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Syntheses of *E*- and *Z*-2- and 4-fluorourocanic acids

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Abstract

Horner–Wadsworth–Emmons olefination of ring-fluorinated *N*-trityl-imidazole carboxaldehydes with dialkyphosphonoacetic acid esters produced ring-fluorinated imidazolyl-*E*- and *Z*-acrylate esters. Stereochemistry was controlled by choice of phoshonate. Acid catalyzed removal of trityl followed by ester saponification gave the target 2- and 4-fluoro-*E*- and *Z*-urocanic acid derivatives. These are being investigated as potential mediators of photo-immunosupression.

Keywords: Fluoroimidazoles; Horner–Wadsworth–Emmons olefination; Urocanic acid; Tritylation

1. Introduction

E-urocanic acid (*E*-**1a**) is the product of histidine ammonia lyase catalyzed elimination of ammonia from histidine in the first step of histidine catabolism (Scheme 1). This metabolite is further degraded by urocanase to produce formamino glutamic acid, a source of one carbon units in subsequent biochemical transformations [1]. Absorption of light by *E*-urocanic acid present in the epidermis prompted speculation that it functioned as a naturally-occurring sun screen [2]. In the process, *E*-urocanic acid is photo-isomerized to the *Z*-isomer (*Z*-**1a**). The discovery that *Z*-urocanic acid functions systemically as an immunosupressive agent has sparked renewed interest in the biology of urocanic acid [3].

As part of our investigation of ring fluorinated imidazoles, several years ago we studied the behavior of 2- and 4-fluoro-*L*-histidine as substrates for histidine ammonia lyase. Both isomers were moderate substrates and provided small amounts of (*E*)-2-fluorourocanic acid (*E*-**1b**) and (*E*)-4-fluorourocanic acid (*E*-**1c**), respectively [4]. Neither of these was a substrate for urocanase, but 2-fluorourocanic acid (*E*-**1b**) was a potent competitive inhibitor of the urocanase [5]. We have extended our studies of fluorinated urocanic acids to include the syntheses of *E*- and *Z*-α-fluorourocanic acids [6][1] and recently have completed the syntheses of *E*- and *Z*-β-fluorourocanic acids [7].

The current intensified interest in the photochemistry and biology of urocanic acid has prompted us to develop syntheses of ring-fluorinated analogues of urocanic acid that would provide both *E*- and *Z*-isomers. In particular, a direct synthesis of the *Z*-isomers seemed particularly important since these analogues could be useful tools in the study of the mechanism of the photo-immunosuppressive activity of *Z*-urocanic acid [3]. This synthetic work is the subject of this report.

2. Chemistry

The availability of methods to control the stereochemistry of the Horner–Wittig olefination reaction to produce predominantly either the *E*- or *Z*-isomer made this approach attractive. We previously had prepared 1-trityl-2-fluoroimidazole-4-carboxaldehyde (**2b**) as an intermediate for the synthesis of radiolabelled 2-fluorohistidine [8]. Reaction of **2b** with the potassium salt of (diethoxy-phosphoryl)-acetic acid ethyl ester in the presence of 18-crown-6 [9] was highly stereoselective and gave (*E*)-3-(2-fluoro-1-trityl-1H-imidazol-4-yl)-acrylic acid ethyl ester (**3b**) in good yield. Removal of the trityl group was accomplished by heating a solution of **3b** in 5% ethanolic acetic acid to give ester **4b**. Saponification of the ester, and isolation of the product by ion exchange chromatography gave (*E*)-2-fluorourocanic acid (*E*-**1b**), identical to material prepared previously by enzymatic degradation of *L*-2-fluorohistidine [4]. Reaction of **2b** with [bis-(2,2,2-trifluoroethyoxy)-phosphoryl]-acetic

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[1] In this report, the scheme we constructed describing the mechanism of action of urocanase was over-simplified and contained incorrect structures. Please see [1] for a thorough discussion of this mechanism.

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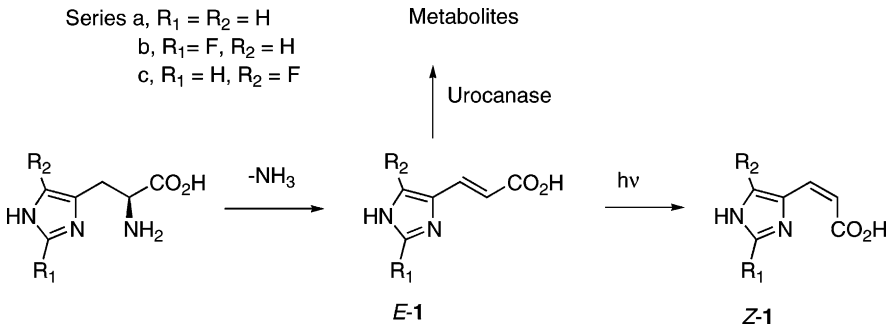
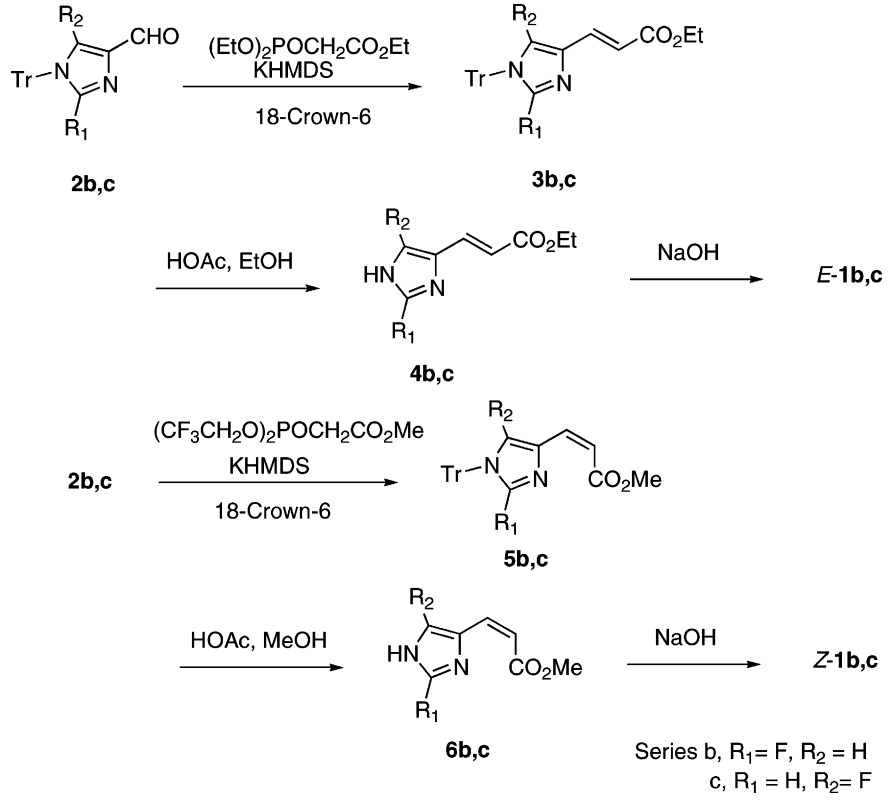


Scheme 1.

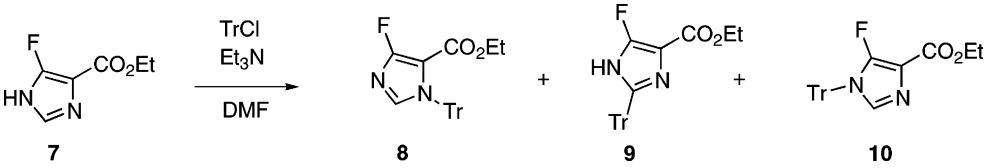
acid methyl ester in the presence of excess 18-crown-6, according to the procedure developed by Still and Gennari [10], stereoselectively produced *Z*-3-(2-fluoro-1-trityl-1H-imidazol-4-yl)-acrylic acid methyl ester (**5b**). Heating a solution of **5b** in 5% methanolic acetic acid in methanol effected removal of the trityl group to give ester **6b**. Saponification and isolation as described for preparation of *E*-**1b** gave *Z*-**1b** (Scheme 2).

Ethyl-4-fluoroimdazole-5-carboxylate (**7**) is readily available by photochemical decomposition of the corresponding diazonium fluoroborate in fluoroboric acid (the photochemical Schiemann reaction) [11].

We were surprised to find that reaction of **7** with trityl chloride gave a mixture of three compounds (two were expected), separated by column chromatography (see Section 4). The high resolution mass spectra (HRMS) and ^{1}H and ^{13}C NMR indicated that each of these was formed by tritylation of the imidazole ring. There are three possible sites of tritylation, corresponding to structures **8–10** (Scheme 3). The structure of compound **9** was assigned based on the following evidence. (1) A broad NH signal is present in the ^{1}H NMR spectrum of **9** (9.06 ppm). (2) The chemical shift of the C-2 carbon in the ^{13}C NMR spectrum of the imidazole ring of **9** is significantly different from the corresponding signals of structures **8** and **10** (see Section 4). (3) This C-2 carbon is coupled ($^{1}J_{CH}$) by the attached proton in **8** and **10** but this coupling is missing in **9**. (4) The benzylic carbon of the trityl group of **9** is at a higher field than in **8** or **10**, as predicted if connected to a less electronegative carbon and not to nitrogen (see Section 4). ^{1}H and ^{13}C NMR were also be used to differentiate between



Scheme 2.



Scheme 3.

structure **8** and **10**. Thus, ^{13}C–^{19}F coupling through three bonds is known to be greater than ^{13}C–^{19}F coupling through four bonds (which is usually zero). The presence of ^{13}C–^{19}F coupling ($^3J_{CF} = 1.7$ Hz) is strong evidence for assignment of structure **10**. Supporting evidence is also found in the higher field chemical shift of the ethyl ester group of compound **8** compared to the corresponding signals of the other two products. This shift to higher field can be ascribed to the anisotropic effect of phenyl rings of trityl group that is situated closer to the ethyl group in structure **8** than in structures **9** and **10**. These structural assignments are tentative but seen consistent with all our data that establish **10** as the major product. In any event, the trityl group is removed from **10** during the synthesis, so the structural assignments are purely of academic interest. At this time we have no explanation for the formation of the unusual C-alkylation product **9**.

Reduction of the major product **10** with DIBAL gave the aldehyde **2c.** The synthetic sequence described for the preparation of *E*-**1b** and *Z*-**1b** was used to prepare *E*- and *Z*-**1c** (Scheme 2).

The ultraviolet spectra of *E*-**1b**,**c** and *Z*-**1b**,**c** (in methanol) are consistent with the data reported for *E*-**1a** and *Z*-**1a** in that $\varepsilon_{trans} > \varepsilon_{cis}$. *E*-**1b**: $\Lambda_{max} = 279$, $\varepsilon = 17{,}800$; *Z*-**1b**: $\Lambda_{max} = 282$, $\varepsilon = 11{,}500$; *E*-**1c**: $\Lambda_{max} = 287.5$, $\varepsilon = 16{,}900$; *Z*-**1c**: $\Lambda_{max} = 290$, $\varepsilon = 10{,}700$. Literature values [12] for urocanic acid (*E*-**1a**): $\Lambda_{max} = 277$, $\varepsilon = 18{,}800$; *Z*-**1a**: $\Lambda_{max} = 277$, $\varepsilon = 13{,}600$.

3. Summary

We have prepared four isomeric ring-fluorinated urocanic acids using stereocontrolled Horner–Wadsworth–Emmons reactions. These compounds, along with side-chain fluorinated analogues, are being investigated with respect to photo-immunosupressive activity. The effect of fluorine substitution on the photochemical reactions of urocanic acids also will be investigated.

4. Experimental details

The ^1H and ^{13}C NMR spectra were recorded at frequencies of 300 and 75.5 MHz, respectively. Chemical shifts (δ) are relative to TMS (0 ppm) ^{19}F NMR (282 MHz) chemical shifts (d) are relative to CF_3CO_2H as external standard. Capillary tube melting points (mp) are not corrected. FAB ionization technique with Xe gas was used to record HRMS. Elemental analyses were done by Atlantic microlab Inc. Silica gel Merck 60 (0.040–0.063 mm) was used for column chromatography, Uniplate^{TM} GF (Analtech) was used for preparative TLC. All reagents and dry solvents were purchased from Aldrich if not otherwise indicated and used without additional purification or drying.

*4.1. (E)-3-(2-Fluoro-1-trityl-1H-imidazol-4-yl)-acrylic acid ethyl ester (**3b**)*

A stirred solution of 337 mg (1.5 mmol) of (diethoxyphosphoryl)-acetic acid ethyl ester and 396 mg (1.5 mmol) of 18-crown-6 ether in 10 ml of THF was cooled in a dry ice/acetone bath. To this was added over 5 min *via* a syringe 3.0 ml (1.5 mmol) of a 0.5 M solution of potassium bis-(trimethylsilyl)amide in toluene. After an additional 15 min stirring, a solution of 358 mg (1.0 mmol) of **2b** in 8 ml of THF was added over 5 min *via* a syringe. The mixture was stirred for 30 min while being cooled in a dry ice/acetone bath, then was allowed to warm to ice-bath temperature, and was stirred for an additional 90 min. The reaction was then quenched with aqueous solution NH_4Cl, water was added, and the solution was extracted three times with EtOAc. The combined organic fractions were washed with water and brine, and then dried over Na_2SO_4. After the removal of volatile solvents by rotary evaporation, the solid residue was chromatographed (9:1 petroleum ether:EtOAc) to give 355 mg (83%) of **3b** as white crystals, mp 151–152 °C (from EtOAc:petroleum ether). ^1H NMR ($CDCl_3$): δ 7.2–7.1 and 7.4–7.3 (multiplets, 16 H, Tr*H*, β*H*), 6.73 (s, 1H, Im-5H), 6.42 (d, 1H, $J = 15.6$ Hz, α*H*), 4.20 (q, 2H, $J = 6.9$ Hz, CH_2), 1.28 (t, 3H, $J = 6.9$ Hz, CH_3). HRMS: Calcd. for $C_{27}H_{23}FN_2O_2$: 426.1733; Found: 426.1733. Anal. Calcd. for $C_{27}H_{23}FN_2O_2$: C, 76.04; H, 5.44; N, 6.57; Found: C, 75.80; H, 5.53; N, 6.54.

*4.2. (Z)-3-(2-Fluoro-1-trityl-1H-imidazol-4-yl)-acrylic acid methyl ester (**5b**)*

A stirred solution of 238 mg (0.75 mmol) of [bis-(2,2,2-trifluoroethyoxy)-phosphoryl]-acetic acid methyl ester and 660 mg (2.5 mmol) of 18-crown-6 ether in 10 ml of THF was cooled in a dry ice/acetone bath. To this was added *via* syringe over a period of 3 min 1.5 ml (0.75 mmol) of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene. After the mixture was stirred for 10 min, a solution of 179 mg (0.5 mmol) of **2b** in 3 ml of THF was added. The reaction was allowed to stir at for 1 h while being cooled in

the dry ice/acetone bath, at which time TLC (5:1 petroleum ether:EtOAc) demonstrated the disappearance of **2b**. The reaction was quenched and worked up as described for the isolation of **3b**, to give, after chromatography (9:1 petroleum ether:EtOAc) 163 mg (79%) of **5b**, mp 140–141 °C (from EtOAc:petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.99 (s, 1H, Im-5*H*), 7.19–7.17 and 7.34–7.36 (multiplets, 15 H, ArH), 6.75 (d, 1H, $J = 12.6$ Hz, βH), 5.74 (d, 1H, $J = 12.6$ Hz, α*H*), 3.61(s, 3H, OCH_3). HRMS: Calcd. for $C_{26}H_{21}FN_2O_2$: 412.1587; Found: 412.1589. Anal. Calcd. for $C_{26}H_{21}FN_2O_2$: C, 75.71; H, 5.13; N, 6.79; Found: C, 75.53; H, 5.08; N, 6.75.

4.3. (E)-3-(2-Fluoro-1H-imidazol-4-yl)-acrylic acid ethyl ester (*4b*)

A solution of 318 mg (0.75 mmol) of **3b** in 4 ml of 5% (v/v) ethanolic acetic acid was refluxed for 3.5 h. The solution was cooled and concentrated by rotary evaporation. The solid residue was purified by column chromatography (5:1 petroluem ether:EtOAc) to give 79 mg (58%) of **4b**, mp 180–183 °C. ^{1}H NMR (CD_3OD): δ 7.43 (dd, 1H, $J = 15$, 2.4 Hz, β*H*), 6.87 (s, 1H, Im-5*H*), 6.47 (d, 1H, $J = 15.3$ Hz, α*H*), 4.23 (q, 2H, $J = 6.9$ Hz, CH_2), 1.31 (t, 3H, $J = 7.2$ Hz, CH_3). HRMS: Calcd. for $C_8H_9FN_2O_2$: 184.0648; Found: 184.0646.

4.4. (Z)-3-(2-Fluoro-1H-imidazol-4-yl)-acrylic acid methyl ester (*6b*)

A solution of 160 mg (0.44 mmol) of **5b** in 4 ml of 5% (v/v) methanolic acetic acid was refluxed for 2.5 h. Volatile solvents were removed by rotary evaporation and the solid residue was chromatographed (5:1 petroleum ether:EtOAc) to give 35 mg (47%) of **6b**, mp 175–190 °C (decomp). ^{1}H NMR (CD_3OD): δ 6.99 (s, 1H, Im-5*H*), 6.69 (dd, 1H, $J = 12.6$, 3.3 Hz, β*H*), 5.65 (d, 1H, $J = 12.3$ Hz, α*H*), 3.80 (s, OCH_3). HRMS: Calcd. for $C_7H_7FN_2O_2$: 170.0492; Found: 170.0494.

4.5. (E)-3-(2-Fluoro-1H-imidazol-4-yl)-acrylic acid (E-2-fluorourocanic acid) (E-*1b*)

A solution of 45 mg (0.28 mmol) of **4b** in 1.0 ml of 1 N NaOH was stored at room temperature for 2 days. The solution was then added to an Amberlite strongly acidic ion exchange column (5 ml wet volume) and the column was eluted with water until the eluant was neutral. The column was eluted with NH_4OH (concentrated diluted 1:4 with distilled water) until TLC indicated all product had been removed. The fractions containing product (TLC) were combined and lyophilized to give 31 mg (71%) of crystalline *E*-**1b**, mp 202–214 °C (decomp). ^{1}H NMR (CD_3OD): δ 7.20 (dd, 1H, $J = 15.9$, 2.7 Hz, β*H*), 6.89 (s, 1H, Im-5*H*), 6.94 (d, 1H, $J = 15.9$ Hz, α*H*). ^{13}C NMR (CD_3OD): δ 169.6, 157.8 133.0, 123.1, 116.6 (d, 246), 102.2 ppm. ^{19}F NMR (CD_3OD): δ −78.1 ppm. HRMS: Calcd. for $C_6H_5FN_2O_2$: 156.0335; Found: 156.0341.

4.6. (Z)-3-(2-Fluoro-1H-imidazol-4-yl)-acrylic acid (Z-2-fluorourocanic acid) (Z-*1b*)

A solution of 35 mg (0.20 mmol) of **6b** in 1.0 ml of 1 N NaOH was stored for 2 days at room temperature. Isolation using Amberlite ion exchange as described for the preparation of the *E*-isomer produced 26 mg (83%) of crystalline *Z*-**1b**, mp 190–197 °C (decomp). ^{1}H NMR (CD_3OD): δ 6.77 (s, 1H, Im-4*H*), 6.47 (dd, 1H, $J = 12.9$, 3.3 Hz, β*H*), 5.69 (d, 1H, $J = 12.6$ Hz, α*H*). ^{13}C NMR (CD_3OD): δ 170.1, 157.6 133.3, 123.5, 116.7 (d, 242) 103.5 ppm. ^{19}F NMR (CD_3OD): δ −75.6 ppm. HRMS: Calcd. for $C_6H_5FN_2O_2$: 156.0335; Found: 156.0332.

4.7. Tritylation of 5-fluoro-1H-imidazole-4-carboxylic acid ethyl ester (*7*)

To an ice-cold solution of 158 mg (1.0 mmol) of 5-fluoro-1H-imidazole-4-carboxylic acid ethyl ester (**7**) and 335 mg (1.2 mmol) of trityl chloride in 3 ml of dry DMF was added 0.2 ml (1.5 mmol) of triethylamine under nitrogen. The solution was stirred for 20 h at room temperature. The reaction mixture was diluted with ethyl acetate and the solution was washed with water and brine. After drying with sodium sulfate, the solvent was evaporated to give a solid that was separated by column chromatography (5:1 hexane:EtOAc → 1:1 hexane:EtOAc).

4.7.1. 4-Fluoro-1-trityl-1H-imidazole-5-carboxylic acid ethyl ester (*8*)

The first compound eluted (5:1 hexane:EtOAc) was identified as **8**, 60 mg (15%). ^{1}H NMR ($CDCl_3$): 7.34–7.29 and 7.17–7.12 (m, 16 H, Tr*H*, Im-2*H*), 3.77 (q, 2H, $J = 7.2$ Hz, CH_2), 0.87 (t, 3H, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 160.7 (d, $J = 252.7$ Hz), 157.6 (d, $J = 5.6$ Hz), 141.4 (3C), 136.7 (d, $J = 15.4$ Hz), 129.8 (6C), 127.9 (3C), 127.7 (6C), 106.2 (d, $J = 26.2$ Hz), 78.0, 60.2, 13.7. HRMS: Calcd. for $C_{25}H_{21}FN_2O_2$: 400.1587; Found: 400.1591.

4.7.2. 4 (5)-Fluoro-2-trityl-1H-imidazole-5 (4)-carboxylic acid ethyl ester (*9b*)

The next product eluted (5:1 hexane:EtOAc) was compound **9**, 27 mg (7%). ^{1}H NMR ($CDCl_3$): δ 9.06 (broad s, 1H, N*H*), 7.34–7.29 and 7.15–7.11 (m, 15 H, Tr*H*), 4.31 (q, 2H, $J = 7.2$ Hz, CH_2), 1.34 (t, 3H, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 159.3 (d, $J = 4.6$ Hz), 157.0 (d, $J = 249.3$ Hz), 149.1 (d, $J = 13.7$ Hz), 143.3 (3C), 130.2 (6C), 128.2 (6C), 127.5 (3C), 101.8 (d, $J = 31.3$ Hz), 61.3, 61.0, 14.3. HRMS: Calcd. for $C_{25}H_{21}FN_2O_2$: 400.1587; Found: 400.1591.

4.7.3. 5-Fluoro-1-trityl-1H-imidazole-4-carboxylic acid ethyl ester (*10*)

The major, most polar fraction, **10**, was eluted with 1:1 hexane:EtOAc and obtained as 313 mg (78%) of a white solid, mp 138–139 °C. ^{1}H NMR ($CDCl_3$): δ 7.39–7.34 and 7.17–7.14 (m, 15 H, Tr*H*), 7.12 (broad s, 1H, Im-2*H*), 4.35 (q, 2H,

$J = 7.2$ Hz, CH_2), 1.35 (t, 3H, $J = 7.2$ Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 161.0 (d, $J = 5.1$ Hz), 150.7 (d, $J = 289.1$ Hz), 139.9 (3C), 130.8 (d, $J = 5.7$ Hz), 128.9 (6C), 128.0 (9C), 112.8, 75.8 (d, $J = 1.7$ Hz), 60.3, 14.0. HRMS: Calcd. for $C_{25}H_{21}FN_2O_2$: 400.1587; Found: 400.1595.

4.8. 5-Fluoro-trityl-1H-imidazole-4-carboxaldehyde (**2c**)

To 400 mg (1 mmol) of **10** in 10 ml of toluene, cooled in a dry ice/acetone bath, was added dropwise 1.0 ml of a 1.5 M solution of DIBAL in toluene. The solution was stirred at the same temperature for 1 h and then quenched with 10 ml of 1 M aqueous potassium tartarate. The aqueous solution was extracted three times with EtOAc, dried (Na_2SO_4) and evaporated to give 333 mg of solid. This was chromatographed (1:1 EtOAc:petroleum ether) to give 191 mg (54%) of **2c**, recrystallized from 1:1 EtOAc:petroleum ether, mp 135–136 °C. ^{1}H NMR ($CDCl_3$): δ 9.83 (s, 1H, C*H*O), 7.39–7.37 and 7.17–7.14 (m, 15 H, Ar*H*), 7.17 (s, 1H, Im-2*H*).

4.9. (E)-3-(5-Fluoro-1-1-trityl-1H-imidazol-4-yl)-acrylic acid ethyl ester (**3c**)

A stirred solution of 95 mg (0.42 mmol) of (diethoxy-phosphoryl)-acetic acid ethyl ester and 110 mg (0.42 mmol) of 18-crown-6 in 8 ml of THF was cooled in a dry ice/acetone bath. To this was added over 5 min *via* a syringe 0.84 ml of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene. After an additional 15 min stirring, a solution of 100 mg (0.28 mmol) of **2c** in 2 ml of THF added over 5 min via a syringe. The mixture was stirred for 30 min while being cooled in a dry ice/acetone bath, then was allowed to come to ice-bath temperature, and was stirred for an additional 90 min. The reaction was then quenched with aqueous solution NH_4Cl, water was added, and the solution was extracted three times with EtOAc. The combined organic fractions were washed with water and brine, and then dried with Na_2SO_4. After removal of volatile solvents by rotary evaporation, the solid residue was chromatographed (1:9 EtOAc:petroleum ether) to give 95 mg (80%) of **3c** as white crystals, mp 118–120 °C (from EtOAc:petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 1H, $J = 15.9$ Hz, αH), 7.37–7.45 (multiplets, 16 H, Ar*H*, Im-2*H*), 6.43 (d, 1H, $J = 15.6$ Hz, βH), 4.21 (q, 2H, $J = 7.2$ Hz, CH_2), 1.29 (t, 3H, $J = 7.2$ Hz, CH_3). HRMS: Calcd. for $C_{27}H_{23}FN_2O_2$: 426.1744; Found: 426.1748.

4.10. (Z)-3-(5-Fluoro-1-trityl-1H-imidazol-4-yl)-acrylic acid methyl ester (**5c**)

A stirred solution of 140 mg (0.42 mmol) of [bis-(2,2,2-trifluoroethyoxy)-phosphoryl]-acetic acid methyl ester and 552 mg (2.1 mmol) of 18-crown-6 in 8 ml of THF was cooled in a dry ice/acetone bath. To this was added via syringe over a period of 3 min 0.84 ml of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene. After the mixture was stirred for 10 min, a solution of 100 mg (0.28 mmol) of **2c** in 2 ml of THF was added. The reaction was allowed to stir while being cooled in a dry ice/acetone bath for 2 h. The reaction was quenched and worked up as earlier for the isolation of **5b** to give, after chromatography (9:1 petroleum ether:EtOAc) 86 mg (72%) of **5c**, mp 102–104 °C (from EtOAc:petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.36–7.16 (multiplets, 16 H, Ar*H*, Im-2*H*), 6.64 (d, 1H, $J = 12.6$ Hz, αH), 5.82 (d, 1H, $J = 12.6$ Hz, βH), 3.78 (s, 3H, OCH_3). HRMS: Calcd. for $C_{26}H_{21}FN_2O_2$: 412.1605; Found: 412.1587.

4.11. (E)-3-(5-Fluoro-1H-imidazol-4-yl)-acrylic acid ethyl ester (**4c**)

A solution of 90 mg (0.21 mmol) of **3c** in 2 ml 5% (v/v) ethanolic acetic acid was heated for 3.5 h at 90 °C. The solution was cooled and concentrated by rotary evaporation. The solid residue was purified by column chromatography (4:1 petroleum ether:EtOAc) to give 19 mg (50%) of **4c**, mp 175–180 °C. ^{1}H NMR (CD_3OD): δ 7.50 (s, 1H, Im-2*H*), 7.47 (d, 1H, $J = 16.2$ Hz, αH), 6.16 (d, 1H, $J = 16.2$ Hz, βH), 4.23 (q, 2H, $J = 7.2$ Hz, CH_2), 1.30 (t, 3H, $J = 7.2$ Hz, CH_3). HRMS: Calcd. for $C_8H_{10}FN_2O_2$ (FAB, MH^+): 185.0726; Found: 185.0735.

4.12. (Z)-3-(5-Fluoro-1H-imidazol-4-yl)-acrylic acid methyl ester (**6c**)

A solution of 80 mg (0.19 mmol) of **5c** in 2 ml 5% (v/v) methanolic acetic acid was heated for 3.5 h at 90 °C. The solution was cooled and concentrated by rotary evaporation. The solid residue was purified by column chromatography (1:4 EtOAc:petroleum ether) to give 27 mg (85%) of **6c**, mp 154–160 °C. ^{1}H NMR (CD_3OD): δ 7.34 (s, 1H, Im-2*H*), 6.81 (d, 1H, $J = 12.6$ Hz, αH), 5.65 (d, 1H, $J = 12.6$ Hz, βH), 3.79 (s, 3H, OCH_3). HRMS: Calcd. for $C_7H_7FN_2O_2$: 170.0492; Found: 170.0498.

4.12.1. (E)-3-(4-Fluoro-1H-imidazol-5-yl)-acrylic acid (E-4-fluorourocanic acid) (E-**1c**)

A solution of 15 mg (0.08 mmol) of **4c** in 1.0 ml of 1 N NaOH was stored for 2 days at room temperature. Isolation using Amberlite ion exchange as described for the preparation of *E*-**1b** produced 10 mg (80%) of crystalline *E*-**1c**, mp 210–218 °C (decomp). ^{1}H NMR (CD_3OD): δ 7.43 (s, 1H, Im-2*H*), 7.30 (d, 1H, $J = 15.9$ Hz, βH), 6.17 (d, 1H, $J = 15.9$ Hz, αH). ^{13}C NMR (CD_3OD): δ 193.4, 157.9 (d, 244), 133.5 (d, 16.4), 129.4, 128.4 (d, 5.15), 117.8 ppm. ^{19}F NMR (CD_3OD): δ −56.9 ppm. HRMS: Calcd. for $C_6H_5FN_2O_2$: 156.0335; Found: 156.0340.

4.13. (Z)-3-(4-Fluoro-1H-imidazol-5-yl)-acrylic acid (Z-**4**-fluorourocanic acid) (Z-**1c**)

A solution of 20 mg (0.12 mmol) of **6c** in 1.0 ml of 1 N NaOH was stored for 2 days at room temperature. Isolation

using Amberlite ion exchange as described for the preparation of the *E*-isomer produced 12 mg (64%) of crystalline *Z*-**1c**, mp 193–205 °C (decomp). ^{1}H NMR (CD_3OD): δ 7.09 (s, 1H, Im*H*), 6.19 (d, 1H, $J = 12.6$ Hz, β*H*), 5.34 (d, 1H, $J = 12.6$ Hz, a*H*). ^{13}C NMR (CD_3OD): δ 173.4, 158.1 (d, 246), 131.2 (d, 16.3) 124.3 (d, 5.16), 117.9, 110.3 ppm. ^{19}F NMR (CD_3OD): δ −58.9 ppm. HRMS: Calcd. for $C_6H_5FN_2O_2$: 156.0333; Found: 156.0329.

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