JOC Article

Construction of a *cis*-Cyclopropane via Reductive Radical Decarboxylation. Enantioselective Synthesis of *cis*- and *trans*-1-Arylpiperazyl-2-phenylcyclopropanes Designed as Antidopaminergic Agents

Kazuya Yamaguchi, Yuji Kazuta, Hiroshi Abe, Akira Matsuda, and Satoshi Shuto*

Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

shu@pharm.hokudai.ac.jp

Received July 8, 2003

(1*S*,2*S*)-, (1*S*,2*R*)-, and (1*R*,2*S*)-1-(2,4-Dimethylphenyl)piperazyl-2-phenylcyclopropane (**2a**, **3**, and ***ent*-3**, respectively), which were designed as conformationally restricted analogues of haloperidol (**1**), a clinically effective antipsychotic agent, were synthesized from chiral epichlorohydrins using the Barton reductive radical decarboxylation as the key step. (1*S*,2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-methyl-2-carboxy-2-phenylcyclopropane (**5**), which was prepared from (*S*)-epichlorohydrin ((*S*)-**7**), was converted into its *N*-hydroxypyridine-2-thione ester **12**, the substrate for the reductive radical decarboxylation. When **12** was treated with TMS_3SiH in the presence of Et_3B or AIBN, the decarboxylation and subsequent hydride attack on the cyclopropyl radical intermediate from the side opposite to the bulky silyloxymethyl moiety occurred, resulting in selective formation of the corresponding reductive decarboxylation product ***4-cis*** with the *cis*-cyclopropane structure. From ***4-cis***, the *cis*-cyclopropane-type target compound **3** was readily synthesized. Starting from (*R*)-epichlorohydrin ((*R*)-**7**), ***ent*-3** was similarly synthesized. Epimerization of the cyclopropanecarboxamide ***ent*-16-*cis***, a synthetic intermediate for ***ent*-3**, on treatment with a base prepared from Bu_2Mg and *i*-Pr_2NH in THF occurred effectively to give the corresponding trans isomer ***16-trans***, which was converted into **2a** with the *trans*-cyclopropane structure.

Introduction

The binding affinity of biologically active compounds for the target molecule can be improved by the conformational restriction as a result of reducing the entropic loss upon binding. In the design of conformationally restricted analogues, it is essential that the analogues are as similar as possible to the parent compound in size, shape, and molecular weight.[1] Because of its characteristic small rigid carbocyclic structural feature, a cyclopropane ring is effective in restricting the conformation of a molecule without significantly changing the chemical and physical properties of the lead compounds.[2,3] Thus, cyclopropanes have already been successfully used to restrict the bioactive conformations of a variety of compounds having pharmacological activity.[2,3,4]

Haloperidol (**1**, Figure 1) is a clinically effective antipsychotic agent, and the pharmacological effect is considered to be due to the antagonism of dopaminergic receptors.[5] One drawback is the side effects from its affinity for other receptors, particularly adrenergic receptors,[5,6] which may be attributed to its conformationally flexible structure. Recently, Thurkauf and co-workers designed and synthesized the arylpiperazine derivatives **2a** and **2b**, which have a *trans*-cyclopropane structure, and identified them as potent dopamine receptor antagonists with reduced adrenergic α_1 receptor affinity.[6] These compounds can be considered as conformationally re-

* Author to whom correspondence may be addressed. Phone: +81-11-706-3229. Fax: +81-11-706-4980.

(1) (a) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, 1992. (b) *Drug Design for Neuroscience*; Kozikowski, A., Ed.; Raven Press: New York, 1993. (c) *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: San Diego, 1996.

(2) For examples, see: (a) Shimamoto, K.; Ofune, Y. *J. Med. Chem.* **1996**, *39*, 407−423. (b) Armstrong, D. P.; Cannon J. G. *J. Med. Chem.* **1970**, *13*, 1037−1039. (c) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305−1318. (d) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284−1298.

(3) (a) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669−1677. (b) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.*, **2003**, *46*, 1980−1988, and references therein.

(4) A new method for restricting the conformation of cyclopropane derivatives based on the fact that adjacent substituents on the ring exert significant mutual steric repulsion because of their eclipsed conformation to each other was devised by us: (a) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamashita, K.; Matsuda, A. *J. Org. Chem.* **1996**, *61*, 915−923. (b) Shuto, S.; Ono, S.; Hase, Y.; Ueno, Y.; Noguchi, T.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1996**, 39, 4844−4852. (c) Shuto, S.; Ono, S.; Imoto, H.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1998**, *41*, 3507−3514. (d) Shuto, S.; Yoshii, K.; Matsuda, A. *Jpn. J. Pharmacol.* **2001**, 85, 207−213.

(5) (a) *The Dopamine Receptors*; Neve, K. A., Neve, R. L., Eds.; Humana Press: Totowa, NJ, 1997. (b) Sibley, D. R.; Monsma, F. J., Jr. *Trends Pharmacol. Sci.* **1992**, *13*, 61−69.

(6) Zhang, X.; Hodgetts, K.; Rachwal, S.; Zhao, H.; Wasley, J. W. F.; Craven, K.; Brodbeck, R.; Kieltyka, A.; Hoffman, D.; Bacolod, M. D.; Girard, B.; Tran, J.; Thurkauf, A. *J. Med. Chem.* **2000**, *43*, 3923−3932.

10.1021/jo0302206 CCC: $25.00
Published on Web 11/06/2003

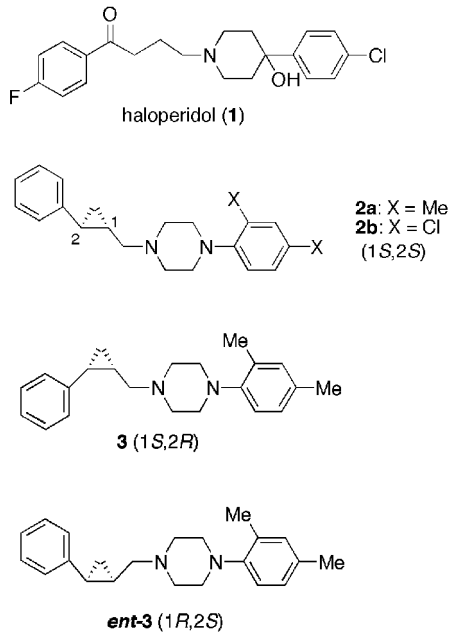


FIGURE 1. Haloperidol (**1**) and its cyclopropane-based conformationally restricted analogues.

stricted analogues of haloperidol, in which the three-dimensional positioning of the two aromatic and basic piperazine rings is restricted by the *trans*-cyclopropane structure.

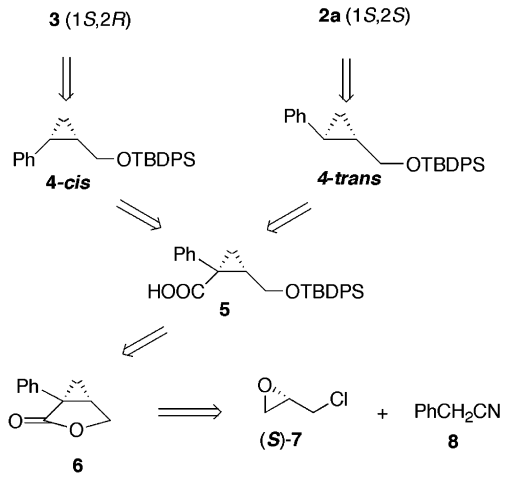
We are interested in the pharmacological effect of the corresponding *cis*-cyclopropane congener **3** and its enantiomer ***ent*-3** (Figure 1), in which the three rings are conformationally restricted differently from those in **2a** and **2b**. In this paper, we describe the synthesis of these conformationally restricted analogues **3** and ***ent*-3** having the *cis*-cyclopropane structure from chiral epichlorohydrins, using the Barton reductive decarboxylation as the key step to construct the *cis*-cyclopropane structure. An alternative synthesis of the potent antipsychotic agent **2a** having the *trans*-cyclopropane ring from an intermediate for the synthesis of ***ent*-3** has also been accomplished.

Results and Discussion

Synthetic Plan. Considerable effort has been devoted to developing efficient methods for preparing cyclopropane derivatives because of their chemical and medicinal chemical importance.[2−4,7−11] Optical resolution of racemic cyclopropane derivatives is one such method for providing chiral cyclopropanes.[9] In fact, Thurkauf and co-workers synthesized **2a** and **2b** via optical resolution of a racemic cyclopropane intermediate with a chiral amine.[6]

In recent years, we have been working to develop a stereoselective synthesis of chiral cyclopropane derivatives.[3,4,11] Throughout these studies, we have shown that (*R*)- and (*S*)-epichlorohydrins, which are commercially available in high optical purity, are efficient synthons for preparing the asymmetric cyclopropane structures.[3,4] On the basis of these findings, we planned to synthesize the target compounds starting from chiral epichlorohydrins.

SCHEME 1



Our synthetic plan for the *cis*-cyclopropane compound **3** with the (1*S*,2*R*) configuration and its trans congener **2a** with the (1*S*,2*S*) configuration is summarized in Scheme 1. The compounds ***4-cis*** and ***4-trans*** were considered effective precursors for the target compounds **3** and **2a**, respectively. The key point in the synthesis is the stereoselective construction of the chiral *cis*- and *trans*-cyclopropane structures. Cyclic radicals can only exist in a reduced number of conformations relative to acyclic ones, and stereochemistry of the radical reactions of cyclic systems, including cyclopropropnes, has been extensively investigated. These studies make prediction of the stereochemical results possible and were nicely documented by Curran et al.[12] Thus, construction of the *cis*- and *trans*-cyclopropanes by radical reaction was planned. We anticipated that both ***4-cis*** and ***4-trans*** might be stereoselectively prepared by the Barton reductive decarboxylation[13,14] of the chiral phenylcyclopropane carboxylic acid **5** under radical conditions by employing

(7) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-Y.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198. (b) Stammer, S. H. *Tetrahedron* **1990**, *46*, 2231−2254. (c) *Small Ring Compounds in Organic Synthesis VI*; De Meijero, A, Ed.; Topic in Current Chemistry 207; Springer: Berlin, 1999.

(8) Reviews on the synthesis of chiral cyclopropanes: (a) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137−149. (b) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919−7946. (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050.

(9) For examples of synthesis of chiral cyclopropanes via chemical or enzymatic optical resolutions, see: (a) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073−2076. (b) Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K. E. *J. Org. Chem.* **1989**, *30*, 1793−1796. (c) Grandjean, D.; Chuche, P. P. J. *Tetrahedron* **1991**, *47*, 1215−1230. (d) Silva, C. B.-D.; Benkouider, A.; Pale, P. *Tetrahedron Lett.* **2000**, *41*, 3077−3081.

(10) For examples of synthesis of chiral cyclopropanes from chiral synthons, see: (a) Yamanoi, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 1181−1184. (b) Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1989**, *30*, 3803−3804. (c) Pirrung, M. C.; Dunlap, S. E.; Trinks, V. P. *Helv. Chim. Acta* **1989**, *72*, 1301−1310. (d) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97−103. (e) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638−6657. (f) Takemoto, Y.; Baba, Y.; Saha, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 3653−3656.

(11) Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511−3521.

(12) Curran, D. P.; Porter, N. D.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.

(13) (a) Barton, D. H. R.; Chen, C.; Wall, G. M. *Tetrahedron* **1991**, *47*, 6127−6138. (b) Barton, D. H. R.; Samadi, M.; *Tetrahedron* **1992**, *48*, 7083−7090.

(14) For the formation of a cyclopropyl radical by the Barton decarboxylation, see: Gawronska, K.; Gawronski, J.; Walborsky, H. M. *J. Org. Chem.* **1991**, *56*, 2193-2197.

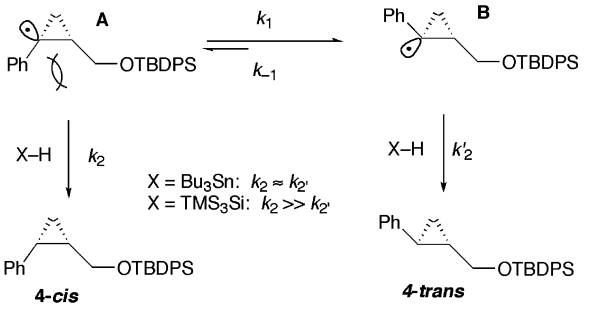


FIGURE 2. Possible reaction pathway for the hydrogen abstraction by the cyclopropyl σ radical generated via the radical decarboxylation of **12**.

the bulky *tert*-butyldiphenylsilyl (TBDPS) protecting group (see below). Compound **5** would be prepared from lactone **6** by functional group transformations. The chiral lactone **6** is readily prepared via condensation of (*S*)-epichlorohydrin (**7**) and phenylacetonitrile (**8**) under basic conditions.[4a] Starting from (*R*)-epichlorohydrin ((*R*)-**7**), ***ent*-3** would also be synthesized.

Cyclopropyl radicals are considered to be σ radicals in which the electron occupies a hybridized orbital.[15] Therefore, in the key Barton radical decarboxylation of **5**, the intermediate radical might be in equilibrium between the σ radicals **A** (cis) and **B** (trans), as shown in Figure 2, which could be isomerized faster than their hydrogen abstraction from a donor X−H, i.e., k_1, $k_{-1} \gg k_2$, k'_2.[15−17] Accordingly, the cis/trans ratio of the products would depend on the **A**/**B** equilibrium, when the rates of the hydrogen transfer from X−H (hydrogen donor) to both radicals **A** and **B** are similar, i.e., $k_2 \approx k'_2$. Because of the steric repulsion between the phenyl and bulky silyloxymethyl moiety, the cis radical **A** might be more unstable than the trans radical **B**, i.e., $k_1 > k_{-1}$.[16,17] Therefore, we expected that **4-*trans*** could be selectively obtained when an effective hydrogen donor, such as PhSH or Bu_3SnH,[17] was used. On the other hand, the hydrogen abstraction could proceed mainly via the cis radical **A** to give **4-*cis*** by using the sterically demanding TMS_3SiH as a donor[19] because the attack of TMS_3SiH on the trans radical **B** would be hampered due to the steric repulsion of the bulky silyloxymethyl group at the position cis to the radical. Thus, we expected that both **4-*cis*** and **4-*trans*** could be selectively obtained by changing the hydrogen donor in the radical reaction.

On the other hand, Boche and Walborsky previously described that delocalizing substituents, such as a carbomethoxy and a cyano group, attached to the radical site could convert the cyclopropyl σ radical to a π radical.[16a] Therefore, the intermediate radical produced from **5**, having the delocalizing phenyl group, might not be in equilibrium between the σ radicals **A** and **B** (Figure 2) but also might be a π radical, in which the electron occupies a p orbital, as shown in Figure 3a. In such a case, **4-*cis*** could be selectively obtained via the hydrogen abstraction from the sterically unhindered face, which can be explained by the antirule.[20]

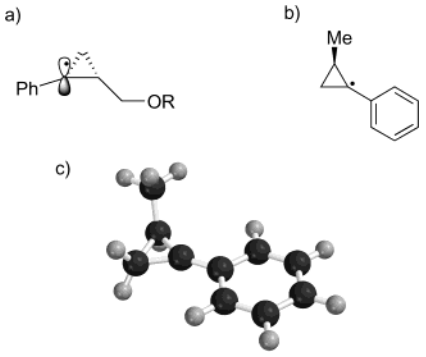
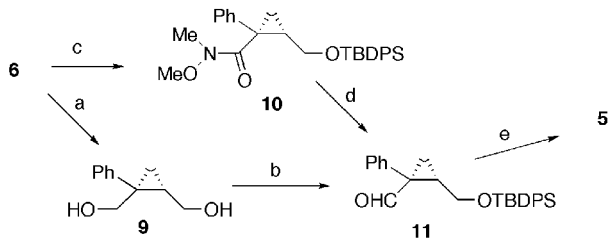


FIGURE 3. Possible cyclopropyl π radical generated by the radical decarboxylation of **12** (a), the model cyclopropyl radical for the calculations (b), and the calculated structure of the model radical (c).

SCHEME 2[a]



[a] Reagents: (a) $NaBH_4$, THF/MeOH, quant.; (b) (1) TBDSCl, imidazole, DMF, 54%, (2) Swern ox., 86%; and (c) Me(MeO)NH, $AlCl_3$, CH_2Cl_2, (2) TBDPSCl, imidazole, DMF, 94%; (d) DIBALH, CH_2Cl_2, 80%; (3) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 86%.

Synthesis of the *cis*-Cyclopropane Targets 3 and *ent*-3. The synthesis of the key intermediate **5** is summarized in Scheme 2. The chiral lactone **6** with 96% ee, prepared from (*S*)-epichlorohydrin ((*S*)-**7**) by our previous method,[4a] was reduced with $NaBH_4$ in THF/MeOH to give the diol **9**. Although treatment of **9** with TBDPSCl/imidazole in DMF at −20 °C and subsequent Swern oxidation gave the desired aldehyde **11**, the yield was low. When the lactone **6** was treated with Me(MeO)NH[21a] in the presence of $AlCl_3$ in CH_2Cl_2 followed by TBDPSCl/imidazole in DMF, the corresponding Weinreb amide **10** was obtained in 94% yield. The DIBALH reduction of the amide **10** by the method reported by Hollenberg[21b] provided the aldehyde **11** in excellent yield. Oxidation of **11** with a $NaClO_2/NaH_2PO_4$/2-methyl-2-butene system[22] gave the desired cyclopropanecarboxylic acid **5**.

The stereoselective radical decarboxylation was next examined. The carboxylic acid **5** was converted into the

(15) Cyclopropyl radicals have been shown to be a rapidly inverting bent σ radical: Johnson, L. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1986**, *108*, 2343−2348. (b) Zerbetto, F.; Zgiarski, M.; Siebrand, W. *J. Am. Chem. Soc.* **1989**, *111*, 2799−2802.

(16) (a) Boche, G.; Walborsky, H. M. In *Cyclopropane Derived Reactive Intermediates*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1990; pp 1−108. (b) Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625−1651.

(17) Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1994**, *116*, 10781−10782.

(18) Chatgilialoglu, C. T. In *Radicals in Organic Synthesis*; Renaud, P., Sibo, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 28−49.

(19) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267−5268.

(20) Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibo, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 400.

(21) (a) Nahn, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Toy, P. H.; Dhanabalasingam, B.; Newcomb, M.; Hanna, I. H.; Hollenberg, P. F. *J. Org. Chem.* **1997**, *62*, 9114−9122.

(22) Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Goto, T. *Tetrahedoron* **1987**, *43*, 4767−4776.

SCHEME 3

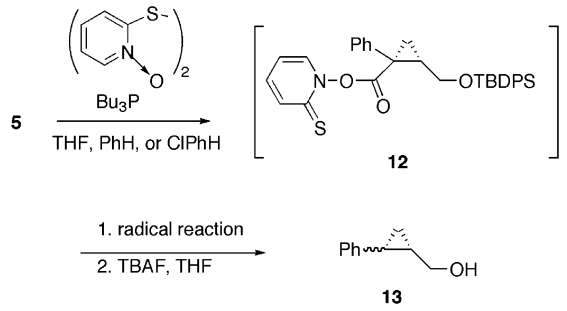


TABLE 1. Radical Decarboxylation of the Barton Ester 12[a]

entry	reductant	initiator	solvent	temp	yield (%)[b]	cis/trans[c]
1	Bu_3SnH	Et_3B	THF	rt	70	2.8:1
2	Bu_3SnH	Me_2Zn	THF	rt	48	2.8:1
3	Bu_3SnH	*hν*	THF	rt	36	2.6:1
4	Bu_3SnH	AIBN	PhH	80 °C	80	2.7:1
5	Bu_3SnH	AIBN	PhCl	130 °C	69	2.6:1
6	*t*-BuSH	Et_3B	THF	rt	80	3.0:1
7	PhSH	Et_3B	THF	rt	70	3.1:1
8	Ph_2SiH_2	AIBN	PhH	80 °C	27	2.5:1
9	TMS_3SiH	Et_3B	THF	rt	74	10:1
10	TMS_3SiH	Et_3B	THF	0 °C	47	14:1
11	TMS_3SiH	Et_3B	THF	−20 °C	22	14:1
12	TMS_3SiH	AIBN	PhH	80 °C	75	11:1

[a] The radical reaction was carried out using 5 equiv of reductant in the presence of an initiator (Et_3B, 0.3 equiv; Me_2Zn, 0.3 equiv; *hν*, high-pressure mercury lamp, 300 W; AIBN, 0.2 equiv). [b] Isolate yield after deprotection. [c] Determined by ^1H NMR.

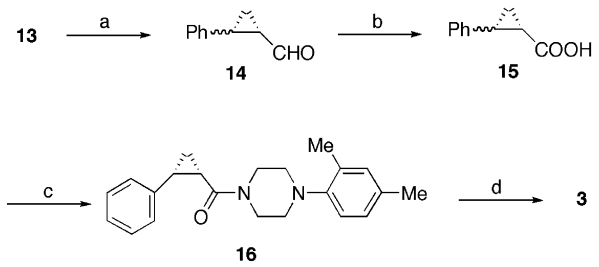
N-hydroxypyridine-2-thione ester **12**,[13] which, without purification, was immediately subjected to the radical reaction (Scheme 3). The yield and cis/trans ratio of the products were determined after removal of the silyl protecting group, and the results are summarized in Table 1. The reaction was first examined with Bu_3SnH, which is an effective hydrogen donor,[18] as the reductant at room temperature by employing different radical initiation methods (entries 1−3). Thus, the desired reductive radical decarboxylation proceeded smoothly, and all three reactions gave the ***4-cis*** as the major product while the selectivity was low (cis/trans = 2.6−2.8:1). The reactions at higher temperature using a Bu_3SnH/AIBN system gave the reduction products in similar cis/trans ratios (entries 4 and 5). Other reductants were subsequently examined. However, use of *t*-BuSH, PhSH, or Ph_2SiH_2 as the reductant did not improve the cis/trans selectivity (entries 6−8).

On the other hand, when the Barton ester **12** was treated with TMS_3SiH/Et_3B at room temperature in THF, ***4-cis*** was obtained highly selectively as expected (entry 9, yield 74%, cis/trans = 10:1). In similar reactions with the TMS_3SiH/Et_3B system at lower temperatures, the cis selectivity was further improved, while the yield decreased (entries 10 and 11). An excellent cis selectivity was also observed by treating **12** with TMS_3SiH and AIBN in refluxing benzene (entry 12, yield 75%, cis/trans = 11:1).

As described, although ***4-trans*** could not be selectively obtained, the cis cyclopropane key intermediate ***4-cis*** was successfully prepared by radical decarboxylation.

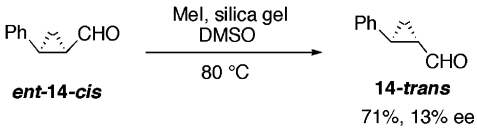
The reduction product, including predominantly ***4-cis*** (cis/trans = 11:1), was successively treated with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 and $NaClO_2/NaH_2PO_4$/2-methyl-2-butene in aqueous acetone to give the carboxylic acid **15** (Scheme 4). When **15** was condensed with *N*-(2,4-dimethylphenyl)piperazine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), the cis isomer **16** was successfully obtained in pure form after silica gel column chromatography. Reduction of **16** with AlH_3 in THF furnished the conformationally restricted target analogue **3** with the *cis*-cyclopropane structure.

SCHEME 4[a]



[a] Reagents: (a) TPAP, NMO, CH_2Cl_2, 88%; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq acetone, 97%; (c) 2,4-dimethylphenylpiperazine, EDC, CH_2Cl_2, 60%; (d) AlH_3, THF, quant.

SCHEME 5



Starting from (*R*)-epichlorohydrin ((*R*)-**7**), ***ent*-3** was similarly synthesized.

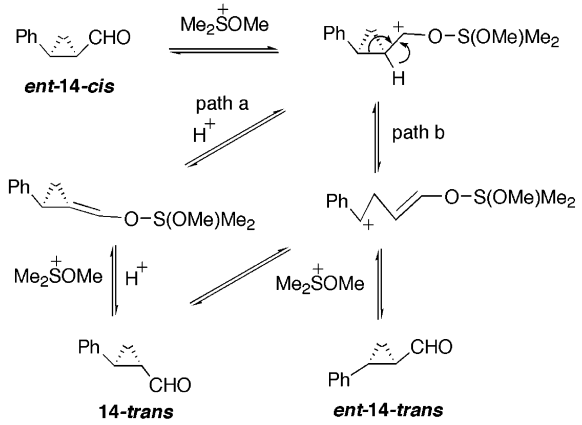
Synthesis of the *trans*-Cyclopropane Target 2a. We next tried to synthesize another target compound **2a** with the *trans*-cyclopropane structure via the cis−trans epimerization of ***ent*-14-*cis***. Sasaki and co-workers reported that when racemic ***14-cis*** was treated with MeI in the presence of silica gel in DMSO at 80 °C, epimerization at the 1-position occurred to form the corresponding cis isomer.[23] Therefore, we heated ***ent*-14-*cis***, which was obtained in pure form by careful silica gel column chromatography, under the same MeI/silica gel/DMSO conditions to give the isomerized trans product ***14-trans*** in 71% yield. However, the optical purity proved to be only 13% (Scheme 5).

In the isomerization reaction, two pathways could be considered, i.e., via the enol intermediate pathway (path a) and the ring-cleaved pathway (path b), as shown in Scheme 6. The experimental results suggest that the epimerization proceeds via the ring-cleaved pathway at least to some extent to result in racemization. Isomerization of ***ent*-14-*cis*** under basic conditions was also examined; however, it was unsuccessful.

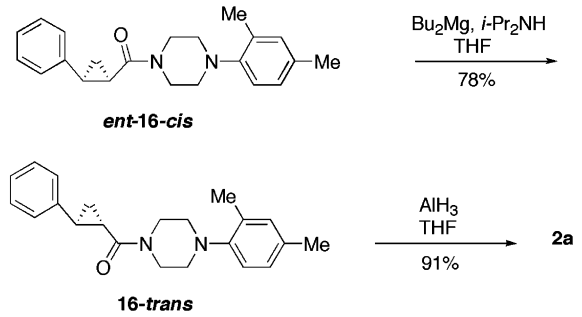
Most recently, Eaton and Zhang reported that a novel base, prepared from Bu_2Mg and *i*-Pr_2NH, effectively removes a proton on the cyclopropane ring at the position adjacent to the amide carbonyl in cyclopropanecarboxamides.[24] They successfully introduced carbon substituents

(23) Sasaki, T.; Eguchi, S.; Ohno, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1469−1470.
(24) Zhang, M.-X.; Eaton, P. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2169−2171.

SCHEME 6



SCHEME 7



on the cyclopropane ring by treating cyclopropanecarboxamides with this base and then electrophiles. During these studies, they observed a cis−trans epimerization of the cyclopropanecarboxamides by the base as a side reaction. We expected that epimerization might occur by treating the *cis*-cyclopropanecarboxamide (***ent*-16-*cis***) with the Eaton base. Thus, when ***ent*-16-*cis*** was treated with the base prepared from Bu_2Mg (2 equiv) and *i*-Pr_2-NH (1 equiv) in THF at room temperature, the desired epimerization actually occurred. After purification by silica gel column chromatography, **16-*trans*** was isolated in 78% yield. Reduction of **16-*trans*** by AlH_3 was ultimately carried out to provide the target **2a**.

Discussion

In this study we showed that the chiral *cis*-cyclopropane structure could be constructed stereoselectively by the radical reduction. Walborsky pointed out that the stereoselectivity of the radical reduction could be determined by the cis/trans equilibrium in the cyclopropyl σ radical intermediate when an effective hydrogen donor was used.[16] The reductions of the Barton ester **12** with Bu_3SnH, *t*-BuSH, PhSH, and Ph_2SiH_2 gave the products in an almost constant cis/trans ratio (2.5−3.1:1). In these cases, the rate of hydrogen transfer from X−H to both the cis radical **A** and the trans radical **B** (Figure 2) might be similar, i.e., $k_2 \approx k'_2$, which is in accord with Walborsky's findings.[16]

On the other hand, the previous studies of the radical reduction of bicyclic cyclopropanes by Apeloig and Nakash suggested that the stereoselectivity could be changed by the hydrogen donor used, i.e., Bu_3SnH or TMS_3SiH.[17] They reported that there is a stronger preference for TMS_3SiH than for Bu_3SnH to transfer a hydrogen atom to the bicyclic cyclopropyl σ radical from the less hindered side. In the reduction of the Barton ester **12**, the significantly bulky TBDPS−O−CH_2 moiety might effectively block the access of the sterically demanding TMS_3SiH to the σ radical orbital of the radical intermediate to form the cis product with high selectivity, similar to the case of Apeloig and Nakash.

Although most of cyclopropyl radicals have been considered to be σ radicals,[15−17] the experimental results in this study also suggest another possibility, namely, that the cyclopropyl radical intermediate derived from **12** is not in equilibrium between the σ radicals **A** and **B** (Figure 2) but is also the π radical due to the delocalizing phenyl group,[16a] as shown in Figure 3a. Thus, we investigated the radical intermediate by theoretical calculations. The structure of the radical was studied using a model radical, 1-phenyl-2-methylcyclopropyl radical (Figure 3b), by DFT calculation using the Gaussian98 program.[25] As shown in Figure 3c, the calculations performed at the UB3LYP/6-31G(d)//UB3LYP/6-31G(d) level clarified that it is a π radical, which is stabilized by the orbital interaction with the p orbitals of the adjacent benzene ring. Accordingly, the stereoselectivity would be explained by the access of the hydrogen donor from the less-hindered side of the π radical intermediate to result in forming mainly the cis product, in which the stereoselectivity can be increased by using a sterically demanding donor such as TMS_3SiH.

Although the selective formation of the trans product by the reductive radical decarboxylation was unsuccessful because of the constrained structure, epimerization of *cis*-cyclopropanes bearing an electron-withdrawing group, such as a carbonyl, often occurs to produce the more stable trans isomer. The target **2a** was actually synthesized via the cis−trans epimerization by using Eaton's base.[24]

Enantioselective olefin cyclopropanation reactions have been extensively studied.[8] Although the methods have been advanced in enantioselectivity, the cis/trans diastereocontrol has remained somewhat elusive.[8,26] In particular, selective preparation of both the chiral *cis*- and *trans*-cyclopropane stereoisomers with high optical purity from the same precursor is often difficult.[27] The procedure developed in this study, i.e., construction of the chiral cyclopropane structures with high optical purity[28] from

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.6; Gaussian, Inc.: Pittsburgh, PA, 1998.

(26) Díaz-Requejo, M. M.; Caballero, A.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pétez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 978−983.

(27) A few examples of the cis-selective asymmetric cyclopropanation of olefins have been recently reported: (a) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3647−3651. (b) Bachmann, S.; Furler, M.; Mezzetti, A. *Organometallics* **2001**, *20*, 2102−2108.

(28) Optical purity was determined by chiral HPLC.

(*R*)- and (*S*)-epichlorohydrins and a carbanion, Barton reductive decarboxylation forming the *cis*-cyclopropanes, and the cis−trans epimerization, is an effective method for preparing all four types of chiral cyclopropane compounds, i.e., the (1*S*,2*S*), (1*S*,2*R*), (1*R*,2*S*), and (1*R*,2*R*) stereoisomers. This method can be applied to the synthesis of various chiral cyclopropane compounds.

Conclusion

The chiral *cis*- and *trans*-1-arylpiperazyl-2-phenylcyclopropanes **2a**, **3**, and ***ent*-3**, designed as conformationally restricted analogues of haloperidol, were synthesized from (*R*)- and (*S*)-epichlorohydrins. Construction of the key *cis*-cyclopropane structure was effectively accomplished by the Barton reductive radical decarboxylation, in which a combination of the bulky *O*-TBDPS protecting group and TMS_3SiH as the reductant was employed. Pharmacological evaluation of the synthesized target compounds as dopaminergic receptor ligands is now in progress.[29]

Experimental Section

(1*S*,2*R*)-1,2-Di(hydroxymethyl)-2-phenylcyclopropane (9). A mixture of **6** (9.69 g, 55.6 mmol) and $NaBH_4$ (4.18 g, 110 mmol) in THF/MeOH (4:1, 100 mL) was stirred at room temperature for 12 h. After addition of H_2O at 0 °C, the solvent was evaporated and the residue was partitioned between AcOEt and 1 N HCl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 1:1 then AcOEt) to give **9** (9.94 g, 100%) as an oil: $[\alpha]^{20}_D$ −56.52 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (1 H, dd, J = 4.6, 5.3 Hz), 1.09 (1 H, dd, J = 5.3, 8.6 Hz), 1.70 (1 H, m), 2.43 (1 H, br s), 2.94 (1 H, br s), 3.44 (1 H, dd, J = 11.5, 11.8 Hz), 3.58 (1 H, d, J = 11.8 Hz), 4.18 (2 H, m), 7.21−7.43 (5 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 25.7, 32.3, 63.4, 67.4, 126.4, 128.1, 129.0, 143.4; LR-MS (EI) *m*/*z* 178 (M^+). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.98. Found: C, 73.73; H, 7.92.

(1*S*,2*R*)-1-(*tert*-Butyldiphenylsilyloxy)methyl-2-(*N*-methoxy-*N*-methylcarbamoyl)-2-phenylcyclopropane (10). A mixture of Me(MeO)NH·HCl (4.52 g, 46.3 mmol) and Et_3N (6.40 mL, 46.3 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 30 min, and the resulting precipitates were filtered off. The filtrate was added slowly to a mixture of **6** (2.02 g, 11.6 mmol) and $AlCl_3$ (3.09 g, 23.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the resulting mixture was stirred at room temperature. After disappearance of **6** on TLC, TBDPSCl (7.60 mL, 25.5 mmol), imidazole (1.75 g, 25.5 mmol), and DMF (50 mL) were added and the mixture was stirred at room temperature for 15 h and then evaporated. The residue was partitioned between AcOEt and 1 N HCl, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 30:1−8:1) to give **10** (5.09 g, 94%) as an oil: $[\alpha]^{24}_D$ +102.76 (*c* 1.040, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (1 H, dd, J = 4.8, 8.9 Hz), 1.11 (9 H, s), 1.54 (1 H, dd, J = 4.8, 5.7 Hz), 2.08 (1 H, m), 3.06 (3 H, s), 3.14 (3 H, br s), 3.72 (1 H, m), 3.77 (1 H, m), 7.20 (1 H, dd, J = 7.0, 7.0 Hz), 7.28 (4 H, dd, J = 8.0, 15.2 Hz), 7.38−7.45 (6 H, m), 7.68 (2 H, d, J = 7.4 Hz), 7.72 (2 H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 26.7, 27.0, 35.0, 126.4, 127.5, 128.3, 129.5, 129.5, 133.6, 133.7, 135.4, 135.5; LR-MS (ESI) *m*/*z* 496 (MNa^+). Anal. Calcd for $C_{29}H_{35}NO_3Si$: C, 73.53; H, 7.45; N 2.96. Found: C, 73.42; H, 7.36; N 2.85.

(1*S*,2*R*)-1-(*tert*-Butyldiphenylsilyloxy)methyl-2-formyl-2-phenylcyclopropane (11) from 9. To a mixture of **9** (1.48 g, 8.3 mmol) and imidazole (0.57 g, 8.3 mmol) in DMF (20 mL) was slowly added TBDPSCl (2.16 mL, 8.3 mmol) at −20 °C, and the mixture was stirred at the same temperature for 10 min. After addition of MeOH, 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), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 30:1) to give the corresponding monosilylated product (1.87 g, 54%) as an oil. A mixture of DMSO (1.28 mL, 18.0 mmol) and CH_2Cl_2 (10 mL) was added slowly to a solution of $(COCl)_2$ (0.79 mL, 9.0 mmol) in CH_2Cl_2 (20 mL) at −78 °C over 30 min, and then a solution of the monosilylated product (1.87 g, 4.5 mmol) in CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred at the same temperature for 2 h, and then Et_3N (5.02 mL, 36.0 mmol) was added. After the mixture was stirred at the same temperature for further 30 min, aqueous saturated NH_4Cl and then $CHCl_3$ and aqueous 10% NaClO were added to the mixture and the whole was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 30:1) to give **11** (3.13 g, 86%) as an oil: $[\alpha]^{25}_D$ +50.66 (*c* 0.930, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (9 H, s), 1.53 (1 H, dd, J = 5.0, 8.6 Hz), 1.74 (1 H, dd, 5.0, 10.8 Hz), 2.03 (1 H, m), 3.69 (1 H, dd, J = 9.6, 11.5 Hz), 4.07 (1 H, dd, J = 5.3, 11.5 Hz), 7.30−7.47 (11 H, m), 7.64−7.71 (4 H, m), 9.66 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 19.3, 26.9, 35.3, 41.7, 61.4, 127.5, 127.6, 129.6, 129.6, 130.0 133.1, 133.4, 135.4, 135.4, 199.8; LR-MS (EI) *m*/*z* 414 (M^+). Anal. Calcd for $C_{27}H_{30}O_2Si$: C, 78.20; H, 7.45. Found: C, 78.22; H, 7.29.

(1*S*,2*R*)-1-(*tert*-Butyldiphenylsililoxy)methyl-2-formyl-2-phenylcyclopropane (11) from 10. To a solution of **10** (23 mg, 0.48 mmol) in CH_2Cl_2 (3 mL) was added DIBALH (0.95 M in hexane, 0.68 mL, 0.65 mmol) at −78 °C, and the mixture was stirred at the same temperature for 2 h. After addition of MeOH, the resulting mixture was partitioned between $CHCl_3$ and 1 N HCl and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 30:1−8:1) to give **11** (16 mg, 80%) as an oil.

(1*S*,2*R*)-1-(*tert*-Butyldiphenylsilyloxy)methyl)-2-carboxy-2-phenylcyclopropane (5). A mixture of **11** (1.30 g, 3.20 mmol), $NaClO_2$ (1.0 g, 11 mmol), NaH_2PO_4·$2H_2O$ (0.50 g, 3.2 mmol), and 2-methyl-2-butene (1.2 mL, 14 mmol) in acetone/H_2O (3:1, 40 mL) was stirred at room temperature for 12 h and then evaporated. The residue 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 column chromatography (silica gel, hexane/AcOEt, 30:1) to give **5** (1.18 g, 86%) as a foam: $[\alpha]^{24}_D$ +22.19 (*c* 1.020, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9 H, s), 1.38 (1 H, dd, J = 4.6, 8.9 Hz), 1.63 (1 H, dd, J = 4.6, 7.3 Hz), 1.95 (1 H, m), 3.96 (1 H, dd, J = 9.0, 11.1 Hz), 4.04 (1 H, dd, J = 5.8, 11.1 Hz), 7.25−7.43(11 H, m), 7.64−7.72 (4 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 20.0, 26.7, 32.7, 33.0, 61.2, 127.0, 127.3. 127.9, 129.3, 130.2, 133.2, 133.4, 135.2, 135.2, 139.7, 177.6. HRMS (FAB) (MH^+) calcd for $C_{27}H_{31}O_3Si$, 431.2041; found, 431.2069 (MH^+).

General Procedure for the Radical Decarboxylation (Table 1, Synthesis of 13 from 5). A mixture of **5** (86 mg, 0.20 mmol), 2,2′-dithiopyridine-1,1′-dioxide (61 mg, 0.24 mmol), Bu_3P (125 μL, 0.50 mmol), and a hydrogen donor (5 equiv) in a solvent (THF, benzene, or chlorobenzene; 5 mL) was stirred at room temperature under shading. After disappearance of **5** on TLC, the radical reaction was carried out by addition of an initiator (Et_3B and Me_2Zn, 0.3 equiv or AIBN, 0.2 equiv) or irradiation with high-pressure mercury lamp (300 W) under the conditions indicated in Table 1. The resulting reaction

(29) Preliminary results of the binding affinities for human dopamine D_4 and adrenaline α_1 receptors using [^{3}H]YM-09151-2 and [^{3}H]-prazosin, respectively: **2a**, 0.20 μM (D_4), 1.79 μM (α_1); **3**, 1.39 μM (D_4), 2.16 μM (α_1); ***ent*-3**, 3.16 μM (D_4), 2.22 μM (α_1).

mixture was evaporated, and the residue was 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, hexane/*i*-Pr_2O, 100:1) to give the reductive decarboxylation products as an oil. A mixture of the oil and TBAF (1.0 M in THF, 400 μL, 0.40 mmol) in THF (5 mL) was stirred at room temperature for 12 h and then evaporated. The residue 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 column chromatography (silica gel, hexane/AcOEt, 9:1) to give **13** as an oil: ^{1}H NMR (270 MHz, $CDCl_3$) for **13-*cis*** δ 0.88 (1 H, dd, J = 5.5, 11.4 Hz), 1.05 (1 H, ddd, J = 5.5, 8.5, 8.5 Hz), 1.50 (1 H, m), 2.30 (1 H, ddd, J = 6.2, 8.5, 8.5 Hz), 3.27 (1 H, dd, J = 8.6, 11.2 Hz), 3.48 (1 H, dd, J = 6.4, 11.2 Hz), 7.20−7.32 (5 H, m); ^{1}H NMR (270 MHz, $CDCl_3$) for **13-*trans*** δ 0.93 (2 H, m), 1.45 (1 H, m), 1.83 (1 H, m), 3.62 (2 H, m), 7.06−7.32 (5 H, m). HRMS (EI) calcd for $C_{10}H_{12}O$, 148.0888 (M^+); found, 148.0887 (M^+).

(1*S*)-1-Formyl-2-phenylcyclopropane (14). A mixture of **13** (cis/trans = 11:1, 343 mg, 2.3 mmol), TPAP (41 mg, 0.12 mmol), and NMO (408 mg, 3.5 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 30 min. The resulting mixture was filtered with Celite, and the filtrate was evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 9:1) to give **14** (cis/trans = 12:1, 297 mg, 88%) as an oil: ^{1}H NMR (270 MHz, $CDCl_3$) for **14-*cis*** δ 1.59 (1 H, m), 1.88 (1 H, m), 2.14 (1H, m), 2.83 (1 H, m), 7.21−7.32 (5 H, m), 8.67 (1 H, d, J = 6.6 Hz); ^{1}H NMR (270 MHz, $CDCl_3$) for **14-*trans*** δ 1.53 (1 H, m), 1.73 (1 H, m), 2.28 (1 H, m), 2.63 (1 H, m), 7.11 (2 H, m), 7.19−7.33 (3 H, m), 9.33 (1 H, d, J = 4.6 Hz). HRMS (EI) calcd for $C_{10}H_{10}O$, 146.0732 (M^+); found, 146.0737 (M^+).

(1*S*)-1-Carboxy-2-phenylcyclopropane (15). A mixture of **14** (cis/trans = 12:1, 298 mg, 2.0 mmol), $NaClO_2$ (643 mg, 7.1 mmol), NaH_2PO_4·$2H_2O$ (317 mg, 2.0 mmol), and 2-methyl-2-butene (767 μL, 9.1 mmol) in acetone/H_2O (3:1, 24 mL) was stirred at room temperature for 15 h and then evaporated. The residue was partitioned between AcOEt and 1 N HCl, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 9:1 then $CHCl_3$/MeOH, 20:1) to give **15** (cis/trans = 12:1, 320 mg, 97%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) for **15-*cis*** δ 1.37 (1 H, m), 1.66 (1 H, m), 2.04 (1 H, m), 2.63 (1 H, m), 7.18−7.29 (5 H, m); ^{1}H NMR (400 MHz, $CDCl_3$) for **15-*trans*** δ 1.41 (1 H, m), 1.66 (1 H, m), 1.91 (1 H, m), 2.61 (1 H, m), 7.11 (2 H, m), 7.16−7.32 (3 H, m). HRMS (EI) calcd for $C_{10}H_{10}O_2$, 162.0681 (M^+); found, 162.0685 (M^+).

(1*S*,2*R*)-1-[4-(2,4-Dimethylpheny)piperazyl]carbonyl-2-phenylcyclopropane (16). A mixture of **15** (14 mg, 88 μmol), 2,4-dimethylphenylpiperazine (17 mg, 88 μmol), and EDC·HCl (19 mg, 97 μmol) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 30 min and then at room temperature for 90 min. The reaction mixture was partitioned between H_2O and $CHCl_3$, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 4:1−1:1) to give **16** (21 mg, 60%) as an oil: $[\alpha]^{25}_D$ −123.16 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (1 H, ddd, J = 5.6, 8.5, 8.5 Hz), 1.85 (1 H, dd, J = 5.6, 12.6 Hz), 2.01 (1 H, m), 2.18 (2 H, m), 2.21 (3 H, s), 2.25 (3 H, s), 2.45 (1 H, ddd, J = 6.2, 9.1, 9.1 Hz), 2.68 (2 H, m), 3.24 (1 H, m), 3.54 (1 H, m), 3.72 (1 H, m), 3.88 (1 H, m), 6.60 (1 H, d, J = 7.9 Hz), 6.94 (2 H, m), 7.15−7.19 (3 H, m), 7.25−7.29 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 17.7, 20.8, 24.2, 24.6, 42.5, 45.8, 51.8, 52.1, 119.0, 126.2, 126.8, 127.3, 127.8, 128.0, 129.1, 131.6, 132.4, 132.9, 137.5, 148.3, 167.0. HRMS (EI) calcd for $C_{22}H_{26}N_2O$, 334.2045 (M^+); found, 334.2044.

(1*S*,2*R*)-1-(2,4-Dimethylphenyl)piperazylmethyl-2-phenylcyclopropane (3). To a suspension of $AlCl_3$ (13 mg, 94 μmol) in THF (0.5 mL) was added $LiAlH_4$ (1 M in THF, 280 μL, 280 μmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. The resulting mixture was added slowly to a solution of **16** (32 mg, 94 μmol) in THF at 0 °C, and the mixture was stirred at room temperature for 90 min. After addition of aqueous NaOH (10%) and $CHCl_3$, the resulting mixture was partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 3:1) to give **3** (31 mg, 100%) as an oil: $[\alpha]^{22}_D$ +48.88 (*c* 0.880, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (1 H, dd, J = 5.6, 11.3 Hz), 1.13 (1 H, ddd, J = 5.6, 8.3, 8.3 Hz), 1.30 (1 H, m), 1.83 (1 H, dd, J = 8.3, 12.8 Hz), 2.20 (1 H, dd, J = 8.7, 11.6 Hz), 2.22 (3 H, s), 2.257 (3 H, s), 2.46 (1 H, dd, J = 4.8, 12.8 Hz), 2.51 (4 H, br s), 2.87 (4 H, m), 6.91−6.97 (3 H, m), 7.18−7.30 (5 H, m). To a solution of **3** (31 mg, 97 μmol) in *i*-PrOH (1 mL) was added aqueous HBr (48%) (33 μL) in which the pH was ca. 3. To the solution was added *i*-Pr_2O to give white precipitates of **3** (47 mg, quant.) as a dihydrobromide: mp 200−204 °C; $[\alpha]^{25}_D$ −43.02 (*c* 0.520, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.37 (1 H, dd, J = 5.7, 11.8 Hz, H-3), 1.50 (1 H, ddd, J = 5.7, 8.4, 8.3 Hz, H-3), 1.73 (1 H, m, H-1), 2.38 (3 H, s, CH_3), 2.39 (3 H, s, CH_3), 2.66 (1 H, dd, J = 8.6, 15.3 Hz, H-2), 2.74 (1 H, dd, J = 9.4, 13.5 Hz, H-1′a) 3.19−3.50 (7 H, m, H-1′b, piperazyl NCH_2), 3.74 (2 H, m, piperazyl NCH_2), 7.10−7.15 (3 H, m, aromatic), 7.40−7.50 (5 H, m, aromatic), the assignment is based on the COSY spectrum; LR-MS (FAB) *m*/*z* 321 (MH^+). Anal. Calcd for $C_{22}H_{30}N_2Br_2$: C, 54.76; H, 6.27; N, 5.81; Br, 33.13. Found: C, 54.13; H, 6.16; N, 5.70; Br, 33.39.

(1*R*,2*S*)-1-(2,4-Dimethylphenyl)piperazylmethyl-2-phenylcyclopropane (*ent*-3). *ent*-3 was prepared from ***ent*-6**[4a] by the same procedure for the synthesis of **3** from **6**. ***ent*-3**·2HBr: mp 208−209 °C; $[\alpha]^{25}_D$ +49.48 (*c* 0.440, CH_3OH). Anal. Calcd for $C_{22}H_{30}N_2Br_2$: C, 54.76; H, 6.27; N, 5.81; Br, 33.13. Found: C, 54.19; H, 6.16; N, 5.68; Br, 33.18.

Treatment of *ent*-14-*cis* with MeI/DMSO. A mixture of ***ent*-14-*cis*** (41 mg, 0.28 mmol), MeI (18 μL, 0.28 mmol), and silica gel (20 mg) in DMSO (1 mL) was stirred at 80 °C for 1 week. The silica gel was filtered off, and the filtrate was 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, hexane/AcOEt, 19:1) to give **14-*trans*** (29 mg, 71%) as an oil: $[\alpha]^{25}_D$ +42.9 (*c* 0.680, $CHCl_3$) (lit. ***ent*-14-*trans***, $[\alpha]^{26}_D$ −324 (*c* 0.333, $CHCl_3$)).[30]

(1*S*,2*S*)-1-(2,4-Dimethylphenyl)piperazylcarbonyl-2-phenylcyclopropane (16-*trans*). A mixture of Bu_2Mg (1.0 M in heptane, 0.22 mL, 0.22 mmol) and *i*-Pr_2NH (14 μL, 0.10 mmol) in THF (1 m) was stirred at room temperature for 20 min and then was added to a solution of ***ent*-16-*cis*** (33 mg, 0.10 mmol), which was synthesized from ***ent*-6** as described above for **16-*cis***, in THF (1 mL). The resulting mixture was stirred at room temperature for 2 days and then partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 15:1−9:1) to give **16-*trans*** (26 mg, 78%) as an oil: $[\alpha]^{25}_D$ +109.46 (*c* 0.670, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (1 H, m), 1.70 (1 H, m), 2.01 (1 H, m), 2.27 (3 H, s), 2.28 (3 H, s), 2.51 (1 H, m), 2.86 (4 H, m), 3.77 (4 H, m), 6.88 (1 H, d, J = 7.9 Hz), 6.99 (2 H, m), 7.12 (2 H, d, J = 7.9 Hz), 7.19 (1 H, m), 7.28 (2 H, m). HRMS (EI) calcd for $C_{22}H_{26}N_2O$, 334.2045 (M^+); found, 334.2044.

(1*S*,2*S*)-1-(2,4-Dimethylphenyl)piperazylmethyl-2-phenylcyclopropane (2a). Compound **2a** (19 mg 91%) was synthesized from **16-*trans*** (22 mg, 66 μmol) as described above for the synthesis of **3**: $[\alpha]^{25}_D$ +82.20 (*c* 0.660, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (1 H, m, H-3), 0.98 (1 H, m, H-3), 1.29 (1 H, m, H-1), 1.71 (1 H, m, H-2), 2.26 (6 H, s, CH_3), 2.44

(30) Kaye, P. T.; Molema, W. E. *Chem. Commun.* **1998**, *22*, 2479−2480.

(1 H, dd, J = 6.6, 12.4 Hz, H-1′a), 2.58 (1 H, dd, J = 6.3, 12.4 Hz, H-1′b), 2.69 (4 H, m, piperazyl NCH_2), 2.92 (4 H, m, piperazyl NCH_2), 6.98−7.27 (8 H, m, aromatic); the ^{1}H NMR chart was identified with that of authentic **2a** and the assignment was based on the COSY spectrum; LR-MS (FAB) m/z 321 (MH^+). Anal. Calcd for $C_{22}H_{30}N_2Br_2$ (dihydrobromide): C, 54.76; H, 6.27; N, 5.81; Br 33.13. Found: C, 54.76; H, 6.22; N, 5.86; Br, 32.80. The optical purity was 97% ee (Chiralcel OD; EtOH, room temperature, 270 nm).

Calculations. All calculations were performed using the Gaussian98 program on a SGI O2 workstation. UHF/6-31G* were taken to be the input geometries for final optimization by UB3LYP/6-31G*. The stationary points were characterized by frequency analysis (minimum with 0).

Acknowledgment. This investigation was supported by a Grant-in-Aid for Creative Scientific Research (13NP0401) (A.M.), a Grant-in-Aid for Scientific Research (S.S.), and Research Fellowships for Young Scientists (H.A.) from the Japan Society for the Promotion of Science. We are grateful to Dr. A. Thurkauf (Achillion Pharmaceuticals) for providing the ^{1}H NMR chart of compound **2a**, to Daiso Co., Ltd., for gift of chiral epichlorohydrins, to Prof. S. Yamada (University of Shizuoka) for pharmacological assay, and to Ms. H. Matsumoto, A. Maeda, and S. Oka (Center for Instrumental Analysis, Hokkaido University) for technical assistance with NMR, MS, and elemental analyses.

Supporting Information Available: General experimental methods, table of atomic coordination for the calculated structure in Figure 3c, and ^{1}H NMR charts of compounds **5**, **13**−**16**, **16-*trans***, and **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0302206