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Trifluoromethyl-substituted hydantoins, versatile building blocks for rational drug design

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

Abstract—Preparatively simple, one-pot syntheses of trifluoromethyl-substituted hydantoins starting from Boc-protected imines of hexafluoroacetone and trifluoropyruvate are described. They represent valuable building blocks for the construction of constrained peptides or as scaffolds for the synthesis of highly potent VLA-4 antagonists.

1. Introduction

A major drawback of peptide drugs is their rapid degradation by proteases, their low lipophilicity and the lack of transport systems to direct peptides into cells. Therefore, cell membranes generally resist passage of most peptides. Consequently, they are rapidly excreted via liver and kidney. The high conformational flexibility of peptides creates another problem: bioactive peptides often bind to different receptor sites causing undesired side effects.[1,2]

Incorporation of α,α-disubstituted α-amino acids into key positions of peptides is an efficient strategy to retard proteolytic degradation and to stabilize secondary structure motifs.[3] Due to the unique properties of the trifluoromethyl group, including high electronegativity, high lipophilicity and high sterical demand, α-trifluoromethyl α-amino acids [α-TfmAAs] are a special subclass of α,α-disubstituted α-amino acids, which may improve the profile of bioactive compounds considerably,[4] by enhancing absorption and transport rates as well as permeability through certain body barriers. An advantage of applying fluoromodification to stabilize peptides and proteins is, that this strategy is complementary to other existing stabilization methods.[5] Another attractive feature of most trifluoromethyl-substituted compounds is their relatively low toxicity and high stability compared to monofluoromethyl and difluoromethyl analogues.[6] Finally, ^{19}F NMR spectroscopy provides a highly efficient method for conformational studies of fluorine-containing peptides as well as for elucidating metabolic processes. Consequently, rational design of mechanism-based fluorinated biologically active compounds is a powerful tool for an efficient drug research.[7,8]

In this context, the development of methodology for incorporation of fluoromodified amino acids into key positions of drug candidates via heterocyclic building blocks, e.g. hydantoins, to improve their therapeutic profile is of current interest.[9] On the other hand, a wide range of therapeutic properties has been reported for hydantions and thiohydantions, including antiviral, antibacterial, antifungal, herbicidal, anticonvulsant, antidiabetic, anti-inflammatory, antiulcer and antiarythmic activities.[10,11] Therefore, the development of new strategies for the synthesis of hydantions, combined with fluoromodification continues to attract the attention of medicinal chemists.[12]

Herein we disclose an efficient, one-pot synthesis of trifluoromethyl- and bis(trifluoromethyl)-substituted hydantoin derivatives which can be used as 'Aib surrogates' starting from Boc-protected imines of 3,3,3-trifluoropyruvates and hexafluoroacetone (Scheme 1).

2. Results an discussion

The highly electrophilic acylimines of hexafluoroacetone[13]

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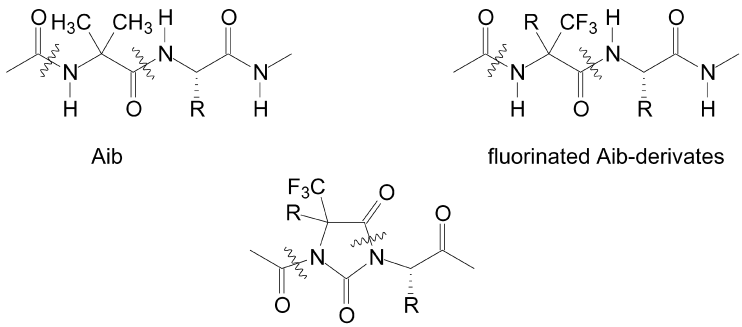


Scheme 1.

and 3,3,3-trifluoropyruvates[14] are excellent traps for isonitriles[15] to give [4+1] cycloadducts,[16,17] which can be readily transformed into dipeptide esters with up to three trifluoromethyl groups[18] on treatment with methanol/1 N HCl. These dipeptide fragments represent interesting lipophilic building blocks for the construction of sterically crowded peptidomimetics.

Surprisingly, when Boc-protected imines derived from methyl 3,3,3-trifluoropyruvate **1a** and hexafluoroacetone **1b** were reacted with isonitriles **2** (substituent pattern see Table 1) in dry benzene at 60 °C for 6–8 h, elemental analyses and mass spectra data reveal that the expected [1:1] adducts are unstable. Under the reaction conditions applied, elimination of $(CH_3)_2C{=}CH_2$ takes place. An analogous isobutene elimination, occurring at rt, was observed on activation of Boc-protected α-TFM amino acids with DCC. At 0 °C oxazolones are formed quantitatively within 20–30 min. The oxazolones turned out to be stable below −30 °C on exclusion of moisture. But on rising the temperature above 0 °C a retro ene reaction starts to convert the oxazolones into Leuchs anhydrides (Scheme 2).[19]

Table 1. Syntheses of hydantoins **5** from Boc-imines **1** and isonitriles **2**

Imine	Isonitrile	Product	R^1	R^2	R^3	R^4
1a	**2a**	**5a**	CO_2Me	H	H	Me
1a	**2b**	**5b**	CO_2Me	CF_3	CH_2Ph	Me
1a	**2c**	**5c**	CO_2Me	CF_3	Ph	Me
1b	**2d**	**5d**	CF_3	H	CH_2CHMe_2	*t*-Bu
1b	**2e**	**5e**	CF_3	H	CH_2-cyclopropyl	*t*-Bu

In analogy, we postulate that in the case of [4+1] cycloadducts **3** a retro ene reaction is the reason for the readily occurring isobutene elimination. Originally, the products isolated we ascribed the structure of 5-imino-1,3-oxazolidin-2-ones **4**.[20] But when we found that these

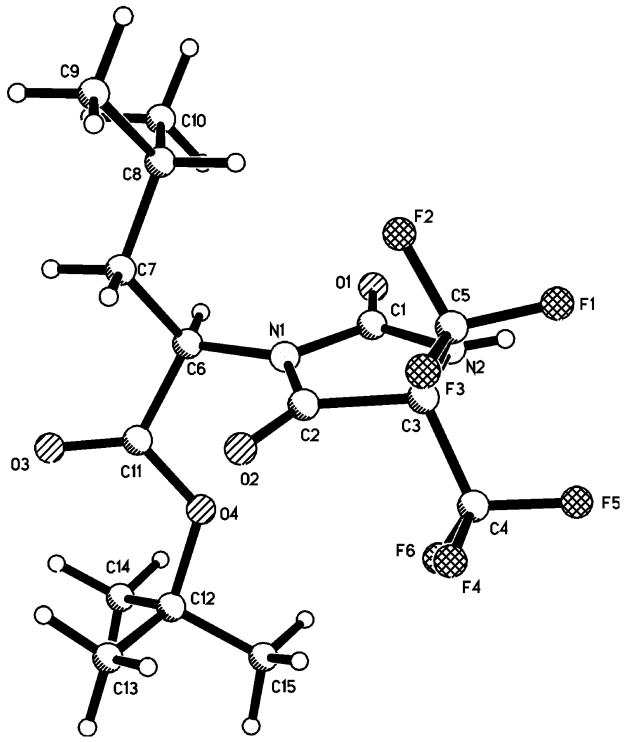
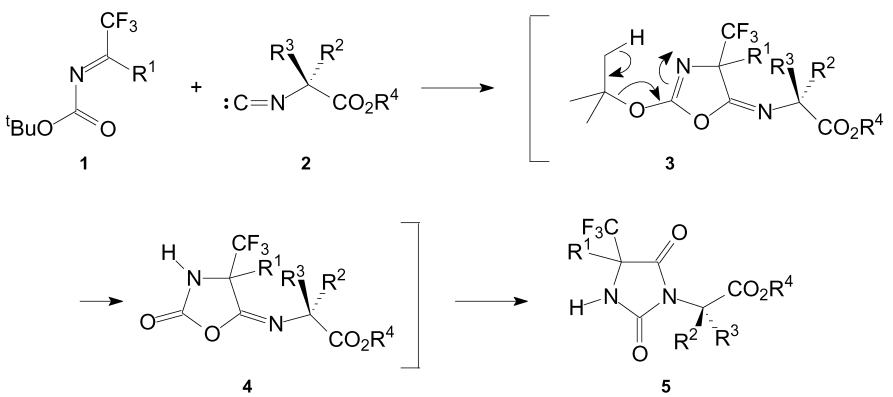
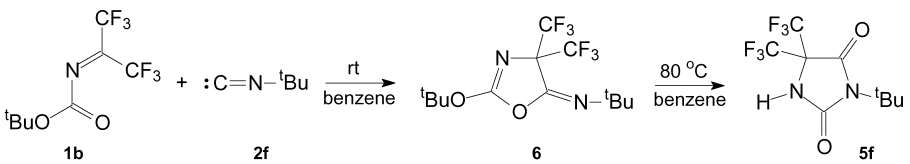


Figure 1. X-ray structure of **5d**.



Scheme 2.



Scheme 3.

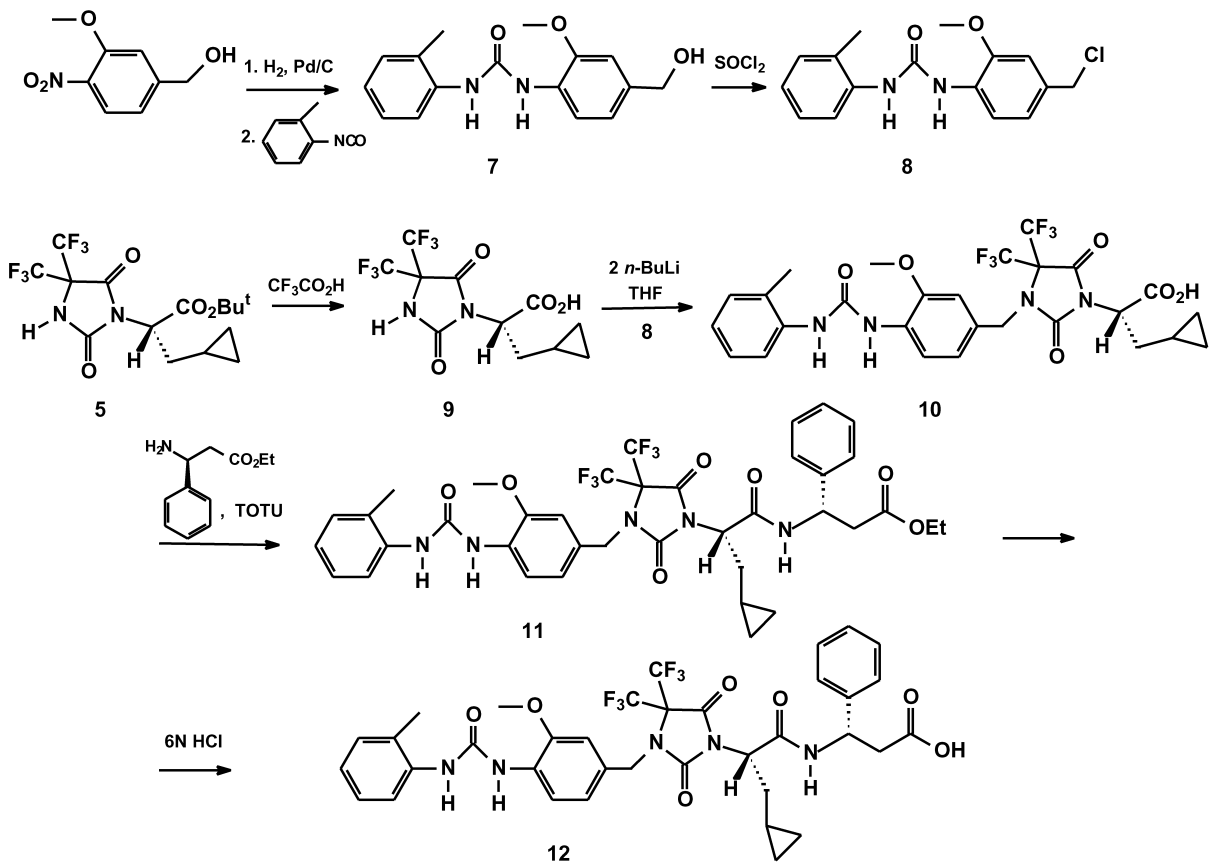
products remained unchanged on treatment with HCl at rt, we reexamined the structural assignment. We found that the [4+1] cycloadducts formed first, undergo a retro ene reaction (**3→4**). However, under the reaction conditions applied the newly formed compounds **4** are unstable too. In a consecutive rearrangement they are converted into hydantoins **5**. A resonance line in the region of δ=154–156 ppm can be assigned to an urea function incorporated into a five-membered ring system.[21]

An X-ray structure analysis[22] (Fig. 1) unequivocally proved that 4,4-bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolidine **5d** is formed in a three step sequence (**1→3→4→5**). When imine **1b** and isonitriles derived from chiral (*S*)-leucine and (*S*)-cyclopropylalanine are used, 5,5-bis(trifluoromethyl)hydantoin-modified dipeptides **5d**,**e** are obtained in very good yields.

To confirm the mechanism for the reaction of imines with isonitriles we investigated a series of similar transformations. We found that imine **1b** and *tert*-butyl isonitrile **2f** afforded a stable [1:1] adduct **6** on reaction at rt in benzene (Scheme 3). **6** was isolated and purified by low temperature crystallization. The rearrangement **6→5f** was achieved on heating under reflux in dry benzene for 16 h.

Structural variability can be generated by chain elongation in N- and C-terminal position. A typical example for a drug candidate is the VLA-4 receptor antagonist **12**[23] (Scheme 3). VLA-4 (=very late antigen 4), a member of the integrin receptor family, is expressed on activated leukocytes, which use the VLA-4 receptors for the adhesion to endothelium cells during inflammatory processes. Blocking of this receptor might be an interesting option to treat inflammatory diseases like asthma, rheumatoid arthritis and multiple sclerosis. The IC_{50} of **12** in a cell attachment assay using VLA-4 expressing U937 cells and its natural ligand VCAM-1 (=vascular cell adhesion molecule 1) was determined to 5.55 nM.

Compound **12** was prepared as shown in Scheme 4. The bis(trifluoromethyl)hydantoin **5e** was deprotected to give acid **9**, which was alkylated using 4-(3-(2-methylphenyl)-ureido-3-methoxybenzyl chloride **8** in the presence of 2 equiv. of *n*-BuLi in THF. **8** was prepared in three steps starting from 3-methoxy-4-nitrobenzyl alcohol, reduction of



Scheme 4.

the nitro group, addition to 2-methylphenyl-isocyanate and transformation of the resulting benzyl alcohol **7** to the corresponding chloride using $SOCl_2$. The VLA-4 antagonist **12** was prepared by coupling of (*S*)-3-amino-3-phenyl-propionic acid ethyl ester to the hydantoin **10** in the presence of TOTU followed by cleavage of the ester group with 6 N HCl (Scheme 4).

3. Conclusion

We developed a highly efficient synthesis for 4-trifluoromethyl- **5a–c** and 4,4-bis(trifluoromethyl)-substituted hydantoins **5d**,**e** which can be used as lipophilic, rigid building blocks for peptide modification. The three step synthesis can be performed as one-pot procedure and represents an impressive example for the high efficiency and elegance of domino reactions.[24,25] **5e** was used as the central scaffold in the synthesis of the highly potent VLA-4 antagonist **12**.

4. Experimental

4.1. General

Melting points were determined on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H NMR spectra were recorded with VARIAN Gemini 2000 spectrometers at 200 and 300 MHz. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ=0 ppm); *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 and 75 MHz. ^{19}F spectra were recorded at 188 and 282 MHz with trifluoroacetic acid (TFA, δ=0 ppm) as external standard. Optical rotations $[\alpha]_D$ were measured using a Polartronic polarimeter (Schmidt and Haensch) in a 5 cm cell. For C, H, N analyses a CHNO-Rapid Elemental Analyzer (Hereaus) was used. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI=70 eV). For flash chromatography, silica gel (32–63 μm) was used with solvent systems given in text. Organic solvents were dried and distilled prior to use.

2-(*N*-Benzoyl)imino- and 2-*N*-(*tert*-butoxycarbonyl)imino-1,1,1,3,3,3-hexafluoropropane were prepared according to the method given in lit.[13b] Methyl 2-[*N*-(benzyloxycarbonyl)imino]- and methyl 2-[*N*-(*tert*-butoxycarbonyl)-imino]-3,3,3-trifluoropropionate were prepared according to the protocol described in lit.[14b] and lit.,[26] respectively. Isonitriles **2a–c** were prepared according to the method given in lit.[17] Isonitriles **2d**,**e** were prepared from *tert*-butyl *N*-formyl-(*S*)-leucinate and *tert*-butyl *N*-formyl-(*S*)-cycloalaninate, respectively, using diphosgene and were taken into reaction with imine **1b** without isolation (see below).

4.2. Trifluoromethyl-substituted hydantoins. General procedure

Equimolar amounts (5 mmol) of an acylimine **1** and an isonitrile **2** were stirred in dry benzene (25 mL) at 60 °C for 6–8 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/hexanes).

4.2.1. Methyl 2-(4-methoxycarbonyl-4-trifluoromethyl-2,5-dioxo-1,3-imidazolin-1-yl)-acetate 5a. Yield: 1.12 g (75%) **5a**; oil. IR (KBr): ν=3360, 3290, 1810, 1780, 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=3.78 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 7.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=40.09, 53.01, 54.92, 68.56 (q, *J*=31.4 Hz), 120.78 (q, *J*=284.9 Hz), 155.38, 161.25, 161.86, 166.60. ^{19}F NMR ($CDCl_3$): δ=4.07 (s, 3F, CF_3). Anal. calcd for $C_9H_9F_3N_2O_6$ (298.16): C, 36.25; H, 3.04; N 9.39. Found: C, 36.40; H 3.19; N, 9.35.

4.2.2. Methyl 2-(4-methoxycarbonyl-4-trifluoromethyl-2,5-dioxo-1,3-imidazolin-1-yl)-2-benzyl-3,3,3-trifluoro-propionate 5b. Yield: 2.00 g (88%) **5b**. *Diastereomer 1*: R_f=0.31 (ethyl acetate/hexanes=1:2); mp 116–119 °C. ^{1}H NMR ($CDCl_3$): δ=3.64 (s, 3H, OCH_3), 3.73 (d, 1H, *J*=14.4 Hz, CH_2), 3.90 (s, 3H, OMe), 4.20 (d, 1H, *J*=14.4 Hz, CH_2), 7.17 (m, 2H, H_{arom}), 7.26 (m, 3H, H_{arom}), 7.40 (m, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=35.86, 53.11, 55.00, 67.52 (q, *J*=31.4 Hz), 120.59 (q, *J*=285.0 Hz), 123.46 (q, *J*=287.4 Hz), 128.08, 128.38, 130.92, 132.13, 154.39, 160.89, 161.60, 163.15. ^{19}F NMR ($CDCl_3$): δ=3.80 (s, 3F, CF_3), 7.46 (3, 3F, CF_3).

Diastereomer 2: R_f=0.26 (ethyl acetate/hexanes=1:2); oil. ^{1}H NMR ($CDCl_3$): δ=3.64 (s, 3H, OCH_3), 3.76 (d, 1H, *J*=14.3 Hz, CH_2), 3.90 (s, 3H, OCH_3), 4.19 (d, 1H, *J*=14.3 Hz, CH_2), 7.15 (m, 2H, H_{arom}), 7.27 (m, 3H, H_{arom}), 7.49 (m, 1H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=35.79, 53.10, 55.01, 67.50 (q, *J*=31.5 Hz), 69.02 (q, *J*=28.4 Hz), 120.60 (q, *J*=285.3 Hz), 123.50 (q, *J*=287.2 Hz), 128.10, 128.40, 130.90, 132.17, 154.43, 160.92, 161.57, 163.26. ^{19}F NMR ($CDCl_3$): δ=3.63 (s, 3F, CF_3), 7.30 (s, 3F, CF_3). Anal. calcd for $C_{17}H_{14}F_6N_2O_6$ (456.28): C, 44.75; H, 3.09; N, 6.14. Found: C, 44.59; H, 3.31; N, 6.17.

4.2.3. Methyl 2-(4-methoxycarbonyl-4-trifluoromethyl-2,5-dioxo-1,3-imidazolin-1-yl)-2-phenyl-3,3,3-trifluoro-propionate 5c. Yield: 1.33 g (60%) **5c**; oil (mixture of diastereomers, ratio 1:1). *Diastereomer 1*: R_f=0.33 (ethyl acetate/hexanes=1:2). ^{1}H NMR ($CDCl_3$): δ=3.80 (s, 3H, OMe), 3.87 (s, 3H, OCH_3), 7.37 (m, 4H, H_{arom}, NH), 7.57 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=54.12, 54.93, 67.70 (q, *J*=31.3 Hz), 69.58 (q, *J*=29.5 Hz), 120.65 (q, *J*=284.8 Hz), 123.37 (q, *J*=287.9 Hz), 127.30 (q, *J*=1.9 Hz), 128.01, 128.66, 129.80, 154.04, 160.62, 161.05, 163.23. ^{19}F NMR ($CDCl_3$): δ=3.95 (s, 3F, CF_3), 11.53 (s, 3F, CF_3).

Diastereomer 2: R_f=0.26 (ethyl acetate/hexanes=1:2). ^{1}H NMR ($CDCl_3$): δ=3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.23 (s, 1H, NH), 7.39 (m, 3H, H_{arom}), 7.58 (s, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$): δ=53.99, 54.86, 67.46 (q, *J*=31.5 Hz), 69.40 (q, *J*=29.5 Hz), 120.49 (q, *J*=284.9 Hz), 123.24 (q, *J*=288.1 Hz), 127.18 (q, *J*=1.8 Hz), 127.93, 128.52, 129.67, 153.61, 160.70, 160.99, 163.08. ^{19}F NMR ($CDCl_3$): δ=3.73 (s, 3F, CF_3), 11.42 (s, 3F, CF_3). Anal. calcd for $C_{16}H_{12}F_6N_2O_6$ (442.25): C, 43.45; H, 2.73; N, 6.33. Found: C, 43.85; H, 2.94; N, 6.21.

4.2.4. *tert*-Butyl *N*-formyl-(*S*)-leucinate.[27] A solution of 4.04 g (40 mmol) of triethylamine in 10 mL of dichloromethane was added to a solution of 8.94 g (40 mmol) of *S*-leucine *tert*-butyl ester hydrochloride and 3.40 g (40 mmol) of cyanomethyl formate[27] in 60 mL of dichloromethane at 0 °C. The reaction solution was allowed to warm up to rt overnight. It was washed twice with brine. The organic phase was dried over $MgSO_4$, filtrated and evaporated. Distillation of the residue under reduced pressure gave *tert*-butyl (*S*)-3-*N*-formyl-3-leucinate (7.5 g, 87%) as an oil; bp 118 °C/0.02 Torr. ^{1}H NMR ($CDCl_3$): δ=0.84 (d, 3H, *J*=5.0 Hz, CH_3), 0.87 (d, 3H, *J*=5.0 Hz, CH_3), 1.36 (s, 9H, $(CH_3)_3$), 1.49 (m, 3H, CH, CH_2), 4.51 (m, 1H, N–CH), 6.75 (br.s, 1H, NH), 8.10 (s, 1H, CH═O).

4.2.5. *tert*-Butyl (*S*)-2-[4,4-bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolin-1-yl]-2-(methyl-propyl)acetate 5d. Diphosgene (2.4 g, 12.1 mmol) was added to a solution of *N*-formyl-(*S*)-leucine *tert*-butyl ester (2.5 g, 11.6 mmol) and triethylamine (2.5 g, 24.7 mmol) in dry dichloromethane (100 mL) at −30 °C. The reaction mixture was allowed to warm up to −10 °C during 1 h and was stirred further at this temperature until the reaction was complete (TLC-control). The reaction solution was washed at rt twice with 7% aqueous $NaHCO_3$ solution. The organic phase was separated and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was taken up in dry benzene (70 mL). Boc-imine of hexafluoroacetone **1b** (3.0 g, 11.3 mmol) in dry benzene (10 mL) was added dropwise to this solution at rt. The reaction mixture was heated to 60 °C overnight, then benzene was removed in vacuo. Column chromatography of the residue over silica gel (eluent: petroleum ether/ethyl acetate=10/1) gave 3.70 g (80%) of **5d** as white crystals; mp 105–106 °C; $[\alpha]^{20}$=−24° (*c*=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.88 (d, 3H, *J*=5.2 Hz, CH_3), 0.92 (d, 3H, *J*=5.2 Hz, CH_3), 1.32 (m, 1H, CH), 1.41 (s, 9H, $(CH_3)_3$), 1.83 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 4.64 (dd, 1H, N–CH, *J*=4.4, 11.7 Hz), 7.93 (br.s, 1H, NH). ^{19}F NMR ($CDCl_3$): δ=4.8 (m, 6F, 2×CF_3). ^{13}C NMR ($CDCl_3$): δ=20.95, 23.41, 25.20, 27.99, 36.68, 53.35, 66.39 sept. (C–CF_3, *J*=32.0 Hz), 83.97, 120.49 q (CF_3, *J*=286.5 Hz), 156.18, 160.54, 167.52. Anal. calcd for $C_{15}H_{20}F_6N_2O_4$ (406.3): C, 44.34; H, 4.96; N, 6.89. Found: C, 44.60; H, 5.28; N 7.02.

4.2.6. *tert*-Butyl (*S*)-3-*N*-formyl-3-cyclopropylalaninate. (*S*)-3-Cyclopropylalanine (3.5 g, 27.1 mmol) was added at rt to a mixture of dioxane (50 mL) and conc. sulfuric acid (5 mL), prepared by cautious dropwise addition of the acid to dioxane at 5 °C. The solution was transferred together with isobutylene (40 mL) in a sealed tube at −78 °C. The sealed tube was shaken at rt for 24 h. The sealed tube was carefully opened (under cooling) and the reaction mixture was cautiously poured into a stirred mixture of triethylamine (30 mL) and water (50 mL), cooled to 5 °C. After removal of the excess of isobutylene, the product was extracted with diethyl ether (2×50 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue-a pale yellow oil (4.2 g, 84%) was used for the following reaction without further purification. ^{1}H NMR ($CDCl_3$): δ=0.10 (m, 2H, CH_2), 0.49 (m, 2H, CH_2), 0.81 (m, 1H, CH), 1.25 (br. m, 2H, NH_2), 1.50 (s, 9H, $C(CH_3)_3$), 1.61 (m, 2H, CH_2), 3.41 (dd, 1H, *J*=1.5, 10.1 Hz, N–CH).

A mixture of (*S*)-cyclopropyl-alanine *tert*-butyl ester (10.0 g, 54 mmol) and cyanomethyl formiate (4.7 g, 55.2 mmol) in dichloromethane (100 mL) was stirred at rt overnight. The solvent was removed in vacuo. Distillation of the residue under reduced pressure gave *tert*-butyl (*S*)-3-*N*-formyl-3-cyclopropylalaninate (8.8 g, 76%) as an oil; bp 120 °C/0.3 Torr. ^{1}H NMR ($CDCl_3$): δ=0.09 (m, 2H, CH_2), 0.48 (m, 2H, CH_2), 0.65 (m, 1H, CH), 1.47 (s, 9H, $C(CH_3)_3$), 1.69 (m, 2H, CH_2), 4.63 (m, 1H, N-CH), 6.31 (1H, NH), 8.20 (s, 1H, CH═O).

4.2.7. *tert*-Butyl (*S*)-2-[4,4-bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolin-1-yl]-2-(cyclopropylmethyl)acetate 5e. Diphosgene (2.4 g, 12.1 mmol) was added to a solution of *tert*-butyl (*S*)-3-*N*-formyl-3-cyclopropylalaninate (2.5 g, 11.7 mmol) and triethylamine (2.5 g, 24.7 mmol) in dry dichloromethane (100 mL) at −30 °C. The reaction solution was allowed to warm up to −15 °C during 1 h and was stirred further at this temperature until the reaction was complete (TLC-control). The organic phase was washed twice with 7% aqueous $NaHCO_3$ solution and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was dissolved in benzene (70 mL). Boc-imine of hexafluoroacetone **1b** (3.05 g, 11.5 mmol) in benzene (10 mL) was added dropwise at rt to this solution. The mixture was heated at 60 °C (bath temperature) overnight, then benzene was removed in vacuo. Column chromatography of the residue over silica gel (eluent: hexanes/ethyl acetate=8/1) gave 3.70 g (78%) **5e** as white crystals; mp 76–77 °C; $[\alpha]^{20}$=−28° (*c*=1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=0.08 (m, 2H, CH_2), 0.42 (m, 2H, CH_2), 0.50 (m, 1H, CH), 1.40 (s, 9H, $(CH_3)_3$), 2.02 (m, 2H, CH_2), 4.67 (dd, 1H, N–CH, *J*=4.4, 11.7 Hz), 7.73 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=3.46, 5.21. 7.76, 27.99, 32.96, 55.41, 66.48 (sept., C-CF_3, *J*=32.0 Hz), 83.94, 120.49 (q, CF_3, *J*=286.5 Hz), 156.19, 160.55, 166.96. ^{19}F NMR ($CDCl_3$): δ=4.89 (m, 6F, 2×CF_3). Anal. calcd for $C_{15}H_{18}F_6N_2O_4$ (404): C, 44.55; H, 4.45; N, 6.93. Found: C, 44.60; H, 4.76; N, 6.72.

4.2.8. 2-*tert*-Butyloxy-4,4-bis(trifluoromethyl)-5-*tert*-butylimino-4*H*-oxazol 6. A mixture of imine **1b** (1.5 g, 5.7 mmol) and *tert*-butylisonitrile (0.47 g, 5.7 mmol) in dry benzene (50 mL) was stirred at rt for 48 h. The solvent was removed under reduced pressure, the remaining solid was recrystallized from hexanes at 0 °C to give 1.7 g (86.3%) **6** as white crystals; mp 73 °C. ^{1}H NMR ($CDCl_3$): δ=1.30 (s, 9H, $NCMe_3$), 1.62 (s, 9H, $OCMe_3$). ^{13}C NMR ($CDCl_3$): δ=29.25, 31.28, 58.39, 78.33 (sept., C-CF_3, *J*=32.0 Hz), 90.62, 123.09 (q, CF_3, *J*=287.5 Hz), 141.19, 164.45. ^{19}F NMR ($CDCl_3$): δ=3.36 (s, 6F, 2×CF_3). Anal. calcd for $C_{13}H_{18}F_6N_2O_2$ (348.3): C, 44.83; H, 5.21; N, 8.04. Found: C, 44.80; H, 5.59; N, 8.32.

4.2.9. 1-*tert*-Butyl-4,4-bis(trifluoromethyl)-2,5-dioxo-imidazolidin 5f. A solution of **6** (1.3 g, 3.7 mmol) in 30 mL benzene was heated at 80 °C for 16 h. After removing of solvent the remaining solid was recrystallized from hexanes to give 0.99 g (90.8%) of **5f** as white crystals; mp 114–115 °C. ^{1}H NMR ($CDCl_3$): δ=1.59 (s, 9H, $NCMe_3$), 7.56 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=29.25, 61.08, 65.73 (sept., C–CF_3, *J*=32.0 Hz), 120.92 (q, CF_3, *J*=287.5 Hz), 159.97, 161.96. ^{19}F NMR ($CDCl_3$):

δ=4.10 (s, 6F, 2×CF_3). Anal. calcd for $C_9H_{10}F_6N_2O_2$ (292.19): C, 37.00; H, 3.45; N, 9.59. Found: C, 37.00; H, 3.39; N, 9.56.

4.3. (*S*)-3-((*S*)-2-(4,4-Bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido-3-methoxy-benzyl)-2,5-dioxo-imidazolin-1-yl)-2-cyclopropylmethyl)acetylamino)-3-phenylpropionic acid 12

4.3.1. 4-[3-(2-Methylphenyl)ureido]-methoxybenzyl alcohol 7. 3-Methoxy-4-nitrobenzyl alcohol (15.0 g, 81.8 mmol) was hydrogenated in methyl *tert*-butyl ether (500 mL) in the presence of a palladium/carbon catalyst while cooling with ice. After the hydrogen uptake ceased, the catalyst was filtered off, and 2-methylphenyl isocyanate (10.14 g, 81.8 mmol) was added to the stirred filtrate within 30 min. The reaction mixture was stirred overnight, and the precipitate was filtered off and washed with methyl *tert*-butyl ether. Yield: 20.5 g (88%) **7**.

^{1}H NMR (DMSO-d_6): δ=2.22 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.43 (d, 2H, *J*=6.0 Hz, CH_2), 5.07 (t, 1H, *J*=6.0 Hz, OH), 6.83 (d, 1H, *J*=8.2 Hz, H_{arom}), 6.95 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.80 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.05 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.45 (s, 1H, NH), 8.56 (s, 1H, NH). MS (ESI): 287.2 $[M+H]^+$.

4.3.2. 4-[3-(2-Methylphenyl)ureido]-3-methoxybenzyl chloride 8. Thionyl chloride (7.65 mL, 104.8 mmol) was added dropwise to a suspension of **7** (15.0 g, 53.4 mmol) in methylene chloride (300 mL) while cooling with ice. The reaction mixture was stirred at rt for 3 h. After standing overnight the mixture was poured into heptane (1000 mL). The heptane was decanted off from the oil, which had separated. The oil was again suspended in heptane, and the heptane was decanted off. This procedure was repeated two times. Then the residue was dissolved in methylene chloride and poured into ice-cold diisopropyl ether (800 mL). The mixture was stirred for 2 h while cooling with ice. The precipitate was filtered off, washed with diisopropyl ether and dried over phosphorus pentoxide to give 12.0 g (75%) of **8**.

^{1}H NMR (DMSO-d_6): δ=2.23 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.73 (m, 2H, CH_2), 6.96 (m, 2H, H_{arom}), 7.15 (m, 3H, H_{arom}), 7.78 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.12 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.55 (s, 1H, NH), 8.70 (s, 1H, NH).

4.3.3. (*S*)-2-[4,4-Bis(trifluoromethyl)-2,5-dioxo-1,3-imidazolin-1-yl]-2-(cyclopropylmethyl)-acetic acid 9. Was obtained from compound **5e** on stirring in a solution of trifluoroacetic acid in dichloromethane (3/7). The solvent and trifluoroacetic acid were removed under reduced pressure. The residue was purified by freeze drying. The crude product **9** was used for the next reaction step.

4.3.4. (*S*)-2-(4,4-Bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido)-3-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)-2-(cyclopropylmethyl)acetic acid 10. A *n*-BuLi solution (3.2 mL. 2.5 M in hexane) was added to a solution of **9** (1.39 g, 4.0 mmol) in dry THF (40 mL) under argon at −40 °C. The reaction mixture was allowed to warm up to 0 °C while stirring, a solution of 4-(3-(2-methylphenyl)-ureido)-3-methoxybenzyl chloride **8** (2.43 g, 8.0 mmol) in dry THF (20 mL) was added, and the reaction mixture was stirred at rt for 3 h. Then 1 N HCl (20 mL) was added and THF removed in vacuo. The aqueous phase was extracted twice with methyl *tert*-butyl ether. The combined organic phase was dried with $NaSO_4$, and after filtration, concentrated in vacuo. The residue was purified by preparative HPLC. Concentration of the product fractions and freeze drying gave 1.41 g (57%) **10**.

^{1}H NMR (DMSO-d_6): δ=0.00 (m, 1H, CH), 0.13 (m, 1H, CH), 0.36 (m, 2H, CH_2), 0.50 (m, 1H, CH), 2.00 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.73 (d, 1H, *J*=15.8 Hz, CH_2), 4.84 (d, 1H, *J*=15.8 Hz, CH_2), 4.94 (dd, 1H, *J*=4.5, 11.3 Hz, CH), 6.82 ('d', 1H, *J*=8.2 Hz, H_{arom}), 6.95 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.77 (d, 1H, *J*=7.1 Hz, H_{arom}), 8.08 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.50 (s, 1H, NH), 8.63 (s, 1H, NH), 13.58 (bs, 1H, COOH). MS (ESI): 617.1 $[M+H]^+$.

4.3.5. Ethyl (*S*)-3-(*S*)-2-(4,4-bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido)-3-methoxybenzyl)-2,5-dioxo-imidazolidin-1-yl)-2-(cyclopropylmethyl)acetylamino-3-phenylpropionate 11. TOTU (728 mg, 2.28 mmol) (*O*-((cyano(ethoxycarbonyl)-methylene)amino-*N*,*N*,*N*′,*N*′-tetramethyluroniumtetrafluoroborate) and *N*,*N*-diisopropylamine (368 μL) were added to a solution of **10** (1.41 g, 2.28 mmol) and of ethyl-(*S*)-3-amino-3-phenylpropionate (442 mg, 2.28 mmol) in dry DMF (20 mL) at 0 °C. After stirring at rt for 1 h, the DMF was removed in vacuo, the residue was dissolved in ethyl acetate, and the organic phase was washed successively with aqueous $KHSO_4/K_2SO_4$ solution, saturated $NaHCO_3$ solution and water. The organic phase was dried over $NaSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography over silica gel, eluent: heptane/ethyl acetate (3:2). After removal of the solvent was obtained 1.48 g (82%) **11**.

^{1}H NMR (DMSO-d_6): δ=0.07 (m, 1H, CH), 0.18 (m, 1H, CH), 0.40 (m, 2H, CH_2), 0.56 (m, 1H, CH), 1.10 (t, 3H, *J*=6.8 Hz, CH_3), 1.97 (m, 1H, CH), 2.22 (m, 1H, CH), 2.23 (s, 3H, CH_3), 2.78 (d, 2H, *J*=7.5 Hz, CH_2), 3.82 (s, 3H, OCH_3), 4.00 (m, 2H, OCH_2), 4.70 (d, 1H, *J*=15.8 Hz, CH_2), 4.75 (m, 1H, CH), 4.80 (d, 1H, *J*=15.8 Hz, CH_2), 5.24 ('q', 1H, *J*=7.5 Hz, CH), 6.80 ('d', 1H, *J*=8.2 Hz, H_{arom}), 6.95 (m, 2H, H_{arom}), 7.15 (m, 2H, H_{arom}), 7.30 (m, 5H, H_{arom}), 7.75 (d, 1H, *J*=8.2 Hz, H_{arom}), 8.06 (d, 1H, *J*=7,5 Hz, H_{arom}), 8.50 (s, 1H, NH), 8.62 (s, 1H, NH), 8.63 (d, 1H, *J*=7.5 Hz, NH). MS (ESI): 792.2 $[M+H]^+$.

4.3.6. (*S*)-3-((*S*)-2-(4,4-Bis(trifluoromethyl)-3-(4-(3-(2-methylphenyl)ureido)-3-methoxybenzyl)-2,5-dioxoimidazolidin-1-yl)-2-(cyclopropylmethyl)-acetylamino)-3-phenylpropionic acid 12. A solution of **11** (1.46 g, 1.84 mmol) in *N*-methyl-2-pyrrolidone (40 mL) was heated with 6N HCl (20 mL) at 60 °C for 6 h. After cooling to rt, the reaction mixture was poured into water (300 mL), and the precipitate was filtered off, washed with water and dried over phosphorus pentoxide. The crude product was subjected twice to column chromatography over silica gel (eluent: dichloromethane/methanol/acetic acid/water=94/5/0.5/0.5). After removal of the solvents, the residue was dissolved in dichloromethane, washed with water and dried

over $NaSO_4$. After removal of the solvent and lypophilization were obtained 1.19 g (85%) **12**.

^{1}H NMR (DMSO-d_6): δ=0.06 (m, 1H, CH), 0.18 (m, 1H, CH), 0.40 (m, 2H, CH_2), 0.55 (m, 1H, CH), 1.97 (m, 1H, CH), 2.22 (m, 1H, CH), 2.23 (s, 3H, CH_3), 2.7 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.68 (d, 1H, J=15.8 Hz, CH_2), 4.77 (m, 1H, CH), 4.82 (d, 1H, J=15.8 Hz, CH_2), 5.18 ('q', 1H, J=7.5 Hz, CH), 6.80 ('d', 1H, J=8.2 Hz, H arom.), 6.95 (m, 2H, H $_{arom}$), 7.15 (m, 2H, H_{arom}), 7.30 (m, 5H, H_{arom}), 7.77 (d, 1H, J=8.2 Hz, H_{arom}), 8.05 (d, 1H, J=7,5 Hz, H_{arom}), 8.50 (s, 1H, NH), 8.56 (d, 1H, J=7.5 Hz, NH), 8.61 (s, 1H, NH), 12.32 (bs, 1H, COOH). MS (ESI): 764.2 $[M+H]^+$.

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