Submitted to Journal of the American Chemical Society

UC-4
LBL-7587
Preprint

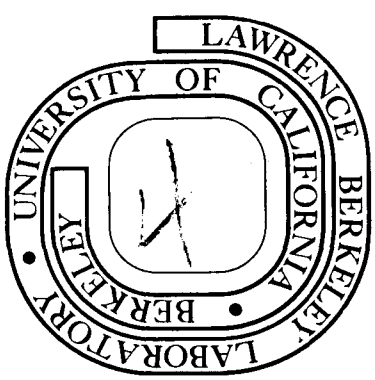
c.1

CYCLOPEPTIDE ALKALOIDS. SYNTHESIS OF THE RING SYSTEM AND ITS ION AFFINITY

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

May 1978

Prepared for the U. S. Department of Energy under Contract W-7405-ENG-48



DISCLAIMER

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, CA 94720.

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^{++}, Mg^{++}) cations.

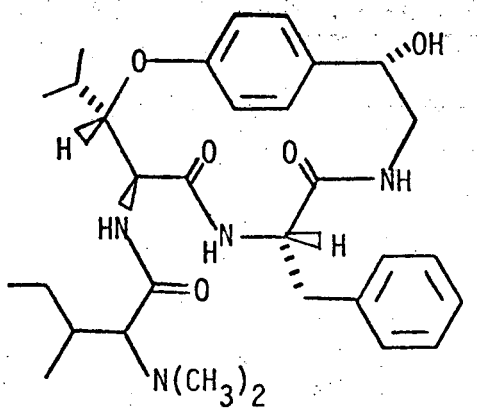
Since the confirmation of the structure of pandamine (1) in 1966,[1] reports of the isolation and structure elucidation of more than seventy cyclopeptide alkaloids have appeared.[2] This class of natural product, particularly prevalent in plants of the Rhamnaceae family, is structurally well illustrated by frangulanine (2). The fourteen 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 of natural product. Recently, 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, has 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.

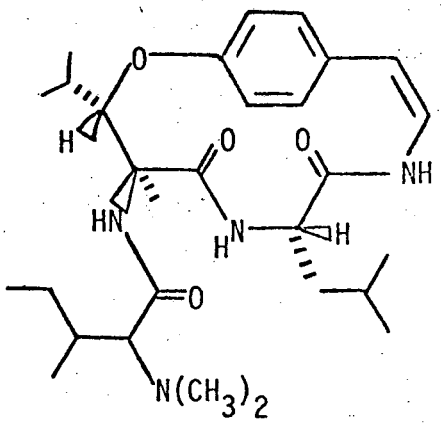
Synthetic goals

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

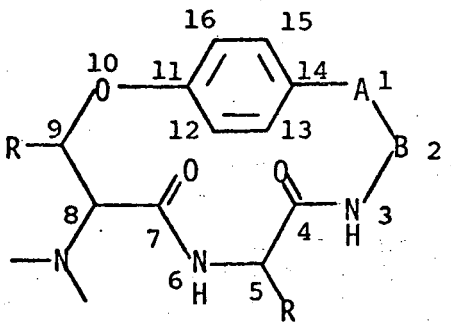
benzylic residues found in the natural products (3a,b,c), perhaps via the saturated models as substrates. As a simplication, we

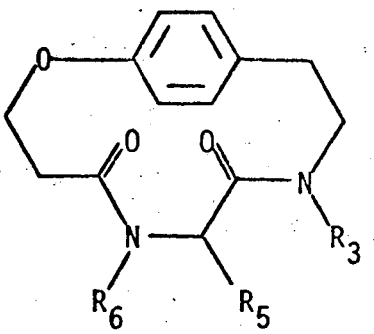


1



2





A-B Components of the Cyclopeptide Alkaloids

3a, A-B = CH=CH

b, A-B = $COCH_2$

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

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

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

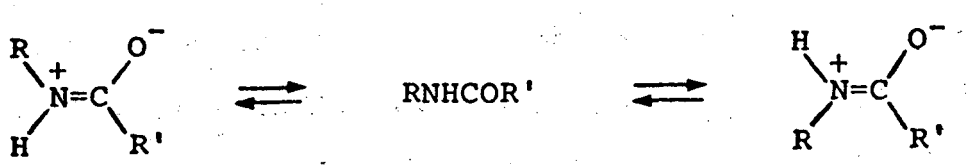
c, $R_3=R_6=CH_3$, $R_5=(CH_3)_2CHCH_2$

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

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

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



trans cis

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. However, in the first step of this sequence we encountered difficulty in para-acylating aryl ether 5 with α-substituted aliphatic acid derivatives (Scheme II). With trifluoromethane-

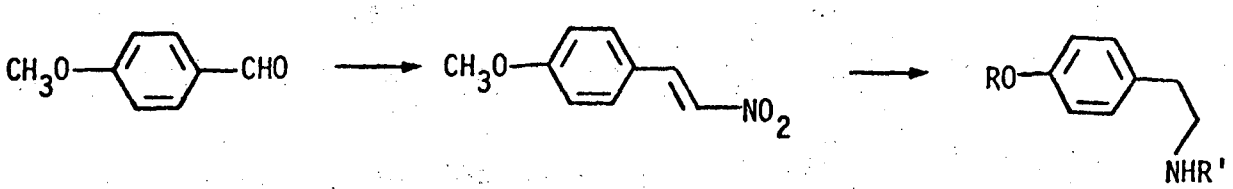
sulfonic-carboxylic anhydride intermediates generated by reaction of carboxylic acid chlorides and silver trifluoromethanesulfonate, exclusive para-acylation of oxygenated aromatics has been reported[6] in some cases. In extending this method, we acylated methyl 3-phenyloxypropanoate (5) with either acetyl chloride or isobutyryl chloride under the reported conditions and obtained greater than 85% yields of isomerically pure para ketones 7a and 7b. However, acylation of 5 with N-trifluoroacetyl-N-methylaminoacetyl chloride (6b) afforded none of the amino ketone. Due to the instability of both aryl ether and ester moieties of 5, no Friedel-Craft procedure successfully effected the desired acylation.

On the other hand, acylation with an α-halogenated acetic acid derivative followed by nucleophilic displacement of the halogen atom with an amine did afford the amino ketone 7d. Unfortunately, the acylation of methyl 3-phenyloxypropanoate (5) via the mixed anhydride formed from trifluoromethane sulfonic acid and chloroacetyl chloride gave a mixture of ortho and para isomers in a 3/2 ratio. A similar isomer mixture was obtained when 5 was acylated with methoxyacetyl chloride by the mixed anhydride procedure. Clearly this acylation method[6] is not a general one for exclusive para acylation of oxygenated aromatic compounds. The amino ketone 7d, alternatively, could be prepared in three steps. The previously synthesized ketone 7a was α-brominated with bromine in ether at 0°C. Displacement of the bromide (7c) by methylamine in methanol then afforded a 79% conversion to the amino ketone 7d.

Catalytic reduction of the ketone 7d always stopped at the

benzyl alcohol stage and failed to give the desired phenylethylamine, although similar catalytic hydrogenation-hydrogenolysis conversions have been reported.[7] Failure in our case was due to decomposition of the 3-aryloxypropanoic acid moiety in both acid and base. This instability of the 3-aryloxypropanoic acid group 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[8] 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.

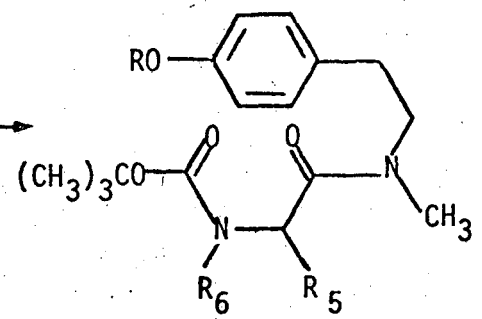


8

9, R=CH_3, R'=H
10, R=H, R'=H
11, R=H, R'=CHO

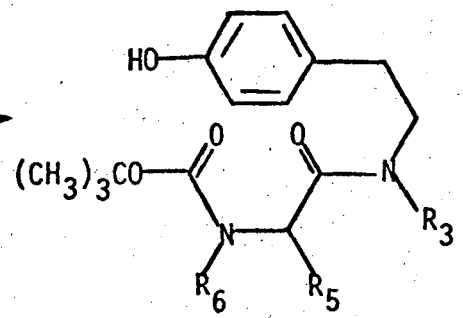
12a, R=CH_3, R'=CHO
12b, R=$C_6H_5CH_2$, R'=CHO
13a, R=CH_3, R'=CH_3
13b, R=$C_6H_5CH_2$, R'=CH_3

The most effective method for the acylation of amines 10 and 13 with N-tert-butoxycarbonylamino acids[9] was a mixed anhydride procedure.[10] 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.



13a, b →

14a, $R=CH_3$, $R_5=R_6=(CH_2)_3$
b, $R=C_6H_5CH_2$, $R_5=(CH_3)_2CHCH_2$, $R_6=H$
c, $R=C_6H_5CH_2$, $R_5=(CH_3)_2CHCH_2$, $R_6=CH_3$



10 →

15a, $R_3=CH_3$, $R_5=R_6=(CH_2)_3$
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, $R_3=R_6=H$, $R_5=(CH_3)_2CHCH_2$

With the phenols (15a-e) in hand, we next considered the alternatives for incorporation of the three carbon propanoate residue (Scheme III). The first attempted alkylation of the phenol (15a) with tert-butyl 3-bromopropanoate or 3-bromopropanoic acid

in acetone over potassium carbonate lead to isolation of the corresponding acrylate and starting phenol. Another method investigated to prepare 3-phenoxypropanate systems was the Michael addition of fn 11 phenols to acrylates.[11] 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 fn 12 Michael addition with propiolate derivatives was successful.[12] 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 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 fn 13 (ONp) 21a-e with p-nitrophenyl trifluoroacetate in pyridine,[13] 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 IV). By NMR, it was clear that this process did not require the presence of a carbonium ion scavenger commonly used during acid catalyzed decomposition of tert-butyl carbamates.[4,5] After evaporation of the excess trifluoroacetic acid, the residual amine salt 21 was dissolved in N,N'-dimethylacetamide and added slowly to pyridine maintained at 90°C. Studies with 21a 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 chromophor. 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 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-15 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 chromophor with the asymmetric center in the cyclic monomers 4. The differential molar extinction coefficient ($\Delta\varepsilon$) 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.[9] The rate of acylation with tert-butoxycarbonylazide decreases in the series proline > leucine >> N-methylleucine. The yields of cyclopeptides follow this sequence of decreased reactivity of the nucleophile, with proline (4a and 4d) > leucine (4b and 4e) >> N-methylleucine (4c).

The spectral data for the cyclopeptide monomers 4a-d indicates 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.

The ion binding properties of the synthetic peptide, cyclo-[3(4-β-aminoethyl)phenyloxypropanoyl-L-prolyl] (4d) and a natural peptide alkaloid, ceanothine B,[14] were determined by circular dichroism studies in acetonitrile.[15] The cyclopeptide 4d showed selectivity for Mg^{++} and Ca^{++} over Li^{+} and did not interact with Na^{+} and K^{+} (Figures 3 and 4). Similarly, ceanothine B interacted with Mg^{++} and Ca^{++} and not with Na^{+} (Figures 5 and 6). Cyclic dimers 23a-e 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] fn 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 MP Apparatus and a Kofler Micro Hot Stage (μmp). Both ^{1}H-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 Brucker 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' x 1/8" glass column, 3% OV-17 (w/w) on Aeropak 30 (100-120 mesh), and (B) a Hewlett Packard Model 5730A GC with a 3' x 1/8" glass column and the same liquid phase and solid support. TLC was done on silica (Eastman sheets #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 home made spectrometer.[17] Ion exchange chromatography was done with a mixed bead resin, BioRex A6501-X8-D, 20-50 mesh, on a column 1.5 x 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 (7a).-- To a suspension of silver trifluoromethanesulfonate (65.1 g, 0.25 mol) in 750 ml of CH_2Cl_2 was added a solution of acetyl chloride (19.9 g, 0.25 mol) in 75 mL of CH_2Cl_2. After the immediate precipitation of silver chloride, a solution of methyl 3-phenyloxypropanoate (5) (45.6 g, 0.25 mol)[11a] in 75 ml of CH_2Cl_2 was introduced. One half hour later the addition of the same amounts of silver salt and acetyl chloride was repeated. After 1 hour, the mixture was filtered, the filtrate was successively washed with water (3 x 300 ml), sat. $NaHCO_3$ (3 x 300 ml), and sat. NaCl (1 x 300 ml), dried, and evaporated. After distillation (Kugelrohr), 53 g (93%) of 7a was obtained: GC (A) R_t at 200°C, 4.3 min; NMR δ 2.55 (s, 3H), 2.83 (t, 2H, J=7Hz), 3.73 (s, 3H), 4.30 (t, 2H, J=7Hz), 6.94 (d, 2H, J=10Hz), 7.76 (d, 2H, J=10 Hz). Anal. ($C_{12}H_{14}O_4$): C, H.

Methyl 3-(4'-Bromoacetylphenyloxy)propanoate (7c). -- Bromine (1.78 g, 11 mmol) was rapidly added to a stirred slurry of ketone 7a (2.48 g, 11 mmol) in 25 ml of Et_2O at 0-5°C. The reaction mixture became homogeneous when allowed to warm to room temperature. After 1 hour, the solution was washed with distilled water (2 x 15 ml), sat $NaHCO_3$ (15 ml), and sat. NaCl (15 ml), dried, and evaporated to afford 2.65 g (80%) of the bromo ketone 7c: mp 68-70°C; GC (A) R_t at 230°C, 2.9 min; NMR δ 2.76 (t, 2H, J=7Hz), 3.67

(s, 3H), 4.27 (t, 2H, J=7Hz), 4.32 (s, 2H), 6.94 (d, 2H, J=10Hz), 7.76 (d, 2H, J=10Hz). Anal. ($C_{12}H_{13}O_4Br$): C, H.

Methyl 3-(4'-N-Methylaminoacetylphenyloxy)propanoate (7d).-- A methanol solution of bromoketone 7c (1.81 g, 6 mmol, in 50 ml) was cooled to -5°C at which time a 25% (w/w) solution of methylamine in methanol (3.60 g, 30 mmol) was introduced. After 4 hours, 1N HCl (32 ml) was added, and on evaporation and SiO_2 chromatography (A), 1.36 g (79%) of the hygroscopic amine hydrochloride 7d was obtained: NMR (DMSO-d_6) δ 2.73 (s, 2H), 2.90 (t, 2H, J=7 Hz), 3.23 (s, 3H), 3.70 (s, 3H), 4.38 (t, 2H, J=7Hz), 4.75 (s, 2H), 7.20 (d, 2H, J=10Hz), 7.92 (d, 2H, J=10Hz).

2-(4'-Methoxyphenyl)ethylamine (9).-- A solution of p-methoxy-
fn 18 ω-nitrostyrene (8, 50 g, 0.28 mol)[18] in 1.7 L of glacial acetic acid was added over an 8 hour period into 1.7 L of glacial acetic acid containing Pd/C (10%, 17.7 g) and conc. H_2SO_4 (46 g, 0.47 mol). Hydrogen was bubbled through the solution with a gas dispersion tube during the addition and for 1 hour afterwards. On subsequent isolation and distillation, the amine 9 (3.3 g, 78%) was isolated: bp 110-112°C (2 mm); NMR δ 1.10 (s, 2H), 2.86 (m, 4H), 3.70 (s, 3H), 6.83 (dd, 4H, J=8,18Hz).

2-(4'-Hydroxyphenyl)ethylamine Hydrobromide (Tyramine Hydrobromide) (10).-- A mixture of the amino methyl ether 9 (10.9 g, 72 mmol) in 300 ml 48% HBr was refluxed for 30 min. After the solution was cooled in an ice bath, the crystalline percipitate was collected and recrystallized from 95% ethanol to yield 10 g (64%) of 10: mp 243-245°C; NMR δ 3.20 (q, 4H, J=6Hz), 4.80 (s, phenolic), 7.0 (dd, 4H, J=8,18Hz).

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 $CHCl_3$ was maintained at 0-5°C, a solution of trichloroacetaldehyde (6.76 g, 46 mmol) in 25 ml $CHCl_3$ was added dropwise over a 1 hour period. After refluxing for 1/2 hour, 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 neg.); NMR δ 2.61 (t, 2H, J=7Hz), 3.27 (q, 2H, J=7Hz), 6.61 (d, 2H, J=8Hz), 6.91 (d, 2H, J=8Hz), 7.86 (m, 1H), 7.92 (s, 1H), 9.0 (s, 1H). 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 $CHCl_3$ cooled to 0-5°C was added dropwise over a 1 hour period, a solution of trichloroacetaldehyde (43 g, 0.29 mol) in 250 ml $CHCl_3$. Following reflux for 45 minutes, the solution was washed with 5% aq. acetic acid (3 x 250 ml), distilled water (1 x 200 ml), sat. $NaHCO_3$ (1 x 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) R_t at 175°C, 9.8 min; NMR δ 2.75 (t, 2H, J=7Hz), 3.43 (q, 2H, J=7Hz), 3.73 (s, 3H), 6.30 (s, 1H), 6.85 (d, 2H, J=9Hz), 7.05 (d, 2H, J=9Hz), 8.0 (s, 1H). 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 acetone was refluxed for 23 hours. 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 sat. $NaHCO_3$ (2 x 75 ml), 1N HCl (2 x 75 ml), distilled water (75 ml) and sat. 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, 2H, J=7Hz), 3.48 (q, 2H, J=7Hz), 4.98 (s, 2H), 5.70 (m, 1H), 6.85 (d, 2H, J=9Hz), 7.05 (d, 2H, J=9Hz), 7.33 (m, 5H), 8.0 (s, 1H). 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 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 THF during a 50 minute period, then the mixture was refluxed for 30 minutes. After cooling the reaction mixture to 5°C, the excess hydride was destroyed by successive addition of 9 ml water, 9 ml 15% NaOH, and 20 ml water and allowed to stir for an additional 30 minutes. Filtration, evaporation, and distillation afforded the N-methylamine 13a (30.5 g, 80%): bp 80-83°C (2 mm); NMR δ 1.20 (s, 1H), 2.40 (s, 3H), 2.77 (s, 4H), 3.62 (s, 3H), 6.77 (dd, 4H, J=8,18Hz). 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, 3H), 2.74 (m, 4H), 4.98 (s, 2H), 6.84 (d, 2H, J=9Hz), 7.06 (d, 2H, J=9Hz), 7.32 (m, 5H). 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[9] (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 hours. Following removal of the urea by filtration, the solution was washed with 5% acetic acid (2 x 500 ml), distilled water (1 x 500 ml), sat. $NaHCO_3$ (2 x 500 ml), and sat. NaCl (500 ml), dried and evaporated to yield 14a as an oil (30 g, 73%): NMR δ 1.45 (s, 9H), 1.85 (m, 4H), 2.8 (m, 2H), 3.0 (d, 3H, N-CH_3), 3.50 (m, 4H), 3.73 (s, 3H), 4.50 (m, 1H), 6.82 (d, 2H, J=8Hz), 7.05 (d, 2H, J=8Hz).

N-Methyl-N,N'-tert-butoxycarbonyl-L-leucyl-2-(4'-benzyl-oxyphenyl)ethylamine (14b). The temperature of a solution of N-tert-butoxycarbonyl-L-leucine[9] (2.77 g, 12 mmol) and N-methyl morpholine (1.16 g, 12 mmol) in 58 ml THF was maintained at -15°C while isobutylchloroformate (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 THF was dripped in during a 2 minute interval while the solution was kept below -15°C. After removal of the cooling bath, the solution was stirred for 4 additional hours, filtered, and evaporated. The resulting oil was dissolved in 100 ml ethyl acetate, washed with 1N HCl (3 x 50 ml), sat. $NaHCO_3$ (3 x 50 ml) and sat. 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, 6H, J=6,12Hz), 1.5 (m, 3H), 1.48 (s, 9H), 2.77 (m, 2H), 2.90 (d, 3H, N-CH_3), 3.55 (m, 2H), 4.55 (m, 1H), 4.98 (s, 2H), 5.14 (m, 1H), 6.82 (dd, 2H, J=3,8Hz), 7.05 (d, 2H, J=8Hz), 7.30 (m, 5H). 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[9,19] [1.86 g, 7.6 mmol, $[\alpha]_D^{25}$ -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, 6H), 1.45 (m, 12H), 2.68 (d, 3H, N-CH_3 carbamate), 2.73 (t, 2H, J=8Hz), 2.89 (m, 3H, N-CH_3), 3.43 (m, 2H), 3.75 (m, 1H), 4.98 (s, 2H), 6.83 (d, 2H, J=8Hz), 7.06 (d, 2H, J=8Hz), 7.30 (m, 5H). 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 hr. After removal of the solvent, the residue was partitioned between 10% NaOH (50 ml) and CH_2Cl_2 (3 x 20 ml). After adjustment of the pH to 9.7, the aqueous layer was washed with CH_2Cl_2 (3 x 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 1N NaOH with a autotitrator. After 2 hr, the pH was adjusted to 2.0, the reaction mixture was extracted with CH_2Cl_2 (3 x 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, 9H), 1.8 (m, 4H), 2.75 (m, 2H), 2.9 (d, 3H, NCH_3), 3.2-3.8 (m, 4H), 4.58 (m, 1H), 6.85 (m, 4H), 8.60 (m, 1H). 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 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 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, 6H, J=6,13 Hz), 1.36-1.61 (m, 3H), 1.41 (s, 9H), 2.78 (m, 2H), 2.90 (d, 3H, NCH_3), 3.50 (m, 2H), 4.52 (m, 1H), 5.18 (m, 1H), 6.68 (d, 2H, J=8Hz), 6.93 (d, 2H, J=8Hz). 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, 6H), 1.44 (s, 9H), 1.43-1.45 (m, 1H), 1.57 (t, 2H, J=8 Hz), 2.70 (m, 5H), 2.90 (m, 3H), 3.47 (m, 2H), 3.76 (m, 2H), 4.59 and 4.80 (m, 1H), 5.00 (m, 1H), 6.70 (m, 2H), 6.95 (m, 2H). 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[9] (7.53 g, 35 mmol) and N-methylmorpholine (3.54 g, 35 mmol) in 175 ml THF was cooled to -15°C, isobutylchloroformate (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 1N HCl (3 x 100 ml), sat. $NaHCO_3$ (3 x 100 ml), and sat. NaCl (1 x 100 ml), dried, and evaporated, giving 11.3 g (97%) of pure 15d: NMR δ 1.40 (s, 9H), 1.70-2.20 (m, 4H), 2.66 (m, 2H), 3.25-3.48 (m, 4H), 4.18 (m, 1H), 6.72 (d, 2H, J=8Hz), 6.91 (d, 2H, J=8Hz), 7.86 (m, 1H). 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[9] (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, 6H, J=6Hz), 1.43 (s, 9H), 1.5 (m, 3H), 2.3 (d, 2H, J=7Hz), 2.6 (t, 2H, J=7Hz), 4.54 (m, 1H), 6.8 (dd, 4H, J=8,18Hz). Anal. ($C_{19}H_{30}N_2O_4$): C, H, N.

Benzyl E-3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolyl-N-methyl-aminoethyl)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 hr at room temperature. After evaporation of the solvent, the residue was dissolved in 60 ml of ethyl acetate, washed with 0.2N HCl (3 x 20 ml), water (20 ml), sat. 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, 9H), 1.6-2.1 (m, 4H), 2.63-3.1 (m, 2H), 2.95 (s, 3H), 3.2-3.75 (m, 4H), 4.55 (m, 1H), 5.18 (s, 2H), 5.58 (d, 1H, J=12Hz), 6.91

(d, 2H, J=8Hz), 7.11 (d, 2H, J=8Hz), 7.38 (s, 5H), 7.83 (d, 1H, J=12Hz). Anal. ($C_{29}H_{36}N_2O_6$): C, H, N.

Benzyl E-3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucyl-N-methyl aminoethyl)phenyloxypropenoate (19b).-- In a manner analogous to above, phenol 15b (3.90 g, 11 mmol) was converted to 19b (5.3 g, 94%) after chromatography (200 g Sephadex LH-20, methanol): NMR δ 0.92 (dd, 6H, J=6,12Hz), 1.1-1.8 (m, 3H), 1.43 (s, 9H), 2.80 (m, 2H), 2.91 (d, 3H), 3.50 (m, 2H), 4.52 (m, 1H), 5.12 (m, 3H), 5.5 (d, 1H, J=12Hz), 6.90 (d, 2H, J=8Hz), 7.13 (d, 2H, J=8Hz), 7.28 (s, 5H), 7.73 (d, 1H, J=12Hz). 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).-- The acrylate 19c (2.32 g, 70%) was prepared from phenol 15c (2.34 g, 6.2 mmol) as above: TLC R_f 0.27 (Et_2O/hexane, 1/1); NMR δ 0.88 (m, 6H), 1.43 (m, 9H), 1.51 (m, 3H), 2.66 (s, 3H, NCH_3), 2.77 (t, 2H, J=7Hz), 2.91 (d, 3H, NCH_3), 3.47-3.68 (m, 3H), 4.98 (m, 1H), 5.10 (s, 2H), 5.50 (d, 1H, J=12Hz), 6.89 (d, 2H, J=8Hz), 7.11 (d, 2H, J=8Hz), 7.27 (s, 5H), 7.70 (d, 1H, J=12Hz). Anal. ($C_{31}H_{42}N_2O_6$): C, H, N.

Benzyl E-3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolylamino-ethyl)phenyloxypropenoate (19d).-- The conversion of phenol 15d (5.37 g, 16 mmol) to 19d (7.9 g, 99%) was accomplished as above: mp 99-101°C; TLC (Et_2O) R_f 0.14; NMR δ 1.41 (s, 9H), 1.82 (m, 4H), 2.82 (m, 2H), 3.30 (m, 2H), 3.45 (q, 2H, J=7Hz), 4.17 (m, 1H), 5.11 (s, 2H), 5.50 (d, 1H, J=12Hz), 6.91 (d, 2H, J=8Hz), 7.11 (d, 2H, J=8Hz), 7.28 (m, 5H), 7.73 (d, 1H, J=12Hz); $[\alpha]_D^{25}$ -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).-- As above, phenol 15e (2.9 g, 8.3 mmol) was converted to 19e (3.98 g, 92%), an oil: NMR δ 0.9 (d, 6H, J=6Hz), 1.4 (s, 9H), 3.0 (t, 2H, J=7Hz), 3.5 (q, 2H, J=7Hz), 5.0 (m, 2H), 5.6 (d, 1H, J=12Hz), 6.89 (d, 2H, J=8Hz), 7.11 (d, 2H, J=8Hz), 7.3 (s, 5H), 7.80 (d, 1H, J=12Hz).

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 ethanol was hydrogenated at 37 psi for 1.5 hr. After filtration and evaporation, 20a (1.25 g, 100%) was obtained: NMR δ 1.43 (s, 9H), 1.6-2.2 (m, 4H), 2.6-3.1 (m, 4H), 2.75 (t, 2H, J=7Hz), 2.95 (s, 3H), 3.28-3.9 (m, 4H), 4.2 (t, 2H, J=7Hz), 4.55 (m, 1H), 6.78 (d, 2H, J=8Hz), 7.1 (d, 2H, J=8Hz), 9.5 (s, 1H). Anal. ($C_{22}H_{32}N_2O_6$): C, H, N.

3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucyl-N-methylaminoethyl) phenyloxypropanoic Acid (20b).-- With the above procedure, the hydrogenation of 19b (1.29 g, 2.5 mmol) afforded the acid 20b (1.03 g, 100%): NMR δ 0.90 (dd, 6H, 6,12Hz, 1.1-1.8 (m, 3H), 1.41 (s, 9H), 2.77 (m, 2H), 2.89 (d, 3H, NCH_3), 3.5 (m, 2H), 4.15 (t, 2H, J=5Hz), 4.55 (m, 1H), 5.48 (m, 1H), 6.73 (d, 2H, J=8Hz), 7.00 (d, 2H, J=8Hz). Anal. ($C_{23}H_{36}N_2O_6$): C, H, N.

3-(4'-β-N,N'-tert-Butoxycarbonyl-N'-methyl-L-leucyl-N-methyl aminoethyl)phenyloxypropanoic Acid (20c).-- The conversion of 19c (2.02 g, 3.8 mmol) to the acid 20c (1.65 g, 97%) was accomplished under the above conditions: UV λ_{max} (ε) 277 nm (1585), 283(1331); NMR δ 0.89 (m, 6H), 1.44 (s, 9H), 1.53 (m, 3H), 2.68 (m, 3H), 2.77 (m, 2H), 2.91 (m, 3H), 3.43 (m, 2H), 4.16 (t, 2H, J=5Hz),

4.98 (m, 1H), 6.76 (d, 2H, J=8Hz), 7.05 (m, 2H). Anal. ($C_{24}H_{38}N_2O_6$): C, H, N.

3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolylaminoethyl)phenyloxy propanoic Acid (20d).-- In a manner exactly as above 19d (5.04 g, 10 mmol) was converted to 20d (4.13 g, 100%): NMR δ 1.43 (s, 9H), 1.82 (m, 4H), 2.70 (m, 2H), 2.77 (t, 2H, J=7Hz), 3.39 (m, 4H), 4.16 (t, 2H, J=7Hz), 4.22 (m, 1H), 6.73 (d, 2H, J=8Hz), 6.98 (d, 2H, J=8Hz), 8.90 (m, 1H); $[\alpha]_D^{25}$ -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)phenyloxy propanoic Acid (20e).-- The conversion of 19e (3.80 g, 7.4 mmol) to 20e (2.88 g, 92%) was accomplished as above: NMR δ 0.88 (d, 6H, J=5Hz), 1.41 (s, 9H), 1.57 (m, 3H), 2.68 (t, 2H, J=7Hz), 2.74 (t, 2H, J=7Hz), 3.41 (q, 2H, J=7Hz), 3.68 and 4.02 (m, 1H), 4.17 (t, 2H, J=7Hz), 5.14 (m, 1H), 6.36 (m, 1H), 6.75 (d, 2H, J=8Hz), 6.98 (d, 2H, J=8Hz). $[\alpha]_D^{25}$ -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[13] (2.64 g, 12 mmol) in 25 ml pyridine was stirred for 4.5 hr. After evaporation, the residue was dissolved in 200 ml of ethyl acetate and washed with 0.3N HCl (3 x 100 ml), sat. $NaHCO_3$ (2 x 100 ml), H_2O (100 ml), and sat. 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, 9H), 1.6-2.3 (m, 4H), 2.6-3.2 (m, 7H), 3.3-3.8 (m, 4H), 4.32 (t, 2H, J=7Hz), 4.55 (m, 1H), 6.83

(d, 2H, J=8Hz), 7.13 (d, 2H, J=8Hz), 7.28 (d, 2H, J=10Hz), 8.18 (d, 2H, J=10Hz). Anal. ($C_{28}H_{35}N_3O_8$): C, H, N.

p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucyl N-methylaminoethyl)phenyloxypropanoate (21b).-- In a manner exactly as above 20b (954 mg, 2.2 mmol) was converted to p-nitrophenyl ester 21b (1.04 g, 82%): TLC (Et_2O) R_f 0.32; NMR δ 0.94 (dd, 6H, J=6,12Hz), 1.43 (s, 9H), 1.62 (m, 3H), 2.77 (t, 2H, J=7Hz), 2.90 (d, 3H, N-CH_3), 3.06 (t, 2H, J=7Hz), 3.55 (m, 2H), 4.31 (t, 2H, J=7Hz), 4.57 (m, 1H), 5.18 (m, 1H), 6.80 (d, 2H, J=8Hz), 7.03 (d, 2H, J=8Hz), 7.24 (d, 2H, J=10Hz), 8.20 (d, 2H, J=10Hz). 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 preparation of the ester 21c from the acid 20c (813 mg, 1.8 mmol) was accomplished as in the earlier examples. The oil was isolated pure (859 mg, 83%) after chromatography (200 g Sephadex LH 20; methanol): TLC (Et_2O) R_f 0.42; NMR δ 0.89 (m, 6H), 1.44 (s, 9H), 1.52 (m, 3H), 2.67 (s, 3H), 2.73 (t, 2H, J=7Hz), 2.89 (d, 3H, N-CH_3), 3.03 (t, 2H, J=7Hz), 3.43 (m, 1H), 3.68 (m, 1H0, 4.28 (t, 2H, J=7Hz), 4.73 and 4.95 (m, 1H), 6.77 (d, 2H, J=8Hz), 7.06 (d, 2H, J=8Hz), 7.20 (d, 2H, J=10Hz), 8.18 (d, 2H, J=10Hz). Anal. ($C_{30}H_{41}N_3O_8$): C, H, N.

p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolylamino ethyl)phenyloxypropanoate (21d). In an analogous manner, 20d (3.45 g, 8.5 mmol) was converted to p-nitrophenyl ester 21d; 3.88 g, 87%, after chromatography (200 g Sephadex LH 20; methanol): NMR δ 1.43 (s, 9H), 1.64-2.18 (m, 4H), 2.7 (m, 2H), 3.05 (t, 2H,

J=7Hz), 3.23-3.52 (m, 4H), 4.18 (m, 1H), 4.30 (t, 2H, J=7Hz), 6.80 (d, 2H, J=8Hz), 7.05 (d, 2H, J=8Hz), 7.24 (d, 2H, J=10Hz), 8.19 (d, 2H, J=10Hz). Anal. ($C_{27}H_{33}N_3O_8$): C, H, N.

p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucylamino-ethyl)phenyloxypropanoate (21e).-- As above 20e (2.70 g, 6.4 mmol) was converted to p-nitrophenyl ester 21e (2.57 g, 74%): mp 116-118°C; TLC (benzene/ethyl acetate), R_f 0.5; NMR δ 0.89 (d, 6H, J=6Hz), 1.41 (s, 9H), 1.61 (m, 3H), 2.70 (t, 2H, J=7Hz), 3.01 (t, 2H, J=7Hz), 3.43 (m, 2H), 3.93 (m, 1H), 4.30 (t, 2H, J=7Hz), 4.75 (m, 1H), 6.03 (m, 1H), 6.80 (d, 2H, J=8Hz), 7.04 (d, 2H, J=8Hz), 7.22 (d, 2H, J=10Hz), 8.17 (d, 2H, J=10Hz). 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 hr 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 hr 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 hrs, 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 Sephadex LH 20; methanol), 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 (21400), 277 (2910), 284 (2510); GC (A) R_t at 275°C, 5.6 min; MS m/e (rel. int.) 604 (0.8), 303 (3), 302 (12), 183 (31), 152 (21), 124 (67), 121 (10), 70 (100), 55 (45); $[\alpha]_D^{25}$ +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); ^1H NMR δ 1.36-2.36 (m, 8H), 2.5-3.1 (m, 12H), 3.0 (s, 6H), 3.14-4.27 (m, 10H), 6.81 (d, 4H, J=8Hz), 7.01 (d, 4H, J=8Hz). 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) R_t at 275°C, 3.2 min; MS m/e $C_{17}H_{22}N_2O_3$ requires 302.1630, found 302.1636; $[\alpha]_D^{25}$ +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, 2H), 1.89 (t, 2H, J=10Hz), 2.22 (dd, 1H, J=5,12Hz), 2.57 (m, 1H), 2.72 (m, 2H), 2.95 (s, 3H), 3.02 (m, 1H), 3.42 (m, 1H), 3.53 (m, 1H), 4.24 (dd, 1H, J=5,12Hz), 4.80 (t, 1H, J=11Hz), 6.77 (dd, 1H, J=2,8Hz), 7.09 (m, 3H). 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 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 hr period to stirred pyridine (600 ml) at 90°C. Stirring was continued for an additional 10 hrs. 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 chroma-

tography 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. int.) 636 (6), 386 (2), 362 (3), 318 (8), 43 (100); CD-$\Delta\varepsilon_{max}$ (λ_{max} nm): -8.70 (218), -3.77 (234), -0.48 (278), -0.45 (283); NMR δ 0.83 (m, 6H), 0.93 (q, 6H, J=5Hz), 1.30 (m, 4H), 1.47 (m, 2H), 2.55 (dq, 4H, J=7Hz), 2.78 (m, 4H), 2.97 (d, 4H, J=4Hz), 3.00 (m, 6H), 4.09 (m, 4H), 4.25 (m, 2H), 6.20 (m, 2H), 6.80 (m, 4H), 7.02 (m, 4H). Anal. ($C_{36}H_{52}N_4O_6$): C, H, N; (3) was 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 (shld, 6052), 275 (690); MS m/e (rel. int.) 319 (4), 318 (17), 276 (6), 275 (36), 44 (100); GC (B) R_t at 230°, 8.6 min; CD-$\Delta\varepsilon_{max}$ (λ_{max} nm): +9.84 (230); +0.23 (275), +0.46 (284); NMR δ 0.84 (dd, 4H, J=4,8Hz), 0.92 (d, 2H, J=6.5Hz), 1.16 (m, 1H), 1.34 (m, 2H), 2.25 (dd, 1H, J=3,8Hz), 2.40 (dd, 0.5H, J=5,15Hz), 2.63 (m, 0.5H), 2.80 (m, 2.5H), 2.94 (s, 1.5H), 3.04 (s, 1.5H), 3.40 (m, 0.5H), 3.61 (m, 0.5H), 3.95 (q, 0.5H, J=6.5Hz), 4.21 (dd, 1H, J=4,11Hz), 4.53 (td, 0.5H, J=5,9Hz), 4.71 (td, 0.5H, J=5.6,12Hz), 4.92 (m, 1H), 5.62 (m, 1H), 6.68 (dd, 0.5H, J=2.3,8Hz), 6.89 (m, 2.5H), 7.17 (m, 1H). 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, CH_3OH) 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) R_t at 230°C: 18 min (20%), 21 min (14%), 32 min (56.4%). These products were isolated by preparative GC (3% OV-17, 6' x 1/4"). 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 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°on crystallization from ethanol; UV λ_{max} (ε) 224 nm (25180), 276.5 (3393), 283.5 (2855). MS m/e 576 (0.8), 374 (2), 368 (2), 124 (100), 70 (100); CD-$\Delta\varepsilon_{max}$ (λ_{max} nm): -6.9 (224), -0.29 (282), -0.45 (274.5); NMR δ 1.73 (m, 2H), 2.05 (m, 4H), 2.52 (m, 4H), 2.68 (m, 4H), 2.86 (m, 2H), 3.32 (m, 6H), 3.73 (m, 4H), 3.97 (m, 2H), 4.58 (d, 2H, J=7.5Hz), 6.81 (d, 4H, J=8Hz), 7.01 (d, 4H, J=8Hz), 7.13 (m, 2H). 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 shld), 271 (568), 276 (513); GC (B) R_t at 230°C, 12 min; MS m/e 289 (4), 288 (19), 231 (13), 70 (100); CD-$\Delta\varepsilon_{max}$ (λ_{max} nm) -12.42 (232), -2.17 (271), -1.91 (277); NMR δ 1.55 (m, 1H), 1.95 (m, 1H), 2.12 (m, 2H), 2.19 (dd, 1H, J=6,13Hz), 2.34 (m, 1H), 2.75 (dd, 1H, J=10,17Hz), 2.89 (m, 2H), 3.31 (dd,

1H, J=10,17Hz), 3.49 (t, 1H, J=8Hz), 3.80 (m, 1H), 4.28 (m, 2H), 4.62 (t, 1H, J=10Hz), 6.36 (m, 1H), 6.85 (s, 2H), 7.17 (dd, 2H, J=8,15Hz). 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 g, 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, CH_3OH) 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, μmp287°C; UV λ_{max} (ε) 224.5 nm (19511), 276 (2680), 283 (2267). MS m/e 609 (1), 608 (3), 306 (2), 305 (14), 304 (69), 86 (100); CD-$\Delta\varepsilon_{max}$ (λ_{max} nm): -5.65 (229), +0.69 (277), +0.74 (284); NMR: δ 0.93 (m, 12H), 1.66 (m, 6H), 2.65 (m, 8H), 3.26 (m, 2H, J=7Hz), 3.45 (m, 2H, J=7Hz), 4.13 (m, 2H), 4.23 (m, 2H), 4.63 (m, 2H), 6.71 (d, 2H, J=8Hz), 6.97 (d, 2H, J=8Hz). 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) R_t at 230°C, 9.5 min: MS m/e 305 (6), 304 (29), 86 (100); CD-$\Delta\varepsilon_{max}$ (λ_{max} nm): +8.12 (226), +0.39 (275), +0.50 (284); NMR δ 0.84 (d, 6H, J=6Hz), 1.33 (m, 3H), 2.31 (m, 2H), 2.52 (m, 1H), 3.06 (m, 2H), 4.00 (dd, 1H, J=7,14Hz), 4.21 (dd, 2H, J=6,13Hz), 4.95 (t, 1H, J=10.5Hz), 5.22 (d, 1H, J=11Hz),

5.53 (d, 1H, J=9Hz), 6.87 (dd, 1H, J=2.4,7Hz), 6.94 (dd, 1H, J=2.4, 7Hz), 7.03 (dd, 1H, J=2.4,7Hz), 7.09 (dd, 1H, J=2.4,7Hz). Anal. ($C_{17}H_{24}N_2O_3$): C, H, N.

ACKNOWLEDGEMENT

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.

REFERENCES AND NOTES

(1) M. Pais, F. X. Jarreau, X. Lusinchi, and R. Goutarel, Ann. Chim. (Paris), 83 (1966).

(2) a) R. Tschesche and E. U. Kaussman, in "The Alkaloids", ed. R.H.F. Manske, Vol. XV, Academic Press, New York, N.Y., 1975, pp. 165-205; b) Y. Ogihara, Ann. Rep. Fac. Pharm. Sci. Nagoya City Univ., 22, 1 (1974); c) E. W. Warnhoff, Fortschr. Chem. Org. Naturst., 28, 162 (1970).

(3) R. A. Ravizzini, C. S. Andreo, and R. H. Vallejos, Plant Cell Physiol., 18, 701 (1977).

(4) a) J. Dale and K. Titlestad, J.C.S. Chem. Comm., 656 (1969); b) M. Rothe, K.-D. Steffen, and I. Rothe, Angew. Chem., 77, 347 (1965); c) R. Schwyzer, J. P. Carrion, B. Gorup, H. Noltung, and A. Tun-Kyi, Helv. Chim. Acta., 47, 441 (1964).

(5) a) J. Meienhofer, J. Am. Chem. Soc., 92, 3771 (1970); b) S. Matsura, M. Waki, S. Makisumi, and N. Izumiya, Bull. Chem. Soc. Japan, 43, 1197 (1970).

(6) F. Eppenberger and G. Epple, Angew. Chem., 84, 294 (1971).

(7) K. W. Rosenmund and E. Karg, Ber., 75, 1850 (1942).

(8) F. F. Blicke and C. J. Lu, J. Am. Chem. Soc., 74, 3933 (1952).

(9) E. Schnabel, Justus Liebigs Ann. Chem., 702, 188 (1967).

(10) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, J. Am. Chem. Soc., 89, 5012 (1967).

(11) a) R. H. Hall and E. S. Stern, J. Chem. Soc., 2035 (1949); b) C. E. Rehberg and M. B. Dixon, J. Am. Chem. Soc., 72, 2205 (1950).

(12) E. Gottesmann, Ber., 66, 1168 (1933).

(13) S. Sakakibara and N. Inukai, Bull. Chem. Soc. Japan., 37, 1231 (1964).

(14) F. K. Klein and H. Rapoport, J. Am. Chem. Soc., 90, 3576 (1968).

(15) V. Madison, M. Atreyi, C. M. Deber and E. R. Blout, J. Am. Chem. Soc., 96, 6725 (1974).

(16) The recently observed effect of cyclopeptide alkaloids on ion selective mitochondrial swelling may be pertinent in this regard [K. Kawai, Y. Nozawa, and Y. Ogihara, Experientia, 33, 1454 (1977).

(17) J. C. Sutherland, L. E. Vickery, and M. P. Klein, Rev. Sci. Instrum., 45, 1089 (1974).

(18) The p-methoxynitrostyrene was prepared analogously to the process of D. E. Worrall, Org. Syn., Coll. Vol. I, 405 (1932).

(19) P. Quitt, J. Hellerbach and K. Vogler, Helv. Chim. Acta., 46, 327 (1963).

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-methylaminoethylphenyloxy)-propanoyl-L-prolyl]$_2$; 23b, cyclo[3-(4-β-N-methylaminoethylphenyloxy)-propanoyl-L-leucyl]$_2$; 23d, cyclo[3-(4-β-aminoethylphenyloxy)-propanoyl-L-prolyl]$_2$; 23e, cyclo[3-(4-β-aminoethylphenyloxy)-propanoyl-L-leucyl]$_2$.

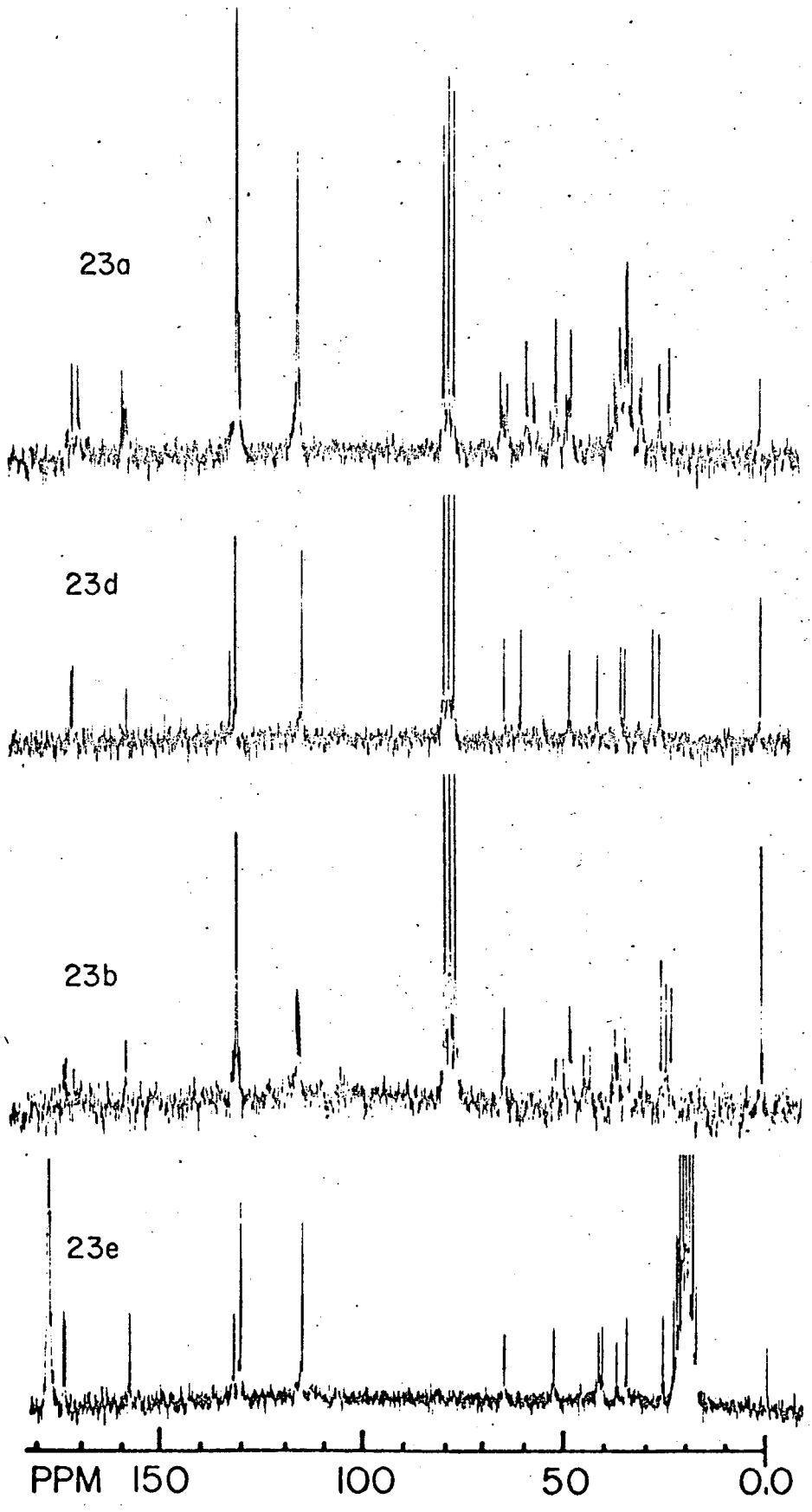

23a
23d
23b
23e
PPM 150
100
50
0.0

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

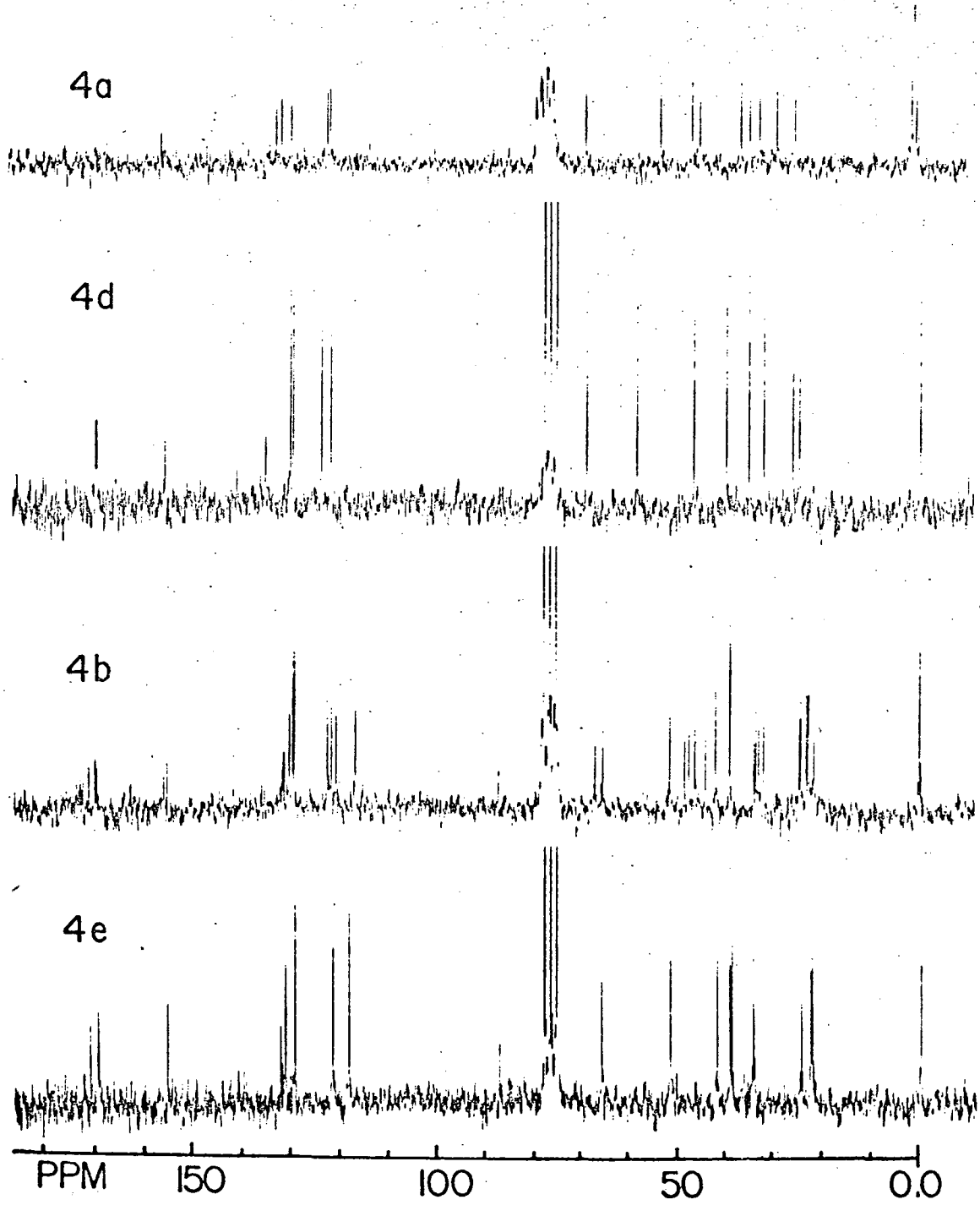

4a
4d
4b
4e
PPM
150
100
50
0.0

Figure 3. Circular dichroism spectra of cyclo[3-(4-β-aminoethylphenyloxy)-propanoyl-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 $Ca(ClO_4)_2$.

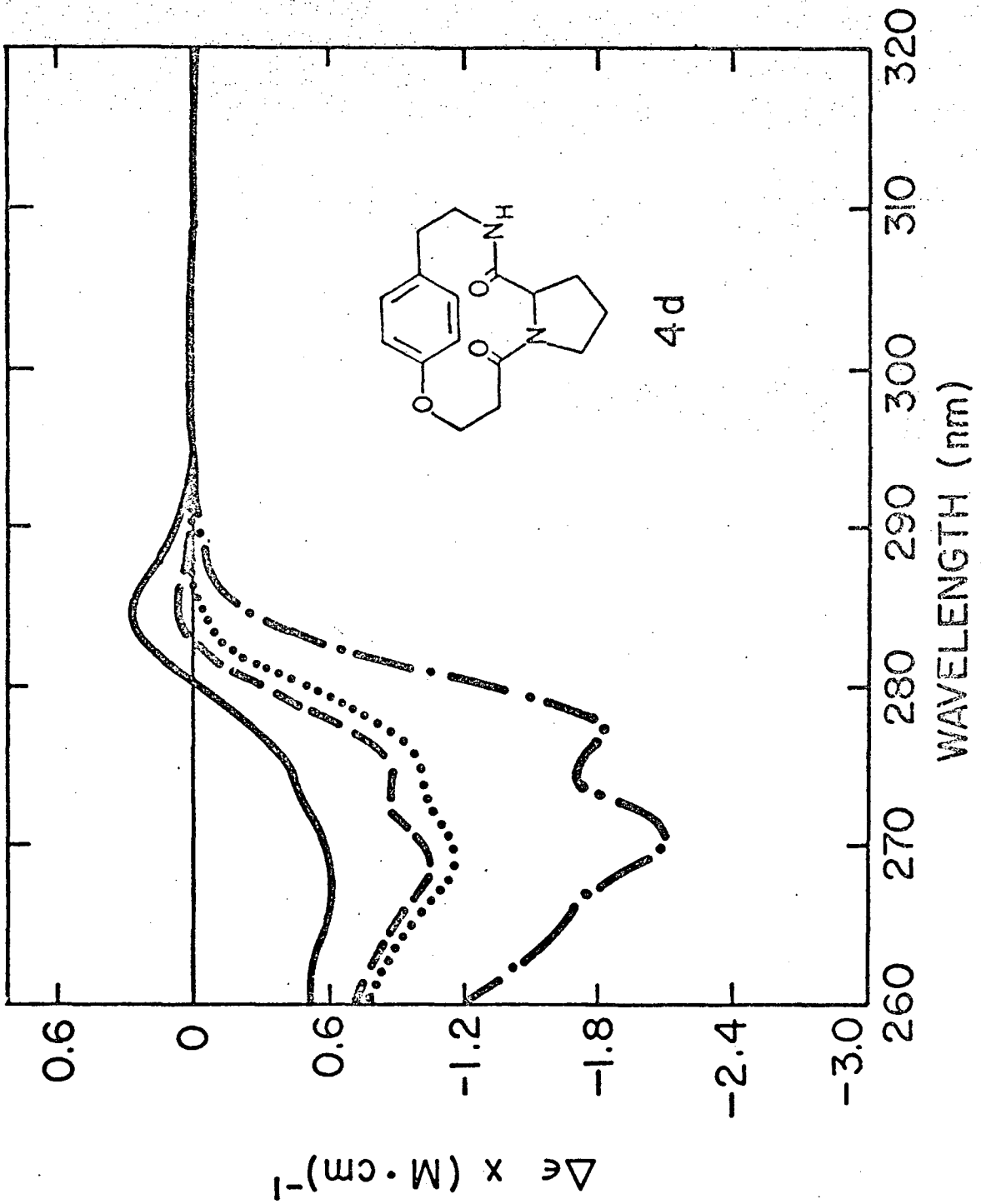

4d
WAVELENGTH (nm)
260
270
280
290
300
310
320
0.6
0
0.6
-1.2
-1.8
-2.4
-3.0
Δε x (M·cm)⁻¹

Figure 4. Circular dichroism spectra of cyclo[3-(4-β-aminoethylphenyloxy)propanolyl-L-prolyl] (4d), 9.4 x 10^{-4} M in CH_3CN with various added salts: — · —, no salt added; — · —, 1.0 x 10^{-2} M $NaClO_4$; ——, 9.3 x 10^{-3} M $Mg(ClO_4)_2$.

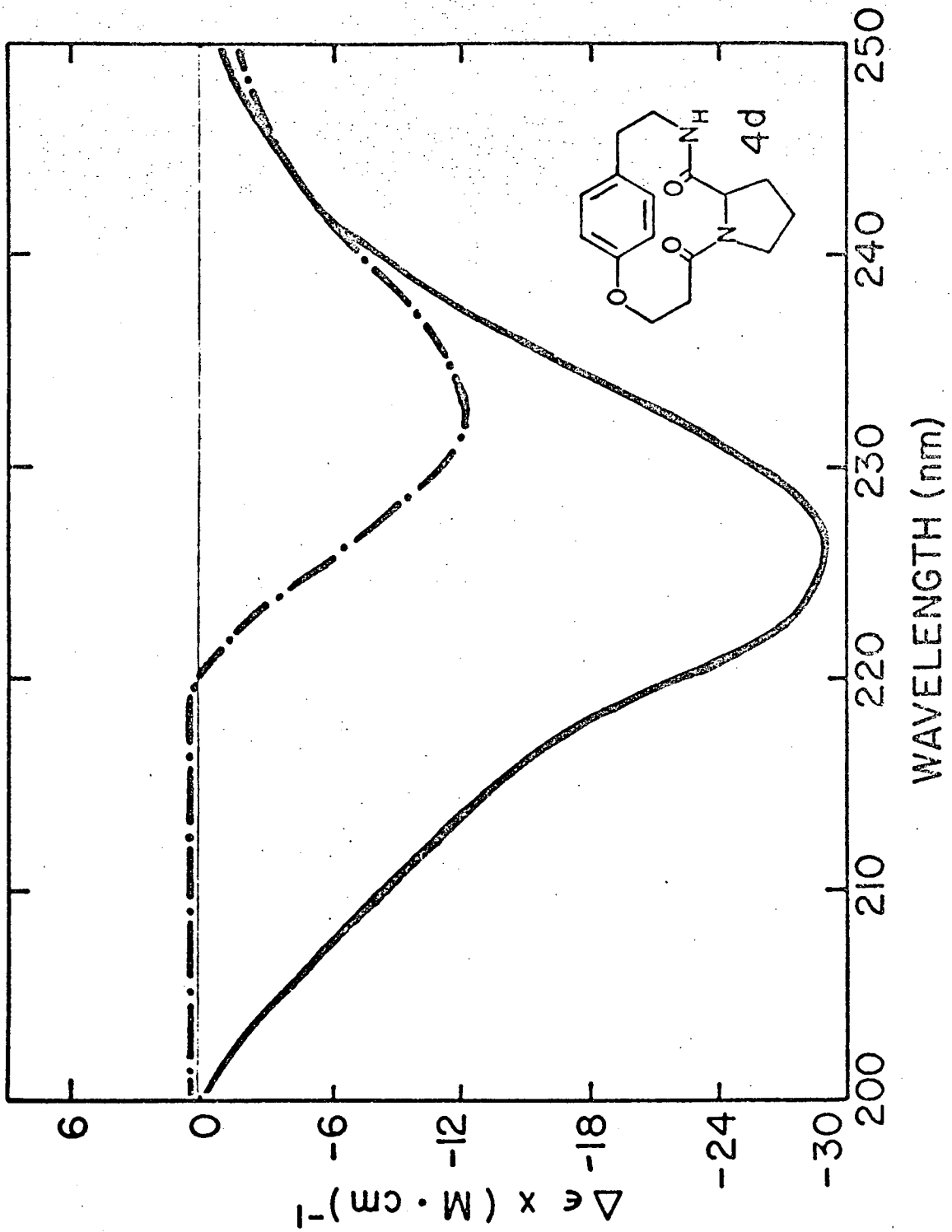

4d
WAVELENGTH (nm)
200
210
220
230
240
250
Δε x (M · cm)⁻¹
6
0
-6
-12
-18
-24
-30

Figure 5. 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 $Ca(ClO_4)_2$.

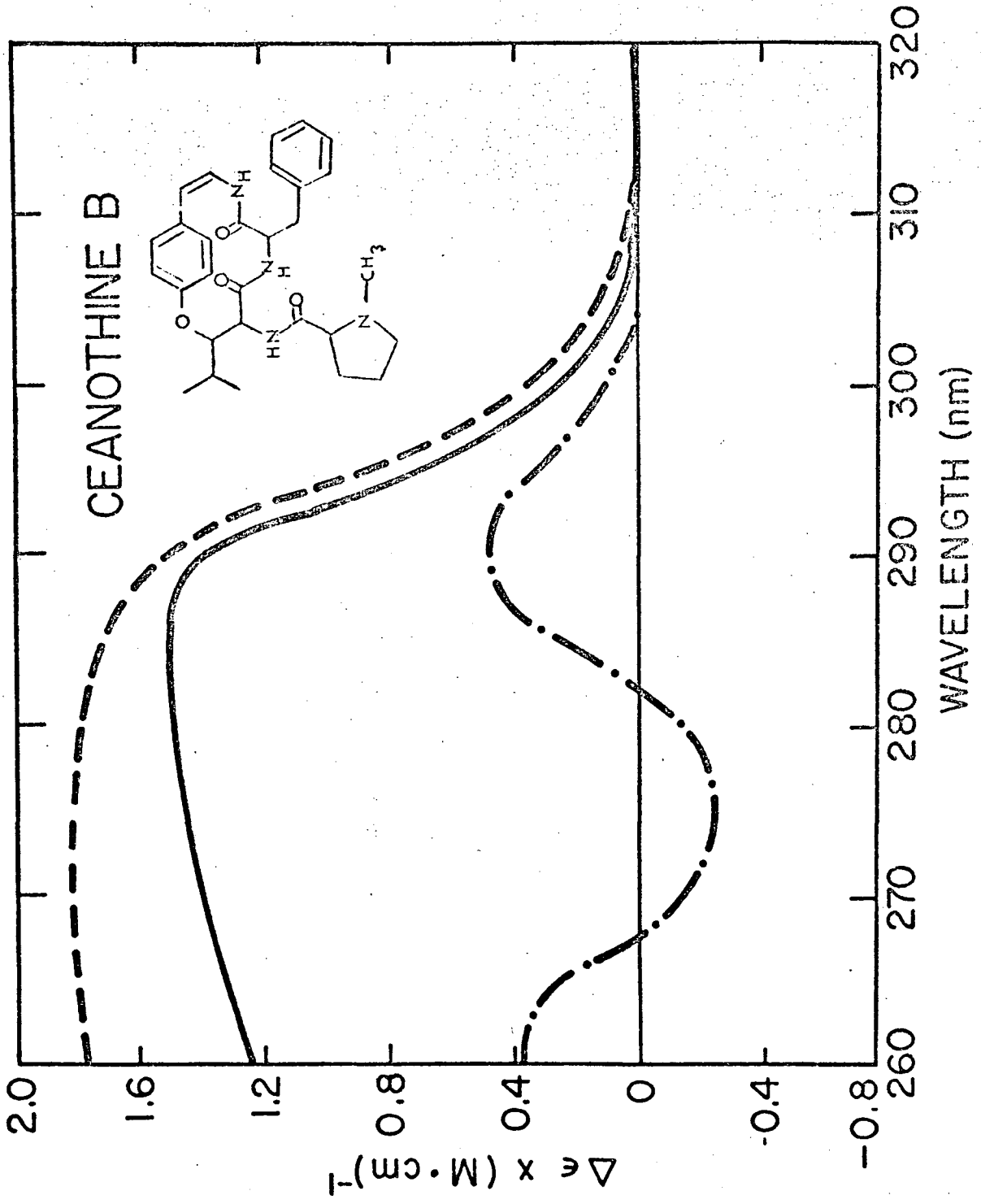
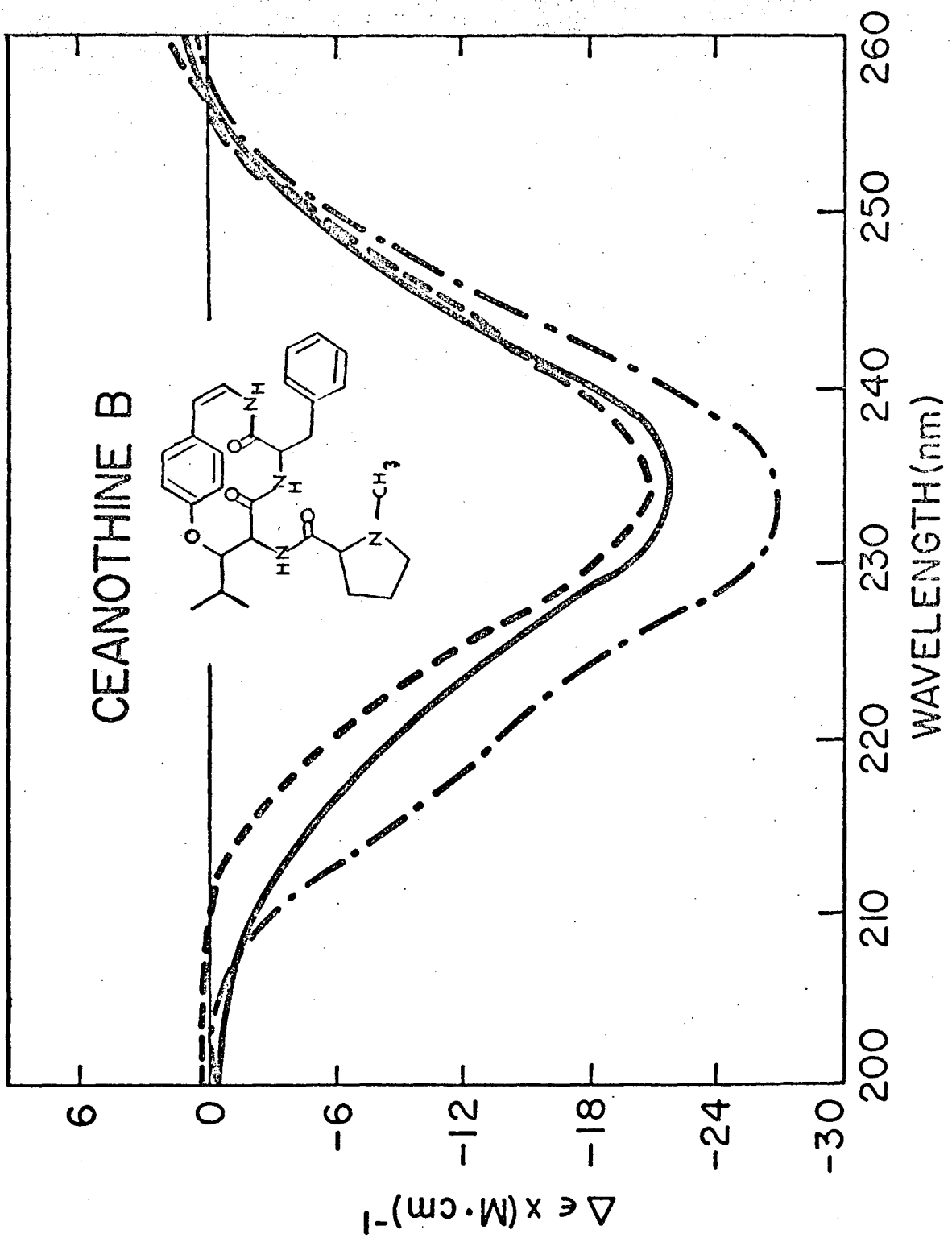
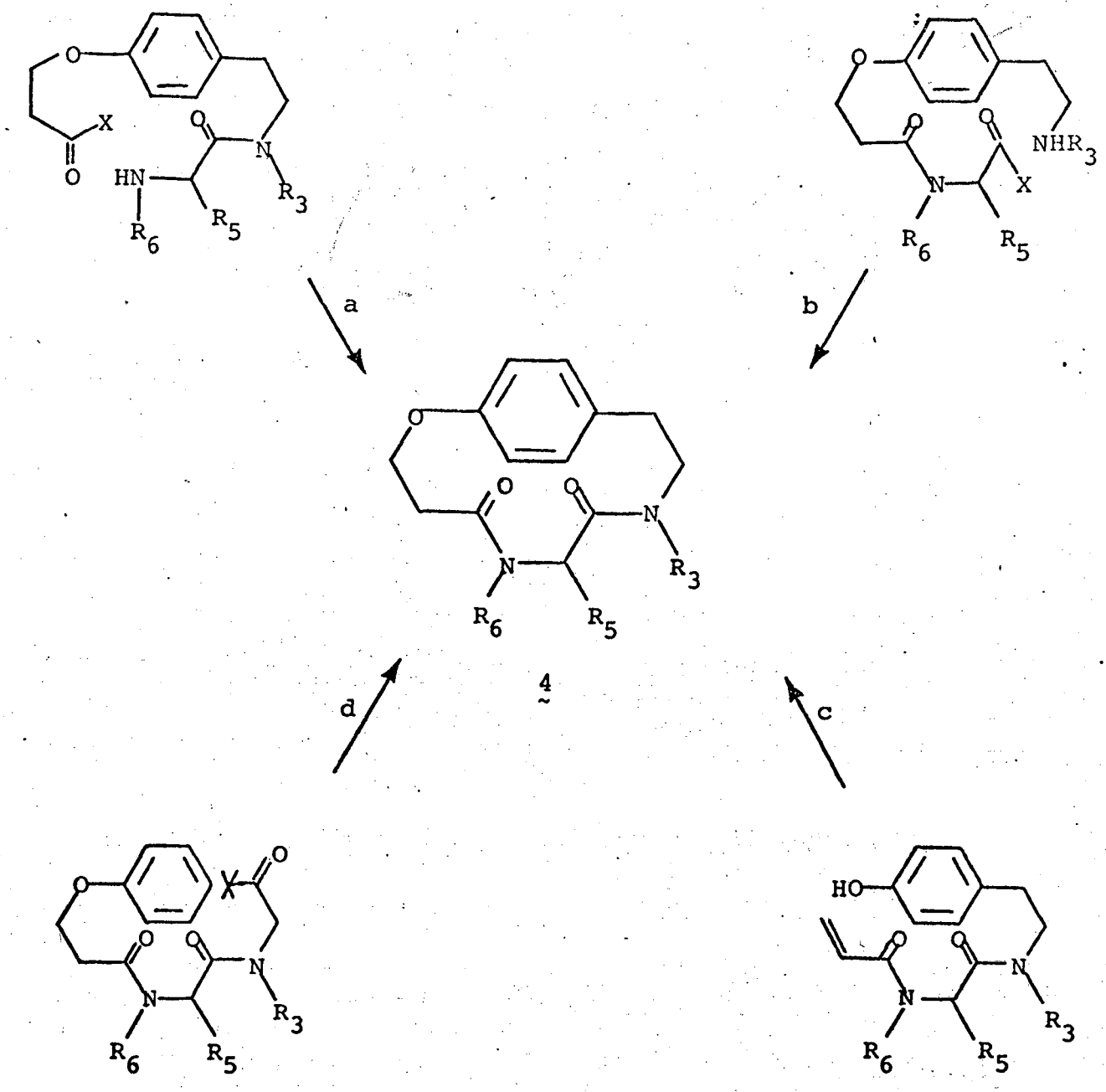

CEANOTHINE B
WAVELENGTH (nm)
260
270
280
290
300
310
320
2.0
1.6
1.2
0.8
0.4
0
-0.4
-0.8
Δε x (M·cm)⁻¹

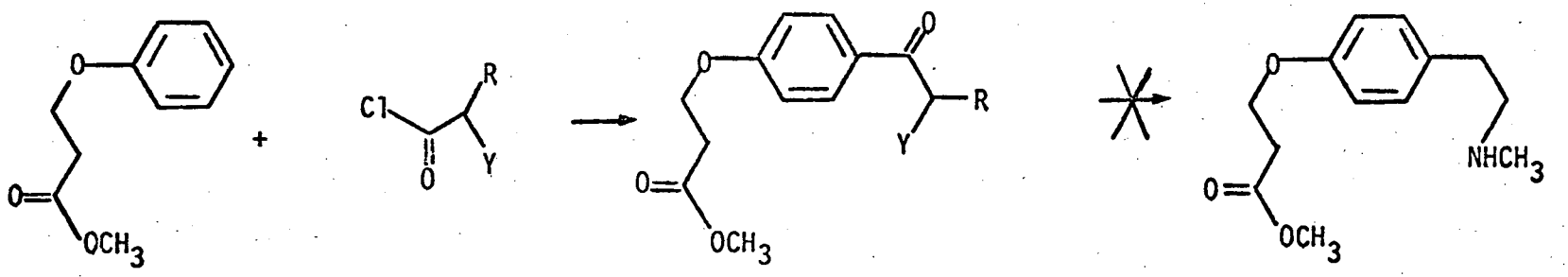
Figure 6. Circular dichroism spectra of ceanothine B, 1.0×10^{-4} M in CH_3CN with various added salts: — · —, no salt added; — · —, 1.1×10^{-3} M $NaClO_4$; ——, 9.2×10^{-4} M $Mg(ClO_4)_2$; ---, 1.5×10^{-3} M $Ca(ClO_4)_2$.


CEANOTHINE B
Δ ε x (M·cm)⁻¹
6
0
-6
-12
-18
-24
-30
200
210
220
230
240
250
260
WAVELENGTH (nm)

Scheme I. Cyclization Modes for the Preparation of Cyclopeptide Alkaloids.



Scheme II. Synthetic Approach via Para Acylation of 2-Phenyloxypropanoates.

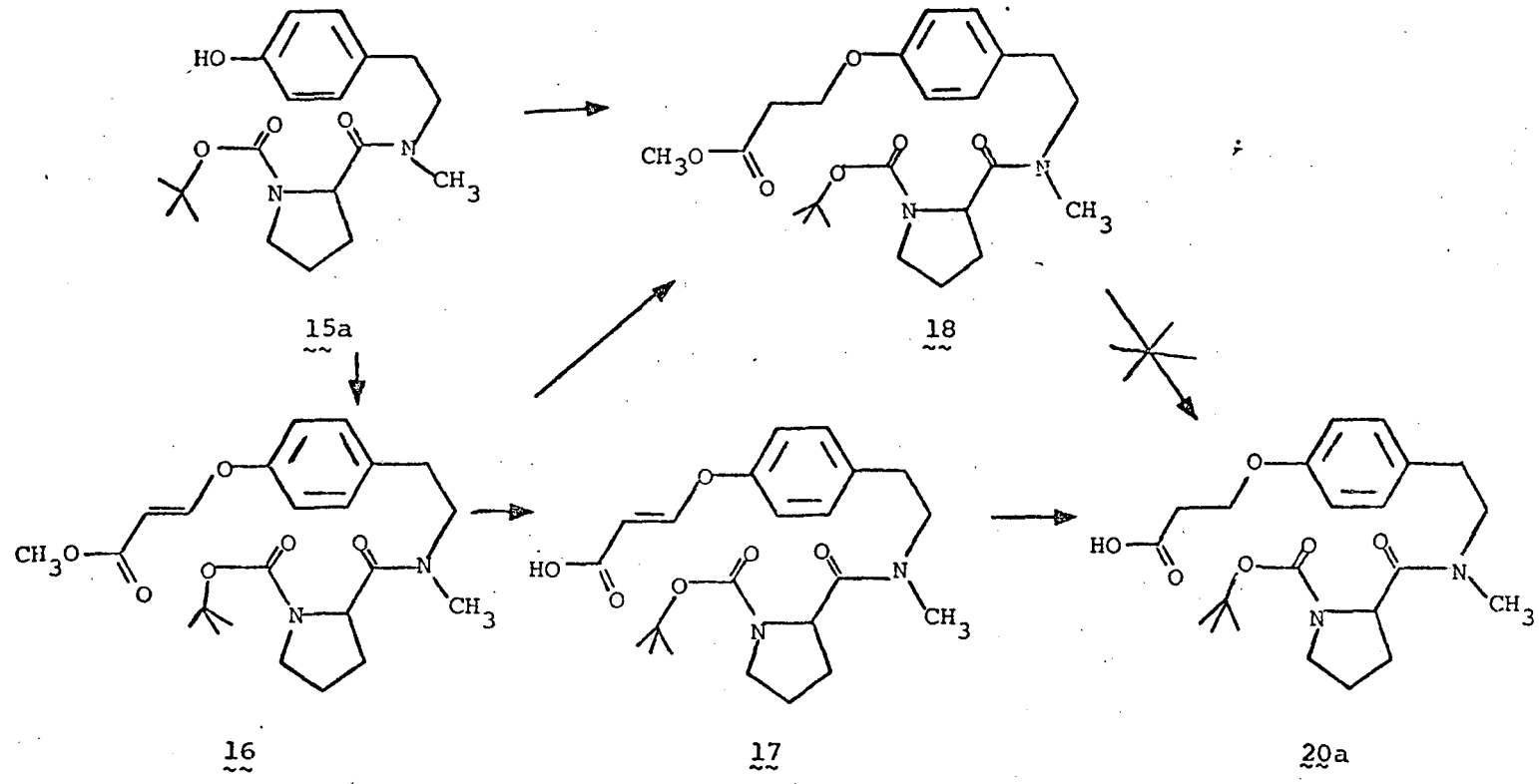


5

6a, R=Y=H
b, R=Y=CH_3
c, R=H, Y=Br
d, R=H, Y=$N(CH_3)COCF_3$

7a, R=Y=H
b, R=Y=CH_3
c, R=H, Y=Br
d, R=H, Y=$NHCH_3 \cdot HCl$

Scheme III. Incorporation of the Three Carbon Propanoate Residue.



15a

18

16

17

20a

15a-e

19a-e

20a-e

21a-e

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

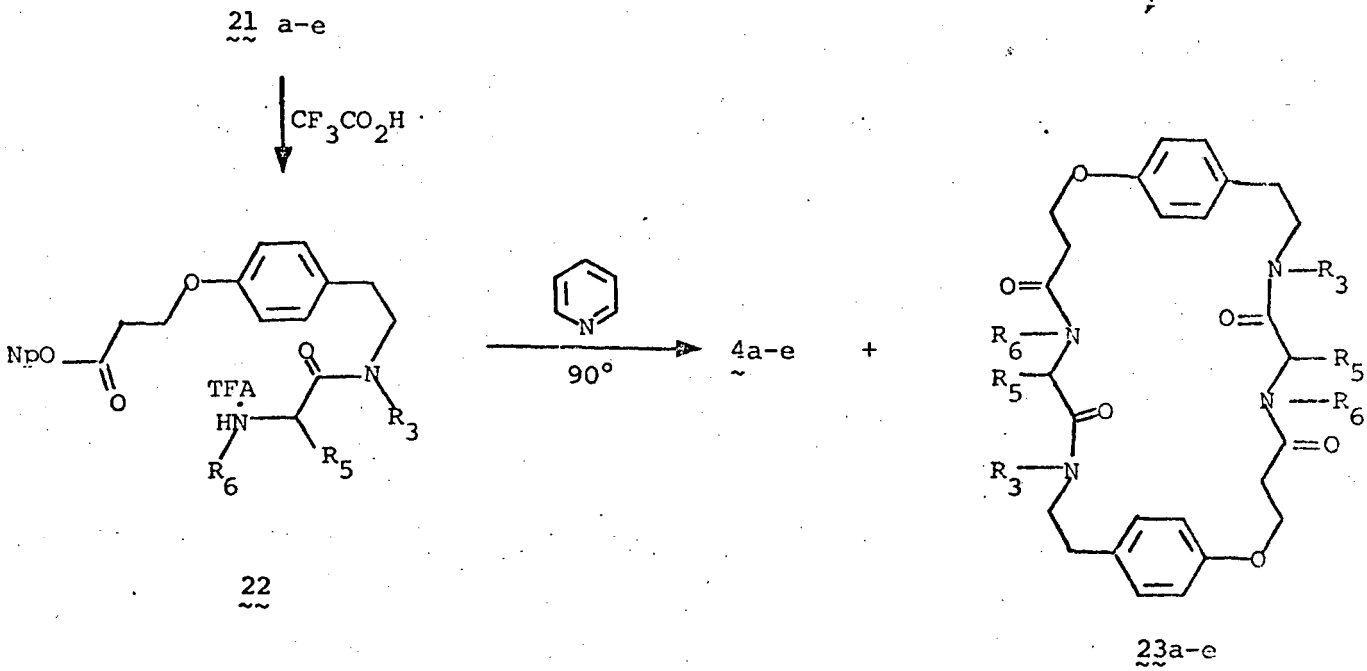
b, $R_3=CH_3$, $R_5=(CH_3)_2CHCH_2$, $R_6=H$

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

Scheme IV. Peptide Cyclization



Appendix. Elemental Analyses.

Compound	Mol. Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	$C_{17}H_{22}N_2O_3$	67.5	7.3	9.3	67.7	7.4	9.1
4b	$C_{18}H_{26}N_2O_3$	67.9	8.2	8.8	67.9	8.2	8.7
4d	$C_{16}H_{20}N_2O_3$	66.6	7.0	9.7	66.5	7.0	9.7
4e	$C_{17}H_{24}N_2O_3$	67.1	8.0	9.2	66.9	8.0	9.1
7a	$C_{12}H_{14}O_4$	64.8	6.3		64.7	6.1	
7c	$C_{12}H_{13}O_4Br$	47.9	4.4		48.0	4.4	
11	$C_9H_{11}NO_2$	65.4	6.7	8.5	65.2	6.7	8.4
12a	$C_{10}H_{13}NO_2$	67.0	7.3	7.8	67.2	7.1	7.9
12b	$C_{16}H_{17}NO_2$	75.3	6.7	5.5	75.2	6.7	5.5
13a	$C_{10}H_{15}NO$	72.7	9.1	8.5	72.9	9.0	8.7
13b	$C_{16}H_{19}NO$	79.6	7.9	5.8	79.6	7.9	5.9
14b	$C_{27}H_{38}N_2O_4$	71.3	8.4	6.2	71.5	8.3	5.9
14c	$C_{28}H_{40}N_2O_4$	71.8	8.6	6.0	72.0	8.6	5.7
15a	$C_{19}H_{28}N_2O_4$	65.5	8.1	8.0	65.3	8.0	8.0
15b	$C_{20}H_{32}N_2O_4$	65.9	8.8	7.7	65.8	8.7	7.5
15c	$C_{21}H_{34}N_2O_4$	66.6	9.0	7.4	66.7	9.0	7.1
15d	$C_{18}H_{26}N_2O_4$	64.6	7.8	8.4	64.5	7.8	8.2
15e	$C_{19}H_{30}N_2O_4$	65.1	8.6	8.0	64.8	8.4	7.9
19a	$C_{29}H_{36}N_2O_6$	68.5	7.1	5.5	68.3	7.1	5.6
19b	$C_{30}H_{40}N_2O_6$	68.7	7.7	5.3	68.6	7.7	5.3
19c	$C_{31}H_{42}N_2O_6$	69.1	7.9	5.2	68.9	7.9	5.1
19d	$C_{28}H_{34}N_2O_6$	68.0	6.9	5.7	67.9	6.9	5.7

Compound	Mol. Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
20a	$C_{22}H_{32}N_2O_6$	62.8	7.7	6.7	62.7	7.6	6.7
20b	$C_{23}H_{36}N_2O_6$	63.3	8.3	6.4	63.3	8.1	6.4
20c	$C_{24}H_{38}N_2O_6$	64.0	8.5	6.2	63.9	8.6	6.0
20d	$C_{21}H_{30}N_2O_6$	62.0	7.4	6.9	61.9	7.4	6.8
20e	$C_{22}H_{34}N_2O_6$	62.5	8.1	6.6	62.4	8.1	6.5
21a	$C_{28}H_{35}N_3O_8$	62.1	6.5	7.8	62.1	6.5	7.8
21b	$C_{29}H_{39}N_3O_8$	62.5	7.0	7.5	62.2	7.0	7.8
21c	$C_{30}H_{41}N_3O_8$	63.0	7.2	7.3	62.7	7.2	7.2
21d	$C_{27}H_{33}N_3O_8$	61.5	6.3	8.0	61.6	6.4	7.9
21e	$C_{28}H_{37}N_3O_8$	61.9	6.9	7.7	61.8	6.9	7.6
23a	$C_{34}H_{44}N_4O_6$	67.5	7.3	9.3	66.4	7.4	9.2
23b	$C_{36}H_{52}N_4O_6$	67.9	8.2	8.8	67.7	8.0	8.7
23d	$C_{32}H_{40}N_4O_6$	66.6	7.0	9.7	66.6	7.0	9.7
23e	$C_{34}H_{48}N_4O_6$	67.1	7.9	9.2	66.8	7.8	9.2

This report was done with support from the Department of Energy. Any conclusions or opinions expressed in this report represent solely those of the author(s) and not necessarily those of The Regents of the University of California, the Lawrence Berkeley Laboratory or the Department of Energy.

TECHNICAL INFORMATION DEPARTMENT
LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA 94720