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Cyclopeptide Alkaloids

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Cyclopeptide alkaloids are a group of cyclic closely related polyamide bases of plant origin. They are primarily composed of simple, natural amino acids linked by amide bonds (-CONH-), except for one non-amino acid unit, a styrylamine portion or derivative thereof. One of the amino acid residues has its amino function either mono- or dimethylated, and it is this group that is responsible for the basicity of these molecules. Therefore, the name cyclopeptide means that these compounds exist as a ring made up of peptide bonds while the term alkaloid is given because they are nitrogenous bases isolated from plants. With one exception, all cyclopeptide alkaloids contain one β -hydroxyamino acid ($-\text{CH}(\text{OH})\text{-CH}(\text{NH}_2)\text{-COOH}$), and it is this unit that determines the various families of compounds. The general structure of cyclopeptide alkaloids is illustrated in Figure 1.

The term *cyclopeptide alkaloid* was first proposed by Goutarel and co-workers (1). Rapoport and co-workers have also suggested the names *ansapeptides* and *phencyclopeptides* (2, 3).

Since the first correct structure determination of a cyclopeptide alkaloid in 1966 (4), over 100 cyclopeptide alkaloids have been isolated from plants and characterized. The widespread occurrence of these compounds makes them an important class of natural products. Their biological function in plants is not known with certainty although there is evidence that they function as ionophores and may be involved in absorption of nutrients from the soil, especially alkali metal ions. In spite of their abundance in plants, yields from dried plant materials are generally low and depend on plant material and method of isolation. The low natural availability of cyclopeptide alkaloids has generated considerable interest in the development of methodology to synthesize these molecules. As a result, cyclopeptide alkaloids are a rapidly expanding field with emphasis on both the development of synthetic methods and the investigation of their biological properties and function.

Discovery, Natural Occurrence, and Isolation

Cyclopeptide alkaloids were observed as early as 1884 in a plant from the family Rhamnaceae, *Ceanothus americanus*, long used in folk medicine (5).

In 1963, Goutarel and co-workers (6) isolated adouetines -X, -Y, and -Z from *Waltheria americana*, and Swiss investigators (7) isolated zizyphine from *Zizyphus oenoplia*. In 1964 the occurrence of alkaloids in *Scutia buxifolia* was reported (8). The same year, the structure of pandamine, extracted from *Panda oleosa*, was shown to have peptide structure whose components were phenylalanine, N,N-di-

methylleucine, β -hydroxyleucine, and 2-(*p*-hydroxyphenyl)ethylamine (1). These results were confirmed in 1966 (4). Shortly after, other cyclopeptide alkaloids were isolated from *Ceanothus americanus* (9,10), *Scutia buxifolia* (11), and *Waltheria americana* (12). Their structures were found to be closely related to that of pandamine. Since then, the number of cyclopeptide alkaloids that have been isolated and characterized has increased steadily, and the reader is referred to previous review articles for more detailed information (13-18).

Cyclopeptide alkaloids are widespread in plants of the family Rhamnaceae but are also present in plants of other families. They are formed in leaves, bark, root bark, and seeds but are often difficult to isolate because they are present in minute amounts. The yields of cyclopeptide alkaloids from dried plant material range from 0.01 to 1%, and are dependent on many factors such as the method of isolation, region of growth, and maturity of the plant used.

The first step in the isolation of a cyclopeptide alkaloid is an extraction procedure that is modified according to the plant source and the bases present. The dried ground plants are usually treated with a dilute basic solution and then extracted with an organic solvent. The bases are separated from the extracts by treatment with a dilute acid solution. Further purification and separation of the individual bases are accomplished by standard chromatographic methods. Detection of the various fractions is accomplished with an ultraviolet source. High-performance liquid chromatography is a valuable technique for the separation of cyclopeptide alkaloids from crude plant extracts. The isolation of a cyclopeptide alkaloid is described in an article reporting a new natural product, sativanine-G from a plant of the family Rhamnaceae, *Zizyphus sativa* (19).

Classification

Several classification methods have been proposed for cyclopeptide alkaloids (16), all based on the various residues that constitute these molecules. A detailed description of these is beyond the scope of this article. The β -hydroxyamino acid and the size of the ring are important in classifying the various families. For instance, several cyclopeptide alkaloids have a *trans*- β -hydroxyproline amino acid and a 14-membered ring (see table). However, rings of different size (13- and 15-membered) and other β -hydroxyamino acids such as β -hydroxyisoleucine and β -hydroxyphenylalanine are also found in other families.

Structural Determination

The structures of the various cyclopeptide alkaloids have been determined by chemical degradation reactions and spectroscopic methods. The structures of two cyclopeptide alkaloids, mauritine-A (20) and frangulanine (21), have been confirmed by X-ray analyses.

Methods used for the chemical degradation of cyclopeptide alkaloids into their components have been summarized in detail (16). Acid hydrolysis is the most commonly used method for amino acid determinations, and it is carried out after reduction or ozonolysis of the styrylamine functionality. Alkaline hydrolysis has also been used to determine the tryptophan content and the nature of the substituents present on the aromatic ring of the aryl ether moiety of these

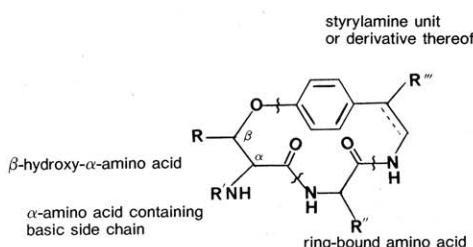


Figure 1. General structure of cyclopeptide alkaloids.

compounds. Direct acid hydrolysis is followed by analysis via chromatographic methods.

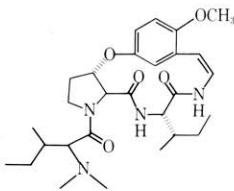
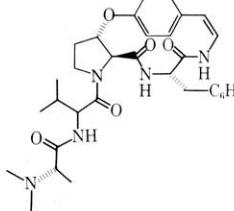
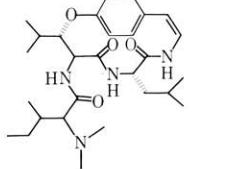
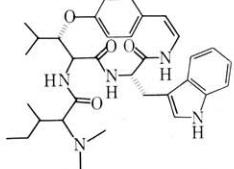
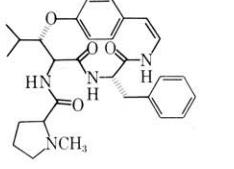
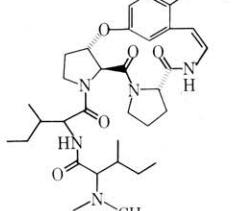
Mass spectroscopy has been used more extensively than any other method for the structural determination of cyclopeptide alkaloids. High-resolution mass spectroscopy gives the elemental composition of the natural product. Electron fragmentation patterns depend on the β -hydroxyamino acid present in the alkaloid. Typical fragmentation patterns have been described (16). These patterns compliment the degradative studies. A novel application of metastable ion and collisional activation spectra to peptides containing leucine and isoleucine now allows unequivocal differentiation between N,N-dimethylated leucine, isoleucine, and norleucine. Analysis of MIKES (metastable ion kinetic energy spectra) of scutianines C and H ascertained the presence of N,N-dimethylisoleucine in both alkaloids (22). Field desorp-

tion mass spectroscopy has been used to examine crude cyclopeptide alkaloid extracts.

Infrared spectroscopy has allowed the determination of several functional groups such as NH, NMe, phenol ether, styryl double-bond, and amide.

Ultraviolet spectroscopy has been used to recognize the tryptophan moiety and to detect strain in the 14-membered cyclopeptide alkaloids. The lack of a characteristic peak indicative of a conjugated styrylamine chromophore led to the assumption that ring strain precluded the coplanarity of the aromatic ring and the enamido chromophore, thereby preventing π -orbital overlap. This supposition was confirmed by X-ray studies. The ultraviolet spectra of 13-membered ring alkaloids confirm that considerably less strain exists in these molecules and therefore π overlap of the styrylamine system is possible. The less strained 15-mem-

Selected Cyclopeptide Alkaloids

Name Ring Size Amino Acids ^{a,b}	Molecular Formula	Melting Point (°C)	Optical Rotation (α°) _D
	C ₂₈ H ₄₂ N ₄ O ₅	92	...
	C ₃₂ H ₄₁ N ₅ O ₅	104	-315 c 0.33, CH ₃ OH
	C ₂₈ H ₄₄ N ₄ O ₄	275-276	-288 c 0.1, CHCl ₃
	C ₃₃ H ₄₂ N ₅ O ₄	235-236	-172 c 0.1, CHCl ₃
	C ₂₉ H ₃₆ N ₄ O ₄	238.5-240.5	-293
	C ₃₃ H ₄₉ N ₅ O ₆	124-126	-411 c 0.086, CH ₃ OH

continued on next page

bered ring bases exhibit characteristic maxima from the styrylamine portion which are very similar to those observed for N-styrylamides. Aromatic substituents that produce bathochromic shifts are also easily identified by the characteristic ultraviolet absorptions.

Nuclear magnetic resonance has been used extensively in the structural elucidation of cyclopeptide alkaloids. Detailed spectral studies have been reported for several members of the hydroxyleucine-containing cyclopeptide alkaloids (16). Compounds containing hydroxyphenylalanine and hydroxyproline have also been examined (16, 22). Distinguishing evidence between 3- and 4-hydroxyprolines was obtained from the NMR spectra of the amphibine type alkaloids.

The conformational aspects of the 14-membered ring alkaloids have been studied by both ^1H and ^{13}C nuclear magnetic resonance (18, 23). The solvent and temperature-dependent chemical shifts of NH protons of both the tryptophan amide and indole ring of discarine-B were investigated. The results suggested a minimal conformational change with solvent and temperature variation. The conformational rigidity of the 14-membered ring of discarine-B was substantiated by the apparent solvent-solute interaction between one face of the peptide frame and polar solvents. Partial stacking of the tryptophan and isoleucine side chains was proposed from the chemical shifts of the isoleucine groups (24).

On the other hand, ^1H NMR, ^{13}C NMR, NOE measurements and variable temperature experiments showed that frangulanine, another 14-membered ring cyclopeptide alkaloid, existed in a γ -turn conformation in CDCl_3 , with the NH of leucine providing the hydrogen bonding proton in the

turn. Frangulanine, unlike discarine-B, undergoes a conformational change in d_6 -DMSO which is evidenced by the disappearance of the γ turn and by the large solvent dependency of the chemical shifts and vicinal coupling constants.

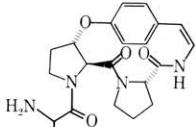
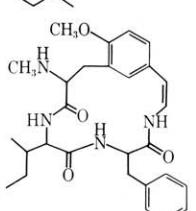
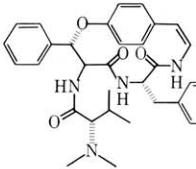
Alkaloids with 13- and 14-membered macrocycles show chemical shifts similar to the unstrained noncyclic derivatives.

Several detailed ^{13}C NMR studies of cyclopeptide alkaloids have been reported (22, 25, 26). Again the 14-membered ring alkaloids show distinctive NMR features that indicate conformational rigidity and macrocyclic ring strain. The β -aryloxyleucine side chain residue in discarine-B reveals a nonequivalence of the δ -methyl resonances. Restricted motion of the aromatic ring results in the four aromatic protons being in dissimilar environments and therefore absorbing at different positions. The two styrene carbons are almost equivalent, consistent with a nonconjugated double-bond system. Acyclic derivatives are strain free and therefore the same carbons exhibit greatly different chemical shifts.

A combined NMR and X-ray crystallographic approach to the analysis of the conformations of two synthetic cyclopeptide alkaloid models illustrates clearly the usefulness of these techniques in determining both solution and solid state conformations. Only subtle differences between the models were observed, they both adopted the same overall geometry with both amides trans. The differences observed reflected the ability of one of the cyclopeptide models to form an intramolecular hydrogen bond similar to those observed in the γ turns of proteins.

Circular dichroism (CD) spectra furnishes complimentary information to the ^1H and ^{13}C NMR studies of cyclope-

Selected Cyclopeptide Alkaloids (Continued)

Name Ring Size Amino Acids ^{a,b}	Molecular Formula	Melting Point (°C)	Optical Rotation (α°) ^c
 Zizyphine-G/ 14-membered β -HOPro Ile Pro	$\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_4$	130	-185 c 0.19, CH_3OH
 Mucronine-B/ 15-membered ... N-MAla Ile Phe	$\text{C}_{28}\text{H}_{38}\text{N}_4\text{O}_4$	222-224	+175 ^k c 0.2, CHCl_3
 Integerissine/ 14-membered β -Phe N,N-DMVal Phe	$\text{C}_{33}\text{H}_{38}\text{N}_4\text{O}_4$	285	-164 c 0.2, CHCl_3

^a β -Hydroxyamino acid, basic amino acid, and ring amino acid.

^b β -Hydroxyproline (β -HOPro), N,N-dimethylisoleucine (N,N-DMIle), proline (Pro), leucine (Leu), N,N-dimethylalanine (N,N-DMAla), phenylalanine (Phe), β -hydroxyleucine (β -HOLeu), tryptophan (Trp), isoleucine (Ile), N-methylalanine (N-MAla), N,N-dimethylvaline (N,N-DMVal).

^c Ref 19.

^d Tschesche, R.; Wilhelm, H.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1972**, 26, 2609.

^e Tschesche, R.; Last, H.; Fehlhaber, H.-W. *Chem. Ber.* **1967**, 100, 3937.

^f Mascaretti, O. A.; Merkuza, U. M.; Ferraro, G. E.; Ruveda, E. A.; Chang, C.-J.; Wenkert, E. *Phytochemistry* **1972**, 11, 1133.

^g Ref 9.

^h Tschesche, R.; Kaussman, E. U.; Eckhardt, G. *Tetrahedron Lett.* **1973**, 26, 2577.

ⁱ Tschesche, R.; Khokhar, I.; Spilles, Ch.; Eckhardt, G.; Cassels, B. K. *Tetrahedron Lett.* **1974**, 34, 2941.

^j Fehlhaber, H.-W.; Uhendorf, J.; David, S. T.; Tschesche, R. *Liebigs Ann. Chem.* **1972**, 759, 195.

^k At 25 °C.

^l Tschesche, R.; Rheingans, J.; Fehlhaber, H.-W.; Legler, G. *Chem. Ber.* **1967**, 100, 3924.

tides. Both theoretical and experimental CD spectra allow the identification of solution conformers.

Binding constants for cations of different groups may be determined. Binding curves confirm the stoichiometry of the complexes as calculated by extraction procedures. The ion binding properties of a synthetic peptide and a natural cyclopeptide alkaloid, ceanothine-B were determined by circular dichroism studies in acetonitrile (27, 28). Ceanothine B interacted with Mg^{2+} and Ca^{2+} but not with Na^+ .

The crystal structures of the 14-membered ring cyclopeptide alkaloids, mauritine-A (20) and a N,N,N-trimethylated derivative of frangulanine (21) were elucidated by X-ray diffraction analysis. In both compounds, all amino acid centers had the L-configuration and the amide bonds had trans stereochemistry. The ring strain that had been postulated from UV, 1H , and ^{13}C NMR studies was also evident in the crystal structures. In mauritine-A, the benzene ring was slightly bent and the attached atoms were out of the benzene plane. The pronounced deviation from coplanarity was more apparent in the styrylamide system preventing π -orbital overlap. The trans stereochemistry of the β -hydroxyproline unit was clearly established, thereby clarifying the ambiguities found in the 1H NMR studies. The erythro stereochemistry of the β -hydroxyleucine unit in frangulanine was confirmed by the X-ray studies.

General and Biological Properties

The free bases of cyclopeptide alkaloids are usually crystalline although the amphibines and mauritines are amorphous. Cyclopeptide alkaloids are usually sparingly soluble in water but readily soluble in alcohols, chloroform, and other organic solvents. They have high melting points, generally above 200 °C. Reduction of the *p*-hydroxystyrylamine unit normally causes an increase in melting point ranging from 20–80 °C. With few exceptions (aralionine-A, +82°, methanol and lasiodine-A, +38°, chloroform and mucronine-B, +175°, chloroform) most of the alkaloids are levorotatory and have large negative rotations ranging from 200° to 400° in either chloroform or methanol. Reduction decreases the rotation. The optical activity of the 15-membered compounds depends both on the solvent and the degree of methylation of the amino group (16).

Cyclopeptide alkaloids are weak bases and often crystallize from aqueous solutions of weak acids. Many of their salts are appreciably soluble in nonpolar solvents.

Plants containing cyclopeptide alkaloids were first investigated because of their therapeutic reputation. However, pharmacological investigations have been hampered by the lack of large quantities of pure products (14).

Cyclopeptide alkaloids are reported to have antibiotic properties and to be weakly active against lower fungi and gram-positive bacteria. The degree of methylation of the amino group is reported to be important. Desmethyl bases are active only against fungi, and antibacterial properties are observed only after methylation of the amino function (16).

The effect of frangulanine on mitochondrial swelling has been investigated. This compound showed ion selectivity on the induction of mitochondrial swelling. Swelling occurred in potassium or rubidium chlorides but not in either sodium or lithium chlorides. The ion selectivity may be caused by the formation of a complex with either potassium or rubidium, which would act as an ionophore in the mitochondrial inner membranes, in a manner similar to valinomycin. This complex may be involved in the absorption of nutrients from the soil, especially alkali metals (29).

Photophosphorylation in isolated spinach chloroplast was inhibited by several cyclopeptide alkaloids (30). All of the cyclopeptide alkaloids assayed inhibited photophosphorylation. Some of them affected ATP synthesis specifically while others behaved like uncouplers. These compounds may become useful tools in the study of energy conservation in chloroplasts. The sensitivity of the photosynthetic energy

conservation machinery to cyclopeptide alkaloids may be related to their biological role in plants.

Synthetic Strategies

Cyclopeptide alkaloids are a new class of heterodetic cyclic peptides that contain an aryl alkyl ether linkage. As it is believed that the biological activity of cyclic peptides will be retained in analogs of different sequence and configuration, if their structures are similarly arranged in space, cyclopeptide alkaloids should show similar biological properties to related depsipeptides. They are already known to transport cations across membranes. Their potential similarity to depsipeptides should be explored further. But in spite of their widespread occurrence in plants, yields from dried plant material do not exceed 1% and depend not only on the plant source but also on the method of isolation. Therefore, practical synthetic methods for these compounds are of utmost importance if their resemblance to biologically active depsipeptides is to be explored.

The synthetic challenges presented by the various families of cyclopeptide alkaloids has attracted the attention of several research groups. However, before describing the efforts of the many groups involved in these synthetic endeavors, we will discuss briefly the challenges presented by these compounds and the possible strategies available.

The steps required for the synthesis of heterodetic cyclic peptides are the formation of peptide bonds, the formation of nonpeptide bonds, and the cyclization of these units, this last step being the most crucial.

Cyclization requires the generation of mutually reactive chains under conditions that favor an intramolecular process. The formation of a peptide bond requires a free amino group and a carboxyl function activated toward nucleophilic attack. The coupling of the ends must proceed at high dilution (10^{-3} – 10^{-4} M); therefore, the carboxyl activation and the cyclization step must be separable. As cyclization is always a slow process, the activated carboxyl group should not undergo unimolecular or solvent-induced decomposition, nor racemize before cyclization takes place.

The synthetic challenges presented by cyclopeptide alkaloids are the preparation of the β -aryloxyamino acid, the formation of the enamide linkage and the generation of the macrocycle. In most of the commonly found 14-membered rings cyclization creates a ring with considerable strain. Synthetic studies have focused on the dihydro derivatives and introduction of unsaturation to form the enamide bond is achieved after cyclization. However, the reduced derivatives present essentially the same synthetic problems as reduction of the vinylic double bonds does not relieve ring strain to an appreciable extent.

As the generation of the macrocycle (1) is the key step in the synthesis, the possible cyclization sites will be examined first. These are shown in Figure 2.

Cyclization at positions 1 or 2 involves standard peptide bond formation methods and high dilution conditions. Because of the mild conditions used for peptide bond formation as compared to other organic transformations, this approach has been favored by most investigators (Fig. 3).

Although the preference for position 1 or 2 was initially debated, more recent work seems to indicate that there is little difference between them. Therefore, the choice of posi-

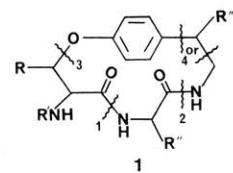


Figure 2. Possible cyclization sites.

tions 1 or 2 as cyclization sites should be determined by the ease of preparation of the required linear precursor.

Cyclization at position 3 requires either an intramolecular Michael addition of the phenol functionality to a dehydroamino acid residue or a nucleophilic attack on the three-membered heterocycle by a phenolate ion (Fig. 4).

A desirable feature of the ring closure at the 3 position is that it utilizes the intact alkaloid structure, including the styrylamide moiety, as a linear precursor.

Finally, ring closure at position 4 requires attack on benzene ring which might be accomplished via Friedel-Crafts-type reactions. This cyclization position is less attractive because of the more rigorous conditions required for such reactions. Alternatively, closure at this position could be effected by using linear precursors that could be cyclized via aldol-type reactions. The disadvantage of this approach is that peptide fragments possess several positions of comparable acidity. Therefore, selective abstraction of the proton needed to generate the required carbanion may not be possible (Fig. 5).

The first attempts to synthesize cyclopeptide alkaloids were carried out by French investigators (31, 32). The target molecule was the dihydro derivative of frangulanine, a 14-membered cyclopeptide alkaloid. Cyclization was attempted at both positions 1 and 2, using standard peptide bond formation methods such as azide or active ester activation, but could not be accomplished. This failure was attributed to the strain of the 14-membered ring.

Rapoport and co-workers (27, 28) at Berkeley reported cyclization studies using simplified models that did not contain the enamide moiety and the β -hydroxy- α -amino acid (Fig. 6).

These models were chosen to examine the effect of amide

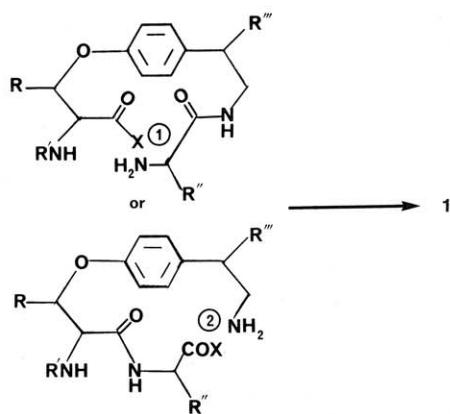


Figure 3. Cyclization at positions 1 or 2.

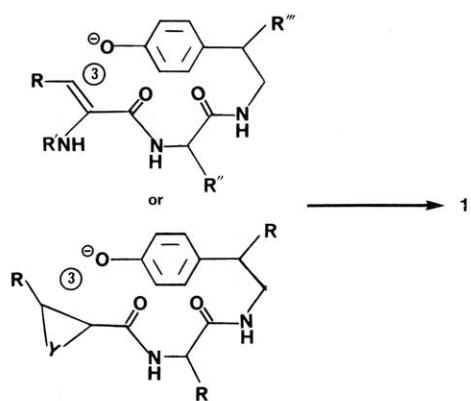


Figure 4. Cyclization at position 3.

substitution on the course of peptide cyclization. Both amide linkages were alkylated either with methyl groups or by incorporation into a proline residue because the preference for a trans arrangement diminishes when peptide bonds are alkylated. In linear peptides, the presence of a cis amide bond causes the peptide to fold in on itself. Therefore, it was expected that this folding at both peptide ends might help cyclization. The conclusion of this study was that the reactivity of the free amino group in the linear precursor is the major factor in determining the yields of the cyclic monomers. The yields of ansapeptides were found to be independent of the degree of amide substitution in the precursors but the configuration of the cyclic products depended on the structure of the amide in the linear precursor. Although these results are interesting, their relevance to the synthesis of a natural cyclopeptide alkaloid has not been explored.

The first total synthesis of a 14-membered dihydrocyclopeptide alkaloid, dihydromauritine-A, was accomplished from L-proline via an S_N2 displacement and three amide-bond-forming steps (33, 34). In this case, cyclization was accomplished at position 1.

The first total synthesis of a 13-membered cyclopeptide alkaloid, zizyphine A, was reported by German investigators (35). Schmidt and co-workers (36, 37) also synthesized several dihydro cyclopeptide alkaloids: dihydrozizyphines A and B (13-membered) and dihydrozizyphine-G (14-membered). These investigators also synthesized a 15-membered derivative, mucronine-B (38). In contrast with the 13-and 14-membered cyclopeptide alkaloids which are biogenetically derived from tyrosine and contain a β -phenoxyamino acid unit in the ring, the members of the mucronine family do not possess an ether linkage but a carbon-carbon bond. Their biogenesis presumably originates from *m*-phenylenediamine. Both cyclizations at positions 1 and 2 were used by the Schmidt group.

Investigations carried out by Lawton and co-workers (39, 40) have focused on the cyclization of linear precursors at position 3. The strategy employed by this research group was

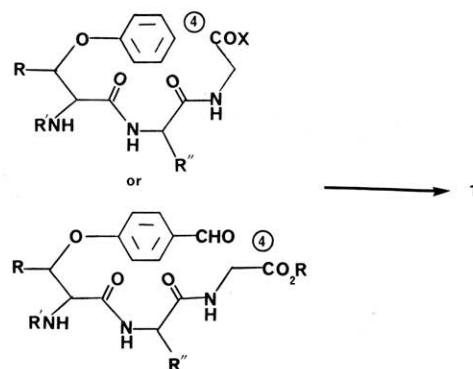


Figure 5. Cyclization at position 4.

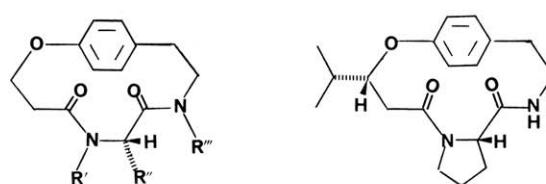


Figure 6. Model ansapeptides.

intended to mimic a possible biosynthetic pathway. In the biogenesis of cyclopeptide alkaloids, there is no evidence for the way this macrocycle is closed. It has been proposed that the oxygen-carbon bond forms last. A number of possible transformations have been proposed (40, 41). A quinone methide composed of a dehydrophenylalanylphenylalanine coupled to an oxidized tyrosine could be a suitable precursor. This compound would then undergo decarboxylation

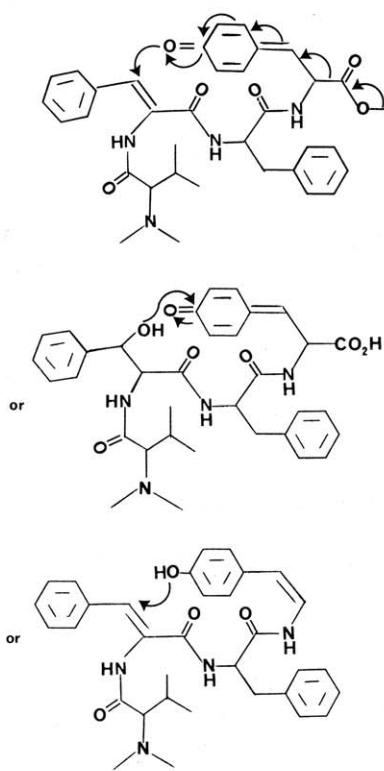


Figure 7. Possible biosynthetic pathways.

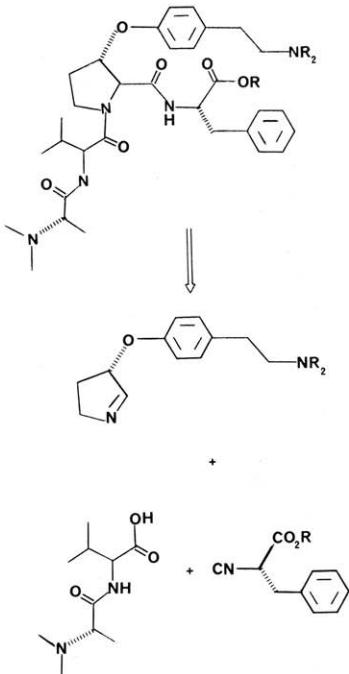


Figure 8. Four-component condensation.

and subsequent Michael addition to form the macrocycle. Alternatively, a phenylserylphenylalanyltyrosine derivative could undergo cyclization via attack of the β -hydroxyl group on the quinone carbonyl, followed by decarboxylation and loss of the phenolate hydroxyl. Equally possible would be attack of a phenolic hydroxyl group on an unsaturated amide (Fig. 7). From a synthetic point of view, none of these pathways appears easily achievable. Lawton and co-workers prepared several tripeptide precursors containing both a dehydrophenylalanine and a tyrosine residue (39, 40). Although many different functionalities and conditions were tried, cyclization of the linear precursors could not be accomplished.

While cyclization remains the most challenging step in the synthesis of cyclopeptide alkaloids, the formation of the linear precursors is far from trivial. Their synthesis is plagued with the separation of diastereomeric products, and racemization of any or all of the several asymmetric centers is an ever present possibility. Consequently, many efforts have been aimed at the development of novel methodology that could make the preparation of linear precursors more efficient and stereoselective.

One such proposed strategy for proline-containing cyclopeptide alkaloids involves a four-component condensation as a way of introducing, in one step, the amino acids containing the basic side chain and the ring-bound α -amino acid (42). This reaction generates a N-acylated amino acid amide from an aldehyde, an amine (present as the corresponding imine), a carboxylic acid and an isonitrile. This strategy generates the N-acyl bond, the bond to the α -carbon of proline, the prolyl amide and the trans stereochemistry of the proline derivative, all in one reaction step (Fig. 8).

A different strategy has been proposed by Lipshutz and co-workers (43) which envisions the use of heterocycles as masked diamide-dipeptide equivalents. The unmasking of these heteroaromatic moieties to their dipeptide equivalents has been demonstrated and model studies for subsequent elaboration to specific heterocyclophanes is under investigation (Fig. 9).

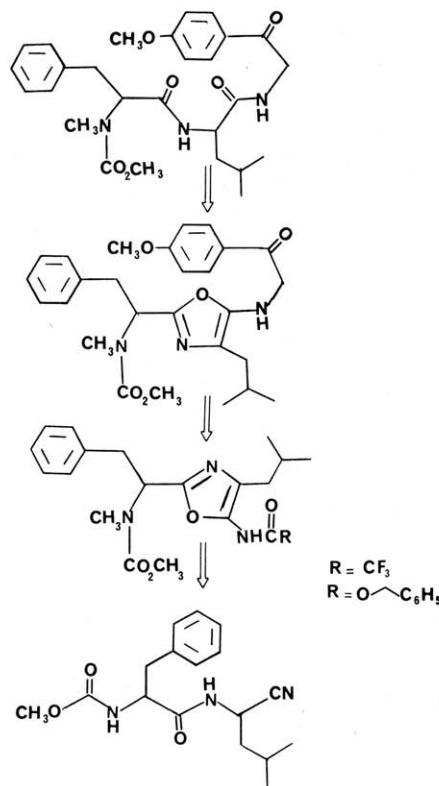


Figure 9. Masked diamide-dipeptide equivalents.

Conclusion

The field of cyclopeptide alkaloids is under active investigation in both this country and abroad. Since the structure elucidation of the first cyclopeptide alkaloid, pandamine, in 1966, over 100 cyclopeptide alkaloids have been isolated and their structures elucidated. New members of this class of natural products are still being reported. The synthetic challenges presented by these macrocycles have attracted several research groups and new developments are reported regularly in this rapidly expanding field. The potential biological activity of cyclopeptide alkaloids, their still uncertain role in plants, and their potential as a new class of naturally occurring ionophores, makes them important synthetic targets.

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