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Synthesis of γ-Fluoro-α-methyl-α-amino Acids. A New Alkylation Procedure for Ester Imines

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Abstract: Deprotonation of alanine ester imines with KO'Bu in DMSO or DMF and alkylation of the formed enolates with several 2-fluoroalkyl halogenides **2** and subsequent hydrolysis of the imino and the ester groups are presented as an efficient three-step sequence for the synthesis of racemic title compounds **5**.

Keywords: Alkylation; Amino acids; Fluorine compounds; Diastereoselection.

Introduction

In recent years non-proteinogenic and uncommon synthetic amino acids have gained much interest concerning the design and synthesis of enzyme inhibitors as potential pharmaceutical agents and also for the investigation of enzyme action [1]. α,α-Dialkyl-α-amino acids, particularly α-methyl derivatives, became most interesting in agricultural and medicinal chemistry as well as in biochemistry. These compounds are recognized as powerful enzyme inhibitors and are able to act as receptor antagonists. When incorporated in peptides these compounds reduce their flexibility and can modify the properties, e.g. reduce the enzymatic metabolism while increasing of lipophilicity [2]. Accordingly, several methods for the synthesis of α,α-dialkyl-α-amino acids have been developed and reviewed [3-5].

Moreover, it is well known that substitution of hydrogen in amino acids and their derived peptides by fluorine induce interesting new chemical and physiological properties. Thus, plenty of fluorinated analogues of natural and non-natural amino acids have been synthesized by several different methods

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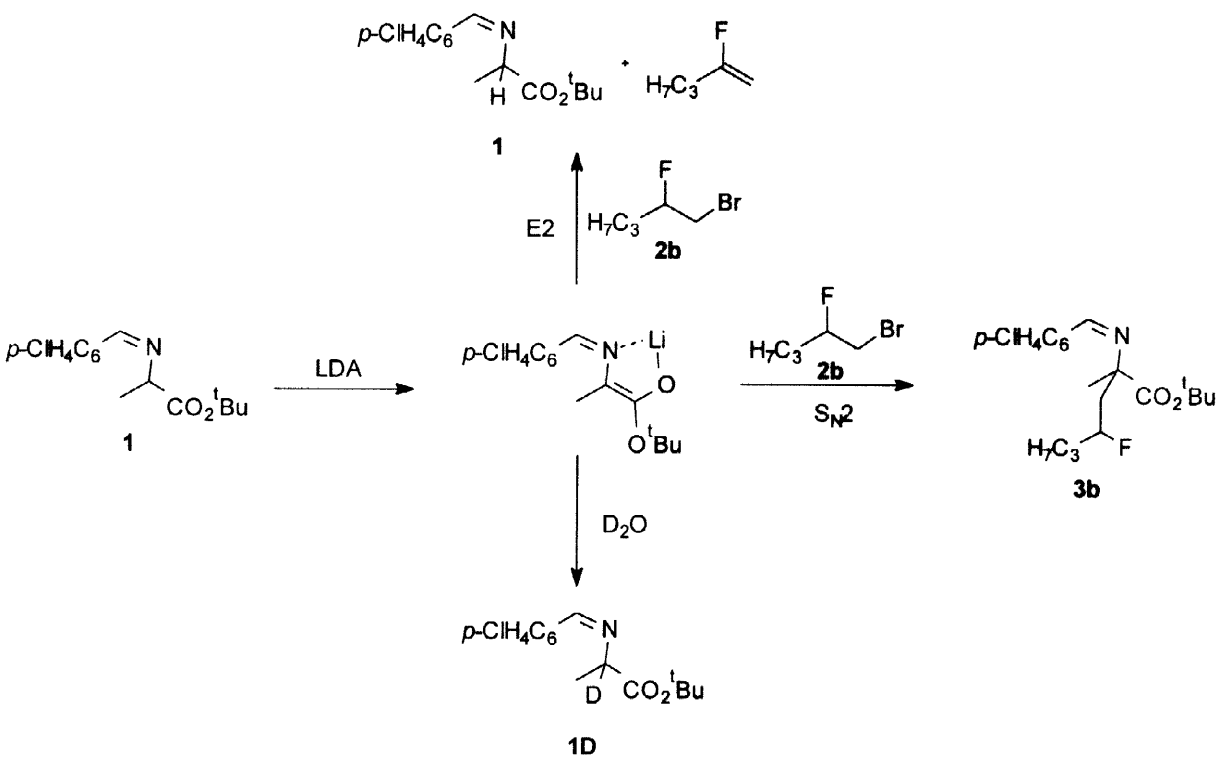
[6-9]. Among these compounds only a few γ-fluoro-α-amino acids have been prepared in the past [10]. However, *threo*-γ-fluoroglutamic acid has been shown to be a substrate of polyglutamate synthetase [11]. The isomeric γ-fluoro-L-glutamates were studied for their effect on bacterial glutamate mutase and the (4*S*)-isomer was found to be a potent inhibitor of this enzyme [12].

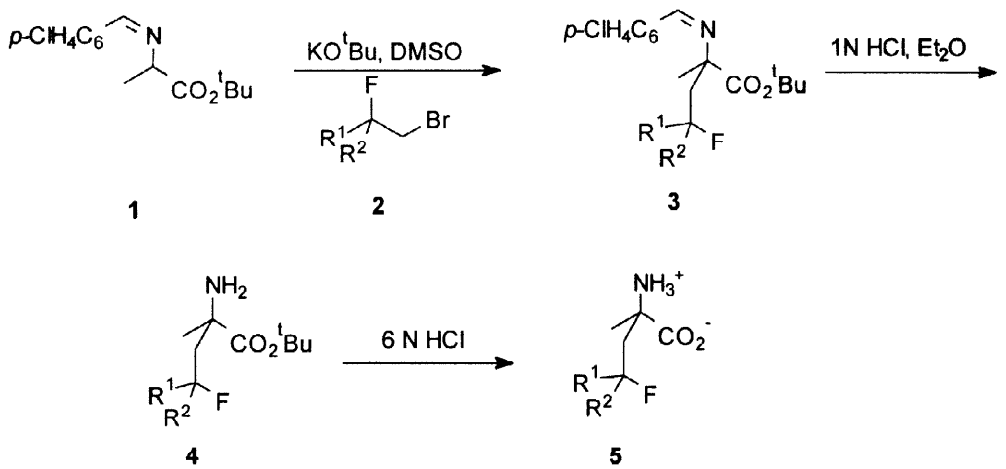
Recently we described the synthesis of racemic [13] and optically active [14] γ- and δ-fluoro-α-amino acids by alkylation of glycine ester imines with 1-bromo-2-fluoroalkanes. However, corresponding α-methyl derivatives are not known yet. We wish to report our results on the synthesis of several 2-amino-4-fluoro-2-methylalkanoic acids.

Results and Discussion

Applying the general alkylation procedure [13] of the Schiff's base **1** of alanine *tert.*-butyl ester and *p*-chlorobenzaldehyde with LDA in THF in the presence of DMPU at -78 °C followed by addition of 1-halo-2-fluoroalkanes only small amounts of the alkylation product were detected by GC. Following the reaction of the lithium enolate of **1** in THF-d_8 with 1-bromo-2-fluoropentane (**2b**) in a NMR tube by ^{19}F NMR spectroscopy at low temperature (-78°C → 20°C) it became obvious that 2-fluoropentene was formed to some extent. Almost no alkylation was observed. Repeating this reaction and quenching the mixture with D_2O after 4 hours at -78°C and warming up over night gave 30% of the starting α-protonated imine **1** and 70% of the α-deuterated analogue **1D** after usual work-up as checked by ^1H NMR spectroscopy.



These experiments show that under these conditions the E2-type elimination dominates the S_N2-type alkylation. In order to favor the alkylation we screened different bases, solvents and temperatures. Finally good results were obtained by treatment of **1** with KO^{t}Bu in DMSO or DMF and subsequent addition of the corresponding 1-halo-2-fluoroalkanes **2** [15] to form alkylation products **3** (Table 1). Furthermore, the alkylation of **1** with 3-bromo-2-fluoropropene (**2f**) succeeded in obtaining **3f** with better yield compared to earlier results [16].



1 **2** **3** **4** **5**

Table 1: Alkylation of the imine **1** with 1-bromo-2-fluoroalkanes **2** (X=Br) and 3-bromo-2-fluoropropene (**2f**) in DMSO.

Entry	1-Bromo-2-fluoroalkane	R^1	R^2	Reaction Time [h]	Reaction Temp. [°C]	Yield **3** [%]
1	**2a**	H	H	6	20	39
2	**2b**	H	C_3H_7	6	20	88
3	**2c**	H	$CH(CH_3)_2$	12	20	73
4	**2d**	CH_3	CH_3	6	90	(20)[a]
5	**2e**	H	C_6H_5	12	20	(36)[a]
6	**2f**		$=CH_2$	3	20	80

[a] GC yield

The imino esters **3** are very sensitive to hydrolysis. Thus, the crude alkylation products **3** are directly hydrolyzed with 1N HCl. Diastereoselectivity of the alkylation does not depend much on solvent (Table 2, entries 8 and 9) and temperature (entries 8-11), but depends on the leaving group (entries 11 and 13) and on substituents attached to the 1-bromo-2-fluoroethane moiety (entries 8, 15-17). The diastereomeric excess was determined by ^{19}F NMR spectroscopic analysis of **4** obtained after mild hydrolysis of the imino group (Table 2). Finally, the *tert.*-butyl esters **4a** - **4c** were hydrolyzed under drastic conditions by refluxing with 6N HCl to give compounds **5** contaminated with small

amounts of the corresponding γ-chloroamino acids (Table 2). The ester **4f** was hydrolyzed with trifluoroacetic acid at room temperature to form **5f** [16].

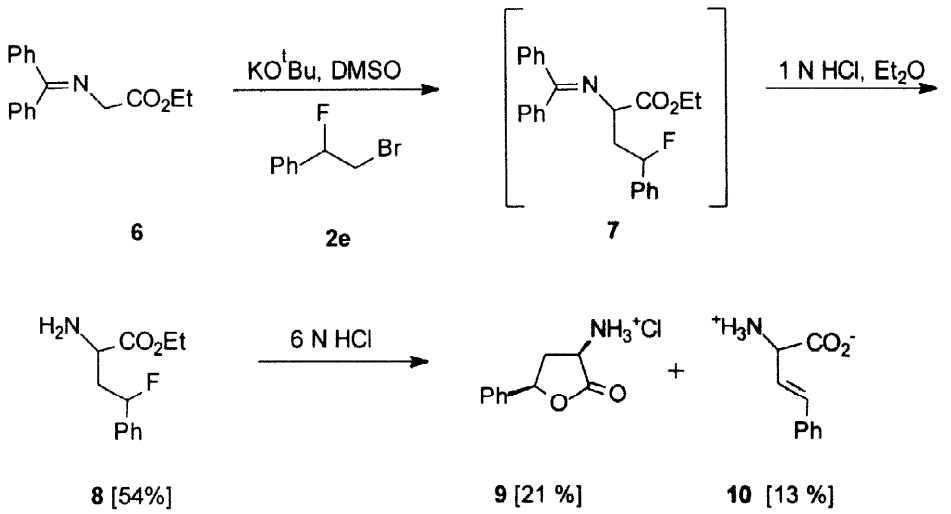
Table 2: Synthesis of *tert.*-butyl 2-amino-4-fluoro-2-methyl carboxylates **4** and 4-fluoro-2-methyl-2-amino acids **5** by alkylation of **1** and subsequent hydrolysis of crude **3**.

Entry	1-Halo-2-fluoro-alkanes	R^1	R^2	X	Alkylation conditions			Yield **4**[a]	Yield **5**
					Solvent	Time [h]	Temp. [°C]	[%] (de)	[%]
7	**2a**	H	H	Br	DMSO	6	20	55	49
8	**2b**	H	C_3H_7	Br	DMSO	6	20	53 (24)	19[b]
9	**2b**	H	C_3H_7	Br	DMF	12	20	53 (24)	--
10	**2b**	H	C_3H_7	Br	DMF	12	0	46 (24)	--
11	**2b**	H	C_3H_7	Br	DMF	12	-20	43 (26)	--
12	**2b**	H	C_3H_7	Br	DMF	12	-40	36 (28)	--
13	**2b**	H	C_3H_7	I	DMF	12	-20	40 (36)	--
14	**2b**	H	C_3H_7	I	DMF	12	-55	29 (38)	--
15	**2c**	H	$CH(CH_3)_2$	Br	DMSO	12	20	62 (66)	35[b]
16	**2e**	H	C_6H_5	Br	DMSO	12	20	19 (18)	[c]
17	**2f**	$=CH_2$		Br	DMSO	3	20	73	52[d]

[a] overall yield from **1**; [b] contaminated with the chloro amino acids 5% in the case of **5b** and 15% in the case of **5c**; [c] decomposition with 6 N HCl; [d] by hydrolysis with F_3CCOOH [16]

Furthermore, also alkylation of benzophenone derived glycine esters (ethyl- and *tert.*-butyl) have been possible using KO'Bu in DMSO to give slightly better yields compared with the corresponding alkylation using LDA in THF [13].

Moreover, alkylation with 2-bromo-1-fluoro-1-phenylethane (**2e**) of the benzophenone glycine ethyl ester imine **6** was successful. However, α-fluorostyrene could be detected by GC in addition to the product **7** indicating that elimination of HBr competes with alkylation. Since **7** decomposed during column chromatography the imino group of **7** was directly hydrolyzed with 1N HCl and the diastereomeric esters **8** (1:1 ratio) were isolated in 54 % overall yield. Unfortunately, dehydrofluorination occurred during hydrolysis with 6N HCl. The lactone **9** [18] and the elimination product **10** [19] were isolated. The *cis*-configuration of **9** was confirmed by NOE experiments.



Experimental

General: *tert.*-Butyl 2-(p-chlorobenzylideneamino)propionate (**1**) [16] and ethyl *N*-(diphenylethylene)-glycinate (**6**) [17] were prepared according to literature methods. All other starting materials were obtained from Acros, Merck and Fluka chemicals.

Melting and boiling points are uncorrected. – ^{1}H (300 MHz), ^{13}C (75.5 MHz) and ^{19}F NMR (282.3 MHz): Bruker WM 300 and ^{1}H (600 MHz): Varian 600 MHz apparatus Unity Plus. TMS was used as standard for ^{1}H-, $CDCl_3$ for ^{13}C- and $CFCl_3$ for ^{19}F NMR spectroscopy. If not stated otherwise $CDCl_3$ was used as solvent. – Mass spectra (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 puls-width, drift length 3 m, expected accuracy of mass +/-0.1%, ionization MALDI. – Elemental analysis: Mikroanalytisches Laboratorium, OC, Universität Münster.

Alkylation of 1: In a Schlenk vessel 340 mg (3 mmol) of KO'Bu were dissolved in 7 mL of DMSO (or DMF) at 20°C. The solution was degassed in vacuum and the vessel was filled with argon. Then 670 mg (2.5 mmol) of **1** in 3 mL of DMSO (or DMF) were added and the mixture was stirred for 30 min. Bromofluoroalkane **2** (3.2 mmol) was added and the mixture was stirred at the temperature given in Tables 1 and 2 for the mentioned time. Subsequently 40 mL of water and 40 mL of diethyl ether were added and stirred for 3 min. The layers were separated and the aq. phase was extracted four times with 20 mL of ether. The combined ethereal layers were washed with saturated sodium bicarbonate solution and sodium chloride solution and dried with magnesium sulfate. The solvent was evaporated and the products **3** were separated by column filtration (3 cm silica gel).

tert.-Butyl 2-(p-chlorobenzylideneamino)-4-fluoro-2-methylbutyrate (**3a**). Preparation from 2.68 g (10 mmol) of **1**. Yield: 302 mg (39%). ^{1}H NMR δ 8.28 (s, 1H, 8-H), 7.3-7.8 (m, 4H, Ph-H), 4.66 (ddd, 2H,

$^2J_{HF}$ = 47.2 Hz, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$= 6.4 Hz, CFH_2), 2.18-2.48 (m, 2H, CH_2), 1.50 (s, 3H, CH_3), 1.46 (s, 9H, $C(CH_3)_3$);^{13}C NMR δ 172.3 (s, COO), 158.4 (d, C=N), 136.8 and 134.9 (s, C-Ph), 129.4 and 128.8 (d, C-Ph), 81.5 (d, $C(CH_3)_3$), 80.9 (dd, $^1J_{CF}$ = 162.8 Hz, CF), 66.8 (ds, $^3J_{CF}$ = 5.1 Hz, $C(CH_3)N$), 40.3 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 27.9 (q, $C(CH_3)_3$), 23.7 (q, CH_3); ^{19}F NMR δ -218.6 (tt, $^2J_{HF}$ = 47.2 Hz, $^3J_{HF}$ = 22.9 Hz, CH_2F). GC/MS m/z (%) 313 (0) [M^+], 256 (3.1) [M^+-C_4H_9], 212 (100) [M^+-$CO_2C_4H_9$].

tert.-Butyl 2(p-chlorobenzylideneamino)-4-fluoro-2-methylheptanoate (**3b**): Yield: 570 mg (64%, 24% de). Mixture of both diastereomers: ^{1}H NMR δ 8.30 (s,1H, CH=N), 8.25 (s,1H, CH=N), 7.70 and 7.38 (m, 4H, Ph-H), 4.75 (dm, 1H, $^2J_{HF}$ = 50.8 Hz, CHF), 2.45-1.30 (m, 6H, 3xCH_2), 0.95 (t, 3H, $^3J_{HH}$ = 7.4 Hz, CH_2CH_3), 1.51 (s, 3H, CH_3), 1.46 (s, 9H, $C(CH_3)_3$);^{13}C NMR δ 172.6 (s, COO), 158.5 (d, CH=N), 158.1 (d, CH=N), 136.8 and 135.0 (s, C-Ph), 128.8, 129.4 and 130.9 (d, C-Ph), 90.1 (dd, $^1J_{CF}$ = 166.5 Hz, CHF), 90.0 (dd, $^1J_{CF}$ = 166.5 Hz, CHF), 81.3 (s, $C(CH_3)_3$), 67.4 (s, $C(CH_3)N$), 67.0 (s, $C(CH_3)N$), 46.0 5 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 44.5 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 38.1 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 28.0 (q,CH_3), 24.6 (q, $C(CH_3)_3$), 18.2 (dt, $^3J_{CF}$ = 2.4 Hz, CH_2), 13.9 (q, CH_2CH_3); ^{19}F NMR δ -177.6 (m, CHF), -177.8 (m, CHF); GC/MS m/z (%) 356 (0) [M^+], 298/300 (7/2) [M^+-C_4H_9], 254/256 (100/35) [M^+-$CO_2C_4H_9$]. Anal. Calcd. for $C_{19}H_{27}ClFNO_2$ (355.88): C 64.13, H 7.65, N 3.94. Found C 64.00, H 7.54, N 4.15.

tert.-Butyl 2-(p-chlorobenzylideneamino)-4-fluoro-2,5-dimethylhexanoate (**3c**): Yield: 650 mg (73%, 66% de). Mixture of both diastereomers: ^{1}H NMR δ 8.29 (s, 1H, CH=N), 8.25 (s, 1H, CH=N), 7.72 and 7.38 (m, 4H, Ph-H), 4.56 (dddd, 1H, $^2J_{HF}$ = 51.6 Hz, $^3J_{HH}$ = 4.2 Hz, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 11.3 Hz, CHF), 4.47 (dddd, 1H, $^2J_{HF}$ = 51.6 Hz, $^3J_{HH}$ = 4.2 Hz, $^3J_{HH}$ = 7.3 Hz, $^3J_{HH}$ = 11.3 Hz, CHF), 1.46 (s, 9H, $C(CH_3)_3$), 1.75-2.40 (m, 3H, CH, CH_2), 1.42 (s, 3H, CH_3), 0.97 (d, 6H, $^3J_{HH}$ = 6.9 Hz, $CH(CH_3)_2$); ^{13}C NMR δ 172.6 (s, COO), 158.5 (d, CH=N), 158.0 (d, CH=N), 136.8 and 135.0 (s, C-Ph), 128.8, 129.4 and 130.9 (d, C-Ph), 95.0 (dd, $^1J_{CF}$ = 170.4 Hz, CHF), 90.0 (dd, $^1J_{CF}$ = 170.4 Hz, CHF), 81.2 (s, $C(CH_3)_3$), 67.4 (s, $C(CH_3)N$), 67.2 (s, $C(CH_3)N$), 43.2 (dt, $^2J_{CF}$= 20.4 Hz, CH_2), 41.8 (dt, $^2J_{CF}$ = 20.4 Hz, CH_2), 33.1 (dd, $^2J_{CF}$ = 20.3 Hz, CH), 28.0 (q, $C(CH_3)_3$), 22.7 (q, CH_3), 18.2 (dq, $^3J_{CF}$ = 5.1 Hz, CH_3), 16.9 (dq, $^3J_{CF}$ = 7.6 Hz, CH_3); ^{19}F NMR δ -183.7 (m, CHF), -184.2 (m, CHF); GC/MS m/z (%) 356 (0) [M^+], 298/300 (5/1) [M^+-C_4H_9], 254/256 (100/40) [M^+-$CO_2C_4H_9$].

tert.-Butyl 2-(p-chlorobenzylideneamino)-4-fluoro-2,4,4-trimethylpentanoate (**3d**): Yield 20% (GC). ^{19}F NMR δ -133.4 (m, $CF(CH_3)_2$); GC/MS m/z (%) 341 (0) [M^+], 240/242 (100/25) [M^+-$CO_2C_4H_9$], 165/167 (18/5) [240-C_4H_8F], 138 (8) [$C_7H_8ClN^+$], 111 (3) [$C_6H_4Cl^+$], 61 (14) [$C_3H_6^+$].

tert.-Butyl 2-(p-chlorobenzylideneamino)-4-fluoro-2-methylpent-4-enoate (**3f**): Preparation from 1.34 g (5 mmol) of **1**. Yield: 1.30 g (80%). The GC/MS, ^{1}H, ^{19}F and ^{13}C NMR data agree with published values [16].

Hydrolysis of the imino group of **3**. The crude product **3** obtained by alkylation of **1** (5.0 mmol) was dissolved in 10 mL of diethyl ether, 10 mL of 1N HCl were added and the mixture was stirred for about 12 h at rt. The layers were separated, the aq. phase was extracted three times with 20 mL of diethyl

ether. The combined ethereal layers were extracted three times with 20 mL of 1N HCl. The combined aq. phases were neutralized with solid potassium carbonate and extracted four times with 40 mL of dichloromethane and 20 mL of ether. The combined organic extracts were dried over sodium sulfate, the solvent was evaporated and the residue was purified by Kugelrohr distillation or column chromatography.

tert.-Butyl 2-amino-4-fluoro-2-methylbutyrate (**4a**). 2.68 g (10.0 mmol) of **1** were alkylated using 1.62 g (12.8 mmol) of **2a** and the crude product was hydrolyzed. Yield: 1.33 g (55%); bp 75°C/18 mbar. ^{1}H NMR δ 4.58 (ddd, 2H, $^2J_{HF}$ = 47.5 Hz, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 6.2 Hz, CFH_2), 1.85-2.20 (m, 2H, CH_2), 1.69 (s, 2H, NH_2), 1.46 (s, 9H, $C(CH_3)_3$), 1.34 (s, 3H, CH_3); ^{13}C NMR δ 175.3 (s, COO), 81.1 (s, $C(CH_3)_3$), 80.8 (dt, $^1J_{CF}$ = 165.8 Hz, CH_2F), 56.5 (s, $C(CH_3)N$), 40.7 (dt, $^2J_{CF}$= 17.9 Hz, CH_2), 28.0 (q, $C(CH_3)_3$), 27.0 (q, CH_3); ^{19}F NMR δ -219.6 (tdd, $^2J_{HF}$ = 47.5 Hz, $^3J_{HF}$ = 26.7 Hz, $^3J_{HF}$ = 24.8 Hz, CH_2F); GC/MS m/z (%) 192 (0.1) [M^++H], 191 (0) [M^+], 90 (100) [M^+-$CO_2C_4H_9$], 70 (50) [$C_4H_8N^+$]; Anal. Calcd. for $C_9H_{18}FNO_2$ (191.24): C 56.52, H 9.44, N 7.32. Found C 56.17, H 9.67, N 7.16.

tert.-Butyl 2-amino-4-fluoro-2-methylheptanoate (**4b**). 1.35 g (5.0 mmol) of **1** were alkylated using 1.08 g (6.0 mmol) of **2b** and the crude product was hydrolyzed. Yield: 615 mg (53%, 24% de); bp 80°C/17 mbar. Mixture of both diastereomers: ^{1}H NMR δ 4.70 (dm, $^2J_{HF}$ = 50.8 Hz, 1H, CHF), 2.27-1.80 (m, 2H, CH_2), 1.75 (s, 2H, NH_2), 1.47 (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.32 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.3-1.7 (m, 4H, 2xCH_2), 0.95 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_2CH_3); ^{13}C NMR δ 176.2 (s, COO), 176.0 (s, COO), 92.0 (dd, $^1J_{CF}$= 165.3 Hz, CHF), 90.6 (dd, $^1J_{CF}$ = 165.3 Hz, CHF), 80.9 (s, $C(CH_3)_3$), 80.7 (s, $C(CH_3)_3$), 57.5 (s, $C(CH_3)_3N$), 55.9 (s, $C(CH_3)N$), 46.1 (dt, $^2J_{CF}$ = 17.8 Hz, CH_2), 45.0 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 38.1 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2CH_2), 37.9 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2CH_2), 27.7 (q, $C(CH_3)_3$), 27.6 (q, CH_3), 27.2 (q, CH_3), 18.1 (dt, $^3J_{CF}$ = 5.1 Hz, CH_2CH_3), 13.7 (q, CH_2CH_3). ^{19}F NMR δ -178.7 (m, CHF), -181.9 (m, CHF). GC/MS m/z (%) 234 (0.4) [M^++H], 233 (0) [M^+], 132 (100) [M^+-$CO_2C_4H_9$], 112 (100) [132-HF]. Anal. Calcd. for $C_{12}H_{24}FNO_2$ (233.33): C 61.77, H 10.37, N 6.00. Found C 61.30, H 10.69, N 6.18.

tert.-Butyl 2-amino-4-fluoro-2,5-dimethylhexanoate (**4c**). 1.35 g (5.0 mmol) of **1** were alkylated using 1.08 g (6.0 mmol) of **2c** and the crude product was hydrolyzed. Yield: 724 mg (62%, 66% de); bp 45°C/1 mbar. Mixture of both diastereomers: ^{1}H NMR δ 4.45 (dddd, $^2J_{HF}$ = 49.8 Hz, $^3J_{HH}$ = 10.73 Hz, $^3J_{HH}$ = 5.24 Hz, $^3J_{HH}$ = 2.14 Hz, CHF), 4.40 (dddd, 1H, $^2J_{HF}$ = 47.8 Hz, $^3J_{HH}$ = 2.6 Hz, $^3J_{HH}$ = 5.2 Hz, $^3J_{HH}$ = 8.8 Hz, CHF), 1.8-1.95 (m, 3H, CH_2, CH), 1.74 (s, 2H, NH_2), 1.47 (s, 9H, $C(CH_3)_3$), 1.44 (s, 9H, $C(CH_3)_3$), 1.33 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.96 (d, 6H, $^3J_{HH}$ = 6.7 Hz, $CH(CH_3)_2$); ^{13}C NMR δ 176.6 (s, COO), 96.3 (dd, $^1J_{CF}$ = 169.3 Hz, CHF), 94.8 (dd, $^1J_{CF}$ = 170.4 Hz, CHF), 80.9 (s, $C(CH_3)_3$), 80.7 (s, $C(CH_3)_3$), 57.5 (s, $C(CH_3)N$), 55.9 (s, $C(CH_3)N$), 42.9 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 41.8 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 33.0 (dd, $^2J_{CF}$ =23.4 Hz, CH), 32.7 (dd, $^2J_{CF}$ = 20.3 Hz, CH), 27.9 (q, $C(CH_3)_3$), 27.8 (q, CH_3), 27.3 (q, CH_3), 18.0 (q, $^3J_{CF}$ = 5.1 Hz, $CH(CH_3)_2$), 16.9 (q, $^3J_{CF}$ = 7.5 Hz, $CH(CH_3)_2$); ^{19}F NMR δ -183.6 (m, CHF), -187.8 (m, CHF); GC/MS m/z (%) 233 (0) [M^+], 176 (0.4) [M^+-C_4H_9], 132 (100) [M^+-$CO_2C_4H_9$], 88 (24) [$C_5H_9F^+$], 43 (12) [$C_3H_7^+$]; Anal. Calcd. for $C_{12}H_{24}FNO_2$ (233.33): C 61.77, H 10.37, N 6.00. Found C 61.38, H 10.21, N 6.36.

tert.-Butyl 2-amino-4-fluoro-2-methyl-4-phenylbutanoate (**4e**): 670 mg (2.5 mmol) of **1** were alkylated using 640 mg (3.0 mmol) of **2e** and the crude product has been hydrolyzed. Yield: 127 mg (19%, 18% de); bp 70°C/0.4 mbar. Mixture of both diastereomers: ^{1}H NMR δ 7.35 (m, 5H, Ph-H$_5$), 5.67 (dm, $^2J_{HF}$ = 49.1 Hz, CHF), 2.60-1.80 (m, 2H, CH_2), 1.84 (s, 2H, NH_2), 1.52 (s, 9H, $C(CH_3)_3$), 1.50 (s, 9H, $C(CH_3)_3$), 1.39 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{19}F NMR δ -174.9 5 (ddd, $^2J_{HF}$ = 49.1 Hz, $^3J_{HF}$ = 17.2 Hz, $^3J_{HF}$ = 40.1 Hz, CHF), -176 (ddd, $^2J_{CF}$ = 47.7 Hz, $^3J_{HF}$ = 11.5 Hz, $^3J_{HF}$ = 40.0 Hz, CHF); GC/MS m/z (%) 270 (0) [M$^+$], 255 (0.2) [M$^+$-CH_3], 210 (12) [M$^+$-C_4H_9], 166 (100) [M$^+$-$CO_2C_4H_9$].

tert.-Butyl 2-amino-4-fluoro-2-methylpent-4-enoate (**4f**): 2.95 g (10.0 mmol) of **1** were alkylated with 1.62 g (12.8 mmol) of **2f** and the crude product was hydrolyzed. Yield: 1.64 g (81%); bp 45 °C/15 mbar. The GC/MS, ^{1}H, ^{19}F and ^{13}C NMR data agree with published values [16].

Hydrolysis of the tert.-butylesters **4**. 2 mmol of the *tert.*-butylesters **4** were mixed with 14 mL of 6N HCl and refluxed for 6 h. The mixture was evaporated to dryness and dissolved in abs. ethanol/diethyl ether. Then 1 mL of propylene oxide was added and refluxed for 30 min. On cooling to rt the amino acids precipitated as white solids which were recrystallized from ethanol/water 1:1.

2-Amino-4-fluoro-2-methylbutanoic acid (**5a**). Preparation from 550 mg (2.9 mmol) of **4a**. Yield: 190 mg (49%); mp 173 °C, decomp. ^{1}H NMR (D_2O) δ 4.75-4.40 (m, 4H, CH_2F), 2.35-2.10 (m, 2H, CH_2), 1.53 (s, 3H, CH_3); ^{13}C NMR (D_2O) d 176.6 (s, COO), 82.2 (dt, $^1J_{CF}$ = 157.7 Hz, CH_2F), 61.0 (s, *C*(CH_3)N), 37.6 (dt, $^2J_{CF}$ = 17.8 Hz, CH_2), 23.1 (q, CH_3); ^{19}F NMR (D_2O) δ -216 (tdd, $^2J_{HF}$ = 47.7 Hz, $^3J_{HF}$ = 32.4 Hz, $^3J_{HF}$ = 28.6 Hz, CH_2F); MS (Maldi-TOF) m/z 136 [M+H$^+$].

2-Amino-4-fluoro-2-methylheptanoic acid (**5b**). Preparation from 443 mg (2.1 mmol) of **4b**. Yield: 70 mg (19%, 24% de); mp 187 °C, decomp. Mixture of both diastereomers: ^{1}H NMR (D_2O) δ 5.02 (m, 1H, CHF), 2.21 (m, 2H, CH_2), 1.57 (s, 3H, CH_3), 1.3.5-1.88 (m, 4H, CH_2CH_2), 0.97 (t, 3H, $^3J_{HH}$ = 7.4 Hz, CH_2CH_3); ^{13}C NMR (D_2O) δ 178.1 (s, COO), 96.1 (dd, $^2J_{CF}$ = 166.5 Hz, CHF), 62.1 (s, *C*(CH_3)N), 44.3 (dt, $^2J_{CF}$ = 18.9 Hz, CH_2), 39.9 (dt, $^2J_{CF}$ = 20.4 Hz, CH_2), 25.9 (q, CH_3), 19.6 (t, CH_2), 15.2 (q, CH_2CH_3); ^{19}F NMR (D_2O) δ -176.3 (m, CHF), -177.8 (m, CHF); MS (Maldi-TOF) m/z: 178 [M+H$^+$].

2-Amino-4-fluoro-2,5-dimethylhexanoic acid (**5c**). Preparation from 663 mg (2.85 mmol) of **4c**. Yield: 176 mg (35%, 88% de); mp 204 °C, decomp. Mixture of both diastereomers: ^{1}H NMR (D_2O) δ 4.6-4.8 (m, 1H, CHF), 2.31 (m, 2H, CH_2), 1.90-2.07 (m, 1H, CH), 1.70 (s, 3H, CH_3), 1.06 (d, 6H, $^3J_{HH}$= 6.9 Hz, $CH(CH_3)_2$); ^{13}C NMR (1N HCl in D_2O, d_4-methanol) δ 174.7 (q, COO), 174.6 (q, COO), 98.7 (dd, $^1J_{CF}$ = 165.3 Hz, CHF), 61.2 (s, *C*(CH_3)N), 60.6 (s, *C*(CH_3)N), 39.8 (dt, $^2J_{CF}$ = 20.3 Hz, CH_2), 33.2 (dt, $^3J_{CF}$ = 17.8 Hz, $CHFCH_2$), 28.8 (q, CH_3), 28.7 (q, CH_3), 24.1 and 22.7 (q, $CH(CH_3)_2$); ^{19}F NMR (1N HCl in D_2O) δ -180.9 (m, CHF), -182.7 (m, CHF); MS (Maldi-TOF) *m/z*: 178 [M + H$^+$].

2-Amino-4-fluoro-2-methylpent-4-enoic acid (**5f**): Preparation from 120 mg (0.59 mmol) of **4f**. Yield: 33 mg (38%); mp 210 °C, decomp. The MS, ^{1}H, ^{19}F and ^{13}C NMR data agree with published values [16].

Ethyl N-(diphenylmethyleneamino)-4-fluoro-4-phenylbutanoate (**7**): Similarly to the alkylation of **1** 1.34 g (5.0 mmol) ethyl *N*-(diphenylmethylene)glycinate (**6**) were alkylated with 1.30 g (6.0 mmol) 2-bromo-1-fluoro-1-phenylethane (**2e**). The product decomposed partially during column chromatography. Yield: 1.59 g (62%, 75% purity, GC, 20% de), a small amount of the pure substance was isolated. Mixture of both diastereomers: ^{1}H NMR δ 7.82-7.05 (m, 15H, Ph-H$_{15}$), 5.66 (ddd, $^2J_{HF}$ = 45.8 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 4.8 Hz, CHF), 5.47 (ddd, 1-H, $^2J_{HF}$ = 49.6 Hz, $^3J_{HH}$ = 10.25 Hz, $^3J_{HH}$ = 3.1 Hz, CHF), 4.44 - 4.04 (m, 3H, CH, C*H*$_2$CH$_3$), 2.66-2.36 (m, 2H, CH$_2$), 1.25 and 1.22 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH$_3$); ^{13}C NMR δ 172.2 (s, COO), 171.6 (s, C=N), 171.5 (s, C=N), 136.2 and 136.1 (s, C-Ph), 130.4 (ds, $^2J_{CF}$ = 7.6 Hz, C-Ph), 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8 and 127.7 (d, C-Ph), 92.5 (dd, $^1J_{CF}$ = 170.4 Hz, CHF), 90.4 (dd, $^1J_{CF}$ = 172.3 Hz, CHF), 62.1 (d, CHN), 61.6 (d, CHN), 61.0 (t, *C*H$_2$CH$_3$), 41.0 (dt, $^2J_{CF}$ = 22.9 Hz, CH$_2$), 14.1 (q, CH$_3$); ^{19}F NMR δ -174.8 (ddd, $^2J_{HF}$ = 45.8 Hz, $^3J_{HF}$ = 26.7 Hz, $^3J_{HF}$ = 17.2 Hz, CHF), -180.4 (ddd, $^2J_{HF}$ = 49.6 Hz, $^3J_{HF}$ = 36.2 Hz, $^3J_{HF}$ = 14.5 Hz, CHF); GC/MS (Ion Trap) m/z (%) 390 (6) [M$^+$+H], 389 (0) [M$^+$], 369 (3) [M$^+$-HF], 316 (55) [M$^+$-CO$_2$C$_2$H$_5$], 109 (100) [C$_7$H$_6$F$^+$]; Anal. Calcd. for C$_{25}$H$_{24}$FNO$_2$ (389.47): C 77.10 H 6.21 N 3.60. Found C 77.34, H 6.56, N 3.55.

Ethyl 2-amino-4-fluoro-4-phenylbutanoate (**8**): 1.34 g (5.0 mmol) **6** were alkylated with 1.30 g (6.0 mmol) **2e** and the crude product was hydrolyzed according to the procedure for **4**. Yield: 603 mg (54%, 10% de); bp 61°C/0.41 mbar. Mixture of both diastereomers: ^{1}H NMR δ 7.60-7.28 (m, 5H, Ph-H$_5$), 5.77 (ddd, $^2J_{FH}$ = 48.4 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 2.6 Hz, CHF), 5.68 (ddd, 1H, $^2J_{HF}$ = 48.6 Hz, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 5.5 Hz, CHF), 4.19 (q, $^3J_{HH}$ = 7.2 Hz, C*H*$_2$CH$_3$), 4.17 (q, $^3J_{HH}$ = 7.2 Hz, C*H*$_2$CH$_3$), 3.72 (dd, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 3.8 Hz, CHN), 3.55 (dd, 1H, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 6.4 Hz, CHN), 2.50-1.75 (m, 2H, CH$_2$), 1.28 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH$_2$C*H*$_3$), 1.27 (t, 2H, $^3J_{HH}$ = 7.2 Hz, CH$_2$C*H*$_3$); ^{13}C NMR δ 175.6 (s, COO), 175.1 (s, COO), 139.8 (ds, $^2J_{CF}$ = 20.3 Hz, C-Ph), 128.3, 125.7 and 125.4 (d, C-Ph), 92.2 (dd, $^1J_{CF}$ = 167.8 Hz, CHF), 91.3 (dd, $^1J_{CF}$ = 170.4 Hz, CHF), 61.0 (t, *C*H$_2$CH$_3$), 51.7 (dd, $^3J_{CF}$ = 5.1 Hz, CHN), 51.3 (dd, $^3J_{CF}$ = 5.1 Hz, CHN), 42.3 (dt, $^2J_{CF}$ = 25.4 Hz, CH$_2$), 41.9 (dt, $^2J_{CF}$ = 25.4 Hz, CH$_2$), 14.1 (p, CH$_2$*C*H$_3$); ^{19}F NMR δ -175.6 (ddd, $^2J_{HF}$ = 48.4 Hz, $^3J_{HF}$ = 28.6 Hz, $^3J_{HF}$ = 13.3 Hz, CHF), -178.9 (ddd, $^2J_{HF}$ = 48.6 Hz, $^3J_{HF}$ = 36.2 Hz, $^3J_{HF}$ = 13.3 Hz, CHF); GC/MS m/z (%) 225 (2) [M$^+$], 152 (45) [M$^+$-CO$_2$C$_2$H$_5$], 132 (100) [152-HF], 109 (35) [C$_7$H$_6$F$^+$]; Anal. Calcd. for C$_{12}$H$_{16}$FNO$_2$ (225.26): C 63.98, H 7.16, N 6.22. Found C 64.38, H 7.24, N 6.13.

Hydrolysis of compound **8**: 980 mg (4.4 mmol) **8** were dissolved in 16 mL of 6N hydrochloric acid and refluxed for 6 h. The solvent was removed in vacuum. The residue was dried over P_2O_5 and recrystallized from ethanol/diethyl ether. The lactone **9** precipitated and was isolated. Propene oxide was added to the solution and the mixture was refluxed for 30 min. The amino acid **10** precipitates as a white solid. The crude product was recrystallized from water.

cis-2-Amino-4-phenylbutyrolactone hydrochloride (**9**): Yield: 208 mg (21%); mp 173 °C (Lit. [18]: Mp 190-195 °C). ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 9.1 (s br, NH$_3^+$), 7.48-7.35 (m, 5H, Ph-H$_5$), 5.53 (dd, 1H, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 5.6 Hz, 4-H), 4.51 (dd, 1H, $^3J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 8.6 Hz, 2-H), 2.91 (ddd,

1H, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 5.6 Hz, 3-H_{trans}), 2.40 (ddd, 1H, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 10.9 Hz, 3-H_{cis}). The IR, ^{1}H and ^{13}C NMR data agree with published values [18].

2-Amino-4-phenylbut-3-enoic acid (**10**): Yield: 98 mg (13%), T_M 207°C. MS (Maldi) m/z: 132.1 [M+H^+-H_2O-CO], 193.1 [M+CH_2^+], 200.1 [M+Na^+], 216.1 [M+K^+], 397.4 [2M-H^++2Na^+], 413.6 [2M-H^++Na^++K^+], 429.5 [2M-H^++2K^+]. The ^{1}H and ^{13}C NMR data agree with published values [19].

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