Hexafluoroacetone as a Protecting and Activating Reagent: Synthesis of New Types of Fluoro-Substituted α-Amino, α-Hydroxy and α-Mercapto Acids

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Dedicated to Prof. Dr. W. Steglich on the occasion of his 70th birthday

Abstract: Starting from (*S*)-aspartic, (*S*)-malic, (*S*)-citramalic and (*S*,*R*)-thiomalic acid, new types of 4,4-difluoro-substituted α-amino-, α-hydroxy- and α-mercaptopentanoic acids have been synthesized, applying hexafluoroacetone as protecting and activating reagent. The new partially fluorinated α-functionalized carboxylic acids represent interesting monomers for peptide and depsipeptide modification and for rational design and elucidation of secondary structure.

Key words: amino acids, hydroxy acids, mercapto acids, fluorine, peptides

Fluorinated analogues of naturally occurring biologically active compounds often exhibit unique physiological activities.[1,2]With increasing success, the design of peptides and proteins of enhanced activity and stability is developed by incorporation of nonproteinogenic and non-natural amino acids.[3] Therefore, there is a steadily growing interest in the development of new methodologies for the incorporation of fluoroamino acids into key positions of peptides.[4,5] The comparable sizes of hydrogen and fluorine preclude undesirable steric inhibition of binding at the active site of the receptor.[6] Incorporation of fluorinated amino acids into proteins and peptides allows monitoring of the chemical environment of the fluorine-containing residues by ^{19}F NMR spectroscopy.

Many important structural questions concerning protein folding cannot be addressed using X-ray crystallography and therefore have to be solved by NMR spectroscopy in solution and in solid phase. Introduction of two or three fluorine atoms into a protein is not expected to significantly perturb its tertiary structure.[3]However, at least in one ^{19}F NMR study,[7] substantial changes have been observed in protein structure after fluoromodification.

In all chiral compounds like amino acids, hydroxy acids, peptides and depsipeptides, the hydrogen atoms of a methylene group are diastereotopic. Thus, on displacement by fluorine diastereotopic fluorine atoms are obtained. They provide an additional stereochemical tool using NMR spectroscopy to address conformational questions, provided that the two fluorine atoms can be assigned individually.

Interactions between the α-hydrogen and carbonyl oxygen in peptide backbones have been virtually ignored by chemists and biologists until recently.[8] However, C^{α}-H···O=C hydrogen bonds seem to be ubiquitous, particularly in β-sheets and helical proteins. It was postulated that its strength is up to 3 kcal mol^{-1}, enough to play a considerable role in determining protein conformation.[9] Under these aspects, α-amino acids (**A**) having additional carbonyl groups in the side chain (**B**) (Figure 1) should be of considerable interest, because they are capable of additional hydrogen bonding, enhancing substrate/enzyme interactions and assisting protein folding.[10]

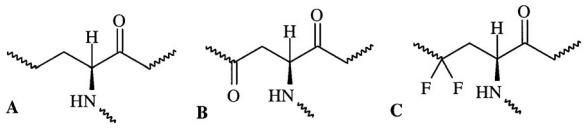

Figure 1 Partial structure of amino acids containing additional moiety in the side chain

In this context, amino acids with extra C=O (**B**) and/or CF_2 groups (**C**) in the side chain, should be excellent model compounds to study new noncovalent interactions of type C=O...H and CF_2...H and to find out whether they are sufficiently strong to have similar impact on the secondary structure and on folding like hydrogen-bonding between C^{α}-hydrogens and carbonyl groups of the peptide bond. C(sp^3)–F fluorine can enter into stronger hydrogen bonds than fluorine of a C(sp^2)–F moiety.[11] Theoretical calculations estimate the strength of a F...H bond between 2 to 3.2 kcal mol^{-1}.[9]

We now report on a new, preparatively simple access to α-amino acids having $CH_2C(=O)$ and CH_2CF_2 subunits in the side chain. To enlarge structural diversity of the building blocks we included α-hydroxy and α-mercapto analogues into our investigations.

Key intermediates of the synthesis are diazoketones **2a**–**d**, which are obtainable from α-functionalized α,ω-dicarboxylic acids **1a**–**d** in three steps. The reaction sequence in-

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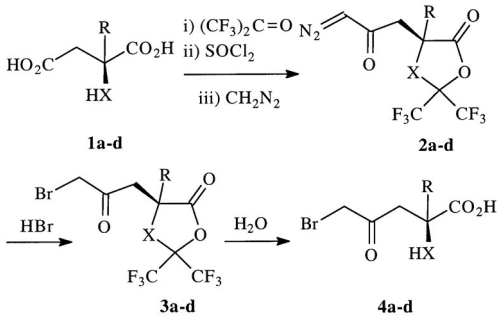
cludes hexafluoroacetone protection, conversion into β-acid chlorides by reaction with thionyl chloride and finally treatment with an excess of diazomethane (>3 equiv) to give compounds **2a**–**d** in very good yields (90%) (Scheme 1).

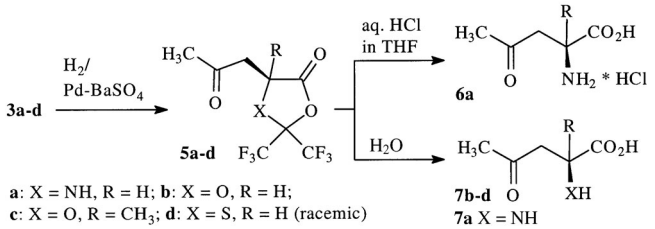


a: X = NH, R = H; **b**: X = O, R = H;
c: X = O, R = CH_3; **d**: X = S, R = H (racemic)

Scheme 1

When diazoketones **2a**–**d** were treated with concentrated HBr at –30 °C in THF spontaneously nitrogen elimination occurred and the corresponding bromoketones **3a**–**d** were formed within minutes. The structural assignment is based on IR, ^1H and ^{13}C NMR data. Compounds **3** are versatile building blocks e.g. for Hantzsch type syntheses of heteroaromatic α-functionalized carboxy acids.[12–14] Simultaneous deprotection of the α-amino and the adjacent carboxy group could be achieved on heating (bath temperature 50 °C) compounds **3** in an acetonitrile–water mixture.

4-Oxonorvaline (**7a**)[12b] was obtained on vigorous stirring of **3a** in boiling toluene under an atmosphere of hydrogen in the presence of a Pd catalyst, followed by hydrolysis with dilute HCl at room temperature and finally treatment with propene oxide (**3a** → **5a** → **6a** →**7a**). The reductive debromination and deprotection of **3b**–**d** to give the corresponding α-hydroxy and α-mercapto acids **7b**–**d** via **5b**–**d** was accomplished using the above protocol (Scheme 2). The final treatment with propene oxide is not necessary since hydrolysis is performed in water–acetonitrile.

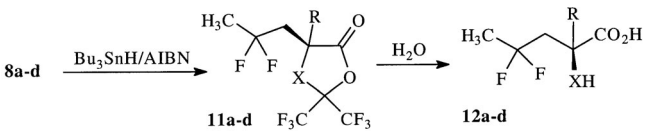


a: X = NH, R = H; **b**: X = O, R = H;
c: X = O, R = CH_3; **d**: X = S, R = H (racemic)

Scheme 2

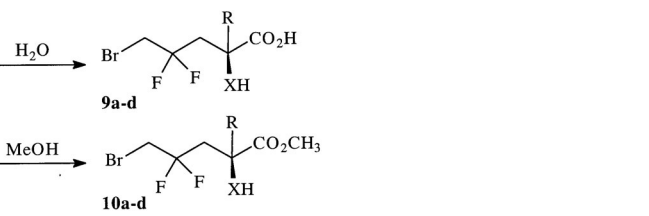
Compounds **3a**–**d** were readily converted into 5-bromo-4,4-difluoropentanoic acid derivatives **8a**–**d** (70–80%) by fluorodeoxygenation with DAST (diethylaminosulfur trifluoride).[15,16] Since hexafluoroacetone protected compounds are carboxy group activated species, simultaneous deprotection of both functional groups (**8** → **9**) as well as simultaneous derivatization of the carboxy group and deprotection (**8** → **10**) can be performed already at room temperature in acceptable yields (65–75%) (Scheme 3).

The debromination of compounds **8a**–**d** could not be achieved in acceptable yields using the protocol applied for transformation **3** → **5**. Finally, we found tributyltin hydride to be the reagent of choice for reductive debromination **8** → **11**. However, the quantitative removal of the tin compounds is in some cases laborious. Since hexafluoroacetone-protected compounds are carboxy group activated species, they readily react with various nucleophiles. Simultaneous deblocking of the carboxy and the adjacent amino group was accomplished by stirring compounds **11** in a mixture of water–propan-2-ol at room temperature. The progress of the reaction can be readily controlled by TLC analysis. The reaction time of the hydrolytic cleavage could be reduced to a few hours, when dilute HCl was used for deblocking (**11** → **12**) (Scheme 4). Concomitantly with the cleavage of the lactone moiety, deprotection of the XH function occurred, which can be derivatized selectively in a subsequent step.



a: X = NH, R = H; **b**: X = O, R = H;
c: X = O, R = CH_3; **d**: X = S, R = H (racemic)

Scheme 3

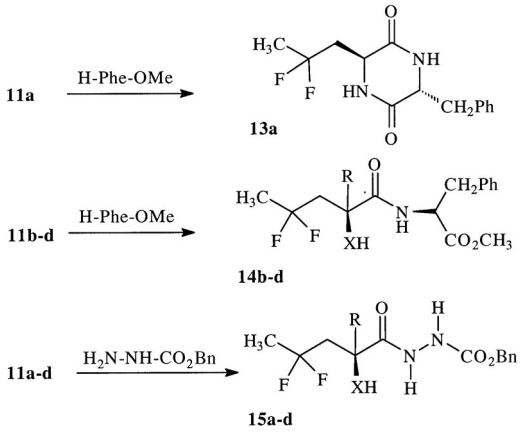


a: X = NH, R = H; **b**: X = O, R = H; **c**: X = O, R = CH_3; **d**: X = S, R = H (racemic)

Scheme 4

Incorporation of the new types of fluorinated amino, hydroxy and mercapto acids into small peptides and depsipeptides provides building blocks of high structural diversity for fragment condensation. When **11** (X = NH) was reacted with amino acid methyl ester partially fluorinated diketopiperazines **13** were formed,[17] while in the case of X = O, S, the open-chain compounds **14** and **15** were stable under the reaction conditions applied

(Scheme 5). Incorporation of α-mercapto acids into peptidomimetics adds a new facet to peptide modification, particulary since disulfide formation offers ready access to symmetric peptidomimetics.[18]



a: X = NH, R = H; **b**: X = O, R = H;
c: X = O, R = CH_3; **d**: X = S, R = H (racemic)

Scheme 5

Examples for the incorporation of α-mercapto acids into peptide hybrides are rare.[19]A β-mercapto acid is a subunit of Captopril, a classical drug for treating hypertension.[20] An α-mercapto subunit is present in Omapatrilat and Gemopatrilat, both are vasopeptidase inhibitors which are currently under clinical evaluation.[21]Compounds containing mercapto and mercaptoacyl moieties[22]often exhibit strong inhibitory effects on metal-containing enzymes (metalloenzymes),[23] similar to hydroxamic acids.[24] Some of the zinc-containing angiotensin converting enzymes (ACE) possess an α-mercaptoacyl substructure.[25]

Since a growing number of reports focus on peptidomimetic compounds built from two or more different types of monomers,[26] the new building blocks are promising candidates for rational design of peptidomimetics with the option of forming weak hydrogen bonds which may play a substantial role in stabilizing and creating new secondary structure motifs and in controlling protein folding.

Solvents were purified and dried prior to use. Reagents were used as purchased. IR spectra were obtained on a Genesis ATI Mattson/ Unicam FTIR spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz and 300 MHz. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ = 0); *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 MHz, 75 MHz with TMS (δ = 0.0) as internal standard. ^{19}F NMR spectra were recorded at 188 MHz and 282 MHz with trifluoroacetic acid (TFA, δ = 0) as external standard. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV). Optical rotations ($[\alpha]_D$) were measured using a Polatronic polarimeter (Schmidt & Haensch) in a 5 cm cell. Melting points were determined on a Boetius heating table. For C, H, N analyses a CHNO-Rapid-Elemental-Analyzer (Hereaus) was used. All new compounds gave satisfactory microanalyses: C ±0.54; H ±0.45; N, ±0.38%. For flash chromatography, silica gel (32–63 μm, ICN Biomedicals) was used with solvent systems given in the text. TLC: compounds were visualized by spraying with ninhydrin (2 mg/mL) in EtOH or with a mixture of $Ce(SO_4)_2$ (0.2%), $(NH_4)_2MoO_4$ (5%) and H_2SO_4 (5%) in H_2O followed by heating.

Reaction of Diazoketones 2 with Concentrated HBr; General Procedure

To a stirred solution of diazoketone **2a–d** (10.0 mmol) in THF (25 mL) at –30 °C was added conc. HBr (7 mL) dropwise. After gas evolution ceased, the mixture was warmed up to 0 °C. Solvents and the excess of HBr were evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (100 mL), washed with cold $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was subjected to column chromatography (eluent: $CHCl_3$–hexanes, 10:1) and then recrystallized from $CHCl_3$–pentane.

(4*S*)-4-(3-Bromo-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (3a)

Yield: 3.18 g (89%); mp 65 °C; $[\alpha]_D$ –3.0 (*c* = 2, CH_2Cl_2).

IR (KBr): 3355, 1820, 1738 cm^{-1}.

For further spectral data, see Lit.[12b,27]

(5*S*)-5-(3-Bromo-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one (3b)

Yield: 2.73 g (76%); bp 54–56 °C/0.1 Torr, mp 56 °C; $[\alpha]_D$ –12.8 (*c* = 1, acetone).

IR (KBr): 1845, 1740 cm^{-1}.

For further spectral data, see Lit.[27]

(5*S*)-5-(3-Bromo-2-oxopropyl)-2,2-bis(trifluoromethyl)-5-methyl-1,3-dioxolan-4-one (3c)

Yield: 2.80 g (75%); oil; $[\alpha]_D$ –49.4 (*c* = 1.7, $CHCl_3$).

IR (KBr): 1840, 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (s, 3 H, CH_3), 3.20 (d, *J* = 16.5 Hz, 1 H, CH_2), 3.26 (d, *J* = 16.5 Hz, 1 H, CH_2), 3.85 (d, *J* = 14.0 Hz, 1 H, CH_2Br), 3.91 (d, *J* = 14.0 Hz, 1 H, CH_2Br).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8 (CH_3), 34.2 (CH_2Br), 45.8 (CH_2), 79.7 [*C*(CH_3)], 97.5 [sept, *J* = 36.0 Hz, *C*(CF_3)$_2$], 119.2 (q, *J* = 287.0 Hz, CF_3), 119.6 (q, *J* = 289.0 Hz, CF_3), 167.2 (lactone C=O), 195.3 (ketone C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –2.7 (q, *J* = 7.0 Hz, 3 F, CF_3), –2.3 (q, *J* = 7.0 Hz, 3 F, CF_3).

MS: *m*/*z* = 347/345 $[M – CO]^+$, 279 $[M – CH_2Br]^+$, 238 $[M – CHCOCH_2Br]^+$, 43 $[HCOCH_2]^+$.

4-(3-Bromo-2-oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (3d)

Yield: 3.07 g (82%); bp 84–87 °C/0.3 Torr; mp 40 °C.

IR (KBr): 1800, 1710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.25 (dd, *J* = 19.0, 10.5 Hz, 1 H, CH_2), 3.78 (dd, *J* = 19.0, 3.0 Hz, 1 H, CH_2), 3.95 (s, 2 H, CH_2Br), 4.45 (dd, *J* = 10.0, 3.0 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.6 (CH_2Br), 41.0 (CH), 44.1 (CH_2), 83.9 [sept, *J* = 35.0 Hz, *C*(CF_3)$_2$], 121.2 (q, *J* = 284.0 Hz, CF_3), 121.4 (q, *J* = 285.0 Hz, CF_3), 170.7 (lactone C=O), 198.5 (ketone C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = 1.0 (q, *J* = 9.0 Hz, 3 F, CF_3), 1.6 (q, *J* = 9.0 Hz, 3 F, CF_3). MS: *m*/*z* = 376/374 $[M]^+$, 295 $[M – Br]^+$, 281 $[M – CH_2Br]^+$, 253 $[M – COCH_2Br]^+$, 87 $[M –COCH_2Br – (CF_3)_2CO]^+$.

Deprotection of Compounds 3; General Procedure
A solution of **3a–d** (5 mmol) was heated in the solvent mixture MeCN–H_2O (10 mL, 1:1) for 2 h (50 °C, bath temperature). After evaporation of the solvent under reduced pressure, the remaining solid was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), evaporated to dryness and the residue was recrystallized from $CHCl_3$ or subjected to column chromatography (eluent: $CHCl_3$–hexanes; 10:1).

(2*S*)-2-Amino-5-bromo-4-oxopentanoic Acid (4a)
Yield: 0.83 g (79%); oil; $[\alpha]_D$ –1.7 (*c* = 1.2, $CHCl_3$).

IR (film): 3700–2500, 1730 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.69–2.75 (m, 1 H, CH_2), 2.81–2.87 (m, 1 H, CH_2), 3.25–3.35 (m, 2 H, CH_2Br), 3.66–3.74 (m, 2 H, NH_2), 3.92–4.01 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.5 (CH_2Br), 40.6 (CH), 41.5 (CH_2), 178.0 (acid C=O), 210.6 (ketone C=O).

MS: *m*/*z* = 211/209 $[M]^+$, 147/145 $[M – CO_2 – HF]^+$, 113 $[M – Br – NH_3]^+$, 100 $[M – BrCH_2 – NH_2]^+$.

(2*S*)-5-Bromo-2-hydroxy-4-oxopentanoic Acid (4b)
Yield: 0.89 g (84%); mp 48 °C; $[\alpha]_D$ –11.2 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3700–2500, 1730 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.12 (dd, *J* = 17.0, 7.0 Hz, 1 H, CH_2), 3.23 (dd, *J* = 17.0, 4.0 Hz, 1 H, CH_2), 4.05 (s, 2 H, CH_2Br), 4.61 (dd, *J* = 7.0, 4.0 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.6 (CH_2Br), 43.2 (CH_2), 66.3 (CH), 174.3 (acid C=O), 198.9 (ketone C=O).

MS: *m*/*z* = 212/210 $[M]^+$, 167/165 $[M – CO_2H]^+$, 123/121 $[COCH_2Br]^+$, 117 $[M – CH_2Br]^+$, 89 $[M – CH_2Br – CO]^+$.

(2*S*)-5-Bromo-2-hydroxy-2-methyl-4-oxopentanoic Acid (4c)
Yield: 0.91 g (81%); oil; $[\alpha]_D$ +12.5 (*c* = 2.4, $CHCl_3$).

IR (film): 3500–3000, 1728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 3.12 (d, *J* = 17.0 Hz, 1 H, CH_2), 3.34 (d, *J* = 17.0 Hz, 1 H, CH_2), 3.89–4.00 (m, 2 H, CH_2Br).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.0 (CH_3), 34.2 (CH_2Br), 48.7 (CH_2), 72.8 (CCH_3), 179.1 (acid C=O), 202.1 (ketone C=O).

MS: *m*/*z* = 226/224 $[M]^+$, 210/208 $[M – H – CH_3]^+$, 182/180 $[M – CO_2]^+$, 131 $[M – CH_2Br]^+$, 113 $[M – CH_2Br – H_2O]^+$.

5-Bromo-4-oxo-2-sulfanylpentanoic Acid (4d)
Yield: 0.66 g (58%); oil.

IR (film): 3300–3100, 1712 cm^{-1}.

^1H NMR (300 MHz, methanol-d_4): δ = 2.72 (dd, *J* = 17.5, 6.9 Hz, 1 H, CH_2), 2.80 (dd, *J* = 17.5, 2.7 Hz, 1 H, CH_2), 3.33 (d, *J* = 16.8 Hz, 1 H, CH_2Br), 3.44 (d, *J* = 16.8 Hz, 1 H, CH_2Br), 3.94–4.05 (m, 1 H, CH).

^{13}C NMR (50 MHz, methanol-d_4): δ = 37.0 (CH_2Br), 42.4 (CH_2), 43.0 (CH), 176.7 (acid C=O), 213.2 (ketone C=O).

MS: *m*/*z* = 227/225 $[M]^+$, 251/249 $[M + Na]^+$, 474 $[2 M + Na]^+$.

Debromination of Compounds 3; General Procedure
To a solution of **3a–d** (10 mmol) in toluene (30 mL) was added the Pd catalyst (0.5 g 5% Pd on $BaSO_4$). The vigorously stirred solution was heated for 12 h (100 °C bath temperature), while a stream of H_2 was bubbled through the mixture until HBr elimination ceased. The catalyst was filtered off and the solvent was removed in vacuo. The remaining colorless liquid was purified by distillation.

(4*S*)-4-(2-Oxopropyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (5a)[12b,27]
Yield: 2.15 g (77%); mp 81–82 °C (subl.); $[\alpha]_D$ –35.0 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3340, 1820, 1720 cm^{-1}.

(5*S*)-5-(2-Oxopropyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one (5b)
Yield: 1.93 g (69%); mp 42 °C; $[\alpha]_D$ –11.7 (*c* = 2.0, $CHCl_3$).

IR (KBr): 3400, 1851, 1728 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, CH_3CO), 2.97 (dd, *J* = 18.3, 6.9 Hz, 1 H, CH_2), 3.12 (dd, *J* = 18.3, 3.7 Hz, 1 H, CH_2), 5.08 (dd, *J* = 6.9, 3.7 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.3 (CH_3), 44.2 (CH_2), 70.9 (CH), 96.9 [m, $C(CF_3)_2$], 119.0 (q, *J* = 287.0 Hz, CF_3), 119.8 (q, *J* = 289.0 Hz, CF_3), 168.0 (acid C=O), 201.1 (ketone C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –4.4 (q, *J* = 8.2 Hz, 3 F, CF_3), –4.1 (q, *J* = 8.2 Hz, 3 F, CF_3).

MS: *m*/*z* = 281 $[M + H]^+$, 304 $[M + H, Na]^+$.

(5*S*)-2,2-Bis(trifluoromethyl)-5-methyl-5-(2-oxopropyl)-1,3-dioxolan-4-one (5c)
Yield: 2.08 g (71%); oil, $[\alpha]_D$ +12.1 (*c* = 2.0, $CHCl_3$).

IR (film): 3500–3300, 1830, 1722 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3CO), 3.16 (d, *J* = 17.9 Hz, 1 H, CH_2), 3.35 (d, *J* = 17.9 Hz, 1 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.3 (CH_3), 29.4 (CH_3), 49.2 (CH_2), 79.8 [$C(CF_3)_2$], 123.2 (q, *J* = 286.0 Hz, CF_3), 123.5 (q, *J* = 285.0 Hz, CF_3), 169.7 (acid C=O), 202.9 (ketone C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –2.8 (q, *J* = 6.0 Hz, 3 F, CF_3), –2.3 (q, *J* = 6.0 Hz, 3 F, CF_3).

MS: *m*/*z* = 621 $[2 M + K]^+$, 295 $[M + H]^+$.

2,2-Bis(trifluoromethyl)-4-(2-oxopropyl)-1,3-oxathiolan-5-one (5d)
Yield: 1.95 g (66%); oil.

IR (film): 2960, 2800, 1810, 1720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, CH_3CO), 3.01 (dd, *J* = 18.6, 11.0 Hz, 1 H, CH_2), 3.50 (dd, *J* = 18.6, 3.0 Hz, 1 H, CH_2), 4.19 (dd, *J* = 11.0, 3.0 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3 (CH_3), 43.9 (CH_2), 55.8 (CH), 83.4–85.2 [m, $C(CF_3)_2$], 119.4 (q, *J* = 284.0 Hz, CF_3), 119.7 (q, *J* = 284.0 Hz, CF_3), 171.0 (acid C=O), 189.0 (ketone C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = 0.9 (q, *J* = 9.0 Hz, 3 F, CF_3), 1.5 (q, *J* = 9.0 Hz, 3 F, CF_3).

MS: *m*/*z* = 296 $[M]^+$, 593 $[2 M + H]^+$.

(2*S*)-4-Oxonorvaline Hydrochloride (6a)
Compound **5a** (2.0 mmol, 0.56 g) was heated with conc. HCl (1 mL) in a mixture of THF–H_2O (10 mL; 1:1) for 24 h (50 °C bath temperature). After evaporation of the solvent under reduced pressure, the remaining substance was purified by lyophylization.

Yield: 0.23 g (70%); mp 135–137 °C; $[\alpha]_D$ +8.0 (*c* = 1.0, H_2O).

IR (KBr): 3700–3300, 1713, 1660 cm^{-1}.

^1H NMR (200 MHz; $CDCl_3$): δ = 2.11 (s, 1 H, CH_3), 3.12–3.24 (m, 2 H, CH_2), 4.10–4.20 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.2 (CH_3), 42.3 (CH_2), 48.7 (CH), 171.7 (acid C=O), 209.9 (ketone C=O).

MS: *m*/*z* = 656 [5 M + H]$^+$, 525 [4 M + H]$^+$, 394 [3 M + H]$^+$, 263 [2 M + H]$^+$, 132 [M + H]$^+$, 74 [M – CH_2COCH_3]$^+$.

Hydrolysis of Compounds 5b–d; General Procedure

A solution of **5** (5 mmol) was heated in a mixture of MeCN–H_2O (10 mL, 1:1) up to 50 °C (bath temperature) for 24 h. After evaporation of the solvent under reduced pressure, the remaining solid was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to dryness.

2-Hydroxy-4-oxopentanoic Acid (7b)

Yield: 0.48 g (73%); oil; $[\alpha]_D$ –23.1 (*c* = 2.0, $CHCl_3$).

IR (film): 3500–3300, 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, CH_3), 2.88 (dd, *J* = 16.7, 7.7 Hz, 1 H, CH_2), 2.99 (dd, *J* = 16.7, 4.2 Hz, 1 H, CH_2), 4.55 (dd, *J* = 7.7, 4.2 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.4 (CH_3), 46.7 (CH_2), 66.6 (CH), 176.9 (acid C=O), 207.9 (ketone C=O).

MS: *m*/*z* = 133 [M + H]$^+$, 115 [M – H_2O]$^+$.

2-Hydroxy-2-methyl-4-oxopentanoic Acid (7c)

Yield: 0.50 g (69%); oil; $[\alpha]_D$ +22.1 (c = 2.0, $CHCl_3$).

IR (film): 3500–3300, 2985, 1716 cm^{-1}.

^{1}H NMR (300 MHz, methanol-d_4): δ = 1.42 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 2.89 (d, *J* = 17.0 Hz, 1 H, CH_2), 3.12 (d, *J* = 17.0 Hz, 1 H, CH_2).

^{13}C NMR (75 MHz, methanol-d_4): δ = 25.7 (CH_3), 29.6 (CH_3), 52.3 (CH_2), 73.0 (*C*CH_3), 177.8 (acid C=O), 208.1 (ketone C=O).

MS: *m*/*z* = 147 [M + H]$^+$, 169 [M + Na]$^+$.

4-Oxo-2-sulfanylpentanoic Acid (7d)

Yield: 0.52 g (70%); oil.

IR (film): 3400–2900, 1712 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 2.26 (d, *J* = 9.3 Hz, 1 H, SH), 2.89 (dd, *J* = 18.0, 5.1 Hz, 1 H, CH_2), 3.15 (dd, *J* = 18.0, 9.3 Hz, 1 H, CH_2), 3.78 (ddd, *J* = 9.3, 9.3, 5.1 Hz, 1 H, CH), 6.3 (br s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.9 (CH_3), 35.0 (CH), 48.3 (CH_2), 177.7 (acid C=O), 205.2 (ketone C=O).

MS: *m*/*z* = 149 [M + H]$^+$, 131 [M + H – H_2O]$^+$, 130 [M – H_2O]$^+$.

Fluorodeoxygenation of Compounds 3; General Procedure

To a solution of the bromoketone **3a–d** (10 mmol) in CH_2Cl_2 (25 mL), was added DAST (11.6 g, 9.5 mL) at –15 °C with stirring. After 20 h, the reaction mixture was quenched with an ice/water mixture. The organic layer was washed with aq sat. $NaHCO_3$ solution, H_2O and dried ($MgSO_4$). Then the solvent was evaporated in vacuo. The residue was purified by distillation under reduced pressure.

(4*S*)-(3-Bromo-2,2-difluoropropyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (8a)

Yield: 2.66 g (70%); bp 80 °C/0.60 Torr; $[\alpha]_D$ –4.0 (*c* = 1.0, $CHCl_3$).

IR (film): 3350, 1820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28–2.47 (m, 1 H, CH_2), 2.66–2.84 (m, 1 H, CH_2), 3.39 (d, *J* = 6.0 Hz, 1 H, NH), 3.64 (t, *J* = 12.9 Hz, 2 H, CH_2Br), 4.31–4.36 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.5 (dd, *J* = 32.0, 32.0 Hz, CH_2Br), 38.4 (dd, *J* = 28.0, 23.0 Hz, CH_2), 50.0 (CH), 88.5 [sept, *J* = 32.0 Hz, *C*$(CF_3)_2$], 119.0 (q, *J* = 289.0 Hz, CF_3), 120.0 (q, *J* = 284.5 Hz, CF_3), 122.1 (t, *J* = 246.0 Hz, CF_2), 169.9 (C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = – 21.4 (d, 1 F, CF_2), –20.1 (d, 1 F, CF_2), –3.13 (q, *J* = 9.0 Hz, 3 F, CF_3), –2.49 (q, *J* = 9.0 Hz, 3 F, CF_3).

MS: *m*/*z* = 379 [M – H]$^+$, 310 [M – CF_3 – H]$^+$, 236 [M – $BrCH_2CF_2$]$^+$, 144 [$BrCH_2CF_2$]$^+$, 70 [HCF_3]$^+$.

(5*S*)-(3-Bromo-2,2-difluoropropyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one (8b)

Yield: 2.76 g (72%); bp 30 °C/0.07 Torr; $[\alpha]_D$ –12.7 (*c* = 1.5, $CHCl_3$).

IR (film): 1850 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.62–2.74 (m, 2 H, CH_2), 3.55–3.67 (m, 2 H, CH_2Br), 4.95 (dd, *J* = 10.0, 2.0 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.6 (dd, *J* = 34.0, 32.0 Hz, CH_2Br), 37.2 (dd, *J* = 26.0, 25.0 Hz, CH_2), 70.4 (dd, *J* = 7.0, 3.0 Hz, CH), 98.1 [sept, *J* = 36.0 Hz, *C*$(CF_3)_2$], 118.8 (q, *J* = 287.0 Hz, CF_3), 119.1 (t, *J* = 245.0 Hz, CF_2), 119.5 (q, *J* = 289.0 Hz, CF_3), 166.7 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –20.7 (d, 1 F, CF_2), –19.1 (d, 1 F, CF_2), –3.3 (m, 6 F, 2 CF_3).

MS: *m*/*z* = 362/360 [M – HF]$^+$, 69 [CF_3]$^+$.

(5*S*)-(3-Bromo-2,2-difluoropropyl)-2,2-bis(trifluoromethyl)-5-methyl-1,3-dioxolan-4-one (8c)

Yield: 2.68 g (68%); bp 80 °C/0.56 Torr; $[\alpha]_D$ –17.0 (*c* = 2.0, $CHCl_3$).

IR (film): 1845 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 2.57–2.68 (m, 2 H, CH_2), 3.51–3.65 (m, 2 H, CH_2Br).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (CH_3), 31.2 (dd, *J* = 33.0, 31.3 Hz, CH_2Br), 41.0 (dd, *J* = 24.7, 37.0 Hz, CH_2), 79.5 (C), 97.5 [sept, *J* = 36.0 Hz, *C*$(CF_3)_2$], 119.1 (q, *J* = 290.0 Hz, CF_3), 119.2 (q, *J* = 285.5 Hz, CF_3), 119.6 (t, *J* = 246.0 Hz, CF_2), 169.3 (C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –18.8 (d, 1 F, CF_2), –13.8 (d, 1 F, CF_2), –2.9 (m, 6 F, 2 CF_3).

MS: *m*/*z* = 396/394 [M – H]$^+$, 376 [M – F]$^+$, 237 [M – $BrCH_2CF_2CH_2$], 182 [$CO_2(CF_3)_2$]$^+$.

(3-Bromo-2,2-difluoropropyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (8d)

Yield: 3.49 g (88%); bp 60 °C/0.07 Torr.

IR ($CHCl_3$): 1810 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.67–2.73 (m, 1 H, CH_2), 3.25–3.30 (m, 1 H, CH_2), 3.72–3.77 (m, 2 H, CH_2Br), 4.55–4.60 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.5 (dd, *J* = 33.0, 32.5 Hz, CH_2Br), 38.5 (dd, *J* = 23.5, 23.0 Hz, CH_2), 39.5 (CH), 84.0 [sept, *J* = 32.0 Hz, *C*(CF_3)], 119.7 (t, *J* = 245.0 Hz, CF_2), 120.9 (q, *J* = 284.0 Hz, CF_3), 121.6 (q, *J* = 284.0 Hz, CF_3), 170.2 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –22.6 (d, 1 F, CF_2), –19.4 (d, 1 F, CF_2), 0.9 (q, *J* = 9.0 Hz, 3 F, CF_3), 1.9 (q, *J* = 9.0 Hz, 3 F, CF_3).

MS: *m*/*z* = 398/396 [M]$^+$, 397/395 [M – H]$^+$, 316 [M – Br]$^+$, 301 [M – Br – O]$^+$, 69 [CF_3]$^+$.

Deprotection of Compounds 8; General Procedure

Compound **8** (5 mmol) was heated in a solvent mixture of propan-2-ol–H_2O (10 mL, 1:1) for 5 h (50 °C, bath temperature). After evaporation of the solvent under reduced pressure, the remaining solid was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was recrystallized from $CHCl_3$.

(2*S*)-2-Amino-5-bromo-4,4-difluoropentanoic Acid (9a)
Yield: 0.84 g (72%); mp 181–183 °C; $[\alpha]_D$ –9.1 (*c* = 1.1, DMSO).

IR (KBr): 3500-3000, 1630 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.59–2.63 (m, 1 H, CH_2), 2.79–2.85 (m, 1 H, CH_2), 3.66 (dt, *J* = 12.0, 9.0 Hz, 2 H, CH_2Br), 4.06 (t, *J* = 15.0 Hz, 1 H), 4.15–4.20 (m, 1 H, CH), 4.52 (t, *J* = 7.5 Hz, 1 H, OH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 37.1 (CH_2Br), 51.5 (CH_2), 57.8 (CH), 128.0 (t, *J* = 244.0 Hz, CF_2), 169.5 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –18.8 (d, 1 F, CF_2), –17.4 (d, 1 F, CF_2).

MS: *m*/*z* = 460 $[2 M – 4 H]^+$, 232 $[M]^+$, 214 $[M – H_2O]^+$.

(2*S*)-5-Bromo-4,4-difluoro-2-hydroxypentanoic Acid (9b)
Yield: 0.89 g (75%); mp 80–81 °C; $[\alpha]_D$ = –15.0 (*c* = 1.2, $CHCl_3$).

IR (KBr): 3600–3100, 1730 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.00–2.06 (m, 1 H, CH_2), 2.05–2.10 (m, 1 H, CH_2), 3.94 (t, *J* = 12.0 Hz, 2 H, CH_2Br), 4.71–4.76 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.8 (t, *J* = 35.5 Hz, CH_2Br), 44.4 (t, *J* = 35.0 Hz, CH_2), 65.9 (CH), 107.3 (t, *J* = 245.0 Hz, CF_2), 176.7 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –19.6 (d, 1 F, CF_2), –16.7 (d, 1 F, CF_2).

MS: *m*/*z* = 465 $[2 M – H]^+$.

GC/MS: *m*/*z* = 233 $[M]^+$.

(2*S*)-5-Bromo-4,4-difluoro-2-hydroxy-2-methylpentanoic Acid (9c)
Yield: 0.85 g (69%); mp >300 °C (dec.); $[\alpha]_D$ –2.0 (*c* = 1.0, DMSO).

IR (KBr): 3600–3200, 1605 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (s, 3 H, CH_3), 2.38–2.43 (m, 2 H, CH_2), 3.95–4.02 (m, 2 H, CH_2Br).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 (CH_3), 35.0 (CH_2), 44.9 (t, *J* = 35.0 Hz, CH_2Br), 71.8 (CH), 121.2 (t, *J* = 238.0 Hz, CF_2), 178.2 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –20.1 (d, 1 F, CF_2), –17.6 (d, 1 F, CF_2).

MS: *m*/*z* = 247 $[M]^+$, 205 $[M – 2 HF – 2 H]^+$.

5-Bromo-4,4-difluoro-2-sulfanylpentanoic Acid (9d)
Yield: 0.98 g (79%); mp 96–98 °C.

IR (KBr): 3500–2900, 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.38 (dd, *J* = 10.0 Hz, 1 H, SH), 2.49–2.56 (m, 1 H, CH_2), 2.85–2.91 (m, 1 H, CH_2), 3.58–3.65 (m, 2 H, CH_2Br), 3.71–3.77 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.3 (t, *J* = 32.5 Hz, CH_2Br), 31.9 (CH), 40.5 (t, *J* = 25.0 Hz, CH_2), 119.7 (t, *J* = 244.5 Hz, CF_2), 177.7 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –20.5 (m, 2 F, CF_2).

MS: *m*/*z* = 249 $[M]^+$, 227 $[M – F – 3 H]^+$, 203 $[M – COOH – H]^+$.

Alcoholysis of Compounds 8b–d; General Procedure
Compound 8b–d (5 mmol) was reacted with an excess of MeOH (20 mL) for 2 h at 50 °C. Then the solvent was evaporated in vacuo, the residue was washed with Et_2O and purified by flash chromatography (eluent: EtOAc).

Methyl 5-Bromo-4,4-difluoro-2-hydroxypentanoate (10b)
Yield: 0.88 g (71%); mp 100–102 °C; $[\alpha]_D$ –9.4 (*c* = 1.7, $CHCl_3$).

IR (KBr): 3500–3100, 1740 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.30–2.38 (m, 1 H, CH_2), 2.55–2.61 (m, 1 H, CH_2), 3.66–3.75 (m, 2 H, CH_2Br), 3.82 (s, 3 H, OCH_3), 4.40–4.49 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.1 (t, *J* = 32.0 Hz, CH_2Br), 38.3 (t, *J* = 25.0 Hz, CH_2), 53.2 (OCH_3), 66.1 (CH), 120.2 (t, *J* = 244.0 Hz, CF_2), 174.1 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –19.6 (d, 1 F, CF_2), –16.3 (d, 1 F, CF_2).

MS: *m*/*z* = 248 $[M]^+$, 209 $[M – F_2]^+$, 187 $[M – CO_2C_2H_3]^+$, 167 $[M – Br]^+$, 89 $[CHOHCO_2CH_3]^+$, 59 $[CO_2CH_3]^+$.

(2*S*)-Methyl 5-Bromo-4,4-difluoro-2-hydroxy-2-methylpentanoate (10c)
Yield: 0.91 g (70%); oil; $[\alpha]_D$ –9.0 (*c* = 1.7, $CHCl_3$).

IR (film): 3600–3100, 1740 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 2.45–2.51 (m, 1 H, CH_2), 2.59–2.68 (m, 1 H, CH_2), 3.50–3.57 (m, 1 H, CH_2Br), 3.58–3.65 (m, 1 H, CH_2Br), 3.71 (s, 3 H, OCH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.5 (CH_3), 31.4 (t, *J* = 33.0 Hz, CH_2Br), 43.4 (t, *J* = 26.0 Hz, CH_2), 52.9 (OCH_3), 71.8 (CCH_3), 120.1 (t, *J* = 245.0 Hz, CF_2), 176.2 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –20.6 (d, 1 F, CF_2), –18.2 (d, 1 F, CF_2).

MS: *m*/*z* = 262 $[M + H]^+$, 223 $[M – 2 F]^+$, 181 $[M – Br]^+$, 59 $[CO_2CH_3]^+$.

Methyl 5-Bromo-4,4-difluoro-2-sulfanylpentanoate (10d)
Yield: 0.80 g (61%); oil.

IR (KBr): 3365, 1735 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.28 (d, *J* = 10.0 Hz, 1 H, SH), 2.48–2.55 (m, 1 H, CH_2), 2.80–2.90 (m, 1 H, CH_2), 3.50–3.62 (m, 2 H, CH_2), 3.65–3.73 (m, 1 H, CH), 3.76 (s, 3 H, OCH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.6 (t, *J* = 32.0 Hz, CH_2Br), 34.4 (CH), 41.0 (t, *J* = 24.0 Hz, CH_2), 53.2 (OCH_3), 119.8 (t, *J* = 244.0 Hz, CF_2), 173.1 (C=O).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –22.1 (m, 2 F, CF_2).

MS: *m*/*z* = 262 $[M – H]^+$, 232 $[M – OCH_3]^+$, 230 $[M – SH]^+$, 204 $[M – CO_2CH_3]^+$, 163 $[M – Br – HF]^+$.

Debromination of Compounds 8a–d with Tributyltin Hydride; General Procedure
To a solution of **8** (10 mmol) in anhyd benzene (5 mL) in an inert gas atmosphere were added Bu_3SnH (2.90 g, 10 mmol) and AIBN (2,2′-azobisisobutyronitrile, 50 mg, 0.3 mmol) in anhyd benzene (4 mL) dropwise during 10 min. The resulting mixture was stirred at r.t. overnight. The solvent was evaporated in vacuo, and the residue was purified by column chromatography.

(4*S*)-4-(2,2-Difluoropropyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (11a)
Yield: 1.98 g (66%) ; bp 65 °C/5 Torr; $[\alpha]_D$ –18.3 (*c* = 2.0, $CHCl_3$).

IR (film): 3450–3350, 1832 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.72 (t, *J* = 18.8 Hz, 3 H, CH_3), 2.08–2.25 (m, 1 H, CH_2), 2.42–2.60 (m, 1 H, CH_2), 3.38 (d, *J* = 4.8 Hz, 1 H, NH), 4.27–4.33 (m, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.0 (t, *J* = 26.6 Hz, CH_3), 41.5 (t, *J* = 24.0 Hz, CH_2), 50.2 (CH), 88.6 [sept, *J* = 34.5 Hz, $C(CF_3)_2$],

121.3 (q, J = 286.6 Hz, 2 CF_3), 122.9 (t, J = 238.0 Hz, CF_2), 170.5 (acid C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –14.8 (d, 1 F, CF_2), –13.1 (d, 1 F, CF_2), –3.1 (q, J = 9.0 Hz, 3 F, CF_3), –2.5 (q, J = 9.0 Hz, 3 F, CF_3),

MS: m/z = 261 $[M – K]^+$ 238 $[M – CH_3CF_2]^+$, 136 $[M – HFA]^+$.

(5*S*)-5-(2,2-Difluoropropyl)-2,2-bis(trifluoromethyl)-1,3-dioxolan-4-one (11b)
Yield: 2.29 g (76%); bp 104 °C/250 Torr; $[\alpha]_D$ –6.2 (c = 2.0, $CHCl_3$).

IR (film): 3500–3200, 2990, 1820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (t, J = 18.5 Hz, 3 H, CH_3), 2.28–2.41 (m, 1 H, CH_2), 2.49–2.59 (m, 1 H, CH_2), 4.92 (d, J = 9.6 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.9 (t, J = 26.5 Hz, CH_3), 40.4 (t, J = 27.3 Hz, CH_2), 70.9 (CH), 97.6 [sept, J = 37.4 Hz, $C(CF_3)_2$], 118.7 (q, J = 287.2 Hz, CF_3), 119.5 (q, J = 288.7 Hz, CF_3), 121.4 (t, J = 240.3 Hz), 167.2 (C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –14.2 (d, 1 F, CF_2), –11.2 (d, 1 F, CF_2), –3.5 (q, J = 6.0 Hz, 3 F, CF_3), –3.3 (q, J = 6.0 Hz, 3 F, CF_3),

MS: m/z = 605 $[2 M + H]^+$, 325 $[M + Na]^+$, 303 $[M + H]^+$.

(5*S*)-5-(2,2-Difluoropropyl)-2,2-bis(trifluoromethyl)-5-methyl-1,3-dioxolan-4-one (11c)
Yield: 2.05 g (65%); bp 78 °C; $[\alpha]_D$ +18.9 (c = 2.0, $CHCl_3$).

IR (film): 3000, 1843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (t, J = 18.0 Hz, 3 H, CH_3), 1.72 (s, CH_3), 2.24–2.36 (m, 1 H, CH_2), 2.41–2.59 (m, 1 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4 (s, CH_3), 24.4 (t, J = 26.7 Hz, CH_3), 44.0 (dd, J = 28.8 Hz, CH_2), 79.7 [d, J = 7.7 Hz, $C(CH_3)$], 97.4 [sept, J = 35.9 Hz, $C(CF_3)_2$], 119.2 (q, J = 288.3 Hz, CF_3), 119.3 (q, J = 289.8 Hz, CF_3), 122.2 (t, J = 238.8 Hz, CF_2), 169.7 (acid C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –10.5 (d, 1 F, CF_2), –9.7 (d, 1 F, CF_2), –3.1 (m, 6 F, 2 CF_3).

HRMS: m/z = 316 $[M]^+$.

4-(2,2-Difluoropropyl)-2,2-bis(trifluoromethyl)-1,3-oxathiolan-5-one (11d)
Yield: 2.13 g (67%); bp 88 °C/50 Torr.

IR (film): 3000, 1824 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73 (t, J = 18.4 Hz, 3 H, CH_3), 2.30–2.39 (m, 1 H, CH_2), 2.83–3.00 (m, 1 H, CH_2), 4.41 (d, J = 11.1 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8 (t, J = 26.9 Hz, CH_3), 39.8 (d, J = 4.0 Hz, CH), 42.3 (t, J = 24.6 Hz, CH_2), 83.5 [sept, J = 35.5 Hz, $C(CF_3)_2$], 120.9 (q, J = 284.6 Hz, CF_3), 121.5 (q, J = 283.4 Hz, CF_3), 121.8 (t, J = 237.3 Hz, CF_2), 170.5 (acid C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –16.1 (d, 1 F, CF_2), –12.7 (d, 1 F, CF_2), 0.8 (q, J = 9.1 Hz, 3 F, CF_3), 1.9 (q, J = 9.1 Hz, 3 F, CF_3).

MS: m/z = 318 $[M]^+$, 299 $[M – F]^+$, 267 $[M – HCF_2]^+$.

Hydrolysis of Compounds 11a–d; General Procedure
A solution of **11** (5 mmol) was heated in a solvent mixture of MeCN–H_2O (10 mL; 1:1) up to 50 °C (bath temperature) for 24 h. After evaporation of the solvent under reduced pressure, the remaining solid was extracted with Et_2O (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to dryness and the residue was recrystallized from $CHCl_3$.

(2*S*)-4,4-Difluoronorvaline (12a)
Yield: 0.46 g (60%); colorless crystals; mp 230 °C; $[\alpha]_D$ –4.6 (c = 2.0, $CHCl_3$).

IR (KBr): 3100–3000, 1599 cm^{-1}.

^{1}H NMR (300 MHz, methanol-d_4): δ = 1.76 (t, J = 19.2 Hz, 3 H, CH_3), 2.39–2.45 (m, 1 H, CH_2), 2.66–2.79 (m, 1 H, CH_2), 3.84 (dd, J = 11.1, 2.4 Hz, 1 H, CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.5 (t, J = 26.0 Hz, CH_3), 40.3 (t, J = 24.7 Hz, CH_2), 52.4 (d, J = 2.7 Hz, CH), 126.7 (t, J = 235.1 Hz, CF_2), 175.7 (acid C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –13.6 (d, 1 F, CF_2), –10.4 (d, 1 F, CF_2).

MS: m/z = 154 $[M + H]^+$, 88 $[M – CH_3CF_2]^+$.

(2*S*)-4,4-Difluoro-2-hydroxypentanoic Acid (12b)
Yield: 0.53 g (69%); colorless crystals; mp 73 °C; $[\alpha]_D$ +11.5 (c = 2.0, $CHCl_3$).

IR (KBr): 3400–3200, 3000, 1719 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (t, J = 19.0 Hz, 3 H, CH_3), 2.25–2.33 (m, 1 H, CH_2), 2.44–2.54 (m, 1 H, CH_2), 4.57 (d, J = 6.5 Hz, 1 H, CH), 7.42 (br s, 1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.1 (t, J = 26.5 Hz, CH_3), 41.5 (t, J = 25.4 Hz, CH_2), 66.5 (s, CH), 123.4 (t, J = 237.6 Hz, CF_2), 177.7 (acid C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –11.7 (d, 1 F, CF_2), –9.8 (d, 1 F, CF_2).

MS: m/z = 153 $[M – H]^+$, 89 $[M – CH_3CF_2]^+$.

(2*S*)-4,4-Difluoro-2-hydroxy-2-methylpentanoic Acid (12c)
Yield: 0.60 g (72%); colorless crystals; mp 108 °C; $[\alpha]_D$ +4.1 (c = 2.0, $CHCl_3$).

IR (KBr): 3420, 3000, 1728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 3 H, CH_3), 1.69 (t, J = 19.2 Hz, 3 H, CH_3), 2.21–2.34 (m, 1 H, CH_2), 2.44–2.59 (m, 1 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.8 (t, J = 27.1 Hz, CH_3), 27.9 (CH_3), 47.6 (t, J = 30.0 Hz, CH_2), 72.8 (t, J = 6.1 Hz, C), 124.6 (t, J = 236.5 Hz, CF_2), 178.7 (acid C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –9.7 (d, 1 F, CF_2), –5.2 (d, 1 F, CF_2).

MS: m/z = 169 $[M + H]^+$, 149 $[M + H – HF]^+$, 133 $[M + H – 2 F]^+$.

4,4-Difluoro-2-sulfanylpentanoic Acid (12d)
Yield: 0.53 g (62%); colorless crystals; mp 95 °C.

IR (KBr): 3500–3300, 3000, 1749, 1660 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (t, J = 18.9 Hz, 3 H, CH_3), 2.21–2.36 (m, 1 H, CH_2), 2.34 (d, J = 9.6 Hz, 1 H, SH), 2.62–2.81 (m, 1 H, CH_2), 3.84 (ddd, J = 9.6, 3.9 Hz, 1 H, CH), 8.1 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.8 (t, J = 27.1 Hz, CH_3), 34.5 (t, J = 4.2 Hz, CH), 43.6 (t, J = 25.5 Hz, CH_2), 122.3 (t, J = 239.6 Hz, CF_2), 178.7 (C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –13.5 (d, 1 F, CF_2), –12.9 (d, 1 F, CF_2),

MS: m/z = 169 $[M]^+$, 104 $[M – CH_3CF_2]^+$.

Aminolysis of Compounds 11a–d; General Procedure
A solution of **11** (1.5 mmol) and amine (2.0 mmol) in a minimum amount of anhyd MeCN was stirred at r.t. for 48 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography.

(3*S*,6*S*)-3-Benzyl-6-(2,2-difluoropropyl)-2,5-diketopiperazine (13a)
Yield: 0.30 g (72%); mp 174 °C; $[\alpha]_D$ +3.4 (c = 2.0, MeCN).

IR (KBr): 3450–2900, 1678 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 1.50 (t, *J* = 19.2 Hz, 3 H, CH_3), 1.72–1.89 (m, 2 H, CH_2Ph), 2.90 (dd, *J* = 13.5, 4.9 Hz, 1 H, CH_2), 3.15 (dd, *J* = 13.5, 4.0 Hz, 1 H, CH_2), 3.84 (d, *J* = 8.7 Hz, 1 H, CH), 4.20–4.29 (m, 1 H, CH), 7.15–7.35 (m, 5 H, C_6H_5), 7.87 (s, 1 H, NH), 8.35 (s, 1 H, NH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 22.9 (t, *J* = 26.5 Hz, CH_3), 38.1 (CH_2Ph), 41.1 (t, *J* = 24.8 Hz, CH_2), 49.9 (t, *J* = 4.0 Hz, CH), 55.3 (CH), 123.6 (t, *J* = 236.9 Hz, CF_2), 126.7, 128.2, 130.4, 136.1 (C_6H_5), 166.3 (2 C=O).

^{19}F NMR (282 MHz, DMSO-d_6): δ = –9.2 (d, 1 F, CF_2), –7.5 (d, 1 F, CF_2).

MS: *m*/*z* = 281 $[M – H]^+$.

Methyl *N*-[(2*S*)-4,4-Difluoro-2-hydroxypentanoyl]phenylalaninate (14b)
Yield: 0.30 g (63%); mp 55 °C; $[\alpha]_D$ –12.4 (*c* = 2.0, MeOH).

IR (KBr): 3380, 3300, 1731, 1639 cm^{-1}.

^1H NMR (300 MHz, methanol-d_4): δ = 1.60 (t, *J* = 19.0 Hz, 3 H, CH_3), 1.82–2.03 (m, 1 H, CH_2), 2.09–2.29 (m 1 H, CH_2), 3.02 (dd, *J* = 14.0, 5.5 Hz, 1 H, CH_2Ph), 3.18 (dd, *J* = 14.0, 8.0 Hz, 1 H, CH_2Ph), 3.69 (s, 3 H, OCH_3), 4.21 (dd, *J* = 1.8, 9.4 Hz, 1 H, CH), 4.74 (dd, *J* = 5.5, 8.0 Hz, 1 H, CH), 7.10–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0 (t, *J* = 26.9 Hz, CH_3), 37.2 (CH_2Ph), 41.9 (t, *J* = 25.8 Hz, CH_2), 51.8 (OCH_3), 53.3 (CH), 67.5 (t, *J* = 5.7 Hz, COH), 123.6 (t, *J* = 236.5 Hz, CF_2), 126.9, 128.4, 129.2, 136.6 (C_6H_5), 172.0 (C=O), 174.5 (C=O).

^{19}F NMR (188 MHz, methanol-d_4): δ = –13.2 (d, 1 F, CF_2), –9.6 (d, 1 F, CF_2).

MS: *m*/*z* = 314 $[M – H]^+$, 254 $[M – CH_3CF_2]^+$.

Methyl *N*-[(2*S*)-4,4-Difluoro-2-hydroxy-2-methylpentanoyl]phenylalaninate (14c)
Yield: 0.33 g (67%); mp 77 °C; $[\alpha]_D$ +26.0 (*c* = 2.0, MeOH).

IR (KBr): 3395, 3380, 3200, 1750, 1670, 1538 cm^{-1}.

^1H NMR (300 MHz, methanol-d_4): δ = 1.40 (s, CH_3), 1.53 (t, *J* = 19.5 Hz, 3 H, CH_3), 2.05–2.20 (m, 1 H, CH_2), 2.40–2.55 (m, 1 H, CH_2), 3.12 (d, 1 H, CH_2Ph), 3.15 (d, 1 H, CH_2Ph), 3.73 (s, 3 H, OCH_3), 4.73 (t, *J* = 6.6 Hz, 1 H, CH), 7.20–7.35 (m, 5H, C_6H_5).

^{13}C NMR (50 MHz, methanol-d_4): δ = 24.5 (t, *J* = 26.9 Hz, CH_3), 28.0 (CH_3), 38.3 (CH_2Ph), 47.0 (t, *J* = 25.0 Hz, CH_2), 52.8 (OCH_3), 54.6 (CH), 73.7 (COH), 124.7 (t, *J* = 235.9 Hz, CF_2), 128.0, 129.6, 130.3, 137.6 (C_6H_5), 173.1 (C=O), 177.7 (C=O).

^{19}F NMR (282 MHz, methanol-d_4): δ = –5.8 (d, 1 F, CF_2), –2.8 (d, 1 F, CF_2).

MS: *m*/*z* = 328 $[M – H]^+$.

Methyl *N*-[(2*S*)-4,4-Difluoro-2-sulfanylpentanoyl]phenylalaninate (14d)
Yield: 0.31 g (64%); mp 102 °C; 1:1 diastereomeric mixture.

IR (KBr): 3325, 2950, 1736, 1647 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (t, *J* = 18.6 Hz, 3 H, CH_3), 2.13–2.16 (m, 1 H, CH_2), 2.17–2.20 (m, 1 H, CH_2), 2.64–2.77 (m, 1 H, CH_2), 3.04–3.08 (m, 1 H, CH_2Ph), 3.11–3.13 (m, 1 H, CH_2Ph), 3.34–3.42 (m, 1 H, CHNH)), 3.66 (s, 3 H, OCH_3), 4.78–4.85 (m, 1 H, CH), 6.42 (d, *J* = 7.4 Hz, 1 H, NH), 7.05–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.9 (t, *J* = 26.9 Hz, CH_3), 36.6 (CH_2Ph), 37.9 (CH), 43.8 (t, *J* = 25.0 Hz, CH_2), 52.5 (OCH_3), 53.7 (CHNH), 123.4 (t, *J* = 235.0 Hz, CF_2), 127.3, 128.7, 129.6, 135.7 (C_6H_5), 171.4 (C=O), 171.7 (C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –13.5 (d, 1 F, CF_2), –11.8 (d, 1 F, CF_2).

MS: *m*/*z* = 330 $[M – H]^+$, 314 $[M – OH]^+$.

Benzyl *N*-[(2*S*)-2-Amino-4,4-difluoropentanoyl]azaglycinate (15a)
Yield: 0.32 g (72%); mp 157 °C; $[\alpha]_D$ –17.2 (*c* = 2.0, MeOH).

IR (KBr): 3400–3000, 1716, 1522 cm^{-1}.

^1H NMR (300 MHz, methanol-d_4): δ = 2.01 (s, 3 H, CH_3), 2.87–2.99 (m, 2 H, CH_2), 3.33–3.35 (m, 1 H, CH), 5.25 (s, 2 H, CH_2Ph), 7.36–7.43 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.7 (CH_3), 38.2 (CH_2), 68.2 (CH_2Ph), 77.1–77.7 (m, CH), 121.5 (q, *J* = 286.4 Hz, CF_2), 129.2, 129.3, 129.5, 137.6 (C_6H_5), 156.6 (urethane C=O), 170.5 (hydrazide C=O).

^{19}F NMR (282 MHz, methanol-d_4): δ = –11.4 (d, 1 F, CF_2), –9.7 (d, 1 F, CF_2).

MS: *m*/*z* = 300 $[M – H]^+$.

Benzyl *N*-[(2*S*)-4,4-Difluoro-2-hydroxypentanoyl]azaglycinate (15b)
Yield: 0.27 g (60%); mp 74 °C; $[\alpha]_D$ +3.4 (*c* = 2.0, MeOH).

IR (KBr): 3400, 3200, 1688, 1662 cm^{-1}.

^1H NMR (300 MHz, methanol-d_4): δ = 2.21 (t, *J* = 14.8 Hz, 3 H, CH_3), 2.19–2.26 (m, 1 H, CH_2), 2.30–2.48 (m, 1 H, CH_2), 4.39–4.42 (m, 1 H, CH), 5.18 (s, 2 H, PhCH_2), 7.30–7.45 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, methanol-d_4): δ = 23.1 (t, *J* = 27.5 Hz, CH_3), 42.0 (t, *J* = 25.8 Hz, CH_2), 67.2 (CH_2Ph), 67.3 (COH), 123.6 (t, *J* = 237.6 Hz, CF_2), 127.9, 128.1, 128.4, 136.5 (C_6H_5), 157.3 (urethane C=O), 174.6 (hydrazide C=O).

^{19}F NMR (282 MHz, methanol-d_4): δ = –10.8 (d, 1 F, CF_2), –6.7 (d, 1 F, CF_2).

MS: *m*/*z* = 301 $[M – H]^+$.

Benzyl *N*-[(2*S*)-2-Hydroxy-4,4-difluoro-2-methylpentanoyl]azaglycinate (15c)
Yield: 0.34 g (71%); mp 67 °C; $[\alpha]_D$ +29.1 (*c* = 2.0, MeOH).

IR (KBr): 3400–3250, 1682 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 1 H, CH_3), 1.66 (t, *J* = 19.5 Hz, 3 H, CH_3), 2.01–2.35 (m, 1 H, CH_2), 2.55–2.71 (m, 1 H, CH_2), 5.17 (s, 2 H, PhCH_2), 7.18 (s, 1 H, NH), 7.25–7.45 (m, 5 H, C_6H_5), 8.79 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (t, *J* = 26.9 Hz, CH_3), 27.7 (CH_3), 45.6 (t, *J* = 23.5 Hz, CH_2), 68.2 (CH_2Ph), 74.3 (t, *J* = 2.9 Hz, COH), 124.4 (t, *J* = 238.2 Hz, CF_2), 128.5, 128.7, 128.8, 135.7 (C_6H_5), 156.6 (urethane C=O), 175.1 (hydrazide C=O).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –9.1 (d, 1 F, CF_2), –6.0 (d, 1 F, CF_2).

MS: *m*/*z* = 339 $[M + Na]^+$, 665 $[2 M + Na]^+$.

Benzyl *N*-(4,4-Difluoro-2-sulfanylpentanoyl)azaglycinate (15d)
Yield: 0.37 g (77%); oil; 1:1 diastereomeric mixture.

IR (KBr): 3400–3200, 3020, 1700, 1530 cm^{-1}.

^1H NMR (300 MHz, methanol-d_4): δ = 1.64 (t, *J* = 18.4 Hz, 3 H, CH_3), 2.32–2.38 (m, 1 H, CH_2), 2.72–2.81 (m, 1 H, CH_2), 3.51–3.72 (m, 1 H, CH), 5.17 (s, 2 H, PhCH_2), 7.25–7.50 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, methanol-d_4): δ = 22.7 (t, J = 26.9 Hz, CH_3), 33.5 (CH), 43.2 (t, J = 25.8 Hz, CH_2), 67.3 (CH_2Ph), 122.9 (t, J = 237.3 Hz, CF_2), 127.9, 128.2, 128.4, 136.2 (C_6H_5), 157.2 (urethane C=O), 173.7 (hydrazide C=O).

^{19}F NMR (282 MHz, methanol-d_4): δ = –14.3 (d, 1 F, CF_2), –10.7 (d, 1 F, CF_2).

MS: m/z = 319 $[M + H]^+$, 341 $[M + Na]^+$, 357 $[M + K]^+$.

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