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Preparation of β-fluoro- and β,β-difluoro-histidinols

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This manuscript is dedicated to Professor Eric Banks on the occasion of his 70th birthday

Abstract

Nucleophilic attack of azide on 2-bromo-3-fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propan-1-ol (**1a**) in aprotic solvent occurs on the 2-position to give the 2-azido derivative (**2a**). Reduction of azide and removal of the trityl group produces β-fluorohistidinol (**6a**). Elimination of HBr from **1a** followed by "FBr" addition to the resulting double bond gives 2-bromo-3,3-difluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propan-1-ol (**1b**). Nucleophilic attack of azide followed by reduction and removal of the trityl group, as for the preparation of **6a**, gives β,β-difluorohistidinol (**6b**). Initial attempts, under a variety of conditions, to oxidize the fluorinated histidinol precursors to carboxylic acids have not been successful.

Keywords: "FBr" addition; Imidazole analogues; Histidine biosynthesis; Solvent effects on halogen mobility

1. Introduction

The essential amino acid histidine is formed in microorganisms and plants by a two-step oxidation of 2-amino-1-(3*H*-imidazol-4-yl)-propane-1,3-diol (histidinol), the immediate biosynthetic precursor. Analogues of histidinol thus have attracted interest as potential herbicidal agents (for example, see [1]). In addition, histidinol has been shown to have unusual and potentially beneficial properties that relate to drug response. For example, Warrington et al. demonstrated that L-histidinol protects normal cells from antineoplastic drugs while enhancing the toxicity of these same drugs to cancer cells [2]. L-Histidinol also has been found to reverse drug resistance [3], and further, has been shown, on its own, to have antineoplastic activity against certain tumors [4]. We recently have developed procedures for the preparation of side-chain fluorinated analogues of biologically important imidazoles and indoles, including α- and β-fluorourocanic acid [5,6], *β*-fluoro- and *β*,*β*-difluorohistamines [7], and a series of tryptamines [8]. We report herein the syntheses of *β*-fluoro- and *β*,*β*-difluorohistidinols (**6a** and **b**). These compounds are designed to probe effects of fluorine substitution on the final side-chain oxidation in histidine biosynthesis. Their toxicities will be examined as well as their effects on activities of chemotherapeutic agents.

2. Chemistry

The starting point for our synthesis (Scheme 1) of *β*-fluorohistidinols is racemic (2*S**, 3*R**) propanol **1a**, which we had prepared previously as an intermediate in our synthesis of *β*-fluorourocanic acid [6]. Treatment of **1a** with NaN_3 in DMF at 110 °C leads to formation of azide **2a** (2*R**,3*R**) in about 30% yield, the result of S_N2 substitution. In addition, *E*-alkene **3** is formed in similar yield, a result of anti elimination. This competing elimination reaction represents no serious problem because **3** is required for the synthesis of **6b**. Trace amounts of compounds **4** also were observed. We found that changing temperature (80 or 130 °C) or using DMSO instead DMF had almost no influence on the ratio **2a**:**3** or on the yields. However, when the substitution was done in dry methanol the course of the reaction was dramatically different. In this solvent, the fluorine atom is substituted instead of bromine, producing a mixture of the two diastereoisomeric azides **4a** and **b** with no traces of compounds **2a** or **3** being detected. The poor leaving group ability of fluoride, particularly in nonprotic solvents, favors S_N2 substitution or E_2 elimination of bromide to give **2a** and **3**. In methanol, apparently hydrogen bonding is sufficient to lead to facile loss of fluoride with formation of a stabilized carbonium ion intermediate, producing the diasteromeric mixture of **4a** and **b** (for a discussion and references to issues of fluoride reactivity, see [9]).

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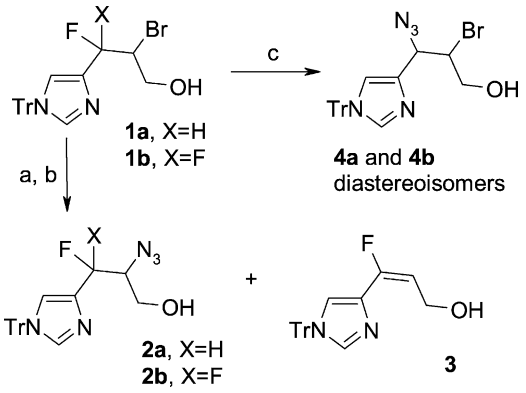
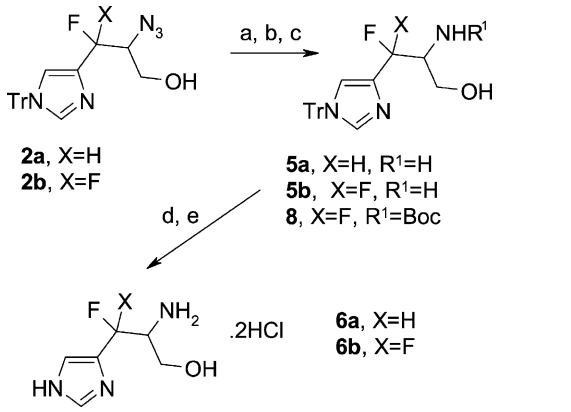


Scheme 1. Substitution of bromine with NaN_3. (a) **1a**, 110 °C, 29% **2a**, 37% **3**; (b) **1b**, 105 °C, DMSO with H_2O, 7 days, 73% **2b** and (c) **1a**, methanol, 50 °C, 3 days, 25% **4a**, 18% **4b**.

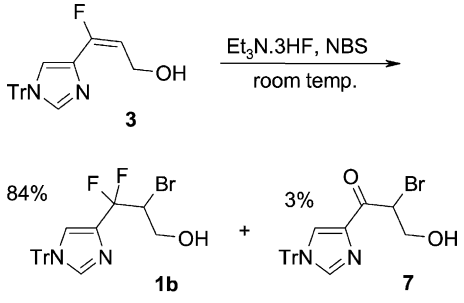


Scheme 3. (a) **2a**, H_2/Pd, 98% **5a**; (b) **2b**, H_2/Pd, 87% **5b**; (c) **2a**, Boc_2O, H_2/Pd, 98% **8**; (d) **5a**, HCl/MeOH, 95% **6a** and (e) **5b**, HCl/MeOH, 84% **6b**.

Using the usual conditions [10] for the addition of "FBr," alkene **3** was converted to difluorobromo derivative **1b**. Ketone **7** was found as a byproduct of this reaction (Scheme 2). Analogous byproducts have been previously reported in "FBr" additions to fluoroalkenes [11]. In this report, ketone formation was ascribed to hydrolysis of originally formed adducts during chromatography on silica during isolation. However, we observed no formation of ketone 7 during chromatography of **1b**. In light of the fact that we isolated products from "HOBr" addition as byproducts of "FBr" addition to vinylimidazole [7], we believe that origin of ketone **7** lies in "HOBr" addition to alkene **3** followed by spontaneous HF loss.

The bromine present in propanol **1b** was replaced with azide to give **2b** using conditions that enhance the reactivity of β,β-difluorobromides toward nucleophilic displacement [12]. The azides **2a** and **b** were then reduced by catalytic hydrogenation to give amines **5a** and **b**. Azide **1b** was also reduced in presence of Boc_2O to give **8**. A subsequent acidic detritylation produced fluorohistidinol **6a** and difluorohistidinol **6b** (Scheme 3).

Our intention to use this approach to also prepare fluorinated histidines has been thwarted to date. We made several attempts to oxidize the hydroxymethyl group of **2b** to a carboxylic acid (histidine derivative). In general, we found that oxidation either does not occur or the reaction



Scheme 2. "FBr" addition.

conditions result in loss of fluorine and decomposition. We obtained similar results in attempts to oxidize **8**. We are continuing in these efforts, and are also exploring alternative approaches to the amino acids.

3. Summary

Fluorinated histidinols **6a** and **b** were prepared in good yields starting from previously prepared bromofluoroimidazolylpropanol **1a**. Selective displacement of bromine with azide was a critical step in this sequence. This was achieved cleanly using dipolar aprotic solvent. However, use of protic solvent led exclusively to fluoride displacement. This example of solvent control of chemoselectivity is quite impressive, and we feel it might be incorporated effectively into other synthetic strategies. Although we have not yet been able to prepare histidine derivatives by the approach presented here, the histidinol derivatives are themselves of considerable biological interest, and appropriate studies are underway.

4. Experimental details

The ^1H, ^{19}F and ^{13}C NMR spectra were recorded at frequencies of 300, 282 and 76 MHz, respectively. Chemical shifts are given in ppm relative to TMS for ^1H and ^{13}C and to $CFCl_3$ for ^{19}F NMR unless otherwise mentioned. Melting points were taken in Unimelt capillary melting point apparatus and were not corrected. High resolution mass spectra (HRMS) were obtained using 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. If not otherwise indicated, all other reagents and dry solvents were purchased and used without additional purification or drying.

4.1. 2-Bromo-3,3-difluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**1b**)

A solution of 911 mg (2.37 mmol) of alkene **3** was cooled to 0 °C and 0.6 ml (3.68 mmol) of $Et_3N{\cdot}3HF$ was added. After 30 min 466 mg (2.62 mmol) of NBS was added. The mixture was stirred at 0 °C for 30 min, then removed from the cooling bath and allowed to stir overnight at RT. The reaction mixture was partitioned between brine and CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, evaporated to dryness and separated by silica gel column chromatography using CH_2Cl_2/Et_2O as eluent to give 958 mg (84%) of **1b** and 35 mg (3%) of **7**. ^{1}H NMR ($CDCl_3$) δ: 7.48 (s, 1H), 7.39–7.31 (m, 9H), 7.16–7.08 (m, 7H), 5.02 (bs, 1H, OH), 4.53 (m, 1H, Σ *J* 34.1, CHBr), 4.17 (dd, 1H, 12.9, 4.2), 4.00 (dd, 1H, 12.8, 5.3). ^{13}C NMR ($CDCl_3$) δ: 141.54 (3C), 139.24 ($C2_{Imi}$), 134.00 (dd, 33.7, 31.2, $C4_{Imi}$), 129.60 (6CH), 128.40 (3CH), 128.24 (6CH), 121.97 (t, 4.5, $C5_{Imi}$), 117.94 (dd, 242.0, 241.6, CF_2), 76.08 (Tr), 62.05 (t, 3.6, CH_2), 54.61 (dd, 30.4, 27.4, CHBr); mp 159.5–160.5 °C (from cyclohexane). Anal. Calcd. for $C_{25}H_{21}BrF_2N_2O$: C, 62.12; H, 4.38; N, 5.80. Found: C, 62.37; H, 4.37; N, 5.92. HRMS (FAB^+): Calcd. for $C_{25}H_{22}BrF_2N_2O$ (MH^+) doublet: 483.0884, 485.0863. Found: 483.0855, 485.0864.

4.2. 2-Bromo-3-hydroxy-1-(1-trityl-1H-imidazol-4-yl)-propan-1-one (**7**)

^{1}H NMR ($CDCl_3$) δ: 7.71 (d, 1H, 1.2), 7.50 (d, 1H, 1.2), 7.39–7.33 (m, 9H,), 7.13–7.08 (m, 6H), 5.42 (dd, 1H, 6.9, 4.8), 4.23–4.03 (m, 2H), 3.29 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ: 189.36 (CO), 141.33 (3C), 139.57 ($C2_{Imi}$), 137.94 ($C4_{Imi}$), 129.59 (6CH), 128.51 (3CH), 128.34 (6CH), 127.72 ($C5_{Imi}$), 76.45 (Tr), 62.97 (CH_2), 47.47 (CHBr); mp 144.5–145.5 °C (from cyclohexane). Anal. Calcd. for $C_{25}H_{21}BrN_2O_2$: C, 65.09; H, 4.59; N, 6.07; Br, 17.32. Found: C, 65.14; H, 4.61; N, 6.02; Br, 17.21.

4.3. 2-Azido-3-fluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**2a**)

A mixture of 999 mg (2.15 mmol) of **1a** [6] and 279 mg of NaN_3 (4.29 mmol) in 30 ml of dry DMF was stirred at 110 °C for 14 h. The mixture was evaporated to dryness and the resulting solid was partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, filtered and evaporated to give crude product. Silica gel column chromatography using CH_2Cl_2/MeOH afforded 306 mg (37%) of olefin **3**. The physical and spectral properties of **3** were identical with those reported previously [6]. The desired azide **2a** was obtained as a non-crystalline solid (262 mg, 29%). ^{1}H NMR ($CDCl_3$) δ: 7.47 (d, 1H, 1.5), 7.38–7.32 (m, 9H), 7.15–7.09 (m, 6H), 7.00 (dd, 1H, 2.2, 1.5), 5.55 (dd, 1H, 46.7, 7.1), 3.96 (m, 1H, Σ *J* 32), 3.75 (dd, 2H, 4.4, 0.9), 3.65 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 141.79 (3C), 139.33 (d, 7.1, J_{CH} 211.4, $C2_{Imi}$), 135.85 (d, 24.0, $C4_{Imi}$), 129.57 (6CH), 128.21 (3CH), 128.12 (6CH), 121.18 (d, 6.0, J_{CH} 192.8 d, $C5_{Imi}$), 88.67 (d, 173.0, J_{CH} 154.2 d, CHF), 75.75 (Tr), 65.36 (d, 21.7, J_{CH} 142.4 d, CHN_3), 60.97 (d, 5.1, J_{CH} 143.5 t, CH_2OH). ^{19}F NMR ($CDCl_3$) δ: −178.8 (dd, 47.0, 12.2). HRMS (FAB^+): Calcd. for $C_{25}H_{22}FN_5O$ (MH^+): 428.1887. Found: 428.1880.

4.4. 2-Azido-3,3-difluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**2b**)

A mixture of 818 mg (1.69 mmol) of **1b**, 721 mg (11.1 mmol) of NaN_3, 1.5 ml water and 40 ml of Me_2SO was stirred at 105 °C for 7 days. The mixture was poured into 400 ml brine and 200 ml of water and the product was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was subjected to silica gel column chromatography using petrol ether/Et_2O as eluent to afford 551 mg (73%) of **2b**. ^{1}H NMR ($CDCl_3$) δ: 7.45 (q, 1H, 1.2), 7.40–7.31 (m, 9H), 7.15 (q, 1H, 1.5), 7.13–7.07 (m, 6H), 4.65 (br s, 1H), 4.47–4.35 (m, 1H), 3.56–3.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 141.68 (3C), 139.15 ($C2_{imi}$), 135.20 (t, 31.9, $C4_{imi}$), 129.64 (6CH), 128.43 (3CH), 128.28 (6CH), 120.88 (t, 3.8, $C5_{imi}$), 117.03 (dd, 241.1, 243.1, CF_2), 76.09 (Tr), 73.24 (dd, 27.0, 29.6, CHN_3), 50.78 (t, 3.3, CH_2). ^{19}F NMR ($CDCl_3$) δ: −102.1 (dd, 1F, 266.5, 6.5), −108.1 (dd, 1F, 266.5, 13.8). M.p. 118–119 °C (from Et_2O). Anal. Calcd. for $C_{25}H_{21}F_2N_5O$: C, 67.41; H, 4.75; N, 15.72. Found: C, 67.42; H, 4.88; N, 15.76. HRMS (FAB^+): Calcd. for $C_{25}H_{22}F_2N_5O$ (MH^+): 446.1792. Found: 446.1797.

4.5. 3-Azido-2-bromo-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**4a**)

A mixture of 950 mg (2.04 mmol) of **1a** and 686 mg (10.6 mmol) of NaN_3 in 60 ml of dry methanol was stirred at 50 °C for 17 h. The mixture was evaporated to dryness and the resulting solid was partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give crude product. Silica gel column chromatography using CH_2Cl_2/MeOH afforded 252 mg of **4a** (25%) and 174 mg (18%) of **4b**. ^{1}H NMR ($CDCl_3$) δ: 7.48 (d, 1H, 1.2), 7.38–7.32 (m, 9H), 7.18–7.10 (m, 6H), 6.91 (d, 1H, 1.2), 5.00 (d, 1H, 6.0), 4.74 (br s, 1H), 4.46 (q, 1H, 6.0), 4.02–3.98 (m, 2H). ^{13}C NMR ($CDCl_3$) *d*: 141.83 (3C), 139.05 (dd, J_{CH} 211.4, 7.0, $C2_{Imi}$), 135.56 ($C4_{Imi}$), 129.65 (6CH), 128.27 (3CH), 128.17 (6CH), 121.38 (d, J_{CH} 192.5, $C5_{Imi}$), 75.74 (Tr), 63.60 (t, J_{CH} 146.7, CH_2), 61.75 (d, J_{CH} 143.5, CHN_3), 55.85 (d, J_{CH} 153.4, CHBr). HRMS (FAB^+): Calcd. for $C_{25}H_{23}BrN_5O$ (MH^+) doublet: 488.1086, 490.1066. Found: 488.1087, 490.1059.

4.6. 3-Azido-2-bromo-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**4b**)

^{1}H NMR ($CDCl_3$) δ: 7.48 (d, 1H, 1.5), 7.37–7.31 (m, 9H), 7.17–7.11 (m, 6H), 6.60 (d, 1H, 1.5), 5.48 (bs, 1H, OH), 5.07

(d, 1H, 4.9), 4.35 (dt, 1H, 6.7, 4.8), 3.96 (dd, 1H, 12.6, 4.5), (1H, 12.3, 6.9). ^{13}C NMR ($CDCl_3$) δ: 141.77 (3C), 139.00 (d, J_{CH} 211.5 $C2_{Imi}$), 136.31 ($C4_{Imi}$), 129.60 (6CH), 128.21 (3CH), 128.13 (6CH), 121.03 (d, J_{CH} 192.7 $C5_{Imi}$), 75.74 (Tr), 63.34 (t, J_{CH} 145.7, CH_2), 61.02 (d, J_{CH} 143.1, CHN_3), 57.42 (d, J_{CH} 152.4, CHBr). HRMS (FAB^+): Calcd. for $C_{25}H_{23}BrN_5O$ doublet: 488.1086, 490.1066. Found: 488.1070, 490.1070.

*4.7. 2-Amino-3-fluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**5a**)*

Azide **2a** (453 mg, 1.06 mmol) was dissolved in 50 ml of methanol and 128 mg of catalyst (10% Pd on C) was added. The atmosphere was changed to hydrogen (balloon) and the mixture was stirred at room temperature until starting azide **2a** was consumed (TLC; 1–3 h). The catalyst was filtered through a pad of celite and pure amine **5a** (419 mg, 98%) was obtained after evaporation of solvent. ^{1}H NMR ($CDCl_3$) δ: 7.43 (d, 1H, 1.2), 7.36–7.30 (m, 9H), 7.14–7.08 (m, 6H), 6.95 (dd, 1H, 2.7, 1.2), 5.36 (dd, 1H, 47.5, 6.2), 3.79–3.39 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 142.02 (3C), 139.33 ($C2_{imi}$), 136.63 (d, 23.3, $C4_{imi}$), 129.68 (6CH), 128.26 (3CH), 128.19 (6CH), 121.49 (d, 6.4), 89.77 (d, 169.0, CHF), 75.68 (Tr), 62.19 (d, 4.4, CH_2OH), 55.42 (d, 23.0, $CHNH_2$). ^{19}F NMR ($CDCl_3$) δ: −103.8 (dd, 1F, 48.0, 13.4). HRMS (FAB^+): Calcd. for $C_{25}H_{25}FN_3O$ (MH^+): 402.1903. Found: 402.1982.

*4.8. 2-Amino-3,3-difluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**5b**)*

Azide **2b** (215 mg, 483 μmol) was dissolved in 20 ml of methanol and 114 mg of catalyst (10% Pd on C) was added. The atmosphere was changed to hydrogen (balloon) and the mixture was stirred at room temperature until starting azide **2** disappeared (TLC; 1–3 h). The catalyst was filtered through a pad of Celite and pure amine **5b** (176 mg, 87%) was obtained after evaporation of solvent. ^{1}H NMR (CD_3OD) δ: 7.43 (s, 1H), 7.37–7.27 (m, 9H), 7.13–7.09 (m, 7H), 4.13 (ddt, 1H, 13.0, 9.2, 5.7), 2.94 (d, 2H, 5.7), 2.53 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ: 141.67 (3C), 139.45 ($C2_{imi}$), 134.60 (t, 31.9, $C4_{imi}$), 129.59 (6CH), 128.12 (9CH), 121.09 (br s, $C5_{imi}$), 118.42 (t, 242.2, CF_2), 75.83 (Tr), 70.41 (t, 28.8, $CHNH_2$), 39.94 (br s, CH_2). ^{19}F NMR ($CDCl_3$) δ: −103.9 (dd, 1F, 264.0, 9.2), −107.5 (1F, 264.0, 13.0). HRMS (FAB^+): Calcd. for $C_{25}H_{23}F_2N_3O$ (MH^+): 420.1809. Found: 420.1893.

*4.9. 2,2-Difluoro-1-hydroxymethyl-2-(1-trityl-1H-imidazol-4-yl)-ethyl]-carbamic acid tert-butyl ester (**8**)*

To a solution of 212 mg (0.476 mmol) of azide **2b** and 0.123 ml (0.575 mmol) of Boc_2O dissolved in 6 ml of EtOAc was added 30 mg of 10% Pd on C. This was stirred in an atmosphere of H_2 (balloon) for 4 h. The catalyst was filtered through a Celite pad and the filtrate was evaporated to dryness. Pure **8** (243 mg, 98%) was obtained by preparative TLC (CH_2Cl_2/Et_2O). ^{1}H NMR ($CDCl_3$) δ: 7.43 (s, 1H), 7.37–7.32 (m, 9H), 7.14–7.08 (m, 7H), 5.17 (br s, 1H), 4.70 (br s, 1H), 4.27 (m, 1H, ΣJ 37), 3.61 (m, 1H, ΣJ 33), 3.23 (m, 1H, ΣJ 33), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 156.51 (CO), 141.69 (3C), 139.11 ($C2_{Imi}$), 135.27 (t, 31.9, $C4_{Imi}$), 129.56 (6CH), 128.24 (3CH), 128.14 (6CH), 120.85 (t, 3.9, $C5_{Imi}$), 117.88 (t, 242.2, CF_2), 79.30 (CMe_3), 75.87 (Tr), 72.45 (t, 27.4, CH), 40.73 (CH_2), 28.25 (3Me). ^{19}F NMR ($CDCl_3$) δ: −103.9 (d, 1F, 265.9), −107.7 (dd, 1F, 265.9, 13.0). HRMS (FAB^+): Calcd. for $C_{30}H_{32}F_2N_3O_3$ (MH^+): 520.2412. Found: 520.2429.

*4.10. 2-Amino-3-fluoro-3-(1H-imidazol-4-yl)-propan-1-ol (**6a**) dihydrochloride*

To 165 mg (0.41 mmol) of the tritylation histidinol **5a** dissolved in 20 ml of methanol in a 50 ml round bottom flask and cooled to 0 °C was added 5 ml of 2N aqueous HCl. The mixture was stirred for 1 h at 0 °C and then overnight at room temperature. After the solvent MeOH was removed by rotary evaporation, the aqueous solution was washed with CH_2Cl_2. The aqueous layer on concentration by lyophilization to afford 87 mg (95%) of the pure product **6a**. ^{1}H NMR (CD_3OD) δ: 9.12 (s, 1H), 7.96 (dd, 3.3, 1.0, 1H), 6.10 (d, 9.0, 1H), 5.95 (d, 9.0, 1H), 4.16–3.83 (m, 2H), 3.82–3.71 (m, 2H), 3.59–3.51 (m, 2H). ^{13}C NMR (CD_3OD) δ: 136.50 (J_{CH} 120.4 d, 6.7 d, $C2_{imi}$), 121.67 (d, 8), 118.66 (d, 26.3), 84.60 (d, 172.0), 72.65 (d, 228.0), 59.44 (d, 5.2). ^{19}F NMR (CD_3OD/TFA) δ: −104.78 (dd, 1F, 48.0, 9.3).

*4.11. 2-Amino-3,3-difluoro-3-(1H-imidazol-4-yl)-propan-1-ol (**6b**) dihydrochloride*

To 102 mg (0.240 mmol) of tritylation histidinol **5b** dissolved in 15 ml of methanol in a 50 ml round bottom flask and cooled to 0 °C was added 4 ml of 2N aqueous HCl. The solution was stirred for 1 h at 0 °C and then overnight at room temperature. After evaporation of MeOH the aqueous layer was washed with CH_2Cl_2. The aqueous solution was lyophilized to produce 51 mg (84%) of the pure product **6b**. ^{1}H NMR (CD_3OD) δ: 9.22 (d, 1H, 1.4), 8.07 (td, 1H, 1.5, 1.4), 4.57 (dddd, 1H, 14.2, 9.6, 6.5, 3.3), 3.36 (dd, 1H, 13.5, 3.3), 3.09 (dd, 1H, 13.5, 9.6). ^{13}C NMR (CD_3OD) δ: 137.61 (J_{CH} 222.4 d, 6.7 d, $C2_{imi}$), 127.49 (t, 34.4, J_{CH} 10.5 d, 5.8 d, $C4_{imi}$), 121.33 (t, 5.4, J_{CH} 204.8 d, 5.5 d, $C5_{imi}$), 117.73 (t, 245.9, CF_2), 70.17 (dd, 31.6, 27.3, J_{CH} 146.1 d, $CHNH_2$), 40.25 (t, 3.4, J_{CH} 143.6 t, CH_2). ^{19}F NMR (CD_3OD) δ: −99.4 (dd, 1F, 275.4, 5.9), −110.1 (dd, 1F, 275.4, 13.7); mp 180–187 °C decomp. (from *i*PrOH). Anal. Calcd. for $C_6H_{11}Cl_2F_2N_3O$: C, 28.82; H, 4.43; N, 16.80; Cl, 28.35. Found: C, 28.86; H, 4.44; N, 16.61; Cl, 28.53.

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