New Building Blocks for Fluorinated Imidazole Derivatives: Preparation of β-Fluoro- and β,β-Difluorohistamine

Bohumil Dolensky and Kenneth L. Kirk*

Laboratory of Bioorganic Chemistry, National Institute of Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892

Kennethk@bdg8.niddk.nih.gov

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We demonstrate that "FBr" addition to 1-trityl-4-vinyl-1*H*-imidazole (**7**) provides a convenient route to side-chain-fluorinated histamines. Thus, addition of "FBr" to the double bond of **7** occurs with Markovnikov regioselectivity to produce 4-(2-bromo-1-fluoroethyl)-1-trityl-1*H*-imidazole (**8**). Substitution with azide, reduction, and removal of the trityl group provide β-fluorohistamine (**1**) as the dihydrochloride. Elimination of HBr from **8** followed by a second addition of "FBr" gives 4-(2-bromo-1,1-difluoroethyl)-1-trityl-1*H*-imidazole (**15**). This was similarly converted to β,β-difluorohistamine (**2**) as the dihydrochloride.

Introduction

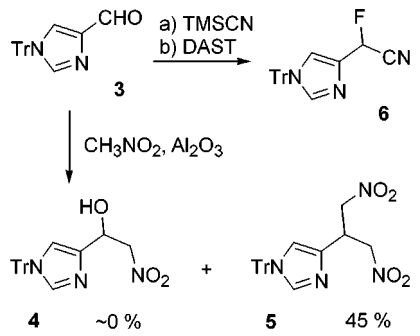
In biotransformations of biologically important imidazoles such as histidine and histamine, the imidazole side chain is usually the site of enzyme action. Whereas substitution of fluorine on the imidazole ring has been shown to affect the interactions of imidazole derivatives with many biological recognition sites,[1,2] fluorine on the side chain could be expected to have different and possibly dramatic effects. Despite this, β-fluorohistamine[3] (**1**) is the only example of a side-chain-fluorinated analogue of either histidine or histamine that we are aware of that has fluorine attached to the methylene group adjacent to the imidazole role. Examples of biologically important imidazoles with more distal side chain fluorine substitution include such compounds as α-fluoromethyl histidine, an inhibitor of histidine decarboxylase,[4] and *E*- and *Z*-α-fluorourocanic acid.[5]

We recently have initiated research to develop general methods for the synthesis of side-chain-fluorinated analogues of biologically important imidazoles. In this report, we describe one such approach and illustrate the application thereof to the synthesis of β-fluorohistamine (**1**) and β,β-difluorohistamine (**2**).

Chemistry

β-Fluorohistamine (**1**) was prepared previously by reaction of β-hydroxyhistamine with SF_4 in HF.[3] This straightforward method has two potential problems. In the first place, hazardous materials such as SF_4 and/or liquid HF must be used. Second, the availability of starting hydroxy or oxo derivative (for a similar preparation of the difluoro compound) could be problematic.

Scheme 1



The availability of stable reagents for fluorodeoxygenation (e.g. DAST, FAR) could provide alternative procedures that would be more convenient, eliminating the first concern. To examine fluorodeoxygenation as a route to additional side chain substituted imidazoles, we explored routes to hydroxy precursors. However, our first attempts, based on reaction of 1-trityl-1*H*-imidazole-4-carboxaldehyde (**3**) with a C_1-synthon and subsequent functional group manipulation, were unsuccessful (Scheme 1). For example, additions of nitromethane to the aldehyde **3** in attempts to prepare adduct **4** proved to be very complicated. Under varied experimental conditions we obtained either no reaction, complex mixtures, or the predominate formation of the bis-adduct of nitromethane **5**. Approaches based on deoxyfluorination[6] of the trimethylsilyl cyanohydrin derived from **3** gave disappointing initial results in that only trace amounts **6** could be detected by MS.

In a different approach, we explored functionallization of the double bond of 4-vinyl-1*H*-imidazoles based an efficient procedure for the electrophilic addition of a stoichiometric equivalent of FBr to a double bond. This is achieved by treatment of an olefin with a source of electrophilic Br^+, usually an *N*-bromo amide, and nu-

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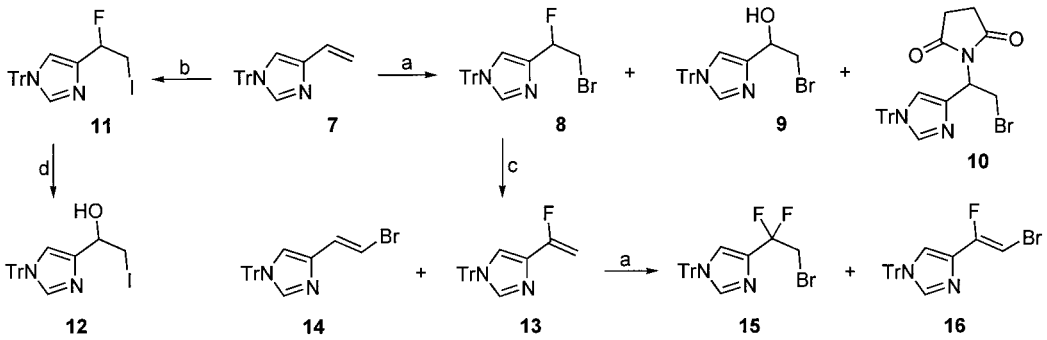
Scheme 2[a]



[a] (a) NBS, $3HF{\cdot}Et_3N$; (b) NIS, $3HF{\cdot}Et_3N$; (c) K_2CO_3; (d) silica.

cleophilic F^-, usually an $(HF)_x$·amine complex. The addition proceeds predominantly with Markovnikov regioselectivity. This method is the subject of recent reviews.[7] A particularly useful procedure using a combination of the unagressive $Et_3N{\cdot}3HF$ and *N*-bromosuccinamide (NBS) has been exploited extensively by Haufe and co-workers.[8] Adding utility to the method is the fact that the resulting bromofluoro product could be used as building blocks for subsequent syntheses of difluoro derivatives.[9] Thus, elimination of HBr[9,10] followed by a second "FBr" addition leads to bromodifluoro adducts.[9,11]

Although the utility of this method for introduction of fluorine has been amply demonstrated, a limitation to its generality would be the presence of other groups that might be susceptible to electrophilic attack or to the action of $Et_3N{\cdot}3HF$. Indeed, we were particularly aware that NBS is an effective reagent for ring-bromination of imidazole.[12] In fact, we determined that the attempted addition of "FBr" to the double bond of 4-vinyl-1*H*-imidazole led to a complex mixture, the ^{19}F NMR spectrum of which indicated the complete absence of any organoflourine compound.

In contrast, we found that reaction of 1-trityl-4-vinyl-1*H*-imidazole (**7**) with NBS and $Et_3N{\cdot}3HF$ (Scheme 2) occurred cleanly to give the desired bromofluoro derivative **8** in 74−80% yield. From ^1H NMR data, it appears that the addition takes place with total Markovnikov regioselectivity. We assume that the bulky trityl group impedes electrophilic bromination at the adjacent imidazole 2- and 5-positions, permitting efficient reaction at the exocyclic double bond. As byproducts we isolated triphenylcarbinol (10%), a result of partial detritylation, and hydroxybromide **9** (6%), apparently due to the presence of water.[13] Smaller amounts (2%) of the adduct **10** were isolated (Scheme 2).[14]

An alternative to addition of "FBr" is addition of "FI", where *N*-iodosuccinamide (NIS) is used[7] as source of I^+. The iodinated product should be more reactive than the brominated product in our intended substitution reactions. The expected fluoroiodo adduct **11** is formed, also with complete Markovnikov selectivity and in high yield. However, we found that the adduct **11** loses the fluorine atom during chromatography and hydroxyiodo compound **12** is obtained. In view of the stability of **8** under these conditions, and the fact that the substitution reaction of **11** with potassium phthalimide results in displacement of iodine, this apparent "substitution" of fluorine is surprising.

To introduce a second fluorine atom into the side chain, we envisioned a repeat of the "FBr" addition to the fluoro olefin **13** prepared by dehydrobromination of **8**. Using K_2CO_3 as base, the expected olefin **13** was isolated in 50% yield as the major product accompanied by bromoolefin **14** isolated in 2% yield, the product of dehydrofluorination. The assignment of the *E* configuration to **14** was based on the presence of a new band in the IR spectrum at 940 cm^{-1} that indicates[15] a trans relationship of the hydrogen atoms on the double bond. We have consistently found that competing formation of olefins **13** and **14** accompanies all substitution reactions of **8** that we have performed.

A repeat of the "FBr" addition to **13** gave 4-(2-bromo-1,1-difluoroethyl)-1*H*-tritylimidazole (**15**) in 71% yield. Difluoroimidazole **15** is accompanied by traces of *Z*-fluorobromoolefin **16** (The *E* isomer has[16] a smaller $^3J_{HF}$; 29.1 vs 15.6 Hz). This presumably is a result of the addition of Br_2 to **13** followed by elimination of HBr (Scheme 3). Dibromo adducts such as **17** frequently have been reported as byproducts of "FBr" additions in these reactions.[7] Another possible origin of bromofluoroolefin **16** would be the addition of "FBr" to bromoolefin **14**, a possible contaminant of starting olefin **13**, and subsequent elimination of HBr from the resulting dibromofluoro compound **18**. This possibility was ruled out by examination of the chemical behavior of **17** and **18**. Thus, we found that **18** is relatively stable in the presence of Et_3N. In contrast, under the same conditions, dibromofluoro compound **17** readily eliminates HBr and is completely converted (^1H NMR) to bromofluoroolefin **16** (Scheme 3).

Compounds **8** and **15** possess functionality that can be used to prepare imidazole derivatives having, respectively, one or two fluorine substituents on the side chain.

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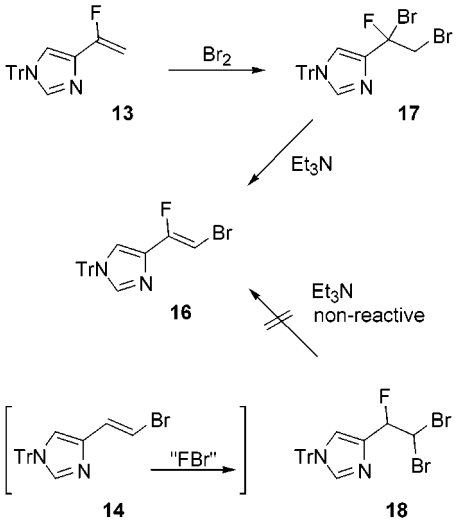
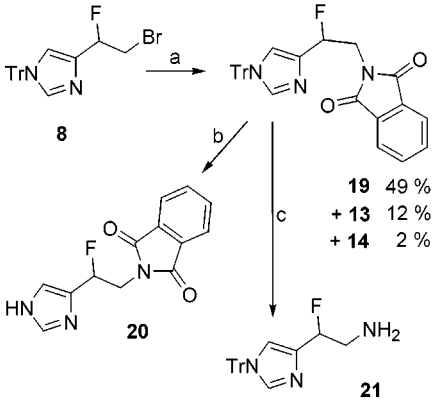
Scheme 3



Scheme 4[a]



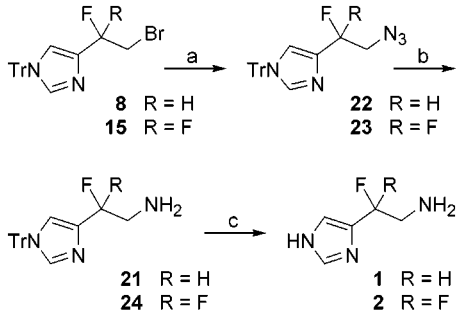
[a] (a) Potassium phthalimide; (b) aq HCl; (c) NH_2NH_2.

As initial targets, we chose side-chain-fluorinated histamines that would result from successful application of the Gabriel synthesis. However, the reaction of compound **8** with potassium phthalimide gave not only substitution product **19**, but also elimination products **13** and **14**. The ratio of substitution vs elimination was found to be quite independent of the reaction temperature (rt, 80 °C or 110 °C), and furthermore the reaction with iodide **11** gave a similar ratio.

The trityl group of **19** was removed readily by treatment with aq HCl to give the protected amine **20.** Attempts to first remove the phthaloyl group using hydrazine produced the tritylated amine **21** (Scheme 4) along with an unidentified byproduct, possibly resulting from partial substitution of fluorine (^{1}H NMR). Consistent with the expected lower reactivity[17] of the difluoro derivative **15**, reaction with potassium phthalimide in DMF, even at 150 °C, gave only 5% conversion (^{1}H NMR) after 24 h.

We next considered azide substitution as an alternative (Scheme 5). The azide anion should be a better nucleophile and weaker base than the phthalimide anion, and the resulting azide should be converted readily to the amine under mild catalytic reduction conditions. Reaction

Scheme 5[a]



[a] (a) NaN_3; (b) H_2/Pd; (c) aq HCl.

of **8** with sodium azide cleanly produced the azide **22** in 87% yield, accompanied by a mixture of olefins **13** and **14**, isolated in 7% yield (**13** + **14**). Difluoro derivative **15** similarly was converted to the azide **23** in 89% yield. Catalytic reductions of azides **22** and **23** proceeded cleanly at atmospheric pressure to give the corresponding amines **21** and **24**. However, hydrogenation of azide **22** at 276 kPa (40 psi) overnight led to reductive loss of fluorine and tritylated histamine was obtained.

The hydrolysis of tritylated β,β-difluorohistamine (**24**) takes place without any problem and the target compound β,β-difluorohistamine (**2**) was obtained in 87% yield as the dihydrochloride. Hydrolysis of trityl β-fluorohistamine (**21**) likewise produced the dihydrochloride of the target β-fluorohistamine (**1**), readily identified in the crude product mixture by NMR and mass spectral data. However, attempts to purify the dihydrochloride of **1** have consistently led to substantial material loss accompanied by formation of intractable material. To date we have been unable achieve satisfactory purification, a disappointing result in light of the previous report[3] on the isolation and facile purification of this compound.

The pK_{a1} and pK_{a2} values for difluorohistamine **2** were determined by titration of a solution of the dihydrochloride of **2** with aqueous NaOH at 25 °C. Analysis of the titration curve gave estimated values of $pK_{a1} = 2.9$ and $pK_{a2} = 6.8$. In comparison with pK_a values of histamine (at 30 °C, $pK_{a1} = 5.9$, $pK_{a2} = 9.7$)[18] it seems that the two fluorine substituents in the β-position have similar effects on both the aromatic amino group ($\Delta pK_{a1} = 3.0$) and the aliphatic amino group ($\Delta pK_{a2} = 2.9$).

Conclusion

The preparation of β-fluoro- and β,β-difluorohistamine demonstrates the applicability of this approach to side-chain-fluorinated imidazoles. The prepared histamines **1** and **2** are now subjects of biological studies. We are continuing this work and are developing routes to other key imidazole derivatives, including fluorourocanic acids,[16] fluorohistidinols, and fluorohistidines.

Experimental Section

The NMR spectra were recorded at frequencies of 300.1 for ^{1}H, 75.5 for ^{13}C, and 282.2 MHz for ^{19}F spectra. Chemical shifts (δ) of protons and carbons are relative to TMS, the fluorine shifts are relative to $CFCl_3$, all in ppm. Coupling constants are presented in Hz. The ^{1}H and ^{19}F signals are presented as δ (intensity, multiplicity, coupling constants). The ^{13}C signals

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are written as δ (number of carbons if not one, multiplicity if not singlet, coupling constants, assignment); after a marker "off:" are given the signal characteristics obtained without decoupling of ^{1}H. The solvent is $CDCl_3$ unless otherwise specified. Melting points (mp) are not corrected. The low resolution MS (LRMS) were done with chemical ionization using ammonia gas. The high-resolution MS (HRMS) were done with FAB ionization with Xe gas. Elemental analyses were done by Atlantic Microlab, Inc. Silica gel Merck 60 (0.040−0.063 mm) was used for column chromatography, Uniplate GF (Analtech) was used for preparative TLC, Merck TLC plates Silica gel 60 F_{254} were used for analytical TLC; UV at 254 nm was used for detection. All reagents and dry solvents were purchased from Aldrich if not otherwise indicated and used without additional purification or drying. 4-Vinyl-1*H*-imidazole was prepared as described[19] previously by thermal decarboxylation (distillation in vacuo) of urocanic acid (Fluka) in yields of 35 to 65%. We found that rapid distillation is necessary to achieve optimum yield. 1-Tritryl-4-vinyl-1*H*-imidazole (**7**) was prepared by tritylation of 4-(hydroxymethyl)-1*H*-imidazole, followed by oxidation to give the aldehyde (**3**),[20] and subsequent Wittig olefination[21] or by direct tritylation of 4-vinyl-1*H*-imidazole.

4-(2-Bromo-1-fluoroethyl)-1-trityl-1*H*-imidazole (8). To a cooled (0 °C) and stirred solution of imidazole **7** (12.93 g, 38.4 mmol) dissolved in 370 mL of CH_2Cl_2 was added 9.9 mL (60.7 mmol) of $Et_3N{\cdot}3HF$. Any undissolved starting imidazole **7** went into solution after the addition of $Et_3N{\cdot}3HF$. After 15 min, 7.50 g (42.1 mmol) of NBS was added in portions. The mixture was allowed to warm to room temperature over 1−2 h and was stirred an additional 10 h. The mixture was then poured into a mixture of 200 mL of water, 200 mL of brine, and 20 mL of concentrated aqueous ammonia. The aqueous solution was extracted with 2 × 200 mL and then 2 × 50 mL of CH_2Cl_2, and the combined extracts were washed twice with 200 mL of brine. The organic layer was dried with $MgSO_4$ and evaporated to give 17.46 g of an oil. This was separated by column chromatography (100 g silica, CH_2Cl_2/ether 99/1 → 95/5 → 0/100) to give triphenylcarbinol (1.00 g, 10%) and the fluorobromo derivate **8** (12.40 g, 74%). ^{1}H NMR: 7.44 (1H, d, 1.2), 7.34−7.30 (9H, m), 7.16−7.09 (6H, m), 6.95 (1H, dd, 2.4, 1.2), 5.60 (1H, dt, 47.4, 6.0), 3.91−3.77 (2H, m). ^{13}C NMR: 142.05 (3C, Tr), 139.30 ($C2_{imi}$), 136.97 (d, 23.8, $C4_{imi}$), 129.71 (6CH, Tr), 128.21 (3CH, Tr), 128.14 (6CH, Tr), 120.64 (d, 5.7, $C5_{imi}$), 87.94 (d, 172.6, CHF), 75.62 (Tr), 32.83 (d, 29.1, CH_2-Br). ^{19}F NMR: −196.1 (dddd, 47.5, 20.3, 17.2, 2.4). Mp 127.5−130.0 °C (decomp. above 175 °C). HRMS calcd for $C_{24}H_{21}BrFN_2$: 435.0872, 437.0852. Found: 435.0872, 437.0846. Polar fractions (3.47 g) isolated from this column were subjected to a second chromatographic separation (60 g silica, CH_2Cl_2/ether 8/2) to give bromides **9** (1.02 g, 6%) and **10** (0.46 g, 2%).

4-(1-Fluoro-2-iodoethyl)-1-trityl-1*H*-imidazole (11). Using conditions similar to those used for bromofluorination, 674 mg (2.00 mmol) of **7**, 0.5 mL (3.07 mmol) of $Et_3N{\cdot}3HF$, and 497 mg (2.21 mmol) of NIS in 10 mL of CH_2Cl_2 was stirred for 15 h under protection from light. As above, the reaction mixture was extracted with brine, to which had been added a small amount of $Na_2S_2O_3$ to remove iodine. After extraction there was obtained 1.04 g of **11** estimated to be ca. 80−90% pure by ^{1}H NMR. ^{1}H NMR: 7.42 (1H, br s), 7.35−7.29 (9H, m), 7.15−7.06 (6H, m), 6.93 (1H, m, ΣJ 6), 5.49 (1H, dt, 47.3, 6.1), 3.71 (1H, ddd, 19.4, 10.5, 5.8), 3.63 (1H, ddd, 16.3, 10.4, 6.5). ^{13}C NMR: 141.99 (3C, Tr), 139.13 ($C2_{imi}$), 137.54 (d, 23.8, $C4_{imi}$), 129.67 (6CH, Tr), 128.14 (3CH, Tr), 128.07 (6CH, Tr), 120.49 (d, 5.6, $C5_{imi}$), 88.09 (d, 172.3, CHF), 75.53 (Tr), 6.35 (d, 28.6, CH_2I). ^{19}F NMR: −161.4 (dt, 47.3, 17.7). HRMS calcd for $C_{24}H_{21}FIN_2$: 483.0734. Found: 483.0716.

Attempted purification by column chromatography on silica gel (60 g, CH_2Cl_2/ether 100/0 → 95/5 → 2/8) gave nonpolar fractions consisting of uncharacterized impurities and a polar fraction of pure (^{1}H NMR) compound **12** (659 mg, 71%). Compound **12** was further purified by preparative TLC (ether/CH_2Cl_2 9/1) to give an analytical sample.

4-(1-Fluorovinyl)-1-trityl-1*H*-imidazole (13). To a solution of 2.05 g (4.71 mmol) of **8** in 65 mL of dry DMF was added 2.02 g (14.62 mmol) of K_2CO_3, and the mixture was stirred at 100 °C for 48 h. The mixture was then evaporated to dryness and partitioned between 100 mL of CH_2Cl_2 and 100 mL of brine. The organic layer was washed with 2 × 100 mL of brine, dried over $MgSO_4$, and evaporated. Separation by silica gel chromatography (100 g, petroleum ether/acetone, 9/1) gave 867 mg of a 20:1 mixture of the olefins **13** (50%) and **14** (2%) and 402 mg (20%) of starting compound **8**. Most of the bromoolefin **14** could be removed by crystallization of the mixture from cyclohexane, during which process **14** separates as the initially formed crystals. Attempts to carry out chromatographic separation were unsuccessful. Data for **13**: ^{1}H NMR: 7.45 (1H, dd, 3.2, 1.5), 7.35−7.29 (9H, m), 7.18−7.12 (6H, m), 7.00 (1H, m, Σ*J* 3.5), 5.16 (1H, dd, 50.9, 3.0), 4.68 (1H, dd, 18.1, 3.0). ^{13}C NMR: 158.86 (d, 241.2, CF), 141.98 (3C, Tr), 139.67 (d, 1.7, $C2_{imi}$), 134.18 (d, 40.1, $C4_{imi}$), 129.63 (6CH, Tr), 128.15 (3CH, Tr), 128.09 (6CH, Tr), 118.87 (d, 1.0, $C5_{imi}$), 87.43 (d, 17.3, CH_2), 75.56 (1C, Tr). ^{19}F NMR: −112.75 (ddd, 50.8, 18.0, 3.3). Mp 130.5−133.5 °C (cyclohexane, white crystals). Anal. Calcd for $C_{24}H_{19}FN_2$: C, 81.33; H, 5.40; N, 7.90. Found: C, 80.44; H, 5.44; N, 7.71. HRMS calcd for $C_{24}H_{19}FN_2$: 354.1532. Found: 354.1535.

4-(2-Bromo-1,1-difluoroethyl)-1-trityl-1*H*-imidazole (15). Using the procedure as described for the reaction with **7**, 858 mg (2.42 mmol) of olefin **13** was subjected to bromofluorination with 0.6 mL (3.68 mmol) of $Et_3N{\cdot}3HF$ and 472 mg (2.65 mmol) of NBS. Separation of the crude product (1.13 g) by column chromatography on silica gel (100 g, petroleum ether/acetone 9/1) gave 779 mg (71%) of bromide **15** and 42 mg (4%) of olefin **16**. Data for **15**: ^{1}H NMR: 7.46 (1H, dt, 1.5, 1.2), 7.37−7.32 (9H, m), 7.16−7.09 (7H, m), 3.95 (2H, t, 13.4). ^{13}C NMR: 141.80 (3C, Tr), 139.51 ($C2_{imi}$), 134.72 (t, 31.7, $C4_{imi}$), 129.69 (6CH, Tr), 128.31 (3CH, Tr), 128.19 (6CH, Tr), 120.96 (t, 2.8, $C5_{imi}$), 116.70 (t, 238.5, CF_2), 75.88 (Tr), 32.39 (t, 33.8, CH_2). ^{19}F NMR: −96.5 (t, 13.4). Mp 140.0−142.5 °C (cyclohexane, white crystals). Anal. Calcd for $C_{24}H_{19}BrF_2N_2$: C, 63.59; H, 4.22; N, 6.18. Found: C, 63.65; H, 4.33; N, 6.17.

2-[2-Fluoro-2-(1-trityl-1*H*-imidazol-4-yl)-ethyl]isoindole-2,5-dione (19). A solution of 645 mg (1.48 mmol) of bromide **8** and 323 mg (1.74 mmol) of potassium phthalimide in 9 mL of dry DMF was stirred at 100 °C for 24 h. The reaction mixture then was evaporated to dryness and partitioned between 100 mL of CH_2Cl_2 and 50 mL of brine. The organic layer was extracted with 2 × 50 mL of brine, dried over $MgSO_4$, and evaporated to give 858 mg of crude product. Separation by column chromatography (40 g, CH_2Cl_2/ether 100/0 → 95/5 → 9/1) afforded 186 mg of mixture olefins **13** and **14** (molar ration 92:8 equal to yields 32% **13**, 3% **14**), 119 mg (46.3%) of phthalimide, and 364 mg (49%) of substitution product **19**. ^{1}H NMR: 7.87−7.80 (2H, m), 7.74−7.67 (2H, m), 7.46 (1H, d, 1.4), 7.35−7.27 (9H, m), 7.15−7.08 (6H, m), 7.01 (1H, dd, 1.4, 3.1), 5.78 (1H, ddd, 49.5, 8.9, 3.8), 4.49 (1H, ddd, 14.3, 12.0, 9.0), 4.09 (1H, ddd, 27.9, 14.4, 3.8). ^{13}C NMR: 167.76 (2CO), 141.95 (3C, Tr), 139.24 ($C2_{imi}$), 136.40 (d, 21.7, $C4_{imi}$), 133.85 (2CH, Ph), 131.83 (2C, Ph), 129.56 (6CH, Tr), 128.02 (3CH, Tr), 127.97 (6CH, Tr), 123.20 (2CH, Ph), 120.45 (d, 6.3, $C5_{imi}$), 85.60 (d, 171.8, CHF), 75.44 (Tr), 41.11 (d, 26.9, CH_2). ^{19}F NMR: −175.6 (dddd, 49.6, 27.9, 11.7, 3.2). Mp 190−192 °C (ethanol, light yellow crystals). Anal. Calcd for $C_{32}H_{24}FN_3O_2$: C, 76.63; H 4,82; N, 8.38. Found: C, 76.34; H; 5.06, N, 8.35. HRMS calcd for $C_{33}H_{24}FN_3O_2$: 502.1931. Found: 502.1924.

2-[2-Fluoro-2-(1*H*-imidazol-4-yl)-ethyl]isoindole-1,3-dione (20). A mixture of 156 mg (311 μmol) of **19** was stirred in 7 mL of methanol and 0.8 mL of concentrated HCl at 50 °C for 2 h. The mixture was cooled to room temperature and, after addition of 10 mL of water, was evaporated to dryness. The resulting solid was partitioned between 5 mL of water and 5 mL of CH_2Cl_2. The aqueous phase was extracted with 2 × 2 mL CH_2Cl_2 and evaporated to dryness. There was obtained

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55 mg (68%) of compound **20** as the solid hydrochloride with a purity of ca. 80% (^{1}H NMR). ^{1}H NMR in CD_3OD: 9.06 (1H, d, 1.5), 7.90−7.79 (5H, m), 6.00 (1H, ddd, 45.9, 6.9, 5.4), 4.37 (1H, td, 14.4, 6.9), 4.24 (1H, ddd, 20.1, 14.4, 5.4). ^{13}C NMR in CD_3OD: 169.30 (2C, C=O), 137.13 ($C2_{imi}$), 135.91 (2CH, Ph), 133.23 (2C, Ph), 130.74 (d, 23.5, $C4_{imi}$), 124.60 (2CH, Ph), 120.06 (d, 6.2, $C5_{imi}$), 83.62 (d, 174.6, CHF), 41.53 (d, 28.8, CH_2). ^{19}F NMR in CD_3OD: −179.7 (dddd, 46.2, 20.2, 14.1, 3.1). HRMS calcd for $C_{13}H_{11}FN_3O_2$: 260.0835. Found: 260.0845.

2-Fluoro-2-(1-trityl-1*H*-imidazol-4-yl)ethylamine (21). To 150 mg (299 μmol) of **19** suspended in 10 mL of ethanol contained in a pressure ampule was added 20 μL (516 μmol) of 80% aqueous hydrazine hydrate. The tube was closed and the mixture was stirred at 85 °C at which time the mixture became homogeneous. After 1.5 h there remained starting **19** so an additional 60 μL (1.55 mmol) of hydrazine hydrate was added. After an additional 2 h, a solid was formed, and the reaction was allowed to cool to room temperature. The mixture was evaporated to dryness and extracted with 3 × 15 mL of CH_2Cl_2. The extracts were combined and evaporated to give 96 mg of solid amine **21** in a purity of ca. 80% (^{1}H NMR).

4-(2-Azido-1,1-difluoroethyl)-1-trityl-1*H*-imidazole (23). The procedure was similar to that used for the reaction with potassium phthalimide. A mixture of 441 mg (0.97 mmol) of bromide **15** and 252 mg (3.88 mmol) of NaN_3 was stirred in 6 mL of dry DMSO and 0.12 mL of water.[23] After 3 days at 80 °C there was 50% conversion as determined by ^{1}H NMR. Further reaction for 3 days at 110 °C resulted in 95% conversion. The mixture was partitioned between 50 mL of CH_2Cl_2 and 200 mL of brine. The aqueous phase was extracted with 50 mL of CH_2Cl_2, and the combined organic phases were extracted with 2 × 100 mL of brine, dried over $MgSO_4$, and evaporated to dryness. The obtained crude product (499 mg) was purified by preparative TLC (petroleum ether/acetone 75/15). There was obtained 360 mg (89%) of azide **23**. ^{1}H NMR: 7.48 (1H, dd, 2.7, 1.2), 7.36−7.31 (9H, m), 7.19 (1H, dd, 3.0, 1.5), 7.15−7.10 (6H, m), 3.88 (2H, t, 13.1). ^{13}C NMR: 141.71 (s, 3C, off: m, ΣJ 17.5, Tr), 139.62 (s, off: dd, 212.1, 7.3, $C2_{imi}$), 134.59 (t, 31.2, off: tddt, 31.2, 11.1, 8.0, 1.6, $C4_{imi}$), 129.56 (s, 6CH, off: dm, 161, Σ*J* 14.5, Tr), 128.25 (s, 3CH, off: dt, 161.5, 7.5, Tr), 128.12 (s, 6CH, off: dm, 162, Σ*J* 10.5, Tr), 120.81 (t, 4.3, off: dq, 194.5, 4.0, $C5_{imi}$), 117.97 (t, 239.6, off: ttd, 239.6, 3.9, 0.9, CF_2), 75.88 (s, off: m), 53.85 (t, 31.0, off: tt, 144.9, 31.0, CH_2). ^{19}F NMR −99.7 (t, 12.8). Mp 120.5−122.0 °C (methanol, white crystals). Anal. Calcd for $C_{24}H_{19}F_2N_5$: C, 69.39; H, 4.61; N, 16.86. Found: C, 69.48; H, 4.60; N, 16.69.

4-(2-Azido-1-fluoroethyl)-1-trityl-1*H*-imidazole (22). A solution of 2.00 g (4.59 mmol) of **8** and 900 mg (13.8 mmol) of NaN_3 in 60 mL of dry DMF was stirred at 100 °C for 24 h. Workup as for **23** gave 1.84 g of crude product that was separated on column chromatography (100 g, petroleum ether/acetone 9/1) to give 125 mg of mixture olefins **13** and **14** (molar ratio 56:44, 4% **13**, 3% **14**) and 1.59 g (87%) of azide **22**. ^{1}H NMR: 7.47 (1H, d, 1.5), 7.33−7.25 (9H, m), 7.17−7.10 (6H, m), 7.01 (1H, dd, 2.7, 1.5), 5.54 (1H, ddd, 48.6, 7.5, 3.9), 3.84 (1H, ddd, 17.1, 13.5, 7.5), 3.67 (1H, ddd, 26.0, 13.4, 3.8). ^{13}C NMR: 141.77 (3C, Tr), 139.10 ($C2_{imi}$), 136.23 (d, 22.9, $C4_{imi}$), 129.40 (6CH, Tr), 127.93 (3CH, Tr), 127.86 (6CH, Tr), 120.37 (d, 5.9, $C5_{imi}$), 87.67 (d, 171.3, CHF), 75.34 (Tr), 53.27 (d, 25.4, CH_2). ^{19}F NMR: −175.3 (dddd, 48.5, 25.9, 17.4, 2.6). Mp 107−108 °C (cyclohexane, white crystals). Anal. Calcd for $C_{24}H_{20}FN_5$: C, 72.53; H, 5.07; N, 17.62. Found: C, 72.62; H, 5.16; N, 17.65.

2,2-Difluoro-2-(1-trityl-1*H*-imidazol-4-yl)-ethylamine (24). To a solution of 329 mg (0.792 mmol) of the azide **23** in 60 mL of methanol under a nitrogen atmosphere was added 152 mg of Pd/C (10%). The flask was attached to a hydrogen-filled balloon and the reaction was vigorously stirred for 2 h. After this time, TLC (CH_2Cl_2/ether 9/1) indicated the absence of starting material. The reaction mixture was filtered through a pad of Celite, and the Celite pad was washed with additional methanol. Evaporation of the combined filtrate and methanol wash gave 319 mg of **24**. Purification by column chromatography (20 g, CH_2Cl_2 → CH_2Cl_2/CH_3OH 9/1) produced 304 mg (99%) of pure amine **24** as a white solid. ^{1}H NMR: 7.44 (1H, q, 1.2), 7.38−7.33 (9H, m), 7.15−7.09 (7H, m), 3.34 (2H, t, 14.3), 1.88 (2H, br s). ^{13}C NMR: 141.85 (3C, Tr), 139.40 ($C2_{imi}$), 135.98 (t, 32.2, $C4_{imi}$), 129.61 (6CH, Tr), 128.25 (3CH, Tr), 128.15 (6CH, Tr), 120.39 (t, 4.3, $C5_{imi}$), 119.30 (t, 236.7, CF_2), 75.76 (Tr), 47.39 (t, 29.3, CH_2). ^{19}F NMR: −102.7 (t, 14.1). Mp 124−125 °C. HRMS calcd for $C_{24}H_{22}F_2N_3$: 390.1782. Found: 390.1782.

2-Fluoro-2-(1-trityl-1*H*-imidazol-4-yl)ethylamine (21). Using an analogous procedure as above for **24**, 884 mg of azide **22** in 120 mL of methanol was reduced over 450 mg Pd/C for 2 h. Crude product (830 mg, white solid) was purified by column chromatography (54 g, CH_2Cl_2/CH_3OH 17/3) to give 826 mg (97%) of amine **21** as a colorless oil. ^{1}H NMR: 7.43 (1H, d, 1.5), 7.36−7.30 (9H, m), 7.16−7.09 (6H, m), 6.91 (1H, ddd, 2.1, 1.5, 0.9), 5.39 (1H, ddd, 48.9, 6.6, 4.2), 3.26 (1H, ddd, 19.5, 14.1, 6.6), 3.16 (1H, ddd, 24.3, 14.1, 4.2), 1.81 (2H, bs). ^{13}C NMR: 141.91 (3C, Tr), 138.93 ($C2_{imi}$), 137.76 (d, 23.5, $C4_{imi}$), 129.42 (6CH, Tr), 127.89 (3CH, Tr), 127.84 (6CH, Tr), 119.87 (d, 5.9, $C5_{imi}$), 90.32 (d, 166.4, CHF), 75.23 (Tr), 45.43 (d, 24.8). ^{19}F NMR: −179.1 (dddd, 49.0, 24.4, 19.7, 2.6). HRMS calcd for $C_{24}H_{23}FN_3$: 372.1876. Found: 372.1881. If higher pressure is used (276 kPa, overnight) the product of the reaction is **2-(1-trityl-1*H*-imidazol-4-yl)ethylamine (tritylated histamine).** ^{1}H NMR: 7.35−7.26 (9H, m), 7.15−7.07 (6H, m), 7.02 (1H, s), 6.62 (1H, s), 3.12 (2H, t, 7.2), 2.85 (2H, t, 7.2). HRMS calcd for $C_{24}H_{24}N_3$: 354.1970. Found: 354.1975.

2,2-Difluoro-2-(1*H*-imidazol-4-yl)ethylamine (2) as dihydrochloride. A solution of 303 mg (778 μmol) of amine **24** in 20 mL of methanol was cooled to 0 °C and treated with 1 mL of hydrochloric acid (12 N diluted 1:5 with water). After stirring 1 h at 0 °C and 6 h at room temperature, TLC (CH_2Cl_2/CH_3OH 9/1) indicated no starting material remained. The mixture was evaporated to dryness at room temperature, and the resulting solid was partitioned between 15 mL of water and 10 mL of CH_2Cl_2. The aqueous layer was extracted with 2 × 10 mL of CH_2Cl_2 and then lyophilized. After additional drying in high vacuum at room temperature and there was obtained 149 mg (87%) dihydrochloride of difluorohistamine **2** as an off white solid. ^{1}H NMR in CD_3OD: 9.09 (1H, d, 1.3), 8.12 (1H, td, 1.8, 1.3), 4.01 (2H, dd, 15.7, 15.2). ^{13}C NMR in CD_3OD: 138.58 ($C2_{imi}$), 127.49 (t, 32.2, $C4_{imi}$), 121.48 (t, 6.1, $C4_{imi}$), 115.95 (t, 241.1, CF_2), 44.44 (t, 26.3, CH_2). ^{19}F NMR in CD_3OD: −97.8 (td, 15.4, 1.7). Mp 175−200 °C (with slow decomposition). HRMS: calcd for $C_5H_8F_2N_3$: 148.0686. Found 148.0691. Anal. Calcd for $C_5H_9Cl_2F_2N_3$: C, 27.29; H, 4.23; N, 19.10. Found: C, 27.53; H, 4.12; N, 18.71.

2-Fluoro-2-(1*H*-imidazol-4-yl)ethylamine (1) as Dihydrochloride. The same conditions as described for **2** above were used. In addition, hydrolyses were carried out in HCl (12 N or diluted 1:5 with water) without using methanol as a cosolvent. Under all conditions examined there was obtained a mixture of compounds that contained as a major component (60−80%) dihydrochloride of **1.** All atempts at further purification led to material of lower purity. ^{1}H NMR in CD_3OD: 9.12 (1H, d, 1.2), 7.95 (1H, ddd, 2.7, 1.5, 0.6), 6.15 (1H, ddd, 48.3, 9.5, 3.0), 3.76 (1H, td, 14.1, 9.4), 3.63 (1H, ddd, 31.1, 14.1, 3.5). ^{13}C NMR in CD_3OD: 137.67 ($C2_{imi}$), 129.35 (d, 22.7, $C4_{imi}$), 120.81 (d, 5.9, $C5_{imi}$), 83.61 (d, 172.7, CHF), 43.26 (d, 23.6, CH_2). ^{19}F NMR in CD_3OD: −179.6 (m, ΣJ 110). HRMS calcd for $C_5H_9N_3F$: 130.0781. Found 130.0781.

Supporting Information Available: Details for the preparation of compound **5**, ^{1}H, ^{13}C, ^{19}F and mass spectral data for **16**, and ^{1}H, ^{13}C, and mass spectral data for **5, 9**, **10**, **12**, and **17**: details for examination of the reactivities of **17** and **18** toward Et_3N. This information is available free of charge via the Internet at http://pubs.acs.org.

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