Review Article

γ-LACTAM ANALOGUES OF β-LACTAM ANTIBIOTICS

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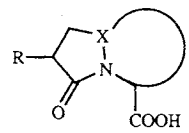
(Received for publication August 25, 1990)

CONTENTS

Introduction

The β-lactam antibiotics[1~5] represent the most important class of antibacterial agents at the present time. However, owing to their widespread use an ever increasing number of resistant bacterial strains are developing due to mutation and β-lactamase gene transfer.[6] To overcome this inactivation by β-lactamases one possibility is to modify the β-lactam ring, the target of these enzymes. Replacement of the β-lactam ring with other four-membered systems, *e.g.* cyclobutanone,[7~11] β-sultam[12] and others[13~16] lead to little success. Attention was turned to five-membered systems, which are somewhat activated towards penicillin-binding proteins (PBPs),[17] the targets of β-lactam antibiotics. Herein we report the chemistry and biology of γ-lactam analogues (γ-lactam, pyrazolidinone and isoxazolidinone (lactivicin) derivatives) represented by the general structure (Fig. 1).

Fig. 1. General structure of γ-lactams reviewed in this article.



R=H, $CH_3CH(OH)$, R'COHN
X=C, N, O

Related molecules, *e.g.* urethanes[18~20] and others[21~27] are not discussed.

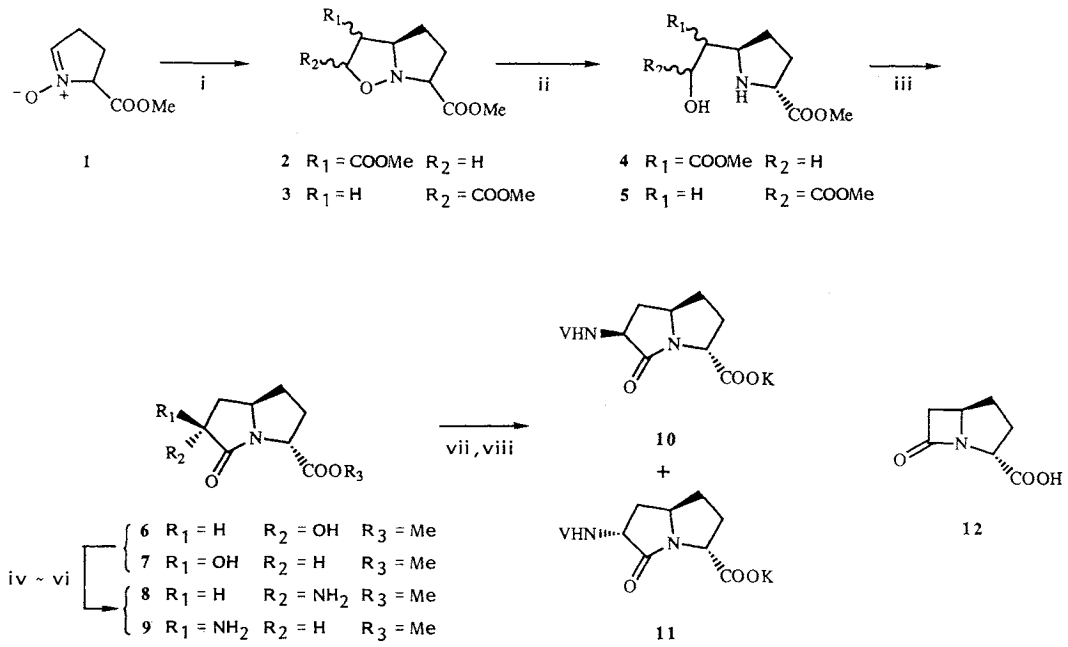
γ-Lactams

Although γ-lactam analogues of penicillins had been prepared earlier[28~30] it was not until the early 1980s that the search for biologically active γ-lactam analogues of the β-lactam antibiotics began in earnest.

In initial reports[31,32] we considered the possibility that the presence of a β-lactam ring was not mandatory for antibiotic activity but that a suitably activated amide bond was the major requirement. Two bicyclic γ-lactams (**10** and **11**), racemic analogues of carbapenicillanic acid (**12**),[33] were synthesised however they exhibited no antibacterial activity when tested against *Bacillus subtilis* ATCC 6633 and *Escherichia coli* supersensitive strain No. 21/30 or β-lactamase inhibition against *Bacillus cereus* β-lactamase II and *Klebsiella aerogenes* BRL 1003.

The two epimers were prepared *via* the nitrone (**1**) (Scheme 1). Reaction of **1** with methyl acrylate provided an inseparable mixture of **2** and **3** which was reduced to the amino alcohols (**4** and **5**). Cyclisation

Scheme 1.



i: CH_2=CHCOOMe, ii: H_2, Raney Ni, iii: MeOH, iv: TsCl, pyridine, v: NaN_3, vi: H_2, Pd-C, vii: $PhOCH_2COCl$, pyridine, viii: K_2CO_3, MeOH.

in refluxing methanol afforded the separable alcohols (**6** and **7**) which were modified *via* standard functional group chemistry to the carbapenam analogues (**10** and **11**).

Our work continued with the synthesis and biological evaluation of fused γ-lactam azetidines[34,35] since molecular modelling studies of these molecules showed similar pyramidal distortions of the lactam nitrogen atom to those observed in penicillins. The degree of pyramidal distortion of the lactam nitrogen in β-lactam antibiotics has been associated with antibacterial activity.[36]

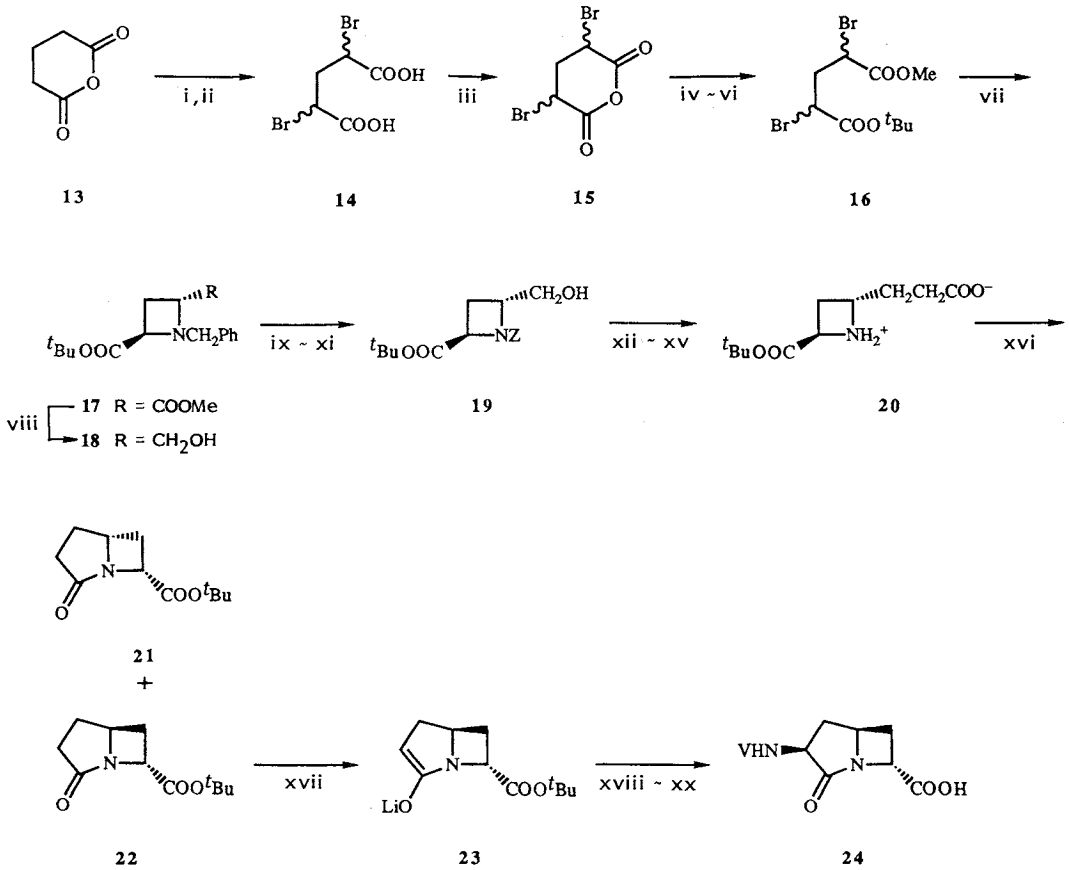
Bromination of glutaric anhydride (**13**) and transformation to the diester (**16**) was followed by cyclisation with benzylamine to give the diastereomeric azetidines (**17**) (Scheme 2). Sodium borohydride reduction provided the alcohols (**18**) separable by fractional crystallisation. After nitrogen deprotection and acylation the alcohols (**19**) were converted to the acids (**20**) *via* a Wittig reaction and two-stage hydrogenation. Intramolecular cyclisation gave the bicyclic γ-lactams (**21** and **22**). Interestingly substitution α to the γ-lactam carbonyl of **22** *via* the lithium enolate (**23**) occurred on the more hindered concave face. Finally elaboration to an acylamino side chain and deprotection provided (**24**).

γ-Lactam (**24**) as well as deprotected **21** and **22** showed no significant antibacterial activity against a panel of Gram-positive and Gram-negative organisms including strains highly sensitive to penicillins. They also showed no β-lactamase inhibitory activity against β-lactamase I (*B. cereus*). However a related compound, the azete (**25**),[37] was reported in a patent to possess antibacterial activity against a wide variety of pathogens (Fig. 2).

The first clear evidence that γ-lactam analogues of β-lactams were active as antibiotics was provided in 1986 by our group and the Eli Lilly research group with the synthesis of **26**[38,39] and **27**[40] (Fig. 3).

In our case the prior preparation of the bicyclic γ-lactams (**11** and **24**) and the discovery that neither

Scheme 2.



i: Br_2, ii: HCOOH, iii: AcCl, iv: Na_2CO_3, MeOH, v: $(COCl)_2$, pyridine, vi: ^tBuOH, pyridine, vii: $PhCH_2NH_2$, viii: $NaBH_4$, ix: cryst./sep., x: H_2, Pd-C, xi: $PhCH_2OCOCl$, pyridine, xii: DCC, DMSO, pyridine, TFA, xiii: $Ph_3P{=}CHCOO\text{-}PNB$, xiv: H_2, $(PPh_3)_3RhCl$, xv: H_2, Pd-C, xvi: 2,2'-dipyridyl disulfide, PPh_3, xvii: $LiN(SiMe_3)_2$, xviii: $Ph_2PO_2NH_2$, xix: $PhOCH_2COOH$, EEDQ, xx: TFA.

Fig. 2. Azete (**25**) possessing antibacterial activity.

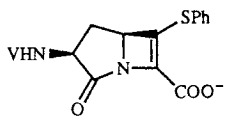
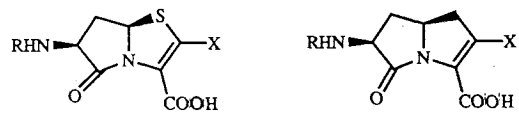


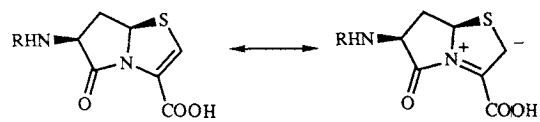
Fig. 3. First γ-lactam analogues possessing activity.



26 **27**

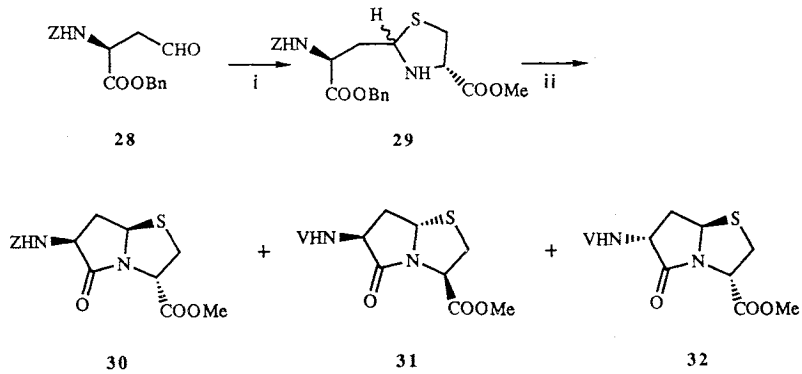
possessed antibacterial activity suggested to us that γ-lactam analogues of penems might show increased reactivity and biological activity due to delocalisation of the lactam nitrogen lone pair through the olefinic bond (Fig. 4).[38,41,42]

Fig. 4. Delocalisation of electron density in penems.



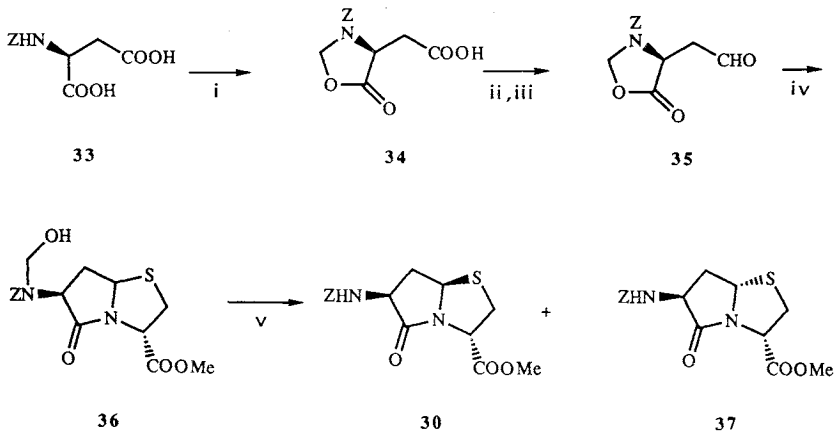
Two synthetic routes to the intermediates (**30** and **31**) were reported. Condensation of the aldehyde (**28**) derived from L-aspartic acid with D-cysteine methyl ester gave the thiazolidines (**29**) (Scheme 3). Subsequent cyclisation provided the three bicyclic compounds **30**~**32**.

Scheme 3.



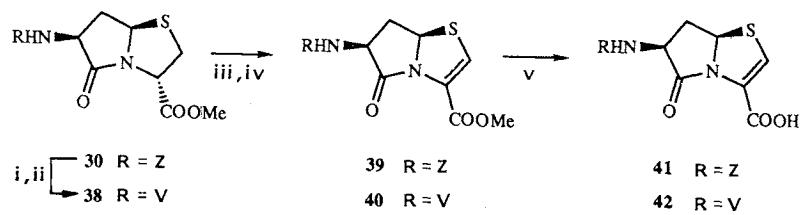
i: D-Cysteine Me ester, pyridine, ii: pyridine, reflux.

Scheme 4.



i: $(H_2CO)_n$, TsOH, ii: $SOCl_2$, iii: Bu_3SnH, iv: D-cysteine Me ester, pyridine, v: MeOH, Na_2CO_3.

Scheme 5.

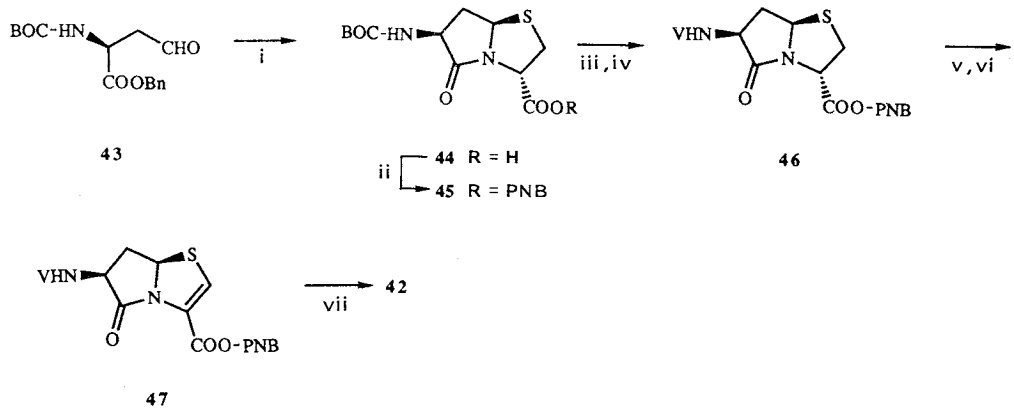


i: HBr, AcOH, ii: $PhOCH_2OCl$, Et_3N, iii: $(PhCO)_2O_2$, iv: $PhNMe_2$, v: LiOH.

Alternatively the aspartic acid (**33**) was reacted with paraformaldehyde to yield the oxazolidinone acid (**34**) (Scheme 4). Transformation to the aldehyde (**35**), condensation with L-cysteine methyl ester and removal of the one-carbon nitrogen appendage gave **30** and **37**.

Deprotection and reacylation of **30** yielded **38** (Scheme 5). Both were treated with benzoyl peroxide and elimination of the resultant benzoates followed by hydrolysis of the methyl esters gave the desired **41** and **42**.

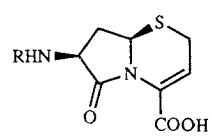
Scheme 6.



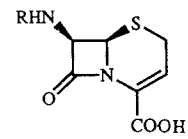
i: D-Cysteine, pyridine, ii: PNB-Br, KI, $KHCO_3$, iii: HCOOH, iv: $PhOCH_2COCl$, Et_3N, v: $(PhCO)_2O_2$, $Cu(acac)_2$, vi: $PhNMe_2$, vii: H_2, Pd-C.

The low yield of the final deprotection step prompted a modified synthesis *via* a *p*-nitrobenzyl (PNB) protected carboxylic acid. Thus reaction of the aldehyde (**43**) with D-cysteine gave the acid (**44**) which was esterified to **45** (Scheme 6). Nitrogen deprotection and subsequent acylation to give the phenoxyacetyl (V) side chain was followed by benzoate formation and elimination. Hydrogenolysis of the ester **47** gave the bicyclic γ-lactam (**42**). This compound was found to show weak but real biological activity against both Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*E. coli* ESS).

Fig. 5. γ-Lactam analogue (**48**) of a 3-unsubstituted cephem (**49**).



48



49

We are now synthesising the related molecules **48**, γ-lactam analogues of the cephalosporins (**49**), *e.g.* ceftizoxime[43] (Fig. 5).

The Eli Lilly work[39,40,44] followed molecular modelling studies which showed that bicyclic γ-lactams possessing an acylamino side chain at C-7 rather than C-6 and in a β orientation are conformationally similar to β-lactam antibiotics. They reasoned that the acylamino side chain would be required in a γ-lactam antibiotic to promote activity diminished by the lower stain of the γ-lactam ring relative to a β-lactam ring. In addition it was thought that electron withdrawing functions at C-3 would increase the reactivity of the lactam by delocalisation of the nitrogen lone pair away from the carbonyl group (Fig. 6).

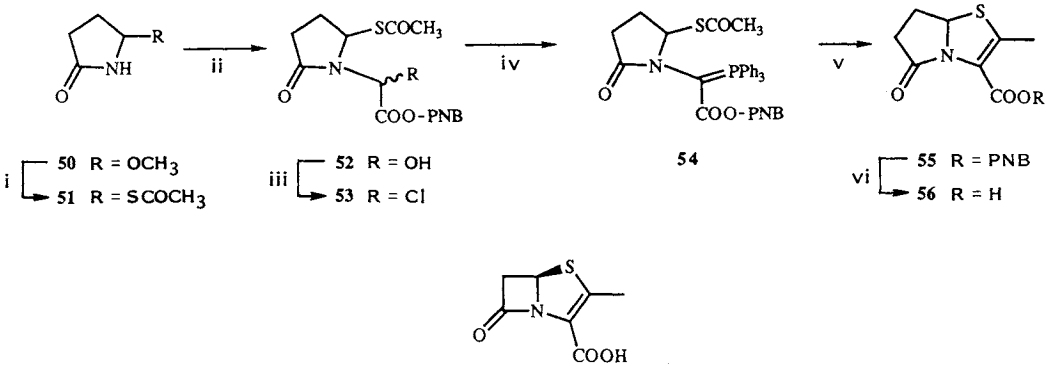
However firstly they synthesised the C-7 unsubstituted γ-lactam (**56**) for direct comparison with the potent β-lactam antibiotics (**57**) (Scheme 7).[45,46]

Solvolysis of the pyrrolidinone (**50**) in thiolacetic acid and subsequent condensation with *p*-nitrobenzylglyoxylate provided the hemiaminals (**52**) which were transformed to the desired racemic product (**56**) *via* WOODWARD's procedure.[47] This compound was devoid of antimicrobial or β-lactamase inhibition activity.

Similar molecules substituted at C-7 with an acylamino side chain were also prepared (Scheme 8). Thus high pressure reduction of the pyrazoline (**58**) provided the monocyclic γ-lactams (**59**) followed by elaboration to the bicyclic derivatives (**63**~**68**) as in Scheme 7. Protecting group removal and acylation

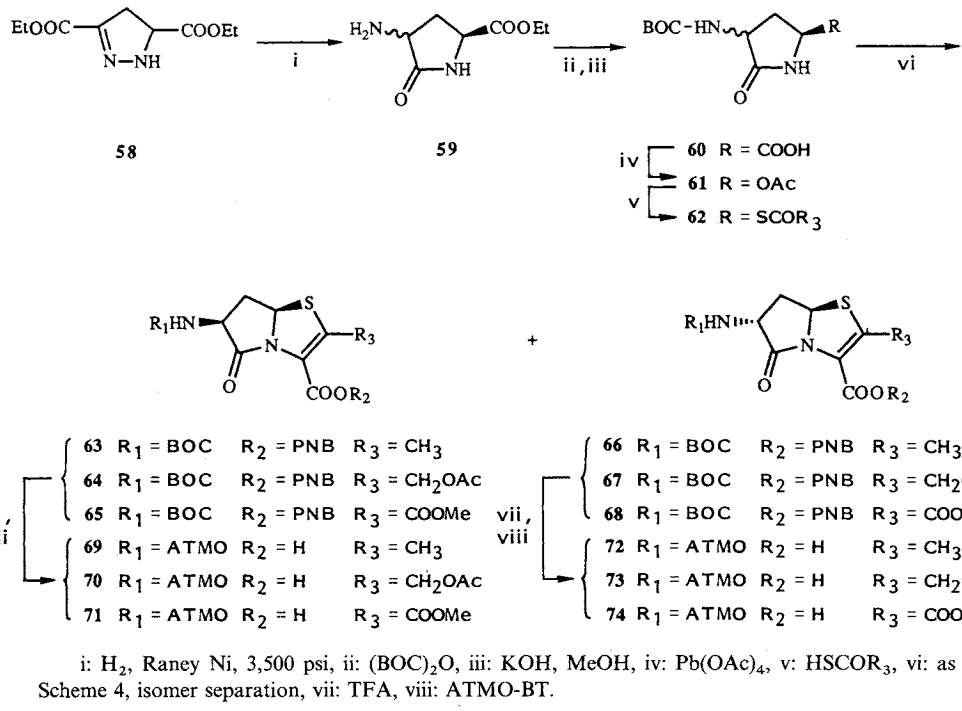
Fig. 6. Delocalisation of electron density in carbapenems stabilised by an electron withdrawing group (X).

Scheme 7.



i: CH_3COSH, ii: HCOCOO-PNB, iii: $SOCl_2$, 2,6-lutidine, iv: PPh_3, 2,6-lutidine, v: toluene, 80°C, 17 hours, vi: H_2, Pd-C.

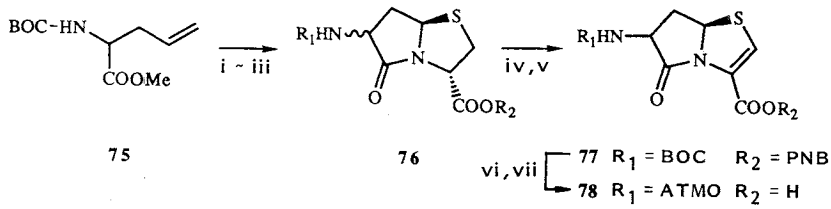
Scheme 8.



i: H_2, Raney Ni, 3,500 psi, ii: $(BOC)_2O$, iii: KOH, MeOH, iv: $Pb(OAc)_4$, v: $HSCOR_3$, vi: as in Scheme 4, isomer separation, vii: TFA, viii: ATMO-BT.

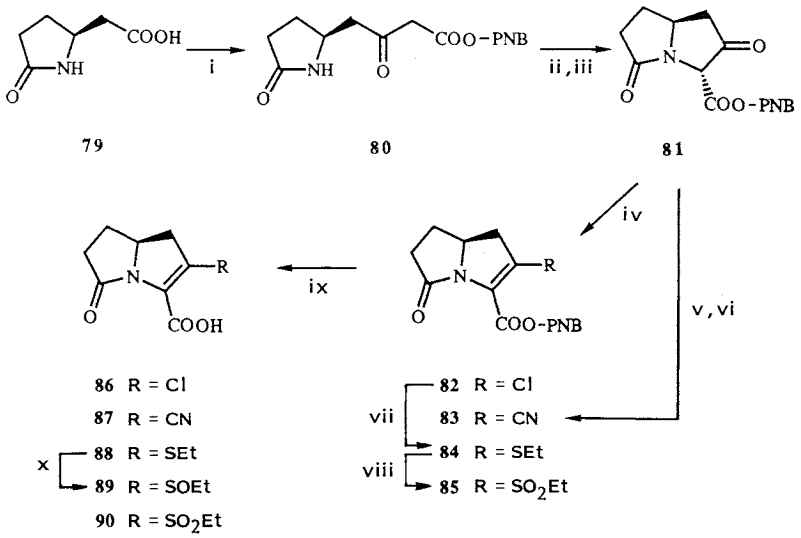
gave the desired products (**69**~**74**). Of these the epimeric **69** (MIC: 64 and 128 μg/ml against *Streptococcus pyogenes* C 203 and *Streptococcus pneumoniae* PARK) and **72** (MIC: 4.0 and 8.0 μg/ml against the same organisms) showed moderate antimicrobial activity.

Scheme 9.



i: O_3, DMS, ii: cysteine, NaOAc, HOAc, iii: PNB-Br, $NaHCO_3$, iv: $(PhCO)_2O_2$, v: DBU, vi: TFA, vii: ATMO-BT.

Scheme 10.



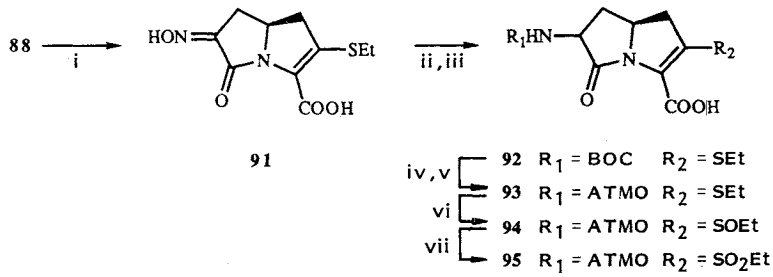
i: CDI, $Mg(O_2CCH_2COO\text{-}PNB)_2$, ii: $HOOCPhSO_3N_3$, Et_3N, iii: cat. $Rh_2(OAc)_4$, iv: $(PhO)_3PCl_2$, Pr^i_2NEt, v: TMS-CN, ZnI_2, 18-C-6/KCN, vi: $POCl_3$, pyridine, vii: EtSH, Pr^i_2NEt, viii: mCPBA, ix: Zn, HCl or HOAc, x: CH_3COOH.

A different route was employed for derivatives unsubstituted at C-3 (Scheme 9). Condensation of the protected allyl glycine (**75**) with cysteine followed by carboxylic acid deprotection gave the bicyclic γ-lactams (**76**). Unsaturation was introduced by treatment with benzoyl peroxide and elimination of the resultant benzoates. Deprotection and *N*-acylation yielded compounds **78**.

A series of C-7 unsubstituted carbapenem analogues were prepared from an optically active pyrrolidone carboxylic acid (**79**) (Scheme 10). Transformation to the bicyclic keto ester (**81**) was followed by conversion to the vinyl chloride (**82**) and the corresponding nitrile (**83**). Displacement of chlorine with ethanethiol gave the sulfide (**84**) which was subsequently oxidised to the sulfone (**85**). Deprotection of **82**~**85** with zinc under acidic conditions and peracetic acid oxidation of the resulting sulfide provided the C-7 unsubstituted bicyclic γ-lactams (**86**~**90**). However only the sulfoxide (**89**) showed trace antimicrobial activity.

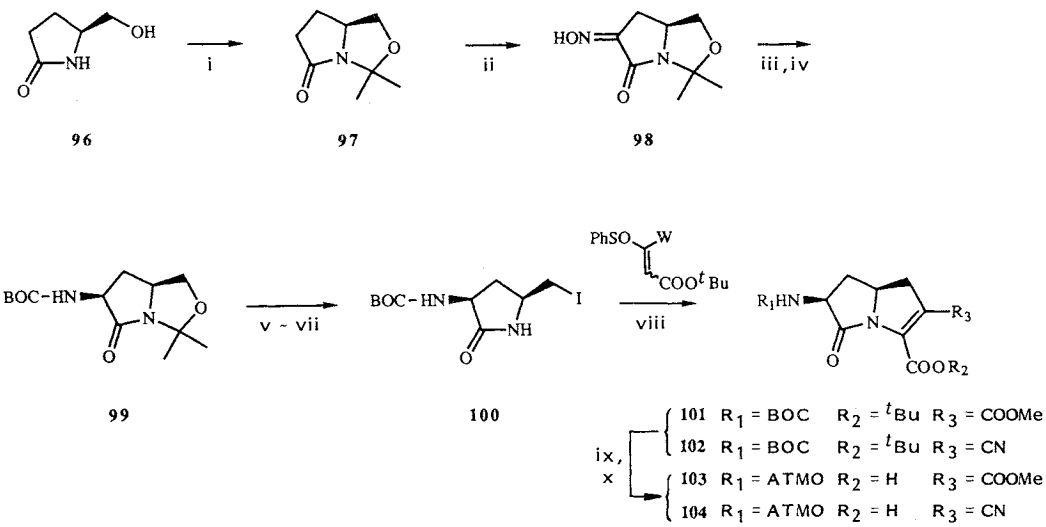
The C-7 acylamino γ-lactam carbapenems were prepared by two different routes. For the thioethyl analogues (**93**~**95**) the C-7 unsubstituted sulfide (**88**) was treated with base then *n*-butylnitrile to give the

Scheme 11.



i: LDA, Bu^{n}CN, ii; Zn, HOAc, iii: $(BOC)_2O$, iv: TFA, v: ATMO-BT, vi: CH_3COOH, vii: mCPBA.

Scheme 12.



i: 2,2-Dimethoxypropane, TsOH, ii, ^{t}BuOK, Bu^{n}CN, iii: H_2, Pd - C, iv: $(BOC)_2O$, $NaHCO_3$, v: HOAc, vi: MsCl, Et_3N, vii: NaI, viii: $LiN(SiMe_3)_2$, ix: TFA, x: ATMO-BT.

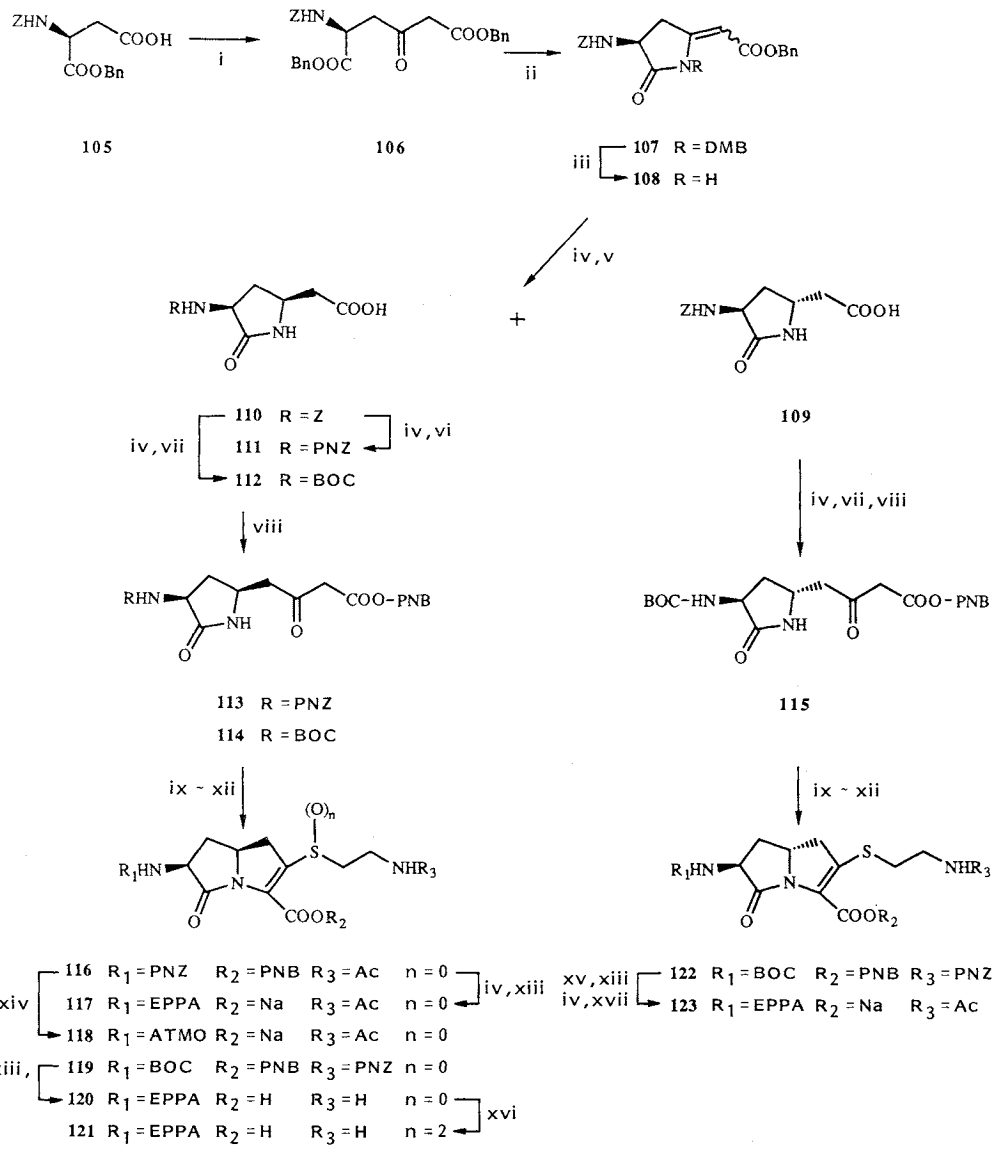
oxime (**91**) (Scheme 11). Acylamino side chain modification and oxidation afforded the required derivatives (**93**~**95**).

For the cyano and carbomethoxy analogues (**103** and **104**) the pyrrolidinone (**96**) was treated with 2,2-dimethoxypropane to give the acetonide (**97**) (Scheme 12). Introduction of the oxime function and conversion to the protected amine (**96**) was followed by a three step sequence to the iodo derivative (**100**). Cyclisation with a vinyl sulfone gave the bicyclic compounds **101** and **102**. Deprotection and acylation provided the desired analogues **103** and **104**. Of these only **103** exhibited slight activity against *E. coli* X161 and *E. coli* X580.

Finally workers in the Takeda laboratories[48] prepared γ-lactam analogues of carbapenems with cysteamine moieties at C-3 starting from L-aspartic acid as a source of chirality. The diprotected amino acid (**105**) was transformed to the keto ester (**106**) followed by condensation with dimethoxybenzylamine and subsequent cyclisation (Scheme 13).

After conversion to the acids (**109** and **110**) the *cis* isomer (**110**), separated by crystallisation, was

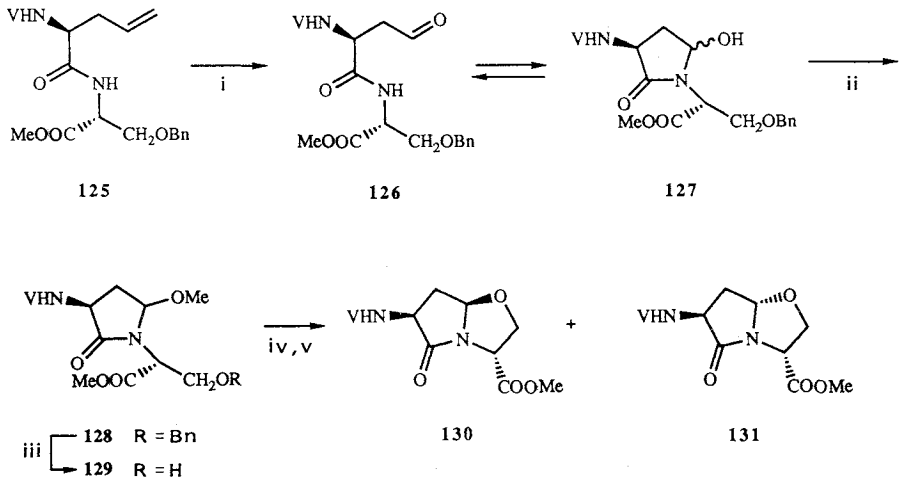
Scheme 13.



i: CDI, $Mg(OOCCH_2COOBn)_2$, ii: DMB-NH_2, iii: CAN, iv: H_2, Pd-C, v: $PhCH_2OCOCl$, $NaHCO_3$, vi: PNZ-Cl, $NaHCO_3$, vii: $(BOC)_2O$, Et_3N, viii: CDI, $Mg(OOCCH_2COO\text{-}PNB)_2$, ix: TsN_3, Et_3N, x: cat. $Rh_2(OAc)_4$, xi: $(PhO)_2POCl$, $Pr^i{}_2NEt$, xii: $HSCH_2CH_2NHR_3$, $Pr^i{}_2NEt$, xiii: EPPA-BT, xiv: ATMO-Cl, xv: TFA, $NaHCO_3$, xvi: mCPBA, $NaHCO_3$, xvii: Ac_2O.

transformed to derivatives (**111** and **112**). The keto esters (**113**, **114** and **115**) were prepared then cyclisation gave the bicyclic γ-lactams (**116**, **119** and **122**). Exchange of the C-7 acylamino side chains and oxidation of one product to its sulfone provided five carbapenem analogues (**117**, **118**, **120**, **121** and **123**) for biological evaluation. All showed slight but appreciable *in vitro* antibacterial activity against the Gram-negative organisms tested. Of particular interest was the sulfone (**121**) (MIC: 50 and 100 μg/ml against *E. coli* PG-85 and *Proteus mirabilis* ATCC 21100, respectively) which was more potent than the sulfide (**120**) (MIC: 100 and >100 μg/ml against the same organisms) possibly due to activation of the C-N bond by the electron

Scheme 14.



i: Cat. OsO_4, $NaIO_4$, ii: H^+, MeOH, iii: H_2, Pd-C, iv: TsOH, v: LiOH.

Fig. 7. Oxapenams (**124**).

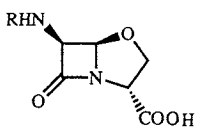


Fig. 8. Oxapenems (**132**).

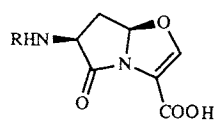
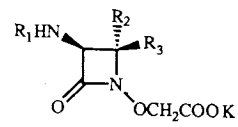


Fig. 9. Oxamazins (**133**).



withdrawing sulfonyl group. Also the *trans* isomer (**123**) (MIC: 25, 6.25 and 25 μg/ml against *E. coli* PG-12, *P. mirabilis* ATCC 21100 and *Klebsiella pneumoniae* IFO 3317) was found to be more active than the *cis* (**117**) (MIC: 100, 25, and 100 μg/ml against the same organisms) contrasting with known results for other antibiotics and their epimers.

Although the major emphasis in this area has been analogues of the penems and carbapenems we recently reported[49] the synthesis of analogues of the oxapenams (**124**)[50] (Fig. 7).

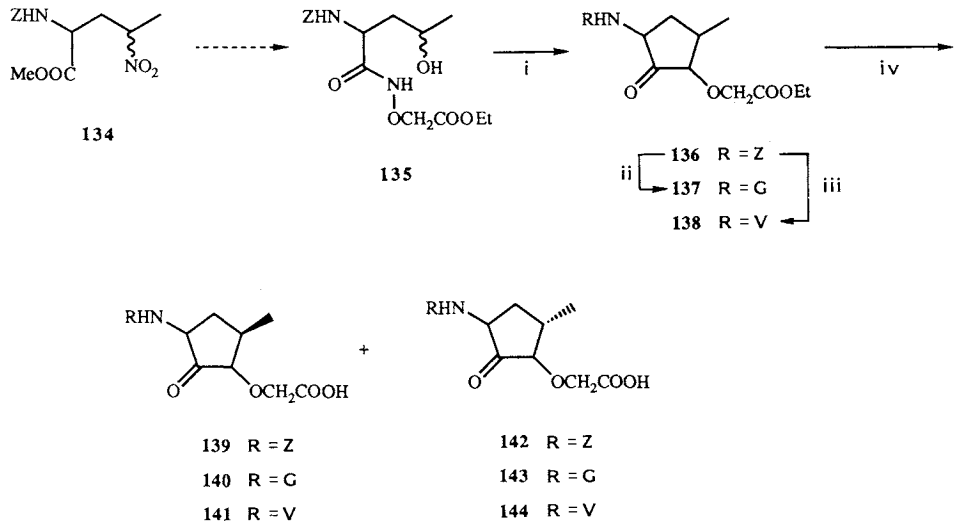
Thus the oxidative cleavage of dipeptide (**125**) afforded an equilibrium mixture of the aldehyde (**126**) and the hydroxylactams (**127**) (Scheme 14). Treatment with acidified methanol gave the methoxy lactams (**128**) separable by chromatography. Hydrogenolysis to the alcohols (**129**), cyclisation and deprotection provided the desired analogues (**130** and **131**). Both were shown to be inactive when tested for antibiotic activity against *S. aureus* NCTC 6571.

Work is currently in progress in our laboratories to prepare the unsaturated derivatives (**132**) which are expected to have increased reactivity (Fig. 8).

Attention has been focussed on the preparation of bicyclic γ-lactams however CROSSLEY *et al.*[51] has shown interest in monocyclic γ-lactams as antibiotics with the synthesis of analogues of the oxamazins (**133**).[52]

Cyclisation of the *O*-alkyl hydroxamates (**135**), prepared from the protected γ-nitro α-amino acid (**134**), gave the γ-lactams (**136**) (Scheme 15). Nitrogen protection was modified by hydrogenolysis and reacylation. Ethyl ester deprotection and HPLC separation of diastereoisomers provided compounds **139**～**144** however none showed significant antibacterial activity against a range of Gram-positive and

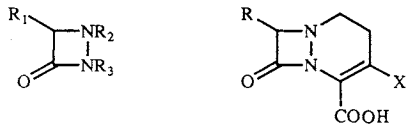
Scheme 15.



i: PPh_3, CCl_4, Et_3N, ii: H_2, Pd-C, $(PhCH_2CO)_2O$, iii: H_2, Pd-C, $(PhOCH_2CO)_2O$, iv: LiOH.

Gram-negative bacteria.

Fig. 10. Aza-β-lactams.



Bicyclic Pyrazolidinones

As part of the continued search for biologically active γ-lactam analogues of the β-lactam antibiotics workers from the Lilly Research laboratories investigated the pyrazolidinone ring as a reactive γ-lactam. Since aza-β-lactams (**145**)[15] (Fig. 10) are highly reactive and attempts to prepare appropriate bicyclic compounds **146**[16] failed they reasoned that aza-γ-lactam analogues might possess a mixture of chemical stability and acylating ability suitable for antimicrobial activity.

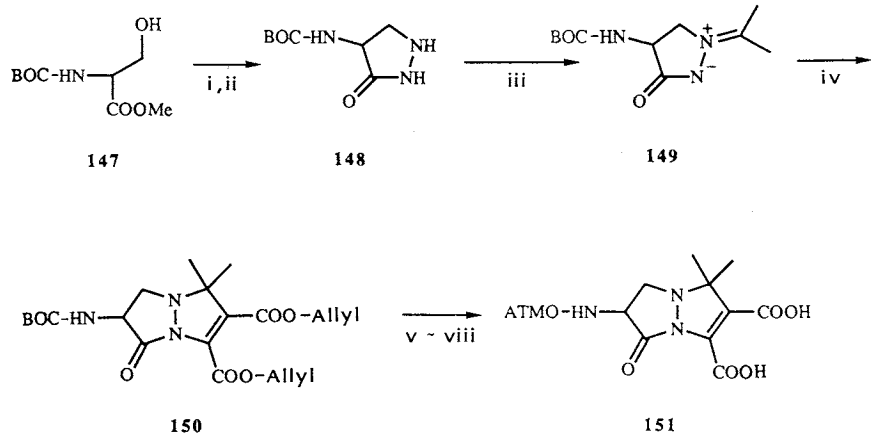
The initial chemistry involved the preparation of the bicyclic pyrazolidinone (**151**) containing the gem-dimethyl moiety in the B ring (Scheme 16).[53] It was envisaged that the 1,3-dipolar cycloaddition of a substituted acetylene to a pyrazolidinium ylide would provide the desired [3.3.0] fused bicycle. Thus treatment of the pyrazolidinone (**148**), readily prepared from diprotected D,L-serine, with 2,2-dimethoxypropane and catalytic acid yielded the dimethyl ylide (**149**).

Cycloaddition with diallyl acetylene dicarboxylate gave the bicyclic pyrazolidinone (**150**) in respectable yield. Removal of the BOC protecting group, acylation then deprotection gave the pyrazolidinone (**151**) containing an appropriate amide side chain. This compound was found to exhibit *in vitro* antimicrobial activity against *S. aureus*.

In order to more closely mimic a typical β-lactam antibiotic a bicyclic unit without the gem-dimethyl unit was preferred.[54~57] This was achieved by reaction of the monocyclic pyrazolidinone (**148**) with aqueous formaldehyde providing the azomethine imine (**152**) which was heated with the acetylene diester to give the C-4 unsubstituted bicyclic unit (**153**) (Scheme 17). Coupling of the amide side chain and deprotection gave compound **154** which showed enhanced *in vitro* antibacterial activity against a variety of Gram-positive and Gram-negative strains relative to the gem-dimethyl analogue.

The electron withdrawing ability of the C-3 substituent (Fig. 11) affects the reactivity of the

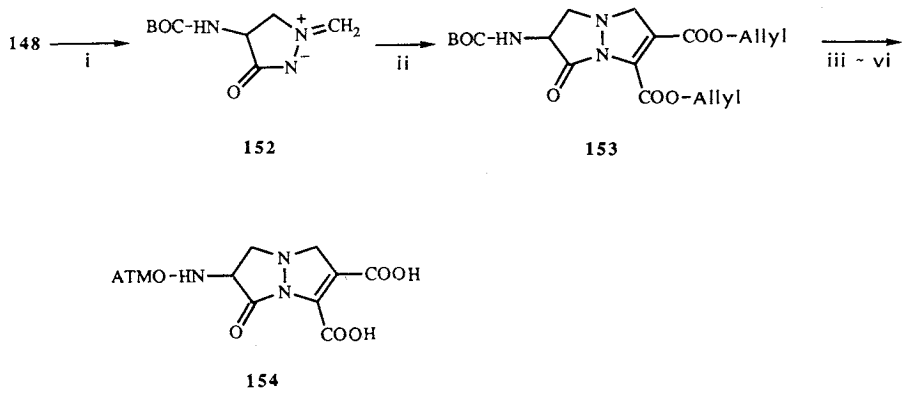
Scheme 16.



147 148 149 150 151

i: TsCl, pyridine, ii: N_2H_4, iii: 2,2-dimethoxypropane, D-10-camphorsulfonic acid, iv: diallyl acetylene dicarboxylate, v: TFA, vi: *N*-formyl ATMO-Cl, $NaHCO_3$, vii: $Pd(PPh_3)_4$, sodium-2-ethylhexanoate, viii: HCl.

Scheme 17.

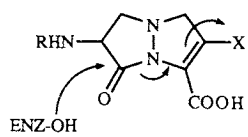


152 153 154

i: aq H_2CO, ii: diallyl acetylene dicarboxylate, iii: TFA, iv: BSTFA then *N*-allylcarbonyl-ATMO-Cl, v: $Pd(PPh_3)_4$, $Bu^n{}_3SnH$, vi: HCl.

pyrazolidinone by providing a more effective acylating agent which may result in increased antibacterial activity. In view of this the scope of the cycloaddition reaction was explored by trapping the unsubstituted pyrazolidinium ylide (**152**) with a variety of acetylenes (Scheme 18).

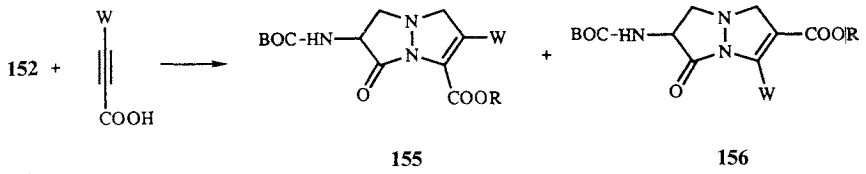
Fig. 11. Increased reactivity of a γ-lactam towards enzymatic hydrolysis by electron withdrawing groups (X).



However this approach suffered from low yields and a lack of regiocontrol. Both isomers (**155** and **156**) were generally obtained with the desired **155** often the minor product.

A substantial improvement to this methodology was achieved by employing vinyl sulfones as acetylene equivalents.[58,59] Thus formation of the cycloadducts (**157** and **158**) followed by base catalysed elimination of phenylsulfinic acid gave the desired bicyclic pyrazolidinones (**155**) with high regioselectivity (Scheme 19).

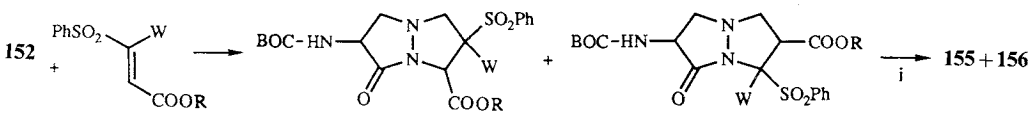
Scheme 18.



155 **156**

W = COOMe, COO-allyl, COMe, CONHPh, COPh, PO_3Me_2, CF_3, CH_2O-THP, CH_2OH, H, Ph, SPh
R = Me, ^{t}Bu, allyl

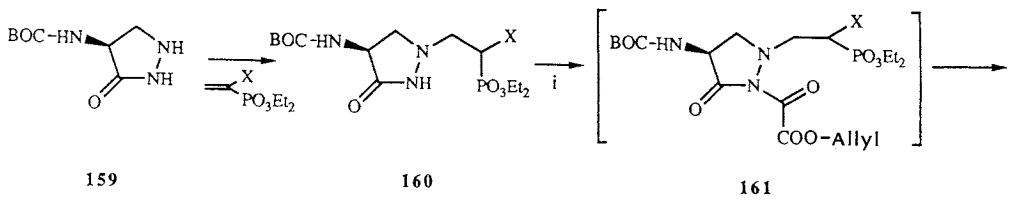
Scheme 19.



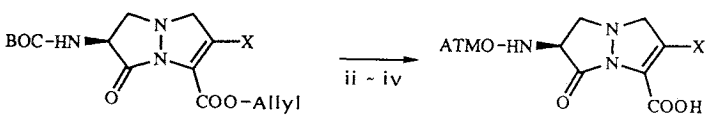
157 **158**

W = COOMe, COMe, COCOOEt, CN, H
R = ^{t}Bu, allyl

Scheme 20.



159 **160** **161**



162 **163**

i: ClCOCOO-allyl, Pr^i_2NEt (2 equiv), ii: HCl, HOAc, ii: *N*-allyloxycarbonyl-ATMO-OH, $POCl_3$, NMM, iv: $Pd(PPh_3)_4$, Bu^n_3SnH.

More recently the bicyclic unit has been prepared *via* an intramolecular Wadsworth-Horner-Emmons condensation.[60~62] The three conditions of regioselectivity, variability of the C-3 substituent and preservation of chirality at C-7 were satisfied. Conjugate addition of the chiral pyrazolidinone (**159**) to the vinyl phosphonate provided the *N*-alkylated product (**160**) (Scheme 20). Subsequent acylation of the amide nitrogen and the addition of 2 equivalents of base instigated ring closure to the bicyclic compounds **162**. Elaboration of the C-7 side chain gave bicyclic pyrazolidinones (**163**) suitable for biological evaluation.

Bicyclic pyrazolidinones (**163**), where X is electron withdrawing (relative to X = COOH), were indeed found to possess greater antimicrobial activity than the diacid (**154**) (Table 1). A study of the activities of the methyl ester (X = COOMe) and acetyl (X = COMe) derivatives[63] showed both to have broad spectrum

antibacterial activity however both were susceptible to inactivation by β-lactamases (only the acetyl derivative was inactivated by *Enterobacter cloacae* 265A).

An investigation of the rates of hydrolysis of the bicyclic pyrazolidinones as a measure of their acylating ability[64] showed a correlation between the rate of reaction with hydroxide ion and antimicrobial activity. The rates of γ-lactam ring opening also correlate with the C-3 substituent constants (σ). Thus the cyano (X=CN) and methyl sulfone ($X=SO_2Me$) analogues revealed greater potency as expected, the latter exhibiting greater overall activity.

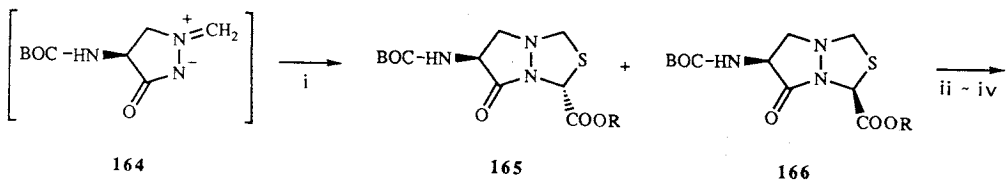
Investigations into structural changes of the [3.3.0]bicyclic pyrazolidinone unit, other than variation of the C-3 substituent, included replacement of C-3 with sulfur, ring enlargement to the [4.3.0]pyrazolidinones and modification of the C-7 side chain.

Reaction of the optically pure intermediate pyrazolidinium ylide (**164**) with a thioaldehyde equivalent gave the two diastereoisomers (**165** and **166**) (Scheme 21). These were transformed to the target molecules (**167** and **168**) however neither isomer exhibited antibacterial activity.[65]

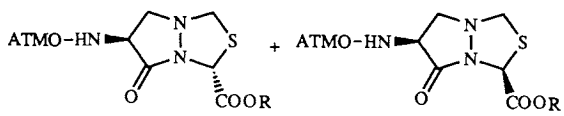
Table 1. Antibacterial activity of bicyclic pyrazolidinones (**163**).

163 X	MIC (μg/ml)		
	Streptococcus pyogenes C 203	*Klebsiella pneumoniae* X68	*Providencia rettgeri* C24
SO_2Me	0.25	0.25	0.06
CN	0.5	0.5	0.25
COMe	0.5	2	0.25
COOMe	4	8	1
$CONHC_6H_5$	1	32	8
COOH	8	64	8
2-Thiophene	>128	>128	>128
C_6H_5	>128	>128	>128

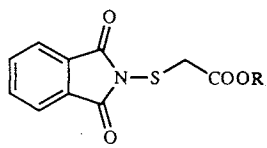
Scheme 21.

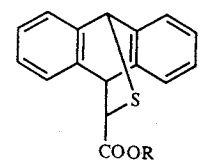


164 **165** **166**



167 **168**





169 **170**

i: **169** or **170**, ii: TFA, iii: ATMO-BT, iv: $Pd(OAc)_2$, PPh_3, sodium-2-ethylhexanoate.

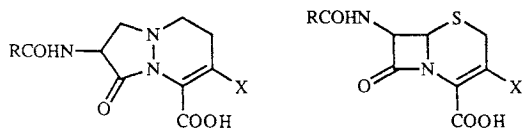
The [4.3.0]byclic pyrazolidinones (**171**) were seen to resemble the cephalosporin skeleton (**172**) (Fig. 12).[66]

Thus compounds **176** were synthesised in the following manner (Scheme 22). Selective alkylation of N-1 of the monocyclic nucleus (**148**) provided the ester (**173**). Reduction to the alcohol and iodination *via* the mesylate gave a suitable precursor (**174**) for cyclisation with an acetylene or acetylene equivalent. Thus Michael addition of N-2 to the vinyl sulfoxides (**177**) followed by ring closure and elimination of phenylsulfinic acid gave the desired bicyclic units (**175**). These were transformed to potential antibiotics (**176**) however neither showed significant antibacterial activity.

The carbapenems PS-5 (**178**)[67] and thienamycin (**179**)[68] (Fig. 13) are potent antibiotics which do not possess the typical C-7 acylamino side chain. The [3.3.0]bicyclic pyrazolidinones (**183**) with the same alkyl or substituted alkyl side chains were prepared (Scheme 23).[69]

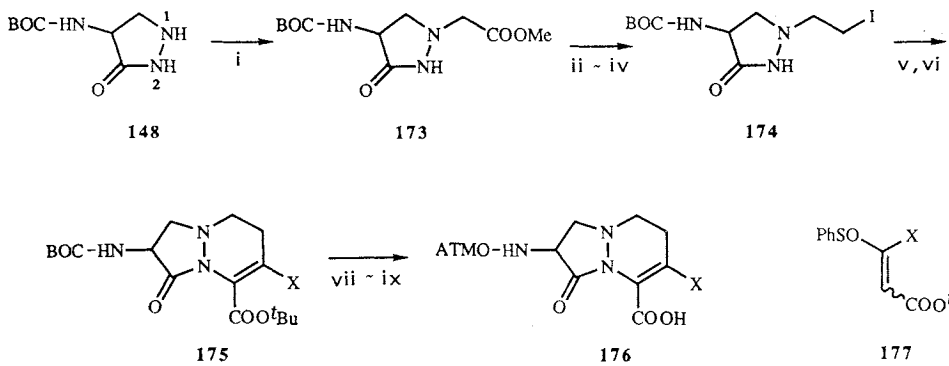
The substituted acrylates (**180**) were condensed with hydrazine and the pyrazolidinium ylides (**181**) formed *via* reaction with aqueous formaldehyde. Reaction with an acetylene or acetylene equivalent followed by deprotection yielded the bicyclic compounds **183**. Of these the cyano derivative was the most potent but all exhibited significantly reduced antibacterial activity relative to **163** (X=COMe).

Fig. 12. Bicyclic[4.3.0]pyrazolidinone analogue (**171**) of cephalosporins (**172**).



171 **172**

Scheme 22.



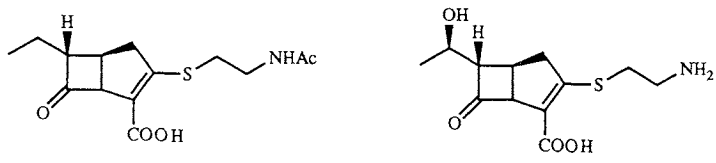
148 **173** **174**

175 **176** **177**

X=COOMe, COMe

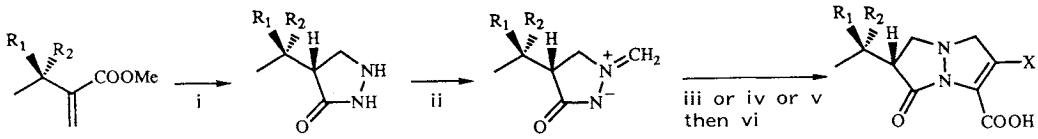
i: NaH, $BrCH_2COOMe$, ii: $NaBH_4$, LiCl, diglyme, iii: MsCl, Et_3N, iv: NaI, v: NaH, **177**, vi: DBU, vii: TsOH, viii: ATMO-BT, Pr^i_2NEt, ix: TFA.

Fig. 13. Carbapenem antibiotics PS-5 (**178**) and thienamycin (**179**).



178 **179**

Scheme 23.



180 181 182 183

184 185

R_1, R_2=H X=COOH, COMe
R_1=H R_2=OH X=COOH, COMe
R_1=OH R_2=H X=COOH, COMe, CN

i: N_2H_4, ii: aq H_2CO, iii: diallyl acetylene dicarboxylate, iv: **184**, NMM, v: **185**, vi: $Pd(OAc)_2$, PPh_3, sodium-2-ethylhexanoate.

7-Unsubstituted pyrazolidinones (**186**)[70] also were synthesised by cycloaddition chemistry (Fig. 14).

Some of these compounds showed moderate to good antibacterial activity. However, no β-lactamase inhibitory properties were reported.

Lactivicins

Using hypersensitive screening methodology[71] Takeda workers discovered lactivicin (LTV: **187**)[72,73] as well as novel β-lactam antibiotics (*e.g.* sulfazecins,[74] cephabacins[75~78] and formadicins[79,80]) of bacterial origin. LTV was isolated from culture filtrates of *Empedobacter lactamgenus* YK-258 and *Lysobacter albus* YK-422. It has the structure [4*S*]-2-(4-acetylamino-3-oxo-isoxazolidinyl)-5-oxo-tetrahydrofuran-2-carboxylic acid,[81,82] whereby an isoxazolidinone moiety and a γ-lactam ring are connected by a single C-N bond. LTV exists as an equilibrium mixture of two epimers in the ratio 53:47 (A:B) (Fig. 15).

The structure contains a cycloserine nucleus, the D-form of which is an antibacterial agent (oxamycin and orientomycin)[83,84] in itself and has been used in the treatment of severe pulmonary tuberculosis. LTV is a non-β-lactam antibiotic having properties[85] previously considered exclusively characteristic of β-lactam antibiotics:

Fig. 14. 7-Unsubstituted[3.3.0]pyrazolidinones (**186**).

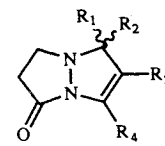
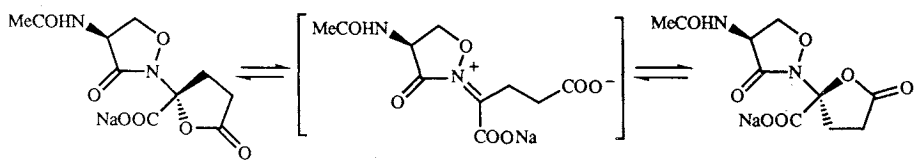


Fig. 15. Lactivicin equilibrium structures.



187A 187B

1) It binds to the essential PBPs,[86] the target proteins of β-lactams[17] (the first non-β-lactam having this affinity).
2) Is highly susceptible to various cephalosporinases and penicillinases.
3) Induces β-lactamase activity.
4) Shows much higher activity against β-lactamase hypersensitive mutants of *E. coli* and *Pseudomonas aeruginosa* than against their parents.
5) Is active against anaerobic bacteria but not mycoplasma or fungi.

Moreover LTV has weak inhibitory activity against a number of β-lactamases and at least two types of activity against *E. coli*; one is that of β-lactam antibiotics (special inhibition of peptidoglycan synthesis) and the other may be inhibition of SH-proteins involved in fundamental membrane functions.

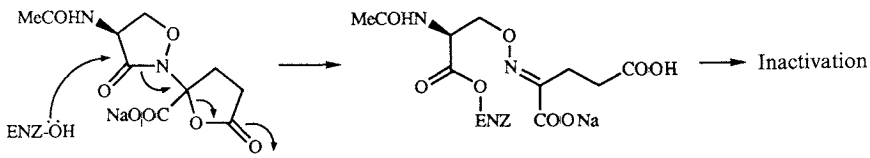
The mode of action of LTV is very similar to that of β-lactam antibiotics and is believed to involve irreversible acylation of the PBPs yielding an acylase enzyme with concomitant opening of the γ-lactone ring. The resultant oxime (**188**) may subsequently degrade further (Fig. 16).[81,85,86]

Since LTV possesses only moderate antibacterial activity[85] (Table 2) and in order to overcome its relatively strong toxicity on parental administration[72] structural modifications were necessary.

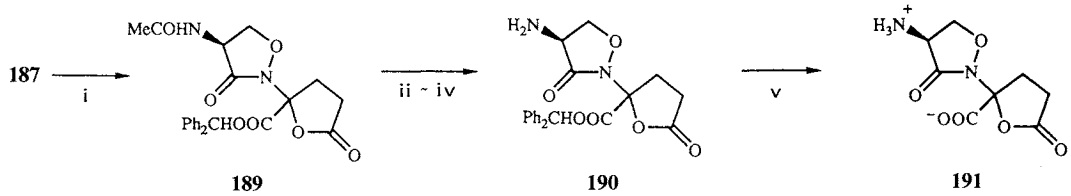
The initial work consisted of the development of a direct route to the LTV nucleus, 4-aminolactivicinic acid (4-ALA: **191**) (Scheme 24).[72,87]

4-ALA was also prepared by formal total synthesis.[88] Selective esterification of 2-oxoglutaric acid and reaction with the cycloserine (**194**) afforded the desired condensation product (**195**) (Scheme 25).

Fig. 16. Proposed mode of action of lactivicin.

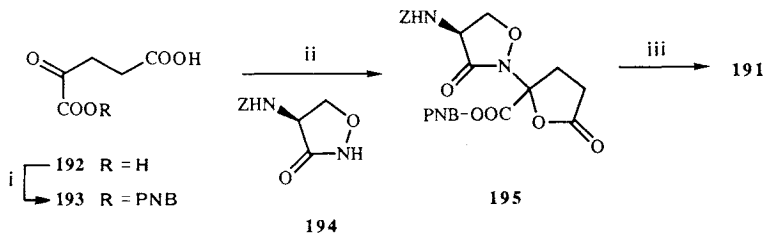


Scheme 24.



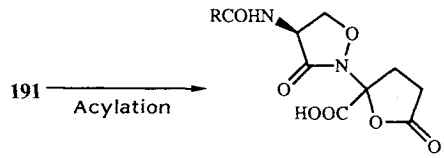
i: Ph_2CN_2, ii: PCl_5, pyridine, iii: MeOH, iv: H^+, v: H_2, Pd-C.

Scheme 25.



i: PNB-Br, $(C_6H_{11})_2NH$, ii: DCC, iii: H_2, Pd-C.

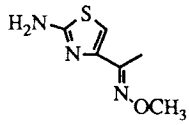
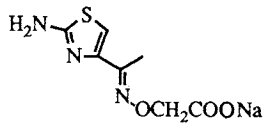
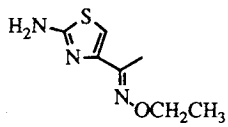
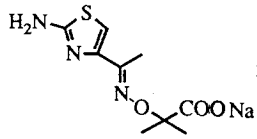
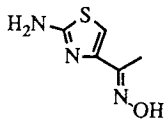
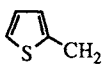
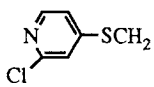
Scheme 26.



196

Acylation methods: i, RCOOH, DCC, HO-BT, DMF; ii, RCOCl, DMA, DCM; iii, RCOCl, $NaHCO_3$, H_2O, Et_2O; iv, RCOS-BT, DMF, THF.

Table 2. Antibacterial activity of lactivicin derivatives (**196**).

	R	*In vitro* MIC (μg/ml)						
		S.a FDA 209P	*E.c.* NIHJ JC-2	*E.c.* O 111	*C.f.* IFO 12681	*K.p.* DT	*S.m.* IFO 12648	*P.v.* IFO 3988
196A	CH_3	3.13	100	100	100	100	>100	100
196B		12.5	1.56	0.39	3.13	0.78	3.13	0.78
196C		100	0.78	<0.1	0.78	0.39	0.78	0.39
196D		6.25	0.39	0.2	0.78	0.39	1.56	0.39
196E	$PhCH_2$	0.2	6.25	3.13	12.5	3.13	50	100
196F	$PhOCH_2$	0.39	50	6.25	50	25	>100	12.5
196G		>100	0.78	<0.1	0.78	0.2	0.39	<0.1
196H		1.56	3.13	1.56	3.13	3.13	6.25	3.13
196I		0.39	6.25	3.13	12.5	6.25	>100	6.25
196J		<0.1	12.5	3.13	100	12.5	>100	6.25
	D-Cycloserine	12.5	25	—	50	—	>100	100

Abbreviations: *S.a.*, *Staphylococcus aureus*; *E.c.*, *Escherichia coli*; *C.f.*, *Citrobacter freundii*; *K.p.*, *Klebsiella pneumoniae*; *S.m.*; *Serratia marcescens*; *P.v.*, *Proteus vulgaris*.

Hydrogenolysis gave the key intermediate (**191**) for preparing LTV derivatives.

With 4-ALA (**191**) in hand the chemistry developed for the modification of 6-aminopenicillanic acid (6-APA), 7-aminocephalosporanic acid (7-ALA) and 3-aminomonobactamic acid (3-AMA) was applied for the preparation of a range of LTV derivatives for biological evaluation (Scheme 26).[72,88,89]

Table 2 contains MIC values for the most active derivatives (for comparison MIC data for LTV and D-cycloserine[85] are also included).

Active esters of the highly *in vitro* active compounds **196B** and **196I** were prepared for *in vivo* use and were found to have improved protective effects after oral administration compared with their parents.[89]

Since D-cycloserine itself is a cell-wall biosynthesis inhibitor we reasoned that the cycloserine nucleus may be the only structural requirement for antibacterial activity thus derivatives lacking the γ-lactone moiety were prepared.[90]

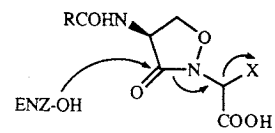
In our laboratory we envisaged that cleavage of the γ-lactam ring would result in elimination of the leaving group (X) (Fig. 17) in a similar manner to that proposed for LTV itself.

Alkylation of the lithium salt of the cycloserine (**197**) with allyl chloro-2-ethoxyacetate afforded the epimeric ethers (**198**) (Scheme 27). Palladium catalysed protecting group removal gave the diastereoisomers (**199**) separable by HPLC.

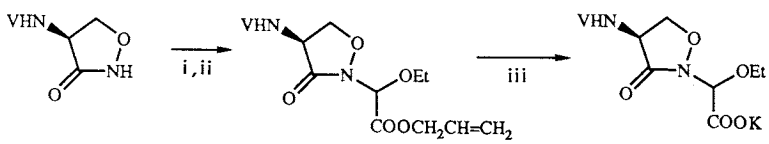
Neither of the epimers (**199**) displayed antibacterial activity against *E. coli* X580 or *S. aureus* NCTC 6571.

In addition the preparation of an enamine (**201**) was carried out.[90] We considered that delocalisation of the nitrogen lone pair might activate the γ-lactam towards nucleophilic attack by the enzyme. Cycloserine (**197**) was treated with base followed by an acetylene dicarboxylate then quenching with acetic acid yielded a single diastereoisomer (unassigned) (**200**) (Scheme 28). Deprotection and HPLC purification provided the diammonium salt

Fig. 17. Increased reactivity of cycloserine derivatives by electron withdrawing groups (X).



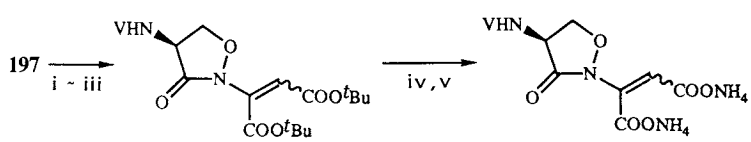
Scheme 27.



197 **198** **199**

i:LDA, ii: allyl chloro-2-ethoxyacetate, iii: $Pd(PPh_3)_4$, PPh_3, potassium 2-ethylhexanoate.

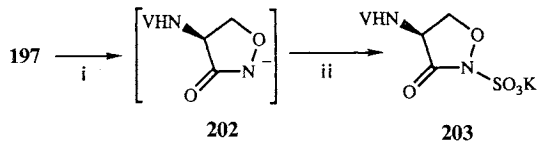
Scheme 28.



200 **201**

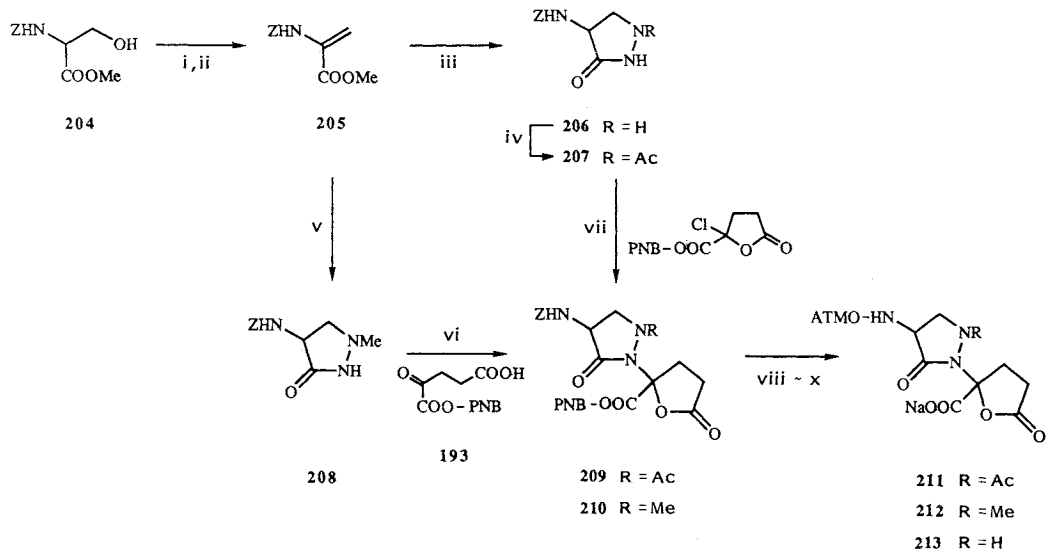
i: LDA, ii: di-^{t}Bu-acetylene dicarboxylate, iii: AcOH, iv: TFA, anisole, v: HPLC.

Scheme 29.



i: LDA, ii: $SO_3 \cdot DMF$.

Scheme 30.



i: PCl_5, ii: DBU, iii: $N_2H_4 \cdot H_2O$, iv: Ac_2O, v: CH_3NHNH_2, vi: DCC, vii: NaH, viii: H_2, Pd-C, ix: $ClCH_2CO$-ATMO-Cl, x: $CH_3NHCSSNa$.

(**201**) which showed only low activity against the above strains.

A γ-lactam analogue of the monobactams also was prepared[91] in our laboratories. Such an *N*-sulfonyl L-cycloserine derivative bearing a penicillin-type side chain might be activated towards acylation due to the cumulative effects of the two electronegative substituents on the amide nitrogen.

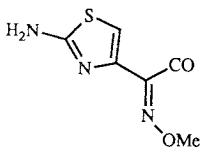
Deprotection of cycloserine (**197**) followed by electrophilic sulfonation and ion exchange chromatography gave compound **203** which proved to be inactive against a number of organisms (Scheme 29).

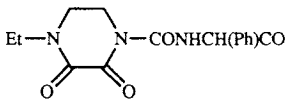
Takeda workers prepared aza analogues of LTV,[92] molecules related to the bicyclic pyrazolidinone antibacterials (previous chapter). Conversion of protected serine (**204**) to the acrylic ester (**205**) was followed by treatment with hydrazine hydrate then acetylation gave pyrazolidinone (**207**) (Scheme 30). Similarly treatment of **205** with methylhydrazine gave **208**. After addition of the lactone unit to give **209** and **210** deprotection and acylation provided the *N*-substituted compounds **211** and **212**. The unsubstituted **213** was produced *via* similar chemistry and exhibited weak activity against *E. coli* O 111 and *S. pyogenes* E-14 whereas **211** and **212** showed none.

Abbreviations

acac: Acetylacetonate, BSTFA: bis(trimethylsilyl)-trifluoroacetimide, Bn: benzyl, BT: benzotriazole, mCPBA: *m*-chloroperoxybenzoic acid, CAN: ceric ammonium nitrate, CDI: 1,1'-carbonyldiimidazole,

DCC: 1,3-dicyclohexylcarbodiimide, DMB: 2,4-dimethoxybenzyl, DMS: dimethyl sulfide, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMA: *N*,*N*-dimethyl acetamide, EEDQ: 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinone, G: phenylacetyl, LDA: lithium diisopropylamide, Ms: mesyl, NMM: *N*-methyl morpholine, PNB: *p*-nitrobenzyl, PNZ: *p*-nitrobenzyloxycarbonyl, THP: tetrahydropyranyl, TMS: trimethylsilyl, Ts: tosyl, V: phenoxyacetyl, Z: benzyloxycarbonyl.

ATMO: 

EPPA: 

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