Development of Versatile *cis*- and *trans*-Dicarbon-Substituted Chiral Cyclopropane Units: Synthesis of (1*S*,2*R*)- and (1*R*,2*R*)-2-Aminomethyl-1-(1*H*-imidazol-4-yl)cyclopropanes and Their Enantiomers as Conformationally Restricted Analogues of Histamine

Yuji Kazuta, 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

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The cyclopropane ring can be used effectively in restricting the conformation of biologically active compounds to improve activity and also to investigate bioactive conformations. We designed (1*S*,2*R*)- and (1*R*,2*R*)-2-aminomethyl-1-(1*H*-imidazol-4-yl)cyclopropanes (**1** and **2**, respectively) and their enantiomers (*ent*-**1** and *ent*-**2**) as conformationally restricted analogues of histamine. The four types of chiral cyclopropanes bearing two differentially functionalized carbon substituents in a *cis* or *trans* relationship on a cyclopropane ring, (1*S*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formylcyclopropane (**7**) and (1*R*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formylcyclopropane (**8**) and their enantiomers (*ent*-**7** and *ent*-**8**), were developed as the key intermediates for synthesizing **1**, **2**, *ent*-**1**, and *ent*-**2**. The reaction between (*R*)-epichlorohydrin [(*R*)-**12**] and phenylsulfonylacetonitrile (**13a**) in the presence of NaOEt in EtOH followed by treatment with acid gave the chiral cyclopropane lactone **11a** with 98% ee in 82% yield. Compound **11a** was converted into both the *cis*- and *trans*-chiral cyclopropane units **7** and **8**, respectively, via reductive desulfonylation with Mg/MeOH as the key step. The corresponding enantiomers, the *cis*-substituted *ent*-**7** and the *trans*-substituted *ent*-**8**, were also prepared starting from (*S*)-epichlorohydrin [(*S*)-**12**]. The four conformationally restricted target histamine analogues **1**, **2**, *ent*-**1**, and *ent*-**2** were successfully synthesized from **7**, **8**, *ent*-**7**, and *ent*-**8**, respectively. The chiral cyclopropane units **7**, **8**, *ent*-**7**, and *ent*-**8** should be useful as versatile intermediates for synthesizing various compounds having an asymmetric cyclopropane structure.

Introduction

Due to its free rotation about single bonds, a biologically active compound, such as a drug or a neurotransmitter, can assume a variety of conformations, with only one of these conformers binding to a receptor. If a compound has low binding affinity for its target molecule, it may simply be because the active conformer is unstable. Therefore, the synthesis of conformationally restricted analogues of a lead compound often results in an improvement of the specific binding affinity for the target molecule.[1] Restricting the conformation of a biologically active compound is also effective in investigating the bioactive conformation,[1c] which is the conformation the compound assumes in binding to its target molecule.[1]

In the design of conformationally restricted analogues, it is essential that the conformationally restricted analogues be as similar as possible to the parent compound in size, shape, and molecular weight.[1a] Conformationally restricted analogues have usually been designed and synthesized by introducing often bulky cyclic moieties into the lead compounds. Consequently, the chemical and physical properties of these analogues can be quite different from those of the original leads. Because of its structure, cyclopropane is likely to be effective in restricting the conformation of a molecule without changing the chemical and physical properties of the lead compound.[2] In fact, cyclopropane has already been successfully used to restrict the bioactive conformations of neurotransmitters,[2a,b] amino acids,[2c] peptides,[2d] and nucleosides.[2e] We also devised a new method for restricting the conformation of cyclopropane derivatives based on the fact that adjacent substituents on the ring exert mutual steric repulsion because of their eclipsed conformation to each other. This method has been successfully used in the design of NMDA (*N*-methyl-D-aspartic acid) receptor antagonists.[3]

* To whom correspondence should 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) Kozikowski, A., Ed. *Drug Design for Neuroscience*; Raven Press: New York, 1993. (c) Wermuth, C. G., Ed. *The Practice of Medicinal Chemistry*; Academic Press: San Diego, 1996.

(2) For examples see: (a) K. 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) Stammer, S. H. *Tetrahedron* **1990**, *46*, 2231−2254. (d) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305−1318. (e) 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) 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.

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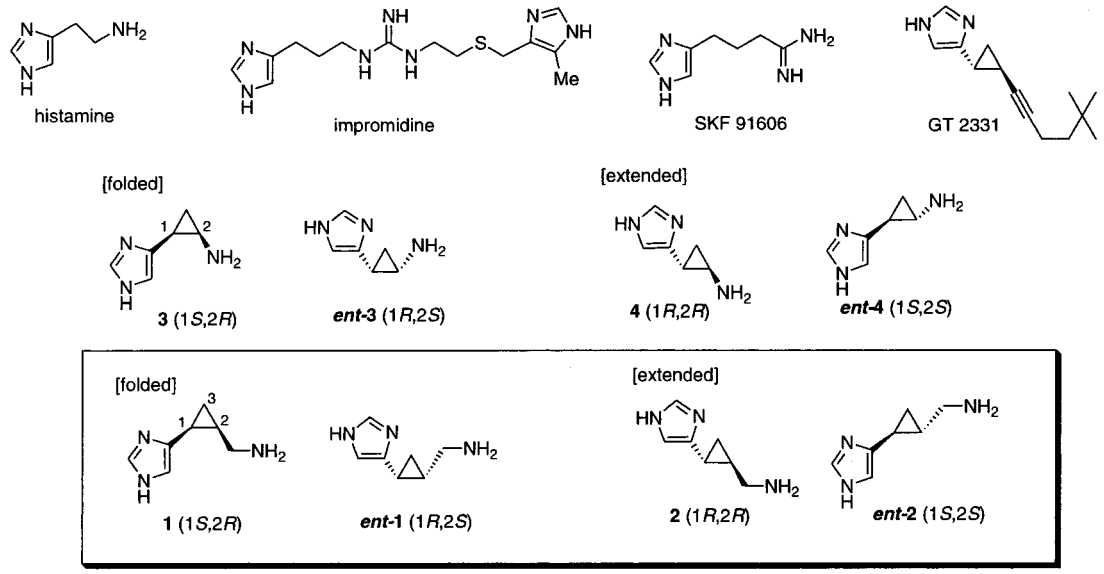

Figure 1. Histamine, known histamine receptor ligands, and novel conformationally restricted analogues of histamine.

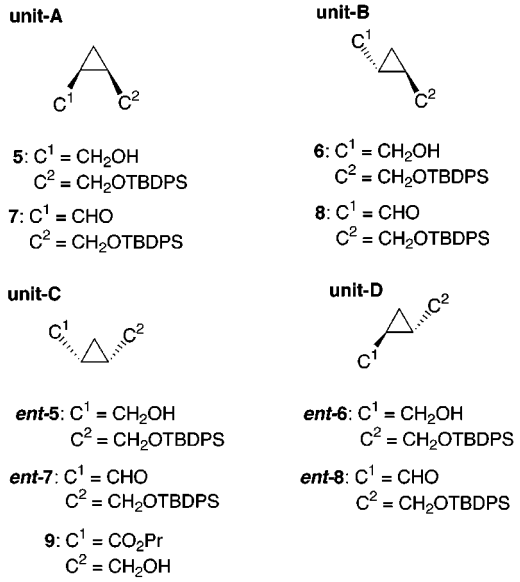

Figure 2. Versatile *cis*- and *trans*-substituted chiral cyclopropane units.

On the basis of the encouraging results using a cyclopropane ring to restrict bioactive conformations, we designed the novel conformationally restricted analogues of histamine having a cyclopropane ring, **1**, *ent*-**1**, **2**, and *ent*-**2**, the structures of which are shown in Figure 1. To synthesize these target compounds, we developed the versatile *cis*- or *trans*-substituted chiral cyclopropane intermediates unit **A** (**5**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$; **7**, $C^1 = CHO$, $C^2 = CH_2OTBDPS$), unit **B** (**6**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$; **8**, $C^1 = CHO$, $C^2 = CH_2OTBDPS$), unit **C** (*ent*-**5**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$; *ent*-**7**, $C^1 = CHO$, $C^2 = CH_2OTBDPS$), and unit **D** (*ent*-**6**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$; *ent*-**8**, $C^1 = CHO$, $C^2 = CH_2OTBDPS$), shown in Figure 2, using (*R*)- and (*S*)-epichlorohydrins as synthons. The four conformationally restricted target histamine analogues **1**, **2**, *ent*-**1**, and *ent*-**2** were successfully synthesized from **7**, **8**, *ent*-**7**, and *ent*-**8**, respectively. In this paper we describe the results on these studies.

Results and Discussion

Design of the Conformationally Restricted Analogues of Histamine. Histamine is a neurotransmitter involved in a variety of homeostatic processes, such as sleep and wakefulness, eating and drinking, learning and memory, or neuroendocrin.[4] These effects of histamine are mediated by the three receptor subtypes termed H_1, H_2, and H_3, and the agonists and antagonists specific to each one of these subtypes can be used as drugs as well as pharmacological tools.[4] Histamine, like other neurotransmitters, is conformationally flexible due to the "aromatic ring$-C(sp_3)-C(sp_3)-$N" backbone. Consequently, histamine can assume a variety of conformations, which may make it possible to bind to several receptor subtypes in the different conformations. Therefore, the conformation binding to the H_1 subtype, i.e., the bioactive conformation for H_1, may be different from those for H_2 and/or H_3. We planned to synthesize conformationally restricted analogues of histamine to investigate the bioactive conformation for each receptor subtype and to develop subtype-specific agonists and/or antagonists.[1,2]

It would appear that the spatial arrangement of the imidazole ring and the basic amino nitrogen is a determining factor in the potency of histamine and its derivatives as receptor ligands. Impromidine,[5] which is a potent H_2 agonist, has the one-carbon-elongated structure "imidazole$-C-C-C-$N" compared with the "imidazole$-C-C-$N" structure of the parent compound histamine. SKF91606,[6] with its two-carbon-elongated structure "imidazole$-C-C-C-C-$N", is the most potent H_3-receptor agonist known to date. Such carbon elongation in impromidine and SKF91606 may relate to their potent and

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(5) Ganellin, C. R. In *The Chemical Regulations of Biological Mechanisms*; Creighton, A. M., Turner, S., Eds.; Royal Society of Chemistry: London, 1982; pp 1−15.

(6) Howson, W.; Parsons, M. E.; Raval, P.; Swayne, T. G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 77−78.

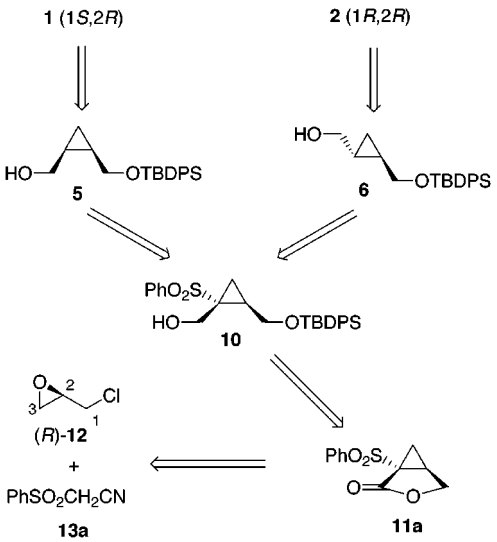
selective affinity for the receptor subtypes. Therefore, we designed the histamine analogues **1**, *ent*-**1**, **2**, and *ent*-**2** restricted conformationally by a cyclopropane, which have the carbon-elongated "imidazole−C(1)−C(2)−C(2′)−N" and/or "imidazole−C(1)−C(2)−C(3)−C(2′)−N" structure. In these conformationally restricted analogues, the spatial relationships between the imidazole ring and the basic nitrogen of *cis*-substituted **1** and *ent*-**1** are restricted in the "folded" form, while those of the *trans*-isomers **2** and *ent*-**2** are in the "extended" form (Figure 1).

Most recently, a very potent H_3-receptor antagonist, GT-2331 (Figure 1), having a cyclopropylimidazole structure, was reported by Ali and co-workers,[7] which suggested that the cyclopropane ring is likely to be effective in restricting the bioactive conformation of histamine.

Esch and co-workers designed four stereoisomers of 2-amino-1-(1*H*-imidazol-4-yl)cyclopropane, i.e., the folded *cis*-isomer **3** and its enantiomer *ent*-**3** and the extended *trans*-isomer **4** and its enantiomer *ent*-**4**, in which the basic amino group is directly attached to the cyclopropane ring. They accomplished the synthesis of the extended analogues **4** and *ent*-**4**, via optical resolution of a racemic intermediate, and identified *ent*-**4** as a potent H_3 subtype-specific agonist.[8] However, they failed to synthesize **3** and *ent*-**3**; therefore, the biological activity of the folded analogues is unknown. Our study will also clarify whether the folded conformation is the active one in the binding of histamine to the receptors.

Synthetic Plan. Chiral cyclopropanes are not only useful for restricting the conformation of biologically active compounds to improve the activity but also important as key fragments in many natural products.[9] Therefore, considerable effort[9−12] has been devoted to developing practical methods for preparing chiral cyclopropanes, which include enantioselective cyclopropanations,[10] chemical or enzymatic optical resolutions,[11] and transformations from chiral synthons.[12] We needed the four types of chiral cyclopropane units bearing two adjacent carbon substituents in a *cis* or *trans* relationship, namely, units **A**−**D**, shown in Figure 2, for the synthesis of the target compounds; in these chiral cyclopropane units, the two carbon substituents on a cyclopropane should be differentially functionalized for further transformations into the target molecules. Such cyclopropane units are useful for the synthesis of a variety of biologically important compounds; e.g., a unit **B** (*ent*-**5**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$) prepared from D-mannitol and a unit **C** (**9**, $C^1 = CO_2Pr$, $C^2 = CH_2OH$) prepared via enzymatic optical resolution were effectively used as the key intermediates for synthesizing marine products constanolactones[11d] and a conformationally restricted γ-aminobutylic acid (GABA) analogue,[12d] respectively. However, a straightforward method for preparing all four types of the units with different stereochemistries, i.e., units **A**−**D**, has not yet been developed.

Scheme 1



In recent years, we have been working to synthesize (1*S*,2*R*)-1-phenyl-2-[(*S*)-1-aminopropyl]-*N*,*N*-diethylcyclopropanecarboxamide and its derivatives, which have an asymmetric cyclopropane backbone, for developing novel effective antagonists of the NMDA receptor.[3,13] Throughout these studies, we successfully used (*R*)- and (*S*)-epichlorohydrins, which are readily available in high optical purity, as the synthons for preparing the asymmetric cyclopropane structures.[13] On the basis of these studies, we planned to develop an efficient method for preparing the chiral cyclopropane units bearing two adjacent carbon substituents in *cis* and *trans* relationships, i.e., units **A**−**D**, shown in Figure 2, starting from (*R*)- or (*S*)-epichlorohydrin as the synthon.

The synthetic plan for the conformationally restricted analogue **1** with the (1*S*,2*R*)-*cis* stereochemistry and its *trans*-diastereomer (1*R*,2*R*)-**2** starting from (*R*)-epichlorohydrin [(*R*)-**12**], via the chiral phenylsulfonylcyclopropane derivative **10** as the key common intermediate, is summarized in Scheme 1. The chiral cyclopropane units bearing 1,2-*cis*- and 1,2-*trans*-substituents, **5** (unit **A**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$) and **6** (unit **B**, $C^1 = CH_2OH$, $C^2 = CH_2OTBDPS$), respectively, were likely to be suitable precursors for the synthesis of the target com-

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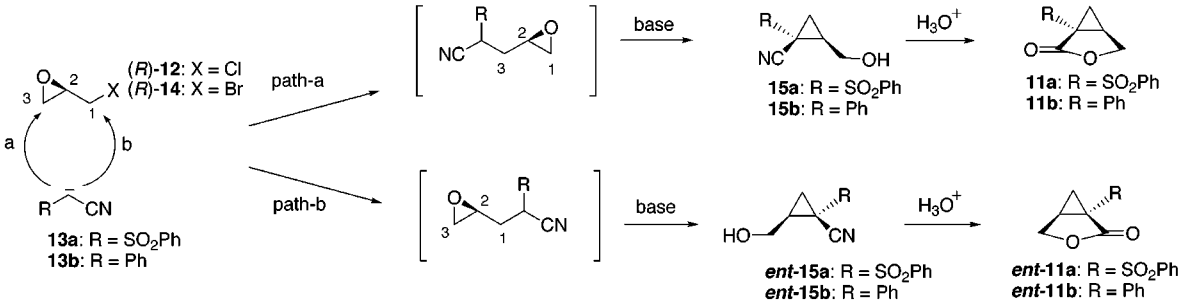
(11) Examples of the synthesis of 1,2-disubstituted chiral cyclopropanes via chemical or enzymatic optical resolutions: (a) Laumen, K.; Schneider, M. *Tetrahedron Lett.* **1985**, *26*, 2073−2076. (b) Ader, U.; Breitgoff, D.; Klein, P.; Laumen, K. E. *J. Org. Chem.* **1989**, *30*, 1793−1796. (c) Grandjean, 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. (e) 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.

(12) Examples of the synthesis of 1,2-disubstituted chiral cyclopropanes from chiral synthons: (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.

(13) (a) Ono, S.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 221−224. (b) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Matsuda, A. *Tetrahedron Lett.* **1996**, *37*, 641−644. (c) Shuto, S.; Shibuya, N.; Yamada, S.; Ohkura, T.; Kimura, R.; Matsuda, A. *Chem. Pharm. Bull.* **1999**, *47*, 1188−1192. (d) Kazuta, Y.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **2000**, *41*, 5373−5377. (e) Kazuta, Y.; Shuto, S.; Abe, H.; Matsuda, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 599−604.

Scheme 2

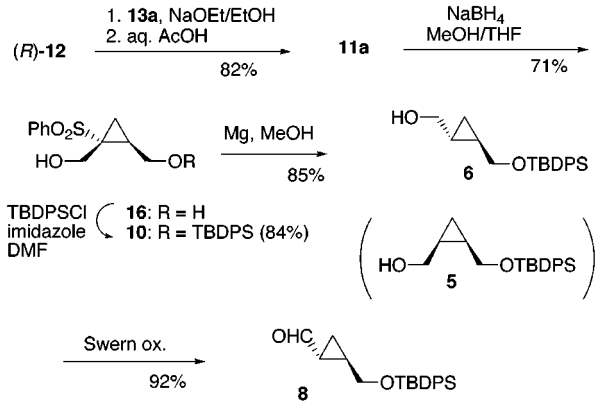


pounds **1** and **2**. Reductive desulfonylation[14] of the chiral phenylsulfonylcyclopropane derivative **10** under kinetic and thermodynamic conditions was expected to provide the desired *cis*- and *trans*-cyclopropane units **5** and **6**, respectively. Compound **10** would be prepared from lactone **11a** by its functional group transformations. The chiral lactone **11a** would be constructed via condensation of (*R*)-**12** and phenylsulfonylacetonitrile (**13a**) under basic conditions.

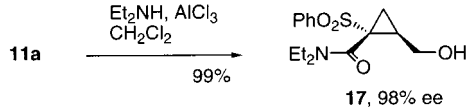
Development of the Versatile Chiral Cyclopropane Units. Benedetti and co-workers reported that the racemic lactone (±)-**11** was obtained by the basic treatment of a mixture of (±)-epibromohydrin [(±)-**14**] and **13a**, followed by acidic hydrolysis of the reaction product.[14a] In the cyclopropane ring-closure reaction between **12** or **14** and the substituted acetonitrile **13a** or **13b**, in the presence of a base, two pathways, namely, paths a and b, would be possible (Scheme 2). If a highly selective nucleophilic attack occurred either through path a or through path b, this would provide an efficient method to access the lactone **11** or *ent*-**11** in an optically active form. MaClure and co-workers studied the mode of nucleophilic substitution on various chiral 2,3-epoxypropanes with a leaving group, such as a chloro, bromo, or trifluoromethanesulfonyloxy group, at the 1-position to show that it is dependent on the leaving group as well as on the conditions used.[15] We planned to prepare the desired chiral cyclopropane lactone **11a** and its enantiomer *ent*-**11a** with (*R*)- and (*S*)-epichlorohydrins as the synthons, since they are stable and readily available in high optical purity. In the previous study, we successfully synthesized the phenylcyclopropane lactone **11b** and its enantiomer *ent*-**11b** with high optical purity (96% ee) by the reaction of (*R*)- or (*S*)-epichlorohydrin and a carbanion of phenylacetonitrile (**13b**), which clearly showed that chiral epichlorohydrins are actually useful as chiral synthons. Compound **11b** was obtained from (*R*)-**12**, while *ent*-**11b** was obtained from (*S*)-epichlorohydrin [(*S*)-**12**], which suggested that the relatively weaker leaving ability of the chloro group compared with the bromo and sulfonyloxy groups would make the highly regioselective attack of the carbanion at the epoxide terminal possible.

We first tried to develop a method for preparing the desired chiral cyclopropane units **5** and **6**, using (*R*)-**12** as the starting material. The results are shown in Scheme 3. Thus, a mixture of (*R*)-**12** and **13a** was treated with an excess of NaOEt in EtOH at room temperature for 12 h, and the unpurified reaction product was

Scheme 3



Scheme 4



subsequently subjected to acidic hydrolysis with aqueous AcOH to give the desired chiral cyclopropane derivative **11a** with 98% ee[16] in 82% yield, the stereochemistry of which was determined as described below.[17] The results showed that the highly regioselective nucleophilic attack at the epoxide terminal of (*R*)-**12** occurred via path a in this reaction, as we expected.

The reductive cleavage of the lactone ring of **11a** with $NaBH_4$ in THF/MeOH afforded the cyclopropane-1,2-dimethanol **16** in 71% yield. When **16** was treated with 1.0 equiv of *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole (1.0 equiv) in DMF at −20 °C, the sterically more unhindered hydroxyl group was selectively protected to give the desired key intermediate **10** in 84% yield. Reductive desulfonylation of compound **10** was next examined. Treatment of **10** with Mg in MeOH[14] at 55 °C produced the expected more thermodynamically stable *trans*-isomer **6** in 85% yield as the sole product.[17] We expected the corresponding *cis*-isomer **5** to be the kinetically favored product formed in the similar reductive treatment of **10** at lower temperature. Although we investigated the reaction at various temperatures, the *cis*-isomer **5** was not formed as the major product; at −20 °C, the reductive cleavage scarcely proceeded, while at 0

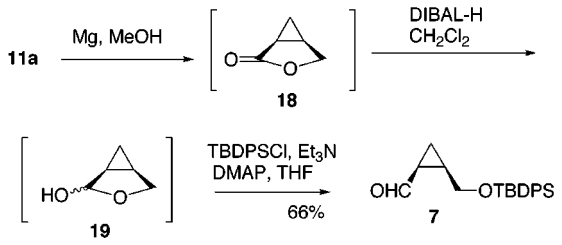
(14) (a) Benedetti, F.; Berti, F.; Risaliti, A. *Tetrahedron Lett.* **1993**, *34*, 6443−6446. (b) Brown A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749−1750.

(15) McClure, D. E.; Arison, B. H.; Baldwin, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666−3668.

(16) The optical purity was determined by chiral HPLC (Chiralcel OJ, Daicel) after conversion of **11a** into the *N*,*N*-diethylcarboxamide **17**.

(17) Compound **6** was previously synthesized from D-mannitol by Taguchi and co-workers (see ref 12d). The physical data including optical rotation of **6** prepared in this study were in accord with those reported previously.

Scheme 5



°C, 18% *cis*-isomer **5** was obtained along with 76% *trans*-isomer **6**. Swern oxidation of the *trans*-isomer **6** gave the corresponding aldehyde **8** (unit **B**, C^1 = CHO, C^2 = CH_2-OTBDPS, Figure 2).

We next tried to prepare the *cis*-substituted chiral cyclopropane **7** (unit **A**, C^1 = CHO, C^2 = CH_2OTBDPS, Figure 2) via the reductive desulfonylation of the lactone **11a** (Scheme 5). When the lactone **11a** was treated with Mg/MeOH,[14a] formation of the desired desulfonylated lactone **18** was observed by ^{1}H NMR analysis of the reaction mixture. However, **18** was not obtained in a pure form. Successive treatment of **11a** with Mg/MeOH and DIBAL-H/CH_2Cl_2 afforded the lactol **19**, which was, without purification,[18] immediately treated with TBDPSCl/Et_3N/THF. After purification by silica gel column chromatography, the desired *cis*-substituted chiral cyclopropane **7** was obtained in 66% yield from **11a**.

The relative stereochemistries of the *cis*-cyclopropylcarboxaldehyde **7** and the corresponding *trans*-isomer **8** were confirmed from NOE experiments as summarized in Figure 3.

Starting from (*S*)-epichlorohydrin, the *cis*-substituted *ent*-**7** (unit **C**, C^1 = CHO, C^2 = CH_2OTBDPS) and the *trans*-substituted *ent*-**8** (unit **D**, C^1 = CHO, C^2 = CH_2-OTBDPS), shown in Figure 2, were also prepared.

As described, an efficient method was developed for preparing the four types of chiral cyclopropane units with different stereochemistries, i.e., units **A**−**D**. These cyclopropane units are versatile intermediates for synthesizing various biologically important compounds having an asymmetric cyclopropane structure.

Synthesis of the Conformationally Restricted Analogues of Histamine. The synthesis of the folded (1*S*,2*R*)-conformationally restricted analogue **1** from the chiral cyclopropane unit **7** is summarized in Scheme 6. The imidazole ring was constructed by treating **7** with tosylmethyl isocyanide followed by ammonia in EtOH. The resulting unpurified imidazole product was further treated with TrCl and Et_3N in CH_2Cl_2 to give *N*-tritylimidazolylcyclopropane **20** in 55% overall yield. After removal of the silyl protecting group of **20**, the resulting cyclopropylmethanol **21** was Swern-oxidized to afford the aldehyde **22**. Introduction of an amino function at the 1′-position was next investigated under reductive amination conditions. Thus, the aldehyde **22** was treated with an $AcONH_4$/$NaBH_3CN$/molecular sieves 3A system in MeOH; however, the reaction gave the cyclopropylmethylamine **24** in only 32% yield. The yield improved significantly when **22** was treated with $BnONH_2$·HCl/molecular sieves 4A in THF followed by $LiAlH_4$ in THF.

(18) When **19** was isolated, the yield was low, probably due to its volatility.

(19) Horne, D. A.; Yakushijin, K.; Buchi, G. A. *Heterocycles* **1994**, *39*, 139−153.

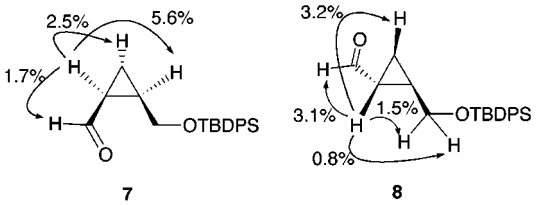
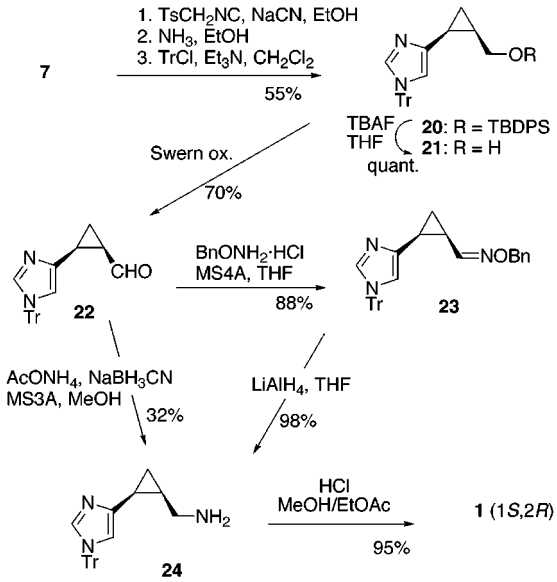
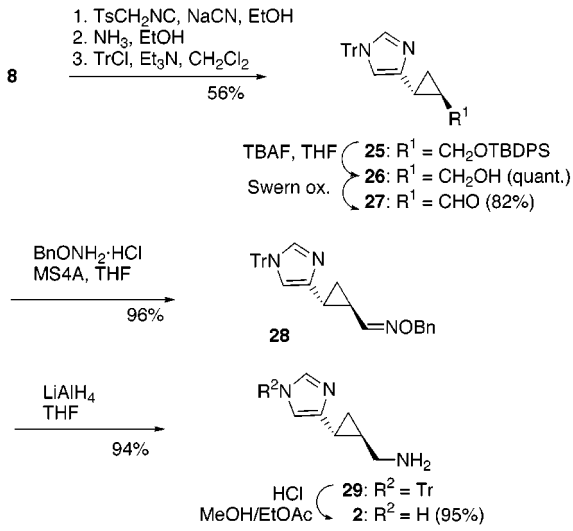


Figure 3. NOE data of compounds **7** and **8**.

Scheme 6



Scheme 7



The two-step reaction via the benzyloxime **23** afforded the desired amine **24** in 86% yield. Acidic removal of the trityl group finally gave the target compound **1** in 95% yield.

As shown in Scheme 7, the extended (1*R*,2*R*)-conformationally restricted analogue **2** was synthesized from the *trans*-disubstituted chiral cyclopropane unit **8**, according to a procedure similar to that used for the synthesis of the folded analogue **1** described above.

Using the cyclopropane units *ent*-**7** and *ent*-**8**, the folded (1*R*,2*S*)-conformationally restricted analogue *ent*-**1** and the extended (1*S*,2*S*)-conformationally restricted analogue *ent*-**2** were similarly synthesized.

Conclusion

We have developed four types of chiral cyclopropane units bearing two differentially functionalized carbon substituents in a *cis* or *trans* relationship on a cyclopropane ring, i.e., (1*S*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)-methyl-1-formylcyclopropane (**7**) and (1*R*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formylcyclopropane (**8**) and their enantiomers (*ent*-**7** and *ent*-**8**). These units were efficiently synthesized from (*R*)- or (*S*)-epichlorohydrin [(*R*)-**12** or (*S*)-**12**] and were successfully converted into (*1S*,2*R*)- and (*1R*,2*R*)-1-aminomethyl-2-(1*H*-imidazole-4-yl)cyclopropanes (**1** and **2**, respectively) and their enantiomers (*ent*-**1** and *ent*-**2**), which were designed as the conformationally restricted analogues of histamine. The chiral cyclopropane units **7**, **8**, *ent*-**7**, and *ent*-**8** should be useful as versatile intermediates for synthesizing various compounds having an asymmetric cyclopropane structure.

Experimental Section

Chemical shifts are reported in parts per million downfield from TMS. All of the ^{1}H NMR assignments described were in agreement with COSY spectra. Thin-layer chromatography was done on a Merck coated plate $60F_{254}$. Silica gel chromatography was done on Merck silica gel 5715. Reactions were carried out under an argon atmosphere.

(1*R*,5*S*)-2-Oxo-1-phenylsulfonyl-3-oxabicyclo[3.1.0]-hexane (11a). A mixture of NaOEt (21% in EtOH, 130 mL) and phenylsulfonylacetonitrile (**13a**; 14.5 g, 80.0 mmol) in EtOH (340 mL) was stirred at room temperature for 30 min, and then (*R*)-epichlorohydrin [(*R*)-**12**; 9.3 mL, 80 mmol] was added. After being stirred at room temperature for 12 h, the resulting mixture was concentrated in vacuo (to remove EtOH) and poured into H_2O (500 mL). After the pH was adjusted to about 3 with AcOH, the resulting mixture was stirred at room temperature for 5 h. To the mixture was added $CHCl_3$ (1 L) was added, 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; AcOEt/hexane, 1:4) to give **11a** as white crystals (15.6 g, 82%): mp (hexane/AcOEt/Et_2O) 113−114 °C; $[\alpha]^{25}_D$ −107.5 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (1 H, dd, J = 5.4, 5.4 Hz), 2.19 (1 H, dd, J = 5.4, 8.7 Hz), 3.18 (1 H, ddd, J = 4.8, 5.4, 8.7 Hz), 4.19 (1 H, d, J = 9.7 Hz), 4.40 (1 H, dd, J = 4.8, 9.7 Hz), 7.60 (2 H, dd, J = 7.3, 7.8 Hz), 7.71 (1 H, dd, J = 7.8, 7.8 Hz), 8.07 (2 H, d, J = 7.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$)_19.32, 26.62, 45.93, 66.90, 128.84, 129.06, 134.27, 138.06, 167.65; LR-MS (EI) *m*/*z* 238 (M^+); HR-MS (EI) calcd for $C_{11}H_{10}O_4S$ 238.0300, found 238.0298 (M^+). Anal. Calcd for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46. Found: C, 55.45; H, 4.37; S, 13.54.

(1*R*,2*S*)-1,2-Bis(hydroxymethyl)-1-phenylsulfonylcyclopropane (16). A mixture of **11a** (11.9 g, 50.0 mmol) and $NaBH_4$ (3.78 g, 100 mmol) in MeOH/THF (4:1, 200 mL) was stirred at room temperature for 12 h. The reaction was quenched with AcOH, and the resulting mixture was 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; AcOEt/hexane, 1:1 and then 2:1) to give **16** as an oil (8.62 g, 71%): $[\alpha]^{25}_D$ −36.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (1 H, dd, J = 4.8, 5.2 Hz), 1.62 (1 H, dd, J = 4.8, 9.8 Hz), 2.52 (1 H, m), 3.25 (1 H, dd, J = 4.2, 11.2 Hz), 3.34 (1 H, m), 3.41−3.53 (2 H, m), 4.13 (1 H, m), 4.35 (1 H, dd, J = 4.2, 13.6 Hz), 7.58 (2 H, t, J = 7.5 Hz), 7.68 (1 H, t, J = 7.5 Hz), 7.92 (2 H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 16.35, 24.99, 47.20, 61.07, 61.50, 128.65, 129.24 133.84, 138.32; LR-MS (EI) *m*/*z* 242 (M^+); HR-MS (EI) calcd for $C_{11}H_{14}O_4S$ 242.0613, found 242.0613 (M^+). Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 54.36; H, 5.82.

(1*R*,2*S*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-hydroxymethyl-1-phenylsulfonylcyclopropane (10). A mixture of **16** (3.27 g, 13.5 mmol), TBDPSCl (3.51 mL, 13.5 mmol), and imidazole (919 mg, 13.5 mmol) in DMF (30 mL) was stirred at −20 °C for 5 h. The reaction was quenched with MeOH, and the resulting mixture 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; AcOEt/hexane, 1:9) to give **10** as an oil (5.47 g, 84%): $[\alpha]^{24}_D$ +37.4 (*c* 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (9 H, s), 0.92 (1 H, dd, J = 5.7, 6.2 Hz), 1.87 (1 H, dd, J = 5.7, 9.7 Hz), 2.22 (1 H, dddd, H-2, J = 5.4, 6.2, 9.7, 10.0 Hz), 3.17 (1 H, dd, J = 2.6, 10.4 Hz), 3.37 (1 H, dd, J = 10.0, 11.8 Hz), 3.77 (1 H, dd, J = 2.6, 13.9 Hz), 4.07 (1 H, dd, J = 5.4, 11.8 Hz), 4.23 (1 H, dd, J = 10.4, 13.9 Hz), 7.33−7.49 (7 H, m), 7.52−7.63 (6 H, m), 7.99−8.00 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.23, 18.87, 25.37, 26.57, 47.84, 61.16, 62.92, 127.88, 127.90, 128.99, 129.01, 130.04, 130.10, 132.23, 132.30, 133.52, 135.34, 135.44, 139.19; LR-MS (EI) *m*/*z* 433 ((M − *t*-Bu)$^+$). Anal. Calcd for $C_{27}H_{32}O_4SSi$: C, 67.46; H, 6.71. Found: C, 67.28; H, 6.83.

(1*R*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-hydroxymethylcyclopropane (6) and (1*S*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-hydroxymethylcyclopropane (5). Into dry MeOH (60 mL) was placed activated Mg turnings (700 mg). The mixture was heated to 55 °C with stirring until gas evolution started (15 min), and then the mixture was cooled to 0 °C. To the mixture was added a solution of **10** (961 mg, 2.00 mmol) in dry MeOH (10 mL) in one portion, and the mixture was stirred at 50 °C for 24 h. The resulting mixture was filtered through Celite, and the filtrate was evaporated. The residue was partitioned between 1 N HCl and AcOEt, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:4) to give the *trans*-isomer **6** (578 mg, 85%) as an oil. When the same reaction was carried out at 0 °C, the *cis*-isomer **5** (125 mg, 18%) was obtained as an oil along with the *trans*-isomer **6** (519 mg, 76%). Data for **6**: $[\alpha]^{25}_D$ −11.2 (*c* 0.83, $CHCl_3$) [lit.[12d] $[\alpha]^{26}_D$ −11.2 (*c* 1.05, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.38−0.46 (2 H, m, H-3), 0.91−0.98 (2 H, m, H-1 and H-2), 1.05 (9 H, s, −C(CH_3)$_3$), 1.55 (1 H, br s, −OH), 3.38−3.48 (3 H, m, H-1′a and H-2′), 3.68 (1 H, dd, H-1′b, $J_{1'b,1}$ = 5.2, $J_{1'b,1'a}$ = 10.8 Hz), 7.36−7.43 (6 H, m, aromatic), 7.66−7.68 (4 H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.68 (C-3), 19.12 (C-1 or C-2), 19.19 (−*C*(CH_3)$_3$), 19.31 (C-1 or C-2), 26.87 (−C(*C*H_3)$_3$), 66.43 (C-1′ or C-2′), 66.46 (C-1′ or C-2′), 127.66, 129.58, 133.87, 135.56 (aromatic); LR-MS (EI) *m*/*z* 283 ((M − *t*-Bu)$^+$); HR-MS (EI) calcd for $C_{17}H_{19}O_2Si$ 283.1154, found 283.1156 ((M − *t*-Bu)$^+$). Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 73.93; H, 8.38. Data for **5**: $[\alpha]^{25}_D$ +11.4 (*c* 1.13, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (1 H, m, H-3a), 0.71 (1 H, m, H-3b), 1.06 (9 H, s, −C(CH_3)$_3$), 1.23 (1 H, m, H-2), 1.44 (1 H, m, H-1), 3.30−3.36 (3 H, m, H-1′a and H-2′a and −OH), 4.01 (1 H, m, H-1′b), 4.08 (1 H, dd, H-2′b, $J_{2'b,2}$ = 5.5, $J_{2'b,2'a}$ = 12.8 Hz), 7.38−7.47 (6 H, m, aromatic), 7.67−7.69 (2 H, m, aromatic), 7.71−7.73 (2 H, m, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.26 (C-3), 17.17 (C-1 or C-2), 18.41 (C-1 or C-2), 19.05 (−*C*(CH_3)$_3$), 26.79 (−C(*C*H_3)$_3$), 63.24 (C-1′ or C-2′), 64.92 (C-1′ or C-2′), 127.77, 127.80, 129.83, 129.86, 133.02, 134.79, 135.49, 135.60 (aromatic); LR-MS (EI) *m*/*z* 283 ((M − *t*-Bu)$^+$); HR-MS (EI) calcd for $C_{17}H_{19}O_2Si$ 283.1154; found 283.1167 ((M − *t*-Bu)$^+$); Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 73.87; H, 8.29.

(1*R*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-formylcyclopropane (8). A mixture of DMSO (1.70 mL, 24.0 mmol) and CH_2Cl_2 (20 mL) was added slowly to a solution of oxalyl chloride (1.05 mL, 12.0 mmol) in CH_2Cl_2 (10 mL) at −78 °C over 30 min, and then a solution of **6** (2.04 g, 6.00 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 (6.75 mL, 48.0 mmol) was added. After the resulting mixture was stirred at the same temperature for a further 30 min, aqueous saturated NH_4Cl and then CH_2Cl_2 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; AcOEt/hexane, 1:9) to give **8** as white crystals (1.86 g, 92%): mp (hexane/

AcOEt/*i*-Pr_2O) 48−49 °C; $[\alpha]^{24}_D$ −37.6 (*c* 1.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (9 H, s, $-C(CH_3)_3$), 1.08 (1 H, m, H-3a), 1.24 (1 H, m, H-3b), 1.73 (1 H, m, H-2), 1.83 (1 H, m, H-1), 3.64 (1 H, dd, H-2′a, $J_{2'a,2}$ = 5.4, $J_{2'a,2'b}$ = 11.0 Hz), 3.76 (1 H, dd, H-2′b, $J_{2'b,2}$ = 4.8, $J_{2'b,2'a}$ = 11.0 Hz), 7.37−7.45 (6 H, m, aromatic), 7.64 (4 H, d, aromatic, *J* = 6.6 Hz), 9.07 (1 H, d, H-1′, $J_{1',1}$ = 5.3 Hz); NOE (400 MHz, $CDCl_3$) H-1 → H-3a (3.2%), H-1 → H-1′ (3.1%), H-1 → H-2′a (1.6%), H-1 → H-2′b (0.8%), H-2 → H-3b (2.7%), H-2 → H-1′ (5.8%), H-2 → H-2′a (2.2%), H-2 → H-2′b (2.0%), H-3b → H-2 (2.2%), H-3b → H-3a (12.4%), H-3b → H-1′ (2.3%), H-1′ → H-1 (2.7%), H-1′ → H-2 (3.7%), H-1′ → H-3b (1.2%); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.75 (C-3), 19.20 ($-C(CH_3)_3$), 23.81 (C-2), 26.79 ($-C(CH_3)_3$), 27.54 (C-1), 63.74 (C-2′), 127.73, 129.77, 133.87, 135.54 (aromatic), 200.62 (C-1′); LR-MS (EI) *m*/*z* 281 ((M − *t*-Bu)$^+$); HR-MS (EI) calcd for $C_{17}H_{17}O_2Si$ 281.0998, found 281.0988 ((M − *t*-Bu)$^+$). Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.20; H, 7.49.

(1*R*,2*S*)-1-Phenylsulfonyl-2-(hydroxymethyl)-*N*,*N*-diethylcyclopropanecarboxamide (17). To a solution of **11a** (3.57 g, 15.0 mmol) and $AlCl_3$ (4.00 g, 30.0 mmol) in CH_2Cl_2 (40 mL) was slowly added Et_2NH (6.3 mL, 60 mmol) at 0 °C, and the mixture was stirred at room temperature for 5 h. To the resulting mixture was added 1 N HCl, and the whole was partitioned. The organic layer was washed with 1 N HCl and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:3) to give **17** as yellow crystals (4.52 g, 97%). The optical purity was determined by chiral HPLC (Chiralcel OJ, 0.46 × 25 cm, Daicel; hexane/EtOH, 1:1; 0.5 mL/min; 265 nm) as 98% ee: mp (hexane/AcOEt/Et_2O) 61 °C; $[\alpha]^{28}_D$ −45.3 (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (3 H, t, $-NCH_2CH_3$, *J* = 7.1 Hz), 1.24 (1 H, dd, *J* = 5.5, 5.5 Hz), 1.26 (3 H, t, *J* = 7.1 Hz), 2.16 (1 H, m), 2.23 (1 H, dd, *J* = 5.5, 9.5 Hz), 2.84 (1 H, ddd, *J* = 1.5, 12.0, 12.0 Hz), 3.23 (1 H, m), 3.47−3.58 (2 H, m), 3.85 (1 H, dd, *J* = 1.5, 12.0 Hz), 3.91−4.00 (2 H, m), 7.56 (2 H, dd, *J* = 7.5, 7.5 Hz), 7.67 (1 H, dd, *J* = 7.5, 7.5 Hz), 7.86 (2 H, d, *J* = 7.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 12.02 ($-NCH_2CH_3$), 13.48 ($-NCH_2CH_3$), 15.89 (C-3), 28.09 (C-2), 40.06 ($-NCH_2CH_3$), 43.13 ($-NCH_2CH_3$), 49.35 (C-1), 62.63 (C-1′), 128.75, 128.79, 133.96, 137.86, 163.56; LR-MS (EI) *m*/*z* 311 (M^+); HR-MS (EI) calcd for $C_{15}H_{21}NO_4S$ 311.1191, found 311.1203 (M^+). Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50; S, 10.30. Found: C, 57.67; H, 6.78; N, 4.42; S, 10.24.

(1*S*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-formylcyclopropane (7). Into dry MeOH (60 mL) was placed activated Mg turnings (700 mg). The mixture was heated to 55 °C with stirring until gas evolution started (15 min). A solution of **11a** (953 mg, 4.00 mmol) in dry MeOH (10 mL) was added to the mixture in one portion, and the mixture was stirred at room temperature for 24 h. The resulting mixture was filtered through Celite, and the filtrate was evaporated. The residue was partitioned between 1 N HCl and AcOEt, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. To a solution of the residue in CH_2Cl_2 (5 mL) was added DIBAL-H (1.0 M in hexane, 4.0 mL, 4.0 mmol) at −78 °C, and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl, and then the solvent was evaporated. The residue was partitioned between 1 N HCl and AcOEt, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. A mixture of the residue, TBDPSCl (1.04 mL, 4.00 mmol), Et_3N (1.69 mL, 12.0 mmol), and DMAP (147 mg, 1.20 mmol) in THF (5 mL) was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:4) to give **7** (887 mg, 66%) as white crystals: mp (hexane/AcOEt) 81−82 °C; $[\alpha]^{23}_D$ +5.8 (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (9 H, s, $-C(CH_3)_3$), 1.19 (1 H, m, H-3a), 1.27 (1 H, m, H-3b), 1.76 (1 H, m, H-2), 1.95 (1 H, m, H-1), 3.67 (1 H, dd, H-2′a, $J_{2'a,2}$ = 8.2, $J_{2'a,2'b}$ = 11.4 Hz), 4.00 (1 H, dd, H-2′b, $J_{2'b,2}$ = 5.6, $J_{2'b,2'a}$ = 11.4 Hz), 7.37−7.45 (6 H, m, aromatic), 7.63−7.67 (4 H, m, aromatic), 9.37 (1 H, d, H-1′, $J_{1',1}$ = 5.5 Hz); NOE (400 MHz, $CDCl_3$) H-1 → H-2 (5.6%), H-1 → H-3b (2.5%), H-1 → H-1′ (1.7%), H-2 → H-1 (6.1%), H-2 → H-3b (4.5%), H-2 → H-2′a (2.6%), H-2 → H-2′b (1.0%); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.18 (C-3), 19.16 ($-C(CH_3)_3$), 25.88 (C-2), 26.78 ($-C(CH_3)_3$), 27.40 (C-1), 62.07 (C-2′), 127.70, 127.72, 129.74, 133.35, 135.55 (aromatic), 200.65 (C-1′); LR-MS (EI) *m*/*z* 281 ((M − *t*-Bu)$^+$); HR-MS (EI) calcd for $C_{17}H_{17}O_2Si$ 281.0998, found 281.0996 ((M − *t*-Bu)$^+$). Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.36; H, 7.74.

(1*S*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (20). To a suspension of tosylmethyl isocyanide (1.07 g, 5.50 mmol) and **7** (1.86 g, 5.50 mmol) in EtOH (10 mL) was added NaCN (40 mg, 0.82 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. A mixture of the resulting solution and saturated NH_3 in EtOH (60 mL) was heated at 125 °C in a stainless steel tube for 24 h. After the mixture was cooled, the solvent was evaporated, and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:1, and then MeOH/$CHCl_3$, 1:19) to give the crude imidazole compound as an oil. A solution of the oil, TrCl (1.53 g, 5.50 mmol), and Et_3N (1.55 mL, 11.0 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h, and then the reaction mixture was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:1, and then MeOH/$CHCl_3$, 1:19) to give **20** as a solid (1.87 g, 55%): $[\alpha]^{24}_D$ +0.27 (*c* 0.78, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.56 (1 H, m), 0.91 (1 H, m), 0.98 (9 H, s), 1.32 (1 H, m), 2.01 (1 H, m), 3.45 (1 H, dd, *J* = 7.2, 11.0 Hz), 3.77 (1 H, dd, *J* = 7.1, 11.0 Hz), 6.50 (1 H, s), 7.06−7.08 (6 H, m), 7.22−7.38 (16 H, m), 7.58−7.63 (4 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.01, 14.18, 19.16, 20.53, 26.90, 64.25, 75.01, 118.62, 127.47, 127.85, 127.91, 129.34, 129.37, 129.71, 134.31, 134.36, 135.53, 135.61, 137.99, 139.46, 142,; LR-MS (FAB) *m*/*z* 619 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{42}H_{43}N_2OSi$ 619.3145, found 619.3143 (M + H)$^+$). Anal. Calcd for $C_{42}H_{42}N_2OSi$: C, 81.51; H, 6.84; N, 4.53. Found: C, 81.84; H, 6.81; N, 4.30.

(1*S*,2*R*)-2-Hydroxymethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (21). A solution of **20** (743 mg, 1.20 mmol) and TBAF (1.0 M in THF, 2.4 mL, 2.4 mmol) in THF (6 mL) was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:1, and then MeOH/$CHCl_3$, 1:19) to give **21** as white crystals (447 mg, 100%): mp (hexane/AcOEt) 164−166 °C; $[\alpha]^{24}_D$ +32.1 (*c* 0.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.60 (1 H, m), 0.95 (1 H, m), 1.47 (1 H, m) 1.97 (1 H, m), 3.05 (1 H, dd, *J* = 9.8, 11.8 Hz), 3.91 (1 H, dd, *J* = 4.2, 11.8 Hz), 6.65 (1 H, s), 7.10−7.13 (6 H, m), 7.31−7.34 (10 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.53, 13.40, 19.61, 62.83, 75.29, 120.53, 128.03, 128.04, 129.70, 137.88, 140.06, 142,32; LR-MS (EI) *m*/*z* 380 (M^+); HR-MS (EI) calcd for $C_{26}H_{24}N_2O$ 380.1889, found 380.1899 (M^+). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.15; H, 6.38; N, 7.17.

(1*S*,2*R*)-2-Formyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (22). A mixture of DMSO (0.14 mL, 2.00 mmol) and CH_2Cl_2 (3 mL) was added slowly to a solution of oxalyl chloride (87 μL, 1.0 mmol) in CH_2Cl_2 (2 mL) at −78 °C over 30 min. A solution of **21** (190 mg, 0.50 mmol) in CH_2Cl_2 was added slowly to the resulting mixture, and the whole was stirred at the same temperature for 2 h. After addition of Et_3N (0.53 mL, 4.0 mmol), the resulting mixture was stirred at −78 °C for a further 30 min, and then saturated aqueous NH_4Cl and CH_2Cl_2 were added and partitioned. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (silica gel; AcOEt/hexane, 1:2) to give **22** as white crystals (133 mg, 70%): mp (hexane/AcOEt) 166−167 °C; $[\alpha]^{25}_D$ +94.8 (*c* 1.21, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.50 (1 H, m), 1.92 (1 H, m), 2.03 (1 H, m), 2.59 (1 H, m), 6.69 (1 H, s), 7.10−7.14 (6 H, m), 7.10−7.14 (10 H, m), 9.10 (1 H, d, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.17, 20.35, 30.10, 75.29, 119.90, 128.04, 128.05, 129.69, 136.81, 136.36, 142.28, 202.03; LR-MS (FAB)

m/*z* 379 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{26}H_{23}N_2O$ 379.1810, found 379.1780 ((M + H)$^+$). Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.43; H, 6.02; N, 7.22.

(1*R*,2*S*)-2-(Benzyloxyimino)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (23). A mixture of **22** (378 mg, 1.00 mmol), *O*-benzylhydroxylamine hydrochloride (319 mg, 2.00 mmol), and molecular sieves 4A (300 mg) in THF (5 mL) was stirred at room temperature for 12 h. The mixture was filtered through Florisil, and the filtrate was evaporated. The residue was purified by short column chromatography (silica gel; AcOEt/hexane, 1:1) to give **23** as white crystals (*E*/*Z* mixture; 425 mg, 88%). The *E*/*Z* mixture (242 mg, 0.5 mmol) was separated further by column chromatography (silica gel; AcOEt/hexane, 1:1) to give the (*E*)-isomer (118 mg) and the (*Z*)-isomer (94 mg). Data for ***(E)-23***: mp (hexane/AcOEt) 150−151 °C; $[\alpha]^{24}_D$ +42.4 (*c* 1.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28−1.36 (2 H, m), 1.94 (1 H, m), 2.33 (1 H, m), 5.02 (2 H, s), 6.60 (1 H, s), 7.09−7.12 (6 H, m), 7.16 (1 H, d, *J* = 8.8 Hz), 7.26−7.34 (15 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.17, 16.77, 18.77, 75.20, 75.44, 119.41 (C-5"), 127.65, 127.97, 128.01, 128.11, 128.29, 129.72, 137.86, 138.21, 138.34, 142.40, 152.64; LR-MS (FAB) *m*/*z* 484 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{33}H_{30}N_3O$ 484.2388, found 484.2387 ((M + H)$^+$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.88; H, 6.02; N, 8.42. Data for ***(Z)-23***: mp (hexane/AcOEt) 148−151 °C; $[\alpha]^{24}_D$ +98.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30−1.40 (2 H, m), 2.36 (1 H, m), 2.56 (1 H, m), 5.09 (2 H, s), 6.40 (1 H, d, *J* = 8.8 Hz), 6.64 (1 H, d, *J* = 0.8 Hz), 7.10−7.13 (6 H, m), 7.30−7.37 (15 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.01, 15.29, 17.33, 75.19, 75.63, 119.42, 127.58, 127.95, 128.00, 128.34, 128.43, 129.70, 137.42, 138.07, 138.35, 142.39, 152.26; LR-MS (FAB) *m*/*z* 484 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{33}H_{30}N_3O$ 484.2388, found 484.2366 ((M + H)$^+$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.88; H, 6.01; N, 8.52.

(1*S*,2*R*)-2-Aminomethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (24). Reductive Amination of 22. A suspension of **22** (38 mg, 0.10 mmol), $AcONH_4$ (77 mg, 1.0 mmol), and molecular sieves 3A (30 mg) in MeOH (3 mL) was stirred at room temperature for 1 h, and then $NaBH_3CN$ (6.3 mg, 0.1 mmol) was added. The resulting mixture was stirred at room temperature for 12 h, and then the solvent was evaporated. The residue was partitioned between $CHCl_3$ 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; MeOH/$CHCl_3$, 1:19 and then 1:4) to give **24** as white crystals (13 mg, 32%).

Reduction of 23. To a solution of **23** (242 mg, 0.50 mmol) in THF (5 mL) was added $LiAlH_4$ (1.0 M in THF, 1.5 mL), and the mixture was stirred at room temperature for 1 h. After the reaction was quenched with MeOH, the solvent was evaporated, and the residue was partitioned between $CHCl_3$ 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; MeOH/$CHCl_3$, 1:19 and then 1:4) to give **24** as white crystals (187 mg, 98%): mp (EtOH/Et_2O) 110−112 °C; $[\alpha]^{24}_D$ +45.97 (*c* 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 0.68 (1 H, m), 1.04 (1 H, m), 1.29 (1 H, m), 2.06 (1 H, m), 2.65 (2 H, m), 6.70 (1 H, s), 7.03−7.05 (6 H, m), 7.28−7.32 (10 H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 10.49, 14.90, 16.02, 41.33, 76.99, 122.00, 129.31, 129.42, 130.79, 139.37, 139.57, 143.56; LR-MS (FAB) *m*/*z* 380 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{26}H_{26}N_3$ 380.1889, found 380.2152 ((M + H)$^+$). Anal. Calcd for $C_{26}H_{25}N_3 \cdot 5H_2O$: C, 66.50; H, 7.51; N, 8.95. Found: C, 66.58; H, 7.53; N, 8.88.

(1*S*,2*R*)-2-Aminomethyl-1-(1*H*-imidazol-4-yl)cyclopropane Dihydrochloride (1). A solution of **24** (20 mg, 53 μmol), HCl (4.0 M in AcOEt, 1.5 mL), and MeOH (0.5 mL) was heated under reflux for 2 h. The solvent was evaporated, and then the residue was treated with Et_2O to give a white amorphous solid of **1** as a dihydrochloride (110 mg, 95%): $[\alpha]^{24}_D$ −24.7 (*c* 0.12, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 0.98 (1 H, m, H-3a), 1.34 (1 H, m, H-3b), 1.54 (1 H, m, H-2), 2.22−2.30 (2 H, m, H-1 and H-1′a), 3.05 (1 H, dd, H-1′b, $J_{1'b,2}$ = 7.0, $J_{1'b,1'a}$ = 12.0 Hz), 7.31 (1 H, s, H-5″), 8.75 (1 H, s, H-2″); ^{13}C NMR (125 MHz, CD_3OD) δ 10.70 (C-3), 11.66 (C-1), 16.85 (C-2), 40.93 (C-1′), 118.33 (C-5″), 132.43 (C-4″), 135.40 (C-2″); LR-MS (FAB) *m*/*z* 138 ((M + H)$^+$); HR-MS (FAB) calcd for $C_7H_{12}N_3$ 138.1031, found 138.0996 ((M + H)$^+$). Anal. Calcd for $C_7H_{13}Cl_2N_3 \cdot H_2O$ C, 36.86; H, 6.63; N, 18.42. Found: C, 36.66; H, 6.82; N, 18.25.

(1*R*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (25). Compound **25** was prepared from **8** (1.86 g, 5.50 mmol) as described for **20**. After purification by column chromatography (silica gel; AcOEt/hexane, 1:1, and then MeOH/$CHCl_3$,1:19), **25** was obtained as a solid (1.90 g, 56%): mp (hexane/AcOEt) 145−147 °C; $[\alpha]^{24}_D$ −38.3 (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (1 H, m), 0.92 (1 H, m), 1.03 (9 H, s), 1.45 (1 H, m), 1.65 (1 H, m), 3.69 (2 H, d, *J* = 7.1 Hz), 6.50 (1 H, d, *J* = 0.9 Hz), 7.13−7.15 (6 H, m), 7.27 (1 H, s), 7.31−7.34 (13 H, m), 7.36−7.39 (2 H, m), 7.65 (4 H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.64, 14.36, 19.24, 22.76, 26.87, 66.19, 75.05, 116.90, 127.53, 127.90, 127.93, 129.46, 129.80, 134.00, 134.05, 135.61, 138.13, 142.48, 142,57; LR-MS (FAB) *m*/*z* 641 ((M + Na)$^+$); HR-MS (FAB) calcd for $C_{42}H_{42}N_2NaOSi$ 641.2964, found 641.2977 ((M + Na)$^+$). Anal. Calcd for $C_{42}H_{42}N_2OSi$: C, 81.51; H, 6.84; N, 4.53. Found: C, 81.54; H, 6.92; N, 4.36.

(1*R*,2*R*)-2-Hydroxymethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (26). Compound **26** was prepared from **25** (743 mg, 1.20 mmol) as described for **21**. After purification by column chromatography (silica gel; AcOEt/hexane, 1:1, and then MeOH/$CHCl_3$, 1:19), **26** was obtained as white crystals (447 mg, 100%): mp (hexane/AcOEt) 146−147 °C; $[\alpha]^{24}_D$ −34.6 (*c* 1.13, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$: CD_3OD, 10:1) δ 0.72 (1 H, m), 0.86 (1 H, m), 1.29 (1 H, m), 1.70 (1 H, m), 3.29 (1 H, dd, *J* = 8.1, 11.4 Hz), 3.69 (1 H, dd, *J* = 5.5, 11.4 Hz), 6.49 (1 H, d, *J* = 0.7 Hz), 7.09−7.12 (6 H, m), 7.30 (1 H, d, *J* = 1.1 Hz) 7.32−7.35 (9 H, m); ^{13}C NMR (125 MHz; $CDCl_3$/CD_3OD, 10:1) δ 10.35, 15.01, 23.32, 65.86, 75.29, 116.90, 127.95, 127.99, 129.61, 137.84, 141.95, 142,12; LR-MS (EI) *m*/*z* 380 (M$^+$); HR-MS (EI) calcd for $C_{26}H_{24}N_2O$ 380.1889, found 380.1883 (M$^+$). Anal. Calcd for $C_{26}H_{24}N_2O \cdot H_2O$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.58; H, 6.53; N, 7.04.

(1*R*,2*R*)-2-Formyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (27). Compound **27** was prepared from **26** (190 mg, 0.50 mmol) as described for **22**. After purification by column chromatography (silica gel; AcOEt/hexane, 1:2), **27** was obtained as white crystals (155 mg, 82%): mp (hexane/AcOEt) 162−163 °C; $[\alpha]^{24}_D$ −105.7 (*c* 1.15, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59−1.66 (2 H, m), 2.30 (1 H, m), 2.50 (1 H, m), 6.67 (1 H, s), 7.11−7.15 (6 H, m), 7.31 (1 H, d, *J* = 0.9 Hz), 7.32−7.34 (9 H, m), 9.27 (1 H, d, *J* = 4.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.32, 20.74, 32.36, 75.26, 118.19, 128.02, 128.18, 129.68, 138.58, 138.76, 142.27, 200.09; LR-MS (FAB) *m*/*z* 401 ((M + Na)$^+$); HR-MS (FAB) calcd for $C_{26}H_{22}N_2NaO$ 401.1630, found 401.1634 ((M + Na)$^+$). Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.66; H, 6.04; N, 7.16.

(1*R*,2*R*)-2-(Benzyloxyimino)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (28). Compound **28** was prepared from **27** (378 mg, 1.00 mmol) as described for **23**. After purification by short column chromatography (silica gel; AcOEt/hexane, 1:1), the *E*/*Z* mixture of **28** was obtained as white crystals (463 mg, 96%). The *E*/*Z* mixture (242 mg, 0.50 mmol) was separated further by column chromatography (silica gel; AcOEt/hexane, 1:1) to give the (*E*)-isomer (129 mg) and the (*Z*)-isomer (85 mg). Data for ***(E)-28***: mp (hexane/AcOEt) 162−163 °C; $[\alpha]^{24}_D$ −76.2 (*c* 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (1 H, m), 1.39 (1 H, m), 1.97 (1 H, m), 2.05 (1 H, m), 5.02 (2 H, s), 6.59 (1 H, d, *J* = 1.2 Hz), 7.10−7.15 (7 H, m), 7.26−7.36 (15 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.88, 18.13, 20.68, 75.13, 75.54, 117.43, 127.74, 127.95, 128.22, 128.32, 128.41, 129.72, 137.40, 138.39, 140.23, 142.40, 153.08; LR-MS (FAB) *m*/*z* 484 ((M + H)$^+$); HR-MS (FAB) calcd $C_{33}H_{30}N_3O$ 484.2388, found 484.2383 ((M + H)$^+$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.66; H, 6.05; N, 8.63. Data for ***(Z)-28***: mp (hexane/AcOEt) 159−160 °C; $[\alpha]^{24}_D$ +80.3 (*c* 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (1 H, m), 1.48 (1 H, m), 2.07 (1 H, m), 2.63 (1 H, m), 5.09 (2 H, s), 6.11 (1 H, d, *J* = 7.9 Hz), 6.61 (1 H, d, *J* =

1.0 Hz), 7.12−7.15 (6 H, m), 7.27−7.37 (15 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.09, 18.05, 18.26, 75.19, 75.68, 117.58, 127.58, 127.93, 127.96, 127.98, 128.27, 129.76, 138.16, 138.49, 140.06, 142.42, 153.62; LR-MS (FAB) *m*/*z* 484 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{33}H_{30}N_3O$ 484.2388, found 484.2384 ((M + H)$^+$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.66; H, 6.05; N, 8.63.

(1*R*,2*R*)-2-Aminomethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (29). Compound **29** was prepared from **28** (*E*/*Z* mixture; 242 mg, 0.50 mmol) as described for **24**. After purification by column chromatography (silica gel; MeOH/$CHCl_3$, 1:19 and then 1:4), **29** was obtained as white crystals (179 mg, 94%): mp (EtOH/Et_2O) 137−139 °C; $[\alpha]^{24}_D$ −43.5 (*c* 0.27, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 0.91 (1 H, m), 1.07 (1 H, m), 1.34 (1 H, m), 1.87 (1 H, m), 2.87 (1 H, dd, *J* = 8.0, 13.2 Hz), 2.96 (1 H, dd, *J* = 7.1, 13.2 Hz), 6.74 (1 H, d, *J* = 1.2 Hz), 7.12−7.15 (6 H, m), 7.35 (1 H, d, *J* = 1.2 Hz), 7.36−7.38 (9 H, m); ^{13}C NMR (125 MHz, CD_3OD) δ 12.87, 16.68, 19.24, 44.71, 76.88, 119.20, 129.25, 129.36, 130.81, 139.36, 141.93, 143.61; LR-MS (FAB) *m*/*z* 380 ((M + H)$^+$); HR-MS (FAB) calcd for $C_{26}H_{26}N_3$ 380.2127, found 380.2152 ((M + H)$^+$). Anal. Calcd for $C_{26}H_{25}N_3 \cdot 5H_2O$: C, 66.50; H, 7.51; N, 8.95. Found: C, 66.68; H, 7.55; N, 8.78.

(1*R*,2*R*)-2-Aminomethyl-1-(1*H*-imidazol-4-yl)cyclopropane Dihydrochloride (2). Compound **2** was prepared from **29** (20 mg, 53 μmol) as described for **1**. After treatment with Et_2O, white crystals of **2** were obtained as a dihydrochloride (11 mg, 95%): mp (EtOH/Et_2O) 182−183 °C; $[\alpha]^{24}_D$ −72.3 (*c* 0.21, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 1.18−1.26 (2 H, m, H-3), 1.56 (1 H, m, H-2), 2.12 (1 H, m, H-1), 2.98 (1 H, dd, H-1′a, $J_{1'a,2}$ = 7.6, $J_{1'a,1'b}$ = 13.3 Hz), 3.10 (1 H, dd, H-1′b, $J_{1'b,2}$ = 7.6, $J_{1'b,1'a}$ = 13.3 Hz), 7.34 (1 H, s, H-5″), 8.79 (1 H, s, H-2″); ^{13}C NMR (125 MHz, CD_3OD) δ 13.78 (C-3), 14.11 (C-1), 20.12 (C-2), 44.75 (C-1′), 117.27 (C-5″), 135.51 (C-2″), 136.42 (C-4″); LR-MS (FAB) *m*/*z* 138 ((M + H)$^+$); HR-MS (FAB) calcd for $C_7H_{12}N_3$ 138.1031, found 138.1048 ((M + H)$^+$). Anal. Calcd for $C_7H_{13}Cl_2N_3$: C, 40.02; H, 6.24; N, 20.00. Found: C, 39.81; H, 6.12; N, 19.60.

Data for (1*S*,5*R*)-2-oxo-1-phenylsulfonyl-3-oxabicyclo-[3.1.0]hexane (*ent*-11a): mp (hexane/AcOEt/Et_2O) 113−114 °C; $[\alpha]^{25}_D$ +111.2 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46. Found: C, 55.37; H, 4. 31; S, 13.49.

Data for (1*S*,2*R*)-1,2-bis(hydroxymethyl)-1-phenylsulfonylcyclopropane (*ent*-16): $[\alpha]^{23}_D$ +37.4 (*c* 1.23, $CHCl_3$). Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82. Found: C, 54.26; H, 5.85.

Data for (1*S*,2*R*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-hydroxymethyl-1-phenylsulfonylcyclopropane (*ent*-10): $[\alpha]^{24}_D$ −35.8 (*c* 1.15, $CHCl_3$). Anal. Calcd for $C_{27}H_{32}O_4SSi$: C, 67.46; H, 6.71. Found: C, 67.34; H, 6.86.

Data for (1*R*,2*S*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-hydroxymethylcyclopropane (*ent*-5): $[\alpha]^{24}_D$ −12.0 (*c* 1.28, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 73.76; H, 8.34.

Data for (1*S*,2*S*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-hydroxymethylcyclopropane (*ent*-6): $[\alpha]^{24}_D$ +11.1 (*c* 0.55, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 74.15; H, 8.22.

Data for (1*R*,2*S*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formylcyclopropane (*ent*-7): mp (hexane/AcOEt) 79−81 °C; $[\alpha]^{25}_D$ −5.1 (*c* 1.75, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.31; H, 7.82.

Data for (1*S*,2*S*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-formylcyclopropane (ent-8): mp (hexane/AcOEt/*i*-Pr_2O) 48−50 °C; $[\alpha]^{23}_D$ +38.2 (*c* 1.04, $CHCl_3$). Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.80; H, 7.76.

Data for (1*R*,2*S*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-20): $[\alpha]^{24}_D$ −0.20 (*c* 2.07, $CHCl_3$). Anal. Calcd for $C_{42}H_{43}N_2OSi$: C, 81.51; H, 6.84; N, 4.53. Found: C, 81.34; H, 6.54; N, 4.35.

Data for (1*R*,2*S*)-2-hydroxymethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-21): mp (hexane/AcOEt) 163−165 °C; $[\alpha]^{24}_D$ −32.5 (*c* 1.25, $CHCl_3$). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 81.98; H, 6.32; N, 7.08.

Data for (1*R*,2*S*)-2-formyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-22): mp (hexane/AcOEt) 167−168 °C; $[\alpha]^{23}_D$ −95.2 (*c* 1.55, $CHCl_3$). Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.41; H, 5.92; N, 7.16.

Data for (1*S*,2*S*)-(*E*)-2-(benzyloxyimino)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane [*ent*-(*E*)-23]: mp (hexane/AcOEt) 150−152 °C; $[\alpha]^{24}_D$ −42.5 (*c* 2.84, $CHCl_3$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.87; H, 6.12; N, 8.77.

Data for (1*S*,2*S*)-(*Z*)-2-(benzyloxyimino)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane [*ent*-(*Z*)-23]: mp (hexane/AcOEt) 149−151 °C; $[\alpha]^{24}_D$ −96.2 (*c* 1.31, $CHCl_3$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.92; H, 6.04; N, 8.69.

Data for (1*R*,2*S*)-2-aminomethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-24): mp (EtOH/Et_2O) 109−110 °C; $[\alpha]^{23}_D$ −46.2 (*c* 0.40, $CHCl_3$). Anal. Calcd for $C_{26}H_{25}N_3 \cdot 5H_2O$: C, 66.50; H, 7.51; N, 8.95. Found: C, 66.62; H, 7.54; N, 8.63.

Data for (1*R*,2*S*)-2-aminomethyl-1-(1*H*-imidazol-4-yl)-cyclopropane Dihydrochloride (*ent*-1): $[\alpha]^{23}_D$ +24.1 (*c* 0.30, MeOH). Anal. Calcd for $C_7H_{13}Cl_2N_3 \cdot H_2O$ C, 36.86; H, 6.63; N, 18.42. Found: C, 36.77; H, 6.53; N, 18.44.

Data for (1*S*,2*S*)-2-(*tert*-butyldiphenylsilyloxy)methyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-25): mp (hexane/AcOEt) 147−148 °C; $[\alpha]^{24}_D$ +38.9 (*c* 1.59, $CHCl_3$). Anal. Calcd for $C_{42}H_{42}N_2OSi$: C, 81.51; H, 6.84; N, 4.53. Found: C, 81.35; H, 6.89; N, 4.38.

Data for (1*S*,2*S*)-2-hydroxymethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-26): mp (hexane/AcOEt) 143−145 °C; $[\alpha]^{25}_D$ +36.4 (*c* 1.06, MeOH). Anal. Calcd for $C_{26}H_{24}N_2O \cdot H_2O$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.48; H, 6.32; N, 7.08.

Data for (1*S*,2*S*)-2-formyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-27): mp (hexane/AcOEt) 162−163 °C; $[\alpha]^{24}_D$ +101.0 (*c* 1.09, MeOH). Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.66; H, 6.04; N, 7.16.

Data for (1*S*,2*S*)-(*E*)-2-benzyloxyiminomethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane [*ent*-(*E*)-28]: mp (hexane/AcOEt) 162−164 °C; $[\alpha]^{24}_D$ +75.2 (*c* 2.84, $CHCl_3$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.75; H, 6.08; N, 8.62.

Data for (1*S*,2*S*)-(*Z*)-2-benzyloxyiminomethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane [*ent*-(*Z*)-28]:mp (hexane/AcOEt) 159−161 °C; $[\alpha]^{24}_D$ −81.3 (*c* 1.31, $CHCl_3$). Anal. Calcd for $C_{33}H_{29}N_3O$: C, 81.96; H, 6.04; N, 8.69. Found: C, 81.59; H, 6.01; N, 8.55.

Data for (1*S*,2*S*)-2-aminomethyl-1-(1-triphenylmethyl-1*H*-imidazol-4-yl)cyclopropane (*ent*-29): mp (EtOH/Et_2O) 138−139 °C; $[\alpha]^{24}_D$ +48.6 (*c* 0.33, MeOH). Anal. Calcd for $C_{26}H_{25}N_3 \cdot 5H_2O$: C, 66.50; H, 7.51; N, 8.95. Found: C, 66.69; H, 7.32; N, 8.72.

Data for (1*S*,2*S*)-2-aminomethyl-1-(1*H*-imidazol-4-yl)-cyclopropane Dihydrochloride (*ent*-2): mp (EtOH/Et_2O) 182−183 °C; $[\alpha]^{24}_D$ +72.9 (*c* 0.18, MeOH). Anal. Calcd for $C_7H_{13}Cl_2N_3$: C, 40.02; H, 6.24; N, 20.00. Found: C, 39.92; H, 6.22; N, 19.88.

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