PARALLEL SOLID-PHASE SYNTHESIS OF PARTIALLY MODIFIED RETRO AND RETRO-INVERSO ψ[NHCH(CF_3)]-Gly PEPTIDES

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Received April 15, 2002
Accepted August 5, 2002

Dedicated to the memory of Professor Miloš Hudlický.

The parallel solid-phase synthesis of small libraries of molecules belonging to a novel class of retro and retro-inverso peptides having a ψ[NHCH(CF_3)] surrogate of the conventional retro-peptide bond (NH–CO) has been accomplished. Key step for the synthesis of the -NHCH(CF_3)- unit is a Michael-type *N*-addition of resin bound α-amino acid esters H-AA^1-OWang (**1**), dipeptide H-Val-Gly-OWang (**8**), and tripeptide H-Val-Val-Ala-OWang (**12**) to (*S*)-3-(*E*-enoyl)-1,3-oxazolidin-2-one (**3**), which took place very effectively under mild condition. Chemoselective exocyclic oxazolidinone cleavage, followed by parallel couplings of the resulting polymer-bound pseudopeptides WangO-AA^1-ψ[NHCH(CF_3)]-Gly-OH (**5**), WangO-Gly-Val-ψ[NHCH(CF_3)]-Gly-OH (**10**), and WangO-Ala-Val-Val-ψ[NHCH(CF_3)]-Gly-OH (**14**) with different α-amino acid esters afforded, after release from the resin, a representative set of ψ[NHCH(CF_3)] retro and retro-inverso tripeptides HO-AA^1-ψ[NHCH(CF_3)]-Gly-AA^2-OX^1 (**7**), tetrapeptides HO-Gly-Val-ψ[NHCH(CF_3)]-Gly-AA^3-OX^2 (**11**), and pentapeptides HO-Ala-Val-Val-ψ[NHCH(CF_3)]-Gly-AA^4-OX^3 (**15**), respectively, with good to excellent purity in all cases.

Keywords: Solid-phase synthesis; Combinatorial synthesis; Peptide mimetics; Michael reactions; Trifluoromethyl group.

While linear peptides have been used extensively at early stages of lead discovery, they have found only limited application as therapeutic agents due to a number of drawbacks, such as poor bioavailability, bioselectivity, biostability, and also conformational flexibility, since often only one conformation of a peptide is responsible for its biological activity and hence function[1]. To circumvent these drawbacks several approaches have been

studied to modify and stabilise linear peptides through construction of peptide mimetics[2]. One of the most popular strategies to modify peptides is to replace one or more peptide bonds with a surrogate X, which is conventionally symbolised as ψ(X). When this modification consists in the reversal of all or some of the peptide bonds (NH–CO instead of CO–NH) the resulting peptides are called retro or partially modified retropeptides (PMR-peptides), respectively[3] (Fig. 1). Recently, we described a new class of PMR-peptides, *i.e.* PMR-ψ[NHCH(CF_3)] peptides[4], in which the conventional retro-peptide bond is replaced by an -NHCH(CF_3)- unit. This surrogate should be stable towards proteolytic degradation, iso-polar with the NH–CO unit, and the stereo-electronically demanding CF_3 is expected to introduce some backbone conformational constraint, thus limiting the number of stable conformational isomers. Moreover the CF_3 group should be able to modify the binding properties, and may act as a hydrogen bond acceptor or coordinative site with enzymes or receptor subsites[5].

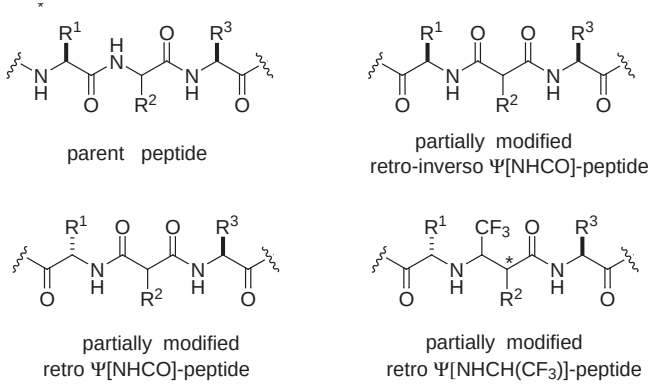


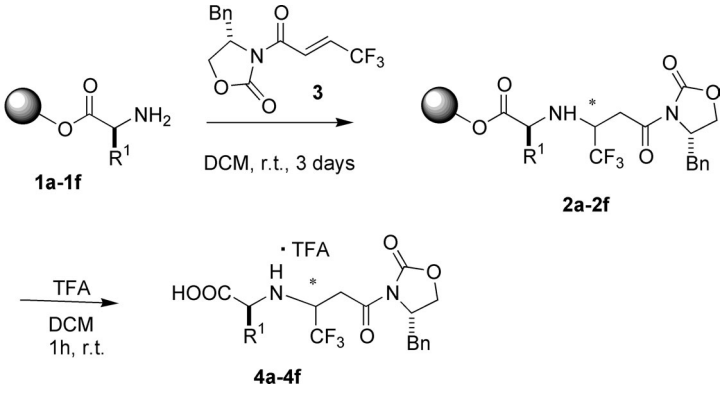
FIGURE 1

In this article we report in full detail the parallel solid-phase synthesis of small libraries of PMR-ψ[NHCH(CF_3)]-Gly tri-[6], tetra-, and pentapeptides, which in perspective should be applicable in the preparation of wider libraries of PMR-ψ[NHCH(CF_3)] polypeptides for high-throughput biological screening[7].

RESULTS AND DISCUSSION

Six different H-AA[1]-OWang resins **1a**–**1f** (Scheme 1, AA means amino acid), prepared by standard Fmoc chemistry using Wang resin as solid support, were engaged in Michael-type *N*-additions with an excess (3 equivalents) of (*S*)-3-(*E*-enoyl)-1,3-oxazolidin-2-one[8] **3**, which took place very efficiently in

3 days at room temperature[9] providing the trifluoromethyl resins **2a**–**2f**. These reactions could be easily monitored by single-bead Fourier Transform Infrared (FT-IR) microscopy through the presence of three distinct and very intense carbonyl bands at *ca* 1 735 (ester CO), 1 780–1 790 (carbamate CO), and *ca* 1 700 cm^{-1} (amide CO) in the spectra of resins **2a**–**2f**.



SCHEME 1

The diastereoselection seems to depend mainly upon the bulkiness of the amino ester side-chain R^1, as already assessed for the solution-phase reactions (Table I)[4a]. The best diastereoselections were in fact achieved with Val (R^1 = iso-Pr, entry 1) and Ile (R^1 = *sec*-Bu, entry 5) whilst an equimolecular

TABLE I
Solid-phase synthesis of pseudodipeptides **4** (Scheme 1)

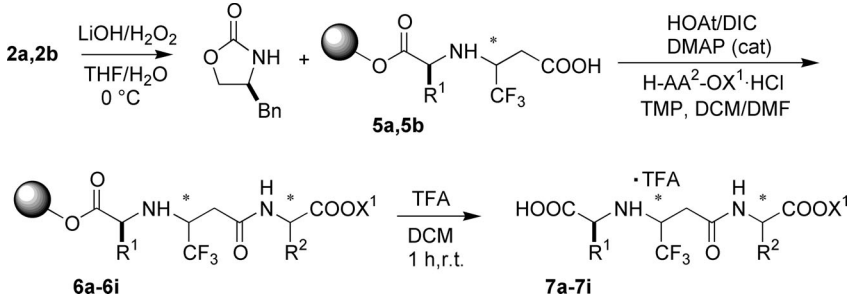
Entry	R^1	Product	d.r.[a]	Yield, %	Purity, %[a]
1	iso-Pr	**4a**	7:1	–[b]	>95
2	H	**4b**	1:1	51[c]	>95
3	Me	**4c**	3:1	77[d]	>95
4	$-CH_2COOt$-Bu	**4d**[e]	1.1:1	98[d]	>95
5	*sec*-Bu	**4e**	6.5:1	100[d]	>95
6	4-*t*-BuO-C_6H_4-CH_2–	**4f**[f]	3:1	98[d]	>95

[a] Diastereoisomeric ratio (d.r.) and purity determined by ^{19}F and ^1H NMR of **4**. [b] See Table II, entries 2–9, for the overall yields of **7b**–**7i** from **1a**. [c] Yield from **1b**, calculated on the isolated amount of **4b**. [d] Yield from Wang resin, calculated on the isolated amount of **4c**–**4f**. [e] R^1 = CH_2COOH. [f] R^1 = 4-HO-C_6H_4-CH_2.

mixture of the two diastereoisomers **4b** was obtained with Gly (R^1 = H, entry 2)[10]. Surprisingly, also in the case of Asp resin (R^1 = CH_2COOt-Bu, entry 4) no stereocontrol was observed, whereas, as expected, moderate stereoselectivity was achieved with Ala (R^1 = Me, entry 3) and Tyr (R^1 = 4-*t*-BuO-C_6H_4-CH_2, entry 6) resins. The observed stereoselectivity can be roughly explained if one considers that, in the absence of a chelating agent, the oxazolidin-2-one **3** should exist in the *S-trans* conformation (as portrayed in Scheme 1) with the benzyl group pointing away from the reactive β-carbon centre, thus exerting little control on the facial selectivity. In contrast, the R^1 side chain of **1a**–**1f** should be spatially close to the C=C bond in the transition state, thus its influence should be more important[11]. However, from the perspective of combinatorial application, a low stereocontrol is not necessarily a drawback, because both epimers at the trifluoromethyl substituted stereocenter can be produced and, eventually, submitted to biological assays.

After cleavage of the resin-bound pseudopeptides **2a**–**2f** by treatment with 20% trifluoroacetic acid (TFA) in dichoromethane (DCM) (1 h at room temperature) the pseudodipeptides **4a**–**4f** were obtained in good yields and excellent purity (Table I). Analytically pure pseudopeptides could be obtained by further purification. For instance, epimers of **4e** were purified by flash chromatography affording the single major diastereoisomer with nearly 100% purity[12].

Exocyclic cleavage of the chiral auxiliary was achieved with excellent chemoselectivity by treatment of the resins **2a**, **2b** with lithium hydroperoxide (Scheme 2) (1 equivalent of LiOH, 4 equivalents of H_2O_2, THF/H_2O, 0 °C)[13] affording the resins **5a**, **5b**. Also in this case the reactions could be reliably monitored by FT-IR microscopy. In fact, the characteristic CO bands of the amide group and the carbamate group at *ca* 1 700 and 1 780–1 790 cm^{-1}, respectively, were progressively replaced by a strong



SCHEME 2

broad band at 1 600 cm^{-1}, characteristic of the CO_2H group. Moreover, the formation of the 4-benzyl-oxazolidin-2-one could be easily detected by TLC analysis of the solution.

The parallel coupling of the resulting resin-bound pseudodipeptides **5a**, **5b** with different α-amino acid esters H-AA^2-OX^1 (Table II), generated *in situ* from the commercial hydrochlorides and 2,4,6-trimethylpyridine (TMP), afforded, in the presence of 1-hydroxy-7-azabenzotiazole (HOAt)/1,3-diisopropylcarbodiimide (DIC) (DCM/DMF, room temperature), a representative library of resin-bound partially modified retro (PMR) (**6a**–**6c**, **6e**–**6i**) and partially modified retro-inverso (PMRI) (**6d**) ψ[NHCH(CF_3)]-Gly tripeptides. As expected FT-IR monitoring of the coupling showed that the CO_2H band at *ca* 1 600 cm^{-1} was progressively replaced by a new strong amide CO band at 1 690–1 650 cm^{-1}.

Finally, treatment of resins **6a**–**6i** with 20% TFA in DCM at room temperature released the target products **7a**–**7i** from the solid support, in good to excellent overall yields and purity in all cases (Table II).

Validation of the method for combinatorial synthesis of PMR-ψ[NHCH(CF_3)]-Gly polypeptides with different lengths was achieved by its extension to resin-bound di- and tripeptides. In fact, H-Val-Gly-OWang dipeptide resin **8** (Scheme 3), which was prepared by conventional Fmoc chemistry, gave the conjugate *N*-addition to **3** affording

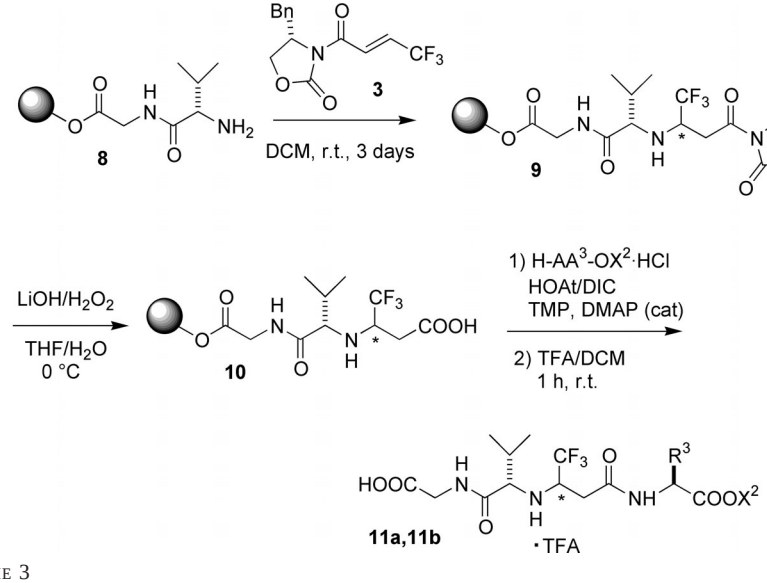
TABLE II
Parallel library of partially-modified ψ[NHCH(CF_3)]-Gly tripeptides **7** (Scheme 2)

Entry	R^1	AA^2	X^1	Product	Yield, %[a]	Purity, %[b]
1	H	L-Phe	Bn	**7a**	49[c]	>90
2	iso-Pr	L-Phe	Bn	**7b**	59	90
3	iso-Pr	L-Ala	Me	**7c**	59	90
4	iso-Pr	D-Ala	Me	**7d**	68	83
5	iso-Pr	L-Leu	Bn	**7e**	53	90
6	iso-Pr	L-Pro	Bn	**7f**	69	93
7	iso-Pr	L-Val	Bn	**7g**	79	89
8	iso-Pr	Gly	Me	**7h**	46	>95
9	iso-Pr	L-Ile	Me	**7i**	65	75

[a] Overall yield from the Wang resin unless otherwise stated. [b] Determined by ^{19}F and ^1H NMR of **7a**–**7i**. [c] Overall yield from **1b**.

the supported tripeptide mimic **9**. Also in this case the reaction could be monitored by FT-IR microscopy following the progressive appearance of the strong band of the CO carbamate bond (1 785 cm^{-1}). This reaction was less stereoselective (diastereoisomeric ratio 4.5 : 1) than that involving the resin H-Val-OWang **1a** (diastereomeric ratio 7 : 1, Table I, entry 1). This observation is in agreement with previous work performed in solution, which showed that the additions of α-amino acid amides to (*S*)-3-(*E*-enoyl)-1,3-oxazolidin-2-one **3** occur with lower stereoselectivity as compared with the parent α-amino acid esters[4b,4c].

After the usual highly chemoselective exocyclic cleavage of the oxazolidin-2-one from the resin **9**, the resulting resin bound pseudo-tripeptide **10** was coupled with two different α-amino acid esters using the



SCHEME 3

TABLE III

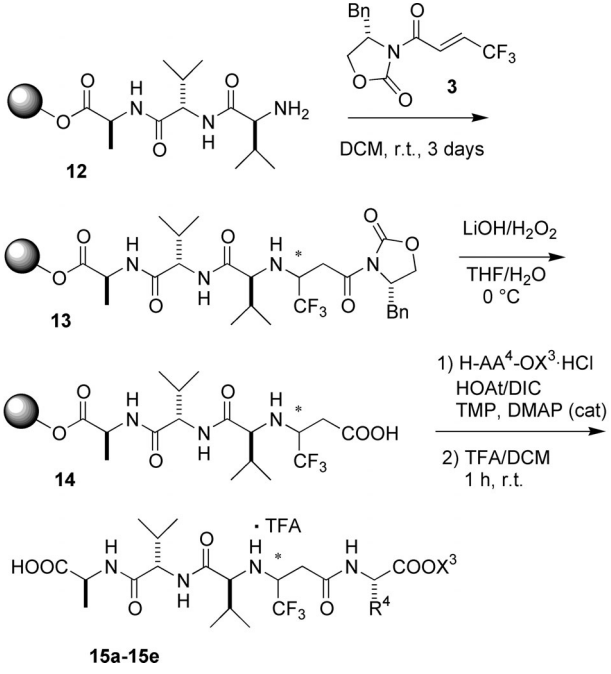
Solid-phase synthesis of partially modified ψ[NHCH(CF_3)]-Gly tetrapeptides **11** (Scheme 3)

Entry	R^3	AA^3	X^2	Product	d.r.	Yield, %[a]	Purity, %[b]
1	Bn	L-Phe	Bn	**11a**	4.5:1	48	89
2	Me	L-Ala	Me	**11b**	4.5:1	68	83

[a] Overall yield from the starting Wang resin. [b] Determined by ^{19}F and ^{1}H NMR.

HOAt/DIC system (Scheme 3). After cleavage from the solid support (20% TFA in DCM), the target PMR-ψ[NHCH(CF_3)]-Gly tetrapeptides **11a**, **11b** were obtained in good overall yields and very good purity (Table III).

Next, we prepared by Fmoc-chemistry the tripeptide resin H-Val-Val-Ala-OWang **12** (Scheme 4), which was subjected to the conjugate addition with **3**, taking place very effectively in 3 days at room tempera-



SCHEME 4

TABLE IV
Parallel library of partially-modified ψ[NHCH(CF_3)]-Gly pentapeptides **15** (Sheme 4)

Entry	R^4	AA^4	X^3	Product	d.r.	Yield, %[a]	Purity, %[b]
1	Me	L-Ala	Me	**15a**	10:1	76	82
2	iso-Bu	L-Leu	Bn	**15b**	10:1	77	83
3	*sec*-Bu	L-Ile	Me	**15c**	10:1	63	86
4	iso-Pr	L-Val	Bn	**15d**	10:1	75	87
5	Bn	L-Phe	Me	**15e**	10:1	74	85

[a] Overall yield from the starting Wang resin. [b] Determined by ^{19}F and ^{1}H NMR.

ture. Interestingly, in this case we observed the highest diastereoselection as compared with the conjugate additions of H-Val-OWang **1a** and H-Val-Gly-OWang **8**. In fact, a 10 : 1 mixture of diastereoisomers **15a**–**15e** was formed (^{1}H and ^{19}F NMR analysis), whereas the addition of **1a** and **8** produced 7 : 1 and 4.5 : 1 mixtures of diastereoisomers **7b**–**7i** and **11a**, **11b**, respectively. This shows that additional stereocenters, even in remote position of the nucleophile, can have a strong influence on the stereochemical outcome of the conjugate additions[14].

Following the same synthetic strategy used for the synthesis of tri- and tetrapeptides **7a**–**7i** and **11a**, **11b**, the resin **13** was chemoselectively hydrolysed at the C-terminus by treatment with lithium hydroperoxide generated *in situ*. The resulting pseudotetrapeptide resin **14** was coupled (HOAt/DIC) with five different α-amino acid esters generating, after release from the resin, the PMR-ψ[NHCH(CF_3)]-Gly pentapeptides **15a**–**15e** with very good overall yields and purity (Table IV).

Analytically pure PMR-ψ[NHCH(CF_3)]-Gly pentapeptides could be obtained either by washing with organic solvents (or mixtures of them), or by flash chromatography (FC). For instance, FC of the pentapeptide **15b** gave a mixture of the two epimers with very high chemical purity[12]. On the other hand, washing of epimeric pentapeptides **15c** with a mixture ethyl acetate–ethyl ether (about 1 : 1) afforded a single diastereomer with nearly 100% chemical purity.

CONCLUSIONS

An effective solid-phase procedure for the preparation of a novel structural family of fluorinated retro and retro-inverso peptides, *i.e.* PMR- and PMRI-ψ[NHCH(CF_3)]-Gly peptides has been developed. Solid supported α-amino acid esters as well as dipeptides and tripeptides effectively gave rise to Michael-type *N*-additions to the chiral fluorinated acceptor **3**, affording the -NHCH(CF_3)- unit. Using this strategy we have been able to prepare small libraries of PMR- and PMRI-ψ[NHCH(CF_3)]-Gly tripeptides, tetrapeptides and pentapeptides with very good yields and excellent purity in all cases. It should be possible to exploit the same strategy for the synthesis of more complex PMR- and PMRI-ψ[NHCH(CF_3)]-AA polypeptides having different substituents at the α-position ($R^2 \neq H$ in Fig. 1) or PMR- and PMRI-ψ[NHCH(R_F)]-AA polypeptides having different fluoroalkyl (R_F) groups. These synthetic issues, as well as others related with the structural, conformational and biological features of PMR- and PMRI-ψ[NHCH(R_F)] polypeptides, are at present being addressed in our laboratories.

EXPERIMENTAL

Methods

NMR spectra were taken on spectrometers Bruker 250 (250 MHz for ^{1}H, 235.4 MHz for ^{19}F and 62.9 MHz for ^{13}C) and Bruker 500 (500 MHz for ^{1}H, 470.6 MHz for ^{19}F and 125.7 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm of the applied field, coupling constants (*J*) in Hz. Me_4Si was used as internal standard (δ_H and δ_C 0.00) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F –162.90) for ^{19}F nuclei. Peak multiplicities are abbreviated: singlet s, doublet d, triplet t, quartet q, multiplet m, *etc.* A three-stage quadrupole instrument DIS (Direct Inlet System) was used for mass spectrometry of pure compounds. Infrared spectra of resins (ν_{max} in cm^{-1}) were recorded on a Perkin–Elmer 2000 FTIR spectrometer preparing samples in KBr pellets or directly using a Perkin–Elmer Multiscope FTIR Microscope. Commercially available reagent-grade solvents were employed without purification. Wang resin (100–200 or 200–400 mesh, loading 1.3 mmol/g) was purchased from Novabiochem.

Solid-Phase Michael Addition: Synthesis of Resins **2a**–**2f**, **9** and **13**. Typical Procedure

A solid-phase reaction vessel was charged with H-Val-O-Wang resin **1a** (1.15 mmol/g, 1.15 equivalents), **3** (1.03 g, 3.45 equivalents) and DCM (24.4 ml), and shaken at room temperature for 3 days. The solution was drained and the solvent evaporated *in vacuo* to recover the unreacted compound **3** (0.69 g, 2.3 equivalents). The resin was washed with DCM (5 × 20 ml) and dried *in vacuo* to constant weight to give **2a**.

Resin **2a**: FTIR (KBr): ν_{max} = 1 785, 1 732, 1 700.
Resin **2b**: FTIR (KBr): ν_{max} = 1 793, 1 735, 1 704.
Resin **2c**: FTIR (KBr): ν_{max} = 1 787, 1 735, 1 719.
Resin **2d**: FTIR (microscope): ν_{max} = 1 792, 1 736, 1 701.
Resin **2e**: FTIR (microscope): ν_{max} = 1 785, 1 727, 1 701.
Resin **2f**: FTIR (microscope): ν_{max} = 1 781, 1 736, 1 700.
Resin **9**: FTIR (microscope): ν_{max} = 1 785, 1 751, 1 676, 1 602.
Resin **13**: FTIR (microscope): ν_{max} = 1 792, 1 737, 1 650.

Solid-Phase Cleavage of the Oxazolidinone; Synthesis of Resins **5a**, **5b**, **10** and **14**. Typical Procedure

In a round-bottom flask the resin **2a** (0.87 mmol/g, 0.87 equivalent) was suspended in a 4 : 1 mixture of THF–H_2O (23 ml). To this suspension was added, at 0 °C and under nitrogen atmosphere, a 30% aqueous solution of H_2O_2 (0.36 ml, 3.48 equivalents), followed by solid LiOH (21 mg, 0.87 mmol). The mixture was stirred for 2 h, then the solution was drained and the resin washed with water (3 × 20 ml), MeOH (3 × 20 ml), DCM (3 × 20 ml) and dried *in vacuo* to a constant weight to give **5a**.

Resin **5a**: FTIR (KBr): ν_{max} = 1 735, 1 618.
Resin **5b**: FTIR (KBr): ν_{max} = 1 735, 1 618.
Resin **10**: FTIR (microscope): ν_{max} = 1 743, 1 618.
Resin **14**: FTIR (microscope): ν_{max} = 1 741, 1 602.

Solid-Phase Coupling with α-Amino Acid Esters and Cleavage from the Resin: Synthesis of the Products **7a**–**7i**, **11a**, **11b** and **15a**–**15e**. Typical Procedure

A solid-phase reaction vessel was charged with resin **5a** (1.00 mmol/g, 0.10 equivalent), L-Ala-OMe·HCl (42 mg, 0.30 equivalent), HOAt (41 mg, 0.30 equivalent), DIC (0.047 ml, 0.30 equivalent), TMP (0.080 ml, 0.6 equivalent), a catalytic amount of DMAP and DMF (2 ml) and then shaken at room temperature overnight. The solution was drained and the resin was washed with DMF (3 × 20 ml), DCM (3 × 20 ml), MeOH (3 × 20 ml), DCM (3 × 20 ml), and dried *in vacuo* to constant weight to give **6c**.

Resin **6a:** FTIR (KBr): ν_{max} = 1 735, 1 685, 1 655.
Resin **6b:** FTIR (KBr): ν_{max} = 1 736, 1 655, 1 613.
Resin **6c:** FTIR (KBr): ν_{max} = 1 735, 1 653, 1 613.
Resin **6d:** FTIR (KBr): ν_{max} = 1 736, 1 658, 1 618.
Resin **6e:** FTIR (KBr): ν_{max} = 1 736, 1 654, 1 615.
Resin **6f:** FTIR (KBr): ν_{max} = 1 736, 1 684, 1 652.
Resin **6g:** FTIR (KBr): ν_{max} = 1 735, 1 685, 1 654.
Resin **6h:** FTIR (KBr): ν_{max} = 1 736, 1 686, 1 655.
Resin **6i:** FTIR (KBr): ν_{max} = 1 736, 1 654, 1 614.
Resin bound **11a**: FTIR (microscope): ν_{max} = 1 744, 1 672.
Resin bound **11b**: FTIR (microscope): ν_{max} = 1 745, 1 672.
Resin bound **15a**: FTIR (microscope): ν_{max} = 1 740, 1 671, 1 655.
Resin bound **15b**: FTIR (microscope): ν_{max} = 1 740, 1 675, 1 655.
Resin bound **15c**: FTIR (microscope): ν_{max} = 1 735, 1 671, 1 655.
Resin bound **15d**: FTIR (microscope): ν_{max} = 1 739, 1 664.
Resin bound **15e**: FTIR (microscope): ν_{max} = 1 741, 1 675, 1 655.

The resulting resin **6c** was shaken with 20 vol.% TFA in CH_2Cl_2 (2 ml) at room temperature for 1 h. The solution was drained and the resin was washed three times with the same mixture. The solvent was evaporated *in vacuo* to recover 31 mg of the PMR-ψ[NHCH(CF_3)]-Gly peptide **7c** (58% overall yields).

NMR and Mass Spectra

4b, *major diastereomer*: ^{1}H NMR (500 MHz, acetone-d_6): 7.36 (m, 5 H, Ar); 4.80 (m, 1 H, -C**H**(CH_2Ph)-); 4.38 (m, 1 H, -OCH**H**-); 4.27 (m, 1 H, -OC**H**H-); 3.95 (m, 1 H, -C**H**(CF_3)-); 3.67 (m, 2 H, -NHC**H**$_2$COOH); 3.32 (m, 2 H, -COCH**H**- + -CH**H**Ph); 3.25 (dd, *J* = 5.4, 3.2, 1 H, -COC**H**H-); 2.99 (dd, *J* = 8.4, 4.6, 1 H, -C**H**HPh). ^{19}F NMR (235.4 MHz, $CDCl_3$): –72.2 (br s, 3 F). EI-MS (70 eV), *m/z* (%): 375 (20) [M^+ + 1], 299 (19), 123 (62), 91 (100).

4b, *minor diastereomer*: ^{19}F NMR (235.4 MHz, $CDCl_3$): –76.5 (br s, 3 F).

4c, *major diastereomer*: ^{1}H NMR (500 MHz, acetone-d_6): 7.36–7.25 (m, 5 H, Ar); 4.79 (m, 1 H, -C**H**(CH_2Ph)-); 4.39 (m, 1 H, -OCH**H**-); 4.26 (m, 1 H, -OC**H**H-); 3.85 (m, 1 H, -C**H**(CF_3)-); 3.66 (m, 1 H, -NHC**H**(CH_3)-); 3.38 (m, 2 H, -COCH**H**- + -CH**H**Ph); 3.23 (m, 2 H, -COC**H**H- + -C**H**HPh); 1.35 (m, 3 H, -CH(C**H**$_3$)-). ^{19}F NMR (470.6 MHz, $CDCl_3$): –76.5 (br s, 3 F). EI-MS (70 eV), *m/z* (%): 389 (88) [M^+ + 1], 343 (100), 124 (35), 91 (52).

4c, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –77.5 (br s, 3 F).

4d, *major diastereomer*: ^{1}H NMR (400 MHz, CD_3OD): 7.36–7.19 (m, 5 H, Ar); 4.74 (m, 1 H, -C**H**(CH_2Ph)-); 4.30 (dd, *J* = 8.2, 2.7, 1 H, -OC**H**H-); 4.21 (dd, *J* = 8.2, 5.7, 1 H, -OCH**H**-); 3.87 (m, 2 H, -NHC**H**(COOH)- and -C**H**(CF_3)-); 3.37 (dd, *J* = 16.2, 3.5, 1 H, -C**H**HCOOH); 3.21 (m, 1 H, -C**H**HPh); 3.03 (dd, *J* = 16.2, 3.7, 1 H, -CH**H**COOH); 2.92 (dd, *J* = 8.4, 6.2, 1 H,

-C**H**HPh); 2.75 (dd, *J* = 16.3, 4.2, 1 H, -COC**H**H-); 2.67 (dd, 1 H, *J* = 16.3, 6.7, -COCH**H**-). ^{19}F NMR (235.4 MHz, CD_3OD): –75.3 (d, *J* = 7.5, 3 F). EI-MS (70 eV), *m/z* (%): 433 (18) [M^+ + 1], 123 (60), 91 (100).

4d, *minor diastereomer*: ^{19}F NMR (235.4 MHz, CD_3OD): –74.2 (d, *J* = 7.3, 3 F).

4e, *major diastereomer*: ^{1}H NMR (400 MHz, CD_3OD): 7.36–7.19 (m, 5 H, Ar); 4.32 (m, 1 H, -OC**H**H-); 4.22 (dd, *J* = 8.8, 2.9 ,1 H, -OCH**H**-); 3.75 (m, 1 H, -NHC**H**(COOH)-); 3.38 (m, 2 H, -C**H**HPh and -C**H**(CF_3)-); 3.25 (dd, *J* = 13.7, 8.8, 1 H, -CH**H**Ph); 3.14 (dd, *J* = 15.7, 9.5 1 H, -COC**H**H-); 2.90 (dd, *J* = 15.7, 8.7, 1 H, -COCH**H**-); 1.72 (m, 1 H, -C**H**(CH_3)-); 1.50 (m, 1 H, -C**H**H(CH_3)); 1.20 (m, 1 H, -CH**H**(CH_3)); 0.97 (d, *J* = 6.8, 3 H, C**H**$_3$CH-); 0.91 (t, *J* = 7.3, 3 H, C**H**$_3$CH_2-). ^{19}F NMR (235.4 MHz, CD_3OD): –74.9 (d, *J* = 7.3, 3 F). EI-MS (70 eV), *m/z* (%): 431 (13) [M^+ + 1], 385 (68), 91 (100).

4e, *minor diastereomer*: ^{19}F NMR (235.4 MHz, CD_3OD): –73.3 (d, *J* = 7.3, 3 F).

4f, *major diastereomer*: ^{1}H NMR (400 MHz, CD_3OD): 7.36–7.13 (m, 5 H, Ar); 7.07–6.90 (m, 2 H, 4-HO-C_6**H**$_4$-); 6.75–6.61 (m, 2 H, 4-HO-C_6**H**$_4$-); 4.61 (m, 1 H, -C**H**(CH_2Ph)-); 4.26 (m, 1 H, -OC**H**H-); 4.17 (m, 1 H, -OCH**H**-); 3.75 (m, 2 H, -NHC**H**(COOH)- and -C**H**(CF_3)-); 3.31 (m, 2 H, -C**H**HPh and 4-HO-C_6H_4-C**H**H-); 3.14 (m, 2 H, -C**H**HPh and 4-HO-C_6H_4-CH**H**-); 2.88 (m, 1 H, -COC**H**H-); 2.79 (m, 1 H, -COCH**H**-). ^{19}F NMR (235.4 MHz, CD_3OD): –74.5 (d, *J* = 7.2, 3 F). EI-MS (70 eV), *m/z* (%): 481 (20) [M^+ + 1], 91 (80), 107 (100).

4f, *minor diastereomer*: ^{19}F NMR (235.4 MHz, CD_3OD): –73.7 (d, *J* = 8.7, 3 F).

7a, *major diastereomer*: ^{1}H NMR (500 MHz, acetone-d_6): 7.44–7.18 (m, 10 H, Ar); 5.13 (s, 2 H, -OCOC**H**$_2$Ph); 4.83 (m, 1 H, -C**H**(CH_2Ph)-); 3.65 (m, 1 H, -C**H**(CF_3)-); 3.54 (m, 2 H, -NHC**H**$_2$COOH); 3.32 (m, 2 H, -C**H**$_2$Ph); 3.07 (m, 1 H, -COCH**H**-); 2.60 (m, 1 H, -COC**H**H-). ^{19}F NMR (470.6 MHz, $CDCl_3$): –76.9 (br s, 3 F). EI-MS (70 eV), *m/z* (%): 453 (2) [M^+ + 1], 120 (18), 91 (100).

7a, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –76.4 (br s, 3 F).

7b, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.18 (m, 8 H, Ar); 7.69 (m, 2 H, Ar); 6.47 (br d, *J* = 7.3, 1 H, -CON**H**-); 5.16 (d, *J* = 11.9, 1 H, -OCOCH**H**Ph); 5.11 (d, *J* = 11.9, 1 H, -OCOC**H**HPh); 4.94 (m, 1 H, -NHC**H**(CH_2Ph)-); 3.53 (m, 1 H, -C**H**(CF_3)-); 3.46 (d, *J* = 4.1, 1 H, -NHC**H**(iPr)-); 3.12 (m, 2 H, -C**H**$_2$Ph); 2.65 (dd, *J* = 16.0, 3.2, 1 H, -COCH**H**-); 2.33 (dd, *J* = 16.0, 10.1, 1 H, -COC**H**H-); 2.12 (m, 1 H, -C**H**(CH_3)$_2$); 1.00 (d, *J* = 6.9, 3 H, -C**H**$_3$CH(CH_3)); 0.92 (d, *J* = 6.9, 3 H, -CH_3CH(C**H**$_3$)). ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.2 (d, *J* = 5.2, 3 F). EI-MS (70 eV), *m/z* (%): 449 (2) [M^+ – CO_2], 120 (2), 91 (100).

7b, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.5 (d, *J* = 5.6, 3 F).

7c, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.20 (br d, *J* = 6.9, 1 H, -CON**H**-); 4.61 (m, 1 H, -NHC**H**(CH_3)-); 3.76 (s, 3 H, -COOC**H**$_3$); 3.63 (m, 1 H, -C**H**(CF_3)-); 3.55 (m, 1 H, -NHC**H**(iPr)-); 2.75 (m, 1 H, -COCH**H**-); 2.50 (m, 1 H, -COC**H**H-); 2.15 (m, 1 H, -C**H**(CH_3)$_2$); 1.44 (br s, 3 H, -CHC**H**$_3$); 1.04 (br s, 3 H, -(CH_3)CHC**H**$_3$); 0.97 (br s, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, $CDCl_3$): –74.9 (br s, 3 F). CI-MS, *m/z* (%): 343 (100) [M^+ + 1].

7c, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.3 (br s, 3 F).

7d, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.30 (br s, 1 H, -CON**H**-); 4.61 (m, 1 H, -NHC**H**(CH_3)-); 3.77 (s, 3 H, -COOC**H**$_3$); 3.73 (m, 1 H, -C**H**(CF_3)-); 3.60 (m, 1 H, -NHC**H**(iPr)-); 2.78 (m, 1 H, -COCH**H**-); 2.60 (m, 1 H, -COC**H**H-); 2.18 (m, 1 H, -C**H**(CH_3)$_2$); 1.44 (br s, 3 H, -CHC**H**$_3$); 1.04 (br s, 3 H, -(CH_3)CHC**H**$_3$); 0.99 (br s, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, $CDCl_3$): –74.3 (br s, 3 F). CI-MS, *m/z* (%): 343 (100) [M^+ + 1].

7d, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.4 (br s, 3 F).

7e, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.39–7.29 (m, 5 H, Ar); 6.77 (br s, 1 H, -CON**H**-); 5.18 (d, *J* = 12.8, 1 H, -OCOCH**H**Ph); 5.13 (d, *J* = 12.8, 1 H, -OCOC**H**HPh); 4.69

(m, 1 H, -NHC**H**(iBu)-); 3.59 (m, 1 H, -C**H**(CF_3)-); 3.53 (m, 1 H, -NHC**H**(iPr)-); 2.74 (m, 1 H, -COCH**H**-); 2.46 (m, 1 H, -COC**H**H-); 2.15 (m, 1 H, -C**H**(CH_3)$_2$Val); 1.65 (m, 2 H, -C**H**$_2$CH(CH_3)$_2$); 1.58 (m, 1 H, -C**H**(CH_3)$_2$ Leu); 1.01 (d, *J* = 6.9, 3 H, -(C**H**$_3$)CHC**H**$_3$Val); 0.93 (d, *J* = 6.9, 3 H, -(CH_3)CHC**H**$_3$Val); 0.91 (d, *J* = 5.0, 6H, -C**H**$_3$CHC**H**$_3$Leu). ^{19}F NMR (470.6 MHz, $CDCl_3$): –74.7 (br s, 3 F). CI-MS, *m/z* (%): 461 (100) [M^+ + 1].

7e, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.4 (br s, 3 F).

7f, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.40–7.30 (m, 5 H, Ar); 5.19 (d, *J* = 12.4, 1 H, -OCOCH**H**Ph); 5.14 (d, *J* = 12.4, 1 H, -OCOC**H**HPh); 4.60 (m, 1 H, -C**H**(COOCH_2Ph)-); 3.78 (m, 1 H, -C**H**(CF_3)-); 3.60 (m, 3 H, -NHC**H**(iPr)- and -C**H**$_2$N(CO)-); 2.82 (m, 1 H, -COCH**H**-); 2.65 (m, 1 H, -COC**H**H-); 2.22 (m, 2 H, -C**H**$_2$CHCOO-); 2.05 (m, 3 H, -C**H**$_2$CH_2N(CO)- + -C**H**(CH_3)$_2$); 1.02 (br s, 3 H, -(CH_3)CHC**H**$_3$); 0.96 (br s, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, $CDCl_3$): –74.2 (br s, 3 F). CI-MS, *m/z* (%): 445 (100).

7f, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.6 (br s, 3 F).

7g, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.35 (m, 5 H, Ar); 7.13 (br s, 1 H, -CON**H**-); 5.23 (d, *J* = 11.9, 1 H, -OCOCH**H**Ph); 5.14 (d, *J* = 11.9, 1 H, -OCOC**H**HPh); 4.55 (m, 1 H, -CONHC**H**(iPr)-); 3.72 (m, 1 H, -C**H**(CF_3)-); 3.57 (m, 1 H, -NHC**H**(iPr)COOH); 2.82 (m, 1 H, -COCH**H**-); 2.61 (m, 1 H, -COC**H**H-); 2.19 (m, 2 H, -C**H**(CH_3)$_2$); 1.03 (br s, 3 H, -(C**H**$_3$)CHCH_3); 0.96 (br s, 3 H, -(CH_3)CHC**H**$_3$); 0.92 (d, *J* = 5.0, 3 H, -(CH_3)CHC**H**$_3$); 0.88 (d, *J* = 5.0, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, $CDCl_3$): –74.2 (br s, 3 F). CI-MS, *m/z* (%): 447 (100) [M^+ + 1].

7g, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –75.5 (br s, 3 F).

7h, *major diastereomer*: ^{1}H NMR (500 MHz, DMSO-d_6): 8.53 (br t, *J* = 5.9, 1 H, -CON**H**-); 3.87 (dd, *J* = 17.4, 5.5, 1 H, -CH**H**COOMe); 3.87 (dd, *J* = 17.4, 5.9, 1 H, -C**H**HCOOMe); 3.62 (s, 3 H, -COOC**H**$_3$); 3.50 (m, 1 H, -C**H**(CF_3)-); 3.05 (d, 1 H, *J* = 5.0, -NHC**H**(iPr)-); 2.53 (dd, *J* = 15.1, 5.5, 1 H, -COCH**H**-); 2.45 (dd, *J* = 15.1, 6.9, 1 H, -COC**H**H-); 1.84 (m, 1 H, -C**H**(CH_3)$_2$); 0.89 (d, *J* = 6.9, 3 H, -(CH_3)CHC**H**$_3$); 0.84 (d, *J* = 6.9, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, DMSO-d_6): –75.2 (d, *J* = 7.6, 3 F). CI-MS, *m/z* (%): 329 (100) [M^+ + 1].

7h, *minor diastereomer*: ^{19}F NMR (470.6 MHz, DMSO-d_6): –73.9 (br s, 3 F).

7i, *major diastereomer*: ^{1}H NMR (500 MHz, $CDCl_3$): 7.20 (br s, 1 H, -CON**H**-); 4.57 (m, 1 H, -C**H**(COOMe)-); 3.84 (m, 1 H, -C**H**(CF_3)-); 3.75 (s, 3 H, -COOC**H**$_3$); 3.66 (m, 1 H, -NHC**H**(iPr)-); 2.87 (m, 1 H, -COCH**H**-); 2.72 (m, 1 H, -COC**H**H-); 2.23 (m, 1 H, -C**H**(CH_2CH_3)-); 1.90 (m, 1 H, -C**H**(CH_3)$_2$); 1.43 (m, 1 H, -CH**H**CH_3); 1.20 (m, 1 H, -C**H**HCH_3); 1.05 (br s, 3 H, -CH(C**H**$_3$)-Ile); 1.01 (br s, 3 H, -(C**H**$_3$)CHCH_3); 0.91 (br s, 6 H, -(CH_3)CHC**H**$_3$ + -CH_2C**H**$_3$). ^{19}F NMR (470.6 MHz, $CDCl_3$): –73.5 (br s, 3 F). CI-MS, *m/z* (%): 385 (100) [M^+ + 1].

7i, *minor diastereomer*: ^{19}F NMR (470.6 MHz, $CDCl_3$): –74.5 (br s, 3 F).

11a, *major diastereomer*: ^{1}H NMR (500 MHz, CD_3OD): 7.25 (m, 10 H, Ar); 5.10 (s, 2 H, -OCOHC**H**$_2$Ph); 4.72 (dd, *J* = 7.3, 6.6, 1 H, -NHC**H**(CH_2Ph)CO-); 3.93 (m, 2 H, -NHC**H**$_2$COOH); 3.65 (m, 1 H -C**H**(CF_3)-); 3.13 (dd, *J* = 13.9, 6.6, 1 H, -C**H**HPh); 3.03 (dd, *J* = 13.9, 7.3, 1 H, -CH**H**Ph); 2.60 (dd, *J* = 15.4, 4.0, 1 H, -COCH**H**-); 2.48 (dd, *J* = 15.4, 9.4, 1 H, -COC**H**H-); 1.95 (m, 1 H, -C**H**(CH_3)$_2$); 0.97 (d, *J* = 6.9, 3 H, -(CH_3)CHC**H**$_3$); 0.93 (d, *J* = 6.9, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, CD_3OD): –75.4 (d, *J* = 6.5, 3 F). ^{13}C NMR (127.7 MHz, CD_3OD): 176.4, 172.9, 172.8, 171.8, 137.9, 136.9, 130.1, 129.5, 129.4, 129.2, 128.1 (q, *J* = 284.9); 127.8, 67.9, 67.3, 55.7 (q, *J* = 28.6); 41.5, 38.4, 36.1, 32.9, 19.6, 18.3. CI-MS, *m/z* (%): 553 (100) [M^+ + 1].

11a, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –76.6 (d, *J* = 7.3, 3 F).

11b, *major diastereomer*: ^{1}H NMR (500 MHz, CD_3OD): 4.43 (q, *J* = 7.3, 1 H, -NHC**H**(CH_3)CO-); 3.95 (m, 2 H, -NHC**H**$_2$COOH); 3.71 (m, 4 H, -COOC**H**$_3$ and -C**H**(CF_3)-); 2.66 (m, 2 H, -C**H**(iPr)- and -COCH**H**-); 2.52 (m, 1 H, -COC**H**H-); 1.97 (m, 1 H, -C**H**(CH_3)$_2$); 1.39 (d, *J* = 7.3, 3 H, -CH(C**H**$_3$)-); 1.01 (d, *J* = 6.9, 3 H, -(CH_3)CHC**H**$_3$); 0.97 (d, *J* = 6.9, 3 H, -(C**H**$_3$)CHCH_3). ^{19}F NMR (470.6 MHz, CD_3OD): –75.7 (d, *J* = 6.5, 3 F). ^{13}C NMR (127.7 MHz, CD_3OD): 176.5, 174.0, 172.8, 171.7, 128.1 (q, *J* = 284.7); 67.3, 56.2 (q, *J* = 27.7); 52.8, 41.6, 36.3, 33.0, 19.6, 18.9, 18.2, 17.3. CI-MS, *m/z* (%): 400 (100) [M^+ + 1].

11b, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –76.7 (d, *J* = 7.3, 3 F).

15a, *major diastereomer*: ^{1}H NMR (500 MHz, CD_3OD): 4.44 (m, 2 H, -NHC**H**(CH_3)$COOCH_3$ and -NHC**H**(CH_3)COOH); 4.14 (d, *J* = 7.8, 1 H, -CONHC**H**(iPr)CO-); 3.83 (m, 1 H, -C**H**(CF_3)-); 3.70 (s, 3 H, -COOC**H**$_3$); 3.43 (d, *J* = 4.9, 1 H, -CHNHC**H**(iPr)CO-); 2.72 (dd, *J* = 15.9, 3.7, 1 H, -COC**H**H-); 2.61 (dd, *J* = 15.9, 10.4, 1 H, -COCH**H**-); 2.18 (m, 1 H, -C**H**(CH_3)$_2$); 2.01 (m, 1 H, -C**H**(CH_3)$_2$); 1.40 (d, *J* = 7.2, 3 H, -CH(C**H**$_3$)-); 1.36 (d, *J* = 7.2, 3 H, -CH(C**H**$_3$)-); 1.02–0.92 (m, 12 H, -CH(C**H**$_3$)$_2$). ^{19}F NMR (470.6 MHz, CD_3OD): –74.5 (d, *J* = 7.3, 3 F). ^{13}C NMR (127.7 MHz, CD_3OD): 175.9, 175.5, 174.6, 173.6, 172.1, 128.2 (q, *J* = 286.6); 66.8, 61.3, 55.5 (q, *J* = 27.7); 52.8, 52.7, 52.6, 35.9, 33.1, 31.5, 19.8, 19.7, 19.5, 18.1, 17.3. CI-MS, *m/z* (%): 513 (100) [M^+ + 1].

15a, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –77.3 (d, *J* = 6.5).

15b, *major diastereomer*: ^{1}H NMR (500 MHz, CD_3OD): 7.37–7.28 (m, 5 H, Ar); 5.16 (d, *J* = 12.2, 1 H, -OCOCH**H**Ph); 5.12 (d, *J* = 12.2, 1 H, -OCOC**H**HPh); 4.50 (t, *J* = 7.1, 1 H, -C**H**(iBu)-); 4.44 (q, *J* = 7.1, 1 H, -C**H**(CH_3)-); 4.14 (d, *J* = 8.1, 1 H, -CONHC**H**(iPr)CO-); 3.86 (m, 1 H, -C**H**(CF_3)-); 3.46 (d, *J* = 4.4, 1 H, CHNHC**H**(iPr)CO-); 2.74 (dd, *J* = 15.8, 4.4, 1 H, -COC**H**H-); 2.62 (dd, *J* = 15.8, 9.9, 1 H, -COCH**H**-); 2.19 (m, 1 H, -C**H**(CH_3)$_2$); 2.03 (m, 1 H, -C**H**(CH_3)$_2$); 1.69 (m, 1 H, -CH_2C**H**(CH_3)$_2$); 1.63 (m, 2 H, -C**H**$_2$(CH_3)$_2$); 1.31 (d, *J* = 7.1, 3 H, -CH(C**H**$_3$)-); 1.02–0.88 (m, 18 H, -CH(C**H**$_3$)$_2$). ^{19}F NMR (470.6 MHz, CD_3OD): –74.2 (d, *J* = 6.5, 3 F). ^{13}C NMR (127.7 MHz, CD_3OD): 175.7, 175.4, 173.8, 172.4, 172.3, 137.1, 130.6, 129.3, 129.1, 128.4 (q, *J* = 286.6); 67.8, 66.5, 61.5, 55.4 (q, *J* = 27.6); 52.6, 41.1, 35.8, 33.0, 31.3, 25.9, 23.1, 21.9, 19.9, 19.8, 19.5, 18.2, 18.1. CI-MS, *m/z* (%): 631 (100) [M^+ + 1].

15b, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –76.5 (d, *J* = 7.3, 3 F).

15c, *major diasteromer*: ^{1}H NMR (500 MHz, CD_3OD): 4.46 (q, *J* = 7.1, 1 H, -C**H**(CH_3)-); 4.42 (d, *J* = 6.0, 1 H, -CONHC**H**(iPr)CO-); 3.86 (m, 1 H, -C**H**(CF_3)-); 3.71 (s, 3 H, -COOC**H**$_3$); 3.46 (d, *J* = 3.7, 1 H, -CHNHC**H**(iPr)CO-); 2.76 (dd, *J* = 15.8, 3.7, 1 H, -COC**H**H-); 2.66 (dd, *J* = 15.8, 9.9, 1 H, -COCH**H**-); 2.20 (m, 1 H, -C**H**(CH_3)$_2$); 2.04 (m, 1 H, -C**H**(CH_3)$_2$); 1.89 (m, 1 H, -C**H**(CH_2CH_3)-); 1.51 (m, 1 H, -CH**H**CH_3); 1.36 (d, *J* = 7.1, 3 H, -CH(C**H**$_3$)-); 1.25 (m, 1 H, -C**H**HCH_3); 0.96–0.87 (m, 18 H, -CH_2C**H**$_3$, -C**H**$_3$CH(CH_2CH_3)- and -CH(C**H**$_3$)$_2$). ^{19}F NMR (470.6 MHz, CD_3OD): –74.2 (d, *J* = 6.5) . ^{13}C NMR (127.7 MHz, CD_3OD): 178.5, 175.4, 173.7, 173.3, 172.3, 128.4 (q, *J* = 286.7); 66.6, 61.7, 58.4, 55.4 (q, *J* = 27.7); 52.4, 38.4, 35.7, 33.0, 31.4, 26.4, 19.8, 19.5, 18.3, 18.2, 16.1, 15.8, 11.7. CI-MS, *m/z* (%): 556 (100) [M^+ + 1].

15c, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –76.6 (d, *J* = 7.3).

15d, *major diastereomer*: ^{1}H NMR (500 MHz, CD_3OD): 7.38–7.25 (m, 5 H, Ar); 5.19 (d, *J* = 12.1, 1 H, -OCOCH**H**Ph); 5.13 (d, *J* = 12.1, 1 H, -OCOC**H**HPh); 4.45 (q, *J* = 7.1, 1 H, -C**H**(CH_3)-); 4.38 (d, *J* = 6.0, 1 H, -COC**H**(iPr)NH-); 4.12 (m, 1 H, -CONHC**H**(iPr)CO-); 3.86 (m, 1 H, -C**H**(CF_3)-); 3.43 (d, *J* = 4.3, 1 H, -CHNHC**H**(iPr)CO-); 2.76 (dd, *J* = 15.9, 4.4, 1 H, -COCH**H**-); 2.66 (dd, *J* = 15.9, 9.9, 1 H, -COC**H**H-); 2.17 (m, 2 H, -C**H**(CH_3)$_2$); 2.02 (m, 1 H, -C**H**(CH_3)$_2$); 1.31 (d, *J* = 7.1, 3 H, -CH(C**H**$_3$)-); 1.02–0.88 (m, 18 H, -CH(C**H**$_3$)$_2$). ^{19}F NMR (470.6 MHz, CD_3OD): –74.3 (d, *J* = 6.5, 3 F). ^{13}C NMR (127.7 MHz, CD_3OD): 175.7, 175.4, 173.7, 172.7, 172.4, 137.2, 129.6, 129.3, 67.9, 66.6, 61.5, 59.6, 55.5 (q, *J* = 27.6); 35.9, 33.1,

33.0, 31.6, 31.5, 19.9, 19.8, 19.6, 19.4, 18.6, 18.3, 18.2; the -CF_3 signal was obscured due to its low intensity. CI-MS, *m/z* (%): 618 (100) [M^+ + 1].

15d, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –76.8 (d, *J* = 7.3, 3 F).

15e, *major diastereomer*: ^{1}H NMR (500 MHz, CD_3OD): 7.31–7.18 (m, 5 H, Ar); 4.68 (dd, *J* = 8.4, 5.6, 1 H, -C**H**(CH_2Ph)-); 4.44 (q, *J* = 7.5, 1 H, -C**H**(CH_3)-); 4.14 (d, *J* = 8.4, 1 H, -CONHC**H**(iPr)CO-); 3.78 (m, 1 H, -C**H**(CF_3)-); 3.39 (d, *J* = 4.7, 1 H, -CHNHC**H**(iPr)CO-); 3.31 (s, 3 H, -COOC**H**$_3$); 3.15 (dd, *J* = 14.1, 5.6, 1 H, -CH**H**Ph); 3.02 (dd, *J* = 14.1 and 8.4, 1 H, -C**H**HPh); 2.71 (dd, *J* = 16.0, 3.8, 1 H, -COC**H**H-); 2.54 (dd, *J* = 16.0, 6.6, 1 H, -COCH**H**-); 2.17 (m, 1 H, -C**H**(CH_3)$_2$); 1.97 (m, 1 H, -C**H**(CH_3)$_2$); 1.34 (d, *J* = 7.5, 3 H, -CH(C**H**$_3$)-); 1.01–0.70 (m, 12 H, -CH(C**H**$_3$)$_2$). ^{19}F NMR (470.6 MHz, CD_3OD): –74.4 (d, *J* = 6.5, 3 F). ^{13}C NMR (127.7 MHz, CD_3OD): 175.4, 174.4, 173.6, 173.4, 172.1, 138.2, 130.2, 129.6, 129.5, 128.0 (q, *J* = 286.7); 66.7, 61.3, 55.8, 55.5 (q, *J* = 26.9); 52.6, 38.3, 35.8, 33.0, 31.5, 19.8, 19.7, 19.6, 18.4, 18.3, 18.2. CI-MS, *m/z* (%): 589 (100) [M^+ + 1].

15e, *minor diastereomer*: ^{19}F NMR (470.6 MHz, CD_3OD): –76.5 (d, *J* = 7.3).

We thank CNR for financial support.

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9. Excess of **3** can be recovered quantitatively in a pure form just evaporating the organic solvent from the solution without any further purification.
10. The absolute configurations of the [CH*(CF_3)NH] stereogenic centres of the PMR-peptides synthesised in this work by solid-phase chemistry were not assessed

experimentally. However, the remarkable analogies (in terms of stereoselectivity, as well as of spectroscopic and analytical properties) existing between the PMR-ψ[NHCH(CF_3)]-Gly peptides prepared in solution[4a] or solid-phase chemistry strongly suggest that the main diastereomers of **4a**, **4c**, **4e**, **4f**, and their derivatives should have (*S*)-configuration at the [CH*(CF_3)NH] center.

11. To our knowledge, these are the first examples reported in literature of solid-phase intermolecular Michael-type *N*-additions involving α-amino acid esters and 4-substituted acceptors. For some rare solution-phase examples, see: a) Leonard N. J., Fischer F. E., Barthel E., Jr., Figueras J., Jr., Wildman W. C.: *J. Am. Chem. Soc.* **1951**, *73*, 2371; b) Urbach H., Henning R.: *Tetrahedron Lett.* **1984**, *25*, 1143. For solid-phase conjugate 1,4-*N*-additions to unsubstituted acceptors, see: c) Morphy J. R., Rankovic Z., Rees D. C.: *Tetrahedron Lett.* **1996**, *37*, 3209; d) Kolodziej S. A., Hamper B. C.: *Tetrahedron Lett.* **1996**, *37*, 5277; e) Garibay P., Nielsen J., Hoeg-Jensen T.: *Tetrahedron Lett.* **1998**, *39*, 2207.
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