Enantiopure β3-Trifluoromethyl-β3-homoalanine Derivatives: Coupling with Boc-Protected Amino Acids and Conformational Studies of Peptides in Solid State

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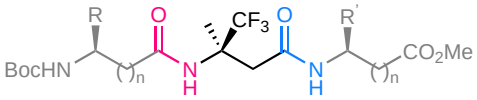
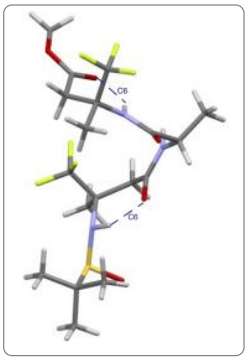


N-coupling: HATU, DIPEA, DMF

C-coupling: EDCI, HOBt, DIPEA, MeCN

(*R*) and (*S*)-b^3-CF$_3$-b^3-homoalanine : gram-scale synthesis
N- and/or *C*-protected derivatives

48 original a/b- and hetero b-di-, tri- and tetrapeptides



Abstract: The use of enantiopure β^3-trifluoromethyl-β^3-alkyl β-amino acids for the design of peptides would contribute to drastically enhance the peptide stability *in vivo*. Moreover, the steric hindrance generated by the substituents on the tetrasubstituted carbon adjacent to the nitrogen function coupled to the electron-withdrawing effect of the trifluoromethyl group are more likely to influence the 3D conformation of the peptide. Herein, we describe a short, scalable and robust method to synthesize *N*- and/or *C*-protected enantiopure (*R*)- and (*S*)-β^3-trifluoromethyl-β^3-methyl β-amino acid derivatives and liquid-phase coupling methods suitable with Boc protected amino acids to incorporate them in short α/β- and β-peptides. Conformational studies of some of these original peptides *via* X-ray diffraction analysis highlighted intraresidue C6 hydrogen bonds into trifluoromethylated amino acids.

Key words fluorine, amino acids, peptides, coupling, conformational analysis.

β-Aminoacids are highly promising building blocks in medicinal chemistry as bioactive peptides containing these units do not present the significant disadvantages of α-peptides, i.e. the high conformational freedom of short fragments and the low proteolytic stability *in vivo*.[1] β-Amino acids are the subunits of β-peptides[2] (made up exclusively of β-amino acids) and α/β-peptides[3] (sequence of β- and natural α-amino acids) that have been the subject of numerous research to determine their preferred secondary structures in solid state and solution. Experimental and molecular dynamic studies have both highlighted the profound influence of the nature of the amino acids, the site of the attachment of the side chain and the configuration of the chiral centers.[2,3] The effect of geminal disubstitution of β-amino acids on the conformation of peptides is intriguing.[4] Focusing on $\beta^{3,3}$-amino acids (disubstitution on the carbon adjacent to the nitrogen), the influence of achiral 1-amino-cyclohexane acetic acid ($\beta^{3,3}$-Ac$_6$c) has been mostly investigated.[5] The presence of geminal disubstituents restricts the torsion angles ϕ (about N-Cβ bond) and θ (about Cα-Cβ bond) and $\beta^{3,3}$-Ac$_6$c residue adopts almost exclusively *gauche* conformations about Cα-Cβ bonds.[5b-d] Despite that no intramolecular hydrogen bonds were observed in many small α/β-peptides,[5a,b] C6 hydrogen-bonded turns were detected in free amino acid and homo-β-dipeptide,[5b] C11 α/β-turns, expanded version of the type II β-turn, were highlighted in two α/β-hybrid dipeptides[5b,c] while longer tetra- and pentapeptide folded in mixed C11/C9 helical structure.[5d] Conformations of peptides containing chiral $\beta^{3,3}$-amino acids have been rarely documented.[4b,6] Homo-β-hexapeptide consisting of amino acids derived from sugar appears to prefer C8 conformation in solution.[6]

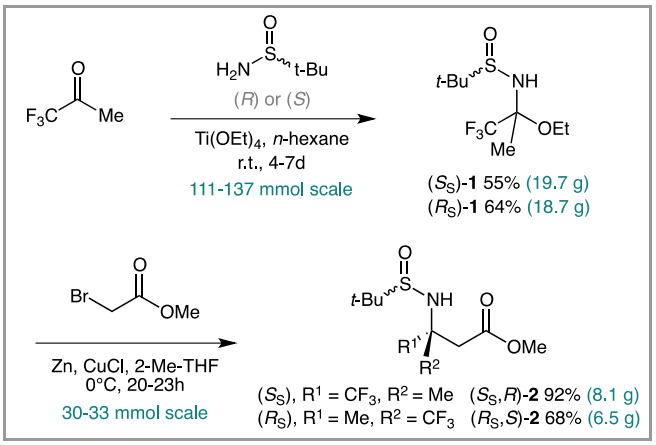
A broad variety of fluorinated amino acids have been reported but most of them are derived from α-amino acids and contained a fluorinated side chain or a fluorinated substituent instead of the α-proton.[7] Their incorporation into peptides and proteins may promote the stabilization of particular secondary structure, increase their metabolic stability and enhance their hydrophobicity and, as a result, improve their biological activities.[7f,8] Moreover, fluorinated amino acids can serve as probes for ^{19}F NMR studies.[8] The influence of fluorinated β-amino acids[7a,c,f-l,9] on the conformation of peptides has been mainly investigated with a backbone-bound fluorine atom on the carbon adjacent to the CO function (β^2-fluoro β-amino acids).[10] The effect of the trifluoromethyl group[11] has been studied only with mono substituted β-alanine derivative and was the subject of two publications.[12] In the first one,[12a] a β-turn-like conformation backbone was obtained with α/β-dipeptides containing (*S*)-2-(aminomethyl)-3,3,3-trifluoropropanoic acid [(*S*)-β^2-trifluoromethyl-β-alanine] through no intramolecular H-bond was observed. In the second one,[12b] two residues of (*R*)-3-amino-4,4,4-trifluorobutanoic acid [(*R*)-β^3-trifluoromethyl-β-alanine] have significantly stabilized the 14-helix structure of a β-hexapeptide thanks to the highly withdrawing fluorinated groups which enhanced the hydrogen-bond donating property of the neighboring amide NH and thus strengthened intramolecular H-bonds.

Only a few stereoselective synthesis of more substituted, linear, β^3-trifluoromethyl β^3-alkyl(aryl) β-amino acids derivatives have

been reported to date,[13] and, thus, synthetic methods for obtaining them in enantiopure form are limited.[13a-c] Our main contribution in this area was the development of the highly diastereoselective Reformatsky reaction on stable precursors of aliphatic and aromatic trifluoromethyl (S_S)-*N*-*tert*-butanesulfinyl ketoimines.[13b] Their incorporation into peptides was rarely reported.[13b] The strongly electron-withdrawing and bulky trifluoromethyl group[14] decreases the nucleophilicity[15] but also greatly increases the steric hindrance of adjacent amine function of β³-trifluoromethyl β³-alkyl(aryl) β-amino acid derivatives. Elongation at the *N*-terminus of β³-trifluoromethyl-β³-homoalanine containing peptide was thus performed using highly reactive amino acid chloride, intrinsically limiting this coupling to Fmoc-protected amino acids.[13b] While this methodology enables to prepare the Fmoc-Ala-(*R*)-β³-Tfm-β³-hAla-Ala-OMe hetero-tripeptide, attempts to perform the reaction of Fmoc-L-Ala-Cl with dipeptide H-(*R*)-β³-Tfm-β³-hAla-Phe-OEt containing a bulkier side chain unfortunately failed.[13b]

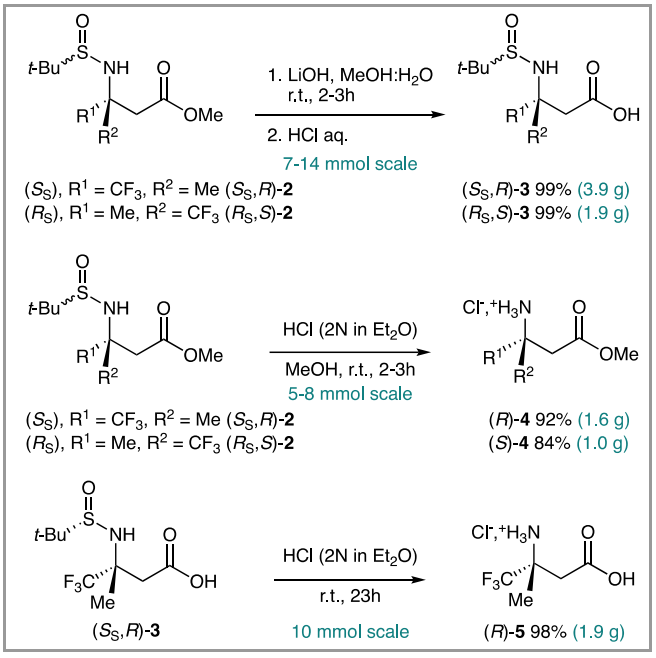
In this publication, we wish to disclose the scalability of the diastereoselective Reformatsky reaction we reported a few years ago[13b] for the multigram synthesis of enantiopure (*R*)- as well as of (*S*)-β³-trifluoromethyl-β³-methyl β-amino acids precursors (named β³-trifluoromethyl-β³-homoalanine or β³-Tfm-β³-hAla precursors). Having in hand various *N*- and *C*-protected derivatives of these amino acids, we desired to study the preparation of short hetero-peptides using a coupling method suitable with Boc strategy, the most convenient approach for liquid phase reactions. Finally, our aim was also to explore the effect of geminal trifluoromethyl and methyl substituents on carbon adjacent the nitrogen function of β-aminoacids on the conformations of short peptides in solid state.

Synthesis of enantiopure (*R*)- and (*S*)-β³-trifluoromethyl-β³-homoalanine derivatives. According to the procedure previously described,[13b] *N*-*tert*-butanesulfinyl trifluoromethyl hemiaminals (S_S)-**1**[13b] and (R_S)-**1** could be easily prepared by reacting over a hundred millimoles of the commercially available 1,1,1-trifluoroacetone with each enantiomer of Ellman chiral auxiliary[16] in *n*-hexane in the presence of an excess of $Ti(OEt)_4$ at room temperature for days (Scheme 1). Reaction of several grams of these bench stable hemiaminals (S_S)-**1** or (R_S)-**1** under Reformatsky conditions in methyl-THF[13b] allowed to release *in situ* the corresponding *N*-tert-butanesulfinyl trifluoromethylketimine. Addition of the metal enolate on this highly electrophilic intermediate led to the *N*-protected amino ester (S_S,*R*)-**2** or (R_S,*S*)-**2** with excellent diastereoselectivity (the minor isomer could not be detected in the ^{19}F NMR spectra of the crude reaction mixture). After purification by chromatography on silica gel, enantiomeric *N*-protected amino esters (S_S,*R*)-**2**[13b] and (R_S,*S*)-**2** were isolated in good to excellent yields (92% and 68% yields, respectively) (Scheme 1). The observed diastereoselectivity is consistent with a Zimmerman-Traxler-type six-membered transition state.[13b]



Scheme 1 Two-steps multigrams scale synthesis of enantiopure *N*-tert-butanesulfinyl β³-trifluoromethyl-β³-homoalanine methyl ester **(S_S,*R*)-2** and **(R_S,*S*)-2** from commercially available 1,1,1-trifluoroacetone.

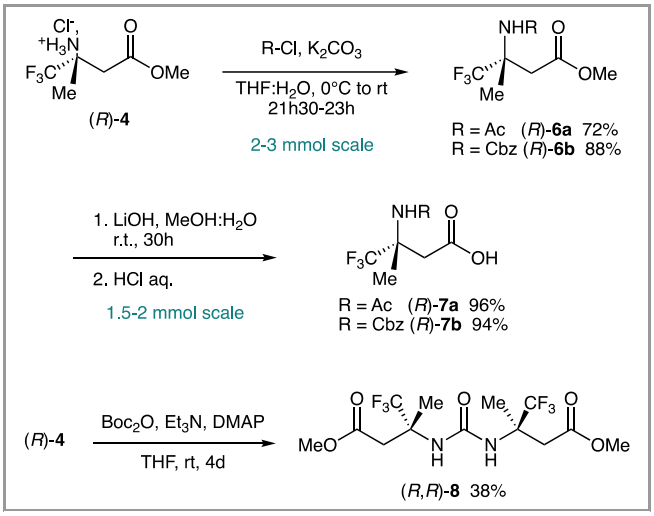
Basic treatment of amino methyl esters (S_S,*R*)-**2** and (R_S,*S*)-**2** gave quantitatively *N*-*tert*-butanesulfinyl protected β³-trifluoromethyl-β³-homoalanine (S_S,*R*)-**3**[13b] and (R_S,*S*)-**3** (Scheme 2). Ellman auxiliary of (S_S,*R*)-**2**, (R_S,*S*)-**2** and (S_S,*R*)-**3** was classically removed under acidic treatment. β³-Trifluoromethyl-β³-homoalanine methyl ester hydrochloride (*R*)-**4** and (*S*)-**4** and β³-trifluoromethyl-β³-homoalanine hydrochloride (*R*)-**5** were thus obtained in excellent yields (Scheme 2). These reactions allowed the multigram synthesis of the desired enantiopure *N*-protected (S_S,*R*)-**3**, (R_S,*S*)-**3** or *C*-protected (*R*)-**4**, (*S*)-**4** as well as of the fully deprotected (*R*)-**5** β³-trifluoromethyl-β³-homoalanine derivatives in only three or four steps from the commercially available 1,1,1-trifluoroacetone.



Scheme 2 Synthesis of enantiopure *N*-*tert*-butanesulfinyl β³-trifluoromethyl-β³-homoalanine (S_S,*R*)-**3** and (R_S,*S*)-**3,** β³-trifluoromethyl-β³-homoalanine methyl ester hydrochloride (*R*)-**4** and (*S*)-**4** and β³-trifluoromethyl-β³-homoalanine hydrochloride (*R*)-**5**.

Attempts were then performed to introduce acetyl (Ac), benzyloxycarbonyl (Cbz) and *tert*-butoxycarbonyl (Boc)

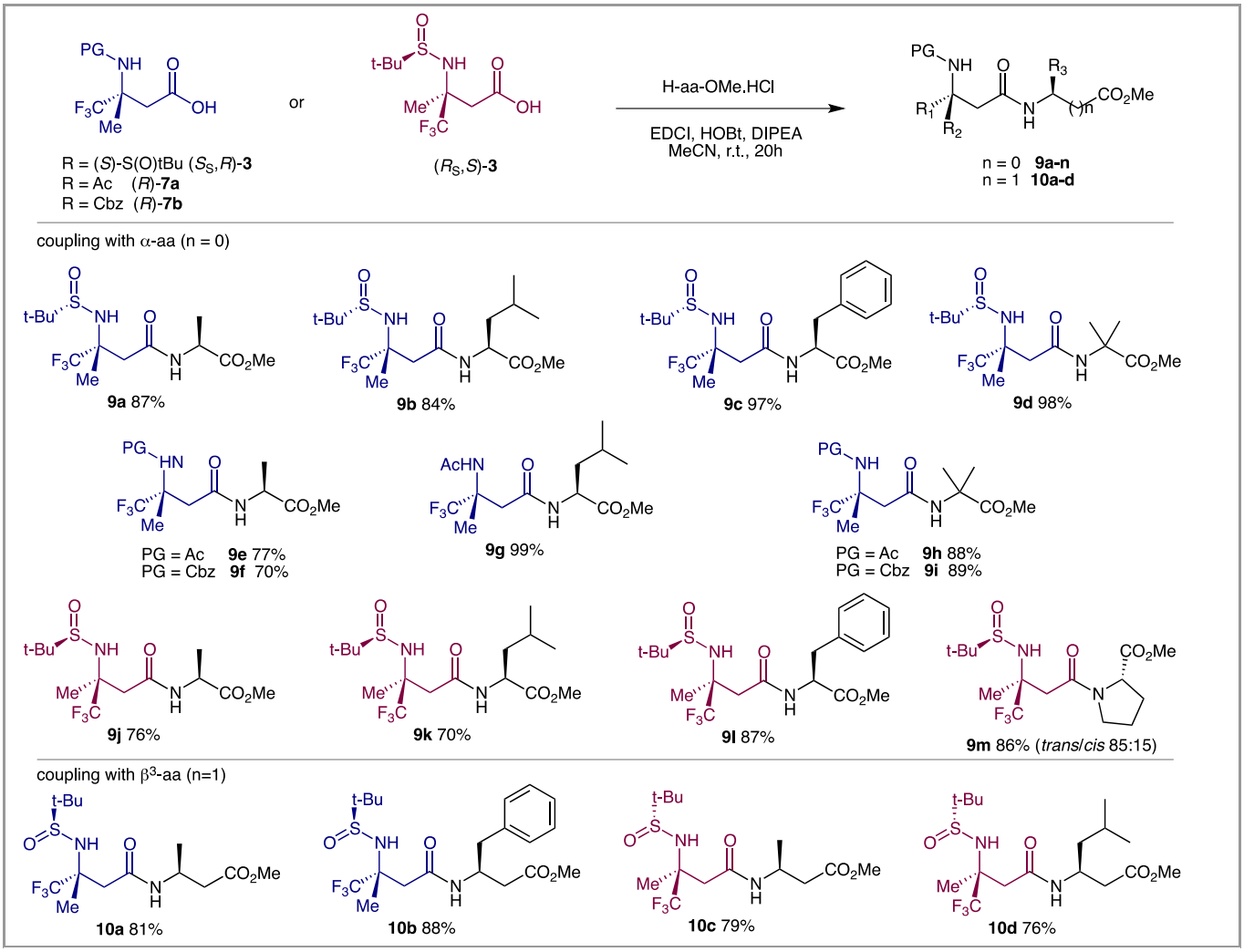
protecting groups on the amine function of the (*R*)-β³-trifluoromethyl-β³-homoalanine methyl ester hydrochloride (*R*)-**4**. Despite the poor nucleophilicity and the steric hindrance of the amine function, Schotten-Baumann-type reaction on millimoles scale of (*R*)-β³-trifluoromethyl-β³-homoalanine methyl ester hydrochloride (*R*)-**4** with acetyl chloride or benzylchloroformate led to the desired *N*-Ac amino ester (*R*)-**6a** and *N*-Cbz amino ester (*R*)-**6b**, which were isolated in very good yields (72% and 88% yields, respectively) (Scheme 3). Saponification of these *N*-protected amino esters (*R*)-**6a** and (*R*)-**6b** gave easily the corresponding amino acids (*R*)-**7a** and (*R*)-**7b** (Scheme 3). Boc-protection of the amino ester (*R*)-**4** was more troublesome even using experimental conditions developed for tetrasubstituted α-trifluoromethyl α-amino acids.[17] Reaction of (*R*)-β³-trifluoromethyl-β³-homoalanine methyl ester hydrochloride (*R*)-**4** with an excess of di-*tert*-butyl carbonate in THF, in the presence of Et_3N and DMAP, afforded only the urea-type derivative having a C_2-symmetry (*R,R*)-**8** which was isolated in 38% yield (Scheme 3). The structure of (*R,R*)-**8** was confirmed by X-ray diffraction.[18] No traces of the formation of other product could be detected by ^{19}F or ^{1}H NMR, during the course of the reaction and in the crude reaction mixture. No further investigations were performed to obtain Boc-protected (*R*)-β³-trifluoromethyl-β³-homoalanine methyl ester as the *tert*-butanesulfinyl group can be considered as a Boc protecting group surrogate as both of them are stable to base and are cleaved under acidic condition.[16,19] *N-tert*-Butanesulfinylamino acids (*S*S,*R*)-**3**, (*R*S,*S*)-**3**, as *N*-acetyl and *N*-benzyloxycarbonyl amino acids (*R*)-**7a**, (*R*)-**7b**, could be further used in peptide coupling at the *C*-terminus of the fluorinated amino acid fragment.



Scheme 3 *N*-protection of (*R*)-**4** with Ac and Cbz protecting groups and attempt for the introduction of Boc group.

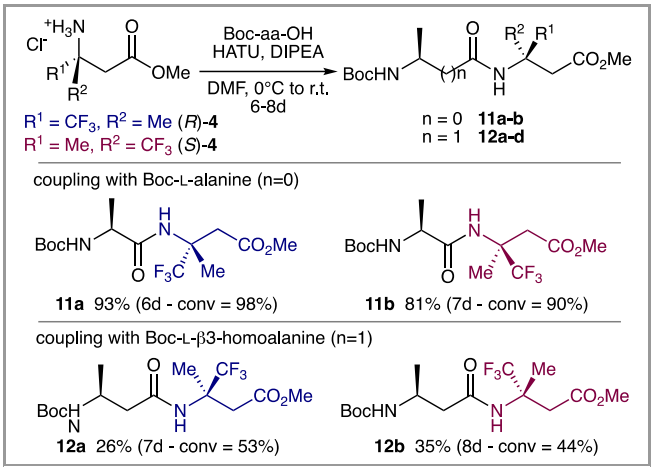
Having in hands enantiopure (*R*)-β³-trifluoromethyl-β³-homoalanine hydrochloride (*R*)-**5** as well as *N*- and *O*-protected derivatives (*S*S,*R*)-**3**, (*R*S,*S*)-**3,** (*R*)-**4,** (*S*)-**4**, (*R*)-**7a** and (*R*)-**7b** we next attempted the synthesis of short peptides containing enantiopure β³-trifluoromethyl-β³-homoalanine fragment in various position.

Synthesis of β/α- and β-dipeptides containing (*R*)- or (*S*)-β³-trifluoromethyl-β³-homoalanine derivatives at the *N*-terminal position by elongation at the *C*-terminus of *N*-protected β³-trifluoromethyl β³-amino acid (*S*S,*R*)-3, (*R*S,*S*)-3, (*R*)-7a and (*R*)-7b. To prepare β/α-and β-heteropeptides whom are the precursors of tripeptides with the β³-trifluoromethyl-β³-homoalanine fragment in central position, the peptide-bond formation at the *C*-terminus position of the trifluororomethylated β-amino acid derivatives was investigated. Considering the poor nucleophilicity and the steric hindrance of the amine adjacent to the trifluoromethyl group, direct coupling at the *C*-terminus of the unprotected (*R*)-β³-trifluoromethyl-β³-homoalanine hydrochloride (*R*)-**5** with L-alanine methyl ester hydrochloride, a strategy validated with tetrasubstituted α-trifluoromethylalanine,[20] was first studied. Unfortunately, the use of EDCI, HOBt and DIPEA in DMF led to a very complex mixture. However, we have previously reported that *N-tert*-butanesulfinyl-β³-trifluoromethyl-β³-homoalanine (*S*S,*R*)-**3** reacted easily with this amino ester under these classical coupling conditions and gave the corresponding dipeptide **9a** which was isolated in 93% yield.[13b] Pleasingly, similar yields could be obtained using CH_2Cl_2 as solvent (89%) but above all with acetonitrile[21] (87%), a friendlier alternative to DMF[22] (Scheme 4). In order to evaluate the scope of this latter condition, variously *N*-protected derivatives of (*R*)-β³-trifluoromethyl-β³-homoalanine (*S*S,*R*)-**3**, (*R*)-**7a** and (*R*)-**7b** or *N-tert*-butanesulfinyl-β³-trifluoromethyl-β³-homoalanine (*R*S,*S*)-**3** reacted with α-amino acid methyl ester having side chains with variable steric demands (L-alanine, L-leucine, L-phenylalanine and the α,α-disubstituted amino ester, α-methylalanine). The corresponding hybrid β/α-dipeptides **9a-l** were isolated in good to very good yields, ranging from 70 to 99% (Scheme 4). Reaction of (*R*S,*S*)-**3** with L-proline methyl ester led to the dipeptide **9m** which was isolated in 86% yield as a 85:15 mixture of *trans*:*cis* rotamers (Scheme 4).[23,24] Reaction of (*S*S,*R*)-**3** or (*R*S,*S*)-**3** with methyl ester derivatives of L-β³-homoalanine, L-β³-homoleucine and/or L-β³-homophenylalanine hydrochloride provided hetero β-dipeptides **10a-d**, isolated in good yields ranging from 76% and 88% (Scheme 4).



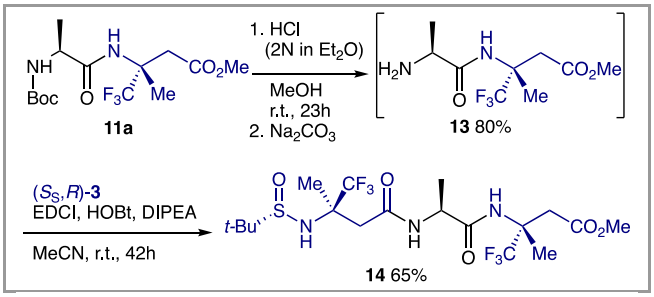
Scheme 4 *C*-Coupling of *N*-protected β³-trifluoromethyl-β³-homoalanine derivatives (*S*S,*R*)-**3**, (*R*S,*S*)-**3**, (*R*)-**7a** and (*R*)-**7b** with α- and β-amino esters.

Synthesis of various dipeptides containing (*R*)- or (*S*)-β³-trifluoromethyl-β³-homoalanine derivatives at the *C*-terminal position by elongation at the *N*-terminus of β³-trifluoromethyl-β³-amino methyl esters (*R*)-4 and (*S*)-4 – Towards α/β-tripeptide containing trifluoromethylated β-amino acid fragments at each end. As mentioned in the introduction, the *N*-coupling of β³-trifluoromethyl β³-alkyl β-amino acid derivatives is the challenging step for their incorporation into peptides and has been reported only once using highly reactive amino acid chloride.[13b] This methodology is thus limited to Fmoc-protected amino acids and requires the prior synthesis of the acid chlorid. In the literature, the closest example describing the *N*-coupling of hindered trifluoromethylated amino acid whose conditions are compatible with Boc-protected amino acid concerns a tetrasubstituted α-trifluoromethyl-α-amino acid derivative, the α-trifluoromethyl alanine.[25] The mixed anhydride approach was used but the target peptide was only obtained in moderate yield (39%). In order to develop easy reaction conditions compatible with Boc strategy for the *N*-coupling of these β³-trifluoromethylated β³,³-amino acid derivatives, we investigated the use of HATU as this reagent can promote amidation reaction with electron deficient and sterically hindered amines.[26] *N*-Coupling of Boc-L-alanine with (*R*)-**4** was successfully achieved in the presence of an excess of HATU and DIPEA in DMF after a long reaction time (98% conversion of the starting material after 6 days of reaction at room temperature, reaction monitored by ^{19}F NMR) (Scheme 5). α/β-Dipeptide **11a** was thus isolated in very good yield (93%) (Scheme 5). Replacement of DMF by MeCN was detrimental for the reaction. A 50% maximal conversion of (*R*)-**4** into peptide **11a** was obtained after 3 days of stirring at room temperature without further evolution of the reaction mixture (39% yield of **11a**). Attempts under microwaves heating only led, at best, to 25% conversion (T=60°C, P_{max}=40W, maximum conversion into **11a** obtained after 10 minutes, longer reaction time didn't improve the conversion into **11a** and led to the formation of side-products). Reaction of (*S*)-**4** with Boc-L-alanine under the best reaction conditions (HATU and DIPEA in DMF) led to 90% conversion of (*S*)-**4** after 7 days of reaction and **11b** was isolated in 81% yield (Scheme 5). The reaction of (*R*)-**4** or (*S*)-**4** with Boc-L-β³-homoalanine was much more sluggish. Only 53% and 44% conversion were obtained after 7 and 8 days of reaction respectively, which explains the low yields for β-heterodipeptides **12a** and **12b** (respectively 26% and 35%) (Scheme 5).



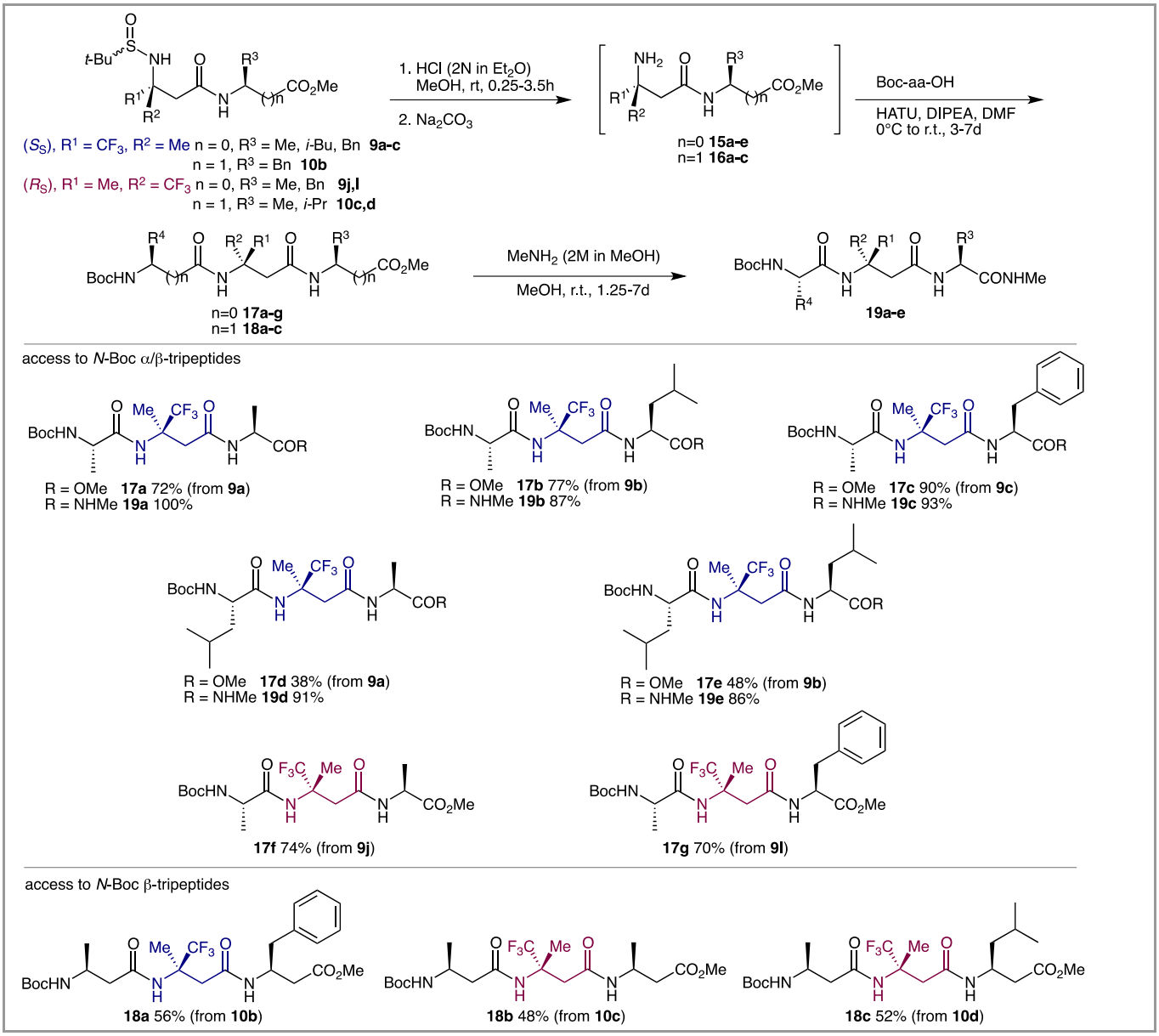
Scheme 5 *N*-Coupling of β³-trifluoromethyl-β³-homoalanine methyl esters (*R*)-**4** and (*S*)-**4** with Boc-L-alanine and Boc-L-β³-homoalanine.

Boc-protecting group of α/β-dipeptide **11a** was then cleaved under acidic conditions giving the dipeptide **13** which was used in the next step without further purification (Scheme 6). Reaction of dipeptide **13** with *N*-*tert*-butanesulfinyl protected β³-trifluoromethyl-β³-homoalanine (*S*S,*R*)-**3** in the presence of EDCI, HOBt and DIPEA in MeCN led to the heterotripeptide **14**. Original β/α/β-tripeptide **14** containing two trifluoromethylated β-amino acid fragments was isolated with a global yield of 52% from dipeptide **11a** (Scheme 6).



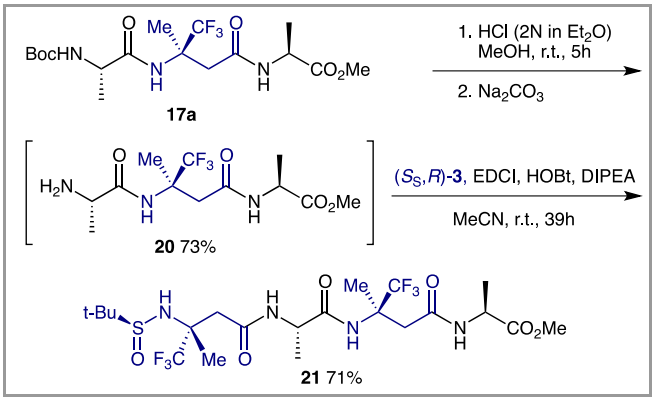
Scheme 6 Synthesis of β/α/β-tripeptide **14** containing β³-trifluoromethyl-β³-homoalanine unit at each end.

Synthesis of α/β/α-tripeptides containing the (*R*)- and (*S*)-β³-trifluoromethyl-β³-homoalanine subunit in central position by elongation at the *N*-terminus of β³-trifluoromethyl-β³-amino acid containing dipeptides 9a-c,j,l and 10b-d – Towards α/β-tetrapeptide containing a repetitive sequence (*R*)-β³-trifluoromethyl-β³-homoalanine-L-alanine. *N*-*tert*-Butanesulfinyl-protecting group of β/α-dipeptides **9a-c,j,l** and β-dipeptides **10b-d** was removed under classical acidic conditions giving the corresponding β/α-dipeptides **15a-e** and β-dipeptides **16a-c**. These dipeptides **15a-e** and **16a-c** were obtained in yields between 87% and 98% and were used in the next step without further purification (Scheme 7). β/α-Dipeptides **15a-c** containing α-amino methyl ester substituted with alkyl or benzyl side chains reacted on the *N*-terminal position with Boc-L-alanine in the presence of HATU and DIPEA in DMF. After purification, the corresponding α/β/α-tripeptides **17a-c** were obtained in good yields (between 72% and 90% yields, for two steps from *N*-*tert*-butanesulfinyl protected dipeptides **9a-c**) (Scheme 7). The reaction of dipeptide **15a,b** with Boc-L-leucine was more troublesome as only average 50% conversion into tripeptides **17d,e** was observed after 5 days of stirring. Dipeptides **17a,b** were thus isolated in 38% and 48% yields respectively (from dipeptides **9a,b**). Diastereomeric dipeptides **9j,l** reacted similarly to **9a,c** leading to the dipeptides **17f,g** in 74% and 70% yields respectively. These few examples show that, with these reaction conditions, the hindrance of the side chain of the α-amino acid of the dipeptide has no influence on the coupling of the amine function of (*R*)-β³-trifluoromethyl-β³-homoalanine fragment, However, the steric hindrance of the side chain of the Boc-protected amino acid has a great impact on its success. Moreover, the configuration of the β³-trifluoromethyl-β³-homoalanine fragment does not appears to exert much influence on the *N*-terminal coupling. As we previously observed, coupling of β-dipeptides **16a-c** with Boc-L-β³-homoalanine under these reaction conditions was more troublesome and the β-tripeptides **18a-c** were isolated in yields ranging only from 48% to 56% (yields for two steps from *N*-protected β-dipeptides **10b-d**) (Scheme 7). Finally, as *C*-terminal amide can have a deep influence on the conformation characteristics of small peptides,[27] α/β-tripeptide methyl esters **17a-e**, containing (*R*)-β³-trifluoromethyl-β³-homoalanine fragment in central position, were then treated with a solution of methylamine in methanol to form the corresponding α/β-tripeptide methyl amides **19a-e**, which were isolated in very good to excellent yields (Scheme7).



Scheme 7 Synthesis of Boc-protected heterotripeptides **17a-g**, **18a-c** and **19a-e** containing (*R*)- or (*S*)-β³-trifluoromethyl-β³-homoalanine fragment in central position.

Treatment of the Boc-protected α/β/α-tripeptide **17a** under acidic conditions gave the tripeptide **20** which was used in the next step without further purification (Scheme 8). Elongation of the peptide **20** was carried out with *N*-*tert*-butanesulfinyl protected β³-trifluoromethyl-β³-homoalanine (*Ss*,*R*)-**3**, EDCI, HOBt and DIEPA in MeCN. Heterotetrapeptide **21**, containing two (*R*)-β³-trifluoromethyl-β³-homoalanine-L-alanine repetitive fragments, was thus isolated in 71% yield (Scheme 8).



Scheme 8 Synthesis of α/β-tetrapeptide **21** containing two (*R*)-β³-trifluoromethyl-β³-homoalanine-L-alanine repetitive fragments.

Having prepared nearly 50 original short α/β- and hetero β-peptides containing (*R*)- or (*S*)-β³-trifluoromethyl β³-homoalanine residue, we next envisaged to investigate their conformation in the solid state by X-ray diffraction as the influence of chiral trifluoromethylated β³,³-amino acid has never been explored.

Crystal structure investigations. Single crystals were obtained for the β/α-dipeptides **9c**,**d**,**h**, the α/β-dipeptide **11a**, the β/α/β-tripeptide **14** as well as for the hetero β-peptides **10b**,**d** and **12a** having all *C*-terminal ester function.[18] Figure 1 illustrates the observed conformations. Backbone torsion angles and hydrogen-bond parameters are listed in Tables 1 and 2, respectively.

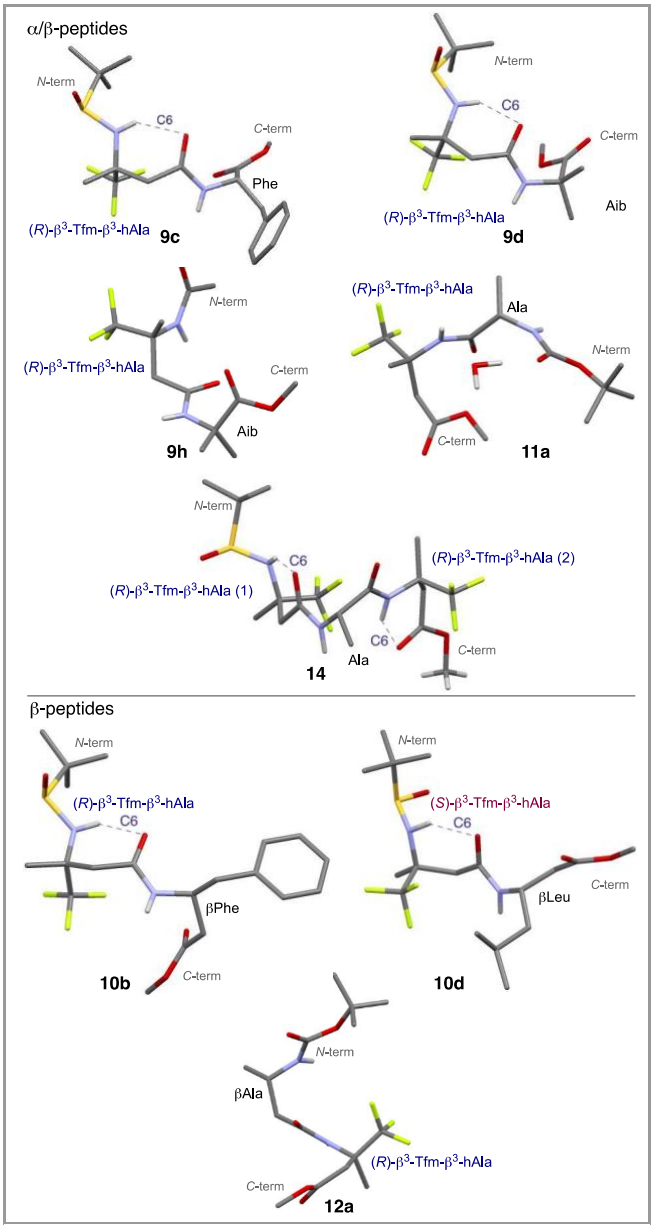


Figure 1 Solid state molecular conformations of α/β-dipeptides **9c**,**d**,**h**, **11a** and tripeptide **14** and of hetero β-dipeptides **10b-d** and **12a**. Intramolecular hydrogen bonds are shown in purple dashed lines. All hydrogen toms except NH and H_2O are removed for the sake of clarity.

In all crystals structures of peptides, geminal di-substitution of (*R*)- and (*S*)-β³-trifluoromethyl-β³-homoalanine residue imposes restrictions on the torsion angle θ (about the Cα-Cβ bond), β³,³-amino acid residue adopts *gauche* conformation with θ torsion values comprised between 41° and 78° with either positive (+) or negative (-) signs (Table 1).

Table 1 Torsional angles for α/β-peptides **9c**,**d**,**h**, **11a**, **14** and β-peptides **10b**,**d**, **12a** determined in crystal structures.

residue	ϕ [°]	θ[°]	ψ[°]	ω[°]
(*S*$_S$)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Phe-OMe **9c**				
(*R*)-β³-Tfm-β³-hAla	-154.8	-49.5	-127.7	-177.7
Phe	-80.5	164.5		
(*S*$_S$)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Aib-OMe **9d**				
(*R*)-β³-Tfm-β³-hAla	-146.1	-41.4	-132.8	-147.0
Aib	-51.9		-43.5	
Ac-(*R*)-β³-Tfm-β³-hAla-Aib-OMe **9h**				
(*R*)-β³-Tfm-β³-hAla	-167.6	72.8	124.7	-177.9
Aib	55.1		-151.4	
Boc-Ala-(*R*)-β³-Tfm-β³-hAla-OMe **11a**				
Ala	-96.3		141.6	-175.7
(*R*)-β³-Tfm-β³-hAla	33.9	68.4	-59.4	
(*S*$_S$)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Ala-(*R*)-β³-Tfm-β³-hAla-OMe **14**				
(*R*)-β³-Tfm-β³-hAla (1)	-111.2	-47.1	-137.4	-176.8
Ala	-73.8		-35.6	-177.6
(*R*)-β³-Tfm-β³-hAla (2)	-159.9	-49.2	-135.6	
(*S*$_S$)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-βhPhe-OMe **10b**				
(*R*)-β³-Tfm-β³-hAla	-112.4	-50.4	-119.5	178.6
βhPhe	89.8	65.7	-124.8	
(*R*$_S$)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-βhLeu-OMe **10d**				
(S)-β³-Tfm-β³-hAla	98.6	54.8	125.7	-175.0
βhLeu	-81.9	171.0	153.0	
Boc-βhAla-(*R*)-β³-Tfm-β³-hAla-OMe **12a**				
βhAla	-122.4	54.0	-126.9	-178.2
(*R*)-β³-Tfm-β³-hAla	22.6	50.6	-165.1	

Intra-residue hydrogen bonds[28] between the sulfinamido NH and CO groups are observed in dipeptides **9c**,**d**, **10b**,**d** and tripeptide **14** [Δ(N…O) = 2.69-2.81 Å, Δ(H…O) = 1.90-2.14 Å, ∢(N-H…O) = 137.8-149.5°] (Table 2). In all of them, *gauche* conformation along the Cα-Cβ bond is associated with a tendency of ϕ (about N-Cβ bond) and/or ψ (about Cα-CO bond) to prefer fully extended conformations[2a,d,3b,5b] and with all three dihedral angles having the same sign (Table 1).[2a,29] No intramolecular hydrogen bond was observed in β/α-dipeptide **9h**, *N*-acetyl analog of β/α-sulfinamidopeptide **9d** [intramolecular C6 H-bond for **9d**: Δ(Nβ³,³…Oα) = 2.69 Å, Δ(Hβ³,³…Oα) = 1.92 Å, ∢(N-Hβ³,³…Oα) = 144.3° (table 2); data for **9h**: Δ(Nβ³,³…Oα) = 2.95 Å, Δ(Hβ³,³…Oα) = 2.64 Å, ∢(N-Hβ³,³…Oα) = 102.2°].[18,28] Hydrogen-bonded C6 conformation[1b,3b,5a,b,30] for sulfinamidopeptides **9c**,**d**, **10b**,**d** and **14** might result from a better hydrogen-bond donor character of sulfinamide NH other than amide[31] or from minimization of steric hindrance and/or of electrostatic repulsion between the Ellman auxiliary and the trifluoromethyl group which imposed a spatial arrangement favorable for the formation of intra-residue H-bond. Nevertheless, it is interesting to note that both residues of (*R*)-β³-trifluoromethyl-β³-homoalanine in β/α/β-tripeptide **14** adopts C6 hydrogen-bonded conformation. Moreover, various intermolecular hydrogen-bonding interactions have also been observed in the crystals, including N-H···O=S hydrogen bonds (Table 2).

Table 2 Hydrogen bond parameters[28a] for α/β-peptides **9c**,**d**,**h**, **11a**, **14** and β-peptides **10b**,**d**, **12a** determined in crystal structures.

Type	Donor (D)	Acceptor (A)	D···A (Å)	H···A (Å)	∢D-H···A (°)
(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Phe-OMe **9c**					
intramol. (C6)	NH(β³,³)	CO(β³,³)	2.79	2.14	137.8
intermol.	NH(α)	SO[a]	2.88	2.04	169.6
(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Aib-OMe **9d**					
intramol. (C6)	NH(β³,³)	CO(β³,³)	2.69	1.92	144.3
intermol.	NH(α)	SO[b]	2.82	1.96	172.9
Ac-(*R*)-β³-Tfm-β³-hAla-Aib-OMe **9h**					
intermol.	NH(β³,³)	CO(α)[c]	2.97	2.10	171.2
intermol.	NH(α)	CO(Ac)[d]	2.87	2.05	168.5
Boc-Ala-(*R*)-β³-Tfm-β³-hAla-OMe **11a**					
intermol.	H_2O	CO(Boc)	2.78	1.74	172.5
intermol.	H_2O	CO(α)[e]	2.78	1.79	162.4
intermol.	NH(α)	H_2O[f]	2.81	2.05	177.7
intermol.	NH(β³,³)	CO(α)[g]	2.93	2.19	148.5
(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Ala-(*R*)-β³-Tfm-β³-hAla-OMe **14**					
intramol. (C6)	NH(β³,³(1))	CO(β³,³(1))	2.75	1.90	149.5
intramol. (C6)	NH(β³,³(2))	CO(β³,³(2))	2.80	2.03	138.9
intermol.	NH(α)	SO[h]	2.76	1.79	178.5
(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-βhPhe-OMe **10b**					
intramol. (C6)	NH(β³,³)	CO(β³,³)	2.80	2.02	145.3
intermol.	NH(β)	SO[i]	2.80	1.96	156.4
(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-βhLeu-OMe **10d**					
intramol. (C6)	NH(β³,³)	CO(β³,³)	2.81	2.02	145.0
intermol.	NH(β)	SO[j]	2.83	1.93	177.4
Boc-βhAla-(*R*)-β³-Tfm-β³-hAla -OMe **12a**					
intermol.	NH(β)	CO(β)[k]	3.04	2.26	152.3
intermol.	NH(β³,³)	CO(Boc)[k]	2.08	2.90	173.7

symmetry operation: [a]: 1-x, 1/2+y, 2-z; [b]: 1-x, -1/2+y, -z; [c]: -1+x, -y, z; [d]: 1-x, 1/2+y, 3/2-z; [e]: -y, -1+x, -1/4+z; [f]: y, -x,1/4+z; [g]: -y, +x, -1/4+z, [h]: -1/2+x, 5/2-y, 1-z; [i]: 2-x, -1/2+y, 1-z; [j]: 1/2+x, 3/2-y, 1-z; [k]: -1/2+x, 1/2-y, 1-z.

In summary, the diastereoselective Reformatsky reaction on chiral *N*-*tert*-butanesulfinyltrifluoromethylketimines was the key reaction of a short and robust synthesis enabling the multigram synthesis of *N*- and/or *C*-protected (*R*)- and (*S*)-β³-trifluoromethyl-β³-homoalanine derivatives. *C*-Coupling of these residues was performed with EDCI in the presence of HOBt and DIPEA in acetonitrile instead of the more conventional solvents, DMF or CH_2Cl_2. Despite the hindrance and the low nucleophilicity of α-trifluoromethyl amine moiety, *N*-coupling of these β³,³-amino acid derivatives was successfully achieved with HATU in the presence of DIPEA in DMF, practical reaction conditions and, above all, suitable with Boc-protected amino acids. These methods allowed the preparation of a small library of original di-, tri- and tetra- α/β- and hetero-β-peptides containing one or two (*R*)- or (*S*)-β³-trifluoromethyl-β³-homoalanine residues in various positions. Investigation of the conformations of some of these peptides by X-ray diffraction analysis highlighted the presence of an intra-residue C6-hydrogen bond within the trifluoromethylated β-amino acid. All the results described herein should contribute to the development of novel peptides containing original trifluoromethyl substituted β-amino acids.

The experimental section has no title; please leave this line here.

CH_2Cl_2 and MeCN were dried using a Pure Solv solvent drying system over aluminum oxide under argon atmosphere. *n*-Hexane (97% extra dry over molecular sieves, Acroseal®) and DMF (99.8% extra dry over molecular sieves, water <0.005%, Acroseal®) were purchased from Acros Organics. $Ti(OEt)_4$ was distilled prior to use. Diisopropylethylamine (DIPEA) was first distilled from ninhydrin and then from potassium hydroxide at atmospheric pressure and was stored under potassium hydroxide. Zn was activated by stirring with a 10% HCl (v/v) solution and successive washing with distilled H_2O, 95% EtOH and Et_2O. Zn was then dried thoroughly in vacuum oven at 70°C for a least 24h (activated Zn can be stored under these conditions for 10 days). Thin-layer chromatography using precoated aluminum backed plates (Merck Kieselgel 60F254) were visualized by UV light and/or by phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin solutions followed by heating. Silica gel (40−63 µm; Macherey-Nagel GmbH & Co KG) was used for flash chromatography. NMR spectra were recorded in $CDCl_3$, D_2O or CD_3CN with 250, 500, or 600 MHz spectrometers. Chemicals shifts (δ) were reported in ppm relative to TMS for ^1H and $^{13}C\{^1H\}$ NMR spectra and to $CFCl_3$ for ^{19}F NMR spectra. In the $^{13}C\{^1H\}$ NMR data (^{13}C NMR or J-MOD), reported signal multiplicities are related to C−F coupling. The following abbreviations were used to indicate the multiplicities: s (singlet), br s (broad singlet), br d (broad doublet), d (doublet), t (triplet), q (quartet), quint (quintuplet), sext (sextuplet), hept (heptuplet), and m (multiplet). HRMS were recorded on an ESI-Q-TOF mass spectrometer using an electrospray source in positive mode. Melting points (mp) were determined on a Tottoli apparatus and were uncorrected. Optical rotations were measured at room temperature (ca. 20 °C). X-ray data were collected on a Bruker D8 venture diffractometer equipped with a PHOTON detector. Data collection were obtained using APEX 3 software. Olex 2 software was used to solve and to refine the structures. The structure were solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation. Hydrogen atoms were added at their geometrically ideal positions and their ADP were refined isotropically (see Table 3 for crystal data and tructure refinements for peptides **9c**,**d**,**h**, **10b**,**d**, **11a**, **12a** and **14**).

The synthesis on smaller scale of **(*S*S)-1**, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OMe **(*S*S,*R*)-2** and of (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** [**(*S*S)-1**: 8,1g, 70%; **(*S*S,*R*)-2**: 648 mg, 86%, **(*S*S,*R*)-3**: 274 mg, 99%], the preparation of dipeptide (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Ala-OMe **9a** using DMF as solvent (742 mg, 93%) and the synthesis of H-(*R*)-β³-Tfm-β³-hAla-Ala-OMe **15a** (569 mg, 87%) have been previously described.[13b]

Procedures

(*R*S)-(-)-*N*-(2-Ethoxy-1,1,1-trifluoropropan-2-yl)-*tert*-butylsulfinamide (*R*S)-1. A solution of 1,1,1-trifluoroacetone (12.5 g, 111.6 mmol), (*R*)-*tert*-butanesulfinamide (16.5 g, 136.5 mmol, 1.2 equiv), and $Ti(OEt)_4$ (47 mL, 224.1 mmol, 2 equiv) in *n*-hexane (150 mL) was stirred at r.t. and under Ar for 7 days. The reaction mixture was then quenched with H_2O and after 5 min of stirring was filtered on a pad of Dicalite 4158 (Et_2O). The organic layer of the filtrate was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (petroleum ether/Et_2O 6:4) afforded hemiaminal **(*R*S)-1** (18.7 g, 64%, dr=100 :0) as a white solid.

Mp 55°C; $[\alpha]_D^{20}$ -75 (*c* 1.04, $CHCl_3$).

IR (KBr): 3160, 2982, 2585, 2165, 1664, 1374, 1329, 1124, 1019, 941, 897, 849, 771 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.89 (br s, 1H), 3.69 (quint, *J*=7.0 Hz, 1H), 3.57 (m, 1H), 1.65 (s, 3H), 1.21 (s, 9H), 1.19 (t, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 123.5 (q, *J*=286.0 Hz), 87.8 (q, *J*=30.0 Hz), 58.5, 56.6, 22.5, 16.5, 15.3.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-84.8 (s).

HRMS-ESI : *m*/*z* $[M+Na]^+$ calcd for $C_9H_{18}F_3NNaO_2S$: 284.0908; found : 284.0908.

(*R*S,*S*)-(-)-*N*-*tert*-butanesulfinyl-β³-trifluoromethyl-β³-homoalanine methyl ester [(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OMe] (*R*S,*S*)-2. A three-necked flask containing activated Zn (21.9 g, 334.1 mmol, 10 equiv) and CuCl (3.29 g, 33.3 mmol, 1 equiv) was heated under Ar with a heat gun for 5 min. The flask was allowed to cool to r.t., 2-Me-THF (160 mL) was added (formation of a black slurry), and the suspension was heated to reflux under vigorous stirring for 30 min under Ar. The heating bath was then removed, methyl bromoacetate (7.9 mL, 83.5 mmol, 2.5 equiv) was added dropwise (caution: exothermic reaction) while

maintaining the vigorous stirring, and the reaction was stirred for an additional 30 min at room temperature and 45 min at 50 °C. The reaction was then cooled to 0 °C, a solution of hemiaminal **(R_S)-1** (8.65 g, 33.1 mmol) in 2-Me-THF (125 mL) was added, and the resulting reaction mixture was stirred at 0 °C under Ar. After 23 h of stirring at this temperature, the reaction mixture was filtered on a pad of Dicalite 4158 (Et_2O). The filtrate was washed with an aq. sol. of HCl 10% (v /v), a sat. aq. sol. of $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (petroleum ether/EtOAc from 8:2 to 3:7) afforded *N-tert*-butanesulfinylamino ester **(R_S,S)-2** (6.52 g, 68%) as a yellow oil.

$[\square]_D^{20}$ -78 (*c* 0.98, $CHCl_3$)

IR (film) : 3456, 3265, 2959, 1730, 1634, 1462, 1362, 1235, 1166, 1074 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.61 (br s, 1H), 3.71 (s, 3H), 2.76 (d, *J*=15.5 Hz, 1H), 2.69 (d, *J*=15.5 Hz, 1H), 1.67 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 170.6; 125.8 (q, *J*=285.0 Hz), 59.1 (q, *J*=28.0 Hz), 56.5, 52.5, 40.4, 22.7, 19.6.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ = -81.0 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{10}H_{18}F_3NNaO_3S$: 312.0857; found : 312.0851.

(R_S,S)-(-)-*N-tert*-butanesulfinyl-β³-trifluoromethyl-β³-homoalanine [(R_S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OH] (R_S,S)-3. A solution of β-amino ester **(R_S,S)-2** (2.03 g, 7.0 mmol) and $LiOH.H_2O$ (590 mg, 14.0 mmol, 2.0 equiv) in a mixture of MeOH and H_2O (3:1, 24 mL) was stirred 2 h at r.t. The residue was diluted with AcOEt and acidified with HCl 1M (pH =1). The organic layer was separated and the aqueous layer was extracted three times with AcOEt. The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure to afford *N-tert*-butanesulfinylamino acid **(R_S,S)-3** (1.93 g, 99%) as a white solid.

Mp 137°C; $[\alpha]_D^{20}$ -60 (*c* 1.00, $CHCl_3$)

IR (KBr plates): 3256, 2993, 2965, 2928, 2725, 2603, 2554, 2355, 1714, 1467, 1419, 1285, 1239, 1155, 1027, 939, 774, 650 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=11.21 (br s, 1H), 5.88 (s, 1H), 2.74 (d, *J*=15.5 Hz, 1H), 2.68 (d, *J*=15.5 Hz, 1H), 1.69 (s, 3H, CH_3), 1.26 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=171.4, 125.8 (q, *J*=284.5 Hz), 59.3 (q, *J*=28.0 Hz), 57.3, 39.7, 22.7, 19.3

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.4 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_9H_{16}F_3NNaO_3S$: 298.0701; found : 298.0696.

(*R*)-(-)-β³-trifluoromethyl-β³-homoalanine methyl ester hydrochloride [H-(*R*)-β³-Tfm-β³-hAla-OMe.HCl] (*R*)-4. A solution of *N-tert*-butanesulfinyl β-amino ester **(S_S,*R*)-2** (2.30 g, 7.95 mmol) in MeOH (20 mL) reacted with HCl (2 N in Et_2O, 10 mL). After 3 h of stirring at r.t. under Ar, the reaction mixture was concentrated under reduced pressure and the residue was triturated with Et_2O to afford β-amino ester hydrochloride **(*R*)-4** (1.62 g, 92%) as a pale yellow hygroscopic solid.

$[\alpha]_D^{20}$ -0.5 (*c* 1.00, MeOH)

IR (KBr plate): 3423, 3168, 3069, 2793, 2574, 2023, 1738, 1575, 1537, 1444, 1370, 1257, 1185, 1123 cm^{-1}.

^1H NMR (500 MHz, D_2O): δ=3.79 (s, 3H), 3.12 (d, *J*=17.0 Hz, 1H), 3.07 (d, *J*=17.0 Hz, 1H), 1.67 (s, 3H).

^{13}C NMR (125.8 MHz, D_2O): δ=170.2, 124.1 (q, *J*=283.0 Hz), 57.1 (q, *J*=30.0 Hz), 53.0, 35.9, 17.4.

^{19}F NMR (235.3 MHz, D_2O): δ=-80.0 (s).

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_6H_{11}F_3NO_2$: 186.0742; found : 186.0745.

(*S*)-(+)-β³-trifluoromethyl-β³-homoalanine methyl ester hydrochloride [H-(*S*)-β³-Tfm-β³-hAla-OMe.HCl] (*S*)-4. A solution of *N-tert*-butanesulfinyl β-amino ester **(R_S,*S*)-2** (1.52 g, 5.24 mmol) in MeOH (16 mL) reacted with HCl (2 N in Et_2O, 8 mL). After 2 h of stirring at r.t. under Ar, the reaction mixture was concentrated under reduced pressure and the residue was triturated with Et_2O to afford β-amino ester hydrochloride **(*S*)-4** (979 g, 84%) as a yellowish hygroscopic solid.

$[\alpha]_D^{20}$ +0.5 (*c* 0.98, MeOH).

IR (KBr plate) 3420, 3165, 2959, 2855, 2569, 2356, 2037, 1737, 1614, 1532, 1445, 1374, 1322, 1279, 1188, 1068, 1007, 961, 898, 856, 773, 647, 584, 550, 444 cm^{-1}.

^1H NMR (500 MHz, D_2O): δ =3.77 (s, 3H), 3.11 (d, *J*=17.0 Hz, 1H), 3.05 (d, *J*=17.0 Hz, 1H), 1.66 (s, 3H).

^{13}C NMR (125.8 MHz, D_2O): δ=170.2, 124.1 (q, *J*=283.0 Hz), 57.1 (q, *J*=30.0 Hz), 53.0, 35.9, 17.4.

^{19}F NMR (235.3 MHz, D_2O): δ=-80.0 (s).

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_6H_{11}F_3NO_2$: 186.0742; found : 186.0740.

(*R*)-(+)-β³-trifluoromethyl-β³-homoalanine hydrochloride [H-(*R*)-β³-Tfm-β³-hAla-OH.HCl] (*R*)-5. *N-tert*-Butanesulfinyl β-amino acid **(S_S,*R*)-3** (2.61 g, 9.46 mmol) reacted with HCl (2 N in Et_2O, 53 mL). After 23 h of stirring at r.t. under Ar, the reaction mixture was concentrated under reduced pressure and the residue was triturated with Et_2O to afford β-amino acid hydrochloride **(*R*)-5** (1.93 g, 98%) as a white solid.

$[\alpha]_D^{20}$ +5 (*c* 0.94, H_2O).

IR (KBr plate): 3490, 3423, 3124, 2969, 2643, 2574, 2016, 1734, 1621, 1536, 1417, 1193, 1135, 853, 820, 532 cm^{-1}.

^1H NMR (500 MHz, D_2O): δ=3.05 (d, *J*=17.0 Hz, 1H), 2.97 (d, *J*=17.0 Hz, 1H), 1.67 (s, 3H, CH_3).

^{13}C NMR (125.8 MHz, D_2O): δ=172.1, 124.3 (q, *J*=283.0 Hz), 57.3 (q, *J*=30.0 Hz), 35.9, 17.4.

^{19}F NMR (235.3 MHz, D_2O): δ=-80.4 (s).

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_5H_9F_3NO_2$: 172.0585; found : 172.0584.

(*R*)-(-)-*N*-acetyl-β³-trifluoromethyl-β³-homoalanine methyl ester [Ac-(*R*)-β³-Tfm-β³-hAla-OMe] (*R*)-6a. A solution of *β*-amino methyl ester hydrochloride **(*R*)-4** (400 mg, 1.81 mmol) and K_2CO_3 (2.50 g, 18.1 mmol, 10 equiv) in a mixture of THF and H_2O (3:2, 10 mL) was stirred under Ar at 0 °C for 10 min. Acetyl chloride (129 µL, 1.81 mmol, 1 equiv) was then added and after 10 min of stirring at this temperature, the reaction mixture was allowed to warm at room temperature. After 19 h of stirring, the mixture was cooled to 0 °C and another amount of K_2CO_3 (2.50 g, 18.1 mmol, 10 equiv) and AcCl (129 µL, 1.81 mmol, 1 equiv) were added following the same procedure. After 21h30 of stirring (reaction monitored by ^{19}F NMR), the reaction was quenched with water (10 mL) and was extracted three times with AcOEt. The combined organic layers were washed with HCl 10% (v/v), a sat. aq. sol. of $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under

reduced pressure. Purification of the residue by chromatography on silica gel (petroleum ether/AcOEt 7:3) afforded the *N*-acetyl aminoester **(*R*)-6a** (297 mg, 72%) as a beige solid.

Mp 49°C; $[\alpha]_D^{20}$ -15 (*c* 0.31, $CHCl_3$) [lit. enantiomer *S*: $[\alpha]^{20}_D$=+2.4 (*c*=0.3 in chloroform)[13a]].

IR (KBr plate): 3287, 3091, 3007, 2959, 2855, 1750, 1667, 1573, 1441, 1380, 1287, 1169, 1097, 1013, 732, 661 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.26 (br s, 1H), 3.67 (s, 3H), 3.31 (d, *J*=15.5 Hz, 1H), 2.64 (d, *J*=15.5 Hz, 1H), 1.98 (s, 3H), 1.64 (s, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=170.4, 170.1, 125.9 (q, *J*=286.0 Hz), 57.8 (q, *J*=28.5 Hz), 52.1, 36.8, 24.5, 20.1.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.0 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_8H_{12}F_3NNaO_3$: 250.0667; found : 250.0670.

(*R*)-(-)-*N*-benzyloxycarbonyl-β³-trifluoromethyl-β³-homoalanine methyl ester [Cbz-(*R*)-β³-Tfm-β³-hAla-OMe] (*R*)-6b. A solution of *β*-amino methyl ester hydrochloride **(*R*)-4** (420 mg, 1.90 mmol) and K_2CO_3 (2.56 g, 18.5 mmol, 9.7 equiv) in a mixture of THF and H_2O (3:2, 10 mL) was stirred under Ar at 0 °C for 10 min. Benzyl chloroformate (270 µL, 1.90 mmol, 1 equiv) was then added and after 10 min of stirring at this temperature, the reaction mixture was allowed to warm at room temperature. After 23h of stirring (reaction monitored by ^{19}F NMR), the reaction was quenched with water (10 mL) and was extracted three times with AcOEt. The combined organic layers were washed with an aq. sol. of HCl 10% (v/v), a sat. aq. sol. of $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (petroleum ether/AcOEt 9:1) afforded the *N*-benzyloxycarbonyl aminoester **(*R*)-6b** (534 mg, 88%) as a colourless oil.

$[\alpha]_D^{20}$ -5 (*c* 0.99, $CHCl_3$).

IR (KBr plate): 3355, 3067, 3034, 2956, 1744, 1534, 1458, 1386, 1260, 1175, 1068, 745, 699 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.39-7.29 (m, 5H), 5.56 (br s, 1H), 5.09 (d, *J*=12.5 Hz, 1H), 5.07 (d, *J*=12.5 Hz, 1H), 3.67 (s, 3H), 3.27 (d, *J*=15.5 Hz, 1H), 2.63 (d, *J*=15.5 Hz, 1H), 1.66 (s, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=169.7, 154.5, 136.2, 128.6, 128.3, 128.2, 125.9 (q, *J*=286.0 Hz), 66.9, 57.3 (q, *J*=29.0 Hz), 52.2, 37.2, 20.0.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.5 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{16}F_3NNaO_4$: 342.0929; found : 342.0925.

(*R*)-(+)-*N*-acetyl-β³-trifluoromethyl-β³-homoalanine [Ac-(*R*)-β³-Tfm-β³-hAla-OH] (*R*)-7a. A solution of β-amino ester **(*R*)-6a** (433 mg, 1.90 mmol) and LiOH.H_2O (161 mg, 3.84 mmol, 2.0 equiv) in a mixture of MeOH and H_2O (3:1, 8 mL) was stirred 30 h at r.t. The residue was diluted with AcOEt and acidified with HCl 1M (pH =1). The organic layer was separated and the aqueous layer was extracted three times with AcOEt. The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure to afford *N*-acetylamino acid **(*R*)-7a** (391 mg, 96%) as a white solid.

Mp 100°C; $[\alpha]_D^{20}$ +8 (*c* 1.00, H_2O).

IR (KBr plate): 3328, 3111, 2906, 2638, 2548, 1714, 1647, 1578, 1268, 1163, 1098, 919, 720, 648 cm^{-1}.

^1H NMR (600 MHz, CD_3CN): δ=9.33 (br s, 1H), 6.65 (br s, 1H), 3.56 (d, *J*=16.0 Hz, 1H), 2.62 (d, *J*=16.0 Hz, 1H), 1.89 (s, 3H), 1.56 (s, 3H).

^{13}C NMR (150.9 MHz, CD_3CN): δ=171.9, 170.8, 127.2 (q, *J*=285.5 Hz), 58.3 (q, *J*=28.5 Hz), 36.1, 24.0, 20.1.

^{19}F NMR (235.3 MHz, CD_3CN): δ=-80.4 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_7H_{10}F_3NNaO_3$: 236.0510; found : 236.0503.

(*R*)-(-)-*N*-benzyloxycarbonyl-β³-trifluoromethyl-β³-homoalanine [Cbz-(*R*)-β³-Tfm-β³-hAla-OH] (*R*)-7b. A solution of β-amino ester **(*R*)-6b** (493 mg, 1.54 mmol) and LiOH.H_2O (131 mg, 3.11 mmol, 2.0 equiv) in a mixture of MeOH and H_2O (3:1, 8 mL) was stirred 30 h at r.t. The residue was diluted with AcOEt and acidified with HCl 1M (pH =1). The organic layer was separated and the aqueous layer was extracted three times with AcOEt. The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure to afford *N*-benzyloxycarbonylamino acid **(*R*)-7b** (444 mg, 94%) as a pale yellow oil.

$[\alpha]_D^{20}$ -5 (*c* 1.05, $CHCl_3$).

IR (film): 3330, 3036, 2958, 2679, 1737, 1532, 1459, 1413, 1183, 1138, 1096, 1070, 974, 745, 699, 632 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=9.47 (br s, 1H), 7.40-7.30 (m, 5H), 5.50 (br s, 1H), 5.09 (m, 2H), 3.43 (d, *J*=16.0 Hz, 1H), 2.68 (d, *J*=16.0 Hz, 1H), 1.64 (s, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.3, 154.9, 135.9, 128.7, 128.4, 128.2, 125.8 (q, *J*=284.0 Hz), 67.2, 57.2 (q, *J*=29.0 Hz), 36.7, 20.1.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.3 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{14}F_3NNaO_4$: 328.0773; found : 328.0778.

(3*R*,3'*R*)-(-)-dimethyl 3,3'-(carbonylbis(azanediyl))bis(4,4,4-trifluoro-3-methylbutanoate) (*R*,*R*)-8. Triethylamine (106 µL, 0.78 mmol, 1.2 equiv) and DMAP (16 mg, 0.13 mmol, 0.2 equiv) were added at r.t. and under Ar to a solution of β-amino ester hydrochloride **(*R*)-4** (145 mg, 0.65 mmol) in THF (2 mL). After 5 min of stirring, Boc_2O (285 mg, 1.31 mmol, 2.0 equiv) was added. After 4 days of stiiring (reaction monitored by ^{19}F NMR), the reaction mixture was diluted with AcOEt and washed with an aq. sol. of HCl 10% (v/v), a sat. aq. sol. of $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by chromatography (petroleum ether/AcOEt 8:2 containing 0.01% Et_3N) afforded the urea **(*R*,*R*)-8** (49 mg, 38%) as a white solid. An analytical sample of **(*R*,*R*)-8** was crystallized from Et_2O-PE by slow evaporation.

Mp 119-120°C; $[\alpha]_D^{20}$ -3 (*c* 1.00, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ=5.38 (s, 2H), 3.68 (s, 6H), 3.24 (d, *J*=15.5 Hz, 2H), 2.65 (d, *J*=15.5 Hz, 2H), 1.62 (s, 6H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=170.3, 154.9, 126.1 (q, *J*=286.5 Hz), 57.6 (q, *J*=28.5 Hz), 52.1, 37.5, 20.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.1 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{18}F_6N_2NaO_5$: 419.1018; found : 419.1026.

General procedure for the coupling reaction with EDCI/HOBt (general procedure A): A solution of $\beta^{3,3}$-amino acid **(*S*s,*R*)-3**, **(*R*s,*S*)-3**, **(*R*)-7a** or **(*R*)-7b**, amino ester or *C*-protected peptide, EDCI.HCl (2.0-2.2 equiv),

HOBt.xH_2O (2.0-2.4 equiv, calculated on anhydrous HOBt) and DIPEA (4.0-5.0 equiv) in acetonitrile was stirred at r.t. and under Ar. The reaction was diluted with AcOEt, washed with HCl 10% (v/v), a sat. aq. sol. of $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure and, if necessary, the residue was purified by chromatography on silica gel.

General procedure for the coupling reaction with HATU (general procedure B): A solution of $\beta^{3,3}$-amino ester **(*R*)-4**, **(S)-4** or dipeptide **15a-e**, **16a-c**, *N*-Boc protected amino acid (1.5 equiv), HATU (2-2.1 equiv), DIPEA (4.0-5.0 equiv) in DMF was stirred at r.t. and under Ar. The reaction was diluted with AcOEt, washed with HCl 10% (v/v), a sat. aq. sol. of $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure and the residue was purified by chromatography on silica gel.

General procedure for the cleavage of Boc or tert-butanesulfinyl groups (general procedure C): A solution of *N-tert*-butanesulfinyl peptides **9a-c**,**j**,**l**, **10b-d** or N-Boc peptides **11a**, **17a** in MeOH reacted with HCl (2 N in Et_2O). The reaction mixture was diluted with an aq. sol. of HCl 5% (v/v) and was washed with Et_2O and *n*-hexane. Na_2CO_3 solid was added to the aqueous layer until pH = 9 and was then extracted with AcOEt. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford deprotected peptide, used in the next step without further purification.

General procedure for the amidation of tripeptides (general procedure D): $MeNH_2$ (2 N in MeOH, 5.0-15.3 equiv) was added portionwise at r.t. and under Ar to a solution of tripeptide methyl ester **17a-e** in MeOH. After completion of the reaction, the mixture was concentrated under reduced pressure to afford the *C*-amide peptide.

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Ala-OMe 9a.[13b] According to the *general procedure A*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (1.52 g, 5.52 mmol) reacted with H-Ala-OMe.HCl (1.58 g, 11.28 mmol, 2.0 equiv), EDCI.HCl (2.34 g, 12.22 mmol, 2.2 equiv), HOBt.xH_2O (1.79 g, 13.26 mmol, 2.4 equiv) and DIPEA (3.85 mL, 22.10 mmol, 4.0 equiv) in CH_3CN (30 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 30:1) afforded the dipeptide **9a** as a yellow oil (1.73 g, 87%).

$[\alpha]_D^{20}$ +49 (*c* 1.10, $CHCl_3$).

IR (film): 3262, 3075, 2986, 2958, 2876, 2615, 1747, 1660, 1555, 1459, 1156, 1054, 757 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.94 (br s, 1H), 6.11 (s, 1H), 4.53 (quint, *J*=7.0 Hz, 1H), 3.72 (s, 3H), 2.62 (d, *J*=14.5 Hz, 1H), 2.57 (d, *J*=14.5 Hz, 1H), 1.64 (s, 3H), 1.39 (d, *J*=7.0 Hz, 3H), 1.23 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.0, 168.6, 125.9 (q, *J*=285.0 Hz), 59.7 (q, *J*=28.0 Hz), 56.5, 52.6, 48.3, 41.9, 22.7, 19.8, 18.1.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.9 (s).

HRMS-ESI: *m/z* [*M*+Na]$^+$ calcd for $C_{13}H_{23}F_3N_2NaO_4S$: 383.1228; found : 383.1235.

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Leu-OMe 9b. According to the *general procedure A*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (507 mg, 1.84 mmol) reacted with H-Leu-OMe.HCl (669 mg, 3.68 mmol, 2.0 equiv), EDCI.HCl (778 mg, 4.06 mmol, 2.2 equiv), HOBt.xH_2O (547 mg, 4.05 mmol, 2.2 equiv) and DIPEA (1.30 mL, 7.46 mmol, 4.1 equiv) in CH_3CN (10 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 30:1) afforded the dipeptide **9b** as a white solid (625 mg, 84%).

Mp 104°C; $[\alpha]_D^{20}$ +35 (*c* 0.85, $CHCl_3$).

IR (KBr plate): 3254, 3075, 2963, 2875, 1748, 1666, 1570, 1470, 1434, 1276, 1160, 1046, 869, 797, 740 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.71 (d, *J*=8.0 Hz, 1H), 6.02 (s, 1H), 4.58 (m, 1H), 3.71 (s, 3H), 2.64 (d, *J*=14.5 Hz, 1H), 2.58 (d, *J*=14.5 Hz, 1H), 1.65 (s, 3H), 1.64-1.55 (m, 3H), 1.24 (s, 9H), 0.912 (d, *J*=6.0 Hz, 3H), 0.909 (d, *J*=6.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.1, 168.8, 125.9 (q, *J*=285.0 Hz), 59.7 (q, *J*=27.5 Hz), 56.5, 52.4, 51.0, 42.2, 41.2, 25.0, 22.9, 22.7, 21.9, 19.9.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.9 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{16}H_{29}F_3N_2NaO_4S$: 425.1698; found : 425.1701.

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Phe-OMe 9c. According to the *general procedure A*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (1.54 g, 5.58 mmol) reacted with H-Phe-OMe.HCl (2.41 g, 11.19 mmol, 2.0 equiv), EDCI.HCl (2.36 g, 12.30 mmol, 2.2 equiv), HOBt.xH_2O (1.67 g, 12.35 mmol, 2.2 equiv) and DIPEA (3.90 mL, 22.39 mmol, 4.0 equiv) in CH_3CN (30 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 13:1) afforded the dipeptide **9c** as a white solid (2.37 g, 97%). An analytical sample of **9c** was crystallized from CH_2Cl_2-*n*-hexane by slow evaporation.

Mp 119°C; $[\alpha]^{20}_D$=+107 (*c* 1.01, $CHCl_3$).

IR (KBr plate): 3257, 3079, 2956, 1755, 1662, 1566, 1414, 1374, 1275, 1219, 1169, 1129, 1093, 1051, 987, 702 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.30-7.27 (m, 2H), 7.25-7.20 (m, 1H), 7.10-7.07 (m, 2H), 6.55 (d, *J*=7.5 Hz, 1H), 6.11 (s, 1H), 4.84 (dt, *J*=7.5 Hz, *J*=6.0 Hz, 1H), 3.72 (s, 3H), 3.17 (dd, *J*=14.0 Hz, *J*=6.0 Hz, 1H), 3.09 (dd, *J*=14.0 Hz, *J*=6.0 Hz, 1H), 2.59 (d, *J*=14.5 Hz, 1H), 2.52 (d, *J*=14.5 Hz, 1H), 1.60 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=171.7, 168.8, 135.8, 129.3, 128.8, 127.3, 125.9 (q, *J*=285.0 Hz), 59.7 (q, *J*=27.5 Hz), 56.5, 53.4, 52.6, 41.9, 37.5, 22.7, 19.8.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.9 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{19}H_{27}F_3N_2NaO_4S$: 459.1541; found : 459.1547.

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Aib-OMe 9d. According to the *general procedure A*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (103 mg, 0.37 mmol) reacted with H-Aib-OMe.HCl (117 mg, 0.76 mmol, 2.0 equiv), EDCI.HCl (160 mg, 0.84 mmol, 2.2 equiv), HOBt.xH_2O (120 mg, 0.88 mmol, 2.4 equiv) and DIPEA (270 µL, 1.52 mmol, 4.1 equiv) in CH_3CN (2 mL) for 20h. After work-up, the dipeptide **9d** (137 mg, 98%) was obtained as a white solid. An analytical sample of **9d** was crystallized from CH_2Cl_2-*n*-hexane by slow evaporation.

Mp 120°C; $[\alpha]_D^{20}$ -2 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3234, 3055, 2992, 1743, 1659, 1555, 1471, 1433, 1382, 1332, 1284, 1181, 1096, 1050, 929, 609, 564 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.24 (s, 1H), 5.66 (s, 1H), 3.70 (s, 3H), 2.57 (br s, 2H), 1.60 (s, 3H), 1.56 (s, 3H), 1.47 (s, 3H), 1.25 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=175.2, 167.8, 125.6 (q, *J*=285.0 Hz), 60.3 (q, *J*=28.0 Hz), 56.9, 56.7, 52.8, 43.9, 25.6, 24.1, 22.7, 20.7.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.2 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{14}H_{25}F_3N_2NaO_4S$: 397.1385; found : 397.1378.

Ac-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe 9e. According to the *general procedure A*, Ac-(*R*)-β^3-Tfm-β^3-hAla-OH **(*R*)-7a** (113 mg, 0.53 mmol) reacted with H-Ala-OMe.HCl (158 mg, 1.13 mmol, 2.1 equiv), EDCI.HCl (230 mg, 1.20 mmol, 2.3 equiv), HOBt.xH_2O (174 mg, 1.29 mmol, 2.4 equiv) and DIPEA (370 µL, 2.12 mmol, 4.0 equiv) in CH_3CN (2 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 30:1) afforded the dipeptide **9e** as a yellow oil (122 mg, 77%).

$[\alpha]_D^{20}$ +32 (*c* 1.01, $CHCl_3$).

IR (film): 3309, 3078, 3000, 2955, 2852, 1746, 1682, 1537, 1456, 1376, 1303, 1159, 1102, 1058, 983, 757, 662 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ=6.84 (d, *J*=7.5 Hz, 1H), 6.42 (s, 1H), 4.50 (quint, *J*=7.5 Hz, 1H), 3.70 (s, 3H), 3.48 (d, *J*=13.5 Hz, 1H), 2.37 (d, *J*=13.5 Hz, 1H), 2.03 (s, 3H), 1.58 (s, 3H), 1.36 (d, *J*=7.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.1, 172.0, 168.5, 126.0 (q, *J*=286.5 Hz), 58.5 (q, *J*=29.0 Hz), 52.5, 48.2, 38.5, 24.8, 20.7, 17.9.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.2 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{11}H_{17}F_3N_2NaO_4$: 321.1038; found : 321.1042.

Cbz-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe 9f. According to the *general procedure A*, Cbz-(*R*)-β^3-Tfm-β^3-hAla-OH **(*R*)-7b** (111 mg, 0.36 mmol) reacted with H-Ala-OMe.HCl (101 mg, 0.73 mmol, 2.0 equiv), EDCI.HCl (154 mg, 0.81 mmol, 2.2 equiv), HOBt.xH_2O (108 mg, 0.80 mmol, 2.2 equiv) and DIPEA (260 µL, 1.46 mmol, 4.0 equiv) in CH_3CN (2 mL) for 20h. Purification on SiO_2 (petroleum ether/AcOEt 1:1 to 0:100) afforded the dipeptide **9f** as a pale yellow oil (99 mg, 70%).

$[\alpha]_D^{20}$ +34 (*c* 0.86, $CHCl_3$).

IR (film): 3327, 3067, 3035, 2997, 2954, 1740, 1662, 1538, 1456, 1384, 1166, 1098, 1067, 971, 748, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ=7.37-7.30 (m, 5H), 6.82 (d, *J*=7.5 Hz, 1H), 5.61 (s, 1H), 5.13 (d, *J*=12.0 Hz, 1H), 5.09 (d, *J*=12.0 Hz, 1H), 4.53 (quint, *J*=7.5 Hz, 1H), 3.69 (s, 3H), 3.45 (d, *J*=13.5 Hz, 1H), 2.40 (d, *J*=13.5 Hz, 1H), 1.57 (s, 3H), 1.33 (d, *J*=7.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.1, 167.9, 155.5, 136.0, 128.6, 128.4, 128.3, 126.1 (q, *J*=287.0 Hz), 67.3, 57.8 (q, *J*=28.5 Hz), 52.5, 48.1, 38.2, 20.6, 18.1.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.0 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{17}H_{21}F_3N_2NaO_5$: 413.1300; found : 413.1292.

Ac-(*R*)-β^3-Tfm-β^3-hAla-Leu-OMe 9g. According to the *general procedure A*, Ac-(*R*)-β^3-Tfm-β^3-hAla-OH **(*R*)-7a** (154 mg, 0.72 mmol) reacted with H-Leu-OMe.HCl (262 mg, 1.44 mmol, 2.0 equiv), EDCI.HCl (304 mg, 1.59 mmol, 2.2 equiv), HOBt.H_2O (216 mg, 1.60 mmol, 2.2 equiv) and DIPEA (510 µL, 2.90 mmol, 4.0 equiv) in CH_3CN (2 mL) for 20h. After work-up, the dipeptide **9g** (244 mg, 99%) was obtained as a white solid.

Mp 95°C; $[\alpha]_D^{20}$+25 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3373, 3310, 3088, 2963, 2874, 1748, 1679, 1563, 1450, 1375, 1308, 1272, 1210, 1167, 1100, 1035, 985, 736, 650 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ=6.70 (br s, 1H), 6.24 (br s, 1H), 4.52 (td, *J*=9.0 Hz, *J*=4.5 Hz, 1H), 3.69 (s, 3H), 3.57 (d, *J*=13.0 Hz, 1H), 2.37 (d, *J*=13.0 Hz, 1H), 2.04 (s, 3H), 1.67-1.59 (m, 2H), 1.57 (s, 3H), 1.52-1.47 (m, 1H), 0.92 (d, *J*=5.0 Hz, 3H), 0.91 (d, *J*=5.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.2, 172.2, 168.7, 126.0 (q, *J*=286.5 Hz), 58.5 (q, *J*=29.0 Hz), 52.3, 51.0, 41.0, 38.4, 25.0, 24.9, 22.9, 21.8, 20.8.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.3 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{14}H_{23}F_3N_2NaO_4$: 363.1508; found : 363.1504.

Ac-(*R*)-β^3-Tfm-β^3-hAla-Aib-OMe 9h. According to the *general procedure A*, Ac-(*R*)-β^3-Tfm-β^3-hAla-OH **(*R*)-7a** (101 mg, 0.47 mmol) reacted with H-Aib-OMe.HCl (145 mg, 0.94 mmol, 2.0 equiv), EDCI.HCl (201 mg, 1.05 mmol, 2.2 equiv), HOBt.H_2O (142 mg, 1.05 mmol, 2.2 equiv) and DIPEA (330 µL, 1.89 mmol, 4.0 equiv) in CH_3CN (2 mL) for 20h. After work-up, the dipeptide **9h** (129 mg, 88%) was obtained as a beige solid. An analytical sample of **9h** was crystallized from EtOAc by slow evaporation.

Mp 143°C; $[\alpha]_D^{20}$ +39 (*c* 1.02, $CHCl_3$).

IR (KBr plate):3371, 3308, 3061, 2992, 2956, 1735, 1678, 1545, 1443, 1384, 1289, 1212, 1167, 1098, 1028, 974, 920, 760, 648, 605 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ=6.77 (s, 1H), 6.75 (s, 1H), 3.70 (s, 3H), 3.19 (d, *J*=14.0 Hz, 1H), 2.34 (d, *J*=14.0 Hz, 1H), 2.01 (s, 3H), 1.62 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.7, 171.3, 168.3, 126.1 (q, *J*=286.5 Hz), 58.5 (q, *J*=28.5 Hz), 56.4, 52.6, 39.1, 24.9, 24.8, 24.6, 20.6.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-78.8 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{12}H_{19}F_3N_2NaO_4$: 335.1195; found : 335.1199.

Cbz-(*R*)-β^3-Tfm-β^3-hAla-Aib-OMe 9i. According to the *general procedure A*, Cbz-(*R*)-β^3-Tfm-β^3-hAla-OH **(*R*)-7b** (106 mg, 0.35 mmol) reacted with H-Aib-OMe.HCl (107 mg, 0.70 mmol, 2.0 equiv), EDCI.HCl (147 mg, 0.77 mmol, 2.2 equiv), HOBt.xH_2O (105 mg, 0.77 mmol, 2.2 equiv) and DIPEA (250 µL, 1.41 mmol, 4.0 equiv) in CH_3CN (2 mL) for 20h. After work-up, the dipeptide **9i** (124 mg, 89%) was obtained as a beige oil.

$[\alpha]_D^{20}$ +30 (*c* 1.01, $CHCl_3$).

IR (film): 3338, 3063, 3034, 2992, 2952, 1737, 1663, 1527, 1458, 1388, 1287, 1254, 1161, 1098, 1067, 1028, 971, 752, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.40-7.29 (m, 5H), 6.63 (s, 1H), 5.80 (s, 1H), 5.11-5.04 (m, 2H), 3.68 (s, 3H), 3.24 (d, *J*=13.5 Hz, 1H), 2.36 (d, *J*=13.5 Hz, 1H), 1.60 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=174.6, 167.8, 155.3, 136.0, 128.7, 128.4, 128.2, 126.1 (q, *J*=286.5 Hz), 67.1, 57.9 (q, *J*=28.5 Hz), 56.4, 52.6, 38.7, 24.7, 24.6, 20.6.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI : *m/z* [M+Na]$^+$ calcd for $C_{18}H_{23}F_3N_2NaO_5$: 427.1457; found : 427.1464.

(R_S)-*t*BuS(O)-(*S*)-β^3-Tfm-β^3-hAla-Ala-OMe 9j. According to the *general procedure A*, (R_S)-*t*BuS(O)-(*S*)-β^3-Tfm-β^3-hAla-OH **(R_S,*S*)-3** (816 mg, 2.97

mmol) reacted with H-Ala-OMe.HCl (831 mg, 5.96 mmol, 2.0 equiv), EDCI.HCl (1.26 g, 6.57 mmol, 2.2 equiv), HOBt.xH_2O (882 mg, 6.53 mmol, 2.2 equiv) and DIPEA (2.60 mL, 14.93 mmol, 5.0 equiv) in CH_3CN (15 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 13:1) afforded the dipeptide **9j** (807 mg, 76%) as a yellow oil.

$[\alpha]_D^{20}$ +1 (*c* 0.60, $CHCl_3$).

IR (film): 3260, 3075, 2986, 2959, 2877, 2613, 1746, 1660, 1557, 1459, 1384, 1331, 1275, 1159, 1101, 1054, 981, 916, 852, 757, 689, 665 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.44 (br d, *J*=7.0 Hz, 1H), 5.89 (s, 1H), 4.54 (quint, *J*=7.0 Hz, 1H), 3.72 (s, 3H), 2.69 (d, *J*=14.0 Hz, 1H), 2.63 (d, *J*=14.0 Hz, 1H), 1.61 (s, 3H), 1.40 (d, *J*=7.5 Hz, 3H), 1.26 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.0, 168.3, 125.5 (q, *J*=285.0 Hz), 60.5 (q, *J*=28.0 Hz), 56.8, 52.7, 48.4, 43.8, 22.7, 20.9, 17.4.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.1 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{23}F_3N_2NaO_4S$: 383.1228; found : 383.1218.

(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-Leu-OMe 9k. According to the *general procedure A*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OH **(*R*S,*S*)-3** (207 mg, 0.75 mmol) reacted with H-Leu-OMe.HCl (278 mg, 1.53 mmol, 2.0 equiv), EDCI.HCl (317 mg, 1.66 mmol, 2.2 equiv), HOBt.xH_2O (225 mg, 1.67 mmol, 2.2 equiv) and DIPEA (530 µL, 3.04 mmol, 4.0 equiv) in CH_3CN (4 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 13:1) afforded the dipeptide **9k** (212 mg, 70%) as a white solid.

Mp 146°C; $[\alpha]_D^{20}$ +15 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3250, 3089, 2962, 2874, 1755, 1653, 1567, 1471, 1436, 1373, 1335, 1273, 1199, 1156, 1056, 988, 920, 764, 723 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.46 (d, *J*=8.0 Hz, 1H), 5.83 (s, 1H), 4.53 (ddd, *J*=10.0 Hz, *J*=8.0 Hz, *J*=5.0 Hz, 1H), 3.70 (s, 3H), 2.71 (d, *J*=14.0 Hz, 1H), 2.64 (d, *J*=14.0 Hz, 1H), 1.70 (m, 1H), 1.60 (s, 3H), 1.59 (m, 2H), 1.26 (s, 9H), 0.93 (d, *J*=6.5 Hz, 3H), 0.90 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.2; 168.5; 125.4 (q, *J*=284.5 Hz), 60.6 (q, *J*=28.0 Hz), 56.9, 52.5, 51.4, 44.1, 40.4, 25.1, 23.0, 22.7, 21.7, 21.1.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.3 ppm (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{16}H_{29}F_3N_2NaO_4S$: 425.1698; found : 425.1697.

(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-Phe-OMe 9l. According to the *general procedure A*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OH **(*R*S,*S*)-3** (809 mg, 2.94 mmol) reacted with H-Phe-OMe.HCl (1.27 g, 5.88 mmol, 2.0 equiv), EDCI.HCl (1.24 g, 6.47 mmol, 2.2 equiv), HOBt.xH_2O (875 mg, 6.47 mmol, 2.2 equiv) and DIPEA (2.60 mL, 14.93 mmol, 5.1 equiv) in CH_3CN (15 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 13:1) afforded the dipeptide **9l** (1.12 g, 87%) as a white solid.

Mp 143°C; $[\alpha]_D^{20}$ +31 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3277, 3205, 3083, 3032, 2958, 2869, 1754, 1655, 1560, 1440, 1371, 1330, 1271, 1219, 1186, 1159, 1125, 1096, 1054, 984, 919, 759, 702 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.37 (m, 1H), 7.28 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 2H), 5.93 (s, 1H), 4.78 (td, *J*=8.0 Hz, *J*=5.0 Hz, 1H), 3.71 (s, 3H), 3.12 (dd, *J*=14.0 Hz, *J*=5.0 Hz, 1H), 2.99 (dd, *J*=14.0 Hz, *J*=8.0 Hz, 1H), 2.64 (d, *J*=14.0 Hz, 1H), 2.56 (d, *J*=14.0 Hz, 1H), 1.58 (s, 3H), 1.26 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.7, 168.5, 136.1, 129.3, 128.7, 127.2, 125.5 (q, *J*=285.0 Hz), 60.4 (q, *J*=28.5 Hz), 56.8, 54.1, 52.6, 43.6, 37.5, 22.7, 20.8.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.2 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{19}H_{27}F_3N_2NaO_4S$: 459.1541; found: 459.1523.

(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-Pro-OMe 9m. According to the *general procedure A*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OH **(*R*S,*S*)-3** (123 mg, 0.45 mmol) reacted with H-Pro-OMe.HCl (152 mg, 0.92 mmol, 2.0 equiv), EDCI.HCl (196 mg, 1.02 mmol, 2.3 equiv), HOBt.xH_2O (135 mg, 1.00 mmol, 2.2 equiv) and DIPEA (390 µL, 2.24 mmol, 5.0 equiv) in CH_3CN (2 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 15:1) afforded the dipeptide **9m** (148 mg, 86%, mixture of *trans*/*cis* rotamers: 85:15) as a colourless oil.

$[\alpha]_D^{20}$ -120 (*c* 1.00, $CHCl_3$).

IR (film): 3462, 3197, 2959, 2882, 1745, 1633, 1451, 1365, 1323, 1277, 1187, 1157, 1123, 1097, 1064, 963, 916, 866, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ=7.23 (s,1H *cis*), 6.74 (s, 1H *trans*), 4.51 (dd, *J*=8.5 Hz, *J*=3.5 Hz, 1H *trans*), 4.37 (dd, *J*=8.0 Hz, *J*=3.0 Hz, 1H *cis*), 3.73 (s, 3H *cis*), 3.70 (s, 3H *trans*), 3.69-3.63 (m, 2H *cis* and *trans*), 3.63-3.50 (m, 2H *cis* and *trans*), 2.77 (d, *J*=15.0 Hz, 1H *trans*), 2.62 (d, *J*=15.0 Hz, 1H *trans*), 2.60 (d, *J*=16.0 Hz, 1H *cis*), 2.53 (d, *J*=16.0 Hz, 1H *cis*), 2.16 (m, 3H *cis* and *trans*), 2.09-1.95 (m, 3H *cis* and *trans*), 1.92 (m, 2H *cis*), 1.70 (s, 3H *trans*), 1.63 (s, 3H *cis*), 1.24 (s, 9H *cis*), 1.21 (s, 9H *trans*).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=172.1 (*trans*), 172.0 (*cis*), 168.8 (*cis*), 168.6 (*trans*), 126.2 (q, *J*=285.5 Hz, *trans*), 126.0 (q, *J*=285.0 Hz, *cis*), 59.70 (q, *J*=27.5 Hz, *cis*), 59.67 (*cis*), 59.60 (q, *J*=27.5 Hz, *trans*), 58.9 (*trans*), 56.4 (*trans*), 56.3 (*cis*), 52.9 (*cis*), 52.5 (*trans*), 47.6 (*trans*), 46.6 (*cis*), 38.7 (*trans*), 38.6 (*cis*), 31.4 (*cis*), 29.2 (*trans*), 24.7 (*trans*), 22.83 (*cis*), 22.80 (*trans*), 22.5 (*cis*), 20.27 (*trans*), 20.26 (*cis*).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.6 (s, major *trans* rotamer), -79.8 (s, minor *cis* rotamer).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{25}F_3N_2NaO_4S$: 409.1385; found : 409.1391.

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-β-hAla-OMe 10a. According to the *general procedure A*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (404 mg, 1.47 mmol) reacted with H-β-hAla-OMe.HCl (451 mg, 2.94 mmol, 2.0 equiv), EDCI.HCl (622 mg, 3.25 mmol, 2.2 equiv), HOBt.xH_2O (439 mg, 3.25 mmol, 2.2 equiv) and DIPEA (1.05 mL, 6.03 mmol, 4.1 equiv) in CH_3CN (6 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 20:1) afforded the dipeptide **10a** (448 mg, 81%) as a white solid.

Mp 145°C; $[\alpha]_D^{20}$ +27 (*c* 1.02, $CHCl_3$).

IR (KBr plate): 3270, 3156, 3088, 2983, 1737, 1651, 1563, 1463, 1437, 1371, 1303, 1195, 1153, 1126, 1096, 1053, 964, 920, 710, 616 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.64 (d, *J*=8.0 Hz, 1H), 6.42 (s, 1H), 4.31 (m, 1H), 3.67 (s, 3H), 2.55 (d, *J*=14.5 Hz, 1H), 2.52 (m, 2H), 2.45 (d, *J*=14.5 Hz, 1H), 1.63 (s, 3H), 1.24 (s, 9H), 1.21 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.1, 168.4, 126.0 (q, *J*=285.0 Hz), 59.7 (q, *J*=27.5 Hz), 56.5, 51.8, 42.4, 42.2, 39.3, 22.8, 20.0, 19.9.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{25}F_3N_2NaO_4S$: 397.1385, found : 397.1390.

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-β-hPhe-OMe 10b. According to the *general procedure A*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (404 mg, 1.47 mmol) reacted with H-β-hPhe-OMe.HCl (517 mg, 2.25 mmol, 1.5 equiv), EDCI.HCl (629 mg, 3.28 mmol, 2.2 equiv), HOBt.xH_2O (437 mg, 3.23 mmol, 2.2 equiv) and DIPEA (1.02 mL, 5.87 mmol, 4.0 equiv) in CH_3CN (6 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 20:1) afforded the dipeptide **10b** (583 mg, 88%) as a white solid. An analytical sample of **10b** was crystallized from CH_2Cl_2-*n*-hexane by slow evaporation.

Mp 163°C; $[\alpha]_D^{20}$ +35 (*c*1.00, $CHCl_3$).

IR (KBr plate): 3755, 3423, 3283, 2959, 2373, 2339, 1748, 1655, 1557, 1431, 1368, 1268, 1197, 1151, 1091, 1055, 992, 920, 759, 702, 569 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.28 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.5 Hz, 1H), 7.15 (d, *J*=7.5 Hz, 2H), 6.58 (d, *J*=8.0 Hz, 1H), 6.32 (s, 1H), 4.47 (m, 1H), 3.67 (s, 3H), 2.94 (dd, *J*=14.0 Hz, *J*=7.0 Hz, 1H), 2.85 (dd, *J*=14.0 Hz, *J*=8.0 Hz, 1H), 2.54 (d, *J*=14.5 Hz, 1H), 2.53 (dd, *J*=16.5 Hz, *J*=5.5 Hz, 1H), 2.48 (dd, *J*=16.5 Hz, *J*=5.5 Hz, 1H), 2.44 (d, *J*=14.5 Hz, 1H), 1.60 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.3, 168.5, 137.3, 129.2, 128.8, 127.0, 126.0 (q, *J*=285.0 Hz), 59.7 (q, *J*=27.5 Hz), 56.5, 51.9, 47.4, 42.5, 39.6, 36.4, 22.8, 20.0.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{20}H_{29}F_3N_2NaO_4S$: 473.1698; found : 473.1700.

(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-β-hAla-OMe 10c. According to the *general procedure A*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OH **(*R*S,*S*)-3** (101 mg, 0.37 mmol) reacted with H-β-HAla-OMe.HCl (114 mg, 0.74 mmol, 2.0 equiv), EDCI.HCl (158 mg, 0.83 mmol, 2.3 equiv), HOBt.xH_2O (110 mg, 0.82 mmol, 2.2 equiv) and DIPEA (260 µL, 1.49 mmol, 4.1 equiv) in CH_3CN (2 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 20:1) afforded the dipeptide **10c** (108 mg, 79%) as a colourless oil.

$[\alpha]_D^{20}$ -58 (*c* 0.95, $CHCl_3$).

IR (KBr plate): 3270, 3210, 3161, 3095, 2982, 1742, 1651, 1566, 1463, 1432, 1376, 1298, 1269, 1216, 1180, 1124, 1098, 1054, 1015, 969, 922, 724, 620, 573 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.87 (d, *J*=8.5 Hz, 1H), 6.23 (s, 1H), 4.33 (m, 1H), 3.66 (s, 3H), 2.61-2.54 (m, 2H), 2.50 (d, *J*=14.5 Hz, 1H), 2.44 (dd, *J*=15.5 Hz, *J*=6.0 Hz, 1H), 1.61 (s, 3H), 1.26 (s, 9H), 1.20 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.3, 168.0, 125.9 (q, *J*=285.0 Hz), 59.9 (q, *J*=27.5 Hz), 56.6, 51.9, 43.1, 42.4, 39.5, 22.8, 20.5, 20.0.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.4 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{14}H_{25}F_3N_2NaO_4S$: 397.1385; found : 397.1380.

(*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-β-hLeu-OMe 10d. According to the *general procedure A*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-OH **(*R*S,*S*)-3** (103 mg, 0.37 mmol) reacted with H-β-hLeu-OMe.HCl (147 mg, 0.75 mmol, 2.0 equiv), EDCI.HCl (159 mg, 0.83 mmol, 2.2 equiv), HOBt.xH_2O (112 mg, 0.83 mmol, 2.2 equiv) and DIPEA (260 µL, 1.49 mmol, 4.0 equiv) in CH_3CN (2 mL) for 20h. Purification on SiO_2 (CH_2Cl_2/MeOH 20:1) afforded the dipeptide **10d** (118 mg, 76%) as a white solid. An analytical sample of **10d** was crystallized from CH_2Cl_2-cyclohexane by slow evaporation.

Mp 163°C; $[\alpha]_D^{20}$ -55 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3421, 3269, 3210, 3171, 3091, 2963, 2875, 1743, 1652, 1564, 1468, 1433, 1372, 1307, 1273, 1215, 1194, 1155, 1125, 1098, 1057, 1022, 986, 919, 767, 714, 617 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.74 (d, *J*=9.0 Hz, 1H), 6.22 (s, 1H), 4.30 (m, 1H), 3.65 (s, 3H), 2.61 (d, *J*=14.5 Hz, 1H), 2.60 (dd, *J*=15.0 Hz, *J*=4.5 Hz, 1H), 2.52 (d, *J* = 14.5 Hz, 1H), 2.39 (dd, *J*=15.0 Hz, *J*=6.0 Hz, 1H), 1.61 (s, 3H), 1.60 (m, 1H), 1.49 (ddd, *J*=14.0 Hz, *J*=9.5 Hz, *J*=5.5 Hz, 1H), 1.27 (s, 9H), 1.26 (m, 1H), 0.892 (d, *J*=6.5 Hz, 3H), 0.888 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.5, 168.0, 125.8 (q, *J*=285.0 Hz), 60.0 (q, *J*=28.0 Hz), 56.7, 51.9, 44.7, 43.3, 43.2, 38.7, 25.0, 23.0, 22.8, 22.1, 20.7.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.4 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{31}F_3N_2NaO_4S$: 439.1854; found : 439.1861.

Boc-Ala-(*R*)-β³-Tfm-β³-hAla-OMe 11a. According to the *general procedure B*, H-(*R*)-β³-Tfm-β³-hAla-OMe.HCl **(*R*)-4** (748 mg, 3.38 mmol) reacted with Boc-Ala-OH (960 mg, 5.08 mmol, 1.5 equiv), HATU (2.59 g, 6.80 mmol, 2.0 equiv) and DIPEA (2.9 mL, 16.65 mmol, 5.0 equiv) in DMF (15 mL) for 6 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the dipeptide **11a** (1.12 g, 93%) as a white solid. An analytical sample of **11a** was crystallized from Et_2O-*n*-hexane by slow evaporation.

Mp 75°C; $[\alpha]_D^{20}$ -41 (*c* 0.50, $CHCl_3$).

IR (KBr plate): 3514, 3438, 3333, 3252, 3087, 2984, 1721, 1682, 1566, 1447, 1372, 1312, 1254, 1167, 1101, 1020, 864, 765, 666, 621, 547 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.10 (br s, 1H), 4.97 (br s, 1H), 4.13 (m, 1H), 3.67 (s, 3H), 3.36 (m, 1H), 2.63 (d, *J*=15.5 Hz, 1H), 1.65 (s, 3H), 1.44 (s, 9H), 1.32 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.6, 169.7, 156.0, 125.9 (q, *J* = 286.0 Hz), 80.5, 57.7 (q, *J* = 27.5 Hz), 52.1, 50.8, 36.9, 28.4, 19.9, 17.4.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.2 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{23}F_3N_2O_5$+Na^+: 379.1457; found : 379.1465.

Boc-Ala-(*S*)-β³-Tfm-β³-hAla-OMe 11b. According to the *general procedure B*, H-(*S*)-β³-Tfm-β³-hAla-OMe.HCl **(*S*)-4** (213 mg, 0.96 mmol) reacted with Boc-Ala-OH (275 mg, 1.45 mmol, 1.5 equiv), HATU (734 mg, 1.93 mmol, 2.0 equiv) and DIPEA (840 µL, 4.82 mmol, 5.0 equiv) in DMF (5 mL) for 7 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the dipeptide **11b** (276 mg, 81%) as a yellow oil.

$[\alpha]_D^{20}$ -22 (*c* 0.87, $CHCl_3$).

IR (film): 3318, 3087, 2982, 1742, 1686, 1527, 1452, 1370, 1290, 1250, 1167, 1098, 859, 758, 658 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.06 (br s, 1H), 5.12 (br s, 1H), 4.13 (br s, 1H), 3.65 (s, 3H), 3.36 (d, *J*=14.0 Hz, 1H), 2.66 (d, *J*=15.5 Hz, 1H), 1.64 (s, 3H), 1.41 (s, 9H), 1.30 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.7, 169.7, 156.0, 125.9 (q, *J*=286.0 Hz), 80.4, 57.8 (q, *J*=28.5 Hz), 52.1, 50.6, 36.6, 28.3, 20.1, 17.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.8 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{23}F_3N_2NaO_5$: 379.1457; found : 379.1452.

Boc-β-hAla-(*R*)-β³-Tfm-β³-hAla-OMe 12a. According to the *general procedure B*, H-(*R*)-β³-Tfm-β³-hAla-OMe.HCl **(*R*)-4** (107 mg, 0.48 mmol) reacted with Boc-β-hAla-OH (150 mg, 0.74 mmol, 1.5 equiv), HATU (373 mg, 0.98 mmol, 2.0 equiv) and DIPEA (430 µL, 2.47 mmol, 5.1 equiv) in DMF (3 mL) for 7 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the dipeptide **12a** (47 mg, 26%) as a white solid. An analytical sample of **12a** was crystallized from $CHCl_3$-pentane by vapour diffusion.

Mp 98°C; $[\alpha]_D^{20}$ -21 (*c* 0.55, $CHCl_3$).

IR (KBr plate): 3355, 3311, 3100, 2984, 2367, 1756, 1679, 1567, 1531, 1456, 1376, 1281, 1164, 1097, 1060, 957, 902, 657 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ=6.27 (s, 1H), 5.16 (m, 1H), 3.96 (m, 1H), 3.69 (s, 3H), 3.43 (d, *J*=16.0 Hz, 1H), 2.64 (d, *J*=16.0 Hz, 1H), 2.39 (d, *J* = 5.5 Hz, 2H), 1.65 (s, 3H), 1.43 (s, 9H), 1.21 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=171.0, 170.0, 155.5, 125.9 (q, *J*=286.0 Hz), 79.5, 57.8 (q, *J* = 28.5 Hz), 52.2, 44.3, 43.9, 36.6, 28.5, 20.4, 20.3.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{25}F_3N_2NaO_5$: 393.1613; found : 393.1611.

Boc-β-hAla-(*S*)-β³-Tfm-β³-hAla-OMe 12b. According to the *general procedure B*, H-(*S*)-β³-Tfm-β³-hAla-OMe.HCl **(*S*)-4** (116 mg, 0.52 mmol) reacted with Boc-β-HAla-OH (160 mg, 0.79 mmol, 1.5 equiv), HATU (398 mg, 1.05 mmol, 2.0 equiv) and DIPEA (460 µL, 2.64 mmol, 5.1 equiv) in DMF (2 mL) for 8 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the dipeptide **12b** (68 mg, 35%) as a white solid.

Mp 143°C. $[\alpha]_D^{20}$ -10 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3293, 3232, 3090, 2981, 2935, 1737, 1674, 1627, 1564, 1534, 1442, 1367, 1285, 1252, 1176, 1099, 1063, 1013, 939, 906, 853, 782, 664, 579, 509, 463, 425, 404 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ=6.41 (br s, 1H), 5.16 (br s, 1H), 3.96 (sext, *J*=7.0 Hz, 1H), 3.69 (s, 3H), 3.34 (d, *J*=15.5 Hz, 1H), 2.68 (d, *J*=15.5 Hz, 1H), 2.39 (m, 2H), 1.66 (s, 3H), 1.42 (s, 9H), 1.21 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=171.0, 170.0, 155.5, 125.9 (q, *J* = 286.0 Hz), 79.5, 57.9 (q, *J*=28.5 Hz), 52.2, 44.3, 44.0, 36.8, 28.5, 20.5, 20.2.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.6 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{25}F_3N_2NaO_5$: 393.1613; found : 393.1608.

H-Ala-(*R*)-β³-Tfm-β³-hAla-OMe 13. According to the *general procedure C*, Boc-Ala-(*R*)-β³-Tfm-β³-hAla-OMe **11a** (537 mg, 1.51 mmol) reacted with HCl (2N in Et_2O, 8.4 mL) in MeOH (16.8 mL) for 23h leading to the deprotected dipeptide **13** (310 mg, 80%) as an orange oil.

^1H NMR (250 MHz, $CDCl_3$): δ=7.98 (br s, 1H), 3.67 (s, 3H), 3.43 (m, 2H), 2.70 (m, 1H), 1.66 (s, 5H), 1.31 (d, *J*=7.0 Hz, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.1 (s).

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Ala-(*R*)-β³-Tfm-β³-hAla-OMe 14. According to the *general procedure A*, H-Ala-(*R*)-β³-Tfm-β³-hAla-OMe **13** (204 mg, 0.80 mmol) reacted with (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (269 mg, 0.98 mmol, 1.2 equiv), EDCI.HCl (307 mg, 1.60 mmol, 2.0 equiv), HOBt.xH_2O (216 mg, 1.60 mmol, 2.2 equiv) and DIPEA (560 µL, 3.22 mmol, 4.0 equiv) in CH_3CN (4 mL) for 42h. Purification on SiO_2 (petroleum ether/EtOAc 1:1 to 1:4) afforded the tripeptide **14** (264 mg, 65%) as a white solid. An analytical sample of **14** was crystallized from MeOH by slow evaporation. An analytical sample of **14** was crystallized from MeOH by slow evaporation.

Mp 151°C; $[\alpha]_D^{20}$ -19 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3342, 3223, 3051, 2981, 2376, 1732, 1707, 1655, 1531, 1437, 1368, 1332, 1290, 1238, 1187, 1160, 1124, 1100, 1053, 1017, 969, 921, 742, 693, 625, 577, 550 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.00 (s, 1H), 6.93 (m, 1H), 6.08 (s, 1H), 4.45 (quint, *J*=7.0 Hz, 1H), 3.66 (s, 3H), 3.37 (d, *J*=15.5 Hz, 1H), 2.66 (d, *J*=15.5 Hz, 1H), 2.65 (d, *J*=14.5 Hz, 1H), 2.60 (d, *J*=14.5 Hz, 1H), 1.65 (s, 3H), 1.61 (s, 3H), 1.35 (d, *J*=7.0 Hz, 3H), 1.24 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=171.6, 169.7, 169.3, 125.9 (q, *J*=285.0 Hz), 125.8 (q, *J*=286.0 Hz), 59.8 (q, *J*=28.0 Hz), 57.9 (q, *J*=29.0 Hz), 56.6, 52.1, 49.9, 41.9, 36.6, 22.7, 19.9, 19.8, 17.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s, 3F), -79.9 (s, 3F).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{18}H_{29}F_6N_3NaO_5S$: 536.1630; found : 536.1611.

H-(*R*)-β³-Tfm-β³-hAla-Leu-OMe 15b. According to the *general procedure C*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Leu-OMe **9b** (625 mg, 1.55 mmol) reacted with HCl (2N in Et_2O, 10 mL) in MeOH (20 mL) for 15 min leading to the deprotected dipeptide **15b** (455 mg, 98%) as a pale yellow oil.

^1H NMR (600 MHz, $CDCl_3$): δ=8.18 (d, *J*=8.0 Hz, 1H), 4.56 (m, 1H), 3.69 (s, 3H), 2.48 (d, *J*=15.0 Hz, 1H), 2.40 (d, *J*=15.0 Hz, 1H), 1.84 (s, 2H), 1.63 (m, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 1.38 (s, 3H), 0.91 (d, *J*=6.0 Hz, 3H), 0.90 (d, *J*=6.0 Hz, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-84.0 (s).

H-(*R*)-β³-Tfm-β³-hAla-Phe-OMe 15c. According to the *general procedure C*, (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Phe-OMe **9c** (2.37 g, 5.42 mmol) reacted with HCl (2N in Et_2O, 33 mL) in MeOH (66 mL) for 2h leading to the deprotected dipeptide **15c** (1.61 g, 91%) as a white solid.

^1H NMR (600 MHz, $CDCl_3$): δ=8.20 (d, *J*=7.0 Hz, 1H), 7.28 (t, *J*=7.5 Hz, 2H), 7.24 (t, *J*=7.5 Hz, 1H), 7.12 (d, *J*=7.5 Hz, 2H), 4.88 (q, *J*=7.5 Hz, 1H), 3.73 (s, 3H), 3.15 (dd, *J*=14.0 Hz, *J*=5.5 Hz, 1H), 3.07 (dd, *J*=14.0 Hz, *J*=7.0 Hz, 1H), 2.42 (d, *J*=15.0 Hz, 1H), 2.38 (d, *J*=15.0 Hz, 1H), 1.68 (s, 2H), 1.33 (s, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-84.0 (s).

H-(*S*)-β³-Tfm-β³-hAla-Ala-OMe 15d. According to the *general procedure C*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-Ala-OMe **9j** (807 mg, 2.24 mmol) reacted with HCl (2N in Et_2O, 14 mL) in MeOH (20 mL) for 3h30 leading to the deprotected dipeptide **15d** (527 mg, 92%) as a yellow oil.

^1H NMR (600 MHz, $CDCl_3$): δ=7.94 (d, *J*=7.0 Hz, 1H), 4.59 (quint, *J*=7.0 Hz, 1H), 3.74 (s, 3H), 2.52 (d, *J*=15.0 Hz, 1H), 2.43 (d, *J*=15.0 Hz, 1H), 2.07 (br s, 2H), 1.42 (d, *J*=7.0 Hz, 3H), 1.34 (s, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-83.6 (s).

H-(*S*)-β³-Tfm-β³-hAla-Phe-OMe 15e. According to the *general procedure C*, (*R*S)-*t*BuS(O)-(*S*)-β³-Tfm-β³-hAla-Phe-OMe **9l** (532 mg, 1.22 mmol) reacted with HCl (2N in Et_2O, 8 mL) in MeOH (16 mL) for 2h30 leading to the deprotected dipeptide **15e** (379 mg, 94%) as a yellow oil.

^1H NMR (600 MHz, $CDCl_3$): δ=7.94 (d, *J*=7.5 Hz, 1H), 7.30-7.27 (m, 2H), 7.23 (m, 1H), 7.17 (d, *J* = 7.0 Hz, 2H), 4.87 (td, *J*=7.5 Hz, *J*=5.5 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J*=14.0 Hz, *J*=5.5 Hz, 1H), 3.03 (dd, *J*=14.0 Hz, *J*=8.0 Hz,

1H), 2.46 (d, *J*=15.5 Hz, 1H), 2.36 (d, *J*=15.5 Hz, 1H), 1.81 (s, 2H), 1.05 (s, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-83.8 (s).

H-(*R*)-β^3-Tfm-β^3-hAla-β-hPhe-OMe 16a. According to the *general procedure C*, (S_S)-*t*BuS(O)-(*R*)-β^3-Tfm-β^3-hAla-β-hPhe-OMe **10b** (272 mg, 0.60 mmol) reacted with HCl (2N in Et_2O, 5 mL) in MeOH (10 mL) for 2h30 leading to the deprotected dipeptide **16a** (204 mg, 98%) as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.70 (br d, *J*=8.5 Hz, 1H), 7.29 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.5 Hz, 1H), 7.18 (d, *J*=7.5 Hz, 2H), 4.51 (m, 1H), 3.68 (s, 3H), 2.94 (dd, *J*=13.5 Hz, *J*=7.0 Hz, 1H), 2.86 (dd, *J*=13.5 Hz, *J*=7.5 Hz, 1H), 2.57 (dd, *J*=16.0 Hz, *J*=5.0 Hz, 1H), 2.49 (dd, *J*=16.0 Hz, *J*=6.0 Hz, 1H), 2.39 (d, *J*=15.0 Hz, 1H), 2.33 (d, *J*=15.0 Hz, 1H), 1.76 (s, 2H), 1.24 (s, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-83.1 (s).

H-(*S*)-β^3-Tfm-β^3-hAla-β-hAla-OMe 16b. According to the *general procedure C*, (R_S)-*t*BuS(O)-(*S*)-β^3-Tfm-β^3-hAla-β-hAla-OMe **10c** (249 mg, 0.67 mmol) reacted with HCl (2N in Et_2O, 5 mL) in MeOH (10 mL) for 3h30 leading to the deprotected dipeptide **16b** (172 mg, 96%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ=7.65 (br d, *J*=7.0 Hz, 1H), 4.35 (m, 1H), 3.67 (s, 3H), 2.52 (d, *J*=5.5 Hz, 2H), 2.43 (d, *J*=15.0 Hz, 1H), 2.37 (d, *J*=15.0 Hz, 1H), 2.06 (s, 2H), 1.32 (s, 3H), 1.23 (d, *J*=7.0 Hz, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-83.3 (s).

H-(*S*)-β^3-Tfm-β^3-hAla-β-hLeu-OMe 16c. According to the *general procedure C*, (R_S)-*t*BuS(O)-(*S*)-β^3-Tfm-β^3-hAla-β-hLeu-OMe **10d** (255 mg, 0.61 mmol) reacted with HCl (2N in Et_2O, 5 mL) in MeOH (10 mL) for 2h30 leading to the deprotected dipeptide **16c** (179 mg, 93%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ=7.52 (s, 1H), 4.30 (m, 1H), 3.65 (s, 3H), 2.54 (dd, *J*=15.5 Hz, *J*=5.5 Hz, 1H), 2.48 (dd, *J*=15.5 Hz, *J*=5.5 Hz, 1H), 2.44 (d, *J*=15.0 Hz, 1H), 2.37 (d, *J*=15.0 Hz, 1H), 1.85 (s, 2H), 1.61 (m, 1H), 1.51 (ddd, *J*=14.0 Hz, *J*=9.5 Hz, *J*=5.5 Hz, 1H), 1.31 (s, 3H), 1.30 (m, 1H), 0.90 (d, *J*=6.5 Hz, 6H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-83.2 (s).

Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe 17a. According to the *general procedure B*, H-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe **15a** (113 mg, 0.44 mmol) reacted with Boc-Ala-OH (126 mg, 0.67 mmol, 1.5 equiv), HATU (336 mg, 0.88 mmol, 2.0 equiv) and DIPEA (385 µL, 2.21 mmol, 5.0 equiv) in DMF (3 mL) for 7 days. Purification on SiO_2 (petroleum ether/EtOAc 2:3) afforded the tripeptide **17a** (156 mg, 83%) as a pale yellow oil.

$[\alpha]_D^{20}$ -48 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3612, 3486, 3278, 3099, 2986, 1755, 1690, 1659, 1584, 1555, 1456, 1389, 1301, 1258, 1177, 1099, 1071, 1026, 988, 962, 889, 852, 780, 673, 628, 568, 519, 486, 454 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.13 (br s, 1H), 6.93 (d, *J*=7.5 Hz, 1H), 5.46 (br s, 1H), 4.46 (m, 1H), 4.15 (br s, 1H), 3.67 (s, 3H), 3.60 (d, *J*=13.0 Hz, 1H), 2.32 (d, *J*=13.0 Hz, 1H), 1.51 (s, 3H), 1.36 (s, 9H), 1.31 (d, *J*=7.0 Hz, 3H), 1.27 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=174.1, 173.8, 168.8, 156.2, 126.0 (q, *J*=286.5 Hz), 80.2, 58.2 (q, *J*=29.0 Hz), 52.4, 50.6, 48.1, 37.9, 28.2, 20.3, 17.7, 17.0.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.4 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{17}H_{28}F_3N_3NaO_6$: 450.1828; found : 450.1833.

Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Leu-OMe 17b. According to the *general procedure B*, H-(*R*)-β^3-Tfm-β^3-hAla-Leu-OMe **15b** (413 mg, 1.39 mmol) reacted with Boc-Ala-OH (394 mg, 2.08 mmol, 1.5 equiv), HATU (1.04 g, 2.77 mmol, 2.0 equiv) and DIPEA (1.20 mL, 6.89 mmol, 5.0 equiv) in DMF (10 mL) for 5 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the tripeptide **17b** (516 mg, 79%) as a pale yellow oil.

$[\alpha]_D^{20}$ -37 (*c* 1.01, $CHCl_3$).

IR (film): 3316, 3079, 2962, 2875, 2252, 1681, 1529, 1452, 1369, 1327, 1248, 1164, 1100, 1067, 1026, 986, 916, 858, 758, 666 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ=6.87 (br s, 1H), 6.62 (br s, 1H), 5.49 (br s, 1H), 4.56 (m, 1H), 4.21 (m, 1H), 3.76 (d, *J*=13.0 Hz, 1H), 3.72 (s, 3H), 2.35 (d, *J*=13.0 Hz, 1H), 1.54 (s, 3H), 1.62 (m, 1H), 1.56 (m, 1H), 1.51 (m, 1H), 1.43 (s, 9H), 1.33 (d, *J*=7.0 Hz, 3H), 0.92 (d, *J*=6.0 Hz, 3H), 0.91 (d, *J*=6.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.3, 174.2, 168.4, 156.6, 126.0 (q, *J*=286.5 Hz), 80.5, 58.2 (q, *J*=29.0 Hz), 52.5, 50.8, 50.6, 41.2, 37.9, 28.4, 25.0, 23.0, 21.8, 20.8, 16.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.5 (s).

HRMS-ESI : *m/z* [M+Na]$^+$ calcd for $C_{20}H_{34}F_3N_3NaO_6$: 492.2297; found : 492.2311.

Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Phe-OMe 17c. According to the *general procedure B*, H-(*R*)-β^3-Tfm-β^3-hAla-Phe-OMe **15c** (336 mg, 1.01 mmol) reacted with Boc-Ala-OH (289 mg, 1.53 mmol, 1.5 equiv), HATU (773 mg, 2.03 mmol, 2.0 equiv) and DIPEA (700 µL, 4.02 mmol, 4.0 equiv) in DMF (6 mL) for 5 days. Purification on SiO_2 (petroleum ether/EtOAc 3:7) afforded the tripeptide **17c** (508 mg, 99%) as a colourless oil.

$[\alpha]_D^{20}$ -11 (*c* 0.80, $CHCl_3$).

IR (film): 3313, 3068, 2980, 2638, 2451, 2289, 1953, 1671, 1530, 1451, 1369, 1249, 1164, 1128, 1100, 1067, 1027, 992, 913, 857, 757, 701, 668, 407 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ=7.29 (t, *J*=7.5 Hz, 2H), 7.24 (t, *J*=7.5 Hz, 1H), 7.11 (d, *J*=7.5 Hz, 2H), 6.92 (br s, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 5.36 (br d, *J*=7.0 Hz, 1H), 4.81 (m, 1H), 4.16 (m, 1H), 3.71 (s, 3H), 3.67 (d, *J*=13.0 Hz, 1H), 3.09 (dd, *J*=14.0 Hz, *J*=5.5 Hz, 1H), 2.98 (dd, *J*=14.0 Hz, *J*=7.5 Hz, 1H), 2.29 (d, *J*=13.0 Hz, 1H), 1.50 (s, 3H), 1.43 (s, 9H), 1.22 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.1, 172.6, 168.2, 156.4, 135.7, 129.2, 128.8, 127.4, 125.9 (q, *J*=286.5 Hz), 80.5, 58.1 (q, *J*=29.0 Hz), 53.4, 52.5, 50.5, 37.9, 28.4, 20.6, 16.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.5 (s).

HRMS-ESI: *m/z* [M+Na]$^+$ calcd for $C_{23}H_{32}F_3N_3NaO_6$: 526.2141; found : 526.2134.

Boc-Leu-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe 17d. According to the *general procedure B*, H-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe **15a** (512 mg, 2.00 mmol) reacted with Boc-Leu-OH (699 mg, 3.02 mmol, 1.5 equiv), HATU (1.53 g, 4.02 mmol, 2.0 equiv) and DIPEA (1.75 mL, 10.05 mmol, 5.1 equiv) in DMF (12 mL) for 5 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the tripeptide **17d** (413 mg, 44%) as a pale yellow oil.

$[\alpha]_D^{20}$ -46 (*c* 1.02, $CHCl_3$).

IR (KBr plate): 3371, 3324, 3284, 3064, 2965, 2874, 2370, 1745, 1702,

1650, 1549, 1457, 1388, 1367, 1286, 1245, 1171, 1103, 1048, 983, 853, 789, 749, 693, 631, 603, 472, 446 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.87 (s, 1H), 6.78 (br s, 1H), 5.26 (br d, *J*=7.0 Hz, 1H), 4.55 (m, 1H), 4.10 (m, 1H), 3.74 (s, 3H), 3.71 (d, *J*=13.0 Hz, 1H), 2.36 (d, *J*=13.0 Hz, 1H), 1.75-1.65 (m, 2H), 1.54 (s, 3H), 1.46 (m, 1H), 1.42 (br s, 9H), 1.37 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.0, 173.9, 168.0, 156.6, 126.0 (q, *J*=286.5 Hz), 80.5, 58.2 (q, *J*=29.0 Hz), 53.5, 52.7, 48.2, 39.6, 38.1, 28.4, 24.8, 23.1, 22.1, 20.7, 18.1.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.4 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{20}H_{34}F_3N_3NaO_6$: 492.2297; found : 492.2318.

Boc-Leu-(*R*)-β³-Tfm-β³-hAla-Leu-OMe 17e. According to the *general procedure B*, H-(*R*)-β³-Tfm-β³-hAla-Leu-OMe **15b** (426 mg, 1.43 mmol) reacted with Boc-Leu-OH (496 mg, 2.14 mmol, 1.5 equiv), HATU (1.09 g, 2.88 mmol, 2.0 equiv) and DIPEA (1.25 mL, 7.18 mmol, 5.0 equiv) in DMF (10 mL) for 5 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the tripeptide **17e** (361 mg, 49%) as a colourless oil.

$[\alpha]_D^{20}$ -39 (*c* 1.00, $CHCl_3$).

IR (film): 3312, 3077, 2960, 2873, 2726, 2401, 2288, 1668, 1536, 1460, 1370, 1158, 1102, 1048, 1022, 987, 922, 873, 851, 757, 665, 616, 410 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.88 (br s, 1H), 6.66 (br d, *J*=7.5 Hz, 1H), 5.32 (br d, *J*=7.5 Hz, 1H), 4.57 (m, 1H), 4.12 (m, 1H), 3.71-3.68 (m, 4H), 2.35 (d, *J*=13.0 Hz, 1H), 1.54 (s, 3H), 1.75-1.47 (m, 6H), 1.42 (s, 9H), 0.94-0.89 (m, 12H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.1, 173.1, 168.3, 156.7, 126.0 (q, *J*=286.5 Hz), 80.4, 58.2 (q, *J* = 28.5 Hz), 53.4, 52.5, 50.8, 41.3, 39.6, 38.0, 28.4, 25.0, 24.8, 23.2, 23.0, 22.0, 21.8, 20.7.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.4 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{23}H_{40}F_3N_3NaO_6$: 534.2767; found : 534.2761.

Boc-Ala-(*S*)-β³-Tfm-β³-hAla-Ala-OMe 17f. According to the *general procedure B*, H-(*S*)-β³-Tfm-β³-hAla-Ala-OMe **15d** (416 mg, 1.63 mmol) reacted with Boc-Ala-OH (463 mg, 2.45 mmol, 1.5 equiv), HATU (1.24 g, 3.26 mmol, 2.0 equiv) and DIPEA (1.20 mL, 6.89 mmol, 4.2 equiv) in DMF (7 mL) for 7 days. Purification on SiO_2 (petroleum ether/EtOAc 3:7) afforded the tripeptide **17f** (559 mg, 80%) as a colourless oil.

$[\alpha]_D^{20}$ -36 (*c* 1.01, $CHCl_3$).

IR (film): 3329, 3083, 2985, 2369, 1748, 1690, 1534, 1457, 1374, 1293, 1252, 1217, 1163, 1099, 1062, 1024, 982, 855, 783, 760, 654, 615, 559, 450 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.42 (br s, 1H), 6.74 (m, 1H), 5.05 (d, *J*=7.0 Hz, 1H), 4.55 (quint, *J*=7.0 Hz, 1H), 4.11 (m, 1H), 3.74 (s, 3H), 3.19 (br d, *J*=13.5 Hz, 1H), 2.53 (d, *J*=13.5 Hz, 1H), 1.66 (s, 3H), 1.42 (s, 9H), 1.36 (d, *J*=7.0 Hz, 3H), 1.32 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.6, 173.4, 168.1, 156.0, 126.0 (q, *J*=288.0 Hz), 80.6, 58.7 (q, *J*=29.0 Hz), 52.7, 50.9, 48.2, 39.3, 28.3, 20.7, 18.0, 17.4.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.0 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{17}H_{28}F_3N_3NaO_6$: 450.1828; found : 450.1824.

Boc-Ala-(*S*)-β³-Tfm-β³-hAla-Phe-OMe 17g According to the *general procedure B*, H-(*S*)-β³-Tfm-β³-hAla-Phe-OMe **15e** (155 mg, 0.47 mmol) reacted with Boc-Ala-OH (136 mg, 0.72 mmol, 1.5 equiv), HATU (357 mg, 0.94 mmol, 2.0 equiv) and DIPEA (330 µL, 1.89 mmol, 4.1 equiv) in DMF (3 mL) for 5 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the tripeptide **17g** (173 mg, 74%) as a colourless oil.

$[\alpha]_D^{20}$ -2 (*c* 1.01, $CHCl_3$).

IR (KBr plate): 3324, 3072, 2982, 2371, 1745, 1688, 1528, 1452, 1372, 1252, 1221, 1167, 1099, 1066, 1027, 858, 749, 701, 664, 605, 449 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.41 (br s, 1H), 7.29 (t, *J*=7.5 Hz, 2H), 7.24 (t, *J*=7.5 Hz, 1H), 7.12 (d, *J*=7.5 Hz, 2H), 6.61 (br s, 1H), 4.99 (br d, *J*=6.5 Hz, 1H), 4.84 (q, *J*=6.5 Hz, 1H), 4.02 (m, 1H), 3.70 (s, 3H), 3.20 (d, *J*=14.0 Hz, 1H), 3.07 (m, 2H), 2.52 (d, *J*=14.0 Hz, 1H), 1.61 (s, 3H), 1.44 (s, 9H), 1.24 (br d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=173.5, 172.0, 168.2, 156.0, 135.9, 129.2, 128.7, 127.3, 126.0 (q, *J*=286.5 Hz), 80.5, 58.6 (q, *J*=28.5 Hz), 53.4, 52.5, 50.6, 39.2, 37.8, 28.3, 20.6, 17.3.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.1 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{23}H_{32}F_3N_3NaO_6$: 526.2141; found : 526.2147.

Boc-β-hAla-(*R*)-β³-Tfm-β³-hAla-β-hPhe-OMe 18a. According to the *general procedure B*, H-(*R*)-β³-Tfm-β³-hAla-β-hPhe-OMe **16a** (103 mg, 0.30 mmol) reacted with Boc-β-hAla-OH (93 mg, 0.46 mmol, 1.5 equiv), HATU (227 mg, 0.60 mmol, 2.0 equiv) and DIPEA (210 µL, 1.21 mmol, 4.1 equiv) in DMF (2 mL) for 3 days. Purification on SiO_2 (petroleum ether/EtOAc 3:7) afforded the tripeptide **18a** (90 mg, 57%) as a colourless oil.

$[\alpha]_D^{20}$ -9 (*c* 0.90, $CHCl_3$).

IR (KBr plate):3325, 3078, 2978, 2934, 1737, 1687, 1531, 1451, 1370, 1308, 1256, 1163, 1099, 1057, 849, 748, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.29 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 2H), 7.03 (s, 1H), 6.63 (d, *J*=8.5 Hz, 1H), 5.21 (br s, 1H), 4.48 (m, 1H), 3.96 (m, 1H), 3.67 (s, 3H), 3.14 (br d, *J*=14.0 Hz, 1H), 2.89 (dd, *J*=13.5 Hz, *J*=7.5 Hz, 1H), 2.83 (dd, *J*=13.5 Hz, *J*=7.5 Hz, 1H), 2.51 (dd, *J*=16.0 Hz, *J*=5.0 Hz, 1H), 2.43-2.39 (m, 2H), 2.34 (m, 1H), 2.31 (d, *J*=14.0 Hz, 1H), 1.58 (s, 3H), 1.42 (s, 9H), 1.20 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.1, 171.9, 168.1, 155.6, 137.4, 129.3, 128.8, 127.0, 126.1 (q, *J*=287.0 Hz), 79.6, 58.4 (q, *J*=28.5 Hz), 51.9, 47.6, 44.3, 44.2, 40.1, 39.4, 37.4, 28.5, 20.7, 20.4.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-78.6 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{25}H_{36}F_3N_3NaO_6$: 554.2454; found : 554.2437.

Boc-β-hAla-(*S*)-β³-Tfm-β³-hAla-β-hAla-OMe 18b. According to the *general procedure B*, H-(*S*)-β³-Tfm-β³-hAla-β-hAla-OMe **16b** (105 mg, 0.39 mmol) reacted with Boc-β-hAla-OH (121 mg, 0.60 mmol, 1.5 equiv), HATU (299 mg, 0.79 mmol, 2.0 equiv) and DIPEA (270 µL, 1.55 mmol, 4.0 equiv) in DMF (2 mL) for 7 days. Purification on SiO_2 (petroleum ether/EtOAc 3:7) afforded the tripeptide **18b** (89 mg, 50%) as a white solid.

Mp 128°C; $[\alpha]_D^{20}$ -28 (*c* 0.90, $CHCl_3$).

IR (KBr plate): 3385, 3294, 3096, 2980, 2938, 1746, 1713, 1650, 1561, 1257, 1173, 1099 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.33 (s, 1H), 6.63 (d, *J*=8.0 Hz, 1H), 5.21 (br s, 1H), 4.31 (m, 1H), 3.99 (m, 1H), 3.68 (s, 3H), 2.90 (d, *J*=14.0 Hz, 1H), 2.53 (dd, *J*=16.0 Hz, *J*=5.5 Hz, 1H), 2.50 (dd, *J*=16.0 Hz, *J*=5.5 Hz, 1H), 2.45 (d, *J*=14.0 Hz, 2H), 2.34 (dd, *J*=14.5 Hz, *J*=6.0 Hz, 1H), 1.68 (s, 3H), 1.41 (s, 9H), 1.20 (d, *J*=6.5 Hz, 3H), 1.19 (d, *J*=6.5 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.1, 171.5, 168.1, 155.6, 126.1 (q, *J*=287.0 Hz), 79.5, 58.6 (q, *J*=28.5 Hz), 51.9, 44.3, 44.2, 42.3, 40.1, 39.7, 28.5, 20.7, 20.5, 19.9.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-78.3 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{19}H_{32}F_3N_3NaO_6$: 478.2141; found : 478.2125.

Boc-β-hAla-(*S*)-β^3-Tfm-β^3-hAla-β-hLeu-OMe 18c. According to the *general procedure B*, H-(*S*)-β^3-Tfm-β^3-hAla-β-hLeu-OMe **16c** (105 mg, 0.34 mmol) reacted with Boc-β-hAla-OH (103 mg, 0.50 mmol, 1.5 equiv), HATU (268 mg, 0.71 mmol, 2.1 equiv) and DIPEA (235 µL, 1.35 mmol, 4.0 equiv) in DMF (2 mL) for 3 days. Purification on SiO_2 (petroleum ether/EtOAc 1:1) afforded the tripeptide **18c** (92 mg, 56%) as a white solid.

Mp 143°C; $[\alpha]_D^{20}$ -30 (*c* 0.90, $CHCl_3$).

IR (KBr plate): 3325, 3078, 2978, 1737, 1687, 1531, 1451, 1370, 1256, 1163, 1099, 1057, 748, 701 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.40 (s, 1H), 6.50 (br d, *J*=8.0 Hz, 1H), 5.18 (br s, 1H), 4.29 (m, 1H), 4.00 (m, 1H), 3.67 (s, 3H), 2.87 (d, *J*=14.0 Hz, 1H), 2.55 (dd, *J*=15.5 Hz, *J*=5.0 Hz, 1H), 2.48-2.44 (m, 3H), 2.32 (dd, *J*=14.5 Hz, *J*=6.0 Hz, 1H), 1.68 (s, 3H), 1.57 (m, 1H), 1.47 (ddd, *J*=14.0 Hz, *J*=9.5 Hz, *J*=5.5 Hz, 1H), 1.42 (s, 9H), 1.26 (ddd, *J*=14.0 Hz, *J*=8.5 Hz, *J*=5.5 Hz, 1H), 1.20 (d, *J*=6.5 Hz, 3H), 0.89 (d, *J*=6.5 Hz, 6H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=172.3, 171.4, 168.2, 155.6, 126.1 (q, *J*=287.0 Hz), 79.5, 58.6 (q, *J*=28.5 Hz), 51.9, 44.5, 44.3, 44.2, 43.1, 40.3, 38.8, 28.5, 25.0, 23.0, 22.0, 20.7, 20.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-78.2 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{22}H_{38}F_3N_3NaO_6$: 520.2610; found : 520.2605.

Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Ala-NHMe 19a. According to the *general procedure D*, reaction of Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe **17a** (104 mg, 0.24 mmol) and $MeNH_2$ (2N in MeOH, 605 µL, 1.21 mmol, 5.0 equiv) in MeOH (750 µL) for 4d gave the dipeptide **19a** (103 mg, 100%) as a colourless oil.

$[\alpha]_D^{20}$ -54 (*c* 1.03, $CHCl_3$).

IR (KBr plate): 3313, 3087, 2983, 2940, 1686, 1536, 1455, 1373, 1291, 1251, 1166, 1099, 1066, 1026, 858, 757, 663, 529, 452 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ=6.91 (br s, 1H), 6.66 (m, 1H), 6.13 (m, 1H), 5.77 (m, 1H), 4.34 (quint, *J*=7.0 Hz, 1H), 4.20 (m, 1H), 3.65 (d, *J*=13.5 Hz, 1H), 2.82 (d, *J*=5.0 Hz, 3H), 2.37 (d, *J*=13.5 Hz, 1H), 1.55 (s, 3H), 1.45 (s, 9H), 1.36 (d, *J*=7.0 Hz, 3H), 1.34 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.5, 173.1, 168.4, 156.6, 126.0 (q, *J*=286.5 Hz), 80.4, 58.2 (q, *J*=29.0 Hz), 50.8, 49.0, 38.3, 28.4, 26.4, 20.6, 18.2, 16.8.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{17}H_{29}F_3N_4NaO_5$: 449.1988; found : 449.1976.

Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Leu-NHMe 19b. According to the *general procedure D*, reaction of Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Leu-OMe **17b** (108 mg, 0.23 mmol) and $MeNH_2$ (2N in MeOH, 3x575 µL, 3x1.15 mmol, 3x5.0 equiv at t = 0, 5d and 6d) in MeOH (650 µL) for 7d gave the dipeptide **19b** (93 mg, 87%) as a white foamy solid.

$[\alpha]_D^{20}$ -51 (*c* 1.02, $CHCl_3$).

IR (KBr plate): 3311, 3088, 2965, 2878, 2815, 2378, 1653, 1540, 1456, 1372, 1286, 1254, 1168, 1100, 1069, 1024, 955, 858, 758, 652, 623, 471 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=6.95 (br s, 1H), 6.71 (m, 1H), 6.33 (m, 1H), 5.89 (br d, *J*=6.5 Hz, 1H), 4.32 (td, *J*=8.5 Hz, *J*=5.5 Hz, 1H), 4.22 (m, 1H), 3.66 (d, *J*=13.0 Hz, 1H), 2.80 (d, *J*=4.5 Hz, 3H), 2.35 (d, *J*=13.0 Hz, 1H), 1.63-1.58 (m, 2H), 1.54 (s, 3H), 1.50-1.46 (m, 1H), 1.44 (s, 9H), 1.36 (d, *J*=7.0 Hz, 3H), 0.92 (d, *J*=6.0 Hz, 3H), 0.89 (d, *J*=6.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.8, 173.0, 168.6, 156.8, 126.0 (q, *J*=286.5 Hz), 80.4, 58.2 (q, *J*=29.0 Hz), 52.0, 50.8, 41.1, 38.2, 28.4, 26.4, 24.9, 23.0, 22.1, 20.7, 16.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{20}H_{35}F_3N_4NaO_5$: 491.2457; found : 491.2456.

Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Phe-NHMe 19c. According to the *general procedure D*, Boc-Ala-(*R*)-β^3-Tfm-β^3-hAla-Phe-OMe **17c** (254 mg, 0.50 mmol) reacted with $MeNH_2$ (2N in MeOH, 1.30 mL, 2.60 mmol, 5.2 equiv) in MeOH (1 mL) for 30h. Purification of the residue on SiO_2 (petroleum ether/EtOAc 1:4) afforded the dipeptide **19c** (237 mg, 93%) as a white solid.

Mp 101°C; $[\alpha]_D^{20}$ -47 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3312, 3086, 3032, 2981, 2939, 2812, 1655, 1540, 1454, 1372, 1288, 1252, 1167, 1100, 1069, 1025, 964, 909, 858, 752, 700, 650, 623, 526, 487, 454 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.27 (t, *J* = 7.0 Hz, 2H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 7.09 (br s, 1H), 6.96 (m, 1H), 6.31 (m, 1H), 5.75 (br s, 1H), 4.57 (q, *J*=7.5 Hz, 1H), 4.22 (m, 1H), 3.51 (d, *J*=13.5 Hz, 1H), 3.01 (dd, *J*=13.5 Hz, *J*=7.5 Hz, 1H), 2.95 (dd, *J*=13.5 Hz, *J*=7.5 Hz, 1H), 2.69 (d, *J*=5.0 Hz, 3H), 2.30 (d, *J*=13.5 Hz, 1H), 1.49 (s, 3H), 1.42 (s, 9H), 1.34 (d, *J*=7.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.5, 171.8, 168.4, 156.6, 136.6, 129.2, 128.8, 127.2, 125.9 (q, *J*=286.5 Hz), 80.4, 58.1 (q, *J*=29.0 Hz), 54.8, 50.7, 38.5, 38.2, 28.4, 26.3, 20.4, 16.9.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.8 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{23}H_{33}F_3N_4NaO_5$: 525.2301; found : 525.2311.

Boc-Leu-(*R*)-β^3-Tfm-β^3-hAla-Ala-NHMe 19d. According to the *general procedure D*, reaction of Boc-Leu-(*R*)-β^3-Tfm-β^3-hAla-Ala-OMe **17d** (105 mg, 0.22 mmol) and $MeNH_2$ (2N in MeOH, 2x560 µL, 2x1.12 mmol, 2x5.0 equiv at t = 0 and 6d) in MeOH (650 µL) for 7d gave the dipeptide **19d** (96 mg, 91%) as a colourless oil.

$[\alpha]_D^{20}$ -58 (*c* 1.02, $CHCl_3$).

IR (KBr plate): 3314, 3083, 2964, 2876, 2815, 1684, 1539, 1457, 1373,

1289, 1252, 1167, 1101, 1049, 1022, 922, 874, 758, 664, 531, 461 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ=6.93 (br s, 1H), 6.64 (m, 1H), 6.21 (m, 1H), 5.49 (m, 1H), 4.38 (m, 1H), 4.09 (m, 1H), 3.57 (d, *J*=13.5 Hz, 1H), 2.82 (br s, 3H), 2.39 (d, *J*=13.5 Hz, 1H), 1.75-1.68 (m, 2H), 1.57 (s, 3H), 1.51 (m, 1H), 1.44 (s, 9H), 1.35 (d, *J*=7.0 Hz, 3H), 0.96 (d, *J*=6.0 Hz, 3H), 0.93 (d, *J*=6.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.3, 173.0, 168.3, 156.7, 126.0 (q, *J*=286.0 Hz), 80.4, 58.2 (q, *J*=29.0 Hz), 53.7, 49.0, 39.8, 38.5, 28.4, 26.5, 24.8, 23.2, 22.0, 20.5, 18.2.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.7 (s).

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{20}H_{35}F_3N_4O_5+Na^+$: 491.2457; found : 491.2465.

Boc-Leu-(*R*)-β³-Tfm-β³-hAla-Leu-NHMe 19e. According to the *general procedure D*, reaction of Boc-Leu-(*R*)-β³-Tfm-β³-hAla-Leu-OMe **17e** (103 mg, 0.20 mmol) and $MeNH_2$ (2N in MeOH, 3x510 µL, 3x1.02 mmol, 3x5.1 equiv at t = 0, 22h and 31h) in MeOH (600 µL) for 4d gave the dipeptide **19e** (89 mg, 86%) as a colourless oil.

$[\alpha]_D^{20}$ -71 (*c* 1.00, $CHCl_3$).

IR (KBr plate): 3311, 3083, 2962, 2876, 2375, 1688, 1658, 1539, 1462, 1387, 1372, 1288, 1253, 1168, 1101, 1049, 1022, 876, 852, 756, 678, 654, 619, 463 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.07 (s, 1H), 6.82 (br s, 1H), 6.52 (br s, 1H), 5.62 (br s, 1H), 4.36 (m, 1H), 4.11 (m, 1H), 3.54 (d, *J*=13.5 Hz, 1H), 2.78 (d, *J*=4.5 Hz, 3H), 2.38 (d, *J*=13.5 Hz, 1H), 1.71-1.65 (m, 2H), 1.64-1.57 (m, 2H), 1.55 (s, 3H), 1.54-1.48 (m, 2H), 1.43 (s, 9H), 0.94 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.0 Hz, 3H), 0.91 (d, *J*=6.5 Hz, 3H), 0.88 (d, *J*=6.0 Hz, 3H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=174.5, 172.9, 168.6, 156.8, 126.0 (q, *J* = 286.5 Hz), 80.4, 58.2 (q, *J*=29.0 Hz), 53.6, 52.0, 41.0, 39.8, 38.5, 28.4, 26.4, 24.9, 24.8, 23.3, 23.0, 22.1, 21.9, 20.5.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.6 (s).

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{23}H_{41}F_3N_4NaO_5$: 533.2927; found : 533.2924.

H-Ala-(*R*)-β³-Tfm-β3-hAla-Ala-OMe 20. According to the *general procedure C*, Boc-Ala-(*R*)-β³-Tfm-β³-hAla-Ala-OMe **17a** (214 mg, 0.50 mmol) reacted with HCl (2N in Et_2O, 3 mL) in MeOH (6 mL) for 5h leading to the deprotected tripeptide **20** (120 mg, 73%) as a yellow oil.

^1H NMR (500 MHz, $CDCl_3$): δ=7.99 (s, 1H), 7.01 (br d, *J*=7.0 Hz, 1H), 4.40 (quint, *J*=7.5 Hz, 1H), 3.70 (d, *J*=13.0 Hz, 1H), 3.65 (s, 2H), 3.41 (q, *J*=7.0 Hz, 1H), 2.34 (d, *J*=13.0 HZ, 1H), 2.11 (s, 2H), 1.52 (s, 3H), 1.30 (d, *J*=7.5 Hz, 3H), 1.27 (d, *J*=7.0 Hz, 3H).

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-80.5 (s).

(*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-Ala-(*R*)-β³-Tfm-β³-hAla-Ala-OMe 21. According to the *general procedure A*, H-Ala-(*R*)-β³-Tfm-β³-hAla-Ala-OMe **20** (92 mg, 0.28 mmol) reacted with (*S*S)-*t*BuS(O)-(*R*)-β³-Tfm-β³-hAla-OH **(*S*S,*R*)-3** (155 mg, 0.56 mmol, 2.0 equiv), EDCI.HCl (117 mg, 0.62 mmol, 2.2 equiv), HOBt.xH_2O (84 mg, 0.62 mmol, 2.2 equiv) and DIPEA (200 µL, 1.15 mmol, 4.1 equiv) in CH_3CN (2 mL) for 39h. Purification on SiO_2 (CH_2Cl_2/MeOH 9:1) afforded the tetrapeptide **21** (116 mg, 71%) as a white solid.

Mp 173°C; $[\alpha]_D^{20}$ -30 (*c* 0.91, $CHCl_3$).

IR (KBr plate): 3300, 3093, 2990, 2960, 1757, 1706, 1657, 1560, 1456, 1385, 1268, 1224, 1157, 1054, 704 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ=7.40 (d, *J*=8.0 Hz, 1H), 6.87 (s, 1H), 6.66 (d, *J*=7.0 Hz, 1H), 5.74 (s, 1H), 4.63 (dq, *J*=8.0 Hz, *J*=7.0 Hz, 1H), 4.46 (quint, *J*=7.0 Hz, 1H), 3.80 (d, *J*=13.0 Hz, 1H), 3.73 (s, 3H), 2.64 (d, *J*=14.5 Hz, 1H), 2.54 (d, *J*=14.5 Hz, 1H), 2.32 (d, *J*=13.0 Hz, 1H), 1.69 (s, 3H), 1.52 (s, 3H), 1.36 (d, *J*=7.5 Hz, 3H), 1.31 (d, *J*=7.0 Hz, 3H), 1.23 (s, 9H).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ=175.1, 173.4, 169.0, 168.2, 126.1 (q, *J*=285.0 Hz), 125.9 (q, *J*=286.5 Hz), 60.0 (q, *J*=27.5 Hz), 58.4 (q, *J*=29.0 Hz), 56.7, 52.6, 49.4, 48.3, 41.8, 37.8, 22.7, 20.6, 19.3, 17.6, 16.8.

^{19}F NMR (235.3 MHz, $CDCl_3$): δ=-79.4 (s, CF_3), -80.4 (s, CF_3).

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}F_6N_4O_6S$: 585.2182; found : 585.2191.

Table 3 Crystal data and structure refinements for peptides **9c**,**d**,**h**, **10b**,**d**, **11a**, **12a** and **14**

peptide	**9c**	**9d**	**9h**	**10b**	**10d**	**11a** . H_2O	**12a**	**14**
empirical formula	$C_{19}H_{27}F_3N_2O_4S$	$C_{14}H_{25}F_3N_2O_4S$	$C_{12}H_{19}F_3N_2O_4$	$C_{20}H_{29}F_3N_2O_4S$	$C_{17}H_{31}F_3N_2O_4S$	$C_{14}H_{25}F_3N_2O_6$	$C_{15}H_{25}F_3N_2O_5$	$C_{18}H_{29}F_6N_3O_5S$
formula weight	436.49	374.42	312.29	450.51	416.50	374.36	370.37	513.50
crystal system	monoclinic	monoclinic	orthorhombic	monoclinic	orthorhombic	tetragonal	orthorhombic	orthorhombic
crystal size (mm^3)	0.2x0.15x0.12	0.2x0.15x0.1	0.24x0.2x0.15	0.2x0.16x0.14	0.2x0.18x0.16	0.25x0.15x0.10	0.16x0.14x0.12	0.24x0.18x0.16
crystallizing solvent	CH_2Cl_2/*n*-hexane	CH_2Cl_2/*n*-hexane	EtOAc	CH_2Cl_2/*n*-hexane	CH_2Cl_2/cyclo-hexane	Et_2O/*n*-hexane	$CHCl_3$/penta-ne	MeOH
space group	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P4_3$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	9.218(5)	8.882(5)	6.259(5)	10.5533(3)	9.2664(2)	9.797(5)	9.6769(2)	9.742(5)
b (Å)	11.973(5)	11.622(5)	13.764(5)	9.0676(3)	11.3591(3)	9.797(5)	11.4809(3)	10.698(5)
c (Å)	9.579(5)	9.576(5)	17.824(5)	12.0900(4)	21.2498(6)	18.900(5)	17.0959(4)	23.475(5)
β (°)	91.032(5)	109.976(5)		101.3260(10)				
volume (Å^3)	1057.0(9)	929.0(8)	1535.5(14)	1134.40(6)	2236.71(10)	1814.0(14)	1899.35(8)	2446.6(18)
Z	2	2	4	2	4	4	4	4
ρ_{calcd} ($g.cm^{-3}$)	1.371	1.338	1.351	1.319	1.237	1.371	1.295	1.394
F (000)	460.0	396.0	656.0	476.0	888.0	792.0	784.0	1072.0
radiation	CuKα	CuKα	CuKα	CuKα	CuKα	CuKα	CuKα	CuKα
T (K)	100(2)	104(4)	100(2)	104(2)	104(2)	100(2)	100(2)	100(2)
2Θ max (°)	144.42	144.6	144.48	149.12	149.26	144.4	149.24	145.328
measured reflns	37228	29987	28331	24944	48077	30403	46605	42555
unique reflns	4152	3661	3023	4585	4576	3567	3883	4824
R_{int}	0.0318	0.0355	0.0284	0.0417	0.0556	0.0294	0.0505	0.0558
final R_1 (all data)	0.0220	0.0242	0.0225	0.0280	0.0302	0.0371	0.0324	0.0545
final wR_2 (all data)	0.0561	0.0633	0.0587	0.0627	0.0650	0.0998	0.0671	0.1338

Conflicts of interest

The authors declare non conflicts of interest.

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Supporting Information

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