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Synthesis of (1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide (PPDC) Derivatives Modified at the Carbamoyl Moiety As a New Class of NMDA Receptor Antagonists

Yuji Kazuta,[a] Ryuichi Tsujita,[b] Kiyoshi Ogawa,[b] Tadami Hokonohara,[b] Kanako Yamashita,[b] Kiyoko Morino,[a] Akira Matsuda[a] and Satoshi Shuto[a,*]

[a]*Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan*
[b]*Institute of Life Science Research, Asahi Chemical Industry Co., Ltd., Ohito-cho, Shizuoka 410-2321, Japan*

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Abstract—(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide (PPDC, **4a**), which is a conformationally restricted analogue of the antidepressant milnacipran [(±)-**1**], represents a new class of potent NMDA receptor antagonists. A series of PPDC analogues modified at the carbamoyl moiety were synthesized. Among these, (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-dipropylcyclopropanecarboxamide (**4d**) was identified as the most potent NMDA receptor antagonist in this series and clearly reduced the MMDA receptor mediated potentiation of rat hippocampal slices, a model of long-term potentiation (LTP). The three-dimensional structure of **4d** was also analyzed in detail to clarify the receptor-binding conformation.

Introduction

Various antagonists of NMDA (*N*-methyl-D-aspartic acid) receptors have been developed,[1–3] since the receptors may be involved in both chronic and acute neurodegenerative disorders.[1] Some have been shown to be effective in experimental models of epilepsy and stroke.[1–3] Unfortunately, the non-competitive inhibitors currently available, such as MK-801, frequently have serious behavioral effects[4] and cause neuronal vacuolization,[5] while competitive inhibitors are often inactive in vivo because of their poor permeability through the blood–brain barrier.[6] Therefore, another type of efficient NMDA receptor antagonist is eagerly desired.

(±)-(*Z*)-2-Aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide [milnacipran, (±)-**1**],[7] a clinically efficient antidepressant due to competitive inhibition of the re-uptake of serotonin (5-HT) in the CNS,[8] is also recognized as a non-competitive NMDA receptor antagonist.[9] Although the binding affinity of (±)-**1** for the NMDA receptor is not very high, the compound has the advantage of sufficiently penetrating into the brain without serious side effects,[8d,e] making it a clinically useful antidepressant and therefore a good lead for an efficient NMDA receptor antagonist. This may be because the structure of milnacipran is clearly different from that of previous NMDA receptor antagonists.

We previously reported the design of conformationally restricted analogues of (±)-**1** using a new method to restrict the conformation of cyclopropane derivatives to increase their specific affinity for the NMDA receptor.[10] Adjacent substituents on a cyclopropane ring exert significant mutual steric repulsion, since 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. Because the primary amino function of (±)-**1** is essential for the binding affinity for the NMDA receptor,[9] we assumed that the conformation of the aminomethyl moiety would significantly affect the activity of the compound. While the aminomethyl moiety is not so bulky and may freely rotate at least to some extent, the conformers A and B may be preferable to conformer C

*Corresponding author. Tel.: +81-11-706-3229; fax: +81-11-706-4980; e-mail: shu@pharm.hokudai.ac.jp

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because of the serious steric repulsion with the bulky diethylcarbamoyl group in conformer C, as shown in Figure 2. Based on these considerations, we designed and synthesized four types of conformationally restricted analogues of (±)-**1** with different stereochemistries, that is, Type-1 and Type-2, and their enantiomers Type-3 and Type-4, as shown in Figure 1.[10a] In these analogues, an alkyl group introduced at the α-position of the amino function of (±)-**1** restricts the location of the amino group in space due to steric repulsion from the diethylcarbamoyl group.[10a] Therefore, the conformation of these compounds can be limited depending on the configuration of the alkyl group introduced; conformer B would be predominant in Type-1 and its enantiomer Type-3, while conformer A would be predominant in Type-2 and its enantiomer Type-4, as shown in Figure 2.

Biological evaluations of these compounds showed: (1) that the conformational restriction can improve the activity; (2) that analogues with a (1*S*,2*R*,1′*S*)-configuration (Type-1) are the most active ones in the four types of analogues, and (3) that C-2 alkyl groups, such as ethyl, ethenyl, and ethynyl groups, are suitable for the 1′-substituents.[10d] Thus, we found that analogues with a Type-1 configuration, that is, **2** (PEDC), **4a** (PPDC), and **6** (PPEDC), were potent non-competitive NMDA receptor antagonists which significantly inhibited the binding of [^{3}H] MK-801, with IC_{50} values about 30-fold stronger than that of (±)-**1**.[10d–f]

These previous studies suggested that PPDC (**4a**) was likely to be the most desirable, since it was a potent NMDA receptor antagonist virtually devoid of the inhibitory effect on 5-HT-uptake, while **2** and **6** are strong 5-HT-uptake inhibitors like the parent compound milnacipran.[10 h] Pharmacological studies on PPDC have shown: (1) that PPDC binds to the receptor in an agonist-independent manner, whereas the binding affinities of known non-competitive NMDA receptor antagonists are affected by agonist concentration;[10h] and (2) that the release of PPDC and the previous non-competitive antagonists, such as MK-801, from their binding sites was quite different with respect to their dependence on the direction of ionic currents flowing through the channel pores of NMDA receptors, that is, outward currents had no effect on the channel block of PPDC, while the release of MK-801 was significantly accelerated under outward current conditions in the voltage-clamp experiments.[10f] These results, together with the structural features of PPDC, which are clearly different from those of the previous antagonists, suggest that PPDC represents a new class of NMDA receptor antagonists.

The above results prompted us to plan further studies on PPDC (**4a**). Thus, we synthesized derivatives of PPDC modified at the 1-carbamoyl moiety for developing useful NMDA receptor antagonists and for further clarifying the structure–activity relationship (SAR). We previously modified the structure of milnacipran, the parent compound of PPDC, and recognized that the substituent having the amide structure (-CONR^{1}R^2) at the 1-position is essential for the NMDA receptor

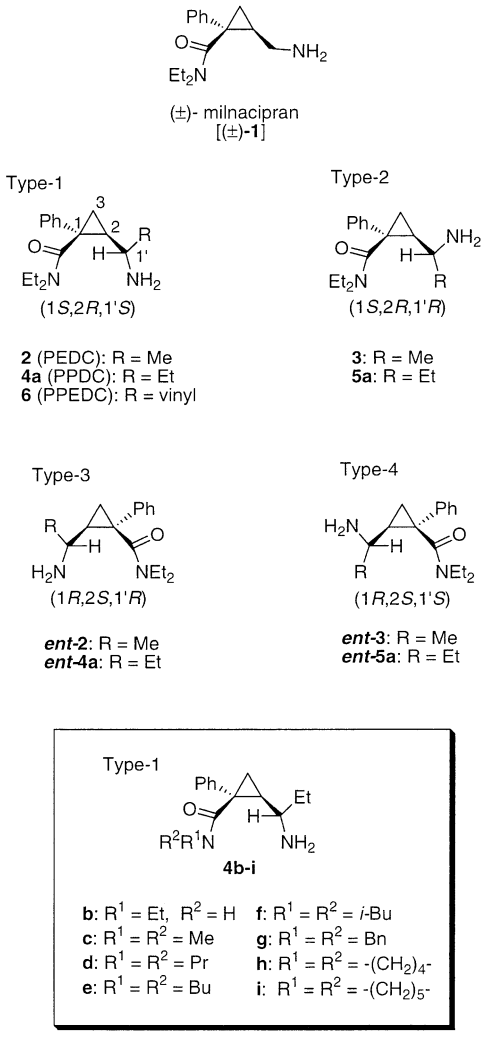


Figure 1. Milnacipran and its conformationally restricted analogues.

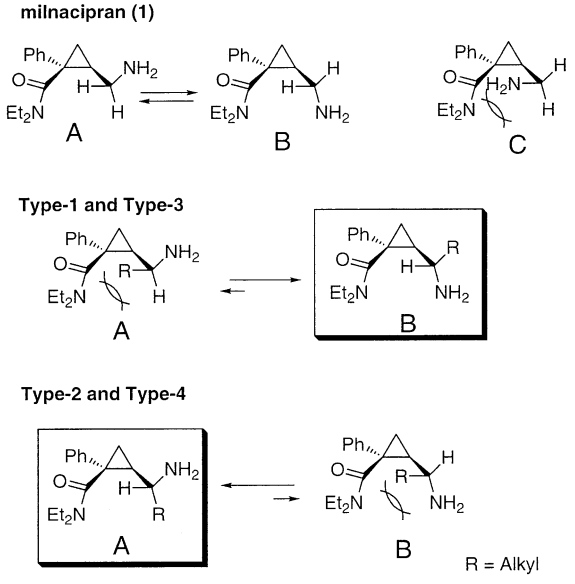
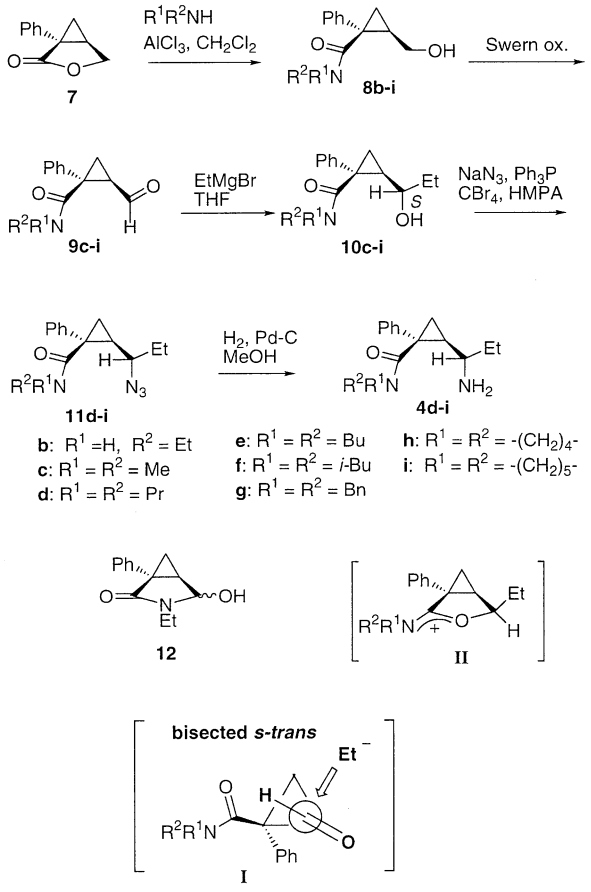
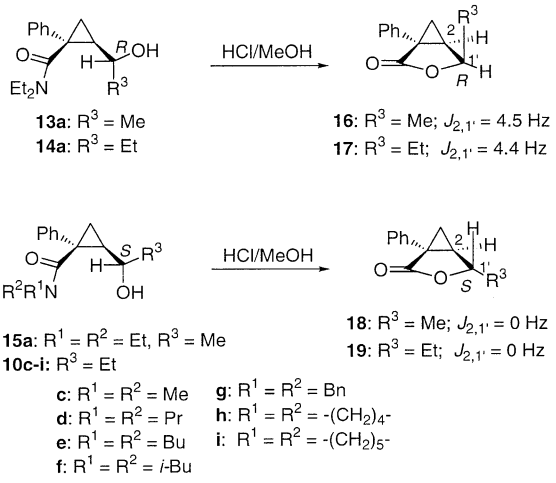


Figure 2. Conformational restriction of milnacipran by introducing an alkyl substituent at the 1′-position.



Scheme 1.



Scheme 2.

antagonist activity.[9] Accordingly, we designed the carbamoyl moiety-modified analogues of PPDC, **4b–i**, preserving the amide structure, as shown in Figure 1. Among the newly synthesized compounds, 1-phenyl-2-[(*S*)-1-amino - 3 - propyl] - *N*,*N* - dipropylcyclopropanecarboxamide (**4d**) was identified as the most potent compound in this series. We also investigated detailed three-dimensional structure of **4d** to clarify the receptor-binding conformation. In this paper we describe the results of these studies.

Results and Discussion

Chemistry

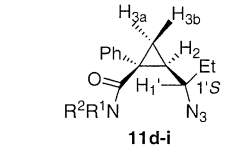
The target compounds were synthesized from an optically active lactone **7** with a (1*S*,2*R*)-configuration, which was readily prepared from (*R*)-epichlorohydrin,[10a] as shown in Scheme 1.

In the previous synthesis of PPDC, the diethylaminolysis of the lactone **7** was performed with $LiNEt_2$ in THF at −78 °C. We found that $AlCl_3$ effectively promoted aminolysis of **7** with various secondary amines in CH_2Cl_2 at room temperature. Consequently, the corresponding ring-opened amides **8b–i** were readily prepared in high yields. From **8d–i**, the target compounds **4d–i** were synthesized according to the procedure developed previously for the synthesis of PPDC.[10a] Thus, after Swern oxidation of **8c–i**, a Grignard reaction of the resulting aldehydes **9c–i** with EtMgBr gave stereoselectively the 1′*S*-addition products **10c–i**. However, Swern oxidation of the *N*-ethylamide **8b** gave none of the corresponding aldehyde but gave instead the cyclized aminal **12**. However, the Grignard reaction of **12** with EtMgBr did not proceed.

We demonstrated earlier that the 1′-configurations of 1′*R*-methyl derivative **13a** and its 1′*S*-diastereomer **15a** can be determined based on the their ^1H NMR coupling constant between the 2-H and the 1′-H after their conversion into the corresponding lactones **16** and **18**,[10a] as shown in Scheme 2. Thus, in this study, after conversion of **14a** and **10c–i** into the 1′-ethyllactones **17** and **19**, respectively, the 1′-configuration of **17** was confirmed as *R* ($J_{2,1'}$=4.4 Hz) and that of **19** as *S* ($J_{2,1'}$=0 Hz). Therefore the Grignard reaction of the cyclopropylaldehydes **9c–i** with EtMgBr would proceed highly stereoselectively via the stereoelectronically favored bisected *s-trans* conformation **I** (Scheme 1), similarly as in previous examples.[10a,d,e]

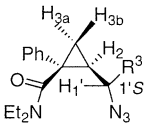
Introduction of an azido group by a Mitsunobu-type reaction was performed by treating **10d–i** with a NaN_3/Ph_3P/CBr_4 system[11] in HMPA to give the corresponding 1′*S*-azides **11d–i**. As we previously reported,[10a,d,e] this reaction is likely to occur via the neighboring group participation intermediate **II** (Scheme 1). Accordingly, the reaction should produce the corresponding configuration-retained azides. On the other hand, when the *N*,*N*-dimethylamide **10c** was treated with the same NaN_3/Ph_3P/CBr_4 system in HMPA, the lactone **17** (Scheme 2) with the 1′*R*-configuration, instead of the expected 1′*S*-azide **11c**, was obtained as the major product. The formation of **17** may support the neighboring group participation reaction pathway, since it should be the hydrolysis product of the intermediate **II**. The 1′-configurations of azides **11d–i** were confirmed by the chemical shifts in ^1H NMR spectra as summarized in Table 1. The table shows the ^1H NMR spectral data of the previously synthesized 1′*R*-azides **20R**[10a] and

Table 1. ^{1}H NMR chemical shifts of the 1′-azide derivatives in $CDCl_3$

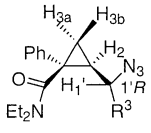


11d-i

d: $R^1 = R^2$ = Pr **g**: $R^1 = R^2$ = Bn
e: $R^1 = R^2$ = Bu **h**: $R^1 = R^2$ = -$(CH_2)_4$-
f: $R^1 = R^2$ = *i*-Bu **i**: $R^1 = R^2$ = -$(CH_2)_4$-



20S: R^3 = Me
21S: R^3 = Et

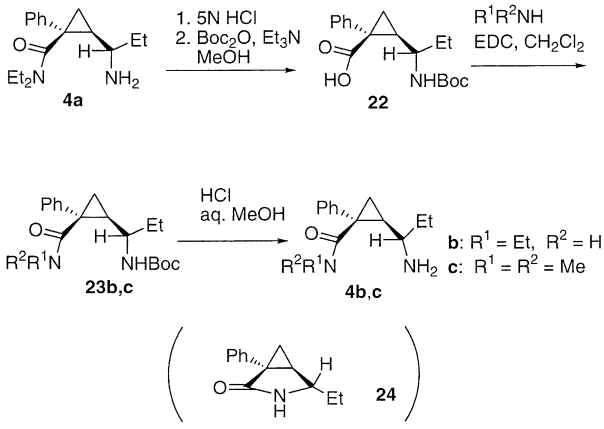


20R: R^3 = Me
21R: R^3 = Et

Compd	R^1R^2N	R^3	1′-config.	Chemical shift, δ (multiplicity)			
				H-1′	H-2	H-3a	H-3b
20S	Et_2N	Me	*S*	2.98–3.08 (m)	1.95 (ddd)	0.91 (dd)	1.61 (dd)
21S	Et_2N	Et	*S*	2.86 (ddd)	1.96 (ddd)	0.95 (dd)	1.65 (dd)
20R	Et_2N	Me	*R*	3.33–3.38 (m)	1.48–1.52 (m)	1.48–1.52 (m)	1.48–1.52 (m)
21R	Et_2N	Et	*R*	3.12–3.26 (m)	1.47–1.60 (m)	1.47–1.60 (m)	1.47–1.60 (m)
11d	Pr_2N	Et	*S*	2.84–2.90 (m)	1.95 (ddd)	0.97 (dd)	1.63 (dd)
11e	Bu_2N	Et	*S*	2.83–2.93 (m)	1.96 (ddd)	0.96 (dd)	1.64 (dd)
11f	*i*-Bu_2N	Et	*S*	3.09 (m)	1.61–1.77 (m)	1.33 (dd)	1.37 (dd)
11g	Bn_2N	Et	*S*	3.05 (m)	1.74–1.85 (m)	1.20 (dd)	1.57 (dd)
11 h	Pyrrodidyl	Et	*S*	3.16 (dt)	1.94 (ddd)	0.92 (dd)	1.63–1.73 (m)
11i	Piperidyl	Et	*S*	2.88 (m)	1.94 (ddd)	1.00 (dd)	1.59 (dd)

21R,[10a] and 1′*S*-azides **20S**,[10a] **21S**,[10a] the stereochemistries of which were determined earlier. The chemical shift pattern of the 1′*S* azides is clearly different from that of the 1′*R*-azides; in the 1′*S*-azide series, the H-2, H-3a, and H-3b signals are separately observed around δ 1.9, 1.0 and 1.6, respectively, while the three protons signals overlap in the spectra of the 1′*R* azides. The signals of the H-2, H-3a, and H-3b in the azides **11d–i**, prepared in the present study, were observed separately as shown in Table 1 supporting their 1′*S*-configurations. Hydrogenation of the azides **11d–i** with Pd-C afforded the target compounds **4d–i**.

The *N*,*N*-dimethyl- and *N*-ethylcarbamoyl analogues, **4c** and **4b**, respectively, which could not be synthesized by the above procedure, were obtained from PPDC (**4a**), as shown in Scheme 3. Acidic hydrolysis of **4a**, followed by protection of the amino group with a Boc group, gave an amino acid derivative **22**. Condensation between **22** and dimethylamine or ethylamine with EDC, and subsequent deprotection gave the desired **4b** and **4c**, even though the overall yields were not high. In the procedure, 1,2-*cis* substituents were easily cyclized to produce the lactam **24**, which made the yields low.



Scheme 3.

Binding affinity for 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, and the results are shown in Table 2.

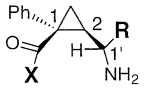
The binding affinity was significantly affected by the alkyl substituents on the nitrogen of the carbamoyl moiety. The binding affinities of the *N*-ethylcarbamoyl (**4b**) and *N*,*N*-dimethylcarbamoyl (**4c**) derivatives were weaker than that of the parent diethyl derivative **4a** (PPDC). Notably, the *N*,*N*-dipropylcarbamoyl derivative **4d** significantly inhibited the binding of [^{3}H] MK-801 with an IC_{50} value of 0.13±0.016 μM, which is about 2-fold stronger than that of PPDC (IC_{50} = 0.20±0.02 μM). The derivatives having a carbamoyl moiety bulkier than dipropylcarbamoyl group, such as **4e**, **4f**, and **4g**, showed a weaker affinity than PPDC. The affinities of the cyclic carbamoyl derivatives, **4 h** and **4i**, were also insignificant.

The *N*,*N*-dipropylcarbamoyl derivative **4d** had the most significant affinity for the receptor among the compounds described.

Inhibitory effects on the uptake of 5-HT

The inhibitory effects of the compounds on the uptake of 5-HT by nerve terminals of cerebral cortical synaptic membrane from rats were evaluated with [^{3}H] paroxetine, one of the most potent competitive 5-HT uptake inhibitor, as a radioligand, and the results are shown in Table 2. Although previous potent NMDA receptor

Table 2. Effects of the compounds on NMDA receptor binding and 5-HT uptake



Type-1 (1*S*,2*R*,1'*S*)

Compd	X	R	NMDA receptor binding[a]	5-HT-uptake[b]	Selectivity index[c]
			(IC_{50}, μM)	(K_i, μM)	(5-HT/NMDA)
(±)-**1**	Et_2N	H	6.3±0.3	0.0085±0.0006	0.0013
2 (PEDC)	Et_2N	Me	0.35±0.08	0.014±0.002	0.040
6 (PPEDC)	Et_2N	$CH{=}CH_2$	0.16±0.02	0.023±0.0007	0.14
4a (PPDC)	Et_2N	Et	0.20±0.02	24±0.9	120
4b	EtHN	Et	2.2±0.52	>100	>45
4c	Me_2N	Et	1.1±0.1	>100	>91
4d	Pr_2N	Et	0.13±0.02	>100	>770
4e	Bu_2N	Et	3.5±0.3	22±4.4	6.3
4f	*i*-Bu_2N	Et	1.5±0.1	11±2.3	7.3
4g	Bn_2N	Et	14±0.11	NT[d]	—
4 h	Pyrrodidyl	Et	1.2±0.3	>100	83
4i	Piperidyl	Et	2.6±0.01	>100	38
Ketamine			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}).
[d]Not tested.

antagonists, such as **2** (PEDC) and **6** (PPEDC), were also strong 5-HT uptake inhibitors like the parent compound milnacipran [(±)-**1**], all of the newly synthesized compounds were virtually inactive in this system. It should be noted that the *N*,*N*-dipropylcarbamoyl derivative **4d**, which showed the most potent binding affinity for NMDA receptor in this series, was completely inactive as a 5-HT-uptake inhibitor, while a weak 5-HT-uptake inhibition activity remained with PPDC (**4a**). Thus the selectivity index on the NMDA receptor binding and the 5-HT uptake inhibition of **4d** (NMDA/5-HT > 770) is clearly superior to that of PPDC (NMDA/5-HT = 120). While, as reported previously, the 5-HT uptake inhibitory effects of the compounds significantly affected by the alkyl group at the 1′ positon,[10d,e] this study showed that the effects are also affected by the structure of the carbamoyl moiety.

Effects on NMDA receptor mediated LTP in rat hippocampal CA1 area

NMDA receptors mediate the induction of long-term potentiation (LTP) in hippocampus. It has been shown that NMDA receptor antagonists block the induction of LTP correlating with their potency as NMDA receptor antagonists.[1–3] We investigated the effect of the most active compound **4d** in this series and a well-known non-competitive antagonist MK-801 on the MMDA receptor mediated LTP with rat hippocampal slices. The LTP was induced by perfusing the slice with Mg^{2+}-free artificial cerebrospinal fluid (ACSF).[13] The results are shown in Figure 3. The application of Mg^{2+} free ACSF evoked an increase of excitability in hippocampal pyramidal cells. This potentiation could only be reversed in part by perfusing with normal ACSF. Although **4d** was inactive at 3×10^{-7} M, it clearly reduced the LTP at 1×10^{-6} M (Fig. 3b), the potency of which was similar to that of MK-801 at 1×10^{-7} M (Fig. 3a). These results suggest that **4d** can prevent the overstimulation of the NMDA receptor which may cause neuronal damage.

Conformational analysis of 4d

Our hypothesis regarding conformational restriction based on the structural feature of the cyclopropane ring described above has been supported by X-ray crystallographic analysis of ***ent*-4a**, the enantiomer of PPDC, and its 1′-diastereomer ***ent*-5a**.[10a] However, the conformation of a compound in the solid state may be different from that in solution. Therefore, we investigated the conformation of **4d** in aqueous solution based on NOE data. The three-dimensional structure in aqueous solution was constructed by MM2 calculations with a simulated annealing method based on the NOE constraints of the intramolecular proton pairs measured in D_2O.[14] The structures of **4d** obtained by the calculation based on the NOE data shown in Figure 4 was in agreement with the speculated conformer B, shown in Figure 2.

The results suggest that the conformation of the substituents on a cyclopropane ring of **4d** would be restricted by the steric effect of adjacent substituents even in solution, as we hypothesized, and that the compound would bind to the NMDA receptor in a conformation like conformer B (Fig. 2).

Conclusion

We have developed a series of conformationally restricted analogues of milnacipran [(±)-**1**] and identified (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-dipropylcyclopropanecarboxamide (**4d**) as the most potent compound in this series of NMDA receptor antagonists. Compound **4d** clearly reduced the MMDA receptor

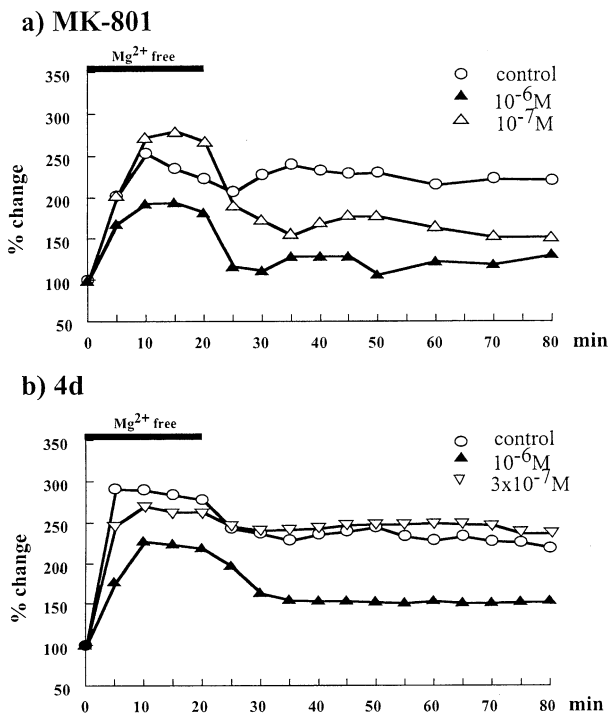


Figure 3. Effects of MK-801 (a) and **4d** (b) on NMDA receptor mediated LTP induced by perfusion of Mg^{2+} free ACSF in rat hippocampal CA1 area ($n=2$). Mg^{2+} free medium was perfused 0–20 min. Compounds were prefused for 65 min before and during perfusion of Mg^{2+} free ACSF. Ordinate: percent of amplitude of population spikes when the amplitude before perfusion of Mg^{2+} free ACSF was defined as 100. Abscissa: time in min with control.

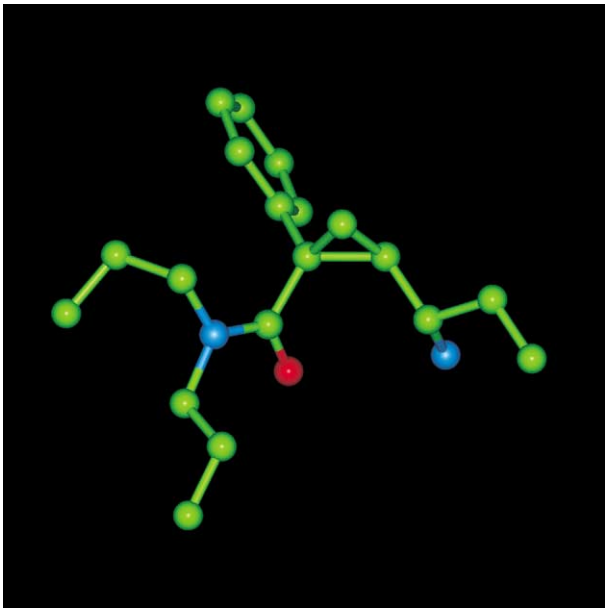


Figure 4. The MM2 calculation structure of **4d** by simulated annealing method based on the NOE data.

mediated potentiation of rat hyppocampal slices, a model of LTP. These results suggest that **4d** is a new candidate as a drug for preventing NMDA receptor related neuronal damage.

Experimental

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 and-400, or Bruker AMX 500 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. Reactions were performed under argon.

General procedure for the preparation of cyclopropylcarboxamides 8b–i

To a solution of **7** (10.5 g, 60.0 mmol) in CH_2Cl_2 (200 mL) was added $AlCl_3$ (16.0 g, 120 mmol) and then the mixture was cooled to 0 °C, and then an amine (240 mmol, a 2.0 M solution of the amine in THF was used in the synthesis of **8b** and **8c**) was added slowly. The mixture was stirred at room temperature for 24 h, and then the reaction was quenched with saturated aqueous NH_4Cl. After addition of CH_2Cl_2 and H_2O, the resulting mixture was partitioned. The organic layer was washed with 1 N HCl and brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:4) to give the corresponding cyclopropylcarboxamide.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*-ethylcyclopropanecarboxamide (8b). Yield 25%, crystal; mp (hexane/AcOEt) 104–105 °C; $[\alpha]_D^{22}$ −56.60 ° (*c* 1.405, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (3H, t,–$NCH_2\underline{CH_3}$, $J=7.2$ Hz), 1.29 (1H, dd, H-3a, $J_{3a,3b}=4.6$, $J_{3a,2}=9.2$ Hz), 1.65 (1H, dd, H-3b, $J_{3b,3a}=4.6$, $J_{3b,2}=6.6$ Hz), 1.78 (1H, dddd, H-2, $J_{2,\ 1'b}=4.1$, $J_{2,3b}=6.6$, $J_{2,1'a}=8.6$, $J_{2,3a}=9.2$ Hz), 3.21 (2H, t,-$N\underline{CH_2}CH_3$), 3.53 (1H, br s,–OH), 3.76 (1H, dd, H-1′a, $J_{1'a,2}=8.6$, $J_{1'a,1'b}=12.0$ Hz), 4.09 (1H, dd, H-1′b, $J_{1'b,2}=4.1$, $J_{1'b,1'a}=12.0$ Hz), 5.63 (1H, br s,–NH–), 7.29 (1H, m, aromatic), 7.31–7.40 (4H, m, aromatic); ^{13} C NMR (125 MHz, $CDCl_3$) δ 14.58 (–$NCH_2\underline{CH_3}$), 17.54 (C-3), 30.32 (C-2), 34.87 (–$N\underline{CH_2}CH_3$), 35.80 (C-1), 60.97 (C-1′), 127.68 (C-4″), 128.91 (C-2″ and C-6″), 129.81 (C-3″ and C-5″), 140.69 (C-1″), 172.76 (C=O); HR-MS (EI) calcd $C_{13}H_{17}NO_2$ 219.1259, found 219.1249 (M^+). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.32; H, 8.00; N, 6.32.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-dimethylcyclopropanecarboxamide (8c). Yield 82%, crystal; mp (hexane/AcOEt) 76–77 °C; $[\alpha]_D^{27}$ −83.30 ° (*c* 0.980, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ1.09 (1H, dd, H-3a, $J_{3a,3b}=5.0$, $J_{3a,2}=5.0$ Hz), 1.60 (1H, dddd, H-2, $J_{2,1'a}=4.6$, $J_{2,3a}=5.0$, $J_{2,3b}=8.7$, $J_{2,1'}=10.4$ Hz), 1.65 (1H, dd, H-3b, $J_{3b,3a}=5.0$, $J_{3b,2}=8.7$ Hz), 2.98 (3H, s,–$N\underline{CH_3}$), 3.01 (3H, s,–$N\underline{CH_3}$), 3.18 (1H, dd, H-1′a, $J_{1'a,2}=10.4$, $J_{1'a,1'b}=12.2$ Hz), 4.04 (1H, dd, H-1′b, $J_{1'b,2}=4.6$, $J_{1'b,1'a}=12.2$ Hz), 4.66 (1H, br s,–OH), 7.20–7.23 (3H, m, aromatic), 7.28–7.31 (2H, m, aromatic);

^{13}C NMR (125 MHz, $CDCl_3$) δ 17.34 (C-3), 32.11 (C-2), 34.19 (C-1), 35.65 (–NCH$_3$), 37.71 (–NCH$_3$), 64.78 (C-1′), 125.76 (C-2″ and C-6″), 126.62 (C-4″), 128.68 (C-3″ and C-5″), 139.84 (C-1″), 171.80 (C=O); HR-MS (EI) calcd $C_{13}H_{17}NO_2$ 219.1259, found 219.1266 (M^+). Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.52; H, 7.81; N, 6.39.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-dipropylcyclopropanecarboxamide (8d). Yield 84%, crystal; mp (hexane/AcOEt) 60–61 °C; $[\alpha]_D^{24}$ +63.74° (*c* 1.020, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (3H, t,–NCH$_2$CH$_2$CH$_3$, *J* = 7.4 Hz), 0.88 (3H, t,–NCH$_2$CH$_2$CH$_3$, *J* = 7.4 Hz), 1.06 (1H, dd, H-3a, $J_{3a,3b}$ = 5.9, $J_{3a,2}$ = 5.9 Hz), 1.16 (1H, m,–NCH$_2$CH$_2$CH$_3$), 1.37 (1H, m,–NCH$_2$CH$_2$CH$_3$), 1.50–1.62 (3H, m–NCH$_2$CH$_2$CH$_3$ and H-2), 1.68 (1H, dd, H-3b, $J_{3b,3a}$ = 5.9, $J_{3b,2}$ = 8.8 Hz), 3.17 (1H, ddd, H-1′a, $J_{1'a,OH}$ = 2.0, $J_{1'a,1'b}$ = 11.8, $J_{1'a,2}$ = 11.8 Hz), 3.14 (1H, ddd, H-1′a, $J_{1'a,\ OH}$ = 2.5, $J_{1'a,1'b}$ = 11.8, $J_{1'a,2}$ = 12.7 Hz), 3.22–3.36 (4H, m,–NCH$_2$CH$_2$CH$_3$), 4.04 (1H, ddd, H-1′b, $J_{1'b,2}$ = 4.9, $J_{1'b,OH}$ = 10.9, $J_{1'b,1'a}$ = 11.8 Hz), 4.86 (1H, dd,–OH, $J_{OH,1'a}$ = 2.0, $J_{OH,1'b}$ = 10.9 Hz), 7.20–7.36 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.15 (–NCH$_2$CH$_2$CH$_3$), 11.45 (–NCH$_2$CH$_2$CH$_3$), 16.52 (C-3), 20.33 (–NCH$_2$CH$_2$CH$_3$), 21.16 (–NCH$_2$CH$_2$CH$_3$), 31.99 (C-2), 34.61 (C-1), 46.65 (–NCH$_2$CH$_2$CH$_3$), 49.43 (–NCH$_2$CH$_2$CH$_3$), 64.96 (C-1′), 125.87 (C-2″ and C-6″), 126.62 (C-4″), 128.58 (C-3″ and C-5″), 140.14 (C-1″), 171.51 (C=O); HR-MS (EI) calcd $C_{17}H_{25}NO_2$ 275.1885, found 275.1867 (M^+). Anal. calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.92; H, 9.32; N, 5.07.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-dibutylcyclopropanecarboxamide (8e). Yield 94%, oil; $[\alpha]_D^{23}$ +59.92 °(*c* 1.040, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (3H, t, –NCH$_2$CH$_2$CH$_2$CH$_3$, *J* = 7.1 Hz), 0.93 (3H, t, –NCH$_2$CH$_2$CH$_2$CH$_3$, *J* = 7.4 Hz), 1.06 (1H, dd, H-3a, $J_{3a,3b}$ = 5.4, $J_{3a,2}$ = 6.0 Hz), 1.09–1.16 (3H, m, –NCH$_2$CH$_2$CH$_2$CH$_3$ × 2 and –NCH$_2$CH$_2$CH$_2$CH$_3$ × 1), 1.24–1.35 (3H, m, –NCH$_2$CH$_2$CH$_2$CH$_3$ × 2 and –NCH$_2$CH$_2$CH$_2$CH$_3$ × 1), 1.47–1.56 (3H, m, –NCH$_2$-CH$_2$CH$_2$CH$_3$ × 2 and H-2), 1.66 (1H, dd, H-3b, $J_{3b,3a}$ = 5.4, $J_{3b,2}$ = 8.7 Hz), 3.17 (1H, ddd, H-1′a, $J_{1'a,OH}$ = 2.6, $J_{1'a,1'b}$ = 10.4, $J_{1'a,2}$ = 12.5 Hz), 3.25–3.41 (4H, m,–NCH$_2$CH$_2$CH$_2$CH$_3$), 4.07 (1H, ddd, H-1′b, $J_{1'b,2}$ = 4.9, $J_{1'b,1'a}$ = 10.4, $J_{1'b,\ OH}$ = 11.0 Hz), 4.76 (1H, dd,–OH, $J_{OH,1'a}$ = 2.6, $J_{OH,\ 1'b}$ = 11.0 Hz), 7.19–7.31 (5H, m, aromatic); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.52 (–NCH$_2$CH$_2$CH$_2$CH$_3$), 13.64 (–NCH$_2$CH$_2$-CH$_2$CH$_3$), 16.46 (C-3), 19.84 (–NCH$_2$CH$_2$CH$_2$CH$_3$), 20.06 (–NCH$_2$CH$_2$CH$_2$CH$_3$), 28.93 (–NCH$_2$CH$_2$CH$_2$-CH$_3$), 29.74 (C-2), 31.63 (–NCH$_2$CH$_2$CH$_2$CH$_3$), 34.38 (C-1), 44.69 (–NCH$_2$CH$_2$CH$_2$CH$_3$), 47.48 (–NCH$_2$-CH$_2$CH$_2$CH$_3$), 64.66 (C-1′), 125.70 (C-2″ and C-6″), 126.45 (C-4″), 128.45 (C-3″ and C-5″), 140.09 (C-1″), 171.28 (C=O); HR-MS (EI) calcd $C_{19}H_{29}NO_2$ 303.2198, found 303.2178 (M^+). Anal. calcd for $C_{19}H_{29}NO_2$: C, 75.12; H, 9.63; N, 4.62. Found: C, 74.96; H, 9.51; N, 4.62.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-di-*i*-butylcyclopropanecarboxamide (8f). Yield: 93%, crystal; mp (hexane/AcOEt) 63–64 °C; $[\alpha]_D^{24}$ +70.87° (*c* 1.175, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.41 (3H, d,–NCH$_2$-CH(CH$_3$)$_2$, *J* = 6.6 Hz), 0.82 (9H, m,–NCH$_2$CH(CH$_3$)$_2$ × 9), 1.00 (1H, dd, H-3a, $J_{3a,3b}$ = $J_{3a,2}$ = 6.0 Hz), 1.46 (1H, m, H-2), 1.76–1.82 (2H, m,–NCH$_2$CH(CH$_3$)$_2$ and H-3b), 1.97 (1H, m,–NCH$_2$CH(CH$_3$)$_2$), 3.02 (1H, dd,–NCH$_2$CH(CH$_3$)$_2$, *J* = 7.0, 13.5 Hz), 3.14 (1H, ddd, H-1′a, $J_{1'a,OH}$ = 2.5, $J_{1'a,1'b}$ = 11.8, $J_{1'a,2}$ = 12.7 Hz), 3.25 (2H, d,–NCH$_2$CH(CH$_3$)$_2$ × 2, *J* = 7.8 Hz), 3.46 (1H, dd,–NCH$_2$CH(CH$_3$)$_2$, *J* = 8.1, 13.5 Hz), 4.04 (1H, ddd, H-1′b, $J_{1'b,2}$ = 4.7, $J_{1'b,1'a}$ = 11.3, $J_{1'b,\ OH}$ = 11.8 Hz), 4.90 (1H, dd,–OH, $J_{OH,1'a}$ = 2.5, $J_{OH,1'b}$ = 11.3 Hz), 7.20 (1H, m, H-4″), 7.29 (2H, m, H-3″ and H-5″), 7.34 (2H, m, H-2″ and H-6″); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.09 (C-3), 19.07 (–NCH$_2$CH(CH$_3$)$_2$), 20.08 (–NCH$_2$CH(CH$_3$)$_2$), 20.19 (–NCH$_2$CH(CH$_3$)$_2$), 20.22 (–NCH$_2$CH(CH$_3$)$_2$), 25.70 (–NCH$_2$CH(CH$_3$)$_2$), 25.80 (–NCH$_2$CH(CH$_3$)$_2$), 32.12 (C-2), 35.04 (C-1), 50.06 (–NCH$_2$CH(CH$_3$)$_2$), 53.89 (–NCH$_2$CH(CH$_3$)$_2$), 65.11 (C-1′), 126.52 (C-2″ and C-6″), 126.74 (C-4″), 128.50 (C-3″ and C-5″), 139.98 (C-1″), 172.47 (C=O); HR-MS (EI) calcd $C_{19}H_{29}NO_2$ 303.2198, found 303.2204 (M^+). Anal. calcd for $C_{19}H_{29}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.92; H, 9.32; N, 5.07.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-dibenzylcyclopropanecarboxamide (8g). Yield 91%, crystal; mp (hexane/AcOEt) 89–90 °C; $[\alpha]_D^{21}$ +31.92° (*c* 1.110, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (1H, dd, H-3a, $J_{3a,3b}$ = 5.3, $J_{3a,2}$ = 5.7 Hz), 1.59 (1H, dddd, H-2, $J_{2,1'b}$ = 5.3, $J_{2,3a}$ = 5.7, $J_{2,3b}$ = 8.8, $J_{2,1'a}$ = 12.0 Hz), 1.65 (1H, dd, H-3b, $J_{3b,3a}$ = 5.3, $J_{3b,2}$ = 8.8 Hz), 3.30 (1H, ddd, H-1′a, $J_{1'a,OH}$ = 2.4, $J_{1'a,2}$ = 12.0, $J_{1'a,1'b}$ = 12.6 Hz), 4.04 (1H, ddd, H-1′b, $J_{1'b,2}$ = 4.6, $J_{1'b,OH}$ = 11.0, $J_{1'b,1'a}$ = 12.6 Hz), 4.41 (1H, d, –NCH$_2$Ph, *J* = 4.7 Hz), 4.55 (1H, d,–NCH$_2$Ph, *J* = 5.9 Hz), 4.58 (1H, d, –NCH$_2$Ph, *J* = 4.7 Hz), 4.68 (1H, d, –NCH$_2$Ph, *J* = 5.9 Hz), 4.76 (1H, dd, –OH, $J_{OH,1'a}$ = 2.4, $J_{OH,1'b}$ = 11.0 Hz), 6.83 (2H, m, aromatic), 7.08 (2H, m, aromatic), 7.21–7.29 (9H, m, aromatic), 7.34 (2H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.71 (C-3), 31.31 (C-2), 34.62 (C-1), 47.00 (–NCH$_2$Ph), 50.20 (–NCH$_2$Ph), 65.02 (C-1′), 126.63, 127.02, 127.09, 127.44, 127.57, 128.16, 128.54, 128.70, 128.78, 135.57, 136.58, 139.55 (aromatic), 172.41 (C=O); HR-MS (EI) calcd $C_{25}H_{25}NO_2$ 371.1885, found 371.1888 (M^+). Anal. calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.88; H, 6.96; N, 3.96.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-cyclopentylenecyclopropanecarboxamide (8h). Yield 90%, crystal; mp (AcOEt, Hexane) 127 °C; $[\alpha]_D^{24}$ +113.41° (*c* 1.095, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (1H, dd, H-3a, $J_{3a,3b}$ = 5.1, $J_{3a,2}$ = 5.1 Hz), 1.46–1.56 (2H, m, H-3b and H-2), 1.66–18.5 (4H, m, –NCH$_2$CH$_2$– × 4), 3.11–3.22 (2H, m, H-1′a and –NCH$_2$CH$_2$– × 1), 3.38–3.49 (3H, m, –NCH$_2$CH$_2$– × 3), 4.04 (1H, ddd, H-1′b, $J_{1'b,2}$ = 4.1, $J_{1'b,OH}$ = 11.0, $J_{1'b,1'a}$ = 12.2 Hz), 4.69 (1H, dd,–OH, $J_{OH,1'a}$ = 2.4, $J_{OH,1'b}$ = 11.0 Hz), 7.12–7.25 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.77 (C-3), 23.99 (–NCH$_2$CH$_2$–), 25.88 (–NCH$_2$CH$_2$–), 31.93 (C-2), 35.40 (C-1), 46.23 (–NCH$_2$CH$_2$–), 46.82 (–NCH$_2$CH$_2$–), 64.79 (C-1′), 125.91 (C-2″ and C-6″), 126.51 (C-4″), 128.53 (C-3″ and C-5″), 139.43 (C-1″),

170.02 (C=O); HR-MS (EI) calcd $C_{15}H_{19}NO_2$ 245.1416, found 245.1416 (M^+). Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.56; H, 7.98; N, 5.71.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-cyclohexylenecyclopropanecarboxamide (8i). Yield: 95%, crystal; mp (AcOEt, Hexane) 105–106 °C; $[\alpha]_D^{22}$ +68.73 ° (*c* 1.060, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (1H, dd, H-3a, $J_{3a,3b}=4.9$, $J_{3a,2}=6.1$ Hz), 1.16 (1H, m,–NCH_2-CH_2CH_2–), 1.38 (1H, m, –$NCH_2CH_2CH_2$–), 1.49–1.66 (6H, m, H-3b and H-2 and-$NCH_2CH_2CH_2$– × 2 and –$NCH_2CH_2CH_2$– × 2), 3.17 (1H, ddd, H-1′a, $J_{1'a,OH}=2.7$, $J_{1'a,2}=10.5$, $J_{1'a,1'b}=12.5$ Hz), 3.46–3.57 (3H, m,–$NCH_2CH_2CH_2$– × 3), 3.66 (1H, m, –NCH_2-CH_2CH_2–), 4.05 (1H, ddd, H-1′b, $J_{1'b,2}=4.6$, $J_{1'b,OH}=11.2$, $J_{1'b,1'a}=12.5$ Hz), 4.74 (1H, dd, –OH, $J_{OH,1'a}=2.7$, $J_{OH,1'b}=11.2$ Hz), 7.19–7.32 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.15 (C-3), 24.20 (–$NCH_2CH_2CH_2$–), 25.40 (–$NCH_2CH_2CH_2$–), 25.58 (–$NCH_2CH_2CH_2$–), 31.66 (C-2), 34.05 (C-1), 43.05 (–$NCH_2CH_2CH_2$–), 46.94 (–$NCH_2CH_2CH_2$–), 64.68 (C-1′), 125.66 (C-2″ and C-6″), 126.40 (C-4″), 128.44 (C-3″ and C-5″), 139.95 (C-1″), 169.86 (C=O); HR-MS (EI) calcd $C_{16}H_{21}NO_2$ 259.1572, found 259.1593 (M^+). Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.94; H, 8.24; N, 5.21.

General procedure for preparing cyclopropylcarbaldehydes 9c–i. To a solution of oxalyl chloride (5.23 mL, 60.0 mmol) in CH_2Cl_2 (30 mL) was added a solution of DMSO (8.53 mL, 120 mmol) in CH_2Cl_2 (20 mL) slowly over 30 min at −78 °C for 30 min. A solution of **8** (30.0 mmol) in CH_2Cl_2 (20 mL) was added, and the mixture was stirred at the same temperature for 2 h. After addition of Et_3N (33.7 mL, 240 mmol), the resulting mixture was further stirred at the same temperature for 30 min, and then the reaction was quenched with saturated aqueous NH_4Cl. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:4) to give **9** as crystals.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-dimethylcyclopropanecarboxamide (9c). Yield 91%; mp (hexane/AcOEt) 73–74 °C; $[\alpha]_D^{26}$ −161.00 °(*c* 0.980, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (1H, dd, H-3a, $J_{3a,3b}=5.5$, $J_{3a,2}=8.5$ Hz), 2.26 (1H, dd, H-3b, $J_{3b,2}=5.5$, $J_{3b,3a}=5.5$ Hz), 2.50 (1H, ddd, H-2, $J_{2,3b}=5.5$, $J_{2,1'}=6.1$, $J_{2,3a}=8.5$ Hz), 2.87 (3H, s,–NCH_3), 2.97 (3H, s,–NCH_3), 7.22–7.36 (5H, m, aromatic), 9.08 (1H, d, H-1′, $J_{1'2}=6.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.67 (C-3), 35.85 (C-2), 36.76 (–NCH_3), 37.26 (–NCH_3), 39.72 (C-1), 125.66 (C-2″ and C-6″), 127.54 (C-4″), 129.05 (C-3″ and C-5″), 137.54 (C-1″), 168.18 (C=O), 198.13 (C-1′); HR-MS (EI) calcd $C_{13}H_{15}NO_2$ 217.1103, found 217.1129 (M^+). Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.75; H, 7.00; N, 6.47.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-dipropylcyclopropanecarboxamide (9d). Yield 94%; mp (hexane/AcOEt) 167–168 °C; $[\alpha]_D^{23}$−116.89 ° (*c* 1.165, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.60 (3H, t, –$NCH_2CH_2CH_3$, $J=7.3$ Hz), 0.87 (3H, t,–$NCH_2CH_2CH_3$, $J=7.3$ Hz), 0.98 (1H, m, –$NCH_2CH_2CH_3$), 1.15 (1H, m, –NCH_2-CH_2CH_3), 1.53 (1H, m, –$NCH_2CH_2CH_3$), 1.76 (1H, dd, H-3a, $J_{3a,3b}=5.5$, $J_{3a,2}=8.3$ Hz), 2.23 (1H, dd, H-3b, $J_{3b,3a}=5.5$, $J_{3b,2}=5.5$ Hz), 3.07 (1H, ddd, H-2, $J_{2,3b}=5.5$, $J_{2,1'}=6.2$, $J_{2,3a}=8.3$ Hz), 3.07 (1H, m,–$NCH_2CH_2CH_3$), 3.17 (1H, m, –$NCH_2CH_2CH_3$), 3.25–3.37 (2H, m, –$NCH_2CH_2CH_3$), 7.26–7.36 (5H, m, aromatic), 9.06 (1H, d, H-1′, $J_{1'2}=6.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.80 (–$NCH_2CH_2CH_3$), 11.26 (–$NCH_2CH_2CH_3$), 19.65 (C-3), 20.12 (–$NCH_2CH_2CH_3$), 20.70 (–NCH_2CH_2-CH_3), 36.20 (C-2), 40.28 (C-1), 46.84 (–$NCH_2CH_2CH_3$), 48.93 (–$NCH_2CH_2CH_3$), 126.00 (C-2″ and C-6″), 127.48 (C-4″), 128.84 (C-3″ and C-5″), 137.95 (C-1″), 167.69 (C=O), 197.98 (C-1′); HR-MS (EI) calcd $C_{17}H_{23}NO_2$ 273.1729, found 273.1724 (M^+). Anal. calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.94; H, 8.16; N, 4.77.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-dibutylcyclopropanecarboxamide (9e). Yield 96%; mp (AcOEt/Hexane/Et_2O) 142–143 °C; $[\alpha]_D^{23}$−145.61 ° (*c* 0.400, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (3H, t, –$NCH_2CH_2CH_2CH_3$, $J=7.1$ Hz), 0.82–0.94 (4H, m, –$NCH_2CH_2CH_2CH_3$ × 3 and –$NCH_2CH_2CH_2CH_3$ × 1), 0.95–1.15 (3H, m,–NCH_2-$CH_2CH_2CH_3$ × 1 and –$NCH_2CH_2CH_2CH_3$ × 2), 1.23–1.33 (2H, m, –$NCH_2CH_2CH_2CH_3$), 1.44–1.52 (2H, m, –$NCH_2CH_2CH_2CH_3$), 1.74 (1H, dd, H-3a, $J_{3a,3b}=5.4$, $J_{3a,2}=8.3$ Hz), 2.25 (1H, dd, H-3b, $J_{3b,3a}=5.4$, $J_{3b,2}=5.8$ Hz), 2.45 (1H, ddd, H-2, $J_{2,3b}=5.8$, $J_{2,1'}=6.3$, $J_{2,3a}=8.3$ Hz), 3.06 (1H, m, –$NCH_2CH_2CH_2CH_3$), 3.17 (1H, m, –$NCH_2CH_2CH_2CH_3$), 3.27–3.42 (2H, m, –NCH_2CH_2-CH_2CH_3), 7.19–7.31 (5H, m, aromatic), 9.04 (1H, d, H-1′, $J_{1'2}=6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.77 (–$NCH_2CH_2CH_2CH_3$), 13.93 (–$NCH_2CH_2CH_2CH_3$), 20.01 (–$NCH_2CH_2CH_2CH_3$), 20.05 (C-3), 20.35 (–$NCH_2CH_2CH_2CH_3$), 29.13 (–$NCH_2CH_2CH_2CH_3$), 29.75 (–$NCH_2CH_2CH_2CH_3$), 36.31 (C-2), 40.33 (C-1), 45.24 (–$NCH_2CH_2CH_2CH_3$), 47.32 (–$NCH_2CH_2CH_2$-CH_3), 125.86 (C-2″ and C-6″), 127.37 (C-4″), 128.77 (C-3″ and C-5″), 137.77 (C-1″), 167.38 (C=O), 197.83 (C-1′); HR-MS (EI) calcd $C_{19}H_{27}NO_2$ 301.2042, found 301.2020 (M^+). Anal. calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.96; H, 9.01; N, 4.62.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-di-*i*-butylcyclopropanecarboxamide (9f). Yield 77%; mp (hexane/AcOEt/Et_2O) 96–97 °C; $[\alpha]_D^{23}$−82.76 ° (*c* 1.260, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.52 (3H, d,–NCH_2-$CH(CH_3)_2$, $J=6.6$ Hz), 0.64 (3H, d,–$NCH_2CH(CH_3)_2$, $J=6.6$ Hz), 0.83 (6H, m,–$NCH_2CH(CH_3)_2$ × 6, $J=6.6$ Hz), 1.76 (1H, m,–$NCH_2CH(CH_3)_2$), 1.94 (1H, m, –$NCH_2CH(CH_3)_2$), 1.95 (1H, dd, H-3a, $J_{3a,3b}=5.7$, $J_{3a,2}=8.3$ Hz), 2.12 (1H, dd, H-3b, $J_{3b,2}=5.7$, $J_{3b,3a}=5.7$ Hz), 2.26 (1H, ddd, H-2, $J_{2,3b}=5.7$, $J_{2,1'}=5.9$, $J_{2,3a}=8.3$ Hz), 3.05 (1H, m,–NCH_2-$CH(CH_3)_2$), 3.16–3.26 (3H, m, –$NCH_2CH(CH_3)_2$), 7.25–7.37 (5H, m, aromatic), 9.11 (1H, d, H-1′, $J_{1'2}=5.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.85 (C-3), 19.38 (–$NCH_2CH(CH_3)_2$), 19.55 (–$NCH_2CH(CH_3)_2$), 20.15 (–$NCH_2CH(CH_3)_2$), 20.19 (–$NCH_2CH(CH_3)_2$), 25.70 (–$NCH_2CH(CH_3)_2$), 25.77 (–$NCH_2CH(CH_3)_2$),

37.04 (C-2), 41.17 (C-1), 50.68 (–$NCH_2CH(CH_3)_2$), 53.66 (–$NCH_2CH(CH_3)_2$), 126.51 (C-2″ and C-6″), 127.54 (C-4″), 128.71 (C-3″ and C-5″), 137.92 (C-1″), 168.45 (C=O), 197.68 (C-1′); HR-MS (EI) calcd $C_{19}H_{27}NO_2$ 301.2042, found 301.2029 (M^+). Anal. calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.67; H, 9.09; N, 4.65.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-dibenzylcyclopropanecarboxamide (9g). Yield 97%; mp (hexane/AcOEt/Et_2O) 67–68 °C; $[\alpha]_D^{21}$ −75.02 ° (*c* 1.185, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.87 (1H, dd, H-3a, $J_{3a,3b}=5.6$, $J_{3a,2}=8.2$ Hz), 1.65 (1H, dd, H-3b, $J_{3b,3a}=5.6$, $J_{3b,2}=5.6$ Hz), 2.39 (1H, m, H-2, $J_{2,1'}=5.3$, $J_{2,3b}=5.6$, $J_{2,3a}=8.2$ Hz), 4.25 (1H, d, –NCH$_2$Ph, $J=4.5$ Hz), 4.35 (1H, d,–NCH$_2$Ph, $J=5.8$ Hz), 4.63 (1H, d, –NCH$_2$Ph, $J=5.8$ Hz), 4.66 (1H, d,–NCH$_2$Ph, $J=4.5$ Hz), 6.75 (2H, m, aromatic), 7.09 (2H, m, aromatic), 7.21–7.31 (9H, m, aromatic), 7.36 (2H, m, aromatic), 9.32 (1H, d, H-1′, $J_{1',2}=5.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.78 (C-3), 36.70 (C-2), 41.16 (C-1), 47.30 (–NCH$_2$Ph), 49.90 (–NCH$_2$Ph), 126.73, 127.17, 127.47, 127.56, 127.84, 128.44, 128.49, 128.63, 129.05, 135.25, 136.52, 137.48 (the above mentioned, aromatic), 168.57 (C=O), 197.76 (C-1′); HR-MS (EI) calcd $C_{25}H_{23}NO_2$ 369.1729, found 369.1721 (M^+). Anal. calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 80.87; H, 6.50; N, 4.04.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-cyclopentylenecyclopropanecarboxamide (9h). Yield 96%; mp (hexane/AcOEt) 120–121 °C; $[\alpha]_D^{24}$ −124.37 ° (*c* 1.565, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.67–1.85 (5H, m, –NCH$_2$CH$_2$– × 4 and H-3a), 2.24 (1H, dd, H-3b, $J_{3b,3a}=5.9$, $J_{3b,3a}=8.5$ Hz), 2.42 (1H, ddd, H-2, $J_{2,3b}=5.9$, $J_{2,1'}=6.3$, $J_{2,3a}=8.1$ Hz), 3.10–3.28 (2H, m, –NCH$_2$CH$_2$– × 2), 3.41–3.51 (2H, m, –NCH$_2$CH$_2$– × 2), 7.17–7.35 (5H, m, aromatic), 9.06 (1H, d, H-1′, $J_{1',2}=6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.00 (C-3), 23.78 (–NCH$_2$CH$_2$–), 25.87 (–NCH$_2$CH$_2$–), 36.17 (C-2), 40.79 (C-1), 46.34 (–NCH$_2$CH$_2$–), 46.49 (–NCH$_2$CH$_2$–), 125.93 (C-2″ and C-6″), 127.31 (C-4″), 128.75 (C-3″ and C-5″), 136.99 (C-1″), 166.25 (C=O), 198.12 (CHO); HR-MS (EI) calcd $C_{15}H_{17}NO_2$ 243.1259, found 243.1264 (M^+). Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.03; H, 7.05; N, 5.70.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-cyclohexylenecyclopropanecarboxamide (9i). Yield 96%; mp (hexane/AcOEt) 80–81 °C; $[\alpha]_D^{24}$ −154.98 ° (*c* 1.240, $CHCl_3$);^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (2H, m, –NCH$_2$CH$_2$CH$_2$–), 1.50 (4H, m,–NCH$_2$CH$_2$CH$_2$– × 2 and –NCH$_2$CH$_2$CH$_2$– × 2), 1.71 (1H, dd, H-3a, $J_{3a,3b}=5.3$, $J_{3a,2}=8.3$ Hz), 2.27 (1H, dd, H-3b, $J_{3b,3a}=5.3$, $J_{3b,2}=5.6$ Hz), 2.52 (1H, dd, H=2, $J_{2,3b}=5.6$, $J_{2,1'}=6.1$, $J_{2,3a}=8.3$ Hz), 3.26–3.41 (2H, m,–NCH$_2$CH$_2$CH$_2$– × 2), 3.52 (1H, m,–NCH$_2$CH$_2$CH$_2$–), 3.62 (1H, m, –NCH$_2$CH$_2$CH$_2$–), 7.24–7.36 (5H, m, aromatic), 9.06 (1H, d, H-1′, $J_{1',2}=6.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.43 (C-3), 24.13 (–NCH$_2$CH$_2$CH$_2$–), 25.32 (–NCH$_2$CH$_2$CH$_2$–), 25.37 (–NCH$_2$CH$_2$CH$_2$–), 36.47 (C-2), 39.58 (C-1), 43.28 (–NCH$_2$CH$_2$CH$_2$–), 46.54 (–NCH$_2$CH$_2$CH$_2$–), 125.51 (C-2″ and C-6″), 127.28 (C-4″), 128.78 (C-3″ and C-5″), 137.65 (C-1″), 166.26 (C=O), 198.03 (C-1′); HR-MS (EI) calcd $C_{16}H_{19}NO_2$ 257.1416, found 257.1403 (M^+). Anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.81; H, 7.62; N, 5.38.

General procedure for the Grignard reaction of 9

To a solution of **9** (3.28 g, 12.0 mmol) in THF (50 mL), EtMgBr (3.0 M in Et_2O, 16.0 mL, 48.0 mmol) was added at −15 °C, and the mixture was stirred at the same temperature for 3 h, and then the reaction was quenched with saturated aqueous NH_4Cl. The resulting mixture was concentrated in vacuo (for removing THF and Et_2O), and then AcOEt and H_2O were added. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:4) to give **10**.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-dimethylcyclopropanecarboxamide (10c). Yield 93%, oil; $[\alpha]_D^{26}$ −12.50 ° (*c* 0.982, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.00 (3H, t, H-3′, $J_{3',2'}=7.5$ Hz), 1.07 (1H, dd, H-3a, $J_{3a,3b}=J_{3a,2}=5.5$ Hz), 1.30 (1H, ddd, H-2, $J_{2,3a}=5.5$, $J_{2,3b}=J_{2,1'}=8.5$ Hz), 1.66 (1H, m, H-2′), 1.71 (1H, dd, H-3b, $J_{3b,3a}=5.5$, $J_{3b,2}=8.5$ Hz), 2.98 (3H, s, –NCH$_3$), 3.02 (3H, s, –NCH$_3$), 3.08 (1H, m, H-1′), 5.38 (1H, br s,–OH), 7.19–7.23 (3H, m, aromatic), 7.28–7.31 (2H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.24 (C-3′), 17.65 (C-3), 29.04 (C-2′), 33.10 (C-1), 35.60 (–NCH$_3$), 36.76 (C-2), 37.71 (–NCH$_3$), 75.64 (C-1′), 125.75 (C-2″ and C-6″), 126.55 (C-4″), 128.62 (C-3″ and C-5″), 139.81 (C-1″), 172.02 (C=O); HR-MS (EI) calcd $C_{15}H_{21}NO_2$ 247.1572, found 247.1579 (M^+). Anal. calcd for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.50; N, 5.67. Found: C, 72.88; H, 8.54; N, 5.67.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-dipropylcyclopropanecarboxamide (10d). Yield 73%, oil; $[\alpha]_D^{22}$ +76.36° (*c* 1.375, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.71 (3H, t, –NCH$_2$CH$_2$CH$_3$, $J=7.4$ Hz), 0.88 (3H, t, –NCH$_2$CH$_2$CH$_3$, $J=7.4$ Hz), 1.00 (3H, t, H-3′, $J_{3',2'}=7.5$ Hz), 1.04 (1H, dd, H-3a, $J_{3a,3b}=5.5$, $J_{3a,2}=6.6$ Hz), 1.18 (1H, m, –NCH$_2$CH$_2$CH$_3$), 1.23 (1H, ddd, H-2, $J_{2,3a}=6.0$, $J_{2,3b}=8.8$, $J_{2,1'}=9.2$ Hz), 1.41 (1H, m, –NCH$_2$CH$_2$CH$_3$), 1.56 (2H, m, –NCH$_2$CH$_2$CH$_3$), 1.65 (2H, m, H-2′), 1.72 (1H, dd, H-3b, $J_{3a,3b}=5.5$, $J_{3a,2}=8.8$ Hz), 3.07 (1H, m, H-1′), 3.22–3.38 (4H, m, –NCH$_2$CH$_2$CH$_3$), 5.47 (1H, d, –OH, $J_{OH,1'}=1.1$ Hz), 7.19–7.30 (5H, m, aromatic): ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.22 (C-3′), 10.98 (–NCH$_2$CH$_2$CH$_3$), 11.27 (–NCH$_2$CH$_2$CH$_3$), 16.75 (C-3), 20.18 (–NCH$_2$CH$_2$CH$_3$), 21.03 (–NCH$_2$CH$_2$CH$_3$), 29.36 (C-2′), 33.43 (C-2), 36.55 (C-1), 46.51 (–NCH$_2$CH$_2$CH$_3$), 49.32 (–NCH$_2$CH$_2$CH$_3$), 75.67 (C-1′), 125.83 (C-2″ and C-6″), 126.52 (C-4″), 128.52 (C-3″ and C-5″), 140.27 (C-1″), 171.80 (C=O); HR-MS (EI) calcd $C_{19}H_{29}NO_2$ 303.2198, found 303.2191 (M^+). Anal. calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.19; H, 9.79; N, 4.46.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-dibutylcyclopropanecarboxamide (10e). Yield 69%, oil; $[\alpha]_D^{27}$

+75.06 ° (*c* 1.340, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (3H, t, –$NCH_2CH_2CH_2CH_3$, J = 7.0 Hz), 0.93 (3H, t, –$NCH_2CH_2CH_2CH_3$, J = 7.2 Hz), 1.00 (3H, t, H-3′, $J_{3',2'}$ = 7.5 Hz), 1.03 (1H, dd, H-3a, $J_{3a,3b}$ = 5.5, $J_{3a,2}$ = 6.0 Hz), 1.09–1.18 (3H, m, H-2′a and–NCH_2-$CH_2CH_2CH_3$ × 2), 1.20–1.40 (4H, m, H-2 and H-2′b and–$NCH_2CH_2CH_2CH_3$ × 2), 1.47–1.57 (2H, m,–NCH_2-$CH_2CH_2CH_3$), 1.66 (2H, m, –$NCH_2CH_2CH_2CH_3$), 1.71 (1H, dd, H-3b, $J_{3b,3a}$ = 5.5, $J_{3b,2}$ = 8.7 Hz), 3.07 (1H, m, H-1′), 3.29–3.38 (4H, m, –$NCH_2CH_2CH_2CH_3$), 5.48 (1H, d, –OH, $J_{OH,\ 1'}$ = 1.7 Hz), 7.18–7.30 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.46 (C-3′), 13.85 (–$NCH_2CH_2CH_2CH_3$), 13.95 (–$NCH_2CH_2CH_2CH_3$), 16.98 (C-3), 20.16 (–$NCH_2CH_2CH_2CH_3$), 20.37 (–NCH_2-$CH_2CH_2CH_3$), 29.18 (–$NCH_2CH_2CH_2CH_3$), 29.22 (–$NCH_2CH_2CH_2CH_3$), 30.06 (C-2′), 33.52 (C-1), 36.79 (C-2), 44.91 (–$NCH_2CH_2CH_2CH_3$), 47.67 (–NCH_2-$CH_2CH_2CH_3$), 75.72 (C-1′), 125.64 (C-2″ and C-6″), 126.39 (C-4″), 128.42 (C-3″ and C-5″), 140.07 (C-1″), 171.42 (C=O); HR-MS (EI) calcd $C_{21}H_{33}NO_2$ 331.2511, found 331.2528 (M^+). Anal. calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.10; H, 10.09; N, 4.15.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-di-*i*-butylcyclopropanecarboxamide (10f). Yield 82%, crystal; mp (hexane/AcOEt) 80–81 °C; $[\alpha]_D^{25}$ +76.76 ° (*c* 1.165, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40 (3H, d, –$NCH_2CH(CH_3)_2$, J = 6.6 Hz), 0.83 (9H, m,–NCH_2-$CH(CH_3)_2$ × 9), 0.97–1.00 (4H, m, H-3a and H-3′), 1.18 (1H, m, H-2), 1.66 (2H, m, H-2′), 1.77–1.85 (2H, m, –$NCH_2CH(CH_3)_2$ and H-3b), 1.98 (1H, m,–NCH_2-$CH(CH_3)_2$), 3.00–3.07 (2H, m, –$NCH_2CH(CH_3)_2$ and H-1′), 3.26 (2H, d, –$NCH_2CH(CH_3)_2$ × 2, J = 7.7 Hz), 3.46 (1H, dd, –$NCH_2CH(CH_3)_2$, J = 8.1, 13.5 Hz), 5.58 (1H, s, –OH), 7.20 (1H, m, H-4″), 7.28 (2H, m, H-3″ and H-5″), 7.34 (2H, m, H-2″ and H-6″); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.39 (C-3′), 16.57 (C-3), 19.07 (–$NCH_2CH(CH_3)_2$), 20.09 (–$NCH_2CH(CH_3)_2$ × 2), 20.20 (–$NCH_2CH(CH_3)_2$), 25.66 (–$NCH_2CH(CH_3)_2$), 25.81 (–$NCH_2CH(CH_3)_2$), 29.14 (C-2′), 33.94 (C-1), 36.64 (C-2), 50.05 (–$NCH_2CH(CH_3)_2$), 53.93 (–NCH_2-$CH(CH_3)_2$), 75.88 (C-1′), 126.48 (C-2″ and C-6″), 126.67 (C-4″), 128.46 (C-3″ and C-5″), 140.03 (C-1″), 172.68 (C=O); HR-MS (EI) calcd $C_{21}H_{33}NO_2$ 331.2511, found 331.2508 (M^+). Anal. calcd for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 75.92; H, 10.03; N, 4.20.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-dibenzylcyclopropanecarboxamide (10g). Yield 90%, oil; $[\alpha]_D^{22}$ +32.33 ° (*c* 1.265, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (3H, t, H-3′, $J_{3',2'}$ = 7.5 Hz), 1.09 (1H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,\ 2}$ = 6.0 Hz), 1.31 (1H, ddd, H-2, $J_{2,3a}$ = 6.0, $J_{2,1'} = J_{2,3b}$ = 9.2), 1.63–1.77 (3H, m, H-3b and H-2′), 3.20 (1H, m, H-1′), 4.38 (1H, d, –NCH_2Ph, J = 4.6 Hz), 4.52 (1H, d, –NCH_2Ph, J = 6.0 Hz), 4.63 (1H, d, –NCH_2Ph, J = 4.6 Hz), 4.71 (1H, d, –NCH_2Ph, J = 6.0 Hz), 5.45 (1H, br s, –OH), 6.85 (2H, m, aromatic), 7.07 (2H, m, aromatic), 7.21–7.29 (9H, m, aromatic), 7.33–7.35 (2H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.35 (C-3′), 16.16 (C-3), 29.15 (C-2′), 33.63 (C-1), 35.89 (C-2), 47.00 (–NCH_2Ph), 50.22 (–NCH_2Ph), 75.82 (C-1′), 126.64, 126.99, 127.09, 127.46, 127.61, 128.20, 128.56, 128.75, 128.79, 135.64, 136.59, 139.65 (aromatic), 172.68 (C=O); HR-MS (EI) calcd $C_{27}H_{29}NO_2$ 399.2198, found 399.2220 (M^+). Anal. calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.04; H, 7.41; N, 3.64.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-cyclopentylenecyclopropanecarboxamide (10h). Yield 82%, oil; $[\alpha]_D^{24}$ +116.01 ° (*c* 1.315, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, H-3′, $J_{3',2'}$ = 7.6 Hz), 1.06 (1H, dd, H-3a, $J_{3a,3b}$ = 5.6, J_{3a2} = 6.2 Hz), 1.27 (1H, m, H-2), 1.61–1.92 (7H, m, –NCH_2CH_2– × 4 and H-3b and H-2′), 3.28 (1H, m, –NCH_2CH_2–), 3.45–3.57 (3H, m, –NCH_2CH_2– × 3), 5.42 (1H, d, –OH, $J_{OH,\ 1'}$ = 1.7 Hz), 7.21–7.32 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.29 (C-3′), 17.04 (C-3), 23.95 (–NCH_2CH_2–), 25.85 (–NCH_2CH_2–), 29.09 (C-2′), 34.31 (C-1), 36.65 (C-2), 46.16 (–NCH_2CH_2–), 46.79 (–NCH_2CH_2–), 75.69 (C-1′), 125.86 (C-2″ and C-6″), 126.40 (C-4″), 128.45 (C-3″ and C-5″), 139.47 (C-1″), 170.20 (C=O); HR-MS (EI) calcd $C_{17}H_{23}NO_2$ 273.1729, found 273.1709 (M^+). Anal. calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.50; H, 8.58; N, 5.01.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxylpropyl]-*N*,*N*-cyclohexylenecyclopropanecarboxamide (10i). Yield 94%, crystal; mp (hexane/AcOEt) 98 °C; $[\alpha]_D^{24}$ +80.06 ° (*c* 1.060, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, H-3′, $J_{3',2'}$ = 7.6 Hz), 1.05 (1H, dd, H-3a, $J_{3a,3b}$ = 5.5, $J_{3a,2}$ = 6.4 Hz), 1.15 (1H, m, –$NCH_2CH_2CH_2$–), 1.28 (1H, ddd, H-2, $J_{2,3a}$ = 6.4, $J_{2,\ 3b}$ = 9.0, $J_{2,\ 1'}$ = 9.8 Hz), 1.40 (1H, m, –$NCH_2CH_2CH_2$–), 1.49–1.61 (4H, m, –$NCH_2CH_2CH_2$– × 2 and –$NCH_2CH_2CH_2$– × 2), 1.62–1.73 (3H, m, H-3b and H-2′), 3.30 (1H, m, H-1′), 3.46–3.54 (3H, m, –$NCH_2CH_2CH_2$– × 3), 3.69 (1H, m, –$NCH_2CH_2CH_2$–), 5.48 (1H, d, –OH, $J_{OH,1'}$ = 2.7 Hz), 7.17–7.31 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.35 (C-3′), 17.46 (C-3), 24.29 (–NCH_2-CH_2CH_2–), 25.47 (–$NCH_2CH_2CH_2$–), 25.69 (–NCH_2-CH_2CH_2–), 29.11 (C-2′), 33.07 (C-1), 36.55 (C-2), 43.12 (–$NCH_2CH_2CH_2$–), 47.04 (–$NCH_2CH_2CH_2$–), 75.62 (C-1′), 125.78 (C-2″ and C-6″), 126.44 (C-4″), 128.49 (C-3″ and C-5″), 140.04 (C-1″), 170.24 (C=O); HR-MS (EI) calcd $C_{18}H_{25}NO_2$ 287.1885, found 287.1867 (M^+). Anal. calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.23; H, 8.80; N, 4.83.

General procedure for preparing cyclopropylmethylazides 11d–i. To a solution of **10** (1.00 mmol) in HMPA (10 mL) were added PPh_3 (787 mg, 3.00 mmol) and CBr_4 (995 mg, 3.00 mmol) at 0 °C, the mixture was stirred for 30 min at the same temperature. After addition of NaN_3 (650 mg, 10.0 mmol), the resulting mixture was stirred at room temperature for 6 h, and then AcOEt and H_2O were added. The resulting mixture was partitioned, and the organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by flash column chromatography (silica gel; AcOEt/hexane, 1:9) to give **11**.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-dipropylcyclopropanecarboxamide (11d). Yield 68%, crystal; mp (hexane/AcOEt) 71–72 °C; $[\alpha]_D^{21}$ −147.16 ° (*c* 1.600,

$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.26 (1H, m, –$NCH_2CH_2CH_3$), 0.47 (3H, t, –$NCH_2CH_2CH_3$, $J = 7.3$ Hz), 0.89 (3H, t, –$NCH_2CH_2CH_3$, $J = 7.4$ Hz), 0.97 (1H, dd, H-3a, $J_{3a,3b} = 4.8$, $J_{3a,2} = 9.2$ Hz), 1.06 (3H, t, H-3′, $J_{3',2'} = 7.4$ Hz), 1.16 (1H, m, –$NCH_2CH_2CH_3$), 1.54 (1H, m, –$NCH_2CH_2CH_3$), 1.60 (1H, m, –$NCH_2CH_2CH_3$), 1.63 (1H, dd, H-3b, $J_{3b,3a} = 4.8$, $J_{3b,2} = 6.2$ Hz), 1.82 (2H, m, H-2′), 1.95 (1H, ddd, H-2, $J_{2,3b} = 6.2$, $J_{2,3a} = J_{2,1'} = 9.2$ Hz), 2.84–2.90 (2H, m, –$NCH_2CH_2CH_3$ and H-1′), 3.10 (1H, m, –$NCH_2CH_2CH_3$), 3.37 (1H, m, –$NCH_2CH_2CH_3$), 3.57 (1H, m, –$NCH_2CH_2CH_3$), 7.19–7.31 (5H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.19 (C-3′), 10.90 (–$NCH_2CH_2CH_3$), 11.45 (–$NCH_2CH_2CH_3$), 19.43 (C-3), 20.24 (–$NCH_2CH_2CH_3$), 20.31 (–$NCH_2CH_2CH_3$), 27.40 (C-2), 28.19 (C-2′), 35.96 (C-1), 47.76 (–$NCH_2CH_2CH_3$), 49.86 (–$NCH_2CH_2CH_3$), 64.04 (C-1′), 126.67 (C-2″ and C-6″), 127.02 (C-4″), 128.64 (C-3″ and C-5″), 140.94 (C-1″), 169.61 (C=O); HR-MS (EI) calcd $C_{19}H_{28}N_4O$ 328.2263, found 328.2254 (M^+). Anal. calcd for $C_{19}H_{28}N_4O$: C, 69.48; H, 8.59; N, 17.06. Found: C, 69.66; H, 8.66; N, 16.80.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-dibutylcyclopropanecarboxamide (11e). Yield 62%, oil; $[\alpha]_D^{25}$ −149.20 ° (*c* 1.155, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (1H, m, –$NCH_2CH_2CH_2CH_3$), 0.62 (3H, t, –$NCH_2CH_2CH_2CH_3$, $J = 7.2$ Hz), 0.81 (1H, m, –$NCH_2CH_2CH_2CH_3$), 0.92 (1H, m, –$NCH_2CH_2CH_2CH_3$), 0.93 (3H, t, –$NCH_2CH_2CH_2CH_3$, $J = 7.2$ Hz), 0.96 (1H, dd, H-3a, $J_{3a,3b} = 4.8$, $J_{3a,2} = 9.5$ Hz), 1.09 (3H, t, H-3′, $J_{3',2'} = 7.4$ Hz), 1.10 (1H, m, –$NCH_2CH_2CH_2CH_3$), 1.31 (2H, m ,–$NCH_2CH_2CH_2CH_3$), 1.47 (1H, m,–$NCH_2CH_2CH_2CH_3$), 1.54 (1H, m, –$NCH_2CH_2CH_2CH_3$), 1.64 (1H, dd, H-3b, $J_{3b,3a} = 4.8$, $J_{3b2} = 6.4$ Hz), 1.72–1.87 (2H, m, H-2′), 1.96 (1H, ddd, H-2, $J_{2,3b} = 6.4$, $J_{2.3a} = 9.5$, $J_{2,1'} = 9.5$ Hz), 2.83–2.93 (2H, m, –$NCH_2CH_2CH_2CH_3$ and H-1′), 3.11 (1H, m, –$NCH_2CH_2CH_2CH_3$), 3.41 (1H, m, –$NCH_2CH_2CH_2CH_3$), 3.60 (1H, m, –$NCH_2CH_2CH_2CH_3$), 7.19–7.32 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.29 (C-3′), 13.70 (–$NCH_2CH_2CH_2CH_3$), 13.87 (–$NCH_2CH_2CH_2CH_3$), 19.65 (C-3), 20.12 (–$NCH_2CH_2CH_2CH_3$), 20.45 (–$NCH_2CH_2CH_2CH_3$), 27.31 (C-2), 28.27 (–$NCH_2CH_2CH_2CH_3$), 29.15 (–$NCH_2CH_2CH_2CH_3$), 29.23 (C-2′), 35.98 (C-1), 45.99 (–$NCH_2CH_2CH_2CH_3$), 48.23 (–$NCH_2CH_2CH_2CH_3$), 64.06 (C-1′), 126.53 (C-4″), 126.93 (C-2″ and C-6″), 128.58 (C-3″ and C-5″), 140.79 (C-1″), 169.44 (C=O); HR-MS (EI) calcd $C_{21}H_{32}N_4O$ 356.2576, found 356.2574 (M^+). Anal. calcd for $C_{21}H_{32}N_4O$: C, 70.75; H, 9.05; N, 15.72. Found: C, 71.02; H, 9.15; N, 15.44.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-di-*i*-butylcyclopropanecarboxamide (11f). Yield 68%, oil; $[\alpha]_D^{23}$ −13.42 ° (c 1.265, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.39 (3H, d, –$NCH_2CH(CH_3)_2$, $J = 6.6$ Hz), 0.53 (3H, d, –$NCH_2CH(CH_3)_2$, $J = 6.6$ Hz), 0.85–0.88 (6H, m, –$NCH_2CH(CH_3)_2$ × 6), 1.01 (3H, t, H-3′, $J_{3',2'} = 7.4$ Hz), 1.33 (1H, dd, H-3a, $J_{3a,3b} = 5.1$, $J_{3a,2} = 6.6$ Hz), 1.37 (1H, dd, H-3b, $J_{3b,3a} = 5.1$, $J_{3b,2} = 9.3$ Hz), 1.61–1.77 (4H, m, H-2 and H-2′ and –$NCH_2CH(CH_3)_2$), 1.97 (1H, m, –$NCH_2CH(CH_3)_2$), 3.05 (1H, m, –$NCH_2CH(CH_3)_2$), 3.09 (1H, m, H-1′), 3.18 (1H, m, –$NCH_2CH(CH_3)_2$), 3.25–3.31 (2H, m, –$NCH_2CH(CH_3)_2$ × 2), 7.19–7.35 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.26 (C-3′), 17.72 (C-3), 19.02 (–$NCH_2CH(CH_3)_2$), 20.59 (–$NCH_2CH(CH_3)_2$), 20.24 (–$NCH_2CH(CH_3)_2$), 20.38 (–$NCH_2CH(CH_3)_2$), 25.71 (–$NCH_2CH(CH_3)_2$), 26.04 (–$NCH_2CH(CH_3)_2$), 28.11 (C-2′), 30.33 (C-2), 35.97 (C-1), 50.90 (–$NCH_2CH(CH_3)_2$), 53.73 (–$NCH_2CH(CH_3)_2$), 63.59 (C-1′), 126.77 (C-4″), 127.02 (C-2″ and C-6″), 128.58 (C-3″ and C-5″), 140.70 (C-1″), 170.38 (C=O); HR-MS (EI) calcd $C_{21}H_{32}N_4O$ 356.2576, found 356.2585 (M^+). Anal. calcd for $C_{21}H_{32}N_4O$: C, 70.75; H, 9.05; N, 15.72. Found: C, 70.40; H, 9.06; N, 15.49.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-dibenzylcyclopropanecarboxamide (11g). Yield 43%, oil; $[\alpha]_D^{22}$ −89.24 ° (*c* 1.085, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (3H, t, H-3′, $J_{3',2'} = 7.5$ Hz), 1.20 (1H, dd, H-3a, $J_{3a,3b} = 5.1$, $J_{3a,2} = 9.2$ Hz), 1.57 (1H, dd, H-3b, $J_{3b,3a} = 5.1$, $J_{3b,2} = 6.6$ Hz), 1.74–1.85 (3H, m, H-2 and H-2′), 3.05 (1H, m, H-1′), 3.95 (1H, d, –NCH_2Ph, $J = 4.6$ Hz), 4.22 (1H, d, –NCH_2Ph, $J = 6.1$ Hz), 4.91 (1H, d,–NCH_2Ph, $J = 6.1$ Hz), 4.96 (1H, d, –NCH_2Ph, $J = 4.6$ Hz), 6.59 (2H, m, aromatic), 7.08–7.30 (11H, m, aromatic), 7.33 (2H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.14 (C-3′), 18.12 (C-3), 27.83 (C-2′), 29.05 (C-2), 35.90 (C-1), 47.63 (–NCH_2Ph), 50.48 (–NCH_2Ph), 63.46 (C-1′), 126.97, 127.06, 127.25, 127.29, 127.62, 128.23, 128.40, 128.51, 128.86, 135.72, 137.18, 140.12 (the above mentioned, aromatic), 170.75 (C=O); HR-MS (EI) calcd $C_{27}H_{28}N_4O$ 424.2263, found 424.2274 (M^+). Anal. calcd for $C_{27}H_{28}N_4O$: C, 76.39; H, 6.65; N, 13.20. Found: C, 76.20; H, 6.78; N, 12.85.

4(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-cyclopentylenecyclopropanecarboxamide (11h). Yield 86%, oil; $[\alpha]_D^{26}$ −136.62 ° (*c* 1.230, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (1H, dd, H-3a, $J_{3a,3b} = 4.6$, $J_{3a,2} = 9.3$ Hz), 1.45 (3H, t, H-2′, $J_{2',1'} = 6.4$ Hz), 1.63–1.76 (4H, m, –NCH_2CH_2– × 3 and H-3b), 1.94 (1H, ddd, H-2, $J_{2,3b} = 6.3$, $J_{2,3a} = 9.3$, $J_{2,1'} = 9.3$ Hz), 2.48 (1H, m, –NCH_2CH_2–), 3.16 (1H, m), 3.60 (1H, m, –NCH_2CH_2–), 7.17–7.32 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.38 (C-3′), 19.91 (C-3), 23.81 (–NCH_2CH_2–), 26.23 (–NCH_2CH_2–), 27.92 (C-2′), 28.23 (C-2), 36.22 (C-1), 47.08 (–NCH_2CH_2–), 47.71 (–NCH_2CH_2–), 64.33 (C-1′), 126.44 (C-4″), 127.02 (C-2″ and C-6″), 128.55 (C-3″ and C-5″), 140.10 (C-1″), 168.41 (C=); HR-MS (EI) calcd $C_{17}H_{22}N_4O$ 298.1793, found 298.1802 (M^+). Anal. calcd for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.42; H, 7.41; N, 18.65.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-cyclohexylenecyclopropanecarboxamide (11i). Yield: 78%, oil; $[\alpha]_D^{25}$ −140.94 ° (*c* 1.460, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (1H, m, –$NCH_2CH_2CH_2$–), 1.00 (1H, dd, H-3a, $J_{3a,3b} = 4.9$, $J_{3a,2} = 9.3$ Hz), 1.07 (3H, t, H-3′, $J_{3',2'} = 7.3$ Hz), 1.13 (1H, m, –$NCH_2CH_2CH_2$–), 1.41–1.56 (4H, m, –$NCH_2CH_2CH_2$– × 2 and –$NCH_2CH_2CH_2$– × 2), 1.59 (1H, dd, H-3b, $J_{3b,3a} = 4.9$, $J_{3b,2} = 6.3$ Hz), 1.71–1.86 (2H, m, H-2′), 1.94 (1H, ddd, H-2, $J_{2,3b} = 6.3$, $J_{2,3a} = 9.3$, $J_{2,1'} = 9.5$ Hz), 2.88 (1H, m, H-1′), 3.11–3.25 (2H, m, –$NCH_2CH_2CH_2$– × 2), 3.55 (1H, m, –$NCH_2CH_2CH_2CH_2$–), 3.97 (1H, m,–$NCH_2CH_2CH_2CH_2$–), 7.19–7.33

(5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.42 (C-3′), 19.93 (C-3), 24.37 (–$NCH_2CH_2\underline{C}H_2$–), 24.75 (–$NCH_2\underline{C}H_2CH_2$–), 25.56 (–$NCH_2\underline{C}H_2CH_2$–), 27.87 (C-2′), 28.41 (C-2), 35.63 (C-1), 43.92 (–$N\underline{C}H_2CH_2$–), 47.37 (–$N\underline{C}H_2CH_2$–), 64.53 (C-1′), 126.23 (C-2″ and C-6″), 126.48 (C-4″), 128.67 (C-3″ and C-5″), 140.66 (C-1″), 168.43 (C=O); HR-MS (EI) calcd $C_{18}H_{24}N_4O$ 312.1950, found 312.1953 (M^+). Anal. calcd for $C_{18}H_{24}N_4O$: C, 69.20; H, 7.74; N, 17.93. Found: C, 69.12; H, 7.54; N, 17.65.

General procedure for preparing the target cyclopropylethylamines 4d–i

A mixture of **11** (1.00 mmol) and 10% Pd-charcoal (50 mg) in MeOH (5 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 18 h, and then the catalyst was filtered off. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel; AcOEt/hexane 1:1 then $CHCl_3$/MeOH 9:1) to give free amine of **11** as an oil. The free amine was dissolved in MeOH, and the solution was put on a column of Diaion WA-30 resin (Cl^- form). The column was developed with MeOH, and the appropriate fractions were evaporated. The residue was treated with Et_2O to give white crystals of amine **4** as a hydrochloride.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-dipropylcyclopropanecarboxamide hydrochloride (4d). Yield 93%; mp (*i*-Pr_2O/Et_2O/*t*-BuOMe/hexane) 200–201 °C; $[\alpha]_D^{26}$ +91.01 ° (*c* 1.110, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 0.59 (3H, t,–$NCH_2CH_2\underline{CH_3}$, *J* = 7.3 Hz), 0.79 (3H, t, –$NCH_2CH_2\underline{CH_3}$, *J* = 7.4 Hz), 0.97 (1H, m, –$NCH_2\underline{CH_2}CH_3$), 0.99 (3H, t, H-3′, $J_{3',2'}$ = 7.5 Hz), 1.08 (1H, ddd, H-2, $J_{2,3a}$ = 6.1, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 10.4 Hz), 1.25 (1H, dd, H-3a, $J_{3a,3b} = J_{3a,2}$ = 6.1 Hz), 1.37 (1H, m, –$NCH_2\underline{CH_2}CH_3$), 1.45 (1H, m, –$NCH_2\underline{CH_2}CH_3$), 1.53 (1H, m, –$N\underline{CH_2}CH_2CH_3$), 1.74 (2H, m, H-2′), 2.10 (1H, dd, H-3b, $J_{3b,3a}$ = 6.1, $J_{3b,2}$ = 9.0 Hz), 2.66 (1H, m, H-1′), 3.17–3.31 (4H, m, –$N\underline{CH_2}CH_2CH_3$), 7.17 (1H, m, H-4″), 7.25–7.28 (4H, m, aromatic); ^{13}C NMR (125 MHz, CD_3OD) δ 10.37 (C-3′), 11.25 (–$NCH_2CH_2\underline{CH_3}$), 11.69 (–$NCH_2CH_2\underline{CH_3}$), 18.49 (C-3), 21.22 (–$N\underline{CH_2}CH_2CH_3$), 21.84 (–$NCH_2\underline{CH_2}CH_3$), 27.69 (C-2′), 32.86 (C-2), 34.64 (C-1), 47.97 (–$N\underline{CH_2}CH_2CH_3$), 50.91 (–$N\underline{CH_2}CH_2CH_3$), 57.86 (C-1′), 127.01 (C-2″ and C-6″), 128.44 (C-4″), 130.09 (C-3″ and C-5″), 140.26 (C-1″), 173.11 (C=O); HR-MS (EI) calcd $C_{19}H_{30}N_2O$ 302.2358, found 302.2361 (M^+). Anal. calcd for $C_{19}H_{31}ClN_2O$: C, 67.33; H, 9.22; Cl, 10.46; N, 8.27. Found: C, 67.03; H, 9.13; Cl, 10.48; N, 8.22.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-dibutylcyclopropanecarboxamide hydrochloride (4e). Yield 96%; mp (*i*-Pr_2O/Et_2O/*t*-BuOMe/hexane) 148 °C; $[\alpha]_D^{24}$ +92.14 ° (*c* 1.145, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.67 (3H, t, –$NCH_2CH_2CH_2\underline{CH_3}$, *J* = 7.3 Hz), 0.85 (3H, t, –$NCH_2CH_2CH_2\underline{CH_3}$, *J* = 7.4 Hz), 0.87 (1H, m, –$NCH_2\underline{CH_2}CH_2CH_3$), 1.00 (4H, m, H-3′ and-$NCH_2CH_2\underline{CH_2}CH_3$), 1.06 (1H, m, H-2), 1.23 (3H, m, H-3a and –$NCH_2CH_2\underline{CH_2}CH_3$ × 2), 1.34 (1H, m, –$NCH_2\underline{CH_2}CH_2CH_3$), 1.41 (1H, m, –$NCH_2\underline{CH_2}CH_2CH_3$), 1.49 (1H, m, –$NCH_2\underline{CH_2}CH_2CH_3$), 1.74 (2H, m, H-2′), 2.11 (1H, dd, H-3b, $J_{3b,3a}$ = 5.9, $J_{3b,2}$ = 9.0 Hz), 2.66 (1H, m, H-1′), 3.20–3.34 (4H, m, –$N\underline{CH_2}CH_2CH_2CH_3$), 7.16 (1H, m, H-4″), 7.17–7.28 (4H, m, H-2″ and H-3″ and H-5″ and H-6″); ^{13}C NMR (100 MHz, CD_3OD) δ 10.43 (C-3′), 14.09 (–$NCH_2CH_2CH_2\underline{C}H_3$), 14.23 (–$NCH_2\underline{C}H_2CH_2CH_3$), 18.53 (C-3), 20.99 (–$NCH_2CH_2\underline{C}H_2CH_3$), 21.28 (–$NCH_2CH_2\underline{C}H_2CH_3$), 27.74 (C-2′), 30.17 (–$NCH_2\underline{C}H_2CH_2CH_3$), 30.17 (–$NCH_2\underline{C}H_2CH_2CH_3$), 33.06 (C-2), 34.60 (C-1), 46.18 (–$N\underline{C}H_2CH_2CH_2CH_3$), 49.15 (–$N\underline{C}H_2CH_2CH_2CH_3$), 57.80 (C-1′), 126.83 (C-2″ and C-6″), 128.31 (C-4″), 129.99 (C-3″ and C-5″), 140.16 (C-1″), 172.78 (C=O); HR-MS (EI) calcd $C_{21}H_{34}N_2O$ 330.2671, found 330.2651 (M^+). Anal. calcd for $C_{21}H_{35}ClN_2O$: C, 68.73; H, 9.61; Cl, 9.66; N, 7.63. Found: C, 68.55; H, 9.60; Cl, 9.71; N, 7.61.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-di-*i*-butylcyclopropanecarboxamide hydrochloride (4f). Yield 87%; mp (*i*-Pr_2O/Et_2O/*t*-BuOMe/hexane) 172–173 °C; $[\alpha]_D^{24}$ +92.46 ° (*c* 1.055, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.29 (3H, d, –$NCH_2CH(\underline{CH_3})_2$, *J* = 6.7 Hz), 0.72–0.78 (9H, m, –$NCH_2CH(\underline{CH_3})_2$), 0.98 (3H, t, H-3′, $J_{3',2'}$ = 7.5 Hz), 1.05 (1H, ddd, H-2, $J_{2,3a}$ = 6.4, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 10.4 Hz), 1.18 (1H, dd, H-3a, $J_{3a,3b}$ = 6.4, $J_{3a,2}$ = 6.4 Hz), 1.67–1.81 (3H, m, H-2′ and –$NCH_2\underline{CH}(CH_3)_2$), 1.90 (1H, m, –$NCH_2\underline{CH}(CH_3)_2$), 2.19 (1H, dd, H-3b, $J_{3b,3a}$ = 6.4, $J_{3b,2}$ = 9.0 Hz), 2.57 (1H, m, H-1′), 3.00 (1H, dd, –$N\underline{CH_2}CH(CH_3)_2$, *J* = 7.0, 13.4 Hz), 3.11–3.23 (2H, m, –$N\underline{CH_2}CH(CH_3)_2$), 3.35 (1H, dd, –$N\underline{CH_2}CH(CH_3)_2$, *J* = 7.0, 13.4 Hz), 7.16–7.33 (5H, m, aromatic); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.48 (C-3′), 18.41 (C-3), 19.43 (–$NCH_2CH(\underline{C}H_3)_2$), 20.48 (–$NCH_2CH(\underline{C}H_3)_2$), 20.54 (–$NCH_2CH(\underline{C}H_3)_2$), 20.65 (–$NCH_2CH(\underline{C}H_3)_2$), 26.91 (C-2′), 26.98 (–$N\underline{C}H_2CH(CH_3)_2$), 27.70 (–$NCH_2\underline{C}H(CH_3)_2$), 32.74 (C-2), 35.12 (C-1), 51.37 (C-1′), 55.38 (–$N\underline{C}H_2CH(CH_3)_2$), 58.09 (–$N\underline{C}H_2CH(CH_3)_2$), 127.52 (C-2″ and C-6″), 128.49 (C-4″), 129.97 (C-3″ and C-5″), 140.04 (C-1″), 173.80 (C=O); HR-MS (EI) calcd $C_{21}H_{34}N_2O$ 330.2671, found 330.2651 (M^+). Anal. cxalcd for $C_{21}H_{35}ClN_2O$: C, 68.73; H, 9.61; Cl, 9.66; N, 7.63. Found: C, 68.57; H, 9.72; Cl, 9.74; N, 7.48.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-dibenzylcyclopropanecarboxamide hydrochloride (4g). Yield 89%; mp (Et_2O, *i*-Pr_2O) 137–139 °C; $[\alpha]_D^{22}$ +92.46 ° (*c* 1.235, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.11 (3H, t, H-3′, $J_{3',2'}$ = 7.5 Hz), 1.23 (1H, ddd, H-2, $J_{2,3a}$ = 6.6, $J_{2,3b}$ = 9.1, $J_{2,1'}$ = 10.4), 1.38 (1H, dd, H-3a, $J_{3a,3b}$ = 6.2, $J_{3a,2}$ = 6.6 Hz), 1.86 (2H, m, H-2′), 2.17 (1H, dd, H-3b, $J_{3b,3a}$ = 6.2, $J_{3b,2}$ = 9.1 Hz), 2.89 (1H, m, H-1′), 4.40 (1H, d, –$N\underline{CH_2}$Ph, *J* = 4.8 Hz), 4.57 (1H, d, –$N\underline{CH_2}$Ph, *J* = 4.8 Hz), 4.61 (1H, d, –$N\underline{CH_2}$Ph, *J* = 6.0 Hz), 4.66 (1H, d, –$N\underline{CH_2}$Ph, *J* = 6.0 Hz), 6.85 (2H, m, aromatic), 7.09 (2H, m, aromatic), 7.20–7.30 (7H, m, aromatic), 7.34 (2H, m, aromatic), 7.43 (2H, m, aromatic); ^{13}C NMR (125 MHz, CD_3OD) δ 10.37 (C-3′), 17.90 (C-3), 27.73 (C-2′), 32.30 (C-2), 34.84 (C-1), 48.61 (–$N\underline{C}H_2$Ph), 52.00 (–$N\underline{C}H_2$Ph), 57.81 (C-1′), 127.70, 128.52, 128.62, 128.76, 128.80, 129.63, 129.71, 129.80, 130.27, 136.56, 137.77, 139.74 (the above mentioned, aromatic), 173.83

(C=O); HR-MS (EI) calcd $C_{27}H_{30}N_2O$ 398.2358; found 398.2377 (M^+). Anal. calcd for $C_{27}H_{31}ClN_2O$: C, 74.55; H, 7.18; Cl, 8.15; N, 6.44. Found: C, 74.88; H, 7.19; Cl, 8.05; N, 6.43.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-cyclopentylenecyclopropanecarboxamide hydrochloride (4 h). Yield 69%; mp (Et_2O/hexane) 187–190 °C; $[\alpha]_D^{24}$ +89.04 ° (*c* 1.030, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.10 (3H, t, H-3′, *J* = 7.6 Hz), 1.23 (1H, ddd, H-2, $J_{2,3a}$ = 6.0, $J_{2,3b}$ = 8.9, $J_{2,1'}$ = 10.5 Hz), 1.46 (1H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.0 Hz), 1.71–1.96 (6H, m, –NCH$_2$CH$_2$– × 4 and H-2′), 2.05 (1H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 8.9 Hz), 2.89 (1H, m, H-1′), 3.19 (1H, m, –NCH$_2$CH$_2$–), 3.39–3.55 (2H, m, –NCH$_2$CH$_2$– × 2), 3.64 (1H, m, –NCH$_2$CH$_2$–), 7.24–7.37 (5H, m, aromatic); ^{13}C NMR (100 MHz, CD_3OD) δ 10.39 (C-3′), 18.81 (C-3), 24.91 (–NCH$_2$CH$_2$–), 26.72 (C-2′), 27.71 (–NCH$_2$CH$_2$–), 32.85 (C-2), 35.31 (C-1), 47.56 (–NCH$_2$CH$_2$–), 48.28 (–NCH$_2$CH$_2$–), 57.70 (C-1′), 126.91 (C-2″ and C-6″), 128.21 (C-4″), 129.92 (C-3″ and C-5″), 139.44 (C-1″), 171.24 (C=O); HR-MS (EI) calcd $C_{17}H_{24}N_2O$ 272.1889, found 272.1872 (M^+). Anal. calcd for $C_{17}H_{24}N_2O$: C, 66.11; H, 8.16; Cl, 11.48; N, 9.07. Found: C, 65.73; H, 8.14 ; Cl, 11.51; N, 8.84.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-cyclohexylenecyclopropanecarboxamide hydrochloride (4i). Yield: 75%; mp (Et_2O/hexane) 236–239 °C; $[\alpha]_D^{24}$ +63.63 ° (*c* 1.040, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.06 (1H, m, –NCH$_2$CH$_2$CH$_2$–), 1.09 (3H, t, H-3′, $J_{3',2'}$ = 7,6 Hz), 1.22 (1H, ddd, H-2, $J_{2,3a}$ = 6.4, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 10.5 Hz), 1.39 (1H, dd, H-3a, $J_{3a,3b}$ = 6.1, $J_{3a,2}$ = 6.4 Hz), 1.45 (2H, m, –NCH$_2$CH$_2$CH$_2$– × 2), 1.55–1.58 (3H, m, –NCH$_2$CH$_2$CH$_2$– × 1 and –NCH$_2$CH$_2$CH$_2$– × 2), 1.84 (2H, m, H-2′), 2.12 (1H, dd, H-3b, $J_{3b,3a}$ = 6.1, $J_{3b,2}$ = 9.0 Hz), 2.79 (1H, m, H-1′), 3.33 (1H, m, –NCH$_2$CH$_2$CH$_2$–), 3.48 (1H, m,–NCH$_2$CH$_2$CH$_2$–), 3.60 (1H, m, –NCH$_2$CH$_2$CH$_2$–), 3.84 (1H, m, –NCH$_2$CH$_2$CH$_2$–), 7.26 (1H, m, H-4″), 7.32–.38 (4H, m, aromatic); ^{13}C NMR (100 MHz, CD_3OD) δ 10.43 (C-3′), 19.05 (C-3), 25.15 (–NCH$_2$CH$_2$CH$_2$–), 26.46 (–NCH$_2$CH$_2$CH$_2$–), 26.67 (–NCH$_2$CH$_2$CH$_2$–), 27.73 (C-2′), 32.74 (C-2), 34.24 (C-1), 44.31 (–NCH$_2$CH$_2$CH$_2$–), 49.64 (–NCH$_2$CH$_2$CH$_2$–), 57.65 (C-1′), 126.88 (C-2″ and C-6″), 128.24 (C-4″), 129.96 (C-3″ and C-5″), 140.10 (C-1″), 171.22 (C=O); HR-MS (EI) calcd $C_{18}H_{26}N_2O$ 286.2045, found 286.2054 (M^+). Anal. calcd for $C_{18}H_{27}ClN_2O$: C, 66.96; H, 8.43; Cl, 10.98; N, 8.68. Found: C, 67.01; H, 8.36; Cl, 10.87; N, 8.49.

General procedure for preparing lactones 17 and 19

To a solution of various alcohols **14a** or **10a**–**c** (1 mmol) in MeOH (5 mL) was added 6 N HCl (5 mL), and the mixture was heated under reflux for 2 h. The solvent was evaporated, and then the residue was partitioned between saturated aqueous $NaHCO_3$ and AcOEt. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane 1:4) to give **17** or **19** as an oil.

(1*S*,4*R*,5*R*)-2-Oxo-4-ethyl-1-phenyl-3-oxabicyclo[3.1.0]-hexane (17). Yield 94% (from **14a**[10a]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, t, H-2′, $J_{2',1'}$ = 7.5 Hz), 1.42 (1H, dd, H-6a, $J_{6a,5}$ = 5.0, $J_{6a,6b}$ = 5.0 Hz), 1.48 (1H, dd, H-6b, $J_{6b,6a}$ = 5.0, $J_{6b,5}$ = 7.7 Hz), 1.65 (1H, m, H-1′a), 1.82 (1H, m, H-1′b), 2.52 (1H, ddd, H-5, $J_{5,4}$ = 4.4, $J_{5,6a}$ = 5.0, $J_{5,6b}$ = 7.7 Hz), 4.36 (1H, dt, H-4, $J_{4,5}$ = 4.4, $J_{4,1'}$ = 6.9 Hz), 7.26–7.43 (5H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.79 (C-2′), 16.78 (C-6), 25.34 (C-5), 28.47 (C-1′), 32.71 (C-1), 79.48 (C-4), 127.55 (C-4″), 128.15 (C-2″ and C-6″), 128.55 (C-3″ and C-5″), 134.32 (C-1″), 175.67 (C=O); HR-MS (EI) calcd $C_{13}H_{14}O_2$ 202.0994, found 202.1003 (M^+).

(1*S*,4*S*,5*R*)-2-Oxo-4-ethyl-1-phenyl-3-oxabicyclo[3.1.0]-hexane (19). Yields 99% (from **10c**), 61% (from **10d**), 97% (from **10e**), 85% (from **10f**), 89% (from **10g**), 90% (from **10 h**), and 99% (from **10i**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, t, H-2′, $J_{2',1'}$ = 7.4 Hz), 1.35 (1H, dd, H-6a, $J_{6a,5}$ = 4.6, $J_{6a,6b}$ = 4.8 Hz), 1.63 (1H, dd, H-6b, $J_{6b,6a}$ = 4.8, $J_{6b,5}$ = 7.8 Hz), 1.82 (2H, m, H-1′), 2.33 (1H, dd, H-5, $J_{5,6a}$ = 4.6, $J_{5,6b}$ = 7.8 Hz), 4.36 (1H, t, H-4, $J_{4,1'}$ = 6.0 Hz), 7.28–7.41 (5H, m, aromatic); ^{13} C NMR (125 MHz, $CDCl_3$) δ 8.60 (C-2′), 19.90 (C-6), 29.32 (C-5), 29.57 (C-1′), 32.20 (C-1), 80.72 (C-4), 127.63 (C-4″), 128.31 (C-2″ and C-6″), 128.58 (C-3″ and C-5″), 134.20 (C-1″), 175.63 (C=O); HR-MS (EI) calcd $C_{13}H_{14}O_2$ 202.0994, found 202.0999 (M^+).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*t*-butoxycarbonylaminopropyl]cyclopropanecarboxylic acid (22). A solution of **4a** (1.35 g, 5.30 mmol) in 5 N HCl (200 mL) was heated at 100 °C for 18 h, and then the solvent was evaporated. A mixture of the residue, Et_3N (7.40 mL, 53.0 mmol), and Boc_2O (2.44 mL, 11.0 mmol) in MeOH (53 mL) was stirred at room temperature for 18 h. The resulting mixture was concentrated in vacuo, and then $CHCl_3$ and 0.1 N HCl was added. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; MeOH/$CHCl_3$, 1:30) to give **22** as crystals (1.40 g, 83%): mp (EtOH) 62–63 °C; $[\alpha]_D^{26}$ −114.10 ° (*c* 0.980, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, H-3′, *J* = 7.5 Hz), 1.21 (1H, br s, H-3a), 1.35 (9H, s, –C(CH$_3$)$_3$), 1.48–1.63 (4H, m, H-2 and H-3b and H-2′), 3.44–3.47 (2H, m, H-1′ and –NH–), 7.08–7.27 (5H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.09 (C-3′), 19.80 (C-3), 28.02 (C-2′), 28.42 (–C(CH$_3$)$_3$), 30.24 (C-2), 34.93 (C-1), 56.10 (C-1′), 126.99 (C-2″ and C-6″), 127.10 (C-4″), 128.63 (C-3″ and C-5″), 135.84 (C-1″), 177.32 (C=O); HR-MS (EI) calcd $C_{13}H_{17}NO_2$ 219.1259, found 219.1271 ((MH-Boc)$^+$).

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-dimethylcyclopropanecarboxamide hydrochloride (4c). A mixture of **22** (315 mg, 1.00 mmol), Me_2NH (0.55 mL, 2.00 M in THF), and EDC (210 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 18 h. After addition of CH_2Cl_2 and H_2O, the resulting mixture was partitioned, and the organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; MeOH/$CHCl_3$, 1:30) to give **23c** as white crystals (84 mg, 24%): ^{1}H NMR

(270 MHz, $CDCl_3$) δ 0.96 (3H, t, H-3′, $J_{3',2'}=7.3$ Hz), 1.10 (1H, br, H-2), 1.44 (9H, s, $(CH_3)_3C$–), 1.56 (1H, br, H-3a), 1.72–1.91 (3H, m, H-2′ and H-3b), 2.80 (3H, s, –NCH_3), 2.97 (3H, s, –NCH_3), 3.22 (1H, m, H-1′), 4.71 (1H, br s, –NH–), 7.17–7.33 (5H, m, aromatic); LR-MS (EI) m/z 346 (M^+). A solution of **23c** (84 mg, 0.24 mmol) in 1 N HCl/MeOH (2.4 mL) was heated under reflux for 90 min. The solvent was evaporated, and then residue was treated with Et_2O to give white crystals of **4c** as a hydrochloride (60 mg, 88%): mp (Et_2O) 116–118 °C; $[\alpha]_D^{25}$ −168.10 ° (*c* 0.975, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (3H, t, H-3′, $J_{3',2'}=7.5$ Hz), 1.23 (1H, ddd, H-2, $J_{2,3a}=6.0$, $J_{2,3b}=J_{2,1'}=9.0$ Hz), 1.43 (1H, dd, H-3a, $J_{3a,3b}=J_{3a,2}=6.0$ Hz), 1.83 (2H, m, H-2′), 2.11 (1H, dd, H-3b, $J_{3b,3a}=6.0$, $J_{3b,2}=9.0$ Hz), 2.79 (1H, m, H-1′), 2.99 (3H, s, –NCH_3), 3.02 (3H, s, –NCH_3), 7.25–7.37 (5H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.33 (C-3′), 19.38 (C-3), 27.72 (C-2′), 33.14 (C-2), 34.31 (C-1), 36.04 (–NCH_3), 38.31 (–NCH_3), 57.68 (C-1′), 126.75 (C-2″ and C-6″), 128.37 (C-4″), 130.13 (C-3″ and C-5″), 139.93 (C-1″), 173.19 (C=O); HR-MS (EI) calcd $C_{15}H_{22}N_2O$ 246.1732, found 246.1728 ($(M\text{-}HCl)^+$). Anal. calcd for $C_{15}H_{23}ClN_2O\cdot0.5H_2O$: C, 61.74; H, 8.29; N, 9.60. Found: C, 61.34; H, 8.15; N, 9.80.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*-ethylcyclopropanecarboxamide hydrochloride (4b). Compound **23b** was obtained as an oil, as described above for the synthesis of **23c** in 18% yield, with EtNH (0.55 mL, 2.00 M in THF) instead of Me_2NH: ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, t, H-3′, $J_{3',2'}=7.3$ Hz), 1.00 (3H, t, –NCH_2CH_3, $J=7.5$ Hz), 1.18–1.29 (2H, m, H-2 and H-3a), 1.46 (9H, s, $(CH_3)_3C$–), 1.69–1.85 (3H, m, H-3b and H-2′), 3.07–3.30 (2H, m, H-1′ and –NCH_2CH_3), 3.57 (1H, m, –NCH_2CH_3), 5.21 (1H, br s, –NH), 5.37 (1H, br s, –NH), 7.26–7.41 (5H, m, aromatic). LR-MS (EI) m/z 346 (M^+). From **23b**, compound **4b** (hydrochloride) was obtained as white crystals in 75% yield, as described above for the synthesis of **4c**: mp (Et_2O) 112–114 °C; $[\alpha]_D^{26}$ +15.90 ° (*c* 0.760, MeOH); ^1H NMR (500 MHz, CD_3OD : $CDCl_3$, 1:4) δ 1.07 (3H, t, –NCH_2CH_3, $J=7.2$ Hz), 1.11 (3H, t, H-3′, $J_{3',2'}=7.5$ Hz), 1.49 (1H, dd, H-3a, $J_{3a,3b}=5.0$, $J_{3a,2}=5.0$ Hz), 1.55–1.62 (2H, m, H-2 and H-3b), 1.84–2.01 (2H, m, H-2′), 3.06 (1H, m, H-1′), 3.18 (1H, m, –NCH_2CH_3), 3.24 (1H, m, –NCH_2CH_3), 5.33 (1H, br s, –NH–), 7.30 (1H, t, aromatic, $J=7.3$ Hz), 7.37 (2H, t, aromatic, $J=7.3$ Hz), 7.44 (2H, t, aromatic, $J=7.3$ Hz); ^{13}C NMR (100 MHz, CD_3OD : $CDCl_3$, 1:4) δ 9.82 (C-3′), 13.88 (–NCH_2CH_3), 18.93 (C-3), 26.51 (C-2′), 28.15 (C-2), 34.83 (–NCH_2CH_3), 35.41 (C-1), 54.36 (C-1′), 127.73 (C-4″), 128.72 (C-2″ and C-3″ and C-5″ and C-6″), 138.60 (C-1″), 172.11 (C=O); HR-MS (EI) calcd $C_{15}H_{22}N_2O$ 246.1732, found 246.1719 (M^+). Anal. calcd for $C_{15}H_{23}ClN_2O\cdot0.25H_2O$: C, 62.71; H, 8.24; N, 9.75. Found: C, 62.90; H, 8.34; N, 9.36.

Binding assay. The binding affinity for the NMDA receptor was investigated according to previously reported methods.[12]

Inhibitory effects on the uptake of 5-HT. The assay was investigated according to the previously reported method.[10d]

Effects on NMDA receptor mediated LTP in rat hippocampal CA1 area

The brains of 7-weeks-old male Wistar rats were rapidly removed and placed in an ice-cold Kreb's solution bubbled continuously with a gas mixture (95% O_2 and 5% CO_2). A block was removed by making cut at a 30 ° angle from the coronal plane. Sections (450 μm in thickness) were cut from the entire block using a vibratome. The slices were allowed to recover in a submersion type slice chamber at 35 °C for at least 1.5 h. The ACSF (pH 7.4) contained NaCl 126 mM, KCl 5 mM, $CaCl_2$ 2.4 mM, $MgSO_4$ 1.3 mM, $NaHPO_4$ 1.26 mM, $NaHCO_3$ 26 mM, and D-glucose 10 mM, and was bubbled continuously with the O_2–CO_2 mixture. The LTP was prolonged upon perfusion with Mg^{2+} free ACSF for 20 min. A single slice was transferred to a recording chamber through which flowed ACSF (3 mL/min) at 35 °C. Field potentials from the pyramidal layer of CA1 to electrical stimulation of the Schaffer collateral–commissural fiber pathway were recorded with a single-barrel micropipette filled with 2 M NaCl. The stimuli were square wave pulses of 0.1 ms duration, applied at a frequency of 0.25 Hz; the intensity of stimulation was submaximal voltage. The micropipette was advanced into the CA1 area until the activity of a neuron was detected on the oscilloscope. Electrode signals were amplified and monitored on an oscilloscope. The compound dissolved in ACSF was applied in the bath. The percentage of the amplitude was calculated by comparing the baseline amplitude. At each concentration of compounds, differences were statistically determined by the Wilcoxon rank sum test to compared the experimental groups with their controls.

Conformational analysis of 4d

The NMR spectra of **4d** (hydrochloride, 15 mM) were measured in D_2O (400 MHz) at 37 °C. NOESY spectra were recorded in the phase-sensitive mode using the methods of States and coworkers.[15] The intensities of the NOE cross peaks in the NOESY spectrum recorded with the mixing time of 200 ms were used to obtained inter-proton distances. NOE cross peaks were separated into three distance categories depending on cross peak intensity. Strong NOE were given an upper distance constraint of 2.5 Å while medium and weak NOEs were given values of 3.0 and 3.5 Å, respectively. For distance constraints that involved nonequivalent methylene, methyl and aromatic ring protons which could not be stereospecifically assigned, the pseudoatom treatment was used. These provided the distance constraints which were used for the subsequent structure calculation. Three-dimensional structures which satisfy the NOE constraints of the intramolecular proton pairs were constructed by simulated annealing calculations[14] using Discover-Insight (MSI) as the program. All calculations of other potential functions were performed following the protocol in the program Discover using the standard parameters on IRIS Indogo2 Solid Impact R10000.

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