New Building Blocks for Fluorinated Bioimidazole Derivatives II: Preparation of β-Fluorourocanic Acids

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Replacement of vinyl hydrogen with fluorine is based on addition of an FBr equivalent to a double bond followed by HBr elimination. This sequence has been adapted to prepare 3-fluoro-3-imidazolylpropenoic acids (β-fluorourocanic acids), and the related fluorinated imidazolyl propenals and prop-2-en-1-ols, from urocanic acid. Tritylation of the imidazole nitrogen was necessary for successful addition of "FBr" to the double bond, and prior reduction of the carboxyl group to the alcohol was required to provide the desired chemoselectivity in the elimination of HX. Reoxidation and deprotection produced the fluorinated urocanic acids.

Introduction

We have been involved for many years in the synthesis and biological evaluation of fluorinated analogues of biologically important imidazoles. As part of this research, we have prepared fluorinated analogues of urocanic acid (**1**), the imidazolyl acrylic acid that is produced in vivo by histidine catabolism.[1] Interest in urocanic acid and derivatives has increased with the discovery that (*Z*)-urocanic acid, formed by photoisomerization of the initially formed (*E*)-isomer in the epidermis, functions systemically as an immunosuppressive agent.[2] To study these and others processes, we have developed methods or used known ones to prepare (*Z*)- and (*E*)-isomers of α-fluorourocanic,[3] 2-fluorourocanic, and 4-fluorourocanic acids.[4] To complete the inventory of monofluorinated urocanic acids, we now have developed synthetic procedures that provide (*E*)- and (*Z*)-β-fluorourocanic acids (**2a** and **2b**, respectively).

Methods to prepare β-fluoro-β-aryl acrylic acids (in large part β-fluorocinnamate derivatives) can be grouped into three general procedures. One procedure[5] involves a multistep construction of the carbon skeleton from CF_2=CH−Li, CO_2, and aryl-MgBr. A second recently published[6] method is based on catalytic coupling reaction of aryl-I with CF_2BrCH_2COOEt. The third procedure is based on addition of HF to a triple-bond precursor.[7] In general, the applicability of these methods depends on the availability of starting compounds and the compatibility of functional groups.

On the basis of literature data, it seems that the addition[8,9] of FX followed by HX elimination[10,11] could provide a direct route to β-aryl-β-fluoro-acrylic acids. Furthermore, we have shown previously that this approach is applicable in imidazole chemistry, as we demonstrated[12] by the preparation of β-fluorohistamines from 1-trityl-4-vinyl-1*H*-imidazole. However, applications of this strategy to compounds with additional functional groups are not well studied. The limitations, problems, and resolution of the problems related to the addition of an FBr equivalent to polyfunctional substrates and a protocol for preparation of β-aryl-β-fluoro-acrylic acids are described in this paper. Application of this protocol to the syntheses of (*E*)- and (*Z*)-β-fluorourocanic acid is detailed.

Chemistry

The facile addition of "FBr" to the double bond of unsaturated compounds containing a carboxylic acid remote from the double bond by $Et_3N{\cdot}3HF$ and NBS is documented.[8,13] Furthermore, the addition of FBr to a double bond that has the carboxyl function directly attached (acrylic acids) also has been described.[14,15] Issues to be considered in regard to the presence of the carboxyl group include the possible intervention of bromodecarboxylation (a variant of the Hunsdiecker reaction) as a competing process.[16]

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(3) Percy, E.; Singh, M.; Takahashi, T.; Takeuchi, Y.; Kirk, K. L. *J. Fluorine Chem.* **1998**, *91*, 5. In this report, the scheme we constructed describing the mechanism of action of urocanase was oversimplified and contained incorrect structures. Please see ref 1 for a thorough discussion of this mechanism.
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(12) Dolensky, B.; Kirk, L. K. *J. Org. Chem.* **2001**, *66*, 4687. Corrections: the ^{19}F NMR shift of compound **8** should be −169.1 ppm; the page in ref 23 should be 3043.
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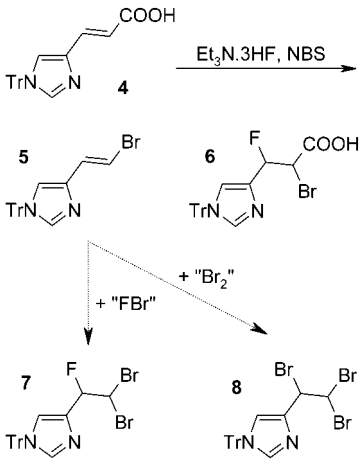
Scheme 1



Attempts to add FBr to urocanic acid (**1**) were unsuccessful, and **1** was unchanged (^{1}H NMR of crude product). The lack of reaction is probably due to insufficient solubility of **1** in the reaction medium (CH_2Cl_2). However, when DMSO was used as a cosolvent to increase solubility, an intractable tar was obtained. Reaction of methyl urocanate (**3**) with FBr in methylene chloride gave a complex reaction mixture, which had very similar features in the ^{1}H NMR to the product mixture obtained from the reaction of FBr with unprotected 4-vinyl-1*H*-imidazole.[12] As before, there was no evidence of any adduct of FBr (on the basis of ^{19}F NMR). Thus, imidazole ring protection is necessary. On the basis of its effectiveness in our previous work,[12] we used the trityl group for this purpose.

Treatment of 1-trityl-*E*-urocanic acid **4** with $Et_3N{\cdot}3HF$ and NBS (Scheme 1) gives four products. Under ordinary conditions of FBr addition (substrate:$Et_3N{\cdot}3HF$:NBS molar ratio = 1:1.5:1.1), bromoolefin **5** is formed as the major product and compounds **6**−**8** as byproducts[17] (23% **4**; 62% **5**; 8% **6**; 4% **7**; 3% **8**). When the ratio of reagents to substrate was increased (1:3:2), the main product was **7** (0% **4**; 0% **5**; 18% **6**; 57% **7**; 25% **8**). From these two experiments, it appears that compound **7** is formed by addition of FBr to the double bond of initially formed **5** instead of by bromodecarboxylation of **6**. This is reasonable since the carboxyl group of **6** should be relatively more resistant to bromodecarboxylation initiated by NBS than **4** (where the carboxyl group is situated on a double bond).

In light of the problems for FBr addition presented by the presence of the free carboxyl group, we concluded that protection of both the imidazole ring and carboxyl group is required. Accordingly, tritylated methyl urocanate **9a** was next considered as the starting compound. We were encouraged by the previous demonstration[18] of successful addition of bromine and chlorine to **9a**. Furthermore, FBr addition has been carried out successfully on cinnamate esters.[15,19]

Unfortunately, we also encountered serious problems with the addition of FBr to **9a**. Under the ordinary conditions, four products were formed, including the desired FBr-adduct **10** and Br_2-adduct **11** (Scheme 2). In addition, α-bromourocanates **12a** and **12b**, products of subsequent dehydrofluorination of **10** and/or dehydrobromination of **11**, were isolated. We found that the outcome of the reaction is strongly affected the by ratio of reagents, reaction time, and reaction mixture workup (Table 1). Under the ordinary conditions, **9a** is converted to FBr-adduct **10** in about 50% yield (row a). When the reaction time is extended, there is no further conversion of **9a** to the FBr-adduct **10**, but there is an increased formation of bromourocanates **12** (row b). When the amount of $Et_3N{\cdot}3HF$ is doubled, the conversion is slightly better (row c). Finally, doubled amounts of both reagents ($Et_3N{\cdot}3HF$ and NBS) produce the best results and the starting urocanate **9a** is converted completely to FBr-adduct **10** and bromourocanates **12** (row d). In the same conditions but with a shorter reaction time, the Br_2-adduct **11** could be detected spectroscopically in the crude product (row e). The product distribution obtained by the ordinary workup of the reaction is shown in row f.

Scheme 2

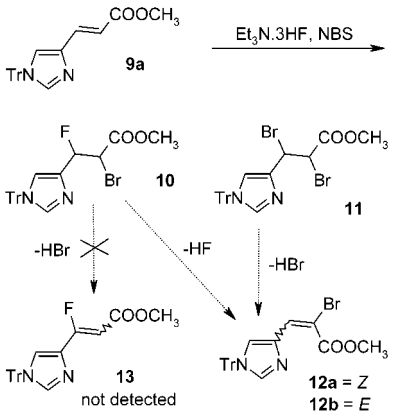


Table 1

	$Et_3N{\cdot}3HF$:NBS	time [h]	**9a**	**10**	**12a**	**12b**	**11**
a	1.5:1.1	12	38	46	6	3	7
b	1.5:1.1	117	49	33	18	+	0
c	3.0:1.1	15	27	52	15	6	0
d	3.0:2.2	16	0	68	22	10	0
e	3.0:2.2	4	7	72	5	+	16
f	3.0:2.2	16	+	12	74	14	0

It is apparent from the above results that the FBr-adduct **10** is quite sensitive to basic conditions, properties not reported for FBr- or FCl-adducts of cinnamates[15,19] or Br_2- of Cl_2-adducts of urocanates.[18] The FBr-adduct **10** eliminates HF to produce the α-bromourocanates **12** and gives no trace of the desired fluorourocanate **13** (on the basis of ^{1}H NMR) when treated with base (Et_3N, $NaHCO_3$, or *t*-BuOK). Elimination to **12** also occurred under attempts to displace the bromine with potassium phthalimide or sodium azide. Since displacement of bromine in FBr-adducts of β-alkylacrylic acids[14] by ammonium can be carried out (10−60%), it is apparent that the aryl substituent is responsible for this extreme reactivity. Treatment of FBr- or FCl-adducts of cinnamates with base[15,19] or heating neat[15] above 50 °C also results in elimination of β-halogen. Similar behavior is seen with Br_2- or Cl_2-adducts of tritylated ethyl urocanate.[18] The fact that preferential HBr elimination occurs with FBr-adducts of styrene or vinyl imidazole reveals the role of the carboxylic function in the loss of HF in the present case. Since there is also preferential loss of HF from FBr-adducts of symmetrically substituted ole-

(17) Compounds **5** and **7** were isolated, while the presence of **6** and **8** was based on MS and NMR spectroscopic evidences.

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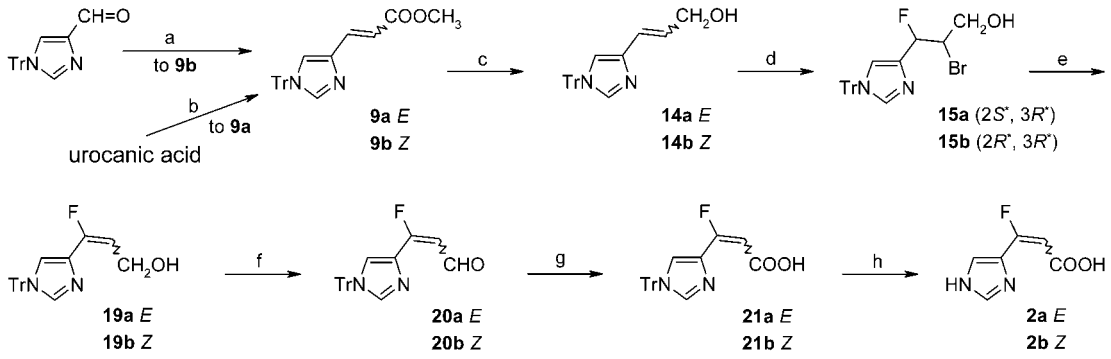
Scheme 3[a]



[a] (a) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, ref 31, **9b** 71−95%; (b) (i) MeOH/H^+, ref 32, (ii) TrCl, Et_3N, ref 33, **9a** 91−95%; (c) DIBAL-H, ref 34, **14a** 46−59%, **14b** 65−76%; when we used reduction by LAH (ref 35), also reduction of the double bond (18%) was found; (d) NBS, 3HF·Et_3N, **15a** 59−76%, **15b** 74%; (e) Et_3N, 110 °C, **19a** 52−62%, **19b** 80%; (f) MnO_2, **20a** 61−80%, **20b** 92%; (g) $NaClO_2$, ref 36, **21a** 68%, **21b** 71%; (h) $CH_3COOH/HCl/H_2O$, **2a** 100%, overall ca. 10%, **2b** 100%, overall ca. 23%.

fins, for example, from α-bromo-α′-fluorosuccinate esters, special effects of fluorine may also be involved.[15,20]

The problem of preferential elimination of HF vs HBr from the product of FBr addition to the furan ring of khellin was partially solved[21] by using KF with DMA as the elimination agent. Unfortunately, these conditions again produced no fluorourocanate **13** (^{1}H NMR) when carried out on **10**. In addition, we found that under these elimination conditions, the initially formed bromourocanates **12** are partially converted 4-methoxycarbonyl-4-ethynyl- and 4-ethynyl-1-trityl-1*H*-imidazoles[22] as result of loss of HBr or both HBr and $COOCH_3$. A similar subsequent reaction is not possible for the five-membered ring of khellin.

It should be noted that, in all cases, the (*Z*)-isomer **12a** was formed as the major isomer. Since the trans addition of FBr gives the erythro isomer of FBr-adduct **10**, mainly cis elimination of HF must occur to give **12a**, rather than trans elimination to give **12b**. In contrast, we found[22] that treatment of Br_2-adduct **11** with base gives mainly **12b**, as a result of expected trans elimination of HBr. The same selective cis HF elimination was also found with cinnamates.[15,19]

From these results, it is clear that the influence of the carboxyl group precludes formation of the *β*-fluorourocanate **13**. To avoid the directive effects of the carboxylic function in the elimination reaction, compounds **9** were reduced to the allyl alcohols **14** and the sequence of reactions to obtain acids **2** was applied (Scheme 3).

At this point, we note that the FBr-adducts **6** and **10** (as well as the Br_2-adduct **11**) were formed as single diastereoisomers (^{1}H NMR). Trans addition of FBr to the (*E*)-olefin would produce the erythro configuration.[9] However, this diastereoselectivity is observed only with (*E*)-olefins. The (*Z*)-olefins produced a mixture of both diastereoisomers.[19,23] Consistent with this previous observation, the addition of FBr to the (*E*)-allylalcohol **14a** takes place cleanly and forms the erythro (*S**,*R**)-isomer **15a** in 60−78% yield. The threo isomer **15b** was found only as a minor impurity (<5%) during chromatographic purification of **15a**. On the other hand, the addition of FBr to the (*Z*)-allylalcohol **14b** proceeded with a good yield but gave a mixture of diastereoisomers **15a** and **15b** in a ratio of 8:2. We note that we did not observe any isomerization of FBr-adducts **6**, **10**, or **15**, a process that may occur at higher temperatures.[15] We attempted to alter the ratio of isomer formation by using a larger excess of Et_3N·3HF or by adding of Et_3N in order to form the more nucleophilic[24] Et_3N·2HF. The effect of HF concentration on the course of FBr addition has been described.[25] As can be seen from Table 2, the ratio of **15a**:**15b** can be affected slightly by addition of Et_3N. However, when more than 0.5 equiv of Et_3N to Et_3N·3HF is used, the overall conversion of **14b** to isomers **15a** and **15b** is dramatically lower.

The FBr addition proceeded with Markovnikov selectivity in accordance with all known FBr additions to *β*-aryl-acrylates, acrylates, or styrene derivatives wherein the Markovnikov product is formed as the major or only one[9] (one surprising exception is addition to *β*-oxiranylstyrene[26]). The total regioselectivity we observe probably results from reinforcing orientation effects of the aryl and carboxyl groups. Although not isolated, we found NMR evidence for the formation **16** ("succinimide-Br" addition) and **17** ("HO-Br" addition) (see Supporting Information, Scheme 4), compounds analogous to byproducts formed from vinylimidazole.[12] Compound **18**, wherein the OH and F groups are transposed (see Supporting Information, Scheme 4) due to a possible rearrangement involving the hydroxy group,[27] was not observed.

Several conditions were investigated for the dehydrobromination of adducts **15**. The best conditions proved to be Et_3N in DMSO at 110 °C, which cleanly produced olefins **19** in yields of 50−80%. We observed no isomerization about the double bond in that dehydrobromination of mixtures of **15a** and **15b** gave the same ratio

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(26) Hedhli, A.; Baklouti, A. *J. Org. Chem.* **1994**, *59*, 5277. Apparently regioselectivity was established only from ^{19}F NMR. We have found such data quite sensitive to sample concentration and to impurities. In contrast, we found analyses of ^{1}H−^{13}C and ^{19}F−^{13}C coupling constants in ^{13}C NMR to be a reliable basis for structure assignment.

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of **19a** and **19b**. Furthermore, we found no NMR evidence for competing HF elimination. The reaction was slower in DMF or Et_3N and did not proceed in toluene at 80 °C. Other bases examined, including K_2CO_3, DBU, or *t*-BuOK, were less satisfactory, possibly because of competing oxirane formation.[27]

The reoxidation of the alcohols to the carboxyl function was done in two steps. The fluoro alcohols **19** were conveniently oxidized to aldehydes **20** using activated MnO_2 in yields better than those reported[28] for nonfluorinated analogues (60−90% vs 30%). However, when the oxidation was carried out with pyridinium dichromate in DMF, mild conditions that are reported to give no isomerization[29] of double bonds, we, in fact, observed substantial isomerization. Thus, the oxidation of (*E*)-fluoro alcohol **19a** gives (*E*)-aldehyde **20a** and (*Z*)-aldehyde **20b** in a ratio of 73:27. Under the same conditions, the oxidation of (*Z*)-fluoro alcohol **19b** gives aldehydes **20a** and **20b** in a ratio of 2:98. In view of the difficulty in preparing **15b** caused by the loss of stereoselectivity in the FBr addition, this second loss of stereoselectivity is actually quite useful and provided a fortuitous alternative route to **2b**. The aldehydes **20** are fairly stable, but we recommend no long-term storage because of the known[7] air oxidation of 3-fluoro-3-phenylpropanal to 3-fluoro-3-phenyl-acrylic acid.

In the second step, the aldehydes **20** were oxidized to acids **21** with $NaClO_2$. Final removal of trityl groups from acids **21** produced β-fluorourocanic acids **2**. The acid **2a** was isolated as the dihydrochloride monohydrate and acid **2b** as the dihydrochloride dihydrate. These "complexes" are surprisingly stable and, even under extended drying (100 Pa, 3 days, 40 °C), there was only partial release of HCl and H_2O, as shown by elemental analyses.

Conclusion

We have completed a synthesis of β-fluorourocanic acids using, as the key step, addition of FBr (Et_3N·3HF with NBS) to a vinyl imidazole derivative. On the basis of our results and literature reports, we make the following generalizations. Addition of an FBr equivalent to β-aryl acrylic acids is complicated by decarboxylation/bromination. The addition of FBr to the N-protectected imidazoyl acrylate esters is successful. In the next step, however, the presence of the ester function causes elimination of HF instead of HBr from the FBr adducts. Chemoselectivity of the elimination can be changed by prior reduction of the carboxyl to hydroxymethyl. Following elimination, reoxidation of the alcohol in two steps gives the β-fluoroacrylates.

Experimental Section

The NMR spectra were recorded at frequencies of 300.1 MHz for ^1H, 75.5 MHz for ^{13}C, and 282.2 MHz for ^{19}F spectra. The solvent is $CDCl_3$ unless otherwise specified. For other details, see Supporting Information.

Addition of FBr to Tritylated Urocanic Acid 4: Procedure A. To a cooled (0 °C) and stirred solution of 301 mg (0.79 mmol) of **4** (prepared according to ref 18) dissolved in CH_2Cl_2 was added 0.20 mL (1.23 mmol) of Et_3N·3HF. After 15 min, 154 mg (0.87 mmol) of NBS was added in portions. After an additional 15 min, the mixture was allowed to come to room temperature, stirred for 2 h, and then evaporated to dryness at room temperature. ^1H NMR analysis of the crude product indicated that the molar ratio of **4**:**5**:**6**:**7**:**8** was 23:62:8:4:3. This mixture was subjected to preparative TLC (9:1 petroleum ether/acetone) to give 115 mg (35%) of compound **5**. **Procedure B.** Using the same conditions as described in procedure A, 304 mg (0.80 mmol) of **4**, 0.40 mL (2.45 mmol) of Et_3N·3HF, and 281 mg (1.58 mmol) of NBS gave a mixture of three products. ^1H NMR analysis of the crude product showed the presence of **6**, **7**, and **8** in a molar ratio of 18:57:25. The products were partially separated by filtration through 4 g of silica. NMR and MS spectroscopic analysis of the mixtures verified the structures of **6** and **8**. In another experiment, 151 mg of **7** (37%) was isolated from the crude product by preparative TLC (CH_2Cl_2).

(*E*)-4-(2-Bromovinyl)-1-trityl-1*H*-imidazole (5). ^1H and ^{13}C NMR characteristics were identical to material we had characterized previously.[12] In addition, the signal for the olefinic protons in ^1H NMR we originally observed as a singlet is resolved into two doublets at δ 7.01 (1H, d, 13.5) and δ 6.87 (1H, d, 13.5) when measured in a slightly acidic pH. These interaction constants confirm the earlier assignment[12] of the (*E*)-configuration.

(2*R,3*S**)-2-Bromo-3-fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propionic Acid (6).** ^1H NMR characteristic signals: δ 5.92 (1H, dd, 45.4, 6.3), 4.90 (1H, dd, 10.4, 6.3). HRMS FAB$^-$: [M − H]$^-$ calcd for $C_{25}H_{19}BrFN_2O_2$, 477.0614, 479.0593; found, 477.0627, 479.0623.

4-(2,2-Dibromo-1-fluoroethyl)-1-trityl-1*H*-imidazole (7). ^1H NMR: δ 7.44 (1H, br s), 7.37−7.32 (9H, m), 7.15−7.10 (6H, m), 7.01 (1H, br s), 6.07 (1H, dd, 13.8, 5.7), 5.65 (1H, dd, 45.6, 5.7). ^{13}C NMR: δ 141.93 (3C, off: m), 139.15 (off: dd, 211.4, 7.2), 135.38 (d, 24.8, off: m), 129.71 (6CH, off: dm), 128.27 (3CH, off: dt), 128.16 (6CH, off: dm), 121.82 (d, 5.2, off: dm, 192), 91.06 (d, 182.8, off: dd, 158.6, 182.8), 75.76 (off: m), 43.91 (d, 30.5, off: dd, 178.5, 30.8). ^{19}F NMR: δ −168.8 (m, ΣJ 150). HRMS FAB$^+$: M$^+$ calcd for $C_{24}H_{20}Br_2FN_2$, 512.9977, 514.9957, 516.9936; found, 512.9962, 514.9951, 516.9921.

4-(1,2,2-Tribromo-ethyl)-1-trityl-1*H*-imidazole (8). ^1H NMR only characteristic signals: δ 6.18 (1H, d, 6.8), 5.43 (1H, d, 6.8), predicted[30] chemical shifts 6.17 and 5.54. LRMS FAB$^+$: MH$^+$ calcd for $C_{24}H_{20}Br_3N_2$, 573, 575, 577, and 579. These peaks were observed but too low in intensity to record the HRMS.

Addition of FBr to Tritylated Urocanic Acid Methyl Ester 9a: Procedure A. To 3.00 g (7.61 mmol) of **9a** in 45 mL of CH_2Cl_2, cooled to 0 °C, was added 3.7 mL (22.7 mmol) of Et_3N·3HF. After 10 min, 2.97 g (16.7 mmol) of NBS was added in portions. The temperature was allowed to warm to room temperature (2 h) and stirred for an additional 14 h. The reaction mixture was poured into a mixture of 250 mL of CH_2Cl_2, 200 mL of water, and 10 mL of concentrated ammonia. The water layer was extracted with 2 × 100 mL of water, and the combined organic layers were washed with 3 × 150 mL of brine and dried over $MgSO_4$. Removal of solvent gave 4.35 g of solid. This was separated by column chromatography (80 g, 95:5 CH_2Cl_2/Et_2O) to give 0.32 g (9%) of **10**, 1.93 g (54%) of **12a**, and 0.35 g (9%) of **12b**. **Procedure B.** According to the same conditions described in procedure A, to 1.00 g (2.54 mmol) of **9a** and 1.2 mL (7.36 mmol) of Et_3N·3HF in 15 mL of CH_2Cl_2 was added 0.91 g (5.11 mmol) of NBS. The reaction mixture was kept for 10 min at 0 °C and for 4 h at room temperature.

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The mixture was quickly partitioned between 150 mL of CH_2Cl_2 and 150 mL of water containing 2 mL of concentrated ammonia. The organic layer was washed with 150 mL of brine and filtered through a pad of silica (5 g), and the solvent was evaporated to dryness. The residue was separated by preparative TLC (98:2 CH_2Cl_2/acetone) to give 0.72 g (58%) of **10** as an off-white solid. **Procedure C.** Optimization experiments were carried out using 129 mg (327 μmol) of **9a** in 2 mL of CH_2Cl_2 according to procedure A. The reaction mixtures were evaporated to dryness, and compositions of product mixtures were estimated by ^{1}H NMR. The equivalents of reagents, reaction times, and product compositions are given in Table 1.

(2*R,3*S**)-2-Bromo-3-fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propanoic Acid Methyl Ester (10).** ^{1}H NMR: δ 7.48 (1H, d, 1.2), 7.38−7.30 (9H, m), 7.16−7.09 (6H, m), 6.99 (1H, dd, 3.6, 1.2), 5.73 (1H, dd, 46.5, 9.9), 4.89 (1H, dd, 9.9, 6.0), 3.84 (3H, s). ^{13}C NMR: δ 168.07, 141.76 (3C), 134.54 (d, 21.7), 129.09 (6CH), 128.09 (3CH), 127.98 (6CH), 122.69 (d, 6.3), 87.01 (d, 173.9), 75.94, 53.01, 42.93 (d, 36.5). ^{19}F NMR: δ −157.0 (ddd, 46.7, 6.3, 3.8). HRMS FAB$^+$: MH$^+$ calcd for $C_{26}H_{23}BrFN_2O_2$, 493.0927, 495.0906; found, 493.0935, 495.0931. Mp: 135−145 °C dec.

(*Z*)-2-Bromo-3-(1-trityl-1*H*-imidazol-4-yl)-acrylic Acid Methyl Ester (12a). ^{1}H NMR: δ 8.31 (1H, d, 0.6), 7.93 (1H, dd, 1.3, 0.6), 7.53 (1H, d, 1.3), 7.39−7.31 (9H, m), 7.19−7.11 (6H, m), 3.84 (3H, s). ^{13}C NMR: δ 163.69 (off: dq, 5.0, 3.8), 141.74 (3C), 139.39 (off: dd, 211.5, 7.5), 135.88 (off: d, 157.5), 135.72 (off: ddd, 11.6, 8.7, 2.4), 129.61 (6CH), 128.29 (3CH), 128.17 (6CH), 125.72 (off: ddd, 185.6, 5.5, 3.3), 109.31 (off: dd, 3.5, 1.0), 76.01, 53.24 (off: q, 147.6). Mp: 200−204.5 °C (from cyclohexane). Anal. Calcd for $C_{26}H_{21}BrN_2O_2$: C, 65.97; H, 4.47; N, 5.92. Found: C, 65.74; H, 4.61; N, 5.84. The (*Z*)-configuration was assigned on the basis of predicted ^{1}H NMR chemical shifts[30] and on analogy with NMR data of the ethyl ester derivative.[18]

(*E*)-2-Bromo-3-(1-trityl-1*H*-imidazol-4-yl)-acrylic Acid Methyl Ester (12b). ^{1}H NMR: δ 7.57 (1H, dd, 1.4, 0.6), 7.43 (1H, d, 1.3), 7.36−7.31 (10H, m), 7.17−7.10 (6H, m), 3.70 (3H, s). ^{13}C NMR: δ 164.37 (off: dq, 10.9, 4.0), 141.87 (3C), 138.96 (off: dd, 211.1, 7.2), 135.53 (off: ddd, 11.6, 8.3, 2.0), 135.13 (off: d, 158.8), 129.61 (6CH), 128.13 (3CH), 128.06 (6CH), 124.79 (off: ddd, 195.7, 5.3, 3.5), 106.81 (off: d, 8.4), 75.68, 52.66 (off: q, 147.8). Mp: 178−185 °C (from chloroform). Anal. Calcd for $C_{26}H_{21}BrN_2O_2$: C, 65.97; H, 4.47; N, 5.92. Found: C, 65.89; H, 4.47; N, 5.91. The (*E*)-configuration was assigned on the basis of predicted ^{1}H NMR chemical shifts[30] and on analogy with NMR data of the ethyl ester derivative.[18]

(2*R,3*S**)-2,3-Dibromo-3-(1-trityl-1*H*-imidazol-4-yl)-propanoic Acid Methyl Ester (11).** ^{1}H NMR: δ 7.59 (1H, s), 7.38−7.32 (9H, m), 7.16−7.09 (6H, m), 6.92 (1H, s), 5.37 (1H, d, 11.4), 5.17 (1H, d, 11.4), 3.86 (3H, s). HRMS FAB$^+$: MH$^+$ calcd for $C_{26}H_{23}Br_2N_2O_2$, 553.0126, 555.0106, 557.0085; found, 553.0111, 555.0102, 557.0080.

Addition of FBr to Allylalcohols 14a and 14b: Procedure A. To 7.88 g (21.5 mmol) of allyl alcohol **14a** dissolved in 360 mL of CH_2Cl_2 was slowly added via syringe 5.4 mL (33.0 mmol) of $Et_3N{\cdot}3HF$. After 10 min, 4.21 g (23.7 mmol) of NBS was added in two portions and the mixture was stirred for 5 h. The reaction mixture then was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The solid residue was separated on column chromatography to give 6.87 g (69%) of **15a**. **Procedure B.** According to the same conditions (procedure A), 1.20 g (3.27 mmol) of allyl alcohol **14b**, 0.80 mL (4.91 mmol) of $Et_3N{\cdot}3HF$, and 642 mg (3.61 mmol) of NBS in 66 mL of CH_2Cl_2 gave 1.30 g (74%) of a mixture of isomers **15a** and **15b** in a molar ratio of 75:25. Column chromatography effected only partial separation, and only enriched fractions were obtained. **Procedure C.** The optimization reactions were carried out on 50 mg (0.14 mmol) of **14b** in 2 mL of CH_2Cl_2. The experiments were done as described for procedure A except that Et_3N was added before the addition of NBS. The reaction mixtures were evaporated to dryness at room temperature, and the product compositions were estimated on the basis of ^{1}H and ^{19}F NMR. The equivalents of reagents and product compositions are given in Table 2. It should be noted that, for estimation of product composition, the signals at δ 5.72 and 5.76 of the CHF groups cannot be used because their order of appearance is often switched. This is caused by their high sensitivity to the conditions under which the NMR measurements are made.

(2*S,3*R**)-2-Bromo-3-fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propan-1-ol (15a).** ^{1}H NMR: δ 7.46 (1H, d, 1.5), 7.38−7.30 (9H, m), 7.16−7.10 (6H, m), 6.96 (1H, dd, 2.4, 1.5), 5.72 (1H, dd, 45.9, 5.4), 4.59 (1H, dddd, 8.1, 6.6, 5.4, 4.8), 4.49 (1H, br s), 4.11 (1H, dd, 12.5, 6.4), 4.02 (1H, ddd, 12.5, 4.3, 1.5). ^{13}C NMR: δ 141.85 (3C, off: m), 138.94 (off: dd, 211.4, 7.1), 135.96 (d, 23.8, off: dddt, 23.8, 10.9, 8.6, 3.1), 129.96 (6CH, off: dm), 128.23 (3CH, off: dt), 128.13 (6CH, off: dm), 121.83 (d, 5.7, off: ddt, 192.8, 5.9, 3.3), 88.44 (d, 174.3, off: ddm, 174.1, 155.5, ΣJ 12), 75.61 (off: m), 62.80 (d, 4.9, off: tm, 146.3, ΣJ 13), 54.71 (d, 25.9, off: dd, 152.5, 26.2). ^{19}F NMR: δ −172.3 (dd, 45.6, 12.5). Mp: 142 °C. Anal. Calcd for $C_{25}H_{22}BrFN_2O$: C, 64.52; H, 4.76; N, 6.02. Found: C, 64.61; H, 4.83; N, 6.06. HRMS FAB$^+$: MH$^+$ calcd for $C_{25}H_{23}BrFN_2O$, 465.0978, 467.0957; found, 465.0956, 467.0966.

(2*R,3*R**)-2-Bromo-3-fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propan-1-ol (15b).** ^{1}H NMR: δ 7.46 (1H, s), 7.36−7.30 (9H, m), 7.16−7.09 (6H, m), 6.98 (1H, s), 5.76 (1H, dd, 45.5, 4.6), 5.35 (1H, bs), 4.45 (1H, ddt, 18.0, 6.9, 4.8), 4.02 (1H, dd, 12.3, 4.8), 3.89 (1H, dd, 12.6, 6.9). ^{13}C NMR: δ 141.79 (3C), 138.89, 136.25 (d, 25.1), 129.61 (6CH), 128.19 (3CH), 128.10 (6CH), 121.28 (d, 5.8), 87.94 (d, 175.0), 75.69, 62.66 (d, 2.8), 55.50 (d, 23.6). ^{19}F NMR: δ −176.9 (dd, 45.8, 17.1).

Elimination of HBr from FBr-Adducts 15 to Fluoroallyl Alcohols 19. A solution of 357 mg (0.77 mmol) of the 1:4 mixture of isomers **15a** and **15b** in 30 mL of dry DMSO was treated with 5 mL of Et_3N and stirred for 21 h at 110 °C. After cooling to room temperature, the mixture was partitioned between a mixture of 200 mL of brine and 200 mL of water and extracted with 3 × 20 mL of CH_2Cl_2. The organic layers were washed with 100 mL of a 10% aqueous solution of citric acid and 100 mL of brine, dried over $MgSO_4$, and evaporated to dryness. Preparative TLC (4:1 CH_2Cl_2/Et_2O) gave 46 mg (78% from **15a**) of **19a** and 190 mg (81% from **15b**) of **19b**. The identical ratio of products (1:4) demonstrates that no isomerization occurs during the elimination.

(*E*)-3-Fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-prop-2-en-1-ol (19a). ^{1}H NMR: δ 7.50 (1H, dd, 3.0, 1.5), 7.36−7.30 (9H, m), 7.17−7.10 (6H, m), 7.06 (1H, t, 1.2), 5.96 (1H, br s), 5.63 (1H, dt, 22.8, 6.9), 4.32 (2H, dd, 6.9, 2.7). ^{13}C NMR: δ 155.46 (d, 235.8, off: ddt, 235.6, 8.2, 5.1), 141.55 (3C), 139.27 (d, 2.0, off: ddd, 212.1, 7.3, 1.7), 133.48 (d, 41.4, off: m), 129.44 (6CH), 128.13 (3CH), 128.04 (6CH), 119.93 (d, 1.0, off: dd, 194.7, 2.9), 106.09 (d, 18.5, off: ddt, 156.7, 18.4, 4.5), 75.70 (off: m), 55.34 (d, 11.6, tdd, 144.2, 12.5, 2.1). ^{19}F NMR: δ −115.4 (dm, 22.9, ΣJ 11). Anal. Calcd for $C_{25}H_{21}FN_2O$: C, 78.10; H, 5.51; N, 7.29. Found: C, 78.04; H, 5.46; N, 7.26. R_f (Et_2O) = 0.77. Mp: 133−134 °C (from cyclohexane).

(*Z*)-3-Fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-prop-2-en-1-ol (19b). ^{1}H NMR: δ 7.44 (1H, dd, 3.1, 1.5), 7.35−7.29 (9H, m), 7.16−7.08 (6H, m), 6.93 (1H, m, ΣJ 4), 5.81 (1H, dt, 38.1, 7.3), 4.33 (2H, dd, 7.4, 1.7), 3.53 (1H, bs). ^{13}C NMR: δ 153.35 (d, 242.1), 141.82 (3C), 139.58 (d, 1.6), 133.87 (d, 39.6), 129.58 (6CH), 128.16 (3CH), 128.10 (6CH), 118.96 (d, 1.2), 103.52 (d, 11.3), 75.62, 55.03 (d, 6.9). ^{19}F NMR: δ −122.1 (d, 38.4). R_f (Et_2O) = 0.36. Mp: 150−152 °C (from petroleum ether).

The Oxidation of Allyl Alcohols 19 to Propenals 20: Procedure A. To a stirred solution of 422 mg (1.10 mmol) of allyl alcohol **19a** in 30 mL of CH_2Cl_2 was added 400 mg (4.60 mmol) of activated MnO_2. The mixture was stirred at room temperature and monitored by TLC (9:1 CH_2Cl_2/Et_2O). After 1 h, an additional 400 mg of activated MnO_2 was added and mixture was stirred overnight. The mixture was filtered through a paper filter to remove most of the MnO_2 and then eluted through 5 g of silica with CH_2Cl_2. The crude product was purified by column chromatography (60 g, 95:5 CH_2Cl_2/Et_2O) to give 336 mg (80%) of propenal **20a**. Using an analogous procedure, propenal **20b** was obtained from **19b** in 92% yield. **Procedure B.** To a stirred solution of 26 mg (68

μmol) of **19a** in 2 mL of dry DMF was added 33 mg (88 μmol) of pyridinium dichromate (PDC), and the mixture was stirred for 3 days at room temperature. The mixture then was diluted with 20 mL of CH_2Cl_2 and eluted through 4 g of silica with 10 mL of Et_2O. After removal of the solvents, the NMR spectrum of the residue was recorded. The mixture of aldehydes **20a** and **20b** was estimated to be 73:27. Oxidation of allyl alcohol **19b** using the same procedure gave **20a** and **20b** in a ratio of 2:98.

(*E*)-3-Fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propenal (20a). ^{1}H NMR: δ 10.85 (1H, ddd, 8.1, 2.4, 0.9), 7.53 (1H, dd, 3.0, 1.5), 7.41−7.35 (9H, m), 7.33 (1H, t, 1.4), 7.16−7.11 (6H, m), 5.82 (1H, dd, 21.0, 8.1). ^{13}C NMR: δ 193.37 (d, 19.3, off: dd, 183.3, 20.2), 168.12 (d, 260.9, off: dd, 261.2, 7.4), 141.38 (3C), 140.87 (d, 2.3, off: ddd, 213.1, 9.1, 2.4), 132.71 (d, 37.4), 129.43 (6CH), 128.36 (3CH, off: dt, 161.6, 7.2), 128.21 (6CH), 124.50 (d, 3.2, off: dm, d 194.7), 109.99 (d, 19.5, off: ddd, 160.4, 26.3, 19.5), 76.03 (off: m). ^{19}F NMR: δ −94.6 (d, 22.0). R_f (9:1 CH_2Cl_2/Et_2O) = 0.69. HRMS FAB$^+$: MH^+ calcd for $C_{25}H_{20}FN_2O$, 383.1560; found, 383.1551. Mp: 162.5−164.0 °C. Anal. Calcd for $C_{25}H_{19}FN_2O$: C, 78.52; H, 5.01; N, 7.32. Found: C, 78.13; H, 5.10; N, 7.34.

(*Z*)-3-Fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-propenal (20b). ^{1}H NMR: δ 10.10 (1H, d, 8.1), 7.52 (1H, dd, 3.2, 1.4), 7.40−7.34 (9H, m), 7.34 (1H, t, 0.9), 7.17−7.10 (6H, m), 6.21 (1H, dd, 34.7, 8.1). ^{13}C NMR: δ 188.16 (d, 11.3), 167.51 (d, 266.6), 141.47 (3C), 141.07 (d, 1.9), 132.04 (d, 34.9), 129.55 (6CH), 128.48 (3CH), 128.32 (6CH), 123.49 (d, 2.7), 105.34 (d, 1.3), 76.22. ^{19}F NMR: δ −112.2 (dd, 34.7, 2.8). R_f (9:1 CH_2Cl_2/Et_2O) = 0.50. HRMS FAB$^+$: MH^+ calcd for $C_{25}H_{20}FN_2O$, 383.1560; found, 383.1568.

Oxidation of Propenals 20 to Acids 21. The propenal **20a** (334 mg, 0.87 mmol) was suspended in 21 mL of *t*-BuOH, and 4.5 mL of isobutylene was added. The stirred mixture was warmed to 30 °C, and a solution of 740 mg (8.18 mmol) of $NaClO_2$ and 736 mg (6.13 mmol) of NaH_2PO_4 in 7.4 mL of water was slowly added (2 min). The reaction was followed by TLC (9:1 CH_2Cl_2/Et_2O). After the disappearance of **20a** (3 h), the mixture was poured into a mixture of 10 mL of brine, 10 mL of 10% aqueous citric acid, and 10 mL of CH_2Cl_2. The aqueous layer was extracted with 3 × 10 mL of CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and evaporated to dryness. The residual solid was separated by preparative TLC (49:1 CH_2Cl_2/CH_3OH) to give 235 mg (68%) of acid **21a**. Oxidation of propenal **20b** (124 mg, 0.32 mmol) using the same procedure (1:1 CH_2Cl_2/Et_2O was used for preparative TLC) gave **21b** in yield 91 mg (71%).

(*E*)-3-Fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-acrylic Acid (21a). ^{1}H NMR: δ 15.96 (1H, br s), 7.66 (1H, dd, 3.0, 1.2), 7.43−7.38 (9H, m), 7.26 (1H, t, 1.2), 7.14−7.08 (6H, m), 5.89 (1H, d, 25.8). ^{13}C NMR: δ 165.55 (d, 22.5), 159.20 (d, 250.7), 140.89 (3C), 138.50 (d, 2.1), 131.17 (d, 41.4), 129.52 (6CH), 128.84 (3CH), 128.55 (6CH), 122.89 (d, 1.9), 103.98 (d, 26.4), 77.00. ^{19}F NMR: δ −104.2 (dd, 25.8, 2.5). Mp: 194−220 °C dec.

(*Z*)-3-Fluoro-3-(1-trityl-1*H*-imidazol-4-yl)-acrylic Acid (21b). ^{1}H NMR: δ 7.54 (1H, dd, 3.0, 1.4), 7.38−7.33 (9H, m), 7.24 (1H, m, ΣJ 3.2), 7.16−7.09 (6H, m), 6.10 (1H, d, 37.5). ^{13}C NMR: δ 168.56, 162.82 (d, 269.7), 141.53 (3C), 140.55, 132.76 (d, 35.7), 129.59 (6CH), 128.43 (3CH), 128.31 (6CH), 122.84 (d), 94.75, 76.17. The pure compound has very broad signals in the NMR.

Detritylation of Acids 21 to Acids 2. To a solution of 91 mg (228 μmol) of **21b** in 5 mL of acetic acid was added 1 mL of 12 N HCl, and the mixture was stirred for 1 h at room temperature. The mixture then was evaporated to dryness at 40 °C, and the residual solid was triturated with 3 × 2 mL of water. The aqueous extracts were combined, filtered, and evaporated to dryness to give 46 mg (77%) of **2b**·2HCl·$2H_2O$ as a slightly yellow solid. By the same procedure was prepared 155 mg (94%) of **2a**·2HCl·H_2O from 234 mg of **21a**.

(*E*)-3-Fluoro-3-(1*H*-imidazol-4-yl)-acrylic Acid Dihydrochloride Hydrate (2a). ^{1}H NMR (CD_3OD): δ 9.07 (1H, s), 8.38 (1H, s), 6.21 (1H, d, 23.1). ^{1}H NMR (CD_3SOCD_3, rt): δ 15.0−4.5 (too broad to integrate), 8.97 (1H, s), 8.28 (1H, s), 6.08 (1H, d, 23.7). ^{1}H NMR (CD_3SOCD_3, 50 °C): δ 11.2−6.6 (6H, br s), 8.78 (1H, s), 8.16 (1H, s), 6.01 (1H, d, 24.0). ^{1}H NMR (CD_3SOCD_3, 70 °C): δ 10.6−7.2 (6H, br s), 8.66 (1H, s), 8.09 (1H, s), 5.96 (1H, d, 24.0). ^{13}C NMR: δ 168.55 (d, 21.6), 158.94 (d, 250.2), 137.20, 125.28 (d, 40.0), 124.46 (d, 5.3), 105.30 (d, 29.0). ^{19}F NMR: δ −99.4 (d, 22.9). Mp: decomp. from 160 °C; melting of residue from 190 to 195 °C. UV: λ_{max} = 269 nm, ε = 17,000 L mol^{-1} cm^{-1} (log ε = 4.2) in methanol. HRMS DCI$^+$: M^+ calcd for $C_6H_5FN_2O_2$, 156.0335; found, 156.0334. Anal. Calcd $C_6H_9Cl_2FN_2O_3$: C, 29.17; H, 3.67; N, 11.34; Cl, 28.70. Found: C, 29.22; H, 3.24; N, 11.24; Cl, 22.22.

(*Z*)-3-Fluoro-3-(1*H*-imidazol-4-yl)-acrylic Acid Dihydrochloride Dihydrate (2b). ^{1}H NMR (CD_3OD): δ 9.09 (1H, t, 1.4), 8.12 (1H, d, 1.3), 6.12 (1H, d, 33.9). ^{1}H NMR (CD_3SOCD_3, rt): δ from 15.5 to −1.1 (too broad to integrate), 8.85 (1H, s), 8.08 (1H, s), 6.24 (1H, d, 35.7). ^{1}H NMR (CD_3SOCD_3, 50 °C): δ 9.0−3.2 (8H, br s), 8.61 (1H, s), 7.95 (1H, s), 6.17 (1H, d, 35.7). ^{1}H NMR (CD_3SOCD_3, 70 °C): δ 8.44 (1H, s), 8.0−4.2 (8H, br s), 7.86 (1H, s), 6.12 (1H, d, 35.7). ^{13}C NMR: δ 165.81 (d, 1.5), 156.42 (d, 268.3), 138.22, 127.29 (d, 39.3), 121.50 (d, 4.0), 101.52 (d, 4.0). ^{19}F NMR: δ −103.3 (dd, 34.0, 1.5). Mp: decomp. from 180 °C; no melting of residue to 250 °C. UV: λ_{max} = 270 nm, ε = 29 000 L mol^{-1} cm^{-1} (log ε = 4.5) in methanol. HRMS DCI$^+$: M^+ calcd for $C_6H_5FN_2O_2$, 156.0335; found, 156.0336. Anal. Calcd $C_6H_{11}Cl_2FN_2O_4$: C, 27.19; H, 4.18; N, 10.57. Found: C, 26.49; H, 4.01; N, 9.94.

Supporting Information Available: General experimental conditions, NMR characteristics of certain nonfluorinated intermediates, Table 2 describing the effects of reaction conditions on the diastereoselectivity of FBr addition, and Scheme 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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