A Novel Pyrrolidine Analog of Histamine as a Potent, Highly Selective Histamine H_3 Receptor Agonist†

Neng-Yang Shih,*,‡ Andrew T. Lupo, Jr.,‡ Robert Aslanian,‡ Steven Orlando,‡ John J. Piwinski,‡ Michael J. Green,‡ Ashit K. Ganguly,‡ Michael A. Clark,§ Salvatore Tozzi,§ William Kreutner,§ and John A. Hey§

Departments of Chemical Research and Allergy, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

Received November 14, 1994®

Employing classical conformational analysis on a known H_3 agonist, (*R*)-α-methylhistamine (**1**), a series of conformationally constrained H_3 agonists were proposed and synthesized. Pyrrolidine (±)-**4a**, a compound proposed to mimic the *anti*-conformation of (*R*)-α-methylhistamine (**1**), was found to be a potent and selective H_3 agonist. The pyrrolidine (±)-**4a** was resolved, and its (+) enantiomer, immepyr [(+)-**4a**], showed a greater separation of H_3 and H_1 activities *in vivo* (H_3/H_1 ratio ≫ 550) than (*R*)-α-methylhistamine (**1**) (H_3/H_1 ratio = 17), the standard H_3 agonist. In fact, no evidence of H_1 activity was detected at doses of immepyr [(+)-**4a**] as high as 100 mg/kg iv. This pyrrolidine, immepyr [(2*R*,3*S*)-(+)-**4a**], represents, to our knowledge, the first reported cyclic, conformationally restricted analog of histamine to possess selective *in vivo* H_3 agonist activity.

Introduction

The discovery by Arrang *et al.*[1] of a unique histamine (H_3) receptor has rekindled interest in exploring the physiological role of histamine and the potential for a new class of therapeutic agent that acts at this receptor. The H_3 receptor is a prejunctional receptor that modulates the synthesis and release of histamine[2] and various other neurotransmitters (such as serotonin,[3] noradrenaline,[4] and acetylcholine[5]) in both the central nervous system (CNS) and peripheral nervous system. The potential therapeutic value of H_3 ligands, regarding treatment of diseases in the CNS as well as in the respiratory and gastrointestinal tracts, is currently under investigation.[6] As a result of our efforts directed toward the discovery of therapeutically useful H_3 receptor agonists devoid of undesired H_1 activity, a novel pyrrolidine analog of histamine, which shows greater separation of H_3 and H_1 activities *in vivo* (H_3/H_1 ≫ 550) than the standard agonist (*R*)-α-methylhistamine (**1**)[1] (H_3/H_1 = 17), has been identified. In fact, (*R*)-α-methylhistamine (**1**) has been found to elicit adverse bronchoconstrictor events by direct activation of H_1 receptors *in vivo*[7] (ED_{50} = 1.7 mg/kg). In this paper we describe our chemical efforts directed toward the identification of this novel analog of histamine, pyrrolidine (+)-**4a** (immepyr); a compound which, to our knowledge, represents the first reported cyclic analog of histamine to possess such an *in vivo* activity profile.

Chemistry

Complete synthetic procedures and analytical data for the compounds presented in this article are contained within the Experimental Section. The compounds shown in Chart 1 were synthesized as racemates by the protocols outlined in Schemes 1–4. For convenience, only one of the corresponding enantiomers is indicated in the schemes and the chart. A brief outline of the synthetic protocols used to prepare these compounds is presented below.

The aminocyclopentane **3** was prepared via a route whose key step was a Michael addition of the Grignard reagent derived from 1-trityl-4-iodoimidazole[8] (**6**) to the 1-nitrocyclopentene (Scheme 1). Treatment of the resulting nitrocyclopentane **7** with aluminum amalgam followed by aqueous acid hydrolysis of the imidazole protecting group provided the desired target compound (±)-**3**.

The α,β-dimethyl-substituted histamines **2a** and **2b** were prepared via a route different from that which had previously been published[9] and which proceeded from the triphenylmethyl-protected imidazole-4-carboxaldehyde[10] (**9**) (Scheme 2). Henry reaction of aldehyde **9** with nitroethane followed by treatment with (2-(trimethylsilyl)ethoxy)methyl chloride in dimethylformamide provided the nitro olefin **11**. Treatment with methyllithium in the presence of boron trifluoride etherate and subsequent reduction with aluminum amalgam gave a diastereomeric mixture (2.5:1) of the imidazole-protected dimethylhistamine analogs **13a** and **13b**. Separation of the two diastereomers was accomplished by flash column chromatography of the *tert*-butyloxycarbonyl derivatives of **13a** and **13b**. Subsequent aqueous acid hydrolysis of the protecting groups provided the desired target compounds (±)-**2a** and (±)-**2b**.

The 2-substituted pyrrolidines (±)-**4a**, (+)-**4a**, and (−)-**4a** were all prepared from the intermediate lactam (±)-**19t**, obtained via a modification of a published procedure.[11] Michael addition of nitroethane to a suitably protected derivative of urocanic acid (**15**) provided the nitro esters **18** (Scheme 3). Reduction of the nitro group and subsequent cyclization to the lactams **19** was accomplished by hydrogenation over Raney nickel. Separation of the diastereomeric mixture of lactams **19** by flash chromatography provided the desired *trans*-lactam (±)-**19t**. Subsequent hydride reduction and acid hydrolysis provided the desired pyrrolidine (±)-**4a**. Resolution of the racemic mixture (±)-**4a** to provide

† Presented in part: New Perspectives in Histamine Research, Satellite Symposium of the XII[th] International Congress of Pharmacology of IUPHAR, Canada, July 20–24, 1994.

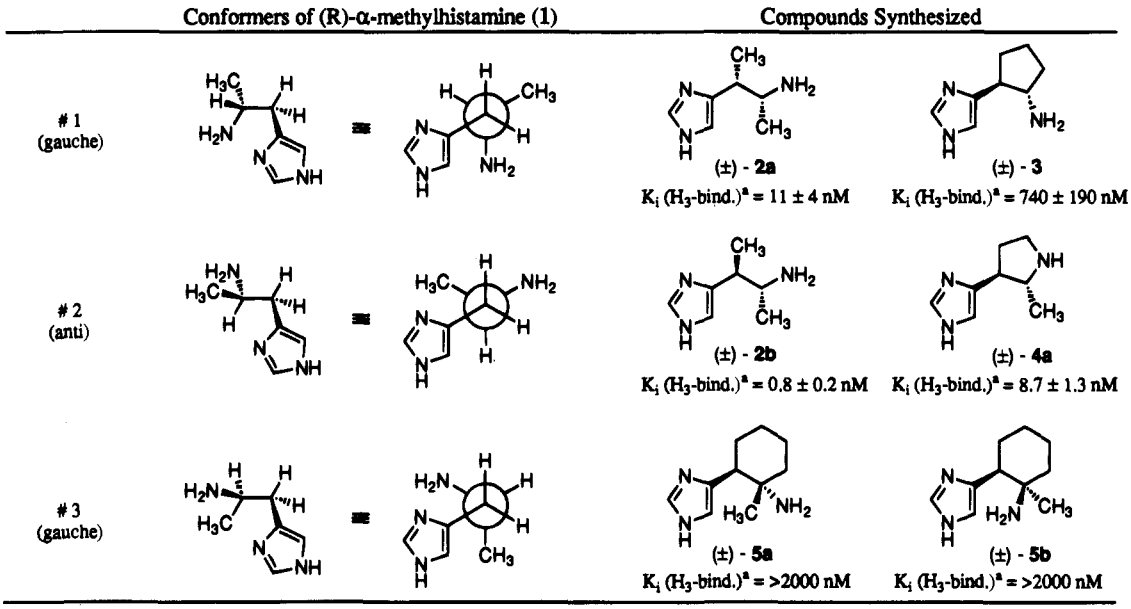
‡ Department of Chemical Research.

§ Department of Allergy.

® Abstract published in *Advance ACS Abstracts*, May 1, 1995.

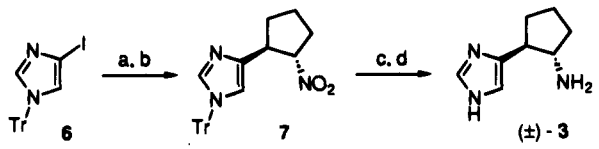
0022-2623/95/1838-1593$09.00/0

Chart 1



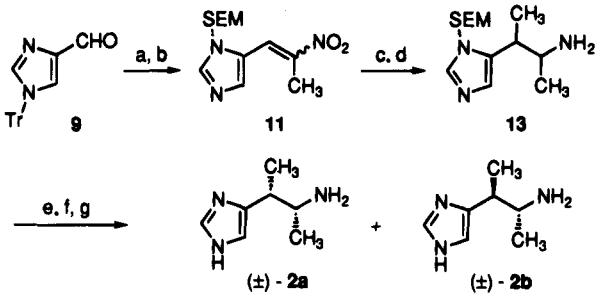
[a] Unless otherwise noted, the K_i value for H_3 receptor binding of each compound represents the mean of two independent experiments with the associated errors representing the range from the mean.

Scheme 1[a]



[a] (a) EtMgBr, CH_2Cl_2; (b) 1-nitrocyclopentene; (c) Al(Hg), THF, H_2O; (d) HCl, H_2O, MeOH.

Scheme 2[a]

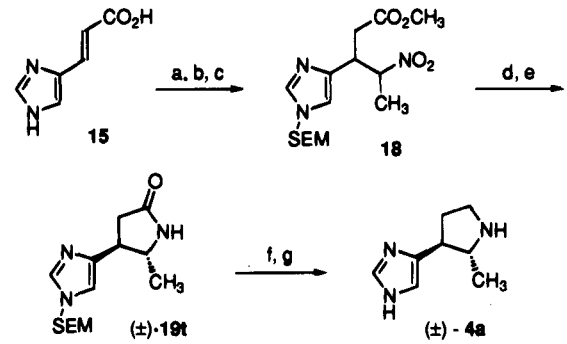


[a] (a) $CH_3CH_2NO_2$, *n*-$BuNH_2$, EtOH; (b) SEMCl, DMF, Δ; (c) CH_3Li, Et_2O, BF_3·Et_2O; (d) Al(Hg); (e) (*t*-BOC)$_2O$, NEt_3, CH_2Cl_2; (f) separate diastereomers; (g) H_2O, HCl, MeOH, Δ.

enantiomerically pure (>99% ee) (+)-**4a** (immepyr) and (−)-**4a** was accomplished via chiral stationary phase HPLC of the corresponding bis(*tert*-butyloxycarbonyl) derivatives of the pyrrolidines (+)-**4a** (immepyr) and (−)-**4a**.

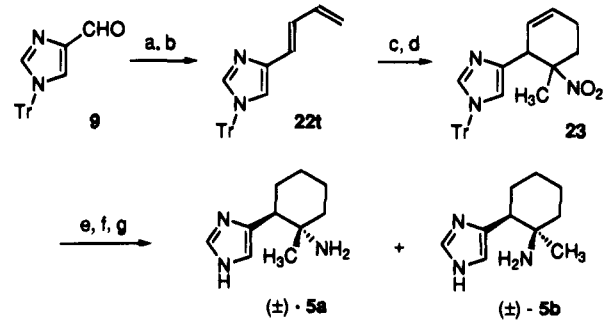
The aminocyclohexanes **5a** and **5b** were prepared from the triphenylmethyl-protected imidazole-4-carboxaldehyde[10] (**9**). Wittig reaction followed by light-induced double-bond isomerization provided the desired *trans* olefin **22t** (Scheme 4). Diels–Alder reaction with 2-nitropropene[12] followed by separation of the resulting diastereomers provided the nitrocyclohexenes **23a** and **23b**. Hydrogenation of **23a** in the presence of palladium on carbon followed by treatment with aluminum amalgam reduced both the double bond and the nitro moieties. Subsequent aqueous acid hydrolysis of the imidazole protecting group provided the desired target compound **5a**. Similar treatment of **23b** provided the diastereomeric **5b**.

Scheme 3[a]



[a] (a) MeOH, H_2SO_4; (b) SEMCl, NEt_3, CH_2Cl_2; (c) $CH_3CH_2NO_2$, DBU, CH_3CN; (d) H_2, RaNi, EtOH, Δ; (e) separate diastereomers; (f) $LiAlH_4$, Et_2O; (g) H_2O, HCl, EtOH, Δ.

Scheme 4[a]

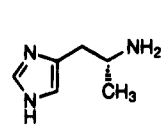


[a] (a) $(C_6H_5)_3P{=}CHCH{=}CH_2$ (b) $C_6H_5SSC_6H_5$, benzene, Δ; (c) 2-nitropropene, benzene, Δ; (d) separate diastereomers; (e) H_2, RaNi, EtOH; (f) Al(Hg); (g) H_2O, HCl, MeOH.

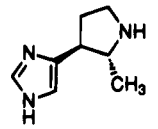
Results and Discussion

Conformational Analysis of (*R*)-α-Methylhistamine (1). Early work[2] in the area of H_3 receptor agonists identified (*R*)-α-methylhistamine (**1**) as a potent and selective H_3 agonist *in vitro* (H_3/H_1 ratio

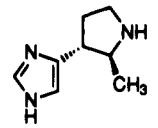
Table 1



(R)-α-methylhistamine (1)



immepyr [(+)-4a]



(-)-4a

compound	H_3 binding (K_i, nM)		guinea pig ileum (pD_2)		*in vivo* (ED_{50}, mg/kg)[c]		H_3/H_1 ratio (*in vivo*)
	H_3	H_1	H_3	H_1	H_3[d]	H_1[e]	[$ED_{50}(H_1)/ED_{50}(H_3)$]
(*R*)-α-methylhistamine (1)	1.5 ± 0.5	>10 000	8.2 ± 0.2	5.4 ± 0.1	0.10 ± 0.03	1.7 ± 0.1	17
immepyr [(+)-**4a**]	2.8 ± 1.5	>10 000	7.1 ± 0.2	NA[b]	0.18 ± 0.05	>100[f]	≫550
(−)-**4a**	33.0 ± 1.0	>10 000	NA[a]	–	30%	–	–

[a] Inactive at 1 μM. [b] Inactive at 10 μM. [c] Via intravenous administration. [d] Determined in the CNS hypertension model (see ref 20) [reported as ED_{50} (mg/Kg) or % (*R*)-α-methylhistamine (1) activity at 0.3 mg/kg]. [e] Determined by an H_1 histamine-mediated bronchospasm (see ref 7) [reported as ED_{50} (mg/kg)]. [f] No evidence of any H_1 activity was detected at doses as high as 100 mg/kg.

~10 000). Although (*R*)-α-methylhistamine (**1**) showed good selectivity *in vitro*, our own work showed substantial *in vivo* H_1 activity (H_3/H_1 ratio = 17, see Table 1). While introduction of an α-methyl group into the histamine side chain imparted the observed selectivity, it was unclear whether this was a manifestation of a steric or a conformational effect. With regard to conformational considerations, our own calculations[13] show only minor energetic differences (<1.5 kcal/mol) between the rotameric conformations of (*R*)-α-methylhistamine (**1**). In an effort to more clearly define the bioactive conformation, to explore the steric requirements of H_3 receptor agonists, and to ultimately identify novel, orally active H_3 agonists devoid of H_1 activity, we chose initially to conformationally restrict the relative spatial orientation of the basic side chain nitrogen and the imidazole moiety.

Neglecting imidazole group rotational freedom, we chose to mimic three predominant conformations of (*R*)-α-methylhistamine (**1**) (determined by classical conformational analysis[14] and confirmed by MM2 calculations[13]) with the conformationally restricted analogs of histamine illustrated in Chart 1. Two of the conformations (1 and 3) possess a gauche relationship between the basic side chain nitrogen and the imidazoyl moiety, and one (2) possesses an anti relationship between these two moieties. For each conformation of (*R*)-α-methylhistamine (**1**) that we chose to mimic, two specifically designed compounds were prepared and examined in our H_3 binding assay;[15] **2a** and **3** mimicked the gauche conformer 1, **2b** and **4a** mimicked the anti conformer 2, and **5a** and **5b** mimicked the gauche conformer 3. Of these three conformers, the only one for which both associated analogs showed substantial H_3 activity was the anti conformer 2 (histamine analogs **2b** [$K_i(H_3$-bind.) = 0.8 nM] and **4a** [$K_i(H_3$-bind.) = 8.7 nM]). A direct result of this conformational analysis approach was the identification of the previously unknown, potent H_3 receptor ligand **4a**.[16]

In light of the known enantioselectivity of the H_3 receptor [(*R*)-α-methylhistamine (**1**) is ~100-fold more potent than the corresponding *S*-enantiomer in H_3 binding studies[17]], we resolved (±)-**4a** and determined the absolute stereochemistry of the constituent enantiomers by single-crystal X-ray analysis.[18] Further binding studies indicated that the dextrorotatory enantiomer (2*R*,3*S*)-(+)-**4a** [$K_i(H_3$-bind.) = 2.8 ± 1.5 nM] was more than 10-fold more active in the H_3 binding assay than the levorotatory (3*S*,2*R*)-(−)-**4a** [$K_i(H_3$-bind.) = 33 ± 5 nM]. Further biological evaluation[19,20] of (+)-**4a** (immepyr), in comparison with (*R*)-α-methylhistamine (**1**), is summarized in the table. *In vitro*, immepyr [(+)-**4a**] was effective at inhibition of an electrically induced contraction in guinea pig ileum tissue. Similarly, it was as effective as (*R*)-α-methylhistamine (**1**) *in vivo* (via intravenous administration) in the inhibition of an electrically induced CNS hypertensive response. Most significantly, immepyr [(+)-**4a**] also exhibited a substantially enhanced *in vivo* selectivity for the H_3 receptor compared to the biological profile of (*R*)-α-methylhistamine (**1**) (H_3/H_1 ratio ≫550 for immepyr [(+)-**4a**]).

Summary

In conclusion, employment of classical conformational analysis on a known H_3 agonist, (*R*)-α-methylhistamine (**1**), led to the proposal and synthesis of a series of conformationally constrained H_3 agonists. Pyrrolidine (±)-**4a**, a compound proposed to mimic the *anti* conformation of (*R*)-α-methylhistamine (1), was found to be a potent and selective H_3 agonist. The pyrrolidine (±)-**4a** was resolved and its (+) enantiomer, immepyr [(+)-**4a**] showed a greater separation of H_3 and H_1 activities *in vivo* (H_3/H_1 ratio ≫ 550) than (*R*)-α-methylhistamine (**1**) (H_3/H_1 ratio = 17). In fact, no evidence of H_1 activity was detected at doses of immepyr [(+)-**4a**] as high as 100 mg/kg iv. This pyrrolidine, immepyr [(2*R*,3*S*)-(+)-**4a**], represents, to our knowledge, the first reported cyclic, conformationally restricted analog of histamine to possess selective *in vivo* H_3 agonist activity.

Experimental Section

General Experimental. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents were either obtained from Aldrich Chemical Co. in Sure/Seal bottles or distilled immediately prior to use (tetrahydrofuran). Unless otherwise noted, all ^1H NMR spectra were recorded at 300 MHz on a Varian Gemini-300 spectrometer. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectral analysis was performed on either a Hewlett-Packard 5989-A mass spectrometer (for CI and EI) or a VG-ZAB-SE double focusing mass spectrometer (for FAB). Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 μm). All flash chromatography was conducted using ICN SiliTech flash grade silica gel (particle size 32−63 μm). Chiral stationary phase HPLC was performed using a Waters DeltaPrep 3000 HPLC system using Daicel analytical (3.6 × 30 mm) columns; the packing material and solvent conditions are indicated in the experimental procedures below. Unless otherwise noted, all compounds were synthesized as racemates. Due to the extreme hygroscopicity of the hydrochloride salts reported in this article,

melting points of these compounds could not determined with any degree of certainty.

1α-Nitro-2β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclopentane (7). To a solution of 4-iodo-1-(triphenylmethyl)-imidazole (**6**) (2.18 g, 5 mmol) in dry CH_2Cl_2 (20 mL) at room temperature was added ethylmagnesium bromide (1.83 mL of a 3 M solution in ether, 5.5 mmol) dropwise, and the pale yellow mixture was stirred for 30 min. After cooling to 0 °C, a solution of 1-nitro-1-cyclopentene (0.62 g, 5.5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. The reaction was quenched after 2.5 h by the addition of half-saturated aqueous NH_4Cl (30 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (60:40 hexane/ethyl acetate) to give **7** as a white foam (1.03 g, 49%): ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 1H), 7.31–7.42 (m, 9H), 7.03–7.20 (m, 6H), 6.67 (s, 1H), 5.10 (q, 1H, J = 7.1 Hz), 3.65 (br q, 1H, J = 8.0 Hz), 2.36 (br q, 2H, J = 7.0 Hz), 2.13–2.31 (m, 1H), 1.88–2.07 (m, 3H).

1α-Amino-2β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)-cyclopentane (8). To a suspension of aluminum amalgam (from 0.96 g of aluminum) in a THF/H_2O mixture (10:1) at 0 °C was added a solution of the nitro compound **7** (1.03 g, 2.43 mmol) in THF (20 mL) over the course of 30 min. After stirring overnight at room temperature, the reaction mixture was filtered through Celite, and the Celite was washed with a 1:1 mixture of CH_2Cl_2 and CH_3OH (100 mL). The solvents were removed *in vacuo*, and the residue was purified by flash chromatography (95:5 CH_2Cl_2:CH_3OH/NH_3) to give the amine **8** (0.44 g, 46%): ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H), 7.31–7.39 (m, 9H), 7.04–7.22 (m, 6H), 6.61 (s, 1H), 3.35 (q, 1H, J = 8.7 Hz), 2.60 (br q, 1H, J = 8.8 Hz), 1.96–2.23 (m, 5H), 1.65–1.89 (m, 3H), 1.38–1.55 (m, 1H).

1α-Amino-2β-(1*H*-imidazol-4-yl)cyclopentane, Dihydrochloride (3). To a solution of the amine **8** (0.44 g, 1.13 mmol) in a small amount of methanol was added 1 N HCl (25 mL). The reaction mixture was heated to 60 °C for 1 h and cooled to room temperature, and the white solid that formed during the reaction was removed by filtration. The aqueous layer was washed once with ether and concentrated *in vacuo* to give the amine **3** as the dihydrochloride salt (0.20 g, 79%): ^{1}H NMR (DMSO) δ 9.14 (s, 1H), 8.63 (br s, 1H, exchanges with D_2O), 7.60 (s, 1H), 3.63–3.79 (br m, 1H), 3.39 (q, 1H, J = 7.5 Hz), 2.03–2.27 (m, 2H), 1.64–1.93 (m, 4H); ^{13}C (DMSO) δ 133.682, 133.015, 115.775, 55.199, 39.589, 31.467, 30.088, 22.366; FAB MS m/z (relative intensity) 152 (M + 1, 100), 135 (28), 130 (15). Anal. ($C_8H_{13}N_3$·2HCl·0.50H_2O) C, H, N.

1-Methyl-2-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)nitroethene (10). A mixture of 1-(triphenylmethyl)-1*H*-imidazole-4-carboxaldehyde[10] (**9**) (12.2 g, 37.4 mmol), nitroethane (2.7 mL, 37.4 mmol), *n*-butylamine (94 μL, 0.94 mmol), absolute ethanol (15 mL), and anhydrous dimethoxyethane (10 mL) was heated to reflux for 5 h. After cooling to room temperature, the precipitate formed was filtered, washed successively with absolute ethanol and diethyl ether, and then dried under vacuum to give **10** as a white solid (12.0 g, 80%): ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.58 (s, 1H), 7.37 (m, 9H), 7.19 (s, 1H), 7.13 (m, 6H), 2.69 (s, 3H); MS (CI, NH_3) m/z 396 (MH^+).

1-Methyl-2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)nitroethene (11). To a solution of the triphenylmethyl-protected imidazole **10** (5.69 g, 14.4 mmol) in dimethylformamide (28 mL) at 90 °C was added (2-(trimethylsilyl)ethoxy)methyl chloride (2.8 mL, 15.8 mmol), and the mixture was stirred at 90 °C for 2 h. The mixture was cooled to room temperature and concentrated under high vacuum (<1 mmHg) to remove the dimethylformamide solvent. The residue was purified by flash chromatography (eluting solvent gradient: hexane/methylene chloride (1:1) to methylene chloride) to give 11 (2.47 g, 61%): ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.73 (s, 1H), 7.39 (s, 1H), 5.32 (s, 2H), 3.52 (t, 2H), 2.73 (s, 3H), 0.93 (t, 2H), 0.00 (s, 9H); MS (EI) m/z 283 (M^+).

2-Nitro-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)butane (12). To a cooled (-78 °C) portion of anhydrous tetrahydrofuran (16 mL) was added successively a solution of methyllithium in hexane (17.5 mL, 1.4 M, 24.5 mmol) and boron trifluoride etherate (4.0 mL, 32.6 mmol). The resulting solution was stirred at −78 °C for 20 min, a cooled (−78 °C) solution of the α,β-unsaturated nitro compound 11 (2.30 g, 8.18 mmol) in anhydrous tetrahydrofuran (30 mL) was added dropwise via cannula over the course of 35 min, and then the resulting yellow solution was stirred at −78 °C for an additional 50 min. To the cooled (−78 °C) reaction mixture was added water (40 mL), the cooling bath was removed, and the mixture was stirred while warming to room temperature. To the mixture were added ethyl acetate (30 mL) and then saturated aqueous sodium bicarbonate until the pH of the aqueous phase reached approximately 6. The mixture was shaken, the layers were separated, and the organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by flash chromatography (eluting solvent gradient: methylene chloride to methylene chloride/ethyl acetate (2:1)) to give **12** as a 1:1 mixture of erythro and threo diastereomers (1.29 g, 46%): ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.56 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 5.24 (s, 2H), 5.22 (s, 2H), 4.95 (dq, 1H), 4.83 (dq, 1H), 3.46 (m, 5H), 3.33 (dq, 1H), 1.53 (d, 3H), 1.44 (d, 3H), 1.33 (d, 3H), 1.31 (d, 3H), 0.91 (dt, 4H), 0.00 (s, 18 H); MS (FAB) m/z 300 (MH^+).

3-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)-2-butanamine (13). To a solution of mercury(II) chloride (61 mL, 2% by weight in water) was added aluminum (1.48 g, granules, 40 mesh), and the mixture was stirred at room temperature for 1 min. The aqueous solution was decanted, and the remaining aluminum amalgam was washed successively with absolute ethanol and diethyl ether. To a suspension of the aluminum amalgam in tetrahydrofuran (60 mL)/water (6 mL) was added slowly (40 min) a solution of the nitro compound **12** (1.11 g, 3.71 mmol) in tetrahydrofuran (20 mL). The mixture was stirred at room temperature for an additional 2 h and filtered through a pad of Celite, and the Celite was washed with methylene chloride/methanol (9:1, 120 mL). The filtrates were combined, dried over anhydrous potassium carbonate, and concentrated to give **13** as a 1:1 mixture of diastereomers (0.91 g, 92%). The material was used directly, without further purification, in the next step: ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 2H), 6.82 (s, 1H), 6.81 (s, 1H), 5.24 (s, 4H), 3.49 (t, 4H), 3.24 (dq, 1H), 3.11 (dq, 1H), 1.97 (br s, 4H), 1.24 (t, 6H), 1.10 (d, 3H), 1.05 (d, 3H), 0.91 (t, 4H), 0.00 (s, 18H).; MS (CI, NH_3) m/z 270 (MH^+).

***threo*-(±)-2-((*tert*-Butyloxycarbonyl)amino)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)butane (14a) and *erythro*-(±)-2-((*tert*-Butyloxycarbonyl)-amino)-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazol-5-yl)butane (14b).** To a solution of diastereomeric amines **13** (1.22 g, 4.53 mmol) in anhydrous methylene chloride (19 mL) were added triethylamine (1.6 mL, 11.3 mmol) and di-*tert*-butyl dicarbonate (2.18 g, 9.5 mmol). The resulting soution was stirred at room temperature for 5 h and concentrated under vacuum, and to the residue were added water and ethyl acetate. The mixture was shaken, the layers were separated, and the organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (eluting solvent gradient: methylene chloride/ethyl acetate, 5:1 to 1:1). The first to elute was the the threo diastereomer **14a** (0.90 g, 54%). The second to elute was the erythro diastereomer **14b** (0.18 g, 11%). Threo diastereomer **14a**: ^{1}H NMR ($CDCl_3$) δ 7.56 (s, 1H), 6.84 (s, 1H), 5.68 (br d, 1H), 5.24 (s, 2H), 3.87 (br s, 1H), 3.49 (t, 2H), 2.85 (m, 1H), 1.46 (s, 9H), 1.31 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H), 0.91 (t, 2H), 0.01 (s, 9H); MS (FAB) m/z 370 (MH^+). Erythro diastereomer **14b**: ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 6.81 (s, 1H), 5.98 (br d, 1H), 5.24 (s, 2H), 3.85 (br s, 1H), 3.48 (t, 2H), 3.03 (br s, 1H), 1.47 (s, 9H), 1.26 (d, J = 7.2 Hz, 3H), 0.92 (d, 3H), 0.91 (t, 2H), 0.01 (s, 9H); MS (FAB) m/z 370 (MH^+).

***threo*-(±)-3-(1*H*-imidazol-4-yl)-2-butanamine, Dihydrochloride (2a).** A suspension of threo diastereomer **14a** (0.59 g 1.60 mmol) in 3 N aqueous hydrochloric acid (8 mL) was heated to reflux for 4.5 h. The mixture was cooled to room

temperature and concentrated under vacuum, and the residue was recrystallized from methanol/diethyl ether to give **2a** as the dihydrochloride salt (0.25 g, 73%): ^{1}H NMR (D_2O) δ 8.63 (s, 1H), 7.36 (s, 1H), 3.58 (dq, J = 6.7, 6.7 Hz, 1H), 3.29 (dq, J = 7.1, 7.1 Hz, 1H), 1.32 (d, J = 7.2 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H); MS (CI, CH_4) m/z 140 (MH^+).

***erythro*-(±)-3-(1*H*-Imidazol-4-yl)-2-butanamine, Dihydrochloride (2b).** A suspension of erythro diastereomer **14b** (0.34 g, 0.92 mmol) in 3 N aqueous hydrochloric acid was heated to reflux for 4.5 h. The mixture was cooled to room temperature and concentrated under vacuum, and the residue was recrystallized from methanol/diethyl ether to give **2b** as the dihydrochloride salt (0.052 g, 41%): ^{1}H NMR (D_2O) δ 8.63 (s, 1H), 7.36 (s, 1H), 3.55 (dq, J = 6.8, 6.8 Hz, 1H), 3.28 (dq, J = 6.9, 6.9 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H); MS (CI, CH_4) m/z 140 (MH^+).

Urocanic Acid, Methyl Ester (16). To a suspension of urocanic acid **15** (13.8 g, 100 mmol) in methanol (250 mL) was added concentrated sulfuric acid (10 mL), and the mixture was heated to reflux for 24 h. The mixture was cooled to 5 °C, and concentrated ammonium hydroxide (25 mL) was added slowly. The solvents were removed by rotary evaporation, and to the residue were added water (50 mL) and ethyl acetate (750 mL). The mixture was shaken, the layers were separated, and the aqueous layer was extracted with ethyl acetate (500 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give **16** as a white solid (14.9 g, 98%): ^{1}H NMR (CD_3COCD_3) δ 7.73 (s, 1H), 7.63 (d, J = 16 Hz, 1H), 7.30 (s, 1H), 6.48 (d, J = 16 Hz, 1H), 3.78 (s, 3H).

3-(1-((2-(Trimethylsilyl)ethoxy)methyl)imidazol-4-yl)-prop-2-enoic Acid, Methyl Ester (17). To a suspension of the methyl ester **16** (12.2 g, 80.0 mmol) in tetrahydrofuran (80 mL) were added triethylamine (28 mL, 200 mmol) and then (2-(trimethylsilyl)ethoxy)methyl chloride (30 mL, 170 mmol). The mixture was stirred at room temperature for 1 h, and then to this mixture were added 5% aqueous sodium hydroxide (200 mL) and methylene chloride (1200 mL). The mixture was shaken vigorously, the layers were separated, and the aqueous layer was extracted with methylene chloride (1200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to give an orange, oily residue which was purified by flash chromatography (ethyl acetate) to give **17** as a slightly yellow solid (10.8 g, 48%): ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.57 (d, J = 16 Hz, 1H), 7.25 (s, 1H), 6.71 (d, J = 16 Hz, 1H), 5.33 (s, 2H), 3.79 (s, 3H), 3.52 (t, J = 8 Hz, 2H), 0.92 (t, J = 8 Hz, 2H), −0.01 (s, 9H).

(±)-4-Nitro-3-(1-((2-(trimethylsilyl)ethoxy)methyl)imidazol-4-yl)pentanoic Acid, Methyl Ester (18). To a solution of unsaturated ester **17** (10.8 g, 38 mmol) in acetonitrile (25 mL) was added nitroethane (15 mL, 209 mmol) and then 1,8-diazabicyclo[5.4.0]undec-7-ene (6 mL, 40 mmol). The mixture was stirred at room temperature for 72 h, the solvents were removed by rotary evaporation, and the dark, oily residue was purified by flash chromatography (ethyl acetate) to give the nitroester **18** as a mixture of diastereomers (13.3 g, 97%): ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H, diast A and diast B), 6.91 (s, 1H, diast A), 6.86 (s, 1H, diast B), 5.21 (s, 2H, diast A), 5.19 (s, 2H, diast B), 4.97 (m, 1H, diast A and diast B), 3.80 (m, 1H, diast A and diast B), 3.62 (s, 3H, diast B), 3.59 (s, 3H, diast A), 3.43 (m, 2H, diast A and diast B), 2.75 (m, 2H, diast A and diast B), 1.56 (d, J = 7 Hz, 3H, diast B), 1.40 (d, J = 7 Hz, 3 H, diast A), 0.87 (t, J = 8 Hz, 2 H, diast A and diast B), −0.04 (s, 9H, diast A and diast B).

(±)-(4β,5α)-5-Methyl-4-(1-((2-(trimethylsilyl)ethoxy)-methyl)imidazol-4-yl)-2-pyrrolidinone (19t) and (±)-(4β,5β)-5-Methyl-4-(1-((2-(trimethylsilyl)ethoxy)methyl)-imidazol-4-yl)-2-pyrrolidinone (19c). A mixture of the nitro esters **18** (8.3 g, 23 mmol) and Raney nickel (8 g) in absolute ethanol (60 mL) was shaken under 60 psi of hydrogen at 55 °C in a Parr apparatus for 6 h. The mixture was filtered, and the filtrate was evaporated to give an oily residue which was purified by flash chromatography [(a) 5% MeOH/NH_3 in CH_2Cl_2, (b) 7% MeOH/NH_3 in THF:hexane, 2:1] to give two compounds. The first compound to elute was the *trans*-diastereomer **19t** (2.64 g, 39%): ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1H), 6.87 (s, 1H), 6.28 (br s, 1H), 5.22 (s, 2H), 3.84 (dq, J = 6, 6 Hz, 1H), 3.48 (t, J = 8 Hz, 2H), 3.13 (ddd, J = 6, 6, 6 Hz, 1H), 2.67 (m, 2H), 1.29 (s, J = 6 Hz, 3H), 0.89 (t, J = 8 Hz, 2H), −0.03 (s, 9H). The second compound to elute was the *cis*-diastereomer **19c** (1.67 g, 26%): ^{1}H NMR ($CDCl_3$) δ 7.62 (s, 1H), 6.87 (s, 1H), 6.18 (br s, 1H), 5.24 (s, 2H), 4.07 (dq, J = 8, 7 Hz, 1H), 3.80 (ddd, J = 8, 8, 8 Hz, 1H), 3.46 (t, J = 8 Hz, 2H), 2.61 (m, 2H), 0.89 (s, 3H), 0.89 (t, J = 8 Hz, 2H), −0.03 (s, 9H).

(±)-(2α,3β)-2-Methyl-3-(1-((2-(trimethylsilyl)ethoxy)-methyl)imidazol-4-yl)pyrrolidine (20t). To a solution of the *trans*-lactam **19t** (2.60 g, 8.8 mmol) in tetrahydrofuran (175 mL) was added a solution of lithium aluminum hydride in diethyl ether (1.0 M, 44.0 mL, 44 mmol). The mixture was stirred at room temperature for 4 h, and to the reaction mixture was added diethyl ether (440 mL) and saturated aqueous sodium sulfate (7 mL) dropwise. The mixture was dried over anhydrous sodium sulfate, filtered, and evaporated to give an oily residue which was purified by flash chromatography (gradient elution; CH_2Cl_2:MeOH/NH_3, 7:1 to 5:1) to give **20t** as a colorless oil (1.15 g, 46%): ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1H), 6.88 (d, J = 1 Hz, 1H), 5.21 (s, 2H), 4.57 (br s, 1H), 3.48 (m, 5H), 3.02 (m, 1H), 2.34 (m, 1H), 2.20 (m, 1H), 1.45 (d, J = 7 Hz, 3H), 0.90 (t, J = 8 Hz, 2H), −0.02 (s, 9H).

(±)-(2α,3β)-2-Methyl-3-(1*H*-imidazol-4-yl)pyrrolidine, Dihydrochloride (4a). To a solution of the pyrrolidine **20t** (563 mg, 2.0 mmol) in 95% ethanol (3 mL) was added concentrated hydrochloric acid (1 mL) and the mixture was heated to reflux for 16 h. The solvents were removed by rotary evaporation, and to the residue was added 1 N aqueous hydrochloric acid (8 mL). This solution was extracted with ethyl acetate (3 × 4 mL), and the aqueous layer was concentrated by rotary evaporation. To the residue was added distilled water (15 mL), and the resulting solution was filtered through a glass wool plug. The filtrate was concentrated by rotrary evaporation to give (±)-**4a** as a cream-colored solid (395 mg, 88%).

Purification of (±)-(2α,3β)-2-Methyl-3-(1*H*-imidazol-4-yl)pyrrolidine, Dihydrochloride (4a). To a solution of (±)-**4a** (336 mg, 1.5 mmol) in dimethylformamide (5.0 mL) was added triethylamine (1.05 mL, 7.53 mmol) and then a solution of di-*tert*-butyl dicarbonate [(*t*-BOC)$_2$O] (720 mg, 3.3 mmol) in dimethylformamide (1 mL). The mixture was stirred at room temperature for 2 h, the solvents were removed by vacuum distillation (1.0 mmHg), and the resulting residue was purified by flash chromatography (gradient elution; EtOAc:hexane, 1:1 to 2:1) to give the corresponding di-*t*-BOC derivative (±)-**21t** (488 mg) as a white solid. This material was dissolved in ethyl acetate (3 mL) and cooled to 5 °C, and to this solution was added a saturated solution of hydrogen chloride in ethyl acetate (14 mL). The mixture was gradually warmed to room temperature (30 min) and stirred at this temperature for 16 h. The ethyl acetate was removed from the precipitated product by pipet, and the precipitate was dried under high vacuum (0.1 mmHg) to give (±)-**4a** as a white solid (286 mg, 85% recovery): ^{1}H NMR (D_2O) δ 8.62 (d, J = 1 Hz, 1H), 7.39 (s, 1H), 4.74 (s, 4H), 3.68 (dq, J = 10, 7 Hz), 3.46 (m, 2H), 3.34 (ddd, J = 10, 10, 8 Hz, 1H), 2.52 (dddd, J = 13, 8, 8, 5 Hz, 1H), 2.18 (dddd, J = 13, 10, 10, 9 Hz, 1H), 1.38 (d, J = 7 Hz, 3H). Anal. ($C_8H_{13}N_3$·2HCl·0.05EtOAc) C, H, N.

Resolution of (±)-(2α,3β)-2-Methyl-3-(1*H*-imidazol-4-yl)pyrrolidine, Dihydrochloride (4a). The racemic *t*-BOC derivatives (±)-**21t** were resolved by high performance liquid chromatography using a Daicel Chiralcel OJ chiral chromatography column (2.0 cm × 50.0 cm, 4% 2-propanol in hexane). Multiple injections (13 injections of about 150 mg each) provided the levorotatory enantiomer (−)-**21t** [950 mg; $[\alpha]^{26}$ = −12.8° (c = 0.50, $CHCl_3$)] and the dextrorotatory enantiomer (+)-**21t** [904 mg; $[\alpha]^{26}$ = +12.0° (c = 0.50, $CHCl_3$)]. Treatment of (−)-**21t** with a saturated solution of hydrogen chloride in ethyl acetate as described above for the purification of (±)-**21t** provided (−)-**4a** [$[\alpha]^{26}$ = −34.6° (c = 1.00, H_2O)]. Anal. ($C_8H_{13}N_3$·2HCl·0.50H_2O) C, H, N. Similar treatment of (+)-**21t** gave (+)-**4a** [$[\alpha]^{26}$ = +39.4° (c = 1.00, H_2O)]. Anal. ($C_8H_{13}N_3$·2HCl·0.33H_2O) C, H, N.

1-(1-(Triphenylmethyl)-1*H*-imidazol-4-yl)-1,3-butadiene (22). To a suspension of allyltriphenylphosphonium

bromide (56 g, 145 mmol) in anhydrous tetrahydrofuran (400 mL) at 0 °C was added a solution of *n*-butyllithium in hexane (58 mL, 2.5 M, 145 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. To the mixture was added a solution of 1-(triphenylmethyl)-1*H*-imidazole-4-carboxaldehyde[10] (**9**) (38 g, 112 mmol) in hot tetrahydrofuran (250 mL), and the mixture was stirred at room temperature for an additional 2.5 h. To the mixture was added water (350 mL), the mixture was shaken, and the phases were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (gradient elution: 2% saturated methanolic ammonia in methylene chloride/hexane; 1: 5 to 1:1) to give the mixture of isomers **22** (**22c**/**22t** = 2.4) as a white solid (28.0 g, 71%). For *Z*-isomer **22c**: ^{1}H NMR ($CDCl_3$) δ 7.59 (ddd, J = 17, 10.5, 10 Hz, 1H), 7.45 (s, 1H), 7.32 (m, 9H), 7.14 (m, 6H), 6.81 (s, 1H), 6.15 (d, J = 10.5 Hz, 1H), 6.08 (dd, J = 11.5, 10.5 Hz, 1H), 5.28 (dd, J = 17, 2 Hz, 1H), 5.17 (dd, J = 10, 2 Hz, 1H). For *E*-isomer **22t**: ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H), 7.35 (m 9H), 7.14 (m, 6H), 6.89 (dd, J = 15.5, 10.5 Hz, 1H), 6.79 (s, 1H), 6.44 (ddd, J = 17, 10.5, 10 Hz, 1H), 6.40 (d, J = 15.5 Hz, 1H), 5.28 (dd, J = 17, 2 Hz, 1H), 5.08 (dd, J = 10, 2 Hz, 1H); MS (FAB) m/z 363 (MH^+).

(*E*)-1-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)-1,3-butadiene (22t). To a solution of the mixture of isomers **22** (15 g, 41.3 mmol) in benzene (450 mL) was added phenyl disulfide (0.9 g, 4.12 mmol), and the mixture was irradiated with a sun lamp at reflux for 24 h. The mixture was cooled to room temperature and concentrated under vacuum. The resulting residue was purified by flash chromatography (2% saturated methanolic ammonia in methylene chloride/hexane; 1:5) to give pure *E*-isomer **22t** (10 g, 66%): ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1H), 7.35 (m 9H), 7.14 (m, 6H), 6.89 (dd, J = 15.5, 10.5 Hz, 1H), 6.79 (s, 1H), 6.44 (ddd, J = 17, 10.5, 10 Hz, 1H), 6.40 (d, J = 15.5 Hz, 1H), 5.28 (dd, J = 17, 2 HZ, 1H), 5.08 (dd, J = 10, 2 Hz, 1H); MS (FAB) m/z 363 (MH^+).

4β-Methyl-4α-nitro-3β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclohex-1-ene (23a) and 4α-Methyl-4β-nitro-3β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclohex-1-ene (23b). A solution of the *trans*-olefin **22t** (10 g, 28 mmol) and 2-nitropropene[12] (8.6 g, 99 mmol) in benzene (40 mL) was heated to reflux for 5 h. The mixture was concentrated under vacuum, and the residue was purified by flash chromatography (5% ethyl acetate in methylene chloride) to give the *anti* diastereomer **23a** (6.14 g, 49%) and the *syn* diastereomer **23b** (1.63 g, 13%). For anti diastereomer **23a**: ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.34 (m, 9H), 7.10 (m, 6H), 6.59 (s, 1H), 5.77 (br t, 2H), 4.38 (br s, 1H), 2.42 (m, 1H), 2.21 (br m, 2H), 2.07 (m, 1H), 1.33 (s, 3H); MS (FAB) m/z 450 (MH^+). For syn diastereomer **23b**: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 10H), 7.10 (m, 6H), 6.54 (s, 1H), 5.80 (br d, 1H), 5.71 (br d, 1H), 3.72 (br s, 1H), 2.60 (m, 1H), 2.41 (dt, 1H), 2.11 (m, 1H), 1.89 (dd, 1H), 1.70 (s, 3H); MS (FAB) m/z 450 (MH^+).

1β-Methyl-1α-nitro-2β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclohexane (24a). A mixture of the anti diastereomer **23a** (5.20 g, 11.6 mmol) and 10% palladium on carbon (0.75 g) in absolute ethanol (150 mL) was shaken under 55 psi of hydrogen gas for 18 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under vacuum to give the nitrocyclohexane **24a** (4.18 g, 80%): ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.32 (m, 9H), 7.13 (m, 6H), 6.53 (s, 1H), 2.49 (dd, 1H), 2.80–1.20 (m, 8H), 0.98 (s, 3H); MS (FAB) m/z 452 (MH^+).

1α-Methyl-1β-nitro-2β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclohexane (24b). A mixture of the *syn* diastereomer **23b** (0.70 g, 1.56 mmol) and 10% palladium on carbon (0.17 g) in absolute ethanol (40 mL) was shaken under 55 psi of hydrogen gas for 18 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under vacuum to give the nitrocyclohexane **24b** (0.50 g, 71%): ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 1H), 7.33 (m, 9H), 7.14 (m, 6H), 6.51 (s, 1H), 2.46 (dd, 1H), 2.90–1.20 (m, 8H), 0.91 (s, 3H); MS (FAB) m/z 452 (MH^+).

1β-Methyl-2β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclohexylamine (25a). To a solution of mercury(II) chloride (133 mL, 2% by weight in water) was added aluminum (3.72 g, granules, 40 mesh), and the mixture was stirred at room temperature for 1 min. The aqueous solution was decanted, and the remaining aluminum amalgam was washed successively with absolute ethanol and diethyl ether. To a suspension of the aluminum amalgam in tetrahydrofuran (140 mL)/water (14 mL) was added slowly (45 min) a solution of the nitro compound **24a** (2.10 g, 4.66 mmol) in tetrahydrofuran (50 mL). The mixture was stirred at room temperature for an additional 18 h and filtered through a pad of Celite, and the Celite was washed with methylene chloride/methanol (9:1, 200 mL). The filtrates were combined and concentrated under vacuum. The resulting residue was purified by preparative thin layer chromatography (5% saturated methanolic ammonia in ethyl acetate) to give **25a** (0.69 g, 35%): ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 10H), 7.13 (m, 6H), 6.30 (s, 1H), 2.49 (dd, J = 12, 4 Hz, 1H), 1.80–1.20 (m, 8H), 0.95 (s, 3H); MS (FAB) m/z 422 (MH^+).

1α-Methyl-2β-(1-(triphenylmethyl)-1*H*-imidazol-4-yl)cyclohexylamine (25b). To a solution of mercury(II) chloride (38 mL, 2% by weight in water) was added aluminum (0.92 g, granules, 40 mesh), and the mixture was stirred at room temperature for 1 min. The aqueous solution was decanted, and the remaining aluminum amalgam was washed successively with absolute ethanol and diethyl ether. To a suspension of the aluminum amalgam in tetrahydrofuran (40 mL)/water (4 mL) was added slowly (45 min) a solution of the nitro compound **24b** (0.60 g, 1.33 mmol) in tetrahydrofuran (14 mL). The mixture was stirred at room temperature for an additional 18 h and filtered through a pad of Celite, and the Celite was washed with methylene chloride/methanol (9:1, 70 mL). The filtrates were combined and concentrated under vacuum. The resulting residue was purified by preparative thin layer chromatography (5% saturated methanolic ammonia in ethyl acetate) to give **25b** (0.28 g, 50%): ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 10H), 7.13 (m, 6H), 6.56 (s, 1H), 2.50 (dd, J = 12.2, 4.0 Hz, 1H), 1.80–1.20 (m, 8H), 0.95 (s, 3H); MS (FAB) m/z 422 (MH^+).

1β-Methyl-2β-(1*H*-imidazol-4-yl)cyclohexylamine, Dihydrochloride (5a). A suspension of the diastereomer **25a** (0.33 g 0.78 mmol) in 0.5 N aqueous hydrochloric acid (25 mL) was heated to reflux for 0.5 h. The cooled aqueous solution was extracted with diethyl ether (3 × 13 mL), and the aqueous phase was concentrated under vacuum. The residue was recrystallized with methanol/diethyl ether to give **5a** as the dihydrochloride salt (0.074 g, 35%): ^{1}H NMR (400 MHz, D_2O) δ 8.66 (s, 1H), 7.37 (s, 1H), 3.15 (m, 1H), 1.94–1.51 (m, 8H), 1.29 (s, 3H); MS (CI) m/z 180 (MH^+). Anal. ($C_{10}H_{17}N_3 \cdot 2HCl \cdot 1.00H_2O$) C, H, N.

1α-Methyl-2β-(1*H*-imidazol-4-yl)cyclohexylamine, Dihydrochloride (5b). A suspension of the diastereomer **25b** (0.27 g 0.64 mmol) in 0.5 N aqueous hydrochloric acid (20 mL) was heated to reflux for 0.5 h. The cooled aqueous solution was extracted with diethyl ether (3 × 10 mL), and the aqueous phase was concentrated under vacuum. The residue was recrystallized with methanol/diethyl ether to give **5b** as the dihydrochloride salt (0.083 g, 51%): ^{1}H NMR (400 MHz, D_2O) δ 8.89 (s, 1H), 7.47 (s, 1H), 3.19 (dd, J = 12.7, 4.1 Hz, 1H), 2.05 (br d, 2H), 2.00–1.80 (m, 4H), 1.53 (br t, 2H), 1.42 (s, 3H). For diastereomer **5b** an NOE effect (3.5%) was observed between the 2-position methine proton (δ = 3.19 ppm) and the 1-position methyl protons (δ = 1.42 ppm). Anal. ($C_{10}H_{17}N_3 \cdot 2HCl \cdot 0.60H_2O$) C, H, N.

Acknowledgment. The authors wish to thank Professor Andrew T. McPhail of Duke University who provided the single-crystal X-ray analysis needed to determine the absolute stereochemistry of (2*R*,3*S*)-(+)-**4a**. The authors also wish to acknowledge the efforts of the Physical and Analytical Chemistry Research and Development (PACRD) group at the Schering-Plough Research Institute who provided the analytical (NMR,

mass spectral, elemental analysis, etc.) data for all the compounds presented in this article.

References

(1) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-Inhibition of Brain Histamine Release Mediated by a Novel Class (H_3) of Histamine Receptor. *Nature (London)* **1983**, *302*, 832–837.

(2) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte, J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. Highly Potent and Selective Ligands for Histamine H_3-Receptors. *Nature (London)* **1987**, *327*, 117–123.

(3) Schlicker, E.; Betz, R.; Göthert, M. Histamine H_3 Receptor-Mediated Inhibition of Serotonin Release in Rat Brain Cortex. *Naunyn-Schmeid. Arch. Pharmacol.* **1988**, *337*, 588–590.

(4) Schlicker, E.; Schunack, W.; Göthert, M. Histamine H_3 Receptor-Mediated Inhibition of Noradrenaline Release in Pig Retina Discs. *Naunyn-Schmeid. Arch. Pharmacol.* **1990**, *342*, 497–501.

(5) Clapham, J.; Kilpatrick, G. J. Histamine H_3 Receptors Modulate the Release of [^{3}H]-Acetylcholine from slices of Rat Entorhinal Cortex: Evidence for Possible Existence of H_3 Receptor Subtypes. *Br. J. Pharmacol.* **1992**, *107*, 919–923.

(6) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C.; Lipp, R.; Stark, H.; Schunack, W.; Lecomte, J.-M. The Histamine H_3-Receptor: Pharmacology, Roles and Clinical Implications Studied with Agonists. In *New Perspectives in Histamine Research*; Timmerman, H., van der Goot, H., Eds.; Birkhäuser Verlag: Basel, 1991; pp 55–67.

(7) Hey, J. A.; del Prado, M.; Egan, R. W.; Kreutner, W.; Chapman, R. (*R*)-α-Methylhistamine Augments Neural, Cholinergic Brochospasm in Guinea Pigs by Histamine H_1 Receptor Activation. *Eur. J. Pharmacol.* **1992**, *211*, 421–426.

(8) Turner, R. M.; Lindell, S. D.; Ley, S. V. A Facile Route to Imidazol-4-yl Anions and Their Reaction with Carbonyl Compounds. *J. Org. Chem.* **1991**, *56*, 5739–5740.

(9) (a) Arrang, J.-M.; Garbarg, M.; Schunack, W.; Schwartz, J.-C.; Lipp, R. O. Dérivé de l'histamine, sa préparation et son application en thérapeutique. Eur. Pat. 0 338 939, 1989. (b) Lipp, R.; Arrang, J.-M.; Buschmann, J.; Garbarg, M.; Luger, P.; Schunack, W.; Schwartz, J.-C. Novel Chiral H_3-Receptor Agonists. In *New Perspectives in Histamine Research*; Timmerman, H., van der Goot, H., Eds.; Birkhäuser Verlag: Basel, 1991; pp 277–282. (c) Lipp, R.; Arrang, J.-M.; Garbarg, M.; Luger, P.; Schwartz, J.-C.; Schunack, W. Synthesis, Absolute Configuration, Stereoselectivity, and Receptor Selectivity of (αR,βS)-α,β-Dimethylhistamine, a Novel Highly Potent Histamine H_3 Receptor Agonist. *J. Med. Chem.* **1992**, *35*, 4434–4441.

(10) Kelley, J. L.; Miller, C. A.; McLean, E. W. Attempted Inhibition of Histidine Decarboxylase with β-Alkyl Analogues of Histidine. *J. Med. Chem.* **1977**, *20*, 721–723.

(11) Langlois, M.; Guillonneau, C.; Vo Van, T.; Maillard, J.; Lannoy, J.; Nguyen, H. N.; Morin, R.; Manuel, C.; Benharkate, M. Synthèse et Propriétés Antidépressives de Dérivés de l'Amino-2 Phényl-4 Delta 1-Pyrroline. *Eur. J. Med. Chem.—Chem. Ther.* **1978**, 161–169.

(12) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *Org. Synth.* **1981**, *60*, 101–103.

(13) Calculations were completed using MacroModel v. 3.5x. The authors gratefully acknowledge the efforts of Dr. Barr E. Bauer who was instrumental in the execution of these computational studies. Recently a more detailed investigation of the conformations of histamine and (α*R*,β*S*)-α,β-dimethylhistamine has appeared: Nagy, P. I.; Durant, G. J.; Hoss, W. P.; Smith, D. A. Theoretical Analyses of the Tautomeric and Conformational Equilibria of Histamine and (αR,βS)-α,β-Dimethylhistamine in the Gas Phase and Aqueous Solution. *J. Am. Chem. Soc.* **1994**, *116*, 4898–4909.

(14) Dauben, W. G.; Pitzer, K. S. Conformational Analysis. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley & Sons, Inc.: New York, 1963; pp 1–60.

(15) The receptor binding assay was performed on guinea pig brain tissue using [^{3}H]-N^α-methylhistamine as ligand: Korte, A.; Myers, J.; Shih, N.-Y.; Egan, R. W.; Clark, M. A. Characterization and Tissue Distribution of H_3 Histamine Receptors in Guinea Pigs by N^α-Methylhistamine. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 979–986.

(16) The acyclic dimethylhistamine derivative **2b** (as well as the diastereomeric **2a**), while quite potent in the H_3 binding assay, had previously been reported. For reports of **2a** and **2b**, see ref 9 above. In addition to (*R*)-α-methylhistamine and (α*R*,β*S*)-α,β-dimethylhistamine, other potent and selective H_3 receptor agonists that have been reported include imetit and immepip. For reports of imetit, see: (a) Howson, W.; Parsons, M. E.; Raval, P.; Swayne, G. T. G. Two Novel, Potent and Selective Histamine H_3 Receptor Agonists. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 77–78. (b) Ganellin, C. R.; Bang-Andersen, B.; Khalaf, Y. S.; Tertiuk, W.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Rouleau, A.; Schwartz, J.-C.; Imetit and N-Methyl Derivatives. The Transition from Potent Agonist to Antagonist at Histamine H_3 Receptors. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1231–1234. (c) Garbarg, M.; Arrang, J.-M.; Rouleau, A.; Ligneau, X.; Tuong, M. D. T.; Schwartz, J.-C.; Ganellin, C. R. S-[2-(4-Imidazolyl)ethyl]isothiourea, a Highly Specific and Potent Histamine H_3 Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304–310. (d) Van der Goot, H.; Schepers, M. J. P.; Sterk, G. J.; Timmerman, H. Isothiourea Analogues of Histamine as Potent Agonists or Antagonists of the Histamine H_3-Receptor. *Eur. J. Med. Chem.* **1992**, *27*, 511–517. For reports of immepip see: (e) Shih, N.-Y.; Green, M. J. Imidazoylalkyl Substituted with a Six Membered Nitrogen Containing Heterocyclic Ring. Intern. Pat. Appl. WO 93-12107, 1993. (f) Vollinga, R. C.; de Koning, J. P.; Jansen, F. P.; Leurs, R.; Menge, W. M. P. B.; Timmerman, H. A New Potent and Selective Histamine H_3 Receptor Agonist, 4-(1*H*-Imidazol-4-ylmethyl)piperidine. *J. Med. Chem.* **1994**, *37*, 332–333.

(17) Arrang, J.-M.; Schwartz, J.-C.; Schunack, W. Stereoselectivity of the Histamine H_3-Presynaptic Autoreceptor. *Eur. J. Pharmacol.* **1985**, *117*, 109–114.

(18) Resolutions were accomplished via chiral stationary phase HPLC of the di-*t*-BOC derivatives of (±)-**4a**. Absolute stereochemistry of the enantiomers of **4a** were assigned based upon a single-crystal X-ray analysis of an (*R*)-α-methylbenzyl urea derivative of (−)-**4a**.

(19) An electrically-stimulated isolated guinea pig ileum preparation was used as the *in vitro* functional assay; an assay which differentiates H_3 agonists and H_3 antagonists. The assay used is based on studies described previously. See: Trzeciakowski, J. P. Inhibition of Guinea Pig Ileum Contractions Mediated by a Class of Histamine Receptor Resembling the H_3 Subtype. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 874–880.

(20) H_3 agonist activity was determined *in vivo* using a model previously described: Hey, J. A.; del Prado, M.; Egan, R. W.; Kreutner, W.; Chapman, R. W. Inhibition of Sympathetic Hypertensive Responses in the Guinea Pig by Prejunctional Histamine H_3-Receptors. *Br. J. Pharmacol.* **1992**, *107*, 347–351.

JM9407670