Synthetic studies for novel structure of α-nitrogenously functionalized α-fluorocarboxylic acids. Part III*. Some reactions of α-bromo-α-fluorocarboxylic acids and their ethyl esters with sodium azide†

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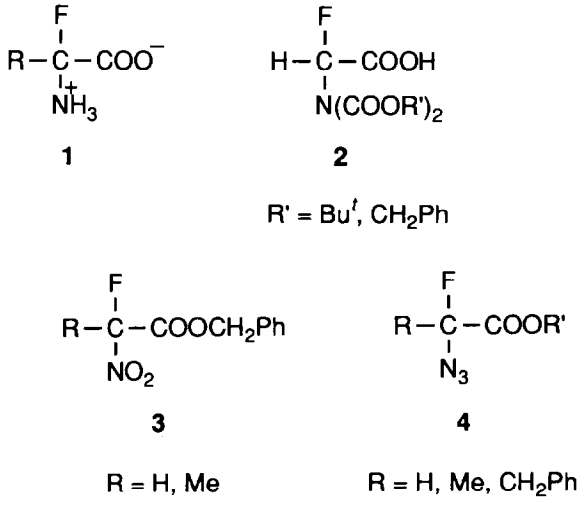
Abstract

Synthesis of a novel group of α-azido-α-fluorocarboxylic acid derivatives has been attempted by azidation of the corresponding α-bromo-α-fluorocarboxylic acids or ethyl esters. Although ethyl azidofluoroacetate was obtained, over-azidation occurred very readily in most cases to afford geminally diazidated compounds. Attempted conversion of ethyl azidofluoroacetate into azidofluoroacetic acid by alkaline hydrolysis or by treatment with trimethylsilyl bromide resulted mainly in the formation of defluorinated products. It was found that, although α-fluorocarboxylates are generally considered stable, defluorination occurs under nucleophilic conditions if an additional labilizing group is present on the same carbon atom as the fluorine.

Introduction

Because of the potential biological activity of organofluorine compounds, the introduction of the fluorine atom into bioactive molecules has recently been studied extensively [1]. However, no compounds have been reported with fluorine on the α-carbon of any α-amino acid, in spite of great interest in such compounds from the viewpoint of structure and potential significance with respect to biological activity. The reason for this seems to be the inherent instability of the CF–NH function [2]. During the course of our continuing investigations for constructing the novel α-fluoro-α-amino acid structure **1**, we developed synthetic pathways to potential precursors of **1**, i.e., *N*-protected α-fluoro-α-amino acids **2** and benzyl α-fluoro-α-nitrocarboxylates **3**. However, the reaction conditions needed for deprotection of *N*-dicarboxylate derivatives **2** were not mild enough to isolate **1** [3]. Also, the α-fluoro-α-nitrocarboxylic acids were found to be unstable and the attempted concurrent conversion of both the nitro and benzyl ester groups in **3** afforded fluorine-free amino acid benzyl esters [4]. Preferential reduction of the nitro group during hydrogenation is not surprising; the loss of fluorine may result from hydrogenation of the imine formed from the α-amino-α-fluoro ester.



Scheme 1.

We then focused on the α-azido acid structure as a precursor of **1**, since an azido group is usually more susceptible to catalytic hydrogenation than a nitro group

*For Part II, see ref. 4.

†This paper is dedicated to Professor Yoshifumi Maki on this occasion of his retirement from Gifu Pharmaceutical University in March 1994.

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[5]. Except for our preliminary studies [6], however, there have been no reports on the synthesis of α-azido-α-fluorocarboxylic esters. Here we present the results of attempted synthesis of a novel group of α-azido-α-fluorocarboxylic esters **4** (R′ = Et) or the corresponding acids **4** (R′ = H), potential precursors of the final structure **1** (Scheme 1).

Results and discussion

Ethyl bromofluoroacetate (**5a**) was treated with a large excess of NaN_3 ($EtOH/H_2O$, room temperature, 10 h) to give the azido derivative **6a**, which was virtually inseparable from the accompanying bis(azido) compound **6b***. However, reaction of **5a** with 5 molar equiv. of NaN_3 under phase-transfer conditions ($Et_2O/Bu_4NBr/H_2O$, room temperature, 3 h) selectively produced **6a** in 87% yield. Saponification of **6a** with 1 N NaOH afforded mainly the unexpected ethoxy acid **7**. Ester cleavage of **6a** with trimethylsilyl bromide (TMSBr) [7] was also attempted, but gave the brominated ester **6c**. These unfavorable results reveal the ease of nucleophilic displacement of the fluorine, which displacement is greatly enhanced by the adjacent ester and azido groups [8].

The alternative approach of reversing the order of functionalization seemed to avoid these problems. Thus, ester **5a** was first saponified with 1 N NaOH to yield the acid **8a** in excellent yield [9]. Azidation of **8a** was attempted with NaN_3 or LiN_3 ($Et_2O/EtOH/H_2O$, rt, 8 h) to give the diazido acid **9a** which was converted, for structural characterization, to the methyl ester **9b** by treatment with CH_2N_2. In order to suppress the undesirable diazidation, we next employed the more reactive iodo analog **8b** in the hope that monoazidation would occur more rapidly and more selectively. The fluoroiodoacetate **5b** obtained from **5a** [10] was treated with 5% NaOH to yield **8b** [9] in 53% yield. The iodo acid **8b** was also obtained directly from **5a** by treatment with trimethylsilyl iodide (TMSI) (CCl_4, reflux) [7]. Monoazidation of **8b** was attempted with $LiN_3/(CD_3)_2CO$, with monitoring by NMR spectroscopy of the characteristic signal for proton coupling with fluorine; however, the product again proved to be **9a**. The stability of fluorine in the conversion of **5** to **8**, in contrast to its lability in the conversion of **8a** to **9a**, shows how extensively the azido group can enhance an adjacent S_N2 displacement. However, ammonolysis (NH_4OH/D_2O) of either **8a** or **8b** failed to produce the target compound **10**, only starting material being recovered (Scheme 2).

*Prolonged reaction resulted in complete conversion of **5a** into the diazido derivative **6b**.

We next tried steric retardation of the S_N2 displacements* by use of the α-alkyl or α-aryl substituted analog **11–13**, obtained according to the procedure of Olah and Welch [11]. Although compounds **11** and **12** were obtained in 56%–60% yield by treatment of the corresponding α-diazo esters [12] with *N*-bromosuccinimide (NBS) and hydrogen fluoride pyridine, the yield of **13** was very low (*c.* 3%), probably due to the poor electrophilicity of NBS toward the electron-deficient α-carbon atom of the α-diazophenylacetate. Reaction of **11** with NaN_3, in an analogous manner to the synthesis of **6a**, unfortunately produced only the diazido ester **14** [13]. Attempted saponification of **11** gave a mixture of dehydrohalogenated products **15a, b**. However, the ethyl ester **11** could be hydrolyzed by treatment with 5% HCl to produce **16** in 52% yield. The acid **16** was treated with the $NaN_3/CH_2Cl_2/H_2O/Bu_4NBr$ system: although NMR and MS spectra indicated the formation of **17a**, the major products isolated were the diazido acid **17b** and α-bromoacrylic acid **15b**†. From these results, defluorination seems to occur readily with α-fluorocarboxylic acids as well as with α-fluoro esters. On the other hand, azidation of **12** with NaN_3 afforded mainly the olefin **18a**. Saponification of **12** with 5% NaOH produced the acid **19** in 76% yield. However, attempted azidation or ammonolysis of **19** gave the dehydrobrominated product **18b** (Scheme 3).

In summary, we have investigated the preparation of several α-azido-α-fluorocarboxylic acids and esters. Although ethyl α-azido-α-fluoroacetate (**6a**) could be isolated successfully, various attempts to obtain α-azido-α-fluorocarboxylic acids failed due to their instability and/or the ease of over-azidation. It was found that α-fluorocarboxylate structures are prone to lose fluorine under nucleophilic conditions, but only if another labilizing group (e.g. azido group) is present on the same carbon atom as the fluorine.

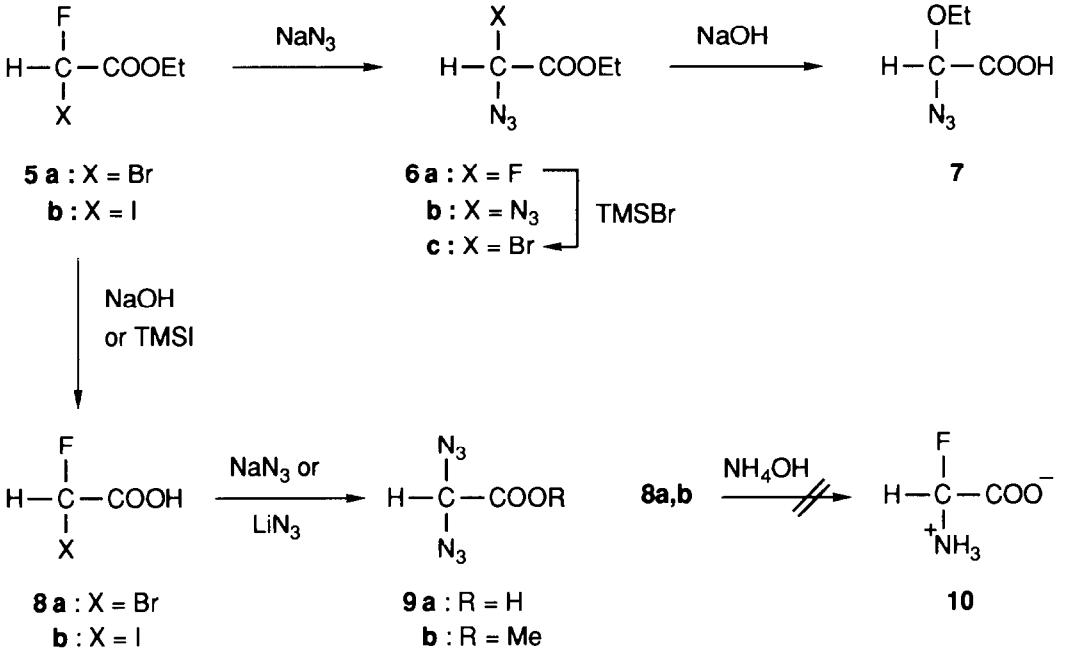
Experimental

General

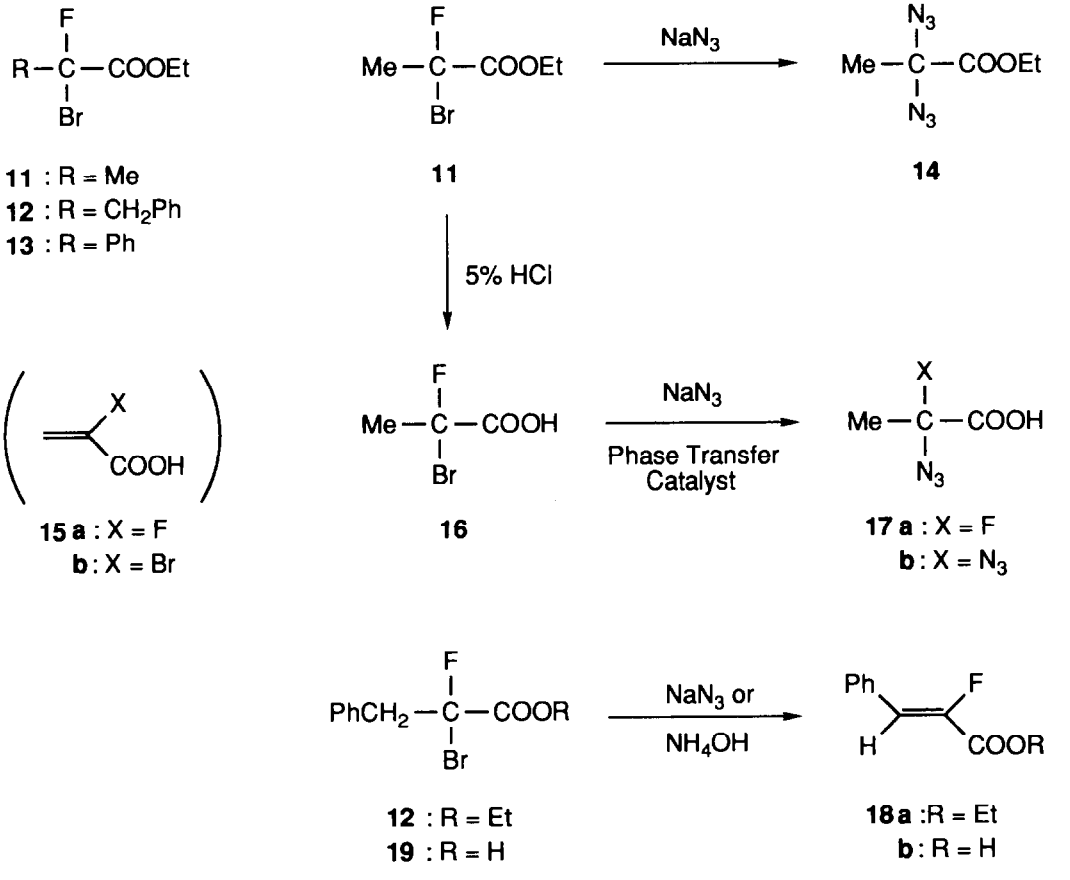
Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 or a Perkin-

*We consider displacement by S_N1 pathways highly unlikely, in view of the strong carbo cation destabilizing effects of both carbonyl and azido groups.

†The characteristic signals at δ 2.13 (3H, d, J = 19.1 Hz, Me) and −108.69 (1F, d, J = 19.3 Hz, F) ppm in the ^1H ($SiMe_4$) and ^{19}F ($CFCl_3$) NMR spectra, respectively, and *m/z* 133 (M^+); 91 ($M^+ - N_3$); and 88 ($M^+ - COOH$) in the mass spectra can be reasonably assigned to structure **17a**. The signal at δ 1.71 (3H, s, Me) ppm in the ^1H NMR spectra and *m/z* 156 (M^+); and 111 ($M^+ - COOH$) in the mass spectra can be assigned to structure **17b**.



Scheme 2.



Scheme 3.

Elmer 1600 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ with Me_4Si as internal standard and were recorded on a JEOL GX-270 (270 MHz), a Varian XL-200 (200 MHz) or a JEOL PMX-60 (60 MHz) spectrometer. ^{19}F NMR spectra were measured in $CDCl_3$ with $CFCl_3$ as internal standard and taken with a JEOL GX-270 (254 MHz) spectrometer. Upfield shifts are quoted in ppm as negative δ values. ^{13}C NMR spectra were measured in $CDCl_3$ with Me_4Si as internal standard and taken with a Varian Unity-500 (125.7 MHz) spectrometer. Electron Impact mass spectra (MS) including high-resolution mass spectra (HRMS) were taken with a JEOL JMS-D300 spectrometer. Column chromatography and preparative TLC were performed on Kieselgel 60 (Merck, Art. 9385 and 7748, respectively).

Ethyl azidofluoroacetate (6a)

A mixture of **5a** (0.61 g, 3.3 mmol), NaN_3 (1.1 g, 16.9 mmol) and Bu_4NBr (0.1 g, 0.31 mmol) in Et_2O (2.5 ml) and H_2O (2.5 ml) was stirred at room temperature for 2 h. The ethereal layer was separated and the aqueous layer was saturated with NaCl and extracted with Et_2O (5 ml×2). The combined ethereal layer was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent gave **6a** in 87% yield (0.42 g) as a colorless oil: b.p. 83–84 °C/18 mmHg. IR (neat) (cm^{-1}): 2110 (N_3); 1765 (CO); 1210 (C–O–C). ^{1}H NMR (60 MHz) δ: 1.40 (3H, t, J=6.8 Hz, Me); 4.33 (2H, q, J=6.8 Hz, CH_2); 5.44 (1H, br d, J(H–F)=51.0 Hz, CH) ppm. ^{19}F NMR δ: −147.8 (d, J(F–H)=51.3 Hz) ppm. MS *m/z*: 147 (M^+); 74 (M^+ − COOEt); 73 ($EtOCO^+$). HRMS *m/z*: Calc. for $C_4H_6FN_3O_2$ (M^+): 147.0444. Found: 147.0462. Calc. for $CHFN_3$ (M^+ − COOEt): 74.0154. Found: 74.0166. Calc. for $C_3H_5O_2$ ($EtOCO^+$): 73.0289. Found: 73.0332. Attempted distillation resulted in an explosion.

Ethyl diazidoacetate (**6b**): colorless oil. IR (neat) (cm^{-1}): 2987 (CH); 2115 (N_3); 1755 (CO); 1198 (C–O–C). ^{1}H NMR (270 MHz) δ: 1.36 (3H, t, J=7.1 Hz, Me); 4.33 (2H, q, J=7.1 Hz, CH_2); 4.86 (1H, br s, CH) ppm. ^{13}C NMR δ: 14.0 (Me); 63.2 (CH_2); 73.4 (CH); 165.1 (CO) ppm. MS *m/z*: 97 (M^+ − COOEt).

Ethyl azidobromoacetate (6c)

To a solution of **6a** (147 mg, 1 mmol) in CCl_4 (0.15 ml) was added TMSBr (0.15 ml, 1.2 mmol) by means of a syringe under an argon atmosphere and the mixture stirred at 65 °C for 6.5 h. Evaporation of the solvent gave an oil which was purified by silica gel column chromatography (Et_2O/hexane) to give **6c** as a colorless oil in 63% yield (131 mg). ^{1}H NMR (60 MHz, CCl_4) δ: 1.37 (3H, t, J=7.2 Hz, Me); 4.30 (2H, q, J=7 Hz, CH_2); 4.30 (1H, br s, CH) ppm. No fluorine signal was observed in the ^{19}F NMR spectrum.

Azidoethoxyacetic acid (7)

A solution of **6a** (221 mg, 1.5 mmol) in 1 N NaOH (3 ml) was stirred at room temperature for 5 h. The solution was acidified with 5% HCl in an ice bath, extracted with Et_2O (10 ml×3) and the ethereal layer dried over $MgSO_4$. Evaporation of the solvent gave **7** as a colorless semisolid in 45% yield (117 mg). IR ($CHCl_3$) (cm^{-1}): 3450 (OH); 2120 (N_3); 1740 (CO); 1220 (C–O–C). ^{1}H NMR (200 MHz) δ: 1.34 (3H, t, J=7.2 Hz, Me); 3.74 (1H, AB q, J=8.5, 7.2 Hz, OCH_aH_b); 3.95 (1H, AB q, J=8.5, 7.2 Hz, OCH_aH_b); 4.77 (1H, s, CH); 5.18 (1H, br s, OH) ppm. MS *m/z*: 128 (M^+ − OH); 103 (M^+ − N_3); 100 (M^+ − OEt and/or M^+ − COOH).

Diazidoacetic acid (9a)

A mixture of **8a** (or **8b**) (1 mmol) and NaN_3 or LiN_3 (5 mmol) in H_2O, MeOH or Me_2CO (2 ml) was stirred at room temperature for 5–7 h. The solvent was evaporated and the residue dissolved in 1 N HCl (5 ml) in an ice bath. The solution was extracted with Et_2O (3 ml×3) and the ethereal layer dried over $MgSO_4$. Evaporation of the solvent gave **9a** as a colorless oil in 15%–35% yield. IR (neat) (cm^{-1}): 3500–2900 (OH); 2130 (N_3); 1740 (CO). ^{1}H NMR (200 MHz) δ: 5.01 (1H, br s, CH); 7.26 (1H, br s, OH) ppm. MS *m/z*: 142 (M^+); 99 (M^+ − HN_3); 97 (M^+ − COOH); 55 (M^+ − N_3 − COOH). HRMS *m/z*: Calc. for $C_2H_2N_6O_2$ (M^+): 142.0239. Found: 142.0184. Calc. for CHN_6 (M^+ − COOH): 97.0262. Found: 97.0294. Calc. for CHN_3 (M^+ − N_3 − COOH): 55.0170. Found: 55.0210.

The structure of the rather unstable acid **9a** was confirmed by converting it into the methyl ester **9b** by treatment of **9a** with CH_2N_2.

Methyl diazidoacetate (**9b**): colorless oil. IR ($CHCl_3$) (cm^{-1}): 2140 (N_3); 1745 (CO); 1230 (C–O–C). ^{1}H NMR (200 MHz) δ: 3.89 (3H, s, Me); 4.92 (1H, br s, CH) ppm. MS *m/z*: 97 (M^+ − COOMe); 59 ($MeOCO^+$).

General procedure for the preparation of ethyl 2-bromo-2-fluorocarboxylates 11–13

To a stirred mixture of well-ground NBS (1.78 g, 10 mmol) in 70% HF/pyridine (4 ml) and Et_2O (5 ml) was added dropwise a solution of ethyl α-diazocarboxylate [11] (6 mmol) in Et_2O (5 ml) at 0 °C and the resulting mixture stirred at 0 °C for 30 min. To the mixture was added ice water (10 ml) and insoluble materials were filtered off. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 ml×2). The combined organic layer was washed with water, saturated $NaHCO_3$ and water, and dried over $MgSO_4$. Evaporation of the solvent gave a crude product which was purified by silica gel (AcOEt/hexane) and/or Sephadex LH-20 (Me_2CO) column chromatography to afford **11–13**.

Ethyl 2-bromo-2-fluoropropionate (**11**): colorless oil in 60% yield. IR (neat) (cm^{-1}): 2961 (CH); 1751 (CO). ^1H NMR (270 MHz) δ: 1.38 (3H, t, $J=7.2$ Hz, CH_2Me); 2.28 (3H, d, $J=19.5$ Hz, CFMe); 4.36 (2H, q, $J=7.2$ Hz, CH_2) ppm. ^{19}F NMR δ: −108.83 (q, $J(F-H)=19.6$ Hz) ppm. MS *m/z*: 198, 200 (M^+); 179, 181 (M^+-F). HRMS *m/z*: Calc. for $C_5H_8BrFO_2$ (M^+): 197.9692. Found: 197.9665. Calc. for $C_5H_8Br^*FO_2$ (M^+): 199.9672. Found: 199.9658.

Ethyl 2-bromo-2-fluoro-3-phenylpropionate (**12**): colorless oil in 56% yield, b.p. 70–72 °C/0.8 mmHg IR (neat) (cm^{-1}): 1765 (CO); 1605 (C=C). ^1H NMR (60 MHz) δ: 1.29 (3H, t, $J=7.0$ Hz, Me); 3.78 (2H, d, $J(H-F)=21.5$ Hz, CH_2Ph); 4.27 (2H, q, $J=7.0$ Hz, OCH_2); 7.37 (5H, s, Ph) ppm. MS *m/z*: 275, 277 ($M^+ + 1$); 255, 257 (M^+-F); 195 (M^+-Br). Analysis: Calc. for $C_{11}H_{12}BrFO_2$: C, 48.02; H, 4.40%. Found: C, 47.91; H, 4.42%.

Ethyl α-bromo-α-fluorophenylacetate (**13**): colorless needles (AcOEt/hexane) in 3.1% yield, m.p. 133–134 °C. IR (KBr) (cm^{-1}): 1735 (CO); 1240 (C−O−C). ^1H NMR (270 MHz) δ: 1.31 (3H, dt, $J=15.9$, 7.1 Hz, Me); 4.23–4.45 (2H, m, CH_2); 7.05–7.35 (5H, m, Ph) ppm. ^{19}F NMR δ: −150.18 (s) ppm. MS *m/z*: 243, 241 (M^+-F); 181 (M^+-Br); 105 (M^+-Ph+1). HRMS *m/z*: Calc. for $C_{10}H_{10}FO_2$ (M^+-Br): 181.0665. Found: 181.0707.

Ethyl 2,2-diazidoproprionate (14)

To a mixture of **11** (36 mg, 0.18 mmol) and Bu_4NBr (29 mg, 0.09 mmol) in CH_2Cl_2 (0.5 ml), H_2O (0.5 ml) and EtOH (0.1 ml) was added NaN_3 until no more NaN_3 dissolved. The mixture was stirred at room temperature for 2 d (checked by TLC). The organic layer was separated, washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil which was purified by preparative TLC. The spectral data of the major product may be assigned to the diazidated compound **14**. IR (neat) (cm^{-1}): 2150 (N_3); 1735 (CO). ^1H NMR (270 MHz) δ: 1.37 (3H, t, $J=7.1$ Hz, CH_2Me); 1.66 (3H, s, N_3CMe); 4.34 (2H, q, $J=7.1$ Hz, CH_2) ppm.

2-Bromo-2-fluoropropionic acid (16)

A solution of **11** (327 mg, 1.64 mmol) in 5% HCl (20 ml) and EtOH (1 ml) was heated at 40 °C for 3 d. The solution was made alkaline with 10% Na_2CO_3 and washed with AcOEt. The aqueous layer was acidified with 10% HCl and extracted with AcOEt (10 ml×3). The organic layer was dried over $MgSO_4$. Evaporation of the solvent gave **16** as a colorless oil in 52% yield (146 mg). IR (neat) (cm^{-1}): 2950–2550 (COOH); 1740 (CO). ^1H NMR (270 MHz) δ: 2.30 (3H, d, $J=19.3$ Hz, Me); 4.16 (1H, br s, COOH) ppm. ^{19}F NMR δ: −109.5 (q, $J=19.0$ Hz) ppm. MS *m/z*: 170, 172 (M^+); 150, 152 (M^+-HF); 125, 127 (M^+-COOH); 91 (M^+-Br). HRMS *m/z*: Calc. for $C_3H_4BrFO_2$ (M^+): 169.9379. Found: 169.9370. Calc. for $C_3H_4Br^*FO_2$ (M^+): 171.9359. Found: 171.9444. Calc. for $C_3H_3BrO_2$ (M^+-HF): 149.9317. Found: 149.9332. Calc. for $C_3H_3Br^*O_2$ (M^+-HF): 151.9270. Found: 151.9283.

(Z)-2-Fluorocinnamic acid (18b)

A solution of **12** in conc. NH_4OH was stirred at room temperature for 1 h. Concentration of the mixture to dryness under reduced pressure gave a colorless semisolid which was characterized as **18b** from the spectral data. IR (Nujol) (cm^{-1}): 1675 (CO). ^1H NMR (60 MHz) δ: 6.80 (1H, d, $J(H-F)=36.0$ Hz, CH); 7.10–7.80 (5H, m, Ph) ppm.

2-Bromo-2-fluoro-3-phenylpropionic acid (19)

A solution of **12** (206 mg, 0.75 mmol) in 5% NaOH (5 ml) was stirred at room temperature for 3 h. The solution was concentrated to half of the original volume under reduced pressure and acidified with conc. HCl. The resulting solution was extracted with Et_2O (2 ml×3) and dried over $MgSO_4$. Evaporation of the solvent gave **19** as a colorless semisolid in 78% yield (144 mg). IR (Nujol) (cm^{-1}): 1700 (CO); 1650 (C=C). ^1H NMR (60 MHz) δ: 3.75 (2H, d, $J(H-F)=23.0$ Hz, CH_2); 7.35 (5H, s, Ph); 9.73 (1H, br s, OH) ppm. MS *m/z*: 246, 248 (M^+); 226, 228 (M^+-HF); 166 (M^+-HBr); 91 ($PhCH_2^+$).

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