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STEREOSELECTIVE SYNTHESIS OF 4(5)-[(2*S*, 3*S*)- AND (2*R*, 3*R*)-3-AMINOTETRAHYDROFURAN-2-YL)IMIDAZOLES USING MODIFIED AND STANDARD MITSUNOBU CYCLIZATIONS: SYNTHETIC STUDIES TOWARD NOVEL HISTAMINE H_3-LIGANDS

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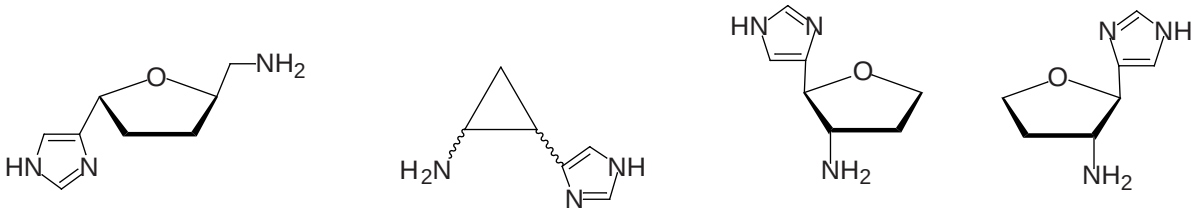
Abstract - 4(5)-[(2*S*,3*S*)-3-Aminotetrahydrofuran-2-yl)imidazole [(+)-**3**] and its enantiomer [(-)-(2*R*,3*R*)-**3**] were stereoselectivity synthesized by using both modified and standard Mitsunobu cyclizations from *L*- and *D*-methionine, respectively.

INTRODUCTION

The histamine H_3 (H_3) receptors[1] exist on histaminergic fibers in the brain and modulate the synthesis and release of histamine as an autoreceptor.[2] Moreover, H_3-receptors have been shown to be heteroreceptors[3] which modulate the release of a number of different neurotransmitters.[3,4] This type of receptor can be also found in many peripheral tissues.[1] The H_3 -agonists are regarded as a target for new therapeutics of bronchial asthma,[5] and H_3-antagonists are now expected to be potential drugs for memory degenerative disorders like Alzheimer's disease.[3,4] We recently reported[6] (+)-4(5)-[(2*R*,5*R*)-5-(aminomethyl)tetrahydrofuran-2-yl]imidazole (imifuramine, **1**)[6a] as a new type of H_3-agonist, whose activity measured by *in vivo* brain microdialysis[7] was approximately equal to that of the current H_3-agonist, immepip.[8] Imifuramine, to the contrary, exhibited weak H_3-agonistic activity in an *in vitro* test using guinea pig ileum preparation.[9] Arrang *et al.* have been reported cyclopropylhistamine (**2**) as a H_3-agonist in a patent application.[10] However, the stereochemical identity of the material tested was not reported.



1 (Imifuramine) **2** (+) - **3** (2*S*, 3*S*) (-) - **3** (2*R*, 3*R*)

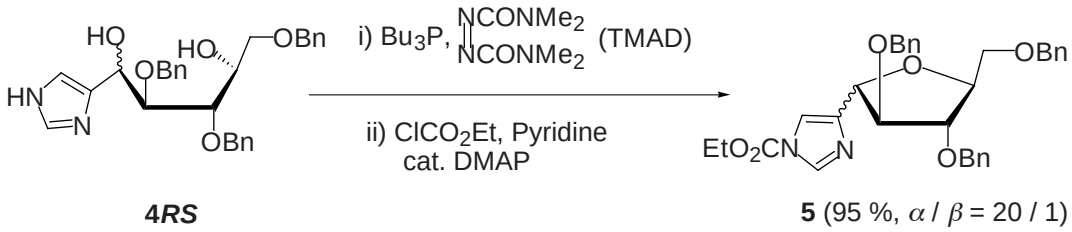
Figure 1

Recently, two groups[11,12] independently reported the synthesis and evaluation of the H_3-agonistic activity of *trans*-cyclopropylhistamine. Khan *et al.*[11] determined that the *trans*-(1*R*,2*R*)- isomer was 1 order of magnitude more active than the (1*S*,2*S*)-isomer. Contrary to the results reported, Timmerman *et al.*[12] concluded that the *trans*-(1*S*,2*S*)-isomer was about 10 times more active than its enantiomer.

From these results, we envisioned that either 4(5)-[(2*S*,3*S*)-3-aminotetrahydrofuran-2-yl]imidazole [*S*,*S*-THF-histamine, (+)-**3**] or its enantiomer [(-)-**3**] might show H_3-agonistic activity. Further, they may be used as a base compound for synthetic study toward novel H_3-antagonists by introduction of a hydrophobic group into the amino group of **3**, since the present H_3-antagonists exhibit three common and essential structural features: an imidazole headgroup, a spacer and a hydrophobic tail group.[4] We report herein an efficient and stereoselectinve synthesis of the novel *trans*-THF-histamines [(+)-**3** and (-)-**3**] using modified and standard Mitsunobu cyclization.

RESULTS AND DISCUSSION

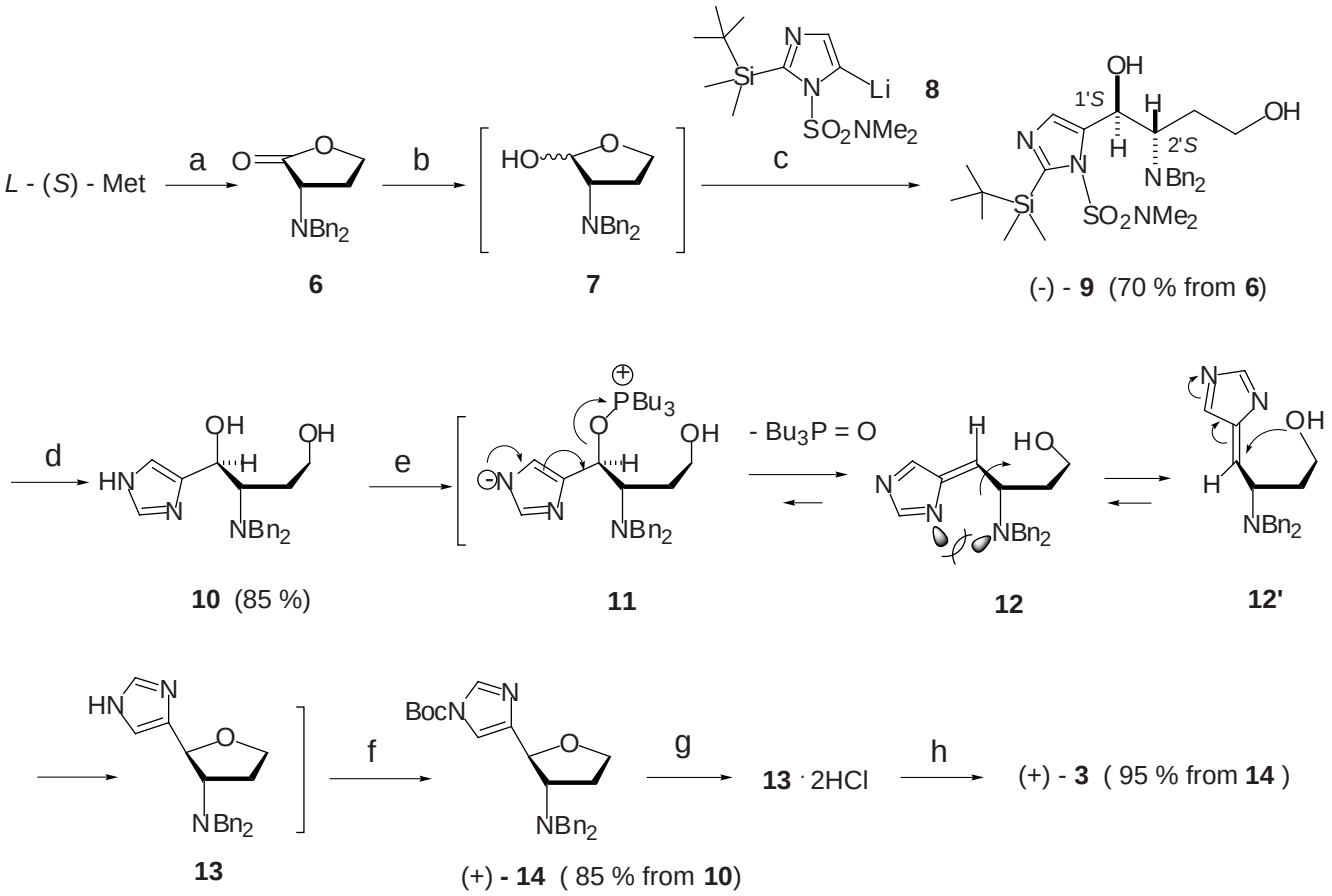
We very recently reported[13] that the modified Mitsunobu cyclization[14] of a 1:1 diastereomeric mixture (**4*RS***) having an unsubstituted imidazole, using *N*,*N*,*N'*,*N'*-tetramethylazodicarboxamide (TMAD)[15] and Bu_3P, stereoselectively afforded α-*L*-arabinofuranosylnucleosides (**5**), in which the benzyloxy group at the C2'-position acted as the directing group to control thermodynamically the stereochemistry of imidazole *C*-nucleosides (Scheme 1). Importantly, the unsubstituted imidazole moiety was indispensable for the exclusive formation of the α-anomer. We thus expected that an unsubstituted imidazole (**10**) having a



4RS **5** (95 %, α / β = 20 / 1)

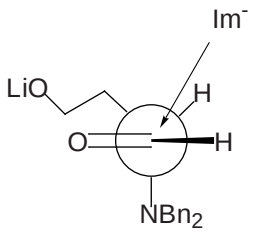
Scheme 1

dibenzylamino group at the C2'-position would form a 1', 2'-*trans*-THF derivative (**13**) (Scheme 2). (*S*)-*N*,*N*-Dibenzylhomoserine lactone (**6**) was easily synthesized from (*S*)-methionine as described by Sendzik *et al.*[16] Reduction of **6** with DIBAL-H followed by an addition of the lithium salt (**8**) of bis-protected imidazole to the resulting lactol (**7**) gave only a diol [(-)-**9** (70 %), mp 132 - 133.5 ℃] as a single isomer with C1'*S* configuration. The configuration at C-1'of **9** was assigned by the relatively large $J_{1',2'}$ coupling constant (5.1 Hz) in ^{1}H-NMR, based on an analogy of our previous reports.[6,13,14] The formation of C-1', 2'-*anti* -configurated compound (**9**) can be assumed by the Felkin-Anh model as illustrated in Figure 2, in which a conformer, with the dibenzylamino group in the position of the largest substituent,[17] governs the addition of **8** and, hence, leads to the *anti*-adduct. Deprotection of **9** in HCl-THF at room temperature afforded a diol (**10**) in 85 % yield. The modified Mitsunobu cyclization of **10** using TMAD and Bu_3P at room temperature in benzene followed by *N*-Boc-protection for the ease of isolation, as expected, produced only a *trans*-THF derivative [(+)-**14**] in 85% overall yield from **10**. The *trans*-selectivity in this reaction may be explained as follows. Preferential elimination of Bu_3P=O from **11** leads to an active form (**12**) of the imidazole ring. This exclusively supplies the *trans*-isomer (**13**) *via* a rotomer (**12'**) which is thermodynamically more stable. Thus, the *trans*-stereoselectivity of **13** may be facilitated by a stereoelectronic repulsion in **12**. Removal of the Boc group of **14** with HCl and subsequent Pd-catalyzed hydrogenolysis of the resulting dihydrochloride (**13**·2HCl) yielded the *trans*-THF-histamine [(+)-**3**] in 95% overall yield from **14.** The correctness of the stereochemical assignment was confirmed by ^{1}H COSY and NOESY experiments of a cyanoguanidine (**15**) derived from **3**, as illustrated in Scheme 3.



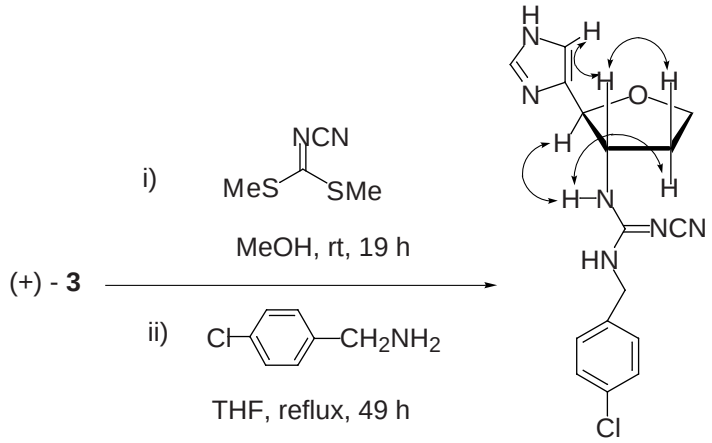
Reagents and conditions : a) ref. 16 ; b) DIBAL, -7**0°C**, 20 min **;** c) (i) **8**, -50**°C** ; (ii) rt, 1 h ; d) 1N HCl, rt, 38 h ; e) TMAD, Bu_3P, benzene-THF, rt, 17 h ; f) Boc_2O, THF, rt, 26 h ; g) 1N HCl, EtOH, rt, 0.5 h ; h) (i) H_2 / 10% Pd-C (3 Kg / cm^2) ; (ii) column chromatography ($CHCl_3$: MeOH : 30% NH_4OH = 20 :10 :1)

Scheme 2



(gives **9**)

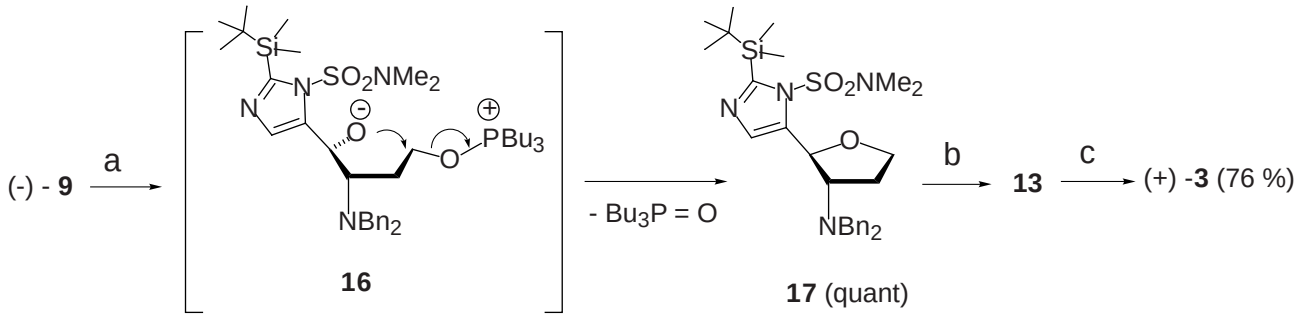
Figure 2



Scheme 3

(Arrows indicate interactions between sets of two protons in NOESY experiments)

Yokoyama *et al.*[18] had reported the synthesis of *C*-ribonucleosides having typical aromatic heterocycles, in which the cyclization of the corresponding diols proceeds through an intramolecular S_N2 reaction under standard Mitsunobu conditions (DEAD, Ph_3P), 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, a β-anomer. Therefore, we anticipated the formation of a *cis*-THF derivative from **9** by the S_N2 reaction *via* the C1'-oxyphosphonium intermediate. However, cyclization of **9** with TMAD and Bu_3P at room temperature in benzene produced the *trans*-**17** in quantitative yield (Scheme 4). This fact indicates that **17** arises from the formation of an oxyphosphonium intermediate (**16**) at the less hindered C-4' hydroxy group. Deprotection of **17** thus obtained followed by removal of the *N*-dibenzyl group also completed the synthesis of (+)-**3** in a shorter route. Accordingly, the modified and standard Mitsunobu cyclizations produced the respective *trans*-THF-intermediats (**13** and **17**), but they proceeded by different reaction mechanisms. It is important to note that simply switching the starting material to *D*-methionine allows the synthesis of the enantiomer [(-)-(2*R*,3*R*)-**3**]. We thus achieved an efficient and stereoselective synthesis of (+)-**3** and (-)-**3** *via* two routes. The biological evaluation of THF-histamines and their related derivatives is under way in our laboratories.



Reagents and condditions : a) TMAD, Bu_3P, benzene, rt, 47 h ; b) 1N HCl, THF, reflux, 1 h; c) (i) 1N HCl, EtOH, rt, 0.5 h ; (ii) H_2 / 10% Pd-C (3 kg / cm^2), 20 h ; (iii) column chromatography ($CHCl_3$: MeOH : 30% NH_4OH = 20 :10 :1)

Scheme 4

EXPERIMENTAL

The melting points were determined on a hot-stage apparatus and are uncorrected. Optical rotations measurements were recorded with a JASCO DIP-1000 digital polarimeter. ^{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. THF was distilled from sodium-benzophenone.

2-*tert*-Butyldimethylsilyl-5-[(1*S*, 2*S*)-2-dibenzylamino-1,4-dihydroxybutyl]-*N*,*N*-dimethylimidazole-1-sulfonamide [(-)-**9**]**.**

To a solution of **6**[16] (1.40 g, 5 mmol) in dry toluene (18 mL) at -70 ℃ was added a 1 M solution of DIBAL in toluene (5.2 mL, 5.2 mmol) over 5 min. After being stirred for 15 min at -70 ℃, the reaction mixture was quenched with MeOH (1 mL) and further stirred at rt. Saturated $NaHCO_3$ solution (2 mL) was then added to the reaction mixture with stirring. 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 solvent was evaporated to give crude lactol (**7**) (1.40 g) as a white solid. The ^{1}H-NMR spectrum of **7** indicated a 1:2 epimeric mixture [e.g., ($CDCl_3$) δ: 5.34 (br s, 1/3H, 2-H), 5.54 (br s, 2/3H, 2-H)]. Next, a solution of 2-*tert*-butyldimetylsilyl-*N*,*N*-dimethyl-1*H*-imidazole- sulfonamide (2.88 g, 9.97 mmol) in THF (5 mL) was cooled to -50 ℃, and 1.6 M BuLi-hexane (6.23 mL, 9.97 mmol) was added dropwise over 5 min to the solution to precipitate the white lithium salt (**8**). The resulting suspension was cooled to -60 ℃, and a solution of **7** in toluene (15 mL) was added slowly at the same temperature. The dry ice bath was removed, and the reaction mixture was stirred at rt to dissolve the salts. After 1 h, the resulting solution was diluted with hexane-EtOAc (2:1), and the solution was washed with H_2O, dried, and evaporated to give a crude oil. The residue was purified by column chromatography to give (-)-**9** (2.00 g,

70 %) as a solid using a gradient solvent system [2:1 to 1:3 in hexane-EtOAc]. (-)-**9** : recrystallized from hexane-benzene to give colorless needles. mp 132-133.5 ℃. $[\alpha]_D$ -52.7° (*c*=1.35, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.40 (s, 3H, $SiCH_3$), 0.42 (s, 3H, $SiCH_3$), 1.03 [s, 9H, $C(CH_3)_3$], 1.73-1.85 (m, 1H, 3'-H), 2.13-2.32 (m, 1H, 3'-H), 2.84 [s, 6H, $N(CH_3)_2$], 3.06-3.26 (2H, br, OH×2), 3.29 (dt, 1H, *J* = 6.6, 4.9 Hz, 2'-H), 3.52 (d, 2H, *J* = 13.0 Hz, CH_2Ph), 3.74 (br s, 2H, 4'-H), 3.78 (d, 2H, *J* = 13.0 Hz, CH_2Ph), 5.29 (d, 1H, *J* = 5.0 Hz, 1'-H), 6.83 (s, 1H, 5-H), 7.11-7.42 (m, 10H, Ph×2). *Anal. Calcd* for $C_{29}H_{44}N_4O_4SSi$: C, 60.80; H, 7.74; N, 9.78. Found: C, 60.78; H, 7.73; N, 9.74.

4(5)-[(1*S*, 2*S*)-2-Dibenzylamino-1,4-dihydroxybutyl]imidazole (10)

A solution of **9** (814 mg, 1.423 mmol) in THF (50 mL) and 1.5 N HCl (10 mL) was stirred at rt. After 15 h, as deprotection of the imidazole moiety was incomplete from TLC, 1.5 N HCl (10 mL) was further added to the reaction mixture, and then the whole was further stirred for 23 h. After neutralization by addition of $NaHCO_3$ powder, the mixture was extracted with EtOAc (×4). The extract was dried and evaporated to give an oil, which was subjected to flash chromatography. Elution with EtOAc followed by MeOH-EtOAc (1:19) afforded **10** (422 mg, 85 %) as a white amorphous product. ^{1}H-NMR (CD_3OD) δ: 1.75-1.90 (m, 1H, 3'-H), 2.05-2.20 (m, 1H, 3'-H), 3.02 (m, 1H, 2'-H), 3.5-3.8 (br m, 2H, 4'-H), 3.63 (d, 1H, *J* = 12.0 Hz, CH_2Ph), 3.82 (d, 1H, *J* = 12.0 Hz, CH_2Ph), 5.09 (d, *J* = 6.0 Hz, 1'-H), 6.82 [s, 1H, 4(5)-H], 7.18-7.39 (br m, 10H, Ph×2), 7.65 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 29.9, 55.3, 62.0, 62.6, 67.8, 118.3, 127.8, 129.0, 130.0, 135.5, 141.1. EIMS *m/z*: 352 (M^++1). HRMS *m/z*: 352.2022 (Calcd for $C_{21}H_{26}N_3O2$: 352.2024).

Conversion of 10 into (+)-14 using the modified Mitsunobu cyclization

To a solution of **10** (417 mg, 1.19 mmol) and Bu_3P (362 mg, 1.79 mmol) in benzene (25 mL) was added TMAD (308 mg, 1.79 mmol) at rt. THF (10 mL) was added to the reaction mixture which was stirred at rt for 17 h. The insoluble material was filtered through a Celite pad, and the filtrate was condensed. The resulting crude oil was diluted with EtOAc, and the organic layer was washed with 5% HCl (×3). The

collected aqueous layer was neutralized with $NaHCO_3$ powder and extracted with EtOAc (×3). The extract was dried, and evaporated to give an oil, which was subjected to chromatography. Elution with gradient solvent [EtOAc to MeOH-EtOAc (1:19)] gave **13** (407 mg) containing a small amount of $Bu_3P=O$. The THF solution (5 mL) of **13** was stirred with Boc_2O (397 mg, 1.82 mmol) at rt for 26 h. The solvent was removed to give a residual oil, purification of which by column chromatography using EtOAc–hexane (3:7) as eluent gave (+)-*tert*-butyl 4-[(2*S*,3*S*)-3-dibenzylaminotetrahydrofuran-2-yl]imidazole-1-carboxylate[19] [(+)-**14**, 440 mg, 85% from **10**] as a colorless oil. (+)-**14**: $[\alpha]_D$ +50.2° (*c*=3.32, $CHCl_3$). IR (neat) cm^{-1}: 1753 (NCOO). ^{1}H-NMR ($CDCl_3$) δ: 1.63 [s, 9H, $C(CH_3)_3$], 2.11 (q, 2H, *J* = 7.3 Hz, 4'-H), 3.63 (d, 2H, *J* = 14.6 Hz, CH_2Ph), 3.76 (d, 2H, *J* = 14.6 Hz, CH_2Ph), 3.79 (1H, q, *J* = 8.1 Hz, 3'-H), 4.01 (td, 2H, *J* = 7.3, 2.3 Hz, 5'-H), 4.92 (d, 1H, *J* = 5.8 Hz, 2'H), 7.12 (s, 1H, 5-H), 7.16-7.39 (m, 10H, Ph×2), 8.00 (s, 1H, 2-H).

(+)-4(5)-[(2*S*, 3*S*)-3-Aminotetrahydrofuran-2-yl]imidazole [(+)-**3**]

A solution of (+)-**14** (395 mg, 0.91 mmol) in EtOH (30 mL) was stirred with 1N HCl (3 mL) at rt for 0.5 h, and evaporated to give a **13**·2HCl (365 mg, 99%) as a white amorphous material. **13**·2HCl: ^{1}H-NMR ($CDCl_3$) δ: 2.65 (m, 1H, 4'-H), 2.83 (m, 1H, 4'H), 3.92 (t, 1H, *J* = 8.4 Hz, 3'-H), 4.1-4.5 (m, 2H, 5'-H), 6.05 (s, 1H, 2'-H), 7.3-7.5 [br, 6H, Ph and (4)5-H], 7.5-7.7 (br, 5H, Ph), 9.00 (s, 1H, 2-H). A solution of **13**·2HCl (365 mg, 0.91 mmol) in EtOH (35 mL) was subsequently hydrogenated with 10% Pd-C (108 mg) at initial pressure of 3.0 kg/cm^2 for 20 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated to give (+)-**3**·2HCl [198 mg, 96 % from (+)-**14**] as anamorphous product. (+)-**3**·2HCl: $[\alpha]_D$ +32.5° (*c*=1.1, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.1-2.3 (m, 1H, 4'-H), 2.4-2.7 (m, 1H, 4'-H), 4.0-4.3 (m, 3H, 2'-H, 5'-H), 5.20 (d, 1H, *J* = 6.7 Hz, 2'-H), 7.74 (s, 1H, 5-H), 9.00 (s, 1H, 2-H). EIMS *m/z*: 153 (M^+). HRMS *m/z*: 153.0896 (Calcd for $C_7H_{11}N_3O$: 153.0901). To a MeOH solution of (+)-**3**·2HCl thus obtained was added a small amount of Chromatorex NH-DM 1020. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column

(Chromatorex NH-DM 1020). Chromatography using $CHCl_3$-MeOH-30% NH_4OH (20:10:1) as the eluent gave (+)-**3** (quant.) as free form. (+)-**3:** colorless oil. $[\alpha]_D$ +69.5° (*c*=2.23, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.8-1.9 (m, 1H, 4'H), 2.3-2.4 (m, 1H, 4'H), 3.59 (dd, 1H, *J* = 12.1, 7.6 Hz, 3'H), 4.0-4.1 (m, 2H, 5'H), 4.53 (d, *J* = 5.3 Hz, 2'-H), 7.07 (s, 1H, 5-H), 7.67 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 35.5, 58.1, 68.0, 83.2, 118.1, 137.2. EIMS *m/z*: 153 (M^+). HRMS *m/z*: 153.0896 (Calcd for $C_7H_{11}N_3O$: 153.0901).

Conversion of (-)-9 into (+)-3 Using the standard Mitsunobu Cyclization.

To a solution of (-)-**9** (487 mg, 0.85 mmol) and Bu_3P (0.32 mL, 1.28 mmol) in benzene (45 mL) was added TMAD (220 mg, 1.28 mmol) at 0 ℃ and the whole was stirred at rt for 47 h. The resulting insoluble material was filtered through a Celite pad, washed with EtOAc and the filtrate was condensed. The residual oil was chromatographed [EtOAc-hexane (10% to 30%)] to give 2-*tert*-butyldimethylsilyl-5-[(2*S*,3*S*)-3-dibenzylaminotetrahydrofuran-2-yl]-*N*,*N*-dimethylimidazole-1-sulfonamide[19] (**17**, 471 mg, quant.) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.40 (s, 3H, $SiCH_3$), 0.42 (s, 3H, $SiCH_3$), 1.04 [s, 9H, $C(CH_3)_3$], 2.0-2.2 (m, 2H, 4'-H), 2.87 [s, 6H, $N(CH_3)_2$], 3.5-4.0 (3H, m, 3' and 5'-H), 3.65 (s, 4H, CH_2Ph), 5.29 (d, 1H, *J*= 6.3 Hz, 1'-H), 6.81 (s, 1H, 5-H), 7.23 (br s, 10H, Ph×2). A solution of **17** (336 mg, 0.61 mmol) in THF (30 mL) and 1N HCl (3 mL) was refluxed for 1 h and then cooled. After neutralization by addition of 30% NH_4OH, the solvent was evaporated to give a residue, which was extracted with EtOAc. The extract was washed with H_2O and brine, dried, and evaporated to give an oil, which was subjected to chromatography. Elution with EtOAc-hexane (50% to 100%) afforded **13** (154 mg, 76%). **13**: ^{1}H-NMR ($CDCl_3$) δ: 2.10 (q, 2H, *J* = 7.2 Hz, 4'-H), 3.60 (d, 2H, *J* = 14.1 Hz, CH_2Ph), 3.75 (overlapped, 1H, 3'-H), 3.78 (d, 2H, *J* = 14.1 Hz, CH_2Ph), 3.91 (q, 1H, *J* = 8.1 Hz, 5'-H), 4.01 (dt, 1H, *J* = 8.1, 7.8 Hz, 5'-H), 4.97 (d, 1H, *J* = 6.6 Hz, 2'-H), 6.79 [s, 1H, 4(5)-H], 7.15-7.35 (br, 10H, Ph×2), 7.50 (s, 1H, 2-H). EIMS *m/z*: 333 (M^+). HRMS *m/z*: 333.1846 (Calcd for $C_{21}H_{23}N_3O$: 333.1840). A solution of **13** (154 mg, 0.46 mmol) in EtOH (10 mL) was stirred with 1N HCl

(0.9 mL) at rt for 0.5 h, and evaporated to give a **13**·2HCl (191 mg, quant) as a white amorphous material. The dihydrochloride was quantitatively converted into (+)-**3** by the same procedure described above.

(-)-4(5)-[(2*R*, 3*R*)-3-Aminotetrahydrofuran-2-yl]imidazole [(-)-**3**]

The configuration counterpart {(-)-(2*R*,3*R*)-**3**, $[\alpha]_D$ -69.9° (*c*=4.01, MeOH)} was synthesized from D-methionine by the present method.

1-Cyano-2-(*p*-chlorobenzyl)-3-{2-[1*H*-imidazol-4(5)-yl]-tetrahydrofuran-3-yl}guanidine [(+)-15]

A solution of (+)-**3** (8 mg, 0.05 mmol) and dimethyl *N*-cyanodithioiminocarbonate (9 mg, 0.06 mmol) in MeOH (1.0 mL) was stirred overnight at rt for 19 h. After evaporation of the solvent, the residue was dissolved in a solution of *p*-chlorobenzylamine (0.007 mL, 0.06 mmol) in THF (2 mL) and the whole was refluxed for 48 h. The solvent was evaporated to give a residue, which was subsequently chromatographed [MeOH-AcOEt (3:7 to 1:1)] to give (+)-**15** (11 mg, 65 %) as a pale yellow oil. $[\alpha]_D$ +95.0° (*c*=2.73, MeOH), ^{1}H-NMR (DMSO-d_6) δ: 1.9-2.0 (m, 1H, 4'-H), 2.2-2.4 (m, 1H, 4'-H), 3.86 (t, 2H, *J* = 6.4 Hz, 5'-H), 4.32 (d, 2H, *J* = 3.7 Hz, CH_2Ph), 4.3-4.4 (m, 1H, 3'-H), 4.66 (d, 1H, *J* = 5.9 Hz, 2'-H), 7.02 (s, 1H, 5-H), 7.21 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.2-7.3 [overlapped, C2'-NH (indicated by D_2O treatment, ^{1}H-COSY and NOESY)], 7.36 (d, 2H, *J* = 3.7 Hz, Ar-H), 7.57 (s, 1H, 2-H), 8.16 (br, 1H, NH), 12.07 (br, 1H, NH). ^{13}C-NMR (DMSO-d_6) δ: 32.3, 43.5, 56.8, 66.0, 78.5, 117.5, 125.2, 127.8, 128.1, 128.8, 131.3, 135.1, 137.8, 159.0. EIMS *m/z*: 344 (M^+). HRMS *m/z*: 344.1155 (Calcd for $C_{16}H_{17}N_6OCl$: 344.1152).

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REFERENCES

1. J. -M. Arrang, M. Garbarg, and J. -C. Schwartz, *Nature (London),* 1983, **302**, 837.
2. J. -M. Arrang, M. Garbarg, J. -C. Lancelot, J. –M. Lecomte, H. Pollard. M. Robba, W. Schunack, and J. -C. Schwartz, *Nature (London),* 1987, **327**, 117.
3. E. Schlicker, B. Malinowska, M. Kathmann, and M. Göthert, *Fundam Clin Pharmacol.*, 1994, **8**, 128.
4. For recent reviews on the medicinal chemistry and therapeutic potentials of ligands of the histamine H_3 receptor, see: (a) W. Schunak, *Actual. Chim. Ther.*, 1993, **20**, 9. (b) W. Schunack, and H. Stark, *Eur. J. Drug Metab. Pharmacokinet.*, 1994, **19**, 173. (c) R. Leurs, R. C. Vollinga, and H. Timmerman, *Prog. Drug Res.*, 1995, **45**, 107. (d) H. Stark, E. Schlicker, and W. Schunack, *Drugs Future*, 1996, **21**, 507. (e) R. Leurs, P. Blandina, C. Tedford, and H. Timmerman, *TiPS* 1998, **19**, 177.
5. N. -Y. Shin, A. T. Lupo Jr, R. Aslanian, S. Orlando, J. J. Piwinski, M. J. Green, A. K. Ganguly, M. A. Clark, S. Tozzi, W. Kreutner, and J. A. Hey, *J. Med. Chem.*, 1995, **38**, 1593
6. (a) S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Yamamoto, and A. Yamatodani, *Tetrahedron Lett.*, 1999, **40**, 2561. (b) S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Sakamoto, Y. Yamamoto, and A. Yamatodani, *J. Org. Chem.*, 1999, **64**, 8608.
7. T. Mochizuki, A. Yamatodani, K. Okakura, M. Takemura, N. Inagaki, and H. Wada, *Naunyn*

Schmiedebergs Arch. Pharmacol., 1991, **343**, 190.

8. Y. Yamamoto, T. Mochizuki, K. Okakura-Mochizuki, A. Uno, and A. Yamatodani, *Methods Find. Exp. Clin. Pharmacol.*, 1997, **19**, 289.
9. S. Harusawa, T. Imazu, S. Takashima, L. Araki, H. Ohishi, T. Kurihara, Y. Sakamoto, Y. Yamamoto, T. Hashimoto, and A. Yamatodani, The 8th Japan-Korea Joint Symposium on Drug and Development (Abstract, p. 37). Tokyo, April 10-12, 2000.
10. J. M. Arrang, M. Garbarg, W. Schunack, and J. C. Schwartz, Eur. Patent Apple, 0214058. 1987 (Chem. Abstr., 1987, **107**, 59036x).
11. M. A. Khan, S. L. Yates, C. E. Tedford, K. Kirschbaum, and J.G. Philips, *J. Bioorg. Med. Chem. Lett*. 1997, **7**, 3017.
12. I. J. P. De Esch, R. C. Vollinga, K. Goubitz, H. Schenk, U. Appelberg, U. Hacksell, S. Lemstra, O. P. Zuiderveld, M. Hoffmann, R. Leurs, W. M. P. B. Menge, and H. Timmerman, *J. Med. Chem.*, 1999, **42**, 1115.
13. L. Araki, S. Harusawa, H. Suzuki, and T. Kurihara, *Heterocycles*, 2000, **53**, 1957.
14. (a) S. Harusawa, Y. Murai, H. Moriyama, H. Ohishi, R. Yoneda, and T. Kurihara, *Tetrahedron Lett*., 1995, **36**, 3165. (b) S. Harusawa, Y. Murai, H. Moriyama, T. Imazu, H. Ohishi, R. Yoneda, and T. Kurihara, *J. Org. Chem.*, 1996, **61**, 4405. (c) S. Harusawa, H. Moriyama, Y. Murai, T. Imazu, H. Ohishi, R. Yoneda, T. Kurihara, H. Hata, and Y. Sakamoto, *Chem. Pharm. Bull.*, 1997, **45**, 53.
15. T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Ito, *Chem. Lett.*, 1994, 539.
16. M. Sendzik, W. Guarnieri, and D. Hoppe, *Synthesis*, 1998, 1287.
17. (a) M. T. Reetz, *Angew. Chem.*, 1991, **103**, 1559. (b) S. Hormuth and H.-U. Reissig, *J. Org. Chem.*, 1994, **59**, 67.
18. (a) M. Yokoyama, A. Toyoshima, T. Akiba, and H. Togo, *Chem. Lett.*, 1994, 265. (b) M.

Yokoyama, H. Toyoshima, M. Shimizu, and H. Togo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 29.

19. The expected MS peaks were not obtained because of thermal instability.