Synthesis and Biological Activity of Conformationally Restricted Analogs of Milnacipran: (1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide, an Efficient Noncompetitive *N*-Methyl-D-aspartic Acid Receptor Antagonist

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We recently demonstrated that (±)-(*Z*)-2-(aminomethyl)-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide [milnacipran, (±)-**1**], an inhibitor of the reuptake of serotonin (5-HT), was a noncompetitive NMDA receptor antagonist. On the basis of the cyclopropane structure of (±)-**1**, conformationally restricted analogs with different stereochemistries, namely 1-phenyl-2-(1-aminoalkyl)-*N*,*N*-diethylcyclopropanecarboxamindes (**2**, **3**, ***ent*-2**, and ***ent*-3**), were designed and synthesized. Among these analogs, **2a**, **2b**, and **2f**, with (1*S*,2*R*,1′*S*)-configuration, were more efficient than milnacipran as NMDA receptor antagonists; these compounds significantly inhibited the binding of [^{3}H]MK-801 at $IC_{50} = 0.35 \pm 0.08$, 0.20 ± 0.024, and 0.16 ± 0.02 μM, respectively, and blocked the response of voltage-clamped oocytes to NMDA, surpassing the effects of (±)-**1**. Although both the 1′-methyl analog **2a** and the 1′-vinyl analog **2f**, like (±)-**1**, strongly inhibited 5-HT uptake in vitro, the corresponding 1′-ethyl analog **2b** was devoid of the inhibitory effect on 5-HT uptake, while it was about 30 times more potent as an NMDA receptor antagonist than (±)-**1**.

Introduction

Because of the potential involvement of NMDA (*N*-methyl-D-aspartic acid) receptors in both chronic and acute neurodegenerative disorders,[1] there have been attempts to develop novel agents that block the activation of NMDA receptors by glutamate or related excitatory neurotransmitters.[1−5]

Recently, various noncompetitive and competitive NMDA receptor antagonists have been developed, and some have been shown to be effective in experimental models of epilepsy and stroke.[1−3] Unfortunately, noncompetitive inhibitors have had serious behavioral effects[4a,b] and caused neuronal vacuolization,[4c] while competitive inhibitors were often inactive *in vivo* because of poor transport to the brain.[5] Therefore, the development of another type of efficient NMDA receptor antagonist is eagerly desired.

We previously reported that (±)-(*Z*)-2-(aminomethyl)-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide [milnacipran, (±)-**1**],[6] as an efficient antidepressant due to competitive inhibition of the re-uptake of serotonin (5-HT) in the CNS,[7] was a new class of noncompetitive NMDA receptor antagonist.[8] Although the binding affinity of (±)-**1** for the NMDA receptor is not strong, its characteristic structure is of importance for the search of novel potent NMDA receptor antagonists other than the known competitive and noncompetitive antagonists.[8] Therefore, we modified the structure of (±)-**1**, to increase its specific affinity for the NMDA receptor as well to decrease its inhibitory effect on 5-HT reuptake, to develop a clinically useful NMDA receptor antagonist. Since our previous study showed that modification of the functional groups of (±)-**1**, such as the aminomethyl or the diethylcarbamoyl group, did not improve its activity,[8] we planned to investigate the effects of conformational changes of the molecule on its activity. Therefore, we designed conformationally restricted analogs of (±)-**1** and accordingly developed a new method for restricting the conformation of cyclopropane derivatives.[9a]

We designed conformationally restricted analogs based on the structural feature of (±)-**1**, as shown in Figure 1. Adjacent substituents on a cyclopropane ring exert significant mutual steric repulsion because they are fixed in an eclipsed conformation relative to each other. Consequently, the conformations of substituents on a cyclopropane ring can be restricted by the steric effects of adjacent substituents, especially when they are bulky enough. Since the primary amino group of (±)-**1** is essential for the binding to the NMDA receptor,[8] we presumed that the conformation of the aminomethyl moiety would significantly affect the activity of the compound. While the aminomethyl moiety is not very bulky and may freely rotate to some extent, conformers A and B may be preferable to conformer C, due to the strong steric repulsion of the bulky *N*,*N*-diethylcarbamoyl group in conformer C, as shown in Figure 2. Introducing an alkyl group into the α-position of the amino function of (±)-**1** would prevent this rotation and restrict the location of the amino group in space due to its steric repulsion from the diethylcarbamoyl group. Therefore, the conformation of the compounds can be limited depending on the configuration of the alkyl group introduced; conformer B would be predominant in **2** and its enantiomer (***ent*-2**), while conformer A would be predominant in **3** and its enantiomer (***ent*-3**),

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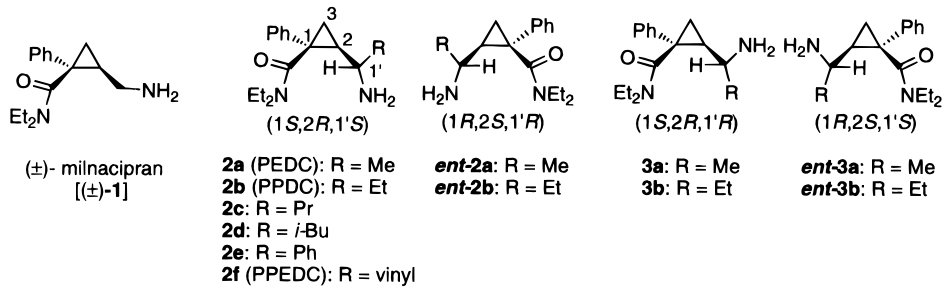


Figure 1. Milnacipran and its conformationally restricted analogs.

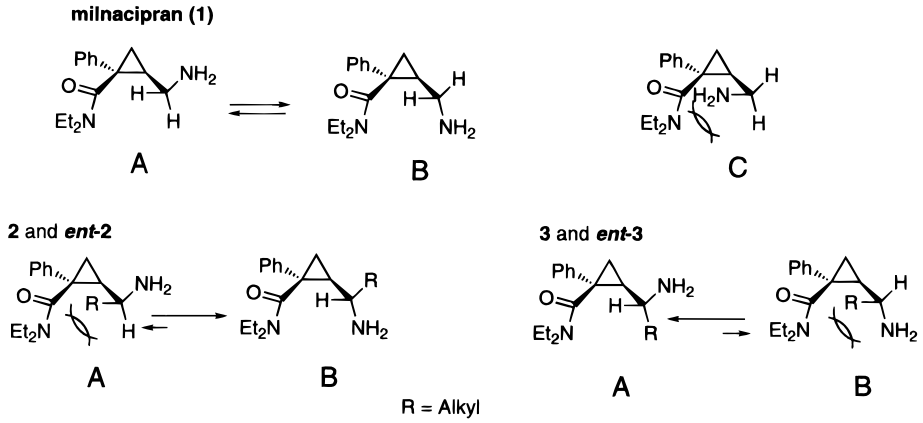


Figure 2. Conformational restriction of milnacipran by introducing an alkyl group.

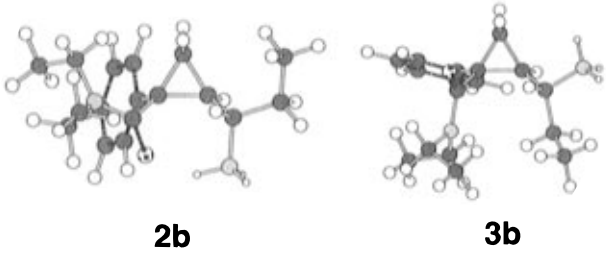


Figure 3. Molecular structures of the low-energy conformers of **2b** and **3b**.

as shown in Figure 2. As the alkyl groups, we selected methyl and ethyl groups, which would be bulky enough to restrict the conformation of the compounds. We carried out molecular orbital calculations on **2b** and **3b**.[10] As shown in Figure 3, the calculated structures of **2b** and **3b** supported our hypothesis.

Four types of conformationally restricted analogs with different stereochemistries, namely, **2a** and **2b**, **3a** and **3b**, ***ent*-2a** and ***ent*-2b**, and ***ent*-3a** and ***ent*-3b**, were synthesized with high stereoselectivity,[11] starting from (*R*)- or (*S*)-epichlorohydrins.[9] X-ray crystallographic analysis clearly showed that the conformations of **2** (***ent*-2**) and **3** (***ent*-3**) were effectively restricted to conformers B and A, respectively, as we hypothesized.[9a]

Among these conformationally restricted analogs, (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminoethyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2a**, PEDC) and (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2b**, PPDC) significantly inhibited the binding of [^{3}H]MK-801 to the NMDA receptor. Considering these findings, to investigate the effects of the alkyl group at the α-position of the amino group on the biological activity, we synthesized other conformationally restricted analogs of milnacipran (**2c**−**f**) with the same stereochemistry as that of **2a** and **2b**.

Results and Discussion

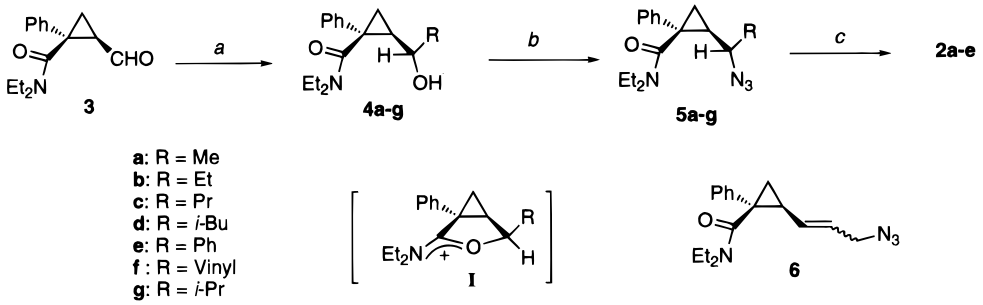
Chemistry. We previously reported the stereoselective syntheses of four types of conformationally restricted analogs of (±)-**1**, namely, **2a** and **2b**, **3a** and **3b**, ***ent*-2a** and ***ent*-2b**, and ***ent*-3a** and ***ent*-3b**.[9] In this study, **2c**−**f** were also synthesized from an optically active cyclopropylcarbaldehyde **3**, a key intermediate in the synthesis of **2a** and **2b**, which was readily prepared from (*R*)-epichlorohydrin (Scheme 1).

We previously recognized that addition reactions of Grignard reagents on the cyclopropylcarbaldehyde **3** proceed from the least hindered *si* face in the bisected *s-trans* conformation which is preferred due to the peculiar stereoelectronic effects of the cyclopropane ring, to give 1′*S*-products highly selectively.[9] The Grignard reaction of **3** with propyl-, isobutyl-, phenyl-, and vinylmagnesium bromides in THF at −20 °C also gave 1′*S*-products **4c**−**g** diastereoselectively in high yields. Treatment of **4c**−**e** with a $NaN_3/CBr_4/Ph_3P$ system in DMF[12] gave azido derivatives **5c**−**e** stereoselectively in good yields. This reaction gave the configuration-retained azido products via the participation of a neighboring group in intermediates **I**.[9a] However, when isopropyl derivative **4g** was treated under the same reaction conditions, nucleophilic substitution did not proceed, and **4g** was recovered. This result is likely due to steric hindrance around the 1′-position. On the other hand, similar treatment of vinyl derivative **4f** did not give the desired 1′*S*-azide **5f**, but S_N2' product **6** was obtained as a mixture of *E*- and *Z*-isomers.

Catalytic hydrogenation of azido derivatives **5c**−**e** with Pd−C in MeOH gave the target conformationally restricted analogs **2c**−**e**, which were isolated as hydrochlorides in good yields (Scheme 1).

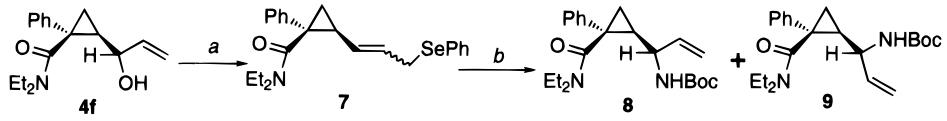
We attempted to synthesize vinyl derivative **2f** using an oxidative 2,3-sigmatropic rearrangement reaction[13] via vinylselenide **7** (Scheme 2). We initially thought

Scheme 1[a]



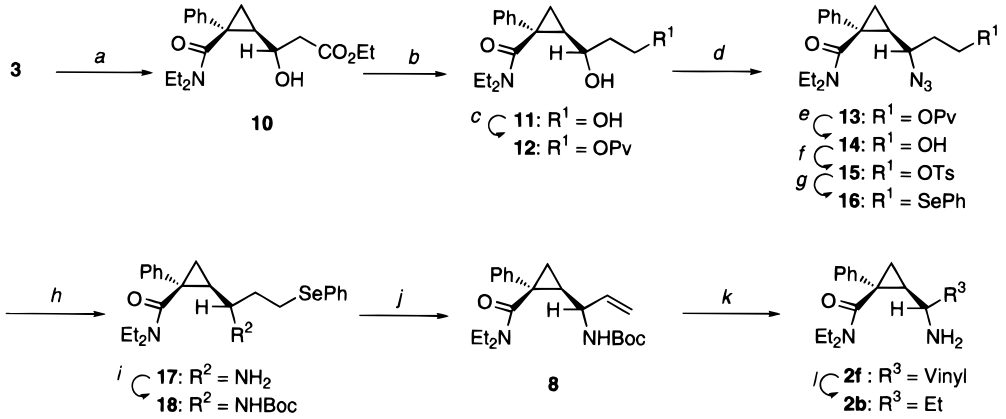
[a] Reagents: (a) RMgBr, THF; (b) NaN_3, CBr_4, Ph_3P, DMF; (c) H_2, Pd−C, MeOH.

Scheme 2[a]



[a] Reagents: (a) (1) $(CF_3CO)_2O$, MeCN, (2) $NaBH_4$, $(PhSe)_2$, EtOH; (b) *t*-BuO_2CNH_2, *i*-Pr_2NH, NCS, MeOH.

Scheme 3[a]



[a] Reagents: (a) $LiCH_2CO_2Et$, THF; (b) $NaBH_4$, MeOH; (c) pivaloyl chloride, py; (d) NaN_3, Ph_3P, CBr_4, DMF; (e) NaOMe, MeOH; (f) TsCl, DMAP, Et_3N, CH_2Cl_2; (g) $NaBH_4$, $(PhSe)_2$, EtOH; (h) Ph_3P, py, then NH_4OH; (i) Boc_2O, CH_2Cl_2; (j) H_2O_2, aqueous THF; (k) TFA, MeOH; (l) H_2, Pd−C, MeOH.

that the phenylseleno derivative **7** could be prepared by treating **4f** with $PhSe^-$, since the nucleophilic substitution reaction of **4f** proceeded in an S_N2' manner to give the corresponding exo-olefin product as described above. In fact, treatment of **4f** with NaSePh, prepared from $(PhSe)_2$ and $NaBH_4$, in EtOH gave the S_N2' product **7** in 76% yield as a mixture of *E*- and *Z*-isomers. When mixture **7** was treated with *N*-chlorosuccinimide in the presence of *tert*-butyl carbamate and *i*-Pr_2NH, an oxidative 2,3-sigmatropic rearrangement proceeded to give the 1′-vinyl derivative as a mixture of 1′-diastereomers in high yield. However, separation of the diastereomeric mixture was unsuccessful.[14]

Next, we planned to construct the vinyl moiety via the oxidative *syn*-elimination reaction of a phenylseleno group after introduction of an amino function at the 1′-position, as outlined in Scheme 3. Treatment of aldehyde **3** with a lithium enolate of EtOAc at −78 °C in THF gave 1′*S*-addition product **10** and the corresponding 1′*R*-diastereomer in 79% and 10% yields, respectively. Reduction of the ester group of **10** with $NaBH_4$ in MeOH gave alcohol **11** of which the primary hydroxyl was protected selectively with a pivaloyl group to give **12** in high yield. The azido function was introduced at this stage; treatment of **12** with the $NaN_3/CBr_4/Ph_3P$ system in DMF[12] gave desired azido derivative **13** in excellent yield. After removal of the protecting group, the hydroxyl was tosylated to give **15**. Nucleophilic substitution reaction of **15** with NaSePh in EtOH afforded phenylseleno derivative **16** in 85% yield. Although catalytic hydrogenation of **16** was unsuccessful, when **16** was treated successively with Ph_3P in pyridine and NH_4OH,[15] the azide group was selectively reduced to give the desired amino derivative **17**, the amino group of which was protected with a Boc group to give **18**. Treatment of **18** with H_2O_2 in aqueous THF at room temperature gave the oxidative *syn*-elimination product **8** in 95% yield. Deprotection of **8** with TFA in aqueous MeOH furnished the target 1′-vinyl derivative **2f**, which was isolated as a hydrochloride in 84% yield. Finally, the stereochemistry at the 1′-position was confirmed to be *S*, since the catalytic hydrogenation of **2f** with Pd−C in MeOH gave 1′*S*-ethyl derivative **2b** (PPDC), the stereochemistry of which was determined previously by X-ray crystallographic analysis.[9a]

Biological Activity.[16] It is important to determine the stereochemistry of the conformationally restricted analogs of (±)-**1** that strongly bind to the NMDA receptor. Therefore, conformationally restricted analogs with different stereochemistries, namely, **2a** and **2b**, **3a** and **3b**, ***ent*-2a** and ***ent*-2b**, and ***ent*-3a** and ***ent*-3b**, were evaluated *in vitro* for their binding affinity for the

Table 1. Effects of Compounds on the NMDA Receptor Binding and the 5-HT Uptake

compound	configuration	2′-substituent	NMDA receptor binding[a] (IC_{50}, μM)	5-HT uptake[b] (K_i, μM)	selectivity index[c] (5-HT/NMDA)
(±)-1			6.3 ± 0.3	0.0085 ± 0.0006	0.0013
2a	1*S*,2*R*,1′*S*	Me	0.35 ± 0.08	0.014 ± 0.002	0.040
2b	1*S*,2*R*,1′*S*	Et	0.20 ± 0.02	24 ± 0.9	125
3a	1*S*,2*R*,1′*R*	Me	6.5 ± 0.5	2.4 ± 0.3	0.37
3b	1*S*,2*R*,1′*R*	Et	8.2 ± 2.1	>100	>12
***ent*-2a**	1*R*,2*S*,1′*R*	Me	19 ± 1.8	0.17 ± 0.003	0.0089
***ent*-2b**	1*R*,2*S*,1′*R*	Et	8.2 ± 2.0	>100	>12
***ent*-3a**	1*R*,2*S*,1′*S*	Me	31 ± 0.1	>100	>3.2
***ent*-3b**	1*R*,2*S*,1′*S*	Et	11 ± 0.05	>100	>9.1
2c	1*S*,2*R*,1′*S*	Pr	1.0 ± 0.05	37 ± 3	37
2d	1*S*,2*R*,1′*S*	*i*-Bu	4.2 ± 0.2	>100	>24
2e	1*S*,2*R*,1′*S*	Ph	17 ± 0.3	>100	>5.9
2f	1*S*,2*R*,1′*S*	Vinyl	0.16 ± 0.02	0.023 ± 0.0007	0.14
phencyclidine			0.009.8 ± 0.005		
ketameine			0.61 ± 0.46		

[a] Assay was done with cerebral cortical synaptic membrane of rats using [^{3}H]MK-801. [b] Assay was done with cerebral cortical synaptic membrane of rats using [^{3}H]paroxetine. [c] The ratio: 5-HT uptake inhibition (K_i)/NMDA receptor binding (IC_{50}).

NMDA receptor of cerebral cortical synaptic membrane from rats, with [^{3}H]MK-801 as a radioligand.[17] The results are shown in Table 1. Generally, conformationally restricted analogs with (1*S*,2*R*)-configuration, **2a**, **2b**, **3a**, and **3b**, showed more potent inhibitory effects than the corresponding enantiomers, ***ent*-2a**, ***ent*-2b**, ***ent*-3a**, and ***ent*-3b**. Notably, conformationally restricted analogs with (1*S*,2*R*,1′*S*)-configuration, namely, **2a** [(1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminoethyl]-*N*,*N*-diethylcyclopropanecarboxamide, PEDC] and **2b** [(1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide, PPDC], significantly inhibited the binding of [^{3}H]MK-801 with IC_{50} values of 0.35 ± 0.08 and 0.20 ± 0.02 μM, respectively, which were about 20- and 30-fold stronger than that of (±)-**1** (IC_{50} = 6.3 ± 0.3 μM).[8] The corresponding diastereomers, **3a** and **3b**, had weaker activities than those of **2a** and **2b**, and their IC_{50} values were similar to that of (±)-**1**. All of the conformationally restricted analogs with (1*R*,2*S*)-configuration, ***ent*-2a**, ***ent*-2b**, ***ent*-3a**, and ***ent*-3b**, showed weaker activity than (±)-**1**.

On the basis of these results, we synthesized conformationally restricted analogs with (1*S*,2*R*,1′*S*)-configuration, **2c**−**f**, which have propyl, isobutyl, phenyl, and vinyl groups at the 1′-position and evaluated their binding affinity for the receptor. The results are also summarized in Table 1. The binding affinity was significantly affected by the alkyl group at the 1′-position; introduction of groups bulkier than the ethyl group clearly decreased the affinity for the receptor. Notably, the 1′-vinyl derivative **2f** [(1*S*,2*R*)-1-phenyl-2-[(*S*)-1-amino-2-propenyl]-*N*,*N*-diethylcyclopropanecarboxamide, PPEDC] strongly bound to the receptor and was more potent than **2a** and **2b**.

We next evaluated the inhibitory effects of the compounds on the uptake of 5-HT by nerve terminals using cerebral cortical synaptic membrane from rats, with [^{3}H]-paroxetine as a radioligand, since milnacipran [(±)-**1**] is a potent inhibitor of 5-HT uptake.[7] As reported previously,[7] (±)-**1** significantly inhibited the 5-HT uptake (K_i = 0.0085 ± 0.0006 μM). Unfortunately, (1*S*,2*R*,1′*S*)-1′-methyl derivative **2a** (PEDC) and -vinyl derivative **2f** (PPEDC), which showed strong binding to the NMDA receptor as described above, also significantly inhibited 5-HT uptake (K_i = 0.014 ± 0.002 and 0.023 ± 0.0007 μM, respectively), similar to (±)-**1**. Surprisingly, the corresponding 1′-ethyl derivative **2b** (PPDC), which also strongly bound to the NMDA receptor, did not affect 5-HT uptake (K_i = 24 ± 0.9 μM). The effect of PPDC (**2b**) was about 1500 times less than the effects of PEDC (**2a**) and PPEDC (**2f**), although they have the same stereochemistry. The enantiomer of PEDC, ***ent*-2a**, which was only a weak NMDA receptor antagonist, considerably inhibited the 5-HT uptake (K_i = 0.17 ± 0.003 μM). All of the 1′-ethyl derivatives had insignificant inhibitory effects on the 5-HT uptake, regardless of their stereochemistry. On the other hand, all of the 1′-methyl derivatives, except ***ent*-3a**, clearly inhibited 5-HT uptake, and the potency depended on their stereochemistries; **2a** [(1*S*,2*R*,1′*S*-)-configuration] > ***ent*-2a** [(1*R*,2*S*,1′*R*)-configuration] > **3a** [(1*S*,2*R*,1′*R*)-configuration] ≫ ***ent*-3a** [(1*R*,2*S*,1′*S*)-configuration]. Consequently, it was suggested that the inhibitory potency against the 5-HT uptake did not correlate with that against NMDA receptor activation in these compounds. These results also suggested that the conformation of milnacipran binding to the NMDA receptor was different from that binding to the 5-HT transporter.

We next investigated the effects of the conformationally restricted analogs with different stereochemistries, as well as (±)-**1**, on the blockade of NMDA receptors expressed by *Xenopus* oocytes. The oocyte expression system has been used to investigate the pharmacological aspects of neurotransmitter receptors, since *Xenopus* oocytes not only translate microinjected exogenous mRNA and assemble functional neurotransmitter receptors of voltage-gated channels but also are appropriate for voltage-clamp experiments. Whole brain mRNA was extracted from 10-day-old Wistar rats by the guanidine/CsCl method, and the injected oocytes were voltage-clamped with two glass electrodes filled with 3 M KCl, as previously described.[18] The injected oocytes were stimulated with 30 μM NMDA and 10 μM Gly in the presence of the compounds tested at different concentrations. All of the compounds tested, including (±)-**1**,[19] decreased the responses to NMDA. The results are summarized in Table 2. The conformationally restricted analogs with (1*S*,2*R*,1′*S*)-configuration, **2a** and **2b**, blocked the response significantly (IC_{50} = 2.3 ± 1.1 and 2.2 ± 2.1 μM, respectively). Although other stereoisomers, **3**, ***ent*-2**, and ***ent*-3**, as well as (±)-**1** also clearly blocked the response, the effects were weaker and those of **2a** and **2b**. Therefore, it is demonstrated that the conformationally restricted analogs clearly

Table 2. Blocking Effects of Compounds on the NMDA Receptors Produced by Oocytes[a]

compound	IC_{50} (μM) or inhibition (%)
1	53 (%)[b]
2a	2.3 ± 1.1 μM
2b	2.2 ± 2.1 μM
3a	50 ± 13 (%)[c]
3b	51 ± 24 (%)[c]
***ent*-2a**	51 ± 3 (%)[c]
***ent*-2b**	39 ± 2.1 μM
***ent*-3a**	59 ± 18 (%)[c]
***ent*-3b**	51 ± 24 (%)[c]
MK-801	98 (%)[d]

[a] Estimated from the inhibition curves obtained from at least three oocytes voltage-clamped at −50 mV. [b] Inhibition at 10 μg/mL. [c] Inhibition at 100 μg/mL. [d] Inhibition at 0.1 μg/mL.

inhibit the function of the NMDA receptor, and there were clear correlations between the inhibition of [^{3}H]-MK-801 binding and blockade of the NMDA receptors by these compounds.[20] The potency of the conformationally restricted analogs as NMDA antagonists depended on their stereochemistry; in the order, **2** [(1*S*,2*R*,1′*S*)-configuration] > **3** [(1*S*,2*R*,1′*R*)-configuration], ***ent*-2** [(1*R*,2*S*,1′*R*)-configuration], ***ent*-3** [(1*R*,2*S*,1′*S*)-configuration].

PPDC may be a desirable NMDA antagonist, since milnacipran, the prototype of PPDC, has been shown clinically to be an antidepressant free from serious side effects[21] and to be transportable to the brain. PPDC is a strong and selective antagonist of the NMDA receptor; with regard to the ratio of selectivity index [5-HT uptake inhibition (K_i)/NMDA receptor binding (IC_{50})], (±)-**1** was 0.0013 and PPDC was 125, respectively. Furthermore, PPDC may be easily transported to the brain because it is more lipophilic than (±)-**1**.

In the design of conformationally restricted analogs, it is imperative that the conformationally restricted analogs and the lead compound be as similar as possible in size, shape, and molecular weight.[22] Conformationally restricted analogs have usually been designed and synthesized by introducing cyclic moieties into lead compounds which were often rather bulky. Consequently, their chemical and physical properties are often changed. On the other hand, it has been considered that an induced fit, namely conformational changes in both the receptor and the ligand coming from their interaction, is important for strong binding.[22a] The introduction of cyclic moieties to restrict the conformation may make the compounds too rigid to be suitable for an induced fit. On the basis of these considerations, our method of restricting the conformation of a key functional group by introducing a small alkyl group, such as a methyl or ethyl group, would be efficient. The alkyl groups introduced in the conformationally restricted analogs may be effective for removing the undesirable side effects when the lead compound interacts with several binding sites. In fact, although the 1′-methyl derivative PEDC (**2a**) and -vinyl derivative PPEDC (**2f**) are significantly active both as NMDA receptor antagonists and as 5-HT-uptake inhibitors, the corresponding 1′-ethyl derivative PPDC (**2b**), which is also an efficient NMDA receptor antagonist, is almost inactive as a 5-HT uptake inhibitor.

In conclusion, we developed conformationally restricted analogs of milnacipran [(±)-**1**] and identified a potent NMDA receptor antagonist, PPDC (**2b**). Although the potency of PPDC as an NMDA receptor antagonist is about 30 times greater than that of the lead compound, milnacipran, it does not inhibit 5-HT uptake, which is the major effect of milnacipran. Thus, we found a new method for restricting the conformation of cyclopropane derivatives.

Experimental Section

Melting points were determined on a Yanagimoto MP-3 micro-melting point apparatus and are uncorrected. The NMR spectra were recorded with a JEOL EX-270 or -400 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), t (triplet), q (quartet), m (multiplet), or br (broad). Mass spectra were measured on a JEOL JMS-D300 spectrometer. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with Merck silica gel 5715.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxybutyl]-*N*,*N*-diethylcyclopropanecarboxamide (4c). To a solution of **3** (245 mg, 1.0 mmol) in THF (8 mL) was slowly added PrMgBr (1.0 M in THF, 2 mL, 2.0 mmol) at −20 °C under argon. The mixture was stirred at the same temperature for 2 h and was quenched with saturated NH_4Cl (20 mL). After the mixture was concentrated *in vacuo*, EtOAc and water were added, and then the mixture was partitioned. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; EtOAc/hexane, 1:4) to give **4c** as an oil (251 mg, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.0 Hz), 0.93 (3 H, t, J = 7.0 Hz), 1.05 (1 H, dd, J = 5.5, 6.5 Hz), 1.14 (3 H, t, J = 7.0 Hz), 1.26 (1 H, ddd, J = 6.5, 8.5, 9.0 Hz), 1.39−1.67 (4 H, m), 1.69 (1 H, dd, J = 5.5, 8.5 Hz), 3.12−3.17 (1 H, m), 3.32−3.46 (3 H, m), 3.52 (1 H, dq, J = 14.0, 7.0 Hz), 5.41 (1 H, s), 7.18−7.30 (5 H, m); HR-MS (EI) calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2053.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxy-3-methylbutyl]-*N*,*N*-diethylcyclopropanecarboxamide (4d). Compound **4d** was prepared as described above for **4c**, with *i*-BuMgBr instead of PrMgBr. After purification by column chromatography (silica gel; EtOAc/hexane, 1:4), **4d** was obtained as an oil (284 mg, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.90−0.94 (9 H, m), 1.04 (1 H, dd, J = 5.5, 6.5 Hz), 1.14 (3 H, t, J = 7.0 Hz), 1.24 (1 H, ddd, J = 6.5, 8.5, 9.0 Hz), 1.37 (1 H, ddd, J = 5.0, 8.5, 13.5 Hz), 1.61 (1 H, ddd, J = 5.5, 8.5, 13.5 Hz), 1.68 (1H, dd, J = 5.5, 8.5 Hz), 1.88 (1 H, m), 3.20 (1 H, m), 3.33−3.55 (4H, m), 5.42 (1H, s), 7.18−7.29 (5 H, m); HR-MS (EI) calcd for $C_{19}H_{29}NO_2$ 303.2198, found 303.2206.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-hydroxy-1-phenylmethyl]-*N*,*N*-diethylcyclopropanecarboxamide (4e). Compound **4e** was prepared as described above for **4c**, with PhMgBr instead of PrMgBr. After purification by column chromatography (silica gel; EtOAc/hexane, 1:4), **4e** was obtained as a white powder (309 mg, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.95 (3 H, t, J = 7.0 Hz), 1.19 (3 H, t, J = 7.0 Hz), 1.29 (1 H, dd, J = 5.5, 6.0 Hz), 1.55 (1 H, ddd, J = 6.0, 8.5, 9.5 Hz), 1.74 (1 H, dd, J = 5.5, 8.5 Hz), 3.40 (1 H, dq, J = 14.0, 7.0 Hz), 3.46−3.58 (3 H, m), 4.25 (1 H, dd, J = 2.0, 9.5 Hz), 5.83 (1 H, d, J = 2.0 Hz), 7.20−7.35 (8 H, m), 7.47 (2 H, d, J = 7.5 Hz); HR-MS (EI) calcd for $C_{21}H_{25}NO_2$ 323.1885, found 323.1893. Anal. ($C_{21}H_{25}NO_2$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxy-2-propenyl]-*N*,*N*-diethylcyclopropanecarboxamide (4f). Compound **4f** was prepared as described above for **4c**, with vinylmagnesium bromide instead of PrMgBr. After purification by column chromatography (silica gel; EtOAc/hexane, 1:4), **4f** was obtained as a white powder (242 mg, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.93 (3 H, t, J = 7.0 Hz), 1.13 (1 H, dd, J = 5.5, 6.5 Hz), 1.15 (3 H, t, J = 7.0 Hz), 1.36 (1 H, ddd, J = 6.5, 9.0, 9.5 Hz), 1.72 (1 H, dd, J = 5.5, 9.0 Hz), 3.33−3.46 (3 H, m), 3.53 (1 H, dq, J = 14.0, 7.0 Hz), 3.66 (1 H, dd, J = 5.5, 9.5 Hz), 5.13 (1 H, d, J = 10.5 Hz), 5.33 (1 H, d, J = 16.0 Hz), 5.54 (1 H, s), 6.00 (1 H, ddd, J = 5.5, 10.5, 16.0 Hz), 7.19−7.31 (5 H, m); HR-MS (EI) calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1712.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxy-2-methylpropyl]-*N*,*N*-diethylcyclopropanecarboxamide (4g). Compound **4g** was

prepared as described above for **4c**, with *i*-PrMgBr instead of PrMgBr. After purification by column chromatography (silica gel; EtOAc/hexane, 1:4), **4f** was obtained as an oil (263 mg, 91%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.3 Hz), 0.99 (3 H, d, J = 6.8 Hz), 1.02 (3 H, d, J = 6.4 Hz), 1.08 (1 H, dd, J = 5.4, 6.6 Hz), 1.14 (3 H, t, J = 7.3 Hz), 1.28 (1 H, ddd, J = 6.6, 8.8, 10.0 Hz), 1.73 (1 H, dd, J = 5.4, 98.8 Hz), 1.85 (1 H, ddd, J = 6.4, 6.4, 6.8 Hz), 2.90 (1 H, dd, J = 6.4, 10.0 Hz), 3.33−3.54 (4 H, m), 7.19−7.31 (5 H, m); MS (EI) *m*/*z* 289 (MH^+).

(1*S*,2*R*′)-1-Phenyl-2-[(*S*)-1-azidobutyl]-*N*,*N*-diethylcyclopropanecarboxamide (5c). To a solution of **4c** (289 mg, 1.0 mmol) in DMF (8 mL) were added at 0 °C NaN_3 (1.24 g, 19 mmol), Ph_3P (787 mg, 3.0 mmol), and CBr_4 (995 mg, 3.0 mmol), and the mixture was stirred at room temperature for 3 h. Water was added, the resulting mixture was evaporated, and then the residue was partitioned between brine and EtOAc. The separated organic layer was dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 1:2) to give **5c** as an oil (210 mg, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.37 (3 H, t, J = 7.0 Hz), 0.94 (1 H, dd, J = 5.0, 9.5 Hz), 0.97 (3 H, t, J = 7.0 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.42−1.61 (2 H, m), 1.66 (1 H, dd, J = 5.0, 5.5 Hz), 1.72−1.77 (2 H, m), 1.96 (1 H, ddd, J = 5.5, 9.5, 10.0 Hz), 2.90 (1 H, ddd, J = 6.5, 6.5, 10.0 Hz), 3.03 (1 H, dq, J = 14.0, 7.0 Hz), 3.17 (1 H, dq, J = 14.0, 7.0 Hz), 3.53 (1 H, dq, J = 14.0, 7.0 Hz), 3.71 (1 H, dq, J = 14.0, 7.0 Hz), 7.20−7.32 (5 H, m); HR-MS (EI) calcd for $C_{18}H_{26}N_4O$ 314.2106, found 314.2089.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-methylbutyl]-*N*,*N*-diethylcyclopropanecarboxamide (5d). Compound **5d** was prepared from **4d** (240 mg, 0.792 mmol) as described above for **5c**. After purification by column chromatography (silica gel; EtOAc/hexane, 1:2), **5d** was obtained as an oil (243 mg, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.37 (3 H, t, J = 7.0 Hz), 0.92 (3 H, d, J = 6.5 Hz), 0.95 (1 H, dd, J = 5.0, 9.5 Hz), 0.97 (3 H, d, J = 6.5 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.54 (1 H, ddd, J = 4.5, 9.5, 14.0 Hz), 1.65 (1H, dd, J = 5.0, 6.5 Hz), 1.74 (1 H, ddd, J = 4.5, 9.5, 14.0 Hz), 1.83−1.90 (1 H, m), 1.96 (1 H, ddd, J = 6.5, 9.5, 9.5 Hz), 2.92 (1 H, ddd, J = 4.5, 9.5, 9.5 Hz), 3.03 (1 H, dq, J = 14.0, 7.0 Hz), 3.16 (1 H, dq, J = 14.0, 7.0 Hz), 3.53 (1 H, dq, J = 14.0, 7.0 Hz), 3.71 (1 H, dq, J = 14.0, 7.0 Hz), 7.20−7.32 (5 H, m); HR-MS (EI) calcd for $C_{19}H_{28}N_4O$ 328.2263, found 328.2256.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-azido-1-phenylmethyl]-*N*,*N*-diethylcyclopropanecarboxamide (5e). Compound **5e** was prepared from **4e** (130 mg, 0.40 mmol) as described above for **5c**. After purification by column chromatography (silica gel; EtOAc/hexane, 1:2), **5e** was obtained as an oil (132 mg, 95% yield): ^{1}H NMR (500 MHz, $CDCl_3$) 0.19 (3 H, t, J = 7.0 Hz), 1.10 (3 H, t, J = 7.0 Hz), 1.23 (1 H, dd, J = 5.0, 9.0 Hz), 2.00 (1 H, dd, J = 5.0, 6.5 Hz), 2.10 (1 H, dq, 14.0, 7.0 Hz), 2.36 (1 H, ddd, J = 6.5, 9.0, 9.0 Hz), 2.95 (1 H, dq, J = 14.0, 7.0 Hz), 3.21 (1 H, dq, J = 14.0, 7.0 Hz), 3.28 (1 H, dq, J = 14.0, 7.0 Hz), 4.28 (1 H, d, J = 9.0 Hz), 7.17−7.43 (10 H, m); HR-MS (EI) calcd for $C_{21}H_{24}N_4O$ 348.1950, found 348.1942.

General Procedure for the Reduction of Azido Derivatives. A mixture of **5c**−**e** (1.00 mmol) and 10% Pd−charcoal (50 mg) in MeOH (10 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 1.5 h, and then the catalyst was filtered off. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 90:20:0.5) to give free amines **2c**−**e** as oil. The oil was partitioned between $CHCl_3$ and 1 N NaOH, and then the $CHCl_3$ phase was washed twice with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (1 mL), the solution was put on a column of Diaion WA-30 resin (2 × 8 cm, Cl^- form), and the column was developed with MeOH. The solvent was evaporated, and the residue was treated with ether to give white crystals of **2c**−**e** as hydrochlorides.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminobutyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride (2c): yield 95%; mp 205−207 °C; $[\alpha]^{27}_D$ = +86.7 (*c* 0.766, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) 0.90 (3 H, t, J = 7.5 Hz), 1.10 (3 H, t, J = 7.0 Hz), 1.06−1.09 (1 H, m), 1.43−1.65 (3 H, m), 1.90 (1 H, dd, J = 6.0, 9.0 Hz), 2.01−2.09 (1 H, m), 2.24−2.31 (1 H, m), 2.65−2.71 (1 H, m), 3.29 (1 H, dq, J = 14.0, 7.0 Hz), 3.33−3.47 (3 H, m), 7.20−7.30 (5 H, m), 9.06 (3 H, br s); MS (EI) *m*/*z* 288 (M^+). Anal. ($C_{18}H_{29}ClN_2O\cdot0.3H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-3-methylbuthyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride (2d): yield 43%; mp 198−199 °C; $[\alpha]^{27}_D$ = +79.9 (*c* 0.670, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 0.89 (3 H, t, J = 7.0 Hz), 0.95 (3 H, d, J = 6.5 Hz), 0.98 (3 H, d, J = 6.5 Hz), 1.08 (1 H, dd, J = 5.5, 6.0 Hz), 1.10 (3 H, t, J = 7.0 Hz), 1.53 (1 H, ddd, J = 6.0, 9.0, 9.0 Hz), 1.89 (1 H, dd, J = 5.5, 9.0 Hz), 1.91−2.03 (2 H, m), 2.13−2.19 (1 H, m), 2.72−2.79 (1 H, m), 3.29 (1 H, dq, N = 14.0, 7.0 Hz), 3.34−3.47 (1 H, m), 7.19−7.30 (5 H, m), 9.07 (3 H, br s); MS (EI) *m*/*z* 302 (M^+). Anal. ($C_{19}H_{31}ClN_2O\cdot0.1H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-amino-1-phenylmethyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride (2e): yield 88%; mp 149−150 °C; $[\alpha]^{27}_D$ = −104.9 (*c* 0.610, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 0.18 (3 H, t, J = 7.0 Hz), 1.01 (3 H, t, J = 7.0 Hz), 1.08−1.12 (1 H, m), 1.83−1.86 (1 H, m), 2.08−2.18 (1 H, m), 2.42−2.47 (1 H, m), 2.89 (1 H, dq, J = 14.0, 7.0 Hz), 3.09 (1 H, dq, J = 14.0, 7.0 Hz), 3.23 (1 H, dq, J = 14.0, 7.0 Hz), 4.07−4.09 (1 H, m), 7.11−7.57 (10 H, m), 8.91 (3 H, br s); MS (EI) *m*/*z* 322 (M^+). Anal. ($C_{21}H_{27}ClN_2O\cdot0.8H_2O$) C, H, N.

(*E* and *Z*)-(1*R*,2*S*)-1-Phenyl-2-[3-(phenylseleno)-1-propenyl]-*N*,*N*-diethylcyclopropanecarboxamide (7). A mixture of **4f** (220 mg, 0.806 mmol) and $(CF_3CO)_2O$ (145 μL, 1.05 mmol) in MeCN (10 mL) was stirred at room temperature for 1 h under argon. The resulting solution was added to a NaSePh solution, which was prepared by stirring a mixture of $NaBH_4$ (95 mg, 2.5 mmol) and $(PhSe)_2$ (328 mg, 1.05 mmol) in EtOH (15 mL) at room temperature for 1 h, and the mixture was heated under reflux for 16 h under argon. The resulting mixture was evaporated, and the residue was partitioned between CH_2Cl_2 and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; MeOH/$CHCl_3$, 1:6) to give **7** as an oil (252 mg, 76%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.51 (t, J = 7.0 Hz), 0.52 (t, J = 7.0 Hz), 1.02−1.10 (m), 1.08 (t, J = 7.0 Hz), 1.67 (dd, J = 5.5, 6.0 Hz), 1.70 (dd, J = 5.0, 6.0 Hz), 2.49 (ddd, J = 6.0, 9.0, 9.5 Hz), 2.58 (ddd, J = 6.0, 9.5, 9.5 Hz), 2.89 (dq, J = 14.0, 7.0 Hz), 2.89−3.54 (m), 3.15 (dq, J = 14.0, 7.0 Hz), 3.41 (dq, J = 14.0, 7.0 Hz), 3.49 (dq, J = 14.0, 7.0 Hz), 3.53 (d, J = 7.5 Hz), 3.78 (d, J = 7.5 Hz), 5.00 (dd, J = 9.5, 10.5 Hz), 5.09 (1 H, dd, J = 9.5, 15.0 Hz), 5.72 (dt, j = 10.5, 7.5 Hz), 5.88 (dt, J = 15.0, 7.5 Hz), 7.16−7.50 (m); HR-MS (EI) calcd for $C_{23}H_{27}NOSe$ 413.1257, found 413.1237.

(1*R*,2*S*)-1-Phenyl-2-[1-(*tert*-butoxycarbonyl)amino]-2-propenyl]-*N*,*N*-diethylcyclopropanecarboxamides (8 and 9). To a solution of **7** (150 mg, 0.364 mmol), *t*-BuO_2CNH_2 (128 mg, 1.09 mmol), and *i*-$PrNH_2$ (0.38 mL, 2.2 mmol) in MeOH (0.5 mL) was added at 0 °C under argon NCS (146 mg, 1.09 mmol), and the mixture was stirred at room temperature for 2 h. The resulting mixture was evaporated and the residue was partitioned between diethyl ether and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 5:1) to give the mixture of **8** and **9** as an oil (135 mg, 99%, **8**:**9** = 1:6): ^{1}H NMR (500 MHz, $CDCl_3$) 0.54 (br t, J = 7.0 Hz), 0.77 (br t, J = 7.0 Hz), 1.12−1.20 (m), 1.40−1.50 (m), 1.57−1.62 (m), 1.83 (dd, J = 8.0, 16.0 Hz), 3.07 (dq, J = 14.0, 7.0 Hz), 3.12−3.23 (m), 3.28 (dq, J = 14.0, 7.0 Hz), 3.32 (dq, J = 14.0, 7.0 Hz), 3.36 (dq, J = 14.0, 7.0 Hz), 3.38 (dq, J = 14.0, 7.0 Hz), 3.52 (dq, J = 14.0, 7.0 Hz), 3.61 (dq, J = 14.0, 7.0 Hz), 3.80−3.90 (m), 4.30−4.40 (1 H, m), 4.95 (br s), 5.11 (d, J = 10.5 Hz), 5.12 (d, J = 10.0 Hz), 5.18 (d, J = 17.0 Hz), 5.20 (d, J = 17.0 Hz), 5.87 (br s), 6.03−6.10 (m), 7.18−7.31 (m); MS (EI) *m*/*z* 372 (M^+).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxy-2-(ethoxycarbonyl)-ethyl]-*N*,*N*-diethylcyclopropanecarboxamide (10). To a solution of $HN(TMS)_2$ (3.93 mL, 18.6 mmol) in THF (20 mL) was added dropwise BuLi solution (1.66 M in hexane, 11.2 mL, 18.6 mmol) at −10 °C under argon. After 20 min the solution was cooled to −78 °C and EtOAc (1.86 mL, 18.6 mmol) was added dropwise, and then the solution was stirred for 20 min at the same temperature. A solution of **3** (3.8 g, 15.5 mmol)

in THF (20 mL) was added dropwise to the solution, and the resulting solution was stirred at the same temperature for 2 h. The cooling bath was removed, and the reaction mixture was quenched by an addition of saturated NH_4Cl (10 mL). After the mixture was concentrated *in vacuo*, EtOAc and water were added, and then the mixture was partitioned. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, hexane/EtOAc, 2:1) to give **10** as an oil (4.1 g, 79%) and the corresponding 1′*R*-diastereomer as an oil (0.49 g, 10%). **10:** ^{1}H NMR (500 MHz, $CDCl_3$) 0.89 (3 H, t, J = 7.0 Hz), 1.14 (3 H, t, J = 7.0 Hz), 1.17 (1 H, dd, J = 5.5, 6.5 Hz), 1.27 (3 H, t, J = 7.0 Hz), 1.37 (1 H, ddd, J = 6.5, 8.5, 9.0 Hz), 1.63 (1 H, dd, J = 5.5, 8.5 Hz), 2.58 (1 H, dd, J = 6.0, 15.0 Hz), 2.70 (1 H, dd, J = 7.5, 15.0 Hz), 3.34 (1 H, dq, J = 14.0, 7.0 Hz), 3.35 (1 H, dq, J = 14.0, 7.0 Hz), 3.43 (1 H, dq, J = 14.0, 7.0 Hz), 3.51 (1 H, dq, J = 14.0, 7.0 Hz), 3.62−3.67 (1 H, m), 4.16 (2 H, q, J = 7.0 Hz), 5.40 (1 H, br s), 7.19−7.30 (5 H, m); MS (EI) m/z 333 (M^+). Anal. ($C_{19}H_{27}NO_4$) C, H, N.

The 1′-diastereomer of 10: ^{1}H-NMR (500 MHz, $CDCl_3$) 0.80 (3 H, t, J = 7.0 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.25 (3 H, t, J = 7.0 Hz), 1.38 (1 H, ddd, J = 6.5, 6.5, 9.0 Hz), 1.48 (1 H, dd, J = 5.5, 6.5 Hz), 1.57 (1 H, dd, J = 5.5, 9.0 Hz), 2.61 (1 H, dd, J = 8.5, 16.0 Hz), 2.87 (1 H, dd, J = 4.0, 16.0 Hz), 3.25−3.51 (4 H, m), 3.43 (1 H, d, J = 4.0 Hz), 4.15 (2 H, q, J = 7.0 Hz), 4.26−4.30 (1 H, m), 7.19−7.31 (5 H, m); MS (EI) m/z 333 (M^+).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1,3-dihydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide (11). A mixture of $NaBH_4$ (4.50 g, 119 mmol) and **10** (3.97 g, 11.9 mmol) in MeOH (40 mL) was stirred for 2 h at room temperature and then heated under reflux for 1 h. The mixture was cooled to room temperature and quenched by an addition of AcOH, and the resulting mixture was evaporated. The residue was partitioned between EtOAc and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; MeOH/$CHCl_3$, 1:6) to give **11** as a white powder (766 mg, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.0 Hz), 1.05 (1 H, dd, J = 5.5, 6.5 Hz), 1.15 (3 H, t, J = 7.0 Hz), 1.33 (1 H, ddd, J = 6.5, 8.5, 9.0 Hz), 1.71 (1 H, dd, J = 5.5, 8.5 Hz), 1.81−1.93 (2 H, m), 2.61 (1 H, br s), 3.32−3.53 (5 H, m), 3.79−3.87 (2 H, m), 5.83 (1 H, br s), 7.17−7.35 (5 H, m); MS (EI) m/z 291 (M^+). Anal. ($C_{17}H_{25}NO_3 \cdot 0.2H_2O$) C, H, N.

(1*S*,2*R*-)-1-Phenyl-2-[(*S*)-1-hydroxy-3-(pivaloyloxy)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (12). A mixture of **11** (1.60 g, 5.50 mmol) and pivaloyl chloride (1.26 mL, 7.59 mmol) in pyridine (30 mL) was stirred at 0 °C for 1.5 h under argon, and then water was added. The resulting mixture was evaporated, and the residue was partitioned between EtOAc and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; EtOAc/hexane, 1:3) to give **12** as an oil (1.81 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.0 Hz), 1.03 (1 H, dd, J = 5.5, 6.5 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.18 (9 H, s), 1.29 (1 H, ddd, J = 6.5, 8.5, 9.0 Hz), 1.70 (1 H, dd, J = 5.5, 8.5 Hz), 1.89−2.03 (2 H, m), 3.23−3.28 (1 H, m), 3.31−3.46 (3 H, m), 3.51 (1 H, dq, J = 14.0, 7.0 Hz), 4.24 (2 H, t, J = 6.5 Hz), 7.20−7.31 (5 H, m); MS (EI) m/z 375 (M^+). Anal. ($C_{22}H_{33}NO_4$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-(pivaloyloxy)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (13). Compound **13** was prepared from **12** (1.50 g, 4.0 mmol) as described above for **5c**. After purification by column chromatography (silica gel; EtOAc/hexane, 1:2), **13** was obtained as an oil (1.46 g, 91%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.41 (3 H, t, J = 7.0 Hz), 1.06 (1 H, dd, J = 5.0, 9.0 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.21 (9 H, s), 1.59 (1 H, dd, J = 5.0, 6.5 Hz), 1.92 (1 H, ddd, J = 6.5, 9.0, 9.5 Hz), 1.98−2.13 (2 H, m), 3.07 (1 H, dq, J = 4.0, 7.0 Hz), 3.11−3.15 (1 H, m), 3.19 (1 H, dq, J = 14.0, 7.0 Hz), 3.49 (1 H, dq, J = 14.0, 7.0 Hz), 3.67 (1 H, dq, J = 14.0, 7.0 Hz), 4.19−4.29 (2 H, m), 7.21−7.32 (5 H, m); MS (EI) m/z 400 (M^+). Anal. ($C_{22}H_{34}N_4O_3$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-hydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide (14). To a solution of **13** (1.33 g, 3.33 mmol) in MeOH (30 mL) was added NaOMe (28% in MeOH, 2.5 mL), and the resulting mixture was stirred at room temperature for 15 h under argon and then neutralized with AcOH. The resulting mixture was evaporated, and the residue was partitioned between EtOAc and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; EtOAc/hexane, 3:1) to give **14** as a white powder (1.04 g, 99%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.44 (3 H, t, J = 7.0 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.10−1.14 (1 H, m), 1.58 (1 H, dd, J = 5.5, 6.0 Hz), 1.83 (1 H, br s), 1.87−2.08 (3 H, m), 3.08 (1 H, dq, J = 14.0, 7.0 Hz), 3.18−3.29 (2 H, m), 3.50 (1 H, dq, J = 14.0, 7.0 Hz), 3.65 (1 H, dq, J = 14.0, 7.0 Hz), 3.84 (2 H, t, J = 6.0 Hz), 7.21−7.33 (5 H, m); MS (EI) m/z 385 (M^+). Anal. ($C_{22}H_{33}N_4O_2$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-(tosyloxy)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (15). A mixture of **14** (400 mg, 1.27 mmol), TsCl (606 mg, 3.18 mmol), Et_3N (0.89 mL, 6.4 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 15 h, and then water and CH_2Cl_2 were added. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; EtOAc/hexane, 1:3) to give **15** as an oil (592 mg, 99%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.49 (3 H, t, J = 7.0 Hz), 1.10 (3 H, t, J = 7.0 Hz), 1.20 (1 H, dd, J = 5.0, 9.5 Hz), 1.41 (1 H, dd, J = 5.0, 6.5 Hz), 1.68 (1 H, ddd, J = 6.5, 9.5, 9.5 Hz), 1.92−1.99 (1 H, m), 2.03−2.10 (1 H, m), 2.45 (3 H, s), 3.09 (1 H, dq, J = 14.0, 7.0 Hz), 3.19−3.26 (2 H, m), 3.46 (1 H, dq, J = 14.0, 7.0 Hz), 3.55 (1 H, dq, J = 14.0, 7.0 Hz), 4.11−4.16 (1 H, m), 4.19−4.24 (1 H, m), 7.22−7.36 (7 H, m), 7.80 (2 H, d, J = 8.0 Hz); MS (EI) m/z 470 (M^+). Anal. ($C_{24}H_{30}N_4O_4S \cdot 0.1H_2O$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-(phenylseleno)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (16). A mixture of $(PhSe)_2$ (165 mg, 0.528 mmol) and $NaBH_4$ (60 mg, 1.58 mmol) in EtOH (10 mL) was stirred at room temperature for 1 h under argon, to which a solution of **15** (190 mg, 0.404 mmol) in EtOH (4 mL) was added. The resulting mixture was stirred at room temperature for 15 h and then evaporated. The residue was partitioned between diethyl ether and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; EtOAc/hexane, 1:3) to give **16** as an oil (156 mg, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.41 (3 H, t, J = 7.0 Hz), 1.01 (1 H, dd, J = 5.0, 9.5 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.54 (1 H, dd, J = 5.0, 6.5 Hz), 1.87 (1 H, ddd, J = 6.5, 9.5, 9.5 Hz), 2.02−2.11 (2 H, m), 2.91−2.97 (1 H, m), 3.02−3.15 (3 H, m), 3.20 (1 H, dq, J = 14.0, 7.0 Hz), 3.50 (1 H, dq, J = 14.0, 7.0 Hz), 3.64 (1 H, dq, J = 14.0, 7.0 Hz), 7.20−7.31 (8 H, m), 7.51−7.53 (2 H, m); MS (EI) m/z 456 (M^+). Anal. ($C_{23}H_{28}N_4O_4Se$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-3-(phenylseleno)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (17). A mixture of **16** (400 mg, 1.27 mmol) and Ph_3P (180 mg, 0.69 mmol) in pyridine (2 mL) was stirred at room temperature for 1 h, 28% NH_4OH (2 mL) was added, and then the mixture was stirred at room temperature for 12 h. The resulting mixture was evaporated, and the residue was partitioned between diethyl ether and water. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 90:10:0.2) to give **17** as an oil (70 mg, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.83 (3 H, t, J = 7.0 Hz), 1.09 (1 H, dd, J = 5.0, 6.5 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.20 (1 H, ddd, J = 6.5, 9.0, 9.5 Hz), 1.49 (1 H, dd, J = 5.0, 9.0 Hz), 1.85−2.01 (2 H, m), 2.22 (2 H, br s), 2.54 (1 H, ddd, J = 5.0, 8.0, 9.5 Hz), 2.99 (1 H, ddd, J = 6.5, 9.5, 12.0 Hz), 3.09 (1 H, ddd, J = 5.5, 9.5, 12.0 Hz), 3.28 (1 H, dq, J = 14.0, 7.0 Hz), 3.31 (1 H, dq, J = 14.0, 7.0 Hz), 3.42 (1 H, dq, J = 14.0, 7.0 Hz), 3.53 (1 H, dq, J = 14.0, 7.0 Hz), 7.17−7.69 (10 H, m); HR-MS (EI) calcd for $C_{23}H_{30}N_2OSe$ 430.1523, found 413.1497.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]-3-(phenylseleno)propyl]-*N*,*N*-diethylcyclopropanecarboxamide (18). A mixture of **17** (400 mg, 1.27 mmol) and Boc_2O (960 mg, 2.11 mmol) in CH_2Cl_2 (35 mL) was stirred at room temperature for 5 h, and then water and CH_2Cl_2 were added. The organic layer separated was washed with brine,

dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; EtOAc/hexane, 1:3) to give **18** as a white powder (1.02 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.57 (3 H, br t), 1.13 (3 H, t, J = 7.0 Hz), 1.19−1.34 (2 H, m), 1.41 (9 H, s), 1.72−1.78 (1 H, m), 2.03−2.12 (1 H, m), 2.32−2.42 (1 H, m), 2.92 (1 H, ddd, J = 7.0, 9.0, 12.0 Hz), 3.01 (1 H, ddd, J = 5.0, 9.5, 12.0 Hz), 3.06−3.15 (1 H, m), 3.27 (1 H, dq, J = 14.0, 7.0 Hz), 3.38 (1 H, dq, J = 14.0, 7.0 Hz), 3.44−3.52 (1 H, m), 3.56 (1 H, dq, J = 14.0, 7.0 Hz), 4.94 (1 H, br s), 7.17−7.29 (8 H, m), 7.47−749 (2 H, m); MS (EI) m/z 530 (M^+). Anal. ($C_{28}H_{38}N_2O_3Se$) C, H, N.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-propenyl]-*N*,*N*-diethylcyclopropanecarboxamide (8). A mixture of **18** (680 mg, 1.28 mmol) and aqueous H_2O_2 (30%, 1.2 mL) in THF (25 mL) was stirred at room temperature for 5 days, and then water and CH_2Cl_2 were added. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH, 20:1) to give **8** as a white powder (449 mg, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.54 (3 H, br t, J = 7.0 Hz), 1.12−1.20 (1 H, m), 1.13 (3 H, t, J = 7.0 Hz), 1.42 (9 H, s), 1.46−1.50 (1 H, m), 1.83 (1 H, dd, J = 8.0, 16.0 Hz), 3.07 (1 H, dq, J = 14.0, 7.0 Hz), 3.32 (1 H, dq, J = 14.0, 7.0 Hz), 3.36 (1 H, dq, J = 14.0, 7.0 Hz), 3.61 (1 H, dq, J = 14.0, 7.0 Hz), 3.80−3.90 (1 H, m), 4.95 (1 H, br s), 5.11 (1 H, d, J = 10.5 Hz), 5.20 (1 H, d, J = 17.0 Hz), 6.03−6.10 (1 H, m), 7.18−7.30 (5 H, m); HR-MS (EI) calcd for $C_{22}H_{32}N_2O_3$ 372.2413, found 372.2419.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-2-propenyl]-*N*,*N*-diethylcyclopropanecarboxamide (2f). A mixture of **19** (100 mg, 0.268 mmol) and aqueous TFA (90%, 3 mL) in MeOH (4.5 mL) was stirred at room temperature for 15 h. The pH of the mixture was adjusted to about 10 with 3 M KOH, and then CH_2Cl_2 was added. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 80:20:0.2) to give an oil. The oil was dissolved in MeOH (1 mL), which was put on a column of Diaion WA-30 resin (1 × 5 cm, Cl^- form), and the column was developed with MeOH. The solvent was evaporated, and the residue was treated with diethyl ether to give white crystals of **2f** as hydrochloride (40 mg, 50%): mp 185−188 °C; $[\alpha]^{27}_D$ = +83.7 (c 0.680, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.0 Hz), 1.09 (1 H, dd, J = 6.0, 6.5 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.72 (1 H, ddd, J = 6.5, 9.0, 10.0 Hz), 1.88 (1 H, dd, J = 6.0, 9.0 Hz), 3.20 (1 H, dd, J = 7.0, 10.0 Hz), 3.30 (1 H, dq, J = 14.0, 7.0 Hz), 3.34−3.49 (3 H, m), 5.42 (1 H, d, J = 10.5 Hz), 5.54 (1 H, d, J = 17.5 Hz), 6.35 (1 H, ddd, J = 7.0, 10.5, 17.5 Hz), 7.20−7.31 (5 H, m), 9.20 (3 H, br s); MS (EI) m/z 272 (M^+). Anal. ($C_{17}H_{25}ClN_2O\cdot 0.2H_2O$) C, H, N.

Catalytic Hydrogenation of 2f. Compound **2f** (hydrochloride, 3.2 mg) was partitioned between $CHCl_3$ (5 mL) and 1 M NaOH (2 mL). The separated organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue and 10% Pd−charcoal (1 mg) in MeOH (2 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 1.5 h, and then the catalyst was filtered off. The filtrate was evaporated to give **2b** as an oil (2.5 mg, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) 0.81 (3 H, t, J = 7.0 Hz), 0.95 (3 H, t, J = 7.5 Hz), 1.11−1.15 (1 H, m), 1.13 (3 H, t, J = 7.0 Hz), 1.19−1.27 (1 H, m), 1.47 (1 H, dd, J = 5.0, 9.0 Hz), 1.48−1.55 (1 H, m), 1.59−1.67 (1 H, m), 2.31−2.34 (3 H, m), 3.26 (1 H, dq, J = 14.0, 7.0 Hz), 3.29 (1 H, dq, J = 14.0, 7.0 Hz), 3.45 (1 H, dq, J = 14.0, 7.0 Hz), 3.57 (1 H, dq, J = 14.0, 7.0 Hz), 7.16−7.29 (5 H, m); MS (EI) m/z 274 (M^+).

Binding Assay. The binding affinity for the NMDA receptors was investigated according to previously reported methods.[17]

Assay with Voltage-Clamped Oocytes. The blocking effects of the compound on the NMDA receptors were investigated according to previously reported methods.[18]

Inhibitory Effects on the Uptake of 5-HT. Under various concentrations of the compounds, cerebral cortical synaptic membrane from rats was incubated at 20 °C for 45 min in the presence of [^{3}H]paroxetine (2 nM) in 50 mM Tris-HCl (pH 7.4) containing NaCl (120 mM) and KCl (5 mM). Nonspecific binding was determined by the addition of femoxetine (10 μM). Incubations were stopped by rapid filtration over GF/C glass-fiber filters that were presoaked in a solution of 0.1% polyethylenimine for at least 1 h before use. Filters were washed with cold Tris-HCl buffer (4 mL × 3), and specific binding was defined as bound radioactivity.

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