Synthesis and Dopamine Receptor Modulating Activity of Novel Peptidomimetics of L-Prolyl-L-leucyl-glycinamide Featuring α,α-Disubstituted Amino Acids

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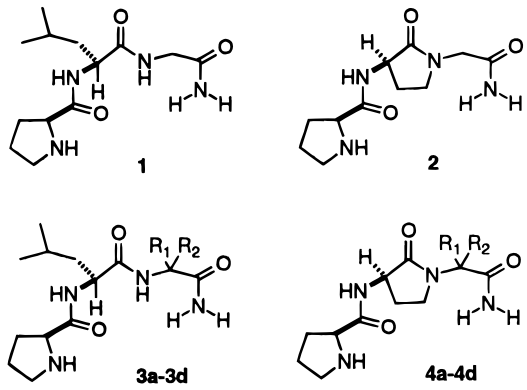
In the present study, L-prolyl-L-leucyl-glycinamide (**1**) peptidomimetics **3a**−**3d** and **4a**−**4d** were synthesized utilizing α,α-disubstituted amino acids. These analogues were designed to explore the conformational effects of constraints at the ϕ_3 and ψ_3 torsion angles. Constrained conformations were verified by the use of X-ray crystallography and circular dichroism. The effects of Pro-Leu-Gly-NH_2 analogues **3a**−**3d** and **4a**−**4d** on enhancing rotational behavior induced by apomorphine in the 6-hydroxydopamine-lesioned animal models of Parkinson's disease were studied. The ability of these peptidomimetics to increase the binding of agonist *N*-propylnorapomorphine (NPA) to the dopamine D_2 receptor was also examined. Extended analogue Pro-Leu-Deg-NH_2 was the most active compound of this series. It was 10 times more potent and almost 2 times more effective than **1** in increasing apomorphine-induced rotations (56 ± 15% at 1.0 mg/kg ip) and in enhancing [^{3}H]NPA specific binding (40%).

Introduction

L-Prolyl-L-leucyl-glycinamide (PLG, **1**) is a tripeptide found in the central nervous system that modulates dopaminergic neurotransmission.[1] Studies have shown that **1** does not modulate dopaminergic neurotransmission by affecting either dopamine synthesis, uptake, or metabolism.[2−5] 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.[6,7] Due to this activity, **1** and its analogues have been postulated to have therapeutic potential for the treatment of extrapyramidal motor disorders and depression.[8]

Proton NMR spectroscopy data[9] and X-ray structural analysis[10] have shown **1** to exist in a type II β-turn. Previously, the peptidomimetic 2-oxo-3(*R*)-[(2(*S*)-pyrrolidinylcarbonyl)amino]-1-pyrrolidineacetamide (**2**) was synthesized by Yu et al.[11] This peptidomimetic of **1**, which utilizes the Freidinger γ-lactam to restrict the ψ_2 torsion angle, was found to be 1 000−10 000 times more potent than **1** in a number of pharmacological assay systems.[11−14] NMR spectroscopy studies[15] suggested this analogue existed in a turn conformation in solution, whereas X-ray analysis[16] showed an extended conformation in the solid state.

The series of compounds **3a**−**3d** and **4a**−**4d** were synthesized in order to investigate the effects of conformationally constraining **1** and peptidomimetic **2**. α,α-Dialkylated glycyl residues were utilized in designing these eight novel mimetics, since work done previously with constraints of this type have shown that the presence of two groups on the α-carbon imposes a marked restriction on the available ϕ_3 and ψ_3 space.[17]



a: $R_1 = R_2 = -CH_2CH_3$ **c**: $R_1 = R_2 = -CH_2CH_2CH_2CH_2-$
b: $R_1 = R_2 = -CH_2CH_2-$ **d**: $R_1 = R_2 = -CH_2CH_2CH_2CH_2CH_2-$

Syntheses

The series of eight peptidomimetics **3a**−**3d** and **4a**−**4d** were synthesized in a similar manner beginning with available α,α-disubstituted amino acids. As shown in Scheme 1, the *N*-*tert*-butoxycarbonyl (Boc)-protected α,α-disubstituted amino acids **5a**−**5d** were converted to amides **6a**−**6d** in excellent yields with ammonia and the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC·HCl).[18] Poorer yields (50%) of the amides were obtained when bromotris(pyrrolidino)-phosphonium hexafluorophosphate (PyBroP)[18] was used as the coupling reagent. Compounds **6a**−**6d** were deprotected with HCl/dioxane to afford the corresponding HCl salts of the amines. The free amines of **6b**−**6d** were

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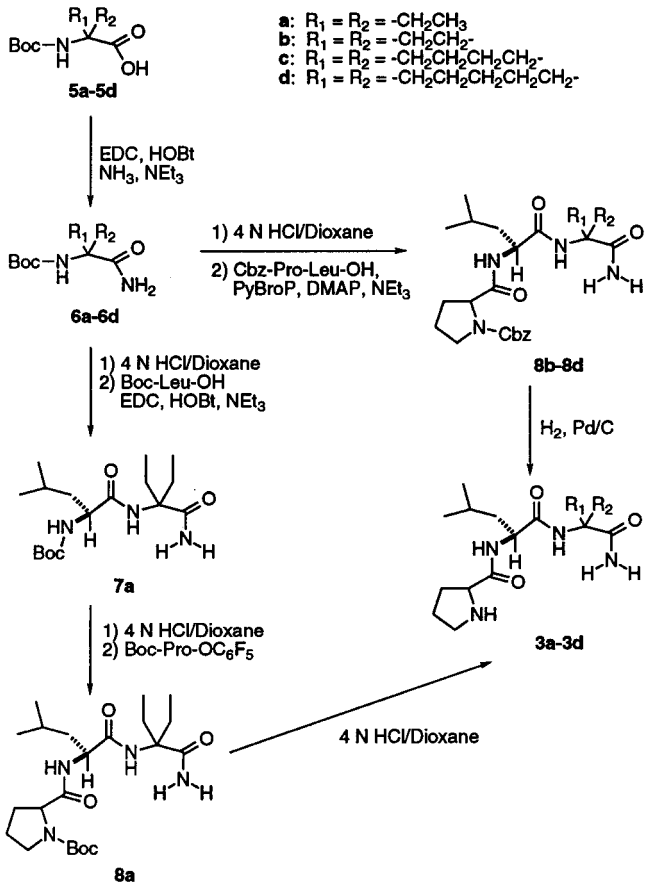
Scheme 1



coupled to *N*-benzyloxycarbonyl-(Cbz)-Pro-Leu-OH to give the protected tripeptides **8b**−**8d**, respectively, while the deprotected derivative of **6a** was coupled to Boc-Leu-OH to give dipeptide **7a**. Coupling reagents EDC·HCl and PyBroP were both utilized in the above coupling reactions to afford either the di- or tripeptides in greater than 50% yields. Dipeptide **7a** was deprotected with HCl/dioxane, and the product obtained was coupled with the pentafluorophenyl ester of Boc-Pro-OH[19] to afford tripeptide **8a** in greater than 80% yields. The Cbz group of **8b**−**8d** and the Boc group of **8a** were removed by hydrogenolysis and HCl/dioxane, respectively, to give the final tripeptides **3a**−**3d**.

Scheme 2 illustrates the synthetic route to peptidomimetics **4a**−**4d**. Boc-protected amides **6a**, **6c**, and **6d** and methyl ester **6b** were deprotected with HCl/dioxane, and the corresponding HCl salts were coupled to Boc-D-Met-OH to afford dipeptides **9a**−**9d**. Freidinger lactam formation was accomplished by stirring these dipeptides in neat iodomethane followed by treatment with NaH.[11,20] The cyclized products **10a**−**10d** were deprotected and then coupled to either Cbz-Pro-OH or Boc-Pro-OH to afford the tripeptides **11a**−**11d** and **12b**. Amidation to afford **13b** or **14b** was accomplished by stirring **11b** or **12b** in a 50% NH_3/MeOH solution for 11 days at 50 °C. Final Pro-Leu-Gly-NH_2 analogues **4a**−**4d** were obtained after either hydrogenolysis or HCl/dioxane treatment of the respective protected precursors. The physical properties of the synthetic intermediates of **3a**−**3d** and **4a**−**4d** are given in Table 1.

Scheme 2

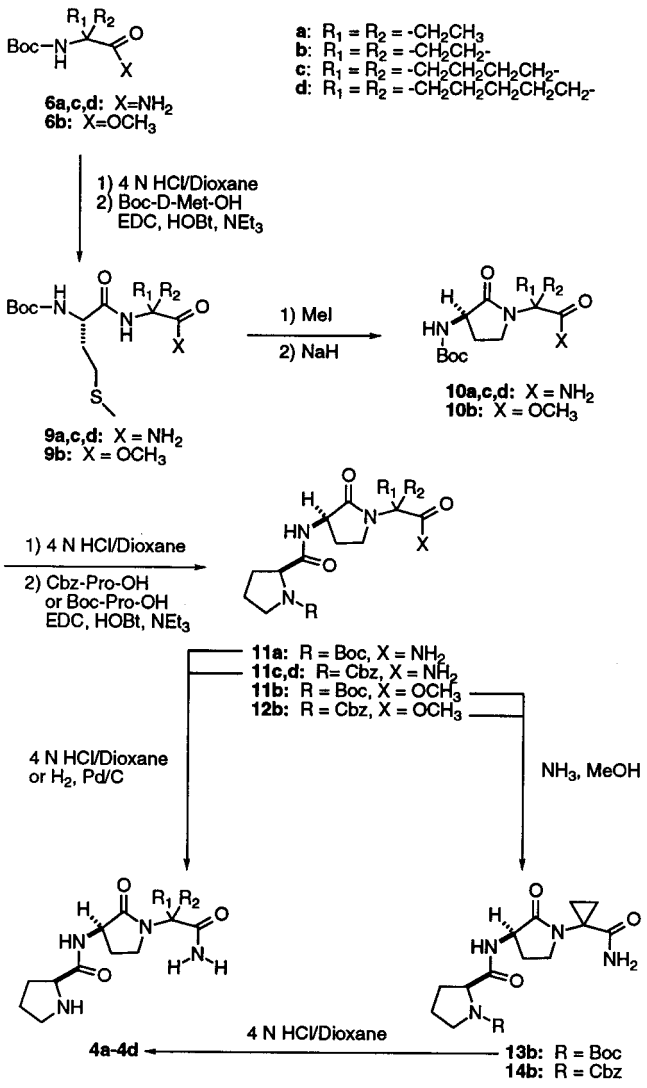


Table 1. Physical Properties of the Synthetic Intermediates of **3a**−**3d** and **4a**−**4d**

compd	yield, %	mp, °C	$[M + H]^+$ [a]	$[\alpha]_D$, deg	formula[b]
6a	92	159−163	231		$C_{11}H_{22}N_2O_3$
7a	63	214−218	345	−20.6 (*c* 0.8, MeOH)	$C_{17}H_{33}N_3O_4$
8b	50	oil	nd	−79.2 (*c* 0.4, MeOH)	nd
8c	50	111−113	473	−84.3 (*c* 0.2, MeOH)	$C_{25}H_{36}N_4O_5$
8d	50	nd	nd	−71.3 (*c* 1.0, MeOH)	nd
9b	60	108−110	347	−28.2 (*c* 1.0, CH_2Cl_2)	$C_{15}H_{26}N_2O_5S$
9c	50	109−111	382	−24.6 (*c* 1.0, CH_2Cl_2)	$C_{16}H_{29}N_3O_4S$
9d	61	98−100	374	−24.6 (*c* 1.0, CH_2Cl_2)	nd
10a	58	86−90	314	+16.1 (*c* 0.4, MeOH)	$C_{15}H_{27}N_3O_4$
10b	43	126−128	299	+39.7 (*c* 0.8, MeOH)	$C_{14}H_{22}N_2O_5$
10c	35	192−194	312	−8.0 (*c* 1.0, CH_2Cl_2)	$C_{15}H_{25}N_3O_4$
10d	60	132−134	343	−15.0 (*c* 1.0, CH_2Cl_2)	$C_{16}H_{27}N_3O_4$
11a	66	118−122	411	−34.7 (*c* 0.63, MeOH)	nd
11b	81	155−157	396	−19.3 (*c* 0.7, MeOH)	$C_{19}H_{29}N_3O_6$
11c	50	92−94	443	−48.0 (*c* 1.0, MeOH)	$C_{23}H_{30}N_4O_5$
11d	50	72−74	457	−48.0 (*c* 1.0, MeOH)	$C_{24}H_{32}N_4O_5$
14b	50	132−136	415	−66.2 (*c* 1.0, MeOH)	$C_{21}H_{26}N_4O_5$

[a] FAB MS *m*/*z*. [b] CHN analyses were found to be within ±0.4% of the calculated data, unless otherwise indicated. nd, not determined.

X-Ray Crystallography

The X-ray crystal structures of **8a** and **14b** were solved and are depicted in Figures 1 and 2, respectively.[21] In the crystals of **8a** there were two unique, but similar, molecules found which defined the unit of

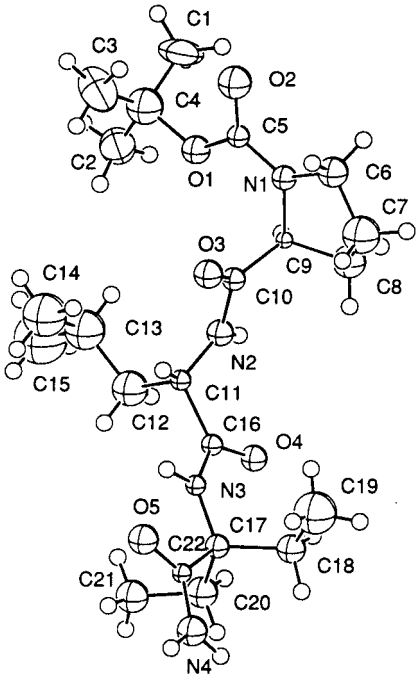


Figure 1. ORTEP drawing of **8a**A with crystallographic numbering system.

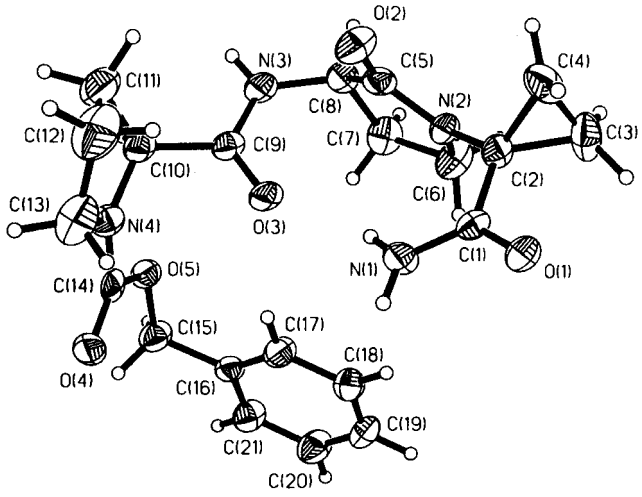


Figure 2. ORTEP drawing of **14b** with crystallographic numbering system.

Table 2. ϕ and ψ Torsion Angles Observed in the Crystal Structures of **8a** and **14b**

	torsion angle, deg			
	ϕ_2	ψ_2	ϕ_3	ψ_3
14b	−49	+134	+85	−4
8a (A)	−136	+139	−176	−176
8a (B)	−124	+145	−177	+177
ideal type II β-turn	−60	120	80	0

pattern. As summarized in Table 2, both solid-state forms for **8a** (A and B) were found to exist in an extended conformation. In contrast, for peptidomimetic **14b**, the ϕ, ψ torsion angles were close to those for an ideal type II β-turn.

CD Spectroscopy

Shown in Figures 3 and 4 are the CD spectra of the leucine-containing compounds **1**, **3a**, and **3c** and the CD spectra of the lactam analogues **2**, **4a**, **4b**, and **4d**,

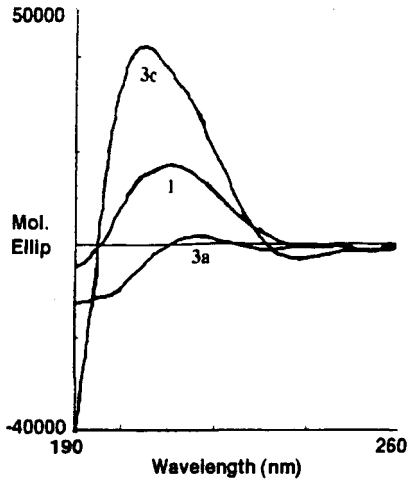


Figure 3. CD spectra of PLG (**1**) and the α,α-dialkylated glycyl analogues **3a** and **3c**.

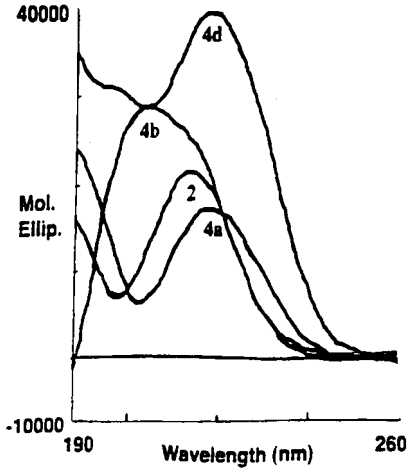


Figure 4. CD spectra of PLG lactam-containing peptidomimetics **2**, **4a**, **4b**, and **4d**.

respectively. Compounds **1**, **3c**, and **4b** exhibited curves of ideal type II β-turns, with broad minima at 230 nm and strong maxima at 208 nm.[22,23] Extended analogue **3a** produced a spectrum with no significant CD signal, indicative of a flexible molecule which exhibits several conformations.[24] The lactam analogues **2**, **4a**, and **4d** produced curves which were shifted from those of the ideal type II β-turn (with maxima around 217 nm). However, such curves have been shown in the literature to represent turn type conformations.[25,26] Incorporation of the lactam constraint changes the amide group environment and takes a secondary amide to a tertiary amide. It can therefore be postulated that the CD spectrum of a lactam would be shifted from that of a typical amide. Circular dichroism previously done on peptides containing α,α-disubstituted amino acids yielded spectra which were suggestive of type II β-turn conformations.[27] These spectra were similar to those obtained in this study.

Pharmacology

The effects of Pro-Leu-Gly-NH_2 analogues **3a**−**3d** and **4a**−**4d** in enhancing rotational behavior induced by apomorphine in the 6-hydroxydopamine-lesioned animal model of Parkinson's disease[13,28] are summarized in Table 3. The analogues were tested at 0.01, 0.1, 1.0, and

Table 3. Effects of PLG Analogues **3a**−**3d** and **4a**−**4d** on Apomorphine-Induced Rotational Behavior in Rats with Unilateral 6-Hydroxydopamine Substantia Nigra Lesions[a]

	% change from control, mean ± SEM			
compd	0.01 μg/kg	0.10 μg/kg	1.0 μg/kg	10.0 μg/kg
2[b]		20	75	191
3a	6 ± 5	31 ± 11	56 ± 15**	1 ± 6
3b	15 ± 10	18 ± 6	8 ± 5	−7 ± 5
3c	−15 ± 6	−1 ± 8	5 ± 2	−26 ± 5
3d	−2 ± 4	14 ± 13	−2 ± 3	−25 ± 6**
4a	2 ± 3	−3 ± 7	17 ± 8	8 ± 14
4b	−6 ± 1	10 ± 4	−8 ± 5	4 ± 4
4c	4 ± 6	−5 ± 2	19 ± 8*	−4 ± 4
4d	7 ± 4	1 ± 4	19 ± 12	−2 ± 6

[a] Apomorphine dose = 0.25 mg/kg ip. Number of contralateral rotations in 10 min expressed as a percentage change from control rotational response ($n = 5$). Statistical difference from the respective control group is indicated as follows: *$p < 0.05$, **$p < 0.01$. Maximal response observed upon PLG administration was found to be 32% at 1 mg/kg.[13,28] [b] Data is from Mishra et al.[13] and is the number of contralateral rotations in 30 min expressed as a percentage change from control rotational response ($n = 5$).

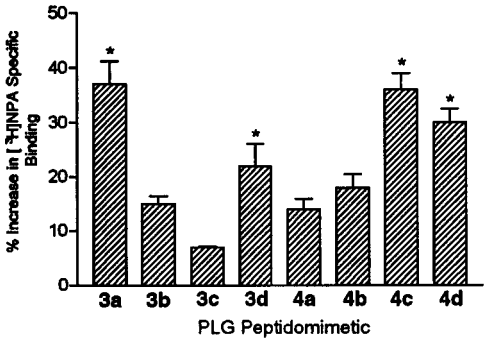


Figure 5. Effect of PLG analogues (0.1 μM) on [^{3}H]-*N*-propylnorapomorphine ([^{3}H]NPA) binding to the dopamine D_2 receptor. *$p < 0.05$ from control.

10.0 μg/kg, ip. Most of the analogues exhibited a bell-shaped dose−response profile, which is characteristic of **1** and its analogues.[6,13] Compounds **3a** and **4c** produced a statistically significant increase in apomorphine-induced rotational behavior at a dose of 1.0 μg/kg. The percent increase for **3a** was 56%, while that for **4c** was 19%. Interestingly, analogue **3d** produced a significant decrease (−25%) in apomorphine-induced rotation at a dose of 10.0 μg/kg. Compound **3c** also produced a decrease at this dose level, but it was not found to be significant.

Analogues **3a**−**3d** and **4a**−**4d** were tested for their ability to increase the binding of agonist *N*-propylnorapomorphine (NPA) to the dopamine D_2 receptor (Figure 5). All of the analogues, except **3c** (∼5%), were shown to increase [^{3}H]NPA specific binding by at least 15% at 0.1 μM. The rank order potency of analogues which exhibited a statistically significant increase in agonist binding was found to be **3a** > **4c** > **4d** > **3d**. Analogue **3a** was the most active compound, increasing [^{3}H]NPA specific binding by 40%. The full dose−response curve for **3a** is shown in Figure 6.

Discussion

α,α-Disubstituted amino acids have demonstrated great versatility as peptide constraints because of the restrictions placed on the residues' ϕ and ψ torsion angles.[17] For example, the diethylglycine (Deg) residue favors formation of a fully extended structure (ϕ and ψ = 180°). In contrast, the 1-aminocyclopropanecarboxylic (Ac_3c) residue favors ϕ and ψ torsion angles of 90° and 0°, respectively and thus promotes a turn conformation. An increase in ring size to the five-membered (Ac_5c) or six-membered (Ac_6c) rings yields residues which promote either turn ($\phi = 90°$, $\psi = 0°$) or helix ($\phi = -60°$, $\psi = -30°$) type structures.

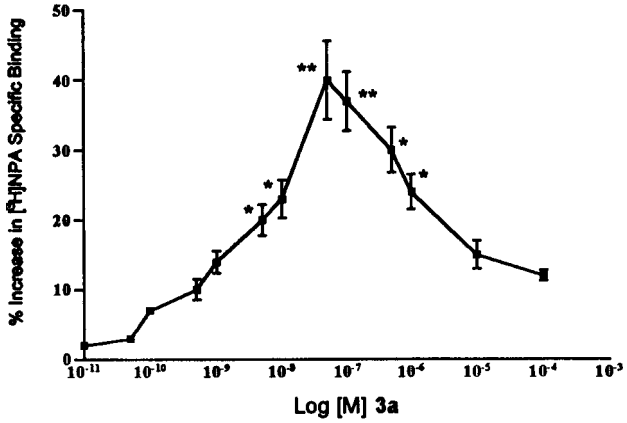


Figure 6. Dose−response effect for **3a** on [^{3}H]-*N*-propylnorapomorphine ([^{3}H]NPA) binding to the dopamine D_2 receptor. *$p < 0.05$, **$p < 0.01$ from control.

Low doses of either **3a** or **4c** significantly potentiated apomorphine-induced rotations (Table 3). The maximal effect observed upon administration of **3a** (56% at 1.0 μg/kg) was about 1.5 times greater than the previously reported maximal response observed upon administration of **1** (32% at 1 mg/kg)[13,28] and occurred at a 1000-fold lower dose. Analogue **4c** (19% at 1.0 μg/kg) was also shown to be more potent, but it produced only about one-half the maximal response of that seen with **1**. Neither analogue **3a** nor **4c** potentiated apomorphine-induced rotations to the degree observed upon administration of peptidomimetic **2**, which showed percentage increases of 191% and 75% at doses of 10 and 1.0 μg/kg, respectively.[13]

Analogues **3a**, **3d**, **4c**, and **4d** produced equal, or greater, percentage increases in [^{3}H]NPA specific binding (Figure 5) compared to that of **1** (24% at 1 μM),[6,7] but at a 10-fold lower dose. In contrast, analogues **3b**, **3c**, **4a**, and **4b** were found to be less active than **1** at 1 μM (data not shown) in increasing the agonist binding to dopamine receptors. Thus, **3a** was the most active compound in increasing apomorphine-induced rotations and [^{3}H]NPA specific binding. In a separate study, **3a** was also found to be the most active of this series in decreasing haloperidol-induced catalepsy.[29] Compound **3d** proved to be an interesting analogue in that at low doses it increased [^{3}H]NPA specific binding and apomorphine-induced rotations, although the latter effect was not shown to be statistically significant. In contrast to the other analogues which lost their modulating activity at high doses, however, **3d** significantly decreased apomorphine-induced rotations suggesting that it may induce an unfavorable conformational change in the D_2 receptor resulting in decreased apomorphine binding.

Our previous studies with conformationally constrained analogues of **1** suggested that its bioactive conformation was a type II β-turn.[11,19,30] Thus, the good activity of **3a** in the tripeptide series **3a**−**3d** was

surprising, since it was predicted that the presence of the diethylglycine residue would promote an extended conformation. Indeed, an X-ray structure of a derivative of **3a**, **8a**, indicated the predicted extended conformation. However, the CD spectrum of **3a** revealed no defined structure indicating that the analogue was quite flexible. This lack of constraint could allow the diethylglycine analogue to adopt the bioactive conformation of **1** at the receptor. What is more difficult to reconcile is the relative inactivity of **3b**−**3d** in comparison to **3a**, since on the basis of the restrictions placed on the ϕ and ψ torsion angles by the cyclic α,α-disubstituted residues one would expect these analogues to be capable of mimicking the postulated bioactive conformation of **1**. Although a previous study showed that cyclic imino acids are tolerated at the C-terminal position of **1**,[31] it is clear that cyclic α,α-disubstituted residues have a detrimental effect. It may be that ethyl side chains of **3a**, which are free to rotate, are able to access hydrophobic binding sites that the cyclic α,α-disubstituted residues cannot.

Combining the γ-lactam constraint with the α,α-disubstituted glycine constraints provided peptidomimetics **4a**−**4d** which showed activity, but none came close to approaching the potency seen with the simple γ-lactam peptidomimetic **2**. Clearly this combination of constraints was detrimental to their activity even though X-ray crystallography and CD spectroscopy indicated that **4a**−**4d** were capable of existing in the postulated type II β-turn bioactive conformation. Interestingly, in this series it was the analogue containing the C-terminal Ac_5c α,α-disubstituted residue, **4c**, that showed the best activity, while the least active compound was **4a** with the diethyl substitution. This profile was opposite of that seen with the α,α-disubstituted tripeptide series **3a**−**3d** suggesting that the two series may be interacting with the Pro-Leu-Gly-NH_2 modulatory site in a different manner. Further studies with a series of Pro-Leu-Gly-NH_2 analogues and lactam peptidomimetics containing flexible, hydrophobic groups at the C-terminal α-carbon should provide some insight on this hypothesis.

Experimental Section

General Aspects. DMF was purchased in Aldrich Sure-Seal bottles, and CH_2Cl_2 was distilled from CaH_2. Thin-layer chromatography was performed on Analtech 250-μm silica gel GF Uniplates and visualized by UV, I_2, and ninhydrin spray (amines). Chromatographic purification on silica gel (Merck, grade 60, 240−400 mesh, 60 Å) was done by gravity methods. Optical rotations were measured on a Rudolph 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 obtained on a GE Omega 300-MHz instrument.

General Deprotection Procedure for the *N*-*tert*-Butoxycarbonyl Group. Compounds **3a**, **4a**, and **4b** were prepared by a general procedure in which *N*-*tert*-butoxycarbonyl-protected tripeptide (1.0 mmol) was dissolved in 4 N HCl/dioxane (10 mL), and the resulting solution was stirred overnight at room temperature. Excess HCl and the dioxane then were removed under aspirator pressure by forming an azeotrope with CH_2Cl_2 (2×).

L-Prolyl-L-leucyl-diethylglycinamide Hydrochloride (3a). Crystallization from EtOH provided 102 mg (74%) of **3a**: mp 158−162 °C; $[\alpha]_D$ −57.8 (*c* 1.25, MeOH); ^{1}H NMR (D_2O) δ 4.30−4.40 (m, 2 H, Pro α-CH, Leu α-CH), 3.30−3.41 (m, 2 H, Pro δ-CH_2), 2.39−2.47 (m, 1 H, Pro β-CH), 1.96−2.10 (m, 5 H, Pro β-CH and γ-CH_2, Leu β-CH_2), 1.72−1.87 (m, 2 H, Deg β-CH_2), 1.53−1.66 (m, 3 H, Deg β-CH_2, Leu γ-CH), 0.91 (d, J = 4.8 Hz, 3 H, Leu δ-CH_3), 0.79 (d, J = 4.8 Hz, 3 H, Leu δ-CH_3), 0.72 (t, J = 7.5 Hz, 6 H, Deg-CH_3); ^{13}C NMR ($CDCl_3$) δ 7.7 (Deg γ-C), 20.8 (Leu δ-C), 22.7 (Pro γ-C), 24.1 (Leu γ-C), 25.3 (Pro β-C), 28.4 (Leu β-C), 30.5 (Deg β-C), 46.6 (Pro δ-C), 54.0 (Leu α-C), 60.2 (Pro α-C), 65.4 (Deg α-C), 169.9 (CONH), 172.0 (CONH), 176.7 ($CONH_2$); FAB MS *m*/*z* 341 $[M + H]^+$. Anal. ($C_{17}H_{33}N_4O_3Cl\cdot 2H_2O$) C, H, N.

2-[3(*R*)-[(2(*S*)-Pyrrolidinylcarbonyl)amino]-2-oxopyrrolidin-1-yl]-2-ethylbutanamide Hydrochloride (4a). Precipitation from MeOH/Et_2O provided 0.11 g (33%) of **4a**: mp 136−141 °C; $[\alpha]_D$ +6.9 (*c* 0.42, MeOH); ^{1}H NMR (D_2O) δ 4.56−4.63 (m, 1 H, Pro α-CH), 4.33−4.38 (m, 1 H, lactam 3-CH), 3.51−3.72 (m, 2 H, lactam 5-CH_2), 3.41−3.45 (m, 2 H, Pro δ-CH_2), 2.41−2.49 (m, 2 H, lactam 4-CH_2), 1.88−2.12 (m, 6 H, Pro γ-CH_2 and β-CH_2, Deg β-CH_2), 1.72−1.83 (m, 2 H, Deg β-CH_2), 0.77−0.85 (m, 6 H, Deg γ-CH_3); ^{13}C NMR (D_2O) δ 7.5, 7.7 (Deg γ-C), 24.5, 24.6 (Deg β-C), 24.9 (Pro γ-C), 25.9 (lactam 4-C), 30.3 (Pro β-C), 44.3 (Pro δ-C), 47.2 (Deg α-C), 52.8 (lactam 5-C), 170.3 (CONH), 174.2 (lactam-CO), 178.7 ($CONH_2$); FAB MS *m*/*z* 311 $[M + H]^+$. Anal. ($C_{15}H_{27}N_4O_3Cl\cdot 2H_2O$) C, H, N.

1-[3(*R*)-[(2(*S*)-Pyrrolidinylcarbonyl)amino]-2-oxopyrrolidin-1-yl]cyclopropane-1-carboxamide Hydrochloride (4b). Precipitation from MeOH/Et_2O provided 190 mg (79%) of **4b**: mp 170−174 °C; $[\alpha]_D$ −7.1 (*c* 0.58, MeOH); ^{1}H NMR (D_2O) δ 4.36−4.42 (m, 2 H, Pro α-CH, lactam 3-CH), 3.35−3.61 (m, 4 H, Pro δ-CH_2, lactam 5-CH_2), 2.02−2.52 (m, 2 H, lactam 4-CH_2), 2.02−2.18 (m, 4 H, Pro γ-CH_2 and β-CH_2), 1.44−1.55 (m, 2 H, Ac_3c β-CH_2), 1.26−1.35 (m, 2 H, Ac_3c β-CH_2); ^{13}C NMR (D_2O) δ 16.1, 17.5 (Ac_3c β-C), 24.4 (Pro γ-C), 25.1 (lactam 4-C), 30.4 (Pro β-C), 38.0 (Pro δ-C), 46.0 (Ac_3c α-C), 47.1 (lactam 5-C), 53.1 (lactam 3-C), 59.1 (Pro α-C), 170.4 (CONH), 176.2 (lactam-CO), 176.3 ($CONH_2$); FAB MS *m*/*z* 281 $[M + H]^+$. Anal. ($C_{13}H_{22}N_4O_3Cl$) C, H, N.

General Deprotection Procedure for the *N*-Benzyloxycarbonyl Group. Compounds **3b**−**3d**, **4c**, and **4d** were made by a general procedure in which a solution of the *N*-benzyloxycarbonyl-protected tripeptide (1.0 mmol) in MeOH (10 mL) containing 5% Pd/C (1 mg) was hydrogenated at 30 psi for 3 h. The solution was filtered through Celite, and solvent was removed from the filtrate under aspirator pressure to yield product which was crystallized from EtOAc/MeOH.

L-Prolyl-L-leucyl-1-aminocyclopropanecarboxamide (3b). Yield = 20 mg (60%): mp 142−144 °C; $[\alpha]_D$ +82.1 (*c* 0.6, MeOH); ^{1}H NMR (D_2O) δ 4.31−4.35 (m, 1 H, Pro α-CH), 4.16 (t, J = 7.8 Hz, 1 H, Leu α-CH), 3.29−3.37 (m, 2 H, Pro δ-CH_2), 2.36−2.40 (m, 1 H, Pro β-CH), 1.90−2.03 (m, 3 H, Pro β-CH, Leu β-CH_2), 1.47−1.60 (m, 4 H, Pro γ-CH_2, Leu γ-CH, Ac_3c β-CH), 1.49−1.75 (m, 1 H, Ac_3c β-CH), 1.02−1.13 (m, 2 H, Ac_3c β-CH), 0.86, 0.83 (d, J = 4.8 Hz, Leu δ-CH_3); ^{13}C NMR (D_2O) δ 17.4 (Ac_3c β-C), 21.8, 22.4 (Leu δ-C), 24.3 (Ac_3c β-C) 30.6 (Leu γ-C), 37.5 (Pro γ-C), 34.6 (Pro β-C), 39.2 (Leu β-C), 47.2 (Pro δ-C), 54.2 (Leu α-C), 60.1 (Pro α-C), 78.2 (Ac_3c α-C), 170.9, 176.8 (CONH), 177.6 ($CONH_2$); FAB HRMS *m*/*z* 311.2107 ($C_{15}H_{26}N_4O_3$ + H^+ requires 311.2085); HPLC ($CHCl_3$/MeOH, 3:1) t_R = 3.9 min.

L-Prolyl-L-leucyl-1-aminocyclopentanecarboxamide (3c). Yield = 30 mg (50%): mp 142−144 °C; $[\alpha]_D$ −74.2 (c 0.6, MeOH); ^{1}H NMR (D_2O) δ 4.23−4.30 (m, 1 H, Pro α-CH), 4.12−4.16 (m, 1 H, Leu α-CH), 3.11−3.25 (m, 2 H, Pro δ-CH_2), 2.27−2.33 (m, 1 H, Pro β-CH), 2.09−2.17 (m, 1 H, Pro β-CH), 1.44−1.91 (m, 13 H, Ac_5c-CH_2, Pro γ-CH_2, Leu γ-CH and β-CH_2), 0.92, 0.86 (d, J = 5.4 Hz, 6 H, Leu δ-CH_3); ^{13}C NMR (D_2O) δ 24.5 (Ac_5c γ-C), 24.9, 25.1 (Leu δ-C), 26.6, 26.7 (Ac_5c β-C), 30.8 (Pro γ-C), 38.1 (Leu γ-C), 40.3 (Leu β-C), 46.8 (Pro β-C), 47.2 (Pro δ-C), 53.3 (Leu α-C), 60.4 (Pro α-C), 67.6 (Ac_5c α-C), 170.0, 174.3 (CONH), 180.4 ($CONH_2$); FAB HRMS *m*/*z* 339.2394 ($C_{17}H_{30}N_4O_3$ + H^+ requires 339.2398); HPLC ($CHCl_3$/MeOH, 3:1) t_R = 4.2 min.

L-Prolyl-L-leucyl-1-aminocyclohexanecarboxamide (3d). Yield = 30 mg (50%): mp 111−116 °C; $[\alpha]_D$ −69.0 (*c* 0.3,

MeOH); ^{1}H NMR (D_2O) δ 4.33−4.42 (m, 2 H, Pro α-CH, Leu α-CH), 3.31−3.40 (m, 2 H, Pro δ-CH_2), 2.38−2.42 (m, 1 H, Pro β-CH), 2.14−2.19 (m, 1 H, Pro β-CH), 1.84−1.97 (m, 3 H, Leu γ-CH and β-CH_2), 1.60−1.70 (m, 9, Ac_6c δ-CH_2, γ-CH_2 and β-CH, Pro γ-CH_2), 1.20−1.29 (m, 3, Ac_6c β-CH_2), 0.88, 0.92 (d, J = 5.4 Hz, 6 H, Leu δ-CH_3); ^{13}C NMR (D_2O) δ 21.6 (Leu δ-C), 21.6 (Ac_6c δ-C), 21.7 (Leu δ-C), 22.4, 24.3 (Ac_6c γ-C), 25.0, 25.2 (Ac_6c β-C), 30.2 (Pro γ-C), 30.6 (Leu γ-C), 33.9 (Leu β-C), 40.2 (Pro β-C), 47.2 (Pro δ-C), 53.7 (Leu α-C), 60.1 (Pro α-C), 60.9 (Ac_6c α-C), 170.3, 174.6 (CONH), 180.7 ($CONH_2$); FAB HRMS m/z 353.2545 ($C_{16}H_{32}N_4O_3$ + H^+ requires 353.2554); HPLC ($CHCl_3$/MeOH, 3:1) t_R = 3.7 min.

1-[3(*R*)-[(2(*S*)-Pyrrolidinylcarbonyl)amino]-2-oxopyrrolidin-1-yl]cyclopentane-1-carboxamide (4c). Yield = 6 mg (85%): mp 142−144 °C; $[\alpha]_D$ −80.5 (c 0.6, MeOH); ^{1}H NMR (D_2O) δ 4.38−4.65 (m, 1 H, Pro α-CH), 4.06−4.17 (m, 1 H, lactam 3-CH), 3.55−3.79 (m, 3 H, Pro δ-CH_2, lactam 5-CH), 3.28−3.38 (m, 1 H, lactam 5-CH), 3.14−3.23 (m, 1 H, Pro β-CH), 2.29−2.57 (m, 2 H, Pro β-CH, lactam 4-CH), 2.16−2.23 (m, 4 H, Pro γ-CH_2, lactam 4-CH, Ac_5c β-CH), 1.93−2.10 (m, 3 H, Ac_5c β-CH and γ-CH_2), 1.64−1.77 (m, 4 H, Ac_5c γ-CH_2); ^{13}C NMR (D_2O) δ 24.3, 24.5 (Ac_5c γ-C), 24.5, 25.0 (Ac_5c β-C), 30.5 (Pro γ-C), 36.0 (Pro β-C), 38.3 (lactam 4-C), 40.0 (Pro δ-C), 47.1 (lactam 5-C), 53.5 (lactam 3-C), 60.1 (Pro α-C), 67.6 (Ac_5c α-C), 170.3 (CONH), 174.7 (lactam-CO), 179.9 ($CONH_2$); FAB MS m/z 309 $[M + H]^+$. Anal. ($C_{15}H_{24}N_4O_3$) C, H, N.

1-[3(*R*)-[(2(*S*)-Pyrrolidinylcarbonyl)amino]-2-oxopyrrolidin-1-yl]cyclohexane-1-carboxamide (4d). Yield = 30 mg (86%): mp 111−115 °C; $[\alpha]_D$ −50.5 (c 1.0, MeOH); ^{1}H NMR (D_2O) δ 4.95−5.12 (m, 1 H, Pro α-CH), 4.37−4.43 (m, 1 H, lactam 3-CH), 3.44−3.80 (m, 4 H, Pro δ-CH_2, lactam 5-CH_2), 2.84−2.98 (m, 2 H, Pro β-CH_2), 1.76−2.38 (m, 10 H, Pro γ-CH_2, lactam 4-CH_2, Ac_6c δ-CH_2 and γ-CH_2), 1.42−1.54 (m, 4 H, Ac_6c β-CH_2); ^{13}C NMR (D_2O) δ 22.4 (Ac_6c δ-C), 22.6, 25.2 (Ac_6c γ-C), 25.4, 25.6 (Ac_6c β-C), 31.0 (Pro γ-C), 31.7 (lactam 4-C), 32.5 (Pro β-C), 43.8 (lactam 5-C), 47.0 (Pro δ-C), 52.9 (lactam 3-C), 60.6 (Pro α-C), 64.5 (Ac_6c α-C), 175.3 (CONH); 176.4 (lactam-CO), 179.3 ($CONH_2$); FAB MS m/z 323 $[M + H]^+$. Anal. ($C_{16}H_{26}N_4O_3$) C, H, N.

General Coupling Procedure with 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (EDC·HCl). Compounds **6a**, **7a**, **11a**, and **11b** were made by the following general procedure**.** In a dry flask, the *N*-*tert*-butoxycarbonyl-protected amino acid (1.15 mmol), the HCl salt of either a C-terminal protected ester or amide (1.0 mmol), and HOBt·H_2O (1.15 mmol) were dissolved in either CH_2Cl_2 or DMF. The solution was cooled to −78 °C in a dry ice/acetone bath after which NEt_3 (2.0 mmol) and EDC·HCl (1.15 mmol) were added. The mixture was stirred at a −78 °C for 30 min and then warmed to room temperature whereupon the reaction was allowed to proceed for 2 days. When DMF was used as the solvent, it was removed under high vacuum and the residue which remained was dissolved in EtOAc. The solution was washed with 1 M $NaHCO_3$, 10% citric acid, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under aspirator pressure. The crude product was purified by either crystallization (**6a**, CH_2Cl_2/MeOH; **7a**, EtOAc/MeOH) or silica gel column chromatography (**11a**, CH_2Cl_2/MeOH, 10:1; **11b**, CH_2Cl_2/MeOH, 15:1).

***N*-*tert*-Butoxycarbonyl-L-prolyl-L-leucyl-diethylglycinamide (8a).** In a dry flask under nitrogen, the HCl salt of the C-terminal amide **7a** (1.0 mmol) was dissolved in CH_2Cl_2. Boc-L-proline pentafluorophenyl ester (1.0 mmol) was added to the solution whereupon the solution was cooled to −78 °C with a dry ice/acetone bath. NEt_3 (1.0 mmol) then was added after which the reaction was allowed to warm to room temperature where it was kept for 2 days. The CH_2Cl_2 was removed under aspirator pressure, and the residue obtained was dissolved in EtOAc. The EtOAc solution was washed successively with 1 M $NaHCO_3$, 10% citric acid, water, and brine. The organic layer then was dried over $MgSO_4$, filtered, and concentrated under aspirator pressure. The crude product was purified by crystallization from EtOAc/MeOH to give 106 mg (88%) of crystals: mp 219−222 °C; $[\alpha]_D$ −67.7 (c 0.51, MeOH). Anal. ($C_{22}H_{40}N_4O_5$) C, H, N.

General Coupling Procedure with Bromotris(pyrrolidino)phosphonium Hexafluorophosphate (PyBroP). Compounds **8b**−**8d**, **9b**−**9d**, **11c**, and **11d** were prepared by the following general procedure. In a dry flask, the *N*-*tert*-butoxycarbonyl-protected amino acid (1.10 mmol) and the HCl salt of either a C-terminal protected amide or ester (1.0 mmol) were dissolved in CH_2Cl_2. PyBroP (1.0 mmol) and DMAP (0.01 mmol) then were added to the solution. The mixture was cooled in an ice bath to 0 °C, and then diisopropylethylamine (3.0 mmol) was added. The reaction was allowed to proceed for 2 days, after the solution to came to room temperature. The solution was washed with 10% citric acid, 1 M $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under aspirator pressure whereupon the crude product was purified by either crystallization (**8c**, EtOAc/hexanes; **9c**, EtOAc/hexanes; **9d**, EtOAc/hexanes; **11c**, EtOAc/hexanes; **11d**, EtOAc/hexanes) or silica gel column chromatography (**8b**, CH_2Cl_2/MeOH, 10:1; **8d**, CH_2Cl_2/MeOH, 10:1; **9b**, EtOAc/hexanes, 1:1).

General Cyclization Procedure for Formation of the Freidinger Lactam Ring. Lactams **10a**−**10d** were synthesized by the following general procedure. In a dry flask, MeI (10 mL) and DMF (2 mL) were added to a Boc-D-methionine dipeptide (**9a**−**9d**; 1.0 mmol). The solution was stirred for 1 day whereupon the excess MeI was completely removed under aspirator pressure by formation of an azeotrope with CH_2Cl_2 (3×). To the sulfonium iodide in DMF was added CH_2Cl_2 to double the volume. The solution was cooled in an ice bath to 0 °C, and NaH (60% dispersion in mineral oil, 2.0 mmol) was added in one portion. The reaction was stirred at 0 °C for 2 h, and then the mixture was allowed to warm to room temperature and react overnight. The solvents were removed under reduced pressure, and the residue remaining was dissolved in EtOAc. Solid citric acid (2.0 mmol) was added, and the mixture was allowed to stir for 10 min. The solution was washed with 10% citric acid, 1 M $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under aspirator pressure after which the crude product was purified by crystallization (**10a**, EtOAc/MeOH; **10b**−**10d**, EtOAc/hexanes).

General Amidation Procedure. Compounds **13b** and **14b** were prepared by reacting the corresponding protected tripeptide methyl ester (1.0 mmol) in 50% NH_3/MeOH (10 mL) at 50 °C for 4 days. After the MeOH and excess NH_3 were removed by evaporation, the product was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) in the case of **13b** and by crystallization (EtOAc/MeOH) in the case of **14b**.

X-ray Diffraction. Yellowish, flat crystals of **8a** were grown from EtOAc/MeOH. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu Kα radiation (λ = 1.541 78 Å). The data were collected at a temperature of 173(1) K using $\omega - 2\theta$ scan technique. Intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SHELXS86[32] and expanded using Fourier techniques.[33] All calculations were performed using the teXsan crystallographic software package.[34] Due to the fact that the crystal was extremely thin, the number of observed reflections was too small to support a complete anisotropic refinement. Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined.

Colorless, prism crystals of **14b** were grown from EtOAc/MeOH. All measurements were made on a Siemens SMART Platform CCD diffractometer at 173(2) K using the hemisphere collection technique. The structure was solved and refined by direct methods using SHELXTL-Plus V5.0.[35] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters.

Circular Dichroism Studies. The peptidomimetics were dissolved in 50 mM potassium phosphate buffer solution (pH = 5.4) with the concentrations of the samples studied ranging

from 500 to 880 μM. CD spectra were measured on a JASCO J-710 spectropolarimeter.

Pharmacological Assays. Evaluation of the effects of **3a**−**3d** and **4a**−**4d** on apomorphine-induced rotational behavior in rats with unilateral 6-hydroxydopamine lesions in the substantia nigra was conducted as described previously.[13] Measurement of the enhancement of [^{3}H]-*N*-propylnorapomorphine binding to the dopamine D_2 receptor was performed as described by Srivastava et al.[7]

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Supporting Information Available: X-ray crystallographic data including tables of positional parameters, bond distances, and bond angles for **8a** and **14b** and ^{1}H and ^{13}C NMR data for the synthetic intermediates of **3a**−**3d** and **4a**−**4d**. This information is available free of charge via the Internet at http://pubs.acs.org.

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