The synthesis of natural β-lactam antibiotics

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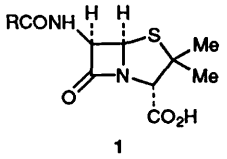
Reviewing the literature published up to February 1994

1 Introduction

Up to 1970 most β-lactam research was concerned with the penicillin **1** and cephalosporin **2** families of antibiotics.[1] In 1970 elucidation of the structure of the β-lactamase stable cephamycins **3**[2] was quickly followed by the isolation from natural sources of several new β-lactams structurally distinct from the penicillins and cephalosporins. These were the nocardicins **4**,[3] clavulanic acid **5**,[4] thienamycin **6**[5] and the olivanic acids **7**.[6] This diversity of structural types, coupled with potent antibacterial or β-lactamase inhibitory activity, provided a new incentive for expansion in the area of β-lactam chemistry directed



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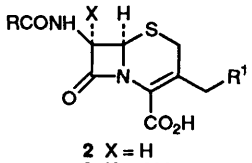
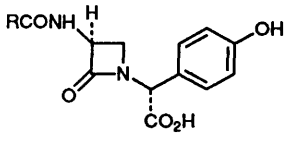


2 X = H
3 X = OMe



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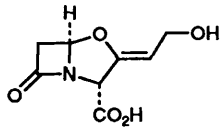

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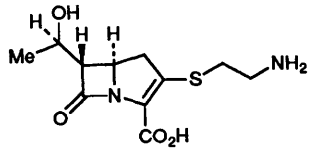
towards semi- or total-synthesis of these new agents and analogues. Over the next two decades these efforts saw the emergence of many new methodologies for the synthesis of such structures, involving aspects of stereo control, β-lactam ring construction and protecting group strategies.

Subsequently, the isolation of the so called monobactams **8** from bacterial sources provided a further impetus to synthesis in the area.[7,8] More recently the cephabacins **9**[9] and formadicins **10**[10] have provided further variations of naturally occurring cephalosporins and monocyclic structures.

In addition to the discovery of these new natural products a substantial effort has been devoted to the synthesis of numerous β-lactams of various structural



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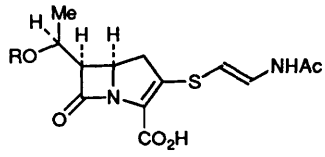

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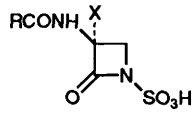
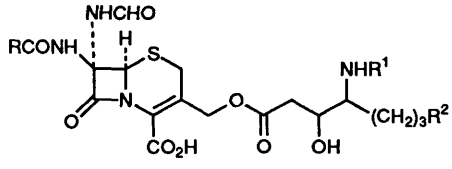


8 X = H, OMe



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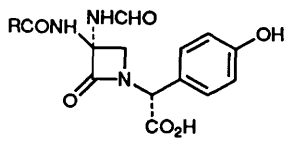

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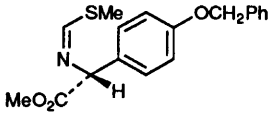
types which have not been found in nature. Although these do not strictly fall within the scope of this review, significant structures of synthetic interest have been included.

2 Monocyclic β-lactams

2.1 Nocardicins

While semi-synthetic approaches to the nocardicins from penicillin derived β-lactams have been described,[11,12] only the totally synthetic methods are covered here. One of the first made use of the classical keten-imine reaction for the construction of the β-lactam **12** by reaction of phthalimido acetyl chloride with the thioimidate **11**. Subsequent removal of the *S*-substituent and deprotection afforded 3-aminonocardicinic acid **13** which could be acylated to afford nocardicins A and D.[13] The Lilly group reported a synthesis starting from the L-cysteine derived thiazolidine **14** followed by one of the first examples of N–C-4 bond ring closure *via* the chloride **15**.[14]



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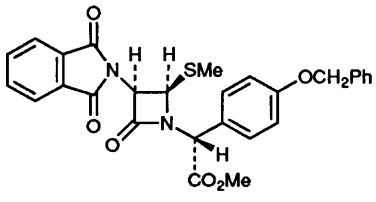

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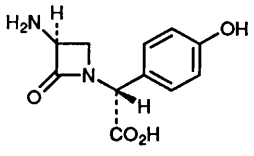

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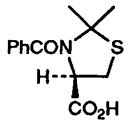

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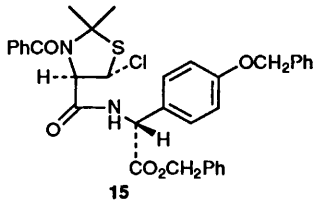

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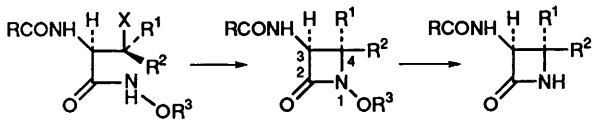
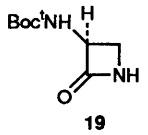
A much more direct synthesis of functionalized β-lactams involving the biomimetic N–C-4 cyclization approach is by the highly versatile and widely used hydroxamate method developed by Miller.[15] Further, it provides the opportunity to use readily accessible chiral amino-acids to form the β-lactam. Whereas N–C-4 cyclizations of amino-acids with β-leaving groups are normally low yielding due to competing side-reactions such as elimination or racemization, the Miller synthesis provides a high yielding process which is applicable to almost any β-lactam. The key to this approach lies in the selective intramolecular displacement of X in intermediates **16** by the nitrogen atom of the hydroxamic acid derivative giving the azetidinone **17** with inversion of configuration at C-4 and retention at C-3. Thus, base-catalysed cyclization of β-halo hydroxamates or use of the Mitsunobu procedure readily provided good yields of the cyclic products **17** ($R^3 = CH_2Ph$).[16] Conversion to the free *N*-hydroxy β-lactam **17** ($R^3 = H$) was followed by reduction with $TiCl_3$[17] to provide an efficient synthesis of β-lactams **18** and applicable to a wide variety of structural variations.



16 **17** **18**

This methodology was used by Miller for the synthesis of the nocardicin ring-system starting from tBoc-L-serine. This provided β-lactam **19**, which on treatment with the diazophenylacetate **20** and rhodium acetate gave a mixture of C-5 disastereoisomers from which the protected 3-aminonorcardicinic acid (3-ANA) nucleus could be separated. Fortunately, the wrong diastereoisomer of **21** could be isomerized with base to allow almost complete conversion into **21** in an overall yield of 45% from the protected amino-acid.[18]



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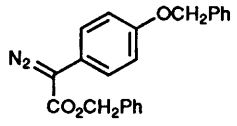

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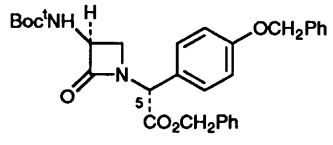

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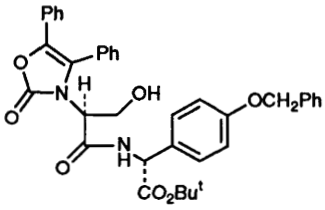
The total synthesis of nocardicins A–G, also by a biomimetic N–C-4 ring closure has been comprehensively described by Townsend.[19] In this case intermediate **22** was cyclized smoothly in a modified Mitsunobu cyclodehydration procedure, substituting triethylphosphite for triphenylphosphine to give a high yield of cyclic product with virtually none of the opposite C-5 diastereoisomer which has plagued many other approaches, even under the mildest conditons of cyclization such as demonstrated by Hanessian using the imidazoylsulfonate leaving group.[20] The use of the 4,5-diphenyl-4-oxazoline-2-one (Ox) protecting group for nitrogen also showed several advantages compared to the more conventionally used phthalimido, being readily removed by hydrogenation with less competing side-reactions. Differential deprotection of the cyclic product provided **23** which by a variety of procedures,



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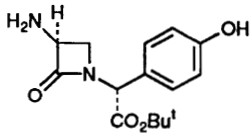

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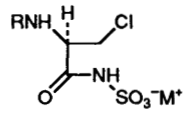
using the appropriate side-chains, was converted into the natural nocardicins A–G. For example, nocardicin A was produced in an overall yield of 22% from L-serine and D-(*p*-hydroxyphenyl) glycine.

2.2 Monobactams

As in the case of the nocardicins, initial approaches to the monobactams were from penicillin derived β-lactams.[21] Total synthesis of the naturally occurring nucleus **25** was achieved by direct base-catalysed cyclization of the acyl sulfamate **24**.[22]



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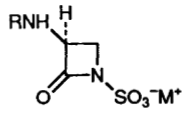

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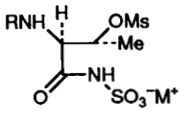
With the monobactams, however, it was found that non-naturally occurring C-4 substituted β-lactam derivatives showed some advantage in their biological properties compared to the natural products. Thus, cyclization of the threonine derived mesylate **26** and deprotection gave 3-amino-4-methylmonobactamic acid **27** from which the highly potent antibiotic aztreonam **28** was obtained.[23]



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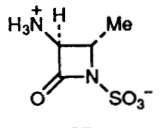

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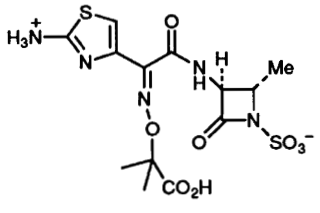

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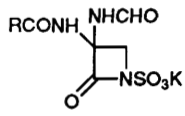
2.3 Formadicins

Of the most recently discovered naturally occurring 3-formamido substituted nocardicins of type **10**, no syntheses have been reported, although formamido monobactam analogues **29** have been synthesized from the penicillin derived sulfone **30**.[24] A wide ranging review of the synthesis of many other analogues of the nocardicins and monobactam family has also been published.[25]



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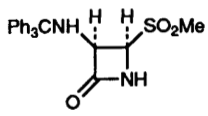

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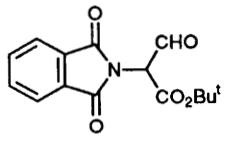
3 Penicillins and cephalosporins

3.1 Penicillins

The first synthesis of a natural penicillin (potassium penicillin V) was described by Sheehan in 1957 following his early pioneering work in this area.[26] Condensation of **31** with D-penicillamine **32** to give **33** was followed by progression to the penicilloate **34** which was cyclized to the natural product **35** using the then newly introduced DCCI (dicyclohexylcarbodiimide) reagent. Subsequent reports outlined the application of such methods to the general synthesis of penicillins.[27] Keten-imine cycloaddition reactions for β-lactam construction as used by Bose also allowed the construction of the penicillin ring-system but gave the unnatural 5,6 *trans*-configuration of the β-lactam protons.[28]



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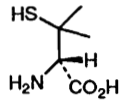

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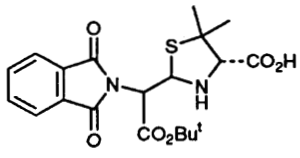
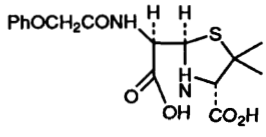


33 (diastereoisomers separated)



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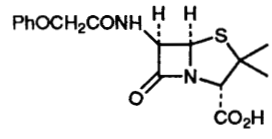

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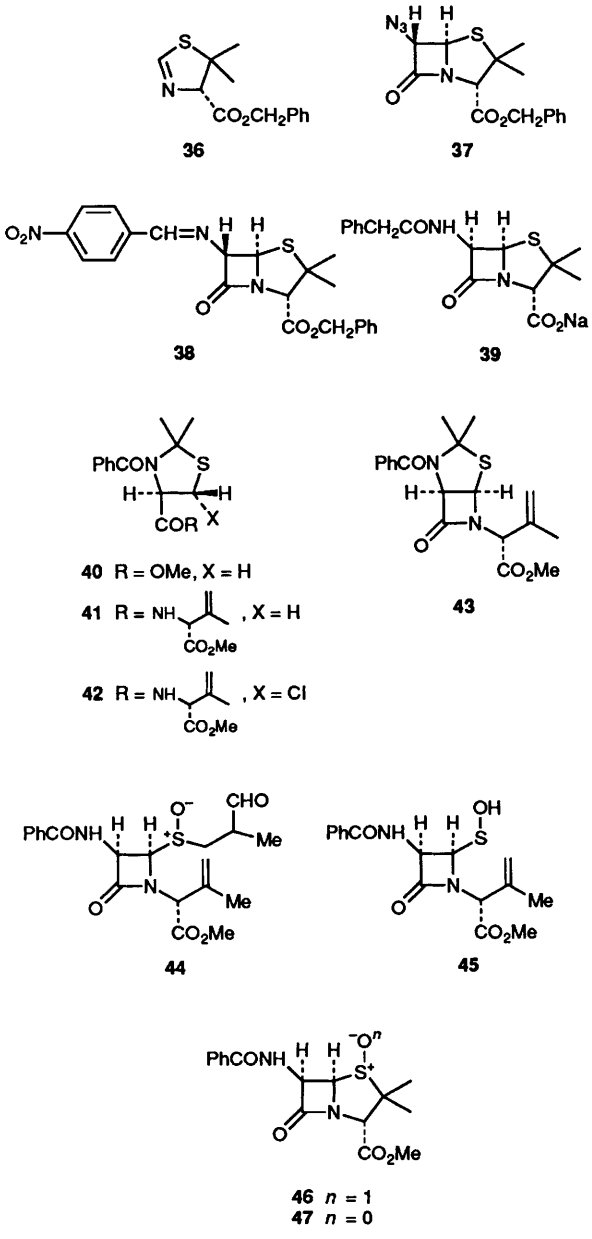
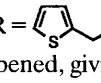
However, a method for correcting this stereochemistry was developed by the Merck group and used in a total synthesis of Penicillin G.[29] Thus, using the keten derived from azido-acetyl chloride and the chiral thiazoline **36** yielded (98%) the α-azido bicyclic system **37**. Elaboration to the Schiff's base **38** allowed ready deprotonation at the C-6 position. Subsequent kinetic reprotonation provided a 2:1 ratio of *cis*:*trans* β-lactam isomers which could be progressed and separated to give synthetic penicillin G **39**.

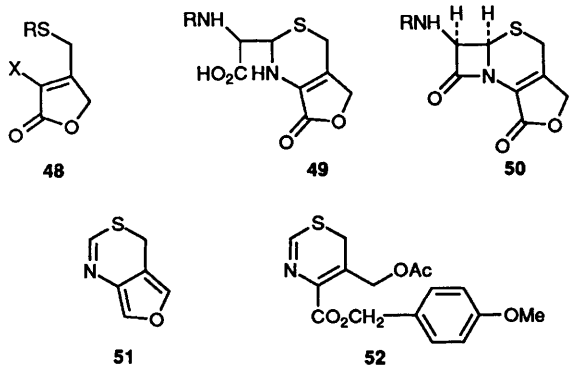
The only highly stereoselective synthesis of the penicillin ring-system remains that described by Baldwin in 1976, using the peptide precursor **41** obtained from the cysteine derived thiazolidine **40** and D-isodehydrovaline methyl ester.[30] Base-catalysed cyclization of the chloride **42** to **43** was followed by a multi-step conversion into the sulfoxide **44**. Generation of the sulfenic acid **45** resulted in



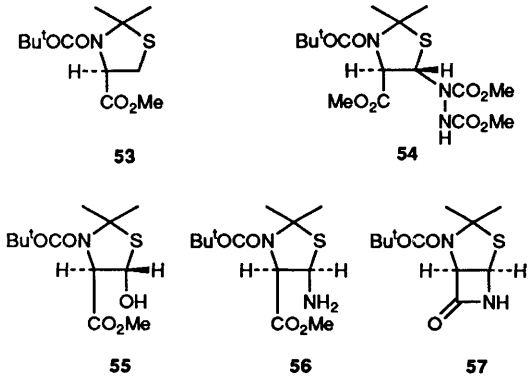
ring-closure to the sulfoxide **46** which on deoxygenation gave the penicillin ester **47**.

3.2 Cephalosporins

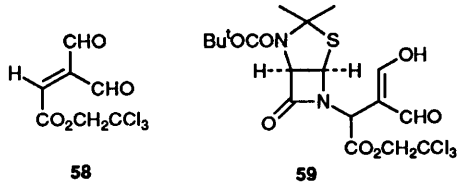
While a large number of nuclear analogues of the cephalosporin ring-system have been synthesized, approaches to the natural products have been limited, the major emphasis being focused on acylamino-derivatives of 7-amino-cephalosporanic acid (7-ACA). Both the Squibb[31] and Roussel[32] groups used intermediates of type **48** to produce the amino-acid **49** which could be cyclized as in the Sheehan penicillin synthesis to provide the cephalosporin lactone ring-system **50**. Deprotection and acylation of the amino-function provided **50** (R = ) in which the lactone ring could be opened, giving deacetylcephalothin.[33] Another approach to the lactone made use of the cycloaddition reaction between the thiazine **51** and the keten generated from azido-acetyl chloride.[34] In a similar manner the Merck group used thiazine **52** to complete a total synthesis of racemic cephalothin.[35]



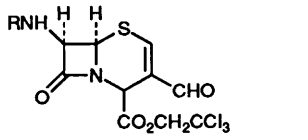
In contrast to these approaches the earlier total synthesis of cephalosporin C described by Woodward in 1966 provides one of the classic examples of natural product synthesis.[36,37] Protection of the nitrogen, sulfur, and carboxylic acid functions of L(+)-cysteine provided the cyclic intermediate **53** which was ideally suited for introduction of the amino-function—this in turn was to become the nitrogen atom of the key β-lactam intermediate **57**. This was achieved in a stereocontrolled manner by introduction of the hydrazino-substituent **54** followed by oxidation and conversion into the *trans*-hydroxy ester **55**. Conversion into the mesylate, inversion of the stereochemistry by displacement with azide, and reduction gave the β-amino-ester **56** which was cyclized to the β-lactam **57** using triisobutylaluminium, the stereochemistry being confirmed by *X*-ray crystallography.



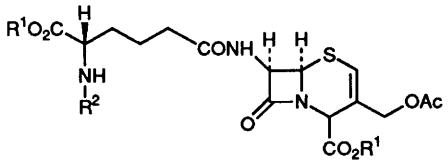
Addition of **57** in a Michael-like manner to the dialdehyde **58** to form **59** was followed by treatment with trifluoroacetic acid to remove both nitrogen and sulfur protecting groups and effect cyclization to the bicyclic cephalosporin precursor **60**. The amino group was acylated with the protected D-α-amino adipic acid side-chain in forming **61**. Reduction, acylation of the primary hydroxyl, and equilibrium provided the cephalosporin C ester **62**. The then novel and subsequently much used trichloroethyl protecting groups were removed using zinc to give the free acid **63** (identical with authenic natural cephalosporin C).



58 59

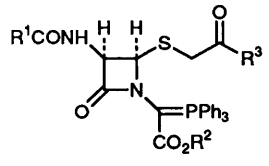


60 R = H
61 R = $Cl_3CCH_2O_2C$, H, $(CH_2)_3CO$, NH, $CO_2CH_2CCl_3$



62 $R^1 = CH_2CCl_3$, $R^2 = CO_2CH_2CCl_3$
63 $R^1 = R^2 = H$

Although not directed specifically towards natural product synthesis, many subsequent outstanding contributions were made by the Woodward group to the area of β-lactam chemistry. None more so than the intramolecular phosphorane cyclization methodology initial developed for constructing novel cephalosporins **65** from **64**,[38] and then the highly active hybrid penicillin-cephalosporin penem ring system **67** by way of **66**.[39] This mild, neutral, and high yielding method has been universally used for constructing an immense variety of bicyclic β-lactam ring-structures over the past twenty years.



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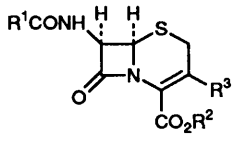

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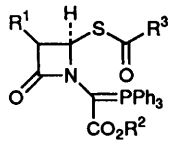

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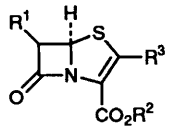

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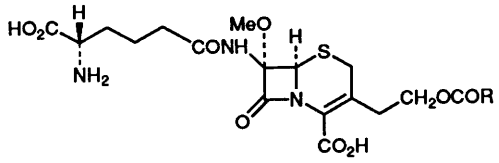
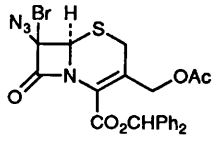


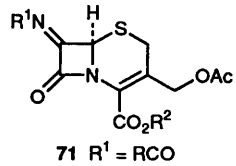
68 R = Me
69 R = NH_2

the α-amino-adipic acid side-chain but vary in the substitution pattern at C-3. As a family they are intrinsically more resistant to degradation by β-lactamases compared to the unsubstituted compounds. As in the case of cephalosporins one of the main areas of chemistry has been concerned with the introduction of new acyl-amino side-chains. However, much effort has also been devoted to methods for synthesizing the 7(α)-methoxy cephalosporin ring-system present in the natural products.

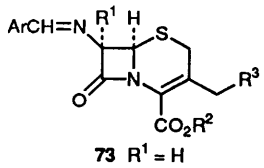
Initial approaches were based on the displacement of halogen from intermediates such as the bromo-azide **70** derived from the C-7-diazo intermediate.[42] Many other methods were subsequently developed for the stereoselective addition of methoxide to acylimine intermediates such as **71**,[43] while addition to sulfenimines **72** is also possible.[44] A common methodology is to use a Schiff's base **73** to facilitate C-7 anion formation, followed by reaction with an electrophile such as methyl methanethiosulfonate to provide **74**. Introduction of the acylamino side-chain followed by solvolysis in methanol in the presence of a mercury salt gives the methoxycephem in good yield.[45–48] Other methods of generating imines followed by addition of methanol make use of **75**[49] and the quinonoid intermediate **76**.[50] In all cases, addition to the imine is from the less-hindered face of the bicyclic ring-system to provide the required α-orientation of the methoxy substituent.



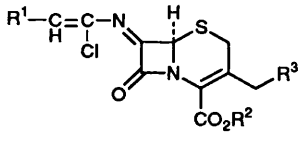
70



71 R^1 = RCO
72 R^1 = RS



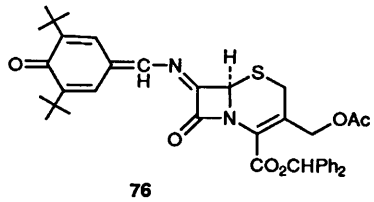
73 R^1 = H
74 R^1 = SMe



75

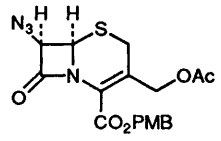
3.3 Cephamycins

In 1971 the isolation and structural elucidation of two naturally occurring cephalosporins **68** and **69** possessing a 7α-methoxy group was reported.[40] Further examples of this type of natural product were subsequently obtained from a variety of Streptomycete strains.[41] Known as the cephamycins, they all possess



76

Cycloaddition using the previously described thiazine **52** and the keten from azido-acetyl chloride produced the azido-cephem **77**, which was progressed to the thiomethyl derivative **78**. This was ideally suited for conversion into **79** and ultimately to provide a total synthesis of (±) cefoxitin **80**.[35]



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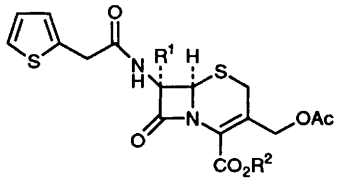
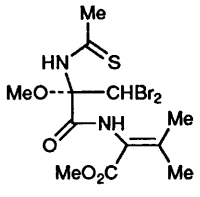


78 R^1 = SMe, R^2 = PMB (*p*-methoxybenzyl)
79 R^1 = OMe, R^2 = PMB
80 R^1 = OMe, R^2 = H

The only other total synthesis of a methoxylated cephalosporin is that reported by Kishi[51] and mimics a possible biogenetic route for β-lactam synthesis.[52] *N*-Acetyl-bromodehydroalanine t-butyl ester was converted in five steps into the bromothioamide **81**. This was successfully used in a double cyclization to give the β-lactam thiazoline **82**. The allylic bromide **83** could then by cyclized to **84** by merely allowing a methylene chloride solution of the bromide to evaporate to dryness at room temperature over three days.



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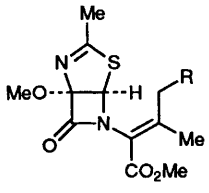
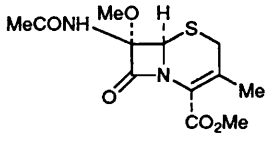
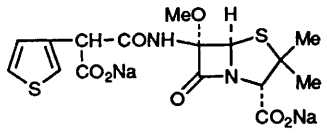


82 R = H
83 R = Br



84

Although not discovered as natural products, considerable effort has also been devoted to the synthesis and development of 6(α)-methoxy substituted penicillins such as temocillin **85** and other variants,[53,54] while mention must also be made of the methoxylated oxacephem moxalactam **86** developed by Shionogi and Lilly, using a multi-stage synthesis starting from the penicillin nucleus.[55]



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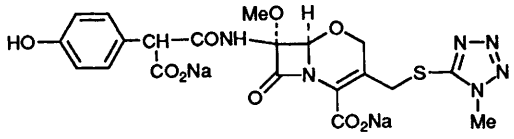
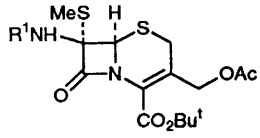


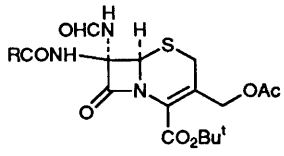
86

3.4 Cephabacins

In 1984 several groups reported on the isolation of naturally occurring 7(α)-formamido substituent cephalosporins **9** from bacterial sources.[9,56,57] Interestingly, during the course of examining a range of 6(α)-substituted penicillins and 7(α)-substituted cephalosporins, the Beecham group had already discovered that this substituent, with an appropriate side-chain, provided a series of highly active antibiotics.[58,59] Conversion of the unsubstituted cephalosporin ring-system into the formamido nucleus could conveniently be carried out starting from the readily available t-butyl 7β-amino-7α-(methylthio)cephalosporanate **87** used for methoxylated analogues.[60] Acylation provides **88** from which the methylthio group is readily displaced by ammonia in the presence of a mercury (II) salt; subsequent formylation with acetic-formic anhydride provides **89**. Alternatively, the formamido group can be introduced directly by treatment of **88** with *N*, *N*-bis(trimethylsilyl)formamide in the presence of mercuric acetate. Removal of the acid protecting t-butyl group from **89** affords the appropriate 7(α)-formamido cephalosporin acid. Other methods for introducing the formamido substituent have been described,[61,62] together with a review of the structural variations prepared.[63]

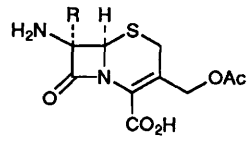


87 R^1 = H
88 R^1 = R^2CO

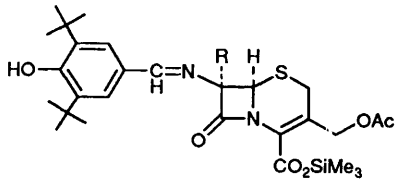


89

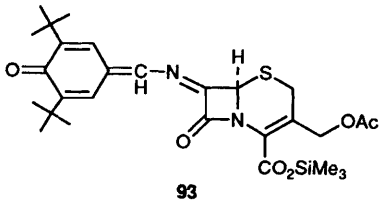
A highly convenient large scale preparation of the 7(α)-formamido nucleus **90** was also developed to provide a readily available intermediate for semi-synthetic manipulation.[64] Protection of 7-ACA **91** as the trimethylsilyl ester was followed by conversion into the Schiff's base **92**. Oxidation *in situ* with DDQ gave the quinone methide **93**, which readily reacted with *N*, *N*-bis(trimethylsilyl)formamide, forming **94**. Subsequent hydrolysis to remove the side-chain and silyl protecting group followed by crystallization gave the pure 7α-formamido nucleus **90**. This 'one-pot' procedure provided an overall yield



90 R = NHCHO
91 R = H



92 R = H
94 R = NHCHO

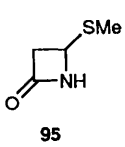


93

of 46% of **90** from **91** on a 1 kg scale, while the DDQ and aldehyde used for oxidation and Schiff's base formation are both recoverable.

4 Clavulanic acid

Streptomyces clavuligerus produces a number of natural products containing the 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane (clavam) ring system, the best known of these being the clinically important β-lactamase inhibitor clavulanic acid **5**.[6,65,66] Although many derivatives and synthetic analogues of this agent have been described,[63] syntheses directed towards the natural product itself have been minimal. Starting from the simple azetidinone **95**, alkylation to provide the keto-ester **96** was followed by conversion into the chloride **97** and base-catalysed cyclization to **98**. The geometry of the double bond was corrected by ultra-violet irradiation and the resulting diester **99** selectively reduced with di-isobutylaluminium hydride to give a low yield of the racemic methyl ester **100** of clavulanic acid.[67] In a second approach the diene **101** was prepared by cyclization of the appropriate keto-ester. The terminal double bond was converted into the ozonide, which on hydrogenation also provided the racemic ester **100**.[68] Since the methyl ester of the natural product can be readily hydrolysed to the parent compound both syntheses constitute a formal total synthesis of racemic **5**.



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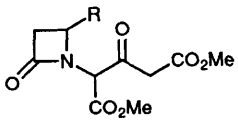
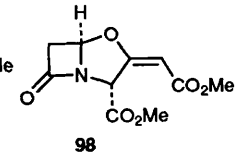


96 R = SMe
97 R = Cl



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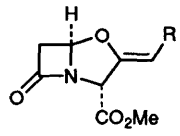
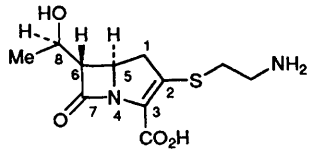


99 R = CO_2Me
100 R = CH_2OH
101 R = $CH{=}CH_2$

5 Carbapenems

Discovered in the mid-1970's the first compounds to be reported were thienamycin **6**[5] from *Streptomyces cattleya* and a group of interrelated metabolites from *S. olivaceus* such as MM 13902 (**7**; R = SO_3H)[6] and MM 22382 (**7**; R = H)[69] known as the olivanic acids.



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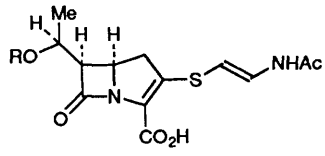
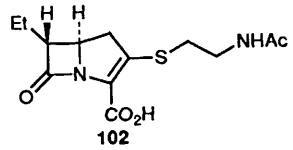


7

Thienamycin has the 8*R* configuration of the hydroxy group with a *trans*- arrangement of β-lactam protons, whereas in the olivanic acids the stereochemistry is 8*S* with a *cis*-substituted β-lactam in the sulfated series and both *cis*- and *trans*-β-lactams in the hydroxy cases. Subsequently, several other structural variations represented by PS-5 **102**,[70] carpetimycin A **103**,[71] asparenomycin C **104**,[72] and pluracidomycin C **105**,[73] were reported. To date over forty variations of these natural products with differing C-2 and C-6 substituents have been described.[41] The simplest



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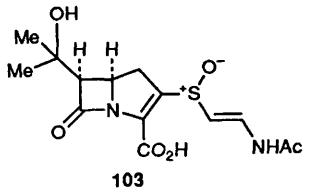

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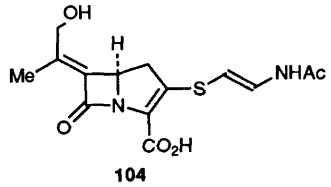
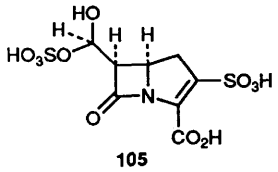


104

member of the series is the rather unstable parent nucleus **106**, shown to occur in certain bacterial strains of *Serratia* and *Erwinia*.[74] Fermentation yields of these Streptomycete metabolites are low and total synthesis methodology has been extensively developed to provide both natural products and analogues. The most common strategy has been to construct an appropriately substituted monocyclic β-lactam with the correct stereochemistry, followed by cyclization to form the highly-strained bicyclic carbapenem ring-system in the last step of the synthesis.



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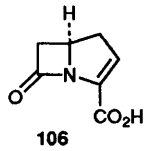
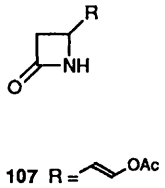
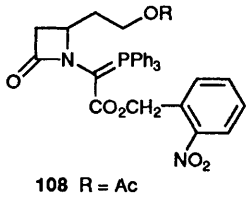


106

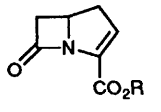
The basic ring system **106** was synthesized in racemic form by several groups prior to the disclosure of the natural product. Merck[75] made use of the azetidinone **107** derived from chlorosulfonyl isocyanate (CSI) and 1,4-acetoxybutadiene. After reduction of the double bond, progression was by way of the phosphorane **108** and **109**. Oxidation and cyclization gave a good yield of the ester **110**. Subsequent removal of the photolabile protecting group provided the unstable sodium salt of racemic **106**. Also, using phosphorane methodology, the CSI derived 4-allylazetidinone **111**[76] was converted, *via* the *p*-nitrobenzyl or acetonyl ester **112**, into the racemic natural product **106**; in this case oxidation of the terminal methylene grouping by ozonolysis provided the aldehyde for the intramolecular Wittig reaction.[77,78]



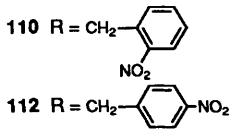
107 R = OAc
111 R =



108 R = Ac
109 R = H



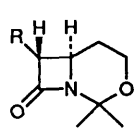
110 R = CH_2-(4-NO_2)



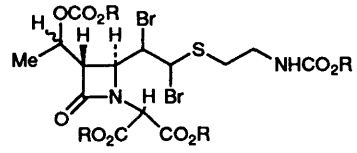
112 R = CH_2-(4-NO_2) or CH_2COCH_3

5.1 Thienamycin

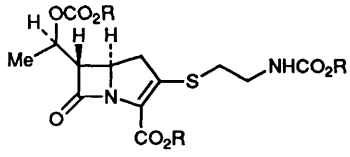
Since its discovery, the highly potent broad spectrum antibiotic thienamycin **6** has been the focal point for a multitude of synthetic studies in the carbapenem area.[79,80] While several novel methods have been developed, many of the original contributions from Merck are still widely used. The first synthesis of racemic material made use of the previously described azetidinone **107**.[81,82] This was converted into the 1,3-tetrahydrooxazine **113** and then by an aldol condensation to the appropriately substituted *trans*-β-lactam **114**. This was elaborated by a lengthy process to the dibromide **115**, which on cyclization, decarboxylation, and elimination gave the ester **116**; deprotection led to (±)-thienamycin.



113 R = H
114 R = MeCH(OH)

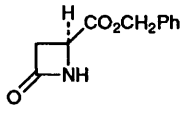


115 R = PNB (*p*-nitrobenzyl)



116 R = PNB

A chiral synthesis soon followed, starting from the L-aspartate derived β-lactam **117**.[83] In this case introduction of the hydroxyethyl side-chain was *via* an acetyl substituent which was subsequently reduced, by a stereocontrolled manner using potassium selectride™, to the alcohol. Homologation to the acid **118** was followed by conversion into the keto-ester, silyl group removal, and diazo-exchange to form **119**. C-3–N-4 cyclization using a catalytic amount of rhodium acetate proceeded extremely efficiently to produce the bicyclic keto-ester **120**. Activation at C-2 by conversion into the enol phosphate allowed the introduction of the cysteamine side-chain and final deprotection afforded (+)-thienamycin. Another



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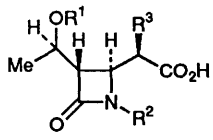
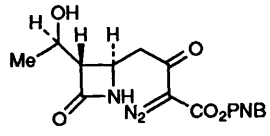


118 $R^1 = R^3 = H$, $R^2 = SiMe_2Bu^t$
129 $R^1 = SiMe_2Bu^t$, $R^2 = R^3 = H$
130 $R^1 = SiMe_2Bu^t$, $R^2 = H$, $R^3 = Me$



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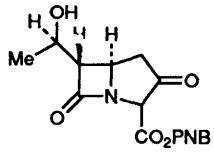
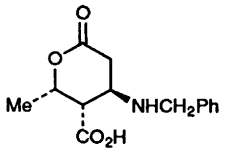


120

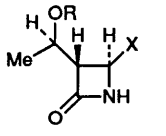
approach to the intermediate **118** starts from the lactone **121** derived from acetone dicarboxylic acid.[84] Conversion of the side-chain stereochemistry from *S* to *R* was required, but nevertheless the overall yield to final product was greater than 10% and offered a practical synthesis of (±)-thienamycin. The method

was later modified to produce homochiral material.[85] The synthesis of **121** from (−)-carvone has also been reported.[86]

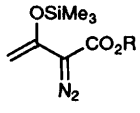


121

Further refinements using the 4-acetoxy or 4-chloro azetidinone **122** and the silyl enol ether **123** in the presence of Lewis acid provided a method for the direct incorporation of the diazo-ketone residue.[87,88] A convenient method for the synthesis of trimethylsilyl and t-butyldimethylsilyl enol ethers of various esters of α-diazoacetoacetic acid for use in this procedure has been reported.[89] Azetidinones **118** and **122** (X = OAc) have become universally recognized as being the key intermediate for the synthesis not only of thienamycin but also of many analogues. Methodology therefore has concentrated on developing routes to these versatile β-lactams. Two of the most conceptually appealing procedures make use of simple readily available chiral starting materials derived from 3-hydroxybutyric or lactic acid.

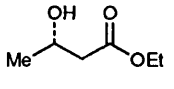


122 X = OAc, Cl
R = H, $SiMe_2Bu^t$



123

Thus, using a dianion-imine cycloaddition approach, **122** (X = OAc, R = $SiMe_2Bu^t$) was synthesized in an overall yield of 44% in eight steps from (*S*)-(+)-ethyl-3-hydroxy-butyrate **124** and the *N*-arylaldimine **125**.[90] A comprehensive account of cyclo-addition procedures using *R* or *S* 3-hydroxybutyric acid derivatives directed towards thienamycin synthesis has been published.[91] The (*S*)-enantiomer of ethyl lactate **126** can be converted into (*S*)-2-benzyloxypropanal which, with di-*p*-anisylmethylamine, gives a chiral imine **127** suitable for a [2 + 2]cycloaddition reaction with diketen. This proceeds in a highly stereoselective manner to the 3,4-*trans*-3-acetyl β-lactam **128** which was elaborated in high yield to either **129** or **122**



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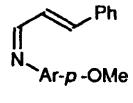

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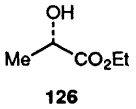

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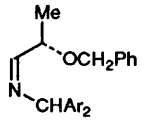

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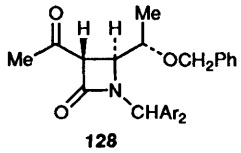
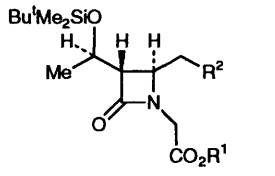


128

(X = OAc, R = $SiMe_2Bu^t$).[92] Synthesis of the latter has advanced to a stage where it is readily available commerically for both carbapenem and penem synthesis.[93] Efficient syntheses of the 4-benzoyloxy analogue **122** (X = OCOPh, R = H) have made use of the intramolecular cyclization of a threonine derived *N*-protected epoxy amide[94] or keten-imine methodology.[95]

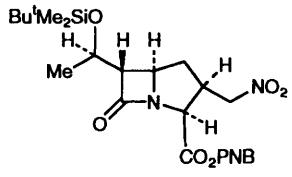
Approaches to non-naturally occurring carbapenems also make use of displacement reactions with **122** (X = OAc, R = $SiMe_2Bu^t$). Many of these have been particularly directed towards 1β-methyl substituted compounds which show a decreased susceptibility to degradation by the renal dehydropeptidase-I (DHP-I) enzyme compared to thienamycin.[96] Examples include the use of tin or boron enolates producing **130** in yields of 70–80% with a ratio of β:α isomers ranging from 24:1 to 60:1.[97–99]

Other formal syntheses of thienamycin, using β-lactams derived from carbohdyrates,[100–102] amino-acids[103,104] and isoxazolidines,[105] have been reported. Alternative methods for bicyclic ring construction include the Dieckmann type cyclization, using the *S*-pyridylthioester **131** (60–65%)[106] which gives the keto-ester directly, and an intramolecular Michael cyclization with **132** to form the saturated ring-system **133** (57%); the latter being elaborated to the bicyclic keto-ester *via* a nitrolefin and ozonolysis.[107] Novel approaches making use of organo-iron or cobalt complexes have been described.



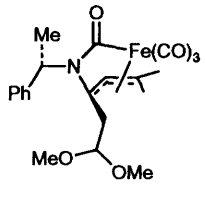
131 R^1 = Me, R^2 = COS– 

132 R^1 = PNB, R^2 = CH=CHNO$_2$



133

Oxidation of the π-allyl-tricarbonyliron lactam complex **134**, derived from (*S*)-(−)-α-methylbenzylamine and the π-allyl-tricarbonyliron lactone, gave a 85% yield of the β-lactam **135** which could be converted into a known thienamycin intermediate.[108] Most recently, Pattenden has shown that heating the carbamoylcobalt salophen **136** in toluene affords a stereoselective cyclization with dehydrocobaltation to the racemic β-lactam **137**; this has also been converted into a known thienamycin precursor.[109]



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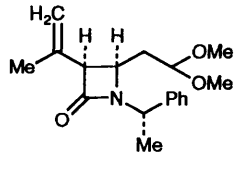

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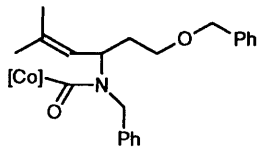
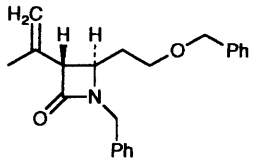


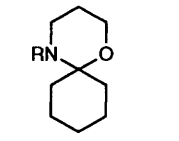
136 [Co] = Co(salophen)



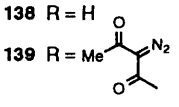
137

5.2 Olivanic acids

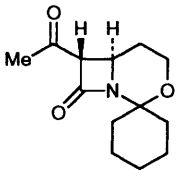
The discovery that thiol esters could participate in the intramolecular Wittig cyclization to form the carbapenem ring-system provided a basis for the total synthesis of the olivanic acid derivative MM 22383 **146**.[110,111] Tetrahydrooxazine **138** was converted into the diazo-intermediate **139** by reaction with diketen and then tosyl azide. Rhodium acetate catalysed cyclization provided the more thermodynamically favoured *trans*-substituted β-lactam **140**. Borohydride reduction gave a 1 : 1 mixture of hydroxy epimers.



138 R = H

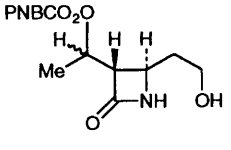


139 R = Me



140

Protection of the hydroxy group and removal of the nitrogen-oxygen blocking group gave the β-lactam **141** in which the primary hydroxyl was oxidized and converted into the Wittig product **142**. This was progressed to the phosphorane **143**, and, after oxidation to the acid, to the thio-ester **144** possessing the required (*E*)-acetamidoethenylthio side-chain. Heating in boiling toluene gave the two epimers of the cyclic product **145** (23%) which were separated and deprotected to afford (±)-MM 22383 **146** and (±)-*N*-acetyldehydrothienamycin **147**.[112] Later, the use of a 1,3-tetrahydroxazine derived from an optically active cyclohexanone or aminopropanol provided the opportunity for the chiral synthesis of other analogues.[113,114]



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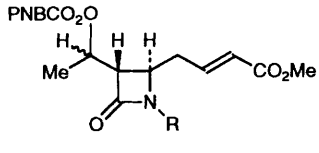
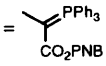
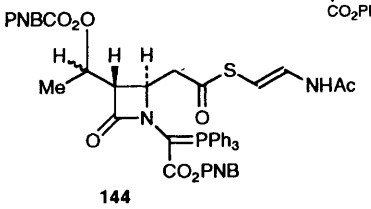


142 R = H



143 R =



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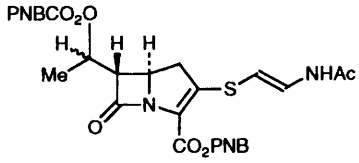

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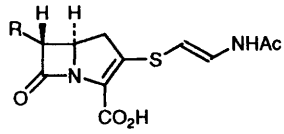
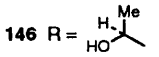
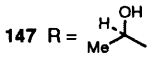


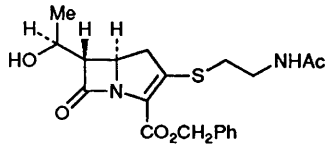


146 R = (*S*)



147 R = (*R*)

One other reported synthesis in the olivanic acid series was of the benzyl ester of racemic MM 22381 **148** by way of thiol addition of the appropriate C-(2)-side-chain to the unsubstituted nucleus **149**.[110,115] This gave, in high yield, the saturated carbapenam isomers **150**, which by a process of oxidation ($PhICl_2$) and double bond isomerization, could be converted into **148**.



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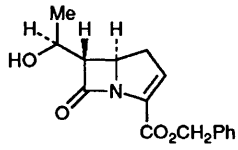

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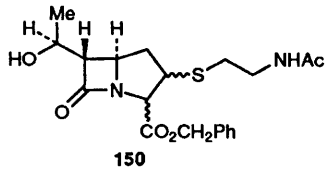
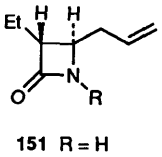


150

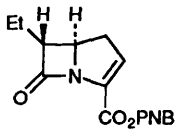
5.3 PS-5

PS-5 **102**[70] and other members of this group (PS-6, PS-7, and PS-8)[41] differ from thienamycin and the olivanic acids in having an unsubstituted ethyl or isopropyl group at C-6 in combination with the acetamidoethylthio or acetamidoethenylthio-substituent at C-2. Synthesis has been primarily directed towards PS-5. One of the earliest successes made use of the thiol addition procedure described for MM 22381.[116,117] Allylazetidinone **111** was alkylated α-to the β-lactam carbonyl and the *trans*-β-lactam **151** converted into the phosphorane **152** and then cyclized to **153**. Addition of acetamidoethanethiol gave a 70% yield of isomers of **154**, which on reintroduction of the double bond and deprotection, afforded (±)-PS-5.
Most other methods have concentrated on using the C-2 to N-4 carbene insertion procedure after the synthesis of an appropriately substituted monocyclic β-lactam. One early synthesis which illustrates this was by Kametani[118] using the 4-acetoxy substituted β-lactam **155** derived from the vinyl acetate **156** and



151 R = H

152 R = 



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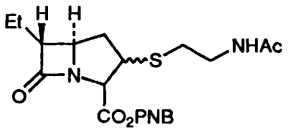

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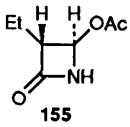

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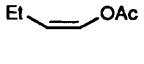

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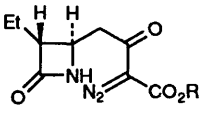
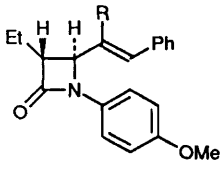
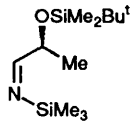


157

CSI. Enolate displacement of the acetate to **157** was followed by cyclization and conversion into (±)-PS-5. A variety of ester-imine condensations have also been used to provide **155** in racemic or chiral form. Thus, a Reformatsky-type reaction with a bromo-ester and imine gave racemic **158**,[119] while a lithium enolate-imine condenstion using a chiral ester gave a 92% e.e. of **159**;[120] both were converted by oxidative procedures into **155**. Similarly, using the lithium enolate of t-butyl butanoate and the silylimine **160** from *S*-lactic aldehyde provided *trans*-β-lactam **161** (96:4 *trans*:*cis*) which after deprotection, conversion into the ketone and Baeyer–Villiger oxidation again gave the acetoxy azetidinone **155**.[121] Alternatively, ester enolate additions to imines can give β-amino-acids such as **162** or **163** suitable for elaboration to either racemic or chiral PS-5.[122–124] Boron or tin(II) enolate-imine condensations also provide suitable β-lactam precursors.[125,126]



158 R = Me
159 R = H



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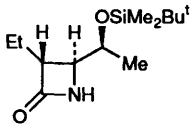

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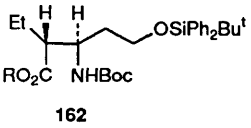

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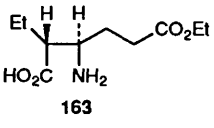
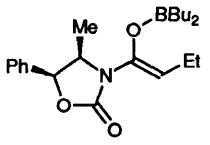


163

An elegant and novel approach which uses a 3-substituted anisole as a masked β-keto ester synthon has been used by Evans[127] in an enantioselective synthesis. Reaction of the chiral boron enolate **164** with the aldehyde **165** established the correct stereochemistry in **166** required for the β-lactam ring **168**. This was achieved after conversion into the hydroxamate **167** and cyclization using the Miller



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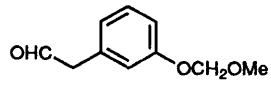

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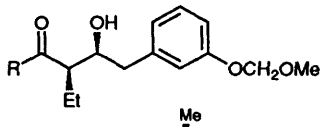
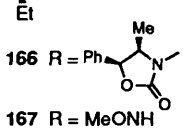
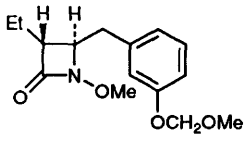


166 R = 

167 R = MeONH

methodology. In the next step, a dissolving metal reduction effected both N–O bond cleavage and aromatic ring reduction. The dihydroanisole derivative **169** was subjected to ozonolysis to give, after reductive work-up, the β-keto-ester **170**. This was converted by the standard procedure into **171**, and the synthesis completed by introduction of the *N*-acetyl-cysteamine side-chain and deprotection to the acid. The route provides enantiomerically pure (+)-PS-5 in 13% overall yield from 3-methoxymethylphenylacetaldehyde.



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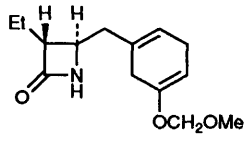

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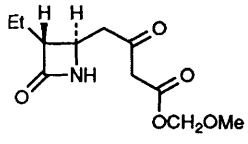

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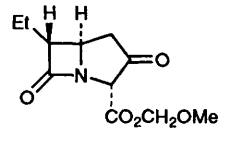
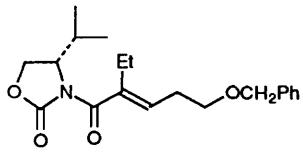


171

One of the most recent routes makes use of a stereoselective addition of thiophenol to the double bond of the chiral imide **172**.[128] The desired 2*S*, 3*S* adduct **173** was then converted into the hydroxamate **174**. Formation of the β-lactam **175** was accomplished in this case through S-alkylation and base-catalysed cyclization (83%). Further elaboration provided **176** in



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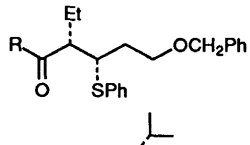
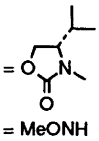
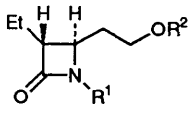


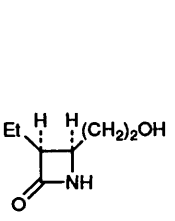
173 R = 

174 R = MeONH



175 R^1 = OMe, R^2 = CH_2Ph
176 R^1 = R^2 = $SiMe_2Bu^t$

42% overall yield from the acid precursor of **172**. A photochemical synthesis of the *cis*-β-lactam **177** from the pyrazolidin-3-one **178** has also been described.[129] Since this can be epimerized to the *trans*-isomer it also affords another route to PS-5. An extensive review of synthetic procedures directed towards PS-5 and PS-6 has been published.[130]



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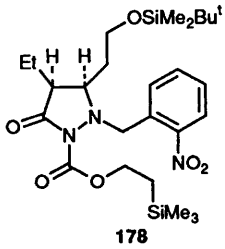
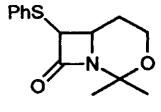


178

5.4 Carpetimycins

Several syntheses of the naturally occurring sulfoxide carpetimycin A **103** have been reported. In contrast to the synthesis of thienamycin, a major problem in this series is the establishment of the *cis* stereochemistry of the β-lactam ring. In one approach[131] mono-sulfenylation of the tetrahydrooxazine **113** to **179** was followed by an aldol reaction with acetone giving a mixture of *cis*- and *trans*-products **180**. Reductive desulfurization using tri-n-butyltin hydride in the presence of a radical initiator gave predominantly the *cis*-azetidinone **181** (71% *cis*:22% *trans*). The same ratio of isomers was obtained irrespective of the stereochemistry of **180**, indicating that the same radical intermediate is formed and that hydrogen transfer from the bulky hydride reagent takes place from the less-hindered α-face. A sequence of protection and oxidation reactions to the acid **182** was followed by conversion into **183**. Cyclization to the bicyclic keto-ester, introduction of the C-2-side-chain, oxidation to the sulfoxide, and deprotection then gave ($\pm$)-carpetimycin A **103**. Two other approaches to the *cis*-substituted intermediate **181** also utilize radical reduction methods. One uses the isonitrile **184**[132] obtained from a penicillin-derived β-lactam, the second uses the bromohydrin **185** which originates from a β-lactam obtained by reaction of an allenyl sulfide with CSI.[133]



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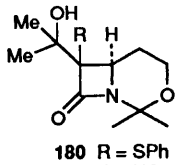
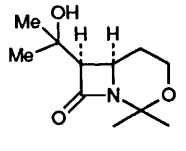


180 R = SPh
184 R = NC
185 R = Br



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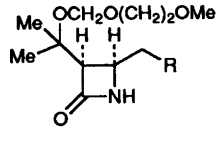
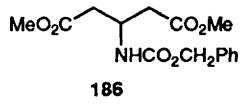


182 R = CO_2H
183 R = $COCH_2CO_2PNB$

An alternative synthesis which introduces chiralilty into the sequence makes use of the enzymic hydrolysis of the prochiral ester **186** to the acid **187** (98% e.e.). Borohydride reduction resulted in formation of the lactone **188**. Stereocontrolled incorporation of the hydroxyisopropyl substituent giving **189** was followed by ring-opening and conversion into the amino-acid **190**. This could be cyclized using the Grignard reagent to the β-lactam and then by known procedures to ($-$)-carpetimycin A.[134]



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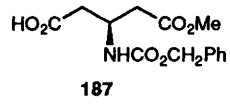

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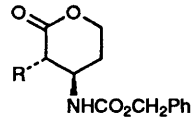
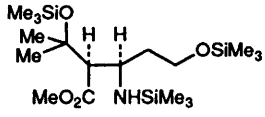
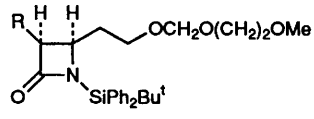


188 R = H
189 R = $Me_2C(OH)$



190

A neat example of a directed aldol condensation has also been used starting from the optically pure methoxyethoxymethoxy (MEM) protected azetidinone **191**.[135] These authors reasoned that on formation of the β-lactam enolate, metal-ion chelation with the neighbouring MEM group on the β-face of the molecule would allow for predominant formation of the *cis*-β-lactam. Thus, condensation with acetone using the titanium enolate and bulky silyl group on nitrogen gave 59% of the *cis*- product **192** and only 22% of *trans*-isomer.

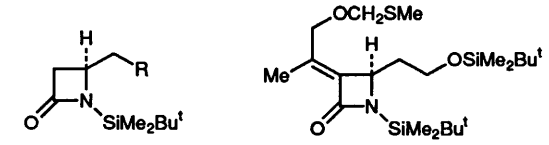


191 R = H
192 R = $Me_2C(OH)$

5.5 Asparenomycins

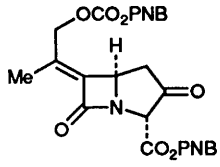
The asparenomycin natural products have an alkylidene substituent at the C-6 position. Synthesis has followed the familiar carbapenem approach by way of a bicyclic keto-ester (*e.g.* **195**) derived from an appropriately functionalized monocyclic azetidinone. The first synthesis of ($-$)-asparenomycin C utilized **193**. This underwent an aldol condensation with methylthiomethoxyacetone followed by elimination to the desired (*E*)-double bond isomer **194** (98%).[136] This was readily progressed to **195**. Introduction of the (*E*)-acetamidoethenylthio side-chain and deprotection led to ($-$)-asparenomycin C (**104**).

Using the allylazetidinone **196** the aldol product from hydroxyacetone, as a mixture of isomers, was readily converted into the carbonate **197**, and ultimately the bicyclic analogues **198**.[137,138] Treatment with DBU gave a single (*E*)-isomer and removal of the *p*-methoxybenzyl group with aluminium trichloride-anisole gave the various racemic asparenomycin natural products. A slightly different



193 R = $CH_2OSiMe_2Bu^t$
196 R = $CH{=}CH_2$

194



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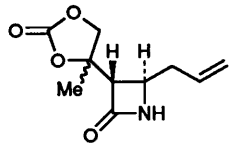

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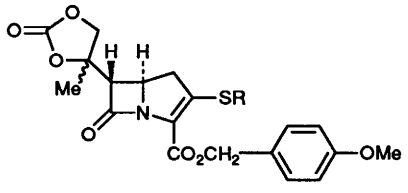
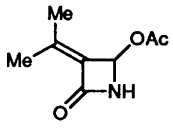


198 R =



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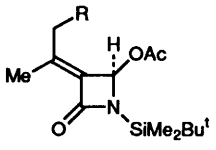

200 R = Br
201 R = OCO_2PNB

approach uses the acetoxy azetidinone **199** derived from 1-acetoxy-3-methylbuta-1,2-diene and CSI.[139] This was converted by way of the allylic bromide **200** into the azetidinone **201**, and then progressed by the diazo-route to (±)-asparenomycin C.

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