A New Strategy for the Synthesis of α-Difluoromethyl-Substituted α-Hydroxy and α-Amino Acids

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A new method for the preparation of α-chlorodifluoromethyl-, α-bromodifluoromethyl-, and α-difluoromethyl-substituted α-hydroxy and α-amino acid esters **11, 19**−**21** is described. The key step of the synthesis is the regioselective alkylation of ketones **5, 7**−**9** and imines **16**−**18** with C-nucleophiles. The ketones **7**−**9** are readily available from 3,3,3-trifluorolactate **1** by a five-step procedure. Subsequent removal of the protecting groups from **19**−**21** provides the corresponding free amino acids **25, 26, 28**.

Introduction

Regulation of enzymatic decarboxylation reactions of amino acids by using specific inhibitors is of fundamental therapeutic interest.[1] In this context a number of *β*-fluorine-containing α-amino acids has received considerable attention during the last 15 years.[2] Among them special attention is paid to α-difluoromethyl-substituted α-amino acids possessing promising properties as irreversible mechanism-based inhibitors of the corresponding pyridoxal phosphate dependent α-amino acid decarboxylases.[3] Several representatives of this class of compounds exhibit antibacterial, antihypertensive, cancerostatic, and cytotoxic activity. For instance, α-difluoromethyl ornithine (eflornithine) is of therapeutic relevance for the treatment of African sleeping disease[4] and of *Pneumocystis carinii* pneumonia,[5] the most frequent opportunistic infection associated with the acquired immune deficiency syndrome (AIDS).

The known synthetic routes for α-fluoromethyl (e.g. α-monofluoromethyl, α-difluoromethyl, α-trifluoromethyl) α-amino acids[6] can be divided into two groups. Direct substitution of an α-hydrogen of a natural α-amino acid by fluoromethyl substituents consists of CH-insertion of the fluorine-containing carbene generated *in situ* from the corresponding freon under strongly basic conditions in a late step of the reaction sequence.[7] The second method involves the transformation of functional groups (e.g. fluorodehydroxylation) and includes the application of special fluorinating agents such as DAST, SF_4, CF_3OF, HF, and others.[8] In both cases the introduction of fluorine is accomplished using highly reactive species which may cause undesired transformations of other functional groups present in the molecule. Consequently, control of regio- and stereoselectivity is often difficult to achieve. Therefore, it is necessary to protect the functional groups, which requires additional synthetic steps. The most important standard protective groups (e.g. Boc and Cbz) for peptide synthesis are not applicable for these purposes as the remaining proton of the amino function can be attacked by the fluorinating reagent. Moreover, many of the currently used fluorinating reagents are expensive, toxic, corrosive, and sometimes explosive.

The building block strategy represents an attractive alternative route to α-fluoromethyl α-amino acids. We developed a preparative method for the synthesis of α-trifluoromethyl α-amino acids based on the amidoalkylation of carbon nucleophiles with highly electrophilic imines of methyl 3,3,3-trifluoropyruvate.[9] This enables direct synthesis of α-trifluoromethyl α-amino acids with orthogonal protective groups and renders this method

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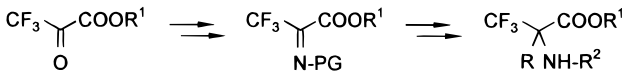
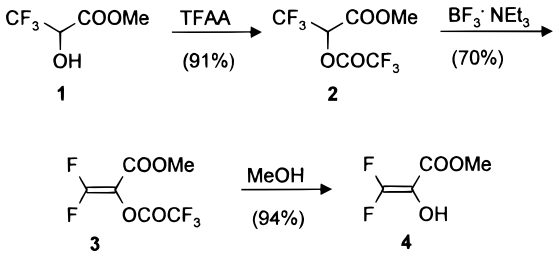
Scheme 1



Scheme 2



convenient for the preparation of free amino acids as well as for their incorporation into peptides[10] (Scheme 1).

Furthermore, the building block strategy provides access to homochiral α-trifluoromethyl α-amino acids via alkylation of *in situ* formed homochiral cyclic α-trifluoromethyl acyl imines with C-nucleophiles[11] or via the alkylation of α-trifluoromethyl imines with homochiral carbanions.[12]

In this paper, we wish to disclose a new convenient synthesis for α-difluoromethyl α-hydroxy and α-amino acids and for the virtually unknown α-chlorodifluoromethyl and α-bromodifluoromethyl α-hydroxy and α-amino acids, respectively, via 3,3-difluoropyruvate, 3-chloro-3,3-difluoropyruvate, and 3-bromo-3,3-difluoropyruvate or via the corresponding acyl imines.

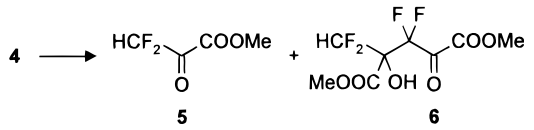
Results and Discussion

In the context with our interest in new fluorine containing building blocks,[13] we recently described a new metastable fluorinated enol, 3,3-difluoro-2-hydroxyacrylate (**4**),[14] using methyl 3,3,3-trifluorolactate (**1**)[15] as starting material (Scheme 2), which can be obtained from easily accessible methyl 3,3,3-trifluoropyruvate.[16]

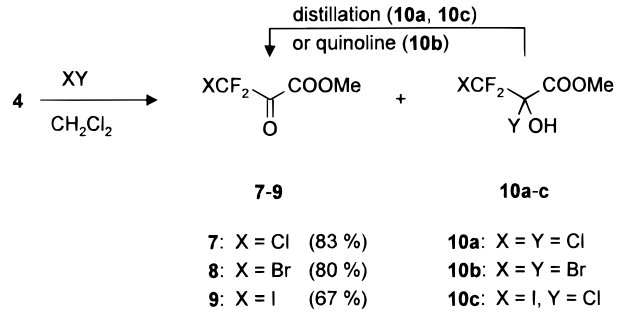
The trifluoroacetyl derivative **2** is obtained in 91% yield on treatment of **1** with trifluoroacetic anhydride (TFAA) in quinoline. Dehydrofluorination with $BF_3{\cdot}NEt_3$ provides acrylate **3** in good yield even on a 100 g scale. Essentially quantitative deprotection of **3** is achieved on treatment with MeOH. Enol **4** is a stable compound and can be distilled (bp 130−133 °C) without substantial decomposition.

The enol of pentafluoroacetone (as an analog of **4**) quantitatively isomerizes to give the ketone in boiling MeOH.[17] All attempts to induce complete transformation

Scheme 3



Scheme 4



of **4** into ketone **5** were unsuccessful so far. Conversion up to 30% only is observed on treatment of **4** with Et_3N in CH_2Cl_2. Compound **6** is the main product of this reaction as the result of an aldol-type condensation (Scheme 3). Nevertheless, methyl 3,3-difluoropyruvate (**5**) was separated from the mixture and characterized by NMR spectra and chemical transformations (Scheme 5 and 6).

The 3-chloro-3,3-difluoro-, 3-bromo-3,3-difluoro-, 3-iodo-3,3-difluoropyruvates, respectively, can be synthesized in a stepwise procedure starting from enol **4**, which readily reacts with halogens (or ICl) to give a mixture of the corresponding ketone (**7**−**9**) and the hydrogen halide adduct **10**[18] (Scheme 4) in a ratio of 3:1 (X = Cl), 3:2 (X = Br), 1:1 (X = I). The HX adducts **10** can be transformed into **7**−**9**.

Two pathways for the formation of **10** seem to be plausible: either the adducts are formed independently as a result of decomposition of the initially formed halogenonium ion or they are the products of a secondary reaction of **7**−**9** with the corresponding hydrogen halide.

The undesired byproducts **10a** or **10c** are converted into **7** or **9**, respectively, by distillation of the reaction mixture under ambient pressure. HBr elimination from **10b** is accomplished by treatment of the mixture with 1 equiv of quinoline. Subsequent distillation under reduced pressure gives pure **8**. Thus, ketones **7**−**9** are obtained from readily available lactate **1** by a five-step procedure in 50, 47, and 35% overall yield, respectively. In addition, every stage has been optimized on a 100 g scale.

Our interest in α-difluoromethyl α-hydroxy acids is connected with the fact that several α-fluoromethyl α-hydroxy acids have been applied as important components of antiandrogenic compounds.[19] Some of them were used for the synthesis of monomers for piezoelectric polymers[20] as well as for the preparation of fluorine-containing sugars.[21]

As expected, the ketones **5, 7**−**9** react regioselectively with Grignard reagents at −78 °C to give α-hydroxy esters **11** (Scheme 5) in high yields.

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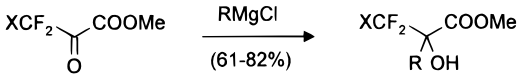
Scheme 5

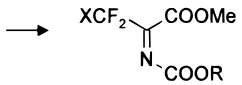


5, **7-9** **11a-f**

11a: X = H, R = Ph
11b: X = H, R = CH_2Ph
11c: X = Cl, R = Ph
11d: X = Br, R = Me
11e: X = Br, R = Ph
11f : X = Br, R = CH_2Ph

Scheme 6

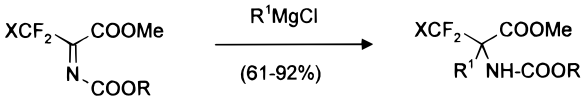
5, **7-9** **12-15**



16-18

12a, **16a:** X = H, R = *t*-Bu
12b: X = H, R = CH_2Ph
13a, **17a:** X = Cl, R = *t*-Bu
13b, **17b:** X = Cl, R = CH_2Ph
14a, **18a:** X = Br, R = *t*-Bu
14b, **18b:** X = Br, R = CH_2Ph
15a: X = I, R = CH_2Ph

Scheme 7



16-18 **19-21**

A protocol described by us earlier for the synthesis of the corresponding α-trifluoromethyl derivatives[9] can be applied for the synthesis of α-difluoromethyl α-amino acid derivatives from ketones **5, 7**−**9** (Schemes 6 and 7). The ketones **5, 7**−**9** readily form the stable hemiamidals **12**−**15** on reaction with benzyl and *tert*-butyl carbamates. The reactions proceed in CH_2Cl_2 or $CHCl_3$ at rt and are complete within 16 h. This process is significantly accelerated (1 h) when the reaction temperature is increased to 50−60 °C. The conversion of compounds **12**−**15** into imines **16**−**18** is carried out with trifluoroacetic anhydride/pyridine as dehydrating agent. Usually, the imines obtained do not require further purification. However, some of them can be distilled under reduced pressure. In analogy to their precursors **5** and **7**−**9**, the imines **16**−**18** smoothly react with Grignard reagents at −78 °C and the corresponding amino acid derivatives **19**−**21** are obtained in good to excellent yields (Table 1).

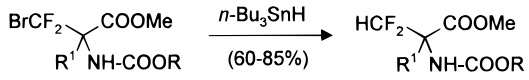
The reactions of the imines with the Grignard reagents proceed regioselectively. Addition to the ester groups or isomerization of **16a** to the enamide are not observed.

As mentioned above, this sequence is of limited value for the synthesis of α-difluoromethyl-substituted α-hydroxy and α-amino acids because of the low yield of **5**. Therefore, we developed an alternative route via radical reduction of the $BrCF_2$-group at the end of the reaction sequence. The (α-$BrCF_2$)-groups in hemiamidals **14** and α-amino esters **21** are readily reduced on treatment with 1.3 equiv of *n*-Bu_3SnH (Scheme 8) in THF. In the case of the hemiamidals **14** the reaction proceeds at rt within 1−2 h. Reduction of compounds **21a**−**d** in boiling THF reaches completion within 2−4 h.

Table 1. Conversion of Imines 16−18 into α-Amino Acid Esters 19−21

entry	X	R	R^1	product	yield (%)
1	H	*t*-Bu	$PhCH_2$	**19e**	72
2	Cl	$PhCH_2$	Me	**20a**	73
3	Cl	$PhCH_2$	$PhCH_2$	**20b**	92
4	Cl	*t*-Bu	$PhCH_2$	**20c**	80
5	Br	$PhCH_2$	Me	**21a**	78
6	Br	$PhCH_2$	$PhCH_2$	**21b**	68
7	Br	$PhCH_2$	*i*-Bu	**21c**	63
8	Br	$PhCH_2$	Ph	**21d**	62
9	Br	$PhCH_2$	Allyl	**21e**	61
10	Br	*t*-Bu	Me	**21f**	80
11	Br	*t*-Bu	$PhCH_2$	**21g**	86

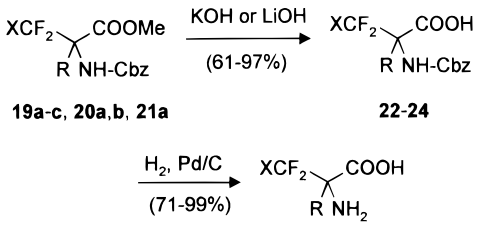
Scheme 8



14a,**b**, **21a-d** **12a**,**b**, **19a-d**

14a, **12a:** R^1 = OH; R = *t*-Bu
14b, **12b:** R^1 = OH; R = CH_2Ph
21a, **19a:** R^1 = Me; R = CH_2Ph
21b, **19b:** R^1 = CH_2Ph; R = CH_2Ph
21c, **19c:** R^1 = *i*-Bu; R = CH_2Ph
21d, **19d:** R^1 = Ph; R = CH_2Ph

Scheme 9



19a-c, **20a**,**b**, **21a** **22-24**

25-26

19a, **22a**, **25a:** X = H, R = Me
19b, **22b**, **25b:** X = H, R = CH_2Ph
19c, **22c**, **25c:** X = H, R = *i*-Bu
20a, **23a**, **26a:** X = Cl, R = Me
20b, **23b**, **26b:** X = Cl, R = CH_2Ph
21a, **24a:** X = Br, R = Me

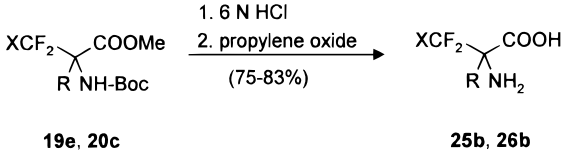
The chloro derivatives **13b**, **20a**,**b** are also reduced with *n*-Bu_3SnH in boiling THF. However, the conversion remained incomplete under the reaction conditions tested (also in the presence of AIBN). Furthermore, partial decomposition is observed especially in the case of hemiamidal **13b**, presumably via elimination of benzyl carbamate.

In order to check the perspectives for the utilization of these protected amino acid derivatives for peptide synthesis we tested methods for the removal of protective groups using standard peptide chemistry protocols.

Selective deprotection of the carboxy group of Cbz-protected derivatives **19**−**21** under mildly basic conditions (KOH/MeOH, rt, 24 h or LiOH/MeOH, 5 °C, 24 h) readily gives the corresponding acids **22**−**24**. Subsequent catalytic hydrogenation (Pd/C, MeOH, 12 h) affords free amino acids **25** and **26**. In the case of the bromo derivative **24a** hydrogenation results in simultaneous reduction of the CF_2Br- and cleavage of Cbz-group to give α-difluoromethyl alanine **25a** (Scheme 9).

Direct hydrolysis of Boc-protected derivatives **19e**, **20c** (6 N HCl, 80 °C, 10 h) proceeds in good yield to give

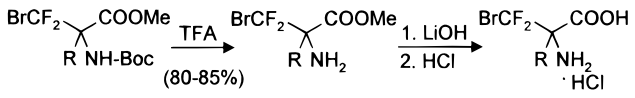
Scheme 10



19e, **20c** **25b**, **26b**

25b: X = H, R = CH_2Ph
26b: X = Cl, R = CH_2Ph

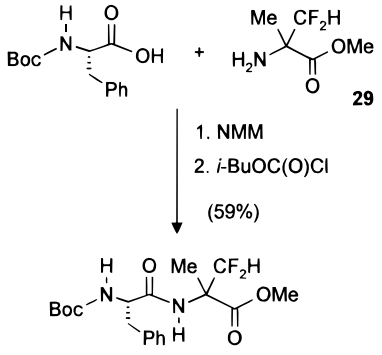
Scheme 11



21f,g **27a,b** **28a,b**

21f, **27a**, **28a:** R = Me
21g, **27b**, **28b:** R = CH_2Ph

Scheme 12



30

α-difluoromethyl and α-chlorodifluoromethyl amino acids **25b**, **26b** (Scheme 10). Bromo derivatives **21f**,**g** decompose under these conditions. Treatment of **21f**,**g** with 40% HBr in acetic acid (20 °C, 3 h) results only in deprotection of the amino group to give **27a**,**b**.

A different strategy was used for the preparation of free α-bromodifluoromethyl α-amino acids **28a**,**b**: deprotection of the amino group in the corresponding Boc-derivatives **21f**,**g** with trifluoroacetic acid (TFA), followed by cleavage of the methyl esters **27a**,**b** (LiOH/MeOH) (Scheme 11). All attempts to purify acids **28a**,**b** (also by ion-exchange chromatography with ion-exchange resin DOWEX 50W-X2) failed. They were characterized spectroscopically as hydrochlorides in a mixture with LiCl.

Noteworthy, the free α-$BrCF_2$-containing α-amino acids are unstable toward heating or basic reagents. However, being protected either on the amino or the carboxy function, they are quite stable compounds.

α-Difluoromethyl-substituted α-amino acids can be readily incorporated into peptides by standard peptide synthesis procedures as demonstrated by the synthesis of dipeptide **30** from Boc-protected L-phenylalanine and methyl α-(difluoromethyl)alaninate (**29**)[22] using the mixed anhydride strategy (Scheme 12). The diastereomers can be separated by flash-chromatography. Investigations concerning SPPS (solid phase peptide synthesis) with α-difluoromethyl-substituted α-amino acids are in progress.

(22) Compound **29**·HBr was especially obtained from compound **21a** by hydrogenation (Pd/C, MeOH, 12 h) as result of simultaneous cleavage of the Cbz-protective group and reduction of the bromodifluoromethyl group to a difluoromethyl group (see Experimental Section).

Conclusion

We developed a new convenient route to 3-chloro-3,3-difluoropyruvate **7** and 3-bromo-3,3-difluoropyruvate **8** via halogenation of enol **4**. The latter is readily prepared via a three-step procedure from 3,3,3-trifluorolactate **1**. The new ketones **7**, **8** are highly electrophilic synthons which can be efficiently used as building blocks for the synthesis of various derivatives of biologically valuable α-difluoromethyl-substituted α-hydroxy and α-amino acids. Scale-up synthesis of these compounds can easily be achieved, thus making them available in sufficient quantities to study their potential pharmacological and therapeutic properties.

Experimental Section

^1H NMR spectra were recorded on 200 and 300 MHz spectrometers with Me_4Si as internal standard. ^{13}C NMR spectroscopy was performed at 50, 75, and 100 MHz. ^{19}F NMR spectra were obtained at 188 and 282 MHz with trifluoroacetic acid as external standard, downfield shifts being designated as positive. Mass spectra were obtained using EI ionization at 70 eV. Elemental microanalyses were carried out by the microanalytical laboratory of the chemistry department, University of Leipzig. All compounds have been fully characterized and gave correct microanalytical data [±0.4%, except **5** (unstable), **10** (undesired side products), **28** (contains salt), **29** (hygroscopic)]. All reactions were routinely monitored with the aid of ^{19}F NMR spectroscopy or TLC. Analytical TLC was performed using Merck precoated silica gel 60F-254 plates (0.25 mm). For flash chromatography, silica gel 60 (30−60 μm) was used with hexanes/ethyl acetate solvent systems. Organic solvents were dried and distilled prior to use.

Methyl *O*-(Trifluoroacetyl)-3,3,3-trifluorolactate (2). TFAA (190.0 g, 0.90 mol) was added at 0 °C to a stirred solution of **1** (130 g, 0.82 mol) in quinoline (380.0 g, 2.90 mol). The mixture was stirred at 0 °C for 1 h and then at rt for 1 h. The reaction flask was connected to a distillation apparatus, and the product was transferred under reduced pressure (1 Torr) into a cooled (−78 °C) receiver. The contents of the receiver was allowed to warm up to rt. Distillation gave 190.1 g (91%) of **2**: bp 72 °C/70 Torr; n^{20}_D 1.3202. ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H); 5.58 (q, $^3J_{HF}$ = 6.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 54.1; 71.3 (q, $^2J_{CF}$ = 35.2 Hz); 113.9 (q, $^1J_{CF}$ = 284.7 Hz); 120.2 (q, $^1J_{CF}$ = 281.2 Hz); 155.6 (q, $^2J_{CF}$ = 42.6 Hz); 160.8. ^{19}F NMR ($CDCl_3$) δ 3.22 (s, 3F); 5.03 (d, $^3J_{HF}$ = 6.5 Hz, 3F).

Methyl 3,3-Difluoro-2-(trifluoroacetoxy)acrylate (3). A mixture of **2** (20.0 g, 0.079 mol), silica gel (Merck, 63−200 μm, 1.6 g), and $Et_3N{\cdot}BF_3$ (40.0 g, 0.23 mol) was heated to 120 °C for 2 h. The reaction flask was then connected to a distillation apparatus, and the volatiles were transferred under reduced pressure (1 Torr) into a cooled (−78 °C) receiver, while the temperature was raised from rt to 90 °C. The contents of the receiver was subjected once more to thermolysis at 120 °C for 42 h with the same amount of $Et_3N{\cdot}BF_3$ (this time without silica gel). The product was collected as above. Distillation gave 12.8 g (70%) of pure **3**: bp 40−42 °C/50 Torr; n^{20}_D 1.3456. ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 53.1; 106.1 (m); 114.1 (q, $^1J_{CF}$ = 285.9 Hz); 158.8; 158.9 (q, $^2J_{CF}$ = 21.3 Hz); 159.0 (dd, $^1J_{CF}$ = 308.4, 303.4 Hz). ^{19}F-NMR ($CDCl_3$) δ −2.14 (d, $^2J_{FF}$ = 6.1 Hz, 1F); 3.29 (d, $^2J_{FF}$ = 6.1 Hz, 1F); 3.40 (s, 3F).

Methyl 3,3-Difluoro-2-hydroxyacrylate (4). MeOH (5.8 g, 0.18 mol) in 5 mL of CH_2Cl_2 was added at −10 °C to a stirred solution of **3** (40.0 g, 0.17 mol) in CH_2Cl_2 (15 mL). The mixture was allowed to warm up to rt and was stirred for 16 h. Volatiles were removed under reduced pressure (60 Torr). Distillation of the residue gave 22.3 g (94%) of **4**: bp 65−66 °C/60 Torr. ^1H NMR ($CDCl_3$) δ 3.92 (s, 3H); 4.54 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 53.3; 109.6 (dd, $^2J_{CF}$ = 35.4, 19.3 Hz); 156.1 (dd, $^1J_{CF}$ = 295.0, 298.2 Hz); 164.7 (dd, $^3J_{CF}$ = 10.3, 7.9 Hz). ^{19}F NMR ($CDCl_3$) δ −19.16 (d, $^2J_{FF}$ = 29.0 Hz, 1F); −9.34 (d, $^2J_{FF}$ = 29.0 Hz, 1F). IR (neat): ν (cm^{-1}) 3400 (OH), 1760 (C=C), 1750 (C=O). MS (EI, *m*/*z*) 138 (M^+); 107 (39); 79 (74).

Isomerization of 4. A solution of Et_3N (3−4 drops) in CH_2Cl_2 (3 mL) was added at rt to a solution of **4** (10.0 g, 7.24 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 10 h. After evaporation of the solvent, the residue was distilled under reduced pressure to give two fractions: methyl 3,3-difluoropyruvate (**5**) (3.1 g, bp 78−80 °C/25 Torr) and dimethyl 4-(difluoromethyl)-3,3-difluoro-4-hydroxy-2-oxopentanedioate (**6**) (4.2 g, bp 101−103 °C/15 Torr).

5: ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H); 6.40 (t, $^2J_{HF}$ = 52.9 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ −53.21 (d, $^2J_{HF}$ = 52.9 Hz). An analytically pure sample was not obtained. **6**·H_2O: ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H); 3.95 (s, 3H); 4.52 (br s, 3H); 6.17 (dd, $^2J_{HF}$ = 54.9, 53.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 54.55; 54.85; 77.25 (m); 92.64 (t, $^2J_{CF}$ = 29.6 Hz); 112.31 (t, $^1J_{CF}$ = 252.9 Hz); 115.64 (t, $^1J_{CF}$ = 276.1 Hz); 167.19 (t, $^2J_{CF}$ = 3.5 Hz); 168.10. ^{19}F NMR ($CDCl_3$) δ −53.53 (ddt, $^2J_{FF}$ = 293.9 Hz, $^2J_{HF}$ = 53.2, $^4J_{FF}$ = 12.0 Hz, 1F); −50.40 (ddt, $^2J_{FF}$ = 293.9 Hz, $^2J_{HF}$ = 53.2, $^4J_{FF}$ = 12.0 Hz, 1F); −38.84 (dt, $^2J_{FF}$ = 274.8, $^4J_{FF}$ = 12.0 Hz, 1F); −37.73 (dt, $^2J_{FF}$ = 274.9, $^4J_{FF}$ = 12.0 Hz, 1F).

Methyl 3-Chloro-3,3-difluoro-2-oxopropionate (7). A cold (−50 °C) solution of chlorine (23.2 g, 32.6 mmol) in CH_2Cl_2 (100 mL) was added under nitrogen in one portion to a stirred solution of **4** (30.0 g, 21.7 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was stirred for 2 h at −60 °C, warmed up to rt, and stirred overnight. The solvent was removed under reduced pressure. The residue was a mixture of **7** and methyl 2,3-dichloro-3,3-difluoro-2-hydroxypropionate (**10a**) (ratio of 3:1; as measured by NMR). **10a**: ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.81 (br s, 1H). ^{19}F ($CDCl_3$) δ 11.39 (d_{AB}, $^2J_{FF}$ = 164.4 Hz, 1F); 15.93 (d_{AB}, $^2J_{FF}$ = 164.4 Hz, 1F). The mixture was distilled to give 31.1 g (83%) of pure **7** (bp 129−130 °C). ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 54.02; 118.27 (t, $^1J_{CF}$ = 304.1 Hz); 157.14; 173.87 (t, $^2J_{CF}$ = 33.2 Hz). ^{19}F NMR ($CDCl_3$) δ 11.31 (s, 2F). MS (EI, *m*/*z*) 172 (M^+); 160 (18); 132 (28); 95 (31); 86 (92); 59 (100).

Methyl 3-Bromo-3,3-difluoro-2-oxopropionate (8). A solution of bromine (50.0 g, 31.25 mmol) in CH_2Cl_2 (100 mL) was slowly (within 1 h) added to a vigorously stirred solution of **4** (40.0 g, 28.9 mmol) in CH_2Cl_2 (50 mL) at −30 °C under nitrogen. The reaction mixture was stirred for 12 h at rt. After removal of the solvent, the residue was distilled under reduced pressure (bp 41−43 °C/10 Torr) to afford 74.5 g of a slightly yellow liquid which was a mixture of **8** and methyl 2,3-dibromo-3,3-difluoro-2-hydroxypropionate (**10b**) (according to NMR spectra) in a ratio of 3:2. **10b**: ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H); 5.46 (br s, 1H). ^{19}F NMR ($CDCl_3$) δ 19.29 (d_{AB}, $^2J_{FF}$ = 162.0 Hz, 1F); 26.17 (d_{AB}, $^2J_{FF}$ = 162.0 Hz, 1F). A 37.4 g (28.9 mmol) amount of quinoline was added at 10 °C to this mixture. After stirring for 1 h the reaction flask was connected to a distillation apparatus and the product was transferred under reduced pressure (1 Torr) into a cooled (−78 °C) receiver, while the temperature of the reaction flask was slowly raised from rt to 50 °C. The product was redistilled from a small amount of phosphorus pentoxide to give 65.7 g (80%) of pure **8** (bp 70−71 °C/70 Torr). ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 54.00; 111.36 (t, $^1J_{CF}$ = 317.9 Hz); 156.88; 173.73 (t, $^2J_{CF}$ = 29.6 Hz). ^{19}F NMR ($CDCl_3$) δ 13.88 (s, 2F). MS (EI, *m*/*z*): 216 (M^+); 176 (13); 129 (52); 82 (31); 59 (100).

Methyl 3-Iodo-3,3-difluoro-2-oxopropionate (9). By analogy to the procedure for **7**, 17.1 g of a mixture of **9** and methyl 2-chloro-3-iodo-3,3-difluoro-2-hydroxypropionate (**10c**) in a ratio of 1:1 were obtained from 10.0 g (7.24 mmol) of **4** and 13.0 g (8.0 mmol) of ICl. **10c**: ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H); 4.45 (br s, 1H). ^{19}F NMR ($CDCl_3$) δ 20.54 (d_{AB}, $^2J_{FF}$ = 185.3 Hz, 1F); 23.58 (d_{AB}, $^2J_{FF}$ = 185.3 Hz, 1F). The mixture was converted into pure **9** (12.8 g, 67%) on distillation under reduced pressure (bp 57−59 °C/12 Torr). ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H). ^{19}F NMR ($CDCl_3$) δ 16.05 (s, 2F).

General Procedure for the Preparation of α-Hydroxy acids 11a−f. A Grignard reagent (solution in THF, 10.0 mmol) was added dropwise to a stirred solution of 10.0 mmol of ketone **5**, **7**, **8**, **9**, respectively, in dry THF (25 mL) at −78 °C. After 1 h at −78 °C the reaction mixture was allowed to warm up to rt within 2 h. The reaction was quenched with 1 N HCl and extracted with ether (2 × 25 mL). The combined organic layer was washed with brine (25 mL), dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography.

Methyl 3,3-difluoro-2-hydroxy-2-phenylpropionate (11a): yield 68%; oil. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 1H); 3.91 (s, 3H); 6.23 (t, $^2J_{HF}$ = 54.4 Hz, 1H); 7.41 (m, 3H); 7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 54.47; 78.61 (t, $^2J_{FC}$ = 21.2 Hz); 115.18 (t, $^1J_{FC}$ = 248.9 Hz); 126.45; 129.14; 129.64; 135.01; 171.15. ^{19}F NMR ($CDCl_3$) δ −55.97 (dd_{ABX}, $^2J_{FF}$ = 278.3 Hz, $^2J_{HF}$ = 54.4 Hz, 1F); −51.22 (dd_{ABX}, $^2J_{FF}$ = 278.3 Hz, $^2J_{HF}$ = 54.4 Hz, 1F).

Methyl 2-(difluoromethyl)-2-hydroxy-3-phenylpropionate (11b): yield 74%; oil. ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 2H); 3.43 (br s, 1H); 3.80 (s, 3H); 5.86 (t, $^2J_{HF}$ = 55.1 Hz, 1H); 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 39.42 (t, $^3J_{CF}$ = 3.0 Hz); 53.87; 78.81 (t, $^2J_{CF}$ = 21.0 Hz); 115.41 (t, $^1J_{CF}$ = 250.2 Hz); 127.91; 128.85; 130.67; 134.03; 171.29. ^{19}F NMR ($CDCl_3$) δ −55.82 (dd_{ABX}, $^2J_{FF}$ = 282.4 Hz, $^2J_{HF}$ = 55.1 Hz, 1F); −49.97 (dd_{ABX}, $^2J_{FF}$ = 282.4 Hz, $^2J_{HF}$ = 55.1 Hz, 1F). MS (EI, *m*/*z*) 230 (M^+); 212 (18); 91 (100).

Methyl 3-chloro-3,3-difluoro-2-hydroxy-2-phenylpropionate (11c): yield 82%; oil. ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H); 4.47 (s, 1H); 7.20 (m, 3H); 7.92 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 55.14; 81.64 (t, $^2J_{CF}$ = 27.3 Hz); 122.59 (t, $^1J_{CF}$ = 303.3 Hz); 127.74; 128.85; 130.14; 133.52; 170.26. ^{19}F NMR ($CDCl_3$) δ 15.07 (d_{AB}, $^2J_{FF}$ = 165.4 Hz, 1F); 17.20 (d_{AB}, $^2J_{FF}$ = 165.4 Hz, 1F).

Methyl 2-(bromodifluoromethyl)-2-hydroxypropionate (11d): yield 70%; oil. ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 3H); 3.91 (s, 3H); 3.97 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.00; 54.71; 79.93 (t, $^2J_{CF}$ = 24.2 Hz); 123.76 (t, $^1J_{CF}$ = 315.9 Hz); 171.30. ^{19}F NMR ($CDCl_3$) δ 18.67 (d_{AB}, $^2J_{FF}$ = 162.2 Hz, 1F); 21.18 (d_{AB}, $^2J_{FF}$ = 162.2 Hz, 1F).

Methyl 3-bromo-3,3-difluoro-2-hydroxy-2-phenylpropionate (11e): yield 74%; oil. ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H); 4.54 (s, 1H); 7.42 (m, 3H); 7.85 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 55.21; 82.40 (t, $^2J_{CF}$ = 24.1 Hz); 123.09 (t, $^1J_{CF}$ = 316.0 Hz); 127.72; 128.81; 130.10; 133.44; 170.00. ^{19}F NMR ($CDCl_3$) δ 20.85 (d_{AB}, $^2J_{FF}$ = 162.4 Hz, 1F); 23.48 (d_{AB}, $^2J_{FF}$ = 162.4 Hz, 1F).

Methyl 2-(bromodifluoromethyl)-2-hydroxy-3-phenylpropionate (11f): yield 61%; oil. ^{1}H NMR ($CDCl_3$) δ 3.20 (d_{AB}, $^2J_{HH}$ = 13.4 Hz, 1H); 3.33 (d_{AB}, $^2J_{HH}$ = 13.4 Hz, 1H); 3.82 (s, 3H); 3.94 (s, 1H); 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 38.03; 54.02; 83.02 (t, $^2J_{CF}$ = 23.4 Hz); 122.79 (t, $^1J_{CF}$ = 316.7 Hz); 127.62; 128.38; 130.42; 133.24; 169.60. ^{19}F NMR ($CDCl_3$) δ 19.62 (d_{AB}, $^2J_{FF}$ = 162.0 Hz, 1F); 22.22 (d_{AB}, $^2J_{FF}$ = 162.0 Hz, 1F). MS (EI, *m*/*z*) 308 (M^+); 290 (5); 211 (17); 91 (100).

General Procedure for Preparation of Hemiamidals 12−15. A mixture of the corresponding ketone (10 mmol) and benzyl carbamate (or *tert*-butyl carbamate; 10 mmol) in dry $CHCl_3$ was stirred at rt for 16 h. The solution was concentrated in vacuo, and the crude product was purified by recrystallization from $CHCl_3$/hexanes.

Methyl 2-[*N*-(*tert*-butyloxycarbonyl)amino]-3,3-difluoro-2-hydroxypropionate (12a): yield 83%; mp 68−70 °C. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H); 3.91 (s, 3H); 4.92 (s, 1H); 5.65 (s, 1H); 5.87 (t, $^2J_{HF}$ = 52.0 Hz). ^{13}C NMR ($CDCl_3$) δ 27.60; 53.77; 80.70 (t, $^2J_{CF}$ = 24.2 Hz); 81.70; 112.11 (t, $^1J_{CF}$ = 242.3 Hz); 153.88; 167.53. ^{19}F NMR ($CDCl_3$) δ −57.01 (dd_{ABX}, $^2J_{FF}$ = 288.1 Hz, $^2J_{HF}$ = 52.0 Hz, 1F); −52.85 (dd_{ABX}, $^2J_{FF}$ = 288.1 Hz, $^2J_{HF}$ = 52.0 Hz, 1F).

Methyl 2-[*N*-(benzyloxycarbonyl)amino]-3,3-difluoro-2-hydroxypropionate (12b): yield 74%; mp 108−109 °C. ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H); 4.89 (s, 1H); 5.11 (d_{AB}, $^2J_{HH}$ = 12.0 Hz, 1H); 5.15 (d_{AB}, $^2J_{HH}$ = 12.0 Hz, 1H); 5.87 (s, 1H); 5.90 (t, $^2J_{HF}$ = 55.3 Hz, 1H); 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 54.82; 68.34; 81.76 (t, $^2J_{CF}$ = 25.0 Hz); 112.89 (t, $^1J_{CF}$ = 252.0 Hz); 128.82, 129.05; 129.11; 135.70; 155.61; 167.98. ^{19}F NMR ($CDCl_3$) δ −57.00 (dd_{ABX}, $^2J_{FF}$ = 294.3 Hz, $^2J_{HF}$ = 55.3 Hz, 1F); −52.92 (dd_{ABX}, $^2J_{FF}$ = 294.3 Hz, $^2J_{HF}$ = 55.3 Hz, 1F).

Methyl 2-[*N*-(*tert*-butyloxycarbonyl)amino]-3-chloro-3,3-difluoro-2-hydroxypropionate (13a): yield 89%; mp 83−84 °C. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H); 3.94 (s, 3H); 5.58 (br s, 1H); 5.73 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 28.09; 54.74; 82.57; 83.96 (t, $^2J_{CF}$ = 28.6 Hz); 126.38 (t, $^1J_{CF}$ = 303.4 Hz); 154.03, 167.01. ^{19}F NMR ($CDCl_3$) δ 11.39 (d_{AB}, $^2J_{FF}$ = 164.1 Hz, 1F); 11.78 (d_{AB}, $^2J_{FF}$ = 164.1 Hz, 1F). MS (EI, *m*/*z*) 271 ($M^+ - H_2O$); 256 (34); 217 (23); 57 (100).

Methyl 2-[*N*-(benzyloxycarbonyl)amino]-3-chloro-3,3-difluoro-2-hydroxypropionate (13b): yield 91%; mp 106−108 °C. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H); 5.11 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 5.17 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 5.53 (br s, 1H); 6.01 (br s, 1H); 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 54.94; 68.09; 84.00 (t, $^2J_{CF}$ = 28.1 Hz); 126.19 (t, $^1J_{CF}$ = 303.4 Hz); 128.46; 128.71; 128.73; 135.05; 154.67; 166.60. ^{19}F NMR ($CDCl_3$) δ 11.34 (d_{AB}, $^2J_{FF}$ = 164.3 Hz, 1F); 11.74 (d_{AB}, $^2J_{FF}$ = 164.3 Hz, 1F). MS (EI, *m*/*z*) 305 ($M^+ - H_2O$); 263 (5); 107 (20); 91 (100).

Methyl 2-[*N*-(*tert*-butyloxycarbonyl)amino]-3-bromo-3,3-difluoro-2-hydroxypropionate (14a): yield 86%; mp 92−95 °C. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H); 3.94 (s, 3H); 5.60 (very br.); 5.72 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.53; 55.21; 83.01; 84.80 (t, $^2J_{CF}$ = 26.5 Hz); 121.20 (t, $^1J_{CF}$ = 315.4 Hz); 154.33; 167.16. ^{19}F NMR ($CDCl_3$) δ 16.80 (d_{AB}, $^2J_{FF}$ = 162.2 Hz, 1F); 18.35 (d_{AB}, $^2J_{FF}$ = 162.2 Hz, 1F). MS (EI, *m*/*z*) 317 ($M^+ - H_2O$); 243 (11); 215 (13); 57 (100).

Methyl 2-[*N*-(benzyloxycarbonyl)amino]-3-bromo-3,3-difluoro-2-hydroxypropionate (14b): yield 93%; mp 99−100 °C. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H); 5.11 (d_{AB}, $^2J_{HH}$ = 12.1 Hz, 1H); 5.16 (d_{AB}, $^2J_{HH}$ = 12.1 Hz, 1H); 5.52 (br s, 1H); 5.97 (br s, 1H); 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 54.92; 68.07; 84.00 (t, $^2J_{CF}$ = 28.6 Hz); 126.21 (t, $^1J_{CF}$ = 303.1 Hz); 128.48; 128.60; 128.72; 135.07; 154.72; 166.65. ^{19}F NMR ($CDCl_3$) δ 16.77 (d_{AB}, $^2J_{FF}$ = 135.5 Hz, 1F); 18.22 (d_{AB}, $^2J_{FF}$ = 135.5 Hz, 1F).

Methyl 2-[*N*-(benzyloxycarbonyl)amino]-3-iodo-3,3-difluoro-2-hydroxypropionate (15): yield 64%; mp 91−92 °C. ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H); 5.11 (d_{AB}, $^2J_{HH}$ = 12.1 Hz, 1H); 5.16 (d_{AB}, $^2J_{HH}$ = 12.1 Hz, 1H); 5.47 (s, 1H); 5.83 (s, 1H); 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 55.39; 68.55; 85.05 (t, $^2J_{CF}$ = 22.5 Hz); 102.10 (t, $^1J_{CF}$ = 321.7 Hz); 128.75; 128.97; 129.17; 135.53; 154.83; 165.93. ^{19}F NMR ($CDCl_3$) δ 16.77 (d_{AB}, $^2J_{FF}$ = 135.5 Hz, 1F); 18.22 (d_{AB}, $^2J_{FF}$ = 135.5 Hz, 1F).

General Procedure for the Preparation of Imines 16−18. Trifluoroacetic anhydride (4.5 mL, 31.9 mmol) was added at 0 °C to a vigorously stirred solution of a hemiamidal (29 mmol) in dry ether (100 mL) over a period of 0.5 h. After stirring for 0.5 h, pyridine (5.2 mL, 64 mmol) was added slowly. Stirring was continued for additional 2 h. The reaction mixture was cooled to −20 °C and the precipitated pyridinium trifluoroacetate was filtered off under an inert gas atmosphere. The filtrate was concentrated in vacuo and triturated with 50 mL of hexanes (4 × 50 mL) to dissolve the imine and separate it from residual pyridinium trifluoroacetate. The combined hexane solutions were evaporated. Frequently, the purity of the products is sufficient for further transformations. If necessary, the imines **16−18** can easily be purified by distillation in vacuo.

Methyl 2-[*N*-(*tert*-butyloxycarbonyl)imino]-3,3-difluoropropionate (16a): yield 88%, bp 68−70 °C/0.25 Torr. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H); 3.85 (s, 3H); 6.35 (t, $^2J_{HF}$ = 53.3 Hz). ^{13}C NMR ($CDCl_3$) δ 28.22; 53.91; 85.14; 110.20 (t, $^1J_{CF}$ = 247.1 Hz); 150.92 (t, $^2J_{CF}$ = 25.9 Hz); 157.26, 158.39. ^{19}F NMR ($CDCl_3$) δ −46.33 (d, $^2J_{HF}$ = 53.3 Hz, 2F).

Methyl 2-[*N*-(*tert*-butyloxycarbonyl)imino]-3-chloro-3,3-difluoropropionate (17a): yield 92%; bp 60−62 °C/0.25 Torr. ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 9H); 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 28.21; 54.21; 85.68; 121.07 (t, $^1J_{CF}$ = 294.6 Hz); 149.55 (t, $^2J_{CF}$ = 30.4 Hz); 156.46; 157.37. ^{19}F NMR ($CDCl_3$) δ 18.45 (s, 2F).

Methyl 2-[*N*-(benzyloxycarbonyl)imino]-3-chloro-3,3-difluoropropionate (17b): yield 98%; oil. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H); 5.34 (s, 2H); 7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 54.03; 69.59; 120.48 (t, $^1J_{CF}$ = 295.2 Hz); 128.77; 129.02; 129.11; 134.43; 155.78 (t, $^2J_{CF}$ = 31.3 Hz); 155.78; 158.51. ^{19}F NMR ($CDCl_3$) δ 18.23 (s, 2F).

Methyl 3-bromo-2-[*N*-(*tert*-butyloxycarbonyl)imino]-3,3-difluoropropionate (18a): yield 94%; bp 78−80 °C/0.25 Torr. ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 9H); 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 28.21; 54.20; 85.61; 112.90 (t, $^1J_{CF}$ = 309.2 Hz); 150.20 (t, $^2J_{CF}$ = 27.7 Hz); 156.39; 157.28. ^{19}F NMR ($CDCl_3$) δ 21.67 (s, 2F).

Methyl 2-[*N*-(benzyloxycarbonyl)imino]-3-bromo-3,3-difluoropropionate (18b): yield 95%; oil. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H); 5.34 (s, 2H); 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 52.99; 68.53; 111.28 (t, $^1J_{CF}$ = 308.9 Hz); 127.72; 127.97; 128.07; 133.35; 149.85 (t, $^2J_{CF}$ = 27.2 Hz); 154.70; 157.44. ^{19}F NMR ($CDCl_3$) δ 21.29 (s, 2F).

Procedure for the Preparation of Amino Esters 19−21. The α-amino esters **19−21** were obtained by Grignard reaction according to the procedure for the synthesis of α-hydroxy esters **11**.

Methyl *N*-(*tert*-butyloxycarbonyl)-2-(difluoromethyl)-phenylalaninate (19e): yield 72%; oil. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H); 3.29 (d, $^2J_{HH}$ = 13.4 Hz, 1H); 3.74 (d, $^2J_{HH}$ = 13.4 Hz, 1H); 3.86 (s, 3H); 5.47 (br s, 1H); 6.42 (t, $^2J_{HF}$ = 55.8 Hz, 1H); 7.09 (m, 2H); 7.29 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 27.82; 34.55; 52.75; 65.71 (t, $^2J_{CF}$ = 21.4 Hz); 80.04; 113.10 (t, $^1J_{CF}$ = 250.9 Hz); 127.03; 128.10; 129.58; 133.63; 153.82; 168.11. ^{19}F NMR ($CDCl_3$) δ −50.34 (d, $^2J_{HF}$ = 55.8 Hz, 2F).

Methyl *N*-(benzyloxycarbonyl)-2-(chlorodifluoromethyl)alaninate (20a): yield 73%; oil. ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H); 3.82 (s, 3H); 5.11 (s, 2H); 5.62 (s, 1H); 7.36 (s, 5H). ^{13}C NMR ($CDCl_3$) δ 19.16; 54.15; 67.20 (t, $^2J_{CF}$ = 24.9 Hz); 67.80; 129.21 (t, $^1J_{CF}$ = 302.5 Hz); 128.71; 128.85; 129.07; 136.28; 154.80; 168.01. ^{19}F NMR ($CDCl_3$) δ 15.67 (d_{AB}, $^2J_{FF}$ = 164.2 Hz, 1F); 16.74 (d_{AB}, $^2J_{FF}$ = 164.2 Hz, 1F).

Methyl *N*-(benzyloxycarbonyl)-2-(chlorodifluoromethyl)phenylalaninate (20b): yield 92%; mp 51−52 °C. ^{1}H NMR ($CDCl_3$) δ 3.04 (d, $^2J_{HH}$ = 13.8 Hz, 1H); 3.84 (s, 3H); 4.29 (d, $^2J_{HH}$ = 13.8 Hz, 1H); 5.05 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 5.26 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 6.01 (s, 1H); 7.08 (m, 5H); 7.19 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 33.40; 54.38; 67.47; 72.21 (t, $^2J_{CF}$ = 25.6 Hz); 128.03; 128.85; 128.99; 129.03; 129.05; 129.09; 130.41 (t, $^1J_{CF}$ = 314.4 Hz); 134.07; 135.22; 154.51; 167.58. ^{19}F NMR ($CDCl_3$) δ 19.00 (d_{AB}, $^2J_{FF}$ = 160.1 Hz, 1F); 20.48 (d_{AB}, $^2J_{FF}$ = 160.1 Hz, 1F).

Methyl *N*-(*tert*-butyloxycarbonyl)-2-(chlorodifluoromethyl)phenylalaninate (20c): yield 80%; mp 62−63 °C. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H); 3.46 (d, $^2J_{HH}$ = 12.6 Hz, 1H); 3.86 (s, 3H); 4.27 (d, $^2J_{HH}$ = 12.6 Hz, 1H); 5.72 (s, 1H); 7.22 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 28.72; 33.79; 54.23; 72.07 (t, $^2J_{CF}$ = 25.1 Hz); 80.97; 127.96; 128.87; 129.32 (t, $^1J_{CF}$ = 307.4 Hz); 130.53, 134.45; 153.82, 167.80. ^{19}F NMR ($CDCl_3$) δ 19.29 (d_{AB}, $^2J_{FF}$ = 160.0 Hz, 1F); 20.63 (d_{AB}, $^2J_{FF}$ = 160.0 Hz, 1F).

Methyl *N*-(benzyloxycarbonyl)-2-(bromodifluoromethyl)alaninate (21a): yield 78%; bp 120−122 °C/0.05 Torr. ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H); 3.82 (s, 3H); 5.12 (s, 2H); 5.68 (br s, 1H); 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.95; 53.82; 67.51 (t, $^2J_{CF}$ = 31 Hz); 67.81; 123.10 (t, $^1J_{CF}$ = 317 Hz); 128.26; 128.42; 128.62; 135.80; 154.21; 167.40. ^{19}F NMR ($CDCl_3$) δ 22.21 (d_{AB}, $^2J_{FF}$ = 161.0 Hz, 1F); 23.82 (d_{AB}, $^2J_{FF}$ = 161.0 Hz, 1F).

Methyl *N*-(benzyloxycarbonyl)-2-(bromodifluoromethyl)phenylalaninate (21b): yield 68%; mp 61−63 °C. ^{1}H NMR ($CDCl_3$) δ 3.44 (d, $^2J_{HH}$ = 13.6 Hz, 1H); 3.85 (s, 3H); 4.29 (d, $^2J_{HH}$ = 13.6 Hz, 1H); 5.07 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 5.27 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 6.03 (s, 1H); 7.19 (m, 5H); 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 33.26; 54.48; 67.55; 73.54 (t, $^2J_{CF}$ = 22.8 Hz); 123.41 (t, $^1J_{CF}$ = 321.8 Hz); 128.06; 128.62; 128.83; 129.00; 129.08; 130.37; 134.08; 136.67; 154.42; 167.75. ^{19}F NMR ($CDCl_3$) δ 25.40 (d_{AB}, $^2J_{FF}$ = 156.5 Hz, 1F); 27.56 (d_{AB}, $^2J_{FF}$ = 156.5 Hz, 1F). MS (EI, *m*/*z*) 441 (M^+); 350 (5); 211 (13); 151 (12); 91 (100).

Methyl *N*-(benzyloxycarbonyl)-2-(bromodifluoromethyl)leucinate (21c): yield 63%; oil. ^{1}H NMR ($CDCl_3$) δ 0.79 (d, $^2J_{HH}$ = 6.6 Hz, 3H); 0.95 (d, $^2J_{HH}$ = 6.1 Hz, 3H); 1.63 (m, 1H); 2.03 (m, 1H); 2.93 (m, 1H); 3.87 (s, 3H); 5.12 (m, 2H); 6.18 (s, 1H); 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 21.87; 23.55; 24.54; 35.76; 53.92; 67.01; 71.54 (t, $^2J_{CF}$ = 22.9 Hz); 123.69 (t, $^1J_{CF}$ = 322.3 Hz); 128.16; 128.29; 128.58; 136.17; 153.56; 168.67. ^{19}F NMR ($CDCl_3$) 24.00 (d_{AB}, $^2J_{FF}$ = 155 Hz, 1F); 26.49 (d_{AB}, $^2J_{FF}$ = 155 Hz, 1F).

Methyl *N*-(benzyloxycarbonyl)-2-(bromodifluoromethyl)-2-phenylglycinate (21d): yield 62%; mp 85−86 °C. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H); 5.11 (s, 2H); 6.06 (s, 1H); 7.40 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 54.26; 68.11; 72.72 (t, $^2J_{CF}$ = 21.7 Hz); 124.21 (t, $^1J_{CF}$ = 321.0 Hz); 127.64, 128.80; 128.90; 129.07; 129.12; 129.90; 133.37; 136.22; 154.55; 166.72. ^{19}F NMR ($CDCl_3$) δ 26.42 (d_{AB}, $^2J_{FF}$ = 159.0 Hz, 1F); 28.16 (d_{AB}, $^2J_{FF}$ = 159.0 Hz, 1F). MS (EI, *m*/*z*) 427 (M^+); 254 (5); 199 (7); 108 (20); 91 (100).

Methyl-2-[*N*-(benzyloxycarbonyl)amino]-2-(bromodifluoromethyl)-4-pentenoate (21e): yield 61%; oil. ^{1}H NMR ($CDCl_3$) δ 2.95 (m, 1H); 3.73 (m, 1H); 3.87 (s, 3H); 5.09 (m, 1H); 5.14 (m, 2H); 5.16 (m, 1H); 5.55 (m, 1H); 6.03 (s, 1H); 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 32.74; 54.12; 67.12; 71.64 (t, $^2J_{CF}$ = 23.0 Hz); 120.90; 122.76 (t, $^1J_{CF}$ = 320.4 Hz); 128.16; 128.31; 128.59; 130.09; 136.05; 153.61; 167.40. ^{19}F NMR ($CDCl_3$) δ 24.21 (d_{AB}, $^2J_{FF}$ = 157.3 Hz, 1F); 26.16 (d_{AB}, $^2J_{FF}$ = 157.3 Hz, 1F).

Methyl *N*-(*tert*-butyloxycarbonyl)-2-(bromodifluoromethyl)alaninate (21f): yield 80%; mp 52−53 °C. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H); 1.85 (s, 3H); 3.83 (s, 3H); 5.29 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 20.03; 28.62; 53.95; 67.88 (t, $^2J_{CF}$ = 22.2 Hz); 81.51; 123.92 (t, $^1J_{CF}$ = 316.6 Hz); 154.08; 167.93. ^{19}F NMR ($CDCl_3$) δ 22.51 (d_{AB}, $^2J_{FF}$ = 162.0 Hz, 1F); 23.89 (d_{AB}, $^2J_{FF}$ = 162.0 Hz, 1F).

Methyl *N*-(*tert*-butyloxycarbonyl)-2-(bromodifluoromethyl)phenylalaninate (21g): yield 86%; mp 66−67 °C. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H); 3.44 (d, $^2J_{HH}$ = 12.0 Hz, 1H); 3.86 (s, 3H); 4.28 (d, $^2J_{HH}$ = 12.0 Hz, 1H); 5.74 (s, 1H); 7.22 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 28.29; 33.01; 53.84; 72.88 (t, $^2J_{CF}$ = 22.6 Hz); 80.52; 123.28 (t, $^1J_{CF}$ = 322.3 Hz); 127.51; 128.42; 130.03; 134.01; 153.30; 167.45. ^{19}F NMR ($CDCl_3$) δ 25.79 (d_{AB}, $^2J_{FF}$ = 155.1 Hz, 1F); 27.81 (d_{AB}, $^2J_{FF}$ = 155.1 Hz, 1F).

Reduction of Bromo Derivative 14a with *n*-Bu_3SnH. Freshly prepared *n*-Bu_3SnH (13.6 g, 46.7 mmol) was added to a stirred solution of **14a** (12.0 g, 36 mmol) in THF (100 mL) over a period of 10 min. During the addition, the reaction warmed up to 50 °C. The mixture was heated to reflux for 1 h to complete the reaction. THF was removed under reduced pressure. The residue was redissolved in ether (80 mL) and treated with a saturated aqueous solution of KF (50 mL) for 0.5 h. Precipitated *n*-Bu_3SnF was filtered off. The aqueous layer was separated and extracted with ether (2 × 20 mL). The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was recrystallized from $CHCl_3$/hexanes to give 5.6 g of pure **12a**. The mother liquor was evaporated and purified by flash chromatography (SiO_2, EtOAc/hexanes) to give further 2.0 g (total yield 75%) of **12a**, whose spectral and analytical data were identical with those reported above. Compound **12b** was obtained in the same manner from bromo derivative **14b** in 83% yield.

Reduction of Bromo Derivative 21a with *n*-Bu_3SnH. Freshly prepared *n*-Bu_3SnH (0.65 g, 2.2 mmol) was added to a stirred solution of **21a** (0.62 g, 1.7 mmol) in THF (10 mL). The mixture was heated to reflux until TLC analysis indicated completion, and workup was done as above. Purification by flash chromatography (SiO_2, EtOAc/hexanes) gave 0.27 g (66%) of pure **19a**. Compounds **19b**−**d** were obtained in the same manner from bromo derivatives **21b**−**d**, respectively.

Methyl *N*-(benzyloxycarbonyl)-2-(difluoromethyl)alaninate (19a): yield 56%; oil. ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3H); 3.80 (s, 3H); 5.10 (s, 2H); 5.46 (s, 1H); 6.22 (t, $^2J_{HF}$ = 56.0 Hz, 1H); 7.36 (s, 5H). ^{13}C NMR ($CDCl_3$) δ 17.30; 53.68; 61.64 (t, $^2J_{CF}$ = 22.5 Hz); 67.76; 113.82 (t, $^1J_{CF}$ = 248.9 Hz); 128.61; 128.84; 129.07; 136.27; 155.31; 170.23. ^{19}F NMR ($CDCl_3$) δ −52.98 (dd_{ABX}, $^2J_{FF}$ = 279.0 Hz, $^2J_{HF}$ = 56.0 Hz, 1F); −50.95 (dd_{ABX}, $^2J_{FF}$ = 279.0 Hz, $^2J_{HF}$ = 56.0 Hz, 1F).

Methyl *N*-(benzyloxycarbonyl)-2-(difluoromethyl)phenylalaninate (19b): yield 84%; mp 59−60 °C. ^{1}H NMR ($CDCl_3$) δ 3.29 (d, $^2J_{HH}$ = 13.3 Hz, 1H); 3.74 (d, $^2J_{HH}$ = 13.3 Hz, 1H); 3.86 (s, 3H); 5.06 (d_{AB}, $^2J_{HH}$ = 12.4 Hz, 1H); 5.23 (d_{AB}, $^2J_{HH}$ = 12.4 Hz, 1H); 5.74 (s, 1H); 6.44 (t, $^2J_{HF}$ = 55.3 Hz, 1H); 7.10 (m, 5H); 7.44 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 35.41; 53.87; 66.85 (t, $^2J_{CF}$ = 22.1 Hz); 67.55; 113.87 (t, $^1J_{CF}$ = 250.9 Hz); 127.97; 128.61; 128.77; 128.56; 129.09; 130.34; 134.10; 136.58; 155.17; 168.69. ^{19}F NMR ($CDCl_3$) δ −50.20 (m, 2F). MS (EI, *m*/*z*) 363 (M^+); 272 (10); 212 (23); 51 (10); 91 (100).

Methyl *N*-(benzyloxycarbonyl)-2-(difluoromethyl)leucinate (19c): yield 61%; oil. ^{1}H NMR ($CDCl_3$) δ 0.80 (d, $^3J_{HH}$ = 6.6 Hz, 3H); 0.92 (d, $^2J_{HH}$ = 6.6 Hz, 3H); 1.61 (m, 1H); 1.85 (m, 1H); 2.48 (m, 1H); 3.85 (s, 3H); 5.10 (s, 2H); 6.00 (s, 1H); 6.23 (t, $^2J_{HF}$ = 55.7 Hz); 7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.71; 24.11; 24.29; 37.63; 53.82; 65.31 (t, $^2J_{CF}$ = 21.3 Hz); 67.45; 114.13 (t, $^1J_{CF}$ = 251.5 Hz); 128.55; 128.77; 129.05; 136.53; 154.85; 170.10. ^{19}F NMR ($CDCl_3$) δ −51.28 (dd_{ABX}, $^2J_{FF}$ = 276.0 Hz, $^2J_{HF}$ = 55.7 Hz, 1F); −50.17 (dd_{ABX}, $^2J_{FF}$ = 276.0 Hz, $^2J_{HF}$ = 55.7 Hz, 1F).

Methyl *N*-(benzyloxycarbonyl)-2-(difluoromethyl)phenylglycinate (19d): yield 60%; mp 83−85 °C. ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H); 5.11 (s, 2H); 5.93 (s, 1H); 6.72 (t, $^2J_{HF}$ = 56.0 Hz, 1H); 7.39 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 53.90; 67.63 (t, $^2J_{CF}$ = 22.6 Hz); 67.95; 113.42 (t, $^1J_{CF}$ = 249.2 Hz); 127.21; 128.65; 128.86; 129.07; 129.36; 129.73; 135.57; 136.27; 155.52; 169.30. ^{19}F NMR ($CDCl_3$) δ −50.44 (dd_{ABX}, $^2J_{FF}$ = 281.2 Hz, $^2J_{HF}$ = 56.0 Hz, 1F); −47.99 (dd_{ABX}, $^2J_{FF}$ = 281.2 Hz, $^2J_{HF}$ = 56.0 Hz, 1F). MS (EI, *m*/*z*) 349 (M^+); 254 (5); 180 (7); 108 (22); 91 (100).

General Procedure for the Saponification of Amino Esters 19a−c, 20a,b, and 21a. A solution of an α-amino acid ester (2 mmol) in ether (20 mL) was stirred with a 1:1 mixture of 1 N aqueous KOH/MeOH (15 mL) for 12 h (method A) or with 10 mmol of $LiOH·H_2O$ in MeOH/water (3:1) for 15 h at 5 °C (method B). The reaction mixture was concentrated to approximately 7 mL, acidified with 2 N HCl to pH 1, and extracted twice with ether (25 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by recrystallization from $CHCl_3$/hexanes.

***N*-(Benzyloxycarbonyl)-2-(difluoromethyl)alanine (22a)** (method A): yield 97%; mp 79−81 °C. ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3H); 5.13 (s, 2H); 5.50 (br s, 1H); 6.25 (t, $^2J_{HF}$ = 56.0 Hz, 1H); 7.36 (m, 5H); 7.63 (br s, 1 H). ^{13}C NMR ($CDCl_3$) δ 17.23; 61.47 (t, $^2J_{CF}$ = 23.1 Hz); 68.29; 113.56 (t, $^1J_{CF}$ = 249.0 Hz); 128.68; 128.96; 129.12; 135.88; 155.93; 174.18. ^{19}F NMR ($CDCl_3$) δ −53.16 (dd_{ABX}, $^2J_{FF}$ = 282.1 Hz, $^2J_{HF}$ = 56.0 Hz, 1F); −51.24 (dd_{ABX}, $^2J_{FF}$ = 282.1 Hz, $^2J_{HF}$ = 56.0 Hz, 1F).

***N*-(Benzyloxycarbonyl)-2-(difluoromethyl)phenylalanine (22b)** (method A): yield 91%; mp 100−101 °C. ^{1}H NMR ($CDCl_3$) δ 3.31 (d, $^2J_{HH}$ = 13.8 Hz, 1H); 3.73 (d, $^2J_{HH}$ = 13.8 Hz, 1H); 5.05 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 5.23 (d_{AB}, $^2J_{HH}$ = 12.2 Hz, 1H); 5.65 (s, 1H); 6.45 (t, $^2J_{HF}$ = 55.2 Hz, 1H); 7.20 (m, 10H); 9.21 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 35.06; 66.20 (t, $^2J_{CF}$ = 22.1 Hz); 67.37; 113.26 (t, $^1J_{CF}$ = 251.3 Hz); 127.65; 128.33; 128.47; 128.53; 128.64; 130.00; 133.12; 135.83; 155.00; 171.21. ^{19}F NMR ($CDCl_3$) δ −50.37 (m, 2F).

***N*-(Benzyloxycarbonyl)-2-(difluoromethyl)leucine (22c)** (method A): yield 80%; mp 127−129 °C.^{1}H NMR ($CDCl_3$) δ 0.87 (d, $^3J_{HH}$ = 5.9 Hz, 3H); 0.93 (d, $^3J_{HH}$ = 5.9 Hz, 3H); 1.70 (m, 1H); 1.90 (m, 1H); 2.45 (m, 1H); 5.12 (s, 2H); 5.90 (s, 1H); 6.27 (t, $^2J_{HF}$ = 56.2 Hz, 1H); 7.05 (br s, 1H); 7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 22.97; 24.03; 24.42; 37.72; 65.23 (t, $^2J_{CF}$ = 20.5 Hz); 67.82; 113.99 (t, $^1J_{CF}$ = 252.6 Hz); 128.63; 128.91; 129.10; 136.19; 155.18; 173.74. ^{19}F NMR ($CDCl_3$) δ −51.36 (dd_{ABX}, $^2J_{FF}$ = 278.2 Hz, $^2J_{HF}$ = 56.2 Hz, 1F); −50.29 (dd_{ABX}, $^2J_{FF}$ = 278.2 Hz, $^2J_{HF}$ = 56.2 Hz, 1F).

***N*-(Benzyloxycarbonyl)-2-(chlorodifluoromethyl)alanine (23a)** (method A): yield 75%; mp 75−77 °C. ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H); 4.26 (br s, 1H); 5.13 (s, 2H); 5.71 (s, 1H); 7.37 (s, 5H). ^{13}C NMR (CD_3OD) δ 20.85; 67.31 (t, $^2J_{CF}$ = 24.2 Hz); 68.18; 129.71; 129.43; 129.82; 131.56 (t, $^1J_{CF}$ = 302.5); 138.10; 157.05; 170.38. ^{19}F NMR ($CDCl_3$) δ 15.90 (d_{AB}, $^2J_{FF}$ = 165.2 Hz, 1F); 16.86 (d_{AB}, $^2J_{FF}$ = 165.2 Hz, 1F).

***N*-(Benzyloxycarbonyl)-2-(chlorodifluoromethyl)phenylalanine (23b)** (method A; reaction time 72 h): yield 93%; mp 138−139 °C. ^{1}H NMR ($CDCl_3$) δ 3.52 (d, $^2J_{HH}$ = 14.4 Hz, 1H); 4.24 (d, $^2J_{HH}$ = 14.4 Hz, 1H); 5.08 (d_{AB}, $^2J_{HH}$ = 12.1 Hz, 1H); 5.24 (d_{AB}, $^2J_{HH}$ = 12.1 Hz, 1H); 5.99 (s, 1H); 7.17 (m, 5H); 7.40 (m, 5H); 8.74 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 33.37; 67.50; 71.56 (t, $^2J_{CF}$ = 24.3 Hz); 127.67; 128.41; 128.42 (t, $^1J_{CF}$ = 307.7 Hz); 128.48; 128.58; 128.64; 130.08; 133.11; 135.80; 154.32; 169.80. ^{19}F NMR ($CDCl_3$) δ 19.24 (d_{AB}, $^2J_{FF}$ = 160.8 Hz, 1F); 20.56 (d_{AB}, $^2J_{FF}$ = 160.8 Hz, 1F).

***N*-(Benzyloxycarbonyl)-2-(bromodifluoromethyl)alanine (24a)** (method B): yield 61%; oil. ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3H); 5.12 (s, 2H); 5.88 (br s, 1H); 7.35 (s, 5H); 8.63 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.69; 67.87 (t, $^2J_{CF}$ = 22.0 Hz); 68.25; 123.62 (t, $^1J_{CF}$ = 317.1 Hz); 128.78; 129.00; 129.15; 135.89; 155.34; 170.86. ^{19}F NMR ($CDCl_3$) δ 22.71 (d_{AB}, $^2J_{FF}$ = 162.6 Hz, 1F); 24.01 (d_{AB}, $^2J_{FF}$ = 162.6 Hz, 1F).

Hydrogenation. A mixture of **22a** (0.135 g, 0.5 mmol) and 10% Pd/C (0.4 g) in methanol (25 mL) was stirred for 14 h under an atmosphere of hydrogen. The catalyst was filtered

off, and the filtrate was concentrated under reduced pressure. The remaining solid was triturated with ether to give 72 mg of **25a**. Purification was performed by sublimation.

2-(Difluoromethyl)alanine (25a): yield 99%; mp 256 °C dec. ^{1}H NMR (D_2O) δ 1.46 (s, 3H); 6.17 (t, $^2J_{HF}$ = 53.0 Hz, 1H). ^{13}C NMR (D_2O) δ 16.65; 61.73 (t, $^2J_{CF}$ = 18.3 Hz); 114.92 (t, $^1J_{CF}$ = 245.2 Hz); 170.49. ^{19}F NMR (D_2O) δ −55.44 (dd_{ABX}, $^2J_{FF}$ = 279.1 Hz, $^2J_{HF}$ = 53.0 Hz, 1F); −49.18 (dd_{ABX}, $^2J_{FF}$ = 279.1 Hz, $^2J_{HF}$ = 53.0 Hz, 1F).

Compounds **25b**,**c**, **26a**,**b** were obtained in the same manner starting from Cbz-derivatives **22b**,**c**, **24a**, respectively.

2-(Difluoromethyl)phenylalanine (25b): yield 89%; mp 220 °C. ^{1}H NMR (D_2O) δ 2.97 (d, $^2J_{HH}$ = 14.3 Hz, 1H); 3.36 (d, $^2J_{HH}$ = 14.3 Hz, 1H); 6.29 (t, $^2J_{HF}$ = 53.0 Hz, 1H); 7.23 (m, 5H). ^{13}C NMR (D_2O) δ 36.65; 66.87 (t, $^2J_{CF}$ = 19.2 Hz); 115.37 (t, $^1J_{CF}$ = 249.5 Hz); 128.42; 129.25; 130.22; 132.10; 169.23. ^{19}F NMR (D_2O) δ −54.32 (dd_{ABX}, $^2J_{FF}$ = 280.3 Hz, $^2J_{HF}$ = 53.0 Hz, 1F); −49.34 (dd_{ABX}, $^2J_{FF}$ = 280 Hz, $^2J_{HF}$ = 53.0 Hz, 1F).

2-(Difluoromethyl)leucine (25c): yield 95%; mp 228−229 °C. ^{1}H NMR (D_2O) δ 0.75 (d, $^3J_{HH}$ = 6.4 Hz, 3H); 0.79 (d, $^3J_{HH}$ = 6.4 Hz, 3H); 1.65 (m, 3H); 6.06 (t, $^2J_{HF}$ = 53.8 Hz, 1H). ^{13}C NMR (D_2O) δ 21.69; 23.10; 23.69; 39.01; 65.60 (t, $^2J_{CF}$ = 20.7 Hz); 115.66 (t, $^1J_{CF}$ = 246.1 Hz); 170.20. ^{19}F NMR (D_2O) δ −55.13 (dd_{ABX}, $^2J_{FF}$ = 276.1 Hz, $^2J_{HF}$ = 53.8 Hz, 1F); −49.15 (dd_{ABX}, $^2J_{FF}$ = 276.1 Hz, $^2J_{HF}$ = 53.8 Hz, 1F).

2-(Chlorodifluoromethyl)alanine (26a): yield 71%; mp > 250 °C. ^{1}H NMR (D_2O) δ 1.56 (s, 3H). ^{13}C NMR (D_2O) δ 20.15; 69.66 (t, $^2J_{CF}$ = 25.1 Hz); 130.00 (t, $^1J_{CF}$ = 297.8 Hz); 171.16. ^{19}F NMR (D_2O) δ 15.55 (d_{AB}, $^2J_{FF}$ = 170.9 Hz, 1F); 16.53 (d_{AB}, $^2J_{FF}$ = 170.9 Hz, 1F).

2-(Chlorodifluoromethyl)phenylalanine (26b): yield 93%; mp 188−189 °C. ^{1}H NMR (D_2O) δ 3.25 (d, $^2J_{HH}$ = 14.3 Hz, 1H); 3.76 (d, $^2J_{HH}$ = 14.3 Hz, 1H); 7.41 (m, 5H). ^{13}C NMR (D_2O) δ 36.21; 71.39 (t, $^2J_{CF}$ = 22.9 Hz); 127.13 (t, $^1J_{CF}$ = 298.7 Hz); 128.68; 129.39; 130.43; 131.42; 166.99. ^{19}F NMR (D_2O) δ 17.33 (s, 2F).

Procedure for Direct Hydrolysis of 19e, 20c. A solution of Boc-protected amino acid ester **19e** (0.5 g, 1.5 mmol) in 6 N HCl (15 mL) was heated at 80 °C for 10 h. The reaction mixture was evaporated under reduced pressure, dissolved in EtOH (10 mL), and stirred with an excess of propylene oxide for 10 h. The volatiles were removed under reduced pressure to give 0.27 g (83%) of amino acid **25b**. Purification was performed by sublimation (100 °C, 0.1 Torr). Compound **26b** was obtained in the same manner starting from Boc-derivative **20c** in 75% yield. NMR spectra of the compounds **25b** and **26b** were identical with those reported above.

Methyl 2-(bromodifluoromethyl)alaninate (27a). A 10 mL volume of TFA was added in one portion to a solution of **21f** (1.0 g, 2.86 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 15 min at 25 °C, volatiles were evaporated and the residue was dissolved in ether and washed with $NaHCO_3$. The aqueous solution was extracted with ether (2 × 20 mL), and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 0.57 g (80%) of **27a** as an oil. ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H); 2.02 (s, 2H); 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 20.93; 53.32; 66.89 (t, $^2J_{CF}$ = 21.7 Hz); 125.94 (t, $^1J_{CF}$ = 316.3 Hz); 169.70. ^{19}F NMR ($CDCl_3$) δ 20.46 (d_{AB}, $^2J_{FF}$ = 157.2 Hz, 1F); 21.89 (d_{AB}, $^2J_{FF}$ = 157.2 Hz, 1F).

Methyl 2-(bromodifluoromethyl)phenylalaninate (27b) (procedure see **27a**): yield 85%; oil. ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 2H); 2.97 (d, $^2J_{HH}$ = 13.0 Hz, 1H); 3.51 (d, $^2J_{HH}$ = 13.0 Hz, 1H); 3.78 (s, 3H); 7.22 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 39.28; 53.67; 71.66 (t, $^2J_{FC}$ = 20.9 Hz); 125.74 (t, $^1J_{FC}$ = 318.8 Hz); 128.22; 129.17; 130.76; 134.21; 169.79. ^{19}F NMR ($CDCl_3$) δ 21.47 (d_{AB}, $^2J_{FF}$ = 156.1 Hz, 1F); 23.96 (d_{AB}, $^2J_{FF}$ = 156.1 Hz, 1F).

2-(Bromodifluoromethyl)alanine Hydrochloride (28a). A 0.3 g (1.3 mmol) amount of **27a** was treated with 7.0 mmol of LiOH·H_2O in MeOH/water (3:1) for 72 h at 10 °C. Methanol was evaporated under reduced pressure. The residue was adjusted to pH 1 with 2 N HCl and evaporated to give 0.4 g of **28a**·*x*LiCl. ^{1}H NMR (D_2O) δ 1.79 (s, 3H). ^{13}C NMR (D_2O) δ 18.65; 68.25 (t, $^2J_{FC}$ = 21.8 Hz); 121.48 (t, $^1J_{FC}$ = 311.4 Hz); 169.68. ^{19}F NMR (D_2O) δ 21.43 (d_{AB}, $^2J_{FF}$ = 171.7 Hz, 1F); 22.31 (d_{AB}, $^2J_{FF}$ = 171.7 Hz, 1F).

2-(Bromodifluoromethyl)phenylalanine hydrochloride (28b) was obtained in analogy to **28a** as a mixture with LiCl. ^{1}H NMR (D_2O) δ 3.07 (d, $^2J_{HH}$ = 16.6 Hz, 1H); 3.58 (d, $^2J_{HH}$ = 16.6 Hz, 1H); 7.25 (m, 5H).^{13}C NMR (D_2O) δ 36.45; 72.47 (t, $^2J_{FC}$ = 22.1 Hz); 119.75 (t, $^1J_{FC}$ = 312.4 Hz); 128.83; 129.51; 130.53; 131.34; 167.06. ^{19}F NMR (D_2O) δ 22.49 (d_{AB}, $^2J_{FF}$ = 177.0 Hz, 1F); 23.46 (d_{AB}, $^2J_{FF}$ = 177.0 Hz, 1F).

Methyl 2-(difluoromethyl)alaninate hydrobromide (29·HBr) was obtained from **21a** by hydrogenation (procedure see **25a**) and purified by recrystallization from $CHCl_3$: yield 77%; mp 124−126 °C. ^{1}H NMR (acetone-d_6) δ 1.07 (s, 3H); 3.95 (s, 3H); 6.71 (t, $^2J_{HF}$ = 54.1 Hz, 1H). ^{13}C NMR (acetone-d_6) δ 16.72; 54.55; 62.58 (t, $^2J_{CF}$ = 23.7 Hz); 114.48 (t, $^1J_{CF}$ = 250.2 Hz); 166.96. ^{19}F NMR (acetone-d_6) δ −47.40 (dd_{ABX}, $^2J_{FF}$ = 286.8 Hz, $^2J_{HF}$ = 54.1 Hz, 1F); −45.72 (dd_{ABX}, $^2J_{FF}$ = 286.8 Hz, $^2J_{HF}$ = 54.1 Hz, 1F).

Synthesis of Methyl *N*-(*tert*-Butyloxycarbonyl)-L-phenylalanyl-*ambo*-α-(difluoromethyl)alaninate (30a,b). A solution of Boc-Phe-OH (0.26 g, 1.0 mmol) in dry THF (5 mL) was cooled to −15 °C and neutralized with *N*-methylmorpholine (0.10 g, 1.0 mmol). Isobutyl chloroformate (0.16 g, 1.2 mmol) was added. After 10 min at −15 °C, a mixture of methyl α-(difluoromethyl)alaninate hydrobromide (0.23 g, 1.0 mmol) and *N*-methylmorpholine (0.10 g, 1.0 mmol) in DMF (5 mL) was added. The reaction mixture was stirred for 4 h at −15 °C and then warmed up to rt. The salts were removed by filtration and washed with THF. The solution was concentrated under reduced pressure and the residue partitioned between water (20 mL) and ethyl acetate (30 mL). The organic layer was washed with 0.5 N $KHSO_4$ (20 mL), water (20 mL), 1 N $NaHCO_3$ (20 mL), and water (20 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded 0.24 g (59%) of **30** as a mixture of diastereomers. The diastereomers were separated by flash chromatography (SiO_2, EtOAc/hexanes). Diastereomer 1: mp 158−158.5 °C; $[\alpha]^{21}_D$ = −36.4 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H); 1.46 (s, 3H); 3.01 (d, $^2J_{HH}$ = 7.0 Hz, 2H); 3.75 (s, 3H); 4.33 (m, 1H); 5.10 (br s, 1H); 6.19 (t, $^2J_{HF}$ = 55.9 Hz, 1H); 6.72 (br s, 1H); 7.10−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.19; 28.22; 37.78; 53.04; 55.46; 60.82 (t, $^2J_{CF}$ = 23.8 Hz); 80.60; 112.84 (t, $^2J_{CF}$ = 248.0 Hz); 127.08; 128.72; 129.39; 136.40; 155.58; 169.35; 171.38. ^{19}F NMR ($CDCl_3$) δ −53.27 (dd_{ABX}, $^2J_{FF}$ = 281.7 Hz, $^2J_{HF}$ = 55.9 Hz, 1F); −50.41 (dd_{ABX}, $^2J_{FF}$ = 281.7 Hz, $^2J_{HF}$ = 55.9 Hz, 1F). Diastereomer 2: mp 120−121 °C; $[\alpha]^{21}_D$ = −57.1 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H); 1.48 (s, 3H); 2.90−3.05 (m, 2H); 3.75 (s, 3H); 4.38 (m, 1H); 5.18 (d, $^2J_{HH}$ = 8.0 Hz, 1H); 6.21 (t, $^2J_{HF}$ = 55.9 Hz, 1H); 6.92 (br s, 1H); 7.10−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 16.52; 28.66; 38.32; 53.49; 56.00; 61.34 (t, $^2J_{CF}$ = 23.8 Hz); 81.05; 113.25 (t, $^2J_{CF}$ = 248.0 Hz); 127.50; 129.12; 129.79; 136.79; 156.06; 169.96; 171.98. ^{19}F NMR ($CDCl_3$) δ −53.12 (dd_{ABX}, $^2J_{FF}$ = 281.7 Hz, $^2J_{HF}$ = 55.9 Hz, 1F); −50.13 (dd_{ABX}, $^2J_{FF}$ = 281.7 Hz, $^2J_{HF}$ = 55.9 Hz, 1F).

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Supporting Information Available: Microanalytical data (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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