Review Article

STEREOSPECIFIC CONSTRUCTIONS OF CHIRAL β-LACTAMS

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It will be clear to those interested in the field of new antibiotics, that the synthesis of azetidines and azetidinones, the basic ring system of β-lactam antibiotics, has gained crucial importance as a result of recent developments in that area. Since the first synthesis of an azetidine in 1888[1] and of a β-lactam in 1907[2], a number of reviews and books have dealt with synthetic methodology[3~13] displaying nearly every conceivable way of elaboration of this structural unit. However, there has been limited focus[14,15] on *enantiospecific* constructions of chiral azetidines, which suggested the present review.

The scope of this review is to underline the principles for the enantiospecific synthesis of azetidines and β-lactams. Emphasis will be placed upon the choice of starting material and ring closure methods. Approaches to chiral azetidines that involve degradation of natural material (penicillins or cephalosporins), modifications of readily available β-lactams (introduction of side-chains, elaboration of a second ring), asymmetric induction (enantioselective cycloadditions) or synthetic processes which have only been carried out with racemic material although theoretically applicable to optically active starting material will not be dealt with in this paper.

The various approaches to be discussed will be presented according to the class of chiral starting materials employed; at first amino acids, then carbohydrates and finally miscellaneous derivatives.

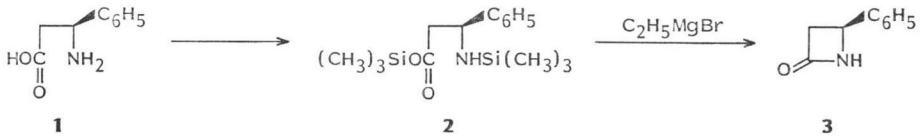
I. Amino Acids

A. Alkylamino Acids

Simple chiral β-amino acids have been used to prepare optically active β-lactams bearing only alkyl

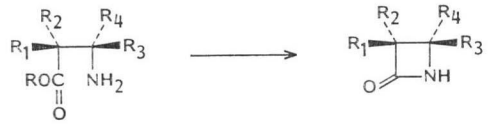
substituents α to nitrogen.

These syntheses are based on modifications[17~19] of the powerful GRIGNARD-mediated cyclization procedure discovered initially by BRECKPOT[16]. For example, β-phenyl-β-*S*-alanine (**1**) whose optical integrity was demonstrated by the absence of peaks for the diastereoisomer in presence of a chiral ^{1}H NMR shift reagent, was transformed into its bistrimethylsilyl derivative **2** and then cyclized to the optically active azetidinone **3** using ethylmagnesium bromide: The (−)-4-phenyl-2-azetidinone (**3**) thus obtained was then further transformed into the naturally-occurring bis 8-membered ring compound, homaline[20,21].



1 **2** **3**

Similarly, optically active α-disubstituted-β-alanines **4** were cyclized using GRIGNARD reagents to give 3,3-disubstituted-β-lactams **5**[22~26,168].

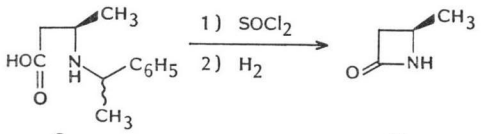


4 **5**

$R_1 = R_2 = R_4 = H$, $R_3 = CH{=}CH_2$
$R_1 = R_2 = H$, $R_3 = CH_3$, $R_4 = C_6H_5$
$R_1 = R_2 = H$, $R_3 = C_6H_5$, $R_4 = CH_3$
$R_1 = R_2 = CH_3$, $R_3 = C_6H_5$, $R_4 = H$
$R_1 = C_6H_5$, $R_2 = C_2H_5$, $R_3 = R_4 = H$
R_1 = cyclo C_5H_{11}, $R_2 = CH_3$, $R_3 = R_4 = H$

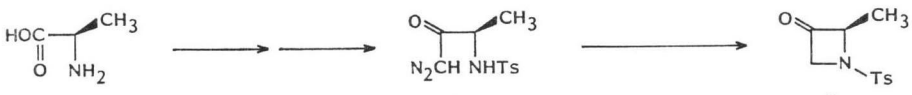
These chiral azetidinones were used in chiroptical studies[25,27] or as intermediates in the syntheses of optically active isocyanides[28] and 3-amino-1-propanols[29].

The simplest optically active substituted β-lactam, (*S*)-2-methylazetidin-4-one (**7**) was prepared from a *N*-protected β-methyl-β-alanine **6** *via* the corresponding acid chloride. After deblocking **7** was obtained[30]. Its configuration was proved by an independent X-ray crystallographic analysis[31] which allowed the correction[32] of a previous misassignment of this structure[33].



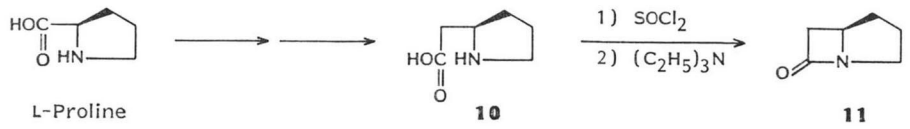
6 **7**

(*R*)-2-Methylazetidin-3-one (**9**) was obtained during an attempted Arndt-Eistert homologation of **8** derived from alanine[34].



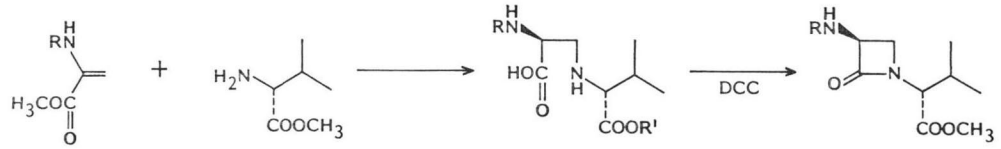
Ts : *p*-Toluenesulfonyl

Another amino acid, L-proline, served as the starting material in the synthesis of the basic skeleton of carbocyclic analogues of penicillins[35]. Thus, in several steps, the homo-proline derivative **10** was obtained without racemization. Formation of the bicyclic system **11** was then effected in low variable



yields (1~12%). However, yields over 40% were estimated by gas chromatography which could be explained in terms of the inherent unstability of **11**[35].

L-Valine methyl ester (**13**) has been used in a MICHAEL-type condensation with dehydroalanine **12** giving rise to **14** (together with its epimer). After purification, ring closure was effected with dicyclohexylcarbodiimide (DCC) to give **15** which was then compared to phenoxymethylpenicillin-derived authentic material. Although the optical rotation was only half that of the expected value, it was shown that racemization had occurred after ring closure[36~39].

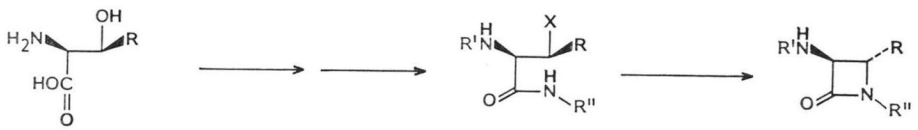


R = H, R' = CH_3

B. Hydroxyamino Acids

Serine and threonine are the most familiar examples of this class and they have been used in a number of approaches to chiral β-lactams and in particular for the total syntheses of monocyclic β-lactams. As the β-hydroxyamino acids, serine and threonine, differ only in the presence of a methyl group they will be discussed simultaneously.

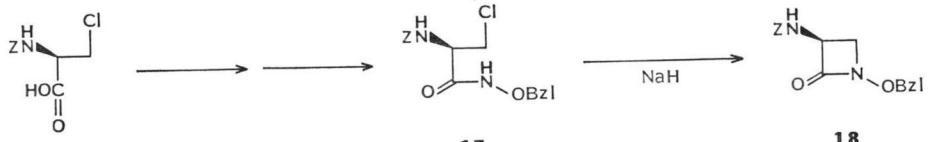
Several research groups have established the basic requirements for ring closure in which a leaving group is displaced by a nitrogen[40], so as to allow formation of the 4-membered ring:



L-Serine R = H

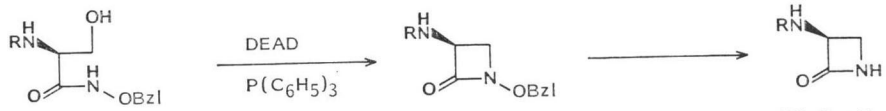
L-Threonine R = CH_3

For example, serine-derived **16** was condensed with *O*-benzylhydroxylamine to give **17** which upon sodium hydride treatment gave **18** in ~80% yield[41,42]. This sequence was considered as a model study and conditions were then sought for efficient direct ring formation route from a simple protected serine.



Bzl : Benzyl

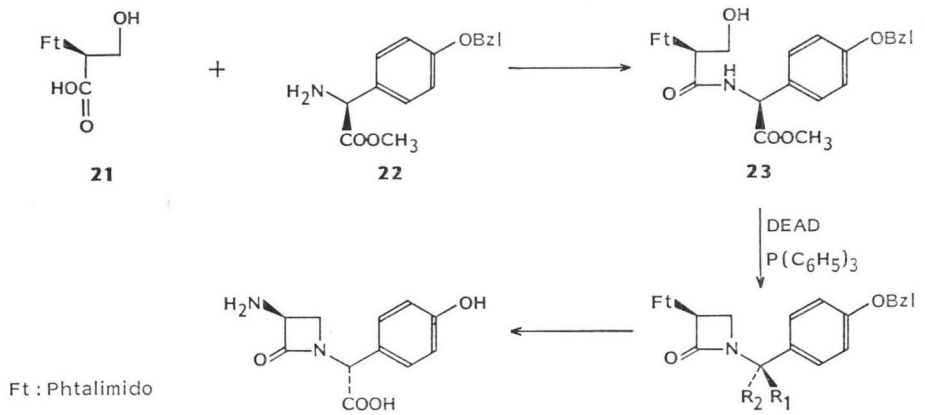
A synthesis was developed whose major feature[42] was the use of a combination of the hydroxamate moiety and a MITSUNOBU type ring closure (diethylazodicarboxylate (DEAD)-triphenylphosphine)[43]. After deblocking[44] the synthon **19** was isolated. Degradation of **19** led to optically pure L-2,3-diaminopropionic acid, thereby confirming the retention of chirality during the synthesis.



19 R = H
20 R = Boc

This short efficient scheme was subsequently applied to the total synthesis of 3-aminonocardicinic acid (3-ANA) derivatives. Use of a *tert*-butyloxycarbonyl (Boc) protective group for the side chain amino function permitted selective deprotection of the hydroxamate to give optically active **20**[45]. More recent work by the same team shed light on the actual mechanistic pathways and disclosed possible reaction intermediates by means of interesting model reactions[46]. As a consequence, previous results and reaction conditions were optimized[46].

Similarly, biogenetically-modeled cyclization of an optically active dipeptide had been proposed earlier[47]. Serine-derived **21** was coupled with optically active **22** to give dipeptide **23**. Under MITSUNOBU conditions[43] **23** was cyclized to a mixture of epimers **24** and **25** which upon hydrogenolysis in acidic medium gave optically pure (−)-aminonocardicinic acid (**26**) identical with natural material[47].



21 **22** **23**

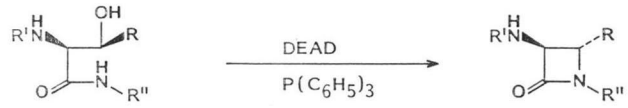
24 R_1 = H, R_2 = $COOCH_3$
25 R_1 = $COOCH_3$, R_2 = H

26

These results were later substantiated by mechanistic studies which showed that the ratio of epimers (2: 1) obtained was independent of the proportion of DEAD to triphenylphosphine employed[43]. If either of the pure isomers was treated under the same reaction conditions, the same 2: 1 product ratio was observed revealing that product formation was equilibrium controlled. When the less nucleophilic reagent triethyl phosphite (1 equivalent) was used, a single isomer could be isolated; however epimerization takes place if an excess of this reagent is used suggesting a unique mechanistic situation[48].

It is clear from other works[49~51] that the choice of protecting groups is also critical. For example, serine-derived **27** was smoothly cyclized to **28** whose enantiomeric purity was demonstrated using a chiral NMR shift reagent. Unfortunately the same reaction failed when carried out with the cor-

responding threonine derivative. If however the side-chain amino group was protected using its phtaloyl derivative, as in **29**, then β-lactam **30** could be prepared.



27 R = H, R' = Z, R'' = *p*-$CH_3C_6H_4$ **28**

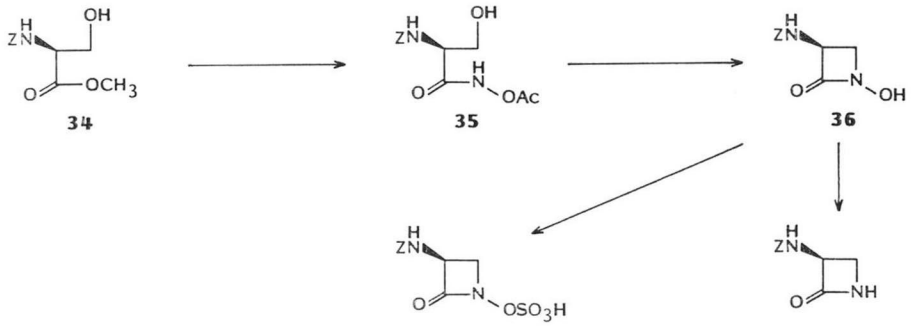
29 R = H, R' = Phtaloyl, R'' = *p*-$CH_3C_6H_4$ **30**

31 R = CH_3, R' = Ac, R'' = OBzl **32**

33 R = H, R' = Z, R'' = 5-(1-Benzoyltetrazol)yl

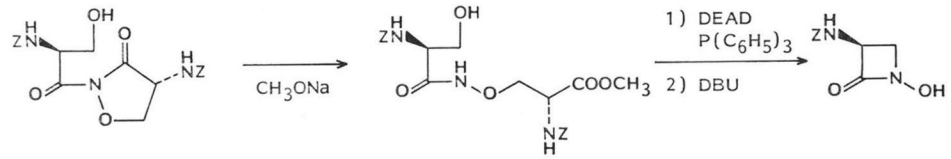
If one changes the nature of the amide nitrogen substituent however application of the MITSUNOBU conditions to threonine-derived **31** leads to **32**. The benzyloxycarbonyl (Z) group can still be used with serine-derived **33**, which enabled the synthesis of an analogue of nocardicin[52].

MILLER and coworkers showed in their most recent contribution[53] that use of expensive reagents can be avoided as demonstrated in their practical synthesis of monobactams. By simply treating Z-serine (**34**) with hydroxylamine followed by acetic anhydride, crystalline **35** was obtained in 63% yield. Ring closure (triethylamine-triphenylphosphine) followed by mild base (sodium hydrogen carbonate) hydrolysis gave **36** in ~50% yield. Compound **36** can either be reduced to **9** or sulfonated to yield synthetic monobactam **37**.



34 **35** **36** **37** **9**

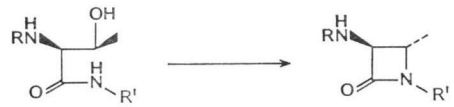
The latter compound has also been made available starting with the condensation product between Z-serine and Z-cycloserine[54]. Upon treatment of product **38** with sodium methoxide, the hydroxylamine derivative **39** was obtained. When MITSUNOBU conditions were applied to **39** a cyclization product was obtained; however it was not isolated but directly treated with a strong non nucleophilic base to afford **36**.



38 **39** **36**

Similarly it was shown that upon reaction of threonine with *ortho*-phenylsulphenyl chloride followed by coupling with *O*-benzylhydroxylamine, the intermediate **40** could be obtained. After sequential

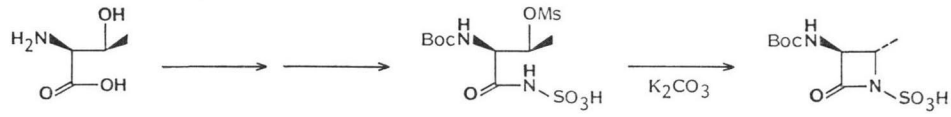
treatment of **40** with mesyl chloride and sodium hydride, internal displacement of the secondary leaving group afforded **41**[54]. The overall yield of this route was later improved by a careful choice of protecting groups. The threonine derivative **42** was thus efficiently cyclized to **43** the product being isolated without the need for chromatographic purification[55].



40 R = *o*-$NO_2C_6H_4S$, R' = OBzl **41**

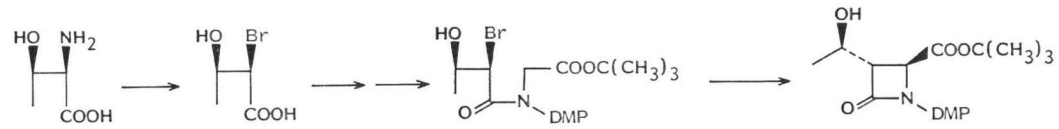
42 R = Boc, R' = OCH_3 **43**

This synthetic methodology was next applied to the synthesis of chiral monobactams starting from sulfonylated acyclic derivatives resulting in a more direct route to these important derivatives. Threonine was converted into **44** upon sequential treatment with mesyl chloride (MsCl) and picoline/sulfur trioxide complex. Ring closure to **45** was then simply achieved (>90%) using potassium or sodium hydrogen carbonate[56,57].



44 **45**

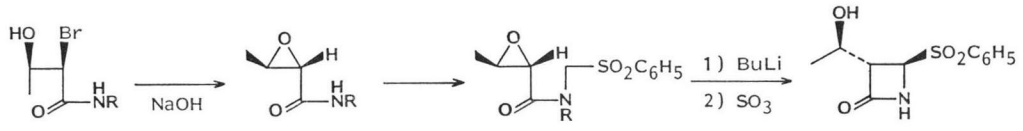
The inherent chirality of threonine has been retained in a totally different approach by a group from Sankyo[58]. Conversion of threonine to the α-bromo acid **46** was achieved with retention of configuration, and this derivative was transformed by conventional means into **47**. When treated with two equivalents of lithium hexamethyldisilazide, **47** cyclized cleanly giving **48** in 61% yield. Interestingly this cyclization was shown to proceed with retention of configuration at the carbon bearing the bromine. This was explained by the formation of an intermediate epoxide through a double inversion process.



L-Threonine **46** **47** **48**

DMP : 2,4-Dimethoxyphenyl

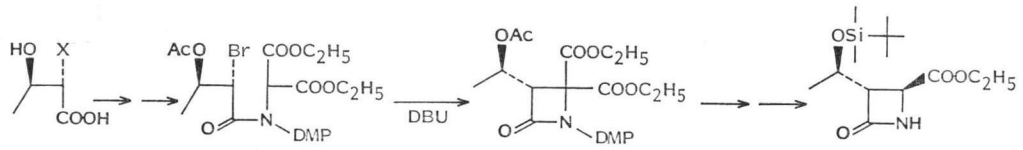
A similar epoxide **50** was later intentionally prepared by base treatment of **49** as an intermediate in the preparation of an optically active sulfone[59]. Alkylation at nitrogen of **49** with phenylthiomethyl chloride followed by oxidation gave **51**. Treatment of **51** with *n*-butyllithium (BuLi) at −50°C in hexamethylphosphotriamide gave a 83% yield of a single isomer which was shown to be the *trans*-derivative. Deblocking then afforded **52**, a carbapenem synthetic intermediate in eight steps from threonine.



49 **50** **51** **52**

R = *p*-$OCH_3C_6H_4$

A closely related chiral starting material is D-allothreonine easily derived from threonine[60], which has been used in the synthesis of chiral monobactams, in the same manner as described above for threonine[57]. It has also been used in a much longer route to such optically active β-lactam sulfones[58]. The bromo derivative **53** obtained (retention of configuration) from allothreonine was converted to **54**. A key transformation relies on the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) mediated ring closure of **54** to give **55** in 95% yield. In this case protection of the hydroxyl group as the acetate avoided formation of an intermediate epoxide thus rendering possible ring closure by a clean S_{N^2} process; nine additional steps were necessary to convert **55** to β-lactam **56**[61].

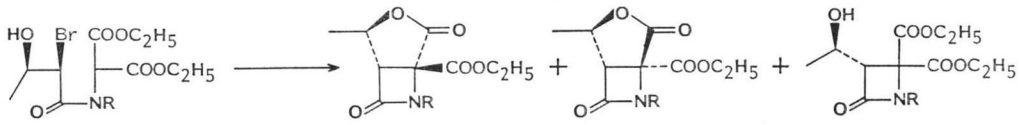


D-Allothreonine **54** **55** **56**

X = NH_2

53 X = Br

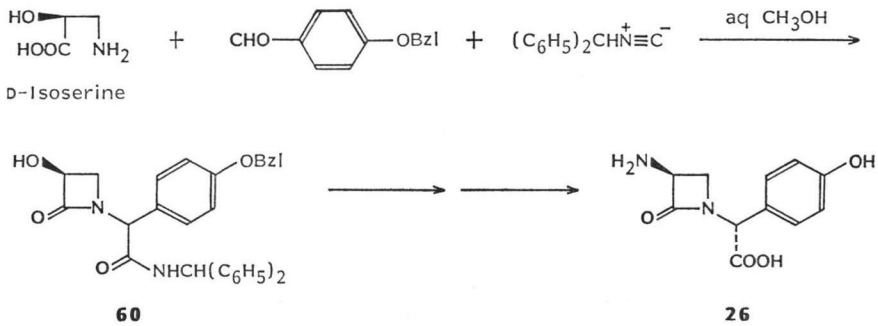
The mechanism of the ring closure was examined in further studies[62] and for example the unprotected alcohol **57** was shown to give three different β-lactams on treatment with DBU. Compound **58** was the major product; the epimeric lactone **59** was shown to result from the opening of an intermediate epoxide.



57 **58** (75 %) **59** (12 %) (7 %)

R = DMP

Another hydroxyamino acid, isoserine (a serine in which hydroxyl and amino groups have been "exchanged"), has been used in a convenient and high yielding synthesis of nocardicin. This was made possible by use of the UGI 4-component condensation reaction (4 CC)[63,64] as shown below:



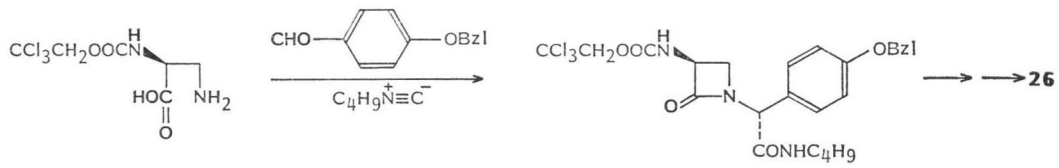
D-Isoserine

60 **26**

Only four steps are then necessary to convert **60** into 3-aminonocardicinic acid (3-ANA) (**26**) in a 30% overall yield[65].

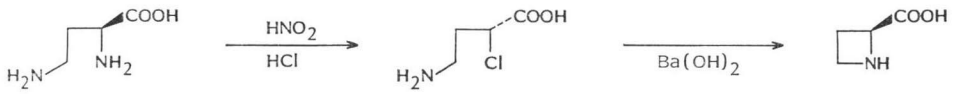
C. Amino-amino Acids

It is interesting to note that the same UGI-type reaction failed with the related L-2,3-diaminopropionic acid (a serine in which the hydroxyl group has been replaced by an amino group)[66]. However, when the *N*-2 protected compound **61** was reacted with *p*-benzyloxybenzaldehyde and butylisonitrile in methanol for three days the desired epimer **62** was obtained in 36% yield. This resulted in another practical synthesis of 3-ANA since the unwanted epimer which was parallely formed in the reaction could later be epimerized. The overall yield from **61** was 38%[67,68].



61 **62**

L-2,4-Diaminobutyric acid (**63**), another ω-amino-amino acid, was used as the chiral starting material[69,70] in the synthesis of naturally occurring azetidine-2 carboxylic acid (**65**). After replacement of the vicinal amino group by a chlorine to give **64**, displacement of the latter by the terminal amino group occurred to give **65**. However the optical purity was not reported.



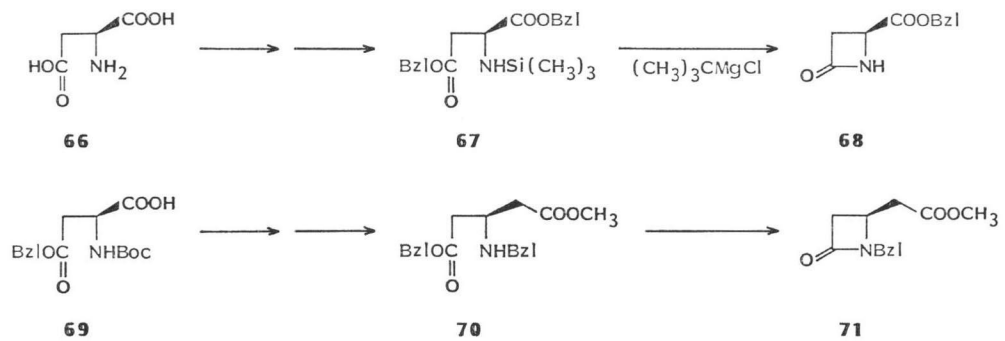
63 **64** **65**

D. Carboxyamino Acids

L-Aspartic acid has been used as a convenient chiral source in several enantiospecific syntheses of azetidinones.

For example, it was chosen as the starting material in a spectacular total synthesis of (+)-thienamycin[71~77]. One of the key steps was the one-pot GRIGNARD reagent-induced ring closure of the monosilylamine **67** derived from aspartic acid (**66**). Azetidinone **68** crystallized directly from the reaction mixture in over 70% yield. The enantiomeric purity of **68** was checked by its reconversion to the starting amino acid **66** which was subsequently shown to retain its optical activity[75,83].

Similarly, aspartic acid was used in a closely related project[78]. The free carboxylic acid group

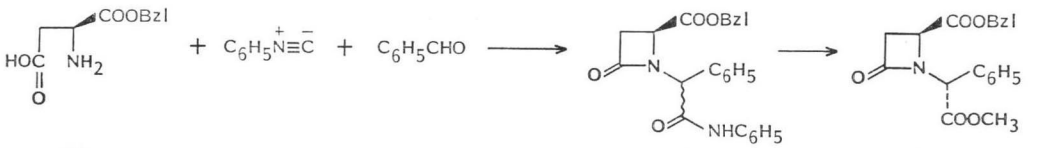


66 **67** **68**

69 **70** **71**

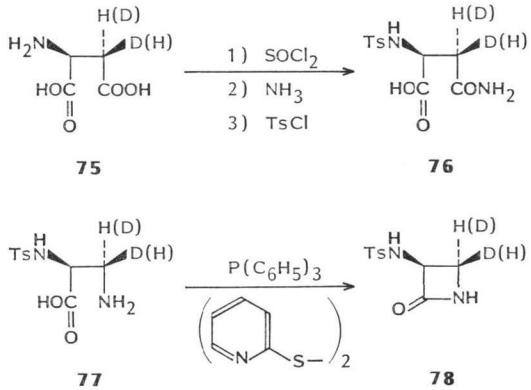
of **69** was homologated to yield an optically active 3-aminopentanedioic acid in which the two carboxylic groups are differentiated (for other synthetic approaches to these diacids, *vide infra*). After amino protecting group exchange and selective deblocking of one of the ester groups to give **70** cyclization was brought about on reacting the corresponding acid chloride with the secondary amine derived anion. Thus a 66% yield of crystalline **71**, an intermediate in carbapenem syntheses, could be obtained[78].

Aspartic acid has also used as a starting material in a four component condensation route[79]. Condensation of the α-benzyl ester **72** with benzaldehyde and phenyl isocyanide gave (30% on a large scale) a mixture of diastereoisomers **73**. Conditions for the successful conversion (PCl_5, then CH_3OH) of the amides **73** to the corresponding ester was a key feature of the synthesis especially since a single isomer **74** was then formed, suggesting a thermodynamic control.



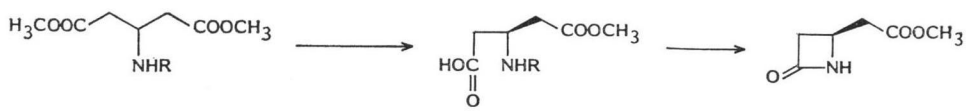
72 **73** **74**

Deuterium-labeled aspartic acid (**75**) has recently been used in the unambiguous determination of NMR resonances of monocyclic β-lactams[80]. Selective esterification of the β-carboxyl group followed by treatment with ammonia then tosyl chloride (TsCl) afforded a labelled sample of **76** which was further transformed into **77** (through an HOFFMANN rearrangment which occurs with retention of configuration). Cyclization to β-lactam **78** occurred, although in low yield, by use of the conditions developed by OHNO and coworkers[81] for such β-amino acids.



75 **76** **77** **78**

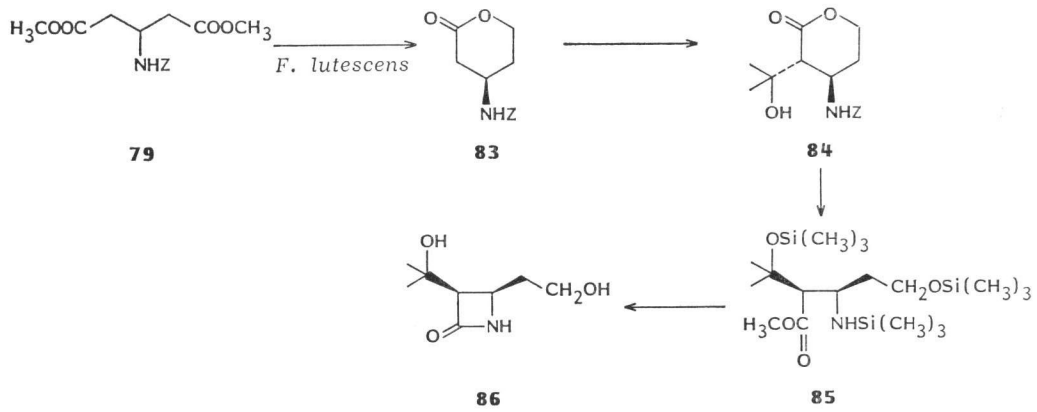
The latter group was involved in a combination of chemical and enzymatic procedures to obtain 3-aminopentanedioic acids in optically active form (for another approach *vide supra*). The key problem was the differentiation of both ester groups of **79** while inducing optical activity. Early experiments[82] showed that pig liver esterase hydrolyzed **79** very efficiently; the optical purity was low however (*ca* 40% enantiomeric excess) which was explained by participation of the amino group in a concomitant chemical hydrolysis. Therefore this amino group was protected as the benzyloxycarbonyl (Z) derivative which upon treatment with pig liver esterase gave **80** in a 93% yield of high optical purity. Hydrogenolysis of **80** then provided **81** and application of the recently established β-lactam forming conditions[81] provided **82** in good yield, which is clearly superior to the 10~30% yield obtained with



79 R = H, Z **80** R = Z **81** R = H **82**

dicyclohexylcarbodiimide (DCC) ring closure method[50]. Ring closure has been brought about as well by treatment of the corresponding acid chloride with triethylamine[84,85].

It was disclosed recently that about 500 species of organisms were screened for enantiospecific hydrolysis of prochiral **79**. An enantiomeric excess of 98.1% has been obtained with *Flavobacterium lutescens*[86]. Incorporation of the hydroxyisopropyl side-chain from **83** thus obtained occurred in a completely stereo-controlled manner; no other isomer could be detected. Then, acid catalyzed cleavage of **84** followed by persilylation gave the derivative **85** which was immediately submitted to a GRIGNARD induced cyclization to yield optically active β-lactam **86**, a key intermediate in the total synthesis[87]. This resulted in a stereo-controlled synthesis of carpetimycin A.

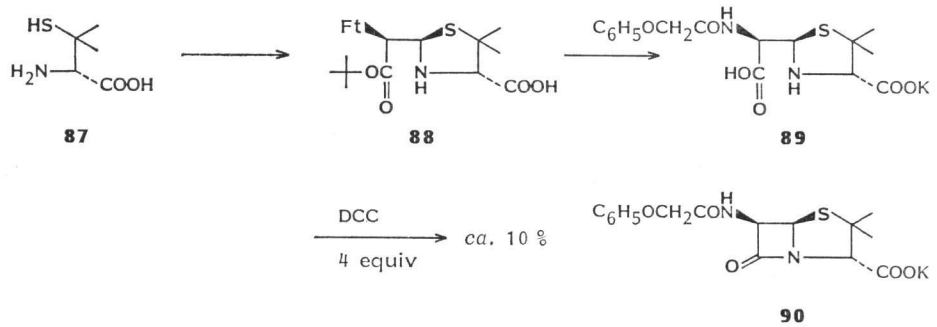


79 **83** **84** **85** **86**

E. Thioamino Acids

The outstanding and pioneering work of SHEEHAN and HENERY-LOGAN which has been central to the early β-lactam forming reactions and which culminated in the syntheses of optically active penicillines[88,89] rely on a degradation product of penicillins, namely the thioamino acid D-penicillamine. The success of the syntheses depended on the choice of protecting groups and on the mild β-lactam ring closure which was brought about late in the reaction scheme. (An earlier attempt by DU VIGNEAUD and coworkers[90] will not be detailed here as yields in the range of 0.1% were obtained in the cyclization step).

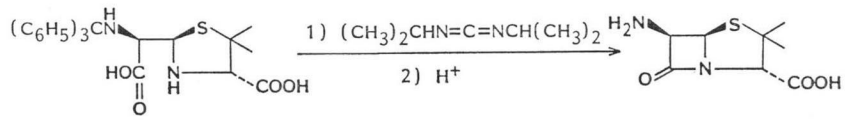
Condensation of D-penicillamine **87** with phtalimidomalonaldehyde afforded among other isomers the suitably derivatized thiazolidine **88**. After replacement of the phtalimido group by the phenoxymethylpenicillin side-chain to give **89** and liberation of the protected groups, the stage was set for the



87 **88** **89** **90**

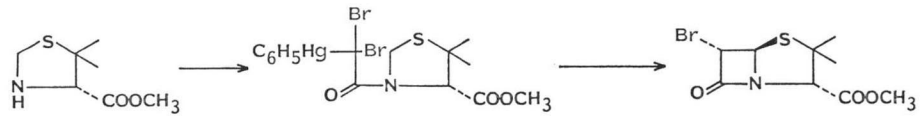
critical ring closure. The discovery[91] that aliphatic carbodiimides are capable of forming amide bonds under very mild conditions suggested their use in the cyclization process. This allowed isolation, for the first time in an efficient manner, of a synthetic penicillin, the potassium salt of phenoxymethylpenicillin (**90**)[88,99]. It is significant to note that β-lactam formation was brought about in the penultimate step of the synthesis.

This critical cyclization step was carried out subsequently at an earlier stage in the synthetic scheme[92,93], which was made possible by the chemical differentiation of both amino groups: D-penicillamine-derived thiazolidine **91** which bears a tritylamino group so as to preclude azlactone formation, could be cyclized with water soluble diisopropylcarbodiimide in 25% yield[93]. This gave access to the characteristic bicyclic system of penicillins. Subsequent deblocking of the amino group allowed (in contrast to previous work) obtaining of 6-aminopenicillanic acid (**92**), thus enabling elaboration of various side-chains.



91 **92**

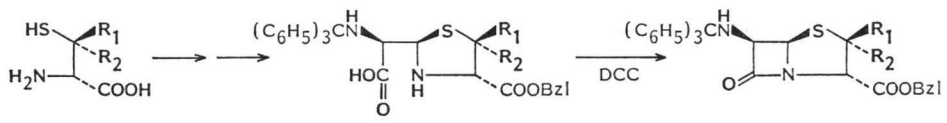
Ring closure from a thiazolidine such as **93** has been achieved using a different approach involving acylation of nitrogen and formation of an organomercury derivative. Thermal decomposition of intermediate **94** thus obtained afforded the lactam **95** as a minor product (10%). It was identical with an authentic sample derived from (+)-penicillanic acid thereby confirming the absolute configuration of the newly created chiral centers[94].



93 **94** **95**

The nor-analogues of phenoxymethylpenicillin *i.e.* compounds lacking a methyl group have been prepared using essentially the same strategy as developed previously by SHEEHAN *et al.*[89,93]. Starting with either *R*- or *S*-methylcysteine[95,96] derivatives **96** and **97** respectively are obtained; cyclization with DCC then affords isomeric β-lactams **98** or **99**[97].

Cysteine from which the optically active thiazolidine **100** is similarly prepared[98] has been used in exactly the same way for the preparation of the bis nor-analogue **101**[99].



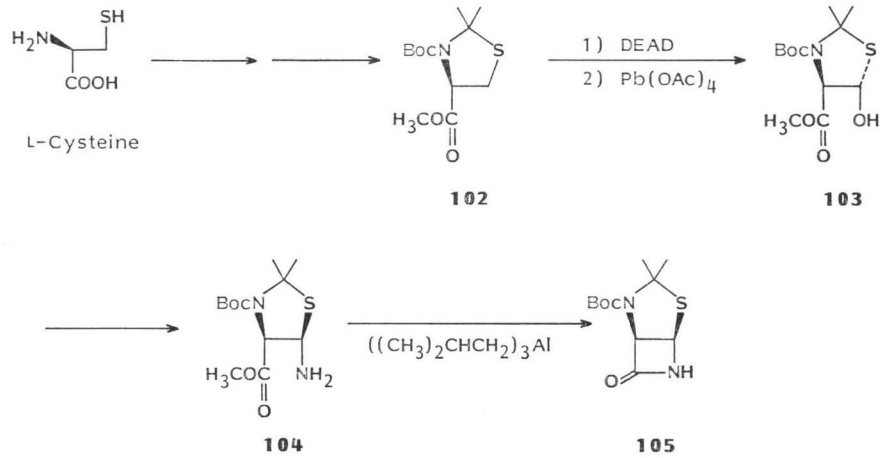
R_1 = H, R_2 = CH_3 **96** **98**

R_1 = CH_3, R_2 = H **97** **99**

R_1 = R_2 = H **100** **101**

Cysteine has also served as the starting material for the mercury induced ring closure which was described above[100].

But one of the most spectacular use of L-cysteine has been in the total synthesis of cephalosporin C by WOODWARD and coworkers[101,102]. Reaction of the thiazolidine derivative **102** with excess dimethyl azodicarboxylate resulted in stereospecific functionalization of the carbon vicinal to the sulfur atom giving **103** after oxidative cleavage. The alcohol group was then conventionally replaced by an amino group with inversion of configuration, the structure of **104** being proven by X-ray analysis. Cyclization to **105** was then achieved using triisobutylaluminium; the structure of **105** was again confirmed by radiocrystallography.

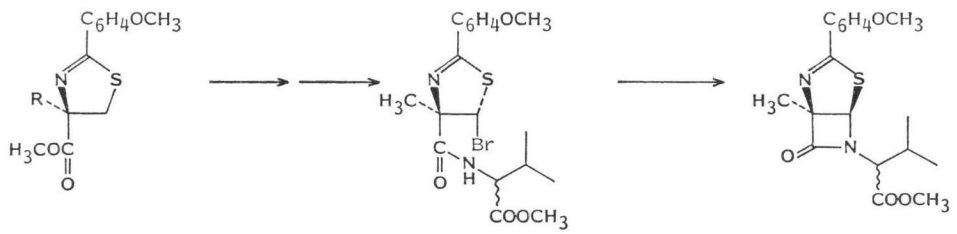


102 **103** **104** **105**

It is of interest to note that **105** contains the structural elements common to both the penicillins and the cephalosporins, and as such can be considered as a key intermediate. Six steps, for example, are necessary for conversion of **105** to cephalothin and eight steps to get cephalosporin C[101,102].

L-Cysteine has also been used by several groups in a biomimetic approach to β-lactams *i.e.* construction of the azetidinone ring from acyclic peptides precursors.

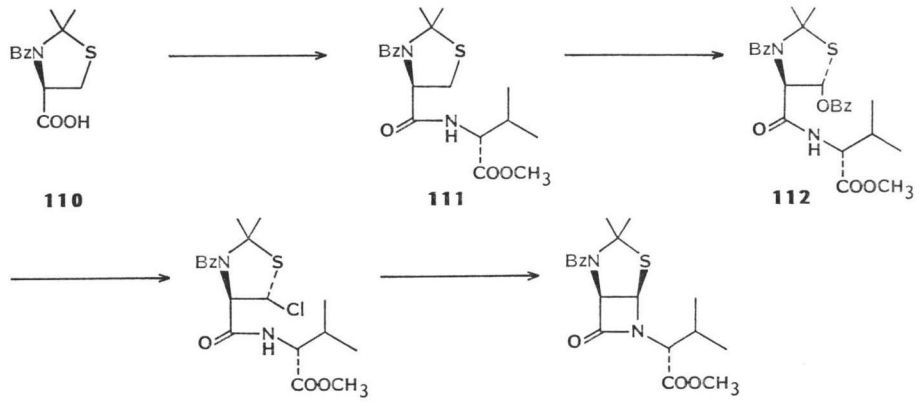
For example, thiazolidine **106** which corresponds to the dehydrated form of an *N*-acyl cysteine derivative, was treated with sodium methoxide and excess methyl iodide to afford **107**. The methyl group thus introduced avoids thiazole formation during the succeeding bromination step which is next carried out on the coupling product with valine. This gave **108** as a mixture of diastereoisomers. Treatment of **108** with potassium hydride in tetrahydrofuran containing lithium perchlorate yielded the bicyclic β-lactam **109** which demonstrated the feasibility of this approach[103].



106 R = H
107 R = CH_3

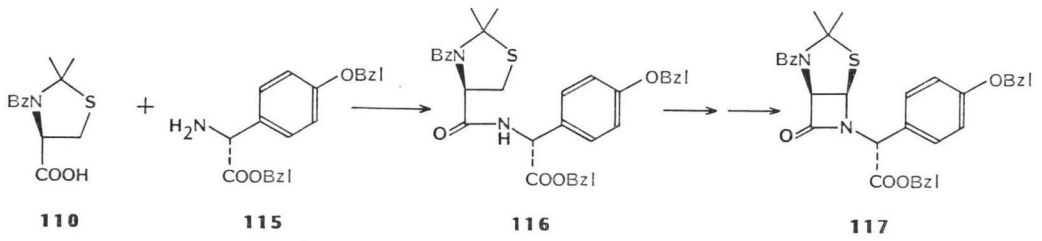
108 **109**

The stereospecific conversion of an acyclic peptide was simultaneously demonstrated to be a viable route by another group[104]. Protected cysteine **110** was coupled with L-valine methyl ester to give the dipeptide **111**. Stereospecific functionalization at C-3 of the cysteine moiety was then achieved using benzoyl peroxide. The high stereo-selectivity observed presumably resulted from shielding of the upper face of the thiazolidine by the valine residue. Treatment of this benzoate **112** with hydrogen chloride afforded **113** with retention of configuration suggesting a cationic intermediate[104]. Ring closure was then brought about with sodium hydride to give **114** in 81% yield[105~107].



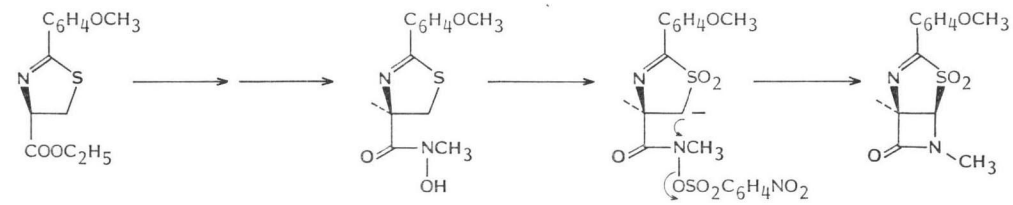
This approach was later used by the same group[108] and by others[109] in a shortened entry to the penicillin ring system.

Similarly, a total synthesis of nocardicin A relied on the same strategy of thiazolidine functionalization and β-lactam ring closure[110]. L-Cysteine-derived **110** was condensed with D-phenyl glycinate **115** to give **116**. Benzoyl peroxide functionalization followed by chlorination and sodium hydride treatment afforded **117** as the major product[110]. Compound **117** was a key intermediate in 3-ANA synthesis.



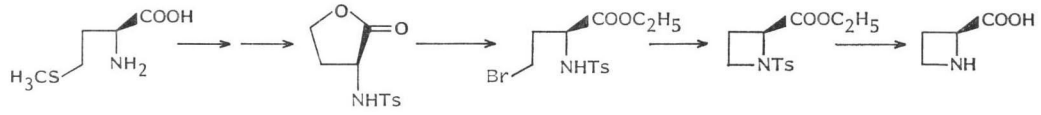
Finally, L-cysteine has been used in a different manner in a successful application[111] of an internal displacement of an hydroxamic ester by a sulfone-stabilized carbanion. L-Cysteine was converted to **118** which was the methylated and further condensed with methyl hydroxylamine to give hydroxamic acid **119** in 55% overall yield. Two steps (introduction of leaving group on the hydroxamic moiety and oxidation of the sulfone) afforded **120** which was viewed as a model biomimetic intermediate. Potassium *tert*-butoxide treatment then gave β-lactam **121** in ~50% yield[111].

Another thioamino acid, L-methionine, has been used as the chiral starting material in the synthesis



118 **119** **120** **121**

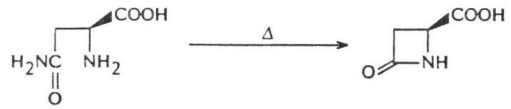
of optically pure azetidine-2-carboxylic acid, which had earlier been prepared in partially racemized form. The present route is advantageous in that substitution reaction does not occur on the asymmetric carbon, thus precluding possible racemization. Tosyl-L-homoserine lactone (**122**) which is easily prepared[112] from tosyl-L-methionine[113] was treated with hydrogen bromide to afford **123**. Cyclization to the desired azetidine **124** was smoothly brought about upon sodium hydride treatment in 95% yield. Final deprotection gave **65**, in good overall yield[114,115].



L-Methionine **122** **123** **124** **65**

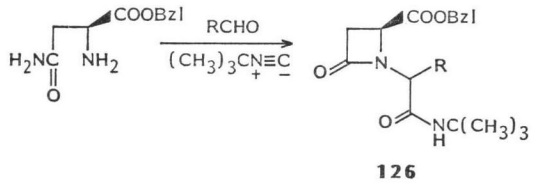
F. Amido-amino Acids

What appears to be the earliest example[116] of chiral azetidinone synthesis is the thermal ring closure of asparagine (100°C, 24 hours, pH 6.7) described to give β-lactam amino acid **125** in 4~5% yield. However, doubt can be cast on these results, since it was stated that **125** was stable to acidic hydrolysis (6 N HCl, 100°C, 24 hours)[116], and subsequent work has since shown that this compound is unstable at room temperature[83,117].



L-Asparagine **125**

A more conclusive use of L-asparagine can be found in its UGI-type condensation with aldehydes such as pyruvaldehyde cinnamaldehyde or benzaldehyde in presence of *tert*-butyl isonitrile. This gave access to the chiral azetidinones **126**[118~120].



126

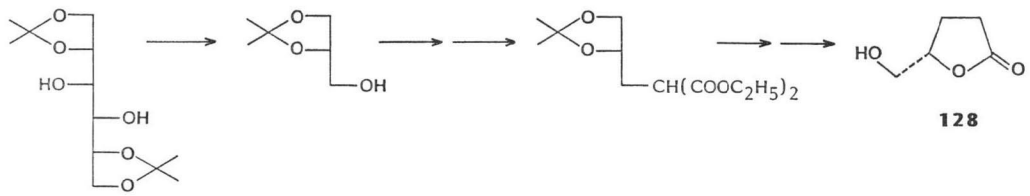
R = $COCH_3$, $CH(CH_3)_2$, C_6H_5, $CH{=}CHC_6H_5$

II. Carbohydrates

Carbohydrates represent another source of abundant chiral material. These can be used to control a single chiral center as will be seen first or a more elaborate use of their stereochemical features can be made as will be seen subsequently.

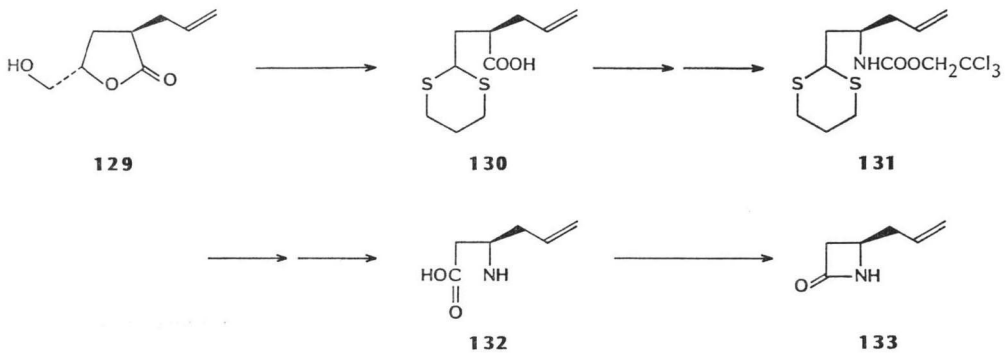
A. D-Mannitol

The inherent symmetry of D-mannitol has been used as a convenient source of 2,3-protected glycerol or glyceraldehyde through oxidative cleavage of its 1,2-5,6-diacetonide **127**.



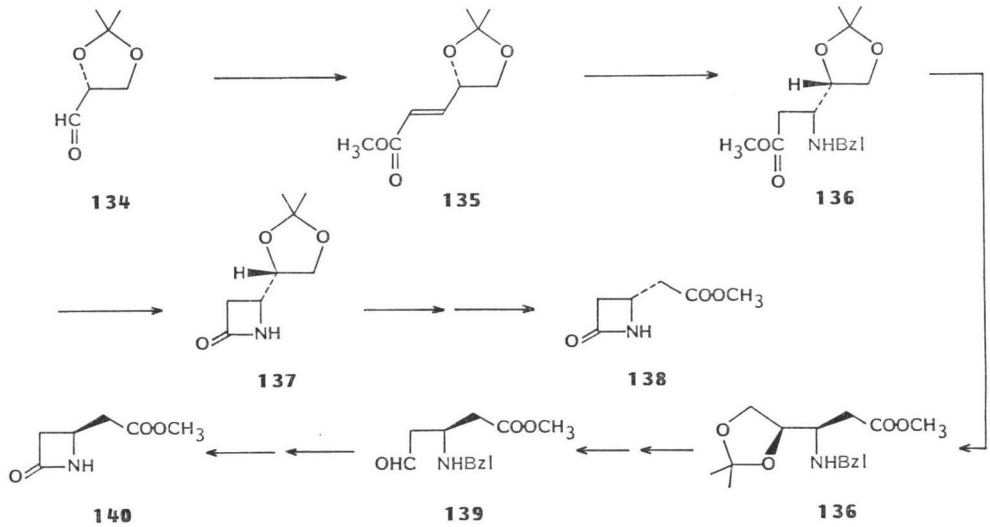
127 **128**

The preparation of optically pure **128** was made possible by a standard sequence of reactions[121]. Further transformations afforded the functionalized lactone **129** which was opened[122] with propane 1,3-dithiol in presence of boron trifluoride etherate to give acyclic carboxylic acid **130**. A CURTIUS-SCHMIDT type rearrangement gave carbamate **131** in 72% yield after saponification and protection of the newly created amine function. Hydrolysis of the protected aldehyde followed by oxidation and removal of the amine protecting group gave the key amino acid **132** which was cyclized to give the desired β-lactam in over 76% yield, employing the procedure developed by OHNO and coworkers[81]. Compound **133** is an intermediate in carbapenem syntheses[123,124]. It should be noted however that 15 steps were required for the preparation of **133** which distracts from the practicability of this route.

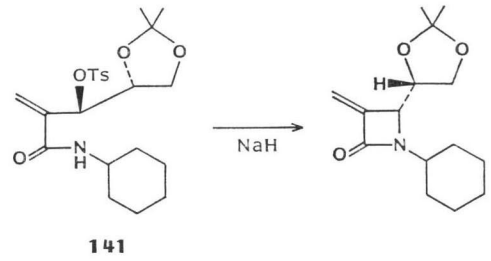


129 **130** **131** **132** **133**

Fewer steps from mannitol were needed to prepare a closely related azetidinone[125]. WITTIG condensation from protected glyceraldehyde **134** afforded **135**. On reacting **135** with benzylamine at −50°C a single isomer **136** was formed in 85% yield. This intermediate **136** was then converted in 46% overall yield to β-lactam **137** using standard procedures. Compound **137** was later converted to azetidinone **138**. Intermediate **136** was also used in the synthesis of the other enantiomer, **140**. Five steps were necessary to convert **136** into aldehyde **139** which was oxidized to the acid and cyclized as above[125].



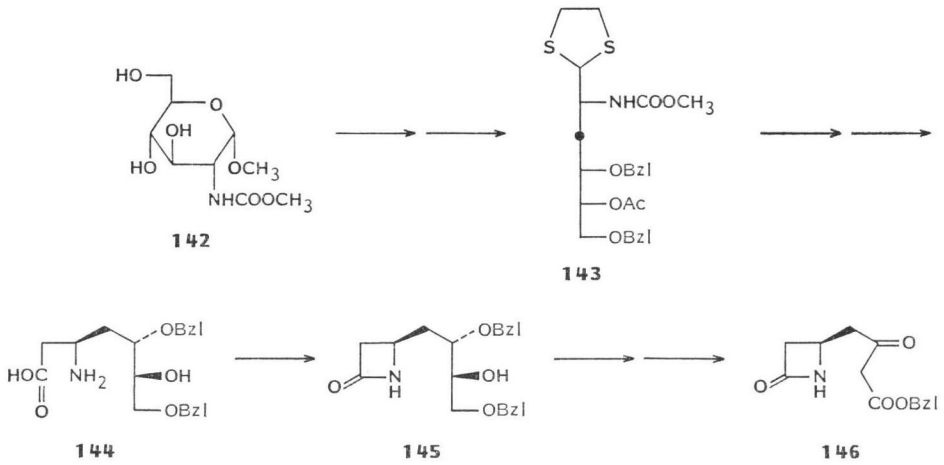
A final use of mannitol can be found in the ring closure of glyceraldehyde-derived **141** (obtained by a SHAPIRO reaction) which is brought about with a strong base.



This has been carried out with both enantiomers[126].

B. D-Glucosamine

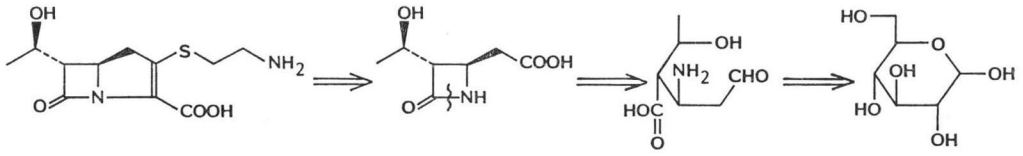
D-Glucosamine is a second example of a carbohydrate in which only one chiral center is retained, in the elaboration of a thienamycin precursor. In a number of classical steps, **142** was transformed into



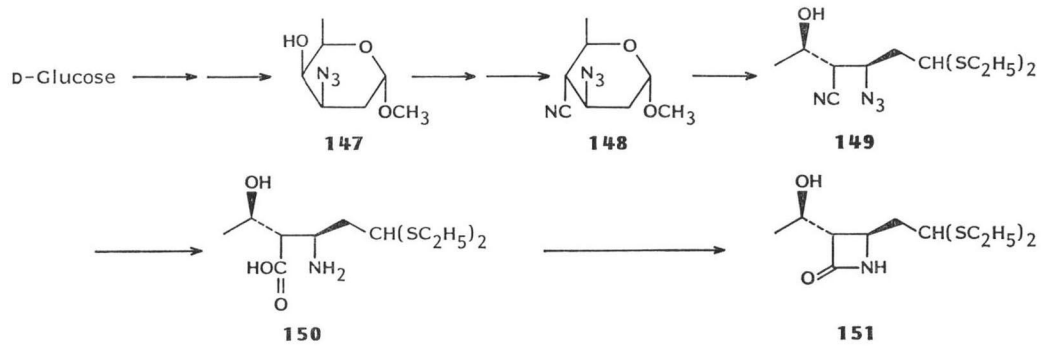
143[127]. After acid hydrolysis, one carbon homologation and deprotection, the amino acid **144** was obtained. This intermediate on treatment with 2,2′-dipyridyl disulfide and triphenylphosphine[81] gave the optically active β-lactam **145** in 89% yield. This was further converted to **146** an key intermediate in thienamycin synthesis[127].

C. D-Glucose

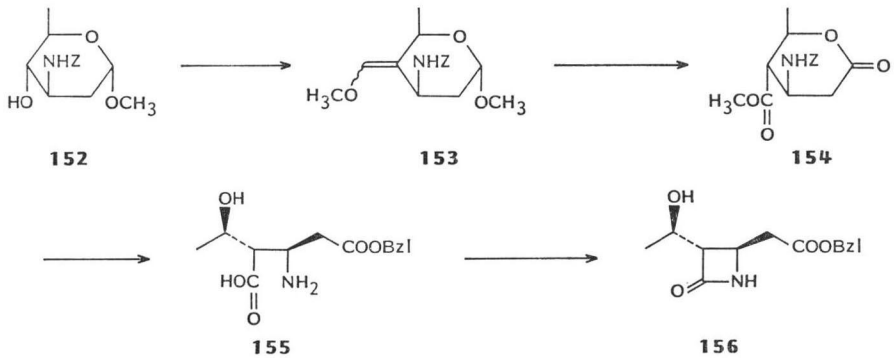
In contrast to all previous examples, glucose has been used as a chiral source in which more than one asymmetric center can still be found in the final ring-closed product. All examples refer to stereocontrolled syntheses of thienamycin: the presence of three contiguous asymmetric centers in thienamycin suggested full use of glucose chiralities according to the following general retrosynthetic analysis:



The first example was announced by DURETTE[128~130]: D-glucose was conventionally converted to **147**. Lateral functionalization was then brought about by S_{N^2} displacement of a triflate by an "naked" cyanide anion to give **148** which was then ring opened in presence of propanedithiol to yield **149**. After hydrolysis to **150**, ring closure to azetidinone **151**, a precursor of thienamycin, could be effected in 51% yield using DCC in acetonitrile.

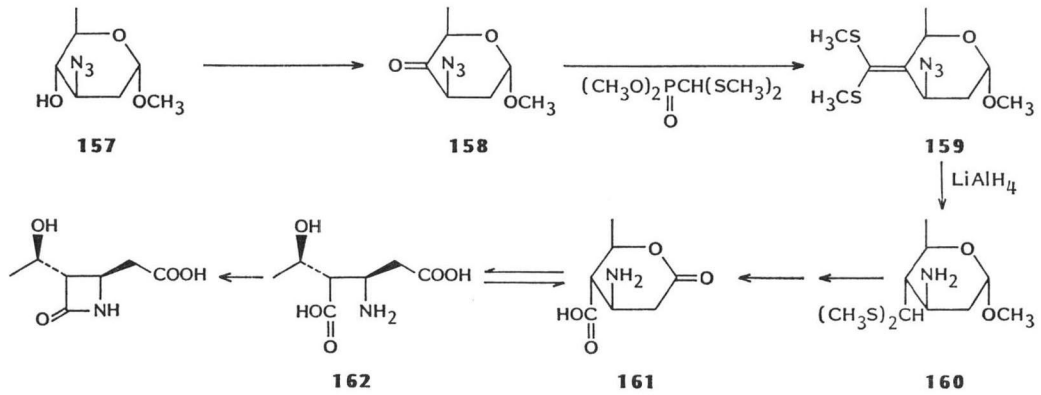


In the second example[131], introduction of the lateral carboxylic acid was obtained by a WITTIG reaction of the D-glucose derivative **152** which was oxidized and reacted with the lithium salt of methoxy-



methyldiphenylphosphine oxide to give **153** (mixture of stereoisomers). Compound **153** was then converted to the ester which was further oxidized to lactone **154**. After hydrogenolysis, ring opening and esterification, amino acid **155** was obtained and then cyclized to β-lactam **156** in 43% isolated yield using DCC.

The third demonstration of glucose chirality transfer was reported almost simultaneously[132]. Compound **157** which was derived from glucose was oxidized to ketone **158** and then reacted with the lithium derivative of *O*,*O*-dimethylformylphosphonate *S*,*S*-dimethyldithioacetal to give **159**. Stereospecific reduction of **159** to **160** was performed with lithium aluminium hydride assuming prior coordination with the neighboring initially formed amine. Conventional manipulation then afforded **161** which is in equilibrium with the open form **162**. As **162** was ring closed with DCC in the racemic series[133,134], the present work is a formal synthesis of (+)-thienamycin[132].

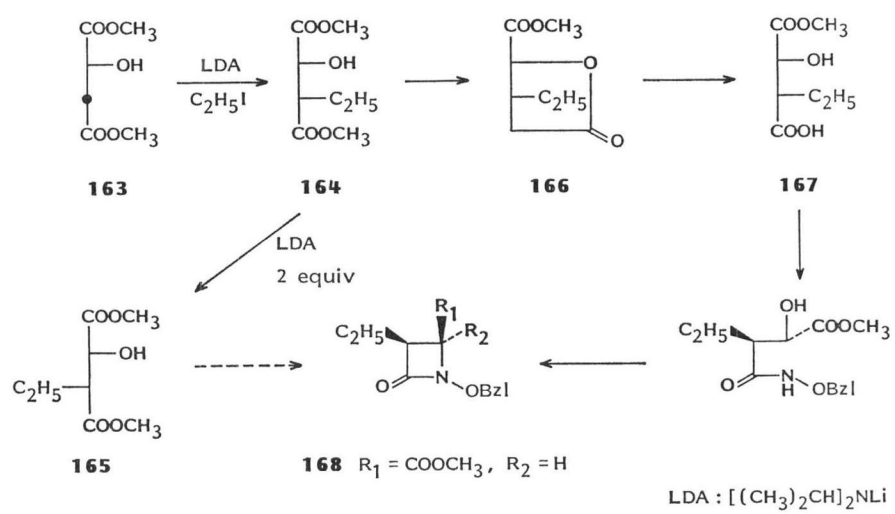


III. Other Chiral Material

A. Acyclic Sources

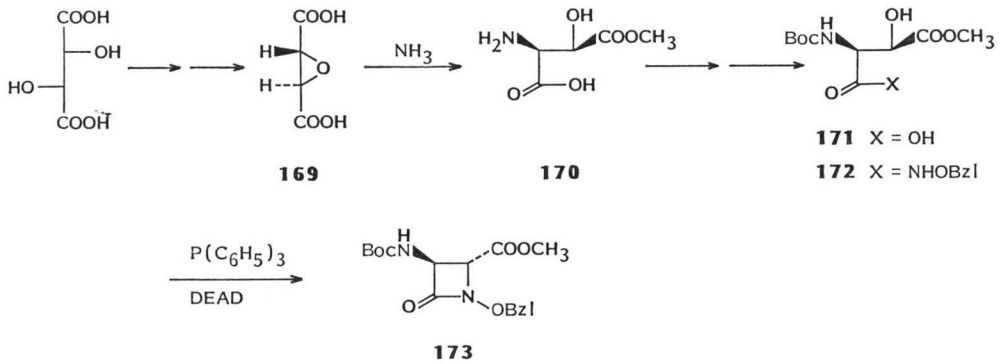
Besides amino acids and carbohydrates several other chiral sources have been used as templates for the preparation of optically active β-lactams.

For example, malic acid which is available in both enantiomeric forms appears to be a good precursor to C-2 and C-3 functionalized β-lactams[135]. Indeed L- (or D-) malic acid dimethyl ester (**163**)



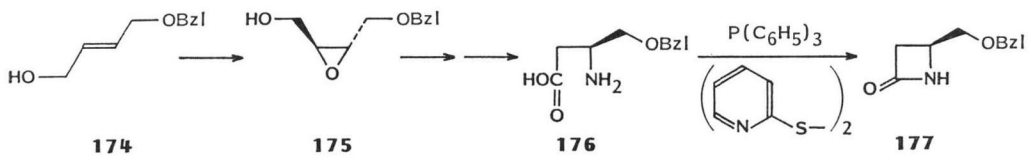
can be alkylated to give **164** and if desired isomerized to **165**. After deprotection to the acid, the monoester **167** can be selectively obtained through formation of intermediate lactone **166**. Reaction of **167** with benzylhydroxylamine followed by application of the MITSUNOBU cyclization conditions afforded **168** whose optical purity was confirmed by NMR chiral shift studies. The same scheme was carried out with **165** and as D-malic acid has been equally chosen as the starting material, the preparation of all four optically pure β-lactam isomers could thus be effected[135,136].

Tartaric acid is another abundant chiral source. In the present case L-tartaric acid has been converted to *trans*-epoxysuccinic acid (**169**)[137] which was opened with ammonia to yield L-*erythro*-β-hydroxyaspartic acid **170**. Selective monoester formation proceeded through a lactone as described above to yield **171** after protection of the amino group. Reaction with benzylhydroxylamine then afforded **172** which was cyclized to **173** ($P(C_6H_5)_3$-DEAD) in ~60% yield. As further transformation gives access to a free β-lactam nitrogen, these syntheses are very powerful especially since all four isomers of β-hydroxyaspartic acid have been described, thus giving access to any corresponding β-lactams[137].

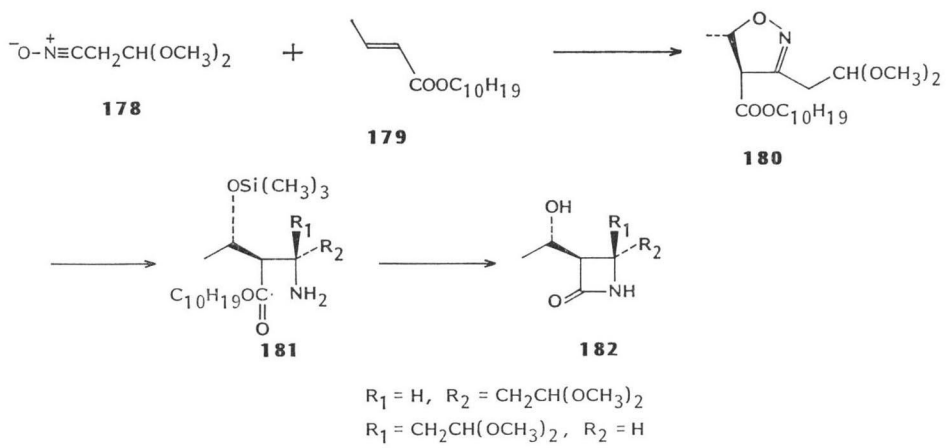


There are two additional examples of use of acyclic optically active material in the construction of β-lactams; although strictly speaking these material are not optically pure, their use will nevertheless be outlined.

Asymmetric epoxidation of *E*-benzyloxybutenol (**174**) using L-diethyl tartarate as chirality control[138] afforded the chiral epoxide **175** in 90% enantiomeric excess and 85% chemical yield. After opening of the epoxide, the corresponding glycol was transformed uneventfully into amino acid **176** which was then cyclized[139] using the OHNO procedure to azetidinone **177**, a usefull synthon in β-lactam chemistry.



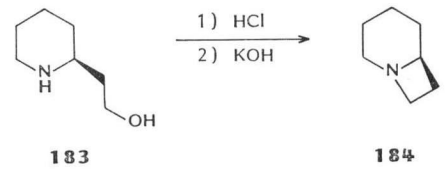
The other example involved the formation of isoxazoline **180** which is obtained by cycloaddition of nitrile oxide **178** and (−)-menthyl crotonate **179** in 85% enantiomeric excess. This oxazoline was reduced to **181** which was cyclized with ethyl magnesium bromide to β-lactam **182** after protection of the alcohol group as its silyl ether[140]. The overall yield was 13%.



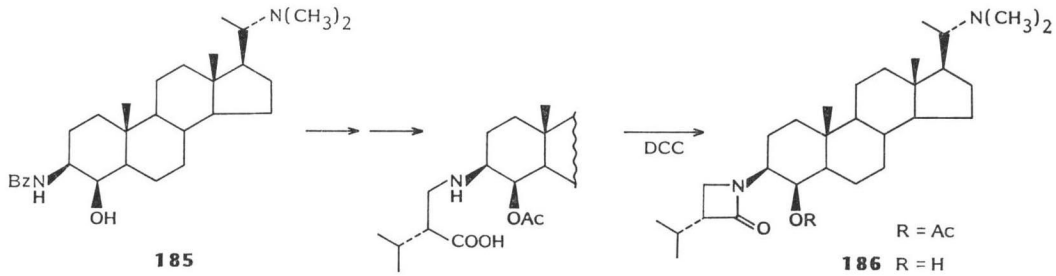
B. Other Natural Products

A few examples of naturally occurring bicyclic azetidines, not related to β-lactam antibiotics, can be found in the literature and as such they will be briefly spoken of herein.

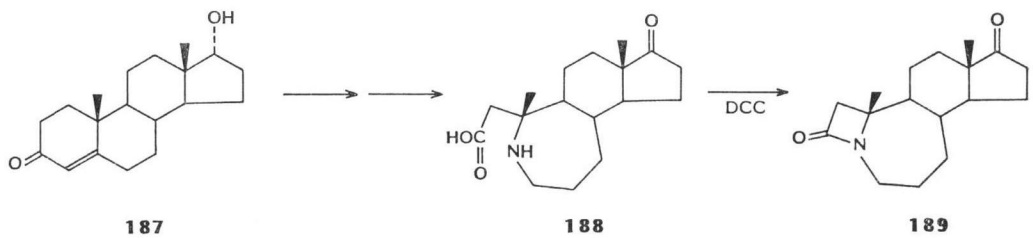
The first of these, conidine (**184**), was synthesized from optically active 2β-hydroxyethylpiperidine (**183**) by sequential treatment with hydrochloric acid, then potassium hydroxide, thus affording **184** in 32% yield[141].



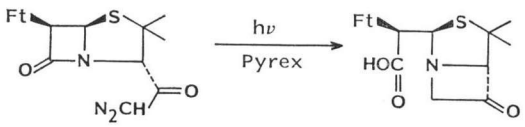
The second example refers to pachystermine (**186**), a naturally occurring alkaloid, which was synthesized in a large number of steps from epipachysandrine A (**185**), a minor alkaloid present in the same source[142,143].



Finally, a steroidal β-lactam has been prepared from A-nortestosterone (**187**). Thirteen steps are necessary to convert **187** into **188** which is then cyclized to **189** with DCC in nitromethane[144,145].



The last example describes the rearrangement which was observed during irradiation of synthetic **190**. The diazoketone on departure of nitrogen opened the β-lactam ring to create a new four-membered nitrogen-containing ring, azetidinone **191**[146].



190 **191**

These examples, however, do not seem to be of practical use in total syntheses.

Conclusion

Today β-lactams represent without doubt the most important family of therapeutically useful antibiotics. This family has given birth to an increasing number of marketed compounds. Lately, organic synthesis and in particular total synthesis have gained importance as is evidenced by the forthcoming marketing of totally synthetic molecules.

It is therefore expected that, due to a number of reasons of which cost is not the least, enantiospecific construction of chiral β-lactams, will prove to be a major tool in the production of new β-lactam antibiotics and other β-lactamase inhibitors.

Addendum in Proof

Since submission of this review article, a number of papers relevant to this subject have appeared in the literature. At first, more general works about azetidines[147~149] and β-lactams[150,151] can be found. Then, additional synthetic uses of L-serine and L-threonine in the stereospecific construction of monobactams[152~154] have been described. Furthermore, the enantioselective synthesis of asparenomycin C, starting with chiral 3-amino pentanedioic acid has been outlined[155] and another use of L-malic acid has been proposed[156]. The chiron approach[157] has been successfully applied to the total synthesis of carbapenems starting with D-glucose[158] or D-glucosamine[159], respectively. Finally, three examples of the stereospecific elaboration of the β-lactam moiety using a neighbouring chiral center as internal control have been recently announced; these make use of: 1) an oxazine derived from commercially available (3*R*)-methylcyclohexanone[160], 2) a *Π*-allyltricarbonyliron complex incorporating (*S*)-α-methylbenzylamine[161] and 3) a chromium carbene addition product with an optically active thiazoline ester[162].

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