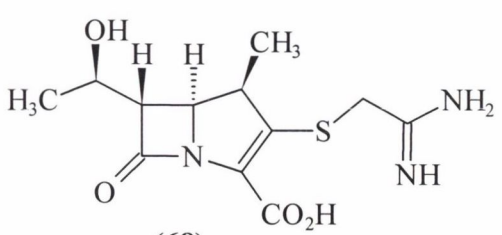
(67)

The mixture of imipenem (**66**) and cilastatin salt (**67**) is called Tienam (Primaxin in the US). Both in laboratory animals and in man cilastatin (MK0791)

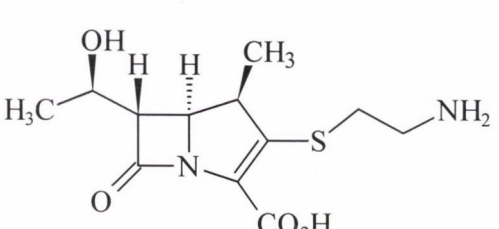
protects imipenem from renal metabolism by DHP-1. Tienam has been used extensively and is a remarkably effective agent against almost all types of bacterial infections. Tienam was approved in the UK in 1988 after it was introduced in the US in December 1985. It is now available in almost all countries as a novel and important antibiotic whose breadth of spectrum and potency remain unsurpassed. It went through one of the most difficult chemical development programmes any pharmaceutical company has faced. Only after modification of the natural product to form a chemically stable derivative with improved biological properties, subsequent design of an inhibitor to prevent unwanted *in vivo* degradation and after manufacture by total synthesis has the commercial production of this unique antibiotic become possible. Tienam is resistant to *Nocardia spp.* and *Mycobacteria.* It is four times more potent than thienamycin (**22**) against *Pseudomonas aeruginosa spp.* Only *Pseudomonas maltophilia, Enterococcus faecium*, some strains of Methicillin-resistant *Staphylococcus aureus* and Methicillin-resistant coagulase-negative *Staphylococci, Pseudomonas cepacia* and *corynebacteria* are generally resistant to imipenem[38] (**66**).

1.9 Biological Properties of 1β-Methylcarbapenems

Imipenem (**66**) showed a broad antibacterial spectrum and an excellent bactericidal activity among β-lactams. In spite of possessing the broadest spectrum of antimicrobial activity of all β-lactam antibiotics in clinical use, imipenem has two serious drawbacks. Those are a high sensitivity to renal dehydropeptidase-1 and a convulsive potential[41,42,23]. The presence of a methyl group tends to stabilize the carbapenem molecule towards DHP-1 and carbapenems such as L 646 591 (**68**)[43] potentially combine DHP-1 stability with antibiotic potency. In 1985, Shih *et al*[44] successfully introduced a 1-β-methyl group on the C-1 position of the pyrroline ring. The 1β-methylcarbapenem (**69**) thus synthesized was found to be resistant to DHP-1 but unfortunately it possesses decreased antibacterial activity.

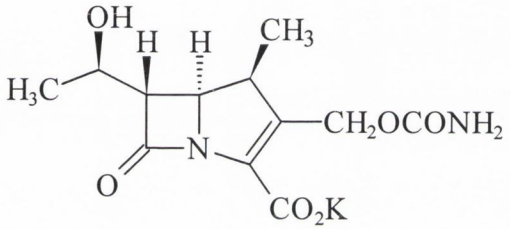


(68)

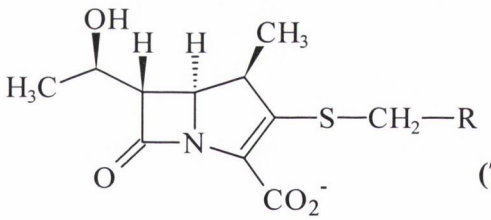


(69)

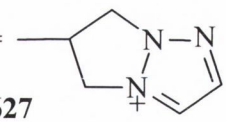
Many of the earlier 1-substituted carbapenems did not possess the antibacterial activity of thienamycin (**22**). A vast number of substituents have been investigated at position 2 of the pyrroline ring. The 2-functionalized methyl-1β-carbapenem (**70**) retained antibacterial activity but was not effective against *Pseudomonas aeruginosa* nor was it resistant to DHP-1[45]. The 1β-methylcarbapenem LJC 10627 (**71**) has been shown to be about twice as active as imipenem against gram negative bacteria *in vitro* and *in vivo*[46]. LJC 10627 (**71**) is stable to renal dehydropeptidase and a pharmacokinetic study indicated 95% urinary recovery in monkeys. In particular the addition of pyrrolidinyl-containing side chains at C-2 has produced a number of stable compounds such as (**72**) with a broad spectrum of activity.



(70)

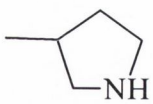


(71) R =

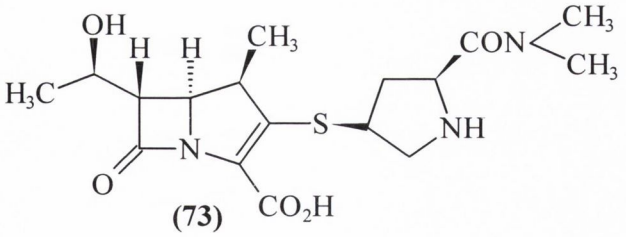


LJC 10627

(72) R =



The most important of these derivatives at C-2 of the pyrroline ring with the hydroxyethyl substituent present at C-6 is known as meropenem (SM 7338, ICI 194, 660) (**73**) containing a pyrrolidin-3`-ylthio group as C-2 side chain. The introduction of the methyl group on C-1 of the five membered pyrroline ring created what is known as the second generation of carbapenem antibiotics. To date the value of meropenem (**73**) as an antimicrobial has not been surpassed by any compound in clinical use due to its antibacterial activity and stability[47,48,23].



(73)

1.9.1 Mechanism of activity of meropenem (73)

Meropenem (**73**) has high affinity for PBPs in *Staphylococcus aureus*[49], *Escherichia coli* and *Pseudomonas aeruginosa*[50, 51]. It is generally agreed that PBP2 is the primary target of both meropenem (**73**) and imipenem (**66**) in *E. coli.* However, there are differences between the PBP affinity patterns of meropenem (**73**) and imipenem (**66**) in *E. coli* and *P. aeruginosa*, particularly with respect to a greater affinity of meropenem (**73**) for PBP3.

1.9.2 β-Lactamase stability

Meropenem (**73**) is unstable to the less common metalloenzymes e.g. from *Xanthomonas maltophilia*, *Flavobacterium spp.*[52,53]. It has been shown that meropenem (**73**) is a relatively poor inducer of Type 1 β-lactamase in strains of *Enterobacter cloacae*, *Proteus mirabilis, Morganella morganii*, *Citrobacter freundii, Serratia marcescens* and *Pseudomonas. aeruginosa.* Meropenem (**73**) was hydrolysed more slowly than imipenem (**66**) by a carbapenemase producing strain of *S. marcescens* and like imipenem (**66**) exhibited depressed activity against *Enterobacteriaceae.* Meropenem (**73**) has been reported to be hydrolysed more rapidly than imipenem (**66**) by some enzymes produced by *S. maltophilia*[54,55].

1.9.3 Postantibiotic effect

The postantibiotic effect (PAE) is the delayed regrowth of bacteria after exposure to antibacterial agents. Reported PAEs vary according to the bacterial strains studied, the concentration of antibacterial drugs, exposure time and method used to assess the effect. Most studies have used viable counts to assess PAE with a variety of clinical isolates and reference bacteria and an inoculum of usually 10^5 or 10^6 cfu (colony forming units). Meropenem (**73**) has been reported to produce a PAE with

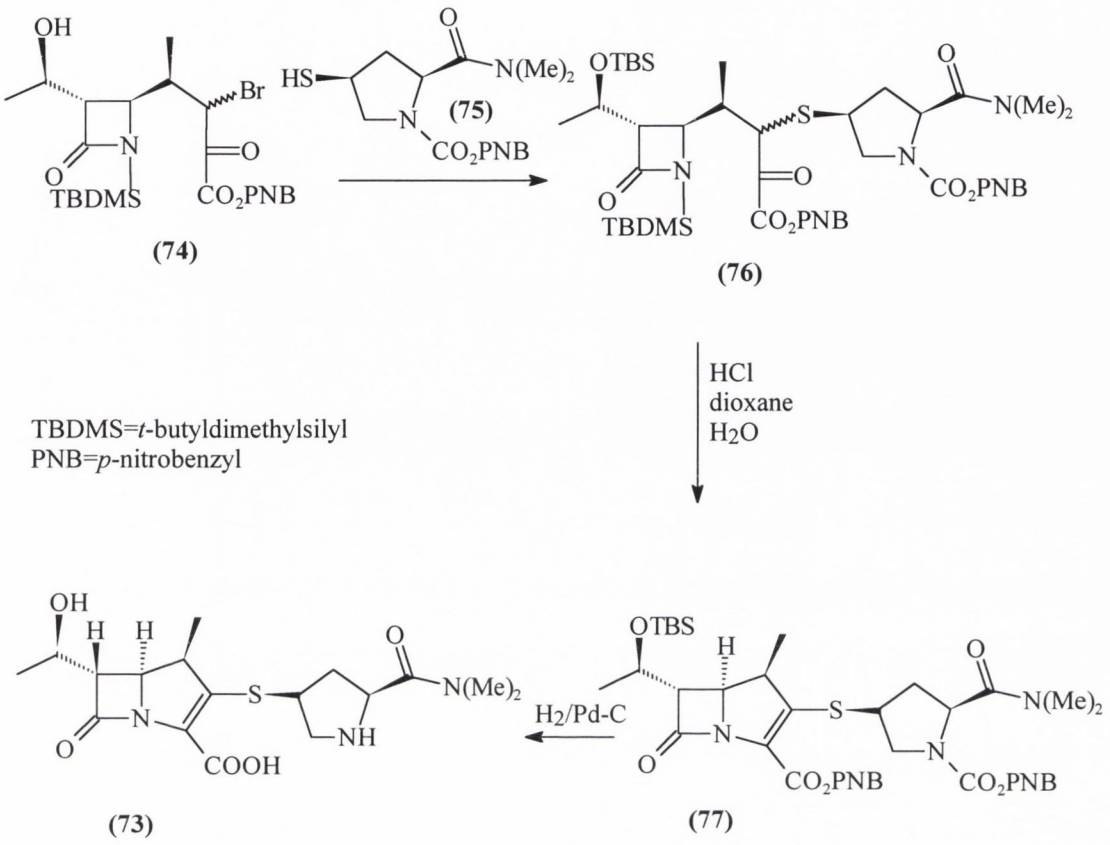
Enterobacteriaceae, *S. aureus, P. aeruginosa, B. fragilis* and *E. faecalis* which in some instances was longer than that with imipenem (**66**) for the same bacteria. When different methods of assessing PAE`s with *Enterobacteriaceae* were compared those determined by viable counts were considered lower (by 0.2 to 2.6 hours) than those assessed by other methods (e.g. bioluminescence). PAE`s for meropenem (**73**) determined by morphological methods were the longest (2.3 to 8.4 hours). Thus meropenem (**73**) has been reported to produce a PAE with Enterobacteriaceae, *S. aureus, P. aeruginosa,* and *Enterococcus faecalis*[56,57] which is useful clincally as there will be delayed regrowth of bacteria.

1.9.4 Antibacterial activity

Meropenem (**73**) is more active *in vitro* than imipenem (**66**) against *Enterobacteriaceae*. The drug is also active against *Staphylococcus aureus* as well as *S. epidermidis* and other coagulase-negative *Staphylococci*. Combinations of meropenem (**73**) with several other antibacterial agents have shown a synergistic antibacterial activity. Methicillin-resistant *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococci pneumoniae* including penicillin resistant strains are inhibited by low concentrations of meropenem (**73**). Meropenem (**73**) (0.06-4mg/l) inhibits the growth of virtually all tested strains of *Bacteroides fragilis*, and *Fusobacterium spp*. Meropenem (**73**) is more active than imipenem (**66**) against clinical isolated *Clostridium perfringens*[58].

1.9.5 Synthesis of meropenem

Prashad *et al* in 1998 described the synthesis of meropenem (**73**)[59] (**Scheme 7**). This method described involves the displacement of the bromine group of the intermediate (**74**) with the heterocyclic thiol (**75**) to afford (**76**). Deprotection and cyclization were both achieved with HCl in ethereal solvents over a wide range of acid concentrations yielding (**77**). Following deprotection of the *para*-nitrobenzyl group by reduction, the product meropenem (**73**) was obtained.



Scheme 7

1.10 Biological Properties of New 1β-Methylcarbapenems

Research on all aspects of carbapenem antibiotics remains very active, reflecting the medical and commercial importance of this group of drugs. Derivatisation together with continuing development of newer antibiotics, and more effective and efficient methods of synthesis is directed towards increasing the stability and broadening the spectrum of activity.

Until recently, imipenem (**66**) was the only carbapenem available for clinical use in the United States. Of all the β-lactams antibiotics in clinical use, it has the broadest spectrum of antimicrobial activity against aerobic and anaerobic gram positive and gram negative bacteria, including many resistant clinical isolates. It is not only stable to hydrolysis by most serine β-lactamases, but is also an effective inhibitor of these serine β-lactamases.

However, imipenem (**66**) has four draw-backs:

(i) It is highly sensitive to renal dehydropeptidase (DHP) inactivation, thus requiring co-adminstration with cilastatin (**67**), a dehydropeptidase inhibitor.

(ii) It has a convulsive potential particularly in patients with impaired renal function and underlying CNS disease.

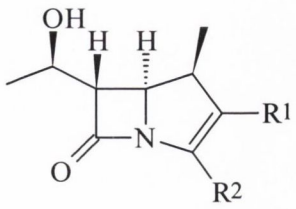
(iii) It is not orally active.

(iv) It has a half–life of only one hour.

The second generation carbapenem, meropenem (**73**) which has antimicrobial activity very similar to that of imipenem (**66**) and was recently approved for clinical use addresses the first two concerns only[60]. The high success of meropenem (**73**) from both a financial and a medical perspective brought considerable interest in analogues with enhanced activity or stability. Some C-6 modifications will be discussed in Chapter 2 and Chapter 4.

A brief review of newer carbapenems reported in the period 1997-1998 is now presented. An impressive series of 1β-methylcarbapenems have been synthesized and tested for antibacterial activity and stability in recent years and some of these are shown in **Table 3**. The majority of substituents have been investigated at position 2 of the pyrroline ring with the hydroxyethyl substituent present at C-6.

Table 3: Recent developments in carbapenem antibiotics



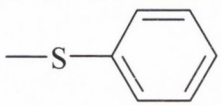
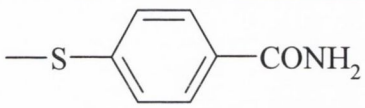
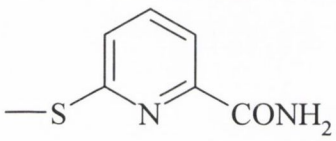
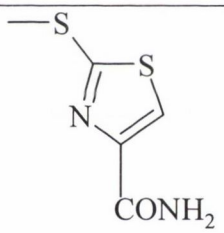
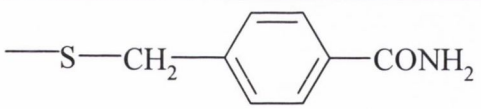
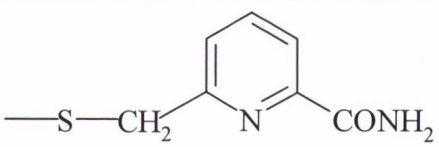
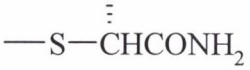
Compound No.	R^1	R^2
78a		CO_2Na
78b		CO_2Na
78c		CO_2Na
78d		CO_2Na
78e		CO_2Na
78f		CO_2Na
78g	$-S-CH_2CONH_2$	CO_2Na
78h	$-S-CH_2CH_2CONH_2$	CO_2Na
78i		CO_2Na

Table 3 continued

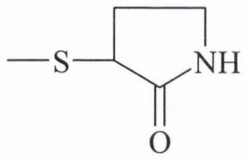
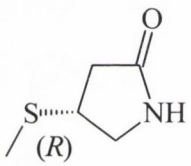
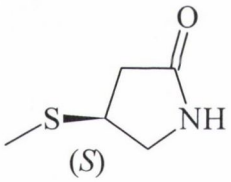
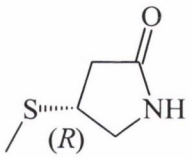
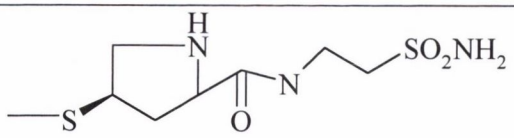
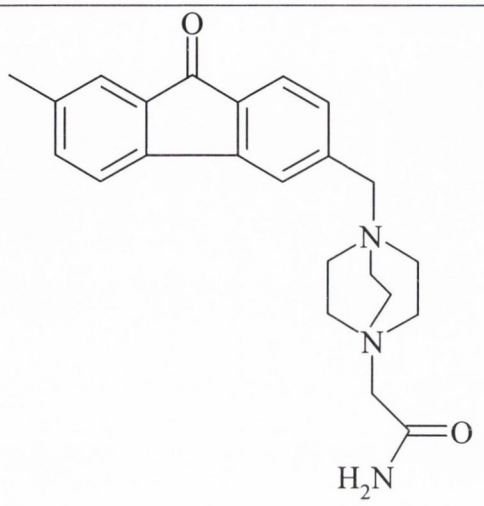
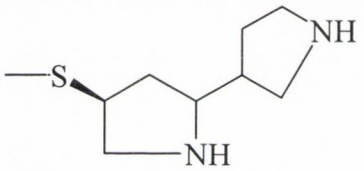
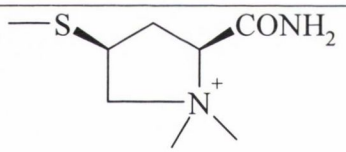
Compound No.	R^1	R^2
78j		CO_2Na
78k		CO_2Na
78l		CO_2Na
78m		CO_2Na
78n		CO_2Na
78o		$CO_2CH_2OCOC(CH_3)_3$
79		CO_2H

Table 3 continued

Compound No.	R^1	R^2
80		CO_2H
81		CO_2H
82		CO_2H

Sankyo[61] research laboratories investigated the synthesis of novel oral carbapenems in order to overcome the problem of oral adminstration. The following derivatives both heterocyclic and non-heterocyclic were synthesized (**Table 3**). An orally active antibiotic with potent activity is of much interest in the clinical realm because oral adminstration and lower dosage are advantageous for patients. The carbapenem (**78a**) which has a phenylthio group at C-2 showed excellent activity against gram positive bacteria such as *Staphylococcus aureus,* but it was inactive against gram negative bacteria. The aromatic and heteroaromatic derivatives (**78b**)-(**78f**) showed improved activity against gram positive bacteria. The aryl and heteroarylthio derivatives (**78e**) and (**78f**) were more active against gram negative bacteria than corresponding aryl and heteroarylthio compounds (**78b**) and (**78c**) respectively.

Secondly, aliphatic carboxamide or carbamate derivatives were examined. The derivatives (**78g**)-(**78j**) having an alkyl carboxamide substituent were potent against gram negative bacteria but were less active against gram positive bacteria. The stereochemistry of the methyl group on the carbon next to the sulphur atom influenced the antibacterial activity. The (*R*)-isomer (**78i**) showed better antibacterial activity than the (*S*) isomer. The carbamate derivative (**78k**) showed potent activity similar to the carboxamides (**78g**) and (**78h**). In order to promote higher activity against gram positive bacteria, a five-membered cyclic amide system similar to that of meropenem (**73**) was introduced. Although oxopyrrolidin-3-ylthio derivative (**78l**) became less active, the 5-oxopyrrolidin-3-ylthio derivatives (**78m**) and (**78n**) exhibited well balanced and potent antimicrobial activity against both gram positive and gram negative bacteria. In order to optimize the oral absorption of the carbapenem (**78m**) the ester derivative (**78o**) was prepared. The oral absorption of a pro-drug can be estiminated from its urinary recovery as the parent compound. The pivaloyloxymethyl ester (**78o**) had an 47% urinary recovery and thus had good therapeutic efficacy.

More recently Shin[62] *et al* in 1998 reported the synthesis of the 1β-methylcarbapenem (**79**) having a new amide function instead of 5`-dimethylaminocarbonyl group in the pyrrolidin-3`-ylthio C-2 side chain of meropenem (**73**). This compound was active against a wide range of gram positive and gram negative organisms including *Pseudomonas.* In 1998 the Merck[63] group reported the synthesis of L-742,728 (**80**) having anti MRSA activity.

Banyu[64] Pharmaceutical Co. Ltd. investigated the synthesis and antibacterial activity and stability to DHP-1 of 1β-methyl-2-(5-substituted pyrrolidin-3-ylthio)carbapenems. The most active synthesized was BO-2502A (**81**). This carbapenem displayed *in vitro* and *in vivo* antibacterial activity against gram positive and gram negative bacteria including methicillin resistant *Staphylococcus aureus* (MRSA) and imipenem resistant *P. aeruginosa.* Ishikawa *et al*[65] synthesized 1β-methylcarbapenems with quaternary ammonium groups at C-2. Compound (**82**) was active against MRSA and *P. aeruginosa.*

1.10.1 Recent heterocyclic derivatives at C-2 of the carbapenem.

Researchers at Wyeth-Ayerst Research have investigated the development of the next generation carbapenems, equal in activity to the clinically effective carbapenems, imipenem (**66**) and meropenem (**73**), and having oral activity together with pharmacokinetic advantages such as longer half life and improved bioavailability[66]. In looking at carbapenem sites for further structural modification, the C-2-position appeared to be the only place that would allow considerable variation without compromising the antimicrobial activity and therefore became the target site for structural innovation.

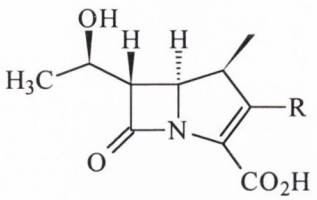
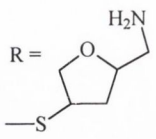
Since hundreds of substituted tetrahydrofuranylthiols can be readily obtained by modification of carbohydrates, extensive efforts were directed towards the synthesis of novel C-2 tetrahydrofuranylthiol substituted 1β-methylcarbapenems with pharmacokinetic and microbiological advantages. These compounds were developed with the objective of obtaining carbapenems with enhanced activity against gram negative bacteria and with oral activity both mediated through the use of peptide transport systems[67].

C-2 aminomethyl-THF-1β-methylcarbapenems were synthesized which exhibited antimicrobial activity against a spectrum of gram positive and gram negative bacteria. A representative of this group of compounds (**83**) is shown in **Table 4** together with its MIC value. Values against different strains of pathogenic bacteria are given. Carbapenem (**83**) exhibited good activity against gram positive organisms particularly against *Enterococcus faecalis*.

Most importantly (**83**) demonstrated moderate oral activity (ED_{50}=2-4mg/kg) against an *E. coli* infection in mice and was 20 times more efficacious than imipenem (**66**) when dosed orally. Compound (**83**) exhibited activity against methicillin resistant *Staphylococcus aureus* and *Xanthomonas maltophilia.* It also demonstrated better stability than imipenem (**66**) to hydrolysis by renal dehydropeptidase and therefore did not require co-adminstration with a dehydropeptidase inhibitor.

Table 4: Antimicrobial activity of 2-aminomethyl-THF-1β-methylcarbapenem

In vitro activity (MIC; μg/ml)

	**(83)** 	**(66)** Imipenem	**(73)** Meropenem
Organism			
E.coli (ATCC 25922)	≤0.06	0.12	≤0.06
E. faecalis (GC 1182)	2.0	1.0	2.0
S. aureus (GC2220)	8.0	1.0	8.0
X. maltophilia (GC 562)	>128	>128	>128
ED $_{50}$ (mg/kg) (Imipenem/cilastatin as reference drug)	3.7	79	Not tested

In related work Burton *et al* at Smithkline Beecham Research Laboratories[68] reported the synthesis of novel C-2 heterocyclic substituted carbapenems i.e compound (**84**). Substitution at C-1 with a β-methyl group is known to result in compounds that combine chemical and metabolic stability with enhanced antibacterial potency as exemplified by meropenem (**73**).

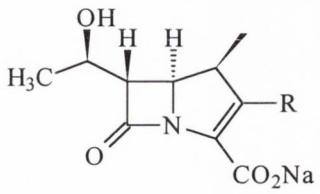
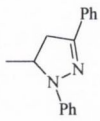
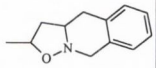
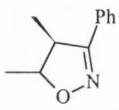
Carbapenems (**84**)-(**87**) were identified as suitable for the treatment of community acquired infections e.g. influenzae and were also stable to DHP-1 enzyme. The DHP-1 stability figure quoted in **Table 5** is the percentage stability of the carbapenem to the enzyme renal dipeptidase dehydropeptidase-1. The antibacterial activities and susceptibility to human DHP-1 of these new carbapenems in comparsion with values for imipenem (**66**) and meropenem (**73**) are reported. Compounds were evaluated *in vitro* against a range of important target organisms associated with community acquired infections. e.g *Haemophilus influenzae.* Compound (**84**) showed better antibacterial activity than meropenem (**73**) to *Haemophilus influenzae* and was more stable to DHP-1 than imipenem (**66**).

Although several synthetic routes to carbapenems[70,71] have been reported the Beecham group[69] developed a methodology that would allow the facile synthesis of several C-2 heterocyclic analogues from a common late stage intermediate. The products studied are illustrated in **Table 5.** The isoxazoline (**86**) and isoxazolidine

(**87**) showed moderate stability to human dehydropeptidase 1 (DHP-1). The pyrazoline (**85**) exhibited excellent stability to DHP-1 but reduced potency against gram negative organisms. Compound (**86**) showed better antibacterial activity to *Haemophilus influenzae* than that observed for meropenem (**73**).

Table 5: Antimicrobial activity of 2-heterocyclic derivatives

In vitro activity (MIC; μg/ml)

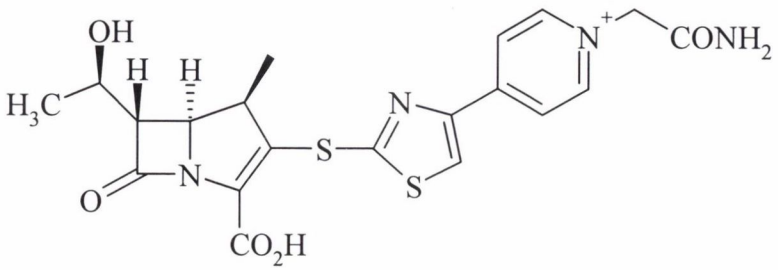
	**(84)** R =  (*S*)-isomer	**(85)** R = 	**(86)** R = 	**(87)** R.= 	**(66)***	**(73)****
Organism						
E. coli	0.13	>64	16	>64	0.12	≤0.03
Haemophilus influenzae	0.13	16	0.25	1	0.06	1
Stability to DHP-1 (%)	74	>98	64	56	66	88

* imipenem

** meropenem

1.10.2 Non-Heterocyclic Carbapenems

Infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) have become a serious problem in the clinic because there are few anti MRSA agents which are clinically effective. Vancomycin[72] is a potent anti-MRSA agent but its adverse effects restrict its clinical use[73]. β-lactam antibiotic 17466 (**88**) was reported to show high affinity for the Penicillin binding protein –2` (PBP-2`) of MRSA which is essential for anti MRSA activity.

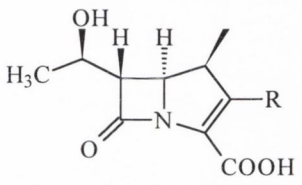


(88)

With a thiazolo structural feature in mind Banyu Pharmaceutical Co. Ltd[73] envisaged a dithiocarbamate moiety at the C-2 side chain by cleaving the 1-5 bond of the thiazole ring. The biological activity of these novel dithiocarbamate are shown in **Table 6**. These compounds showed activity against *E. faecalis* and *E. Coli* but were all inactive against *P. aeruginosa.*

Table 6: Antimicrobial activity of novel C-2 dithiocarbamate–1β-methylcarbapenems

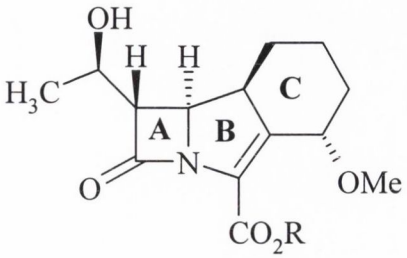
In vitro activity activity (MIC; μg/ml)

	**(89a)** R= -SC=SN(Me)$_2$	**(89b)** R= - SC=SNMe(CH$_2$)$_2$OH	**(66)** Imipenem
Organism			
E faecalis (MB 4996)	5.91	4.80	200
E. coli (NIH 5502)	12.5	6.25	Not tested
P. aeruginosa (MB 5002)	25	25	Not tested
In vivo anti-MRSA activity ED$_{50}$ (μg/ml)	25	25	Not tested

1.10.3 Tribactams

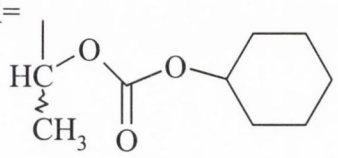
Glaxo Research Laboratories reported the synthesis of tricyclic β-lactams (tribactams, or trinems) in 1992. This new class of antibacterial agent has exhibited a broad spectrum of activity together with β-lactamase inhibitory properties[74,75]. The characteristic feature of these tricyclic β-lactam derivatives is the presence of the reactive four-membered β-lactam ring A fused to the unsaturated five membered pyrroline ring B (i.e the carbapenem structure) which is itself fused to a third ring C which in theory could be a five, six or seven-membered carbocyclic or heterocyclic

structure. The tricyclic β-lactam GG-326 (formely known as GV-104326) (**90**) and its orally active prodrug (**91**) are the most promising of this class of antibiotic synthesized to date. They display an unprecedented range of antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidase-1-enzyme[76]. GG326 (**90**) is currently in phase II clinical trials.



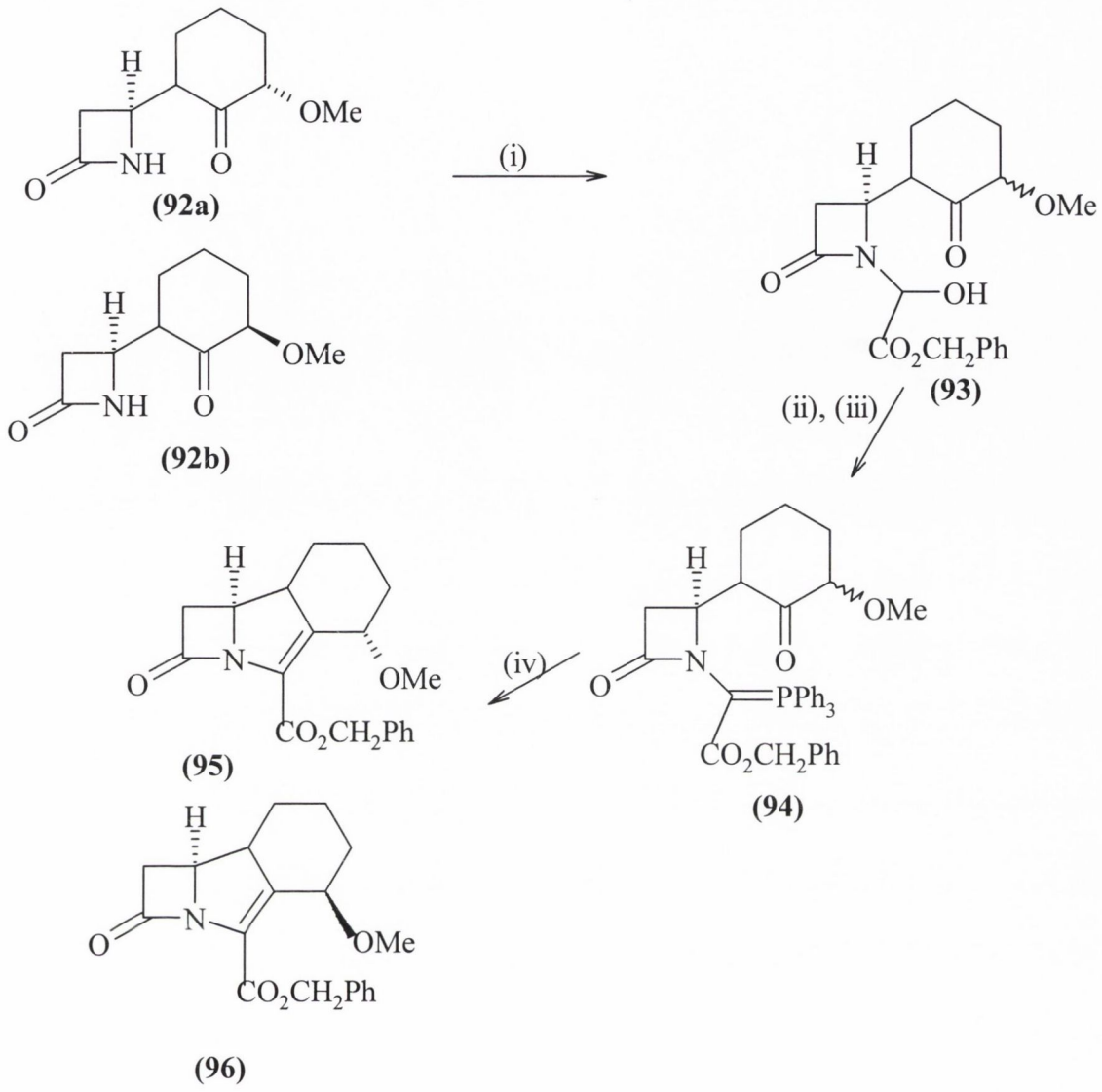
(90) R=H

(91) R=



1.10.4 Synthesis of trienem ring system

The formation of the trienem ring system (in racemic form) involves two general methods for the conversion of ketoazetidinones into trinems. The first involves an intramolecular Wittig reaction of a phosphorane[77a,77b]. The second involves heating an oxalimide with triethylphosphite[78,79]. The Wittig method is now described (**Scheme 8**). Treatment of the ketoazetidinones (**92a**), (**92b**) with benzylglyoxylate gave the alcohol (**93**) in 74% yield. Reaction of the alcohols (**93**) with thionyl chloride followed by triphenylphosphine gave the phosphoranes (**94**) in 36% yield. The phosphoranes underwent intramolecular Wittig reaction on heating in refluxing toluene containing a single crystal of hydroquinone to give the trienem (**95**) in 40% yield. The trienem (**96**) resulting from the cyclisation of the ketoazetidinone (**92b**) was not isolated.



(i) $HCOCO_2CH_2Ph$, C_6H_6, reflux;

(ii) $SOCl_2$, 2,6-lutidine, THF;

(iii) PPh_3, 2,6-lutidine, THF;

(iv) PhMe, reflux

Scheme 8

1.10 Summary

The interest in the synthesis of carbapenems is due to their broad spectrum activity, their low fermentation yields, their β-lactamase inhibitory properties and their chemical structure. This chapter described in detail the synthesis and biological evaluation of both natural and synthetic carbapenems. Some recently synthesized carbapenems were examined against a broad range of bacteria. The development of new synthetic methods in the search for carbapenems more resistant to *E. coli*, *E. faecalis*, *S. aureus* and *H. influenzae* is ongoing. In this thesis the synthesis of monocyclic β-lactams as precursors of the carbapenem nucleus is described in the search for carbapenems with activity against a wide range of bacteria and a high degree of stability towards β-lactamase enzymes.

1.11 Objectives

Previous extensive studies have concentrated on the formation of carbapenem bicyclic ring system containing various C-2 side chains. Few studies have focused on modification of the C-6 hydroxyethyl side chain.

The aims of this thesis is as follows:

(i) To design a stereocontrolled synthesis of 3-vinyl, 3-isopropenyl and 3-alkyl-4-formylazetidin-2-ones as potential intermediates for the preparation of novel carbapenem antibiotics.

(ii) To epoxidise a series of 3-vinylazetidin-2-ones, followed by a study of regioselective ring opening reactions allowing access to β–lactams with OH or OR side chain.

(iii) To investigate the isomerisation of 3-vinyl-4-substituted β-lactams as a possible route to the introduction of side chains present in the asparenomycin series of carbapenems.

(iv) To oxidise the 4-formyl group of 3-vinyl, 3-isopropenyl and 3-alkyl-4-formyl azetidin-2-ones, with sulphur ylides to afford highly reactive oxiranes which themselves are suited to further chemical manipulation.

(v) To synthesize β-lactam derivatives containing the α,β-unsaturated ketone substituent at C-3 as potential versatile precursors to carbapenem compounds.

The work in this part of the thesis is presented as follows:

(a) The stereocontrolled synthesis of C-3 substituted α-vinyl β-lactams, via an acid chloride method, and secondly by an activated ester route is investigated, yielding both model β-lactams and potential carbapenem precursor structures (Chapter 2 and Chapter 3).

(b) The epoxidation of 3-vinylazetidin-2-ones followed by a study of the regioselective ring opening reactions is then undertaken (Chapter 2).

(c) Chapter 3 is concerned with the synthesis of asparenomycin related precursors displaying C-3 ethylidene and C-3 isopropylidene side chains are obtained following chemical transformations carried out on the C-3 alkene group of a series of 3-vinylazetidin-2-ones. The reduction of 4-formylazetidin-2-ones to

the corresponding 4-hydroxymethyl β-lactam group of these 3-ethylidene and 3-isopropylidene compounds is discussed. Conversion of the alcohol moiety of these compounds to a mesylate, followed by nucleophilic substitution reactions to provide carbapenem intermediates is described.

(d) The formation of α,β-unsaturated ketone C-3 substituted β-lactam derivatives is studied in Chapter 4 as versatile side chains in the formation of novel C-6 substituted carbapenem precursors.

(e) A radical induced synthesis of 3,3-disubstituted azetidin-2-ones containing C-3 acyl and C-3 benzyl groups is discussed in Chapter 4.

(f) The objective of Chapter 5 is to synthesize C-3 substituted alkyl β-lactams which have an epoxide moiety at C-4, recognised as useful carbapenem precursors.

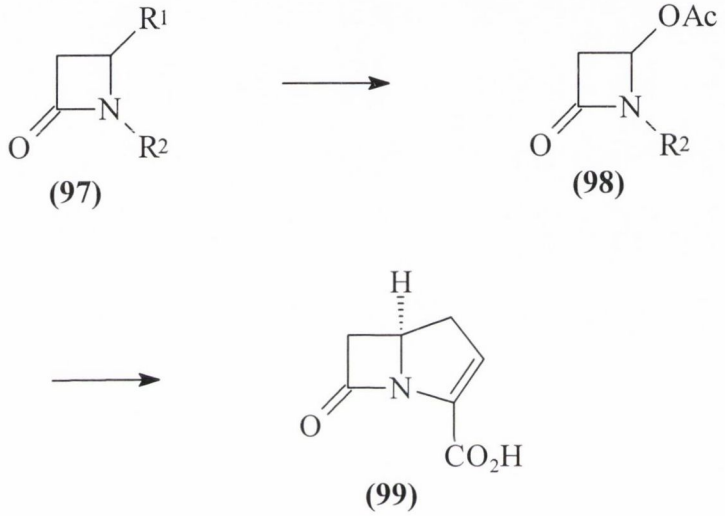
(g) Chapter 5 is focused on the conversion of 4-formyl-3-vinylazetidin-2-one to a pyrrolidinone structure via reaction with a sulphur ylide.

Chapter 2

Synthesis and Chemical Modification of 3-Vinylazetidin-2-ones

2.1 Introduction.

The low fermentation yields reported for the carbapenem antibiotics has meant that much effort has been devoted to developing suitable methods for their synthesis. The main strategies towards carbapenem synthesis involves the construction of an appropriately substituted monocyclic β-lactam with the correct stereochemistry at C-3 and C-4 of the β-lactam ring. Chemical manipulation at C-4 of (**97**) gives (**98**), followed by subsequent ring closure affords the bicyclic ring system (**99**) (**Scheme 9**).



Scheme 9

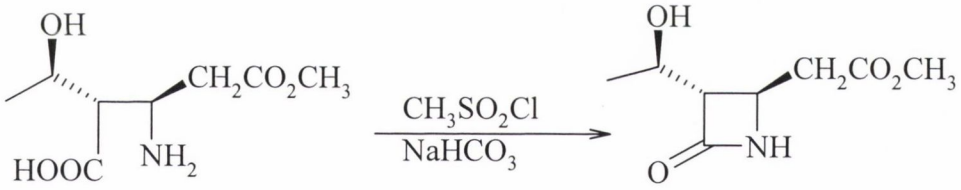
The synthesis of model 3-vinyl-4-substituted azetidin-2-ones are examined in this chapter as intermediates to potential carbapenems. The 4-methoxyphenyl group is chosen as the most appropriate N-1 protecting group due to its facile removal with cerium ammonium nitrate and this is demonstrated in Chapter 3. Synthetic process for the formation of β-lactams have been extensively reviewed in the scientific literature[80]. Methods for the formation of the amide bond involve either the synthesis of one bond or the simultaneous formation of two bonds. Cycloaddition reactions resulting in the simultaneous formation of two of the β-lactam bonds are divided into the following sections; isocyanate-alkene method, ketene-imine method, bromoester-imine condensations, metal-enolate–imine approach. This chapter discusses the most common route i.e. the ketene-imine approach in detail. The bromo-ester procedure is discussed in Chapter 4.

A short summary of the synthetic methods available for the preparation of β-lactams is now presented.

2.2 Preparation of Monocyclic β-Lactams

2.2.1 Formation of the amide bond (N_1-C_2)

Stezhko *et al*[81] prepared the parent azetidin-2-one ring by heating 3-aminopropanoic acid in dimethylsulphoxide at 150°C. Sheehan and Hess[82] were early investigators in the use of dicyclohexylcarbodiimide (DCC) as a condensing agent in peptide synthesis. Tanner and Somfai utilised DCC as a dehydrating agent in the enantioselective synthesis of precursors to the carbapenem antiobiotic (+)-PS-5[83,84]. Formation of β-lactam (**101**) was also achieved by Watanabe and Mukaiyama[85] obtaining good yields from the corresponding β-amino acid (**100**) utilizing a tetrabutylammonium salt as a phase transfer catalyst in the presence of methanesulfonyl chloride and potassium hydrogen carbonate in a chloroform-water system (**Scheme 10**).



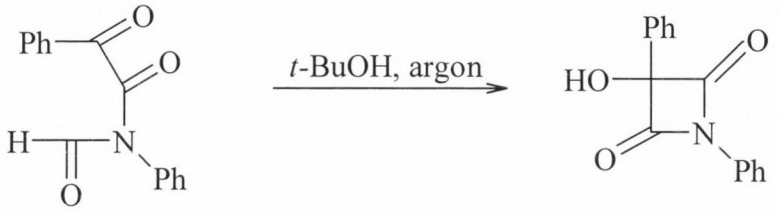
(100) **(101)**

Scheme 10

Another example of β-lactam formation involving the closure of the amide bond has been the synthesis of α-(1-hydroxy)alkylazetidin-2-ones, by cyclisation of the condensation product of a primary amine and ethyl-2-hydroxyalkylacrylate, yielding the desired β-lactam product[86].

2.2.2 Formation of C_2-C_3 bond

Few examples involving the formation of the azetidin-2-one C_2-C_3 bond presently exist. Recent advances include a photochemical transformation of compound (**102**) into the corresponding 4-keto-β-lactam (**103**) (**Scheme 11**)[87-89].

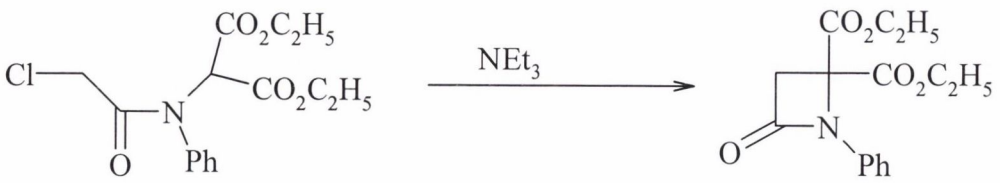


(102) **(103)**

Scheme 11

2.2.3 Formation of C_3-C_4 bond.

Both enolate-imine condensations and ketene-imine type cycloadditions lead to the formation of C_3-C_4 β-lactam bond in addition to the N_1-C_2 bond. In a simplistic approach, C_3-C_4 bond formation alone should occur when C-3 has a nucleophilic centre and C-4 an electrophilic centre or vice versa. This nucleophilic intramolecular displacement reaction was first demonstrated by Sheehan and Bose in the cyclisation of α-haloacetanilidomalonates such as (**104**) to the corresponding azetidin-2-one (**105**) in the presence of base (**Scheme 12**)[90,91].

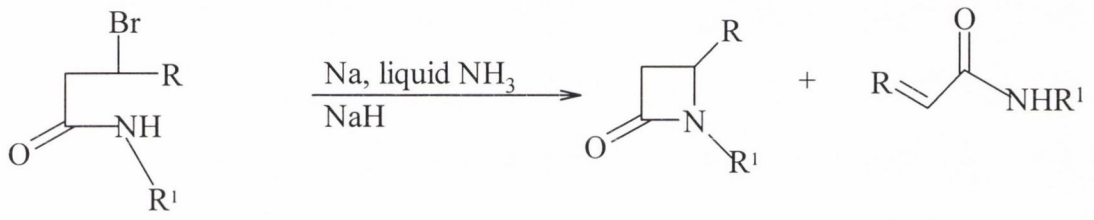


(104) **(105)**

Scheme 12

2.2.4 Formation of N_1-C_4 bond

Strategies for the synthesis of N_1-C_4 bond of the azetidin-2-one ring have evolved around an intramolecular S_N2 nucleophilic displacement of a leaving group at C-4 of the β-lactam. Knunyants and Gambaryan first demonstrated the cyclodehydrohalogenation of 3-halopropionamides (**106**) by employing strong bases at high temperature to afford 3-unsubstituted azetidin-2-ones (**107**) accompanied by a portion of the acrylamide side product (**108**) (**Scheme 13**)[92]. Milder conditions with phase transfer catalysis are now employed[93].

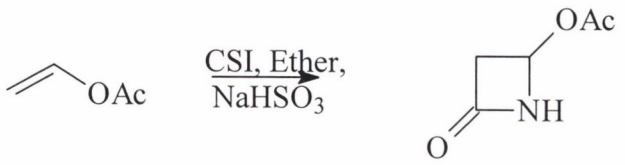


(106) **(107)** **(108)**

Scheme 13

2.2.5 Isocyanate-Alkene method

Cycloaddition of an alkene across the C=N function of an isocyanate leads to the simultaneous formation of bonds N_1-C_4 and C_2-C_3 of the β-lactam[94,95]. For this reaction to proceed efficiently, activation of the alkene by an electron donating group or of the isocyanate by an electron withdrawing group is required. Chlorosulfonyl isocyanate (CSI) is the most popularly employed isocyanate, producing under mild conditions a variety of monocyclic, bicyclic and spirocyclic β-lactams. The ease of removal of the sulphonylchloride moiety from the β-lactam using aqueous sodium bisulphite or sodium hydrogen carbonate ensures the use of CSI as a facile method of preparing *N*-unsubstituted azetidin-2-ones. Reaction with vinyl acetate (**109**) yields azetidin-2-one (**110**) which is a useful synthon for carbapenems (**Scheme 14**)[96,97].



(109) **(110)**

Scheme 14

2.2.6 Metal enolate-imine condensations

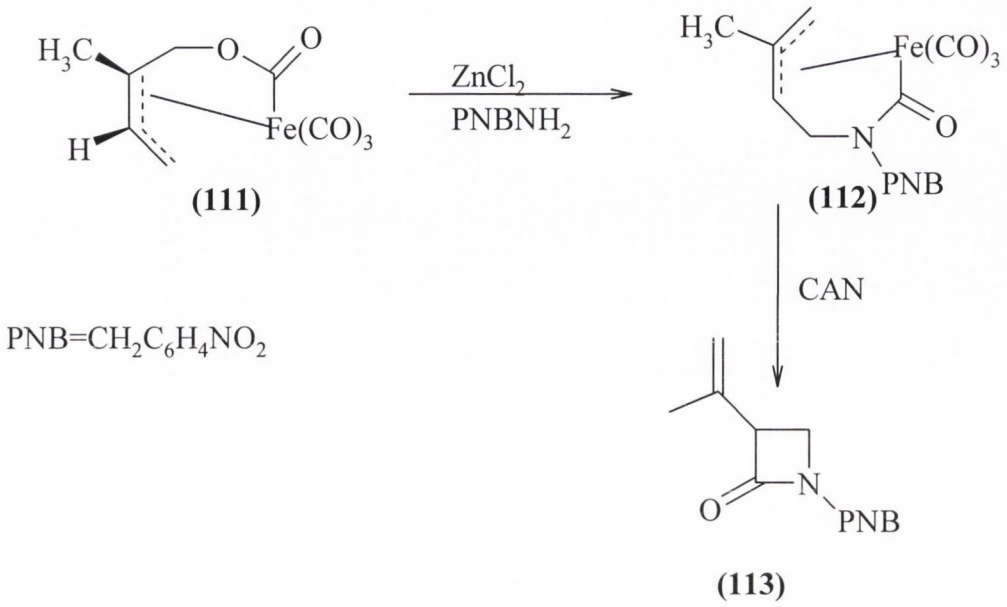
Metal enolates derived from esters can interact with imines derived from non-enolizable aldehydes to form azetidin-2-ones. Brown[98] in his review of this subject discussed the cyclisation of *N*-arylimines, *N*-alkylimines and *N*-heteroimines with simple alkylester enolates, α-heteroester enolates and 3-hydroxybutyrate enolates.

This reaction was first demonstrated by Gluchowski *et al* in 1980[99] in their synthesis of azetidin-2-ones from lithium enolates and aryl imines. Palomo *et al*[100] successfully synthesized the carbapenem (+)-PS-5 prescursor by treating α-methylcinnamylidineaniline with the lithium enolate of ethyl butyrate.

2.3 3-Vinyl and 3-Isopropenylazetidin-2-ones

The presence of an alkene moiety at C-3 of the β-lactam ring in the products synthesized in this work, provides a manipulable functional group for further chemical transformations. A short summary of the synthetic methods available for the preparation of 3-vinyl and 3-isopropenylazetidin-2-ones is now presented. The introduction of the vinyl group at C-3 of the β-lactam has been investigated by many research groups.

One of the earlier approaches was reported by Annis *et al*[101]. They examined the synthesis of thienamycin analogues. π-Allyltricarbonyliron (lactone) complexes were used as precursors in the construction of the corresponding lactam complexes. Synthesis of the following 3-vinylazetidin-2-one (**113**) is achieved by reaction of (**111**) (**Scheme 15**) with zinc chloride and *para*nitrobenzylamide yielding the intermediate (**112**) which on reaction with cerium ammonium nitrate (CAN) yields the 3-vinyl-azetidin-2-one (**113**).



Scheme 15

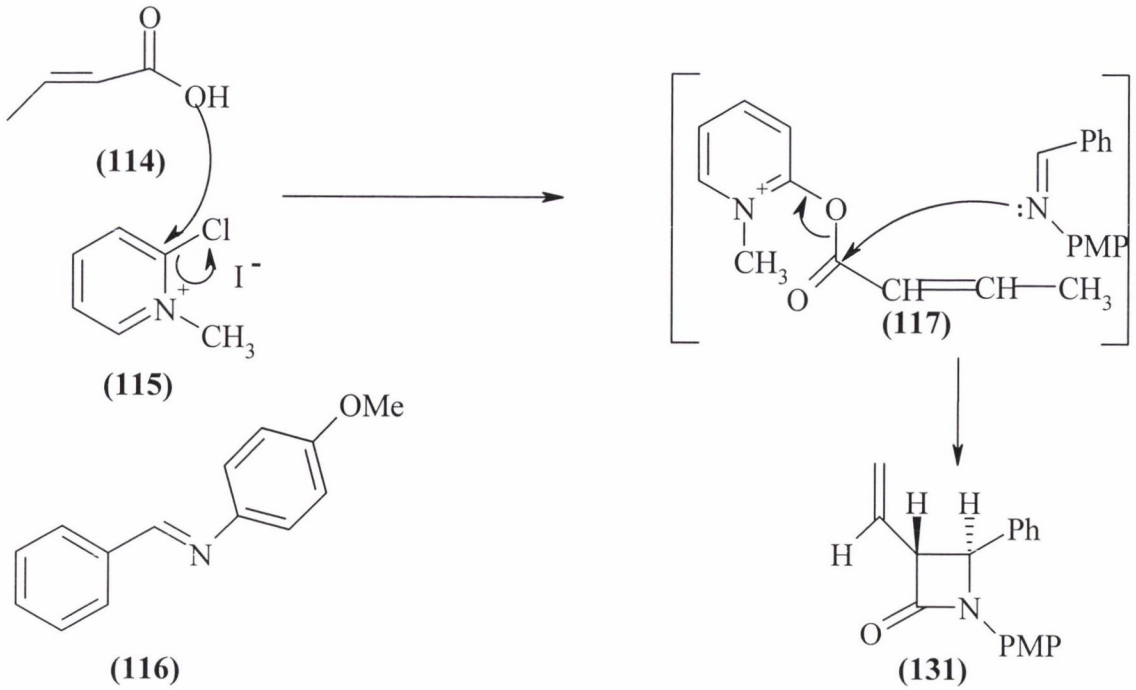
Buynak and co-workers described the synthesis of 6-vinylidenepenam from allenyl iodides[102]. Kano *et al* condensed 1-phenyl-β-lactams with ketones to afford 3-alkylidene azetidin-2-ones which were isomerized by LDA in THF at 0°C to give the corresponding 3-vinylazetidin-2-ones[103,104]. Foulds and co-workers prepared derivatives of penicillins in which the C-6 amide group was replaced by an olefinic moiety. Selective addition of thiols to 6-alkylidene penicillanic acids produced 6β-substituted penicillinates. The conjugate addition of Grignard derivatives derived from 6,6-dibromopenicillinates to substituted acrylates and acrylamides, followed by selective reduction of the remaining 6-bromo group afforded the 6-vinyl-substituted penicillanates[105].

Torii and co-workers[106] in 1993 and Zhou and Alper[107] in 1996 utilised the palladium catalysed carbonylation of allyl diethylphosphate in the presence of imines under CO pressure gave *cis* or *trans* 3-vinyl β-lactam compounds depending on the nature of the imine employed.

2.3.1 Carboxylic Acid Route

In the present work two routes will be used for 3-vinyl and 3-isopropenylazetidin-2-one syntheses i.e via Georg`s acid method[108a] and the acid chloride route reported by Zamboni and Just[111a]. One of the most versatile methods for the one step construction of the β-lactam ring system is the reaction between an activated carboxylic acid with an imine in the presence of a tertiary base. Acid activating agents include several phosphorus derived reagents, ethyl chloroformate, trifluoroacetic anhydride and *p*-toluenesulfonyl chloride[108a].

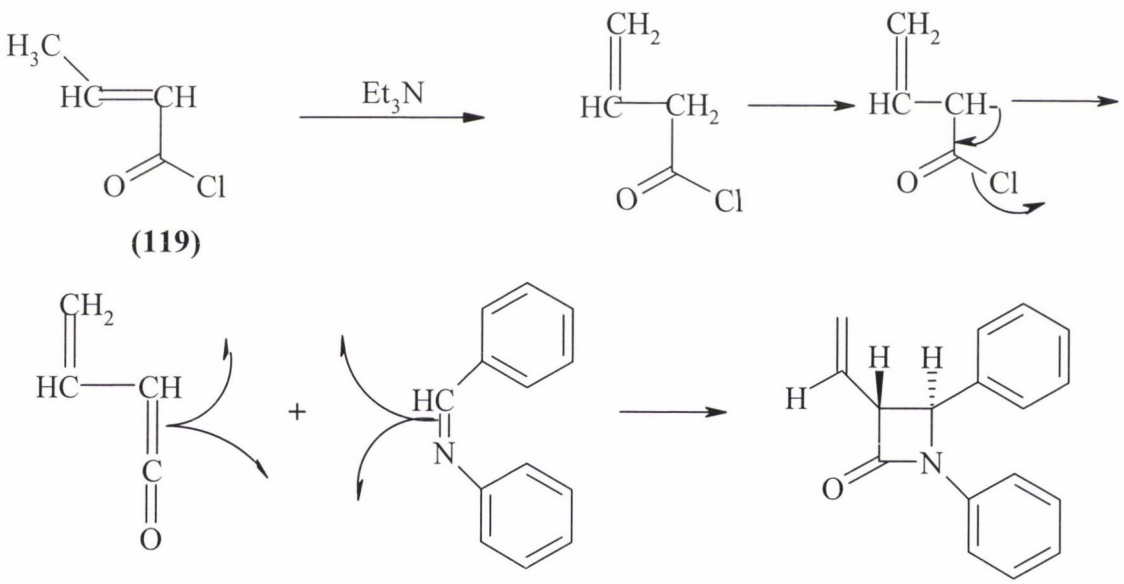
Georg *et al* have reported that carboxylic acids activated with Mukaiyama`s reagent (2-chloro-*N*-methylpyridinium iodide) (**115**) reacted with imines in the presence of a teritary amine base to produce β-lactams with good stereoselectivity [108a]. The stereochemical outcome of the reaction is dependent on the reaction conditions and substituents present and thus is difficult to predict[109]. The reaction of crotonic acid (**114**) and Mukaiyama`s reagent (**115**) with three equivalents of tripropylamine and the appropriate Schiff base (**116**) yields the desired 3-vinylazetidin-2-one (**131**). The proposed mechanism for the formation of β-lactams *via* this route is given in (**Scheme 16**). The activated ester (**117**) acts as an intermediate which reacts with an imino compound (**116**) and triethylamine to produce the four-membered heterocycle. The cyclization is generally considered to be a non-concerted, two step reaction resulting in formation of the *trans* product[108b].



Scheme 16

2.3.2 Acid-Chloride/Imine Reaction

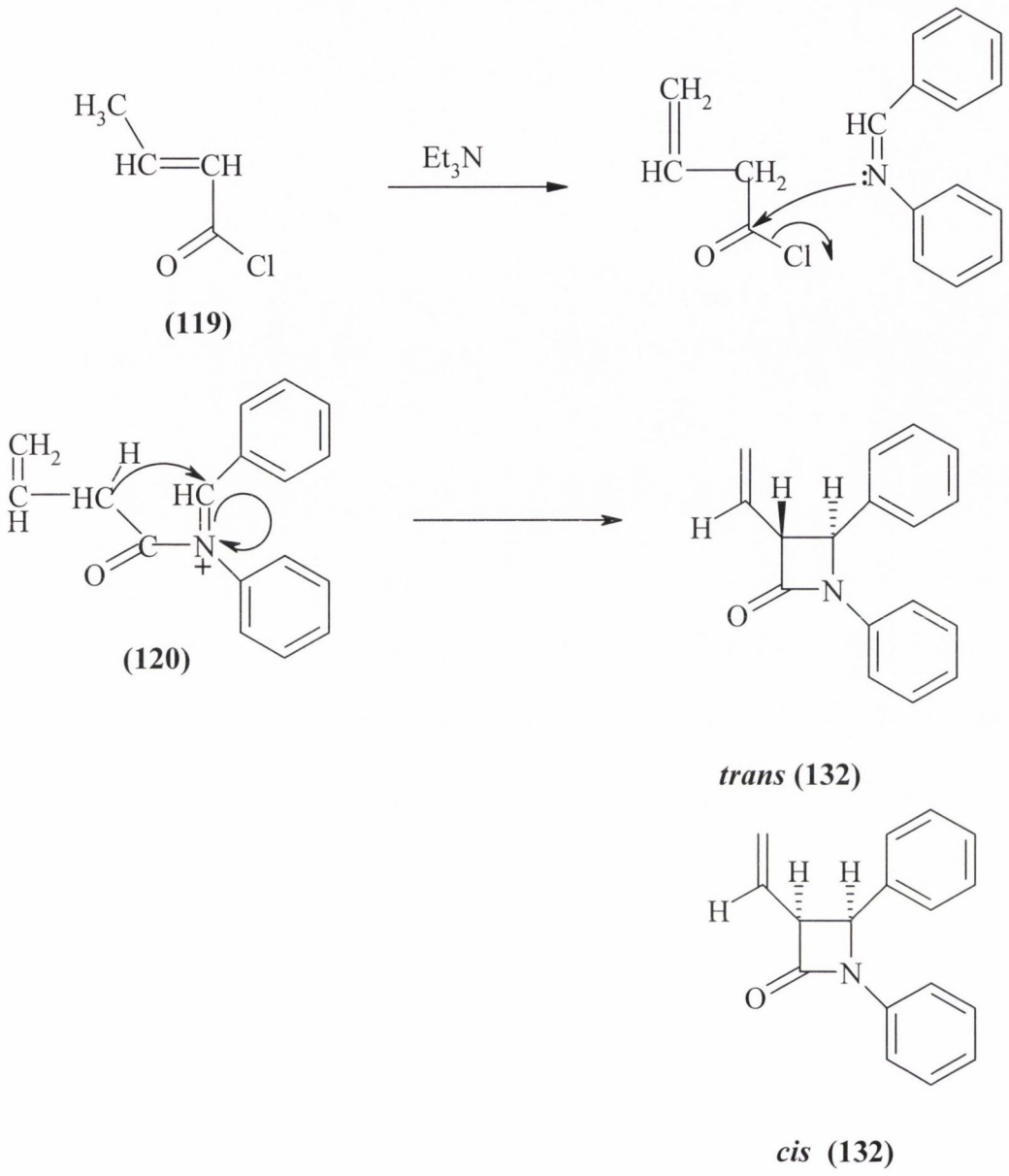
Bose *et al* reported the formation of 3-vinyl and 3-isopropenylazetidin-2-ones by reaction of benzylidene anilines and crotonyl chloride in the presence of triethylamine[110]. This reaction gave the corresponding *trans* β-lactam when carried out in dichloromethane. Later Zamboni and Just[111a] utilized this reaction for preparing several *cis* and *trans* 3-vinyl β-lactams as potential synthons for β-lactam antibiotics. The *trans* 3-vinylazetidin-2-ones can be formed by either a concerted or a two-step non-concerted reaction mechanism. The concerted mechanism usually leads exclusively to the *trans* isomer (**131**) using the acid chloride (**119**) (**Scheme 17**), while a two-step non-concerted process can result in *cis* or *trans* β–lactams (**Scheme 18**)[111b, 111c] via the intermediate (**120**).



(**119**)

trans **(132)**

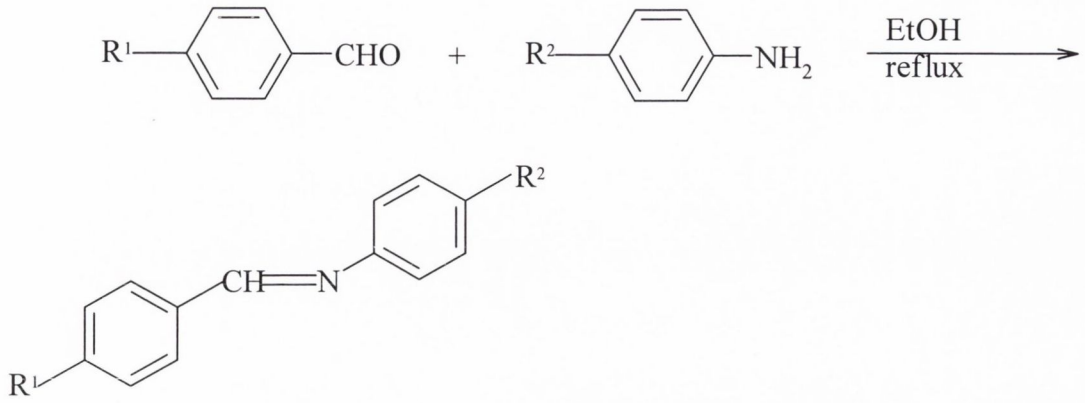
Scheme 17



Scheme 18

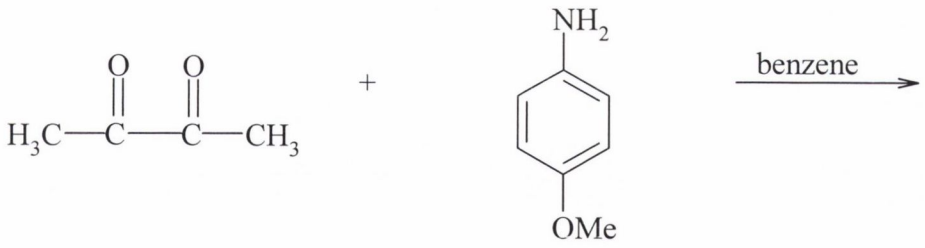
2.4 Preparation of Schiff Bases

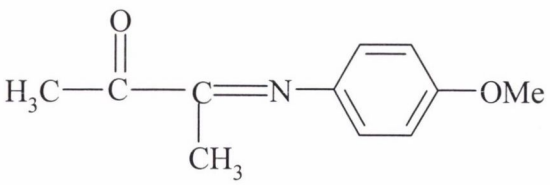
In the present work the Schiff bases (**121**)-(**127**) required for the synthesis of 3-vinylazetidin-2-ones were prepared by the condensation of a primary amine with an aromatic aldehyde (**Scheme 19**) or by using a dione instead of an aldehyde (**Scheme 20**).



(121) R^1=3, 4-OCH_2O, R^2=CO_2CH_3
(122) R^1=3, 4-OCH_2O, R^2=OCH_3
(123) R^1=Cl, R^2=CO_2CH_3
(124) R^1=H, R^2=OCH_3
(125) R^1=H, R^2=H
(126) R^1=F, R^2=CO_2CH_3

Scheme 19





(127)

Scheme 20

The yields, melting points, molecular formulae and spectroscopic details of compounds (**121**)-(**127**) are given in **Table 7-Table 9**.

Table 7: Yield and melting point data for compounds (121)-(126)

Compound No.	R^1	R^2	% Yield	m.p. °C (Lit.)
121	3, 4-OCH_2O-	CO_2CH_3	80	129-130 (130-131)[112]
122	3, 4-OCH_2O-	OCH_3	92	98-99 (98-99)[102]
123	Cl	CO_2CH_3	60	155-156 (155-156)[102]
124	H	OCH_3	60	63-64 (62)[112]
125	H	H	86	54 (53)[102]
126	F	CO_2CH_3	39	113-114 (113-114)[113]

Table 8: Yield and melting point data for compound (127)

Compound No	R^1	R^2	R^3	% Yield	m.p. °C (Lit.)
127	OCH_3	CH_3	CH_3	55	31-33 (33)[114]

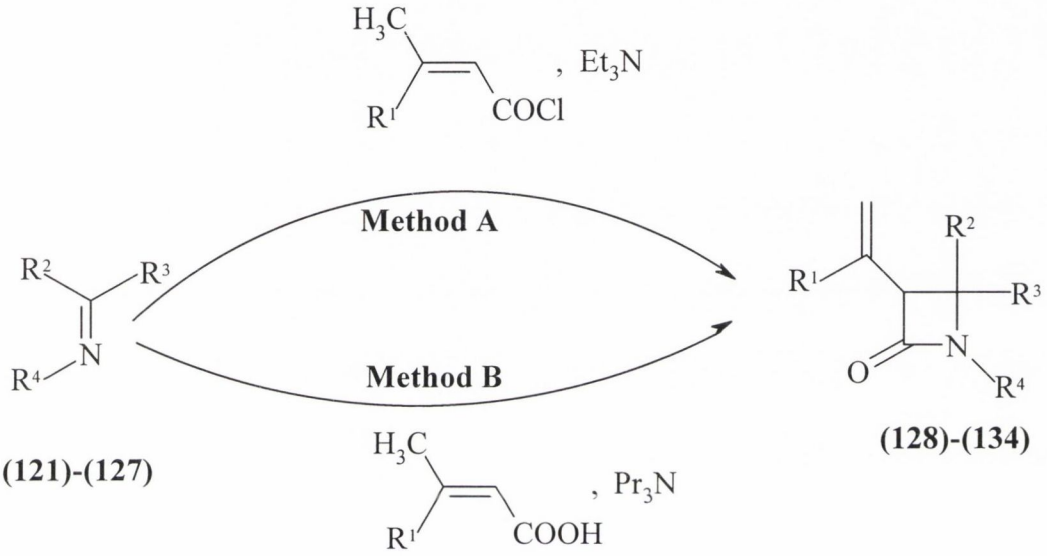
The infrared spectra for all compounds displays the characteristic imine double bond stretching frequency in the range ν1620-1630cm^{-1}. In the case of compounds (**121**), (**123**), (**126**), the carbonyl group gives rise to a peak at ν1710cm^{-1} which is typical of the ester functionality. In the ^{1}H-NMR spectra the methine group of the imine bond resonates downfield as a singlet in the region δ8.27-8.43. Methoxy groups give rise to sharp singlets at δ3.78-3.85. The methylene-dioxy group protons in compounds (**121**) and (**122**) appear as singlets at δ5.90 and δ5.96 respectively. The aromatic hydrogens for this series of compounds appear usually as multiplets at δ6.70-8.19. Spectroscopic details for compounds (**121**)-(**127**) are given in **Table 9**.

Table 9:Spectroscopic Data for Schiff Bases (121)-(127)

Compound No	IR Data ν_{max} cm^{-1} (KBr or film)	^{1}H-NMR Data δ($CDCl_3$)
121	1625 (C=N) 1710 (CO_2CH_3)	3.91 (3H, s, CO_2CH_3) 5.90 (2H, s, OCH_2O), 6.86-8.07 (7H, m, aromatic Hs), 8.27 (1H, s, CH=N).
122	1630 (C=N)	3.78 (3H, s, OCH_3) 5.96 (2H, s, OCH_2O), 6.70-7.57 (7H, m, aromatic Hs), 8.31 (1H, s, CH=N).
123	1625 (C=N) 1710 (CO_2CH_3)	3.96 (3H, s, CO_2CH_3) 6.78-8.19 (8H, m, aromatic Hs), 8.43 (1H, s, CH=N).
124	1620 (C=N)	3.85 (3H, s, OCH_3), 6.90-7.38 (9H, m, aromatic Hs), 8.38 (1H, s, CH=N).
125	1630 (C=N)	6.95-7.43 (10H, m, aromatic Hs), 8.43 (1H, s, CH=N).
126	1620 (C=N) 1710 (CO_2CH_3)	3.93 (3H, s, CO_2CH_3), 6.85-8.15 (8H, m, aromatic Hs), 8.42 (1H, s, CH=N).
127	1698 (C=O) 1630 (C=N)	1.99 (3H, s, CH_3), 2.48 (3H, s, $COCH_3$), 3.79 (3H, s, -OCH_3), 6.62-6.91 (4H, m, aromatic Hs).

2.5 1,4-Diaryl-3-vinylazetidin-2-ones

A series of *trans* 3-vinylazetidin-2-ones were synthesized from their corresponding imines, via the Zamboni and Just acid-chloride procedure[108a] (method A) and secondly by the carboxylic acid route (method B) reported by Georg *et al*[111a] (**Scheme 21**). The yields and melting point data for the azetidin-2-ones (**128**)-(**134**) are given in **Table 10**.



Compound No.	R^1	R^2	R^3	R^4
128	H	H	3,4-$C_6H_3OCH_2O$	4-$C_6H_4CO_2CH_3$
129	H	H	3, 4-$C_6H_3OCH_2O$	4-$C_6H_4OCH_3$
130	H	H	4-C_6H_4Cl	4-$C_6H_4CO_2CH_3$
131	H	H	C_6H_5	4-$C_6H_4OCH_3$
132	H	H	C_6H_5	C_6H_5
133	H	H	4-C_6H_4F	4-$C_6H_4CO_2CH_3$
134	H	CH_3	$COCH_3$	4-$C_6H_4OCH_3$

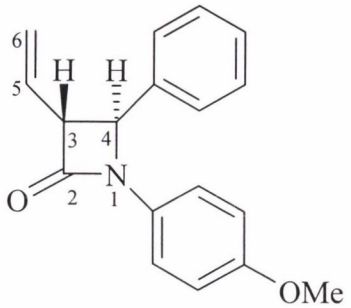
Scheme 21

In general, of the two methods, the carboxylic acid route affords the higher yield.

Table 10: Yield, melting point and molecular formula data for 1,4-diaryl-3-vinylazetidin-2-ones (128)-(134)

Compound No.	% Yield Method A & B	m.p. ^{o}C (Lit.)	Molecular Formula
128	A:26	115-116 (115-116)[122]	$C_{20}H_{17}NO_5$
129	A:47 B:52	110-111 (110-111)[122]	$C_{19}H_{17}NO_4$
130	A:19	91-92 (91-92)[122]	$C_{19}H_{16}ClNO_3$
131	A:18	127-128 (127-128)[122]	$C_{18}H_{17}NO_2$
132	A:31 B:32	102-103 (100-102)[122]	$C_{17}H_{15}NO$
133	A:39	96-97 (95-97)[113]	$C_{19}H_{16}FlNO_3$
134	A:89 B:76	79-81 (79-80)[116]	$C_{15}H_{17}NO_3$

The β-lactams were characterized by infrared, high resolution ^{1}H-NMR and ^{13}C-NMR spectroscopy. In the infrared spectra all products showed strong absorbance in the region ν1750cm^{-1} indicating the presence of the carbonyl group in the strained four-membered ring. The ester carbonyls which occur in compounds (**128**), (**130**), (**133**) absorb in the ν1710cm^{-1} region. ^{1}H-NMR spectroscopy exhibits seventeen non-exchangeable hydrogens for 1-(4-methoxyphenyl)-4-phenyl-3-vinylazetidin-2-one (**131**) a representative of this series of compounds.

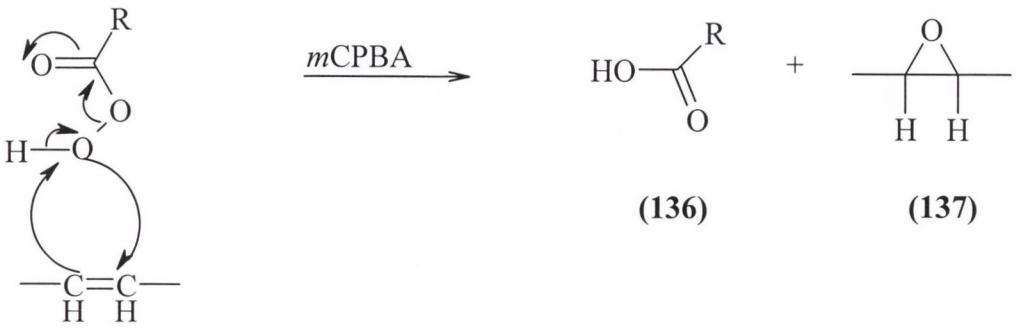


(131)

The doublet which is seen at δ3.65 is assigned to H-3 which is coupled to H-4 at δ4.75 $J_{3,4trans}$=2.5Hz. H-4 resonates as a doublet at δ4.75. The small coupling constant value of 2.5Hz is indicative of *trans* coupling to H-3. The vinylic protons give rise to a typical arrangement of two multiplets in the δ5.10-6.12 region. The methoxy hydrogens appear as a singlet at δ3.72. The aromatic protons resonate as an unresolved multiplet in the δ6.61-7.54 region.

2.6 Synthesis of 1,4-Diaryl-3-(1,2-epoxyethyl)azetidin-2-ones

Transformation of 3-vinylazetidin-2-ones to their corresponding epoxides is examined in this section. Epoxides (or oxiranes) are versatile intermediates in organic synthesis, and are potential intermediates for carbapenems with known and novel substituents at C-3 of the β-lactam ring. Not only are the epoxides easily prepared from a variety of vinyl starting materials, but the inherent polarity and strain of the three membered ring makes them susceptible to ring opening reactions with a large number of reagents i.e. electrophiles, nucleophiles, acids, bases, reducing and some oxidising agents. These reactions will be discussed in Section 2.7. The epoxidation of the vinyl group of 1,4-diaryl-azetidin-2-ones provides a gateway to novel substituted side chains at C-3 of the β-lactam ring. Methods of producing epoxides have been well reviewed[115,117-119]. The use of peracids, such as *m*CPBA is the most useful method of preparing epoxides. The reaction is called the ``Prilezhaev reaction``. The following one step mechanism has been proposed (**Scheme 22**)[120]. The reaction proceeds by the addition of an oxygen atom across the double bond (**135**) affording the compound (**136**) and the epoxide (**137**).

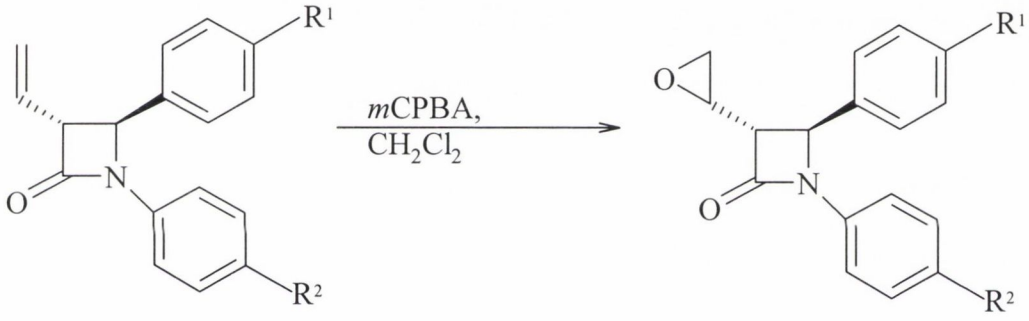


(135) **(136)** **(137)**

Scheme 22

Yields of epoxides using *m*CPBA are high and conditions are mild which makes *m*CPBA a suitable oxidising agent for β-lactam compounds. Epoxides may also be prepared by treating an olefin with oxygen or alkyl peroxide catalysed by a complex of Ti, V, Co, or Mo[120]. More recently reported peroxyacids include, trifluroperoxyacetic acid or magnesium monoperphthalate hexahydrate (MMPP)[121].

In the present work a series of 3-vinylazetidin-2-ones (**138**)-(**142**) were treated with *m*CPBA in anhydrous dichloromethane for 24 h under a nitrogen atmosphere. Optimum results were achieved using 1mmol of *m*CPBA and a reaction time of 24 h (**Scheme 23**). The yields obtained were moderate. For reasons of simplicity, only one enantiomer of the β-lactam compounds synthesised is shown throughout the thesis.



(128)-(132)

(138) R^1=3, 4-OCH_2O, R^2=CO_2CH_3
(139) R^1=3, 4-OCH_2O, R^2=OCH_3
(140) R^1=Cl, R^2=CO_2CH_3
(141) R^1=H, R^2=OCH_3
(142) R^1=H, R^2=H

Scheme 23

The epoxides (**138**)-(**142**) were obtained as diastereomeric mixtures which apart from compound (**142**) were inseparable by column chromatography. All diastereoisomers possessed exclusively *trans* stereochemistry for the β-lactam protons H-3 and H-4. The products were characterized by spectroscopic analysis. Satisfactory high resolution mass spectrometry or microanalysis was obtained in each case. These epoxides proved to be relatively unstable and were obtained in low yield. The yields

and spectroscopic details for epoxide compounds (**138**)-(**142**) are provided in **Table 11**.

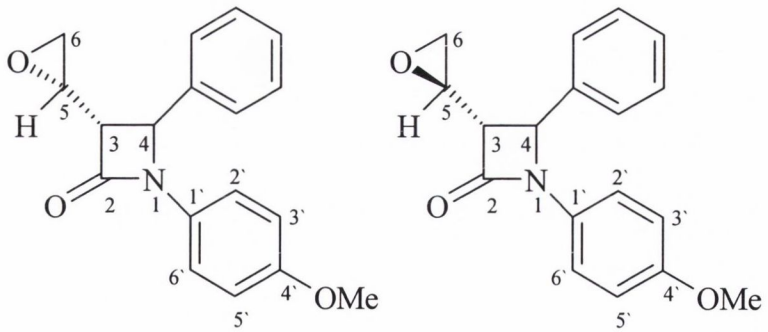
Table 11: Yields and Spectroscopic data for compounds (138)-(142)

Compound No.	**% Yield**	**IR Data $\nu_{max}cm^{-1}$ (KBr or film)**	**^{1}HNMR $\delta(CDCl_3)$**
138	46	1760 (C=O) 1720 (CO_2CH_3) 1148, 941, 748 (epoxy C-O)	2.65-3.62 (4H, m, epoxy Hs, H-3), 3.84 (3H, s, -CO_2CH_3), 4.81 (0.63H, d, $J_{4,3\ trans}$=3Hz, H-4), 4.96 (0.36H, $J_{4,3trans}$=3Hz, H-4), 5.97 (2H, m, -OCH_2O-), 6.87-8.10 (7H, m, aromatic Hs).
139	36	1750 (C=O)	2.15-3.61 (4H, m, epoxy Hs, H-3), 3.68 (3H, s, -OCH_3), 4.75 (0.7H, d, $J_{4,3trans}$=3Hz, H-4), 4.85 (0.3H, d, $J_{4,3trans}$=3Hz, H-4), 5.95 (2H, m, -OCH_2O-), 6.60-7.51 (7H, m, aromatic Hs).
140	52	1750 (C=O) 1720 (CO_2CH_3)	2.18-3.70 (4H, m, epoxy Hs, H-3), 3.85 (3H, s, -OCH_3), 4.97 (0.7H, d, $J_{4,3trans}$=2.59Hz, H-4), 4.86 (0.3H, d, $J_{4,3trans}$=2.63Hz, H-4), 6.69-7.90 (8H, m, aromatic Hs).
141	46	1746 (C=O) 1247, 943, 757 (epoxy C-O)	2.72 (1H, dd, J_{gem}=4.6Hz, $J_{6,5}$=2.6Hz, H-6), 2.96 (1H, dd, J_{gem}=4.6Hz, $J_{6,5}$=4.1Hz, H-6), 3.27-3.29 (1H, m, H-3), 3.33-3.54 (1H, m, H-5), 3.73, 3.74 (3H, s, -OCH_3), 4.84 (0.72H, d, $J_{4,3trans}$=2.4Hz, H-4), 4.96 (0.28H, d, $J_{4,3trans}$=2.6Hz, H-4), 6.75-7.37 (9H, m, aromatic Hs).

Table 11 continued

Compound No.	% Yield	IR Data $\nu_{max}cm^{-1}$ (KBr or film)	^{1}HNMR $\delta(CDCl_3)$
142	42	1760 (C=O) 1248, 940, 748 (epoxy C-O)	2.73 (1H, dd, J_{gem}=4.5Hz, $J_{6,5}$=2.6Hz, H-6), 2.98 (1H, dd, J_{gem}=4.5Hz, $J_{6,5}$=4.1Hz, H-6), 3.25 (1H, dd, $J_{3,4\ trans}$=2.5Hz, $J_{3,5}$=5.0Hz, H-3), 3.42-3.44 (1H, m, H-5), 4.89 (1H, d, $J_{4,3trans}$=2.5Hz, H-4), 7.03-7.41 (10H, m, aromatic Hs).

In the infrared spectra of compounds (**138**)-(**142**) the β-lactam carbonyl function was evident in each case by the appearance of a distinctive absorbance at ν1746-1760cm^{-1}. For compounds (**138**) and (**140**) the ester carbonyl was seen to resonate at the lower frequency of ν1720cm^{-1}. From the ^{1}H-NMR spectrum of 3-(1,2-epoxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**141**) it is evident that the product was obtained as a diastereomeric mixture.



Diastereomers (141)

In the diastereomeric compound, one of the H-6 signals is seen at δ2.72 as a double doublet integrating for one hydrogen, J_{gem}=4.6Hz, $J_{6,5}$=2.6Hz and the other double doublet appears at δ2.96 integrating for one proton J_{gem}=4.6Hz, $J_{6,5}$=4.1Hz. The multiplets integrating in the region δ3.27-3.29 and δ3.33-3.54 are attributable to H-3 and H-5. The methoxy hydrogens appear as two signals at δ3.73 and δ3.74. One of the H-4 signals is seen as a doublet integrating for 0.72H, $J_{4,3}$=2.4Hz, and the other doublet appears at δ4.96 integrating for 0.28H, $J_{4,3}$=2.6Hz.

In the ^{1}H-NMR spectrum of the starting material 1-(4-methoxyphenyl)-4-phenyl-3-vinylazetidin-2-one (**131**), H-3 is seen as a broad doublet at δ3.65, coupled to H-4 at δ4.75 $J_{3,4trans}$=2.5Hz. Hence it is apparent that the addition of the epoxide has exerted an upfield shift on H-3. Proof of the formation of a diastereomeric mixture is obtainable from the ^{1}H-NMR splitting pattern of the H-4 signal. H-4 appears as two doublets one of which is at δ4.84 integrating for 0.72H, and the other at δ4.96 integrating for 0.28H, indicating the addition of the epoxide above and below the double bond. The aromatic protons are seen typically downfield as a multiplet in the δ6.75-7.37 region.

The ^{13}C-NMR spectrum of 3-(1,2-epoxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**141**) displays the readily assignable carbonyl carbons i.e. 162.33ppm, 163.06ppm (β-lactam C=O). The appearance of the two carbon signals is indicative of the diasteromeric mixture. The other quaternary carbons are visible at 156.11ppm (C-4`), 137.18ppm (C-1``) and 130.83ppm (C-1`). These signals are absent in the DEPT spectrum. (This NMR technique allows the user to distinguish between differently substituted carbons. The DEPT 135° technique used in this thesis, gives positive signals for methyl and methines, and negative signals for methylene carbons, while quaternary signals disappear). The aromatic carbons C-2` and C-6` are equivalent in chemical shift and appear as one signal at 118.36ppm. Similarly C-3` and C-5` are located at 114.18ppm. The remaining aromatic carbons give rise to a cluster of signals in the 125.89-129.15ppm region. C-4 of the β-lactam at 60.25ppm, 61.66ppm is slightly downfield from the C-3 which is seen as two signals at 56.77ppm and 56.08ppm. The methoxy signal resonates at 53.34ppm. C-5 of the epoxy group appears as two signals at 48.24ppm and 48.64ppm. C-6 of the epoxy group is seen at 45.70ppm, 45.93ppm. The peak is inverted in the DEPT 135 spectrum indicating that a methylene group is present. Elemental analysis confirms the proposed structure.

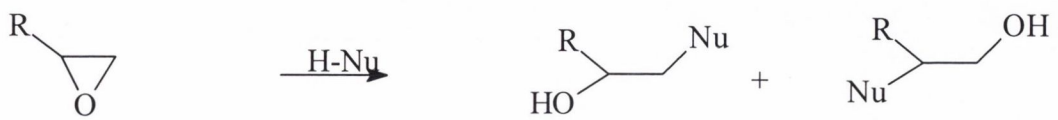
2.7 Selective Opening of 3-(1,2-epoxyethyl)azetidin-2-ones with Alcohols Catalysed by Ceric (IV) Ammonium Nitrate

2.7.1 Introduction

Epoxides are susceptible to reaction with oxygen nucleophiles (alcohols), nitrogen nucleophiles (amines and azides), sulphur nucleophiles and various carbon nucleophiles due to the inherent polarity and strain of the three membered ring. Ring opening can occur in either neutral, basic or acidic solution, but it is known that the presence of acid accelerates ring opening. In neutral and basic media, the reaction proceeds via nucleophilic attack on the neutral epoxide. In acidic media, protonation of the epoxide precedes nucleophilic attack. It is generally agreed that the reaction follows an S_N2 mechanism in neutral or basic solution.

In acid-solution the mechanism has most often been termed borderline S_N2 but has been the subject of much discussion. Normally backside attack of the nucleophile occurs on the epoxide carbon resulting in a Walden inversion at this centre. The 1,2-disubstituted products necessarily have a *trans* relationship of the nucleophile to the oxygen leaving group.

With unsymmetrical epoxides for example epoxides with an azetidin-2-one substituent, nucleophilic attack is governed by both the structure of the epoxide and the exact reaction conditions. With the monosubstituted epoxide (**143**) nucleophilic attack can occur at either the less or more substituted side of the epoxide to form the products (**144**) and (**145**) respectively (**Scheme 24**).



(143) **(144)** **(145)**

Scheme 24

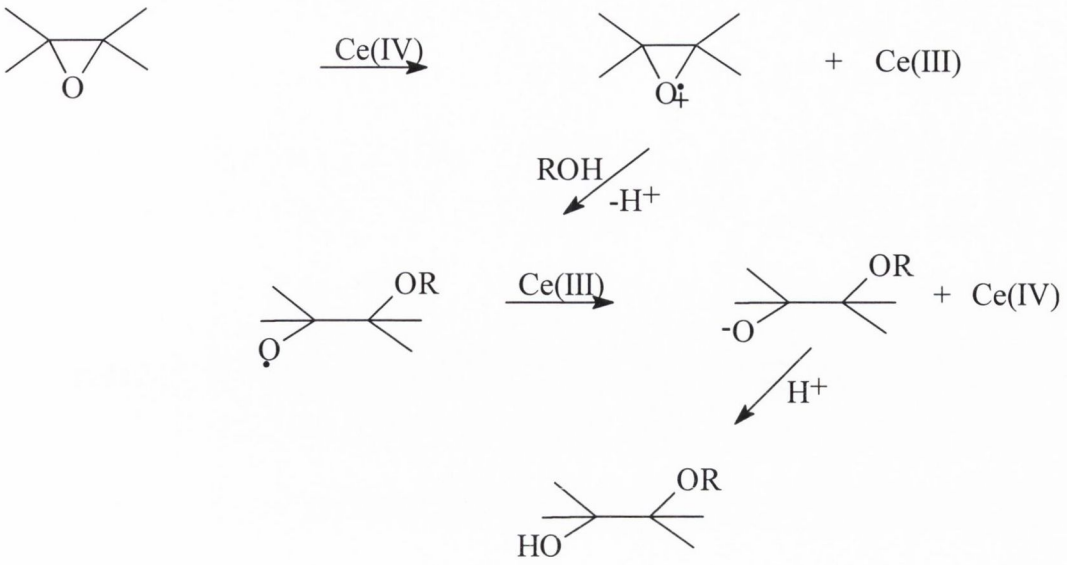
In neutral and basic solution, attack at the sterically less hindered site occurs predominantly yielding (**144**). In acid solution, there is usually a greater tendency for nucleophilic attack at the carbon atom which can better accommodate a positive

charge in the transition state, that is the more substituted carbon to form the addition adduct (**145**)[123].

Ring opening of epoxides with sulphur nucleophiles has been carried out with tris[ethylthio]borane[124] and phenylthioborane[125]. A number of catalysts have been examined in the nucleophilic opening of epoxides. Cobalt (I) salts[126], cobalt (II) salts[127] and ceric ammonium nitrate (CAN)[128] have been successfully employed in the regioselective opening of a variety of symmetrical and unsymmetrical epoxides. Nucleophilic ring opening of epoxides by alcohols is a synthetically useful method for the preparation of β-alkoxy alcohols. Alcholoysis reactions have been extensively studied but many of the methods reported have limited applicability in modern synthesis due to the high temperatures and acidic conditions involved.

Recently a number of efficent, mild, neutral and highly regioselective methods of epoxide opening with alcohols have been reported. One method involves the treatment with a nucleophile in the presence of unactivated, commercially available Woelm-200 neutral alumina[122]. Nucleophiles found to be successfully incorporated under these conditions include primary alcohols, thiols and amines. Secondary and tertiary alcohols do not react under these conditions. Iranpoor and Baltork[129] have reported that amounts of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) catalyses highly regioselective ring opening reactions of epoxides under neutral conditions by primary, secondary and tertiary alcohols to afford the corresponding β-alkoxy alcohols in excellent yields.

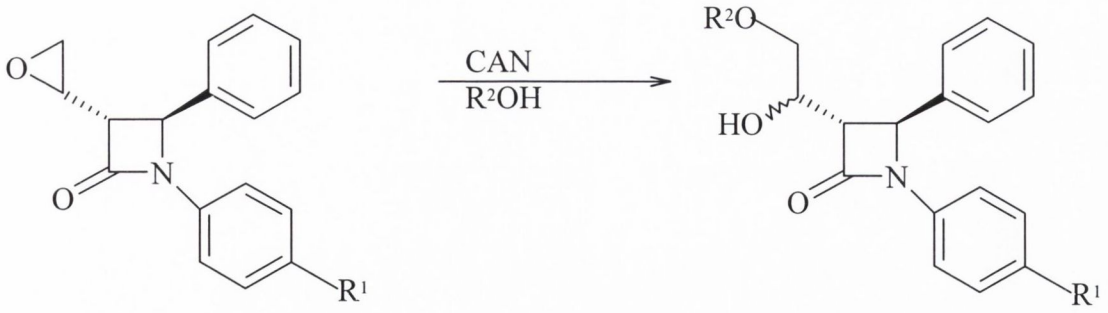
The same authors reported that commercially available ceric(IV) ammonium nitrate (CAN) catalyses nucleophilic ring opening of epoxides by primary, secondary and tertiary alcohols under mild conditions affording the corresponding β–alkoxy alcohols in high yields and high regiostereoselectivity[128]. In this section the CAN method was investigated in the synthesis of novel 1,4-diaryl-3-[1-(2-alkoxy-1-hydroxy)ethyl]azetidin-2-ones with the aim of introducing a hydroxy substituent at C-5 adjacent to the azetidin-2-one ring a feature which is characteristic of carbapenems. The reaction most probably occurs through a one electron transfer reaction with the initial formation of the epoxonium radical cation (**Scheme 25**).



Scheme 25

2.7.2 3-[1-(2-Alkoxy-1-hydroxy)ethyl]-1,4-diarylazetidin-2-ones

The β-lactam epoxides (**141**) and (**142**) were treated with CAN and methanol, ethanol or ispropanol using the method described by Iranpoor[128] (**Scheme 26**). The epoxide ring was opened regioselectively each case to afford the corresponding β-alcohol as a diastereomeric mixture. The *trans* nature of the β-lactam protons was retained throughout this procedure. The products were obtained in moderate yields and were purified by column chromatography. Yields and relevant spectroscopic data are given in **Table 12**. All compounds gave satisfactory molecular ion on high resolution mass spectrometry analysis.



(141), (142)

(146) $R^1=CH_3$, $R^2=CH_3$
(147) $R^1=OCH_3$, $R^2=CH_2CH_3$
(148) $R^1=OCH_3$, $R^2=CH_3$
(149) $R^1=OCH_3$, $R^2=CH(CH_3)_2$

Scheme 26

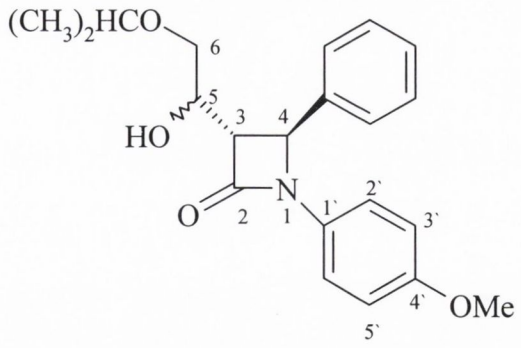
Table 12: Yields and spectroscopic data for 3-[1-(2-alkoxy-1-hydroxy)ethyl]-1,4-diarylazetidin-2-ones (146)-(149)

Compound No	**R^1**	**R^2**	**% Yield**	**^{1}H-NMR δ(CDCl$_3$)**
146	H	OCH_3	56	3.23 (1H, m, $J_{3,4trans}$=2.52Hz, H-3), 3.41 (2.32H, s, -OCH_3), 3.42 (0.68H, s, -OCH_3), 3.52-3.61 (2H, m, -CH_2OCH_3), 4.31-4.33 (1H, m, H-5), 5.08 (0.2H, d, $J_{4,3trans}$=2.52Hz, H-4), 5.16 (0.8H, d, $J_{4,3trans}$=2.52Hz, H-4), 7.06-7.40 (10H, m, aromatic Hs).
147	OCH_3	OCH_2CH_3	56	1.08-1.10 (3H, m, -$OCH_2C\underline{H}_3$), 3.11-3.13 (1H, m, H-3), 3.43-3.50 (2H, m, $OC\underline{H}_2CH_3$), 3.50-3.60 (2H, m, $C\underline{H}_2OCH_2CH_3$), 3.71 (3H, s, OCH_3), 4.19-4.27 (1H, m, C<u>H</u>OH), 4.92 (0.7H, d, $J_{4,3trans}$=2.52Hz, H-4), 4.94 (0.3H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.71-7.40 (9H, m, aromatic Hs).

Table 12 continued

Compound No	R^1	R^2	% Yield	^{1}H-NMR δ($CDCl_3$)
148	OCH_3	OCH_3	50	3.17-3.18 (1H, m, H-3), 3.38 (2.1H, s, -OCH_3), 3.40 (0.9H, s, OCH_3), 3.48-3.50 (2H, m, $C\underline{H}_2OCH_3$), 3.78 (3H, m, -OCH_3), 4.26-4.28 (1H, m, H-5), 4.99 (0.3H, d, $J_{4,3trans}$=2.5Hz, H-4), 5.07 (0.7H, d, $J_{4,3trans}$=2.5Hz, H-4), 6.76-7.35 (9H, m, aromatic Hs).
149	OCH_3	$OCH(CH_3)_2$	40	1.05-1.07 (6H, m, 2xCH_3), 2.65 (1H, s, OH), 3.13 (1H, dd, $J_{3,4trans}$=2.52Hz, $J_{3,5}$=6.52Hz, H-3), 3.44-3.57 (3H, m, $OC\underline{H}(CH_3)_2$, $C\underline{H}_2OCH_2(CH_3)_2$), 3.65 (3H, s, OCH_3), 4.15-4.17 (1H, m, H-5), 4.96 (0.2H, d, $J_{4,3trans}$=2.52Hz, H-4), 4.99 (0.8H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.68-7.29 (9H, m, aromatic Hs).

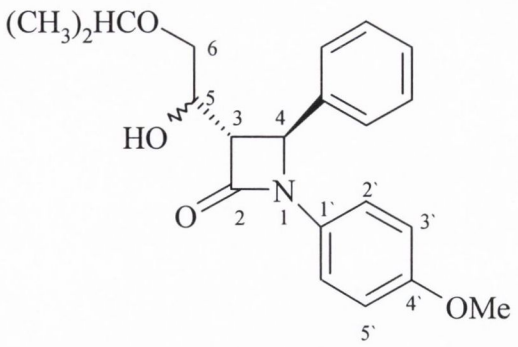
In the infrared spectrum of each alcohol product the β-lactam carbonyl appears at ν1750cm^{-1}. The broad band which occurs in the region ν3400-3428cm^{-1} for all products is assigned to the hydroxy group at position 5. The high resolution ^{1}H-NMR spectrum of 3-[1-(1-hydroxy-2-propoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**149**) is illustrated in **Figure 3** reveals the presence of a diastereomeric mixture of products.



(149)

A multiplet present in the region δ1.05-1.07 integrating for six hydrogens is assigned to the methyl groups. The hydroxy group resonates as a broad singlet at δ2.65. The double doublet at δ3.13 is assigned to the H-3 signal which is coupled to the H-4 at δ4.96 and δ4.99, $J_{4,3}$=2.52Hz and the methine proton at C-5, $J_{3,5}$=6.52Hz. The multiplet in the region δ3.44-3.57 is assigned to the H-6 methylene protons and the proton attached to the two methyl groups of the propoxy substituent. The characteristic methoxy hydrogens resonating at δ3.65 are slightly upfield in relation to H-5, a multiplet which occurs at δ4.15-4.17. The presence of a diastereomeric mixture is evident from the appearance of two doublet signals for H-4 at δ4.96 integrating for 0.2H, $J_{3,4trans}$=2.52Hz and δ4.99 $J_{4,3trans}$=2.52Hz, integrating for 0.8H. The aromatic protons appear typically in the δ6.68-7.29 region.

The ^{13}C-NMR spectrum of 3-[1-(1-hydroxy-2-propoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**149**) is illustrated in **Figure 4**. Four quaternary carbons at 164.01ppm (β-lactam carbonyl carbon), 155.58ppm (C-4`), 137.60 (C-1``) and 130.81 (C-1`) are easily assigned as each disappeared in the DEPT spectrum. Three aromatic signals at 125.70ppm, 126.39ppm and 128.58ppm are grouped together due to their proximity in chemical shift values and therefore cannot be specifically assigned to C-2``, C-6``, C-3``, C-5`` and C-4``. The remaining characteristic aromatic signals at 118.87ppm and 113.86ppm representing the pairs C-2` and C-6` and C-3` and C-5`. The signal at 72.31ppm is assigned to the propoxy carbon of the substituent at C-6. The C-6 signal at 69.92ppm is inverted in the DEPT spectrum and is slightly further downfield than C-5 at 68.72ppm and 68.71ppm. In the major diastereoisomer C-4 of the β-lactam ring resonated at 62.70ppm and 62.69ppm is assigned to the less abundant isomer. The signals at 57.46ppm and 57.45ppm is assigned to C-3. The methoxy signal resonates at 55.38ppm slightly further downfield than the two methyl signals at 21.65ppm and 21.48ppm.



(149)

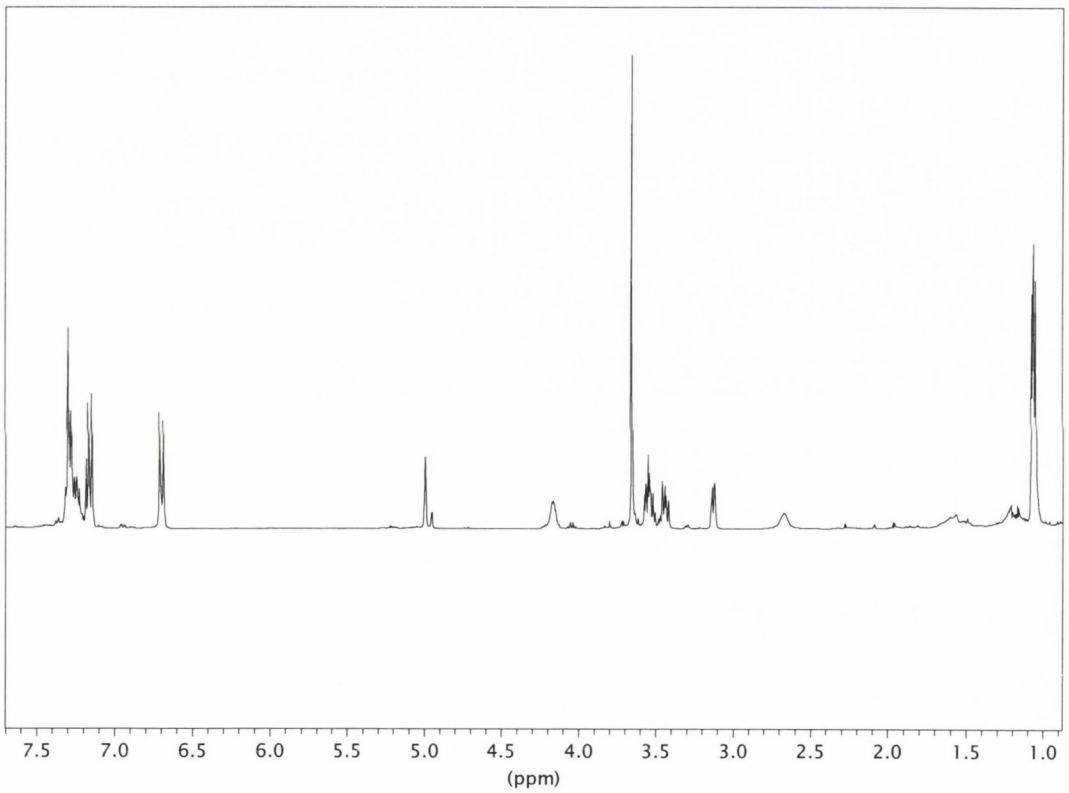
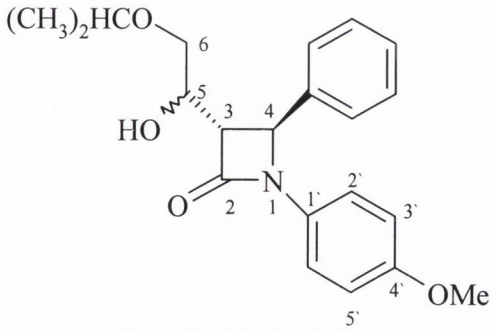


Figure 3: *^{1}H-NMR spectrum of 3-[1-(1-hydroxy-2-propoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one* (**149**)



(149)

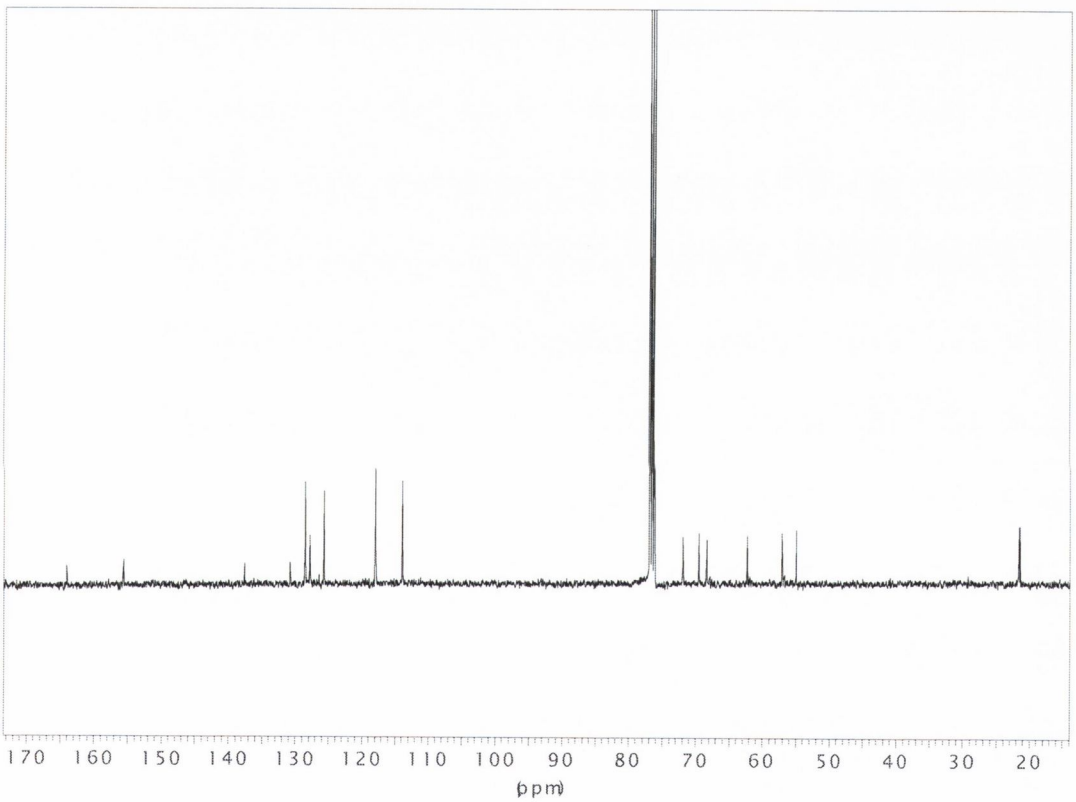


Figure 4: *^{13}C-NMR spectrum of 3-[1-(1-hydroxy-2-propoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one* (**149**)

Jackson *et al*[130a] have described two possible fragmentation patterns A and B for azetidin-2-ones illustrated in **Figure 5**. Process A involves 2.3/4.1 cleavage and results in the formation of an imine fragment and a ketene ion as the principal peaks. Process B involves a 1.2/3.4 cleavage and results in formation of the isocyanate ion and olefin radical ion .

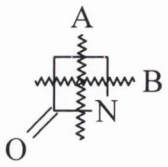
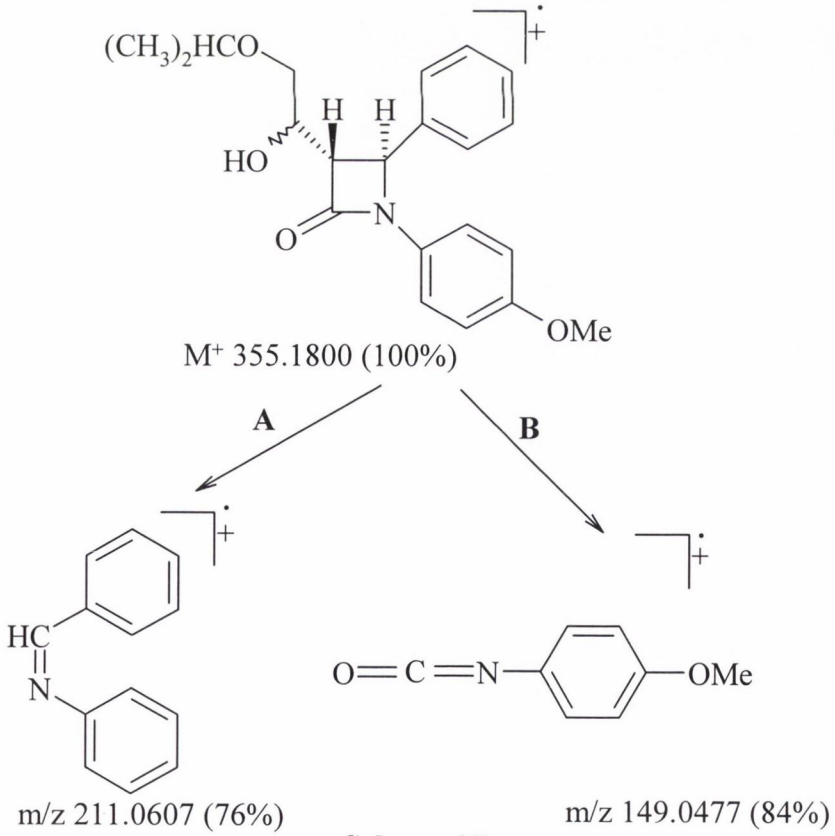


Fig 5

The high resolution mass spectrum fragmentation of 3-[1-(1-hydroxy-2-propoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**149**) is illustrated in (**Scheme 27**). The molecular ion peak is seen at m/z 355.1800 in an abundance of 100%. Type A fragmentation generates an imine fragment at m/z 211.0607 at an abundance of 76%. Type B fragmentation leads to an isocyanate ion at m/z 149.0477 in 84% abundance.



Scheme 27

2.8 Summary

The synthesis of 3-[1-(2-alkoxy-1-hydroxy)ethyl]azetidin-2-ones was achieved by the regioselective opening of 3-(1,2-epoxyethyl)azetidin-2-ones by ethanol, methanol and isopropanol using cerium ammonium nitrate as the catalyst. The β-alkoxy alcohols were characterized by spectroscopic analysis. Nucleophilic addition occurs exclusively at the unsubstituted carbon of the epoxide with the introduction of the hydroxy substituent at the C-3 position of the β-lactam ring which is a characteristic feature of many carbapenem antibiotics. The Schering-Plough group in 1995 reported that 1-phenyl-3-[1-hydroxy-2-(4-fluorophenoxy)ethyl]-4-(4-methoxyphenyl)-2-azetidinone is a useful hypocholesterolemic agent in the treatment of atherosclerosis[130b].

Chapter 3

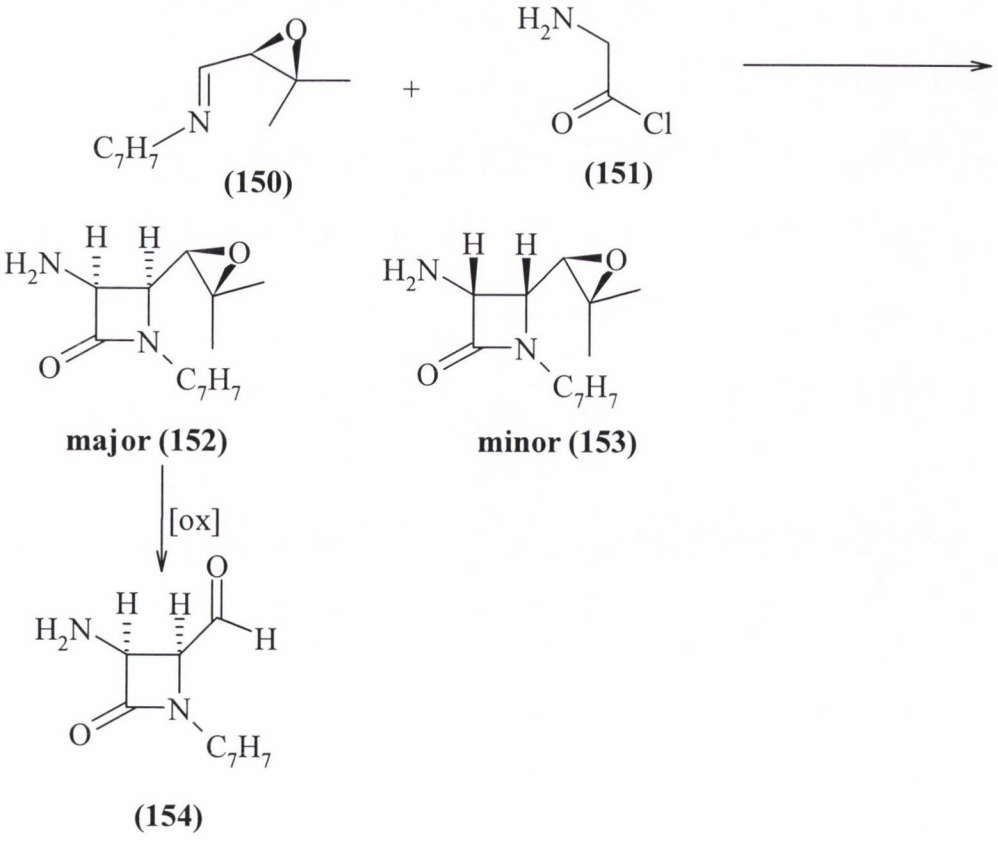
Synthesis and Chemical Modification of 4-Formyl-3-vinylazetidin-2-ones and Related compounds

3.1 Introduction

4-Formylazetidin-2-ones appropriately substituted at C-3 are versatile building blocks for the synthesis of biologically active β-lactam antibiotics including *trans* and *cis* carbapenems[131-133]. This chapter describes the synthesis of novel *cis*-4-formyl-3-vinylazetidin-2-ones which can undergo further oxidation or reduction reactions to provide intermediates for both known and novel carbapenem structures.

3.2 Methods for the synthesis of 4-formylazetidin-2-ones

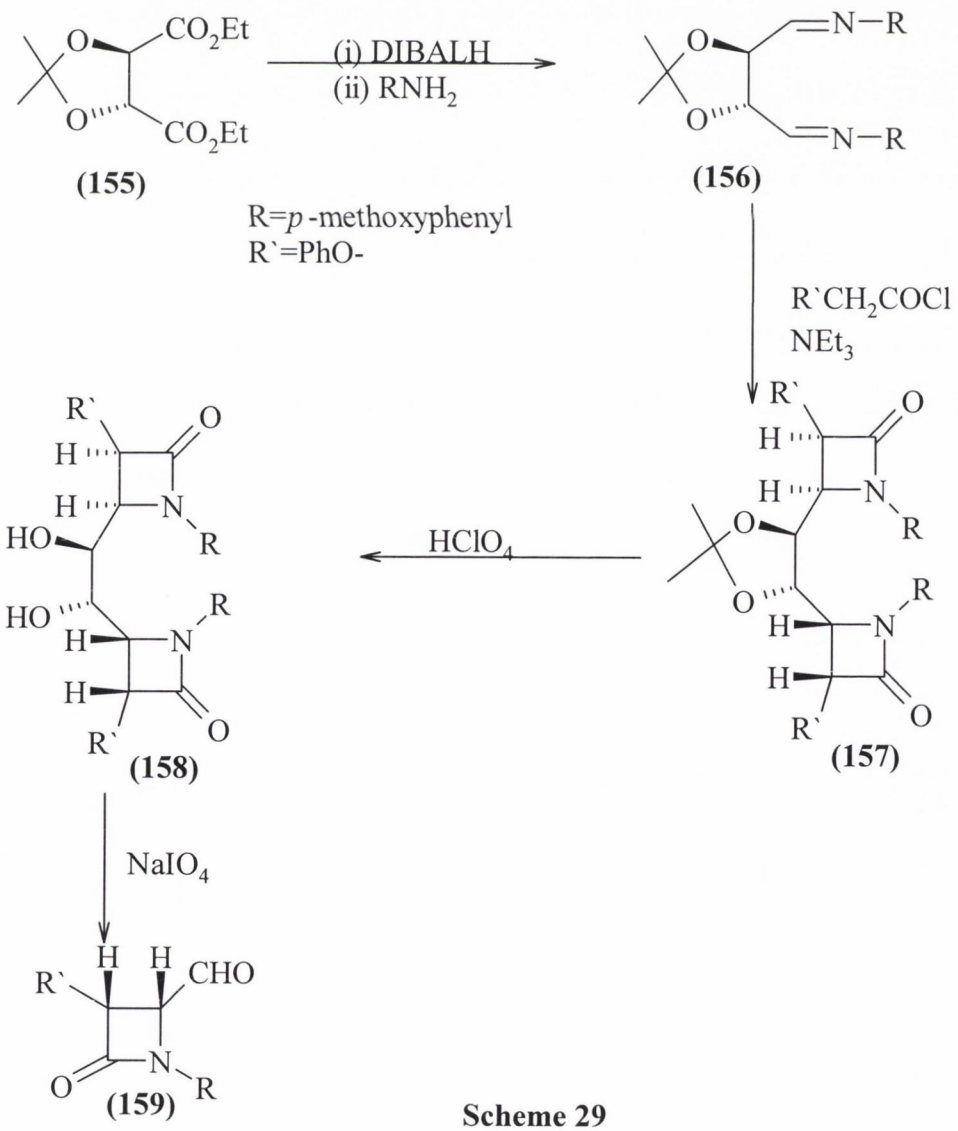
There are many reported examples of the synthesis of 4-formylazetidin-2-ones involving either oxidative degradation or multistep functional group transformation of appropriate 4-substituted β-lactams i.e 4-styryl or 4-alkoxycarbonyl β-lactams[131, 134-136]. Evans *et al*[137] reported the reaction of (**150**) with glycine acid chloride (**151**) to give rise to two β-lactam products (**152**) and (**153**) (**Scheme 28**). Cleavage of epoxide (**152**) which is the major product with periodic acid provides exclusively *cis* substituted 3-amino-4-formylazetidin-2-one (**154**).



Scheme 28

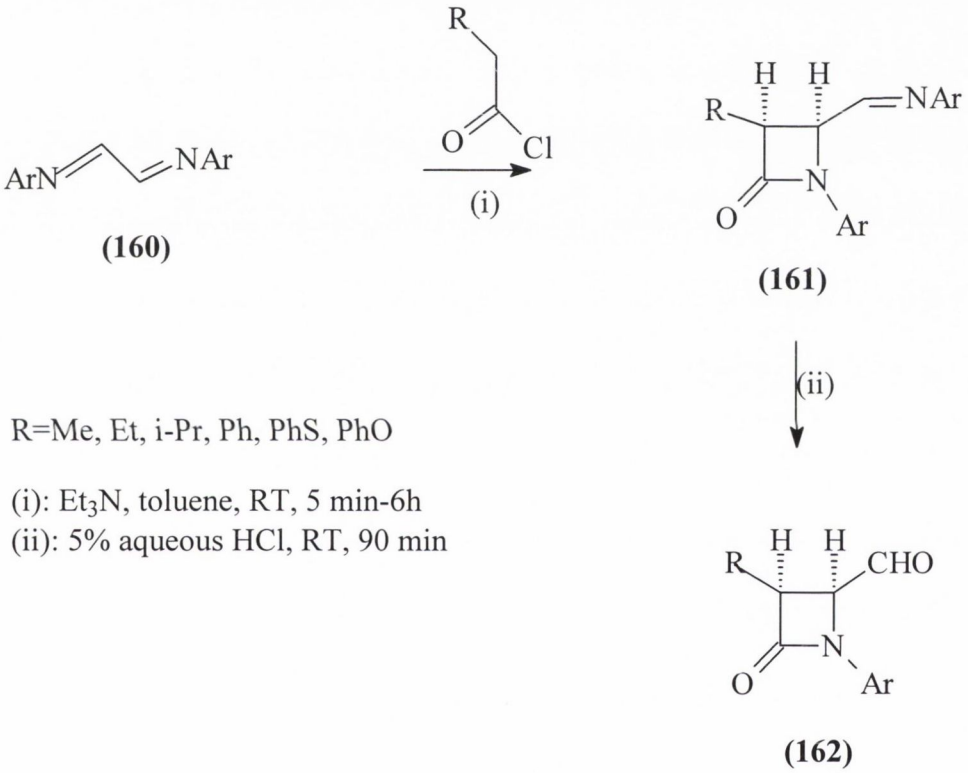
The intermediate (**154**) is regarded as one of the most useful chiral synthons for the production of new β-lactam antibiotics and has been employed in the synthesis of both monobactam and isocepham antibiotics.

Jayaraman *et al* demonstrated the efficient asymmetric synthesis of *cis*-4-formyl β-lactams from L-(+)-tartaric acid[138]. (4*R*,5*R*)-(-)-Diethyl-2,3-*O*-isopropylidene-L-tartrate (**155**) was prepared from L-(+)-tartaric acid using a reported procedure (**Scheme 29**)[139]. Diimine (**156**) was obtained from (**155**) in two steps in a one pot reduction with diisobutylaluminum hydride (DIBALH), followed by treatment with amines. The diimine (**156**) on annelation with acid chloride in the presence of triethylamine gave the β-lactam (**157**). Treatment of (**157**) with $HClO_4$ in THF provided the deprotected dihydroxy β-lactam (**158**), treatment with $NaIO_4$ under usual conditions[140] afforded homochiral *cis*-4-formyl β-lactam (**159**).



Scheme 29

A synthetic route to *cis*-substituted β-lactams was developed by Alcaide and co-workers[141]. They reported in 1991, a one pot procedure for the synthesis of C-3-substituted 4-formylazetidin-2-ones, having alkyl, aryl or electron withdrawing substituents at C-3. This involved the treatment of the easily accessible α–diimines (**160**) with acid chlorides in toluene at room temperature in the presence of triethylamine to yield *cis*-4-imino β-lactams (**161**) which were hydrolysed *in situ* under mild acid conditions to yield the desired *cis*-4-formyl β-lactam (**162**) in good yield (**Scheme 30**).



(160)

(161)

(162)

R=Me, Et, i-Pr, Ph, PhS, PhO

(i): Et_3N, toluene, RT, 5 min-6h
(ii): 5% aqueous HCl, RT, 90 min

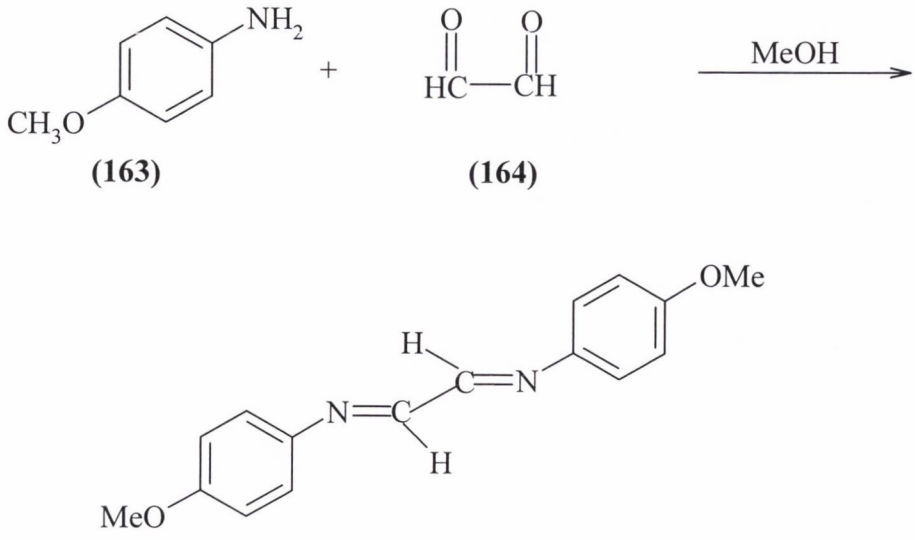
Scheme 30

In the present study a variety of novel 3-substituted-4-formylazetidin-2-ones were prepared using the one pot synthetic method. These compounds could upon further chemical elaboration lead to various carbapenem precursors in good yield. The two synthetic pathways used (i.e. acid chloride and an activated carboxylic acid route) have been reported previously within this research group[116].

3.2.1 *N*-Substituted-1,2-diimines

In the present work it was therefore necessary to first investigate the preparation of *N*-substituted 1,2-diimines. Kliegman and Barnes[142] have reported the synthesis of a number of *N*-substituted 1,2-diimines by the reaction of glyoxal with primary amines. The diimine used in this present work was *N-N'-bis-*(*p*-anisyl)ethylenediimine (**165a**) which was prepared by reaction of glyoxal (**164**) with *p*-ansidine (**163**) in methanol (**Scheme 31**). The diimine was assigned the stable *E*-s-*trans*-*E*-configuration. The s-*trans* refers to tortional isomers around the central carbon-carbon bond of the 1,3-diene.

The infrared spectrum of *N-N'-bis-*(*p*-anisyl)ethylenediimine (**165a**) displays a strong absorption band at $\nu 1610 cm^{-1}$ corresponding to the stretching frequency of the imine double bond. In the ^{1}H-NMR spectrum of *N-N'-bis-*(*p*-anisyl)ethylenediimine (**165a**) a sharp singlet is seen at δ3.80 integrating for six protons and is assigned to the methoxy protons. Due to the symmetrical nature of the compound (*E*-s-*trans*-*E*-configuration) there is no evidence of another methoxy signal since the methoxy protons are chemical shift equivalent. A double doublet at δ7.15 integrating for eight hydrogens is attributed to the aromatic protons on the *p*-substituted rings. The singlet at δ8.40 integrating for two protons is due to the two equivalent imine hydrogens.

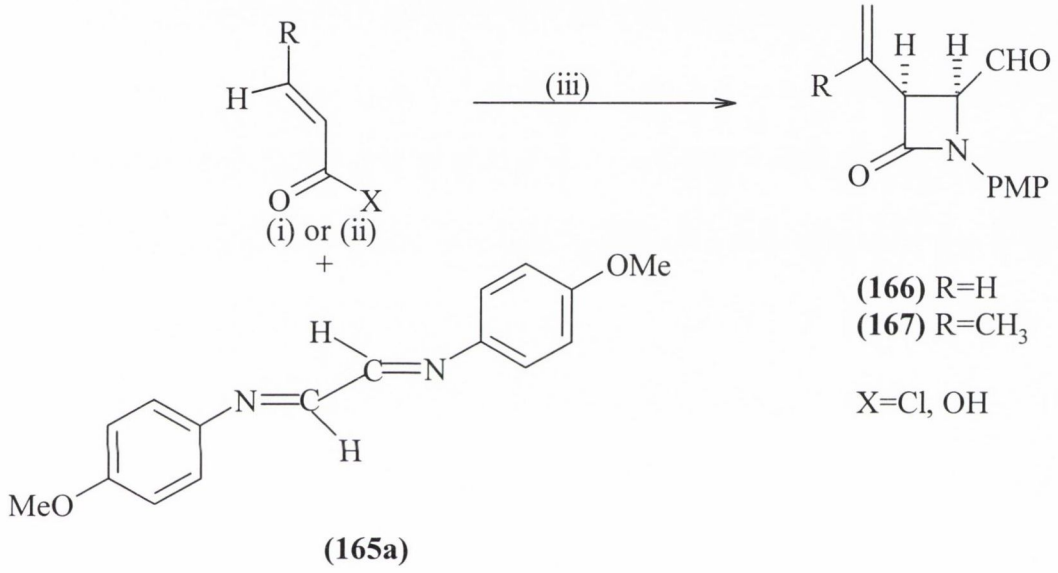


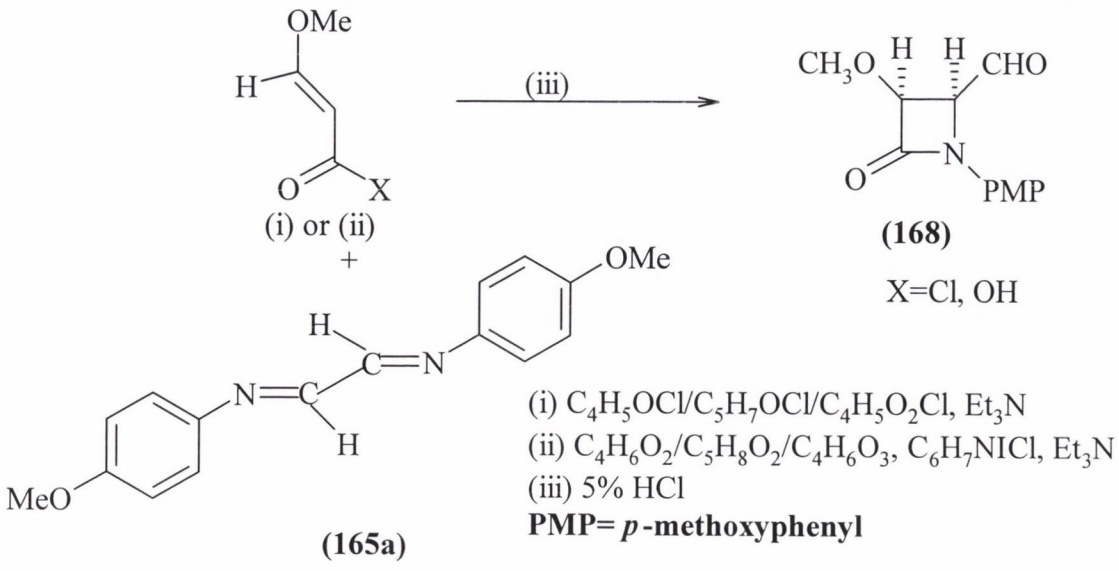
(163) **(164)** **(165a)**

Scheme 31

3.2.2 4-Formyl-3-vinylazetidin-2-ones and related compounds (166)-(168)

The cycloaddition of *N-N'-bis*-(*p*-anisyl)ethylenediimine (**165a**) and the appropriate acid chloride (i.e. crotonyl chloride, 3,3-dimethylacryloyl chloride and methoxyacetyl chloride) or alternatively with the appropriate carboxylic acid (i.e. crotonic acid, 3,3-dimethylacrylic acid and methoxyacetic acid) provided a one pot synthesis for 4-formyl-3-vinyl, 4-formyl-3-methoxy and 4-formyl-3-isopropenylazetidin-2-ones (**Scheme 32**).





Scheme 32

The preparation of the 4-formyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**168**) is now discussed as a prototype. 4-Formyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**168**) was obtained according to the method described by Alcaide *et al*[141] in 32% yield. Secondly the approach of reacting methoxyacetic acid with the diimine using the Mukaiyama reagent as described by Georg[108a] in the synthesis of 3-vinyl β-lactams in Chapter 2 was investigated as an alternative method and yielded the desired product in 40% yield (**Scheme 32**).

The infrared spectrum of 4-formyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**168**) displays a sharp absorption in the region ν1750-1755cm^{-1} which is assigned to the β-lactam carbonyl. The carbonyl peak in the region ν1720cm^{-1} is attributed to the aldehyde group. In the ^{1}H-NMR spectrum the two singlets each integrating for three protons at δ3.68 and δ3.85 are assigned to the two methoxy groups. The doublet seen at δ4.36 is assigned to H-3 coupled to H-4 with a coupling constant of 6.0Hz indicating a *cis* arrangement of the β-lactam protons. H-4 resonates as a double doublet downfield at δ4.58, $J_{4,3}$=6.0Hz, $J_{4,5}$=3.5Hz due to the deshielding influence of the adjacent aldehyde function. The aromatic protons give rise to a pair of apparent doublets (H-2` and H-6` are chemically equivalent but not magnetically equivalent, also the same applies for H-3` and H-5`) each integrating for two protons, typical of *para* substituted phenyl rings. The apparent doublet at δ6.88, J=9.0Hz, is assigned to H-3` and H-5` which are chemical shift equivalent and the apparent doublet at δ7.32, J=9.0Hz is assigned to equivalent aromatic protons on C-2` and C-6`. The doublet integrating for one proton at δ9.80 is the aldehydic proton coupled to H-4, J=3.5Hz which is downfield due to the deshielding influence of the carbonyl group and is characteristic of aldehyde protons.

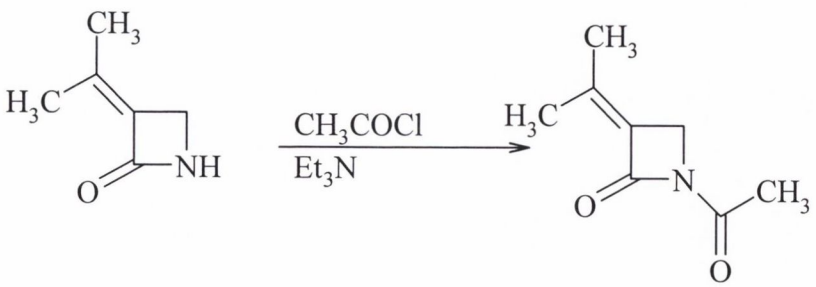
Nine signals are observed in the ^{13}C-NMR spectrum of 4-formyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**168**). They are assigned as follows: 199.98ppm (representing the aldehyde carbonyl carbon), 162.78ppm (the β-lactam C=O), 156.95ppm (C-4`) and 130.47ppm (C-1`). These two quaternary carbons disappear in the DEPT spectrum. The remaining aromatic carbons are seen at 114.59ppm (C-3` and C-5`) and 118.04ppm (C-2`and C-6`). The β-lactam carbons C-4 and C-3 are seen as two signals at 85.10ppm (C-4) and 63.17ppm (C-3). The carbons of the methoxy groups resonate at 59.47ppm and 55.59ppm.

3.3 Chemical Transformations of 4-formylazetidin-2-ones and Related Compounds

The reduction of 4-formyl β-lactams to afford the corresponding 4-hydroxymethylazetidinones and the subsequent hydride mediated isomerisation of the vinyl substituent at C-3 affording the corresponding 3-ethylidene and 3-isopropylideneazetidin-2-ones was now investigated. These alcohols are valuable intermediates for carbapenem synthesis and therefore an efficent route to their synthesis is of interest. The first reported synthesis of (+)-thienamycin employed 4-hydroxymethylazetidin-2-ones[34]. Since the recognition of 4-hydroxymethylazetidin-2-ones as useful intermediates for carbapenems synthesis, many efforts have been made to develop short, high yielding methods for their preparation. Thomas has employed the ketene-imine route for the large scale synthesis of enantiomerically pure *N*-protected-3-amino-4-hydroxymethylazetidin-2-ones[145].

Ethylidene compounds are of interest because of the following:

(i) Brickner *et al* reported the synthesis of *N*-acyl-3-alkylidenyl a new class of monocyclic β-lactam antibacterial agents. They designed monocyclic β-lactams doubly activated by an exocyclic C-C double bond at position C-3 and an appropriate electron withdrawing moiety of the lactam N-1. The rationale behind this template design hinged on the rudimentary concept of creating additional ring strain through the juxtapositioning of two sp^2 hybridised carbons within the 4-membered ring[144,146] (**Scheme 33**). These compounds displayed potent *in vitro* antibacterial activity.

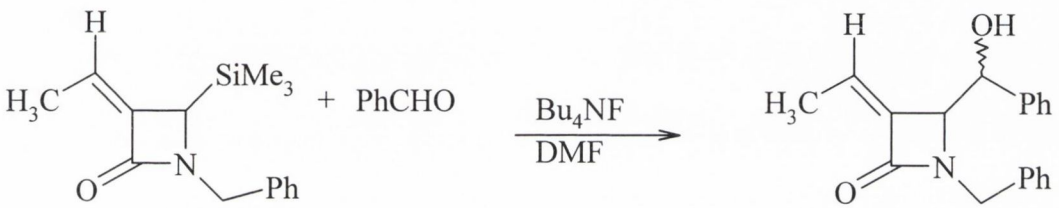


(169) **(170)**

Scheme 33

(ii) One of the fundamental subjects in the synthetic studies on these compounds is how to introduce a carbon substituent into the C-4 position of azetidin-2-ones.

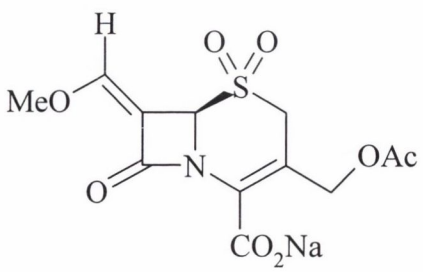
Although substitution reactions with carbon nucleophiles e. g. enol silylethers, allyltin reagents and carbene species, etc, are well established processes for carbon-carbon bond formation at the C-4 position of azetidin-2-ones, electrophilic carbon-carbon bond formation at the C-4 position is very much limited. Hotoda *et al* 1996[147] reported the electrophilic substitution of 3-alkylidene-4-trimethylsilyl-azetidin-2-ones (**171**) with aldehydes in the presence of Bu_4NF to give 4-(α-hydroxy)alkyl derivatives (**172**) in good yields (**Scheme 34**). Since the trimethylsilyl group in (**171**) can be smoothly displaced not only by nucleophiles such as alcohols, acetic acid and flourine ion under anodic oxidation[148] conditions but also by electrophiles at the C-4 position, substrate (**172**) will be a versatile synthetic intermediate in β-lactam chemistry.



(171) **(172)**

Scheme 34

(iii) Buynak *et al* in 1997[149a] reported that 7-alkylidene cephalosporin esters as inhibitors of human leukocyte elastase (**173**) obtained by Wittig procedures on 7-oxo compounds.



(173)

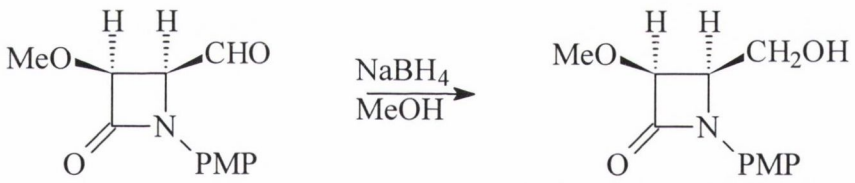
(iv) Kawashima reported that the 2-oxoalkylidene moiety at the 3 position of *Z*-3-(2-oxopropylidene)-4-methyl-1-phenylazetidin-2-one was essential for the platelet aggregation inhibitory activities of this compound[149b].

Hence 3-ethylidene and 3-isopropylidene hydroxymethylazetidin-2-ones are key intermediates in the synthesis of novel carbapenems. The 3-ethylidene and 4-

hydroxymethyl substituents can be converted to several substituents by known methods providing an entry to a wide variety of functional groups at positions 3 and 4 of the β-lactam ring. This chapter investigates a number of oxidation, reduction and nucleophilic displacement reactions of 4-formyl-3-vinylazetidin-2-ones, 4-formyl-3-methoxyazetidin-2-ones and 4-phenyl-3-vinylazetidin-2-ones with a view to synthesizing novel carbapenem intermediates such as 3-ethylidene, 3-isopropylidene, 4-acetoxy and 4-hydroxymethyl β-lactams.

3.3.1 Synthesis of 4-Hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (174)

4-Formyl-3-methoxyazetidin-2-one (**168**) was reacted with four equivalents of sodium borohydride in anhydrous methanol at room temperature (**Scheme 35**). One product was isolated in 53% yield from the reaction mixture. Using the usual spectroscopic techniques the product was identified as 4-hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**174**).



(168) **(174)**

Scheme 35

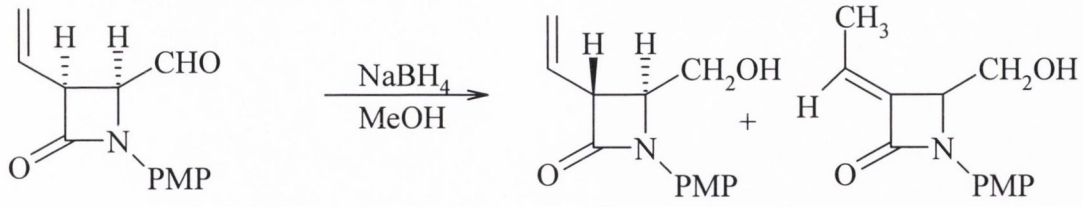
The infrared spectrum of 4-hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**174**) shows the β-lactam carbonyl stretching frequency at ν1750cm^{-1}. A broad band in the region ν3300-3400cm^{-1} is due to the stretching frequency of the hydroxy group. In the ^{1}H-NMR spectrum of 4-hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**174**) the methoxy protons appear as two singlets at δ3.61 and δ3.62 each integrating for three protons. The H-5 protons appear as a multiplet in the region δ3.97-4.00 integrating for two protons. H-4 resonates as a multiplet at δ4.22. H-3 is seen as a doublet at δ4.60 $J_{3,4cis}$=5.2Hz, thus illustrating that H-3 and H-4 are in a *cis* arrangement and the stereochemistry is retained. The aromatic protons are easily assignable, an apparent

doublet at δ6.82 representing H-3` and H-5` J=8.76Hz, while H-2` and H-6` resonate at δ7.32 as the corresponding doublet, J=8.76Hz.

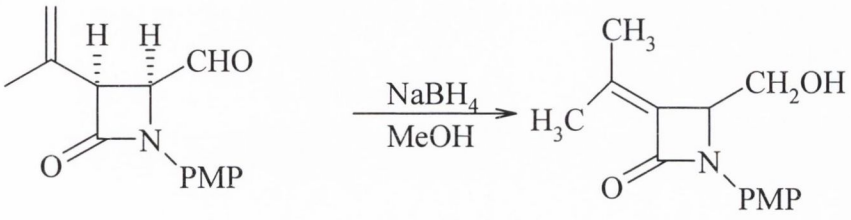
In the ^{13}C-NMR spectrum of 4-hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**174**) ten signals are observed. Three quaternary signals are evident as the signals disappear in the DEPT spectrum. They may be assigned as follows: 164.13ppm (the β-lactam carbonyl), 156.43ppm (C-4`), 130.41ppm (C-1`). The aromatic carbons are seen at 118.76ppm (C-2` and C-6`) and 114.38ppm (C-3` and C-5`). C-3 and C-4 appear at 82.97ppm and 59.54ppm. The C-5 carbon is inverted in the DEPT spectrum resonating at 57.23ppm; the methoxy signals resonating at 57.80ppm and 55.40ppm respectively.

3.3.2 Reaction of 4-formyl-3-vinyl-1-(4-methoxyphenyl)azetidin-2-one (166) and 4-formyl-3-isopropenyl-1-(4-methoxyphenyl)azetidin-2-one (167) with sodium borohydride.

In this work 4-formyl-3-vinyl-1-(4-methoxyphenyl)azetidin-2-one (**166**) was reacted with sodium borohydride to afford a mixture of 4-hydroxymethyl-3-vinyl-1-(4-methoxyphenyl)azetidin-2-one (**175**) and 3-ethylidene-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**176**) (**Scheme 36**). The crude mixture was separated by column chromatography to provide the *trans*-3-vinyl-β-lactam (**175**) in 35% yield and the 3-ethylidene alcohol (**176**) in 60% yield. Likewise 3-isopropenyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**167**) was reduced with sodium borohydride in dry methanol at room temperature to afford 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**177**) in 75% yield.



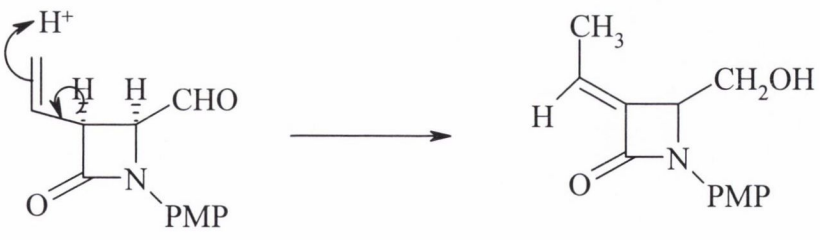
(166) **(175)** **(176)**



(167) **(177)**

Scheme 36

The reduction of 4-formylazetidin-2-ones to the corresponding 4-hydroxymethyl compounds is a useful reaction in the synthesis of carbapenem intermediates. Isomerisation of the double bond at C-3 was also observed. The following isomerisation mechanism is proposed (**Scheme 37**). The observed isomerisation is the result of proton abstraction at C-3 by the hydride. Formation of the exocyclic double bond is followed by protonation of the terminal alkene carbon.

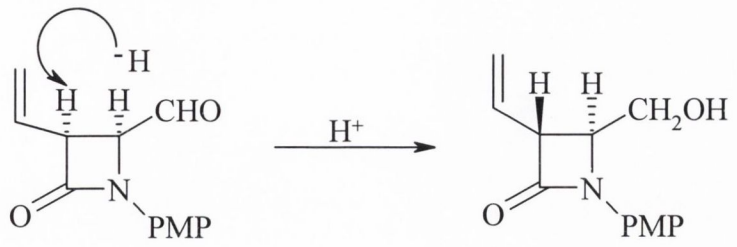


(166) **(176)**

Scheme 37

Isomerisation of the 3-vinyl substituent of monocyclic β-lactams has also been reported by Manhas[150] while attempting to epimerize one of the β-lactam centres with the cyclic base DBU (1,8-diazobicyclo[5.4.0]undec-7-ene). This is a non-nucleophilic base in which the bridgehead nitrogen is sterically encumbered for nucleophilic attack. Compound (**175**) was obtained as the *trans* isomer. Clearly base promoted

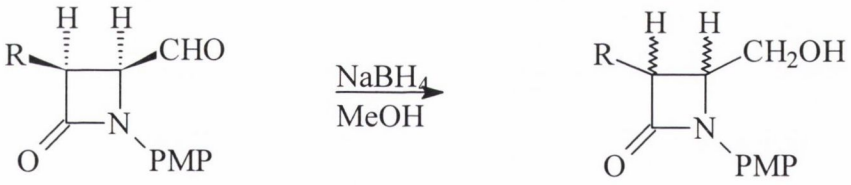
epimerisation at C-3 is occuring before or after the reduction takes place. It is proposed that proton abstraction at C-3 induced by sodium borohydride followed by addition of H^+ from the β-face affords the less hindered *trans* product (**Scheme 38**).



(166) **(175)**

Scheme 38

Alcaide *et al* reported sodium borohydride reduction of the aldehyde group of compound (**181**) yielded cleanly the 4-hydroxymethyl derivatives (**Scheme 39**). The *trans* isomer was the main reaction product for (**184**), the *cis* isomers were the main reaction products for compounds (**182**) and (**183**). The ability of the PhS group to stabilize a carbanion accounts for the observed isomerisation to the thermodynamically more stable *trans* isomer[152].



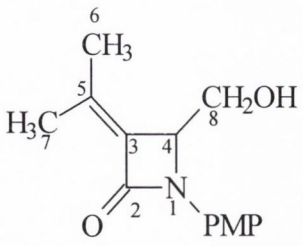
(181)

(182) R=Et
(183) R=Pr
(184) R=PhS

Scheme 39

Fortunately 3-alkylidene-β-lactams are regarded as valuable synthetic intermediates for the introduction of side chains common to the asparenomycin series. The alcohols (**175**)-(**177**) were identified by spectroscopic methods.

The infrared spectrum of 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**177**) shows the β-lactam carbonyl stretching frequency at $\nu 1750 cm^{-1}$. A broad band which occurs in the region $\nu 3300\text{-}3400 cm^{-1}$ is due to the absorbance of the OH group.



(177)

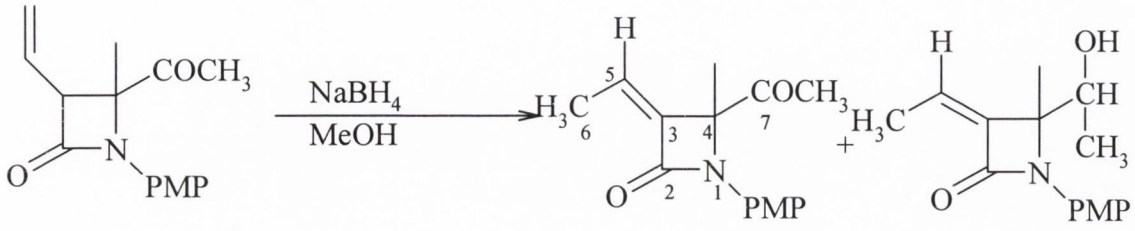
In the ^{1}H-NMR spectrum of 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**177**) the sharp singlets at δ1.82 and δ2.10 integrating for three protons are assigned to the methyl groups. The singlet at δ3.60 is due to the methoxy substitutent of the phenyl ring. A multiplet in the region δ4.10-4.21 represents the H-8 protons. H-4 resonates as a multiplet at δ4.50-4.52. The aromatic protons appear downfield in the δ6.80-7.42 region.

In the ^{13}C-NMR spectrum of 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**177**) twelve signals are observed. Five quaternary carbons are distinguishable at 155.72 (the β-lactam carbonyl), 155.49ppm (C-4), 138.23ppm (C-3), 131.52ppm (C-1`) and 130.67ppm (C-5). The characteristic aromatic signals at 118.18ppm, 114.30ppm representing the pairs C-2` and C-6` and C-3` and C-5` respectively are also observed. C-8 resonating at 61.54ppm appears slightly further downfield than C-4 at 61.08ppm. The former signal is inverted in the DEPT spectrum. A signal at 55.40ppm is assigned to the methoxy carbon. The methyl carbons appear at 20.81ppm and 20.27ppm respectively.

3.3.3 *Z*-4-Acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (178) and *Z*-3-Ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (179).

To further explore the utility of the previous reaction, 4-acetyl-1(-4-methoxyphenyl)-4-methyl-3-vinylazetidin-2-one (**134**) was reacted with 4-equivalents of sodium borohydride. The following two compounds were isolated: *Z*-4-acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**178**) and *Z*-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**179**). The products were identified by spectroscopic methods and by mass spectrometry.

Compounds (**178**) and (**179**) were separated by flash column chromatography to provide the 3-ethylidene ketone (**178**) in 33% yield and 3-ethylidene alcohol (**179**) in 20% yield (**Scheme 40**).



(134) **(178)** **(179)**

Scheme 40

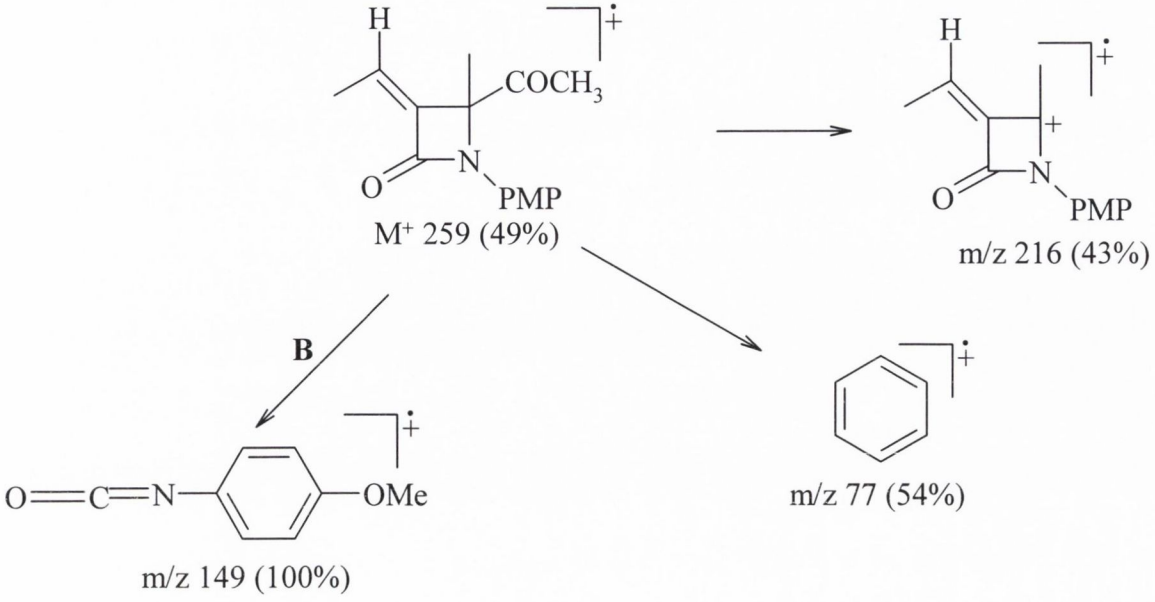
The infrared spectrum of *Z*-4-acetyl-3-ethylidene-4-methyl–1-(4-methoxyphenyl)azetidin-2-one (**178**) shows the β-lactam carbonyl stretching frequency at ν1750cm^{-1} and the ketone carbonyl stretching frequency at ν1721cm^{-1}.

In the ^{1}H-NMR spectrum of *Z*-4-acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**178**) (**Figure 6**) the methyl signal at C-4 resonating at δ1.66 appears as a singlet integrating for three protons. The methyl substituent at C-5 can exist in either the *E* configuration or the *Z* configuration. Hence the possibilty of two possible isomers for the β-lactam ketone. The alkene (**178**) is more likely to exist in the *E*-configuration since a lesser degree of steric hindrance occurs in this isomer. Comparsion of the chemical shift value with similar compounds suggests the *Z*-configuration[122,151]. The methyl substituent at C-5 resonates as a doublet integrating for three protons at δ2.11 due to coupling with the methine proton at H-5 which appears downfield as a quartet at δ5.70, J=7.26Hz integrating for one proton. The methyl signal appears further downfield when compared with *E*-isomers of related structures, this is due to the deshielding effect of the neighbouring carbonyl substituent. The absence of another methyl signal in the ^{1}H-NMR spectrum demonstrates the presence of only one geometrical isomer. The methyl group would be expected to resonate in the region δ1.82 further upfield if the *E*-configuration was adopted as this methyl group would not be deshielded by the carbonyl at C-2. The methyl substituent attached to the carbonyl at C-6 integrating for three protons appears as a singlet downfield at δ2.13 with respect to the other methyl groups due to the

deshielding effect of the carbonyl group. The sharp singlet at δ3.77 is assigned to the methoxy substituent on the phenyl ring. The aromatic protons appear downfield in the region δ6.86-7.23.

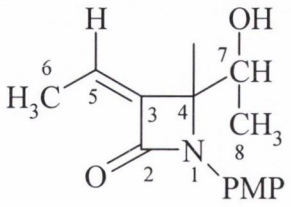
The ^{13}C-NMR and DEPT of *Z*-4-acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**178**) spectra (**Figure 7**) displays more convincing evidence that the ethylidene substituent is now present in the structure. The ^{13}C-NMR spectrum displays the readily assignable carbonyl carbons i.e. 207.01ppm (ketone C=O), and 160.34ppm (β-lactam C=O). The other quaternary carbons visible are 156.23ppm (C-4`), 141.50ppm (C-3), 130.34ppm (C-1`). C-5 appears at 126.98ppm. The aromatic carbon C-2` and C-6` are chemical shift equivalent and appear as one signal at 117.74ppm; similarly C-3` and C-5` are located at 114.68ppm. C-4 of the β-lactam ring at 71.95ppm is slightly downfield from the methoxy carbon at 55.39ppm which itself is followed by the acetyl group methyl carbon at 24.62ppm. The methyl carbon at C-5 appears at 17.05 ppm and finally the C-4 methyl carbon at 14.86ppm completes the spectrum.

Structural elucidation of *Z*-4-acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**178**) is confirmed by low resolution mass spectrometry (**Scheme 41**). The high resolution mass spectrum for compound (**178**) follows the typical pattern reported by Jackson *et al*[130a]. The molecular ion M^+ for $C_{15}H_{17}NO_3$ is seen at m/z 259.12046 in an abundance of (49%) which corresponds with the theoretical value of m/z 259.12084. The fragment at m/z 216 (43%) is due to loss of the acetyl group. Type B fragmentation leads to the base peak isocyanate ion at m/z 149 in 100% abundance and an aromatic fragment at m/z 77 in 54% abundance. Type A fragmentation is not evident.



Scheme 41

The infrared spectrum of *Z*-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**179**) shows the β-lactam carbonyl stretching frequency at ν1750cm^{-1}. The broad band which occurs in the region ν3000-3400cm^{-1} is due to the stretching frequency of the OH group. The broad nature of the bond is due to the intermolecular hydrogen bonding.



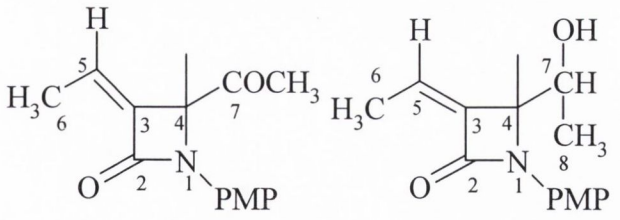
(179)

The ^{1}H-NMR spectrum of *Z*-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**179**) (**Figure 8**) the methyl group (C-8) appears as a doublet integrating for three protons $J_{8,7}$=6.36Hz at δ1.16. The C-4 substituted methyl appears as a singlet integrating for three protons at δ1.58 . The methyl substituent at C-5 resonates as a doublet integrating for three protons at δ2.05 J=7.23Hz, due to coupling with the methine proton and thus this confirms that this is the *Z*-isomer as the methyl group is closer to the carbonyl in the *Z* isomer than in the *E* isomer and is therefore more deshielded and therefore appears further downfield in the ^{1}H-NMR

spectrum. H-5 appears downfield as a quartet at δ5.64 J=7.23Hz. A broad singlet at δ2.43 integrating for one proton is assigned to the hydroxy group. The sharp singlet at δ3.56 is assigned to the methoxy substituent on the phenyl ring. A doublet at δ4.12 $J_{7,8}$=6.36Hz is assigned to the methinyl proton on C-7. The arrangement of two doublets in the region δ6.83-7.54 is due to aromatic protons H-3`, H-5`, H-2` and H-6`.

In the ^{13}C-NMR spectrum of *Z*-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**179**) (**Figure 9**) the β-lactam carbonyl appears at 161.51ppm. The other remaining quaternary carbons in this region of the spectrum are visible at 156.02ppm (C-4`), 142.76ppm (C-3), 130.90ppm (C-1`). C-5 appears at 124.63ppm. The aromatic carbons C-2` and C-6` are equivalent and resonate at 119.21ppm, similarly C-3` and C-5` are observed at 114.41ppm. C-4 resonates at 71.67ppm. C-7 is seen at 69.99ppm. The methoxy carbon appears at 55.34ppm which is slightly downfield from the methyl carbon of C-5 at 19.40ppm. The hydroxymethyl carbon appears at 18.31ppm. The methyl carbon attached to C-4 appears at 14.59ppm and completes the spectrum.

The high resolution mass spectrum of *Z*-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**179**) displays the molecular ion M^+ $C_{15}H_{19}NO_3$ at m/z 261.13702 in an abundance of 40%.



(178) **(179)**

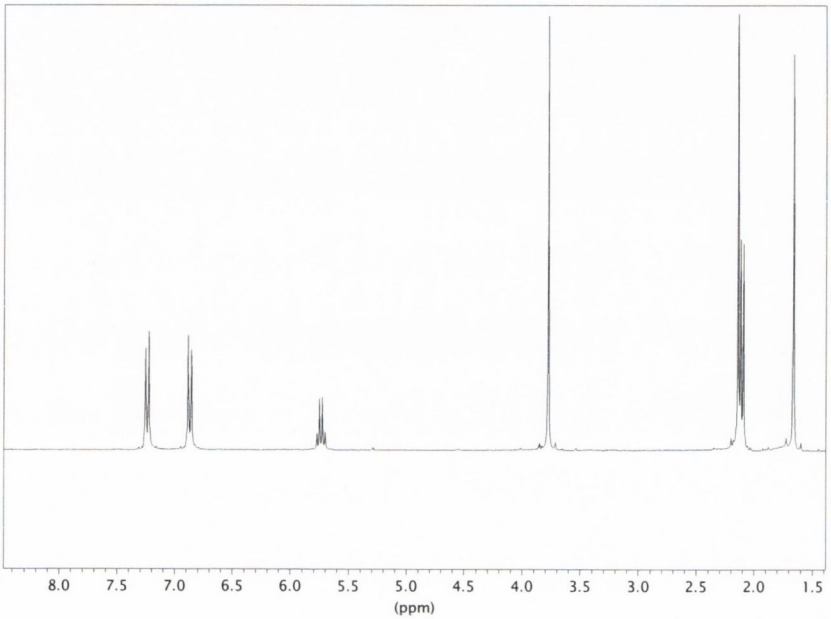


Figure 6: *^{1}H-NMR spectrum of Z-4-acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**178**)*

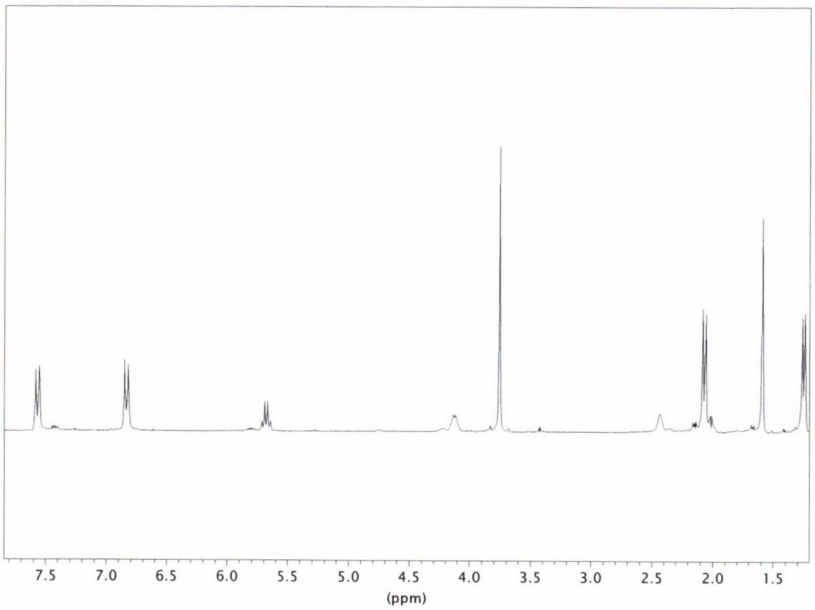
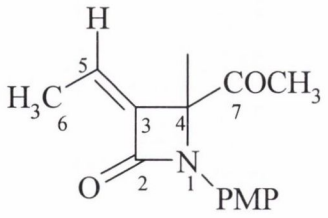


Figure 8: *^{1}H-NMR spectrum of Z-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**179**)*



(178)

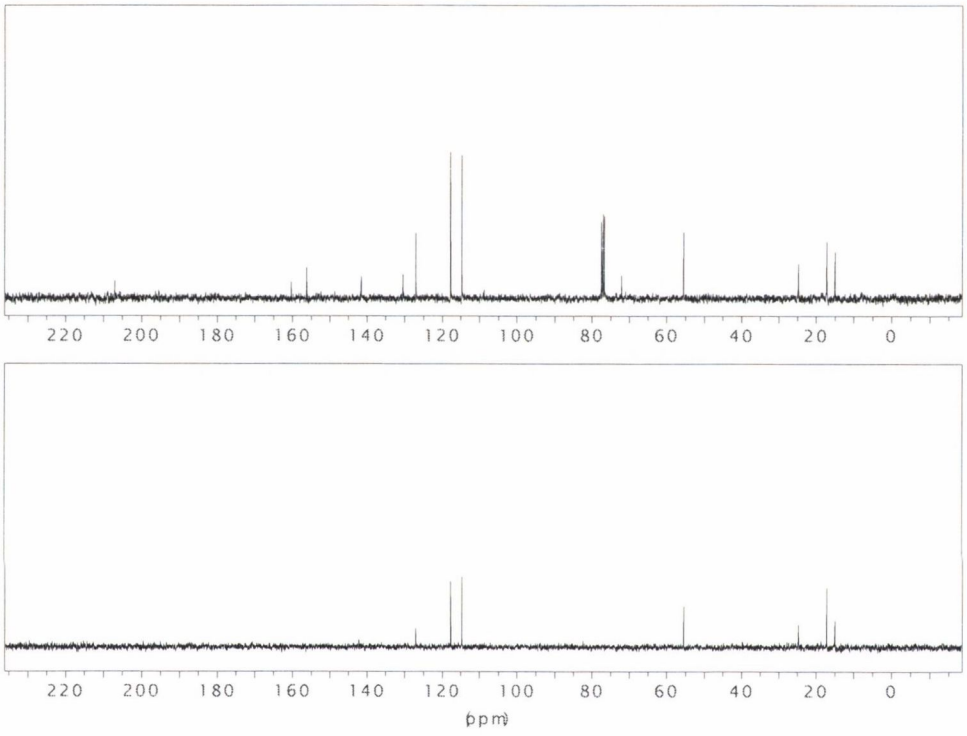
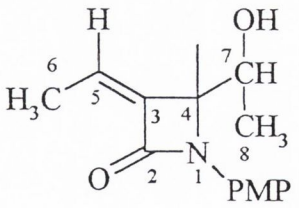


Figure 7: *^{13}C-NMR and DEPT spectra of Z-4-acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (**178**)*



(179)

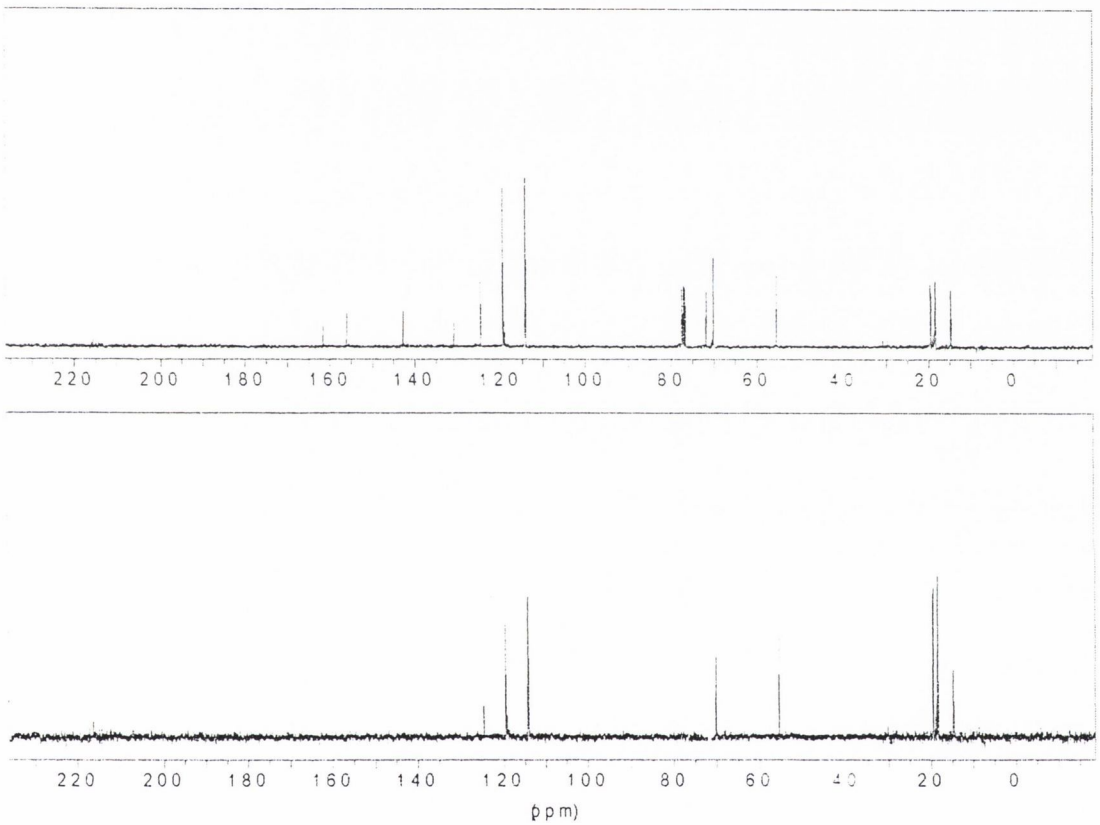
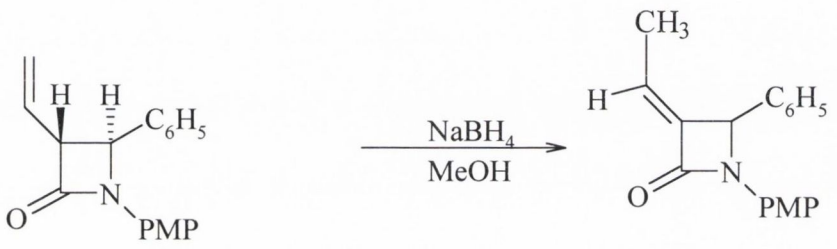


Figure 9: *^{13}C-NMR and DEPT spectra of Z-3-ethylidene-4-(1-hydroxyethyl)-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (179)*

3.3.4 *E*-3-Ethylidene-1(-4-methoxyphenyl)-4-phenylazetidin-2-one (180)

In order to further demonstrate the observed isomerisation at C-3, the hydroxy at C-4 was replaced by a less functionalised phenyl group. Reaction with sodium borohydride could now only occur at C-3 and not C-4. Reaction of 4-phenyl-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (**131**) with four equivalents of sodium borohydride gave *E*-3-ethylidene-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**180**) as the sole product in 63% yield (**Scheme 42**). This product was characterised by spectroscopic analysis.



(131) **(180)**

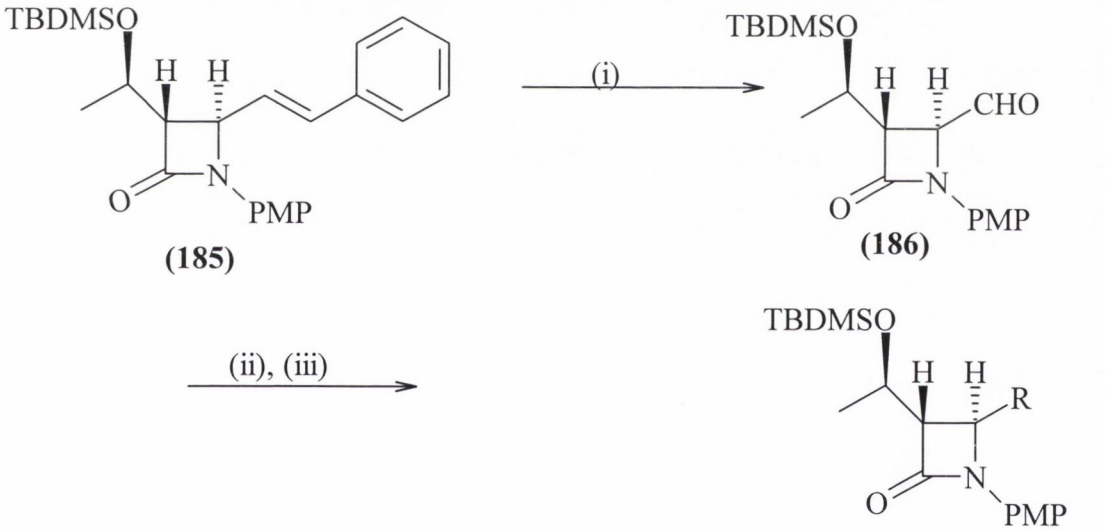
Scheme 42

In the infrared spectrum of *E*-3-ethylidene-1-(4-methoxyphenyl)-4-phenyl-azetidin-2-one (**180**) indicates the β-lactam carbonyl absorbance at ν1750cm^{-1}. In the ^{1}H-NMR spectrum of *E*-3-ethylidene-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**180**) the methyl protons resonate as a doublet at δ1.81, J=7.11Hz. H-5 appears as a quartet at δ6.26, J=7.11Hz. The methoxy hydrogens appear as a singlet at δ3.71. Further downfield H-4 appears as a singlet at δ5.38 while the aromatic protons occur as a multiplet in the region δ6.78-7.42.

In the ^{13}C-NMR spectrum of *E*-3-ethylidene-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**180**) sixteen signals are evident. Four quaternary carbons are present and are assigned as follows: 160.58ppm (the β-lactam carbonyl), 155.52ppm (C-4`), 142.39ppm (C-3), 136.36ppm (C-1`). C-5 appears at 130.97ppm. The remaining nine aromatic carbons are grouped and appear in the region 113.91ppm-128.46ppm. C-4 resonates at 62.46ppm and the methoxy carbon is seen at 54.94ppm. Further upfield the methyl carbon appears at 12.73ppm.

3.4 Chemical Transformations of *E*-3-ethylidene-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (176).

4-Acetoxy β-lactams are key intermediates in carbapenem synthesis and there is considerable interest in the development of efficient, mild, high yielding methods for their preparation. The 4-acetoxy group can be easily substituted by oxygen, sulphur, nitrogen and carbon nucleophiles providing a range of carbapenem intermediates[153] and related systems[154]. In 1987 Georg *et al*[136] reported the oxidative cleavage of the double bond in the optically active β-lactam (**185**) with osmium tetroxide and sodium periodate to yield the aldehyde (**186**) which was converted to the corresponding acid (**187**) which on oxidative decarboxylation and acetoxylation with lead tetraacetate produced the *trans* 4-acetoxy derivative (**188**) (**Scheme 43**).

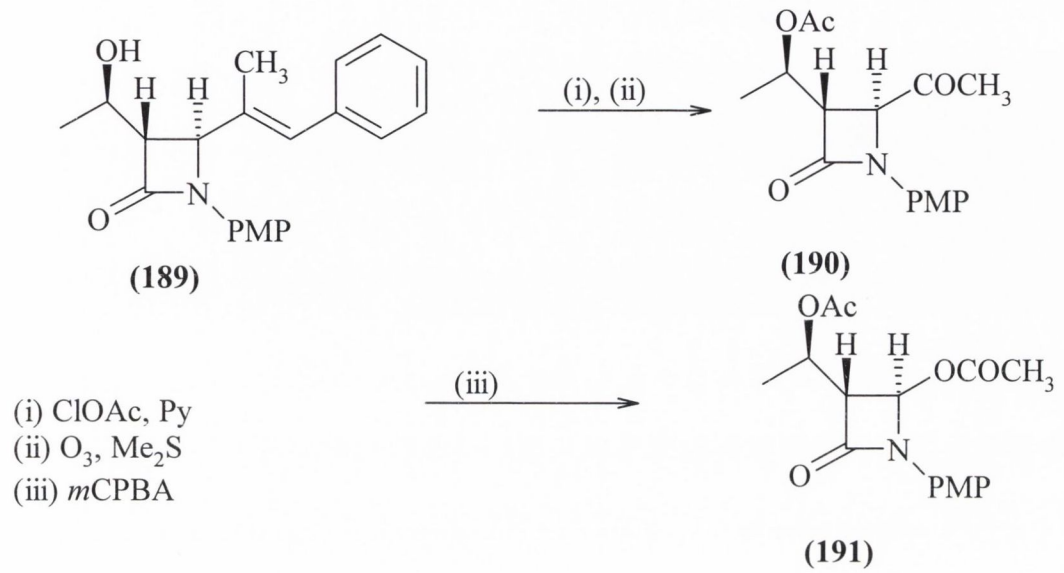


(187) R= CO_2H
(188) R= OAc

(i) OsO_4, $NaIO_4$, THF/H_2O, 25°C (ii) $KMnO_4$, THF/H_2O, 25°C
(iii) $Pb(OAc)_4$, DMF/H_2O, 70°C

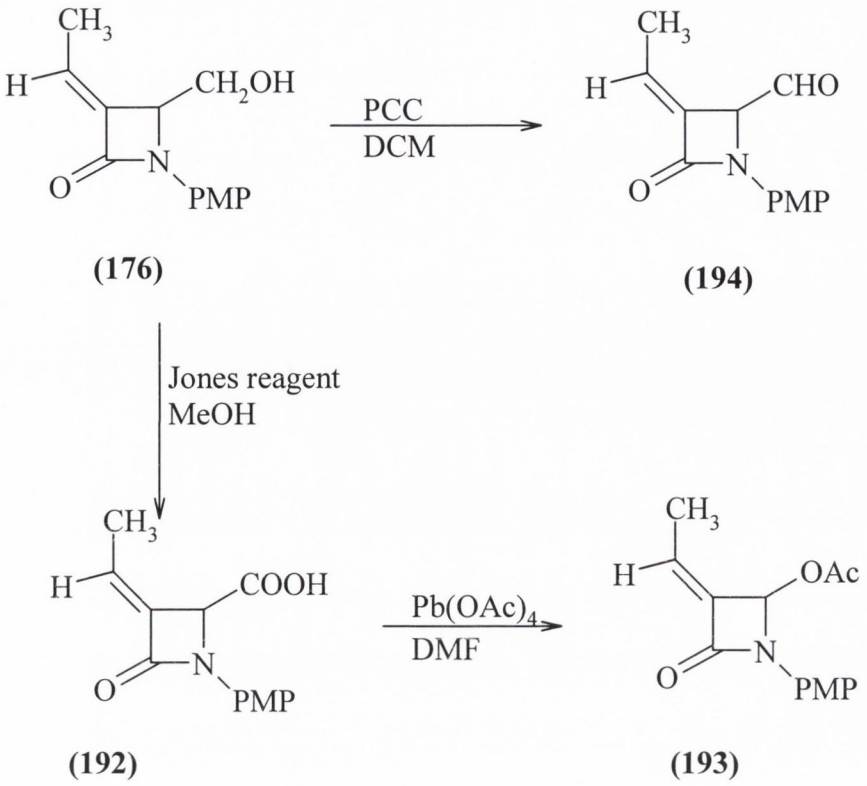
Scheme 43

Palomo and co-workers[100] converted a 4-styryl substituted azetidin-2-one (**189**) to the methyl ketone (**190**) which was converted to the 4-acetoxy derivative (**191**) via a Baeyer Villiger oxidation reaction on treatment with *m*CPBA (**Scheme 44**).



Scheme 44

In this work, in order to demonstrate the utility of the sodium borohydride isomerization, product *E*-3-ethylidene-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**176**) was oxidised to *E*-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (**192**) with Jones reagent in 65% yield (**Scheme 45**). The reaction of the above *E*-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (**192**) with lead tetra-acetate afforded the corresponding 4-acetoxy compound (**193**). Oxidation of 3-ethylidene-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**176**) with pyridinium chlorochromate (PCC) afforded 3-ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**194**) providing an alternative route to the synthesis of 4-formyl compounds in good yield.



(176) **(194)** **(192)** **(193)**

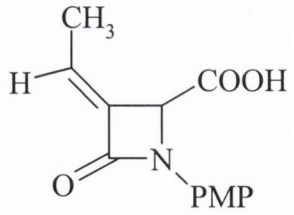
Scheme 45

Yields, melting points and mass spectrometry details for compounds (**192**)-(**194**) are given in **Table 13**.

Table 13: Yield, molecular formula and mass spectrometry data for compounds (192)-(194).

Compound No	Yield %	Molecular formula	Molecular ion M^+
192	65	$C_{13}H_{13}NO_4$	_
193	60 [116]	$C_{14}H_{15}NO_4$	261.1040
194	55	$C_{13}H_{13}NO_3$	231.0895

In the infrared spectrum of *E*-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (**192**) the carboxylic acid group OH gives rise to a very distinct broad OH stretching band ν2800-3400cm^{-1}. A broad band in the region ν1750cm^{-1} arising from the β-lactam carbonyl and the acid functional group carbonyl is also observed.



(192)

In the 400MHz ^{1}H-NMR spectrum of *E*-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (**192**) a doublet integrating for three protons at δ1.82, J=7.80Hz is assigned to the methyl group of the ethylidene side chain. The methoxy substituent on the phenyl ring gives rise to a three proton singlet at δ3.70. The β-lactam H-4 appears as a singlet at δ4.85. The methine proton H-5 gives rise to a quartet at δ6.27, J=7.80Hz as a result of coupling to the adjacent methyl group. The aromatic protons appear downfield as a pair of apparent doublets at δ6.78 (H-3` and H-5`) J=9.0Hz, δ7.23 (H-2` and H-6`), J=9.0Hz. The acid proton resonates as a singlet at δ13.20 proving that the desired oxidation has taken place. In the ^{13}C-NMR spectrum of *E*-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (**192**) the five quaternary carbons could readily be assigned as follows:170.60ppm (the acid group carbon), 159.88ppm (β-lactam C=O), 156.06ppm (C-4`), 136.43ppm (C-3), 136.06ppm (C-1`). C-5 appears at 124.87ppm. Para-substitution of the aromatic ring produces two sets of equivalent carbons which are observed as two signals resonating at 117.63ppm (C-2` and C-6) and 114.31ppm (C-3` and C-5`). The signal at 55.37ppm is assigned to the methoxy substituent on the phenyl ring which is further downfield than the methyl signal at 13.75ppm.

In the infrared spectrum of *E*-4-acetoxy-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one (**193**) the β-lactam carbonyl appears at ν1760cm^{-1} overlapping with the acetoxy carbonyl band. In the ^{1}H-NMR spectrum the acetoxy methyl hydrogens resonate at δ2.19. A doublet integrating for three protons at δ1.89 is assigned to the methyl group of the ethylidene side chain. The methoxy substituent on the phenyl ring gives rise to a three proton signal at δ3.83. The β-lactam H-4 appears as a singlet at δ7.01 due to the deshielding influence of the neighbouring acetoxy group. The methine proton at H-5 gives rise to a quartet at δ6.34, J=5.23Hz, as a result of coupling to the adjacent methyl group. The aromatic protons appear

downfield as a pair of apparent doublets at δ6.92 (H-3` and H-5`), J=6.78Hz, δ7.40 (H-2` and H-6`), J=6.78Hz.

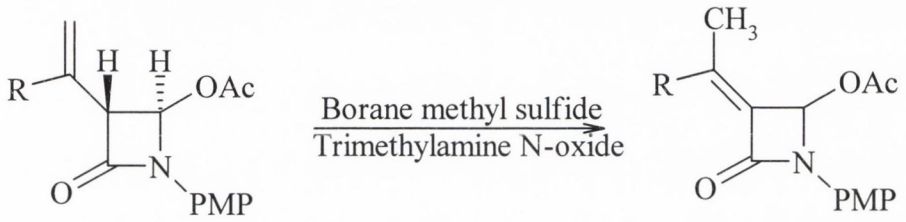
In the ^{13}C-NMR of *E*-4-acetoxy-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one (**193**) five quaternary carbons could readily be assigned as follows: 170.50ppm ($\underline{C}OCH_3$), 157.81ppm (β-lactam C=O), 156.67ppm (C-4`), 138.71ppm (C-3), 127.61ppm (C-1`). C-5 appears at 125.33ppm. These signals disappear in the DEPT spectrum. Para substitution of the aromatic rings produced two sets of equivalent carbons which are observed as two signals resonating at 118.26ppm and 114.56ppm. The signals at 78.77ppm and 55.43ppm are assigned to C-4 and the methoxy substituent on the phenyl ring. Finally the acetoxy methyl carbon and methyl carbon is assigned to 20.88ppm and 14.10ppm. High resolution mass spectrum was obtained for compound (**193**). The molecular ion peak M^+ ($C_{15}H_{17}NO_5$) is observed at m/z 261.1040 in 29% abundance. Process B splitting is observed with the isocyanate fragment at m/z 149 in 60% abundance.

In the infrared spectrum of 3-ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**194**) the β-lactam carbonyl appears at ν1760cm^{-1} overlapping with the formyl band. In the ^{1}H-NMR spectrum of 3-ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**194**) a doublet integrating for three protons at δ1.84, J=5.64Hz is assigned to the methyl group of the ethylidene side chain. The methoxy substituent resonates at δ3.81. The β-lactam H-4 appears as a singlet at δ4.82. The methine proton H-5 gives rise to a quartet at δ6.53, J=6Hz. The aromatic protons appear downfield as a pair of apparent doublets at δ6.89 (H-3` and H-5`), J=9.39Hz and δ7.29 (H-2` and H-6`), J=9.39Hz. The aldehyde proton appears as a doublet at δ9.60, J=3.75Hz.

In the ^{13}C-NMR spectrum of 3-ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**194**) five quaternary carbons could readily be assigned as follows: 197.90ppm (CHO), 159.04ppm (β-lactam C=O), 155.01ppm (C-4`), 135.01ppm (C-1`). C-5 appears at 127.43ppm. H-3`, H-5`, H-2` and H-6` appear as two signals at 117.29ppm and 114.51ppm. The signal at 65.31ppm is assigned to C-4. Further downfield the methoxy substituent on the phenyl ring appears at 55.48ppm. The signal at 13.80ppm representing C-6 completes this spectrum. High resolution mass spectrum was obtained for compound (**194**). The molecular ion peak M^+

($C_{13}H_{13}NO_3$) is observed at m/z 231.08948 in 61% abundance. Process B splitting is observed with the isocyanate fragment at m/z 149 in 39% abundance.

Our research group reported the treatment of *trans* α-vinyl β-lactams (**195**) and (**196**) with borane methylsulfide in diglyme followed by the addition of triethylamine *N*-oxide[116]. The reaction did not give the expected C-3 hydroxy side chains to the β-lactam ring. The reaction proceeded via the Markovnikov addition of the hydroxy group forming the intermediate alcohol which on dehydration and rearrangement afforded the products (**193**) and (**197**) (**Scheme 46**).



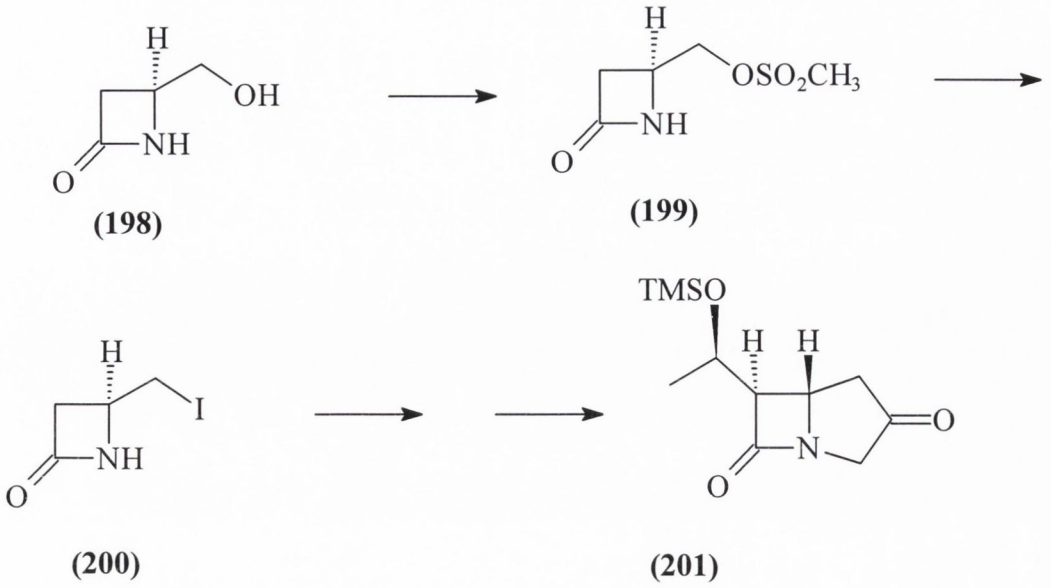
(195) R=H
(196) R=CH_3

(193) R=H
(197) R=CH_3

Scheme 46

3.5 Esterification and Nucleophilic Displacement of 4-hydroxymethylazetidin-2-ones.

4-Hydroxymethylazetidin-2-ones are useful synthons for carbapenem antibiotics. The following transformation of 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-ones is now described. Mesylates are recognized as useful derivatives of alcohols in organic synthesis which undergo a variety of nucleophilic displacement reactions. Nucleophilic displacement of methylsulfonyloxy substituent at C-4 of β-lactam is investigated. The first reported synthesis of (+)-thienamycin (**22**) by Salzmann *et al*[34] involved the mesylation of 4-hydroxymethylazetidin-2-one (**198**) to afford the mesylate product (**199**) followed by reaction with sodium iodide to afford 4-iodomethylazetidin-2-one (**200**). A series of reactions then followed to afford the bicyclic ketoester (**201**) (**Scheme 47**). Georg and Durst[156] also reported the nucleophilic displacement of iodine from 4-iodomethylazetidin-2-ones while retaining the β-lactam ring yielding an intermediate which could be alkylated to the known carbapenem intermediate.

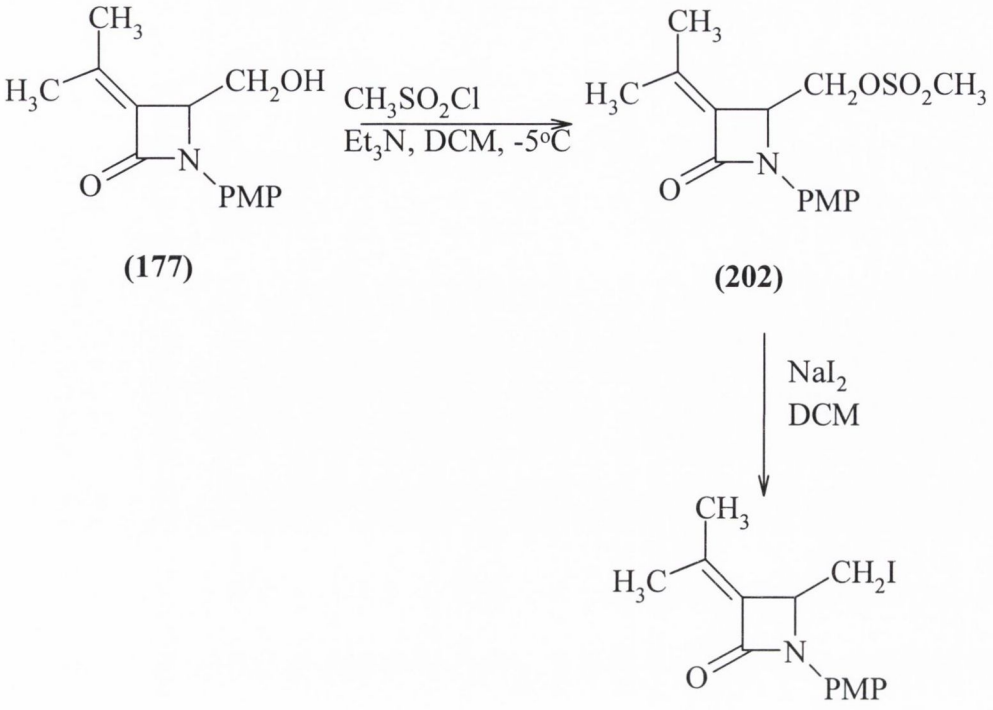


Scheme 47

Fetter *et al*[155] in 1994 reported the synthesis of structure activity relationships of new 2-oxaazetidine-1-sulphonic acids or 1-sulphonates carrying heterocyclyl or heterocyclylalkyl groups attached at C-4 of the β-lactam ring. Methylsulphonyloxymethyl or 4-chlorophenylsulphonyloxymethyl-azetidinones and iodomethylazetidinones were used as the starting compounds with the corresponding quaternary compounds as the intermediates.

3.5.1 3-Isopropenyl-4-methanesuphonyloxymethyl-1-(4-methoxyphenyl)azetidin-2-one (202) and 4-iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (203)

In this work 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**177**) was converted to the corresponding mesylate (**202**) by the addition of mesyl chloride at –5°C. Displacement of the mesylate group with sodium iodide resulted in the synthesis of 4-iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**203**) in 75% yield. (**Scheme 48**). 3-Isopropenyl-4-methanesulphonyloxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**202**) and 4-iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**203**) were identified by spectroscopic methods, mass spectrometry and microanalysis.

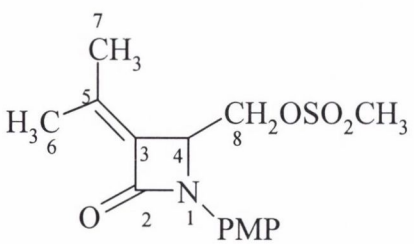


(177) **(202)**

(203)

Scheme 48

In the infrared spectrum of 3-isopropenyl-4-methanesulphonyloxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**202**) the β-lactam absorbance is seen at ν1743 cm^{-1}. S=O stretching frequencies occur in the fingerprint region, an absorbance at ν1350cm^{-1} is assigned to asymmetric stretching, while symmetric stretching gives rise to an absorbance at ν1175cm^{-1}.



(202)

In the 400MHz ^{1}H-NMR spectrum of 3-isopropenyl-4-methanesulphonyloxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**202**) two singlets at δ1.86 and δ2.13 are assigned to the two methyl groups of the isopropylidene side chain. The methyl (C-6) resonating further downfield due to the neighbouring carbonyl at C-2. A sharp singlet integrating for three protons at δ2.88 is due to the

methyl protons of the mesylate function. The methoxy substituent on the phenyl ring is seen typically at δ3.78. A double doublet at δ4.25 integrating for one hydrogen J_{vic}=5.25Hz, J_{gem}=4.38Hz and another double doublet at δ4.59 integrating for one hydrogen J_{vic}=3.51Hz, J_{gem}=4.38Hz are assigned to the methylene protons H-8. H-4 resonates as an apparent triplet at δ4.75, J=4.38Hz due to splitting by the methylene protons on C-8. The aromatic protons are seen as an apparent pair of doublets centered at δ6.86 and δ7.36.

In the ^{13}C-NMR spectrum of 3-isopropenyl-4-methanesulphonyloxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**202**) five quaternary carbons are present which are assigned as follows: 161.53ppm (β-lactam carbonyl), 157.56ppm (C-4`), 139.56ppm (C-3), 129.56ppm (C-5). The signal at 118.17ppm and 114.48ppm is due to the aromatic carbons C-2`, C-6` and C-3`, C-5`. A signal appearing at 66.67ppm is assigned to C-8 which is inverted in the DEPT 135 spectrum. The β-lactam C-4 occurs at 57.89ppm. A signal at 55.90ppm is assigned to the methoxy substituent at C-4` of the phenyl ring while an upfield signal at 39.67ppm is assigned to the methyl group of the mesylate . The signals at 20.56ppm and 19.88ppm are assigned to the methyl substituents at C-5 of the ethylidene group. Characterisation of this compound using elemental analysis proved satisfactory.

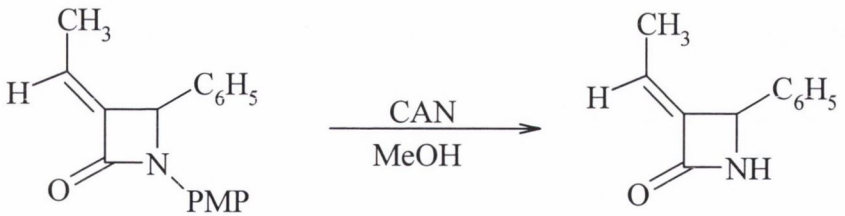
In the infrared spectrum of 4-iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**203**) shows the β-lactam carbonyl absorbance at 1736cm^{-1}. In the ^{1}H-NMR spectrum of 4-iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**203**) two singlets at δ1.80 and δ2.13 integrating each for three protons are assigned to the methyl protons. The protons at C-8 are geminally coupled to one another and vicinally coupled to H-4 and appear as a multiplet in the region δ3.62-3.74. The methoxy substituent of the phenyl ring appears as a singlet at δ3.78 integrating for three protons. The H-4 signal occurs as an apparent triplet $J_{4,8}$=3Hz, due to coupling with each of the adjacent methylene protons on C-8. The aromatic protons gives rise to a pair of doublets at δ6.87 and δ7.20.

In the ^{13}C-NMR spectrum of 4-iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**203**) five quaternary carbons are present which are assigned as follows: 156.03ppm (β-lactam carbonyl), 144.98ppm (C-4`), 138.51ppm (C-3), 133.58ppm (C-1`) and 130.53ppm (C-5). The aromatic carbons C-2` and C-6` give rise to a single peak at 118.35ppm, C-3` and C-5` are also equivalent and give

rise to a single peak at 114.59ppm. The methoxy substituent of the phenyl ring appears typically at 57.62ppm. C-4 resonates at 55.45ppm. The methyl substituents give rise to two signals at 20.90ppm and 20.30ppm. The upfield signal at 6.06ppm which is inverted in the DEPT 135 spectrum is assigned to the methylene carbon at C-8. The molecular ion peak M^+ ($C_{14}H_{16}NO_2I$) is observed at m/z 357.02235 in 100% abudance. Process B splitting shows the isocyanate ion at m/z 149 in 39% abundance.

3.6 *E*-3-Ethylidene-4-phenylazetidin-2-one (204)

Further elaboration of β-lactam to carbapenem requires the availability of deprotected NH of β–lactam. It is apparent from the literature that the 4-methoxyphenyl substituent is considered one of the most appropriate N-1 protecting groups available due to its facile removal under mild conditions[80]. Kronenthal *et al* in 1982 reported the deprotection at N-1 of *p*-methoxyphenylazetidin-2-ones on reaction with ceric ammonium nitrate (CAN)[157]. *E*-3-Ethylidene–1-(4-methoxyphenyl)-4-phenyl-azetidin-2-one (**180**) was reacted with CAN at –5°C to afford *E*-3-ethylidene-4-phenylazetidin-2-one (**204**) in 60% yield (**Scheme 49**). This reaction demonstrates the stability of ethylidene groups to CAN oxidation and possible utility in total synthesis. This product was identified by spectroscopic methods and mass spectrometry.



(180) **(204)**

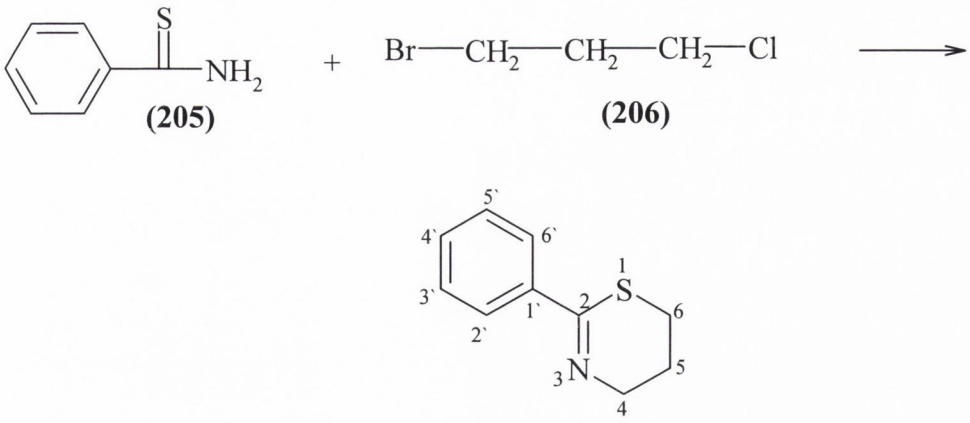
Scheme 49

In the infrared spectrum of *E*-3-ethylidene-4-phenylazetidin-2-one (**204**) reveals the N-H absorption frequency band at ν3348cm^{-1} together with a sharp singlet at ν1741cm^{-1} representing the carbonyl stretching frequency. In the ^{1}H-NMR spectrum of *E*-3-ethylidene-4-phenylazetidin-2-one (**204**) a singlet at δ1.54 represents the methyl group of the ethylidene side chain coupled with H-5 which appears downfield as a quartet at δ6.25Hz J=7.84Hz. *E* stereochemistry is adopted as the methyl group is seen upfield. H-4 appears as a doublet at δ5.13. The –NH proton appears as a broad

singlet resonating at δ6.52 . It is apparent from the ^{1}H-NMR spectrum that the *p*-methoxyphenyl group has been cleaved. The aromatic protons appear as a multiplet in the region δ7.31-7.54. In the ^{13}C-NMR spectrum of *E*-3-ethylidene-4-phenylazetidin-2-one (**204**) three quaternary carbons are visible and are assigned as follows: 164.50ppm (β-lactam carbonyl), 144.00ppm (C-3), 136.06ppm (C-5). The aromatic carbons are seen in the region 138.18-123.13ppm. The β-lactam carbon resonates at 58.24ppm and the methyl carbon at 12.65ppm. Mass spectrometry shows the molecular ion peak m/z 173.08392 in 100% abundance. Type B fragmentation leads to an aromatic fragment at m/z 77 in 37% yield.

3.7 6-Phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-ones (6-phenyl-7-vinyl cephams)

The biologically active principalconstituent of all β-lactam antibiotics is the azetidinone ring whose reactivity with penicillin binding proteins (PBPs) is thought to be favourably enhanced by the additional strain induced by fused ring systems[158]. Bose *et al* in 1969 reported novel cepham structures which were synthesized by the base catalysed cycloaddition reaction between acid chlorides and 2-aryl-5,6-dihydro-4H-1,3-thiazines[159]. Merck workers reported that certain cepham sulphone esters demonstrate activity as elastase inhibitors[160]. In this present work both the acid chloride-imine approach which has been successfully used by Bose to synthesize various cephams and the activated acid method described by Georg *et al* in Chapter 2 are investigated in the synthesis of 7-substituted–6-phenyl cephams. The imine chosen in this study was 2-phenyl-5,6-dihydro-4H-1,3-thiazine (**207**) by reaction of 1-bromo-3-chloropropane with thiobenzamide (**Scheme 50**).

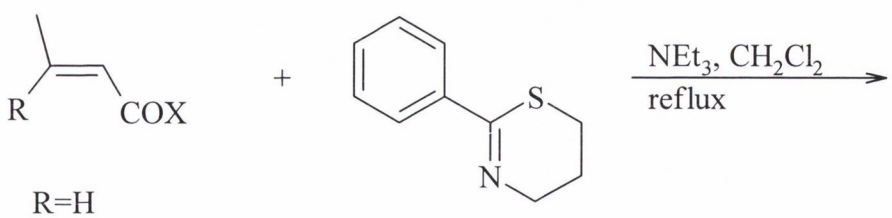


(205) **(206)**

(207)

Scheme 50

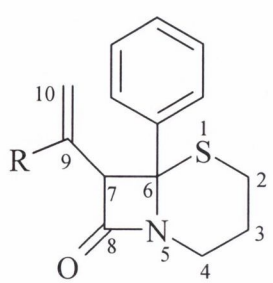
Reaction of 2-phenyl-5,6-dihydro-4H-1,3-thiazine (**207**) and the appropriate acid chloride or carboxylic acid e.g. crotonyl chloride (crotonic acid), 3,3-dimethylacryloylchloride (3,3-dimethylacrylic acid) in the presence of triethylamine afforded the cepham products (**208**) and (**209**) respectively (**Scheme 51**). The activated carboxylic acid route by Georg *et al*[108a] gave better yields for compounds (**208**) (60%) and (**209**) (70%) in comparsion to yields of 56% and 65% respectively via the acid-chloride method prevously reported in our research group[122].



R=H
R=CH_3

X=Cl or OH

(207)



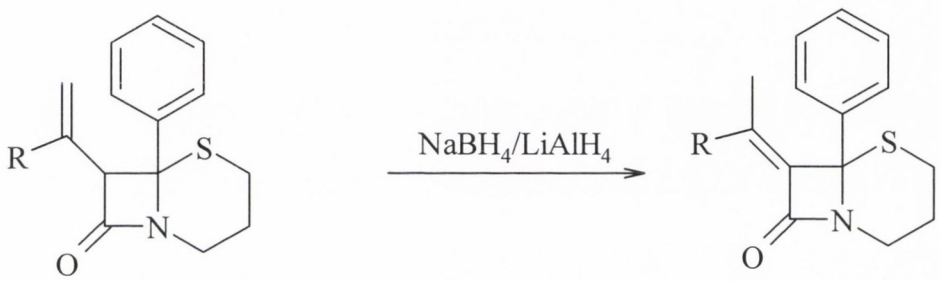
(208) R=H

(209) R=CH_3

Scheme 51

3.7.1 Isomerisation studies of 6-Phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-ones

In the earlier sections in this chapter the isomerization of 3-vinyl β-lactams giving rise to a double bond directly attached to the β-lactam ring was discussed. This was achieved by stirring 3-vinyl-6-phenylazetidin-2-ones in methanol in the presence of sodium borohydride and resulted in the formation of ethylidene and isopropylidene β-lactams. In this present work the isomerization of (**208**) and (**209**) is examined using both sodium borohydride and lithium aluminium hydride (**Scheme 52**).



(208) R=H

(209) R=CH_3

(210) R=H

(211) R=CH_3

Scheme 52

In 1994 our research group reported that 7-vinylcephams when treated with the base DBU[152] gave the corresponding 7-alkylidenecepham[122]. In this section the isomerization of the 6-phenyl-7-vinyl cephams using the sodium borohydride method described earlier was investigated in an attempt to introduce an asparenomycin type substituent to the cepham nucleus. Lithium aluminum hydride was used in an attempt to increase the yields of compounds (**210**) and (**211**). The yields using the three methods of compounds (**210**) and (**211**) are given in **Table 14**. The products were characterized by infrared, ^{1}H-NMR and ^{13}C-NMR spectroscopy. 7-Ethylidene-6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (**210**) was obtained as a mixture of geometric isomers in 60% and 10% using sodium borohydride and lithium aluminium hydride respectively. These yields when compared to that of the DBU method which gave a 85% yield were much lower. 7-Isopropylidene-6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (**211**) was obtained as a single isomer as *E* and *Z* isomers were not possible.

Table 14: Yield and melting point for compounds (210) and (211)

(A) $LiAlH_4$ method, (B) $NaBH_4$ method, (C) DBU method.

Compound No.	Yield %	m.p. °C (lit.)
210	A:10, B:60, C: 85[122]	oil
211	B: 50, C: 87[122]	131-132 (131-132)[122]

In the infrared spectrum of 7-ethylidene-6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (**210**) a β-lactam carbonyl is evident at $\nu 1760 cm^{-1}$. Such a high frequency absorbance is a result of the strain induced by the fused dihydrothiazine ring and the additional strain arising from the conjugated exocyclic double bond. In the ^{1}H-NMR spectrum a mixture of geometric isomers is evident. The methyl substituent resonates as two doublets at δ1.52 and δ1.93 in a 1:1 ratio. The signal at δ1.92 is assigned to the Z isomer. The Z isomer is seen further downfield due to the deshielding influence of the neighbouring carbonyl at C-2. The doublet signal is the result of coupling to the adjacent methine proton which appears as two quartet signals at δ5.49-5.59 and δ5.96-6.02, each integrating for 0.5H, J=7.2Hz. The protons of the dihydrothiazine ring show a similar pattern to the parent vinyl compound. The protons on C-2 give rise to an unresolved multiplet at δ2.54-2.64. The multiplet at δ1.71-1.92 is assigned to the methylene protons at C-3. The multiplet at δ2.84-δ3.06 is due to H-4ax, H-4eq is seen at δ4.03-4.15. The aromatic protons are seen typically downfield in the δ7.26-7.55 region.

In the infrared spectrum of 7-isopropylidene-6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (**211**) the β-lactam carbonyl stretching frequency occurs at $1770 cm^{-1}$ which is indicative of a highly strained ring. In the ^{1}H-NMR spectrum the singlets at δ1.44 and δ2.00 each integrating for three protons are assigned to the methyl substituents. The signal at δ1.44 is assigned to the methyl group on the opposite side of the double bond to the β-lactam ring i.e. the *E* position. The signal at δ2.00 is assigned to the *Z*-methyl group. The multiplet at δ1.62-1.78 is attributed as

before to the protons at the dihydrothiazine ring. The protons on C-2 resonate as a multiplet at δ2.46-2.61. The axial proton on C-4 is seen as a multiplet in the δ2.76-2.83 region while the equatorial proton appears downfield at δ3.94-4.01 region.

3.9 Summary

This chapter describes a number of chemical transformations at C-3 and C-4 of a series of monocyclic β-lactams. Reaction of *cis*-4-formyl-3-methoxyazetidin-2-one (**168**) with sodium borohydride gave *cis*-4-hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (**174**). Using the same reaction conditions and the starting material *cis*-4-formyl-3-vinylazetidin-2-one (**166**) gave *trans*-4-hydroxymethyl-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (**175**) and 3-ethylidine-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**176**). Epimerisation at C-3 was observed for compound (**166**) to afford the more stable product. These compounds are intermediates to potential carbapenem antibiotics suitably substituted at C-6. The hydroxymethyl group can be easily converted to its mesylate and a number of nucleophilic displacement reactions at C-4 of the mesylate derivative were demonstrated.

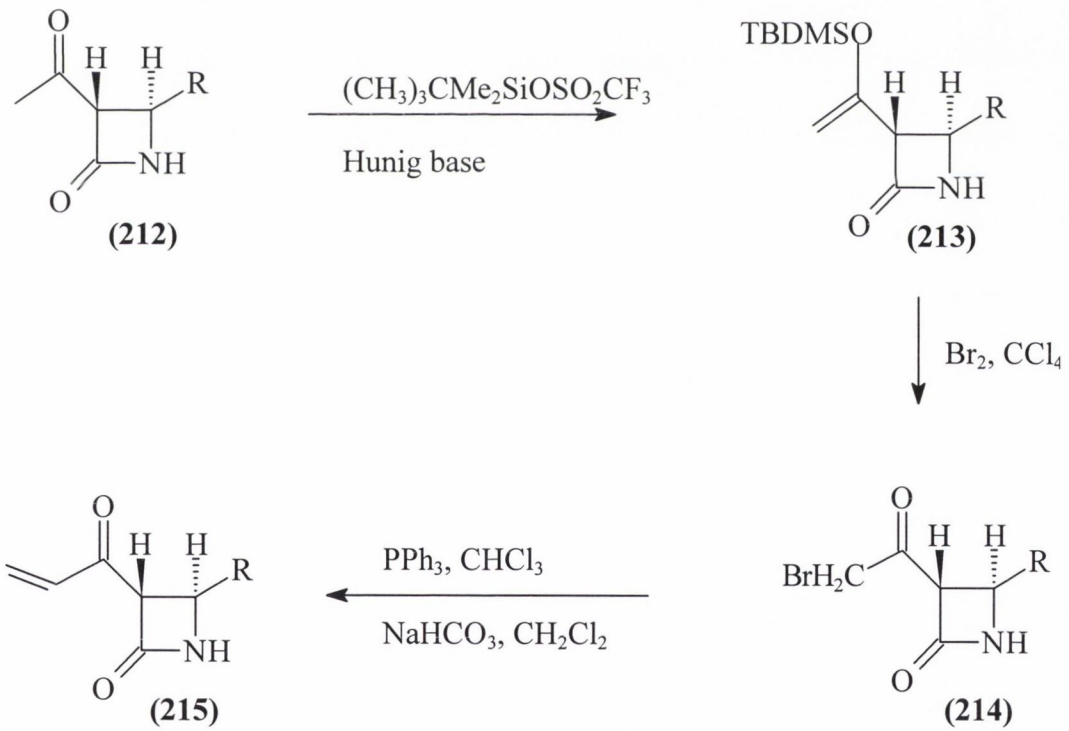
Chapter 4

Synthesis and Chemistry of Azetidin-2-ones with α,β–unsaturated Ketone Substituent at C-3

4.1 Introduction

As an extension to the work carried out on the synthesis of versatile C-3-α-vinyl-substituted azetidin-2-ones, the formation of C–3α–vinylketone substituted azetidin-2-ones is now investigated. The following synthetic approach is utilised in this work: addition of appropriate aldehydes to C-3 unsubstituted azetidin-2-ones by an aldol condensation reaction, followed by an oxidation reaction, to afford α, β unsaturated products.

Bouthillier *et al*[162,163a.,163b] reported the synthesis of α,β-unsaturated ketones at the C-3 position of azetidin-2-ones. The methyl ketone (**212**) can be easily converted to the corresponding silyl enol ether (**213**) on reaction with the appropriate silylating reagent in the presence of base. This bromoketone compound (**214**) can then be transformed via a Wittig reaction to the α, β-unsaturated ketone (**215**) (**Scheme 53**).



Scheme 53

The first of these methods is investigated in this chapter. These compounds are of interest as they demonstrate the introduction of versatile functional groups at C-3 position of monocyclic β-lactams. When these products are suitably substituted at the C-4 and N-1 positions they may be considered as potential precursors for the formation of novel carbapenems.

4.2 The Synthesis of 1-Alkylazetidin-2-ones under Phase Transfer Conditions.

In order to investigate the introduction of an α,β-unsaturated ketone at C-3 a number of 3-unsubstituted β-lactams are first prepared. 3-Bromo-*N*-(4-methoxyphenyl)propionamide (**218**) and 3-chloro-*N*-(4-methylphenyl)propionamide (**219**) were obtained in 84% and 50% yield by a Schotten-Baumann reaction of 3-bromopropionyl chloride and of 3-chloropropionyl chloride with the appropriate amines (**216**) and (**217**) (**Scheme 54**)[164].

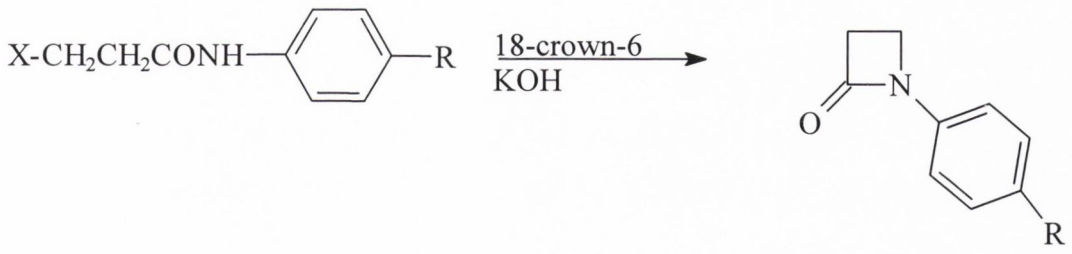
(**216**) R=OCH_3
(**217**) R=CH_3

(**218**) X=Br, R=OCH_3
(**219**) X=Cl, R=CH_3

Scheme 54

The 3-haloproponamides were characterised by spectroscopic analysis. In the infrared spectrum the amides showed a characteristic N-H stretching in the range ν3250cm^{-1} to 3280cm^{-1}, while the carbonyl stretching was in the range ν1650-1665cm^{-1}. The ^{1}H-NMR spectra of the 3-halopropionamides displayed the H-2 protons as a triplet in the range δ2.70-2.85 ($J_{2,3}$=6.0-6.5Hz) with the 3-chloropropionamide protons slightly more upfield than observed for the 3-bromopropionamide as expected. The H-3 protons appeared as a triplet in the range δ3.65-3.80 ($J_{3,2}$=6.0-6.5Hz). The aromatic protons appeared as two apparent doublets in the range δ6.79-7.50, J=9.0Hz.

18-Crown-6 was used as a phase transfer catalyst in the base catalysed cyclodehydrohalogenation of (**218**) and (**219**) to the corresponding 1-alkylazetidin-2-ones in dichloromethane using pulverised potassium hydroxide as base (**Scheme 55**).



(218) X=Br, R=OCH_3
(219) X=Cl, R=CH_3

(220) R=OCH_3
(221) R=CH_3

Scheme 55

Wasserman *et al*[164] reported that the proportion of β-elimination producing the acrylamide side product was minimised when there was a slow rate of addition of the amide to the base and when high dilution conditions were employed. The spectroscopic details, melting points and yields for compounds (**220**) and (**221**) are displayed in **Table 15**. All products are known compounds and were identified by comparsion of their melting points and spectroscopic data (^{1}H-NMR and IR) with literature values.

In the infrared spectrum of the two compounds a characteristic carbonyl absorbance in the range ν1731cm^{-1} to ν1730cm^{-1} was observed. The ^{1}H-NMR spectrum of compounds (**220**) and (**221**) displayed the H-3 and H-4 protons as triplets in the range δ2.98-3.06 ($J_{3,4}$=4.00-4.41Hz) and δ3.48-3.57 ($J_{4,3}$=4.00-4.41Hz).

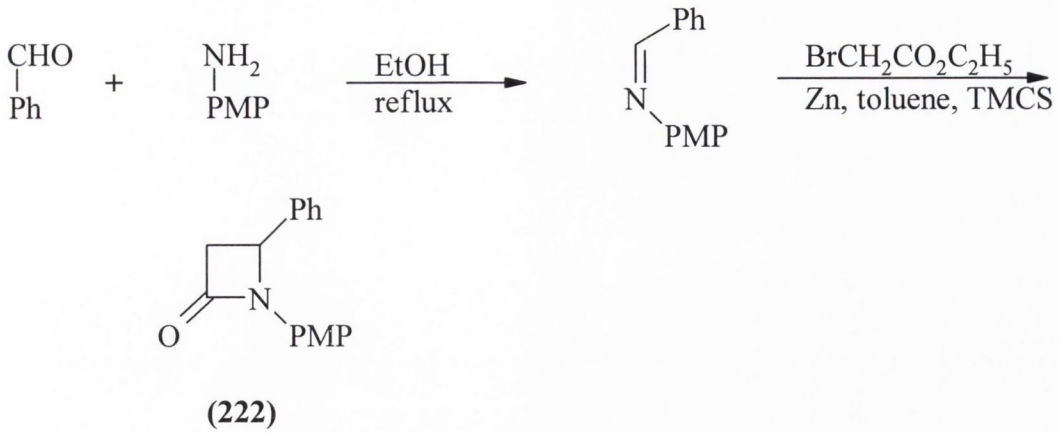
It has been shown that 18-crown-6 is an effective phase transfer catalyst for the synthesis of monocyclic β-lactams by dehydrohalogenation of 3-halopropionamides[93].

Table 15: Yield, melting point and spectroscopic data for compounds (220) and (221)

Compound No.	% Yield	m.p. ^{o}C (lit)	IR Data ν_{max} (KBr)cm^{-1}	^{1}H-NMR Data δ ($CDCl_3$)
220	80	101-102 (98-99[186]) (104-105[187])	1731 (C=O)	3.06 (2H, t, $J_{3,4}$=4.0Hz, H-3), 3.57 (2H, t, $J_{4,3}$=4.0Hz, H-4), 3.78 (3H, s, -OCH_3), 6.95 (2H, d, J=9.0Hz, H-3` and H-5`), 7.29 (2H, d, J=9.0Hz, H-2`and H-6`).
221	73	100-101 (97-98[165])	1730 (C=O)	2.26 (3H, s, CH_3), 2.98 (2H, t, $J_{3,4}$=4.41Hz, H-3), 3.48 (2H, t, $J_{4,3}$=4.41Hz, H-4), 7.06 (2H, d, J=8.19Hz, H-3` and H-5`), 7.19 (2H, d, J=8.19Hz, H-2`and H-6`).

4.3 1-(4-Methoxyphenyl)-4-phenylazetidin-2-one (222) and 1-(4-Methoxyphenyl)-4-styrylazetidin-2-one (224)

1-(4-Methoxyphenyl)-4-phenylazetidn-2-one (**222**) was prepared by a Reformatsky reaction of benzylideneaniline and ethylbromoacetate in the presence of zinc dust and trimethylchlorosilane according to the conditions of Gilman and Speeter[166]. The Schiff base was synthesized as described in Chapter 2 by a reaction between benzaldehyde and *p*-ansidine (**Scheme 56**).



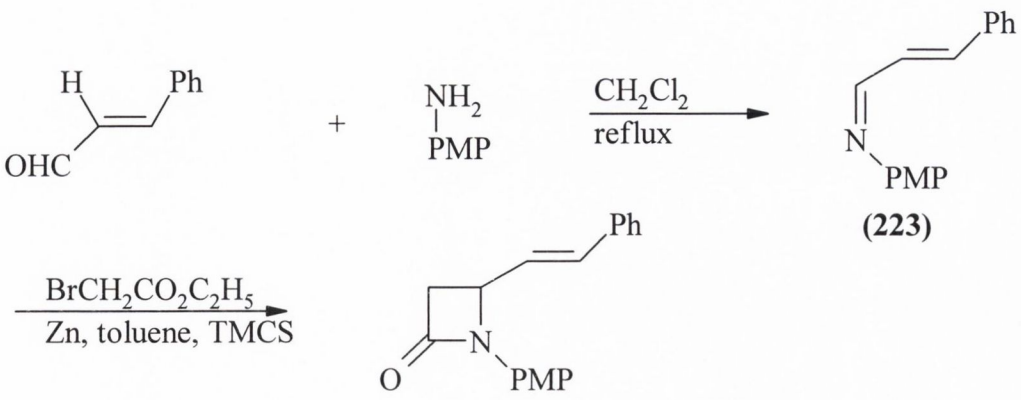
(222)

Scheme 56

1-(4-Methoxyphenyl)-4-phenylazetidn-2-one (**222**) was characterised by spectroscopic analysis. In the infrared spectrum the carbonyl absorbance of 1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**222**) was observed at $\nu 1740 cm^{-1}$. In the ^{1}H-NMR spectrum of (**222**) the H-4 proton at δ4.85 ($J_{4,3\alpha cis}$=5.0Hz, $J_{4,3\beta trans}$=2.5Hz) appears as a double doublet due to the strongly deshielding influence of the C-4 aryl substituent and of the anisotropic carbonyl group. H-3β is orientated *trans* to H-4 and thus experiences the shielding influence of the C-4 phenyl substituent. It is assigned at δ2.78 ($J_{3\beta,4trans}$=2.5Hz, J_{gem}=14.0Hz) and is more downfield due to the deshielding influence of the phenyl ring substituent. H-3α is isolated at δ3.45 ($J_{3\alpha,4cis}$=5.0Hz, J_{gem}=14.0Hz). The aromatic protons appear as a multiplet in the region δ6.66-7.41 integrating for nine protons.

4-Styrylazetidin-2-one (**224**) was synthesized for use as a substrate in reaction with a series of aldehydes via an aldol condensation reaction in order to prepare useful synthons for carbapenems with novel substituents at C-6. Palomo *et al*[100] successfully prepared 3-(1-hydroxyethyl)-4-(α-methylstyryl)azetidin-2-one employing an aldol condensation reaction by treatment of 4α-methylstyrylazetidin-2-one with LDA followed by reaction with acetaldehyde in THF at –78°C. This compound subsequently underwent an ozonolysis Baeyer Villiger sequence of transformations to provide *trans*-4-acetoxy-3-(1-acetoxyethyl)azetidin-2-one, an intermediate for thienamycin (**22**).

A Reformatsky reaction between ethylbromoacetate and cinnamylidene-*p*-ansidine (**223**) in the presence of zinc and trimethylchlorosilane (TMCS) was employed to prepare compound (**224**) (**Scheme 57**).



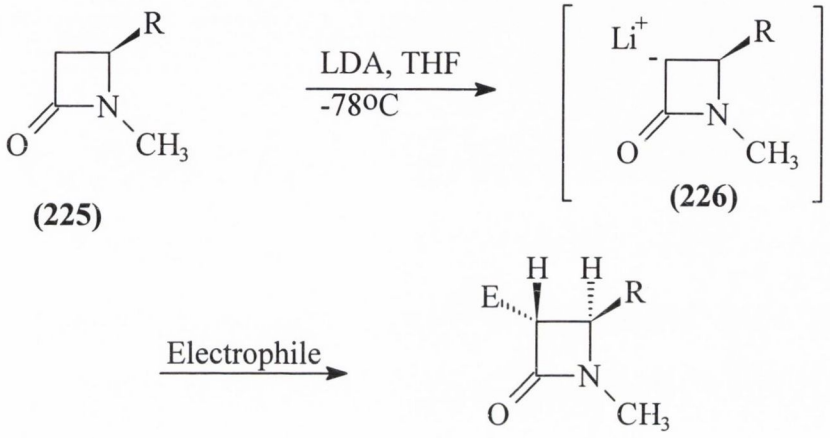
Scheme 57

The imine (**223**) was prepared by reaction of the arylamine with cinnamaldehyde. The Schiff base (**223**) displayed its imine proton at δ8.26 in the ^{1}H-NMR spectrum while the infrared spectrum illustrated the imine stretching absorbance at ν1605cm^{-1}. In the infrared spectrum of compound (**224**) the β-lactam carbonyl stretching was observed at 1743cm^{-1}. In ^{1}H-NMR spectrum of (**224**) the H-3 proton appeared at δ2.91 ($J_{3\beta,4trans}$=2.21Hz, J_{gem}=15.05Hz) occupying a position *trans* to H-4. H-3β is assigned upfield with respect to H-3α at δ3.39 ($J_{3\alpha,4cis}$=5.53Hz, J_{gem}=15.05Hz) due to the respective shielding and deshielding influence of the 4-(methylstyryl) substituent on each of these protons. H-4 resonates as a multiplet at δ4.59-4.63 integrating for one proton. The methoxy group is seen as a singlet at δ3.75. H-5 appears as a double doublet at δ6.27 (IH, dd, $J_{5,4}$=8.34Hz, $J_{5,6}$=15.8Hz). The aromatic protons are seen as a multiplet in the region δ6.84-7.41 integrating for nine protons. It is now possible to introduce C-3 substituents on compounds (**220**)-(**222**) and (**224**).

4.4: Aldol condensations reactions

Ruf and Otto in 1995[167] reported the synthesis of C-3 propylidene and cycloalkenylideneazetidin-2-one derivatives, on reaction of α,β-unsaturated ketones with a solution of LDA and 3-silylated β-lactam in THF (i.e. Peterson olefination reaction).

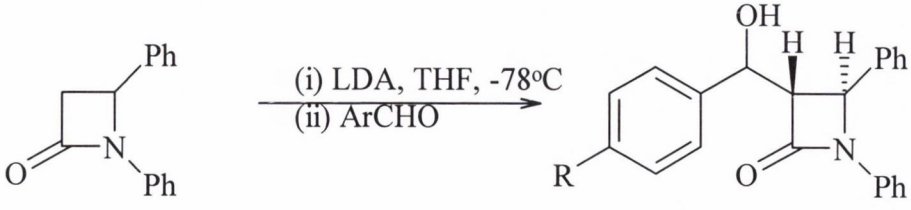
Durst and LeBelle[168] in 1972 reported the deprotonation of the monocyclic azetidin-2-ones (**225**) to form the lithiocarbanions (**226**) on treatment with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at –78°C. These carbanions subsequently underwent reaction with a variety of electrophiles such as ketones, esters and reactive alkyl halides to form 3-substituted products such as (**227**) and (**228**) (**Scheme 58**).



(227) R=CH=CH_2, E=$(CH_3)_2C(OH)$
(228) R=Ph, E=$Ph_2C(OH)$

Scheme 58

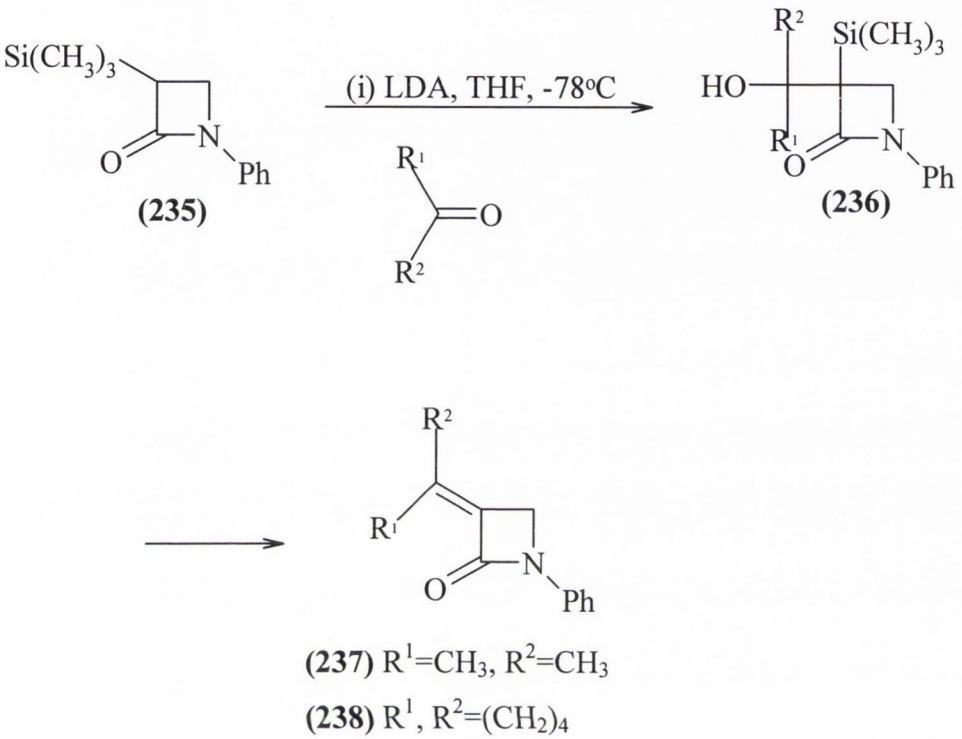
Hamlett and Durst[169] prepared *trans*-3,4-disubstituted azetidin-2-ones from *N*-pyrrolidinomethyl protected 4-vinylazetidin-2-one using a range of electrophiles including acetaldehyde, acetone, ethyl acetate, benzaldehyde. Otto *et al*[170,171,13] reported the preparation of a series of 3-[(aryl)(hydroxy)methyl]-1,4-diphenylazetidin-2-ones (**230**)-(**234**) by an aldol type reaction between 1,4-diphenylazetidin-2-one (**229**) and arylaldehydes (**Scheme 59**).



(230) R=H
(231) R=4-Cl
(232) R=4-NO_2
(233) R=2-NO_2
(234) R=3-NO_2

Scheme 59

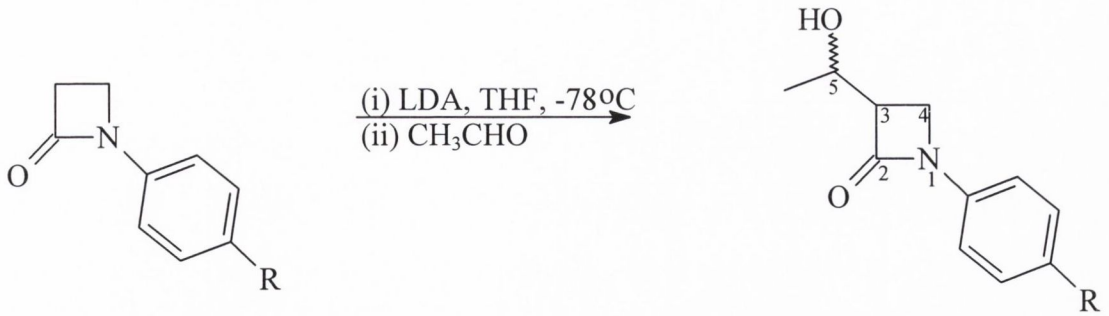
3-Alkylidene azetidin-2-ones (**237**)-(**238**) have been prepared by Kano *et al*[172] using a Peterson olefination to react 3-trimethylsilylazetidin-2-one (**235**) with carbonyl compounds (**Scheme 60**).



Scheme 60

In a similar fashion Gürtler and Otto[173,174] further investigated substituted 3-conjugated methyleneazetidin-2-ones via the 3-trimethylsilyl derivative. Few investigations have occurred on the synthesis of thienamycin (**22**) and other carbapenems containing α,β-unsaturated ketone type substituents at C-6.

In the present work the preparation of 3-[1-(1-hydroxyethyl)]-1-(4-methoxyphenyl)azetidin-2-one (**239**) and 3-[1-(1-hydroxyethyl]-1-(4-methylphenyl)azetidin-2-one (**240**) in which the C-4 position of the β-lactam is unsubstituted was first investigated. The C-3 unsubstituted azetidin-2-ones (**220**) and (**221**) were treated with acetaldehyde in THF at –78°C using LDA as the base (**Scheme 61**). The products were obtained as diastereomeric mixtures which were inseparable by column chromatography.

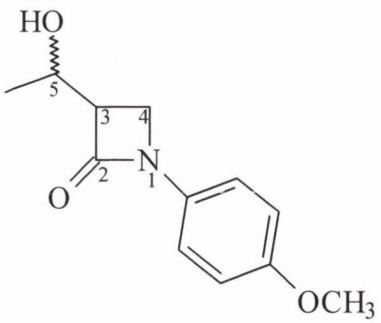


(220) R=OCH_3
(221) R=CH_3

(239) R=OCH_3
(240) R=CH_3

Scheme 61

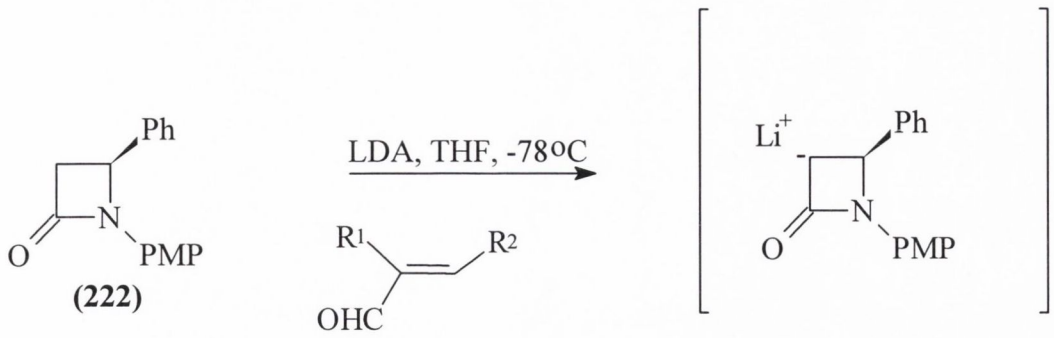
Spectroscopic details for compounds (**239**) and (**240**) are shown in **Table 16**. The yields, molecular formula and mass spectrometry for compounds (**239**) and (**240**) are shown in **Table 17.** The infrared spectrum of compound (**239**) displays the carbonyl stretching frequency at 1736cm^{-1}. The broad OH band is observed at ν3400cm^{-1}.



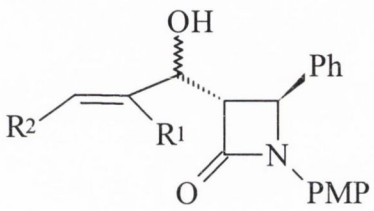
(239)

The ^{1}H-NMR spectrum of (**239**) reveals the presence of a diastereomeric mixture. A singlet at δ1.30 integrating for one proton and at δ1.35 integrating for two protons is assigned to the methyl protons. The OH proton gives rise to a broad singlet at δ3.00. H-4 appears as two double doublets at δ3.39 and δ3.46, J=5.52Hz, J=2.52Hz. A multiplet in the region of the spectrum δ3.57-3.59 represents H-3. The methoxy protons appear as a singlet in the characteristic region δ3.74. H-5 appears as a multiplet in the region δ4.11-4.24. The aromatic protons H-3` and H-5` are chemically equivalent at δ6.83, J=9.04Hz due to coupling with H-2` and H-6` which appear as a doublet at δ7.26 (J=9.04Hz).

In the ^{13}C-NMR spectrum of compound (**239**) six quaternary carbons are present and can be easily assigned at 166.55ppm, 164.79ppm (the β-lactam carbonyl), 155.62ppm, 155.65ppm (C-4`) and 131.43ppm, 131.53ppm (C-1`). The remaining aromatic carbons further upfield, C-2` and C-6` are equivalent and appear as one signal at 117.12ppm. Similarly C-3` and C-5` are assigned at 113.90ppm. The diastereomeric nature of the product is apparent in the ^{13}C-NMR spectrum. C-5 is observed as two signals at 64.57ppm and 65.65ppm slightly more downfield than C-4 at 55.03ppm and 55.10ppm. C-4 appears at 40.58ppm and 40.78ppm and is inverted in the DEPT spectrum. The methyl carbon is seen at 21.05ppm and 20.51ppm. In the high resolution mass spectrum of compound (**239**) the molecular ion peak $M^+(C_{12}H_{15}NO_3)$ is seen at m/z 221.10489 in an abudance of 100% (theoretical value at M^+ 221.10519). In the present work the preparation of 3-[(hydroxy)(1-propenyl)methyl] (**241**), 3-[(hydroxy)(styryl)methyl)] (**242**), 3-[(hydroxy)(α-methylstyryl)methyl] (**243**) and 3-[hydroxy)(1-vinyl)methyl]azetidin-2-one (**244**) in which the C-4 position of the β-lactam is occupied by a phenyl group is now demonstrated. The C-3 unsubstituted azetidin-2-one (**222**) was treated with the appropriate aryl or alkyl aldehyde in THF at –78°C using LDA as the base (**Scheme 62**).



(222)

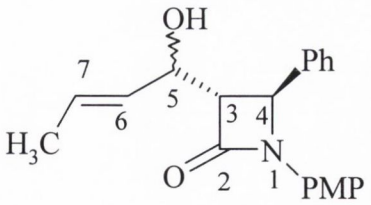


(241) R^1=H, R^2=CH_3
(242) R^1=H, R^2=C_6H_5
(243) R^1=CH_3, R^2=C_6H_5
(244) R^1=H, R^2=H

Scheme 62

All products were obtained in moderate yields as diastereomeric mixtures. Exclusively *trans* products were obtained in these C-4 phenyl substituted compounds (**241**)-(**244**). This selectivity may be due to the steric effect of the bulky C-3 side chain favouring addition to the opposite side of the ring to the C-4 substituent. Spectroscopic details for compounds (**241**)-(**244**) are shown in **Table 16**. Yields, molecular formulae and mass spectrometry for compounds (**241**)-(**244**) are shown in **Table 17**. The spectroscopic details of 3-[(hydroxy)(1-propenyl)methyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**241**) are now discussed in detail.

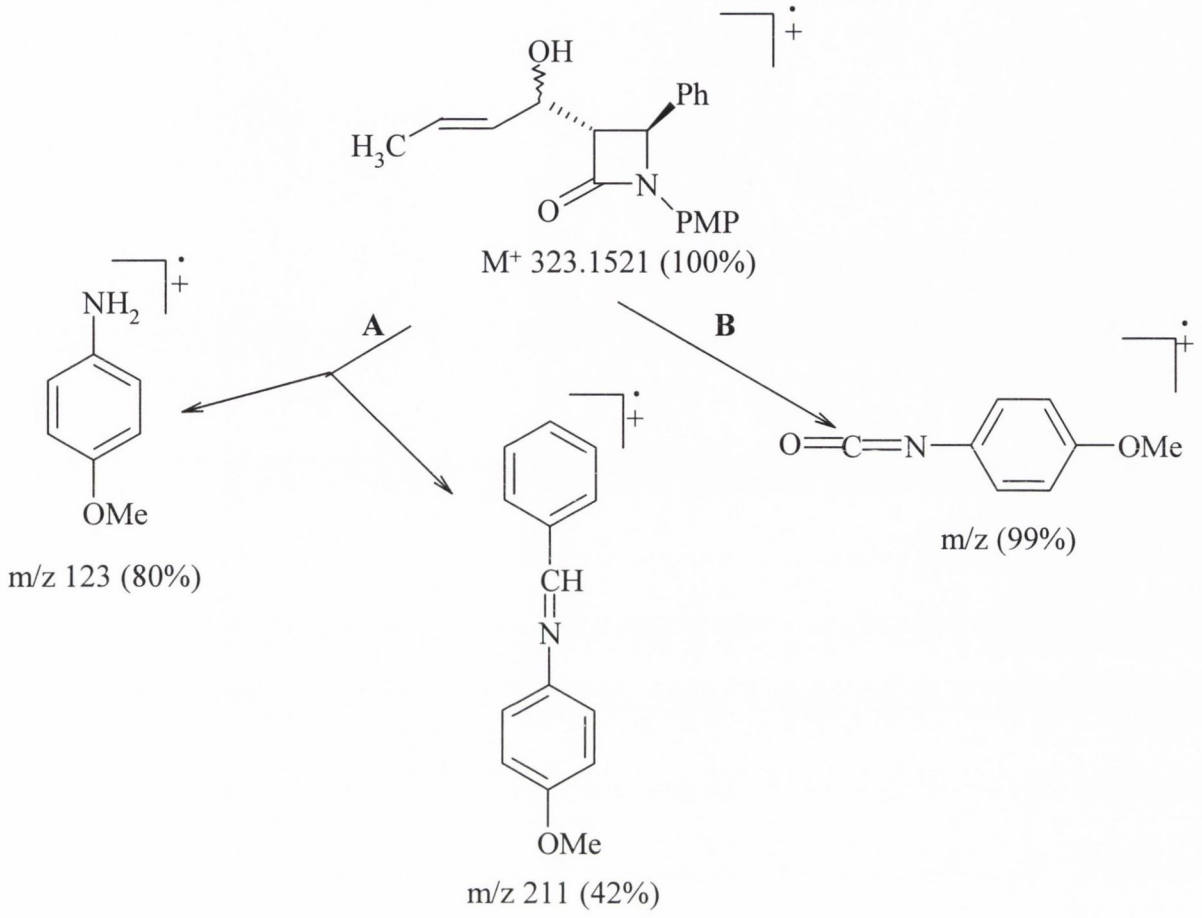
In the infrared spectrum of compound (**241**) the broad OH band is observed at ν3423cm^{-1} while the stretching frequency at ν1733cm^{-1} is assigned to the β-lactam carbonyl.



(241)

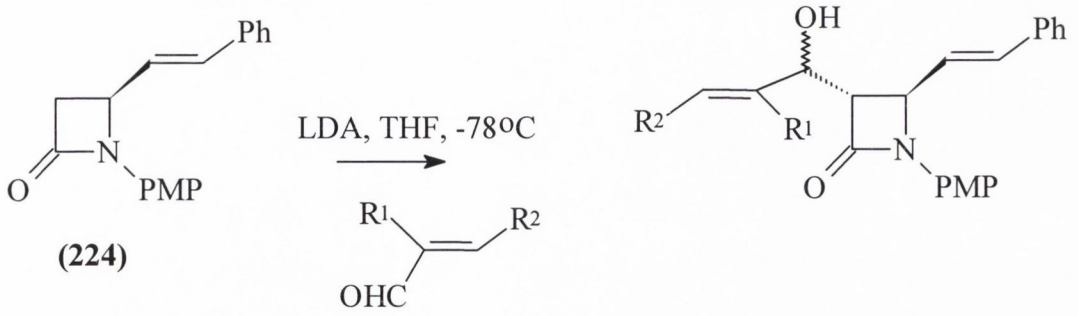
In the ^{1}H-NMR spectrum of compound (**241**) the methyl protons appear as a multiplet at δ1.70 integrating for three hydrogens. H-3 resonates as a double doublet at δ3.24, $J_{3,4trans}$=2.48Hz, $J_{3,5}$=6.2Hz due to coupling with H-4 and H-5. H-5 (0.5H) resonates as a broad triplet $J_{5,3}$=6.2Hz at δ4.54. The remainder H-5 (0.5H) resonates at δ4.69. H-4 is seen at δ4.89 (0.5H, $J_{4,3trans}$=2.52Hz). The remainder H-4 (0.5H) resonates at δ5.08. H-6 and H-7 appear as a multiplet in the region δ5.50-5.60. A multiplet in the region δ6.74-7.20 accounts for nine aromatic protons.

In the ^{13}C-NMR spectrum of compound (**241**) a diastereomeric mixture of products is obvious. The signals at 165.12ppm and 165.05ppm is the β-lactam carbonyl. C-4` appears at 155.78ppm. The aromatic carbons together with C-6 and C-7 are grouped in the region 137.95ppm-125.57ppm. The remaining aromatic carbons C-2` and C-6` resonate at 118.21ppm and 118.28ppm. Similarly C-3` and C-5` are assigned to 114.09ppm and 114.05ppm. Two signals are observed for C-5 and the two β-lactam carbons C-4 and C-3 at 70.65ppm, 68.43ppm, 65.30ppm, 65.04ppm, 57.23ppm and 56.23ppm. Further upfield the methoxy carbon resonates at 55.17ppm, while the methyl carbon at 17.45ppm completes the spectrum. High resolution mass spectrometry confirmed the molecular formula of compound (**241**) as $M^{+}(C_{20}H_{21}NO_3)$. The molecular ion is observed at m/z 323.1521 in an abundance of 100%. Process A yields the imine fragment at m/z 211 (42%) and the amine derivative at m/z 123 in a relative abudance of 80%. Fragmentation via process B yields the isocyanate fragment m/z 149 in 99% abudance (**Scheme 63**).



Scheme 63

In the present work the preparation of 3-[(hydroxy)(1-propenyl)methyl] (**245**), 3-[(hydroxy)(styryl)methyl)] (**246**), 3-[(hydroxy)(α-methylstyryl)methyl] (**247**) and 3-[hydroxy)(1-vinyl)methyl]azetidin-2-one (**248**) in which the C-4 position of the β-lactam is occupied by a styryl group is demonstrated. C-4 styryl groups can be easily converted to the carbapenem precursor acetoxy substituent and therefore are frequently utilised in total synthesis sequencies for carbapenems. The C-3 unsubstituted azetidin-2-one (**224**) was treated with the appropriate aryl or alkyl aldehyde in THF at –78°C using LDA as the base (**Scheme 64**).

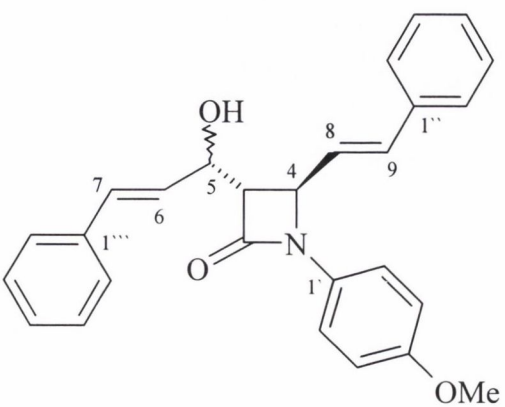


(224)

(245) R_1=H, R_2=CH_3
(246) R_1=H, R_2=C_6H_5
(247) R_1=CH_3, R_2=C_6H_5
(248) R_1=H, R_2=H

Scheme 64

All products were obtained in moderate yields as diastereomeric mixtures. Exclusively *trans* products were obtained in these C-4 styryl substituted compounds (**245**)-(**248**). This selectivity may be due to the steric effect of the bulky C-3 side chain favouring addition to the opposite side of the ring to the C-4 substituent. Spectroscopic details for compounds (**245**)-(**248**) are shown in **Table 16**. Yields, molecular formulae and mass spectrometry for compounds (**245**)-(**248**) are shown in **Table 17.** Spectroscopic details of 3-[(hydroxy(styryl)methyl]-1-(4-methoxyphenyl)-4-(styryl)azetidin-2-one (**246**) a representative of these novel structures is now discussed in detail. In the infrared spectrum of compound (**246**) the broad OH band is observed at ν3422cm^{-1}, while a stretching frequency at ν1731cm^{-1} is assigned to the β-lactam carbonyl.



(246)

In the ^{1}H-NMR spectrum of compound (**246**) H-3 appears as a double doublet at δ3.21 ($J_{3,4trans}$=1.89Hz, $J_{3,5}$=3.0Hz) due to coupling with H-4 and H-5 in the diastereomeric mixture. The methoxy proton resonates as a singlet at δ3.61. A double doublet integrating for 0.5H ($J_{4,3trans}$=1.89Hz, $J_{4,7}$=6.2Hz) at δ4.48 represents H-4, the remainder (0.5H) resonates at δ4.66. H-5 (0.5H) resonates as a broad triplet at δ4.61 (J=4.5Hz). The remainder H-5 (0.5H) resonates at δ4.80 (J=4.5Hz). H-6 and H-7 appear as a multiplet in the region δ6.10-6.40. A multiplet in the range δ6.50-7.23 integrating for sixteen hydrogens accounts for the fourteen aromatic protons together with H-8 and H-9. These alkene hydrogens are located downfield due to the deshielding effects of the aromatic rings.

In the ^{13}C-NMR spectrum of compound (**246**) a mixture of products is obvious. The signal at 163.46ppm is the β-lactam (C=O). C-4` appears as two signals at 154.95ppm and 154.98ppm. C-1`` and C-1``` of the aromatic rings appear at 135.35ppm and 135.37ppm. These are all quaternary carbons and disappear in the DEPT spectrum. C-6, C-7, C-8 and C-9 appear in the region 131.22ppm-129.71ppm. The aromatic carbons are located in their characteristic regions. Two signals are observed for C-5 and the two β-lactam carbons C-4 and C-3 resonating at 69.55ppm, 67.27ppm, 61.28ppm, 59.21ppm and 55.51ppm. The methoxy carbon at 54.25ppm completes the spectrum. These compounds have now the versatile alkene and hydroxy groups at C-3 substituent enabling synthetic elaboration towards further novel compounds.

Table 16: Spectroscopic details for compounds (239)-(248)

Compound No.	IR Data ν_{max} (film)cm^{-1}	^{1}H-NMR Data $\delta(CDCl_3)$
239	3400 (OH) 1736 (C=O)	1.30 (1H, d, J=6.52Hz, CH_3), 1.35 (2H, d, J=6.52Hz, CH_3), 3.00 (1H, bs, -OH), 3.39 (1H, dd, J=5.52Hz, J=2.52Hz, H-4), 3.46 (1H, dd, J=5.52Hz, J=2.52Hz, H-4), 3.57-3.59 (1H, m, H-3), 3.74 (3H, s, -OCH_3), 4.11-4.24 (1H, m, H-5), 6.83 (2H, d, J=9.04Hz, H-3` and H-5`), 7.26 (2H, d, J=9.04Hz, H-2` and H-6`).
240	3400 (OH) 1736 (C=O)	1.19 (1H, d, J=6.52Hz, CH_3), 1.30 (2H, d, J=6.52Hz, CH_3), 2.13 (3H, s, CH_3), 3.39 (1H, dd, J=5.52Hz, 2.52Hz, H-4), 3.45 (1H, dd, J=5.52Hz, 2.52Hz, H-4), 3.59-3.66 (1H, m, H-3), 4.10-4.20 (1H, m, H-5), 6.83 (2H, d, J=9.04Hz, H-3` and H-5`), 7.26 (2H, d, J=9.04Hz, H-2`and H-6`).
241	3423 (OH) 1733 (C=O)	1.70 (3H, m, CH_3), 3.24 (1H, dd, $J_{3,4trans}$=2.48Hz, $J_{3,5}$=6.2Hz, H-3), 4.54 (0.5H, br t, $J_{5,3}$=6.2Hz, H-5), 4.69 (0.5H, br s, H-5), 4.89 (0.5H, d, $J_{4,3trans}$=2.52Hz, H-4), 5.08 (0.5H, $J_{4,3trans}$=2.52Hz, H-4), 5.50-5.60 (2H, m, H-6, H-7), 6.74-7.20 (9H, m, aromatic Hs).
242	3425 (OH) 1750 (C=O)	3.36-3.37 (1H, m, H-3), 3.76 (3H, s, OCH_3), 4.59 (0.25H, d, $J_{4,3trans}$=2.48Hz, H-4), 4.62 (0.25H, d, $J_{4,3trans}$=2.48Hz), 4.71-4.93 (1.5H, m, H-4 and H-5), 6.28 (1H, m, H-6), 6.43 (1H, d, $J_{7,6}$=15Hz, H-7), 7.32-7.43 (14H, m, aromatic Hs).

Table 16 continued

243	3423 (OH) 1749 (C=O)	1.88 (0.9H, s, CH_3), 2.07 (2.1H, s, CH_3), 3.46 (1H, dd, $J_{3,4trans}$=2.4Hz, $J_{3,5}$=8.04Hz, H-3), 3.70 (0.9H, s, OCH_3), 3.72 (2.1H, s, -OCH_3), 4.13 (0.30H, d, $J_{5,3}$=7.02Hz, H-5), 4.16 (0.70H, d, $J_{5,3}$=7.02Hz, H-5), 4.84 (1H, d, $J_{4,3trans}$=2.52Hz, H-4), 5.23 (1H, bs, H-7), 6.82-7.43 (14H, m, aromatic Hs).
244	3450 (OH) 1734 (C=O)	2.50 (1H, br s, -OH), 3.26 (1H, dd, $J_{3,4trans}$=1.90Hz, $J_{3,5}$=4.5Hz, H-3), 3.60 (3H, s, -OCH_3), 4.89 (0.5H, d, $J_{4,3trans}$=1.89Hz, H-4), 5.06 (0.5H, d, $J_{4,3}$=1.89Hz, H-4), 4.61 (0.5H, br t, $J_{5,3}$=4.89Hz, H-5), 4.76 (0.5H, br t, H-5), 5.23-6.12 (2H, m, H-6 and H-7), 6.77-7.30 (9H, m, aromatic Hs).
245	3426 (OH) 1736 (C=O)	1.63-1.65 (3H, m, CH_3), 3.12-3.14 (1H, m, H-3), 3.64 (3H, s, -OCH_3), 4.40-4.61 (2H, m, H-4 and H-5), 5.51-5.59 (2H, m, H-6 and H-7), 6.68-7.35 (11H, m, aromatic Hs, H-8 and H-9).
246	3422 (OH) 1731 (C=O)	3.21 (1H, dd, $J_{3,4trans}$=1.89Hz, $J_{3,5}$=3.0Hz, H-3), 3.61 (3H, s, -OCH_3), 4.48 (0.5H, dd, $J_{4,3trans}$=1.5Hz, $J_{4,7}$=6.5Hz, H-4), 4.66 (0.5H, dd, $J_{4,3}$=1.89Hz, $J_{4,7}$=6.2Hz, H-4), 4.61 (0.5H, t, J=4.5Hz, H-5), 4.80 (t, 0.5H, J=4.5Hz, H-5), 6.10-6.40 (2H, m, H-6 and H-7), 6.50-7.23 (16H, m, aromatic Hs, H-8 and H-9).

Table 16 continued

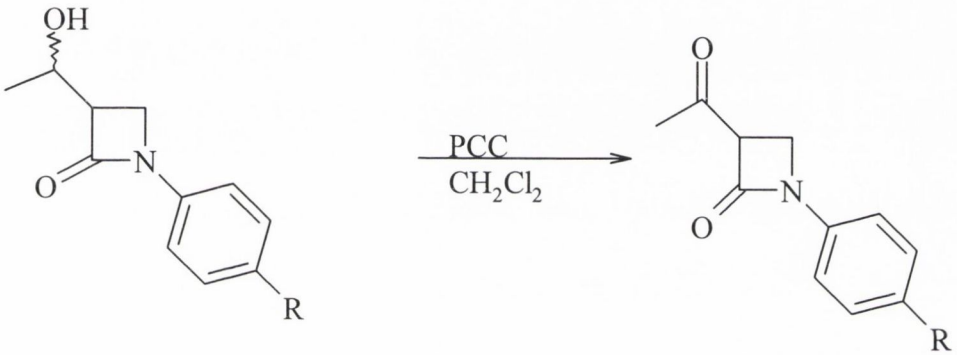
247	3410 (OH) 1739 (C=O)	1.90 (1H, s, CH_3), 1.91 (2H, s, CH_3), 3.55 (1H, dd, $J_{3,4trans}$=1.5Hz, $J_{3,5}$=8.6Hz, H-3), 3.73 (1H, s, -OCH_3), 3.76 (2H, s, -OCH_3), 4.47-4.83 (2H, m, H-4 and H-5), 6.28-6.31 (1H, m, H-7), 6.33-7.32 (16H, m, aromatic Hs, H-8 and H-9).
248	3450 (OH) 1734 (C=O)	3.27-3.31 (1H, m. H-3), 3.77 (3H, s, -OCH_3), 4.54 (0.5H, dd, $J_{4,3}$=1.8Hz, $J_{4,5}$=6.40Hz, H-4), 4.71 (0.5H, dd, $J_{4,3}$=1.8Hz, $J_{4,5}$=6.40Hz, H-4), 4.60 (0.5H, br t, J=4.53Hz, H-5), 4.75 (0.5H, br t, J=3.36Hz, H-5), 5.24-6.33 (2H, m, H-6 and H-7), 6.39-7.51 (11H, m, aromatic Hs, H-8 and H-9).

Table 17: Yield, molecular formula and mass spectrometry details for compounds (239)-(248)

Compound No.	**R^1**	**R^2**	**% Yield**	**Molecular formula**	**Mass spectrometry M^+**
239	-	-	63	$C_{12}H_{15}NO_3$	221
240	-	-	55	$C_{12}H_{15}NO_2$	205
241	H	CH_3	70	$C_{20}H_{21}NO_3$	323
242	H	C_6H_5	70	$C_{25}H_{23}NO_3$	385
243	CH_3	C_6H_5	85	$C_{26}H_{25}NO_3$	399
244	H	H	58	$C_{19}H_{19}NO_3$	309
245	H	CH_3	47	$C_{22}H_{23}NO_3$	349
246	H	C_6H_5	59	$C_{27}H_{25}NO_3$	411
247	CH_3	C_6H_5	65	$C_{28}H_{27}NO_3$	425
248	H	H	47	$C_{21}H_{21}NO_3$	335

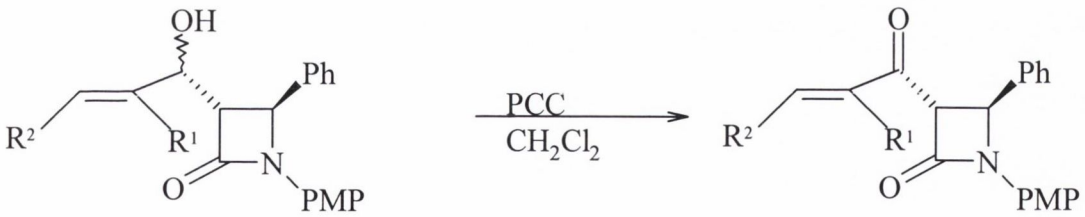
4.5 Oxidation Reactions with pyridinium chlorochromate (PCC)

In order to introduce a carbonyl function at C-3 it was now possible to oxidise the hydroxy function of compounds (**239**) and (**240**) with pyridinum chlorochromate (PCC), thus preventing possible dehydration reactions at C-5 in further chemical transformations. Pyridinum chlorochromate allows the efficent oxidation of a wide range of alcohols to carbonyl compounds in which only a modest excess of oxidant is needed[175]. On treatment of (**239**) and (**240**) with PCC in dichloromethane at room temperature compounds (**249**) and (**250**) were obtained. Similar treatment of (**241**), (**245**), (**246**) resulted in the single *trans* products (**251**)-(**253**) being obtained (**Scheme 65**).

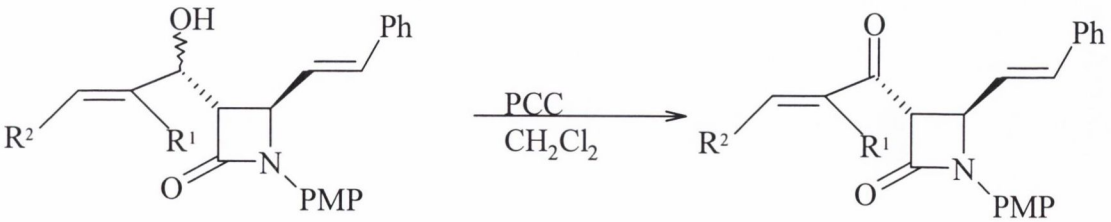


(239) R=OCH_3 **(249)** R=OCH_3

(240) R=CH_3 **(250)** R=CH_3



(241) R^1=H, R^2=CH_3 **(251)** R^1=H, R^2=CH_3



(245) R^1=H, R^2=CH_3 **(252)** R^1=H, R^2=CH_3

(246) R^1=H, R^2=Ph **(253)** R^1=H, R^2=Ph

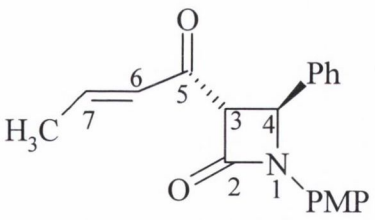
Scheme 65

Table 18 shows the yields, molecular formulae and mass spectrometry for the ketone compounds obtained.

Table 18: Yield, molecular formula and mass spectrometry data for compounds (249)-(253)

Compound No.	Yield %	R^1	R^2	Molecular formula	Mass spectrometry M^+
249	70	_	_	$C_{12}H_{13}NO_3$	219
250	65	_	_	$C_{12}H_{13}NO_2$	203
251	38	H	CH_3	$C_{20}H_{19}NO_3$	321
252	85	H	CH_3	$C_{22}H_{21}NO_3$	349
253	70	H	C_6H_5	$C_{27}H_{23}NO_3$	409

All compounds were analysed by spectroscopic methods. 1-(4-Methoxyphenyl)-3-[1-(1-oxo-but-2-enyl)]-4-phenylazetidin-2-one (**251**) is a representative of these compounds. The infrared spectrum of compound (**251**) displays the β-lactam C=O and ketone carbonyl at ν1752cm^{-1} and ν1679cm^{-1} respectively.

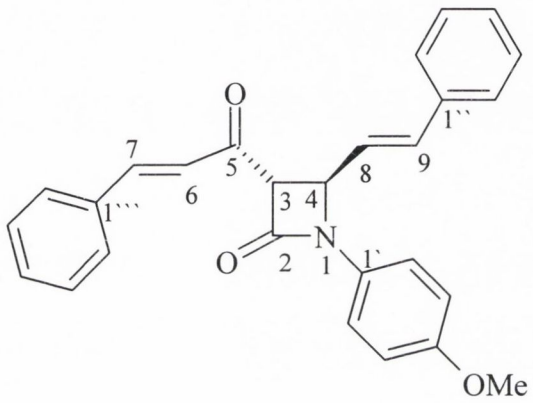


(251)

In the ^{1}H-NMR spectrum H-3, H-4, and H-6 are shifted to δ4.32, δ5.52 and δ6.31 in relation to the chemical shift values in the starting material (**241**) due to the deshielding effect of the carbonyl compound. The methyl group appears as a double doublet at δ1.98 (J=1.5Hz, J=6.5Hz). A multiplet in the region δ7.09-7.39 integrates for nine aromatic protons and H-7. H-5 has disappeared as expected due to the oxidation of the hydroxy group. The ^{13}C-NMR spectrum of (**251**) reveals all the carbon signals. C-7 has shifted downfield to 147.08ppm, while the remaining signals differ only slightly from the values observed in compound (**241**). The molecular ion

$M^+(C_{20}H_{19}NO_3)$ for compound (**251**) is observed at m/z 321.1327 in a relative abundance of 99%. Fragmentation via process B yields the isocyanate fragment m/z 149 as the base peak. Type A fragmentation is not observed.

The infrared spectrum of 1-(4-methoxyphenyl)-3-[1-(1-oxo-3-phenyl)prop-2-enyl]-4-styrylazetidin-2-one (**253**) displays the β-lactam carbonyl and the ketone carbonyl absorptions at $\nu 1748cm^{-1}$ and $\nu 1654cm^{-1}$ respectively.



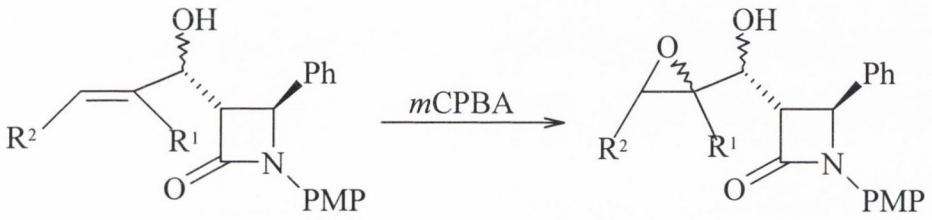
(253)

In the ^{1}H-NMR spectrum of (**253**) the methoxy protons appear as a singlet at δ3.81. H-3 is seen as a doublet $J_{4,3trans}$=2.5Hz at δ4.74. Further downfield the multiplet present at δ6.81-6.85 integrating for three protons is assigned to H-6, H-8 and H-9. A multiplet in the range δ7.23-7.60 integrating for fifteen hydrogens accounts for fourteen hydrogens and H-7. The alkene hydrogens are located downfield due to the deshielding effects of the aromatic rings.

In the ^{13}C-NMR spectrum of compound (**253**) five quaternary carbons are present and are assigned as follows: 190.13ppm (C=O), 159.49ppm (β-lactam C=O), 145.80ppm, 145.90ppm and 130.56ppm (C-1), (C-1``) and (C-1```). The aromatic carbons together with C-6, C-8 and C-9 appear in the region 124.73ppm-133.77ppm. The remaining aromatic carbons are further upfield at 118.00ppm C-2` and C-6` are equivalent, similarly C-3` and C-5` are assigned at 113.92ppm. C-3 and C-4 resonate at 55.33ppm and 54.94ppm. The methoxy carbon appears at 52.92ppm and completes the spectrum. High resolution mass spectrometry confirmed the molecular formula of this compound. The molecular ion $M^+(C_{20}H_{21}NO_3)$ is observed at m/z 409.17279. These novel β-lactam products containing a vinyl ketone substituent at C-3 are readily accesible via the aldol procedure. The next section now investigates further chemical transformations of the α, β–unsaturated C-3 side chain of some of these compounds.

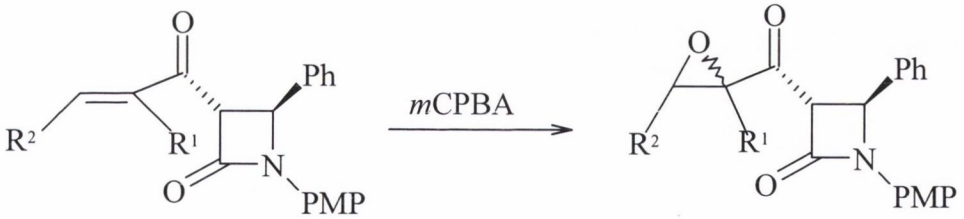
4.6 Epoxidation Studies

Epoxidation of the alkene moiety in compounds (**241**), (**244**) and (**251**) affords readily accessible epoxy alcohol and epoxy ketone C-3 substituted β-lactams. 3-(1,2-Epoxyethyl)-substituted β-lactams are well known structures (i.e. similar to those reported in Chapter 2) while the formation of 3-(2,3-epoxypropan-1-ol) and 3-(2,3-epoxypropan-1-one) substituted azetidin-2-ones reported in this chapter is not common. Reaction of *meta*chloroperbenzoic acid with the compounds (**241**), (**244**) and (**245**) afforded the *trans* products (**254**)-(**256**) in good yields (**Scheme 66**).



(241) R^1=H, R^2=CH_3 **(254)** R^1=H, R^2=CH_3

(244) R^1=H, R^2=H **(255)** R^1=H, R^2=H



(251) R^1=H, R^2=CH_3 **(256)** R^1=H, R^2=CH_3

Scheme 66

Diastereomeric mixtures were obtained for the 3-hydroxy derivatives (**254**) and (**255**) which were inseparable by column chromatography. Compound (**256**) was obtained as a single isomer. The yields, molecular formulae and mass spectrometry data for compounds (**254**) to (**256**) is shown in **Table 19**. The spectroscopic details for these compounds is shown in **Table 20**.

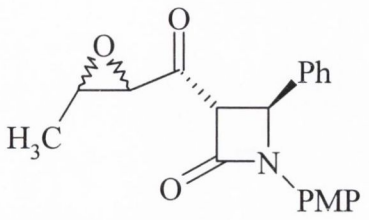
Table 19: Yield, molecular formula and mass spectrometry details for compounds (254)-(256)

Compound No.	Yield %	Molecular formula	Mass spectrometry M^+
254	63	$C_{20}H_{21}NO_4$	339
255	58	$C_{19}H_{19}NO_4$	325
256	65	$C_{20}H_{19}NO_4$	337

Table 20 Spectroscopic data for compounds (254)-(256)

Compound No.	IR Data νmax (film)cm^{-1}	^{1}H-NMR Data δ($CDCl_3$)ppm
254	3440 (OH) 1750 (C=O) 1251, 947, 760 (epoxy C-O)	1.30-1.36 (3H, m, CH_3), 2.88-3.37 (3H, m, H-3, H-6, and H-7), 3.92-4.44 (1H, m, H-5), 5.03 (0.4H, d, $J_{3,4trans}$=2Hz, H-4), 5.10 (0.3H, d, J=2Hz, H-4), 5.14 (0.3H, d, J=2Hz, H-4), 6.75 (2H, d, J=8.52Hz, H-3` and H-5`), 7.23-7.31 (7H, m, aromatic Hs).
255	3500 (OH) 1734 (C=O) 1247,932, 750 (epoxy C-O)	2.76-3.37 (3H, m, H-3, H-6, and H-7), 3.76 (3H, s, OCH_3), 4.13-4.49 (1H, m, H-5), 5.03-5.14 (3xd, $J_{3,4trans}$=2Hz, H-4), 6.79 (2H, d, H-3` and H-5`), 7.20-7.39 (7H, m, aromatic Hs).
256	1760 (C=O) 1686 (C=O) 1239, 931, 751 (epoxyC-O)	1.57-2.01 (3H, m, CH_3), 2.50-3.43 (2H, m, H-6 and H-7), 3.93 (3H, s, OCH_3), 4.07-4.34 (1H, m, H-3), 5.43 (1H, d, $J_{3,4trans}$=2.52Hz, H-4), 6.81-8.16 (9H, m, aromatic Hs).

The infrared spectrum of 3-[1-(2,3-epoxy-1-oxobutyl)]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**256**) displays the β-lactam carbonyl stretch and ketone carbonyl at ν1760cm^{-1} and ν1686cm^{-1} respectively. The C-O epoxy bands are seen at ν1239, 931 and 751cm^{-1}.



(256)

In the ^{1}H-NMR spectrum of compound (**256**) a multiplet resonating at δ1.57-2.01 represents the methyl protons. H-6 and H-7 appear as a multiplet in the region δ2.50-3.43. The methoxy protons are seen at δ3.93. One multiplet signal is observed for H-3 at δ4.07-4.34. The doublet at δ5.43, $J_{4,3trans}$=2.52Hz is assigned to H-4. Nine aromatic hydrogens appear as a multiplet at δ6.81-8.16. In the ^{13}C-NMR spectrum of (**256**) quaternary carbon signals are observed at 160.13ppm representing the β-lactam carbonyl and 190.00ppm (C=O), while the aromatic signals are located in the general region 130.40ppm-113.90ppm. The signals appearing at 64.27ppm, 60.53ppm, 54.96ppm and 53.90ppm are assigned to C-6, C-7, C-3 and C-4. The methoxy carbon resonates at 53.12ppm, further downfield than the methyl signal at 22.21ppm. High resolution mass spectroscopy affords the molecular ion $M^{+}(C_{20}H_{19}NO_4)$ 337.12977. The scope for chemical manipulation provided by such novel and versatile C-3 substituted β-lactams is vast and will therefore be exploited in future research carried out in this group and will include ring opening reactions of the epoxy moiety of these compounds.

4.7 4-Benzoyloxyazetidin-2-ones

4-Acetoxy and 4-benzoyloxy substituted azetidin-2-ones have been extensively used as precursors of β-lactam antibiotics as these ester groups can undergo nucleophilic displacement reactions[176-178]. A method for the synthesis of 4-benzoyloxy-substituted azetidin-2-ones through the copper catalysed reactions of β-lactams with *t*-butylperesters is attempted in this section. Other alternative reports to

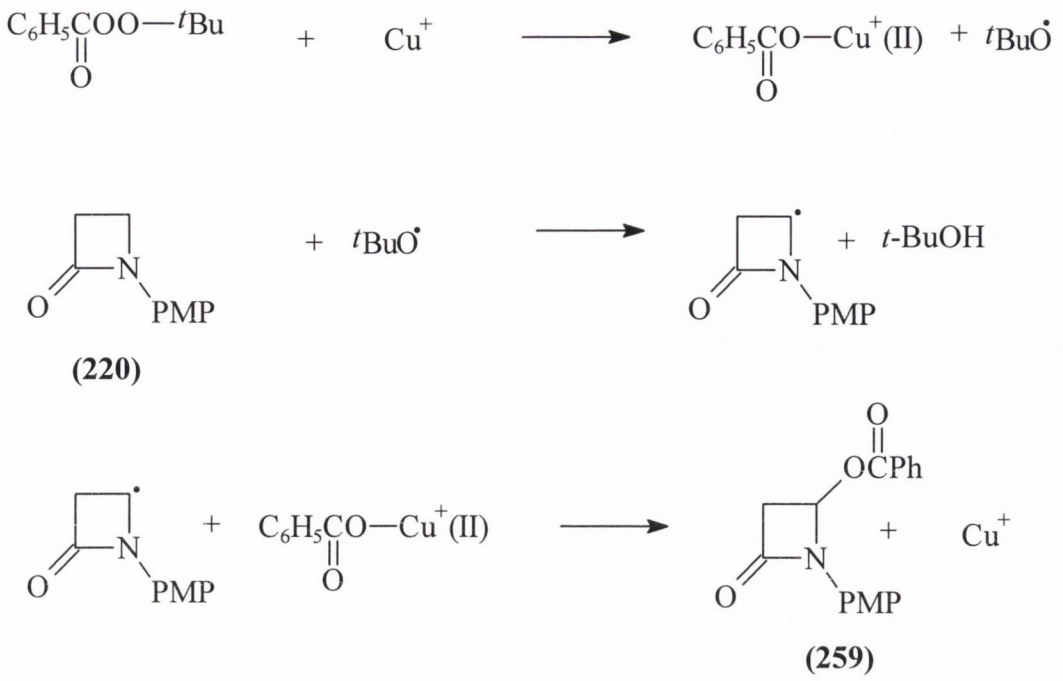
the synthesis of 4-benzoyloxy-substituted azetidin-2-ones involves the conversion of 1-aryl-4-benzoylazetidin-2-ones (**257**) to the corresponding ester (**258**) by employing *m*CPBA (**Scheme 67**)[93].

(257) **(258)**

Scheme 67

The only alternative procedure that has been reported for the direct acyloxylation of β-lactams at the C-4 position involves the electrochemical oxidation of azetidin-2-ones in acetic acid-acetonitrile[179]. This method is an extension of previous work on the introduction of alkoxy substituents through electrolysis of β-lactams[180,181]. It has also been reported that oxidation of *N*-hydroxyazetidines with lead tetraacetate gives the corresponding 1,4-diacetoxyazetidinones, but this process is thought to occur by 1,4 addition of the oxidizing agent to intermediate nitrones, not by direct substitution of β-lactams[182].

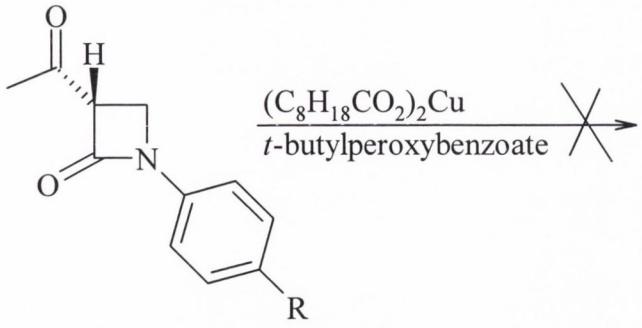
Easton *et al*[183] in 1990 reported that the reaction of 1-(4-methoxyphenyl)azetidin-2-one (**220**) with *t*-butylperbenzoate in the presence of cupric octonate afforded after column chromatography the 4-benzoyloxy-substituted β-lactam in 46% yield. The major features of the mechanism of reactions involving *t*-butylperbenzoate have been elucidated (**Scheme 68**)[184]. Formation of (**259**) may be attributed to hydrogen transfer from (**220**) to the *t*-butoxy radical, followed by benzoate incorporation at the site of hydrogen abstraction. The reaction requires a catalyst i.e. cupric octonate (cuprous ion is the actual catalyst, but a trace is only necessary). Clearly the methylene at the C-4-position is more reactive than the corresponding methylene at the 3-position, and more reactive towards hydrogen transfer presumably because of the activating effect of the adjacent amide nitrogen[185]. This procedure was verified in the present work in an initial experiment and compound (**259**) was obtained in 46% yield.



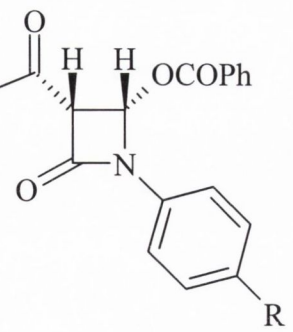
Scheme 68

In the infrared spectrum of 4-benzoyloxy-1-(4-methoxyphenyl)azetidin-2-one (**259**) a broad carbonyl absorption is seen at ν1740cm^{-1} representing the β-lactam carbonyl and the ester. In the ^{1}H-NMR spectrum of (**259**) two double doublets are observed at δ3.17, J=2, J=16Hz and at δ3.63 representing the two protons at C-3. The methoxy protons resonate at δ3.80. H-4 appears as a double doublet at δ6.75, J=2, J=4Hz. A multiplet in the region δ6.80-8.30 represents the remaining aromatic protons.

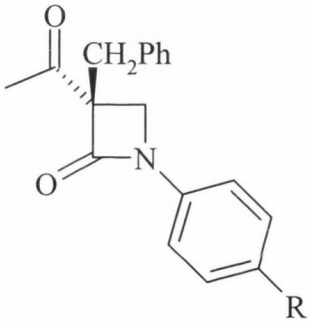
The above methodology was then extended by reacting the following two compounds 3-acetyl-1-(4-methoxyphenyl)azetidin-2-one (**249**) and 3-acetyl-1-(4-methylphenyl)azetidin-2-one (**250**) with *t*-butylperbenzoate and cupric octonate as a possible route to the introduction of a benzoyloxy group at C-4 of the β-lactam ring. The expected products 3-acetyl-4-benzoyloxy-1-(4-methoxyphenyl)azetidin-2-one (**260**) and 3-acetyl-4-benzoyloxy-1-(4-methylphenyl)azetidin-2-one (**261**) were not isolated (**Scheme 69**). Using a combination of spectroscopic techniques together with mass spectrometry the compounds were identified as 3-acetyl-3-benzyl-1-(4-methoxyphenyl)azetidin-2-one (**262**) and 3-acetyl-3-benzyl-1-(4-methylphenyl)azetidin-2-one (**263**).



(249) R=OCH_3
(250) R=CH_3



(260) R=OCH_3
(261) R=CH_3



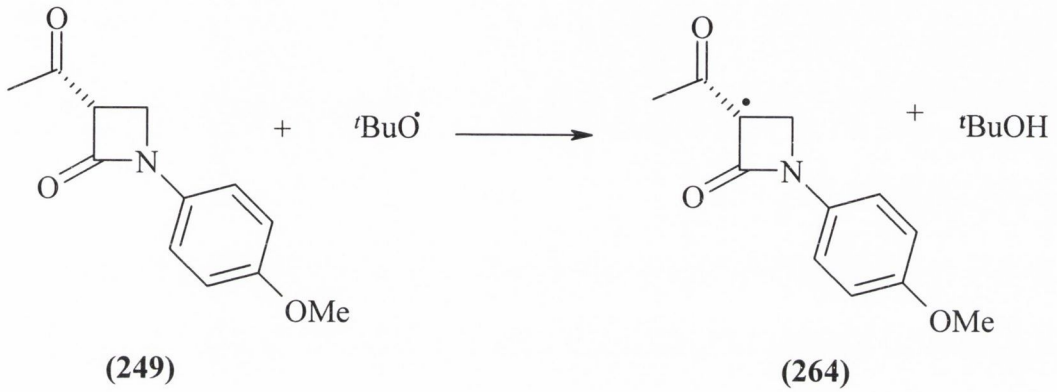
(262) R=OCH_3
(263) R=CH_3

Scheme 69

The following mechanism is proposed for this novel reaction in which a benzyl group has been inserted at C-3 (**Scheme 70**). Step 1 involves the reaction of *t*-butylperoxybenzoate with the Cu^+ complex forming the *t*-butoxyradical and copper (II) complex. In step 2 hydrogen transfer from the more reactive C-3 to the *t*-butoxy radical forming the radical (**264**) is proposed. Hydrogen transfer from toluene to the *t*-butoxy radical forming the radical (**265**) and *t*-butylalcohol. In step 3 the reaction is terminated when the radical (**264**) reacts with the radical (**265**) to form the product (**262**).

STEP 1

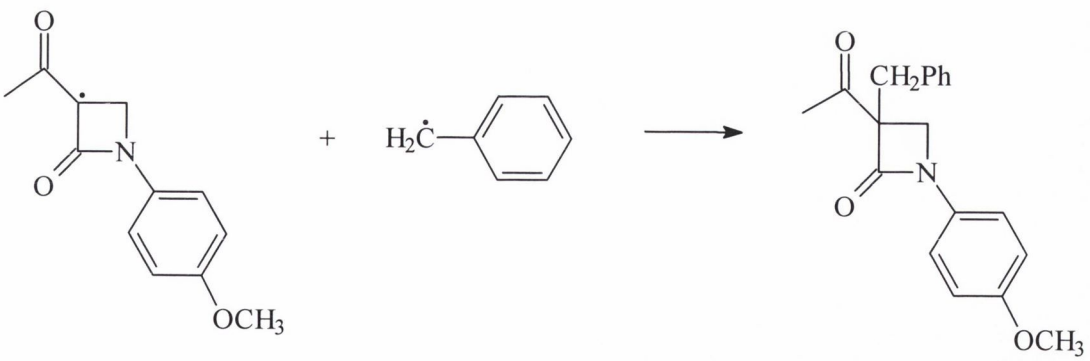
STEP 2



(249) **(264)**

(265)

STEP 3



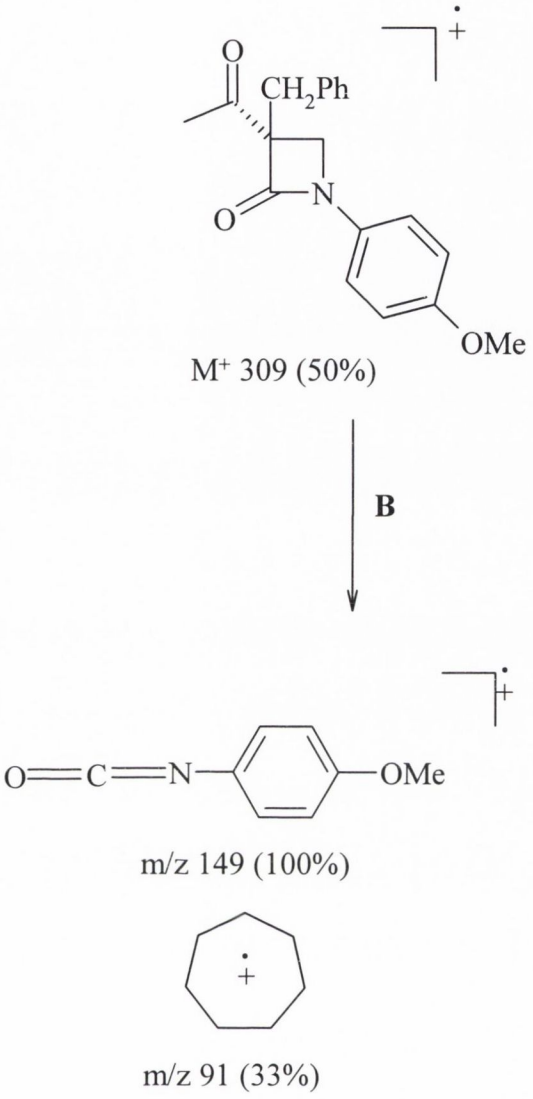
(264) **(262)**

Scheme 70

To attempt to introduce the benzoyloxy group at C-4 the reaction was carried out in benzene but no reaction occurred. It was evident that H-3 of substrates (**249**) and (**250**) was more acidic and more reactive than the H-4 protons under these conditions. Reaction of 3-benzoyl-1-(4-methoxyphenyl)azetidin-2-one was not successful under these conditions in an attempt to introduce the benzoyloxy group at C-4. In conclusion the reaction of C-4 unsubstituted azetidin-2-ones with *t*-butylperoxybenzoate in the presence of a copper catalyst in toluene is a novel method of preparation of 3,3-disubstituted azetidin-2-ones containing C-3 acyl and C-3 benzyl groups. Simple dialkylsubstituted azetidin-2-ones are usually obtained by the Staudinger reaction[80].

Compounds (**262**) and (**263**) were identified by spectroscopic analysis and have not been previously reported. A representative of the two compounds (**262**) is now discussed. In the infrared spectrum of (**262**) the β-lactam carbonyl is seen at $\nu 1747 cm^{-1}$ while the ketone carbonyl is seen at $\nu 1714 cm^{-1}$. In the ^{1}H-NMR spectrum the methyl group at C-3 resonates at δ2.39. The multiplet integrating for three protons at δ3.41-3.49 is due to the methylene group and one of the H-4`s. The other H-4 resonates as a doublet downfield at δ4.10, J=6Hz. The aromatic protons integrating for nine hydrogens appear as a multiplet in the region δ6.80-8.16ppm.

In the ^{13}C-NMR spectrum five quaternary carbons are visible which as expected disappear in the DEPT spectrum. These signals are assigned as follows; 202.46 (ketone carbonyl), 162.50ppm (β-lactam carbonyl), 156.03ppm (C-4`), 134.68 ppm (C-1`), 70.56ppm (C-3). Two signals at 117.40ppm and 113.97ppm are readily assigned to C-2` and C-6` and C-3` and C-5`. The other aromatic carbons appear in the region 126.87ppm to 134.67ppm. The methoxy carbon resonates at δ55.04 downfield from C-4 at 44.88ppm and the methylene and methyl carbons at 36.46ppm and 26.92ppm complete the spectrum. The molecular ion $M^{+}C_{19}H_{19}NO_3$ is observed at m/z 309.13852 in 50% abundance. Process B splitting can also be noted with the isocyanate fragment at m/z 149 as the base peak. The benzyl fragment is seen at m/z 91 in an abundance of 33% (**Scheme 71**).



Scheme 71

4.8: Summary

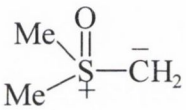
Investigation of benzoyloxyation at the C-4 position of azetidin-2-ones resulted in the novel synthesis of 3-acyl, 3-benzyl disubstituted azetidin-2-ones. The formation of azetidin-2-ones with α, β-unsaturated ketone substituent at C-3 was achieved with the future objective of utilising these compounds as intermediates for the corresponding novel C-6 carbapenems. The aldol condensation, oxidation and epoxidation reaction sequence offers an efficent route to additional C-3 functionalised azetidin-2-ones.

Chapter 5

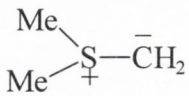
Reactions of 3-Alkyl and 3-Vinyl-4-formylazetidin-2-ones with Sulphur ylides

5.1 Introduction

The objective of this chapter is the reaction of 3-vinyl and 3-alkyl β-lactams containing a 4-formyl group with sulphur ylides as a method for the introduction of an epoxide at C-4. The ready accessibility of a wide variety of epoxides in racemic or chiral form has made them popular intermediates in organic synthesis[192]. For example numerous methods are available for their conversion to the corresponding allylic alcohols already mentioned[193]. Epoxides can also be alkylated by phosphorus and oxosulphonium ylides leading generally to phosphoranes[194] and oxetanes[195] respectively. The use of dimethyloxosulphonium methylide (**266**) and dimethylsulphonium ylide (**267**) to generate epoxides from carbonyl compounds is well known[196].

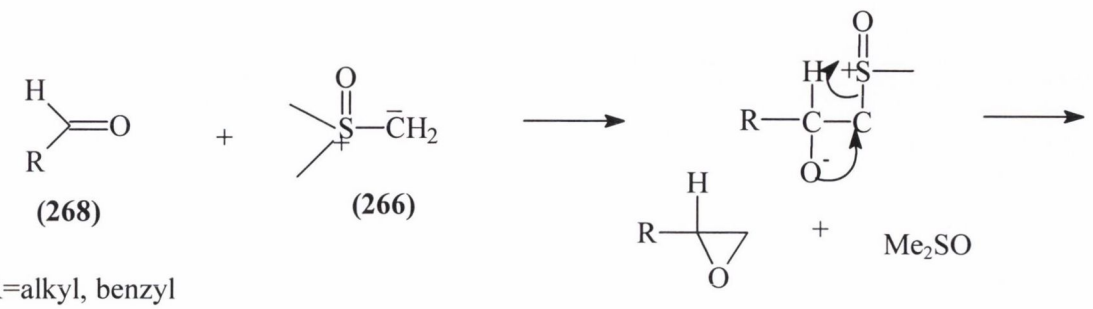


(266)



(267)

There are many examples of the formation of epoxides via reaction of carbonyl compounds with sulphur ylides reported in the literature e.g. Ihara *et al*[197] reported that reaction of excess trimethyloxosulphonium iodide with an aldehyde in dimethylsulphoxide afforded the corresponding epoxide. The generally accepted mechanism[120] for the reaction between sulphur ylides and aldehydes or ketones is shown in **Scheme 72**. The base sodium hydride abstracts a proton from the sulphur ylide (trimethyloxosulphonium iodide) generating the ion dimethyloxosulphonium methylide (**266**) which undergoes nucleophilic substitution at the carbonyl centre of the appropriate aldehyde or ketone (**268**). Loss of Me_2SO generates the epoxide (**269**).

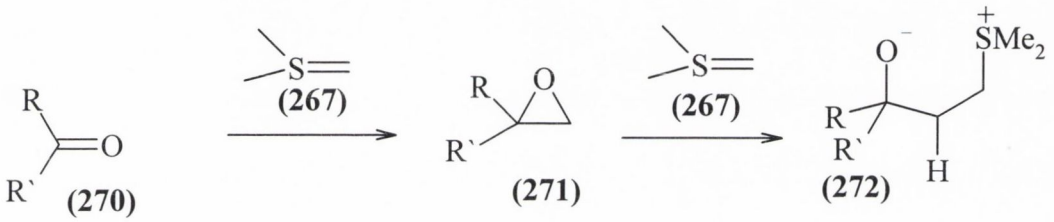


(268) **(266)** **(269)**

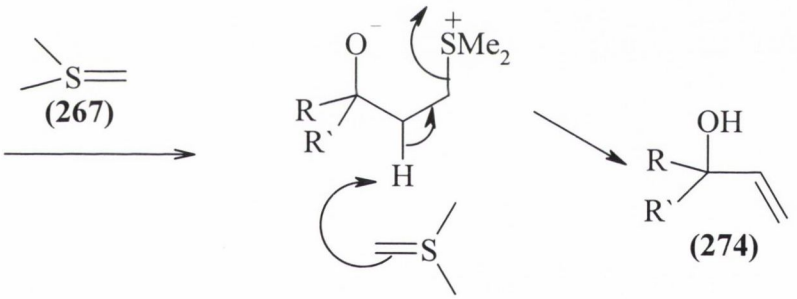
R=alkyl, benzyl

Scheme 72

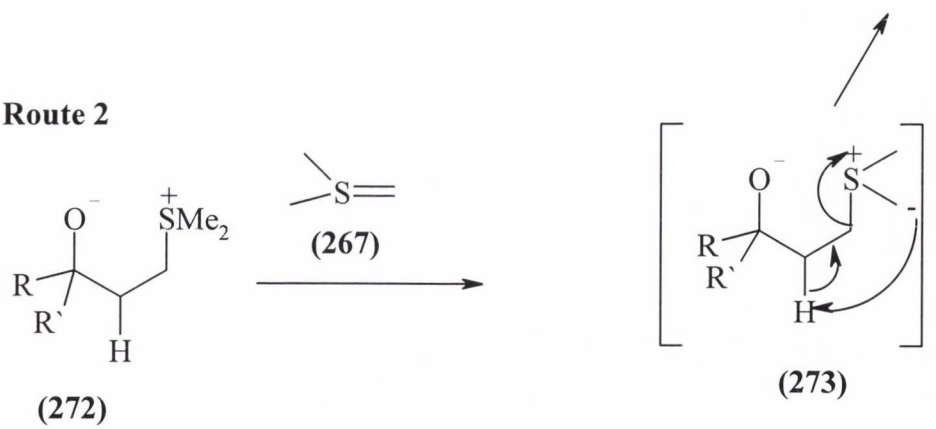
Harnett *et al* in 1994[198] demonstrated further synthetic utility, reaction of excess dimethylsulphonium ylide (**267**) with various ketones and aldehydes resulted in a convenient synthesis of homologated allylic alcohols in moderate to good yields. Their data suggest that the allylic alcohol (**274**) obtained from the carbonyl (**270**) results from a double methylene transfer by two molecules of ylide (**267**) via the initially formed epoxide (**271**) and intermediate (**272**) as shown in (**Scheme 73**). The two routes described can be envisioned to account for the formation of (**274**) whether the betaine intermediate undergoes α, β-elimination (**route 1**) or is deprotonated to the species (**273**) which then undergoes an α, β-elimination (**route 2**).



Route 1



Route 2

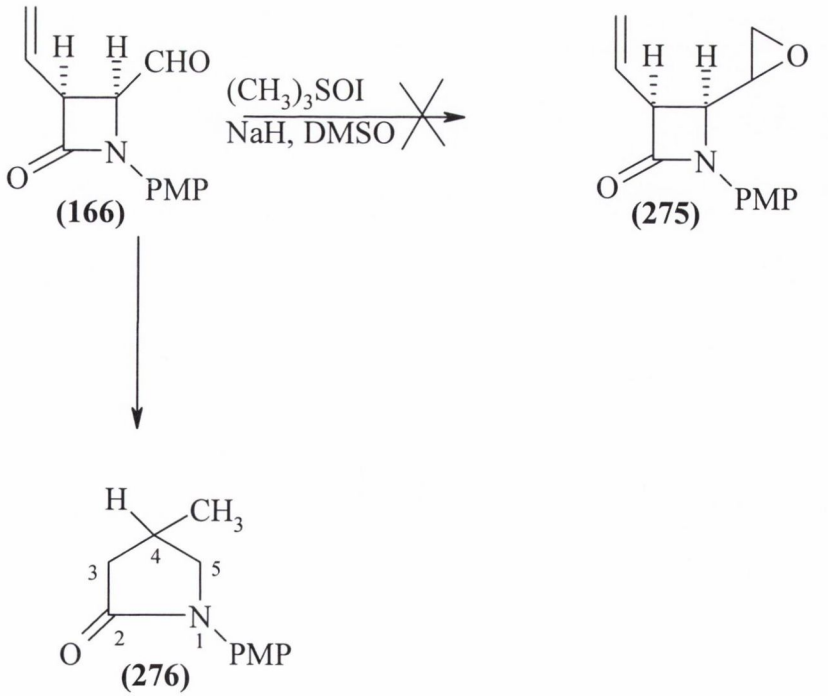


R=alkyl, H
R`=alkyl, benzyl

Scheme 73

5.2 4-Methyl-1-(4-methoxyphenyl)-2-pyrrolidinone

Harnett's method[198] was applied to the following work by reacting 4-formyl-3-vinylazetidin-2-one (**166**) previously prepared in Chapter 3 with *n*-butyllithium and trimethylsulphonium iodide as a possible route to the introduction of an allylic type substituent at C-4 of the β-lactam ring. The reaction product could not be isolated as extensive decomposition was observed during column chromatography. Ihara's literature procedure[197] was also applied to the following work. 4-Formyl-3-vinylazetidin-2-one (**166**) was reacted with sodium hydride and excess dimethyloxosulphonium iodide in DMSO. The expected epoxide (**275**) was not obtained (**Scheme 74**). The reaction was carried out under reaction conditions varying from two equivalents of sodium hydride and dimethyloxosulphonium iodide to seven equivalents. Reaction of 4-formyl-3-vinyl-1-(4-methoxyphenyl)azetidin-2-one (**166**) was observed when both seven equivalents of trimethyloxosulphonium iodide and sodium hydride were used yielding the unexpected product (**276**).



Scheme 74

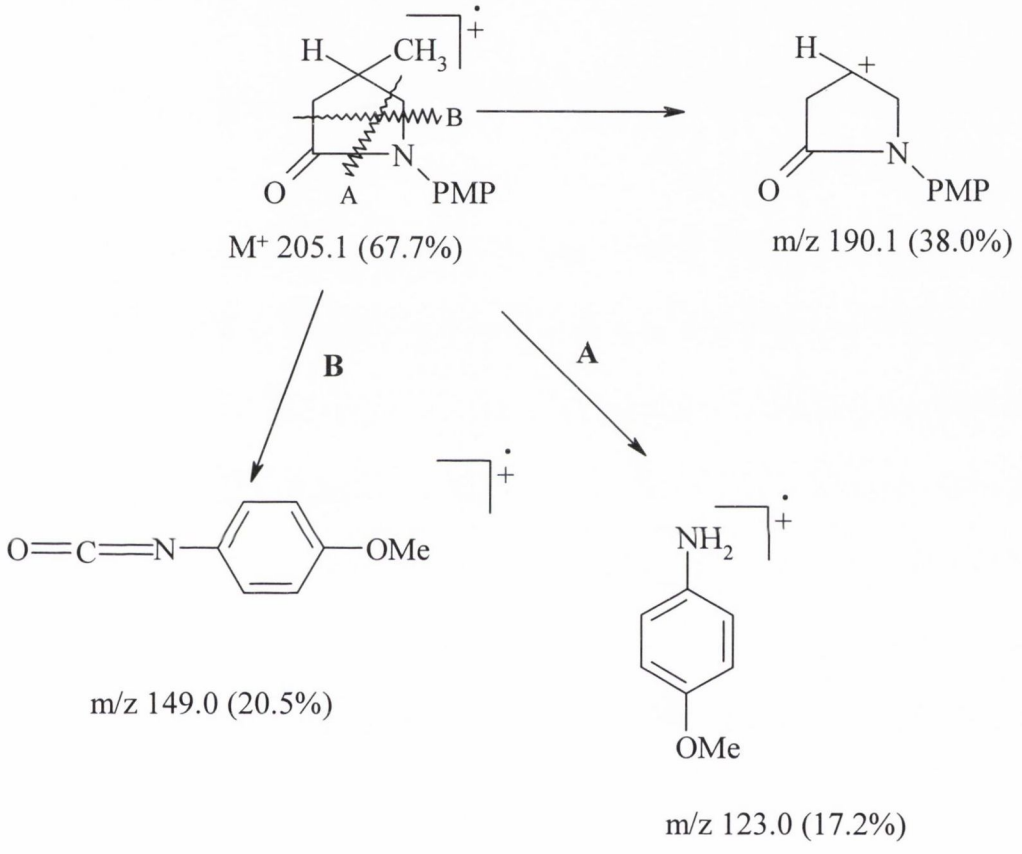
This product was obtained as a colourless oil in 65% yield, and proved on spectroscopic analysis not to be the expected product (**275**). Using a combination of spectroscopic techniques together with the high resolution mass spectrometry the pyrrolidinone structure (**276**) was proposed as the product.

The infrared spectrum for compound (**276**) displays the carbonyl stretching frequency at $\nu 1700 cm^{-1}$ indicating that the β-lactam carbonyl is no longer present and indicating the presence of a pyrrolidinone carbonyl. The ^{1}H-NMR spectrum reveals a doublet at δ1.22 integrating for three hydrogens which is assigned to the methyl protons (J=6.6Hz). A double doublet at δ2.25 is assigned to one of the H-3 protons (J_{gem}=16.57Hz, $J_{3a,4}$=7.02Hz). The other H-3 proton also appears as a double doublet at δ2.75 (J_{gem}=16.57Hz, $J_{3b,4}$=8.53Hz) due to geminal coupling and coupling with the proton at C-4. H-4 appears as a multiplet at δ2.55 due to its coupling with both the methylene protons at C-3, C-5 and the methyl protons at C-4. One of the H-5 protons resonates at δ3.43 integrating for one proton as a double doublet (J_{gem}=19.07Hz, $J_{5a,4}$=6.53Hz) and the other H-5 proton appearing at δ3.91 (J_{gem}=19.06Hz, $J_{5b,4}$=7.53Hz). The methoxy protons appear at δ3.83 while the chemically equivalent aromatic hydrogens H-3` and H-5` resonate at δ6.90, as an apparent doublet displaying coupling to H-2` and H-6` at δ7.47, J=9.04Hz. The 2D H-H COSY NMR spectrum showed coupling of H-4 to H-3 and H-5. (The H-H COSY NMR technique identifies protons which are coupled to each other in a compound).

In the ^{13}C-NMR spectrum three quaternary carbons are identified which as expected disappear in the DEPT spectrum. These signals are assigned as follows 175.24ppm (C=O), 156.03ppm (C-4`), 136.97ppm (C-1`). Two signals at 121.36ppm and 113.35ppm are readily assigned to the pairs C-2` and C-6`, C-3` and C-5` respectively. The methoxy carbon resonates at 55.40ppm. The signals seen at 56.29ppm and 40.76ppm are assigned to C-5 and C-3 and are inverted in the DEPT 135 spectrum while C-4 appears at 26.30ppm. The methyl carbon at 13.69ppm completes the spectrum. The chemical shift values were confirmed by analysing the C-H COSY (HETCOR) NMR spectrum. (The C-H COSY NMR technique shows the correlation between carbon signals and signals for hydrogens to which they are bonded).

High resolution mass spectrometry proved satisfactory for the pyrrolidinone compound (**276**) (**Scheme 75**). The proposed fragmentation patterns A and B are

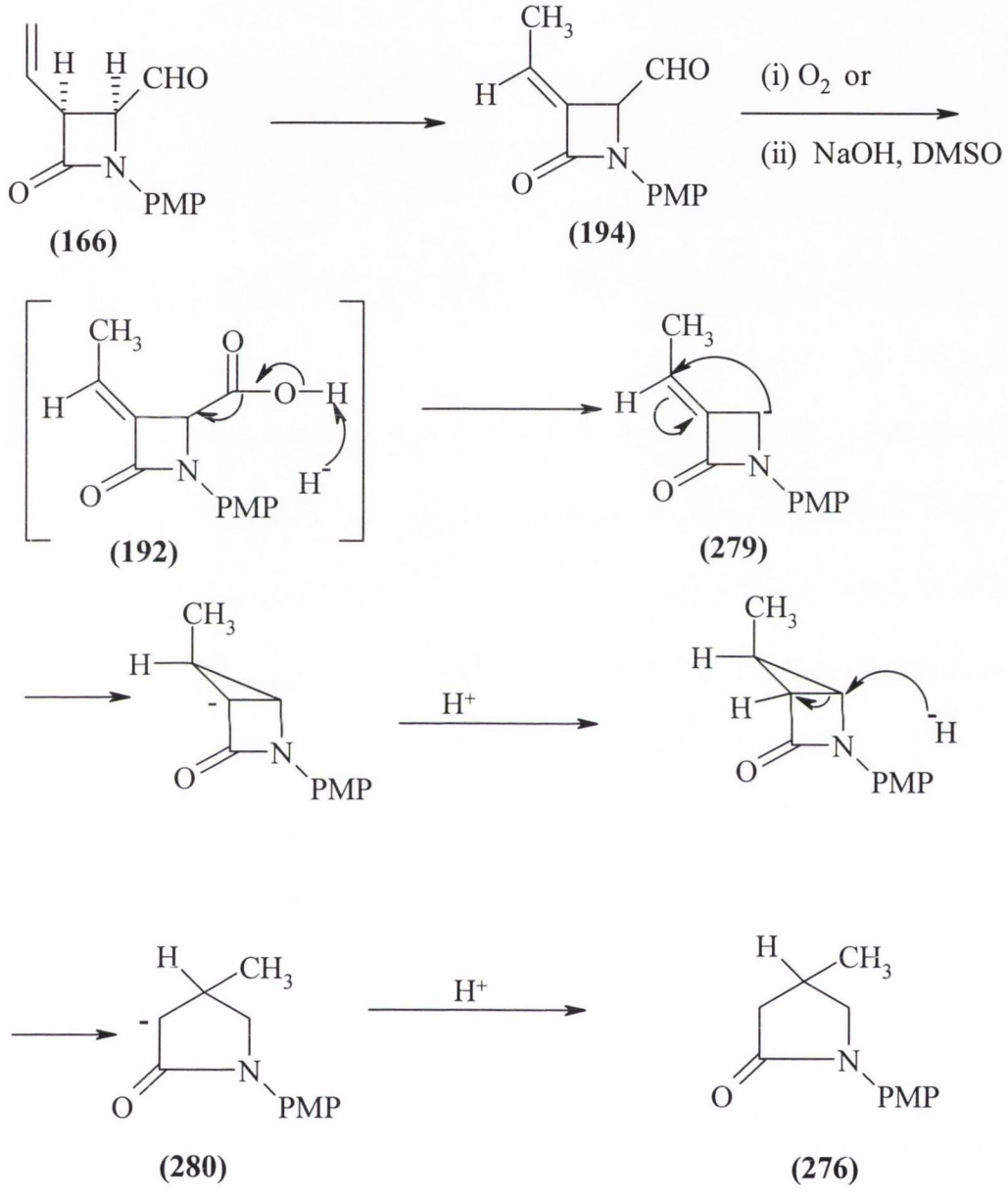
shown which are similar to those previously discussed for the azetidin-2-one ring. The molecular ion M^+ ($C_{12}H_{15}NO_2$) is observed at m/z 205.1119 in 67.7% abundance. Fragmentation shown by process A yields the amine fragment at m/z 123.0 in 17.2% abundance. Process B splitting can also be noted with the isocyanate fragment at m/z 149.0 in 20.5% yield. Loss of a methyl group yields the fragment at 190.1 in 38.0% abundance.



Scheme 75

The following mechanism has been proposed for the formation of compound (**276**) (**Scheme 76**). It is believed that the vinyl group at C-3 of 4-formyl-3-vinyl-1-(4-methoxyphenyl)azetidin-2-one (**166**) undergoes hydride mediated isomerisation with sodium hydride yielding *E*-3-ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**194**). This isomerisation was previously discussed for the reaction with $NaBH_4$. This compound subsequently is converted to the acid derivative (**192**) either via oxidation in air or via a Cannizzaro type reaction. It is proposed that this reaction occurs in the workup. The alcohol product is not isolated and it is proposed that this compound degraded as extensive decomposition was observed after column chromatography. Loss of CO_2 in the presence of base[120] resulted in the formation of the intermediate

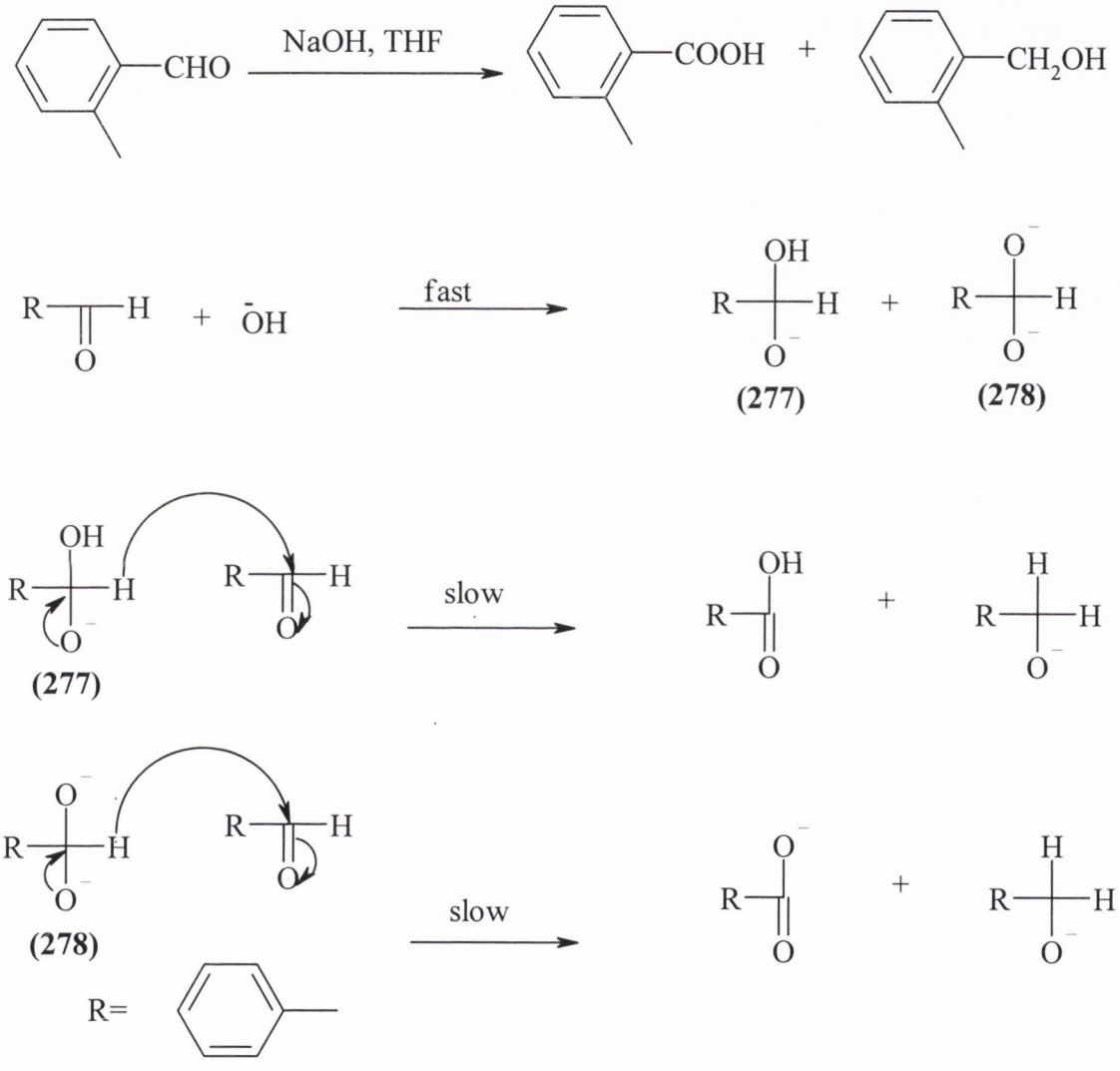
(**279**). This compound (**279**) subsequently forms a five membered ring (**280**) (However, Baldwin *et al* [199a] reported that for trig reactions exo trig reactions are more favourable than endo) and addition of H^+ generates the product 4-methyl-1-(4-methoxyphenyl)-2-pyrrolidinone (**276**).



Scheme 76

Support for the proposed mechanism comes from the following. There are many reported examples of oxidation of an aldehyde to an acid while leaving to stand in air[120, 199b]. Ashby *et al*[200] reported that the Cannizzaro reaction proceeds well with substituted aldehydes i.e 2-methylbenzaldehyde with sodium hydroxide resulted in the formation of the corresponding acid and alcohol products. The mechanism[120, 201] of the Cannizzaro reaction involves the addition of a hydroxy ion to the C=O to give (**277**) which may lose a proton in the basic solution to give the diion (**278**). The strong electron donating character of O^- greatly facilites the ability of the aldehydic hydrogen

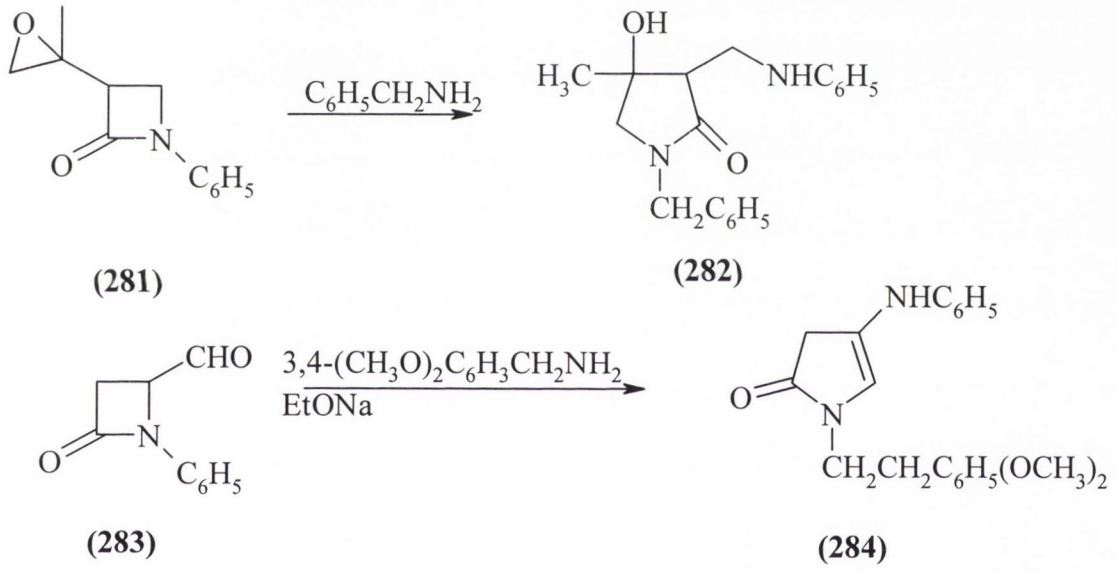
to leave with its electron pair. Of course this effect is even stronger in (**278**). When the hydride does leave it attacks another molecule of aldehyde. The hydride can come from (**277**) or (**278**). If the hydride ion comes from (**277**), the final step is a rapid proton transfer. In the other case the acid salt is formed directly and the alkoxide acquires a proton from the solvent. The overall outcome of the Cannizzaro reaction is the formation of both acid and alcohol products (**Scheme 76**).



Scheme 77

This ring transformation is unexpected but however there are many examples of structurally diverse heterocycles formed from β-lactams. The four membered heterocyclic β-lactam ring possesses high chemical activity as its amide bond may be easily cleaved readily by weak nucleophiles such as amines and alcohols. Therefore azetidin-2-ones have been utilised as starting materials for the synthesis of many heterocyclic compounds, while the ring transformation of β-lactams to indenones,

quinolones, butenolides and pyrroles has also been reported[202,204a]. Kano and co-workers have carried out extensive studies in this area, reporting the aminolysis of β-lactam epoxides and aldehydes to afford pyrrolidinone type compounds[203]. They investigated the aminolysis of 3-(α, β-epoxyisopropyl)-1-phenyl-2-azetidin-2-one (**281**) yielding 3-anilinomethyl-1-benzyl-4-hydroxy-4-methyl-2-pyrrolidinone (**282**). They also examined the aminolysis of 4-formyl-1-phenyl-2-azetidin-2-one (**283**) with 3,4-dimethoxyphenylamine in ethanol under reflux, followed by further heating in the presence of sodium ethoxide under reflux afforded 4-anilino-2,3-dihydro-1-(3,4-dimethoxyphenethyl)-2-oxopyrrole (**284**) (**Scheme 78**). It is of interest these 2-azetidinones are found to be useful precursors for the preparation of the 4-hydroxy-2-pyrrolidinone system and the pyrrolidin-2,4-dione analogues.



(281) **(282)**

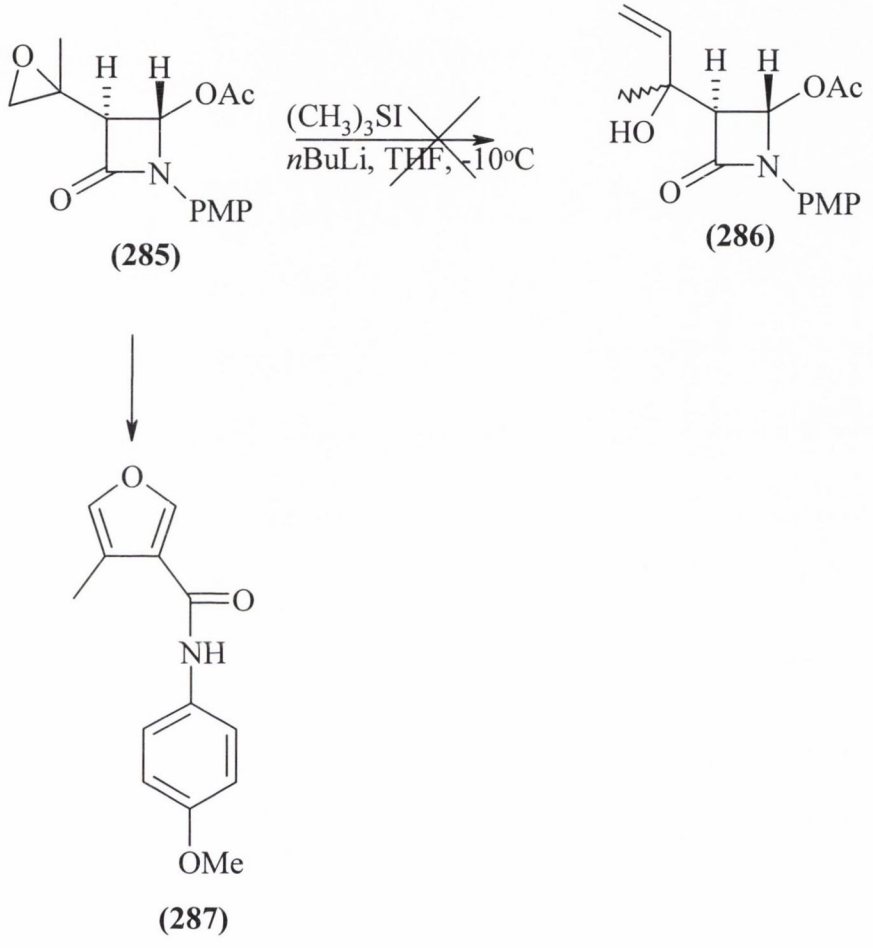
(283) **(284)**

Scheme 78

Work carried out in our research group[116] reported that reaction of 4-acetoxy-3-[2-(1,2-epoxy)propyl]-1-(4-methoxyphenyl)azetidin-2-one (**285**) with *n*-butyllithium and trimethylsulphonium iodide, as a possible route to the introduction of an allylic alcohol type substituent at C-3 of the β-lactam ring did not yield the expected product (**286**) but the unexpected 4-methylfuran-3-[1-(4-methoxyphenyl]carboxamide (**287**) (**Scheme 79**).

Bhagwat *et al*[204b] in 1996 reported the synthesis of 2-pyrrolidinones as endothelin receptor antagonists via a [2+2] cycloaddition of the appropriate amine and an enantiomerically pure acid chloride to give the β-lactam product, which rearranged

in acid and methanol to give the corresponding pyrrolidinone. The formation of 2-pyrrolidinone by Rh(I)-catalysed hydrocarbonylation of alkynes in the presence of primary amines has been reported previously in the literature[204c]. These structures are claimed to be anticonvulsant agents[204d]. Compound (**276**) has not been synthesised or reported before.

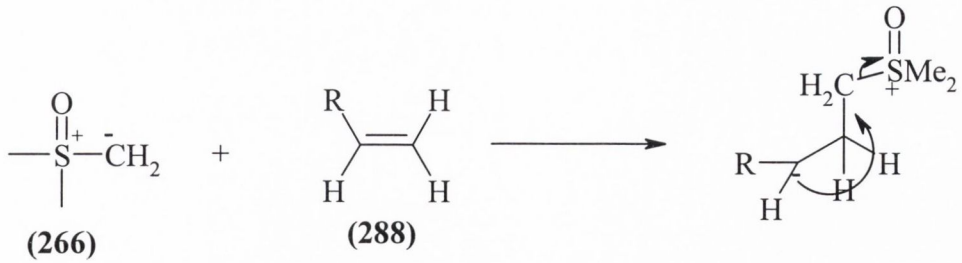


Scheme 79

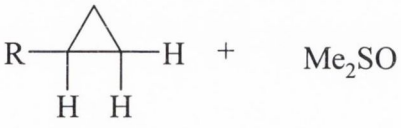
5.3 Reaction of 3-alkyl-4-formylazetidin-2-ones with sulphur ylides

Aldehydes and ketones can be converted to epoxides in good yields with the sulphur ylides dimethyloxosulphonium iodide and dimethylsulphonium iodide in the presence of base. Alkenes also react with sulphur ylides to form cyclopropane derivatives. The mechanism is shown (**Scheme 80**). Base abstracts a proton from trimethyloxosulphonium iodide forming the dimethylsulphonium methylide (**266**)

which then undergoes nucleophilic addition with the vinyl compound (**288**). Loss of Me_2SO yields the compound (**289**)[120].



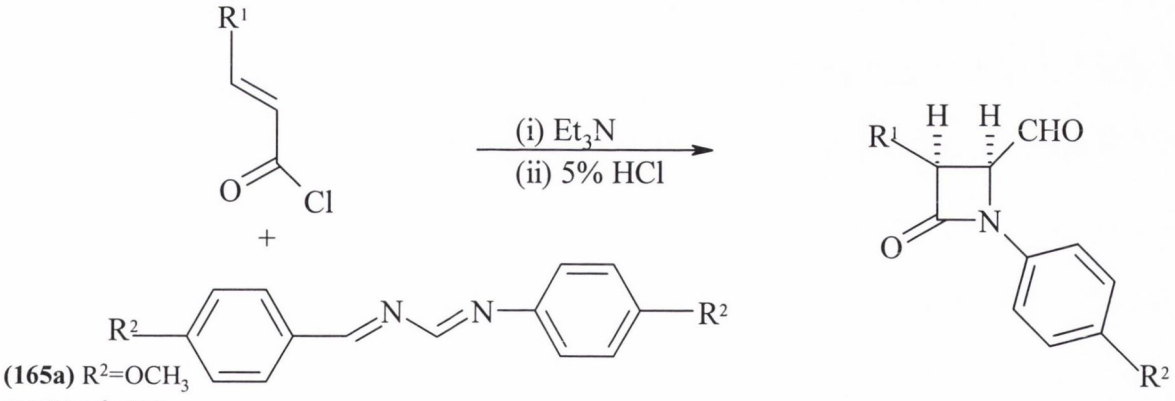
(266) **(288)**



(289)

Scheme 80

The following 3-alkyl-4-formyl β-lactams were prepared with the objective of reacting these less functionalised compounds at C-3 with sulphur ylides eliminating possible chemical transformation seen with 3-vinyl substituents. A series of 3-alkyl-4-formylazetidin-2-ones (**290**)-(**297**) were obtained from their corresponding diimines (**165a**) and (**165b**) via the procedure described in Chapter 2 (**Scheme 81**). The spectroscopic details of compounds of (**290**)-(**297**) are given in **Table 21**.



(165a) $R^2=OCH_3$
(165b) $R^2=CH_3$

(290) $R^1=CH_3$, $R^2=OCH_3$
(291) $R^1=CH_2CH_3$, $R^2=OCH_3$
(292) $R^1=CH_2CH_2CH_3$, $R^2=OCH_3$
(293) $R^1=CH(CH_3)_2$, $R^2=OCH_3$
(294) $R^1=CH_3$, $R^2=CH_3$
(295) $R^1=CH_2CH_3$, $R^2=CH_3$
(296) $R^1=CH_2CH_2CH_3$, $R^2=CH_3$
(297) $R^1=CH(CH_3)_2$, $R^2=CH_3$

Scheme 81

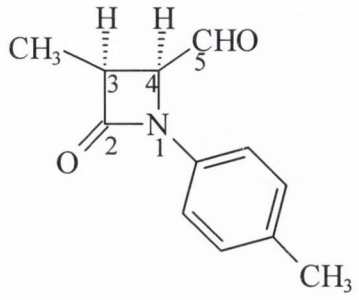
Table 21: Spectroscopic details for compounds (290)-(297)

Compound No.	IRν_{max} (KBr or film)cm^{-1}	^{1}H-NMR Data δ ($CDCl_3$)
290	1750 (C=O) 1735 (CHO)	1.24 (3H, d, J=15Hz, CH_3), 3.68 (1H, dd, $J_{3,4cis}$=6.42Hz, $J_{3,5}$=15.0Hz, H-3), 3.74 (3H, s, -OCH_3), 4.45 (1H, dd, $J_{4,3cis}$=6.42Hz, $J_{4,6}$=3.0Hz, H-4), 6.83 (2H, d, J=9Hz, H-3` and H-5`), 7.19 (2H, d, J=9Hz, H-2` and H-6`), 9.80 (1H, d, $J_{6,4}$=3.0Hz, H-6).
291	1751 (C=O) 1736 (CHO)	1.08 (3H, t, J=7.02Hz, CH_3), 2.56 (2H, m, CH_2), 3.54 (1H, dd, $J_{3,4cis}$=6.56Hz, $J_{3,5}$=6.0Hz, H-3), 3.81 (3H, s, -OCH_3), 4.46 (1H, dd, $J_{4,3cis}$=6.56Hz, $J_{4,6}$=3.52Hz), 6.84 (2H, d, J=9.04Hz, H-3` and H-5`), 7.21 (2H, d, J=9.04Hz, H-2` and H-6`), 9.85 (1H, d, $J_{6,4}$=3.52Hz, -CHO).
292	1750 (C=O) 1732 (CHO)	0.97 (3H, t, J=7.52 Hz, CH_3), 1.45-1.85 (4H, m, 2xCH_2), 3.65 (1H, dd, $J_{3,4cis}$=6.52Hz, $J_{3,5}$=7.52Hz, H-3), 3.81 (3H, s, -OCH_3), 4.47 (1H, dd, $J_{4,3cis}$=6.52Hz, $J_{4,8}$=3.04Hz, H-4), 6.87 (2H, d, J=9.04Hz, H-3` and H-5`), 7.24 (2H, d, J=9.04Hz, H-2` and H-6`), 9.87 (1H, d, $J_{8,4}$=3.04Hz, –CHO).
293	1755 (C=O) 1735 (CHO)	0.94 (3H, d, J=6.6Hz, CH_3), 1.19 (3H, d, J=6.6Hz, CH_3), 2.02-2.20 (1H, m, CH), 3.34 (1H, dd, $J_{3,4cis}$=6.0Hz, $J_{3,5}$=10.3Hz, H-3), 3.76 (3H, s, -OCH_3), 4.43 (1H, dd, $J_{4,3cis}$=6.0Hz, $J_{4,6}$=4.2Hz, H-4), 6.84 (2H, d, J=9.3Hz, H-3` and H-5`), 7.21 (2H, d, J=9.3Hz, H-2` and H-6`), 9.88 (1H, d, $J_{6,4}$=4.2Hz).

Table 21 continued

Compound No.	IRν_{max} (KBr or film)cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
294	1755 (C=O) 1735 (CHO)	1.35 (3H, d, J=8.04Hz, CH_3), 2.10 (3H, s, CH_3), 3.73 (1H, m, H-3), 4.49 (1H, dd, $J_{4,3cis}$=6.52Hz, $J_{4,5}$=3.52Hz, H-4), 7.16 (2H, d, J=8.56Hz, H-2` and H-5`), 7.20 (1H, d, J=8.56Hz), H-2` and H-6`), 9.86 (1H, d, $J_{5,4}$=3.52Hz, CHO).
295	1751 (C=O) 1733 (CHO)	1.11 (3H, t, J=7.56Hz, CH_3), 2.20 (3H, s, CH_3), 3.58 (1H, dd, $J_{3,4cis}$=6.04Hz, $J_{3,5}$=8.52Hz, H-3), 3.00-3.75 (2H, m, CH_2), 4.48 (1H, dd, $J_{4,3cis}$=6.04Hz, $J_{4,6}$=3.48Hz), 7.16 (2H, d, J=8.04Hz, H-3` and H-5`), 7.19 (2H, d, J=8.04Hz, H-2` and H-6`), 9.88 (1H, d, $J_{6,4}$=3.48Hz, CHO).
296	1753 (C=O) 1731 (CHO)	0.97 (3H, t, J=7Hz, CH_3), 1.20-1.80 (4H, m, 2x CH_2), 2.31 (3H, s, CH_3), 3.65 (1H, dd, $J_{3,4\ cis}$=6.26Hz, $J_{3,5}$=14.3Hz, H-3), 4.48 (1H, dd, $J_{4,3cis}$=6.26Hz, $J_{4,8}$=3.52Hz, H-4), 7.19 (2H, d, J=8.04Hz, H-3` and H-5`), 7.23 (2H, d, J=8.04Hz, H-2` and H-6`), 9.87 (1H, d, $J_{8,4}$=3.52Hz, CHO).
297	1755 (C=O) 1731 (CHO)	0.97 (3H, d, J=6.52Hz, CH_3), 1.24 (3H, d, J=6.52Hz, CH_3), 2.14-2.17 (1H, m, CH), 2.31 (3H, s, CH_3), 3.38 (1H, dd, $J_{3,4cis}$=6.04Hz, $J_{3,5}$=10.5Hz, H-3), 4.47 (1H, dd, $J_{4,3cis}$=6.04Hz, $J_{4,6}$=4.02Hz, H-4), 7.15 (2H, d, J=8.52Hz, H-3` and H-5`), 7.20 (2H, d, J=8.52Hz, H-2` and H-6`), 9.92 (1H, d, $J_{6,4}$=4.02Hz, CHO).

The infrared spectrum for 4-formyl-3-methyl-1-(4-methylphenyl)azetidin-2-one (**294**) displays the characteristic β-lactam carbonyl band at ν1755cm^{-1} downfield from the aldehyde absorption at ν1730cm^{-1}.



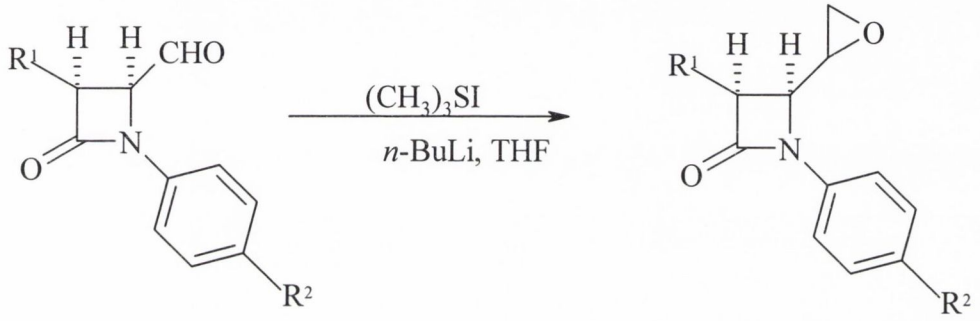
(294)

The ^{1}H-NMR spectrum exhibits the aromatic methyl protons as a singlet at δ2.10, downfield from the C-3 methyl at δ1.35 which appears as a doublet due to its coupling with a nearby proton with a coupling constant of 8.04Hz. A multiplet integrating for one hydrogen can be assigned to H-3 at δ3.73-3.75 which couples to both H-4 and the neighbouring methyl group. A double doublet integrating for one hydrogen can be assigned to H-4 at δ4.49 and is coupled to both H-3 and H-5, ($J_{4,3cis}$=6.52Hz, $J_{4,5}$=3.52Hz) illustrating that H-3 and H-4 are in a *cis* arrangement. The aromatic protons are easily assignable: a doublet at δ7.16 representing H-3` and H-5`, J=8.56Hz, while H-2` and H-6` resonate at δ7.20, J=8.56Hz. A doublet resonating at δ9.86 represents the aldehyde hydrogen which couples to H-4, $J_{5,4}$=3.52Hz. This chemical shift value is characteristic of aldehyde protons in general which are deshielded by the carbonyl group present resulting in their downfield position.

Ten signals are observed in the ^{13}C-NMR spectrum. Four quaternary carbons are evident as the signals disappear in the DEPT spectrum. They may be assigned as follows: 199.70ppm (representing the aldehyde carbonyl carbon), 165.33ppm (β-lactam carbonyl), 159.45 (C-4`), and 131.31 (C-1`). The aromatic carbons C-2`, C-6` and C-3`, C-5` are seen at 129.39ppm and 115.81ppm. C-4 and C-3 both appear within the same region 56.69ppm and 47.91ppm. They are followed by the methyl carbons appearing at 20.41ppm and 9.52ppm respectively. The molecular ion $M^{+}(C_{12}H_{13}NO_2)$ is observed at m/z 203 in 65% abudance.

In the present work transformation of 3-alkyl-4-formyl-1-(4-methoxyphenyl) and 3-alkyl-4-formyl-1-(4-methylphenyl)azetidin-2-ones to their corresponding 3-

alkyl-4-(1,2-epoxyethyl)azetidin-2-ones is discussed. When the aldehydes (**291**), (**292**) and (**296**) were reacted with a suspension of trimethylsulphonium iodide and *n*-butyllithium in tetrahydrofuran at –70°C the following epoxides (**298**)-(**300**) were obtained in low yield (**Scheme 82**). Reaction of the remaining aldehydes (**293**)-(**295**) and (**297**) with a suspension of trimethylsulphonium iodide and *n*-butyllithium in tetrahydrofuran at –70°C gave relatively unstable compounds which could not be isolated as extensive decomposition was observed after column chromatography.



(292) R^1=$CH_3CH_2CH_2$, R^2=OCH_3
(291) R^1=CH_3CH_2, R^2=OCH_3
(296) R^1=$CH_3CH_2CH_2$, R^2=CH_3

(298) R^1=$CH_3CH_2CH_2$, R^2=OCH_3
(299) R^1=CH_3CH_2, R^2=OCH_3
(300) R^1=$CH_3CH_2CH_2$, R^2=CH_3

Scheme 82

Compounds (**298**)-(**300**) were isolated by column chromatography and these epoxides proved to be very unstable and were thus obtained in poor yield. Characterisation of each compound using spectroscopic analysis and high resolution mass spectrometry proved to be satisfactory. The yields, molecular formulae, molecular ions and reaction conditions are given in **Table 22**, while the spectroscopic details are given in **Table 23**.

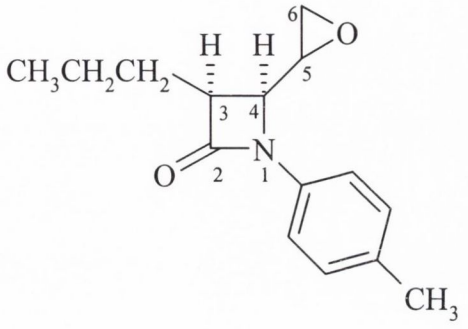
Table 22: Yield, molecular formula, molecular ion and reaction conditions for compounds (298)-(300)

Compound No.	Yield %	Molecular formula	Mass spectrometry M^+	NaH (eq)	Me_3SI (eq)
298	37	$C_{15}H_{19}NO_3$	261.1351	3.3	6
299	40	$C_{14}H_{17}NO_3$	247.1186	3.3	6
300	30	$C_{15}H_{19}NO_2$	245.1395	3.3	6

Table 23: Spectroscopic details for compounds (298)-(300)

Compound No.	IR ν_{max} (film)cm^{-1}	^{1}H-NMR Data δ ($CDCl_3$)
298	1750 (C=O) 1231, 942, 750 (epoxy C-O)	1.00 (3H, t, J=6Hz, CH_3), 1.65 (2H, m, CH_2), 1.85 (2H, m, CH_2), 2.67 (1H, dd, J_{gem}=5.04Hz, $J_{6,5}$=3Hz, H-6), 3.13 (1H, dd, J_{gem}=5.04Hz, $J_{6,5}$=2.6Hz, H-6), 3.17-3.19 (1H, m, H-5), 3.41-3.44 (1H, m, H-3), 3.55 (1H, dd, $J_{4,3cis}$=6.04Hz, J=7.78Hz, H-4), 3.79 (1H, s, -OCH_3), 6.88 (2H, d, J=9.04Hz, C-3` and C-5`), 7.55 (2H, d, J=9.04Hz, C-2` and C-6`).
299	1750 (C=O) 1235, 950, 751 (epoxy C-O)	1.17 (3H, t, J=8.52Hz, CH_3), 1.80-2.00 (2H, m, CH_2), 2.70 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=2.52Hz, H-6), 2.97 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=3Hz, H-6), 3.13-3.16 (1H, m, H-5), 3.31-3.37 (1H, m, H-3), 3.58 (1H, dd, $J_{4,3cis}$=5.52Hz, $J_{4,5}$=7.78Hz, H-4), 3.80 (3H, s, -OCH_3), 6.90 (2H, d, J=9.04Hz, H-3` and H-5`), 7.56 (2H, d, J=9.04Hz, H-2` and H-6`).
300	1750 (C=O) 1230, 940, 751 (epoxy C-O)	0.97 (3H, t, J=7Hz, CH_3), 1.45-1.81 (4H, m, 2x CH_2), 2.32 (3H, s, CH_3), 2.69 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=2.52Hz, H-6), 3.01 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=3Hz, H-6), 3.12-3.16 (1H, m, H-5), 3.41-3.43 (1H, m, H-3), 4.47-4.49 (1H, m, H-4), 7.16 (2H, d, J=8.04Hz, H-3` and H-5`), 7.52 (2H, d, J=8.04Hz, H-2` and H-6`).

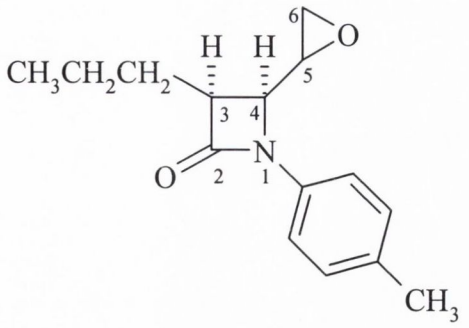
The infrared spectrum of compound 4-(1,2-epoxyethyl)-1-(4-methylphenyl)-3-propylazetidin-2-one (**300**) a representative of this group of compounds displays the β-lactam carbonyl at ν1750cm^{-1}. The epoxy C-O stretching bonds are observed at ν1230, ν940, ν751 cm^{-1}.



(300)

In the ^{1}H-NMR spectrum of compound (**300**) (**Figure 10**) the triplet at δ0.97 is assigned to the methyl of the propyl group which is coupled to the adjacent methylene protons, J=7Hz. A multiplet in the region δ1.45-1.81 integrating for four protons is assigned to the two methylene groups of the propyl side chain. The characteristic methyl group appears as a singlet integrating for three protons at δ2.32. The epoxide protons give rise to two double doublets at δ2.69, δ3.01 each integrating for one proton (J_{gem}=4.76Hz, $J_{6,5}$=2.52Hz). H-5 appears as a multiplet in the region δ3.13-3.16 due to the coupling with H-4 and adjacent epoxy protons. Further downfield both H-3 and H-4 appear as multiplets in the region δ3.31-3.43 and δ3.60-3.62. A doublet at δ7.16 (J=8.04Hz) represents the aromatic protons H-3` and H-5` while the aromatic protons H-2` and H-6` appear further downfield at δ7.52Hz, (J=8.04Hz).

In the ^{13}C-NMR and DEPT spectra of compound (**300**) (**Figure 11**) three quaternary carbons are present and are easily assigned as follows: 166.83ppm (β-lactam carbonyl), 135.12ppm (C-4`), 133.11ppm (C-1`). All of these three signals disappear in the DEPT spectrum. C-2` and C-6` are equivalent and appear as one signal at 129.15ppm. Similarly C-3`and C-5` are assigned to 116.49ppm. C-4 shows at 57.81ppm slightly more downfield than C-3 and C-5 which appear at 51.28ppm and 50.52ppm respectively. The epoxy C-6 carbon resonating at 44.05ppm together with the methylene groups of the propyl side chain at C-3 appearing at 27.34ppm and 21.04ppm are inverted in the DEPT spectrum. The methyl groups occur at 20.42ppm and 13.55ppm. The high resolution mass spectrum for compound (**300**) displayed the molecular ion peak M^{+} ($C_{15}H_{19}NO_2$) seen at m/z 245.1395.



(300)

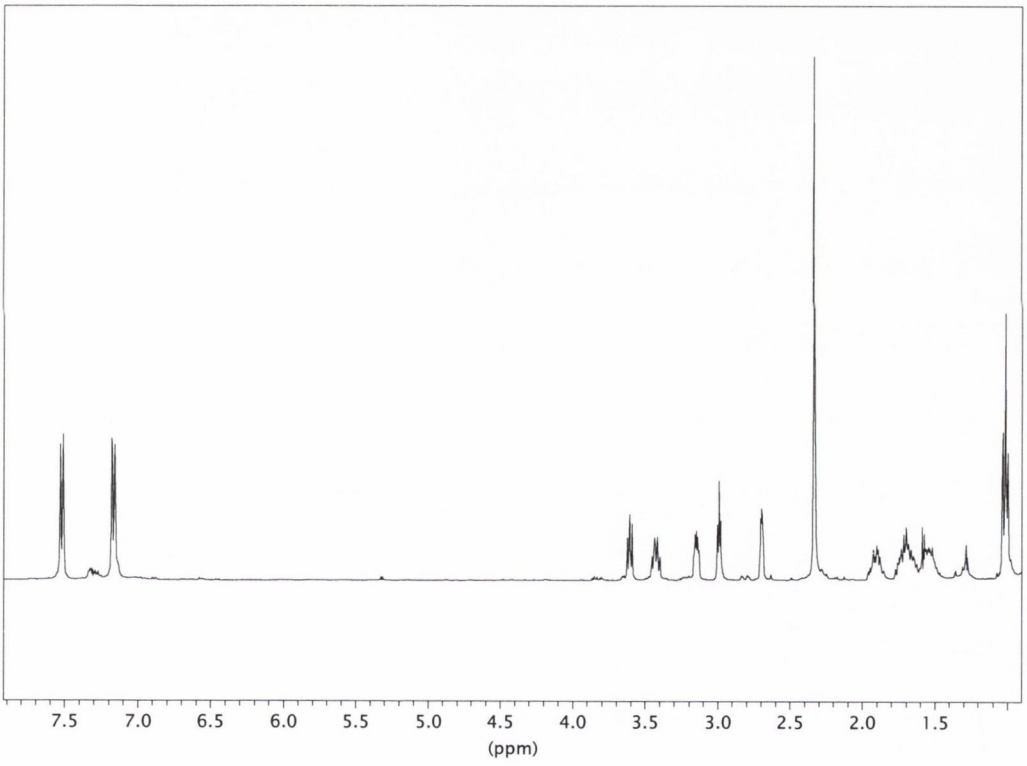
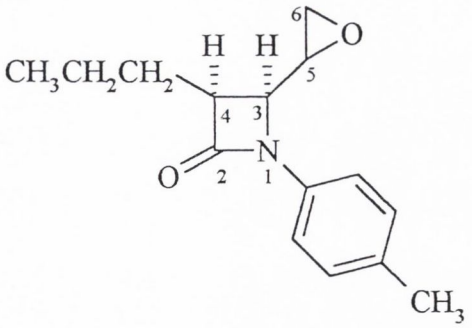


Figure 10: *^{1}H-NMR spectrum of 4-(1,2-epoxyethyl)-1-(4-methoxyphenyl)-3-propylazetidin-2-one (**300**)*



(300)

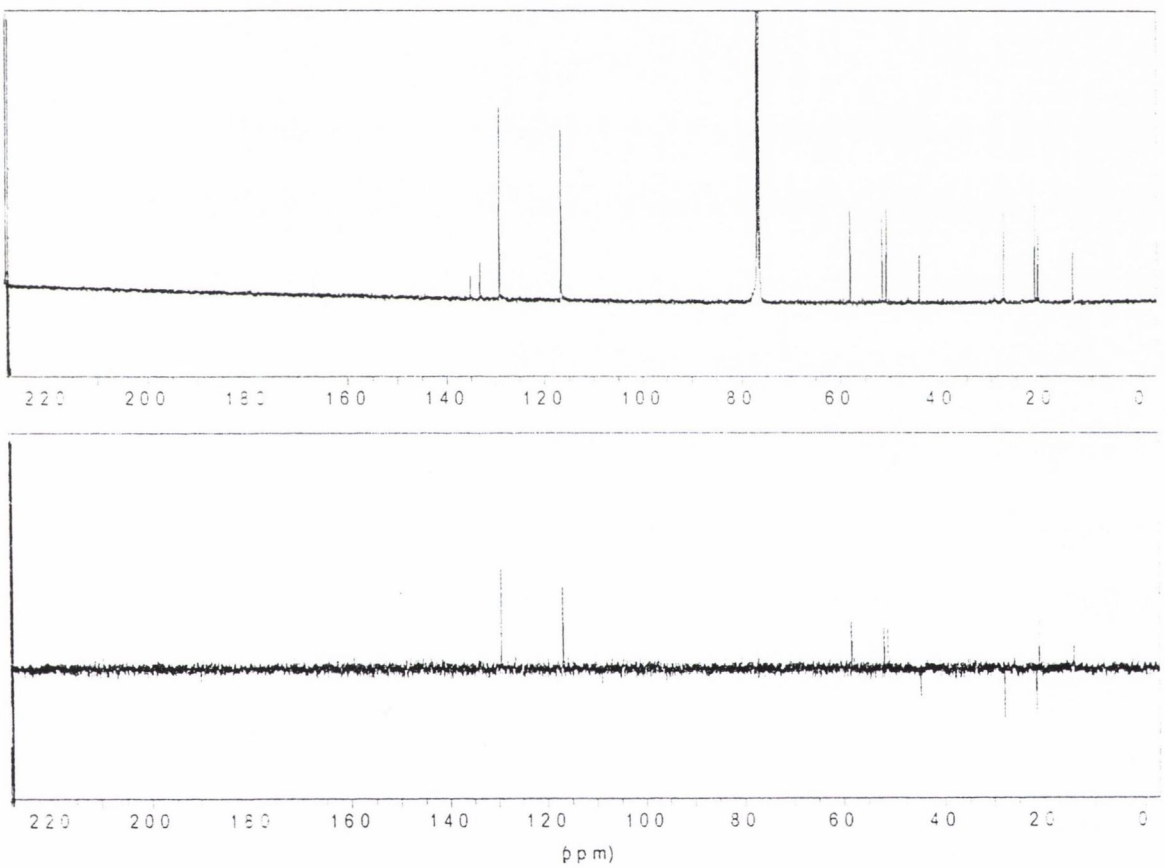
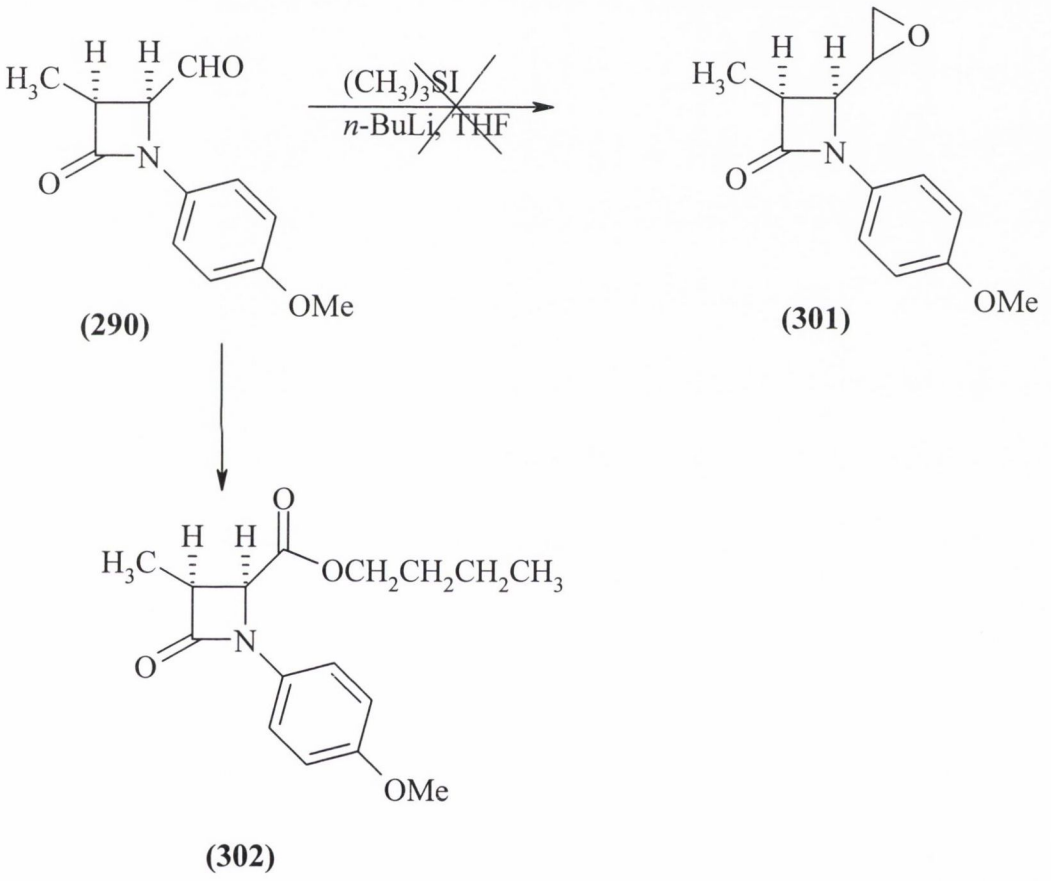


Figure 11: *^{13}C-NMR and DEPT spectra of 4-(1,2-epoxyethyl)-1-(4-methoxyphenyl)-3-propylazetidin-2-one (**300**)*

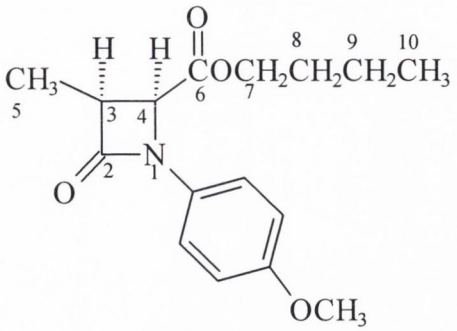
5.4 Isolation of ester compound (302)

4-Formyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (**290**) was treated with a $-10^{o}C$ suspension of four equivalents of trimethylsulphonium iodide and 2.5 equivalents of 2.5M *n*-butyllithium as a possible route to the introduction of an epoxide type substituent at C-3 of the β-lactam ring. The expected product (**301**) was not obtained (**Scheme 83**). One product was obtained from this reaction mixture in 45% yield as a colourless oil. Using a combination of spectroscopic techniques the ester structure (**302**) was proposed rather than the expected product (**301**).



Scheme 83

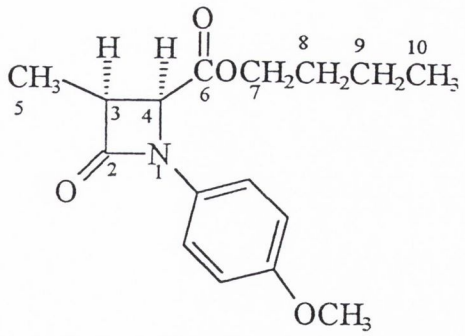
The infrared spectrum of 4-butoxycarbonyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (**302**) displays a carbonyl stretching frequency at $\nu 1749 cm^{-1}$ indicating that the β-lactam carbonyl is still present.



(302)

^{1}H-NMR spectroscopy of compound (**302**) reveals a triplet at δ0.87 integrating for three hydrogens which is assigned to the butyl methyl protons due to coupling with neighbouring methylene protons. The C-3 methyl appears as a doublet at δ1.28 due to coupling with H-3, J=7.52Hz. Two multiplets in the range δ1.23-1.64 is assigned to the four methylene protons. The methoxy protons appear at δ3.89. A multiplet in the region δ3.61-3.64 is assigned to H-3 due to coupling with H-4 and adjacent methyl protons. Further downfield the multiplet seen at δ4.09 is assigned to the methylene protons adjacent to the oxygen at C-7 and is further downfield due to the deshielding effect of the carbonyl. H-4 appears as a doublet at δ4.57 due to coupling with H-3 in a *cis* arrangement J=5.52Hz, while the equivalent aromatic hydrogens H-3` and H-5` resonate at δ6.83 as a doublet displaying coupling to H-2` and H-6` at δ7.22, J=9.02Hz. In the 2D H-H COSY NMR spectrum (**Figure 12**) the correlation between the methylene protons and the methyl group is observed. The chemical shift values were confirmed by analysing the C-H COSY (HETCOR) NMR spectrum (**Figure 13**) (The C-H COSY NMR technique shows the correlation between carbon signals and signals for hydrogens to which they are bonded).

In the ^{13}C-NMR spectrum of compound (**302**) four quaternary signals are assigned as follows:168.43ppm (ester carbonyl), 165.58ppm (β-lactam carbonyl), 155.87 ppm (C-4`) and 130.64ppm (C-1`). Two signals at 117.51ppm and 113.80ppm were readily assigned to the pairs C-2` and C-6`, C-3` and C-5`. C-7 resonates at 65.36ppm. The remaining methylene carbons resonate at 30.09ppm and 18.49ppm. C-4 resonates at 55.86ppm downfield from the methoxy carbon at 55.40ppm and C-3 at 47.74ppm. The methyl signals are seen at 9.16ppm and 13.05ppm.



(302)

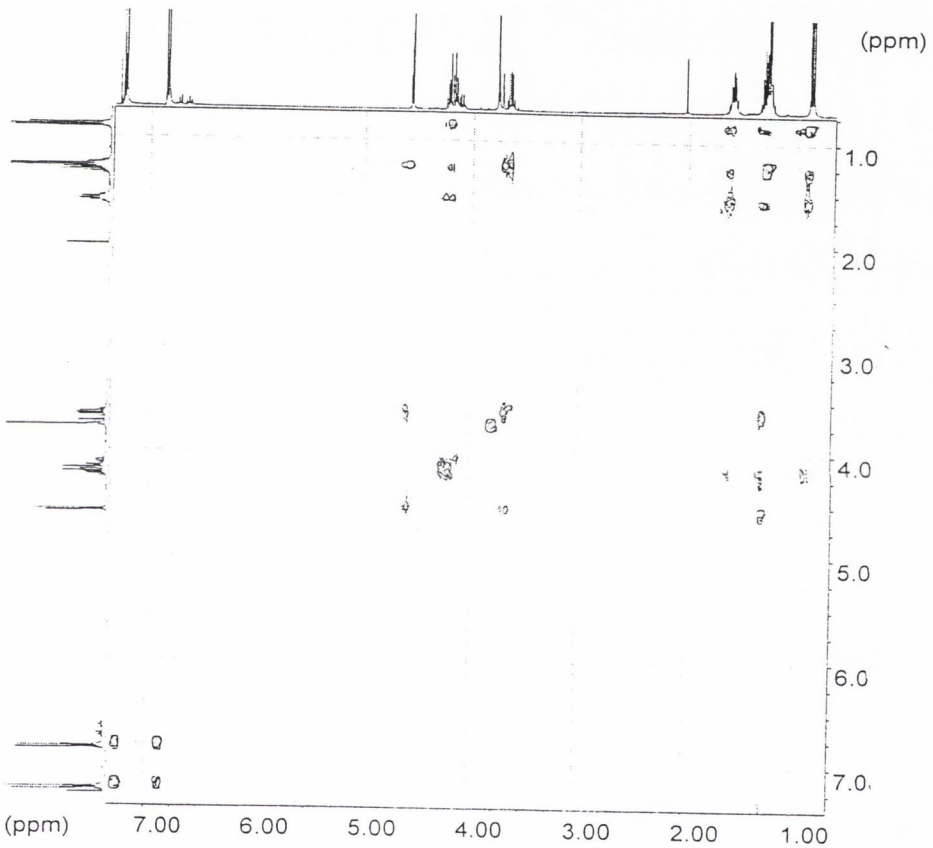
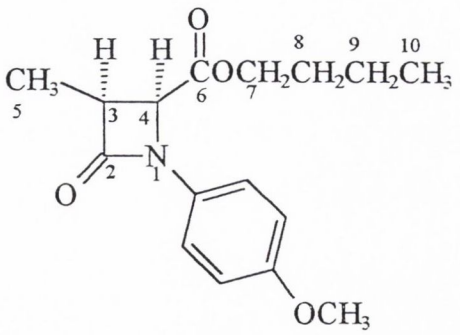


Figure 12: *H-H COSY spectrum of 4-butoxycarbonyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (302)*



(302)

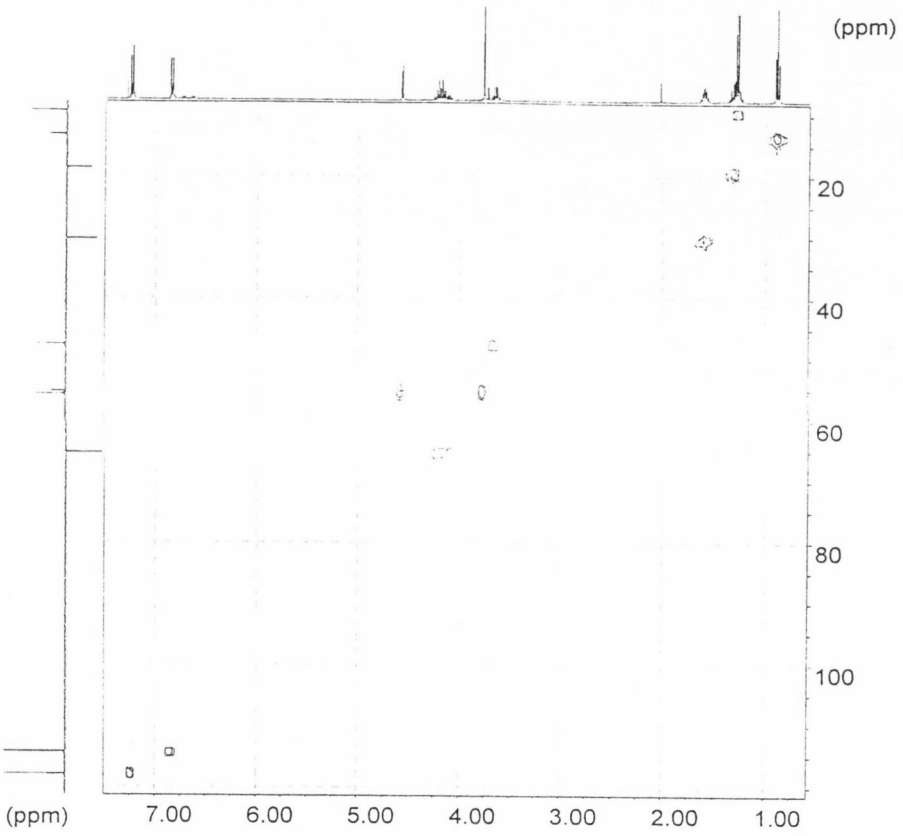
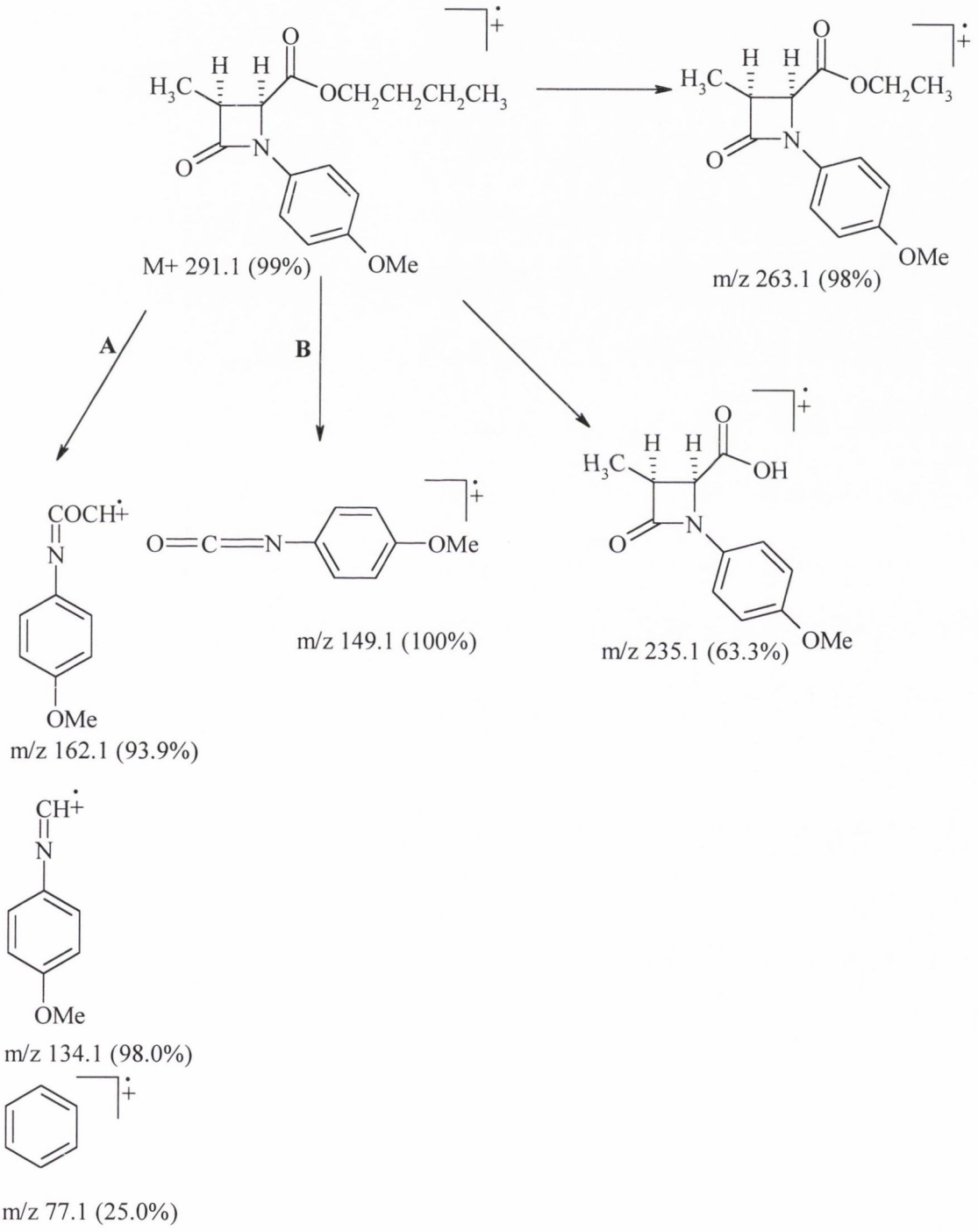


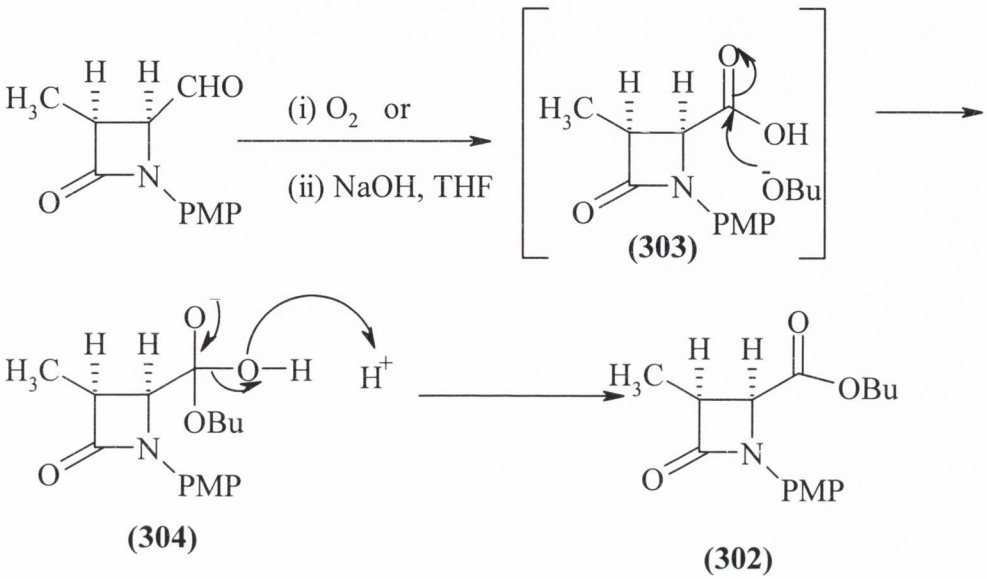
Figure 13*: C-H COSY spectrum of 4-butoxycarbonyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (**302**)*

High resolution mass spectrometry confirmed the molecular formula of compound (**302**) as $M^+(C_{16}H_{21}NO_4)$. The molecular ion is observed at m/z 291.1451 in 99% abudance (**Scheme 84**). Loss of alkyl fragments affords the two fragments at m/z 263.1 in 98% abudance and at m/z 235.1 in 63.3% abudance. Type B fragmentation affords an isocyanate ion at m/z 149.1 in 100% abudance. Type A fragmentation reveals the imine fragments at m/z 162.1 in 93.9% abudance and at m/z 134.1 in 98.0% abudance and a phenyl group at m/z 77.1 in 25.0% abudance.



Scheme 84

A reaction mechanism for this novel transformation has been proposed (**Scheme 85**). 3-Methyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**290**) is oxidised to the corresponding carboxylic acid (**303**) by air or the Cannizzaro method. Nucleophilic attack of the alkoxide yields the intermediate (**304**). Transfer of a proton converts the OH group into a good leaving group. Loss of H_2O generates the ester product (**302**).



Scheme 85

5.4 Summary

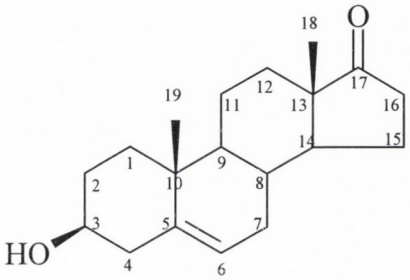
This chapter demonstrated the use of sulphur ylides in the transformation of the formyl group of C-3 alkyl-4-formylazetidin-2-ones to an epoxyethyl substituent. The manipulation of the chemistry at C-4 of these β-lactam rings is of interest as the 4-epoxysubstituted compounds are useful intermediates and many further chemical transformations can be achieved on such a reactive functional group at C-4. The novel pyrrolidin-2-one product was obtained via sulphur ylide chemistry illustrating the unexceptional reactivity of the β-lactam ring and potential for heterocyclic transformations.

Chapter 6

Dehydroepiandrosterone

6.1 Introduction

Dehydroepiandrosterone (**305**), is also referred to as DHEA, 3β-hydroxyandrost-5-ene-17-one, prasterone, dehydroisoandrosterone, hydroandrosterone, Δ^5-androsten-3β-ol-17-one, astenile, deandros, diandrone and psicosterone. In this thesis the most common name DHEA will be used throughout. The carbon atoms of (**305**) are numbered as below in accordance with I.U.P.A.C.



(305)

For many years DHEA (**305**) was considered a physiologically inert steroid produced in large quantities by the human adrenal cortex. No function for DHEA was known except to serve as a precursor of sex hormones such as testosterone (**306**). In the past fifteen years there has been a tremendous surge in research on the biological role of DHEA. Extensive data published so far have shown that DHEA has many diverse physiological, biological and biochemical effects[205, 206]. DHEA (**305**) has been shown to have effects in diseases such as diabetes and cancer and may also play a role in the following conditions obesity, stress, immune responses and pregnancy and the process of ageing. The structure of DHEA (**305**) has been elucidated by ^{13}C-NMR and single crystal X-ray diffraction methods[207, 208].

6.2 History of DHEA

DHEA was first isolated from human urine by Butenandt and Dannenbaum in 1934[209]. In this study DHEA itself was not isolated, the substance isolated was its 3-chloro derivative. The chlorine containing substance was immediately recognized as an artifact produced from DHEA by boiling the urine with HCl. What was not known until 1944 was that the most probable chemical precursor of the chloro compound was the conjugate dehydroepiandrosterone-3-sulfate (DHEAS) (**307**) which was isolated from human urine by Munson[210] in 1944. DHEA (**305**) is converted to DHEAS by hydrosteroid sulphatase. In the brain the cytochrome P450 catalyses the conversion of cholesterol (**308**) to pregnenolone (**309**).

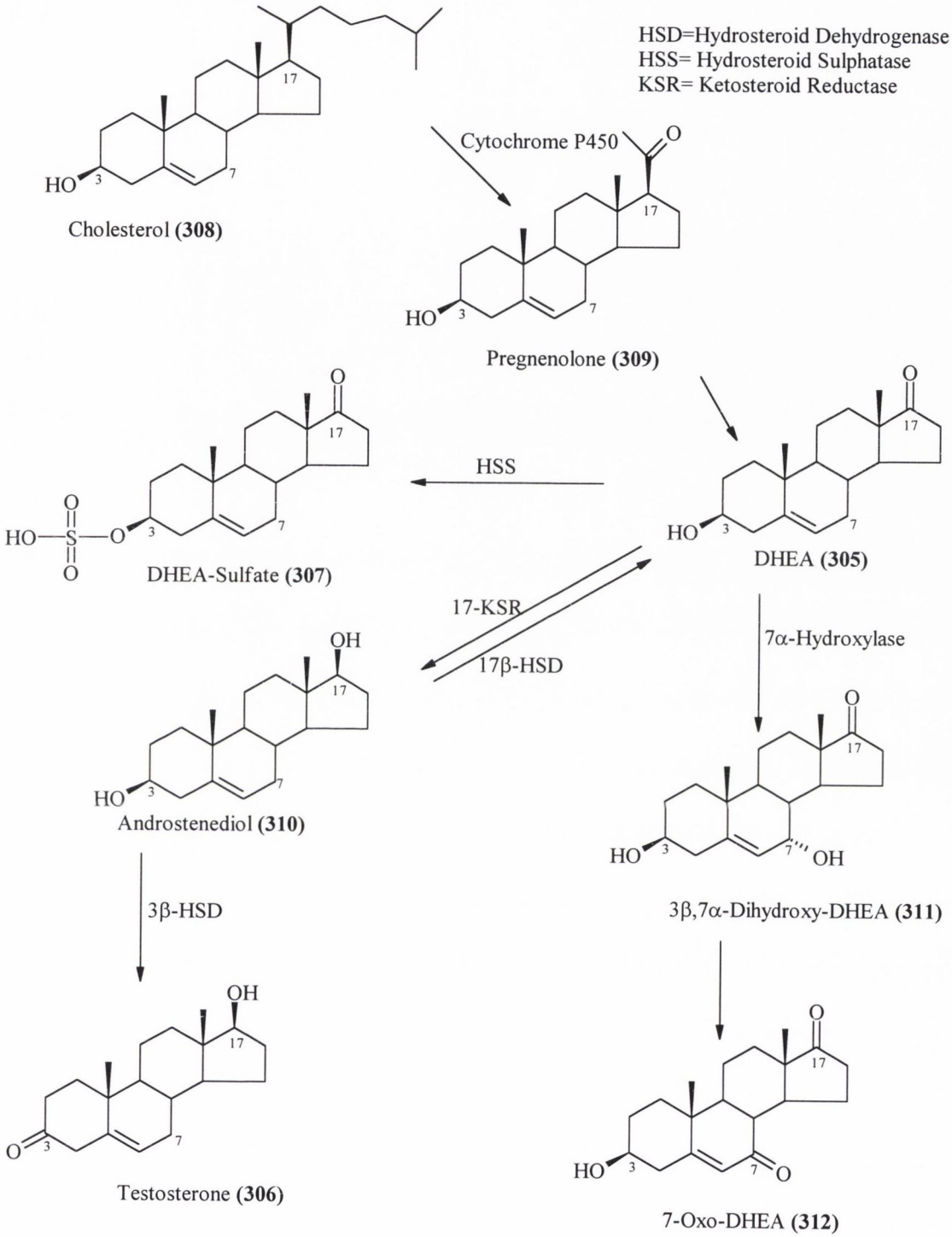
Pregnenolone (**309**) had been isolated from pig testes[211]. Pregnenolone (**309**) may be formed enzymatically or by non-enzymatic autooxidation from the hydroperoxides or dioxetanes present in non-ketonic fractions. As shown in **Scheme 86**, DHEA (**305**) is an intermediate in the biosynthesis of testosterone (**306**) whereby DHEA is converted to androstenediol (**310**) by the enzyme ketosteroid reductase. Thus androstenediol (**310**) is converted to testosterone (**306**) by the enzyme Δ^5-3β-hydrosteroid dehydrogenase. The scheme shown here is merely to illustrate that DHEA can serve as a biosynthetic precursor of testosterone (**306**).

Liberman and co-workers[212] isolated 7-oxo-DHEA (**312**) from human urine. Schneider and Mason[213] independently found it to be produced from DHEA (**305**) by rabbit liver slices but neither group characterized it. DHEA (**305**) is converted to 7-oxo-DHEA (**312**) via the intermediate 3β, 7α-dihydroxy-DHEA (**311**) by the enzyme 7α-hydroxylase which is then converted to 7-oxo-DHEA (**312**). Much remains to be learned about the conversion of 3β,7α-dihydroxy-DHEA (**311**) to 7-oxo-DHEA (**312**) in primates and rodents.

6.3 Properties of DHEA

DHEA is an intermediate in the metabolic conversion of cholesterol (**308**) to testosterone (**306**) and also exerts several physiological effects. In relatively large doses DHEA caused weight loss in genetically obese[214] and normal[215] animals without affecting food intake and depresses blood cholesterol levels in man, rats and dogs[216,217]. It decreases blood sugar concentration in diabetic mice[218] and also enhances resistance of mice to viral infections[219,220]. DHEA (**305**) induces the incidence of spontaneous[221] and carcinogen induced tumours in mice and improves memory in aged mice[222]. Body weight responses in humans treated with DHEA are questionable[223].

It is not unusual for a hormone to have more than one mode of action. Some steroids may function by binding to a site on a cell membrane and influence events directly in that cell. The same steroid may also function by combining with a specific receptor to form a complex that will be recognized by a response element on specific promoters.


HSD=Hydrosteroid Dehydrogenase
HSS= Hydrosteroid Sulphatase
KSR= Ketosteroid Reductase
Cholesterol (308)
Cytochrome P450
Pregnenolone (309)
HSS
DHEA-Sulfate (307)
DHEA (305)
17-KSR
17β-HSD
7α-Hydroxylase
Androstenediol (310)
3β-HSD
3β,7α-Dihydroxy-DHEA (311)
Testosterone (306)
7-Oxo-DHEA (312)

Scheme 86

6.4 Active analogues of DHEA

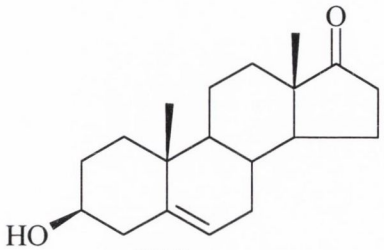
Steroids that are produced from DHEA (**305**) or that could be formed metabolically from DHEA (**305**) by hydroxylation, hydrogenation, oxidation or other reactions to determine their biological activities have been synthesized[224a,224b]. Lardy *et al* postulated that the 7α-hydroxy DHEA (**311**) and the 7-oxo DHEA (**312**) derivatives are involved in the metabolic pathway from DHEA (**305**) to more active steroid hormones[224a]. In order to carry out this program a convenient assay to guide progress was needed. The thermogenic functions of DHEA were considered. The thyroid hormone, a classic thermogenic agent was tested for its effect on the activity of mitochondrial glycerol-3-phosphate dehydrogenase (G3PDH) and liver cytosolic malic enzyme. Several other enzymes are increased in hyperthyroid animals but the magnitude of their responses to the thyroid hormone is not nearly as great as those of G3PDH and cytosolic malic enzyme.

In 1989 Tagliaferro *et al*[225] reported that DHEA increased heat production in rats and could thus be used as a thermogenic hormone. Lardy *et al* found that DHEA induced the level of mitchondrial G3PDH and cytosolic malic enzyme in rats. The responses of these two enzymes provided an effective assay for one type of activity for synthetic steroids related in structure to DHEA (**305**). Increasing the amount of DHEA (**305**) in the diet of rats would therefore result in increased heat production and associated weight loss. Enhancement of mitchondrial G3PDH and cytosolic malic enzyme were used as a semiquantitative assay for activity of nearly 150 steroid structures. The compounds (**305**), (**305a**), (**311**), (**311a**), (**311b**), (**312**) and (**312a**) found capable of inducing both G3PDH and malic enzyme are shown in **Figure 14**. **Figure 15** depicts compounds (**305**), (**305b**), (**311**), (**311c**), (**312**) and (**312c**) that induce malic enzyme but not G3PDH. Among the compounds studied 7-oxo-DHEA (**312**) was found to be the most active.

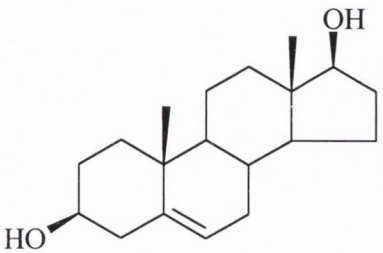
DHEA is not useful as a therapeutic agent for promoting weight loss or controlling weight gain because the dose rate of DHEA (**305**) necessary to achieve these desired characteristics may also stimulate the production of sex hormones which is associated with various undesired side effects. Accordingly a therapeutic agent possessing the weight loss characteristic of DHEA without the associated sex-hormone stimulating characteristic would be extremely useful.

The 7-oxo-steroids may prove to be more useful as therapeutic agents than DHEA (**305**) for they cannot be converted to testosterone (**306**) and hence an

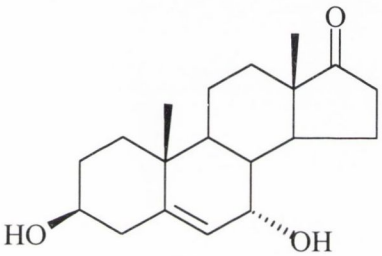
investigation of the synthesis of 7-oxo-DHEA (**312**) and related compounds was undertaken in this work. As part of this project, the biochemical effects of the 7-oxo-DHEA (**312**) derived products will be assessed by Dr. R.Porter, Biochemistry Department, Trinity College Dublin.



(305)



(305a)



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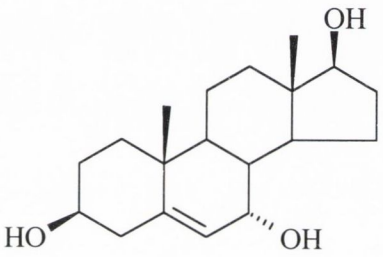

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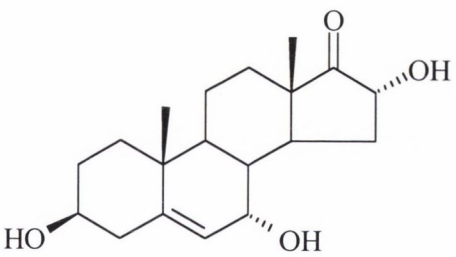
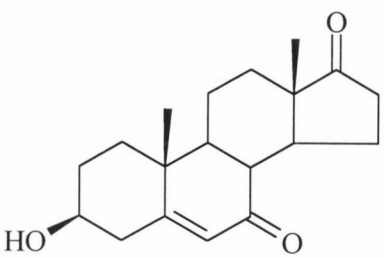


(311b)



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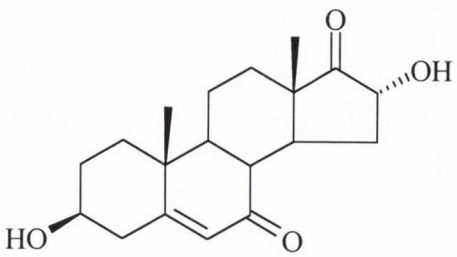
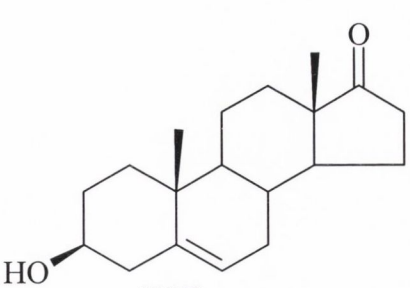


(312a)

Figure 14



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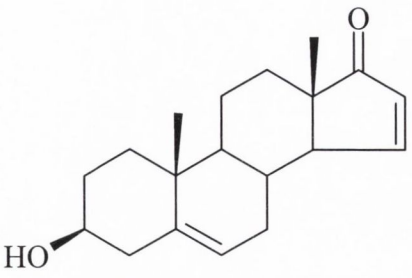
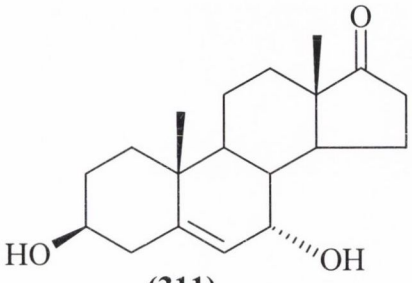


(305b)



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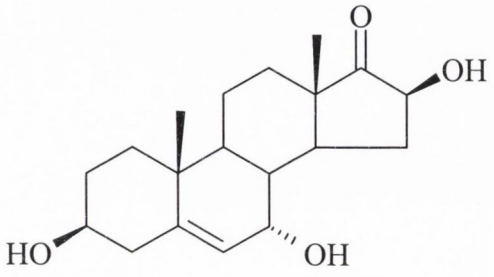
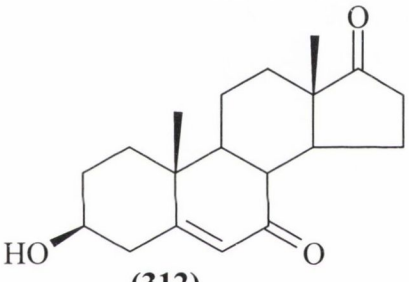
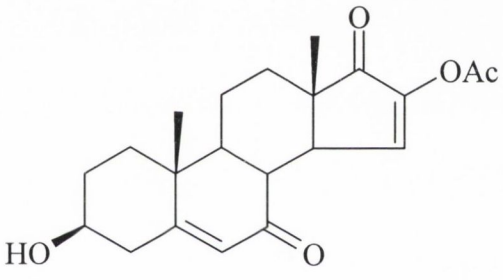


(311c)



(312)



(312c)

Figure 15

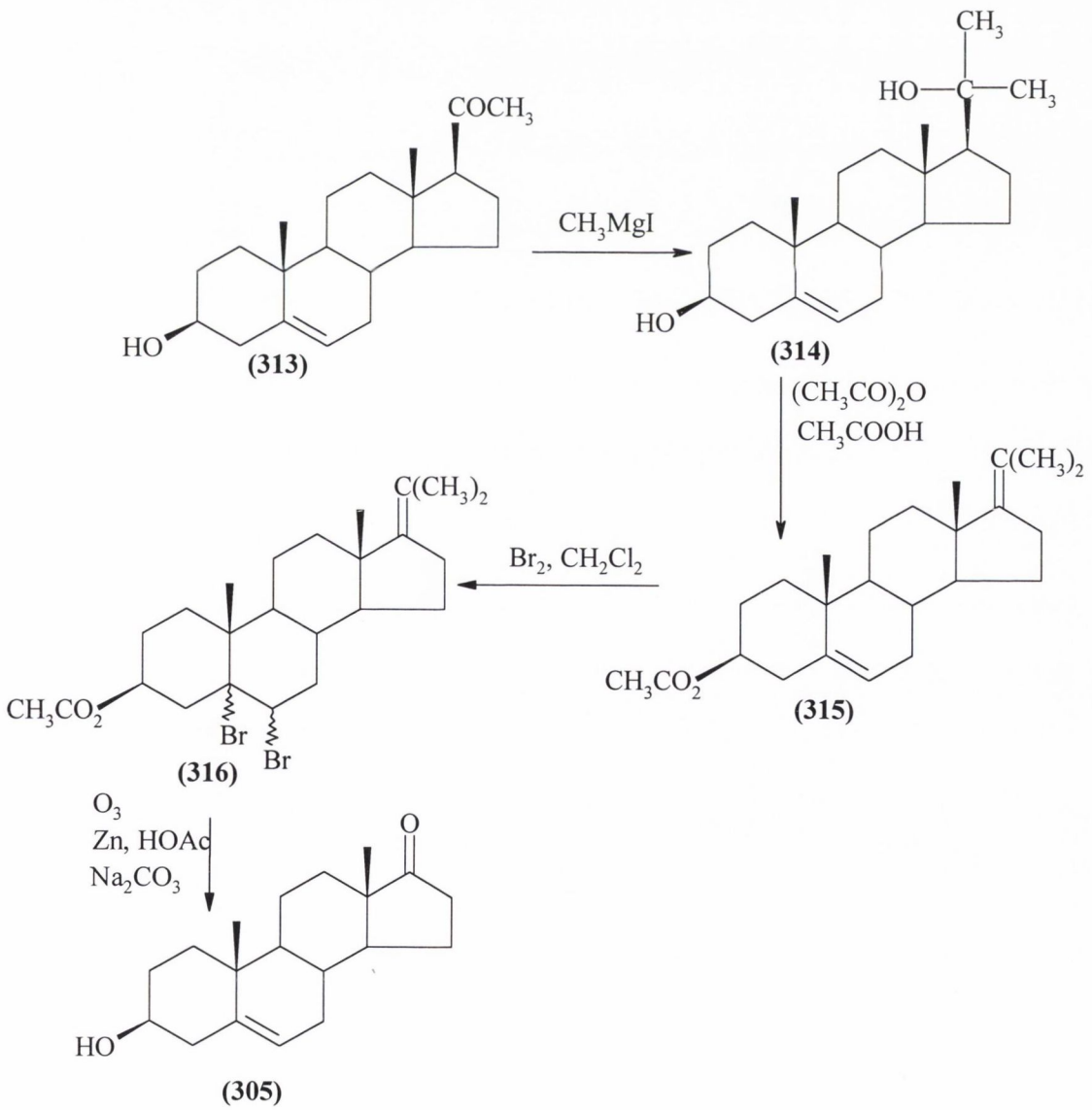
6.5 Synthesis of DHEA

The earliest preparation of DHEA (**305**) was reported by Wallis[226] in 1934 from cholesterol (**308**). In that communciation it was pointed out that the preparation of this substance from cholesterol (**308**) located definitely the position of the double bond at C-5 and also the β–stereochemistry of the 3-hydroxy group as in cholesterol (**308**). Cholesteryl acetate dibromide is formed by refluxing cholesterol (**308**) in acetic acid followed by the addition of bromine. Treatment of cholesteryl acetate dibromide with chromic oxide followed by zinc dust completed debromination. Addition of semicarbazide hydrochloride and chromium trioxide forms DHEA-acetate semicarbazone. DHEA is obtained when DHEA-acetate semicarbazone is treated with 2.5M H_2SO_4

Marker *et al*[227, 228] in 1942 showed that treatment of compound (**313**) with methylmagnesium iodide gave the diol (**314**). The diol (**314**) on treatment with acetic

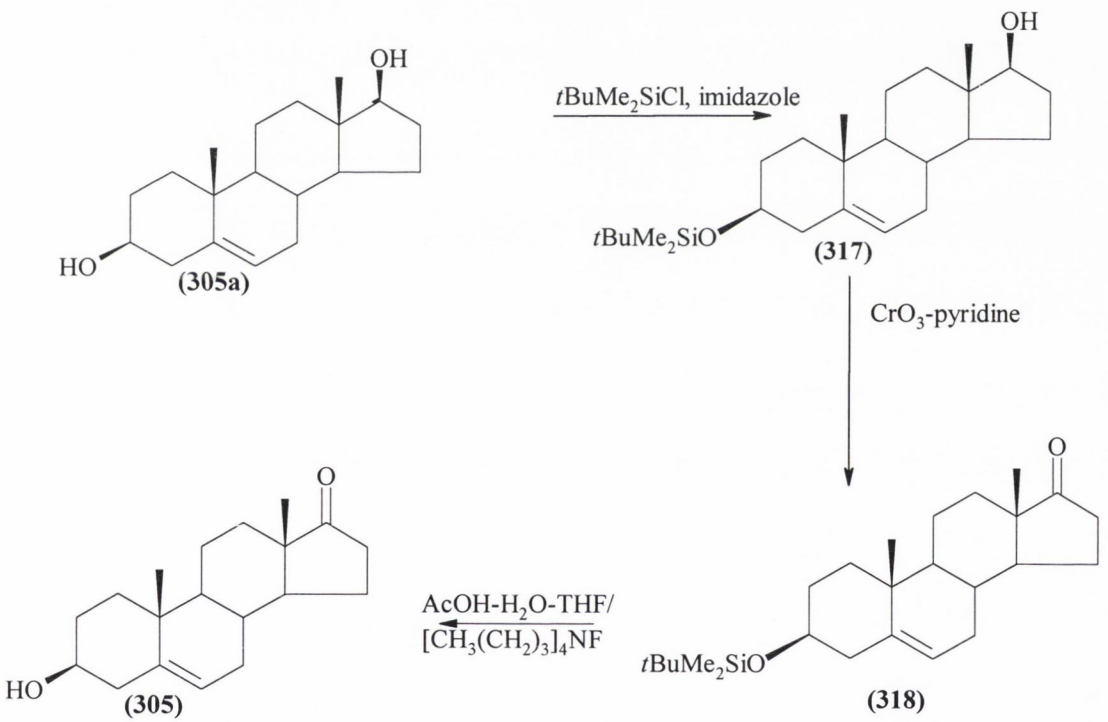
acid and acetic anhydride giving a mixture of isomers from which $\Delta^{5,17}$-20-methylpregnadien-3β-ol-acetate (**315**) was isolated. By treating (**315**) with bromine in chloroform at –5°C it was possible to brominate the double bond in the 5,6 position yielding Δ^{17}-5,6-dibromo-20-methylpregnen-3β-ol-acetate (**316**). Subsequent ozonolysis, debromination, followed by removal of the acetate group with sodium carbonate solution yielded DHEA (**305**) (**Scheme 87**).

Glazer and Gut[229] in 1961 described an alternative synthesis of DHEA. Androst-4-ene-3,17-diene-3-enolacetate[230] is treated with semicarbazide under basic conditions to give androst-4-ene-3,17-diene-3-enolacetate-17-semicarbazone in 88% yield. This semicarbazone compound now makes possible the reduction of the 3-enolacetate with sodium borohydride after which the keto group can be regenerated by treating it with pyruvic acid yielding DHEA (**305**) .



Scheme 87

Hosoda[231] *et al* in 1973 reported a high yield conversion of androst-5-ene-3β,17β-diol (**305a**) to DHEA (**305**). Since selective oxidation of the 17-hydroxy function was not promising[232], selective protection of the 3β-hydroxy group appeared to offer the best chance of success. Androst-5-ene-3β,17β-diol (**305a**) when treated with dimethyl-*tert*-butylsilylchloride in dimethylformamide in the presence of imidazole yielded the desired protected androst-5-ene (**317**) in 71% yield. Oxidation of (**317**) with CrO_3-pyridine complex gave (**318**) in quantitative yield. Clevage of the 3β-dimethyl-*tert*-butylsilylgroup of (**318**) was performed in a mixture of AcOH-H_2O-THF or by exposure to tetra-*n*-butylammonium flouride . The overall yield of DHEA (**305**) from (**305a**) was 64% (**Scheme 88**).



Scheme 88

6.6 Chemistry of DHEA

Because of the functionality of DHEA at C-3, C-5, C-6 and C-17 a number of structural modifications of DHEA (**305**) have been investigated and are shown in **Scheme 89**. They are divided into the following groups with the objective of producing compounds with similar biologically activity to that of DHEA (**305**)[233,236];

(i) alkylation at C-2,

(ii) alkenylation at C-2,

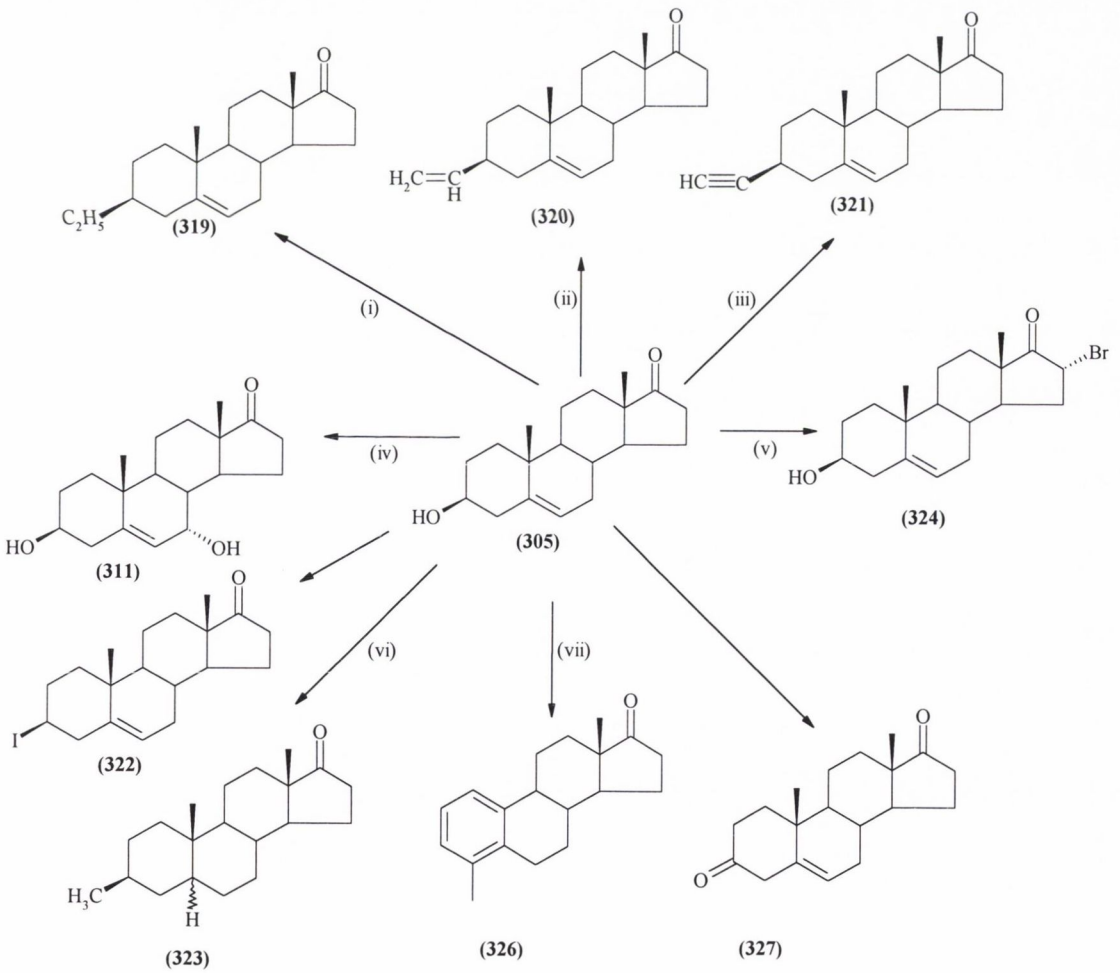
(iii) alkynylation at C-3,

(iv) hydroxylation at C-7,

(v) halogenation at C-16,

(vi) catalytic hydrogenation reactions,

(vii) aromatization reactions.

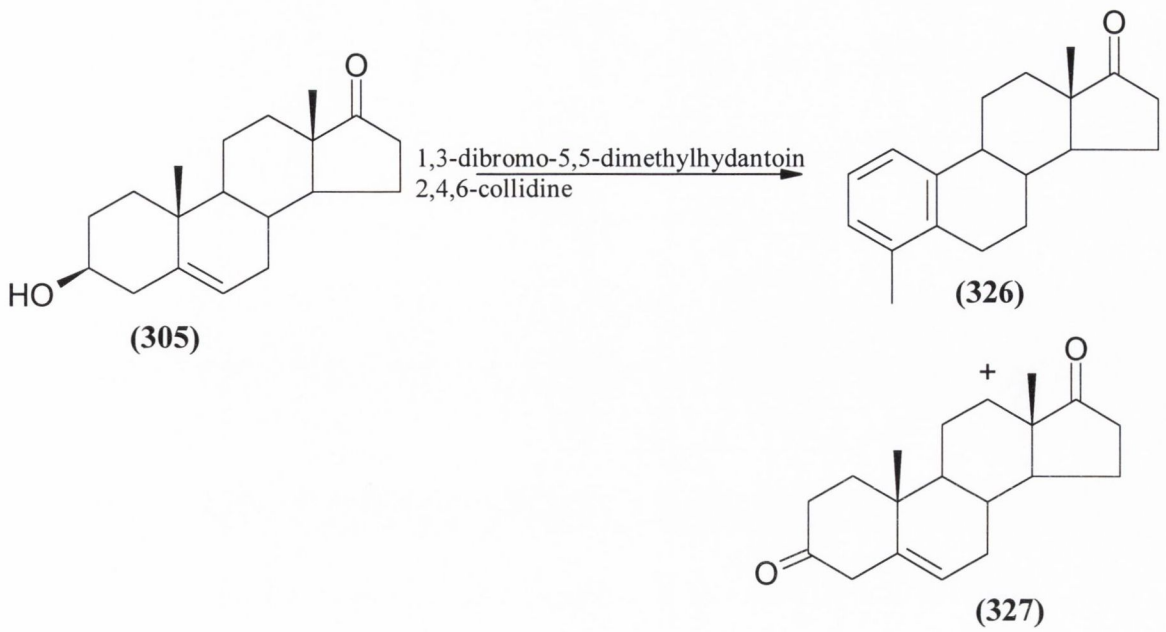


Scheme 89

DHEA was iodonated at C-3 with catechol phosphochloridate followed by iodine yielding 3β-iodoandrost-5-ene-17-one (**322**) which was ketalised then alkylated with a mixture of ethyllithium and cuprous cyanide to yield 3β-ethylandrost-5-ene-17-ethyleneketal. Hydrolysis of the ketal afforded 3β-ethylandrost-5-ene-17-one (**319**).

Alkenylation at C-3 was performed by reacting 3β-iodoandrost-5-ene-17-one-17-ketal with vinyl lithium cuprate forming 3β-vinyl-androst-5-ene-17-one (**320**). Reaction of 3β-iodoandrost-5-ene-17-one-17-ketal with tri-*n*-butylstannylacetylenelithiumcuprate resulted in the synthesis of 3β-ethylenylandrost-5-ene-17-one (**321**). DHEA (**305**) reacts with singlet oxygen to yield 5α-hydroperoxy-3β-hydroxyandrost-6-ene-17-one. This hydroperoxide undergoes a rearrangement when in chloroform solution to yield 7α-hydroxyperoxy-3β-hydroxyandrost-5-ene-17-one. Catalytic reduction of the hydroperoxide yields 3β,7α-dihydroxyandrost-5-ene-17-one (**311**). Also catalytic hydrogenation of 3β-methylandrost-5-ene-17-one yielded 3β-methyl-5α-androstan-17-one (**323**). Reaction of DHEA with cupric bromide yields 16α-bromo-3β-hydroxyandrost-5-ene-17-one (**324**)[233].

Hanson and Dargon[236] reported a novel steroidal aromatization reaction utilising DHEA (**305**) as the starting material providing a novel route to the synthesis of an oestrogen type structure. DHEA (**305**) was brominated with 1,3-dibromo-5,5-dimethylhydantoin followed by debromination with 2,4,6-collidine afforded 4-methyloestra-1,3,5-triene-17-one (**326**) and androst-5-ene-3,17-dione (**327**) (**Scheme 90**). Compound (**326**) is of interest due to its similarity to the oestrogens i.e. oestrone and oestriol. The oestrogens are responsible for the development of the female sex organs. In most species the naturally occuring oestrogens contain a phenolic ring A[237].



(305) (326) (327)

Scheme 90

6.7 Biological activity of DHEA and related compounds

In 1991 initial biochemical studies showed that DHEA (**305**) treatment in mice resulted in lower body weight gain[215,234]. Subsequent studies have shown that DHEA treatment in rats has a similar effect. In adult rodents weight loss is a consequence of DHEA treatment. In general these effects are independent of changes in food intake and are accompanied by lower body fat. DHEA treatment has been shown in some circumstances to alter a number of serum factors including glucose, insulin, cholesterol and triacylglycerol. Recent studies have focused on the effects of DHEA (**305**) on liver metabolism. Studies have been undertaken to determine whether the antiobesity effect of DHEA is mediated by the inhibition of glucose-6-phosphate dehydrogenase (G6PDH) by this steroid. Hypothetically, inhibition of G6PDH would result in limited NADPH production and subsequently lowered rates of fatty acid synthesis. G6PDH was found to be lower in the adipose tissue of obese rats treated with DHEA for 15 weeks than in non treated obese rats. It is not clear at present how these effects of DHEA on adipose tissue growth and metabolism are mediated.

Previously reported in 1985[233] compounds shown in **Table 24** were screened as inhibitors of purified bovine adrenal G6PDH activity as one predictor of cancer preventive action. 16α-Bromo-3β-hydroxyandrost-5-ene-17-one (**324**) shows the highest precentage of inhibition.

Table 24: Inhibition of G6PDH with compounds (305), (319) and (324).

Compound No.	**Conc (μm)**	**Inhibition %**
(305)	10	53
	1.0	36
	0.1	12
(319)	10	73
	1.0	55
	0.1	58
(324)	10	74

The following studies have been carried out on DHEA (**305**) and related compounds.

(i) Inhibition of Tumor Promoter Stimulation of Mouse Epidermal DNA.

The inhibition of tumor promoter stimulation of mouse epidermal DNA synthesis rate by steroids may also contribute to cancer preventive activity[233]. The data are expressed as counts per minute (cpm) of tritium per μg of DNA (**Table 25**) for DHEA (**305**) and (**319**).

Table 25: Inhibition of TPA with compounds (305) and (319)

Steroid	cpm/μg DNA
Control (no TPA, no steroid)	55 ± 3.7
TPA + DHEA (400mg/kg)	50 ± 2.8
TPA + DHEA (200mg/kg)	155 ± 1.6
TPA + DHEA (100mg/kg)	169 ± 11
TPA + (319) (400mg/kg)	39 ± 1.1
TPA + (319) (200mg/kg)	44 ± 2.5
TPA + (319) (100mg/kg)	100± 19

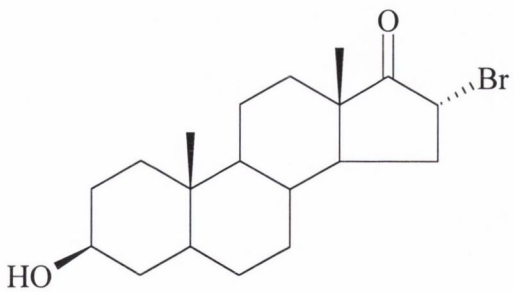
In conclusion of this experiment compound (**319**) is more active than DHEA (**305**)

(ii) Anti-Hyperglycemic Activity

Adminstration of DHEA (0.4% of the diet) produced a marked hypoglycemic effect in mice and significantly prolonged their lifespan[233]. It was noted that diabetes is more severe and develops more rapidly in males and can be improved or circumvented by combined estradiol and progesterone treatment and suggested that the therapeutic effect of DHEA (**305**) might result from its metabolism to estrogens[233]. Compound (**319**) was tested in this model. When mice were taken off diets containing DHEA or compound (**319**) and placed on control diet, blood glucose levels increased at 24 and 48 h for (**305**), but significantly more slowly in mice that had received compound (**319**).

(iii) Anti-Hypercholesterolemic Activity

In this experiment the effect of DHEA (**305**) and compound (**325**) on serum cholesterol was examined[233]. Cholesterol was measured according to the procedure of Rao[235]. It can be concluded that treatment of DHEA (**305**) and compound (**325**) reduced serum cholesterol levels in mice after one week.



(325)

DHEA (**305**) and related compounds has been shown to have effects in diseases such as diabetes and cancer and can effect weight control. DHEA (**305**) is a useful starting material because of the functionality at C-3, C-5, C-6 and C-17 and a number of structural modifications have been carried out synthesizing compounds with therapeutic properties.

6.8 Summary

Various procedures for the synthesis of DHEA are known. The interest in this compound is due to its biological role. DHEA has been shown to have effects in diseases such as cancer and in many conditions i.e. obesity and in the process of ageing. However DHEA is not useful as a therapeutic agent because the dose rate of DHEA necessary to achieve these desired characteristics may also stimulate the production of sex hormones. A derivative of DHEA, i.e. 7-oxo-DHEA, has been reported to have biologically properties with no side effects. The development of analogues of 7-oxo-DHEA with potential therapeutic properties is ongoing.

6.9 Objectives

Previous extensive studies have concentrated on the formation of analogues of DHEA. Few studies have focused on the synthesis of analogues of 7-oxo-DHEA.

The aims of this thesis is as follows:

(i) To synthesis analogues of DHEA and 7-oxo-DHEA bearing a halide, azide and tosylate substituents at C-3.

(ii) To synthesis 3α,4α-epoxyandrost-5-ene-7,17-dione.

(iii) To obtain 3-alkoxy-4-hydroxyandrost-5-ene-17-one via ring opening reactions of 3α,4α-epoxyandrost-5-ene-7,17-dione with alcohol catalysed with cerium ammonium nitrate.

(iv) To design a stereocontrolled synthesis of 3β,4β-dihydroxyandrost-5-ene-7,17-dione a potential novel therapeutic agent.

Chapter 7

Chemical Transformations of DHEA

7.1 Introduction

DHEA is not useful as a therapeutic agent for controlling weight gain or promoting weight loss because the dose rate of DHEA necessary to achieve these desired characteristics may also stimulate the production of sex hormones which is associated with various undesired side effects[233]. In this work the chemical modifications of DHEA and 7-oxo-DHEA (**312**) were investigated with the aim of synthesizing analogues of DHEA and 7-oxo-DHEA (**312**) with the potential of having anti-obesity and anti-ageing properties without toxic effects. The following chemical reactions of DHEA and 7-oxo-DHEA (**312**) were investigated:

(i) Halogenation, tosylation at C-3.

(ii) Epoxidation of $\Delta^{3,5}$-androstadiene-7,17-dione (**342**).

(iii) Ring opening reactions of 3α,4α-epoxyandrost-5-ene-7,17-dione (**328**)

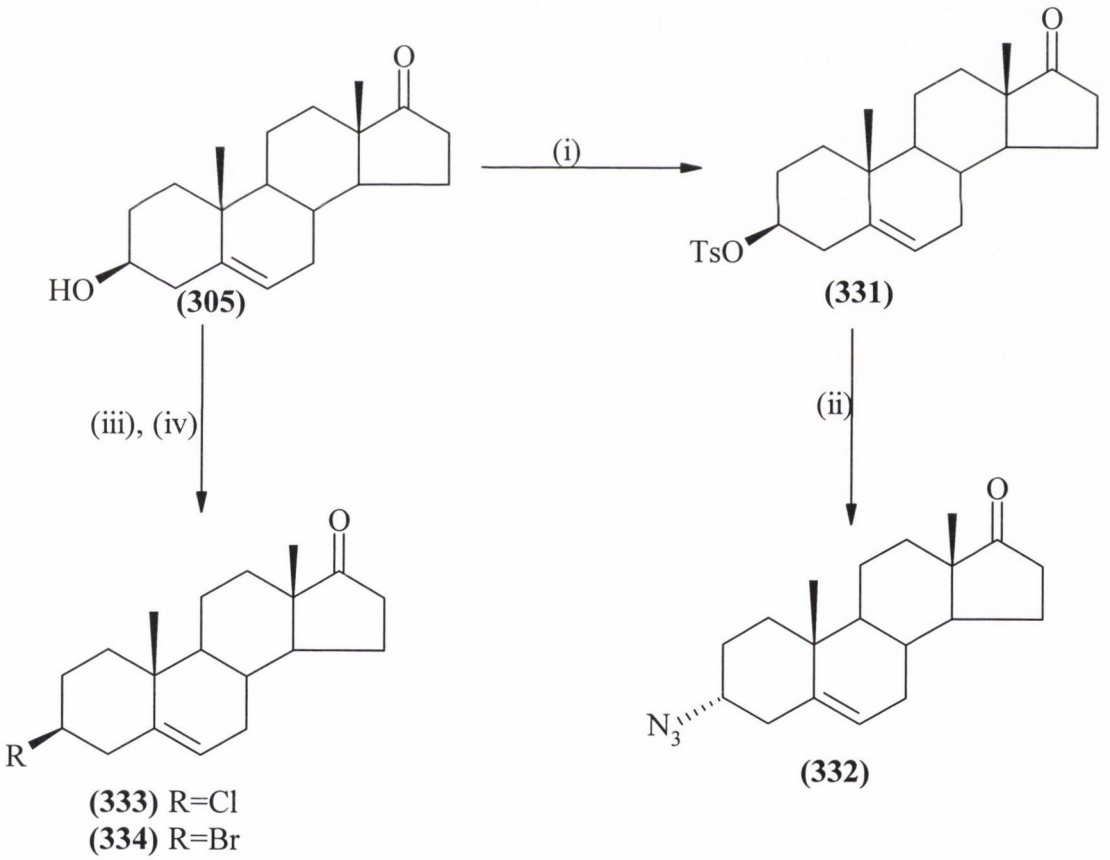
(iv) Synthesis of 3β,4β-dihydroxyandrost-5-ene-7,17-dione (**330**).

7.2 Chemical transformation at C-3 of DHEA

In the present work a number of chemical transformations were carried out with the objective of synthesizing 7-oxo derivatives of DHEA modified at C-3. Paulet and Bascoul[238] reported the synthesis of a number of DHEA derivatives using 3β-tosyloxyandrost-5-ene–17-one (**331**) as an intermediate as the tosylate group is easily replaced by various nucleophiles. Hanson and Wadsworth in 1980[239] reported the hydrogenolysis of 3β-tosyloxyandrost-5-ene-17-one (**331**) with lithium aluminium deuteride and with zinc-^{2}H acetic acid. Sterospecifically deuteriated steroids have been widely used in mechanistic, spectroscopic and biosynthetic studies[240]. Deuteriated steroids have played a central role in determining the stereochemistry of enzymatic hydroxylation[241] and in the mechanism of some rearrangement reactions[242]. In the present work 3β-tosyloxyandrost-5-ene-17-one (**331**) was prepared by reaction of DHEA with *p*-toluenesulphonyl chloride and pyridine by a known literature procedure[238] (**Scheme 91**). Lai *et al*[243] reported the stereospecific synthesis of steroid azides from alcohols with diphenylphosphoryl azide. DHEA was allowed to react with triphenylphosphine and diethylazidiocarboxylate to yield 3α-azidoandrost-5-ene-17-one (**332**). Novoka *et al*[244] in 1995 reported the synthesis of amino steroids via azide derivatives. Amino steroids have not been isolated in nature and thus using tosyl

steroids as an intermediate provided an efficient method for the preparation of amino steroids. In the present work 3α-azidoandrost-5-ene-17-one (**332**) was prepared via the traditional route (alcohol-tosylate-azide) demonstrating the use of tosyl compounds as intermediates. 3α–Azidoandrost-5-ene-17-one (**332**) was prepared on reaction of 3β-tosyloxy-DHEA (**331**) with sodium azide in DMF and resulted in inversion of the stereochemistry .

A convenient route to 3β-chloroandrost-5-ene-17-one (**333**) was via reaction of DHEA (**305**) with thionyl chloride for 30 minutes at room temperature. 3β-Bromoandrost-5-ene-17-one (**334**) was synthesized by the reaction of DHEA (**305**) with phosphorous tribromide at 0°C (**Scheme 91**). The yields, melting points and $[\alpha]_D$ values for compounds (**331**)-(**334**) are shown in **Table 26**. Characterisation of each compound using spectroscopic analysis proved to be satisfactory. Relevant spectroscopic data of the products (**331**)-(**334**) are illustrated in **Table 27**.



(i) $CH_3C_6H_4SO_2Cl$, C_6H_5N, 24 h, 25°C, (ii) NaN_3, DMF, reflux, 20 h, (iii) $SOCl_2$, 30 min, 25°C, (iv) PBr_3, diethylether, 0°C.

Scheme 91

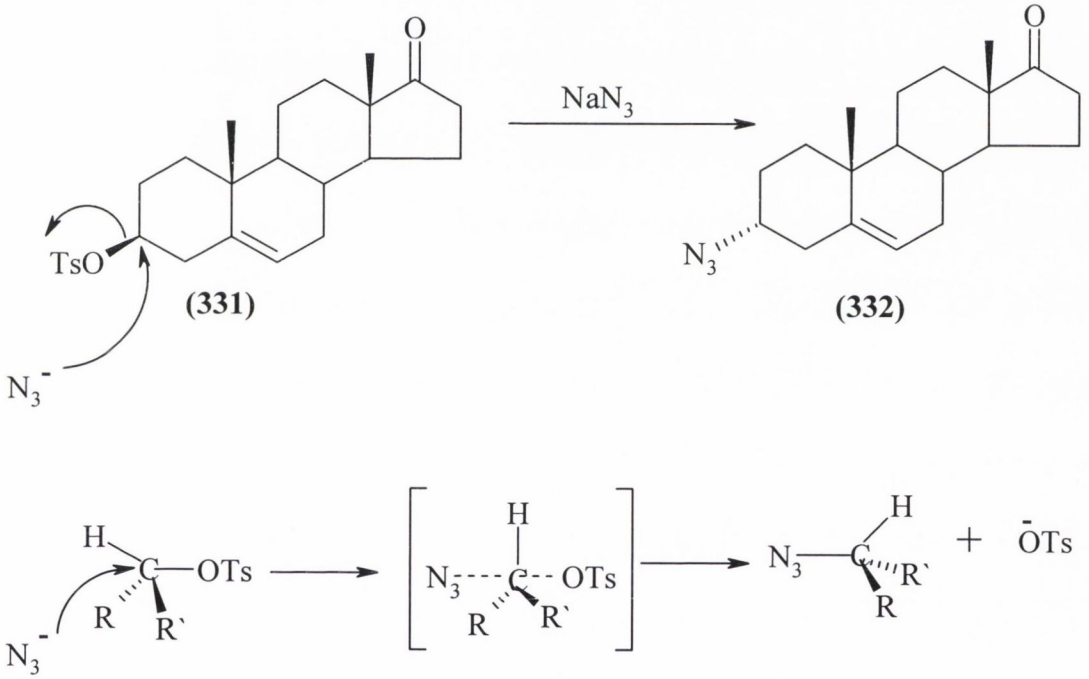
Table 26: Yield, melting point and $[\alpha]_D$ data for compounds (331)-(334)

Compound No.	% Yield	m.p. °C (Lit.)	$[\alpha]_D^{20}$ (Lit.)
331	55	157-158 (157-158)[238]	+40° (C=1, $CHCl_3$) (no lit.)
332	60	156-158 (156-159)[244]	+43° (44.2) (C=0.8, $CHCl_3$)
333	50	155-157 (155.5-156)[245]	+14° (13.5) (C=0.8, $CHCl_3$)
334	20	175-176 (174)[246]	+24° (C=1, $CHCl_3$) (no lit.)

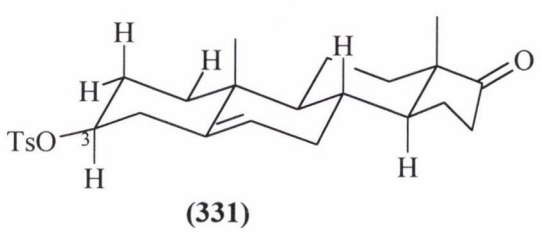
Table 27: Selected spectroscopic details for compounds (331)-(334)

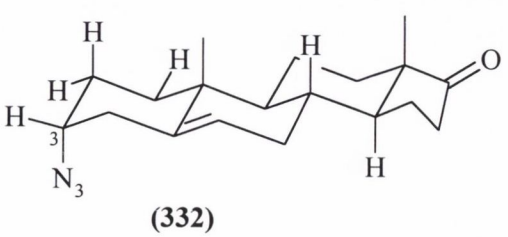
Compound No	IR Data ν_{max} (KBr)cm^{-1}	Selected ^{1}H-NMR Data ($CDCl_3$)ppm
331	1732 (C=O) 1356 (SO_2)	0.84 (3H, s, H-18), 1.23 (3H, H-19), 4.26-4.33 (1H, m, H-3α), 5.32 (1H, d, J=4Hz, H-6), 7.31 (2H, d, J=8.04Hz, H-3` and H-5`), 7.76 (2H, d, J=8.04Hz, H-2`and H-6`).
332	2115 (N_3) 1750(C=O)	0.73 (3H, s, H-18), 1.12 (3H, s, H-19), 3.83-3.87 (1H, m, H-3β), 5.27-5.28 (1H, d, J=5Hz, H-6).
333	1735 (C=O)	0.82 (3H, s, H-18), 1.25 (3H, s, H-19), 3.79-3.83 (1H, m, H-3α), 5.46 (1H, d, J=5Hz, H-6).
334	1735 (C=O)	0.88 (3H, s, H-18), 1.19 (3H, s, H-19), 3.85-3.90 (1H, m, H-3α), 5.46 (1H, d, J=5Hz, H-6).

It is proposed that compound (**332**) is formed via an S_N2 mechanism, whereas the halogen compounds (**333**) and (**334**) are formed via an S_Ni mechanism. The following mechanism is proposed for compound (**332**) (**Scheme 92**). The azide ion attacks the chiral C-3 from the α side of the steroid. C-3 undergoes inversion of its configuration. It has been suggested[247] that a transition state is formed in which the attacking azide ion becomes partially bonded to the reacting carbon atom before the incipient tosylate ion has become wholly detached from it. The stereochemistry of this compound was confirmed by the $[\alpha]_D$ reported in the literature. In the 3D drawing of compound (**332**) it can be seen that the azide at C-3 is in an axial position whereas in the starting material (**331**) the tosyloxy was in an equatorial position.

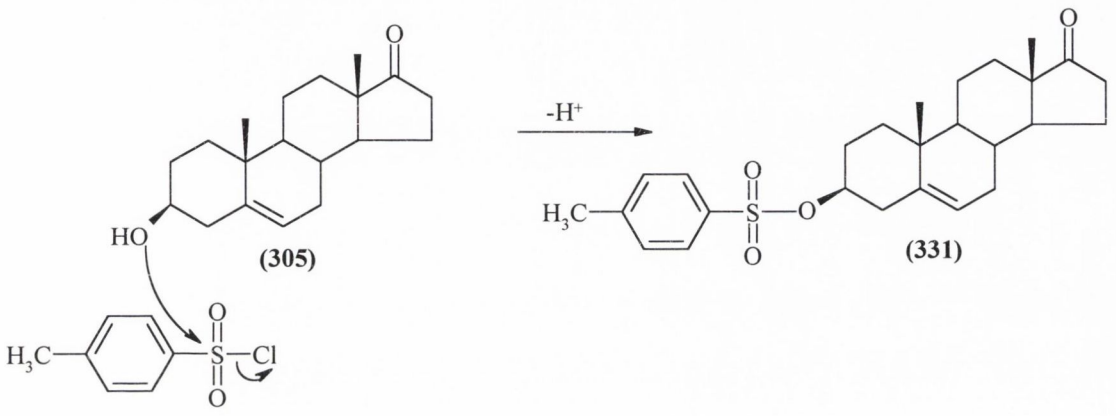


Scheme 92





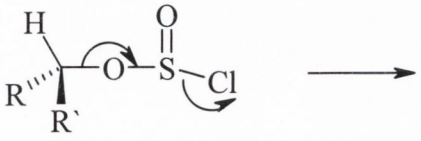
In the above mechanism shown for formation of the chiral compound (**332**), a reaction occurs in which a bond joining the tosylate group to the chiral C-3 is broken and thus the C-3 undergoes inversion of configuration. In the nucleophilic attack by the oxygen at C-3 of DHEA (**305**) on the sulphur of *p*-toluenesulphonyl chloride the bond from the chiral center is not broken and thus the configuration at C-3 in (**331**) product remains unchanged (**Scheme 93**). Here DHEA is the nucleophile.



Scheme 93

Reaction of DHEA (**305**) with thionyl chloride is an example of an S_Ni reaction that proceeds with retention of configuration[247] and the mechanism illustrated in **Scheme 94**. The sulphur atom is the most electron deficient atom and so is prone to attack by the hydroxy group to form a chlorosulphite intermediate (**335**). The C-O bond has not been broken in this step and so there cannot have been any change in the configuration at this center. The chlorosulphite intermediate now fragments. The C-O bond breaks to form the chlorosulphite anion. This further decomposes to form sulphur dioxide and a chlorine ion. This is the rate determining step of the reaction. Once the sulphur dioxide has escaped, the chlorine ion attacks the carbonium ion (**336**) to form the substituted compound (**333**). The nucleophile is formed on the same side as the original C-O. It then attacks the carbonium ion from this side and so results in the retention of configuration. The stereochemistry of this compound was confirmed by the $[\alpha]_D$ reported in the literature. In the 3D drawing of compound (**333**) it can be seen that the hydrogen at C-3 is in an axial position and in the starting material (**305**) the hydrogen is also in an axial position as retention of configuration has taken place.

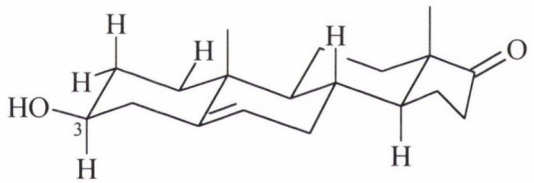
(305)



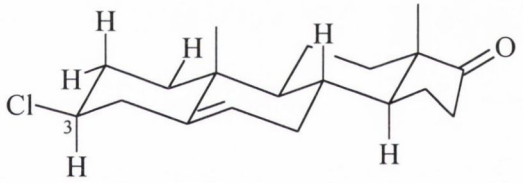
(335)

(336) (333)

Scheme 94

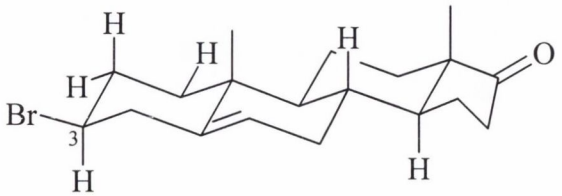


(305)

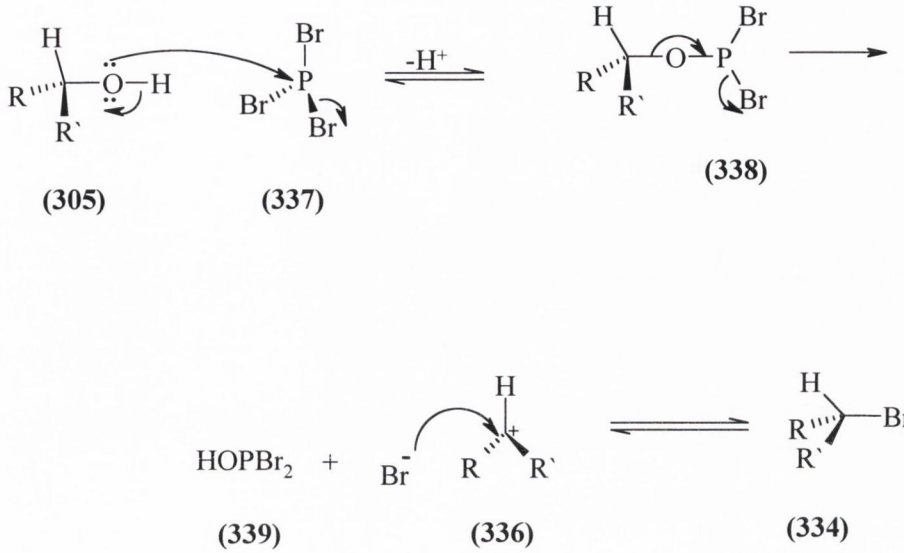


(333)

It is proposed that compound (**334**) is formed via a similar reaction mechanism with retention of configuration (**Scheme 95**). The phosphorus atom of phosphorus tribromide (**337**) is the most electron deficent atom and so is prone to attack by the hydroxy group to form the intermediate (**338**). The C-O bond breaks to form the cation (**336**) and (**339**). The cation (**336**) undergoes nucleophilic substitution from the bromine ion yielding compound (**334**).

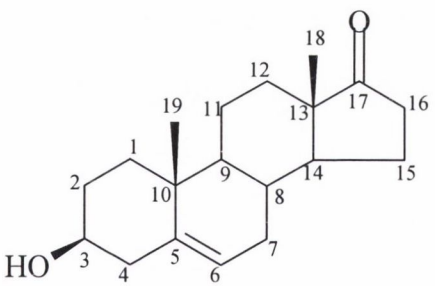


(334)



Scheme 95

To assist in the ^{1}H-NMR assignment of compounds (**331**)-(**334**) the spectroscopic data for DHEA is first described. In the infrared spectrum of DHEA (**305**) exhibits a broad OH band at ν3486cm^{-1}. The carbonyl at C-17 is observed at ν1741cm^{-1} .



(305)

Nineteen signals are observed in the ^{13}C-NMR spectrum of DHEA (**305**). Blunt and Stothers[207] using the following techniques assigned the carbon signals of DHEA:

(i) Shielding data.

(ii) Off-resonance decoupled spectra.

(iii) Comparsion with spectra of closely related compounds.

(iv) Selective proton decoupling.

(v) Isotopic labelling.

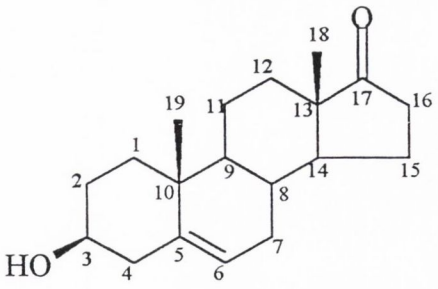
(vi) Lanthananide shift reagents.

(vii) Spin-lattice relaxation time (T1) values.

Owing to the complexity of the ^{1}H-NMR and ^{13}C-NMR spectra of DHEA the assignments are discussed in detail. In the present work four quaternary carbons are evident as the signals disappear in the DEPT 135 spectrum. They may be assigned as follows: 220.98ppm (C-17), 142.40ppm (C-5), 47.31ppm (C-13), 36.43ppm (C-10). The signal at 120.70ppm is typical of an alkene carbon (C-6). Further upfield C-3 appears at 71.33ppm. The remaining methine carbons are assigned as follows: 51.55ppm (C-14), 50.05ppm (C-9) and 31.28ppm (C-8). Eight methylene carbons are evident as the signals are inverted in the DEPT 135 spectrum and are assigned as follows: 41.94ppm (C-4), 37.80ppm (C-1), 35.61ppm (C-16), 31.28ppm (C-12), 31.24ppm (C-2), 30.56 (C-7), 21.64ppm (C-15), 20.14ppm (C-11). C-18 and C-19 are seen further upfield at 19.20ppm and 13.27ppm respectively.

^{1}H-NMR spectroscopy indicated the presence of twenty eight protons. Two singlets, each integrating for three hydrogens, which appears at δ0.80 and δ0.90 are assigned to H-18 and H-19. A multiplet in the region δ1.20-1.80 integrating for 11 protons is assigned to the following protons H-15, H-12, H-11, H-2, H-14, H-7, H-8 and H-1. One of the protons of H-15 is observed as a multiplet in the region δ1.85-1.91. One of the H-16 and H-7 protons is seen as a multiplet in the region δ1.96-2.07. H-4 is observed further downfield as a multiplet integrating for two protons δ2.07-2.37 due to the deshielding effect of the neighbouring hydroxy and alkene functionality. One of the H-16 protons appears as a multiplet at δ2.35-2.42. The hydroxy proton is seen as a broad singlet at δ2.62. H-3α appears as a multiplet at δ3.40-3.48 due to coupling with neighbouring H-2 and H-4. The alkene proton H-6 resonates as a doublet at δ5.29 integrating for one proton with a coupling constant of J=5.52Hz due to coupling with H-7.

In the present work a 2D H-H COSY NMR spectrum was also obtained for this compound which helped to assign the above signals (**Figure 16**). (The H-H COSY NMR technique identifies protons that are coupled to each other). A C-H COSY spectrum was also obtained which also helped in the assignment of the above signals (**Figure 17**). (The C-H COSY NMR technique shows the correlation between carbon signals and signals for hydrogens to which they are bonded).



(305)

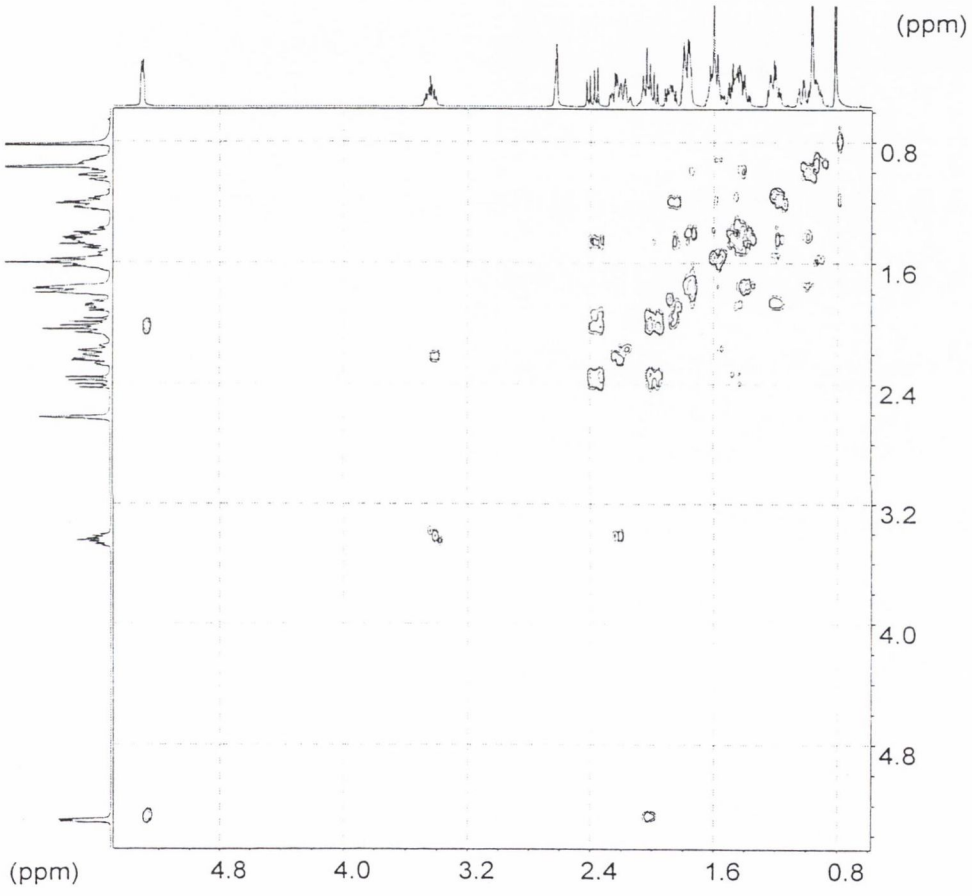
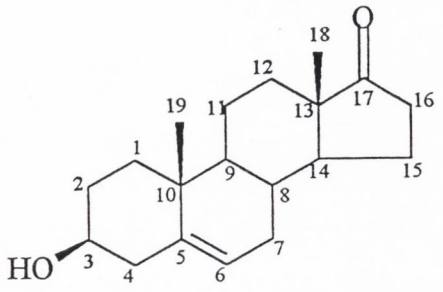


Figure 16*: H-H COSY spectrum of DHEA (**305**)*



(305)

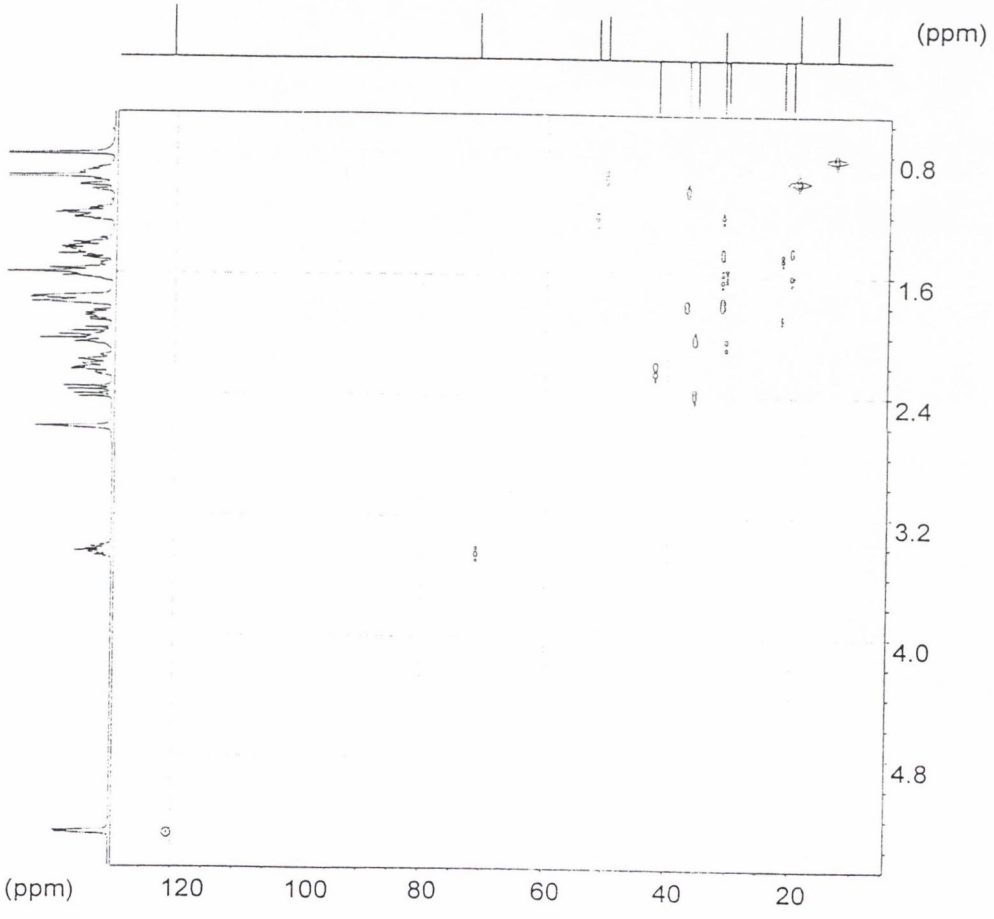


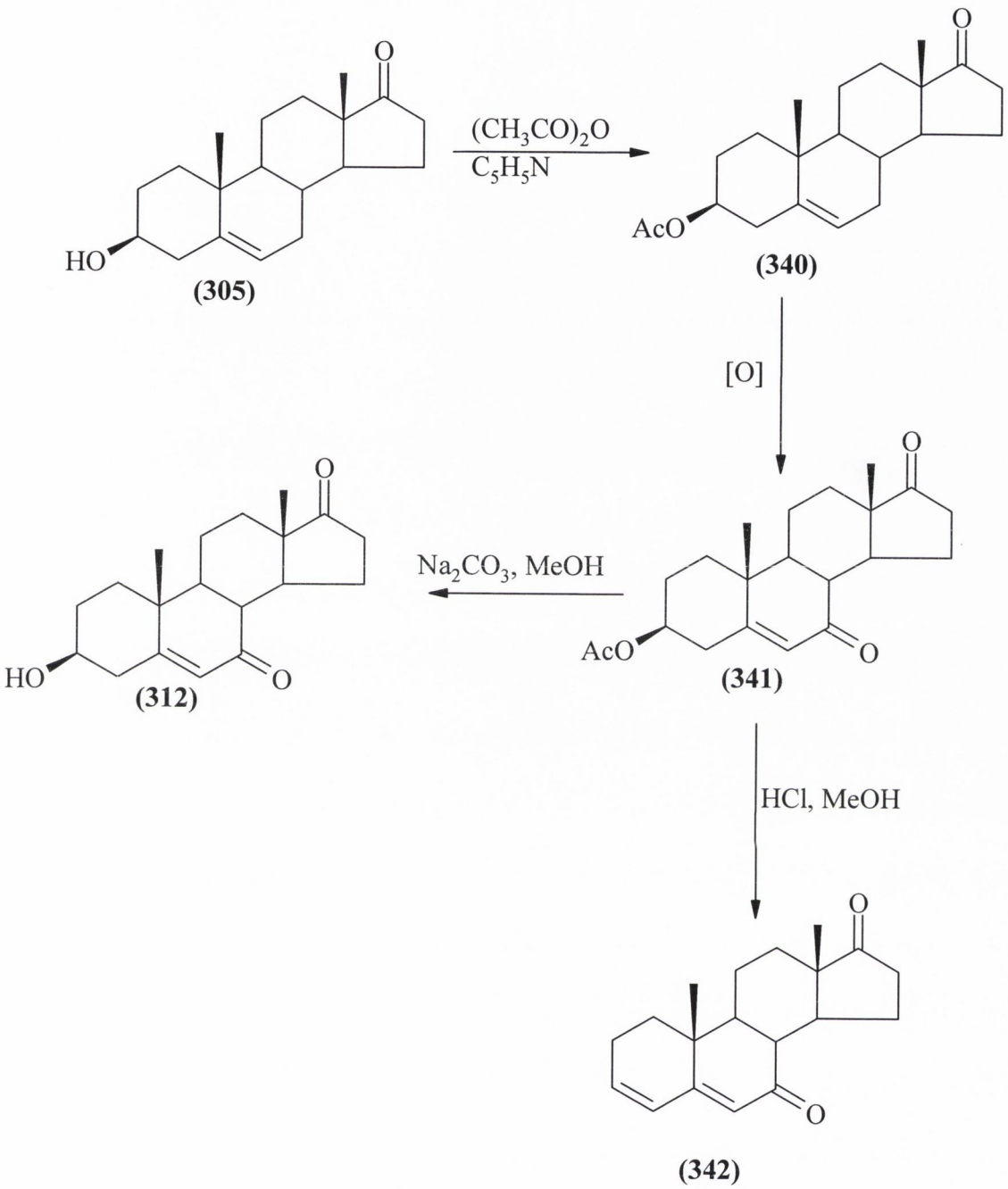
Figure 17*: C-H COSY spectrum of (305)*

7.3 Synthesis of 7-oxo-DHEA (312)

Billeter[248] attempted the synthesis of 7-oxo-DHEA (**312**) via reaction of DHEA (**305**) with acetic anhydride and pyridine forming 3β-acetoxyandrost-5-ene-17-one (**340**). Oxidation of (**340**) with chromium (VI) oxide resulted in the formation of the 7-oxo-derivative (**341**). Removal of the acetate protecting group at C-3 with conc. hydrochloric acid did not give the expected 7-oxo-DHEA (**312**) but the unexpected product $\Delta^{3,5}$-androstadien-7,17-dione (**342**) arising by initial hydrolysis of the acetate group and subsequent acid catalysed dehydration of the alcohol product formed (**Scheme 96**).

Later Lardy *et al*[251] reported the oxidation at C-7 of (**340**) with acetic anhydride and sodium chromate. In the present work a new examination of the oxidation of DHEA (**305**) at C-7 with various oxidizing reagents and reaction conditions was investigated (**Table 28**). Chromium trioxide and sodium acetate (Method 2), sodium chromate and acetic anhydride (Method 3) and *N*-hydroxyphthalimide (Method 5) have previously been used as oxidising agents, for successfully inserting a ketone at C-7[250, 251]. The highest yield for the synthesis of 3β-acetoxyandrost-5-ene-7,17-dione (**341**) was obtained when sodium chromate in acetic anhydride at 42°C for 72h was employed as the reaction conditions. Novel procedures (**1**) and (**4**) using chromium trioxide as the oxidising agent gave low to moderate yields and have not previously been reported in the synthesis of 3β-acetoxyandrost-5-ene-7,17-dione (**341**). The lowest yield was obtained for compound (**341**) when method (**2**) was employed using chromium trioxide and sodium acetate as the oxidising conditions.

The removal of the acetate protecting group of (**341**) was examined with the objective of maximizing the yield of 7-oxo-DHEA (**312**). The conditions used and the yields obtained for compound (**312**) is shown in **Table 29**. The highest yield for the synthesis of 7-oxo-DHEA (**312**) was obtained when either sodium carbonate or potassium carbonate were employed as base for hydrolysis of the acetate group. The novel procedure (**3**) gave a moderate yield, NH_3 has not been previously reported in the removal of the acetate group of 3β-acetoxyandrost-5-ene-7,17-dione (**341**).
Characterisation of compounds (**340**)-(**342**) and (**312**) using spectroscopic analysis proved to be satisfactory.


HO
O
(305)
$(CH_3CO)_2O$
C_5H_5N
AcO
O
(340)
[O]
AcO
O
O
(341)
Na_2CO_3, MeOH
HO
O
O
(312)
HCl, MeOH
O
O
(342)

Scheme 96

Table 28: Syntheses of 3β-acetoxyandrost-5-ene-7,17-dione (341)

Method	DHEA (mol)	Oxidising Reagent (mol)	Solvent (volume)	Time (h)	Temperature (°C)	Yield %
1	0.0015	CrO_3 (0.004)	CH_3CO_2H (24ml)	1	55	40
2	0.006	CrO_3 (0.02) CH_3CO_2Na (0.02)	CH_3CO_2H (23ml) $(CH_3CO)_2O$ (6.5ml)	1	56	20
3	0.0015	Na_2CrO_4 (0.002)	$(CH_3CO)_2O$ (20ml)	72	42	80
4	0.0015	CrO_3 (0.0068)	CCl_4 (4ml) $C_4H_{10}OH$ (0.5ml)	20	60	60
5	0.03	*N*-hydroxyphthalimide (0.003) $(C_6H_5CO)_2O_2$ (0.0002)	CH_3COCH_3 (10ml)	9	60	50

Table 29: Syntheses of 7-oxo-DHEA (312)

Method	(341) (mmol)	Base (mmol)	Solvent (volume)	Time (h)	Temperature (°C)	Yield %
1	0.2	Na_2CO_3 (0.02)	CH_3OH (2ml)	1	60	72
2	0.2	K_2CO_3 (0.02)	CH_3OH (2ml)	1	60	72
3	0.2	NH_3 (0.008)	CH_3OH (2ml)	2.5	60	58

In the infrared spectrum of 3β-acetoxyandrost-5-ene-17-one (**340**) the carbonyl at C-17 and the ester carbonyl at C-3 are seen as a broad peak at $\nu 1743 cm^{-1}$. In the ^{1}H-NMR spectrum of (**340**) H-3 is shifted to δ4.56 downfield in relation to the chemical shift value of H-3 in the starting material (**305**) at δ3.40-3.48. The methyl group of the acetate at C-3 appears as a singlet at δ2.30 integrating for three protons. The remaining signals differ only slightly from the values observed in compound (**305**). In the ^{13}C-NMR spectrum of (**340**) reveals all the required carbon signals. C-3 has shifted further downfield to 73.31ppm from 71.33ppm, while the acetate carbonyl carbon is seen at 169.93ppm.

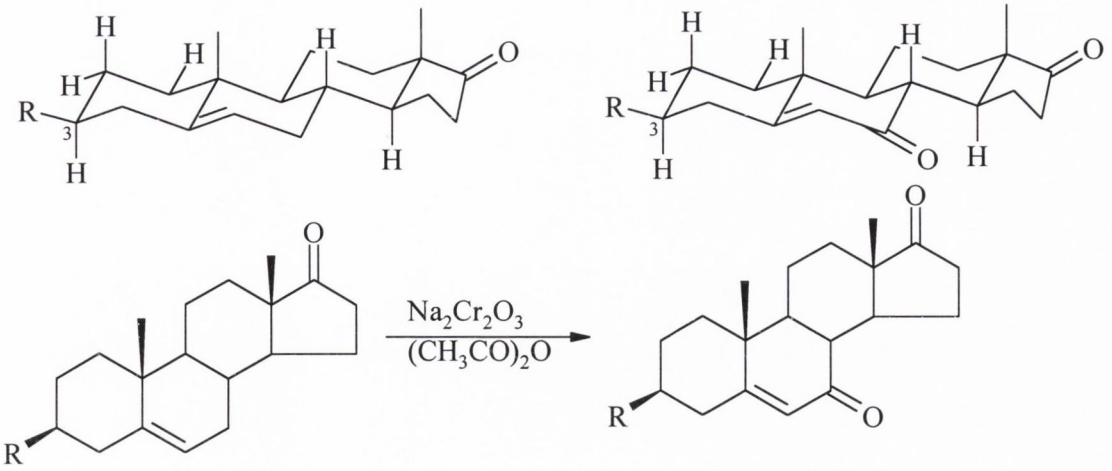
The infrared spectrum of 3β-acetoxyandrost-5-ene-7,17-dione (**341**) provides proof of succesful oxidation at C-7 by the appearance of an absorption at $\nu 1672 cm^{-1}$. In the ^{1}H-NMR spectrum H-6 now resonates as a singlet at δ5.74 providing further proof that oxidation has occurred at C-7. In the ^{13}C-NMR spectrum C-7 has shifted downfield to 202.82ppm due to the deshielding effect of the carbonyl group. The remaining signals differ only slightly from the values observed in compound (**340**).

In the infrared spectrum of 7-oxo-DHEA (**312**) it is obvious that the protecting acetate group has successfully been removed at C-3 by the apperance of an OH stretch at $\nu 3486 cm^{-1}$. In the ^{1}H-NMR spectrum the acetate methyl singlet at δ2.06 has disappeared, while in the ^{13}C-NMR spectrum C-3 has shifted upfield to 69.73ppm providing further proof of removal of the protecting group. The remaining signals differ only slightly from the values observed in compound (**341**).

In the ^{1}H-NMR spectrum of $\Delta^{3,5}$-androstadien-7,17-dione (**342**) the appearance of a multiplet integrating for two protons in the region δ6.10-6.20 is indicative that H-3 and H-4 are alkene protons. The ^{13}C-NMR spectrum further confirms that initial hydrolysis of the acetate group and subsequent acid catalysed dehydration of the alcohol product formed has occurred as H-3 and H-4 are shifted downfield to the region 123.45ppm-136.71ppm. The remaining signals differ only slightly from the values observed in compound (**341**).

7.4 Oxidation at C-7 of analogues of DHEA

A series of analogues of DHEA (**305**) e.g. 3β-tosylandrost-5-ene-17-one (**331**), 3β-chloroandrost-5-ene-17-one (**333**) and 3β-bromoandrost-5-ene-17-one (**334**) were reacted with sodium chromate in acetic anhydride at 42°C for 72h yielding the products 3β-tosylandrost-5-ene-7,17-dione (**343**), 3β-chloroandrost-5-ene-7,17-dione (**344**) and 3β-bromoandrost-5-ene-7,17-dione (**345**) (**Scheme 97**).



(331) R=OTs
(333) R=Cl
(334) R=Br

(343) R=OTs
(344) R=Cl
(345) R=Br

Scheme 97

By TLC analysis it was obvious that compounds (**344**) and (**345**) were unstable towards silica and were immediately purified by recrystallisation from ethanol. Joska[252] previously reported the synthesis of 3β-tosylandrost-5-ene-7,17-dione (**343**) by reaction of 3β-androst-5-ene-7,17-dione (**312**) with *p*-toluenesulphonylchloride and pyridine for 40h at room temperature. The yields, melting points and $[\alpha]_D^{20}$ values for compounds (**343**)-(**345**) are shown in **Table 30**. Characterisation of each compound using spectroscopic analysis proved to be satisfactory. Relevant spectroscopic data of the products (**343**)-(**345**) are illustrated in **Table 31**. In each of the compounds isolated it is proposed that the stereochemistry at C-3 remained unchanged as no chemical reaction was taking place at C-3.

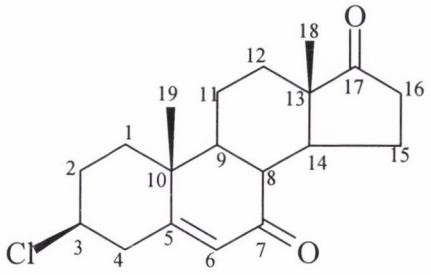
Table 30: Yield, melting point and $[\alpha]_D^{20}$ data for compounds (343)-(345)

Compound No.	Yield %	m.p. °C (Lit.)	$[\alpha]_D^{20}$ (lit.)
343	60	132-134 (131-132)	+63° (64) (C=1.95, $CHCl_3$)
344	30	161-162	+109° (C=1, $CHCl_3$)
345	20	151-153	+116° (C=1, $CHCl_3$)

Table 31: Spectroscopic data of compounds (343)-(345)

Compound No	IR Data ν_{max} (KBr)cm^{-1}	Selected ^{1}H-NMR Data ($CDCl_3$)ppm
343	1734 (C=O) 1674 (C=O)	0.84 (3H, s, H-18), 1.17 (3H, s, H-19), 4.34-4.39 (1H, m, H-3α), 5.62 (1H, bs, H-6), 7.33 (2H, d, J=8.04Hz, H-3` and H-5`), 7.76 (2H, d, J=8.04Hz, H-2` and H-6`).
344	1751 (C=O) 1674 (C=O)	0.93 (3H, s, H-18), 1.39 (3H, s, H-19), 3.90-4.04 (1H, m, H-3α), 5.70 (1H, s, H-6).
345	1734 (C=O) 1674 (C=O)	0.90 (3H, s, H-18), 1.35 (3H, s, H-19), 4.10-4.17 (1H, m, H-3α), 5.71 (1H, s, H-6).

In the infrared spectrum of 3β-chloroandrost-5-ene-17-one (**344**) a representative of this group of compounds exhibits the C-17 carbonyl absorption at ν1751cm^{-1} and the C-7 carbonyl absorption at ν1674cm^{-1} proving that the oxidation had been successful.



(344)

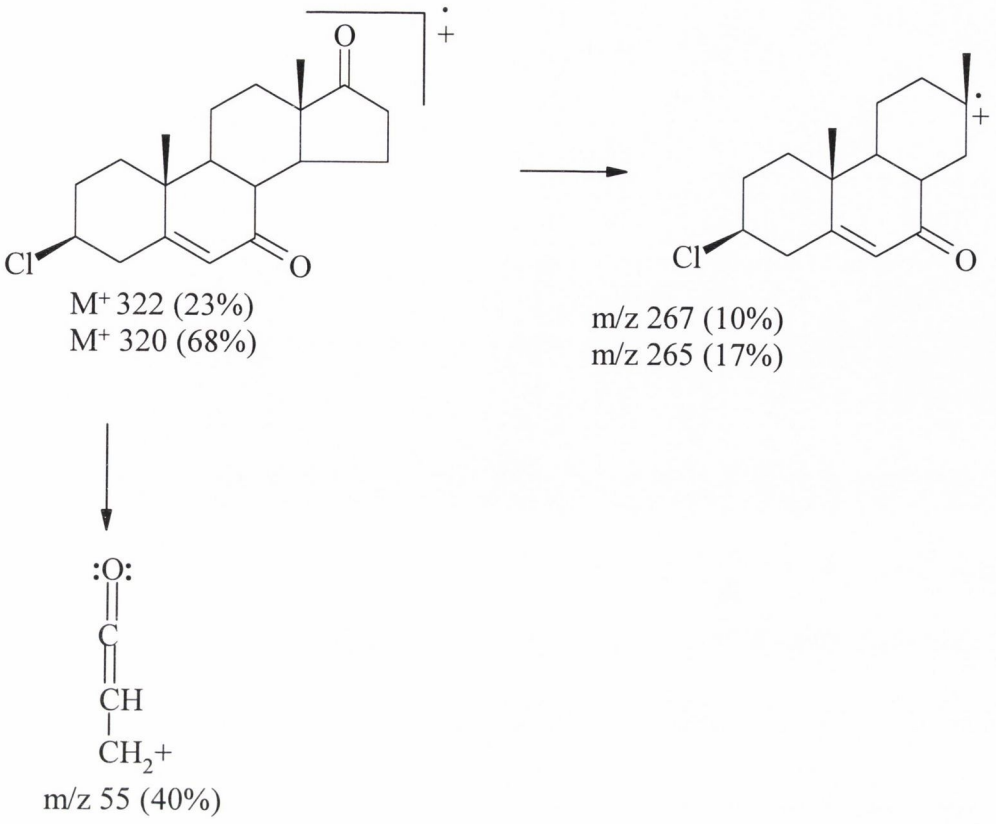
Nineteen signals are observed in the ^{13}C-NMR spectrum of (**344**). Five quaternary carbons are evident as the signals disappear in the DEPT spectrum and may be assigned as follows: 200.54ppm (C-17), 165.32ppm (C-7), 140.10ppm (C-5), 47.97ppm (C-13) and 38.31ppm (C-10). C-6 is observed at 126.09ppm while C-3 appears further upfield at 58.53ppm due to the deshielding effect of the chlorine atom. The methine carbons (C-14), (C-9), (C-8) resonate at 50.62ppm, 46.23ppm and 31.35ppm. The signals for C-4, C-1, C-16, C-12 and C-2 are seen at 42.85ppm, 38.64ppm, 35.39ppm, 33.24ppm and 31.35ppm respectively. C-15 and C-11 resonate

further upfield at 24.35ppm and 20.85ppm. The methyl carbons C-18 and C-19 appear as two signals at 17.19ppm and 13.66ppm completing this spectrum. In the ^{1}H-NMR spectrum of (**344**) the two singlets at δ0.93 and δ1.39 are assigned to H-18 and H-19 each integrating for three protons. H-3α is observed as a multiplet resonating at δ3.90-4.04. H-6 integrating for one proton appears as a singlet at δ5.70 providing further proof of the successful oxidation at C-7.

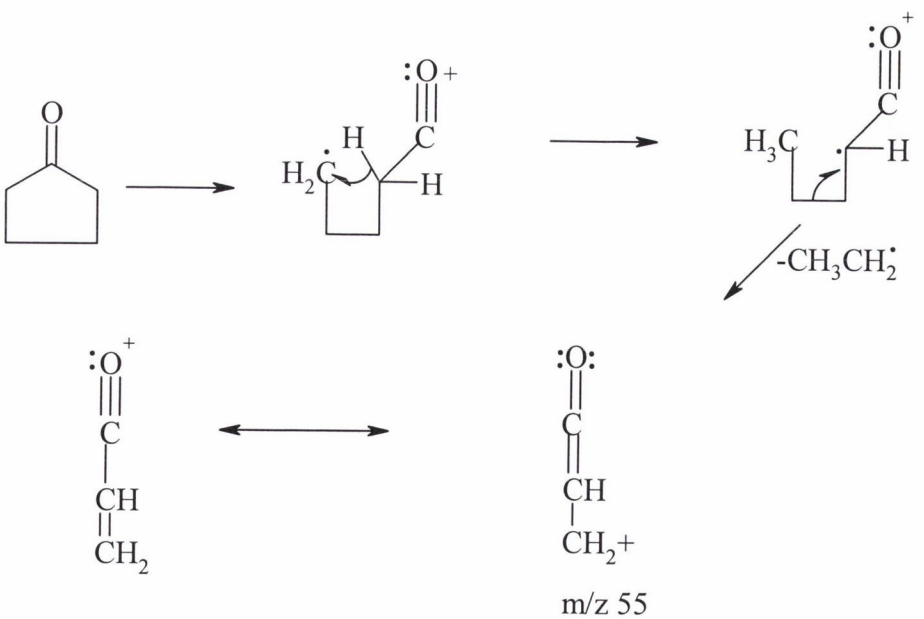
A low resolution mass spectrum for compound (**344**) was obtained. Molecular ions containing chlorine can be readily recognised and therefore are of value for inferring the presence of a chlorine. The ease of detection of chlorine containing ions is due to their characteristic isotope pattern. A compound that contains one chlorine will have two M^+ peaks because of the presence of the 37 isotope and 35 isotope[253]. (Chlorine consists of two stable isotopes ^{35}Cl and ^{37}Cl in the ratio of about 3:1). The observed fragmentation pattern for compound (**344**) is shown (**Scheme 98**). The molecular ion peak M^+ ($C_{19}H_{25}{}^{37}ClO_2$) is seen at m/z 322 in an abundance of 23% and the M^+ ($C_{19}H_{25}{}^{35}ClO_2$) at m/z 320 in 68% due to the Cl isotopes.

Fragmentation of ring D gives rise to a detectable ion at m/z 267 in 10% abundance and at m/z 265 in 17% abundance due to the chlorine isotopes. The mechanism for this fragmentation is similar to that observed in cyclopentanone[254] (**Scheme 99**). Hydrogen shift to convert a primary radical to a conjugated secondary radical followed by the formation of the resonance-stable ion m/z 55 is observed for cyclopentanone. A peak at m/z 55 is observed for compound (**344**) in 40% abundance.

In the mass spectrum of DHEA (**305**) the detectable ions at m/z 55 and m/z 233 are observable in 60% and 13% providing further proof that fragmentation of ring D is occurring. In the mass spectrum of (**345**) which contains one bromine and should have two M^+ peaks stemming from the presence of the ^{81}Br and ^{79}Br isotopes. (Bromine consists of two stable isotopes ^{79}Br and ^{81}Br in approximately equal amounts). The molecular ion peak M^+ ($C_{19}H_{25}{}^{79}BrO_2$) is seen at m/z 366 in an abundance of 100% and at M^+ ($C_{19}H_{25}{}^{81}BrO_2$) m/z 364 in 99% due to the Br isotopes. A peak at m/z 55 in 33% abundance is observed thus confirming the fragmentation pattern obtained for (**343**) and (**305**).



Scheme 98



Scheme 99

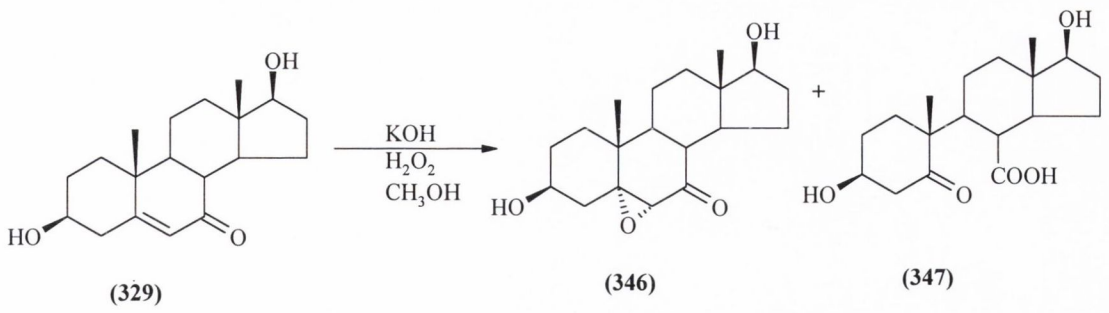
7.5 Epoxidation of $\Delta^{3,5}$-androstadien-7,17-dione (342)

Transformation of $\Delta^{3,5}$-androstadien-7,17-dione (**342**) to the corresponding epoxide is discussed in this section. Epoxides are extremely useful for the introduction of extra functionality on the steroid nucleus. As mentioned in Chapter 2, epoxides (oxiranes) are highly strained three membered rings which are extremely reactive in the presence of various reagents. Nucleophilic ring opening of these compounds is the most common reaction observed but they can also react with electrophiles, acids, bases, reducing agents and some oxidising agents[123-129].

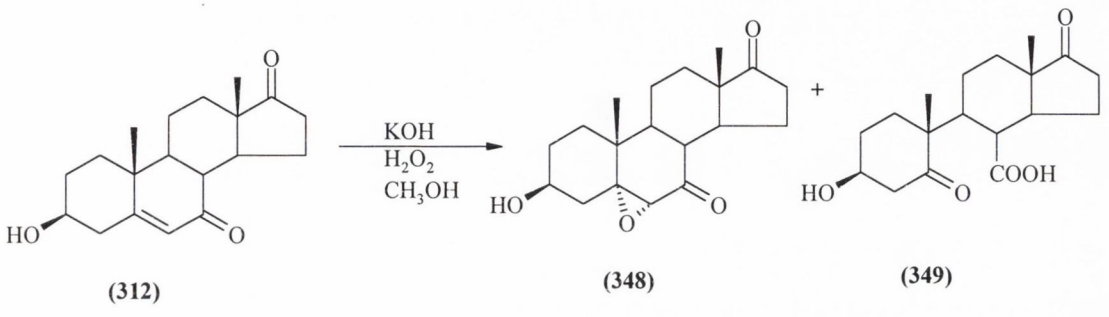
The objective of this work was the addition of alkoxide and alcohol functional groups at position C-3 and C-4 to $\Delta^{3,5}$-androstadien-7,17-dione (**342**). In the present work 3α,4α-epoxyandrost-5-ene-17-one (**328**) was prepared by treating $\Delta^{3,5}$-androstadien-7,17-dione (**342**) with *m*CPBA, followed by a ring opening reaction with cerium ammonium nitrate (CAN) and alcohol.

Kolek and Molunowick[255] reported the epoxidation of 3β,17β-dihydroxyandrost-5-ene-7-one (**329**) with potassium hydroxide and hydrogen peroxide in methanol to give 3β-17β-dihydroxy-5α,6α-epoxyandrostan-7-one (**346**) and the transformation product carboxylic acid (**347**). Reaction of 7-oxo-DHEA (**312**) with similar reagents formed 3β-hydroxy-5α,6α-epoxyandrostan-7,17-dione (**348**) and the carboxylic (**349**) with an increase in reaction rate (**Scheme 100**).

Hanson *et al*[256] showed that the epoxidaton of some steroid 4 and 5-enes with biphasic systems derived from permanganate-metal sulphates affords β-epoxides whereas epoxidation with peracids affords α–epoxides[257]. The epoxidation of 3β,17β–diacetoxyandrost-4-ene (**350**) was not stereospecific with the copper sulphate system. A mixture of α and β epoxides was obtained (**Scheme 101**).

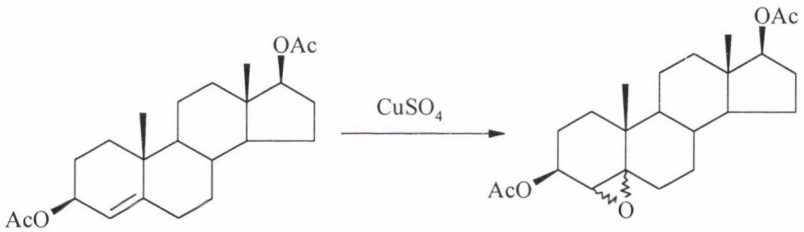


(329) (346) (347)



(312) (348) (349)

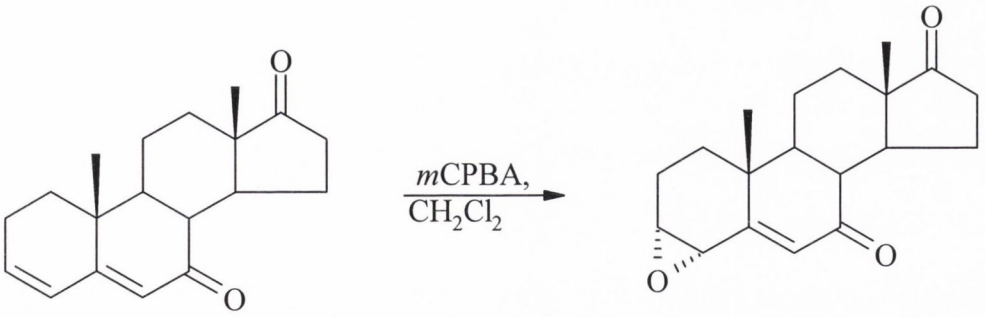
Scheme 100



(350) (351)

Scheme 101

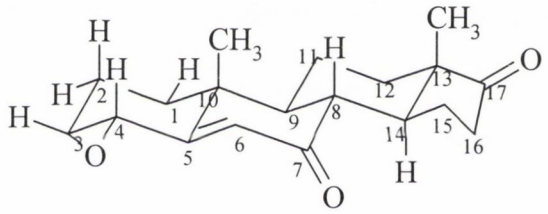
In the present work using Bourban`s[258] procedure, 3α,4α-epoxyandrost-5-ene (**328**) was prepared by treating $\Delta^{3,5}$-androstadien-7,17-dione (**342**) with *m*CPBA at room temperature for 24h under a nitrogen atmosphere (**Scheme 102**). Epoxidation of such steroids with peracids is expected to afford α–epoxides[257]. In this case addition of oxygen occurs on the α-face of the C_3-C_4 bond[258]. This reaction is known as the ``Prilezhaev reaction`` and discussed in Chapter 2. By T.L.C analysis it was apparent that the reaction did not go to completion, and by varying the reaction conditions and the amounts of reagents used it was found that two equivalents of the oxidising reagent afforded optimum yields. On examination of the proton NMR spectra it was evident that the epoxide was obtained as a single isomer which was isolated by column chromatography.



(342) **(328)**

Scheme 102

The infrared spectrum of 3α,4α-epoxyandrost-5-ene-7,17-dione (**328**) shows the characteristic carbonyl absorbances for C-17 and C-7 present at ν1745cm^{-1} and 1680cm^{-1} respectively. The epoxy C-O stretching bands are observed at ν1250, ν899 and ν735 cm^{-1}.



(328)

In the ^{1}H-NMR spectrum of (**328**) the methyl hydrogens are seen as two signals at δ0.64 and δ0.86 integrating each for three protons. H-4β appears as a doublet at δ3.19, J=3.0Hz due to coupling with H-3β. The stereochemistry at C-3 and C-4 is examined by looking at the 3D conformation of 3α,4α-epoxyandrost-5-ene-7,17-dione (**328**). H-3β is in an equatorial position and H-4β is in an axial position. The J_{ab} typical for eq-eq coupling is 2-3Hz[254]. J_{ab} typical for eq-ax is also 2-3Hz but it is known that peracids afford α-epoxides[257] and therefore it is proposed that eq-ax coupling is observed and hence the oxygen has added on to the α face of the C_3-C_4 double bond. H-3β appears as a multiplet at δ3.22 due to coupling with the neighbouring H-4β proton and H-2. H-6 appears as a singlet at δ5.78 integrating for one proton.

In the ^{13}C-NMR spectrum of (**328**) five quaternary carbons are evident as they disappear in the DEPT spectrum. They may be assigned as follows: 219.36ppm (C-

17), 199.24ppm (C-7), 160.70ppm (C-5), 47.31ppm (C-13) and 35.14ppm (C-10). The signal at 130.15ppm is assigned to C-6. The disappearance of the two other alkene carbons in the starting material and the appearance of two signals at 51.54ppm and 45.48ppm is indicative that epoxidation has been successful. The remaining methine carbons are assigned as follows: 51.55ppm (C-14), 49.12ppm (C-9) and 44.70ppm (C-8). The following methylene signals are observed and are inverted in the DEPT 135 spectrum: 34.88ppm (C-1), 23.48ppm, 25.67ppm, and 30.10ppm (C-12, C-16, C-2), 19.87ppm and 19.96ppm (C-15 and C-11). C-18 and C-19 are seen at 13.17ppm and 17.01ppm.

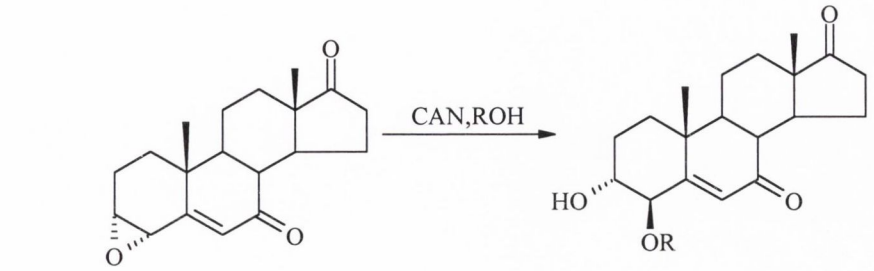
7.6 Regioselective ring opening of 3α,4α-epoxyandrost-5-ene-7,17-dione (328)

The purpose of this investigation was the regioselective ring opening of 3α,4α-epoxyandrost-5-ene-7,17-dione (**328**) with the appropriate alcohols catalysed by CAN with the objective of synthesizing novel 3-alkoxy-4-hydroxyandrost-5-ene-7,17-diones (**Scheme 103**) and hence introducing an alkoxy substituent at C-3 and a hydroxy group at C-4 of the DHEA structure (**305**).

Epoxide ring opening can occur in either neutral, basic or acidic solution, but it is known that the presence of acid accelerates ring opening. In neutral and basic media, the reaction proceeds via nucleophilic attack on the neutral epoxide. In acidic media protonation of the epoxide precedes nucleophilic attack. It is generally agreed that the reaction follows an S_N2 mechanism in neutral or basic solution. In acid-solution the mechanism has most often been termed borderline S_N2 but has been the subject of much discussion. Normally backside attack of the nucleophile occurs on the epoxide carbon resulting in a Walden inversion at this centre. The 1,2 disubstituted products necessarily have a *trans* relationship of the nucleophile to the oxygen leaving group[123].

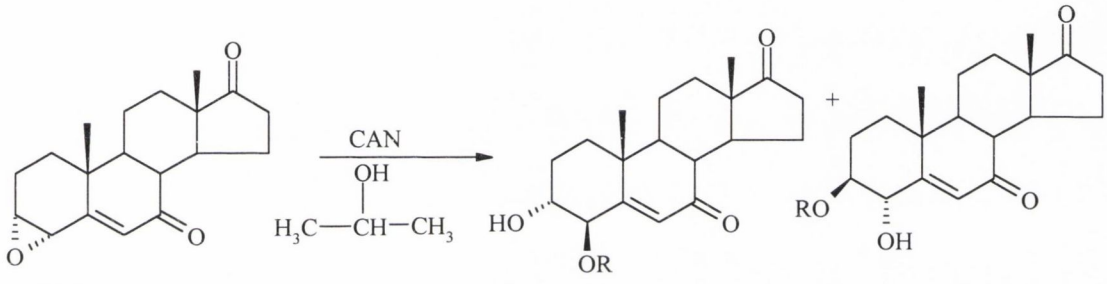
With unsymmetrical epoxides nucleophilic attack is governed by both the structure of the epoxide and the exact reaction conditions. With a monosubstituted epoxide nucleophilic attack can occur at either the less or more substituted end of the epoxide as shown in **Scheme 24**, Chapter 2 in this thesis. In neutral and basic solution, attack at the less sterically hindered site predominantly occurs. In acid solution, there is usually a greater tendancy for nucleophilic attack at the carbon atom

which can better accommodate a positive charge in the transition state, that is the more substituted carbon[123]. Equatorial substitution is generally more favourable than axial for steric reasons.



(328)

(352) R=CH_3
(353) R=CH_2CH_3



(328)

(354a) R=$(CH_3)_2CH$ **(354b)** R=$(CH_3)_2CH$

Isomers

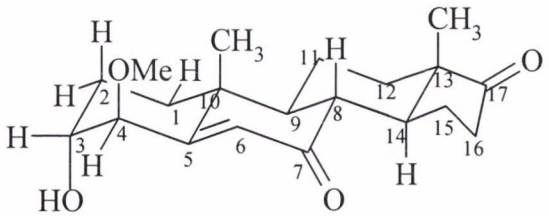
Scheme 103

3α,4α-Epoxyandrost-5-ene-7,17-dione (**328**) was treated with CAN and the appropriate alcohol. The epoxide (**328**) was opened regioselectively with methanol and ethanol to afford the following products: 3α-hydroxy-4β-methoxy androst-5-ene-7,17-dione (**352**) and 4β-ethoxy-3α-hydroxyandrost-5-ene-7,17-dione (**353**). On examination of the proton NMR spectra it was evident that the products (**352**) and (**353**) were obtained as single isomers. 3α-Hydroxy-4β-isopropoxyandrost-5-ene-7,17-dione (**354a**) and 3β-isopropoxy-4α-hydroxyandrost-5-ene-7,17-dione (**354b**) were obtained as regioisomers and this was evident from the proton NMR spectrum. The products were obtained in moderate yields and were purified by flash column chromatography over silica gel. The relevant spectroscopic data for compounds (**352**)-(**354**) are shown in **Table 32**. All compounds gave satisfactory molecular ions when examined by EI.

Table 32: Spectroscopic Data for compounds (352)-(354)

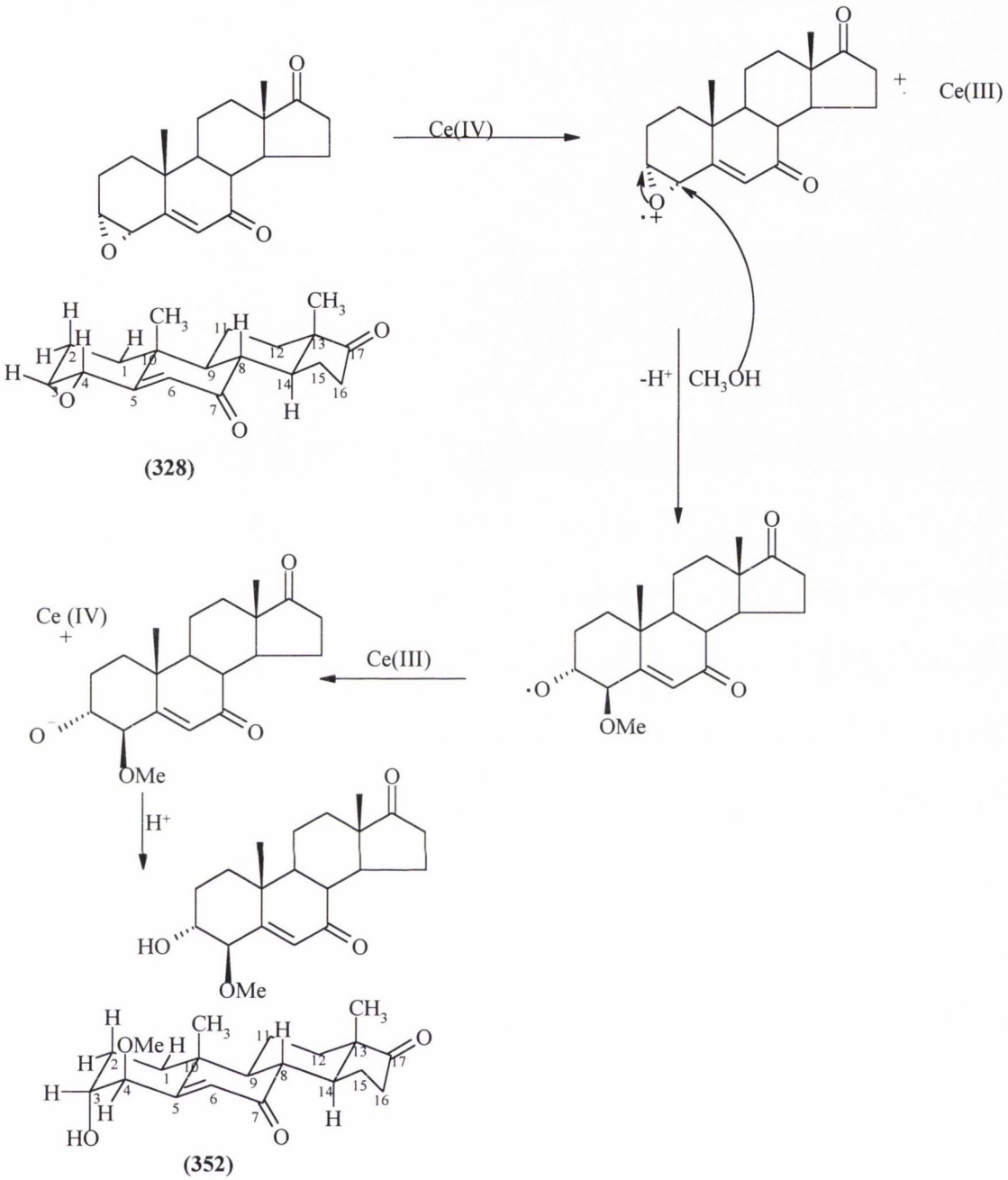
Compound No	IR Data ν_{max} (film)cm^{-1}	Selected ^{1}H-NMR Data δ ($CDCl_3$)
352	3447 (OH) 1734 (C=O) 1670 (C=O)	0.89 (3H, s, H-18), 1.32 (3H, s, H-19), 3.55 (3H, s, OCH_3), 3.55 (1H, d, J=3Hz H-4β), 4.10 (1H, m, H-3α), 5.85 (1H, s, H-6).
353	3448 (OH) 1737 (C=O) 1670 (C=O)	0.90 (3H, s, H-18), 1.24 (3H, s, H-19), 1.34 (3H, t, $OCH_2C\underline{H}_3$), 3.28-3.45 (2H, m, $OC\underline{H}_2CH_3$), 3.66 (1H, d, J=2.52Hz, H-4β), 4.08-4.13 (1H, m, H-3α), 5.83 (1H, s, H-6).
354	3444 (OH) 1736 (C=O) 1671 (C=O)	0.86 (3H, s, H-18), 1.28 (2H, s, H-19), 1.30 (1H, s, H-19), 1.50-1.53 (6H, 2x s, $OCH(C\underline{H}_3)_2$), 3.12-3.19 (1H, m, $OC\underline{H}(CH_3)_2$), 3.62–5.32 (2H, m, H-4, H-3), 5.79 (0.33H, s, H-6), 6.02 (0.67H, s, H-6).

In the infrared spectrum of 3α-hydroxy-4β-methoxy androst-5-ene-7,17-dione (**352**) the carbonyl absorptions of C-17 and C-7 appear at ν1734cm^{-1} and ν1670cm^{-1} respectively. In the infrared spectrum, the broad band which occurs in the region ν3477cm^{-1} is assigned to the hydroxy group at position 3.



(352)

In assigning the ^{1}H-NMR spectrum of (**352**) the mechanism of the ring opening reaction was considered. The reaction most probably occurs through a one electron transfer reaction with the initial formation of the epoxonium radical cation (**Scheme 104**). It was thought that commerically available CAN catalyses the nucleophilic ring opening of (**352**) at the less hindered carbon i.e C-3. However by examination of the ^{1}H-NMR spectrum this is not observed.



Scheme 104

Examination of the chair configuration of 3α,4α-epoxyandrost-5-ene-7,17-dione (**328**) showed that H-3β is in an equatorial position, H-4β is in an axial position. If nucleophilic attack occurred at C-3 inversion, of configuration would have occurred thus the proton at C-3 would now be in an axial position and H-4β would remain in an axial position. The J_{ab} typical for axial-axial coupling is 8-10Hz. The coupling constant observed for $J_{3,4}$ is 3Hz. It is proposed that substitution has not occurred at C-3. If nucleophilic ring opening occurred at C-4, with inversion of configuration, H-3β would remain in an equatorial and H-4 would now be in an equatorial position. J_{ab}

typical for equatorial–equatorial coupling is 2-3Hz. It is proposed from examination of the ^{1}H-NMR spectrum that substitution has occurred at C-4.

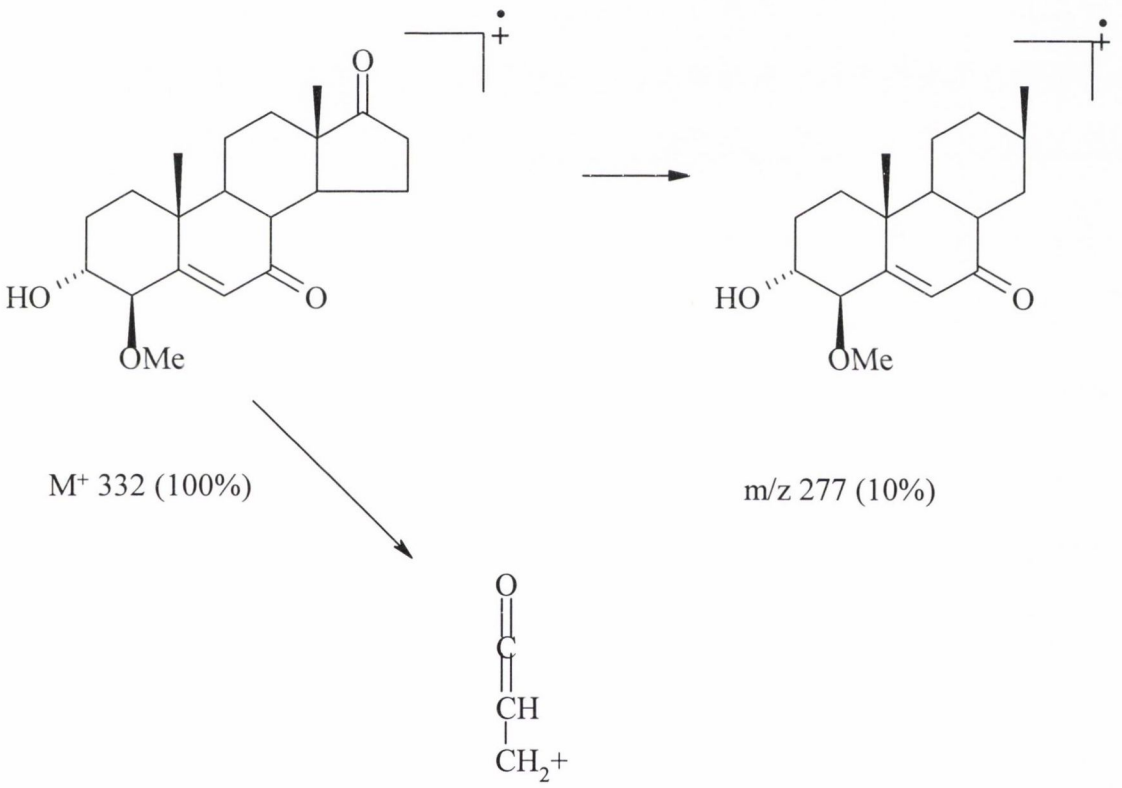
In the ^{1}H-NMR spectrum of (**352**) H-18 and H-19 resonate at δ0.89 and δ1.32 respectively as two singlets each integrating for three protons. The methoxy signal resonates as a singlet at δ3.55. H-4α is seen as a doublet at δ3.55, J=3Hz due to coupling with H-3β. H-3β resonates as a multiplet at δ4.10-δ4.12 due to coupling with neighbouring H-2 and H-4α protons. The singlet at δ5.85 integrating for one proton represents the alkene proton H-6.

In the ^{13}C-NMR spectrum of 3α-hydroxy-4β-methoxyandrost-5-ene-7,17-dione (**352**) five quaternary carbons are evident as the signals disappear in the DEPT spectrum. They may be assigned as follows: 219.93ppm (C-17), 200.65ppm (C-7), 161.05ppm (C-5), 47.46ppm (C-13), 38.16ppm (C-10). C-6 resonates at 130.36ppm while C-3 and C-4 appear at 84.79ppm and 68.72ppm. The signals for C-3 and C-4 assignments were confirmed by analysing the C-H COSY spectrum for this compound. The H-4α signal at δ3.55 in the ^{1}H-NMR spectrum corresponded to a signal in the ^{13}C-NMR spectrum at 84.79ppm. The H-3β signal at δ4.10 in the ^{1}H-NMR spectrum corresponded with a signal at 68.72ppm in the ^{13}C-NMR spectrum. C-14, C-9 and C-8 appear at 45.39ppm, 44.55ppm and 38.16ppm. The methylene signals which are inverted in the DEPT 135 spectrum appear in the general region 44.55ppm-19.36ppm. C-18 and C-19 are seen more upfield at 17.04ppm and 13.24ppm.

^{1}H-NMR spectroscopy of 3α-hydroxy-4β-isopropoxyandrost-5-ene-7,17-dione (**354a**) and 3β-isopropoxy-4α-hydroxyandrost-5-ene-7,17-dione (**354b**) reveals the presence of regioisomers. A singlet at δ0.86 intregrating for three hydrogens is assigned to H-18; H-19 protons are observed as two singlets at δ1.28 and δ1.30 each integrating for two and one proton respectively. The methyls of the isopropoxy group appear as two singlets at δ1.50 and δ1.53. H-6 appears as two singlets. The first regioisomer is observed as a singlet at δ5.79 integrating for 0.33H. H-6 in the second regioisomer appears as a singlet at δ6.02 integrating for 0.67H. H-3, H-4 and the methine of the isopropoxy group appear as a multiplet integrating for three protons in the range δ3.12-5.32. The ^{13}C-NMR spectrum of (**354a**) and (**354b**) provides further proof of a regioisomeric product by the appearance of two signals for the respective

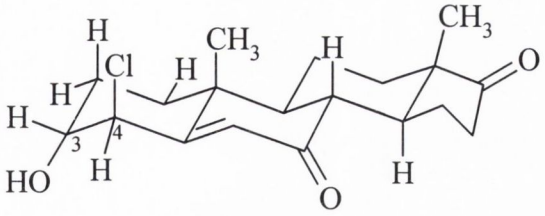
carbons. C-17, C-7, C-5, C-6 resonate as two signals at 219.87ppm, 220.22ppm (C-17), 200.49ppm, 200.97ppm (C-7), 156.62ppm, 162.24ppm, (C-5) 130.0ppm and 132.29ppm (C-6). C-19 also appears as two signals at 17.07ppm and 17.38ppm. It is proposed that for compounds (**352**) and (**353**) nucleophilic substitution only occurred at C-4 whereas for compound (**354**) substitution occurred at both C-3 and C-4.

A high resolution mass spectrum for compound (**352**) was examined. The observed fragmentation pattern is shown in (**Scheme 105**). The molecular ion $M^+(C_{19}H_{28}O_4)$ is seen at m/z 332.20002 in an abudance of 100%. The characteristic fragment at m/z 277 in 10% abudance is observed together with another fragment at m/z 55 (25%).



Scheme 105

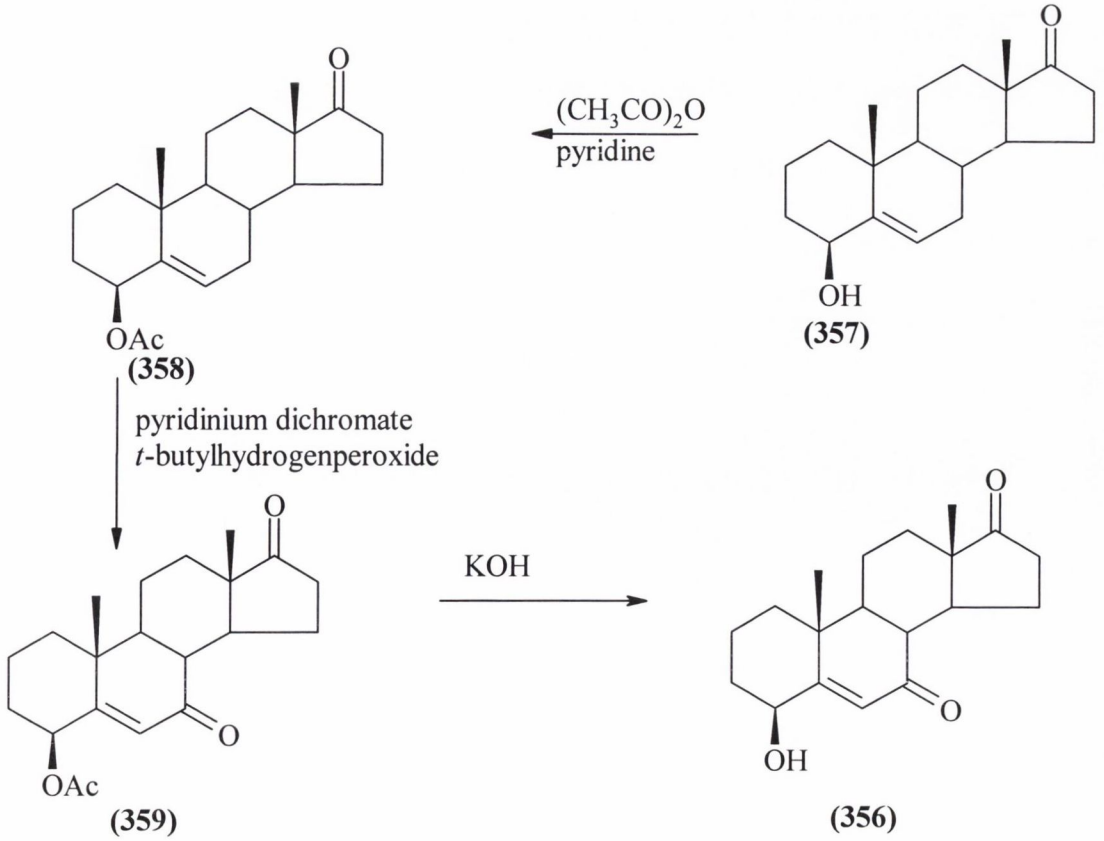
In support of the structural assignment, the work of Bourban *et al*[258] on the hydrolysis of 3α,4α-epoxyandrost-5-ene-7,17-dione (**328**) with HCl gave 4β-chloro-3α–hydroxyandrost-5-ene-7,17-dione (**355**). This reaction takes place in an acid solution. Substitution occurs at C-4 with inversion of configuration via an S_N2 mechanism. $J_{H\text{-}4\beta,H\text{-}3\alpha}$ observed was 3.5Hz which is indicative of equatorial–equatorial



(355)

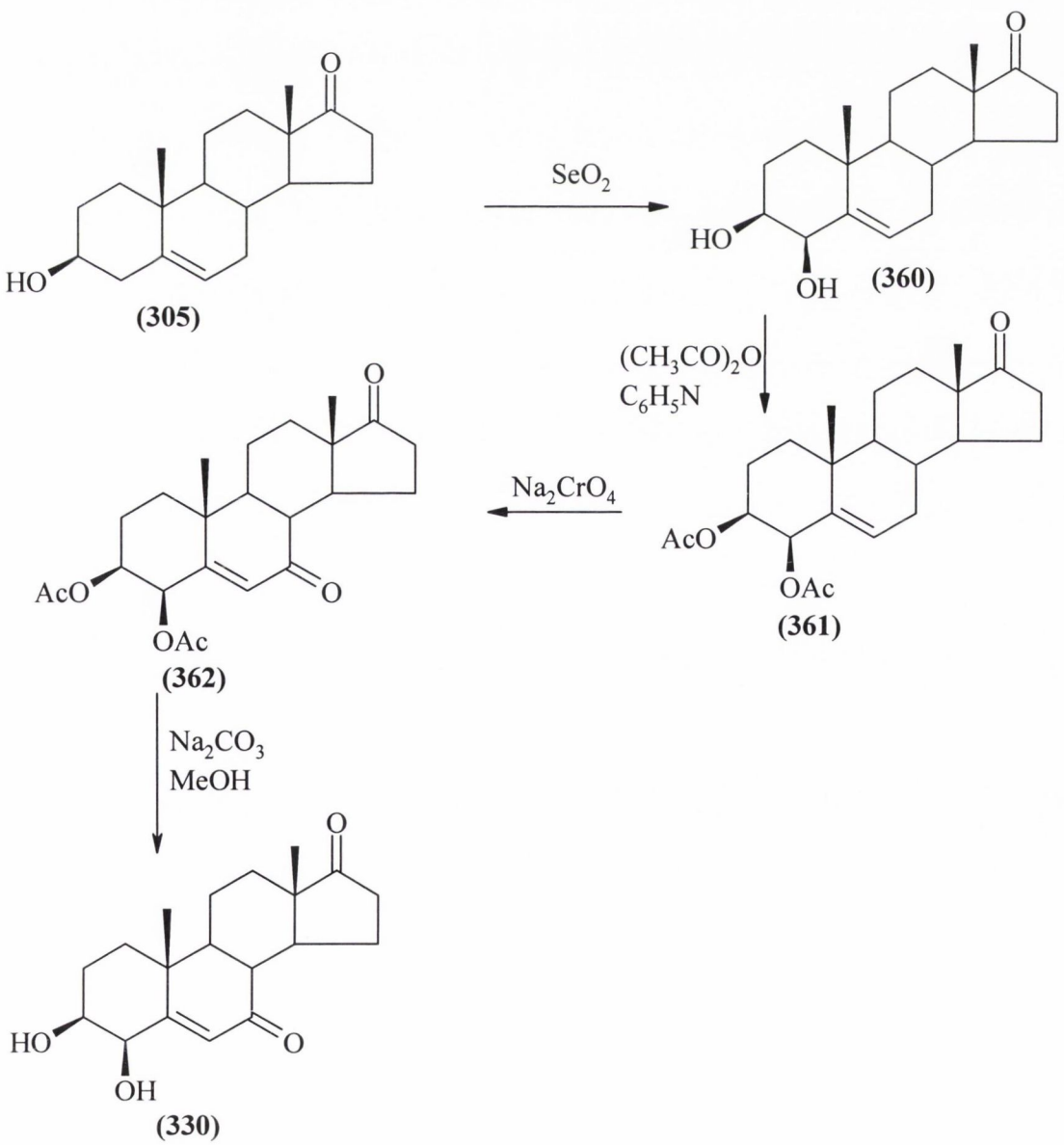
7.7 Synthesis of 3β,4β-androst-5-ene-7,17-dione (330)

Numazawa *et al*[259] reported that aromatase is the cytochrome P-450-enzyme complex responsible for estrogen biosynthesis *in vivo*[260-262]. Inhibitors of this complex might serve to modulate estrogen dependent processes and have a role in treating estrogen dependent diseases such as breast cancer[263]. For this reason various steroids have been tested in a number of laboratories as inhibitors of aromatase. Numazawa[259] reported the synthesis and biochemical evaluations of 4β-hydroxyandrost-5-ene-7,17-dione (**356**). 4β-Hydroxyandrost-5-ene-17-one (**357**) was reacted with acetic anhydride and pyridine to give 4β-acetoxyandrost-5-ene-17-one (**358**) which was oxidised at C-7 to give 4β-acetoxyandrost-5-ene-7,17-dione (**359**) with pyridinium dichromate and *t*-butylhydrogenperoxide. Subsequent alkaline hydrolysis with potassium hydroxide gave 4β-hydroxyandrost-5-ene-7,17-one (**356**) (**Scheme 106**).



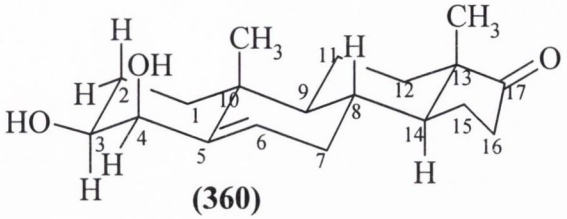
Scheme 106

It was observed that the introduction of a hydroxy group at C-4β markedly enhanced affinity of the active site of aromatase. In the present work a hydroxy analogue of 7-oxo-DHEA was synthesized with the objective of investigating similar biological properties as those described by Numazawa. DHEA (**305**) was treated with selenium dioxide under reflux conditions to afford 3β,4β-dihydroxyandrost-5-ene-17-one (**360**)[233]. (**360**) was reacted with acetic anhydride and pyridine yielded 3β,4β-acetoxyandrost-5-ene-17-one (**361**). Reaction of (**361**) with sodium chromate in acetic anhydride at 42°C for 72 h gave 3β,4β-diacetoxyandrost-5-ene-7,17-dione (**362**). Compound (**362**) was not characterised due to its instability on silica gel and was immediately converted to (**330**) by reaction of the crude (**362**) with sodium carbonate in methanol (**Scheme 107**). All compounds apart from (**362**) were purified by flash column chromatography over silica gel.



Scheme 107

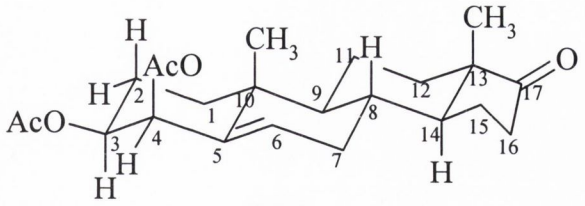
Characterisation of (**360**), (**361**) and (**330**) using spectroscopic analysis proved to be satisfactory. In the infrared spectrum of compound (**360**) the hydroxy groups absorb at $\nu 3340 cm^{-1}$. The C-17 carbonyl is seen at $\nu 1743 cm^{-1}$.



(360)

In the ^{1}H-NMR spectrum of compound (**360**) twenty eight protons are observed. Two singlets each integrating for three hydrogens, which appear at δ0.95 and δ1.08 are assigned to H-18 and H-19. A multiplet in the region δ3.50-3.55 is assigned to H-3α. H-4α is seen further downfield at δ4.13, J=3Hz due to coupling with H-3. Examination of the chair conformation of the known compound (**360**) shows that H-3α is in an axial position while H-4α is in an equatorial position. If H-4 and H-3 were both in axial positions then the coupling constant $J_{ax\text{-}ax}$ would have to be in the range 8-10Hz[254]. However from the ^{1}H-NMR spectrum the coupling constant observed is 3Hz therefore H-4 cannot be in an axial position and is thus in an equatorial position. Therefore β-hydroxylation has occurred at C-4. The stereochemistry of this compound was confirmed by the $[\alpha]_D$ reported in the literature [265] ($[\alpha]_D$ Lit[-28.5]$_D$). H-6 resonated as a doublet, J=5Hz at δ5.70.

In the ^{13}C-NMR spectrum of compound (**360**) four quaternary carbons are present as the signals disappear in the DEPT spectrum. They may be assigned as follows: 220.55ppm (C-17), 141.01ppm (C-5), 47.08ppm (C-13) and 35.70ppm (C-10). The signal at 127.24ppm is assigned to C-6. Further upfield C-3 and C-4 appear at 71.11ppm and 76.59ppm. The remaining methine carbons are assigned as follows: 51.45ppm (C-14), 49.87ppm (C-9) and 30.99ppm (C-8). Seven methylene signals are visible as the signals are inverted in the DEPT 135 spectrum and may be grouped as follows: 36.45ppm, 35.33ppm, 30.91ppm, 30.49ppm, 24.72ppm, 21.37ppm and 20.49ppm (C-16, C-1, C-7, C-2, C-12, C-15 and C-11). C-18 and C-19 are further downfield at 19.36ppm and 13.08ppm.

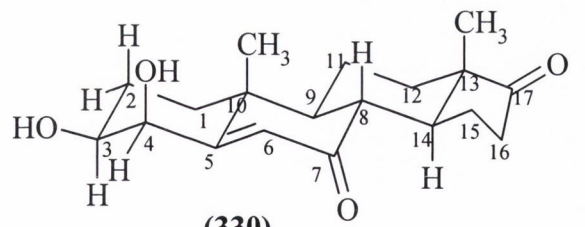


(361)

In the ^{1}H-NMR of compound (**361**) the appearance of two singlets at δ2.09 and δ2.16 each integrating for three protons is proof that protection of both hydroxy groups with an acetate at C-3 and C-4 was successful. H-3α, H-4α and H-6 are shifted to δ4.74-4.79, δ5.54, and δ5.87 respectively, downfield in relation to their chemical shift values in the starting material (**360**) due to the deshielding effect of the ester groups at C-3 and C-4.

In the ^{13}C-NMR spectrum of (**361**) the appearance of two new signals at 20.58ppm and 20.94ppm is further proof that there are two acetate groups present. The acetate carbonyls at C-3 and C-4 appear at 169.76ppm and 169.55ppm, while the remaining signals differ only slightly from the values observed in compound (**360**). In the formation of compound (**361**) by reacting (**360**) with acetic anhydride and pyridine the C-O bonds at C-3 and C-4 are not being broken, therefore it is proposed that the configuration at C-3 and C-4 remains the same as it is in the starting material (**360**).

In the infrared spectrum of (**330**) the C-17 and C-7 carbonyl band absorbances are seen at ν1732cm^{-1} and ν1665cm^{-1}. The hydroxy absorbs at ν3400cm^{-1}.



(330)

The ^{1}H-NMR spectrum displays two singlets resonating close to each other at δ0.92 and δ1.20 these are assigned to H-18 and H-19. A multiplet occurring in the region δ3.50-3.91 is assignable to H-3α. The H-4α resonates as a doublet at δ4.17, J=3Hz. This confirms that the stereochemistry at C-3 and C-4 has been retained. Further downfield H-6 appears as a singlet at δ5.87. The fact that H-6 is now a singlet and not a doublet is further proof of successful oxidation at C-7.

The ^{13}C-NMR spectrum displays more convincing evidence that the C-7 carbonyl substituent is now present in the structure. The appearance of the carbonyl at 200.12ppm displays more convincing evidence that oxidation has been successful at C-7. The remaining C-17 carbonyl is seen at 220.12ppm. The quaternary C-5 at 139.12ppm disappears in the DEPT 135 spectrum. C-6 appears in the alkene region at 120.04ppm. A C-H COSY was useful in the assignment of C-3 and C-4 at 79.81ppm and 83.22ppm. The H-4β signal at δ4.17 in the ^{1}H-NMR spectrum corresponded to a signal in the ^{13}C-NMR spectrum at 83.22ppm. The H-3β signal at δ3.50 in the ^{1}H-NMR spectrum corresponded with a signal at 79.81ppm in the ^{13}C-NMR spectrum. The readily assignable methyl carbons appear in the region 13.10ppm (C-18) and 19.39ppm (C-19).

Structural confirmation of compound (**330**) was obtained by high resolution mass spectrometry. The high resolution mass spectrum for compound (**330**) shows the molecular ion M^{+}318.18315 in an abudance of 100%. For identification purposes by low resolution mass spectrometry (1mg) (**330**) was reacted with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide 97% (0.5ml) in chloroform (1ml) to give the TMS derivative of (**330**).

7.8 Conclusion

DHEA can be easily modified at C-3, C-4 and C-7 and a number of chemical transformations of DHEA has been demonstrated. This work also involved the synthesis of 7-oxo-DHEA analogues. Thus DHEA (**305**) and 7-oxo-DHEA (**312**) provides a gateway to known and novel steroids with potential therapeutic properties and without toxic effects. Future work on this project could include :

(i) Extension of ring opening reactions of 3α,4α-epoxyandrost-5-ene-7,17-dione with various nucleophiles providing a route to novel substituents at C-3 and C-4 of the DHEA steroid.

(ii) Alkylation at C-3 of DHEA and 7-oxo-DHEA.

(iii) Hydroxylation studies at C-7 and C-16 of DHEA and displacement of the hydroxy group with various nucleophiles.

(iv) Eludication of the novel compounds for thermogenic activity is to be investigated by Dr. R. Porter, Department of Biochemistry, Trinity College Dublin.

Experimental Data

Experimental Note

Melting points were determined on a Gallenkamp melting point appartus and were not corrected. The infrared spectra were recorded on a Nicolet 205-FT-IR spectrometer. ^{1}H-NMR spectra were recorded in deutrated chloroform with tetramethylsilane (TMS) as an internal standard unless other wise stated. These were recorded on a Bruker spectrometer DPX 400 (400.14MHz) and on a Bruker MSL-300 spectrometer (300.13MHz). ^{13}C-NMR were recorded in deutrated chloroform on a Bruker spectrometer MSL-300 (75.46MHz) and a Bruker DPX 400 spectrometer (100.62MHz) unless otherwise stated. Column chromatography was undertaken using Merck Kieselgel $PF_{254+366}$. Optical measurement were measured on an Optical Activity AA-10 Automatic Polarimeter using monochromatic sodium line at 589nm. High resolution mass spectrometry was carried out in the Department of Pharmaceutical Sciences, University of Strathclyde and Department of Chemistry, University College Cork. Elemental analysis was carried out in the Microanalysis Laboratory, Department of Chemistry, University College Dublin.

All solvents were distilled before use. Anhydrous solvents were prepared according to literature methods. THF was dried and distilled from calcium hydride followed by a second drying and distillation over sodium wire. Dichloromethane was dried by refluxing from calcium hydride. Diethyl ether and toluene were dried by refluxing over sodium wire. Benzene was dried by slow and very careful fractional distillation from sodium. Methanol and DMSO were dried over calcium hydride. Pyridine was dried and distilled from potassium hydroxide.

Chapter 2

General Preparation of Schiff Bases (121)-(127)

A solution of the appropriately substituted aryl aldehyde (0.1mol) and the appropriately substituted aryl amine (0.1mol) in ethanol (50ml) was heated to reflux for 3 h. The reaction mixture was then reduced to 10ml *in vacuo* and on standing the Schiff base product recrystallised from ethanol.

3,4-Methylenedioxybenzylidene-4-methoxycarboxyaniline (121) was obtained as yellow crystals in 80% yield, m.p. 129-130°C and recrystallised from EtOH, (lit. m.p.[112] 130-131°C).

IRν_{max} (KBr) 1625 (C=N), 1710 (CO_2CH_3) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.91 (3H, s, CO_2CH_3), 5.90 (2H, s, 3,4-OCH_2O), 6.86-8.07 (7H, m, aromatic Hs), 8.27 (1H, s, CH=N).

3,4-Methylenedioxybenzylidene-4-methoxyaniline (122) was obtained as yellow crystals in 92% yield, m.p. 98-99°C (lit. m.p.[102] 98-99°C).

IRν_{max} (KBr) 1630 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.78 (3H, s, OCH_3), 5.96 (2H, s, 3,4-OCH_2O), 6.70-7.57 (7H, m, aromatic Hs), 8.31 (1H, s, CH=N).

4-Chlorobenzylidene-4-methoxycarbonylaniline (123) was obtained as yellow crystals in 60% yield, m.p.155-156°C (lit. m.p.[102] 155-156°C).

IRν_{max} (KBr) 1625 (C=N), 1710 (CO_2CH_3) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.96 (3H, s, CO_2CH_3), 6.78-8.19 (8H, m, aromatic Hs), 8.43 (1H, s, CH=N).

Benzylidene-4-methoxybenzylidene aniline (124) was obtained as colourless crystals in 60% yield, m.p. 63-64°C (lit. m.p.[112] 62°C).

IRν_{max} (KBr) 1620 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.85 (3H, s, $-OCH_3$), 6.90-7.38 (9H, m, aromatic Hs), 8.38 (1H, s, CH=N).

Benzylideneaniline (125) was obtained as colourless crystals in 86% yield, m.p. 54°C, (lit. m.p.[102] 53°C).

IRν_{max} (KBr) 1630 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 6.95-7.43 (10H, m, aromatic Hs), 8.43 (1H, s, CH=N).

4-Fluorobenzylidene-4-methoxycarbonylaniline (126) was obtained as yellow crystals in 39% yield, m.p. 113-114°C (lit. m.p.[113] 113-114°C).

IRν_{max} (KBr) 1620 (C=N), 1710 (CO_2CH_3) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.93 (3H, s, CO_2CH_3), 6.85-8.15 (8H, m, aromatic Hs), 8.42 (1H, s, CH=N).

1-Acetyl-N-(4-methoxyphenyl)ethanimine (127)

Equimolar quantites of *p*-anisidine (5g, 0.04mol) and butanedione (0.04mol) were mixed at room temperature. Anhydrous benzene (1ml) was added to obtain a homogenous solution. The mixture was allowed to stand at room temperature for 15 h

and then diluted with benzene (5ml of benzene/3ml of mixture). The solution was then dried with sodium sulphate, the solvent evaporated and the imine isolated by vacuum distillation to afford a yellow solid in 55% yield, m.p. 31-33°C (lit. m.p.[114] 33°C).

IR ν_{max} (KBr) 1698 (C=O), 1630 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.99 (3H, s, $-CH_3$), 2.48 (3H, s, $-COCH_3$), 3.79 (3H, s, $-OCH_3$), 6.62-6.91 (4H, m, aromatic Hs).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 13.89 ($\underline{C}H_3$), 24.47 ($CO\underline{C}H_3$), 55.32 ($O\underline{C}H_3$), 114.15 (C-3`and C-5`), 121.90 (C-2` and C-6`) 142.22 (C-1`), 157.17, 165.26 (C-4` and $\underline{C}$=N), 200.53 ($\underline{C}$=O).

General Preparation of 1,4-diaryl-3-vinyl-azetidin-2-ones (128)-(134)

Method A:

To a solution of Schiff base (10mmol) and triethylamine (1.0g, 10mmol) in dichloromethane (50ml) at reflux under nitrogen was added dropwise over 45 min a solution of crotonyl chloride (1.045g, 10mmol) in dichloromethane (25ml). The reaction mixture was then refluxed for 1 h and washed with water (2x50ml). The dichloromethane layer was dried over anhydrous (Na_2SO_4) and evaporated to yield the crude product. The required β-lactams were obtained by column chromatography over silica gel (eluent, light petroleum (b.p. 40-60°C): diethyl ether, solvent gradient 9:1 to 7:3 for compounds (**128**)-(**131**) and (**133**), in the case of compounds (**132**) and (**134**) 100% dichloromethane. The products were recrystallised from ethanol.

Method B:

Crotonic acid (0.002mol) was mixed with 2-chloro-*N*-methylpyridinium iodide (0.0024mol) and tri-*n*-propylamine (0.006mol) in anhydrous dichloromethane (30ml) under a nitrogen atmosphere at room temperature. The suspension was heated to

reflux. After the suspension became clear, a solution of the appropriate imine (0.002mol) in dichloromethane (10ml) was added and the reaction mixture was refluxed overnight. The solution was then washed with water, 2% HCl (2x50ml) aqueous solution, and water again. The organic layer was dried over (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel as outlined in Method A.

1,4-(Methoxycarbonylphenyl)-4-(3,4-methylenedioxyphenyl)-3-vinylazetidin-2-one (128) was obtained as colourless crystals in 26% yield (method A), m.p. 115-116°C (lit. m.p.[122] 115-116°C).

IRν_{max} (KBr) 1750 (C=O), 1710 ($\underline{C}OOCH_3$) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.77 (1H, d (br), $J_{3,4trans}$=3.0Hz, H-3), 3.85 (3H, s, -CO_2CH_3), 4.76 (1H, d, $J_{4,3trans}$=3.0Hz, H-4), 5.15-6.39 (3H, m, -CH=CH_2), 5.94 (2H, m, OCH_2O), 6.74-8.07 (7H, m, aromatic Hs).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 52.01 ($CO_2\underline{C}H_3$), 61.34 (C-3), 64.31 (C-4), 105.62 ($O\underline{C}H_2O$), 120.01(C-6), 108.79, 109.21, 129.94, 130.44, 130.83, 141.03, (aromatic Cs, C-5), 148.08 (C-4`), 166.42, 166.43 (β-lactam $\underline{C}$=O, $\underline{C}OOCH_3$).

1-(4-Methoxyphenyl)-4-(3,4-methylenedioxyphenyl)-3-vinylazetidin-2-one (129) was obtained as colourless crystals in 47% (method A) and 52% (method B) yield, m.p. 110-111°C (lit.[122] 110-111°C).

IRν_{max} (KBr) 1750 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.60 (1H, d (br), $J_{3,4trans}$=2.5Hz, H-3), 3.67 (3H, s, -OCH_3), 4.72 (1H, d, $J_{4,3trans}$=2.5Hz, H-4), 5.05-6.40 (3H, m, CH=CH_2), 5.95 (2H, s, -OCH_2O), 6.62-7.49 (7H, m, aromatic Hs).

^{13}C-NMR (75MHz)

(CDCl$_3$)ppm 55.37 (O<u>C</u>H$_3$), 61.15 (C-4), 64.05 (C-3), 101.30 (O<u>C</u>H$_2$O), 105.79, 108.65, 125.29 (aromatic Cs), 117.73 (C-3` and C-5`), 119.06 (C-2` and C-6`), 122.06 (C-6), 130.61 (C-1`), 130.63 (C-5), 147.86 (C-1``), 156.00 (C-4`), 164.69 (β-lactam <u>C</u>=O).

4-(4-Chlorophenyl)-1-(4-methoxycarbonylphenyl)-3-vinylazetidin-2-one (130) was obtained as colourless crystals in 19% yield (Method A), m.p. 91-92°C (lit.[122] 91-92°C).

IRν_{max} (KBr) 1750 (C=O), 1710 (COOCH$_3$) cm^{-1}

^{1}H-NMR (300MHz)

δ (CDCl$_3$) 3.76 (1H, br (d), $J_{3,4trans}$=2.47Hz, H-3), 3.83 (3H, s, -CO$_2$CH$_3$), 4.80 (1H, $J_{4,3trans}$=2.47Hz, H-4), 5.36-6.36 (3H, m, -CH=CH$_2$), 6.74-8.06 (8H, m, aromatic Hs).

^{13}C-NMR (75MHz)

(CDCl$_3$)ppm 52.06 (CO$_2$<u>C</u>H$_3$), 60.72 (C-3), 64.31 (C-4), 120.60 (C-6), 119.81, 125.54, 127.10, 129.57, 13.90 (aromatic Cs and C-5), 134.50 (C-1`), 134.67 (C-1``), 140.80 (C-4), 165.30, 166.34 (β-lactam <u>C</u>=O, <u>C</u>OOCH$_3$).

1-(4-Methoxyphenyl)-4-phenyl-3-vinylazetidin-2-one (131) was obtained as colourless crystals in 18% yield (Method A), m.p. 127-128°C (lit. m.p.[122] 127-128°C).

IRν_{max}(KBr) 1750 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ (CDCl$_3$) 3.65 (1H, br (d) $J_{3,4trans}$=2.5Hz, H-3), 3.72 (3H, s, -OCH$_3$), 4.75 (1H, d, $J_{4,3trans}$=2.5Hz, H-4), 5.10-6.12 (3H, m, -CH=CH$_2$), 6.61-7.54 (9H, m, aromatic Hs).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 55.26 ($O\underline{C}H_3$), 60.86 (C-3), 64.08 (C-4), 114.52 (C-3` and C-5`), 117.00 (C-2` and C-6`), 119.82 (C-6), 123.86, 127.11, 128.98 (C-2``, C-6``, C-3``, C-5``, C-4``), 130.05 (C-5), 155.96 (C-4`), 164.58 (β-lactam $\underline{C}$=O).

1,4-Diphenyl-3-vinylazetidin-2-one (132) was obtained as colourless crystals in 31% (Method A) and 32% (Method B) yield, m.p. 102-103°C (lit. m.p.[122] 100-102°C).

IRν_{max} (KBr) 1737 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.76 (1H, dd, $J_{3,4trans}$=2.5Hz, $J_{3,5}$=7.7Hz, H-3), 4.83 (1H, d, $J_{4,3trans}$=2.5Hz, H-4), 5.32-5.43 (2H, m, -CH=C$\underline{H}_2$), 5.99-6.11 (1H, m, -C$\underline{H}$=CH_2), 7.02-7.42 (10H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 61.17 (C-3), 63.95 (C-4), 116.98, 123.86, 125.76, 128.48, 128.96, 129.12 (aromatic Cs), 119.81 (C-6), 130.47 (C-5), 137.32, 137.53 (C-1` and C-1``), 165.21 (β-lactam $\underline{C}$=O).

4-(4-Fluorophenyl)-1-(4-methoxycarbonylphenyl)-3-vinylazetidin-2-one (133) was obtained as colourless crystals in 39% yield (Method A) m.p. 96-97°C (lit.[113] 95-97°C).

IRν_{max} (KBr) 1750 (C=O), 1710 (CO_2CH_3) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.73 (1H, d (br), $J_{3,4trans}$=2.5Hz, H-3), 3.88 (3H, s, -CO_2CH_3), 5.23-6.43 (3H, m, -CH=CH_2), 6.88-8.23 (8H, m, aromatic Hs), 7.88 (1H, d, $J_{4,3trans}$=2.5Hz, H-4).

Elemental Analysis

$C_{19}H_{16}NO_3$	Requires:	C;70.13,	H;4.96,	N;4.30%
	Found:	C;69.92,	H;4.96,	N;4.23%

4-Acetoxy-1-(4-methoxyphenyl)-4-methyl-3-vinylazetidin-2-one (134) was obtained as a colourless solid in 89% (method A) and 76% (method B) yield, m.p. 79-81°C (lit. m.p.[116] 79-80°C).

IRν_{max} (KBr) 1755 (β-lactam C=O), 1714 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.81 (3H, s, CH_3), 2.18 (3H, s, $COCH_3$), 3.74-3.85 (4H, m, H-3 and OCH_3), 5.34-5.78 (3H, m, -CH=CH_2), 6.87-7.28 (4H, m, aromatics).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 19.62 ($\underline{C}H_3$), 27.86 ($CO\underline{C}H_3$), 55.34 ($O\underline{C}H_3$), 64.22 (C-3), 70.37 (C-4), 114.41 (C-3` and C-5`), 116.23 (C-6), 118.41 (C-2` and C-6`), 127.09 (C-5), 130.03 (C-1`), 156.22 (C-4`), 163.40 (β-lactam $\underline{C}$=O), 207.10 ($\underline{C}OCH_3$).

General preparation of 3-(1,2-epoxyethyl)azetidin-2-ones (138)-(142)

To a solution of 1,4-diaryl-3-vinylazetidin-2-one (1mmol) in dry dichloromethane (10ml) was added *m*-chloroperbenzoic acid (173mg, 1mmol) and the mixture allowed to stir at room temperature for 24 h. The mixture was washed with $NaHCO_3$ solution (5%) and water and dried over anhydrous (Na_2SO_4). Evaporation of the solvent afforded the required epoxide which was purified by column chromatography over silica gel (eluent, dichloromethane:diethyl ether, 9:1). The products were then recrystallised from dichloromethane-diethyl ether, 1:1.

3-(1,2-Epoxyethyl)-1-(4-methoxycarbonylphenyl)-4-(3,4-methylenedioxyphenyl) azetidin-2-one (138) was obtained as colourless crystals as a diastereomeric mixture in 46% yield m.p. 99-100°C (lit.[122] 99-100°C).

IRν_{max} (KBr) 1760 (C=O), 1720 (CO_2CH_3), 1248, 941, 748 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.65-3.62 (4H, m, epoxy Hs, H-3), 3.84 (3H, s, -CO_2CH_3), 4.81 (0.64H, d, $J_{4,3trans}$=3Hz, H-4), 4.96 (0.36H, $J_{4,3trans}$=3Hz, H-4), 5.97 (2H, m, -OCH_2O), 6.87-8.10 (7H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 45.54, 45.61 (C-6), 48.23, 51.98 (C-5), 56.60, 56.90 (C-3), 61.70, 61.81 (C-4), 101.42 (O<u>C</u>H_2O), 105.71, 108.81, 115.12, 119.79, 125.51 (aromatic Cs), 133.12 (C-1`), 140.80 (C-1``), 148.13, 148.64 (C-4`), 164.18, 166.34 ($COOCH_3$, β-lactam <u>C</u>=O).

High Resolution Mass Spectrum

$C_{20}H_{17}NO_6$ Requires: M^+=367.1056

Found: M^+=367.1114

Mass Spectrum (m/z)

367.1 (M^+, 11.0%), 351.1 (M-16.0, 4.2%), 343.0 (M-24.1, 5.7%), 307.2 (M-59.9, 9.3%), 283.0 (M-84.1, 17.5%), 279.1 (M-88.0, 20.9%), 251.1 (M-116.0, 9.4%), 239.2 (M-127.8, 5.9%), 231.0 (M-136.1, 12.6%), 190.0 (M-177.1, 24.6%), 155.9 (M-211.1, 76.7%), 149.0 (M-218.1, 100.0%), 138.9 (M-228.2, 90.7%), 110.1 (M-257.0, 52.7%).

3-(1,2-Epoxyethyl)-1-(4-methoxyphenyl)-4-(3,4-methylenedioxyphenyl)azetidin-2-one (139) was obtained as a colourless oil as a diastereomeric mixture in 36% yield[122].

IRν_{max}(film) 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.15-3.61 (4H, m, epoxy Hs, H-3), 3.68 (3H, s, -OCH_3), 4.75 (0.7H, d, $J_{4,3trans}$=3Hz, H-4), 4.85 (0.3H, d, $J_{4,3trans}$=3Hz, H-4), 5.95 (2H, m, -OCH_2O), 6.60-7.51 (7H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 45.68, 45.91 (C-6), 48.20, 48.62 (C-5), 55.37 (O<u>C</u>H_3), 56.72, 58.03 (C-3), 60.28, 61.71 (C-4), 101.31 (O<u>C</u>H_2O), 114.27 (C-3` and C-5`), 119.80 (C-2` and C-6`), 105.87, 108.68, 120.12 (aromatic Cs), 130.80, 130.88 (C-1`), 147.91, 148.51 (C-1``), 156.15 (C-4`), 163.06 (β-lactam <u>C</u>=O).

High Resolution Mass Spectrum

$C_{19}H_{17}NO_5$ Requires: M^+=339.1106

Found: M^+=339.1075

Mass Spectrum (m/z)

339.1 (M^+, 59.8%), 271.0 (M-68.1, 30.7%), 240.0 (M-99.1, 42.7%), 216.9 (M-122.2, 28.4%), 190.0 (M-149.1, 84.6%), 175.0 (M-164.1, 34.3%), 162.1 (M-177.0, 10.0%), 149.0 (M-190.1, 100.0%).

3-(2-Epoxyethyl)-4-(4-chlorophenyl)-1-methoxycarbonylphenyl)azetidin-2-one (140) was obtained as a colourless oil in 52% yield[122].

IRν_{max} (film) 1750 (C=O), 1720 ($COOCH_3$) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.18-3.70 (4H, m, epoxy Hs, H-3), 3.85 (3H, s, -OCH_3), 4.97 (0.7H, d, $J_{4,3trans}$=2.59Hz, H-4), 4.86 (0.3H, d, $J_{4,3trans}$=2.63Hz, H-4), 6.69-7.90 (8H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 45.66, 45.97 (C-6), 48.04, 48.25 (C-5), 51.99 (CO_2<u>C</u>H_3), 56.13, 57.70 (C-3), 60.69, 61.93 (C-4), 116.51 (C-3`and C-5`), 125.68 (C-2` and C-6`), 127.24, 128.14, 129.57, 130.80, 130.86, 134.70 (aromatic C's), 135.05 (C-1`), 140.60 (C-1``), 162.99 (C-4`), 166.24 (β-lactam <u>C</u>=O, <u>C</u>OOCH_3).

High Resolution Mass Spectrum

$C_{19}H_{16}ClNO_4$	Requires:	M^+=357.0767
	Found:	M^+=357.0743

Mass Spectrum (m/z)

357.1 (M^+, 100.0%), 326.1 (M-31.0, 23.9%), 275.1 (M-82.0, 26.1%), 273.1 (M-86.0, 70.3%), 244.1 (M-113.0, 32.0%), 242.1 (M-115.0, 86.9%), 180.1 (M-177.0, 88.5%), 153.9 (M-203.2, 99.9%), 151.9 (M-205.2, 99.8%), 117.1 (M-242.0, 99.7%).

3-(1,2-Epoxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (141) was obtained as a colourless solid, as a diastereomeric mixture in 46% yield, m.p. 132-134°C (lit. m.p[116] 132-134°C).

IRν_{max} (KBr) 1746 (C=O), 1247, 943, 757 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.72 (1H, dd, J_{gem}=4.6Hz, $J_{6,5}$=2.6Hz, H-6), 2.96 (1H, dd, J_{gem}=4.6Hz, $J_{6,5}$=4.1Hz, H-6), 3.27-3.29 (1H, m, H-3), 3.33-3.54 (1H, m, H-5), 3.73, 3.74 (3H, s, -OCH_3), 4.84 (0.72H, d, $J_{4,3trans}$=2.4Hz, H-4), 4.96 (0.28H, d, $J_{4,3trans}$=2.6Hz, H-4), 6.75-7.37 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 45.70, 45.93 (C-6), 48.24, 48.64 (C-5), 55.34 ($O\underline{C}H_3$), 56.77, 58.08 (C-3), 60.25, 61.66 (C-4), 114.18 (C-3`and C-5`), 118.36 (C-2` and C-6`), 125.89, 128.55, 129.15 (C-2``, C-6``, C-3``, C-5`` and C-4``), 130.83 (C-1`), 137.18 (C-1``), 156.11 (C-4`), 162.33, 163.06 (β-lactam $\underline{C}$=O).

Elemental Analysis

$C_{18}H_{17}NO_3$	Requires:	C, 73.20;	H, 5.80;	N, 4.74%
	Found:	C, 72.75;	H, 5.77;	N, 4.51%

1,4-Diphenyl-3-(1,2-epoxyethyl)azetidin-2-one (142) was obtained as a colourless crystalline solid in 42% yield, m. p. 125-127°C (lit.[122] m.p. 125-126°C).

IRν_{max} (KBr) 1738 (C=O), 1248, 940, 748 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.73 (1H, dd, J_{gem}=4.5Hz, $J_{6,5}$=2.6Hz, H-6), 2.98 (1H, dd, J_{gem}=4.5Hz, $J_{6,5}$=4.1Hz, H-6), 3.25 (1H, dd, $J_{3,4trans}$=2.5Hz, $J_{3,5}$=5.0Hz, H-3), 3.42-3.44 (1H, m, H-5), 4.89 (1H, d, $J_{4,3trans}$=2.5Hz, H-4), 7.03-7.41 (10H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 45.68 (C-6), 48.57 (C-5), 56.64 (C-3), 61.65 (C-4), 117.04, 124.08, 125.85, 128.60, 128.99, 129.19 (aromatic Cs), 136.99 (C-1`), 137.26 (C-1``), 163.67 (β-lactam C=O).

Ring opening of 3-(1,2-epoxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (141), 1,4-diphenyl-3-(1,2-epoxyethyl)azetidin-2-one (142) with alcohols catalysed with Ceric (IV) Ammonium Nitrate

The appropriate epoxide (**141 or 142**) (1mmol) in methanol (10ml) was treated with cerium ammonium nitrate (0.2mmol) and stirred at reflux temperature for 15 min. The methanol was evaporated. After cooling to room temperature the solution was diluted with diethyl ether (10ml), washed with water (2x10ml) and dried (Na_2SO_4). The solvent was evaporated and purification was carried out by column chromatography over silica gel (eluent, dichloromethane:ethyl acetate 9:1) yielding compounds (**146**) and (**148**).

3-(1,2-Epoxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (141) (1mmol) in ethanol (10ml) was treated with cerium ammonium nitrate (0.4mmol) and stirred at reflux temperature for 30 min. The work-up was similar to the previous reaction. Purification was carried out by column chromatography over silica gel (eluent:dichloromethane:ethyl acetate 8:2) yielding (**147**).

3-(1,2-Epoxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (141), (1mmol) in isopropanol (10ml) was treated with cerium ammonium nitrate (0.4mmol) and stirred at reflux temperature for 30 min. Work-up and purification similar to previous reaction yielding (**149**).

1,4-Diphenyl-3-[1-(1-hydroxy-2-methoxy)ethyl]azetidin-2-one (146) was obtained as a colourless oil in 56% yield[113, 122].

IRν_{max} (film) 3400 (br OH), 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.23 (1H, m, $J_{3,4trans}$=2.52Hz, H-3), 3.41 (2.40H, s, -OCH_3), 3.42 (0.60H, s, -OCH_3), 3.52-3.61 (2H, m, -$C\underline{H}_2OCH_3$), 4.31-4.33 (1H, m, H-5), 5.08 (0.2H, d, $J_{4,3trans}$=2.52Hz, H-4), 5.16 (0.8H, d, $J_{4,3trans}$=2.52Hz, H-4), 7.06-7.40 (10H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 53.21 (O$\underline{C}H_3$), 54.63 (C-3), 56.28 (C-4), 67.77 (C-5), 74.19 (C-6), 111.21, 116.64, 125.59, 125.70, 128.63, 132.21 (aromatic Cs), 164.57 (β-lactam $\underline{C}$=O).

3-[1-(2-Ethoxy-1-hydroxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidn-2-one (147) was obtained as a colourless oil in 56% yield as a diastereomeric mixture.

IRν_{max} (film) 3450 (br OH), 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.08-1.10 (3H, m, -$OCH_2C\underline{H}_3$), 3.11-3.13 (1H, m, H-3), 3.43-3.50 (2H, m, $OC\underline{H}_2CH_3$), 3.50-3.60 (2H, m, $C\underline{H}_2OCH_2CH_3$), 3.71 (3H, s, -$OCH_3$), 4.19-4.27 (1H, m, C$\underline{H}$OH), 4.92 (0.7H, d, $J_{4,3trans}$=2.52Hz, H-4), 4.94 (0.3H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.71-7.40 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 14.02 ($\underline{C}H_3$), 57.11 ($O\underline{C}H_3$), 57.24 (C-3), 62.27, 62.70 (C-4), 66.81, 66.82 ($O\underline{C}H_2CH_3$), 68.09, 68.24 (C-5), 72.29, 72.44 (C-6), 114.24, 118.45, 118.39, 126.04, 126.10, 128.21, 128.39, 128.84, 128.96, 129.04, 131.07, 133.31, 134.51 (aromatic Cs), 137.91 (C-1``), 156.02 (C-4`), 164.64 (β-lactam $\underline{C}$=O).

High Resolution Mass Spectrum

$C_{20}H_{23}NO_4$ Requires: M^+=341.1627

Found: M^+=341.1673

Mass Spectrum (m/z)

341.2 (M^+, 63.1%), 293.0 (M-48.2, 20.9%), 279.2 (M-62.0, 100.0%), 261.2 (M-80.0, 15.6%), 243.2 (M-98.0, 15.5%).

3-[1-(1-Hydroxy-2-methoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (148) was obtained as a colourless oil in 50% yield as a diasteromeric mixture.

IRν_{max} (film) 3440 (br OH), 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.17-3.18 (1H, m, H-3), 3.38 (2.1H, s, -OCH_3), 3.40 (0.9H, s, OCH_3), 3.48-3.50 (2H, m, $C\underline{H}_2OCH_3$), 3.78 (3H, m, -OCH_3), 4.26-4.28 (1H, m, H-5), 4.99 (0.3H, d, $J_{4,3trans}$=2.5Hz, H-4), 5.07 (0.7H, d, $J_{4,3trans}$=2.5Hz, H-4), 6.76-7.35 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 55.38, 57.10 ($O\underline{C}H_3$), 59.03 (C-3), 62.66 (C-4), 68.31 (C-5), 74.21 (C-6), 114.27 (C-3`and C-5`), 118.36 (C-2` and C-6`), 126.03-129.07 (aromatic Cs), 165.31 ($\underline{C}$=O).

High Resolution Mass Spectrum

$C_{19}H_{21}NO_4$ Requires: M^+=327.1470

Found: M^+=327.1469

Mass Spectrum (m/z)

327.1 (M^+, 99.0%), 279.1 (M-48.0, 37.2%), 251.1 (M-76.0, 10.4%), 210.9 (M-116.2, 38.3%), 184.0 (M-143.1, 16.8%), 133.0 (M-194.1, 100.0%).

3-[1-(1-Hydroxy-2-propoxy)ethyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (149) was obtained as a colourless oil in 40% yield.

IRν_{max} (film) 3428 (br OH), 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.05-1.07 (6H, m, 2x CH_3), 2.65 (1H, s, -OH), 3.13 (1H, dd, $J_{3,4trans}$=2.52Hz, $J_{3,5}$=6.52Hz, H-3), 3.44-3.57 (3H, m, OC<u>H</u>$(CH_3)_2$, C<u>H</u>$_2$OCH$(CH_3)_2$), 3.65 (3H, s, OCH_3), 4.15-4.17 (1H, m, H-5), 4.96 (0.2H, d, $J_{4,3trans}$=2.52Hz, H-4), 4.99 (0.8H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.68-7.29 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 21.48, 21.65 (<u>C</u>H_3), 55.38 (O<u>C</u>H_3), 57.46, 57.45 (C-4), 62.69, 62.70 (C-3), 68.71, 68.72 (C-5), 69.92 (C-6), 72.31 (O<u>C</u>H$(CH_3)_2$), 113.86 (C-3` and C-5`), 118.87 (C-2` and C-6`), 125.70, 126.39, 128.58 (aromatic Cs), 130.81 (C-1`), 137.60 (C-1``), 155.58 (C-4`), 164.01 (β-lactam <u>C</u>=O).

High Resolution Mass Spectrum

$C_{21}H_{25}NO_4$ Requires: M^+=355.1783

Found: M^+=355.1800

Mass Spectrum (m/z)

355.1 (M^+100.0%), 306.1 (M-49.0, 34.8%), 279.2 (M-75.9, 20.2%), 260.1 (M-95.0, 24.4%), 243.2 (M-111.9, 27.5%), 211.0 (M-144.1, 76.5%), 149.0 (M-206.2, 84%).

Chapter 3

N,N'-bis-(*p*-anisyl)ethylenediimine (165a)

Glyoxal (36.3g, 0.25mol) was added dropwise to a hot solution of *p*-anisidine (61.6g, 0.5mol) in methanol (300ml). A solid precipitated to which isopropyl alcohol was added. This was then heated to reflux for 2 min. When cooled to room temperature the yellow needles which precipitated were filtered and dried. *N,N'-bis*-(*p*-anisyl)ethylenediimine (**165a**) was obtained as yellow crystals in 55% yield, m.p. 157-159°C (lit.[142] m.p. 159°C).

IRν_{max}(KBr) 1610 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.80 (6H, s, 2x-OCH_3), 7.15 (8H, dd, aromatic Hs), 8.40 (2H, s, 2x-CH=N).

N,N'-bis-(*p*-tolyl)ethylenediimine (165b)

Glyoxal (14.3g, 0.1mol) was added dropwise to a cooled solution (0-10°C) of *p*-toluidine (21.4g, 0.2mol) in isopropyl alcohol (100ml). The resultant yellow solid was collected on a filter and quickly recrystallised from isopropyl alcohol. The recrystallised material was collected by filtration giving yellow crystals.
N,N'-bis-(*p*-tolyl)ethylenediimine (**165b**) was obtained as yellow crystals in 25% yield, m. p. 164-165°C (lit.[142] m.p. 164-165°C).

IRν_{max}(KBr) 1612 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 2.40 (6H, s, CH_3), 7.70 (8H, dd, aromatic Hs), 8.42 (2H, s, 2x-CH=N).

4-Formyl-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (166), 4-formyl-3-isopropenyl-1-(4-methoxyphenyl)azetidin-2-one (167) and 4-formyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (168)

Method A:

A solution of the appropriate acid chloride (0.04mol) in dry toluene (75ml) was added dropwise to a vigorously stirred suspension of *N,N'-bis*-(*p*-anisyl)ethylenediimine (**165a**) (0.02mol) and triethylamine (0.024mol) in dry toluene (150ml) at room temperature under nitrogen. The reaction was stirred under nitrogen at room temperature overnight. 5% Aqueous HCl (200ml) was then added and the heterogenous mixture was vigorously stirred for 3 h. The organic layer was diluted with toluene (50ml) and successively washed with 5% HCl (2x100ml), 5% $NaHCO_3$ (2x100ml), brine (200ml) and water (200ml), and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography over silica gel (eluent: dichloromethane:ethyl acetate, 95:5) to give the pure 4-formyl-3-substituted azetidin-2-ones.

Method B:

To a solution of the appropriate acid chloride (0.024mol) in dry dichloromethane (50ml) was added dropwise over 45 min to a solution of diimine (0.02mol) and triethylamine (0.024mol) in dry dichloromethane (100ml) at reflux under nitrogen. The reaction mixture was then refluxed for 6 h. Then 5% aqueous HCl (200ml) was added and the heterogenous mixture was vigorously stirred for 3 h. The organic layer was diluted with dichloromethane (50ml) and successively washed with 5% HCl (2x200ml), 5% $NaHCO_3$ (2x200ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography over silica gel (eluent, dichloromethane:ethyl acetate, 95:5) to afford the desired 4-formyl products.

4-Formyl-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (166) was obtained as colourless crystals in 77% (method A), 50% (method B) yield, m.p. 114-115°C (lit. m.p.[122] 114-115°C).

IRν_{max} (KBr) 1750 (β-lactam C=O), 1720 (CHO) cm^{-1}.

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.78 (3H, s, $-OCH_3$), 4.33 (1H, m, H-3), 4.58 (1H, dd, $J_{4,3cis}$=6.3Hz, $J_{4,7}$=3.5Hz, H-4), 5.38-5.86 (3H, m, $-CH=CH_2$), 6.86 (2H, d, J=9.2Hz, H-3` and H-5`), 7.25 (2H, d, J=9.2Hz, H-2` and H-6`), 9.74 (1H, d, $J_{7,4}$=3.5Hz, H-7).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 55.44 ($O\underline{C}H_3$), 56.40, 60.68 (C-3 and C-4), 114.49 (C-3`and C-5`), 117.78 (C-2` and C-6`), 122.77 (C-6), 126.56 (C-5), 130.87 (C-1`), 156.61 (C-4`), 163.16 (β-lactam $\underline{C}$=O), 199.48 ($\underline{C}$HO).

4-Formyl-3-isopropenyl-1-(4-methoxyphenyl)azetidin-2-one (167) was obtained as colourless crystals in 77% (method A), 74% (method B) yield, m.p. 70-71°C (lit. m.p.[122] 70°C).

IRν_{max} (KBr) 1750 (β-lactam C=O), 1720 (CHO) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.65 (3H, s, $-CH_3$), 3.68 (3H, s, $-OCH_3$), 4.15 (1H, d, $J_{3,4cis}$=6.4Hz, H-3), 4.42 (1H, dd, $J_{4,3cis}$=6.4Hz, $J_{4,7}$=3.8Hz, H-4), 5.02-5.22 (2H, m, $-C=CH_2$), 6.77 (2H, d, J=9.1Hz, H-3` and H-5`), 7.17 (2H, d, J=9.1Hz, H-2` and H-6`), 9.59 (1H, d, $J_{7,4}$=3.8Hz, H-7).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 21.88 ($\underline{C}H_3$), 55.34 ($O\underline{C}H_3$), 59.13, 60.14 (C-3 and C-4), 114.39 (C-3` and C-5`), 116.98 (C-6), 117.61 (C-2` and C-6`), 130.98 (C-1`), 134.78 (C-5), 156.48 (C-4`), 163.26 (β-lactam $\underline{C}$=O), 199.59 ($\underline{C}$HO).

4-Formyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (168) was obtained as a colourless solid in 32% yield (method A), 40% yield (method B) m.p. 97-99°C (lit. m.p.[143] 97-99°C).

IRν_{max} (KBr) 1755 (C=O), 1720 (-CHO) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.68 (3H, s, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 4.36 (1H, dd, $J_{3,4cis}$=6.0Hz, $J_{3,6}$=3.5Hz, H-3), 4.58 (1H, dd, $J_{4,3cis}$=6.0Hz, $J_{4,5}$=3.5Hz, H-4), 6.88 (2H, d, J=9Hz, H-3` and H-5`), 7.32 (2H, d, J=9Hz, H-2` and H-6`), 9.80 (1H, d, J=3.5Hz, -CHO).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 55.59 ($O\underline{C}H_3$), 59.47 ($O\underline{C}H_3$), 63.17 (C-3), 85.10 (C-4), 114.59 (C-3` and C-5`), 118.04 (C-2` and C-6`), 130.47 (C-1`), 156.95 (C-4`), 162.78 ($\underline{C}$=O), 198.98 ($\underline{C}$HO).

Reduction studies of compounds (131), (134) and (166)-(168)

The appropriate β-lactam (1mmol) was dissolved in dry MeOH (10ml) and $NaBH_4$ (4.05 mmol, 0.15g) was added in portions. The solvent was removed and the crude product was then poured onto water and extracted with diethyl ether (3x20ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (eluent, light petroleum (b.p. (40-60°C): ethyl acetate, 7:3) to provide the alcohol products (**174**)-(**180**).

4-Hydroxymethyl-3-methoxy-1-(4-methoxyphenyl)azetidin-2-one (174) was obtained as a colourless oil in 53% yield.

IRν_{max} (film) 1750 (C=O), 3300 (OH) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.61, (3H, s, $-OCH_3$), 3.62 (3H, s, $-OCH_3$), 3.97-4.00 (2H, m, H-5), 4.22 (1H, m, H-4), 4.60 (1H, d, $J_{3,4cis}$=5.2Hz, H-3), 6.82 (2H, d, J=8.76Hz, H-3` and H-5`), 7.32 (2H, d, J=8.76Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 55.40 ($O\underline{C}H_3$), 57.80 ($O\underline{C}H_3$), 57.23 (C-5), 59.54 (C-4), 82.97, (C-3), 114.38 (C-3` and C-5`), 118.76 (C-2` and C-6`), 130.41 (C-1`), 156.43 (C-4`), 164.13 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{12}H_{15}NO_4$ Requires: M^+=237

Found : M^+=237

High Resolution Mass Spectrum

$C_{12}H_{15}NO_4$ Requires: M^+=237.10011

Found: M^+=237.10030

Mass Spectrum (m/z)

237 (M^+, 16.6%), 178 (M-59, 8.8%), 164 (M-73, 8.7%), 149 (M-88, 100%), 134 (M-103, 60.0%), 121 (M-116, 10.1%), 106 (M-131, 13.3%), 92 (M-145, 15.6%), 77 (M-160, 16.6%), 64 (M-173, 10.0%)

4-Hydroxymethyl-1-(4-methoxyphenyl)-3-vinylazetidin-2-one (175) was obtained as a yellow oil in 35% yield[122].

IRν_{max}(film) 3428 (OH), 1752 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 2.85 (1H, s, OH), 3.77 (3H, s, -OCH_3), 3.85-4.04 (4H, m, H-3, H-4, Hs-7), 5.22-5.47 (2H, m, Hs-6), 5.78-5.97 (1H, m, H-5), 6.80 (2H, d, J=8.99Hz, H-3` and H-5`), 7.38 (2H, d, J=8.99Hz, H-2`and H-6`).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 55.02 ($O\underline{C}H_3$), 55.35 (C-3), 59.23 (C-4), 60.46 (C-7), 114.29 (C-3` and C-5`), 118.61 (C-2` and C-6`), 121.90 (C-6), 128.49 (C-1`), 130.78 (C-5), 156.11 (C-4`), 165.06 (β-lactam $\underline{C}$=O).

***E*-3-Ethylidene-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (176)** was obtained as colourless crystals in 60% yield, m.p. 125-127°C (lit. m.p. 125-126°C[122]), (recrystallised from CH_2Cl_2).

IRν_{max} (film) 3400 (OH), 1750 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.82 (3H, d, J=7.80Hz, $C\underline{H}_3$-CH=), 3.09 (1H, s, OH), 3.75 (3H, s, -OCH_3), 3.95 (1H, d, J_{gem}=13.05Hz, H-7), 4.02 (1H, d, J_{gem}=13.05Hz, H-7), 4.64 (1H, m, H-4), 6.27 (1H, q, J=7.80Hz, H-5), 6.80 (2H, d, J=8.99Hz, H-3` and H-5`), 7.36 (2H, J=8.99Hz, H-2`and H-6`).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 14.15 (C-6), 55.30 ($O\underline{C}H_3$), 61.07 (C-7), 61.52 (C-4), 114.28 (C-3` and C-5`), 118.37 (C-2` and C-6`), 123.96 (C-5), 131.17 (C-1`), 137.54 (C-3), 155.59 (C-4`), 161.14 (β-lactam $\underline{C}$=O).

4-Hydroxymethyl-3-isopropylideneazetidin-2-one (177) was obtained as a colourless oil in 75% yield.

IRν_{max} (film) 3400 (OH), 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.82 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.60 (3H, s, -OCH_3), 4.10-4.21 (2H, m, H-8), 4.50-4.52 (1H, m, H-4), 6.80 (2H, d, J=8.70Hz, H-3` and H-5`), 7.42 (2H, d, J=8.70Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 20.27 (C-6), 20.81 (C-7), 55.40 ($O\underline{C}H_3$), 61.08 (C-4), 61.54 (C-8), 114.30 (C-3` and C-5`), 118.18 (C-2` and C-6`), 130.67 (C-5), 131.52 (C-1`), 138.23 (C-3), 155.49 (C-4`), 155.72 (β-lactam $\underline{C}$=O).

High Resolution Mass Spectrum

$C_{14}H_{17}NO_3$ Requires: M^+=247.12084

Found: M^+=247.12125

Mass Spectrum (m/z)

247 (M^+, 72%), 232 (M-15, 3%), 216 (M-31, 100%), 200 (M-47, 13%), 188 (M-59, 14%), 173 (M-74, 25%), 134 (M-113, 99%), 123 (M-124, 98%), 108 (M-139, 45%), 92 (M-155, 29%), 77 (M-170, 43%).

***Z*-4-Acetyl-3-ethylidene-4-methyl-1-(4-methoxyphenyl)azetidin-2-one (178)** was obtained as a colourless oil in 33% yield.

IRν_{max} (film) 1750 (β-lactam C=O), 1721 ($\underline{C}OCH_3$) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.66 (3H, s, CH_3), 2.11 (3H, d, J=7.26Hz, Hs-6), 2.13 (3H, s, -$COCH_3$), 3.77 (3H, s, -OCH_3), 5.70 (1H, q, J=7.26Hz, H-5), 6.86 (2H, d, J=9.3Hz, H-3` and H-5`), 7.23 (2H, d, J=9.3Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 14.86 ($\underline{C}H_3$), 17.02 ($\underline{C}H_3$), 24.62 ($CO\underline{C}H_3$), 55.39 ($O\underline{C}H_3$), 71.95 (C-4), 114.68 (C-3`and C-5`), 117.74 (C-2` and C-6`), 126.98 (C-5), 130.34 (C-1`), 141.50 (C-3), 156.23 (C-4`), 160.34 (β-lactam $\underline{C}$=O), 207.01 ($\underline{C}OCH_3$).

Low Resolution Mass Spectrum

$C_{15}H_{17}NO_3$ Requires: M^+=259

Found: M^+=259

High Resolution Mass Spectrum

$C_{15}H_{17}NO_3$ Requires: M^+=259.12084

Found: M^+=259.12046

Mass Spectrum (m/z)

259 (M^+, 49%), 216 (M-43, 43%), 173 (M-86, 27%), 149 (M-110, 100%), 134 (M-125, 13%), 107 (M-152, 18%), 92 (M-167, 40%), 77 (M-182, 54%).

***Z*-3-Ethylidene-4-(1-hydroxyethyl)-1-(4-methoxyphenyl)-4-methyl-azetidin-2-one (179)** was obtained as a colourless oil in 20% yield.

IRν_{max} (film) 1750 (C=O), 3000-3400 (br, OH) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.16 (3H, d, J=6.36, Hs-8), 1.58 (3H, s, CH_3), 2.05 (3H, d, J=7.23Hz, H-6), 2.43 (1H, s, OH), 3.56 (3H, s, -OCH_3), 4.12 (1H, m, H-7), 5.64 (1H, q, J=7.23Hz, H-5), 6.83 (2H, d, J=9.21Hz, H-3` and H-5`), 7.54 (2H, d, J=9.21Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 14.59 ($\underline{C}H_3$), 18.31 (C-8), 19.40 (C-6), 55.34 ($O\underline{C}H_3$), 69.99 (C-4), 71.67 (C-7), 114.41 (C-3` and C-5`), 119.21 (C-2` and C-6`), 124.63 (C-5), 130.90 (C-1`), 142.76 (C-3), 156.02 (C-4`), 161.51 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{15}H_{19}NO_3$ Requires: M^+=261

Found: M^+=261

High Resolution Mass Spectrum

$C_{15}H_{19}NO_3$	Requires:	M^+=261.13649
	Found:	M^+=261.13702

Mass Spectrum (m/z)

261 (M^+, 40%), 246 (M-15, 15%), 216 (M-45, 100%), 173 (M-88, 15%), 148 (M-113, 99%), 123 (M-138, 16%), 92 (M-169, 25%), 77 (M-184, 36%).

***E*-3-Ethylidene-1-(4-methoxyphenyl)-4-phenyl-azetidin-2-one (180)** was obtained as a colourless oil in 63% yield.

IRν_{max} (film) 1750 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.82 (3H, d, J=7.11Hz, $C\underline{H}_3$-CH=), 3.71 (3H, s, -OCH_3), 5.38 (1H, s, H-4), 6.26 (1H, q, J=7.11Hz, H-5), 6.78-7.42 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 12.73 (C-6), 54.94 (O$\underline{C}H_3$), 62.46 (C-4), 113.91, 117.69, 122.34, 125.44, 126.64, 126.68, 127.76, 128.46 (aromatic Cs), 130.97 (C-5), 136.36 (C-1`), 142.39 (C-3), 155.52 (C-4`), 160.58 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{18}H_{17}NO_2$	Requires:	M^+=279
	Found:	M^+=279

High Resolution Mass Spectrum

$C_{18}H_{17}NO_2$	Requires:	M^+=279.12593
	Found:	M^+=279.12620

Mass Spectrum (m/z)

279 (M^+, 72%), 211 (M-68, 10%), 196 (M-83, 25%), 167 (M-112, 17%), 149 (M-130, 100%), 129 (M-150, 62%), 115 (M-164, 67%), 106 (M-173, 17%), 77 (M-202, 25%).

***E*-3-Ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (192)**

Preparation of oxidising agent

The oxidising agent, Jones reagent (2.67M), was prepared by suspending 26.7g of Cr (VI) oxide in 25ml of conc. H_2SO_4 and pouring slowly with stirring into 75ml of water. The deep orange-red solution was cooled to room temperature before use.

Oxidation procedure

Jones reagent (2.67M; 1ml) was added dropwise at 0°C to a solution of the alcohol (**176**) (0.7142mmol) in acetone (15ml). After 1 h, methanol (1ml) was added and the mixture was filtered, washed with brine and evaporated under reduced pressure to give the corresponding acid. The residue was chromatographed on silica gel (eluent, dichloromethane:ethyl acetate, 9:1) to provide the acid product.
3-Ethylidene-1-(4-methoxyphenyl)azetidin-2-one-4-carboxylic acid (**192**) was obtained as a yellow oil in 65% yield.

IRν_{max} (film) 2800-3400 (br, CO<u>OH</u>), 1750 (br, C=O, <u>C</u>OOH) cm^{-1}.

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.82 (3H, d, J=7.80Hz, C<u>H</u>$_3$-CH=), 3.70 (3H, s, -OCH_3), 4.85 (1H, s, H-4), 6.27 (1H, q, J=7.80Hz, H-5), 6.78 (2H, d, J=9Hz, H-3` and H-5`), 7.23 (2H, d, J=9Hz, H-2` and H-6`), 13.20 (1H, s, COOH).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.75 (C-6), 55.37 (O<u>C</u>H_3), 59.15 (C-4), 114.31 (C-3` and C-5`), 117.63 (C-2` and C-6`), 124.87 (C-5), 131.06 (C-1`), 136.43 (C-3), 156.06 (C-4`), 159.88 (β–lactam <u>C</u>=O), 170.60 (<u>C</u>OOH).

Low Resolution Mass Spectrum

$C_{13}H_{13}NO_4$ Requires: M^+=247

Found: M^+= (not observed)

***E*-4-Acetoxy-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one (193)**

To a solution of the appropriate acid (**192**) (10mmol) in 20ml of DMF was added 5ml of acetic acid at room temperature. The reaction mixture was heated to 60°C on an oil bath. Lead tetraacetate (15mmol) was added to the reaction mixture. The reaction mixture was heated for an additional 5 min, cooled to room temperature, diluted with excess of water and extracted with ethyl acetate. The organic layer was washed with aqueous $NaHCO_3$ (2x20ml) and brine (2x20ml) and dried (Na_2SO_4) and evaporated to dryness to give the corresponding acetate. The residue was chromatographed on silica gel (eluent, dichloromethane:ethyl acetate 95:5). *E*-4-Acetoxy-3-ethylidene-1-(4-methoxyphenyl)azetidin-2-one (**193**) was obtained as a yellow oil in 60% yield.

IRν_{max} (film) 1760 (br, β-lactam C=O, O<u>C</u>OCH_3) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.89 (3H, d, J=5.64Hz, C<u>H</u>$_3$-CH=), 2.19 (3H, s, -$COCH_3$), 3.83 (3H, s, -OCH_3), 6.34 (1H, q, J=5.23Hz, H-5), 6.92 (2H, d, J=6.78Hz, H-3`and H-5`), 7.01 (1H, s, H-4), 7.40 (2H, d, J=6.78Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 14.10 (C-6), 20.88 (CO<u>C</u>H_3), 55.43 (O<u>C</u>H_3), 78.77 (C-4), 114.56 (C-3` and C-5`), 118.26 (C-2` and C-6`), 125.33 (C-5), 127.61 (C-1`), 138.71 (C-3), 156.67 (C-4`), 157.81 (β-lactam <u>C</u>=O), 170.50 (<u>C</u>OCH_3).

Low Resolution Mass Spectrum

$C_{14}H_{15}NO_4$ Requires: M^+=261

Found: M^+=261

High Resolution Mass Spectrum

$C_{14}H_{15}NO_4$ Requires: M^+=261.1001

Found: M^+=261.1040

Mass Spectrum (m/z)

261 (M^+, 29%), 219 (M-42, 60%), 149 (M-112, 60%).

_E_-3-Ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (194)

Pyridinium chlorochromate (0.06g, 0.29mmol) was suspended in dry dichloromethane (5ml) and 3-ethylidene-4-hydroxymethyl-1-(4-methoxyphenyl)azetidin-2-one (**176**) (0.05g, 0.21mmol) was rapidly added at room temperature. The solution became briefly homogenous before depositing the black insoluble reduced reagent. After 12 h the reaction mixture was diluted with anhydrous diethyl ether (50ml), the solvent was decanted and the black solid washed twice with ether. The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to give the corresponding aldehyde. The residue was chromatographed on slica gel (eluent, diethyl ether:ethyl acetate:petroleum ether 90:5:5). *E*-3-Ethylidene-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (**194**) was obtained as a colourless oil in 55% yield.

IRν_{max} (film) 1760 (br, β–lactam C=O, CHO) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.84 (3H, d, J=5.64Hz, $C\underline{H}_3$-CH=), 3.81 (3H, s, -OCH_3), 4.82 (1H, s, H-4), 6.53 (1H, q, J=6Hz, H-5), 6.89 (2H, d, J=9.39Hz, H-3`and H-5`), 7.29 (2H, d, J=9.39Hz, H-2` and H-6`), 9.60 (1H, d, $J_{7,4}$=3.75Hz, -CHO).

^{13}C-NMR

($CDCl_3$)ppm 13.80 (C-6), 55.48 ($O\underline{C}H_3$), 65.31 (C-4), 114.51 (C-3` and C-5`), 117.29 (C-2` and C-6`), 127.43 (C-5), 159.04 (β-lactam $\underline{C}$=O), 135.01 (C-1`), 155.04 (C-4`), 197.90 ($\underline{C}$HO).

Low Resolution Mass Spectrum

$C_{13}H_{13}NO_3$	Requires:	M^+=231
	Found:	M^+=231

High Resolution Mass Spectrum

$C_{13}H_{13}NO_3$	Requires:	M^+=231.08954
	Found:	M^+=231.08948

Mass Spectrum (m/z)

231 (M^+, 61%), 202 (M-29, 99%), 159 (M-72, 28%), 149 (M-82, 39%), 134 (M-97, 100%), 107 (M-124, 21%), 77 (M-154, 42%), 69 (M-162, 43%).

3-Isopropylidene-4-methanesulphonyloxymethyl-1-(4-methoxyphenyl)azetidin-2-one (202)

To a stirred solution of 4-hydroxymethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**177**) (2mmol) in dichloromethane (25ml) was added triethylamine (0.42ml) followed by methanesulfonyl chloride (0.18ml) at -5°C. The mixture was stirred in an ice bath for 20 min and then washed successively with cold water (2x20ml), 3N HCl (2x20ml), 10% $NaHCO_3$ (2x20ml), and again with water (2x20ml). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to afford the mesylate which was recrystallised from ethanol to afford the pure product. 3-Isopropylidene-4-methanesulphonyloxy-1-(4-methoxyphenyl)azetidin-2-one (**202**) was obtained as a colourless solid in 70% yield m.p. 110-111°C.

IRν_{max} (KBr) 1743 (C=O), 1350, 1175 (S=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.86 (3H, s, CH_3), 2.13 (3H, s, CH_3), 2.88 (3H, s, CH_3), 3.78 (3H, s, -OCH_3), 4.25 (1H, dd, J_{vic}=5.25Hz, J_{gem}=4.38Hz, H-8`), 4.59 (1H, dd, J_{vic}=3.51Hz, J_{gem}=4.38Hz, H-8``), 4.75 (1H, t, $J_{4,7}$=4.38Hz, H-4), 6.86 (2H, d, J=9Hz, H-3` and H-5`), 7.36 (2H, d, J=9Hz, H-2`and H-6`).

^{13}C-NMR (101MHz)

(CDCl$_3$)ppm 19.88 (C-6), 20.56 (C-7), 39.67 ($OSO_2\underline{C}H_3$), 55.90 ($O\underline{C}H_3$), 57.89 (C-4), 66.67 (C-8), 115.78 (C-3` and C-5`), 118.56 (C-2` and C-6`), 129.56 (C-5), 130.45 (C-1`), 139.56 (C-3), 157.56 (C-4`), 161.53 ($\underline{C}$=O).

Elemental Analysis

$C_{15}H_{19}NO_5S$	Requires:	C, 55.37; H, 5.89; N, 4.30%.
	Found:	C, 55.63; H, 5.88; N, 4.17%.

4-Iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (203)

Sodium iodide (3mmol) was added to a solution of 3-isopropenyl-4-methanesulphonyloxy-1-(4-methoxyphenyl)azetidin-2-one (**202**) (1mmol) in acetone (10ml). The solution was brought to reflux for 4 h, filtered and evaporated to dryness. Dichloromethane (25ml) was added and the organic layer was washed twice with water (2x25ml). The organic phase was dried with (Na_2SO_4). Evaporation of the solvent yielded the 4-iodomethyl-β-lactam, which was recrystallised from dichloromethane to afford the pure product. 4-Iodomethyl-3-isopropylidene-1-(4-methoxyphenyl)azetidin-2-one (**203**) was obtained as colourless oil in 75% yield .

IRν_{max} (KBr) 1736 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ (CDCl$_3$) 1.80 (3H, s, CH_3), 2.13 (3H, s, CH_3), 3.62-3.74 (2H, m, Hs-8), 3.78 (3H, s, -OCH_3), 4.25 (1H, t, $J_{4,8}$=3Hz, H-4), 6.87 (2H, d, H-3` and H-5`), 7.20 (2H, d, H-2`and H-6`).

^{13}C-NMR (101MHz)

(CDCl$_3$)ppm 6.06 (C-8), 20.30 (C-6), 20.90 (C-7), 55.45 (C-4), 57.62 ($O\underline{C}H_3$), 114.59 (C-3` and C-5`), 118.35 (C-2`and C-6`), 130.53 (C-5), 133.58 (C-1`), 138.51 (C-3), 144.98 (C-4`), 156.03 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{14}H_{16}NO_2I$	Requires:	M^+=357
	Found:	M^+=357

High Resolution Mass Spectrum

$C_{14}H_{16}NO_2I$	Requires:	M^+=357.02258
	Found:	M^+=357.02235

Mass Spectrum (m/z)

357 (M^+, 100%), 230 (M-127, 43%), 216 (M-141, 20%), 202 (M-155, 20%), 149 (M-208, 38%), 134 (M-223, 37%), 122 (M-235, 25%), 92 (M-265, 13%), 79 (M-278. 36%).

_E_-3-Ethylidene-4-phenylazetidin-2-one (204)

Ammonium cerium (IV) nitrate (0.406g, 0.742mmol) dissolved in water (1.25ml) was added to a cooled solution (0-5°C) of *E*-3-ethylidene-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**180**) (0.06g, 0.246mmol) in acetonitrile (4.94ml). The reaction mixture was stirred at 0-5°C for 30 min and then poured into water (7.40ml). The resulting solution was extracted with ethyl acetate (4x3.7ml) and the organic layer washed with aqueous $NaHCO_3$ (3.0ml, saturated solution). The aqueous layer was again extracted with ethyl acetate (1.5ml). The combined extracts were washed with 40% $NaHCO_3$ (4x3.7ml), aqueous $NaHCO_3$ (3.0ml, saturated solution) and brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded a residue which was purified by column chromatography over silica gel (eluent:dichloromethane:ethyl acetate 85:15). *E*-3-Ethylidene-4-phenylazetidin-2-one (**204**) was obtained as a brown oil in 60% yield.

IRν_{max} (film)	3348 (N-H), 1741 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$)	1.54 (3H, d, J=7.84Hz, C<u>H</u>$_3$-CH=), 5.13 (1H, s, H-4), 6.25 (1H, q, J=7.84Hz, H-5), 6.52 (1H, s, NH), 7.31-7.54 (5H, m, aromatic Hs).

^{13}C-NMR (101MHz)

(CDCl$_3$)ppm 12.65 (<u>C</u>H$_3$), 58.25 (C-4), 123.13, 126.48, 138.18, (aromatic Cs), 136.06 (C-5), 144.00 (C-3), 164.50 (β-lactam <u>C</u>=O).

Low Resolution Mass Spectrum

$C_{11}H_{11}NO$ Requires: M^+=173

Found: M^+=173

High Resolution Mass Spectrum

$C_{11}H_{11}NO$ Requires: M^+=173.08406

Found: M^+=173.08392

Mass Spectrum (m/z)

173 (M^+, 31%), 144 (M-29, 37%), 130 (M-43, 100%), 115 (M-58, 74%), 104 (M-69, 43%), 77 (M-96, 37%), 51 (M-122, 36%).

2-Phenyl-5, 6-dihydro-4<u>H</u>-1, 3-thiazine (207)

A mixture of thiobenzamide (10g) and 1-bromo-3-chloropropane (100ml) was heated to boiling under an air condenser. The mixture was refluxed gently for 2-2.5 h, during which time gases were given off by the liquid. When the gaseous development had almost completely stopped, the liquid was allowed to cool and was extracted with water. The aqueous extract was shaken with diethyl ether to remove the 1-bromo-3-chloropropane and the ether layer was discarded. The aqueous layer was then made alkaline using conc. NaOH solution and extracted three times with diethyl ether. The extract was evaporated to dryness under reduced pressure to afford the crude product as dirty yellow crystals. The crude product was purified by column chromatography over silica gel, (eluent, diethyl ether:light petroleum (b.p. 40-60°C), 30:70 to give yellow crystals in 70% yield, m.p. 43°C (lit. m.p.[161] 44-45°C).

IRν_{max} (KBr) 1600 (C=N) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.47-1.98 (2H, m, Hs-5), 3.02 (2H, t, J=6Hz, Hs-6), 3.77 (2H, t, J=4.80Hz, Hs-4), 7.15 (3H, m, H-3`, H-4`and H-5`), 7.80 (2H, m, H-2` and H-6`).

6-Phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-ones (208), (209)

Method A:

To a solution of 2-phenyl-5,6-dihydro-4H-1,3-thiazine (**207**) (10mmol) and triethylamine (1.0g, 10mmol) in CH_2Cl_2 (50ml) at reflux under nitrogen was added dropwise over 45 min a solution of crotonyl chloride or 3,3-dimethylacryloyl chloride (10mmol) in CH_2Cl_2 (25ml). The reaction mixture was then refluxed for one hour and washed with water (2x50ml). The dichloromethane layer was dried over anhydrous (Na_2SO_4) and evaporated to yield the crude product. The required β-lactams were obtained by column chromatography (eluent, light petroleum (b.p. 40-60°C):diethyl ether, 7:3) as colourless oils.

Method B:

To a solution of crotonic acid or 3, 3-dimethylacrylic acid (0.009mol) in CH_2Cl_2 (100ml) was added 2-chloro-*N*-methylpyridinium iodide (2.75g, 0.011mol) and tri-*n*-propylamine (5.12ml, 0.027mol) in dry CH_2Cl_2 (50ml) under a nitrogen atmosphere at room temperature. The reaction mixture was refluxed gently. When all the solids had dissolved 2-phenyl-5,6-dihydro-4H-1,3-thiazine (**207**) (2g, 0.009mol) was added . The reaction mixture was then refluxed for 24h and washed with water (2x50ml). The dichloromethane layer was dried over anhydrous (Na_2SO_4) and evaporated to yield the crude product. The crude product was purified by column chromatography over silica gel as discussed in method A.

7-vinyl-6-phenyl-1-thia-5-azabicyclo[4.2.0]-octan-8-one (208) was obtained as a colourless oil in 56% (method A)[122] and 60% (method B) yield as a colourless oil.

IRν_{max} (film) 1755 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ($CDCl_3$) 1.83-1.89 (2H, m, H-3), 2.61-2.69 (2H, m, H-2), 3.03-3.13 (1H, m, J_{gem}14.55Hz, J_{ax-eq}3.20Hz, J_{ax-ax}8.95Hz, H-4ax), 4.10-4.14 (1H, m, J=0.71-2.09Hz, H-4eq), 4.16 (1H, d, J=7.28Hz, H-7), 4.98-5.30 (3H, m, H-9, H-10), 7.26-7.49 (5H, m, aromatic H`s).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 23.80 (C-3), 25.65 (C-2), 37.76 (C-4), 67.36 (C-6), 69.68 (C-7), 120.74 (C-10), 127.67 (C-3` and C-5`), 128.05 (C-9), 128.33 (C-2` and C-6`), 128.61 (C-1`), 137.58 (C-4`), 165.98 (C=O).

7-(1-methylvinyl)-6-phenyl-1-thia-5-azabicyclo[4.2.0]-octan-8-one (209) was obtained as a colourless oil in 65% (method A)[122] and 70% yield (method B) as a colourless oil.

IRν_{max} (film) 1760 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ($CDCl_3$) 1.20 (3H, s, CH_3), 1.80-1.85 (2H, m, H-3), 2.54-2.70 (2H, m, H-2), 2.99-3.05 (1H, m, H-4ax), 4.10-4.16 (1H, m, H-4eq), 4.15 (1H, s, H-7), 4.77 (1H, d, J_{gem}=1.32Hz, H-10), 5.98 (1H, d, J_{gem}=1.32Hz, H-10), 7.26-7.55 (5H, m, aromatic H).

^{13}C-NMR (75MHz)

($CDCl_3$)ppm 21.40 ($\underline{C}H_3$), 23.73 (C-3), 25.80 (C-2), 37.42 (C-4), 67.90 (C-6), 73.36 (C-7), 116.48 (C-10), 127.88 (C-3` and C-5`) 128.10 (C-9`), 128.26 (C-2` and C-6`), 136.29 (C-1`), 136.60 (C-4`), 165.89 ($\underline{C}$=O).

Isomerisation studies of 6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-ones (208) and (209)

Method A:

The appropriate 6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (1mmol) was dissolved in dry MeOH (10ml) and $NaBH_4$ (4.05mmol, 0.15g) was added in portions. The mixture was stirred at room temperature for 65 min. The solvent was removed and the crude product was then poured on water and extracted with diethyl ether (3x20ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residues were chromatographed on silca gel (eluent, light petroleum (b.p. 40-60°C):diethyl ether 5:5) to afford the products (**210**) and (**211**).

Method B:

The appropriate 6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (0.0009mol) was dissolved in dry THF (10ml). $LiAlH_4$ (0.0036mol) was added under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min. The crude product was gently poured onto water. The solution was washed with 2% HCl (2x10ml), 10% $NaHCO_3$ (2x10ml) and brine (2x10ml) and extracted with diethylether (2x10ml) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded a residue which was purified by column chromatography over silica gel as mentioned in method A.

7-Ethylidene-6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (210) was obtained as a colourless oil in 10% (method A) and 60% (method B) yield[122].

IRν_{max} (film) 1760 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.52 (1.5H, d, $J_{10,9}$=7.22Hz, *E* isomer H-10), 1.71-1.92 (2H, m, H-3), 1.93 (1.5H, d, J=7.22Hz, *Z*-isomer H-10), 2.54-2.64 (2H, m, H-2), 2.84-3.06 (1H, m, H-4ax), 4.03-4.15 (1H, m. H-4eq), 5.49-5.59 (0.5H, q, $J_{9,10}$=7.22Hz, *E* isomer H-9), 5.96-6.02 (0.5H, q, $J_{9,10}$=7.22Hz, *Z* isomer H-9), 7.26-7.77 (5H, m, aromatic H).

7-Isopropylidene-6-phenyl-1-thia-5-azabicyclo[4.2.0]octan-8-one (211) was obtained as colourless crystals in 50% yield (method A) m.p. 131-132°C (lit. m.p. 130-132°C[122]) recrystallised from MeOH.

IRν_{max} (film) 1770 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 1.44 (3H, s, CH_3 *trans* to C=O), 2.00 (3H, s, CH_3 *cis* to C=O), 1.62-1.78 (2H, m, H-3), 2.46-2.61 (2H, m, H-2), 2.76-2.83 (1H, m, H-4ax), 3.94-4.01 (1H, m, H-4eq), 7.20-7.69 (5H, m, aromatic H).

Chapter 4

General preparation of *N*-aryl-3-halopropionamides (218), (219)

A suspension of 3-bromopropionyl chloride (1.073g, 0.00625mol) or of 3-chloropropionyl chloride (0.793g, 0.00625 mol) in dry dichloromethane (12.5ml) was added dropwise with stirring to a solution of *N,N*-dimethylaniline (1.6ml, 0.0125mol) and the appropriately substituted aryl amine (0.00625mol) in dry dichloromethane (75ml) at 0°C. The reaction mixture was stirred at room temperature for 2 h. The mixture was washed with 5% HCl solution (2x50ml), water (2x50ml), saturated $NaHCO_3$ solution (2x50ml) and brine (2x50ml). The organic phase was dried over anhydrous (Na_2SO_4) and concentrated *in vacuo* to afford a solid product.

3-Bromo-*N*-(4-methoxyphenyl)propionamide (218) was crystallised from dichloromethane as colourless crystals in 84% yield m.p.105-109°C (lit.m.p.[186] 111-112°C, lit. m.p[187], 112-114°C).

IRν_{max}(KBr) 3250 (NH), 1650 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.85 (2H, t, $J_{3,4}$=6.5Hz, H-3), 3.65 (2H, t, $J_{4,3}$=6.5Hz, H-4), 3.74 (3H, s, -OCH_3), 6.79 (2H, d, J=9.0Hz, H-3`and H-5`), 7.36 (2H, d, J=9.0Hz, H-2` and H-6`).

3-Chloro-*N*-(4-methylphenyl)propionamide (219) was crystallised from dichloromethane as colourless crystals in 50% yield m.p. 120-123°C (lit. m.p.[188]121°C).

IRν_{max}(KBr) 3280 (NH), 1665 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.25 (3H, s, CH_3), 2.70 (2H, t, $J_{3,4}$=6.0Hz, H-3), 3.80 (2H, t, $J_{4,3}$=6.0Hz, H-4), 6.80 (2H, d, J=9.0Hz, H-3`and H-5`), 7.50 (2H, d, J=9.0Hz, H-2` and H-6`).

1-(4-Methoxyphenyl)azetidin-2-one (220) and 1-(4-methyphenyl)azetidin-2-one (221)

A solution containing the appropriate *N*-aryl-3-halopropionamide (0.0025mol) in 25ml of dichloromethane was added to a suspension of pulverised potassium hydroxide (0.003mol) and 18-crown-6 (0.0005mol) in dichloromethane (25ml) over a period of 3 h with stirring. After the completion of the addition, the reaction mixture was stirred for 30 min. The precipitate was filtered and then washed with dichloromethane. After removal of the combined solvent, the residue was purified by crystallization from methanol.

1-(4-Methoxyphenyl)azetidin-2-one (220) was obtained as colourless crystals in 80% yield m.p.101-102°C (lit. m.p.[186] 98-99°C, lit. m.p.[187] 104-105°C).

IRν_{max}(KBr) 1731 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.06 (2H, t, $J_{3,4}$=4.0Hz, H-3), 3.57 (2H, t, $J_{4,3}$=4.0Hz, H-4), 3.78 (3H, s, -OCH_3), 6.95 (2H, d, J=9.0Hz, H-3` and H-5`), 7.29 (2H, d, J=9.0Hz, H-2`and H-6`).

1-(4-Methylphenyl)azetidin-2-one (221) was obtained as colourless crystals in 73% yield m. p. 100-101°C (lit. m.p.[165] 97-98°C).

IRν_{max}(KBr) 1730 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.26 (3H, s, CH_3), 2.98 (2H, t, $J_{3,4}$=4.41Hz, H-3), 3.48 (2H, t, $J_{4,3}$=4.41Hz, H-4), 7.06 (2H, d, J=8.19Hz, H-3` and H-5`), 7.19 (2H, d, J=8.19Hz, H-2`and H-6`).

***N*-cinnamylidene-*p*-anisidine (223)**

A mixture of cinnamaldehyde (0.2mol), *p*-anisidine (24.6g, 0.2mol) and magnesium sulphate (1.00g) in dichloromethane (200ml) was refluxed for 2 h. The resulting mixture was filtered and the solvent was evaporated *in vacuo* to give the crude imine which was crystallised from ethanol.

***N*-cinnamylidene-*p*-anisidine (223)** was afforded as yellow plates in 73% yield m.p 121-122°C (lit. m.p.[189] 118-119°C).

IRν_{max} (KBr) 1605 (C=N) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 8.26 (1H, d, J=4Hz, -C<u>H</u>=N-), 6.55-7.45 (11H, m, aromatic H, -CH=CH-), 3.77 (3H, s, $-OCH_3$).

1-(4-Methoxyphenyl)-4-phenylazetidin-2-one (222) and 1-(4-methoxyphenyl)-4-styrylazetidin-2-one (224)

To a suspension of zinc dust (0.9g, 0.0138mol) in dry toluene (20ml) under nitrogen, trimethylchlorosilane (0.65ml, 0.005mol) was added, and the resulting mixture was stirred at room temperature for 15 min and then under reflux conditions for 2 min. The suspension was cooled and the appropriate imine (0.010mol) and ethyl bromoacetate (1.33ml, 0.012mol) were added. The reaction mixture was refluxed under nitrogen for 2.5 h and then cooled in an ice-water bath and poured over a solution of NH_4Cl (20ml, saturated solution) and 25% NH_4OH (20ml). Dichloromethane (20ml) was added, and the organic layer was washed with 0.1M HCl (20ml) and water (20ml). The organic solution was dried over anhydrous (Na_2SO_4) and the solvent evaporated under reduced pressure to yield the crude β-lactam.

1-(4-Methoxyphenyl)-4-phenylazetidin-2-one (222) was purified by column chromatography over silica gel [eluent:petroleum ether (b.p. 60-40°C): diethyl ether; 75:25] followed by crystallization from methanol to afford cream coloured needles in 17% yield m.p. 96°C (lit. m.p.[190] 86°C, lit. m.p.[191] 95-97°C)

IRν_{max} (KBr) 1740 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.78 (1H, dd, $J_{3\beta,4trans}$=2.5Hz, J_{gem}=14.0Hz, H-3β), 3.45 $J_{3\alpha,4cis}$=5.0Hz, J_{gem}=14.0Hz, H-3α), 3.75 (3H, s, -OCH_3), 4.85 (1H, dd, $J_{4,3\alpha cis}$=5.0Hz, $J_{4,3\beta trans}$=2.5Hz, H-4), 6.66-7.41 (9H, m, aromatic H).

1-(4-Methoxyphenyl)-4-styrylazetidin-2-one (224) was purified by column chromatography over silica gel [eluent:light petroleum (b.p. 60-40°C):diethyl ether; 80:20 v/v] followed by crystallization from ethanol to yield pale yellow crystals in 53% yield m.p. 140-142°C (lit.m.p.[100] 139-142°C).

IRν_{max} (KBr) 1743 (C=O) cm^{-1}.

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.91 (1H, dd, $J_{3\beta,4trans}$=2.21Hz, J_{gem}=15.05Hz, H-3β), 3.39 (1H, dd, $J_{3\alpha,4cis}$=5.53Hz, J_{gem}=15.05Hz, H-3α), 3.75 (3H, s, OCH_3), 4.59-4.63 (1H, m, H-4), 6.27 (1H, dd, $J_{5,4}$=8.34Hz, $J_{5,6}$=15.81Hz, H-5), 6.77-6.84 (3H, m, H-3`, H-5`, H-6), 7.27-7.41 (7H, m, aromatic Hs).

General preparation of compounds (239), (240) and (241)-(248)

All reactions were carried out in a nitrogen atmosphere. THF was dried over calcium hydride followed by a second drying over sodium wire with benzophenone as an indicator. The THF changed from a clear colour to a blue colour when dry.

To a solution of lithium diisopropylamide [prepared from diisopropylamine (0.7ml, 0.005mol) and *n*-butyllithium (1.79ml of 2.5M solution in hexane 0.005mol) in dry THF (2.5ml)] was added a solution of the appropriate azetidin-2-one (0.0025mol) in THF (25ml) at -78°C. After 5 min, a solution of the appropriate arylaldehyde or alkylaldehyde was added to the reaction mixture at the same temperature. After stirring at -78°C for 30 min, the reaction mixture was poured into water (50ml) and saturated with sodium chloride. The organic layer was separated, dried over (Na_2SO_4), and evaporated to dryness.

Compounds **(239), (240)** were isolated as diastereomeric mixtures by column chromatography over silica gel (eluent: 100% dichloromethane) and obtained as yellow oils in 63 % yield, and 55% yield respectively.

3-[1-(1-Hydroxyethyl)]-1-(4-methoxyphenyl)azetidin-2-one (239)

IRν_{max} (film) 3400 (br OH), 1736 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.30 (1H, s, CH_3), 1.35 (2H, s, CH_3), 3.00 (1H, bs, -OH), 3.39 (1H, dd, J=5.52Hz, J=2.52Hz, H-4), 3.46 (1H, dd, J=5.52Hz, J=2.52Hz, H-4), 3.57-3.59 (1H, m, H-3), 3.74 (3H, s, -OCH_3), 4.11-4.24 (1H, m, H-5), 6.83 (2H, d, J=9.04Hz, H-3` and H-5`), 7.26 (2H, d, J=9.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 20.51, 21.05 (CH_3), 40.58, 40.78 (C-4), 54.85 (OCH_3), 55.03, 55.10, (C-3), 64.57, 65.65 (C-5), 113.90 (C-3` and C-5`), 117.12 (C-2`and C-6`), 131.43, 131.53 (C-1`), 155.62, 155.65 (C-4`), 164.55, 164.79 (β-lactam C=O).

Low Resolution Mass Spectrum

$C_{12}H_{15}NO_3$ Requires: M^+=221
Found: M^+=221

High Resolution Mass Spectrum

$C_{12}H_{15}NO_3$ Requires: M^+=221.10519
Found: M^+=221.10489

Mass Spectrum (m/z)

221 (M^+, 50%), 177 (M-44, 45%), 149 (M-72, 70%), 135 (M-86, 100%), 120 (M-101, 75%).

3-[1-(1-Hydroxyethyl]-1-(4-methylphenyl)azetidin-2-one (240)

IRν_{max} (film) 3400 (br OH), 1736 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.19 (1H, d, J=6.52Hz, CH_3), 1.30 (2H, d, J=6.52Hz, CH_3), 2.13 (3H, s, CH_3), 3.39 (1H, dd, J=5.52Hz, J=2.52Hz, H-4), 3.45 (1H, dd, J=5.52Hz, J=2.52Hz, H-4), 3.59-3.66 (1H, m, H-3), 4.10-4.20 (1H, m, H-5), 6.83 (2H, d, J=9.04Hz, H-3` and H-5`), 7.26 (2H, d, J=9.04Hz, H-2`and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 17.74, 18.07 (CH_3) 20.67, 20.92 (CH_3), 40.58, 40.61 (C-4), 54.74, 54.80 (C-3), 65.17, 65.20 (C-5), 115.85 (C-3` and C-5`), 129.10 (C-2` and C-6`), 132.99 (C-1`), 135.40 (C-4`), 165.17, 165.38 (β-lactam C=O).

Low Resolution Mass Spectrum

$C_{12}H_{15}NO_2$ Requires: M^+=205

Found: M^+=205

Mass Spectrum (m/z)

205 (M^+, 65%), 190 (M-15, 15%), 120 (M-85, 30%).

3-[(Hydroxy)(1-propenyl)methyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (241) was purified by flash chromatography over silica gel (eluent, dichloromethane:ethyl acetate; 9:1) to yield a diastereomeric product as a colourless oil in 70% yield.

IRν_{max}(film) 3423 (br OH), 1733 (β-lactam C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.70 (3H, m, CH_3), 3.24 (1H, dd, $J_{3,4trans}$=2.48Hz, $J_{3,5}$=6Hz, H-3), 4.54 (0.5H, br t, $J_{5,3}$=6.2Hz, H-5), 4.69 (0.5H, br s, H-5),

4.89 (0.5H, d, $J_{4,3trans}$=2.52Hz, H-4), 5.08 (0.5H, $J_{4,3trans}$=2.52Hz, H-4), 5.50-5.60 (2H, m, H-6, H-7), 6.74-7.20 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 17.45 ($\underline{C}H_3$), 55.17 ($O\underline{C}H_3$), 56.23, 57.23 (C-4), 65.04, 65.30 (C-3), 68.43, 70.65 (C-5), 114.05, 114.09 (C-3`and C-5`), 118.21, 118.28 (C-2` and C-6`), 125.57, 125.95, 127.24, 127.94, 128.14, 128.81, 128.88, 129.00, 130.45, 130.94 , 137.59, 137.95 (aromatic Cs, C-6 and C-7), 155.78 (C-4`), 165.05, 165.12 ($\underline{C}$=O).

High Resolution Mass Spectrum

$C_{20}H_{21}NO_3$ Requires: M^+=323.1521

Found: M^+=323.1521

Mass Spectrum (m/z)

323.1 (M^+, 100%), 253.1 (M-70.0, 26%), 211.0 (M-112.1, 42%), 196.0 (M-127.1, 40%), 148.9 (M-174.2, 99%), 123.0 (M-200.1, 80%).

3-[1-(Hydroxy)(styryl)methyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (242) was purified by flash chromatography over silica gel (eluent, dichloromethane:ethyl acetate, 9:1) to afford a diasteromeric product as a yellow oil in 70% yield. For identification purposes by low resolution mass spectrometry (**242**) (1mg) was reacted with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide 97% (0.5ml) in chloroform (1ml) to give the TMS derivative of (**242**).

IRν_{max}(film) 3425 (br OH), 1750 (β-lactam C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.36-3.37 (1H, m, H-3), 3.76 (3H, s, OCH_3), 4.59 (0.25H, d, $J_{4,3trans}$=2.48Hz, H-4), 4.62 (0.25H, d, $J_{4,3trans}$=2.48Hz, H-4), 4.71-4.93 (1.5H, m, H-4 and H-5), 6.28 (1H, m, H-6), 6.43 (1H, d, $J_{7,6}$=15Hz, H-7), 7.32-7.43 (14H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 55.00, 55.06 (C-3), 56.29 ($O\underline{C}H_3$), 61.91, 62.22 (C-4), 68.10, 70.50 (C-5), 113.90, 117.97, 126.19, 126.55, 127.40, 127.79, 127.91, 128.15 (aromatic Cs), 131.11, 132.13 (C-6), 133.63, 133.88 (C-7), 135.24, 135.36, 135.74, 135.96 (C-1`, C-1``, and C-1```), 155.69, 155.73 (C-4`), 164.05 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{25}H_{23}NO_3$ Requires : M^+=385

Found: M^+72=457 (TMS derivative)

High Resolution Mass Spectrum

$C_{25}H_{23}NO_3$ Requires : M^+=385.16779

Found: M^+=385.17133

Mass Spectrum (m/z)

457 (M^+, 30%), 325 (M-132, 20%), 205 (M-252, 100%), 73 (M-384, 100%).

3-[1-(Hydroxy)(α-methylstyryl)methyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (243) was purified by flash chromatography over silica gel (eluent, dichloromethane:ethyl acetate 9:1) to afford a diastereomeric product as a yellow oil in 85% yield .

IRν_{max}(film) 3423 (br OH), 1749 (β-lactam C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.88 (0.9H, s, CH_3), 2.07 (2.1H, s, CH_3), 3.46 (1H, dd, $J_{3,4trans}$=2.4Hz, $J_{3,5}$=8.04Hz, H-3), 3.70 (0.9H, s, OCH_3), 3.72 (2.1H, s, -OCH_3), 4.13 (0.30H, br d, $J_{5,3}$=7.02Hz, H-5), 4.16 (0.70H, br d, $J_{5,3}$=7.02Hz, H-5), 4.84 (1H, br d, $J_{4,3trans}$=2.52Hz, H-4), 5.23 (1H, bs, H-7), 6.82-7.43 (14H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 12.55, 12.95 (CH_3), 53.12 (C-3), 54.93, 54.97 ($O\underline{C}H_3$), 57.37, 60.00 (C-4), 74.29, 71.34 (C-5), 113.87, 113.96 (C-3` and C-5`), 117.96, 118.12 (C-2` and C-6`), 124.75, 125.55, 125.73, 126.09, 126.43, 127.43, 127.75, 127.76, 127.85, 128.00, 128.63 (aromatic Cs), 130.73 (C-7), 136.68, 137.05, 137.28, 137.38 (C-1`, C-1``, C-1``` and C-6), 155.59, 155.70 (C-4`), 165.40 (β-lactam $\underline{C}$=O).

High Resolution Mass Spectrum

$C_{26}H_{25}NO_3$ Requires: M^+=399.1834

Found: M^+=399.1826

Mass Spectrum (m/z)

399.2 (M^+, 100%), 253.1 (M-146.1, 41.6%), 211.1 (M-188.1, 49.4%), 149.0 (M-250.2, 97.1%), 131.0 (M-268.2, 91.8%), 123.0 (M-276.2, 87.9%).

3-[(Hydroxy)(1-vinyl)methyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (244) was purified by flash chromatography over silica gel (eluent: 100% dichloromethane) to afford a diastereomeric product as a yellow oil in 58% yield.

IRν_{max} (film) 3450 (br OH), 1734 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.50 (1H, br s, -OH), 3.26 (1H, dd, $J_{3,4trans}$=1.90Hz, $J_{3,5}$=4.5Hz, H-3), 3.60 (3H, s, -OCH_3), 4.89 (0.5H, d, $J_{4,3trans}$ =1.89Hz, H-4), 5.06 (0.5H, d, $J_{4,3}$=1.89Hz, H-4), 4.61 (0.5H, br t, $J_{5,3}$=4.89Hz, H-5), 4.76 (0.5H, br t, H-5), 5.23-6.12 (2H, m, H-6 and H-7), 6.77-7.30 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 54.97 ($O\underline{C}H_3$), 55.79, 55.68 (C-3), 64.23, 64.49 (C-4), 68.42, 70.83 (C-5), 113.84, 113.88 (C-3` and C-5`), 117.95, 118.02 (C-2`and C-6`), 125.71, 128.00, 128.58, 128.67, 136.00 (aromatic

Cs, C-5 and C-6), 136.76, 137.12, 137.46 (C-1`, C-1``, C-1```), 155.63, 155.68 (C-4`), 165.58 (β-lactam C=O).

Low Resolution Mass Spectrum

$C_{19}H_{19}NO_3$	Requires:	M^+=309
	Found:	M^+=309

High Resolution Mass Spectrum

$C_{19}H_{19}NO_3$	Requires:	M^+=309.13649
	Found:	M^+=309.13704

Mass Spectrum (m/z)
309 (M^+, 25%), 211 (M-98, 20%), 196 (M-113, 25%), 149 (M-160, 100%), 77 (M-232, 20%).

3-[(Hydroxy)(1-propenyl)methyl]-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (245) was purified by flash chromatography over silica gel (eluent, dichloromethane:ethyl acetate, 9:1) to afford a diastereomeric product as a colourless oil in 47% yield.

IRν_{max} (film) 3426 (br OH), 1736 (β-lactam C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.63-1.65 (3H, m, CH_3), 3.12-3.14 (1H, m, H-3), 3.64 (3H, s, -OCH_3), 4.40-4.61 (2H, m, H-4 and H-5), 5.51-5.59 (2H, m, H-6 and H-7), 6.68-7.35 (11H, m, aromatic Hs, H-8 and H-9).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 16.55 (CH_3), 55.56 (OCH_3), 59.27, 61.62 (C-3 and C-4), 67.65, 69.60 (C-5), 113.21 (C-3` and C-5`), 117.29 (C-2` and C-6`), 125.49, 127.55, 129.22, 129.26, 130.48, 132.79 (aromatic Cs, C-6, C-8, C-9 and C-7), 154.96 (C-4`), 163.76 (β-lactam C=O).

Low Resolution Mass Spectrum

$C_{22}H_{23}NO_3$	Requires:	M^+=349
	Found:	M^+=349

High Resolution Mass Spectrum

$C_{22}H_{23}NO_3$	Requires:	M^+=349.16779
	Found:	M^+=349.16822

Mass Spectrum (m/z)

349 (M^+, 30%), 279 (M-70, 46%), 236 (M-113, 38%), 202 (M-147, 58%), 157 (M-192, 61%), 69 (M-280, 100%).

3-[(Hydroxy)(styryl)methyl]-1-(4-methoxyphenyl)-4-styrylazetidin-2-one (246) was purified by column chromatography over silica gel (eluent, dichloromethane:ethyl acetate; 9:1) to afford a diastereomeric product as a yellow oil in 59% yield.

IRν_{max} (film) 3422 (OH), 1731 (C=O) cm^{-1}

^{1}H-NMR (300MHz)

δ ($CDCl_3$) 3.21 (1H, dd, $J_{3,4trans}$=1.89Hz, $J_{3,5}$=3.0Hz, H-3), 3.61 (3H, s, -OCH_3), 4.48 (0.5H, dd, $J_{4,3trans}$=1.5Hz, $J_{4,7}$=6.5Hz, H-4), 4.66 (0.5H, dd, $J_{4,3}$=1.89Hz, $J_{4,7}$=6.2Hz, H-4), 4.61 (0.5H, br t, 0.5H, J=4.5Hz, H-5), 4.80 (br t, 0.5H, J=4.5Hz, H-5), 6.10-6.40 (2H, m, H-6 and H-7), 6.50-7.23 (16H, m, aromatic Hs, H-8 and H-9).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 54.25 (O<u>C</u>H_3), 55.51 (C-3), 59.21, 61.28 (C-4), 67.27, 69.55 (C-5), 113.17 (C-3` and C-5`), 117.26 (C-2` and C-6`), 125.46, 125.55, 125.90, 126.60, 126.81, 127.04, 127.16, 127.25, 127.36, 127.43, 127.69 (aromatic Cs), 129.71 (C-6), 130.43, 131.22 (C-7 and C-9), 132.85 (C-1`), 134.68 (C-8), 135.35, 135.37 (C-1`` and C-1```), 154.95, 154.98 (C-4`), 163.46 (β-lactam <u>C</u>=O).

High Resolution Mass Spectrum

$C_{27}H_{25}NO_3$ Requires: M^+=411.18344

Found: M^+=411.18384

3-[(Hydroxy)(α-methylstyryl)methyl]-1-(4-methoxyphenyl)-4-styryl-azetidin-2-one (247) was purified by flash chromatography over silica gel (eluent, dichloromethane:ethylacetate, 9:1) to afford a diastereomeric product as a yellow oil in 65% yield. For identification purposes by low resolution mass spectrometry (**247**) (1mg) was reacted with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide 97% (0.5ml) in chloroform (1ml) to give the TMS derivative of (**247**).

IRν_{max}(film) 3410 (br OH), 1739 (C=O) cm^{-1}

^{1}H-NMR(400MHz)

δ ($CDCl_3$) 1.90 (1H, s, CH_3), 1.91 (2H, s, CH_3), 3.55 (1H, dd, $J_{3,4trans}$=1.5Hz, $J_{3,5}$=8.6Hz, H-3), 3.73 (1H, s, -OCH_3), 3.76 (2H, s, -OCH_3), 4.47-4.83 (2H, m, H-4 and H-5), 6.28-6.31 (1H, m, H-7), 6.33-7.32 (16H, m, aromatic Hs, H-8 and H-9).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.76, 23.08 ($\underline{C}H_3$), 54.97 (O$\underline{C}H_3$), 57.22 (C-3), 59.91, 60.40 (C-4), 71.57 (C-5), 113.89, 113.97 (C-3` and C-5`), 117.85, 117.96 (C-2` and C-6`), 125.06, 126.12, 126.26, 126.37, 126.89, 127.23, 127.79, 128.31, 128.66 (aromatic Cs, C-7 and C-9), 131.31 (C-1`), 133.98, 135.69 (C-6 and C-8), 135.27. 135.48, 136.71, 137.21 (C-1`` and C-1```), 155.73 (C-4`), 165.12 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{28}H_{27}NO_3$ Requires: M^+=425

Found: M^+72=497 (TMS derivative)

High Resolution Mass Spectrum

$C_{28}H_{27}NO_3$ Requires: M^+=425.19909

Found: M^+=425.19833

Mass Spectrum (m/z)

497 (M^+, 20%), 351 (M-146, 40%), 219 (M-278, 100%), 73 (M-424, 99%).

3-[(Hydroxy)(1-vinyl)methyl]-1-(4-methoxyphenyl)-4-styryl-azetidin-2-one (248) was purified by flash chromatography over silica gel (eluent; 100% dichloromethane) to afford a diastereomeric product as a yellow oil in 47% yield.

IRν_{max} (film) 3450 (br OH), 1734 (β-lactam C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.27-3.31 (1H, m, H-3), 3.77 (3H, s, -OCH_3), 4.54 (0.5H, dd, $J_{4,3}$=1.8Hz, $J_{4,5}$=6.40Hz, H-4), 4.71 (0.5H, dd, $J_{4,3}$=1.8Hz, $J_{4,5}$=6.40Hz, H-4), 4.60 (0.5H, br t, J=4.53Hz, H-5), 4.75 (0.5H, br t, J=3.36Hz, H-5), 5.24-6.33 (2H, H-6 and H-7), 6.39-7.51 (11H, m, aromatic Hs, H-8 and H-9).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 54.80, 55.71 (-O<u>C</u>H_3, C-3), 61.50 (C-4), 61.80 (C-5), 68.30, 70.55 (C-5), 113.88, 113.91 (C-3` and C-5`), 117.89, 117.96 (C-2` and C-6`), 126.09, 126.15, 126.19, 126.48, 127.83, 128.22, 128.25 (aromatic Cs, C-6 and C-7), 131.07, 131.14 (C-9), 133.60, 133.85 (C-1`), 135.21, 135.36 (C-8), 136.76, 136.89 (C-1``, C-1```), 155.32, 155.68, 164.01 (β-lactam <u>C</u>=O).

Low Resolution Mass Spectrum

$C_{21}H_{21}NO_3$ Requires: M^+=335

Found: M^+=335

High Resolution Mass Spectrum

$C_{21}H_{21}NO_3$ Requires: M^+=335.15214

Found: M^+=335.15156

Mass Spectrum (m/z)

335 (M^+, 335, 60%), 279 (M-56, 40%), 236 (M-99, 75%), 202 (M-133, 70%), 157 (M-178, 65%), 149 (M-186, 100%), 115 (M-220, 99%), 91 (M-244, 98%), 82 (M-253, 90%), 55 (M-280, 80%).

General oxidation procedure for the preparation of compounds (249)-(253)

Pyridinium chlorochromate (0.0041mol) was suspended in dichloromethane (5.47ml), and the appropriately substituted alcohol (0.0027mol) dissolved in dichloromethane (4.1ml) was rapidly added at room temperature. The solution became briefly homogenous before depositing the black insoluble reduced reagent. After 12 h the reaction mixture was diluted with 5 volumes of anhydrous diethyl ether, the solvent was decanted and the black solid washed twice with ether. The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness, yielding a residue which was purified by flash chromatography to afford the pure product. Compounds **(251)-(253)** were purified by flash column chromatography over silica gel (100% dichloromethane).

Compounds **(249)** and **(250)** were purified by flash column chromatography over silica gel [eluent, petroleum ether (b.p. 40-60°C): diethyl ether 2:8] and obtained as yellow oils in 70% yield and 65% yield respectively.

3-Acetyl-1-(4-methoxyphenyl)azetidin-2-one (249)

IRν_{max}(film) 1747 (β-lactam C=O), 1714 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.39 (3H, s, CH_3), 3.58 (1H, t, J=5.52Hz, H-3), 3.78 (3H, s, -OCH_3), 4.04 (1H, dd, J=2.52Hz, J=5.78Hz, H-4), 4.32 (1H, dd, J=2.52Hz, J=5.52Hz, H-4), 6.87 (2H, d, J=9.04Hz, H-3` and H-5`), 7.26 (2H, d, J=9.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

(CDCl$_3$)ppm 29.25 (CH_3), 39.42 (C-4), 55.04 (O<u>C</u>H$_3$), 61.04 (C-3), 114.00 (C-3`and C-5`), 117.21 (C-2` and C-6`), 131.09 (C-1`), 155.97 (C-4`), 158.97 (β-lactam <u>C</u>=O), 199.12 (<u>C</u>=O).

Low Resolution Mass Spectrum

$C_{12}H_{13}NO_3$ Requires: M^+=219

Found: M^+=219

Low Resolution Mass Spectrum

$C_{12}H_{13}NO_3$ Requires: M^+=219.08954

Found: M^+=219.09012

Mass Spectrum (m/z)

219 (M^+, 72%), 149 (M-70, 44%), 135 (M-84, 100%), 120 (M-99, 80%).

3-Acetyl-1-(4-methyphenyl)azetidin-2-one (250)

IRν_{max}(film) 1743 (β-lactam C=O), 1713 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ (CDCl$_3$) 2.32 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.58 (1H, t, J=5.52Hz, H-3), 4.04 (1H, dd, J=2.52Hz, J=5.76Hz, H-4), 4.32 (1H, dd, J=2.52Hz, J=5.76Hz, H-4), 7.12 (2H, d, J=9.04Hz, H-3` and H-5`), 7.22 (2H, d, J=9.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

(CDCl$_3$)ppm 20.04 (CH_3), 29.25 (CH_3), 39.27 (C-3), 60.98 (C-4), 115.86 (C-3` and C-5`), 129.21 (C-2` and C-6`), 133.55 (C-1`), 135.07 (C-4`), 159.27 (β-lactam <u>C</u>=O), 199.04 (<u>C</u>=O).

Low Resolution Mass Spectrum

$C_{12}H_{13}NO_2$ Requires: M^+=203
Found: M^+=203

Mass Spectrum (m/z)
203 (M^+, 50%), 149 (M-54, 10%), 91 (M-112, 68%), 77 (M-126, 11%).

1-(4-methoxyphenyl)-3-[(1-(1-oxo-but-2-enyl)]-4-phenylazetidin-2-one (251) was obtained as a colourless oil in 38% yield.

IRν_{max} (film) 1752 (β-lactam C=O), 1679 (C=O) cm^{-1}

^{1}H-NMR (400MHz)
δ ($CDCl_3$) 1.98 (3H, dd, J=1.5Hz, J=6.5Hz, CH_3), 3.71 (3H, s, -OCH_3), 4.32 (1H, d, $J_{3,4trans}$=2.52Hz, H-3), 5.52 (1H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.31–6.36 (1H, m, H-6), 7.09-7.39 (10H, m, aromatic Hs and H-7).

^{13}C-NMR (101MHz)
($CDCl_3$)ppm 18.27 (CH_3), 54.93 (C-3), 55.61 (OCH_3), 68.68 (C-4), 113.90 (C-3`and C-5`), 117.99 (C-2`and C-6`), 125.75, 128.21, 128.73, 130.42, 130.67 136.57, 147.08, (aromatic Cs and C-6, C-1`, C-1``, C-1``` and C-7, 155.83 (C-4`), 159.47 (β-lactam C=O), 189.91 (C=O).

Low Resolution Mass Spectrum

$C_{20}H_{19}NO_3$ Requires: M^+=321
Found: M^+=321

High Resolution Mass Spectrum

$C_{20}H_{19}NO_3$ Requires: M^+=321.1364
Found: M^+=321.1327

Mass Spectrum (m/z)

321.1 (M^+, 99%), 278.1 (M-43.0, 25%), 196.1 (M-125.0, 65%), 149.0 (M-172.1, 100%), 131.0 (M-190.1, 70%), 69.0 (M-252.1, 39%).

1-(4-Methoxyphenyl)-3-[1-(1-oxo-but-2-enyl)]-4-styrylazetidin-2-one (252) was obtained as a colourless oil in 85% yield.

IRν_{max}(film) 1746 (β-lactam C=O), 1654 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.06 (3H, d, J=2.2Hz), 3.69 (3H, s, OCH_3), 4.63 (0.5H, d, $J_{3,4trans}$=2Hz, H-4), 5.23 (0.5H, d, $J_{4,3trans}$=2Hz, H-4), 6.24 (0.5H, d, J=16Hz, H-6), 6.28 (0.5H, d, J=16Hz, H-6), 7.20-7.36 (11H, aromatic Hs, H-8 and H-9), 7.42 (1H, d, J=16Hz, H-7).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.44 ($\underline{C}H_3$), 55.85 ($O\underline{C}H_3$), 65.91 (C-3), 77.06, 77.38 (C-4), 114.79 (C-3` and C-5`), 118.82 (C-2` and C-6`), 126.25, 127.05, 128.86, 129.19, 129.38, 130.40 (aromatic Cs, C-6 and C-9), 131.75 (C-1`), 135.59, 135.97 (C-8), 136.02, 136.93 (C-1``), 144.38 (C-7), 156.74 (C-4`), 160.00 (β-lactam $\underline{C}$=O), 192.78 ($\underline{C}$=O).

High Resolution Mass Spectrum

$C_{22}H_{21}NO_3$ Requires: M^+=347.0374

Found: M^+2=349.1897

Mass Spectrum (m/z)

349 (M^+2, 10%), 284(M-65, 100%), 217 (M-132, 80%).

1-(4-methoxyphenyl)-3-[1-(1-oxo-3-phenyl-prop-2-enyl)]-4-styrylazetidin-2-one (253) was obtained as a yellow oil in 70% yield.

IRν_{max} (film) 1748 (β-lactam C=O), 1654 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.81 (3H, s, OCH_3), 3.82 (1H, d, $J_{3,4}$=2.52Hz, H-3), 4.74 (1H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.81-6.82 (1H, m, H-6), 6.83-6.85 (2H, m, H-8 and H-9), 7.23-7.60 (15H, aromatics and H-7).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 52.92 (O<u>C</u>H$_3$), 54.96 (C-3), 55.53 (C-4), 113.92 (C-3` and C-5`), 118.00 (C-2` and C-6`), 124.73, 125.79, 128.22, 128.53 (aromatic Cs , C-6 and C-9), 130.56 (C-1`), 133.77 (C-8), 145.80, 145.90 (C-1``, C-1```), 147.85 (C-7), 155.88 (C-4`), 159.49 (β-lactam <u>C</u>=O), 190.13 (<u>C</u>=O).

High Resolution Mass Spectrum

$C_{27}H_{23}NO_3$	Requires:	M^+=409.16779
	Found:	M^+=409.17279

General preparation of epoxides (254)-(256)

m-Chloroperbenzoic acid (519mg, 0.003mol) was added to a solution of the appropriate azetidin-2-one (0.001mol) in dry dichloromethane (10ml) under nitrogen, and the mixture was allowed to stir at room temperature for 24 h. It was then washed with $NaHCO_3$ solution (5%) (2x10ml), water (2x10ml) and dried over anhydrous (Na_2SO_4). Evaporation of the solvent afforded the required epoxide which was purified by flash chromatography over silica gel [eluent, light petroleum (b.p. 40-60°C):diethyl ether 1:1] for all compounds.

3-[1-(2,3-Epoxy-1-hydroxy)butyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (254) was obtained as a colourless oil in 63% yield.

IRν_{max} (film) 3440 (br OH), 1750 (C=O), 1251, 947, 760 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.30-1.36 (3H, m, CH_3), 2.88-3.37 (3H, m, H-3, H-6, and H-7), 3.92-4.44 (1H, m, H-5), 5.03 (0.4H, d, $J_{3,4trans}$=2Hz, H-4), 5.10

(0.3H, d, J=2Hz, H-4), 5.14 (0.3H, d, J=2Hz, H-4), 6.75 (2H, d, J=8.52Hz, H-3` and H-5`), 7.23-7.31 (7H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 16.54, 16.59 ($\underline{C}H_3$), 51.01 (O$\underline{C}H_3$), 51.86, 52.01, 52.29, 52.24, 54.94, 55.98, 56.48, 59.33, 59.65, 59.72, 60.44, 62.03, 62.21, 62.47, 63.17, 65.83, 67.35, 68.52, 76.38, 76.69, 77.01 (C-3, C-4, C-5, C-6 and C-7), 113.59, 113.86, 118.06, 125.44, 125.85, 126.36, 126.92, 127.16, 127.87, 128.04, 128.11, 128.30, 128.69, 130.07, 130.52 137.15, 137.28 (aromatic Cs), 155.68 (C-4`), 163.64, 163.83, 163.91, 164.13 (β-lactam $\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{20}H_{21}NO_4$ Requires: M^+=339
Found: M^+=339

High Resolution Mass Spectrum

$C_{20}H_{21}NO_4$ Requires: M^+=339.14706
Found: M^+=339.14698

Mass Spectrum (m/z)
339 (M^+, 8%), 211 (M-128, 80%), 196 (M-143, 100%), 167 (M-172, 25%), 77 (M-262, 8%).

3-[1-(2,3-Epoxy-1-hydroxy)propyl]-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (255) was obtained as a colourless oil in 58% yield. For identification purposes by low resolution mass spectrometry (**255**) (1mg) was reacted with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide 97% (0.5ml) in chloroform (1ml) to give the TMS derivative of (**255**).

IRν_{max} (film) 3500 (br OH), 1734 (C=O), 1247 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.76-3.37 (3H, m, H-3, H-6, and H-7), 3.76 (3H, s, OCH_3), 4.13-4.49 (1H, m, H-5), 5.03-5.14 (1H, 3xd, $J_{4,3trans}$=2Hz, H-4), 6.79 (2H, d, H-3` and H-5`), 7.20-7.39 (7H, m, aromatic Hs).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 54.97 (OCH_3), 59.27, 61.87, 62.00, 62.30, 67.63, 67.72, 69.25, 76.21, 76.53, 76.84 (C-3, C-4, C-5, C-6 and C-7), 113.89, 117.99, 125.56, 128.75, 131.40, 131.67 (aromatic Cs), 155.72 (β-lactam C=O).

Low Resolution Mass Spectrum

$C_{19}H_{19}NO_4$ Requires: M^+=325

Found: M^+72=397 (TMS derivative)

High Resolution Mass Spectrum

$C_{19}H_{19}NO_4$ Requires: M^+=325.13141

Found: M^+=325.13079

Mass Spectrum (m/z)

397 (M^+, 40%), 205 (M-192, 50%), 149 (M-248, 100%), 73 (M-324, 50%).

3-[1-(2,3-epoxy-1-oxobutyl)]-1-(4-methoxyphenyl)-4-azetidin-2-one (256) was obtained as a yellow oil in 65% yield.

IRν_{max} (film) 1760 (β-lactam C=O), 1686 (C=O), 1239, 931, 751 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.57-2.01 (3H, m, CH_3), 2.50-3.43 (2H, m, H-6 and H-7), 3.93 (3H, s, OCH_3), 4.07-4.34 (1H, m, H-3), 5.43 (1H, d, $J_{4,3trans}$=2.52Hz, H-4), 6.81-8.16 (9H, m, aromatic Hs).

^{13}C-NMR (101MHz)

δ ($CDCl_3$) 22.21 ($\underline{C}H_3$), 53.12 ($O\underline{C}H_3$), 53.90, 54.96, 60.53, 64.27 (C-3, C-4, C-6, and C-7), 113.90, 118.00, 124.28, 125.74, 128.27, 130.40 (aromatic C's), 160.13 (β-lactam $\underline{C}$=O, 190.00 ($\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{20}H_{19}NO_4$ Requires: M^+=337
Found: M^+=337

High Resolution Mass Spectrum

$C_{20}H_{19}NO_4$ Requires: M^+=337.13141
Found: M^+=337.12977

Mass Spectrum (m/z)

337 (M^+, 100%), 308 (M-29, 50%), 280 (M-57, 49%), 159 (M-178, 75%), 131 (M-206, 40%), 103 (M-234, 35%), 77 (M-260, 30%), 57 (M-280, 20%).

4-Benzoyloxy-1-(4-methoxyphenyl)azetidin-2-one (259)

A solution of the azetidin-2-one (**259**) (0.63mmol), *t*-butyl perbenzoate (0.44ml, 2.3mmol) and cupric octanoate (10mg, 0.02mmol) in toluene was heated at reflux under nitrogen for 6 h. The solution was then washed with saturated aqueous sodium metabisulphite (3x25ml), dried (Na_2SO_4), and concentrated under reduced pressure and purified by column chromatography over silica gel [(eluent, petroleum ether (b.p. 40-60°C):diethyl ether, 7:3] for compound (**259**). 4-Benzoyloxy-1-(4-methoxyphenyl)azetidin-2-one (**259**) was obtained as a colourless solid in 46% yield, m.p. 135-136°C (lit. m.p.[202] 135-136°C).

IRν_{max}(film) 1740 (β-lactam C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 3.17 (1H, dd, J=2Hz, J=16Hz, H-3), 3.63 (1H, dd, J=4Hz, J=16Hz, H-3), 3.80 (3H, s, OCH_3), 6.75 (1H, dd, J=2Hz, J=4Hz, H-4), 6.80-8.30 (9H, m, aromatic Hs).

General preparation of 4-Benzoyloxyazetidin-2-ones (262) and (263)

A solution of the azetidin-2-one (0.63mmol), *t*-butyl perbenzoate (0.44ml, 2.3mmol) and cupric octanoate (10mg, 0.02mmol) in toluene was heated at reflux under nitrogen for 6 h. The solution was then washed with saturated aqueous sodium metabisulphite (3x25ml), dried (Na_2SO_4), and concentrated under reduced pressure and purified by column chromatography over silica gel (eluent, petroleum ether (b.p. 40-60°C):diethyl ether, 5:5).

3-Acetyl-3-benzyl-1-(4-methoxyphenyl)azetidin-2-one (262) was obtained as a colourless oil in 63% yield.

IR ν_{max}(film) 1747 (β-lactam C=O), 1714 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.39 (3H, s, CH_3), 3.78 (3H, s, -OCH_3), 3.41-3.49 (3H, m, CH_2, H-4), 4.10 (1H, d, J=6Hz, H-4), 6.80-8.16 (9H, m, aromatics).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 26.94 ($\underline{C}H_3$), 36.46 ($\underline{C}H_2$), 44.88 (C-4), 55.04 ($O\underline{C}H_3$), 70.56 (C-3), 113.97 (C-3` and C-5`), 117.40 (C-2` and C-6`), 126.87-134.67 (aromatics), 134.68 (C-1`), 156.03 (C-4`), 162.50 (β-lactam $\underline{C}$=O), 202.46 ($\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{19}H_{19}NO_3$ Requires: M^+=309
Found: M^+=309

High Resolution Mass Spectrum

$C_{19}H_{19}NO_3$ Requires: M^+=309.13649
Found: M^+=309.13852

Mass Spectrum (m/z)

309 ($M^{+\cdot}$ 50%), 149 (M-160, 100%), 135 (M-174, 60%), 120 (M-189, 33%), 91 (M-218, 33%).

3-Acetyl-3-benzyl-1-(4-methylphenyl)azetidin-2-one (263) was obtained as a colourless oil in 60% yield.

IR ν_{max}(film) 1744 (β-lactam C=O), 1710 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 2.31 (3H, s, CH_3,), 2.41 (3H, s, CH_3), 3.43-3.49 (3H, m, CH_2, H-4), 4.10 (1H. d, J=6Hz, H-4), 7.13-7.63 (9H, m, aromatics).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 20.42 ($\underline{C}H_3$), 26.93 ($\underline{C}H_3$), 36.48 ($\underline{C}H_2$), 44.74 (C-4), 70.51 (C-3), 116.02 (C-3` and C-5`), 119.98 (C-2` and C-6`), 126.64-134.81 (aromatics) 162.80 (β-lactam $\underline{C}$=O), 202.35 ($\underline{C}$=O).

Low Resolution Mass Spectrum

$C_{19}H_{19}NO_2$ Requires: M^+=293

Found: M^+=293

High Resolution Mass Spectrum

$C_{19}H_{19}NO_2$ Requires: M^+=293.14158

Found: M^+=293.14210

Mass Spectrum (m/z)

293 (M^+, 90%), 159 (M-134, 50%), 133 (M-160, 100%), 119 (M-174, 85%), 91 (M-202, 99%), 65 (M-228, 55%), 51 (M-242, 25%).

Chapter 5

4-Methyl-1-(4-methoxyphenyl)-2-pyrrolidinone (276)

To a stirred solution of sodium hydride (60% oil dispersion) (7eq) was added slowly at room temperature a solution of trimethyloxosulphonium iodide (7eq) in dry DMSO (10ml) and stirred for 10 min. To the resulting mixture was added 4-formyl-3-vinylazetidin-2-one (**166**) (1eq) in DMSO (5ml) and the mixture was stirred at room temperature for 25 min and for 2 h at 50°C. After the addition of water (20ml) at 0°C, the mixture was extracted with dichloromethane (2x20ml). The extract was washed with saturated NaCl (2x20ml), 5% NaOH (2x20ml), dried (Na_2SO_4), and concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography over silica gel (eluent, light petroleum (b. p. 40-60°C):diethyl ether 1:9) to afford (**276**) as a colourless oil in 65% yield.

IRν_{max} (film) 1700 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.22 (3H, d, J=6.6Hz, CH_3), 2.25 (1H, dd, J_{gem}=16.57Hz, $J_{3a,4}$=7.02Hz, H-3a), 2.55 (1H, m, CH), 2.75 (1H, dd, J_{gem}=16.57Hz, $J_{3b,4}$=8.53Hz, H-3b), 3.43 (1H, dd, J_{gem}=19.07Hz, $J_{3a,4}$=6.53Hz, H-5a), 3.83 (3H, s, -OCH_3), 3.91 (1H, dd, J_{gem}=19.07Hz, $J_{5b,4}$=7.53Hz, H-5b), 6.90 (2H, d, J=9.04Hz, H-3`and H-5`), 7.47 (2H, d, J=9.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.69 ($\underline{C}H_3$), 26.30 (C-4), 40.67 (C-3), 56.29 (C-5), 55.40 (O$\underline{C}H_3$), 113.35 (C-3` and C-5`), 121.36 (C-2` and C-6`), 136.97 (C-1`), 156.03 (C-4`), 175.24 ($\underline{C}$=O).

High Resolution Mass Spectrum

$C_{12}H_{15}NO_2$ Requires: M^+=205.1102

Found : M^+=205.1119

Mass Spectrum (m/z)

205.1 (M^+, 67.7%), 190.1 (M-15.0, 38.0%), 149.0 (M-56.1, 20.5%), 136.0 (M-69.1, 100%), 123.0 (M-82.1, 17.2%), 108.0 (M-97.0, 17.3%).

3-Alkyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-ones (290)-(293) and 3-Alkyl-4-formyl-1-(4-methylphenyl)azetidin-2-ones (294)-(297).

A solution of the appropriate acid chloride (0.04mol) in dry toluene (75ml) was added dropwise to a vigorously stirred suspension of diimine (**165a**) or (**165b**) (0.02mol) and triethylamine (0.024mol) in dry toluene (150ml) at room temperature under nitrogen. The reaction was stirred under nitrogen at room temperature overnight. Then 5% aqueous HCl (200ml) was added and the heterogenous mixture was vigorously stirred for 3 h. The organic layer was diluted with toluene (50ml) and successively washed with 5% HCl (2x100ml), 5% $NaHCO_3$ (2x100ml), brine (200ml) and water (200ml), and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a residue which was purified by column chromatography over silica gel (eluent, dichloromethane:ethyl acetate, 99:1) to give the pure 4-formyl-3-substituted azetidin-2-ones.

4-Formyl-3-methyl-1-(4-methoxyphenyl)azetidin-2-one (290) was obtained as a colourless solid in 90% yield m.p. 118-120°C (lit. m.p.[152] 118-120°C).

IRν_{max}(KBr) 1750 (C=O), 1735 (CHO) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.24 (3H, d, J=15Hz, CH_3), 3.68 (1H, dd, $J_{3,4cis}$=6.42Hz, $J_{3,5}$=15.0Hz, H-3), 3.74 (3H, s, -OCH_3), 4.45 (1H, dd, $J_{4,3cis}$=6.42Hz, $J_{4,6}$=3.0Hz, H-4), 6.83 (2H, d, J=9Hz, H-3` and H-5`), 7.19 (2H, d, J=9Hz, H-2` and H-6`) 9.80 (1H, d, $J_{6,4}$=3.0Hz, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 9.09 ($\underline{C}H_3$), 48.28 (O$\underline{C}H_3$), 55.40 (C-3), 60.30 (C-4), 114.15 (C-3` and C-5`), 129.53 (C-2` and C-6`), 131.0 (C-1`), 156.3 (C-4`), 160.11 (β-lactam $\underline{C}$=O), 199.99 ($\underline{C}$HO).

3-Ethyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (291) was obtained as a colourless solid in 73% yield m.p. 90-91°C (lit. m.p.[152] 90-91°C).

IRν_{max}(KBr) 1751 (C=O), 1736 (CHO) cm^{-1}

^{1}H-NMR

δ ($CDCl_3$)(400MHz) 1.08 (3H, t, J=7.02Hz, CH_3), 2.56 (2H, m, CH_2), 3.54 (1H, dd, $J_{3,4cis}$=6.56Hz, $J_{3,5}$=6.0Hz, H-3), 3.81 (3H, s, -OCH_3), 4.46 (1H, dd, $J_{4,3cis}$=6.56Hz, $J_{4,6}$=3.52Hz, H-4), 6.84 (2H, d, J=9.04Hz, H-3` and H-5`), 7.21 (2H, d, J=9.04Hz, H-2` and H-6`), 9.85 (1H, d, $J_{6,4}$=3.52Hz, CHO).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 11.68 ($\underline{C}H_3$), 18.57 ($\underline{C}H_2$), 55.03 ($O\underline{C}H_3$), 55.16 (C-3), 59.90 (C-4), 117.14 (C-3` and C-5`), 118.12 (C-2` and C-6`), 130.72 (C-1`), 156.08 (C-4`), 165.35 (β-lactam $\underline{C}$=O), 199.41 ($\underline{C}$HO).

4-Formyl-1-(4-methoxyphenyl)-3-propylazetidin-2-one (292) was obtained as a colourless oil in 76% yield.

IRν_{max}(KBr) 1750 (C=O), 1732 (CHO) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.97 (3H, t, J=7.52 Hz, CH_3), 1.45-1.85 (4H, m, 2x CH_2), 3.65 (1H, dd, $J_{3,4cis}$=6.52Hz, $J_{3,5}$=7.52Hz, H-3), 3.81 (3H, s, -OCH_3), 4.47 (1H, dd, $J_{4,3cis}$=6.52Hz, $J_{4,8}$=3.04Hz, H-4), 6.87 (2H, d, J=9.04Hz, H-3` and H-5`), 7.24 (2H, d, J=9.04Hz, H-2` and H-6`), 9.87 (1H, d, $J_{8,4}$=3.04Hz, CHO).

^{13}C-NMR(101MHz)

($CDCl_3$)ppm 13.29 ($\underline{C}H_3$), 20.49 , 27.13 (2x $\underline{C}H_2$), 53.47 ($O\underline{C}H_3$), 55.06 (C-3), 55.06 (C-4), 114.16 (C-3` and C-5`), 117.23 (C-2` and C-6`), 130.76 (C-1`), 156.12 (C-4`), 165.42 (β-lactam C=O), 199.56 ($\underline{C}$HO).

Low Resolution Mass Spectrum

$C_{14}H_{17}NO_3$	Requires:	M^+=247
	Found:	M^+=247

Mass Spectrum (m/z)

247 (M^+, 60%), 190 (M-57, 75%), 149 (M-98, 50%), 134 (M-113, 100%), 77 (M-170, 25%).

4-Formyl-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (293) was obtained as a colourless crystalline solid in 80% yield m.p. 91-93 °C (lit.m.p.[152] 91-93°C).

IRν_{max}(KBr) 1755 (C=O), 1735 (CHO) cm^{-1}

^{1}H-NMR(400MHz)

δ ($CDCl_3$) 0.94 (3H, d, J=6.6Hz, CH_3), 1.19 (3H, d, J=6.6Hz, CH_3), 2.02-2.20 (1H, m, CH), 3.34 (1H, dd, $J_{3,4cis}$=6.0Hz, $J_{3,5}$=10.3Hz, H-3), 3.76 (3H, s, -OCH_3), 4.43 (1H, dd, $J_{4,3cis}$=6.0Hz, $J_{4,6}$=4.2Hz, H-4), 6.84 (2H, d, J=9.3Hz, H-3` and H-5`), 7.21 (2H, d, J=9.3Hz, H-2` and H-6`), 9.98 (1H, d, $J_{6,4}$=4.2Hz, CHO)

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 20.50 ($\underline{C}H_3$), 21.40 ($\underline{C}H_3$), 25.70 ($\underline{C}H$), 55.30 ($O\underline{C}H_3$), 60.30 (C-3), 61.50 (C-4), 114.40 (C-3` and C-5`), 117.40 (C-2` and C-6`), 131.00 (C-1`), 156.30 (C-4`), 165.10 (β-lactam $\underline{C}$=O), 199.90 ($\underline{C}$HO).

4-Formyl-3-methyl-1-(4-methylphenyl)azetidin-2-one (294) was obtained as a colourless oil in 70% yield.

IRν_{max} (KBr) 1755 (C=O), 1730 (CHO) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.35 (3H, d, J=8.04Hz, CH_3), 2.10 (3H, s, CH_3), 3.73 (1H, m, H-3), 4.49 (1H, dd, $J_{4,3cis}$=6.52Hz, $J_{4,5}$=3.52Hz, H-4), 7.16 (2H, d,

J=8.56Hz, H-2` and H-5`), 7.20 (1H, d, J=8.56Hz, H-2` and H-6`), 9.86 (1H, d, $J_{5,4}$=3.52Hz, CHO).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 9.52 ($\underline{C}H_3$), 20.41 ($\underline{C}H_3$), 47.91 (C-3), 56.69 (C-4), 115.81 (C-3` and C-5`), 129.39 (C-2`and C-6`), 131.31 (C-1`), 159.45 (C-4`), 165.33 (β-lactam $\underline{C}$=O), 199.70 ($\underline{C}$HO).

Low Resolution Mass Spectrum

$C_{12}H_{13}NO_2$ Requires: M^+=203

Found: M^+=203

Mass Spectrum (m/z)

203 (M^+, 65%), 174 (M-29, 33%), 146 (M-57, 85%), 133 (M-70, 50%), 118 (M-85, 100%), 104 (M-99, 15%), 91 (M-112, 70%), 77 (M-126, 14.1%), 65 (M-138, 40%).

3-Ethyl-4-formyl-1-(4-methylphenyl)azetidin-2-one (295) was obtained as a colourless oil in 69% yield.

IRν_{max}(KBr) 1751 (C=O), 1733 (CHO) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.11 (3H, t, J=7.56Hz, CH_3), 2.20 (3H, s, CH_3), 3.58 (1H, dd, $J_{3,4cis}$=6.04Hz, $J_{3,5}$=8.52Hz, H-3), 3.00-3.75 (2H, m, CH_2), 4.48 (1H, dd, $J_{4,3cis}$=6.04Hz, $J_{4,6}$=3.48Hz, H-4), 7.16 (2H, d, J=8.04Hz, H-3` and H-5`), 7.19 (2H, d, J=8.04Hz, H-2` and H-6`), 9.88 (1H, d, $J_{6,4}$=3.48Hz, CHO).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 9.61 ($\underline{C}H_3$), 19.41 ($\underline{C}H_2$), 20.41 ($\underline{C}H_3$), 57.31 (C-3), 61.13 (C-4), 115.31 (C-3` and C-5`), 130.61 (C-2` and C-6`), 132.31 (C-1`), 165.32 (β-lactam $\underline{C}$=O), 199.73 (CHO).

Low Resolution Mass Spectrum

$C_{13}H_{15}NO_2$ Requires : M^+=217

Found : M^+=217

Mass Spectrum (m/z)

217 (M^+, 75%), 188 (M-29, 21%), 160 (M-57, 98%), 133 (M-84, 75%), 118 (M-99, 100%), 104 (M-113, 19%), 91 (M-126, 80%), 77 (M-140, 18%), 65 (M-152, 40%), 51 (M-166, 15%).

4-Formyl-1-(4-methylphenyl)-3-propylazetidin-2-one (296) was obtained as a colourless solid in 65% yield m.p. 99-100°C.

IRν_{max} (KBr) 1753 (C=O), 1731 (CHO) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.97 (3H, t, J=7Hz, CH_3), 1.20-1.80 (4H, m, 2x CH_2), 2.31 (3H, s, CH_3), 3.65 (1H, dd, $J_{3,4cis}$=6.26Hz, $J_{3,5}$=14.3Hz, H-3), 4.48 (1H, dd, $J_{4,3cis}$=6.26Hz, $J_{4,8}$=3.52Hz, H-4), 7.19 (2H, d, J=8.04Hz, H-3` and H-5`), 7.23 (2H, d, J=8.04Hz, H-2` and H-6`), 9.87 (1H, d, $J_{8,4}$=3.52Hz, CHO).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.29 ($\underline{C}H_3$), 20.40 ($\underline{C}H_3$), 20.48 ($\underline{C}H_2$), 27.10 ($\underline{C}H_2$), 53.35 (C-3), 59.67 (C-4), 115.77 (C-3` and C-5`), 129.36 (C-2` and C-6`), 133.79 (C-1`), 134.77 (C-4`), 165.67 (β-lactam $\underline{C}$=O), 199.54 ($\underline{C}$HO).

Low Resolution Mass Spectrum

$C_{14}H_{17}NO_2$ Requires: M^+=231

Found: M^+=231

Mass Spectrum (m/z)

231 (M^+, 25%), 186 (M-45, 14%), 149 (M-82, 100%), 134 (M-97, 10%), 106 (M-125, 10%), 77 (M-154, 15%).

Elemental analysis

$C_{14}H_{17}NO_2$	Requires:	C, 72.70; H, 7.40; N, 6.05.
	Found	C, 72.57; H, 7.36; N, 6.01.

4-Formyl-3-isopropyl-1-(4-methylphenyl)azetidin-2-one (297) was obtained as a colourless solid in 60% yield m.p. 103-105°C.

IRν_{max} (KBr) 1755 (C=O), 1731 (CHO) cm^{-1}

^{1}H-NMR (400MHz)

($CDCl_3$)ppm 0.97 (3H, d, J=6.52Hz, CH_3), 1.24 (3H, d, J=6.52Hz, CH_3), 2.14-2.17 (1H, m, CH), 2.31 (3H, s, CH_3), 3.38 (1H, dd, $J_{3,4cis}$=6.04Hz, $J_{3,5}$=10.5Hz, H-3), 4.47 (1H, dd, $J_{4,3cis}$=6.04Hz, $J_{4,6}$=4.02Hz, H-4), 7.15 (2H, d, J=8.52Hz, H-3` and H-5`), 7.20 (2H, d, J=8.52Hz, H-2` and H-6`), 9.92 (1H, d, $J_{6,4}$=4.02Hz, CHO).

^{13}C-NMR (101MHz)

δ ($CDCl_3$) 20.18 ($\underline{C}H_3$), 20.40 ($\underline{C}H_3$), 21.07 ($\underline{C}H_3$), 25.39 (C-5), 59.92 (C-3), 61.15 (C-4), 119.19 (C-3` and C-5`), 129.37 (C-2` and C-6`), 133.21 (C-1`), 135.76 (C-4`), 166.00 (β-lactam C=O), 199.54 (CHO).

Elemental analysis

$C_{14}H_{17}NO_2$	Requires:	C, 72.70; H, 7.40; N, 6.05.
	Found	C, 72.62; H, 7.48; N, 6.03.

3-Alkyl-4-(1,2-epoxyethyl)azetidin-2-ones (298)-(300)

To a suspension of trimethylsulphonium iodide at -10°C (4eq for compound (**302**), 6eq for compounds (**298**)-(**300**) in dry THF (10ml) was added *n*-butyllithium (2.5eq for compound (**302**), 3.3 eq for compounds (**298**)-(**300**)) of 2.5M solution in hexane. After 30 min the appropriate aldehyde in dry THF (5ml) was introduced, producing a milky yellow suspension. The reaction was allowed to warm to 0°C over 30 min and then to room temperature while stirring for 2 h. The solution was then treated with water (50ml) at 0°C, extracted with diethyl ether (2x20ml) and the ether extracts washed with saturated NaCl (2x20ml), 5% NaOH (2x100ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica gel (eluent, light petroleum (b.p. 40-60°C): diethyl ether 1:9 for compounds (**298**)-(**300**), diethyl ether:ethyl acetate 9:1 for compound (**302**).

4-(1,2-Epoxyethyl)-1-(4-methoxyphenyl)-3-propylazetidin-2-one (298) was obtained as a colourless oil in 37% yield.

IRν_{max} (film) 1750 (C=O), 1231, 942, 750 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 1.00 (3H, t, J=6Hz, CH_3), 1.65 (2H, m, CH_2), 1.85 (2H, m, CH_2), 2.67 (1H, dd, J_{gem}=5.04Hz, $J_{6,5}$=3Hz, H-6), 3.13 (1H, dd, J_{gem}=5.04Hz, $J_{6,5}$=2.6Hz, H-6), 3.17-3.19 (1H, m, H-5), 3.41-3.44 (1H, m, H-3), 3.55 (1H, dd, $J_{4,3cis}$=6.04Hz, J=7.78Hz, H-4), 3.79 (1H, s, -OCH_3), 6.88 (2H, d, J=9.04Hz, C-3` and C-5`), 7.55 (2H, d, J=9.04Hz, C-2` and C-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.53 ($\underline{C}H_3$), 20.98 ($\underline{C}H_2$), 27.32 ($\underline{C}H_2$), 44.03, 44.09 (C-6), 49.99, 50.49 (C-5), 51.88 (O$\underline{C}H_3$), 54.99, 55.10 (C-3), 57.95 (C-4), 115.15 (C-3` and C-5`), 118.09 (C-2`and C-6`), 131.16 (C-1`), 155.67 (C-4`), 166.56 (β-lactam $\underline{C}$=O).

High Resolution Mass Spectrum

$C_{15}H_{19}NO_3$	Requires:	M^+=261.1364
	Found:	M^+=261.1351

Mass Spectrum (m/z)

261.1 (M^+, 100.0%), 177.0 (M-84.1, 60.2%), 149.0 (M-112.1, 79.4%).

4-(1,2-Epoxyethyl)-3-ethyl-1-(4-methoxyphenyl)azetidin-2-one (299) was obtained as a colourless oil in 40% yield.

IRν_{max} (film) 1750 (C=O), 1235, 950, 751 (epoxy C-O) cm^{-1}

^{1}H-NMR) (400MHz)

δ ($CDCl_3$) 1.17 (3H, t, J=8.52Hz, CH_3), 1.80-2.00 (2H, m, CH_2), 2.70 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=2.52Hz, H-6), 2.97 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=3Hz, H-6), 3.13-3.16 (1H, m, H-5), 3.31-3.37 (1H, m, H-3), 3.58 (1H, dd, $J_{4,3cis}$=5.52Hz, $J_{4,5}$=7.78Hz, H-4), 3.80 (3H, s, -OCH_3), 6.90 (2H, d, J=9.04Hz, H-3` and H-5`), 7.56 (2H, d, J=9.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 12.28 ($\underline{C}H_3$), 18.68 ($\underline{C}H_2$), 44.06 (C-6), 50.43 (C-5), 53.11 ($O\underline{C}H_3$), 55.02 , 55.13 (C-3), 58.01 (C-4), 117.95 (C-3` and C-5`), 119.28 (C-2`and C-6`), 131.62 (C-1`), 155.70 (C-4`), 166.43 (β-lactam $\underline{C}$=O).

High Resolution Mass Spectrum

$C_{14}H_{17}NO_3$	Requires:	M^+=247.1208
	Found:	M^+=247.1186

Mass Spectrum (m/z)

247.1 (M^+, 100%), 177.0 (M-70.1, 82.5%), 149.0 (M-98.1, 47.9%), 134.0 (M-113.1, 47.9%), 83.9 (M-163.2, 45.1%).

4-(1,2-Epoxyethyl)-1-(4-methylphenyl)-3-propylazetidin-2-one (300) was obtained as a colourless oil in 30% yield.

IRν_{max}(film) 1750 (C=O), 1230, 940, 751 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.97 (3H, t, J=7Hz, CH_3), 1.45-1.81 (4H, m, 2xCH_2), 2.32 (3H, s, CH_3), 2.69 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=2.52Hz, H-6), 3.01 (1H, dd, J_{gem}=4.76Hz, $J_{6,5}$=3Hz, H-6), 3.12-3.16 (1H, m, H-5), 3.41-3.43 (1H, m, H-3), 4.47-4.49 (1H, m, H-4), 7.16 (2H, d, J=8.04Hz, H-3` and H-5`), 7.52 (2H, d, J=8.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.55 ($\underline{C}H_3$), 20.42 ($\underline{C}H_3$), 21.01 ($\underline{C}H_2$), 27.34 ($\underline{C}H_2$), 44.05 (C-6), 50.52 (C-5), 51.28 (C-3), 57.81 (C-4), 116.49 (C-3` and C-5`), 129.15 (C-2` and C-6`), 133.11 (C-1`), 135.12 (C-4`), 166.83 (β-lactam $\underline{C}$=O).

High Resolution Mass Spectrum

$C_{15}H_{19}NO_2$ Requires: M^+=245.1415

Found: M^+=245.1395

Mass Spectrum (m/z)

245.1 (M^+, 100.0%), 202.0 (M-43.1, 17.9%), 161.0 (M-84.1, 99.0%), 133.0 (M-112.1, 98.0%), 118.0 (M-127.1, 78.1%), 91.0 (M-154.1, 53.7%).

4-Butoxycarbonyl-1-(4-methoxyphenyl)-3-methylazetidin-2-one (302) was obtained as a colourless oil in 45% yield.

IRν_{max} (film) 1749 (br, C=O, β-lactam, C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.87 (3H, t, J=7.52Hz, CH_3), 1.28 (3H, d, J=7.52Hz, CH_3), 1.23-1.34 (2H, m, CH_2), 1.56-1.64 (2H, m, CH_2), 3.61-3.64 (1H, m, H-3), 3.82 (3H, s, -OCH_3), 4.09 (2H, m, -OCH_2), 4.57 (1H, d, J=5.52Hz, H-4), 6.83 (2H, d, J=9.04Hz, H-3` and H-5`), 7.22 (2H, d, J=9.04Hz, H-2` and H-6`)

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 9.16 ($\underline{C}H_3$), 13.05 (CH_3), 18.49 ($\underline{C}H_2$), 30.09 ($\underline{C}H_2$), 47.74 (C-3), 55.40 (O$\underline{C}H_3$), 55.86 (C-4), 65.36 (-O$\underline{C}H_2$), 113.80 (C-3` and C-5`), 117.51 (C-2` and C-6`), 130.64 (C-1`), 155.87 (C-4`), 165.58 (β-lactam $\underline{C}$=O), 168.43 ($\underline{C}$=O).

High Resolution Mass Spectrum

$C_{16}H_{21}NO_4$ Requires: M^+=291.1470

Found : M^+=291.1451

Mass Spectrum (m/z)

291.1 (M^+, 99.0%), 263.1 (M-28.0, 98.0%), 235.1 (M-56.0, 63.3%), 162.1 (M-129.0, 93.9%), 149.1 (M-142.0, 100.0%), 134.1 (M-157.0, 98.0%), 77.1 (M-214.0, 25.0%).

Chapter 7

Spectroscopic characterisation of DHEA (305)

IRν_{max} (KBr) 3486 (OH), 1741 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.80 (3H, s, H-18), 0.90 (3H, s, H-19), 0.94-1.02 (2H, m, H-9, H-1), 1.20-1.80 (11H, m, H-15, H-12, H-11, H-2, H-14, H-8, H-1, H-7), 1.85-1.91 (1H, m, H-15), 1.96-2.07 (2H, m, H-16, H-7), 2.07-2.27 (2H, m, H-4), 2.35-2.42 (1H, m, H-16), 2.62 (1H, s, -OH), 3.40-3.48 (1H, m, H-3α), 5.29 (1H, d, J=5.52Hz, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.27 (C-18), 19.20 (C-19), 20.14 (C-11), 21.64 (C-15), 30.56 (C-7), 31.24 (C-2), 31.28 (C-12), 31.28 (C-8), 35.61 (C-16), 36.43 (C-10), 37.80 (C-1), 41.94 (C-4), 47.31 (C-13), 50.05 (C-9), 51.55 (C-14), 71.33 (C-3), 120.70 (C-6), 142.40 (C-5), 220.98 (C-17).

Low Resolution Mass Spectrum

$C_{19}H_{28}O_2$ Requires: M^+=288

Found : M^+=288

Mass Spectrum (m/z)

288 (M^+, 100.0%), 270 (M-18, 50%), 255 (M-33, 70%), 233 (M-55, 13%), 203 (M-85, 51%), 55 (M-233, 60%).

3β–Toluene-*p*-sulphonyloxyandrost-5-ene-17-one (331)

Dry redistilled pyridine (5ml) was added to toluene-*p*-sulphonyl chloride (0.71g, 3.74mmol) with cooling. This solution was allowed to stand for 30 min at room temperature. DHEA (**305**) (0.5g, 1.7mmol) was added with shaking and cooling. The solution was allowed to stand for 1 day at room temperature. The solution was poured

onto crushed ice (10g), stirred vigorously for 1 h. The product was extracted with diethyl ether (2x10ml), washed with water (2x10ml), dried (Na_2SO_4), and concentrated in *vacuo* to yield the crude product. The crude product was recrystallised from ethanol as colourless crystals in 55% yield m.p. 157-158°C, (lit. m.p.[238]157-158°C), $[\alpha]_D^{20}$ +40° (C=1, $CHCl_3$).

IRν_{max} (KBr) 1732 (C=O), 1356 (-SO_2) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.84 (3H, s, H-18), 1.23 (3H, s, H-19), 1.23-1.48 (19H, m, H-1, H-2, H-4, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 2.5 (3H, s, CH_3), 4.26-4.33 (1H, m, H-3α), 5.32 (1H, d, J=4Hz, H-6), 7.31 (2H, d, J=8.04Hz, H-3` and H-5`), 7.76 (2H, d, J=8.04Hz, H-2`and H-6`).

^{13}C-NMR (101MHz)

δ ($CDCl_3$)ppm 13.39 (C-18), 19.03 (C-19), 20.16 (CH_3), 21.48 (C-11), 21.69 (C-15), 28.41, 30.57, 30.58, 31.24, 35.63 (C-7, C-2, C-12, C-16), 35.63 (C-8), 36.35 (C-10), 36.68 (C-1), 38.74 (C-4), 47.31 (C-13), 49.90 (C-9), 51.52 (C-14), 79.10 (C-3), 122.63 (C-6), 127.47 (C-3`and C-5`), 129.64 (C-2` and C-6`), 134.55 (C-1``), 138.98 (C-5), 144.33 (C-4`), 220.52 (C-17).

3α-Azidoandrost-5-ene-17-one (332)

A solution of 3β-toluene-*p*-sulphonyloxyandrost-5-ene-17-one (**331**) (0.81g, 1.84mmol) and sodium azide (0.7g, 0.01mol) in dimethylformamide (130ml) was refluxed for 20 h. The reaction mixture was washed with water (2x200ml) and extracted with diethyl ether (2x200ml). The ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield 3α-azidoandrost-5-ene-17-one (**332**) as a colourless solid which was recrystallised from ethanol in 60% yield m.p. 156-158°C (lit.m.p.[244]156-159°C). $[\alpha]_D^{20}$ +44.2 (C=0.8, $CHCl_3$).

IRν_{max} (KBr) 2115 (N_3), 1750 (C=O) cm^{-1}

^{1}H-NMR(400MHz)

δ ($CDCl_3$) 0.73 (3H, s, H-18), 1.12 (3H, s, H-19), 1.16-2.61 (19H, m, H-1, H-2, H-4, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.83-3.87 (1H, m, H-3β), 5.27 (1H, d, J=5Hz, H-6).

^{13}C-NMR(101MHz)

δ ($CDCl_3$)ppm 12.62 (C-18), 18.14 (C-19), 19.61 (C-11), 21.21 (C-15), 28.04 (C-8), 31.28, 31.05, 30.31, 33.31, 34.83 (C-2, C-12, C-7, C-16, C-1), 35.29 (C-4), 36.83 (C-10), 46.83 (C-13), 51.33, 50.09 (C-9, C-14), 69.10 (C-3), 121.72 (C-6), 138.30 (C-5), 218.17 (C-17).

3β-Chloroandrost-5-ene-17-one (333)

DHEA (**305**) (0.54g, 1.875mmol) was dissolved in thionyl chloride (2ml, 0.02mol). The solution was allowed to stand for 30 min at 25°C. The solution was poured into an ice-water mixture (10ml). The mixture was extracted with diethyl ether (2x10ml). The combined ether extracts were washed with saturated sodium bicarbonate solution (2x10ml) and water (2x10ml). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude product which was recrystallised from ethanol as a colourless solid in 50% yield m.p. 155-157°C, (lit. m.p.[245] 155.5-156 °C), $[\alpha]_D^{20}$ +13.5 (C=0.8$CHCl_3$).

IRν_{max}(KBr) 1735 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

(CD_3COCD_3) 0.82 (3H, s, H-18), 1.25 (3H, s, H-19), 1.25-2.61 (19H, m, H-1, H-2, H-4, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.79-3.83 (1H, m, H-3α), 5.46 (1H, d, J=5Hz, H-6).

^{13}C-NMR (101MHz)

(CD_3COCD_3)ppm 12.43 (C-18), 19.20 (C-19), 20.94 (C-11), 27.77 (C-15), 30.05 (C-7), 30.85 (C-8), 31.06, 32.80 (C-16, C-12, C-2), 35.89 (C-10), 38.37 (C-15), 42.68, 42.78 (C-1, C-4), 46.56 (C-13), 49.89

(C-9), 51.10 (C-14), 59.43 (C-3), 121.31 (C-6), 140.49 (C-5), 221.12 (C-17).

3β-Bromoandrost-5-ene-17-one (334)

A solution of DHEA (**305**) (0.5g, 1.7mmol) in dry ether (5ml) was stirred in a dry atmosphere and cooled to 0°C. Phosphorus tribromide (1.48g, 0.005mol), was added dropwise and cooling was maintained to keep the temperature below 5°C during the addition. After completion of the addition the solution was allowed to warm to room temperature and stand for 2h. The reaction mixture was poured onto crushed ice, the organic layer was extracted with diethyl ether, washed with water (2x10ml) and 10% sodium bicarbonate solution (2x20ml). The solution was evaporated to yield a yellow oil. The product was recrystallised from ethanol as colourless crystals in 20% yield m.p.175-176°C, (lit. m.p[246]174°C), $[\alpha]_D^{20}$=+24°.

IRν_{max} (KBr) 1735 (C=O) cm^{-1}

^{1}H-NMR(400MHz)

δ (CD_3COCD_3) 0.88 (3H, s, H-18), 1.19 (3H, s, H-19), 1.20-2.01 (19H, m, H-1, H-2, H-4, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.85-3.90 (1H, m, H-3α), 5.46 (1H, d, J=5Hz, H-6).

^{13}C-NMR (101MHz)

δ (CD_3COCD_3)ppm 12.41 (C-18), 18.25 (C-19), 19.73 (C-11), 21.03 (C-15), 30.01, 30.13, 30.78, 30.91 (C-16, C-12, C-2, C-7), 31.05 (C-8), 36.35 (C-10), 39.53, 43.68 (C-1, C-4), 46.55 (C-13), 51.09, 51.14, 51.61 (C-9, C-14, C-3),121.15 (C-6), 141.22 (C-5), 217.98 (C-17).

3β-Acetoxyandrost-5-ene-17-one (340)

Dry, redistilled pyridine (4ml) and acetic anhydride (4ml) were added dropwise to DHEA (**305**) (1.0g, 0.003mol). The solution was allowed to stand for 24 h at room temperature. After the mixture had been poured onto water, the crude acetate was

recrystallised from aqueous alcohol as a crystalline colourless solid in 80% yield, m.p. 168-169°C (lit. m.p.[249] 171-172°C).

IRν_{max} (KBr) 1743 (br, C=O, $COOCH_3$) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.88 (3H, s, H-18), 1.05 (3H, s, H-19), 1.18-2.49 (19H, m, H-1, H-2, H-4, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 2.30 (3H, s, $COOC\underline{H}_3$), 4.56-4.64 (1H, m, H-3α), 5.40 (1H, d, J=5.04Hz, H-6).

^{13}C-NMR (101MHz)

δ ($CDCl_3$) 13.18 (C-18), 18.99 (C-19), 21.52 (C-15), 19.99 (C-11), 20.97 ($OCO\underline{C}H_3$), 27.36 (C-7), 30.43, 31.10 (C-12 ,C-16, C-2), 31.13 (C-8), 36.38 (C-10), 36.61 (C-1), 37.75 (C-4), 47.09 (C-13), 49.84 (C-9), 51.36 (C-14), 73.31 (C-3), 121.49 (C-6), 139.59 (C-5), 169.93 ($O\underline{C}OCH_3$), 220.17 (C-17).

3β-Acetoxyandrost-5-ene-7,17-dione (341)

Method 1

Chromium (VI) oxide (0.4g, 0.004mol) was dissolved in a mixture of water (0.4ml) and glacial acetic acid (4ml). This mixture was added dropwise to 3β-acetoxyandrost-5-ene-17-one (**340**) (0.5g, 0.0015mol) dissolved in glacial acetic acid (20ml) at 55°C over 45 min. The solution was stirred for 1 h at 55°C and after cooling the excess chromic acid was neutralized with sodium metasulphite. The solution was filtered, washed with diethyl ether (2x50ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (eluent, dichloromethane:ethyl acetate 90:10) to afford 3β-acetoxyandrost-5-ene-7,17-dione (**341**) as a colourless crystalline solid in 40% yield m.p 187-188°C (lit. m.p.[248] 184°C).

IRν_{max} (KBr) 1728 (C=O, CO_2CH_3), 1672 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.80 (3H, s, H-18), 1.23 (3H, s, H-19), 1.59-2.82 (17H, m, H-1, H-2, H-4, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 2.06 (3H, s, $OCOC\underline{H}_3$), 4.68-4.74 (1H, m, H-3α), 5.74 (1H, s, H-6).

^{13}C-NMR (101MHz)

δ ($CDCl_3$)ppm 13.67 (C-18), 17.30 (C-19), 20.48 (C-11), 21.11 ($OCO\underline{C}H_3$), 24.07 (C-15), 27.22, 30.64, 35.53, 35.90, 37.76 (C-12, C-2, C-4, C-16, C-1), 38.12 (C-10), 44.29, 45.68, 49.92 (C-8, C-9, C-14), 48.10 (C-13), 71.86 (C-3), 121.76 (C-6), 164.70 (C-5), 167.90 ($O\underline{C}OCH_3$), 202.82 (C-7), 219.95 (C-17).

Method 2

Acetic anhydride (6.5ml), glacial acetic acid (23ml), anhydrous sodium acetate (1.7g, 0.02mol) and 3β-acetoxyandrost-5-ene-17-one (**340**) (2.0g, 0.006mol) were stirred for 30 min. Chromium trioxide (2.0g, 0.02mol) was added over a 30 min period. This mixture was maintained at a constant temperature of 56-58°C and continously stirred during the addition of chromium trioxide. The mixture was then cooled and slowly poured to an ice-water mixture (600ml) to form a precipitate. The flocculent precipitate was filtered and washed with water, dried *in vacuo*, yielding 3β-acetoxyandrost-5-ene-7,17-dione (**341**) as a colourless solid in 20% yield.

Method 3

To a solution of 3β-acetoxyandrost-5-ene-17-one (**340**) (0.5g, 0.0015mol) in acetic anhydride (20ml) was added anhydrous sodium chromate (0.425g, 0.002mol) in portions with stirring and cooling. Heat of reaction was noted which lasted for several hours. The reaction mixture was kept at 42°C. After 72 h the mixture was poured onto an ice-water mixture. After stirring for 1 h, the precipitate was filtered and then slurried three times with water. The solid was filtered off, dried *in vacuo* and recrystallised from ethanol to yield 3β-acetoxyandrost-5-ene-7,17-dione (**341**) as a crystalline colourless solid in 80% yield.

Method 4

To a solution of 3β-acetoxyandrost-5-ene-17-one (**340**) (0.5g, 0.0015mol) in carbon tetrachloride (4ml) was added glacial acetic acid (1ml), acetic anhydride (0.26ml) and the mixture warmed to 55°C. Over a 45 min period at 55-60°C, was added a solution of acetic acid (1ml), acetic anhydride (0.26ml) and chromium trioxide (0.68g, 0.0068mol) in *t*-butylalcohol (0.5ml). The mixture was stirred at 60-65°C for 20 h. The solution was then washed with water (2x50ml) and extracted with chloroform (2x50ml). The solution was dried (Na_2SO_4) and concentrated *in vacuo* to yield a residue which was purified as described in method 1 yielding 3β-acetoxyandrost-5-ene-7,17-dione (**341**) as a colourless crystalline solid in 60% yield.

Method 5

Into a refluxing mixture of *N*-hydroxyphthalimide (0.51g) in acetone was added 3β-acetoxyandrost-5-ene-17-one (1.0g, 0.003mol) and dibenzoyl peroxide (0.05g, 0.0002mol). A weak stream of compressed air was introduced into the flask. The mixture was heated to reflux and maintained at this temperature for 9 h. The refluxed mixture was cooled down, the solvent evaporated *in vacuo* and the residue treated with carbon tetrachloride (10ml) at 50°C for 30 min to form a white precipitate of *N*-hydroxyphthalimide which was filtered off under suction. The filtrate was evaporated *in vacuo* to give an oily residue that was dissolved in pyridine (6.25ml), heated to 50°C then cooled to 5-10°C and treated with acetic anhydride (0.625ml). This mixture was stirred for 24h at room temperature then concentrated *in vacuo* yielding a residue which was purified as described in method 1 resulting in the isolation of the product 3β-acetoxyandrost-5-ene-7,17-dione (**341**) as a colourless solid in 50% yield.

3β-Hydroxyandrost-5-ene-7,17-dione (312)

Method 1 and Method 2

Sodium carbonate or potassium carbonate (0.02mol) was added to a solution of 3β-acetoxyandrost-5-ene-7,17-dione (**341**) (0.06g, 0.2mol) in dry methanol (2ml). The reaction mixture was stirred at room temperature for 1 h. The methanol was removed *in vacuo*. The residue was diluted with dichloromethane, then washed with water

(2x2.5ml) and dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude product. The crude product was purified by column chromatography over silica gel (eluent, dichloromethane:ethyl acetate, 99:1) to afford the product 3β-hydroxyandrost-5-ene-7,17-dione (**312**) as a colourless crystalline solid in 72% yield m.p. 237-238°C (lit. m.p.[250] 235-238°C).

IRν_{max} (KBr) 3486 (OH), 1721 (C=O), 1658 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.91 (3H, s, H-18), 1.19 (3H, s, H-19), 1.20-2.33 (17H, m, H-1, H-2, H-4, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.64-3.70 (1H, m, H-3α), 5.36 (1H, s, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.27 (C-18), 16.96 (C-19), 20.11 (C-11), 23.68 (C-15), 30.26, 30.61 (C-12, C-2), 35.15 (C-16), 35.86 (C-1), 38.20 (C-10), 41.43 (C-4), 43.87 (C-8), 45.29 (C-9), 47.13 (C-13), 49.65 (C-14), 69.73 (C-3), 125.34 (C-6), 165.92 (C-5), 200.59 (C-7), 219.87 (C-17).

Method 3

3β-Acetoxyandrost-5-ene-7,17-dione (**341**) (0.685g, 0.2mmol) was suspended in dilute methanolic ammonia (2ml, prepared by diluting 2.0M ammonia with an equal volume of methanol at 20°C). The reaction mixture was stirred at 25°C for 2.5 h, then the methanol was evaporated. The residue was washed with water and extracted with dichloromethane (10ml). The organic phase was dried (Na_2SO_4) and purified according to the procedure described in method 1 yielding 3β–hydroxyandrost-5-ene-7,17-dione (**312**) in 58% yield.

$\Delta^{3,5}$-Androstadien-7,17-dione (342)

Concentrated hydrochloric acid (0.25ml) was added to a solution of 3β-acetoxyandrost-5-ene-7,17-dione (341) (0.15g, 0.0004mol) in dry methanol (5ml). The solution was refluxed for 1 h. The reaction was cooled and water added dropwise until crystallization occurred. The crystals were filtered and recrystallised from methanol yielding a colourless crystalline solid in 70% yield m.p. 162-163°C, (lit. m.p.[248] 164°C).

IRν_{max} (KBr) 1750 (C=O), 1665 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.84 (3H, s, H-18), 1.21 (3H, s, H-19), 1.23-2.49 (15H, m, H-1, H-2, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 5.63 (1H, s, H-6), 6.10-6.20 (2H, m, H-3, H-4).

^{13}C-NMR (101MHz)

($CDCl_3$) 13.90 (C-18), 16.21 (C-19), 20.07 (C-11), 22.91 (C-15), 32.33, 32.91, 33.84 (C-2, C-12, C-16), 35.21 (C-1), 35.89 (C-10), 47.69 (C-13), 44.49, 49.01, 49.34 (C-8, C-9, C-14), 123.45, 127.12, 136.71 (C-4, C-3, C-6), 161.15 (C-5), 200.62 (C-7), 219.86 (C-17).

3β-Toluene-*p*-sulphonyloxyandrost-5-ene-7,17-dione, (343) 3β-Chloroandrost-5-ene-7,17-dione (344), 3β-Bromoandrost-5-ene-7,17-dione (345)

To a solution of the appropriate steroid (**343**)-(**345**) (0.0015mol) in acetic anhydride (20ml) was added anhydrous sodium chromate (0.425g, 0.002mol) in portions with stirring and cooling. Heat of reaction was noted which lasted for several hours. The reaction mixture was kept at 42°C. After 72 h the mixture was poured onto an ice-water mixture. After stirring for 1h, the precipitate was filtered and then slurried three times with water (20ml). The solid was filtered and dried *in vacuo*. All compounds were purified by recrystallisation from ethanol yielding crystalline solids.

3β-Toluene-*p*-sulphonyloxyandrost-5-ene-7,17-dione (343) was obtained as a colourless solid in 60% yield, m. p. 132-134°C, (lit. m.p.[252] 131-132°C), $[\alpha]_D^{20} = +63^\circ$ (C=1.95, $CHCl_3$)

IRν_{max} (KBr) 1734 (C=O), 1674 (C=O)cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.84 (3H, s, H-18), 1.17 (3H, s, H-19), 1.48-2.43 (17H, m, H-1, H-2, H-4, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 4.34-4.39 (1H, m, H-3α), 5.62 (1H, bs, H-6), 7.33 (2H, d, J=8.04Hz, H-3` and H-5`), 7.76 (2H, d, J=8.04Hz, H-2` and H-6`).

^{13}C-NMR (101MHz)

δ ($CDCl_3$)ppm 13.23 (C-18), 20.04 (C-19), 21.15 (CH_3), 23.58 (C-11), 27.69, 30.16, 30.17 (C-12, C-16, C-15, C-2), 35.01 (C-1), 37.73 (C-10), 38.00 (C-4), 47.25 (C-13), 45.17, 49.37, 50.00 (C-8, C-9, C-14), 79.05 (C-3), 127.16 (C-6), 129.47 (C-3` and C-5`), 133.62 (C-2` and C-6`), 133.62 (C-1`), 144.45 (C-4`), 162.93 (C-5), 199.91 (C-7), 219.33 (C-17).

3β-Chloroandrost-5-ene-7,17-dione (344) was obtained as a yellow solid in 30% yield m.p. 161-162°C, $[\alpha]_D^{20} = +109^\circ$(C=1, $CHCl_3$)

IRν_{max} (KBr) 1751 (C=O), 1674 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ (CD_3COCD_3) 0.93 (3H, s, H-18), 1.39 (3H, s, H-19), 1.11-2.56 (17H, m, H-1, H-2, H-4, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.9-4.04 (1H, m, H-3α), 5.70 (1H, s, H-6).

^{13}C-NMR (101MHz)

(CD_3COCD_3)ppm 13.66 (C-18), 17.19 (C-19), 20.85 (C-11), 24.35 (C-15), 31.35 (C-8), 33.24, 31.35, 38.64, 35.39, (C-12, C-2, C-16, C-1), 38.31 (C-10), 42.85 (C-4), 47.97 (C-13), 46.23 (C-9), 58.53 (C-3),

50.62 (C-14), 126.09 (C-6), 140.10 (C-5), 165.32 (C-7), 200.54 (C-17).

Low Resolution Mass Spectrum

$C_{19}H_{25}ClO_2$ Requires: M^+=322 / 320

Found: M^+=322 / 320

Mass Spectrum (m/z)

322 (M^+ 23%), 320 (M^+ 68%), 267 (M^+-55, 10%). 265 (M-55, 17%), 223 (M-98, 25%), 170 (M-151, 30%),161 (M-160, 63%), 105 (M-216, 51%), 91 (M-230, 100%), 79 (M-242, 74%), 55 (M-266, 40%).

3β-Bromoandrost-5-ene-7,17-dione (345) was obtained as a yellow solid in 20% yield m. p.151-153°C, $[\alpha]_D^{20} = +116°$(C=1, $CHCl_3$).

IRν_{max} (KBr) 1734 (C=O), 1674 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ (CD_3COCD_3) 0.90 (3H, s, H-18), 1.35 (3H, s, H-19), 1.13-2.60 (17H, m, H-1, H-2, H-4, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 4.10-4.17 (1H, m, 3-Hα), 5.71 (1H, s, H-6).

^{13}C-NMR (101MHz)

(CD_3COCD_3)ppm 13.68 (C-18), 17.29 (C-19), 20.45 (C-11), 24.35 (C-15), 31.35 (C-8), 33.14, 31.75, 34.64, 35.49 (C-12, C-2, C-1, C-16), 35.31 (C-10), 43.85 (C-4), 45.97 (C-13), 46.13 (C-9), 59.53 (C-3), 50.62 (C-14), 126.19 (C-6), 141.10 (C-5), 164.32 (C-7), 200.64 (C-17).

Low Resolution Mass Spectrum

$C_{19}H_{25}BrO_2$ Requires: M^+=366 / 364

Found: M^+=366 / 364

Mass Spectrum (m/z)

366 (M^+, 100%), 364 (M^+, 99%), 321 (M-45, 10%), 311 (M-55, 13%), 309 (M-55, 12%), 267 (M-99, 12%), 243 (M-123, 15%), 187 (M-179, 24%), 161, (M-205, 40%), 147 (M-219, 4%), 91 (M-275, 74%), 79 (M-287, 20%), 55 (M-310, 33%).

3α,4α-Epoxyandrost-5-ene-7, 17-dione (328)

$\Delta^{3,5}$-Androstadien-7,17-dione (**342**) (1.6g, 0.005mol) in chloroform (50ml) was treated with *m*CPBA (2.0eq) overnight. The solution was diluted with aqueous sodium sulphite (2x100ml), washed with aqueous $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed under vacuum to yield a colourless solid. Purification by flash column chromatography over silica gel, (eluent, dichloromethane:ethyl acetate, 90:10) afforded a colourless solid in 80% yield m.p. 196-198°C (lit. m.p.[258] 196-198°C).

IRν_{max} (KBr) 1745 (C=O), 1680 (C=O), 1250, 899, 735 (epoxy C-O) cm^{-1}

^{1}H-NMR (400MHz)

δ($CDCl_3$) 0.64 (3H, s, H-18), 0.86 (3H, s, H-19), 0.97-2.50 (15H, m, H-1, H-2, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.19 (1H, d, J=3.00Hz, H-3), 3.22 (1H, m, H-4), 5.78 (1H, s, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.17 (C-18), 17.01 (C-19), 19.87, 19.96 (C-15, C-11), 23.48, 25.67, 30.10 (C-12, C-16, C-2), 34.88 (C-1), 35.14 (C-10), 44.70 (C-8), 45.48 (C-3), 47.31 (C-13), 49.12 (C-9), 51.15 (C-14), 51.54 (C-4), 130.15 (C-6), 160.70 (C-5), 199.24 (C-7), 219.36 (C-17).

3α-Hydroxy-4β-methoxy-androst-5-ene-7,17-dione (352)

3α,4α-Epoxyandrost-5-ene-7,17-dione (**328**) (0.300g, 1mmol) in methanol (10ml) was treated with cerium ammonium nitrate (0.109g, 0.2mmol) and stirred under reflux for 15 min. The methanol was evaporated under vacuum, and the resulting product was extracted with diethylether (2x10ml) and washed with water (2x10ml). The ether

extract was dried (Na_2SO_4). The crude product was purified by column chromatography over silica gel (100% dichloromethane) resulting in a colourless oil in 64% yield.

IRν_{max} (film) 3447 (OH), 1734 (C=O), 1670 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

$\delta(CDCl_3)$ 0.89 (3H, s, H-18), 1.32 (3H, s, H-19), 1.22-2.82 (15H, m, H-1, H-2, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.55 (3H, s, OCH_3), 3.55 (1H, d, J=3Hz, H-4), 4.10-4.12 (1H, m, H-3), 5.85 (1H, s, H-6).

^{13}C-NMR (101MHz)

$(CDCl_3)$ppm 13.24 (CH_3), 17.04 (CH_3), 19.36 (C-11), 23.72 (C-15), 30.19, 31.15 (C-12, C-16, C-2), 38.16 (C-10), 44.55 (C-1), 47.46 (C-13), 50.31 ($O\underline{C}H_3$), 44.55, 45.39, 55.72 (C-8, C-9, C-14), 68.72 ($\underline{C}OH$), 84.79 ($\underline{C}OCH_3$), 130.63 (C-6), 161.05 (C-5), 200.65 (C-7), 219.93 (C-17).

Low Resolution Mass Spectrum

$C_{20}H_{28}O$	Requires:	M^+=332
	Found:	M^+=332

High Resolution Mass Spectrum

$C_{20}H_{28}O_4$	Requires:	M^+=332.19876
	Found:	M^+=332.20002

Mass Spectrum (m/z)

332 (M^+, 100%), 277 (M-55, 10%), 137 (M-195, 25%), 79 (M-253, 25%), 55 (M-277, 25%).

3α-Hydroxy-4β-ethoxyandrost-5-ene-7,17-dione (353)

3α,4β-Epoxyandrost-5-ene-7,17-dione (**328**) (0.300g, 1mmol) in ethanol (10ml) was treated with cerium ammonium nitrate (0.109g, 0.2mmol) and stirred under reflux conditions for 1 h. The ethanol was evaporated and the resulting product was extracted with diethylether (2x10ml) and washed with water (2x10ml). The ether extract was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (100% dichloromethane) resulting in a colourless oil in 64% yield. $[\alpha]_D^{20} = -40^{\circ}$(C=1, $CHCl_3$).

IRν_{max} (film) 3448 (OH), 1737 (C=O), 1670 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.90 (3H, s, H-18), 1.24 (3H, s, H-19), 1.34 (3H, t, $OCH_2C\underline{H}_3$), 1.41-2.79 (15H, m, H-1, H-2, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.28-3.45 (2H, m, $OC\underline{H}_2CH_3$), 3.66 (1H, d, J=2.52Hz, H-4), 4.08-4.13 (1H, m, H-3), 5.83 (1H, s, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.23 (C-18), 14.52 ($OCH_2C\underline{H}_3$), 17.08 (C-19), 19.37 (C-11), 23.74 (C-15), 30.20, 31.23, 38.10 (C-12, C-16, C-2, C-1), 35.17 (C-10), 44.52, 45.39, 50.32 (C-8, C-9, C-14), 47.00 (C-13), 63.37 ($O\underline{C}H_2CH_3$), 69.02 ($\underline{C}$-OH), 82.84 ($\underline{C}$-OCH_2CH_3), 130.29 (C-6), 161.76 (C-5), 200.69 (C-7), 219.89 (C-17).

Low Resolution Mass Spectrum

$C_{21}H_{30}O_4$	Requires:	M^+=346
	Found:	M^+=346

High Resolution Mass Spectrum

$C_{21}H_{30}O_4$	Requires:	M^+=346.21441
	Found:	M^+=346.21449

3α-Hydroxy-4β-isopropoxyandrost-5-ene-7,17-dione (354a)

4α-Hydroxy-3β-isopropoxyandrost-5-ene-7,17-dione (354b)

3α,4α-epoxyandrost-5-ene-7,17-dione (**328**) (0.300g, 1mmol) in isopropanol (10ml) was treated with cerium ammonium nitrate (0.109g, 0.2mmol) and stirred under reflux temperature for 1 h. The solvent was evaporated and the resulting product was extracted with diethylether (2x10ml) and washed with water (2x10ml) and the ether extracts dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (100% dichloromethane) resulting in a regioisomeric product as a colourless oil as in 70% yield. $[\alpha]_D^{20}$=+100 (C=1, $CHCl_3$).

IRν_{max}(film) 3444 (OH), 1736 (C=O), 1671 (C=O) cm^{-1}

^{1}H-NMR(400MHz)

δ ($CDCl_3$) 0.86 (3H, s, C-18), 1.28 (2H, s, H-19), 1.30 (1H, s, H-19), 1.50 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.19–2.79 (15H, m, H-1, H-2, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.12-3.19 (1H, m, OC<u>H</u>$(CH_3)_2$), 3.62–5.32 (2H, m, H-3, H-4), 5.79 (0.33H, s, H-6), 6.02 (0.67H, s, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 10.17 (OCH(<u>C</u>H_3)), 13.20 (C-18), 17.07, 17.38 (C-19), 19.34, 19.52, 22.37, 23.57, 23.71, 23.90 (C-11, C-15), 30.08, 30.15, 30.39, 31.19 (C-12, C-16, C-2), 35.09, 35.16 (C-1), 37.65, 38.09 (C-10), 47.35, 47.48 (C-13), 44.45, 44.49, 45.16, 45.34, 50.05, 50.27 (C-9, C-8, C-14), 65.64 (O<u>C</u>H$(CH_3)_2$), 68.83 (<u>C</u>-OH), 83.06, 83.67 (<u>C</u>OCH$(CH_3)_2$), 130.04, 132.29 (C-6), 156.62, 162.24 (C-5), 200.49, 200.97 (C-7), 219.87, 220.22 (C-17).

Low Resolution Mass Spectrum

$C_{22}H_{32}O_4$	Requires:	M^+=360
	Found:	M^+=360

High Resolution Mass Spectrum

$C_{22}H_{32}O_4$	Requires:	M^+=360.23006
	Found:	M^+=360.23085

3β,4β-Dihydroxyandrost-5-ene-17-one (360)

Dioxane (0.3ml) and selenium dioxide (0.05g, 0.05mol) and water (0.1ml) was heated to 50-55°C and stirred until the solid dissolved. DHEA (**305**) (0.144g, 0.0005mol) was added. The mixture was refluxed for 4 h. The selenium dioxide was filtered from the hot solution and the dioxane removed under reduced pressure. The product was diluted with dichloromethane (10ml) and washed with water (3x10ml) dried (Na_2SO_4) and reduced *in vacuo*. The product was purified by column chromatography over silica gel (eluent, dichloromethane: ethyl acetate; 99:1) yielding a colourless solid in 55% yield m.p.204-205°C (lit. m.p.[264] 204-205°C, lit. m.p.[265] 204-205°C). $[\alpha]_D^{20}$ = -28.5° (C=0.22, $CHCl_3$).

IR ν_{max} (KBr)	3340 (br-OH), 1743 (C=O) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$)	0.95 (3H, s, H-18), 1.08 (3H, s, H-19), 1.19–2.79 (17H, m, H-1, H-2, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.50-3.55 (1H, m, H-3α), 4.13 (1H, d, J=3Hz, H-4α), 5.70 (1H, d, J=5Hz, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm	13.08 (C-18), 19.36 (C-19), 20.49 (C-11), 21.37 (C-15), 24.72, 30.49, 30.91 35.33, 36.45, (C-12, C-2, C-7, C-1, C-16), 30.99 (C-8), 35.70 (C-10), 47.08 (C-13), 49.87, 51.45 (C-9, C-14), 71.11, 76.59 (C-3, C-4), 127.24 (C-6), 141.01 (C-5), 220.55 (C-17).

3β,4β-Diacetoxy-androst-5-ene-17-one (361)

Dry, redistilled pyridine (0.4ml) and acetic anhydride (0.4ml) was added dropwise to 3β,4β-dihydroxyandrost-5-ene-17-one (**360**) (0.09g, 0.0003mol). The solution was allowed to stand for 24 h at room temperature. The solution was diluted with diethyl ether (10ml), washed with water (3x10ml) and brine (3x10ml). The ether extracts were dried (Na_2SO_4) and reduced *in vacuo*. The crude product was purified by flash column chromatography on silica gel (eluent, 100% dichloromethane) yielding the desired product in 70% yield as a colourless oil[266] .

IRν_{max} (KBr) 1735 (C=O), 1710 ($COCH_3$) cm^{-1}

^{1}H-NMR (400MHz)

δ ($CDCl_3$) 0.90 (3H, s, H-18), 1.26 (3H, s, H-19), 2.09 (3H, s, OCOC$\underline{H}_3$), 1.19–2.93 (17H, m, H-1, H-2, H-7, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 2.16 (3H, s, OCOC$\underline{H}_3$), 4.74-4.79 (1H, m, H-3α), 5.54 (1H, d, J=3Hz, H-4α), 5.87 (1H, d, J=5Hz, H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.04 (C-18), 19.92 (C-19), 19.39 (C-11), 20.58, 20.94 (OCO$\underline{C}H_3$) 21.35, 21.97, 30.42, 30.87 35.36, 36.28 (C-15, C-7, C-12, C-2, C-1, C-16), 35.83 (C-10), 47.00 (C-13), 49.86, 51.33 (C-9, C-14), 72.19, 75.31 (C-3, C-4), 130.32 (C-6), 149.00 (C-5),169.55, 169.76 (O$\underline{C}OCH_3$) 220.12 (C-17).

3β,4β-Dihydroxyandrost-5-ene-7, 17-dione (330)

To a solution of 3β,4β-diacetoxyandrost-5-ene-17-one (**361**) (0.06g, 0.00015mol) in acetic anhydride (2ml) was added anhydrous sodium chromate (0.04g, 0.0002mol) in portions with stirring and cooling. Heat of reaction was noted which lasted for several hours. The reaction mixture was kept at 42°C. After 72 h the mixture was diluted with diethyl ether (10ml) and washed with water (2x10ml), 10% aqueous $NaHCO_3$ (2x10ml) and brine (2x10ml). The ether extracts were dried (Na_2SO_4) and

concentrated *in vacuo*. The crude product was stirred at room temperature for 1 h in dry methanol (2ml). The methanol was evaporated *in vacuo* The crude product was purified by flash column chromatography over silica gel (eluent: 95:5 dichloromethane:ethyl acetate) yielding 3β,4β-dihydroxyandrost-5-ene-7,17-dione (**330**) in 10% yield as a colourless oil. $[\alpha]_D^{20} = -30^\circ$ (C=1, $CHCl_3$). For identification purposes by low resolution mass spectrometry (1mg) (**330**) was reacted with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide 97% (0.5ml) in chloroform (1ml) to give the TMS derivative of (**330**).

IRν_{max} (KBr) 3400 (OH), 1732 (C=O), 1665 (C=O) cm^{-1}

^{1}H-NMR(400MHz)

δ ($CDCl_3$) 0.92 (3H, s, H-18), 1.20 (3H, s, H-19), 1.10-2.50 (15H, m, H-1, H-2, H-8, H-9, H-11, H-12, H-14, H-15, H-16), 3.50-3.91 (1H, m, H-3α), 4.17 (1H, d, J=3Hz, H-4α), 5.87 (1H, s H-6).

^{13}C-NMR (101MHz)

($CDCl_3$)ppm 13.10 (C-18), 19.39 (C-19), 79.81, 83.22 (C-3, C-4), 120.04 (C-6), 139.12, (C-5), 200.12 (C-7), 220.12 (C-17).

Low Resolution Mass Spectrum

$C_{19}H_{26}O_4$	Requires:	M^+=318
	Found:	M^+154=462 (TMS derivative)

High Resolution Mass Spectrum

$C_{19}H_{26}O_4$	Requires:	M^+=318.18311
	Found:	M^+=318.18315

Mass Spectrum (m/z)

462 (M^+, 10%), 333 (M-129, 15%), 195 (M-267, 40%), 73 (M-389, 100%).

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Appendix 1

Publication.

3-(2-Alkoxy-1-hydroxyethyl)azetidin-2-ones: Potential Intermediates for the Synthesis of Novel Carbapenems, Aisling C. O`Leary, Caroline M. Waldron, Catherine M. Burke, Raymond D. Keaveny and Mary J. Meegan, *Journal of Chemical Research (S),* 1998, 64, *Journal of Chemical Research (M)*, 1998, 434.

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3-(2-Alkoxy-1-hydroxyethyl)azetidin-2-ones: Potential Intermediates for the Synthesis of Novel Carbapenems

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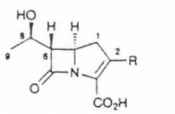
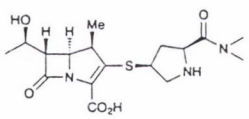
3-Vinyl and 3-isopropenylazetidin-2-ones can be transformed into the corresponding 3-(2-alkoxy-1-hydroxyethyl)azetidin-2-ones and 3-(1-alkoxy-2-hydroxypropan-2-yl)azetidin-2-ones by regioselective alcoholysis of 3-(1,2-epoxyethyl)azetidin-2-ones; 4-acetoxy-3-(1-hydroxy-2-methoxyethyl)-1-(4-methoxyphenyl)azetidin-2-one **14** is a synthetic precursor for carbapenems having both alcohol and alkoxyalcohol substituents at C-8.

The 1-hydroxyethyl substituent at C-6 is a characteristic feature of many carbapenems isolated and synthesised to date and the presence of this group consistently demonstrates potent antibacterial activity *e.g.* thienamycin **1a**, imipenem **1b** and meropenem **2**.[1] Extensive carbapenem modifications have been reported, the vast majority of which involve the substituents at C-1 and C-2.[2] However, Mastalerz *et al.* have reported a study on the synthesis and antibacterial activity of 6-aminoalkylcarbapenems[4] and related compounds. Other C-6 modifications that have been investigated include 6-(1-fluoroethyl),[5] 6-ethylidene,[6] 6-heteroethylidene[7] and 6-[1-(hydroxymethyl)ethylidene] carbapenems (asparenomycins).[8] The cholesterol absorption inhibition of 3-(2-aryloxy-1-hydroxyethyl)azetidin-2-ones has also been reported.[9]



1a R = $SCH_2CH_2NH_2$
1b R = $SCH_2CH_2NH{-}CH{=}NH$



2

The synthesis of a 4-acetoxy-3-(1-hydroxy-2-methoxyethyl)-1-(4-methoxyphenyl)azetidin-2-one **14** and related compounds is now described with a view to the introduction of alkoxyalkyl and related substituents at C-8 of carbapenems. We investigated the regioselective epoxide ring opening of 3-(1,2-epoxyethyl)azetidin-2-ones with alcohols and other oxygen nucleophiles under the mild and neutral conditions[12,14,15] required for β-lactam chemistry. The required epoxides **5a–f** were obtained as illustrated in Scheme 1.

The 3-vinyl-β-lactams **4a–f** were obtained by reaction of crotonyl chloride or 3,3-dimethylacryloyl chloride with the appropriate Schiff bases **3a–f**. We have reported the use of 3-vinylazetidin-2-ones as intermediates in the synthesis of asparenomycin type carbapenem antibiotics[10] while Manhas *et al.* have reported their use as intermediates for the PS series of carbapenems.[11] The epoxides **5a–f** were prepared by oxidation of the 3-vinyl β-lactams **4a–f** with *m*CPBA and were obtained as diastereomeric mixtures. Treatment of the epoxides **5a–f** with methanol, ethanol or acetic acid with Woelm 200 neutral alumina[12] was then carried out and the epoxides **5a–f** were opened regioselectively in each case to afford the corresponding β-alkoxyalcohols **6a–h** and related esters as diastereomeric mixtures. The *trans* nature of the β-lactam protons was maintained throughout the procedure. The regioselectivity of the process was evident from the ^1H NMR spectrum. Diol **8** is produced in 25% yield from epoxide **5a** together with required β-alkoxy alcohol **6a** if conditions are not anhydrous. Oxidation of the β-alkoxyalcohols **6a–c** to the corresponding carbonyl compounds **7a–c** with pyridinium chlorochromate provided conclusive proof of the regioselectivity of the alumina method for opening the 3-(1,2-epoxyethyl)azetidin-2-ones with alcohols. This procedure allowed the introduction of the alcohols methanol and ethanol at C-6 while the use of acetic acid as nucleophile allowed the introduction of an ester substituent of C-6.

Regioselective methanolysis of 3-(1,2-epoxyethyl)-4-(4-methoxyphenyl)-1-phenylazetidin-2-one **5b** by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[14] was achieved giving rise to the corresponding β-methoxy alcohol **6b** as a diastereomeric mixture in 49% yield. A similar alcoholysis reaction was carried out on β-lactam epoxides **5a, f** using cerium ammonium nitrate (CAN) as the catalyst[15] to afford the β-alkoxyalcohol products **6a, i, j, k**. The alumina, CAN and DDQ methods are suitable for use in β-lactam chemistry where mild neutral conditions are required to avoid unwanted reactions.

In order to demonstrate the utility of the procedure for carbapenem synthesis we then examined the preparation of suitably modified 4-acetoxyazetidin-2-ones, well recognised as intermediates for carbapenem synthesis.[19] This regioselective alcoholysis of 3-(1,2-epoxyethyl)azetidin-2-ones was therefore applied to a 4-acetoxy substituted azetidin-2-one which would afford products which could be considered as precursors for carbapenems having the β-alkoxy alcohol type substituent at C-6. The 4-acetoxy-3-vinylazetidin-2-one **12** was obtained from the corresponding 4-formyl-3-vinylazetidin-2-one[20] (Scheme 2) by oxidation to the carboxylic acid followed by decarboxylation–acetoxylation.[10] Epoxidation of the vinyl compound **12** afforded the epoxide product **13** as a diastereomeric mixture which was then reacted with methanol in the presence of alumina to afford the corresponding β-methoxy alcohol **14** as a diastereomeric mixture.

A procedure for the synthesis of β-lactams containing a β-alkoxy alcohol type substituent at C-3 is described. This reaction gives access to β-lactam products which have the characteristic hydroxy group at C-5 of the side chain as found in clinically important carbapenems, and contain an additional alkoxyalkyl substituent at C-6. The development of this methodology for the stereoselective introduction of varied nucleophiles at C-9 of carbapenems is currently in progress.

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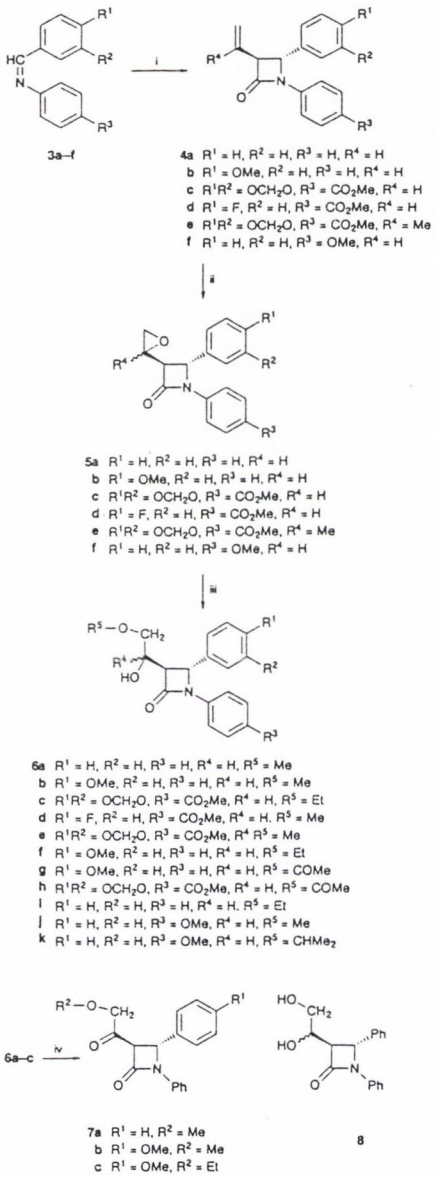
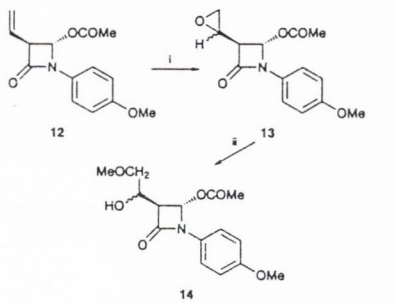


Scheme 1 *Reagents and conditions*: i, MeCH=CHCOCl or $(Me)_2C$=CHCOCl, Et_3N; ii, *m*CPBA; iii, R^5OH, alumina, DDQ, or CAN; iv, pyridinium chlorochromate



Scheme 2 *Reagents and conditions*: i, *m*CPBA, CH_2Cl_2; ii, MeOH, alumina

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Techniques used: ^1H and ^{13}C NMR, IR, mass spectrometry, TLC

Schemes: 2

Tables: 1

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