Efficient Synthesis of *trans*- or *cis*-4(5)-(5-Aminomethyltetrahydrofuran-2-yl)imidazoles *via* Diazafulvene Intermediates: Synthetic Approach toward Human Histamine H_4-Ligands

Shinya HARUSAWA,[a] Lisa ARAKI,[a] Hirotaka TERASHIMA,[a] Makoto KAWAMURA,[a] Seiichiro TAKASHIMA,[a] Yasuhiko SAKAMOTO,[b] Takeshi HASHIMOTO,[c] Yumiko YAMAMOTO,[c] Atsushi YAMATODANI,[c] and Takushi KURIHARA*,[a]

[a] *Department of Synthetic Organic Chemistry, Osaka University of Pharmaceutical Sciences; 4–20–1 Nasahara, Takatsuki, Osaka 569–1094, Japan:* [b] *R&D Division, AZWELL, Inc.; 2–24–3, Sho, Ibaraki, Osaka 567–0806, Japan: and* [c] *Department of Bioinformatics, Graduate School of Allied Health Sciences, Faculty of Medicine, Osaka University; 1–7 Yamadaoka, Suita, Osaka 565–0871, Japan.* Received March 17, 2003; accepted April 21, 2003

(+)-4(5)-[(2*R*,5*R*)-5-Aminomethyltetrahydrofuran-2-yl]imidazole [(+)-1, imifuramine] and its 2*R*,5*S*-stereoisomer (+)-2 were expected as base compounds to develop selective human histamine H_4-receptor ligands. The improved synthesis of (+)-1 was done *via* cyclization of a diazafulvene intermediate generated by Bu_3P/*N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) treatment of a diol 17ab bearing an unsubstituted imidazole moiety in good yields. This methodology also afforded an alternative synthetic route to *trans*- and *cis*-ethyl 4(5)-(5-hydroxymethyltetrahydrofuran-2-yl)imidazole carboxylates (5 and 6), reported previously. Also, 4(5)-[(2*R*,5*S*)-5-aminomethyltetrahydrofuran-2-yl]imidazole (+)-2 was synthesized from ethyl 4(5)-(2-deoxy-β-D-ribofuranosyl)imidazole-1-carboxylate (35) *via* the four steps involving deoxygenation.

Key words imifuramine; diazafulvene; H_4-receptor

Histamine H_4 (H_4)-receptor is the most recently discovered histamine receptor which has approximately 35% overall homology to the human histamine H_3 (H_3)-receptor.[1—7] However, the tissue distribution of the two receptors is quite different. The H_3-receptor is mainly found in the central nervous system, whereas the mRNA of the H_4-receptor is expressed exclusively in peripheral tissues, such as bone marrow,[1,4] small intestine,[1,6,7] spleen,[4,6,7] and leukocytes.[7] The physiological and pathophysiological functions of the receptor are unknown. However, the abundant expression of human H_4-receptor mRNA in the hematopoietic and lymphatic tissues indicates that the receptor might be related to regulation of hematopoiesis and/or an immune function. To investigate the pharmacology of the receptor, specific ligands are indispensable, but most H_3-ligands are active at the H_4-receptor as well and no specific ligands for the H_4-receptor are available.[8]

We very recently examined the binding affinity and functional activity of 2,5-disubstituted tetrahydrofuranylimidazoles for human H_3- and H_4-receptors expressed in SK-N-MC cells.[9] Among them, (+)-4(5)-[(2*R*,5*R*)-5-aminomethyltetrahydrofuran-2-yl] imidazole [(+)-**1**, imifuramine][10,11] exhibited potent agonistic activities for the H_3-receptor, while its enantiomer (−)-**1** was found to be a selective H_3-agonist, which was approximately 300-fold more active at the H_3-receptor than the H_4-receptor (Fig. 1). It is of particular interest to find that methylcyanoguanidine derivatives (−)-**3** (OUP-16) and (+)-**4** (OUP-13) exhibited full agonistic activities for the H_4-receptor with 40- to 45-fold selectivity over the H_3-receptor. Hence, the two OUP compounds would be lead compounds to develop selective human H_4-receptor ligands.[8]

We previously reported a stereodivergent synthesis of *trans*- or *cis*-4(5)-(5-aminomethyltetrahydrofuran-2-yl- or 5-aminomethyl-2,5-dihydrofuranyl)imidazoles, which is characterized by use of α- or β-phenylselenenyl nucleosides **7** or **8** as key intermediates (Fig. 1).[10—12] Although the synthetic strategy was effective as an initial step for accessing these compounds, it lacks the stereoselective formation of **7** or **8** and, further, requires phenylselenenylation and deselenenylation steps in the synthetic sequence. On the other hand, we reported an efficient and stereoselective synthesis of β-imidazole C-nucleosides bearing 4(5)-substituted imidazole as a

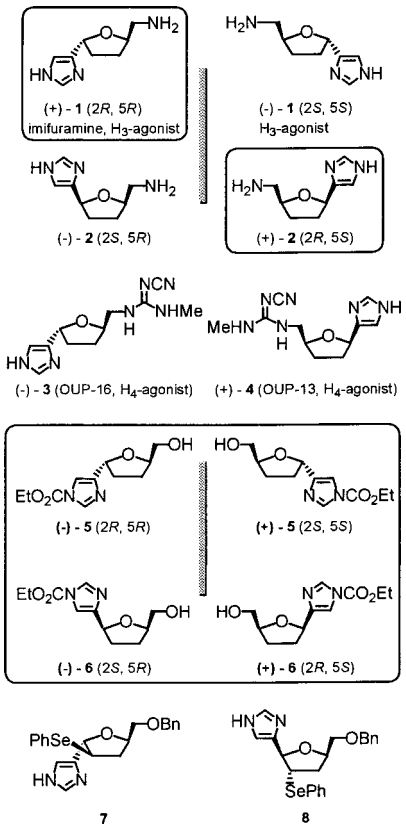


Fig. 1

* To whom correspondence should be addressed. e-mail: kurihara@gly.oups.ac.jp

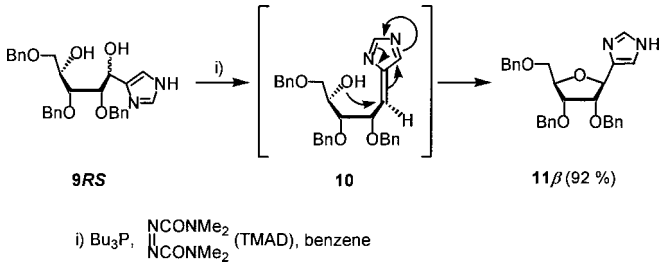
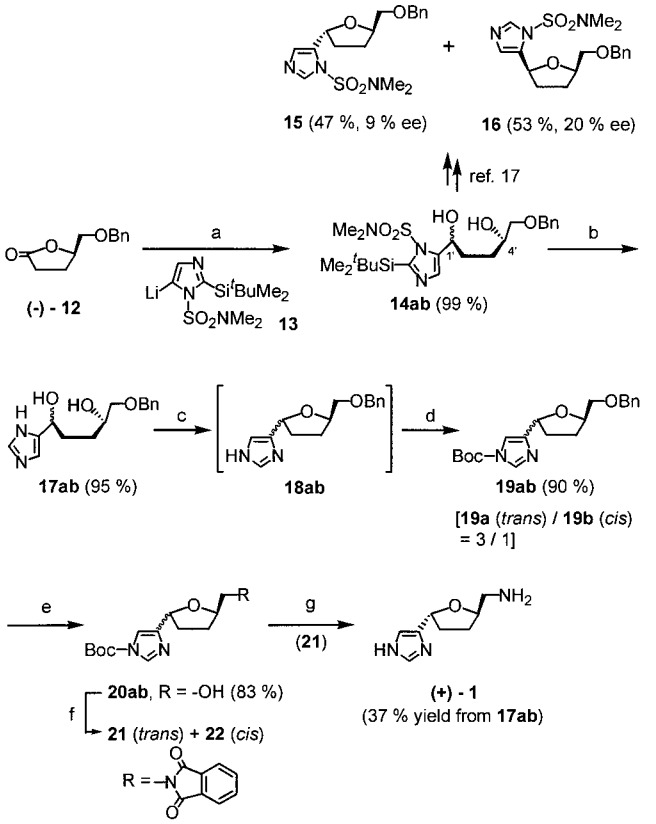


Chart 1

common structural unit, using the cyclization of 1,3-diazafulvene generated *in situ* (Chart 1).[13,14] In that report, we also indicated that an unsubstituted imidazole moiety is indispensable for the generation of the diazafulvene **10**, and the benzyloxy group at the C2′-position of the substrate 9*RS* (diastereomeric mixtue at C1′) acts as the directing group to control the stereochemistry of β-imidazole C-nucleoside 11β.[13,14] The methodology was recently extended to stereocontrolled synthesis of heterocyclic C-nucleosides (indole, C-2 linked imidazole, benzimidazole, and 6-iodobenzimidazole) by Benhida *et al.*[15,16] In such circumstances, the findings of OUP-16 and 13 encouraged us to synthesize *trans*- or *cis*-tetrahydrofuranylimidazoles using the diazafulvene-cyclization.

We herein describe a simple and effective synthesis of imifuramine [(+)-**1**] *via* a diazafulvene intermediate. Also, this synthetic method was independently used for the synthesis of *trans*- and *cis*-ethyl 4-(5-hydroxymethyltetrahydrofuranyl)-imidazole-1-carboxylates **5** and **6**, useful intermediates in our quest for specific H_4-ligands. Further, 4(5)-[(2*R*,5*S*)-5-aminomethyltetrahydrofuran-2-yl]imidazole [(+)-**2**], which is a substrate of OUP-13, was efficiently synthesized from ethyl 4(5)-(2-deoxy-β-D-ribofuranosyl)imidazole-1-carboxylate (35).

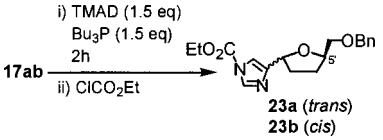
Synthesis of Imifuramine We recently reported that intramolecular Mitsunobu reaction of a diol **14ab**[17] (1 : 1 diastereomeric mixture), which was prepared starting from (*R*)-benzyloxymethyl-γ-butyrolactone (**12**),[18] with *N*,*N*,*N*″,*N*″-tetramethylazodicarboxamide (TMAD)[19] and Bu_3P followed by desilylation affords *trans*- and *cis*-cyclization products **15** (47%, 9% ee) and **16** (53%, 20% ee) with low optical purities (Chart 2). The low optical purities were attributed to indistinguishable activities between two hydroxy groups of **14ab**.[17] Thus, we directed our attention to imifuramine synthesis using diazafulvene cyclization. Hydrolysis of **14ab** in refluxing 1.5 N HCl afforded a diol **17ab** having unsubstituted imidazole in 95% yield. The cyclization of **17ab** was examined under various conditions to optimize the yield of the *trans*-product.[14,20] The results are summarized in Table 1. When the reaction of **17ab** was first carried out using TMAD and Bu_3P at rt in tetrahydrofuran (THF) for 2 h, a crude tetrahydrofuranylimidazole **18ab** was obtained. The crude mixture was then treated with ethyl chloroformate to separate it from the Bu_3P=O by-product, followed by column chromatography to afford a 2.3 : 1 mixture of *trans*- and *cis*-*N*-ethoxycarbonylated products **23a** and **23b** in only 12% overall yield from **17ab** (Table 1, run 1). In the case of THF (Table 1, run 1—3), the reaction was suppressed to give low yields, but the yields of **23ab** were improved to 56% or 50% yields in benzene or toluene, respectively (run 4 and 5). Further, the use of CH_2Cl_2 at 0 °C increased the yield to 80% with a 3 : 1 ratio of *trans*- and *cis*-products (run 7). The predominant formation of the *trans*-isomer was also observed in CH_2Cl_2 at −35 °C, but in only 15% yield (run 8). From these results, it became clear that the reaction was significantly influenced by the selection of solvents.



Reagents and conditions : a) (i) DIBAL, -70°C; (ii) **13**, THF, -70 to -50°C then rt; b) aq.1.5 N HCl - THF (1 : 1), reflux, 4h; c) Bu_3P (1.5 eq), TMAD (1.5 eq), CH_2Cl_2, 0°C, 15h; d) Boc_2O; e) H_2, 10 % Pd-C; f) (i) Phthalimide, Ph_3P, DEAD; (ii) SiO_2 separation; g) hydrazine hydrate.

Chart 2

Table 1. Solvent Effects of Cyclization to **23ab**



Run	Solvent	Temp. (°C)	Yield (%)	**23a**/**23b**
1	THF	rt	12	2.3/1
2	THF	0	12	3/1
3	THF	Reflux	15	2/1
4	Benzene	rt	56	2/1
5	Toluene	0	50	2/1
6	CH_2Cl_2	rt	68	1/1
7	CH_2Cl_2	0	80	3/1
8	CH_2Cl_2	−35	15	5/1

The structures of **23a** and **23b** were assigned on the basis of ^{1}H-NMR. The C5′-H (δ 4.32—4.55, m, 5′H and $CO_2C\underline{H}_2$)

in *trans*-**23a** was observed in lower field in comparison with that (δ 4.16—4.31, m) in *cis*-**23b**, because of the deshielding effect of the imidazole ring located *syn* in **23a**.[17]

At a practical level, a serious drawback of the *N*-ethoxycarbonyl product **23ab** is the difficulty in separating the respective *trans*- and *cis*-isomers **23a** and **23b** by SiO_2 column chromatography. It required a large column to avoid contamination of the *trans*-product by the *cis*-isomer. After many trials, we found that *N*-Boc-phthalimides **21** and **22** could be separated more easily by column chromatography. Thus, the Boc derivatives were prepared from **17ab** (Chart 2). The cyclodehydration of **17ab** with TMAD and Bu_3P in CH_2Cl_2 at 0 °C for 15 h followed by *N*-Boc-protection was carried out to produce a 3 : 1 mixture of **19a** and **19b** in 90% yield from **17ab**. Debenzylation of **19ab** using H_2/Pd-C and subsequent Mitsunobu phthaloylimination afforded crude phthalimides. After chromatographic separation of the *trans*-isomer **21** contaminated by diethyl 1,2-hydrazine-dicarboxylate formed in the Mitsunobu reaction, deprotection of the crude **21** with hydrazine hydrate and purification yielded (+)-**1**, imifuramine,[12] in 37% overall yield[21] from the diol intermediate **17ab**. Similarly, *cis*-(−)-**2**[12] was obtained from crude **22** in 6% overall yield from **17ab**. This synthetic process allows the synthesis of the enantiomer (−)-**1** by simply switching the starting material to (+)-**12**.

Synthesis of *trans*- and *cis*-Ethyl 4-(5-Hydroxymethyltetrahydrofuranyl)imidazole-1-carboxylates Schunack *et al.* used 3-(1*H*-imidazole-4-yl)propanol,[22] which is easily synthesized from urocanic acid, as the central building block to develop many potent H_3-agonists or antagonists.[23] Thus, *trans*- or *cis*-alcohols **5** and **6** may be useful intermediates to supply a variety of derivatives (Fig. 1). Since hydrogenolysis of benzyl ethers **19ab** or **23ab** synthesized above afforded an inseparable mixture of the corresponding alcohols, we intended an easy isolation of **5** and **6** by the cyclization of a diol **29ab** having a bulky trityloxy group at the C5′-position (Chart 3).

Novel *N*-[2-(trimethylsilyl)ethoxy]methyl (SEM) protected 4- and 5-iodoimidazoles **24** and **25** were first prepared from 4(5)-iodoimidazole[24,25] in 55% and 37% yields, respectively (Chart 3, Eq. 1). The *N*-SEM compounds **24** and **25** were assigned by the respective NOE experiments, as illustrated in Chart 3. According to the Lindell procedure,[26] **24** or **25** was treated with ethylmagnesium bromide to generate C4 or C5-imidazole anions, which were then reacted with lactol **28**,[27] which was prepared by reduction of 2,3-dideoxy-5-*O*-trityl-L-glyceropentanoic acid γ-lactone[27] with DIBAL-H, to give the corresponding diols **26ab** or **27ab** in 81% and 56% yields, respectively (Chart 3, Eq. 2). Thus, without their isolation, the mixture of **24** and **25** was treated as above to give an isomeric mixture (**26ab**, **27ab**) in 78% yield (Chart 3). The following cleavage of the SEM group with tetra-*n*-butyl ammonium fluoride sluggishly proceeded in refluxing THF to give unsubstituted imidazole **29ab** (41%), but this reaction was improved to give a much higher yield (84%) under coexisting ethylenediamine[28] in refluxing THF for 20 h. Cyclization (TMAD-Bu_3P) of **29ab** in CH_2Cl_2, followed by ethoxycarbonylation of the resulting **30ab** produced *trans*- and *cis*-isomers **31** and **32** after flash column chromatography. The better result [**31** (43 %) and **32** (25%)] for the cyclization was attained in refluxing CH_2Cl_2 for 2 h in this case. Detritylation of **31** with $Pd(OH)_2$-C in cyclohexene gave the desirable (−)-**5** (57%) and 4-(5-hydroxymethyltetrahydrofuranyl)-imidazole **33** (37%), the latter of which could revert to **5** by *N*-ethoxycarbonylation.[12] In a similar manner, *cis*-isomer (−)-**6** (63%) and **34** (25%) were obtained from **32**.

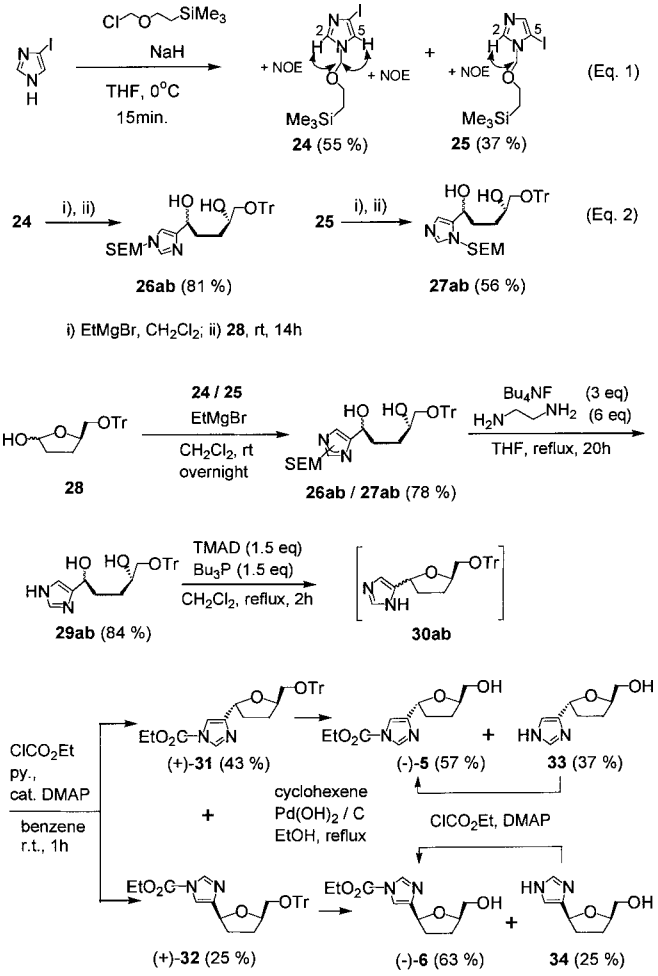


Chart 3

Their configuration counterparts (+)-**5** and (+)-**6** were also synthesized from 2,3-dideoxy-5-*O*-trityl-D-glyceropentanoic acid γ-lactone[27] by the same methodology. The conversion of **5** or **6** into *trans*-**1** or its *cis*-isomer **2** has already been described in our previous report.[12] Accordingly, the present method may become a more efficient stereodivergent synthetic route to the *trans*- and *cis*-amino compounds than the previous method using the PhSe group.

Synthesis of 4(5)-[(2*R*,5*S*)-5-Aminomethyltetrahydrofuran-2-yl]imidazole [(+)-2] We reported an efficient and stereoselective synthesis of ethyl 4(5)-(2-deoxy-β-ribofuranosyl)imidazole-1-carboxylate (**35**) by using the cyclization *via* a diazafulvene intermediate.[14] An advantageous feature of this approach is that it enables the supply of a multigram scale of **35** from D-2-deoxyribose. Thus, we selected **35** for the synthesis of (+)-**2** (Chart 4).

After phthaloylimination of **35**, the deoxygenation of the resulting secondary alcohol **36** was achieved as follows.[28] Reaction of **36** with 1,1′-thiocarbonyldiimidazole in DMF gave crude thiocarbonylimidazolide **37**, which was subsequently treated with Bu_3SnH and AIBN to give an ethoxycar-

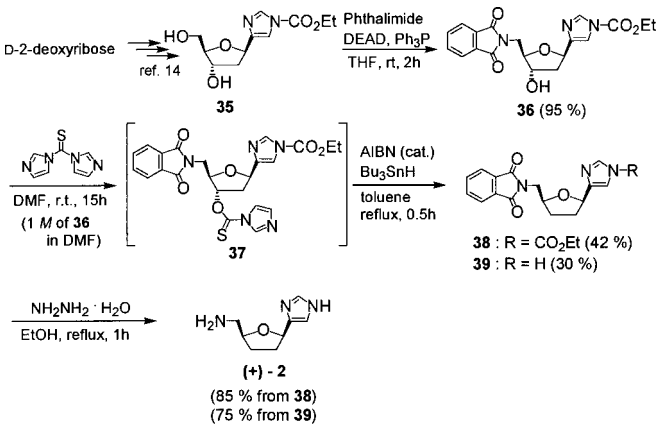


Chart 4

bonyl compound **38** and unsubstituted imidazole **39** in 42% and 30% yields from **36**, respectively. We first encountered a low yield of **37**, but the problem was solved by high concentration (1 M concentration of **36**) of DMF. This result indicates the close contact of 1,1′-thiocarbonyldiimidazole and **36** in high concentration is essential to promote the reaction.[30] Deprotection of **38** and **39** with hydrazine hydrate afforded (+)-**2** in 85% and 75% yields, respectively.

In conclusion, we have described a simple and efficient synthesis of imifuramine (+)-**1** and *N*-ethoxycarbonyl intermediates **5** and **6** *via* diazafulvene intermediates. Further, (+)-*cis*-amino compound **2** was obtained from **35**. The synthetic processes would supply a variety of derivatives by which the H_4-receptor activities of tetrahydrofuranylimidazoles can be assessed.

Experimental

The melting points were determined on a hot-stage apparatus and were 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. Bu_3P (>90%) was purchased from Tokyo Kasei Kogyou Co., Ltd. For column chromatography, BW-127ZH, FL-60D, and Chromatorex NH-DM 1020 (Fuji Silysia Chemical Ltd.) were used. THF was distilled from sodium-benzophenone. HPLC analyses were 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]. TLC were performed on pre-coated TLC plates with $60F_{254}$ (silica gel, Merck).

4(5)-[(1*RS*,4*R*)-5-Benzyloxy-1,4-dihydroxypentyl]imidazole (17ab) A solution of **14ab** (439 mg, 0.88 mmol) in THF (10 ml) was refluxed with 1.5 N HCl (7 ml) for 4 h and then cooled. After neutralization by addition of 28% NH_4OH, the solvent was evaporated to give a residue, which was extracted with EtOAc (×3) by salting-out techniques. The extract was washed with brine, dried, and concentrated to give an oil, which was subjected to chromatography. Elution with MeOH–EtOAc (3 : 7) afforded **17ab** (231 mg, 95%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30—2.12 (4H, m), 3.43 (2H, d, J=7.6 Hz), 3.70—3.85 (1H, m), 4.54 (2H, s), 4.68 (1H, t, J=6.0 Hz), 6.96 (1H, s), 7.21—7.42 (5H, m), 7.62 (1H, s).

***tert*-Butyl 4-[(2*RS*,5*R*)-5-Benzyloxymethyltetrahydrofuran-2-yl]imidazole-1-carboxylate (19ab)** To a solution of **17ab** (1.058 g, 3.83 mmol) and Bu_3P (1.52 ml, 5.75 mmol) in CH_2Cl_2 (195 ml) at 0 °C was added TMAD (989 mg, 5.75 mmol). The resulting mixture was stirred at 0 °C for 15 h. The solvent was evaporated to give a residual oil, which was dissolved with $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed with brine, dried, and concentrated to give a crude oil of **18ab**. The solution of **18ab** in THF (8 ml) was stirred with Boc_2O (1.671 g, 7.67 mmol) and Et_3N (1.06 ml, 7.67 mmol) at room temperature (rt) for 22 h. The solvent was evaporated, and the residue was extracted twice with EtOAc. The extract was washed with H_2O, brine, dried, and concentrated. The residual oil was subjected to flash chromatography using EtOAc–hexane (1 : 4) for elution to give **19ab** [1.232 g (90%), **19a**/**19b**=3 : 1]. Although the separation of **19a** (55%) and **19b** (13%) was not required for the following experiment, **19a** and **19b** were carefully isolated by column chromatography by use of EtOAc–hexane (3 : 7) and characterized spectroscopically. **19a**: Colorless oil, *Rf* (ethyl acetate) 0.6. IR (nujol) cm^{-1}: 1750. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.60 (9H, s), 1.77—1.97 (1H, m), 2.03—2.20 (2H, m), 2.24—2.40 (1H, m), 3.54 (2H, d, J=5.1 Hz), 4.39 (1H, quint, J=5.7 Hz), 4.60 (2H, s), 5.04 (1H, t, J=6.2 Hz), 7.23—7.40 (6H, m), 8.00 (1H, s). HR-MS *m/z*: 358.1878 (Calcd for $C_{20}H_{26}N_2O_4$: 358.1891). EI-MS *m/z*: 358 (M^+). **19b**: Colorless oil; *Rf* (ethyl acetate) 0.55; IR (nujol) cm^{-1}: 1750. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.60 (9H, s), 1.77—1.96 (1H, m), 1.98—2.16 (2H, m), 2.21—2.46 (1H, m), 3.48—3.64 (2H, m), 4.23 (1H, quint, J=5.9 Hz), 4.58 (2H, s), 4.95 (1H, t, J=6.2 Hz), 7.23—7.40 (6H, m), 8.00 (1H, s). HR-MS *m/z*: 358.1878 (Calcd for $C_{20}H_{26}N_2O_4$: 358.1891). EI-MS *m/z*: 358 (M^+).

Ethyl 4-(5-Benzyloxymethyltetrahydrofuran-2-yl)imidazole-1-carboxylate (23ab) By the same procedure as for the preparation of **18ab**, a mixture of **17ab** (130 mg, 0.47 mmol), Bu_3P (0.14 ml, 0.52 mmol), and TMAD (89 mg, 0.52 mmol) in benzene (15 ml) was stirred for 2 h at rt to give crude **18ab**, which was refluxed with ethyl chloroformate (0.05 ml, 0.52 mmol), pyridine (0.04 ml, 0.52 mmol), and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in benzene (20 ml) for 15 min to give a 2 : 1 mixture (87 mg, 56%) of **23a** and **23b** as an oil: ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.3 Hz), 1.75—2.41 (4H, m), 3.54 (4/3H, d, J=5.0 Hz), 3.59 (2/3H, dd, J=5.0, 1.6 Hz), 4.16—4.31 (1/3H, m), 4.32—4.55 (8/3H, m), 4.60 (2H, s), 4.98 (1/3H, t, J=6.4 Hz), 5.06 (2/3H, t, J=6.4 Hz), 7.24—7.40 (6H, m), 8.10 (1H, s).

***tert*-Butyl 4-[(2*RS*,5*R*)-5-Hydroxymethyltetrahydrofuran-2-yl]imidazole-1-carboxylate (20ab)** A solution of **19ab** (680 mg, 1.90 mmol) in MeOH (20 ml) was hydrogenated over 10% Pd–C (408 mg) at 3.0 kg/cm^2 for 12 h. After filtration through Celite, the filtrate was concentrated to give a crude oil, which was purified by column chromatography [MeOH–EtOAc (3 : 97)] to give **20ab** (421 mg, 83%) as a colorless oil. IR (nujol) cm^{-1}: 1750. ^{1}H-NMR (CD_3OD) δ: 1.62 (9H, s), 1.76—1.92 (1H, m), 2.02—2.37 (3H, m), 3.48—3.73 (2H, m), 4.05—4.16 (1/4H, m), 4.22 (3/4H, m), 4.84—5.02 (1H, overlapped with H_2O in CD_3OD), 7.62 (3/4H, s), 7.67 (1/4H, s), 8.17 (1H, s). HR-MS *m/z*: 269.1513 (Calcd for $C_{13}H_{21}N_2O_4$: 269.1500). SI-MS *m/z*: 269 (M^++1).

4(5)-[(2*R*,5*R*)-5-Aminomethyltetrahydrofuran-2-yl]imidazole [(+)-1] Phthalimide (440 mg, 2.99 mmol) and PPh_3 (1.809 g, 6.90 mmol) were dissolved in a solution of **20ab** (618 mg, 2.30 mmol) in THF (13 ml). To this mixture was added DEAD (1.07 ml, 6.90 mmol) with stirring at 0°C. The reaction mixture was stirred at rt for 1 h, and then the whole was concentrated to give a residue, which was subsequently dissolved in EtOAc. The solution was washed with H_2O and brine, dried, and concentrated to give a crude oil, which was subjected to chromatography {*Rf* (80% EtOAc in hexane); 0.68 (**21**), 0.62 (**22**)}. Elution with EtOAc–hexane (19 : 31) afforded a mixture (1.1 g) of **21** and diethyl 1,2-hydrazinedicarboxylate. **21**: ^{1}H-NMR ($CDCl_3$) δ: 1.60 (9H, s), 1.75—1.90 (1H, m), 2.11—2.40 (3H, m), 3.68 (1H, dd, J=13.8, 5.0 Hz), 3.89 (1H, dd, J=13.8, 8.2 Hz), 4.56 (1H, quint, J=6.5 Hz), 5.10 (1H, t, J=6.3 Hz), 7.24 (1H, s), 7.66—7.88 (4H, m), 7.99 (1H, s). **22**: ^{1}H-NMR ($CDCl_3$) δ: 1.60 (9H, s), 1.74—1.94 (1H, m), 2.00—2.20 (3H, m), 3.80 (1H, dd, J=13.3, 4.9 Hz), 3.95 (1H, dd, J=13.3, 7.4 Hz), 4.33—4.49 (1H, m), 4.98 (1H, t, J=6.2 Hz), 7.56 (1H, s), 7.66—7.92 (4H, m), 7.99 (1H, s). A solution of the crude **21** thus obtained and $NH_2NH_2 \cdot H_2O$ (813 mg, 16.25 mmol) 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, the solvent was evaporated to give a residual oil. It was purified by chromatography (Chromatorex NH-DM 1020) with MeOH–EtOAc (1 : 9) to give (+)-**1**[12,21] (170 mg, 64% converted from a 3 : 1 mixture of **20a** and **20b**) as an oil: ORD (c=3.35, EtOH) [α] (nm) +7.8° (589), +11.1° (550), +16.1° (500), +22.2° (450), +38.2° (400), +73.0° (350). ^{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).

4- and 5-Iodo-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-imidazole (24, 25) A suspension of NaH (60% in mineral oil, 134 mg, 3.30 mmol) in hexane was stirred for 5 min. After removal of the supernatant solution, THF (4 ml) was added therein. A solution of 4(5)-iodoimidazole[24,25] (582 mg,

3.00 mmol) in THF (3 ml) was added to the resulting suspension of NaH at 0 °C. The whole was stirred for 0.5 h at rt, and then 2-(trimethylsilyl)-ethoxymethyl chloride (0.60 ml, 3.15 mmol) was added to the mixture at 0 °C. After 15 min at the same temperature, the reaction was quenched with saturated NH_4Cl solution and the THF was concentrated. The residue was extracted twice with CH_2Cl_2, and the solution was subsequently washed with H_2O, brine, dried, and concentrated to give a crude oil. Chromatography using EtOAc and hexane (1 : 3) as eluent gave **24** (535 mg, 55%) and **25** (362 mg, 37%). **24**: Colorless oil, ^{1}H-NMR ($CDCl_3$) δ: 0—0.10 (9H, m), 0.92 (2H, t, J=8.0 Hz), 3.49 (2H, t, J=8.0 Hz), 5.26 (2H, s), 7.15 (1H, s), 7.50 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: −0.9, 18.1, 66.8, 76.0, 124.1, 138.2. HR-MS m/z: 324.0158 (Calcd for $C_9H_{17}IN_2OSi$: 324.0156). EI-MS m/z: 324 (M^+). **25**: Colorless oil, ^{1}H-NMR ($CDCl_3$) δ: 0—0.16 (9H, m), 0.93 (2H, t, J=8.0 Hz), 3.54 (2H, t, J=8.0 Hz), 5.28 (2H, s), 7.15 (1H, s), 7.75 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: −0.9, 18.1, 66.5, 76.0, 137.0, 139.8. HR-MS m/z: 324.0156 (Calcd for $C_9H_{17}IN_2OSi$: 324.0156). EI-MS m/z: 324 (M^+).

1-(2-Trimethylsilyl)ethoxymethyl-4-[(1*RS*,4*R*)-1,4-dihydroxy-5-trityloxypentyl]imidazole (26ab) A solution of **24** (925 mg, 2.86 mmol) in dry CH_2Cl_2 (11 ml) was added to a 3 M Et_2O solution of EtMgBr (0.95 ml, 2.86 mmol) at 0 °C. After 40 min at rt, **28**[27] (411 mg, 1.14 mmol) in dry CH_2Cl_2 (2.5 ml) was added dropwise at 0 °C, and the mixture was stirred at rt for 14 h. Saturated NH_4Cl solution was then added, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue yielded **26ab** (517 mg, 81%) as a colorless oil. ^{1}H-NMR (CD_3OD) δ: −0.03 (9/2H, s), 0.01 (9/2H, s), 0.85 (2H, t, J=9.4 Hz), 1.25—2.08 (4H, m), 2.90—3.14 (2H, m), 3.50 (2H, t, J=9.4 Hz), 3.74 (1H, m), 4.60 (1H, t, J=6.3 Hz), 5.38 (2H, s), 7.09 (1H, s), 7.13—7.50 (15H, m), 7.71 (1H, s). HR-MS m/z: 559.2992 (Calcd for $C_{33}H_{43}N_2O_4Si$: 559.2990). SI-MS m/z: 559 (M^++1).

1-(2-Trimethylsilyl)ethoxymethyl-5-[(1*RS*,4*R*)-1,4-dihydroxy-5-trityloxypentyl]imidazole (27ab) In the same manner as **26ab**, a solution of **28**[27] (443 mg, 1.23 mmol) in CH_2Cl_2 (2 ml) was added to a mixture of **25** (997 mg, 3.01 mmol) and 3 M Et_2O solution of EtMgBr (1.00 ml, 3.00 mmol) to give **27ab** (387 mg, 56%) as a colorless oil. ^{1}H-NMR (CD_3OD) δ: 0.00 (9H, s), 0.86 (2H, t, J=8.0 Hz), 1.37—2.12 (4H, m), 2.95—3.18 (2H, m), 3.44—3.59 (2H, m), 3.70—3.84 (1H, m), 4.77 (1H, t, J=7.2 Hz), 5.28—5.59 (2H, m), 6.92 (1H, s), 7.16—7.53 (15H, m), 7.76 (1H, s). HR-MS m/z: 559.2991 (Calcd for $C_{33}H_{43}N_2O_4Si$: 559.2990). SI-MS m/z: 559 (M^++1).

1-(2-Trimethylsilyl)ethoxymethyl-4(5)-[(1*RS*,4*R*)-1,4-dihydroxy-5-trityloxypentyl]imidazole (26ab/27ab) By the same procedure as for the preparation of **26ab**, a 1 : 1 mixture (2.309 g, 7.13 mmol) of **24** and **25** in dry CH_2Cl_2 (29 ml) was added to a 3 M Et_2O solution of EtMgBr (2.38 ml, 7.13 mmol) at 0 °C. After 0.5 h at rt, **28**[27] (1.026 g, 2.85 mmol) in dry CH_2Cl_2 (6 ml) was added at 0 °C, and the mixture was stirred at rt for 14 h followed by column chromatography to yield a 3.6 : 1 mixture of **26ab** and **27ab** (1.243 g, 78%) as an oil.

4(5)-[(1*RS*,4*R*)-1,4-Dihydroxy-5-trityloxypentyl]imidazole (29ab) To a solution of **26ab**/**27ab** (200 mg, 0.36 mmol) in THF (1.5 ml) 1 M THF solution of tetra-*n*-butylammonium fluoride (1.08 ml, 1.07 mmol) and ethylenediamine (0.14 ml, 2.15 mmol) were added, and the resulting mixture was refluxed for 20 h. A small amount of silica gel was added to the cooled solution. The solvent was evaporated to give a coated silica gel, which was subsequently placed in a column. Chromatography using MeOH–EtOAc (1 : 9) gave **29ab** (129 mg, 84%) as white amorphous product. ^{1}H-NMR (CD_3OD) δ: 1.28—2.04 (4H, m), 2.91—3.15 (2H, m), 3.64—3.80 (1H, m), 4.66 (1H, t, J=6.4 Hz), 6.97 (1H, s), 7.12—7.51 (15H, m), 7.70 (1H, s). HR-MS m/z: 429.2199 (Calcd for $C_{27}H_{28}N_2O_3$: 429.2176). SI-MS m/z: 429 (M^++1).

Ethyl 4-[(2*R*,5*R*)-(5-Trityloxymethyl)tetrahydrofuran-2-yl]imidazole-1-carboxylate (31) and Its 2*S*,5*R*-Isomer (32) To a solution of **29ab** (320 mg, 0.75 mmol) in CH_2Cl_2 (25 ml) were added Bu_3P (0.31 ml, 1.12 ml) and TMAD (193 mg, 1.12 ml). The mixture was refluxed for 2 h and then washed with H_2O, dried ($MgSO_4$), and evaporated to give a crude oil of **30ab**. A solution of the crude **30ab**, ethyl chloroformate (0.14 ml, 1.50 mmol), pyridine (0.12 ml, 1.50 mmol), and DMAP (10 mg) in benzene (2.5 ml) was stirred at rt for 1 h. After addition of H_2O, the solvent was evaporated and the residue was extracted twice with EtOAc–hexane (2 : 1). The extract was washed with H_2O, dried, and concentrated. The residual oil was purified by flash column chromatography using EtOAc–hexane (3 : 7) for elution to give **31** (153 mg, 43%), and then **32** (91 mg, 25%). (+)-**31**: Colorless oil, *Rf* (50% EtOAc in hexane); 0.47. IR (nujol) cm^{-1}: 1755. $[\alpha]_D$=+21.9° (c=3.57, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.1 Hz), 1.82—1.93 (1H, m), 2.04—2.21 (2H, m), 2.23—2.38 (1H, m), 3.11 (1H, dd, J=9.6, 5.1 Hz), 3.19 (1H, dd, J=9.6, 5.1 Hz), 4.38—4.49 (3H, m), 5.04 (1H, t, J=6.3 Hz), 7.16—7.53 (16H, m), 8.09 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.6, 29.0, 32.1, 64.4, 66.4, 75.3, 78.4, 113.1, 126.5, 127.3, 128.3, 136.6, 143.6, 145.0, 148.1. HR-MS m/z: 482.2199 (Calcd for $C_{30}H_{30}N_2O_4$: 482.2204). EI-MS m/z: 482 (M^+). (+)-**32**: Colorless oil, *Rf* (50% EtOAc in hexane) 0.40. $[\alpha]_D$=+18.3° (c=3.60, MeOH). IR (nujol) cm^{-1}: 1755. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.1 Hz), 1.77—1.92 (1H, m), 1.95—2.14 (2H, m), 2.21—2.35 (1H, m), 3.14 (1H, dd, J=9.6, 4.5 Hz), 3.27 (1H, dd, J=9.6, 5.4 Hz), 4.23 (1H, m), 4.33—4.49 (2H, m), 5.00 (1H, t, J=6.1 Hz), 7.17—7.51 (16H, m), 8.06 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.5, 28.5, 31.9, 64.3, 66.5, 76.0, 79.1, 113.0, 126.5, 127.3, 128.3, 136.4, 143.6, 145.5, 148.0. HR-MS m/z: 482.2208 (Calcd for $C_{30}H_{30}N_2O_4$: 482.2204). EI-MS m/z: 482 (M^+). The configuration counterparts (−)-**31** and (−)-**32** were synthesized by the present method from L-glutamic acid. (−)-**31**: $[\alpha]_D$=−20.1° (c=1.80, MeOH), (−)-**32**: $[\alpha]_D$=−17.3° (c=1.92, MeOH).

(−)-Ethyl 4-[(2*R*,5*R*)-5-Hydroxymethyltetrahydrofuran-2-yl]imidazole-1-carboxylate [(−)-5] A mixture of **31** (126 mg, 0.26 mmol), 20% $Pd(OH)_2$–C (76 mg), and cyclohexene (0.79 ml, 7.83 mmol) was refluxed for 2.5 h. After filtration through a Celite pad, the filtrate was concentrated to give a residue. It was purified by column chromatography using MeOH–EtOAc (1 : 19) to give (−)-**5**[12] (36 mg, 57%) as a colorless oil. Further elution with MeOH provided **33** (16 mg, 37%) as an oil, which was subsequently reverted to (−)-**5** (53%) by treatment with ethyl chloroformate and DMAP.[12] (−)-**5**: *Rf* (10% MeOH in EtOAc); 0.42. ^{1}H-NMR (CD_3OD) δ: 1.41 (3H, t, J=6.9 Hz), 1.77—1.89 (1H, m), 1.97—2.16 (2H, m), 2.22—2.36 (1H, m), 3.53 (1H, dd, J=11.0, 5.1 Hz), 3.60 (1H, dd, J=11.0, 4.2 Hz), 4.22 (1H, quint, J=5.5 Hz), 4.47 (2H, q, J=6.9 Hz), 4.98 (1H, t, J=6.5 Hz), 7.46 (1H, s), 8.22 (1H, s). **33**: ^{1}H-NMR (CD_3OD) δ: 1.76—1.92 (1H, m), 1.96—2.19 (2H, m), 2.24—2.42 (1H, m), 3.54 (1H, dd, J=11.8, 5.4 Hz), 3.62 (1H, dd, J=11.8, 3.7 Hz), 4.17—4.27 (1H, m), 5.09 (1H, t, J=6.9 Hz), 7.30 (1H, s), 8.38 (1H, s). The configuration counterpart (+)-**5** was synthesized by the present method from L-glutamic acid. (+)-**5**: $[\alpha]_D$=+3.20° (c=1.97, $CHCl_3$).[31] HPLC (flow rate 2 ml/min; t_R 15.6 min) exhibited a single peak.

(−)-Ethyl 4-[(2*S*,5*R*)-5-Hydroxymethyltetrahydrofuran-2-yl]imidazole-1-carboxylate [(−)-6] The mixture of **32** (70 mg, 0.15 mmol), cyclohexene (0.44 ml, 4.35 mmol), and 20% $Pd(OH)_2$–C (42 mg) in EtOH (4 ml) was refluxed to give (−)-**6**[12] (22 mg, 63%) and **34** (6 mg, 25%) as colorless oils by the same procedure for the preparation for **5**. (−)-**6**: *Rf* (10% MeOH in EtOAc); 0.33. ^{1}H-NMR (CD_3OD) δ: 1.41 (3H, t, J=7.1 Hz), 1.77—2.11 (3H, m), 2.14—2.35 (1H, m), 3.55 (1H, dd, J=11.9, 5.3 Hz), 3.67 (1H, dd, J=11.9, 3.9 Hz), 4.10 (1H, quint, J=5.7 Hz), 4.48 (2H, q, J=7.1 Hz), 4.84—4.94 (1H, m, overlapped with H_2O in CD_3OD), 7.52 (1H, s), 8.23 (1H, s). **34**: ^{1}H-NMR (CD_3OD) δ: 1.80—2.14 (3H, m), 2.20—2.36 (1H, m), 3.57 (1H, dd, J=11.7, 5.0 Hz), 3.70 (1H, dd, J=11.7, 3.6 Hz), 4.06—4.18 (1H, m), 5.00 (1H, t, J=6.6 Hz), 7.23 (1H, s), 8.20 (1H, s).

The configuration counterparts were synthesized by the present method from L-glutamic acid. (+)-**6**: $[\alpha]_D$=+9.78° (c=1.64, $CHCl_3$).[31] HPLC (flow rate 2 ml/min; t_R 10.4 min) exhibited a single peak.

Ethyl 4-(2,5-Dideoxy-5-phthaloylamino-β-ribofuranosyl)imidazole-1-carboxylate (36) Phthalimide (828 mg, 5.63 mmol) and PPh_3 (1.48 g, 5.63 mmol) were dissolved in a solution of **35** (1.31 g, 5.12 mmol) in THF (70 ml). To this mixture was added DEAD (0.96 ml, 5.63 mmol) with stirring. The reaction mixture was stirred at rt for 2 h, and then the THF was evaporated to give a residue. It was purified by flash chromatography with EtOAc–hexane (11 : 9) to give **36** (1.795 g, 95%) as a white amorphous product. IR (KBr) cm^{-1}: 3400, 1762, 1712. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.0 Hz), 2.30 (2H, dd, J=7.0, 4.5 Hz), 3.00 (1H, br s), 3.88 (2H, m), 4.18 (1H, m), 4.45 (3H, m), 5.16 (1H, t, J=7.0 Hz), 7.38 (1H, s), 7.64—7.75 (2H, m), 7.78—7.89 (2H, m), 8.00 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.7, 40.6, 40.8, 64.9, 74.6, 74.9, 84.2, 114.4, 123.8, 132.5, 134.5, 137.5, 144.8, 149.0, 169.0. HR-MS m/z: 386.1352 (Calcd for $C_{19}H_{20}N_3O_6$: 386.1351). SI-MS m/z: 386 (M^++1).

Deoxygenation of 36 A mixture of **36** (237 mg, 0.615 mmol) and thiocarbonyldiimidazole (135 mg, 0.737 mmol) in DMF (0.6 ml) was stirred at rt for 13 h. The resulting mixture was dissolved with EtOAc, and the solution was washed with H_2O and brine, dried, and concentrated to give a crude **37**. To a toluene solution (15 ml) of the crude **37** were added a mixture of Bu_3SnH (0.20 ml, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) in toluene (0.5 ml), and then the whole was refluxed for 0.5 h. Evaporation of the solvent afforded a residual oil, which was subsequently dissolved with CH_3CN. The solution was washed with hexane and evaporated to give a residue. Flash chromatography using EtOAc–hexane (1 : 1) as eluent gave ethyl 4-[(2*R*,5*S*)-5-phthaloylaminotetrahydrofuran-2-yl]imidazole-1-carboxylate **38**[12] (96 mg, 42%) as a white solid. Further elution with EtOAc–MeOH

(97 : 3) provided 4(5)-[(2*R*,5*S*)-5-phthaloylaminotetrahydrofuran-2-yl]imidazole **39**[12] (56 mg, 30%) as an amorphous product. **38**: IR (KBr) cm^{-1}: 1760, 1722. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.3 Hz), 1.73—1.94 (1H, m), 2.00—2.22 (2H, m), 2.22—2.40 (1H, m), 3.81 (1H, dd, J=14.1, 5.6 Hz), 3.94 (1H, dd, J=14.1, 5.6 Hz), 4.38 (1H, td, J=7.0, 5.6 Hz), 4.47 (2H, q, J=7.3 Hz), 4.97 (1H, dd, J=4.7, 3.7 Hz), 7.54 (1H, s), 7.70—7.73 (2H, m), 7.84—7.88 (2H, m), 8.03 (1H, s). HR-MS *m/z*: 369.1320 (Calcd for $C_{19}H_{19}N_3O_5$: 369.1323). EI-MS *m/z*: 369 (M^+). **39**: ^{1}H-NMR ($CDCl_3$) δ: 1.74—1.84 (1H, m), 2.01—2.18 (3H, m), 3.75—3.83 (2H, m), 4.37—4.44 (1H, m), 5.11 (1H, dd, J=5.1, 3.6 Hz), 6.94 (1H, s), 7.11 (1H, s), 7.69—7.79 (2H, m), 7.81—7.93 (2H, m). Although the separation of **37** was not required for the following experiment, it could be isolated as a white solid by use of MeOH–$CHCl_3$ (1 : 100) as eluent: mp 176—178 °C. IR (KBr) cm^{-1}: 1760, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.5 Hz), 2.65 (2H, m), 3.99 (2H, d, J=7.5 Hz), 4.49 (2H, q, J=7.5 Hz), 4.60 (1H, t, J=7.5 Hz), 5.26 (1H, dd, J=9.8, 6.9 Hz), 6.00 (1H, d, J=3.9 Hz), 7.02 (1H, s), 7.46 (1H, s), 7.55 (1H, s), 7.75 (2H, m), 7.87 (2H, m), 8.09 (1H, s), 8.28 (1H, s). HR-MS *m/z*: 496.1287 (Calcd for $C_{23}H_{22}N_5O_6S$: 496.1289). SI-MS *m/z*: 496 (M^++1).

(+)-4(5)-[(2*R*,5*S*)-5-Aminomethyltetrahydrofuranyl]imidazole [(+)-2] By the same procedure for the preparation of (+)-**1**, a solution of **38** (382 mg, 1.04 mmol) and hydrazine hydrate (0.25 ml, 5.18 mmol) in EtOH (20 ml) was refluxed for 1 h to yield (+)-**2** (147 mg, 85%) as an oil. Similarly, **41** (149 mg, 0.50 mmol) was converted into (+)-**2** (63 mg, 75%) as an oil. $[\alpha]_D$=+27.0° (c=3.40, MeOH). IR (film) cm^{-1}: 3700—2200, 1038. ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.92 (1H, m), 1.96—2.33 (3H, m), 2.72 (1H, dd, J=12.2, 7.0 Hz), 2.80 (1H, dd, J=12.2, 5.2 Hz), 4.03 (1H, ddd, J=12.2, 7.0, 5.2 Hz), 4.94 (overlapped with H_2O in CD_3OD), 7.03 (1H, s), 7.65 (1H, s). HR-MS *m/z*: 168.1134 (Calcd for $C_8H_{14}N_3O$: 168.1136). SI-MS *m/z*: 168 (M^++1).

Acknowledgement This work was partially supported by a grant (No. 11672127) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and Notes

1) Lin C., Ma X. J., Jiang X., Wilson S. J., Hofstra C. L., Blevitt J., Pyati J., Li X., Chai W., Carruthers N., Lovenberg T. W., *Mol. Pharmacol.*, **59**, 420—426 (2001).
2) Nakamura T., Itadani H., Hidaka Y., Ohta M., Tanaka K., *Biochem. Biophys. Res. Commun.*, **279**, 615—620 (2000).
3) Morse K. L., Behan J., Laz T. M., West R. E., Greenfeder S. A., Anthes J. C., Umland S., Wan Y., Hipkin R. W., Gonsiorek W., Shin N., Gustafson E. L., Qiao X., Wang S., Hedrick J. A., Greene J., Bayne M., Monsma F. J., *J. Pharmacol. Exp. Ther.*, **296**, 1058—1066 (2001).
4) Zhu Y., Michalovich D., Wu H. L., Tan K. B., Dytko G. M., Mannan I. J., Boyce R., Alston J., Tierney L. A., Li X., Herrity N. C., Vawter L., Sarau H. M., Ames R. S., Davenport C. M., Hieble J. P., Wilson S., Bergsma D. J., Fitzgerald L. R., *Mol. Pharmacol.*, **59**, 434—441 (2001).
5) Nguyen T., Shapiro D. A., George S. R., Setola V., Lee D. K., Cheng R., Rauser L., Lee S. P., Lynch K. R., Roth B. L., O'Dowd B. F., *Mol. Pharmacol.*, **59**, 427—433 (2001).
6) Oda T., Morikawa N., Saito Y., Masuho Y., Matsumoto S., *J. Biol. Chem.*, **275**, 36781—36786 (2000).
7) Coge F., Guenin S. P., Rique H., Boutin J. A., Galizzi J. P., *Biochem. Biophys. Res. Commun.*, **284**, 301—309 (2001).
8) For a review, see: Hough L. B., *Mol. Pharmacol.*, **59**, 415—419 (2001).
9) Hashimoto T., Harusawa S., Araki L., Zuiderveld O. P., Smit M. J., Imazu T., Takashima S., Yamamoto Y., Sakamoto Y., Kurihara T., Leurs R., Bakker R. A., Yamatodani A., *J. Med. Chem.*, in press (JM0300025).
10) We recently reported imifuramine as a new type of H_3-agonist, whose activity measured by *in vivo* rat brain microdialysis was approximately equal to that of the current H_3-agonist, immepip: Harusawa S., Imazu T., Takashima S., Araki L., Ohishi H., Kurihara T., Yamamoto Y., Yamatodani A., *Tetrahedron Lett.*, **40**, 2561—2564 (1999).
11) Harusawa S., Imazu T., Takashima S., Araki L., Ohishi H., Kurihara T., Sakamoto Y., Yamamoto Y., Hashimoto T., Yamatodani A., "Histamine Reseach in the New Millennium," ed. by Watanabe T., Timmerman H., Yanai K., Elsevier, Amsterdam, 2001, pp. 83—88.
12) Harusawa S., Imazu T., Takashima S., Araki L., Ohishi H., Kurihara T., Sakamoto Y., Yamamoto Y., Yamatodani A., *J. Org. Chem.*, **64**, 8608—8615 (1999).
13) Harusawa S., Murai Y., Moriyama H., Ohishi H., Yoneda R., Kurihara T., *Tetrahedron Lett.*, **36**, 3165—3168 (1995).
14) Harusawa S., Murai Y., Moriyama H., Imazu T., Ohishi H., Yoneda R., Kurihara T., *J. Org. Chem.*, **61**, 4405—4411 (1996).
15) Guianvarc'h D., Benhida, R., Fourrey J.-L., *Tetrahedron Lett.*, **42**, 647—650 (2001).
16) Guianvarc'h D., Fourrey J.-L., Dau M.-E. T. H., Guerineau V., Benhida R., *J. Org. Chem.*, **67**, 3724—3732 (2002).
17) Harusawa S., Araki L., Imazu T., Ohishi H., Sakamoto Y., Kurihara T., *Chem. Pharm. Bull.*, **51**, 325—329 (2003).
18) Taniguchi M., Koga K., Yamada S., *Tetrahedron*, **30**, 3547—3552 (1974).
19) Tsunoda T., Otsuka J., Yamamiya Y., Ito S., *Chem. Lett.*, **1994**, 539—542 (1994).
20) Araki L., Harusawa S., Suzuki H., Kurihara T., *Heterocycles*, **53**, 1957—1973 (2000).
21) This approach supplied 234 mg (37%) of imifuramine [(+)-**1**] from 1058 mg of **17ab**.
22) Stark H., Purand K., Huls A., Ligneau X., Garbarg M., Schwartz J.-C., Schunack W., *J. Med. Chem.*, **39**, 1220—1226 (1996).
23) Stark H., Schlicker E., Schunack W., *Drug Future*, **21**, 507 (1996).
24) Iddon B., Lim B. L., *J. Chem. Soc.*, *Perkin Trans. I*, **1983**, 735—739 (1983).
25) Bensusan H. B., Naidu M. S. R., *Biochemistry*, **6**, 12—15 (1967).
26) Turner R. M., Lindell S. D., *J. Org. Chem.*, **56**, 5739—5740 (1991).
27) Xiang Y., Du J., Chu C. K., *Nucleosides Nucleotides*, **15**, 1821—1834 (1996).
28) Muchowski J. M., Solas D. R., *J. Org. Chem.*, **49**, 203—205 (1984).
29) Barton D. H., McCombie S. W., *J. Chem. Soc.*, *Perkin Trans. I*, **1975**, 1574—1585 (1975).
30) Hagiwara H., Ohtsubo S., Kato M., *Tetrahedron*, **53**, 2415—2420 (1997).
31) The optical rotation measurements were recorded in $CHCl_3$, since **5** and **6** were unstable in CH_3OH.