Synthesis of (±)-*trans*- or *cis*-(5-Aminomethyltetrahydrofuranyl)imidazole by Mitsunobu Cyclization: Synthetic Studies toward Novel Histamine H_3 or H_4-Ligands

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The (±)-*trans*- or *cis*-4(5)-(5-aminomethyltetrahydrofuranyl)imidazole [1 and 2] were synthesized by the Mitsunobu cyclization, starting from L-glutamic acid.

Key words Mitsunobu reaction; cyclization; 1,4-diol; H_3; H_4

A new histamine receptor designed as histamine $H_4(H_4)$-receptor has been characterized through homology searching of genomic databases by several groups in 2000.[1] The H_4-receptor has a very similar amino acid sequence and pharmacological characteristics to the histamine $H_3(H_3)$-receptor.[2,3] Thus, all the well-known H_3-receptor ligands bind to the H_4-receptor. To investigate the possible physiological function of the H_4-receptor, a specific ligand is required.

The H_3-agonistic activity of (±)-*trans*-4(5)-(5-aminomethyltetrahydrofuranyl)imidazole [(±)-1] was found from the preliminary results of an *in vivo* rat microdialysis.[4—6] The H_3-agonistic activity of (±)-1 was approximately equal to that of the current H_3-agonist, immepip. Further, (+)-(2*R*,5*R*)-1 (imifuramine) was identified as the eutomer exhibiting H_3-agonistic activity (Fig. 1). We very recently revealed that the enantiomer (−)-1 of imifuramine showed approximately 300-fold higher selectivity at the human H_3-receptor than the human H_4-receptor.[7] More interestingly, a cyanoguanidine derivative [(−)-3, OUP-16] of imifuramine and its *cis*-stereoisomer [(+)-4, OUP-13] having the 2*R*,5*S*-configuration exhibited the full agonistic activities for the human histamine H_4-receptor with a 40- to 45-fold selectivity over the human H_3-receptor.[7]

We herein describe the synthesis of *trans*- or *cis*-4(5)-(5-aminomethyltetrahydrofuranyl)imidazole [(±)-1 and 2], which was the clue to the development of H_3- or H_4-ligands, starting from L-glutamic acid. It was also found that Mitsunobu cyclization in this synthesis gave products with low optical purities owing to indistinguishable activation between two hydroxy groups of a chiral 1,4-diol intermediate.

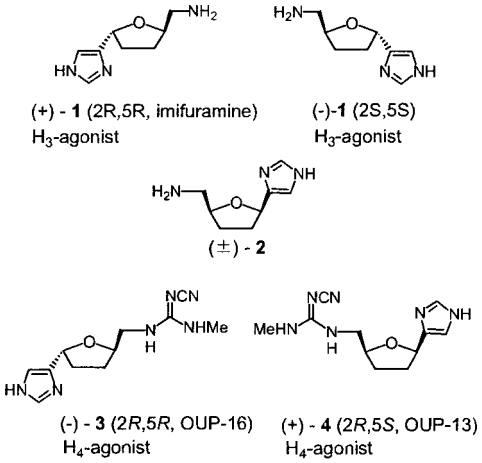

Fig. 1

Results and Discussion

Reduction of (*S*)-benzyloxymethyl-γ-butyrolactone (**5**)[8] with DIBAL-H followed by an addition of lithium salt **6**[9] of 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide[10] afforded adduct **7ab** in quantitative yield as an inseparable 1 : 1 diastereomeric mixture (Chart 1). Yokoyama *et al.* previously reported[11] the synthesis of *C*-ribonucleosides having typical aromatic heterocycles using standard Mitsunobu conditions (DEAD, Ph_3P),[12] in which the cyclization of the corresponding diols proceeds through an intramolecular S_N2 reaction of the C1′-oxyphosphonium intermediate, and the orientation of the glycosidic linkage is controlled by the C1′ configuration of the substrate: one isomer affords an α-anomer and the other, β-anomer (Chart 2). Thus, Mitsunobu cyclizations of **7a** (1′*R*) or 1′*S*-diastereomer **7b** are required selective formations of C1′-oxyphosphonium intermediates to obtain products with high optical purities.

The cyclization of **7ab** using *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[13] and Bu_3P at room temperature for 18 h afforded an inseparable 1 : 1 mixture of *trans*- and *cis*-cyclization product **8ab** in 97% yield. Desilylation of **8ab** using tetrabutylammonium fluoride, followed by flash chromatography provided **9a** and the less polar **9b**, in 47% and 53% yields, respectively. In ^{1}H-NMR, two C5′-protons (δ 3.51, 3.55) of *cis*-isomer **9b** were individually observed and shifted downfield compared to those (δ 3.49) of the *trans*-isomer. These results presumably reflect the rotational hindrance of the C4′–C5′ bond and deshielding effects due to imidazole. However, since nuclear Overhauser effect (NOE) experiments of **9a** and **9b** did not show significant differences, their relative configurations were not established at this stage. On the other hand, in the measurements of the optical rotatory dispersion (ORD) of **9a** and **9b**, their ORD curves did not, unexpectedly, show variations of optical activities with respect to wavelengths. Furthermore, HPLC on a chiral stationary column demonstrated that compounds **9a**

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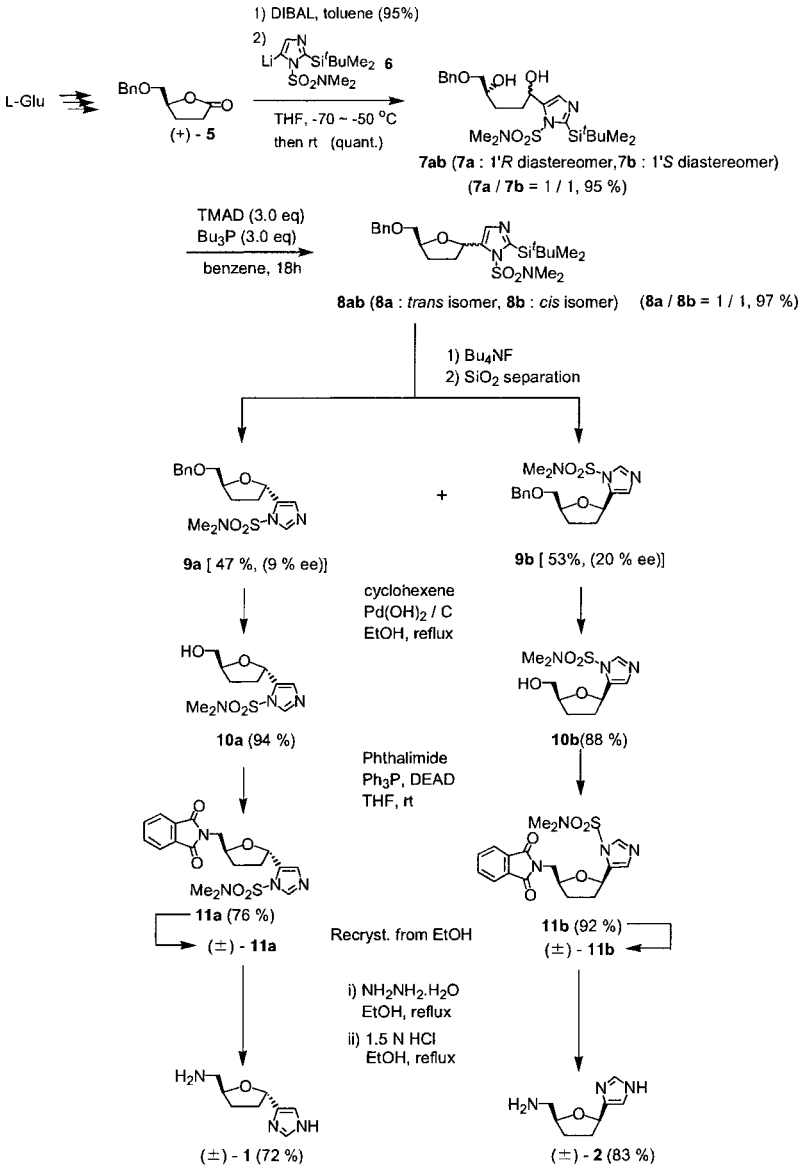


Chart 1

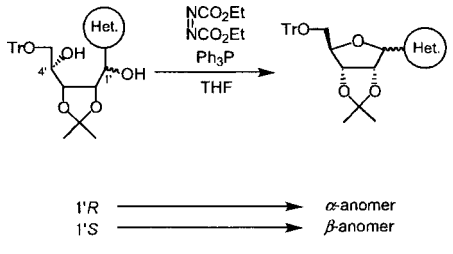


Chart 2

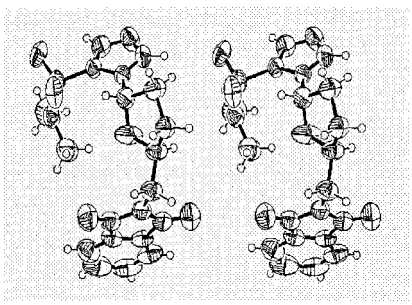
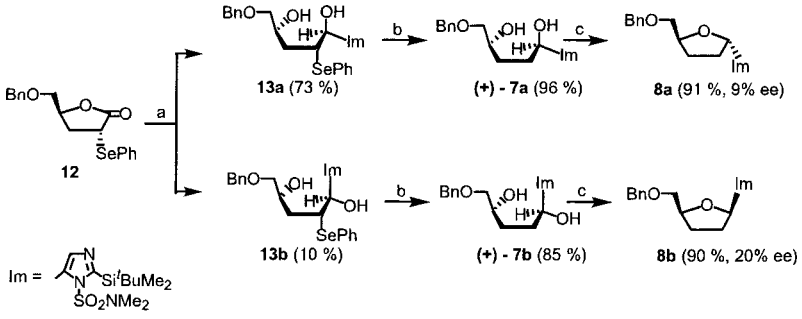


Fig. 2. X-Ray Determined Structure of (±)-**11a**

and **9b** were 1 : 1.2 (9% ee) and 1 : 1.5 (20% ee) enantiomeric mixtures, respectively. These results suggested that the cyclization of **7ab** proceeded through simultaneous cyclization *via* C1′ and C4′-oxyphosphonium salts.

Debenzylation of **9a** and **9b** using $Pd(OH)_2$–C in cyclohexene afforded primary alcohols **10a** and **10b** in 94% and 88% yields, respectively, which were subjected to phthalimidation using DEAD, Ph_3P, and phthalimide to yield **11a** (76%) and **11b** (92%), respectively. To determine the relative configuration, phthalimide **11a** was recrystallized from EtOH to afford a racemic crystal, which was analyzed using X-ray crystallography indicating *trans*-configuration between C2′ and C5′ of **11a**, as shown in Fig. 2. The space group of the single crystal **11a** from the X-ray analysis belonged to P-1, which indicated a racemic compound. It has been reported that in some cases, racemates crystallize more readily than



[a] Reagents : (a) reference 6; (b) Et_3B, Bu_3SnH; (c) Bu_3P, TMAD

Chart 3

their optically pure compounds.[14] Deprotection of phthalimides (±)-**11a** using hydrazine hydrate, followed by hydrolysis using aqueous 1.5 N HCl produced (±)-*trans*-amine **1** in 72% yields. In a similar manner, the (±)-*cis*-amine **2** was synthesized from phthalimide **11b**, as shown in Chart 1.

To clarify the mechanism of the cyclization reaction, we obtained the corresponding diol intermediates **7a** and **7b** *via* an alternative route using phenylselenenyldiols **13a** and **13b**, which was reported in our previous paper[6] (Chart 3). The PhSe groups at the C2′ position of diols **13a** and **13b** were removed by treatment with *n*-Bu_3SnH and Et_3B to give **7a** and **7b** in 96% and 85% yields, respectively. Mitsunobu cyclization of **7a** afforded exclusively *trans*-product **8a** in 91% yield, while that of **7b** afforded exclusively *cis*-product **8b** in 90% yield.

The HPLC analysis on a chiral stationary column demonstrated that diols **7a** and **7b** showed a single peak, respectively, while it indicated that cyclization products **8a** and **8b** were 1 : 1.2 and 1 : 1.5 enantiomeric mixtures, respectively. The decrease of regioselectivity of the cyclodehydration during the Mitsunobu cyclization of **7ab** may be due to the lack of C2′ and/or C3′-oxygen functional groups, which is present in linear heterocyclic sugar derivatives.

Experimental

The melting points were determined on a hot-stage apparatus and are uncorrected. Optical rotation measurements were recorded with a JASCO DIP-1000 digital polarimeter. IR spectra were recorded on a Shimadzu IR-435 spectrometer. ^{1}H- and ^{13}C-NMR spectra were taken with tetramethylsilane as an internal standard on a Varian Gemini-200, Varian Mercury-300, and Varian UNITY INOVA-500 spectrometers. Reactions with air- and moisture-sensitive compounds were carried out under an argon atmosphere. Unless otherwise noted, all extracts were dried over Na_2SO_4, and the solvent was removed in a rotary evaporator under reduced pressure. Tetrahydrofuran (THF) was distilled from sodium-benzophenone. HPLC analysis was carried out with a Waters Associates instrument [column; Daicel CHIRALPAK® AD, 0.46 cm×25 cm; eluent, 10% 2-propanol in hexane; detection 254 nm].

5-[(1*RS*,4*S*)-5-Benzyloxy-1,4-dihydroxypentyl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (7ab) To a solution of **5**[8] (618 mg, 3.00 mmol) in dry toluene (6 ml) at −70 °C was added a 1.0 M solution of DIBAL in toluene (4.50 ml, 4.50 mmol) over 15 min. After being stirred for 5 min at −70 °C, the reaction mixture was quenched with MeOH (2.5 ml) and further stirred for 1 h at room temperature (rt). Saturated $NaHCO_3$ solution (1.5 ml) and EtOAc (4.0 ml) were added to the resulting mixture, which was further stirred for 25 min. After anhydrous $MgSO_4$ was added to the resulting suspension, the reaction mixture was stirred for a while, filtered through a Celite pad, and washed with EtOAc. The filtrate was evaporated to give a crude oil, which was subjected to chromatography. Elution with EtOAc–hexane (3 : 17) afforded 5*S*-benzyloxymethyltetrahydrofuran-2-ol (590 mg, 95 %) as a colorless oil.

IR (neat) cm^{-1}: 3400 (OH). ^{1}H-NMR ($CDCl_3$) δ: 1.56—2.22 (4H, m), 3.30 (1/2H, br), 3.40—3.68 (2H, m), 3.80 (1/2H, d, J=6.5 Hz), 4.30 (1/2H, m), 4.44 (1/2H, m), 4.56 (2/4H, s), 4.60 (2/4H, s), 5.45 (1/2H, br d, J=6.5 Hz), 5.60 (1/2H, br d, J=6.5 Hz), 7.32 (5H, m). Electron impact (EI)-MS *m/z*: 208 (M$^+$).

A solution of 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide[10] (1.04 g, 3.61 mmol) in THF (10 ml) was cooled to −70 °C and was treated dropwise with 1.6 M BuLi–hexane (2.31 ml, 3.61 mmol), and the resulting mixture was stirred for 30 min at −50 °C to precipitate the white lithium salt (**6**). The resulting suspension was again cooled to −70 °C, and a THF solution (5 ml) of the lactol (280 mg, 1.34 mmol) in THF (5 ml) was added slowly. The dry ice bath was removed, and the reaction mixture was stirred at rt. After 30 min, the reaction was quenched with H_2O, and the THF was removed under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with H_2O, dried, and evaporated to give a crude oil. Flash chromatography on silica gel using 40% EtOAc–hexane as eluent gave **7ab** (670 mg, quant) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.39 (6H, s), 0.99 (9H, s), 1.40—2.11 (4H, m), 2.82 (6H, s), 3.35 (1H, t, J=7.7 Hz), 3.50 (1H, dd, J=7.7, 3.6 Hz), 3.90 (1H, m), 4.58 (2H, s), 4.93 (1H, m), 7.22 (1H, s), 7.35 (5H, m). High resolution (HR)-MS *m/z*: 498.2447 (Calcd for $C_{23}H_{40}N_3O_5SSi$: 498.2456). EI-MS *m/z*: 498 (M$^+$+1).

5-[(*trans* and *cis*-2,5)-5-Benzyloxymethyltetrahydrofuran-2-yl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethy-1*H*-imidazolesulfonamide (8ab) To a solution of **7ab** (665 mg, 1.34 mmol) in dry benzene (45 ml) was added Bu_3P (1.10 ml, 4.02 mmol) at rt. TMAD (691 mg, 4.02 mmol) was then added rapidly to the mixture at ice bath temperature. After a few minutes, the reaction mixture was warmed to rt and the stirring was continued for 18 h. The insoluble material was removed by filtration, and the filtrate was condensed to give a residue, which was diluted with EtOAc. The solution was washed with H_2O (×2) and brine, dried, and evaporated. The residual oil was purifed by flash chromatography using EtOAc–hexane (3 : 17) for elution to give **8ab** (621 mg, 97%) as a brown oil of inseparable mixture. ^{1}H-NMR ($CDCl_3$) δ: 0.38 (6H, s), 1.00 (9H, s), 1.72—2.50 (4H, m), 2.84 (6H, s), 3.50 (2/2H, d, J=2.7 Hz), 3.55 (2/2H, d, J=5.6 Hz), 4.17 (1/2H, quint, J=5.6 Hz), 4.32 (1/2H, quint, J=5.6 Hz), 4.54 (2/2H, s), 4.57 (2/2H, s), 5.17 (1/2H, t, J=6.5 Hz), 5.28 (1/2H, t, J=6.5 Hz), 7.18 (1/2H, s), 7.23 (1/2H, s), 7.32 (5H, m). HR-MS *m/z*: 480.2352 (Calcd for $C_{23}H_{38}N_3O_4SSi$: 480.2350). EI-MS *m/z*: 480 (M$^+$+1).

5-[(*trans*-2,5)-5-Benzyloxymethyltetrahydrofuan-2-yl]-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (9a) and Its *cis*-2′,5′-Isomer (9b) To a solution of **8ab** (172 mg, 0.36 mmol) in THF (25 ml) was added a 1 M solution of a Bu_4NF (0.40 ml, 0.40 mmol) at 0 °C. The mixture was stirred at rt for 20 min. The THF was evaporated to give a crude oil, which was then purified by column chromatography [EtOAc–hexane (2 : 3)] to give **9b** (70 mg, 53%) and **9a** (62 mg, 47%), in that order. **9b**: oil, 20% e.e. by chiral HPLC (flow rate 2 ml/min; t_R 10.0 and 11.4 min). ^{1}H-NMR ($CDCl_3$) δ: 1.72—2.12 (3H, m), 2.21—2.42 (1H, m), 2.89 (6H, s), 3.51 (1H, d, J=2.5 Hz), 3.55 (1H, s), 4.20 (1H, m), 4.55 (2H, s), 5.20 (1H, t, J=6.6 Hz), 7.09 (1H, s) 7.31 (5H, m), 7.89 (1H, s). HR-MS *m/z*: 366.1486 (Calcd for $C_{17}H_{24}N_3O_4S$: 366.1486). EI-MS *m/z*: 366 (M$^+$+1). **9a**: oil, 9% e.e. by chiral HPLC (flow rate 2 ml/min; t_R 9.5 and 13.4 min). ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.89 (1H, m), 1.94—2.20 (2H, m), 2.27—2.45 (1H, m), 2.85 (6H, s), 3.49 (2H, d, J=4.5 Hz), 4.29 (1H, m), 4.52 (2H, s), 5.30 (1H, t, J=6.5 Hz), 7.05 (1H, s), 7.30 (5H, m), 7.88 (1H, s). HR-MS *m/z*: 366.1495 (Calcd for $C_{17}H_{24}N_3O_4S$: 366.1486). EI-MS *m/z*: 366 (M$^+$+1).

5-[(*cis*-2,5)-5-Hydroxymethyltetrahydrofuran-2-yl]-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (10b) A mixture of **9b** (460 mg, 1.27 mmol), 20%

$Pd(OH)_2$–C (230 mg), and cyclohexene (3.2 ml, 31.7 mmol) in EtOH (50 ml) was refluxed for 30 min. After filtration through Celite, the filtrate was evaporated to give a residue which was purified by column chromatography [MeOH–EtOAc (1 : 20)] to give **10b** (300 mg, 87%) as a colorless oil. ^{1}H-NMR (CD_3OD) δ: 1.76—2.16 (3H, m), 2.27—2.46 (1H, m), 2.95 (6H, s), 3.59 (2H, m), 4.10 (1H, m), 5.23 (1H, t, J=6.5 Hz), 7.19 (1H, s), 8.08 (1H, s). HR-MS m/z: 276.1015 (Calced for $C_{10}H_{18}N_3O_4S$: 276.1017). EI-MS m/z: 276 (M^++1).

5-[(*cis*-2,5)-5-Phthaloylaminotetrahydrofuran-2-yl]-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide [(±)-11b] Phthalimide (160 mg, 1.12 mmol) and Ph_3P (530 mg, 2.03 mmol) were dissolved in a solution of **10b** (280 mg, 1.02 mmol) in THF (15 ml). To this mixture was added DEAD (0.35 ml, 2.03 mmol) with stirring. The reaction mixture was stirred at rt for 30 min, and then the whole was evaporated to give a residue, which was subsequently dissolved in EtOAc. The solution was washed with H_2O and brine, dried, and evaporated to give a crude oil. It was purified by flash chromatography with EtOAc–hexane (3 : 2) to **11b** (380 mg, 92%) as a white solid, which was recrystallized from EtOH to give white leaflets [(±)-**11b**]. mp 98—100 °C. IR (KBr) cm^{-1}: 1770 (N–CO), 1710 (N–CO), 1390, 1175 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.79—2.22 (3H, m), 2.29—2.50 (1H, m), 2.85 (6H, s), 3.80 (1H, dd, J=14.1, 5.0 Hz), 3.90 (1H, dd, J=14.1, 6.0 Hz), 4.37 (1H, m), 5.17 (1H, t, J=6.0 Hz), 7.16 (1H, s), 7.68—7.77 (2H, m), 7.80—7.86 (2H, m), 7.86 (1H, s). *Anal.* Calcd for $C_{18}H_{20}N_4O_5S$: C, 53.45; H, 4.98; N, 13.85. Found: C, 53.65; H, 4.94; N, 13.84.

4(5)-[(*cis*-2,5)-5-Aminomethyltetrahydrofuran-2-yl]imidazole [(±)-2] A solution of (±)-**11b** (340 mg, 0.85 mmol) and $NH_2NH_2\cdot H_2O$ (0.21 ml, 4.24 mmoli) in EtOH (30 ml) was refluxed for 2 h and then cooled. A small amount of 10% Pd–C was then added to the solution, and the reaction mixture was further refluxed for 10 min. After removal of the catalyst by filtration through a Celite pad, a small amount of silica gel was added to the filtrate. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column (Chromatorex NH-DM 1020). Chromatography using EtOAc as the eluent gave 5-[(*cis*-2,5)-5-aminomethyltetrahydrofuran-2-yl]-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (210 mg, 92%) as an oil. IR (nujol) cm^{-1}: 3370, 1580 (NH), 1375, 1170 (SO_2). ^{1}H-NMR (CD_3OD) δ: 1.63—1.90 (1H, m), 1.97—2.20 (2H, m), 2.29—2.46 (1H, m), 2.76 (2H, d, J=6.1 Hz), 2.99 (6H, s), 4.04 (1H, m), 5.23 (1H, t, J=6.6 Hz), 7.17 (1H, s), 8.10 (1H, s). EI-MS m/z: 275 (M^++1). To a EtOH solution (5 ml) of the sulfonamide (48 mg, 0.17 mmol) thus obtained was added 1.5 N HCl (2 ml). The resulting mixture was refluxed for 90 min and neutralized by addition of 30% NH_4OH. The whole was diluted with EtOH and evaporated to remove water as an azeotrope under reduced pressure. The residue was further diluted with EtOH and the resulting white salts were filtered off. A small amount of silica gel (Chromatorex NH-DM 1020) was added to the filtrate. The solvent was evaporated to give a coated silica gel, which was placed in a column (Chromatorex NH-DM 1020). Chromatography using MeOH–AcOEt (2 : 23) gave (±)-**2** (26 mg, 90%) as a colorless oil.[6] IR (nujol) cm^{-1}: 3350, 1585 (NH). ^{1}H-NMR (CD_3OD) δ: 1.68—2.35 (4H, m), 2.75 (2H, m), 4.04 (1H, m), 4.93 (overlapped with H_2O in CD_3OD), 7.03 (1H, s), 7.65 (1H, s). HR-MS m/z: 167.1060 (Calcd for $C_8H_{13}N_3O$: 167.1058). EI-MS m/z: 167 (m^+).

5-[(*trans*-2,5)-5-Hydroxymethyltetrahydrofuran-2-yl]-*N*,*N*-dimethylimidazole-1-sulfonamide (10a) By the same procedure as **10b**, benzylether **9a** (48 mg, 0.13 mmol) was converted to **10a** (34 mg, 94%) as a colorless oil. ^{1}H-NMR (CD_3OD) δ: 1.72—1.94 (1H, m), 1.98—2.22 (2H, m), 2.33—2.50 (1H, m), 2.95 (6H, s), 3.54 (1H, dd, J=12.0, 5.5 Hz), 3.62 (1H, dd, J=12.0, 4.1 Hz), 4.19 (1H, m), 5.36 (1H, t, J=6.4 Hz), 7.12 (1H. s). 8.10 (1H, s). HR-MS m/z: 276.1018 (Calced for $C_{10}H_{18}N_3O_4S$: 276.1017). EI-MS m/z: 276 (M^++1).

5-[(*trans*-2,5)-5-Phthaloylaminotetrahydrofuran-2-yl]-*N*,*N*-dimethylimidazole-1-sulfonamide [(±)-11a] By the same procedure as **11b**, **10a** (33 mg, 0.12 mmol) was converted to **11a** (37 mg, 76%), which was recrystallized from EtOH to give colorless prisms. mp 133—135 °C. IR (KBr) cm^{-1}: 1790 (N–CO), 1710 (N–CO), 1395, 1175 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.74—1.90 (1H, m), 2.00—2.28 (2H, m), 2.39—2.52 (1H, m), 2.88 (6H, s), 3.70 (1H, dd, J=14.1, 5.0 Hz), 3.85 (1H, dd, J=14.1, 7.1 Hz) 4.43 (1H, m), 5.38 (1H, t, J=6.8 Hz), 7.00 (1H, s), 7.69—7.75 (2H, m), 7.80—7.85 (2H, m), 7.85 (1H, s). *Anal.* Calcd for $C_{18}H_{20}N_4O_5S$: C, 53.45; H, 4.98; N, 13.85. Found: C, 53.69; H, 4.91; N, 13.84.

5-[(*trans*-2,5)-5-Aminomethyltetrahydrofuran-2-yl]imidazole [(±)-1] By the same procedure as (±)-**2**, **11a** (160 mg, 0.41 mmol) was converted to 5-[(*trans*-2,5)-5-aminomethyltetrahydrofuran-2-yl]-*N*,*N*-dimethylimidazole-1-sulfonamide (120 mg, quant). IR (nujol) cm^{-1}: 3350, 1585 (NH), 1375, 1170 (SO_2). ^{1}H-NMR (CD_3OD) δ: 1.71—1.95 (1H, m), 2.00—2.26 (2H, m), 2.33—2.52 (1H, m), 2.75 (2H, d, J=6.0 Hz), 2.95 (6H, s), 4.16 (1H, m), 5.36 (1H, t, J=6.4 Hz), 7.15 (1H, s), 8.12 (1H, s). EI-MS m/z: 275 (M^++1). By the same procedure as (±)-**2**, the sulfonamide (109 mg, 0.40 mmol) was converted to (±)-**1** (48 mg, 72%).[6] IR (nujol) cm^{-1}: 3350, 1585 (NH). ^{1}H-NMR (CD_3OD) δ: 1.61—1.82 (1H, m), 2.02—2.38 (3H, m), 2.73 (2H, d, J=6.0 Hz), 4.17 (1H, m), 5.02 (1H, t, J=6.5 Hz), 7.02 (1H, s), 7.64 (1H, s). HR-MS m/z: 167.1060 (Calcd for $C_8H_{13}N_3O$: 167.1058). EI-MS m/z: 167 (M^+).

5-[(1*R*,4*S*)-5-Benzyloxy-1,4-dihydroxypentyl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (7a) A mixture of **13a**[6] (204 mg, 0.31 mmol), 1 M hexane solution of Et_3B (0.34 ml, 0.34 mmol), and Bu_3SnH (0.095 ml, 0.34 mmol) in benzene (6 ml) was stirred at room temperature for 15 min. The benzene was removed under reduced pressure. The residue was dissolved in CH_3CN, and the solution was washed with hexane and evaporated. The resulting residue was purified by column chromatography using a gradient solvent from 30 to 70% EtOAc in hexane to give **7a** (148 mg, 96%) as an oil. $[\alpha]_D$ +3.30° (c=2.4, $CHCl_3$). HPLC (flow rate 3 ml/min; t_R 7.2 min) exhibited a single peak. ^{1}H-NMR ($CDCl_3$) δ: 0.38 (6H, s), 1.00 (9H, s), 1.45—1.80 (2H, m), 2.00 (2H, quint, J=6.0 Hz), 2.80 (6H, s), 3.34 (1H, t, J=7.5 Hz), 3.48 (1H, dd, J=7.5, 3.0 Hz), 3.87 (1H, m), 4.55 (1H, s), 4.94 (1H, dd, J=6.0, 5.0 Hz), 7.25—7.45 (5H, br s). HR-MS m/z: 498.2452 (Calcd for $C_{23}H_{40}N_3O_5SSi$: 498.2456). EI-MS m/z: 498 (M^++1).

5-[(*trans*-2,5)-5-Benzyloxymethyltetrahydrofuran-2-yl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (8a) By the same procedure as the preparation of **8ab**, a mixture of **7a** (43 mg, 0.09 mmol), Bu_3P (0.07 ml, 0.26 mmol), and TMAD (45 mg, 0.26 mmol) in benzene (3 ml) was stirred for 18 h at rt to give **8a** (38 mg, 91%) as an oil. 9% e.e. by chiral HPLC (flow rate 2 ml/min; t_R 2.9 and 4.7 min). ORD (c=1.18, EtOH) [α] (nm) 0 (589), +5.1 (450). ^{1}H-NMR ($CDCl_3$) δ: 0.39 (6H, s), 1.00 (9H, s), 1.78—1.91 (1H, br m), 1.97—2.21 (2H, m), 2.31—2.48 (1H, m), 2.84 (6H, s), 3.52 (2H, br s), 4.32 (1H, quint, J=5.0 Hz), 4.55 (2H, s), 5.28 (1H, t, J=6.6 Hz), 7.25—7.45 (5H, m). HR-MS m/z: 480.2351 (Calcd for $C_{23}H_{38}N_3O_4SSi$: 480.2350). EI-MS m/z: 480 (M^++1).

5-[(1*S*,4*S*)-5-Benzyloxy-1,4-dihydroxypentyl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (7b) The same procedure as used for the preparation of **7a** provided **7b** (30 mg, 85%) as an oil from **13b**[6] (46 mg, 0.07 mmol). $[\alpha]_D$ +3.00° (c=1.4, $CHCl_3$). HPLC (flow rate 3 ml/min; t_R 6.4 min) exhibited a single peak. ^{1}H-NMR ($CDCl_3$) δ: 0.38 (6H, s), 0.99 (9H, s), 1.55—1.72 (2H, m), 2.03 (2H, q, J=7.5 Hz), 2.83 (6H, s), 3.36 (1H, t, J=7.5 Hz), 3.50 (1H, dd, J=7.5, 3.0 Hz), 3.80—3.97 (1H, m), 4.55 (1H, s), 4.90 (1H, t, J=6.0 Hz), 7.25—7.45 (5H, br s). HR-MS m/z: 498.2450 (Calcd for $C_{23}H_{40}N_3O_5SSi$: 498.2456). EI-MS m/z: 498 (M^++1).

5-[(*cis*-2,5)-5-Benzyloxymethyltetrahydrofuran-2-yl]-2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (8b) By the same procedure as the preparation of **8ab**, a mixture of **7b** (62 mg, 0.13 mmol), Bu_3P (0.10 ml, 3.7 mmol), and TMAD (64 mg, 3.7 mmol) in benzene (10 ml) was stirred for 18 h at room temperature to give **8b** (54 mg, 90%) as an oil. 20% e.e. by chiral HPLC (flow rate 2 ml/min; t_R 2.3 and 4.3 min). ORD (c=2.69, EtOH) [α] (nm) −9.2 (589), −11.6 (550), −14.2 (500), −18.1 (450). ^{1}H-NMR ($CDCl_3$) δ: 0.39 (6H, s), 1.00 (9H, s), 1.75—2.12 (3H, br m), 2.12—2.42 (1H, m), 2.85 (6H, s), 3.55 (2H, br s), 4.17 (1H, quint, J=7.5 Hz), 4.55 (2H, quint, J=5.0 Hz), 4.55 (2H, s), 5.15 (1H, t, J=7.5 Hz), 7.2—7.45 (5H, m). HR-MS m/z: 480.2353 (Calcd for $C_{23}H_{38}N_3O_4SSi$: 480.2350). EI-MS m/z: 480 (M^++1).

X-Ray Structure Determination The 6300 reflections were collected up to 0.89 Å resolution with cell dimensions a=11.868(6) Å, b=20.476(6) Å, c=7.931(6) Å, α=95.62(1)°, β=97.22(1)°, γ=93.82(1)°, crystal system triclinic, space group P-1, Z=2 and calculated density 1.416 g/cm^3. The structure of **10b** was determined by direct method using program SHELXS-97[15] and refined by full matrix least-squares method using program SHELXSL-97.[15] The final R-value was 0.0589 with 5973 reflections (F_O>4σF_O).

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