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Design and Synthesis of Conformationally Constrained Amino Acids as Versatile Scaffolds and Peptide Mimetics

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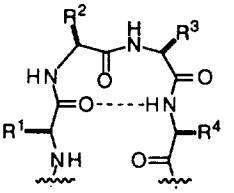
I. INTRODUCTION

The field of amino acids has gained enormous popularity and relevance in recent years, particularly with the emergence of unnatural analogs as components of molecules with therapeutic potential.[1] The need to replace natural amino acids in peptides with non-proteinogenic counterparts in order to obtain drug-like target molecules has stimulated a great deal of innovation on several fronts.[2] Different areas of expertise have come together to allow a better understanding of interactions of small molecules with biological targets such as enzymes or receptors.[3] These efforts have led to the design of molecules as potentially useful medicinal agents often based on intriguing biological rationales and hypotheses. A scenario in which a clinically important enzyme is co-crystallized with its natural substrate, thus providing crucial and "visual" information for realistic drug design through synthesis of unnatural analogs, is in fact, a practice of common occurrence today.[4] The medicinal chemist is well versed in understanding biological phenomena, and admirably served by physical tools such as X-ray crystallography, molecular modeling, NMR, and SAR data.[5] Armed with such valuable information, in addition to other tools such as computer aided methods, and the ever-expanding arsenal of synthesis methods, it is now possible to design specific molecules for a variety of therapeutic purposes.

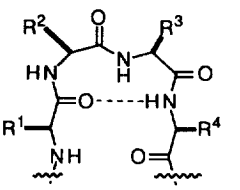
One of the more exciting areas of research in drug design has been the synthesis of so-called peptidomimetic molecules[2,3] that are expected to have the same therapeutic effects as natural peptide counterparts, with the added advantage of metabolic stability. Of particular interest has been the replacement

of a dipeptide motif in a given natural substrate with a constrained or rigidified counterpart that simulates a so-called β-turn.[2,3,6] According to a well-accepted classification,[6] these motifs can exist as type I and type II β-turns where the peptide backbone adopts a U-shaped conformation (Figure 1). These motifs are characterized by specific angular and torsional parameters in addition to an important 10-membered intramolecular H-bond that orient two peptide units from each end.[7] It is therefore clear that the synthesis of constrained dipeptide motifs would nicely mimic the natural β-turn in a given target molecule, particularly if it incorporated a carboxyl and amino group in geometrically suitable positions for peptide coupling. Expression **1** in Figure 1 is a composite representation of such a constrained dipeptide mimetic which we shall categorize under the general name of a 1-azaoxobicycloalkane skeleton. The attachment of one or more rings to the basic structure is also possible.

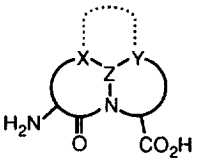
Figure 1



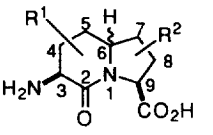
Type I-β-turn



Type II-β-turn



1



2

By its very nature, such a motif could also encompass heteroatom analogs, in which carbon is replaced by sulfur, oxygen or nitrogen, at different synthetically attainable sites. The presence of functional groups as pendant substituents on the basic ring system or its heteroatom congeners would also provide opportunities for diversification. The nature of such substituents can be modulated so as to engage them into hydrophobic, hydrophilic and related interactions with biological targets. Thus, the synthesis of dipeptide motifs such as **1** (Figure 1) with specific substituents on either ring and with amide appendages at each end, could be the ultimate objective as a drug-like molecule. Synthesis strategies for such motifs must therefore be versatile to allow the inclusion of substituents. This will entail stereochemical problems that will only heighten the challenge of synthesis even further.

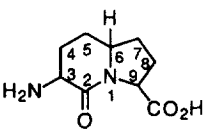
An added bonus to the availability of such strategies is that the originally intended constrained motif can also be considered as a scaffold for chemical and functional diversity. In essence, the deployment of other functional groups that can be manipulated at will, and independently of each other, can enhance the utility of the original motif by making it a spatially defined chemical platform. The application of combinational methods of diversification could lead to libraries of compounds based on a constrained

dipeptide scaffold of the type shown in expression **2**, and related heteroatom analogs or ring-size variants (Figure 1). The judicious choice of orthogonally manipulatable functional groups will provide useful scaffolds for combinatorial chemistry.[8]

The objective of this Report is to provide an up-to-date overview of molecules related to 1-azaoxobicycloalkane amino acids and analogs that incorporate a complete dipeptide unit only. The examples are thus confined to those motifs that harbor at least a six-atom subunit with one carboxyl "end", a central amide group, and an amino "end" as part of the dipeptide unit. Because of angular and torsional parameters discussed above in connection with the β-turn types, we have chosen the indolizidinone skeleton (Figure 1) as a prototype. Other ring size modifications, including heteroatom variants are presented in the same order, i.e. 5,6-fused, 5,7-fused, etc. Since this review is intended mostly for organic, medicinal, and biologically orientated chemists who are engaged in the act of synthesis, we chose to adopt a more visual and graphical representation format. The 1-azaoxobicycloalkane amino acids are grouped under different structural types, and the general synthesis methods for each type are briefly outlined. The tabular form of representation also includes pertinent information that the reader may find useful before going to the primary literature for molecules of special interest. Because of the expansive nature of the subject matter, coverage is not exhaustive. Nevertheless, it is hoped that the information given provides a general overview and an appreciation of the topic.

II. AZABICYCLOALKANE AMINO ACIDS

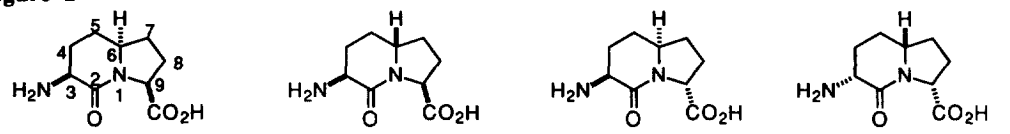
1. 5,6-Fused 1-Aza-2-oxobicycloalkane Amino Acids (Indolizidinone-type)



This section will focus on the synthesis and structural features of bicyclic lactams that encompass an Ala-Pro type dipeptide unit with an all-carbon backbone (indolizidinone). In order to simulate the proline-like motif, and to maintain the overall features of a dipeptide unit, we shall consider first the 1-aza-2-oxobicyclo[4.3.0]nonane skeleton.

Although such a 5,6-fused structure seems to be intuitively an obvious target as a constrained Ala-Pro type dipeptide, it was not the first to be synthesized in this series, as it was preceded by the corresponding 7-thia analog (see section III.1). There is a practical reason for this, since the 7-thia derivative can be synthesized from L-cysteine, thus securing one stereogenic center from the natural amino acid template at the outset. The structures and absolute stereochemistry of four representative indolizidinone amino acids are shown in Figure 2.

Figure 2

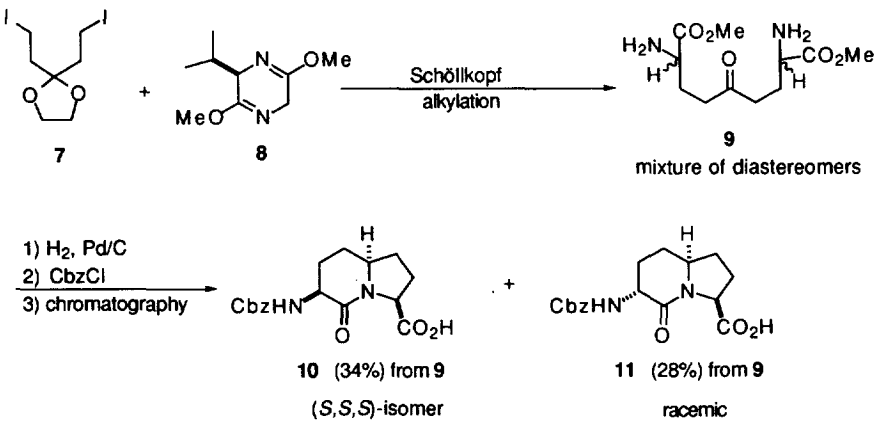


3 (3*S*, 6*S*, 9*S*)- **4** (3*S*, 6*R*, 9*S*)- **5** (3*S*, 6*S*, 9*R*)- **6** (3*R*, 6*R*, 9*R*)-

An obvious advantage of such a system compared to the 7-thia or 5-oxa analogs is their greater stability under acidic conditions. It is clear that a number of strategies can be adopted to access this general structure, and to secure the desired absolute stereochemistry. In general, these strategies have consisted in intramolecular cyclizations of cyclic iminium ions and related derivatives. The incorporation of substituents on the backbone would obviously add to the challenge of stereocontrol.

Although the obvious choice of starting material for the 5,6-fused indolizidinone amino acids is a proline or pyroglutamic acid type template, the first syntheses relied in fact on the intramolecular cyclization of acyclic precursors. A diastereoselective synthesis of a bis-diamino acid derivative as an acyclic precursor to the target 5,6-fused indolizidinone is shown in Scheme 1.[9] After a Schöllkopf alkylation and hydrolysis,

Scheme 1



7 **8** **9** mixture of diastereomers

10 (34%) from **9** (*S,S,S*)-isomer **11** (28%) from **9** racemic

the mixture of diastereomeric 5-keto-diamino azelate diesters **9** was subjected to reductive amination. The indolizidinone amino acids could be easily separated as their Cbz derivatives to provide the (3*S*,6*S*,9*S*)-isomer in 34% yield. According to the authors,[9] the method has allowed them to produce multigram quantities of enantiomerically pure indolizidinone **10**, in spite of the stereochemical limitations of the process.

An expedient entry into the indolizidinone amino acid structure utilizes L-glutamic acid as a chiral educt (Scheme 2, PhF = 9-(9-Phenyfluorenyl)).[10] L-*N*-(PhF)Glutamate diesters **12a** and **12b** were subjected to Claisen condensations to give respectively β-keto esters **13a** and **13b**, which upon hydrolysis and decarboxylation, yielded the *C2* symmetrical and enantiomerically pure 5-keto-diamino azelates **14a** and

14b. Indolizidinone amino acid **16** was synthesized from diamino azelate **14** via two different routes: one featuring reductive amination of symmetric amino ketone **14** (Scheme 2), the other involving hydride reduction of **14** followed by activation and intramolecular displacement of the resulting symmetric amino alcohol (Scheme 3). In the reductive amination sequence, simply increasing hydrogen pressure was found to augment the diastereoselectivity in the reductive amination step with (2*S*, 8*S*)-**14** such that the ratio of (6*S*)-**15** to (6*R*)-**15** could be varied from 1:2 up to 49:1 (Table 1). The Claisen condensation/reductive amination/lactam cyclization sequence provided enantiopure (3*S*, 6*S*, 9*S*)-indolizidinone amino acid **16** in 61% (7 steps), and 41% (6 steps) respective overall yields from **12a** and **12b**. Epimerization of the C-9 stereocenter of (3*S*, 6*S*, 9*S*)-*N*-(Boc)amino indolizidinone methyl ester **15** with $NaN(SiMe_3)_2$ followed by hydrolysis gave (3*S*, 6*S*, 9*R*)-indolizidinone amino acid (3*S*, 6*S*, 9*R*)-**16**. The synthesis of all stereoisomers of enantiopure indolizidinone amino acid **16** is possible by employing both L- and D-glutamate in this approach. In addition, the alkylation of ketone **14** now provides alkyl-branched diaminoazelate intermediates and thus opens the route for the synthesis of 5- and 7-alkyl substituted indolizidinone amino acids.[10e]

Scheme 2

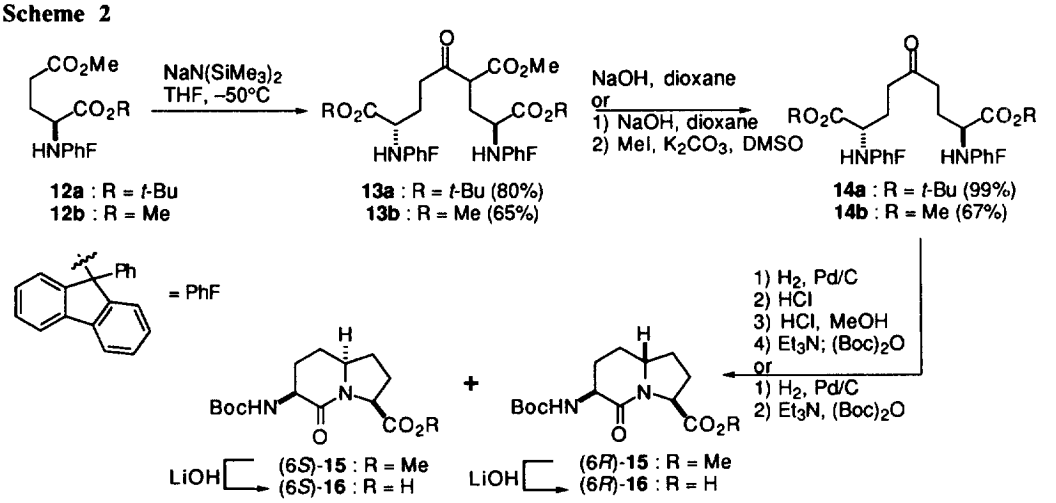
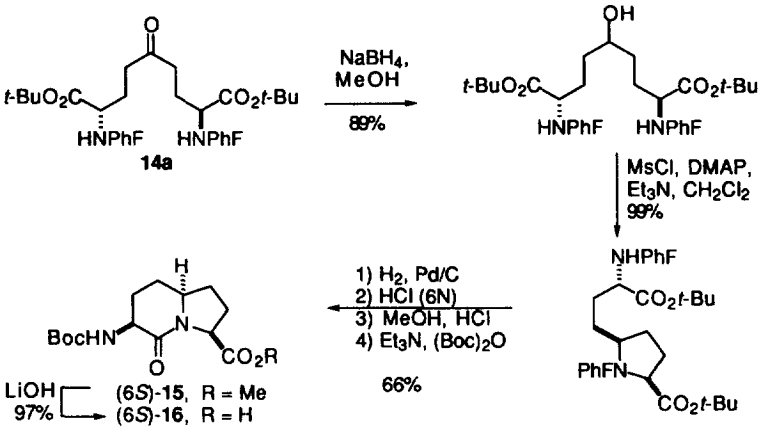


Table 1. Influence of H_2 Pressure on Reductive Amination of 14.[a]

14	R	H_2 (atm)	% (6*S*)-15	% (6*R*)-15	dr
a	*t*-Bu	1	45	22	67:33
a	*t*-Bu	11	66	3	96:4
b	Me	1	27	62	33:67
b	Me	6	81	2	98:2

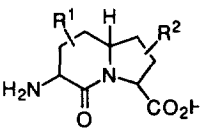
[a]isolated yields

Scheme 3



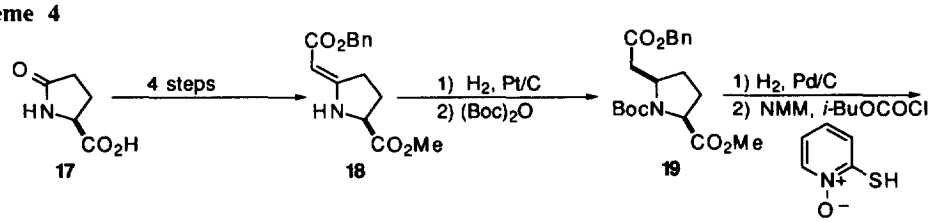
The analog [IAA$^{4\text{-}5,4'\text{-}5'}$]-GS, in which indolizidinone amino acid (6*S*)-**16** replaced the D-Phe-Pro residues in the cyclic-peptide antibiotic gramicidin S (GS; cyclo-[Val$^{1.1'}$-Orn$^{2.2'}$-Leu$^{3.3'}$-D-Phe$^{4.4'}$-Pro$^{5.5'}$]$_2$) exhibited similar antibacterial activity and reduced hemolytic activity.[10b,e]

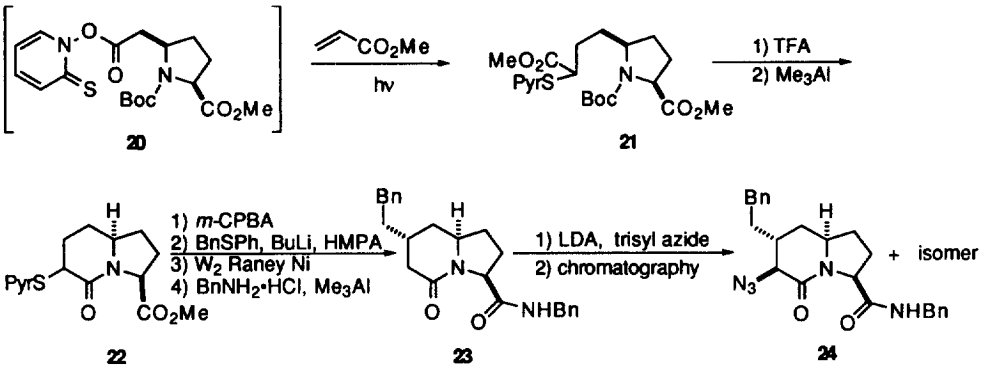
2. Substituted 5,6-Fused 1-Aza-2-oxobicycloalkane Amino Acids



As previously mentioned, a synthesis of the constrained Ala-Pro dipeptide motif in the indolizidinone series would be much more useful if it were to incorporate substituents in the bicyclic ring system. L-Proline or L-pyroglutamic acid are ideal precursors to the indolizidinone ring system. The advantage of L-pyroglutamic acid is the presence of the lactam function which can serve the dual purpose of allowing chemical manipulations in the five-membered ring, in addition to providing a reactive site at the intended C-6 carbon atom through carbonyl reactions. An example of the implementation of this strategy can be seen in Scheme 4.[11]

Scheme 4

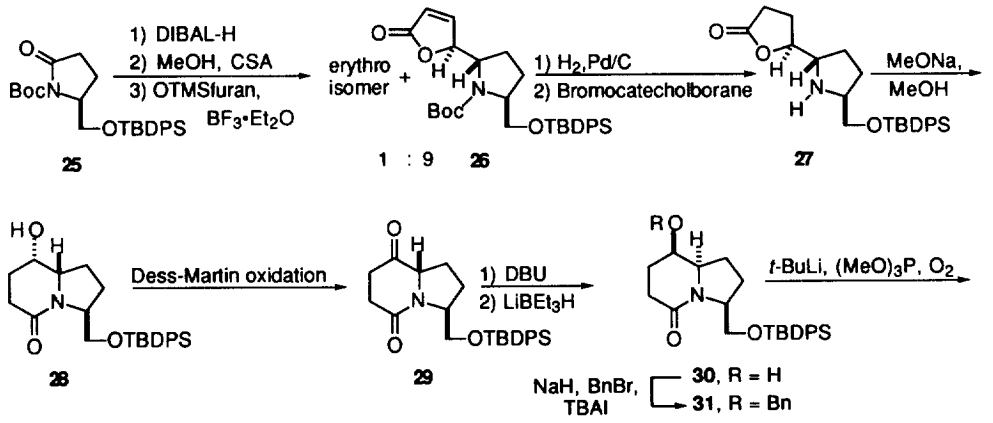


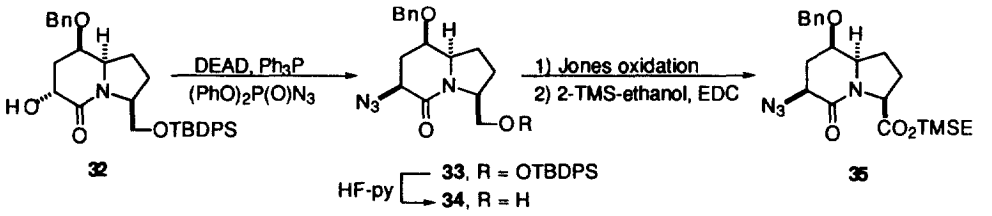


The desired *cis*-substitution pattern, which was required for a (6*S*)-stereochemistry, was obtained by a known two-carbon extension followed by a stereoselective reduction to **19**. A key step was the application of the free-radical Barton thiopyridinyl hydroxamate fragmentation[12] of the ester **20** in the presence of methyl acrylate to give **21**. Manipulation of amine and ester functionality led to the indolizidinone **22**, in which a strategically placed 2-pyridylthio group served as a site for an elimination-conjugate addition sequence leading to the amide **23**. Lactam enolate formation, and electrophilic azidation then led to a 1:1 mixture of the desired (3*S*)-azido lactams which could be separated by chromatography. The strategy is flexible to accommodate other substituents at the C-4 position by a selection of an appropriate carbon nucleophile in the conjugate addition step. Furthermore, diversification can be assured by selecting different amide functions from the carboxyl and azide (amine) ends. For example, the 3-indole 3-acetamide derivative was prepared and found to have a low (3μM) but selective binding affinity to the NK-2 receptor.[11]

A versatile method for the stereocontrolled synthesis of 5,6-fused 1-aza-2-oxobicycloalkane amino acids is shown in Scheme 5.[13]

Scheme 5

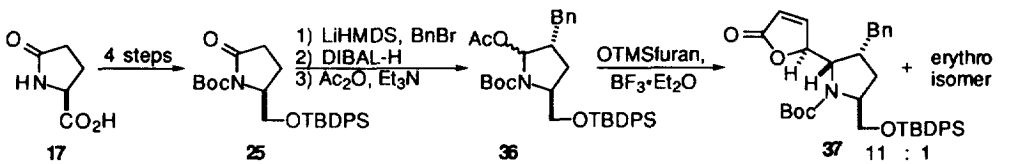


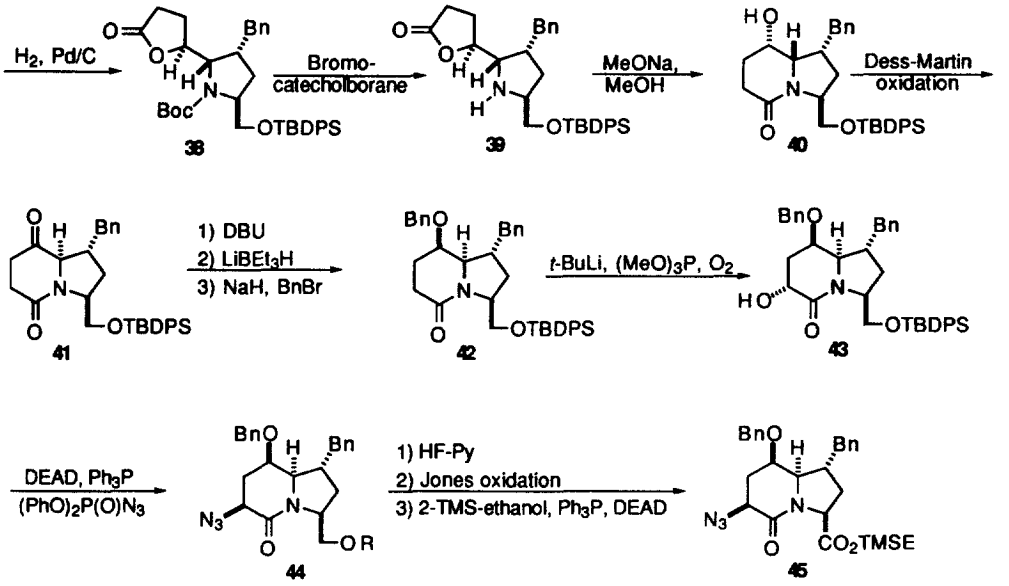


Condensation of the readily available lactam **25** with OTMS-furan gave a 9:1 *threo-erythro* mixture of butenolides which was manipulated by standard methods to give the crystalline indolizidinone **28**. The stereochemical outcome at C-6 could be exploited further to provide the (6*R*)-isomers of the intended structures. However, the (6*S*)-configuration could be easily obtained by an oxidation epimerization-reduction sequence proceeding from **28** to **29** to **30**. Protection as a benzyl ether allowed a stereocontrolled hydroxylation of the lactam enolate en route to a single C-3 hydroxy isomer **32**. The azide group was introduced via a Mitsunobu reaction to produce **33**, the structure of which was definitively assigned by X-ray crystal analysis on the alcohol **34**. Finally, oxidation to the acid and esterification gave **35** with three orthogonally protected functional groups. Transformation to the 3-indole 2-acetamido-5-*O*-benzyl carboxamide derivative led to a selective NK-2 activity (49% binding at 1μM).

The utilization of a benzyl substituted L-pyroglutamic acid analog in the synthesis of a C-7 benzyl indolizidinone amino acid is shown in Scheme 6.[14] Benzylation of the lithium enolate of **25** led to essentially one isomer **36** which was activated as the *N*-Boc iminium ion precursor **36**. Treatment with OTMS-furan under Lewis acid catalyzed conditions gave the *threo*-product **38** as the major isomer. Manipulation of functionality as in the case of the unsubstituted analog (Scheme 5), through a series of highly stereocontrolled reactions, led to the desired indolizidinone **45**. A number of intermediates were characterized by X-ray crystal structure analysis. This strategy allows a number of other carbon (or heteroatom) substituents to be incorporated at C-7 of the intended target. The orientation of the resident groups are largely responsible for the stereocontrolled introduction of new substituents, and a single center originally present in L-pyroglutamic acid is responsible for all new centers introduced through cooperative effects. The strategies shown in Schemes 5 and 6 can be easily adapted to the creation of libraries of β-turn mimetics by attachment of the 1-aza-2-oxobicycloalkane motif to a solid phase support and manipulation of the amino acid extremities individually.[15]

Scheme 6

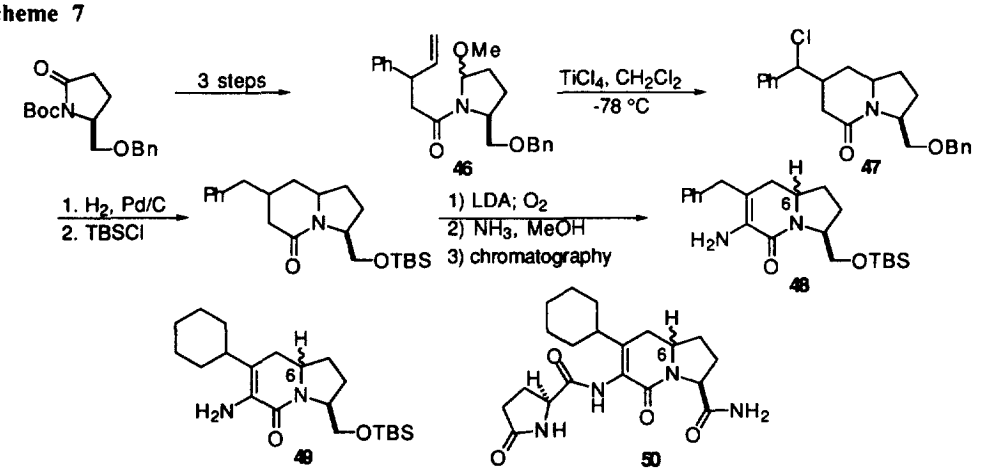




A free-radical approach to carbocyclization has been described in which the bond-forming step leads to substitution at the amine-bearing carbon atom C-3 on a structure related to **3** (Figure 2).[16] In addition to the expected (3*R*,6*S*,9*S*)-3-benzyl-3-acetamido indolizidinone *tert*-butyl ester (34%), a significant amount (44%) of reduction was also observed (see also Scheme 10).

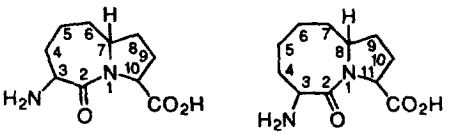
A method that leads to a substituted α,β-unsaturated indolizidinone amino acid precursor related to **24** except for the absence of two stereogenic centers is illustrated in Scheme 7.[17a] It is of interest that the 5,6-fused system **47** was the product of an unexpected ring contraction from treatment of **46** with $TiCl_4$. The basic strategy was intended to involve the generation of an iminium ion and a cyclization to a 5,7-bicyclic system; however, this method led to the 5,6-bicyclic system **48**.

Scheme 7



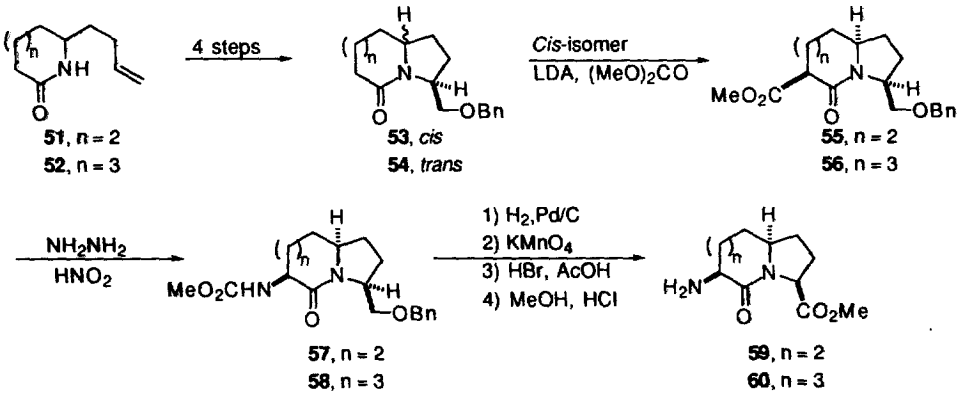
In light of this result, the 4-cyclohexyl Δ^3-indolizidinone anolog **49** was synthesized using a similar procedure.[17b] Introduction of **49** into thyrotropin-releasing-hormone (TRH) gave mimetic **50** that exhibited receptor affinity and bioactivity contingent upon the ring-fusion stereochemistry. A comparison of **50** with the unrestricted analog cyclohexyl-Ala^2-TRH concluded that (6*R*)-stereochemistry interfered with binding and potency while the (6*S*)-isomer showed 3.4 times better affinity and proved to be 4.7 times more potent.

3. 5,7- and 5,8-Fused 1-Aza-2-oxobicycloalkane Amino Acids



The earliest syntheses of the 5,7- and 5,8-fused skeletons exemplified by the general structures shown above, started with the lactam portion.[18] Seven- and eight-membered lactams **51** and **52** were elaborated through their unsaturated side-chains to produce isomeric bicyclic lactams **53** and **54** (Scheme 8). Functionalization of the *cis*-lactam enolate led to the ester which was rearranged to the corresponding carbamate via the hydrazide. Functional group manipulation gave the racemic 5,7- and 5,8-fused bicyclic amino acid derivatives. It is of interest that the corresponding analogs comprising a 4-phenyl butyric acid group attached to the C-3 amine showed potent ACE inhibitor activity in both 5,7- and 5,8-fused ring systems.[18]

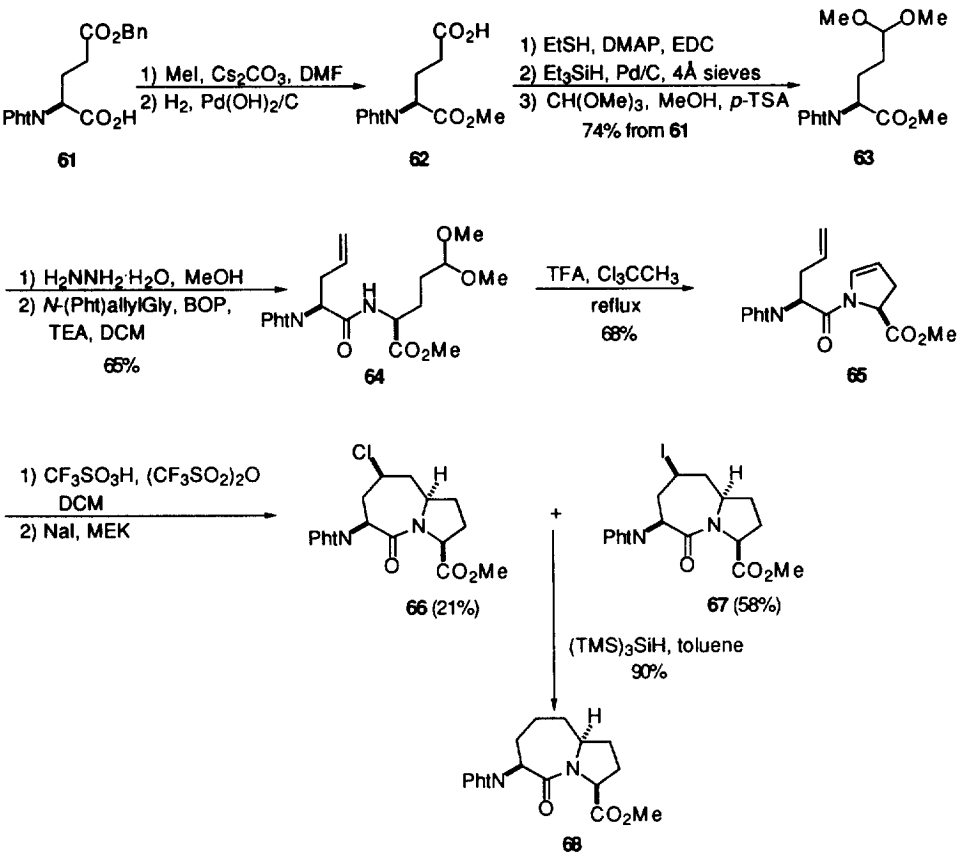
Scheme 8



A different strategy to assemble the 5,7-fused system starting with L-glutamic acid derivative **61** is shown in Scheme 9.[19] Selective functionalization of **61** through intermediates **62** and **63** led to the peptide **64** which was transformed into the cyclic enamide **65**. In a key acyliminium ion cyclization reaction, enamide **65** was transformed into the intended 5,7-fused skeleton as a mixture of halides **66** and **67**.

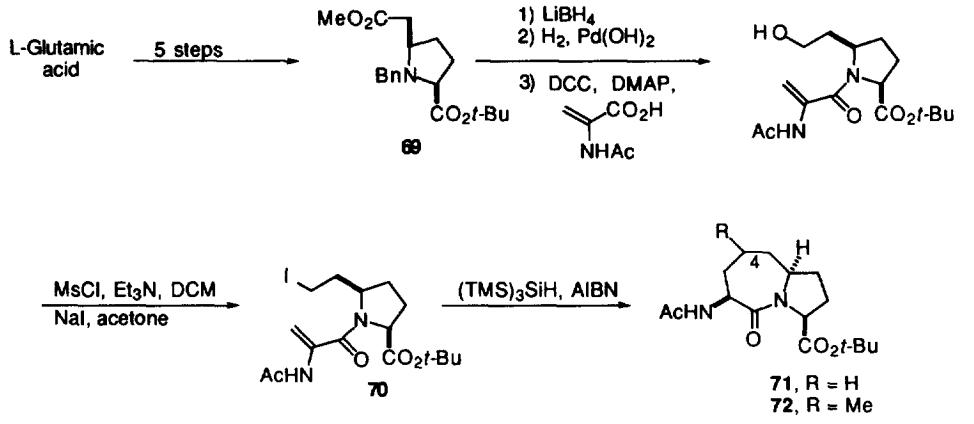
Radical-mediated dehalogenation afforded the *N*-phthalimido ester **68**, the structure of which was ascertained by nOe studies.

Scheme 9



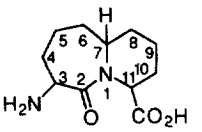
Another approach starting from L-glutamic acid features a free-radical cyclization to form the 5,7-fused ring system (Scheme 10).[20] Glutamate was transformed into the known *cis*-disubstituted derivative **69** which was in turn subjected to catalytic hydrogenation to liberate the free pyrrolidine derivative. Amide formation with the acrylic acid derivative, and further manipulation led to iodide **70.** The key reaction relies on a *7-endo-trig* cyclization of intermediate **70** to afford the intended target **71** in a yield of 42% with excellent diastereoselectivity. Improved yield (61%) of **71** was achieved in the free-radical cyclization when the iodide group was changed to a phenylselenyl function. Use of a dehydro amido butyrate in a similar sequence gave a 1:1 diastereomeric mixture of (4*RS*)-methyl analogues **72** in 52% yield.

Scheme 10



The structures of 3,4-unsaturated 4-phenyl, 5,7-fused compounds prepared by intramolecular Lewis-acid mediated cyclizations[21,22] have been revised and shown to be 5,6-fused systems.[17a]

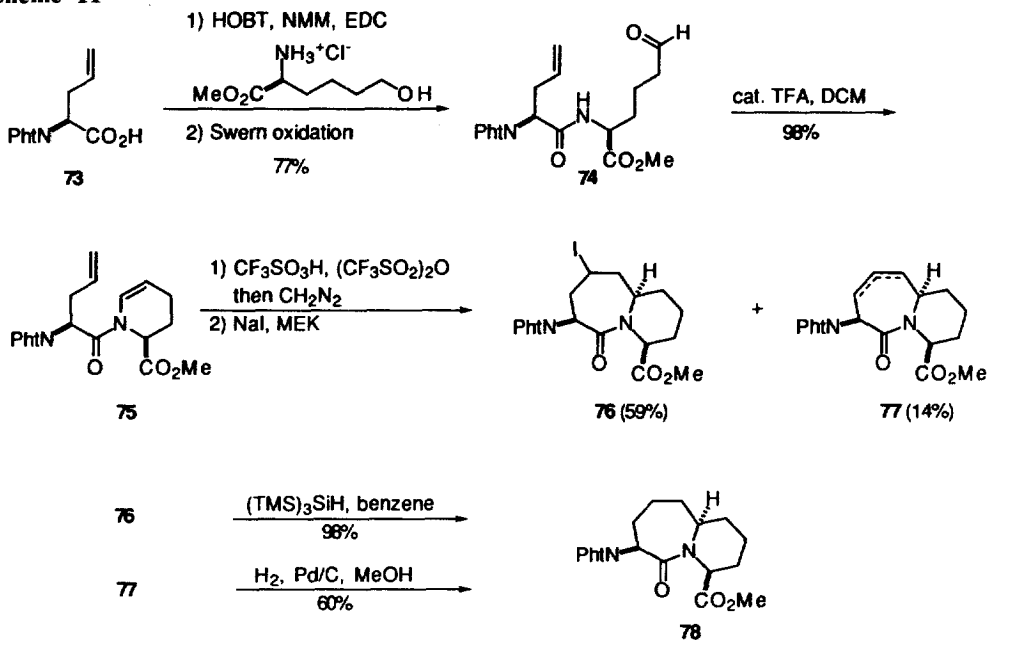
4. 6,7-Fused 1-Aza-2-oxobicycloalkane Amino Acids



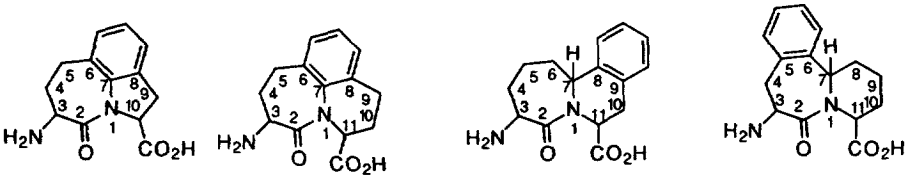
The synthesis of the 6,7-fused bicyclic systems shown above, was accomplished essentially by the same general reactions previously described for the 5,7-analog[19] (Scheme 9).

N-Phthalimido L-allylglycine **73** was transformed to the corresponding amide **74**, and the latter was cyclized to the enamide **75** (Scheme 11). The seven-membered ring was constructed using an iminium ion cyclization as in the synthesis of the 5,7-fused analog shown in Scheme 9. Reduction of the two products **76** and **77** led to the desired compound **78** as a single isomer.

Scheme 11

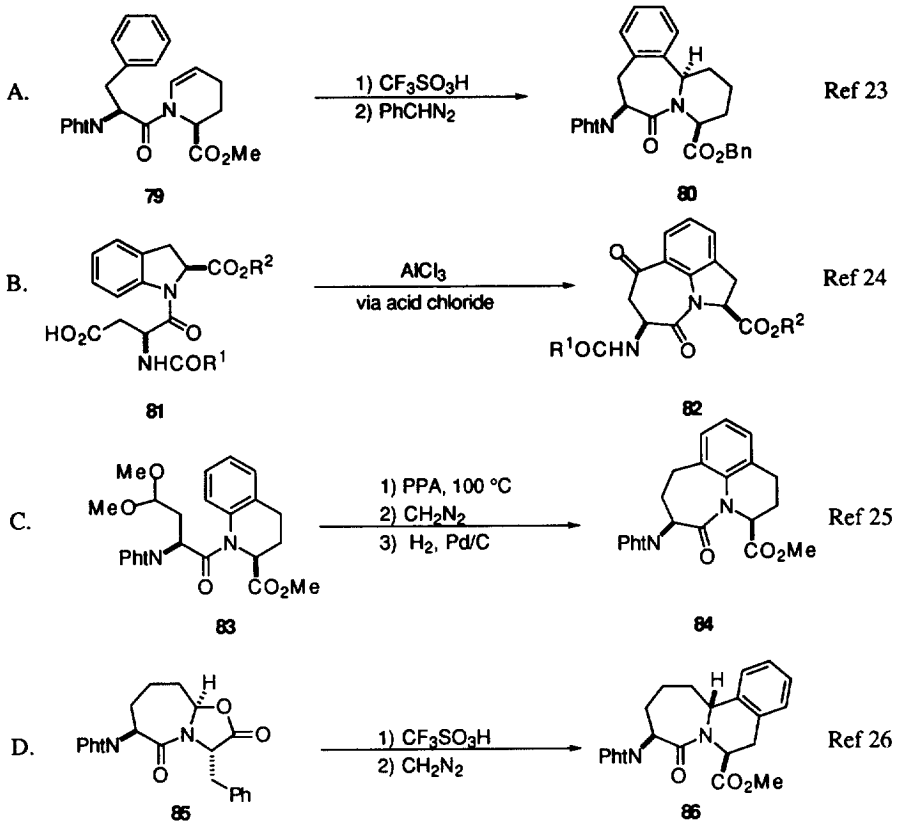


5. 5,7- and 6,7-Fused 1-Aza-2-oxobicycloalkane Amino Acids with Appended Aromatic Units

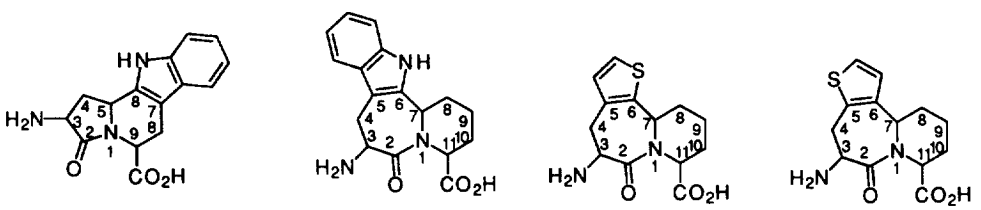


The propensity of phenylalanine in natural and unnatural molecules that have demonstrated therapeutic potential has instigated the exploration of tricyclic structures that incorporate the phenyl ring. The synthesis strategy for these tricyclic structures involves intramolecular electrophilic aromatic substitutions of activated groups as shown in Scheme 12.[23-26] Some C-3 aminoalkyl analogs in this series have exhibited enzymatic activity as ACE inhibitors.[23-26]

Scheme 12

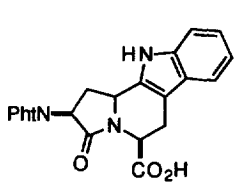


6. 5,6- and 6,7-Fused 1-Aza-2-oxobicycloalkane Amino Acids with Appended Heteroaromatic Units.



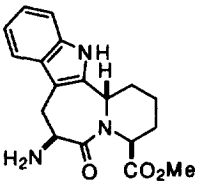
The preceding 5,6- and 6,7-fused bicyclic motifs have been synthesized[27a,28] with appended heteroaromatic units as represented by the general structures **87-90** shown in Figure 3.

Figure 3



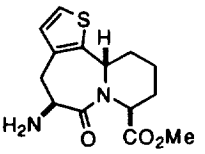
87

Ref 27



88

Ref 28



89

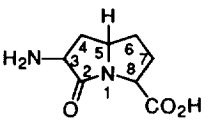
Ref 28

90

Ref 28

The introduction of **87** at the 4 and 5 positions of a [Lys$^{2.2'}$]-GS analog gave similar antibacterial activity with the (5*R*)-isomer and caused a marked decrease in antibacterial potency with the (5*S*)-isomer.[27b]

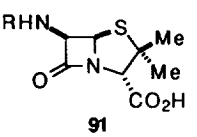
7. 5,5-Fused 1-Aza-2-oxobicycloalkane Amino Acids (Pyrrolizidinone type)



Extensive work on the synthesis and chemical modification of β-lactam antibiotics over the years has produced a multitude of biologically active analogs and novel structural entities in this area.[29] In view of the relatively limited possibilities left for structural and functional variations of the β-lactam motif while maintaining a rational approach to the accepted modes of antibacterial action, chemists have turned to the exploration of γ-lactams and related heterocycles[30] as potential antibacterial agents. The structural similarity of these analogs to the 1-aza-2-oxobicycloalkane amino acid motifs discussed in this review, warrants their inclusion, as well as some discussion of their methods of synthesis and their potential as dipeptide mimetics.

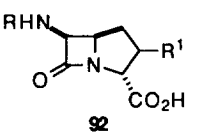
The synthesis and biological evaluation of a series of γ-lactam analogs of penicillanic and carbapenicillanic acids **91-93** (Figure 4) have been areas of intense research efforts since 1983.[31]

Figure 4



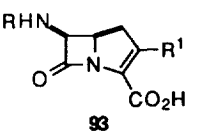
91

Penicillin type



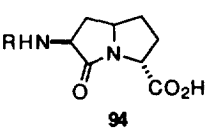
92

Carbapenicillin type



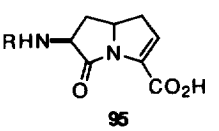
93

Carbapenem type



94

γ-Lactam variant

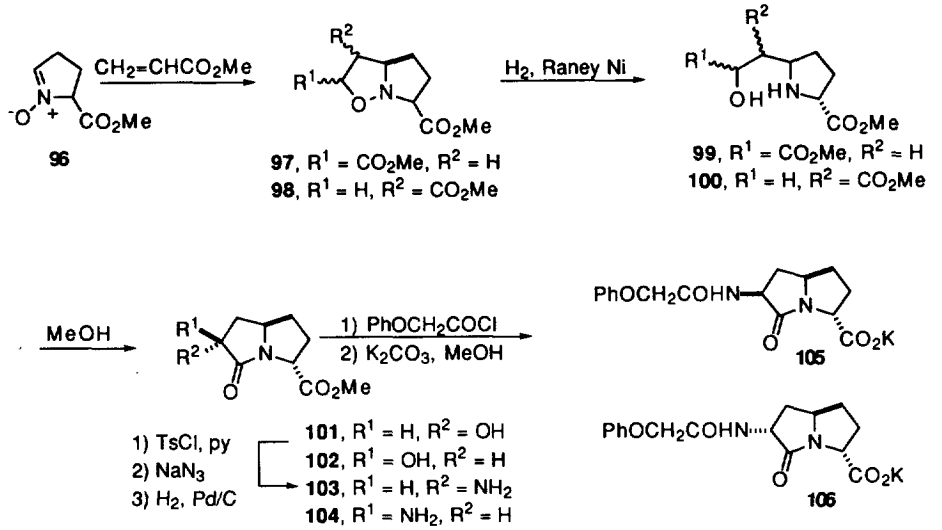


95

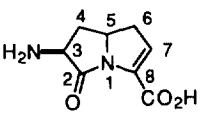
Unsaturated γ-Lactam variant

In one strategy,[32] the nitrone **96** was subjected to a 1,3-dipolar cycloaddition reaction with methyl acrylate to give a mixture of adducts **97** and **98** (Scheme 13). Reductive cleavage of the N-O bond, introduction of the amine group via azide ion, followed by cyclization gave a mixture of *N*-protected bicyclic γ-lactams. Finally, deprotection afforded a mixture of racemic products **105** and **106** which did not exhibit antibacterial activity.

Scheme 13



8. 5,5-Fused 1-Aza-2-oxobicycloalkene Amino Acids.



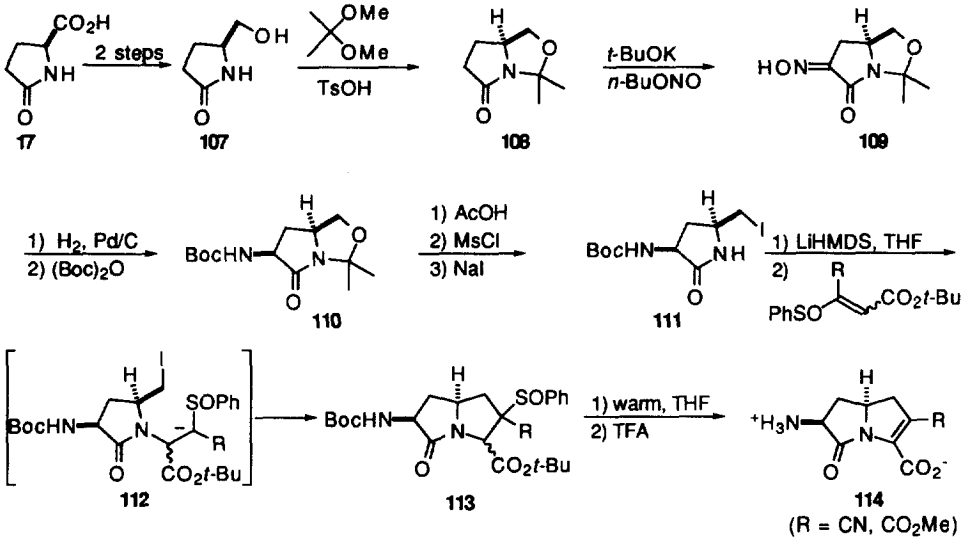
An obvious extension of the work described above[31] involves the synthesis of the corresponding unsaturated bicyclic γ-lactams. Here, the effect of ring strain would be expected to manifest itself by rendering the molecules more susceptible to enzymes such as the penicillin binding proteins,[29] that are prone to be acylated by the original β-lactams.

A strategy that capitalized on the ready availability of L-pyroglutamic acid as a chiral educt is shown in Scheme 14.[33] The known alcohol **107** was protected as the acetonide **108**, and the amino group was introduced by oximation of the corresponding enolate to give **109**. Catalytic hydrogenation and *N*-protection afforded the *N*-Boc derivative **110** with the expected stereochemistry because of the bias offered by the bicyclic structure. An X-ray crystal analysis confirmed the structure. The key step in the sequence was an annulation reaction involving a conjugate addition of a lithium imidate derived from **111** to provide the

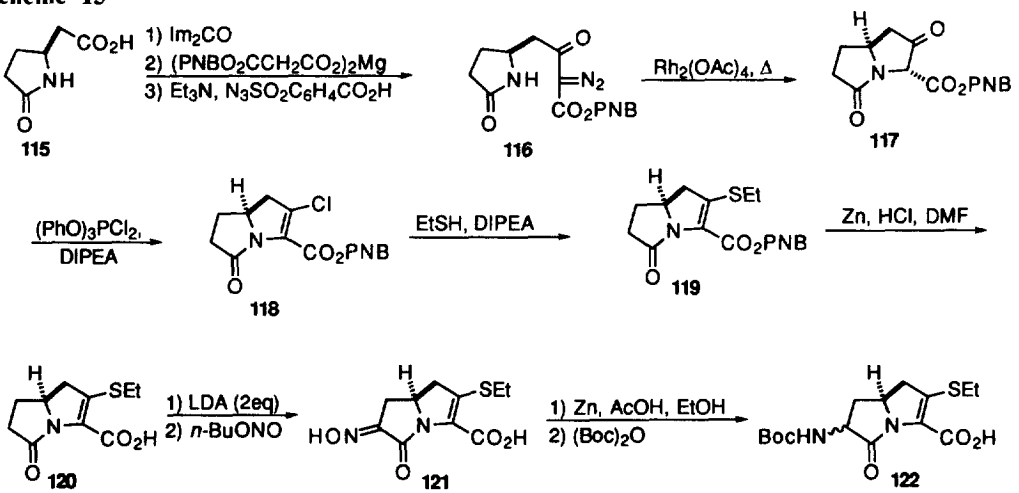
bicyclic lactam **113** via the sulfoxide intermediate **112**. β-Elimination followed by deprotection afforded the desired motif **114**. Only slight levels of antibacterial activity were observed in this series.

In an alternative strategy, the unsaturated γ-lactam analogs with vinylic sulfoxides and sulfones have been prepared[34] (Scheme 15). The homologated L-pyroglutamic acid **115** was transformed into the diazo ester **116**. Application of a Rh(II)-catalyzed insertion reaction[35] led to the bicyclic lactam **117**, which was further manipulated to produce a mixture of *N*-Boc derivatives expressed as **122**. These were then transformed into specific amide derivatives for biological evaluation. No antibacterial activity was detected with these γ-lactam analogs.

Scheme 14

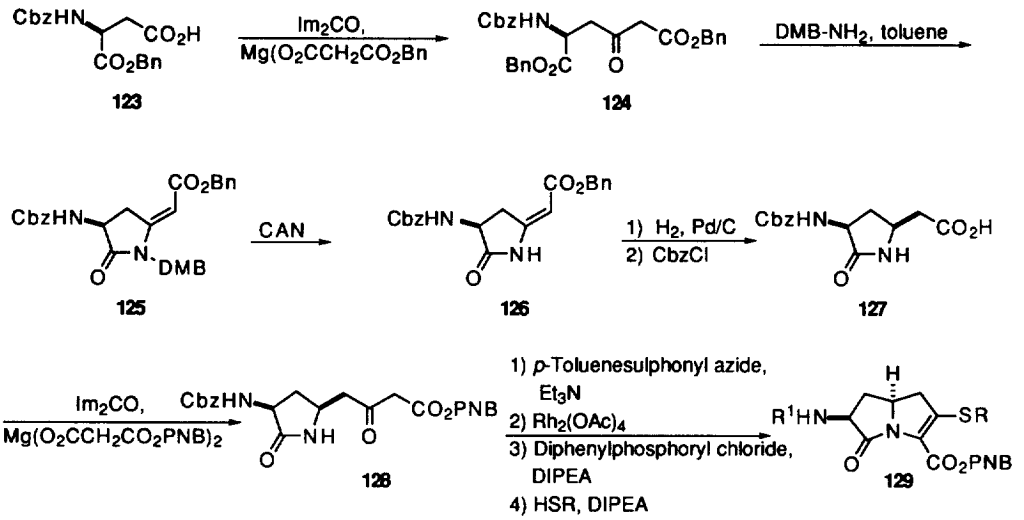


Scheme 15

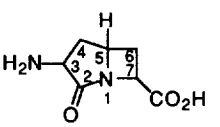


Another group[36] has reported a synthesis of unsaturated γ-lactam analogs of carbapenems starting from L-aspartic acid derivative **123** (Scheme 16). Chain extension using a malonate synthon led to the β-keto ester **124**. Lactam formation in the presence of dimethoxybenzylamine led to **125** which was deprotected to enamido ester **126**. Catalytic hydrogenation followed by *N*-protection gave intermediate **127**, which was transformed into the γ-lactam carbapenem analog following known methods. In contrast to the lack of antibacterial activity for this class of compounds in general,[31,34] the authors report "slight but appreciable *in vitro* antibacterial activity against the Gram-negative organisms tested", for a series of analogs.[36]

Scheme 16



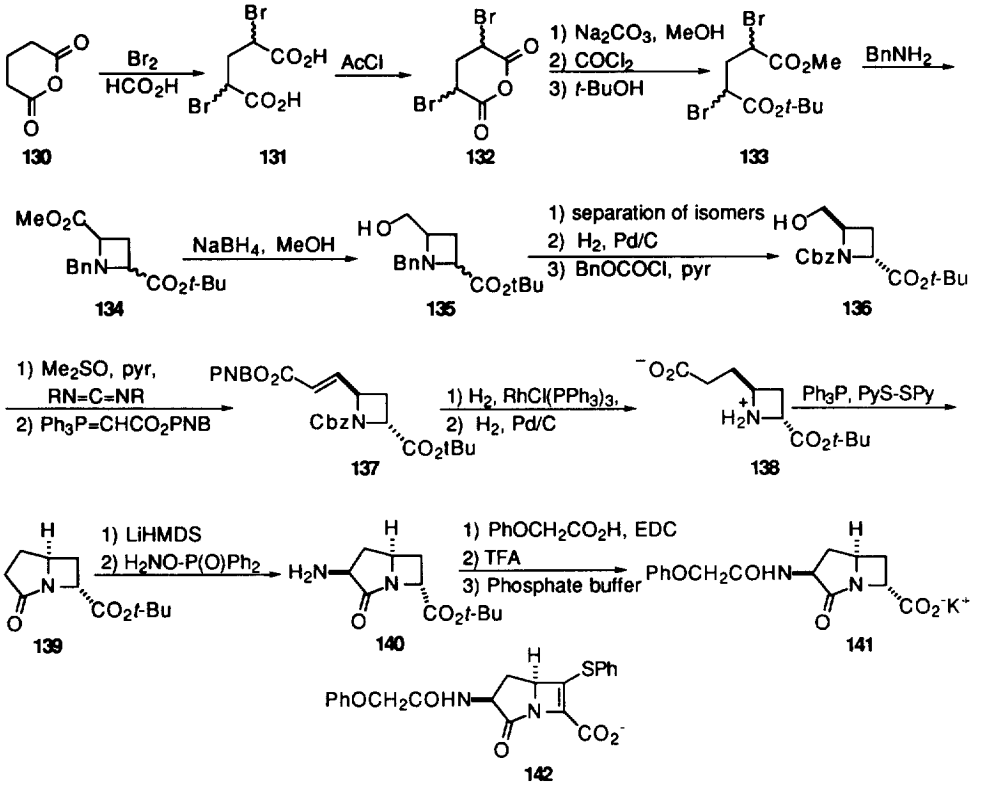
9. 4,5-Fused 1-Aza-2-oxobicycloalkane and 1-Aza-2-oxobicycloalkene Amino Acids



Based on molecular modeling studies it was proposed that the hybridization characteristics of the nitrogen atom in a bicyclic azetidine analog[37] would better approximate the situation found in penicillin. Accordingly, the synthesis of such analogs and their azete counterparts was undertaken (Scheme 17). Glutaric anhydride (**130**) was transformed into α,α'-dibromo diester **133** by conventional methods. Azetidine formation was achieved by treatment with benzylamine. Preferential reduction of the methyl ester in **134** followed by separation of *cis*/*trans* isomers and further manipulation led to **136**. Chain-extension and catalytic reduction gave azetidine **138** which was subjected to γ-lactam formation, affording *trans*-isomer **139**. Introduction of the amino group was achieved via enolate chemistry utilizing *O*-diphenylphosphinoyl

hydroxylamine as the nitrogen source[38] to give **140**, which was transformed into the *N*-phenoxyacetyl penam surrogate **141**. Unfortunately, no significant antibacterial activity was detected with **141** or its *cis*-aminoacyl isomer.

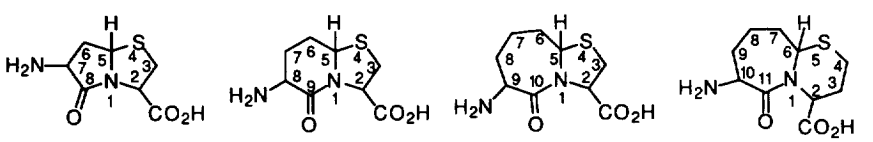
Scheme 17



It is of interest to point out that azete analog **142** (Scheme 17), disclosed in a patent,[39] possesses antibacterial activity.

III. THIAZABICYCLOALKANE AMINO ACIDS

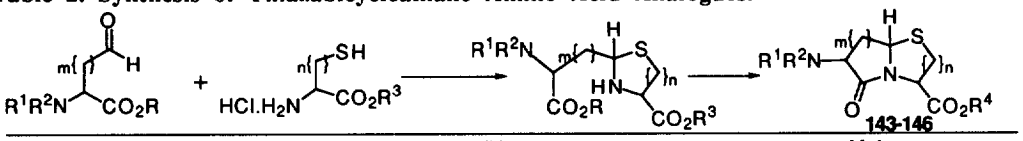
1. 5,5-, 5,6-, 5,7- and 6,7-Fused 1-Azaoxobicycloalkane Amino Acids Encompassing Sulfur



The first 1-azaoxobicyclo[X.Y.0]alkane amino acids that were synthesized for use as conformationally rigid dipeptide mimetics were those possessing sulfur in the heterocycle ring.[40-42] Since

they are prepared by a common synthesis method, we will discuss these different ring systems within the same section. The general method for synthesizing thiazabicycloalkane amino acid involves condensation of an ω-formyl α-amino acid analog with a cysteine derivative to provide a thiazolidine intermediate that is treated directly under conditions to effect intramolecular *N*-acylation and furnish the bicyclic lactam. The *N*-protected bicyclo amino acid or ester is then usually purified by chromatography.

Table 2. Synthesis of Thiazabicycloalkane Amino Acid Analogues.



m	n	R, R^1, R^2	R^3	conditions condensation / lactam cyclization	R^4	%Yield[a]	Major Product	Ref
1	1	Bn, H, Boc	H	pyridine, Δ; CH_2N_2	Me	68	(2*S*, 5*R*, 7*R*)-**143**	43
1	1	Bn, H, Cbz	Me	pyridine, Δ	Me	38	(2*S*, 5*R*, 7*S*)-**143**	44
1	1	Bn, H, Cbz	Me	pyridine, Δ	Me	45	(2*R*, 5*S*, 7*S*)-**143**	44
2	1	-CH_2-, Cbz	H	H_2O / DMSO, pH 7, Δ; CH_2N_2	Me	35	(2*S*, 5*R*, 8*R*)-**144**	43
2	1	$(CH_2)_2$TMS, Pht	Et	HOAc, H_2O / $BnNMe_3F$, DMF	Et	50	(2*R*, 5*S*, 8*S*)-**144**	45
2	1	-CH_2-, Cbz	Me	pyridine; K_2CO_3, MeOH	Me	46	(2*R*, 5*S*, 8*S*)-**144**	46
2	1	Me, Pht	H	NaOAc, H_2O, EtOH, Δ	H	51	(2*R*, 5*S*, 8*S*)-**144**	41
2	1	-CH_2-, Cbz	Me	pyridine; K_2CO_3, MeOH	Me	70	(2*S*, 5*R*, 8*S*)-**144**[b]	47
3	1	H, Pht	Me	MeOH / EEDQ	Me	74	(2*R*, 5*RS*, 9*S*)-**145**[c]	42
3	2	H, Pht	Me	MeOH / EEDQ	Me	25	(2*S*, 6*S*, 10*S*)-**146**[d]	48

[a]Unless otherwise noted, yields refer to the major isomer isolated. [b](2*S*, 5*S*, 8*S*)-**144** was also isolated in 12% yield. [c]**145** was isolated as a 1:1 mixture. [d](2*R*, 5*R*, 10*S*)-, (2*R*, 5*S*, 10*S*)- and (2*S*, 5*R*, 10*S*)-**146** were also isolated in 21%, 8% and 1% yields.

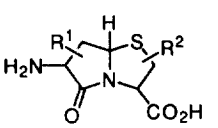
Syntheses of thiazabicyclo[X.Y.0]alkane amino acids using ordinary ω-formyl α-amino acids and esters with cysteine and homocysteine are summarized in Table 2.[41,43-48] Yields of bicyclic products from cysteine derivatives are generally moderate to good.[41,43-49] The stereochemistry about the bicyclic products can be controlled by employing enantiopure amino acid substrates in the condensation/lactam cyclization sequence. In the case of 5,5- and 6,5-bicyclic systems, the major diastereomer that is ordinarily formed possesses the ring-junction hydrogen and the cysteine-derived carboxylate, on the same side of the thiazolidine ring (Table 2).[41,43-47]

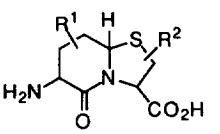
The ω-formyl α-amino acids were protected to avoid intramolecular cyclization in those cases that could lead to the formation of dehydropyrrolidines and dehydropiperidines. Although phthalimides were initially used for amino protection,[41,42] *N*-(Cbz)oxazolidinones have been used more recently to protect both the amine and acid groups, thereby preventing intramolecular cyclization, and simultaneously activate the α-carboxylate for intramolecular lactam formation.[43,47,49] The hydroxymethyl group that resulted from ring opening of the *N*-(Cbz)oxazolidinone was subsequently removed under mildly alkaline conditions.

Thiapyrrolizidinone amino acid **143** (Table 2) was originally synthesized as a γ-lactam analog of the penems.[40,44,49] Although **143** did not possess bioactivity, the related 2,3-unsaturated analog showed weak antibacterial activity against *Staphylococcus aureus*.[44,50-52,30a-c] A systematic examination of Pro-Leu-Gly-NH_2 using a variety of thiapyrrolizidinone amino acids related to **143**, and substituted thiapyrrolizidinone amino acid **152** (Section III.2) has provided strong evidence that this tripeptide adopts a type II β-turn conformation when exhibiting modulatory effects on the dopamine receptor.[43,53]

The use of thiaindolizidinone amino acid **144** in conjunction with studies of different biologically active peptides has led to several potent conformationally-constrained surrogates. For example, similar antibacterial activity and circular dichroism spectra indicate that (2*R*, 5*S*, 8*S*)-**144** mimics the type II' β-turn in gramicidin S, replacing D-Phe at the $i + 1$ and Pro at the $i + 2$ positions.[45,54-56] Analogs with reduced potency were obtained upon replacing (2*R*, 5*S*, 8*S*)-**144** for Gly^2-Gly^3 in enkephalin (H-Tyr-Gly-Gly-Phe-Leu-NH_2, 1/1000 activity)[55,57] and for Gly^6-Leu^7 in LH-RF (Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2, 1/10 activity).[55,56,58] Substitution of thiaindolizidinone amino acid (2*S*, 5*R*, 8*S*)-**144** for L-Ala^7-D-Ala^8 in cyclosporin A (CsA) furnished a more potent inhibitor of the T-cell receptor signaling pathway in a signaling assay. Tricyclic cyclosporin A (TCsA) exhibits three times greater affinity for cyclophilin (CyP) and the affinity of TCsA-CyP for calcineurin was also determined to be three times greater than that of CsA-CyP.[47] Examples in which thiaindolizidinone amino acid **144** have been incorporated into peptide analogs lacking biological activity may result from mimicking an inactive conformation and from structural features that interfere with receptor recognition. For example, NMR and computational studies of an inactive cyclic hexapeptide mimetic of Tendamistat showed that (2*R*, 5*S*, 8*S*)-**144** adopted a conformation in which the constrained dipeptide occupied the i and $i + 1$ positions rather than the $i + 1$ and $i + 2$ positions of a type II' β-turn.[46] On the other hand, (2*R*, 5*S*, 8*S*)-**144** was recently shown to adopt the desired type II' β-turn, and to stabilize a bioactive geometry in a cyclic hexapeptide inhibitor of the interaction between integrin $\alpha_4\beta_1$ and vascular cell adhesion molecule-1.[59] In addition, 5,7- and 6,7-fused thiazabicycloalkane amino acids **145** and **146** have been incorporated into the peptide frameworks of several potent metalloprotease inhibitors.[18,48,60]

2. Substituted 5,5- and 5,6-Fused 1-Aza-2-oxobicycloalkane Amino Acids Encompassing Sulfur

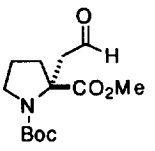




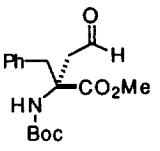
α-Alkyl ω-formyl α-amino esters **147** and **148**, β-alkyl cysteines **149** and **150**, as well as δ-keto α-amino acid **151**, all have been employed to synthesize thiazabicyclo[X.Y.0]alkane amino acid analogs possessing side-chain groups attached to the ring carbons (Figure 5). α-Alkyl ω-formyl α-amino esters react with cysteine to furnish the desired α-branched heterocycles.[61,62] For example, the condensation between

aldehyde **147**, derived from (*R*)-2-allylproline, and (*S*)-cysteine·HCl in aqueous ethanol followed by cyclization with triethylamine in DMF at 70 °C furnished the bicyclic lactam which was isolated as its methyl ester **152** in 37% overall yield.[62] Condensation of α-methyl α-benzyl-*N*-(Boc)aspartate β-aldehyde **148** with (*R*)-cysteine in pyridine at reflux gave the thiapyrrolizidine amino acid **153** in 46% yield after acidification.[61] The reaction between α-methyl L-*N*-(Cbz)aspartate β-aldehyde and (*S*)-penicillamine **149** in refluxing pyridine was claimed to provide 5,5-fused bicyclic lactam **154**.[63] On the other hand, condensation of α-methyl *N*-phthalyl-L-glutamate γ-aldehyde with (*R*)-penicillamine **149** gave **155** in only 2% overall yield.[55,56] The condensation of β-phenylcysteine methyl ester hydrochloride **150** with the same aldehyde was reported to also give a poor yield of **156**.[64] However, the bicyclic lactam **157** was obtained in good yield when β-phenylcysteine•HCl **150** (R = H) was condensed with the δ-keto α-amino acid **151**.[64]

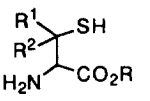
Figure 5



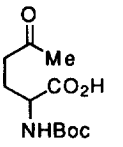
147



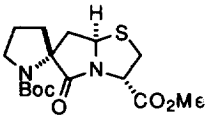
148



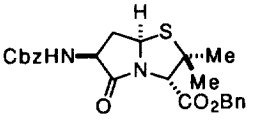
149 : R^1, R^2 = Me; R = H
150 : R^1 = H; R^2 = Ph; R = Me



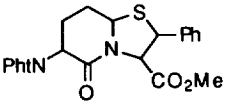
151



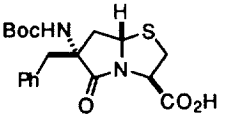
(2*S*, 5*R*, 7*R*)-**152**



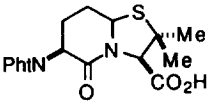
(2*S*, 5*R*, 7*S*)-**154**



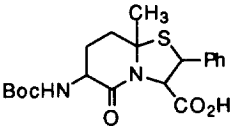
156



(2*R*, 5*S*, 7*R*)-**153**



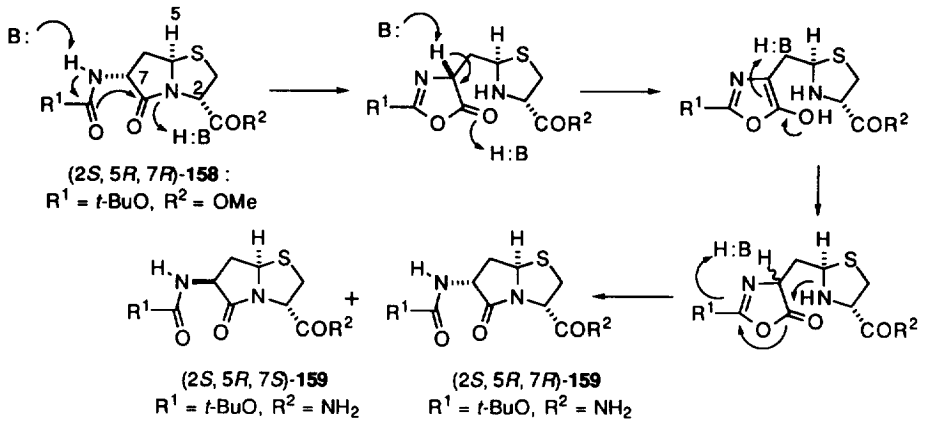
155



157

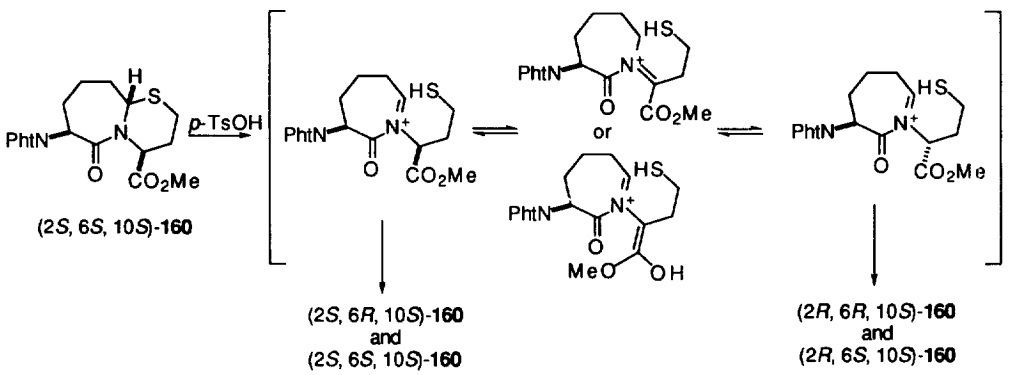
3. Epimerization of Thiazabicycloalkane Amino Acids

Scheme 18



Epimerization has been encountered during the synthesis and further transformations of 1-azaoxobicyclo[X.Y.0]alkane amino acids.[43,48] For example, treatment of (2*S*, 5*R*, 7*R*)-*N*-(Boc)amino thiapyrrolizidinone methyl ester **158** with NH_3 in methanol gave a 9:1 mixture of (2*S*, 5*R*, 7*R*)- and (2*S*, 5*R*, 7*S*)-*N*-(Boc)amino thiapyrrolizidinone carboxamides **159** (Scheme 18, R^1 = *t*-BuO, $R^2 = NH_2$).[43] The suggested mechanism for the epimerization of **158** under these conditions involves the formation and enolization of an oxazolone intermediate, similar to the racemization of amino acids during peptide synthesis.[65] In the case of **158**, the release of ring strain was proposed as a driving force for oxazolone formation.[43]

Scheme 19

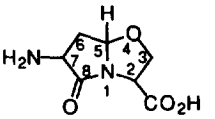


Acid-induced epimerization was observed during the preparation of thiazabicyclo[5.4.0]alkane phthalimido ester **160**.[48] Treatment of pure ester **160** of either (2*S*, 6*S*, 10*S*)-, (2*R*, 6*S*, 10*S*)- or (2*R*, 6*R*, 10*S*)-configuration with *p*-toluenesulfonic acid in benzene at reflux for 2-4 h furnished a 10:30:<1:15 ratio of (2*S*, 6*S*, 10*S*)-, (2*R*, 6*S*, 10*S*)-, (2*R*, 6*R*, 10*S*)- and (2*S*, 6*R*, 10*S*)-diastereomers **160**. The mechanism for

epimerization of **160** may involve enolization of an imino ester intermediate or equilibration of iminium ion intermediates under the acidic conditions as illustrated in Scheme 19.

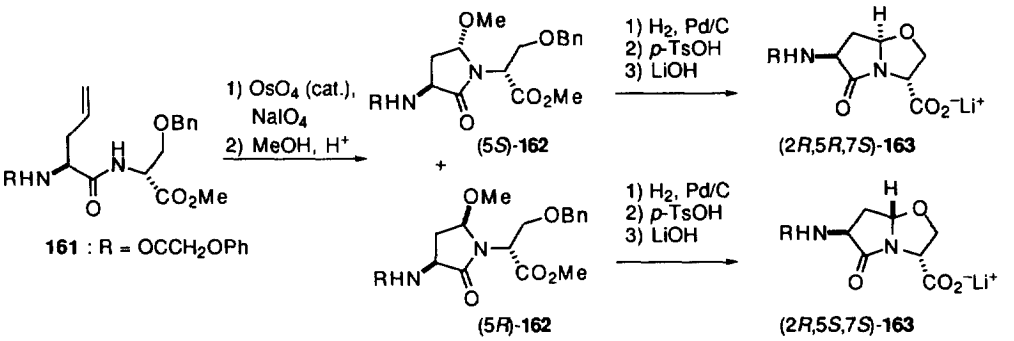
IV. OXAZABICYCLOALKANE AMINO ACIDS

1. 5,5-Fused 1-Aza-8-oxobicycloalkane Amino Acids Encompassing Oxygen

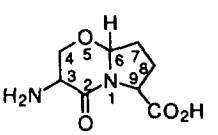


Interest in the synthesis of biologically active γ-lactam analogs of the β-lactam antibiotics led to the preparation of 5,5-fused azabicycloalkane amino acids encompassing oxygen.[66] Thus, *N*-phenoxyacetyl-(2*S*)-allylglycyl-D-(*O*-benzyl)serine methyl ester **161** was first oxidized with a combination of catalytic OsO_4 and $NaIO_4$ in dioxane/water followed by treatment with acidified methanol in order to provide a separable 3:1 mixture of diastereomeric methoxy lactams (5*S*)- and (5*R*)-**162** (Scheme 20). Hydrogenolysis of the benzyl ether and acid-catalyzed cyclization with inversion of configuration at the bridge-head center, followed by ester hydrolysis gave 5,5-fused bicyclic compounds (2*R*,5*R*,7*S*)- and (2*R*,5*S*,7*S*)-**163** as their lithium salts which did not exhibit antibiotic activity.

Scheme 20

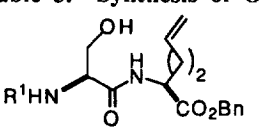


2. 5,6-Fused 1-Aza-2-oxobicycloalkane Amino Acids Encompassing Oxygen

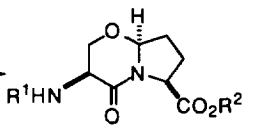


In a related process, oxidative cleavage of *N*-acyl-L-serinyl-(2*S*)-but-3-enylglycine benzyl esters **164** followed by acid catalyzed cyclization gave 3-carbamato-5-oxaindolizidinone-9-carboxylates **165** in good to excellent yields (Table 3).[67,68] The diastereoselectivity of the cyclization to form the bridgehead center was found to be influenced by the absolute configuration of the serine residue. For example, dipeptide **164** incorporating an L-serine provided a >8:1 ratio of (3*S*, 6*S*, 9*S*)- and (3*S*, 6*R*, 9*S*)-diastereomers **165**. Under the same conditions, dipeptide **164** with a D-serine residue gave a >7:1 ratio of diastereomers (3*R*, 6*R*, 9*S*)- and (3*R*, 6*S*, 9*S*)-**165**.[67] Major diastereomers (3*S*, 6*S*, 9*S*)-**165a** and (3*S*, 6*S*, 9*S*)-**165c** (R^1 = Cbz and Fmoc) could be epimerized to (3*S*, 6*R*, 9*S*)-**165a** and (3*S*, 6*R*, 9*S*)-**165c** respectively on prolonged acid treatment (CF_3CO_2H). Alkaline hydrolysis of (3*S*, 6*S*, 9*S*)-**165a** resulted in epimerization, such that *N*-protected oxazabicyclo[4.3.0]alkane amino acid (3*S*, 6*S*, 9*S*)-**166a** was accompanied by some of the diastereomeric acid (3*R*, 6*S*, 9*S*)-**166a** (R^1 = Cbz).[67] Hydrogenolysis of benzyl esters **165b** and **165c** (R^1 = Boc and Fmoc) gave diastereomerically pure *N*-protected amino acids **166b** and **166c** respectively.[67,68]

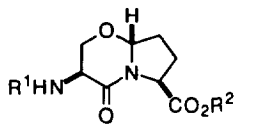
Table 3. Synthesis of Oxazabicycloalkane Amino Acid Esters 165.[67,68]



164



(3*S*, 6*S*, 9*S*)-**165** : R^2 = Bn
(3*S*, 6*S*, 9*S*)-**166** : R^2 = H

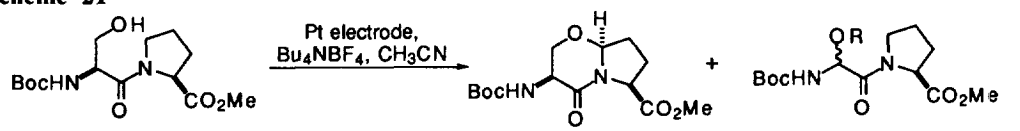


(3*S*, 6*R*, 9*S*)-**165** : R^2 = Bn
(3*S*, 6*R*, 9*S*)-**166** : R^2 = H

entry	R^1	1	2	%Yield	6*S* / 6*R*	Ref
a	Cbz	OsO_4 (cat.), $NaIO_4$ (2 eq.)	F_3CCO_2H (cat.), CH_2Cl_2, Δ	57	>8 / 1	67
b	Boc	OsO_4 (cat.), $NaIO_4$ (2 eq.)	F_3CCO_2H (cat.), CH_2Cl_2, Δ	77	10 / 1	67
c	Fmoc	O_3, CH_2Cl_2, –78°C; Ph_3P	F_3CCO_2H (cat.), CH_2Cl_2, Δ	87	9 / 1	68

Electrochemical oxidation of *N*-Boc-L-serinyl-L-proline methyl ester **167** was recently used to generate the oxaindolizidinone ester (3*S*, 6*S*, 9*S*)-**168** in 15% yield on 10 mmol scale[69] in a diastereoselective fashion. The major drawback to the electrochemical oxidation was the cleavage of the hydroxymethyl side-chain of the serine residue of **167** which gave Boc-α-alkoxyglycylproline methyl esters **169**. Formation of **169** predominated when the anodic amide oxidation was conducted in alcoholic solutions with tetrabutylamonium tetrafluoroborate as the electrolyte. Employment of dry acetonitrile as solvent was important to the cyclization; however, exclusion of water from the system was impossible and some Boc-α-hydroxyglycylproline methyl ester **170** was always isolated as a by-product[69] (Scheme 21).

Scheme 21

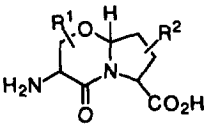


167

(3*S*, 6*S*, 9*S*)-**168** (10-25%)

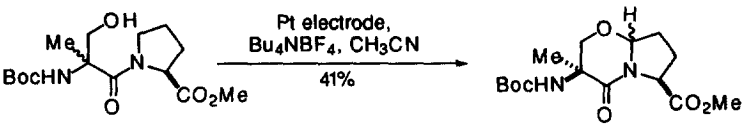
169 : R = Me
170 : R = H

3. Substituted 5,6-Fused 1-Aza-2-oxobicycloalkane Amino Acids Encompassing Oxygen



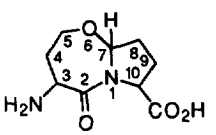
In an attempt to prepare oxaindolizidinone amino acids possessing a 3-methyl substituent, the electrochemical cyclization of *N*-Boc-(*RS*)-α-methylserinyl-L-proline methyl esters **171** yielded (3*S*,6*RS*, 9*S*)-methyl 3-methyl 3-*N*-(Boc)amino-5-oxaindolizidin-2-one-9-carboxylate **172** in 41% yield as a 6:4 mixture of diastereomers. However, this product was found to be very acid labile and decomposed on treatment with dilute TFA[69] (Scheme 22).

Scheme 22



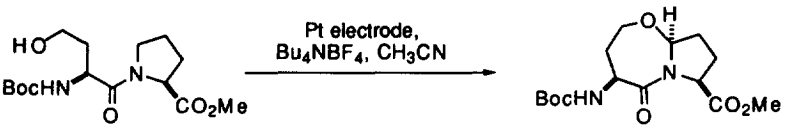
171 (3*S*, 6*RS*, 9*S*)-**172**

4. 5,7-Fused 1-Aza-2-oxobicycloalkane Amino Acids Encompassing Oxygen



Electrochemical oxidation of *N*-Boc-L-homoserinyl-L-proline methyl ester (*S*,*S*)-**173**, and *N*-Boc-L-homoserinyl-D-proline methyl ester (*S*,*R*)-**173**, proved effective for generating 5,7-fused 1-aza-2-oxobicycloalkane amino esters encompassing oxygen[70,71] (Scheme 23). Bicyclic compounds (3*S*, 7*S*, 10*S*)-**174** and (3*S*, 7*S*, 10*R*)-**174** were obtained in 48% and 52% respective yields on 40 and 1 mmol scales respectively.[70,71] In the synthesis of the 5,7-system, diminishing the current density from 19.5 mA/cm^2 to 6.9 mA/cm^2 augmented the yield of **174** from 21% to 48%. The diastereoselectivity in the cyclization was not influenced by the proline residue and peptide **173** with *S*-homoserine furnished the isomer with an *S*-configuration at the bridgehead as the predominant product (>15:1).[70,71]

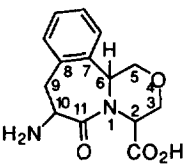
Scheme 23



173 (3*S*, 7*S*, 10*S*)-174 (48%)

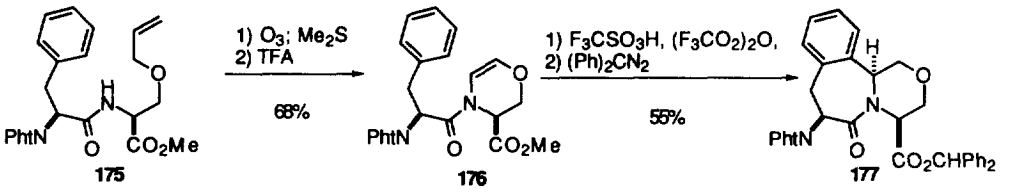
Exposure of *N*-(Boc)amino azabicycloalkane esters encompassing oxygen, 5,6- and 5,7-fused bicycles **168** and **174**, to TFA for 2 h at room temperature and to HF for 1h at 0°C caused only deprotection of the Boc group without epimerization of the bridgehead stereocenter.[69,70] In the presence of carbocation scavengers such as anisole and dimethylsulfide, HF deprotection was accompanied by the formation of side products that were presumed to result from ring opening of the bicyclic ring systems, and intermolecular trapping of the *N*-acyliminium ion.[69,70] Because of the configurational lability of oxaindolizidinone amino acids under acidic conditions, the use of *N*-(Boc)amino acid **166b** was not ideal for peptide synthesis and *N*-(Fmoc)amino oxaindolizidinone acid **166c** was employed in the preparation of a leucine-enkephalin analog by solution-phase techniques.[68]

5. 6,7-Fused 1-Aza-11-oxobicycloalkane Amino Acids Encompassing Oxygen with Appended Aromatic Units



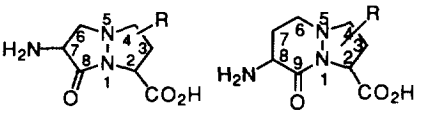
Intramolecular electrophilic addition of an acyliminium ion to an aromatic ring has been used to synthesize 6,7-fused 1-azaoxobicycloalkane amino acid encompassing oxygen. In this approach, *N*-phthalimido-L-phenylalaninyl-L-serine methyl ester was treated with allyl trichloroacetimidate to furnish the allyl ether **175**.[72] Ozonolysis of **175** followed by acid-catalyzed cyclization afforded the morpholinoenamine derivative **176** (Scheme 24). Oxazatricycloalkane amino ester **177** was then synthesized via an acid catalyzed intramolecular acyliminium ion cyclization on **176** using conditions similar to those employed for the synthesis of azatricycloalkane amino acid **80** (Scheme 12). The methyl ester was solvolyzed during this procedure, and esterification of the tricyclic acid with diphenyldiazomethane led to the isolation of ester **177** in 55% yield after chromatography.[72]

Scheme 24



V. Diazabicycloalkane Amino Acids

1 Substituted 5,5- and 5,6-Fused 1,5-Diazaoxobicycloalkene Amino Acids (Fused Pyrazolidinones and Pyridazinones)



The majority of the known diazabicycloalkane amino acid motifs incorporate generally the two ring nitrogens at the ring-junction sites, a feature which simplifies their synthesis. In the mid 1980's several research groups became interested in the possibility of utilizing 5,5-fused pyrazolidinones as constrained aza-γ-lactam mimics of the carbapenem class of antibacterial drugs. Several compounds of this type bearing electron-withdrawing appendages at C-3 have shown promising antibacterial properties.[73] Although their use as constrained dipeptide mimetics is limited by their instability towards basic hydrolysis of the amide, [74] their preparation and structural features are amenable towards their use as scaffolds for other purposes.

The first 5,5-fused pyrazolidinones synthesized harbored a carbonyl group at C-3 and a gem dimethyl group at C-4.[75] Their synthesis utilized a 1,3-dipolar cycloaddition reaction as the key ring forming step (Scheme 25).

Scheme 25

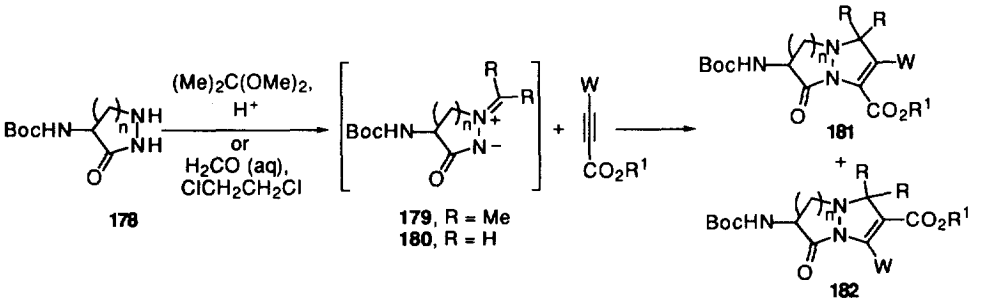
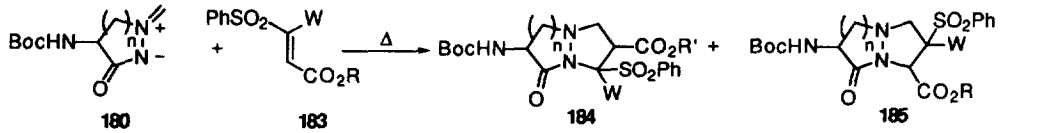


Table 4.

n	R	W	R^1	Isolated products	% Yield	Ref
1	Me	CO_2allyl	allyl	181 ≡ 182	67	76
1	H	CO_2Me	Me	181 ≡ 182	88	77
1	H	H	allyl	182	23	77
1	H	COMe	allyl	2:3;181:182	26	77
1	H	CO_2allyl	allyl	181 ≡ 182	49	75
1	H	CH_2OTHP	allyl	182	10	77
1	H	Ph	allyl	182	10	77
1	H	CO_2Me	allyl	1:1;181:182	38	77
2	H	CO_2allyl	allyl	181 ≡ 182	17	83

The starting pyrazolidinone template **178** (n = 1) was readily prepared in 2 steps from *N*-(Boc)serine methyl ester in 60% yield. Treatment of **178** with 2,2-dimethoxypropane and a catalytic amount of acid in boiling methanol afforded ylide **179** in quantitative yield after recrystallization. Prolonged exposure of **179** to diallyl acetylene dicarboxylate in CH_2Cl_2 at ambient temperature gave the racemic bicyclic system **181** (R = Me, W = CO_2allyl, R^1 = allyl) in 67%. Similarly, the addition of aqueous formaldehyde to **178** provided azomethine imine ylide **180**, which could not be isolated and was directly heated with acetylene dicarboxylates in 1,2-dichloroethane to furnish 5,5-fused pyrazolidinones **181** (R = H, Table 4).[76] Because of the instability of the amide towards base, the exocyclic amine was typically protected as a Boc derivative and the carboxylates were introduced as either their *tert*-butyl or allyl esters. When unsymmetrical dipolarophiles were employed,[77] regioisomeric mixtures of bicyclic products were usually obtained, the desired regioisomer often being the minor product (Table 4). This problem could be overcome by the use of phenyl vinyl sulfones as the acetylenic equivalent in the 1,3-dipolar cycloaddition step (Scheme 26).[78] For example, (*E*)-substituted phenyl vinyl sulfones **183** reacted with **180** in refluxing 1,2-dichloroethane to give predominantly the desired bicyclic compound **185** (>95:5). On the other hand, (*Z*)-substituted phenyl vinyl sulfones gave the undesired regioisomer **184**. Base-promoted elimination of the sulfonyl moiety in **187** using *N*-methylmorpholine or DBU at 0 °C afforded the unsaturated product **181** in moderate yields (21-61%, Table 5). In practice, ylide formation, 1,3-dipolar cycloaddition, and alkene formation were typically performed without purification of the intermediates. Enantiomerically pure 5,5-fused pyrazolidinones[78] have been prepared starting with enantiopure forms of the pyrazolidinone template **178**.[79] *N*-Methylmorpholine was used for the elimination of the sulfonyl group in these cases because DBU caused racemization.

Scheme 26

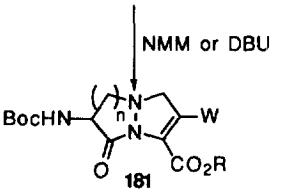


180 **183** **184** **185**

Table 5.

n	W	R	% Yield of 181[a]	Ref
1	CO_2Me	allyl	47	83
1	CO_2Me	allyl	61	83
1	COMe	*t*-Bu	32	83
1	$COCO_2Et$	allyl	38	83
1	CN	*t*-Bu	44	83
1	H	allyl	49	83
2	COMe	allyl	21	78

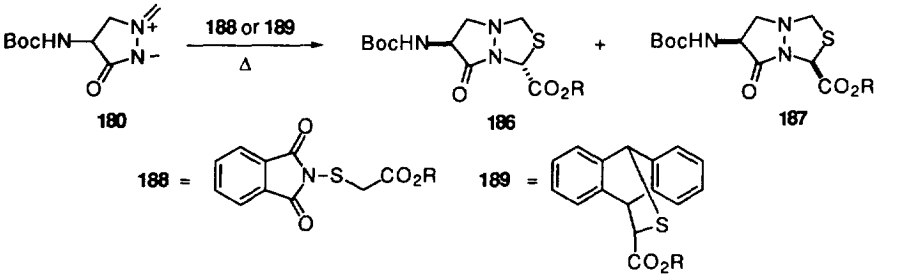
[a] overall yield from **180**



181

A related 1,3-dipolar cycloaddition reaction has been used to regioselectively obtain the 2-thia-analogs[80] **186** and **187** (Scheme 27). Treatment of **180** with a catalytic amount of NMM followed by the dropwise addition of a thioaldehyde precursor, **188** or **189**, and heating at reflux in 1,2-dichloroethane furnished in 65% yield a 3:1 mixture of diastereoisomers **186** and **187** which could be separated.

Scheme 27



180 **186** **187**

188 = **189** =

An intramolecular Horner-Wadsworth-Emmons reaction[81] has been used in a "one-pot" preparation of C-3-substituted 5,5-fused pyrazolidinones (Scheme 28).[82] Treatment of α-substituted phosphonate esters **190** with acetic anhydride and tetramethyl diaminomethane gave vinyl phosphonates **191** that were immediately reacted with the pyrazolidinone **178** to afford selectively the Michael adduct **192**. Subsequent addition of an oxalyl chloride mono-ester and Hünig's base gave the acylated intermediate **193** which cyclized to **181** (Scheme 28, Table 6).

The above mentioned strategies in Schemes 25-28 have been successfully employed for the preparation of the corresponding 5,6-analogs (see Tables 4-6).[83]

Scheme 28

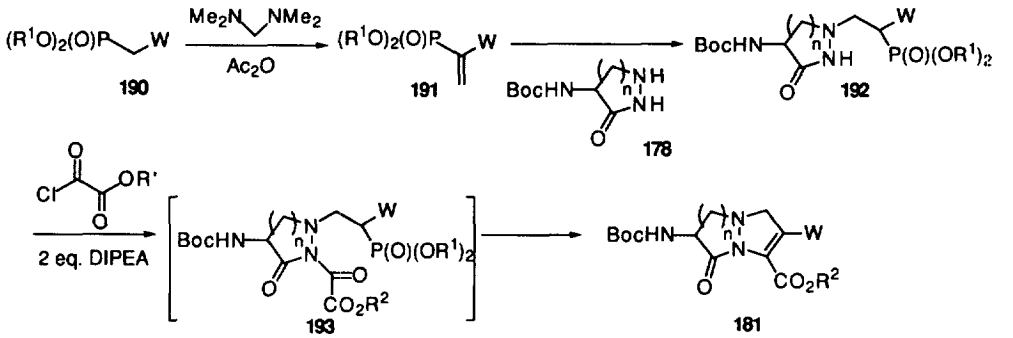
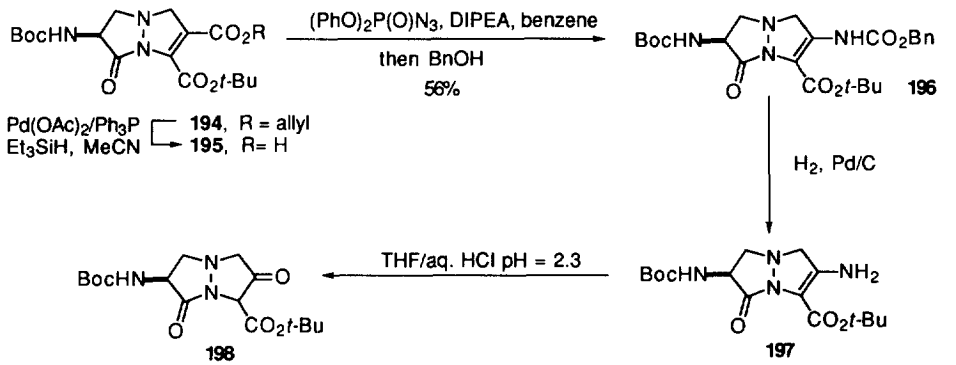


Table 6.

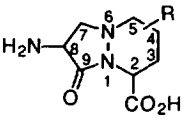
n	W	R^2	% Yield of **181**	Ref
1	CO_2allyl	*t*-Bu	58	85
1	CN	allyl	25	82
1	CO_2Et	allyl	20	86
1	CO_2Ph	allyl	63	86
1	COEt	allyl	6	86
1	CN	allyl	28	86
1	SO_2Me	allyl	35	86
2	CN	allyl	11	83

A noteworthy means to modify C-3 involves a selective Curtius rearrangement[84] of the C-3 carboxylate (Scheme 29).[85]

Scheme 29

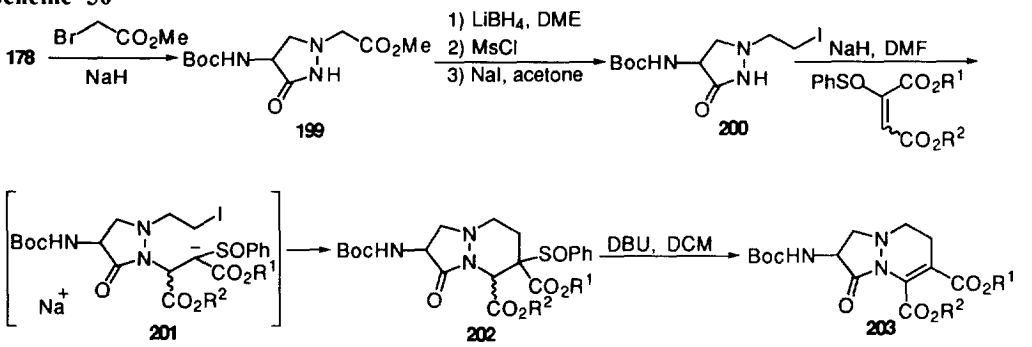


2. Substituted 5,6-Fused 1,6-Diaza-9-oxobicycloalkene Amino Acids (5,6-Fused Pyrazolidinones)



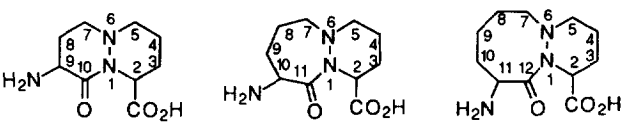
Synthesized initially as core analogues of the cephalosporin class of antibacterial agents, the 5,6-fused 1,6-diaza-9-oxobicycloalkene amino acid derivatives were found to be less active than their corresponding 5,5-fused systems (section V.1). Their syntheses proceed generally via a selective chain extension from the amine group of pyrazolidinone **178** followed by a ring annulation utilizing an acetylene equivalent (Scheme 30). [86]

Scheme 30



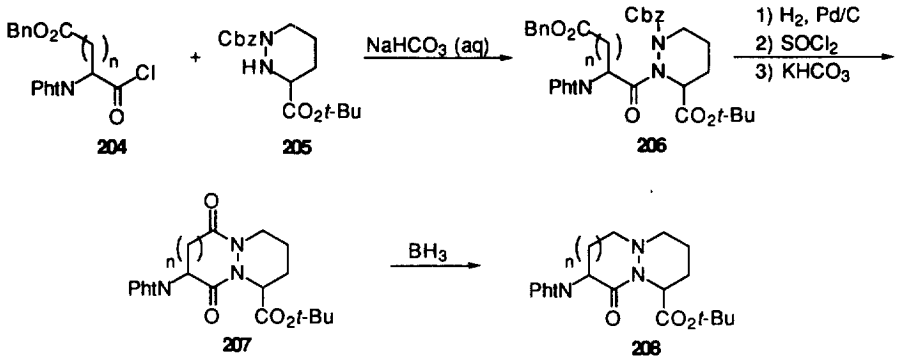
For example, alkylation of **178** with methyl bromoacetate afforded **199** in 36% yield, which was subsequently converted into the primary iodide **200**. Treatment with NaH in DMF followed by the addition of a phenyl vinyl sulfoxide led to a regioselective Michael addition resulting in stabilized anion intermediate **201**, which upon intramolecular displacement of the iodide furnished a diastereomeric mixture of bicyclic products **202**. Base-induced elimination of phenylsufinic acid afforded the desired bicycloalkene amino ester **203** in 36% overall yield from **200**.

3. 6,6-, 6,7- and 6,8-Fused 1,6-Diazaoxobicycloalkane Amino Acids (6,6-, 6,7- and 6,8-Pyridazine Based Structures)



Designed and synthesized to act as conformationally restrained analogues of the angiotensin converting enzyme inhibitors Captopril and Enalapril,[87] these diazabicyclo[X.Y.0]alkane amino acids possess a hexahydropyridazine fused either to an appropriately functionalized tetrahydropyridazinedione, hexahydro[1,2]diazepinedione or octahydro[1,2]diazocanedione. These systems are prepared in the same general manner, via the condensation of an α-aminodicarboxylate and a protected hexahydropyridazine-3-carboxylate (piperazic acid, Scheme 31).

Scheme 31

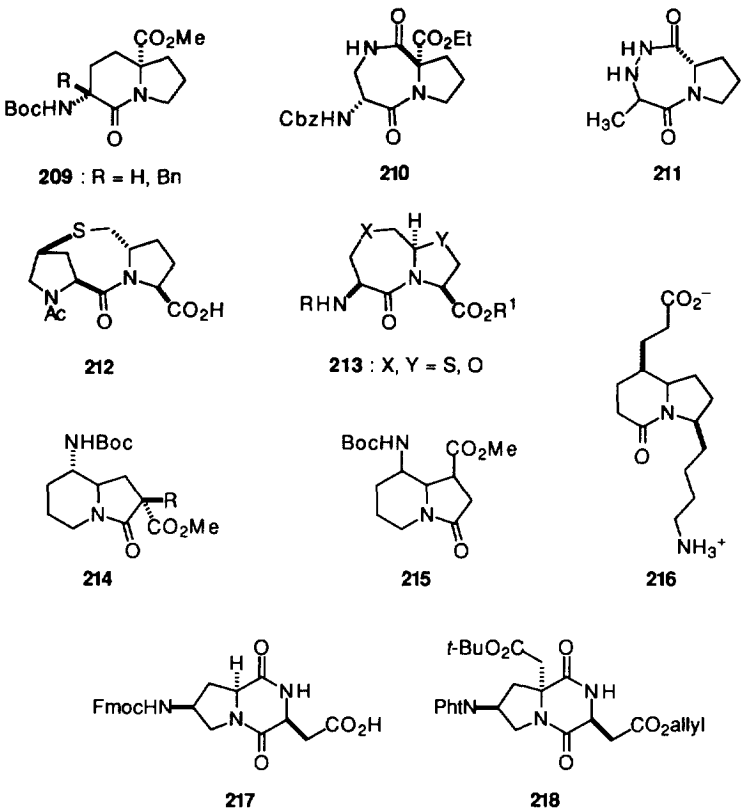


N-Acylation of *N'*-(Cbz)piperazate **205** with ω-benzyl aspartic, glutamic or α-aminoadipic α-acid chlorides **204** furnished amides **206**. Deprotection of the benzyl and Cbz groups via hydrogenolysis, generation of the corresponding acid chloride and treatment with aqueous $KHCO_3$ afforded bicyclic compounds **207** with yields above 70%. The corresponding mono-oxo systems **208** were obtained in excellent yields (>90%) by selective reduction of the less hindered lactam using borane in THF.[87] The use of enantiopure starting materials has led to the efficient preparation of numerous chiral, non-racemic 6,6-, 6,7- and 6,8-pyridazino based bicyclic systems of this type in multigram quantities.

VI. MISCELLANEOUS EXAMPLES

Mimetics of other peptide structures have been based on related azacycloalkane amino acid motifs (Figure 6). For example, indolizidinone amino acid **209**,[88-90] 5,7-fused diazabicycloalkane amino acid **210**,[91] and 5,7-fused triazabicycloalkane amino acid **211**,[92] all have been synthesized to serve as mimetics of X-Pro *cis*-amide rotamers and type IV β-turns. Tricyclic-diprolyl structure **212** has been used as a template for α-helix induction.[93] In addition, several 5,7-fused azabicycloalkane amino acid analogs **213** have been synthesized that encompass two heteroatoms in the ring system.[94] Finally, some representative structures of other 5,6-fused bicyclo motifs **214-218**,[95-97] that do not encompass the Ala-Pro type dipeptide mimic simulated by the corresponding indolizidinone prototype (Section II.1), have been included in this Report as examples of interesting bicyclic amino acid scaffolds (Figure 6).

Figure 6



VII. PERSPECTIVES

Our knowledge of the relationship between structure, function and conformation of natural peptides and proteins is steadily growing and has shown that among these molecules, enzymes and protein receptors play primordial roles in physiological events that bear directly on life processes. Understanding of the interactions of peptide structures at the molecular level is now essential for tackling any therapeutically relevant area of drug design. In this regard, the vast majority of peptide-based interactions with peptidic substrates are ultimately translated into non-peptidic counterparts often called peptidomimetics. In this Report, we have addressed the synthesis of bicyclic amino acid motifs that may be used as scaffolds upon which pharmacologically relevant groups can be appended. Alternatively, the motifs can be utilized as conformationally constrained entities that mimic parts of natural peptidic substrates. These templates in which the peptide backbone geometry and side-chain functionality are restrained in bicycloalkane ring systems have already found important use as antibacterials and as constituents of metalloprotease inhibitors. Their incorporation into larger structures has given fundamental insight of the mechanism of action of relevant biologically active peptides and proteins. Future developements in this area of peptide mimicry should lead to

both greater understanding of protein biochemistry as well as novel drug candidates for a variety of pathological and therapeutic indications.

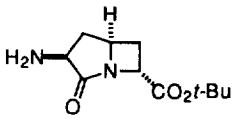
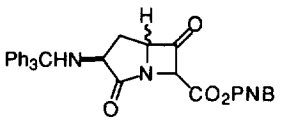
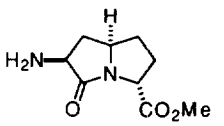
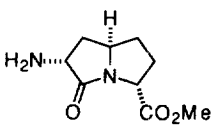
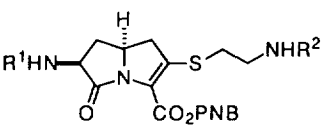
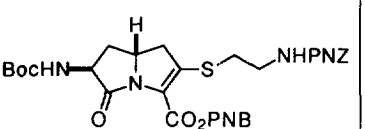
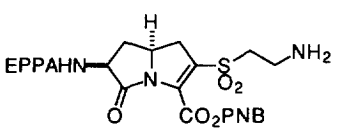
The medicinal chemist's role is more crucial than ever, especially in the advent of combinatorial methods for drug discovery and lead optimization. Biologically active molecules of a peptidic nature will ultimately require "redesigning" into structural types that are metabolically stable while maintaining their biological activities. The initial objectives in drug design reside in achieving better binding to specific receptors, and more potent inhibition of target enzymes. While the structures covered in this review may be distant from such noble goals at first glance, it is our hope that they can be cleverly and beneficially used to design new medicinal agents.[†]

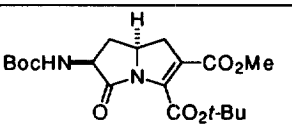
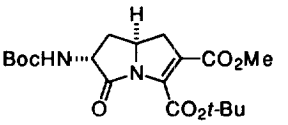
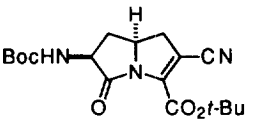
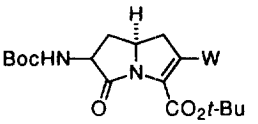
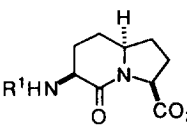
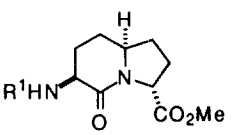
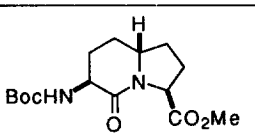
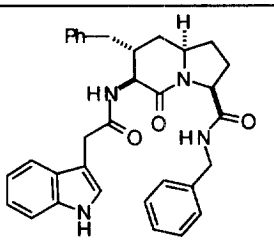
VIII. ABBREVIATIONS

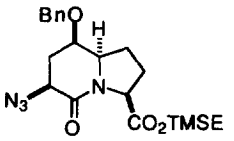
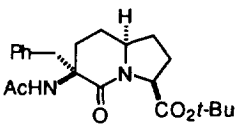
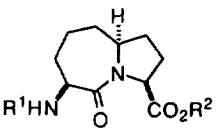
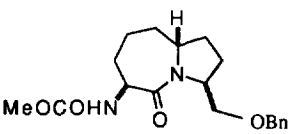
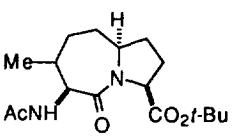
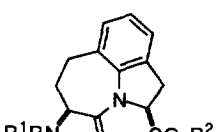
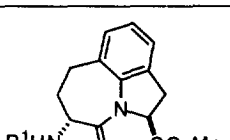
Ac	Acetyl
ACE	Angiotensin-Converting-Enyzme
ADTN	2-Amino-dihydroxy-1,2,3,4-tetrahydronapthalene
Boc	*tertiary*-Butyloxycarbonyl
Bn	Benzyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CoA	Co-enzyme A
COSY	Correlated Spectroscopy
DBU	Diazabicyclo[5.4.0]undecene
DCM	Dichloromethane
DIPEA	*N-N*-Diisopropylethylamine
DMB	Dimethoxybenzyl
EPPA	D-2-(4-Ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-2-phenylacetic acid
Fmoc	9-Fluorenylmethyloxycarbonyl
HMBC	Heteronuclear Multiple Bond Correlation
NEP	Neutral endopeptidase
NK-2	Neurokinin-2 receptor
NMM	*N*-Methylmorpholine
nOe	Nuclear Overhauser Effect
OTMS furan	2-(Trimethylsilyloxy)furan
Pht	Phthalimido
PNB	p-Nitrobenzyl
PNZ	p-Nitrobenzyloxycarbonyl
ROESY	Rotational-frame Overhauser Enhancement Spectroscopy
TBDMS	*tertiary*-Butyldimethylsilyl
TBDPS	*tertiary*-Butyldiphenylsilyl
TMSE	Trimethylsilylethyl

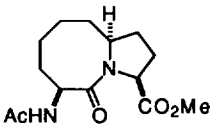
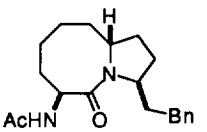
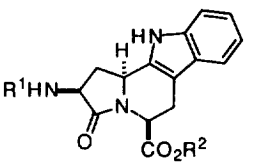
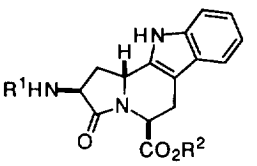
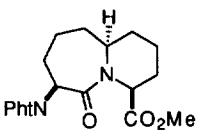
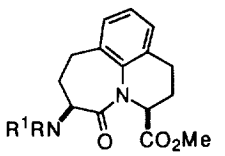
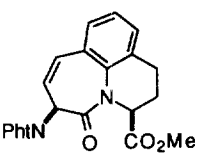
IX. TABULAR SUMMARY OF AZABICYCLOALKANE AMINO ACIDS AND DERIVATIVES

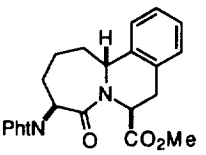
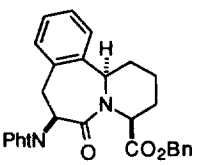
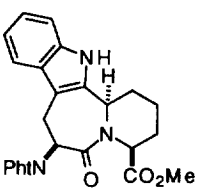
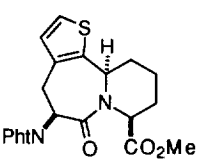
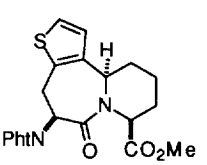
The following tabular summary has been ordered in the same general manner as the preceding text, i.e. the compounds are categorized as carbo-, thio-, oxa- and diaza-bicycloalkane amino acids in that order, and generally arranged from the smallest bicyclic system to the largest, in that particular series.

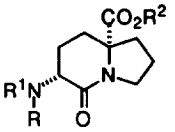
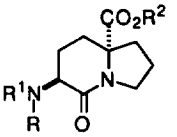
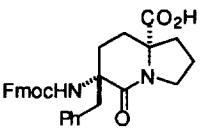
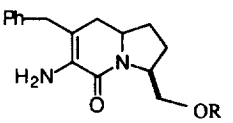
Type	Compounds	Comments	References
4,5-fused		X-ray of the $PhOCH_2CO$- derivative Designed as a β-lactam analog. No significant antibacterial activity against Gram-positive and Gram-negative organisms nor β-lactamase 1 (from *Bacillus cereus*).	37
4,5-fused		Designed as a β-lactam analog. Antibacterial activity against both Gram-positive and Gram-negative bacteria.	30b 39
5,5-fused		X-ray of the C-3 alcohol derivative. Designed as a β-lactam analog. No significant antibacterial nor β-lactamase inhibitory activity.	31 32
5,5-fused		Designed as a β-lactam analog. No significant antibacterial nor β-lactamase inhibitory activity.	31 32
5,5-fused		R^1 = PNZ, R^2 = Ac R^1 = Boc, R^2 = PNZ Designed as β-lactam analogs. Antibacterial activity against both Gram-positive and Gram-negative bacteria.	36
5,5-fused		Designed as a β-lactam analog. Antibacterial activity against both Gram-positive and Gram-negative bacteria.	36
5,5-fused		Designed as a β-lactam analog. Antibacterial activity against both Gram-positive and Gram-negative bacteria.	36

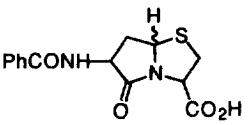
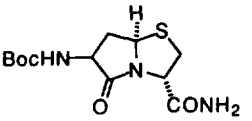
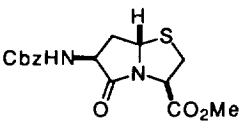
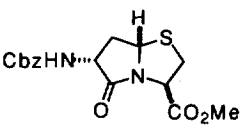
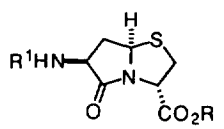
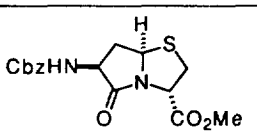
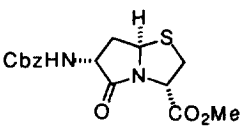
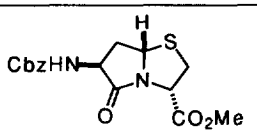
Type	Compounds	Comments	References
5,5-fused		Designed as a β-lactam analog. No activity against *E. Coli* X161 and X850.	33
5,5-fused		Designed as a β-lactam analog. No activity against *E. Coli* X161 and X850.	33
5,5-fused		Designed as a β-lactam analog. No activity against *E. Coli* X161 and X850.	33
5,5-fused		W = CO_2Me, CN, SEt, SOEt, SO_2Et W = SEt (α/β 2:3) Designed as β-lactam analogs.	34 30 34
5,6-fused		R^1 = Boc, X-ray analysis, nOe experiments R^1 = Cbz Designed as a type II' β-turn mimetic. Introduced into a Gramicidin S analog exhibiting antibacterial activity.	10 9 10b,e
5,6-fused		R^1 = Boc, nOe experiments R^1 = Cbz (racemic)	10 9
5,6-fused		Designed as a type II' β-turn mimetic.	10
5,6-fused		Selective antagonist for the NK-2 receptor.	11

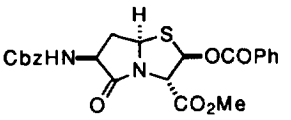
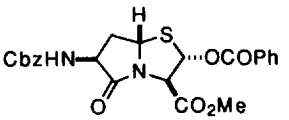
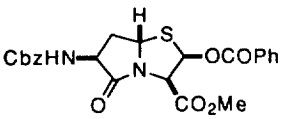
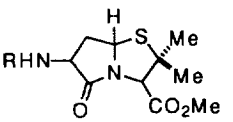
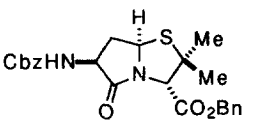
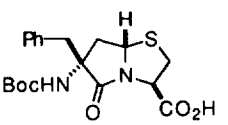
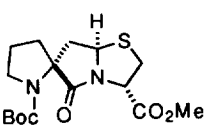
Type	Compounds	Comments	References
5,6-fused		Intermediate in the production of a selective antagonist for the NK-2 receptor.	13
5,6-fused			20
5,7-fused		R^1 = Ac, R^2 = *t*-Bu R^1 = Ac, R^2 = Me, X-ray analysis R^1 = Pht, R^2 = Me, nOe experiments R^1 = H, R^2 = Me Designed for use in metalloprotease inhibitors (ACE/NEP).	20, 16 20, 16 19, 28 18
5,7-fused		X-ray analysis.	18
5,7-fused			20
5,7-fused		R = R^1 = Pht, R^2 = Et R = H, R^1 = Ac, R^2 = Me R= H, R^1 = $COCF_3$, R^2 = Me, X-ray analysis. Designed for use in metalloprotease inhibitors (ACE/NEP).	28, 25 24 24
5,7-fused		R^1 = $COCF_3$, R^1 = H, X-ray analysis Designed for use in metalloprotease inhibitors (ACE/NEP).	24

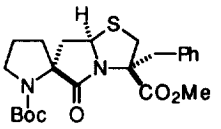
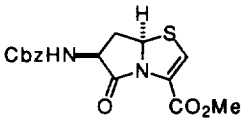
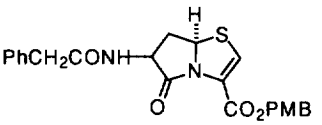
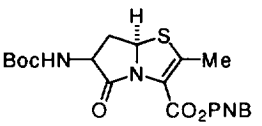
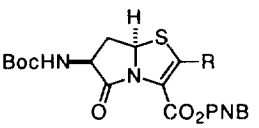
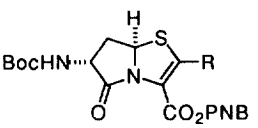
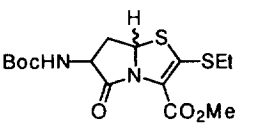
Type	Compounds	Comments	References
5,8-fused		Designed for use in metalloprotease inhibitors (ACE).	18
5,8-fused		Designed for use in metalloprotease inhibitors (ACE).	18
5,6-fused		R^1 = Cbz, R^2 = Me R^1 = Boc, R^2 = Me R^1 = Cbz, R^2 = Bn, nOe experiments Designed as a type II' β-turn mimetic. Introduced into GS analog.	27
5,6-fused		R^1 = Cbz, R^2 = Me R^1 = Boc, R^2 = Me R^1 = Cbz, R^2 = Bn, nOe experiments Designed as a type II' β-turn mimetic. Introduced into GS analog.	27
6,7-fused		X-ray analysis Designed for use in metalloprotease inhibitors (ACE).	19
6,7-fused		$R = R^1$ = Pht $R = R^1$ = H, X-ray analysis Designed for use in metalloprotease inhibitors (ACE).	28, 25
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	28, 25

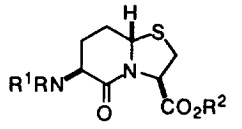
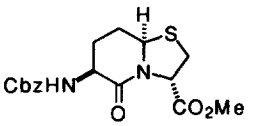
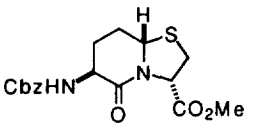
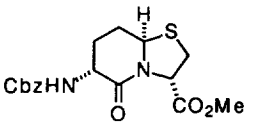
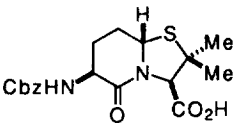
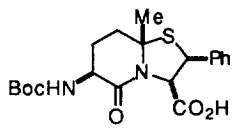
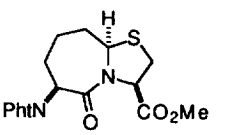
Type	Compounds	Comments	References
6,7-fused		X-ray analysis Designed for use in metalloprotease inhibitors (ACE/NEP).	26
6,7-fused		X-ray analysis Designed for use in metalloprotease inhibitors (ACE/NEP).	23
6,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	28
6,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	28
6,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	28

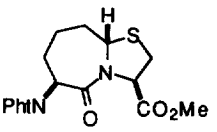
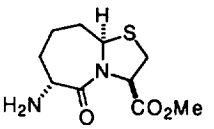
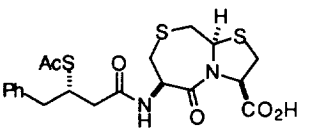
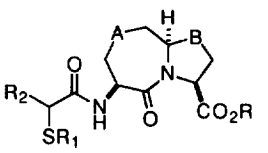
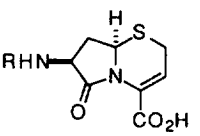
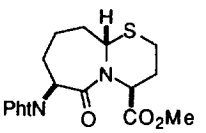
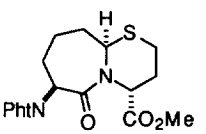
Type	Compounds	Comments	References
5,6-fused		R = H, R^1 = Boc R^2 = Me, X-ray analysis. R = Boc, R^1 = NHBoc, R^2 = *t*-Bu 1:9 mixture of diastereoisomers at C-3 R = H, R^1 = Fmoc, R^2 = H Designed as a type VI β-turn mimetic.	88 88, 90 88, 90
5,6-fused		R = Boc, R^1 = NHBoc, R^2 = *t*-Bu 9:1 mixture of diastereoisomers at C-3 R^1 = Fmoc, R = R^2 = H ROESY experiments Designed as a type VI β-turn mimetic.	88, 90
5,6-fused		Designed as a type VI β-turn mimetic.	90
5,6-fused		R = TBDMS, Me	17

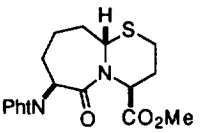
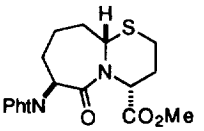
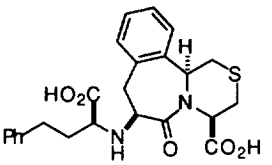
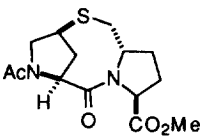
Type	Compounds	Comments	References
5,5-fused		Designed as a β-lactam analog. No significant antibiotic nor β-lactamase inhibitory activity.	40
5,5-fused		9(*R*):1(*S*) mixture of diastereoisomers nOe and NOESY experiments Designed as a type-II β-turn mimetic. In a derivative, it increased the binding of receptor agonist ADTN to the dopamine receptor.	43
5,5-fused		nOe experiments Designed as a β-lactam analog.	44 49 50
5,5-fused		nOe experiments Designed as a β-lactam analog.	44
5,5-fused		R^1 = Cbz, R^2 = Me, nOe experiments R^1 = Boc, R^2 = H Designed as a β-lactam analog. No biological activity against *S. aureus*.	44 49
5,5-fused		nOe experiments Designed as a β-lactam analog.	44
5,5-fused		nOe experiments Designed as a β-lactam analog.	44
5,5-fused		nOe experiments Designed as a β-lactam analog.	49

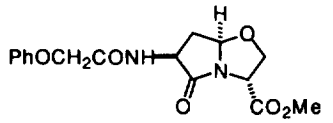
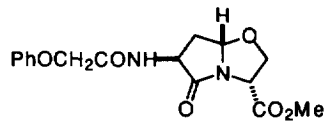
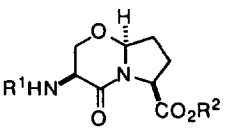
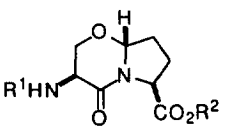
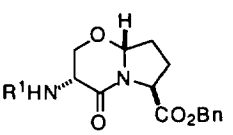
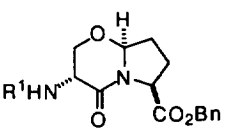
Type	Compounds	Comments	References
5,5-fused		Designed as a β-lactam analog.	44 50
5,5-fused		3(*S*):1(*R*) mixture of diastereoisomers at C-3. Designed as a β-lactam analog.	44 50
5,5-fused		1(*R*):3(*S*) mixture of diastereoisomers at C-3. Designed as a β-lactam analog.	44 50
5,5-fused		R = COPh and Bn Designed as a β-lactam analog. No significant antibiotic nor β-lactamase inhibitory activity.	40
5,5-fused		Designed as a β-lactam analog.	63
5,5-fused		nOe experiments. Designed as a β-lactam analog.	61
5,5-fused		nOe experiments. Designed as a type II β-turn mimetic. In a derivative, it increased the binding of receptor agonist ADTN to the dopamine receptor.	53 62

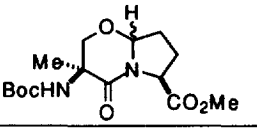
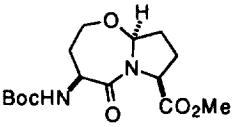
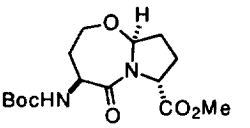
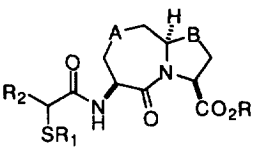
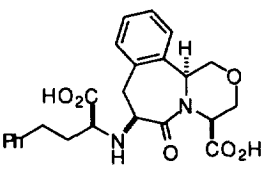
Type	Compounds	Comments	References
5,5-fused		Designed as a type II' β-turn mimetic.	98
5,5-fused		1:1 mixture of diastereoisomers at C-5. Designed as a β-lactam analog. Weak biological activity against *S. aureus*.	34 44 50
5,5-fused		3(*S*):1(*R*) mixture of diastereoisomers at C-3. NOESY experiments. Designed as a β-lactam analog. No antibacterial nor β-lactamase inhibitory activity.	44
5,5-fused		3.75(*R*):1(*S*) mixture of diastereoisomers at C-7. Designed as a β-lactam analog. Low activity against both Gram-positive and Gram-negative bacteria.	51
5,5-fused		R = Me, CH_2OAc, CO_2Me Racemic and optically active. Designed as β-lactam analogs.	30a 30b 34
5,5-fused		R = Me, CH_2OAc, CO_2Me. Racemic. Designed as β-lactam analogs.	30a 30b 34
5,5-fused		1(*cis*):3(*trans*) mixture of diastereoisomers. Designed as a β-lactam analog.	52

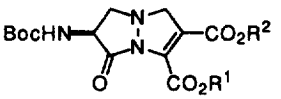
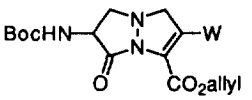
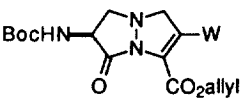
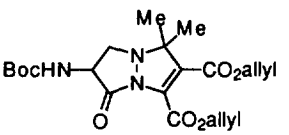
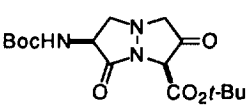
Type	Compounds	Comments	References
5,6-fused		R^1 = Boc, R = R^2 = H, X-ray analysis R,R^1 = Pht, R^2 = H R^1 = Fmoc, R = R^2 = H R^1 = Cbz, R = H, R^2 = Me nOe experiments. Designed as a type II' β-turn mimetic. Diverse biological applications.	41 55 46
5,6-fused		Designed for use in an analog of CsA.	47
5,6-fused			47
5,6-fused		nOe experiments. Designed as a type II β-turn. Used in Tendamistat analogs.	43 46
5,6-fused			55 56
5,6-fused		Designed for use in a Dermorphine analog.	55 64
5,7-fused		1:1 mixture of diastereoisomers at C-5 X-ray analysis. Designed for use in metalloprotease inhibitors (ACE).	18 60 42

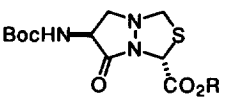
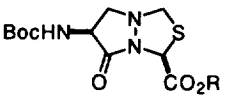
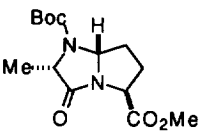
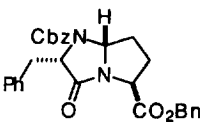
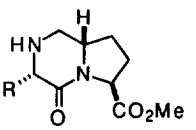
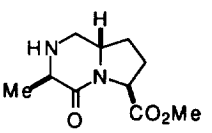
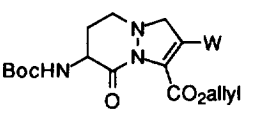
Type	Compounds	Comments	References
5,7-fused		1:1 mixture of diastereoisomers at C-5. Designed for use in metalloprotease inhibitors (ACE).	18 60 42
5,7-fused		Designed for use in metalloprotease inhibitors (ACE).	60
5,7-fused		Designed for use as a metalloprotease inhibitor (ACE).	94
5,7-fused		R = H, alkyl, ArY, $CH_2OCH_2CCMe_3$, Ph_2CH R_1 = H, Ac, PhCO, $CH_2O_2CCMe_3$, Q_1 R_2 = H, alkyl, $CH_2OCH_2CH_2OMe$, ArY A = CH_2, O, S B = S, O ArY = (substitued) arylalkyl Q_1 = $COCH_2$-Morpholine Designed for use in metalloprotease inhibitors (ACE/NEP).	94
5,6-fused		Designed as a β-lactam analog.	30a
5,7-fused		nOe and COSY experiments. Designed for use in metalloprotease inhibitors (ACE/NEP).	48
5,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	48

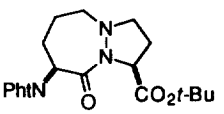
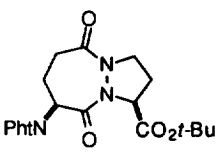
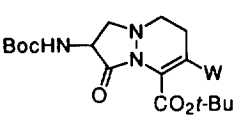
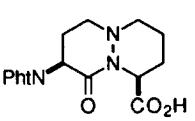
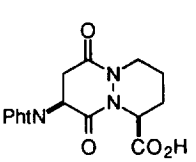
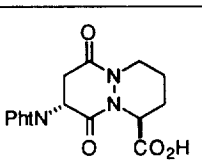
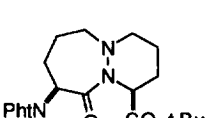
Type	Compounds	Comments	References
6,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	48
6,7-fused			48
6,7-fused		Designed for use as a metalloprotease inhibitors (ACE).	72
5,8,5-fused		X-ray of the acid derivative. Designed as a template for α-helix formation.	93

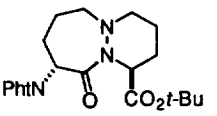
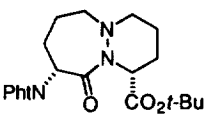
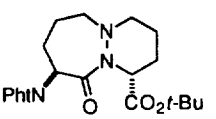
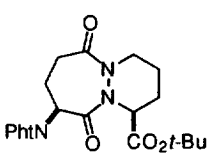
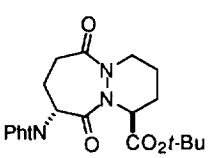
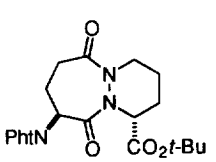
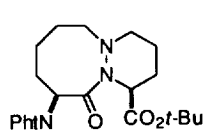
Type	Compounds	Comments	References
5,5-fused		Designed as a β-lactam analog. Inactive against *S. aureus* NCTC-6571.	66
5,5-fused		Design as a β-lactam analog. Inactive against *S. aureus* NCTC-6571.	66
5,6-fused		R^1 = Cbz, R^2 = Bn, nOe experiments. >8:1 mixture of diastereoisomers at C-6. R^1 = Boc, R^2 = Bn, 10:1 mixture of diastereoisomers at C-6. R^1 = Boc, R^2 = Me, nOe experiments. R^1 = Fmoc, R^2 = Bn, 9 : 1 mixture of diastereoisomers at C-6. Designed as a β-turn mimetic.	67 67 69 68
5,6-fused		R^1 = Cbz, R^2 = Bn, nOe experiments 1:>8 mixture of diastereoisomers at C-6. R^1 = Boc, R^2 = Bn, 1:10 mixture of diastereoisomers at C-6. R^1 = Fmoc, R^2 = Bn, 1:9 mixture of diastereoisomers at C-6. Designed as a β-turn mimetic.	67 67 68
5,6-fused		R^1 = Cbz, X-ray analysis, nOe experiments. >10:1 mixture of diastereoisomers at C-6. R^1 = Boc, >7:1 mixture of diastereoisomers at C-6.	67
5,6-fused		R^1 = Cbz, nOe experiments 1:>10 mixture of diastereoisomers at C-6. R^1 = Boc, 1:>7 mixture of diastereoisomers at C-6.	67

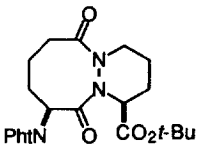
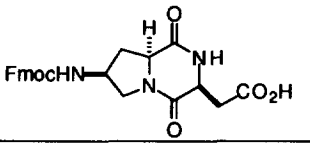
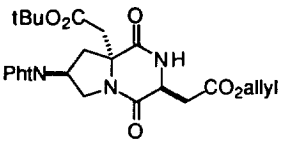
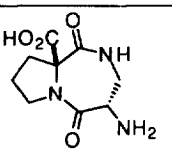
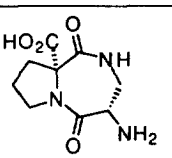
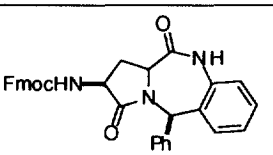
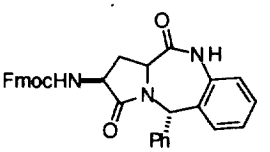
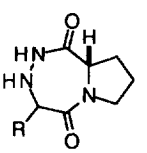
Type	Compounds	Comments	References
5,6-fused		6:4 mixture of diastereoisomers at C-6.	69
5,7-fused		Designed as a β-turn mimetic.	70
5,7-fused			71
5,7-fused		R = H, alkyl, ArY, $CH_2OCH_2CCMe_3$, Ph_2CH R_1 = H, Ac, PhCO, $CH_2O_2CCMe_3$, Q_1 R_2 = H, alkyl, $CH_2OCH_2CH_2OMe$, ArY A = CH_2, O, S B = S, O ArY = (substituted) arylalkyl Q_1 = $COCH_2$-Morpholine Designed for use as metalloprotease inhibitors (ACE/NEP).	94
6,7-fused		Designed for use as a metalloprotease inhibitor (ACE/NEP).	72

Type	Compounds	Comments	References
5,5-fused		R^1 = allyl, R^2 = allyl R^1 = Me, R^2 = allyl R^1 = allyl, R^2 = Me, X-ray analysis. Designed as β-lactam analogs. Antibacterial activity against both Gram-positive and Gram-negative bacteria.	100 76 76 76, 77
5,5-fused		W = COMe, COPh, CONHPh, PO_3Me_2, CF_3, CH_2OH, H W = CO_2Me, COMe, $COCO_2Et$, H W = COMe, CN for *t*-Bu ester W = COMe, CO_2Me, CO_2Et, CO_2Pr, CO_2Bn, COEt, CN, SO_2Me W = CO_2Et, CO_2CH_2Ph, COEt, CN, SO_2Me Designed as β-lactam analogs.	100, 101 77 78 78 73b 86a
5,5-fused		W = CO_2Me, COMe, X-ray analysis W = CN, SO_2Me W = CN, SO_2Me, SO_2Et, SO_2Ph W = CN, SO_2Me, SO_2Et, SO_2n-Pr, SO_2n-Bu, SO_2Ph, allyl, COMe, CO_2Me, SO_3Me X-ray analyses for W =COMe; CO_2t-Bu. Designed as β-lactam analogs. Antibacterial activity.	100, 101 77 82 73b 73c
5,5-fused		Designed as a β-lactam analog. *In vitro* antimicrobial activity against *S. aureus*.	75
5,5-fused		Designed as a β-lactam analog.	85

Type	Compounds	Comments	References
5,5-fused		R = Me, *t*-Bu, $HC(Ph)_2$, Et, allyl 3(*R*):1(*S*) mixture of diastereoisomers at C-2. nOe experiments. Designed as β-lactam analogs.	80
5,5-fused		R = Me, *t*-Bu, $HC(Ph)_2$, Et, allyl, H 1(*S*):3(*R*) mixture of diastereoisomers at C-2. nOe experiments. Designed as β-lactam analogs.	80
5,5-fused		nOe experiments.	71
5,5-fused		X-ray of the acid derivative. Designed as a β-lactam analog.	102
5,6-fused		R = Me, CH_2Ph NOESY and HMBC experiments.	103
5,6-fused			103
5,6-fused		W = CO_2allyl, CN, COMe Designed as β-lactam analogs. Antibacterial activity.	80

Type	Compounds	Comments	References
5,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	104 28
5,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	104 28
5,6-fused		W = CO_2Me, X-ray analysis. W = COMe Designed as β-lactam analogs.	100 86a 73b 86b
6,6-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	60 87a
6,6-fused		Designed for use in metalloprotease inhibitors (ACE).	87a 87c
6,6-fused		Designed for use in metalloprotease inhibitors (ACE).	87a 87c
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	104, 28 60 87a 87b

Type	Compounds	Comments	References
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	87a
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	87a
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	87a
6,7-fused		Designed for use in metalloprotease inhibitors (ACE/NEP).	104, 28 60 87a, 87b
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	87b
6,7-fused		Designed for use in metalloprotease inhibitors (ACE).	87a
6,8-fused		Designed for use in metalloprotease inhibitors (ACE).	87a

Type	Compounds	Comments	References
6,8-fused		Designed for use in metalloprotease inhibitors (ACE).	87a
5,6-fused		Used to stabilize loop conformations in cyclic peptides having NPNA and RGD motifs.	96a
5,6-fused		Used in cyclic peptides having NPNA motifs.	96b
5,7-fused		1:1 mixture of diastereoisomers at C-7. Designed for use as Xaa-Pro amide *cis*-rotamer and type VI β-turn mimetics.	91
5,7-fused		1:1 mixture of diastereoisomers at C-7. Designed for use as Xaa-Pro amide *cis*-rotamer and type VI β-turn mimetics.	91
5,7-fused		5(*R*):1(*S*) mixture of diastereoisomers at C-2. nOe experiments.	105
5,7-fused		1(*S*):5(*R*) mixture of diastereoisomers at C-2. nOe experiments.	105
5,7-fused		R = H, X-ray analysis. R = Me, X-ray analysis for the *R* derivative. Designed for use as Xaa-Pro amide *cis*-rotamer and type VI β-turn mimetics.	92

IX. ACKNOWLEDGEMENT

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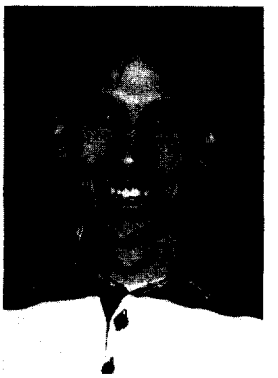
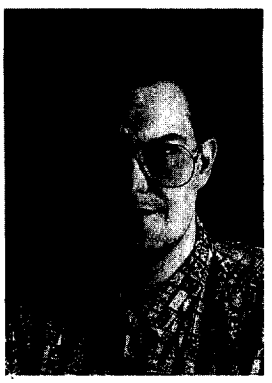


Grant McNaughton-Smith



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