Total Synthesis of Zizyphine A. Synthesis of Peptide Alkaloids. 8.[1,2] Amino Acids and Peptides. 40

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Zizyphine A (3) has been synthesized via 11 → **26a** → 3.

About 45 years after definition and introduction of the nomenclature of ansa compounds (1 and 2, Chart I) and of the construction of simple models by Lüttringhaus,[3] syntheses of the natural ansa compounds maitansine[4] and rifamycine[5] were recently reported. Both are ansa lactams, maitansine having a 16-membered meta bridge or handle (ansa) across the benzene nucleus and rifamycine having a 19-membered bridge across the naphthoquinone nucleus.

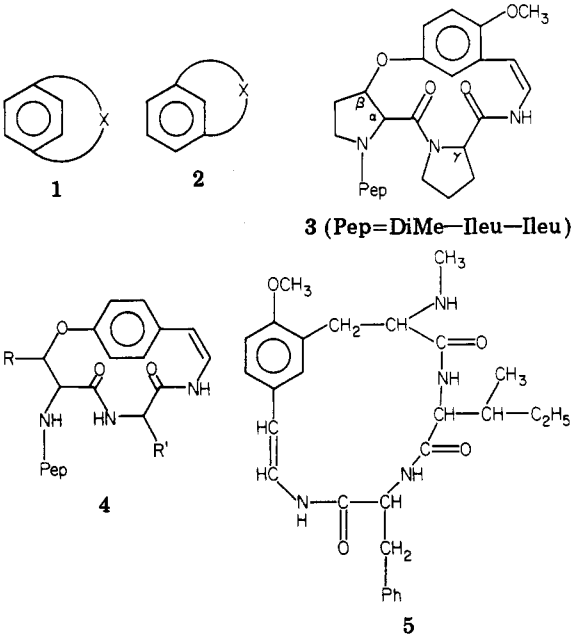
The peptide alkaloids,[6] a further group of biologically active[7] natural ansa compounds, have a bridge or handle (ansa) which is significantly tighter and contains 10 members in meta-ansa compounds of the zizyphine A type (3) and in para-ansa compounds of the frangulanine type (4). The mucronine type (5) with a 15-membered ring bears a meta handle with 12 members.

The shortest bridge (handle) in a para-ansa compound which can be formed in satisfactory yield by ring closure of a para-substituted aromatic compound contains 10 sp^3-hybridized members.[3] In a meta-ansa compound the shortest unstrained bridge (handle) contains 9 members.[3] In peptide alkaloids with a 14-membered ring and a 10-membered handle (frangulanine type) the two *s*-trans amide groups make the system more rigid and thus the synthesis more difficult. In peptide alkaloids with a 13-membered ring system (zizyphine A type) the 10-membered meta bridge (handle) contains one more member than the shortest bridge in a meta-ansa compound, and therefore the handle is flexible.

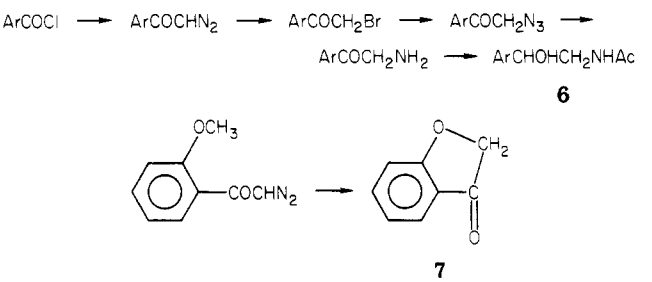
Until now only few approaches to the synthesis of peptide alkaloids have been reported. Rapoport described[9b,10] the synthesis of simple models with a phenoxypropionic acid unit instead of the *erythro*-β-phenoxyamino acid. Ring closure leading to a saturated 10-membered ansa bridge was achieved by the nitrophenyl ester method. Pais, Jarreau, Rocchiccioli, and Marchand[11,12] developed an elegant synthesis of *erythro*-β-phenoxyamino acids, but ring closure of these compounds by using the azide method failed.[13] Instead of an ansa lactam with a 10-membered bridge an ansa urea with an 11-membered bridge was formed by way of a Curtius degradation. Only the synthesis of an ansa peptide with a 13-membered ansa bridge could be achieved. These results taken together with our observations indicate that a higher reaction temperature is required to form the 10-membered ansa bridge of the peptide alkaloids. Therefore, only thermostable carboxylic acid derivatives (and not azides) are suitable for this ring closure reaction.

Recently[14] we described a new cyclization method for the synthesis of ansa peptides which involves hydrogen-

Chart I



Scheme I



(1) Parts 7 and 38, respectively: Schmidt, U.; Bökens, H.; Lieberknecht, A.; Griesser, H. *Justus Liebigs Ann. Chem.*, in press.

(2) For a preliminary communication see: Schmidt, U.; Lieberknecht, A.; Bökens, H.; Griesser, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1026.

(3) Lüttringhaus, A. *Justus Liebigs Ann. Chem.* **1936**, *528*, 181.

(4) (a) Meyers, A. J.; Reider, P. J.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6597. (b) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *Ibid.* **1980**, *102*, 6613.

(5) Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965.

(6) Review: (a) Warnhoff, E. W. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 162. (b) Tschesche, R.; Kaussmann, E. V. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. XV, pp 165–203.

(7) Reports on the isolation and structure elucidation of about 100 cyclopeptide alkaloids found in plants of the Rhamnaceae and Sterculiaceae families have been published during the last 20 years. Some of these peptide alkaloids are active against lower fungi and gram-positive bacteria.[8] Discarine B is a specific inhibitor of energy-transfer reactions in chloroplasts.[8] Experimental evidence points to their function as ionophores in plants.[9a,b]

(8) Ravizzine, R. A.; Andreo, C. S.; Vallejos, R. H. *Plant Cell Physiol.* **1977**, *18*, 701.

(9) (a) Kawai, K.; Nozawa, Y.; Ogihara, Y. *Experientia* **1975**, *33*, 1454. (b) Lagarias, J. C.; Houghten, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202.

(10) Goff, D.; Lagarias, J. C.; Shih, W. C.; Klein, M. P.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4813.

(11) Frappier, F.; Rocchiccioli, R.; Jarreau, F. X.; Pais, M. *Tetrahedron* **1978**, *34*, 2911.

(12) Marchand, J.; Rocchiccioli, F.; Pais, M.; Jarreau, F. X. *Bull. Soc. Chim. Fr.* **1972**, 4699.

(13) Rocchiccioli, F.; Jarreau, F. X.; Pais, M. *Tetrahedron* **1978**, *34*, 2917.

(14) Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 280; *J. Org. Chem.* **1982**, *47*, 3261.

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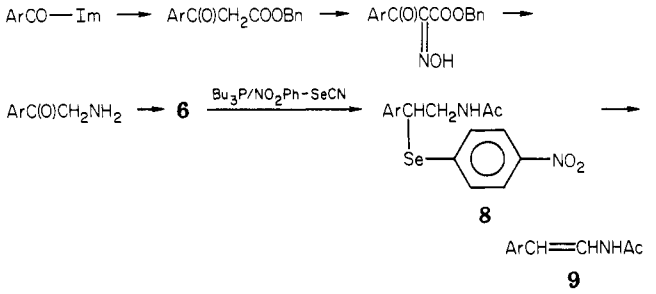
Scheme II



olysis of (*Z*)-pentafluorophenyl esters. We applied this reaction to the syntheses of the para-ansa compound dihydrozizyphine G,[15] of the meta-ansa compounds dihydrozizyphine A and B,[16] and of the 13-membered mucronine B[17] and obtained ring closure yields in the range of 50% and 95%, respectively, at temperatures above 95 °C. Below this reaction temperature mainly dimers were formed. Herein we report the first total synthesis of a peptide alkaloid, the synthesis of zizyphine A with a 10-membered meta-ansa bridge.[18]

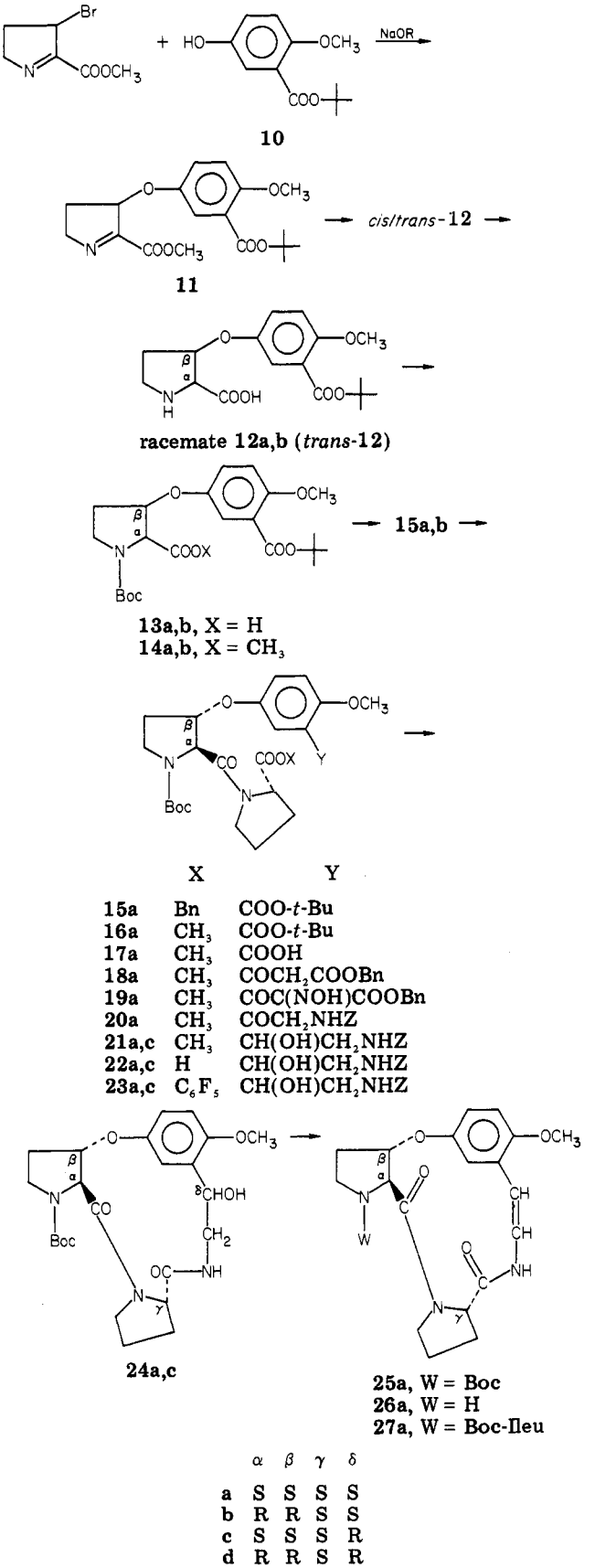
Synthesis of the Styrylamino Unit. The styrylamino unit is presumably biosynthesized from a dehydrotyrosine by decarboxylation. Although this decarboxylation reaction can be realized in vitro[19] by using model substrates, we preferred a route to this system which involves an elimination reaction starting with an ethanol amide. As ring closure is achieved by catalytic hydrogenation, introduction of the double bond in the peptide alkaloid can be effected only *after* the ring has been built.

Two ways for the construction of the ethanolamide moiety from an aromatic carboxylic acid[20] were elaborated.

(1) Hydrogenation in acetic acid of an azido ketone, prepared from the acid chloride via a diazo ketone and bromo ketone, gave the amino ketone (Scheme I). Acylation with an acylamino acid hydroxysuccinimide ester and reduction with cyanoborohydride afforded the hydroxy amide **6**. Although these reactions proceed smoothly, this sequence is not applicable to the synthesis of zizyphine A, for *o*-methoxyphenyl diazo ketones cannot be transformed into bromo ketones but produce benzofuranones **7**.[21] However, it is suitable for the synthesis of ortho-unsubstituted naturally occuring styrylamides, e.g., clionamide.[22]

(2) By the method of Masamune,[23] reaction of a carboxylic acid imidazolide with the magnesium salt of benzyl malonate affords the benzyl aroylacetate and on subsequent reaction with nitrite affords the oxime (Scheme II). Catalytic hydrogenation of the latter reduces the oximino group and simultaneously cleaves the benzyl ester. Subsequent decarboxylation forms the amino ketone. As the transformation of the hydroxy amide **6** into the enamide **9** via the chloride and bromide can be realized in low yields only and is hard to reproduce, we adopted the selenoxide elimination procedure. The nitrophenyl selenides **8** were prepared by redox condensation by using tributylphosphine and *p*-nitrophenyl selenocyanate;[24] oxidation

Scheme III



	α	β	γ	δ
a	S	S	S	S
b	R	R	S	S
c	S	S	S	R
d	R	R	S	R

(15) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Häusler, J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 281; *Liebigs Ann. Chem.* **1982**, 2153.
(16) Schmidt, U.; Bökens, H.; Lieberknecht, A.; Griesser, H. *Tetrahedron Lett.* **1981**, *22*, 4949; *Liebigs Ann. Chem.*, in press.
(17) Schmidt, U.; Schanbacher, U. *Angew. Chem., Int. Ed. Engl.*, in press.
(18) Isolation and structure elucidation: (a) Zbiral, E.; Ménard, E. L.; Müller, J. M. *Helv. Chim. Acta* **1963**, *48*, 1801. (b) Pailer, M.; Haslinger, E.; Zbiral, E. *Monatsh. Chem.* **1969**, *100*, 1608. (c) Revised structure: Tschesche, R.; Kaussmann, E.; Eckhardt, G. *Tetrahedron Lett.* **1973**, 2577. (d) Cassels, G.; Eckhardt, G.; Kaussmann, E.; Tschesche, R. *Tetrahedron* **1974**, *30*, 2461.
(19) Schmidt, U.; Lieberknecht, A. *Angew. Chem., Int. Ed. Engl.*, in press.
(20) These model experiments will be published separately.
(21) Bose, A. K.; Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 4703.
(22) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Bökens, H. *Tetrahedron Lett.* **1982**, *23*, 4911.
(23) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.

and elimination produced the olefin **9**.

In case of the linear aromatic hydroxy amides this elimination sequence leads to the *E* enamide; in case of cyclic ansa hydroxy amides, it produces the *Z* compounds of lower energy.[25]

Synthesis of the *trans*-β-Phenoxy Unit. As the starting material for the synthesis of the *trans*-phenoxyproline unit of zizyphine A we needed a *trans*-phenoxyproline with a protected aromatic carboxylic group which could be deblocked easily later on for construction of the styrylamino residue. The bromodehydroproline was reacted with phenol **10** by a standard method[26] to give the methyl dehydro-3-aryloxyprolinate **11** (Scheme III) which was saponified and reduced with dimethylaminoborane. This gave a mixture of the *cis*- and *trans*-(aryloxy)prolines **12**, the crystallization of which afforded a part of the racemic trans compound **12a,b**.[27] We did not succeed in rearranging the cis into the trans isomer by bases or heating with acetic anhydride. Introduction of the Boc group provided starting material **13a,b** for the sequences described below.

Ring Closure on Phenylethylamine Nitrogen. Whereas in the synthesis of the saturated ansapeptide dihydrozizyphine G,[15] with a rigid 10-membered para-ansa handle, ring closure toward the proline nitrogen proceeded more readily (67%) than toward the phenylethylamine nitrogen (35%), ring closure yields in the construction of the saturated meta-ansa compounds dihydrozizyphine A and B,[16] with a 10-membered flexible handle, at both positions were excellent and equal (95%). In the case in question ring closure on the phenylethylamine nitrogen provided an opportunity for separating the diastereomeric dipeptides **15a** and **15b**, prepared from **13a** + **13b** and benzyl (*S*)-prolinate by DCC condensation, by medium-pressure chromatography. On the basis of our experience with the analogous compounds in the synthesis[15] of dihydrozizyphine G, the compound with higher R_f value was suspected of being the *S,S,S* isomer **15a**. After hydrogenolysis of the benzyl ester and reaction with diazomethane to give methyl ester **16a**, cleavage of the *tert*-butyl ester and reacylation formed the carboxylic acid **17a**, further transformation of which by way of **18a** → **20a** gave the amino ketone unit in high yields. Sodium cyanoborohydride reduced **20a** nonstereoselectively to the diastereomers **21a** and **21c**. Saponification of the methyl esters and formation of a mixture of the two diastereomeric pentafluorophenyl esters **23a** and **23c** by DCC condensation yielded starting material for the ring-closure step. Catalytic hydrogenation of **23a,c** for 5 h by using dilution techniques afforded in about 80% yield a mixture of the cyclic alcohols **24a** and **24c** which were separated by chromatography, the yield of each isomer being 60%.[28] The introduction of a hydroxy group which is eliminated in the final steps of the synthesis increases the number of diastereomers and hence leads to mixtures which are difficult to purify. However, this disadvantage is balanced out by high yields, particularly in the ring-closure step. By contrast, ring closure using ketone **20a** (X = C_6F_5) proceeds in poor yield only and with partial reduction of the ketone to a hydroxyl group. The hydroxyl required for the eventual elimination reaction was therefore introduced before the ring-closure step.

Transformation of diastereomeric alcohols **24a** and **24c** into the selenides and oxidative elimination was realized with both isomers separately, the yield of olefin **25a** being identical (65%). After cleavage of the Boc group by trifluoroacetic acid, the amine **26a** was first reacted with (*tert*-butoxycarbonyl)isoleucine hydroxysuccinimide ester, forming **27a**, and after cleavage of the protecting group by trifluoroacetic acid the resulting amine was treated with dimethylisoleucine pentafluorophenyl ester to yield zizyphine A (**3**). The synthetic product (38% yield from **25a**) was identical with zizyphine A in every respect.[29]

Ring Closure at Proline Nitrogen. The ring closure at proline nitrogen proceeds with a yield of 80%, but the separation of the diastereomers can be achieved only after the ring has been closed. Therefore, the olefin **25a** has to be separated from the diastereomer **25b**, which makes this sequence less advantageous.

Experimental Section

Melting points (Kofler) are uncorrected. ^1H NMR spectra were recorded on Bruker Spectrospin 80-MHz spectrometer and a Bruker HX-90E spectrometer. An MAT 711 was used for determining mass spectra. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Circular dichroism (CD) was recorded with a JASCO J 500A spectropolarimeter. TCL was done on silica (Merck silica 60 F_{254} sheets), and medium-pressure column chromatography used 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.

***tert*-Butyl 5-(Benzyloxy)-2-methoxybenzoate.** To a mixture of 31 g (0.12 mol) of 5-(benzyloxy)-2-methoxybenzoic acid (the acid was obtained by the hydrolysis of the corresponding methyl ester with sodium hydroxide in dioxane[30]) and 10 mL of *tert*-butyl alcohol in 40 mL of CH_2Cl_2 was condensed 50 mL of isobutene at −40 °C. After addition of 1.8 mL of H_2SO_4(concn) the reaction vessel was closed and shaken vigorously at room temperature over a period of 50 h. After evaporation the residue was diluted with diethyl ether, and the unreacted acid was collected by filtration. The filtrate was washed with 0.5 N NaOH and water. After acidification of the water layers, the total yield of unreacted acid was 12 g (37%). The organic phase was dried, filtered, and evaporated. The residue was treated with petroleum ether, and the resulting suspension was filtered to yield 20.05 g (52%) of the *tert*-butyl ester as a white solid compound: mp 58–59 °C; R_f 0.54 (petroleum ether/ethyl acetate, 8:2); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.60 (s, 9 H), 3.85 (s, 3 H), 5.10 (s, 2 H), 6.85–7.25 (m, 3 H), 7.45 (s, 6 H). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.04. Found: C, 72.59; H, 7.01.

***tert*-Butyl 5-Hydroxy-2-methoxybenzoate (10).** A 12-g (38.2 mmol) sample of the *tert*-butyl ester of 5-(benzyloxy)-2-methoxybenzoic acid dissolved in 100 mL of ethanol was hydrogenated (3 bar) in the presence of palladium/charcoal (1 g, 5%) overnight. After filtration from the catalyst and evaporation, the solution of the residue in diethyl ether was treated with petroleum ether under stirring. The resulting crude product was filtered, washed with petroleum ether, and dried: yield 7.8 g (91%); R_f 0.23 (petroleum ether/ethyl acetate, 2:8); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.55 (s, 9 H), 3.80 (s, 3 H), 6.5–7.4 (m, 4 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.18. Found: C, 64.17; H, 7.08.

Methyl 3-[[3-(*tert*-Butoxycarbonyl)-4-methoxyphenyl]oxy]-1-pyrroline-2-carboxylate (11). To 30.45 mmol of a 1 N sodium methylate solution in methanol was added 6.33 g (30.45 mmol) of **10**. After evaporation of the solvent and drying in vacuo (0.001 mm) the solution of the residue in 100 mL of *N,N*-di-

(24) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(25) Models of cyclic olefins of type **3** with an *E* configuration are rather strained.

(26) Häusler, J.; Schmidt, U. *Liebigs Ann. Chem.* **1979**, 1881.

(27) The isomers in the mother liquor were converted into a mixture of the *cis*- and *trans*-Boc methyl ester, *cis*- + *trans*-**20**, and the isomers were separated by chromatography. The yield of the trans compound **19a** + **19b** from **17** was 43% all together.

(28) In the chromatography of the cyclic alcohols with a polar eluent some loss of material is observed.

(29) High-resolution MS, HPLC, NMR, CD: we thank Dr. J. M. Müller (Ciba-Geigy) and Dr. G. Eckhardt for providing samples of zizyphine A.

(30) Tschesche, R.; Spilles, C.; Eckhardt, G. *Chem. Ber.* **1974**, *107*, 686.

methylformamide was cooled to −30 °C. Then over a period of 3 h a solution of 6.39 g (31 mmol) of methyl 3-bromo-1-pyrroline-2-carboxylate[26] was continuously added under stirring. After an additional 20 h at room temperature the reaction was complete. The solvent was evaporated, and the residual product was dried in vacuo (0.001 mm) and dissolved in diethyl ether followed by extraction with water. After the organic phase was dried and filtered and the solvent evaporated, the residue was filtered on silica gel first with 8:2 petroleum ether/ethyl acetate and then with 4:6 petroleum ether/ethyl acetate. The second eluent was evaporated and dried in vacuo, affording 7 g (67%) of **11** as a pale yellow oil: R_f 0.54 (petroleum ether/ethyl acetate, 3:7); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.60 (s, 9 H), 1.75–2.60 (br s, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.55 (t, 3 H), 5.40–5.65 (m, 1 H), 6.85–7.45 (m, 3 H). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.00. Found: C, 61.70; H, 6.56; N, 3.83.

Sodium 3-[[3-(*tert*-Butoxycarbonyl)-4-methoxyphenyl]oxy]-1-pyrroline-2-carboxylate. To a solution of 6 g (17.2 mmol) of methyl ester **11** in 20 mL of dioxane was added 17.2 mL of 1 N NaOH. After 4 h the dioxane was evaporated, and the aqueous residue was diluted with water and extracted with ethyl acetate. Evaporation the aqueous phase and drying in vacuo (0.001 mm) afforded 6.15 g (100%) of sodium salt: R_f 0.05 (ethyl acetate); ^{1}H NMR (Me_2SO-D_6, Me_4Si) δ 1.40–2.60 (m, 2 H), 3.50–4.10 (m, 7 H), 5.30–5.65 (m, 1 H), 7.00 (s, 3 H).

***trans*-3-[[3-(*tert*-Butoxycarbonyl)-4-methoxyphenyl]oxy]proline (12a,b).** To a solution of 6 g (17 mmol) of sodium 3-[[3-(*tert*-butoxycarbonyl)-4-methoxyphenyl]oxy]pyrroline-2-carboxylate in 30 mL of acetic acid at 10 °C was added 1.4 g of dimethylaminoborane. After 2 h the solvent was evaporated and pumped at 0.001 mm for 1 h. The residue was dissolved in water and extracted with diethyl ether, followed by concentration of the aqueous phase to a total volume of 10 mL. After the mixture was kept overnight at 0 °C, separation of a white solid took place. Filtering yielded 1.47 g (26%) **12a,b**. [The filtrate containing a mixture of *cis*- and *trans*-prolines **12a–d** was transformed into the corresponding Boc esters **14a–d** which could be separated by medium-pressure chromatography on silica gel with ethyl acetate/petroleum ether (1:1)]. *cis*-**12c,d**, R_f 0.27. *trans*-**12a,b**: R_f 0.37 (*n*-butanol/acetic acid/water, 8:1:1); ^{1}H NMR (D_2O, Me_4Si) δ 1.45 (s, 9 H), 2.0–3.0 (s, 2 H), 3.35–3.75 (m, 2 H), 3.75 (s, 3 H), 4.20 (s, 1 H), 5.0–5.20 (m, 2 H), 6.90–7.40 (m, 3 H). Anal. Calcd for $C_{22}H_{31}NO_8$: C, 60.40; H, 7.14; N, 3.20. Found: C, 59.79; H, 6.99; N, 3.06.

***trans*-*N*-(*tert*-Butoxycarbonyl)-3-[[3-(*tert*-butoxycarbonyl)-4-methoxyphenyl]oxy]proline (13a,b).** To a solution of 6 g (17.8 mmol) of *trans*-prolines **12a,b** dissolved in 100 mL of dioxane were added 17.8 mL of 1 N NaOH and 3.88 g (17.8 mmol) of di-*tert*-butyl dicarbonate, and the reaction mixture was stirred at room temperature overnight. Then the dioxane was evaporated in vacuo, and the remaining water solution was extracted with ethyl acetate, acidified with $KHSO_4$ at 0–5 °C, and again extracted with ethyl acetate. After the organic layer was dried and evaporated, the residue was filtered on silica gel with ethyl acetate. Addition of petroleum ether to the filtrate afforded 7.51 g (97%) of *trans*-(*tert*-butoxycarbonyl)prolines **13a,b**: R_f (trans) 0.09 (ethyl acetate); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.55 (s, 9 H), 1.70 (s, 9 H), 2.15–2.60 (m, 2 H), 3.5–4.0 (m, 3 H), 4.00 (s, 3 H), 4.50–4.95 (m, 1 H), 5.00–5.35 (m, 1 H), 6.90–7.65 (m, 3 H).

Methyl Esters of *trans*-*N*-(*tert*-Butoxycarbonyl)-3-[[3-(*tert*-butoxycarbonyl)-4-methoxyphenyl]oxy]proline (14a,b). A solution of 7.4 g (17 mmol) of **13a,b** in methanol was treated with CH_2N_2/diethyl ether until the yellow color persisted. Evaporation and chromatography of the residue on silica gel (ethyl acetate/petroleum ether, 1:1) afforded 7.3 g (95%) of *trans*-methyl esters **14a,b**: R_f 0.41 (ethyl acetate/petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.60 (s, 9 H), 2.0–2.35 (m, 2 H), 3.50–3.95 (m, 2 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 4.55 (d, 1 H, J = 3 Hz), 4.85 (m, 1 H), 6.90–7.45 (m, 3 H). Anal. Calcd for $C_{23}H_{33}NO_8$: C, 61.05; H, 7.58; N, 3.09. Found: C, 61.20; H, 7.50; N, 3.27.

Corresponding to the upper two prescriptions, the crystallization filtrate containing a mixture of *cis*- and *trans*-prolines **12a–d** was transformed into the *cis*- and *trans*-Boc esters **14a–d**. Separation by chromatography on silica gel with ethyl acetate/petroleum ether (1:1) afforded additional *trans*-methyl esters **20a,b**. Thus, the overall yield of available *trans*-phenoxyproline compounds was 43% from **11**.

Benzylic Ester of *N*-[3-[[3-(*tert*-Butoxycarbonyl)-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (15a) and Benzylic Ester of *N*-[3-[[3-(*tert*-Butoxycarbonyl)-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*R*,3*R*)-prolyl]-(*S*)-proline (15b). To a mixture of 5.54 g (12.7 mmol) of **13a,b**, 3.22 g (13.33 mmol) of the hydrochloride of the benzylic ester of proline, and 1.348 g (13.33 mmol) of *N*-methylmorpholine in 50 mL of CH_2Cl_2(abs) at 0 °C was added 2.74 g (13.33 mmol) of *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was stirred overnight at room temperature, filtered from the urea, and evaporated. The following chromatography on silica gel with ethyl acetate/petroleum ether (7:3) afforded the separated diastereomeric dipeptides **15a** and **15b** in a total yield of 7.42 g (93%).

For diastereomeric dipeptide **15a**: 3.71 g (46.5%); R_f 0.48 (petroleum ether/ethyl acetate, 7:3); $[\alpha]^{20}_D$ +11.09° (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.45 (d, 9 H), 1.60 (s, 9 H), 1.75–2.50 (m, 6 H), 3.25–3.90 (m, 4 H), 3.85 (s, 3 H), 4.40–4.80 (m, 3 H), 5.5 (q, 2 H), 6.85 (s, 2 H), 7.20–7.40 (m, 2 H), 7.30 (s, 5 H). Anal. Calcd for $C_{34}H_{44}N_2O_9$: C, 65.37; H, 7.10; N, 4.48. Found: C, 64.99; H, 7.03; N, 4.55.

For diastereomeric dipeptide **15b**: 3.71 g (46.5%); R_f 0.36 (petroleum ether/ethyl acetate, 7:3); $[\alpha]^{20}_D$ −74.8° (*c* 0.99, $CHCl_3$).

Methyl Ester of *N*-[3-[[3-(*tert*-Butoxycarbonyl)-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (16a). A solution of 3.5 g (5.6 mmol) of benzylic ester **15a** in 100 mL of absolute ethanol was hydrogenated in the presence of Pd/activated charcoal (0.5 g, 5%) over a period of 1 h. After filtration from the catalyst and evaporation, the residue was dissolved in 50 mL of ethyl acetate/methanol (9:1) followed by addition of diazomethane in diethyl ether until the pale yellow color persisted. Evaporation and filtration on silica gel with ethyl acetate yields 2.9 g (96.6%) of methyl ester **16a**: R_f 0.42 (ethyl acetate); $[\alpha]^{20}_D$ +14.15° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.55 (s, 9 H), 1.95–2.60 (m, 6 H), 3.25–3.90 (m, 4 H), 3.80 (s, 6 H), 4.25–5.00 (m, 3 H), 6.75–7.35 (m, 3 H). Anal. Calcd for $C_{28}H_{40}N_2O_9$: C, 61.30; H, 7.35; N, 5.11. Found: C, 61.17; H, 7.52; N, 5.14.

Methyl Ester of *N*-[3-[[3-Carboxy-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (17a). A mixture of 2.90 g (5.29 mmol) of **16a** and 1 g of *m*-dimethoxybenzene in 30 mL of trifluoroacetic acid was stirred for 3 h at 0 °C. After evaporation, the residue and 1.24 g (5.7 mmol) of di-*tert*-butyl dicarbonate were dissolved in dioxane, made alkaline with 1 N $KHCO_3$, and stirred overnight. Following evaporation of the reaction mixture, the solution of the residue in water was acidified with oxalic acid and extracted with ethyl acetate. The organic phase was dried, filtered, and evaporated in vacuo (0.001 mm) to yield 2.5 g (95%) of the acid **17a**: R_f 0.1 (ethyl acetate); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.50–2.60 (m, 6 H), 3.20–4.00 (m, 4 H), 3.70 (s, 6 H), 4.20–5.2 (m, 3 H), 6.75–7.40 (m, 3 H), 8.5 (s, 1 H). Anal. Calcd for $C_{24}H_{32}N_2O_9$: C, 58.53; H, 6.55; N, 5.69. Found: C, 58.71; H, 6.60; N, 5.44.

Methyl Ester of *N*-[3-[[3-[1-Oxo-2-(benzyloxycarbonyl)-ethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (18a). A 2.4-g (4.88 mmol) sample of **17a** and 0.89 g (5.5 mmol) of *N,N*-carbonyldiimidazole in 10 mL of absolute THF were stirred for 2 h at room temperature. After addition of 2 g (5 mmol) of the magnesium salt of benzyl malonate to the reaction mixture stirring was continued at 50 °C for additional 5 h. Following evaporation the suspension of the residue in ethyl acetate was extracted with 1 N $KHSO_4$ and 1 N $KHCO_3$. The organic phase was dried, filtered, and evaporated in vacuo (0.001 mm) to afford 2.7 g (87%) of compound **18a**: R_f 0.40 (ethyl acetate); $[\alpha]^{20}_D$ +5.0° (*c* 1.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.65–2.50 (m, 6 H), 3.30–3.90 (m, 4 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 4.0 (s, 2 H), 4.40–4.90 (m, 3 H), 5.10 (s, 2 H), 6.75–7.50 (m, 8 H). Anal. Calcd for $C_{33}H_{40}N_2O_{10}$: C, 63.45; H, 6.45; N, 4.48. Found: C, 63.30; H, 6.45; N, 4.62.

Methyl Ester of *N*-[3-[[3-[1-Oxo-2-(benzyloxycarbonyl)-2-hydroximinoethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (19a). To a solution of 1.34 g (2.15 mmol) of **18a** in 3 mL of acetic acid/H_2O (9:1) at 0 °C was added $NaNO_2$ in portions until the reaction was

complete (monitored by TLC in ethyl acetate). After evaporation, the solution of the residue in ethyl acetate was washed with 1 N $KHCO_3$ and 1 N $KHSO_4$, dried, filtered, and reduced in vacuo to yield 1.25 g (88%) of hydroximino compound **19a**: R_f 0.35 (ethyl acetate); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.65–2.80 (m, 6 H), 3.30–4.00 (m, 4 H), 3.60 (s, 3 H), 3.80 (s, 3 H), 4.40–5.10 (m, 4 H), 5.30 (s, 2 H), 6.70–7.75 (m, 8 H). Anal. Calcd for $C_{33}H_{39}N_3O_{10}$: C, 60.63; H, 6.01; N, 6.43. Found: C, 60.54; H, 6.08; N, 6.54.

Methyl Ester of *N*-[3-[[3-[2-(Carbobenzoxyamino)-1-oxoethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (20a). A 1.2-g (1.84 mmol) sample of **19a** dissolved in 30 mL of acetic acid was hydrogenated in the presence of Pd/charcoal (0.25 g, 5%) for 5 h. After filtration from the catalyst and evaporation the solution, the residue in dioxane was treated at 0 °C with 0.39 g (2.3 mmol) of benzyl chloroformate, made alkaline with 1 N $KHCO_3$, and stirred at room temperature overnight. Following evaporation of the solvent, the solution of the residue in ethyl acetate was extracted with 1 N $KHCO_3$ and 1 N $KHSO_4$. The organic layer was dried, filtered, evaporated, and chromatographed on silica gel with ethyl acetate/petroleum ether (9:1) to afford **20a**: 0.93 g (79%); R_f 0.35 (ethyl acetate); $[\alpha]^{20}_D$ −0.439° (*c* 1.92, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.40 (s, 9 H), 1.65–2.55 (m, 6 H), 3.25–4.00 (m, 4 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 4.65 (d, 2 H, J = 5 Hz), 4.0–4.95 (m, 3 H), 5.10 (s, 2 H), 5.6–6.0 (br s, 1 H), 6.80–7.55 (m, 8 H). Anal. Calcd for $C_{33}H_{41}N_3O_{10}$: C, 61.96; H, 6.46; N, 6.57. Found: C, 61.14; H, 6.29; N, 6.72.

Diastereomers of the Methyl Ester of *N*-[3-[[3-[2-(Carbobenzoxyamino)-1-hydroxyethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (21a,c). To a solution of 0.93 g (1.46 mmol) of **20a** in 10 mL of THF/acetic acid (9:1) was added 0.200 g of $NaCNBH_3$. After being stirred overnight, the reaction mixture was concentrated in vacuo and the solution of the residue in ethyl acetate extracted with 1 N $KHSO_4$ and 1 N $KHCO_3$. The organic layer was dried, filtered, and evaporated in vacuo (0.001 mm) to yield 0.91 g (98%) of the hydroxy compounds **21a,c**: R_f 0.32 (ethyl acetate); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.75–2.75 (m, 6 H), 3.25–4.00 (m, 4 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 4.3–5.5 (m, 8 H), 5.1 (s, 2 H), 6.75–7.4 (m, 8 H). Anal. Calcd for $C_{33}H_{43}N_3O_{10}$: C, 61.75; H, 6.75; N, 6.55. Found: C, 61.69; H, 6.54; N, 6.50.

Diastereosiomers of *N*-[3-[[3-[2-(Carbobenzoxyamino)-1-hydroxyethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (22a,c). A 1.45-mL sample of 1 N LiOH was added to a solution of 0.91 g (1.42 mmol) of **21a,c** in 2 mL of dioxane. After evaporation of the dioxane the water solution of the residue was washed with diethyl ether, acidified with 1 N $KHSO_4$, and extracted with ethyl acetate. The organic layer was dried, filtered, and reduced in vacuo to afford 0.74 g (83%) of carboxylic acids **21a,c**: R_f 0.1 (ethyl acetate); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.65–2.40 (m, 7 H), 3.20–4.10 (m, 8 H), 4.10–5.30 (m, 4 H), 5.25 (s, 2 H), 6.75–7.30 (m, 4 H), 7.40 (s, 5 H). Anal. Calcd for $C_{32}H_{41}N_3O_{10}$: C, 61.23; H, 6.59; N, 6.69. Found: C, 61.05; H, 6.55; N, 6.53.

Diastereoisomers of the Pentafluorophenyl Ester of *N*-[3-[[3-[2-(Carbobenzoxyamino)-1-hydroxyethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-proline (23a,c). A 0.752-g (1.2 mmol) sample of **22a,c** and 0.22 g (1.2 mmol) of pentafluorophenol were dissolved in 5 mL of ethyl acetate and then treated with 0.247 g (1.2 mmol) of DCC. After the solution was stirred for 1 h at 0 °C and an additional hour at room temperature the reaction mixture was filtered from urea and evaporated. The residue was chromatographed on silica gel first with 8:2 petroleum ether/ethyl acetate as the eluent and then with 3:7 petroleum ether/ethyl acetate. The second eluent was evaporated and dried in vacuo to afford 0.84 g (90%) of pentafluorophenyl esters **23a,c**: R_f 0.60 (ethyl acetate); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.50 (s, 9 H), 1.70–2.60 (m, 7 H), 3.30–4.20 (m, 6 H), 3.95 (s, 3 H), 4.20–5.50 (m, 4 H), 5.25 (s, 2 H), 6.80–7.25 (m, 9 H). Anal. Calcd for $C_{38}H_{40}N_3O_{10}F_5$: C, 57.50; H, 5.08; N, 5.29. Found: C, 57.12; H, 5.14; N, 5.42.

Diastereoisomers of Cyclo[*N*-[3-[[3-(2-amino-1-hydroxyethyl)-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-prolyl] (24a,c). To a rapidly stirred solution of 350 mL of dioxane (90 °C) containing 8 mL of absolute ethanol, 4-pyrrolidinopyridine (120 mg, 0.68 mmol), and Pd/activated charcoal (0.6 g, 5%) was injected a solution of the pentafluorophenyl esters **23a,c** (0.66 g, 0.84 mmol) in 48 mL of dioxane continuously over a period of 4 h. At the same time hydrogen was passed through the reaction solution. After filtration and evaporation, chromatography on silica gel with CH_2Cl_2/CH_3OH (9:1) afforded the two diastereomeric cyclic alcohols **24a** and **24c**.

For the first diastereomeric alcohol: 124 mg (63%); R_f 0.36 (CH_2Cl_2/*i*-PrOH, 92:8), R_f 0.15 (ethyl acetate); $[\alpha]^{20}_D$ −146.9° (*c* 0.44, $CHCl_3$); MS (20 eV), *m/e* (relative intensity) 475 (M^+, 100); high-resolution MS, calcd for $C_{24}H_{33}N_3O_7$ *m/e* 475.2318, found *m/e* 475.2315.

For the second diastereomeric alcohol: 118 mg (60%); R_f 0.28 (CH_2Cl_2/*i*-PrOH, 92:8), R_f 0.22 (ethyl acetate); $[\alpha]^{20}_D$ −143.9° (*c* 0.62, $CHCl_3$); MS (20 eV), *m/e* (relative intensity) 475 (M^+, 94), 375 (M^+ − Boc, 100); high-resolution MS, calcd for $C_{24}H_{33}N_3O_7$ *m/e* 475.2318, found *m/e* 475.2317.

Cyclo[*N*-[3-[[3-[2-(*Z*)-aminovinyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-prolyl] (25a). A 0.056-mL (0.23 mmol) sample of tributylphosphine was added to a solution of 83 mg (0.17 mmol) of the diastereoisomer **24a** or **24c** and 51.6 mg (0.23 mmol) *p*-nitrophenyl selenocyanate in 3 mL of absolute THF under argon. After being stirred 2 h at room temperature, the reaction mixture was evaporated in vacuo, and the residue was chromatographed on silica gel with ethyl acetate/petroleum ether (7:3) to yield 85 mg (72%) of the selenides.

For the diastereosiomeric selenide generated from the first diastereoisomeric alcohol: 85 mg (72%); R_f 0.31 (petroleum ether/ethyl acetate, 3:7); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.45–2.50 (m, 6 H), 2.95 (m, 2 H), 3.15–3.95 (m, 4 H), 3.80 (s, 3 H), 3.95–4.40 (m, 2 H), 4.70 (m, 1 H), 5.05–5.65 (m, 2 H), 6.85 (m, 3 H), 7.80 (m, 4 H).

For the diastereoisomeric selenide generated from the second diastereoisomeric alcohol: 85 mg (72%); R_f 0.30 (petroleum ether/ethyl acetate, 3:7); ^1H NMR ($CDCl_3$, Me_4 Si) δ 1.40 (s, 9 H), 1.50–2.50 (m, 6 H), 2.90 (m, 2 H), 3.10–3.90 (m, 4 H), 3.80 (s, 3 H), 3.90–4.35 (m, 2 H), 4.70 (m, 1 H), 5.05–5.60 (m, 2 H), 6.80 (m, 3 H), 7.80 (m, 4 H).

A solution of 85 mg (0.129 mmol) of the mixture of both diastereosiomers of cyclo[*N*-[3-[[3-[2-amino-1-[(*p*-nitrophenyl)-selenyl]ethyl]-4-methoxyphenyl]oxy]-*N*-(*tert*-butoxycarbonyl)-(2*S*,3*S*)-prolyl]-(*S*)-prolyl] in 3 mL of CH_2Cl_2 containing 10 mg of pyridine was treated under vigorous stirring with 0.07 mL of H_2O_2 (30%) in 0.3 mL of water at room temperature. After 1 h the reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with 1 N $KHSO_4$. Drying, evaporation of the solvent, and chromatography on silica gel with ethyl acetate/petroleum ether (7:3) afforded 53 mg (90%) of elimination product **25a**.

If the reaction was done with the two separated selenides, both reactions gave identical elimination products in equal yields: R_f 0.36 (ethyl acetate/petroleum ether 7:3); $[\alpha]^{20}_D$ −499.6° (*c* 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.45 (s, 9 H), 1.75–2.50 (m, 6 H), 3.10–4.00 (m, 4 H), 3.75 (s, 3 H), 4.30 (d, J = 5 Hz, 1 H), 4.65 (m, 1 H), 5.25 (m, 1 H), 5.90 (d, J = 8 Hz, 1 H), 6.70–7.10 (m, 4 H), 8.35 (d, J = 11 Hz, 1 H); high-resolution MS, calcd for $C_{24}H_{31}N_3O_6$ *m/e* 457.2212, found *m/e* 457.2213.

Cyclo[*N*-[3-[[3-[2-(*Z*)-aminovinyl]-4-methoxyphenyl]oxy]-*N*-[*N*-(butoxycarbonyl)isoleucyl]-(2*S*,3*S*)-prolyl]-(*S*)-prolyl] (27a). A 100-mg (0.21 mmol) sample of **25a** was treated with 10 mL of trifluoroacetic acid at room temperature in the presence of 0.1 mL of *m*-dimethoxybenzene. After evaporation in vacuo the residue was dissolved in 1 N $KHCO_3$ followed by extraction with ethyl acetate. After the organic phase was dried, the solution was evaporated. Recrystallization from ethyl acetate/petroleum ether afforded **27a**: 70 mg (92%); R_f 0.1 (ethyl acetate); $[\alpha]^{20}_D$ −480° (*c* 0.26, $CHCl_3$). A 57-mg (0.16 mmol) sample of the upper product was dissolved together with 40 mg (0.17 mmol) *N*-(*tert*-butoxycarbonyl)-L-isoleucine in 2 mL of CH_2Cl_2. At 0 °C 35 mg (0.17 mmol) of DCC was added. After being stirred 4 h at room temperature, the reaction mixture was filtered from urea. After the organic phase was dried, the solution was filtered, evaporated, and chromatographed on silica gel with ethyl acetate/petroleum ether (7:3) to afford **27a**: 65 mg (71%); R_f 0.32 (ethyl acetate/petroleum ether (7:3); $[\alpha]^{20}_D$ −415.9° (*c* 1.21, $CHCl_3$);

MS (70 eV), m/e (relative intensity) 570 (M^+, 62), 70 (100); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.96 (m, 6 H), 1.00–2.60 (m, 9 H), 1.45 (s, 9 H), 2.75–4.00 (m, 4 H), 3.80 (s, 3 H), 4.00–4.70 (m, 3 H), 5.00–5.50 (m, 2 H), 5.90 (d, J = 8.5 Hz, 1 H), 6.50–7.05 (m, 4 H), 8.35 (d, J = 11 Hz, 1 H); high-resolution MS, calcd for $C_{30}H_{42}N_4O_7$ m/e 570.3054, found m/e 570.3052.

Zizyphine A (3). A solution of 60 mg (0.105 mmol) of **27a** and 0.1 mL of *m*-dimethoxybenzene in 5 mL of trifluoroacetic acid was stirred for 0.5 h at room temperature and then evaporated in vacuo. The solution of the residue in CH_2Cl_2 was washed with 1 N $KHCO_3$, dried, filtered, and evaporated. Recrystallization of the residue from ethyl acetate/petroleum ether afforded 50 mg (100%) of cyclo[*N*-[3-[[3-[2-(*Z*)-aminovinyl]-4-methoxyphenyl]oxy]-*N*-isoleucyl-(2*S*,3*S*)-prolyl]-(*S*)-prolyl]. This product was added to a solution of 25 mg of 4-(dimethylamino)pyridine and 100 mg (0.3 mmol) of the pentafluorophenyl ester of *N*-(dimethylamino)-L-isoleucine in 3 mL of absolute dioxane. The reaction mixture was kept at 80 °C for 7 h and then evaporated, and the residue was chromatographed on silica gel with CH_2Cl_2/*i*-PrOH (92.5:7.5) to yield zizyphine A (**3**): 35 mg (54%); $[\alpha]^{20}_D$ −430° (*c* 0.093, $CHCl_3$) (lit.[18a] $[\alpha]^{24}_D$ −464° (*c* 1, $CHCl_3$); lit.[18c] $[\alpha]^{20}_D$ −411° (*c* 0.086, $CHCl_3$)). The CD of the synthetic product was identical with the CD of the natural product (Ciba-Geigy): CD Δ_{emax} (λ_{max},nm) −32.7 (258), −15.7 (318); ^1H NMR ($CDCl_3$, Me_4Si) δ 0.9 (m, 12 H), 1.19 (m, 3 H), 1.6 (m, 2 H), 1.8 (m, 3 H), 1.97 (m, 2 H), 2.25 (s, 6 H), 2.42 (m, 4 H), 3.33 (m, 1 H), 3.67 (m, 1 H), 3.8 (s, 3 H), 4.32 (m, 3 H), 4.55 (m, 2 H), 5.26 (m, 1 H), 5.96 (d, 1 H, J = 9.0 Hz), 6.89 (m, 4 H), 8.34 (d, 1 H, J = 11.7 Hz); MS (20 eV) m/e (relative intensity) 611 (M^+, 2), 114 (100); high-resolution MS, calcd for $C_{33}H_{49}N_5O_6$ m/e 611.3683, found m/e 611.3677.

The synthetic product and the natural compound were identical by HPLC [ethanol/H_2O (7:3), LiChroprep Si 60 (15–25 μm) treated with $C_{18}H_{37}SiCl_3$].

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Registry No. **3**, 51059-42-8; **10**, 86272-64-2; **11**, 86272-65-3; **11**-Na, 86288-21-3; (±)-*trans*-**12**, 79816-21-0; (±)-*cis*-**12**, 79816-22-1; (±)-*trans*-**13**, 86272-66-4; (±)-*trans*-**14**, 79816-23-2; **15a**, 86272-67-5; **15b**, 86272-68-6; **16a**, 86272-69-7; **17a**, 86272-70-0; **18a**, 86272-71-1; **19a**, 86272-72-2; **20a**, 86272-73-3; **21a**, 86272-74-4; **21c**, 86333-64-4; **22a**, 86333-89-3; **22c**, 86272-75-5; **23a**, 86272-76-6; **23c**, 86333-65-5; **24a**, 79816-29-8; **24a** *p*-nitrophenyl selenide, 86272-77-7; **24c**, 79854-70-9; **24c** *p*-nitrophenyl selenide, 86333-66-6; **25a**, 79816-31-2; **26a**, 79816-32-3; **27a**, 86288-22-4; *N*,*N*-dimethyl-L-isoleucine pentafluorophenyl ester, 86272-78-8; 5-(benzyloxy)-2-methoxybenzoic acid, 84923-68-2; *tert*-butyl 5-(benzyloxy)-2-methoxybenzoate, 86272-63-1; methyl 3-bromo-1-pyrrolin-2-carboxylate, 72978-15-5; proline benzylic ester hydrochloride, 16652-71-4; benzyl malonate magnesium salt, 79816-35-6; pentafluorophenol, 771-61-9.

A New Approach for the Total Synthesis of Pentacyclic *Aspidosperma* Alkaloids. Total Synthesis of *dl*-16-Methoxytabersonine[1]

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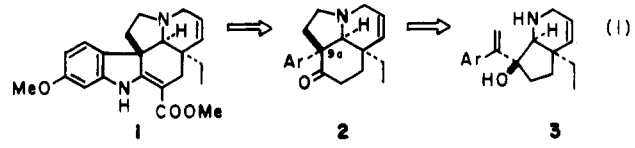
The pentacyclic *Aspidosperma* alkaloid *dl*-16-methoxytabersonine (**1**) has been synthesized by an efficient convergent sequence. The key step in the synthesis is the "ring-enlarging pyrrolidine annulation" reaction of 7-styrylhydropyridin-7-ols **17** and **18** to give 9a-arylhydrolilolidine **19** and 16-methoxy-1,2,6,7-tetradehydroaspidospermidine (**20**), respectively.

Continuing intense interest in the synthesis of pentacyclic *Aspidosperma* alkaloids[2,3] stems in part from the occurrence of the highly functionalized indoline vindoline in the clinically used antineoplastic agents vincaleukoblastine and leurocristine.[4]

We recently outlined[5] a fundamentally new approach to the pentacyclic *Aspidosperma* skeleton in which tricyclic hydrolilolidines, which incorporate the synthetically demanding quaternary aryl function, are key intermediates (eq 1).[6] The central feature of this scheme is the "ring-



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enlarging pyrrolidine annulation" reaction[7] of the formaldehyde iminium ion derived from pyridinol **3**. If the

(1) Part 10 in the series "Synthesis Applications of Aza-Cope Rearrangements". For part 9 see: Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2741–2744.

(2) For a recent review, see: Cordell, G. A. "The Alkaloids"; Manske, R. H. F., Rodrigo, R., Eds.; Academic Press: New York, 1979; Vol. XVII, Chapter 3.

(3) Recent examples include: (a) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335–1343. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1140–1141. Pearson, A. J.; Rees, D. C. *Ibid.* **1982**, *104*, 1118–1119. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *Ibid.* **1981**, *103*, 6990–6992. Speckamp, W. N.; Veenstra, S. J. *Ibid.* **1981**, *103*, 4645–4646. Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443–3447.

(4) Cf.: Neuss, N. In "Indole and Biogenetically Related Alkaloids"; Phillipson, J. D., Zenk, M. H., Ed; Academic Press: New York, 1980; Chapter 17.

(5) Overman, L. E.; Sworin, M.; Bass, L. S.; Clardy, J. *Tetrahedron* **1981**, *37*, 4041–4045.

(6) Hydrolilolidines with 9a-hydrogen substituents were intermediates in the original Stork and Ban syntheses of the *Aspidosperma* skeleton; see: Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry"; Academic Press: New York, 1975; Vol. 2, pp 400–405.

(7) (a) Cf.: Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579–5581. (b) We wish to stress that, although we have chosen for simplicity to discuss this reaction[1,5,7a] as a [3,3]-sigmatropic rearrangement followed by a Mannich cyclization, alternate mechanisms with similar topological constraints are not excluded by data currently available. For example, with electron-rich styrenyl substrates, cyclization to a benzylic cation followed by pinacolic rearrangement is a conceivable alternative.

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