3-Bromo-2-fluoropropene – A Fluorinated Building Block. 2-Fluoroallylation of Glycine and Alanine Ester Imines

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Abstract: 3-Bromo-2-fluoropropene **(4)** is prepared in a new three-step synthesis from ammonium α-fluoroacrylate **(1)** in 31% overall yield. Glycine and alanine ester imines are efficiently alkylated by **4** to give, after deprotection, 2-amino-4-fluoropent-4-enoic acid **(9)** in 63% overall yield, and the α-methylated derivative **13** in 26% overall yield, respectively. Preliminary results indicate that **4** is potentially a new α-carbonyl cation equivalent.

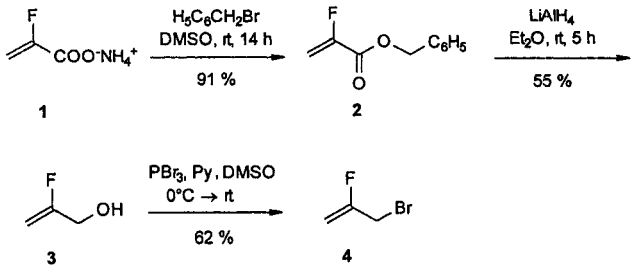
Key words: alkylation, amino acid ester imines, β-fluoroallyl bromide, 2-amino-4-fluoropent-4-enoic acid, α-carbonyl cation equivalent

The interest in partially fluorinated organic compounds has grown continuously over the last few years.[1] Nevertheless, the synthesis of highly functionalized molecules containing a limited number of fluorine atoms still remains a significant challenge to synthetic organic chemists.

Recently, we reported the syntheses of racemic[2] and optically active[3] γ- and δ-fluoro-α-amino acids using easily accessible fluorinated building blocks. Glycine ester imines have been alkylated with 1-bromo-2-fluoroalkanes[4] in good yields, in spite of the deactivating influence of the fluorine substituent in β-position to the reaction center.[5] We then became interested in the application of 3-bromo-2-fluoropropene **(4)**, which should be a more reactive alkylating reagent compared to the saturated β-fluorinated alkyl bromides.

Until now β-fluoroallylic compounds have been infrequently used as building blocks. Only a few C–C bond formation reactions of these compounds have been described in the literature.[6] For example, one such compound has been used for the alkylation of Schöllkopf's bislactim ether.[6, 7] However, they have been already shown to participate well in substitution reactions with non-carbon nucleophiles[6] and esters of β-fluoroallylic alcohols have also been used for hetero-Cope rearrangements.[8] 3-Bromo-2-fluoropropene **(4)**, previously prepared in a three-step synthesis from methyl vinyl ether in low overall yield, has been used for *O*-alkylation by Schlosser et al.[9] We report here a more efficient preparation of **4** and its use for *C*-alkylation of amino acid ester imines.

Attempts to prepare 3-bromo-2-fluoropropene **(4)** by bromofluorination of allylic bromide followed by dehydrobromination have been thwarted by lack of regioselectivity in the addition step.[10, 11] However, we found that 3-bromo-2-fluoropropene **(4)** could be efficiently obtained in three steps via 2-fluoroallylic alcohol **3** starting with ammonium α-fluoroacrylate **(1)**[12] (Scheme 1**)**. The direct reduction of **1** with $LiAlH_4$ could not be accomplished. However, compound **3** could be synthesized by treatment of **1** with $SOCl_2$, followed by reduction of the α-fluoroacrylic acid chloride with $LiAlH_4$ in diethyl ether at –20 °C. Although the reduction step was nearly quantitative, the overall yield of **3** was only 37% in this sequence. The most convenient synthesis of **3** involved the reduction of the benzyl ester **2** with $LiAlH_4$ in diethyl ether. The ester **2** was prepared under mild conditions by esterification of **1** with benzyl bromide in DMSO. Under these conditions, reduction of the C=C double bond or elimination of fluorine were not observed. Finally, the bromide **4** was obtained from the alcohol **3** by treatment with PBr_3[9] in the presence of catalytic amounts of DMSO. Starting from **1** the product **4** was isolated on a gram scale in 31% overall yield.

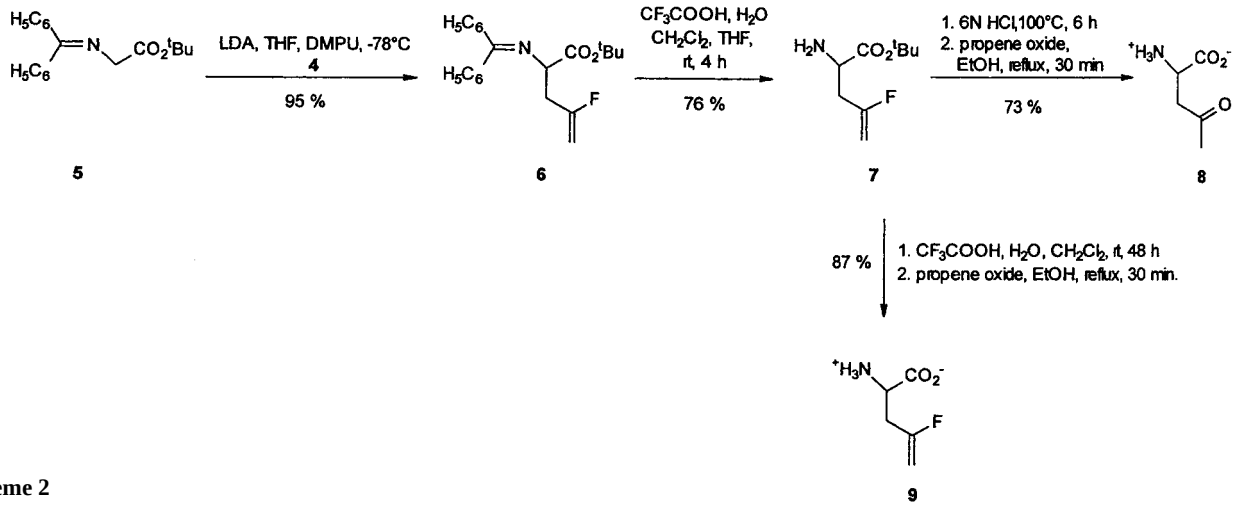


Scheme 1

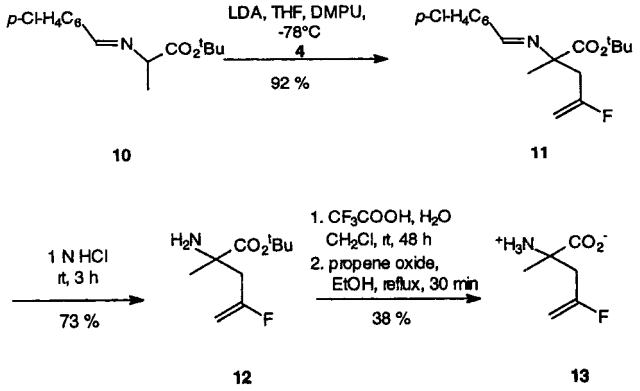
With a convenient synthesis of **4** in hand, we next examined its reactivity as an alkylating agent. Deprotonation of the Schiff's base of glycine *tert*-butyl ester **5**[13] by LDA in THF in the presence of DMPU[14] (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone, 2 mol equiv) at –78 °C[2] and alkylation with **4** gave the fluorinated product **6** in almost quantitative yield.

The protecting groups were subsequently removed stepwise under mild acidic conditions with dilute aqueous trifluoroacetic acid to give first the ester **7** and subsequently 2-amino-4-fluoropent-4-enoic acid **(9)** in 63% overall yield. Refluxing the ester **7** in 6 N HCl for six hours (the usual conditions for deprotection[15]) gave 2-amino-4-oxopentanoic acid **(8)** by hydrolysis of the *tert*-butyl ester group and the fluorovinyl moiety. The fluorovinyl group seems to be more readily hydrolyzed than either the chloro- or bromovinyl moiety, both of which require equimolar amount of mercury salts or concentrated sulfuric acid.[16, 17] Thus, 3-bromo-2-fluoropropene **(4)** can be viewed as a new α-carbonyl cation equivalent, but this potential has yet to be explored.

In order to have access to the corresponding α-methylated analog of **7** we turned our attention to the alkylation of alanine ester imine.



Scheme 2



Scheme 3

Because of the low reactivity of the corresponding benzophenone imine, the *p*-chlorobenzylidene imine **10**[18] was used. Compound **10** was treated in the same way as the glycine derivatives above. The alkylation product **11** was isolated in 92% yield. The imine **11** was hydrolyzed with aqueous 1 N HCl, and finally, the *tert*-butyl ester **12** was treated with trifluoroacetic acid to give the amino acid **13** in 26% overall yield, after crystallization.

All air- and moisture-sensitive reactions were performed under argon in flame dried flasks using standard Schlenk technique. tert-Butyl *N*-(diphenylmethylene)glycinate **(5)** was prepared by a literature method.[13] Ammonium α-fluoroacrylate **(1)** was a gift from Hoechst AG, Frankfurt am Main. All other starting materials were obtained from Acros, Merck and Fluka chemicals. *i*-Pr_2NH and DMPU were dried over molecular sieves (4 Å) and THF was distilled from Na/benzophenone before use.

Mps and bps are uncorrected. ^1H (300 MHz), ^{13}C (75.5 MHz), and ^{19}F NMR (282.3 MHz): Bruker WM 300. TMS for ^1H, $CDCl_3$ for ^{13}C and $CFCl_3$ for ^{19}F NMR as internal standard. If not stated otherwise $CDCl_3$ was used as solvent. The multiplicity of the ^{13}C NMR signals concerning the ^{13}C–^1H coupling was determined by the DEPT method. IR spectra: Nicolet 5DXC-FT-IR spectrometer. MS (70 eV): GC/MS coupling: Varian GC 3400/MAT 8230 and data system SS 300 of Finnigan MAT and Varian GC 3400/Varion Saturn IT (Ion Trap) and data system NIST. TOF "Lazarus III", self-construction by Dr. H. Luftmann, Organisch-Chemisches Institut, Universität Münster, ionization N_2 laser 337 nm, 3 ns pulse width, drift length 3 m, expected accuracy of mass +/–0.1%, ionization MALDI. Elemental analysis: Mikroanalytisches Laboratorium, OC, Universität Münster.

Benzyl α-Fluoroacrylate (2):
Benzyl bromide (22.7 g, 208 mmol) was added to a suspension of ammonium α-fluoroacrylate **(1)** (20.0 g, 189 mmol) in DMSO (80 mL) at r.t. After stirring overnight a brownish clear solution was obtained. Water (75 mL) and Et_2O (40 mL) were added, the organic layer was separated and the aqueous layer extracted with Et_2O (2 × 40 mL). The combined organic layers were washed with water (50 mL), sat. aq $NaHCO_3$ (50 mL), finally with sat. aq NaCl (50 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residual product was filtered through a short silica gel column (pentane/Et_2O 9:1); yield: 30.4 g (91%). The ester undergoes polymerization very easily and is sensitive to direct sunlight. It should be reduced to alcohol **3** immediately.
The ^{19}F NMR data agree with published values.[19]
^1H NMR: δ = 5.25 (s, 2H, CH_2Ph), 5.32 [dd, 1H, $^2J_{H,H}$ = 3.1 Hz, $^3J_{H,F}$ = 13.1 Hz, =CH(*Z*)], 5.68 [dd, 1H, $^2J_{H,H}$ = 3.1 Hz, $^3J_{H,F}$ = 43.2 Hz, =CH(*E*)], 7.40 (m, 5H, H_{arom}).
^{13}C NMR: δ = 67.4 (t, CH_2Ph), 102.8 (dt, $^2J_{F,C}$ = 15.3 Hz, $=CH_2$), 128.3, 128.5, and 128.6 (d, CH_{arom}), 134.9 (s, C_{arom}), 151.3 (ds, $^1J_{F,C}$ = 264.5 Hz, CF), 160.2 (ds, $^2J_{C,F}$ = 35.3 Hz, COO).
MS: *m/z* (%) = 180 (45) [M^+], 91 (100) [$C_7H_7^+$].
IR (film): ν = 1742 (s, C=O), 1656 cm^{-1} (s, C=C).

2-Fluoroprop-2-en-1-ol (3):
A solution of benzyl α-fluoroacrylate **(2)** (30.4 g, 163 mmol) in anhyd Et_2O (120 mL) was added to a suspension of $LiAlH_4$ (2.30 g, 66 mmol) in anhyd Et_2O (120 mL) over 30 min while cooling with an ice bath. The reaction was stirred at r.t. for 5 h, then aq 2 N HCl (200 mL) was added, the organic layer separated and the aqueous layer extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (50 mL), sat. aq NaCl (50 mL) and dried ($MgSO_4$). The solvent was removed by distillation (30 cm Vigreux column) and the product was isolated by vacuum distillation; yield: 7.05 g (55%); bp 65–70 °C/250 mbar.
The ^1H, ^{19}F NMR and MS data agree with published values.[20]
^{13}C NMR: δ = 60.3 (dt, $^2J_{C,F}$ = 33.1 Hz, CH_2OH), 90.9 (dt, $^2J_{H,F}$ = 15.3 Hz, $=CH_2$), 164.5 (ds, $^1J_{C,F}$ = 260.0 Hz, CF).
IR (film): ν = 3381 (s, O–H), 1684 cm^{-1} (s, C=C).

3-Bromo-2-fluoropropene (4):
In a modification of a procedure given in ref,[9] PBr_3 (1.50 mL, 16 mmol) was added to a mixture of **3** (2.98 g, 33 mol), pyridine (1 mL, 1.2 mmol) and DMSO (0.5 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and for 1 h at r.t. **4** was isolated by distillation; yield: 3.34 g (62%); bp 80 °C (Lit.[9] bp 85–86 °C, n_D^{20} 1.4671).

The ^{1}H and ^{19}F NMR data agree with published values.[9]
^{13}C NMR: δ = 26.9 (dt, $^2J_{C,F}$ = 33.2 Hz, CH_2Br), 94.3 (dt, $^2J_{C,F}$ = 20.3 Hz, $=CH_2$), 161.2 (ds, $^1J_{C,F}$ = 254.3 Hz, CF).
GC/MS: *m/z* (%) = 140/138 (25) [M^+], 59 (100) [M^+ – Br].
IR (film): ν = 1670 (s, C=C), 1282 cm^{-1} (s, C–F).

***tert*-Butyl 2-(*p*-Chlorobenzylideneamino)propionate (10):**
In a modified procedure appearing in ref,[21] *rac*-alanine *tert*-butyl ester[22] (18.0 g, 124 mmol) and *p*-chlorobenzaldehyde (10.0 g, 71 mmol) were dissolved in CH_2Cl_2 (150 mL) and $MgSO_4$ (12.0 g) was added. The mixture was stirred for two days at r.t. The solution was filtered and the solvent removed in vacuo. The residue was dissolved in Et_2O (80 mL) and washed subsequently with water (50 mL) and sat. aq NaCl (50 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated; yield: 15.53 g (83%); mp 42 °C (pentane).
^{1}H NMR: δ = 1.45 [s, 9H, $C(CH_3)_3$], 1.47 (d, 3H, $^3J_{H,H}$ = 6.9 Hz, CH_3), 4.03 (q, 1H, $^3J_{H,H}$ = 6.9 Hz, CHN), 7.38 and 7.72 (m, 4H, H_{arom}), 8.24 (s, 1H, HC=N).
^{13}C NMR: δ = 14.1 [q, $C(CH_3)_3$], 19.2 (q, CH_3), 61.0 [s, $C(CH_3)_3$], 128.7 and 129.5 (d, CH_{arom}), 134.1 (q, *C*CH=N) 136.9 (q, CCl), 161.0 (t, HC=N), 171.6 (q, COO).
GC/MS (Ion Trap): *m/z* (%) = 267 (8) [M^+], 166/168 (100/30) [M^+ – $COOC_4H_9$].
IR (KBr): ν = 1729 (s, C=O), 1634 cm^{-1} (s, C=N).
Anal. calcd for $C_{14}H_{18}ClNO_2$ (267.76): C 62.80, H 6.78, N 5.23, found: C 62.71, H 6.71, N 5.37.

Alkylation of Imines; General Procedure:[2]
To a stirred solution of *i*-Pr_2NH (0.23 mL, 3.0 mmol) in anhyd THF (7.5 mL) were added at –78 °C 1.6 M BuLi in hexane (1.86 mL, 3.0 mmol) and DMPU (0.60 mL, 5 mmol). The cooling bath was removed for 5 min. A solution of the corresponding imino ester (2.5 mmol), dissolved in anhyd THF (7.5 mL) was added at –78 °C. After 1 h, 3-bromo-2-fluoropropene **(4)** (417 mg, 3.0 mmol) was injected, and stirring was continued for 2 h at –78 °C before the mixture was allowed to warm up to r.t. overnight. Water (30 mL) was added, the organic layer separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (10 mL), sat. aq $NaHCO_3$ (10 mL), sat. aq NaCl (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the product was filtered through a short silica gel column (cyclohexane/Et_2O 2:1).

***tert*-Butyl 2-(Diphenylmethyleneamino)-4-fluoropent-4-enoate (6):**
From **5** (774 mg, 2.5 mmol) and **4** (417 mg, 3.0 mmol) was obtained **6**; yield: 840 mg (95%); mp 66–67 °C (pentane).
^{1}H NMR: δ = 1.43 [s, 9H, $C(CH_3)_3$], 2.70–2.85 (m, 2H, CH_2), 4.18 (dd, 1H, $^3J_{H,H}$ = 4.8 Hz, $^3J_{H,H}$ = 8.3 Hz, CHN), 4.31 [ddd, 1H, $^2J_{H,H}$ = 2.6 Hz, $^3J_{H,F}$ = 49.8 Hz, $^4J_{H,H}$ = 0.7 Hz, =CH(*E*)], 4.54 [dd, 1H, $^2J_{H,H}$ = 2.6 Hz, $^3J_{H,F}$ = 16.9 Hz, =CH(*Z*)], 7.44–7.16 (m, 10H, H_{arom}).
^{13}C NMR: δ = 28.0 [q, $C(CH_3)_3$], 36.2 (dt, $^2J_{C,F}$ = 25.4 Hz, CH_2), 81.5 [s, $C(CH_3)_3$], 63.0 (d, CHN), 92.3 (dt, $^2J_{C,F}$ = 14.5 Hz, $=CH_2$), 130.2, 128.8, 128.7, 128.6, 128.3, 128.0 and 127.7 (d, C–H_{arom}), 139.6 and 136.2 (s, C_{arom}), 163.2 (ds, $^1J_{C,F}$ = 256.8 Hz, CF), 170.1 (s, C=N), 171.2 (s, COO).
^{19}F NMR: δ = –95.5 (m).
GC/MS: *m/z* (%) = 353 (16) [M^+], 294 (4) [M^+ – C_3H_4F], 252 (100) [M^+ – $C_5H_9O_2$], 192 (30) [$Ph_2C{=}NC^+$].
IR (KBr): ν = 1714 (s, C=O), 1681 (s, C=C), 1624 cm^{-1} (m, C=N).
Anal. calcd for $C_{22}H_{24}FNO_2$ (353.44): C 74.76, H 6.84, N 3.96, found: C 74.59, H 6.84, N 4.14.

***tert*-Butyl 2-(*p*-Chlorobenzylideneamino)-4-fluoro-2-methylpent-4-enoate (11):**
From **10** (668 mg, 2.5 mmol) and **4** (417 mg, 3.0 mmol) was obtained **11** as an oil; yield: 750 mg (92%).
^{1}H NMR: δ = 1.39 [s, 9H, $C(CH_3)_3$], 1.44 (s, 3H, CH_3), 2.6–2.9 (AB, 2H, $^2J_{HH}$ = 14.5 Hz, CH_2), 4.36 [dd, 1H, $^2J_{H,H}$ = 2.6 Hz, $^3J_{H,F}$ = 49.6 Hz, =CH(*E*)], 4.55 dd, 1H, $^2J_{H,H}$ = 2.6 Hz, $^3J_{H,F}$ = 17.4 Hz, =CH(*Z*)], 7.27–7.34 and 7.59–7.65 (m, 4H, H_{arom}), 8.18 (s, 1H, CH=N).
^{13}C NMR: δ = 22.8 (q, CH_3), 28.0 [q, $C(CH_3)_3$], 42.1 (dt, $^2J_{F,C}$ = 25.4 Hz, CH_2), 67.4 [s, $C(CH_3)N$], 81.6 [s, $C(CH_3)_3$], 93.7 (dt, $^2J_{F,C}$ = 20.3 Hz, $=CH_2$), 128.6, 128.7, 129.4 and 130.8 (d, CH_{arom}), 134.9 and 136.8 (s, C_{arom}), 158.2 (d, CHN), 163.0 (ds, $^1J_{F,C}$ = 292.5 Hz, CF), 171.8 (s, COO).
^{19}F NMR: δ = –86.8 (m).
GC/MS: *m/z* (%) = 325/327 (10/4) [M^+], 183/185 (100/33).
IR (film): ν = 1728 (s, C=O), 1672 (s, C=C), 1643 cm^{-1} (s, C=N).
Anal. calcd for $C_{17}H_{21}ClFNO_2$ (325.81): C 62.67, H 6.50, N 4.30, found: C 62.30, H 6.63, N 4.45.

***tert*-Butyl 2-Amino-4-fluoropent-4-enoate (7):**
Similarly to a known hydrolysis procedure for imines,[23] to *tert*-butyl 2-(diphenylmethyleneamino)-4-fluoropent-4-enoate **(6)** (1.73 g, 4.9 mmol) in CH_2Cl_2 (56 mL) and THF (56 mL) were added CF_3COOH (11 mL) and water (14 mL) and the mixture stirred at r.t. for 4 h. Sat. $NaHCO_3$ (20 mL) and then solid $NaHCO_3$ (10 g) were added to neutralize the solution. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with sat. aq NaCl (20 mL), dried ($MgSO_4$), and the solvent was evaporated. The crude product was purified by bulb-to-bulb distillation; yield: 700 mg (76%); bp 40–45 °C/15 mbar.
^{1}H NMR: δ = 1.45 [s, 9H, $C(CH_3)_3$], 1.59 (s, 2H, NH_2), 2.48 (ddd, 1H, $^2J_{H,H}$ = 14.5 Hz, $^3J_{H,F}$ = 20.5 Hz, $^3J_{H,H}$ = 7.4 Hz, C*H*H), 2.65 (ddd, 1H, $^2J_{H,H}$ = 14.5 Hz, $^3J_{H,F}$ = 17.6 Hz, $^3J_{H,H}$ = 5.2 Hz, CH*H*), 3.57 (dd, 1H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 5.2 Hz, CHN), 4.36 [dd, 1H, $^2J_{H,H}$ = 2.9 Hz, $^3J_{H,F}$ = 49.4 Hz, =CH(*E*)], 4.65 [dd, 1H, $^2J_{H,H}$ = 2.9 Hz, $^3J_{H,F}$ = 17.2 Hz, =CH(*Z*)].
^{13}C NMR: δ = 27.9 [q, $C(CH_3)_3$], 34.6 (dt, $^2J_{C,F}$ = 25.4 Hz, CH_2), 52.1 (d, CHN), 81.5 [s, $C(CH_3)_3$], 92.9 (dt, $^2J_{C,F}$ = 20.3 Hz, $=CH_2$), 162.8 (ds, $^1J_{C,F}$ = 257.7 Hz, =CF), 173,6 (s, COO).
^{19}F NMR: δ = –95.8 (dddd, $^3J_{H,F}$ = 49.4 Hz, $^3J_{H,F}$ = 20.5 Hz, $^3J_{H,F}$ = 17.6 Hz, $^3J_{H,F}$ = 17.2 Hz).
GC/MS: *m/z* (%) = 189 (0.2) [M^+], 130 (8) [M^+ – C_3H_4F], 88 (100) [M^+ – $COOC_4H_9$].
IR (film): ν = 3387 (m, N–H), 1734 (s, C=O), 1676 cm^{-1} (s, C=C).
Anal. calcd for $C_9H_{16}FNO_2$ (189.23): C 57.13, H 8.52, N 7.40, found: C 56.83, H 8.64, N 7.21.

***tert*-Butyl 2-Amino-4-fluoro-2-methylpent-4-enoate (12):**
tert-Butyl 2-(*p*-chlorobenzylideneamino)-4-fluoro-2-methylpent-4-enoate **(11)** (2.95 g, 10 mmol) was dissolved in Et_2O (30 mL) and 1 N HCl (15 mL) was added. The mixture was stirred for 3 h at r.t. The aqueous layer was separated and the organic layer was extracted with 1 N HCl (3 × 15 mL). The combined aqueous layers were neutralized with solid K_2CO_3 (15 g) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were washed with sat. aq NaCl (30 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by bulb-to-bulb distillation; yield: 1.64 g (73%); bp 45 °C/15 mbar.
^{1}H NMR: δ = 1.34 (s, 3H, CH_3), 1.47 [s, 9H, $C(CH_3)_3$], 1.70 (s, 2H, NH_2), 2.43 (dd, 1H, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,F}$ = 24.3 Hz, C*H*H), 2.71 (dd, 1H, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,F}$ = 17.4 Hz, CH*H*), 4.35 [dd, 1H $^2J_{H,H}$ = 2.9 Hz, $^3J_{H,F}$ = 49.4 Hz, =CH(*E*)], 4.66 [dd, 1H, $^2J_{H,H}$ = 2.9 Hz, $^3J_{H,F}$ = 17.2 Hz, =CH(*Z*)].
^{13}C NMR: δ = 26.8 (q, CH_3), 27.8 [q, $C(CH_3)_3$], 43.2 (dt, $^2J_{F,C}$ = 25.4 Hz, CH_2), 56.6 [s, $C(CH_3)N$], 81.3 [s, $C(CH_3)_3$], 93.7 (dt, $^2J_{F,C}$ = 22.9 Hz, $=CH_2$) 163.1 (ds, $^1J_{F,C}$ = 259 Hz, CF), 175.5 (s, COO).
^{19}F NMR: δ = –92.4 (dddd, $^3J_{F,H}$ = 17.2 Hz, $^3J_{F,H}$ = 17.4 Hz $^3J_{F,H}$ = 24.3 Hz, $^3J_{F,H}$ = 49.4 Hz).
GC/MS (Ion Trap): *m/z* (%) = 202 (5) [M^+ – H], 102 (75) [M^+ – COO^tBu], 42 (100) [$C_2H_4N^+$].
Anal. calcd for $C_{10}H_{18}FNO_2$ (203.25): C 59.10, H 8.93, N 6.89, found: C 58.75, H 9.10, N 6.89.

Hydrolysis of the *tert*-Butyl Esters:

2-Amino-4-oxopentanoic Acid (8):
tert-Butyl 2-amino-4-fluoropent-4-enoate **(7)** (568 mg, 3.0 mmol) was refluxed in 6 N HCl (20 mL) for 6 h. The solvent was evaporated and the residue dissolved in EtOH (8 mL). Propene oxide (6.5 mL) was added and the solution was refluxed for 30 min. The precipitated **8** was isolated by suction and recrystallized ($EtOH/H_2O$); yield: 364 mg (73%); mp 138 °C ($EtOH/Et_2O$) [Lit.[24] 135–137 °C (EtOH)]. The ^1H and ^{13}C NMR data agree with published values.[25]

2-Amino-4-fluoropent-4-enoic Acid (9); Typical Procedure:
To *tert*-butyl 2-amino-4-fluoropent-4-enoate **(7)** (460 mg, 2.4 mmol), dissolved in CH_2Cl_2 (16 mL) were added water (4 mL) and CF_3COOH (5 mL) and the mixture was stirred at r.t. for 2 d. Then water (10 mL) was added, the layers were separated and the organic phase extracted with 6 N HCl (3 × 5 mL). The combined aqueous layers were evaporated. The residue was dissolved in EtOH (10 mL), propene oxide (2 mL) was added and the solution refluxed for 30 min. The precipitated product was isolated by suction and recrystallized ($EtOH/Et_2O$); yield: 280 mg (87%); mp 180–182 °C (dec) (H_2O/EtOH).
^1H NMR (D_2O): δ = 2.98 (m, 2H, CH_2), 4.08 (dd, 1H, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 4.8 Hz, CHN), 4.67 [dd, 1H, $^2J_{H,H}$ = 3.3 Hz, $^3J_{H,F}$ = 51.0 Hz, =CH(*E*)], 4.95 [dd, 1H, $^2J_{H,H}$ = 3.3 Hz, $^3J_{H,F}$ = 17.7 Hz, =CH(*Z*)].
^{13}C NMR (D_2O/CD_3OD): δ = 34.7 (t, $^2J_{C,F}$ = 28.0 Hz, CH_2), 53.4 (d, CHN), 95.5 (dt, $^2J_{C,F}$ = 17.8 Hz, $=CH_2$), 162.5 (ds, $^1J_{C,F}$ = 256.8 Hz, CF), 191.1 (s, COO).
^{19}F NMR (D_2O): δ = –95.2 (dddd, $^3J_{H,F}$ = 51.0 Hz, $^3J_{H,F}$ = 22.9 Hz, $^3J_{H,F}$ = 17.7 Hz, $^3J_{H,F}$ = 17.2 Hz).
MS (Maldi-TOF): *m/z* = 134 [M + H^+].
Anal. calcd for $C_5H_8FNO_2$ (133.12): C 45.11, H 6.06, N 10.52, found: C 45.15, H 5.93, N 10.58.

2-Amino-4-fluoro-2-methylpent-4-enoic Acid (13):
tert-Butyl 2-amino-4-fluoro-2-methylpent-4-enoate **(12)** (120 mg, 0.59 mmol) was hydrolyzed according to the procedure given for the synthesis of **9**; yield: 33 mg (38%); mp 210 °C (dec) ($EtOH/Et_2O$).
^1H NMR (D_2O): δ = 0.85 (s, 3H, CH_3), 2.10 (AB, 2H, $^2J_{H,H}$ = 15.5 Hz CH_2), 3.90 [dd, 1H, $^2J_{H,H}$ = 3.3 Hz, $^3J_{H,F}$ = 51.3 Hz, =CH(*E*)], 4.15 [dd, 1H, $^2J_{H,H}$ = 3.3 Hz, $^3J_{H,F}$ = 17.9 Hz, =CH(*Z*)].
^{13}C NMR: δ = 22.6 (q, CH_3), 39.7 (dt, $^2J_{C,F}$ = 28.0 Hz, CH_2), 60.5 [s, *C*(CH_3)N], 96.0 (dt, $^2J_{C,F}$ = 20.4 Hz, $=CH_2$), 161.2 (ds, $^1J_{C,F}$ = 254.3 Hz, CF), 176.0 (s, COO).
^{19}F NMR (D_2O): δ = –93.3 (m).
MS (Maldi-TOF): *m/z* = 148 [M + H^+].
Anal. calcd for $C_6H_{10}FNO_2 \cdot 0.5\ H_2O$ (155.71): C 46.17, H 7.09, N 8.96, found: C 46.15, H 7.10, N 8.97.

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