the D_2O layer and was used to prepare 10 mL of a CH_2Cl_2 (c 2.13) solution which gave the following rotations.

λ nm	α obsd	$[\alpha]_\lambda^{25}$	% opt purity	CSF
578	−1.003	−47.1°	29.3	1.83
546	−1.153	−54.1°	29.3	1.83
436	−2.093	−98.3°	28.9	1.81

From the original equilibrated $CDCl_3$ layer was recovered 91.7 mg of free amino ester, which was used to prepare a 5-mL solution of amino ester in CH_2Cl_2 (c 1.83), whose rotations were as follows.

λ, nm	α obsd	$[\alpha]_\lambda^{25}$	% opt purity	CRF
578	2.623	143.3	89.0	17.18
546	3.020	165.0	89.2	17.51
436	5.515	301.4	88.6	16.54

Since EDC = CRF·CSF, then EDC = 17.08 × 1.82 = 31.1.

Deviations from Standard Procedure in EDC Determinations. In runs 7, 8, and 15-22, $CDCl_3$–CD_3CN (9:1 v:v) was employed as the organic medium, instead of the $CDCl_3$ alone used in the other runs. In runs 30 and 40, $C_6H_5CH(CO_2CH_3)NH_3ClO_4$ was employed in the aqueous solution directly in the absence of $LiClO_4$. In runs 4-8, 13, 14, 33, 34, and 38, the G/H ratios were determined only by integrations of ^1H NMR signals of the $CDCl_3$ layer. In all other runs, the G/H ratios reported in Table II were determined from CRF and CSF factors and eq 3. Many were checked by ^1H NMR integrations and were found to be within 0.1. In runs 2-8, 9-14, 16-18, and 20-22, the EDC values were calculated from CRF and CSF values based on rotations of the vacuum dried hydrochloride salts precipitated from final dry (HCl gas saturated) CH_2Cl_2 extracts of the amino esters obtained from each layer in the distribution experiments. In representative runs, the CRF and CSF values were determined from both the free amino ester and HCl salts. The optical purities of the amino esters came out about 1% higher than those of the HCl salts. In runs 15, 19, 31, and 32 that involved p-$HOC_6H_4CH(CO_2CH_3)NH_2$, which is a solid, the ethyl acetate extraction procedure outlined for run 7 of Table II[4] was used to avoid optical fractionation during recovery of amino ester. In runs that involved $CH_3SCH_2CH_2CH(CO_2CH_3)NH_2$ (34 and 38), the CRF values were calculated from ^1H NMR integrations of the $CDCl_3$ phases because of the low rotations of this ester and its salts. The CH_3S diastereomeric singlets differed by about 0.08 ppm and were integrated against each other to determine CRF values. With these and the ^1H NMR determined G/H ratios, the CSF values in the aqueous phase were calculated by difference. The signs of rotations of material isolated from each layer identified the more stable diastereomer in the $CDCl_3$ layer.

Determination of EDC for α-Phenylethylamine Salts. Host (*SS*)-**2** (741 mg, 1.00 mmol) in 5.0 mL of $CDCl_3$ solution (0.20 M) was used to extract at 0 °C 6.0 mL of a D_2O solution that was 0.50 M in α-phenylethylammonium perchlorate (665.2 mg, 3.00 mmol). From the aqueous layer was obtained 105 mg of free amine that provided CSF = 1.18 with a preponderance of *S*-(−) enantiomer. From the $CDCl_3$ layer was obtained 30.4 mg of amine enriched in the *R*-(+) enantiomer to give CRF = 1.61. The EDC value was 1.9 and G/H = 0.78. Optically pure (*R*)-(+)-α-phenylethylamine[6] gave $[\alpha]_{578}^{25}$ 36.9°, $[\alpha]_{546}^{25}$ 43.7°, $[\alpha]_{436}^{25}$ 73.5° (c 2.6, CH_2Cl_2), and our rotations were taken at the same concentrations in the same solvent.

Host (*SS*)-**2** (741 mg, 1.00 mmol) in 5 mL of $CDCl_3$ solution was used to extract at 0 °C 3 mL of a D_2O solution (0.75 M in $LiPF_6$) containing 473 mg (3.00 mmol) of racemic α-phenylethylammonium chloride (1.0 M). From the aqueous layer was obtained 171 mg of amine which gave a CSF of 1.13 (enriched in the *S*=(−) enantiomer). From the $CDCl_3$ was obtained 36 mg of amine which gave a CRF of 1.57 (enriched in the *R*-(+) enantiomer). The values produced an EDC of 1.8 and G/H = 0.65.

References and Notes

(1) This work was supported by the U.S. Public Health Service, Grant GM-12640, from the Department of Health, Education, and Welfare, and by a grant from the National Science Foundation, CHE 72-04616 A04.
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Cyclopeptide Alkaloids. Synthesis of the Ring System and Its Ion Affinity

J. Clark Lagarias, Richard A. Houghten, and Henry Rapoport*

Contribution from the Department of Chemistry and Lawrence Berkeley Laboratory, University of California, Berkeley, California 94720.

Received May 4, 1978

Abstract: Several examples of the 14-membered, para-bridged ring system of the cyclopeptide alkaloids have been synthesized via an active ester cyclization. The yield of monomeric cyclopeptide varied from 1 to 33% and was affected by the amino acid substitution pattern and amide conformation of the linear peptide precursors. Both the synthetic models and a naturally occurring cyclopeptide alkaloid, ceanothine B, bind monovalent (Li^+) and divalent (Ca^{2+}, Mg^{2+}) cations.

Since the confirmation of the structure of pandamine (**1**) in 1966,[1] reports of the isolation and structure elucidation of more than 70 cyclopeptide alkaloids have appeared.[2] This class of natural product, particularly prevalent in plants of the Rhamnaceae family, is structurally well illustrated by frangulanine (**2**). The 14-membered ring, containing two amides and incorporating a variously functionalized benzylic position (**3**), is the feature common to almost all of these natural products.

Although antibiotic, hypotensive, and antitussive properties have been ascribed to the cyclopeptide alkaloids, no definitive pharmacological activity has been demonstrated[2a] for this class

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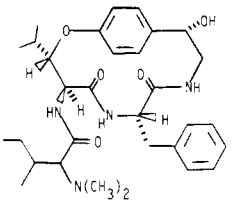
of natural product. On the other hand, peptide alkaloids have shown photophosphorylation inhibitor activity in spinach chloroplasts, an observation which may be related to their function in the plant in which they are produced.[3] The difficulty of isolating sufficient quantities of pure alkaloids, however, and the absence of any method for synthesis have hampered further biological study. In this account we present the synthesis of several examples of this unusual macrocyclic system and provide evidence for specific ion binding of the cyclopeptide alkaloids.

Synthetic Goals

Our initial experimental approach was designed to develop a general synthetic pathway to the saturated cyclopeptides **4**. Successful preparation of these saturated models would then be followed by syntheses directed to compounds with the functionalized benzylic residues found in the natural products (**3a–c**), perhaps via the saturated models as substrates. As a



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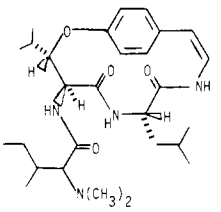

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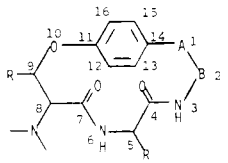
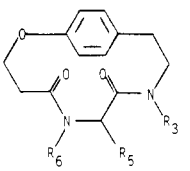




A-B Components of the Cyclopeptide Alkaloids

3a, A-B = CH=CH

b, A-B = $COCH_2$

c, A-B = $CH(CH)CH_2$

4a, R_3=CH_3, R_5+R_6=$(CH_2)_3$

b, R_3=CH_3, R_5=$(CH_3)_2CHCH_2$, R_6=H

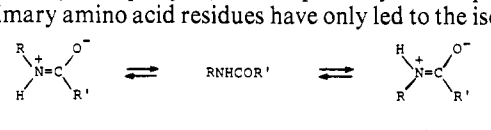
c, R_3=R_6=CH_3, R_5=$(CH_3)_2CHCH_2$

d, R_3=H, R_5+R_6=$(CH_2)_3$

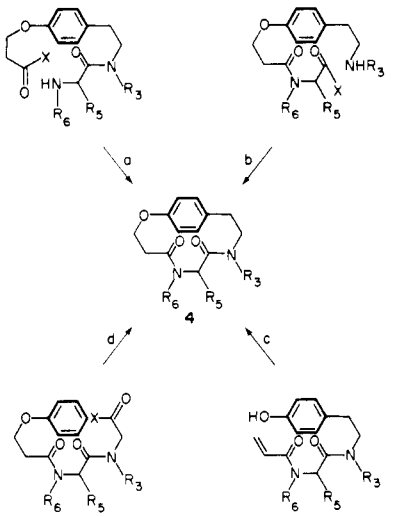
e, R_3=R_6=H, R_5=$(CH_3)_2CHCH_2$

simplification, we chose to omit the nitrogen and alkyl residues on C-8 and C-9, respectively, in our model systems. The exclusion of the β-hydroxy-α-amino acid moiety found in the natural product would eliminate diastereomer separations during the planned synthesis, and the choice of a proline or leucine residue for R_5 was made on the basis of convenience.

The cyclopeptide models **4a–e** were chosen to test the hypothesis that amide substitution should affect the course of peptide cyclization. These models differ in the degree of substitution of the amide nitrogens in both of the component amino acids. It is commonly accepted that amide resonance stabilizes their planar conformation and that trans conformations are preferred to cis (neglecting hydrogen bonds). The strong trans preference for the amide bond disappears when peptides are N-methylated.[4a] That intramolecular reaction between the ends of the linear peptide is influenced by the amide conformation has been demonstrated in the case of cyclotripeptide synthesis. Thus nine-membered ring cyclotripeptide can be prepared only when the amides are tertiary (i.e., cyclotrisarcosyl[4a] and cyclotriprolyl[4b]). Attempts to cyclize tripeptides with primary amino acid residues have only led to the isolation



Scheme I. Cyclization Modes for the Preparation of Cyclopeptide Alkaloids

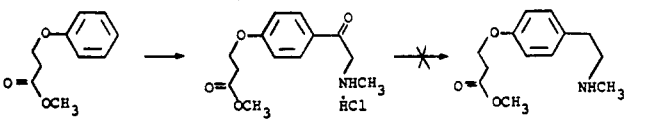


of cyclohexapeptides.[4c] Therefore we chose the five peptide models (**4a–e**) as our first synthetic goals to test the amide conformational factors.

Synthetic Strategy

The key reaction of our synthesis of the cyclopeptide alkaloids involves the cyclization step. Initially, we considered four types of ring closure, as illustrated in Scheme I. Among these, a strong choice was high-dilution cyclization of an active ester (pathway a), a peptide cyclization successful in the preparation of cyclotripeptides[4a,b] and analogues of the antibiotics actinomycin[5a] and gramicidin.[5b] Intramolecular Michael addition (pathway c) was questionable because of the reversibility of this reaction, especially when forming a strained ring. Cyclization via formation of the 3,4-peptide bond (pathway b) was rejected since this cyclization would require activation of a carbonyl adjacent to a chiral carbon and might lead to racemization of this asymmetric center if forcing conditions were necessary. Final formation of the 1,14 bond by Friedel–Crafts acylation was briefly considered (pathway d); however, reaction conditions necessary to effect this cyclization were considered too vigorous to be compatible with the aryl ether and amide functionalities. For these reasons the 6,7-peptide cyclization of pathway a was our first choice.

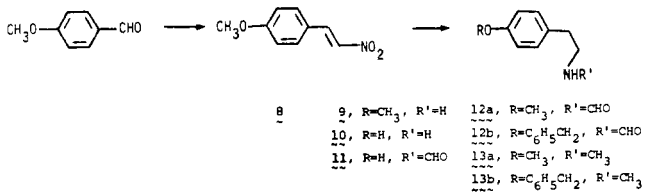
Approach a. Beginning with a 3-phenyloxypropanoate system, our initial synthetic design comprised the early preparation of a para-acylated aryl ether derivative followed by formation of the 3,4-peptide bond and ultimately by the 6,7-peptide cyclization. The instability of the 3-aryloxypropanoate moiety to a variety of Friedel–Crafts conditions prevented the direct conversion of methyl 3-phenyloxypropanoate (**5**) to the amino ketone **7**. Instead, the amino ketone **7** was prepared by



5 7

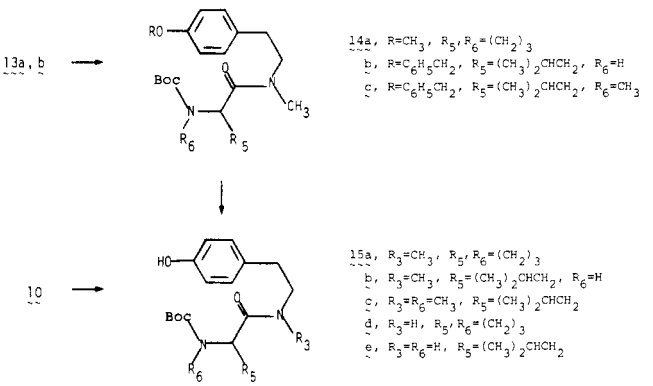
a three-step procedure in 60% overall yield from **5**. Catalytic reduction of this ketone always stopped at the benzyl alcohol stage, thus failing to give the desired phenylethylamine, although similar hydrogenation–hydrogenolysis conversions have been reported.[6] Failure in our case was due to the facile cleavage of the aryl ether in both acid and base. This instability of the 3-aryloxypropanoate moiety necessitated devising a new approach to the cyclopeptide model **4** in which this functionality was introduced near the end of the synthesis.

To overcome these difficulties, we envisioned the preparation of the 9,10 ether linkage after the preparation of the 3,4-peptide bond. The synthesis of the *p*-hydroxyphenylethylamine system, the key intermediate, proceeded via catalytic reduction of the nitrostyrene **8** in acetic acid. The amine **9**, on refluxing in concentrated hydrobromic acid, afforded tyramine hydrobromide **10** in 64% yield. Modifying the trichloroacetaldehyde



(chloral) procedure[7] by adding triethylamine led to formylation of tyramine **10**. Without the addition of triethylamine, the Schiff's base was the exclusive product of this reaction. The resultant phenol **11** was then converted to the benzyl ether **12b** under standard conditions (benzyl chloride in refluxing acetone) and was subsequently reduced with lithium aluminum hydride to the *N*-methylamine **13b**.

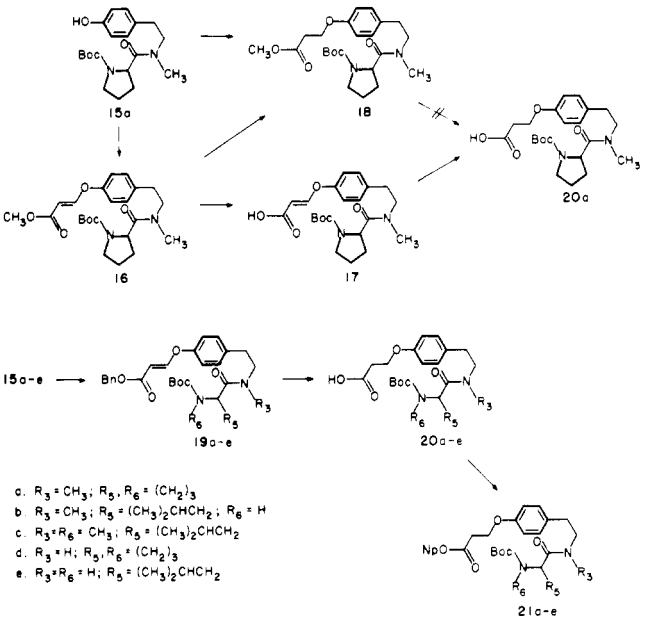
The most effective method for the acylation of amines **10** and **13** with *N*-*tert*-butoxycarbonylamino acids[8] was a mixed anhydride procedure.[9] The yields of peptides **14b** and **14c** from **13** and peptides **15d** and **15e** from **10** were greater than 90%. In the case of the preparation of **14a** via a dicyclohexylcarbodiimide (DCC) coupling, the yield was substantially lower. However, following ether cleavage with BBr_3 and subsequent carbamate formation, the pure phenol **15a** was obtained. The *N*-methyl peptides **14b,c** were converted in high yield to the phenols **15b,c** by hydrogenolysis.



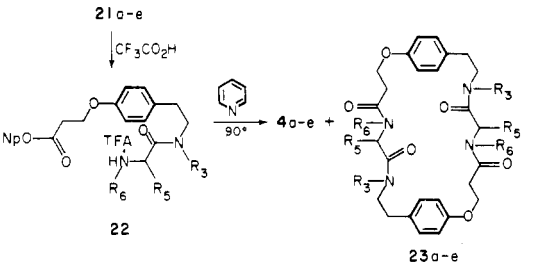
With the phenols (**15a–e**) in hand, we next considered the alternatives for incorporation of the three-carbon propanoate residue (Scheme II). The first attempted alkylation of the phenol **15a** with *tert*-butyl 3-bromopropanoate or 3-bromopropanoic acid in acetone over potassium carbonate led to isolation of the corresponding acrylate and starting phenol. Another method investigated to prepare 3-phenoxypropanoate systems was the Michael addition of phenols to acrylates.[10] Using *p*-cresol as a model, we developed conditions for this conversion which gave ether formation in 80% yield. Employing these conditions, however, we observed no reaction of phenol **15a** with *tert*-butyl acrylate.

A method for the three-carbon homologation of phenols by Michael addition with propiolate derivatives was successful.[11] Thus we prepared methyl (*E*)-3-phenoxypropenoate (**16**) by addition of phenol **15a** to methyl propiolate. If the sodium salt of the phenol was used, prepared with sodium hydride previous to condensation, the *Z* isomer was the predominant product. Catalytic hydrogenation of (*E*)-3-phenoxypropenoate (**16**) afforded the propanoate **18** but this product was extremely sensitive to alkali. Attempted hydrolysis of the methyl ester **18** in alcoholic sodium hydroxide lead to rapid and complete

Scheme II. Incorporation of the Three Carbon Propanoate Residue



Scheme III. Peptide Cyclization



β-elimination. In contrast, hydrolysis of methyl 3-phenoxypropenoate (**16**) with sodium hydroxide was easily accomplished. The resulting acid **17** could be hydrogenated to yield the saturated compound **20a**. The general homologation of phenols **15a–e** to the corresponding 3-phenoxypropanoic acids which were then converted to their *p*-nitrophenyl esters **21a–e** is diagrammed in Scheme III. The reaction of phenols **15a–e** with benzyl propiolate followed by complete reduction afforded the respective 3-phenoxypropanoic acids **20a–e** in high yield. After preparation of *p*-nitrophenyl esters (ONp) **21a–e** with *p*-nitrophenyl trifluoroacetate in pyridine,[12] the conditions for peptide cyclization were next examined.

Cyclization. Removal of the *N*-*tert*-butoxycarbonyl protecting group was accomplished by dissolving the *p*-nitrophenyl esters **21** in anhydrous trifluoroacetic acid at 0–5 °C (Scheme III). After evaporation of the excess trifluoroacetic acid, the residual amine salt **22** was dissolved in *N,N'*-dimethylacetamide and added slowly to pyridine maintained at 90 °C. Studies with **22a** as the model established acceptable conditions for peptide cyclization (see Experimental Section). Owing to the susceptibility of the 3-phenoxypropanoate system to β-eliminate in alkali, the stability of the *p*-nitrophenyl esters **21** and the products **4** to these reaction conditions was also tested; both were stable. Using these conditions, the synthesis of each of the cyclopeptide monomers **4a–e** on a preparative scale was accomplished. The yields are outlined in Table I.

In each case, cyclic monomer **4** was separated from the respective dimer **23** by Sephadex LH-20 chromatography. The spectral data (UV, CD, and ^{13}C NMR) manifest the difference between cyclic monomers and dimers, especially with respect to the aromatic chromophore. In the UV, the absorption maxima of the cyclic dimers **23** are shifted to longer wavelengths with a fivefold increase in extinction coefficient relative to the corresponding cyclic monomer **4**. In the ^{13}C NMR

Table I. Isolated Yields[a] (%) of Cyclopeptides from Cyclization of Esters **21**

ester, **21**	monomer, **4**	dimer, **23**	other neutrals[b]	total
a	24 (33)[c]	22	11	57
b	13	32	35	80
c	~0.4[d]	3	6	~3
d	24	34	17	75
e	9	15	27	51

[a] After mixed bed ion exchange and Sephadex LH-20 chromatography. [b] Uncharacterized neutral products, consisting in part of oligomers. [c] This is a GC yield based on 5α-cholestane as internal standard added to the reaction mixture. [d] Preparative GC followed by high-resolution mass spectrometry established the structure of monomer **4c**.

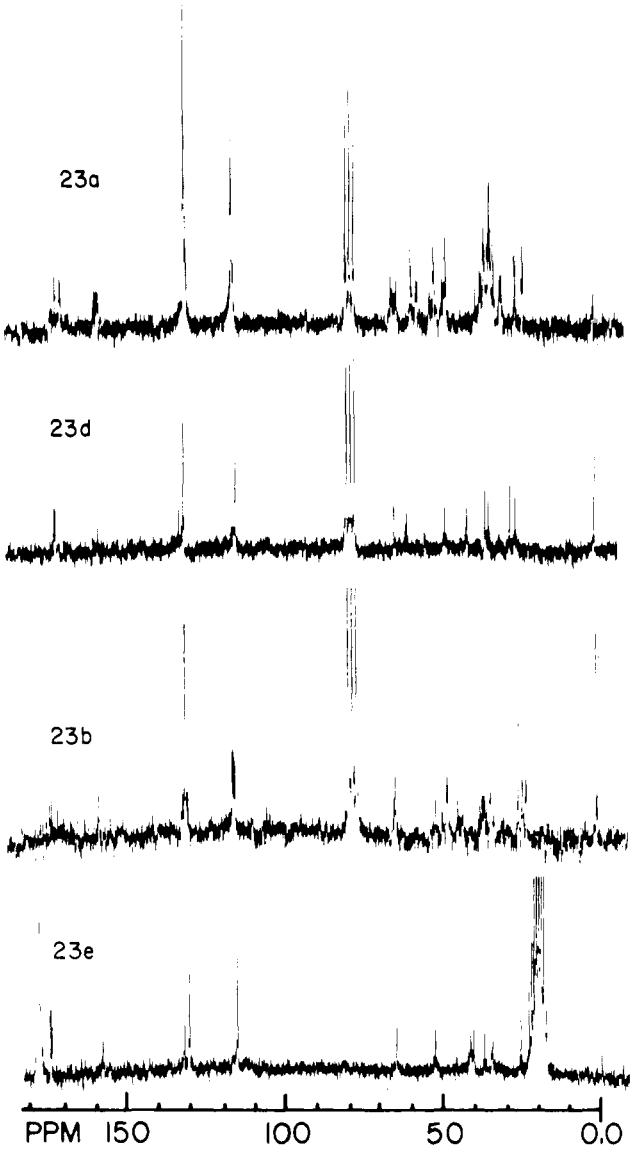


Figure 1. Fourier-transform ^{13}C NMR spectra of cyclic dimers in $CDCl_3$ (~0.05 M): **23a**, *cyclo*-[3-(4-β-*N*-methylaminoethyl)phenyloxypropanoyl-L-prolyl]$_2$; **23b**, *cyclo*-[3-(4-β-*N*-methylaminoethyl)phenyloxypropanoyl-L-leucyl]$_2$; **23d**, *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-prolyl]$_2$; **23e**, *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-leucyl]$_2$.

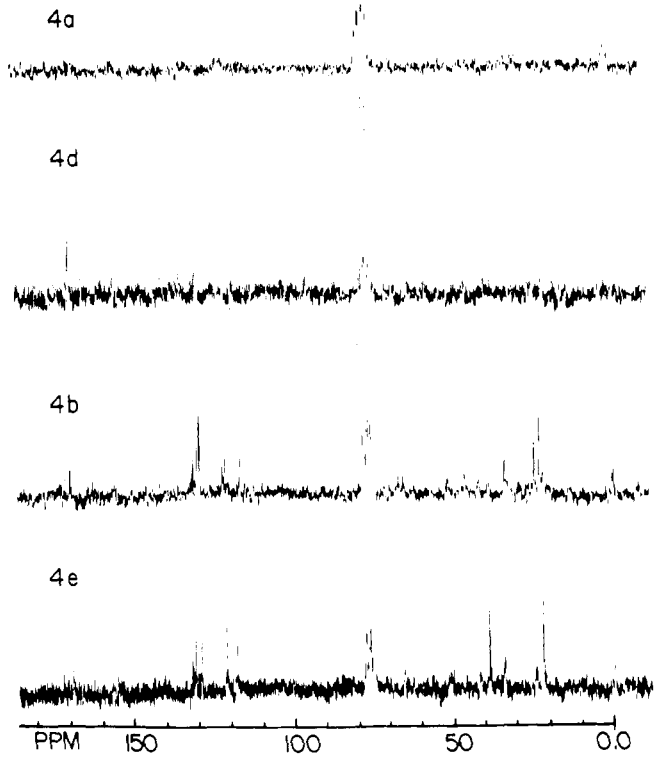


Figure 2. Fourier-transform ^{13}C NMR spectra of cyclic monomers in $CDCl_3$ (~0.05 M): **4a**, *cyclo*-[3-(4-β-*N*-methylaminoethyl)phenyloxypropanoyl-L-prolyl]; **4b**, *cyclo*-[3-(4-β-*N*-methylaminoethyl)phenyloxypropanoyl-L-leucyl]; **4d**, *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-prolyl]; **4e**, *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-leucyl].

spectra of the cyclic dimers **23**, each pair of ortho carbons, C-12, C-16, and C-13, C-15, show a single resonance (Figure 1). On the other hand, each of the four ortho carbons C-12, C-13, C-15, and C-16 of the cyclic monomers **4** has a unique resonance (Figure 2). The CD spectra in the 250–300-nm range show the expected larger interaction of the aromatic chromophore with the asymmetric center in the cyclic monomers **4**. The differential molar extinction coefficient ($\Delta\epsilon$) in this region is greater for the monomers than for the dimers.

Discussion

Contrary to the results of cyclotripeptide synthesis,[4] our data show that the yield of cyclopeptide alkaloid model **4** is independent of the substitution of the amide (N-3, C-4) not involved in the formation of the final peptide bond. Although the linear peptides **21a** and **21d** differ by the substitution pattern of one amide, the yields of the cyclic peptides **4a** and **4d** are similar. The yields of cyclopeptides **4b** and **4e** are also comparable, but less than that of **4a**. Cyclopeptide **4c** was obtained in very low yield. Our results show that the reactivity of the free amino group (N-6) in the linear peptide is the major factor affecting the different yields of cyclic monomers. That the rate of acylation of amines is greatly influenced by their degree of substitution is well illustrated by the preparation of *N-tert*-butoxycarbonylamino acids.[8] The rate of acylation with *tert*-butoxycarbonyl azide decreases in the series proline > leucine ≫ *N*-methylleucine. The yields of cyclopeptides follow this sequence of decreased reactivity of the nucleophile, with proline

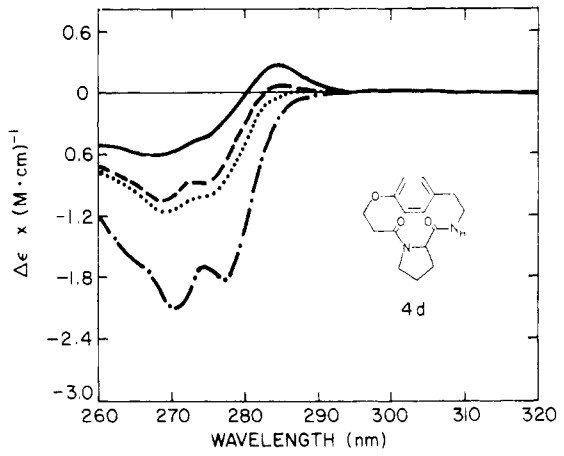


Figure 3. Circular dichroism spectra of *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-prolyl] (**4d**), 9.4×10^{-4} M in CH_3CN, with various added salts: — · —, no salt added; — · —, 9.4×10^{-3} M $NaClO_4$; — · —, 8.6×10^{-3} M KPF_6; ····, 8.3×10^{-3} M $LiClO_4$; —, 9.2×10^{-4} M $Mg(ClO_4)_2$; - - -, 1.5×10^{-3} M $Ca(ClO_4)_2$.

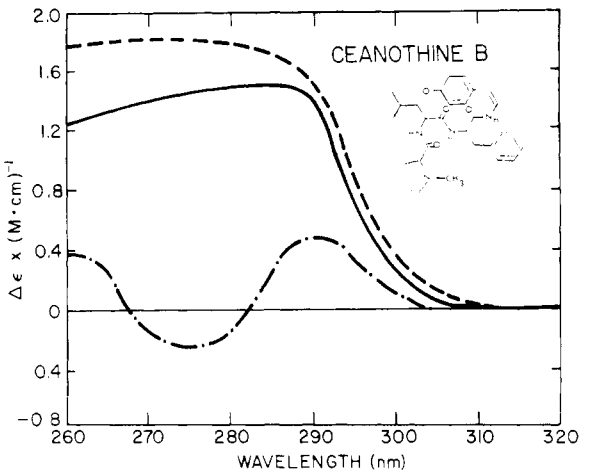


Figure 4. Circular dichroism spectra of ceanothine B, 1.0×10^{-4} M in CH_3CN, with various added salts: — · —, no salt added; — · —, 1.1×10^{-3} M $NaClO_4$; —, 9.2×10^{-4} M $Mg(ClO_4)_2$; - - -, 1.5×10^{-3} M $Ca(ClO_4)_2$.

(**4a** and **4d**) > leucine (**4b** and **4e**) ≫ *N*-methylleucine (**4c**).

The spectral data for the cyclopeptide monomers **4a**, **4b**, **4d**, and **4e** indicate that each macrocycle has a unique geometry. Although the yield of cyclic peptide is independent of the degree of amide substitution in the linear peptide, the configuration of the cyclic product greatly depends on the structure of the amide in the linear peptide. A discussion of configurational isomerization, its effect on the synthesis of this type of ring system, and its effect on ion affinity of these cyclopeptides will be dealt with in a future report, as will the unusual ^1H and ^{13}C NMR spectra of these cyclopeptides.

The ion binding properties of the synthetic peptide, *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-prolyl] (**4d**), and a natural cyclopeptide alkaloid, ceanothine B,[13] were determined by circular dichroism studies in acetonitrile.[14] The cyclopeptide **4d** showed selectivity for Mg^{2+} and Ca^{2+} over Li^+ and did not interact with Na^+ and K^+ (Figure 3).[15] Similarly, ceanothine B interacted with Mg^{2+} and Ca^{2+} and not with Na^+ (Figure 4).[15] Cyclic dimer **23d** as well as the linear free acid **20d** did not exhibit metal complexing when observed by circular dichroism.

It is significant to note that the amino acid components of the cyclopeptide alkaloids contain only hydrophobic residues. Such low molecular weight peptides would probably have a high solubility in the lipid layer of a biomembrane and with respect to their ion affinities, these cyclopeptides could possess ionophoric activity. The high concentration of the cyclopeptide alkaloids in the root bark of plants may indicate an ion solubilizing and transporting function for these alkaloids in plant roots. Also, the reported[3] effect of the cyclopeptide alkaloids on photophosphorylation may be due to alteration of an ion-mediated process.

Our results indicate that this class of natural products possesses an affinity for metal ions. The determination of ion binding constants and ionophoric activity for the cyclopeptide models **4** and various natural peptide alkaloids is presently being further investigated. The implication that the cyclopeptide alkaloids may function as ionophores in the plant that produces them is clearly suggested by the data presented above.[16]

Our synthetic method can be generalized and modified to include the preparation of cyclopeptides of this type in addition to the synthesis of peptide alkaloids. Functionalization of the benzylic position (C-1) of our model system **4**, perhaps via a radical process, will lead to systems found in the natural products **3**. By means of a substituted propiolate the positioning of a variety of groups on C-9 can easily be included into our synthetic scheme, as can substituents on the aromatic nucleus. The 3-phenyloxypropenoate **19** may offer a way to incorporate a nitrogen or other substituents on C-8. Through synthesis of these 14-membered cyclopeptides, **3** or **4**, we can answer the question of what variation in structure affects metal complexing ability, and experiments along these lines are under investigation.

Experimental Section

Methods. All reactions were performed under a nitrogen atmosphere. Solutions were dried over Na_2SO_4 and evaporations were done in vacuo with a Berkeley rotary evaporator. Uncorrected melting points were determined on a Thomas-Hoover capillary melting point apparatus and a Kofler Micro Hot Stage (μmp). Both ^1H NMR and ^{13}C NMR spectra were taken in $CDCl_3$ solution using internal Me_4Si (δ 0) on a Varian HR-220 and a TT-23 (with a Bruker WH-90 console equipped with an NIC-80 computer and a Varian 25.14-MHz magnet), respectively. UV spectra were taken in methanol on a Cary 118 instrument. A Model AEI-MS12 mass spectrometer with INCOS data system was used for determining mass spectra. The gas chromatography was done on (A) a F and M Model 402 high efficiency GC with a 5 ft × 1/8 in. glass column, 3% OV-17 (w/w) on Aeropak 30 (100–120 mesh), and (B) a Hewlett-Packard Model 5730A GC with a 3 ft × 1/8 in. glass column and the same liquid phase and solid support. TLC was done on silica (Eastman sheets no. 6060) and column chromatography used silica gel 60 (EM Reagents) with solvent systems (A) CH_3OH/benzene/acetone, 1/1/1; (B) benzene/acetone, 4/1; and (C) benzene/Et_2O, 1/1. Optical rotations were determined on a Bendix Ericsson ETL-NPL automatic polarimeter, type 43A. CD spectra were taken in acetonitrile on a homemade spectrometer.[17] Ion exchange chromatography was done with a mixed bed resin, BioRex A6501-X8-D, 20–50 mesh, on a column 1.5 × 50 cm. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Materials. The following solvents were routinely distilled prior to use: tetrahydrofuran from sodium benzophenone ketyl, pyridine (predried over NaOH pellets) from BaO, and *N,N'*-dimethylacetamide from 4A molecular sieves. Spectral grade acetonitrile and analytical reagent grade salts were employed for the ion studies.

Methyl 3-(4'-acetylphenyloxy)propanoate (6a), methyl 3-(4'-bromoacetylphenyloxy)propanoate (6b, mp 68–70 °C), **methyl 3-(4'-*N*-methylaminoacetylphenyloxy)propanoate (7), 2-(4'-methoxyphenyl)ethylamine (9,** bp 110–112 °C (2 mm)), and **2-(4'-hydroxyphenyl)ethylamine hydrobromide (10,** tyramine hydrobromide, mp 243–245 °C) are described in detail in the supplementary material.

***N*-Formyl-2-(4'-hydroxyphenyl)ethylamine (11).** While a suspension of tyramine hydrobromide (**10,** 10 g, 46 mmol) and triethylamine (9.3 g, 92 mmol) in 75 mL of $CHCl_3$ was maintained at 0–5 °C, a solution

of trichloroacetaldehyde (6.76 g, 46 mmol) in 25 mL of $CHCl_3$ was added dropwise over a 1-h period. After refluxing for 0.5 h, the resultant solution was evaporated and the residue recrystallized from water yielding 4.6 g (62%) of the *N*-formyl derivative **11**: mp 97–99.5 °C; TLC (B) R_f 0.35 (ninhydrin negative); NMR δ 2.61 (t, 2 H, J = 7 Hz), 3.27 (q, 2 H, J = 7 Hz), 6.61 (d, 2 H, J = 8 Hz), 6.91 (d, 2 H, J = 8 Hz), 7.86 (m, 1 H), 7.92 (s, 1 H), 9.0 (s, 1 H). Anal. ($C_9H_{11}NO_2$) C, H, N.

***N*-Formyl-2-(4′-methoxyphenyl)ethylamine (12a).** To a solution of amine **9** (40 g, 0.27 mol) and triethylamine (29.5 g, 0.29 mol) in 250 mL of $CHCl_3$ cooled to 0–5 °C was added dropwise over a 1-h period a solution of trichloroacetaldehyde (43 g, 0.29 mol) in 250 mL of $CHCl_3$. Following reflux for 45 min, the solution was washed with 5% aqueous acetic acid (3 × 250 mL), distilled water (1 × 200 mL), and saturated $NaHCO_3$ (1 × 200 mL), dried, and evaporated. The residue was distilled to afford 44 g (92%) of the amine **12a**: bp 159–161 °C (2 mm); GC (A) t_R at 175 °C, 9.8 min; NMR δ 2.75 (t, 2 H, J = 7 Hz), 3.43 (q, 2 H, J = 7 Hz), 3.73 (s, 3 H), 6.30 (s, 1 H), 6.85 (d, 2 H, J = 9 Hz), 7.05 (d, 2 H, J = 9 Hz), 8.0 (s, 1 H). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

***N*-Formyl-2-(4′-benzyloxyphenyl)ethylamine (12b).** A mixture of **11** (4.0 g, 24 mmol), finely powdered, anhydrous K_2CO_3 (7.9 g, 57 mmol), and benzyl chloride (3.2 g, 25 mmol) in 100 mL of acetone was refluxed for 23 h. After filtration and evaporation, the residue was partitioned between $CHCl_3$ (150 mL) and distilled water (100 mL). The organic phase was successively washed with saturated $NaHCO_3$ (2 × 75 ml), 1 N HCl (2 × 75 mL), distilled water (75 mL), and saturated NaCl (75 mL). Following drying and evaporating, 4.7 g (76%) of **12b** was isolated: mp 109–110 °C; TLC (B) R_f 0.49; NMR δ 2.73 (t, 2 H, J = 7 Hz), 3.48 (q, 2 H, J = Hz), 4.98 (s, 2 H), 5.70 (m, 1 H), 6.85 (d, 2 H, J = 9 Hz), 7.05 (d, 2 H, J = 9 Hz), 7.33 (m, 5 H), 8.0 (s, 1 H). Anal. ($C_{16}H_{17}NO_2$) C, H, N.

***N*-Methyl-2-(4′-methoxyphenyl)ethylamine (13a).** To a rapidly stirred slurry of lithium aluminum hydride (9.10 g, 0.24 mol) in 180 mL of THF kept at 0–5 °C was added a solution of the *N*-formyl compound **12a** (42.9 g, 0.24 mol) in 100 mL of THF during a 50-min period, then the mixture was refluxed for 30 min. After the reaction mixture was cooled to 5 °C, the excess hydride was destroyed by successive addition of 9 mL of water, 9 mL of 15% NaOH, and 20 mL of water and allowed to stir for an additional 30 min. Filtration, evaporation, and distillation afforded the *N*-methylamine **13a** (30.5 g, 80%): bp 80–83 °C (2 mm); NMR δ 1.20 (s, 1 H), 2.40 (s, 3 H), 2.77 (s, 4 H), 3.62 (s, 3 H), 6.77 (dd, 4 H, J = 8, 18 Hz). Anal. ($C_{10}H_{15}NO$) C, H, N.

***N*-Methyl-2-(4′-benzyloxyphenyl)ethylamine (13b).** In a manner exactly as above, the amide **12b** (4.72 g, 18.5 mmol) was reduced to amine **13b** (4.2 g, 94%): bp 136 °C (0.1 mm); NMR δ 2.39 (s, 3 H), 2.74 (m, 4 H), 4.98 (s, 2 H), 6.84 (d, 2 H, J = 9 Hz), 7.06 (d, 2 H, J = 9 Hz), 7.32 (m, 5 H). Anal. ($C_{16}H_{19}NO$) C, H, N.

***N*-Methyl-*N*,*N*′-*tert*-butoxycarbonyl-L-prolyl-2(4′-methoxyphenyl)ethylamine (14a).** A solution of *N*-*tert*-butoxycarbonyl-L-proline[8] (24.5 g, 0.11 mol), the amine **13a** (18.8 g, 0.11 mol), and DCC (14.3 g, 0.11 mol) in 1.0 L of $CHCl_3$ was stirred for 12 h. Following removal of the urea by filtration, the solution was washed with 5% acetic acid (2 × 500 mL), distilled water (1 × 500 mL), saturated $NaHCO_3$ (2 × 500 mL), and saturated NaCl (500 mL), dried, and evaporated to yield **14a** as an oil (30 g, 73%): NMR[18] δ 1.45 (s, 9 H), 1.85 (m, 4 H), 2.8 (m, 2 H), 3.0 (d, 3 H, NCH_3), 3.50 (m, 4 H), 3.73 (s, 3 H), 4.50 (m, 1 H), 6.82 (d, 2 H, J = 8 Hz), 7.06 (d, 2 H, J = 8 Hz).

***N*-Methyl-*N*,*N*′-*tert*-butoxycarbonyl-L-leucyl-2-(4′-benzyloxyphenyl)ethylamine (14b).** The temperature of a solution of *N*-*tert*-butoxycarbonyl-L-leucine[8] (2.77 g, 12 mmol) and *N*-methylmorpholine (1.16 g, 12 mmol) in 58 mL of THF was maintained at −15 °C while isobutyl chloroformate (1.57 g, 12 mmol) was rapidly added. One minute later, a solution of the *N*-methylamine **13b** (2.77 g, 12 mmol) in 23 mL of THF was dripped in during a 2-min interval while the solution was kept below −15 °C. After removal of the cooling bath, the solution was stirred for an additional 4 h, filtered, and evaporated. The resulting oil was dissolved in 100 mL of ethyl acetate, washed with 1 N HCl (3 × 50 mL), saturated $NaHCO_3$ (3 × 50 mL), and saturated NaCl (50 mL), dried, and evaporated, yielding **14b** as a clear oil (4.80 g, 92%): TLC (B) R_f 0.63; NMR δ 0.92 (dd, 6 H, J = 6, 12 Hz), 1.5 (m 3 H), 2.90 (d, 3 H, NCH_3), 3.55 (m, 2 H), 4.98 (s, 2 H), 5.14 (m, 1 H), 7.30 (m, 5 H). Anal. ($C_{27}H_{38}N_2O_4$) C, H, N.

***N*-Methyl-*N*,*N*′-*tert*-butoxycarbonyl-*N*′-methyl-L-leucyl-2-(4′-benzyloxyphenyl)ethylamine (14c).** The coupling of *N*-*tert*-butoxycarbonyl-*N*-methyl-L-leucine[8,19] [1.86 g, 7.6 mmol, $[\alpha]^{25}_D$ −37.9° (c 0.7, CH_3CO_2H)] and *N*-methylamine **13** (1.83 g, 7.6 mmol) was accomplished with the mixed anhydride procedure utilized for the preparation of **14a**. The peptide **14c** was isolated in 91% yield (3.24 g): TLC (C) R_f 0.56; NMR δ 0.89 (m, 6 H), 2.68 (d, 3 H, NCH_3), 3.43 (m, 2 H), 3.75 (m, 1 H), 4.98 (s, 2 H), 7.30 (m, 5 H). Anal. ($C_{28}H_{40}N_2O_4$) C, H, N.

***N*-Methyl-*N*,*N*′-*tert*-butoxycarbonyl-L-prolyl-2-(4′-hydroxyphenyl)ethylamine (15a).** To a benzene solution (20 mL) of the peptide **14a** (3.09 g, 8.5 mmol) was added boron tribromide (2.56 g, 10.2 mmol). The resultant heterogeneous mixture was refluxed for 6 h. After removal of the solvent, the residue was partitioned between 10% NaOH (50 mL) and CH_2Cl_2 (3 × 20 mL). After adjustment of the pH to 9.7, the aqueous layer was washed with CH_2Cl_2 (3 × 25 mL) and evaporated to a light yellow oil weighing 1.40 g (67%). That the *O*-methyl group was completely removed was established by NMR. This oil (1.40 g, 5.6 mmol) was dissolved in 10 mL of dioxane and 10 mL of water, and the pH was maintained at 8.6 with 1 N NaOH with an autotitrator. After 2 h, the pH was adjusted to 2.0, the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), the CH_2Cl_2 was evaporated, and the residue was chromatographed (B) affording the phenol **15a** (1.37 g, 70%) as an oil: TLC (B) R_f 0.2, ninhydrin negative, $FeCl_3/K_3Fe(CN)_6$ positive; NMR δ 1.43 (s, 9 H), 1.8 (m, 4 H), 2.75 (m, 2 H), 2.9 (d, 3 H, NCH_3), 3.2–3.8 (m, 4 H), 4.58 (m, 1 H), 6.85 (m, 4 H), 8.60 (m, 1 H). Anal. ($C_{19}H_{28}N_2O_4$) C, H, N.

***N*-Methyl-*N*,*N*′-*tert*-butoxycarbonyl-L-leucyl-2-(4′-hydroxyphenyl)ethylamine (15b).** After a slurry of Pd/C (700 mg, 10%) in 25 mL of ethanol was treated with H_2 at 32 psi for 30 min, a solution of benzyl ether **14b** (4.77 g, 11 mmol) in 70 mL of ethanol was introduced and was hydrogenated at 30 psi for 3 h. After filtering, the solution was evaporated to **15b**, an oil weighing 3.82 g (100%): NMR δ 0.91 (dd, 6 H, J = 6, 13 Hz), 1.36–1.61 (m, 3 H), 2.90 (d, 3 H, NCH_3), 3.50 (m, 2 H), 5.18 (m, 1 H). Anal. ($C_{20}H_{32}N_2O_4$) C, H, N.

***N*-Methyl-*N*,*N*′-*tert*-butoxycarbonyl-*N*-methyl-L-leucyl-2-(4′-hydroxyphenyl)ethylamine (15c).** In a manner exactly as above, benzyl ether **14c** (3.10 g, 6.6 mmol) was converted to phenol **15c** (2.5 g, 100%): TLC (C) R_f 0.49, $FeCl_3/K_3Fe(CN)_6$ positive; NMR δ 0.89 (m, 6 H), 1.43–1.45 (m, 1 H), 1.57 (t, 2 H, J = 8 Hz), 2.70 (m, 5 H), 2.90 (m, 3 H), 3.47 (m, 2 H), 3.76 (m, 2 H), 5.00 (m, 1 H). Anal. ($C_{21}H_{34}N_2O_4$) C, H, N.

***N*,*N*′-*tert*-Butoxycarbonyl-L-prolyl-2-(4′-hydroxyphenyl)ethylamine (15d).** As a solution of *N*-*tert*-butoxycarbonyl-L-proline[8] (7.53 g, 35 mmol) and *N*-methylmorpholine (3.54 g, 35 mmol) in 175 mL of THF was cooled to −15 °C, isobutyl chloroformate (4.78 g, 35 mmol) was rapidly added. After 1 min, a solution of tyramine hydrobromide (**10**, 7.63 g, 35 mmol) and triethylamine (3.54 g, 35 mmol) in 70 mL of DMF was added in a 2-min period while the temperature was maintained at −12 °C. Four hours after the removal of the cooling bath, the reaction mixture was filtered and evaporated. The residue was dissolved in ethyl acetate (200 mL), washed with 1 N HCl (3 × 100 mL), saturated $NaHCO_3$ (3 × 100 mL), and saturated NaCl (1 × 100 mL), dried, and evaporated, giving 11.3 g (97%) of pure **15d**: NMR δ 1.7–2.2 (m, 4 H), 3.3–3.5 (m, 4 H), 4.18 (m, 1 H), 7.86 (m, 1 H). Anal. ($C_{18}H_{26}N_2O_4$) C, H, N.

***N*,*N*′-*tert*-Butoxycarbonyl-L-leucyl-2-(4′-hydroxyphenyl)ethylamine (15e).** The coupling of *N*-*tert*-butoxycarbonyl-L-leucine[8] (2.31 g, 10 mmol) and tyramine hydrobromide (**10**, 2.18 g, 10 mmol) was accomplished exactly as above to give pure **15e** as an oil (3.2 g, 89%): NMR δ 0.87 (d, 6 H, J = 6 Hz), 1.5 (m, 3 H), 2.3 (d, 2 H, J = 7 Hz). Anal. ($C_{19}H_{30}N_2O_4$) C, H, N.

Benzyl (*E*)-3-(4′-β-*N*,*N*′-*tert*-Butoxycarbonyl-L-prolyl-*N*-methylaminoethyl)phenyloxypropenoate (19a). A mixture of phenol **15a** (1.18 g, 3.4 mmol), *N*-methylmorpholine (0.34 g, 3.4 mmol), and benzyl propiolate (1.09 g, 6.8 mmol) in 20 mL of THF was allowed to stand for 3 h at room temperature. After evaporation of the solvent, the residue was dissolved in 60 mL of ethyl acetate, washed with 0.2 N HCl (3 × 20 mL), water (20 mL), and saturated NaCl (20 mL), dried, and evaporated. The resultant oil was chromatographed (SiO_2, 100 g, Et_2O) to give 1.55 g (90%) of **19a**: NMR δ 1.47 (s, 9 H), 1.6–2.1 (m, 4 H), 2.6–3.1 (m, 2 H), 2.95 (s, 3 H), 3.2–3.7 (m, 4 H), 4.55 (m, 1 H), 5.18 (s, 2 H), 5.58 (d, 1 H, J = 12 Hz), 6.91 (d, 2 H, J = 8 Hz), 7.11 (d, 2 H, J = 8 Hz), 7.38 (s, 5 H), 7.83 (d, 1 H, J = 12 Hz). Anal. ($C_{29}H_{36}N_2O_6$) C, H, N.

The following propenoates were prepared in a similar manner.

Benzyl (*E*)-3-(4′-β-*N*,*N*′-*tert*-butoxycarbonyl-L-leucyl-*N*-methylaminoethyl)phenyloxypropenoate (19b) was obtained in 94% yield after chromatography (200 g of Sephadex LH-20, MeOH): NMR

δ 0.92 (dd, 6 H, J = 12 Hz), 1.1-1.8 (m, 3 H), 2.91 (d, 3 H), 3.50 (m, 2 H), 5.12 (m, 3 H), 5.5 (d, 1 H, J = 12 Hz), 7.28 (s, 5 H), 7.73 (d, 1 H, J = 12 Hz). Anal. ($C_{30}H_{40}N_2O_6$) C, H, N.

Benzyl (*E*)-3-(4′-β-*N,N′-tert*-butoxycarbonyl-*N′*-methyl-L-leucyl-*N*-methylaminoethyl)phenyloxypropenoate (19c) was isolated in 70% yield: TLC R_f 0.27 (Et_2O/hexane, 1/1); NMR δ 0.88 (m, 6 H), 1.51 (m, 3 H), 2.66 (s, 3 H, NCH_3), 2.91 (d, 3 H, NCH_3), 3.5-3.7 (m, 2 H), 5.10 (s, 2 H), 5.50 (d, 1 H, J = 12 Hz), 7.27 (s, 5 H), 7.70 (d, 1 H, J = 12 Hz). Anal. ($C_{31}H_{42}N_2O_6$) C, H, N.

Benzyl (*E*)-3-(4′-β-*N,N′-tert*-butoxycarbonyl-L-propylaminoethyl)phenyloxypropenoate (19d) was isolated in 99% yield: mp 99-101 °C; TLC (Et_2O) R_f 0.14; NMR δ 1.82 (m, 4 H), 3.30 (m, 2 H), 3.45 (q, 2 H, J = 7 Hz), 5.11 (s, 2 H), 5.50 (d, 1 H, J = 12 Hz), 7.28 (m, 5 H), 7.73 (d, 1 H, J = 12 Hz); $[\alpha]^{25}_D$ −52.6° (c 0.73, CH_3OH). Anal. ($C_{28}H_{34}N_2O_6$) C, H, N.

Benzyl (*E*)-3-(4′-β-*N,N′-tert*-butoxycarbonyl-L-leucylaminoethyl)phenyloxypropenoate (19e) was obtained in 92% yield as an oil: NMR δ 0.9 (d, 6 H, J = 6 Hz), 3.0 (t, 2 H, J = 7 Hz), 3.5 (q, 2 H, J = 7 Hz), 5.0 (m, 2 H), 5.6 (d, 1 H, J = 12 Hz), 7.3 (s, 5 H), 7.80 (d, 1 H, J = 12 Hz).

3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-prolyl-*N*-methylaminoethyl)phenyloxypropanoic Acid (20a). A mixture of **19a** (1.51 g, 3.0 mmol) and Pd/C (10%, 100 mg) in 15 mL of ethanol was hydrogenated at 37 psi for 1.5 h. After filtration and evaporation, **20a** (1.25 g, 100%) was obtained: NMR δ 1.43 (s, 9 H), 1.6-2.2 (m, 4 H), 2.6-3.1 (m, 2 H), 2.75 (t, 2 H, J = 7 Hz), 2.95 (s, 3 H), 3.3-3.9 (m, 4 H), 4.2 (t, 2 H, J = 7 Hz), 4.55 (m, 1 H), 6.78 (d, 2 H, J = 8 Hz), 7.1 (d, 2 H, J = 8 Hz), 9.5 (s, 1 H). Anal. ($C_{22}H_{32}N_2O_6$) C, H, N.

With the above procedure the following propanoic acids were isolated in >90% yield. **3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-leucyl-*N*-methylaminoethyl)phenyloxypropanoic Acid (20b):** NMR δ 0.90 (dd, 6 H, J = 12 Hz), 1.1-1.8 (m, 3 H), 2.77 (m, 4 H), 2.89 (d, 3 H), 4.15 (t, 2 H, J = 5 Hz). Anal. ($C_{23}H_{36}N_2O_6$) C, H, N.

3-(4′-β-*N,N′-tert*-Butoxycarbonyl-*N′*-methyl-L-leucyl-*N*-methylaminoethyl)phenyloxypropanoic Acid (20c): UV λ_{max} (ε) 277 nm (1585), 283 (1331); NMR δ 0.89 (m, 6 H), 1.53 (m, 3 H), 2.68 (m, 3 H), 2.77 (m, 4 H), 2.91 (m, 3 H), 4.16 (t, 2 H, J = 5 Hz). Anal. ($C_{24}H_{38}N_2O_6$) C, H, N.

3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-prolylaminoethyl)phenyloxypropanoic Acid (20d): NMR δ 1.82 (m, 4 H), 2.77 (t, 2 H, J = 7 Hz), 4.16 (t, 2 H, J = 7 Hz); $[\alpha]^{25}_D$ −56.4° (c 0.87, CH_3OH). Anal. ($C_{21}H_{30}N_2O_6$) C, H, N.

3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-leucylaminoethyl)phenyloxypropanoic Acid (20e): NMR δ 0.88 (d, 6 H, J = 5 Hz), 1.57 (m, 3 H), 2.74 (t, 2 H, J = 7 Hz), 4.17 (t, 2 H, J = 7 Hz); $[\alpha]^{25}_D$ −26.7° (c 1.1, CH_3OH). Anal. ($C_{22}H_{34}N_2O_6$) C, H, N.

***p*-Nitrophenyl 3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-prolyl-*N*-methylaminoethyl)phenyloxypropanoate (21a).** A mixture of the acid **20a** (4.94 g, 12 mmol) and *p*-nitrophenyl trifluoroacetate[12] (2.64 g, 12 mmol) in 25 mL of pyridine was stirred for 4.5 h. After evaporation, the residue was dissolved in 200 mL of ethyl acetate and washed with 0.3 N HCl (3 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), H_2O (100 mL), and saturated NaCl (100 mL). Chromatography (C) of the residue after evaporation afforded the *p*-nitrophenyl ester **21a** (4.48 g, 70%): NMR δ 1.42 (s, 9 H), 1.6-2.3 (m, 4 H), 2.6-3.2 (m, 7 H), 3.3-3.8 (m, 4 H), 4.32 (t, 2 H, J = 7 Hz), 4.55 (m, 1 H), 6.83 (d, 2 H, J = 8 Hz), 7.13 (d, 2 H, J = 8 Hz), 7.28 (d, 2 H, J = 10 Hz), 8.18 (d, 2 H, J = 10 Hz). Anal. ($C_{28}H_{35}N_3O_8$) C, H, N.

Utilizing this procedure, *p*-nitrophenyl esters **21b-e** were obtained in 70-90% yield.

***p*-Nitrophenyl 3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-leucyl-*N*-methylaminoethyl)phenyloxypropanoate (21b):** TLC (Et_2O) R_f 0.32; NMR δ 0.94 (dd, 6 H, J = 6, 12 Hz), 1.62 (m, 3 H), 2.90 (d, 3 H), 7.24 (d, 2 H, J = 10 Hz), 8.20 (d, 2 H, J = 10 Hz). Anal. ($C_{29}H_{39}N_3O_8$) C, H, N.

***p*-Nitrophenyl 3-(4′-β-*N,N′-tert*-Butoxycarbonyl-*N′*-methyl-L-leucyl-*N*-methylaminoethyl)phenyloxypropanoate (21c).** The oil **21c** was isolated pure in 83% yield after chromatography (200 g of Sephadex LH 20; MeOH): TLC (Et_2O) R_f 0.42; NMR δ 0.89 (m, 6 H), 1.52 (m, 3 H), 2.67 (s, 3 H), 2.89 (d, 3 H, NCH_3), 7.20 (d, 2 H, J = 10 Hz), 8.18 (d, 2 H, J = 10 Hz). Anal. ($C_{30}H_{41}N_3O_8$) C, H, N.

***p*-Nitrophenyl 3-(4′-β-*N,N′-tert*-butoxycarbonyl-L-prolylaminoethyl)phenyloxypropanoate (21d)** was obtained in 87% yield after chromatography (200 g of Sephadex LH 20; MeOH): NMR δ 1.64-2.18 (m, 4 H), 2.7 (m, 2 H), 7.24 (d, 2 H, J = 10 Hz), 8.19 (d, 2 H, J = 10 Hz). Anal. ($C_{27}H_{33}N_3O_8$) C, H, N.

***p*-Nitrophenyl 3-(4′-β-*N,N′-tert*-Butoxycarbonyl-L-leucylaminoethyl)phenyloxypropanoate (21e):** mp 116-118 °C; TLC (benzene/ethyl acetate) R_f 0.5; NMR δ 0.89 (d, 6 H, J = 6 Hz), 1.61 (m, 3 H), 7.22 (d, 2 H, J = 10 Hz), 8.17 (d, 2 H, J = 10 Hz). Anal. ($C_{28}H_{37}N_3O_8$) C, H, N.

***cyclo*-[3-(4-β-*N*-Methylaminoethyl)phenyloxypropanoyl-L-prolyl] (4a) and *cyclo*-[3-(4-β-*N*-Methylaminoethyl)phenyloxypropanoyl-L-prolyl]$_2$ (23a).** The *p*-nitrophenyl ester **21a** (719 mg, 1.33 mmol) was dissolved in 10 mL of anhydrous trifluoroacetic acid at 0-5 °C. After 1 h the solvent was evaporated to give an oil (1.20 g) which was dissolved in 600 mL of *N,N′*-dimethylacetamide. The resultant solution was added over a 50-h period with a metering pump to 600 mL of mechanically stirred pyridine maintained at 90 °C. The solution was stirred and heated for an additional 10 h and evaporated, and the residue was dissolved in methanol and filtered through a mixed bed ion exchange resin. The first 100 mL of eluant was collected and evaporated to give a solid residue (223 mg, 56%) from which, after chromatography (200 g of Sephadex LH 20; MeOH), three fractions were isolated. Eluted first was 45 mg (11%) of cyclic oligomers which was not further purified. Next was the cyclic dimer **23a**, 88 mg (22%): μmp 251 °C dec; UV λ_{max} (ε) 226 nm (21 400), 277 (2910), 284 (2510); GC (A) t_R at 275 °C, 5.6 min; MS *m/e* (rel intensity) 604 (0.8), 303 (3), 302 (12), 70 (100); $[\alpha]^{25}_D$ +27.5° (c 0.2, CH_3OH); CD ΔE_{max} (λ_{max}, nm) +2.67 (228), −0.11 (268), −0.14 (275.6), −0.14 (283), +0.07 (287); ^{1}H NMR δ 1.36-2.36 (m, 8 H), 2.5-3.1 (m, 12 H), 3.0 (s, 6 H), 3.14-4.27 (m, 10 H), 6.81 (d, 4 H, J = 8 Hz), 7.01 (d, 4 H, J = 8 Hz). Anal. ($C_{34}H_{44}N_4O_6$) C (calcd 67.5, found 66.4), H, N.

Eluted last was **4a** (97 mg, 24%) obtained after sublimation at 100 °C (0.01 mm): μmp 188 °C; UV λ_{max} (ε) 270 nm (508), 276 (492); GC (A) t_R at 275 °C, 3.2 min; MS *m/e* $C_{17}H_{22}N_2O_3$ requires 302.1630, found 302.1636; $[\alpha]^{25}_D$ +6.3° (c 0.2, CH_3OH); CD ΔE_{max} (λ_{max}, nm) +8.72 (222), −1.74 (241), −1.01 (270), −0.97 (275.5); NMR δ 1.74 (m, 2 H), 1.89 (t, 2 H, J = 10 Hz), 2.22 (dd, 1 H, J = 5, 12 Hz), 2.57 (m, 1 H), 2.72 (m, 2 H), 2.95 (s, 3 H), 3.02 (m, 1 H), 3.42 (m, 1 H), 3.53 (m, 1 H), 4.24 (dd, 1 H, J = 5, 12 Hz), 4.80 (t, 1 H, J = 11, Hz), 4.86 (m, 2 H), 6.77 (dd, 1 H, J = 2, 8 Hz), 7.09 (m, 3 H). Anal. ($C_{17}H_{22}N_2O_3$) C, H, N.

***cyclo*-[3-(4-β-*N*-Methylaminoethyl)phenyloxypropanoyl-L-leucyl] (4b) and *cyclo*-[3-(4-β-*N*-Methylaminoethyl)phenyloxypropanoyl-L-leucyl]$_2$ (23b).** Dissolution of *p*-nitrophenyl ester **21b** (665 mg, 1.2 mmol) in 10 mL of anhydrous trifluoroacetic acid at 0-5 °C as above afforded an oil (1.03 g) after evaporation which was dissolved in dimethylacetamide (620 mL) and added dropwise over a 50-h period to stirred pyridine (600 mL) at 90 °C. Stirring was continued for an additional 10 h. The pyridine was evaporated and the residue was dissolved in methanol and filtered through a mixed bed ion exchange resin to give an oil (332 mg). The crude product was purified by column chromatography on Sephadex LH-20 in methanol, isolating four fractions: (1) 95 mg (25%) of cyclic oligomers; (2) dimer **23b** (123 mg, 32%), crystallized from ethanol [μmp 234 °C; UV λ_{max} (ε) 224 nm (25 245), 276 (3234), 283 (2691); MS *m/e* (rel intensity) 636 (6), 318 (8), 43 (100); CD $\Delta\epsilon_{max}$ (λ_{max}, nm) −8.70 (218), −3.77 (234), −0.48 (278), −0.45 (283); NMR δ 0.83 (m, 6 H), 0.93 (q, 6 H, J = 5 Hz), 1.30 (m, 4 H), 1.47 (m, 2 H), 2.55 (dq, 4 H, J = 7 Hz), 2.78 (m, 4 H), 2.97 (d, 4 H, J = 4 Hz), 3.00 (m, 6 H),4.09 (m, 4 H), 4.25 (m, 2 H), 6.20 (m, 2 H), 6.80 (m, 4 H), 7.02 (m, 4 H). Anal. ($C_{36}H_{52}N_4O_6$) C, H, N]; (3) a mixture of compounds (36 mg, 10%) not further characterized; (4) cyclic monomer **4b** (49 mg, 13%) [μmp 119 °C after sublimation at 100 °C (0.01 mm); UV λ_{max} (ε) 226 nm (sh, 6052), 275 (690); MS *m/e* (rel intensity) 319 (4), 318 (17), 44 (100); GC (B) t_R at 230 °C, 8.6 min; CD $\Delta\epsilon_{max}$ (λ_{max}, nm) +9.84 (230), +0.23 (275), + 0.46 (284); NMR δ 0.84 (dd, 4 H, J = 4, 8 Hz), 0.92 (d, 2 H, J = 6.5 Hz), 1.16 (m, 1 H), 1.34 (m, 2 H), 2.25 (dd, 1 H, J = 3, 8 Hz), 2.40 (dd, 0.5 H, J = 5, 15 Hz), 2.63 (m, 0.5 H), 2.80 (m, 2.5 H), 2.94 (s, 1.5 H), 3.04 (s, 1.5 H), 3.40 (m, 0.5 H), 3.61 (m, 0.5 H), 3.95 (q, 0.5 H, J = 6.5 Hz), 4.21 (dd, 1 H, J = 4, 11 Hz), 4.53 (td, 0.5 H, J = 5, 9 Hz), 4.71 (td, 0.5 H, J = 5.6, 12 Hz), 4.92 (m, 1 H), 5.62 (m, 1 H), 6.68 (dd, 0.5 H, J = 2.3, 8 Hz), 6.89 (m, 2.5 H), 7.17 (m, 1 H). Anal. ($C_{18}H_{26}N_2O_3$) C, H, N].

***cyclo*-[3-(4-β-*N*-Methylaminoethyl)phenyloxypropanoyl-*N*-methyl-L-leucyl] (4c).** The conversion of *p*-nitrophenyl ester **21c** (665 mg, 1.2 mmol) to the cyclopeptides was accomplished as described above. After ion exchange a colorless oil (21 mg) was isolated. Sephadex chromatography (200 g LH-20, MeOH) afforded two fractions: (1) 12 mg (3.5%) which was not further characterized; (2) 8 mg, 2.2%, contained three major components by GC (B) t_R at 230 °C 18 (20%), 21 (14%), 32 min (56.4%). These products were isolated by preparative

GC (3% OV-17, 6 ft × ¼ in.). The 18-min component was the desired cyclic peptide **4c** (1.6 mg, 0.4%): MS *m/e* $C_{19}H_{28}N_2O_3$ requires 332.2100, found 332.2091. The other components were not further characterized.

***cyclo*-[3-(4-β-Aminoethyl)phenyloxypropanoyl-L-prolyl] (4d) and *cyclo*-[3-(4-β-Aminoethyl)phenyloxypropanoyl-L-prolyl]$_2$ (23d).** The conversion of *p*-nitrophenyl ester **21d** (591 mg, 1.1 mmol) to the cyclopeptides was accomplished exactly as previously described. After ion exchange a light yellow oil (244 mg) was isolated. Sephadex chromatography (200 g of LH-20, MeOH) gave three fractions. Fraction 1 was 54 mg (17%), cyclic oligomers. Fraction 2 was cyclic dimer **23d** (110 mg, 34%): μmp 221 °C on crystallization from ethanol; UV λ_{max} (ε) 224 nm (25 180), 276.5 (3393), 283.5 (2855); MS *m/e* 576 (0.8), 368 (2), 70 (100), CD $\Delta\epsilon_{max}$ (λ_{max}, nm) −6.9 (224), −0.29 (282), −0.45 (274.5); NMR δ 1.73 (m, 2 H), 2.05 (m, 4 H), 2.52 (m, 4 H), 2.68 (m, 4 H), 2.86 (m, 2 H), 3.32 (m, 6 H), 3.73 (m, 4 H), 3.97 (m, 2 H), 4.58 (d, 2 H, *J* = 7.5 Hz), 6.81 (d, 4 H, *J* = 8 Hz), 7.01 (d, 4 H, *J* = 8 Hz), 7.13 (m, 2 H). Anal. ($C_{32}H_{40}N_4O_6$) C, H, N. Fraction 3 was cyclic monomer **4d** (75 mg, 24%), an oil: UV λ_{max} (ε) 223 nm (6198 sh), 271 (568), 276 (513); GC (B) t_R at 230 °C, 12 min; MS *m/e* 289 (4), 288 (19), 70 (100); CD $\Delta\epsilon_{max}$ (λ_{max}, nm) −12.43 (232), −2.17 (271), −1.91 (277); NMR δ 1.55 (m, 1 H), 1.95 (m, 1 H), 2.12 (m, 2 H), 2.19 (dd, 1 H, *J* = 6, 13 Hz), 2.34 (m, 1 H), 2.75 (dd, 1 H, *J* = 10, 17 Hz), 2.89 (m, 2 H), 3.31 (dd, 1 H, *J* = 10, 17 Hz), 3.49 (t, 1 H, *J* = 8 Hz), 3.80 (m, 1 H), 4.28 (m, 2 H), 4.62 (t, 1 H, *J* = 10 Hz), 6.36 (m, 1 H), 6.85 (s, 2 H), 7.17 (dd, 2 H, *J* = 8, 15 Hz). Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

***cyclo*-[3-(4-β-Aminoethyl)phenyloxypropanoyl-L-leucyl] (4e) and *cyclo*-[3-(4-β-Aminoethyl)phenoxypropanoyl-L-leucyl]$_2$ (22e).** With the same cyclization procedure, *p*-nitrophenyl ester **21e** (588 mg, 1.1 mmol) was converted to the cyclopeptides. The resulting brown solid was triturated in methanol and filtered. The insoluble portion (40.2 mg, 12%) was later identified as cyclic dimer **22e**. The methanol filtrate was eluted through a mixed bed ion exchange resin and evaporated to give a solid residue (137 mg). Following Sephadex chromatography (200 g, LH-20, MeOH) three fractions were isolated. Fraction 1 was 48 mg (15%) of cyclic oligomers, not further characterized. Fraction 2 was cyclic dimer **22e** (51 mg, 15%): crystallized from ethanol, μmp 287 °C; UV λ_{max} (ε) 224.5 nm (19 511), 276 (2680), 283 (2267); MS *m/e* 609 (1), 608 (3), 304 (69), 86 (100); CD $\Delta\epsilon_{max}$ (λ_{max}, nm) −5.65 (229), +0.69 (277), +0.74 (284); NMR δ 0.93 (m, 12 H), 1.66 (m, 6 H), 2.65 (m, 8 H), 3.26 (m, 2 H, *J* = 7 Hz), 3.45 (m, 2 H, *J* = 7 Hz), 4.13 (m, 2 H), 4.23 (m, 2 H), 4.63 (m, 2 H), 6.71 (d, 2 H, *J* = 8 Hz), 6.97 (d, 2 H, *J* = 8 Hz). Anal. ($C_{34}H_{48}N_4O_6$) C, H, N. Fraction 3 was the cyclopeptide **4e** (31 mg, 9%): μmp 199 °C; UV λ_{max} (ε) 226 nm (6127), 276 (734); GC (B) t_R at 230 °C, 9.5 min; MS *m/e* 305 (6), 304 (29), 86 (100); CD $\Delta\epsilon_{max}$ (λ_{max}, nm) +8.12 (226), +0.39 (275), +0.50 (284); NMR δ 0.84 (d, 6 H, *J* = 6 Hz), 1.33 (m, 3 H), 2.31 (m, 2 H), 2.52 (m, 1 H), 3.06 (m, 2 H), 4.00 (dd, 1 H, *J* = 7, 14 Hz), 4.21 (dd, 2 H, *J* = 6, 13 Hz), 4.95 (t, 1 H, *J* = 10.5 Hz), 5.22 (d, 1 H, *J* = 11 Hz), 5.53 (d, 1 H, *J* = 9 Hz), 6.87 (dd, 1 H, *J* = 2.4, 7 Hz), 6.94 (dd, 1 H, *J* = 2.4, 7 Hz), 7.03 (dd, 1 H, *J* = 2.4, 7 Hz), 7.09 (dd, 1 H, *J* = 2.4, 7 Hz). Anal. ($C_{17}H_{24}N_2O_3$) C, H, N.

Acknowledgment. The assistance of Sanford Melzer, an undergraduate research student, is gratefully acknowledged. This research was supported in part by the Division of Biomedical and Environmental Research of the U.S. Department of Energy.

Supplementary Material Available: Experimental details for the preparation of methyl 3-(4′-acetylphenyloxy)propanoate (**6a**), methyl 3-(4′-bromoacetylphenyloxy)propanoate (**6b**), methyl 3-(4′-*N*-methylaminoacetylphenyloxy)propanoate (**7**), 2-(4′-methoxyphenyl)ethylamine (**9**), 2-(4′-hydroxyphenyl)ethylamine hydrobromide (**10**, tyramine hydrobromide); Figure S1, circular dichroism spectra in the far UV of *cyclo*-[3-(4-β-aminoethyl)phenyloxypropanoyl-L-prolyl] (**4d**); and Figure S2, circular dichroism spectra of ceanothine B, in the presence of various added salt (6 pages). Ordering information is given on any current masthead page.

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