Synthesis and Dopamine Receptor Modulating Activity of Substituted Bicyclic Thiazolidine Lactam Peptidomimetics of L-Prolyl-L-leucyl-glycinamide

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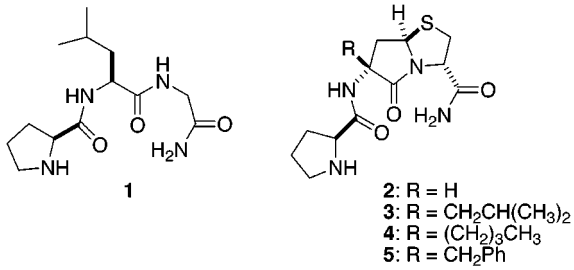
6-Substituted bicyclic thiazolidine lactam peptidomimetics of Pro-Leu-Gly-NH_2 (**1**) were synthesized to test the hypothesis that incorporation of a hydrophobic side chain into the bicyclic thiazolidine lactam scaffold would further enhance the dopamine receptor modulating activity of such peptidomimetics. The substituents employed were the isobutyl, butyl, and benzyl groups to give peptidomimetics **3**−**5**, respectively. These peptidomimetics were evaluated in vivo as modulators of apomorphine-induced rotational behavior in the 6-hydroxydopamine-lesioned rat model of hemiparkinsonism and were compared with the unsubstituted bicyclic thiazolidine lactam Pro-Leu-Gly-NH_2 peptidomimetic **2**. Peptidomimetics **3**−**5** each affected rotational behavior in a bell-shaped dose−response relationship producing maximal increases of 44% (1 μg/kg, ip), 56% (0.1 μg/kg, ip), and 30% (1 μg/kg, ip), respectively. In comparison, unsubstituted peptidomimetic **2** increased rotational behavior by only 23% at a dose of 0.1 μg/kg, ip.

Introduction

The endogenous tripeptide L-prolyl-L-leucyl-glycinamide (**1**, PLG), also known as melanocyte-stimulating hormone release-inhibiting factor (MIF-1),[1] is able to modulate dopaminergic neurotransmission in the CNS. This modulatory activity has been demonstrated through in vitro and in vivo studies.[2−7] In vitro receptor binding studies have shown that **1** and its analogues induce an increase in agonist binding to dopamine receptors in the striatum, which is due to an increase in the affinity of the dopamine receptor for agonists.[3,6] Peptide **1** and its active analogues also are capable of preventing the 5′-guanylylimidodiphosphate [Gpp(NH)p]-induced conversion of D_2 dopamine receptors from a high-affinity to a low-affinity state, suggesting that modulation of dopamine receptors by **1** may involve guanine nucleotide regulatory proteins (G-proteins).[6]

In the rat nigrostriatal 6-hydroxydopamine lesion rotational model,[8] **1** has been shown to potentiate the contralateral rotational behavior induced by apomorphine.[2,5,7,9] Further evidence supporting the ability of **1** to modulate dopamine receptor activity is shown in studies of neuroleptic induced dopamine receptor supersensitivity where it antagonizes the up-regulation of dopamine receptors produced by chronic haloperidol treatment.[4,10,11]

Numerous conformationally constrained analogues of **1** have been synthesized and tested in an effort to elucidate the peptide's bioactive conformation.[12−17] One such analogue is the bicyclic thiazolidine lactam **2**.[14] Although this analogue lacked the side chain that corresponds to the isobutyl group of the leucine residue found in **1**, it proved to be one of the most effective analogues tested thus far. Nevertheless, since earlier SAR studies with linear tripeptide analogues of **1** modified at the leucine position showed that a hydrophobic residue at this position was important for activity,[18] we postulated that incorporation of the hydrophilic side chain into the structure of **2** would enhance further the activity of this peptidomimetic. To test this hypothesis, the synthesis of the 6-substituted bicyclic thiazolidine lactams **3**−**5** was undertaken. In addition to the isobutyl side chain, the butyl and benzyl side chains were also chosen because the SAR studies with linear tripeptide analogues of **1** showed that replacing the leucyl residue with either the norleucine or phenylalanine residue provided analogues equal in potency and efficacy to that of the parent peptide.



Synthesis

The α,α-disubstituted amino acids **8**, **17**, and **18** served as the starting materials for the synthesis of peptidomimetics **3**−**5**. Two different routes were employed in obtaining these compounds. In the synthesis of **8**, a modification of the method by Karady et al.[19] was used as depicted in Scheme 1. L-Cbz-Phe-OH was converted to oxazolidinones **6a** and **6b**, which were separated by a combination of chromatography and crystallization. Consistent with previously published

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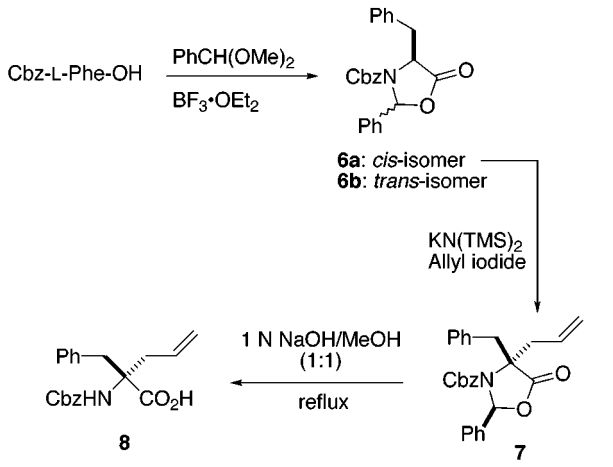
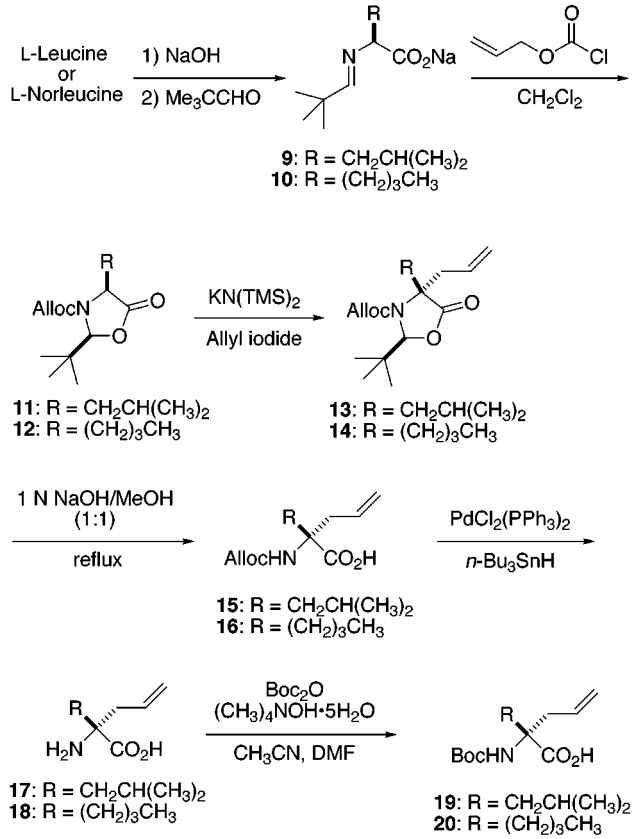
Scheme 1



Scheme 2



work by Cheng et al.,[20] the major isomer obtained was the *cis*-oxazolidinone **6a**. This compound was stereoselectively alkylated with potassium hexamethyldisilazide and allyl iodide to give the α-allyloxazolidinone **7**. Basic hydrolysis of the lactone furnished the benzyloxycarbonyl-protected amino acid **8** quantitatively.

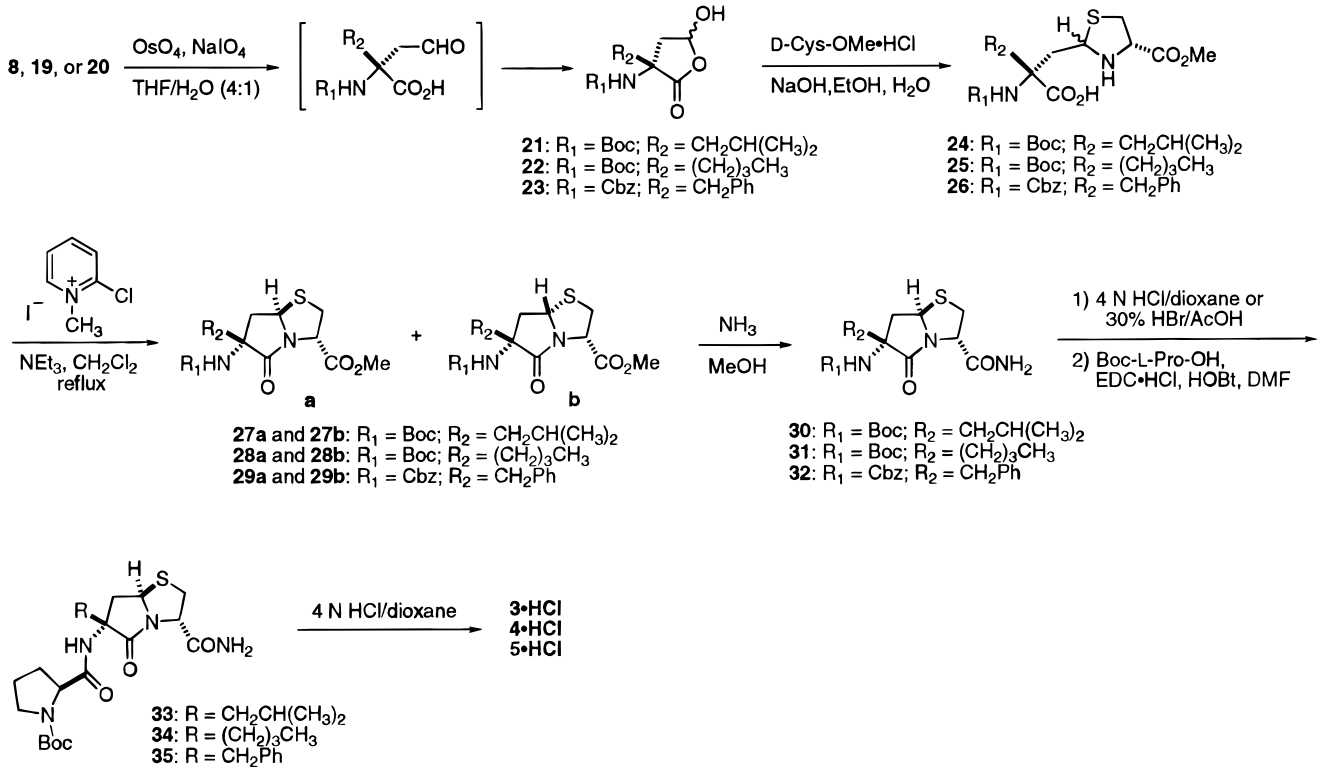
Initially, the above approach was tried for the synthesis of **17**. However, the mixture of *cis*/*trans*-oxazolidinones that was obtained proved very difficult to separate. As an alternative, the procedure of Seebach and Fadel[21] as modified by Smith et al.[22,23] was applied and found to work. As shown in Scheme 2, the sodium salt of L-leucine was condensed with pivalaldehyde to form imine **9**. This Schiff base was cyclized to the corresponding *cis*-oxazolidinone **11** by N-acylation with allyl chloroformate. The relative configuration of this oxazolidinone was determined on the basis of NOE difference experiments which showed a reciprocal NOE between the H_2 and H_4 hydrogens. The results were in agreement with those of Seebach and Fadel[21] and Smith et al.[22] The potassium enolate of **11** was diastereoselectively alkylated with allyl iodide to give **13** which was hydrolyzed to give the allyloxycarbonyl α-allyl amino acid **15** in an excellent overall yield. The same sequence of reactions was carried out on L-norleucine. Since the allyloxycarbonyl group of **15** and **16** was incompatible with the rest of the synthesis, it was removed[24] in each case, and the corresponding amino acids **17** and **18** were reprotected to give the *tert*-butoxycarbamate derivatives **19** and **20**, respectively.

The conversion of the α-allyl amino acids **8**, **19**, and **20** to peptidomimetics **3**−**5**, respectively, was carried out as outlined in Scheme 3. Oxidative cleavage of each of the α-allyl amino acids to the corresponding aldehydes was accomplished with OsO_4 and $NaIO_4$. However, in each case the product actually isolated after workup was a diastereoisomeric mixture of γ-hydroxy lactones **21**−**23**. Condensation of each lactone with D-cysteine methyl ester under conditions previously described by Genin and Johnson[25] afforded, in each case, a diastereoisomeric mixture of thiazolidines **24**−**26**. Ring closure of **24**−**26** to form the epimeric mixture of bicyclic lactams **27a**/**27b**−**29a**/**29b**, respectively, was carried out with Mukaiyama's reagent.[26] In all three cases, the isomer with the bridgehead stereochemistry of 7a-*R* (**a**) was the major isomer isolated. The ratio of **a**:**b** ranged from 2−3:1. Separation of each pair of isomers was possible by chromatographic techniques. However, in the case of compounds **27a**/**27b** and **28a**/**28b**, the separation was very laborious and it proved more expedient to accomplish this in the subsequent carboxamidation step where a differential rate of reaction was observed. Upon treatment of **27a**/**27b** and **28a**/**28b** with methanolic ammonia, the desired isomers in each case, **27a** and **28a**, were found to undergo a much more rapid reaction than their diastereoisomeric counterparts. Thus, it was possible to readily obtain the carboxamides **30** and **31** in pure form after a simple flash chromatographic step. In the case of **29a** and **29b**, the two isomers were easily separated from one another, and the desired isomer **29a** was converted to the carboxamide derivative **32** with NH_3/MeOH.

The stereochemistry at the bridgehead carbon (7a-C) of the 6-substituted bicyclic thiazolidine lactams was assigned on the basis of extensive NOE difference experiments performed on the methyl ester (**27**−**29**) and carboxamide (**30**−**32**) derivatives (Figure 1). For example, in the experiment performed on **28b**, weak reciprocal NOEs (∼1%) were observed between H_3 and H_{7a}, with stronger reciprocal NOEs seen between H_3 and H_{2a} and between H_{7a} and H_{2a}. These data support the assignment of an *S*-configuration at 7a-C. In support of this assignment, NOEs observed for the bicyclic lactam derived from the 7a-epimer of **27b**, **31**, are consistent with an *R*-configuration at 7a-C. As indicated in Figure 1 similar results were seen with bicyclic lactams **27b, 29b**, **30**, and **32**.

The X-ray crystal structure of lactam **29a** was solved, and an ORTEP representation is shown in Figure 2.[27] In addition to confirming the NOE stereochemical

Scheme 3



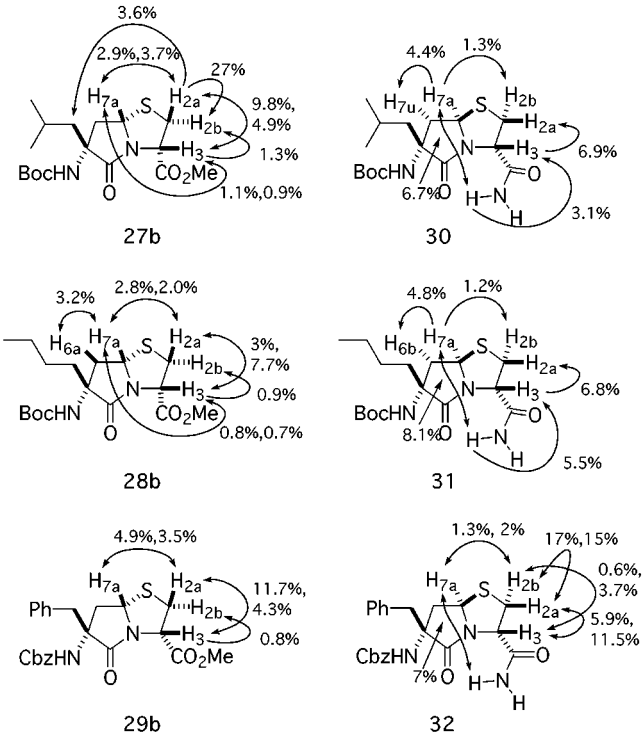


Figure 1. Graphical summary of the NOEs observed for the bicyclic thiazolidine lactams **27b**−**29b** and **30**−**32**.

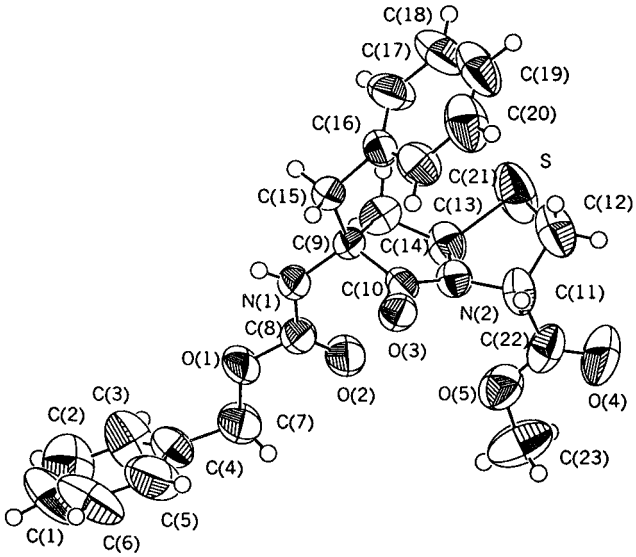


Figure 2. ORTEP plot of 6-benzyl bicyclic thiazolidine lactam **29a**. Hydrogen atoms are drawn as spheres of arbitrary radius.

assignment, the solid-state structure of **29a** provides detailed information on the accessible peptide backbone conformation of this bicyclic thiazolidine lactam scaffold. A comparison of the ϕ, ψ dihedrals defining the turn region of **29a** with those of the classical type II β-turn reveals that the two torsion angles constrained by the heterocycle ($\psi_2 = 123°$ and $\phi_3 = 113°$) as well as the nonconstrained angles ($\phi_2 = -53°$ and $\psi_3 = -26°$) fall within the acceptable range of an ideal type II β-turn.[28]

The final conversions of the dipeptide β-turn mimics **30**−**32** to **3**−**5** were carried out with standard coupling methods as outlined in Scheme 3. In removing the *tert*-butoxycarbonyl group from **33** and **34**, epimerization was observed at the bridgehead carbon (7a-C). This is in accord with a previously proposed mechanism for epimerization involving acid-catalyzed ring opening.[29] This problem was overcome by carrying out the reaction at 0 °C for short periods of time (<45 min).

Pharmacology

The substituted bicyclic lactams **2**−**5** were evaluated

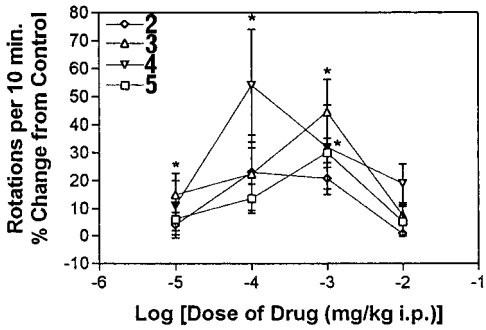


Figure 3. Effect of ip administered peptidomimetics **2**−**5** on contralateral behavior of ip administered apomorphine (0.25 mg/kg) in rats (n = 4) with unilateral lesions. Number of contralateral rotations in 10 min expressed as a percentage change from control rotational response. Dosage expressed as log (mg/kg) from −5 or 0.00001 mg/kg to −2 or 0.01 mg/kg. Each point represents the mean percent change ± SEM. Statistical significance: $*p < 0.05$.

in the rat nigrostriatal 6-hydroxydopamine lesion rotational model. When administered in the absence of apomorphine, peptidomimetics **2**−**5** did not produce any contralateral rotations or other observable changes in behavior. Peptidomimetics **3**−**5** each produced a bell-shaped dose-response curve when administered with apomorphine (Figure 3). The maximal effect for **3**−**5** was a 44%, 56%, and 30% increase in rotations, respectively, compared to apomorphine administration alone. For peptidomimetics **3** and **5**, the maximal response was observed at a dose of 1 μg/kg ip. In the case of **4**, the maximal response was observed at a dose of 0.1 μg/kg, ip. The comparison compound, peptidomimetic **2**, produced a maximal dose response at 0.1 μg/kg ip and resulted in a nonsignificant 23% increase in the number of rotations over a 10-min period compared to apomorphine alone.

Discussion

The numerous pharmacological studies that have been conducted on **1** have clearly shown that this tripeptide enhances dopaminergic neurotransmission within the CNS.[30] Studies have shown that **1** does not modulate dopaminergic neurotransmission by affecting either dopamine synthesis, uptake, or metabolism.[31−34] Rather, biochemical and pharmacological studies indicate that this modulation is brought about by a mechanism in which **1** renders the dopamine receptor more responsive to agonists.[3,6] The ability of **1** and its analogues to enhance apomorphine-induced rotations in 6-hydroxydopamine-lesioned rats is believed to be due to this enhanced responsiveness of the dopamine receptor to the agonist apomorphine.[2,5,7,9]

Compound **2** was originally synthesized as a peptidomimetic of Pro-Leu-Gly-NH_2 wherein the bicyclic thiazolidine lactam scaffold was designed to mimic the type II β-turn conformation that had been postulated to be the bioactive conformation of Pro-Leu-Gly-NH_2.[14] Molecular modeling of the bicyclic thiazolidine lactam ring system had predicated that this template would constrain the ψ_2 and ϕ_3 torsion angles of a type II β-turn to values that were in the range of the idealized values for such a turn. The X-ray structure obtained for **29a** in the current study shows that the ψ_2 and ϕ_3 torsion angles possess values of 123° and 113°, respectively. This result resembles the ψ_2 and ϕ_3 torsion angle values of 142.7° and 120.5°, respectively, that were obtained for the unsubstituted bicyclic thiazolidine lactam scaffold.[17] Both of these X-ray crystallography studies confirm the prediction of molecular modeling[14] that the bicyclic thiazolidine lactam scaffold is a good mimic of a type II β-turn as an idealized β-turn has values of 120° ± 30° for the ψ_2 torsion angle and 80° ± 30° for the ϕ_3 torsion angle.[28]

Pro-Leu-Gly-NH_2 peptidomimetic **2** previously was shown to possess very good activity in enhancing the binding of the dopamine receptor agonist 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene to isolated bovine dopamine receptors even though it lacked the isobutyl side chain present in the parent peptide.[14] Previous work had shown this side chain to be important for the activity of Pro-Leu-Gly-NH_2 as replacing the side chain with lower alkyl moieties resulted in analogues that posessed little or no activity.[18] In contrast, replacing the isobutyl side chain with the butyl or benzyl group yielded analogues that retained the ability to modualte dopamine receptors.

We postulated that placement of lipophilic side chains on the bicyclic thiazolidine lactam scaffold would enhance the activity of these Pro-Leu-Gly-NH_2 peptidomimetics by virture of their ability to access the binding site with which the leucyl side chain interacts. Thus, peptidomimetics **3**−**5** were synthesized in which position 6 of the bicyclic thiazolidine lactam ring scaffold was substituted with the isobutyl, butyl, and benzyl groups, respectively. As illustrated in Figure 3, all three 6-substituted peptidomimetics possessed activity greater than that seen with **2** in terms of enhancing rotational behavior by apomorphine in 6-hydroxydopamine-lesioned rats. The relative ranking of activity was **4** > **3** > **5** > **2**.

Previously, Pro-Leu-Gly-NH_2 was found to increase rotational behavior by 30 ± 7% with this maximal response occurring at a dose of 1.0 mg/kg, ip.[7] The results obtained in this study show that the substituted bicyclic thiazolidine lactams **3**−**5** are much more potent than Pro-Leu-Gly-NH_2, since the maximal responses for these compounds occur at doses that are 1000−10000 times lower. These results support the hypothesis that incorporation of a hydrophobic substituent on the 6-position of the bicyclic thiazolidine lactam scaffold leads to enhanced dopamine receptor modulatory activity through the ability of these peptidomimetics to access the binding site with which the leucine side chain interacts.

Experimental Section

General Aspects. Thin-layer chromatography was performed on Analtech 250-μm silica gel HLF Uniplates visualized by UV, I_2, ninhydrin spray (amines), 2,6-dichlorophenol indophenol spray (acids), and 2,4-dinitrophenylhydrazine (aldehydes). Chromatographic purification on silica gel (Merck, grade 60, 240−400 mesh, 60 Å) was done by flash or gravity methods and semipreparative HPLC was done with a Waters Associates 25- × 100-mm PrepPak cartridge. Optical rotations were measured on a Rudolph Research Autopol III polarimeter at the 589-nm Na D-line. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 and 75.5 MHz, respectively, with $CDCl_3$ as the internal reference for ^{1}H (δ 7.26) and ^{13}C (δ 77.06).

(2*S*,4*S*)- and (2*R*,4*S*)-2-Phenyl-3-*N*-(benzyloxycarbonyl)-4-benzyloxazolidinone (6a and 6b). Oxazolidinone **6a**

was synthesized by a modification of the Karady method[19] that was developed by Cheng et al.[20] Cbz-L-Phe-OH (30 g, 100 mmol) and benzaldehyde dimethyl acetal (14.4 mL, 96 mmol) in Et_2O (500 mL) were cooled to −78 °C. $BF_3{\cdot}Et_2O$ (60.2 mL, 489 mmol) was added dropwise, and the mixture was then allowed to warm to room temperature where it was stirred for 4 days under an atmosphere of N_2. The mixture was cooled to 0 °C, and excess $BF_3{\cdot}Et_2O$ was quenched by adding saturated $NaHCO_3$, initially in 1-mL portions until the strong bubbling ceased. The aqueous layer was separated and extracted with Et_2O (3 × 150 mL). The combined Et_2O extracts were dried with $MgSO_4$ and concentrated under vacuum to give a crude solid that was crystallized from EtOAc/Et_2O to give a total of 13.8 g (37%) of **6a**. The mother liquor contained a mixture of **6a** and its (2*R*,4*S*)-epimer which was difficult to separate cleanly by silica gel chromatography alone (Et_2O/EtOAc/hexanes, 5:1:20). Fractions were obtained from the column that when combined and concentrated gave a tan solid which was highly enriched with the (2*R*,4*S*)-*trans*-epimer **6b** (9 g, 24%). The pure *trans*-epimer was then obtained by recrystallization from EtOAc/hexanes.

6a: mp 126−127 °C (lit.[20] mp = 123−125 °C); $[\alpha]_D$ +45.6 (*c* 1.6, $CHCl_3$); EI MS *m*/*z* 387 $[M]^+$.

6b: mp 136−137 °C; $[\alpha]_D$ +205.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 323 K) δ 3.24 (d, *J* = 14 and 2.4 Hz, 1 H, C*H*$_2$Ph), 3.7 (m, 1 H, C*H*$_2$Ph), 4.82−4.83 (m, 1 H, 4-CH), 5.03−5.06 (m, 2 H, OC*H*$_2$Ph), 5.57 (s, 1 H, 2-CH), 7.12−7.42 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$, 323 K) δ 34.4 (*C*H$_2$Ph), 57.9 (4-C), 67.4 (O*C*H$_2$-Ph), 89.9 (2-C), 126.5, 127.4, 127.9, 128.0, 128.3, 128.5, 128.6, 129.6, 129.8, 134.4, 135.2, and 137.4 (Ph), 151.7 (Cbz C=O), 170.7 (5-C=O); EI MS *m*/*z* 387 $[M]^+$. Anal. ($C_{24}H_{21}NO_4$) C, H, N.

(2*S*,4*S*)-2-Phenyl-3-(benzyloxycarbonyl)-4-benzyl-4-allyloxazolidinone (7). Oxazolidinone **6a** (12.8 g, 33 mmol) was dissolved in dry THF (175 mL) and the solution cooled to −78 °C. A solution of $KN(TMS)_2$ in toluene (0.5 M, 73 mL, 36.5 mmol) was added to the solution dropwise under an atmosphere of Ar. After 30 min of stirring, allyl iodide (4.5 mL, 49.5 mmol) was added dropwise over 5 min. The reaction changed color from deep orange after addition of $KN(TMS)_2$ to yellow after addition of allyl iodide. The mixture was stirred for another 3 h at −78 °C and then allowed to warm to room temperature over 4 h. The reaction was worked up at −78 °C by addition of saturated $NaHCO_3$ followed by removal of the THF in vacuo. The remaining solution was extracted with EtOAc (3 × 200 mL). The combined extracts were washed twice with 200 mL of each of the following: H_2O, saturated $NaHCO_3$, and brine. Drying and removal of solvents under vacuum gave 13.3 g of a crude oil which was purified using flash silica gel chromatography (10% EtOAc in hexanes). The pure product, **7**, was obtained in 54% yield (7.6 g) as a tan solid which was crystallized from CH_2Cl_2/hexanes mixture: mp 108−109 °C; $[\alpha]_D$ +69.8 (*c* 1.6, $CHCl_3$); ^{1}H and ^{13}C NMR show the presence of two rotamers about the carbamate bond in a ratio of 3:1; ^{1}H NMR ($CDCl_3$) δ 2.69 (dd, *J* = 13.4 and 6.1 Hz, 1 H, C*H*$_2$CH=CH$_2$), 3.01 and 3.29−3.37 (dd, *J* = 13.4 and 9.8 Hz and m, 2 H, C*H*$_2$CH=CH$_2$ and C*H*$_2$Ph), 3.66 (d, *J* = 13.4 Hz, 1 H, C*H*$_2$Ph), 4.89 (d, *J* = 12.2, 1 H, OC*H*$_2$Ph), 5.08 (d, *J* = 12.2 Hz, 1 H, OC*H*$_2$Ph), 5.20−5.39 (m, 2 H, CH=C*H*$_2$), 5.69−5.89 (m, 1 H, C*H*=CH$_2$), 6.05 (s, 1 H, 2-CH), 6.12 and 6.30 (d, *J* = 7.3 Hz, 1 H, Ph), 6.78 (d, *J* = 7.3 Hz, 1 H, Ph), 6.97−7.06 (m, 2 H, Ph), 7.14−7.48 (m, 12 H, Ph); ^{13}C NMR ($CDCl_3$) δ 40.6, 41.9, 42.5, and 42.6 (*C*H$_2$Ph and *C*H$_2$CH=CH$_2$), 67.1, 67.9, 68.9, and 69.1 (4-C and O*C*H$_2$Ph), 89.8 and 90.0 (2-C), 121.9, 127.1, 127.3, 127.4, 127.7, 127.9, 128.1, 128.8, 129.1, 129.2, 129.3, 129.9, 130.5, 135.2, 135.8, and 135.9 (Ph), 152.1 and 153.3 (Cbz C=O), 172.9 and 173.1 (5-C=O); FAB MS *m*/*z* 428 $[M + H]^+$. Anal. ($C_{27}H_{25}NO_4$) C, H, N.

(2*S*)-*N*-(Benzyloxycarbonyl)-2-allylphenylalanine (8). Oxazolidinone **7** (4.69 g, 11 mmol) was dissolved in a mixture of MeOH and 1 N NaOH (50 mL each) and the reaction mixture then heated at reflux for 16 h. The reaction mixture was concentrated under vacuum, and the resulting residue was redissolved in H_2O (100 mL). This solution was washed with Et_2O (200 mL) and then extracted with EtOAc (3 × 200 mL) after its pH was adjusted to 1 with 1 N HCl. The combined organic extracts were dried with $MgSO_4$, and the solvents were evaporated in vacuo to give 3.7 g (100%) of **8** as a tan oil which became a glassy solid on standing: $[\alpha]_D$ +41.5 (*c* 2.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.74 (dd, *J* = 14.7 and 7.5 Hz, 1 H, C*H*$_2$-CH=CH$_2$), 3.23−3.33 (m, 2 H, C*H*$_2$CH=CH$_2$ and C*H*$_2$Ph), 3.67 (d, *J* = 13.5 Hz, 1 H, C*H*$_2$Ph), 5.11−5.31 (m, 4 H, OC*H*$_2$Ph and CH=C*H*$_2$), 5.66 (s, 1 H, NH), 5.70−5.79 (m, 1 H, C*H*=CH$_2$), 7.09−7.54 (m, 15 H, Ph), 10.76 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 39.7 and 40.4 (*C*H$_2$Ph and *C*H$_2$CH=CH$_2$), 64.8 and 66.5 (α-C and O*C*H$_2$Ph), 119.6, 126.9, 128.1, 128.2, 128.4, 128.9, 129.8, 130.2, 131.6, 134.0, 135.6, and 136.4 (Ph), 154.5 (Cbz C=O), 177.4 (COOH); FAB MS *m*/*z* 340 $[M + H]^+$, 250 $[M - PhCH_2]^+$. Anal. ($C_{20}H_{21}NO_4$) C, H, N.

(2*S*,4*R*)-2-*tert*-Butyl-3-(allyloxycarbonyl)-4-(2-methylpropyl)-4-allyloxazolidinone (13). Oxazolidinone **11** (10.8 g, 38.1 mmol), prepared according to a procedure by Smith et al.,[22] was transferred to an oven-dried 500-mL round-bottom flask that was purged with Ar. Dry THF (180 mL) was introduced via a cannula, and the flask was cooled to −78 °C. A solution of $KN(TMS)_2$ in toluene (0.5 M, 91.4 mL, 45.7 mmol) was added to the solution dropwise over 15 min under Ar. After another 15 min of stirring, allyl iodide (7.0 mL, 76.2 mmol) was added dropwise. The reaction was stirred for 3 h and then quenched with 10% $NaHSO_4$ at −78 °C. The reaction mixture was extracted with EtOAc (2 × 300 mL), and the combined extracts were washed with saturated $NaHCO_3$ (200 mL) and brine, dried ($MgSO_4$), and evaporated under vacuum. The resulting residue was loaded onto a 5.5- × 58-cm silica gel column and eluted with 10% EtOAc in hexanes to give 11.1 g (90% yield) of **13** as a clear oil: $[\alpha]_D$ +4.8 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84−0.89 (m, 15 H, $(CH_3)_3$ and $(CH_3)_2$), 1.77 (dd, *J* = 14.6 and 4.9 Hz, 1 H, C*H*$_2$CH$(CH_3)_2$), 1.85 (dd, *J* = 14.6 and 6.1 Hz, 1 H, C*H*$_2$CH$(CH_3)_2$), 1.96−2.04 (m, 1 H, C*H*$(CH_3)_2$), 2.37 (dd, *J* = 13.4 and 6.1 Hz, 1 H, C*H*$_2$CH=CH$_2$), 3.04−3.12 (m, 1 H, C*H*$_2$CH=CH$_2$) 4.44 (dd, *J* = 12.2 and 6.1 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 4.56 (dd, *J* = 12.2 and 6.1 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 4.99−5.05 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.16−5.29 (m, 2 H, OCH$_2$CH=C*H*$_2$), 5.34 (s, 1 H, 2-CH), 5.36−5.48 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.79−5.88 (m, 1 H, OCH$_2$C*H*=CH$_2$); ^{13}C NMR ($CDCl_3$) δ 23.4 (*C*H$(CH_3)_2$), 24.4 and 24.6 (CH(*C*H$_3)_2$), 25.1 ((*C*C$H_3)_3$), 37.7 ((*C*CH$_3)_3$), 40.1 (*C*H$_2$CH=CH$_2$), 45.9 (*C*H$_2$-CH$(CH_3)_2$), 66.3 (O*C*H$_2$CH=CH$_2$), 66.7 (4-C), 94.8 (2-C), 119.0 (OCH$_2$CH=*C*H$_2$), 121.1 (CH$_2$CH=*C*H$_2$), 130.4 (CH$_2$*C*H=CH$_2$), 131.5 (OCH$_2$*C*H=CH$_2$), 154.4 (Alloc C=O), 173.9 (5-C=O); FAB MS *m*/*z* 324 $[M + H]^+$. Anal. ($C_{18}H_{29}NO_4$) C, H, N.

(2*S*,4*R*)-2-*tert*-Butyl-3-(allyloxycarbonyl)-4-butyl-4-allyloxazolidinone (14). Oxazolidinone **12** (3.0 g, 10.2 mmol) was treated in the same manner as described above for the synthesis of **13**. The product of the reaction was chromatographed on a 4- × 45-cm silica gel column (10% EtOAc in hexanes) to give 2.8 g (85% yield) of **14** as a clear oil: $[\alpha]_D$ +9.1 (*c* 4.4, $CHCl_3$); ^{1}H NMR (COSY assignment, $CDCl_3$, 323 K) δ 0.88 (t, *J* = 7.3 Hz, 3 H, $(CH_2)_3CH_3$), 0.94 (s, 9 H, $(CH_3)_3$), 1.24−1.41 (m, 3 H, $(CH_2)_2CH_2CH_3$ and $CH_2CH_2CH_2CH_3$), 1.61−1.74 (m, 1 H, $CH_2CH_2CH_2CH_3$), 1.88−2.09 (m, 2 H, $CH_2(CH_2)_2CH_3$), 2.48 (dd, *J* = 13.4 and 6.1 Hz, 1 H, C*H*$_2$CH=CH$_2$), 3.13−3.48 (dd, *J* = 13.4 and 8.6 Hz, 1 H, C*H*$_2$CH=CH$_2$), 4.50 (dd, *J* = 12.2 and 6.1 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 4.64 (dd, *J* = 12.2 and 4.9 Hz, 1 H, OC*H*$_2$CH=CH$_2$), 5.07−5.13 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.23−5.36 (m, 2 H, OCH$_2$CH=C*H*$_2$), 5.42 (s, 1 H, 2-CH), 5.44−5.57 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.86−5.99 (m, 1 H, OCH$_2$C*H*=CH$_2$); ^{13}C NMR (DEPT assignment, $CDCl_3$, 323 K) δ 13.7 $(CH_2)_3CH_3$), 22.9 and 26.4 ($CH_2(CH_2)_2CH_3$), 25.6 ((C*C*H$_3)_3$), 37.5 (*C*H$_2(CH_2)_2CH_3$), 38.0 (*C*$(CH_3)_3$), 39.5 (*C*H$_2$CH=CH$_2$), 66.4 (O*C*H$_2$CH=CH$_2$), 66.8 (4-C), 95.05 (2-C), 119.0 and 121.1 (OCH$_2$CH=*C*H$_2$ and CH$_2$CH=*C*H$_2$), 130.8 and 131.9 (OCH$_2$*C*H=CH$_2$ and CH$_2$*C*H=CH$_2$), 154.6 (Alloc C=O), 174.2 (5-C=O); FAB MS *m*/*z* 324 $[M + H]^+$. Anal. ($C_{18}H_{29}NO_4$) C, H, N.

(2*R*)-*N*-(Allyloxycarbonyl)-2-allylleucine (15). Oxazolidinone **13** (10.5 g, 32.5 mmol) was dissolved in a mixture of MeOH and 1 N NaOH (200 mL, 1:1) and the reaction mixture

then heated at reflux for 24 h. The reaction mixture was concentrated under vacuum to about one-half its volume, and the resulting solution was washed with Et_2O (150 mL). The aqueous layer was acidified to pH 1 with 1 N HCl and then extracted with EtOAc (3 × 300 mL). The combined organic extracts were dried with $MgSO_4$, and solvents were evaporated in vacuo to give 8.3 g (100% yield) of **15** as a tan oil. This material was used without further purification: $[\alpha]_D$ −15.0 (*c* 1.6, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 7.3 Hz, 3 H, $(CH_3)_2$), 0.90 (d, J = 7.0 Hz, 3 H, $(CH_3)_2$), 1.59−1.77 (m, 2 H, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 2.35 (dd, J = 13.4 and 6.1 Hz, 1 H, $CH_2CH{=}CH_2$), 2.47 (dd, J = 14.6 and 7.3 Hz, 1 H, $CH_2CH(CH_3)_2$), 3.11 (dd, J = 13.4 and 7.3 Hz, 1 H, $CH_2CH{=}CH_2$), 4.53 (d, J = 6.1 Hz, 1 H, $OCH_2CH{=}CH_2$), 5.05−5.11 (m, 2 H, $CH_2CH{=}CH_2$), 5.18−5.32 (m, 2 H, $OCH_2CH{=}CH_2$), 5.55−5.69 (m, 1 H, $CH_2CH{=}CH_2$), 5.83−5.97 (m, 1 H, $OCH_2CH{=}CH_2$), 5.86 (s, 1 H, NH), 11.41 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 22.6, 23.6, and 24.6 ($CH(CH_3)_2$ and $CH(CH_3)_2$), 40.6 and 43.5 ($CH_2CH{=}CH_2$ and $CH_2CH(CH_3)_2$), 63.2 and 65.2 ($OCH_2CH{=}CH_2$ and α-C), 117.5 and 119.2 ($OCH_2CH{=}CH_2$ and $CH_2CH{=}CH_2$), 131.7 and 132.7 ($CH_2CH{=}CH_2$ and $OCH_2CH{=}CH_2$), 154.01 (Alloc C=O), 178.9 (COOH); FAB MS *m*/*z* 256 $[M + H]^+$. Anal. ($C_{13}H_{21}NO_4$) C, H, N.

(2*R*)-*N*-(Alloxycarbonyl)-2-allylnorleucine (16). Oxazolidinone **14** (2.7 g, 8.3 mmol) was hydrolyzed with the same procedure as that described above for the synthesis of **15**. The product was obtained as a tan oil in a yield of 2.1 g (100% yield). This material was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 6.7 Hz, 3 H, $(CH_2)_3CH_3$), 0.93−1.33 (m, 4 H, $CH_2(CH_2)_2CH_3$), 1.72−1.80 (m, 1 H, $CH_2(CH_2)_2CH_3$), 2.22−2.29 (m, 1 H, $CH_2(CH_2)_2CH_3$), 2.48−2.54 (m, 1 H, $CH_2CH{=}CH_2$), 2.99−3.03 (m, 1 H, $CH_2CH{=}CH_2$), 4.49−4.50 (m, 2 H, $OCH_2CH{=}CH_2$), 5.03−5.29 (m, 4 H, $CH_2CH{=}CH_2$ and $OCH_2CH{=}CH_2$), 5.55−5.68 (m, 1 H, $CH_2CH{=}CH_2$), 5.81−5.92 (m, 1 H, $OCH_2CH{=}CH_2$), 5.80 (s, 1 H, NH), 11.23 (br s, 1 H, COOH); ^{13}C NMR (DEPT assignment, $CDCl_3$) δ 13.7 ($(CH_2)_3CH_3$), 22.3 and 26.0 ($CH_2(CH_2)_2CH_3$), 34.8 and 39.4 ($CH_2CH{=}CH_2$ and $CH_2(CH_2)_2CH_3$), 63.5 and 65.2 ($OCH_2CH{=}CH_2$ and α-C), 117.4 and 118.9 ($OCH_2CH{=}CH_2$ and $CH_2CH{=}CH_2$), 131.9 and 132.5 ($CH_2CH{=}CH_2$ and $OCH_2CH{=}CH_2$), 154.1 (Alloc C=O), 177.2 (COOH); FAB MS *m*/*z* 256 $[M + H]^+$. Anal. ($C_{13}H_{21}NO_4$) C, H, N.

(2*R*)-2-Allylleucine (17). In a round-bottom flask equipped with a stir bar, **15** (4.47 g, 17.5 mmol), $PdCl_2(PPh_3)_2$ (0.246 g, 0.35 mmol), and H_2O (1.6 mL, 97 mmol) were dissolved in CH_2Cl_2 (200 mL). To that mixture was added *n*-Bu_3Sn (5.6 mL, 21.0 mmol) rapidly via a syringe, and the reaction was stirred for 2 h at room temperature under Ar. The solvent was removed under vacuum, and the residue was triturated with Et_2O producing a white precipitate. Filtration of the mixture afforded 1.1 g (37% yield) of pure **17** as a white solid. The filtrate was extracted with H_2O (5 × 100 mL), and the combined aqueous extracts were evaporated in vacuo. The resulting solid was triturated with Et_2O to give another 1.1 g of product as a tan solid (74% combined yield): mp 266−267 °C dec; $[\alpha]_D$ +51.6 (*c* 1.26, MeOH); ^{1}H NMR (CD_3OD) δ 0.94 (s, 3 H, $(CH_3)_2$), 0.95 (s, 3 H, $(CH_3)_2$), 1.62−1.68 (m, 1 H, $CH_2CH(CH_3)_2$), 1.75−1.85 (m, 2 H, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 2.40 (dd, J = 14.0 and 7.9 Hz, 1 H, $CH_2CH{=}CH_2$), 2.63 (dd, J = 14.0 and 6.7 Hz, 1 H, $CH_2CH{=}CH_2$), 5.18−5.25 (m, 2 H, $CH_2CH{=}CH_2$), 5.73−5.87 (m, 1 H, $CH_2CH{=}CH_2$); ^{13}C NMR (CD_3OD) δ 23.3 ($CH(CH_3)_2$), 25.0 and 25.2 ($CH(CH_3)_2$), 43.4 and 45.9 ($CH_2CH{=}CH_2$ and $CH_2CH(CH_3)_2$), 64.7 (α-C), 121.2 ($CH_2CH{=}CH_2$), 132.6 ($CH_2CH{=}CH_2$), 175.6 (COOH); FAB MS *m*/*z* 172 $[M + H]^+$. Anal. ($C_9H_{17}NO_2$) C, H, N.

(2*R*)-2-Allylnorleucine (18). (2*R*)-*N*-(Allyloxycarbonyl)-2-allylnorleucine (**16**; 2.1 g, 8.2 mmol) was converted to product by the same procedure as that described above for **17** to give the product as a tan solid in a total yield of 61%. This material was successfully crystallized from MeOH/Et_2O: mp 254−256 °C dec; $[\alpha]_D$ +27.9 (*c* 1.4, MeOH); ^{1}H NMR (CD_3OD) δ 0.92 (t, J = 7.3 Hz, 3 H, $(CH_2)_3CH_3$), 1.22−1.42 (m, 4 H, $CH_2(CH_2)_2CH_3$), 1.61−1.71 (m, 1 H, $CH_2(CH_2)_2CH_3$), 1.79−1.88 (m, 1 H, $CH_2(CH_2)_2CH_3$), 2.42 (dd, J = 14.0 and 7.9 Hz, 1 H, $CH_2CH{=}CH_2$), 2.63 (dd, J = 14.0 and 6.7 Hz, 1 H, $CH_2CH{=}CH_2$), 5.18−5.24 (m, 2 H, $CH_2CH{=}CH_2$), 5.72−5.86 (m, 1 H, $CH_2CH{=}CH_2$); ^{13}C NMR (CD_3OD) δ 14.2 ($(CH_2)_3CH_3$), 23.9 and 26.8 ($CH_2(CH_2)_2CH_3$), 37.2 and 42.3 ($CH_2CH{=}CH_2$ and $CH_2(CH_2)_2CH_3$), 65.3 (α-C), 121.0 ($CH_2CH{=}CH_2$), 132.1 ($CH_2CH{=}CH_2$), 175.4 (COOH); FAB MS *m*/*z* 172 $[M + H]^+$. Anal. ($C_9H_{17}NO_2$) C, H, N.

(2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-allylleucine (19). (2*R*)-2-Allylleucine (**17**; 2.1 g, 12.26 mmol), tetramethylammonium hydroxide pentahydrate (TMAH; 2.2 g, 12.26 mmol), and Boc_2O (5.3 g, 24.5 mmol) were added to a 4:1 mixture of CH_3CN/DMF (150 mL). A clear solution was obtained after about 30 min, and the reaction was stirred for 2 days at room temperature. On the third day, another 0.5 equiv of Boc_2O (1.3 g, 6.1 mmol) was added, and the mixture was stirred for another day. The CH_3CN and DMF were removed in vacuo, and the resulting residue was redissolved in H_2O (100 mL). This solution was washed with Et_2O (2 × 100 mL). The aqueous layer was acidified with solid citric acid to pH 3 and then extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with H_2O and dried with $MgSO_4$, and the EtOAc was removed in vacuo to give **19** as a tan oil (2.7 g, 82% yield) which was used without further purification: $[\alpha]_D$ −13.1 (*c* 1.4, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.1 Hz, 3 H, $(CH_3)_2$), 0.92 (d, J = 6.1 Hz, 3 H, $(CH_3)_2$), 1.43 (s, 9 H, Boc CH_3), 1.58−1.74 (m, 2 H, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 2.32 (dd, J = 13.2 and 3.6 Hz, 1 H, $CH_2CH{=}CH_2$), 2.47 (dd, J = 13.2 and 7.5 Hz, 1 H, $CH_2CH(CH_3)_2$), 3.10 (dd, J = 13.2 and 7.2 Hz, 1 H, $CH_2CH{=}CH_2$), 5.06−5.12 (m, 2 H, $CH_2CH{=}CH_2$), 5.58 (s, 1 H, NH), 5.6−5.7 (m, 1 H, $CH_2CH{=}CH_2$), 10.34 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 22.95, 23.67, and 24.65 ($CH(CH_3)_2$ and $CH(CH_3)_2$), 40.54 and 43.50 ($CH_2CH{=}CH_2$ and $CH_2CH(CH_3)_2$), 63.08 (α-C), 79.37 (Boc C−O), 119.13 ($CH_2CH{=}CH_2$), 132.12 ($CH_2CH{=}CH_2$), 153.92 (Boc C=O), 178.81 (COOH); FAB MS *m*/*z* 272 $[M + H]^+$, 216 $[M-(CH_3)_3C]^+$, 172 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{14}H_{25}NO_4$) C, H, N.

(2*R*)-*N*-(*tert*-Butoxycarbonyl)-2-allylnorleucine (20). (2*R*)-2-Allylnorleucine (**18**; 0.6 g, 3.5 mmol) was converted to **20** under the same reaction conditions described above for the synthesis of **19**. The product was obtained as a clear oil (0.84 g, 89% yield): $[\alpha]_D$ +2.8 (*c* 1.6, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3 H, $(CH_2)_3CH_3$), 1.15−1.35 (m, 4 H, $CH_2(CH_2)_2CH_3$), 1.43 (s, 9 H, Boc CH_3), 1.75−1.83 (m, 1 H, $CH_2(CH_2)_2CH_3$), 2.2−2.3 (m, 1 H, $CH_2(CH_2)_2CH_3$), 2.54−2.61 (m, 1 H, $CH_2CH{=}CH_2$), 2.9−3.1 (m, 1 H, $CH_2CH{=}CH_2$), 5.08−5.14 (m, 2 H, $CH_2CH{=}CH_2$), 5.41 (br s, 1 H, NH), 5.63−5.72 (m, 1 H, $CH_2CH{=}CH_2$), 11.51 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$) δ 13.9 ($(CH_2)_3CH_3$), 22.5 and 26.1 ($CH_2(CH_2)_2CH_3$), 28.3 (Boc CH_3), 34.9 and 39.5 ($CH_2CH{=}CH_2$ and $CH_2(CH_2)_2CH_3$), 63.3 (α-C), 79.5 (Boc C−O), 119.1 ($CH_2CH{=}CH_2$), 132.4 ($CH_2CH{=}CH_2$), 154.1 (Boc C=O), 178.4 (COOH); FAB MS *m*/*z* 272 $[M + H]^+$, 216 $[M - (CH_3)_3C]^+$, 172 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{14}H_{25}NO_4$) C, H, N.

(2*RS*,4*S*)-2-[2(*R*)-[*N*-(*tert*-Butoxycarbonyl)amino]-2-carboxy-4-methyl-1-pentyl]thiazolidine-4-carboxylic Acid Methyl Ester (24). The procedures described for the preparation of **26** were followed. Reaction of **19** (2.3 g, 8.48 mmol) with OsO_4 (107 mg, 0.42 mmol) and $NaIO_4$ (4.5 g, 21.2 mmol) in THF/H_2O (4:1, 150 mL) afforded 2.4 g of (2*RS*,4*R*)-4-[*N*-(*tert*-butoxycarbonyl)amino]-4-(2-methylpropyl)-2-hydroxy-5-oxotetrahydrofuran (**21**) as a tan oil: ^{13}C NMR ($CDCl_3$) δ 96.8 (2-C); FAB MS *m*/*z* 274 $[M + H]^+$, 218 $[M - (CH_3)_3C]^+$.

Reaction of the γ-hydroxybutyrolactone **21** (2.2 g, 8.05 mmol) with $NaHCO_3$ (0.67 g, 8.05 mequiv) and D-cysteine methyl ester hydrochloride (1.4 g, 8.05 mmol) in H_2O/95% EtOH (1:1, 60 mL) afforded 2.6 g (84% yield) of the crude thiazolidine mixture **24** as a pink foam which was used without further purification: FAB MS *m*/*z* 391 $[M + H]^+$, 335 $[M - (CH_3)_3C]^+$.

(2*RS*,4*S*)-2-[2(*R*)-[*N*-(*tert*-Butoxycarbonyl)amino]-2-carboxy-1-hexyl]thiazolidine-4-carboxylic Acid Methyl Ester (25). The procedures described for the preparation of **26** were followed. Reaction of **20** (0.63 g, 2.3 mmol) with OsO_4 (0.031 g, 0.12 mmol) and $NaIO_4$ (1.3 g, 6.0 mmol) in THF/H_2O (4:1, 50 mL) afforded 1.0 g of crude (2*RS*,4*R*)-4-[*N*-(*tert*-

butoxycarbonyl)amino]-4-butyl-2-hydroxy-5-oxotetrahydrofuran (**22**) as a yellow semisolid: ^{13}C NMR ($CDCl_3$) δ 96.6 (2-C); FAB MS *m/z* 274 $[M + H]^+$, 218 $[M - (CH_3)_3C]^+$.

Reaction of the γ-hydroxybutyrolactone **22** (0.63 g, 2.3) with $NaHCO_3$ (0.19 g, 2.3 mequiv) and D-cysteine methyl ester hydrochloride (0.395 g, 2.3 mmol) in H_2O/95% EtOH (1:1, 20 mL) afforded 0.59 g (66% yield) of the crude thiazolidine mixture **25** as a clear oil which was used without further purification: FAB MS *m/z* 391 $[M + H]^+$, 335 $[M - (CH_3)_3C]^+$.

(2*RS*,4*S*)-2-[2(*R*)-[*N*-(Benzyloxycarbonyl)amino]-2-benzyl-2-carboxyethyl]thiazolidine-4-carboxylic Acid Methyl Ester (26). To a solution of compound **8** (3.26 g, 9.6 mmol) in THF/H_2O (4:1, 150 mL) was added OsO_4 (170 mg, 0.67 mmol) under Ar. After 5 min of stirring, $NaIO_4$ (5.1 g, 24 mmol) was added as a suspension in H_2O (8 mL) over 10 min. The reaction mixture was stirred under Ar for 24 h and then filtered to remove a white solid. The filtrate was concentrated under vacuum and the residue partitioned between Et_2O (100 mL) and 1 N $NaHCO_3$ (200 mL). The aqueous layer was acidified with 1 N HCl to pH 1 and then extracted with EtOAc (3 × 250 mL). The extracts were dried ($MgSO_4$) and then stripped of solvent in vacuo to give 3.4 g of (2*RS*,4*R*)-4-[*N*-(benzyloxycarbonyl)amino]-4-benzyl-2-hydroxy-5-oxotetrahydrofuran (**23**) as a white foam:^{13}C NMR ($CDCl_3$) δ 97.6 and 97.8 (2-C); FAB MS *m/z* 342 $[M + H]^+$, 206 $[M - PhCH_2OCO]^+$.

The crude γ-hydroxybutyrolactone **23** (3.2 g, 9.37 mmol) in 95% EtOH (40 mL) was cooled to −20 °C in a salt/ice/water bath. One equivalent of $NaHCO_3$ (0.78 g, 9.37 mequiv) in H_2O (39 mL) was added followed by D-cysteine methyl ester hydrochloride (1.6 g, 9.37 mmol). The pH of the resulting solution was adjusted to around 6.5 with 2% $NaHCO_3$. After warming to room temperature, the mixture was stirred for 12 h. The reaction mixture was concentrated to about one-half its volume, and the pH was adjusted to 6 with 1 N HCl. The product was extracted into EtOAc (3 × 250 mL) with readjustment of the pH to 6 between extractions. The combined extracts were dried ($MgSO_4$), and the solvent was evaporated under vacuum to give 4.5 g of **26** as a pink foam which was used without further purification: FAB MS *m/z* 459 $[M + H]^+$.

Methyl [3*S*-(3α,6α,7aα)]-6-[*N*-(*tert*-Butoxycarbonyl)-amino]-6-(2-methylpropyl)-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxylate (27a) and Methyl [3*S*-(3α,6α,7aβ)]-6-[*N*-(*tert*-Butoxycarbonyl)amino]-6-(2-methylpropyl)-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxylate (27b). To a solution of the thiazolidine mixture **24** (2.6 g, 6.7 mmol) in freshly distilled CH_2Cl_2 (400 mL) was added 2-chloro-1-methylpyridinium iodide (1.9 g, 7.6 mmol). This was followed by addition of NEt_3 (2.1 mL, 15.2 mmol) in 15 mL of CH_2Cl_2. The resulting solution was heated at reflux for 16 h. The reaction mixture was allowed to cool and then was washed with 200 mL of each of the following solutions: 10% citric acid, 1 N $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), and then the solvent was removed under vacuum to give a crude mixture of the bridgehead carbon (7a-C) epimers **27a** and **27b** in a ratio of 2-3:1, respectively. Chromatographic separation of the epimers was accomplished with 3% MeOH in benzene. The combined yield of both epimers after chromatography was 2.3 g (92%).

27a: clear oil; $[\alpha]_D$ +128.0 (*c* 1.1, $CHCl_3$); TLC R_f = 0.30 (3% MeOH in benzene); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.0 Hz, 3 H, $(CH_3)_2$), 0.94 (d, *J* = 6.0 Hz, 3 H, $(CH_3)_2$), 1.40 (s, 9 H, Boc CH_3), 1.62 (dd, *J* = 14.7 and 6.0 Hz, 1 H, CH_2CH$(CH_3)_2$), 1.73 (dd, *J* = 14.7 and 4.8 Hz, 1 H, CH_2CH$(CH_3)_2$), 1.81−1.89 (m, 1 H, $CH_2CH(CH_3)_2$), 2.35−2.40 (m, 1 H, 7-CH_2), 2.95 (m, 1 H, 7-CH_2), 3.37 (apparent d, *J* = 6.1 Hz, 2 H, 2-CH_2), 3.74 (s, 3 H, OCH_3), 4.89 (s, 1 H, NH), 4.99−5.02 (m, 1 H, 3-CH), 5.23−5.35 (m, 1 H, 7a-CH); ^{13}C NMR (C_6D_6) δ 23.9, 24.2 and 24.5 ($CH(CH_3)_2$ and $CH(CH_3)_2$), 28.3 (Boc CH_3), 34.9 and 36.2 (7-C and $CH_2CH(CH_3)_2$), 46.1 (2-C), 52.0 (OCH_3), 58.6 (3-C), 62.4 and 63.4 (6-C and 7a-C), 79.4 (Boc C−O), 154.6 (Boc C═O), 169.9 and 175.3 (5-C═O and CO_2CH_3); FAB MS *m/z* 373 $[M + H]^+$, 317 $[M - (CH_3)_3C]^+$, 273 $[M - (CH_3)_3COCO]^+$.

27b: clear oil; $[\alpha]_D$ −46.9 (*c* 1.3, $CHCl_3$); TLC R_f = 0.36 (3% MeOH in benzene); ^{1}H NMR (NOE difference assignment, $CDCl_3$) δ 0.87 (d, *J* = 6.1 Hz, 3 H, $(CH_3)_2$), 0.95 (d, *J* = 6.1 Hz, 3 H, $(CH_3)_2$), 1.42 (s, 9 H, Boc CH_3), 1.61 (dd, *J* = 14.6 and 4.9 Hz, 1 H, CH_2CH$(CH_3)_2$), 1.72−1.92 (m, 1 H, $CH_2CH(CH_3)_2$), 2.14 (dd, *J* = 14.6 and 7.3 Hz, 1 H, CH_2CH$(CH_3)_2$), 2.56 (dd, *J* = 12.2 and 8.6 Hz, 1 H, *pro-S* 7-CH_2), 3.02 (dd, *J* = 12.2 and 4.9 Hz, 1 H, *pro-R* 7-CH_2), 3.51 (d, *J* = 12.2, 1 Hz, *pro-R* 2-CH_2), 3.67 (dd, *J* = 12.2 and 7.3 Hz, 1 H, *pro-S* 2-CH_2), 3.80 (s, 3 H, OCH_3), 4.32 (d, *J* = 7.3 Hz, 1 H, 3-CH), 5.10 (dd, *J* = 8.6 and 4.9 Hz, 1 H, 7a-CH), 5.47 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 23.8, 23.9 and 24.5 ($CH(CH_3)_2$ and $CH(CH_3)_2$), 28.3 (Boc CH_3), 38.9 ($CH_2CH(CH_3)_2$), 42.9 (7-C), 44.2 (2-C), 52.8 (OCH_3), 56.9 (3-C), 64.7 and 65.3 (6-C and 7a-C), 79.4 (Boc C−O), 154.2 (Boc C═O), 168.4 and 172.8 (5-C═O and CO_2CH_3); FAB MS *m/z* 373 $[M + H]^+$, 317 $[M - (CH_3)_3C]^+$, 273 $[M - (CH_3)_3COCO]^+$.

Methyl [3*S*-(3α,6α,7aα)]-6-[*N*-(Benzyloxycarbonyl)amino]-6-benzyl-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxylate (29a) and Methyl [3*S*-(3α,6α,7aβ)]-6-[*N*-(Benzyloxycarbonyl)amino]-6-benzyl-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxylate (29b). To a solution of the thiazolidine mixture **26** (0.5 g, 1.1 mmol) in freshly distilled CH_2Cl_2 (100 mL) was added 2-chloro-1-methylpyridinium iodide (0.27 g, 1.2 mmol). This was followed by addition of NEt_3 (0.34 mL, 2.4 mmol) in 2 mL of CH_2Cl_2. The resulting solution was heated at reflux for 8 h. The reaction mixture was allowed to cool and then was washed with 10% citric acid (30 mL), 1 N $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and then stripped of solvent under vacuum to give a crude mixture of the bridgehead carbon (7a-C) epimers **29a** and **29b** in a ratio of about 3:1, respectively. These epimers were separated by silica gel chromatography (EtOAc/hexanes, 1:3→1:1).

29a: obtained 195 mg (41%) as a white solid which was crystallized from EtOAc/hexanes; mp 142−143 °C; $[\alpha]_D$ +69.9 (*c* 0.9, $CHCl_3$); TLC R_f = 0.52 (EtOAc/hexanes, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.56 (dd, *J* = 14.7 and 2.4 Hz, 1 H, 7-CH_2), 2.7−2.9 (m, 1 H, 7-CH_2), 3.00−3.30 (m, 4 H, 2-CH_2 and CH_2Ph), 3.75 (s, 3 H, OCH_3), 5.04−5.12 (m, 3 H, 3-CH and OCH_2Ph), 5.29 (br s, 1 H, 7a-CH), 5.43 (s, 1 H, NH), 7.19−7.33 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 33.5 and 36.0 (7-C and CH_2Ph), 42.4 (2-C), 52.8 (OCH_3), 57.8 (3-C), 62.4 (7a-C), 63.1 (6-C), 66.8 (OCH_2-Ph), 127.4, 128.1, 128.4, 128.6, 130.5, 134.4, and 135.8 (Ph), 154.6 (Cbz C═O), 169.6 and 174.1 (5-C═O and CO_2CH_3); FAB MS *m/z* 441 $[M + H]^+$. Anal. ($C_{23}H_{24}N_2O_5S$) C, H, N, S.

29b: obtained 66 mg (14%) as a clear oil which solidified in EtOAc/hexanes; mp 147−148 °C; $[\alpha]_D$ +15.2 (*c* 1.3, $CHCl_3$); TLC R_f = 0.46 (EtOAc/hexanes, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.66 (dd, *J* = 13.4 and 8.6 Hz, 1 H, 7-CH_2), 3.14−3.20 (m, 2 H, 7-CH_2 and CH_2Ph), 3.27−3.32 (apparent d, *J* = 13.4 Hz, 2 H, *pro-R* 2-CH_2 and CH_2Ph), 3.42 (dd, *J* = 13.4 and 7.3 Hz, 1 H, *pro-S* 2-CH_2), 3.77 (s, 3 H, OCH_3), 4.02 (dd, *J* = 8.5 and 6.1 Hz, 1 H, 7a-CH), 4.17 (d, *J* = 7.3 Hz, 1 H, 3-CH), 5.06−5.18 (m, 2 H, OCH_2Ph), 5.72 (s, 1 H, NH), 7.17−7.73 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 38.8, 40.9, and 42.0 (7-C, CH_2Ph, and 2-C), 52.8 (OCH_3), 56.4 (3-C), 64.3 (7a-C), 66.6 (OCH_2Ph), 66.9 (6-C), 127.4, 128.0, 128.1, 128.3, 128.5, 130.0, 134.7, and 136.2 (Ph), 154.8 (Cbz C═O), 168.2 and 171.0 (5-C═O and CO_2CH_3); FAB MS *m/z* 441 $[M + H]^+$. Anal. ($C_{23}H_{24}N_2O_5S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[*N*-(*tert*-Butoxycarbonyl)amino]-6-(2-methylpropyl)-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide (30). A mixture of bicyclic lactams **27a** and **27b** (1.9 g, 5.1 mmol) was treated with a concentrated solution of methanolic ammonia (6 mL). The reaction vessel was sealed, and the reaction was stirred for 1 h at room temperature. TLC of the reaction showed complete conversion of the 7a-(*R*)-epimer **27a** to its amide, while the majority of the 7a-(*S*)-epimer **27b** remained unreacted. The solvents and excess ammonia were evaporated in vacuo to give 1.8 g (95%) of a white foam that was purified on a 3- × 42-cm flash silica gel column (5% MeOH in benzene). Pure **30** was obtained as a white foam in a 56% yield (1.1 g). From the column were also obtained 0.48 g (25%) of **27b** and a fraction corresponding to a mixture of **30** and the amide conversion product of **27b** (0.25 g, 25%): total mass balance 1.8 g (95%); mp 68−73 °C; $[\alpha]_D$ +140.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (NOE difference assignment, $CDCl_3$) δ 0.90 (d, *J* = 6.1 Hz, 3 H, $(CH_3)_2$), 0.97 (d, *J* = 7.3 Hz,

3 H, $(CH_3)_2$), 1.36 (s, 9 H, Boc CH_3), 1.52−1.69 (m, 1 H, CH_2-CH$(CH_3)_2$), 1.70−1.84 (m, 2 H, CH_2CH$(CH_3)_2$ and CH_2-C$H(CH_3)_2$), 2.39 (dd, J = 14.6 and 4.9 Hz, 1 H, *pro-R* 7-CH_2), 2.62 (dd, J = 14.6 and 8.6 Hz, 1 H, *pro-S* 7-CH_2), 3.50 (dd, J = 12.2 and 8.5 Hz, *pro-S* 2-CH_2), 3.58 (dd, J = 12.2 and 4.9 Hz, 1 H, *pro-R* 2-CH_2), 4.79 (dd, J = 8.6 and 4.9 Hz, 1 H, 3-CH), 5.14 (s, 1 H, NH), 5.22 (dd, J = 8.6 and 4.9 Hz, 1 H, 7a-CH), 5.93 (br s, 1 H, *cis* NH_2), 7.23 (br s, 1 H, *trans* NH_2); ^{13}C NMR (DEPT assignment, $CDCl_3$) δ 24.1 (*C*H$(CH_3)_2$), 23.1 and 24.4 (CH$(CH_3)_2$), 28.2 (Boc CH_3), 36.1 and 36.7 (7-C and *C*H_2CH-$(CH_3)_2$), 45.6 (2-C), 57.2 (3-C), 62.7 (7a-C), 63.4 (6-C), 80.6 (Boc C−O), 155.1 (Boc C═O), 171.8 and 172.7 (5-C═O and *C*ON); FAB MS *m/z* 358 $[M + H]^+$, 302 $[M - (CH_3)_3C]^+$, 258 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{16}H_{27}N_3O_4S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[*N*-(*tert*-Butoxycarbonyl)amino]-6-butyl-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide (31). To a solution of the thiazolidine mixture **25** (590 mg, 1.5 mmol) in freshly distilled CH_2Cl_2 (200 mL) was added 2-chloro-1-methylpyridinium iodide (375 mg, 1.7 mmol). This was followed by addition of NEt_3 (0.46 mL, 3.3 mmol) in 3 mL of CH_2Cl_2. After 24 h of heating at reflux, the reaction mixture was allowed to cool to room temperature. It was then washed with 10% citric acid, 1 N $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$. Removal of solvent under vacuum gave a crude mixture of the 7a-C epimeric lactams **28a** and **28b** (R_f = 0.55 and 0.50, respectively, 5% MeOH in benzene). Chromatographic separation of these epimers with 3% MeOH in benzene was only partially successful. Fractions from the column possessing both epimers were combined and concentrated in vacuo, and the residue was treated with concentrated ammonia in MeOH (5 mL) at room temperature. After the reaction mixture stirred for 3 h, TLC showed virtual disappearance of **28a**, whereas **28b** remained largely unreacted. Excess ammonia and MeOH were evaporated under vacuum, and the resulting residue was chromatographed on a 3- × 43-cm silica gel column (CH_2Cl_2/MeOH, 50:1→20:1) affording 230 mg (43% over two steps) of pure **31** as a clear oil: $[\alpha]_D$ +128.1 (*c* 1.3, $CHCl_3$); TLC R_f = 0.46 (CH_2Cl_2/MeOH, 20:1), 0.22 (CH_2Cl_2/MeOH, 50:1); ^{1}H NMR (NOE difference assignment, $CDCl_3$, 319 K) δ 0.89 (t, J = 6.8 Hz, 3 H, $(CH_2)_3CH_3$), 1.27−1.37 (m, 4 H, $CH_2(CH_2)_2CH_3$), 1.35 (s, 9 H, Boc CH_3), 1.39−1.71 (m, 2 H, C$H_2(CH_2)_2CH_3$), 2.29 (dd, J = 14.6 and 4.3 Hz, 1 H, *pro-R* 7-CH_2), 2.60 (dd, J = 14.0 and 7.9 Hz, 1 H, *pro-S* 7-CH_2), 3.48 (dd, J = 11.6 and 8.5 Hz, *pro-S* 2-CH_2), 3.58 (dd, J = 11.6 and 4.9, 1 H, *pro-R* 2-CH_2), 4.79 (dd, J = 8.6 and 4.9 Hz, 1 H, 3-CH), 5.12 (br s, 1 H, NH), 5.20 (dd, J = 7.9 and 4.3 Hz, 1 H, 7a-CH), 5.73 (br s, 1 H, *cis* NH_2), 7.14 (br s, 1 H, *trans* NH_2); ^{13}C NMR ($CDCl_3$) δ 13.7 ($(CH_2)_3CH_3$), 22.6 and 25.2 ($CH_2(CH_2)_2CH_3$), 28.2 (Boc CH_3), 36.1 and 36.3 (7-C and $CH_2(CH_2)_2CH_3$), 37.4 (2-C), 57.0 (3-C), 62.5 (7a-CH), 63.5 (6-C), 80.6 (Boc C−O), 155.1 (Boc C═O), 171.9 and 172.6 (5-C═O and *C*ON); FAB MS *m/z* 358 $[M + H]^+$, 302 $[M - (CH_3)_3C]^+$, 258 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{16}H_{27}N_3O_4S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[*N*-(Benzyloxycarbonyl)amino]-6-benzyl-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide (32). Bicyclic lactam **29a** (165 mg, 0.375 mmol) in CH_2Cl_2 (2 mL) was treated with a concentrated solution of methanolic ammonia (4 mL). The reaction vessel was sealed, and the reaction was stirred for 45 min at room temperature at which time TLC showed complete disappearance of the starting material. The solvents and excess ammonia were evaporated in vacuo to give 160 mg (100%) of **32** as a white foam. An analytical sample of **32** was obtained by silica gel column chromatography (EtOAc/hexanes, 1:1→3:1): mp 138−139 °C; $[\alpha]_D$ +142.1 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.53−2.59 (m, 2 H, 7-CH_2), 2.97 (d, J = 13.4 Hz, 1 H, CH_2Ph), 3.18 (d, J = 13.4 Hz, 1 H, CH_2Ph), 3.24−3.28 (m, 1 H, *pro-S* 2-CH_2), 3.51 (dd, J = 11.0 and 4.9 Hz, 1 H, *pro-R* 2-CH_2), 4.83 (dd, J = 8.5 and 4.9 Hz, 1 H, 3-CH), 4.98−5.09 (m, 2 H, OCH_2Ph), 5.14 (m, 1 H, 7a-CH), 5.72 (s, 1 H, CbzNH), 6.10 (s, 1 H, *cis* $CONH_2$), 7.07 (s, 1 H, *trans* $CONH_2$), 7.20−7.38 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 35.7 and 35.8 (7-C and *C*H_2Ph), 42.8 (2-C), 57.6 (3-C), 62.3 (7a-C), 64.1 (6-C), 67.2 (O*C*H_2Ph), 127.7, 128.1, 128.3, 128.5, 128.8, 130.3, 133.9, and 135.5 (Ph), 155.3 (Cbz C═O), 171.5 and 172.4 (*C*ON); FAB MS *m/z* 426 $[M + H]^+$. Anal. ($C_{22}H_{23}N_3O_4S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[[[1-(*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-6-(2-methylpropyl)-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide (33). Compound **30** (0.70 g, 1.96 mmol) was treated with excess HCl (4 N in dioxane, 7 mL) for 18 h at room temperature. Excess HCl and dioxane were removed under vacuum, and the resulting residue was stored under high vacuum overnight and then dissolved in DMF (20 mL). Boc-L-Pro-OH (2.1 g, 9.8 mmol) and HOBt•H_2O (1.3 g, 9.8 mmol) were added, and the solution was cooled to −40 °C (CH_3CN/CO_2 bath). Et_3N (0.4 mL, 2.9 mmol) was added, followed by EDC•HCl (1.9 g, 9.8 mmol) after 5 min of stirring. The mixture was stirred for 4 days under an atmosphere of Ar. Removal of DMF in vacuo gave a residue that was partitioned between EtOAc (220 mL) and 10% citric acid (150 mL). The organic layer was washed with 150 mL of 1 N $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and then stripped of solvents under vacuum to give 1.8 g of a white foam. The crude product was twice subjected to silica gel chromatography (3- × 40-cm column, CH_2Cl_2/MeOH, 20:1) to give 756 mg (85%) of pure product as a white foam which was crushed to a white solid: mp 88−91 °C; $[\alpha]_D$ +22.9 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 318 K) δ 0.93 (d, J = 6.1 Hz, 3 H, $(CH_3)_2$), 1.00 (d, J = 6.1 Hz, 3 H, $(CH_3)_2$), 1.46 (s, 9 H, Boc CH_3), 1.54−1.69 (m, 1 H, CH_2CH$(CH_3)_2$), 1.73−1.93 (m, 5 H, CH_2CH$(CH_3)_2$, $CH_2CH(CH_3)_2$, Pro β-CH_2, and Pro γ-CH_2), 2.02−2.20 (m, 1 H, Pro β-CH_2), 2.38 (dd, J = 14.6 and 4.3 Hz, 1 H, 7-CH_2), 2.56 (dd, J = 14.6 and 7.8 Hz, 1 H, 7-CH_2), 3.32−3.36 (m, 2 H, Pro δ-CH_2), 3.49 (dd, J = 11.0 and 8.6 Hz, 1 H, 2-CH_2), 3.61 (dd, J = 11.6 and 4.9 Hz, 1 H, 2-CH_2), 4.16 (m, 1 H, Pro α-CH), 4.80 (dd, J = 8.6 and 4.9 Hz, 1 H, 3-CH), 5.23 (dd, J = 7.8 and 4.3 Hz, 1 H, 7a-CH), 5.65 (br s, 1 H, NH), 7.25 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 23.1, 24.2, and 24.5 (*C*H$(CH_3)_2$ and CH$(CH_3)_2$), 27.3 (Pro γ-C), 28.3 (Boc CH_3), 31.0 (Pro β-C), 36.2 and 37.8 (7-C and $CH_2CH(CH_3)_2$), 45.6 (2-C), 47.1 (Pro δ-C), 57.3 (3-C), 59.5 (Pro α-C), 62.7 (7a-C), 63.4 (6-C), 80.6 (Boc C−O), 156.0 (Boc C═O), 171.9, 172.3, and 172.4 (CON); FAB MS *m/z* 455 $[M + H]^+$, 399 $[M - (CH_3)_3C]^+$, 355 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{21}H_{34}N_4O_5S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[[[1-(*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-6-butyl-5-oxo-(5*H*)-pyrrolo-[2,1-*b*]thiazolidine-3-carboxamide (34). This compound was prepared from bicyclic lactam **31** (0.15 mg, 0.42 mmol) in the same manner as described for **33**. The crude product was twice subjected to silica gel chromatography (2.2- × 40-cm column, CH_2Cl_2/MeOH, 20:1) to give 170 mg (89%) of pure product as a white foam which was crushed to a white solid: mp 93−96 °C; $[\alpha]_D$ +20.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 323 K) δ 0.92 (t, J = 7.3 Hz, 3 H, $(CH_2)_3CH_3$), 1.30−1.50 (m, 4 H, Pro γ-CH_2 and $CH_2(CH_2)_2CH_3$), 1.47 (s, 9 H, Boc CH_3), 1.64−1.87 (m, 5 H, C$H_2(CH_2)CH_3$, Pro γ-CH_2, and Pro β-CH_2), 2.23 (m, 1 H, Pro β-CH_2), 2.29 (dd, J = 14.0 and 4.3 Hz, 1 H, 7-CH_2), 2.52 (dd, J = 14.0 and 7.9 Hz, 1 H, 7-CH_2), 3.38 (m, 2 H, Pro δ-CH_2), 3.50 (dd, J = 12.2 and 8.5 Hz, 1 H, 2-CH_2), 3.61 (dd, J = 11.0 and 4.9 Hz, 1 H, 2-CH_2), 4.23 (m, 1 H, Pro α-CH), 4.82 (dd, J = 8.6 and 4.9 Hz, 1 H, 3-CH), 5.23 (dd, J = 7.9 and 4.3 Hz, 1 H, 7a-CH), 5.57 (br s, 1 H, NH), 7.19 (br s, 1 H, NH); ^{13}C NMR (DEPT assignment, $CDCl_3$) δ 13.8 ($(CH_2)_3CH_3$), 22.8, 24.7, and 25.2 (Pro γ-C and $CH_2(CH_2)_2CH_3$), 27.2 (Pro β-C), 28.3 (Boc CH_3), 36.2, 36.9, and 37.4 (7-C, $CH_2(CH_2)_2CH_3$, and 2-C), 47.2 (Pro δ-C), 57.1 (3-C), 59.4 (Pro α-C), 62.6 (7a-C), 63.6 (6-C), 80.6 (Boc C−O), 156.1 (Boc C═O), 171.9, 172.2, and 172.4 (CON); FAB MS *m/z* 455 $[M + H]^+$ 399 $[M - (CH_3)_3C]^+$ 355 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{21}H_{34}N_4O_5S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[[[1-(*tert*-Butoxycarbonyl)-2(*S*)-pyrrolidinyl]carbonyl]amino]-6-benzyl-5-oxo-(5*H*)-pyrrolo-[2,1-*b*]thiazolidine-3-carboxamide (35). The same general procedure as that used to make **33** was used. The crude product was twice subjected to silica gel chromatography (2.2- × 40-cm column, CH_2Cl_2/MeOH, 20:1) to give 1.16 g (73%) of pure **35**: mp 232−233 °C; $[\alpha]_D$ +93.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 328 K) δ 1.47 (s, 9 H, Boc CH_3), 1.75−1.90 (m, 2 H,

Pro γ-CH_2), 1.92−2.17 (m, 2 H, Pro β-CH_2), 2.41 (dd, J = 13.4 and 7.3 Hz, 1 H, 7-CH_2), 2.54 (dd, J = 13.4 and 4.9 Hz, 1 H, 7-CH_2), 3.04 (d, J = 13.4 Hz, 1 H, CH_2Ph), 3.15 (d, J = 13.4 Hz, 1 H, CH_2Ph), 3.22−3.40 (m, 3 H, 2-CH_2 and Pro δ-CH_2), 3.57 (dd, J = 12.2 and 4.9 Hz, 1 H, 2-CH_2), 4.17 (m, 1 H, Pro α-CH), 4.84 (dd, J = 8.6 and 4.9 Hz, 1 H, 3-CH), 5.19 (dd, J = 7.3 and 4.9 Hz, 1 H, 7a-CH), 5.69 (br s, 1 H, NH), 7.22−7.38 (m, 7 H, $CONH_2$ and Ph); ^{13}C NMR ($CDCl_3$, 328 K) δ 24.1 (Pro γ-C), 28.3 (Boc CH_3), 30.0 (Pro β-C), 35.9 and 37.2 (7-C and CH_2Ph), 43.3 (2-C), 47.0 (Pro δ-C), 57.7 (3-C), 60.6 (Pro α-C), 62.5 (7a-C), 63.6 (6-C), 80.9 (Boc C−O), 127.8, 129.0, 130.3, and 134.2 (Ph), 155.0 (Boc C═O), 171.4, 171.5, and 172.8 (CON); FAB MS m/z 489 $[M + H]^+$, 433 $[M - (CH_3)_3C]^+$, 389 $[M - (CH_3)_3COCO]^+$. Anal. ($C_{23}H_{31}N_4O_5S$) C, H, N, S.

[3*S*-(3α,6α,7aα)]-6-[[2(*S*)-Pyrrolidinylcarbonyl]amino]-6-(2-methylpropyl)-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide Hydrochloride (3·HCl). Peptidomimetic **33** (46 mg, 0.116 mmol) was treated with 4 N HCl in dioxane (3 mL) at 0 °C under an atmosphere of Ar. After the reaction stirred for 45 min, TLC showed complete disappearance of starting material. The solvent and excess HCl were removed in vacuo, and the residue was twice suspended in CH_2Cl_2 and evaporated to dryness under high vacuum. The resulting white solid was dissolved in H_2O (∼0.5 mL) and lyophilized to give the pure product as a hygroscopic white solid (30 mg, 65%): mp 131−135 °C; $[\alpha]_D$ +94.3 (c 3.0, MeOH); ^{1}H NMR (COSY assignment, $CDCl_3$) δ 0.93 (d, J = 6.1 Hz, 3 H, $(CH_3)_2$), 0.97 (d, J = 6.1 Hz, 3 H, $(CH_3)_2$), 1.35 (dd, J = 14.6 and 6.1 Hz, 1 H, CH_2CH$(CH_3)_2$), 1.63−1.72 (m, 1 H, CH_2C$H$$(CH_3)_2$), 1.85−193 (m, 2 H, Pro γ-CH_2), 1.98 (dd, J = 13.4 and 6.1 Hz, 1 H, 7-CH_2), 2.04−2.21 (m, 2 H, Pro β-CH_2 and Pro γ-CH_2), 2.60−2.69 (m,1 H, Pro β-CH_2), 2.89−2.96 (m, 2 H, CH_2CH$(CH_3)_2$ and 2-CH_2), 3.31 (dd, J = 13.4 and 6.1 Hz, 1 H, 7-CH_2), 3.60−3.81 (m, 3 H, 2-CH_2 and Pro δ-CH_2), 4.37 (m, 1 H, Pro α-CH), 5.14 (d, J = 6.1, 1 H, 3-CH), 5.78 (t, J = 6.1, 1 H, 7a-CH), 7.17 (s, 1 H, NH), 7.84 (br s, 1 H, $^+$NH), 8.00 (br s, 1 H, $^+$NH), 8.28 (s, 1 H, NH), 9.81 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 23.3, 23.5, 24.4, and 24.7 ($CH(CH_3)_2$, Pro γ-C, and $CH(CH_3)_2$), 31.2 and 32.5 (Pro β-C and $CH_2CH(CH_3)_2$), 39.5 (2-C), 43.6 (7-C) 47.8 (Pro δ-C), 56.4 (3-C), 59.7 (Pro α-C), 60.4 (7a-C), 66.0 (6-C), 169.9, 170.8, and 170.9 (CON); FAB HRMS m/z 355.1829 ($C_{16}H_{26}N_4O_3S + H^+$ requires 355.1806). Anal. ($C_{16}H_{26}N_4O_3S$•HCl) C, H, N, S, Cl.

[3*S*-(3α,6α,7aα)]-6-[[(2(*S*)-Pyrrolidinyl)carbonyl]amino]-6-butyl-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide Hydrochloride (4•HCl). Peptidomimetic **34** (31 mg, 0.068 mmol) was deprotected by the same procedure used above to make **3**. The pure product was obtained as a lyophilized hygroscopic white solid (25 mg, 91%): $[\alpha]_D$ +109.8 (c 2.5, MeOH); ^{1}H NMR (COSY assignment, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3 H, $(CH_2)_3CH_3$), 1.25−1.36 (m, 4 H, $CH_2(CH_2)_2$-CH_3), 1.51−1.60 (m, 1 H, CH_2CH$(CH_3)_2$), 1.89−1.96 (m, 2 H, Pro γ-CH_2 and 7-CH_2), 2.01−2.12 (m, 1 H, Pro β-CH_2) 2.14−2.25 (m, 1 H, Pro γ-CH_2), 2.63−2.72 (m, 1 H, Pro β-CH_2), 2.82−3.00 (m, 2 H, C$H_2$$(CH_2)CH_3$ and 2-CH_2), 3.17 (dd, J = 12.8 and 4.9 Hz, 1 H, 7-CH_2), 3.5−3.8 (m, 3 H, 2-CH_2 and Pro δ-CH_2), 4.38 (m, 1 H, Pro α-CH), 5.11 (d, J = 6.0, 1 H, 3-CH), 5.84 (t, J = 6.0, 1 H, 7a-CH), 7.14 (s, 1 H, NH), 7.80 (br s, 1 H, $^+$NH), 8.09 (br s, 1 H, $^+$NH), 8.30 (s, 1 H, NH), 9.78 (s, 1 H, NH); ^{13}C NMR (CD_3OD) δ 14.1 ($(CH_2)_3CH_3$), 23.8, 24.9, and 26.6 (Pro γ-C and $CH_2(CH_2)_2CH_3$), 31.2 (Pro β-C), 36.5, 37.2, and 37.8 (7-C, $CH_2(CH_2)_2CH_3$, and 2-C), 47.6 (Pro δ-C), 59.1 (3-C), 60.9 (Pro α-C), 64.4 (7a-C), 65.5 (6-C), 170.1, 174.0, and 174.4 (CON); FAB HRMS m/z 355.1823 ($C_{16}H_{26}N_4O_3S + H^+$ requires 355.1806). Anal. ($C_{16}H_{26}N_4O_3S$·HCl·H_2O) C, H, N, S, Cl.

[3*S*-(3α,6α,7aα)]-6-[[2(*S*)-Pyrrolidinylcarbonyl]amino]-6-benzyl-5-oxo-(5*H*)-pyrrolo[2,1-*b*]thiazolidine-3-carboxamide Hydrochloride (5·HCl). Peptidomimetic **35** (154 mg, 0.32 mmol) was deprotected by the same procedure used above to make **3**. The pure product was obtained as a lyophilized hygroscopic white solid (130 mg, 97%): mp 150−160 °C; $[\alpha]_D$ +167.8 (c 0.82, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.71−1.88 (m, 3 H, Pro γ-CH_2 and β-CH_2), 2.24−2.30 (m, 2 H, Pro β-CH_2 and 7-CH_2), 2.58 (dd, J = 14.0 and 7.3 Hz, 1 H, 7-CH_2), 2.86 (dd, J = 10.4 and 7.9 Hz, 1 H, Pro δ-CH_2), 2.97−3.16 (m, 5 H, Pro δ-CH_2, 2-CH_2, and CH_2Ph), 4.22 (br s, 1 H, Pro α-CH), 4.60 (dd, J = 7.3 and 3.7 Hz, 1 H, 3-CH), 5.07 (dd, J = 7.3 and 3.7 Hz, 1 H, 7a-CH), 7.06 (s, 1 H, NH), 7.14−7.28 (m, 5 H, Ph), 7.41 (s, 1 H, NH), 8.61 (br s, 1 H, $^+$$NH_2$), 9.21 (s, 1 H, NH), 9.99 (br s, 1 H, $^+$$NH_2$); ^{13}C NMR (DMSO-$d_6$) δ 23.5 (Pro γ-C), 29.7 (Pro β-C), 35.1 and 35.5 (7-C and CH_2Ph), 41.0 (2-C), 45.6 (Pro δ-C), 57.7 and 58.6 (3-C and Pro α-C), 62.4 (7a-C), 64.4 (6-C), 127.0, 128.2, 130.6, and 134.9 (Ph), 168.4, 170.5, and 171.6 (CON); FAB HRMS m/z 389.1666 ($C_{19}H_{24}N_4O_3S + H^+$ requires 389.1650). Anal. ($C_{19}H_{24}N_4O_3S$·HCl·$3H_2O$) C, H, N, S, Cl.

X-ray Diffraction. Colorless needles of **29a** were grown from EtOAc and hexanes. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54178 Å) with the $\omega - 2\theta$ scan mode at 173(1) K by using a Molecular Structure Corp. low-temperature device. Intensities were corrected for Lorentz and polarization effects. Equivalent reflections were merged, and absorption effects were corrected using the psi-scan method.[35] The structure was solved by direct methods using SHELXS86[36] and refined using the TEXSAN structure analysis package.[37] All non-hydrogen atoms were refined anisotropically. Hydrogens bonded to carbon atoms were placed in calculated positions (0.95 Å) and were not refined. Hydrogens bonded to heteroatoms (excluding the water atom) were located in difference Fourier maps, and their positional parameters were refined.

6-Hydroxydopamine-Lesioned Rat Model of Hemiparkinsonism. Male Sprague−Dawley rats with weights ranging from 275 to 300 g were procured from the Charles River breeding facility at St. Constant, Quebec, Canada. Prior to surgery, all animals were given 1 week to acclimate to a 12-h light and 12-h dark photoperiodicity cycle, during which time they were handled in order to minimize stress evoked from naive human contact. Before any drug administration each animal was accurately weighed to ensure all dosages were precise. To spare noradrenergic pathways from the neurotoxic effects of 6-hydroxdopamine, the rats were pretreated with desipramine hydrochloride (15 mg/kg, ip) 30 min prior to anesthesia with Somnotol (sodium pentobarbitol) given at 50 mg/kg, ip. Atropine (0.03 mg/kg, ip) was given to decrease respiratory tract mucous secretions. The foot pinch reflex test was used to determine the effectiveness of the anesthetic (unresponsive animals were considered to be anesthetized). Animals not passing this behavioral measure were administered a mixture of 100 mg/kg ketamine and 20 mg/kg xylazine in a volume of ∼0.01−0.05 mL/kg. Once full anesthesia of the animals was reached, they were then prepared by shaving the fur off the top of their scalps and disinfecting the area with iodine. To prevent unnecessary moisture loss from the eyes, the ocular lubricant Lacri-Lube (Allergan Inc., Markham, Ontario) was applied topically to the eyes of each animal. Animals were then secured in the stereoscopic apparatus, and a single skull incision running form anterior to posterior was made. The membrane covering the surface of the skull (periosteum) was then clipped back exposing the surface of the skull. A Hamilton syringe was centered on bregma, and three-dimensional coordinates for bregma were determined in accordance with the atlas of Paxinos and Watson (A/P −4.8, L/M +1.8, D/V −7.5).[38] Once the coordinates were marked a hand drill was used to make a small access hole into the surface of the skull so that the 30-gauge Hamilton syringe could easily enter into the brain. 6-Hydroxydopamine was infused at a dose of 8 μg in 4 μL of 0.9% isotonic saline with 0.1% ascorbic acid directly into the substantia nigra at a rate of 1 μL/min. The syringe was removed after a 4-min latency period to ensure that the placement of the drug was effective. The surgical wound was then closed using surgical staples, and an antibiotic agent Vetropolycin (Janssen, North York, Ontario) was applied topically. Postoperative care included careful observation of vital signs and the subcutaneous administration of 10 mL of 0.9% isotonic saline.

To evaluate the effectiveness of the lesioning procedure, testing of the animals began 10 days postoperatively. Apomorphine at a dose of 0.25 mg/kg, ip was administered to each animal. Only those animals exhibiting 40 contralateral rotations over a 10-min period were admitted as viable experimental subjects. All rats were observed in the same round, transparent, flat-bottom bowl. A 5-min habituation period in the bowl was allocated to each animal before each trial. Injections were administered after the 5-min habituation, followed by a further 5-min latency period (from time of drug administration) in order to ensure adequate time for physiological distribution of the drugs to the target sites of action. Rotational counts were then taken at 5-min intervals. This process was repeated 4 times after at a 48-h washout period between each injection. This established a stable individual control measure for each animal.

Testing of peptidomimetics **2**−**5** was analogous to the apomorphine protocol described above. Within this experimental design, each individual peptidomimetic's ability to modify the rotational response to apomorphine was evaluated. Injection of a peptidomimetic was administered directly before apomorphine.

To ensure results were not generated by an enhanced sensitivity to increasing doses of drugs, a Latin Square design was implemented. Rotational counts for each animal were then generated into a percent change compared to the individual control apomorphine-induced rotations. Results were analyzed by a one-way analysis of variance (ANOVA), followed by a post hoc comparison (Dunnett's multiple comparison test). Apart from producing an increase in the number of rotations over a 10-min period, administration of peptidomimetics **2**−**5** also yielded a tendency toward stereotypical behaviors (e.g., grooming of the contralateral side of body).[8]

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Supporting Information Available: X-ray crystallographic data including tables of positional parameters, bond distances, and bond angles for **29a**. This information is available free of charge via the Internet at http://pubs.acs.org.

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