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

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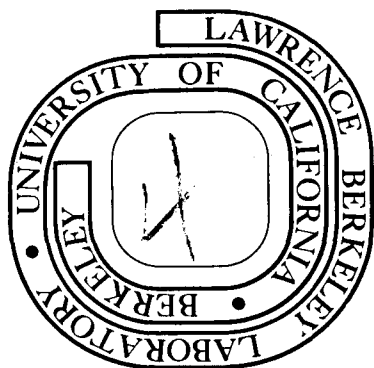
J. Clark Lagarias, Richard A. Houghten, and
Henry Rapoport

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1 Cyclopeptide Alkaloids. Synthesis of the Ring
2 System and Its Ion Affinity.

3
4 J. Clark Lagarias, Richard A. Houghten and Henry Rapoport*

5
6 Contribution from the Department of Chemistry and Lawrence
7 Berkeley Laboratory, University of California, Berkeley, CA 94720.

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

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

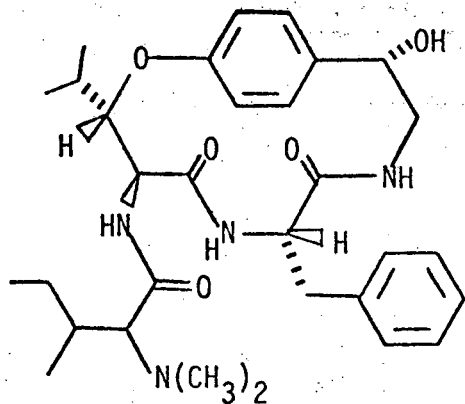
10 Although antibiotic, hypotensive, and antitussive properties
11 have been ascribed to the cyclopeptide alkaloids, no definitive
12 pharmacological activity has been demonstrated^{2a} for this class
13 of natural product. Recently, peptide alkaloids have shown photo-
14 phosphorylation inhibitor activity in spinach chloroplasts, an
15 observation which may be related to their function in the plant in
16 which they are produced.³ The difficulty of isolating sufficient
17 quantities of pure alkaloids, however, and the absence of any
18 method for synthesis, has hampered further biological study. In
19 this account we present the synthesis of several examples of
20 this unusual macrocyclic system and provide evidence for specific
21 ion binding of the cyclopeptide alkaloids.

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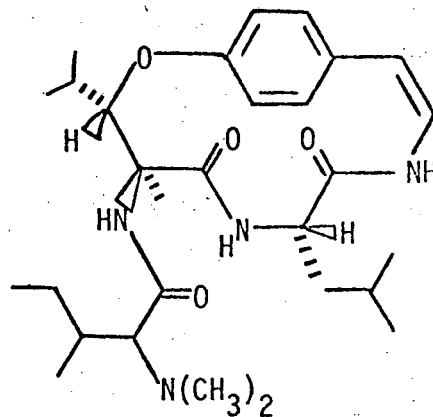
23 Synthetic goals

24 Our initial experimental approach was designed to develop
25 a general synthetic pathway to the saturated cyclopeptides 4.
26 Successful preparation of these saturated models would then be
27 followed by syntheses directed to compounds with the functionalized

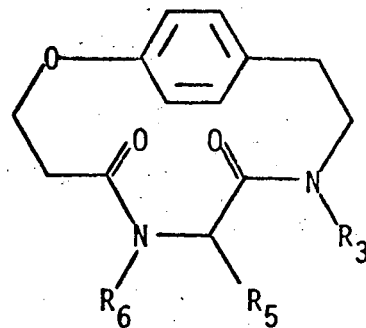
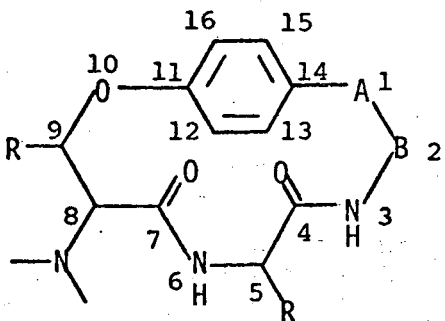
1 benzylic residues found in the natural products (3a,b,c), perhaps
 2 via the saturated models as substrates. As a simplification, we



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A-B Components of the Cyclopeptide Alkaloids

3a, A-B = CH=CH

b, A-B = COCH₂

c, A-B = CH(OH)CH₂

4a, R₃=CH₃, R₅=R₆=(CH₂)₃

b, R₃=CH₃, R₅=(CH₃)₂CHCH₂, R₆=H

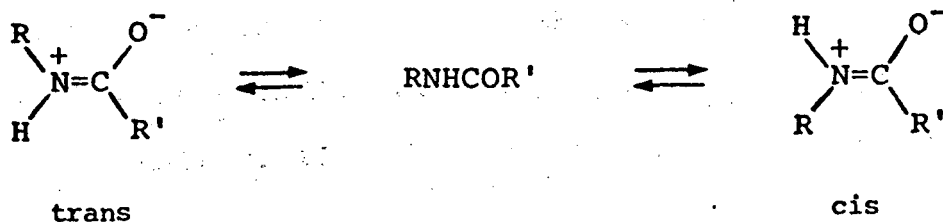
c, R₃=R₆=CH₃, R₅=(CH₃)₂CHCH₂

d, R₃=H, R₅=R₆=(CH₂)₃

e, R₃=R₆=H, R₅=(CH₃)₂CHCH₂

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

7 The cyclopeptide models 4a-e were chosen to test the hypothesis
 8 that amide substitution should affect the course of peptide
 9 cyclization. These models differ in the degree of substitution
 10 of the amide nitrogens in both of the component amino acids.
 11 It is commonly accepted that amide resonance stabilizes their
 12 planar conformation and that trans conformations are preferred
 13 to cis (neglecting hydrogen bonds). The strong trans preference
 14 for the amide bond disappears when peptides are N-methylated.^{4a}
 15 That intramolecular reaction between the ends of the linear
 16 peptide is influenced by the amide conformation has been demon-
 17 strated in the case of cyclotriptide synthesis. Thus 9-
 18 membered ring cyclotriptide can be prepared only when the amides
 19 are tertiary (i.e. cyclotrisarcosyl^{4a} and cyclotriprolyl^{4b}).
 20 Attempts to cyclize tripeptides with primary amino acid residues
 21 have only lead to the isolation of cyclohexapeptides.^{4c} There-
 22 fore we chose the five peptide models (4a-e) as our first
 23 synthetic goals to test the amide conformational factors.



1 Synthetic strategy

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

21 Approach a. Beginning with a 3-phenyloxypropanoate system,
22 our initial synthetic design comprised the early preparation of
23 a para-acylated aryl ether derivative followed by formation of the
24 3,4-peptide bond and ultimately by the 6,7-peptide cyclization.
25 However, in the first step of this sequence we encountered
26 difficulty in para-acylating aryl ether 5 with α -substituted
27 aliphatic acid derivatives (Scheme II). With trifluoromethane-

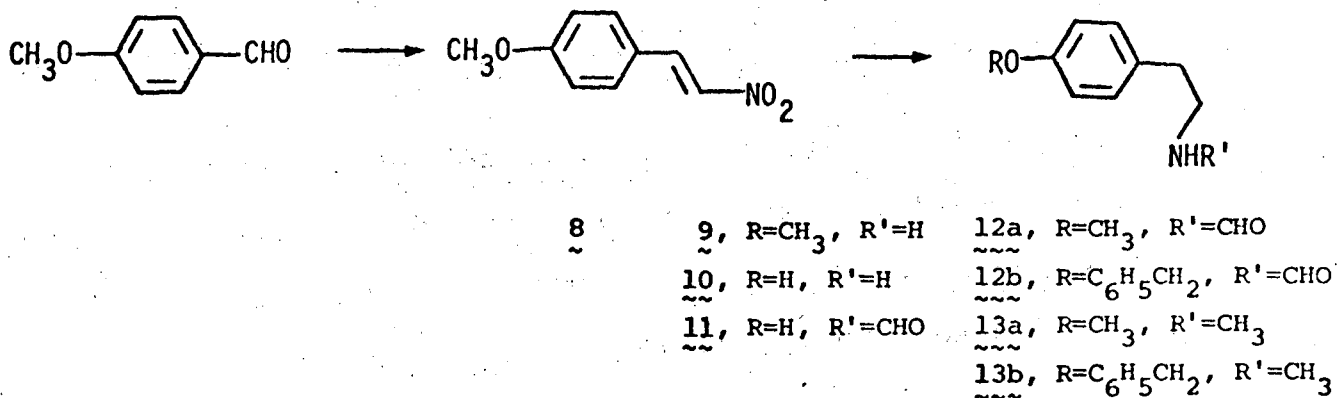
1 sulfonic-carboxylic anhydride intermediates generated by reaction
2 of carboxylic acid chlorides and silver trifluoromethanesulfonate,
3 exclusive para-acylation of oxygenated aromatics has been reported⁶
4 in some cases. In extending this method, we acylated methyl 3-
5 phenoxypropanoate (5) with either acetyl chloride or isobutyryl
6 chloride under the reported conditions and obtained greater than
7 85% yields of isomerically pure para ketones 7a and 7b. However,
8 acylation of 5 with N-trifluoroacetyl-N-methylaminoacetyl chloride
9 (6b) afforded none of the amino ketone. Due to the instability
10 of both aryl ether and ester moieties of 5, no Friedel-Craft pro-
11 cedure successfully effected the desired acylation.

12 On the other hand, acylation with an α -halogenated acetic
13 acid derivative followed by nucleophilic displacement of the
14 halogen atom with an amine did afford the amino ketone 7d.
15 Unfortunately, the acylation of methyl 3-phenoxypropanoate (5)
16 via the mixed anhydride formed from trifluoromethane sulfonic acid
17 and chloroacetyl chloride gave a mixture of ortho and para isomers
18 in a 3/2 ratio. A similar isomer mixture was obtained when 5
19 was acylated with methoxyacetyl chloride by the mixed anhydride
20 procedure. Clearly this acylation method⁶ is not a general one
21 for exclusive para acylation of oxygenated aromatic compounds.
22 The amino ketone 7d, alternatively, could be prepared in three
23 steps. The previously synthesized ketone 7a was α -brominated
24 with bromine in ether at 0°C. Displacement of the bromide (7c)
25 by methylamine in methanol then afforded a 79% conversion to the
26 amino ketone 7d.

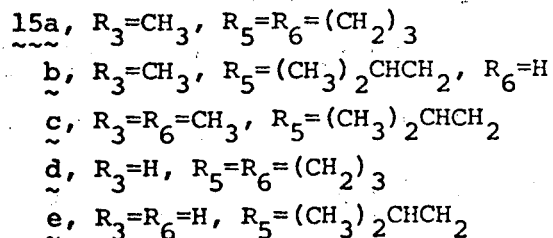
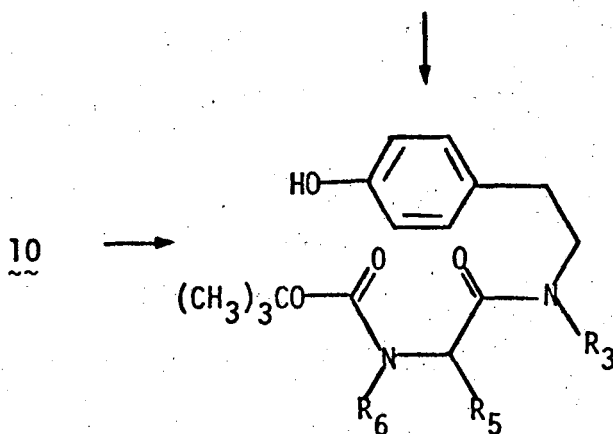
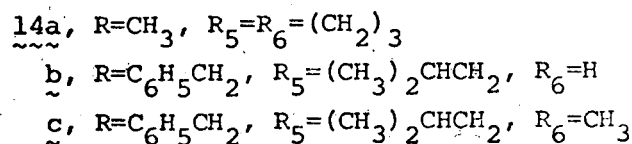
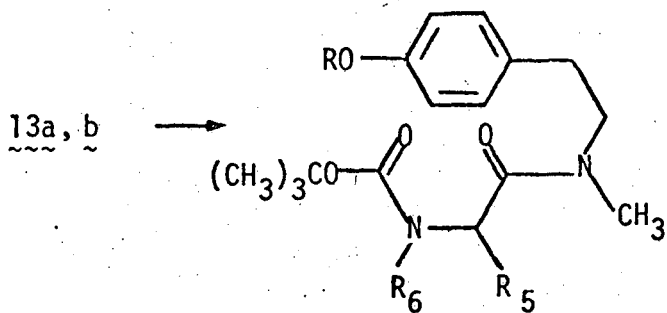
27 Catalytic reduction of the ketone 7d always stopped at the

1 benzyl alcohol stage and failed to give the desired phenylethyl-
 2 amine, although similar catalytic hydrogenation-hydrogenolysis
 fn 7 3 conversions have been reported.⁷ Failure in our case was due to
 4 decomposition of the 3-aryloxypropanoic acid moiety in both acid
 5 and base. This instability of the 3-aryloxypropanoic acid group
 6 necessitated devising a new approach to the cyclopeptide model 4
 7 in which this functionality was introduced near the end of the
 8 synthesis.

9 To overcome these difficulties, we envisioned the preparation
 10 of the 9,10 ether linkage after the preparation of the 3,4-peptide
 11 bond. The synthesis of the p-hydroxyphenylethylamine system, the
 12 key intermediate, proceeded via catalytic reduction of the nitro-
 13 styrene 8 in acetic acid. The amine 9, on refluxing in concentrated
 14 hydrobromic acid, afforded tyramine hydrobromide 10 in 64% yield.
 fn 8 15 Modifying the trichloroacetaldehyde (chloral) procedure⁸ by adding
 16 triethylamine led to formylation of tyramine 10. Without the
 17 addition of triethylamine, the Schiff's base was the exclusive
 18 product of this reaction. The resultant phenol 11 was then con-
 19 verted to the benzyl ether 12b under standard conditions (benzyl
 20 chloride in refluxing acetone) and was subsequently reduced with
 21 lithium aluminum hydride to the N-methylamine 13b.



The most effective method for the acylation of amines 10 and 13 with N-tert-butoxycarbonylamino acids⁹ 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.



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

1 in acetone over potassium carbonate lead to isolation of the cor-
2 responding acrylate and starting phenol. Another method investigated
3 to prepare 3-phenoxypropanoate systems was the Michael addition of
fn 11 4 phenols to acrylates.¹¹ Using p-cresol as a model, we developed
5 conditions for this conversion which gave ether formation in 80%
6 yield. Employing these conditions, however, we observed no reaction
7 of phenol 15a with tert-butyl acrylate.

8 A method for the three carbon homologation of phenols by
fn 12 9 Michael addition with propiolate derivatives was successful.¹²
10 Thus we prepared methyl E-3-phenoxypropenoate (16) by addition of
11 phenol 15a to methyl propiolate. If the sodium salt of the phenol
12 was used, prepared with sodium hydride previous to condensation,
13 the Z-isomer was the predominant product. Catalytic hydrogenation
14 of E-3-phenoxypropenoate (16) afforded the propanoate 18 but this
15 product was extremely sensitive to alkali. Attempted hydrolysis of
16 the methyl ester 18 in alcoholic sodium hydroxide lead to rapid
17 and complete β -elimination. In contrast, hydrolysis of methyl 3-
18 phenoxypropenoate (16) with sodium hydroxide was easily accomplished.
19 The resulting acid 17 could be hydrogenated to yield the saturated
20 compound 20a. The general homologation of phenols 15a-e to the
21 corresponding 3-phenoxypropanoic acids which were then converted
22 to their p-nitrophenyl esters 21a-e is diagrammed in Scheme III.
23 The reaction of phenols 15a-e with benzyl propiolate followed by
24 complete reduction afforded the respective 3-phenoxypropanoic acids
25 20a-e in high yield. After preparation of p-nitrophenyl esters
fn 13 26 (ONp) 21a-e with p-nitrophenyl trifluoroacetate in pyridine,¹³ the
27 conditions for peptide cyclization were next examined.

1 Cyclization. Removal of the N-tert-butoxycarbonyl protecting
2 group was accomplished by dissolving the p-nitrophenyl esters 21
3 in anhydrous trifluoroacetic acid at 0-5°C (Scheme IV). By NMR,
4 it was clear that this process did not require the presence of a
5 carbonium ion scavenger commonly used during acid catalyzed
6 decomposition of tert-butyl carbamates.^{4,5} After evaporation of
7 the excess trifluoroacetic acid, the residual amine salt 21 was
8 dissolved in N,N'-dimethylacetamide and added slowly to pyridine
9 maintained at 90°C. Studies with 21a as the model established
10 acceptable conditions for peptide cyclization (see Experimental
11 Section). Owing to the susceptibility of the 3-phenoxypropanoate
12 system to β-eliminate in alkali, the stability of the p-nitrophenyl
13 esters 21 and the products 4 to these reaction conditions was also
14 tested; both were stable. Using these conditions, the synthesis
15 of each of the cyclopeptide monomers 4a-e on a preparative scale
16 was accomplished. The yields are outlined in Table I.

17 In each case, cyclic monomer 4 was separated from the respective
18 dimer 23 by sephadex LH-20 chromatography. The spectral data (UV,
19 CD, and ¹³C NMR) manifest the difference between cyclic monomers
20 and dimers, especially with respect to the aromatic chromophor.
21 In the UV, the absorption maxima of the cyclic dimers 23 are
22 shifted to longer wavelengths with a fivefold increase in extinction
23 coefficient relative to the corresponding cyclic monomer 4. In the
24 ¹³C NMR spectra of the cyclic dimers 23, each pair of ortho carbons,
25 C-12, C-16, and C-13, C-15, show a single resonance (Figure 1). On
26 the other hand each of the four ortho carbons C-12, C-13, C-15, and
27 C-15 of the cyclic monomers 4 has a unique resonance (Figure 2).

1 The CD spectra in the 250-300 nm range show the expected larger
2 interaction of the aromatic chromophor with the asymmetric center
3 in the cyclic monomers 4. The differential molar extinction coef-
4 ficient ($\Delta\epsilon$) in this region is greater for the monomers than for
5 the dimers.

6 7 Discussion

8 Contrary to the results of cyclotriptide synthesis,⁴ our
9 data show that the yield of cyclopeptide alkaloid model 4 is
10 independent of the substitution of the amide (N-3, C-4) not involved
11 in the formation of the final peptide bond. Although the linear
12 peptides 2la and 2ld differ by the substitution pattern of one amide,
13 the yields of the cyclic peptides 4a and 4d are similar. The yields
14 of cyclopeptides 4b and 4e are also comparable, but less than that
15 of 4a. Cyclopeptide 4c was obtained in very low yield. Our results
16 show that the reactivity of the free amino group (N-6) in the
17 linear peptide is the major factor affecting the different yields
18 of cyclic monomers. That the rate of acylation of amines is
19 greatly influenced by their degree of substitution is well illus-
20 trated by the preparation of N-tert-butoxycarbonylamino acids.⁹
21 The rate of acylation with tert-butoxycarbonylazide decreases in
22 the series proline > leucine >> N-methylleucine. The yields of cyclo-
23 peptides follow this sequence of decreased reactivity of the nucleo-
24 phile, with proline (4a and 4d) > leucine (4b and 4e) >> N-methyl-
25 leucine (4c).

26 The spectral data for the cyclopeptide monomers 4a-d indicates
27 that each macrocycle has a unique geometry. Although the yield

1 of cyclic peptide is independent of the degree of amide substitution
2 in the linear peptide, the configuration of the cyclic product
3 greatly depends on the structure of the amide in the linear peptide.
4 A discussion of configurational isomerization, its effect on the
5 synthesis of this type of ring system, and its effect on ion affinity
6 of these cyclopeptides will be dealt with in a future report.

7 The ion binding properties of the synthetic peptide, cyclo-
8 [3(4- β -aminoethyl)phenoxypropanoyl-L-prolyl] (4d) and a natural
9 peptide alkaloid, ceanothine B,¹⁴ were determined by circular di-
10 chroism studies in acetonitrile.¹⁵ The cyclopeptide 4d showed
11 selectivity for Mg⁺⁺ and Ca⁺⁺ over Li⁺ and did not interact with
12 Na⁺ and K⁺ (Figures 3 and 4). Similarly, ceanothine B interacted
13 with Mg⁺⁺ and Ca⁺⁺ and not with Na⁺ (Figures 5 and 6). Cyclic
14 dimers 23a-e did not exhibit metal complexing when observed by
15 circular dichroism.

16 It is significant to note that the amino acid components of
17 the cyclopeptide alkaloids contain only hydrophobic residues.
18 Such low molecular weight peptides would probably have a high
19 solubility in the lipid layer of a biomembrane and with respect
20 to their ion affinities, these cyclopeptides could possess iono-
21 phoric activity. The high concentration of the cyclopeptide
22 alkaloids in the root bark of plants may indicate an ion
23 solubilizing and transporting function for these alkaloids in
24 plant roots. Also, the reported³ effect of the cyclopeptide alka-
25 loids on photophosphorylation may be due to alteration of an ion-
26 mediated process.

27 Our results indicate that this class of natural products

1 possesses an affinity for metal ions. The determination of ion
2 binding constants and ionophoric activity for the cyclopeptide
3 models 4 and various natural peptide alkaloids is presently being
4 further investigated. The implication that the cyclopeptide alka-
5 loids may function as ionophores in the plant that produces them,
fn 16 6 is clearly suggested by the data presented above.¹⁶

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

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1 EXPERIMENTAL SECTION

2 Methods. All reactions were performed under a nitrogen
3 atmosphere. Solutions were dried over Na_2SO_4 and evaporations
4 were done in vacuo with a Berkeley rotary evaporator. Uncorrected
5 melting points were determined on a Thomas-Hoover Capillary MP
6 Apparatus and a Kofler Micro Hot Stage (μmp). Both ^1H -NMR and
7 ^{13}C -NMR spectra were taken in CDCl_3 solution using internal Me_4Si
8 (δ 0) on a Varian HR-220 and a TT-23 (with a Bruker WH-90 console
9 equipped with an NIC-80 computer and a Varian 25.14 MHz magnet)
10 respectively. UV spectra were taken in methanol on a Cary 118
11 instrument. A model AEI-MS12 mass spectrometer with INCOS data
12 system was used for determining mass spectra. The gas chroma-
13 tography was done on (A) a F and M Model 402 High Efficiency GC
14 with a 5' x 1/8" glass column, 3% OV-17 (w/w) on Aeropak 30 (100-
15 120 mesh), and (B) a Hewlett Packard Model 5730A GC with a 3' x
16 1/8" glass column and the same liquid phase and solid support. TLC
17 was done on silica (Eastman sheets #6060) and column chromatography
18 used silica gel 60 (EM Reagents) with solvent systems: (A) $\text{CH}_3\text{OH}/$
19 benzene/acetone, 1/1/1; (B) benzene/acetone, 4/1; and (C) benzene/
20 Et_2O , 1/1. Optical rotations were determined on a Bendix Ericsson
21 ETL-NPL Automatic Polarimeter Type 43A. CD spectra were taken
22 in acetonitrile on a home made spectrometer.¹⁷ Ion exchange
23 chromatography was done with a mixed bead resin, BioRex A6501-X8-D,
24 20-50 mesh, on a column 1.5 x 50 cm. Elemental analyses were per-
25 formed by the Analytical Laboratory, Department of Chemistry,
26 University of California, Berkeley.

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

6 Methyl 3-(4'-Acetylphenyloxy)propanoate (7a).-- To a suspension
7 of silver trifluoromethanesulfonate (65.1 g, 0.25 mol) in 750 ml
8 of CH₂Cl₂ was added a solution of acetyl chloride (19.9 g, 0.25
9 mol) in 75 mL of CH₂Cl₂. After the immediate precipitation of
10 silver chloride, a solution of methyl 3-phenyloxypropanoate (5)
11 (45.6 g, 0.25 mol)^{11a} in 75 ml of CH₂Cl₂ was introduced. One half
12 hour later the addition of the same amounts of silver salt and
13 acetyl chloride was repeated. After 1 hour, the mixture was
14 filtered, the filtrate was successively washed with water (3 x 300
15 ml), sat. NaHCO₃ (3 x 300 ml), and sat. NaCl (1 x 300 ml), dried,
16 and evaporated. After distillation (Kugelrohr), 53 g (93%) of 7a
17 was obtained: GC (A) R_t at 200°C, 4.3 min; NMR δ 2.55 (s, 3H),
18 2.83 (t, 2H, J=7Hz), 3.73 (s, 3H), 4.30 (t, 2H, J=7Hz), 6.94 (d,
19 2H, J=10Hz), 7.76 (d, 2H, J=10 Hz). Anal. (C₁₂H₁₄O₄): C, H.

20 Methyl 3-(4'-Bromoacetylphenyloxy)propanoate (7c). -- Bromine
21 (1.78 g, 11 mmol) was rapidly added to a stirred slurry of ketone
22 7a (2.48 g, 11 mmol) in 25 ml of Et₂O at 0-5°C. The reaction
23 mixture became homogeneous when allowed to warm to room temperature.
24 After 1 hour, the solution was washed with distilled water (2 x 15
25 ml), sat NaHCO₃ (15 ml), and sat. NaCl (15 ml), dried, and
26 evaporated to afford 2.65 g (80%) of the bromo ketone 7c: mp 68-70°C;
27 GC (A) R_t at 230°C, 2.9 min; NMR δ 2.76 (t, 2H, J=7Hz), 3.67

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

3 Methyl 3-(4'-N-Methylaminoacetylphenoxy)propanoate (7d).--

4 A methanol solution of bromoketone 7c (1.81 g, 6 mmol, in 50 ml)
 5 was cooled to $-5^{\circ}C$ at which time a 25% (w/w) solution of methyl-
 6 amine in methanol (3.60 g, 30 mmol) was introduced. After 4 hours,
 7 1N HCl (32 ml) was added, and on evaporation and SiO_2 chroma-
 8 tography (A), 1.36 g (79%) of the hygroscopic amine hydrochloride
 9 7d was obtained: NMR ($DMSO-d_6$) δ 2.73 (s, 2H), 2.90 (t, 2H, J=7
 10 Hz), 3.23 (s, 3H), 3.70 (s, 3H), 4.38 (t, 2H, J=7Hz), 4.75 (s, 2H),
 11 7.20 (d, 2H, J=10Hz), 7.92 (d, 2H, J=10Hz).

12 2-(4'-Methoxyphenyl)ethylamine (9).-- A solution of p-methoxy-

fn 18 13 ω -nitrostyrene (8, 50 g, 0.28 mol)¹⁸ in 1.7 L of glacial acetic
 14 acid was added over an 8 hour period into 1.7 L of glacial acetic
 15 acid containing Pd/C (10%, 17.7 g) and conc. H_2SO_4 (46 g, 0.47 mol).
 16 Hydrogen was bubbled through the solution with a gas dispersion tube
 17 during the addition and for 1 hour afterwards. On subsequent
 18 isolation and distillation, the amine 9 (3.3 g, 78%) was isolated:
 19 bp $110-112^{\circ}C$ (2 mm); NMR δ 1.10 (s, 2H), 2.86 (m, 4H), 3.70 (s, 3H),
 20 6.83 (dd, 4H, J=8,18Hz).

21 2-(4'-Hydroxyphenyl)ethylamine Hydrobromide (Tyramine Hydro-

22 bromide) (10).-- A mixture of the amino methyl ether 9 (10.9 g,
 23 72 mmol) in 300 ml 48% HBr was refluxed for 30 min. After the
 24 solution was cooled in an ice bath, the crystalline precipitate was
 25 collected and recrystallized from 95% ethanol to yield 10 g (64%) of
 26 10: mp $243-245^{\circ}C$; NMR δ 3.20 (q, 4H, J=6Hz), 4.80 (s, phenolic),
 27 7.0 (dd, 4H, J=8,18Hz).

1 N-Formyl-2-(4'-hydroxyphenyl)ethylamine (11).-- While a
2 suspension of tyramine hydrobromide (10, 10 g, 46 mmol) and
3 triethylamine (9.3 g, 92 mmol) in 75 ml CHCl_3 was maintained at
4 0-5°C, a solution of trichloroacetaldehyde (6.76 g, 46 mmol) in
5 25 ml CHCl_3 was added dropwise over a 1 hour period. After
6 refluxing for 1/2 hour, the resultant solution was evaporated and
7 the residue recrystallized from water yielding 4.6 g (62%) of
8 the N-formyl derivative 11: mp 97-99.5°C; TLC (B) R_f 0.35
9 (ninhydrin neg.); NMR δ 2.61 (t, 2H, J=7Hz), 3.27 (q, 2H, J=7Hz),
10 6.61 (d, 2H, J=8Hz), 6.91 (d, 2H, J=8Hz), 7.86 (m, 1H), 7.92
11 (s, 1H), 9.0 (s, 1H). Anal. ($\text{C}_9\text{H}_{11}\text{NO}_2$): C, H, N.

12 N-Formyl-2-(4'-methoxyphenyl)ethylamine (12a).-- To a solution
13 of amine 9 (40 g, 0.27 mol) and triethylamine (29.5 g, 0.29 mol)
14 in 250 ml CHCl_3 cooled to 0-5°C was added dropwise over a 1 hour
15 period, a solution of trichloroacetaldehyde (43 g, 0.29 mol)
16 in 250 ml CHCl_3 . Following reflux for 45 minutes, the solution
17 was washed with 5% aq. acetic acid (3 x 250 ml), distilled water
18 (1 x 200 ml), sat. NaHCO_3 (1 x 200 ml), dried, and evaporated.
19 The residue was distilled to afford 44 g (92%) of the amine 12a:
20 bp 159-161°C (2 mm); GC (A) R_t at 175°C, 9.8 min; NMR δ 2.75 (t,
21 2H, J=7Hz), 3.43 (q, 2H, J=7Hz), 3.73 (s, 3H), 6.30 (s, 1H),
22 6.85 (d, 2H, J=9Hz), 7.05 (d, 2H, J=9Hz), 8.0 (s, 1H). Anal.
23 ($\text{C}_{10}\text{H}_{13}\text{NO}_2$): C, H, N.

24 N-Formyl-2-(4'-benzyloxyphenyl)ethylamine (12b). A mixture
25 of 11 (4.0 g, 24 mmol), finely powdered, anhydrous K_2CO_3 (7.9 g,
26 57 mmol), and benzyl chloride (3.2 g, 25 mmol) in 100 ml acetone
27 was refluxed for 23 hours. After filtration and evaporation, the

1 residue was partitioned between CHCl_3 (150 ml) and distilled
2 water (100 ml). The organic phase was successively washed with
3 sat. NaHCO_3 (2 x 75 ml), 1N HCl (2 x 75 ml), distilled water
4 (75 ml) and sat. NaCl (75 ml). Following drying and evaporating,
5 4.7 g (76% of 12b) was isolated: mp 109-110°C; TLC (B) $R_f = 0.49$;
6 NMR δ 2.73 (t, 2H, J=7Hz), 3.48 (q, 2H, J=7Hz), 4.98 (s, 2H),
7 5.70 (m, 1H), 6.85 (d, 2H, J=9Hz), 7.05 (d, 2H, J=9Hz), 7.33
8 (m, 5H), 8.0 (s, 1H). Anal. ($\text{C}_{16}\text{H}_{17}\text{NO}_2$): C, H, N.

9 N-Methyl-2-(4'-methoxyphenyl)ethylamine (13a). -- To a rapidly
10 stirred slurry of lithium aluminum hydride (9.10 g, 0.24 mol) in
11 180 ml THF kept at 0-5°C was added a solution of the N-formyl
12 compound 12a (42.9 g, 0.24 mol) in 100 ml THF during a 50 minute
13 period, then the mixture was refluxed for 30 minutes. After
14 cooling the reaction mixture to 5°C, the excess hydride was
15 destroyed by successive addition of 9 ml water, 9 ml 15% NaOH,
16 and 20 ml water and allowed to stir for an additional 30 minutes.
17 Filtration, evaporation, and distillation afforded the N-methyl-
18 amine 13a (30.5 g, 80%): bp 80-83°C (2 mm); NMR δ 1.20 (s, 1H),
19 2.40 (s, 3H), 2.77 (s, 4H), 3.62 (s, 3H), 6.77 (dd, 4H, J=8,18Hz).
20 Anal. ($\text{C}_{10}\text{H}_{15}\text{NO}$): C, H, N.

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

26 N-Methyl-N,N'-tert-butoxycarbonyl-L-prolyl-2(4'-methoxy
27 phenyl)ethylamine (14a). -- A solution of N-tert-butoxycarbonyl

1 L-proline⁹ (24.5 g, 0.11 mol), the amine 13a (18.8 g, 0.11 mol)
2 and DCC (14.3 g, 0.11 mol) in 1.0 L of CHCl₃ was stirred for 12
3 hours. Following removal of the urea by filtration, the solution
4 was washed with 5% acetic acid (2 x 500 ml), distilled water (1 x
5 500 ml), sat. NaHCO₃ (2 x 500 ml), and sat. NaCl (500 ml), dried
6 and evaporated to yield 14a as an oil (30 g, 73%): NMR δ 1.45
7 (s, 9H), 1.85 (m, 4H), 2.8 (m, 2H), 3.0 (d, 3H, N-CH₃), 3.50 (m,
8 4H), 3.73 (s, 3H), 4.50 (m, 1H), 6.82 (d, 2H, J=8Hz), 7.05 (d, 2H,
9 J=8Hz).

10 N-Methyl-N,N'-tert-butoxycarbonyl-L-leucyl-2-(4'-benzyl-
11 oxyphenyl)ethylamine (14b). The temperature of a solution of
12 N-tert-butoxycarbonyl-L-leucine⁹ (2.77 g, 12 mmol) and N-methyl
13 morpholine (1.16 g, 12 mmol) in 58 ml THF was maintained at -15°C
14 while isobutylchloroformate (1.57 g, 12 mmol) was rapidly added.
15 One minute later, a solution of the N-methylamine 13b (2.77 g, 12
16 mmol) in 23 ml THF was dripped in during a 2 minute interval
17 while the solution was kept below -15°C. After removal of the
18 cooling bath, the solution was stirred for 4 additional hours,
19 filtered, and evaporated. The resulting oil was dissolved in
20 100 ml ethyl acetate, washed with 1N HCl (3 x 50 ml), sat. NaHCO₃
21 (3 x 50 ml) and sat. NaCl (50 ml), dried and evaporated, yielding
22 14b as a clear oil (4.80 g, 92%): TLC (B) R_f 0.63; NMR δ 0.92
23 (dd, 6H, J=6,12Hz), 1.5 (m, 3H), 1.48 (s, 9H), 2.77 (m, 2H), 2.90
24 (d, 3H, N-CH₃), 3.55 (m, 2H), 4.55 (m, 1H), 4.98 (s, 2H), 5.14
25 (m, 1H), 6.82 (dd, 2H, J=3,8Hz), 7.05 (d, 2H, J=8Hz), 7.30 (m,
26 5H). Anal. (C₂₇H₃₈N₂O₄): C, H, N.

27

1 N-Methyl-N,N'-tert-butoxycarbonyl-N'-methyl-L-leucyl-2-(4'-
2 benzyloxyphenyl)ethylamine (14c).--- The coupling of N-tert-butoxy-
3 carbonyl-N-methyl-L-leucine^{9,19} [1.86 g, 7.6 mmol, $[\alpha]_D^{25}$ -37.9°
4 (c 0.7, CH₃CO₂H) and N-methylamine 13 (1.83 g, 7.6 mmol) was
5 accomplished with the mixed anhydride procedure utilized for the
6 preparation of 14a. The peptide 14c was isolated in 91% yield
7 (3.24 g): TLC (C) R_f 0.56; NMR δ 0.89 (m, 6H), 1.45 (m, 12H),
8 2.68 (d, 3H, N-CH₃ carbamate), 2.73 (t, 2H, J=8Hz), 2.89 (m, 3H,
9 N-CH₃), 3.43 (m, 2H), 3.75 (m, 1H), 4.98 (s, 2H), 6.83 (d, 2H,
10 J=8Hz), 7.06 (d, 2H, J=8Hz), 7.30 (m, 5H). Anal. (C₂₈H₄₀N₂O₄):
11 C, H, N.

12 N-Methyl-N,N'-tert-butoxycarbonyl-L-prolyl-2-(4'-hydroxy
13 phenyl)ethylamine (15a).--- To a benzene solution (20 ml) of the
14 peptide 14a (3.09 g, 8.5 mmol) was added boron tribromide (2.56
15 g, 10.2 mmol). The resultant heterogeneous mixture was refluxed
16 for 6 hr. After removal of the solvent, the residue was
17 partitioned between 10% NaOH (50 ml) and CH₂Cl₂ (3 x 20 ml).
18 After adjustment of the pH to 9.7, the aqueous layer was washed
19 with CH₂Cl₂ (3 x 25 ml) and evaporated to a light yellow oil
20 weighing 1.40 g (67%). That the O-methyl group was completely
21 removed was established by NMR. This oil (1.40 g, 5.6 mmol) was
22 dissolved in 10 ml of dioxane and 10 ml of water, and the pH
23 was maintained at 8.6 with 1N NaOH with a autotitrator. After
24 2 hr, the pH was adjusted to 2.0, the reaction mixture was
25 extracted with CH₂Cl₂ (3 x 25 ml), the CH₂Cl₂ was evaporated and
26 the residue was chromatographed (B) affording the phenol 15a (1.37 g,
27 70%) as an oil: TLC (B) R_f 0.2, ninhydrin negative, FeCl₃/K₃Fe(CN)₆

1 positive; NMR δ 1.43 (s, 9H), 1.8 (m, 4H), 2.75 (m, 2H), 2.9 (d,
2 3H, NCH₃), 3.2-3.8 (m, 4H), 4.58 (m, 1H), 6.85 (m, 4H), 8.60 (m,
3 1H). Anal. (C₁₉H₂₈N₂O₄): C, H, N.

4 N-Methyl N,N'-tert-butoxycarbonyl-L-leucyl-2-(4'-hydroxy
5 phenyl)ethylamine (15b).-- After a slurry of Pd/C (700 mg, 10%)
6 in 25 ml ethanol was treated with H₂ at 32 psi for 30 min, a
7 solution of benzyl ether 14b (4.77 g, 11 mmol) in 70 ml ethanol
8 was introduced and was hydrogenated at 30 psi for 3 h. After
9 filtering, the solution was evaporated to 15b, an oil weighing
10 3.82 g (100%): NMR δ 0.91 (dd, 6H, J=6,13 Hz), 1.36-1.61 (m, 3H),
11 1.41 (s, 9H), 2.78 (m, 2H), 2.90 (d, 3H, NCH₃), 3.50 (m, 2H), 4.52
12 (m, 1H), 5.18 (m, 1H), 6.68 (d, 2H, J=8Hz), 6.93 (d, 2H, J=8Hz).
13 Anal. (C₂₀H₃₂N₂O₄): C, H, N.

14 N-Methyl-N,N'-tert-butoxycarbonyl-N-methyl-L-leucyl-2-(4'-
15 hydroxyphenyl)ethylamine (15c).-- In a manner exactly as above,
16 benzyl ether 14c (3.10 g, 6.6 mmol) was converted to phenol 15c
17 (2.5 g, 100%): TLC (C) R_f 0.49, FeCl₃/K₃Fe(CN)₆ positive; NMR δ
18 0.89 (m, 6H), 1.44 (s, 9H), 1.43-1.45 (m, 1H), 1.57 (t, 2H, J=8
19 Hz), 2.70 (m, 5H), 2.90 (m, 3H), 3.47 (m, 2H), 3.76 (m, 2H), 4.59
20 and 4.80 (m, 1H), 5.00 (m, 1H), 6.70 (m, 2H), 6.95 (m, 2H).
21 Anal. (C₂₁H₃₄N₂O₄): C, H, N.

22 N,N'-tert-Butoxycarbonyl-L-prolyl-2-(4'-hydroxyphenyl)
23 ethylamine (15d). -- As a solution of N-tert-butoxycarbonyl-L-
24 proline⁹ (7.53 g, 35 mmol) and N-methylmorpholine (3.54 g, 35
25 mmol) in 175 ml THF was cooled to -15°C, isobutylchloroformate
26 (4.78 g, 35 mmol) was rapidly added. After 1 min, a solution of
27 tyramine hydrobromide (10, 7.63 g, 35 mmol) and triethylamine

1 (3.54 g, 35 mmol) in 70 ml of DMF was added in a 2 min period
2 while the temperature was maintained at -12°C . Four hours after
3 the removal of the cooling bath, the reaction mixture was filtered
4 and evaporated. The residue was dissolved in ethyl acetate
5 (200 ml), washed with 1N HCl (3 x 100 ml), sat. NaHCO_3 (3 x 100 ml),
6 and sat. NaCl (1 x 100 ml), dried, and evaporated, giving 11.3 g
7 (97%) of pure 15d: NMR δ 1.40 (s, 9H), 1.70-2.20 (m, 4H), 2.66
8 (m, 2H), 3.25-3.48 (m, 4H), 4.18 (m, 1H), 6.72 (d, 2H, $J=8\text{Hz}$),
9 6.91 (d, 2H, $J=8\text{Hz}$), 7.86 (m, 1H). Anal. ($\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_4$): C, H, N.

10 N,N'-tert-Butoxycarbonyl-L-leucyl-2-(4'-hydroxyphenyl)
11 ethylamine (15e).-- The coupling of N-tert-butoxycarbonyl-L-leucine⁹
12 (2.31 g, 10 mmol) and tyramine hydrobromide (10) (2.18 g, 10 mmol)
13 was accomplished exactly as above to give pure 15e as an oil
14 (3.2 g, 89%): NMR δ 0.87 (d, 6H, $J=6\text{Hz}$), 1.43 (s, 9H), 1.5 (m,
15 3H), 2.3 (d, 2H, $J=7\text{Hz}$), 2.6 (t, 2H, $J=7\text{Hz}$), 4.54 (m, 1H), 6.8
16 (dd, 4H, $J=8,18\text{Hz}$). Anal. ($\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_4$): C, H, N.

17 Benzyl E-3-(4'- β -N,N'-tert-Butoxycarbonyl-L-prolyl-N-methyl-
18 aminoethyl)phenyloxypropenoate (19a).-- A mixture of phenol 15a
19 (1.18 g, 3.4 mmol), N-methylmorpholine (0.34 g, 3.4 mmol) and
20 benzyl propiolate (1.09 g, 6.8 mmol) in 20 ml of THF was allowed
21 to stand for 3 hr at room temperature. After evaporation of the
22 solvent, the residue was dissolved in 60 ml of ethyl acetate,
23 washed with 0.2N HCl (3 x 20 ml), water (20 ml), sat. NaCl (20 ml),
24 dried, and evaporated. The resultant oil was chromatographed
25 (SiO_2 , 100 g, Et_2O) to give 1.55 g (90%) of 19a: NMR δ 1.47 (s,
26 9H), 1.6-2.1 (m, 4H), 2.63-3.1 (m, 2H), 2.95 (s, 3H), 3.2-3.75
27 (m, 4H), 4.55 (m, 1H), 5.18 (s, 2H), 5.58 (d, 1H, $J=12\text{Hz}$), 6.91

1 (d, 2H, J=8Hz), 7.11 (d, 2H, J=8Hz), 7.38 (s, 5H), 7.83 (d, 1H,
2 J=12Hz). Anal. (C₂₉H₃₆N₂O₆): C, H, N.

3 Benzyl E-3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucyl-N-methyl
4 aminoethyl)phenyloxypropenoate (19b).-- In a manner analogous to
5 above, phenol 15b (3.90 g, 11 mmol) was converted to 19b (5.3 g,
6 94%) after chromatography (200 g Sephadex LH-20, methanol): NMR
7 δ 0.92 (dd, 6H, J=6,12Hz), 1.1-1.8 (m, 3H), 1.43 (s, 9H), 2.80
8 (m, 2H), 2.91 (d, 3H), 3.50 (m, 2H), 4.52 (m, 1H), 5.12 (m, 3H),
9 5.5 (d, 1H, J=12Hz), 6.90 (d, 2H, J=8Hz), 7.13 (d, 2H, J=8Hz),
10 7.28 (s, 5H), 7.73 (d, 1H, J=12Hz). Anal. (C₃₀H₄₀N₂O₆): C, H, N.

11 Benzyl E-3-(4'-β-N,N'-tert-Butoxycarbonyl-N'-methyl-L-leucyl-
12 N-methylaminoethyl)phenyloxypropenoate (19c).-- The acrylate 19c
13 (2.32 g, 70%) was prepared from phenol 15c (2.34 g, 6.2 mmol) as
14 above: TLC R_f 0.27 (Et₂O/hexane, 1/1); NMR δ 0.88 (m, 6H), 1.43
15 (m, 9H), 1.51 (m, 3H), 2.66 (s, 3H, NCH₃), 2.77 (t, 2H, J=7Hz),
16 2.91 (d, 3H, NCH₃), 3.47-3.68 (m, 3H), 4.98 (m, 1H), 5.10 (s, 2H),
17 5.50 (d, 1H, J=12Hz), 6.89 (d, 2H, J=8Hz), 7.11 (d, 2H, J=8Hz),
18 7.27 (s, 5H), 7.70 (d, 1H, J=12Hz). Anal. (C₃₁H₄₂N₂O₆): C, H, N.

19 Benzyl E-3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolylamino-
20 ethyl)phenyloxypropenoate (19d).-- The conversion of phenol 15d
21 (5.37 g, 16 mmol) to 19d (7.9 g, 99%) was accomplished as above:
22 mp 99-101°C; TLC (Et₂O) R_f 0.14; NMR δ 1.41 (s, 9H), 1.82 (m, 4H),
23 2.82 (m, 2H), 3.30 (m, 2H), 3.45 (q, 2H, J=7Hz), 4.17 (m, 1H),
24 5.11 (s, 2H), 5.50 (d, 1H, J=12Hz), 6.91 (d, 2H, J=8Hz), 7.11
25 (d, 2H, J=8Hz), 7.28 (m, 5H), 7.73 (d, 1H, J=12Hz); [α]_D²⁵ -52.6°
26 (c 0.73, CH₃OH). Anal. (C₂₈H₃₄N₂O₆): C, H, N.

1 Benzyl E-3-(4'- β -N,N'-tert-Butoxycarbonyl-L-leucylaminoethyl)
2 phenyloxypropenoate (19e).-- As above, phenol 15e (2.9 g, 8.3 mmol)
3 was converted to 19e (3.98 g, 92%), an oil: NMR δ 0.9 (d, 6H,
4 J=6Hz), 1.4 (s, 9H), 3.0 (t, 2H, J=7Hz), 3.5 (q, 2H, J=7Hz), 5.0
5 (m, 2H), 5.6 (d, 1H, J=12Hz), 6.89 (d, 2H, J=8Hz), 7.11 (d, 2H,
6 J=8Hz), 7.3 (s, 5H), 7.80 (d, 1H, J=12Hz).

7 3-(4'- β -N,N'-tert-Butoxycarbonyl-L-prolyl-N-methylaminoethyl)
8 phenyloxypropanoic Acid (20a).-- A mixture of 19a (1.51 g, 3.0 mmol)
9 and Pd/C (10%, 100 mg), in 15 ml ethanol was hydrogenated at 37 psi
10 for 1.5 hr. After filtration and evaporation, 20a (1.25 g, 100%)
11 was obtained: NMR δ 1.43 (s, 9H), 1.6-2.2 (m, 4H), 2.6-3.1 (m,
12 4H), 2.75 (t, 2H, J=7Hz), 2.95 (s, 3H), 3.28-3.9 (m, 4H), 4.2 (t,
13 2H, J=7Hz), 4.55 (m, 1H), 6.78 (d, 2H, J=8Hz), 7.1 (d, 2H, J=8Hz),
14 9.5 (s, 1H). Anal. (C₂₂H₃₂N₂O₆): C, H, N.

15 3-(4'- β -N,N'-tert-Butoxycarbonyl-L-leucyl-N-methylaminoethyl)
16 phenyloxypropanoic Acid (20b).-- With the above procedure, the
17 hydrogenation of 19b (1.29 g, 2.5 mmol) afforded the acid 20b
18 (1.03 g, 100%): NMR δ 0.90 (dd, 6H, 6,12Hz, 1.1-1.8 (m, 3H),
19 1.41 (s, 9H), 2.77 (m, 2H), 2.89 (d, 3H, NCH₃), 3.5 (m, 2H), 4.15
20 (t, 2H, J=5Hz), 4.55 (m, 1H), 5.48 (m, 1H), 6.73 (d, 2H, J=8Hz),
21 7.00 (d, 2H, J=8Hz). Anal. (C₂₃H₃₆N₂O₆): C, H, N.

22 3-(4'- β -N,N'-tert-Butoxycarbonyl-N'-methyl-L-leucyl-N-methyl
23 aminoethyl)phenyloxypropanoic Acid (20c).-- The conversion of 19c
24 (2.02 g, 3.8 mmol) to the acid 20c (1.65 g, 97%) was accomplished
25 under the above conditions: UV λ_{\max} (ϵ) 277 nm (1585), 283(1331);
26 NMR δ 0.89 (m, 6H), 1.44 (s, 9H), 1.53 (m, 3H), 2.68 (m, 3H),
27 2.77 (m, 2H), 2.91 (m, 3H), 3.43 (m, 2H), 4.16 (t, 2H, J=5Hz),

1 4.98 (m, 1H), 6.76 (d, 2H, J=8Hz), 7.05 (m, 2H). Anal. (C₂₄H₃₈N₂O₆):
2 C, H, N.

3 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolylaminoethyl)phenyloxy
4 propanoic Acid (20d).-- In a manner exactly as above 19d (5.04 g,
5 10 mmol) was converted to 20d (4.13 g, 100%): NMR δ 1.43 (s, 9H),
6 1.82 (m, 4H), 2.70 (m, 2H), 2.77 (t, 2H, J=7Hz), 3.39 (m, 4H),
7 4.16 (t, 2H, J=7Hz), 4.22 (m, 1H), 6.73 (d, 2H, J=8Hz), 6.98 (d,
8 2H, J=8Hz), 8.90 (m, 1H); [α]_D²⁵ -56.4° (c 0.87, CH₃OH). Anal.
9 (C₂₁H₃₀N₂O₆): C, H, N.

10 3(4'-β-N,N'-tert-Butoxycarbonyl-L-leucylaminoethyl)phenyloxy
11 propanoic Acid (20e).-- The conversion of 19e (3.80 g, 7.4 mmol)
12 to 20e (2.88 g, 92%) was accomplished as above: NMR δ 0.88
13 (d, 6H, J=5Hz), 1.41 (s, 9H), 1.57 (m, 3H), 2.68 (t, 2H, J=7Hz),
14 2.74 (t, 2H, J=7Hz), 3.41 (q, 2H, J=7Hz), 3.68 and 4.02 (m, 1H),
15 4.17 (t, 2H, J=7Hz), 5.14 (m, 1H), 6.36 (m, 1H), 6.75 (d, 2H,
16 J=8Hz), 6.98 (d, 2H, J=8Hz). [α]_D²⁵ -26.7° (C 1.1, CH₃OH).
17 Anal. (C₂₂H₃₄N₂O₆): C, H, N.

18 p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolyl-
19 N-methylaminoethyl)phenyloxypropanoate (21a).-- A mixture of the
20 acid 20a (4.94 g, 12 mmol) and p-nitrophenyl trifluoroacetate¹³
21 (2.64 g, 12 mmol) in 25 ml pyridine was stirred for 4.5 hr. After
22 evaporation, the residue was dissolved in 200 ml of ethyl acetate
23 and washed with 0.3N HCl (3 x 100 ml), sat. NaHCO₃ (2 x 100 ml),
24 H₂O (100 ml), and sat. NaCl (100 ml). Chromatography (C) of the
25 residue after evaporation afforded the p-nitrophenyl ester 21a
26 (4.48 g, 70%): NMR δ 1.42 (s, 9H), 1.6-2.3 (m, 4H), 2.6-3.2
27 (m, 7H), 3.3-3.8 (m, 4H), 4.32 (t, 2H, J=7Hz), 4.55 (m, 1H), 6.83

1 (d, 2H, J=8Hz), 7.13 (d, 2H, J=8Hz), 7.28 (d, 2H, J=10Hz), 8.18
2 (d, 2H, J=10Hz). Anal. (C₂₈H₃₅N₃O₈): C, H, N.

3 p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucyl
4 N-methylaminoethyl)phenyloxypropanoate (21b).-- In a manner
5 exactly as above 20b (954 mg, 2.2 mmol) was converted to p-
6 nitrophenyl ester 21b (1.04 g, 82%): TLC (Et₂O) R_f 0.32; NMR δ
7 0.94 (dd, 6H, J=6,12Hz), 1.43 (s, 9H), 1.62 (m, 3H), 2.77 (t,
8 2H, J=7Hz), 2.90 (d, 3H, N-CH₃), 3.06 (t, 2H, J=7Hz), 3.55 (m,
9 2H), 4.31 (t, 2H, J=7Hz), 4.57 (m, 1H), 5.18 (m, 1H), 6.80
10 (d, 2H, J=8Hz), 7.03 (d, 2H, J=8Hz), 7.24 (d, 2H, J=10Hz), 8.20
11 (d, 2H, J=10Hz). Anal. (C₂₉H₃₉N₃O₈): C, H, N.

12 p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-N'-methyl-L-
13 leucyl-N-methylaminoethyl)phenyloxypropanoate (21c).-- The
14 preparation of the ester 21c from the acid 20c (813 mg, 1.8 mmol)
15 was accomplished as in the earlier examples. The oil was isolated
16 pure (859 mg, 83%) after chromatography (200 g Sephadex LH 20;
17 methanol): TLC (Et₂O) R_f 0.42; NMR δ 0.89 (m, 6H), 1.44 (s, 9H),
18 1.52 (m, 3H), 2.67 (s, 3H), 2.73 (t, 2H, J=7Hz), 2.89 (d, 3H,
19 N-CH₃), 3.03 (t, 2H, J=7Hz), 3.43 (m, 1H), 3.68 (m, 1H), 4.28 (t,
20 2H, J=7Hz), 4.73 and 4.95 (m, 1H), 6.77 (d, 2H, J=8Hz), 7.06
21 (d, 2H, J=8Hz), 7.20 (d, 2H, J=10Hz), 8.18 (d, 2H, J=10Hz).
22 Anal. (C₃₀H₄₁N₃O₈): C, H, N.

23 p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-prolylamino
24 ethyl)phenyloxypropanoate (21d). In an analogous manner, 20d
25 (3.45 g, 8.5 mmol) was converted to p-nitrophenyl ester 21d;
26 3.88 g, 87%, after chromatography (200 g Sephadex LH 20; methanol):
27 NMR δ 1.43 (s, 9H), 1.64-2.18 (m, 4H), 2.7 (m, 2H), 3.05 (t, 2H,

1 J=7Hz), 3.23-3.52 (m, 4H), 4.18 (m, 1H), 4.30 (t, 2H, J=7Hz),
2 6.80 (d, 2H, J=8Hz), 7.05 (d, 2H, J=8Hz), 7.24 (d, 2H, J=10Hz),
3 8.19 (d, 2H, J=10Hz). Anal. (C₂₇H₃₃N₃O₈): C, H, N.

4 p-Nitrophenyl 3-(4'-β-N,N'-tert-Butoxycarbonyl-L-leucylamino-
5 ethyl)phenyloxypropanoate (21e). -- As above 20e (2.70 g, 6.4 mmol)
6 was converted to p-nitrophenyl ester 21e (2.57 g, 74%): mp 116-
7 118°C; TLC (benzene/ethyl acetate), R_f 0.5; NMR δ 0.89 (d, 6H,
8 J=6Hz), 1.41 (s, 9H), 1.61 (m, 3H), 2.70 (t, 2H, J=7Hz), 3.01 (t,
9 2H, J=7Hz), 3.43 (m, 2H), 3.93 (m, 1H), 4.30 (t, 2H, J=7Hz), 4.75
10 (m, 1H), 6.03 (m, 1H), 6.80 (d, 2H, J=8Hz), 7.04 (d, 2H, J=8Hz),
11 7.22 (d, 2H, J=10Hz), 8.17 (d, 2H, J=10Hz). Anal. (C₂₈H₃₇N₃O₈):
12 C, H, N.

13 Cyclo[3-(4-β-N-methylaminoethyl)phenyloxypropanoyl-L-prolyl] (4a)
14 and Cyclo[3-(4-β-N-methylaminoethyl)phenyloxypropanoyl-L-prolyl]₂ (23a)

15 The p-nitrophenyl ester 21a (719 mg, 1.33 mmol) was dissolved in
16 10 ml of anhydrous trifluoroacetic acid at 0-5°C. After 1 hr the
17 solvent was evaporated to give an oil (1.20 g) which was dissolved
18 in 600 ml of N,N'-dimethylacetamide. The resultant solution was
19 added over a 50 hr period with a metering pump to 600 ml of mech-
20 anically stirred pyridine maintained at 90°C. The solution was
21 stirred and heated for an additional 10 hrs, evaporated, and the
22 residue was dissolved in methanol and filtered through a mixed bed
23 ion exchange resin. The first 100 ml of eluant was collected and
24 evaporated to give a solid residue (223 mg, 56%) from which, after
25 chromatography (200 g Sephadex LH 20; methanol), three fractions
26 were isolated. Eluted first was 45 mg (11%) of cyclic oligomers
27 which was not further purified. Next was the cyclic dimer 23a,

1 88 mg (22%): μmp 251°C (dec); UV λ_{max} (ϵ); 226 nm (21400), 277
 2 (2910), 284 (2510); GC (A) R_t at 275°C, 5.6 min; MS m/e (rel. int.)
 3 604 (0.8), 303 (3), 302 (12), 183 (31), 152 (21), 124 (67),
 4 121 (10), 70 (100), 55 (45); $[\alpha]_D^{25}$ +27.5° (c 0.2, CH₃OH); CD- ΔE_{max}
 5 (λ_{max} nm) +2.67 (228), -0.11 (268), -0.14 (275.6), -0.14 (283),
 6 +0.07 (287); ¹H NMR δ 1.36-2.36 (m, 8H), 2.5-3.1 (m, 12H), 3.0
 7 (s, 6H), 3.14-4.27 (m, 10H), 6.81 (d, 4H, J=8Hz), 7.01 (d, 4H,
 8 J=8Hz). Anal. (C₃₄H₄₄N₄O₆): C (calcd. 67.5, found 66.4), H, N.

9 Eluted last was 4a (97 mg, 24%) obtained after sublimation
 10 at 100°C (0.01 mm): μmp 188°C; UV λ_{max} (ϵ) 270 nm (508), 276
 11 (492). GC (A) R_t at 275°C, 3.2 min; MS m/e C₁₇H₂₂N₂O₃ requires
 12 302.1630, found 302.1636; $[\alpha]_D^{25}$ +6.3 (c 0.2, CH₃OH); CD- ΔE_{max}
 13 (λ_{max} nm); +8.72 (222), -1.74 (241), -1.01 (270), -0.97 (275.5);
 14 NMR δ 1.74 (m, 2H), 1.89 (t, 2H, J=10Hz), 2.22 (dd, 1H, J=5,12Hz),
 15 2.57 (m, 1H), 2.72 (m, 2H), 2.95 (s, 3H), 3.02 (m, 1H), 3.42 (m,
 16 1H), 3.53 (m, 1H), 4.24 (dd, 1H, J=5,12Hz), 4.80 (t, 1H, J=11Hz),
 17 6.77 (dd, 1H, J=2,8Hz), 7.09 (m, 3H). Anal. (C₁₇H₂₂N₂O₃): C, H, N.

18 Cyclo[3-(4- β -N-methylaminoethyl)phenoxypropanoyl-L-leucyl (4b)
 19 and Cyclo[3-(4- β -N-methylaminoethyl)phenoxypropanoyl-l-leucyl]₂ (23b)
 20 Dissolution of p-nitrophenyl ester 21b (665 mg, 1.2 mmol) in 10 ml
 21 anhydrous trifluoroacetic acid at 0-5°C as above, afforded an oil
 22 (1.03 g) after evaporation which was dissolved in dimethylacetamide
 23 (620 ml) and added dropwise over a 50 hr period to stirred pyridine
 24 (600 ml) at 90°C. Stirring was continued for an additional 10 hrs.
 25 The pyridine was evaporated and the residue was dissolved in methanol
 26 and filtered through a mixed bed ion exchange resin to give an
 27 oil (332 mg). The crude product was purified by column chroma-

1 tography on Sephadex LH-20 in methanol, isolating four fractions:
2 (1) 95 mg (25%) of cyclic oligomers; (2) dimer 23b (123 mg, 32%),
3 crystallized from ethanol: μmp 234°C; UV λ_{max} (ϵ) 224 nm (25,245),
4 276 (3234), 283 (2691); MS m/e (rel. int.) 636 (6), 386 (2), 362 (3),
5 318 (8), 43 (100); CD- $\Delta\epsilon_{\text{max}}$ (λ_{max} nm): -8.70 (218), -3.77 (234),
6 -0.48 (278), -0.45 (283); NMR δ 0.83 (m, 6H), 0.93 (q, 6H, J=5Hz),
7 1.30 (m, 4H), 1.47 (m, 2H), 2.55 (dq, 4H, J=7Hz), 2.78 (m, 4H),
8 2.97 (d, 4H, J=4Hz), 3.00 (m, 6H), 4.09 (m, 4H), 4.25 (m, 2H),
9 6.20 (m, 2H), 6.80 (m, 4H), 7.02 (m, 4H). Anal. ($\text{C}_{36}\text{H}_{52}\text{N}_4\text{O}_6$):
10 C, H, N; (3) was a mixture of compounds (36 mg, 10%) not further
11 characterized; (4) cyclic monomer 4b (49 mg, 13%): μmp 119°C
12 after sublimation at 100°C (0.01 mm); UV λ_{max} (ϵ) 226 nm (shld,
13 6052), 275 (690); MS m/e (rel. int.) 319 (4), 318 (17), 276 (6),
14 275 (36), 44 (100); GC (B) R_t at 230°, 8.6 min; CD- $\Delta\epsilon_{\text{max}}$ (λ_{max} nm):
15 +9.84 (230); +0.23 (275), +0.46 (284); NMR δ 0.84 (dd, 4H,
16 J=4,8Hz), 0.92 (d, 2H, J=6.5Hz), 1.16 (m, 1H), 1.34 (m, 2H), 2.25
17 (dd, 1H, J=3,8Hz), 2.40 (dd, 0.5H, J=5,15Hz), 2.63 (m, 0.5H), 2.80
18 (m, 2.5H), 2.94 (s, 1.5H), 3.04 (s, 1.5H), 3.40 (m, 0.5H), 3.61
19 (m, 0.5H), 3.95 (q, 0.5H, J=6.5Hz), 4.21 (dd, 1H, J=4,11Hz), 4.53
20 (td, 0.5H, J=5,9Hz), 4.71 (td, 0.5H, J=5.6,12Hz), 4.92 (m, 1H),
21 5.62 (m, 1H), 6.68 (dd, 0.5H, J=2.3,8Hz), 6.89 (m, 2.5H), 7.17
22 (m, 1H). Anal. ($\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3$): C, H, N.

23 Cyclo[3-(4- β -N-methylaminoethyl)phenoxypropanoyl-N-methyl
24 L-leucyl] (4c).-- The conversion of p-nitrophenyl ester 21c (665 mg,
25 1.2 mmol) to the cyclopeptides was accomplished as described above.
26 After ion exchange a colorless oil (21 mg) was isolated. Sephadex
27 chromatography (200 g LH-20, CH_3OH) afforded two fractions:

1 (1) 12 mg (3.5%) which was not further characterized; (2) 8 mg,
 2 2.2%, contained three major components by GC (B) R_t at 230°C:
 3 18 min (20%), 21 min (14%), 32 min (56.4%). These products were
 4 isolated by preparative GC (3% OV-17, 6' x 1/4"). The 18 min
 5 component was the desired cyclic peptide 4c (1.6 mg, 0.4%):
 6 MS m/e $C_{19}H_{28}N_2O_3$ requires 332.2100, found 332.2091. The other
 7 components were not further characterized.

8 Cyclo[3-(4- β -aminoethyl)phenoxypropanoyl-L-prolyl] (4d) and
 9 Cyclo[3-(4- β -aminoethyl)phenoxypropanoyl-L-prolyl]₂ (23d).-- The
 10 conversion of p-nitrophenyl ester 21d (591 mg, 1.1 mmol) to the
 11 cyclopeptides was accomplished exactly as previously described.
 12 After ion exchange a light yellow oil (244 mg) was isolated.
 13 Sephadex chromatography (200 g LH-20, MeOH) gave three fractions.
 14 Fraction 1 was 54 mg (17%), cyclic oligomers. Fraction 2 was cyclic
 15 dimer 23d (110 mg, 34%): μmp 221° on crystallization from ethanol;
 16 UV λ_{max} (ϵ) 224 nm (25180), 276.5 (3393), 283.5 (2855). MS m/e
 17 576 (0.8), 374 (2), 368 (2), 124 (100), 70 (100); CD- $\Delta\epsilon_{max}$ (λ_{max} nm):
 18 -6.9 (224), -0.29 (282), -0.45 (274.5); NMR δ 1.73 (m, 2H), 2.05
 19 (m, 4H), 2.52 (m, 4H), 2.68 (m, 4H), 2.86 (m, 2H), 3.32 (m, 6H),
 20 3.73 (m, 4H), 3.97 (m, 2H), 4.58 (d, 2H, J=7.5Hz), 6.81 (d, 4H,
 21 J=8Hz), 7.01 (d, 4H, J=8Hz), 7.13 (m, 2H). Anal. ($C_{32}H_{40}N_4O_6$):
 22 C, H, N. Fraction 3 was cyclic monomer 4d (75 mg, 24%), an oil;
 23 UV λ_{max} (ϵ) 223 nm (6198 shld), 271 (568), 276 (513); GC (B)
 24 R_t at 230°C, 12 min; MS m/e 289 (4), 288 (19), 231 (13), 70 (100);
 25 CD- $\Delta\epsilon_{max}$ (λ_{max} nm) -12.42 (232), -2.17 (271), -1.91 (277); NMR δ
 26 1.55 (m, 1H), 1.95 (m, 1H), 2.12 (m, 2H), 2.19 (dd, 1H, J=6,13Hz),
 27 2.34 (m, 1H), 2.75 (dd, 1H, J=10,17Hz), 2.89 (m, 2H), 3.31 (dd,

1 1H, J=10,17Hz), 3.49 (t, 1H, J=8Hz), 3.80 (m, 1H), 4.28 (m, 2H),
2 4.62 (t, 1H, J=10Hz), 6.36 (m, 1H), 6.85 (s, 2H), 7.17 (dd, 2H,
3 J=8,15Hz). Anal. (C₁₆H₂₀N₂O₃): C, H, N.

4 Cyclo[3-(4-β-aminoethyl)phenyloxypropanoyl-L-leucyl] (4e) and
5 Cyclo[3-(4-β-aminoethyl)phenoxypropanoyl L-leucyl]₂ (22e). -- With
6 the same cyclization procedure, p-nitrophenyl ester 21e (588 mg,
7 1.1 mmol) was converted to the cyclopeptides. The resulting brown
8 solid was triturated in methanol and filtered. The insoluble
9 portion (40.2 g, 12%) was later identified as cyclic dimer 22e.
10 The methanol filtrate was eluted through a mixed bed ion exchange
11 resin and evaporated to give a solid residue (137 mg). Following
12 Sephadex chromatography (200 g, LH-20, CH₃OH) three fractions were
13 isolated. Fraction 1 was 48 mg (15%) of cyclic oligomers, not
14 further characterized. Fraction 2 was cyclic dimer 22e (51 mg,
15 15%): crystallized from ethanol, μmp 287°C; UV λ_{max} (ε) 224.5 nm
16 (19511), 276 (2680), 283 (2267). MS m/e 609 (1), 608 (3), 306 (2),
17 305 (14), 304 (69), 86 (100); CD-Δε_{max} (λ_{max} nm): -5.65 (229),
18 +0.69 (277), +0.74 (284); NMR: δ 0.93 (m, 12H), 1.66 (m, 6H),
19 2.65 (m, 8H), 3.26 (m, 2H, J=7Hz), 3.45 (m, 2H, J=7Hz), 4.13 (m,
20 2H), 4.23 (m, 2H), 4.63 (m, 2H), 6.71 (d, 2H, J=8Hz), 6.97 (d,
21 2H, J=8Hz). Anal. (C₃₄H₄₈N₄O₆): C, H, N. Fraction 3 was the
22 cyclopeptide 4e (31 mg, 9%): μmp 199°C; UV λ_{max} (ε) 226 nm (6127),
23 276 (734). GC (B) R_t at 230°C, 9.5 min: MS m/e 305 (6), 304
24 (29), 86 (100); CD-Δε_{max} (λ_{max} nm): +8.12 (226), +0.39 (275),
25 +0.50 (284); NMR δ 0.84 (d, 6H, J=6Hz), 1.33 (m, 3H), 2.31 (m, 2H),
26 2.52 (m, 1H), 3.06 (m, 2H), 4.00 (dd, 1H, J=7,14Hz), 4.21 (dd,
27 2H, J=6,13Hz), 4.95 (t, 1H, J=10.5Hz), 5.22 (d, 1H, J=11Hz),

1 5.53 (d, 1H, J=9Hz), 6.87 (dd, 1H, J=2.4,7Hz), 6.94 (dd, 1H, J=2.4,
2 7Hz), 7.03 (dd, 1H, J=2.4,7Hz), 7.09 (dd, 1H, J=2.4,7Hz). Anal.
3 (C₁₇H₂₄N₂O₃): C, H, N.

4

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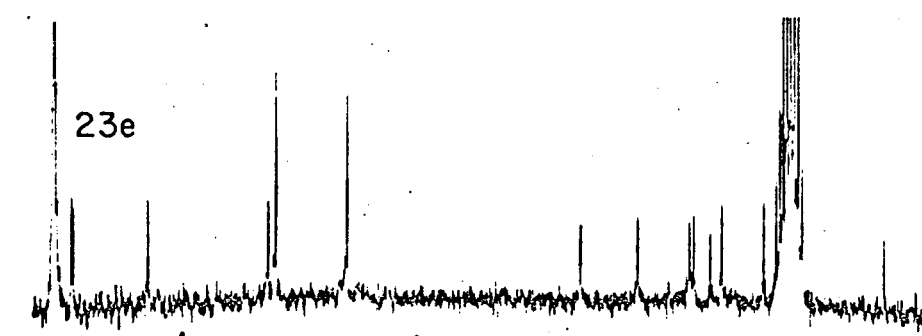
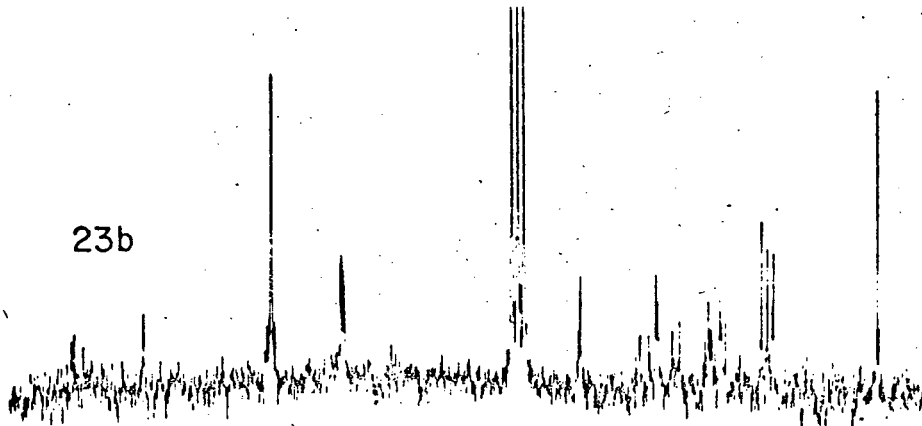
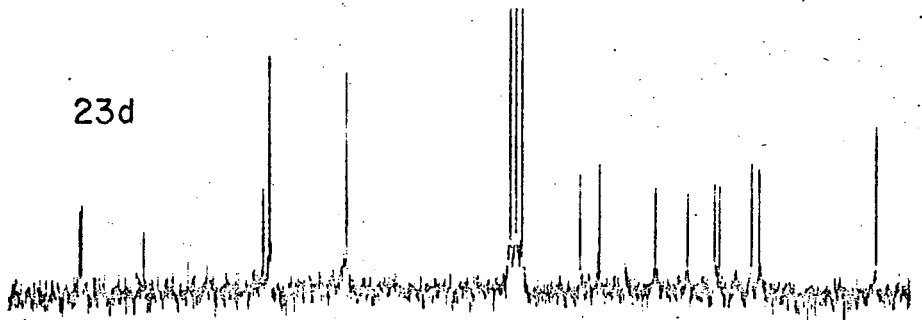
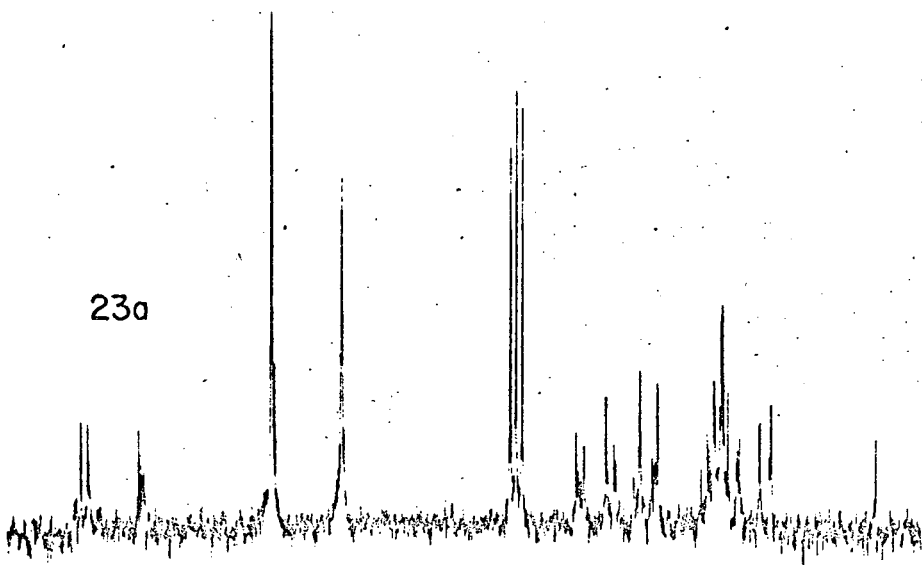
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Table I. Isolated Yields^a of Cyclopeptides from Cyclization of Esters 21.

<u>Ester, 21</u>	<u>Monomer, 4</u>	<u>Dimer, 23</u>	<u>Other neutrals^b</u>	<u>Total</u>
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 5 α -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-methylaminoethylphenoxy)-propanoyl-L-prolyl] $_2$; 23b, cyclo[3-(4- β -N-methylaminoethylphenoxy)-propanoyl-L-leucyl] $_2$; 23d, cyclo[3-(4- β -aminoethylphenoxy)-propanoyl-L-prolyl] $_2$; 23e, cyclo[3-(4- β -aminoethylphenoxy)-propanoyl-L-leucyl] $_2$.



PPM 150 100 50 0.0

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

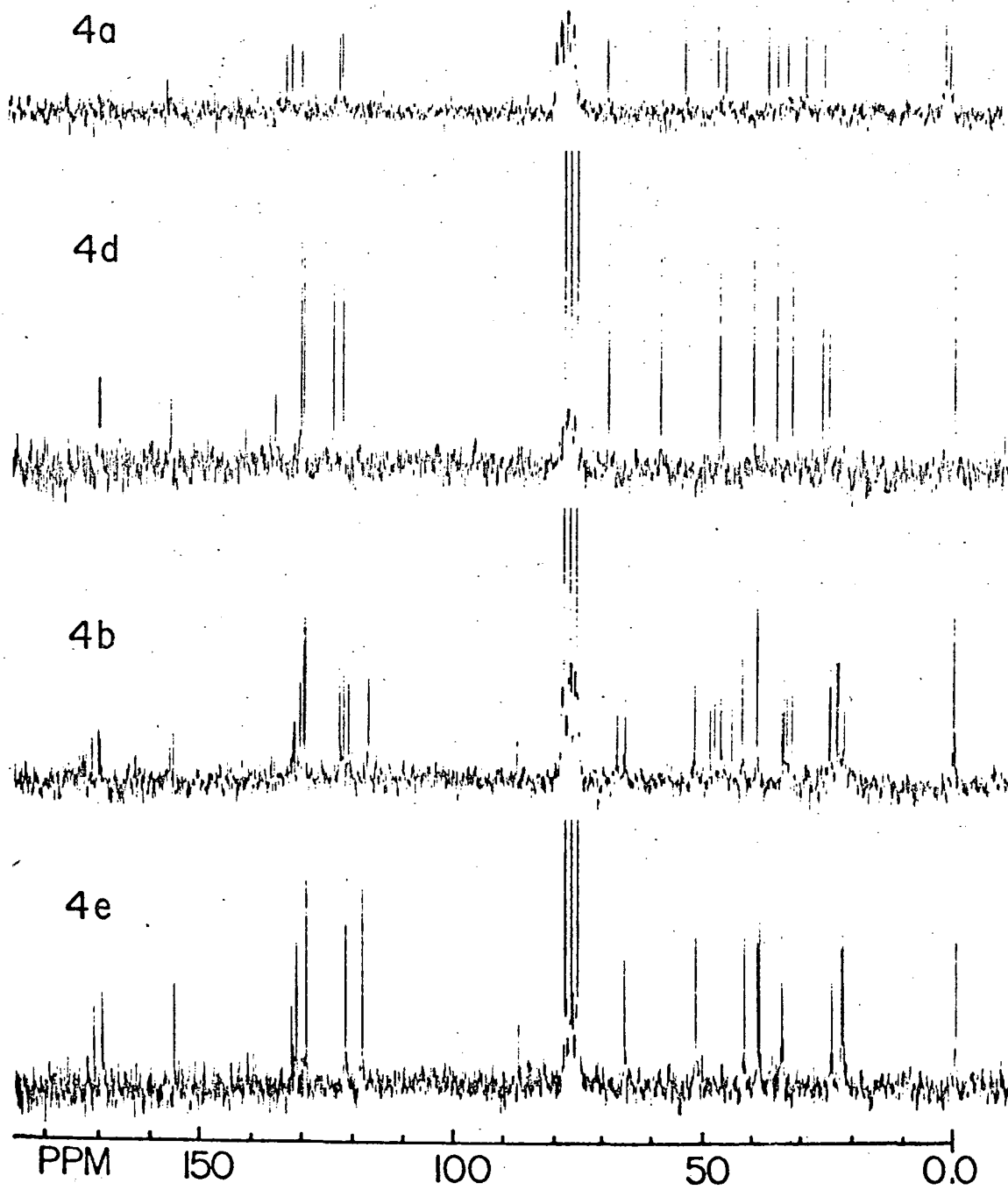


Figure 3. Circular dichroism spectra of cyclo[3-(4- β -amino-ethylphenoxy)-propanoyl-L-prolyl] (4d), 9.4×10^{-4} M in CH_3CN , with various added salts: — · —, no salt added; — · —, 9.4×10^{-3} M NaClO_4 ; — · —, 8.6×10^{-3} M KPF_6 ; ····, 8.3×10^{-3} M LiClO_4 ; ———, 9.2×10^{-4} M $\text{Mg}(\text{ClO}_4)_2$; ---, 1.5×10^{-3} M $\text{Ca}(\text{ClO}_4)_2$.

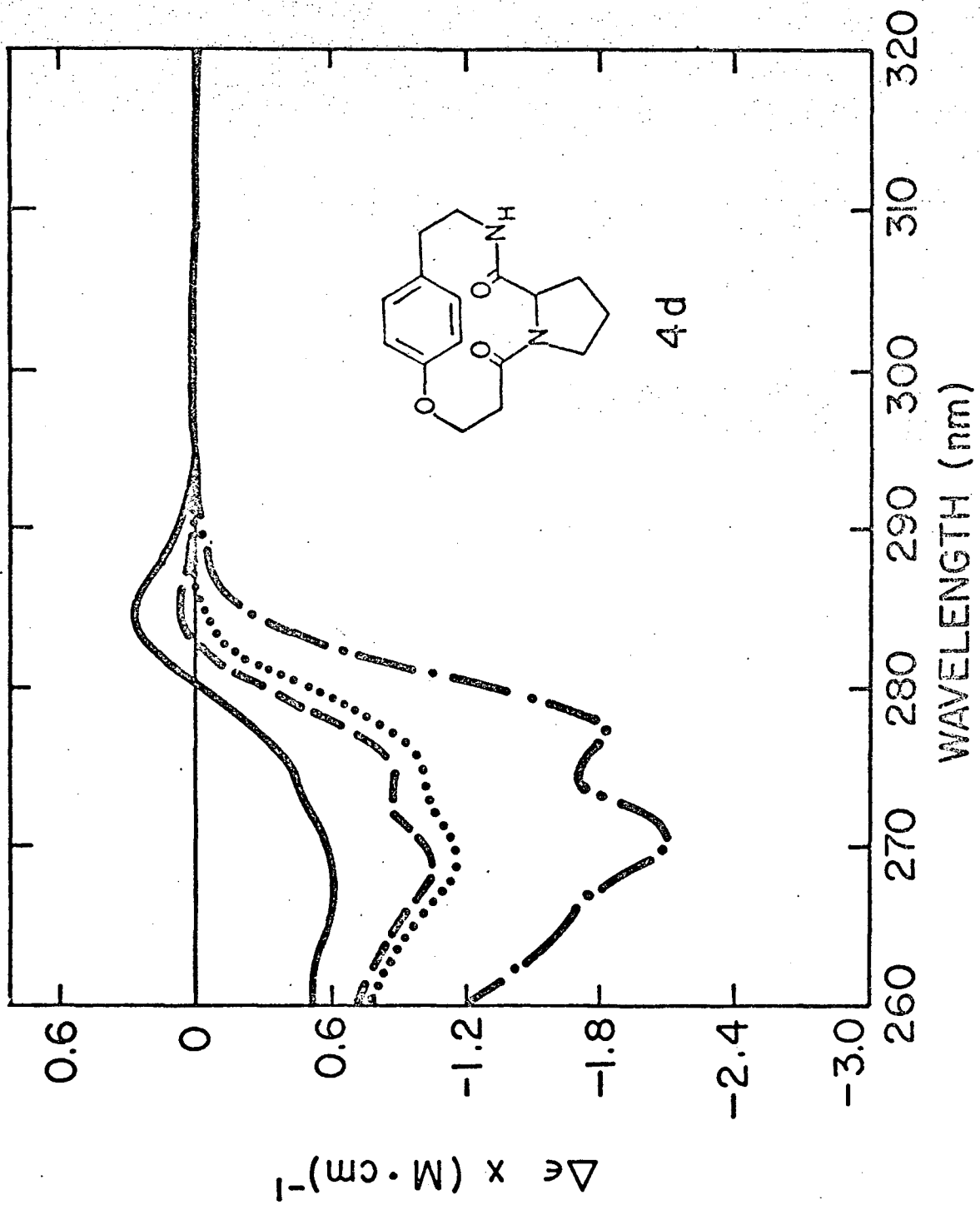


Figure 4. Circular dichroism spectra of cyclo[3-(4- β -amino-ethylphenoxy)propanolyl-L-prolyl] (4d), 9.4×10^{-4} M in CH_3CN with various added salts: — · —, no salt added; — · —, 1.0×10^{-2} M NaClO_4 ; —, 9.3×10^{-3} M $\text{Mg}(\text{ClO}_4)_2$.

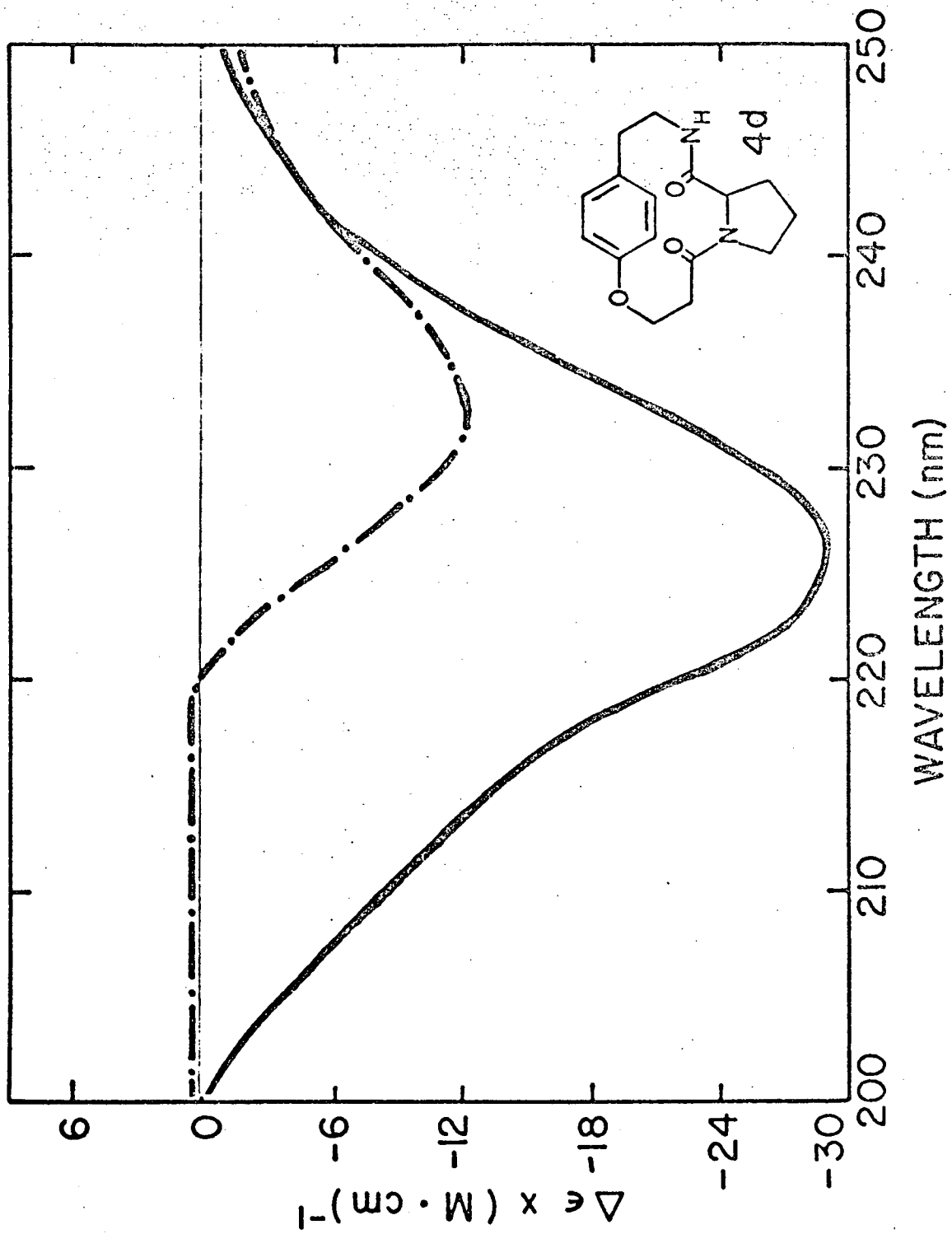


Figure 5. Circular dichroism spectra of ceanothine B, 1.0×10^{-4} M in CH_3CN , with various added salts: — · —, no salt added; — · —, 1.1×10^{-3} M NaClO_4 ; ———, 9.2×10^{-4} M $\text{Mg}(\text{ClO}_4)_2$; ----, 1.5×10^{-3} M $\text{Ca}(\text{ClO}_4)_2$.

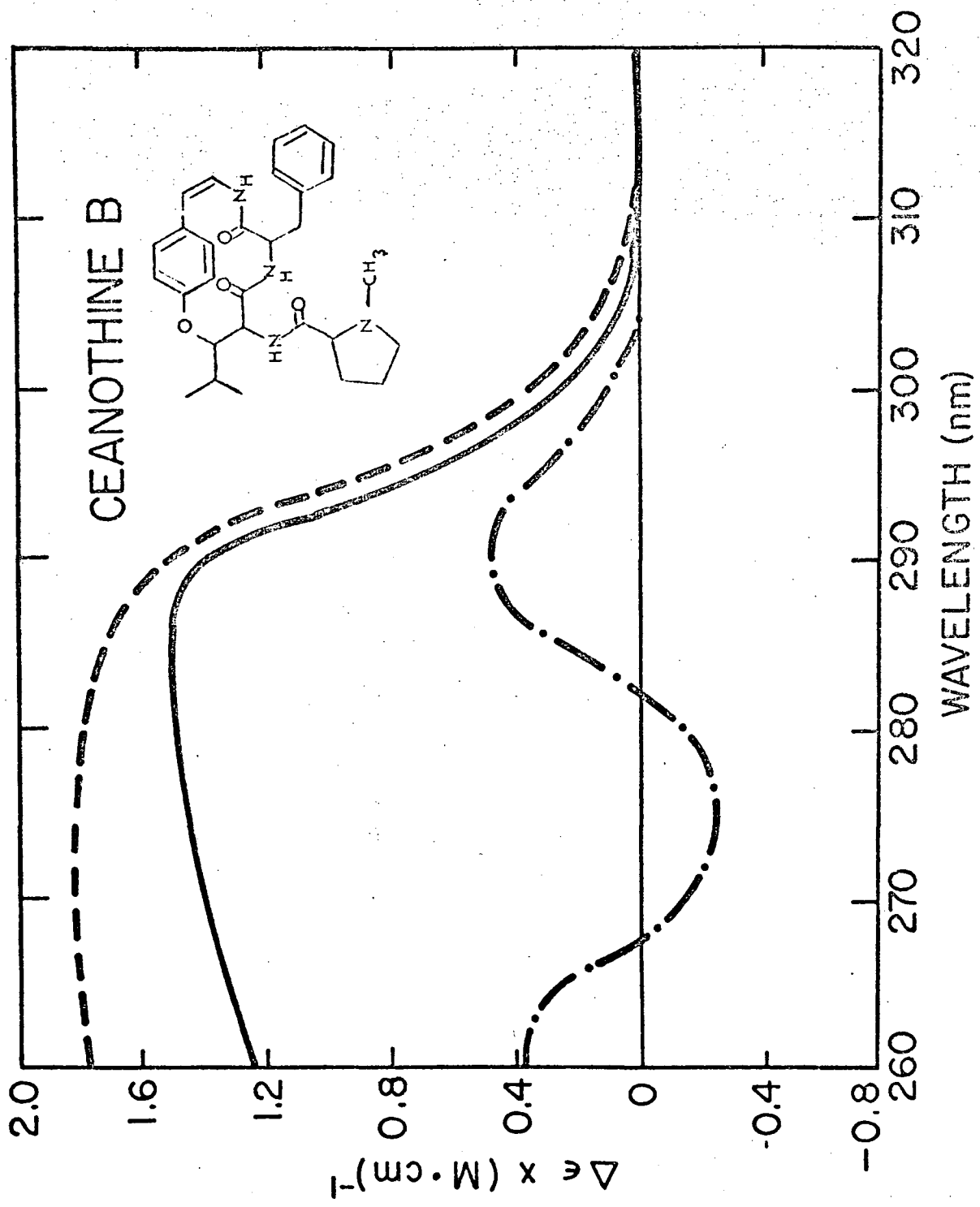
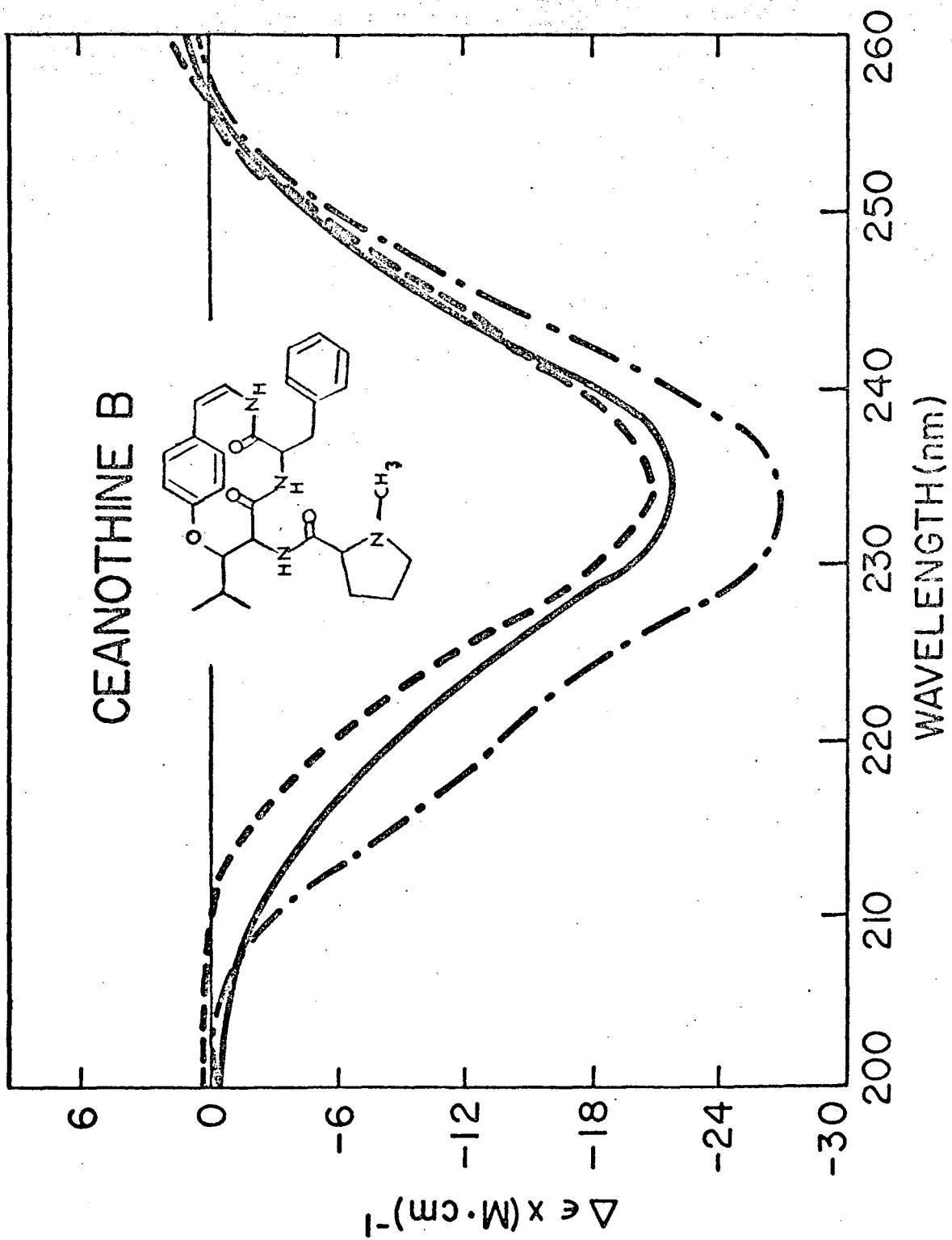
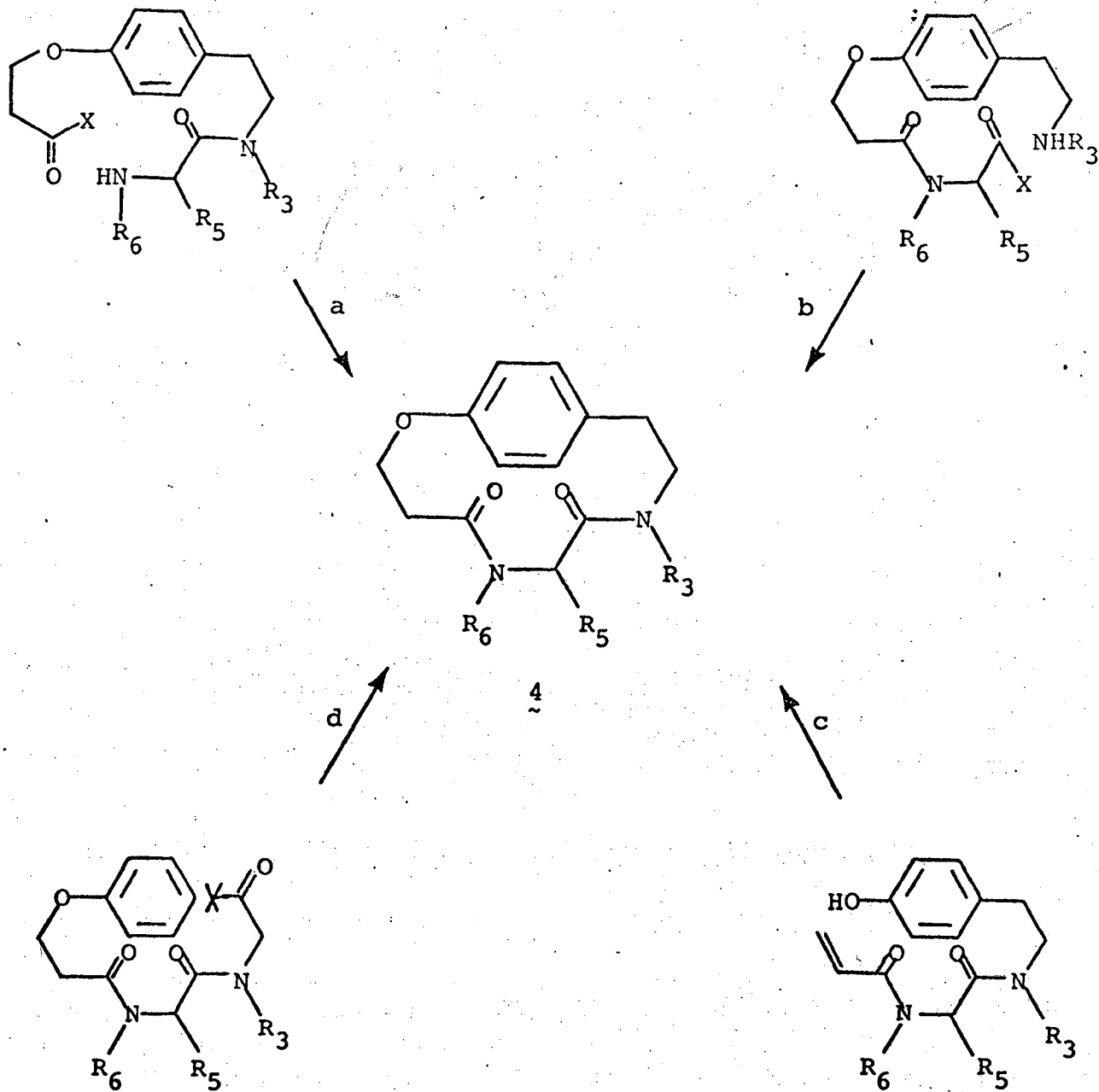


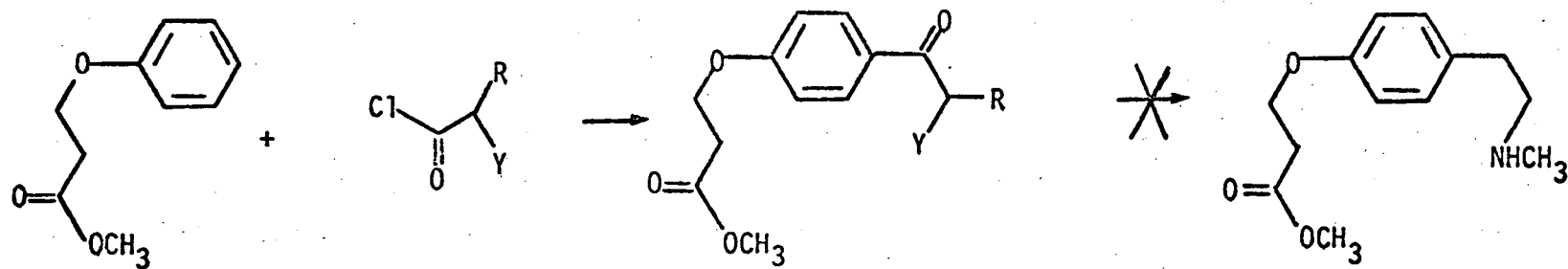
Figure 6. Circular dichroism spectra of ceanothine B, 1.0×10^{-4} M in CH_3CN with various added salts: — · —, no salt added; — · —, 1.1×10^{-3} M NaClO_4 ; —, 9.2×10^{-4} M $\text{Mg}(\text{ClO}_4)_2$; ---, 1.5×10^{-3} M $\text{Ca}(\text{ClO}_4)_2$.



Scheme I. Cyclization Modes for the Preparation of Cyclo-peptide Alkaloids.



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

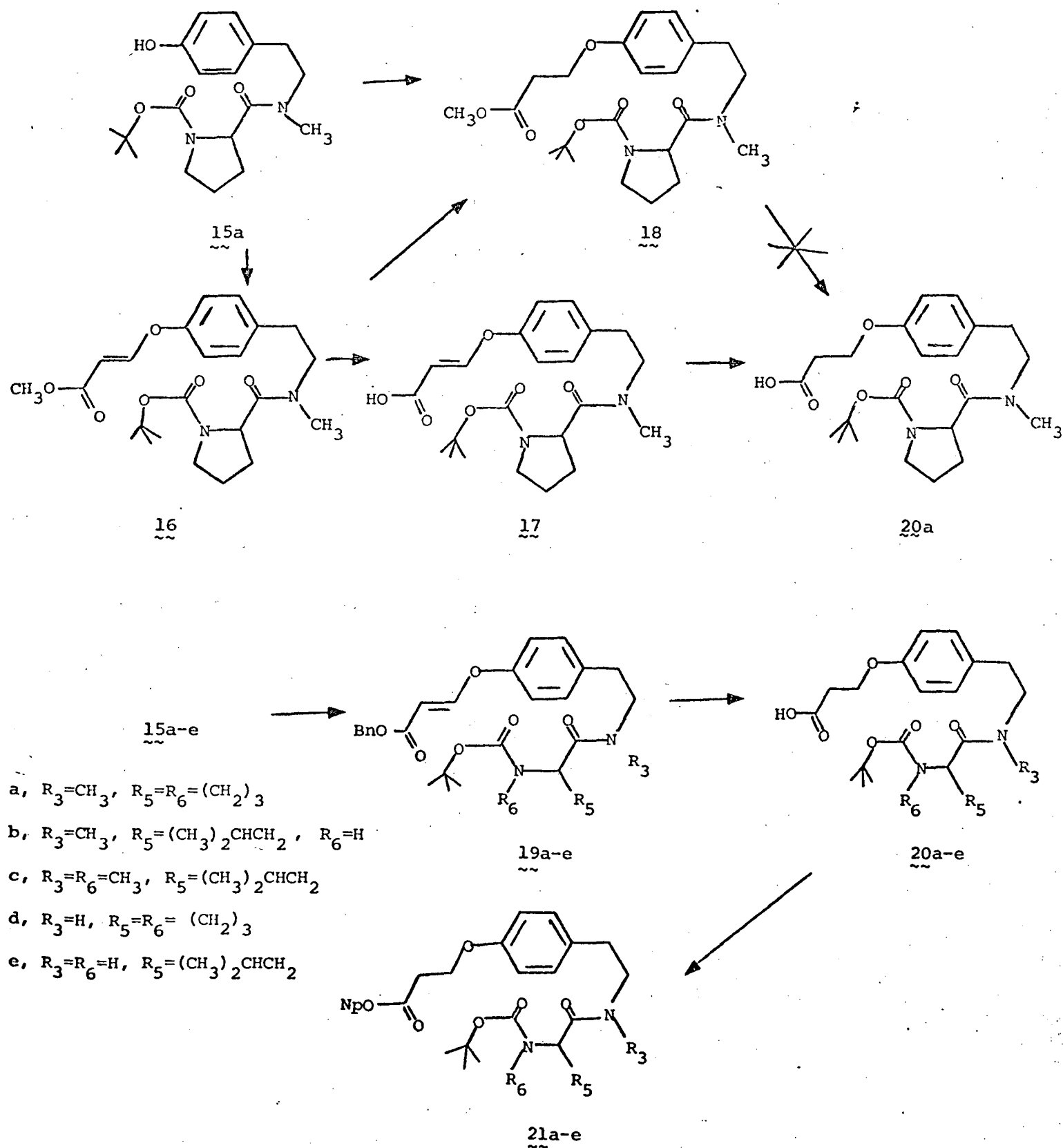


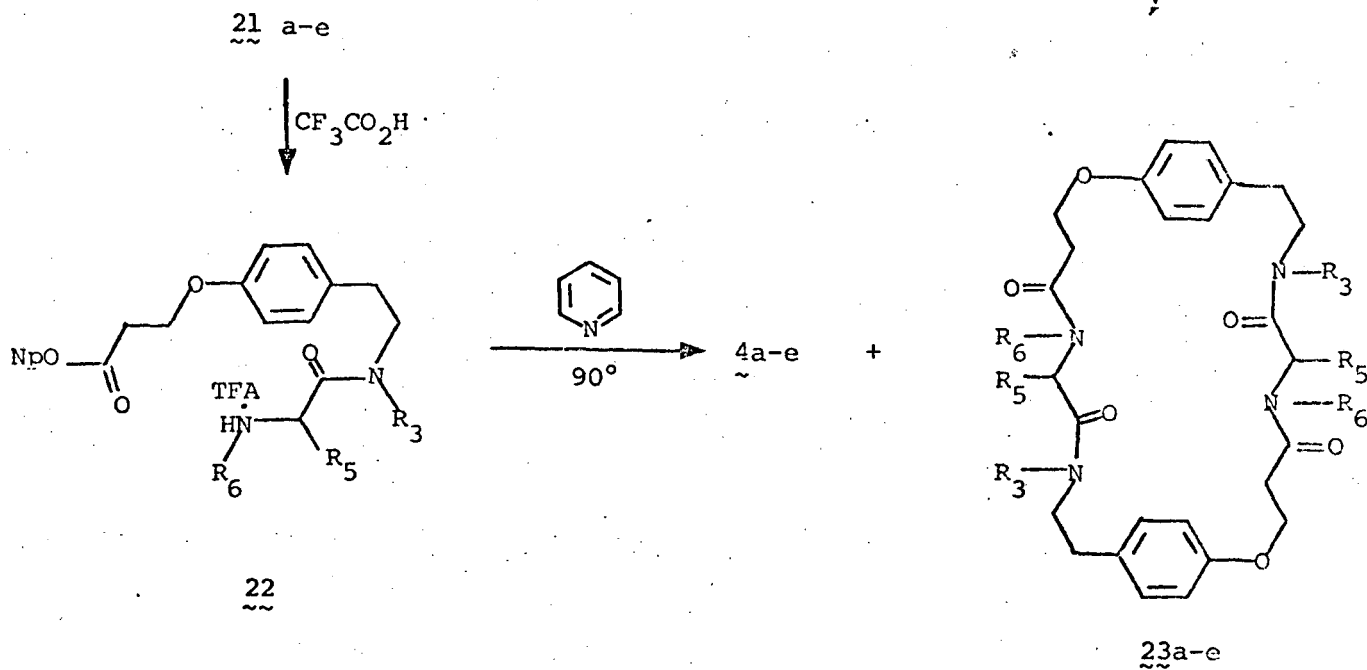
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- 6a, R=Y=H
- 6b, R=Y=CH₃
- 6c, R=H, Y=Br
- 6d, R=H, Y=N(CH₃)COCF₃

- 7a, R=Y=H
- 7b, R=Y=CH₃
- 7c, R=H, Y=Br
- 7d, R=H, Y=NHCH₃•HCl

Scheme III. Incorporation of the Three Carbon Propanoate Residue.



Scheme IV. Peptide Cyclization

Appendix. Elemental Analyses.

Compound	Moi. Formula	Calcd.			Found		
		C	H	N	C	H	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

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

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