A Method for Designing Conformationally Restricted Analogues Based on Allylic Strain: Synthesis of a Novel Class of Noncompetitive NMDA Receptor Antagonists Having the Acrylamide Structure

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A series of conformationally restricted analogues of milnacipran, a weak NMDA receptor antagonist, were designed by a method based on allylic strain. The conformational analysis study showed that the allylic-strain-based conformational restriction indeed occurred and that the affinity for the NMDA receptor was efficiently improved by the conformational restriction.

Introduction

Neurotransmitters such as serotonin and acetylcholine perform many functions because of their impressive conformational flexibility to bind several receptor subtypes in their various conformations. For example, the conformation of a transmitter binding to a receptor subtype, i.e., the bioactive conformation for a subtype, may be different from those for other receptor subtypes. Accordingly, one can expect to get high selectivity by controlling the conformation of the substrate for a certain target receptor subtype. Therefore, the synthesis of conformationally restricted analogues of a lead compound often results in improvement of the specific binding affinity for the target molecule.[1] Restricting the conformation of a biologically active compound is also effective in determining the bioactive conformation.[1c]

In the design of conformationally restricted analogues, it is essential that the analogues should be as similar as possible to the parent compound in size, shape, and molecular weight.[1a] Conformationally restricted analogues have usually been designed and synthesized by introducing bulky cyclic moieties into the lead compounds. Consequently, the chemical and physical properties of these analogues can be quite different from those of the original leads. Because of the small and rigid ring structure, cyclopropane is likely to be effective in restricting the conformation of a molecule without significantly changing the chemical and physical properties of the lead compound.[2] We recently devised a new method for restricting the conformation of cyclopropane derivatives based on the "cyclopropylic strain".[3,4] Adjacent substituents on a cyclopropane ring exert significant mutual steric repulsion, because they are fixed in the eclipsed orientation, which we call "cyclopropylic strain". Consequently, conformations of the substituents on a cyclopropane ring can be restricted by the steric effect of adjacent substituents, especially when they are bulky, as indicated in Figure 1.[3]

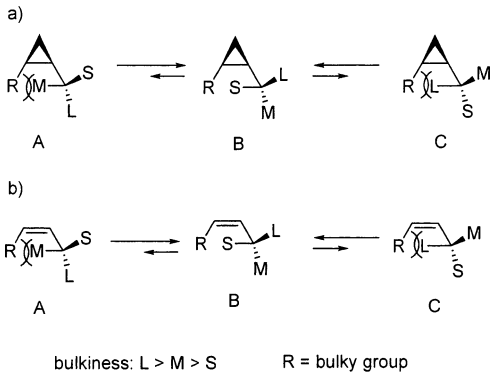

Figure 1. Conformational restriction based on the cyclopropylic strain (a) and the allylic strain (b).

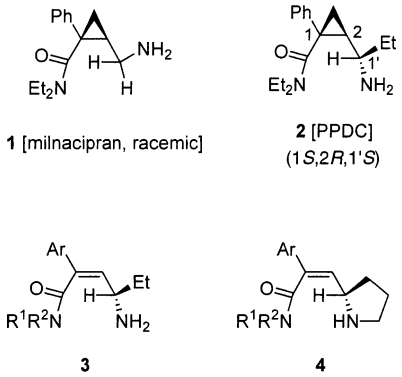

Figure 2. Structure of milnacipran and its conformationally restricted analogues.

Milnacipran (**1**, Figure 2) a clinically effective antidepressant due to competitive inhibition of the reuptake of serotonin (5-HT) and noradrenaline in the central nervous system, is also recognized as a noncompetitive NMDA receptor channel blocker.[4a,5] Although the binding affinity of milnacipran for the NMDA receptor is not high enough, it may be a desirable lead for an efficient NMDA receptor antagonist, since its structural feature is clearly different from those of the known antagonists showing serious side effects and its clinical studies have shown that it can be transported to the brain.[4f] The cyclopropylic-strain-based method has been successfully applied to the design of the conformational restriction

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of milnacipran to result in the development of a new class of NMDA receptor antagonists, PPDC (**2**, Figure 2).[4] PPDC binds to the NMDA receptor in an agonist-independent manner, whereas the binding affinities of known noncompetitive NMDA receptor antagonists are affected by agonist concentration,[4c] and the release of PPDC and the previous noncompetitive antagonists, such as MK-801, from their binding sites was quite different with respect to their dependence on the direction of ionic currents.[4c] Furthermore, the NMDA receptor subtype selectivity of PPDC was shown to be different from those of the previous antagonist.[4e] The conformation of the aminomethyl moiety of PPDC, which is essential for the biological activity,[5] proved to be restricted to the B conformer in Figure 1a by X-ray crystallographic, ^{1}H NMR, and computational analyses.[3] However, one drawback of this conformational restriction method with the cyclopropylic strain is that the synthesis of the target compounds is rather troublesome because of the contiguous three asymmetric carbons.

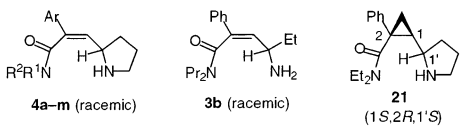
On the basis of these findings and considerations, we newly designed the conformationally restricted analogues of milnacipran based on allylic strain to develop efficient NMDA receptor antagonists. In this report, we describe the results of these studies.

Result and Discussion

Design of the Compounds Using the Allylic-Strain-Based Conformational Restriction Method. We speculated that the conformational restriction, similar to the above-mentioned method using a cyclopropane ring shown in Figure 1a, might possibly occur when the cyclopropane ring is replaced with an ethylene group, since the cyclopropane ring system is known to have a chemical and structural feature similar to a C−C double bond.[6] It is known that, in the 3-disubstituted allylic system, the minima in conformational energy are given by Figure 1b with one substituent (or proton) in the allylic position eclipsing the double bond.[7] Accordingly, the adjacent cis-substituents on an alkenyl bond mutually exert quite significant steric repulsion because of their eclipsed conformation. This kind of steric repulsion is known as "allylic strain",[7,8] which is often the determining factor for regio- and/or stereoselectivity in organic reactions.[7,9] Conformation of the allylic position can be restricted to avoid allylic strain, as shown in Figure 1b,[10] as in a cyclopropane ring (Figure 1a). Therefore, we assumed that an ethylene group could be used as a conformational restriction unit similar to the cyclopropane ring in our previous study.[3,4] On the other hand, the synthesis of these allylic strain-based conformationally restricted analogues would be easier than those of the corresponding cyclopropane-based analogues having three contiguous asymmetric carbons.

To test this hypothesis and also to develop novel NMDA receptor antagonists, we designed the allylic strain-based acrylamide-type analogues of milnacipran, **3**, and **4** (Figure 2). The conformation of **3** and **4** can be restricted by an alkyl group introduced at the α-position to the amino function, which is essential for binding to the NMDA receptor,[5] due to steric repulsion with the *N*,*N*-diethylcarbamoyl group. Accordingly, their conformations can be restricted to the conformer B, as shown in Figure 1b. If this is indeed true, in these acrylamide-type analogues, the three important functional groups, i.e., the phenyl, carbamoyl, and amino groups, should assume the three-dimensional arrangement similar to that in PPDC. Thus, a new acrylamide-type NMDA receptor antagonist would be produced.

Table 1. Binding Affinity of Compounds for the NMDA Receptor



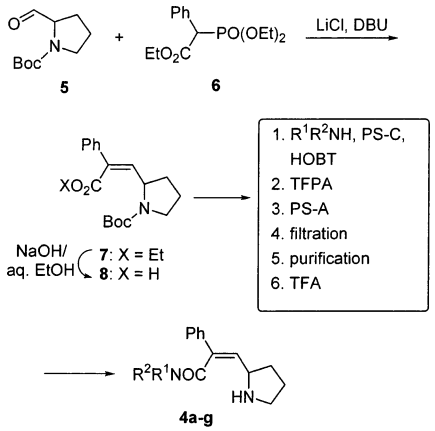
compound	R^1	R^2	Ar	receptor binding[a] (IC_{50}, μM)
1 (milnacipran, racemic)				6.3 ± 0.3
2 (PPDC, 1*S*,2*R*,1'*S*))				0.20 ± 0.02
21 (1*S*,2*R*,1'*S*))				1.0 ± 0.2
4a	Et	Et	Ph	3.6 ± 1.0
4b	Pr	Pr	Ph	0.54 ± 0.10
4c	Bu	Bu	Ph	4.2 ± 0.06
4d	2-Me-allyl	Et	Ph	0.52 ± 0.30
4e	Pr	$cPrCH_2$	Ph	0.74 ± 0.11
4f	$(CH_2)_6$-		Ph	16 ± 0.4
4g	-$(CH_2)_2$-NH-$(CH_2)_2$-		Ph	>1000
4h	Pr	Pr	3-Me-Ph	1.1 ± 0.4
4i	Pr	Pr	4-Me-Ph	>1000
4j	Pr	Pr	2-F-Ph	1.7 ± 0.6
4k	Pr	Pr	3-F-Ph	0.42 ± 0.07
4l	Pr	Pr	4-F-Ph	13 ± 4.3
4m	Pr	Pr	4-MeO-Ph	160 ± 7
3b	Pr	Pr	Ph	0.53 ± 0.16

[a] Assay was done with cerebral cortical synaptic membrane of rats using [^{3}H]MK-801.

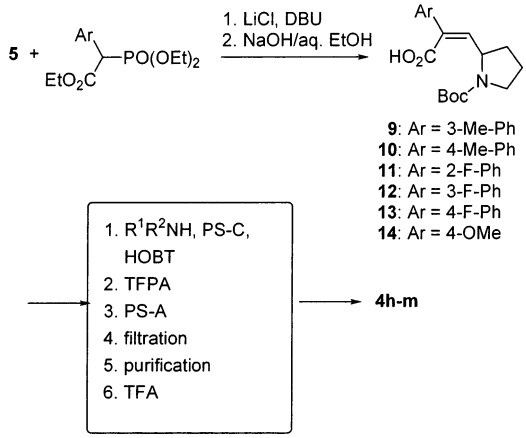
The NMDA receptor, one of the ionotropic glutamate receptor subtypes, is associated with various neurodegenerative disorders.[11a] A number of studies have indicated that the competitive and noncompetitive antagonists are effective in experimental models of epilepsy and stroke.[11] However, clinical studies of these NMDA receptor antagonists have been unsuccessful.[11] Noncompetitive inhibitors, such as the channel blocker MK-801, have had serious behavioral effects[12] and have caused neuronal vacuolization,[13] while competitive inhibitors were often inactive in vivo because of poor transport to the brain.[14] Although the glycine site antagonists and subtype selective antagonists, such as ifenprodil, have also been developed, their pharmacological effects in the clinical studies are unclear.[11] Consequently, the development of another type of efficient NMDA receptor antagonist for use in the treatment of epilepsy, stroke, Huntington's, and/or Parkinson's diseases is desired.

Chemistry. It was important to determine whether the allylic-strain-based conformational restriction occurs and also whether the acrylamide-type compounds actually bind to the NMDA receptor. Therefore, we planned to prepare a series of the acrylamide-type conformationally restricted analogues, the structures of which are shown in Table 1, as racemates because of the ease of synthesis. As shown in Schemes 1 and 2, we synthesized the target compounds via *Z*-alkenes, which could be prepared by the Horner−Wadsworth−Emmons (HWE) reaction.[15]

Scheme 1



Scheme 2

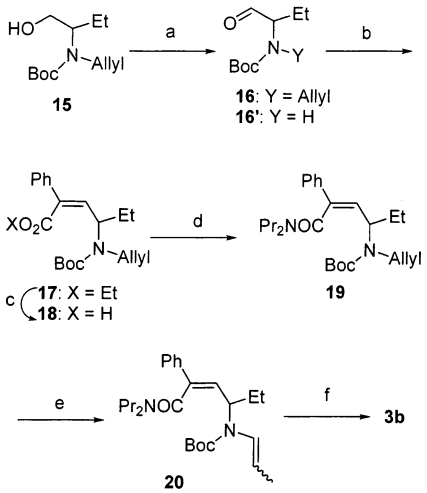


We first examined the HWE reaction of *N*-Boc-prolinal **5**, which was easily prepared from Boc-proline, and triethyl phenylphosphonoacetate (**6**) (Scheme 1). The HWE reaction conditions using LiCl/DBU reported by Masamune *et al.*[16] were employed to give the *Z*-alkene **7** with excellent stereoselectivity (*Z*/*E* = 11/1). After hydrolysis of **7**, which provided the carboxylic acid **8**, the amidation was carried out using a solution-phase combinatorial technique with various commercially available amines. As shown in Scheme 1, the procedure consisted of (1) mixing the carboxylic acid, the resin-bound carbodiimide (PS−C), 1-hydroxybenzotriazole (HOBT), and the amine in CH_2Cl_2, (2) addition of tetrafluorophthalic anhydride (TFPA) to trap the excess amine as its salt, (3) addition of resin-bound amine (PS-A) to trap the unreacted carboxylic acid and TFPA-derived carboxylic acids, (4) filtration of the resins, (5) silica gel column chromatography, if needed, and (6) deprotection of the Boc group with TFA. After this sequence, evaporation of the TFA gave the pyrrolidine-type analogues **4a**−**g** with >95% purity on HPLC.

As mentioned below, among the pyrrolidine-type analogues **4a**−**g**, the *N*,*N*-dipropylamide **4b** was shown to have potent binding affinity for the NMDA receptor. We synthesized a series of dipropylamide-type analogues **4h**−**m** having a substituent on the phenyl group by the same procedure via the HWE reaction products **9**−**14** (Scheme 2).

We next tried to synthesize the ethyl congener **3b** by a method similar to the one described above (Scheme 3). However, the HWE reaction of **6** and *N*-Boc-2-aminobutanal **16′** under Masamune conditions did not give the desired *Z*-alkene but only the corresponding *E*-alkene. Although a variety of HWE conditions were examined, the desired *Z*-alkene was not obtained. We found that when the fully protected aminoalkanal **16** was used, the HWE reaction gave the desired *Z*-alkene **17**, although the yield was low. Hydrolysis of the alkene **17** followed by condensation with dipropylamine gave the *N*,*N*-dipropylamide **19**, which was further treated with $RuHCl(CO)(PPh_3)_3$ [17] to provide **20**. Acidic removal of the protecting groups of **20** resulted in **3b**.

Scheme 3[a]



[a] Reagents: (a) Swern oxidation; (b) **6**, LiCl, DBU; (c) NaOH/aq EtOH; (d) Pr_2NH, EDC, BOP, TEA; (e) $RuHCl(CO)(PPh_3)_3$; (f) aq TFA.

Binding Affinity for the NMDA Receptor. The synthesized compounds were evaluated for their binding affinity for the NMDA receptor of cerebral cortical synaptic membranes from rats with [^{3}H]MK-801 as a radioligand.[18] As seen in Table 1, most of the compounds showed the expected binding affinity for the NMDA receptor. Initially, we tested the effect of the carbamoyl alkyl substituents of the pyrrolidine-type analogues **4a**−**g** on the affinity. The *N*,*N*-diethylamide analogue **4a** showed weak activity (IC_{50} = 3.6 ± 1.0 μM) similar to the parent milnacipran (IC_{50} = 6.3 ± 0.3 μM), which was 18 times less active than PPDC (**2**, IC_{50} = 0.20 ± 0.02 μM), although these have the same *N*,*N*-diethylcarbamoyl moiety. Although the racemic *N*,*N*-diethylamide **4a** was somewhat weaker than the corresponding cyclopropane-type chiral congener **21** (IC_{50} = 1.0 ± 0.2 μM),[4f] it may be because **21** is the eutomer. The affinity of the *N*,*N*-dipropylamide **4b** (IC_{50} = 0.54 ± 0.10 μM)[19,20] was about 7 times greater than those of **4a** and the *N*,*N*-dibutylamide **4c**. The *N*-(2-methylallyl)-*N*-ethyl amide **4d** and the *N*-propyl-*N*-cyclopropylmethyl amide **4e** showed efficient IC_{50} values of 0.52 ± 0.30 and 0.74 ± 0.11 μM, which were similar to those of the *N*,*N*-dipropylamide **4b**. The cyclic amides **4f** and **4g** showed only weak activity, with the piperazine-derived amide **4g** being inactive. Therefore, bulkiness of the carbamoyl moiety is likely to significantly affect their affinity.

On the basis of the binding affinities described above, the compounds having an *N*,*N*-dipropylcarbamoyl group were synthesized for further studies. The effect of the substituent on the benzene ring was next examined. All of the para-substituted derivatives showed low affinity. Compounds **4h**, with a *m*-methyl group, and **4j**, with

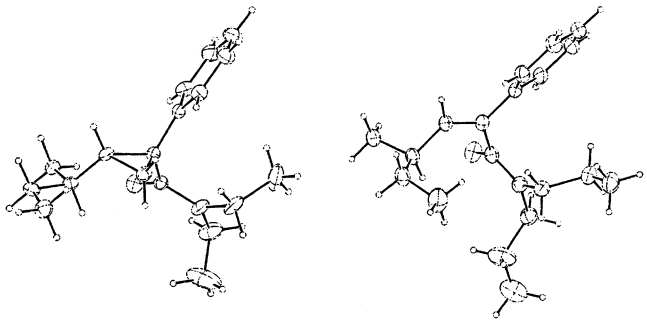


Figure 3. X-ray crystallographic structures of PPDC (**2**, left) and **3b** (right).

an *o*-fluoro group, showed moderate IC_{50} values of 1.1 ± 0.4 and 1.7 ± 0.6 μM, respectively. In this series, the *m*-fluoro compound **4k** showed the strongest affinity (IC_{50} = 0.42 ± 0.07 μM). These results suggested that although the presence of a substituent at the *ortho*- or *meta*-position of the 2-phenyl moiety is tolerated in the binding to the receptor, a para-substituent is likely to disturb the binding, probably due to a steric effect in these acrylamide-type derivatives.

On the other hand, the acyclic primary amino compound **3b**, which is the ethylene congener of the cyclopropane-type compound PPDC, showed a high affinity (IC_{50} = 0.53 ± 0.16 μM) comparable not only to **4b** but also to PPDC.

As described above, the acrylamide-type conformationally restricted analogues showed greater binding affinity to the NMDA receptor than the parent milnacipran, and the affinity was comparable to that of PPDC.

Conformational Analyses. We analyzed the conformation of the allylic strain based conformational restriction analogue **3b** by X-ray crystallography. The X-ray crystallographic structures of **3b** as well as PPDC (**2**)[3] are shown in Figure 3. The crystallographic structure of **3b** clearly demonstrates that it is restricted to the conformation corresponding to the conformer B in Figure 1b, in which the aminopropyl moiety is arranged to avoid the allylic strain, as we hypothesized. When the structure is compared with that of PPDC, the ethylene moiety proved to be structurally equivalent to the cyclopropane in PPDC, which determines the orientation of the three important functional groups, i.e., the phenyl, carbamoyl, and amino groups.

The calculations based on the modified Karplus equation[21] with the coupling constant (9.9 Hz) between the vinylic and allylic protons of **3b** suggested that the $H_{allylic}-C-C-H_{vinylic}$ torsion angle is 168° (or 192°), in which the two protons are trans, similar to the $H_{allylic}-C-C-H_{vinylic}$ torsion angle (178.5° ± 5°) obtained by the X-ray crystallographic analysis of **3b**. These results suggest that the conformation detected in the solid state would also be stable in solution.

We also carried out conformational analysis by theoretical calculations. Thus, the Monte Carlo calculations of PPDC and compound **3a**, which has the same *N*,*N*-diethylcarbamoyl group as PPDC, were performed by the MacroModel v6.5 program.[22] As shown in Figure 4, both calculated structures of PPDC and **3a** are very similar.[3] Moreover, We calculated the rotational barrier around the $H_{allylic}-C-C-H_{vinylic}$ dihedral angle of **3a**. The dihedral angle of the minimum energy conformer

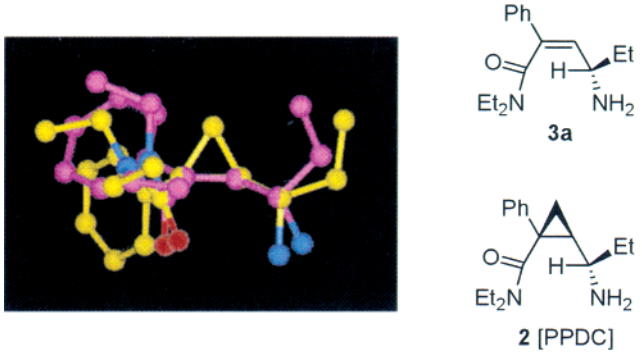


Figure 4. Superimposition of the calculated structures of PPDC (**2**, yellow) and **3a** (magenta).

of **3a** obtained by the above calculations was rotated from 0° to 360° at 30° intervals, the conformations of which were optimized. The minimum-energy conformer was observed around 180°, where the dihedral angle was similar to those observed in the above X-ray and NMR analyses. Although two other local minimum energy values were observed around 60° and 300°, these were more than 3.5 kcal/mol higher compared with the minimum energy at 180°. These results support our hypothesis of the allylic-strain-based conformational restriction.

These conformational analyses showed that the allylic-strain-based conformational restriction actually occurred. Thus, the conformational results together with the above biological results suggest that the allylic-strain-based method can be applicable for the design of various conformational restriction analogues of pharmacologically active compounds.

Conclusion. A method for designing conformationally restricted analogues based on allylic strain, which can be an alternative for the efficient "cyclopropylic-strain"-based method, was devised and applied to the design of a series of conformationally restricted analogues of milnacipran. Compound **3b**, the ethylene congener of the cyclopropane derivative PPDC (**2**), showed high affinity for the NMDA receptor, comparable to that of PPDC, and the structural analysis confirmed that the conformational restriction took place as we had hypothesized. Thus, the method can be effective for conformational restriction of various pharmacologically active compounds.

Experimental Section

The NMR spectra were recorded with a JEOL EX-270 or AL-300 spectrometer with tetramethylsilane as an internal standard. Chemical shifts were reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), q (quartet), m (multiplet), or br (broad). MASS spectra were measured on a JEOL JMS-SX102 spectrometer. Purity measurement was performed by Shimadzu LC-10Avp series chromatograph (column:, YMC-pack A-303; solvent, 0.1% trifluoroacetic acid−MeCN; flow rate, 1.0 mL/min; detect, 254 nm). Thin-layer chromatography was done on Merck silica gel coated plates ($60F_{254}$). Silica gel chromatography was done with Merck silica gel 5715.

(±)-(*Z*)-2-Phenyl-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (8). To a solution of oxalyl chloride (1.3 mL, 15 mmol) in CH_2Cl_2 (30 mL) was added slowly a mixture of DMSO (2.3 mL, 32 mmol) at −78 °C under argon, and the mixture was stirred at the same temperature for 30 min. To the resulting mixture was added slowly *N*-*tert*-butoxycarbonylpyrrolidinemethanol (2.5 g, 12 mmol) in CH_2Cl_2 (20 mL). The resulting solution was stirred at the same

temperature for 1 h, and then Et_3N (8.6 mL, 62 mmol) was added at −78 °C. The mixture was further stirred at the same temperature for 20 min and 0 °C for 40 min. After addition of water, the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous saturated NH_4Cl, aqueous saturated Na_2CO_3, and brine, dried ($MgSO_4$), and evaporated to give crude **5** (2.7 g) as an oil, which was used immediately in the next reaction. A mixture of LiCl (0.62 g, 15 mmol), triethyl 2-phenylphosphonoacetate **6** (4.0 g, 13 mmol), and DBU (2.2 mL, 15 mmol) in MeCN (100 mL) was stirred at room temperature under an atmosphere of argon for 10 min, and then the crude **5** (2.7 g) in MeCN (20 mL) was added. After stirring of the mixture at room temperature overnight, aqueous saturated NH_4Cl and $CHCl_3$ were added. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; hexane/EtOAc 17:3) to give **7** (*Z*/*E* = 11:1, 2.5 g, 49%) as an oil. The *Z*/*E* ratio was determined by ^{1}H NMR spectrum (the peak areas of the hydrogen adjacent to the amino groups in both isomers).[24]

To a solution of **7** (*Z*/*E* = 11:1, 2.5 g, 7.4 mmol) in EtOH (43 mL) was added 1 N NaOH (43 mL) at room temperature, and the mixture was heated at 70 °C overnight. After addition of $CHCl_3$ and aqueous saturated citric acid, the resulting mixture was partitioned, and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; $CHCl_3$/MeOH, 100: 1) to give **8** (2.1 g, 90%) as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$) 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.79−2.06 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.18−2.28 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 3.45 (2H, t, CHNC*H*$_2$CH$_2$CH$_2$, *J* = 6.6 Hz), 4.58−4.66 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.79 (1H, d, C=C*H*, *J* = 10.9 Hz), 7.32−7.48 (5H, m, aromatic). Anal. ($C_{18}H_{23}NO_4$): C, H, N.

(±)-(*Z*)-2-(3-Methylphenyl)-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (9). Compound **9** was obtained in 66% yield from **5** using triethyl 2-(3-methylphenyl)-phosphonoacetate as described for the synthesis of **8**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.77−2.08 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.18−2.33 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 2.35 (3H, s, C*H*$_3$), 3.45 (2H, t, CHNC*H*$_2$-CH$_2$CH$_2$, *J* = 6.6 Hz), 4.56−4.64 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.78 (1H, d, C=C*H*, *J* = 10.8 Hz), 7.13−7.20 (1H, m, aromatic), 7.21−7.30 (3H, m, aromatic); MS (FAB) *m*/*z* 332 (MH$^+$).

(±)-(*Z*)-2-(4-Methylphenyl)-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (10). Compound **10** was obtained in 64% yield from **5** using triethyl 2-(4-methylphenyl)-phosphonoacetate as described for the synthesis of **8**: ^{1}H NMR (270 MHz, $CDCl_3$) 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.75−2.11 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.15−2.29 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 2.34 (3H, s, C*H*$_3$), 3.44 (2H, t, CHNC*H*$_2$-CH$_2$CH$_2$, *J* = 6.6 Hz), 4.55−4.64 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.76 (1H, d, C=C*H*, *J* = 10.9 Hz), 7.13−7.21 (2H, m, aromatic), 7.34−7.37 (2H, m, aromatic); MS (FAB) *m*/*z* 332 (MH$^+$).

(±)-(*Z*)-2-(2-Fluorophenyl)-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (11). Compound **11** was obtained in 5% yield from **5** using triethyl 2-(2-fluorophenyl)-phosphonoacetate as described for the synthesis of **8**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.47 (9H, s, C(C*H*$_3$)$_3$), 1.79−2.08 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.21−2.32 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 3.44 (2H, t, CHNC*H*$_2$CH$_2$CH$_2$, *J* = 6.6 Hz), 4.66−4.73 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.84 (1H, d, C=C*H*, *J* = 10.8 Hz), 7.02−7.20 (2H, m, aromatic), 7.25−7.38 (2H, m, aromatic); MS (FAB) *m*/*z* 336 (MH$^+$).

(±)-(*Z*)-2-(3-Fluorophenyl)-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (12). Compound **12** was obtained in 71% yield from **5** using triethyl 2-(3-fluorophenyl)-phosphonoacetate as described for the synthesis of **8**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.79−2.06 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.19−2.28 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 3.46 (2H, t, CHNC*H*$_2$CH$_2$CH$_2$, *J* = 6.6 Hz), 4.57−4.64 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.82 (1H, d, C=C*H*, *J* = 10.8 Hz), 6.97−7.04 (1H, m, aromatic), 7.17−7.34 (3H, m, aromatic); MS (FAB) *m*/*z* 336 (MH$^+$).

(±)-(*Z*)-2-(4-Fluorophenyl)-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (13). Compound **13** was obtained in 48% yield from **5** using triethyl 2-(4-fluorophenyl)-phosphonoacetate as described for the synthesis of **8**: ^{1}H NMR (270 MHz, $CDCl_3$) 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.75−2.10 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.19−2.31 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 3.45 (2H, t, CHNC*H*$_2$CH$_2$CH$_2$, *J* = 6.6 Hz), 4.56−4.64 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.75 (1H, d, C=C*H*, *J* = 10.9 Hz), 6.98−7.07 (2H, m, aromatic), 7.41−7.48 (2H, m, aromatic); MS (FAB) *m*/*z* 336 (MH$^+$).

(±)-(*Z*)-2-(4-Methoxyphenyl)-3-(2-*N*-*tert*-butoxycarbonylpyrrolidinyl)propenoic Acid (14). Compound **15** was obtained in 23% yield from **5** using triethyl 2-(4-methoxyphenyl)phosphonoacetate as described for the synthesis of **8**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.45 (9H, s, C(C*H*$_3$)$_3$), 1.75−2.07 (3H, m, CHNCH$_2$CH$_2$C*H*$_2$, CHNCH$_2$C*H*$_2$CH$_2$), 2.18−2.29 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 3.44 (2H, t, CHNC*H*$_2$CH$_2$CH$_2$, *J* = 6.6 Hz), 3.80 (3H, s, OC*H*$_3$), 4.56−4.62 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 5.72 (1H, d, C=C*H*, *J* = 10.5 Hz), 6.84−6.89 (2H, m, aromatic), 7.37−7.42 (2H, m, aromatic); MS (FAB) *m*/*z* 348 (MH$^+$).

General Procedure for the Synthesis of the Pyrrolidine-Type Derivatives (4a−m). To a solution of a carboxylic acid **8**−**15** (0.10 mmol) were added Argonaut PS-carbodiimide (300 mg), HOBT (27 mg, 0.20 mmol) in CH_2Cl_2 (4 mL), and dipropylamine (15 μL, 0.11 mmol). After stirring of the mixture at room temperature overnight, tetrafluorophthalic anhydride (110 mg, 0.50 mmol) was added, and the resulting mixture was further stirred at room temperature overnight. To the mixture was added Argonaut PS-trisamine (400 mg), and the resulting mixture was stirred at room temperature for 5 h. After filtration of mixture, the filtrate was evaporated, and the residue was purified by flash chromatography (silica gel; hexane/EtOAc, 3:1) to give a colorless oil. A solution of the oil obtained in trifluoroacetic acid (1 mL) was stirred at 0 °C for 30 min. After the mixture was evaporated, **4a**−**m** were yielded as an oil. Typical instrumental analysis data for **4b**: ^{1}H NMR (300 MHz, $CDCl_3$) 0.57 (3H, t, NCH$_2$CH$_2$C*H*$_3$, *J* = 7.2 Hz), 0.94 (3H, t, NCH$_2$CH$_2$C*H*$_3$, *J* = 7.5 Hz), 1.14−1.29 (2H, m, NCH$_2$C*H*$_2$-CH$_3$), 1.59−1.70 (2H, m, NCH$_2$C*H*$_2$CH$_3$), 1.89−2.14 (3H, m, CHNCH$_2$C*H*$_2$CH$_2$, CHNCH$_2$CH$_2$C*H*$_2$), 2.24−2.32 (1H, m, CHNCH$_2$CH$_2$C*H*$_2$), 2.97−3.03 (2H, m, NC*H*$_2$CH$_2$CH$_3$), 3.26−3.44 (4H, m, NC*H*$_2$CH$_2$CH$_3$, CHNC*H*$_2$CH$_2$CH$_2$), 4.15−4.23 (1H, m, C*H*NCH$_2$CH$_2$CH$_2$), 6.12 (1H, d, C=C*H*, *J* = 9.3 Hz), 7.26−7.35 (5H, m, aromatic). Anal. ($C_{21}H_{29}F_3N_2O_3\cdot H_2O$): C, H, N.

(±)-(*Z*)-*N*,*N*-Diethyl-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4a): 92% yield (purity 96% on HPLC); MS (FAB) *m*/*z* 273 (MH$^+$).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4b): 69% yield (purity 100% on HPLC); MS (FAB) *m*/*z* 301 (MH$^+$).

(±)-(*Z*)-*N*,*N*-Dibutyl-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4c): 74% yield (purity 99% on HPLC); MS (FAB) *m*/*z* 329 (MH$^+$).

(±)-(*Z*)-*N*-Ethyl-*N*-(2-methylallyl)-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4d): 90% yield (purity 100% on HPLC); MS (FAB) *m*/*z* 299 (MH$^+$).

(±)-(*Z*)-*N*-Cyclopropylmethyl-*N*-propyl-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4e): 94% yield (purity 96% on HPLC); MS (FAB) *m*/*z* 313 (MH$^+$).

(±)-(*Z*)-Piperidinyl-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4f): 83% yield (purity 100% on HPLC); MS (FAB) *m*/*z* 285 (MH$^+$).

(±)-(*Z*)-Piperazinyl-2-phenyl-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4g): 94% yield (purity 100% on HPLC); MS (FAB) *m*/*z* 286 (MH$^+$).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-(3-methylphenyl)-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4h): 93% yield (purity 95% on HPLC); MS (FAB) *m*/*z* 315 (MH$^+$).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-(4-methylphenyl)-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4i): 18% yield (purity 96% on HPLC); MS (FAB) *m*/*z* 315 (MH$^+$).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-(2-fluorophenyl)-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4j): 20% yield (purity 96% on HPLC); MS (FAB) *m*/*z* 319 (MH$^+$).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-(3-fluorophenyl)-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4k): 32% yield (purity 97% on HPLC); MS (FAB) *m*/*z* 319 (MH^+).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-(4-fluorophenyl)-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4l): 37% yield (purity 96% on HPLC); MS (FAB) *m*/*z* 319 (MH^+).

(±)-(*Z*)-*N*,*N*-Dipropyl-2-(4-methoxyphenyl)-3-pyrrolidin-2-ylacrylamide trifluoroacetate (4m): 79% yield (purity 96% on HPLC); MS (FAB) *m*/*z* 331 (MH^+).

(±)-*N*-Allyl-*N*-*tert*-butoxycarbonyl-*N*-1-(hydroxymethyl)propylamine (15). A solution of dl-2-aminobutanol (890 mg, 10 mmol), diisopropylethylamine (3.5 mL, 20 mmol), and allyl bromide (870 μL, 10 mmol) was stirred at room temperature overnight. The resulting mixture was partitioned between $CHCl_3$ and water, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; $CHCl_3$/MeOH, 50:1) to give a colorless oil of 1-(2-hydroxymethyl)propylallylamine (230 mg, 18%), which was used immediately in the next reaction.

A solution of 1-(2-hydroxymethyl)propylallylamine (190 mg, 1.5 mmol), Et_3N (280 μL, 2.0 mmol), and Boc_2O (440 mg, 2.0 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature overnight. The resulting mixture was partitioned between $CHCl_3$ and water, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; $CHCl_3$/MeOH, 100:1) to give **15** (300 mg, 13%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) 0.91 (3H, t, CH_2CH_3, J = 7.4 Hz), 1.46 (9H, s, $C(CH_3)_3$), 1.50−1.67 (2H, m, CH_2CH_3), 1.77−1.86 (1H, br, OH), 2.85−2.95 (1H, m, $NCHCH_2CH_3$), 3.60−3.82 (4H, m, $NCH_2CH{=}CH_2$, OCH_2-CH), 5.10−5.19 (2H, m, $CH{=}CH_2$), 5.86−5.92 (1H, m, $CH{=}CH_2$). Anal. ($C_{12}H_{23}NO_3{\cdot}0.2H_2O$): C, H, N.

(±)-(*Z*)-Ethyl 4-(*N*-Allyl-*N*-*tert*-butoxycarbonylamino)-2-phenyl-2-hexenoate (17). To a solution of oxalyl chloride (220 μL, 2.5 mmol) in CH_2Cl_2 (20 mL) was added slowly DMSO (390 μL, 5.5 mmol) at −78 °C, and the mixture was stirred at the same temperature under argon for 30 min. To the resulting mixture was added slowly **15** (260 mg, 1.1 mmol), and the resulting mixture was stirred at the same temperature for 1 h. After addition of Et_3N (1.3 mL, 9.1 mmol), the mixture was stirred at the same temperature for 30 min further. The mixture was allowed to warm to room temperature over 1.5 h and was partitioned between $CHCl_3$ and water. The organic layer was washed with aqueous saturated NH_4Cl, aqueous saturated Na_2CO_3, and brine, dried ($MgSO_4$), and evaporated to give **16′** (250 mg, 96%), which was used immediately in the next reaction.

To a solution of LiCl (25 mg, 0.60 mmol) in MeCN (3 mL) were added **6** (160 mg, 0.54 mmol) and DBU (89 μL, 0.54 mmol) in MeCN (1 mL) at 0 °C under argon. After stirring of the mixture at room temperature for 30 min, **17′** (23 mg, 0.54 mmol) in MeCN (1 mL) was added, and the mixture was stirred room temperature overnight. The resulting mixture was partitioned between aqueous saturated NH_4Cl and $CHCl_3$, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; hexane/EtOAc 20:1) to give **17** (24 mg, 12% from **15**) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) 0.91 (3H, t, $CHCH_2CH_3$, J = 7.2 Hz), 1.32 (3H, t, OCH_2CH_3, J = 7.2 Hz), 1.46 (9H, s, $C(CH_3)_3$), 1.67−1.86 (2H, m, $CHCH_2CH_3$), 3.74 (1H, dd, $NCH_2CH{=}CH_2$, J = 16.2, 6.0 Hz), 3.88−4.00 (1H, m, $NCH_2CH{=}CH_2$), 4.20−4.38 (2H, m, OCH_2CH_3), 4.72 (1H, dd, $NCHCH_2CH_3$, J = 15.9, 8.4 Hz), 5.08−5.17 (2H, m, $CH{=}CH_2$), 5.78−5.91 (1H, m, $CH{=}CH_2$), 6.24 (1H, d, C=CH, J = 9.6 Hz), 7.26−7.38 (5H, m, aromatic). Anal. ($C_{22}H_{31}NO_4$): C, H, N.

(±)-(*Z*)-4-(*N*-Allyl-*N*-*tert*-butoxycarbonylamino)-2-phenyl-2-hexenoic Acid (18). A mixture of **17** (24 mg, 0.064 mmol) and 1 N NaOH (1.3 mL) in EtOH (1.3 mL) was stirred at room temperature at 70 °C overnight. The mixture was neutralized with aqueous saturated citric acid and then extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; $CHCl_3$/MeOH, 20:1) to give **18** (20 mg, 91%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) 0.94 (3H, t, CH_2CH_3, J = 7.4 Hz), 1.46 (9H, s, $C(CH_3)_3$), 1.56−1.90 (2H, m, CH_2CH_3), 3.78 (1H, dd, $NCH_2CH{=}CH_2$, J = 16.4, 6.3 Hz), 3.96 (1H, dd, $NCH_2CH{=}CH_2$, J = 16.4, 5.4 Hz), 5.12−5.19 (3H, m, $NCHCH_2CH_3$, $CH{=}CH_2$), 5.81−5.94 (1H, m, $CH{=}CH_2$), 6.02 (1H, d, C=CH, J = 8.7 Hz), 7.26−7.51 (5H, m, aromatic). Anal. ($C_{20}H_{27}NO_4{\cdot}0.5H_2O$): C, H, N.

(±)-(*Z*)-*N*,*N*-Dipropyl 4-(*N*-Allyl-*N*-*tert*-butoxycarbonylamino)-2-phenyl-2-hexenamide (19). A solution of **18** (1.6 g, 4.7 mmol), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (3.6 g, 19 mmol), BOP (8.5 g, 19 mmol), dipropylamine (5.1 mL, 38 mmol), and Et_3N (5.2 mL, 38 mmol) in CH_2Cl_2 (47 mL) was stirred at room temperature overnight. The resulting mixture was partitioned between $CHCl_3$ and water, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; hexane/EtOAc, 5:1) to give **19** (1.1 g, 52%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) 0.57 (3H, t, $NCH_2CH_2CH_3$, J = 7.4 Hz), 0.88 (3H, t, $NCH_2CH_2CH_3$, J = 7.4 Hz), 0.95 (3H, t, $NCHCH_2CH_3$, J = 7.4 Hz), 1.46 (9H, s, $C(CH_3)_3$), 1.65−1.73 (6H, m, $NCH_2CH_2CH_3$, $NCH_2CH_2CH_3$, $NCHCH_2CH_3$), 3.01−3.04 (2H, m, $NCH_2CH_2CH_3$), 3.18−3.40 (1H, m, $NCH_2CH_2CH_3$), 3.41−3.61 (1H, m, $NCH_2CH_2CH_3$), 3.67 (1H, dd, $NCH_2CH{=}CH_2$, J = 16.2, 6.6 Hz), 3.91−4.20 (1H, m, $NCH_2CH{=}CH_2$), 4.35−4.50 (1H, m, $NCHCH_2CH_3$), 5.11−5.21 (2H, m, $CH{=}CH_2$), 5.81−5.94 (1H, m, $CH{=}CH_2$), 6.02 (1H, d, C=CH, J = 8.7 Hz), 7.26−7.51 (5H, m, aromatic). Anal. ($C_{26}H_{40}N_2O_3$): C, H, N.

(±)-(*Z*)-*N*,*N*-Dipropyl-4-(*N*-*tert*-butoxycarbonyl-N-propenyl)amino-2-phenyl-2-hexenamide (20). A mixture of **19** (11 mg, 0.026 mmol) and $RuHCl(CO)(PPh_3)_3$ (2.4 mg, 2.5 μmol) in xylene (130 μL) was stirred at 60 °C under argon overnight. The resulting mixture was partitioned between $CHCl_3$ and water, and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; hexane/EtOAc, 10:1) to give **20** (9.0 mg, 82%) as an oil: ^{1}H NMR (270 MHz, $CDCl_3$) 0.51 (3H, t, $NCH_2CH_2CH_3$, J = 7.2 Hz), 0.86−0.97 (6H, m, $NCH_2CH_2CH_3$, $NCHCH_2CH_3$),1.47−1.65 (4H, m, $NCH_2CH_2CH_3$, $NCHCH_2$-CH_3), 1.52 (9H, s, $C(CH_3)_3$), 1.69 (3H, d, J = 6.3 Hz), 1.72−2.00 (2H, m, $NCH_2CH_2CH_3$), 2.82−2.97 (1H, m, $NCH_2CH_2CH_3$), 2.99−3.11 (1H, m, $NCH_2CH_2CH_3$), 3.13−3.26 (1H, m, NCH_2-CH_2CH_3), 3.34−3.48 (1H, m, $NCH_2CH_2CH_3$), 4.47 (1H, q, $NCHCH_2CH_3$, J = 7.9 Hz), 5.06−5.19 (1H, m, $NCH{=}CHCH_3$), 6.30 (1H, d, C=CH, J = 7.9 Hz), 6.63 (1H, d, $NCH{=}CHCH_3$, J = 13.9 Hz), 7.21−7.40 (5H, m, aromatic). Anal. ($C_{26}H_{40}$-N_2O_3): C, H, N.

(±)-(*Z*)-*N*,*N*-Dipropyl-4-amino-2-phenyl-2-hexenamide Trifluoroacetate (3b). A solution of **20** (5.0 mg, 0.012 mmol) and trifluoroacetic acid (30 μL) in 1,4-dioxane (60 μL) and water (30 μL) was stirred at 50 °C for 3 h and then evaporated. The residue was dissolved in CH_2Cl_2 and Et_2O, and the resulting solution was concentrated in vacuo to give **3a** (4.0 mg, 82%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) 0.47 (3H, t, $NCH_2CH_2CH_3$, J = 7.2 Hz), 0.87−0.93 (6H, m, $NCH_2CH_2CH_3$, $NH_2CHCH_2CH_3$), 1.01−1.20 (2H, m, NH_2-$CHCH_2CH_3$), 1.51−1.80 (4H, m, $NCH_2CH_2CH_3$, NCH_2CH_2-CH_3), 2.94−3.06 (2H, m, $NCH_2CH_2CH_3$), 3.24−3.58 (2H, m, $NCH_2CH_2CH_3$), 3.58 (1H, dt, $NH_2CHCH_2CH_3$, J = 4.6, 9.9 Hz), 5.92 (1H, d, C=CH, J = 9.9 Hz), 7.36−7.47 (5H, m, aromatic). Anal. ($C_{20}H_{29}F_3N_2O_3{\cdot}H_2O$): C, H, N.

Binding Assay. The binding affinity for the NMDA receptor was investigated according to previously reported methods.[18]

X-ray Crystallographic Analysis of 3b. $C_{20}H_{31}F_3N_2O_4$, M = 420.47 Monoclinic, $C2/c$, a = 21.034(9) Å, b = 7.595(3) Å, c = 29.466(8) Å, β = 97.75(3)°, V = 4664(3) Å^3, Z = 8, D_{calc} = 1.350. Cell parameters were determined and 26 reflections refined in the range 26.5° < θ < 30.0°. A colorless crystal (0.50 × 0.40 × 0.30 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu−Kα radiation (λ = 1.541 78 Å). Data collection using the $\omega/2\theta$ scan technique gave 3848 reflections at room temperature, 3666 being unique, of which 2640 with $I > 3.00\sigma(I)$ reflections were

used in calculations. The intensities were corrected for Lorentz and polarization factors and for absorption and extinction effects. The structure was solved by direct method and refined by the full-matrix least-squares technique using maXus (v4.3) as the computer program. The non-hydrogen atoms were refined isotropically. The unweighted and weighted *R* values were 0.081 and 0.140, respectively.

Calculations. The three-dimensional structures of PPDC and **3a** were determined by conformational analysis (MMFF94) using the BatchMin program included in the MacroModel v6.5 package.[22] A 10 000−35 000 step Monte Carlo search was performed on each compound. The energy minimizations were performed in a vacuum and water, respectively.

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Supporting Information Available: HPLC charts of the final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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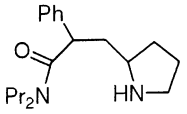
(19) Compound **4b** was almost inactive as a 5HT-uptake inhibitor (K_i > 10 μM).
(20) Compound **4b** was hydrogenated to give a diastereomeric mixture of the corresponding saturated products **22**, the binding affinity of which to the NMDA receptor was low (IC_{50} = 3.6 μM).



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