Synthesis of Conformationally Restricted Analogs of Baclofen, a Potent $GABA_B$ Receptor Agonist, by the Introduction of a Cyclopropane Ring

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Conformationally restricted analogs of baclofen (2), *i.e.*, 5, 6, and their enantiomers *ent*-5, and *ent*-6 , the conformations of which were restricted by introducing a cyclopropane ring, were designed as potential $GABA_B$ receptor ligands. Reaction of (*R*)-epichlorohydrin [(*R*)-7] and (4-chlorophenyl)acetonitrile in the presence of $NaNH_2$ in benzene/tetrahydrofuran gave chiral cyclopropane derivatives 11 and 12, which were then converted into the target compounds 5 and 6, respectively. Their corresponding enantiomers, *ent*-5 and *ent*-6, were also synthesized starting from (*S*)-epichlorohydrin [(*S*)-7].

Key words γ-aminobutyric acid; conformationally restricted analog; baclofen; cyclopropane

γ-Aminobutyric acid (GABA, **1**) is an inhibitory neurotransmitter. Its two major receptor subtypes, $GABA_A$ and $GABA_B$ receptors, have been identified based on electrophysiological[1] and binding[2] studies. Although several specific agonists or antagonists at $GABA_A$ receptor sites have been developed,[3,4] 3-(4-chlorophenyl)-4-aminobutyric acid (baclofen, **2**)[5] is the only clinically useful selective $GABA_B$ agonists. Therefore, additional efficient $GABA_B$ receptor agonists and antagonists are eagerly awaited. Phaclofen (**3**)[6] and 2-hydroxy-saclofen (**4**)[7] have been reported to be selective $GABA_B$ antagonists *in vitro*. However, these have not been used to investigate the pharmacology of $GABA_B$ antagonists *in vivo*, perhaps due to their inability to penetrate the blood brain barrier.[8,9]

Conformationally restricted analogs of a lead compound often improve the specific binding affinity for the receptor.[10] Conformationally restricted analogs have usually been designed and synthesized by introducing cyclic moieties, which are often rather bulky, into lead compounds. As a consequence, their chemical and physical properties are often changed. From this perspective, restricting the conformation of a key functional group by introducing a small cyclopropane ring should be effective. For instance, Ohfune and co-workers have developed useful probes for excitatory amino acid receptors by restricting the conformation of glutamate by introducing a cyclopropane structure into the molecule.[11] We also recently developed potent *N*-methyl-D-aspartic acid (NMDA) receptor antagonists by a novel conformation-restricting method based on the structural feature of a cyclopropane ring.[12]

In the present study, we designed conformationally restricted analogs of (*R*)- and (*S*)-baclofen, *i.e.*, **5**, **6**, and their enantiomers *ent*-**5**, and *ent*-**6**, as shown in Chart 1, to identify efficient agonists and/or antagonists for the $GABA_B$ receptor. The conformations of these compounds are locked into folded or extended forms by introducing a cyclopropane structure to the molecule.[13] In this report, we describe the synthesis and binding affinity of these conformationally restricted analogs to $GABA_B$ receptor.

Chemistry The synthesis of optically active cyclopropane derivatives has been extensively studied in recent years because of their biological importance.[14] We recently reported the efficient synthesis of optically active phenylcyclopropane lactones, starting from chiral epichlorohydrins.[12a—c] This procedure using (*R*)- or (*S*)-epichlorohydrin as a synthon is one of the most useful methods for preparing chiral cyclopropanes; phenylcyclopropane products of high optical purity can be obtained on a large scale from chiral epichlorohydrins, which are stable and readily available in high optical purity. In this reaction, the carbon nucleophile attacks with high regioselectively at the 3-position of epichlorohydrin, and (1*S*,2*R*)-lactone **10** is obtained from (*R*)-**7** while the corresponding enantiomer, (1*R*,2*S*)-lactone *ent*-**10**, is obtained from (*S*)-**7** (Chart 2). We planned to synthesize the target compounds in this study by using this reaction from chiral epichlorohydrins.

We investigated the reaction of (*R*)-**7** and a carbanion derived from (4-chlorophenyl)acetonitrile under various conditions. The best results were obtained when the reaction was carried out with $NaNH_2$ as a base in benzene/tetrahydrofuran (THF) at room temperature; (1*S*,2*R*)-lactone **11** with 93% e.e.[15] was isolated in 68% yield after alkaline hydrolysis of the nitrile group followed by treatment with HCl (Chart 3). In this reaction, the corresponding *trans*-product **12** was also obtained as a minor product.[16]

Ammonolysis of **11** with NH_3/MeOH followed by reduction of the resulting amide with $BH_3 \cdot THF$ gave aminoalcohol **15**. After the amino function was protected with a *tert*-butyloxycarbonyl (Boc) group, it was oxidized with pyridinium dichromate (PDC) in the presence of 4A molecular sieves to give lactam **17**. Following removal of the Boc group with trifluoroacetic acid (TFA), the resulting *N*-free lactam was heated under reflux in HCl to give the conformationally restricted analog **5** as a hydrochloride.

The scheme for preparing the *trans*-analog **6** is shown in Chart 4. Successive treatment of crude **12** with Ac_2O in pyridine, $ClCO_2Oiso\text{-}Bu$, and NH_3 in $CHCl_3$ gave *trans*-acetate **18** in a pure form in 10% yield from (*R*)-**7**. After the acetyl group of **18** was removed, it was converted into the target conformationally restricted analog **6**[17] by a procedure similar to that for synthesizing the *cis*-analog **5** described above.

The corresponding enantiomers, *ent*-**5**, and *ent*-**6** were also

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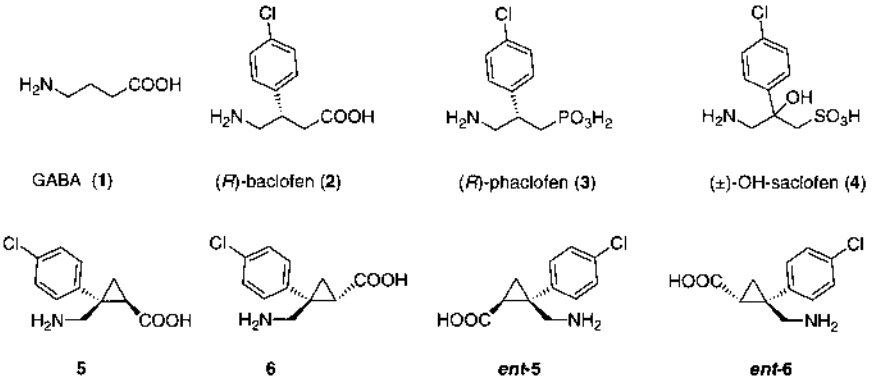

Chart 1

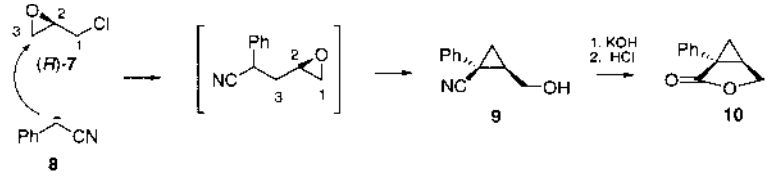

Chart 2

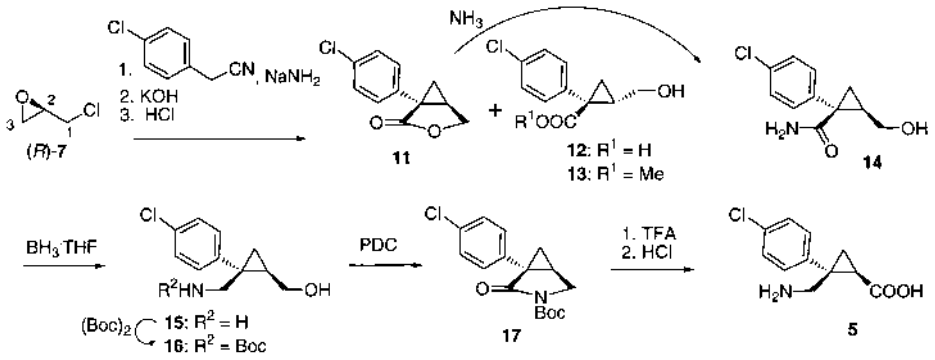

Chart 3

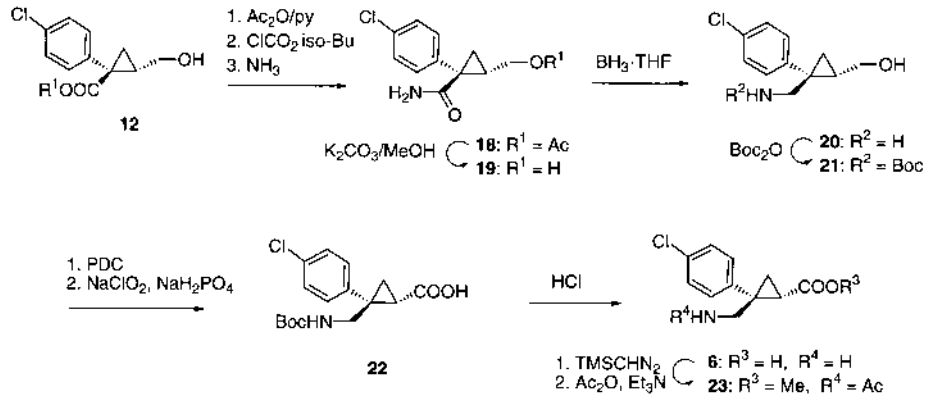

Chart 4

synthesized starting from (+)-epichlorohydrin [(*S*)-**5**].

Effect on Brain $GABA_B$ Receptors The binding of these compounds to $GABA_B$ receptor in rat brain was measured in the presence of isoguvacine (40 μM) to block $GABA_A$ receptors.[18] None of the four conformationally restricted analogs of baclofen synthesized in this study significantly competed with [^{3}H]GABA for $GABA_B$ receptors at concentrations of 10 nM to 100 μM in crude synaptic membranes of rat brain. In the same experiment, (±)-baclofen (10 nM—10 μM), (*R*)-baclofen (10 nM—10 μM) and (*S*)-baclofen (10 μM—1 mM) competed with [^{3}H]GABA for brain $GABA_B$ receptors in a concentration-dependent manner, and their IC_{50} values

(mean±S.E., $n=3$) to displace 50% of control specific binding were 0.36±0.16, 0.30±0.12, and 526±68 μM, respectively.

These results suggest that the three-dimensional structures of compounds **5**, **6**, *ent*-**5**, and *ent*-**6** may be different from the conformation of baclofen at the binding site of $GABA_B$ receptor.

Experimental

Melting points were measured on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. NMR spectra were recorded with a JEOL FX-270, a GSX-400, or a Bruker ARX-500 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded with a JEOL JMS-HX110 spectrometer. Chemical shifts are reported in parts per million (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), m (multiplet), or br (broad), and coupling constants are indicated in Hz. Thin-layer chromatography was done on Merck precoated plates $60F_{254}$. Chromatography was conducted with Merck Silica gel 9025. Reactions were done under argon.

(1*S*,5*R*)-1-(4-Chlorophenyl)-3-oxabicyclo[3.1.0]hexan-2-one (11) and (1*S*,2*S*)-1-(4-Chlorophenyl)-2-hydroxymethylcyclopropanecarboxylic Acid (12) A solution of (4-chlorophenyl)acetonitrile (25.0 g, 323 mmol) in benzene/THF (10 : 1. 200 ml) was added slowly to a suspension of $NaNH_2$ (25.8 g, 660 mmol) in benzene/THF (10 : 1. 1.25 l) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the resulting mixture, a solution of (*R*)-epichlorohydrin [(*R*)-**7**, 25.3 ml, 323 mmol] in benzene/THF (10 : 1. 200 ml) was added at 0 °C, and the whole was stirred at room temperature for 3 h. After EtOH (100 ml) was added, the solvent was evaporated. EtOH (200 ml) and 3 N KOH (70 ml) were added to the residue, and the mixture was heated under reflux for 12 h and then acidified with 12 N HCl at 0 °C (pH of the mixture was about 1). The resulting mixture was evaporated, and EtOAc and saturated aqueous $NaHCO_3$ were added and partitioned. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; hexane/EtOAc, 5 : 2 then hexane/EtOAc/AcOH, 50 : 50 : 1) to give **11** (oil, 45.9 g, 68%) and crude **12** (oil, 10.2 g), the structure of which was confirmed as below. **11**: The optical purity was determined by a chiral HPLC (Chiralcel-OJ, 0.46×25 cm, Daicel Chemical Industries Co., Ltd.; hexane/iso-PrOH, 7 : 3, 0.4 ml/min; 230 nm): 93% e.e. $[\alpha]_D^{29}=-64.8°$ ($c=1.13$, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) 1.38 (1H, dd, $J=4.6$, 4.6 Hz), 1.60 (1H, dd, $J=4.6$, 7.7 Hz), 2.56 (1H, ddd, $J=4.6$, 4.6, 7.7 Hz), 4.29 (1H, d, $J=9.3$ Hz), 4.46 (1H, dd, $J=4.6$, 9.3 Hz), 7.31 (2H, d, $J=8.8$ Hz), 7.37 (2H, d, $J=8.9$ Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 20.46 (CH_2), 25.17 (CH), 31.18 (C), 68.06 (CH_2), 128.79 (CH), 129.67 (CH), 132.75 (C), 133.63 (C), 175.61 (C). MS (EI) *m/z*: 208 (M^+, 100%). High resolution (HR)-EI-MS *m/z*: 208.0308 (Calcd for $C_{11}H_9ClO_2$: 208.091). *Anal*. Calcd for $C_{11}H_9ClO_2$: C, 63.32; H, 4.35; Cl, 16.99. Found: C, 63.51; H, 4.55; Cl, 16.94.

(1*S*,2*R*)-1-(4-Chlorophenyl)-2-hydroxymethylcyclopropane Carboxamide (14) Ammonia gas was bubbled into a solution of **11** (44.9 g, 215 mmol) in MeOH (1000 ml) at −78 °C for 20 min. After the resulting solution was allowed to warm to room temperature, the solvent was evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 10 : 1) to give **14** (white solids, 39.6 g, 82%): mp 123—124 °C ($CHCl_3$/Et_2O). $[\alpha]_D^{25}=+118.8°$ ($c=1.04$, MeOH). ^{1}H-NMR (270 MHz, $CDCl_3$) 1.30 (1H, dd, $J=4.2$, 8.9 Hz), 1.72—1.88 (2H, m), 2.29 (1H, dd, $J=6.2$, 6.3 Hz), 3.77—3.87 (1H, m), 4.13—4.05 (1H, m), 5.47 (1H, br s), 5.74 (1H, br s), 7.29—7.43 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 18.36 (CH_2), 31.22 (CH), 34.65 (C), 60.54 (CH_2), 129.30 (CH), 131.56 (CH), 133.99 (C), 139.24 (C), 175.11 (C). MS (EI) *m/z*: 225 (M^+, 95 %). HR-EI-MS *m/z*: 225.0535 (Calcd for $C_{11}H_{12}ClNO_2$: 225.0556). *Anal*. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.55; H, 5.36; N, 6.21. Found: C, 58.51; H, 5.38; N, 6.18.

(1*R*,2*S*)-2-Aminomethyl-2-(4-chlorophenyl)cyclopropylmethanol (15) A solution of BH_3·THF (1.03 M in THF, 400 ml, 412 mmol) was added slowly to a solution of **14** (39.6 g, 176 mmol) in THF (900 ml) at 0 °C, and then the mixture was heated under reflux for 7 h. After the mixture was cooled to room temperature, MeOH (100 ml) was added, and the solvent was evaporated. EtOAc and 3 N HCl were added to the residue and partitioned. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH/28% NH_4OH, 100 : 10 : 1) to give **15** (oil, 28.0 g, 75%): $[\alpha]_D^{26}=-69.3°$ ($c=0.996$, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) 0.85 (1H, dd, $J=4.8$, 4.8 Hz), 1.04 (1H, dd, $J=4.8$, 8.7 Hz), 1.77—1.84 (1H, m), 2.56 (2H, br s), 2.73 (1H, d, $J=12.6$ Hz), 3.39 (1H, dd, $J=11.3$, 11.8 Hz), 3.52 (1H, d, $J=12.6$ Hz), 3.56 (1H, s), 4.21 (1H, dd, $J=5.4$, 11.8 Hz), 7.36 (2H, d, $J=8.8$ Hz), 7.42 (2H, d, $J=8.7$ Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 18.19 (CH_2), 25.32 (CH), 31.00 (C), 46.35 (CH_2), 63.11 (CH_2), 128.72 (CH), 131.05 (CH), 132.68 (C), 142.32 (C). MS (FAB) *m/z*: 212 (MH^+, 98%). HR-FAB-MS *m/z*: 212.0846 (Calcd for $C_{11}H_{15}ClNO$: 212.0842). *Anal*. Calcd for $C_{11}H_{14}ClNO\cdot 1/3H_2O$: C, 60.69; H, 6.79; N, 6.43. Found: C, 60.93; H, 6.55; N, 6.33.

***tert*-Butyl [(1*S*,2*R*)-1-(4-Chlorophenyl)-2-hydroxymethylcyclopropyl]-methylcarbamate (16)** A solution of **15** (1.06 g, 5.0 mmol) and di-*tert*-Bu dicarbonate (Boc_2O, 1.40 ml, 6.0 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 4 h. After water (50 ml) was added, the resulting mixture was partitioned. The organic layer separated was washed with brine, dried (Na_2SO_4), evaporated, and purified by column chromatography (silica gel; $CHCl_3$/MeOH, 10 : 1) to give **16** (oil, 1.41 g, 90%): $[\alpha]_D^{23}=+36.7°$ ($c=1.14$, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) 0.58 (1H, dd, $J=4.8$, 5.4 Hz), 0.96 (1H, dd, $J=4.8$, 8.9 Hz), 1.38 (9H, s), 1.53—1.63 (1H, m), 3.25—3.33 (1H, m), 3.45—3.55 (2H, m), 4.08—4.16 (2H, m), 4.79 (1H, br s), 7.23—7.33 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 14.76 (CH_2), 27.04 (CH), 28.39 (CH_3), 28.41 (C), 44.07 (CH_2), 62.18 (CH_2), 79.84 (C), 128.58 (CH), 131.13 (CH), 132.59 (C), 142.34 (C). MS (EI) *m/z*: 311 (M^+, 0.03 %), 255 [(M−*tert*-Bu)$^+$, 8%]. *Anal.* Calcd for $C_{16}H_{22}ClNO_3$: C, 61.63; H, 7.11; Cl, 11.37; N, 4.49. Found: C, 61.47; H, 7.17; Cl, 11.18; N, 4.37.

(1*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-1-(4-chlorophenyl)-3-azabicyclo[3,1,0]hexan-2-one (17) A mixture of **16** (1.06 g, 3.4 mmol), PDC (2.56 g, 6.8 mmol), and molecular sieves 4Å (powder, 3.4 g) in CH_2Cl_2 (30 ml) was stirred at room temperature for 4 h. After Et_2O was added, the resulting mixture was filtered with Celite, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 10 : 1) to give **17** (white solids, 573 mg, 55%): mp 131—132 °C (Et_2O). $[\alpha]_D^{21}=-75.1°$ ($c=1.18$, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) 1.31 (1H, dd, $J=3.5$, 4.5 Hz), 1.52—1.57 (10H, m), 2.26 (1H, ddd, $J=1.2$, 3.5, 9.1 Hz), 3.91 (1H, d, $J=11.2$ Hz), 4.02 (1H, dd, $J=11.2$, 1.2 Hz), 7.19 (2H, d, $J=8.5$ Hz), 7.33 (2H, d, $J=8.5$ Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 19.67 (CH_2), 27.08 (C), 28.10 (CH_3), 29.05 (CH), 52.98 (CH_2), 83.17 (C), 129.14 (CH), 133.67 (C), 136.98 (C), 150.11 (C), 172.78(C). MS (EI) *m/z*: 307 (M^+, 2%), 251 [(M−*tert*-Bu)$^+$, 4%]. HR-EI-MS *m/z*: 307.0997 (Calcd for $C_{16}H_{18}ClNO_3$: 307.0975). *Anal.* Calcd for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; Cl, 11.52; N, 4.49. Found: C, 62.59; H, 5.98; Cl, 11.56; N, 4.62.

[(1*S*,2*R*)-2-Carboxy-1-(4-chlorophenyl)cyclopropylmethyl]ammonium Cloride (5) A mixture of **17** (154 mg, 0.50 mmol) and TFA (578 μl, 7.5 μmol) in CH_2Cl_2 (1.0 ml) was stirred at room temperature for 8 h. After the solvent was evaporated, $CHCl_3$ and saturated aqueous $NaHCO_3$ were added, and the resulting mixture was partitioned. The organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 12 : 1) to give yellow solids, which were heated in 6 N HCl (5 ml) under reflux for 17 h. The solvent was evaporated, and the residue was crystallized from EtOH to give **5** as a hydrochloride (white crystals, 83 mg, 63%): mp 184—186 °C. $[\alpha]_D^{25}=-34.1°$ ($c=0.985$, 1 N HCl). ^{1}H-NMR (500 MHz, CD_3OD) 1.46 (1H, dd, $J=5.2$, 5.7 Hz), 1.56 (1H, dd, $J=5.2$, 8.6 Hz), 2.60 (1H, dd, $J=5.7$, 8.6 Hz), 3.45 (1H, d, $J=13.5$ Hz), 3.53 (1H, d, $J=13.5$ Hz), 7.32 (2H, d, $J=8.5$ Hz), 7.35 (2H, d, $J=8.5$ Hz). ^{13}C-NMR (125 MHz, CD_3OD) 21.28 (CH_2), 28.10 (CH), 33.94 (C), 44.65 (CH_2), 131.26 (CH), 132.80 (CH), 135.99 (C), 140.37 (C), 175.42 (C). MS (FAB) *m/z*: 226 (MH^+, 8%). HR-FAB-MS *m/z*: 226.0649 (Calcd for $C_{11}H_{13}ClNO_2$: 226.0634). *Anal.* Calcd for $C_{11}H_{13}Cl_2NO_2\cdot 2/5H_2O$: C, 48.41; H, 5.24; N, 5.13. Found: C, 48.19; H, 4.83; N, 5.05.

Methyl (1*S*,2*S*)-1-(4-Chlorophenyl)-2-hydroxymethylcyclopropanecarboxylate (13) A mixture of **12** (113 mg, 0.50 mmol) and $TMSCHN_2$ (2 M in hexane, 0.30 ml. 0.60 mmol) in benzene (3 ml) and MeOH (2 ml) was stirred at room temperature for 18 h. After addition of AcOH (1 M in benzene, 100 μl), the solvent was evaporated. The residue was partitioned between EtOAc and water, and the organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; hexane/EtOAc, 2 : 1) to give **13** (oil, 63 mg, 67%): the optical purity was determined as 94% e.e. by a chiral HPLC (Chiralcel-OJ, 0.46×25 cm, Daicel Chemical Industries Co., Ltd.; hexane/iso-PrOH, 3 : 1, 0.5 ml/min; 230 nm). $[\alpha]_D^{26}=-7.69°$ ($c=0.586$, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) 1.22 (1H, dd, $J=4.5$, 6.7 Hz), 1.74 (1H, dd, $J=4.5$, 9.3 Hz), 2.24—2.13 (1H, m), 3.15 (1H, dd, $J=8.2$, 11.6 Hz), 3.49 (1H, s), 3.49 (1H, dd, $J=5.7$, 11.6 Hz), 3.63 (3H, s), 7.23—7.45 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 18.59 (CH_2), 29.90 (CH), 33.31 (C), 52.58 (CH_3), 60.27 (CH_2), 128.42 (CH), 132.63 (CH), 133.45 (C), 134.09 (C), 174.07 (C). MS (EI) *m/z*: 240 (M^+, 69%). HR-EI-MS *m/z*: 240.0542 (Calcd for $C_{12}H_{13}ClO_3$:

240.0553. *Anal*. Calcd for $C_{12}H_{13}ClO_3 \cdot 1/3H_2O$: C, 58.43; H, 5.58. Found: C, 58.51; H, 5.37.

(1*S*,2*S*)-2-Acetoxymethyl-1-(4-chlorophenyl)cyclopropanecarboxamide (18) A mixture of crude **12** (10.2 g, obtained from 323 mmol of (*R*)-**7**) and Ac_2O (5.1 ml, 54 mmol) in pyridine (300 ml) was stirred at room temperature for 19 h. After MeOH was added, the solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 15 : 1) to give yellow oil. The oil was dissolved in $CHCl_3$ (300 ml), to which $ClCO_2$iso-Bu (7.0 ml, 54 mmol) and Et_3N (9.4 ml, 68 mmol) were added at −15 °C, and the resulting solution was stirred at the same temperature for 2 h. NH_3 gas was bubbled into the resulting solution at −15 °C for 10 min, and then the mixture was allowed to warm to room temperature. After water was added, the mixture was partitioned, and the organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; hexane/EtOAc, 1 : 1) to give **18** (yellow solid, 9.3 g, 10% from (*R*)-**7**): mp 115—117 °C ($CHCl_3$). $[\alpha]_D^{23} = +18.1°$ (c=0.772, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 1.25 (1H, dd, J=4.3, 6.6 Hz), 1.74 (1H, dd, J=4.3, 9.3 Hz), 2.30—2.36 (1H, m), 3.48 (1H, dd, J=8.4, 12.0 Hz), 3.96 (1H, dd, J=6.0, 12.0 Hz), 5.25 (1H, br s), 5.45 (1H, br s), 7.34 (2H, d, J=8.5 Hz), 7.38 (2H, d, J=8.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 18.97 (CH_2), 20.85 (CH_3), 24.72 (CH), 34.32 (C), 64.23 (CH_2), 129.44 (CH), 132.79 (CH), 134.22 (C), 134.56 (C), 170.67 (C), 175.08 (C). MS (EI) *m*/*z*: 267 (M^+, 6%). HR-EI-MS *m*/*z*: 267.0665 (Calcd for $C_{13}H_{14}ClNO_3$: 267.0661). *Anal.* Calcd for $C_{13}H_{14}ClNO_3$: C, 58.32; H, 5.27; Cl, 13.24; N, 5.23. Found: C, 58.30; H, 5.29; Cl, 13.39; N, 5.21.

(1*S*,2*S*)-1-(4-Chlorophenyl)-2-hydroxymethylcyclopropanecarboxamide (19) A mixture of **18** (9.3 g, 32 mmol) and K_2CO_3 (5.7 g, 54 mmol) in MeOH (80 ml) was stirred at room temperature for 5 h. After neutralization with aqueous $KHSO_4$ (1 M), $CHCl_3$ and saturated aqueous $NaHCO_3$ were added to the resulting mixture, and then the whole was partitioned. The organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 12 : 1) to give **19** (yellow foam, 7.2 g, 99%): $[\alpha]_D^{28} = -5.30°$ (c=1.29, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 1.06 (1H, dd, J=4.1, 6.7 Hz), 1.64 (1H, s), 1.69 (1H, dd, J=4.1, 9.2 Hz), 2.23—2.28 (1H, m), 3.15 (1H, m), 3.52 (1H, dd, J=5.4, 11.4 Hz), 5.25 (1H, br s), 5.52 (1H, br s), 7.38 (2H, d, J=8.5 Hz), 7.41 (2H, d, J=8.4 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 18.87 (CH_2), 28.70 (CH), 34.45 (C), 62.39 (CH_2), 129.36 (CH), 132.97 (CH), 134.26 (C), 134.74 (C), 175.92 (C). MS (EI) *m*/*z*: 225 (M^+, 100%). HR-EI-MS *m*/*z*: 225.0585 (Calcd for $C_{11}H_{12}ClNO_2$ 225.0556).

(1*S*,2*S*)-2-Aminomethyl-2-(4-chlorophenyl)cyclopropylmethanol (20) Compound **20** (white solid, 4.7 g, 69%) was obtained from **19** (7.2 g, 32 mmol) as described above for synthesizing **15**: $[\alpha]_D^{26} = -20.9°$ (c=0.259, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.72 (1H, dd, J=5.1, 5.1 Hz), 0.92 (1H, dd, J=5.1, 8.7 Hz), 1.32—1.34 (1H, m), 2.58 (1H, d, J=13.2 Hz), 2.83 (1H, d, J=13.2 Hz), 2.99 (1H, s), 3.06 (1H, dd, J=8.4, 11.2 Hz), 3.34 (1H, dd, J=6.0, 11.2 Hz), 3.39 (2H, br s), 7.28 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 14.15 (CH_2), 25.38 (CH), 33.48 (C), 52.13 (CH_2), 62.82 (CH_2), 128.68 (CH), 131.89 (CH), 132.83 (C), 137.72 (C). MS (FAB) *m*/*z*: 212 (MH^+, 20%). HR-FAB-MS *m*/*z*: 212.0852 (Calcd for $C_{11}H_{15}ClNO$ 212.0842). *Anal*. Calcd for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.02; H, 6.64; N, 6.25.

***tert*-Butyl [(1*S*,2*S*)-1-(4-Chlorophenyl)-2-hydroxymethylcyclopropyl]-methylcarbamate (21)** Compound **21** (oil, 583 mg, 75%) was obtained from **20** (529 mg, 2.5 mmol), as described above for synthesizing **16**: $[\alpha]_D^{25} = -8.65°$ (c=1.01, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) 0.78 (1H, dd, J=5.3, 5.2 Hz), 1.02 (1H, m), 1.34—1.44 (10H, m), 1.73 (1H, br s), 3.10—3.17 (2H, m), 3.34—3.42 (2H, m), 4.58 (1H, br s), 7.25—7.33 (4H, m). ^{13}C-NMR (125 MHz, $CDCl_3$) 13.78 (CH_2), 25.16 (CH), 28.38 (CH_3), 31.40 (C), 50.23 (CH_2), 63.34 (CH_2), 79.39 (C), 128.76 (CH), 131.71 (CH), 132.98 (C), 137.82 (C), 156.49 (C). MS (EI) *m*/*z*: 311 (M^+, 0.1%), 255 [(M−*tert*-Bu)$^+$, 12%]. HR-EI-MS *m*/*z*: 255.0666 (Calcd for $C_{12}H_{14}ClNO_3$ 255.0661). *Anal*. Calcd for $C_{16}H_{22}ClNO_3$: C, 61.63; H, 7.11; Cl, 11.37; N, 4.49. Found: C, 61.22; H, 7.10; Cl, 11.33; N, 4.35.

(1*S*,2*S*)-2-(4-Chlorophenyl)-2-[*N*-(*tert*-butoxycarbonyl]aminomethyl]-cyclopropanecarboxylic Acid (22) A mixture of **21** (529 mg, 1,7 mmol), PDC (1.28 g, 3.4 mmol), and molecular sieves 4Å (powder, 1.7 g) in CH_2Cl_2 (17 ml) was stirred at room temperature for 3 h. After Et_2O was added, the resulting mixture was filtered with Celite, and the filtrate was evaporated. To the residue, $NaClO_2$ (561 mg, 6.0 mmol), NaH_2PO_4 (296 mg, 1.7 mmol), water (3.4 ml), and acetone (13.6 ml) were added, and the mixture was stirred at room temperature for 9.5 h. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ and water. The organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 5 : 1) to give **22** (foam, 208 mg, 64%): ^{1}H-NMR (270 MHz, $CDCl_3$) 1.39—1.47 (10H, m), 1.57—1.63 (1H, m), 2.02—2.07 (1H, m), 3.17 (1H, dd, J=6.7, 13.4 Hz), 3.41 (1H, dd, J=4.9, 13.4 Hz), 4.52 (1H, br s), 7.17 (2H, d, J=8.0 Hz), 7.27 (2H, d, J=7.4 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) 17.77 (CH_2), 25.22 (CH), 28.35 (CH_3), 36.54 (C), 49.59 (CH_2), 79.82 (C), 128.69 (CH), 131.05 (CH), 133.25 (C), 136.56 (C), 155.95 (C), 176.22 (C). MS (FAB) *m*/*z*: 326 (MH^+, 2%), 270 [(MH−*tert*-Bu)$^+$, 7%)]. HR-FAB-MS *m*/*z*: 326.1131 (Calcd for $C_{16}H_{21}ClNO_4$ 326.1131).

[(1*S*,2*S*)-2-Carboxy-1-(4-chlorophenyl)cyclopropylmethyl]ammonium Cloride (6) HCl gas was bubbled into a solution of **22** (230 mg, 0.71 mmol) at room temperature for 10 min, and the resulting solution was stirred at room temperature for 22 h. The solvent was evaporated to give **2** as a hydrochloride (foam, 157 mg, quant.): ^{1}H-NMR (500 MHz, CD_3OD) 1.47 (1H, dd, J=5.4, 8.2 Hz), 1.84 (1H, dd, J=5.4, 5.6 Hz), 2.25 (1H, dd, J=5.6, 8.2 Hz), 2.85 (1H, d, J=13.1 Hz), 3.57 (1H, d, J=13.1 Hz), 7.40 (2H, d, J=8.5 Hz), 7.40 (2H, d, J=8.6 Hz). MS (FAB) *m*/*z*: 225 (M^+, 9%). HR-FAB-MS *m*/*z*: 225.0530 (Calcd for $C_{11}H_{12}ClNO_2$ 225.0556).

Methyl (1*S*,2*S*)-2-Acetylaminomethyl-2-(4-chlorophenyl)cyclopropanecarboxylate (23) A mixture of **6** (hydrochloride, 52 mg, 0.23 mmol) and trimethylsilyldiazomethane ($TMSCHN_2$, 2 M in hexane, 0.11 ml, 0.22 mmol) in benzene (1.2 ml) and MeOH (0.8 ml) was stirred at room temperature for 1.5 h. After AcOH (1 M in benzene, 20 μl) was added, the solvent was evaporated. A mixture of the residue, Ac_2O (23 μl, 0.24 mmol), and Et_3N (84 μl, 0.60 mmol) in MeCN (2 ml) was stirred at room temperature for 1.5 h. After MeOH (1 ml) was added, the solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer separated was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; $CHCl_3$/MeOH, 15 : 1) to give **23** (foam, 27 mg, 43%): $[\alpha]_D^{25} = -8.55°$ (c=0.230, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$) 1.43 (1H, dd, J=5.1, 8.3 Hz), 1.68 (1H, dd, J=5.2, 5.3 Hz), 1.92 (3H, s), 2.13 (1H, dd, J=5.4, 8.3 Hz), 3.35 (1H, d, J=13.9 Hz), 3.47 (3H, s), 3.51 (1H, d, J=13.9 Hz), 5.30 (1H, br s), 7.1 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=8.5 Hz). MS (EI) *m*/*z*: 281 (M^+, 6%). HR-EI-MS *m*/*z*: 281.0815 (Calcd for $C_{14}H_{16}ClNO_3$). *Anal.* Calcd for $C_{14}H_{16}ClNO_3 \cdot 1/2H_2O$: C, 57.84; H, 5.89; N, 4.82. Found: C, 57.65; H, 5.85; N, 4.97.

$GABA_B$ Receptor Binding Assay $GABA_B$ receptor binding assay using crude synaptic membrane (P_2) fraction from rat brain was performed according to the method of Ohmori *et al*.[18] Briefly, crude synaptic membrane (P_2) (approximately 300 μg protein) from rat brain was incubated with 5 nM [^{3}H]GABA (1.4 TBq/mmol, DuPont-NEN Co. Ltd., Boston, MA) in a total volume of 1 ml in 50 mM Tris–HCl buffer (containing 5 mM $CaCl_2$ and 0.5 mM $MgSO_4$, pH 7.4) for 30 min at 4 °C in the presence of isoguvacine (40 μM) to block $GABA_A$ receptors. The reaction was terminated by rapid filtration under a vacuum through Whatman GF/B glass filters. Filters were immediately washed three times with 3 ml of ice-cold buffer. Tissue-bound radioactivity was extracted from the filters overnight in 3 ml of a scintillation fluid (2 l of toluene, 1 l of Triton X-100, 15 g of 2,5-diphenyloxazole and 0.3 g of 1,4-bis[2-(5-phenyloxazolyl)]benzene), and the radioactivity was determined by a liquid scintillation counter. Specific binding of [^{3}H]GABA was determined experimentally from the difference between counts in the absence and presence of (−)-baclofen (100 μM). All assays were conducted in duplicate.

References and Notes

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15) (1*S*,2*R*)-lactone **11** is obtained from (*R*)-epichlorohydrin [(*R*)-**7**], since carbon nucleophiles attack the epoxide terminal of (*R*)-**7** highly selectively (see ref. 12*a*), and the enantiomeric purity of **11** was measured by HPLC with a Chiralcel-OJ column (Daisel Chemical Co., Ltd.).
16) Compound **12** was not isolated at this stage, but was obtained in a pure form after its conversion into acetate **18**.
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