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SYNTHESIS OF *CIS*- OR *TRANS*-2,4-DISUBSTITUTED TETRAHYDROFURANS BEARING AMINO AND IMIDAZOLE GROUPS BY EFFICIENT USE OF THE MODIFIED OR STANDARD MITSUNOBU CYCLIZATION: SYNTHETIC STUDIES TOWARD NOVEL HISTAMINE H_3-LIGANDS

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Abstract - 4(5)-[(2*R*,4*S*) or (2*S*,4*S*)-4-Aminotetrahydrofuran-2-yl]imidazole [(-)-**1a** or (-)-**1b**] and its enantiomers [(+)-**2a** and (+)-**2b**] were synthesized by efficient use of the modified or standard Mitsunobu cyclization.

INTRODUCTION

We recently reported1 that the activity of (+)-4(5)-[(2*R*,5*R*)-5-aminomethyltetrahydrofuran-2-yl]imidazole (imifuramine)[1a] as a new type of histamine H_3 (H_3)-agonist, whose activity measured by *in vivo* brain microdialysis,[2] was approximately equal to that of the current H_3-agonist, immepip.[3] The H_3-agonists are now regarded as a target for new therapeutics of bronchial asthma.[4,5] In our study of the structure-activity relationship in imifuramine, we were interested in the synthesis and biological evaluation of novel disubstituted tetrahydrofurans bearing imidazole and amino groups.

We have recently reported[6] an efficient and stereoselective synthesis of 4(5)-[(2*R*,3*R*)- and (2*S*,3*S*)-3-aminotetrahydrofuran-2-yl]imidazoles [**3a** and **3b**, THF-histamines] (Figure 1) by using the modified[7] or standard Mitsunobu cyclization[8] from D- and L-methionines, respectively (Scheme 1). In the modified Mitsunobu cyclization *via* 5-*exo*-*trig* process, a bulky C2'-dibenzylamino group of a diol

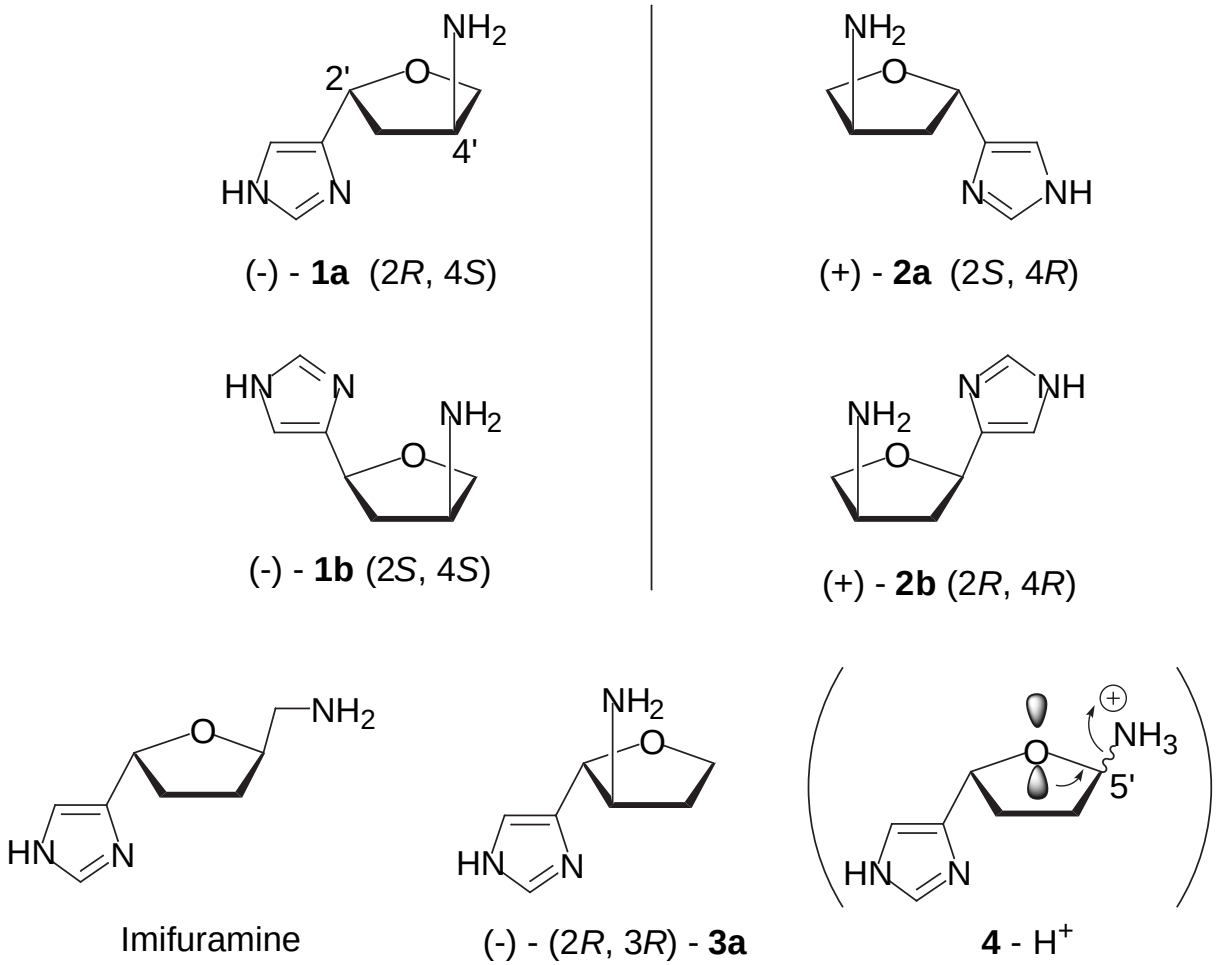
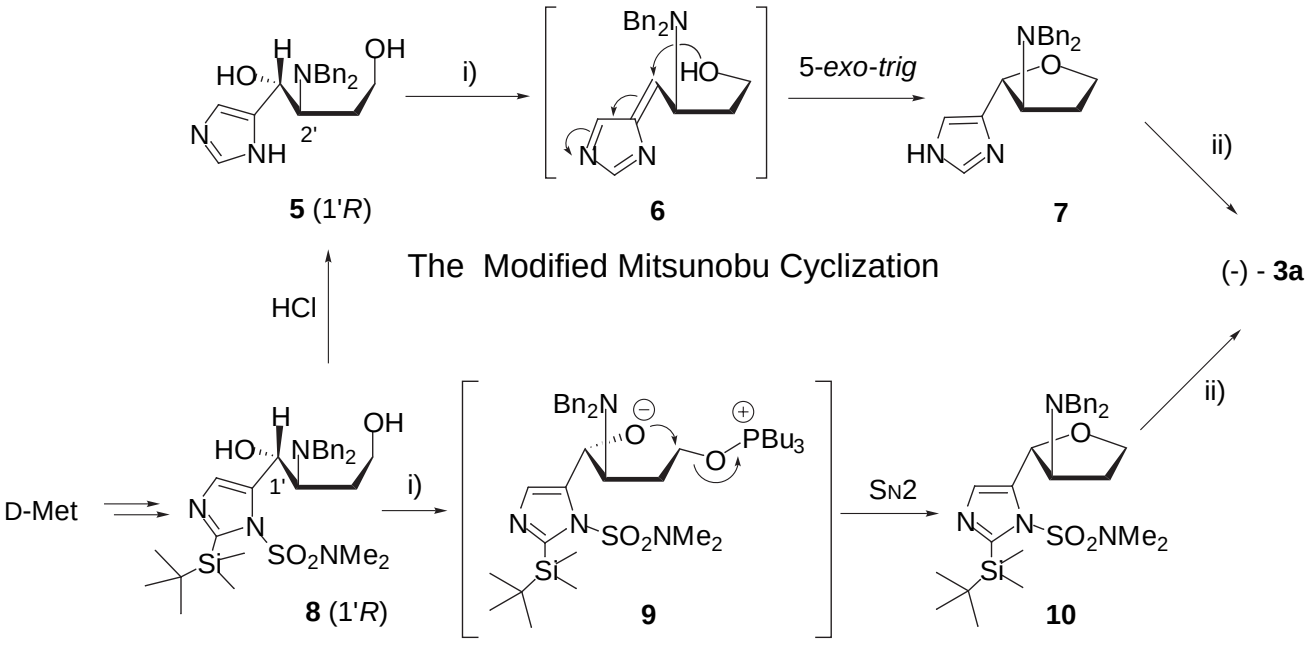


Figure 1

intermediate (**5**) acted as the directing group to control the *trans* stereochemistry of the THFderivative (**7**), while the standard Mitsunobu cyclization produced **10** with the same *trans* system by the SN2 reaction *via* the C4'-oxyphosphonium intermediate (**9**). Accordingly, the modified and standard Mitsunobu cyclizations produced the respective *trans*-THF-intermediates (**7** and **10**), but they proceeded by different reaction mechanisms. As a nor-analog of imifuramine, 4(5)-[5-aminotetrahydrofuran-2-yl]imidazole (**4**) was designed, but it is apparently easily decomposed under physiological pH owing to its *a*-amino ether structure as shown in Figure 1. Then, we focused on synthesis of 4(5)-(4-aminotetrahydrofuran-2-yl)imidazoles (**1a** and **1b**) as a nor-imifuramine analog, because these are spaced by three atoms (C2'-C3'-C4') on the THF ring between the imidazole and amino group analogously to that (C2'-O-C5') of **4**. In this paper, we describe the stereoselective synthesis of the four stereoisomers (**1a**,**1b**, **2a**, and **2b**) of the C4'-amino compound using the modified or standard Mitsunobu cyclizations.

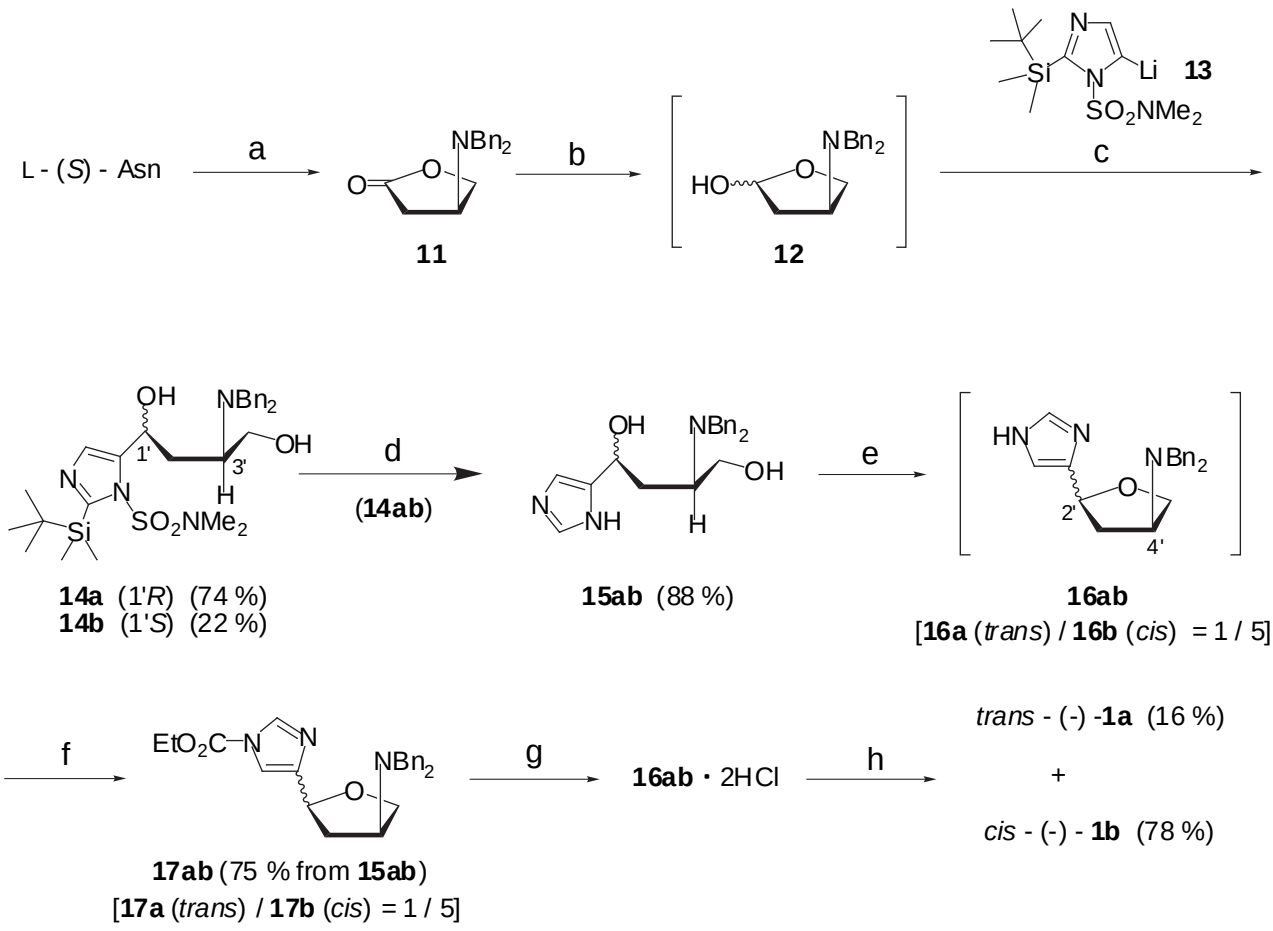


i) Bu_3P, $\begin{matrix} NCONMe_2 \\ | \\ NCONMe_2 \end{matrix}$ (TMAD) ii) ref. 6

Scheme 1

RESULTS AND DISCUSSION

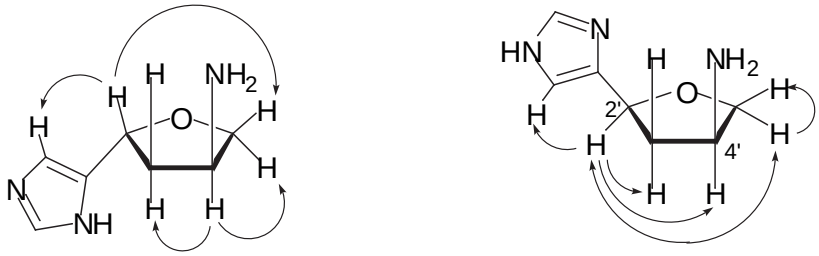
The starting *S*-(+)-4-dibenzylamino-γ-lactone (**11**)[9] was easily synthesized from L-(*S*)-asparagine as described by Gmeiner *et al*. Reduction of **11** with DIBAL-H followed by an addition of the lithium salt (**13**)[7b] of bis-protected imidazole to the resulting lactol (**12**) gave a 4:1 diastereomixture of **14ab**. Although the separation of **14a** and **14b** was not required for the modified Mitsunobu cyclization, they could be separated by SiO_2 chromatography to give the respective diastereomer (**14a**)(polar, 74%) and (**14b**)(less polar, 22%), the configuration at C1' of which was assigned later. Hydrolysis of the diastereomixture (**14ab**) in refluxing 1.5N HCl afforded diol (**15ab**) having unsubstituted imidazole in 88% yield. We here expected that a diol intermediate (**15ab**) having an unsubstituted imidazole might form preferentially a C2', 4'-*trans* isomer (**16a**) by the modified Mitsunobu cyclization (Scheme 2), in which a bulky C3'-dibenzylamino group of **15ab** could control the stereochemistry of **16**, as in the case of THF-histamine synthesis.[6] The Mitsunobu cyclization of **15ab** with *N*,*N*,*N'*,*N'*- tetramethyl-



Reagents and conditions : a) ref. 9 ; b) DIBAL, -70℃, 25 min ; c) (i) **13**, -50℃ ; (ii) rt, 1 h ; d) 1.5 N HCl, reflux, 4 h ; e) TMAD, Bu_3P, benzene-THF, 0℃, 1 h ; f) $ClCO_2Et$, Py, cat. 4-DMAP ; g) 1N HCl, EtOH, reflux, 0.5 h ; h) (i) H_2 (3 Kg / cm^2) / 10% Pd-C ; (ii) column chromatography ($CHCl_3$: MeOH : 30% NH_4OH = 299 : 1 : 10)

Scheme 2

azodicarboxamide (TMAD)[10] and Bu_3P at 0℃ in benzene-THF for 1 h unexpectedly produced a 1:5 mixture (**16ab**) of *trans*- and *cis*-THF-intermediates. The ratio was assigned from the methine protons at C2' in ^{1}H-NMR (δ 5.15 for **16a** *vs*. 4.82 for **16b**). The mixture was converted into ethoxycarbonyl intermediates (**17ab**) owing to the difficulty in production separation from Bu_3P=O. The major component (**17b**) was assigned as *cis*-form from NOE experiments of the final amino compounds (**1a** and **1b**), as described later. Deprotection of the ethoxycarbonyl group of **17ab** with HCl and subsequent Pd-catalyzed hydrogenolysis yielded a mixture of *trans*- and *cis*-isomers (**1a** and **1b**). Separation of the mixture by column chromatography completed the synthesis of the *cis*-isomer [(-)-**1b**, 78%], together with the *trans*-isomer



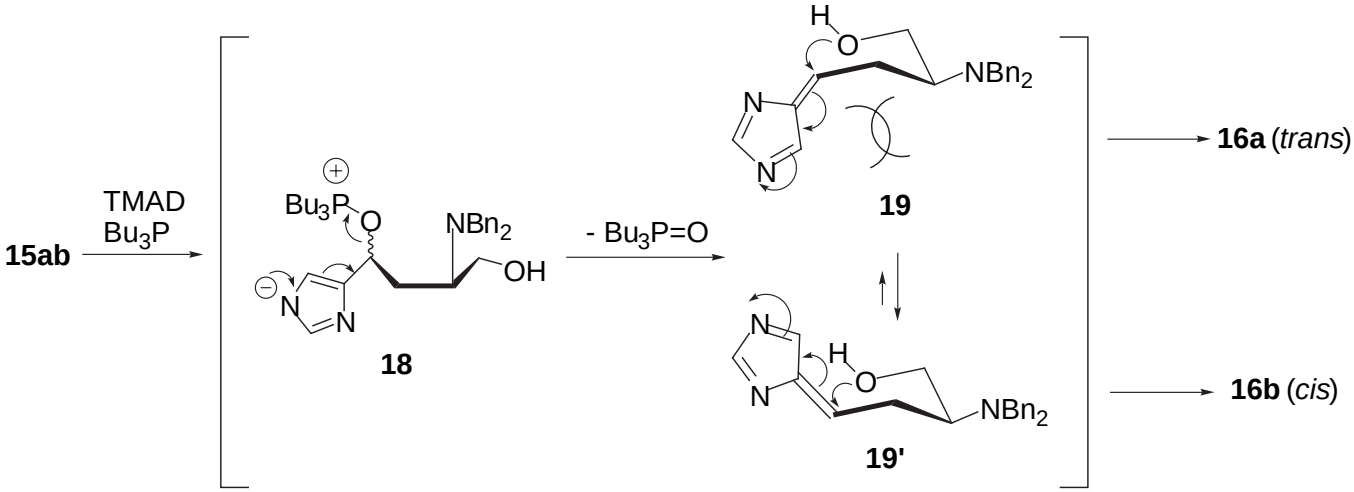
trans -**1a** *cis* - **1b**

Figure 2

[(-)-**1a**, 16%]. The relative configurations of **1a** and **1b** were indicated by the NOE experiments as illustrated in Figure **2**, in which the C2'-H in **1b** was found to have proper interaction with C4'-H, showing *cis* configuration at C2' and C4'.

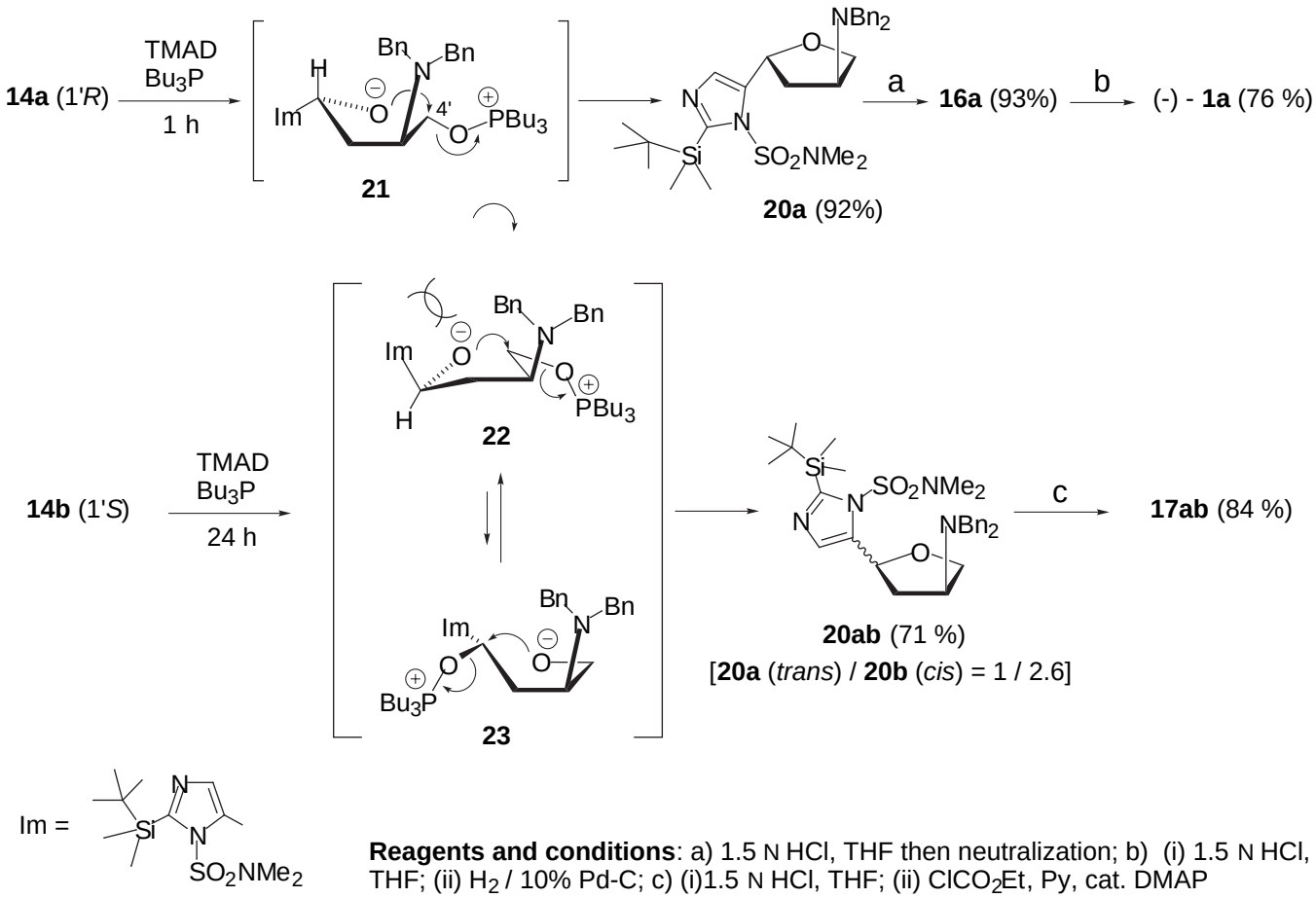
The formation of tetrahydrofurans (**16a** and **16b**) may be explained by a postulated mechanism of the modified Mitsunobu cyclization (Scheme 3): i) elimination of $Bu_3P=O$ from the oxyphosphonium intermediate (**18**) to lead to active forms (**19** and **19'**) of the imidazole, ii) the respective cyclization of **19** and **19'** to **16a** and **16b**.[11] The *cis*-stereoselectivity (**16a** / **16b** = 1 / 5) may be accounted for by the conformational preferance of **19'** over **19** which involves additional $A^{(1,3)}$ -strain.[12]

In the case of the THF-histamine described previously (Scheme 1), cyclization of diol intermediate (**8**)



Scheme 3

using the standard Mitsunobu cyclization proceeded *via* activation of the primary hydroxy group. We thus anticipated that an alternative synthesis of a *trans*-THF intermediate (**20a**) may be attained from **14a** by the SN2 reaction *via* the C4'-oxyphosphonium intermediate[6] (Scheme 4). Cyclization of **14a** with TMAD and Bu_3P at room temperature for 1 h produced **20a** with a *trans* system in 92% yield. The *trans* isomer (**20a**) was transformed into the (-)-**1a** by deprotection of the imidazole moiety followed by debenzylation. On the other hand, cyclization of the minor isomer (**14b**) having C1'*S* configuration proceeded very slowly (24 h) and gave a 1 : 2.6 inseparable mixture (**20ab**) of **20a** (*trans*) and **20b** (*cis*). The structure of **20ab** was confirmed by transformation into **17ab.** The cyclization of **14b** *via* C4'-oxyphosphonium intermediate (**22**) may be suppressed by steric repulsion between the C1'-disubstituted imidazole and



Scheme 4

C3'-dibenzylamino substituent. This interaction may cause the competitive formation of C1'-oxyphosphonium intermediate (**23**), yielding the minor product (**20a**) as illustrated in Scheme 4. Therefore, the C1' configuration in the original compounds (**14a** and **14b**) was tentatively assigned as *R* and *S*, respectively, based on the stereochemistry of the products. The enantiomers (**2a** and **2b**) were synthesized by the same reaction sequence described herein from D-(*R*)-asparagine. We thus achieved an efficient and stereoselective synthesis of the four isomers of 4(5)-(4-aminotetrahydrofuran-2-yl)imidazole by efficient use of the modified and standard Mitsunobu cyclizations.

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. ^{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*R*,3*S* or 1*S*,3*S*)-3-dibenzylamino-1,4-dihydroxybutyl]-*N*,*N*-dimethylimidazole-1-sulfonamide [**14a** (**1'*R***) and **14b** (**1'*S***)]

To a solution of **11**9(613 mg, 2.18 mmol) in dry toluene (13 mL) at -70 ℃ was added a 1 M solution of DIBAL in toluene (3.3 mL, 3.30 mmol) over 15 min. After being stirred for 25 min at -70℃, the reaction mixture was quenched with MeOH (2 mL) and further stirred for 20 min at rt. Saturated $NaHCO_3$ solution (1 mL) and EtOAc (2 mL) were added to the reaction mixture, which was further stirred for 10 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 crude lactol (**12**,

627 mg) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ : 1.77-2.41 (m, 2H, 3-H), 3.72-4.17 (m, 7H, 4-H, 5-H and $CH_2Ph \times 2$), 5.84 (dd, 1/3H, *J* = 5.5, 2.9 Hz, 2-H), 5.63 (dd, 2/3H, *J* = 5.5, 2.0 Hz, 2-H), 7.13-7.40 (m, 10H, Ph × 2). Alternatively, a solution of 2-*tert*-butyldimetylsilyl-*N*,*N*-dimethyl-1*H*-imidazolesulfonamide (1.89 g, 6.54 mmol) in THF (4 mL) was cooled to -50℃, and 1.6 M BuLi-hexane (4.1 mL, 6.54 mmol) was added dropwise over 20 min to the solution to precipitate the white lithium salt (**13**). The resulting suspension was stirred for 15 min and cooled to -65℃, and then a solution of **12** prepared above in toluene (4.5 mL) was added slowly over 10 min at the same temperature and the whole was stirred for 5 min. The dry ice bath was removed, and the reaction mixture was stirred at rt to dissolve the salts. After 1 h, a small amount of H_2O was added to the resulting brown suspension and the solvent was evaporated to give a residue, which was extracted twice with EtOAc. The extract was washed with H_2O and brine, dried, and evaporated to give a crude oil, which was purified by column chromatography [20 % to 50 % EtOAc-hexane (1:1)] to give **14b** (269 mg, 22 %) and **14a** (924 mg, 74 %), in that order, as white amorphous materials. **14a** (more polar)**:** ^{1}H-NMR ($CDCl_3$) δ : 0.38 [s, 3H, $Si(CH_3)_2$], 0.41 [s, 3H, $Si(CH_3)_2$], 1.04 [s, 9H, $C(CH_3)_3$], 1.84 (dt, 1H, *J* = 13.5, 6.6 Hz, 2'-H), 2.33 (dt, 1H, *J* = 13.5, 4.6 Hz, 2'-H), 2.68 [s, 6H, $N(CH_3)_2$], 2.83 (m, 1H, 3'-H), 3.55 (d, 2H, *J* = 13.5 Hz, CH_2Ph), 3.64 (m, 2H, 4'-H), 3.76 (d, 2H, *J* = 13.5 Hz, CH_2Ph), 5.01 (t, 1H, *J* = 6.5 Hz, 1'-H), 7.18-7.34 (m, 11H, 5-H and $Ph \times 2$). ^{13}C-NMR ($CDCl_3$) δ : 18.6, 27.3, 33.3, 37.6, 53.6, 56.9, 61.9, 63.1, 127.1, 128.3, 128.9, 130.0, 137.2, 139.1. SIMS *m/z*: 573 (M^++1). HRMS *m/z*: 573.2925 (Calcd for $C_{29}H_{45}N_4O_4SSi$: 573.2928). **14b** (less polar) **:** ^{1}H-NMR ($CDCl_3$) δ : 0.38 [s, 3H, $Si(CH_3)_2$], 0.41 [s, 3H, $Si(CH_3)_2$], 0.98 [s, 9H, $C(CH_3)_3$], 1.77 (ddd, 1H, *J* = 14.2, 5.9, and 3.3 Hz, 2'-H), 2.13 (m, 1H, 2'-H), 2.68 [s, 3H, $N(CH_3)_2$], 2.78 [s, 3H, $N(CH_3)_2$], 3.25 (m, 1H, 3'-H), 3.66 (d, 2H, *J* = 12.2 Hz, CH_2Ph), 3.69 (d, 1H, *J* = 10.7 Hz, 4'-H), 3.80 (d, 1H, *J* = 10.7 Hz, 4'-H), 3.84 (d, 2H, *J* = 12.2 Hz, CH_2Ph), 4.72 (dd, 1H, *J* = 10.5, 2.3 Hz, 1'-H), 7.20-7.42 (m, 11H, 5-H and $Ph \times 2$). ^{13}C-NMR ($CDCl_3$) δ : 18.5, 27.3, 33.7, 37.6, 37.9, 53.7, 58.5, 59.8, 61.2, 64.8, 127.3, 128.4, 129.4, 129.8, 132.2, 134.7, 137.1, 138.3.

SIMS *m/z*: 573 (M^++1). HRMS *m/z*: 573.2931 (Calcd for $C_{29}H_{45}N_4O_4SSi$: 573.2928).

Hydrolysis of a diasteremeric mixture (14ab)

To a THF solution (25 mL) of **14ab** (1.19 g, 2.08 mmol) was added 1.5 N HCl (20 mL). The resulting mixture was refluxed for 4 h and neutralized by addition of 30% NH_4OH. The solvent was evaporated to give a residue, which was added to EtOAc and brine. After the EtOAc layer was separated, the aqueous layer was further extracted twice with EtOAc. The combined organic layer was dried and evaporated to give a crude oil, which was subjected to flash chromatography using 10% and 15 % MeOH in EtOAc as eluent to give 4(5)-(3-dibenzylamino-1,4-dihydroxybutyl)imidazole (**15ab**)(440 mg, 88 %) as an amorphous product. ^{1}H-NMR (CD_3OD) δ : 1.84 [m, 1H, 2'-H], 2.08-2.21 (m, 2/9H, 2'-H (1'*S*)], 2.28 [dt, 7/9H, *J* = 13.7, 5.9 Hz, 2'-H (1'*R*)], 2.87 [quint, 7/9H, *J* = 6.0 Hz, 3'-H (1'*R*)], 2.92-3.00 [m, 2/9H, 3'-H (1'*S*)], 3.50-3.86 (m, 6H, 4'-H and CH_2Ph×2), 4.67 [dd, 2/9H, *J* = 7.8, 5.4 Hz, 1'-H (1'*S*)], 4.84 [t, 7/9H, *J* = 5.4 Hz, 1'-H (1'*R*)], 6.60 [s, 7/9H, 5-H (1'*R*)], 6.69 (s, 2/9H, 5-H (1'*S*)], 7.17-7.36 (m, 10H, Ph×2), 7.58 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ : 35.5, 35.6, 54.8, 57.5, 58.9, 62.0, 62.7, 67.5, 68.1, 128.0, 128.1, 129.2, 129.3, 130.1, 130.3, 136.0, 140.5, 140.8. SIMS *m/z*: 352 (M^++1). HRMS *m/z*: 352.2017 (Calcd for $C_{21}H_{26}N_3O_2$: 352.2024).

Conversion of 15ab into 17ab using the modified Mitsunobu cyclization

To a solution of **15ab** (640 mg, 1.82 mmol) and Bu_3P (0.67 ml, 2.73 mmol) in THF (15 mL) - benzene (30 mL) was added TMAD (470 mg, 2.73 mmol) at 0℃. The reaction mixture was stirred at 0℃ for 1 h. After the resulting insoluble material was filtered through a Celite pad, and the filtrate was condensed to give a crude oil which was dissolved in EtOAc. The organic layer was washed with H_2O, dried and evaporated to give a crude oil (**16ab**). The solution of **16ab** in benzene (30 mL) was refluxed with ethyl chloroformate (0.35 mL, 3.64 mmol), pyridine (0.22 mL, 2.73 mmol), and a catalytic amount of 4-DMAP for 0.5 h. After a few drops of H_2O was added to the reaction mixture, solvent was evaporated to give a residue, which was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried, and

evaporated to give an oil, which was subjected to chromatography. Elution with 15 % EtOAc-hexane afforded **17ab** (550 mg, 75%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ : 1.41 (t, 3H, J = 7.0 Hz, CH_3), 2.13 [m, 5/6H, 3'-H, (2'*S*)], 2.22 [m, 1/6H, 3'-H, (2'*R*)], 2.40 (m, 1H, 3'-H), 3.55 (d, 2H, J = 14.0 Hz, CH_2Ph), 3.65-3.72 (m, 1H, 5'-H), 3.71 (d, 2H, J = 14.0 Hz, CH_2Ph), 3.78-3.90 (m, 1H, 5'-H), 3.97-4.05 (m, 1H, 4'-H), 4.44 (q, 2H, J = 7.0 Hz, $COCH_2$), 4.76 [dd, 5/6H, J = 9.7, 6.6 Hz, 2'-H (2'*S*)], 5.10 [dd, 1/6H, J = 8.3, 5.4 Hz, 2'-H, (2'*R*)], 7.18-7.38 (m, 11H, Ph × 2 and 5-H), 8.06 [s, 1/6H, 2-H, (2'*R*)], 8.09 [s, 5/6H, 2-H, (2'*S*)]. EIMS *m/z*: 406 (M^++1). HRMS *m/z*: 406.2133 (Calcd for $C_{24}H_{28}N_3O_3$: 406.2129).

4(5)-[(2*R*, 4*S*)-4-Aminotetrahydrofuran-2-yl]imidazole [(-)-1a] and 4(5)-[(2*S*, 4*S*)-4-aminotetrahydrofuran-2-yl]imidazole [(-)-1b]

A solution of **17ab** (142 mg, 0.35 mmol) in EtOH (4.5 mL) was refluxed with 1N HCl (1.8 mL) for 2 h, and evaporated to give a **16ab**·2HCl (152 mg) as a white amorphous material. **16ab**·2HCl: ^{1}H-NMR (CD_3OD) δ : 2.74 (m, 1H, 3'-H), 2.94 [dt, 5/6H, J = 14.4, 6.8 Hz, 3'-H (2'*S*)], 3.18 [m, 1/6H, 3'-H (2'*R*)], 3.97-4.12 (m, 1H, 4'-H), 4.26-4.65 (m, 6H, 5'-H and CH_2Ph × 2), 5.06 [dd, 5/6H, J = 9.1, 6.8 Hz, 2'-H (2'*S*)], 5.59 [dd, 1/6H, J = 8.3, 5.7 Hz, 2'-H (2'*R*), 7.41-7.58 (m, 10H, Ph × 2), 7.66 [s, 1/6H, 5-H (2'*R*), 7.85 (s, 5/6H, 5-H), 8.95 [s, 1/6H, 2-H (2'*S*)], 8.99 [s, 5/6H, 2-H (2'*R*)]. ^{13}C-NMR ($CDCl_3$) δ : 33.5, 56.8, 64.8, 64.9, 68.8, 69.7, 73.0, 118.1, 130.4, 130.4, 131.1, 132.2, 133.0, 136.0. SIMS *m/z*: 334 (M^++1). HRMS *m/z*: 334.1919 (Calcd for $C_{21}H_{24}N_3O$: 334.1918). A solution of **16ab**·2HCl obtained above in EtOH (8 mL) was subsequently hydrogenated with 10% Pd-C (249 mg) at initial pressure of 3.0 kg/cm^2 for 16 h. The catalyst was removed by fluted filter paper, and the filtrate was concentrated to give a residual oil, which was chromatographed [Chromatorex NH-DM 1020, $CHCl_3$ - MeOH - 30% NH_4OH (299:1:10)] to give *cis* - **1b** (42 mg, 78 %) and *trans* - **1a** (8 mg, 16 %) in that order. *cis* - **1b**: colorless oil. $[\alpha]_D$ -11.4° (*c*=1.97, MeOH). ^{1}H-NMR (CD_3OD) δ : 1.78-1.90 (m, 1H, 3'-H), 2.46-2.58 (m, 1H, 3'-H), 3.55-3.70 (m, 2H, 5'-H), 3.85-3.94 (m, 1H, 4'-H), 4.91 (t, 1H, J = 7.7

Hz, 2'-H), 7.04 (s, 1H, 5-H), 7.64 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ : 41.3, 53.4, 75.3, 75.5, 117.6, 136.7, 139.7. EIMS *m/z*: 153 (M^+). HRMS *m/z*: 153.0906 (Calcd for $C_7H_{11}N_3O$: 153.0901). *trans* - **1a**: colorless oil. $[\alpha]_D$ -33.1° (*c*=2.19, MeOH, as dihydrochloride). ^{1}H-NMR (CD_3OD) δ : 2.03 (ddd, 1H, *J*= 13.7, 7.7, and 3.9Hz, 3'-H), 2.24-2.36 (m, 1H, 3'-H), 3.56 (dd, 1H, *J* = 8.6, 3.9 Hz, 5'-H), 3.71 (m, 1H, 4'-H), 4.12 (dd, 1H, *J* = 8.6, 5.6 Hz, 5'-H), 5.14 (t, 1H, *J* = 7.8 Hz, 2'-H), 7.00 (s, 1H, 5-H), 7.63 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ : 41.9, 53.1, 74.7, 76.0, 117.6, 136.7. EIMS *m/z*: 153 (M^+). HRMS *m/z*: 153.0890 (Calcd for $C_7H_{11}N_3O_1$: 153.0901).

Conversion of 14a into (-)-20a Using the standard Mitsunobu Cyclization.

To a solution of **14a** (260 mg, 0.46 mmol) and Bu_3P (0.17 ml, 0.68 mmol) in benzene (7 mL) was added TMAD (118 mg, 0.68 mmol) at 0℃ and the whole was stirred at rt for 1 h. The resulting insoluble material was filtered through a Celite pad and the solvent was evaporated to give a residue. It was diluted with EtOAc and H_2O, and the aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with brine, dried and evaporated. The residual oil was chromatographed using 15 % EtOAc-hexane for elution to give 2-*tert*-butyldimethylsilyl-5-[(2*S*,4*S*)-4-dibenzylaminotetrahydrofuran-2-yl]-*N*,*N*-dimethylimidazole-1-sulfonamide (**20a**, 230 mg, 92 %) as a colorless oil. $[\alpha]_D$ -14.5° (*c*=2.24, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.39 [s, 6H, $Si(CH_3)_2$], 0.99 [s, 9H, $C(CH_3)_3$], 2.06-2.17 (m, 1H, 3'-H), 2.38-2.52 (m, 1H, 3'-H), 2.83 [s, 6H, $N(CH_3)_2$], 3.55 (d, 2H, *J* = 14.0 Hz, CH_2Ph), 3.62-3.74 (m, 1H, 4'-H or 5'-H), 3.76 (d, 2H, *J* = 14.0 Hz, CH_2Ph), 3.81 (dd, 1H, *J* = 9.1, 4.9 Hz, 4'-H or 5'-H), 3.95 (dd, 1H, *J* = 9.1, 7.2 Hz, 4'-H or 5'-H), 5.36 (dd, 1H, *J* = 8.0, 5.3 Hz, 2'-H), 7.08 (s, 1H, 5-H), 7.17-7.40 (m, 10H, Ph×2). ^{13}C-NMR ($CDCl_3$) δ: 18.5, 27.3, 34.5, 37.4, 55.4, 60.8, 70.1, 71.5, 126.9, 128.2, 128.5, 129.8, 135.0, 139.2. EIMS *m/z*: 554 (M^+). HRMS *m/z*: 554.2748 (Calcd for $C_{29}H_{42}N_4O_3SSi$: 554.2745).

4(5)-[(2*R*, 4*S*)-4-Dibenzylaminotetrahydrofuran-2-yl]imidazole [(-)-**16a**]

To a THF solution (8 mL) of **20a** (257 mg, 0.46 mmol) was added 1.5 N HCl (4.5 mL). The resulting

mixture was refluxed for 1 h and neutralized by addition of $NaHCO_3$ powder. The solvent was evaporated to give a residue, which was extracted with EtOAc (×2). The extract was dried and evaporated to give a crude oil, which was purified by flash chromatography using 5 % MeOH in EtOAc to give **16a** (143 mg, 93 %) as a colorless oil. $[\alpha]_D$ -5.84° (*c*=2.58, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.16-2.48 (m, 2H, 3'-H), 3.57 (d, 2H, *J* = 14.3 Hz, CH_2Ph), 3.65-4.06 (m, 3H, 4'-H and 5'-H), 3.77 (d, 2H, *J* = 14.3 Hz, CH_2Ph), 5.16 (t, 1H, *J* = 7.2 Hz, 2'-H), 6.90 (s, 1H, 5-H), 7.08-7.41 (m, 10H, Ph×2), 7.57 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 34.6, 56.4, 62.5, 71.2, 75.7, 117.2, 127.9, 129.1, 129.7, 136.5, 140.0, 140.7. SIMS *m/z*: 334 (M^++1). HRMS *m/z*: 344.1917 (Calcd for $C_{21}H_{24}N_3O$: 334.1918).

Conversion of (-)-16a into (-)-1a

A solution of (-)-**16a** (212 mg, 0.64 mmol) in EtOH (7 mL) was stirred with 1N HCl (1.5 mL) at rt for 3 h, and evaporated to give a **16a**·2HCl (263 mg) as a white amorphous material. **16a**·2HCl : $[\alpha]_D$ -21.8° (*c*=1.46, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.60-2.79 (m, 1H, 3'-H), 3.07-3.24 (m, 1H, 3'-H), 4.00-4.12 (m, 1H, 4'-H), 4.23-4.64 (m, 6H, 5'-H and CH_2Ph×2), 5.60 (dd, 1H, *J* = 5.2, 7.5 Hz, 2'-H), 7.48 (m, 10H, Ph×2), 7.66 (s, 1H, 5-H), 8.94 (s, 1H, 2-H). A solution of **16a**·2HCl in EtOH (23 mL) was subsequently hydrogenated on 10% Pd-C (81 mg) at initial pressure of 3.0 kg/cm^2 for 24 h. The catalyst was removed by fluted filter paper, and the filtrate was evaporated to give a white amorphous material (144 mg) of (-)-**1a**·2HCl [^{1}H-NMR (CD_3OD) δ: 2.49-2.58 (m, 2H, 3'-H), 3.88-4.20 (m, 3H, 4'-H and 5'-H), 5.40 (t, 1H, *J* = 7.5 Hz, 2'-H), 7.60 (s, 1H, 5-H), 8.90 (s, 1H, 2-H). ^{13}C-NMR (CD_3OD) δ: 37.1, 52.8, 71.7, 72.1, 117.6, 134.9, 136.0.]. To a MeOH solution of the dihydrochlodide 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 (25:5:1) as the eluent gave (-)-**1a** (85 mg, 86% from **16a**) as free form.

Conversion of 14b into 20ab.

TMAD (63 mg, 0.37 mmol) was added to a mixture of **14b** (140 mg, 0.25 mmol) and Bu_3P (0.11 mL,

0.37 mmol) at 0℃ and the whole was stirred at rt for 6 h. Bu_3P (0.03 mL, 0.13 mmol) was then added to the resulting mixture, which was further stirred for 18 h at rt to give a 1 : 2.6 mixture (96 mg, 71 %) of **20a** and **20b** by the same procedure as used for the preparation of **1a.** **20ab**: white amorphous material. ^{1}H-NMR (CD_3OD) δ: 0.39 [s, 6H, $Si(CH_3)_2$], 1.00 [s, 9H, $C(CH_3)_3$], 1.97-2.26 [m, 1H, 3'-H], 2.39-2.51 (m, 1H, 3'-H), 2.83 [s, 6H, $N(CH_3)_2$], 3.55 (d, 2H, *J* = 14.3 Hz, CH_2Ph), 3.60-3.85 (m, 2H, 4'-H and 5'-H), 3.73 (d, 2H, *J* = 14.3 Hz, CH_2Ph), 3.94 (m, 1H, 5'-H), 4.98 [dd, 13/18H, *J* = 9.4, 7.2 Hz, 2'-H (2'*S*)], 5.36 [dd, 5/18H, *J* =7.2, 4.5 Hz, 2'-H (2'*R*)], 7.08 [s, 5/18H, 5-H (2'*R*)], 7.20-7.40 [overlapped, 13/18H, 5-H (2'*S*) and 10H, Ph × 2]. The structure of **20ab** was confirmed by transformation into **17ab**, in which hydrolysis followed by ethoxycarbonylation of **20ab** (96 mg, 0.17 mmol) afforded a 1 : 2.6 diastereomeric mixture (96 mg, 84%) of **17a** and **17b** as an oil { ^{1}H-NMR (CD_3OD) δ: 4.76 [dd, 13/18H, *J* = 9.7, 6.6 Hz, 2'-H (2'*S*)], 5.10 [dd, 5/18H, *J* = 8.3, 5.4 Hz, 2'-H, (2'*R*). EIMS *m/z*: 406 (M^++1). HRMS *m/z*: 406.2133 (Calcd for $C_{24}H_{28}N_3O_3$: 406.2129) }.

(+)-4(5)-[(2*S*, 4*R*) and (2*R*, 4*R*)-4-Aminotetrahydrofuran-2-yl]imidazole {[(+)-2a] and [(+)-2b]}

The configuration counterparts {(+)-(2*S*,4*R*)-**2a**, $[\alpha]_D$ +23.0° (*c*=1.20, MeOH) / (+)-(2*R*,4*R*)-**2b**, $[\alpha]_D$ +8.5° (*c*=3.54, MeOH) } were synthesized from D-asparagine by the present method.

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