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Synthesis of some racemic γ-fluoro-α-amino acids*

S. Kröger and **G. Haufe**

Organisch-Chemisches Institut, Universität Münster, Federal Republic of Germany

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Summary. Versatile three-step procedures for syntheses of seven racemic γ-fluoro-α-amino acids are described. Alkylation of *tert*-butyl N-(diphenylmethylene)glycinate with 1-bromo-2-fluoroalkanes gave N-protected aminoacid esters both in anhydrous medium using lithium-diisopropylamide as base at low temperature or in a two phase system of 50% aqueous sodium hydroxide and methylene chloride with triethylbenzylammonium chloride as the phase transfer catalyst at room temperature. Subsequent two-step deprotection with citric acid and hydrochloric acid gave the title compounds in 13–33% overall yields.

Keywords: Fluorinated amino acids – Alkylation – *tert*-Butyl N-(diphenylmethylene)glycinate – 1-Bromo-2-fluoroalkanes – Phase transfer catalysis

Introduction

Fluorinated amino acids and derived peptides – both analogues of naturally occurring compounds and synthetic substances – claim an extraordinary interest in chemistry and biochemistry as well as in medicinal research because of their enormous variety of biological activity (Welch and Eswarakrishnan, 1991; Filler et al., 1993). Furthermore, the determination of structure and dynamics of these compounds becomes easier and more precise using ^{19}F NMR spectroscopy. Among the fluorinated amino acids γ-fluoro-α-amino acids have been synthesized relatively infrequently (Kukhar and Soloshonok, 1995; Haufe and Kröger, 1996), though γ-fluoroisoleucine (Gershon et al., 1978; Butina and Hudlický, 1980), γ-fluoroornithine (Tolman and Benes, 1976), γ-fluoro-α-aminobutyric acid (Lettré and Wölke, 1967; Raasch, 1958), and γ-fluoroglutamic acid (Hudlický and Kakac, 1966; Bergman and Chin-

* Dedicated to Professor Dr.mult., Dr.h.c. Alois Haas on the occasion of his 65th birthday

Hsu, 1973; Hudlický and Merola, 1990; Hudlický, 1993; Tolman, 1993; Tolman and Vlasáková, 1993) exhibit a variety of biological activities. However, the origin of biological activity of these compounds has not been investigated in detail.

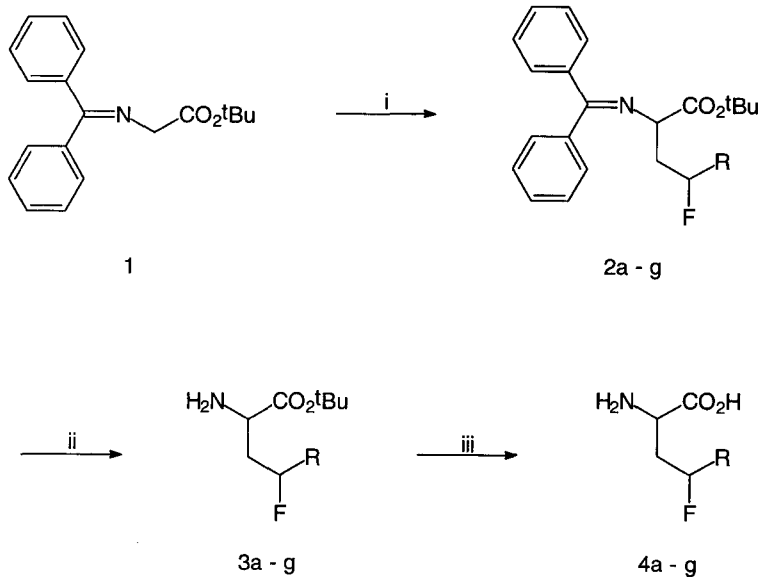
Mostly, γ-fluoro-α-amino acids have been synthesized by introduction of a fluorine substituent into the amino acid or by nucleophilic substitution of a leaving group like bromine with an amino function (Cavalleri et al., 1966; Letté and Wölcke, 1967; Gershorn et al., 1978). On the other hand the four enantiomerically pure stereoisomeric 4-fluoroglutamic acids were built from the corresponding 4-hydroxyprolines in three-step procedures with stereoselective fluorodehydroxylation using diethylaminosulfur trifluoride (DAST) (Hudlický, 1993) as the key-step. Analogously Yarovenko's reagent (Yarovenko and Rakshar, 1959) has been used to substitute a *tert*-butoxy group with fluorine (Bergmann and Chun-Hsu, 1973). Direct fluorination of a tertiary hydrogen with fluorine using perchloryl fluoride has also been described (Tolman and Veres, 1966, 1967).

An attractive alternative concept to substitution reactions is the building block strategy. The alkylation with a fluorinated carbon fragment of acetamidomalonate can be the key-step. In this way a series of monofluorinated aliphatic amino acids has been prepared (Raasch, 1958; Hudlkcký, 1960, 1961; Tolman et al., 1967, 1983, 1993). Alternatively 2-fluoromalonate and ethyl 2-acetamidoacrylate have been used for the Michael-type bond formation (Buchanan et al., 1962). Furthermore, Schöllkopf's (1983) bis-lactimether methodology has been used for the synthsis of ethyl (+)-γ-fluoroleucinate (Papageorgiou et al., 1994).

Results and discussion

The interest in these compounds led us to develop generally applicable strategies for the synthesis of racemic γ-fluoro-α-amino acids.

We started our investigation with alkylation of the Schiff's base **1** derived from glycine *tert*-butylester and benzophenone. This type of alkylation is more difficult using vicinal bromofluorides compared with reactions of simple alkyl bromides or ω-fluoroalkyl bromides (Kröger, 1996). The fluorine substituent in the β-position causes an increased electron density in the terminal position, which means it lowers the electrophilicity of this alkylating agent. However, the alkylation [by analogy to the reaction with ethyl bromide (O'Donnell et al., 1978)] proceeds quite smoothly with bromofluoroethane giving the protected *tert*-butyl γ-fluoro-α-aminobutyrate (**2a**) in 73% yield. Hydrolysis of the imino function with 15% citric acid and subsequent ester hydrolysis with 6N hydrochloric acid gave the amino acid hydrochloride, which was libereted according to a known procedure (Schöllkopf et al., 1981) with propylene oxide in ethanol. In this way γ-fluoro-α-aminobutyric acid (**4a**) has been obtained in 31% overall yield. Similarly other vicinal bromo fluoroalkanes, which are easily available by bromofluorination of 1-alkenes using a combination of N-bromosuccinimide



Scheme 1. *i*) LDA, THF, DMPU, $RCHFCH_2Br$, 8h, −78°C → r.t. or 50% NaOH (20 equiv.), CH_2Cl_2, TEBA, $RCHFCH_2Br$, 48h, 0°C → r.t.; *ii*) 15% citric acid, THF, ethyl acetate; *iii*) 6N HCl, 6h reflux, lyophilization to dryness, liberation of the amino acid with propene oxide, EtOH

Table 1. Synthesis of racemic γ-fluoro-α-amino acids by alkylation in anhydrous medium

Compound	a	b	c	d	e	f	g
R	H	CH_3	C_2H_5	C_3H_7	$(CH_3)_2CH$	C_4H_9	C_5H_{11}
Yield of **3** (%)*	39	37	38	34	21	24	29
Ratio**	–	(42:58)	(44:56)	(34:66)	(39:61)	(37:63)	(43:57)
Yield of **4** (%)	78	74	70	70	71	–	–
Ratio**	–	(42:58)	(32:68)	(34:66)	(39:61)	–	–

*Overall yield of steps i and ii, **determined by ^{19}F NMR spectroscopy.

and triethylamine tris-hydrofluoride (Haufe et al., 1996) were used for the alkylation giving mixtures of the racemic diastereomers of N-protected γ-fluoro-α-amino acid *tert*-butyl esters **2b–2g**. It has been impossible to purify these alkylated imino esters either by liquid chromatography or by distillation. Thus the imino function was hydrolyzed with 15% aqueous citric acid and the esters of the amino acids **3a–3g** were isolated by bulb-to-bulb distillation (Table 1).

Alternatively treatment of the Schiff's base **1** with vicinal bromo fluoroalkanes and 50% aqueous sodium hydroxide in a two-phase system with methylene chloride in the presence of triethylbenzylammonium chloride (TEBA) as phase transfer catalyst gave racemic mixtures of the diastereomeric *tert*-butylesters **3a–3g** in 18–42% overall yield after deprotection and

Table 2. Synthesis of racemic γ-fluoro-α-amino acid tert-butyl esters by phase transfer reaction

Compound	a	b	c	d	e	f	g
R	H	CH_3	C_2H_5	C_3H_7	$(CH_3)_2CH$	C_4H_9	C_5H_{11}
Yield of **3** (%)*	42	28	26	33	18	20	21
Ratio**	–	(42:58)	(43:57)	(34:66)	(31:69)	(20:80)	(43:57)

*Overall yield of steps i and ii **determined by ^{19}F NMR spectroscopy.

in nearly the same ratio as the reaction under anhydrous conditions (Table 2). Subsequent hydrolysis of the ester group with 6N hydrochloric acid gave racemic mixtures of diastereomeric γ-fluoro-α-amino acids **4a–4e** (Table 1).

This both methods are useful for the syntheses of the title compounds. However, the anhydrous method gave better yields on a small scale, whereas the two-phase reaction is cheaper and easier to scale up.

Materials and methods

All air- and moisture-sensitive reactions were performed under an argon atmosphere in flame-dried flasks using standard Schlenk methodology. *tert*-Butyl N-(diphenylmethylene)glycinate was prepared by a literature method (O'Donnell and Polt, 1982).

Melting and boiling points are uncorrected. – Refraction indices: Carl Zeiss, Jena, Abbé refractometer, – ^1H (300 MHz), ^{13}C NMR (75.5 MHz): Bruker WM 300, TMS for ^1H and $CDCl_3$ for ^{13}C NMR as internal standards. – ^{19}F NMR: Bruker WM 300 (282.3 MHz) and Bruker AC 200 (188.0 MHz), α,α,α-trifluorotoluene ($\delta = -63.0$ from $CFCl_3$) as internal standard. If not stated otherwise $CDCl_3$ was used as solvent. – Mass spectra (70 eV): GLC/MS coupling: Varian GC 3,400/MAT 8,230 and data system SS 300 of Finnigan/MAT. – Elemental analyses: Mikroanalytisches Laboratorium, OC, Universität Münster. – Propene and butene were provided by Hüls AG, Marl, triethylamine trishydrofluoride was supplied by Hoechst AG, Frankfurt and 1-bromo-2-fluoroethane was a gift of Bayer AG, Leverkusen. All other starting materials and applied reagents were obtained from Acros and Fluka chemicals. Diisopropylamine was dried by distillation over KOH and tetrahydrofuran was distilled before use over sodium/benzophenone.

Synthesis of the alkylated imines **2**

Method a

Alkylation in an anhydrous medium: Lithium diisopropylamide (LDA) solution was prepared by adding of 4.18 ml (7.5 mmol) n-butyllithium (1.6 N in n-hexane) to a solution of 1.15 ml (7.5 mmol) diisopropylamine in 15 ml tetrahydrofuran under argon at −78°C. The cooling bath was removed and the mixture was stirred for 15 min whereupon 2.21 g (7.5 mmol) of the Schiff base **1** in 8 ml THF were added to the LDA solution at −78°C. After 90 min 1.92 g (1.8 ml; 15.0 mmol) of 1,3-dimethyl-tetrahydro-2(1H)-pyrimidinone (DMPU) was added and the solution was stirred for another 15 min. Then the vicinal bromofluoroalkane (7.5 mmol) dissolved in 8 ml THF was added, the resulting mixture was stirred at −78°C for 2 h and slowly warmed up to room temperature overnight. The

reaction mixture was quenched with 25 ml of brine. The organic layer was separated and the aqueous layer was extracted three times with 40 ml of ether. The combined organic layers were washed with water (4 × 25 ml) and dried with magnesium sulfate. Removal of the solvent under reduced pressure gave the crude alkylated imine **2**, which was filtered over silica gel (cyclohexane/ethyl acetate, 1:1).

Method b

Phase transfer-catalyzed alkylation: To a solution of 3.0 g (10.17 mmol) N-(diphenylmethylene)glycine-tert.-butylester (**1**) in 30 ml CH_2Cl_2, 16 ml 50% aqueous NaOH (8.2 g; 20.4 mmol) and 0.48 g (2.03 mmol) triethylbenzylammonium chloride (TEBA) were added. The light yellow solution were vigorously stirred at 0°C and 51 mmol of the 1-bromo-2-fluoroalkane were added dropwise from a dropping funnel over a period of two hours. The reaction mixture was stirred for additional two hours at 0°C. Stirring was then continued for additional 48 hours at room temperature. The reaction mixture was poured into a separatory funnel which contained 90 ml CH_2Cl_2 and 120 ml water. The organic layer was separated and the aqueous layer extracted three times with 25 ml of CH_2Cl_2. The combined organic layers were washed with water (4 × 25 ml) and saturated aqueous sodium chloride and dried with sodium sulfate. Removal of the CH_2Cl_2 gave the crude alkylated imins **2**.

*2-Benzhydrylideneamino-4-fluorobutanoic acid tert-butyl ester (**2a**)*

Method a: Yield 1.86 g (73%); method b: Yield 2.77 g (80%), m.p. 63–65°C. – ^{1}H NMR: δ = 1.34 (s, 9H, —C(CH_3)$_3$); 2.05–2.36 (m, 2H, —CH_2—); 4.05 (dd, 1H, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 8.5 Hz, =N—CH); 4.24–4.58 (m, 2H, —CH_2F); 7.07–7.59 (10H, aromatic H). – ^{13}C NMR: δ = 27.9 (q, —C(CH_3)$_3$); 34.1 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 62.0 (d, =N—CH); 80.8 (dt, $^1J_{CF}$ = 165.3 Hz, —CH_2F); 81.1 (s, —C(CH_3)$_3$); 127.7; 128.0; 128.4; 128.5; 128.7; 129.9; 130.2; 132.3 (d. aromatic CH); 136.3; 139.5 (s, ipso—C); 170.6 (s, C=N—); 171.2 (s, —CO_2C(CH_3)$_3$). — ^{19}F NMR: δ = −221.1 (ddt, $^2J_{HF}$ = 47.1, $^3J_{HF}$ = 31.2, $^3J_{HF}$ = 20.6 Hz, —CH_2F). – MS (70 eV), m/z (%): 341 (22) [M^+]; 326 (4) [M^+—CH_3]; 295 (18) [M^+—C_2H_3F, McLafferty]; 284 (13) [M^+—C_4H_9]; 240 (89) [M^+—CO_2C(CH_3)$_3$]; 220 (33) [240-HF]; 194 (41) [295-CO_2C(CH_3)$_3$]; 180 (29) [$C_{13}H_{10}N^+$]; 91 (100) [$C_7H_7^+$]; 77 (39) [$C_6H_5^+$]; 65 (36) [$C_5H_5^+$]; 57 (62) [$C_4H_9^+$]; 51 (41) [$C_4H_3^+$]. – $C_{21}H_{24}O_2NF$ (341.4): calcd. C 73.88, H 7.09, N 4.10; found C 73.90, H 7.06, N 3.93.

Synthesis of fluoro amino acid tert-butyl esters

The alkylated imine **2** (7.5 mmol) was dissolved in 30 ml of ethyl acetate and stirred with a mixture of 45 ml of 15% aqueous citric acid and 22 ml tetrahydrofuran at room temperature for 36 hours. The layers were separated and the aqueous phase was extracted three times with 15 ml of ether. The volume of the aqueous layer was reduced to 15 ml and neutralized with staturated aqueous $NaHCO_3$ (pH = 7.0 to 7.5) and extracted with dichloromethane (4 × 20 ml). The combined organic layers were washed with saturated aqueous sodium chloride and dried with sodium sulfate. Removal of the dichloromethane under reduced pressure gave the crude product, which was purified by bulb-to-bulb distillation.

*2-Amino-4-fluorobutanoic acid tert-butyl ester (**3a**)*

Method a: Yield 701 mg (53%), b.p. 89°–90°C/18 Torr, n_D^{20} = 1.4241. – ^{1}H NMR: δ = 1.39 (s, 9H, —C(CH_3)$_3$); 1.48 (bs. 2H, —NH_2); 1.63–2.15 (m, 2H, —CH_2—); 3.39 (dd, 1H, $^3J_{HH}$ = 8.2, $^3J_{HH}$ = 4.9 Hz, H_2N—CH); 4.52 (dm, 2H, $^2J_{HF}$ = 47.2 Hz, —CH_2F). – ^{13}C NMR: δ = 27.7 (q, —C(CH_3)$_3$); 32.3 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 51.5 (dd, $^3J_{CF}$ = 5.1 Hz, H_2N—CH); 80.8 (dt, $^1J_{CF}$ = 165.3 Hz, —CH_2F); 80.9 (s, —C(CH_3)$_3$); 174.6 (s, —CO_2C(CH_3)$_3$). – ^{19}F

NMR: δ = −221.0 (ddt, $^2J_{HF}$ = 47.1, $^3J_{HF}$ = 29.0, $^3J_{HF}$ = 22.8 Hz, —CH_2F). – GC/MS, m/z (%): 177 (3) [M^+]; 162 (2) [M^+—CH_3]; 122 (15) [acid + 1, McLafferty]; 102 (2) [$C_4H_8O_2N^+$]; 76 (100) [M^+—$CO_2C(CH_3)_3$)]; 57 (24) [$C_4H_9^+$]; 56 (52) [$C_3H_6N^+$] 41 (29). – $C_8H_{16}O_2NF$ (177.2): calcd. C 54.22, H 9.10, N 7.90; found C 53.77, H 9.10, N 7.92.

2-Amino-4-fluoropentanoic acid tert-butyl ester ***(3b)***

Method a: Yield 531 mg (37%); method b: Yield 544 mg (28%), b.p. 120°C/18 Torr. – ^{1}H NMR: δ = 1.29 (dd, 3H, $^3J_{HF}$ = 23.8 Hz, —CH_3); 1.39 (s, 9H, —$C(CH_3)_3$); 1.45–2.06 (m, 4H, —CH_2— and —NH_2); 3.40 (dd, 1H, $^3J_{HH}$ = 7.9, $^3J_{HH}$ = 6.4 Hz, H_2N—CH) [minor diastereomer]; 3.43 (dd, 1H, $^3J_{HH}$ = 9.8, $^3J_{HH}$ = 3.8 Hz, H_2N—CH); 4.65–5.00 (dm, 1H, $^2J_{HF}$ = 49.4 Hz, —CHF—). – ^{13}C NMR [major diastereomer]: δ = 21.2 (dq, $^2J_{CF}$ = 22.5 Hz, —CH_3); 27.9 (q, —$C(CH_3)_3$); 41.7 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 51.7 (d, H_2N—CH); 81.1 (s, —$C(CH_3)_3$); 87.8 (dd, $^1J_{CF}$ = 165.3 Hz, —CHF—); 174.4 (s, —$CO_2C(CH_3)_3$). – ^{13}C NMR [minor diastereomer]: δ = 21.0 (dq, $^2J_{CF}$ = 22.9 Hz, —CH_3); 27.9 (q, —$C(CH_3)_3$); 41.7 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 52.3 (d, H_2N—CH); 81.0 (s, —$C(CH_3)_3$); 88.5 (dd, $^1J_{CF}$ = 162.8 Hz, —CHF—); 175.0 (s, —$CO_2C(CH_3)_3$). – ^{19}F NMR: δ = −173.4 and −175.2 (m, —CHF—). – GC/MS, m/z (%): 191 (8) [M^+]; 176 (2) [M^+—CH_3]; 135 (2) [M^+—C_4H_8, McLafferty]; 90 (100) [M^+—$CO_2(CH_3)_3$]; 70 (40); 57 (23); 41 (39). – $C_9H_{18}NO_2F$ (191.2): calcd. C 56.52, H 9.49, N 7.32; found C 56.15, H 9.40, N 7.00.

2-Amino-4-fluorohexanoic acid tert-butyl ester ***(3c)***

Method a: Yield 584 mg (38%); method b: Yield 541 mg (26%), b.p. 120°C/18 Torr. – ^{1}H NMR: δ = 0.91 (t, 3H, $^3J_{HH}$ = 7.5 Hz, —CH_3) [minor diastereomer]; 0.92 (t, 3H, $^3J_{HH}$ = 7.5 Hz, —CH_3); 1.40 (s, 9H, —$C(CH_3)_3$); 1.43–2.04 (m, 4H, —CH_2— and —CH_2—CH_3); 3.43 (dd, 1H, $^3J_{HH}$ = 6.3, $^3J_{HH}$ = 6.3 Hz, H_2N—CH) [minor diastereomer]; 3.45 (dd, 1H, $^3J_{HH}$ = 3.7, $^3J_{HH}$ = 9.9 Hz, H_2N—CH); 4.58 (dm, 1H, $^2J_{HF}$ = 49.6 Hz, —CHF—). – ^{13}C NMR [major diastereomer]: δ = 9.2 (dq, $^3J_{CF}$ = 5.1 Hz, —CH_3); 27.9 (q, —$C(CH_3)_3$); 28.3 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—CH_3); 39.4 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 51.7 (d, H_2N—CH); 81.0 (s, —$C(CH_3)_3$); 92.3 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 175.1 (s, —$CO_2C(CH_3)_3$). – ^{13}C NMR [minor diastereomer]: δ = 9.0 (dq, $^3J_{CF}$ = 5.1 Hz, —CH_3); 27.9 (q, —$C(CH_3)_3$); 28.1 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—CH_3); 39.7 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 52.3 (d, H_2N—CH); 81.0 (s, —$C(CH_3)_3$); 92.9 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 174.4 (s, —$CO_2C(CH_3)_3$). — ^{19}F NMR: δ = −182.8 and −184.0 (m, —CHF—). – GC/MS, m/z (%): 205 (11) [M^+]; 190 (1) [M^+—CH_3]; 150 (17) [acid + 1; McLafferty]; 104 (100) [M^+—$CO_2C(CH_3)_3$)]; 84 (25); 74 (7); 57 (17); 41 (28). – $C_{10}H_{20}NO_2F$ (205.3): calcd. C 58.51, H 9.82, N 6.82; found C 58.30, H 9.83, N 6.52.

2-Amino-4-fluoroheptanoic acid tert-butyl ester ***(3d)***

Method a: Yield 558 mg (34%); method b: Preparation from 38.3 g (100 mmol) of the alkylated imine 2d; yield 7.2 g (33%), b.p. 122°–124°C/18 Torr, n_D^{20} = 1.4250. – ^{1}H NMR: δ = 0.87 (t, 3H, $^3J_{HH}$ = 7.0 Hz, —CH_3); 1.31–1.67 (m, 6H, —CH_2—); 1.40 (s, 9H, —$C(CH_3)_3$); 3.45 (dd, 1H, $^3J_{HH}$ = 9.9, $^3J_{HH}$ = 3.9 Hz, H_2N—CH); 4.49–4.82 (m, 1H, —CHF—). – ^{13}C-NMR [major diastereomer]: δ = 13.7 (q, —CH_3); 18.2 (dt, $^3J_{CF}$ = 5.1 Hz, —CH_2—CH_3); 27.8 (q, —$C(CH_2)_3$); 37.4 (dt, $^2J_{CF}$ = 20.3 Hz, —CH_2—); 40.0 (dt, $^2J_{CF}$ = 22.9 Hz, —CH_2—); 51.7 (d, H_2N—CH); 80.9 (s, —$C(CH_3)_3$); 90.9 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 175.1 (s, —$CO_2C(CH_3)_3$). – ^{13}C NMR [minor diastereomer]: δ = 13.7 (q, —CH_3); 18.8 (dt, $^3J_{CF}$ = 5.1 Hz, —CH_2—CH_3); 27.8 (q, —$C(CH_3)_3$); 37.4 (dt, $^2J_{CF}$ = 20.3 Hz, —CH_2—); 40.0 (dt, $^2J_{CF}$ = 20.3 Hz, —CH_2—); 52.3 (d, H_2N—CH); 80.9 (s, —$C(CH_3)_3$); 91.5 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 174.4 (s, —$CO_2C(CH_3)_3$). – ^{19}F NMR: δ = −181.0 and −182.5 (m, —CHF—). – GC/MS, m/z (%): 220 (3) [M^++1]; 164 (6) [acid − 1]; 118 (100) [M^+ − $CO_2C(CH_3)_3$]; 98 (36); 81 (22); 56 (38); 41 (43). – $C_{11}H_{22}O_2NF$ (219.3): calcd. C 60.25, H 10.11, N 6.39; found C 59.85, H 9.96, N 6.09.

2-Amino-4-fluoro-5-methylhexanoic acid tert-butyl ester ***(3e)***

Method a: Yield 346 mg (21%); method b: Yield 401 mg (18%), b.p. 120°C/18 Torr. – ^{1}H NMR: δ = 0.82 (d, 3H, $^3J_{HH}$ = 6.7 Hz, —CH_3); 0.85 (d, 3H, $^3J_{HH}$ = 6.7 Hz, —CH_3); 1.32–2.03 (m, 3H, —CH_2— and —$CH(CH_3)_2$); 1.40 (s, 9H, —$C(CH_3)_3$; 1.52 (brs, 2H, —NH_2); 3.43 (dd, 1H, $^3J_{HH}$ = 9.9, $^3J_{HH}$ = 3.7 Hz, H_2N—CH); 4.38 (dddd, 1H, $^2J_{HF}$ = 49.2, $^3J_{HH}$ = 10.3, $^3J_{HH}$ = 5.7, $^3J_{HH}$ = 1.8 Hz, —CHF—). – ^{13}C NMR [major diastereomer]: δ = 17.0 (dq, $^3J_{CF}$ = 5.1 Hz, —CH_3); 18.0 (dq, $^3J_{CF}$ = 7.6 Hz, —CH_3); 27.8 (q, —$C(CH_3)_3$); 32.4 (dd, $^2J_{CF}$ = 17.8 Hz, —$CH(CH_3)_2$); 37 (dt, $^2J_{CF}$ = 22.9 Hz, —CH_2—); 51.8 (d, H_2N—CH); 80.8 (s, —$C(CH_3)_3$); 95.1 (dd, $^1J_{CF}$ = 170.4 Hz, —CHF—); 175.2 (s, —$CO_2C(CH_3)_3$). – ^{13}C NMR [minor diastereomer]: δ = 16.6 (dq, $^3J_{CF}$ = 5.1 Hz, —CH_3); 18.0 (dq, $^3J_{CF}$ = 7.6 Hz, —CH_3); 27.8 (q, —$C(CH_3)_3$); 32.2 (dd, $^2J_{CF}$ = 20.4 Hz, —$CH(CH_3)_2$); 37.3 (dt, $^2J_{CF}$ = 22.9 Hz, —CH_2—); 52.3 (d, H_2N—CH); 80.8 (s, —$C(CH_3)_3$); 95.6 (dd, $^1J_{CF}$ = 170.4 Hz, —CHF—); 174.4 (s, —$CO_2C(CH_3)_3$). – ^{19}F NMR: δ = −187.3 and −187.8 (m, —CHF—). – GC/MS, m/z (%): 219 (8) [M^+]; 204 (1) [M^+—CH_3]; 164 (14) [acid + 1, McLafferty]; 144 (1) [$C_7H_{14}O_2N^+$]; 118 (100) [M^+—$CO_2C(CH_3)_3$]; 98 (25) [$C_6H_{12}N^+$]; 81 (45); 74 (12); 57 (19); 41 (30). – $C_{11}H_{22}O_2NF$ (219.3): calcd. C 60.25, H 10.11, N 6.39; found C 59.88, H 10.10, N 6.05.

2-Amino-4-fluorooctanoic acid tert-butyl ester ***(3f)***

Method a: Yield 426 mg (24%); method b: Yield 473 mg (20%), b.p. 130°–140°C/18 Torr. – ^{1}H NMR: δ = 0.84 (t, 3H, $^3J_{HH}$ = 7.0 Hz, —CH_3); 1.17–2.05 (m, 8H, —CH_2—); 1.39 (s, 9H, —$C(CH_3)_3$); 1.55 (brs, 2H, —NH_2); 3.42 (dd, 1H, $^3J_{HH}$ = 6.3, $^3J_{HH}$ = 6.3 Hz, H_2N—CH) [minor diastereomer]; 3.44 (dd, 1H, $^3J_{HH}$ = 9.9, $^3J_{HH}$ = 3.7 Hz, H_2N—CH); 4.47–4.81 (m, 1H, —CHF—). – ^{13}C NMR [major diastereomer]: δ = 13.8 (q, —CH_3); 22.3 (t, —CH_2—); 27.1 (dt, $^3J_{CF}$ = 5.1 Hz, —CH_2—); 27.9 (q, —$C(CH_3)_3$); 35.0 (dt, $^2J_{CF}$ = 20.3 Hz, —CH_2—); 40.0 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 51.8 (d, H_2N—CH); 80.9 (s, —$C(CH_3)_3$); 91.2 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 175.1 (s, —$CO_2C(CH_3)_3$). – ^{13}C NMR [minor diastereomer]: δ = 13.8 (q, —CH_3); 22.3 (t, —CH_2—); 26.9 (dt, $^3J_{CF}$ = 5.1 Hz, —CH_2—); 27.9 (q, —$C(CH_3)_3$); 34.9 (dt, $^2J_{CF}$ = 20.3 Hz, —CH_2—); 40.2 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 52.3 (d, H_2N—CH); 81.0 (s, —$C(CH_3)_3$); 91.8 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 174.4 (s, —$CO_2C(CH_3)_3$). – ^{19}F NMR: δ = −180.7 and −182.1 (m, —CHF—). – GC/MS, m/z (%): 233 (10) [M^+]; 178 (17) [acid + 1]; 132 (100) [M^+—$CO_2C(CH_3)_3$]; 112 (58) [$C_7H_{14}N^+$]; 95 (27); 69 (18); 56 (29); 41 (48). – $C_{12}H_{24}O_2NF$ (233.3): calcd. C 61.77, H 10.37, N 6.00; found C 61.49, H 10.28, N 5.86.

2-Amino-4-fluorononanoic acid tert-butyl ester ***(3g)***

Method a: Yield 431 mg (29%); method b: Yield 528 mg (21%), b.p. 140°C/18 Torr. – ^{1}H NMR: δ = 0.82 (t, 3H, $^3J_{HH}$ = 6.7 Hz, —CH_3); 1.14–2.05 (m, 10H, —CH_2—); 1.39 (s, 9H, —$C(CH_3)_3$); 3.39–3.49 (m, 1H, H_2N—CH); 4.47–4.82 (dm, 1H, $^2J_{HF}$ = 50.3 Hz, —CHF—). – ^{13}C NMR [major diastereomer]: δ = 13.8 (q, —CH_3); 22.4 (t, —CH_2—); 24.6 (dt, $^3J_{CF}$ = 5.1 Hz, —CH_2—); 27.9 (q, —$C(CH_3)_3$); 31.5 (t, —CH_2—); 35.3 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 40.0 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 51.8 (d, H_2N—CH); 80.9 (s, —$C(CH_3)_3$); 91.5 (dd, $^1J_{CF}$ = 167.8 Hz, —CHF—); 175.1 (s, —$CO_2C(CH_3)_3$). – ^{13}C NMR [minor diastereomer]: δ = 13.8 (q, —CH_3); 22.4 (t, —CH_2—); 24.4 (dt, $^3J_{CF}$ = 5.1 Hz, —CH_2—); 27.9 (q, —$C(CH_3)_3$); 31.5 (t, —CH_2—); 35.2 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 40.2 (dt, $^2J_{CF}$ = 22.9 Hz, —CH_2—); 52.3 (d, H_2N—CH); 81.0 (s, —$C(CH_3)_3$); 91.8 (dd, $^1J_{CF}$ = 165.3 Hz, —CHF—); 174.4 (s, —$CO_2C(CH_3)_3$). – ^{19}F NMR: δ = −180.7 and −181.9 (m, —CHF—). – GC/MS, m/z (%): 247 (3) [M^+]; 192 (5) [M^+—C_4H_7, McLafferty + 1]; 146 (100) [M^+—$CO_2C(CH_3)_3$]; 145 (9) [M^+—$C_6H_{11}F$]; 126 (37) [146-HF]; 74 (18) [191-$C_7H_{14}F$]; 56 (30); 41 (48). – $C_{13}H_{26}NO_2F$ (247.4): calcd. C 63.12, H 10.60, N 5.66; found C 62.74, H 10.63, N 5.33.

Hydrolysis of the fluoro amino acid tert-butyl esters

A solution of the amino acid ester **3** (2.5 mmol) in 15 ml 6 N hydrochloric acid was refluxed over a period of 6 hours. The solvent was then evaporated in vacuum and the residual crude amino acid hydrochloride dried over phosphorus pentoxide. The hydrochloride was dissolved in 7 ml of dry ethanol, 4–5 ml of methyloxirane (propene oxide) were added and the mixture was refluxed for 15–20 min. The precipitated product was isolated by suction and dried over phosphorus pentoxide.

2-Amino-4-fluorobutanoic acid ***(4a)***

Preparation from 774 mg (4.37 mmol) of the fluoro amino acid ester **3a**; yield 411 mg (78%), m.p. 168°C (decomp.). – ^{1}H NMR (D_2O): δ = 2.05–2.43 (m, 2H, —CH_2—); 3.85 (dd, 1H, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 7.2 Hz, H_2N—CH); 4.64 (dm, 2H, $^2J_{HF}$ = 46.6 Hz, —CH_2F). – ^{13}C NMR (D_2O): δ = 31.5 (dt, $^2J_{CF}$ = 20.3 Hz, —CH_2—); 53.2 (d, H_2N—CH); 82.4 (dt, $^1J_{HF}$ = 160.2 Hz, —CH_2F); 174.3 (s, —COOH). – ^{19}F NMR (D_2O without standard): δ = −213.9 (tt, $^2J_{HF}$ = 46.8, $^3J_{HF}$ = 29.1 Hz, —CH_2F). – $C_4H_8O_2NF$ (121.1): calcd. C 39.67, H 6.66, N 11.56; found C 39.36, H 6.50, N 11.24.

2-Amino-4-fluoropentanoic acid ***(4b)***

Preparation from 530 mg (2.78 mmol) of the fluoro amino acid ester **3b**; yield 272 mg (74%), m.p. 189°C (decomp.). – ^{1}H NMR (D_2O): δ = 1.33 (dd, 3H, $^3J_{HF}$ = 25.0, $^3J_{HH}$ = 6.2 Hz, —CH_3); 1.94–2.29 (m, 2H, —CH_2—); 3.88 (dd, 1H, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 4.1 Hz, N_2N—CH); 4.87 (dm, 1H, $^2J_{HF}$ = 52.4 Hz, —CHF—). The ^{1}H NMR data of the second diastereomer could not be obtained on a pure sample. – ^{13}C NMR (D_2O) [major diastereomer]: δ = 20.4 (dq, $^2J_{CF}$ = 17.1 Hz, —CH_3); 37.0 (dt, $^2J_{CF}$ = 20.4 Hz, —CH_2—); 52.6 (d, H_2N—CH); 90.2 (dd, $^1J_{CF}$ = 162.8 Hz, —CHF—); 174.3 (s, —COOH). – ^{13}C NMR (D_2O) [minor diastereomer]: δ = 37.9 (dt, $^2J_{CF}$ = 17.8 Hz, —CH_2—); 53.6 (d, H_2N—CH); 91.5 (dd, $^1J_{CF}$ = 160.2 Hz, —CHF—); 174.3 (s, —COOH). The ^{13}C NMR data of the second diastereomer could not be obtained on a pure sample. – The ^{19}F NMR (D_2O, without standard): δ = −170.3 and −170.7 (m, —CHF—).

2-Amino-4-fluorohexanoic acid ***(4c)***

Preparation from 584 mg (2.85 mmol) of the fluoro amino acid ester **3c**; yield 300 mg (70%), m.p. 204°C (decomp.). – ^{1}H NMR (D_2O): δ = 0.95 (t, $^3J_{HH}$ = 7.2 Hz, —CH_3); 1.35–2.24 (m, 4H, —CH_2—); 3.56–3.75 (m, 1H, H_2N—CH); 4.32–4.69 (m, 1H, —CHF—). The ^{1}HNMR data of the second diastereomer could not be obtained on a pure sample. – ^{13}C NMR (D_2O): δ = 19.5 (q, —CH_3); 29.5 (dt, $^2J_{CF}$ = 19.6 Hz, —CH_2); 41.0 (dt, $^2J_{CF}$ = 20.9 Hz, —CH_2—); 54.7 (d, H_2N—CH); 95.7 (dd, $^1J_{CF}$ = 165.7 Hz, —CHF—); 174.8 (s, —COOH). – ^{13}C NMR (D_2O) [minor diastereomer]: δ = 96.4 (dd, $^1J_{CF}$ = 164.5 Hz, —CHF—); 174.1 (s, —COOH). The ^{13}C NMR data of the second diastereomer could not be obtained on a pure sample. – ^{19}F NMR (D_2O, without standard): δ = −178.4 and −178.6 (m, —CHF—).

2-Amino-4-fluoroheptanoic acid ***(4d)***

Preparation from 526 mg (2.4 mmol) of the fluoro amino acid ester **3d**; yield 274 mg (70%), m.p. 215°C (decomp.). – ^{1}H NMR (D_2O): δ = 0.85 (t, 3H, $^3J_{HH}$ = 7.3 Hz, —CH_3); 1.24–1.78 (m, 4H, —CH_2—); 1.95–2.30 (m, 2H, —CH_2—); 3.87–3.90 (m, 1H, H_2N—CH); 4.58–4.96 (m, 1H, —CHF—). The ^{1}H NMR data of the second diastereomer could not be obtained on a pure sample. – ^{13}C NMR (CF_3COOD) [major diastereomer]: δ = 14.4 (q, —CH_3); 19.8 (t, —CH_2—); 36.1 (dt, $^2J_{CF}$ = 19.1 Hz, —CH_2—); 38.8 (dt, $^2J_{CF}$ = 20.2 Hz, —CH_2—); 54.8 (d, H_2N—CH); 95.5 (dd, $^1J_{CF}$ = 162.5 Hz, —CHF—); 174.4 (s, —COOH). – ^{13}CNMR (CF_3COOD) [minor diastereomer]: δ = 14.4 (q, —CH_3); 19.8 (t, —CH_2—); 37.2 (dt, $^2J_{CF}$

= 19.0 Hz, —CH_2—); 39.2 (dt, $^2J_{CF}$ = 20.2 Hz, —CH_2—); 56.0 (d, H_2N—CH); 97.2 (dd, $^1J_{CF}$ = 162.9 Hz, —CHF—); 174.8 (s, —COOH). – ^{19}F NMR (D_2O, without standard): δ = −177.96 and −178.02 (m, —CHF—).

2-Amino-4-fluoro-5-methylhexanoic acid ***(4e)***

Preparation from 346 mg (1.58 mmol) of the fluoro amino acid ester **3e**; yield 183 mg (71%), m.p. 202.5°C (decomp.). – ^1H NMR (CF_3COOD): δ = 1.01 (d, 3H, $^3J_{HH}$ = 6.9 Hz, —CH_3); 1.06 (d, 3H, $^3J_{HH}$ = 6.9 Hz, —CH_3); 1.84–2.13 (m, 1H, —$CH(CH_3)_2$); 2.31–2.71 (m, 2H, —CH_2—); 4.38–4.83 (m, 2H, H_2N—CH u. —CHF—). The ^1H NMR data of the second diastereomer could not be obtained on a pure sample. – ^{13}C NMR (CF_3COOD) [major diastereomer]: δ = 17.8 (q, —CH_3); 18.3 (q, —CH_3); 33.6 (dd, $^2J_{CF}$ = 19.1 Hz, —$CH(CH_3)_2$); 34.7 (dt, $^2J_{CF}$ = 19.2 Hz, —CH_2—); 54.9 (d, H_2N—CH); 99.8 (dd, $^1J_{CF}$ = 165.6 Hz, —CHF—); 174.5 (s, —COOH). – ^{13}C NMR (CF_3COOD) [minor diastereomer]: δ = 56.0 (d, H_2N—CH); 101.4 (dd, $^1J_{CF}$ = 166.2 Hz, —CHF—); 174.9 (s, —COOH). The ^{13}C NMR data of the second diastereomer could not be obtained on a pure sample. – ^{19}F NMR (D_2O, without standard): δ = −177.96 and −178.02 (m, —CHF—).

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Authors' address: Prof. Dr. G. Haufe, Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, D-48149 Münster, Federal Republic of Germany.

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