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Synthesis of New δ-(Polyfluoroalkyl)-δ-hydroxy-α-amino Acids

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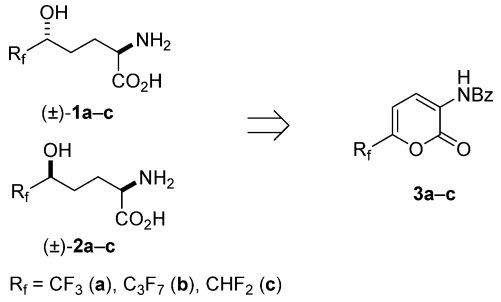
New δ-(polyfluoroalkyl)-δ-hydroxy-α-amino acids were synthesized from the corresponding starting 3-(benzoylamino)-6-(polyfluoroalkyl)-2*H*-pyran-2-ones. The key step of the synthesis was the hydrogenation of the pyrone ring. Stereoselectivity and yields depended dramatically on the reaction conditions and the nature of the polyfluoroalkyl group. Various conditions were used for the preparation of both mixtures of diastereomers and pure diastereomers of the target amino acids. The obtained δ-(polyfluoroalkyl)-δ-hydroxy-α-amino acids are of interest as analogues of 2-amino-5-hydroxyvaleric acid and glutamic acid.

Introduction

Fluorinated analogues of naturally occurring substances play an important role in the design of new biologically active compounds.[1] In this field, fluorinated α-amino acids represent one of the most popular classes of compounds that are particularly interesting as potential reversible or irreversible inhibitors of enzymes. Moreover, these compounds are useful as building blocks for peptides, to modify their properties, and as starting materials in fluoroorganic synthesis.[1,2] Although a large number of diverse fluorinated amino acids have been synthesized during the past 50 years, research interest has not decreased, and each new synthesized fluorinated amino acid attracts considerable attention.[3]

In this article we present the synthesis of the new fluoroalkylated δ-hydroxy-α-amino acids **1** and **2** (Scheme 1). These compounds can be considered polyfluoroalkyl analogues of 2-amino-5-hydroxyvaleric acid, which plays an important role in proline biosynthesis.[4] Moreover, compounds **1** and **2** can also be regarded as glutamic acid analogues, because the $CF_3CH(OH)$ unit is in some cases a bioisostere of the CO_2H group (high acidity; C–CF_3 is substantially isopolar with the C=O group[5]). The properties of the α-(trifluoromethyl) alcohol moiety as a mimetic of the carboxylic acid function are widely used in the design of numerous efficient inhibitors of proteolytic enzymes.[6] By way of example, the amino acids **1a** and **2a** are of interest as potential modulators of processes involving 2-amino-5-hydroxyvaleric acid or glutamic acid as substrates.



Scheme 1. Target amino acids **1a**–**c** and **2a**–**c** and their precursor pyrones **3a**–**c**.

Some fluorinated glutamate analogues have successfully been used to study glutamate hydrolase (GH) activity,[7] to modulate folate poly-γ-glutamate biosynthesis, and to prepare methotrexate (MTX) analogues, which have been shown to be inhibitors of dihydrofolate reductase (DHFR).[8] Because of the great interest in glutamic acid analogues, compounds **1a** and **2a**, as well as other fluorinated analogues such as **1b**–**c** and **2b**–**c**, are interesting as potential enzyme modulators.

We have previously reported the synthesis[9] and reactivities[9,10] of pyrones **3**, which in this paper have served as convenient precursors of the target amino acids **1** and **2**. The pyrones **3** have the same carbon skeletons and necessary functional groups. Obviously, their hydrogenation and simple functional-group transformation should be the most efficient approach to compounds **1** and **2**.

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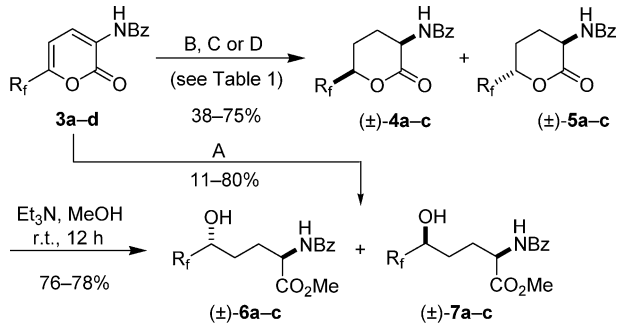
Results and Discussion

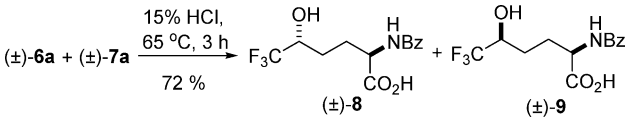
Catalytic reduction of double bonds of pyrones with subsequent ring-opening by nucleophiles is a well-known synthetic protocol.[11] Initially, we used standard conditions ($H_2/PdCl_2$, atmospheric pressure, room temperature, MeOH/Et_3N) for the transformations of pyrones **3a**–**c** (Scheme 2). Accordingly, the first step led to the tetrahydropyrones **4** and **5**, which were transformed into the corresponding benzoylamino acid esters **6** and **7** by methanolysis. The selectivities of the reactions can be easily established from the ^{19}F NMR spectra of the crude product mixtures.



Scheme 2. Reduction of the pyrones **3a**–**3d**.

It has been shown that both the yields and the selectivities of the reactions dramatically depend on the nature of the polyfluoroalkyl group (Table 1, Entries 1–4). In all cases mixtures of diastereomeric benzoylamino acid esters were formed. The stereoselectivity of the reduction of the CF_3-substituted pyrone **3a** was quite low, and the reduction of the C_3F_7-substituted pyrone **3b** did not show any stereoselectivity at all. In contrast, high stereoselectivity was observed in the case of the CHF_2-substituted pyrone **3c**, but several inseparable by-products were also formed, and the isolated yield after column chromatography was low. All attempts to separate the diastereomers **6a/7a** and **6b/7b** from each other by chromatography or crystallization failed.

Careful treatment of a mixture of the CF_3 diastereomers **6a/7a** with 15% HCl (Scheme 3) led to a mixture of the corresponding diastereomeric benzoylamino acids **8** and **9**. Fractional crystallization of the mixture provided the major compound **8** as a pure diastereomer in 43% yield. The correct assignment of structures **6a** and **7a** was confirmed by X-ray analysis of **8** (Figure 1).



Scheme 3. Preparation of diastereomerically pure benzoylamino acid **8**.

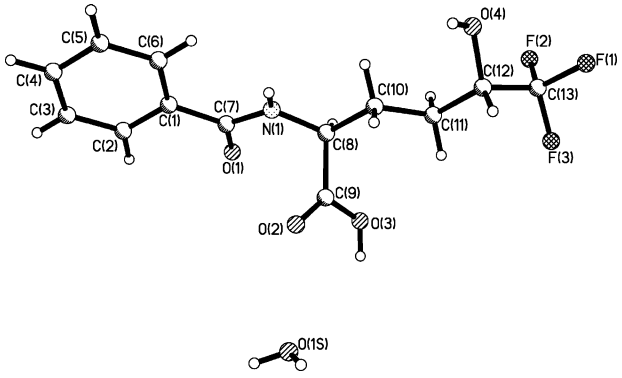


Figure 1. X-ray structure of compound **8** (as monohydrate).

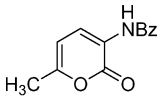
The reduction of the CF_2Cl-substituted pyrone **3d** under the same conditions occurred in a different way (Table 1, Entry 4), with hydrogenation of the pyrone ring being accompanied by transformation of the CF_2Cl group into a CF_2H group. Consequently, the major products were compounds **6c** and **7c**, identical to the products obtained from pyrone **3c**. Compounds **2c** and **10**[9] (Figure 2) were also isolated from the reaction mixture as by-products in 20% and 6% yields, respectively.

From the mixture of **6c** and **7c**, the diastereomerically pure amide **6c** was isolated in 40% yield by fractional crystallization from $CHCl_3$. The structure of **6c** was verified

Table 1. Reduction of the pyrones **3a**–**c**.

Entry	Starting compound	Conditions[a]	Isolated products (ratio)	General yield [%]
1	**3a**	A	**6a/7a** (7:3)	80
2	**3b**	A	**6b/7b** (1:1)	76
3	**3c**	A	**6c/7c** (19:1)	11
4	**3d**	A	**6c/7c** (9:1)	33
5	**3d**	B	**6c/7c** (1:1)	75
6	**3a**	C	**4a**	conversion ca. 10%[b]
7	**3a**	D	**4a**	86
8	**3b**	D	**4b/5b** (17:3)	59
9	**3c**	D	**4c**	38
10	**3d**	D	unresolved mixture	–

[a] For the conditions see Scheme 2. [b] The product was not isolated.



10

Figure 2. By-product **10** derived from the reduction of pyrone **3d** by treatment with $H_2/PdCl_2$, Et_3N, MeOH (Table 1, Entry 4).

by X-ray analysis, which confirms its relative stereochemistry (Figure 3). The X-ray data show that two rotamers (ratio 16:84) with different orientations of the difluoromethyl group exist in the crystal. The configurations of compounds **6a** and **6b** were anticipated to be the same as that of **6c** according to the similar spectroscopic data for these compounds.

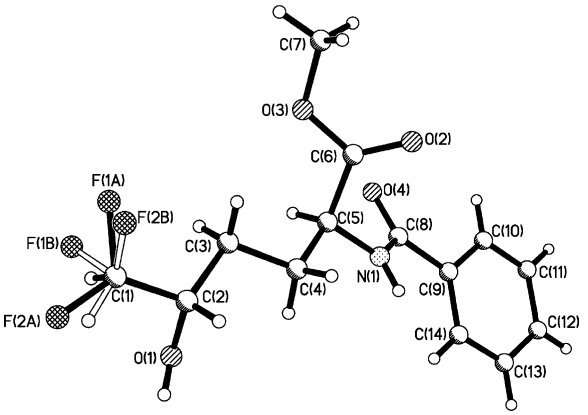


Figure 3. X-ray structure of compound **6c**.

The reduction of the CF_2Cl-substituted pyrone **3d** under forced conditions and without Et_3N (Table 1, Entry 5) proceeded without stereoselectivity, again giving a mixture of the CHF_2-substituted products **6c** and **7c**. This mixture was not separated. It should be noted that the intermediate lactones **4** or **5** were not detected, although Et_3N was not used.

In order to increase the stereoselectivity and/or to allow the separation of the diastereomeric products, we performed the hydrogenation of pyrones **3a**–**c** in aprotic solvents (Table 1, Entries 6–9) and without Et_3N. It was shown that the hydrogenation of compound **3a** in EtOAc (Entry 6) proceeds slowly; after 2 weeks, the degree of conversion was only 10%. In contrast, the reaction of **3a** in THF (under 20 atm pressure, Table 1, Entry 7) proceeded in 2–3 h, and compound **4a** was isolated as a pure diastereomer in 86% yield. Compounds **3b**–**c** were reduced in the same way at 30 atm (Table 1, Entries 8–9). The C_3F_7-substituted pyrone **3b** gave a mixture of the diastereomeric tetrahydropyrones **4b** and **5b**. The major diastereomer **4b** was isolated in 25% yield (based on pyrone **3b**) by fractional crystallization from $CHCl_3/CCl_4$ (3:5). The hydrogenation of the CHF_2-substituted pyrone **3c** led to a complex mixture (as in the case of the reaction in MeOH/Et_3N, Table 1, Entry 3), and the pure diastereomer **4c** was isolated in 38% yield (Table 1, Entry 9). Under the same conditions, the CF_2Cl-substituted pyrone **3d** gave an inseparable mixture of products (Table 1, Entry 10). Compounds **2c** and **10** (among other by-products) were detected in this mixture by NMR spectroscopy, but there was no evidence of compounds **4** or **5**, nor of **6** or **7**.

The configurations of the tetrahydropyrones **4** and **5** were confirmed by NOE experiments (irradiation of 3-C*H*) for compound **4a** (Figure 4). The NOE experiments confirmed an interaction between 3-C*H* and 6-C*H*, which suggests the *cis* orientation of the CF_3 and NHCOPh groups.

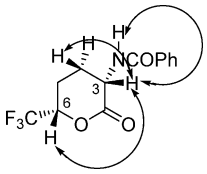
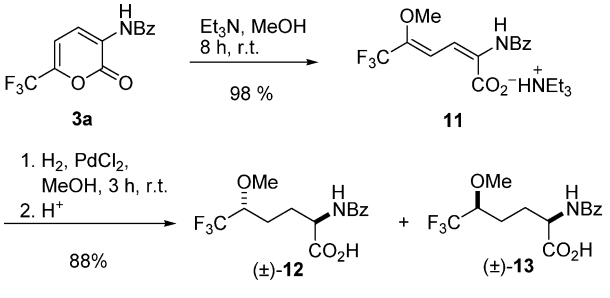


Figure 4. Confirmation of relative configuration of compound **4a** by NOE experiments.

Ring-opening of the diastereomerically pure lactones **4a** and **4b** was easily achieved by treatment with Et_3N/MeOH (see Scheme 2). The products of the reaction were identified as **6a** and **6b**, respectively, from the similarity of their spectroscopic data with those for the compounds obtained by reduction in MeOH/Et_3N. The two-step procedure (hydrogenation under conditions D and ring-opening) thus provided the opportunity to obtain the pure diastereomers **6a** and **6b**.

A different result was obtained on reversing the reaction sequence (i.e., ring-opening and subsequent hydrogenation). Ring-opening of compound **3a** led to the salt **11**, containing a methoxy group adjacent to the CF_3 moiety (Scheme 4). After hydrogenation of **11** under conditions A, an inseparable mixture of the diastereomers **12** and **13** (1:1) was obtained.

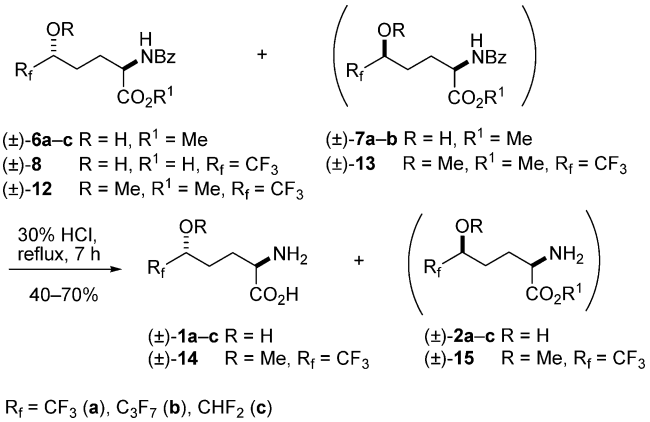


Scheme 4. Preparation of a mixture of diastereomers **12** and **13**.

In summary, conditions A and D (with subsequent ring-opening) gave mixtures of diastereomers **6a/7a** (7:3), **6b/7b** (1:1), and **6c/7c** (9:1), as well as the pure diastereomers **6a**, **6b**, and **6c** by fractional crystallization.

All mixtures of diastereomers and pure diastereomers were easily transformed into the corresponding amino acids (either as mixtures of diastereomers **1a**–**c** and **2a**–**c** or as pure diastereomers **1a**–**c**) by acidic hydrolysis in HCl (30%) at reflux (Scheme 5, Table 2, Entries 1–6). The isolation and purification were performed by ion-exchange chromatography, giving the target compounds in good yields. The

same conditions were used to obtain mixtures of the diastereomeric δ-methoxy-α-amino acids **14** and **15** from the mixture of the benzoylamino acids **12** and **13** (Scheme 5, Table 2, Entry 7).



Scheme 5. Preparation of amino acids **1**, **2**, **14**, and **15**.

Table 2. Deprotection of the benzamides **6a**–**c** and **7a**–**c**.

Entry	Starting materials	Isolated products[a] (ratio)	Overall yield [%]
1	**6a/7a** (7:3)	**1a/2a** (7:3)	45
2	**6b/7b** (1:1)	**1b/2b** (1:1)	47
3	**6a**	**1a**	57
4	**6b**	**1b**	56
5	**6c**	**1c**	43
6	**8**	**1a**	77
7	**12/13** (1:1)	**14/15** (1:1)	28

[a] For the conditions see Scheme 5.

Conclusions

The new δ-(polyfluoroalkyl)-δ-hydroxy-α-amino acids **1** and **2** were prepared from the corresponding starting pyrones **3**. The synthetic pathway included the hydrogenation of pyrones **3** to the tetrahydropyrones **4** with subsequent ring-opening and hydrolysis of the amide and ester functions. The first two steps can also be achieved in a one-pot fashion under conditions A [H_2, $PdCl_2$ (10–20 mol-%), 1 atm, Et_3N/MeOH, room temp., 6 h], but in this case the stereoselectivity was low. The reaction conditions D [H_2, Pd/C (5%), 20–30 atm, THF, room temp., 2 h] are most convenient for the preparation of the diastereomerically pure fluorinated δ-lactones **4**, which were used to synthesize the corresponding pure δ-hydroxy-α-amino acids **1**. The selective preparation of the diastereomers **2**, as well as the synthesis of pure enantiomers of **1** and **2**, is under investigation and will be published in due course.

Experimental Section

General: Melting points are uncorrected. NMR spectra were recorded with a Varian VXR 300 instrument at 300 MHz (^{1}H), 75.4 MHz (^{13}C), or 282 MHz (^{19}F) or with a Bruker Avance DRX instrument at 500 MHz (^{1}H), 126 MHz (^{13}C), or 470 MHz (^{19}F) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. IR spectra were recorded with a Specord M-80 spectrometer. The reaction progress was monitored by TLC (silica gel 60 F254 plates, Merck). Column chromatography was carried out with silica gel 60 (Merck No. 109385, particle size 0.040–0.063). Ion-exchange chromatography was performed on Amberlite IR-120 by standard techniques.[12]

Starting Materials: All starting materials were of the highest commercial quality and were used without further purification. The pyrones **3a**–**d** were prepared according to our previously published procedures.[9]

Hydrogenation of Pyrones 3a–d

Conditions A: Hydrogen was passed through a mixture of the corresponding pyrone (**3a**–**c**, 0.5 mmol), $PdCl_2$ (17 mg, 0.1 mmol), and triethylamine (76 mg, 0.75 mmol) in dry methanol (20 mL) for ca. 6 h. The reaction progress was monitored by TLC. After the hydrogenation was complete, the solid residue was filtered off, and the solvent was evaporated in vacuo. The residue was crystallized or purified by column chromatography. Isolated yields are given in Table 1 (Entries 1–4). In the case of hydrogenation of pyrone **3d**, compounds **2c** and **10** were also isolated [column chromatography, hexane/EtOAc (2:1)] from the reaction mixture as by-products in 20% and 6% yields, respectively. Spectral data are identical to those described in a previous paper.[9]

Methyl 2-(Benzoylamino)-6,6,6-trifluoro-5-hydroxyhexanoate [Mixture of Diastereomers 6a/7a (7:3)]: These compounds were obtained from pyrone **3a** (141 mg) by the General Procedure and were purified by crystallization from $CHCl_3$/hexane (1:3). The diastereomeric ratio was not changed by recrystallization. Yield: 127 mg (80%), white solid, m.p. 143–144 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 1.79 (m, 2 H, CH_2), 2.12 (m, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 4.12 (m, 1 H, CF_3C*H*), 4.74 (m, 1 H, C*H*NH), 5.41 (br. s, 1 H, O*H*), 7.51 (m, 3 H, Ph), 7.93 (m, 2 H, Ph), 8.04 (br. d, $J_{H,H}$ = 8.4 Hz, 1 H, N*H*) ppm. ^{19}F NMR (282 MHz, [D$_6$]acetone): δ = –79.12 (d, $J_{F,H}$ = 9.2 Hz, CF_3 group of compound **7a**), –79.19 (d, $J_{F,H}$ = 9.2 Hz, CF_3 group of compound **6a**) ppm; integration of these signals showed a 7:3 ratio of **6a/7a**. $C_{14}H_{16}F_3NO_4$ (319.1): calcd. C 52.67, H 5.05, N 4.39; found C 52.70, H 5.03, N 4.40.

Methyl 2-(Benzoylamino)-6,6,7,7,8,8,8-heptafluoro-5-hydroxyoctanoate [Mixture of Diastereomers 6b/7b (1:1)]: These compounds were obtained from pyrone **3b** (191 mg) and were purified by crystallization from $CHCl_3$/hexane (1:2). The ratio of diastereomers did not change after crystallization. Yield: 160 mg (76%), white solid, m.p. 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68–2.32 (m, 4 H, CH_2CH_2), 3.80 (s, 3 H, CH_3 of compound **6b**), 3.82 (s, 3 H, CH_3 of compound **7b**), 4.22 (m, 1 H, CF_2C*H*), 4.87 (m, C*H*NH of compound **6b**), 5.01 (m, C*H*NH of compound **7b** and OH), 7.04 (d, $J_{H,H}$ = 7.4 Hz, N*H* of compound **6b**), 7.08 (d, $J_{H,H}$ = 7.4 Hz, N*H* of compound **7b**), 7.40–7.59 (m, 3 H, Ph), 7.81 (m, 2 H, Ph) ppm. ^{19}F NMR (470 MHz, [D$_6$]DMSO): δ = –81.44 (br. m, 3 F, CF_3), –121.43 (d, $J_{F,F}$ = 287 Hz, CF*F*CF_2CF_3 of compound **7b**), –121.62 (d, $J_{F,F}$ = 283.3 Hz, CF*F*CF_2CF_3 of compound **6b**), –125.35 (d, $J_{F,F}$ = 293.5 Hz, C*F*FCF_3 of compound **7b**), –125.60 (d, $J_{F,F}$ = 293.5 Hz, C*F*FCF_3 of compound **6b**), –127.01 (d, $J_{F,F}$ = 293.5 Hz, CF*F*CF_3 of compound **6b**), –127.35 (d, $J_{F,F}$ = 293.5 Hz, CF*F*CF_3 of compound **7b**), –128.00 (d, $J_{F,F}$ = 278.4 Hz, C*F*FCF_2CF_3 of compound **6b**), –129.48 (d, $J_{F,F}$ = 278.4 Hz, C*F*FCF_2CF_3 of compound **7b**) ppm; integration of these signals showed a 1:1 ratio of **6b/7b**. $C_{16}H_{16}F_7NO_4$ (419.3): calcd. C 45.83, H 3.85, N 3.34; found C 45.80, H 3.87, N 3.38.

Methyl 2-(Benzoylamino)-6,6-difluoro-5-hydroxyhexanoate [Mixture of Diastereomers 6c/7c (19:1 or 9:1)]: These compounds were ob-

tained either from pyrone **3c** (132 mg) or from pyrone **3d** (150 mg) and were purified by column chromatography [EtOAc/hexane (1:2), $R_f \approx 0.3$]. The ratio of diastereomers had not changed after purification. Yield: 17 mg (11%) from pyrone **3c** and 50 mg (33%) from pyrone **3d**, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.59 (m, 1 H, C*H*HCH$_2$), 1.74 (m, 1 H, CH*H*CH$_2$), 2.12 (m, 1 H, CH$_2$C*H*H), 2.14 (m, 1 H, CH$_2$CH*H*), 3.68 (m, CHF$_2$C*H* of compound **7c**), 3.78 (s, C*H*$_3$ of compound **6c**), 3.79 (s, C*H*$_3$ of compound **7c**), 3.82 (m, CHF$_2$C*H* of compound **6c**), 4.85 (m, C*H*NH of compound **6c**), 4.92 (m, C*H*NH of compound **7c**), 5.60 (td, $J_{H,F}$ = 56.1, $J_{H,H}$ = 3.8 Hz, C*H*F$_2$ of compound **6c**), 5.62 (td, $J_{H,F}$ = 56.1, $J_{H,H}$ = 3.8 Hz, C*H*F$_2$ of compound **7c**), 6.90 (d, $J_{H,H}$ = 7.5 Hz, N*H* of compound **6c**), 7.00 (d, $J_{H,H}$ = 7.5 Hz, N*H* of compound **7c**), 7.43 (m, 2 H, Ph), 7.51 (m, 1 H, Ph), 7.78 (m, 2 H, Ph) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –128.37 (ddd, $J_{F,F}$ = 10.1, 286.8, $J_{F,H}$ = 56.1 Hz, CH*F*F of compound **7c**), –122.4 (m, CH*F*F of compound **6c**), –129.58 (m, CHF*F* of compound **6c**), –121.16 (ddd, $J_{F,F}$ = 10.1, 286.8, $J_{F,H}$ = 56.1 Hz, CH*F*F of compound **7c**) ppm; the ratio of signal integrals for compounds **6c/7c** is 19:1 or 9:1, depending on the starting material (**3c** or **3d**, respectively). $C_{14}H_{17}F_2NO_4$ (301.1): calcd. C 55.81, H 5.69, N 4.65; found C 55.78, H 5.70, N 4.62.

Methyl (3*R*,6*R*/3*S*,6*S*)-2-(Benzoylamino)-6,6-difluoro-5-hydroxyhexanoate (6c): This compound was obtained from a mixture of diastereomers **6c/7c** (50 mg) by fractional crystallization from $CHCl_3$. Yield: 20 mg (40%), white solid, m.p. 129–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.59 (m, 1 H, C*H*HCH$_2$), 1.74 (m, 1 H, CH*H*CH$_2$), 2.12 (m, 1 H, CH$_2$C*H*H), 2.14 (m, 1 H, CH$_2$CH*H*), 3.78 (s, 3 H, C*H*$_3$), 3.82 (m, 1 H, CHF$_2$C*H*), 4.85 (m, C*H*NH), 5.60 (td, $J_{H,F}$ = 56.1, $J_{H,H}$ = 3.8 Hz, C*H*F$_2$), 6.90 (d, $J_{H,H}$ = 7.5 Hz, N*H*), 7.43 (m, 2 H, Ph), 7.51 (m, 1 H, Ph), 7.78 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.5 (t, *C*H$_2$), 28.5 (*C*H$_2$), 52.1 (*C*H$_3$), 52.8 (*C*HNH), 70.6 (t, $J_{C,F}$ = 23.8 Hz, *C*HOH), 116.1 (t, $J_{C,F}$ = 244.3 Hz, *C*HF$_2$), 127.1 (Ph), 128.7 (Ph), 132.0 (Ph), 133.6 (Ph), 167.4 (*C*ONH), 172.9 (*C*O$_2$Me) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –122.4 (m, CH*F*F), –129.58 (m, CHF*F*) ppm. $C_{14}H_{17}F_2NO_4$ (301.11): calcd. C 55.81, H 5.69, N 4.65; found C 55.79, H 5.66, N 4.63.

Conditions B

Methyl 2-(Benzoylamino)-6,6-difluoro-5-hydroxyhexanoate [Mixture of Diastereomers 6c/7c (1:1)]: A mixture of pyrone **3d** (299 mg, 1 mmol) in MeOH (20 mL) and Pd/C (0.05 g) was stirred in an autoclave under hydrogen pressure (50 atm) at room temp. for 6 h. The reaction progress was monitored by TLC. After the reduction was complete, the residue was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography [hexane/EtOAc (2:1), $R_f \approx 0.3$]. Yield: 225 mg (75%). The spectroscopic data for the mixture are presented above.

Conditions C

A mixture of the pyrone **3a** (299 mg, 1 mmol) in EtOAc (20 mL) and Pd/C (5%, 0.05 g) was stirred in an autoclave under hydrogen pressure (10 atm) at room temp. The reaction progress was monitored by TLC and ^{19}F NMR spectroscopy. After 2 weeks, just 10% conversion was observed. The reaction product **4a** was not isolated.

Conditions D

A mixture of a pyrone (**3a**–**d**, 1 mmol) in dry THF (30 mL) and Pd/C (5%, 0.05 g) was stirred in an autoclave under hydrogen pressure (10 atm) at room temp. for 2 h. The reaction progress was monitored by TLC and ^{19}F NMR spectroscopy. After complete hydrogenation, the residue was filtered through a short pad of silica gel, and the solvent was evaporated in vacuo. The residue was purified (if necessary) by crystallization. Yields are presented in Table 1 (Entries 7–10). In the case of the pyrone **3d**, an unresolved mixture was obtained.

(3*R*,6*R*/3*S*,6*S*)-*N*-[2-Oxo-6-(trifluoromethyl)-tetrahydropyran-3-yl]-benzamide (4a): This compound was obtained from pyrone **3a** (283 mg) and was crystallized from toluene. Yield: 247 mg (86%), white solid, m.p. 221–222 °C. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 2.12 (m, 2 H, C*H*$_2$), 2.42 (m, 1 H, C*H*H), 2.54 (m, 1 H, CH*H*), 5.11 (m, 1 H, C*H*CF$_3$), 5.33 (m, 1 H, C*H*NH), 7.47 (m, 2 H, Ph), 7.55 (m, 1 H, Ph), 7.92 (m, 2 H, Ph), 8.30 (br. d, $J_{H,H}$ = 4.9 Hz, 1 H, N*H*) ppm. ^{13}C NMR (126 MHz, [D$_6$]acetone): δ = 19.9 (*C*H$_2$), 22.7 (*C*H$_2$), 47.4 (*C*HNH), 73.5 (q, $J_{C,F}$ = 34.7 Hz, *C*HCF$_3$), 123.4 (q, $J_{C,F}$ = 278.8 Hz, *C*F$_3$), 127.3 (Ph), 128.3 (Ph), 131.5 (Ph), 134.1 (Ph), 166.4 (*C*O), 169.2 (*C*O) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –77.29 (d, $J_{F,H}$ = 6.0 Hz, C*F*$_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3388, 1764, 1662, 1600, 1552, 1488, 1448, 1367, 1296, 1184, 1117, 1077, 984 cm^{-1}. $C_{13}H_{12}F_3NO_3$ (287.1): calcd. C 54.36, H 4.21, N 4.88; found C 54.33, H 4.17, N 4.97.

***N*-[6-(Heptafluoropropyl)-2-oxo-tetrahydropyran-3-yl]benzamide [Mixture of Diastereomers 4b/5b (17:3)]:** These compounds were obtained from pyrone **3b** (383 mg) without additional purification. Yield: 228 mg (59%), white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (m, C*H*H of compound **4b**), 2.06 (m, C*H*H of compound **5b**), 2.20–2.37 (m, 2 H, C*H*$_2$), 2.70 (m, CH*H* of compound **5b**), 2.87 (m, CH*H* of **4b**), 4.52 (m, C*H*CF$_2$ of **5b**) 4.98 (m, C*H*NH and C*H*CF$_2$ of compound **4b**), 7.06 (br. d, $J_{H,H}$ = 5.0 Hz, 1 H), 7.46 (m, 2 H, Ph), 7.55 (m, 1 H, Ph), 7.82 (m, 2 H, Ph) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –81.25 (t, $J_{F,F}$ = 11.00 Hz, C*F*$_3$ of compound **4b**), –81.30 (t, $J_{F,F}$ = 11.00 Hz, C*F*$_3$ of compound **5b**), –122.60 (d, $J_{F,F}$ = 287.0 Hz, C*F*FCF$_2$CF$_3$ of compound **4b**), –123.23 (d, $J_{F,F}$ = 287.0 Hz, C*F*FCF$_2$CF$_3$ of compound **5b**), –125.89 (d, $J_{F,F}$ = 293.0 Hz, C*F*FCF$_3$ of compound **5b**), –126.03 (d, $J_{F,F}$ = 291.5 Hz C*F*FCF$_3$ of compound **4b**), –126.80 (d, $J_{F,F}$ = 293 Hz, CF*F*CF$_3$ of compound **5b**), –126.87 (d, $J_{F,F}$ = 291.5 Hz, CF*F*CF$_3$ of compound **4b**), –127.23 (d, $J_{F,F}$ = 287.0 Hz, CF*F*CF$_2$CF$_3$ of **4b**), –127.38 (d, $J_{F,F}$ = 287.0 Hz, CF*F*CF$_2$CF$_3$ of compound **5b**) ppm; integration of these signals showed a 17:3 ratio of compounds **4b/5b**.

(3*R*,6*R*/3*S*,6*S*)-*N*-[6-(Heptafluoropropyl)-2-oxo-tetrahydropyran-3-yl]-benzamide (4b): This compound was obtained by recrystallization of the mixture of diastereomers **4b/5b** (17:3, 228 mg) from toluene or $CHCl_3$/CCl_4 (3:5). Yield: 97 mg (25%, based on pyrone **3b**), m.p. 180–182 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (m, 1 H, C*H*H), 2.20–2.37 (m, 2 H, C*H*$_2$), 2.87 (m, 1 H, CH*H*), 4.98 (m, 2 H, C*H*NH and C*H*CF$_2$), 7.06 (br. d, $J_{H,H}$ = 5.0 Hz, 1 H), 7.46 (m, 2 H, Ph), 7.55 (m, 1 H, Ph), 7.82 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.1 (*C*H$_2$), 22.7 (*C*H$_2$), 47.1 (*C*HNH), 72.6 (t, $J_{C,F}$ = 28.3 Hz, *C*HCF$_2$), 127.3 (Ph), 128.3 (Ph), 131.0 (Ph), 134.0 (Ph), 166.6 (*C*O), 169.1 (*C*O) ppm; low-intensity and high-multiplicity signals of C_3F_7-fragment C atoms are in the δ = 110–130 ppm range. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –81.25 (t, $J_{F,F}$ = 11.00 Hz, 3 F, C*F*$_3$), –122.60 (d, $J_{F,F}$ = 287.0 Hz, 1 F, C*F*FCF$_2$CF$_3$), –126.03 (d, $J_{F,F}$ = 291.5 Hz, 1 F, C*F*FCF$_3$), –126.87 (d, $J_{F,F}$ = 291.5 Hz, 1 F, CF*F*CF$_3$), –127.23 (d, $J_{F,F}$ = 287.0 Hz, 1 F, CF*F*CF$_2$CF$_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 1758, 1648, 1600, 1537, 1372, 1264, 1224, 1194, 1128, 1076, 960 cm^{-1}. $C_{15}H_{12}F_7NO_3$ (387.1): calcd. C 46.52, H 3.12, N 3.62; found C 46.54, H 3.10, N 3.59.

(3*R*,6*R*/3*S*,6*S*)-*N*-[6-(Difluoromethyl)-2-oxo-tetrahydropyran-3-yl]-benzamide (4c): This compound was obtained from pyrone **3c** (265 mg) and was crystallized from $CHCl_3$/hexane (1:2). Yield:

102 mg (38%), white solid, m.p. 159–160 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.76 (m, 1 H, C*H*H), 2.03 (m, 1 H, CH*H*), 2.16 (m, 1 H, C*H*H), 2.72 (m, 1 H, CH*H*), 4.64 (m, 1 H, C*H*NH), 4.98 (m, 1 H, C*H*CHF_2), 7.87 (t, $J_{H,F}$ = 53.1 Hz, 1 H, C*H*F_2), 7.18 (br. s, 1 H, N*H*), 7.47 (m, 3 H, Ph), 7.81 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.1 (t, $J_{C,F}$ = 3.0 Hz, *C*H_2), 23.5 (*C*H_2), 48.2 (C*H*NH), 75.1 (t, $J_{C,F}$ = 27.8 Hz, *C*$HCHF_2$), 113.2 (t, $J_{C,F}$ = 244.5 Hz, *C*F_3), 127.1 (Ph), 128.6 (Ph), 133.1 (Ph), 133.2 (Ph), 167.4 (*C*O), 171.0 (*C*O) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –130.44 (ddd, $J_{F,F}$ = 9.3, 53.3, 294.6 Hz, 1 F, CH*F*F), –134.80 (ddd, $J_{F,F}$ = 9.3, 53.3, 294.6 Hz, 1 F, CHF*F*) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 1764, 1665, 1515, 1488, 1150, 1088 cm^{-1}. $C_{13}H_{13}F_2NO_3$ (269.1): calcd. C 57.99, H 4.87, N 5.20; found C 58.00, H 4.89, N 5.21.

Synthesis of Hydroxy-(benzoylamino) Acids 8 and 9

2-(Benzoylamino)-6,6,6-trifluoro-5-hydroxyhexanoic Acid [Mixture of Diastereomers 8/9 (7:3)]: A mixture of the diastereomers **6a/7a** (300 mg, 0.98 mmol) was dissolved in hydrochloric acid (15%, 15 mL). The solution was stirred at 65 °C for 4 h and was then allowed to cool to room temp. The formed precipitate was filtered and recrystallized from EtOH/H_2O (1:4). Yield: 216 mg (72%), white solid. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 1.65 (m, 1 H, C*H*H), 1.75 (m, 1 H, CH*H*), 2.32 (m, 2 H, C*H*$_2$), 4.09 (m, 1 H, C*H*NH), 4.65 (m, 1 H, C*H*CF_3), 5.10 (br. s, 1 H, N*H*), 7.33 (m, 2 H, Ph), 7.41 (m, 1 H, Ph), 7.81 (m, 3 H, Ph and O*H*) ppm. ^{19}F NMR (282 MHz, [D$_6$]acetone): δ = –80.53 (d, $J_{F,H}$ = 6.9 Hz, C*F*$_3$ of compound **8**), –80.60 (d, $J_{F,H}$ = 6.9 Hz, C*F*$_3$ of compound **9**) ppm; integration of these signals showed a 7:3 ratio of **8/9**.

(2*R*,5*R*/2*S*,5*S*)-2-(Benzoylamino)-6,6-difluoro-5-hydroxyhexanoic Acid (8): This compound was obtained by fractional crystallization of the **8/9** mixture (7:3, 200 mg, 0.66 mmol) from EtOH/H_2O (1:4). Yield: 86 mg (43%), white solid, m.p. 115–116 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 1.63–1.95 (m, 2 H, C*H*$_2$), 1.75 (m, 1 H, CH*H*), 2.15 (m, 2 H, C*H*$_2$), 4.14 (m, 1 H, C*H*NH), 4.77 (m, 1 H, C*H*CF_3), 5.39 (br. s, 1 H, N*H*), 7.33 (m, 2 H, Ph), 7.41 (m, 1 H, Ph), 7.81 (m, 3 H, Ph and O*H*) ppm. ^{13}C NMR (126 MHz, [D$_6$]acetone): δ = 25.4 (*C*H_2), 26.5 (*C*H_2), 51.3 (*C*HNH), 68.2 (q, $J_{C,F}$ = 29.8 Hz, *C*HCF_3), 125.5 (q, $J_{C,F}$ = 280.5 Hz, *C*F_3), 126.9 (Ph), 127.9 (Ph), 131.0 (Ph), 133.9 (Ph), 166.5 (*C*ONH), 172.3 (*C*O_2Me) ppm. ^{19}F NMR (282 MHz, [D$_6$]acetone): δ = –80.50 (d, $J_{F,H}$ = 6.9 Hz, C*F*$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3569, 1720, 1656, 1576, 1536, 1491, 1464, 1430, 1336, 1288, 1272, 1224, 1192, 1168, 1136, 1040 cm^{-1}. $C_{13}H_{14}F_3NO_4$ (305.1): calcd. C 51.15, H 4.62, N 4.59; found C 51.10, H 4.59, N 4.61.

Synthesis of Pure Diastereomers of Hydroxy-(benzoylamino) Acid Esters 6a and 6b: Triethylamine (200 mg, 2 mmol) was added with stirring to a solution of compound **4a** or **4b** (1 mmol) in MeOH (20 mL), and the mixture was left at room temp. for 24 h. The solvent was then evaporated in vacuo, and the residue was dissolved in EtOAc and washed with citric acid solution (15%, 10 mL). The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by crystallization, giving pure compounds **6a** or **6b**.

Methyl (2*R*,5*R*/2*S*,5*S*)-2-(Benzoylamino)-6,6,6-trifluoro-5-hydroxyhexanoate (6a): This compound was obtained from compound **4a** (287 mg) and was crystallized from $CHCl_3$/hexane (1:1). Yield: 242 mg (76%), white solid, m.p. 96–97 °C. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.74 (m, 1 H, CH*H*), 1.85 (m, 1 H, C*H*H), 2.12 (m, 2 H, C*H*$_2$), 3.70 (s, 3 H, C*H*$_3$), 4.12 (m, 1 H, C*H*NH), 4.75 (m, 1 H, C*H*CF_3), 5.35 (br. s, 1 H, O*H*), 7.46 (m, 2 H, Ph), 7.57 (m, 1 H, Ph), 7.93 (m, 2 H, Ph), 8.00 (br. d, $J_{H,H}$ = 6.8 Hz, 1 H, N*H*) ppm. ^{13}C NMR (126 MHz, [D$_6$]acetone): δ = 26.2 (*C*H_2), 26.3 (*C*H_2), 52.2 (*C*H_3), 52.4 (*C*HNH), 67.9 (q, $J_{C,F}$ = 28.7 Hz, *C*HCF_3), 126.4 (q, $J_{C,F}$ = 283.6 Hz, *C*F_3), 127.9 (Ph), 128.7 (Ph), 132.0 (Ph), 134.2 (Ph), 167.2 (*C*ONH), 172.8 (*C*O_2Me) ppm. ^{19}F NMR (470 MHz, [D$_6$]acetone): δ = –79.12 (d, $J_{F,H}$ = 7.1 Hz, C*F*$_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 1746, 1640, 1551, 1448, 1202, 1160, 1144, 1048 cm^{-1}. $C_{14}H_{16}F_3NO_4$ (319.10): calcd. C 52.67, H 5.05, N 4.39; found C 52.64, H 5.00, N 4.43.

Methyl (2*R*,5*R*/2*S*,5*S*)-2-(Benzoylamino)-6,6,7,7,8,8,8-heptafluoro-5-hydroxyoctanoate (6b): This compound was obtained from compound **4b** (387 mg) and was crystallized from $CHCl_3$/hexane (1:1), yield 327 mg (78%), white solid, m.p. 106–108 (decomposition). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (m, 1 H, C*H*H), 1.89 (m, 1 H, CH*H*), 2.08 (m, 1 H, C*H*H), 2.17 (m, 1 H, CH*H*), 3.79 (s, 3 H, C*H*$_3$), 4.22 (m, 1 H, C*H*CF_2), 4.87 (m, 1 H, C*H*NH), 7.00 (br. d, $J_{H,H}$ = 7.3 Hz, 1 H, N*H*), 7.43 (m, 2 H, Ph), 7.53 (m, 1 H, Ph), 7.93 (m, 2 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.7 (*C*H_2), 28.4 (*C*H_2), 52.1 (C*H*$_3$), 52.8 (*C*HNH), 69.3 (t, $J_{C,F}$ = 28.4 Hz, *C*HCF_2), 127.1 (Ph), 128.7 (Ph), 132.1 (Ph), 133.3 (Ph), 167.8 (*C*ONH), 172.8 (*C*O_2Me) ppm; low-intensity and high-multiplicity signals of C_3F_7-fragment C atoms are in the δ = 110–130 ppm range. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –81.44 (t, $J_{F,F}$ = 9.5 Hz, 3 F, C*F*$_3$), –121.62 (d, $J_{F,F}$ = 278.4 Hz, 1 F, C*F*FCF_2CF_3), –125.71 (d, $J_{F,F}$ = 293.5 Hz, 1 F, C*F*FCF_3), –127.01 (d, $J_{F,F}$ = 293.5 Hz, 1 F, CF*F*CF_3), –127.95 (d, $J_{F,F}$ = 278.4 Hz, 1 F, CF*F*CF_2CF_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 1747, 1661, 15253, 1477, 1429, 1356, 1210, 1110 cm^{-1}. $C_{16}H_{16}F_7NO_4$ (419.3): calcd. C 45.83, H 3.85, N 3.34; found C 45.81, H 3.89, N 3.30.

Triethylammonium Salt of 2-(Benzoylamino)-6,6,6-trifluoro-5-methoxyhexa-2,4-dienoic Acid (11): The pyrone **3a** (320 mg, 1.13 mmol) was added to a solution of triethylamine (0.5 mL) in MeOH (15 mL), and the mixture was stirred at room temp. for 5 h. The solution was then concentrated in vacuo (bath temperature 30–40 °C, 30–60 Torr). The residue was crystallized from CH_3CN to give compound **11**. Yield: 390 mg (83%). Light yellow solid, m.p. 127–129 °C (decomposition). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.15 (t, $J_{H,H}$ = 6.9 Hz, 9 H, 3 × C*H*$_3$), 3.05 (q, $J_{H,H}$ = 6.9 Hz, 6 H, 3 × C*H*$_2$), 3.56 (s, 3 H, OC*H*$_3$), 5.00 (d, $J_{H,H}$ = 10.9 Hz, 1 H, C*H*), 7.44 (m, 2 H, Ph), 7.50 (m, 1 H, Ph), 7.60 (br. m, 1 H, C*H*), 7.92 (m, 2 H, Ph), 8.59–9.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 9.1 (*C*H_3), 46.3 (*C*H_2), 46.3 (O*C*H_3), 88.6 (*C*H), 111.6 (*C*H), 121.0 (q, $J_{C,F}$ = 289.3 Hz, *C*F_3), 128.0 (Ph), 128.7 (Ph), 131.6 (Ph), 135.2 (Ph), 165.3 (*C*O), 166.6 (*C*O) ppm. ^{19}F NMR (470 MHz, [D$_6$]DMSO): δ = –64.65 (s, C*F*$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3200, 3250, 1720, 1670, 1595, 1580, 1430, 1323, 1220, 1180, 1100, 895, 715 cm^{-1}. $C_{20}H_{27}F_3N_2O_3$ (416.4): calcd. C 57.68, H 6.54, N 6.73; found C 57.70, H 6.53, N 6.73.

2-(Benzoylamino)-6,6,6-trifluoro-5-methoxyhexanoic Acid [Mixture of Diastereomers 12/13 (1:1)]: Hydrogen was passed through a mixture of the salt **11** (400 mg, 1 mmol) in dry MeOH (30 mL) and Pd/C (5%, 0.05 g) at room temp. for 8 h. The reaction progress was monitored by TLC. After complete reduction, the residue was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc and washed with aq. citric acid (15%). The organic layer was separated, dried with $MgSO_4$, and concentrated in vacuo (bath temperature 30–40 °C, 30–60 Torr). The residue was purified by crystallization from $CHCl_3$/CH_3CN (5:1) to give a white solid. Yield: 280 mg (88%), m.p. 105–106 °C. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 1.85 (m, 2 H, C*H*$_2$), 2.19 (m, 2 H, C*H*$_2$), 3.65 (s, 3 H, C*H*$_3$), 4.10 (m, 1 H, C*H*CF_3), 4.73 (m, 1 H, C*H*NH), 5.35 (br. s, 1 H, N*H*), 7.46 (m, 2 H, Ph), 7.54 (m, 1 H, Ph), 7.93 (m, 2 H, Ph), 10.22 (br. s, 1 H, O*H*) ppm. ^{19}F NMR (470 MHz, [D$_6$]acetone): δ = –79.12 (d, $J_{F,H}$ = 6.9 Hz, C*F*$_3$ of compound **12**), –78.20 (d, $J_{F,H}$ = 6.9 Hz, C*F*$_3$ of

compound **13**) ppm; integration of these signals showed an 1:1 mixture of compounds **12** and **13**. IR (KBr): $\tilde{\nu}$ = 2960, 1755, 1648, 1536, 1280, 1216, 1168, 1128 cm^{-1}. $C_{14}H_{16}F_3NO_4$ (319.1): calcd. C 52.67, H 5.05, N 4.39; found C 52.68, H 5.04, N 4.37.

Synthesis of Amino Acids 1 and 2: Either a mixture of diastereomers (**6a–b/7a–b** or **12/13**) or a pure diastereomer (**6a–c** or **8**) (1 mmol) was dissolved in HCl (30%, 6–7 mL), and the mixture was heated at reflux for 7 h. After cooling, the precipitate of the formed benzoic acid was filtered off, and the filtrate was concentrated in vacuo (bath temperature 30–40 °C, 30–60 Torr). The residue was dissolved in water, and the corresponding amino acid was isolated by ion-exchange chromatography either as a mixture of diastereomers (**1a–c/2a–c** or **14/15**) or as a pure diastereomer (**1a–c**). The obtained ammonia solutions were concentrated, dissolved in water, and concentrated in vacuo again in order to remove traces of ammonia. Yields are given in Table 2.

2-Amino-6,6,6-trifluoro-5-hydroxyhexanoic Acid [Mixture of Diastereomers 1a/2a (7:3)]: These compounds were obtained from the mixture of diastereomers **6a/7a** (7:3, 319 mg). Yield: 90 mg (45%), white solid, m.p. >300 °C (decomposition). ^{1}H NMR (300 MHz, D_2O): δ = 1.81 (m, 4 H, CH_2CH_2), 3.71 (m, 1 H, C*H*NH$_2$), 4.04 (br. m, 1 H, C*H*CF$_3$) ppm. ^{19}F NMR (280 MHz, D_2O): δ = –79.12 (d, $J_{F,H}$ = 6.9 Hz, CF_3 of compound **1a**), –79.20 (d, $J_{F,H}$ = 6.9 Hz, CF_3 of compound **2a**) ppm. Integration of these signals showed a 7:3 ratio of compounds **1a/2b**.

(2*R*,5*R*/2*S*,5*S*)-2-Amino-6,6,6-trifluoro-5-hydroxyhexanoic Acid (1a): This compound was obtained from pure diastereomers **6a** (319 mg) or **8** (305 mg). Yield: 115 mg (57%) from **6a** and 155 mg (77%) from **8**, white solid, m.p. >300 °C (decomposition). ^{1}H NMR (500 MHz, D_2O): δ = 1.65 (m, 1 H, CH*H*), 1.84–2.14 (m, 3 H, CH_2 and CH*H*), 3.76 (t, $J_{H,H}$ = 6.7 Hz, 1 H, C*H*NH$_2$), 4.1 (br. m, 1 H, C*H*CF$_3$) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 24.9 (*C*H$_2$), 26.2 (*C*H$_2$), 54.4 (*C*HNH$_2$), 68.8 (q, $J_{C,F}$ = 30.7 Hz, *C*HCF$_3$), 125.1 (q, $J_{C,F}$ = 281.1 Hz, *C*F$_3$), 174.2 (*C*O) ppm. ^{19}F NMR (470 MHz, D_2O): δ = –79.12 (d, $J_{F,H}$ = 6.9 Hz, CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3042, 1616, 1584, 1502, 1442, 1368, 1336, 1304, 1273, 1176, 1128, 1096, 1080, 944 cm^{-1}. $C_6H_{10}F_3NO_3$ (201.1): calcd. C 35.83, H 5.01, N 6.96; found C 35.85, H 4.98, N 6.94.

2-Amino-6,6,7,7,8,8,8-heptafluoro-5-hydroxyoctanoic Acid [Mixture of Diastereomers 1b/2b (1:1)]: These compounds were obtained from a mixture of diastereomers **6b/7b** (1:1, 420 mg). Yield: 142 mg (47%), white solid, m.p. >300 °C (decomposition). ^{1}H NMR (500 MHz, D_2O): δ = 1.85 (m, 4 H, CH_2CH_2), 3.62 (m, 1 H, C*H*NH$_2$), 4.13 (br. m, 1 H, C*H*CF$_2$) ppm. ^{19}F NMR (470 MHz, D_2O): δ = –84.01 (br. m, 3 F, CF_3), –122.61 (d, $J_{F,F}$ = 282.9 Hz, C*F*FCF$_2$CF$_3$ of compound **1b**), –122.72 (d, $J_{F,F}$ = 282.9 Hz, C*F*FCF$_2$CF$_3$ of compound **2b**), –127.67 (d, $J_{F,F}$ = 294.8 Hz, C*F*FCF$_3$ of compound **1b**), –127.73 (d, $J_{F,F}$ = 294.8 Hz, CF*F*CF$_3$ of compound **2b**), –129.42 (d, $J_{F,F}$ = 288.8 Hz, C*F*FCF$_3$ of compound **1b**), –129.47 (d, $J_{F,F}$ = 288.8 Hz, CF*F*CF$_3$ of compound **2b**), –130.49 (d, $J_{F,F}$ = 282.9 Hz, CF*F*CF$_2$CF$_3$ of compound **1b**), –130.62 (d, $J_{F,F}$ = 282.9 Hz, CF*F*CF$_2$CF$_3$ of compound **2b**) ppm. Integration of these signals showed a 1:1 ratio of compounds **1b/2b**.

(2*R*,5*R*/2*S*,5*S*)-2-Amino-6,6,7,7,8,8,8-heptafluoro-5-hydroxyoctanoic Acid (1b): This compound was obtained from pure diastereomer **6b** (420 mg). Yield: 169 mg (56%), white solid, m.p. >300 °C (decomposition). ^{1}H NMR (300 MHz, D_2O): δ = 1.48–2.12 (m, 4 H, CH_2CH_2), 3.65 (m, 1 H, C*H*NH$_2$), 4.16 (m, 1 H, C*H*CF$_2$) ppm. ^{13}C NMR (126 MHz, D_2O): δ = 24.1 (*C*H$_2$), 26.3 (*C*H$_2$), 54.3 (*C*HNH$_2$), 68.0 (t, $J_{C,F}$ = 22.5 Hz, C*H*CF$_2$), 174.1 (*C*O$_2$H) ppm; low-intensity and high-multiplicity signals of C_3F_7-fragment C atoms are in the δ = 110–130 ppm range. ^{19}F NMR (280 MHz, D_2O): δ = –83.3 (dd, $J_{F,F}$ = 8.2, 10.7 Hz, 3 F, CF_3), –122.60 (d, $J_{F,F}$ = 282.9 Hz, 1 F, C*F*FCF$_2$CF$_3$), –127.55 (d, $J_{F,F}$ = 294.8 Hz, 1 F, C*F*FCF$_3$), –129.42 (d, $J_{F,F}$ = 288.8 Hz, 1 F, C*F*FCF$_3$), –129.47 (d, $J_{F,F}$ = 288.8 Hz, CF*F*CF$_3$ of compound **2b**), –130.3 (d, $J_{F,F}$ = 282.9 Hz, 1 F, CF*F*CF$_2$CF$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 2943, 1680, 1592, 1537, 1464, 1412, 1342, 1226, 1184, 1121, 964 cm^{-1}. $C_8H_{10}F_7NO_3$ (301.1): calcd. C 31.91, H 3.35, N 4.65; found C 31.89, H 3.32, N 4.68.

2-Amino-6,6-difluoro-5-hydroxyhexanoic Acid (1c): This compound was obtained from pure diastereomer **6c** (300 mg). Yield: 78 mg (43%), white solid, m.p. >300 °C (decomposition). ^{1}H NMR (500 MHz, D_2O): δ = 1.64 (m, 2 H, CH_2), 2.07 (m, 2 H, CH_2), 3.82 (m, 1 H, C*H*NH), 4.13 (br. m, 1 H, C*H*CHF$_2$), 5.77 (br. t, $J_{H,F}$ = 52.3 Hz, 1 H, C*H*F$_2$) ppm. ^{13}C NMR (126 MHz, D_2O): δ = 25.8 (*C*H$_2$), 26.4 (*C*H$_2$), 53.6 (*C*HNH$_2$), 70.1 (t, $J_{C,F}$ = 22.9 Hz, *C*HCHF$_2$), 117.0 (t, $J_{C,F}$ = 241.1 Hz, *C*HF$_2$), 171.9 (*C*O) ppm. ^{19}F NMR (470 MHz, D_2O): δ = –128.90 (ddd, $J_{F,H}$ = 9.8, 55.1, $J_{F,F}$ = 283.2 Hz, 1 F, CH*F*F), –131.85 (ddd, $J_{F,H}$ = 9.8, 55.1, $J_{F,F}$ = 283.2 Hz, 1 F, CH*F*F) ppm. IR (KBr): $\tilde{\nu}$ = 1734, 1653, 1539, 1223, 1134, 1061, 879 cm^{-1}. $C_6H_{11}F_2NO_3$ (183.15): calcd. C 39.35, H 6.05, N 7.65; found C 39.37, H 6.02, N 7.62.

2-Amino-6,6,6-trifluoro-5-methoxyhexanoic Acid [Mixture of Diastereomers 13/14 (1:1)]: These compounds were obtained from a mixture of diastereomers **11/12** (1:1, 319 mg). Yield: 60 mg (28%), white solid, m.p. >300 °C (decomposition). ^{1}H NMR (500 MHz, D_2O): δ = 1.94 (m, 4 H, CH_2CH_2), 3.76 (m, 1 H, C*H*NH), 4.03 (br. m, 1 H, C*H*CF$_3$), 4.50 (br. s, 3 H, CH_3) ppm. ^{13}C NMR (126 MHz, D_2O): δ = 24.5 (*C*H$_2$), 25.1 (*C*H$_2$), 26.2 (*C*H$_2$), 26.3 (*C*H$_2$), 54.4 (*C*HNH$_2$), 54.5 (*C*HNH$_2$), 68.8 (q, $J_{C,F}$ = 31.8 Hz, *C*HCF$_3$), 68.9 (q, $J_{C,F}$ = 31.8 Hz, *C*HCF$_3$), 125.2 (q, $J_{C,F}$ = 280.5 Hz, *C*F$_3$), 174.2 (*C*O) ppm. ^{19}F NMR (470 MHz, D_2O): δ = –74.72 (d, $J_{F,H}$ = 7.0 Hz, CF_3 of compound **13**), –74.79 (d, $J_{F,H}$ = 7.0 Hz, CF_3 of compound **14**) ppm. IR (KBr): $\tilde{\nu}$ = 3065, 1619, 1587, 1508, 1448, 1347, 1328, 1298, 1274, 1175, 1123, 1090, 1040 cm^{-1}. $C_7H_{12}F_3NO_3$ (215.1): calcd. C 39.07, H 5.62, N 6.51; found C 39.05, H 5.60, N 6.49.

X-ray Crystallographic Study: The data sets were collected with an Xcalibur-3 diffractometer (Mo-K_α radiation, CCD detector, graphite monochromator, ω-scanning) at –173 °C (for compound **8**) and at room temperature (for compound **6c**). The structures were refined by SHELXTL PLUS.[13] Crystals of **6c** were monoclinic, a = 8.002(2), b = 22.727(3), c = 8.868(2) Å, β = 113.22(2)°, V = 1482.1(5) Å^3, M_r = 301.29, Z = 4, space group $P2_1/n$, $d_{calcd.}$ = 1.350 g cm^{-3}, μ(Mo-K_α) = 0.114 mm^{-1}, F(000) = 632. Crystals of **8** were triclinic, a = 7.562(1), b = 8.169(1), c = 12.395(2) Å, α = 79.16(1)°, β = 80.25(1)°, γ = 72.91(1)°, V = 713.5(2) Å^3, M_r = 323.27, Z = 2, space group $P\bar{1}$, $d_{calcd.}$ = 1.505 g cm^{-3}, μ (Mo-K_α) = 0.139 mm^{-1}, F(000) = 336. CCDC-735717 (for **6c**) and CCDC-735718 (for **8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): NMR spectra of compounds **4a–c**, **6a–c**, **1a–c**; COSY and NOE of compound **4a**.

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