Synthesis of (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminoalkyl]-*N*,*N*-diethylcyclopropanecarboxamides as novel NMDA receptor antagonists having a unique NMDA receptor subtype selectivity

1 PERKIN

Yuji Kazuta,[a] Ryuichi Tsujita,[b] Shigeo Uchino,[c] Noriko Kamiyama,[a] Daisuke Mochizuki,[b] Kanako Yamashita,[b] Yutaka Ohmori,[b] Akitake Yamashita,[b] Tamotsu Yamamoto,[b] Shinich Kohsaka,[c] 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. E-mail: shu@pharm.hokudai.ac.jp; Fax: +81117064980; Tel: +8111 7063229*

[b] *Institute of Life Science Research, Asahi Chemical Co., Ltd., Ohito-cho, Shizuoka 410-23, Japan*

[c] *Department of Neurochemistry, National Institute of Neuroscience, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan*

Received (in Cambridge, UK) 18th December 2001, Accepted 8th March 2002
First published as an Advance Article on the web 4th April 2002

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2b**), which is a conformationally restricted analog of the antidepressant milnacipran [(±)-**1**], is a new class of potent NMDA (*N*-methyl-D-aspartic acid) receptor antagonists. A series of analogs of **2b** modified at the 1′-position were designed and synthesized starting from (*R*)-epichlorohydrin *via* the key intermediate an optically active cyclopropanecarbaldehyde derivative **8** with a (1*S*,2*R*)-configuration. Among these analogs, (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminobut-3-enyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2i**) and (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminobut-3-ynyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2j**) were identified as more potent NMDA receptor antagonists than **2b**. The subtype selectivity of **2i** and **2j** together with **2b** was investigated to show that **2i** inhibited the GluRε3/ζ1 and GluRε4/ζ1 subtypes four times more strongly than GluRε1/ζ1 and GluRε2/ζ1 subtypes. Compound **2i** is the first GluRε3/ζ1 and GluRε4/ζ1 subtype-selective antagonist, while the selectivity is not so high.

Introduction

The excitatory neurotransmitter L-glutamic acid (glutamate) has been shown to cause neuronal death in instances of stroke, ischaemia, and head trauma.[1] Glutamate receptor overstimulation may also play a role in chronic neurodegenerative conditions, such as Alzheimer's disease and Parkinson's disease.[1,2] A number of studies strongly suggest that the toxicity of high levels of glutamate is mediated primarily by NMDA (*N*-methyl-D-aspartic acid) receptors, one of the ionotropic glutamate receptor (iGluR) subclasses.[3] There have been attempts to develop novel agents that block the activation of NMDA receptors by glutamate or related excitatory neurotransmitters, and a large number of competitive and non-competitive NMDA receptor antagonists have been developed.[1–3] Several of their structures are shown in Fig. 1. A number of studies have indicated that these competitive and noncompetitive antagonists are effective in experimental models of epilepsy and stroke.[1–3] However, clinical studies of these NMDA receptor antagonists have not been as successful.[1–3] Non-competitive inhibitors, such as channel blocker MK-801, have had serious behavioral effects[4] and have caused neuronal vacuolization[5] while competitive inhibitors were often inactive *in vivo* because of poor transport to the brain.[6] Consequently, the development of another type of efficient NMDA receptor antagonist for use in the treatment of epilepsy, stroke, Huntington's and/or Parkinson's diseases is not only strongly required but also eagerly desired.

It is known that NMDA receptors are composed of GluRε (NR2) and GluRζ (NR1) subunits.[7,8] The GluRε subunit contains the glutamate binding site, while the GluRζ subunit bears the glycine binding site. Mammalian NMDA receptors are heterooligomeric combinations of GluRζ subunits and at least one of four GluRε subunits (GluRε1–4).[1,2] Studies on subtype selectivity of the NMDA receptor antagonists have been reported.[7] Competitive antagonists, such as (*R*)-AP5 or (*R*)-CPP-ene, the non-competitive channel blocker MK-801,[7a] and the polyamine spider toxin argiotoxin[7b] somewhat selectively antagonize the GluRε1/ζ1 (NR1/2A) and/or GluRε2/ζ1 (NR1/2B) subtypes,[7c] while the channel blockers phencyclidine (PCP), ketamine or SKF-10047 do not show any apparent subtype selectivity.[7a] The glycine site antagonist 7-chlorokynurenic acid inhibits the NMDA receptor subtypes in the order of GluRε3/ζ1 (NR1/2C) > GluRε2/ζ1 > GluRε1/ζ1 > GluRε4/ζ1 (NR1/2D).[7d,e] In recent years, ifenprodil[7i] and its analogs, such as CP-101,606,[7j–l] have been identified as highly GluRε2/ζ1 subtype-selective antagonists.

Subtype-selective NMDA receptor antagonists may retain therapeutic activity without the side effects observed in the previous antagonists.[7j–l] Thus, development of novel antagonists with a subtype selectivity different from those of previous antagonists showing serious neuronal side effects, may be desired. The subtype selective antagonists should also be useful as tools for pharmacological studies on the NMDA receptors.

(±)-(*Z*)-2-Aminomethyl-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide [milnacipran, (±)-**1**],[9] a clinically effective antidepressant due to competitive inhibition of the re-uptake of serotonin (5-HT) in the CNS,[10] is also recognized as a non-competitive NMDA receptor antagonist.[11] Although the binding affinity of (±)-**1** to the NMDA receptor is not high enough, it may be a useful starting point in the development of an efficient NMDA receptor antagonist, since structurally it is

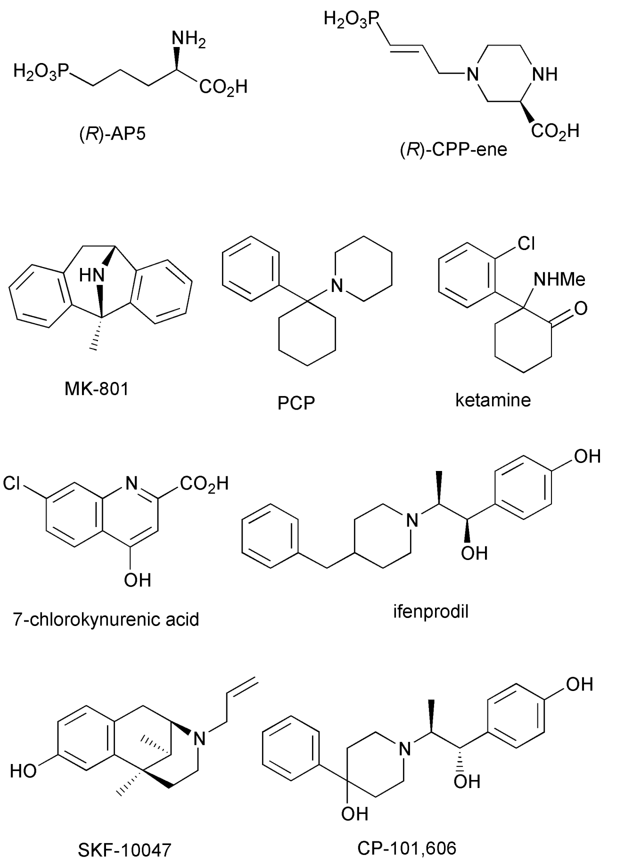


Fig. 1 Known NMDA receptor antagonists.

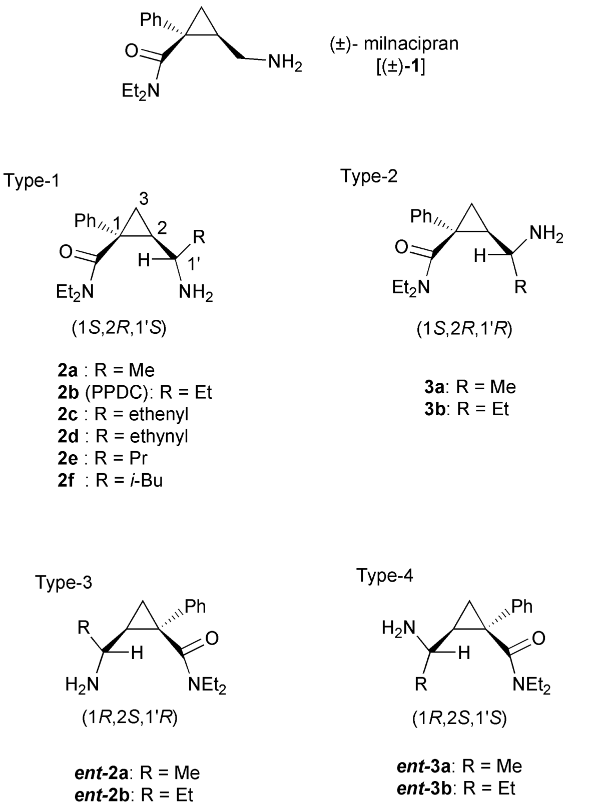


Fig. 2 Milnacipran and the previously synthesized conformationally restricted analogs.

clearly different from the known antagonists that show serious side-effects, and it has been shown in clinical studies that it can be transported to the brain.[10d,e] We previously reported the design and synthesis of four types of conformationally restricted analogs of (±)-**1** with different stereochemistries; *i.e.*, **2** (Type-1) and **3** (Type-2) and their enantiomers ***ent*-2** (Type-3) and ***ent*-3** (Type-4), as shown in Fig. 2. In these conformationally restricted analogs, the conformation can be limited by an alkyl group introduced at the α-position of the amino function of (±)-**1**, which is essential for binding to the NMDA receptor,[11] due to steric repulsion with the diethylcarbamoyl group.[12a]

The biological evaluation of these conformationally restricted analogs of milnacipran showed: 1) that the conformational restriction can improve the activity;[12d] 2) that the analogs with a (1*S*,2*R*,1′*S*)-configuration (Type-1) are more potent than the analogs with the other configurations (Type-2, Type-3, and Type-4) and 3) that introduction of a substituent bulkier than an ethyl group, such as a propyl or isobutyl group, at the 1′-position significantly reduces the activity.[12d] Thus, we found that analogs with a Type-1 configuration, *i.e.*, **2a**, **2b**, **2c** and **2d**, (Fig. 2) were efficient NMDA receptor antagonists, significantly inhibiting the binding of [^{3}H]MK-801, with IC_{50} values about 30-fold stronger than that of (±)-**1**.[12e,f] These previous studies suggested that **2b** 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 **2a**, **2c** and **2e** are strong 5-HT-uptake inhibitors like the parent compound milnacipran.[12h] Pharmacological studies on **2b** have shown: 1) that **2b** 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;[12h] and 2) that the release of **2b** 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, *i.e.*, outward currents had no effect on the channel block of **2b**, while the release of MK-801 was significantly accelerated under outward current conditions in the voltage-clamp experiments.[12f] These results, together with the structural features of **2b**, that are clearly different from those of the previous antagonists, suggest that **2b** is a new class of NMDA receptor antagonist.

The above findings prompted us to carry out further studies, which we report herein. We designed and synthesized the additional conformationally restricted analogs **2g**–**m**, which have a sterically small carbon substituent at the 1′-position, with the same configuration as that for **2b**. The *N*-methyl analog **4** and cyclic amine analogs **5**–**7**, the structures of which are shown in Fig. 3, were also synthesized. Among the newly synthesized compounds, 1-phenyl-2-[(*S*)-1-aminobut-3-enyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2i**) and 1-phenyl-2-[(*S*)-1-aminobut-3-ynyl]-*N*,*N*-diethylcyclopropanecarboxamide (**2j**)

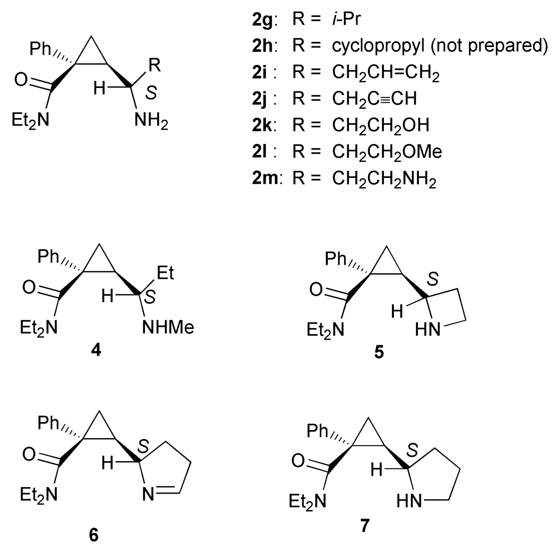
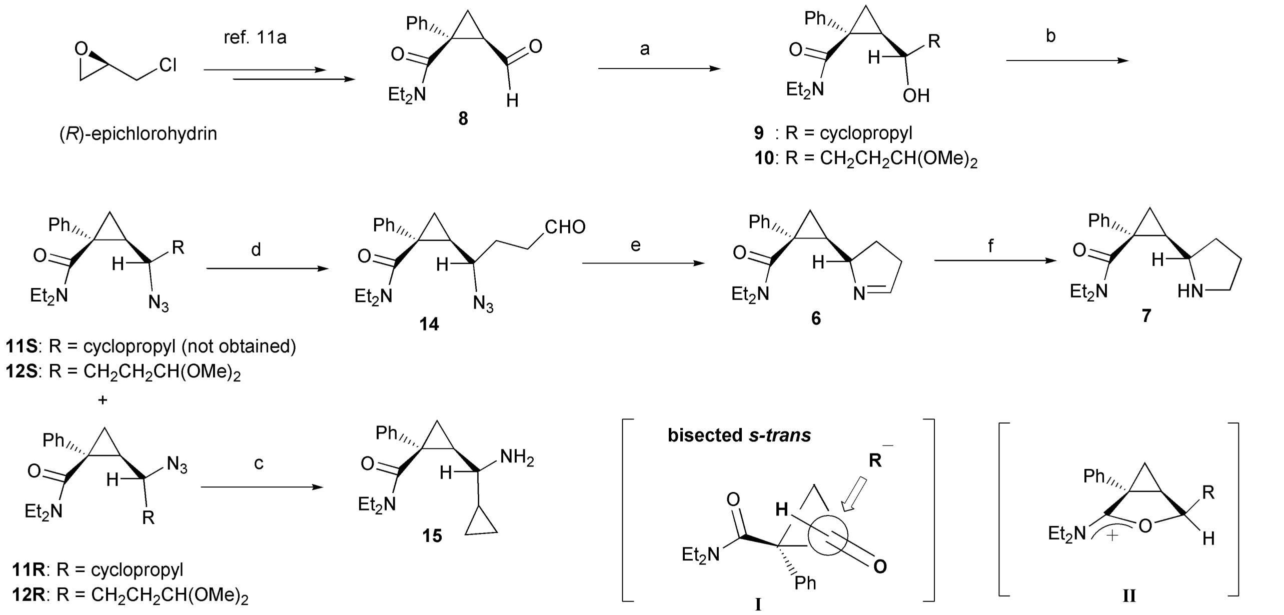


Fig. 3 The newly designed conformationally restricted analogs of milnacipran.



Scheme 1 *Reagents*: (a) RMgBr, THF; (b) NaN_3, PPh_3, CBr_4, DMF; (c) H_2, Pd–C, MeOH; (d) TFA, CH_2Cl_2–H_2O; (e) 1) H_2, Pd–C, MeOH, 2) molecular sieves 5 Å, CH_2Cl_2; (f) $NaBH_3CN$, MeOH.

were identified as the most potent compounds in this series of NMDA receptor antagonists. The subtype selectivity of **2i** and **2j** together with **2b** was also investigated to show that **2i** is the first GluRε3/GluRζ1 and GluRε4/GluRζ1 subtypes-selective antagonist, though the subtype selectivity is not so high.

Results and discussion

Synthesis of 2b derivatives

All of the target compounds were synthesized from an optically active cyclopropanecarbaldehyde derivative **8** with a (1*S*,2*R*)-configuration, which was prepared from (*R*)-epichlorohydrin according to a previously reported method.[12a]

Syntheses of the 1′-cyclopropyl, -pyrrolinyl and -pyrrolidinyl analogs (**2h**, **6** and **7**, respectively) were undertaken *via* Grignard reactions of **8** (Scheme 1). Thus, reaction of **8** with cyclopropyl- or 3,3-dimethoxypropylmagnesium bromide in THF was performed to give the corresponding 1′*S*-products **9** and **10** with high diastereoselectivity in 79% and 96% yields, respectively. We previously showed that the addition reaction of Grignard reagents to **8** proceeds from the least-hindered *si*-face in the bisected s-*trans* conformation **I**, which would be preferred due to the peculiar stereo-electronic effect of the cyclopropane ring, to produce 1′*S*-addition products highly stereoselectively.[12a,b] Treatment of **10** with the NaN_3–PPh_3–CBr_4 system[13] gave the 1′*S*-azide **12S** as the major product in 49% yield along with the 1′*R*-diastereomer **12R** in 15% yield. We have demonstrated that this reaction occurs *via* the neighboring group participation intermediate **II** to give the corresponding configuration-retained azidomethylcyclopropane derivatives as the major products.[12a,d,e] The 1′-configurations of **12S** and **12R** were further supported by the chemical shifts in the ^{1}H NMR spectra as summarized in Table 1. We observed that a series of the 1′-azido-cyclopropane derivatives show a typical chemical shift pattern depending on the 1′-configuration. Table 1 shows the ^{1}H NMR spectral data of the previously synthesized 1′*R*-azides **29R**[12a] and **30R**,[12a] and 1′*S*-azides **29S**,[12a] **30S**,[12a] **31S**[12d] and **32S**,[12d] the stereochemistries of which were determined earlier. The ^{1}H NMR data of 1′*S*-azides **16**–**19**, the stereochemistries of which were confirmed as described below, are also summarized in Table 1. 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 proton signals overlap in the spectra of the 1′*R*-azides. Thus the 1′-configuration of the major product **12S** from **10** was confirmed as *S* based on the signals of the three protons observed separately at δ 1.92, 1.01 and 1.63 respectively, as shown in Table 1.

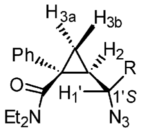
After acidic treatment of **12S**, the resulting aldehyde **14** was treated with H_2/Pd–C in MeOH and then with molecular sieves (5 Å in CH_2Cl_2) causing spontaneous cyclization giving the desired 1′*S*-cyclic-imino derivative **6**. Further reduction of the imino moiety of **6** with $NaBH_3CN$ in MeOH furnished the corresponding pyrrolidine derivative **7**.

Treatment of the 1′-cyclopropyl derivative **9** with the NaN_3–PPh_3–CBr_4 system, similar to that for **10** described above, unexpectedly gave the configuration-inverted 1′*R*-azide **11R**, and not the desired 1′*S*-product **11S**. The 1′*R*-configuration was suggested by the ^{1}H NMR chemical shifts shown in Table 1 and was further confirmed by the X-ray crystallographic analysis of the corresponding amine **15** derived from **11R**. The stereochemical result showed that the nucleophilic substitution between an azide anion and the carbocation generated from **9** did not proceed *via* the neighboring group participation intermediate **II** (Scheme 1). It has been recognized that cyclopropylmethyl carbocations can be significantly stabilized by the interaction between a vacant p-orbital on the carbocation and electrons of the cyclopropane ring, which are characterized as strong π-donors.[14] Therefore, the reaction was likely to proceed *via* an S_N1 reaction pathway due to highly effective stabilization of the 1′-carbocation by the adjacent two cyclopropane rings. The reaction gave stereoselectively the undesired 1′*R*-azide **11b**, since, with regard to the intermediate carbocation, a conformation of the bisected s-*trans*-form would be preferred over the bisected s-*cis*-form due to steric repulsion between the 1′-cyclopropyl group and the *N*,*N*-diethylcarbamoyl group. Therefore an azide anion would attack the intermediate from the less-hindered face forming the undesired product **11b**, as shown in Scheme 2. Catalytic hydrogenation of **11R** with Pd–C in MeOH gave 1′*R*-cyclopropylamine **15**, the X-ray crystallographic structure of which is shown in Fig. 4. Consequently, the synthesis of the 1′*S*-cyclopropyl analog **2h** was unsuccessful.

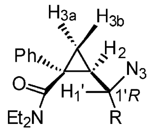
The syntheses of the analogs **2i**–**l** and **5**, having allyl, propargyl†, 2-hydroxyethyl, 2-methoxyethyl, or azetidinyl substituents at the 1′-position, are shown in Scheme 3. All of these compounds were synthesized from the (1′*S*)-1′-azido-1′-(2-pivaloyloxyethyl) derivative **16**, which was prepared from **8**

† The IUPAC name for propargyl is prop-2-ynyl.

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

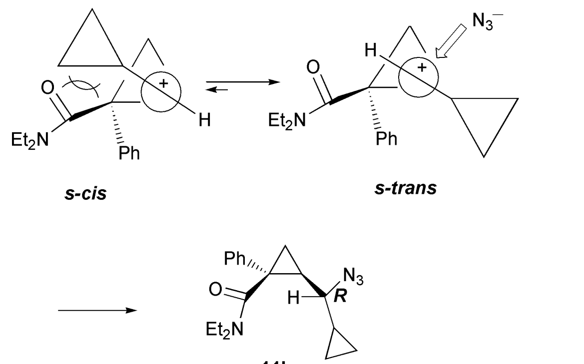


29S: R = Me
30S: R = Et
31S: R = Pr
32S: R = *i*-Bu
12S: R = $CH_2CH_2CH(OMe)_2$
16: R = CH_2CH_2OPiv
17: R = CH_2CH_2OH
18: R = CH_2CH_2OMe
19: R = CH_2CH_2OTs
27S: R = $CH_2CH_2N_3$



29R: R = Me
30R: R = Et
11R: R = cyclopropyl
12R: R = $CH_2CH_2CH(OMe)_2$
27R: R = $CH_2CH_2N_3$

Compd	R	1′-Config.	Chemical shift, δ (multiplicity)			
			H-1′	H-2	H-3a	H-3b
29S	Me	*S*	2.98–3.08 (m)	1.95 (ddd)	0.91 (dd)	1.61 (dd)
30S	Et	*S*	2.86 (ddd)	1.96 (ddd)	0.95 (dd)	1.65 (dd)
31S	Pr	*S*	2.90 (ddd)	1.96 (ddd)	0.94 (dd)	1.66 (dd)
32S	i-Bu	*S*	2.92 (ddd)	1.96 (ddd)	0.95 (dd)	1.65 (dd)
12S	$(MeO)_2CH_2CH_2CH_2$	*S*	2.97 (m)	1.92 (ddd)	1.01 (dd)	1.63 (dd)
16	$PvOCH_2CH_2$	*S*	3.14 (m)	1.92 (ddd)	1.06 (dd)	1.59 (dd)
17	$HOCH_2CH_2$	*S*	3.18–3.29 (m)	1.89 (ddd)	1.12 (dd)	1.58 (dd)
18	$TsOCH_2CH_2$	*S*	3.19–3.26 (m)	1.68 (ddd)	1.10 (dd)	1.41 (dd)
19	$MeOCH_2CH_2$	*S*	3.13–3.23 (m)	1.87–1.98 (m)	1.02 (dd)	1.62 (dd)
27S	$N_3CH_2CH_2$	*S*	3.17 (m)	1.74–1.85 (m)	1.20 (dd)	1.57 (dd)
29R	Me	*R*	3.33–3.38 (m)	1.48–1.52 (m)	1.48–1.52 (m)	1.48–1.52 (m)
30R	Et	*R*	3.12–3.26 (m)	1.47–1.60 (m)	1.47–1.60 (m)	1.47–1.60 (m)
11R	Cyclopropyl	*R*	3.27–3.35 (m)	1.62–1.69 (m)	1.42 (dd)	1.62–1.69 (m)
12R	$(MeO)_2CH_2CH_2CH_2$	*R*	3.33 (m)	1.48 (ddd)	1.56–1.65 (m)	1.56–165 (m)
27R	$N_3CH_2CH_2$	*R*	3.38–3.52 (m)	1.48 (ddd)	1.48–1.52 (m)	1.48–1.52 (m)



11b

Scheme 2 A possible reaction mechanism for the formation of **11b** *via* a S_N2 reaction pathway.

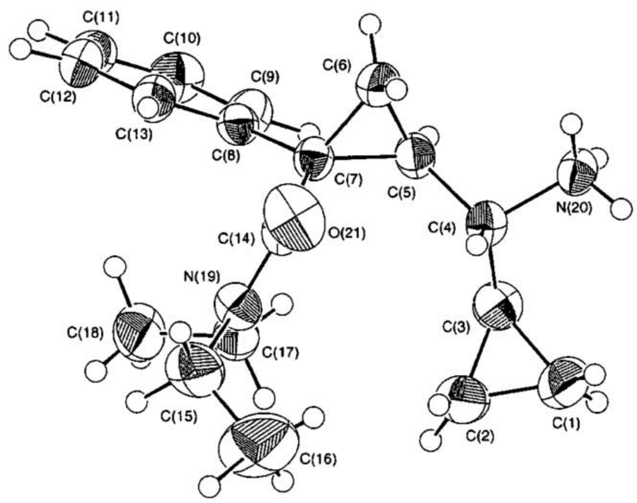


Fig. 4 X-Ray crystallographic structure of **15**.

according to the previous method.[12d] Removal of the pivaloyl group of **16** gave the 1′-hydroxyethyl derivative **17**, which after treatment with MeI–NaH gave the corresponding *O*-methyl derivative **18**. The usual hydrogenation of **17** and **18** gave the corresponding amines **2k** and **2l**, respectively. After treatment of **17** with TsCl–Et_3N–DMAP, the resulting tosyloxy derivative**19** was hydrogenated with Pd–C in MeOH to cause spontaneous cyclization giving the azetidine derivative **5**. Hydrogenation of **16** with Pd–C in the presence of Boc_2O gave the Boc-protected amine **20**, which was treated with NaOMe–MeOH to afford the 1′-(2-hydroxyethyl) derivative **21**. Wittig reaction of the aldehyde **22**, which was prepared by Swern oxidation of **21**, with $Ph_3P{=}CH_2$ produced the corresponding 1′-allyl derivative **23**. The corresponding dibromo derivative **24** was obtained by a similar Wittig-type reaction of **22** with a CBr_4–PPh_3 system, and subsequent treatment of **24** with BuLi[15] gave the propargyl derivative **25**. Removal of the Boc group of **23** and **25** under acidic conditions furnished **2i** and **2j**.

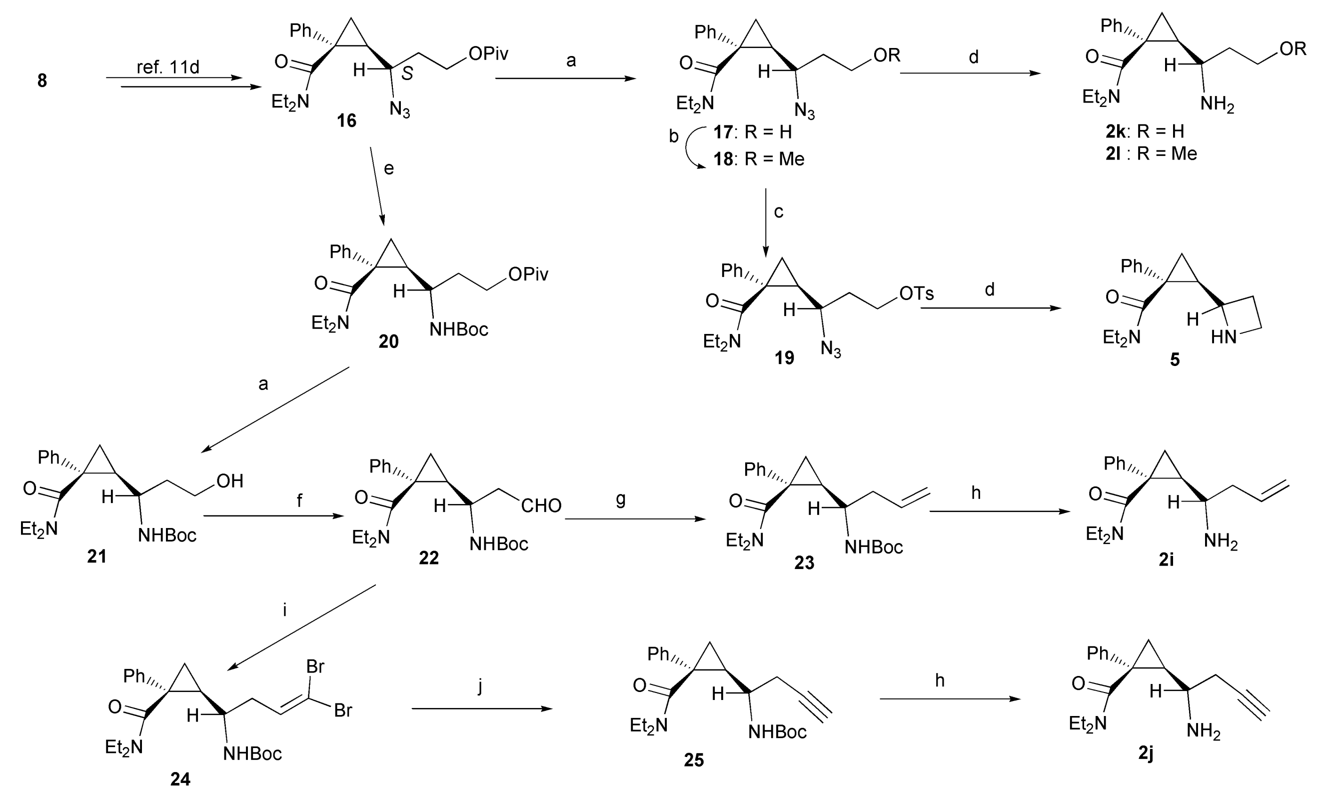
The 1′-(2-aminoethyl) derivative **2m** and the *N*-methylated analog **4** were prepared readily by the usual chemistry as summarized in Schemes 4 and 5.

Affinity for the NMDA receptor of rat cerebral cortex

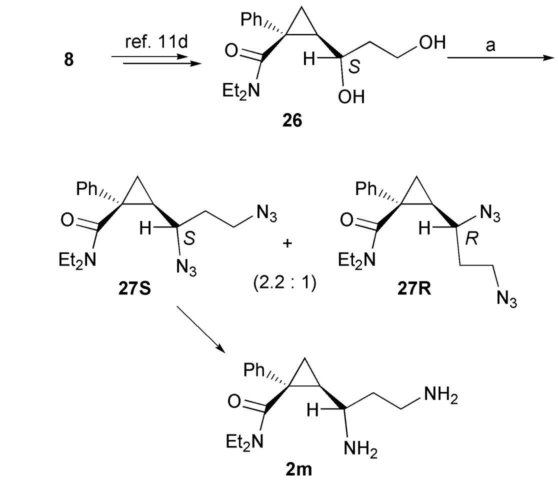
The synthesized compounds were evaluated for their binding affinity to the NMDA receptor of cerebral cortical synaptic membranes from rats with [^{3}H]MK-801 as a radioligand.[16] The results, together with those of several previously reported compounds,[12d,e] are shown in Table 2.

The binding affinity was significantly affected by the substituent at the 1′-position. Compounds **2e**, **2k**, **2l** and **2m**, in which a proton at the terminal carbon of the 1′-ethyl group of **2b** is replaced with a methyl, hydroxy, methoxy, or an amino group, showed binding affinities with IC_{50} values between 1.0–2.0 μM, *i.e.* weaker than for **2b** (IC_{50} = 0.20 ± 0.02 μM). Branching in the 1′-substituent, such as the isopropyl derivative **2g** as well as the previously reported isobutyl derivative **2f**,[12d] significantly decreased the activity.

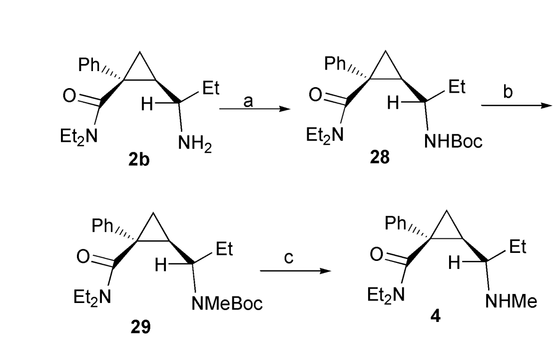
It is worth noting that introduction of an unsaturated bond at the terminal carbon of the 1′-ethyl group of **2b** improved the binding affinity; the 1′-allyl analog **2i** and the 1′-propargyl analog **2j** significantly inhibited the binding of [^{3}H]MK-801 with IC_{50} values of 0.12 ± 0.008 and 0.10 ± 0.03 μM, respectively, which are the strongest binding affinities in the compounds synthesized so far.



Scheme 3 *Reagents*: (a) NaOMe, MeOH; (b) MeI, NaH, THF; (c) TsCl, Et_3N, DMAP, CH_2Cl_2; (d) H_2, Pd–C, MeOH; (e) H_2, Pd–C, Boc_2O, MeOH; (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (g) $Ph_3P{=}CH_2$, THF; (h) HCl, aq. MeOH; (i) CBr_4, PPh_3, CH_2Cl_2; j) BuLi, THF.



Scheme 4 *Reagents*: (a) NaN_3, PPh_3, CBr_4, HMPA; (b) H_2, Pd–C, MeOH.



Scheme 5 *Reagents*: (a) Boc_2O, Et_3N, CH_2Cl_2; (b) MeI, BuLi, THF; (c) HCl, aq. MeOH.

Although the cyclic amine derivatives **5** and **7** showed rather potent binding affinities for the receptor (IC_{50} values of 0.62 ± 0.01 and 1.0 ± 0.2 µM, respectively), they were weaker than for **2b**. The pyrroline derivative **6** was almost inactive (IC_{50} = 13 ± 2.6 µM), which suggested that the presence of a proton on the 1′-amino nitrogen would be important for the binding.

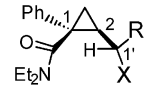
Inhibition of the 5-HT-uptake

The inhibitory effects of the compounds on the uptake of 5-HT by nerve terminals of the cerebral cortical synaptic membrane from rats were next evaluated with [^{3}H]paroxetine as a radioligand,[12d] since milnacipran [(±)-**1**], the parent compound, is a potent inhibitor of 5-HT uptake.[10] The results are also summarized in Table 2. All of the newly synthesized compounds (**2i**–**l** and **4**–**7**), except the 1′-isopropyl derivative **2g** and the 1′-(2-aminoethyl) derivative **2m**, showed no appreciable effect on the uptake of 5-HT. From these results, it appears that the inhibitory potency of the conformationally restricted analogs with Type-1 configuration against the 5-HT uptake is significantly affected by the bulkiness of the 1′-substituent (Me, CH=CH$_2$ > C≡CH ⩾ Et, Pr, *etc.*). It is important that, although the 1′-ethenyl and -ethynyl derivatives (**2c** and **2e**) have a significant inhibitory effect, their homologs, the 1′-allyl derivative **2i** and the 1′-propargyl derivative **2j**, are virtually inactive as 5-HT uptake inhibitors. In particular, the 1′-allyl derivative **2i** showed a remarkable selectivity index [5-HT uptake (K_i)/NMDA receptor binding (IC_{50})] of >830, which is clearly superior to that of **2b** (selectivity index = 120).

NMDA receptor subtype selectivity

We have established Chinese hamster ovary (CHO) cell lines carrying NMDA receptor subtype cDNAs (*i.e.*, GluRζ1 and each of GluRε1, GluRε2, GluRε3, or GluRε4) under the control of the *Drosophila* hsp70 promoter.[17] Heat treatment of the cell lines by incubation at 43 °C for 30–60 min induced the functional expression of NMDA receptor subtypes, since the heat-treated cells showed robust responses to co-application of 30 µM L-glutamate and 30 µM glycine, as shown by an increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). Thus, using these clonal cell lines and calcium fluorometry, we determined the antagonistic potency and subtype selectivity of NMDA receptor antagonists.

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] (IC_{50}/μM)	5-HT-uptake[b] (K_i/μM)	Selectivity index[c] (5-HT/NMDA)
(±)-**1**	NH_2	H	6.3 ± 0.3	0.0085 ± 0.0006	0.0013
2a	NH_2	Me	0.35 ± 0.08	0.014 ± 0.002	0.040
2b	NH_2	Et	0.20 ± 0.02	24 ± 0.9	120
2c	NH_2	$CH{=}CH_2$	0.16 ± 0.02	0.023 ± 0.0007	0.14
2d	NH_2	C≡CH	0.29 ± 0.2	0.19 ± 0.2	0.66
2e	NH_2	Pr	1.0 ± 0.05	37 ± 3	37
2f	NH_2	*i*-Bu	4.2 ± 0.2	> 100	> 24
2g	NH_2	*i*-Pr	17 ± 0.9	4.4 ± 0.1[c]	0.26
2i	NH_2	$CH_2CH{=}CH_2$	0.12 ± 0.008	> 100	> 830
2j	NH_2	$CH_2C{\equiv}CH$	0.10 ± 0.03	20 ± 1	200
2k	NH_2	CH_2CH_2OH	1.2 ± 0.02	24 ± 1	20
2l	NH_2	CH_2CH_2OMe	1.7 ± 0.4	> 100	> 59
2m	NH_2	$CH_2CH_2NH_2$	1.4 ± 0.2	0.48 ± 0.002	0.34
4	NHMe	Et	0.37 ± 0.0	30 ± 0.2	81
5	Azetidin-2-yl		0.62 ± 0.01	32 ± 2	52
6	Pyrrolin-5-yl		13 ± 3	20 ± 1	1.5
7	Pyrrolidin-2-yl		1.0 ± 0.2	32 ± 0.5	32
Ketamine			0.61 ± 0.46		
PCP			0.0098 ± 0.005		

[a] Assay was performed with cerebral cortical synaptic membrane of rats using [^{3}H]MK-801 (*n* = 2; ±, standard error). [b] Assay was performed with cerebral cortical synaptic membrane of rats using [^{3}H]paroxetine (*n* = 2; ±, standard error). [c] The ratio: 5-HT uptake inhibition (K_i) : NMDA receptor binding (IC_{50}).

Table 3 Effects of PPDC, **2i**, and **2j** on GluRε1/ζ1, GluRε2/ζ1, GluRε3/ζ1 and GluRε4/ζ1 subtypes

Compd	IC_{50}/μM[a] (Hill coefficient) GluRε1/ζ1	GluRε2/ζ1	GluRε3/ζ1	GluRε4/ζ1
PPDC (**2b**)	41.7 ± 1.5 (0.9 ± 0.1)	13.3 ± 0.5 (1.1 ± 0.1)	12.6 ± 0.5 (1.0 ± 0.1)	11.5 ± 1.2 (1.0 ± 0.1)
2i	43.0 ± 3.9 (1.2 ± 0.1)	37.9 ± 3.0 (1.2 ± 0.1)	10.6 ± 1.1 (1.2 ± 0.1)	9.8 ± 0.6 (1.1 ± 0.1)
2j	36.4 ± 2.2 (1.1 ± 0.2)	12.3 ± 1.0 (1.1 ± 0.04)	14.5 ± 1.8 (1.0 ± 0.02)	14.1 ± 1.1 (1.0 ± 0.04)
(±)-AP5	0.88 ± 0.03 (1.2 ± 0.04)	1.45 ± 0.10 (1.0 ± 0.1)	2.39 ± 0.03 (1.2 ± 0.1)	17.5 ± 1.5 (0.8 ± 0.03)
Ifenprodil	>100	0.35 ± 0.03 (2.0 ± 0.2)	>100	>100

[a] Assay was performed with the CHO cell lines carrying NMDA receptor subtype cDNAs (*n* = 3; ±, standard error).

We initially tested the sensitivity of the four NMDA receptor subtypes to two well-characterized NMDA receptor antagonists, (±)-AP5 and ifenprodil. The values were obtained by the three independent experiments and are shown in Table 3. The four NMDA receptor subtypes showed differential sensitivity to (±)-AP5. The IC_{50} values of (±)-AP5 were 0.88 ± 0.03 μM for GluRε1/ζ1, 1.45 ± 0.10 μM for GluRε2/ζ1, 2.39 ± 0.03 μM for GluRε3/ζ1 and 17.5 ± 1.48 μM for GluRε4/ζ1. The observed rank order is in accordance with that found in the *Xenopus* oocytes expression system.[7i] Ifenprodil is a GluRε2/ζ1 subtype selective antagonist acting at the polyamine modulatory site.[7l,m] As expected, the GluRε2/ζ1 subtype was highly sensitive to ifenprodil, whereas concentrations of greater than 100 μM were required to affect the responses to other receptor subtypes. The IC_{50} value of 0.35 ± 0.03 μM (Hill coefficient = 2.0 ± 0.2) was similar to that obtained using GluRε2/ζ1 expressed in the *Xenopus* oocytes (0.34 μM) reported previously.[7m] These results indicate that the established clonal cell lines are useful in characterizing the pharmacological properties of drugs that act on NMDA receptors.

We next determined the antagonistic potency of 1′-ethyl derivative **2b**, 1′-allyl derivative **2i**, and 1′-propargyl derivative **2j** to the subtypes. The results obtained by the three independent experiments, and the IC_{50} values are summarized in Table 3. Fig. 5 clearly shows that the NMDA receptor subtype carrying CHO cell lines are very effective for the subtype selectivity evaluation of the compounds. Thus, we determined the antagonistic potency and subtype selectivity of the novel antagonists **2b**, **2j** and **2i**. The compounds **2b** and **2j** were similar in effect for the four NMDA receptor subtypes, the rank-order of sensitivity being GluRε2/ζ1 ≈ GluRε3/ζ1 ≈ GluRε4/ζ1 > GluRε1/ζ1. In contrast, compound **2i** inhibits the GluRε3/ζl and/or GluRε4/ζl subtypes four times more strongly than GluRε1/ζl and/or GluRε2/ζl subtypes. This difference in sensitivity of the compounds provide new insights into development of subtype-selective drugs.

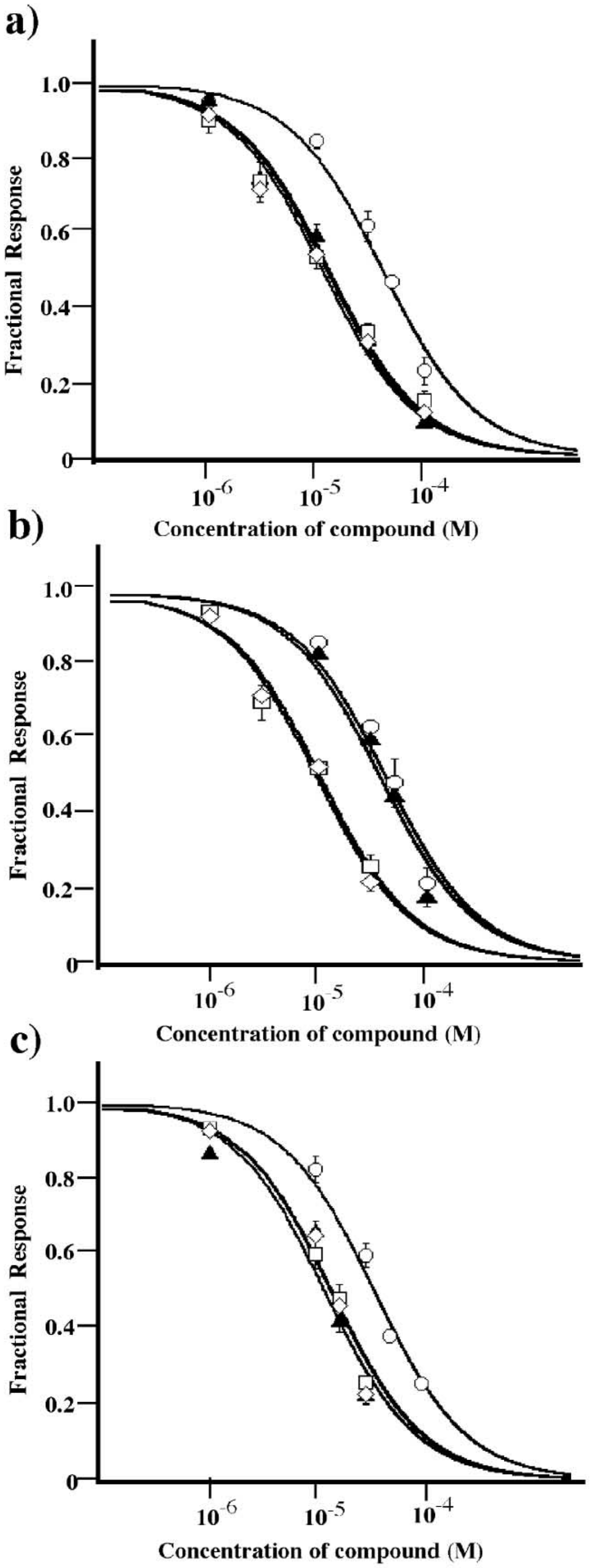


Fig. 5 Effects of PPDC (a), **2i** (b), and **2j** (c) on NMDA receptor subtypes expressed in CHO cell lines: ○, GluRε1/ζ1; ▲, GluRε2/ζ1; □, GluRε3/ζ1; ◇, GluRε4/ζ1.

Excessive activation of the NMDA receptor may lead to an excessive increase in $[Ca^{2+}]_i$ followed by neurodegeneration.[18] Thus, NMDA receptor antagonists would be useful in protecting neurons from brain diseases, such as epilepsy, stroke, ischaemia and Parkinson's syndrome.[1–3,19] However, NMDA receptor antagonists may have various adverse side effects, especially psychotomimetic effects and motor impairment.[4,5] The availability of subtype-selective drugs may minimize the adverse side effects of NMDA receptor antagonists. In fact, the GluRε2 subunit-selective antagonist, CP-101 606 and its derivatives suppress mechanical hyperalgesia and inhibit capsaicin- and 4β-phorbol-12-myristate-12-acetate-induced nociceptive responses without producing any behavioural side effects.[7j,k]

As described above, the studies on subtype selectivity of the NMDA receptor antagonists have shown that the previous antagonists were nonselective or selective to the GluRε1/ζ1, GluRε2/ζ1 and/or GluRε3/ζ1 subtypes.[7] The present study showed that **2b** and **2j** are selective to GluRε2/ζ1, GluRε3/ζ1 and GluRε4/ζ1 subtypes and that **2i** is selective to GluRε3/ζ1 and GluRε4/ζ1 subtypes, although the selectivity is not so high. The compounds **2b**, **2i** and **2j** proved to be a new class of NMDA receptor antagonist from the viewpoint of subtype selectivity.

Conclusion

We designed a series of conformationally restricted analogs of milnacipran [(±)-**1**], which was efficiently synthesized starting from (*R*)-epichlorohydrin. Among the compounds studied, **2i** and **2j** were identified as a new class of the potent NMDA receptor antagonists, which have subtype selectivity different from those of previous antagonists. These results proved that our conformational restriction strategy using the structural feature of the cyclopropane ring is very effective.

Experimental

Melting points were determined on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The NMR spectra were recorded with a JEOL EX-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. Specific optical rotations were measured on a JASCO DIP-370 in 10^{-1} deg cm^2 g^{-1}. Thin-layer chromatography was done on Merck silica gel coated plates ($60F_{254}$). Silica gel chromatography was done with Merck silica gel 5715. Reactions were performed under argon.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-cyclopropylhydroxymethyl]-*N*,*N*-diethylcyclopropanecarboxamide 9

To a suspension of Mg turnings (1.31 g, 54.0 mmol) in THF (10 mL) was added a solution of cyclopropyl bromide (4.30 mL, 54.0 mmol) in THF (60 mL), and the mixture was stirred at room temperature for 2 h. To the resulting solution was added slowly a solution of **8** (4.41 g, 18.0 mmol) in THF (180 mL) at −20 °C. The mixture was stirred at the same temperature for 2.5 h and was quenched with saturated aqueous NH_4Cl. The resulting mixture was concentrated *in vacuo* (for removal of THF), and then partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, Et_2O–hexane, 1 : 3) to give **9** as white crystals (4.09 g, 79%): mp (AcOEt–hexane) 70–72 °C; $[a]_D^{26}$ −50.6 (*c* 0.990, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.32 (1 H, m, H-3′), 0.41 (1 H, m, H-3′), 0.46–0.54 (2 H, m, H-3′), 0.90 (3 H, t, $-NCH_2CH_3$, J = 7.1 Hz), 1.07 (1 H, m, H-2′), 1.08 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.4, $J_{3a,2}$ = 8.7 Hz), 1.13 (3 H, t, $-NCH_2CH_3$, J = 7.1 Hz), 1.44 (1 H, ddd, H-2, $J_{2,3b}$ = 6.4, $J_{2,3a}$ = 8.7, $J_{2,1'}$ = 9.2 Hz), 1.73 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.4, $J_{3b,2}$ = 8.7 Hz), 2.65 (1 H, ddd, H-1′, $J_{1',OH}$ = 5.4, $J_{1',2'}$ = 8.7, $J_{1',2}$ = 9.2 Hz), 3.35 (2 H, m, $-NCH_2CH_3$), 3.42 (1 H, m, $-NCH_2CH_3$), 3.49 (1 H, m, $-NCH_2CH_3$), 5.32 (1 H, d, –OH, $J_{OH,1'}$ = 1.7 Hz), 7.18–7.23

(3 H, m, aromatic), 7.27–7.31 (2 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 1.59 (C-3′a), 2.19 (C-3′b), 12.30 (–NCH_2*C*H_3), 13.08 (–NCH_2*C*H_3), 16.06 (C-2′), 17.13 (C-3), 33.18 (C-1), 36.69 (C-2), 39.40 (–N*C*H_2CH_3), 41.91 (–N*C*H_2CH_3), 77.71 (C-1′), 125.60 (C-2″ and C-6″), 126.52 (C-4″), 128.64 (C-3″ and C-5″), 140.33 (C-1″), 171.39 (C=O); HR-MS (EI) 287.1874 (M^+, $C_{18}H_{25}NO_2$ requires *m*/*z* 287.1885). Found: C, 75.11; H, 8.74; N, 4.70. $C_{18}H_{25}NO_2$ requires C, 75.26; H, 8.71; N, 4.87%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxy-4,4-dimethoxybutyl]-*N*,*N*-diethylcyclopropanecarboxamide 10

To a suspension of Mg turnings (680 mg, 28.0 mmol) and I_2 (10 mg, 0.04 mmol) in THF (20 mL) was added a solution of 3-bromopropionaldehyde dimethyl acetal (3.82 mL, 28.0 mmol) in THF (20 mL), and the mixture was stirred at room temperature for 2 h. To the resulting solution was added slowly a solution of **8** (1.72 g, 7.00 mmol) in THF (20 mL) at −15 °C. The mixture was stirred at the same temperature for 2.5 h and was quenched with saturated aqueous NH_4Cl. The resulting mixture was concentrated *in vacuo* (for removal of THF), and then partitioned between AcOEt and H_2O. The organic layer 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 **10** as an oil (2.23 g, 91%): $[\alpha]_D^{22}$ +65.0 (*c* 0.635, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.92 (3 H, t, –NCH_2*C*H_3, *J* = 7.0 Hz), 1.06 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.0 Hz), 1.14 (3 H, t, –NCH_2*C*H_3, *J* = 7.0 Hz), 1.27 (1 H, ddd, H-2, $J_{2,3a}$ = 6.0, $J_{2,3b}$ = 9.2, $J_{2,1'}$ = 9.2 Hz), 1.66–1.89 (5 H, m, H-3b and H-2′ and H-3′), 3.16 (1 H, m, H-1′), 3.32 (3 H, s, –O*C*H_3), 3.33 (3 H, s, –O*C*H_3), 3.28–3.45 (3 H, m, –N*C*H_2CH_3), 3.51 (1 H, m, –N*C*H_2CH_3), 4.39 (1 H, t, H-4′, $J_{4',3'}$ = 5.5 Hz), 5.43 (1 H, br s, –OH), 7.19–7.30 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.33 (–NCH_2*C*H_3), 13.12 (–NCH_2*C*H_3), 16.95 (C-3), 28.99 (C-3′), 31.05 (C-2′), 33.70 (C-1), 36.83 (C-2), 39.46 (–N*C*H_2CH_3), 41.95 (–N*C*H_2CH_3), 52.54 (–O*C*H_3), 53.11 (–O*C*H_3), 74.10 (C-1′), 104.81 (C-4′), 125.70 (C-2″ and C-6″), 126.59 (C-4″), 128.65 (C-3″ and C-5″), 140.23 (C-1″), 171.39 (C=O); LR-MS (EI) *m*/*z* 349 (M^+). Found: C, 68.94; H, 9.02; N, 4.21. $C_{20}H_{31}NO_4$ requires C, 68.74; H, 8.94; N, 4.01%.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-azido(cyclopropyl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide 11R

After a solution of **9** (5.74 g, 20.0 mmol), PPh_3 (15.7 g, 60.0 mmol), and CBr_4 (19.9 g, 60.0 mmol) in DMF (150 mL) was stirred at 0 °C for 30 min, NaN_3 (24.7 g, 380 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for 3 h and then was quenched with H_2O. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography (silica gel, AcOEt–hexane, 1 : 14) to give **11R** as an oil (2.81 g, 45%): $[\alpha]_D^{26}$ −117.5 (*c* 0.984, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.36 (1 H, m, H-3′), 0.44–0.57 (2 H, m, H-3′), 0.61 (1 H, m, H-3′), 0.70 (3 H, t, –NCH_2*C*H_3, *J* = 7.1 Hz), 1.12 (3 H, t, –NCH_2*C*H_3, *J* = 7.1 Hz), 1.26 (1 H, m, H-2′), 1.42 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.0, $J_{3a,2}$ = 8.6 Hz), 1.62–1.69 (2 H, m, H-3b and H-2), 3.19 (1 H, m, –N*C*H_2CH_3), 3.27–3.35 (2 H, m, H-1′ and –N*C*H_2CH_3), 3.39 (1 H, m, –N*C*H_2CH_3), 3.54 (1 H, m, –N*C*H_2-CH_3), 7.20–7.36 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 2.16 (C-3′a), 2.70 (C-3′b), 12.42 (–NCH_2*C*H_3), 12.69 (–NCH_2*C*H_3), 15.76 (C-2′), 17.54 (C-3), 31.53 (C-2), 33.50 (C-1), 39.59 (–N*C*H_2CH_3), 42.09 (–N*C*H_2CH_3), 64.75 (C-1′), 126.22 (C-2″ and C-6″), 126.57 (C-4″), 128.68 (C-3″ and C-5″), 140.87 (C-1″), 169.36 (C=O); HR-MS (EI) 312.1945 (M^+, requires *m*/*z* $C_{18}H_{24}N_4O$ 312.1950). Found: C, 69.03; H, 7.74; N, 17.91. $C_{18}H_{24}N_4O$ requires C, 69.23; H, 7.69; N, 17.95%.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-amino(cyclopropyl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 15

A mixture of **11R** (2.50 g, 8.00 mmol) and 10% Pd–charcoal (200 mg) in MeOH (110 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, AcOEt–hexane, 1 : 1, then $CHCl_3$–MeOH 9 : 1) to give the free amine as an oil. After the oil was dissolved in MeOH, the resulting solution was put on a column of Diaion WA-30 resin (Cl^- form), and the column was developed with MeOH. The solvent of appropriate fractions was evaporated, and the residue was treated with Et_2O to give white crystals of **15** as a hydrochloride salt (2.20 g, 85%): mp (Et_2O) 172–174 °C; $[\alpha]_D^{25}$ +11.4 (*c* 0.982, $CHCl_3$); ^{1}H-NMR (500 MHz, CD_3OD : $CDCl_3$, 1 : 1) δ 0.48 (1 H, m, H-3′), 0.59 (1 H, m, H-3′), 0.70–0.76 (3 H, m, H-3′ and H-2′), 0.87 (3 H, t, –NCH_2*C*H_3, *J* = 7.1 Hz), 1.14 (3 H, t, –NCH_2*C*H_3, *J* = 7.1 Hz), 1.65 (1 H, ddd, H-2, $J_{2,3a}$ = 7.0, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 9.5 Hz), 1.72 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.8, $J_{3a,2}$ = 9.0 Hz), 1.90 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.8, $J_{3b,2}$ = 9.0 Hz), 2.91 (1 H, dd, H-1′, $J_{1',2'}$ = 7.0, $J_{1',2}$ = 9.5 Hz), 3.33–3.45 (3 H, m, –N*C*H_2CH_3), 3.54 (1 H, m, –N*C*H_2CH_3), 7.25–7.29 (3 H, m, aromatic), 7.34–7.37 (2 H, m, aromatic); ^{13}C-NMR (125 MHz, CD_3OD : $CDCl_3$, 1 : 1) δ 3.69 (C-3′a), 4.33 (C-3′b), 10.30 (C-2′), 11.71 (–NCH_2*C*H_3), 12.39 (–NCH_2*C*H_3), 16.58 (C-3), 29.84 (C-2), 33.39 (C-1), 39.85 (–N*C*H_2CH_3), 42.45 (–N*C*H_2CH_3), 56.66 (C-1′), 125.35 (C-2″ and C-6″), 127.07 (C-4″), 128.73 (C-3″ and C-5″), 138.55 (C-1″), 170.98 (C=O); HR-MS (EI) 286.2037 (M^+ − HCl, $C_{18}H_{26}N_2O$ requires *m*/*z* 286.2045). Found: C, 66.84; H, 8.44; N, 8.63. $C_{18}H_{27}ClN_2O$ requires C, 66.98; H, 8.37; N, 8.68%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-4,4-dimethoxybutyl]-*N*,*N*-diethylcyclopropanecarboxamide 12S and (1*S*,2*R*)-1-phenyl-2-[(*R*)-1-azido-4,4-dimethoxybutyl]-*N*,*N*-diethylcyclopropanecarboxamide 12R

Compound **10** (699 mg, 2.00 mmol) was treated as described above for the synthesis of **11R** from **9**. After purification by column chromatography (silica gel, AcOEt–hexane, 3 : 17), **12S** as an oil (368 mg, 49%) and **12R** as an oil (110 mg, 15%) were obtained, respectively. **12S**: $[\alpha]_D^{21}$ −123.3 (*c* 0.505, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.39 (3 H, t, –NCH_2*C*H_3, *J* = 7.0 Hz), 1.01 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.0, $J_{3a,2}$ = 9.2 Hz), 1.12 (3 H, t, –NCH_2*C*H_3, *J* = 7.0 Hz), 1.63 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.0, $J_{3b,2}$ = 6.7 Hz), 1.74–1.84 (4 H, m, H-2′ and H-3′), 1.92 (1 H, ddd, H-2, $J_{2,3b}$ = 6.7, $J_{2,3a}$ = 9.2, $J_{2,1'}$ = 9.6 Hz), 2.97 (1 H, m, H-1′), 3.04 (1 H, m, –N*C*H_2CH_3), 3.18 (1 H, m, –N*C*H_2CH_3), 3.34 (6 H, s, –O*C*H_3), 3.50 (1 H, m, –N*C*H_2CH_3), 3.67 (1 H, m, –N*C*H_2CH_3), 4.39 (1 H, t, H-4′, $J_{4',3'}$ = 4.5 Hz), 7.20–7.32 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.87 (–NCH_2*C*H_3), 12.29 (–NCH_2*C*H_3), 19.42 (C-3), 27.95 (C-2), 28.82 (C-2′), 30.09 (C-3′), 35.98 (C-1), 39.97 (–N*C*H_2CH_3), 42.05 (–N*C*H_2CH_3), 52.96 (–O*C*H_3), 53.37 (–O*C*H_3), 62.58 (C-1′), 104.18 (C-4′), 126.69 (C-4″), 126.90 (C-2″ and C-6″), 128.74 (C-3″ and C-5″), 140.70 (C-1″), 169.34 (C=O); HR-MS (EI) 374.2297 (M^+, $C_{20}H_{30}N_4O_3$ requires *m*/*z* 374.2318). Found: C, 64.39; H, 8.10; N, 14.68. $C_{20}H_{30}N_4O_3$ requires C, 64.15; H, 8.07; N, 14.96%. **12R**: $[\alpha]_D^{21}$ −44.2 (*c* 0.430, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.67 (3 H, t, –NCH_2*C*H_3, *J* = 7.0 Hz), 1.11 (3 H, t, –NCH_2*C*H_3, *J* = 7.0 Hz), 1.48 (1 H, m, H-2), 1.56–1.65 (2 H, m, H-3a and H-3b), 1.66–1.75 (2 H, m, H-3′), 1.85 (1 H, m, H-2′a), 2.01 (1 H, m, H-2′b), 3.16 (1 H, m, –N*C*H_2CH_3), 3.25 (1 H, m, –N*C*H_2CH_3), 3.30 (3 H, s, –O*C*H_3), 3.31 (3 H, s, –O*C*H_3), 3.33 (1 H, m, H-1′), 3.43–3.52 (2 H, m, –N*C*H_2CH_3), 4.40 (1 H, t, H-4′, $J_{4',3'}$ = 5.2 Hz), 7.20–7.32 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.39 (–NCH_2*C*H_3), 12.61 (–NCH_2*C*H_3), 18.08 (C-3), 29.14 (C-3′), 30.20 (C-2′), 31.35 (C-2), 33.75 (C-1), 39.47 (–N*C*H_2CH_3), 42.01 (–N*C*H_2CH_3), 52.54 (–O*C*H_3), 52.99

(–OCH_3), 63.24 (C-1′), 104.17 (C-4′), 126.14 (C-2″ and C-6″), 126.74 (C-4″), 128.78 (C-3″ and C-5″), 140.48 (C-1″), 169.16 (C=O); HR-MS (EI) 374.2323 (M^+, $C_{20}H_{30}N_4O_3$ requires *m*/*z* 374.2318). Found: C, 63.99; H, 7.98; N, 14.89. $C_{20}H_{30}N_4O_3$ requires C, 64.15; H, 8.07; N, 14.96%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-formylpropyl]-*N*,*N*-diethylcyclopropanecarboxamide 14

A mixture of **12S** (749 mg, 2.00 mmol) and TFA (80% aqueous solution, 5 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h and was then neutralized with $NaHCO_3$. The resulting mixture was evaporated, and the residue was purified by column chromatography (silica gel, AcOEt–hexane, 1 : 4 then 1 : 2) to give **14** as an oil (375 mg, 57%): $[\alpha]_D^{21}$ −123.0 (*c* 0.675, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.42 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.12 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.15 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.2, $J_{3a,2}$ = 9.5 Hz), 1.56 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.2, $J_{3b,2}$ = 6.6 Hz), 1.83 (1 H, ddd, H-2, $J_{2,3b}$ = 6.6, $J_{2,3a}$ = 9.5, $J_{2,1'}$ = 9.5 Hz), 2.01 (1 H, m, H-2′a), 2.09 (1 H, m, H-2′a), 2.58–2.74 (2 H, m, H-3′), 3.04–3.12 (2 H, m, H-1′ and –NCH_2CH_3), 3.22 (1 H, m, –NCH_2CH_3), 3.49 (1 H, m, –NCH_2CH_3), 3.62 (1 H, m, –NCH_2CH_3), 7.21–7.40 (5 H, m, aromatic), 9.82 (1 H, br s, H-4′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.98 (–NCH_2CH_3), 12.31 (–NCH_2CH_3), 18.76 (C-3), 27.37 (C-2′), 28.58 (C-2), 35.91 (C-1), 39.92 (–NCH_2CH_3), 40.24 (C-3′), 41.97 (–NCH_2CH_3), 62.05 (C-1′), 126.71 (C-2″ and C-6″), 126.80 (C-4″), 128.79 (C-3″ and C-5″), 140.33 (C-1″), 169.20 (C=O), 200.82 (C-4′); LR-MS (EI) *m*/*z* 328 (M^+); HR-MS (EI) 328.1917 (M^+, $C_{18}H_{24}N_4O_2$ requires *m*/*z* 328.1899). Found: C, 66.21; H, 7.49; N, 16.97. $C_{18}H_{24}N_4O_2$ requires C, 65.83; H, 7.37; N, 17.06%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-(pyrrolin-5-yl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide 6

A mixture of **14** (65.7 mg, 0.20 mmol) and 10% Pd–charcoal (20 mg) in MeOH (10 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 1 h, and then the catalyst was filtered off. After the filtrate was evaporated, a mixture of the residue and molecular sieves (5 Å in CH_2Cl_2, 3 mL) was stirred at room temperature for 14 h, and then the molecular sieves were filtered off. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel, AcOEt–hexane, 1 : 1 then 2 : 1) to give **6** as an oil (47 mg, 83%): $[\alpha]_D^{22}$ −136.6 (*c* 0.135, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.40 (3 H, t, –NCH_2CH_3, J = 7.1 Hz), 0.83 (1 H, dd, H-3a, $J_{3a,3b}$ = 4.8, $J_{3a,2}$ = 9.3 Hz), 1.08 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.61 (1 H, m, H-4′a), 1.70 (1 H, dd, H-3b, $J_{3b,3a}$ = 4.8, $J_{3b,2}$ = 6.3 Hz), 1.97 (1 H, ddd, H-2, $J_{2,3b}$ = 6.3, $J_{2,3a}$ = 9.3, $J_{2,1'}$ = 9.3 Hz), 2.12 (1 H, m, H-4′b), 2.44 (1 H, m, H-3′a), 2.65 (1 H, m, H-3′b), 3.10 (1 H, m, –NCH_2CH_3), 3.18 (1 H, m, –NCH_2CH_3), 3.48–3.57 (2 H, m, H-5′ and –NCH_2CH_3), 3.90 (1 H, m, –NCH_2CH_3), 7.17–7.30 (5 H, m, aromatic), 7.64 (1 H, t, H-2′, $J_{2',3'}$ = 1.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.04 (–NCH_2CH_3), 12.28 (–NCH_2CH_3), 19.62 (C-3), 27.69 (C-4′), 29.02 (C-2), 36.45 (C-3′), 37.02 (C-1), 39.75 (–NCH_2CH_3), 42.78 (–NCH_2CH_3), 73.01 (C-5′), 126.31 (C-4″), 126.99 (C-2″ and C-6″), 128.52 (C-3″ and C-5″), 141.55 (C-1″), 166.67 (C-2′), 170.21 (C=O); HR-MS (EI) 284.1890 (M^+, $C_{18}H_{24}N_2O$ requires *m*/*z* 284.1889). Found: C, 75.66; H, 8.38; N, 9.79. $C_{18}H_{24}N_2O$ requires C, 76.02; H, 8.51; N, 9.85%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-(pyrrolidin-2-yl)methyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 7

A mixture of **6** (28 mg, 0.10 mmol) and $NaBH_3CN$ (13 mg, 0.20 mmol) in MeOH (2 mL) was stirred at room temperature for 14 h. The resulting mixture was evaporated, and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, $CHCl_3$–MeOH, 1 : 9) to give the free amine as an oil. After the free amine was dissolved in MeOH, the resulting solution was put on a column of Diaion WA-30 resin (Cl^- form), and the column was developed with MeOH. The solvent was evaporated, and the residue was treated with Et_2O to give white crystals of **7** as a hydrochloride salt (30 mg, 93%): mp (Et_2O) 57–59 °C; $[\alpha]_D^{22}$ +46.0 (*c* 0.205, MeOH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.87 (3 H, t, –NCH_2CH_3, J = 7.1 Hz), 1.15 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.28–1.36 (3 H, m, H-3a and H-3b and H-2), 1.82 (1 H, m, H-3′a), 2.00 (1 H, m, H-3′b), 2.08 (2 H, m, H-4′), 2.29 (1 H, m, H-2′), 3.21 (1 H, m, –NCH_2CH_3), 3.27–3.50 (5 H, m, H-5′ and –NCH_2CH_3), 7.24–7.36 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CD_3OD) δ 12.63 (–NCH_2CH_3), 13.23 (–NCH_2CH_3), 17.99 (C-3), 24.34 (C-3′), 30.96 (C-4′), 31.63 (C-2), 35.73 (C-1), 40.65 (–NCH_2CH_3), 43.22 (–NCH_2CH_3), 45.96 (C-5′), 65.02 (C-2′), 126.79 (C-2″ and C-6″), 128.27 (C-4″), 130.01 (C-3″ and C-5″), 140.43 (C-1″), 171.77 (C=O); HR-MS (EI) 286.2054 (M^+, $C_{18}H_{27}ClN_4O_3$ requires *m*/*z* 286.2045). Found: C, 66.61; H, 8.33; N, 8.29. $C_{18}H_{27}ClN_4O_3$ requires C, 66.96; H, 8.43; N, 8.68%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-hydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide 17

A mixture of **16** (200 mg, 0.50 mmol) and NaOMe (28% in MeOH, 0.50 mL) in MeOH (5.0 mL) was stirred at room temperature for 1 h and then neutralized with AcOH. The resulting mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt–hexane, 1 : 1) to give **17** as an oil (140 mg, 86%): mp (hexane–AcOEt) 77–79 °C; $[\alpha]_D^{23}$ −129.1 (*c* 0.700, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.44 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.12 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.2, $J_{3a,2}$ = 8.9 Hz), 1.13 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.58 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.2, $J_{3b,2}$ = 6.2 Hz), 1.70 (1 H, br s, –OH), 1.89 (1 H, ddd, H-2, $J_{2,3b}$ = 6.2, $J_{2,3a}$ = 8.9, $J_{2,1'}$ = 8.9 Hz), 1.95–2.02 (2 H, m, H-2′), 3.08 (1 H, m, –NCH_2CH_3), 3.18–3.29 (2 H, m, H-1′ and –NCH_2CH_3), 3.50 (1 H, m, –NCH_2CH_3), 3.65 (1 H, m, –NCH_2CH_3), 3.84 (2 H, t, H-3′, $J_{3',2'}$ = 6.0 Hz), 7.21–7.33 (5 H, m, aromatic); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.94 (–NCH_2CH_3), 12.33 (–NCH_2CH_3), 19.06 (C-3), 28.60 (C-2), 36.05 (C-1), 37.71 (C-2′), 40.02 (–NCH_2CH_3), 42.06 (–NCH_2CH_3), 59.33 (C-3′), 60.24 (C-1′), 126.76 (C-2″ and C-6″), 126.81 (C-4″), 128.79 (C-3″ and C-5″), 140.56 (C-1″), 169.48 (C=O); HR-MS (EI) 316.1915 (M^+, $C_{17}H_{24}N_4O_2$ requires *m*/*z* 316.1899). Found: C, 64.73; H, 7.77; N, 17.47. $C_{17}H_{24}N_4O_2$ requires C, 64.53; H, 7.65; N, 17.71%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-3-hydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 2k

Compound **2k** was prepared from **17** (200 mg, 0.60 mmol), as described above for the synthesis of **15** from **11R**. After application of the resulting solution to a column of Diaion WA-30 resin (Cl^- form), white crystals of **2k** (188 mg, 96%) were obtained as a hydrochloride: mp (Et_2O) 107–109 °C; $[\alpha]_D^{20}$ +77.0 (*c* 1.200, MeOH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (3 H, t, –NCH_2CH_3, J = 7.1 Hz), 1.15 (3 H, t, –NCH_2CH_3, J = 7.1 Hz), 1.24 (1 H, ddd, H-2, $J_{2,3a}$ = 6.3, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 9.0 Hz), 1.41 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.3 Hz), 1.91–2.05 (2 H, m, H-2′), 2.14 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 9.0 Hz), 3.02 (1 H, m, H-1′), 3.38 (1 H, m, –NCH_2CH_3), 3.44–3.51 (3 H, m, –NCH_2CH_3), 3.75–3.84 (2 H, m, H-3′), 7.26–7.37 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CD_3OD) δ 12.53 (–NCH_2CH_3), 13.20 (–NCH_2CH_3), 18.32 (C-3), 32.93 (C-2), 35.12 (C-1), 36.23 (C-2′), 40.92 (–NCH_2CH_3), 43.55 (–NCH_2CH_3), 54.91 (C-1′), 59.33 (C-3′), 126.83 (C-2″ and C-6″), 128.41 (C-4″), 130.13 (C-3″ and C-5″), 140.28 (C-1″), 172.63 (C=O); HR-MS (EI) 290.2007 (M^+, $C_{17}H_{26}N_2O_2$ requires *m*/*z* 290.1994). Found: C, 62.47;

H, 8.54; N, 8.28. $C_{17}H_{27}ClN_4O_2$ requires C, 62.47; H, 8.83; N, 8.57%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-methoxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide 18

After a mixture of NaH (60% in paraffin liquid, 24 mg, 0.60 mmol) and **17** (158 mg, 0.50 mmol) in THF (5 mL) was stirred at 0 °C for 40 min, MeI (93 µL, 1.5 mmol) was added to the mixture, and the resulting mixture was stirred at the same temperature for 30 min and at room temperature for a further 3 h. After quenching with MeOH, the mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 4) to give **18** as an oil (149 mg, 90%): $[a]_D^{22}$ −169.7 (*c* 0.455, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.40 (3 H, t, $-NCH_2CH_3$, $J = 7.0$ Hz), 1.02 (1 H, dd, H-3a, $J_{3a,3b}$ = 4.8, $J_{3a,2}$ = 9.2 Hz), 1.13 (3 H, t, $-NCH_2CH_3$, $J = 7.0$ Hz), 1.62 (1 H, dd, H-3b, $J_{3b,3a}$ = 4.8, $J_{3b,2}$ = 6.0 Hz), 1.87–1.98 (2 H, m, H-2 and H-2′a), 2.05 (1 H, m, H-2′b), 3.06 (1 H, m, $-NCH_2CH_3$), 3.13–3.23 (2 H, m, H-1′ and $-NCH_2CH_3$), 3.34 (1 H, m, $-NCH_2CH_3$), 3.48–3.57 (3 H, m, H-3′ and $-NCH_2CH_3$), 3.71 (1 H, m, $-NCH_2CH_3$), 7.21–7.33 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 11.92 ($-NCH_2CH_3$), 12.34 ($-NCH_2CH_3$), 19.25 (C-3), 28.26 (C-2), 35.29 (C-2′), 36.10 (C-1), 39.97 ($-NCH_2CH_3$), 41.98 ($-NCH_2CH_3$), 58.62 (–O*Me*), 60.37 (C-1′), 68.89 (C-3′), 126.67 (C-4″), 126.89 (C-2″ and C-6″), 128.72 (C-3″ and C-5″), 140.73 (C-1″), 169.27 (C=O); HR-MS (EI) 330.2035 (M^+, $C_{18}H_{26}N_4O_2$ requires *m*/*z* 330.2056). Found: C, 65.33; H, 7.92; N, 16.63. $C_{18}H_{26}N_4O_2$ requires C, 65.43; H, 7.93; N, 16.96%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-amino-3-methoxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 2l

Compound **2l** was prepared from **18** (83 mg, 0.25 mmol), as described above for the synthesis of **15** from **11R**. After application of the resulting solution to a column of Diaion WA-30 resin (Cl^- form), white crystals of **2l** (79 mg, 93%) were obtained as a hydrochloride salt: mp (Et_2O) 151–152 °C; $[a]_D^{21}$ +88.3 (*c* 0.430, MeOH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.90 (3 H, t, $-NCH_2CH_3$, $J = 7.0$ Hz), 1.14 (3 H, t, $-NCH_2CH_3$, J = 7.0 Hz), 1.24 (1 H, ddd, H-2, $J_{2,3a}$ = 6.7, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 10.4 Hz), 1.36 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.7 Hz), 1.99 (2 H, m, H-2′a), 2.08 (2 H, m, H-2′b), 2.15 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 9.0 Hz), 2.98 (1 H, m, H-1′), 3.36 (3 H, s, –O*Me*), 3.38 (1 H, m, $-NCH_2CH_3$), 3.44–3.50 (3 H, m, $-NCH_2CH_3$), 3.59–3.64 (2 H, m, H-3′), 7.26–7.34 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CD_3OD) δ 12.54 ($-NCH_2CH_3$), 13.22 ($-NCH_2CH_3$), 18.29 (C-3), 32.76 (C-2), 33.78 (C-2′, 35.29 (C-1), 40.92 ($-NCH_2CH_3$), 43.56 ($-NCH_2CH_3$), 55.19 (C-1′), 59.09 (–O*Me*), 70.13 (C-3′), 126.86 (C-2″ and C-6″), 128.42 (C-4″), 130.12 (C-3″ and C-5″), 140.24 (C-1″), 172.61 (C=O); HR-MS (EI) 304.2154 (M^+, $C_{18}H_{28}N_2O_2$ requires 304.2151). Found: C, 63.69; H, 8.47; N, 8.12. $C_{18}H_{29}ClN_2O_2$ requires C, 63.42; H, 8.57; N, 8.22%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azido-3-tosyloxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide 19

A mixture of **17** (127 mg, 0.40 mmol), TsCl (229 mg, 1.20 mmol), Et_3N (0.34 mL, 2.40 mmol) and DMAP (14.7 mg, 0.12 mmol) in CH_2Cl_2 (5.00 mL) was stirred at room temperature for 9 h, and the resulting solution was partitioned with H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 3) to give **19** as an oil (186 mg, 99%): $[a]_D^{22}$ −66.1 (*c* 0.140, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.49 (3 H, t, $-NCH_2CH_3$, $J = 7.0$ Hz), 1.10 (3 H, t, $-NCH_2CH_3$, J = 7.0 Hz), 1.10 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.2, $J_{3a,2}$ = 9.2 Hz), 1.41 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.1, $J_{3b,2}$ = 6.5 Hz), 1.68 (1 H, ddd, H-2, $J_{2,3b}$ = 6.2, $J_{2,3a}$ = 9.2, $J_{2,1'}$ = 9.2 Hz), 1.95 (1 H, m, H-2′a), 2.07 (1 H, m, H-2′b), 2.45 (3 H, s, CH_3PhSO_2–), 3.09 (1 H, m, $-NCH_2CH_3$), 3.19–3.26 (2 H, m, H-1′ and $-NCH_2CH_3$), 3.46 (1 H, m, $-NCH_2CH_3$), 3.55 (1 H, m, $-NCH_2CH_3$), 4.14 (1 H, t, H-3′a), 4.22 (1 H, t, H-3′b), 7.22–7.36 (7 H, m, aromatic), 7.80 (2 H, d, aromatic, $J = 8.2$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 12.14 ($-NCH_2CH_3$), 12.35 ($-NCH_2CH_3$), 18.07 (C-3), 29.52 (C-2), 34.38 (C-2′), 35.86 (C-1), 39.85 ($-NCH_2CH_3$), 41.84 ($-NCH_2CH_3$), 59.25 (C-1′), 66.75 (C-3′), 126.52, 126.85, 127.93, 128.82, 129.92, 132.77, 140.16, 144.93 (aromatic), 169.02 (C=O); HR-MS (EI) 470.1965 (M^+, $C_{24}H_{30}N_4O_4S$ requires *m*/*z* 470.1988). Found: C, 61.21; H, 6.58; N, 12.21. $C_{24}H_{30}N_4O_4S$ requires C, 61.25; H, 6.43; N, 11.91%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-(azetidin-2-yl)]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 5

A mixture of **19** (188 mg, 0.40 mmol) and 10% Pd–charcoal (50 mg) in THF (30 mL) and MeOH (2 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 12 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 the free amine as an oil. After the free amine was dissolved in MeOH, the resulting solution was put on a column of Diaion WA-30 resin (Cl^- form), and the column was developed with MeOH. The solvent was evaporated, and the residue was treated with Et_2O to give white crystals of **5** as a hydrochloride salt (93 mg, 75%): mp (Et_2O) 83–85 °C; $[a]_D^{24}$ +62.7 (*c* 1.105, MeOH); ^{1}H-NMR (500 MHz, CD_3OD) δ 0.91 (3 H, t, $-NCH_2CH_3$, $J = 7.0$ Hz), 1.14 (3 H, t, $-NCH_2CH_3$, J = 7.0 Hz), 1.23 (1 H, ddd, H-2, $J_{2,3a}$ = 6.5, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 9.5 Hz), 1.35 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.5 Hz), 1.98 (1 H, m, H-3′a), 2.06 (1 H, m, H-3′b), 2.14 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 9.0 Hz), 2.97 (1 H, m, H-1′), 3.36 (1 H, m, $-NCH_2CH_3$), 3.44–3.62 (3 H, m, $-NCH_2CH_3$), 3.59–3.62 (2 H, m, H-4′), 7.25–7.37 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CD_3OD) δ 12.53 ($-NCH_2CH_3$), 13.21 ($-NCH_2CH_3$), 18.26 (C-3), 32.80 (C-2), 33.80 (C-3′), 35.30 (C-1), 40.93 ($-NCH_2CH_3$), 43.56 ($-NCH_2CH_3$), 55.20 (C-2′), 59.04 (C-4′), 126.84 (C-2″ and C-6″), 128.44 (C-4″), 130.13 (C-3″ and C-5″), 140.24 (C-1″), 172.62 (C=O); HR-MS (EI) 272.1902 (M^+, $C_{17}H_{24}N_2O$ requires 272.1889). Found: C, 66.01; H, 8.24; N, 9.00. $C_{17}H_{25}ClN_2O$ requires C, 66.11; H, 8.16; N, 9.07%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*tert*-butoxycarbonylamino-3-(pivaloyloxy)propyl]-*N*,*N*-diethylcyclopropanecarboxamide 20

A mixture of **16** (801 mg, 2.00 mmol), 10% Pd–charcoal (100 mg) and $(Boc)_2O$ (0.51 mL, 2.2 mmol) in MeOH (5 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 12 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 : 2) to give **20** as white crystals (812 mg, 86%): mp (hexane–AcOEt) 139–141 °C; $[a]_D^{21}$ −70.3 (*c* 1.015, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.60 (3 H, br s, $-NCH_2CH_3$), 1.13 (3 H, t, $-NCH_2CH_3$, J = 7.0 Hz), 1.19 (9 H, s, $-COC(CH_3)_3$), 1.20 (1 H, br s, H-3a), 1.32 (1 H, br s, H-3b), 1.41 (9 H, s, $-OCOC(CH_3)_3$), 1.78 (1 H, br s, H-2), 2.09 (1 H, m, H-2′a), 2.34 (1 H, m, H-2′b), 3.14 (1 H, m, H-1′), 3.27 (1 H, m, $-NCH_2CH_3$), 3.35 (1 H, m, $-NCH_2CH_3$), 3.47 (1 H, m, $-NCH_2CH_3$), 3.56 (1 H, m, $-NCH_2CH_3$), 4.11–4.21 (2 H, m, H-3′), 5.00 (1 h, br s, –NH–), 7.18–7.36 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.27 ($-NCH_2CH_3$), 12.52 ($-NCH_2CH_3$), 17.23 (C-3), 27.17 ($-COC(CH_3)_3$), 28.37 ($-OCOC(CH_3)_3$), 30.83 (C-2), 33.70 (C-2′), 34.03 (C-1), 38.68 ($-COC(CH_3)_3$), 39.94 ($-NCH_2CH_3$), 42.34 ($-NCH_2CH_3$), 48.25 (C-1′), 61.55 (C-3′), 78.90 ($-OCOC(CH_3)_3$), 126.38 (C-2″ and C-6″), 126.48 (C-4″), 128.66 (C-3″ and C-5″), 140.99 (C-1″), 155.38 (C=O), 170.72 (C=O), 178.58 (C=O); HR-MS (EI) 474.3091 (M^+, $C_{27}H_{42}N_2O_5$ requires *m*/*z* 474.3093). Found: C, 68.12; H, 8.91; N, 5.79. $C_{27}H_{42}N_2O_5$ requires C, 68.32; H, 8.92; N, 5.90%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*tert*-butoxycarbonylamino-3-hydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide 21

Compound **21** was prepared from **20** (712 mg, 1.50 mmol), as described above for the synthesis of **17** from **16**. After purification by column chromatography (silica gel, AcOEt–hexane, 1 : 1), **21** was obtained as white crystals (413 mg, 71%): mp (hexane–AcOEt) 126–128 °C; $[a]_D^{23}$ −106.1 (*c* 0.810, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.54 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.13 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.21 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.0, $J_{3a,2}$ = 9.0 Hz), 1.43 (9 H, s, –OCOC(CH_3)$_3$), 1.48 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.0, $J_{3b,2}$ = 6.2 Hz), 1.74 (1 H, ddd, H-2, $J_{2,3b}$ = 6.2, $J_{2,3a}$ = 9.0, $J_{2,1'}$ = 9.0 Hz), 1.86 (1 H, m, H-2′a), 2.01 (1 H, m, H-2′b), 3.09 (1 H, m, –NCH_2CH$_3$), 3.22–3.42 (3 H, m, H-1′ and –NCH_2CH$_3$), 3.58–3.68 (4 H, m, H-3′ and –OH and –NCH_2CH$_3$), 5.10 (1 H, d, –NH–, $J_{NH,1'}$ = 8.2 Hz), 7.19–7.32 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.41 (–NCH_2CH_3), 12.52 (–NCH_2CH_3), 17.91 (C-3), 28.34 (–OCOC(CH_3)$_3$), 30.79 (C-2), 34.87 (C-1), 40.13 (–NCH_2CH$_3$), 42.37 (–NCH_2CH$_3$), 47.45 (C-1′), 58.90 (C-3′), 79.47 (–OCO*C*(CH$_3$)$_3$), 126.39 (C-2″ and C-6″), 126.51 (C-4″), 128.67 (C-3″ and C-5″), 141.02 (C-1″), 156.52 (C=O), 170.46 (C=O); HR-MS (EI) 390.2498 (M^+, $C_{22}H_{34}N_2O_4$ requires *m*/*z* 390.2518). Found: C, 67.79; H, 8.86; N, 7.03. $C_{22}H_{34}N_2O_4$ requires C, 67.66; H, 8.78; N, 7.17%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*tert*-butoxycarbonylamino-2-formylethyl]-*N*,*N*-diethylcyclopropanecarboxamide 22

To a solution of oxalyl chloride (0.17 mL, 2.0 mmol) in CH_2Cl_2 (5 mL) was slowly added a solution of DMSO (0.28 mL, 4.0 mmol) in CH_2Cl_2 (3 mL) at −78 °C over 30 min. After slow addition of a solution of **21** (391 mg, 1.00 mmol) in CH_2Cl_2 (5 mL), the resulting mixture was stirred at the same temperature for 1 h, and then Et_3N (1.12 mL, 8.00 mmol) was added. After stirring the mixture at −78 °C for a further 10 min, saturated aqueous NH_4Cl, and then CH_2Cl_2 were added and partitioned. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 3) to give **22** as white crystals (275 mg, 71%): mp (hexane–AcOEt) 158–160 °C; $[a]_D^{21}$ −76.0 (*c* 0.545, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.59 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.14 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.27 (1 H, br s, H-3a), 1.37 (1 H, br s, H-3b), 1.41 (9 H, s, –OCOC(CH_3)$_3$), 1.92 (1 H, m, H-2), 2.93 (1 H, dd, H-1′, $J_{1',2'a}$ = 5.2, $J_{1',2}$ = 7.2 Hz), 3.08–3.15 (2 H, m, H-2′a and –NCH_2CH$_3$), 3.28–3.40 (2 H, m, –NCH_2CH$_3$), 3.57 (1 H, m, –NCH_2CH$_3$), 3.82 (1 H, br s, H-2′b), 5.26 (1 H, br s, –NH–), 7.19–7.31 (5 H, m, aromatic), 9.79 (1 H, br s, H-3′); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.50 (–NCH_2CH_3), 12.52 (–NCH_2CH_3), 17.47 (C-3), 28.34 (–OCOC(CH_3)$_3$), 30.29 (C-2), 34.83 (C-1), 39.97 (–NCH_2CH$_3$), 42.33 (–NCH_2CH$_3$), 46.65 (C-1′), 48.87 (C-2′), 79.25 (–OCO*C*(CH$_3$)$_3$), 126.35 (C-2″ and C-6″), 126.63 (C-4″), 128.72 (C-3″ and C-5″), 140.61 (C-1″), 155.23 (C=O), 170.37 (C=O), 200.93 (C-3′); HR-MS (EI) 388.2380 (M^+, $C_{22}H_{32}N_2O_4$ requires *m*/*z* 388.2362). Found: C, 67.78; H, 8.38; N, 7.14. $C_{22}H_{32}N_2O_4$ requires C, 68.01; H, 8.30; N, 7.21%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminobut-3-enyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 2i

To a suspension of methyltriphenylphosphonium bromide (286 mg, 0.80 mmol) in THF (5 mL) was added a BuLi solution (1.50 M in hexane, 0.53 mL, 0.80 mmol) at −78 °C, and the resulting mixture was warmed slowly to 0 °C and then stirred for 30 min. After the mixture was cooled to −40 °C, a solution of **22** (68 mg, 0.20 mmol) was added, and the resulting mixture was stirred at the same temperature for a further 10 min. Saturated aqueous NH_4Cl and AcOEt were added to the reaction mixture, and the resulting mixture was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 4) to give **23** as a white powder (26 mg, 34%). A solution of **23** (26 mg, 0.068 mmol) in 1.0 M HCl–MeOH (2 mL) was heated under reflux for 1 h. The solvent was evaporated, and the residue was treated with Et_2O to give white crystals of **2i** as a hydrochloride salt (19 mg, 88%): mp (Et_2O) 178–180 °C; $[a]_D^{21}$ +82.1 (*c* 0.200, MeOH); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.14 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.20 (1 H, ddd, H-2, $J_{2,3a}$ = 6.5, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 10.4 Hz), 1.36 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.5 Hz), 2.13 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 9.0 Hz), 2.51–2.59 (2 H, m, H-2′), 2.92 (1 H, m, H-1′), 3.39 (1 H, m, –NCH_2CH$_3$), 3.42–3.49 (3 H, m, –NCH_2CH$_3$), 5.22–5.28 (2 H, m, H-4′), 5.88 (1 H, m, H-3′), 7.26–7.37 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.52 (–NCH_2CH_3), 13.17 (–NCH_2CH_3), 18.55 (C-3), 32.85 (C-2), 35.18 (C-1), 38.68 (C-2′), 40.93 (–NCH_2CH$_3$), 43.56 (–NCH_2CH$_3$), 56.00 (C-1′), 120.41 (C-4′), 126.84 (C-2″ and C-6″), 128.45 (C-4″), 130.14 (C-3″ and C-5″), 140.25 (C-1″), 172.61 (C=O); HR-MS (EI) 284.2022 ((M − HCl)$^+$, $C_{18}H_{26}N_2O$ requires *m*/*z* 286.2045). Found: C, 66.65; H, 8.16; N, 8.50. $C_{18}H_{27}ClN_2O$ requires C, 66.96; H, 8.43; N, 8.68%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*tert*-butoxycarbonylamino-4,4-dibromobut-3-enyl]-*N*,*N*-diethylcyclopropanecarboxamide 24

To a solution of **22** (117 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) were added PPh_3 (315 mg, 1.20 mmol) and CBr_4 (199 mg, 0.60 mmol) at 0 °C, and the mixture was stirred at the same temperature for 5 min and then quenched with saturated aqueous $NaHCO_3$. The resulting mixture was evaporated, and the residue was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 4) to give **24** as white crystals (103 mg, 61%): mp (hexane–AcOEt) 195–196 °C; $[a]_D^{21}$ −64.5 (*c* 0.450, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.55 (3 H, br s, –NCH_2CH_3), 1.12 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.25 (1 H, br s, H-3a), 1.43 (9 H, s, –OCOC(CH_3)$_3$), 1.44 (1 H, br s, H-2), 1.78 (1 H, br s, H-3b), 2.58 (1 H, m, H-2′a), 2.71 (1 H, m, H-2′b), 3.08 (1 H, m, H-1′), 3.24–3.40 (2 H, m, –NCH_2CH$_3$), 3.47 (1 H, m, –NCH_2CH$_3$), 3.58 (1 H, m, –NCH_2CH$_3$), 4.99 (1 H, d, –NH–, $J_{NH,1'}$ = 8.5 Hz), 6.49 (1 H, t, H-3′, $J_{3',2'}$ = 7.3 Hz), 7.19–7.31 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.44 (–NCH_2CH_3), 12.57 (–NCH_2CH_3), 17.87 (C-3), 28.39 (–OCOC(CH_3)$_3$), 30.10 (C-2), 34.78 (C-1), 38.82 (C-2′), 40.05 (–NCH_2CH$_3$), 42.34 (–NCH_2CH$_3$), 50.09 (C-1′), 79.26 (–OCO*C*(CH$_3$)$_3$), 90.40 (C-4′), 126.49 (C-2″ and C-6″), 126.61 (C-4″), 128.69 (C-3″ and C-5″), 135.40 (C-1′), 140.74 (C-1″), 155.25 (C=O), 170.29 (C=O); HR-MS (EI) 388.2380 (M^+, $C_{24}H_{36}N_2O_4$ requires *m*/*z* 388.2362). Found: C, 51.18; H, 6.37; N, 5.13. $C_{22}H_{32}N_2O_4$ requires C, 51.44; H, 6.48; N, 5.00%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*tert*-butoxycarbonylaminobut-3-ynyl]-*N*,*N*-diethylcyclopropanecarboxamide 25

To a solution of **24** (56 mg, 0.10 mmol) in THF (5 mL) was slowly added a BuLi solution (1.5 M in hexane, 0.20 mL, 0.30 mmol) at −78 °C, and the mixture was warmed slowly to −50 °C over 2 h. To the resulting mixture, saturated aqueous NH_4Cl and AcOEt were added and partitioned. The separated organic layer was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 4) to give **25** as white crystals (23 mg, 60%): mp (hexane–AcOEt) 177–178 °C; $[a]_D^{21}$ −98.0 (*c* 0.125, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.50 (3 H, br s, –NCH_2CH_3), 1.12 (3 H, t, –NCH_2CH_3, *J* = 7.0 Hz), 1.14 (1 H, br s, H-3a), 1.43 (9 H, s, –OCOC(CH_3)$_3$), 1.45–1.55 (2 H, m, H-2 and H-3b), 2.03 (2 H, d, H-2′, $J_{2',1'}$ = 10.2 Hz), 2.73 (1 H, br s, H-4′), 3.04

(1 H, m, H-1′), 3.28–3.37 (2 H, m, –NCH_2CH$_3$), 3.52 (1 H, m, –NCH_2CH$_3$), 3.62 (1 H, m, –NCH_2CH$_3$), 5.06 (1 H, br s, –NH–), 7.19–7.31 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 12.33 (–NCH$_2$$CH_3$), 12.52 (–NCH$_2$$CH_3$), 18.41 (C-3), 24.99 (C-2′), 28.37 (–OCOC(CH_3)$_3$), 28.39 (C-2), 35.16 (C-1), 40.07 (–NCH$_2$CH$_3$), 42.36 (–NCH$_2$CH$_3$), 49.62 (C-1′), 70.35 (C-4′), 79.24 (–OCOC(CH$_3$)$_3$), 81.15 (C-3′), 126.56 (C-2″ and C-6″), 126.65 (C-4″), 128.65 (C-3″ and C-5″), 140.90 (C-1″), 155.02 (C=O), 170.13 (C=O); HR-MS (EI) 384.2393 (M$^+$, $C_{24}H_{36}N_2O_4$ requires *m/z* 384.2413). Found: C, 71.50; H, 8.50; N, 7.18. $C_{22}H_{32}N_2O_4$ requires C, 71.84; H, 8.39; N, 7.29%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminobut-3-ynyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 2j

Compound **2j** was prepared from **25** (19 mg, 0.050 mmol), as described above for the synthesis of **2i** from **23**. After treatment with Et$_2$O, white crystals of **2j** were obtained as a hydrochloride salt (16 mg, 94%): mp (Et$_2$O) 160–162 °C; $[\alpha]^{23}_{D}$ +78.4 (*c* 0.170, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ 0.89 (3 H, t, –NCH$_2$$CH_3$, J = 7.1 Hz), 1.15 (3 H, t, –NCH$_2$$CH_3$, J = 7.1 Hz), 1.37 (1 H, ddd, H-2, $J_{2,3a}$ = 6.5, $J_{2,3b}$ = 8.9, $J_{2,1'}$ = 10.2 Hz), 1.44 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.1, $J_{3a,2}$ = 6.5 Hz), 2.15 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.1, $J_{3b,2}$ = 8.9 Hz), 2.60 (1 H, t, H-4′, $J_{4',2'}$ = 2.6 Hz), 2.74 (2 H, m, H-2′), 3.05 (1 H, m, H-1′), 3.38 (1 H, m, –NCH_2CH$_3$), 3.42–3.49 (3 H, m, –NCH_2CH$_3$), 7.27–7.38 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 12.52 (–NCH$_2$$CH_3$), 13.15 (–NCH$_2$$CH_3$), 18.18 (C-3), 23.30 (C-2′), 32.21 (C-2), 35.45 (C-1), 40.95 (–NCH$_2$CH$_3$), 43.57 (–NCH$_2$CH$_3$), 54.76 (C-1′), 74.48 (C-4′), 78.19 (C-3′), 126.84 (C-2″ and C-6″), 128.54 (C-4″), 130.17 (C-3″ and C-5″), 140.07 (C-1″), 172.52 (C=O); HR-MS (EI) 284.1875 (M$^+$, $C_{18}H_{24}N_2O$ requires *m/z* 284.1889). Found: C, 67.19; H, 7.64; N, 8.47. $C_{18}H_{25}ClN_2O$ requires C, 67.38; H, 7.85; N, 8.73%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1,3-diazidopropyl]-*N*,*N*-diethylcyclopropanecarboxamide 27S and (1*S*,2*R*)-1-phenyl-2-[(*R*)-1,3-diazidopropyl]-*N*,*N*-diethylcyclopropanecarboxamide 27R

Compound **26** (583 mg, 2.00 mmol) was treated as described above for the synthesis of **11R** from **9**. After purification by column chromatography (silica gel, AcOEt–hexane, 1 : 9), **27S** as an oil (337 mg, 49%) and **27R** as an oil (150 mg, 22%) were obtained, respectively. **27S**: $[\alpha]^{23}_{D}$ −127.9 (*c* 1.390, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ 0.45 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.13 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.15 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.0, $J_{3a,2}$ = 9.2 Hz), 1.56 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.0, $J_{3b,2}$ = 6.2 Hz), 1.85 (1 H, ddd, H-2, $J_{2,3b}$ = 6.2, $J_{2,3a}$ = 9.2, $J_{2,1'}$ = 9.6 Hz), 1.90–2.02 (2 H, m, H-2′), 3.10 (1 H, m, –NCH_2CH$_3$), 3.17 (1 H, m, H-1′), 3.23 (1 H, m, –NCH_2CH$_3$), 3.45–3.55 (3 H, m, H-3′ and –NCH_2CH$_3$), 3.63 (1 H, m, –NCH_2CH$_3$), 7.22–7.35 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 12.03 (–NCH$_2$$CH_3$), 12.35 (–NCH$_2$$CH_3$), 18.71 (C-3), 28.68 (C-2), 34.27 (C-2′), 35.99 (C-1), 39.99 (–NCH$_2$CH$_3$), 41.97 (–NCH$_2$-CH$_3$), 47.99 (C-3′), 60.24 (C-1′), 126.75 (C-2″ and C-6″), 126.85 (C-4″), 128.83 (C-3″ and C-5″), 140.34 (C-1″), 169.11 (C=O); HR-MS (EI) 341.1976 (M$^+$, $C_{17}H_{23}N_7O$ requires *m/z* 341.1964). Found: C, 60.00; H, 6.99; N, 28.48. $C_{17}H_{23}N_7O$ requires C, 59.81; H, 6.79; N, 28.72%. **27R**: $[\alpha]^{23}_{D}$ +12.8 (*c* 1.310, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ 0.74 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.12 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.48 (1 H, ddd, H-2, $J_{2,3a}$ = 6.8, $J_{2,3b}$ = 8.7, $J_{2,1'}$ = 9.0 Hz), 1.53 (1 H, dd, H-3a, $J_{3a,3b}$ = 5.2, $J_{3a,2}$ = 6.8 Hz), 1.67 (1 H, dd, H-3b, $J_{3b,3a}$ = 5.2, $J_{3b,2}$ = 8.7 Hz), 1.83 (1 H, m, H-2′a), 2.37 (1 H, m, H-2′b), 3.21 (1 H, m, –NCH_2CH$_3$), 3.26 (1 H, m, –NCH_2CH$_3$), 3.38–3.52 (4 H, m, H-3′ and –NCH_2CH$_3$ × 2), 7.22–7.27 (3 H, m, aromatic), 7.30–7.33 (3 H, m, aromatic); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 12.38 (–NCH$_2$$CH_3$), 12.76 (–NCH$_2$$CH_3$), 17.59 (C-3), 32.18 (C-2), 33.48 (C-1), 34.33 (C-2′), 39.45 (–NCH$_2$CH$_3$), 41.91 (–NCH$_2$-CH$_3$), 48.41 (C-3′), 61.19 (C-1′), 125.87 (C-2″ and C-6″), 126.86 (C-4″), 128.85 (C-3″ and C-5″), 140.04 (C-1″), 169.04 (C=O); HR-MS (EI) 341.1935 (M$^+$, $C_{17}H_{23}N_7O$ requires *m/z* 341.1964). Found: C, 59.98; H, 7.02; N, 28.58. $C_{17}H_{23}N_7O$ requires C, 59.81; H, 6.79; N, 28.72%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1,3-diaminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide dihydrochloride 2m

Compound **2m** was prepared from **27S** (171 mg, 0.50 mmol), as described above for the synthesis of **2i** from **23**. After treatment with Et$_2$O, white crystals of **2m** were obtained as a hydrochloride salt (175 mg, 97%): mp (Et$_2$O) 199–200 °C; $[\alpha]^{24}_{D}$ +62.7 (*c* 1.105, MeOH); ^{1}H-NMR (500 MHz, CD$_3$OD) δ 0.90 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.15 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.26 (1 H, ddd, H-2, $J_{2,3a}$ = 6.5, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 10.3 Hz), 1.50 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3a,2}$ = 6.5 Hz), 2.19 (1 H, m, H-2′a), 2.20 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 9.0 Hz), 2.25 (1 H, m, H-2′b), 3.09 (1 H, m, H-1′), 3.19 (2 H, m, H-3′), 3.36 (1 H, m, –NCH_2CH$_3$), 3.44–3.51 (3 H, m, –NCH_2CH$_3$), 7.26–7.38 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CD$_3$OD) δ 12.53 (–NCH$_2$-CH$_3$), 13.14 (–NCH$_2$$CH_3$), 18.30 (C-3), 32.48 (C-2′), 32.55 (C-2), 34.90 (C-1), 37.31 (C-3′), 40.96 (–NCH$_2$CH$_3$), 43.57 (–NCH$_2$CH$_3$), 53.69 (C-1′), 126.89 (C-2″ and C-6″), 128.51 (C-4″), 130.16 (C-3″ and C-5″), 139.98 (C-1″), 172.41 (C=O); HR-MS (EI) 289.2126 (M$^+$, $C_{17}H_{27}N_3O$ requires *m/z* 289.2154). Found: C, 56.04; H, 8.23; N, 11.39. $C_{17}H_{29}Cl_2N_3O$ requires C, 56.35; H, 8.07; N, 11.60%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-*tert*-butoxycarbonylaminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide 28

A mixture of **2b** (310 mg, 1.00 mmol), (Boc)$_2$O (0.25 mL, 1.10 mmol) and Et$_3$N (0.21 mL, 1.5 mmol) in CH$_2$Cl$_2$ (5 mL) was stirred at room temperature for 14 h. The mixture was evaporated, and the residue was partitioned between AcOEt and H$_2$O. The organic layer was washed with brine, dried (Na$_2$SO$_4$), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 1) to give **28** as white crystals (160 mg, 43%): mp (hexane–AcOEt) 193–194 °C; $[\alpha]^{22}_{D}$ −130.8 (*c* 0.530, CHCl$_3$); ^{1}H-NMR (500 MHz, CDCl$_3$) δ 0.54 (3 H, br s, –NCH$_2$$CH_3$), 0.95 (3 H, t, H-3′, $J_{3',2'}$ = 7.4 Hz), 1.14 (3 H, t, –NCH$_2$$CH_3$, J = 7.0 Hz), 1.18 (1 H, br s, H-3a), 1.42 (9 H, s, –C(CH_3)$_3$), 1.44 (1 H, br s, H-2), 1.73–1.87 (3 H, m, H-3b and H-2′), 3.08 (1 H, m, H-1′), 3.25–3.41 (3 H, m, –NCH_2CH$_3$), 3.62 (1 H, m, –NCH_2CH$_3$), 3.62 (1 H, m, –NCH_2CH$_3$), 4.81 (1 H, br s, –NH–), 7.18–7.30 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 10.58 (C-3′), 12.42 (–NCH$_2$$CH_3$), 12.58 (–NCH$_2$$CH_3$), 17.90 (C-3), 28.26 (C-2′), 28.40 (–C(CH$_3$)$_3$), 30.42 (C-2), 34.24 (C-1), 40.07 (–NCH$_2$CH$_3$), 42.39 (–NCH$_2$CH$_3$), 52.31 (C-1′), 78.69 (–C(CH$_3$)$_3$), 126.36 (C-2″ and C-6″), 126.57 (C-4″), 128.58 (C-3″ and C-5″), 141.39 (C-1″), 155.51 (C=O), 170.65 (C=O); MS (EI) *m/z* 374 (M$^+$). Found: C, 70.53; H, 9.11; N, 7.41. $C_{22}H_{34}N_2O_3$ requires C, 70.55; H, 9.15; N, 7.48%.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-(*N*-methylamino)propyl]-*N*,*N*-diethylcyclopropanecarboxamide hydrochloride 4

To a solution of **28** (112 mg, 0.30 mmol) in THF (3 mL) was slowly added a BuLi solution (1.50 M in hexane, 0.24 mL, 0.36 mmol) at −78 °C, and the mixture was slowly warmed to −15 °C. To the mixture was added MeI (56 µL, 0.90 mmol), and the resulting mixture was stirred at the same temperature for 1 h. After addition of saturated aqueous NH$_4$Cl, the mixture was concentrated (for removal of THF), and the residue was partitioned between AcOEt and H$_2$O. The organic layer was washed with brine, dried (Na$_2$SO$_4$), evaporated, and purified by column chromatography (silica gel, AcOEt–hexane, 1 : 4) to give **29** as a white powder (107 mg, 92%), which was treated as described for the synthesis of **2i** from **23**. After treatment with Et$_2$O, white crystals of **4** were obtained as a hydrochloride salt (85 mg, 95%): mp (Et$_2$O) 126–127 °C; $[\alpha]^{22}_{D}$ −106.0 (*c* 0.415, MeOH); ^{1}H-NMR (500 MHz, CDCl$_3$) δ 0.88 (3 H, t, –NCH$_2$-

CH_3, J = 7.0 Hz), 1.05 (3 H, t, H-3′, $J_{3',2'}$ = 7.4 Hz), 1.15 (3 H, t, –NCH_2CH_3, J = 7.0 Hz), 1.21 (1 H, ddd, H-2, $J_{2,3a}$ = 6.4, $J_{2,3b}$ = 9.0, $J_{2,1'}$ = 9.0 Hz), 1.43 (1 H, dd, H-3a, $J_{3a,3b}$ = 6.0, $J_{3b,2}$ = 6.4 Hz), 1.72–1.89 (2 H, m, H-2′), 2.25 (1 H, dd, H-3b, $J_{3b,3a}$ = 6.0, $J_{3b,2}$ = 9.0 Hz), 2.69 (3 H, s, –NH–*Me*), 2.84 (1 H, m, H-1′), 3.37 (1 H, m, –NCH_2CH_3), 3.43–3.52 (3 H, m, –NCH_2CH_3), 7.27–7.39 (5 H, m, aromatic); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 10.21 (C-3′), 12.49 (–NCH_2CH_3), 13.10 (–NCH_2CH_3), 19.00 (C-3), 24.03 (C-2′), 29.38 (–NH–*Me*), 31.91 (C-2), 34.50 (C-1), 41.07 (–NCH_2CH_3), 43.67 (–NCH_2CH_3), 64.18 (C-1′), 126.78 (C-2″ and C-6″), 128.52 (C-4″), 130.24 (C-3″ and C-5″), 140.01 (C-1″), 172.89 (C=O); HR-MS (EI) 288.2210 (M^+, $C_{18}H_{28}N_2O$ requires *m*/*z* 288.2202). Found: C, 66.31; H, 8.81; N, 8.58. $C_{18}H_{29}ClN_2O$ requires C, 66.54; H, 9.00; N, 8.62%.

X-Ray crystallographic analysis of 15 ‡

$C_{18}H_{27}ClN_2O$, M = 322.88, monoclinic, $C2$, a = 23.900 (4) Å, b = 6.065 (2) Å, c = 16.073 (3) Å, β = 128.08 (1)°, V = 1833.8 (7) Å^3, Z = 4, D_x = 1.169 Mg cm^{-3}. Cell parameters were determined and refined from 24 reflections in the range 26.5° < θ < 30.0°. A colorless crystal (0.30 × 0.25 × 0.15 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å). Data collection using the $\omega/2\theta$ scan technique gave 1620 reflections at room temperature, 1513 unique, of which 1508 with $I > 0.00\sigma(I)$ reflections were used in calculations. The intensities were corrected for Lorentz and polarization factors, and for absorption and extinction effects. The structure was solved by the direct method and refined by the full-matrix least squares technique using maXus (version 2.0) as the computer program. The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were refined isotropically. The unweighted and weighted values were 0.024 and 0.055, respectively. There was no peak above 0.10 eÅ^{-3} in the last Fourier-difference map.

Binding assay on NMDA receptors

The binding affinity for the NMDA receptor was carried out according to previously reported methods.[15]

Inhibitory effects on the uptake of 5-HT

The assay was carried out according to the previously reported method.[11]

Cell culture and heat-induction of NMDA receptors subtypes

The CHO cell lines introduced expression vectors carrying GluRζ1 and GluRε1, GluRε2, GluRε3, or GluRε4 subunit cDNAs under the promotion of the *Drosophila* heat-shock protein HSP70 which was established as described previously.[16] The CHO cells expressing GluRε1/ζ1 and GluRε2/ζ1 subtypes were maintained at 37 °C in eRDF-1 medium (1 : 1 : 2 mixture of Dulbecco's modified Eagle's medium, Ham's Nutrient Mixture F-12 and RPMI1640, without L-glutamate, glycine and L-aspartate) supplemented with 10% fetal bovine serum (FBS) (Gibco BRL/Life Technologies, Inc., Grand Island, NY), 400 µg mL^{-1} geneticin (Sigma, St. Louis, MO), 2 µg mL^{-1} blasticidin S hydrochloride (Funakoshi, Tokyo, Japan), and 10 µg mL^{-1} puromycin (Sigma) in a humidified atmosphere containing 5% CO_2. The CHO cells expressing GluRε3/ζ1 and GluRε4/ζ1 subtypes were maintained in eRDF-1 medium supplemented with 10% FBS, 1200 µg mL^{-1} geneticin and 2 µg mL^{-1} blasticidin S hydrochloride. For heat-induction of NMDA receptors, the CHO cells were plated on collagen-coated glass coverslips with a silicon rubber wall (Flexiperm Disc; Heraeus, Germany) at a density of 1.5–2.5 × 10^4 cells cm$^{2-1}$, and incubated at 37 °C for 24–36 h. They were then incubated at 43 °C for 30–60 min and maintained at 37 °C for 6–18 h in an appropriate selective growth medium containing 1 mM DL-APV (Sigma), a specific competitive antagonist of the NMDA receptor added to prevent toxicity due to possible activation of the NMDA receptors.

Measurement of $[Ca^{2+}]_i$ with the CHO cells

The CHO cells were incubated for 45 min with 5.0 µM fura-2-AM (Dojindo, Kumamoto, Japan), dispersed by brief sonication in a balanced salt solution (BSS), consisting of 130 mM NaCl, 5.4 mM KCl, 2.0 mM $CaCl_2$, 5.5 mM glucose and 10 mM HEPES (pH 7.3), supplemented with 0.001% cremophore EL (a solubility enhancer; Sigma). The fura-2-loaded cells were then placed on the stage of an inverted fluorescence microscope (IX50; Olympus, Tokyo, Japan) and perfused with BSS at a rate of 2.0 mL min^{-1}. Using alternate illumination at 340 and 380 nm excitation, fluorescence images were obtained using a magnification objective lens (UApo 20x/340; Olympus) and an emission filter (510–550 nm).The images were captured using a silicon-intensified-target video camera (C2400–8; Hamamatsu Photonics, Hamamatsu, Japan) and digitized using an image processor (Argus 50/CA; Hamamatsu Photonics). Finally, the data were fed into a personal computer (Venturis FXs, Digital). For ratiometry, ratio images were obtained by dividing the fluorescence intensity at 340 nm excitation (F340) by that at 380 nm excitation (F380) using the computer and the image processor.

Concentration–inhibition curves were fitted by the logistic equation:

$$I/I_{control} = 1/\{1 + ([antagonist]/IC_{50})^n\}, \qquad (1)$$

where $I_{control}$ is the response in the absence of the antagonist, IC_{50} is the concentration of the drug that inhibits 50% of this response and n is the Hill coefficient.

Acknowledgements

This investigation was supported by a Grant-in-Aid for Creative Scientific Research (13NP0401) from the Japan Society for Promotion of Science. We are grateful to Daiso Co., Ltd. for the gift of chiral epichlorohydrins and also to Ms H. Matsumoto, A. Maeda, S. Oka, and N. Hazama (Center for Instrumental Analysis, Hokkaido University) for technical assistance with NMR, MS, and elemental analysis.

References and notes

1 R. Dingledine, K. Borges, D. Bowie and S. Traynelis, *Pharmacol. Rev.*, 1999, **51**, 7–61.
2 H. Bräuner-Osbornel, J. Egebjerg, E. O. Nielsen, U. Madsen and P. Krogsgaad-Larsen, *J. Med. Chem.*, 2000, **43**, 2609–2645.
3 G. L. Collingridge, J. C. Watkins, *The NMDA Receptor*, IRL Press at Oxford University Press, Oxford, UK, 1994.
4 (*a*) J. Willetts, R. L. Balster and J. D. Leander, *Trends Pharmacol. Sci.*, 1990, **11**, 423–428; (*b*) M. D. Tricklebank, L. Singh, R. J. Oles, C. Preston and S. D. Iversoen, *Eur. J. Pharmacol.*, 1989, **167**, 127–135; (*c*) M. A. Rogawski, *Trends Pharmacol. Sci.*, 1993, **14**, 325–331.
5 J. W. Olney, J. Labruyere and M. T. Price, *Science*, 1989, **244**, 1360–1362.
6 (*a*) B. S. Meldrum, M. J. Croucher, S. J. Czuczwar, J. F. Collins, K. Curry, M. Joseph and T. W. Stone, *Neuroscience*, 1983, **9**, 925–930; (*b*) M. J. Hogan, A. Gjedde and A. M. Hakem, *J. Neurochem.*, 1992, **58**, 186–191.
7 (*a*) T. Kutsuwada, N. Kashiwabuchi, H. Mori, K. Sakimura, E. Kushiya, K. Araki, H. Meguro, H. Masaki, T. Mumanishi, M. Arakawa and M. Mishina, *Nature*, 1992, **358**, 36–41; (*b*) T. Yamakura, H. Mori, H. Masaki, K. Shimoji and M. Mishina, *Neuroreport*, 1993, **4**, 687–690; (*c*) M. Raditsch, P. R. Ruppersberg, T. Kuner, W. Günther, R. Schoepfer, P. H. Seeburg, W. Jahn and V. Witzemann, *FEBS Lett.*, 1993, **324**, 63–66; (*d*) D. J. Laurie

‡ CCDC reference number 176579. See http://www.rsc.org/suppdata/p1/b1/b111540p/ for crystallographic files in .cif or other electronic format.

and P. H. Seeburg, *Eur. J. Pharmacol.*, 1994, **268**, 335–345; (*e*) T. Priestley, P. Laughton, J. Myers, B. Le Bourdelles, J. Kerby and P. J. Whiting, *Mol. Pharmacol.*, 1995, **48**, 841–848; (*f*) H. Mori and M. Mishina, *Neuropharmacology*, 1995, **34**, 1219–1237; (*g*) N. J. Sucher, M. Awobuluyi, Y.-B. Choi and S. A. Lipton, *Trends Pharmacol. Sci.*, 1996, **17**, 348–355; (*h*) V. I. Ilyin, E. R. Whittemore, J. Guastell, E. Weber and R. M. Woodward, *Mol. Pharmacol.*, 1996, **50**, 1541–1550; (*i*) A. L. Buller and D. T. Monaghan, *Eur. J. Pharmocol.*, 1997, **320**, 87–94; (*j*) T. W. Butler, J. F. Blake, J. Bordner, P. Butler, B. L. Chenaed, M. A. Collins, D. DeCosta, M. J. Ducat, M. E. Eisenhard, F. S. Menniti, M. J. Pagnozzi, S. B. Sands, B. E. Segelstein, W. Volberg, W. F. White and D. Zhao, *J. Med. Chem.*, 1998, **41**, 1172–1184; (*k*) K. Taniguchi, K. Shinjo, M. Mizutani, K. Shimada, Y. Ishikawa, F. S. Menniti and A. Nagahisa, *Br. J. Pharmacol.*, 1997, **122**, 809–812; (*l*) R. M. Schelkun, P. Yuen, K. Serpa, T. M. Leonard and D. W. Lawrence, *J. Med. Chem.*, 2000, **43**, 1892–1897; (*m*) K. Williams, *Mol. Pharmacol*, 1993, **44**, 851–859.

8 Mouse NMDA receptor subunits GluRζ1, GluRε1, GluRε2, GluRε3, and GluRge4 correspond to NR1, NR2A, NR2B, NR2C, and NR2D subunits of rat, respectively.

9 Compound (±)-**1** had previously been called "midalcipran". However, since the clinical studies began, the name "milnacipran" has generally been used for (±)-**1**.

10 (*a*) M. Briley, *Drugs Future*, 1986, **11**, 21–23; (*b*) C. Moret, M. Charveron, J. P. M. Finberg, J. Cozinier and M. Briley, *Neuropharmacology*, 1985, **24**, 1211–1219; (*c*) B. Bonnaud, H. Cousse, G. Mouzin, M. Briley, A. Stenger, F. Fauran and J.-P. Couzinier, *J. Med. Chem.*, 1987, **30**, 318–325; (*d*) M. Ansseau, P. Papart, B. Troisfontaines, F. Bartholome, M. Bataille, G. Charles, M. Schittecatte, P. Darimont and J. M. Devoitille, *Psychopharmacology*, 1994, **114**, 131–137; (*e*) F. Artigas, *CNS Drugs*, 1995, **4**, 79–89.

11 S. Shuto, H. Takada, D. Mochizuki, R. Tsujita, Y. Hase, S. Ono, N. Shibuya and A. Matsuda, *J. Med. Chem.*, 1995, **38**, 2964–2968.

12 (*a*) S. Shuto, S. Ono, Y. Hase, N. Kamiyama, H. Takada, K. Yamashita and A. Matsuda, *J. Org. Chem.*, 1996, **61**, 915–923; (*b*) S. Ono, S. Shuto and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 221–224; (*c*) S. Shuto, S. Ono, Y. Hase, N. Kamiyama and A. Matsuda, *Tetrahedron Lett.*, 1996, **37**, 641–644; (*d*) S. Shuto, S. Ono, Y. Hase, Y. Ueno, T. Noguchi, K. Yoshii and A. Matsuda, *J. Med. Chem.*, 1996, **39**, 4844–4852; (*e*) S. Shuto, S. Ono, H. Imoto, K. Yoshii and A. Matsuda, *J. Med. Chem.*, 1998, **41**, 3507–3514; (*f*) T. Noguchi, K. Ishii, H. Imoto, Y. Otubo, S. Shuto, S. Ono, A. Matsuda and K. Yoshii, *Synapse*, 1999, **31**, 87–96; (*g*) Y. Kazuta, S. Shuto and A. Matsuda, *Tetrahedron Lett.*, 2000, **41**, 5373–5377; (*h*) S. Shuto, K. Yoshii and A. Matsuda, *Jpn. J. Pharmacol.*, 2001, **85**, 207–213; (*i*) Y. Kazuta, S. Shuto, H. Abe and A. Matsuda, *J. Chem. Soc., Perkin Trans. 1*, 2001, 599–604.

13 The reaction of alcohols with a NaN_3–PPh_3–CBr_4 system has been known to give the corresponding azide derivatives *via* the S_N2 reaction pathway: I. Yamamoto, M. Sekine and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, 1980, 306–310.

14 (*a*) J. Haywood-Farmer, *Chem. Rev.*, 1974, **74**, 315–350; (*b*) C. F. Wilcox, M. M. Loew and R. Hoffmann, *J. Am. Chem. Soc.*, 1973, **95**, 8192–8193.

15 E. J. Corey and P. L. A. Fuchs, *Tetrahedron Lett.*, 1972, **36**, 2369–3772.

16 T. Asano, I. Ikegaki, S. Satoh, D. Mochizuki, H. Hidaka, Y. Suzuki, M. Shibuya and K. Sugita, *Br. J. Pharmacol.*, 1991, **103**, 1935–1938.

17 S. Uchino, Y. Kudo, W. Watanabe, S. Nakajima-Iijima and M. Mishina, *Mol. Brain Res.*, 1997, **44**, 1–11.

18 (*a*) J. M. Olney, *Ann. Rev. Pharmacol. Toxicol.*, 1990, **30**, 47–71; (*b*) D. W. Choi, *Neuron*, 1998, **1**, 623–634.

19 (*a*) R. Dingledine, C. J. Mcbain and J. O. Mcnamara, *Trends Pharmacol. Sci.*, 1990, **11**, 334–338; (*b*) J. McCulloch, *Br. J. Clin. Pharmac.*, 1992, **34**, 106–114; (*c*) E. R. Wood, T. J. Bussey and A. G. Phillips, *Neurosci. Lett.*, 1992, **145**, 10–14; (*d*) S. A. Lipton, *Trends Neurosci.*, 1993, **16**, 527–532.