of DIEA (1 × 10 min); (13) wash, methylene chloride (3x); (14) wash, ethanol/methylene chloride (1:2; 3x). Recoupling was performed after each coupling of AocArg(Tos). The resulting hexapeptide resin (3.0 g, 0.89 mmol based on the substitution level of the first amino acid attached to the resin) was suspended in 50 mL of trifluoroethanol, which had been saturated at 0 °C with ammonia freshly distilled from sodium. The suspension was sealed in a pressure bottle and shaken for 3 days at room termperature. The flask was then cooled to 0 °C and the trifluoroethanol removed by filtration. The peptide resin was washed several times with methanol, and then the peptide was eluted from the resin with warm DMF. Evaporation of the solvent and trituration of the residue with ether gave 850 mg of peptide (60%). This product was dissolved in 7 mL of DMF, applied to a 2.5 × 80 cm column of LH-20 Sephadex, and eluted with DMF. The major peak corresponding to the appropriate molecular weight was collected, and the solvent was removed under reduced pressure; yield 737 mg (52%). The peptide was still heterogeneous by criteria of TLC, so the product was dissolved in hot methanol, and upon cooling a homogeneous product precipitated: yield 0.42 g (30%); mp 133-136 °C; R_f(F) 0.38, R_f(G) 0.80.

Acknowledgment. We acknowledge financial support by USPHS Program Project HL-18577. We express our appreciation to Dr. Rei Matsueda for many helpful discussions, to Drs. A. B. Shenvi, C. Kettner, J. C. Kauer, and S. Nakagawa, and also to H. P. Tao and J. W. Taylor for careful reading of this manuscript.

Registry No. III, 82190-46-3; IV, 82190-47-4; V, 82198-68-3; VI, 82190-48-5; VII, 82198-69-4; VIII, 38024-17-8; IX, 82190-49-6; Leu-O-*t*-Bu·HCl, 2748-02-9; NPSLeu symmetric anhydride, 82190-50-9; BocSer(Bzl) symmetric anhydride, 64817-69-2; BocGln symmetric anhydride, 68623-39-2; BocGln, 13726-85-7; AocArg(Tos) symmetric anhydride, 76802-47-6; BocLys (2-ClZ) symmetric anhydride, 70889-80-4; *p*-nitrobenzoyl chloride, 122-04-3; melittin, 37231-28-0.

Synthesis of Peptide Alkaloids. 5.[1,2] New Method for Synthesis of Ansa Peptides. Amino Acids and Peptides. 34

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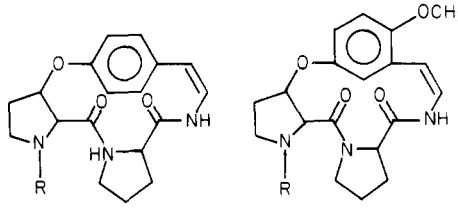
Received December 17, 1981

Fourteen-membered para-ansa copounds and 13-membered meta-ansa compounds have been synthesized by catalytic hydrogenation of the pentafluorophenyl esters of ω-(*Z*)-amino carboxylic acids in 50% and 80% yields, respectively.

Reports on the isolation and structure elucidation of about 100 cyclopeptide alkaloids[3] have appeared during the last 15 years. These compounds typically contain a para or meta ansa bridge consisting of an enamine function and dipeptide of a β-hydroxy amino acid. This structural characteristic is illustrated by zizyphine G (1) or A (2),



1 2

containing a 13- or 14-membered ring, respectively. The synthesis of zizyphine A has been published in a preliminary report.[4]

The cyclic alkaloid peptides have been found in plants of the Rhamnaceae and Sterculiaceae families only. Presumably, the biosynthesis of the β-phenoxy unit happens by radical or ionic addition of the phenol group of tyrosin to the double bond of an α,β-dehydro amino acid. This assumption is supported by the isolation of a "linear" peptide alkaloid from Rhamnaceae containing a free phenolic group and a dehydro amino acid residue. It is interesting that "linear" peptide alkaloids have recently been found in marine sponges.[5] Some of these peptide alkaloids are active against lower fungi and gram-positive bacteria.[3] Discarine B is a specific inhibitor of energy-transfer reactions in chloroplasts.[6] Experimental evidence points to their function as ionophores in plants.[7,8]

Several approaches to the synthesis of peptide alkaloids have been published. The synthesis of analogous but larger 17-membered dihydro ring systems have been described.[9] The ring closure of model systems containing a β-phenoxy carboxylic acid instead of a β-phenoxy amino acid residue was studied.[8,10] The azido and *p*-nitrophenyl ester methods were used for ring formation. In synthesizing peptide alkaloids, the three main difficulties are forming the styrylamino unit, forming the (*S*,*S*)-β-phenoxy amino acid, and the ring closure. A practical solution to the last problem will be given here.

The shortest bridge in a para-ansa compound which can be formed by ring closure of a para-substituted aromatic compound in satisfactory yield contains 10 sp^3-hybridized members.[11] In peptide alkaloids with a 14-membered ring

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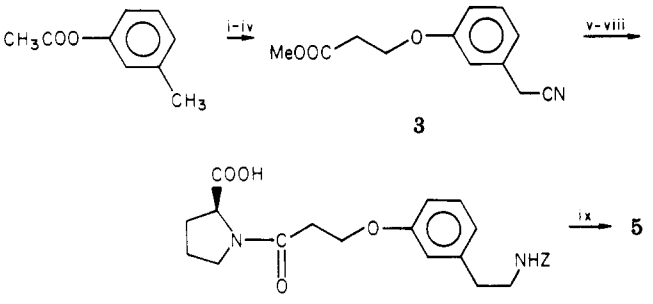
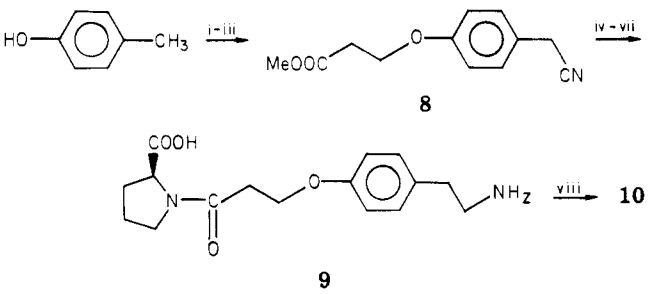
Scheme I[a]



[a] (i) NBS; (ii) $Et_4N^+CN^-$; (iii) NH_3; (iv) CH_2=CHCOOMe; (v) HCl; (vi) Pro-OBZL/DCC; (vii) H_2/Rh; (viii) ZCl; (ix) HOPFP/DCC.

Scheme II[a]



[a] (i) CH_2=CHCOOMe, (ii) NBS, (iii) $Et_4N^+CN^-$, (iv) HCl, (v) Pro-OBZL/DCC, (vi) H_2/Rh, (vii) ZCl, (viii) HOPFP/DCC.

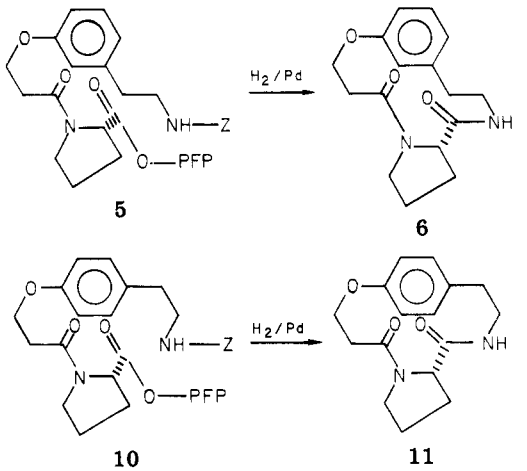
and a 10-membered para bridge the two *s-trans*-amide groups make the system more rigid and thus the synthesis even more difficult. In peptide alkaloids with a 13-membered ring system the 10-membered meta bridge contains one more member than the shortest bridge in a meta-ansa compound.[11] The synthesis of 14-membered peptide alkaloids is indeed much more difficult than the synthesis of 13-membered ones and gives poorer yields.

Up to now the ring closure giving rise to cyclopeptides and ansa peptides has mainly been performed by the nitrophenyl ester method. The disadvantages of this method are a long reaction time and a diffucult separation of the reaction product from a high-boiling solvent (*N,N*-dimethylacetamide), from the base (pyridine), and from trifluoroacetic acid. In addition, the yields are moderate, e.g., 24% only in synthesizing model 11.[8] A similar model with a β-phenoxyhexanoic acid residue was formed in 36% yield.[10] These yields were considered to be too low and the isolation of the reaction product to be too difficult for the synthesis of more complicated systems such as peptid alkaloids.

Results

We have developed a new cyclization method for synthesizing cyclopeptides, particularly applicable in the field of 13- and 14-membered ansa peptides. The main feature of this method is the catalytic hydrogenation of carbobenzoxy–peptide–pentafluorophenyl esters on Pd/charcoal. Using the model compounds **5** and **10**, the synthesis of which is described in Schemes I and II, we obtained the 14-membered ring in 50% yield and the 13-membered ring in a yield up to 80%. **11** and modified models with a substituent on the phenylethylamine nitrogen and other amino acids instead of proline were synthesized by Rapoport and cyclisized by using the nitrophenyl ester method. The best yield of **11** and its *N*-methyl derivative was 24% after isolation by Sephadex chromatography.[8]

The conditions giving optimal yields are very limited. The most suitable solvent is dioxane with addition of a catalytic amount of pyrrolidinopyridine and 2% ethanol. The reaction temperature should exceed 90 °C. If it is lower (75 °C) and the reaction is carried out in ethyl acetate, the dimeric cyclopeptide **11** will be obtained in 45% yield. Alumina of low-absorption activity is added to remove pentafluorophenol formed from the reaction solution. Compared with similar cyclizations, the reaction time is rather short. It amounts to 5 h for the ring closure to form **11** and to only 0.5 h for **6**, but under condition of



dilution. This suggests that the reaction proceed on the surface of the palladium catalyst. It is likely that on the surface of palladium an amino group is adsorbed tighter than an amide group; after hydrogenolytic deblocking of the carbobenzoxy group, the amino function remains on the surface until ring formation with the activated carboxylic function is accomplished. This process favors an intramolecular reaction.

The workup is very easy. After filtration and concentration, chromatography of the residue on silica gel gives the cyclopeptide which is easily separated from its dimer. To optimize the reaction conditions, one can determine the yields of **6** and **11** by gas chromatography.

Racemization amounted to about 2–3%. In forming (*S*)-**11** from (*S*)-**10**, the racemate (*RS*)-**11** precipitated from the solution of the chromatographically pure reaction product. (*RS*)-**11** and (*S*)-**11** have the same spectra and retention times as determined by GC/MS. (*RS*)-**11** crystallized in space group $P2_1/c$; from its center of symmetry this must be the racemate (a = 11.28 Å, b = 14.70 Å, c = 12.60 Å, β = 134.1°, Z = 4) (determined by Dr. J. J. Stezowski). Unfortunately Rapoport did not characterize his compound **11** by optical rotation. On comparison of his CD values for **11**[8] with the CD value of our compound, about 6–7% racemization in the ring-closure reaction by the *p*-nitrophenyl ester method is obvious.

Experimental Section

Melting points (Kofler) are uncorrected. ^{1}H NMR spectra were recorded on Varian T 60, Bruker Spectrospin 80-MHz, and Bruker Spectrospin 250-MHz spectrometers. A MAT 711 was used for determining mass spectra. The gas chromatography was done on a Carlo Erba Frakto Vap, Series 4160, fitted with a HMDS/DPTMDS SE 52 20 m × 0.15 μm column. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. UV spectra were performed with a Zeiss BMR 10 and CD spectra with a JASCO J 500 A. TLC was done on silica (Merck silica 60 F_{254} sheets), and medium-pressure column chromatography used

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Merck Lichroprep Si 60 (15–25 μm). The dioxane for the ring closure reaction was filtered through basic aluminum oxide and distilled from sodium benzophenone ketyl.

Methyl 3-[(4-Methylphenyl)oxy]propanoate. A mixture of *p*-cresol (108.14 g, 1 mol), hydroquinone (0.2 g), sodium (0.8 g), and 500 mL of methyl acrylate was boiled under reflux for 100 h. After neutralization with acetic acid and evaporation of the excess methyl acrylate in vacuo, the residue was dissolved in 400 mL of ether, washed with water (2 × 300 mL), and dried. Filtration, evaporation, and distillation afforded pure methyl 3-[(4-methylphenyl)oxy]propanoate: 132.7 g (68%); bp 80–86 °C (0.05 mm); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.25 (s, 3 H), 2.67 (t, 2 H, J = 7 Hz), 3.63 (s, 3 H), 4.10 (t, 2 H, J = 7 Hz), 6.76 (d, 2 H, J = 9 Hz), 7.04 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26; Found: C, 67.99; H, 7.36.

Methyl 3-[[4-(Bromomethyl)phenyl]oxy]propanoate. A mixture of methyl 3-[(4-methylphenyl)oxy]propanoate (97.11 g, 0.5 mol), *N*-bromosuccinimide (89 g, 0.5 mol), and 2,2′-azobis-(isobutyronitrile) (0.5 g, 3.05 mmol) was stirred under reflux in 850 mL of CCl_4. After termination of the reaction (indicated by the complete formation of succinimide) the cold reaction mixture was filtered and evaporated in vacuo. Recrystallization from petroleum ether yielded methyl 3-[[(4-(bromomethyl)phenyl]-oxy]propanoate: 89.7 g (66%); mp 63–65 °C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.80 (t, 2 H, J = 7 Hz), 3.75 (s, 3 H), 4.25 (t, 2 H, J = 7 Hz), 4.50 (s, 2 H), 6.86 (d, 2 H, J = 9 Hz), 7.32 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.80; Br, 29.26. Found: C, 48.14; H, 4.78; Br, 29.27.

Methyl 3-[[4-(Cyanomethyl)phenyl]oxy]propanoate (8). Methyl 3-[[4-(bromomethyl)phenyl]oxy]propanoate (81.94 g, 0.3 mol) and tetraethylammonium cyanide (48.9 g, 0.31 mol) were dissolved in 700 mL of absolute CH_2Cl_2 and stirred for 24 h at 20 °C. Evaporation of the solvent and distillation afforded methyl 3-[[4-(cyanomethyl)phenyl]oxy]propanoate (8) as a pale yellow solid: 50.5 g (77%); bp 105 °C (0.001 mm); mp 43 °C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.80 (t, 2 H, J = 7 Hz), 3.70 (s, 2 H), 3.75 (s, 3 H), 4.27 (t, 2 H, J = 7 Hz), 6.94 (d, 2 H, J = 9 Hz), 7.29 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.97; N, 6.39. Found: C, 65.78; H, 5.95; N, 6.36.

3-[[4-(Cyanomethyl)phenyl]oxy]propionic Acid. Methyl 3-[[4-(cyanomethyl)phenyl]oxy]propanoate (15.35 g, 70 mmol) was added to 750 mL of HCl (19%). This heterogeneous mixture was heated under stirring until solution was complete, cooled to room temperature, and extracted with ethyl acetate (2 × 200 mL). After extraction of the organic phase with saturated $NaHCO_3$ solution (2 × 200 mL), the water layer was acidified with HCl and extracted again with ethyl acetate (3 × 200 mL). The combined organic layers were washed with saturated NaCl solution, dried, and evaporated. Recrystallization of the residue from water yielded 3-[[4-(cyanomethyl)phenyl]oxy]propionic acid: 13 g (91%); mp 124 °C; ^{1}H NMR (Me_2SO-d_6, Me_4Si) δ 2.72 (t, 2 H, J = 7 Hz), 3.97 (s, 2 H), 4.20 (t, 2 H, J = 7 Hz), 6.97 (d, 2 H, J = 9 Hz), 7.32 (d, 2 H, J = 9 Hz), 12.33 (s, 1 H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 63.89; H, 5.42; N, 6.50.

Benzyl Ester of *N*-[3-[[4-(Cyanomethyl)phenyl]-propanoyl]-L-proline. To a solution of 3-[[4-(cyanomethyl)-phenyl]oxy]propionic acid (8.21 g, 40 mmol) and L-proline benzyl ester (8.23 g, 40 mmol) in 150 mL of CH_2Cl_2 was added *N*,*N*′-dicyclohexylcarbodiimide (8.25 g, 40 mmol) at 0 °C. The solution was kept at 0 °C for 4 h and at 20 °C for 12 h, filtered, washed with 1 N HCl (100 mL) and with saturated $NaHCO_3$ (100 mL), dried, and evaporated. Filtration of the residue with ethyl acetate on silica gel, concentration, and drying in vacuo yielded the benzyl ester of *N*-[3-[[4′-(cyanomethyl)phenyl]oxy]propanoyl]-L-proline: 15.5 g (98%); mp 65 °C; $[\alpha]^{20}_D$ −49.7° (*c* 1.33, ethanol); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.33 (m, 6 H), 3.58 (m, 4 H), 4.42 (m, 3 H), 5.17 (s, 2 H), 6.89 (d, 2 H, J = 9 Hz), 7.24 (d, 2 H, J = 9 Hz), 7.40 (s, 5 H). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.18; H, 6.39; N, 7.04.

***N*-[3-[[4-[β-[(Benzyloxycarbonyl)amino]ethyl]phenyl]-oxy]propanoyl]-L-proline (9).** A mixture of 140 mL of ethanol, 95 mL of water, and 7 mL of HCl (25%) containing the benzyl ester of *N*-[3-[[4-(cyanomethyl)phenyl]oxy]propanoyl]-L-proline (7.85 g, 20 mmol) and 1.9 g of PdO was hydrogenated at 3 atm. After filtration of the PdO, the solution was neutralized with 1 N NaOH and the volume reduced in vacuo. The residue was dissolved in 500 mL of water, and 10.5 mL of 2 N NaOH was added. After filtration of insoluble material, the solution was cooled to 0 °C, and benzyl chloroformate (2.85 mL, 20 mmol) was added under stirring. the reaction mixture was maintained at 0 °C for an additional 4 h, extracted with ether (2 × 300 mL), and acidified with 1 N $NaHSO_4$. Extraction with ethyl acetate (2 × 300 mL) followed. The combined organic layers were dried, filtered, evaporated, and pumped at 10^{-3} mm for 2 h to yield *N*-[3-[[4-[β-[(benzyloxycarbonyl)amino]ethyl]phenyl]oxy]-propanoyl]-L-proline (9): 6.2 g (70%); $[\alpha]^{20}_D$ −32.6° (*c* 0.8, ethanol); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.32 (m, 8 H), 3.5 (m, 4 H), 4.35 (m, 3 H), 5.08 (s, 2 H), 6.80 (d, 2 H, J = 9 Hz), 7.37 (d, 2 H, J = 9 Hz), 8.12 (s, 2 H). Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.43; H, 6.41; N, 6.36. Found: C, 64.51; H, 6.77; N, 5.89.

Pentafluorophenyl Ester of *N*-[3-[[4-[β-[(Benzyloxy-carbonyl)amino]ethyl]phenyl]oxy]propanoyl]-L-proline (10). *N*,*N*′-Dicyclohexylcarbodiimide (0.62 g, 3 mmol) was added to a solution of *N*-[3-[[4-[β-[(benzyloxycarbonyl)amino]ethyl]-phenyl]oxy]propanoyl]-L-proline (9; 1.32 g, 3 mmol) and pentafluorophenol (0.61 g, 3.3 mmol) in 25 mL of absolute ethyl acetate at 0 °C, and the mixture was stirred at 0 °C for 1 h and at 20 °C for 2 h. After removal of urea by filtration and evaporation of the solvent, the residue was filtered on silica gel (petroleum ether/ethyl acetate 7:3), affording the pentafluorophenyl ester of *N*-[3-[[4-[β-[(benzyloxycarbonyl)amino]ethyl]phenyl]oxy]-propanoyl]-L-proline (10): 1.47 g (81%); mp 86 °C; $[\alpha]^{20}_D$ −48.7° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.2 (m, 4H), 2.79 (m, 4 H), 3.5 (m, 4 H), 4.3 (m, 2 H), 4.82 (m, 2 H), 5.10 (s, 2 H), 6.87 (d, 2 H, J = 9 Hz), 7.05 (d, 2 H, J = 9 Hz), 7.38 (s, 5 H). Anal. Calcd for $C_{30}H_{27}F_5N_2O_6$: C, 59.40; H, 4.49; N, 4.62. Found: C, 59.16; H, 4.65; N, 4.40.

3-Acetoxybenzyl Bromide. A solution of 3-acetoxytoluene (59.49 g, 0.4 mol) and *N*-bromosuccinimide (85.4 g, 0.48 mol) in 1400 mL of boiling CCl_4 was irradiated with a tungsten lamp for 16 h. Filtration of the succinimide from the cold reaction solution, evaporation of the solvent under reduced pressure, and distillation afforded 3-acetoxybenzyl bromide: 53 g (58%); bp 72–78 °C (0.01 mm); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.27 (s, 3 H), 4.45 (s, 2 H), 7.17 (m, 4 H). Anal. Calcd for $C_9H_9BrO_2$: C, 47.18; H, 3.96; Br, 34.89. Found: C, 47.20; H, 3.95; Br, 34.78.

3-Hydroxybenzyl Cyanide. To 3-acetoxybenzyl bromide (32.1 g, 0.14 mol) in 100 mL of absolute CH_2Cl_2 was added a solution of tetraethylammonium cyanide (28.4 g, 0.18 mol) in 50 mL of absolute CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 20 °C for 24 h and washed with water. The organic layer was dried and evaporated. After filtration of the residue on silica gel (100 g; petroleum ether/ethyl acetate 7:3), the filtrate was reduced in vacuo. The resulting 3-acetoxybenzyl cyanide was dissolved in 100 mL of C_2H_5OH saturated with ammonia and the mixture stirred for 12 h at 20 °C, followed by evaporation of the solvent, solution of the residue in 150 mL of $CHCl_3$, and extraction with water (3 × 100 mL). The organic layer was dried and concentrated, and distillation yielded 3-hydroxybenzyl cyanide: 11.72 g (63%); bp 106 °C (0.03 mm); mp 54–55 °C; ^{1}H NMR ($CDCl_3$, Me_4Si) δ 3.65 (s, 2 H), 7.0 (m, 5 H). Anal. Calcd for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.93; H, 5.50; N, 10.24.

Methyl 3-[[3-(Cyanomethyl)phenyl]oxy]propanoate (3). A mixture of 3-hydroxybenzyl cyanide (6 g, 45 mmol), hydroquinone (0.01 g), sodium (0.07 g), and 60 mL of methyl acrylate was boiled under reflux for 24 h. After neutralization with acetic acid and evaporation of the excess methyl acrylate in vacuo, the residue was dissolved in $CHCl_3$, washed with water, and dried. Filtration, evaporation, and distillation afforded 3: 7.5 g (76%); bp 140 °C (0.03 mm); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.77 (t, 2 H, J = 7 Hz), 3.67 (s, 2 H), 3.72 (s, 3 H), 4.20 (t, 2 H, J = 7 Hz), 7.0 (m, 4 H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.97; N, 6.39. Found: C, 65.94; H, 6.15; N, 6.14.

The workup for the following synthetic steps is identical with that of the corresponding para compounds.

3-[[3-(Cyanomethyl)phenyl]oxy]propionic Acid. Methyl 3-[[3-(cyanomethyl)phenyl]oxy]propanoate (3; 4.38 g, 20 mmol) in 400 mL of HCl (19%) was heated under stirring until solution was complete. After the usual workup the yield of 3-[[3-(cyanomethyl)phenyl]oxy]propionic acid was 3.98 g (97%): mp 94 °C (H_2O); ^{1}H NMR (Me_2SO-d_6, Me_4Si) δ 2.67 (t, 2 H, J = 7 Hz), 3.97 (s, 2 H), 4.15 (t, 2 H, J = 7 Hz), 7.03 (m, 4 H), 12.33 (s, 1

H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.13; H, 5.51; N, 6.60.

Benzyl Ester of *N*-[3-[[3-(Cyanomethyl)phenyl]oxy]propanoyl]-L-proline. *N,N*-Dicyclohexylcarbodiimide (3.71 g, 18 mmol) was added to a solution of 3-[[3-(cyanomethyl)-phenyl]oxy]propionic acid (3.69 g, 18 mmol) and L-proline benzyl ester (4.36 g, 18 mmol) in 70 mL of absolute CH_2Cl_2 at 0 °C. The workup afforded the benzyl ester of *N*-[3-[[3-(cyanomethyl)-phenyl]oxy]propanoyl]-L-proline: 4.6 g (65%); $[\alpha]^{20}_D$ −57.7° (*c* 0.9, ethanol); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.97 (m, 4 H), 2.78 (t, 2 H, *J* = 7 Hz), 3.57 (m, 4 H), 4.32 (m, 3 H), 5.13 (s, 2 H), 6.8 (m, 3 H), 7.21 (m, 6 H). Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.20; H, 6.30; N, 6.92.

***N*-[3-[[3-[β-[(Benzyloxycarbonyl)amino]ethyl]phenyl]-oxy]propanoyl]-L-proline (4).** The benzyl ester of *N*-[3-[[3-(cyanomethyl)phenyl]oxy]propanoyl]-L-proline (3.14 g, 8 mmol) was dissolved in a mixture of 80 mL of ethanol, 50 mL of H_2O and 2 mL of HCl (25%) and hydrogenated at 3 atm in presence of 1.0 g of PdO. Acylation with benzyl chloroformate (1.4 mL, 9.8 mmol), the usual workup, and chromatography on silica gel (9:1 CH_2Cl_2/CH_3OH) afforded, **4**: 2.64 g (75%); $[\alpha]^{20}_D$ −37.8° (*c* 0.85, ethanol); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.0 (m, 5 H), 2.7 (m, 4 H), 3.45 (m, 4 H), 4.31 (m, 3 H), 5.05 (s, 2 H), 6.65 (m, 3 H), 7.14 (m, 6 H), 10.28 (s, 1 H). Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 62.86; H, 6.60; N, 6.11. Found: C, 62.53; H, 6.28; N, 5.93.

Pentafluorophenyl Ester of *N*-[3-[[3-[β-[(Benzyloxy-carbonyl)amino]ethyl]phenyl]oxy]propanoyl]-L-proline (5). *N,N'*-Dicyclohexylcarbodiimide (2.89 g, 14 mmol) was added to a solution of **4** (6.17 g, 14 mmol) and pentafluorophenol (2.94 g, 16 mmol) in 100 mL of absolute ethyl acetate at 0 °C. The usual workup by filtration on silica gel (petroleum ether/ethyl acetate, 1:3) afforded **5**: 5.3 g (62%); $[\alpha]^{20}_D$ −52.3° (*c* 1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 2.22 (m, 4 H), 2.77 (m, 4 H), 3.58 (m, 4 H), 4.32 (m, 2 H), 4.81 (m, 2 H), 5.12 (s, 2 H), 6.74 (m, 3 H), 7.21 (m, 6 H). Anal. Calcd for $C_{30}H_{27}F_5N_2O_6$: C, 59.40; H, 4.49; N, 4.62. Found: C, 59.00; H, 4.77; N, 4.82.

***cyclo*-[*N*-[3-[[4-(β-Aminoethyl)phenyl]oxy]propanoyl]-L-prolyl] (11) and *cyclo*-[*N*-[3-[[3-β-Aminoethyl)phenyl]-oxy]propanoyl]-L-prolyl] (6).** To a rapidly stirred solution of 350 mL of dioxane (90 °C) containing 8 mL of absolute C_2H_5OH, 4-pyrrolidinopyridine (40 mg, 0.27 mmol), and Pd/activated charcoal (0.6 g, 5%) was injected a solution of pentafluorophenyl ester **10** or **5** (165 mg, 0.27 mmol) in 22 mL of dioxane continuously over a period of 5 h. In the case of pentafluorophenyl ester **5** the injection time could be reduced to only 0.5 h. At the same time hydrogen was passed through the reaction solution. Stirring was continued for 1 h. The cold reaction solution was filtered and evaporated in vacuo. Chromatography of the residue on silica gel in CH_2Cl_2/CH_3OH (98/2) afforded compound **11** (39 mg, 50%) or compound **6** (62 mg, 80%), respectively. The yields were identical with those determined by gas chromatography. Cyclopeptide **6** was obtained as a solid optically pure material. After solution of cyclopeptide **11** in absolute ether, a solid racemic product (2 mg, mp 202–205 °C) precipitated. The mother liquor was removed in vacuo, leaving **11** as an optically pure oily material (37 mg). The racemate and *S* enantiomer had the same spectra and retention times as those determined by GC/MS. There could be observed only traces of the dimeric cyclopeptide 11_2. Both monomeric cyclopeptides **6** and **11** could be sublimed at 180 °C (0.001 mm). When larger amounts of the pentafluorophenyl esters **5** or **10** were cyclized, basic aluminum oxide (deactivated with 30% C_2H_5OH) was added to the reaction solution now containing catalytic amounts of 4-pyrrolidinopyridine only. For example, pentafluorophenyl ester **5** (3 g, 4.95 mmol) was injected into a mixture of 550 mL of dioxane and 15 mL of C_2H_5OH containing 4-pyrrolidinopyridine (70 mg, 0.47 mmol), 2.5 g of Pd/activated charcoal, and 30 g of basic aluminum oxide (30% C_2H_5OH).

Cyclopeptide 11: $[\alpha]^{20}_{546}$ −28.1° (*c* 0.56, ethanol); R_f 0.24 (CH_2Cl_2/CH_3OH, 98:2); GC t_R (217 °C) 33 min; CD $\Delta_{\epsilon_{max}}$ (λ_{max}, nm) −14.3 (235), −2.42 (272), −2.02 (278); UV λ_{max} (271 nm (ε 665.5), 276 (556.6); MS (70 eV), *m/e* (relative intensity) 289 (4), 288 (21), 70 (100); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.51 (m, 1 H), 1.91 (m, 1 H), 2.10 (m, 1 H), 2.17 (dd, 1 H, *J* = 6, 16 Hz), 2.34 (m, 1 H), 2.71 (dd, 1 H, *J* = 10, 17 Hz), 2.88 (m, 3 H), 3.28 (dd, 1 H, *J* = 10, 17 Hz), 3.46 (t, 1 H, *J* = 9 Hz), 3.74 (m, 1 H), 4.23 (m, 2 H), 4.58 (t, 1 H, *J* = 10 Hz), 6.31 (m, 1 H), 6.81 (s, 2 H), 7.13 (dd, 2 H, *J* = 8, 16 Hz). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.71. Found: C, 66.41; H, 6.93; N, 9.72.

Cyclopeptide 6: mp 166–168 °C; $[\alpha]^{20}_{364}$ −50°, $[\alpha]^{20}_{578}$ −4.1° (*c* 0.4, ethanol); R_f 0.24 (CH_2Cl_2/CH_3OH, 98:2); GC t_R (219 °C) 34 min; MS (70 eV), *m/e* (relative intensity) 289 (4), 288 (20), 70 (100); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.62 (m, 1 H), 1.88 (m, 2 H), 2.32 (m, 1 H), 2.44 (dd, 1 H, *J* = 6, 14 Hz), 2.59 (m, 1 H), 2.86 (m, 2 H), 3.12 (m, 1 H), 3.36 (m, 2 H), 3.78 (m, 1 H), 4.35 (m, 1 H), 4.57 (d, 1 H, *J* = 8 Hz), 4.88 (t, 1 H, *J* = 11 Hz), 6.75 (m, 3 H), 7.0 (m, 1 H), 7.16 (m, 1 H). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.71. Found: C, 66.53; H, 6.96; N, 9.72.

***cyclo*-Bis[*N*-[3-[[4-(β-aminoethyl)phenyl]oxy]-propanoyl]-L-prolyl] (11_2).** Cyclizing pentafluorophenyl ester **10** (165 mg, 0.27 mmol) in pure ethyl acetate 350 mL containing 4-pyrrolidinopyridine (35 mg, 0.27 mmol) and Pd/activated charcoal (600 mg, 5%) gave cyclic dimer $(11)_2$ as the major product (35 mg, 45%). Only small amounts of cyclic monomer **11** (1.6 mg, 2%) were obtained. For 11_2: mp 252 °C; R_f 0.06 (CH_2Cl_2/CH_3OH, 98:2); $[\alpha]^{20}_{364}$ −98°, $[\alpha]^{20}_{378}$ −11° (*c* 0.05, ethanol); MS (70 eV), *m/e* (relative intensity) 576 (3.7), 288 (30), 70 (100). Anal. Calcd for $C_{32}H_{40}N_4O_6$: C, 66.65; H, 6.99; N, 9.71. Found: C, 66.51; H, 6.99; N, 9.52.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the BASF AG, and the Deutsche Forschungsgemeinschaft for their generous support of this research, Dr. W. Rozdzinski for recording numerous mass spectra, Professor Dr. H. Rau for recording the CD spectrum, and Degussa A.G. for the gift of amino acids and noble-metal catalysts.

Registry No. **3**, 82134-66-5; **4**, 82134-67-6; **5**, 82134-68-7; **6**, 78003-67-5; **8**, 82134-69-8; **9**, 82134-70-1; **10**, 76847-29-5; (±)-**11**, 82188-45-2; (*S*)-**11**, 69100-22-7; 11_2, 68898-96-4; methyl 3-[(4-methylphenyl)oxy]propanoate, 7497-92-9; methyl 3-[[4-(bromomethyl)phenyl]oxy]propanoate, 82134-71-2; 3-[[4-(cyanomethyl)-phenyl]oxy]propionic acid, 82134-72-3; *N*-[3-[[4-(cyanomethyl)-phenyl]oxy]propanoyl]-L-proline benzyl ester, 82134-73-4; 3-acetoxybenzyl bromide, 49617-80-3; 3-hydroxybenzyl cyanide, 25263-44-9; 3-[[3-(cyanomethyl)phenyl]oxy]propionic acid, 82134-74-5; *p*-cresol, 106-44-5; methyl acrylate, 96-33-3; L-proline benzyl ester, 41324-66-7; pentafluorophenol, 771-61-9; 3-acetoxytoluene, 122-46-3; benzyl chloroformate, 501-53-1; *N*-[3-[[3-(cyanomethyl)phenyl]-oxy]propanoyl]-L-proline benzyl ester, 82134-75-6.