Conformational Restriction by Repulsion between Adjacent Substituents on a Cyclopropane Ring: Design and Enantioselective Synthesis of 1-Phenyl-2-(1-aminoalkyl)-*N*,*N*-diethylcyclopropanecarboxamides as Potent NMDA Receptor Antagonists

Satoshi Shuto,*[,†] Shizuka Ono,[†] Yukako Hase,[†] Noriko Kamiyama,[†] Hironao Takada,[‡] Kanako Yamasihita,[‡] and Akira Matsuda[†]

Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan and Institute for Life Science Research, Asahi Chemical Industry Co., Ltd., Mifuku, Ohito-cho, Shizuoka 410-23, Japan

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Adjacent substituents on a cyclopropane ring mutually exert steric repulsion quite significantly, because they are fixed in eclipsed conformation to each other. Based on this structural feature of the cyclopropane ring, conformationally restricted analogs of milnacipran (**1**), namely 1-phenyl-2-(1-aminoalkyl)-*N*,*N*-diethylcyclopropanecarboxamides (**2**, **3**, *ent*-**2**, and *ent*-**3**) were designed as potent NMDA receptor antagonists and were synthesized highly enantioselectively. Reaction of (*R*)-epichlorohydrin [(*R*)-**5**] and phenylacetonitrile (**6**) in the presence of $NaNH_2$ in benzene gave a chiral cyclopropane derivative that was isolated as lactone **4** with 96% ee in 67% yield, after alkaline hydrolysis of the cyano group. The nucleophilic addition reaction of Grignard reagents to aldehyde **10**, which was readily prepared from **4**, proceeded highly selectively from the *si*-face to afford addition products **11** in high yields. Although hydride reduction of the corresponding ketone **15b**, prepared from **11b**, with L-Selectride also proceeded highly diastereoselectively, the facial selectivity was reversed to give the *re*-face addition product **11b**. On the other hand, reduction of **15** with DIBAL-H afforded the *si*-face addition product **12** in high yields. These results suggested that these nucleophilic addition reactions proceeded via either the bisected *s-trans* or *s-cis* conformation of the cyclopropylcarbonyl derivatives. From **11** and **12**, the target conformationally resticted analogs, **2** and **3**, were synthesized, respectively. Starting from (*S*)-epichlorohydrin [(*S*)-**5**], their corresponding enantiomers, *ent*-**2** and *ent*-**3**, were also synthesized. The structures of the conformationally restricted analogs detected by the X-ray crystallographic analysis suggested that their conformations can be restricted as we hypothesized. Thus, a new method for restricting the conformation of cyclopropane derivatives has been developed.

Introduction

Activation of *N*-methyl-D-aspartate (NMDA) receptor, a subclass of glutamate receptors, has been implicated in the initiation of neuronal cell death due to hypoxia and in the pathophysiology of epilepsy.[1] Because of the potential involvement of the NMDA receptor in both chronic and acute neurodegenerative disorders, an extensive effort to identify novel agents that block activation of NMDA receptor by glutamate, or related excitatory neurotransmitters, has been undertaken.[1−3] MK-801 [10,11-dihydro-5-methyl-*5H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine][2] and CGS 19755 [(±)*cis*-4-(phosphonomethyl)-2-piperidinecarboxylic acid],[3] which are typical noncompetitive and competitive NMDA receptor antagonists, respectively, are effective in experimental models of epilepsy and stroke. Disadvantages of these compounds are that noncompetitive inhibitors had serious behavioral effects[4ab] probably due to neuronal vacuolization,[4c] while the competitive ones were often inactive *in vivo* because of poor transport to the brain.[5] Therefore, development of other types of efficient NMDA receptor antagonists has been awaited.

Recently we reported that (±)-(*Z*)-2-(aminomethyl)-1-phenyl-*N*,*N*-diethylcyclopropanecarboxamide (milnacipran, (±)-**1**), known as an efficient antidepressant due to inhibiting the reuptake of serotonin by the nerve terminal in CNS,[6,7] was a new class of NMDA receptor antagonists.[8] Although the binding affinity of **1** for the NMDA receptor is not strong enough, it has vital importance as a prototype for novel potent NMDA receptor antagonists because of the characteristic structure, which is clearly different from those of known competitive and noncompetitive antagonists of the receptor.[8] In recent years, we

* Author to whom correspondence should be addressed.
† Hokkaido University.
‡ Asahi Chemical Industry Co.
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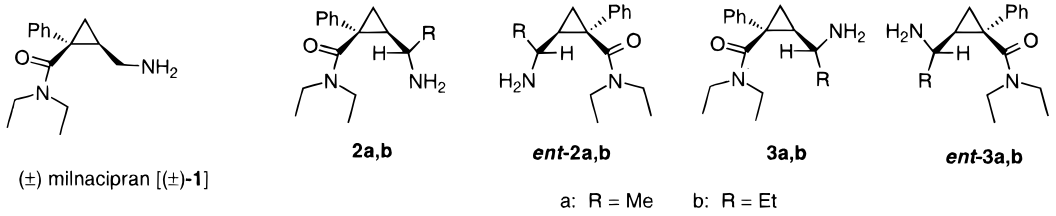


Figure 1. Milnacipran and its conformationally restricted analogs.

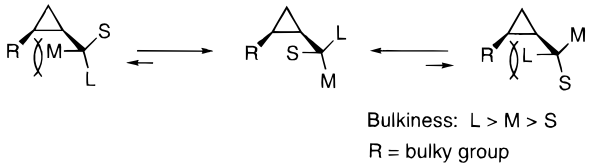


Figure 2. Conformational restriction by the repulsion between adjacent substituents on a cyclopropane ring.

have been engaged in a modification study of milnacipran, increasing the specific affinity for the NMDA receptor, to develop a clinically useful agent. Because our previous study showed that modification of functional groups of milnacipran did not improve the activity,[8] we planned to investigate the effects of conformational changes of the molecule on the activity. Therefore, we designed conformationally restricted analogs of **1**, in which a new method for restricting the conformation of cyclopropane derivatives has been developed.

Design of Conformationally Restricted Analogs of Milnacipran

It is known that as a result of free rotation about single bonds in compounds, a drug molecule can assume a variety of conformations. Only one of these conformers would bind to a receptor. If the lead compound has low binding affinity for the receptor, it may only be because the population of the active conformer in solution is low. So, the synthesis of conformationally restricted analogs of a lead compound can bring an improvement of the specific binding affinity for the receptor.[9]

We designed the conformationally restricted analogs based on the structural feature of **1**, as shown in Figure 1. Adjacent substituents on a cyclopropane ring mutually exert steric repulsion quite significantly, because they are fixed in eclipsed conformation to each other. Consequently, conformations of the substituents on a cyclopropane can be restricted by the steric effect of adjacent substituents, especially when they are bulky as indicated in Figure 2. Because the primary amino function of **1** is essential for the binding affinity for the NMDA receptor,[8] we presumed 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, because of the serious steric repulsion for the bulky diethylcarbamoyl group in conformer C as shown in Figure 3. Introducing an alkyl group into the α-position of the amino function of **1** would prevent the rotation, to restrict the location of the amino function in space due to its steric repulsion for the diethycarbamoyl group. Therefore, depending on the configuration of the alkyl

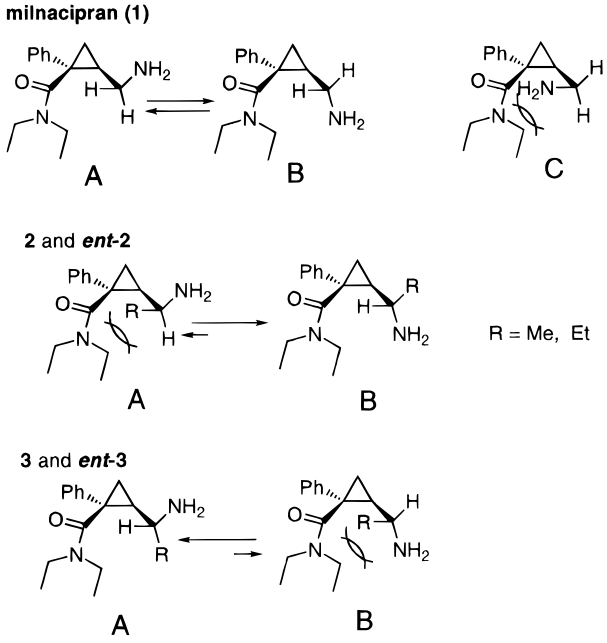
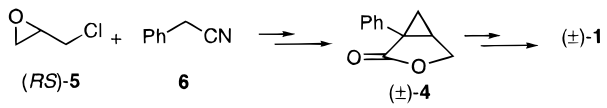
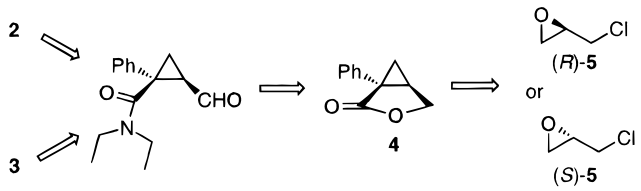


Figure 3. Conformational restriction of milnacipran by introducing an alkyl group.

Scheme 1



Scheme 2



group introduced, the conformation of the compounds can be restricted; conformer B would be predominant in **2** and *ent*-**2**, conversely, conformer A would be predominant in **3** and *ent*-**3** (Figure 3).

Results and Discussion

We have reported an easy synthetic method for (±)-milnacipran [(±)-**1**] and its derivatives via racemic lactone (±)-**4** as the key intermediate as shown in Scheme 1.[8] The racemic lactone (±)-**4** is readily prepared from epichlorohydrin [(*RS*)-**5**] and phenylacetonitrile (**6**).[10] The corresponding optically active lactones **4** and *ent*-**4** were thought to be efficient intermediates for the target compounds as shown in Scheme 2. In the cyclopropane

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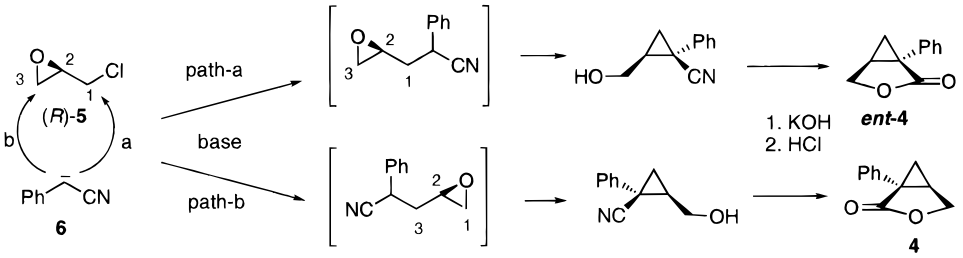
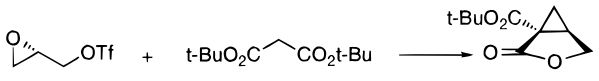
Scheme 3



Scheme 4



ring-closure reaction of **5** and **6** in the presence of a base, two pathways, namely path-a and -b, could be considered (Scheme 3). If a nucleophilic attack occurs highly selectively either through path-a or -b, this would provide an efficient method to access both lactone **4** and *ent*-**4** in optically active forms, because both (*R*)- and (*S*)-epichlorohydrins are available. Chiral epoxypropanes including epichlorohydrins have been widely used as chiral synthons for synthesizing various optically active compounds.[11] MaClure and co-workers studied the mode of nucleophilic substitution on various chiral 2,3-epoxypropanes with a leaving group at the 1-position; they concluded that the mode of nucleophilic attacks depends on the leaving group as well as the conditions used, in which a few highly selective reactions were observed.[12]

When carbanions are used as a nucleophile in the reaction, the corresponding cyclopropane derivatives can be produced in the reaction.[13,14] Burgess and Ho reported that when an optically active triflate **7** was treated with a carbanion of di-*tert*-butyl malonate, nearly all of the optical activity of **7** was transferred to the cyclopropane product **8** (yield 50%, 91% ee; Scheme 4). However, a significant instability of **7**, which would decrease the optical purity, has also been recognized.[11a] On the other hand, when a chiral epichlorohydrin is used instead of the corresponding triflate in similar reactions, decreases of optical activity of the products have been observed.[14] This is a consequence of direct displacement of the chloride with a nucleophile (path-a) competing with an attack at the epoxide (path-b), the latter being the major pathway, as suggested by McClure and co-workers.[12] In recent years, both (*R*)-**5** and (*S*)-**5** of high optical purity (>98% ee) have been commercially available[15] and are significantly more stable than the corresponding triflate. However, cyclopropane-ring-closure reactions with optically active epichlorohydrins have not been studied in detail. Therefore, we decided to try synthesizing chiral lactones **4** and *ent*-**4** of high optical purity starting from chiral epichlorohydrins, (*R*)-**5** and (*S*)-**5**.

We investigated the reaction of (*R*)-**5** and an anion of phenylacetonitrile under various conditions. The resulting cyclopropane product was isolated as lactone **4**, after alkaline hydrolysis of the nitrile group followed by treatment with HCl (Scheme 3). When the reaction was done with $NaNH_2$, as a base, in benzene at room temperature, the result was the most desirable; (1*S*,2*R*)-lactone **4** with 96% e.e was isolated in 67% yield. This reaction can be readily done on a large scale; more than 30 g of chiral product **4** was prepared in one experiment. Use of other bases such as LDA, NaH, or $LiNH_2$ and solvents such as THF or toluene decreased the yield and/or optical purity of **4**. The absolute stereochemistry of **4** was assigned as 1*S*,2*R*, from X-ray crystallographic analysis of the final product (*ent*-**2**) as described below. This result indicates that the nucleophile attacks highly selectively at the epoxide through path-b. Therefore, it is suggested that chiral epichlorohydrins can be efficient synthons for preparing chiral cyclopropanes.

Treatment of **4** with $LiNEt_2$ in THF at −78 °C afforded a ring-opened product **9**, which was subjected to Swern oxidation to give aldehyde **10** in high yield (Scheme 5). Reaction of aldehyde **10** and MeMgBr at −20 °C in THF gave addition product **11a** highly stereoselectively, which was isolated in 92% yield, with a trace of diastereomer **12a**. The corresponding ethyl derivative **11b** was also obtained with EtMgBr in high yield. While the reaction with MeLi, instead of MeMgBr, also afforded **11a** as a major product, the stereoselectivity was reduced (**11a**:**12a** = 70:23).

The 2′-configuration of **11** and **12** was confirmed as follows. Compound **11a** was heated with HCl in MeOH to give lactone **13** in 63% yield (Scheme 6).[16] Similarly, the corresponding diastereomer **14** was obtained from **12a**. The relative configuration between 2-H and 2′-H was assigned from the ^1H NMR spectra of conformationally rigid lactones **13** and **14** based on the Karplus equation; the coupling constant between H-2 and H-2′ of **14** was 4.5 Hz, while the coupling was not observed in **13**. Thus, the stereochemistry of **11** was assigned as 1*S*,2*R*,2′*S*, and **12** as 1*S*,2*R*,2′*R*.[17]

It has been recognized that cyclopropyl carbaldehydes and cyclopropyl ketones preferentially exist in bisected conformations, namely *s-trans* and *s-cis* conformers, due to the characteristic stereoelectronic effects of the cyclopropane ring; the *s-trans* conformer is predominant in cyclopropyl carbaldehydes, conversely, the *s-cis* conformer is predominant in cyclopropyl ketones,[18] as shown in Figure 4. In fact the X-ray crystallographic analysis of aldehyde **10** (Figure 5) indicates the bisected *s-trans* conformation is preferable, as expected. The nucleophilic

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(13) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931−5936.

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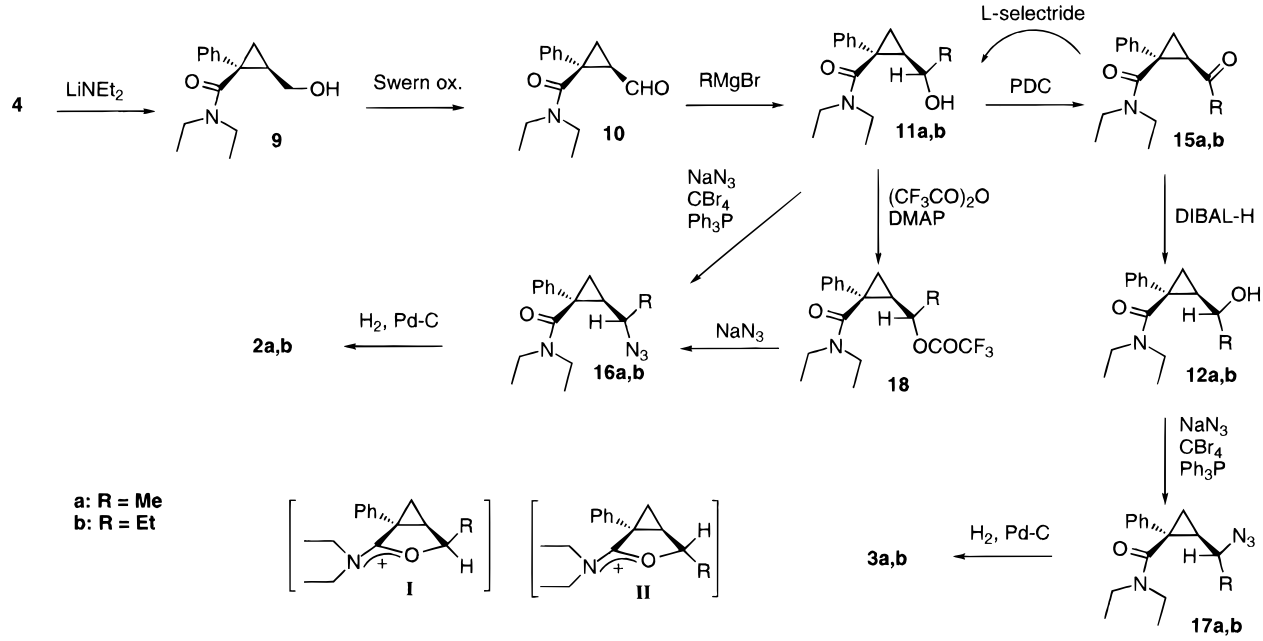
(15) Available from Daiso Co., Ltd.

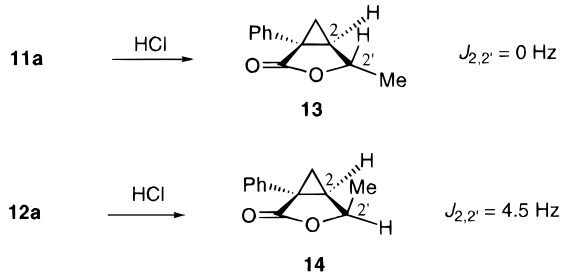
(16) Successive treatment of **11a** with KOH/ethylene glycol and DCC/MeOH also gave **13**.

(17) The configuration of 2′-position of **11a** was also assigned as *S* by modified Mosher's method: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

Scheme 5



Scheme 6



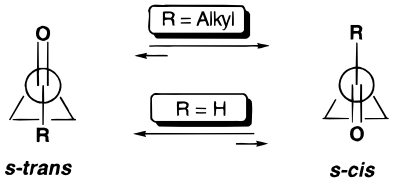


Figure 4. Bisected conformations of cyclopropyl carbaldehyde and cyclopropyl ketone.

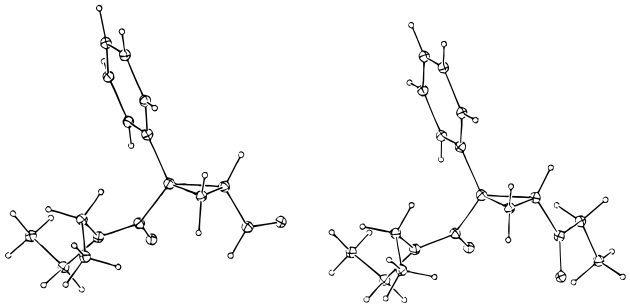


Figure 5. X-ray crystallographic structures of **10** (left) and **15b** (right).

addition reactions would proceed from the least hindered *si*-face of **10** in the *s-trans* conformation to give **11** highly diastereoselectively.

Since we required both diastereomers **11** and **12** to access the target compounds, **2** and **3**, inversion of the configuration at the 2′-position of **11** was investigated. First, mesylation or tosylation of the 2′-hydroxyl group of **11a** was attempted; however, these reactions did not proceed due probably to steric hindrance around the hydroxyl group. Although the Mitsunobu reaction of **11a** with DEAD (diethyl azodicarboxylate), Ph_3P, and chloroacetic acid gave the corresponding 2′-chloroacetate, the configuration was retained.[19] Next, stereoselective reduction of the ketone **15**, which was readily prepared by PDC oxidation of **11**, was attempted. Reduction of **15b** with $NaBH_4$ in MeOH afforded the undesired 2′*S*-alcohol **11b** as the major product in 70% yield (**11b**:**12b** = 4:1). When L-Selectride was used, **11b** was obtained highly selectively (91%, **11b**:**12b** = 50:1[20]). If the conformation of **15b** in the reaction course is similar to that in crystals observed by its X-ray crystallographic analysis as shown in Figure 5, the stereoselectivity of the reaction with these nucleophilic hydride reagents can be explained as the hydride attack occurring from the least hindered face (*re*-face) to the carbonyl of **15b**. The result is also consistent with the previous reports that cyclopropyl ketones preferentially exist in the bisected *s-cis* conformation.[18] Surprisingly, when **15b** was treated with DIBAL-H in THF at −78 °C, the reaction gave the desired 2′*R*-alcohol **12b** highly selectively in 95% yield (**11b**:**12b** = 1:50).[20] A similar desirable result was also obtained in the DIBAL-H reduction of methyl ketone **15a** (yield 90%, **11a**:**12a** = 1:33[20]). When DIBAL-H, which is considered to be a relatively electrophilic reducing reagent for carbonyl groups, coordinates to the carbonyl of

(18) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-Y.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165−198. (b) Gerasimos, J. K.; Nelsom, J. *J. Am. Chem. Soc.* **1965**, *87*, 2864−2870. (c) Pierre, J. L.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1966**, 1690−1693. (d) Bartell, L. S.; Guillory, J. P.; Parks, A. T. *J. Phys. Chem.* **1965**, *69*, 3043−3048. (e) Bartell, L. S.; Guillory, J. P. *J. Phys. Chem.* **1965**, *43*, 647−654. (f) Bordner, J.; Jones, L. A.; Johnson, R. L. *Cryst. Struct. Commun.* **1972**, *1*, 389−391. (g) Lute, C. N. A.; Stam, C. H. *Rec. Trav. Chim. Pays-Bas (Rec. J. R. Neth. Chem. Soc.)* **1976**, *95*, 130−132. (h) Roques, R.; Crasnier, F.; Declercq, J. P. Germain, G.; Cousse, H.; Mouzin, G. *Acta Crystallogr.* **1982**, *B38*, 1375−1377. (i) Crasnier, F.; Labarre, J. F.; Cousse, H.; D'Hinterland, L. D.; Mouzin, G. *Tetrahedron* **1975**, *31*, 825−829.

(19) Removal of the chloroacetyl group by treating with NaOMe/MeOH gave *2′S*-alcohol **11a**.

(20) The ratio of diastereomers produced was measured by the ^1H NMR spectrum (500 MHz) of the crude product.

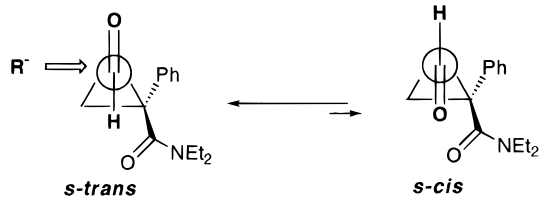


Figure 6. Conceivable reaction pathway of the nucleophilic addition reaction in aldehyde **10**.

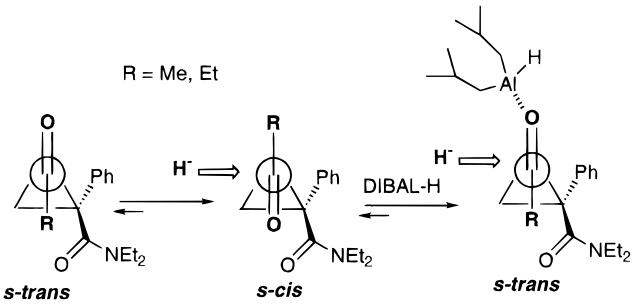


Figure 7. Conceivable reaction pathway of the nucleophilic addition reaction of ketone **15**.

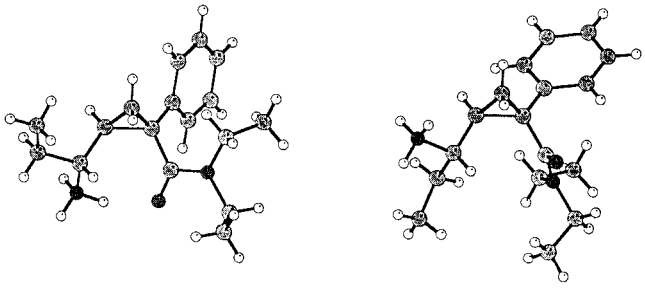


Figure 8. X-ray crystallographic structures of *ent*-**2b** (left) and *ent*-**3b** (right).

15, a conformation like *s-trans* (shown in Figure 7) would be preferred due to steric repulsion between the two bulky isobutyl and diethylcarbamoyl groups. The hydride attack from the least hindered face (*si*-face) to the intermediate would give the desired product highly selectively. These results showed the stereoselectivity of the hydride reduction almost completely reversed when the reaction was done by nucleophilic or electrophilic reducing reagents. To our knowledge, only one example on steroid derivatives that showed almost complete reversion of stereoselectivity in hydride reductions[21] similar to our results, has appeared.

Treatments of **11a** and **11b** with the $NaN_3/CBr_4/Ph_3P$ system in DMF[22] gave azide derivatives, **16a** and **16b**, with retention of the configuration at the 2′-position in excellent yields, respectively. Similar treatments of the corresponding 2′-diastereomers, **12a** and **12b**, also afforded azide derivatives, **17a** and **17b**, respectively, of which the 2′-configurations were also retained. The configurations at the 2′-position were confirmed from X-ray crystallographic analysis of an enantiomer of the final product (*ent*-**2b**) as shown in Figure 8. Although the reaction conditions, namely treatment of an alcohol with the $NaN_3/CBr_4/Ph_3P$ system in DMF, has been known to give the corresponding azide derivative via the S_N2 reaction pathway,[22] in our study, the reaction gave configuration-retained azide derivatives **16** and **17**. On the other hand, when 2′-trifluoroacetyl derivative **18**, which was readily prepared from **11a**, was treated with NaN_3 in DMF, the configuration of the azide product **16a** was also retained. These results suggest a reaction pathway via the neighboring group participated intermediates **I** and **II** (Scheme 5) in the nucleophilic substitution reaction at the 2′-position of the compounds. This assumption would also be consistent with the result of a reaction under the Mitsunobu reaction conditions described above.

Catalytic hydrogenations of azide derivatives, **16a**, **16b**, **17a**, and **17b**, with Pd−C in MeOH gave the target conformationally restricted analogs, **2a**, **2b**, **3a**, and **3b**, in high yields, respectively.

Starting from (+)-epichlorohydrine [(*S*)-**5**], the corresponding enantiomers, *ent*-**2a**, *ent*-**2b**, *ent*-**3a**, and *ent*-**3b**, were also synthesized.

Studies on synthesizing optically active cyclopropane derivatives have been done in recent years due to their biological importance.[23] This procedure with (*R*)- or (*S*)-epichlorohydrin as a synthon for chiral cyclopropanes would be one of the most useful methods; both chiral epichlorohydrins are available readily in high optical purity and are stable, and cyclopropane products of high optical purity can be obtained on a large scale as demonstrated in this study.

Cyclopropyl carbaldehydes and cyclopropyl ketones have been shown to exist preferentially in the bisected *s-trans* and *s-cis* conformations, respectively,[18] from their NMR analyses,[18b,c] electron diffraction studies,[18d,e] X-ray crystallographic analyses,[18f−h] and theoretical calculations.[18i] This study may be the first experimental result that demonstrates the stereochemical pathways of the nucleophilic attack on the cyclopropyl carbonyl can depend upon the predominant bisected conformation of cyclopropane derivatives which is predictable from the stereoelectronic effects. In this study, the predominant conformations of the cyclopropyl carbaldehyde and the corresponding ketone were also suggested from their X-ray crystallographic analyses. Especially, X-ray crystallographic analysis of cyclopropyl carbaldehyde **10** is important, because it is the first one that detects the bisected *s-trans* conformation of cyclopropyl carbaldehyde in crystal structure, though X-ray structures of cyclopropyl ketones of bisected conformations have been reported.[18f−h] In the reaction course of the nucleophilic addition reaction, electrons of the cyclopropane ring, which can be characterized as a strong π-donor, interact with the antibonding orbital of the incipient bond between the nucleophile and the carbonyl carbon.[24] The nucleophilic addition reaction can be facilitated by this interaction, which is maximal when the cyclopropyl carbonyl derivatives exist either in the bisected *s-trans* or *s-cis* conformations. In nucleophilic substitution reactions at the cyclopropylmethyl position, similar significant facilitation of the reaction when the substrates can exist in the bisected conformation has been already recognized.[25]

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(24) Importance of the antibonding orbital in the reaction course of nucleophilic addition reactions on carbonyls has been recognized: (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552. (b) Cieplak, A. S.; Tait, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 5875−5876. (c) Satoh, M.; Murakami, M.; Sunami, S.; Kaneko, C.; Furuya, T.; Kurihara, H. *J. Am. Chem. Soc.* **1995**, *117*, 4279−4287.

The structures of X-ray crystallographic analysis of *ent*-**2b** and *ent*-**3b**, indicated in Figure 8, clearly demonstrate that **2** (*ent*-**2**) and **3** (*ent*-**3**) exist in conformer B and A, respectively, as we hypothesized. Although the conformations detected in this study were in the solid state, this result suggests that the conformation of substituents on a cyclopropane ring would be restricted by the steric effect of adjacent substituents even in the solution. In design of conformationally restricted analogs, it should be imperative that the conformationally restricted analogs and the lead drug molecule should be as similar as possible in size, shape, and molecular weight.[9] Conformationally restricted analogs have usually been designed and synthesized by introducing cyclic moieties into lead compounds that were often rather bulky. Consequently, the chemical and physical properties can be changed. From these points of view, our methodology for restricting the conformation of a key functional group, due to the repulsion of the adjacent substituents by introducing only a small alkyl group such as a methyl or ethyl group, would be useful. This method can be applicable for conformational restriction of various cyclopropane derivatives.

In a preliminary binding study of the compound on NMDA receptor, **2a** and **2b** showed about 30 times stronger binding affinity for the receptor, compared with milnacipran.[8] The details of the biological activity of the compounds will be reported elsewhere.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded at 270, 400, or 500 MHz (^{1}H) and at 100 or 125 MHz (^{13}C) and are reported in ppm downfield from TMS. Mass spectra were obtained by electron ionization. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography and flash silica gel chromatography were done with Merck silica gel 5715 and 9385, respectively.

(1*S*,2*R*)-2-Oxo-1-phenyl-3-oxabicyclo[3.1.0]hexane (4). A solution of phenylacetonitrile (34.5 mL, 300 mmol) in benzene (60 mL) was added slowly to a suspension of $NaNH_2$ (25.8 g, 660 mmol) in benzene (120 mL) at 0 °C under argon, and the mixture was stirred at room temperature for 3 h. To the resulting mixture, a solution of (*R*)-epichlorohydrin [(*R*)-**5**, 20.4 mL, 261 mmol] in benzene (60 mL) was added at 0 °C, and the whole was stirred at room temperature for 2 h. After the solvent was evaporated, EtOH (60 mL) and 1 N KOH (30 mL) were added to the residue, and the mixture was heated under reflux for 15 h and then acidified with 12 N HCl at 0 °C (pH of the mixture was about 1). The resulting mixture was evaporated, and AcOEt (900 mL) was added to the residue. Insoluble salts were filtered off, and the filtrate was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:3) to give **4** as orange crystals (30.3 g, 67%). The optical purity was determined by a chiral HPLC (CHIRALCEL-OJ, 0.46 × 25 cm, Daicel Chemical Industries Co., Ltd.; hexane/2-propanol, 4:1; 0.4 mL/min; 200 nm): 96% ee, mp 56−57 °C. $[\alpha]^{20}_D = -78.5$ (*c* 1.42, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$) 1.36 (1 H, dd, J = 4.5, 5.0 Hz), 1.65 (1 H, dd, J = 5.0, 8.0 Hz), 2.55 (1 H, ddd, J = 4.5, 4.5, 8.0 Hz), 4.29 (1 H, d, J = 9.0 Hz), 4.46 (1 H, dd, J = 4.5, 9.0 Hz), 7.28−7.44 (5 H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 20.41, 25.36, 31.95, 68.34, 127.92, 128.57, 128.85, 134.40, 176.29. HR-MS (EI) calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0684. Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.96; H, 5.87.

(1*S*,2*R*)-1-Phenyl-2-(hydroxymethyl)-*N*,*N*-diethylcyclopropanecarboxamide (9). To a solution of Et_2NH (1.7 mL, 16 mmol) in THF (20 mL), BuLi (1.64 M in hexane, 11 mL, 16 mmol) was added slowly at 0 °C under argon, and then the mixture was cooled to −78 °C. To the resulting cooled mixture, a solution of **4** (1.7 g, 10 mmol) in THF (20 mL) was added slowly, and the whole was stirred at the same temperature. After 2 h, the reaction was quenched with saturated NH_4Cl (10 mL), and the resulting mixture was concentrated *in vacuo* (for removing THF) and then AcOEt was added. The separated organic phase was dried (Na_2SO_4), evaporated, and purified by flash column chromatography (silica gel; AcOEt/hexane, 1:1) to give **9** as an oil (2.1 g, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$) 0.91 (3 H, t, J = 7.0 Hz), 1.08 (1 H, dd, J = 5.0, 6.5 Hz), 1.14 (3 H, t, J = 7.0 Hz), 1.55 (1 H, dddd, J = 5.0, 6.5, 9.0, 10.5 Hz), 1.65 (1 H, dd, J = 5.0, 9.0 Hz), 3.17 (1 H, ddd, J = 2.5, 10.5, 12.0 Hz), 3.32−3.56 (4 H, m), 4.40 (1 H, ddd, J = 5.0, 11.0, 12.0 Hz), 4.74 (1 H, dd, J = 2.5, 11.0 Hz), 7.19−7.32 (5 H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 12.60, 13.33, 17.07, 32.09, 34.64, 39.77, 42.24, 65.06, 125.97, 126.85, 128.92, 140.55, 171.46. HR-MS (EI) calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1564. Anal. Calcd for $C_{15}H_{21}NO_2 \cdot 0.1H_2O$: C, 72.31; H, 8.50; N, 5.57. Found: C, 72.29; H, 8.77; N, 5.57.

(1*S*,2*R*)-1-Phenyl-2-formyl-*N*,*N*-diethylcyclopropanecarboxamide (10). To a solution of oxalyl chloride (0.55 mL, 6.4 mmol) in CH_2Cl_2 (4 mL) was added a mixture of DMSO (0.91 mL, 13 mmol) and CH_2Cl_2 (4 mL) slowly at −78 °C for 30 min under argon. To the resulting mixture was added a solution of **9** (805 mg, 3.26 mmol) in CH_2Cl_2 (4 mL) slowly, the whole was stirred at the same temperature for 2 h, and then Et_3N (1.9 mL, 26 mmol) was added. After being stirred at −78 °C for further 1 h, the reaction mixture was quenched with saturated NH_4Cl (5 mL), and then $CHCl_3$ (10 mL) was added. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:2) to give **10** as a white crystal (766 mg, 96%). Mp 56−57 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) 0.69 (3 H, t, J = 7.0 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.71 (1 H, dd, J = 5.5, 8.5 Hz), 2.28 (1 H, dd, J = 5.5, 6.0 Hz), 2.50 (1 H, ddd, J = 6.0, 6.0, 8.5 Hz), 3.18 (1H, dq, J = 14.0, 7.0 Hz), 3.26 (1H, dq, J = 14.0, 7.0 Hz), 3.42 (1H, dq, J = 14.0, 7.0 Hz), 3.46 (1H, dq, J = 14.0, 7.0 Hz), 7.23−7.38 (5 H, m), 9.05 (1 H, d, J = 6.0 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 12.50, 13.00, 20.23, 36.63, 39.88, 40.35, 41.79, 126.13, 127.74, 129.21, 138.18, 167.54, 198.30. HR-MS (EI) calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1431. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.48; H, 7.92; N, 5.66.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxyethyl]-*N*,*N*-diethylcyclopropanecarboxamide (11a). To a solution of **10** (1.59 g, 6.5 mmol) in THF (40 mL) was added MeMgBr (0.99 M in THF, 16.5 mL, 16.3 mmol) slowly at −20 °C under argon. The mixture was stirred at the same temperature for 2 h and was quenched with saturated NH_4Cl (20 mL). The resulting mixture was concentrated *in vacuo* (for removing THF), and then AcOEt was added. The separated organic phase was dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:2) to give **11a** as white crystals (1.55 g, 93%). Mp 72−73 °C. $[\alpha]^{28}_D = -27.5$ (*c* 1.12, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) 0.93 (3 H, t, J = 7.0 Hz), 1.03 (1 H, dd, J = 5.5, 6.5 Hz), 1.14 (3 H, t, J = 7.0 Hz), 1.28 (1 H, ddd, J = 6.5, 9.0, 9.0 Hz), 1.31 (3 H, d, J = 6.5 Hz), 1.67 (1 H, dd, J = 5.5, 9.0 Hz), 3.26−3.34 (1 H, m), 3.35−3.46 (3 H, m), 3.52 (1 H, dq, 14.0, 7.0 Hz), 5.41 (1H, s), 7.19−7.31 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 12.38, 13.19, 16.79, 21.45, 34.35, 38.15, 39.52, 42.01, 70.74, 125.68, 126.59, 128.68, 140.27, 171.45. HR-MS (EI) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1722. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.52; H, 9.04; N, 5.30.

(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-hydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide (11b). Compound **11b** was prepared as described above for **11a**, with EtMgBr instead of MeMgBr. After purification by column chromatography (silica gel; AcOEt/hexane, 1:3), **11b** was obtained as an oil (3.22 g, 90% yield). $[\alpha]^{26}_D = -17.6$ (*c* 1.11, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.93 (3 H, t, J = 7.0 Hz), 1.00 (3 H, t, J = 7.5 Hz), 1.06 (1 H, dd, J = 5.5, 6.5 Hz), 1.14 (3 H, t, J = 7.0 Hz), 1.26 (1 H, ddd, J = 6.5, 9.0, 9.5 Hz), 1.61−1.73 (2 H, m), 1.70 (1 H, dd, J = 5.5, 9.0 Hz), 3.08 (1 H, ddd, J = 6.5, 9.5, 9.5 Hz),

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3.33−3.46 (3 H, m), 3.48−3.55 (1 H, dq, J = 14.0, 7.0 Hz), 5.44 (1 H, br s), 7.18−7.30 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 10.24, 12.29, 13.08, 17.05, 29.08, 33.25, 36.61, 39.39, 41.90, 75.66, 125.62, 126.48, 128.58, 140.29, 171.41. HR-MS (EI) calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1909. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.88; H, 9.20; N, 5.09.

(1*S*,2*R*)-1-Phenyl-2-acetyl-*N*,*N*-diethylcyclopropanecarboxamide (15a). A mixture of **11a** (1.33 g, 5.10 mmol), PDC (7.67 g, 20.4 mmol), and molecular sieves 4A (6.65 g) in CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h, and the resulting mixture was filtered through Celite. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:1) to give **15a** as white crystals (1.24 g, 94%). Mp 73−74 °C. $[\alpha]^{28}_D$ = −220.3 (*c* 0.91, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) 0.86 (3 H, t, J = 7.0 Hz), 1.09 (3 H, t, J = 7.0 Hz), 1.66 (1 H, dd, J = 5.0, 8.0 Hz), 2.22 (1 H, dd, 5.0, 6.5 Hz), 2.38 (3 H, s), 2.44 (1 H, dd, J = 6.5, 8.0 Hz), 3.24 (1 H, dq, J = 14.0, 7.0 Hz), 3.25 (1 H, dq, J = 14.0, 7.0 Hz), 3.39 (1 H, dq, J = 7.0, 14.0 Hz), 3.45 (1 H, dq, J = 7.0, 14.0 Hz), 7.24−7.35 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 12.40, 13.19, 19.78, 31.46, 37.02, 39.32, 41.64, 41.95, 126.06, 127.25, 128.80, 139.10, 167.76, 204.33. HR-MS (EI) calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1601. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.23; H, 8.21; N, 5.35.

(1*S*,2*R*)-1-Phenyl-2-propanoyl-*N*,*N*-diethylcyclopropanecarboxamide (15b). Compound **15b** was prepared as described above for **15a**. After purification by column chromatography (silica gel; AcOEt/hexane, 1:3), **15b** was obtained as white crystals (600 mg, 87% yield). Mp 84−85 °C. $[\alpha]^{27}_D$ = −220.3 (*c* 0.73, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) 0.88 (3 H, t, J = 7.0 Hz), 1.08 (3 H, t, J = 7.0 Hz), 1.14 (3 H, t, J = 7.5 Hz), 1.65 (1 H, dd, J = 5.0, 8.0 Hz), 2.23 (1 H, dd, J = 5.0, 6.5 Hz), 2.42 (1 H, dd, J = 6.5, 8.0 Hz), 2.61 (1 H, dq, J = 17.5, 7.5 Hz), 2.78 (1 H, dq, J = 17.5, 7.5 Hz), 3.21 (1 H, dq, 14.0, 7.0 Hz), 3.22 (1 H, dq, 14.0, 7.0 Hz), 3.41 (1 H, dq, 14.0, 7.0 Hz), 3.47 (1 H, dq, 14.0, 7.0 Hz), 7.24−7.35 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 7.99, 12.36, 13.22, 19.53, 36.05, 37.60, 39.28, 41.57, 126.10, 127.19, 128.79, 139.26, 167.72, 206.91. HR-MS (EI) calcd $C_{17}H_{23}NO_2$ 273.1729, found 273.1701. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.58; H, 8.60; N, 5.01.

(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-hydroxyethyl]-*N*,*N*-diethylcyclopropanecarboxamide (12a). To a solution of **15a** (100 mg, 0.386 mmol) in THF (5 mL) was added DIBAL-H (0.93 M in hexane, 0.83 mL, 0.97 mmol) slowly at −78 °C under argon. The mixture was stirred at the same temperature for 1 h and quenched with 1 N HCl. The resulting mixture was concentrated *in vacuo* (for removing THF), and then AcOEt and H_2O was added. The separated organic phase was dried (Na_2SO_4), evaporated, and purified by flash column chromatography (silica gel; AcOEt/hexane, 1:1) to give **12a** (91 mg, 90%). $[\alpha]^{28}_D$ = −127.0 (*c* 0.98, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.76 (3 H, t, J = 7.0 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.27 (3 H, d, J = 6.5 Hz), 1.39−1.46 (2 H, m), 1.50 (1 H, dd, 4.0, 6.5 Hz), 3.00 (1 H, brs), 3.26 (1 H, dq, J = 14.0, 7.0 Hz), 3.31 (1 H, dq, J = 14.0, 7.0 Hz), 3.41 (1 H, dq, J = 14.0, 7.0 Hz), 3.49 (1 H, dq, J = 14.0, 7.0 Hz), 4.17 (1 H, dt, J = 10.0, 6.5 Hz), 7.20−7.30 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 12.29, 12.71, 14.91, 22.51, 33.40, 36.19, 39.59, 42.28, 64.89, 125.69, 126.39, 128.68, 140.98, 171.62. HR-MS (EI) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1724. Anal. Calcd for $C_{16}H_{23}NO_2 \cdot 0.1H_2O$: C, 73.02; H, 8.89; N, 5.32. Found: C, 73.07; H, 9.01; N, 5.15.

(1*S*,2*R*)1-Phenyl-2-[(*R*)-1-hydroxypropyl]-*N*,*N*-diethylcyclopropanecarboxamide (12b). Compound **12b** was prepared as described above for **12a**. After purification by column chromatography (silica gel; AcOEt/hexane, 1:2), **12b** was obtained as an oil (130 mg, 95% yield). $[\alpha]^{27}_D$ = −125.0 (*c* 0.99, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.75 (3 H, t, J = 7.0 Hz), 1.00 (3 H, t, J = 7.5 Hz), 1.12 (3 H, t, J = 7.0 Hz), 1.37−1.44 (2 H, m), 1.52−1.64 (3 H, m), 2.88 (1 H, brs), 3.26 (1 H, dq, J = 14.0, 7.0 Hz), 3.31 (1 H, dq, J = 14.0, 7.0 Hz), 3.41 (1 H, dq, J = 14.0, 7.0 Hz), 3.47 (1 H, dq, J = 14.0, 7.0 Hz), 4.00 (1 H, ddd, 4.0, 4.0, 8.0 Hz), 7.17−7.22 (3 H, m), 7.27−7.31 (2 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 10.22, 12.29, 12.66, 14.45, 29.72, 32.79, 34.95, 39.52, 42.21, 69.29, 125.62, 126.30, 128.64, 141.11, 171.87. HR-MS (EI) calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1858. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.75; H, 9.26; N, 4.96.

Reducton of 15b with L-Selectride. Reaction was done as described above for the reduction of **15b**, with L-Selectride (1.0 M in THF) instead of DIBAL-H. After purification by column chromatography (silica gel; AcOEt/hexane, 1:1), a mixture of **11b** and **12b** was obtained as an oil (114 mg, 91%, **11b**:**12b** = 50:1).

Reducton of 15b with $NaBH_4$. To a solution of **15b** (82 mg, 0.30 mmol) in MeOH (0.5 mL) was added $NaBH_4$ (9.8 mg, 0.26 mmol). The mixture was stirred at room temperature for 2 h and then quenched with saturated NH_4Cl. The resulting mixture was concentrated *in vacuo*, then AcOEt was added. The separated organic phase was dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; AcOEt/hexane, 1:1) to give **11a** (46 mg, 56%) and **12b** (12 mg, 15%).

(1*S*,4*S*,5*R*)-4-Methyl-2-oxo-1-phenyl-3-oxabicyclo[3.1.0]-hexane (13). To a solution of **11a** (750 mg, 2.87 mmol) in MeOH (5 mL) was added 6 N HCl (5 mL), and the whole was heated under reflux for 45 min. The solvent was evaporated, and then the residue was partitioned between saturated $NaHCO_3$ and AcOEt. The organic phase washed with brine was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:3) to give **13** as white powder (340 mg, 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) 1.38 (1 H, dd, J = 4.5, 5.0 Hz), 1.52 (3 H, d, J = 6.5 Hz), 1.63 (1 H, dd, J = 5.0, 8.0 Hz), 2.32 (1 H, dd, J = 4.5, 8.0 Hz), 4.54 (1 H, q, J = 6.5 Hz), 7.28−7.42 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 20.12, 22.62, 31.26, 32.48, 75.99, 127.76, 128.51, 128.66, 134.25, 175.46. MS (EI) m/z 188 (M^+). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.59; H, 6.42.

(1*S*,4*R*,5*R*)-4-Methyl-2-oxo-1-phenyl-3-oxabicyclo[3.1.0]-hexane (14). Compound **14** was prepared as described above for **13**. After purification by column chromatography (silica gel; AcOEt/hexane, 1:3), **14** was obtained as white powder (44 mg, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$) 1.42 (3 H, d, J = 6.0 Hz), 1.41−1.43 (1 H, m), 1.48 (1 H, dd, J = 5.0, 8.0 Hz), 2.51 (1 H, ddd, J = 4.5, 5.0, 8.0 Hz), 4.90 (1 H, dq, J = 4.5, 6.0 Hz), 7.27−7.43 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 16.75, 17.59, 29.78, 33.12, 74.27, 127.56, 128.16, 128.55, 134.25, 175.79. HR-MS (EI) calcd $C_{12}H_{12}O_2$ 188.0837, found 188.0824. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.37; H, 6.59.

General Procedure for Preparing Azide Derivatives 16a, 16b, 17a, and 17b. To a solution of 2′-alcohol (**11** or **12**, 3.30 mmol) in DMF (25 mL) were added NaN_3 (3.20 g, 65.0 mmol), Ph_3P (2.60 g, 19.9 mmol), and CBr_4 (3.30 g, 10.0 mmol) at 0 °C, and the whole was stirred at room temperature for 3 h. Water was added and the resulting mixture was evaporated, and then the residue was partitioned between brine and AcOEt. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:5) to give azide **16** or **17** as an oil. **(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidoethyl]-*N*,*N*-diethylcyclopropanecarboxamide (16a).** Yield 62% (585 mg). $[\alpha]^{28}_D$ = −137.3 (*c* 0.99, MeOH).^{1}H-NMR (400 MHz, $CDCl_3$) 0.37 (3 H, t, J = 7.0 Hz), 0.91 (1 H, dd, J = 5.0, 9.5 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.45 (3 H, d, J = 7.0 Hz), 1.61 (1 H, dd, J = 5.0, 6.5 Hz), 1.95 (1 H, ddd, J = 6.5 Hz, 9.5 Hz, 10.0 Hz), 2.98−3.08 (2 H, m), 3.12 (1 H, dq, J = 14.0, 7.0 Hz), 3.57 (1 H, dq, J = 14.0, 7.0 Hz), 3.68 (1 H, dq, J = 14.0, 7.0 Hz), 7.19−7.32 (5 H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 12.11, 12.47, 19.71, 19.99, 28.99, 36.82, 40.06, 42.48, 58.47, 126.90, 127.18, 128.98, 141.02, 169.65. MS (EI) m/z 286 (M^+). Anal. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56. Found: C, 67.30; H, 7.84; N, 19.67. **(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-azidopropyl]-*N*,*N*-diethylcyclopropanecarboxamide (16b).** Yield 72% (713 mg). $[\alpha]^{26}_D$ = −160.0 (*c* 0.91, MeOH).^{1}H-NMR (400 MHz, $CDCl_3$) 0.37 (3 H, t, J = 7.0 Hz), 0.95 (1 H, dd, J = 5.0, 9.5 Hz), 1.07 (3 H, t, J = 7.5 Hz), 1.13 (3 H, t, J = 7.0 Hz), 1.66 (1 H, dd, J = 5.0, 6.5 Hz), 1.74−1.87 (2 H, m), 1.96 (1 H, ddd, J = 6.5, 9.5, 10.0 Hz), 2.86 (1 H, ddd, J = 5.0, 8.0, 10.0 Hz), 3.04 (1 H, dq, J = 14.0,

7.0 Hz), 3.17 (1 H, dq, J = 14.0, 7.0 Hz), 3.53 (1 H, dq, J = 14.0, 7.0 Hz), 3.72 (1 H, dq, J = 14.0, 7.0 Hz), 7.19−7.32 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 10.22, 11.80, 12.29, 19.62, 27.27, 28.24, 35.88, 39.96, 42.08, 64.17, 126.63, 126.99, 128.71, 140.82, 169.48. HR-MS (EI) calcd for $C_{17}H_{24}N_4O$ 300.1950, found 300.1978. Anal. Calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 68.15; H, 8.08; N, 18.43. **(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-azidoethyl]-*N*,*N*-diethylcyclopropanecarboxamide (17a).** Yield 86% (812 mg). $[\alpha]^{28}_D$ = −118.4 (*c* 1.25, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.69 (3 H, t, J = 7.0 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.48−1.52 (3 H, m), 1.51 (3 H, d, J = 6.5), 3.18 (1 H, dq, J = 14.0, 7.0 Hz), 3.23 (1 H, dq, J = 14.0, 7.0 Hz), 3.33−3.38 (1 H, m), 3.45 (1 H, dq, J = 14.0, 7.0 Hz), 3.49 (1 H, dq, J = 14.0, 7.0 Hz), 7.20−7.32 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 12.31, 12.66, 18.20, 20.37, 32.90, 34.15, 39.43, 41.95, 59.20, 126.04, 126.70, 128.75, 140.47, 169.22. HR-MS (EI) calcd for $C_{16}H_{22}N_4O$ 286.1793, found 286.1765. Anal. Calcd for $C_{16}H_{22}N_4O$: C, 67.11; H, 7.74; N, 19.56. Found: C, 67.10; H, 7.82; N, 19.37. **(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-azidopropyl]-*N*,*N*-diethylcyclopropanecarboxamide (17b).** Yield 93% (921 mg). $[\alpha]^{28}_D$ = −101.4 (*c* 0.73, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.69 (3 H, t, J = 7.0 Hz), 1.04 (3 H, t, J = 7.5 Hz), 1.11 (3 H, t, J = 7.0 Hz), 1.47−1.60 (3 H, m), 1.61−1.72 (1 H, m), 2.01 (1 H, ddq, J = 14.5, 3.5, 7.5 Hz), 3.12−3.26 (3 H, m), 3.48 (1 H, dq, J = 14.0, 7.0 Hz), 3.49 (1 H, dq, J = 14.0, 7.0 Hz), 719−7.32 (5 H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) 10.65, 12.35, 12.68, 17.98, 28.37, 31.35, 33.82, 39.43, 41.92, 64.98, 126.12, 126.70, 128.79, 140.62, 169.28. HR-MS (EI) calcd for $C_{17}H_{24}N_4O$ 300.1950, found 300.1926. Anal. Calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 68.26; H, 8.28; N, 18.27.

Synthesis of 16a via 18. To a solution of **11a** (141 mg, 0.54 mmol) and DMAP (132 mg, 1.08 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic anhydride (150 μL, 1.08 mmol), and the mixture was stirred at room temperature for 15 h. To the resulting mixture were added DMF (2 mL) and NaN_3 (53 mg, 0.81 mmol), and the whole was sttired at room temperature for 45 min and further stirred at 45 °C for 15 min. Water was added, the resulting mixture was evaporated, and then the residue was partitioned between brine and AcOEt. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:5) to give **16a** as an oil (128 mg, 83%).

General Procedure for the Reduction of Azide Derivatives. A mixture of **16** or **17** (3.00 mmol) and 10% Pd−charcoal (200 mg) in MeOH (35 mL) was stirred under atmospheric pressure of hydrogen at room temperature for 1.5 h, and then the catalyst was filtered off. The filtrate was evaporated, and the residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 90:20:0.5) to give free amine **2** or **3** as an oil. The oil was partitioned between $CHCl_3$ and 1 N NaOH, and then $CHCl_3$ phase was washed twice with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in MeOH (3 mL), the solution was put on a column of Diaion WA-30 resin (3 × 10 cm, Cl^- form), and the column was developed with MeOH. The solvent was evaporated, and the residue was treated with ether to give white crystals of **2** or **3** as hydrochloride. **(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminoethyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (2a).** Yield 60% (529 mg). Mp 210−213 °C. $[\alpha]^{18}_D$ = +90.1 (*c* 0.260, MeOH). ^{1}H-NMR (400 MHz, $CDCl_3$) 0.92 (3 H, t, J = 7.0 Hz), 1.05 (1 H, dd, J = 6.0, 6.5 Hz), 1.10 (3 H, t, J = 7.0 Hz), 1.60 (1 H, ddd, J = 6.5, 9.5, 10.5 Hz), 1.73 (3 H, d, J = 6.5 Hz), 1.85 (1 H, dd, J = 6.0, 9.5 Hz), 2.79 (1 H, dq, J = 10.5, 6.5 Hz), 3.25−3.50 (4 H, m), 7.17−7.31 (5 H, m), 8.99 (3 H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) 12.27, 13.10, 17.63, 18.33, 32.17, 35.00, 39.65, 42.01, 52.43, 125.91, 127.34, 129.01, 138.13, 170.85. MS (EI) m/z 260 (M^+). Anal. Calcd for $C_{16}H_{24}N_2O$·HCl: C, 64.74; H, 8.49; N, 9.44. Found: C, 64.78; H, 8.62; N, 9.32. **(1*S*,2*R*)-1-Phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (2b).** Yield 76% (707 mg). Mp 200−203 °C. $[\alpha]^{21}_D$ = +100.8 (*c* 0.900, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.90 (3 H, t, J = 7.0 Hz), 1.08−1.12 (7 H, m), 1.50 (1 H, ddd, J = 6.5, 9.0, 10.0 Hz), 1.92 (1 H, dd, J = 5.5, 9.0 Hz), 2.05−2.14 (1 H, m), 2.30−2.38 (1 H, m), 2.63 (1 H, ddd, J = 5.0, 10.0, 10.0 Hz), 3.29 (1 H, dq, J = 14.0, 7.0 Hz), 3.34−3.48 (3 H, m), 7.20−7.23 (3 H, m), 7.27−7.31 (2 H, m), 9.00 (3 H, br s). ^{13}C-NMR (125 MHz, $CDCl_3$) 11.01, 12.45, 13.29, 18.59, 26.78, 30.66, 33.28, 39.92, 42.21, 57.77, 126.26, 127.53, 129.21, 138.36, 171.12. HR-MS (EI) calcd for $C_{17}H_{26}N_2O$ 274.2045, found 274.2046. Anal. Calcd for $C_{17}H_{26}N_2O$·HCl·0.1H_2O: C, 64.93; H, 8.78; N, 8.91. Found: C, 65.04; H, 9.11; N, 8.98. **(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-aminoethyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (3a).** Yield 68% (604 mg). Mp 179−182 °C. $[\alpha]^{21}_D$ = +41.8 (*c* 0.968, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.75 (3 H, t, J = 7.0 Hz), 1.09 (3 H, t, J = 7.0 Hz), 1.55 (1 H, dd, J = 5.5, 5.5 Hz), 1.60−1.70 (2 H, m), 1.65 (3 H, d, J = 6.5 Hz), 3.21−3.30 (2 H, m), 3.35−3.50 (3 H, m), 7.19−7.29 (5 H, m), 8.58 (3 H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) 12.35, 12.82, 17.68, 18.87, 31.46, 35.15, 39.56, 42.03, 50.24, 126.15, 126.92, 128.79, 139.54, 169.38. HR-MS (EI) calcd for $C_{16}H_{24}N_2O$ 260.1889, found 260.1870. Anal. Calcd for $C_{16}H_{24}N_2O$·HCl·0.6H_2O: C, 62.47; H, 8.58; N, 9.11. Found: C, 62.45; H, 8.58; N, 9.14. **(1*S*,2*R*)-1-Phenyl-2-[(*R*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide Hydrochloride (3b).** Yield 81% (753 mg). Mp 165−167 °C. $[\alpha]^{21}_D$ = +52.9 (*c* 0.648, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.75 (3 H, t, J = 7.0 Hz), 1.09 (3 H, t, J = 7.0 Hz), 1.20 (3 H, t, J = 7.5 Hz), 1.51−1.59 (2 H, m), 1.73 (1 H, dd, J = 5.5, 8.0 Hz), 1.94−2.03 (1 H, m), 2.26−2.31 (1 H, m), 3.16−3.28 (3 H, m), 3.39 (1 H, dq, J = 14.0, 7.0 Hz), 3.43 (1 H, dq, J = 14.0, 7.0 Hz), 7.18−7.30 (5 H, m), 8.55 (3 H, br s). ^{13}C-NMR (100 MHz, $CDCl_3$) 10.55, 12.38, 12.84, 17.83, 26.94, 31.04, 35.43, 39.43, 41.86, 56.26, 125.97, 126.94, 128.84, 139.79, 169.11. HR-MS (EI) calcd for $C_{17}H_{26}N_2O$ 274.2045, found 274.2025. Anal. Calcd for $C_{17}H_{26}N_2O$·HCl·0.4H_2O: C, 64.19; H, 8.81; N, 8.81. Found: C, 64.11; H, 9.09; N, 8.76.

X-ray Crystallographic Data of 10. $C_{15}H_{19}NO_2$, M = 245.32, monoclinic, $P2_1$ (no. 4), a = 8.056(2) Å, b = 14.108(4) Å, c = 6.627(1) Å, β = 112.76(1) Å, V = 694.6(2) Å, Z = 2, D_{calcd} = 1.17 g cm^{-3}. Cell parameters were determined and refined from 20 reflections in the range 56° < 2θ < 60°. A colorless crystal (0.35 × 0.20 × 0.20 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.54178 Å). Data collection using the ω/2θ scan technique to a maximum 2θ value of 120° gave 1174 reflections at room temperature, 1051 unique, of which 983 with $I > 3.00\sigma(I)$ reflections were used in calculations. The intensities were corrected for the Lorentz and polarization factors but not for the absorption or the extinction effect. The structure was solved by direct method and refined by full-matrix least squares technique (Crystan-GM system[26] as the computer program and SIR92[27] as the structure solution method). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation, but these positions were not refined. The unweighted and weighted values (with a weighting scheme $W = \exp(15 \sin^2\theta/\lambda^2)/\sigma^2(F_o)$) were 0.057 and 0.064, respectively. No peak above 0.18 e Å^{-3} in the last Fourier-difference map.

X-ray Crystallographic Data of 15b.[28] $C_{17}H_{23}NO_2$, M = 273.38, orthorhombic, $P2_12_12_1$ (no. 19), a = 13.450(4) Å, b = 17.846(5) Å, c = 6.672(4) Å, V = 1602(1) Å^3, Z = 4, D_{calcd} = 1.13 g cm^{-3}. Cell parameters were determined and refined from 15 reflections in the range 57° < 2θ < 60°. A colorless prism (0.5 × 0.3 × 0.1 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.54178 Å). Data collection using the ω/2θ scan technique to a maximum 2θ value of 120° gave 1463 reflections at room temperature, 1396 unique, of which 1280 with $I > 3.00\sigma(I)$ reflections were used in calculations. The intensities were corrected for the Lorentz and polarization factors but not for the absorption or the extinction effect. The structure was solved by direct method and refined by full-matrix least squares technique (Crystan-GM system[26] as the computer program and SIR92[27] as the structure solution method). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation, but these positions were not refined. The unweighted and weighted values (with a weighting scheme $W = \exp(20 \sin^2\theta/\lambda^2)/\sigma^2(F_o)$) were 0.059 and 0.063, respectively. No peak above 0.20 e Å^{-3} in the last Fourier-difference map.

X-ray Crystallographic Data of *Ent*-2b Hydrochloride.[28] $C_{17}H_{27}ClN_2O$, $M = 310.91$, orthorhombic, $P2_12_12_1$ (no. 19), $a = 8.571(2)$ Å, $b = 26.996(5)$ Å, $c = 7.981(2)$ Å, $V = 1846.7(7)$ Å^3, $Z = 4$, $D_{calcd} = 1.12$ g cm^{-3}. Cell parameters were determined and refined from 22 reflections in the range $53° < 2\theta < 60°$. A colorless plate (0.4 × 0.4 × 0.1 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). Data collection using the $\omega/2\theta$ scan technique to a maximum 2θ value of 120° gave 1874 reflections at room temperature, 1791 unique, of which 1275 with $I > 3.00\sigma(I)$ reflections were used in calculations. The intensities were corrected for the Lorentz and polarization factors but not for the absorption or the extinction effect. The structure was solved by direct method and refined by full-matrix least squares technique (Crystan-GM system[26] as the computer program and SIR92[27] as the structure solution method). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation, but these positions were not refined. Both enantiomorphous structures were refined with final disagreement factors $R_1 = 0.079$, $R_{1w} = 0.082$ and $R_2 = 0.085$, $R_{2w} = 0.086$ (with a weighting scheme $W = \exp(10 \sin^2 \theta/\lambda^2)/\sigma^2(F_o)$) for the two enantiomers, respectively. The correct absolute configuration was assigned to the enantiomer displaying the lower values of the disagreement factors. No peak above 0.51 e Å^{-3} in the last Fourier-difference map.

X-ray Crystallographic Data of *Ent*-3b Hydrochloride.[28] $C_{17}H_{27}ClN_2O$, $M = 310.91$, monoclinic, C2 (no. 5), $a = 23.794(6)$ Å, $b = 6.024(2)$ Å, $c = 16.350(4)$ Å, $\beta = 128.66(2)°$, $V = 1830(1)$ Å^3, $Z = 4$, $D_{calcd} = 1.13$ g cm^{-3}. Cell parameters were determined and refined from 20 reflections in the range $53° < 2\theta < 60°$. A colorless crystal (0.50 × 0.15 × 0.05 mm) was mounted on a Mac Science MXC18 diffractometer with graphite-monochromated Cu Kα radiation ($\lambda = 1.54178$ Å). Data collection using the $\omega/2\theta$ scan technique to a maximum 2θ value of 120 Å gave 1614 reflections at room temperature, 1509 unique, of which 1390 with $I > 3.00\sigma(I)$ reflections were used in calculations. The intensities were corrected for the Lorentz and polarization factors, but not for the absorption or the extinction effect. The structure was solved by direct method and refined by full-matrix least squares technique (Crystan-GM system[26] as the computer program and SIR92[27] as the structure solution method). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation, but these positions were not refined. Both enantiomorphous structures were refined with final disagreement factors $R_1 = 0.043$, $R_{1w} = 0.049$ and $R_2 = 0.046$, $R_{2w} = 0.051$ (with a weighting scheme $W = \exp(10 \sin^2 \theta/\lambda^2)/\sigma^2(F_o)$) for the two enantiomers, respectively. The correct absolute configuration was assigned to the enantiomer displaying the lower values of the disagreement factors. No peak above 0.14 e Å^{-3} in the last Fourier-difference map.

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(28) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.