= 7 Hz), 1.45 (4 H, m), 2.12 (2 H, m), 2.55 (2 H, m), 3.20 (3 H, m), 4.03 (2 H, q, J = 7 Hz), 4.23 (2 H, q, J = 7 Hz), 4.59 (AB q, J = 10, 18 Hz), 7.29 (4 H, m).

To **10** (R^1 = n-Pr) (9.0 g, 23 mmol) in 90 mL of EtOH at 0 °C was added a solution of NaOH (830 mg, 21 mmol) in 10 mL of H_2O over 30 min. The reaction was stirred for 3 h at room temperature and evaporated. The residue in 200 mL of H_2O was extracted with 200 mL of diethyl ether. The aqueous layer was acidified to pH 4.3 with 1 N HCl and extracted with 2 × 200 mL of ethyl acetate. The combined ethyl acetate portions were dried (Na_2SO_4) and evaporated to give 6.3 g of a foam. A solution of the foam in 200 mL of CH_2Cl_2 was acidified by bubbling in HCl gas, evaporated, and crystallized from 3-pentanone to give 5.8 g of **5y**·HCl; mp 204–205 °C; $[\alpha]_D$ −180° (c 1.2, EtOH); NMR ($CDCl_3$) δ 0.82 (3 H, t, J = 7 Hz), 1.07 (3 H, t, J = 7 Hz), 1.40 (2 H, m), 1.82 (2 H, m), 2.45 (4 H, m), 3.28 (1 H, m), 3.98 (1 H, m), 4.02 (2 H, q, J = 7 Hz), 4.67 (2 H, s), 7.38 (4 H, s), 10.6 (2 H, br s); IR (Nujol) 3350, 3175, 2950, 2620, 2512, 1740, 1720, 1660, 1535, 1465, 1378, 1212 cm^{-1}. Anal. ($C_{19}H_{27}N_2O_5Cl$) C, H. N.

Acknowledgment. The authors express their thanks to Drs. H. W. Gschwend and H. B. Renfroe for their encouragement and support of this work, Drs. B. Petrack and J. Norman, J. Ansell, and H. Hankin for the biochemical data, Drs. F. Goodman, M. Zimmerman, and B. E. Watkins, D. Miller, and R. A. Dotson for the in vivo biological data, L. Raabis for the NMR spectra, M. Brzechffa for the mass spectral data, G. Robertson and R. Oekinghaus for microanalyses, and M. Makar for typing the manuscript.

Registry No. **5a**, 97878-35-8; **5b**, 97878-67-6; **5b**·HCl, 97878-49-4; **5c**, 95384-35-3; **5c**·HCl, 94793-91-6; **5d**, 97878-68-7; **5d**·HCl, 95384-40-0; **5e**, 97878-50-7; **5f**·HCl, 95384-34-2; (*S,S*)-**5g**, 97878-69-8; (*R,S*)-**5g**, 97878-70-1; (*S,S*)-**5g**·HCl, 97878-51-8; (*R,S*)-**5g**·HCl, 97878-52-9; (*S,S*)-**5h**·HCl, 97878-53-0; (*R,S*)-**5h**·HCl, 97878-54-1; (*S,R*)-**5i**, 95384-22-8; (*R,R*)-**5i**, 97878-41-6; (*S,R*)-**5i**·HCl, 97878-42-7; (*R,R*)-**5i**·HCl, 97878-43-8; (*S,R*)-**5j**, 97878-37-0; (*R,R*)-**5j**, 97878-38-1; (*S,R*)-**5j**·HCl, 97878-39-2; (*R,R*)-**5j**·HCl, 97878-40-5; **5k**, 95384-23-9; **5l**, 95384-24-0; (*S,R*)-**5m**·HCl, 95384-30-8; (*R,R*)-**5m**·HCl, 97878-55-2; **5n**, 97878-56-3; **50**·HCl, 97878-57-4; (*S,S*)-**5p**, 97878-59-6; (*R,S*)-**5p**, 97878-58-5; (*S,S*)-**5q**, 97889-70-8; (*R,S*)-**5q**, 97889-71-9; (*S,S*)-**5q**·HCl, 97878-60-9; (*R,S*)-**5q**·HCl, 97878-61-0; **5r**, 97878-62-1; **5s**, 97878-71-2; **5s**·HCl, 97878-63-2; **5t**, 97878-64-3; **5u**, 97878-72-3; **5u**·HCl, 97878-65-4; **5v**, 95384-25-1; **5w**·HCl, 95384-32-0; **5x**, 97878-66-5; **5y**, 97878-47-2; **5y**·HCl, 97878-48-3; (±)-**6**, 88391-85-9; **7**, 88372-49-0; **8** (R^1 = $(CH_2)_4NHCl_2$ z, methyl ester), 1155-64-2; **8** (R^1 = SCH_2Ph), 953-18-4; **8** (R^1 = n-Pr), 39256-85-4; **9** (R^1 = $(CH_2)_4NHCb$ z, methyl ester), 97878-34-7; **9** (R^1 = CH_2SCH_2Ph), 97878-36-9; **9** (R^1 = n-Pr), 97878-44-9; (*S,S*)-**10** (R^1 = $(CH_2)_4NHCbz$, methyl ester), 94811-71-9; (*R,S*)-**10** (R^1 = $(CH_2)_4NHCbz$, methyl ester), 95102-10-6; (*S,R*)-**10** (R^1 = SCH_2Ph), 95393-15-0; (*R,R*)-**10** (R^1 = SCH_2Ph), 95384-21-7; (*S,S*)-**10** (R^1 = n-Pr), 97878-46-1; (*R,S*)-**10** (R^1 = n-Pr), 97878-45-0; ACE, 9015-82-1.

Angiotensin Converting Enzyme Inhibitors: N-Substituted D-Glutamic Acid γ Dipeptides†

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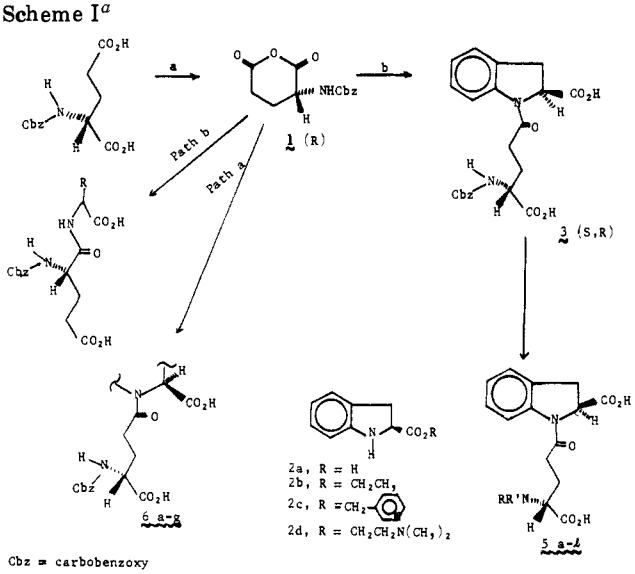
The preparation of two series of *N*-carbobenzoxy-γ-D-glutamyl secondary 2*S* amino acids and (N-substituted γ-D-glutamyl)indoline-2(*S*)-carboxylic acid dipeptides is described. In vitro inhibition of angiotensin converting enzyme (ACE) is reported for each compound, and the structure–activity relationship is discussed. Oral and iv inhibition of AI pressor response in vivo of selected compounds in Table II is also discussed. The most potent compounds in vitro, **3** and **6a**, had an ACE IC_{50} of 7 and 2.7 × 10^{-9} M, respectively.

Since the pioneering work of the Squibb group[1] numerous reports[2] on angiotension converting enzyme (ACE) inhibitors have appeared. Clinical studies[3] have shown ACE inhibitors to be useful in the treatment of hypertension. Bearing in mind the basic stereochemical and active-site model developed from a number of carboxyalkyl tripeptides and 2,4-disubstituted glutaric acid dipeptides, the effects of varying substituents within subsites for this model using D-glutamic acid as the backbone was investigated. Specifically, the importance of the S_2' and S_1, binding sites[4] in the absence of a S_1' site substituent was looked at by varying the substituent on the glutamyl nitrogen and by varying the C-terminal amino acid of the dipeptide.

Chemistry. D-Glutamic acid was converted to *N*-Cbz-glutamic anhydride (**1**) by a previously described[5] procedure. The literature[6] suggests that nucleophilic opening of **1** with amino acids (esters) affords mixtures of α- and γ-dipeptides, with the former predominating. However, the reaction of **1** with secondary amino acids in pyrridine afforded γ-dipeptides (path a), which provided a series of compounds **3** and **6a–g** listed in Table I, while reaction with primary amino acids gave predominantly α-dipeptides (path b, Scheme I).

Scheme I[a]



[a] Reagents: (a) Ac_2O; (b) 2a, pyridine, 50 °C.

†Ksander, G. M., paper presented in part at the 19th National Medicinal Chemistry Symposium, Tuscon, AZ, June 1984.

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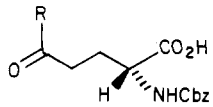
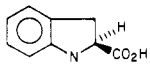
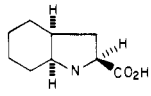
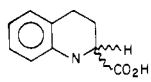
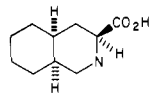
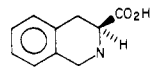
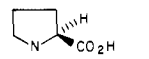
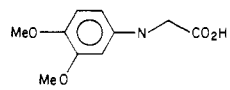
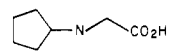
Table I. *N*-Carbobenzoxy-γ-D-glutamyl Dipeptides



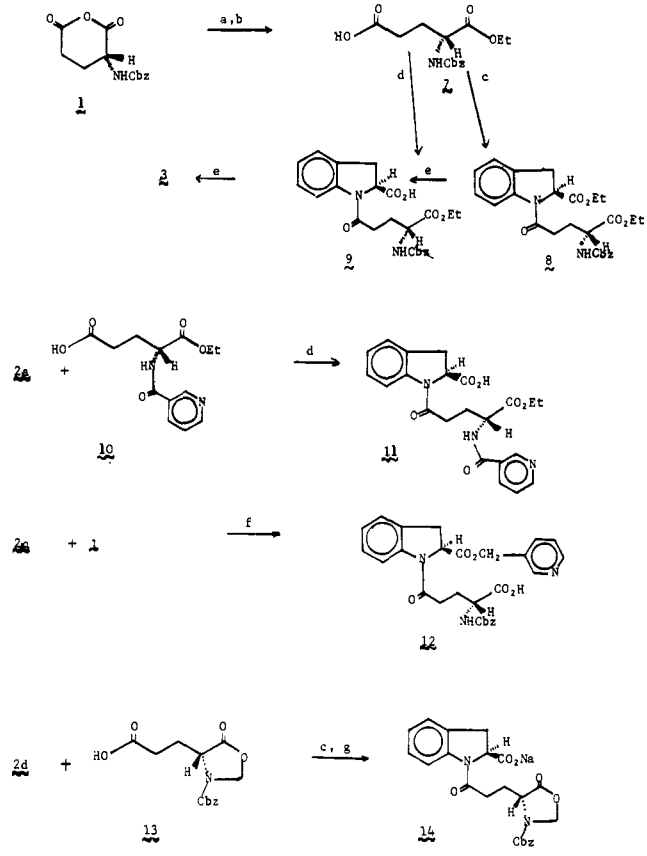
compd	R	mp,[a] °C	$[\alpha]_D$,[b] deg	ACE IC_{50},[c] nM
3		186–188	−60.0	7
6a		79–82	−21.0	2.7
6b		77–80		88
6c		61–64	+7.8	17
6d		87–89	+14.0	14
6e		53–55	−33.0	50
6f		75–79	+0.5[d]	21
6g[e]		67–70	+8.0[f]	40

[a] All compounds had satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structure. [b] Concentrations are given in the Experimental Section. [c] See ref 2e for details of procedure. [d] See ref 9. [e] Prepared analogous to the method described for compound **6a**. [f] *C* 0.5, methanol.

Hydrogenolysis of **3**, followed by alkylation or acylation of the glutamylamine, provided a series of compounds **5a–l** listed in Table II. The structure of **3** was verified as outlined in Scheme II. The mixed-acid ester **7** was prepared by a modification of known methodology.[7] The mixed-acid ester **7** was activated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and coupled with ethylindoline-2(*S*)-carboxylate (**2b**) to give the dipeptide **8**. Saponification provided diacid **3**, identical[8] with the diacid prepared from the nucleophilic opening of **1** with **2a** in pyridine.

Potential prodrugs were prepared by the following procedures, outlined in Scheme II. Regiospecific saponification of **8** with lithium hydroxide afforded the desired ester acid **9**. The structure of the hydrolysis product **9** was confirmed by comparison with a sample prepared in low yield by 1,1′-carbonyldiimidazole-mediated coupling of **7** with **2a**. The unstable oxazolinone **14** was prepared from activated ester coupling of the (dimethylamino)ethyl ester **2d** with **13**. Hydrolysis of the labile (dimethylamino)ethyl

Scheme II



[a] Reagents: (a) EtOH, dicyclohexylamine; (b) 1 N HCl; (c) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (**2b**). (d) 1,1′-Carbonyldiimidazole (**2a**). (e) 1 equiv of 1 N LiOH. (f) Pyridine. (g) Aqueous Na_2CO_3.

(1) (a) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science (Washington, D.C.)* **1977**, *No. 196*, 441. (b) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16*, 5484.

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(3) (a) Jacot des Combes, B.; Turini, G.; Brunner, H. R.; Porchet, M.; Chen, D. S.; Sen, S. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 511. (b) Witte, P. U.; Metzger, H.; Irmisch, R. *IRCS Med. Sci.* **1983**, *11* (12), 1053. (c) Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1980**, *20*, 409. (d) Ferguson, R. K.; Vlasses, P. H.; Swanson, B. N.; Cooper, D. L.; Davies, R. O.; Abrams, W. B. *Am. J. Cardiol.* **1981**, *47*, 1001. (e) Biollaz, J.; Burnier, M.; Turini, G. A.; Gomex, H.; Ferber, F.; Fotis, C.; Jones, K.; Lutterbeck, P.; Gavras, H.; Brunner, H. R. *Clin. Pharmacol. Ther.* **1983**, 234.

(4) We are using the same nomenclature to identify binding sites as those described in ref 2b.

(5) Harrington, C.; Mead, T. *Biochem. J.* **1935**, *29*, 1602.

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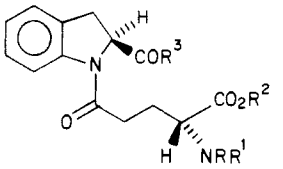
(7) Weygard, G.; Hunger, K. *Z. Naturforsch.* **1958**, *13B*, 50; *Chem. Abstr.* **1958**, *52*, 10880*a*.

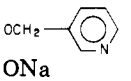
(8) Melting points and mixed melting point for both samples were 186–188 °C. The optical rotations of each sample was $[\alpha]_D$ −60° (*c* 1, CH_3OH).

(9) Due to the low optical rotation we looked at chiral shift reagents to determine optical purity. Unfortunately we were unable to determine enantiomeric purity of this sample.

(10) The in vitro ACE activity is primarily due to hydrolysis to the diacid **3**.

Table II. 1-(N-Substituted γ-D-glutamyl)indoline-2(S)-carboxylic Acids



compd	R	R^1	R^2	R^3	mp,[a] °C	$[\alpha]_D$,[b] deg	ACE IC_{50},[c] nM
3	CO_2CH_2Ph	H	H	OH	186-188	-60.0	7
3a[e]	CO_2CH_2Ph (S isomer)	H	H	OH	174-176	-77.3	500
4	H	H	H	OH	193-195	-110.0	10000
5a	$CO(CH_2)_2Ph$	H	H	OH	196-198	-65.9	40
5b	COPh	H	H	OH	120-123	-70.2	28
5c	CONHPh	H	H	OH	158-161	-88.4	44
5d	$SO_2C_6CH_3$-p	H	H	OH	138-140	-90.0	20
5e	SO_2CH_2Ph	H	H	OH	168-170	-65.0	29
5f	CO_2CH_2Ph	CH_2Ph	H	OH	95-99	-28.7	10000
5g	CO-3-py	H	H	OH	178-180	-63.6	24
5h	CO-2-py	H	H	OH	159-161	-77.0	57
5i	CH_2Ph	H	H	OH	188-190	-96.0	300
5j	$COCH_3$	H	H	OH	200-202	-110.0	95
5k	N,N'-$(Cbz)_2$-lysyl	H	H	OH	125-127	-46.0	61
5l	lysyl	H	H	OH	203-205	-71.8	188
9	CO_2CH_2Ph	H	CH_2CH_3	OH	68-71	-46.0	~1000
11	CO-3-py	H	CH_2CH_3	OH	231-235	-40.0	2200
12	CO_2CH_2Ph	H	H		157-158	-63.0	350
14	CO_2CH_2Ph	—CH_2—		ONa	140 dec	-64.4	52
15[e]	CO_2CH_2Ph	H	H	$O(CH_2)_3N(CH_3)_2$	167-169	-34.5[f]	37
16[e]	CO_2CH_2Ph	H	H	$O(CH_2)_2N(CH_3)_2$	178-179	-51.0[f]	7[d]
17[e]	CO_2CH_2Ph	H	H	NH_2	190-192	-85.6[f]	160
18[e]	CO_2CH_2Ph	H	H	OCH_2CH_3	74-77	-59.4[f]	4700

[a] All compounds had satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structure. [b] Concentrations are given in the Experimental Section. [c] See ref 2e for details of procedure. [d] See ref 10. [e] Prepared analogous to the method described for compounds 3 and 6a. [f] c 0.5, methanol.

ester with sodium carbonate gave **14**. 1,1'-Carbonyldiimidazole-mediated coupling of **2a** with the appropriate nicotinoyl derivative **10** gave the acid ester **11**. Refluxing β-picolylindoline-2(S)-carboxylate (**2c**) with **1** in tetrahydrofuran gave the acid ester **12**.

Biological Results and Discussion

The in vitro ACE inhibitory activities for the two series are listed in Table I and II. In the series of compounds with constant N-Cbz-glutamyl side chain and varied terminal amino acids (Table I), the 2-carboxyindoline (**3**) and the perhydroindoline (**6a**) were the most active. The increasing inhibitory activity of the series, proline **6e**, indoline **3** to perhydroindoline **6a** could be that the fused rings of **3** and **6a** force the side chain to occupy a more favorable position in space for interaction with the enzyme. One important conformation positions the amide carbonyl syn to the ring carboxylate. This assumption can be extrapolated from the structure of a potent 1-benzazaepin-2-one derivative,[11] which has a rigid amide bond that can occupy this conformation.

In the series where the glutamyl nitrogen substitution was varied (Table II), the N-Cbz derivative **3** was found to be at least 3 times as potent as other groups studied. The 6-fold difference in the activity of **3** compared to **5a**, different only in the carbamate oxygen being substituted for a methylene group, cannot be ascribed to chain length alone. Possibly the carbamate causes the acyl chain to occupy a more favorable geometry for enzyme interaction.

(11) Watthey, J.; Desai, M.; Babiarz, J.; Gavin, T.; Finn, B.; Stanton, J. "Abstract of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept. 2, 1983; American Chemical Society: Washington, DC, 1983; Abstr MEDI 93.

Table III. Biological Results

compd	ACE[a] IC_{50}, nM	AI[a,b] % inhibn, mg/kg iv	AI[c] % inhibn, mg/kg po
3	7	70 (0.1)	0 (1)
5a	40	76 (1)	
5b	28	55 (0.1)	
5g	24	79 (0.1)	0 (1)
9	1000	57 (1)	0 (1)
11	2200	100 (1)	30 (10)
12	350	70 (1)	15 (10)

[a] See ref 2e for details of procedure. [b] Tabulated results indicate percent inhibition of angiotensin I pressor response 15 min after intravenous administration of test compound. [c] Tabulated results indicated maximum percent inhibition of angiotensin I pressor response 2 h after oral administration of test compound.

Other acylated nitrogen entries including carboxyaralkyl, benzoyl, tosyl, phenylurea, or carboxypyridyl all had inhibitory values within the (2–5) × 10^{-8} M range. Compounds **4** and **5i**, having a basic nitrogen, showed a >10-fold decrease in activity, which possibly arose from decreased coordination ability of the glutamyl carboxyl group with the zinc atom at the active site of the enzyme. Compound **5f**, the N-benzyl analogue of **3**, had a 10^3-fold decrease in potency compared to **3**, possibly due to steric effects.

The in vivo ACE inhibitory activity of the more active diacid members of this series was evaluated in normotensive rats as summarized in Table III. Compounds **3** and **5g** when administered intravenously at a dose of 0.1 mg/kg produced 70% and 79% inhibition, respectively. The pyridyl-containing dipeptide **5g** showed increased in vivo activity relative to the other N-acylated compounds of comparable in vitro strength. Oral administration of

these diacids did not result in inhibition of AI pressor response.

A number of ester prodrugs[12] were prepared with the aim of improving the oral activity. The potential prodrugs **9**, **11**, and **12**, when administered intravenously at 1 mg/kg, produced 57%, 100%, and 70% inhibition, respectively, indicating that these prodrugs are apparently converted to the active diacids. Unfortunately significant oral activity was still not observed. The pyridyl derivative **11** showed minimal oral activity (30% inhibition) at a 10 mg/kg dose, whereas upon intravenous administration a 100% inhibition of the AI pressor response was achieved at 1 mg/kg.

In summary, for the compounds presented in this paper the *N*-Cbz group was optimal for enzyme inhibition within the S_1 sector of the active site. The lack of a substituent in the S_1' sector is compensated for by replacing proline with indoline-2(*S*)-carboxylic acid or perhydro-*cis*-indoline-2(*S*)-carboxylic acid.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton NMR spectra were determined on a Varian EM-390 and XL 200 spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 457 or Perkin-Elmer Model 137 spectrophotometers. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Compounds **3a**, **6g**, and **15–18** were prepared by methods identical with those described below.

1-(*N*-Carbobenzoxy-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (3). To the solution of 22.5 g of indoline-2-(*S*)-carboxylic acid hydrochloride (**2a**)[2e] (0.113 mol) in 150 mL of pyridine under an atmosphere of nitrogen was added 30.0 g (0.114 mol) of *N*-carbobenzoxy-D-glutamic anhydride (**1**),[5] $[\alpha]_D$ +44.1° (*c* 1.9, methanol). The mixture was heated to 80 °C for 5 h and left to stir at room temperature overnight. The solvent was removed, and the residue was cooled in an ice bath, diluted with 100 mL of water, and acidified with 40 mL of concentrated HCl, giving a viscous gum. The gum was solidified, broken up, washed with methylene chloride and water, and air-dried. The solid was suspended in 70 mL of $CHCl_3$, filtered, washed with $CHCl_3$, and dried at high vacuum to yield 24.5 g (51%) of **3** as a colorless solid melting at 186–188 °C: $[\alpha]_D$ −60.0° (*c* 1, ethanol); IR (KBr) 3400 (NH), 3150 (OH), 1740 (CO), 1725 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.0 (br s, 2, CO_2H), 8.04 (d, 1 H, *J* = 8 Hz, Ar H), 7.57 (d, 1 H, *J* = 7 Hz, NH), 7.31 (s, 5 H, C_6H_5), 7.20 (m, 2 H, Ar H), 7.00 (t, 1 H, *J* = 8 Hz, Ar H), 5.13 (br d, 1 H, *J* = 9 Hz, NCH), 5.00 (s, 2 H, OCH_2), 4.13 (m, 1 H, NCH), 3.7–2.1 (m, 6 H). Anal. ($C_{22}H_{22}N_2O_7$) C, H, N.

General Procedure for the Formation of γ-Dipeptides (6a–g) from *N*-Cbz-D-glutamic Anhydride (1). 1-(*N*-Carbobenzoxy-γ-D-glutamyl)-*cis*-perhydroindoline-2(*S*)-carboxylic Acid (6a). To a solution of 0.5 g of perhydroindoline-2(*S*)-carboxylic acid hydrochloride[15] (2.4 mmol) in 10 mL of pyridine under an atmosphere of nitrogen was added 0.64 g (2.4 mmol) of **1**. The mixture was heated to 70 °C for 5 h. The solvent was removed, and the residue was cooled in an ice bath, acidified (2 N HCl) to pH ~2, and extracted with methylene chloride. The organic extract was concentrated. The residue was treated with 5% sodium bicarbonate and shaken with ether. The basic aqueous layer was cooled, reacidified (2 N HCl), extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated, suspended in hexanes, and filtered to give 0.55 g (53%) of **6a** as a colorless solid melting at 79–82 °C: $[\alpha]_D$ −21.0° (*c* 1.8, methanol); IR (Nujol) 3300, 1720, 1510, 1220 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.5 (br s, 2 H), 7.62 (d, 1 H, *J* = 7 Hz), 7.42 (s, 5 H), 5.06 (s, 2 H), 4.3–3.6 (m, 3 H), 2.4–1.1 (m, 15 H). Anal. ($C_{22}H_{28}N_2O_7$) C, H, N.

1-(*N*-Carbobenzoxy-γ-D-glutamyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (6b) was prepared as described above (73%) to give a colorless solid: mp 77–80 °C; IR (Nujol) 3300, 1720, 1220 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.7 (br s, 2 H), 7.6–7.0 (m, 9 H), 7.38 (s), 5.05–4.90 (m, 3 H), 5.00 (br s), 3.95 (m, 1 H), 2.70–1.20 (m, 8 H). Anal. ($C_{23}H_{24}N_2O_7$) C, H, N.

1-(*N*-Carbobenzoxy-γ-D-glutamyl)-*cis*-octahydroisoquinoline-3(*S*)-carboxylic acid (6c) was prepared as described above (39%) to give a colorless solid: mp 61–64 °C; $[\alpha]_D$ +7.8° (*c* 1.9, methanol); IR (Nujol) 3300, 1720, 1510, 1220 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.0 (br s, 2 H), 7.19 (d, 1 H, *J* = 7 Hz), 7.00 (s, 5 H), 4.80 (s, 2 H), 4.70 (m, 1 H), 3.80 (m, 1 H), 2.42–1.20 (m, 18 H). Anal. ($C_{23}H_{30}N_2O_7 \cdot {}^1/_2H_2O$) C, H, N.

1-(*N*-Carbobenzoxy-γ-D-glutamyl)-1,2,3,4-tetrahydroisoquinoline-3(*S*)-carboxylic acid (6d) was prepared as described above (55%) to give a colorless solid: mp 87–89 °C; $[\alpha]_D$ +14.0° (*c* 1.5, methanol); IR (Nujol) 3300, 1720, 1510, 1210 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.0 (br s, 2 H), 7.61 (d, 1 H, *J* = 7 Hz), 7.47 (s, 5 H), 7.32 (s, 4 H), 5.22 (m, 1 H), 5.10 (s, 2 H), 4.7–4.2 (m, 3 H), 3.19 (m, 2 H), 2.7–1.7 (m, 4 H). Anal. ($C_{23}H_{24}N_2O_7$) C, H, N.

1-(*N*-Carbobenzoxy-γ-D-glutamyl)proline (6e) and the α-regioisomer were isolated as the mixture following the described general procedure in the ratio of 6 to 1, respectively. The pure γ isomer **6e** was obtained by esterification, chromatographic separation (silica gel, eluting with ethyl acetate), and saponification to the diacid **6e** (49%): mp 53–55 °C; $[\alpha]_D$ −33.2° (*c* 0.5, methanol); IR (KBr) 3400 (br), 1725 (br), 1525, 1210 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.5 (br s, 2 H), 7.62 (d, *J* = 7 Hz, 1 H), 7.46 (br s, 5 H), 5.02 (s, 2 H), 4.03 (m, 2 H), 3.25 (m, 2 H), 1.86 (m, 8 H). Anal. ($C_{18}H_{22}N_2O_7$) C, H, N.

***N*-[1-(*N*-Carbobenzoxy-γ-D-glutamyl)-3,4-dimethoxyphenyl]glycine (6f)** was prepared as described above (34%) to give a solid that was contaminated with a small amount of *N*-Cbz-glutamic acid. The dipeptide could be isolated via esterification, chromatographic separation (silica gel eluting with ethyl acetate–methylene chloride (1:1), and saponification to the diacid **6f**.[9] In this case it was more convenient to react *N*-(3,4-dimethoxyphenyl)glycine ethyl ester with **1** in pyridine followed by esterification, chromatographic separation, and saponification to the diacid **6f** (32%): mp 75–79 °C; IR ($CHCl_3$) 3400 (br), 1720, 1650, 1595, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) 9.05 (br s, 2 H), 7.40 (s, 5 H), 6.93 (br s, 3 H), 6.0 (br, 1 H), 5.10 (s, 2 H), 4.37 (br s, 2 H), 3.90 (s, 6 H), 2.32 (m, 4 H). Anal. ($C_{23}H_{26}N_2O_9 \cdot 0.67H_2O$) C, H, N.

1-(γ-D-Glutamyl)indoline-2(*S*)-carboxylic Acid (4). A solution of **3** (18.0 g, 42.2 mmol) in 450 mL of EtOH with 3.6 g of suspended 10% Pd/C was hydrogenated at atmospheric pressure for 16 h. The product crystallized out of solution and was removed by filtration. The crude product was separated from the catalyst by treating the mixture with 400 mL of hot H_2O, filtering, and washing the solid with another 100-mL aliquot of hot H_2O. The aqueous filtrate was concentrated to about 250 mL and cooled in an ice bath. The precipitate was collected and dried to yield 9.2 g (74%) of **4** as a colorless solid melting at 193–195 °C; $[\alpha]_D$ −116° (*c* 1, EtOH); IR (Nujol) 3200, 17058 1650, 1600 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.55 (br s, 4 H, exchangeable), 8.15 (d, 1 H, *J* = 8 Hz), 7.2 (m, 3 H), 4.98 (m, 1 H), 3.70 (m, 1 H), 3.5–2.0 (m, 6 H). Anal. ($C_{14}H_{16}N_2O_5$) C, H, N.

1-(*N*-Carbophenethyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5a). To a solution of NaOH (0.33 g, 8.25 mmol) and **4** (1.2 g, 4.05 mmol) in 4 mL of H_2O cooled to 0 °C were simultaneously added NaOH (0.16 g, 4.1 mmol) in 2 mL of H_2O and dihydrocinnamoyl chloride (0.69 g, 4.1 mmol). The mixture was stirred at room temperature overnight, filtered, cooled, and acidified with 2.5 mL of 12 N HCl. The colorless solid was collected and dried at 50 °C under high vacuum to give 1.3 g (71%) of **5a** melting at 196–198 °C: $[\alpha]_D$ −65.9° (*c* 1, CH_3OH); IR (Nujol) 3380, 3100, 1730, 1695, 1670 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.5 (br s, 2 H, exchangeable), 8.20 (m, 2 H), 7.27 (s, 5 H), 7.20 (m, 3 H), 5.07 (br d, 1 H, *J* = 9 Hz), 4.30 (m, 1 H), 3.7–1.9 (m, 10 H). Anal. ($C_{23}H_{24}N_2O_6$) C, H, N.

1-(*N*-Benzoyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5b) was prepared as described for **5a** to give a colorless solid

(12) Oral activity of other compounds have previously been shown to be improved through esterification: Gross, D. M.; Sweet, C. S.; Ulm, E. H.; Borklund, E. P.; Morris, A. A.; Weitz, D.; Bohn, D. L.; Wenger, H. C.; Vassil, T. C.; Stone, C. A. *J. Pharmacol. Exp. Ther.* **1981**, *216*, 552.

(13) Itoh, M. *Chem. Pharmacol. Bull.* **1969**, *17*, 1683.

(14) This material was hygroscopic and contained a detectable amount of dimethylethanolamine.

(15) Vincent, M.; Rémond, G.; Portvein, B.; Sertiz, B.; Laubie, M. *Tetrahedron Lett.* **1982**, 1677.

(72%) melting at 120–123 °C; $[\alpha]_D$ –70.2° (*c* 1, CH_3OH); IR (Nujol) 3300, 3100, 1730, 1645 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.0 (br s, 2 H, exchangeable), 8.7 (d, 1 H, *J* = 7.5 Hz), 8.2–6.9 (m, 9 H), 5.10 (br d, 1 H, *J* = 8 Hz), 4.47 (m, 1 H), 3.7–1.9 (m, 6 H). Anal. ($C_{21}H_{20}N_2O_6$) C, H, N.

1-[*N*-(Phenylcarbamoyl)-γ-D-glutamyl]indoline-2(*S*)-carboxylic Acid (5c). To a suspension of **4** (1.0 g, 3.4 mmol) in 20 mL of DMF was added phenyl isocyanate (0.407 g, 3.42 mmol). The mixture was stirred for 2 days at room temperature. A small amount of insoluble material was removed by filtration. The filtrate was concentrated and partitioned between Et_2O and 15 mL of 5% aqueous $NaHCO_3$. The basic aqueous layer was separated, washed with ether, cooled, and acidified with 3 mL of 12 N HCl. The solid was collected, washed with H_2O, stirred vigorously in ether, filtered, and dried under high vacuum to give 0.95 g (67%) of **5c** melting at 158–161 °C: $[\alpha]_D$ –88.4 (*c* 0.25, CH_3OH); IR (Nujol) 3400–3300, 1720, 1670 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.5 (br s, exchangeable), 8.74 (s, 1 H), 8.15 (m, 1 H), 7.2 (m, 8 H), 6.53 (d, 1 H, *J* = 7.5 Hz), 5.10 (br d, 1 H, *J* = 9 Hz), 3.72–2.0 (m, 6 H). Anal. ($C_{21}H_{21}N_3O_6$) C, H, N.

1-[*N*-(*p*-Tolylsulfonyl)-γ-D-glutamyl]indoline-2(*S*)-carboxylic Acid (5d). To a solution of **4** (1.2 g, 4.1 mmol) and NaOH (0.49 g, 12.3 mmol) in 5 mL of H_2O cooled in an ice bath was added *p*-toluenesulfonyl chloride (0.78 g, 4.1 mmol). The mixture was stirred at room temperature overnight, cooled in an ice bath, acidified with 1 mL of 12 N HCl, and extracted three times with EtOAc. The organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a form that solidified after stirring 12 h with 25 mL of Et_2O. The solid was collected and dried under high vacuum to give 0.68 g (38%) of **5d** melting at 138–140 °C: $[\alpha]_D$ –90° (*c* 0.25, CH_3OH); IR (Nujol) 3280, 1720, 1655, 1630, 1595, 1160, 1090 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.10 (m, 2 H), 7.70 (d, 2 H, *J* = 8 Hz), 7.20 (m, 5 H), 4.92 (m, 1 H), 3.9–2.0 (m, 7 H), 2.22 (s, 3 H). Anal. ($C_{21}H_{22}N_2O_7S$) C, H, N.

1-[*N*-(Benzylsulfonyl-γ-D-glutamyl]indoline-2(*S*)-carboxylic Acid (5e) was prepared as described for **5d** to give a colorless solid (34%), melting at 168–170 °C: $[\alpha]_D$ –65° (*c* 1, CH_3OH); IR (KBr) 1712, 1668, 1487, 1412 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 11.1 (br s, 2 H, exchangeable), 8.37 (d, 1 H, *J* = 7.5 Hz), 7.55–7.0 (m, 9 H), 5.07 (dd, 1 H, *J* = 3 and 4 Hz), 4.35 (s, 2 H), 4.04 (m, 1 H), 3.65–1.9 (m, 6 H). Anal. ($C_{21}H_{22}N_2O_7S$) C, H, N.

1-(*N*-Carbobenzoxy-*N*-benzyl-γ-D-glutamyl)indoline-2-(*S*)-carboxylic Acid (5f). To a solution of **5i** (0.118 g, 0.319 mmol) and K_2CO_3 (0.220 g, 1.6 mmol) in 10 mL of water was added benzyl chloroformate (0.271 g, 1.6 mmol). The mixture was stirred vigorously for 15 h and then diluted with 15 mL of H_2O containing 0.1 g of K_2CO_3. The basic aqueous mixture was extracted two times with Et_2O and acidified with 1 N HCl to pH 2. The colorless solid was collected, rinsed with water, and dried under high vacuum to give 0.11 g (67%) of **5f**, melting at 95–99 °C: $[\alpha]_D$ –28.7° (*c* 0.4, CH_3OH); IR (KBr) 1740, 1720, 1700, 1595, 1485; ^1H NMR ($CDCl_3$) δ 10.4 (br s, 2 H, exchangeable), 8.28 (d, 1 H, *J* = 9 Hz), 7.29 (s, 5 H), 7.14 (m, 8 H), 5.14 (s, 2 H), 4.84 (m, 1 H), 4.56 (AB q, 2 H, *J* = 9 and 15 Hz), 3.80 (m, 1 H), 3.25 (m, 1 H), 2.4 (m, 4 H). Anal. ($C_{29}H_{28}N_2O_7$) C, H. N.

1-(*N*-Nicotinoyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5g). To a solution of nicotinic acid (1.05 g, 8.6 mmol) and *N*-hydroxy-5-norbornene-2,3-dicarboximide (1.6 g, 8.9 mmol) in 30 mL of dimethylformamide was added DCC (1.94 g, 9.8 mmol). The mixture was stirred for 3.5 h at room temperature and filtered, and to the filtrate was added **4** (2.5 g, 8.6 mmol). The mixture was heated to 70 °C overnight, concentrated, and triturated with 20 mL of cold H_2O. The solid was collected and partitioned between 100 mL of hot EtOAc and 25 mL of warm water. The aqueous layer was separated, and upon cooling **5g** crystallized and was collected by filtration to give 0.5 g (15%) of colorless solid, melting at 178–180 °C: $[\alpha]_D$ –63.6° (*c* 0.5, CH_3OH); IR (Nujol) 3370, 1727, 1650 cm^{-1}; ^1H NMR (Me_2SO-d_6) 11.5 (br s, 2 H, exchangeable), 8.92 (m, 3 H), 8.18 (m, 2 H), 7.50 (m, 1 H), 7.19 (m, 3 H), 5.14 (m, 1 H), 4.50 (m, 1 H), 3.17–1.9 (m, 6 H). Anal. ($C_{20}H_{19}N_3O_6$) C, H, N.

1-(*N*-Picolinoyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5h). A solution of **4** (1.0 g, 3.4 mmol) and *N*-[(2-pyridylcarbonyl)oxy]succinimide (0.75 g, 3.4 mmol) and 15 mL of dimethylformamide was heated at 80 °C for 2 h and then stirred at room temperature overnight. The mixture was concentrated and stirred with 40 mL of H_2O which initiated crystallization. The solid was collected and dried to give 1.0 g (75%) of **5h**. Recrystallization of **5h** from a water–2propanol mixture (9:1) gave the product (46%), melting at 159–161 °C: $[\alpha]_D$ –77° (*c* 0.25, CH_3OH); IR (KBr) 3340, 1740, 1665, 1634, 1600, 1490 cm^{-1}; ^1H NMR (Me_2SO-d_6) 11.5 (br s, 2 H, exchangeable), 8.95 (d, 1 H, *J* = 7.5 Hz), 8.77 (d, 1 H, *J* = 3 Hz), 8.10 (m, 3 H), 7.70 (d, 1 H, *J* = 3 Hz), 7.1k (m, 3 H), 5.15 (m, 1 H), 4.55 (m, 1 H), 3.9–2.0 (m, 6 H). Anal. ($C_{20}H_{19}N_3O_6$) C, H, N.

1-(*N*-Benzyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5i). To a solution of NaOH (0.33 g, 8.25 mmol) and **4** (1.2 g, 4.05 mmol) in 20 mL of H_2O was added benzaldehyde (0.44 g, 4.1 mmol). The mixture was stirred for 15 min and cooled in an ice bath, and $NaBH_4$ (0.052 g, 1.4 mmol) was added. The additions of benzaldehyde (0.44 g) and sodium borohydride (0.052 g) were repeated. The mixture was slowly warmed to room temperature and stirred overnight. The suspension was filtered and cooled in an ice bath, and pH was adjusted to 3.5 with 12 N HCl. The precipitate was collected, suspended in 20 mL of hot H_2O, filtered, washed with H_2O, collected, and dried at 80 °C under high vacuum to give 1.3 g (84%) of **5i**, melting at 188–190 °C: $[\alpha]_D$ –96° (*c* 0.5, 1 N NaOH); IR (Nujol) 3100, 1720, 1655, 1600 cm^{-1}; ^1H NMR (CF_3CO_2D) 8.18 (m, 1 H), 7.52 (s, 5 H), 7.33 (m, 3 H), 5.34 (m, 1 H), 4.50 (br s, 2 H), 4.32 (m, 1 H), 3.9–2.3 (m, 6 H). Anal. ($C_{21}H_{22}N_2O_5$) C, H, N.

1-(*N*-Acetyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5j). To a solution of acetic anhydride (3.5 mL), HOAc (7 mL), and 10 mL of H_2O was added **4** (0.70 g, 2.4 mmol). The mixture was stirred for 15 h and concentrated under reduced pressure. The resulting solid was dissolved in 10 mL of CH_3OH and triturated with H_2O. The colorless solid was collected and dried under high vacuum to give 0.59 g (74%) of **5j**, melting at 200–202 °C: $[\alpha]_D$ –110° (*c* 0.25, CH_3OH); IR 3280, 1720, 1648, 1620, 1480 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.1 (br s, 2 H, exchangeable), 8.17 (m, 2 H), 7.16 (m, 3 H), 5.07 (d, 1 H, *J* = 9 Hz), 4.22 (m, 1 H), 3.7–1.9 (m, 6 H), 1.78 (s, 3 H). Anal. ($C_{16}H_{18}N_2O_6$) C, H, N.

1-[*N*-(*N*′,*N*″-Dicarbobenzoxy-L-lysyl)-γ-D-glutamyl]-indoline-2(*S*)-carboxylic Acid (5k). To a cold solution of *N*,*N*′-dicarbobenzoxy-L-lysine (1.77 g, 4.27 mmol) and *N*-hydroxy-5-norbornene-2,3-dicarboximide (0.80 g, 4.5 mmol) in 15 mL of EtOAc and 20 mL of THF was added DCC (0.97 g, 4.7 mmol). After 0.5 h the ice bath was removed, and stirring was continued for 2 h. The mixture was filtered and concentrated, and the resulting oil was dissolved in 50 mL of DMF and filtered. To the filtrate was added **4** (1.25 g, 4.27 mmol). The mixture was heated to 70 °C overnight, concentrated at 40 °C under high vacuum, and partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, washed with 1 N HCl and H_2O, dried (Na_2SO_4), filtered, and concentrated. The resulting foam was suspended in Et_2O, and the solid was collected and dried at 60 °C under high vacuum to give 1.9 g (66%) of **5k**, melting at 125–127 °C: $[\alpha]_D$ –46° (*c* 1, CH_3OH); IR (Nujol) 3330, 3290, 1735, 1645 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.18 (m, 2 H), 7.40 (s, 10 H), 7.15 (m, 5 H), 5.07 (s, 2 H), 5.02 (s, 2 H), 4.40 (m, 1 H), 4.10 (m, 1 H), 3.6–1.2 (m, 14 H). Anal. ($C_{36}H_{40}N_4O_{10}$) C, H, N.

1-(L-Lysyl-γ-D-glutamyl)indoline-2(*S*)-carboxylic Acid (5l). A solution of **5k** (1.2 g, 1.7 mmol) in 70 mL of EtOH containing 1.0 g of suspended 10% Pd/C was hydrogenated under 50 psi for 2 h. The reaction vessel was evacuated, recharged with hydrogen, shaken 1 h, reevacuated, then recharged with hydrogen, and shaken overnight. The crystallized product along with the catalyst was collected by filtration. The mixture was suspended in hot H_2O, filtered, and washed well with H_2O. The filtrate was concentrated, and the residue was slurried with 15 mL of EtOH. The colorless solid was collected and dried under high vacuum to give 0.52 g (71%) of **5l**, melting at 203–205 °C: $[\alpha]_D$ –71.8 (*c* 0.5, 1 N NaOH); IR (Nujol) 3400–3100 (br), 1600 (br) cm^{-1}; ^1H NMR (D_2O) δ 8.14 (m, 1 H), 7.32 (m, 3 H), 5.00 (m, 1 H), 4.19 (m, 2 H), 3.7–1.5 (m, 14 H). Anal. ($C_{20}H_{28}N_4O_6$) C, H, N.

α-Ethyl D-***N*-carbobenzoxyglutamate (7)** was prepared by a modified literature[7] procedure. To a solution of 7.26 g of dicyclohexylamine (40 mmol) in 80 mL of anhydrous ethanol at 0 °C was added 10.8 g of **1** (40 mmol) in 40 mL of dry tetrahydrofuran dropwise. After the addition of complete, the solution was gradually warmed to room temperature and stirred for an

additional 15 h. Concentrating the solution, triturating with ether–hexane, and recrystallizing from water gave 14.6 g of **7** as the dicyclohexylamine salt (77%): mp 158–160 °C; $[\alpha]_D$ +12.4 (*c* 0.5, methanol); [lit.[7] mp 160–161 °C; $[\alpha]_D$ −7.84° (*c* 1, in methanol)].

Free acid **7** could be generated as previously described[7] or dissolving the dicyclohexylamine salt in methylene chloride and shaking with cold 1 N hydrochloric acid.

Ethyl 1-[4-(*N*-Carbobenzoxyamino)-4-carboethoxy-4-(*R*)-butyryl]indoline-2(*S*)-carboxylic Acid (8). The solution of 1.0 g (3.8 mmol) of **3** in 40 mL of EtOH containing 0.2 mL of 36 N H_2SO_4 was refluxed 3 h, concentrated, diluted with Et_2O, washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4), filtered, and concentrated. The residue was suspended in hexane–Et_2O (5:1). The solid was collected and dried under high vacuum to give 0.83 g (70%) of **8** as a colorless solid, melting at 119–120 °C. This material was identical with the diester prepared from the coupling of **7** with **2b**: $[\alpha]_D$ −55.3 (*c* 0.9, CH_3OH); IR ($CHCl_3$) 3400, 1745, 1670 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.17 (d, 1 H, *J* = 8 Hz), 7.82 (d, 1 H, *J* = 7 Hz), 7.48 (s, 5 H), 7.20 (m, 3 H), 5.27 (m, 1 H), 5.07 (s, 2 H), 4.14 (m, 5 H), 3.8–2.0 (m, 6 H), 1.20 (q, 6 H, *J* = 8 Hz). Anal. ($C_{26}H_{30}N_2O_7$) C, H, N.

1-[4-(*N*-Carbobenzoxyamino)-4-(ethoxycarbonyl)-4(*R*)-butyryl]indoline-2(*S*)-carboxylic Acid (9). To a solution of **8** (1.3 g, 2.69 mmol) in 200 mL EtOH was added 2.66 mL of 1 N LiOH. The cloudy solution was stirred for 15 h, filtered, and concentrated. The residue was partitioned between Et_2O and H_2O. The aqueous layer was separated, washed with Et_2O, cooled in an ice bath, acidified with 12 N HCl, and extracted with CH_2Cl_2. The organic layer was concentrated and flash chromatographed on silica gel eluting with EtOAc–CH_3OH (9:1), giving 0.34 g (28%) of **9** as a colorless solid after stirring with hexanes: mp 68–71 °C; $[\alpha]_D$ −46° (*c* 0.9, CH_3OH); IR (Nujol) 3320, 1730, 1660, 1595, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.5 (br s, 1 H, exchangeable), 8.21 (m, 1 H), 7.30 (s, 5 H), 7.15 (m, 3 H), 6.05 (m, 1 H), 5.02 (s, 2 H), 4.95 (m, 1 H), 4.25 (m, 1 H), 4.10 (q, 2 H, *J* = 7 Hz), 3.5–2.0 (m, 6 H), 1.12 (t, 3 H, *J* = 7 Hz). Anal. ($C_{24}H_{27}N_2O_7 \cdot 0.5H_2O$) C, H, N.

1-[4-(*N*-Nicotinoylamino)-4-(ethoxycarbonyl)-4(*R*)-butyryl]indoline-2(*S*)-carboxylic Acid (11). To a solution of the dicyclohexylamine salt of **7** (11.0 g, 22.4 mmol) in 150 mL of CH_2Cl_2 at 0 °C was added 150 mL of 1 N HCl. The mixture was vigorously stirred for 1 h and filtered. The CH_2Cl_2 layer was separated, washed with H_2O, dried (Na_2SO_4), filtered, and concentrated to give 6.9 g of **7**.

A solution of **7** (6.9 g, 22.4 mmol) in 70 mL of EtOH with 1.0 g of suspended 10% Pd/C was hydrogenated 1 h at room temperature and atmospheric pressure. The flask was evacuated, recharged with hydrogen, and shaken for 4 h. At this time the flask was again evacuated, recharged with hydrogen, and shaken 4 h. The mixture was filtered through Celite. The filtrate was concentrated to give 2.9 g (74%) of α-ethyl D-glutamate as a colorless powder, melting at 97–99 °C; $[\alpha]_D$ −14.2° (*c* 1, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 6.18 (s, 3 H, exchangeable), 4.10 (q, 2 H, *J* = 7 Hz), 3.41 (dd, 1 H, *J* = 6 and 4.5 Hz), 2.25 (t, 2 H, *J* = 7 Hz), 1.74 (m, 2 H), 1.20 (t, 3 H, *J* = 7 Hz); IR (KBr) 3400, 1735, 1620, 1560 cm^{-1}.

A solution of α-ethyl D-glutamate (1.0 g, 5.7 mmol) and *N*-[(3-pyridylcarbonyl)oxy]succinimide (1.25 g, 5.7 mmol) in 20 mL of dimethylformamide was heated 2 h at 80 °C. The mixture was concentrated, and 10 mL of cold H_2O was added. The colorless solid was collected, washed with cold H_2O, and dried under high vacuum to give 1.1 g (63%) of **10** melting at 157–159 °C: $[\alpha]_D$ +18.4° (*c* 1, CH_3OH); IR (KBr) 3300, 1740, 1700, 1595, 1530 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.2 (br s, 1 H), 9.12 (d, 1 H, *J* = 2 Hz), 8.98 (d, 1 H, *J* = 8 Hz), 8.80 (dd, 1 H, *J* = 2 and 5 Hz), 8.27 (dt, 1 H, *J* = 2 and 8 Hz), 7.55 (dd, 1 H, *J* = 8 and 3 Hz), 4.50 (q, 1 H, *J* = 8 Hz), 4.15 (q, 2 H, *J* = 7.5 Hz), 2.40 (t, 2 H, *J* = 8 Hz), 2.05 (m, 2 H), 1.23 (t, 3 H, *J* = 7.5 Hz).

To a suspension of **10** (1.0 g, 3.57 mmol) in 20 mL of CH_2Cl_2 at 0 °C was added 1,1′-carbonyldiimidazole (0.60 g, 3.7 mmol)in 10 mL of CH_2Cl_2. After the mixture was stirred for 1.5 h, **2a** (0.71 g, 3.57 mmol) in 8 mL of pyridine was added. The reaction mixture was stirred 15 h at room temperature and concentrated to give a gummy residue. The residue was treated with 20 mL of 5% aqueous $NaHCO_3$ and extracted twice with Et_2O. The basic aqueous phase was cooled in an ice bath, and the pH of the solution was adjusted to 4.0 with 6 N HCl. The precipitate was collected, washed with H_2O, and dried under high vacuum to give 0.32 g (21%) of **11**, melting at 231–233 °C; $[\alpha]_D$ −40° (*c* 0.5, CH_3OH); IR (KBr) 3310, 1750, 1662, 1650, 1490, 1220 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.08 (m, 2 H), 8.80 (d, 1 H, *J* = 5 Hz), 8.22 (m, 2 H), 7.54 (dd, 1 H, *J* = 8 and 3 Hz), 7.18 (m, 3 H), 5.12 (m, 1 H), 4.57 (m, 1 H), 4.15 (q, 2 H, *J* = 7 Hz), 3.8–2.0 (m, 6 H), 1.2 (t, 3 H, *J* = 7 Hz). Anal. ($C_{22}H_{23}N_3O_6$) C, H, N.

3-Pyridylmethyl 1-(*N*-Carbobenzoxy-γ-D-glutamyl)-indoline-2(*S*)-carboxylate (12). The solution of **1**[5] (1.25 g, 4.75 mmol) and **2c** (1.20 g, 4.75 mmol) in 10 mL of THF was refluxed 18 h. The mixture was concentrated and recrystallized from 20 mL of EtOAc–EtOH (3:1). The colorless solid was collected, rinsed with cold EtOAc, and dried under high vacuum to give 0.60 g (25%) of **12**, melting at 157–158 °C; $[\alpha]_D$ −63° (*c* 0.5, CH_3OH); IR (KBr) 3350, 1740, 1690, 1655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.64 (m, 2 H), 8.19 (d, 1 H, *J* = 8 Hz), 7.79 (m, 2 H), 7.43 (s, 5 H), 7.17 (m, 5 H), 5.34 (m, 1 H), 5.25 (s, 2 H), 5.07 (s, 2 H), 4.15 (m, 1 H), 3.7–1.8 (m, 6 H). Anal. ($C_{28}H_{27}N_3O_7$) C, H, N.

Sodium 1-[[(*R*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidinyl]propionyl]indoline-2(*S*)-carboxylate (14). To the solution of **2d** (1.27 g, 5.42 mmol) and **13**[13] (1.60 g, 5.46 mmol) in 5 mL of CH_2Cl_2 was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.22 g, 6.3 mmol). The reaction mixture was stirred at room temperature for 15 h. The solution was diluted with 150 mL of EtOAc and washed two times with 20% NaCl, 5% cold $NaHCO_3$, and saturated NaCl. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to give 1.5 g (54%) of the (dimethylamino)ethyl ester of **14** as a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.92 (m, 1 H), 7.12 (s, 5 H), 6.9 (m, 3 H), 5.22 (AB q, 2 H, *J* = 14 and 7.5 Hz), 5.03 (s, 2 H), 4.89 (m, 1 H), 4.10 (m, 3 H), 3.22 (m, 2 H), 2.5–2.0 (m, 6 H), 2.14 (s, 6 H). To the above ester (0.40 g, 0.78 mmol) in 3 mL of THF was added 0.78 mL of 1 N NaOH and the resultant mixture stirred for 2 h. The solvent was evaporated, and the resulting oil was dissolved in 5 mL of CH_3OH and triturated with Et_2O. The solvent was decanted off, Et_2O was added to the semisolid, and the suspension was stirred overnight. The fine powder was collected and dried under high vacuum to give 0.2 g (53%) of **14**,[14] melting at 140 °C dec: $[\alpha]_D$ −64.4° (*c* 1, CH_3OH); IR (KBr) 3400, 1695, 1600, 1480 cm^{-1}; ^1H NMR (Me_2SO-d_6) 8.20 (d, 1 H, *J* = 7.5 Hz), 7.45 (s, 5 H), 7.45–6.9 (m, 3 H), 5.14 (s, 2 H), 5.3–4.5 (m, 4 H), 3.23 (m, 2 H), 2.4–1.9 (m, 4 H).

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Registry No. 1, 71869-80-2; **2a**, 79815-20-6; **2b**, 82923-81-7; **2c**, 97975-29-6; **2d**, 97975-30-9; **3**, 97975-31-0; **3a**, 97975-32-1; **4**, 97975-33-2; **5a**, 97975-34-3; **5b**, 97975-35-4; **5c**, 97975-36-5; **5d**, 97975-37-6; **5e**, 97975-38-7; **5f**, 97975-39-8; **5g**, 97975-40-1; **5h**, 97975-41-2; **5i**, 97975-42-3; **5j**, 97975-43-4; **5k**, 97975-44-5; **5l**, 97975-45-6; **6a**, 97975-46-7; **6b**, 97975-47-8; **6c**, 97975-48-9; **6d**, 97975-49-0; **6e**, 97975-50-3; **6f**, 97975-51-4; **6g**, 97975-52-5; **7**, 97996-97-9; 7·dicyclohexylamine salt, 97997-00-7; **8**, 97975-53-6; **9**, 97975-54-7; **10**, 97996-98-0; **11**, 97975-55-8; **12**, 97975-56-9; **13**, 97975-57-0; **14**, 97975-58-1; **14** (dimethylamino)ethyl ester, 97975-62-7; **15**, 97975-59-2; **16**, 97975-60-5; **17**, 97975-61-6; **18**, 97996-99-1; dihydrocinnamoyl chloride, 645-45-4; phenyl isocyanate, 103-71-9; *p*-toluenesulfonyl chloride, 98-59-9; benzyl chloroformate, 501-53-1; nicotinic acid, 59-67-6; *N*-[(2-pyridylcarbonyl)oxy]succinimide, 97975-64-9; benzaldehyde, 100-52-7; *N*,*N*′-dicarbobenzoxy-L-lysine, 405-39-0; *N*-hydroxy-5-norbornene-2,3-dicarboximide, 21715-90-2; 5-norbornene-2,3-dicarboximidyl-*N*,*N*′-dicarbobenzoxy-L-lysine, 97975-65-0; α-ethyl D-glutamate, 97975-66-1; angiotensin converting enzyme, 9015-82-1; perhydroindoline-2(*S*)-carboxylic acid hydrochloride, 97975-67-2; 1-(*N*-carbobenzoxy-α-D-glutamyl)proline, 97975-63-8.