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Synthesis of (*E*)- and (*Z*)-α,β-difluorourocanic acid

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Abstract

Horner–Emmons fluoroolefination of an aryl aldehyde followed by introduction of a second fluorine via "FBr" addition provides an original approach to the preparation of 1-alkyl-2-aryl-1,2-difluoroethenes. The utility of this procedure is demonstrated by the preparation of (*E* and *Z*)-α,β-difluorourocanic acid.
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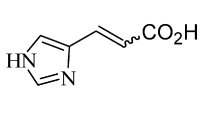
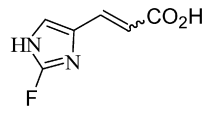
Keywords: Fluoroimidazole; Urocanic acid; Fluoroolefins; FBr addition; Regiochemistry

1. Introduction

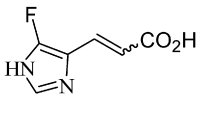
(*E*)-Urocanic acid **1a** is elaborated in vivo by histidine ammonia lyase-catalyzed loss of ammonia from histidine. The photochemistry and biological properties of urocanic acid continue to receive attention, in part because of evidence that (*Z*)-urocanic acid (**1b**), formed in the body by photo-isomerization of the *E* isomer, is a mediator of photo-immunosuppression [1]. As part of our program to prepare fluorinated analogues of biologically important imidazoles, we have reported the synthesis of (*E*)- and (*Z*)-2- and 4-fluorourocanic acid (**2a**,**b** and **3a**,**b**, respectively) [2], (*E*)- and (*Z*)-α-fluorourocanic acid (**4a**,**b**) [3] and (*E*)- and (*Z*-β)-fluorourocanic acid (**5a**,**b**) [4]. Ring-fluorinated analogues **2** and **3** were prepared from ring-fluorinated aldehyde precursors using a Horner–Emmons olefination with triethyl phosphonoacetate [2]. A similar olefination of 1-trityl-(1H)imidazole-4-carboxaldehyde with triethyl flourophosphonoacetate was the key step in the synthesis of **4a**,**b** [3]. To access the β-fluoroanalogues **5a**,**b**, addition of "FBr" to a vinyl imidazole derivative to place fluorine adjacent to the imidazole ring was the key step [4]. Missing from the inventory of side-chain fluorinated analogues of urocanic acid is α,β-difluorourocanic acids (**6a**,**6b**), compounds that should have interesting chemical and biological behavior by virtue of the difluoroacrylate functionality.



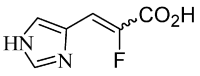
1a *E* (trans)
1b *Z* (cis)



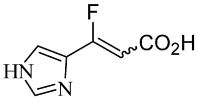
2a *E* (trans)
2b *Z* (cis)



3a *E* (trans)
3b *Z* (cis)



4a *Z* (trans)
4b *E* (cis)



5a *Z* (trans)
5b *E* (cis)

6a *E* (trans)
6b *Z* (cis)

Published routes to compounds of the general structure Aryl-CF=CF-Alkyl would not seem readily applicable to the synthesis of **6a** and **6b**. One approach based on reaction of CF_2=CF_2 or R–CF=CFX (where X is H or halogen) with ArLi has been applied to heteroaryl compounds [5]. However, in general, this method would not readily tolerate functional groups. A second approach that involves elimination of "X–X" from R–CFX–CFX–R [6] requires lengthy and, in our case, problematic preparation of precursors. A third approach would be direct addition of F_2 diluted with N_2 to a triple bond. In one example, addition of F_2 to a series of tolanes give mixtures of products, including α,α′-difluorostilbenes [7]. We did not consider this approach because of the complex reaction products and requirement for special equipment.

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We have approached the synthesis of **6a**,**b** by combining chemistry we used for the preparation of **4** and **5**. In a key reaction in our synthesis of α-fluorourocanic acids, Horner–Emmons olefination of 1-trityl-(1H)imidazole-4-carboxaldehyde with triethyl fluorophosphonoacetate produces α-fluoropropenoates **7** [3]. In our synthesis of β-fluorourocanic acids, we took advantage of regiospecific ''FBr'' addition to a vinyl imidazole derivative followed by HBr elimination to install fluorine in the β-position [4]. In contemplating a combination of these two approaches in order to place fluorine at both the α- and β-positions, a critical question involves regioselectivity of the ''FBr'' addition to 1-alkyl-2-aryl-1-fluoroalkenes. If the directive effect of fluorine (resulting in stabilization of an α-carbonium ion) is strong enough to take precedence over aryl carbonium ion stabilization, ''FBr'' addition would be predicted to lead to the geminal instead of the desired vicinal difluoro compounds. Indeed, this is the observed product of addition of FBr to vinyl fluorides where an aryl group is not present [8] or when the aryl group and fluorine are on the same carbon [9]. To our surprise, we have found no examples of electrophilic additions to 1-alkyl-2-aryl-1-fluoroalkenes.

Having found no precedent wherein addition of ''FBr'' to a vinyl monofluoride produces the vicinal difluoride, we were pleased to find that addition of ''FBr'' to 3-(1-trityl-1(H)-imidazol-4-yl)-1-hydroxymethyl-2-fluoro-2-propene (**8**) in fact proceeds with regioselectivity to produce the vicinal difluoride. This somewhat unexpected direction of addition provides a convenient route to α,β-difluorourocanic acids. In addition, this discovery should make possible the synthesis of other 1-aryl-1,2-difluoroalkenes by the same route.

2. Chemistry

(*E*)- and (*Z*)-Ethyl 2-fluoro-3-(1-trityl-1-H-imidazol-4-yl)-prop-2-enoate (**7a**,**b**) were prepared as described [4]. Based on our experience with the preparation of **5**, we were aware that reduction of the ester to alcohol was necessary to achieve the desired chemoselectivity of halide elimination (bromide vs. fluoride) in the sequence [4]. Previously, we also found that the carboxyl function of urocanic acid deactivates the double bond to the extent that ''FBr'' addition via $Et_3N{\cdot}3HF$ and NBS becomes a sluggish process [4]. In a related example, we were unable to effect ''FBr'' addition to ethoxycabonylalkynylimidazole [10]. Consistent with these results, we found that no FBr-adducts are formed from α-bromourocanate or α-fluorourocanate **7** using our usual conditions. Therefore, we reduced the deactivating ester function to the hydroxymethyl electron donating group to obtain 2-fluoropropenols **8a** and **8b**. These were then used as substrates to study FBr adduct formation. In subsequent reactions, since addition of ''FBr'' to either olefin produced diasteromeric mixtures of products that were extremely difficult to separate, it was convenient to carry out addition of ''FBr'' and elimination of HBr on mixtures of **8a/8b**.

The reactivity of the 2-fluoropropenols **8a**,**b** proved to be lower in comparison to their nonfluorinated analogs [4] or isomeric 3-fluoropropenols [9], where the conversion is about 100%. Under the usual conditions, the conversion of 2-fluoropropenols to products **9a** and **9b** was only 84% of **8a** and 52% of **8b**. As is usual in the cases of poorly reactive olefins, in addition to the desired FBr adducts, the dibromo adducts **10** were also formed in about 25% yield. Thus the reactivity is similar to trityl urocanic methyl ester (conversion 62%) [4]. As in that case, the conversion of **8** can be increased by increasing the reagent amounts (see Table 1). We found no evidence (^1H and ^{19}F NMR) of reversed regioselectivity with formation of geminal difluoro compound.

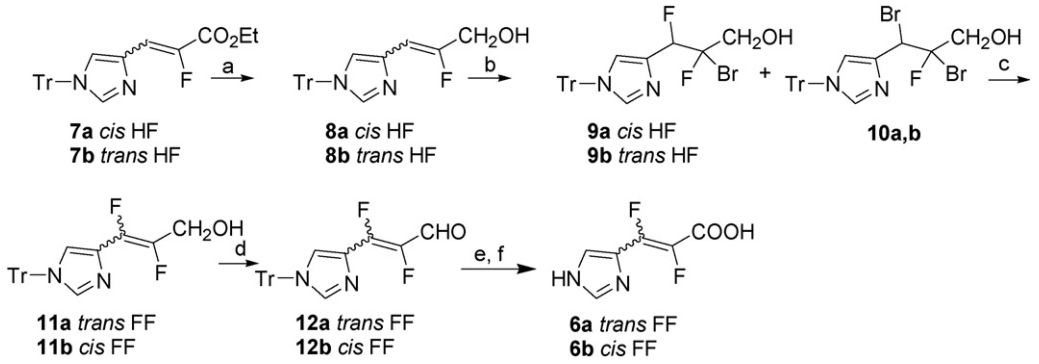
Table 1
Results of addition of ''FBr'' on **6a** or **6b**

Starting isomer	Reaction conditions[a]			Products molar ratio (%)				
	''HF''	NBS	Time	**9a**	**9b**	**10a**	**10b**	**8**[b]
(a) **8a**	1.5	1.1	2	41	17	13	13	16
(b) **8a**	1.5	1.1	5	51	18	6	6	19
(c) **8b**	1.5	1.1	14	3	24	12	13	48
(d) **8b**	2.5	1.8	44	6	41	11	15	27
(e) **8b**	3.2	2.2	19	8	59	15	18	0

[a] Content of columns is as follows: equivalents of $Et_3N{\cdot}3HF$, equivalents of NBS, reaction time in hours.
[b] Starting isomer **8a** or **8b**.

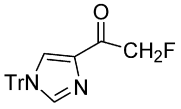
It is well documented that in these reactions, *trans* alkenes give mainly the product of *anti* addition, but *cis* alkenes give mixture of *anti* and *syn* addition [4]. However, there are few precedents for reactions of alkenes having a halogen substituent in place of hydrogen on the double bond. We found that isomer **8b**, where the carbon substituents are *trans* to each other, gives diastereoisomeric adducts in a ratio of 88:12, tentatively assigned as products from *anti* (**9b**, $2R^*,3S^*$-configuration) and *syn* (**9a**, $2R^*,3R^*$-configuration) additions, respectively. This is slightly lower diastereoselectivity than found with the nonfluorinated analog (95:5) [4]. Isomer **8a**, where the carbon substituents are in a *cis* orientation, gives a diastereoisomeric mixture in a ratio of 75:25, tentatively assigned as products from *anti* (**9a**) and *syn* (**9b**) additions. This is significantly higher *anti* diastereoselectivity than found with the *cis*-configured nonfluorinated analog, which gave an *anti*/*syn* addition ratio of 20:80 [4]. It is interesting to note that byproduct Br_2-adducts, two diastereoisomers **10a** and **10b** are formed in ratio of about 1:1 in both cases. These results are summarized in Table 1.

Dehydrobromination of mixture **9a** and **9b** gives corresponding difluoropropenols **11a** and **11b** in the usual yields of 60–70%. Double bond configuration was readily assigned to the two geometrical isomers based on ^{19}F NMR data. The (*E*)-isomer **11a** has a significantly higher F–F coupling constant (126 Hz) than does the (*Z*)-isomer **11b** (21 Hz). The oxidation to aldehyde **12a** and **12b** by MnO_2 surprisingly proceeds with formation of byproduct **13**, the yield of which increases with longer reaction times or increased reaction temperature. The isomer **11b** is significantly less reactive than **11a** and compound **13** becomes the main product of the oxidation (see Section 4.8). We have found no precedent for this conversion and any mechanistic proposals would be entirely speculative. For acceptable yield of the aldehydes **12** (30–50%), it is necessary



Scheme 1. (a) DIBAL-H, CH_2Cl_2, 74% **8a**, 72% **8b**; (b) $Et_3N{\cdot}3HF$, NBS, CH_2Cl_2, 58% **9a**,**b**; (c) Et_3N, DMSO, 47% **11a**, 29% **11b**; (d) MnO_2, CH_2Cl_2, 53% **12a**, 33% **12b**; (e) $NaHPO_4$, $NaClO_2$, *t*-BuOH/H_2O; (f) HCl, CH_3CO_2H, 96% **6a**, 37% **6b**.

to use a large excess of MnO_2 and to monitor the reaction by TLC in order to stop the reaction immediately after full conversion of the starting material.



13

Subsequent one pot oxidation and deprotection of aldehydes **12** afforded the desired α,β-difluorourocanic acids **6a** and **6b**. We did not purify and characterize the immediate products of the oxidation due to complications with their purification that led to decomposition. This was especially true for the product of oxidation of aldehyde **12b**. By this one pot procedure, we obtained (*E*)-α,β-difluorourocanic acid (**6a**) in high yield (96%) and (*Z*)-α,β-difluorourocanic acid (**6b**) in moderate yield (37%) (Scheme 1).

3. Conclusion

We report here the synthesis of new fluorinated analogues of urocanic acid. The methodology developed includes a procedure for the preparation of functionalized 1-alkyl-2-aryl-1,2-difluoroethenes from readily available starting materials. For this synthesis, there was no requirement for hydroxyl group protection. This procedure should be applicable to other aryl and heteroaryl systems as borne out by our preliminary successful experiments with benzaldehydes. Studies on the biology and photochemistry of fluorinated urocanic acids are a subject of continued research. Neither **6a** nor **6b** was an inhibitor of urocanase.

4. Experimental

4.1. General

The NMR spectra were recorded at 22 °C on a Varian Mercury-300 instrument at frequencies of 300.1 for ^1H, 75.5 for ^{13}C and 282.2 MHz for ^{19}F spectra. All ^{13}C NMR spectra are proton-decoupled. Tetramethylsilane (TMS) was used as the internal standard; ^{13}C NMR chemical shifts: $CDCl_3$, $\delta = 77.23$; DMSO-d_6, $\delta = 39.51$ ppm. For ^{19}F NMR, fluorotrichloromethane was used as the internal standard. HRMS spectra were recorded on a Waters LCT Premier TOF mass spectrometer. Flash chromatography was performed on Biotage SP4. LC/MS was performed on Agilent 1100 system.

4.2. (E)-Ethyl 2-fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-enoate (7a)

Compound **7a** was prepared as published in ref. [4]. We report here the additional spectral data. ^{13}C NMR ($CDCl_3$): 160.68 (d, $^2J_{CF} = 34.1$, CO), 144.76 (d, $^1J_{CF} = 250.2$, CF), 142.01 (3C, Tr), 138.78 (s, $C2_{Imi}$), 131.56 (d, $^3J_{CF} = 11.2$, $C4_{Imi}$), 129.63 (6CH, Tr), 128.06 (3CH, Tr), 128.03 (6CH, Tr), 125.75 (d, $^4J_{CF} = 5.4$, $C5_{Imi}$), 117.23 (d, $^2J_{CF} = 30.8$; *C*H=CF), 75.70 (s, 1C, Tr), 61.07 (s, CH_2), 13.96 (s, CH_3). ^{19}F NMR ($CDCl_3$): −124.3 (d, $^3J_{HF} = 24.0$).

4.3. (Z)-Ethyl 2-fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-enoate (7b)

Compound **7b** was prepared as published in ref. [4]. We report here the additional spectral data. ^{13}C NMR ($CDCl_3$): 161.09 (d, $^2J_{CF} = 33.8$, CO), 145.83 (dd, $^1J_{CF} = 259.7$, CF), 141.88 (3C, Tr), 139.47 (s, $C2_{Imi}$), 132.43 (d, $^3J_{CF} = 3.32$, $C4_{Imi}$), 129.66 (6CH, Tr), 128.25 (3CH, Tr), 128.16 (6CH, Tr), 125.13 (d, $^4J_{CF} = 13.4$, $C5_{Imi}$), 112.73 (d, $^2J_{CF} = 8.2$, *C*H=CF), 75.88 (s, 1C, Tr), 61.45 (s, CH_2), 14.15 (s, CH_3). ^{19}F NMR ($CDCl_3$): −123.9 (dd, $^3J_{HF} = 36.2$, $^5J_{HF} = 1.6$).

4.4. (E)- and (Z)-2-Fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (8a,b)

To a stirred solution of propenoates **7** (6.37 g, 14.9 mmol, **7a**:**7b** 5:9) in 370 mL of dry CH_2Cl_2 was slowly added 33 mL of DIBAL-H (1 M in CH_2Cl_2, 33 mmol) at −65 °C. The mixture was allowed to warm to room temperature and was stirred overnight. After addition of 30 mL of water, the mixture was partitioned between CH_2Cl_2 and water/brine.

The organic part was dried over $MgSO_4$ and evaporated to dryness. The resulting solid was separated by column chromatography (250 g, CH_2Cl_2:Et_2O, 9:1) to give pure **8a** (1.51 g, 74% based on **7a**). Isomer **8b** was eluted with CH_2Cl_2:CH_3OH (9:1) and purified by column chromatography (100 g, CH_2Cl_2:EtOAc 1:1) to give pure **8b** (2.65 g, 72% based on **7b**).

*4.4.1. (E)-2-Fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**8a**)*

^{1}H NMR ($CDCl_3$): 7.42 (1H, d, J = 1.5, Imi), 7.38–7.32 (9H, m, Tr), 7.17–7.09 (6H, m, Tr), 7.04 (1H, bs, Tr), 6.74 (1H, d, J = 1.5, Imi), 6.05 (1H, d, $^3J_{HF}$ = 20.8, CH=CF), 4.44 (2H, d, $^3J_{HF}$ = 14.8, CH_2). ^{13}C NMR ($CDCl_3$): 162.09 (d, $^1J_{CF}$ = 259.3, CF), 141.87 (3C, Tr), 138.77 (s, $C2_{Imi}$), 134.30 (d, $^3J_{CF}$ = 15.1, $C4_{imi}$), 129.64 (6CH, Tr), 128.21 (3CH, Tr), 128.13 (6CH, Tr), 120.24 (d, $^4J_{CF}$ = 8.1, $C5_{Imi}$), 101.69 (d, $^2J_{CF}$ = 30.8, *C*H=CF), 75.57 (s, 1C, Tr), 59.97 (d, $^2J_{CF}$ = 37.9, CH_2). ^{19}F NMR ($CDCl_3$): −102.7 (dt, $^3J_{HF}$ = 20.7, $^3J_{HF}$ = 15.0). mp: 194.5–195.5 °C (CH_2Cl_2/Et_2O). HRMS: for M + H, i.e. $C_{25}H_{22}FN_2O$ calculated: 385.1716; found: 385.1729. Elemental analysis for $C_{25}H_{21}FN_2O$ calculated: 78.10%C, 5.51%H, 7.29%N, found: 77.99%C, 5.51%H, 7.32%N.

*4.4.2. (Z)-2-Fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**8b**)*

^{1}H NMR ($CDCl_3$): 7.39 (1H, d, J = 1.4, Imi), 7.34–7.28 (9H, m, Tr), 7.16–7.10 (6H, m, Tr), 7.09 (1H, t, J = 1.6, Imi), 6.01 (1H, d, $^3J_{HF}$ = 40.1, CH=CF), 5.24 (1H, bs, OH), 4.16 (2H, d, $^3J_{HF}$ = 12.6, CH_2). ^{13}C NMR ($CDCl_3$): 158.86 (d, $^1J_{CF}$ = 264.2, CF), 142.07 (3C, Tr), 138.04 (s, $C2_{Imi}$), 133.50 (d, $^3J_{CF}$ = 1.0, $C4_{imi}$), 129.71 (6CH, Tr), 128.09 (3CH, Tr), 128.07 (6CH, Tr), 121.31 (d, $^4J_{CF}$ = 11.7, $C5_{Imi}$), 101.07 (d, $^2J_{CF}$ = 9.7, *C*H=CF), 75.58 (s, 1C, Tr), 60.30 (d, $^2J_{CF}$ = 32.2, CH_2). ^{19}F NMR ($CDCl_3$): −109.7 (dt, $^3J_{HF}$ = 40.1, $^3J_{HF}$ = 12.6). mp: 194–195 °C (ethyl acetate). Elemental analysis for $C_{25}H_{21}FN_2O$ calculated: 78.10%C, 5.51%H, 7.29%N, found: 77.98%C, 5.53%H, 7.32%N.

*4.5. 2-Bromo-2,3-difluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**9a**,**b**)*

To a solution of compound **8a**,**b** (3.11 g, 8.1 mmol) in 40 mL of anhydrous dichloromethane was slowly added $Et_3N{\cdot}3HF$ (1.94 g, 12.0 mmol) at 0 °C. After the solution was stirred for 10 min, 1.59 g of NBS (8.9 mmol) was added. The cooling bath was removed and the reaction was stirred for 2 days at which time TLC indicated that almost all the starting material had disappeared. The solvent was evaporated and 150 mL of ethyl acetate was added. The resulting solution was washed with water (2 × 20 mL), brine (2 × 20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by chromatography on silica gel (hexane/ethyl acetate 2:1) afforded 2.27 g (58%) of a mixture of compound **9a** and compound **9b** as a white solid. ^{1}HNMR indicated the ratio of the two compounds to be 40:60.

HRMS (CI^+): for M + H, i.e. $C_{25}H_{22}BrF_2N_2O$ calculated: 483.0884; found: 483.0833.

4.5.1. (2R,3R*)-2-Bromo-2,3-difluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**9a**)*

^{1}H NMR ($CDCl_3$): 7.47 (1H, d, J = 1.4, Imi), 7.35 (9H, m, Tr), 7.11 (6H, m, Tr), 7.07 (1H, dd, J = 3.2, 1.4, Imi), 6.24 (1H, bs, OH), 5.77 (1H, dd, $^2J_{HF}$ = 45.9, $^3J_{HF}$ = 10.6), 4.44 (1H, ddd, $^2J_{HH}$ = 13.0, $^3J_{HF}$ = 5.4, $^4J_{HF}$ = 1.4), 3.94 (1H, dm, $^2J_{HH}$ = 14.2). ^{13}C NMR ($CDCl_3$): 141.63 (3C, Tr), 139.15 (s, $C2_{Imi}$), 133.23 (dd, $^2J_{CF}$ = 22.6, $^3J_{CF}$ = 7.1, $C4_{Imi}$), 129.66 (6CH, Tr), 128.43 (3CH, Tr), 128.27 (6CH, Tr), 123.79 (dd, $^3J_{CF}$ = 5.9, $^4J_{CF}$ = 1.2, $C5_{Imi}$), 109.68 (dd, $^1J_{CF}$ = 260.0, $^2J_{CF}$ = 26.4, CFBr), 89.86 (dd, $^1J_{CF}$ = 183.9, $^2J_{CF}$ = 26.5, CHF), 76.03 (s, 1C, Tr), 65.08 (dd, $^3J_{CF}$ = 31.0, $^4J_{CF}$ = 2.2, CH_2). ^{19}F NMR ($CDCl_3$): −120 (1F, m), −169.4 (1F, dd, $^2J_{HF}$ = 45.8, $^3J_{FF}$ = 22.2).

4.5.2. (2R,3S*)-2-Bromo-2,3-difluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**9b**)*

^{1}H NMR ($CDCl_3$): 7.46 (1H, t, J = 1.5, Imi), 7.35 (9H, m, Tr), 7.11 (6H, m, Tr), 7.05 (1H, dt, J = 2.3, 1.0, Imi), 6.24 (1H, bs, OH), 5.87 (1H, ddd, $^2J_{HF}$ = 45.0, $^3J_{HF}$ = 9.5, $^4J_{HH}$ = 1.0), 4.17 (1H, dd, $^2J_{HH}$ = 13.4, $^3J_{HF}$ = 3.5), 4.04 (1H, dd, $^3J_{HF}$ = 26.9, $^2J_{HH}$ = 13.4). ^{13}C NMR ($CDCl_3$): 141.74 (3C, Tr), 138.75 (s, $C2_{Imi}$), 134.12 (dd, $^2J_{CF}$ = 25.8, $^3J_{CF}$ = 7.3, $C4_{Imi}$), 129.66 (6CH, Tr), 128.36 (3CH, Tr), 128.23 (6CH, Tr), 121.81 (dd, $^3J_{CF}$ = 5.0, $^4J_{CF}$ = 3.3, $C5_{Imi}$), 110.64 (dd, $^1J_{CF}$ = 263.7, $^2J_{CF}$ = 22.6, CFBr), 90.18 (dd, $^1J_{CF}$ = 182.2, $^2J_{CF}$ = 26.9, CHF), 76.01 (s, 1C, Tr), 67.81 (dd, $^3J_{CF}$ = 23.7, $^4J_{CF}$ = 2.5, CH_2). ^{19}F NMR ($CDCl_3$): −120 (1F, m), −189.1 (1F, dd, $^2J_{HF}$ = 45.3, $^3J_{FF}$ = 21.6).

*4.5.3. 2,3-Dibromo-2-fluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**10a**)*

^{1}H NMR ($CDCl_3$): 7.46 (1H, dd, J = 1.4, 0.4, Imi), 7.37–7.32 (9H, m, Tr), 7.15–7.09 (6H, m, Tr), 6.98 (1H, d, J = 1.4, Imi), 6.36 (1H, bs, OH), 5.63 (1H, dd, $^3J_{HF}$ = 8.1, $^4J_{HH}$ = 0.9), 4.63 (1H, dd, $^2J_{HH}$ = 13.0, $^3J_{HF}$ = 4.5), 3.94 (1H, ddd, $^2J_{HH}$ = 13.0, $^3J_{HF}$ = 12.2, $^4J_{HH}$ = 1.0). ^{13}C NMR ($CDCl_3$): 141.48 (3C, Tr), 139.04 (s, $C2_{Imi}$), 135.88 (d, $^3J_{CF}$ = 7.0, $C4_{Imi}$), 129.60 (6CH, Tr), 128.40 (3CH, Tr), 128.22 (6CH, Tr), 122.05 (d, $^4J_{CF}$ = 1.9, $C5_{Imi}$), 110.85 (d, $^1J_{CF}$ = 269.9, CF), 76.05 (s, 1C, Tr), 66.55 (d, $^2J_{CF}$ = 30.9, CHBr), 51.49 (d, $^2J_{CF}$ = 28.1, CH_2). ^{19}F NMR ($CDCl_3$): −105.28 (1F, bs).

*4.5.4. 2,3-Dibromo-2-fluoro-3-(1-trityl-1H-imidazol-4-yl)-propan-1-ol (**10b**)*

^{1}H NMR ($CDCl_3$): 7.44 (1H, d, J = 1.5, Imi), 7.37–7.32 (9H, m, Tr), 7.15–7.09 (6H, m, Tr), 7.08 (1H, m, Imi), 6.36 (1H, bs, OH), 5.61 (1H, dd, $^3J_{HF}$ = 11.2, $^4J_{HH}$ = 0.7), 4.22 (1H, dd, $^2J_{HH}$ = 13.1, $^3J_{HF}$ = 11.5), 4.07 (1H, dd, $^3J_{HF}$ = 23.5, $^2J_{HH}$ = 13.1). ^{13}C NMR ($CDCl_3$): 141.62 (3C, Tr), 139.10 (s, $C2_{Imi}$), 136.39 (d, $^3J_{CF}$ = 4.5, $C4_{Imi}$), 129.60 (6CH, Tr), 128.32 (3CH, Tr), 128.18 (6CH, Tr), 123.17 (d, $^4J_{CF}$ = 3.4, $C5_{Imi}$), 112.57 (d, $^1J_{CF}$ = 265.5, CF), 76.05 (s, 1C, Tr), 68.34 (d, $^2J_{CF}$ = 24.9, CHBr), 49.68 (d, $^2J_{CF}$ = 26.2, CH_2). ^{19}F NMR ($CDCl_3$): −111.73 (1F, bs).

*4.5.5. Reaction of "FBr" with pure (E)-2-fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**8a**)*

To a solution of compound **8a** (1.44 g, 3.7 mmol) in 40 mL of anhydrous dichloromethane was slowly added $Et_3N{\cdot}3HF$ (0.94 g, 5.8 mmol) at 0 °C. After the solution was stirred for 30 min, 0.73 g of NBS (4.1 mmol) was added. The cooling bath was removed after 60 min and the reaction was stirred for an additional 4 h at which time TLC indicated that almost all the starting material had disappeared. The solvent was evaporated and 70 mL of ethyl acetate was added. The resulting solution was washed with water (2 × 10 mL), brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by chromatography on silica gel (dichloromethane/ethyl acetate 9:1) afforded 1.00 g (55%) of a mixture of compound **9a** and compound **9b** as a white solid. ^{1}H NMR indicated the ratio of the two compounds to be 75:25.

*4.5.6. Reaction of "FBr" with pure (Z)-2-fluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**8b**)*

To a solution of compound **8b** (870 mg, 2.26 mmol) in 40 mL of anhydrous dichloromethane was slowly added $Et_3N{\cdot}3HF$ (547 mg, 3.39 mmol) at 0 °C. After the solution was stirred for 30 min, 445 mg of NBS (2.50 mmol) was added. The cooling bath was removed after 60 min and the reaction was stirred for an additional 2 days at which time TLC indicated that almost all the starting material had disappeared. The solvent was evaporated and 70 mL of ethyl acetate was added. The resulting solution was washed with water (2 × 10 mL), brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by chromatography on silica gel (dichloromethane/ethyl acetate 1:1) afforded 226 mg (18%) of a mixture of compound **9b** and compound **9a** as a white solid. ^{1}H NMR indicated the ratio of the two compounds to be 88:12.

*4.6. (E)- and (Z)-2,3-Difluoro-3-(1-trityl-1-H-imidazol-4-yl)-prop-2-en-1-ol (**11a** and **11b**)*

In a 100 mL flask, 1.51 g of a mixture of compounds **9a** and **9b** (3.13 mmol) was dissolved in 50 mL of anhydrous DMF and 5 mL of triethylamine (∼36 mmol) at room temperature. The mixture was heated to 100 °C and stirred overnight. After evaporation of the solvent, the residue was dissolved in 200 ml of ethyl acetate. The resulting mixture was washed with water (2 × 30 mL), brine (2 × 30 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate 2:1) to give 585 mg of compound **11a** (47%) and 365 mg of compound **11b** (29%) as white solids. The ratio **11a**:**11b** in the crude mixture was 60:40 (calculated from LC and ^{19}F NMR).

*4.6.1. (E)-2,3-Difluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**11a**)*

^{1}H NMR ($CDCl_3$): 7.51 (1H, bs, Imi), 7.36–7.31 (9H, m, Tr), 7.16–7.10 (7H, m, Tr, Imi), 4.46 (2H, dd, $^3J_{HF}$ = 22.9, $^4J_{HF}$ = 5.5), 3.21 (1H, bs, OH). ^{13}C NMR ($CDCl_3$): 148.65 (dd, $^1J_{CF}$ = 244.9, $^2J_{CF}$ = 50.0, CF), 144.44 (dd, $^1J_{CF}$ = 228.7, $^2J_{CF}$ = 46.8, CF), 141.86 (3C, Tr), 139.33 (s, $C2_{Imi}$), 130.23 (dd, $^2J_{CF}$ = 29.0, $^3J_{CF}$ = 6.1, $C4_{Imi}$), 129.66 (6CH, Tr), 128.26 (3CH, Tr), 128.18 (6CH, Tr), 121.39 (dd, $^3J_{CF}$ = 11.1, $^4J_{CF}$ = 5.6, $C5_{Imi}$), 75.85 (s, 1C, Tr), 55.88 (d, $^2J_{CF}$ = 24.3, CH_2). ^{19}F NMR ($CDCl_3$): −156.0 (1F, dt, $^3J_{FF}$ = 125.5, $^3J_{HF}$ = 22.9), −161.6 (1F, dt, $^3J_{FF}$ = 125.5, $^2J_{HF}$ = 5.3). HRMS (FAB^+): for MH, i.e. $C_{25}H_{21}F_2N_2O$ calculated: 403.1622; found: 403.1623; mp: 157–158 °C (ethylacetate). Elemental analysis for $C_{25}H_{20}F_2N_2O$ calculated: 74.61%C, 5.01%H, 6.96%N, found: 74.50%C, 5.14%H, 6.91%N.

*4.6.2. (Z)-2,3-Difluoro-3-(1-trityl-1H-imidazol-4-yl)-prop-2-en-1-ol (**11b**)*

^{1}H NMR ($CDCl_3$): 7.47 (1H, dd, J = 2.8, 1.5, Imi), 7.38–7.33 (9H, m, Tr), 7.16–7.70 (6H, m, Tr), 7.06 (1H, bs, Imi), 5.25 (1H, bs, OH), 4.51 (2H, dd, $^3J_{HF}$ = 20.8, $^4J_{HF}$ = 4.1, CH_2). ^{13}C NMR ($CDCl_3$): 146.84 (dd, $^1J_{CF}$ = 258.1, $^2J_{CF}$ = 13.3, CF), 142.30 (dd, $^1J_{CF}$ = 237.7, $^2J_{CF}$ = 19.8, CF), 141.71 (3C, Tr), 139.44 (d, $^4J_{CF}$ = 1.7, $C2_{Imi}$), 131.60 (dd, $^2J_{CF}$ = 33.7, $^3J_{CF}$ = 1.4, $C4_{Imi}$), 129.65 (6CH, Tr), 128.41 (3CH), 128.28 (6CH), 119.95 (dd, $^3J_{CF}$ = 9.3, $^4J_{CF}$ = 1.0, $C5_{Imi}$), 76.03 (s, 1C, Tr), 58.27 (dd, $^2J_{CF}$ = 29.0, $^3J_{CF}$ = 2.2, CH_2). ^{19}F NMR ($CDCl_3$): −136.1 (1F, td, $^3J_{HF}$ = 20.7, $^3J_{FF}$ = 10.3), −147.6 (1F, dtd, $^3J_{FF}$ = 10.3, $^4J_{HF}$ = 3.8, $^4J_{HF}$ = 3.2). HRMS (FAB^+): for MH, i.e. $C_{25}H_{21}F_2N_2O$ calculated: 403.1622; found: 403.1630; mp: 140–141 °C (ethylacetate). Elemental analysis for $C_{25}H_{20}F_2N_2O$, calculated: 74.61%C, 5.01%H, 6.96%N; found: 74.44%C, 4.90%H, 6.90%N.

*4.7. (E)-α,β-Difluoro-3-(1-trityl-1H-imidazol-4-yl)-propenal (**12a**)*

To a solution of compound **11a** (380 mg, 0.95 mmol) in 10 mL of anhydrous dichloromethane (20 mL) was added activated MnO_2 (804 mg, 9.25 mmol). The mixture was stirred at room temperature for 12 h until TLC indicated complete disappearance of starting material. The mixture was filtered and solvent was evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate 1:1). Purification afforded 200 mg (53%) of the desired product **12a** in yield along with 52 mg (15%) of byproduct **13**. The ratio **12a/13** was 80:20 (calculated from LC and ^{19}F NMR of the crude product).

^{1}H NMR ($CDCl_3$): 9.86 (1H, ddd, $^3J_{HF}$ = 18.9, $^4J_{HF}$ = 2.5, $^6J_{HH}$ = 0.6, CHO), 7.64 (1H, dq, J = 1.4, 0.7, Imi), 7.52 (1H, td, J = 1.4, 0.6, Imi), 7.41–7.34 (9H, m, Tr), 7.18–7.11 (6H, m, Tr). ^{13}C NMR ($CDCl_3$): 178.63 (dd, $^2J_{CF}$ = 17.0, $^3J_{CF}$ = 4.2, CHO), 157.62 (dd, $^1J_{CF}$ = 256.5, $^2J_{CF}$ = 39.9, CF), 144.94 (dd, $^1J_{CF}$ = 244.7, $^2J_{CF}$ = 35.6, CF), 141.31 (3C, Tr), 140.98 (bs, $C2_{Imi}$), 129.49 (6CH, Tr), 128.51 (3CH, Tr), 128.31 (6CH, Tr), 126.53 (dd, $^3J_{CF}$ = 13.9, $^4J_{CF}$ = 7.2, $C5_{Imi}$), 76.44 (s, 1C, Tr), $C4_{Imi}$ is covered by signals of trityl group. ^{19}F NMR ($CDCl_3$): −152.4 (1F, dd, 120.8, 2.5), −168.4 (1F, dddt, 120.8, 18.9, 1.4, 0.7). HRMS (DCI): for $C_{25}H_{18}F_2N_2O$ (M), calculated: 400.1387, found: 400.1389; mp: 139–141 °C (ethylacetate). Elemental analysis for $C_{25}H_{18}F_2N_2O$, calculated: 74.99%C, 4.53%H, 7.00%N; found: 74.91%C, 4.48%H, 7.02%N.

4.8. (Z)-α,β-Difluoro-3-(1-trityl-1H-imidazol-4-yl)-propenal (**12b**)

To a solution of compound **11b** (232 mg, 0.58 mmol) in anhydrous dichloromethane (10 mL) was added activated MnO_2 (501 mg, 5.77 mmol). The mixture was stirred at room temperature for 6 days until TLC indicated complete disappearance of starting material. The mixture was filtered, solvent was evaporated and crude product was purified by column chromatography. The crude product was purified by column chromatography (hexane/ethyl acetate 4/1) to give 76 mg (33%) of the desired product **12b** and 90 mg (42%) of byproduct **13**. The ratio **12b/13** was 40:60 (calculated from LC and ^{19}F NMR of the crude product).

^1H NMR ($CDCl_3$): 10.58 (1H, dd, $^3J_{HF}$ = 19.1, $^4J_{HF}$ = 2.3, CHO), 7.53 (1H, dd, J = 2.9, 1.4, Imi), 7.42–7.34 (9H, m, Tr), 7.18–7.10 (7H, m, Tr, Imi). ^{13}C NMR ($CDCl_3$): 184.71 (dd, $^2J_{CF}$ = 15.4, $^3J_{CF}$ = 7.7), 156.12 (dd, $^1J_{CF}$ = 262.8, $^2J_{CF}$ = 16.2), 143.26 (dd, $^1J_{CF}$ = 254.6, $^2J_{CF}$ = 12.7), 141.46 (3C, Tr), 141.08 (d, $^4J_{CF}$ = 1.8, $C2_{Imi}$), 139.56 (d, $^2J_{CF}$ = 23.9, $C4_{Imi}$), 129.56 (6CH, Tr), 128.55 (3CH, Tr), 128.37 (6CH, Tr), 124.37 (dd, $^3J_{CF}$ = 8.9, $^4J_{CF}$ = 3.3, $C5_{Imi}$), 76.32 (s, 1C, Tr). ^{19}F NMR ($CDCl_3$): −123.6 (1F, d, $^3J_{FF}$ = 12.0), −159.4 (1F, dd, $^3J_{HF}$ = 19.1, $^3J_{FF}$ = 12.0). HRMS (DCI): for $C_{25}H_{18}N_2F_2O$ (M), calculated: 400.1387; found: 400.1389. mp: 136–137 °C (ethylacetate).

4.9. 2-Fluoro-1-(1-trityl-1H-imidazol-4-yl)-ethanone (**13**)

^1H NMR ($CDCl_3$): 7.70 (1H, d, J = 1.4, Imi), 7.44 (1H, d, J = 1.4, Imi), 7.39–7.33 (9H, m, Tr), 7.14–7.08 (6H, m, Tr), 5.29 (2H, d, $^2J_{HF}$ = 47.4, CH_2F). ^{13}C NMR ($CDCl_3$): 189.28 (d, $^2J_{CF}$ = 15.8, CO), 141.45 (3C, Tr), 139.62 (s, $C2_{Imi}$), 137.46 (s, $C4_{Imi}$), 129.58 (6CH, Tr), 128.50 (3CH, Tr), 128.35 (6CH, Tr), 126.16 (d, $^4J_{CF}$ = 4.2, $C5_{Imi}$), 83.55 (d, $^2J_{CF}$ = 179.1, CH_2F), 76.31 (s, 1C, Tr). ^{19}F NMR ($CDCl_3$): −235.7 (t, $^2J_{HF}$ = 47.5). mp: 193–194 °C (ethylacetate). HRMS (FAB^+): for MH, i.e. $C_{24}H_{20}FN_2O$ calculated: 371.1560; found: 371.1553. Elemental analysis for $C_{24}H_{19}FN_2O$, calculated: 77.82% C, 5.17% H, 7.56% N; found: 77.78% C, 5.09% H, 7.75% N.

4.10. (E)-α,β-Difluorourocanic acid (**6a**)

Compound **12a** (108 mg, 0.27 mmol) was dissolved in 8.0 mL of *t*-BuOH and 3.2 mL of 2-methyl-2-butene. Then the mixture was cooled to 0 °C and a solution of $NaClO_2$ (162 mg, 1.79 mmol) and NaH_2PO_4 (218 mg, 1.82 mmol) in 4.0 mL of H_2O was added. The resulting mixture was stirred at room temperature until TLC indicated complete disappearance of the aldehyde. Dichloromethane (80 mL) was added and the mixture was washed with water (2 × 10 mL), brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. The mixture was filtered and evaporated. The residue was then washed with water (2 × 5 mL) and dissolved in 10 mL of CH_3COOH and 1.0 mL of concentrated HCl. The mixture was stirred at room temperature for 3 h. After this period, the solvent was evaporated and the residue was washed subsequently with ethylacetate (2 × 5 ml) and 2 mL of H_2O. The residue was then dried on vacuum and 45 mg (96%) of the final product **6a** was obtained as a white solid.

^1H NMR (DMSO-d_6): 7.91 (bs, 1H), 7.69 (bs, 1H). ^{13}C NMR (DMSO-d_6): 160.73 (dd, $^2J_{CF}$ = 46.4, $^3J_{CF}$ = 29.3, CO), 152.32 (dd, $^1J_{CF}$ = 254.2, $^2J_{CF}$ = 46.4, CF), 137.63 (bs, $C2_{Imi}$), 137.47 (dd, $^1J_{CF}$ = 237.8, $^2J_{CF}$ = 39.5, CF), 127.56 (d, $^2J_{CF}$ = 31.9, $C4_{Imi}$), 121.89 (dd, $^3J_{CF}$ = 13.7, $^4J_{CF}$ = 6.0, $C5_{Imi}$). ^{19}F NMR (DMSO-d_6): −138.90 (d, 1F, $^3J_{FF}$ = 125.0), −160.88 (d, 1F, $^3J_{CF}$ = 128.1). HRMS (ESI): for M − H, i.e. $C_6H_3F_2N_2O_2$ calculated: 173.0163; found: 173.0164; mp: decomposition between 250 and 270 °C. Elemental analysis for $C_6H_4F_2N_2O_2$, calculated: 41.39% C, 2.35% H, 16.09% N; found 40.98% C, 2.33% H, 15.76% N.

4.11. (Z)-α,β-Difluorourocanic acid (**6b**)

Compound **12b** (70 mg, 0.18 mmol) was dissolved in 8 mL of *t*-BuOH and 3 mL of 2-methyl-2-butene. The solution was then cooled to 0 °C and a solution of $NaClO_2$ (160 mg, 1.78 mmol) and NaH_2PO_4 (214 mg, 1.78 mmol) in 4.0 mL of H_2O was added. The mixture was stirred at room temperature until TLC indicated the complete disappearance of aldehyde. Dichloromethane (80 mL) was added and the mixture was washed with water (2 × 10 mL), brine (2 × 10 mL) and dried over anhydrous Na_2SO_4. The mixture was filtered and evaporated. The residue was washed with water (2 × 5 mL) and dissolved in 10 mL of CH_3COOH and 1.0 mL of concentrated HCl. After the mixture was stirred at room temperature for 3 h, the solvent was evaporated and the residue was washed with ethyl acetate (2 × 5 ml) and 2 mL of H_2O. Vacuum drying of the residue gave 11 mg (37%) of the final product **6b** as a white solid.

^1H NMR (DMSO-d_6): 8.42 (d, 1H, $^4J_{HF}$ = 1.5), 7.99 (bs, 1H). ^{13}C NMR (DMSO-d_6): 164.65 (dd, $^2J_{CF}$ = 26.1, $^3J_{CF}$ = 6.0, CO), 154.92 (dd, $^1J_{CF}$ = 250.8, $^2J_{CF}$ = 21.8, CF), 141.81 (s, $C2_{Imi}$), 142.33 (dd, $^1J_{CF}$ = 245.9, $^2J_{CF}$ = 14.6, CF), 131.49 (d, $^2J_{CF}$ = 35.3, $C4_{Imi}$), 125.10 (d, $^3J_{CF}$ = 8.6, $C5_{Imi}$). ^{19}F NMR (DMSO-d_6): −132.95 (bs, 1F), −141.99 (bs, 1F). HRMS (ESI): for M − H, i.e. $C_6H_3F_2N_2O_2$ calculated: 173.0163; found: 173.0166; mp: decomposition between 250 and 270 °C. Elemental analysis for $C_6H_4F_2N_2O_2$, calculated: 41.39% C, 2.35% H, 16.09% N; found: 41.16% C, 2.35% H, 15.81% N.

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