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Synthesis of α,ω-polyfluorinated α-amino acid derivatives and δ,δ-difluoronorvaline†

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Intending to synthesize ω,ω-difluoroalkyl amino acid derivatives by oxidative desulfurization–fluorination reactions of suitable arylthio-2-phthalimido butanoates and pentanoates, in addition to small amounts of the target products, mainly α,ω-polyfluorinated amino acid derivatives were formed by additional sulfur-assisted α-fluorination. This novel structural motif was verified spectroscopically as well as by X-ray analysis. A plausible mechanism of formation is suggested. Using a different approach, δ,δ-difluoronorvaline hydrochloride was synthesized with at least 36% enantiomeric excess *via* deoxofluorination of the corresponding aldehyde.

Introduction

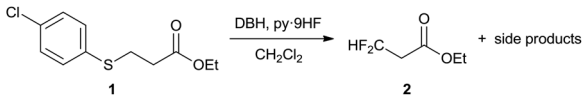
Fluorinated organic molecules play equally important roles in industry[1] as well as for medical[2–5] and agricultural applications.[6–8] For industrial uses especially polyfluorinated materials are of great interest whereas for medicinal or pesticidal purposes interest lies mainly in molecules containing single fluorine substituents or small fluorinated groups. Due to the characteristics of the fluorine substituent, particularly its strong electronegativity and low polarizability, the physical–chemical and pharmacokinetic properties of the respective molecules can be directly influenced. These include the compounds' chemical reactivity, polarity, solubility, *etc*. Additionally, fluorine substitution in strategic positions can increase the metabolic stability of pharmaceuticals *e.g.* by preventing cytochrome mediated oxidation of the oxidation prone sites of the corresponding molecules.

Amino acids are omnipresent in all organisms. They are not only found as monomers, but mostly in the polymerized form as peptides and proteins.[9] The enzymes formed from these polymers are crucial for every living organism as they catalyse chemical reactions inside and outside of cells. Fluorinated amino acids (FAAs)[10–13] can be used to stabilize certain peptides or enzymes and sometimes even increase enzymatic activity.[14–23] Thus the inclusion of FAAs in enzymes can cause valuable improvements in industrial as well as medicinal applications.[24–26] In this publication we present the syntheses of α,δ-polyfluorinated amino acid derivatives by oxidative desulfurization–fluorination as well as the first synthesis of 2-amino-5,5-difluoropentanoic acid (δ,δ-difluoronorvaline).

Results and discussion

In the course of our research it was our aim to synthesize the previously unknown 2-amino-5,5-difluoropentanoic acid (δ,δ-difluoronorvaline). To achieve this, we thought oxidative desulfurization–difluorination was a promising method.[27] As previously reported,[28,29] this kind of reaction can be employed to convert alkyl aryl thioethers like **1** to the corresponding ω,ω-difluoromethyl compounds such as **2** (Scheme 1).

For the synthesis of FAAs by oxidative desulfurization–difluorination first of all suitable starting materials had to be prepared. The alkylation of Schiff bases **3** using sodium hexamethyl disilazide (NaHMDS) and 3-bromoprop-1-yl-arylthioethers **4** was generally possible (Scheme 2, condition A). However, alkylation with potassium *tert*-butoxide in DMSO as a base, which is already known to be very effective for synthesizing α-amino acid derivatives bearing aliphatic side chains,[30] provided simpler access to the required 5-arylthio amino pentanoic acid derivatives **5** (Scheme 2, condition B).



1 2

Scheme 1 Conversion of alkyl aryl thioethers to difluorides by oxidative desulfurization–fluorination.

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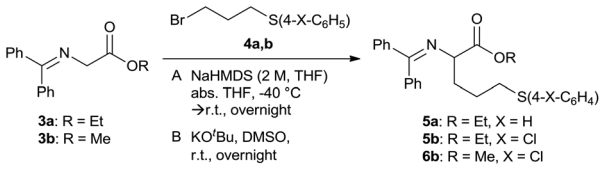
†Electronic supplementary information (ESI) available: Copies of NMR spectra of compounds **5–10**, **12–15**, **21**, **26–29**, **36–41**, and spectroscopic data of new starting materials. CCDC 1429375 and 1429376. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob00131a

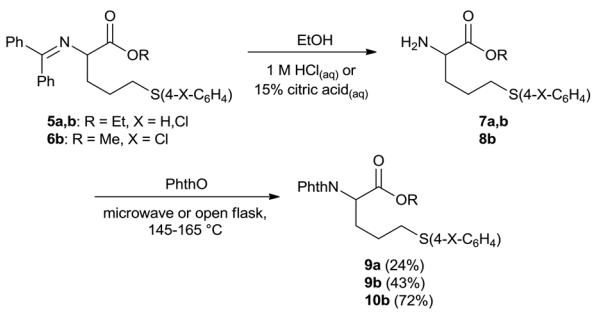


Scheme 2 Alkylation of Schiff bases **3a** and **3b**.

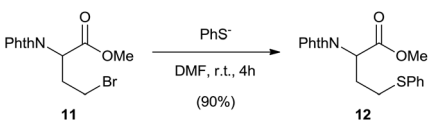
Due to the possible hydrolysis on silica gel, the products were not subjected to chromatography. In the following steps, a nitrogen protection group that is sufficiently stable under the highly acidic conditions of the fluorination step had to be introduced. In previous experiments, the phthalimide group had already proved to be a good choice in this respect. Therefore, after acidic hydrolysis of the diphenylmethylene imines **5a**, **5b** and **6b**, the obtained free amino acids **7** and **8** were condensed with phthalic anhydride to yield thioethers **9** and **10** in moderate overall yields after three steps from diphenylmethylene imines **3** (Scheme 3).

The lower homologue **12** of thioether **10b** was accessible from methyl 4-bromo-2-phthalimidobutanoate[31,32] by the substitution of bromide against phenyl thiolate (Scheme 4).

The subsequent reaction of the aforementioned thioethers **9a** and **10b** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and Olah's reagent yielded only a small amount of the target ω,ω-polyfluoroamino acid derivatives. Quite surprisingly, we primarily observed the formation of trifluorides **13c**, **14c** and **15c** as the major products (Scheme 5). Thus, we found a method to simultaneously introduce fluorine atoms on two remote C-atoms separated by one or two methylene groups creating a new structural motif. It is noteworthy that in contrast to previous reports of β-hydrogen containing α-FAAs,[33–40] our example represents the first method employing a nucleophilic fluorine source.



Scheme 3 Introduction of the phthalimide protecting group.

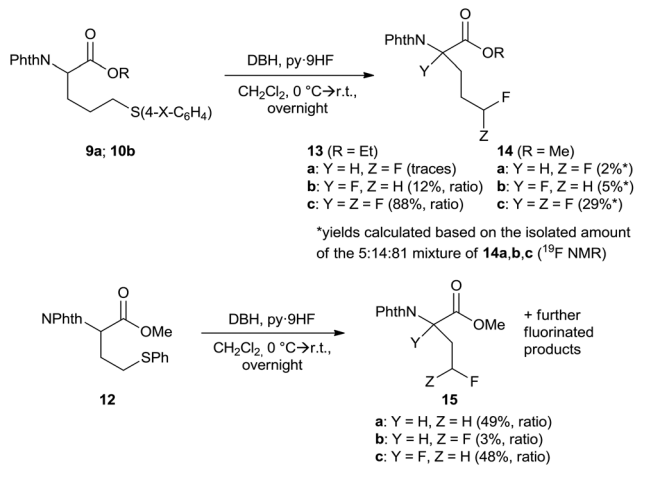


Scheme 4 Synthesis of methyl 4-phenylthio-2-phthalimido-butanoate (**12**).

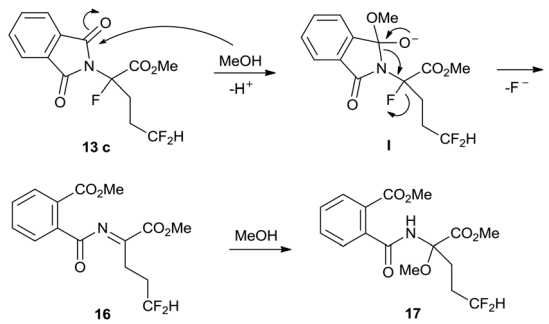
Although the α-fluorinated products **13b** and **13c** of the reaction of **9a** could not be separated by column chromatography, the obtained mixture was extensively investigated by NMR spectroscopy. The FH-HETCOR NMR spectrum clearly shows two fluorine signals with shifts of δ = −123.7 ppm and δ = −116.8/−117.6 ppm that couple with the C-3 and C-4 methylene moieties respectively. While the first is split into a doublet of doublets of triplets ($^3J_{F,H}$ = 26.0, 11.2 Hz, $^5J_{F,F}$ = 1.5 Hz, 1 F, 2-CF), the latter is an AB signal ($^2J_{F,F}$ = 281.9 Hz, $^2J_{F,H}$ = 56.4 Hz, $^3J_{F,H}$ = 16.2 Hz, $^5J_{F,F}$ = 1.3 Hz/$^2J_{F,F}$ = 281.9 Hz, $^2J_{F,H}$ = 56.2 Hz, $^3J_{F,H}$ = 18.7, 16.6 Hz, $^5J_{F,F}$ = 1.7 Hz, 2 F, 5-CF_2H), which shows a distinctive roof effect. While the long range coupling of the fluorine atoms in the ^{1}H coupled ^{19}F NMR spectrum can only be surmised based on the relatively broad signals, they can clearly be seen in the ^{1}H decoupled fluorine spectrum. Further proof for the proposed structures was obtained from the ^{13}C NMR spectrum which clearly shows coupling of the side chain methylene units with a monofluoro as well as a difluoro group (see ESI†).

Looking at the ESI-MS spectrum, in addition to the expected sodium adduct peaks we also noticed a peak that has to be assigned to the sodium adduct of the α-methoxy compound **17**, which originates from the reaction of trifluoride **13c** with methanol (Scheme 6) in a fashion first described by Hudhomme and Duguay.[41] We later recognized that the formation of such products under ESI conditions is characteristic for all of the obtained α-fluorinated α-amino acid derivatives. No reaction, however, was observed when **13c** was dissolved in methanol and maintained at room temperature for 24 hours.

The oxidative desulfurization–fluorination of thioether **10b** leads to similar results. After chromatography, a mixture of products **14a–c** was isolated (Scheme 5). The traces of the δ,δ-difluoride **14a** could subsequently be removed by crystallization. Although we were not able to separate the two α-fluorinated products **14b** and **14c** from each other chromatographically, the crystallization yielded single crystals of methyl 2,5,5-trifluoro-2-phthalimidopentanoate (**14c**), which



Scheme 5 Reaction of thioethers **9**, **10** and **12** with DBH and Olah's reagent.



Scheme 6 Reaction of **13c** with methanol during ESI-MS.

were analyzed by X-ray diffraction (Fig. 1). Thus, we gained definite proof of the constitution of the unexpectedly obtained polyfluorides.

The application of oxidative desulfurization–fluorination conditions to thioether **12** also yielded only 3% of the target γ,γ-difluoride **15b** (^{19}F NMR), which could not be separated chromatographically from the α-fluorides **15a** (49%) and **15c** (48%) (Scheme 5).

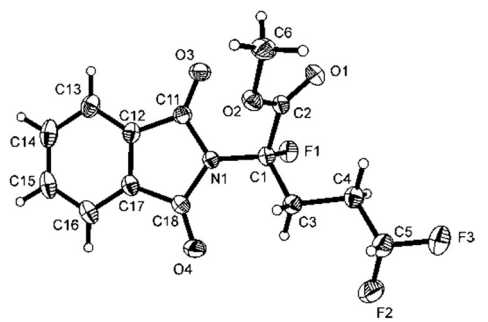
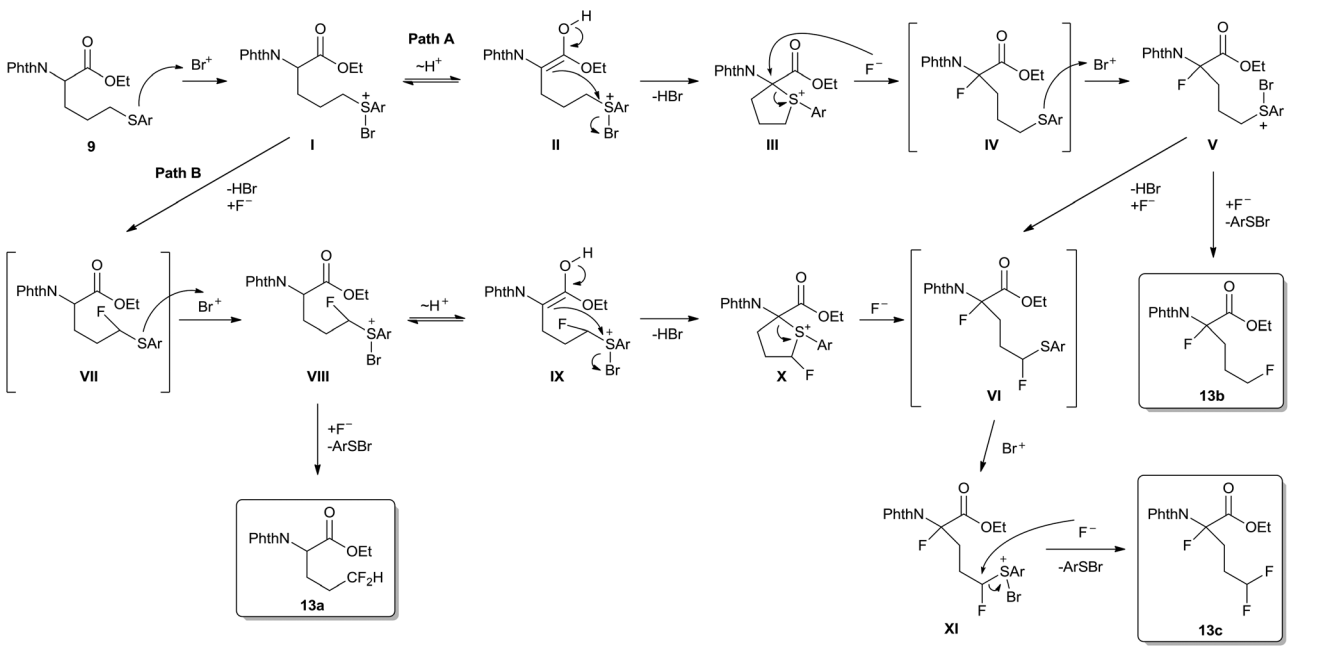


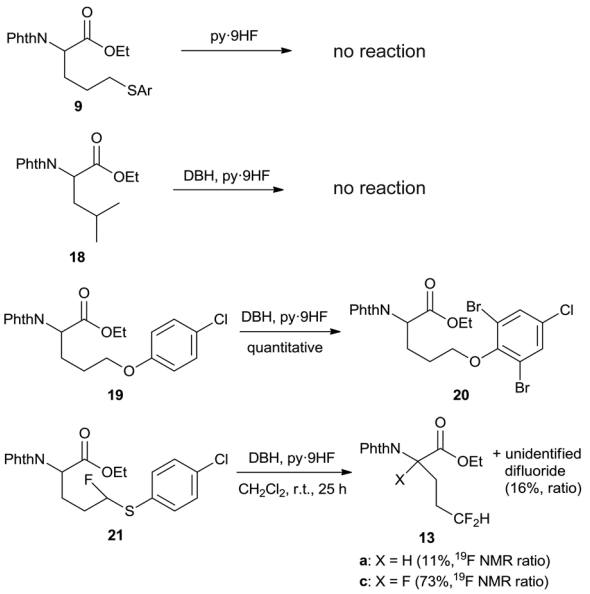
Fig. 1 X-ray crystal structure of **14c** (CCDC 1429376).

To the best of our knowledge, this type of reaction has never been reported before. We anticipate that the products **13a–c** are formed according to the mechanism depicted in Scheme 7 that is based on postulations by Hugenberg.[29,42] Notably, compound **13c** can be formed either *via* pathway A – first introduction of the α-fluorine atom (**IV**) and afterwards oxidative desulfurization fluorination in the δ-position – or *via* pathway B, which starts with δ-monofluorination (**VII**) followed by α-fluorination (**X**) and finally introduction of the second δ-fluorine atom.

To further elucidate the proposed mechanism, several control experiments (Scheme 8) were conducted. Simple addition of pyridine polyhydrofluoride to substrate **9a** proved the stability of the starting material under acidic conditions in the absence of an electrophile and thus the involvement of a bromonium species in δ- as well as in α-fluorination. Exposure of the protected leucine **18** to DBH and Olah's reagent also did not lead to any reaction so that the initial bromination in the α-position followed by substitution with fluoride could be ruled out. To prove the importance of the sulfur atom for the α-fluorination, an ether analogue **19** of thioether **9a** was synthesized and subjected to standard conditions for oxidative desulfurization–fluorination. Instead of fluorination, however, only bromination of the aromatic system resulting in the formation of **20** occurred. To check the probability of the two suggested pathways, following a procedure by Robins and Wnuk[43] we furthermore synthesized a 5-fluoro derivative **21** of thioether **9** and subsequently applied our fluorination protocol. Among the products were δ,δ-difluoride **13a** as well as α,δ,δ-trifluoride



Scheme 7 Proposed mechanisms leading to fluorides **13a–c**.



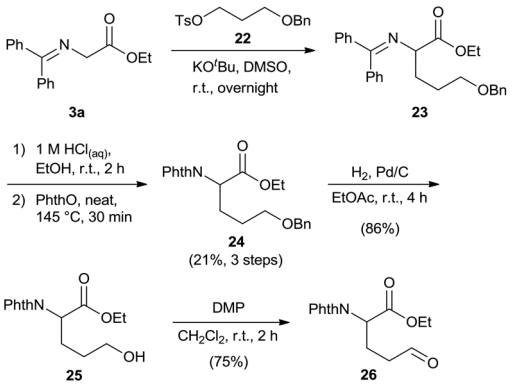
Scheme 8 Control experiments to confirm the proposed mechanism.

13c, whereas expectedly the α,δ-difluoride **13b** was not observed. This shows that the generation of **13c** *via* pathway **B** is probable, although pathway A cannot be definitely excluded.

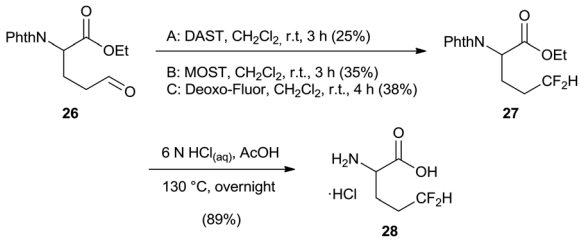
Based on the difficulties experienced in selectively synthesizing ω,ω-difluorinated amino acids by oxidative desulfurization–difluorination reactions of thioethers, we looked for alternative routes to our initial target molecules. As deoxofluorination reactions are commonly used to generate difluoromethyl moieties from aldehydes,[44] we aimed at employing this convenient methodology for our purposes. At first we planned to test the applicability of the method with our system by synthesizing protected *rac*-2-amino-5-oxopentanoic acid and reacting it with the deoxofluorinating agents diethylaminosulfur trifluoride (DAST), morpholinosulfur trifluoride (MOST) and bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor). The aldehyde **26** was synthesized in a similar fashion as used for thioethers **9** and **10**. Beginning with Schiff base **3a**, *rac*-methyl 5-oxo-2-phthalimido-pentanoate (**26**) was synthesized in 5 steps that included alkylation of **3a**, hydrolysis of the formed imine **23**, phthalimide protection of the free amino group to form **24**, hydrogenation of the benzyl ester to **25** and finally oxidation of the terminal hydroxy functionality to aldehyde **26** (Scheme 9).

In the following step, aldehyde **26** was reacted with different deoxofluorinating agents, namely DAST, MOST and Deoxo-Fluor to yield difluoride **27** (Scheme 10). The reaction was feasible with all of these reagents, although the yields of 25, 35 and 38% were rather low in all cases.

Having the protected δ,δ-difluorinated amino acid ester **27** in hand, we adapted a method by Griesbeck and Hirt[45] to obtain the free racemic amino acid in the form of the hydrochloride salt **28** in 89% yield after solid phase extraction (SPE). While the pK_a value of the amino function was determined to be 9.01, similar to that of δ-fluoronorvaline (p$K_a(NH_2)$ = 8.8,



Scheme 9 Synthesis of aldehyde **26**.

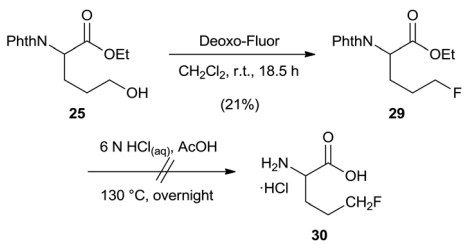


Scheme 10 Fluorination of **26** and deprotection of **27**.

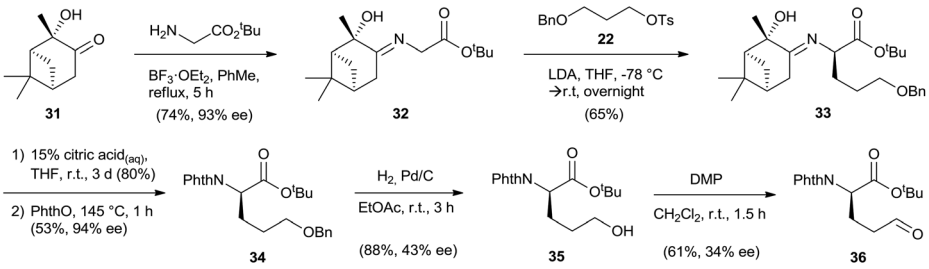
pK_a(COOH) = 2.3 (ref. 46)), and almost one magnitude more acidic than norvaline (p$K_a(NH_2)$ = 9.81, pK_a(COOH) = 2.32 (ref. 47)), the corresponding value of the carboxy moiety of 2.23 was slightly lower than expected.

One could also imagine a direct route to the analogous monofluoride **30** by reacting the alcohol **25** with Deoxo-Fluor and subsequent deprotection. Although the fluorination step to form **29** was indeed successful, the deprotection step using the above mentioned method led to a complex mixture of unidentified, partly defluorinated products (Scheme 11). Thus, the original procedure to prepare **30** is the only option to date.[46]

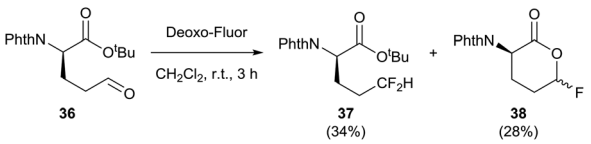
Now that we had proven the general applicability of our method for synthesizing δ,δ-difluoronorvaline, we approached the asymmetric synthesis of the target molecule. To make this happen, the alkylation step had to be carried out in a stereoselective manner, for which the assignment of the hydroxypinanone auxiliary seemed promising.[48–52] Consequently,



Scheme 11 Failed synthesis of δ-fluoronorvaline **30**.



Scheme 12 Synthesis of (*R*)-*tert*-butyl 5-oxo-2-phthalimido-pentanoate (**36**).

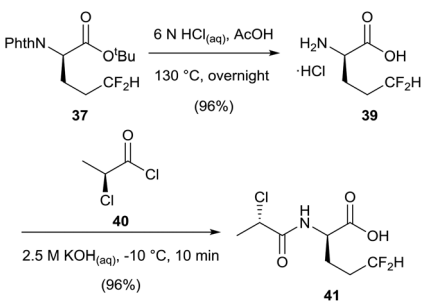


Scheme 13 Deoxofluorination of (*R*)-*tert*-butyl 5-oxo-2-phthalimido-pentanoate (**36**).

(*R*)-*tert*-butyl 5-oxo-2-phthalimidopentanoate was synthesized from (1*S*,2*S*,5*S*)-(−)-2-hydroxypinane-3-one (**31**) and *tert*-butyl glycine in six steps (Scheme 12).

In contrast to the reaction of the racemic aldehyde **26**, treatment of **36** with Deoxo-Fluor besides the desired difluoride **37** (34%) also yielded one dominating diastereomer of the fluorinated lactone **38** (28%) (Scheme 13) that was presumably formed from the difluoride by lactonization after loss of the *tert*-butyl group by acidic hydrolysis due to traces of hydrogen fluoride in the reaction mixture. Attempts to carry out the fluorination reaction in a non-acidic environment by addition of substoichiometric amounts of triethyl amine only yielded the product in small amounts of up to 9%, although cyclization was not observed in these cases.

Subsequent deprotection analogous to the already mentioned method[45] delivered δ,δ-difluoronorvaline hydrochloride (**39**) in 96% yield. For the determination of the enantiomeric excess a derivatization with (*S*)-2-chloropropionic acid chloride (**40**) (Scheme 14)[50,53–55] was necessary, after which an ee value of 36% was calculated from the ^{19}F NMR signal integrals of the diastereoisomers.



Scheme 14 Deprotection of **37** and derivatization of **39** with (*S*)-2-chloropropionic acid chloride (**40**).

Conclusions

The attempt to synthesize ω,ω-difluorinated α-amino acids from thioethers by oxidative desulfurization difluorination only yielded traces of the desired products. Surprisingly, α,ω-polyfluorinated amino acid derivatives **13b,c**, **14b,c** and **15c**, respectively, were formed predominantly. The structure of compound **14c** was verified by X-ray crystallography. The structures of the other products were determined by NMR investigations. A plausible mechanism for these remarkable and yet unknown reactions by the neighbouring group participation of the thioether function was proposed and elucidated by several control experiments. Subsequently, the first synthesis of previously unreported δ,δ-difluoronorvaline was achieved by the deoxofluorination of a suitable aldehyde precursor. Additionally, enantiomerically enriched (*R*)-δ,δ-difluoronorvaline was obtained by making use of the hydroxypinanone auxiliary. The pK_a value of the target molecule's amino function was determined to be 9.01 showing the remarkable influence of the fluorine in the δ-position. The respective value of the carboxy function was measured to be 2.23 indicating no effect of fluorine on this group.

Experimental section

General methods

Column chromatography was performed on Merck silica gel 60 (40–63 μm). NMR spectra were recorded on Bruker AV300 and Bruker DPX300 (^{1}H NMR, 300 MHz, ^{13}C NMR, 75 MHz, ^{19}F NMR, 282 MHz), Bruker AV400 (^{1}H NMR, 400 MHz, ^{13}C NMR, 101 MHz) and Agilent DD2 600 (^{1}H NMR: 600 MHz, ^{13}C NMR: 151 MHz, ^{19}F NMR: 564 MHz) spectrometers. TMS (^{1}H), $CDCl_3$ (^{13}C) and $CFCl_3$ (^{19}F) were used as internal standards. Mass spectra were recorded on Waters-Micromass Triplequad Quattro Micro GC (EI), Waters-Micromass Quattro LCZ (ESI), and Bruker Daltonics MicroTof (ESI) instruments. All air and moisture-sensitive reactions were performed under an argon atmosphere. Solvents were purified and dried by literature methods where necessary. Enantiomeric excesses were determined by using a chiral GC (HP 5890 Series II (FID) with integrator HP 3396A; Beta-Dex™ 120, 30 m, 0.25 mm, 0.25 μm, Supelco Co.) or chiral HPLC (for details see ESI†). pK_a

measurements were conducted using the titrator SI Analytics TitroLine® 7000 with the dosing unit WA 20 mL. The values were calculated by using the TitriSoft 3.0 software. For the titration app. 189.65 mg substance were dissolved in 0.1 M hydrochloric acid (10 mL) and titrated against 1 M NaOH solution.

Synthesis of *N*,*O*-protected thioether containing amino acids

Ethyl 5-phenylthio-2-(diphenylmethylene)aminopentanoate (5a). Method A: ethyl *N*-(diphenylmethylene)glycinate (2.673 g, 10.0 mmol) was dissolved in abs. THF (20 mL) under an argon atmosphere and the solution was cooled to −40 °C before adding a 2 M solution of NaHMDS (0.55 mL, 11 mmol) and stirring for 30 min. Subsequently, a solution of 1-bromo-3-phenylthiopropane (2.543 g, 11.0 mmol) in abs. THF (11 mL) was added dropwise. After stirring for 2 h at −40 °C and at r.t. overnight, the reaction was quenched with half concentrated NaCl solution and the mixture was extracted with Et_2O (2 × 15 mL). The organic phase was washed with H_2O (15 mL) and sat. NaCl solution (15 mL) and dried over $MgSO_4$. Evaporation of the solvent delivered the product as an orange oil (4.393 g). The crude product was used in the following step without purification.

Method B:[30] ethyl *N*-(diphenylmethylene)glycinate (1.951 g, 7.3 mmol) was dissolved in DMSO (15 mL) and reacted with KO^{t}Bu (819 mg, 7.3 mmol) for 20 min. 1-Bromo-3-phenylthiopropane (1.699 g, 7.4 mmol) was added and the mixture was stirred overnight. The reaction was quenched with half concentrated NaCl solution (20 mL) and the mixture was extracted with Et_2O (30 mL). After washing with H_2O and sat. NaCl solution (2 × 30 mL each) the organic phase was dried over $MgSO_4$ and the solvent was evaporated. The product was obtained as a yellow oil (2.622 g) that was used in the next step without purification.

^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, OCH_2CH_3), 1.48–1.77 (m, 2 H, SCH_2CH_2), 2.00–2.12 (m, 2 H, $CHCH_2$), 2.83 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, SCH_2), 4.04 (dd, $^3J_{H,H}$ = 7.3, 5.7 Hz, 1 H, C*H*), 4.09–4.23 (m, 2 H, OCH_2), 7.09–7.66 (m, 15 H, 15 × Ph–C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.2 (CH_3), 25.6 (SCH_2CH_2), 32.6 ($CHCH_2$), 33.4 (SCH_2), 60.9 (OCH_2), 64.8 (*C*H), 125.8 (Ph–*C*H), 127.8 (Ph–*C*H), 128.0 (Ph–*C*H), 128.3 (Ph–*C*H), 128.5 (Ph–*C*H), 128.8 (Ph–*C*H), 128.8 (Ph–*C*H), 129.3 (Ph–*C*H), 130.1 (Ph–*C*H), 130.4 (Ph–*C*), 136.3 (Ph–*C*), 136.4 (Ph–*C*), 170.7 (N=*C*), 172.1 (*C*=O). Exact mass (ESI): $[M + H]^+$ calcd for $C_{26}H_{27}NO_2SH^+$: 418.1835; found: 418.1837. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{26}H_{27}NO_2SNa^+$: 440.1655; found: 440.1657.

Ethyl 5-(4-chlorophenyl)thio-2-(diphenylmethylene)aminopentanoate (5b). Compound **5b** was synthesised according to method B described above for **5a**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, OCH_2CH_3), 1.46–1.72 (m, 2 H, SCH_2CH_2), 1.95–2.16 (m, 2 H, $CHCH_2$), 2.80 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, SCH_2), 4.03 (dd, $^3J_{H,H}$ = 7.5, 5.5 Hz, 1 H, C*H*), 4.07–4.24 (m, 2 H, OCH_2), 7.09–7.16 (m, 2 H, 2 × Ph–C*H*), 7.19 (s, 4 H, C_6H_4Cl), 7.29–7.39 (m, 2 H, 2 × Ph–C*H*), 7.39–7.47 (m, 4 H, 4 × Ph–C*H*), 7.58–7.63 (m, 2 H, 2 × Ph–C*H*). Exact mass (ESI): $[M + H]^+$ calcd for $C_{26}H_{26}ClNO_2SH^+$: 452.1446; found: 452.1449. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{26}H_{26}ClNO_2SNa^+$: 474.1265; found: 474.1271.

Methyl 5-(4-chlorophenyl)thio-2-(diphenylmethylene)aminopentanoate (6b). Compound **6b** was synthesised according to method A described above for **5a**. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.49–1.71 (m, 2 H, SCH_2CH_2), 1.99–2.10 (m, 2 H, $CHCH_2$), 2.79 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, SCH_2), 3.70 (s, 3 H, OCH_3), 4.07 (dd, $^3J_{H,H}$ = 7.5, 5.5 Hz, 1 H, C*H*), 7.11–7.14 (m, 2 H, 2 × Ph–C*H*), 7.19 (s, 4 H, C_6H_4Cl), 7.30–7.35 (m, 2 H, 2 × Ph–C*H*), 7.38–7.43 (m, 4 H, 4 × Ph–C*H*), 7.57–7.62 (m, 2 H, 2 × Ph–C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 25.3 (SCH_2CH_2), 32.6 ($CHCH_2$), 33.6 (SCH_2), 52.2 (OCH_3), 64.7 (*C*H), 127.8 (Ph–*C*H), 128.1 (Ph–*C*H), 128.6 (Ph–*C*H), 128.7 (Ph–*C*), 128.8 (Ph–*C*H), 128.9 (2 × *C*HCCl), 130.5 (Ph–*C*H), 130.7 (2 × SC*C*H), 131.9 (*C*Cl), 134.9 (S*C*CH), 136.2 (Ph–*C*), 139.2 (Ph–*C*), 170.8 (N=*C*), 172.5 (*C*=O). Exact mass (ESI): $[M + H]^+$ calcd for $C_{25}H_{24}{}^{35}ClNO_2SH^+$: 438.1289; found: 438.1287. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{25}H_{24}{}^{35}ClNO_2SNa^+$: 460.1108; found: 460.1107.

Ethyl 5-phenylthio-2-phthalimidopentanoate (9a). Method A:[45] after acidic hydrolysis (2 M $HCl_{(aq.)}$, r.t., 24 h) of the Schiff base, the free amine was mixed with phthalic anhydride and heated to 140 °C in an open vessel in a microwave at 165 W for 7 min. Column chromatography (CyH/EtOAc 5 : 1) yielded a yellow oil (527 mg, 1.4 mmol, 18% over 3 steps from ethyl *N*-(diphenylmethylene)glycinate).

Method B: after acidic hydrolysis the amine was mixed with finely powdered phthalic anhydride and stirred in a pre-heated oil bath at 145 °C for 1 h. Chromatographic purification gave the product as a yellow oil (675 mg, 1.8 mmol, 24% over 3 steps from **5a**). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.22 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, OCH_2CH_3), 1.55–1.75 (m, 2 H, SCH_2CH_2), 2.35–2.43 (m, 2 H, $CHCH_2$), 2.93 (m, 2 H, SCH_2), 4.20 (m, 2 H, OCH_2), 4.82 (dd, $^3J_{H,H}$ = 8.6, 7.1 Hz, 1 H, C*H*), 7.08–7.14 (m, 1 H, *para*-C*H*), 7.16–7.23 (m, 2 H, *meta*-C*H*), 7.25–7.30 (m, 2 H, *ortho*-C*H*), 7.72–7.78 (m, 2 H, 2 × Phth–CCHC*H*), 7.83–7.89 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.1 (OCH_2CH_3), 25.9 (SCH_2CH_2), 27.8 ($CHCH_2$), 33.0 (SCH_2), 51.8 (*C*H), 61.9 (OCH_2), 123.6 (2 × Phth–C*C*H), 126.0 (C-*para*), 128.8 (2 × C-*meta*), 129.5 (2 × C-*ortho*), 131.7 (Phth–C), 134.2 (Phth–CCH*C*H), 136.0 (C-*ipso*), 167.7 (Phth–*C*=O), 169.0 (CO_2Et). Exact mass (ESI): $[M + H]^+$ calcd for $C_{21}H_{21}NO_4SH^+$: 384.1264; found: 384.1256. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{21}H_{21}NO_4SNa^+$: 406.1083; found: 406.1077.

Ethyl 5-(4-chlorophenyl)thio-2-phthalimidopentanoate (9b). Compound **9b** (2.950 g, 7.3 mmol, 43% (3 steps from ethyl *N*-(diphenylmethylene)glycinate)) was synthesised according to method B described above for **9a**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 1.22 (t, $^3J_{H,H}$ = 8.5 Hz, 3 H, OCH_2CH_3), 1.52–1.72 (m, 2 H, SCH_2CH_2), 2.32–2.45 (m, 2 H, $CHCH_2$), 2.79–3.01 (m, 2 H, SCH_2), 4.20 (m, 2 H, OCH_2), 4.77–4.84 (m, 1 H, C*H*), 7.12–7.23 (m, 4 H, C_6H_4Cl), 7.72–7.79 (m, 2 H, 2 × Phth–CCHC*H*), 7.82–7.89 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.1 (OCH_2CH_3), 25.7 (SCH_2CH_2), 27.6 ($CHCH_2$), 33.2 (SCH_2), 51.6 (*C*H), 62.0 (OCH_2), 123.5 (2 × Phth–C*C*H), 128.9

(2 × C-*meta*), 130.9 (2 × C-*ortho*), 131.6 (Phth–C), 132.0 (*C*-*para*), 134.3 (Phth–CCH*C*H), 134.4 (C-*ipso*), 167.6 (Phth–*C*=O), 168.9 (*C*O$_2$Et). Exact mass (ESI): [M + H]$^+$ calcd for $C_{21}H_{20}{}^{35}ClNO_4SH^+$: 418.0874; found: 418.0870. Exact mass (ESI): [M + Na]$^+$ calcd for $C_{21}H_{20}ClNO_4SNa^+$: 440.0694/442.0666; found: 440.0687/442.0665.

Methyl 5-(4-chlorophenyl)thio-2-phthalimidopentanoate (10b). Compound **10b** (1.120 g, 2.8 mmol, 72% (3 steps from methyl *N*-(diphenylmethylene)glycinate)) was synthesised according to method A described above for **9a**. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.52–1.72 (m, 2 H, SCH$_2$C*H*$_2$), 2.34–2.42 (m, 2 H, CHC*H*$_2$), 2.80–3.00 (m, 2 H, SC*H*$_2$), 3.73 (s, 3 H, OC*H*$_3$), 4.83 (dd, $^3J_{H,H}$ = 8.5, 7.2 Hz, 1 H, C*H*), 7.13–7.22 (m, 4 H, C$_6$*H*$_4$Cl), 7.73–7.79 (m, 2 H, 2 × Phth–CCHC*H*), 7.82–7.88 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 25.6 (SCH$_2$*C*H$_2$), 27.6 (CH*C*H$_2$), 33.2 (S*C*H$_2$), 51.4 (*C*H), 123.6 (2 × Phth–C*C*H), 128.9 (2 × C-*meta*), 130.9 (2 × C-*ortho*), 131.6 (Phth–C), 132.0 (*C*-*para*), 134.3 (Phth–CCH*C*H), 134.4 (C-*ipso*), 167.6 (Phth–*C*=O), 169.5 (*C*O$_2$Et). Exact mass (ESI): [M + H]$^+$ calcd for $C_{20}H_{18}{}^{35}ClNO_4SH^+$: 404.0718; found: 404.0724. Exact mass (ESI): [M + Na]$^+$ calcd for $C_{20}H_{18}ClNO_4SNa^+$: 426.0537/428.0509; found: 426.0537/428.0512.

Methyl 4-phenylthio-2-phthalimidobutanoate (12). To a solution of thiophenol (0.11 mL, 1.1 mmol) in DMF (3 mL) was added ethyldiisopropylamine (0.18 mL, 1.1 mmol) and stirred at r.t. for 10 min. Methyl 4-bromo-2-phthalimidobutanoate[31] (341 mg, 1.05 mmol) in DMF (3 mL) was added and after stirring for 4 h at r.t. the reaction was quenched with 1 M HCl solution. Then the mixture was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic phases were washed with water and sat. NaCl solution (2 × 25 mL each), dried over $MgSO_4$ and the solvent evaporated. Column chromatography delivered the product as a yellow oil that gradually solidified to a yellow solid (335 mg, 0.94 mmol, 90%); mp 80–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 2.43–2.64 (m, 2 H, CHC*H*$_2$), 2.81–3.08 (m, 2 H, SC*H*$_2$), 3.72 (s, 3 H, OCH_3), 5.13 (dd, $^3J_{H,H}$ = 9.2, 5.8 Hz, 1 H, C*H*), 7.13–7.22 (m, 1 H, *para*-C*H*), 7.22–7.30 (m, 2 H, *meta*-C*H*), 7.30–7.36 (m, 2 H, *ortho*-C*H*), 7.72–7.78 (m, 2 H, Phth–CCHC*H*), 7.84–7.90 (m, 2 H, Phth–CC*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.5 (CH*C*H$_2$), 30.9 (S*C*H$_2$), 50.8 (*C*H), 52.9 (O*C*H$_3$), 123.6 (Phth–C*C*H), 126.4 (C-*para*), 129.0 (C-*meta*), 129.9 (C-*ortho*), 131.7 (Phth–C), 134.3 (Phth–CCH*C*H), 135.3 (C-*ipso*), 167.6 (2 × Phth–*C*=O), 169.4 (*C*O$_2$Me). Exact mass (ESI): [M + Na]$^+$ calcd for $C_{19}H_{17}NO_4SNa^+$: 378.0770; found: 378.0771. Exact mass (ESI): [M + MeOH + Na]$^+$ calcd for $C_{19}H_{17}NO_4SCH_3OHNa^+$: 410.1033; found: 410.1033. The structure was confirmed by X-ray diffraction (CCDC 1429375).

Oxidative desulfurization–fluorination reactions

Oxidative desulfurization–fluorination of ethyl 5-phenylthio-2-phthalimidopentanoate (9a). Ethyl 5-phenylthio-2-phthalimidopentanoate (97 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (2 mL), the solution was cooled to 0 °C and treated with Olah's reagent (0.28 mL, 1.2 mmol, 4.8 eq.) and 1,3-dibromo-5,5-dimethylhydantoin (DBH) (214 mg, 0.75 mmol, 3.0 eq.). The red solution was stirred for 30 min at 0 °C and overnight at r.t. The mixture was neutralized with ice/sat. $NaHCO_3$ solution and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 0.1 M HCl solution and 5% $NaHCO_3$ solution before the solvent was evaporated. After chromatography (CyH/EtOAc, 5 : 1) a product mixture (29 mg) that according to ^{19}F NMR spectroscopy consisted of ethyl 2,5,5-trifluoro-2-phthalimidopentanoate (88%) and ethyl 2,5-difluoro-2-phthalimidopentanoate (12%) was obtained.

Ethyl 2,5,5-trifluoro-2-phthalimidopentanoate (13c). Identified out of the mixture received from the above reaction. ^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ = 1.36 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, OCH$_2$C*H*$_3$), 1.87–2.00 (m, 1 H, CF$_2$HC*H*^{a}), 2.08–2.22 (m, 1 H, CF$_2$HC*H*^{b}), 2.57–2.69 (m, 1 H, CFC*H*^{a}), 3.16–3.24 (m, 1 H, CFC*H*^{b}), 4.34–4.45 (m, 2 H, OC*H*$_2$), 5.94 (tt, $^2J_{H,F}$ = 56.5 Hz, $^3J_{H,H}$ = 4.3 Hz, 1 H, CF$_2$*H*), 7.79–7.83 (m, 2 H, Phth–CCHC*H*), 7.88–7.92 (m, 2 H, Phth–CC*H*). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 14.0 (OCH$_2$*C*H$_3$), 26.9 (dt, $^2J_{C,F}$ = 25.4 Hz, $^3J_{C,F}$ = 6.2 Hz, CF*C*H$_2$), 28.6 (td, $^2J_{C,F}$ = 22.3 Hz, $^3J_{C,F}$ = 3.7 Hz, CF$_2$H*C*H$_2$), 63.1 (O*C*H$_2$), 96.4 (d, $^1J_{C,F}$ = 219.8 Hz), 116.1 (t, $^1J_{C,F}$ = 239.6 Hz, *C*F$_2$H), 124.1 (Phth–C*C*H), 131.1 (Phth–*C*), 135.0 (Phth–CCH*C*H), 165.7 (d, $^2J_{C,F}$ = 32.0 Hz, *C*O$_2$Et), 166.6 (d, $^3J_{C,F}$ = 1.8 Hz, Phth–*C*=O). ^{19}F NMR (564 MHz, $CDCl_3$, $CFCl_3$) δ = −116.8/−117.6 (AB signal, $^2J_{F,F}$ = 281.9 Hz, $^2J_{F,H}$ = 56.4 Hz, $^3J_{F,H}$ = 16.2 Hz, $^5J_{F,F}$ = 1.3 Hz/$^2J_{F,F}$ = 281.9 Hz, $^2J_{F,H}$ = 56.2 Hz, $^3J_{F,H}$ = 18.7, 16.6 Hz, $^5J_{F,F}$ = 1.7 Hz, 2 F, C*F*$_2$H), −123.7 (ddt, $^3J_{F,H}$ = 26.0, 11.2 Hz, $^5J_{F,F}$ = 1.5 Hz, 1 F, C*F*). Exact mass (ESI): [M + Na]$^+$ calcd for $C_{15}H_{14}F_3NO_4Na^+$: 352.0767; found: 352.0764. Exact mass (ESI): [M − F$^-$ + MeO$^-$ + MeOH + Na]$^+$ calcd for $C_{17}H_{21}F_2NO_6Na^+$: 396.1229; found: 396.1226.

Ethyl 2,5-difluoro-2-phthalimidopentanoate (13b). Identified out of the mixture received from the above reaction of **9a**. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ = −123.9 (ddd, $^3J_{F,H}$ = 28.0, 11.3 Hz, $^5J_{F,F}$ = 1.3 Hz, 1 F, 2-CF), −219.9 (tddd, $^2J_{F,H}$ = 47.0 Hz, $^3J_{F,H}$ = 26.9 Hz, $^3J_{F,H}$ = 23.3 Hz, $^5J_{F,F}$ = 1.3 Hz, 1 F, CFH$_2$). Exact mass (ESI): [M + Na]$^+$ calcd for $C_{15}H_{15}F_2NO_4Na^+$: 334.0861; found: 334.0856. Exact mass (ESI): [M − F$^-$ + MeO$^-$ + MeOH + Na]$^+$ calcd for $C_{17}H_{21}F_2NO_6Na^+$: 378.1320; found: 378.1323.

Oxidative desulfurization–fluorination of methyl 5-(4-chlorophenyl)thio-2-phthalimidopentanoate (10b). Methyl 5-(4-chlorophenyl)thio-2-phthalimidopentanoate (503 mg, 1.25 mmol) was dissolved in CH_2Cl_2 (8 mL), the solution cooled to 0 °C and treated with Olah's reagent (1.7 mL, 7.5 mmol, 6 eq.) and DBH (1.430 g, 5.0 mmol, 4 eq.). The red solution was stirred for 30 min at 0 °C and overnight at r.t. The mixture was neutralized with ice/sat. $NaHCO_3$ solution and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$, 0.1 M HCl and 5% aqueous $NaHCO_3$. The solution was dried over $MgSO_4$ before the solvent was evaporated. Chromatography (CyH/EtOAc, 5 : 1) yielded a 81 : 14 : 5 (^{19}F NMR) mixture (140 mg) of methyl 2,5,5-trifluoro-2-phthalimidopentanoate (**14c**) (29% yield calcd from ^{19}F NMR ratio), methyl 2,5-difluoro-2-phthalimidopentanoate (**14b**) (5%) and methyl 5,5-difluoro-2-phthalimidopentanoate (**14a**) (2%). Recrystallization led to isolation

of a mixture of **14c** and **14b** (85 : 15) that was subjected to X-ray analysis.

Methyl 2,5,5-trifluoro-2-phthalimidopentanoate (14c). Identified out of the mixture received from the above reaction of **10b**. ^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ = 1.87–1.99 (m, 1 H, CF_2HCH^a), 2.07–2.21 (m, 1 H, CF_2HCH^b), 2.55–2.70 (m, 1 H, $CFCH^a$), 3.14–3.27 (m, 1 H, $CFCH^b$), 3.91 (s, 3 H, OCH_3), 5.94 (tt, $^{2}J_{H,F}$ = 56.4 Hz, $^{3}J_{H,H}$ = 4.3 Hz, 1 H, CF_2H), 7.78–7.84 (m, 2 H, Phth–CCHCH), 7.88–7.93 (m, 2 H, Phth–CCH). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 27.0 (dt, $^{2}J_{C,F}$ = 25.5 Hz, $^{3}J_{C,F}$ = 6.2 Hz, $CFCH_2$), 28.8 (td, $^{2}J_{C,F}$ = 22.3 Hz, $^{3}J_{C,F}$ = 3.6 Hz, CF_2HCH_2), 53.7 (OCH_3), 96.5 (d, $^{1}J_{C,F}$ = 219.8 Hz, CF), 116.2 (t, $^{1}J_{C,F}$ = 239.6 Hz, CF_2H), 124.3 (Phth–CCH), 131.2 (Phth–C), 135.2 (Phth–CCHCH), 166.4 (d, $^{2}J_{C,F}$ = 32.1 Hz, CO_2Et), 166.7 (d, $^{3}J_{C,F}$ = 1.9 Hz, Phth–C=O). ^{19}F NMR (564 MHz, $CDCl_3$, $CFCl_3$) δ = −117.1/−117.5 (AB signal, $^{2}J_{F,F}$ = 281.9 Hz, $^{2}J_{F,H}$ = 56.5 Hz, $^{3}J_{F,H}$ = 16.7 Hz, $^{5}J_{F,F}$ = 1.7 Hz/$^{2}J_{F,F}$ = 281.9 Hz, $^{2}J_{F,H}$ = 56.5 Hz, $^{3}J_{F,H}$ = 16.7 Hz, $^{5}J_{F,F}$ = 1.9 Hz, 2 F, CF_2H), −123.6 (ddt, $^{3}J_{F,H}$ = 26.1, 10.9 Hz, $^{5}J_{F,F}$ = 1.5 Hz, 1 F, CF). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{14}H_{12}F_3NO_4Na^+$: 338.0611; found: 338.0614. Exact mass (ESI): $[M - F^- + MeO^- + MeOH + Na]^+$ calcd for $C_{16}H_{19}F_2NO_6Na^+$: 382.1073; found: 382.1075.

Methyl 2,5-difluoro-2-phthalimidopentanoate (13b). Identified out of the mixture received from the above reaction of **10b**. Only identified signals are listed. ^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ = 4.54 (dm, $^{2}J_{H,F}$ = 47.0 Hz, 2 H, CH_2F. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 24.9 (dd, $^{2}J_{C,F}$ = 20.3 Hz, $^{3}J_{C,F}$ = 3.1 Hz, $CFCH_2$), 24.9 (dd, $^{2}J_{C,F}$ = 24.9 Hz, $^{3}J_{C,F}$ = 5.8 Hz, CF_2HCH_2), 53.5 (OCH_3), 83.1 (d, $^{1}J_{C,F}$ = 166.5 Hz, CF), 97.1 (d, $^{1}J_{C,F}$ = 219.5 Hz, CF_2H), 124.2 (Phth–CCH), 131.3 (Phth–C), 135.1 (Phth–CCHCH), 166.7 (d, $^{2}J_{C,F}$ = 32.4 Hz, CO_2Et), 166.8 (ds, $^{3}J_{C,F}$ = 2.0 Hz, Phth–C=O). ^{19}F NMR (564 MHz, $CDCl_3$, $CFCl_3$) δ = −123.8 (ddd, $^{3}J_{F,H}$ = 27.9, 11.0 Hz, $^{5}J_{F,F}$ = 1.2 Hz, 1 F, CF), −220.0 (tddd, $^{2}J_{F,H}$ = 47.1 Hz, $^{3}J_{F,H}$ = 26.9 Hz, $^{3}J_{H,F}$ = 23.0 Hz, $^{5}J_{F,F}$ = 1.2 Hz, 1 F, CH_2F). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{14}H_{13}F_2NO_4Na^+$: 320.0705; found: 320.0709. Exact mass (ESI): $[M - F^- + MeO^- + MeOH + Na]^+$ calcd for $C_{16}H_{20}FNO_6Na^+$: 364.1167; found: 364.1172.

Methyl 5,5-difluoro-2-phthalimidopentanoate (13a). Identified in the mixture obtained by the above reaction of **10b**. Only identified signals are listed. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 5.85 (tt, $^{2}J_{H,F}$ = 56.2 Hz, $^{3}J_{H,F}$ = 4.1 Hz, 2 H, CF_2H). ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ = −116.8/−116.8 (AB signal*, $^{3}J_{F,H}$ = 17.3 Hz, 2 F, 5-CF_2H). *The $^{2}J_{F,H}$ coupling could not be determined because the signal was partially covered by the analogous signal of **13c**. The $^{2}J_{F,F}$ coupling was not possible to determine due to the small outer signals. The ESI results are already listed above for molecule **13b** with the same molecular weight.

Oxidative desulfurization–fluorination of methyl 4-phenylthio-2-phthalimidobutanoate (12). Methyl 4-phenylthio-2-phthalimidobutanoate (355 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with Olah's reagent (1.4 mL, 6.0 mmol, 6 eq.) and cooled to 0 °C. After addition of DBH (858 mg, 3.0 mmol, 3 eq.) the solution was stirred for 30 min at 0 °C and overnight at r.t. The mixture was neutralized with ice/sat. $NaHCO_3$ solution and extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with 1 M aqueous HCl, 10% aqueous $Na_2S_2O_3$, and 5% aqueous $NaHCO_3$. The solution was dried over $MgSO_4$ before the solvent was evaporated. Chromatography (CyH/EtOAc, 5 : 1) yielded a mixture of methyl 4-fluoro-2-phthalimidobutanoate (49%, ^{19}F NMR), methyl 2,4-difluoro-2-phthalimidobutanoate (48%) and methyl 4,4-difluoro-2-phthalimidobutanoate (3%).

Methyl 4-fluoro-2-phthalimidobutanoate (15a). Identified out of the mixture received from the above reaction of **12**. Only identified signals are listed. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ = −222.5 (tdd, $^{2}J_{H,F}$ = 47.2 Hz, $^{3}J_{H,F}$ = 24.0, 30.3 Hz, 1 F, CH_2F). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{13}H_{12}FNO_4Na^+$: 288.0643; found: 288.0639.

Methyl 4,4-difluoro-2-phthalimidobutanoate (15b). Identified out of the mixture received from the above reaction of **12**. Only identified signals are listed. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ = −116.2/−119.1 (AB signal, $^{2}J_{F,F}$ = 287.8 Hz, $^{2}J_{H,F}$ = 55.7 Hz, $^{3}J_{H,F}$ = 16.4 Hz/$^{2}J_{F,F}$ = 287.8 Hz, $^{2}J_{H,F}$ = 55.8 Hz, $^{3}J_{H,F}$ = 18.3, 15.9 Hz, 2 F, CF_2H). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{13}H_{11}F_2NO_4Na^+$: 306.0548; found: 306.0538. $[M - F^- + MeO^- + MeOH + Na]^+$ calcd for $C_{13}H_{11}F_2NO_4Na^+$: 350.1010; found: 350.1015.

Methyl 2,4-difluoro-2-phthalimidobutanoate (15c). Identified out of the mixture received from the above reaction of **12**. Only identified signals are listed. ^{19}F NMR (282 MHz, $CDCl_3$, $CFCl_3$) δ = −124.7 (ddd, $^{3}J_{H,F}$ = 28.3, 10.4 Hz, $^{4}J_{F,F}$ = 2.1 Hz, 1 F, CF), −220.4 (tddd, $^{2}J_{H,F}$ = 46.7 Hz, $^{3}J_{H,F}$ = 33.3, 19.3 Hz, $^{4}J_{F,F}$ = 2.1 Hz, 1 F, CH2F). The ESI results are already listed for molecule **15b** with the same molecular weight above.

Synthesis of racemic δ,δ-difluoronorvaline

Ethyl 5-benzyloxy-2-(diphenylmethylene)aminopentanoate (23). Ethyl *N*-(diphenylmethylene)glycinate (2.760 g, 10.3 mmol) was dissolved in DMSO (10 mL) and according to method B described for the synthesis of **5a** reacted with KO^{t}Bu (1.268 g, 11.3 mmol, 1.1 eq.) and *O*-tosyl-3-benzyloxy-1-propanol (3.308 g, 10.3 mmol). The product (3.947 g) was used in the following step without purification. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.25 (t, $^{3}J_{H,H}$ = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.45–1.73 (m, 2 H, CH_2CH_2OBn), 1.91–2.11 (m, 2 H, $CHCH_2$), 3.41 (t, $^{3}J_{H,H}$ = 6.6 Hz, 2 H, CH_2OBn), 4.06 (dd, $^{3}J_{H,H}$ = 7.9, 5.3 Hz, 1 H CH), 4.10–4.31 (m, 2 H, CO_2CH_2), 4.44 (s, 2 H, OCH_2Ph), 7.09–7.20 (m, 2 H, 2 × Ph–CH), 7.21–7.38 (m, 8 H, 5 × Bn–CH, 3 × Ph–CH), 7.38–7.45 (m, 3 H, 3 × Ph–CH), 7.60–7.66 (m, 2 H, 2 × Ph–CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.2 ($CO_2CH_2CH_3$), 26.3 (CH_2CH_2OBn), 30.3 ($CHCH_2$), 60.8 (CO_2CH_2), 65.2 (CH), 70.0 (CH_2OBn), 72.8 (OCH_2Ph), 127.6 (2 × Bn–CH-*ortho*), 127.8 (2 × Ph–CH), 128.0 (2 × Bn–CH-*meta*), 128.3 (2 × Ph–CH), 128.3 (Bn–CH-*para*), 128.5 (2 × Ph–CH), 128.6 (Ph–CH), 128.8 (2 × Ph–CH), 130.3 (Ph–CH), 136.4 (Ph–C), 138.5 (Bn–C), 139.5 (Ph–C), 170.5 (C=N), 172.2 (CO_2Et). Exact mass (ESI): $[M + H]^+$ calcd for $C_{27}H_{29}NO_3H^+$: 416.2220; found: 416.2220. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{27}H_{29}NO_3Na^+$: 438.2040; found: 438.2037.

Ethyl 5-benzyloxy-2-phthalimidopentanoate (24). Ethyl 5-benzyloxy-2-(diphenylmethylene)aminopentanoate (**23**) (3.947 g, crude from reaction above) was dissolved in EtOH (40 mL) and treated with 1 M aqueous HCl (40 mL) for 2 h at r.t. The mixture was washed with Et_2O (50 mL) and the ethereal phase extracted with 1 M aqueous HCl (20 mL). The combined aqueous phases were then neutralized with $NaHCO_3$ and extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with sat. aqueous $NaHCO_3$ (30 mL), dried over $MgSO_4$ and the solvent evaporated. The residue (1.675 g) and finely mortared phthalic anhydride (992 mg, 6.7 mmol) were mixed and stirred at 145 °C in a pre-heated oil bath for 30 min. The crude product was dissolved in CH_2Cl_2 and the solution dried over $MgSO_4$. After evaporation of the solvent the product (836 mg, 2.2 mmol, 21% over 3 steps from ethyl *N*-(diphenylmethylene)glycinate) was purified chromatographically (CyH/EtOAc, 5 : 1). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.23 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.54–1.74 (m, 2 H, CH_2CH_2OBn), 2.25–2.43 (m, 2 H, $CHCH_2$), 3.48 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2OBn), 4.20 (m, 2 H, CO_2CH_2), 4.47 (s, 2 H, OCH_2Ph), 4.85 (dd, $^3J_{H,H}$ = 10.4, 5.4 Hz, 1 H, C*H*), 7.22–7.35 (m, 5 H, 5 × Ph–C*H*), 7.70–7.78 (m, 2 H, 2 × Phth–CCHC*H*), 7.83–7.89 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.1 ($CO_2CH_2CH_3$), 25.6 ($CHCH_2$), 26.6 (CH_2CH_2OBn), 52.1 (*C*H), 61.8 (CO_2CH_2), 69.3 (CH_2OBn), 73.0 (OCH_2Ph), 123.5 (Phth–C*C*H), 127.5 (C-*para*), 127.6 (C-*ortho*), 128.3 (C-*meta*), 131.8 (Phth–C), 134.2 (PhthCCH*C*H), 138.3 (C-*ipso*), 167.7 (2 × Phth–*C*=O), 169.2 (CO_2Et). Exact mass (ESI): $[M + H]^+$ calcd for $C_{22}H_{23}NO_5H^+$: 382.1649; found: 382.1656. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{22}H_{23}NO_5Na^+$: 404.1468; found: 404.1473.

Ethyl 5-hydroxy-2-phthalimidopentanoate (25). To a solution of Ethyl 5-benzyloxy-2-phthalimidopentanoate (**24**) in abs. EtOH (10 mL) was added Pd/C (10% w/w, 100 mg) and the suspension was stirred for 4 h at r.t. under a 2 bar atmosphere of H_2. The catalyst was removed by filtration over celite and the solvent evaporated which yielded the product as a yellowish oil (560 mg, 1.9 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.23 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.48–1.69 (m, 2 H, CH_2CH_2OH), 2.21–2.43 (m, 2 H, $CHCH_2$), 3.67 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, CH_2OH), 4.20 (m, 2 H, CO_2CH_2), 4.88 (dd, $^3J_{H,H}$ = 10.4, 5.4 Hz, 1 C*H*), 7.72–7.80 (m, 2 H, 2 × Phth–CCHC*H*), 7.82–7.92 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.1 ($CO_2CH_2CH_3$), 25.3 ($CHCH_2$), 29.3 (CH_2CH_2OH), 52.1 (*C*H), 61.9 (CO_2CH_2 and CH_2OH), 123.6 (Phth–C*C*H), 131.8 (Phth–C), 134.3 (PhthCCH*C*H), 167.8 (2 × Phth–*C*=O), 169.3 (CO_2Et). Exact mass (ESI): $[M + H]^+$ calcd for $C_{15}H_{17}NO_5H^+$: 292.1179; found: 292.1183. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{15}H_{17}NO_5Na^+$: 314.0999; found: 314.1002.

Ethyl 5-oxo-2-phthalimidopentanoate (26). Ethyl 5-hydroxy-2-phthalimidopentanoate (**25**) (595 mg, 2.0 mmol) was dissolved in CH_2Cl_2 (5 mL) and reacted with Dess–Martin-periodinane (1.038 g, 2.5 mmol, 1.2 eq.) for 2 h at r.t. The reaction was quenched with sat. aqueous $NaHCO_3$ and sat. aqueous Na_2SO_3. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the solvent evaporated. Filtration over silica yielded the product as a colorless oil (427 mg, 1.5 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.38–2.71 (m, 4 H, CH_2CHO and $CHCH_2$), 4.22 (m, 2 H, CO_2CH_2), 4.87 (dd, $^3J_{H,H}$ = 10.4, 5.4 Hz, 1 H, C*H*), 7.71–7.82 (m, 2 H, 2 × Phth–CCHC*H*), 7.83–7.92 (m, 2 H, 2 × Phth–CC*H*), 9.74 (t, $^3J_{H,H}$ = 1.0 Hz, 1 H, C*H*O). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.1 ($CO_2CH_2CH_3$), 21.7 ($CHCH_2$), 40.5 (CH_2CHO), 51.4 (*C*H), 62.1 (CO_2CH_2), 123.7 (Phth–C*C*H), 131.7 (Phth–*C*), 134.4 (PhthCCH*C*H), 167.6 (2 × Phth–*C*=O), 168.6 (CO_2Et), 200.4 (*C*HO). Exact mass (ESI): $[M + H]^+$ calcd for $C_{15}H_{15}NO_5H^+$: 290.1023; found: 290.1024. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{15}H_{15}NO_5Na^+$: 312.0842; found: 312.0842.

Ethyl 5,5-difluoro-2-phthalimidopentanoate (27). A solution of ethyl 5-oxo-2-phthalimidopentanoate (**26**) (595 mg, 2.1 mmol) in abs. CH_2Cl_2 (5 mL) was treated with Deoxo-Fluor (2.7 M in PhMe, 1.0 mL, 2.7 mL, 1.3 eq.) and the now yellow solution was stirred for 4 h at r.t. After neutralization with sat. aqueous $NaHCO_3$, the phases were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent evaporated. Chromatographic purification (CH/EtOAc, 5 : 1) yielded the product as a yellow, viscous oil (245 mg, 0.8 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.75–2.05 (m, 2 H, CH_2CF_2H), 2.27–2.54 (m, 2 H, $CHCH_2$), 4.22 (m, 2 H, CO_2CH_2), 4.85 (dd, $^3J_{H,H}$ = 10.2, 5.3 Hz, 1 H, C*H*), 5.85 (tt, $^2J_{H,F}$ = 56.4, $^3J_{H,H}$ = 4.3 Hz, 1 H, CHF_2), 7.72–7.82 (m, 2 H, 2 × Phth–CCHC*H*), 7.85–7.94 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 14.1 ($CO_2CH_2CH_3$), 21.9 (t, $^3J_{C,F}$ = 5.8 Hz, $CHCH_2$), 31.1 (t, $^2J_{C,F}$ = 21.7 Hz, CH_2CF_2H), 51.5 (*C*H), 62.1 (CO_2CH_2), 116.4 (t, $^1J_{C,F}$ = 239.5 Hz, CHF_2), 123.7 (Phth–C*C*H), 131.6 (Phth–*C*), 134.4 (Phth–CCH*C*H), 167.6 (2 × Phth–*C*=O), 168.5 (CO_2Et). ^{19}F NMR (282 MHz, $CDCl_3$) δ = −116.78/−116.81 (AB signal, $^2J_{F,F}$ = 281.6 Hz, $^2J_{F,H}$ = 56.5 Hz, $^3J_{F,H}$ = 17.3 Hz, 2 F, CF_2H). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{15}H_{15}F_2NO_4Na^+$: 334.0861; found: 334.0853. Exact mass (ESI): $[M + MeOH + Na]^+$ calcd for $C_{15}H_{15}F_2NO_4CH_3OHNa^+$: 366.1124; found: 366.1124.

2-Amino-5,5-difluoropentanoic acid hydrochloride (28). Similar to a literature procedure,[45] ethyl 5,5-difluoro-2-phthalimidopentanoate (**27**) (299 mg, 0.96 mmol) was stirred with 6 N aqueous HCl (5 mL) and HOAc (0.5 mL) in a pressure tube at 130 °C for 16 h. The volatile components were evaporated and the brown residue was dissolved in ice-cold water (3 mL). Solid-phase extraction (Chromabond C-18 ec, 500 mg) with ice-cold water as an eluent yielded the product as a white solid (162 mg, 0.85 mmol, 89%). If necessary, residues of phthalic anhydride can be removed by repeated washing with hot Et_2O. Mp 209–210 °C (dec.); ^{1}H NMR (400 MHz, CD_3OD, TMS) δ = 1.89–2.21 (m, 4 H, $CHCH_2$ and CH_2CF_2H), 4.07 (t, $^3J_{H,H}$ = 5.8 Hz, 1 H, C*H*), 6.00 (tt, $^2J_{H,F}$ = 56.3, $^3J_{H,H}$ = 3.6 Hz, 1 H, CHF_2). ^{1}H NMR (300 MHz, $(CD_3)_2SO$, TMS) δ = 1.72–2.23 (m, 4 H, $CHCH_2$ and CH_2CF_2H), 3.96 (t, $^3J_{H,H}$ = 5.3 Hz, C*H*), 6.16 (tt, $^2J_{H,F}$ = 57.0, $^3J_{H,H}$ = 3.5 Hz, 1 H, CHF_2), 8.60 (br s, 3 H, NH_3^+). ^{13}C NMR (101 MHz, CD_3OD) δ = 24.1 (t, $^3J_{C,F}$ = 6.2 Hz, $CHCH_2$), 30.9 (t, $^2J_{C,F}$ = 21.9 Hz, CH_2CF_2H), 53.2 (*C*H), 117.8 (t,

$^1J_{C,F}$ = 238.0 Hz, *C*HF_2), 168.5 (*C*O_2H). ^{19}F NMR (282 MHz, CD_3OD) δ = −117.2 (dt, $^2J_{F,H}$ = 56.5 Hz, $^3J_{F,H}$ = 16.7 Hz, 2 F, C*F*$_2$H). Exact mass (ESI): $[M + H]^+$ calcd for $C_5H_9F_2NO_2H^+$: 154.0674; found: 154.0670. Exact mass (ESI): $[M + Na]^+$ calcd for $C_5H_9F_2NO_2Na^+$: 176.0494; found: 176.0493. Exact mass (ESI): $[M + Na]^+$ calcd for $C_5H_8F_2NO_2^-$: 152.0529; found: 152.0530. Elemental analysis: calcd for $C_5H_{10}ClF_2NO_2$: C 31.68%, H 5.32%, N 7.39%; found: C 31.76%, H 5.29%, N 7.49%.

(*R*)-*tert*-Butyl 5-benzyloxy-2-{[(1*S*,2*S*,5*S*,*E*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]-heptan-3-ylidene]amino}pentanoate (33). A solution of diisopropylamine (0.28 mL, 2.0 mmol, 2.0 eq.) in abs. THF (2 mL) was cooled to −78 °C and dropwise treated with *n*-butyllithium (1.6 N in hexane, 1.25 mL, 2.0 mmol, 2.0 eq.). The solution was stirred at r.t. for 15 min and then again cooled to −78 °C. Subsequently a solution of *tert*-butyl 2-{[(1*R*,2*S*,5*R*,*E*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]-heptane-3-ylidene]amino}acetate (**32**) (281 mg, 1.0 mmol) in abs. THF (1 mL) was added dropwise and the solution was stirred for 90 min at the same temperature. After that *O*-tosyl-3-benzyloxy-1-propanol (**22**) (352 mg, 1.1 mmol, 1.1 eq.) in THF (1.1 mL) was added and the mixture was stirred for 2 h at −78 °C and overnight at r.t. The reaction was quenched by addition of half conc. aqueous NaCl (2.5 mL), the organic phase separated and the aqueous phase extracted with Et_2O (4 × 8 mL). The combined organic phases were washed with H_2O and sat. aqueous NaCl (2 × 20 mL each) and dried over $MgSO_4$. After evaporation of the solvent the crude product was obtained as a yellow wax. Purification by column chromatography (CyH/EtOAc, 10 : 1 → 1 : 1) gave a yellow oil (279 mg, 0.65 mmol, 65%). It was also possible to use the crude product for the following reaction. $[\alpha]_D^{20}$ = −25.6 (*c* = 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 0.88 (s, 3 H, C*H*$_3$), 1.32 (s, 3 H, C*H*$_3$), 1.43 (s, 9 H, OC(C*H*$_3$)$_3$), 1.50 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, C*H*^{a}CHCH$_2$), 1.50 (s, 3 H, C(OH)C*H*$_3$), 1.56–1.69 (m, 2 H, C*H*$_2$CH$_2$OBn), 1.83–1.94 (m, 1 H, CO$_2$CHC*H*^{a}), 1.94–2.07 (m, 2 H, CO$_2$CHC*H*^{b}, CH$_2$C*H*CH$_2$), 2.07 (t, $^3J_{H,H}$ = 5.9 Hz, CH$_2$C*H*C(OH)CH$_3$), 2.32 (m, 1 H, C*H*^{b}CHCH$_2$), 2.49–2.52 (m, 2 H, CHC*H*$_2$CN), 3.49 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, C*H*$_2$OBn), 4.07 (dd, $^3J_{H,H}$ = 8.2, 5.1 Hz, 1 H, C*H*CO$_2$), 4.50 (s, 2 H, OC*H*$_2$Ph), 7.25–7.30 (m, 1 H, *para*-C*H*), 7.31–7.37 (m, 4 H, 2 × *ortho*-C*H* and 2 × *meta*-C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 23.0 (*C*H$_3$), 26.2 (*C*H$_2$CH$_2$OBn), 27.3 (*C*H$_3$), 28.0 (CH*C*H$_2$CH and CO$_2$C(*C*H$_3$)$_3$), 28.4 (C(OH)*C*H$_3$), 29.8 (CO$_2$CH*C*H$_2$), 33.5 (CH*C*H$_2$CN), 38.4 (CH$_2$*C*HCH$_2$), 38.5 (CH$_3$*C*CH$_3$), 50.0 (*C*HC(OH)CH$_3$), 62.9 (CO$_2$*C*H), 70.1 (*C*H$_2$OBn), 72.9 (O*C*H$_2$Ph), 76.7 (*C*(OH)CH$_3$), 81.0 (*C*(CH$_3$)$_3$), 127.5 (C-*para*), 127.7 (2 × C-*ortho*), 128.3 (2 × C-*meta*), 138.5 (C-*ipso*), 170.8 (*C*O$_2$^{t}Bu), 178.4 (*C*=N). Exact mass (ESI): $[M + H]^+$ calcd for $C_{26}H_{39}NO_4H^+$: 430.2952; found: 430.2948. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{26}H_{39}NO_4Na^+$: 452.2771; found: 452.2766.

(*R*)-*tert*-Butyl 2-amino-5-benzyloxypentanoate (42). (*R*)-*tert*-Butyl 5-benzyloxy-2-{[(1*S*,2*S*,5*S*,*E*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylidene]amino}pentanoate (**33**) (279 mg, 0.65 mmol) was dissolved in THF (1.2 mL) and treated with 15% citric acid (1.2 mL) at 0 °C. After stirring at r.t. for 3 d, the organic solvent was evaporated and the aqueous residue was washed with *n*-pentane (3 × 5 mL). Then $NaHCO_3$ was added to the aqueous phase until it reached pH > 7. The solution was extracted with Et_2O (4 × 5 mL) and the combined organic phases dried over $MgSO_4$. After evaporation of the solvent the product (145 mg, 0.52 mmol, 80%) could be used without further purification. $[\alpha]_D^{20}$ = 2.2 (*c* = 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.46 (s, 9 H, CO$_2$C(C*H*$_3$)$_3$), 1.56–1.83 (m, 4 H, CO$_2$CHC*H*$_2$ and C*H*$_2$CH$_2$OBn), 3.32 (dd, $^3J_{H,H}$ = 7.4, 5.2 Hz, 1 H, C*H*), 3.50 (t, $^3J_{H,H}$ = 6.1 Hz, 2 H, C*H*$_2$OBn), 4.50 (s, 2 H, OC*H*$_2$Ph), 7.24–7.31 (m, 1 H, *para*-C*H*), 7.31–7.36 (m, 4 H, 2 × *ortho*-C*H* and 2 × *meta*-C*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 25.9 (*C*H$_2$CH$_2$OBn), 28.0 (CO$_2$C(*C*H$_3$)$_3$), 31.8 (CO$_2$CH*C*H$_2$), 54.8 (CO$_2$*C*H), 69.9 (*C*H$_2$OBn), 72.8 (O*C*H$_2$Ph), 80.9 (*C*(CH$_3$)$_3$), 127.5 (C-*para*), 127.6 (2 × C-*ortho*), 128.3 (2 × C-*meta*), 138.5 (C-*ipso*), 175.4 (*C*O$_2$^{t}Bu). Exact mass (ESI): $[M + H]^+$ calcd for $C_{16}H_{25}NO_3H^+$: 280.1907; found: 280.1904. Exact mass (ESI): $[M + Na]^+$ calcd for $C_{16}H_{25}NO_3Na^+$: 302.1727; found: 302.1724.

(*R*)-*tert*-Butyl 5-benzyloxy-2-phthalimidopentanoate (34). (*R*)-*tert*-Butyl 2-amino-5-benzyloxypentanoate (**42**) (559 mg, 2.0 mmol) and finely mortared phthalic anhydride (296 mg, 2.0 mmol) were mixed and in a pre-heated oil bath stirred at 145 °C for 1 h. The cold residue was purified chromatographically (CyH/EtOAc, 5 : 1) which gave a colorless oil (433 mg, 1.06 mmol, 53%, 94% ee, determined by chiral HPLC). $[\alpha]_D^{20}$ = 1.2 (*c* = 1.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 1.43 (s, 9 H, CO$_2$C(C*H*$_3$)$_3$), 1.56–1.71 (m, 2 H, C*H*$_2$CH$_2$OBn), 2.23–2.38 (m, 2 H, CO$_2$CHC*H*$_2$), 3.48 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, C*H*$_2$OBn), 4.47 (s, 2 H, OC*H*$_2$Ph), 4.77 (dd, $^3J_{H,H}$ = 9.7, 6.2 Hz, 1 H, C*H*), 7.22–7.28 (m, 1 H, *para*-C*H*), 7.28–7.35 (m, 4 H, 2 × *ortho*-C*H* and 2 × *meta*-C*H*), 7.68–7.75 (m, 2 H, 2 × Phth–CCHC*H*), 7.81–7.88 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.6 (CO$_2$CH*C*H$_2$), 26.8 (*C*H$_2$CH$_2$OBn), 27.9 (CO$_2$C(*C*H$_3$)$_3$), 52.9 (CO$_2$*C*H), 69.3 (*C*H$_2$OBn), 72.9 (O*C*H$_2$Ph), 82.4 (*C*(CH$_3$)$_3$), 123.4 (2 × Phth–C*C*H), 127.5 (C-*para*), 127.6 (2 × C-*ortho*), 128.3 (2 × C-*meta*), 131.8 (2 × Phth–*C*), 134.1 (2 × Phth–CCH*C*H), 138.4 (C-*ipso*), 167.8 (2 × Phth–*C*=O), 168.2 (*C*O$_2$^{t}Bu). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{24}H_{27}NO_5Na^+$: 432.1781; found: 432.1782.

(*R*)-*tert*-Butyl 5-hydroxy-2-phthalimidopentanoate (35). To a solution of (*R*)-*tert*-butyl 5-benzyloxy-2-phthalimido-pentanoate (**34**) (524 mg, 1.3 mmol) in EtOAc (6 mL) was added Pd/C (10% w/w, 50 mg) and the suspension was stirred under a 2 bar atmosphere of H_2 for 3 h at r.t. After filtration over celite the product was obtained as a colorless oil (360 mg, 1.1 mmol, 88%, 43% ee, determined by chiral HPLC). $[\alpha]_D^{20}$ = 1.4 (*c* = 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 1.43 (s, 9 H, CO$_2$C(C*H*$_3$)$_3$), 1.50–1.66 (m, 2 H, C*H*$_2$CH$_2$OH), 2.22–2.37 (m, 2 H, CO$_2$CHC*H*$_2$), 3.67 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, C*H*$_2$OH), 4.80 (dd, $^3J_{H,H}$ = 9.1, 6.6 Hz, 1 H, C*H*), 7.70–7.79 (m, 2 H, 2 × Phth–CCHC*H*), 7.81–7.91 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.3 (CO$_2$CH*C*H$_2$), 27.9 (CO$_2$C(*C*H$_3$)$_3$), 52.9 (CO$_2$*C*H), 62.1 (*C*H$_2$OH), 82.6 (*C*(CH$_3$)$_3$), 123.5 (Phth–*C*CH), 131.8 (2 × Phth–*C*), 134.2 (Phth–CCH*C*H), 167.9 (2 × Phth–*C*=O), 168.2 (*C*O$_2$^{t}Bu). Exact mass (ESI): $[M + Na]^+$ calcd for

$C_{17}H_{21}NO_5Na^+$: 342.1312; found: 342.1318. Exact mass (ESI): $[M + MeOH + Na]^+$ calcd for $C_{17}H_{21}NO_5CH_3OHNa^+$: 374.1574; found: 374.1576.

(*R*)-*tert*-Butyl 5-oxo-2-phthalimidopentanoate (36). (*R*)-*tert*-Butyl 5-hydroxy-2-phthalimidopentanoate (**35**) (335 mg, 1.1 mmol) was dissolved in CH_2Cl_2 and treated with Dess–Martin periodinane (534 mg, 1.3 mmol, 1.2 eq.). The mixture was stirred for 1.5 h at r.t. before being quenched with sat. aqueous Na_2SO_3 and sat. aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (3 × 10 mL) the combined organic phases were dried over $MgSO_4$ and the solvent evaporated. Chromatographic purification (CyH/EtOAc 2 : 1) led to a yellow, viscous oil (203 mg, 0.64 mmol, 61%, 34% ee, determined by chiral HPLC). $[\alpha]_D^{20}$ = −0.3 (*c* = 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ = 1.43 (s, 9 H, $CO_2C(CH_3)_3$), 2.38–2.66 (m, 4 H, CH_2CHO and CO_2CHCH_2), 4.75–4.86 (m, 1 H, C*H*), 7.72–7.80 (m, 2 H, 2 × Phth-CCHC*H*), 7.84–7.91 (m, 2 H, 2 × Phth–CC*H*), 9.74 (t, $^3J_{H,H}$ = 0.9 Hz, 1 H, C*H*O). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 21.7 (CO_2CHCH_2), 27.8 ($CO_2C(CH_3)_3$), 40.7 (CH_2CHO), 52.1 (CO_2CH), 82.9 ($C(CH_3)_3$), 123.5 (Phth–*C*CH), 131.7 (2 × Phth–*C*), 134.3 (Phth–C*C*H), 167.5 ($CO_2{}^tBu$), 167.7 (2 × Phth–*C*═O), 200.5 (*C*HO). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{17}H_{19}NO_5Na^+$: 340.1155; found: 340.1153. Exact mass (ESI): $[M + MeOH + Na]^+$ calcd for $C_{17}H_{19}NO_5CH_3OHNa^+$: 372.1418; found: 372.1415.

(*R*)-*tert*-Butyl 5,5-difluoro-2-phthalimidopentanoate (37). Under an argon atmosphere a solution of (*R*)-*tert*-butyl 5-oxo-2-phthalimidopentanoate (**36**) (252 mg, 0.79 mmol) in CH_2Cl_2 (7 mL) was reacted with Deoxo-Fluor (2.7 M in PhMe, 0.44 mL, 1.19 mmol, 1.5 eq.) for 3 h at r.t. The reaction was quenched with sat. aqueous $NaHCO_3$ and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography (CyH/EtOAc, 2 : 1) to give a yellow oil (93 mg, 0.27 mmol, 34%), $[\alpha]_D^{20}$ = 1.1 (*c* = 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ = 1.43 (s, 9 H, $CO_2C(CH_3)_3$), 1.71–2.06 (m, 2 H, CH_2CF_2H), 2.25–2.48 (m, 2 H, CO_2CHCH_2), 4.77 (dd, $^3J_{H,H}$ = 9.7, 5.8 Hz, 1 H, C*H*), 5.84 (tt, $^2J_{H,F}$ = 56.5 Hz, $^3J_{H,H}$ = 4.4 Hz, 1 H, CF_2H), 7.73–7.80 (m, 2 H, 2 × Phth–CCHC*H*), 7.85–7.92 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.9 (t, $^3J_{C,F}$ = 5.8 Hz, CO_2CHCH_2), 27.8 ($CO_2C(CH_3)_3$), 31.2 (t, $^2J_{C,F}$ = 21.6 Hz, CH_2CF_2H), 52.2 (CO_2CH), 83.0 ($C(CH_3)_3$), 116.5 (t, $^1J_{C,F}$ = 239.4 Hz, CF_2H), 123.6 (Phth–C*C*H), 131.7 (2 × Phth–*C*), 134.3 (Phth–CCHC*H*), 167.5 ($CO_2{}^tBu$), 167.7 (2 × Phth–*C*═O). ^{19}F NMR (282 MHz, CD_3OD) δ = −116.7/−116.8 (AB signal, $^2J_{F,F}$ = 281.5 Hz, $^2J_{F,H}$ = 56.5 Hz, $^3J_{F,H}$ = 17.2 Hz/$^2J_{F,F}$ = 281.5 Hz, $^2J_{F,H}$ = 56.5 Hz, $^3J_{F,H}$ = 17.3 Hz, 2 F, CF_2H). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{17}H_{19}F_2NO_4Na^+$: 362.1174; found: 362.1172.

2-[(3*R*)-6-Fluoro-2-oxotetrahydro-2*H*-pyran-3-yl]isoindoline-1,3-dione (38). Isolated as a white solid product in addition to **37**. Yield: 58 mg (0.22 mmol, 28%), mp 172–173 °C, $[\alpha]_D^{20}$ = −0.7 (*c* = 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.01–2.11 (m, 1 H, CHNC*H*^{a}), 2.12–2.32 (m, 2 H, CHFC*H*^{a}), 2.34–2.44 (m, 1 H, CHFC*H*^{b}), 2.88–3.06 (m, 1 H, CHNC*H*^{b}), 4.96 (dd, $^3J_{H,H}$ = 12.7, 6.6 Hz, 1 H, C*H*N), 6.14 (ddd, $^2J_{H,F}$ = 53.7 Hz, $^3J_{H,H}$ = 1.8, 1.8 Hz, 1 H, C*H*F), 7.72–7.80 (m, 2 H, 2 × Phth–CCHC*H*), 7.84–7.92 (m, 2 H, 2 × Phth–CC*H*). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 20.3 (dt, $^3J_{C,F}$ = 2.4 Hz, CHNCH_2), 27.6 (dt, $^2J_{C,F}$ = 23.3 Hz, CHFCH_2), 48.4 (d, *C*HN), 106.9 (dd, $^1J_{C,F}$ = 228.4 Hz, *C*HF), 123.8 (d, 2 × Phth–C*C*H), 131.7 (s, 2 × Phth–*C*), 134.5 (d, 2 × Phth–CCHC*H*), 165.0 (d, $^3J_{C,F}$ = 1.7 Hz, CO_2), 166.9 (s, 2 × Phth–*C*═O). ^{19}F NMR ($CDCl_3$, 282 MHz): δ = −119.4 (ddd, $^2J_{H,F}$ = 53.4 Hz, $^3J_{H,F}$ = 36.3, 6.7 Hz, 1 F, C*F*H). Exact mass (ESI): $[M + Na]^+$ calcd for $C_{13}H_{10}FNO_4Na^+$: 286.0486; found: 286.0486; $[M + MeOH + Na]^+$, calcd for $C_{13}H_{10}FNO_4CH_3OHNa^+$: 318.0748; found: 318.0740.

(*R*)-2-Amino-5,5-difluoropentanoic acid hydrochloride (39). In a pressure tube (*R*)-*tert*-butyl 5,5-difluoro-2-phthalimido-pentanoate (**37**) (93 mg, 0.27 mmol) was dissolved in HOAc (0.5 mL) and 6 N aqueous HCl (5 mL) and the solution heated to 130 °C for 15 h. The volatile components were evaporated and the residue was purified by SPE (Chromabond C18ec, 500 mg, 3 mL ice-cold H_2O) which gave the product as a white solid (50 mg, 0.26 mmol, 96%, 36% ee, determined by ^{19}F NMR of the (*S*)-2-chloropropionyl amide). Mp 214–215 °C (dec.); $[\alpha]_D^{20}$ = 3.5 (*c* = 1.00, 1 M $HCl_{(aq.)}$). The spectroscopic and spectrometric data are consistent with those already listed for **28**.

Crystallographic data

X-Ray diffraction. Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (R. W. W. Hooft, Bruker AXS, 2008, Delft, The Netherlands); data reduction, Denzo-SMN;[56] absorption correction, Denzo;[57] structure solution, SHELXS-97;[58] structure refinement, SHELXL-97.[59] *R*-Values are given for observed reflections, and wR^2 values are given for all reflections.

X-ray crystal structure analysis of 12 (CCDC 1429375). Formula $C_{19}H_{17}NO_4S$, *M* = 355.40, colourless crystal, 0.15 × 0.07 × 0.05 mm, *a* = 7.6727(2), *b* = 8.5813(3), *c* = 14.3778(6) Å, α = 82.996(1)°, β = 79.762(1)°, γ = 67.718(2)°, *V* = 860.5(1) Å^3, ρ_{calc} = 1.372 g cm^{-3}, μ = 0.212 mm^{-1}, empirical absorption correction (0.968 ≤ *T* ≤ 0.989), *Z* = 2, triclinic, space group $P\bar{1}$ (no. 2), λ = 0.71073 Å, *T* = 223(2) K, ω and φ scans, 7846 reflections collected (±*h*, ±*k*, ±*l*), 3456 independent (R_{int} = 0.035) and 2985 observed reflections [$I > 2\sigma(I)$], 227 refined parameters, *R* = 0.049, wR^2 = 0.107, max. (min.) residual electron density 0.29 (−0.29) e Å^{-3}; hydrogen atoms were calculated and refined as riding atoms.

X-ray crystal structure analysis of 14c (CCDC 1429376). Formula $C_{14}H_{12}F_3NO_4$, *M* = 315.25, colourless crystal, 0.36 × 0.22 × 0.04 mm, *a* = 13.6630(1), *b* = 7.8244(1), *c* = 13.7079(1) Å, β = 109.783(1)°, *V* = 1378.9(1) Å^3, ρ_{calc} = 1.518 g cm^{-3}, μ = 1.204 mm^{-1}, empirical absorption correction (0.671 ≤ *T* ≤ 0.953), *Z* = 4, monoclinic, space group $P2_1/c$ (no. 14), λ = 1.54178 Å, *T* = 223(2) K, ω and φ scans, 9087 reflections collected (±*h*, ±*k*, ±*l*), 2376 independent (R_{int} = 0.038) and 2161 observed reflections [$I > 2\sigma(I)$], 200 refined parameters, *R* = 0.049, wR^2 = 0.139, max. (min.) residual electron density 0.22 (−0.24) e Å^{-3}. The hydrogen at N1 atom was refined freely; others were calculated and refined as riding atoms.

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Notes and references

1 *Organofluorine Chemistry: Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York, 1994.
2 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2013.
3 *Fluorine and Health - Molecular Imaging, Biomedical Materials and Pharmaceuticals*, ed. A. Tressaud and G. Haufe, Elsevier, Amsterdam, 2008.
4 *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, John Wiley & Sons Ltd, Chichester, 2009.
5 J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Imperial College Press, Hoboken, 2008.
6 G. Theodoridis, in *Advances in Fluorine Science*, ed. A. Tressaud, Elsevier, Amsterdam, 2006, pp. 121–175.
7 P. Jeschke, *ChemBioChem*, 2004, **5**, 570–589.
8 T. Pitterna, M. Böger and P. Maienfisch, *Chimia*, 2004, **58**, 108–116.
9 N. Sewald and H.-D. Jakubke, *Peptides: Chemistry and Biology*, Wiley-VCH, Weinheim, 2003.
10 *Fluorine-containing Amino Acids - Synthesis and Properties*, ed. V. P. Kukhar and V. A. Soloshonok, John Wiley & Sons, Chichester, 1994.
11 A. Sutherland and C. L. Willis, *Nat. Prod. Rep.*, 2000, **17**, 621–631.
12 X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711–6745.
13 X.-L. Qiu and F.-L. Qing, *Eur. J. Org. Chem.*, 2011, 3261–3273.
14 V. Asante, J. Mortier, G. Wolber and B. Koksch, *Amino Acids*, 2014, **46**, 2733–2744.
15 B. Koksch, N. Sewald, H.-J. Hofmann and K. Burger, *J. Pept. Sci.*, 1997, **3**, 157–167.
16 H. Biava and N. Budisa, *Eng. Life Sci.*, 2014, **14**, 340–351.
17 *Enzyme Catalysis in Organic Synthesis*, ed. K. Drauz, H. Gröger and O. May, Wiley-VCH, Weinheim, 2012.
18 C. Jäckel, M. Salwiczek and B. Koksch, *Angew. Chem., Int. Ed.*, 2006, **45**, 4198–4203.
19 Y. Tang, G. Ghirlanda, W. A. Petka, T. Nakajima, W. F. DeGrado and D. A. Tirrell, *Angew. Chem., Int. Ed.*, 2001, **40**, 1494–1496.
20 E. Pourabed, F. G. Golmohamadi, S. M. Monfared, S. M. Ravazi and Z.-S. Shobbar, *Mol. Biotechnol.*, 2015, **57**, 12–26.
21 E. N. G. Marsh, *Acc. Chem. Res.*, 2014, **47**, 2878–2886.
22 P. Baker and J. Montclare, *ChemBioChem*, 2011, **12**, 1845–1848.
23 U. I. M. Gerling, M. Salwiczek, C. D. Cadikamo, H. Erdbrink, S. L. Grage, P. Wadwani, A. S. Ulrich, M. Behrends, G. Haufe, C. Czekelius and B. Koksch, *Chem. Sci.*, 2014, **5**, 819–830.
24 B. Davis and V. Boyer, *Nat. Prod. Rep.*, 2001, **18**, 618–640.
25 D. P. McGregor, *Curr. Opin. Pharmacol.*, 2008, **8**, 616–619.
26 P. C. Michels, Y. L. Khmelnitsky, J. S. Dordick and D. S. Clark, *Trends Biotechnol.*, 1998, **16**, 210–215.
27 M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214–231.
28 V. Hugenberg, R. Fröhlich and G. Haufe, *Org. Biomol. Chem.*, 2010, **8**, 5682–5691.
29 V. Hugenberg and G. Haufe, *J. Fluorine Chem.*, 2010, **131**, 942–950.
30 G. Haufe, K. W. Laue, M. U. Triller, Y. Takeuchi and N. Shibata, *Tetrahedron*, 1998, **54**, 5929–5938.
31 E. W. Logusch, *Tetrahedron Lett.*, 1986, **27**, 5935–5938.
32 G. Talbot, R. Gaudry and L. Berlinguet, *Can. J. Chem.*, 1958, **36**, 593–596.
33 A. Tarui, N. Kawashima, K. Sato, M. Omote and A. Ando, *Tetrahedron Lett.*, 2010, **51**, 4246–4249.
34 A. Tarui, N. Kawashima, K. Sato, M. Omote, Y. Miwa, H. Minami and A. Ando, *Tetrahedron Lett.*, 2010, **51**, 2000–2003.
35 S. C. Kim and F. M. Raushel, *J. Enzyme Inhib.*, 1988, **2**, 153–161.
36 D. Baba and T. Fuchigami, *Tetrahedron Lett.*, 2002, **43**, 4805–4808.
37 J. Kwiatkowski and Y. Lu, *Org. Biomol. Chem.*, 2015, **13**, 2350–2359.
38 P.-F. Zheng, Q. Ouyang, S.-L. Niu, L. Shuai, Y. Yuan, K. Jiang, T.-Y. Liu and Y.-C. Chen, *J. Am. Chem. Soc.*, 2015, **137**, 9390–9399.
39 L. Hu, C. Che, Z. Tan and G. Zhu, *Chem. Commun.*, 2015, **51**, 16641–16644.
40 A. M. Paloyan, L. A. Stepanyan, S. A. Dadayan, A. A. Hambardzumyan, G. P. Halebyan and A. S. Saghiyan, *Appl. Biochem. Microbiol.*, 2013, **49**, 106–112.
41 P. Hudhomme and G. Duguay, *Tetrahedron*, 1990, **46**, 5263–5272.
42 V. Hugenberg, S. Wagner, K. Kopka, O. Schober, M. Schäfers and G. Haufe, *J. Org. Chem.*, 2010, **75**, 6086–6095.
43 M. J. Robins and S. F. Wnuk, *J. Org. Chem.*, 1993, **58**, 3800–3801.
44 W. Dmowski, in *Organo-Fluorine Compounds*, ed. B. Baasner, H. Hagemann and J. C. Tatlow, Houben-Weyl, Stuttgart, 2000.
45 A. G. Griesbeck and J. Hirt, *Liebigs Ann. Chem.*, 1995, **11**, 1957–1961.
46 S. Kröger and G. Haufe, *Amino Acids*, 1996, **11**, 409–424.
47 *Data for Biomedical Research*, ed. R. M. C. Dawson, D. C. Elliott, W. H. Elliott and K. M. Jones, Oxford University Press, London, 1974.

48 N. Minowa, M. Hirayama and S. Fukatsu, *Tetrahedron Lett.*, 1984, **25**, 1147–1150.
49 N. Minowa, M. Hirayama and S. Fukatsu, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1761–1766.
50 K. W. Laue, S. Kröger, E. Wegelius and G. Haufe, *Eur. J. Org. Chem.*, 2000, 3737–3743.
51 R. G. Carlson and J. K. Pierce, *J. Org. Chem.*, 1971, **36**, 2319–2324.
52 K. W. Laue, PhD thesis, University of Münster, 1998.
53 W. Kruizinga, J. Bolster, R. M. Kellogg, J. Kamphuis, W. H. J. Boesten, E. M. Meijer and H. E. Shoemaker, *J. Org. Chem.*, 1988, **53**, 1826–1827.
54 S. Kröger and G. Haufe, *Liebigs Ann./Recl.*, 1997, 1201–1206.
55 K. Watabe, S.-C. Chang, E. Gil-Av and B. Koppenhoefer, *Synthesis*, 1987, 225–228.
56 Z. Otwinowski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307–326.
57 Z. Otwinowski, D. Borek, W. Majewski and W. Minor, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2003, **59**, 228–234.
58 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1990, **46**, 467–473.
59 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112–122.