Design, Synthesis, and Dopamine Receptor Modulating Activity of Diketopiperazine Peptidomimetics of L-Prolyl-L-leucylglycinamide

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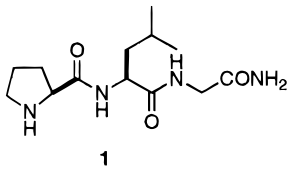
The diketopiperazine "C5" conformational mimic has been incorporated into the L-prolyl-L-leucylglycinamide (PLG, **1**) structure and into the bicyclic lactam PLG peptidomimetic structure **3** to give compounds **5** and **6**, respectively. These analogues were designed to explore the idea that the N-terminal "C5" conformation, which was found in the crystal structure of **2** and which was mimicked in **4** by the diketopiperazine function, was a factor in the high potency of these two agents. Through the use of the [^{3}H]spiroperidol/*N*-propylnorapomorphine (NPA) D_2 receptor competitive binding assay, both **5** and **6** were found to increase the affinity of the dopamine receptor for agonists and both were found to increase the percentage of D_2 receptors which existed in the high-affinity state. These effects were observed when Gpp(NH)p was either absent or present, and they were analogous to the effects observed previously for PLG and the PLG peptidomimetics **2** and **4**. However, the potency seen with **5** and **6** was less than that seen for **2** and **4**, suggesting that while the N-terminal "C5" conformation may play a role in the potency of the γ-lactam peptidomimetics of PLG, it does not appear to be the primary factor. In the 6-hydroxydopamine-lesioned animal model of Parkinson's disease, **5** altered apomorphine-induced rotational behavior in a dose-dependent manner. The maximum effect occurred at a dose of 0.01 mg/kg ip and resulted in a 52.27 ± 13.96% ($p < 0.001$, $n = 7$) increase in rotations compared to apomorphine administered alone.

Introduction

L-Prolyl-L-leucylglycinamide (PLG, **1**) is able to modulate the dopamine D_2 receptor by increasing the affinity of the receptor for agonists[1,2] and by increasing the percentage of D_2 receptors that exist in the high-affinity state.[2] This modulatory action on dopamine D_2 receptors also has been observed for several PLG peptidomimetics that have been synthesized.[3−8] In earlier work, PLG peptidomimetics **2** and **3**, which contain the γ-lactam and bicyclic lactam conformational constraints, respectively, were designed to mimic the postulated bioactive type II β-turn conformation of PLG.[3,6] Peptidomimetic **2** was found to be substantially more potent than PLG in a number of pharmacological assay systems.[3,4] In contrast, peptidomimetic **3** was found to be about 5 times more effective than PLG in enhancing the binding of the dopamine receptor agonist 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) to the dopamine receptor.[6]

In an attempt to discern the structural basis behind the high potency of **2**, the diketopiperazine peptidomimetic **4** was synthesized.[8] This analogue was designed to mimic an N-terminal "C5" conformation involving an intramolecular hydrogen bond between the prolyl nitrogen and the lactam NH, which had been found in the crystal structure of **2**.[9] Peptidomimetic **4**, like **2**, was found to be quite potent in the [^{3}H]spiroperidol/*N*-propylnorapomorphine competition assay, thereby suggesting that an N-terminal "C5" conformation might be a factor in the potency of peptidomimetics **2** and **4**. In order to explore this issue further, diketopiperazines **5** and **6** have been designed. In **5**, the diketopiperazine "C5" conformational mimic has been incorporated into the PLG structure, while in **6** this structural component has been incorporated into the structure of the bicyclic lactam PLG analogue **3**.



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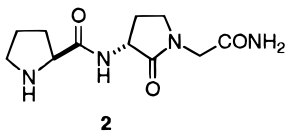

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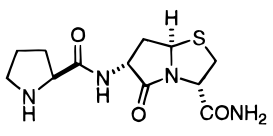

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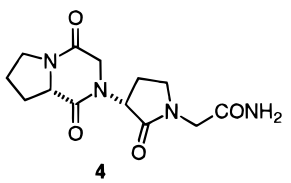

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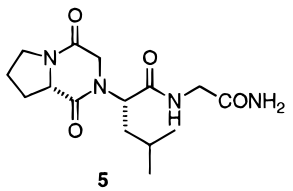

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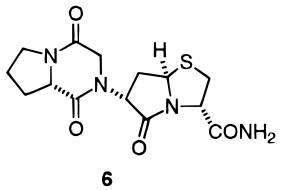

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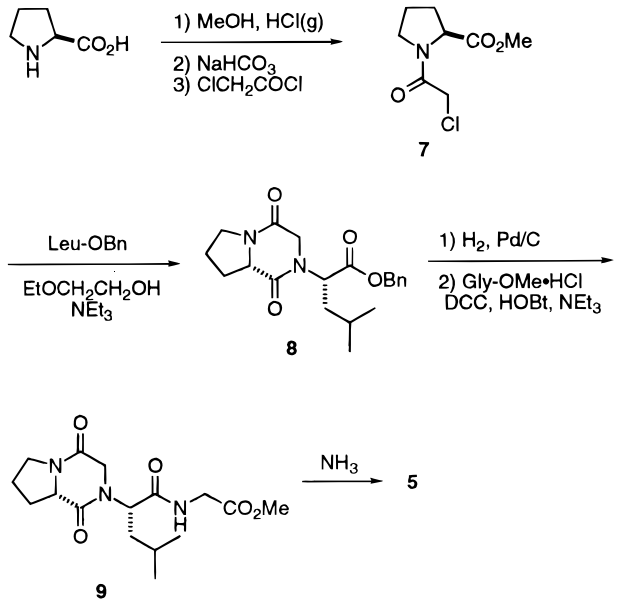
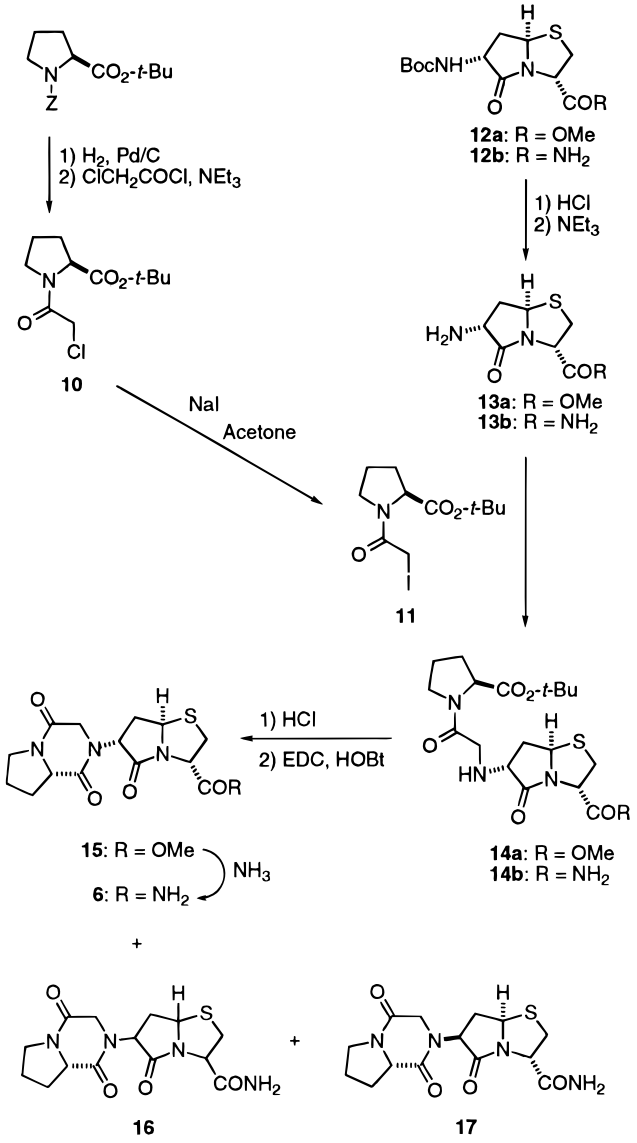
Scheme 1



Scheme 2



Chemistry

In the synthesis of **5** (Scheme 1), the *N*-chloroacetyl derivative **7** was reacted with L-leucine benzyl ester to give **8**, using reaction conditions previously reported in the literature to make diketopiperazines.[10] Conversion of **8** to the desired PLG diketopiperazine analogue **5** was accomplished as shown in Scheme 1.

A similar approach to that above was used to generate the diketopiperazine bicyclic lactam analogue **6** (Scheme 2). The *N*-(chloroacetyl)proline derivative **10** was converted to its α-iodo derivative **11**. This material was immediately reacted with bicyclic lactam **13a**, which had been obtained from the previously described protected bicyclic lactam **12a**,[6] to give **14a** in a 61% yield after chromatographic purification. Deprotection of **14a** followed by cyclization of the resulting intermediate gave the desired diketopiperazine product **15** in a 36% yield. Treatment of **15** with NH_3/MeOH gave primarily the desired PLG analogue **6** along with two of its diastereoisomers (**16** and **17**). Separation of **17** from **6** and **16** was accomplished by preparative TLC. Compounds **6** and **16** then were separated from one another by preparative HPLC. Subsequently, it was found that formation of the epimerization products **16** and **17** could be avoided by using bicyclic lactam amide **13b** in the reaction with **11**, as the product of this condensation reaction, **14b**, could be cleanly and directly converted to **6**.

Stereochemical assignments of the bicyclic ring stereocenters of **6** and **17** were made from their X-ray crystal structures.[11] The crystal structure of **6** is shown in Figure 1.[12] The bicyclic ring stereocenters of **6** possessed the desired 2*S*,5*R*,7*R* configurations, while the configurations of the bicyclic ring stereocenters of **17** were 2*S*,5*R*,7*S*. The stereochemistry of the bicyclic ring stereocenters of **16** could not be assigned because of the inability to obtain a crystal structure and because the very small amount of material which was obtained precluded extensive spectroscopic studies from being carried out.

The diketopiperazine moiety was incorporated into **5** and **6** in order to mimic a "C5" conformation. The torsion angle which defines the "C5" conformation is the ψ_1 torsion angle. From the crystal structure of **6** (Figure 1), the ψ_1 torsion angle (N3−C8−C9−N4) was found to have a value of 21.1(6)°. This is similar to the value of 31.2(2)° observed in **4**[8] and to the value of −0.8(2)° seen in the crystal structure of **2**.[9]

Pharmacology

The ability of the PLG peptidomimetics **5** and **6** to modulate dopamine receptors was determined by measuring the activity of these compounds in a [^{3}H]spiroperidol/*N*-propylnorapomorphine (NPA) D_2 receptor competitive binding assay in the presence or absence of 5′-guanylylimidodiphosphate (Gpp(NH)p), a nonhydrolyzable analogue of GTP. The graphical presentation of the competition experiment for **5** is illustrated in Figure 2. A similar set of curves was obtained for compound **6**. Computer analysis of the competition curves yielded kinetic data for **5** and **6**, which are summarized in Table 1. Also included in Table 1 for comparison are the data obtained previously for PLG (**1**)[2] and the lactam diketopiperazine PLG peptidomimetic **4**.[8]

Peptidomimetics **5** and **6** showed the same ability to increase the affinity of the dopamine receptor for

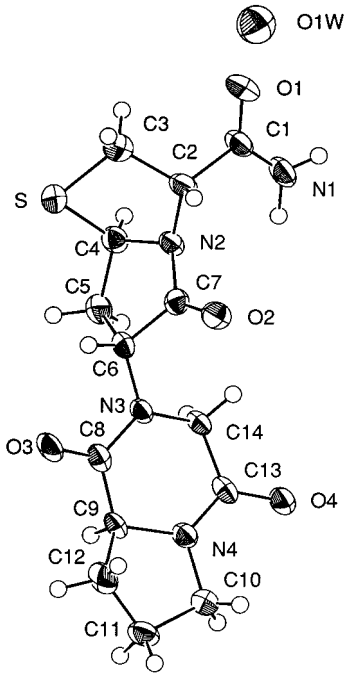


Figure 1. ORTEP drawing of **6** with crystallographic numbering system. The non-hydrogen atoms are shown at the 50% probability level.

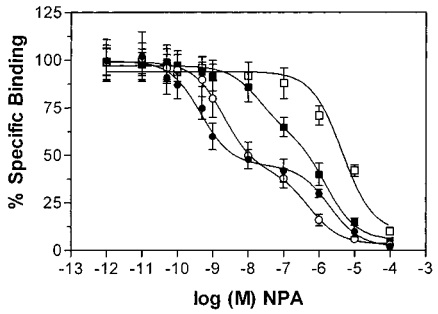


Figure 2. Competition curves of [^{3}H]spiroperidol/NPA in control as well as in membranes treated with **5** and the effect of Gpp(NH)p: (○) control minus Gpp(NH)p, (●) **5** minus Gpp(NH)p, (□) control plus Gpp(NH)p, and (■) **5** plus Gpp(NH)p. The concentration of [^{3}H]spiroperidol in the assay was 0.2 nM. Gpp(NH)p concentration was 100 μM, and the concentration of **5** was 100 nM. Computer analysis of the curves revealed two sites, high- and low-affinity sites of agonist binding with binding parameters as described in Table 1. Each value is an average of four separate experiments ± SEM.

agonists in the [^{3}H]spiroperidol/*N*-propylnorapomorphine D_2 receptor competitive binding assay as that found previously for PLG and the PLG peptidomimetics **2** and **4**.[2,4,8] The only difference was the concentration at which the effects were observed. For both **5** and **6**, this concentration was 100 nM. In comparison, it had been shown previously that the concentration at which the effects were observed for PLG was 1 μM, while that for **2** and **4** was 1 nM. As has been demonstrated previously for PLG and its peptidomimetics,[2,4,8] both **5** and **6** decreased the dissociation constant of the high-affinity state of the dopamine receptor for the agonist NPA. This was seen when Gpp(NH)p was either absent or present, although in these particular experiments statistical significance was clear only in the case where Gpp(NH)p was present. In the presence of Gpp(NH)p, compound **5** decreased the high-affinity receptor state agonist dissociation constant from a control value of 0.12 nM to a value of 0.08 nM. An even greater decrease (52%) in the high-affinity receptor state agonist dissociation constant was seen upon treatment with **6**, where the dissociation constant went from a control value of 0.14 nM to a value of 0.067 nM. No significant change in the dissociation constant of NPA for the low-affinity state of the receptor was observed.

Peptidomimetics **5** and **6** also increased the percentage of D_2 receptors that existed in the high-affinity state. This effect was seen in both the presence and absence of Gpp(NH)p. In the absence of Gpp(NH)p, treatment with **5** increased the ratio of the percentage of receptors in the high- and low-affinity states (R_H/R_L) from 1.35 to 1.97. Similarly, treatment with **6** resulted in an increase in R_H/R_L from 0.96 to 1.36. As can be seen in Table 1, the R_H/R_L ratio was significantly altered by the presence of Gpp(NH)p. Both **5** and **6**, however, were able to attenuate significantly the Gpp(NH)p-induced shift to the low-affinity state. Thus, treatment with **5** resulted in a change in the ratio from 0.257 to 1.47, while in the case of **6** the change in the ratio was from 0.225 to 0.985. What is significant is that even with Gpp(NH)p present, **5** and **6** were able to return the R_H/R_L ratios to values observed in the respective controls where Gpp(NH)p was absent.

Since peptidomimetic **6** had been found previously to be effective in enhancing rotational behavior induced by apomorphine in the 6-hydroxydopamine-lesioned animal model of Parkinson's disease,[13] peptidomimetic **5** was tested for its effects on apomorphine-induced rotational behavior in 6-hydroxydopamine-lesioned rats. Administration of apomorphine (0.25 mg/kg ip) in the absence of **5** resulted in a mean response of 75.0 ± 5.96 contralateral rotations over a 10 min observation period. Besides producing contralateral rotations, the administration of apomorphine produced stereotypical behaviors in the 6-hydroxydopamine-lesioned rats (e.g., grooming of the contralateral side). When administered in the absence of apomorphine, **5** did not produce any observable change in behavior, and it did not result in any contralateral rotations. Peptidomimetic **5**, however, altered apomorphine-induced rotational behavior in a dose-dependent manner displaying a bell-shaped dose−response relationship, which is typical of PLG and its analogues (Figure 3). The maximal effects of **5** occurred at a dose of 0.01 mg/kg ip, resulting in a 52.27 ± 13.96% ($p < 0.001$, $n = 7$) increase in rotations compared to apomorphine administered alone. In comparison, PLG and **6** previously had been shown to produce their maximum increase of approximately 30% at doses of 1 mg/kg ip and 0.1 mg/kg, respectively,[13] while **2** increased apomorphine-induced rotations by 191 ± 15% at 0.01 mg/kg ip.[14]

The above data show that peptidomimetics **5** and **6** possess the same ability to modulate dopamine receptors as PLG and the previously synthesized PLG peptidomimetics **2**−**4**. In the [^{3}H]spiroperidol/*N*-propylnorapomorphine D_2 receptor competitive binding assay, the potency of **5** and **6** was greater than that seen for **1** (PLG) but not as great as that observed for **2** or the analogue of **2** which possesses the diketopiperazine moiety, compound **4**. A slightly different profile was seen in the assay measuring apomorphine-induced rotational behavior in 6-hydroxydopamine-lesioned rats. In this case, **5** was 10 times more potent than **6**, which in turn was 10 times more potent than **1** (PLG).

Table 1. Modulation of [^{3}H]Spiroperidol/*N*-Propylnorapomorphine Binding Competition by **5** and **6**[a]

	binding parameters				
experiment	$K_{H\ (nM)}$	$K_{L\ (nM)}$	$R_{H\ (\%)}$	$R_{L\ (\%)}$	$R_{H/RL}$
control for **5**					
−Gpp(NH)p	0.080 ± 0.001	120 ± 5	56.25 ± 3.52	43.75 ± 3.52	1.35 ± 0.18
+Gpp(NH)p	0.120 ± 0.009	172 ± 7	18.75 ± 3.09	81.25 ± 3.09	0.257 ± 0.023
pretreatment with **5** (100 nM)					
−Gpp(NH)p	0.068 ± 0.007	91 ± 6	63.75 ± 3.43	36.25 ± 3.42	1.97 ± 0.12[b]
+Gpp(NH)p	0.080 ± 0.010[b]	104 ± 2	59.25 ± 2.28[e]	40.75 ± 2.29[e]	1.47 ± 0.137[c]
control for **6**					
−Gpp(NH)p	0.098 ± 0.009	171 ± 18	49.0 ± 2.12	51.0 ± 2.12	0.96 ± 0.081
+Gpp(NH)p	0.140 ± 0.064	183 ± 7	18.50 ± 1.71	81.5 ± 1.71	0.225 ± 0.026
pretreatment with **6** (100 nM)					
−Gpp(NH)p	0.066 ± 0.019	122 ± 15	57.25 ± 2.59[b]	42.75 ± 2.59[b]	1.363 ± 0.14[b]
+Gpp(NH)p	0.067 ± 0.007[c]	106 ± 5	49.25 ± 2.72[e]	50.75 ± 2.72[e]	0.985 ± 0.104[c]
control for **1**[f]					
−Gpp(NH)p	0.09 ± 0.005	73.2 ± 5.5	49 ± 5	51 ± 3	0.96 ± 0.05
+Gpp(NH)p	0.13 ± 0.01	60.0 ± 8.6	19 ± 2	82 ± 5	0.23 ± 0.01
pretreatment with **1** (1 μM)[f]					
−Gpp(NH)p	0.04 ± 0.002[c]	60.1 ± 5.4	61 ± 4[b]	41 ± 2	1.48 ± 0.06[c]
+Gpp(NH)p	0.06 ± 0.006[c]	78.0 ± 9.9	32 ± 3[c]	72 ± 6	0.44 ± 0.03[c]
control for **4**[g]					
−Gpp(NH)p	0.08 ± 0.005	69 ± 3.5	46 ± 1	55 ± 1.8	0.83 ± 0.001
+Gpp(NH)p	0.19 ± 0.02	50 ± 3	22 ± 0.8	78 ± 1.2	0.28 ± 0.002
pretreatment with **4** (1 nM)[g]					
−Gpp(NH)p	0.02 ± 0.003[e]	56 ± 2.5	65 ± 4[d]	33 ± 3.8	1.97 ± 0.007[e]
+Gpp(NH)p	0.05 ± 0.006[e]	64 ± 3.5	42 ± 3[d]	59 ± 1.8	0.71 ± 0.003[e]

[a] Competition data were computer-analyzed as described in the Experimental Section. K_H and K_L represent the inhibitor constant (K_i) of agonist calculated for the high- and low-affinity components of the [^{3}H]spiroperidol binding, respectively. R_H and R_L are the percentage of receptors in the high- and low-affinity form for the agonist, respectively. Values for each preparation are the mean ± SEM of three to four separate experiments with each experiment carried out in duplicate or triplicate. Concentration of Gpp(NH)p was 100 μM. Statistical difference from the respective control group is indicated as follows: [b] $p < 0.05$; [c] $p < 0.01$; [d] $p < 0.005$; [e] $p < 0.001$. [f] Data for **1** from ref 2. [g] Data for **4** from ref 8.

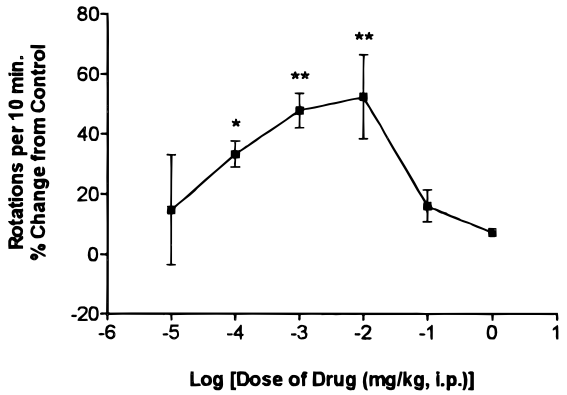


Figure 3. Effect of **5** (dosage ranging from 0.000 01 to 1 mg/kg ip) on contralateral rotational behavior of apomorphine (0.25 mg/kg ip) in rats with unilateral 6-hydroxydopamine substantia nigra lesions ($n = 7$). Number of contralateral rotations in 10 min are expressed as a percentage change from control rotational response. Each point represents the mean percentage change ± SEM. Statistical significance is expressed as *$p < 0.01$, **$p < 0.001$.

Peptidomimetic **5** was as potent as **2** in this *in vivo* assay system; however, **2** produced a much greater percent increase in apomorphine-induced rotations than did **5**. These results suggest that while an N-terminal "C5" conformation may play a part in the potency of the γ-lactam peptidomimetics of PLG, it does not appear to be the primary factor.

Experimental Section

General Aspects. All apparatus were oven-dried and cooled in a desiccator. THF and CH_2Cl_2 were distilled from Na/benzophenone and CaH_2, respectively. Thin-layer chromatography was performed on Analtech 250 μm silica gel HLF Uniplates and visualized by UV, I_2, ninhydrin spray (amines), and 2,6-dichlorophenol indophenol spray (acids). Chromatographic purification on silica gel (Merck, grade 60, 240−400 mesh, 60 Å) was done by flash or gravity methods, and preparative 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*)-1-(Chloroacetyl)-2-(methoxycarbonyl)pyrrolidine (7). L-Proline (10 g, 7.0 mmol) was suspended in anhydous MeOH, and HCl gas was bubbled into the suspension until all the solid was dissolved and the solution became warm. The reaction mixture was stirred for 15 min before it was concentrated to a viscous oil. The resulting Pro-OMe·HCl was partitioned between CH_2Cl_2 and 1 M $NaHCO_3$. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure while keeping the temperature below 20 °C. Anhydrous benzene was added to this oil followed by the dropwise addition of chloroacetyl chloride (6.9 mL, 7.0 mmol). The solution was refluxed for 2 h while it was stirred vigorously. The solution was then concentrated under aspirator pressure and the resulting residue partitoned between CH_2Cl_2 and H_2O. The organic phase was washed with 10% citric acid, 1 M $NaHCO_3$, H_2O, and saturated NaCl. The organic phase was dried ($MgSO_4$) and then stripped of solvent to give a light golden oil. Passage of this material through a pad of silica gel with EtOAc/hexanes (1:1) as the eluant removed final traces of impurities and provided the product in a yield of 5.6 g (24%): $[\alpha]_D = -91.4$ (*c* 2.25, MeOH); FAB MS *m*/*z* 206 [M + H]$^+$.

Benzyl (2*S*)-[(8a*S*)-Hexahydro-1,4-dioxopyrrolo[1,2-*a*]-pyrazin-2(1*H*)-yl]-4-methylpentanoate (8). (2*S*)-1-(Chloroacetyl)-2-(methoxycarbonyl)pyrrolidine (**7**; 0.70 g, 3.40 mmol) and L-leucine benzyl ester (0.90 g, 3.76 mmol) were dissolved in 20 mL of 2-ethoxyethanol. To this solution was added Et_3N (0.47 mL, 3.40 mmol) dropwise. The solution was refluxed for 60 h before the solvent was removed under vacuum. The residue was partitioned between CH_2Cl_2 and 10% citric acid. The organic fraction was washed with 1 M $NaHCO_3$ and

saturated NaCl before it was dried over $MgSO_4$. This solution was stripped of solvent to give an oil which was purified by column chromatography on silica gel with EtOAc/*i*-PrOH (25:1) as the eluant. The material obtained from the column was dissolved in CH_2Cl_2 and this solvent then removed *in vacuo*. This process was carried out several times to remove traces of the eluting solvents. The product was obtained as 740 mg (64%) of a clear oil: $[\alpha]_D = -78.4$ (*c* 1.15, MeOH); TLC R_f (EtOAc/*i*-PrOH, 25:1) = 0.43; ^{1}H NMR ($CDCl_3$) δ 7.26−7.36 (m, 5 H, Ph-H), 5.26−5.31 (m, 1 H, 2-CH), 5.04−5.18 (m, 2 H, $PhCH_2$), 4.09−4.12 (m, 1 H, 8a-CH), 4.09 (d, J = 15.9 Hz, 1 H, NCH_2CO), 3.72 (d, J = 15.9 Hz, 1 H, NCH_2CO), 3.46−3.62 (m, 2 H, 6-CH_2), 2.31−2.41 (m, 1 H, 8-CH_2), 1.78−2.11 (m, 3 H, 7- and 8-CH_2), 1.64−1.80 (m, 2 H, 3-CH_2), 1.35−1.45 (m, 1 H, 4-CH), 0.90 (d, J = 7.2 Hz, 3 H, CH_3), 0.85 (d, J = 7.5 Hz, 3 H, CH_3); ^{13}C NMR (DEPT, $CDCl_3$) δ 171.6, 169.6, 164.2 (CO), 135.8, 129.3, 129.2, 129.1, 129.0, 128.9 (Ph C), 67.9 (CH_2Ph), 59.8, 54.1 (2- and 8a-C), 48.1 (NCH_2CO), 45.7 (6-C), 37.1, 29.3 (3- and 8-C), 25.4 (4-C), 23.7 (7-C), 23.4, 21.7 (CH_3); FAB MS m/z 359 $[M + H]^+$. Anal. ($C_{20}H_{26}N_2O_4 \cdot 0.25CH_2Cl_2$) C, H, N.

Methyl [*N*-[(2*S*)-[(8a*S*)-Hexahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-2(1*H*)-yl]-4-methylpentanoyl]amino]acetate (9). Compound **8** (400 mg, 1.18 mmol) was dissolved in MeOH, and this solution then was added to a suspension of 40 mg of Pd/C in MeOH. This mixture was hydrogenated in a Parr vessel for 8 h. The Pd/C was collected by gravity filtration through a paper filter, and the MeOH was removed under aspirator pressure. The resultant oil was azeotroped (2×) from CH_2Cl_2 before finally being dissolved in CH_2Cl_2. 1-Hydroxybenzotriazole monohydrate (160 mg, 1.18 mmol) and glycine methyl ester hydrochloride (163 mg, 1.30 mmol) were added all at once to this solution. Triethylamine (181 μL, 1.30 mmol) was added dropwise followed by the addition of dicyclohexylcarbodiimide (268 mg, 1.30 mmol) all at once. The solution was stirred for 20 h at room temperature. The precipitated dicyclohexylurea was removed by filtration, and the CH_2Cl_2 filtrate was washed with 10% citric acid, 1 M $NaHCO_3$, and saturated NaCl before it was dried over $MgSO_4$. This solution was stripped of solvent to give an oil which was purified by column chromatography on silica gel with EtOAc/MeOH (9:1) as the eluant. A yield of 162 mg (37%) was obtained: $[\alpha]_D = -30.3$ (*c* 1.5, MeOH); TLC R_f (EtOAc/MeOH, 9:1) = 0.34; ^{1}H NMR ($CDCl_3$) δ 6.70 (t, J = 6.0 Hz, 1 H, NH), 5.07 (t, J = 8.0 Hz, 1 H, 2-CH), 3.71−4.15 (m, 5 H, 8a-CH, NCH_2CON), 3.67 (s, 3 H, OCH_3), 3.48−3.61 (m, 2 H, 6-CH_2), 2.30−2.40 (m, 1 H, 8-CH_2), 1.84−2.10 (m, 3 H, 7- and 8-CH_2), 1.56−1.75 (m, 2 H, 3-CH_2), 1.38−1.47 (m, 1 H, 4-CH), 0.89 (d, J = 6.0 Hz, 3 H, CH_3), 0.84 (d, J = 6.0 Hz, 3 H, CH_3); ^{13}C NMR (DEPT, $CDCl_3$) δ 170.9, 170.6, 170.6, 164.1 (CO), 59.9, 53.9 (2- and 8a-C), 53.0 (OCH_3), 47.7, 41.5 (NCH_2CON, NHCH_2CO), 45.6 (6-C), 36.1, 29.3 (3- and 8-C), 25.3 (4-C), 23.2 (7-C), 23.4, 22.6 (CH_3); FAB MS m/z 340 $[M + H]^+$. Anal. ($C_{16}H_{25}N_3O_5$) C, H, N.

[*N*-[(2*S*)-[(8a*S*)-Hexahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-methylpentanoyl]amino]acetamide (5). Compound **9** (117 mg, 0.34 mmol) was dissolved in MeOH saturated with NH_3. The solution was stirred at room temperature for 12 h. Removal of the MeOH and NH_3 from the solution provided **5** as a foam in quantitative yield: $[\alpha]_D = -76.9$ (*c* 0.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.54 (t, J = 6.0 Hz, 1 H, CONH), 6.77 (bs, 1 H, $CONH_2$), 6.51 (bs, 1 H, $CONH_2$), 5.06 (t, J = 8.4 Hz, 1 H, 2-CH), 3.67−4.17 (m, 7 H, 8a-CH, NHCH_2CO, NCH_2CO), 3.44−3.58 (m, 2 H, 6-CH_2), 2.28−2.35 (m, 1 H, 8-CH_2), 1.80−2.06 (m, 3 H, 7- and 8-CH_2), 1.64−1.69 (m, 2 H, 3-CH_2), 1.31−1.45 (m, 1 H, 4-CH), 0.89 (d, J = 6.0 Hz, 3 H, CH_3), 0.82 (d, J = 6.0 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.6, 171.6, 170.3, 164.4 (CO), 59.9, 54.8 (2 and 8a-C), 48.4, 43.2 (NCH_2CO, NHCH_2CO), 45.7 (6-C), 37.1, 29.3 (3- and 8-C), 25.4 (4-C), 23.4 (7-C), 23.7, 22.3 (CH_3); FAB MS m/z 325 $[M + H]^+$. Anal. ($C_{15}H_{24}N_4O_4$) C, H, N.

(2*S*)-1-(Chloroacetyl)-2-(*tert*-butoxycarbonyl)pyrrolidine (10). Z-Pro-*t*-OBu (8.35 g, 27.3 mmol) was hydrogenated at 40 psi of H_2 in the presence of 500 mg of Pd/C for 4 h. The mixture was filtered through filter paper and the filtrate concentrated under vacuum. The residue was azeotroped from CH_2Cl_2 (2×), and the oil which remained was dissolved in 75 mL of CH_2Cl_2. This solution was cooled to −30 °C, after which NEt_3 (3.81 mL, 27.3 mmol) was added slowly followed by the dropwise addition of chloroacetyl chloride (2.39 mL, 30 mmol) as a solution in 10 mL of CH_2Cl_2. After 2 h at room temperature, 75 mL of a 10% citric acid solution was added, and the layers were separated. The organic layer was washed with 75 mL each of 1 M $NaHCO_3$ and saturated NaCl. The organic layer was dried over $MgSO_4$ and then concentrated to an oil, which was purified by chromatography on silica gel with EtOAc/hexane (1:1) as the eluant. The purified oil was obtained in a yield of 4.9 g (72%): $[\alpha]_D = -97.8$ (*c* 0.55, MeOH); TLC R_f (EtOAc/hexane, 1:1) = 0.39; ^{1}H NMR (shows rotamers about the amide bond present; $CDCl_3$) δ 4.18−4.21 (m, 1 H, α-CH), 3.82−3.95 (m, 2 H, CH_2Cl), 3.38−3.56 (m, 2 H, δ-CH_2), 1.97−2.07 (m, 1 H, β-CH_2), 1.77−1.93 (m, 3 H, β- and γ-CH_2), 1.25−1.31 (m, 9 H, $C(CH_3)_3$); ^{13}C NMR (of major rotamer; $CDCl_3$) δ 171.3, 165.4 (CO), 81.9 ($C(CH_3)_3$), 60.6 (α-C), 47.6 (δ-C), 42.4 (CH_2Cl), 29.6 (β-C), 28.4 ($C(CH_3)_3$), 25.3 (γ-C); FAB MS m/z 248 $[M + H]^+$. Anal. ($C_{11}H_{18}NO_3Cl \cdot 0.8H_2O$) C, H, N, Cl.

Methyl (2*S*,5*R*,7*R*)-1-Aza-7-[[[[(2*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl]carbonyl]methyl]amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (14a). Compound **10** (332 mg, 1.34 mmol) was dissolved in 10 mL of spectroscopic grade acetone, and NaI (201 mg, 1.34 mmol) was added all at once to this solution. This solution was refluxed for 15 min after which the precipitate was removed by filtration and the golden-colored filtrate was concentrated under vacuum to give (2*S*)-1-(iodoacetyl)-2-(*tert*-butoxycarbonyl)pyrrolidine (**11**) as an oil. This material was dissolved in 2 mL of DMF, and the solution was added dropwise to a solution of methyl (2*S*,5*R*,7*R*)-1-aza-7-amino-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (**13a**) in DMF [This solution was prepared by reacting methyl (2*S*,5*R*,7*R*)-1-aza-7-[(*tert*-butoxycarbonyl)amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (**12a**)[6] (385 mg, 1.22 mmol) with 4 N HCl in dioxane for 1 h. The dioxane and excess HCl were removed under vacuum, and the resultant hydrochloride salt was azeotroped from CH_2Cl_2 (3×). The hydrochloride salt was dissolved in 2 mL of DMF at 0 °C, and NEt_3 (356 μL, 2.56 mmol) was added dropwise]. The reaction mixture was stirred for 12 h at room temperature before the solution was concentrated under vacuum to a golden solid. The solid was partitioned between 15 mL of 1 M $NaHCO_3$ and 50 mL of EtOAc. The aqueous phase was again extracted with 50 mL of EtOAc. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated to give a crude oil which was purified by silica gel chromatography with CH_2Cl_2/MeOH (10:1) as the eluant. This provided 316 mg (61%) of a light-gold oil: $[\alpha]_D = +103.3$ (*c* 0.3, MeOH); TLC R_f (CH_2Cl_2/MeOH, 10:1) = 0.56; ^{1}H NMR (of major rotamer; $CDCl_3$) δ 5.18−5.21 (m, 1 H, 5-CH), 4.99−5.04 (m, 1 H, 2-CH), 4.36−4.40 (m, 1 H, 7-CH), 3.74 (s, 3 H, OCH_3), 3.52−3.63 (m, 4 H, NCH_2CO, pyrrolidine 2-CH, pyrrolidine 5-CH_2), 3.29−3.46 (m, 3 H, NCH_2CO, 3-CH_2), 2.61 (bs, 1 H, NH), 2.43−2.52 (m, 1 H, 6-CH_2), 2.30−2.38 (m, 1 H, 6-CH_2), 1.85−2.18 (m, 4 H, pyrrolidine 3- and 4-CH_2), 1.43 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (of the two rotamers; $CDCl_3$) δ 176.6, 176.5, 171.9, 170.8, 170.8, 170.4, 169.9 (CO), 83.0, 82.0 ($C(CH_3)_3$), 65.1, 65.0 (5-C), 60.3, 60.0, 59.9, 59.2, 58.5, 58.4 (2- and 7-C, pyrrolidine 2-C), 53.5 (OCH_3), 49.7, 49.2 (NCH_2CO), 47.2, 46.6 (pyrrolidine 5-C), 37.3 (CH_2S), 33.3, 33.0 (6-C), 32.1, 29.7 (pyrrolidine 3-C), 28.6, 28.6 ($C(CH_3)_3$), 25.1, 22.9 (pyrrolidine 4-C); FAB MS m/z 428 $[M + H]^+$. Anal. ($C_{19}H_{29}N_3O_6S$) C, H, N.

(2*S*,5*R*,7*R*)-1-Aza-7-[[[[(2*S*)-(*tert*-butoxycarbonyl)pyrrolidin-1-yl]carbonyl]methyl]amino]-8-oxo-4-thiabicyclo-[3.3.0]octane-2-carboxamide (14b). This material was prepared in the same manner as that described above for **14a**. Thus, **10** (633 mg, 2.56 mmol) was converted to its iodo derivative **11** with NaI (383 mg, 2.56 mmol) which was then reacted with (2*S*,5*R*,7*R*)-1-aza-7-amino-8-oxo-4-thiabicyclo-[3.3.0]octane-2-carboxamide (**13b**) that had been prepared from the deprotection of (2*S*,5*R*,7*R*)-1-aza-7-[(*tert*-butoxycarbonyl)-amino]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (**12b**)[6] (770 mg, 2.56 mmol). Product was obtained as an oil in a 70% (770 mg) yield: $[\alpha]_D = +77.9$ (*c* 1.35, MeOH); ^{1}H NMR (of major rotamer; $CDCl_3$) δ 7.57 (s, 1 H, CONH), 5.58 (s, 1 H, CONH),

5.23 (t, J = 6.0 Hz, 1 H, 5-CH), 4.73−4.77 (m, 1 H, 2-CH), 4.23−4.27 (m, 1 H, 7-CH), 3.33−3.67 (m, 7 H, NCH_2CO, 3-CH_2, pyrrolidine 2-CH, pyrrolidine 5-CH_2), 2.51 (bs, 1 H, NH), 2.38−2.42 (m, 1 H, 6-CH_2), 2.10−2.19 (m, 1 H, pyrrolidine 3-CH_2), 1.86−2.03 (m, 3 H, pyrrolidine 3- and 4-CH_2), 1.41 (s, 9 H, $C(CH_3)_3$); ^{13}C NMR (of major rotamer; $CDCl_3$) δ 176.0, 172.0, 171.8, 171.0 (CO), 82.1 ($C(CH_3)_3$), 64.8 (5-C), 62.3, 60.4, 59.0 (2- and 7-C, pyrrolidine 2-C), 49.2 (NCH_2CO), 46.6 (pyrrolidine 5-C), 41.6 (CH_2S), 34.6 (6-C), 29.6 (pyrrolidine 3-C), 28.6 ($C(CH_3)_3$), 25.2 (pyrrolidine 4-C); FAB MS m/z 413 $[M + H]^+$.

Methyl (2*S*,5*R*,7*R*)-1-Aza-7-[(8a*S*)-hexahydro-1,4-dioxopyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxylate (15). Compound **14a** (316 mg, 0.74 mmol) was dissolved in 4 N HCl in dioxane after which the solution was stirred for 3 h at room temperature. The dioxane and excess HCl were removed under vacuum, and the residue was azeotroped from CH_2Cl_2 (2×). The product was dried under high vacuum for 3 h before being dissolved in 30 mL of CH_2Cl_2. The solution was cooled to −20 °C before 1-hydroxybenzotriazole monohydrate (100 mg, 0.74 mmol) and NEt_3 (206 μL, 1.48 mmol) were added consecutively. The ice bath was removed, and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (283 mg, 1.48 mmol) was added in four portions over a 3 min period. This solution then was stirred for 16 h at room temperature. An additional 50 mL of CH_2Cl_2 was added to the solution before it was washed consecutively with 50 mL each of 1 N HCl, 1 M $NaHCO_3$, and a saturated NaCl solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a light-gold oil. Final purification was done by silica gel chromatography with EtOAc/MeOH (9:1). A yield of 95 mg (36%) was obtained. A portion of this material was transferred to a vial as a solution in CH_2Cl_2 in order to obtain a sample for elemental analysis: $[\alpha]_D$ = +140.7 (c 0.6, MeOH); TLC R_f (EtOAc/MeOH, 9:1) = 0.29; ^{1}H NMR ($CDCl_3$) δ 5.23 (dd, J = 2.4, 6.0 Hz, 1 H, 5-CH), 5.07 (dd, J = 3.6, 8.7 Hz, 1 H, 2-CH), 4.78 (t, J = 8.7 Hz, 1 H, 7-CH), 4.25 (d, J = 17.1 Hz, 1 H, NCH_2CO), 4.12 (t, J = 8.7 Hz, 1 H, 8a-CH), 3.80 (d, J = 17.1 Hz, 1 H, NCH_2CO), 3.78 (s, 3 H, OCH_3), 3.51−3.68 (m, 2 H, NCH_2), 3.35−3.50 (m, 2 H, SCH_2), 2.48−2.56 (m, 2 H, 6-CH_2), 2.34−2.46 (m, 1 H, 8-CH_2), 1.87−2.16 (m, 3 H, 7- and 8-CH_2); ^{13}C NMR ($CDCl_3$) δ 173.6, 170.6, 168.5, 163.0 (CO), 64.4 (5-C), 59.6, 59.0, 57.3 (2-, 7-, and 8a-C), 53.7 (OCH_3), 51.7 (NCH_2C), 46.0 (NCH_2), 37.5 (CH_2S), 29.4 (8-C), 26.9 (6-C), 23.2 (7-C); FAB MS m/z 354 $[M + H]^+$. Anal. ($C_{15}H_{19}N_3O_5S\cdot CH_2Cl_2$) C, H, N.

(2*S*,5*R*,7*R*)-1-Aza-7-[(8a*S*)-hexahydro-1,4-dioxopyrrolo-[1,2-*a*]pyrazin-2(1*H*)-yl]-8-oxo-4-thiabicyclo[3.3.0]octane-2-carboxamide (6). Method A. Ester **15** (70 mg, 0.20 mmol) was dissolved in cold NH_3 in MeOH, and this solution was stirred for 5 h at room temperature. The solvents were removed, and the resulting oil was purified by using normal phase preparatory TLC. Two bands were obtained with an R_f (CH_2Cl_2/MeOH, 10:1) of 0.49 and 0.41, respectively. The top band contained the two diastereoisomers, **6** and **16**, while the bottom band consisted of diastereoisomer **17**, as determined from X-ray crystallography. Diastereoisomers **6** and **16** were separated by HPLC with EtOAc/MeOH (9:1) as the eluant. Retention times for **6** and **16** were 18.4 and 15.6 min, respectively.

Method B. A solution of 4 N HCl in dioxane was added to **14b** (700 mg, 1.7 mmol). This solution was stirred for 3 h, after which time the dioxane and excess HCl were removed under aspirator pressure to give an oily residue. This material was azeotroped from a mixture of CH_2Cl_2/MeOH (2×) and then left under vacuum to remove all traces of solvents. The resulting material was dissolved in 30 mL of dry DMF. To this stirred solution at 0 °C were added consecutively NEt_3 (249 μL, 1.7 mmol), 1-hydroxybenzotriazole monohydrate (230 mg, 1.7 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (650 mg, 3.4 mmol). The reaction mixture was stirred at room temperature for 48 h. The DMF was removed under vacuum, and the resulting residue was purified by chromatography with EtOAc/MeOH (9:1) as the eluant. Final traces of impurities were removed by preparative HPLC on silica gel with EtOAc/MeOH (9:1) to give a homogeneous white solid. Crystallization from CH_2Cl_2/MeOH provided 75 mg (13%) of **6**: mp 249−252 °C; $[\alpha]_D$ = +66.0 (c 1.0, MeOH); TLC R_f (CH_2Cl_2/MeOH, 10:1) = 0.25; TLC R_f (EtOAc/MeOH, 9:1) = 0.10; ^{1}H NMR ($CDCl_3$/MeOH-d_4) δ 7.14 (s, 1 H, CONH), 6.01 (s, 1 H, CONH), 5.12 (dd, J = 2.4, 3.6 Hz, 1 H, 5-CH), 4.79 (dd, J = 4.2, 4.8 Hz, 1 H, 2-CH), 4.38 (d, J = 15.6 Hz, 1 H, NCH_2CO), 4.23 (dd, J = 2.4, 7.5 Hz, 1 H, 7-CH), 4.12−4.17 (m, 1 H, 8a-CH), 3.82 (d, J = 15.6 Hz, 1 H, NCH_2CO), 3.39−3.63 (m, 4 H, NCH_2, SCH_2), 2.45−2.57 (m, 2 H, 6-CH_2), 2.29−2.39 (m, 1 H, 8-CH), 1.83−2.04 (m, 3 H, 7- and 8-CH_2); ^{13}C NMR ($CDCl_3$/MeOH-d_4) δ 173.1, 172.3, 172.3, 163.5 (CO), 64.5 (5-C), 61.1, 60.5, 59.6, 59.4 (2-, 7-, and 8a-C, NCH_2CO), 46.0 (NCH_2), 36.8 (CH_2S), 29.1 (6-C), 28.8 (8-C), 23.2 (7-C); FAB MS m/z 339 $[M + H]^+$. Anal. ($C_{14}H_{18}N_4O_4S\cdot H_2O$) C, H, N, S.

Isomer 16: TLC R_f (CH_2Cl_2/MeOH, 10:1) = 0.25; $[\alpha]_D$ = +139.5 (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.77 (s, 1 H, CONH), 5.53 (s, 1 H, CONH), 5.15 (dd, J = 3.6, 5.1 Hz, 1 H, 5-CH), 4.83 (dd, J = 4.8, 8.7 Hz, 1 H, 2-CH), 4.58−4.65 (m, 1 H, 7-CH), 4.29 (d, J = 15.6 Hz, 1 H, NCH_2CO), 4.13−4.18 (m, 1 H, 8a-CH), 3.88 (d, J = 15.6 Hz, 1 H, NCH_2CO), 3.45−3.72 (m, 4 H, NCH_2, SCH_2), 2.58−2.66, 2.33−2.48 (m, 3 H, 6- and 8-CH_2), 1.89−2.16 (m, 3 H, 7- and 8-CH_2).

Isomer (2*R*,5*R*,7*R*)-17: TLC R_f (CH_2Cl_2/MeOH, 10:1) = 0.18; $[\alpha]_D$ = +60.7 (c 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.62 (s, 1 H, CONH), 5.58 (s, 1 H, CONH), 5.66 (t, J = 9.9 Hz, 1 H, 5-CH), 5.03−5.07 (m, 1 H, 7-CH), 4.80−4.85 (m, 1 H, 2-CH), 4.18−4.23 (m, 2 H, 8a-CH, NCH_2CO), 3.70−3.79 (m, 2 H, NCH_2CO, SCH_2), 3.52−3.62 (m, 2 H, NCH_2), 3.38 (dd, J = 3.6, 8.4 Hz, 1 H, SCH_2), 2.89−2.99 (m, 1 H, 6-CH_2), 2.35−2.46 (m, 1 H, 8-CH_2), 1.81−2.21 (m, 4 H, 6-, 7-, and 8-CH_2).

X-ray Diffraction. Colorless crystals of **6** monohydrate and **17** were grown from chloroform/methanol. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation (λ = 1.541 78 Å) using 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 ψ-scan method.[15] The structures were solved by direct methods using SHELXS86[16] and refined using the TEXSAN structure analysis package.[17] 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.

[^{3}H]Spiroperidol/*N*-Propylnorapomorphine Binding Competition Assay. Bovine striatal membranes were prepared essentially as described in previous reports.[2,18] The tissues were homogenized in 10 volumes of 0.25 M sucrose in a Potter-Elvehjem homogenizer and centrifuged at 1000g for 15 min. The supernatant was then centrifuged for 1 h at 100000g. The resulting pellet was resuspended in 50 mM Tris-HCl−1 mM EDTA buffer (pH 7.4) and stored at −80 °C in small aliquots. On the day of use, the membrane preparations were thawed and diluted with Tris-HCl buffer containing 1 mM EDTA, 5 mM $MgCl_2$, 0.1 mM dithiothreitol, 0.1 mM phenylmethanesulfonyl fluoride, 0.1 mM benzamide, and 1 mg/mL soybean trypsin inhibitor before using for the ligand binding assay.

The [^{3}H]spiroperidol/*N*-propylnorapomorphine binding competition assays were performed using 150−200 μg of the above membrane protein preparation in a total volume of 1.0 mL of buffer. [^{3}H]Spiroperidol (0.2 nM) and varying concentrations of *N*-propylnorapomorphine were added to the reaction mixture in the absence and presence of 100 μM Gpp(NH)p and the PLG peptidomimetics **5** and **6**; 50 nM ketanserin was included in the [^{3}H]spiroperidol binding assays to occlude the presence of serotonergic sites. Incubation of membranes with ligands was carried out for 1 h at 22 °C. At the end of the incubation the bound and free ligands were separated by rapid filtration on Whatman GF/B filters. The filters were washed with 3 × 5 mL of Tris−EDTA buffer, and the radioactivity was determined on a Beckman Model 1780 scintillation counter. Nonspecific binding was determined in parallel assays in the presence of 1.0 μM (+)-butaclamol.

The binding data were analyzed as previously described.[19] In brief, curves were analyzed using the weighted nonlinear curve-fitting Prism program (Graph Pad Software, San Diego, CA). Data were subjected to analysis for either one site or multiple binding sites together with statistical analysis comparing "goodness of fit" between one or two affinity state models. A two-site model was selected only if a statistically significant improvement of the fit data was obtained over a one-site model. The IC_{50} values obtained from the competition curves were converted to K_i values via the Prism software program, which employs the Cheng and Prusoff equation.[20]

Rotational Behavior Assay. Male Sprague−Dawley rats weighing 250−300 g (Charles River, St. Constant, Quebec) were individually housed under constant temperature and humidity with a 12 h light/12 h dark cycle and were allowed free access to food and water. 6-Hydroxydopamine lesions of the substantia nigra were made in these rats in the following manner. The rats were pretreated with desipramine (15 mg/kg ip) 30 min prior to surgery, in order to spare noradrenergic pathways from the neurotoxic effects of 6-hydroxydopamine. Also, in order to decrease respiratory distress, atropine (0.06 mg/kg ip) was administered prior to anesthesia with sodium pentobarbital (50 mg/kg ip). 6-Hydroxydopamine (8 μg in 4 μL of 0.9% saline with 0.1% ascorbic acid) was infused directly into the substantia nigra pars compacta (coordinates −4.8 A, +1.9 L, −7.5 D to bregma, according to the atlas of Paxinos and Watson[21]) at a rate of 1 μL/min using a 30 gauge Hamilton syringe. Each rat was given 10 mL of sterilized saline (sc) to limit dehydration and 0.2 mL (0.03 mg/mL sc) of Temgesic to limit pain after the surgery.

Ten days postoperatively all animals were tested for rotational behavior by administering only apomorphine (0.25 mg/kg ip) for a total of three times with a 10 day washout period between tests. Only those rats exhibiting a minimum of 40 contralateral rotations over a 10 min period were considered to be lesioned successfully and were included in the study. The animals were observed in a clear round flat-bottom plastic bowl to which they were allowed to acclimate for 10 min before testing was started. Rotational counts were taken manually at 5 min intervals after a 5 min latency period from the point of drug administration to allow for distribution of drug.

The ability of **5** to modify the rotational response to apomorphine (0.25 mg/kg ip) was tested at several doses (Figure 3) with a 2 day washout period between testing. Compound **5** was given at the same time as apomorphine through the ip route of administration. Solutions of **5** were made by dissolving the compound in MeOH and then diluting the solution with 0.9% saline containing 0.1% ascorbic acid. Control experiments were carried out with vehicle (0.9% saline solution containing 0.1% ascorbic acid). A Latin square design was used for the administration of drugs in order to rule out any potential enhanced sensitivity due to increasing drug doses. The rotational counts were compared to baseline apomorphine-induced rotations for each animal and analyzed using repeated measures ANOVA. Results are expressed as the percent change compared to control.

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Supporting Information Available: X-ray crystallographic data including tables of positional parameters, bond distances, and bond angles for **6** and **17** (20 pages). Ordering information is given on any current masthead page.

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(11) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

(12) The crystal structure of **6**, to our knowledge, provides the first reported crystal structure of a compound containing the 5,5-bicyclic thiazolidine lactam β-turn mimic, which restricts the ψ_2 and ϕ_3 torsional angles of a β-turn. In **6**, the ψ_2 (N2−C7−C6−N3) and ϕ_3 (C1−C2−N2−C7) torsional angles possess values of 142.7(4)° and 120.5(4)°, respectively. These can be compared to the corresponding values for an ideal type II β-turn, which are $\psi_2 = 120°$ and $\phi_3 = 80°$.

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