33, 124400-69-7; 34, 124400-70-0; 35, 124400-71-1; 36, 124400-72-2; 37, 124400-73-3; 38, 124400-74-4; CC-1065, 69866-21-3; 4-nitroaniline, 100-01-6; *N*-benzoyl-4-nitroaniline, 3393-96-2; N^1-benzoyl-1,4-diaminobenzene, 17625-83-1; N^4-benzoyl-N^1-(phenylsulfonyl)-1,4-diaminobenzene, 124400-29-9; 2-amino-5-nitrophenol, 121-88-0; *N*-(*tert*-butyloxycarbonyl)-2-amino-5-nitrophenol, 124400-31-3; *N*-(*tert*-butyloxycarbonyl)-*O*-benzyl-2-amino-5-nitrophenol, 124400-32-4; N^2-(*tert*-butyoxycarbonyl)-*O*-benzyl-2,5-diaminophenol, 124400-33-5; N^5-benzoyl-N^2-(*tert*-butyloxycarbonyl)-*O*-benzyl-2,5-diaminophenol, 124400-34-6; N^5-benzoyl-*O*-benzyl-2,5-diaminophenol, 124400-35-7; N^5-benzoyl-N^2-(phenylsulfonyl)-*O*-benzyl-2,5-diaminophenol, 124400-36-8; 1-piperidino-1-propene, 7182-09-4; dimethyl malonate, 108-59-8; methyl acetoacetate, 105-45-3; N^2-benzoyl-N^5-(phenylsulfonyl)-2,5-diaminophenol, 124400-46-0; 2-propenyl-tri-*n*-butylstannane, 24850-33-7; 2-butenyl-tri-*n*-butylstannane, 31197-41-8; 5-nitroindole, 6146-52-7; 5-nitro-1-(phenylsulfonyl)indole, 124400-51-7; 5-amino-1-(phenylsulfonyl)indole, 124400-52-8; N^5-benzoyl-N^2-(phenylsulfonyl)-2,5-diaminophenol, 124400-75-5; N^5-(phenylsulfonyl)-1-benzoyl-5-aminoindole, 124400-76-6.

Supplementary Material Available: Tabular compilation of the ^{1}H NMR spectra of **1–38** (3 pages). Ordering information is given on any current masthead page.

Synthesis of Rigid, Heterocyclic Dipeptide Analogues[1]

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Received September 11, 1989

The preparation of rigid analogues of peptides can be a valuable technique for gaining information about the active conformation of biological ligands and/or for enhancing the proteolytic stability and bioavailability of such systems. In the course of our studies directed toward the design of novel inhibitors of human renin,[2] the aspartic proteinase responsible for initiation of the renin–angiotensin system, we desired a rigid, heterocyclic mimic of an N-terminal phenylalanine containing dipeptide. The analogue that we chose to pursue (**2**) can be conceptually derived from a Phe-Xaa dipeptide **1** by a series of rigidifying events (Figure 1): (a) fixing the dihedral angle between the α and β carbons of phenylalanine;[3] (b) blocking rotation of the side-chain phenyl group;[4] and (c) fixing the directionality of the amide carbonyl group with respect to the indole ring and prohibiting C–N amide-bond rotation.[5] Attachment of **2** to any of a variety of transition-state

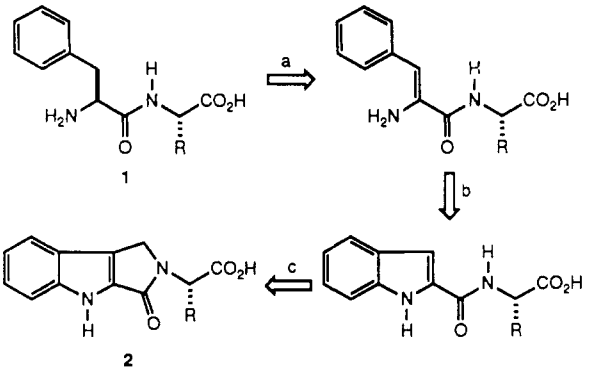

Figure 1. Rigidification of Phe-Xaa dipeptides.

Table I. Synthesis of Heterocyclic Dipeptide Analogues 5a–e

product	R^3	yield,[a] %
5a	(*S*)-4-imidazolylmethyl	31
5b	(*RS*)-4-thiazolylmethyl	61
5c	(*RS*)-3-pyrazolylmethyl	47
5d	(*S*)-$(CH_3)_2CHCH_2$	67
5e	H	16

[a] Overall yield based on **3a**.

analogues[6] designed to occupy the P_1/P_1' subsites of renin was expected to produce a series of potent inhibitors.

Our synthetic approach to **2** is outlined in Scheme I. Benzyl indole-2-carboxylate was subjected to Vilsmeier formylation[7] to give aldehyde **3a** (80%). Reductive amination of **3a** with L-histidine methyl ester dihydrochloride led to **4a** (R = imidazolylmethyl) in 91% yield. Lactam formation[8] was achieved by catalytic hydrogenolysis of **4a** and cyclization using *N*-ethyl-*N*'-[2-(dimethylamino)-ethyl]carbodiimide hydrochloride (EDC) and 4-(dimethylamino)pyridine (DMAP), to give tricyclic ester **5a**. Overall yields for the preparation of **5a–e** from **3a** using a variety of α-amino esters are given in Table I. Hydrolysis of **5a–e** gave the desired tricyclic peptide analogues **2a–e**.[9]

The coupling of **2b–e** to the amino group of a previously described amino glycol transition-state analogue[10] proceeded uneventfully, to give renin inhibitors **6b–e** (Scheme II). Substantial racemization was observed, however, in the coupling of **2a**.[11] This could be avoided through use of an additional protection/deprotection sequence[12] whereby the lithium salt of **2a**, formed in the hydrolysis of **5a**, was treated in the same pot with excess of di-*tert*-butyl dicarbonate. The resulting Boc-protected acid **2f** (R = Boc-imidazolylmethyl) was coupled via its mixed

(1) Presented in part at the 11th American Peptide Symposium, San Diego, CA, July 1989.

(2) (a) Kempf, D. J.; de Lara, E.; Stein, H. H.; Cohen, J.; Plattner, J. J. *J. Med. Chem.* **1987**, *30*, 1978. (b) Kempf, D. J.; de Lara, E.; Stein, H. H.; Cohen, J.; Egan, D. A.; Plattner, J. J. *J. Med. Chem.* In press.

(3) We have previously reported renin inhibitors that contain (*Z*)-dehydrophenylalanine: Plattner, J. J.; Marcotte, P. A.; Kleinert, H. D.; Stein, H. H.; Greer, J.; Bolis, G.; Fung, A. K. L.; Bopp, B. A.; Luly, J. R.; Sham, H. L.; Kempf, D. J.; Rosenberg, S. H.; Dellaria, J. F.; De, B.; Merits, I.; Perun, T. J. *J. Med. Chem.* **1988**, *31*, 2277.

(4) A series of renin inhibitors containing indole-2-carboxylic acid as a phenylalanine replacement has been disclosed: Buhlmayer, P.; Rasetti, V.; Fuhrer, W.; Stanton, J. L.; Goschke, R. U.S. Patent 4,727,060, Feb 23, 1988.

(5) Lactam-containing Phe-Xaa analogues based on cyclizing from the amine nitrogen to the α-carbon of phenylalanine have been reported: (a) Thaisrivongs, S.; Pals, D. T.; Turner, S. R.; Kroll, L. T. *J. Med. Chem.* **1988**, *31*, 1369. (b) Zydowsky, T. M.; Dellaria, J. F.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607.

(6) For an excellent review, see: Greenlee, W. J. *Pharm. Res.* **1987**, *4*, 364.

(7) Shabica, A. C.; Howe, E. E.; Ziegler, J. B.; Tishler, M. *J. Am. Chem. Soc.* **1946**, *68*, 1156.

(8) Lactam formation by thermolysis of acyclic esters, which has been used in less rigid cases (ref 5b), was unsuccessful in the case of **4** due to decomposition via an alkylidene-3*H*-indole intermediate.

(9) A conceptually more efficient approach to racemic **5** via alkylation of **5e** failed due to decomposition, again via an alkylidene-3*H*-indole. The corresponding indole-*N*-Boc derivative of **5e** underwent competitive proton removal from both the α-carbon and the 1-position of the tricyclic nucleus.

(10) Luly, J. R.; BaMung, N.; Soderquist, J.; Fung, A. K. L.; Stein, H. H.; Kleinert, H. D.; Marcotte, P. A.; Egan, D. A.; Bopp, B. A.; Merits, I.; Bolis, G.; Greer, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1988**, *31*, 2264.

(11) We would not have detected racemization of **2b** or **2c** since the starting materials were racemic; however, leucine analogue **2d** did not racemize under the hydrolysis and coupling conditions.

(12) Rosenberg, S. Unpublished results.

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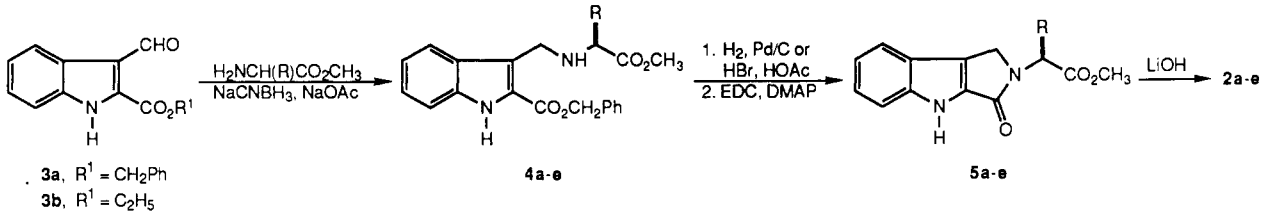
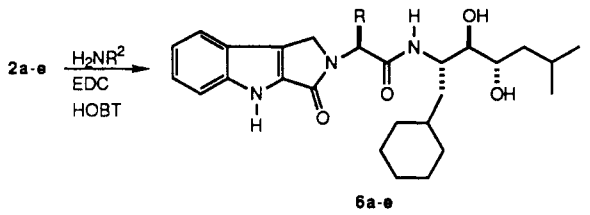
Scheme I



Scheme II



anhydride (isobutyl chloroformate, 4-methylmorphine) to the amino glycol and subsequently deprotected with trifluoroacetic acid in methanol, to give **6a** (43% overall from **5a**) with <5% racemization.

We have also investigated the synthesis of dipeptide analogue **9**, which incorporates a six-membered lactam and thus places the phenyl side chain in a different position relative to the peptide backbone. Two routes to inhibitors containing **9** were investigated. In the first (Scheme III), double deprotonation of known β-carbolinone **7**[13] with 2 equiv of lithium diisopropylamide followed by alkylation with ethyl 2-bromohexanoate gave ester **8** (39%), which was hydrolyzed to afford the racemic Phe-Nle analogue **9a** (R^1 = *n*-butyl). Coupling to the amino glycol[10] gave the renin inhibitor **10a** as a mixture of two diastereomers, which were chromatographically separated. The moderate yields encountered in the alkylation of **14** in addition to our desire to prepare Phe-His analogue **9b** (R^1 = imidazolylmethyl) prompted us to investigate a second route to **10** (Scheme IV). Thus, aldehyde **3b**[7] was homologated in standard fashion[14] to afford aldehyde **11**. Reductive amination with the histidine amide of the amino glycol provided **12**, which was hydrolyzed and cyclized to give the renin inhibitor **10b**. Unfortunately, substantial racemization of the histidine was again observed, this time in the reductive amination step. Presumably this could be avoided by sequential homologation of **3a** to the benzyl analogue of **11**, reductive amination with histidine methyl ester, cyclization, and coupling to the amino glycol via the above protection/deprotection sequence.

Compounds **6** and **10** have been found to be potent inhibitors of purified human renin. Biological activities will be published elsewhere.[15] Retention of activity in these compounds not only provides information on the active conformation of renin inhibitors but also indicates that the conformationally restricted dipeptide analogues **2** and **9** are potentially useful for incorporation at the N-terminus of a variety of bioactive peptides.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were measured on a Nicolet QE-300 (300 MHz) instrument using tetramethylsilane as an internal standard. Elemental analyses were performed by the Analytical Research Department, Abbott Laboratories. Flash column chromatography was performed on silica gel 60, 0.04–0.063 mm (E. Merck). Thin-layer chromatoraphy was performed on precoated silica gel F-254 plates (0.25 mm; E. Merck) and was visualized with phosphomolybdic acid.

Benzyl Indole-2-carboxylate. A solution of 19.9 g (124 mmol) of indole-2-carboxylic acid, 16 mL (155 mmol) of benzyl alcohol, and 3.0 g (25 mmol) of 4-(dimethylamino)pyridine in 800 mL of dichloromethane was treated with 25.6 g (124 mmol) of *N,N'*-dicyclohexylcarbodiimide and stirred at ambient temperature for 2.5 h. The resulting mixture was filtered, concentrated in vacuo, taken up in 1 L of ethyl acetate, and filtered. The solution was subsequently washed sequentially with 1 N HCl, H_2O, saturated $NaHCO_3$, and saturated brine, dried over $MgSO_4$, and concentrated. Recrystallization of the residue from ethyl acetate/hexane gave three crops of crystalline material containing 15.79 g, 11.13 g, and 2.25 g (94%) of benzyl indole-2-carboxylate: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2 H), 7.26 (br t, 1 H), 7.3–7.5 (m, 8 H), 7.69 (br d, 1 H), 8.9 (br s, 1 H); MS *m/z* 252 $(M + H)^+$. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.13; H, 5.53; N, 5.87.

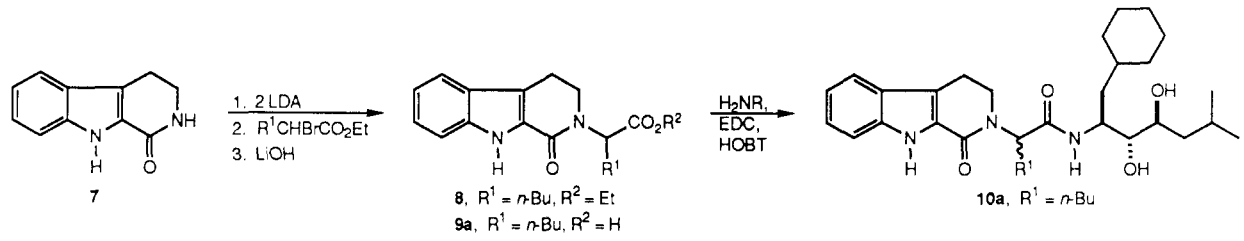
Benzyl 3-Formylindole-2-carboxylate (3a). A mixture of 6.5 mL (70 mmol) of phosphorus oxychloride and 9.3 mL (70 mmol) of *N*-methylformanilide was stirred at ambient temperature. The resulting mixture was diluted with 90 mL of 1,2-dichloroethane, treated with 15.0 g (59.8 mmol) of benzyl indole-2-carboxylate, and heated at reflux for 1 h. After being allowed to cool for 5 min, the warm solution was poured into an ice-cold solution of 60 g of sodium acetate hydrate in 200 mL of water. The resulting mixture was stirred for 1 h and filtered. The yellow solid was washed twice with water and twice with ether and air-dried. The filtrate was treated with 400 mL of hexane and filtered. The combined solids were digested with hot ethyl acetate, cooled to 0 °C, and filtered, to give 13.41 g (80%) of **3a** as an off-white solid: mp 197–198 °C dec; ^{1}H NMR ($CDCl_3/CD_3OD$) δ 5.50 (s, 2 H), 7.3–7.55 (m, 8 H), 8.38 (d, *J* = 9 Hz, 1 H); MS *m/z* 280 $(M + H)^+$. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.51; H, 4.74; N, 4.88.

General Procedure for the Formation of 4. *N*-[[3-[2-(Benzyloxycarbonyl)indolyl]]methyl]histidine Methyl Ester (4a, R = (*S*)-4-Imidazolylmethyl). A mixture of 2.00 g (7.17 mmol) of **3a**, 1.82 g (7.53 mmol) of histidine methyl ester dihydrochloride, 1.42 g (21.5 mmol) of anhydrous sodium acetate, and 0.67 g (10.8 mmol) of sodium cyanoborohydride in 200 mL of isopropyl alcohol was stirred at ambient temperature. After 16 h, an additional 0.22-g portion of sodium cyanoborohydride was added, and stirring was continued for 4.5 h. After removal of the solvent in vacuo, the residue was taken up in ethyl acetate, washed sequentially with saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 7.5% methanol in chloroform gave 2.83 g (91%) of **4a** (R = (*S*)-4-imidazolylmethyl): mp 82–86 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.76 (dd, *J* = 15, 9 Hz, 1 H), 3.01 (dd, *J* = 15, 4 Hz, 1 H), 3.55 (dd, *J* = 9, 4 Hz, 1 H), 3.66 (s, 3 H), 4.78 (s, 2 H), 5.40 (AA', 2 H), 6.74 (br s, 1 H), 7.19 (m, 1 H), 7.31 (br s, 1 H), 7.35–7.5 (m, 7 H), 7.73 (d, *J* = 9 Hz, 1 H), 9.05 (br s, 1 H); MS *m/z* 433 $(M + H)^+$. Anal. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.38; H, 5.84; N, 12.48.

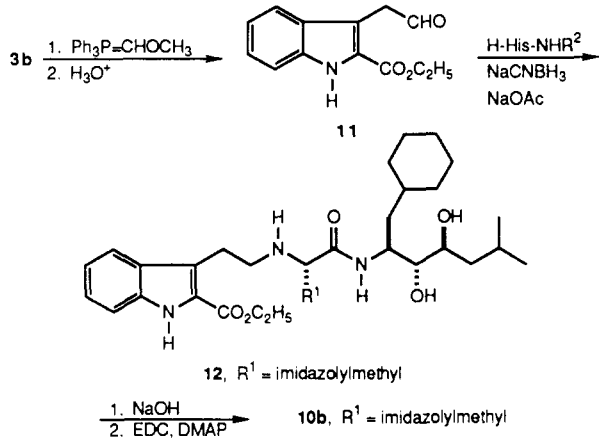
***N*-[[3-[2-(Benzyloxycarbonyl)indolyl]]methyl]-*dl*-β-4-thiazolylalanine methyl ester (4b, R = (*RS*)-4-thiazolylmethyl):** mp 103–112 °C; ^{1}H NMR ($CDCl_3$) δ 3.11 (dd, *J* = 15, 8 Hz, 1 H), 3.17 (dd, *J* = 15, 6 Hz, 1 H), 3.59 (s, 3 H), 3.76 (m, 1 H), 4.28 (AA', 2 H), 5.36 (s, 2 H), 6.96 (d, *J* = 2 Hz, 1 H), 7.13 (ddd, *J* = 8, 6, 2 Hz, 1 H), 7.3–7.5 (m, 6 H), 7.69 (d, *J* = 8 Hz, 1 H), 8.65 (d, *J* = 2 Hz, 1 H), 8.81 (br s, 1 H); MS *m/z* 450 (M

(13) Pelchowitz, Z.; Bergmann, E. D. *J. Chem. Soc.* **1960**, 4699.
(14) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.
(15) Kempf, D. J.; Condon, S. L.; de Lara, E.; Plattner, J. J.; Baker, W. R.; Stein, H.; Cohen, J.; Kleinert, H. D. In *Proceedings of the Eleventh American Peptide Symposium*; Rivier, J., Ed.; ESCOM: Leiden. In press.

Scheme III



Scheme IV



+ H)$^+$. Anal. Calcd for $C_{24}H_{23}N_3O_4S \cdot 0.25H_2O$: C, 63.49; H, 5.22; N, 9.25. Found: C, 63.56; H, 4.95; N, 9.02.

***N*-[[3-[2-(Benzyloxycarbonyl)indolyl]]methyl]-*dl*-β-3-pyrazolylalanine methyl ester (4c, R = (*RS*)-3-pyrazolylmethyl)**: mp 124–127 °C; ^{1}H NMR (DMSO-d_6) δ 2.82 (m, 2 H), 3.45 (s, 3 H), 4.13 (m, 2 H), 5.37 (s, 2 H), 5.91 (m, 1 H), 7.06 (br t, J = 8 Hz, 1 H), 7.26 (br t, J = 8 Hz, 1 H), 7.35–7.55 (m, 6 H), 7.73 (br d, J = 8 Hz, 1 H), 11.66 (br s, 1 H), 12.47 (br s, 1 H); MS m/z 433 (M + H)$^+$. Anal. Calcd for $C_{24}H_{24}N_4O_4$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.55; H, 5.66; N, 12.91.

***N*-[[3-[2-(Benzyloxycarbonyl)indolyl]]methyl]leucine methyl ester (4d, R = (*S*)-isobutyl)**: ^{1}H NMR ($CDCl_3$) δ 0.78 (d, J = 7 Hz, 3 H), 0.87 (d, J = 7 Hz, 3 H), 1.43 (m, 2 H), 1.63 (m, 1 H), 3.34 (t, J = 7 Hz, 1 H), 3.59 (s, 3 H), 4.23 (AA′, 2 H), 5.41 (AA′, 2 H), 7.17 (ddd, J = 8, 6, 2 Hz, 1 H), 7.3–7.5 (m, 7 H), 7.80 (dd, J = 8, 0.5 Hz, 1 H), 8.81 (br s, 1 H); MS m/z 409 (M + H)$^+$. Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 71.05; H, 6.97; N, 6.88.

***N*-[[3-[2-(Benzyloxycarbonyl)indolyl]]methyl]glycine methyl ester (4e, R = H)**: mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 2 H), 3.67 (s, 3 H), 4.29 (s, 2 H), 5.41 (s, 2 H), 7.18 (ddd, J = 8, 6, 2 Hz, 1 H), 7.3–7.5 (m, 7 H), 7.81 (d, J = 9 Hz, 1 H), 8.84 (br s, 1 H); MS m/z 353 (M + H)$^+$. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.98; H, 5.89; N, 7.83.

Procedure A for Lactam Formation. (1′*S*)-2-[2-(4-Imidazolyl)-1-(methoxycarbonyl)ethyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (5a). A mixture of 12.1 g of **4a** and 1.2 g of 10% palladium on carbon in 250 mL of methanol was shaken under 4 atmospheres of H_2. After filtration, removal of the solvent in vacuo gave 10.4 g of the crude substituted indole-2-carboxylic acid. A solution of 5.93 g (17.3 mmol) of the above acid, 0.42 g (3.5 mmol) of 4-(dimethylamino)pyridine, and 1.9 mL (17.3 mmol) of 4-methylmorpholine in 40 mL of dimethylformamide was treated with 4.00 g (20.8 mmol) of *N*-ethyl-*N*′-[2-(dimethylamino)ethyl]carbodiimide hydrochloride and stirred at ambient temperature for 16 h. After removal of the solvent in vacuo, the residue was dissolved in ethyl acetate, washed sequentially with saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 5% methanol in chloroform followed by recrystallization from chloroform/hexane gave 1.76 g (31%) of **5a** as an off-white solid: mp 195–197 °C; ^{1}H NMR ($CDCl_3$) δ 3.25 (dd, J = 15, 11 Hz, 1 H), 3.42 (dd, J = 15, 5 Hz, 1 H), 3.72 (s, 3 H), 4.48 (AA′, 2 H), 5.31 (dd, J = 11, 4 Hz, 1 H), 6.73 (s, 1 H), 7.11 (br t, J = 7 Hz, 1 H), 7.25 (br t, J = 7 Hz, 1 H), 7.34 (d, J = 1 Hz, 1 H), 7.47 (d, J = 8 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H); MS m/z 325 (M + H)$^+$. Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.63; H, 5.05; N, 17.14.

Procedure B for Lactam Formation. 2-[1-(Methoxycarbonyl)-2-(4-thiazolyl)ethyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (5b). A solution of 7.19 g (16.0 mmol) of **4b** in 100 mL of 30% HBr in acetic acid was stirred at ambient temperature for 3.25 h, whereupon a light brown precipitate was observed. The solvent was removed in vacuo, and the residue was taken up in water, washed with ether, concentrated in vacuo, diluted with water, and concentrated by lyophilization, to give 8.5 g of the crude acid dihydrobromide, which was cyclized by the method of procedure A to give **5b** in 86% yield: mp 197–198 °C; ^{1}H NMR ($CDCl_3$) δ 3.59 (dd, J = 15, 11 Hz, 1 H), 3.70 (dd, J = 15, 5 Hz, 1 H), 3.28 (s, 3 H), 4.52 (s, 2 H), 5.45 (dd, J = 11, 5 Hz, 1 H), 7.12 (m, 1 H), 7.18 (br t, J = 8 Hz, 1 H), 7.32 (br t, J = 8 Hz, 1 H), 7.53 (br d, J = 8 Hz, 1 H), 7.59 (br d, J = 8 Hz, 1 H), 8.70 (d, J = 2 Hz, 1 H), 9.83 (br s, 1 H); MS m/z 342 (M + H)$^+$. Anal. Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31. Found: C, 60.04; H, 4.59; N, 12.26.

2-[1-(Methoxycarbonyl)-2-(3-pyrazolyl)ethyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (5c): procedure A; mp 83–90 °C; ^{1}H NMR ($CDCl_3$) δ 3.42 (dd, J = 15, 10 Hz, 1 H), 3.57 (dd, J = 15, 5 Hz, 1 H), 3.77 (s, 3 H), 4.49 (AA′, 2 H), 5.41 (dd, J = 10, 5 Hz, 1 H), 6.17 (d, J = 3 Hz, 1 H), 7.11 (br t, J = 8 Hz, 1 H), 7.27 (br t, J = 8 Hz, 1 H), 7.39 (br d, J = 2 Hz, 1 H), 7.50 (br t, J = 8 Hz, 2 H); MS m/z 325 (M + H)$^+$; exact mass calcd for $C_{17}H_{17}N_4O_3$ (M + H) 325.1301, found 325.1328.

(1′*S*)-2-[1-(Methoxycarbonyl)-3-methylbutyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (5d): procedure A; mp 181–182 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (d, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 1.58 (m, 1 H), 1.90 (m, 2 H), 3.72 (s, 3 H), 4.42 (d, J = 17 Hz, 1 H), 4.67 (d, J = 17 Hz, 1 H), 5.19 (dd, J = 10, 6 Hz, 1 H), 7.70 (br t, J = 8 Hz, 1 H), 7.33 (br t, J = 8 Hz, 1 H), 7.55 (br d, J = 8 Hz, 1 H), 7.62 (br d, J = 8 Hz, 1 H), 9.85 (br s, 1 H); MS m/z 301 (M + H)$^+$. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.08; H, 6.79; N, 9.36.

2-[(Methoxycarbonyl)methyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (5e): procedure A; mp 215–217 °C; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3 H), 4.44 (s, 2 H), 4.59 (s, 2 H), 7.20 (t, J = 8 Hz, 1 H), 7.33 (t, J = 8 Hz, 1 H), 7.55 (d, J = 8 Hz, 1 H), 7.62 (d, J = 8 Hz, 1 H), 9.83 (br s, 1 H); MS m/z 245 (M + H)$^+$. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.01; H, 5.05; N, 11.47.

General Procedure for Hydrolysis and Coupling of 5. (1′*S*,2″*S*,3″*R*,4″*S*)-2-[1-[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]-2-(4-imidazolyl)ethyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (6a). A solution of 1.18 g (3.64 mmol) of **5a** in 15 mL of 1,4-dioxane was cooled to 0 °C and treated with 8.5 mL (4.25 mmol) of aqueous lithium hydroxide. The resulting solution was stirred at 0 °C for 3.5 h and concentrated in vacuo, to give the lithium salt of **2a** as a light yellow solid. A solution of 1.63 mmol of **2a** lithium salt, 1.63 mmol of (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane hydrochloride,[10] and 0.26 g (1.95 mmol) of 1-hydroxybenzotriazole in 8 mL of dimethylformamide was treated with 0.22 mL (1.95 mmol) of 4-methylmorpholine, cooled to −23 °C, and treated with 0.38 g (1.95 mmol) of *N*-ethyl-*N*′-[3-(diethylamino)propyl]carbodiimide hydrochloride. The resulting solution was allowed to come slowly to ambient temperature while being

stirred overnight. Following dilution with ethyl acetate, the solution was washed sequentially with aqueous $NaHCO_3$, water, and saturated brine, dried over $MgSO_4$, and concentrated in vacuo to a 2:1 mixture of **6a** and the corresponding 1′*R* diastereomer. Flash chromatography using methanol/chloroform mixtures afforded 0.39 g (45%) of **6a**: mp 149–154 °C dec; ^1H NMR ($CDCl_3$) δ 0.5–1.0 (br envelope), 0.73 (d, J = 7 Hz, 3 H), 0.89 (d, J = 7 Hz, 3 H), 1.2–1.6 (br envelope), 1.84 (m, 2 H), 3.17 (m, 2 H), 3.28 (br d, J = 8 Hz, 1 H), 3.47 (dd, J = 15, 8 Hz, 1 H), 4.48 (m, 1 H), 4.57 (br s, 1 H), 5.56 (br t, J = 7 Hz, 1 H), 6.83 (br s, 1 H), 7.19 (t, J = 7 Hz, 1 H), 7.33 (m, 2 H), 7.49 (d, J = 7 Hz, 1 H), 7.51 (br s, 1 H), 7.61 (d, J = 7 Hz, 1 H), 9.86 (br, 1 H); MS m/z 536 $(M + H)^+$. Anal. Calcd for $C_{30}H_{41}N_5O_4 \cdot 0.75H_2O$: C, 65.61; H, 7.80; N, 12.75. Found: C, 65.50; H, 7.81; N, 12.69.

(1′*S*,2″*S*,3″*R*,4″*S*)-2-[1-[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]-2-(4-thiazolyl)ethyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (6b). Coupling as above gave a 1:1 mixture of 1′*S* and 1′*R* diastereomers, which were separated by flash chromatography using 3% methanol in dichloromethane, to give **6b**, mp 226–231 °C, in 11% yield: ^1H NMR ($CDCl_3$) δ 0.41 (d, J = 7 Hz, 3 H), 0.74 (d, J = 7 Hz, 3 H), 0.8–1.8 (br envelope), 3.05 (m, 1 H), 3.25 (m, 2 H), 3.44 (dd, J = 14, 8 Hz, 1 H), 3.67 (dd, J = 14, 8 Hz, 1 H), 4.3 (m, 2 H), 4.61 (d, J = 17 Hz, 1 H), 4.76 (d, J = 17 Hz, 1 H), 5.47 (t, J = 8 Hz, 1 H), 7.16 (br t, J = 8 Hz, 1 H), 7.19 (d, J = 3 Hz, 1 H), 7.30 (br t, J = 8 Hz, 1 H), 7.32 (br d, J = 9 Hz, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.57 (d, J = 8 Hz, 1 H), 8.71 (d, J = 3 Hz, 1 H), 9.41 (s, 1 H); MS m/z 553 $(M + H)^+$. Anal. Calcd for $C_{30}H_{40}N_4O_4S \cdot 0.75H_2O$: C, 63.64; H, 7.39; N, 9.89. Found: C, 63.53; H, 7.22; N, 9.93.

(1′*S*,2″*S*,3″*R*,4″*S*)-2-[1-[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]-2-(3-pyrazolyl)ethyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (6c). Coupling as above gave a 1:1 mixture of 1′*S* and 1′*R* diastereomers, which were separated by flash chromatography using 2% methanol in dichloromethane, to give **6c**, mp 152–161 °C, in 38% yield: ^1H NMR ($CDCl_3/CD_3OD$) δ 0.48 (d, J = 7 Hz, 3 H), 0.77 (d, J = 7 Hz, 3 H), 0.8–1.8 (br envelope), 3.06 (m, 2 H), 3.30 (dd, J = 15, 9 Hz, 1 H), 3.43 (dd, J = 15, 8 Hz, 1 H), 4.25 (m, 2 H), 4.60 (d, J = 17 Hz, 1 H), 4.81 (d, J = 17 Hz, 1 H), 5.15 (t, J = 8 Hz, 1 H), 6.18 (d, J = 3 Hz, 1 H), 7.18 (br t, J = 8 Hz, 1 H), 7.32 (br t, J = 8 Hz, 1 H), 7.45 (d, J = 3 Hz, 1 H), 7.49 (d, J = 8 Hz, 1 H), 7.62 (d, J = 8 Hz, 1 H); MS m/z 536 $(M + H)^+$. Anal. Calcd for $C_{30}H_{41}N_5O_4 \cdot H_2O$: C, 65.08; H, 7.83; N, 12.64. Found: C, 64.97; H, 7.57; N, 12.62.

(1′*S*,2″*S*,3″*R*,4″*S*)-2-[1-[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]-3-methylbutyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (6d). Coupling as above gave a crude product, which was purified by flash chromatography using 3:2 ethyl acetate/chloroform, to give **6d**, mp 205–208 °C, in 83% yield: ^1H NMR ($CDCl_3$) δ 0.5–1.7 (br envelope), 0.82 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H), 1.94 (m, 1 H), 2.16 (m, 1 H), 3.31 (m, 2 H), 4.14 (m, 1 H), 4.38 (m, 1 H), 4.45 (m, 1 H), 4.53 (br s, 2 H), 5.23 (dd, J = 9, 6 Hz, 1 H), 7.21 (br t, J = 7 Hz, 1 H), 7.28 (br d, 1 H), 7.35 (ddd, J = 8, 7, 1 Hz, 1 H), 7.52 (d, J = 8 Hz, 1 H), 7.61 (d, J = 8 Hz, 1 H), 9.64 (s, 1 H); MS m/z 512 $(M + H)^+$. Anal. Calcd for $C_{30}H_{45}N_3O_4 \cdot 0.25H_2O$: C, 69.80; H, 8.88; N, 8.14. Found: C, 69.75; H, 9.10; N, 7.84.

(2′*S*,3′*R*,4′*S*)-2-[[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]methyl]-1,2,3,4-tetrahydropyrrolo[3,4-*b*]indol-3-one (6e). Coupling as above gave a crude product, which was purified by flash chromatography using 2% methanol in dichloromethane, to give **6e**, mp 115–116 °C, in 16% yield: ^1H NMR (DMSO-d_6) δ 0.82 (d, J = 7 Hz, 3 H), 0.89 (d, J = 7 Hz, 3 H), 1.1–1.8 (br envelope), 2.55 (m, 1 H), 2.99 (m, 1 H), 3.15 (m, 1 H), 3.35 (m, 2 H), 4.20 (m, 3 H), 4.48 (m, 3 H), 4.86 (d, J = 6 Hz, 1 H), 7.12 (ddd, J = 8, 7, 1 Hz, 1 H), 7.26 (ddd, J = 8, 7, 1 Hz, 1 H), 7.47 (d, J = 8 Hz, 1 H), 7.64 (d, J = 8 Hz, 1 H), 7.83 (d, J = 8 Hz, 1 H), 11.89 (s, 1 H); MS m/z 456 $(M + H)^+$. Anal. Calcd for $C_{26}H_{37}N_3O_4 \cdot H_2O$: C, 65.94; H, 8.30; N, 8.87. Found: C, 66.21; H, 8.02; N, 8.80.

Preparation of 6a via 2f. A suspension of 1.51 g (4.66 mmol) of **5a** in 20 mL of dioxane was cooled to 0 °C and treated with 10.4 mL of 0.5 M aqueous LiOH. After being stirred for 2 h, the solution was treated with 1.12 g (5.13 mmol) of di-*tert*-butyl dicarbonate, stirred at ambient temperature for 2 h, and concentrated in vacuo, to give 2.15 g of the crude lithium salt of **2f**. A portion of the salt (237 mg, ca. 0.52 mmol) was taken up in 5 mL of dichloromethane and 2.5 mL of dimethylformamide, cooled to 0 °C, and treated sequentially with 60 μL (0.55 mmol) of 4-methylmorpholine and 81 μL (0.62 mmol) of isobutyl chloroformate. After being stirred for 10 min, the solution was treated with a solution of 150 mg (0.62 mmol) of (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane,[10] stirred at ambient temperature for 2 h, diluted with ethyl acetate, washed sequentially with aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 5% methanol in chloroform gave 0.32 g of the imidazole-*N*-Boc derivative of **6a**, which was taken up in 5 mL of methanol, treated with 0.5 mL of trifluoroacetic acid, and stirred at ambient temperature for 16 h. After quenching with aqueous $NaHCO_3$, the solution was concentrated in vacuo, diluted with ethyl acetate, washed with saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 10% methanol in chloroform gave 120 mg (43% from **5a**) of pure **6a**.

2-[1-(Ethoxycarbonyl)pentyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-one (8). A solution of 0.38 mL (2.8 mmol) of diisopropylamine in 25 mL of anhydrous tetrahydrofuran was cooled under a N_2 atmosphere to −78 °C and treated with 1.1 mL (2.8 mmol) of *n*-butyllithium. The resulting solution was warmed to 0 °C for 15 min, recooled to −78 °C, and treated with a solution of 250 mg (1.34 mmol) of **7**[13] in 5 mL of tetrahydrofuran. The solution was allowed to warm to 0 °C, followed by treatment with 0.25 mL (1.4 mmol) of ethyl 2-bromohexanoate. The resulting solution was stirred at ambient temperature for 16 h, partitioned between ether and aqueous ammonium chloride, washed with saturated brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel chromatography using 3:1 hexane/ethyl acetate gave 172 mg (39%) of **8** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.91 (br t, 3 H), 1.27 (t, J = 7 Hz, 3 H), 1.4 (m, 4 H), 1.86 (m, 1 H), 2.10 (m, 1 H), 3.10 (m, 2 H), 3.66 (ddd, J = 13, 8, 6 Hz, 1 H), 3.81 (ddd, J = 13, 8, 6 Hz, 1 H), 4.2 (m, 2 H), 5.39 (dd, J = 10, 5 Hz, 1 H), 7.15 (td, J = 7, 1 Hz, 1 H), 7.31 (td, J = 7, 1 Hz, 1 H), 7.47 (d, J = 7 Hz, 1 H), 7.60 (d, J = 7 Hz, 1 H), 9.81 (br s, 1 H); MS m/z 329 $(M + H)^+$. Anal. Calcd for $C_{19}H_{24}N_2O_3 \cdot 0.5H_2O$: C, 67.63; H, 7.47; N, 8.30. Found: C, 67.15; H, 7.04; N, 8.24.

(1′*S*,2″*S*,3″*R*,4″*S*)-2-[1-[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]pentyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-one (10a). Ester **8** was hydrolyzed and coupled as above, to give a mixture of two diastereomeric products, which were separated by silica gel chromatography using 2:1 hexane/ethyl acetate, to give a 30% yield of **10a**: mp 115–117 °C; ^1H NMR ($CDCl_3/CD_3OD$) δ 0.7–2.2 (br envelope), 0.85–0.97 (m, 18 H), 3.06 (m, 4 H), 3.14 (m, 2 H), 3.26 (m, 2 H), 3.70 (m, 6 H), 4.28 (dd, J = 10, 4 Hz, 2 H), 5.15 (t, J = 8 Hz, 2 H), 7.16 (br t, J = 8 Hz, 2 H), 7.33 (br t, J = 8 Hz, 2 H), 7.45 (d, J = 8 Hz, 2 H), 7.61 (d, J = 8 Hz, 2 H), 9.90 (br s, 1 H); MS m/z 526 $(M + H)^+$. Anal. Calcd for $C_{31}H_{47}N_3O_4 \cdot 0.25H_2O$: C, 70.22; H, 9.03; N, 7.92. Found: C, 70.12; H, 9.10; N, 7.65.

[3-[2-(Ethoxycarbonyl)indolyl]]acetaldehyde (11). A suspension of 11.95 g (34.9 mmol) of (methoxymethyl)triphenylphosphonium chloride in 200 mL of anhydrous tetrahydrofuran was cooled to 0 °C under a N_2 atmosphere and treated dropwise with 14.3 mL (35.8 mmol) of *n*-butyllithium. The resulting solution was stirred for 15 min, treated with 3.70 g (17 mmol) of **3b**,[7] and stirred at ambient temperature for 3 h. After concentration of the solvent in vacuo, the residue was taken up in ethyl acetate, washed sequentially with water and saturated brine, dried over $MgSO_4$, and concentrated. The crude mixture of vinyl ethers was partially purified by silica gel chromatography using 6:1 hexane/ethyl acetate. The mixture (2.98 g, 71%) was subsequently treated with 20 mL of 1 M HCl and 40 mL of tetrahydrofuran. After being heated at reflux for 6 h, the cooled solution was partitioned between ether and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography using 4:1 hexane/ethyl acetate provided 1.35 g (48%) of **11**, which was recrystallized from ethyl acetate/hexane, to give a white, crystalline solid: mp 122–123 °C; ^1H NMR ($CDCl_3$) δ 1.42 (t, J = 7 Hz, 3 H), 4.17 (d, J = 2 Hz, 2 H), 4.42 (q, J = 7 Hz, 2 H), 7.19 (ddd, J = 8, 7, 1 Hz, 1 H), 7.37 (ddd, J = 8, 7, 1 Hz), 7.43 (br d, J = 8 Hz, 1 H), 7.61 (br d, J = 8 Hz, 1 H), 8.94

(br s, 1 H), 9.73 (t, J = 2 Hz, 1 H); MS m/z 232 (M + H). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.84; H, 5.75; N, 6.07.

(1′*S*,2″*S*,3″*R*,4″*S*)-2-[1-[*N*-(1-Cyclohexyl-3,4-dihydroxy-6-methyl-2-heptyl)carbamoyl]-2-(4-imidazolyl)ethyl]-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indol-1-one (10b). Reductive amination as above with **11** and the L-histidine amide of (2*S*,3*R*,4*S*)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane gave **12** in 89% yield as a 2:1 mixture of diastereomers after flash chromatography using 10% methanol in chloroform. A sample of **12** (325 mg, 0.55 mmol) in 8 mL of dioxane was treated with 4.5 mL (1.3 mmol) of 0.3 M aqueous NaOH and heated at 60 °C. After 6 h, the solvent was removed in vacuo, and the crude salt was cyclized as above, to give **10b** (mp 153–159 °C) in 13% yield after separation of diastereomers by silica gel chromatography using 7.5% methanol in chloroform: ^{1}H NMR ($CDCl_3$) δ 0.6–1.9 (br envelope), 0.78 (d, J = 7 Hz, 1 H), 0.93 (d, J = 7 Hz, 3 H), 3.0 (m, 3 H), 3.25 (m, 3 H), 3.5 (m, 1 H), 3.83 (m, 2 H), 4.33 (m, 2 H), 5.73 (dd, J = 10, 5 Hz, 1 H), 6.89 (s, 1 H), 7.16 (t, J = 8 Hz, 1 H), 7.32 (t, J = 8 Hz, 1 H), 7.43 (m, 2 H), 7.60 (d, J = 8 Hz, 1 H), 10.05 (br, 1 H); MS m/z 550 $(M + H)^+$. Anal. Calcd for $C_{31}H_{43}N_5O_4 \cdot 0.5H_2O$: C, 66.64; H, 7.94; N, 12.53. Found: C, 66.99; H, 7.94; N, 12.30.

Acknowledgment. The assistance of the Analytical Research Department at Abbott Laboratories in providing spectra is gratefully acknowledged.

Registry No. **2a**·Li, 124156-50-9; **2b**·Li, 124156-51-0; **2c**·Li, 124156-52-1; **2d**·Li, 124156-53-2; **2e**·Li, 124156-54-3; **2f**·Li, 124156-60-1; **3a**, 124156-40-7; **3b**, 18450-27-6; **4a**, 124156-42-9; **4b**, 124156-43-0; **4c**, 124175-16-2; **4d**, 124156-44-1; **4e**, 124156-45-2; **5a**, 124156-46-3; **5b**, 124175-17-3; **5c**, 124156-47-4; **5d**, 124156-48-5; **5e**, 124156-49-6; **6a**, 124156-55-4; **6a** (N^{im}-BOC deriv), 124156-61-2; **6a** (1′*R*-diastereomer), 124223-56-9; **6b**, 124156-56-5; **6b** (1′*R*-diastereomer), 124223-57-0; **6c**, 124156-57-6; **6c** (1′*R*-diastereomer), 124223-58-1; **6d**, 124156-58-7; **6e**, 124156-59-8; **7**, 17952-82-8; **8**, 124156-62-3; **9a**, 124156-63-4; **10a** (1′*S*-diastereomer), 124175-18-4; **10a** (1′*R*-diastereomer), 124262-95-9; **10b** (1′*S*-diastereomer), 124156-67-8; **10b** (1′*R*-diastereomer), 124223-60-5; **11**, 80364-01-8; **12** (1′*S*-diastereomer), 124156-66-7; **12** (1′*R*-diastereomer), 124223-59-2; H-His-OMe·2HCl, 7389-87-9; H-Leu-OMe, 2666-93-5; H-Gly-OMe, 616-34-2; (2*S*,3*R*,4*S*)-(c-C_6H_{11})CH_2CH(NH_2)CH(OH)CH(OH)CH_2CHMe_2·HCl, 104882-45-3; (2*S*,3*R*,4*S*)-(c-C_6H_{11})CH_2CH(NH_2)CH(OH)CH(OH)CH_2CHMe_2, 122621-77-6; (±)-$CH_3(CH_2)_3$CHBrCOOEt, 63927-44-6; $Ph_3(MeOCH_2)P^+Cl^-$, 4009-98-7; (2*S*,3*R*,4*S*)-(c-C_6H_{11})CH_2CH(H-His-NH)CH(OH)CH(OH)CH_2CHMe_2, 116183-33-6; indole-2-carboxylic acid, 1477-50-5; benzyl indole-2-carboxylate, 78277-27-7; methyl (±)-2-amino-3-(4-thiazolyl)propanoate, 119357-61-8; methyl (±)-2-amino-3-(3-pyrazolyl)propanoate, 124156-41-8; ethyl (*E*)-3-(2-methoxyethenyl)indole-2-carboxylate, 124156-64-5; ethyl (*Z*)-3-(2-methoxyethenyl)indole-2-carboxylate, 124156-65-6.

Synthesis of *endo,endo*-2,5-Bis((diphenylphosphino)methyl)bicyclo[2.2.1]heptane, a Chelating Diphosphine with a Natural Bite Angle of 120°

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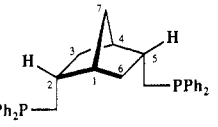
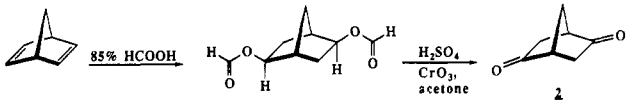
Received August 21, 1989

One of the key intermediates in rhodium-catalyzed hydroformylation reactions is a trigonal-bipyramidal rhodium diphosphine species. The two phosphines in $(R_3P)_2(CO)_2RhH$ have the possibility of occupying two axial, two equatorial, or one axial and one equatorial position. Use of chelating ligands such as DIPHOS, $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$, which has a preferred bite angle (P–M–P) of about 90° allows study of locked axial, equatorial diphosphine catalysts. However, few ligands are available to selectively occupy diequatorial positions in trigonal bipyramids. Because of our interest in hydroformylation, we have initiated a program to design and synthesize chelating diphosphines which have a constrained bite angle near 120° for selective diequatorial coordination.

Our design process begins with molecular models and progresses to molecular mechanics calculations. If molecular models indicate a promising candidate, we use molecular mechanics to predict the "natural bite angle" (β_n) of the chelate.[1] We define the natural bite angle as the preferred chelation angle determined only by ligand backbone constraints and not by metal valence angles.[2] Since the natural bite angle depends on the metal–phosphorus bond length, we input a typical Rh–P bond length of 2.30 Å. In addition, we calculate the potential energy well for distortions from the natural bite angle to estimate how flexible the chelate will be. Using this molecular mechanics procedure, we have calculated that Rh(I) complexes of *endo,endo*-2,5-bis((diphenylphosphino)methyl)bicyclo[2.2.1]heptane (**1**) will have a natural bite angle of 122.6°. It should be pointed out that **1** is a chiral molecule with a C_2 axis of symmetry and it may prove useful in enantioselective syntheses. Here we describe the synthesis and characterization of racemic diphosphine **1**.



The starting material for our four step synthesis of diphosphine **1** is bicyclo[2.2.1]heptane-2,5-dione (**2**). Diketone **2** is readily obtained by addition of formic acid to norbornadiene followed by Jones oxidation of the resulting diformate ester.[3]



Reaction of dione **2** with 2 equiv of $CH_2{=}PPh_3$ in DMSO led to the formation of 2,5-bis(methylene)bicyclo[2.2.1]heptane (**3**) in 66% yield. Use of DMSO as solvent gave substantially higher yields than diethyl ether (37%) as has been noted previously.[4]

Hydroboration–oxidation of diene **3** was anticipated to occur from the exo face since Brown had reported 85% exo selectivity in the hydroboration of 2-methylenenorbornane.[5] In practice, hydroboration–oxidation of diene **3** led to the selective formation of *endo,endo*-2,5-bis(hydroxymethyl)bicyclo[2.2.1]heptane (**4**) in 87% yield (Scheme I). No other isomer was detected by ^{1}H or ^{13}C NMR analyses. The presence of only five resonances in the ^{13}C NMR spectrum establishes the C_2 symmetry of diol **4**. In the ^{1}H NMR spectrum of **4**, the equivalent endo protons on C3 and C6 appear at δ 0.90 (dd, J_{gem} = 14.6 Hz, J = 5.7 Hz) upfield from the exo protons at δ 1.3; a similar

(1) Casey, C. P.; Whiteker, G. T., submitted to *Isr. J. Chem.*
(2) This is accomplished by using a bending force constant of 0 kcal mol^{-1} rad^{-2} for the P–M–P angle.
(3) Hawkins, R. T.; Hsu, R. S.; Wood, S. G. *J. Org. Chem.* **1978**, *43*, 4648.
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(5) Brown, H. C.; Kawakami, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 1990.

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