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Incorporation of α-Trifluoromethyl Substituted α-Amino Acids into C-and N-terminal Position of Peptides and Peptide Mimetics Using Multicomponent Reactions

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Abstract: Methodology for incorporation of α-trifluoromethyl substituted amino acids into the C- and N-terminal position of peptides and peptide mimetics via multicomponent reactions of the Passerini and Ugi type is described.

Dedicated to Prof. Dr. H.-D. Jakubke on the occasion of his 65th birthday

Introduction

Metabolic and conformational stabilization of pharmacologically active peptides can be achieved by incorporation of sterically hindered amino acids, e.g. $C^{\alpha,\alpha}$-disubstituted amino acids [1-5]. α-Trifluoromethyl substituted amino acids (α-Tfm amino acids), a subclass of $C^{\alpha,\alpha}$-disubstituted amino acids, also fullfil this requirements while featuring additional properties based on the high electronegativity of fluorine. Therefore, they are interesting building blocks for peptide synthesis [6].

A trifluoromethyl group in α-position of an amino acid exerts considerable polarization effects on the neighbouring substituents. This structural alteration influences the hydrolytic stability of peptides containing Tfm amino acids resulting in retarded degradation by peptidases [7,8] and, consequently, in prolonged intrinsic activity. Upon incorporation of α-Tfm amino acids, severe conformational restrictions are exerted on the peptide chain. Furthermore, due to the high electron density, the trifluoromethyl group is capable of participating in hydrogen bonding as a hydrogen acceptor. In contrast to an α-methyl group this property enables α-Tfm substituted peptides to interact in a unique way with enzyme or receptor subsites [8].

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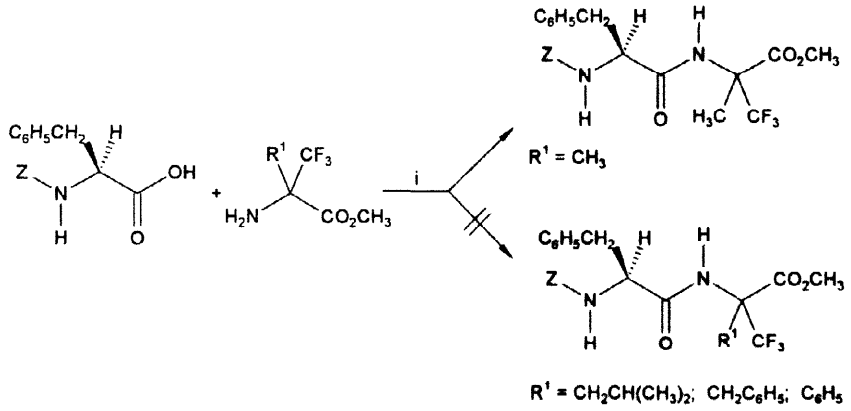
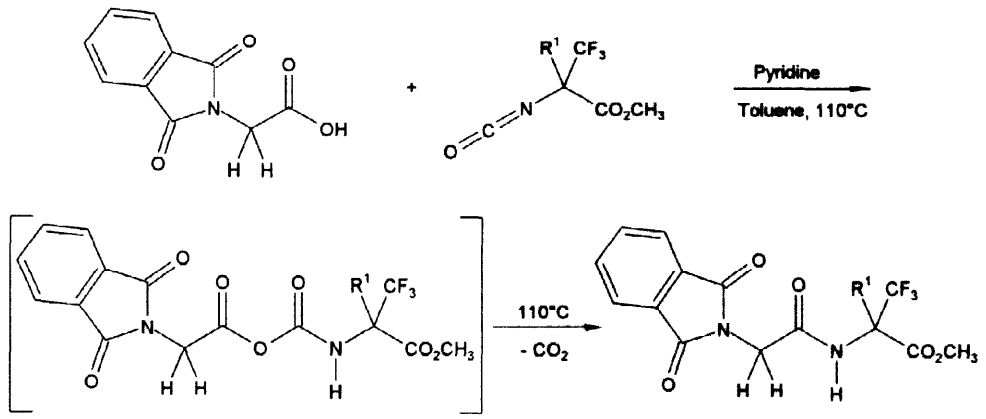
Incorporation of α-Tfm amino acids into the C-terminal position of peptides

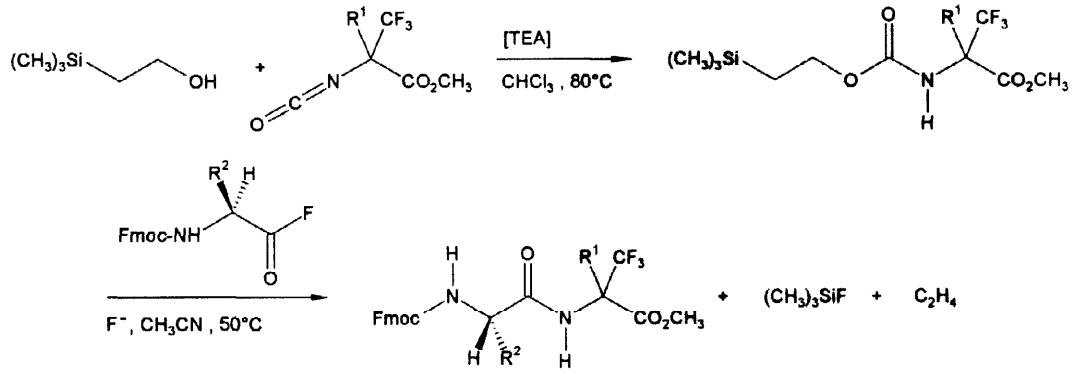
The low nucleophilicity of the amino group (pK_a values of Ala-NH_2: 9.87; TfmAla-NH_2: 5.91) [9] and the steric bulk of the trifluoromethyl group [10] in α-trifluoromethyl α-amino acids (Tfm amino acids) requires modification of the standard protocols of peptide synthesis. Only the least bulky amino acid esters H-(α-Tfm)Gly-OMe and H-(α-Tfm)Ala-OMe can be coupled with reasonable yields using classical methodology [11,12]. For other Tfm amino acids with bulkier side chains, all classical activation strategies failed so far or resulted in substantial epimerization of the non-fluorinated N-terminal amino acid because of the drastic reaction conditions necessary for peptide bond formation.



However, peptide coupling involving the amino group of α-Tfm amino acids can be achieved via conversion into the corresponding isocyanate. The isocyanate can be coupled directly with N-protected amino acids via a mixed anhydride [12].



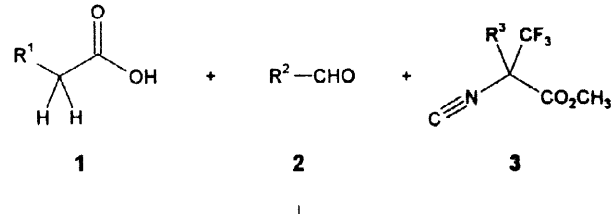
Likewise, a mixed anhydride is involved in an in situ deprotection / coupling process of Teoc- (2-trimethylsilylethoxycarbonyl) protected α-Tfm amino acids. The introduction of the Teoc group is achieved by reaction of the trifluoromethyl substituted isocyanates with 2-trimethylsilyl ethanol. In the presence of catalytic amounts of fluoride ions Teoc-protected α-Tfm amino acid esters react with Fmoc amino acid fluorides to give Fmoc protected dipeptide esters with the Tfm amino acid esters in C-terminal position in acceptable yields[12,13].

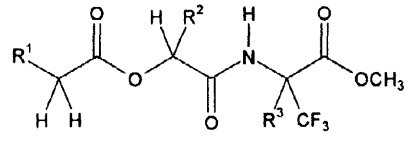


We now report on a general method for C-terminal incorporation of α-Tfm amino acids into depsipeptide and peptide fragments using multicomponent reactions (MCR's) of the Passerini[14] and Ugi [15] type. The 2-isocyano-3,3,3-trifluoropropionates are obtained from N-formyl Tfm amino acid esters [16] on treatment with diphosgene / triethylamine [17].

Passerini Reaction

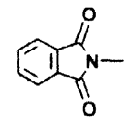
When equimolar amounts of acid **1**, aldehyde **2** and the corresponding 2-isocyano-3,3,3-trifluoropropionate **3** are stirred at room temperature in absolute ethyl acetate or acetonitrile the protected hydroxyacyl amino acid derivatives **4a-d** are obtained as diastereomeric mixtures since the isocyanides **3** are introduced as racemates. In the case of **4a** one isomer can be isolated by crystallization. In most cases the diastereomers can be separated easily by flash chromatography. When N-protected amino acids are used as carboxylic component a diastereomeric mixture (1:1) of tripeptide analogues is obtained. The progress of the reaction can conveniently be monitored by ^{19}F NMR spectroscopy since the resonance absorption of the product is significantly shifted downfield by 3 ppm.





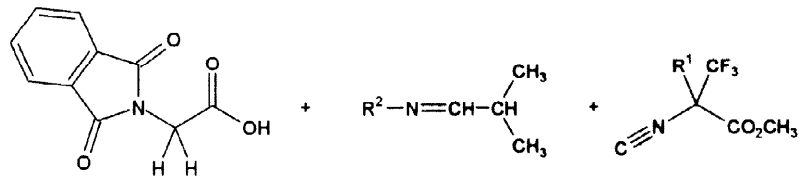
4	R^1	R^2	R^3
a	Cl	$CH(CH_3)_2$	C_6H_5
b	Cl	$CH_2C_6H_5$	$CH_2CH(CH_3)_2$
c	PHT=N	$CH(CH_3)_2$	$CH_2C_6H_5$
d	PHT=N	$CH(CH_3)_2$	C_6H_5

PHT=N :



Ugi Reaction

Because of the problems observed on application of conventional methodology for the C-terminal incorporation of α-Tfm amino acids into peptides we tested the Ugi 4CR [15]. When we applied the classical Ugi protocol the yields were unsatisfactory. Therefore, the imines prepared from isobutyraldehyde and cyclohexyl- and benzylamine *in situ* were treated with phthaloylglycine and 2-isocyano-3,3,3-trifluoropropionate in a 3CR to avoid competition of the Passerini reaction [18].



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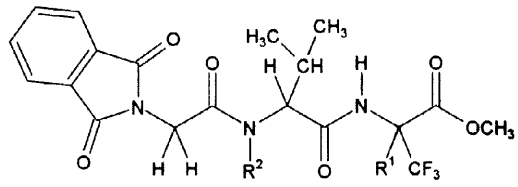

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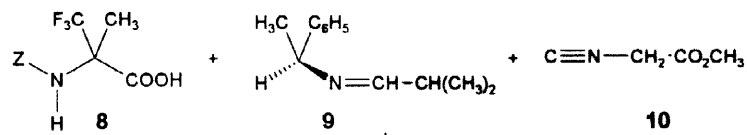
7	R^1	R^2
a	CH_3	C_6H_{11}
b	$C_6H_5CH_2$	C_6H_{11}
c	$C_6H_5CH_2$	$CH_2C_6H_5$
d	C_6H_5	C_6H_{11}
e	$(CH_3)_2CHCH_2$	(S)-$C_6H_5CH(CH_3)$

Stereochemistry is a serious problem of the 4CR. Reaction of the imine formed *in situ* from isobutyraldehyde and (S)-1-phenylethylamine with phthaloylglycine **5** and 3,3,3-trifluoropropionate **3** yields a mixture of four diastereomers in a 2:1:1:2 ratio, independent on the reaction temperature.

Incorporation of α-Tfm amino acids into the N-terminal position of peptides

The Ugi 4CR is also applicable for the introduction of α-Tfm amino acids in N-terminal position of peptide fragments [18]. Consequently, tripeptides can be synthesized with Tfm amino acids in position 1 and 3 via Ugi 4CR.



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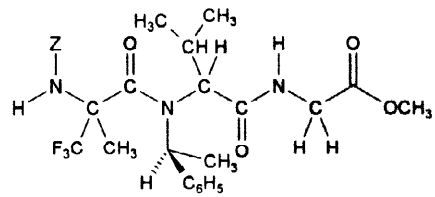

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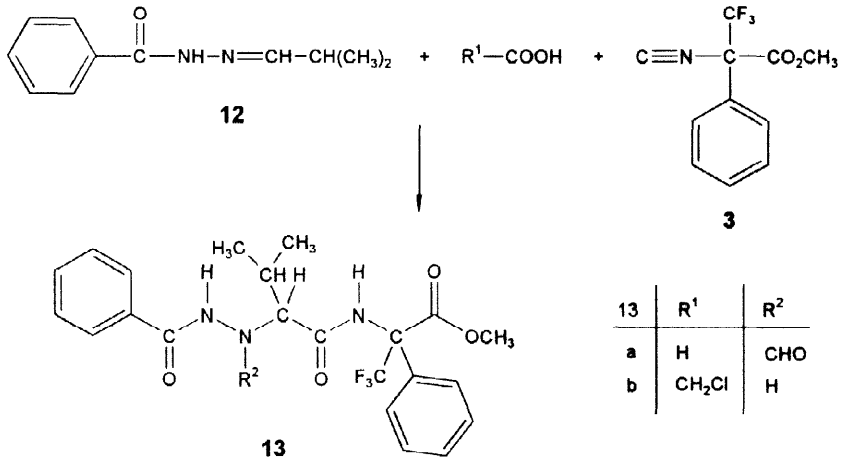
Hydrazinopeptides

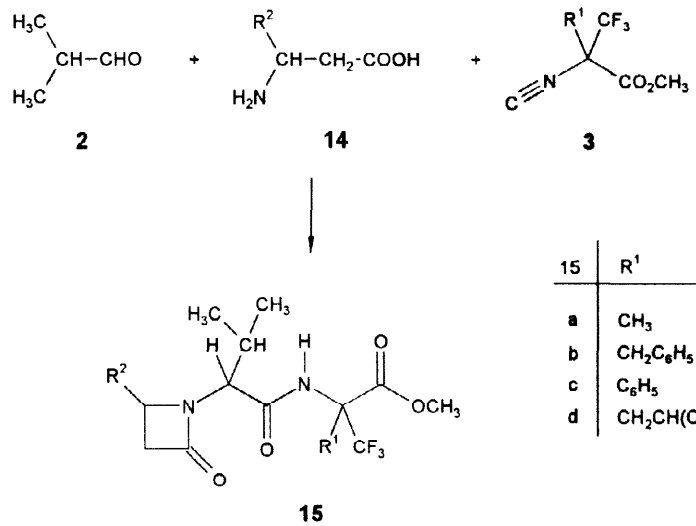
When N-benzoylisobutyraldehyde hydrazone **2**, formic acid and 2-isocyano-3,3,3-trifluoropropionates **3** are treated in a „one pot procedure" N-formyl hydrazino peptide derivatives **13a** with a α-Tfm amino acid in C-terminal position are obtained as diastereomeric mixtures. In the case of monochloroacetic acid as carboxylic component, deprotection of the N-chloroacetyl group during work up is observed. One of the diastereomers (**13b**) can be separated by crystallization.



13	R^1	R^2
a	H	CHO
b	CH_2Cl	H

β-Lactams

Furthermore, in the Ugi 4CR some of the starting materials can have two or three different functional groups, now special types of products are formed [19]. For example, β-amino acids **14** are converted into β-lactam derivatives on reaction with aldehydes and isocyanides. 2-Isocyano-trifluoropropionates **3** can be introduced successfully into this type of transformation to give lactames **15** with an α-Tfm amino acid moiety in the side chain.



15	R^1	R^2
a	CH_3	H
b	$CH_2C_6H_5$	H
c	C_6H_5	H
d	$CH_2CH(CH_3)_2$	C_6H_5

Conclusion

Multicomponent reactions of the Passerini and Ugi type are excellently suited for incorporation of α-fluoroalkyl substituted amino acids into C-and N-terminal position of peptides, peptide mimetics and β-lactams. Therefore, fluoroalkyl substituted amino acids, which are also accessible optically pure [21], should become interesting candidates for combinatorial chemistry to generate libraries of fluoroalkyl substituted peptides and peptide mimetics.

Experimental part

Melting points (not corrected) were determined using a Tottoli apparatus (Büchi SMP-20). Elemental microanalyses were carried out with a Heraeus CHN-elemental analyzer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AM 360 spectrometer at 360, 90 and 339 MHz, respectively. ^{19}F NMR spectra were obtained using a Bruker AC 250 (235 MHz) spectrometer. TMS was used as reference standard for ^{1}H and ^{13}C NMR spectra (internal), trifluoroacetic acid for ^{19}F NMR spectra (external). Mass spectra were recorded using electron ionization (EI, 70 eV) on a Varian MAT CH5 instrument and with chemical ionization (CI) on a Varian MAT M 112S instrument. Solvents were dried using standard methods. α-Tfm amino acids and their protected derivatives were obtained as racemates via known procedures [20, 22-24]. Flash chromatography was performed using silica gel (0.032-0.064 μm) from Riedel de Haën with chloroform/methanol and ethyl acetate/hexanes as eluent, respectively.

Passerini Reaction

General procedure: A mixture of 1 mmol of the corresponding acid **1** (monochloro acetic acid or phthaloylglycine), 1 mmol of the aldehyde **2** (phenyl acetaldehyde, isobutyraldehyde), and 1 mmol of the isonitrile **3** (methyl 2-isobutyl-2-isocyano-3,3,3-trifluoropropionate; methyl 2-benzyl-2-isocyano-3,3,3-trifluoropropionate; methyl 2-isocyano-2-phenyl-3,3,3-trifluoropropionate) in absolute ethyl acetate or acetonitrile was stirred at room temperature until the ^{19}F NMR analysis indicated complete conversion of the isonitrile. The organic solvent was evaporated, the crude product dissolved in dichloromethane, the organic layer was washed three times with saturated $NaHCO_3$ and dried ($MgSO_4$). After removal of the solvent *in vacuo* the product was purified by flash chromatography.

Methyl N-[2-(Chloroacetoxy)-3-phenylpropanoyl]-2-trifluoromethylleucinate ***(4a)***. (73%, mixture of diastereomers, ratio 1:1); Oil; IR (KBr) ν 3370, 1745, 1705 cm^{-1}; m/z: 422 ($M-CH_3$); Anal. Calcd. for $C_{19}H_{23}ClF_3NO_5$: C, 52.12; H, 5.29; N, 3.20. Found: C, 52.14; H, 5.29; N, 3.13.

Diastereomer I: R_f (ethyl acetate/hexanes 1/3): 0.47; ^{1}H NMR ($CDCl_3$) δ 0.71 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H); 1.52 (m, 1H), 1.92 (m, 1H), 2.92 (dd, J=14.2; J=4.1 Hz, 1H), 3.16 (m, 1H), 3.27 (m, 1H), 3.84 (s, 3H), 4.07 (d, J=15.0 Hz, 1H), 4.14 (d, J=15.0 Hz, 1H), 5.44 (m, 1H), 7.09 (s, 1H), 7.19-7.31 (m, 5H);

^{13}C NMR ($CDCl_3$) δ 21.46, 23.63, 23.87, 35.89, 37.51, 40.40, 54.03, 65.86 (q, J=29 Hz), 76.15, 123.77 (q, J=288 Hz), 127.24, 128.57, 129.54, 134.88, 165.95, 167.39, 168.36; ^{19}F NMR ($CDCl_3$) δ 3.68 (s).

Diastereomer II: R_f (ethyl acetate/hexanes 1/3): 0.32; ^{1}H NMR ($CDCl_3$) δ 0.67 (d, J=6.6 Hz, 3H), 0.90 (d, J=6.6 Hz, 3H); 1.42 (m, 1H), 1.92 (dd, J=14.1; J=3.3 Hz, 1H), 2.83 (dd, J=14.1; J=4.1 Hz, 1H), 3.16 (m, 1H), 3.26 (m, 1H), 3.84 (s, 3H), 4.06 (d, J=15.0 Hz, 1H), 4.12 (d, J=15.0 Hz, 1H), 5.44 (m, 1H), 7.07 (s, 1H), 7.19-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.47, 23.68, 23.71, 36.45, 37.36, 40.40, 53.94, 65.83 (q, J=29 Hz), 75.98, 123.86 (q, J=289 Hz), 127.24, 128.57, 129.59, 135.09, 165.85, 167.20, 168.10; ^{19}F NMR ($CDCl_3$) δ 3.72 (s).

Methyl N-[2-(Chloroacetoxy)-3-methylbutanoyl]-2-trifluoromethylphenylglycinate ***(4b)***. (47%); mp: 134-135°C; IR (KBr) ν 3350, 1770, 1735, 1715, 1540 cm^{-1}; m/z: 409 (M); Anal. Calcd. for $C_{17}H_{19}ClF_3NO_5$: C, 49.83; H, 4.67; N, 3.42. Found: C, 49.76; H, 4.58; N, 3.56.

Diastereomer I: ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J=6.6 Hz, 3H), 1.03 (d, J=6.6 Hz, 3H), 2.35 (m, 1H), 3.82 (s, 3H), 4.14 (d, J=14.5 Hz, 1H), 4.21 (d, J=14.5 Hz, 1H), 5.23 (d, J=4.3 Hz, 1H), 7.16 (s, 1H), 7.43-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.62, 18.30, 30.99, 40.47, 53.55, 66.65 (q, J=29 Hz), 79.30, 123.48 (q, J=287 Hz), 126.45, 128.96, 129.73, 131.56, 165.82, 167.56; ^{19}F NMR ($CDCl_3$) δ 6.57 (s).

Methyl N-[3-Methyl-2-(N'-phthaloylglycyloxy)butanoyl]-2-trifluoromethylphenylalaninate ***(4c)***. (72%, mixture of diastereomers, ratio 1:1); Oil; IR (film) ν 3390, 1760, 1725, 1515 cm^{-1}; m/z: 534 (M); Anal. Calcd. for $C_{26}H_{25}F_3N_2O_7$: C, 58.42; H, 4.72; N, 5.24. Found: C, 57.76; H, 4.73; N, 5.19.

^{1}H NMR ($CDCl_3$) δ 0.73/0.89 (d/d, J=6.8/6.8 Hz, 3H), 0.89/0.94 (d/d, J=7.0/7.0 Hz, 3H), 2.22-2.28 (m, 2H), 3.43/3.53 (d/d, J=14/14 Hz, 1H), 4.11/3.92 (d/d, J=14/14 Hz, 1H), 3.85/3.86 (s/s, 3H), 4.43/4.57 (d/d, J=17.4/17.4 Hz, 1H), 4.43-4.44 (m, 2H), 5.13/5.14 (d/d, J=4.1/3.8 Hz, 1H), 6.77/6.96 (s/s, 1H), 7.01-7.13 (m, 2H), 7.15-7.18 (m, 2H), 7.23/7.29 (m, 6H), 7.75-7.79 (m, 4H), 7.86-7.92 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.17/16.53, 18.41/18.59, 30.66/30.77, 34.60/35.77, 38.73/38.85, 53.61/53.77, 65.98/66.47 (q/q, J=28/28 Hz), 79.06/79.40, 123.86 (q, J=290 Hz), 123.72/123.77, 127.81/127.85, 128.53/128.60, 129.98/130.35, 131.83/131.88, 132.71/132.90, 134.46/134.55, 166.00, 166.41/166.57, 167.26/167.46, 168.15/168.21; ^{19}F NMR ($CDCl_3$) δ 5.65/5.72 (s/s).

Methyl N-[3-Methyl-2-(N'-phthaloylglycyloxy)butanoyl]-2-trifluoromethylphenylglycinate ***(4d)***.

(73%, mixture of diastereomers, ratio 1:1); IR (film) ν 3350, 1770, 1720, 1525 cm^{-1} m/z: 520 (M); Anal. Calcd. for $C_{25}H_{23}F_3N_2O_7$: C, 57.69; H, 4.45; N, 5.38. Found: C, 57.35; H, 4.38; N, 5.22.

Diastereomer I: mp: 119-120°C; R_f (diethyl ether/hexanes 2/1): 0.40; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J=7.0 Hz, 3H), 0.92 (d, J=7.0 Hz, 3H), 2.25-2.38 (m, 1H), 3.76 (s, 3H), 4.54 (d, J=17.5 Hz, 1H), 4.65 (d, J=17.5 Hz, 1H), 5.23 (d, J=3.9 Hz, 1H), 7.16 (s, 1H), 7.41-7.52 (m, 5H), 7.74-7.77 (m, 2H), 7.86-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.20, 18.47, 30.79, 38.96, 53.43, 66.60 (q, J=28 Hz), 79.03, 123.58 (q, J=287 Hz), 123.82, 131.74, 134.64, 126.66, 128.97, 129.54, 131.39, 165.76, 166.36, 167.39, 167.70; ^{19}F NMR ($CDCl_3$) δ 6.26 (s).

Diastereomer II: mp: 150-153 °C; R_f (diethyl ether/hexanes 2/1): 0.34; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J=7.0 Hz, 3H), 0.96 (d, J=7.0 Hz, 3H), 2.27-2.31 (m, 1H), 3.81 (s, 3H), 4.59 (d, J=17.4 Hz, 1H), 4.65 (d, J=17.4 Hz, 1H), 5.13 (d, J=4.4 Hz, 1H), 7.17 (s, 1H), 7.42-7.50 (m, 5H), 7.76-7.77 (m, 2H), 7.86-7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 16.63, 18.32, 30.61, 38.86, 53.60, 66.96 (q, J=29 Hz), 79.33, 123.44 (q, J=287 Hz), 123.72, 126.61, 128.90, 129.45, 131.73, 131.76, 134.45, 166.16, 166.26, 167.31, 167.55; ^{19}F NMR ($CDCl_3$) δ 7.22 (s).

Ugi Reaction

General procedure: A mixture of 1 mmol of the corresponding acid, 1 mmol of the imine (prepared *in situ* from 1 mmol aldehyde and 1 mmol of the corresponding amine) and 1 mmol of the isonitrile in 2 mL of absolute methanol was stirred at room temperature until the ^{19}F NMR analysis indicated complete conversion of the starting material. The solvent was evaporated, the crude product was dissolved in trichloromethane, the organic layer was washed three times with saturated $NaHCO_3$ and water and then dried ($MgSO_4$). After removal of the solvent *in vacuo* the product was purified by flash chromatography.

Methyl Phthaloylglycyl-(N-cyclohexylvalyl)-2-trifluoromethylalaninate ***(7a)***.

Starting material: N-phthaloylglycine, cyclohexylamine, isobutyraldehyde, methyl 2-isocyano-2-methyl-3,3,3-trifluoropropionate

(74%; mixture of diastereomers, ratio 1:1); mp: 198-200°C; IR (KBr) ν 3250, 1775, 1755, 1720, 1695, 1680, 1640 cm^{-1}; m/z: 539 (M+1); Anal. Calcd. for $C_{26}H_{31}F_3N_3O_6$: C, 57.98; H, 5.80; N, 7.80. Found: C, 57.78; H, 5.74; N, 7.83.

Diasteromer I: R_f (ethyl acetate/hexanes 1/2): 0.40; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H), 1.22 (m, 1H), 1.32-1.38 (m, 2H), 1.53 (m, 1H), 1.67-1.75 (m, 3H), 1.87-1.90 (m, 3H), 1.58 (s, 3H), 2.92 (m, 1H), 3.22 (d, J=11.0 Hz, 1H), 3.55-3.62 (m, 1H), 3.76 (s, 3H), 4.44 (d, J=16.2 Hz, 1H), 4.68 (d, J=16.2 Hz, 1H), 7.74-7.76 (m, 2H), 7.89-7.91 (m, 2H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.75, 19.45, 20.16, 24.84, 25.74, 26.07, 26.86, 31.08, 31.26, 40.01, 52.83, 58.85, 60.85 (q, J=29 Hz), 69.61, 123.65, 124.15 (q, J=286 Hz), 132.18, 134.17, 167.02, 167.53, 167.74, 171.86; ^{19}F NMR ($CDCl_3$) δ 1.52 (s).

Diasteromer II: R_f (ethyl acetate/hexanes 1/2): 0.36; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H), 1.20 (m, 1H), 1.35-1.42 (m, 2H), 1.54 (m, 1H), 1.67-1.75 (m, 3H), 1.87-1.90 (m, 3H), 1.59 (s, 3H), 2.90 (m, 1H), 3.22 (d, J=11.0 Hz, 1H), 3.55-3.61 (m, 1H), 3.76 (s, 3H), 4.48 (d, J=16.2 Hz, 1H), 4.66 (d, J=16.2 Hz, 1H), 7.74-7.78 (m, 2H), 7.87-7.92 (m, 2H), 8.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.56, 19.40, 20.14, 24.81, 25.73, 26.08, 26.92, 31.09, 31.36, 40.09, 52.79, 58.85, 60.84 (q, J=29 Hz), 69.79, 123.65, 124.12 (q, J=285 Hz), 132.16, 134.24, 167.01, 167.48, 167.87, 171.73; ^{19}F NMR ($CDCl_3$) δ 1.70 (s).

Methyl Phthaloylglycyl-(N-cyclohexylvalyl)-2-trifluoromethylphenylalaninate ***(7b)***.

Starting material: N-phthaloylglycine, cyclohexylamine, isobutyraldehyde, methyl 2-benzyl-2-isocyano-3,3,3-trifluoropropionate

(29%, single diastereomer); mp: 148°C; IR (KBr) ν 3290, 1765, 1715, 1685, 1635 cm^{-1}; m/z: 615 (M); Anal. Calcd. for $C_{32}H_{35}F_3N_3O_6$: C, 62.53; H, 5.74; N, 6.84. Found: C, 62.50; H, 5.94; N, 6.84.

^1H NMR ($CDCl_3$) δ 0.86 (d, J=6.6 Hz, 6H), 1.15 (m, 1H), 1.30-1.41 (m, 2H), 1.50-1.69 (m, 4H), 1.84-1.90 (m, 3H), 2.82 (m, 1H), 3.18 (d, J=11.0 Hz, 1H), 3.27 (d, J=14.2, 1H), 3.42 (d, J=14.2 Hz, 1H), 3.49-3.53 (m, 1H), 3.68 (s, 3H), 4.44 (d, J=16.1 Hz, 1H), 4.72 (d, J=16.1 Hz, 1H), 7.11-7.19 (m, 2H), 7.21-7.27 (m, 3H), 7.72-7.77 (m, 2H), 7.86-7.92 (m, 2H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.45, 20.20, 24.83, 25.72, 26.12, 26.77, 31.03, 31.17, 38.19, 40.09, 52.58, 58.80, 65.22 (q, J=27 Hz), 70.09, 123.67, 124.21 (q, J=288 Hz), 127.49, 128.13, 130.47, 132.19, 133.07, 134.23, 166.04, 167.34, 167.84, 171.62; ^{19}F NMR ($CDCl_3$) δ 6.10 (s).

Methyl Phthaloylglycyl-(N-benzylvalyl)-2-trifluoromethylphenylalaninate ***(7c)***.

Starting material: N-phthaloylglycine, benzylamine, isobutyraldehyde, methyl 2-benzyl-2-isocyano-3,3,3-trifluoropropionate

(52%, mixture of diastereomers, ratio 1:1); mp: 82-85°C; IR (KBr) ν 3480-3380, 1760-1750, 1720, 1665-1645 cm^{-1}; m/z: 623 (M), Anal. Calcd. for $C_{33}H_{32}F_3N_3O_6$: C, 63.56; H, 5.17; N, 6.74. Found: C, 63.95; H, 5.37; N, 6.52.

Diastereomer I: R_f (diethyl ether/hexanes 3/1): 0.57; ^1H NMR ($CDCl_3$) δ 0.79 (d, J=6.4 Hz, 3H), 0.84 (d, J=6.4 Hz, 3H), 2.50 (m, 1H), 3.38 (d, J=14.2 Hz, 1H), 3.64 (m, 1H), 3.68 (s, 3H), 3.91 (m, 1H), 4.32 (d, J=16.3 Hz, 1H), 4.41 (d, J=16.3 Hz, 1H), 4.57 (s, 2H), 7.14-7.36 (m, 11H), 7.70-7.76 (m, 2H), 7.83-7.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.17, 19.43, 27.22, 37.02, 40.00, 52.96, 65.37 (q, J=28 Hz), 71.18, 123.44, 123.97 (q, J=288 Hz), 126.91, 127.54, 127.93, 128.32, 128.98, 130.22, 132.13, 132.86, 134.07, 135.20, 166.02, 167.61, 168.56, 169.33; ^{19}F NMR ($CDCl_3$) δ 5.77 (s).

Diastereomer II: R_f (diethylether/hexanes 3/1): 0.55; ^1H NMR ($CDCl_3$) δ 0.83 (d, J=6.5 Hz, 3H), 0.84 (d, J=6.5 Hz, 3H), 2.44-2.29 (m, 1H), 3.42 (d, J=14.2 Hz, 1H), 3.57 (d, J=14.2 Hz, 1H), 3.71 (s, 3H), 3.78-3.92 (m, 1H), 4.38 (d, J=16.3 Hz, 1H), 4.43 (d, J=16.3 Hz, 1H), 4.58 (s, 2H), 7.15-7.17 (m, 2H), 7.21-7.37 (m, 9H), 7.70-7.76 (m, 2H), 7.84-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.23, 19.61, 27.22, 37.31, 40.00, 52.96, 65.37 (q, J=28 Hz), 71.18, 123.47, 123.97 (q, J=288 Hz), 126.91, 127.54, 127.93, 128.32, 128.98, 130.26, 132.10, 133.03, 134.07, 135.20, 166.02, 167.61, 168.80, 169.51; ^{19}F NMR ($CDCl_3$) δ 5.92 (s).

Methyl Phthaloylglycyl-(N-cyclohexylvalyl)-2-trifluoromethylphenylglycinate ***(7d)***.

Starting material: N-phthaloylglycine, cyclohexylamine, isobutyraldehyde, methyl 2-isocyano-2-phenyl-3,3,3-trifluoropropionate

(65%, mixture of diastereomers, ratio 1:1); mp: 169-175°C; IR (KBr) ν 3270, 1760, 1715, 1630, 1525 cm^{-1} m/z: 601 (M+1), Anal. Calcd. for $C_{31}H_{33}F_3N_3O_6$: C, 61.99; H, 5.54; N, 7.00. Found: C, 61.90; H, 5.60; N, 7.03.

^{1}H NMR ($CDCl_3$) δ 0.89/0.92 (d/d, J=6.6/6.6 Hz, 3H), 0.93/1.01 (d/d, J=6.6/6.6 Hz, 3H), 1.13-1.38 (m, 3H), 1.54-1.95 (m, 7H), 2.99-3.02 (m, 1H), 3.31/3.33 (d/d, J=10.8/11.0 Hz, 1H), 3.55-3.66 (m, 1H), 3.72/3.76 (s/s, 3H), 4.49/4.56 (d/d, J=16.2/16.2 Hz, 1H), 4.70/4.72 (d/d, J=16.2/16.2 Hz, 1H), 7.25-7.33 (m, 3H), 7.36-7.41 (m, 2H), 7.76-7.84 (m, 2H), 7.90-7.95 (m, 2H), 9.41/9.46 (s/s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.38/19.51, 20.16/20.27, 24.76/24.85, 25.61/25.72, 26.05/26.85, 27.04, 30.89, 30.91, 31.13, 31.16, 31.33, 40.07/40.14, 52.59/52.66, 58.85/58.98, 66.25/66.57 (q/q, J=28/28 Hz), 69.79/70.06, 123.58/123.63, 123.75 (q, J=287 Hz), 126.53/126.74, 128.81/128.88, 129.36/129.39, 131.30/131.82, 132.22/132.27, 134.25/134.30, 166.29/166.48, 167.79/167.86, 167.83, 171.89/171.92; ^{19}F NMR ($CDCl_3$) δ 4.21/4.86 (s/s);

Methyl Phthaloylglycyl[N-(S)-1-phenylethylvalyl)]-2-trifluoromethylleucinate (7e).

Educts: N-phthaloylglycine, (S)-1-phenylethylamine, isobutyraldehyde, methyl 2-isobutyl-2-isocyano-3,3,3-trifluoropropionate

(62%, mixture of diastereomers, ratio 2:1:1:2); IR (KBr) ν 3280-3240, 1775, 1755, 1730-1720, 1700, 1640 cm^{-1}; m/z: 603 (M), Anal. Calcd. for $C_{31}H_{36}F_3N_3O_6$: C, 61.68; H, 6.01; N, 6.96. Found: C, 61.63; H, 6.01; N, 6.94; the two major diastereomers have been separated.

Diastereomer I: R_f (ethyl acetate/hexanes 1/2): 0.47; ^{1}H NMR ($CDCl_3$) δ 0.24 (d, J=6.6 Hz, 3H), 0.69 (d, J=6.5 Hz, 3H), 0.83 (d, J=6.5 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H), 1.74 (d, J=7.1 Hz, 3H), 1.82 (m, 1H), 1.87-1.90 (m, 1H), 2.06 (m, 1H), 2.76 (m, 1H), 3.05 (m, 1H), 3.74 (s, 3H), 4.73 (d, J=16.1 Hz, 1H), 4.90 (d, J=16.1 Hz, 1H), 5.25 (q, J=7.0 Hz), 7.38-7.49 (m, 5H), 7.76-7.80 (m, 2H), 7.90-7.93 (m, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.28, 19.27, 19.59, 23.16, 23.63, 23.68, 27.35, 40.08, 40.83, 52.62, 57.09, 63.91 (q, J=28 Hz), 69.58, 123.60, 124.45 (q, J=288 Hz), 128.69, 128.74, 128.84, 132.24, 134.17, 137.41, 166.74, 167.24, 167.75, 171.99; ^{19}F NMR ($CDCl_3$) δ 4.97 (s).

Diastereomer II: R_f (ethyl acetate/hexanes 1/2): 0.31; ^{1}H NMR ($CDCl_3$) δ 0.74 (d, J=6.6 Hz, 3H), 0.78 (d, J=6.6 Hz, 3H), 0.90 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 1.58 (m, 1H), 1.74 (d, J=6.8 Hz, 3H), 1.79 (m, 1H), 1.94 (m, 1H), 2.86 (m, 1H), 3.12 (m, 1H), 3.62 (s, 3H), 4.56-4.83 (m, 2H), 5.23 (q, J=6.8 Hz, 1H), 7.30-7.41 (m, 5H), 7.74-7.79 (m, 2H), 7.88-7.92 (m, 2H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.94, 19.38, 20.56, 23.30, 23.35, 23.39, 27.30, 40.12, 40.87, 52.48, 56.23, 63.88 (q, J=28 Hz), 70.77, 123.55, 124.26 (q, J=288 Hz), 127.33, 128.49, 129.17, 132.28, 134.13, 137.52, 166.75, 167.60, 167.75, 169.61; ^{19}F NMR ($CDCl_3$) δ 5.42 (s).

Methyl (N-Benzyloxycarbonyl-2-trifluoromethylalanyl)-[N-(S)-1-phenylethylvalyl]-glycinate (11).

Educts: N-Benzyloxycarbonyl-2-trifluoromethylalanin, (S)-1-phenylethylamine, isobutyraldehyde, methyl isocyanoacetate

(42%, mixture of diastereomers, ratio 2:1:1:2); IR (KBr) ν 3390, 3240, 1765, 1725, 1665-1655 cm^{-1}; m/z: 565 (M), Anal. Calcd. for $C_{28}H_{34}F_3N_3O_6$: C, 59.46; H, 6.06; N, 7.43. Found: C, 60.03; H, 6.24; N, 7.52; the two major diastereomers have been separated.

Diastereomer I: R_f (ethyl acetate/hexanes 1/2): 0.16; ^{1}H NMR ($CDCl_3$) δ 0.32 (d, J=6.6 Hz, 3H), 0.75 (d, J=6.6 Hz, 3H), 1.54 (d, J=6.8 Hz, 3H), 2.18 (s, 3H), 2.79 (m, 1H), 3.17 (d, J=9.7 Hz, 1H), 3.68 (m, 1H), 3.70 (s, 3H),

4.25 (dd, J=17.8, J=7.5 Hz, 1H), 5.12 (s, 2H), 5.55 (q, J=6.8 Hz, 1H), 6.32 (s, 1H), 7.25-7.42 (m, 10H), 7.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.88, 19.53, 20.33, 20.41, 29.15, 40.94, 52.18, 56.90, 64.87 (q, J=26 Hz), 67.38, 69.86, 125.02 (q, J=287 Hz), 126.66, 128.08, 128.41, 128.46, 128.50, 128.57, 135.65, 138.31, 154.60, 168.27, 170.86, 173.72; ^{19}F NMR ($CDCl_3$) δ 1.88 (s).

Diastereomer II: R_f (ethyl acetate/hexanes 1/2): 0.11; ^{1}H NMR ($CDCl_3$) δ 0.38 (m, 3H), 0.70 (d, J=6.6 Hz, 3H), 1.70 (d, J=7.1 Hz, 3H), 2.05 (s, 3H), 2.78 (m, 1H), 3.19 (d, J=10.4 Hz, 1H), 3.71 (s, 3H), 3.71 (dd, J=17.8 Hz, J=4.6 Hz, 1H), 4.29 (dd, J=17.8, J=7.6 Hz, 1H), 5.13 (d, J=12.2 Hz, 1H), 5.19 (d, J=12.2 Hz, 1H), 5.68 (s, 1H), 5.74 (m, 1H), 7.25-7.41 (m, 10H), 8.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.24, 19.02, 19.89, 20.06, 27.78, 40.77, 52.04, 56.71, 65.01 (q, J=26 Hz), 67.88, 70.18, 125.04 (q, J=285 Hz), 128.39, 128.45, 128.57, 128.60, 128.69, 128.82, 135.25, 137.84, 154.38, 168.32, 170.30, 173.92; ^{19}F NMR ($CDCl_3$) δ 3.46 (s).

Hydrazinopeptides

General procedure: A mixture of 1 mmol of the corresponding acid, 1 mmol of the hydrazone (prepared in situ from 1 mmol aldehyde and 1 mmol benzoic acid hydrazide) and 1 mmol of the isonitrile in 2 ml of dichloromethane (or a mixture of dichlormethane/methanol, 1:1) was stirred at room temperature until 19F NMR analysis indicated complete conversion of the isocyanide. Diastereomeric mixtures are formed in a 1:1 ratio.

Methyl N-(N'-Benzoylamino-N'-formylvalyl)-2-trifluoromethylphenylglycinate ***(13a)***.

(41%, mixture of diastereomers, ratio 1:1); 239-240°C; IR (KBr) ν 3550-3300, 1840, 1800-1725, 1590, 1570 cm^{-1}; m/z: 479 (M); Anal. Calcd. for $C_{23}H_{24}F_3N_3O_5$: C, 57.62; H, 5.05; N, 8.76 . Found: C, 57.41; H, 5.05; N, 8.43.

Diastereomer I: ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H), 2.24 (m, 1H), 3.62 (s, 3H), 4.74 (d, J=7.8 Hz, 1H), 7.45-7.92 (m, 10 H), 8.20 (s, 1H), 9.63 (s, 1H), 10.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.47, 20.05, 27.80, 52.49, 66.20 (q, J=27 Hz), 68.29, 123.59 (q, J=287 Hz), 127.33, 127.89, 128.37, 128.50, 129.19, 131.75, 132.10, 132.40, 164.96, 165.92, 168.30, 169.54; ^{19}F NMR ($CDCl_3$) δ 7.05 (s).

Diastereomer II: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J=6.6 Hz, 3H), 1.04 (d, J=6.6 Hz, 3H), 2.24 (m, 1H), 3.64 (s, 3H), 4.35 (d, J=9.1 Hz, 1H), 7.45-7.92 (m, 10 H), 8.30 (s, 1H), 9.45 (s, 1H), 10.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.66, 19.22, 29.00, 52.62, 66.20 (q, J=27 Hz), 63.18, 123.54 (q, J=286 Hz), 127.16, 128.01, 128.31, 128.53, 129.37, 131.75, 131.93, 132.18, 160.31, 165.83, 168.30, 169.39; ^{19}F NMR ($CDCl_3$) δ 7.11 (s).

Methyl N-(N'-Benzoylaminovalyl)-2-trifluoromethylphenylglycinate ***(13b)***.

(33%, single diastereomer); 195-197°C; IR (KBr) ν 3300, 3250-3210, 1760, 1670 cm^{-1}; m/z: 451 (M); Anal. Calcd. for $C_{22}H_{24}F_3N_3O_4$: C, 58.53; H, 5.36; N, 9.31; Found: C, 58.03; H, 5.36; N, 9.43.

^1H NMR ($CDCl_3$) δ 1.10 (d, J=6.9 Hz, 3H), 1.13 (d, J=6.9 Hz, 3H), 2.14 (m, 1H), 3.44 (d, J=6.1 Hz, 1H), 3.83 (s, 3H), 7.37-7.51 (m, 9H), 7.66-7.68 (m, 2H), 7.85 (s, 1H), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.74, 18.80, 30.37, 53.46, 66.99 (q, J=29 Hz), 71.61, 123.57 (q, J=287 Hz), 126.56, 126.92, 128.65, 129.04, 129.76, 132.11, 132.29, 166.75, 167.20, 171.64; ^{19}F NMR ($CDCl_3$) δ 7.1 (s).

β-Lactams

General Procedure: A suspension of 1 mmol of the β-amino acid (0.09 g β-alanine or 0.17 g D,L-β-phenyl-β-alanine) in absolute methanol was treated with 1 mmol (0.07 g) of isobutyraldehyde and 1 mmol of the corresponding isonitrile at room temperature. The reaction mixture was stirred until ^{19}F NMR analysis indicated complete conversion of the isocyanide. After removal of the solvent in vacuo the crude product was dissolved with trichloromethane and washed three times with saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$), the solvent evaporated and the product purified by flash chromatography.

Methyl N-[3-Methyl-2-(2-oxo-azetidin-1-yl)butanoyl]-2-trifluoromethylalaninate ***(15a)***.

(42%, mixture of diastereomers, ratio 1:1); mp: 116-120°C; IR (KBr) ν 3290, 1765, 1740, 1700, 1550 cm^{-1} m/z: 325 (M+1); Anal. Calcd. for $C_{13}H_{19}F_3N_2O_4$: C, 48.15; H, 5.91; N, 8.64. Found: C, 48.32; H, 5.83; N, 8.53.

^1H NMR ($CDCl_3$) δ 0.96 (d, J=6.7 Hz, 12H), 1.68 (s, 6H), 2.19-2.23 (m, 2H), 2.92-2.94 (m, 4H), 3.34-3.40 (m, 2H), 3.44-3.48 (m, 2H), 3.79 (s, 6H), 3.94/3.97 (d/d, J=9.1 Hz/J=9.4 Hz, 1H), 7.99/8.05 (s/s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.43, 18.59, 18.70, 19.27/19.35, 28.91/29.12, 35.91/35.95, 39.18/39.24, 53.03, 61.37 (q, J=29 Hz), 62.34/62.43, 124.03 (q, J=285 Hz), 166.87, 168.41/168.45, 168.87/168.97; ^{19}F NMR ($CDCl_3$) δ 1.78/1.97 (s/s);

Methyl N-[3-Methyl-2-(2-oxo-azetidin-1-yl)butanoyl]-2-trifluoromethylphenylalaninate ***(15b)***.

(75%, mixture of diastereomers, ratio 1:1); mp: 144-145°C; IR (KBr) ν 3300, 1750, 1735, 1700, 1555 cm^{-1} m/z: 400 (M); Anal. Calcd. for $C_{19}H_{23}F_3N_2O_4$: C, 57.03; H, 5.74; N, 6.99. Found: C, 57.29; H, 5.68; N, 7.21.

Diastereomer I: ^1H NMR ($CDCl_3$) δ 0.95 (d, 6H, J=6.5 Hz), 2.24 (m, 1H), 2.86-2.88 (m, 2H), 3.29-3.31 (m, 2H), 3.48 (d, 1H, J=14.4 Hz), 3.94 (d, 1H, J=14.4 Hz), 3.74 (d, 1H, J=9.7 Hz), 3.86 (s, 3H), 7.13-7.26 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 18.84, 19.25, 28.66, 35.17, 36.15, 39.18, 53.69, 63.35, 66.25 (q, J=28 Hz), 123.85 (q, J=288 Hz), 127.64, 128.33, 129.99, 133.10, 166.49, 168.04, 168.83; ^{19}F NMR ($CDCl_3$) δ 5.65 (s).

Diastereomer II: ^1H NMR ($CDCl_3$) δ 0.88 (d, J=6.6 Hz, 6H), 2.24 (m, 1H), 2.90-2.92 (m, 2H), 3.27-3.32 (m, 2H), 3.51 (d, J=14.2 Hz, 1H), 3.94 (d, J=14.2 Hz, 1H), 3.82 (m, 1H), 3.85 (s, 3H), 7.10-7.16 (m, 2H), 7.23-7.32 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 18.71, 19.32, 28.38, 35.47, 36.15, 39.13, 53.55, 63.92, 66.25 (q, J=28 Hz), 123.85 (q, J=288 Hz), 127.60, 128.33, 130.19, 133.10, 166.49, 168.04, 168.78; ^{19}F NMR ($CDCl_3$) δ 5.77 (s).

Methyl N-[3-Methyl-2-(2-oxo-azetidin-1-yl)butanoyl]-2-trifluoromethylphenylglycinate ***(15c)***.

(51%, mixture of diastereomers, ratio 1:1); IR (KBr) ν 3540-3220, 1760, 1735, 1695 cm^{-1}; m/z: 386 (M); Anal. Calcd. for $C_{18}H_{21}F_3N_2O_4$: C, 55.95; H, 5.48; N, 7.25 . Found: C, 55.53; H, 5.41; N, 7.03.

Diastereomer I: mp: 168-171°C; R_f (ethyl acetate/hexanes 1/1): 0.46; ^1H NMR ($CDCl_3$) δ 1.00 (d, J=6.7 Hz, 6H), 2.30 (m, 1H), 2.89-2.91 (m, 2H), 3.37 (m, 1H), 3.45 (m, 1H), 3.80 (s, 3H), 4.05 (d, J=10 Hz, 1H), 7.41-7.45 (m, 3H), 7.52-7.54 (m, 2H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.90, 19.39, 28.87, 35.93, 39.49, 53.12, 63.39, 66.86 (q, J=28 Hz), 123.73 (q, J=287 Hz), 126.76 (q, J=1 Hz), 128.81, 129.59, 131.71, 166.19, 168.82, 169.07; ^{19}F NMR ($CDCl_3$) δ 5.53 (s).

Diastereomer II: R_f (ethyl acetate/hexanes 1/1): 0.37; ^1H NMR ($CDCl_3$) δ 0.97-1.02 (m, 6H), 2.35 (m, 1H), 2.93-2.98 (m, 2H), 3.35-3.44 (m, 2H), 3.77 (d, J=10.3 Hz, 1H), 3.81 (s, 3H), 7.42-7.44 (m, 3H), 7.50-7.52 (m, 2H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.78, 19.59, 29.24, 35.89, 40.21, 53.07, 65.69, 66.94 (q, J=28 Hz), 123.68 (q, J=287 Hz), 126.76, 128.85, 129.60, 131.68, 166.13, 168.85, 169.08; ^{19}F NMR ($CDCl_3$) δ 5.76 (s).

Methyl N-[3-Methyl-2-(2-oxo-4-phenylazetidin-1-yl)butanoyl]-2-trifluoromethylleucinate ***(15d)***.

(57%, mixture of diastereomers, ratio 1:1); oil; IR (KBr) ν 3280-3240, 1750-1680 cm^{-1}; m/z: 442 (M); Anal. Calcd. for $C_{22}H_{29}F_3N_2O_4$: C, 59.72; H, 6.61; N, 6.33 . Found: C, 59.75; H, 6.69; N, 6.34.

Diastereomer I: R_f (ethyl acetate/hexanes 1/2): 0.33; ^1H NMR ($CDCl_3$) δ 0.84 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H), 0.95 (d, J=6.7 Hz, 3H), 1.01 (d, J=6.7 Hz, 3H), 1.73 (m, 1H), 1.99 (dd, J=14.4, J=8.1 Hz, 1H), 2.57 (dd, J=14.4, J=4.9 Hz, 1H), 2.70 (m, 1H), 2.95-3.04 (m, 2H), 3.33 (dd, J=15.1, J=5.4 Hz, 1H), 3.87 (s, 3H), 4.51 (dd, J=5.2; J=2.5 Hz, 1H), 7.26-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.13, 20.53, 22.19, 23.63, 23.91, 28.98, 38.59, 45.64, 53.55, 54.72, 65.30 (q, J=28 Hz), 69.04, 124.25 (q, J=288 Hz), 127.08, 128.90, 128.98, 137.01, 167.46, 168.37, 169.46; ^{19}F NMR ($CDCl_3$) δ 4.41 (s).

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