

= 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 H₂O over 30 min. The reaction was stirred for 3 h at room temperature and evaporated. The residue in 200 mL of H₂O 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 (Na₂SO₄) and evaporated to give 6.3 g of a foam. A solution of the foam in 200 mL of CH₂Cl₂ 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; $[\alpha]_D^{25} -180^\circ$ (c 1.2, EtOH); NMR (CDCl₃) 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. (C₁₉H₂₇N₂O₅Cl) C, H, N.

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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; 5o·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; ($\pm$)-6, 88391-85-9; 7, 88372-49-0; 8 ($R^1 = (CH_2)_4NHCbz$, methyl ester), 1155-64-2; 8 ($R^1 = SCH_2Ph$), 953-18-4; 8 ($R^1 = n$ -Pr), 39256-85-4; 9 ($R^1 = (CH_2)_4NHCbz$, 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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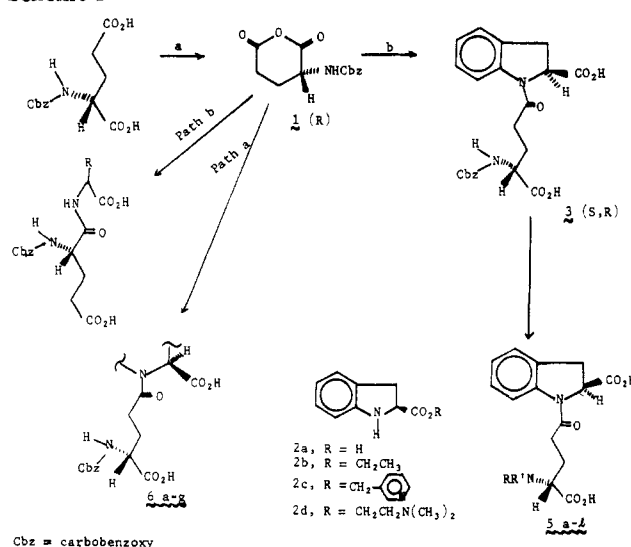
Received September 25, 1984

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 IC₅₀ of 7 and 2.7×10^{-9} M, respectively.

Since the pioneering work of the Squibb group¹ numerous reports² on angiotensin converting enzyme (ACE) inhibitors have appeared. Clinical studies³ 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 S₂' and S₁, binding sites⁴ in the absence of a S₁' 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 described⁵ procedure. The literature⁶ 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 pyridine afforded γ -dipeptides (path a), which provided a series of compounds 3 and 6a–g listed in Table I, while reaction

Scheme I^a

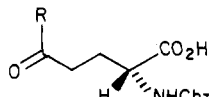
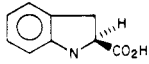
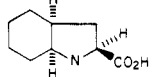
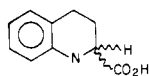
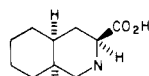
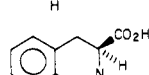
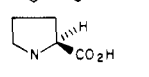
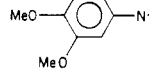
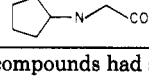


^a Reagents: (a) Ac₂O; (b) 2a, pyridine, 50 °C.

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

with primary amino acids gave predominantly α -dipeptides (path b, Scheme I).

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

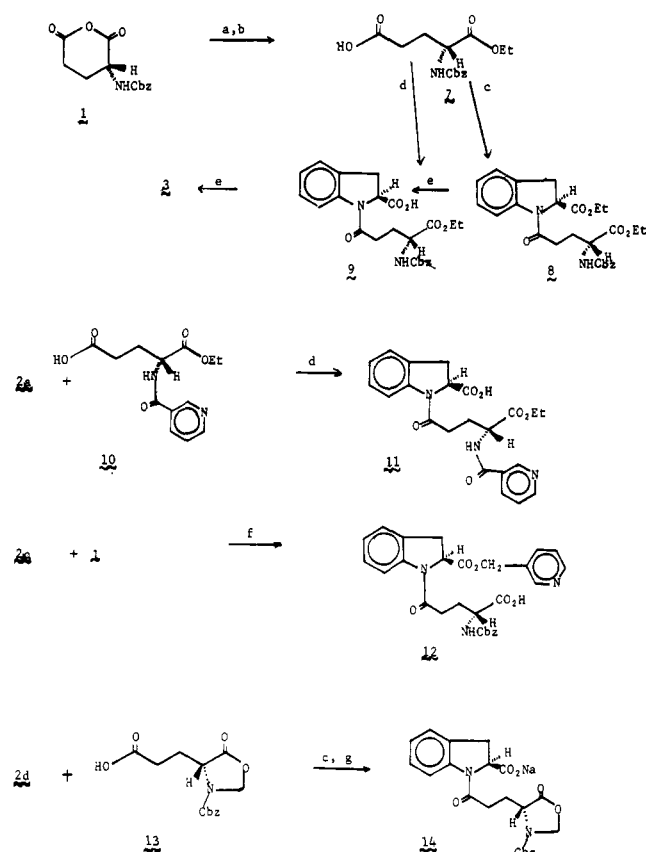
				
compd	R	mp, °C	$[\alpha]_D^{25}$, deg	ACE IC ₅₀ , nM
3		186–188	–60.0	7
6a		79–82	–21.0	2.7
6b		77–80		88
6c		61–64	+7.8	17
6d		87–89	+14.0	14
6e		53–55	–33.0	50
6f		75–79	+0.5 ^d	21
6g ^e		67–70	+8.0 ^f	40

^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 0.5, methanol.

Hydrogenolysis of 3, followed by alkylation or acylation of the glutamylamine, provided a series of compounds 5a–1

- (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.
- (2) (a) Condon, M.; Petrillo, E.; Ryono, D.; Reid, J.; Neubeck, R.; Puar, M.; Heikes, J.; Sabo, E.; Losee, K.; Cushman, D.; Ondetti, M. *J. Med. Chem.* **1982**, *25*, 250. (b) Petrillo, E.; Ondetti, M. *Med. Res. Rev.* **1982**, *2*, 1. (c) Patchett, A.; Harris, E.; Tristram, E.; Wyvratt, M.; Wu, M.; Taub, D.; Peterson, E.; Ikeler, T.; Broeke, J.; Payne, L.; Ondeyka, D.; Thorsett, E.; Greenlee, W.; Lohr, N.; Hoffsommer, R.; Joshua, H.; Rayle, W.; Rothrock, J.; Aster, S.; Maycock, A.; Robinson, F.; Hirschman, R.; Sweet, C.; Ulm, E.; Gross, D.; Vassil, T.; Stone, C. *Nature (London)* **1980**, *288*, 280. (d) Almquist, R.; Crase, J.; Jennings-White, C.; Meyer, R.; Hoefle, M.; Smith, R.; Essenburg, A.; Kaplan, H. *J. Med. Chem.* **1982**, *25*, 1292. (e) Stanton, J.; Gruenfeld, N.; Babiarz, J.; Ackerman, M.; Friedmann, R.; Yuan, A.; Macchia, W. *J. Med. Chem.* **1983**, *26*, 1267. (f) Gruenfeld, N.; Stanton, J.; Yuan, A.; Ebetino, F.; Browne, L.; Gude, C.; Huebner, C. *J. Med. Chem.* **1983**, *26*, 1277. (g) McEvoy, F.; Lai, F.; Albright, J. *J. Med. Chem.* **1983**, *26*, 381.
- (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.

Scheme II

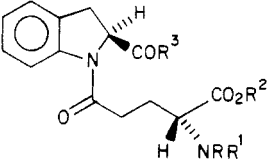


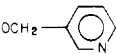
^a Reagents: (a) EtOH, dicyclohexylamine; (b) 1 N HCl; (c) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2b). (d) 1,1'-Carbonyldiimidazole (2a). (e) 1 equiv of 1 N LiOH. (f) Pyridine. (g) Aqueous Na₂CO₃.

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, identical⁸ 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

- (6) (a) Schröder, E.; Lübke, K. "The Peptides"; Academic Press: New York, and London, 1965; Vol. 1, p 182. (b) Magnan, S.; Shirota, F.; Nagasawa, H. *J. Med. Chem.* **1982**, *25*, 1018. (c) Gross, E.; Meienhofer, J. "The Peptides"; Academic Press: New York, 1979; Vol. 1, p 73.
- (7) Weygard, G.; Hunger, K. *Z. Naturforsch.* **1958**, *13B*, 50; *Chem. Abstr.* **1958**, *52*, 10880a.
- (8) Melting points and mixed melting point for both samples were 186–188 °C. The optical rotations of each sample was $[\alpha]_D^{25}$ –60° (c 1, CH₃OH).
- (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	[α] _D , ^b deg	ACE IC ₅₀ , ^c nM
3	CO ₂ CH ₂ Ph	H	H	OH	186-188	-60.0	7
3a ^e	CO ₂ CH ₂ Ph (<i>S</i> isomer)	H	H	OH	174-176	-77.3	500
4	H	H	H	OH	193-195	-110.0	10000
5a	CO(CH ₂) ₂ Ph	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 ₂ C ₆ H ₄ - <i>p</i>	H	H	OH	138-140	-90.0	20
5e	SO ₂ CH ₂ Ph	H	H	OH	168-170	-65.0	29
5f	CO ₂ CH ₂ Ph	CH ₂ Ph	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 ₂ Ph	H	H	OH	188-190	-96.0	300
5j	COCH ₃	H	H	OH	200-202	-110.0	95
5k	<i>N,N'</i> -(Cbz) ₂ -lysyl	H	H	OH	125-127	-46.0	61
5l	lysyl	H	H	OH	203-205	-71.8	188
9	CO ₂ CH ₂ Ph	H	CH ₂ CH ₃	OH	68-71	-46.0	~1000
11	CO-3-py	H	CH ₂ CH ₃	OH	231-235	-40.0	2200
12	CO ₂ CH ₂ Ph	H	H		157-158	-63.0	350
14	CO ₂ CH ₂ Ph		-CH ₂ -	ONa	140 dec	-64.4	52
15 ^e	CO ₂ CH ₂ Ph	H	H	O(CH ₂) ₃ N(CH ₃) ₂	167-169	-34.5 ^f	37
16 ^e	CO ₂ CH ₂ Ph	H	H	O(CH ₂) ₂ N(CH ₃) ₂	178-179	-51.0 ^f	7 ^d
17 ^e	CO ₂ CH ₂ Ph	H	H	NH ₂	190-192	-85.6 ^f	160
18 ^e	CO ₂ CH ₂ Ph	H	H	OCH ₂ CH 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 -picolyndoline-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-benzazepin-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.

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 $(2-5) \times 10^{-8}$ 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 10³-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

(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.

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

A number of ester prodrugs¹² 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 S₁ 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)^{2a} (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 [α]_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 CHCl₃, filtered, washed with CHCl₃, and dried at high vacuum to yield 24.5 g (51%) of 3 as a colorless solid melting at 186–188 °C: [α]_D -60.0° (c 1, ethanol); IR (KBr) 3400 (NH), 3150 (OH), 1740 (CO), 1725 (CO) cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 12.0 (br s, 2, CO₂H), 8.04 (d, 1 H, *J* = 8 Hz, Ar H), 7.57 (d, 1 H, *J* = 7 Hz, NH), 7.31 (s, 5 H, C₆H₅), 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, OCH₂), 4.13 (m, 1 H, NCH), 3.7–2.1 (m, 6 H). Anal. (C₂₂H₂₂N₂O₇) 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 hydrochloride¹⁵ (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 CH₂Cl₂, dried (Na₂SO₄), concentrated, suspended in hexanes, and filtered to give 0.55 g (53%) of 6a as a colorless solid melting at 79–82 °C: [α]_D -21.0° (c 1.8, methanol); IR (Nujol) 3300, 1720,

1510, 1220 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₂H₂₈N₂O₇) 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 (Me₂SO-*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. (C₂₃H₂₄N₂O₇) 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; [α]_D +7.8° (c 1.9, methanol); IR (Nujol) 3300, 1720, 1510, 1220 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₃H₃₀N₂O₇·1/2H₂O) 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; [α]_D +14.0° (c 1.5, methanol); IR (Nujol) 3300, 1720, 1510, 1210 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₃H₂₄N₂O₇) 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; [α]_D -33.2° (c 0.5, methanol); IR (KBr) 3400 (br), 1725 (br), 1525, 1210 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₁₈H₂₂N₂O₇) 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 (32%): mp 75–79 °C; IR (CHCl₃) 3400 (br), 1720, 1650, 1595, 1135 cm⁻¹; ¹H NMR (CDCl₃) 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. (C₂₃H₂₆N₂O₉·0.67H₂O) 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 H₂O, filtering, and washing the solid with another 100-mL aliquot of hot H₂O. 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; [α]_D -116° (c 1, EtOH); IR (Nujol) 3200, 1705, 1650, 1600 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₁₄H₁₆N₂O₅) 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 H₂O cooled to 0 °C were simultaneously added NaOH (0.16 g, 4.1 mmol) in 2 mL of H₂O 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: [α]_D -65.9° (c 1, CH₃OH); IR (Nujol) 3380, 3100, 1730, 1695, 1670 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₃H₂₄N₂O₆) 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

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- (13) Itoh, M. *Chem. Pharmacol. Bull.* **1969**, *17*, 1683.
- (14) This material was hygroscopic and contained a detectable amount of dimethylethanamine.
- (15) Vincent, M.; R  mond, G.; Portevin, B.; Sertiz, B.; Laubie, M. *Tetrahedron Lett.* **1982**, 1677.

(72%) melting at 120–123 °C; $[\alpha]_D -70.2^\circ$ (c 1, CH₃OH); IR (Nujol) 3300, 3100, 1730, 1645 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₁H₂₀N₂O₆) 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 Et₂O and 15 mL of 5% aqueous NaHCO₃. 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 H₂O, 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, CH₃OH); IR (Nujol) 3400–3300, 1720, 1670 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₁H₂₁N₃O₆) 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 H₂O 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 (Na₂SO₄), filtered, and concentrated to give a form that solidified after stirring 12 h with 25 mL of Et₂O. The solid was collected and dried under high vacuum to give 0.68 g (38%) of 5d melting at 138–140 °C: $[\alpha]_D -90^\circ$ (c 0.25, CH₃OH); IR (Nujol) 3280, 1720, 1655, 1630, 1595, 1160, 1090 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₁H₂₂N₂O₇S) 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: $[\alpha]_D -65^\circ$ (c 1, CH₃OH); IR (KBr) 1712, 1668, 1487, 1412 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₁H₂₂N₂O₇S) 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 K₂CO₃ (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 H₂O containing 0.1 g of K₂CO₃. The basic aqueous mixture was extracted two times with Et₂O 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: $[\alpha]_D -28.7^\circ$ (c 0.4, CH₃OH); IR (KBr) 1740, 1720, 1700, 1595, 1485; ¹H NMR (CDCl₃) 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. (C₂₉H₂₈N₂O₇) 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 H₂O. 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: $[\alpha]_D -63.6^\circ$ (c 0.5, CH₃OH); IR (Nujol) 3370, 1727, 1650 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 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. (C₂₀H₁₉N₃O₆) 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 H₂O which initiated crystallization. The solid was collected and dried to give 1.0 g (75%) of 5h. Recrystallization of 5h from a water–2-propanol mixture (9:1) gave the product (46%), melting at 159–161 °C: $[\alpha]_D -77^\circ$ (c 0.25, CH₃OH); IR (KBr) 3340, 1740, 1665, 1634, 1600, 1490 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 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. (C₂₀H₁₉N₃O₆) 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 H₂O was added benzaldehyde (0.44 g, 4.1 mmol). The mixture was stirred for 15 min and cooled in an ice bath, and NaBH₄ (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 H₂O, filtered, washed with H₂O, collected, and dried at 80 °C under high vacuum to give 1.3 g (84%) of 5i, melting at 188–190 °C: $[\alpha]_D -96^\circ$ (c 0.5, 1 N NaOH); IR (Nujol) 3100, 1720, 1655, 1600 cm⁻¹; ¹H NMR (CF₃CO₂D) δ 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. (C₂₁H₂₂N₂O₆) 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 H₂O 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 CH₃OH and titrated with H₂O. The colorless solid was collected and dried under high vacuum to give 0.59 g (74%) of 5j, melting at 200–202 °C: $[\alpha]_D -110^\circ$ (c 0.25, CH₃OH); IR 3280, 1720, 1648, 1620, 1480 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₁₆H₁₈N₂O₆) 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 CH₂Cl₂ and H₂O. The organic layer was separated, washed with 1 N HCl and H₂O, dried (Na₂SO₄), filtered, and concentrated. The resulting foam was suspended in Et₂O, 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: $[\alpha]_D -46^\circ$ (c 1, CH₃OH); IR (Nujol) 3330, 3290, 1735, 1645 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₃₆H₄₀N₄O₁₀) 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 H₂O, filtered, and washed well with H₂O. 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 (D₂O) 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. (C₂₀H₂₈N₄O₆) C, H, N.

α -Ethyl D-*N*-carbobenzoxyglutamate (7) was prepared by a modified literature⁷ 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; $[\alpha]_D -7.84^\circ$ (c 1, in methanol)].

Free acid 7 could be generated as previously described⁷ 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 H₂SO₄ was refluxed 3 h, concentrated, diluted with Et₂O, washed with NaHCO₃ and H₂O, dried (Na₂SO₄), filtered, and concentrated. The residue was suspended in hexane-Et₂O (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, CH₃OH); IR (CHCl₃) 3400, 1745, 1670 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₆H₃₀N₂O₇) 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 Et₂O and H₂O. The aqueous layer was separated, washed with Et₂O, cooled in an ice bath, acidified with 12 N HCl, and extracted with CH₂Cl₂. The organic layer was concentrated and flash chromatographed on silica gel eluting with EtOAc-CH₃OH (9:1), giving 0.34 g (28%) of 9 as a colorless solid after stirring with hexanes: mp 68–71 °C; $[\alpha]_D -46^\circ$ (c 0.9, CH₃OH); IR (Nujol) 3320, 1730, 1660, 1595, 1200 cm⁻¹; ¹H NMR (CDCl₃) 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. (C₂₄H₂₇N₂O₇·0.5H₂O) 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 CH₂Cl₂ at 0 °C was added 150 mL of 1 N HCl. The mixture was vigorously stirred for 1 h and filtered. The CH₂Cl₂ layer was separated, washed with H₂O, dried (Na₂SO₄), 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; $[\alpha]_D -14.2^\circ$ (c 1, CH₃OH); ¹H NMR (Me₂SO-*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 H₂O was added. The colorless solid was collected, washed with cold H₂O, and dried under high vacuum to give 1.1 g (63%) of 10 melting at 157–159 °C: $[\alpha]_D^{+18.4^\circ}$ (c 1, CH₃OH); IR (KBr) 3300, 1740, 1700, 1595, 1530 cm⁻¹; ¹H NMR (Me₂SO-*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 CH₂Cl₂ at 0 °C was added 1,1'-carbonyldiimidazole (0.60 g, 3.7 mmol) in 10 mL of CH₂Cl₂. 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 NaHCO₃ and extracted twice with Et₂O. 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 H₂O, and dried under high vacuum to give 0.32 g (21%) of 11, melting at 231–233 °C; $[\alpha]_D -40^\circ$ (c 0.5, CH₃OH); IR (KBr) 3310, 1750, 1662, 1650, 1490, 1220 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₂H₂₃N₃O₆) C, H, N.

3-Pyridylmethyl 1-(*N*-Carbobenzoxy- γ -D-glutamyl)-indoline-2(*S*)-carboxylate (12). The solution of 1⁵ (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; $[\alpha]_D -63^\circ$ (c 0.5, CH₃OH); IR (KBr) 3350, 1740, 1690, 1655 cm⁻¹; ¹H NMR (Me₂SO-*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. (C₂₈H₂₇N₃O₇) 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 13¹³ (1.60 g, 5.46 mmol) in 5 mL of CH₂Cl₂ 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 NaHCO₃, and saturated NaCl. The organic layer was separated, dried (MgSO₄), filtered, and concentrated to give 1.5 g (54%) of the (dimethylamino)ethyl ester of 14 as a light yellow oil: ¹H NMR (CDCl₃) 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 CH₃OH and triturated with Et₂O. The solvent was decanted off, Et₂O 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: $[\alpha]_D -64.4^\circ$ (c 1, CH₃OH); IR (KBr) 3400, 1695, 1600, 1480 cm⁻¹; ¹H NMR (Me₂SO-*d*₆) δ 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.