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Fabienne GRELLEPOIS

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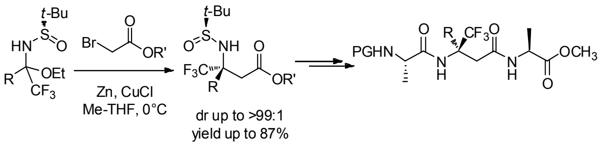
Enantiopure trifluoromethylated $\beta^{3,3}$-amino acids: Synthesis by asymmetric Reformatsky reaction with stable analogues of trifluoromethyl *N*-*tert*-butanesulfinyl ketoimines and incorporation into α/β-peptides.

Fabienne Grellepois*

Université de Reims Champagne-Ardenne, Institut de Chimie Moléculaire de Reims, CNRS UMR 7312, UFR des Sciences Exactes et Naturelles, BP 1039, 51687 Reims Cedex 2, France

fabienne.grellepois@univ-reims.fr



Addition of a Reformatsky reagent to α-aryl(alkyl) α-trifluoromethyl *N*-*tert*-butanesulfinyl hemiaminals, bench stable surrogates of trifluoromethyl ketoimines, provided β-alkyl(aryl) β-trifluoromethyl β-amino acids derivatives in good yields and high diastereoselectivities. The *N*-*tert*-butanesulfinyl $\beta^{3,3}$-amino esters were further utilized as versatile intermediates for the elaboration of hetero-di- and tripeptides.

Introduction

Enantiopure β-amino acids are very attractive building blocks for the synthesis of peptidomimetics and many others bioactive compounds.[1] They are in particular the subunits of β-[2] and α/β-peptides[3] which have received a great deal of attention due to their unique folding properties and their specific biological activities.[2,3] Despite this tremendous interest in β-amino acids[1b,4] and considering the beneficial effects of the substitution of hydrogen by fluorine,[5] very little is known about the synthesis and the biological properties of their fluorinated and fluoroalkylated analogues.[6]

Amongst the various substitution patterns of fluoroalkylated β-amino acids, enantiopure β-trifluoromethyl β-amino acids (β^3-amino acids[7]) have been extensively studied. Numerous diastereoselective[8] and enantioselective[9] syntheses of (*R*)- or (*S*)-3-amino-4,4,4-trifluorobutanoic acid derivatives have been reported to date. These compounds have been incorporated into partially modified retropeptides leading to a nine membered β-turn like conformation and into peptidomimetics having MMP inhibitory activities.[10] Despite the promising studies showing new secondary structures provided by β-peptides containing chiral gem-disubstituted β-amino acids in nonfluorinated series,[11] enantiopure geminally disubstituted β-trifluoromethyl β-amino acids derivatives (β-alkyl(aryl) β-trifluoromethyl β-amino acids) have been scarcely reported. Only one derivative belonging to this subclass of $\beta^{3,3}$-amino acids, an *N*-acetyl β-methyl β-trifluoromethyl β-amino ester, has been described to date.[8i] Its synthesis involved the highly stereoselective addition of 2-(*p*-tolylsulfinyl)-benzylic carbanion to a trifluoromethylated imine and phenyl ring oxidation into a carboxylic acid function as key steps. This approach is consequently limited to β-alkyl substituents and required numerous steps to obtain the target building block. The development of a short, efficient and general synthesis of enantiopure β-trifluoromethyl β-amino acids containing a quaternary stereogenic center in the β-position is still missing and constitutes a challenge for organic chemists.

Since its first report 15 years ago,[12] chiral *N*-*tert*-butanesulfinamides developped by Ellman have been increasingly used for the preparation of a wide range of chiral mono- and poly-functionalized amines derivatives, including variously substituted *β*-amino acids.[13] While the 1,2-addition of ester enolate[14] with *tert*-butanesulfinyl ketoimines is the favored reaction for the synthesis of a variety of nonracemic *N*-protected $\beta^{3,3}$-amino esters, the use of the Reformatsky reagent appeared to be more suitable when the target building block is required on a large scale.[15] In spite of the obvious interesting properties of Ellman's chiral auxiliary such as the availability of both enantiomers and the mild conditions required for its cleavage,[13] only a few publications deal with the applications of trifluoromethyl-substituted *N*-*tert*-butanesulfinyl ketoimines.[16] The presence of the activating substituent on the nitrogen atom makes the aliphatic and aromatic trifluoromethyl *N*-*tert*-butanesulfinyl ketoimines significantly more electrophilic than their *N*-alkyl or *N*-aryl analogues. They have to be generated and isolated quickly prior to use[16a] since they are unstable at room temperature and easily hydrolyzed or decomposed during work-up or purification on silica gel. Only trifluoromethyl α,β-unsatured *N*-*tert*-butanesulfinyl ketoimines are quite stable.[16b,d] According to the authors, the conjugative stabilizing effect of the C-C double bond on the C-N double bond might explain this higher stability.

In this paper, we wish to disclose our results for the one-step synthesis of various enantiopure *N*-*tert*-butanesulfinyl trifluoromethyl $\beta^{3,3}$-amino esters from bench stable analogues of aliphatic and aromatic trifluoromethyl *N*-*tert*-butanesulfinyl ketoimines. We also report the coupling of one of the target building-blocks with natural *α*-amino acid derivatives to elaborate an original α/β/α-tripeptide.

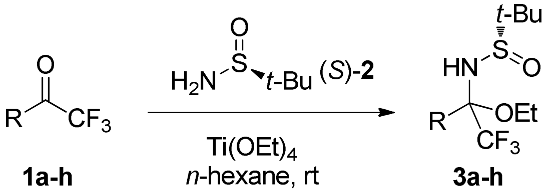
Results and Discussion

The low hydrostability of aliphatic and aromatic trifluoromethyl *N*-*tert*-butanesulfinyl ketoimines significantly diminishs their potential synthetic value and thus our initial efforts focused on developing bench stable surrogates.

As perfluoroalkyl groups adjacent to imines are known to increase their reactivity towards nucleophiles and to have a stabilizing effect for the obtained quaternary species, hemiaminals appeared to be the most convenient precursors for our work.[17,18]

2,2,2-Trifluoroacetophenone **1a** reacted with a slight excess of (*S*)-2-methyl-2-propanesulfinamide (*S*)-**2** (1.2 equivalents) in the presence of $Ti(OEt)_4$ (2 equivalents) in hexane at room temperature for 4 days to give the hemiaminal **3a** (Table 1, entry 1). Hemiaminal **3a** was isolated in 75% yield as a mixture of two diasteroisomers. The separation of both diastereomers and the unequivocal assignment of their stereochemistry were irrelevant for the pursuit of our study (*vide infra*). Monitoring of the reaction by ^{19}F NMR indicated that the ketone **1a** was slowly converted into the corresponding ketoimine (small signal, broad singlet at -70.8 ppm) which was then rapidly converted into hemiaminal **3a**. Although this transformation was extremely slow, hemiaminal **3a** was easily isolated and purified by chromatography on silica gel and found to be highly stable.[19] These conditions were then applied to variously substituted trifluoromethylketones **1b-h** (Table 1). They were effective for most electron rich and electron poor aromatic ketones **1b,c-e,f** and aliphatic ketones **1g,h** (the isolated yields ranged from 64-76%) (entries 2, 5-8). 4-Nitrophenyl hemiaminal **3c** was isolated in only 45% yield due to the formation of many trifluoromethylated by-products during the course of the reaction (entry 3). The limitation of this approach was observed for the ketone **1d** which didn’t lead to the corresponding hemiaminal as the condensation stopped at the ketoimine stage (Table 1, entry 4 and Scheme 1). Ketoimine **4** was isolated in 67% yield and was stable enough to be stored several days in the freezer (around 5% of decomposition into ketone **1d** was detected by ^{19}F NMR after 4 days in the freezer). The bulky methoxy group close to the imine function seemed to prevent nucleophilic addition. Finally, it should be noted that a small amount of enamine **5** was also formed when the reaction was performed with 1,1,1-trifluorobutan-2-one **1h** (Scheme 2). The *Z* geometry of the enamine **5** was determined by an heteronuclear nOe experiment.

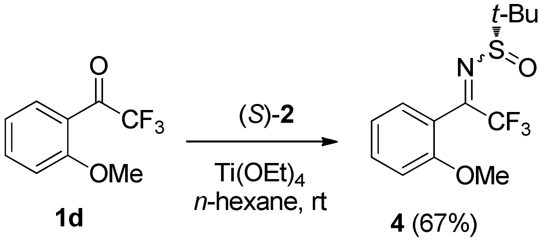
Table 1. Synthesis of hemiaminals 3a-g.



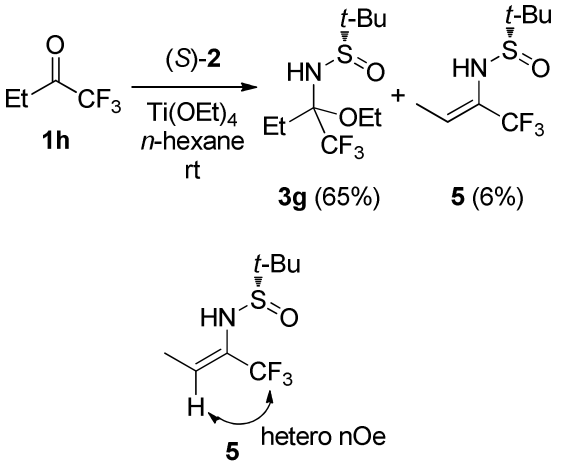
entry	**1**	R	time	hemi-aminal	yield (%)
1	**1a**	Ph	4 d	**3a**	75
2	**1b**	4-FC$_6$H$_4$	3 d	**3b**	76
3	**1c**	4-NO$_2$C$_6$H$_4$	3 d	**3c**	45
4	**1d**	2-MeOC$_6$H$_4$	6 d	-[a]	-
5	**1e**	3-MeOC$_6$H$_4$	6 d	**3d**	64
6	**1f**	4-MeOC$_6$H$_4$	4 d	**3e**	69
7	**1g**	Me	4 d	**3f**	70
8	**1h**	Et	2 d	**3g**	65[b]

[a] only ketimine **4** was formed and isolated, see Scheme 1. [b] 6% of enamine **5** was also isolated, see Scheme 2.

Scheme 1. Synthesis of imine 4 from ketone 1d.

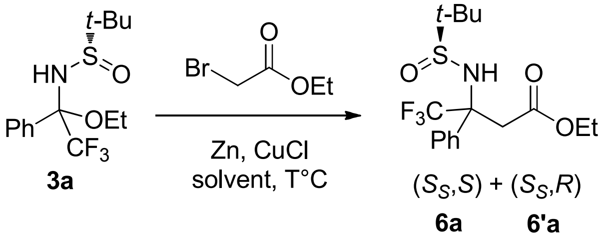


Scheme 2. Reaction of ketone 1h with Ellman's chiral auxiliary (*S*)-2 in the presence of Ti(OEt)$_4$.



To carry out the synthesis of $\beta^{3,3}$-amino acids, we first explored the effect of solvent and temperature on the diastereoselectivity and yield of the addition process of Reformatsky reagent. This reaction being tolerant to a large range of solvents,[20] addition of organozinc reagent to **3a** was explored in DME, Et_2O, THF, 2-Me-THF, CH_2Cl_2, DMF and MeCN (Table 2). The Reformatsky reagent was formed *in situ* by reacting ethyl bromoacetate (2.5 equivalents) in the presence of a large excess of Zn (10 equivalents) and CuCl (1 equivalent) 30 min at room temperature and 45 min at 50°C (or at reflux in Et_2O or CH_2Cl_2). The reaction was successful at room temperature in Et_2O, THF and 2-Me-THF but not in DME (entries 1-4). The facial stereoselectivity of the addition was better in 2-Me-THF than THF and Et_2O (86:14 instead of 78:22 and 80:20, entries 2-4). In 2-Me-THF, decreasing the temperature from room temperature to 0°C had a slightly beneficial effect on the diastereoselectivity (88:12 instead of 86:14) and on the yield of β-amino acids **6a** and **6'a** (respectively 69 and 77%, entries 4-5). Starting from a diastereoisomeric pure sample of **3a** led to the same diastereomeric ratio (entry 6) as that obtained from a mixture (entry 5). This strongly implies that the addition of the reagent occurred on the intermediate ketoimine and thus the separation of both diastereoisomers of hemiaminals **3a-g** was unnecessary for this reaction. The stereoselectivity could not be improved by lowering the temperature as the addition was inhibited at -10°C (entry 7). Changing the solvent to CH_2Cl_2 gave no improvement in stereoselectivity (53:47, entry 8). Finally, in polar aprotic solvents such as DMF and MeCN the reaction failed (entries 9-10). Based on these results, using 2-Me-THF[21] at 0°C appeared to be the best conditions for the synthesis of the target $\beta^{3,3}$-amino-acids **6** and **6'**.

Table 2. Optimisation of Reformatsky reagent additions to *N*-sulfinyl hemiaminal 3a.



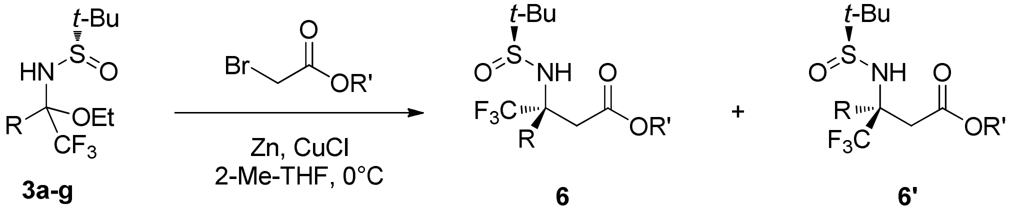
entry	solvent	T°C	dr (6a:6'a)[a]	yield (%)[b]
1	DME	rt	-[c]	-[c]
2	Et_2O	rt	80:20	75
3	THF	rt	78:22	70
4	2-Me-THF	rt	86:14	69
5[d]	2-Me-THF	0°C	88:12	77
6[e]	2-Me-THF	0°C	88:12	79
7	2-Me-THF	-10°C	-[c]	-[c]
8	CH_2Cl_2	rt	53:47	63
9	DMF	rt	-[c]	-[c]
10	MeCN	rt	-[c]	-[c]

[a] diastereomeric ratios **6a**:**6'a** determined by ^{19}F NMR of the crude mixture. [b] isolated yield after silica gel purification. The two diastereoisomers **6a** and **6'a** were not separated. [c] No addition

observed. [d] reaction performed with the mixture of two diastereoisomers of hemiaminal **3a**. [e] reaction performed on the major diastereoisomer of hemiaminal **3a**.

The addition of various simple Reformatsky reagents to the aromatic and aliphatic hemiaminals **3a-g** was thus explored under these optimized conditions. Results are collected in Table 3. For aromatic derivatives (entries 1-10), the diastereomeric ratio ranges from moderate to very high (82:18 to 96:4). Notably, switching from ethyl bromoacetate to the more sterically encumbered *tert*-butyl bromoacetate always improved the facial stereoselectivity. Except for β-4-fluorophenyl β-trifluoromethyl β-amino ethyl ester **6d**/**6'd** (entries 4), the major diastereomers could be separated by silica gel chromatrography. In most cases, a small amount of pure minor diastereomer was also isolated (entries 1-3, 5-6, 8-9). The reaction of methyl and ethyl hemiaminal **3f-g** with methyl, ethyl or *tert*-butyl bromoacetate gave the corresponding $\beta^{3,3}$-amino esters **6k-o** with excellent stereoselectivity (>99:1) regardless the bromoacetate used (entries 11-15).

Table 3. Synthesis of trifluoromethyl $\beta^{3,3}$-amino esters.



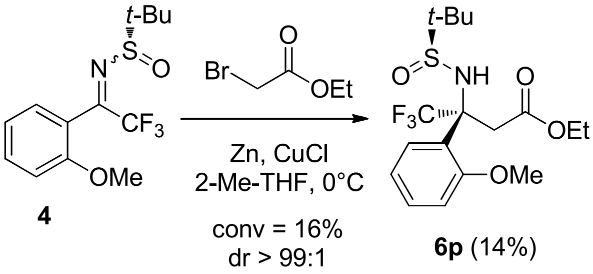
entry	hemiaminal	R	R'	dr (6:6')[a]	product 6	yield (%)	product 6'	yield (%)
1	**3a**	Ph	Et	88:12	**6a**	59	**6'a**	9
2	**3a**	Ph	Bn	87:13	**6b**	58	**6'b**	11
3	**3a**	Ph	*t*-Bu	93:7	**6c**	65	**6'c**	3
4	**3b**	4-FC$_6$H$_4$	Et	86:14	**6d/ 6'd**	77[b]		

5	**3b**	4-FC_6H_4	*t*-Bu	93:7	**6e**	67	**6’e**	2
6	**3c**	4-$NO_2C_6H_4$	*t*-Bu	96:4	**6f**	79	**6’f**	3
7	**3d**	3-$MeOC_6H_4$	Et	90:10	**6g**	64		
8	**3d**	3-$MeOC_6H_4$	*t*-Bu	93:7	**6h**	70	**6’h**	2
9	**3e**	4-$MeOC_6H_4$	Et	82:18	**6i**	57	**6’i**	9
10	**3e**	4-$MeOC_6H_4$	*t*-Bu	90:10	**6j**	71		
11	**3f**	Me	Me	>99:1[c]	**6k**	86		
12	**3f**	Me	Et	>99:1[c]	**6l**	79		
13	**3f**	Me	*t*-Bu	>99:1[c]	**6m**	68		
14	**3g**	Et	Et	>99:1[c]	**6n**	85		
15	**3g**	Et	*t*-Bu	>99:1[c]	**6o**	87		

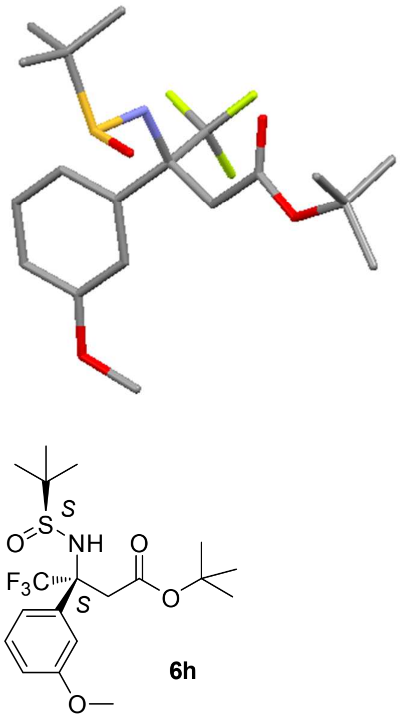
[a] diastereomeric ratios **6a**: **6’a** determined by ^{19}F NMR of the crude mixture. [b] the two diastereomers **6d** and **6’d** could not be separated by silica gel purification. [c] the minor isomer was not detected by ^{19}F NMR of the crude reaction mixture.

These conditions were also applied to the imine **4** using ethyl bromoacetate. Only a small conversion of imine into amino ester **6p** was observed which might be due to the steric hindrance around the electrophilic carbon of the imine function (16% of conversion according to the ^{19}F NMR of the crude reaction mixture) (Scheme 3). However, the diastereoselectivity of the addition was excellent (dr >99:1).

Scheme 3. Reformatsky reaction of imine 4 with ethyl bromoacetate.



The absolute configuration of the amino ester **6h** was determined by X-ray crystallography (figure 1).[22] The absolute configurations of other amino esters **6** and **6’** were assigned by analogy.

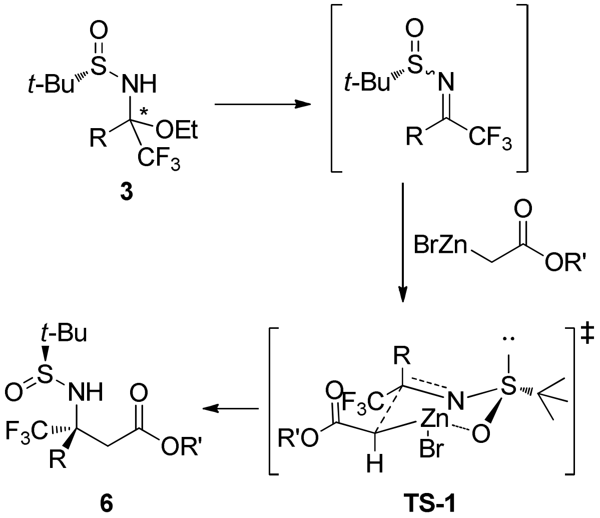


6h

Figure 1. Structure of compound 6h from single crystal X-ray data.

The observed diastereoselectivity (*vide supra*) for the addition of the Reformatsky reagent is consistent with a Zimmerman-Traxler-type six-membered transition state **TS-1** with coordination of the sulfinyl oxygen of the intermediate imine to zinc (Scheme 4).[13,15,16b,c,e,20] In this six-membered chair transition state, the trifluoromethyl group prefers to occupy the equatorial position rather than the axial one due to steric hindrance (its Van der Waals radius lies between those of *i*Pr and *t*Bu) and to the electrostatic repulsion between the trifluoromethyl group and the lone pair of the sulfur atom.[5b,16b,c,e,23]

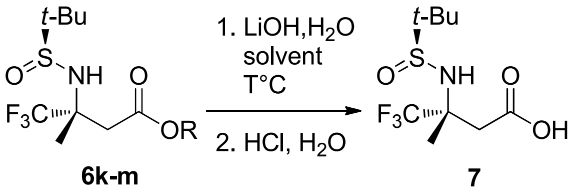
Scheme 4. Rationalization of the observed diastereoselectivity.



Because application of β-trifluoromethyl β-amino acids in peptide design is still in the early stages of development,[6c,10] we then focused on the elaboration of hetero-di- and tripeptides containing β-trifluoromethyl β-methyl amino acid **7**.

$\beta^{3,3}$ Amino acid **7** was prepared by basic hydrolysis of methyl, ethyl or *tert*-butyl amino esters **6k-m** in very good yields (78%-99%) (Table 4).

Table 4. Preparation of trifluoromethyl $\beta^{3,3}$-amino acid 7.

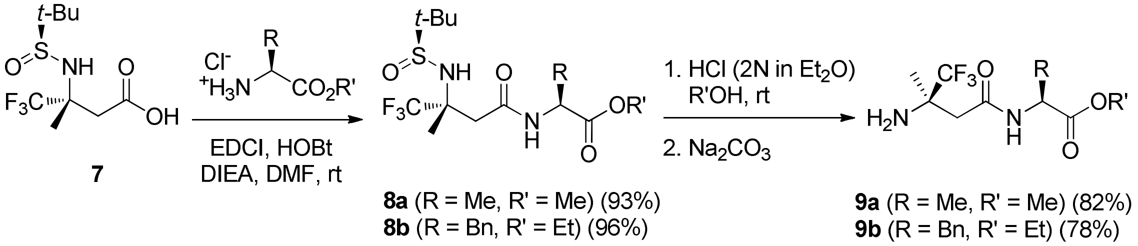


6	R	solvent	T°C	yield **7** (%)
6k	Me	MeOH:H_2O (3:1)	rt	99
6l	Et	EtOH:H_2O (3:1)	rt	92

6m	*t*-Bu	THF:H_2O (1:1)	reflux	78

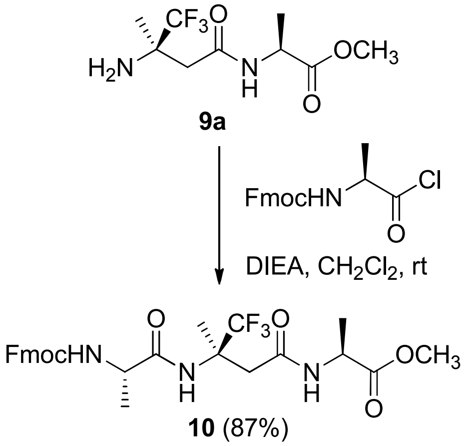
The coupling at the *C*-termini of the *N*-protected $\beta^{3,3}$ amino acid **7** with L-alanine methyl ester hydrochloride or L-phenylalanine ethyl ester hydrochloride was achieved using a conventional procedure[24] (EDCI, HOBT, DIEA, DMF) (Scheme 5). *N*-Protected dipeptides **8a-b** were obtained in excellent yield (93-96%). Removal of the sulfinyl protecting group of dipeptides **8a-b** was easily performed by reaction with HCl (2N in Et_2O) in an alcoholic solvent.[14b,15] After basic aqueous work-up, dipeptides **9a-b** were isolated in respectively 82 and 78% yield.

Scheme 5. *C*-coupling of $\beta^{3,3}$ amino acid 7 with alanine and phenylalanine amino esters: Access to β/α-dipeptides 9a-b.



To prove that these new trifluoromethyl $\beta^{3,3}$-amino acid derivatives were also suitable for incorporation into peptide *via* their *N*-termini, coupling of the β/α-peptide **9a** was then investigated. Because of the low nucleophilicity and steric hindrance of amine adjacent to the electron withdrawing and bulky trifluoromethyl group, specific activating methods (amino acid bromide[25] or chloride,[26] highly electrophilic mixed anhydride[27]) have been developed for the *N*-terminal coupling of α-trifluoromethylated α-amino acids. Based on these results, we performed the reaction of dipeptide **9a** with freshly prepared Fmoc alanine acid chloride[26,28] in the presence of DIEA in CH_2Cl_2. Under these coupling conditions, the heterotripeptide **10** was obtained and isolated in very good yield (87%). Attempts to perform the reaction with the more stable Fmoc alanine acid fluoride[29] failed.

Scheme 6. *N*-coupling of dipeptide 9a with *N*-Fmoc L-alanine acid chloride: Access to the original α/β/α-tripeptide 10.



Conclusion

In conclusion, the asymmetric synthesis of *β*-alkyl(aryl) *β*-trifluoromethyl *β*-amino esters has been described *via* an highly stereoselective imino-Reformatsky reaction with bench stable trifluoromethyl *N*-*tert*-butanesulfinyl ketoimine surrogates. This approach is the first efficient and general preparation of *β*-trifluoromethyl *β*-amino acid derivatives containing a quaternary stereocenter adjacent to the amine function. The versatility of these *N*-*tert*-butanesulfinyl *β*-alkyl(aryl) *β*-trifluoromethyl *β*-amino esters was further proved by their incorporation into peptides. *C*- as well as *N*-terminal coupling with natural *α*-amino acid derivatives was successfully performed. We expect that the reported synthesis will find utility in the synthesis of new peptidomimetics and foldamers.

Experimental section

n-Hexane and DME (monoglyme) were distilled from CaH_2. THF, Et_2O and MeCN were dried using a Pure Solv solvent drying system over aluminium oxide under an Argon atmosphere. CH_2Cl_2 (extra-dry, water < 0,003%), DMF (extra-dry, water < 0,005%) and 2-Me-THF (extra-dry, water < 0,005%, on molecular sieves) were purchased from Acros Organics. $Ti(OEt)_4$ and DIEA were distilled prior to use. Zn was activated by stirring with a 2% HCl solution and successive washing with distilled H_2O, 95% EtOH, and Et_2O.[30] Zn was then dried thoroughly in a vacuum oven at 70°C for at least 24h[15] (activated Zn can be stored under these conditions for 10 days). Thin–layer chromatography using precoated aluminium backed plates (Merck Kieselgel 60F254) were visualized by UV light and/or by phosphomolybdic acid. Silicagel 40-63 μm (Macherey-Nagel GmbH & Co KG) was used for flash chromatography. Silicagel 15-40 μm (Merck) was used for the separation of diastereomers **6** and **6'**. NMR spectra were recorded in $CDCl_3$ with 250 MHz, 500 MHz, or 600 MHz spectrometers. Chemicals shifts (δ) are reported in ppm relative to TMS for ^1H and ^{13}C NMR spectra and to $CFCl_3$ for ^{19}F NMR spectra. In the ^{13}C NMR data, reported signal multiplicities are related to C-F coupling. The following abbreviations are used to indicate the multiplicities: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet). Diastereomeric ratios (dr) were determined by ^{19}F NMR. 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 (c.a. 20 °C).

General procedure for the reaction of ketones 1a-h with (S)-*tert*-butanesulfinamide (*S*)-2 in the presence of $Ti(OEt)_4$.

A solution of trifluoromethyl ketone **1**, (*S*)-*tert*-butanesulfinamide (*S*)-**2** (1.2 equiv) and $Ti(OEt)_4$ (2 equiv) in *n*-hexane was stirred at room temperature under Ar for 2-6 days . The reaction mixture was then quenched with H_2O and after 5 min of stirring was filtered on a pad of celite (Et_2O). The organic layer of the filtrate was extracted, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether:Et_2O).

(S_S)-N-(1-ethoxy-2,2,2-trifluoro-1-phenylethyl)-tert-butylsulfinamide ***3a***. Following the general procedure, 2,2,2-trifluoroacetophenone **1a** (5.0 g, 28.7 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (4.2 g, 34.5 mmol) and $Ti(OEt)_4$ (12.0 mL, 57.4 mmol) in *n*-hexane (70 mL) for 4 days. Purification on silica gel (petroleum ether:Et_2O 1:1 to 2:3) afforded hemiaminal **3a** (7.0 g, 75%, dr = 74:26) as a colorless oil. IR (film) ν_{max} 1079, 1100, 1175, 2982 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -78.5 (s, CF_3, major), -78.9 (s, CF_3, minor); NMR ^{1}H (250 MHz, $CDCl_3$) δ 1.25-1.37 (m, 12H, minor and major), 3.44 (m, 1H, minor), 3.76 (m, 1H, major), 3.88 (m, 1H, minor and major), 4.38 (s, 1H, minor), 4.62 (s, 1H, major), 7.35-7.70 (5H, minor and major); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ 14.6 (minor), 14.9 (major), 22.2 (minor), 22.5 (major), 57.1 (minor), 57.3 (major), 59.2 (minor), 60.2 (major), 86.8 (q, J = 30.5 Hz, minor), 89.4 (q, J = 29.0 Hz, major), 122.7 (q, J = 290.0 Hz, minor), 123.2 (q, J = 290.0 Hz, major), 127.6 (minor), 127.8 (major), 128.7 (minor), 129.0 (major), 129.6 (major), 129.9 (minor), 133.1 (major), 134.1 (minor). HRMS (ESI$^+$): *m/z* calcd for $C_{14}H_{20}F_3NaNO_2S$ $[M+Na]^+$ 346.1065, found 346.1079.

(S_S)-N-(1-ethoxy-2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-tert-butylsulfinamide ***3b***. Following the general procedure, 2,2,2,4'-tetrafluoroacetophenone **1b** (2.15 g, 11.2 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (1.63 g, 13.4 mmol) and $Ti(OEt)_4$ (4.7 mL, 22.4 mmol) in *n*-hexane (30 mL) for 3 days. Purification on silica gel (petroleum ether:Et_2O 1:1 to 2:3) afforded hemiaminal **3b** (2.9 g, 76%, dr = 64:36) as a yellow oil. IR (film) ν_{max} 1089, 1161, 1183, 2983 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -78.3 (s, CF_3, major), -78.9 (s, CF_3, minor), -111.1 (m, CF, minor), -112.1 (m, CF, major); NMR ^{1}H (250 MHz, $CDCl_3$) δ 1.29-1.37 (m, 12H, minor and major), 3.39 (m, 1H, minor), 3.73 (m, 1H, major), 3.90 (m, 1H,

minor and major), 4.26 (s, 1H, minor), 4.65 (s, 1H, major), 7.10 (ddd, *J* = 4.0 Hz, *J* = 8.5 Hz, *J* = 16.0 Hz, 2H, minor and major), 7.46 (m, 1H, minor), 7.52 (dd, *J* = 5.5 Hz, *J* = 9.0 Hz, 1H, major), 7.65 (dd, *J* = 5.5 Hz, *J* = 8.5 Hz, 1H, minor and major); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ 14.3 (minor), 14.7 (major), 21.9 (minor), 22.2 (major), 56.9 (minor), 57.0 (major), 59.0 (minor), 60.1 (major), 88.9 (q, *J* = 29.0 Hz, minor), 89.6 (q, *J* = 30.0 Hz, major), 114.6 (d, *J* = 21.5 Hz, minor and major), 115.1 (d, *J* = 22.5 Hz, minor), 115.5 (d, *J* = 22.0 Hz, major), 122.5 (q, *J* = 290.0 Hz, minor), 123.0 (q, *J* = 296.0 Hz, major), 129.1 (d, *J* = 3.0 Hz, major), 129.8 (d, *J* = 8.5 Hz, major), 130.3 (d, *J* = 3.0 Hz, minor), 130.4 (d, *J* = 9.0 Hz, minor), 131.0 (d, *J* = 8.5 Hz, minor and major), 163.3 (d, *J* = 250.0 Hz, major), 163.4 (d, *J* = 250.0 Hz, minor). HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{19}F_4NaNO_2S$ $[M+Na]^+$ 364.0970, found 364.0954.

(S_S)-N-(1-ethoxy-2,2,2-trifluoro-1-(4-nitrophenyl)ethyl)-tert-butylsulfinamide ***3c***. Following the general procedure, 4’-nitro-2,2,2-trifluoroacetophenone **1c** (1.82 g, 8.3 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (1.21 g, 10.0 mmol) and $Ti(OEt)_4$ (3.5 mL, 16.6 mmol) in *n*-hexane (40 mL) for 3 days. Purification on silica gel (petroleum ether:Et_2O 2:1 to 1:3) afforded hemiaminal **3c** (1.40 g, 45%, dr = 71:29) as a yellow oil. IR (film) ν_{max} 1092, 1183, 1351, 1528 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -77.3 (s, CF_3, major), -78.1 (s, CF_3, minor); NMR ^{1}H (250 MHz, $CDCl_3$) δ 1.24 (s, 9H, major), 1.27 (s, 9H, minor), 1.29 (m, 3H, minor and major), 3.34 (m, 1H, minor), 3.71 (m, 1H, major), 3.92 (m, 1H, minor and major), 4.51 (s, 1H, minor), 4.83 (s, 1H, major), 7.71 (d, *J* = 8.5 Hz, 2H, minor), 7.84 (d, *J* = 8.5 Hz, 2H, major), 8.16 (d, *J* = 9.0 Hz, 2H, major), 8.21 (d, *J* = 10.0 Hz, 2H, minor); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ 14.6 (minor), 14.9 (major), 22.2 (minor), 22.5 (major), 57.5 (minor), 57.7 (major), 59.7 (minor), 60.6 (major), 88.8 (q, *J* = 29.0 Hz, major), 89.7 (q, *J* = 30.0 Hz, minor), 122.3 (q, *J* = 288.0 Hz, minor), 122.7 (q, *J* = 289.0 Hz, major), 122.9 (major), 123.7 (minor), 129.3 (minor), 130.4 (major), 140.7 (major), 141.0 (minor), 148.6 (major), 148.8 (minor). HRMS (ESI$^+$): *m*/*z* calcd for $C_{14}H_{19}F_3NaN_2O_4S$ $[M+Na]^+$ 391.0915, found 391.0910.

(S$_S$)-N-(1-ethoxy-2,2,2-trifluoro-1-(3-methoxyphenyl)ethyl)-tert-butylsulfinamide ***3d***. Following the general procedure, 3'-methoxy-2,2,2-trifluoroacetophenone **1e** (1.29 g, 6.3 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (917 mg, 7.6 mmol) and Ti(OEt)$_4$ (2.65 mL, 12.6 mmol) in *n*-hexane (30 mL) for 6 days. Purification on silica gel (petroleum ether:Et$_2$O 3:2 to 1:2) afforded hemiaminal **3d** (1.42 g, 64%, dr = 57:43) as a yellow oil. IR (film) ν_{max} 1089, 1104, 1162, 1183, 1264, 2981 cm^{-1}; NMR ^{19}F (235 MHz, CDCl$_3$) δ -78.3 (s, CF$_3$, major), -78.8 (s, CF$_3$, minor); NMR ^{1}H (250 MHz, CDCl$_3$) δ 0.80-1.43 (m, 12H, minor and major), 3.46 (m, 1H, minor), 3.75 (m, 1H, major), 3.82 (d, *J* = 1.0 Hz, 3H, minor), 3.83 (s, 3H, major), 3.88 (m, 1H, minor and major), 4.36 (s, 1H, minor), 4.60 (s, 1H major), 6.94-7.40 (m, 4H, minor and major); NMR ^{13}C (62.9 MHz, CDCl$_3$) δ 14.9 (minor), 15.2 (major), 22.4 (minor), 22.8 (major), 55.4 (minor), 55.5 (major), 57.4 (minor), 57.6 (major), 59.5 (major), 60.5 (minor), 89.5 (q, *J* = 29.0 Hz, major), 89.9 (q, *J* = 29.5 Hz, minor), 114.2 (minor), 115.0 (major), 115.2 (major), 115.5 (minor), 119.8 (minor), 121.6 (major), 122.8 (q, *J* = 287.0 Hz, minor), 123.3 (q, *J* = 291.0 Hz, major), 129.0 (minor), 130.0 (major), 134.7 (major), 135.9 (minor), 159.4 (major), 160.0 (minor). HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{22}F_3NaNO_3S$ [M+Na]$^+$ 376.1170, found 376.1158.

(S$_S$)-N-(1-ethoxy-2,2,2-trifluoro-1-(4-methoxyphenyl)ethyl)-tert-butylsulfinamide ***3e***. Following the general procedure, 4'-methoxy-2,2,2-trifluoroacetophenone **1f** (808 mg, 3.96 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (576 mg, 4.75 mmol) and Ti(OEt)$_4$ (1.66 mL, 7.92 mmol) in *n*-hexane (20 mL) for 4 days. Purification on silica gel (petroleum ether:Et$_2$O 3:2 to 1:2) afforded hemiaminal **3e** (966 mg, 69%, dr = 62:38) as a yellow oil. IR (film) ν_{max} 1091, 1173, 1258, 2981 cm^{-1}; NMR ^{19}F (235 MHz, CDCl$_3$) δ -78.8 (s, CF$_3$, major), -79.0 (s, CF$_3$, minor); NMR ^{1}H (250 MHz, CDCl$_3$) δ 1.18 (t, *J* = 7.5 Hz, 3H, minor), 1.28 (s, 9H, major), 1.30 (s, 9H, minor), 1.31 (m, 3H, major), 3.44 (m, 1H, minor and major), 3.73 (m, 1H, minor), 3.80 (s, 3H, minor and major), 3.84 (m, 1H, major), 4.31 (s, 1H, minor), 4.58 (s,

1H, major), 6.90 (m, 2H, minor and major), 7.42 (d, *J* = 9.0 Hz, 2H, minor), 7.54 (d, *J* = 9.0 Hz, 2H, major); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ 14.8 (minor), 15.1 (major), 22.4 (minor), 22.7 (major), 55.3 (major), 55.4 (minor), 57.2 (minor), 57.4 (major), 59.2 (minor), 60.3 (major), 89.5 (q, *J* = 29.0 Hz, major), 89.8 (q, *J* = 30.0 Hz, minor), 113.3 (major), 114.2 (minor), 122.9 (q, *J* = 287.0 Hz, minor), 123.3 (q, *J* = 290.5 Hz, major), 125.7 (minor), 126.0 (major), 129.1 (minor), 130.6 (major), 160.0 (major), 160.9 (minor). HRMS (ESI$^+$): *m*/*z* calcd for $C_{15}H_{22}F_3NaNO_3S$ $[M+Na]^+$ 376.1170, found 376.1161.

(S_S)-(+)-N-(2-ethoxy-1,1,1-trifluoropropan-2-yl)-tert-butylsulfinamide ***3f***. Following the general procedure, 1,1,1-trifluoroacetone **1g** (5.0 g, 44.5 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (6.5 g, 53.4 mmol) and $Ti(OEt)_4$ (18.6 mL, 89.0 mmol) in *n*-hexane (80 mL) for 4 days. Purification on silica gel (petroleum ether:Et_2O 1:1) afforded hemiaminal **3f** (8.1 g, 70%, dr = 100:0) as a white solid. mp 52-53°C; $[\alpha]_D^{20}$ +73 (*c* 1.04, $CHCl_3$); IR (film) ν_{max} 939, 1062, 1131, 1169, 2984 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -84.8 (s, CF_3); NMR ^{1}H (250 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.5 Hz, 3H), 1.23 (s, 3H), 1.67 (s, 3H), 3.59 (m, 1H), 3.71 (td, *J* = 7.5 Hz, *J* = 14.5 Hz, 1H), 3.90 (s, 1H); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ 15.2, 16.4, 22.4, 56.6, 58.4, 87.8 (q, *J* = 30.0 Hz), 123.5 (q, *J* = 123.5 Hz). HRMS (ESI$^+$): *m*/*z* calcd for $C_9H_{19}F_3NO_2S$ $[M+H]^+$ 262.1089, found 262.1087.

(S_S)-N-(2-ethoxy-1,1,1-trifluorobutan-2-yl)-tert-butylsulfinamide ***3g*** *and (S_S,Z)-2-methyl-N-(1,1,1-trifluorobut-2-en-2-yl)propane-2-sulfinamide* ***5***. Following the general procedure, 1,1,1-trifluoro-2-butanone **1h** (588 mg, 4.67 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (679 mg, 5.60 mmol) and $Ti(OEt)_4$ (1.95 mL, 9.34 mmol) in *n*-hexane (8 mL) for 2 days. Purification on silica gel (petroleum ether:Et_2O 1:1 to 1:2) afforded hemiaminal **3g** (835 mg, 65%, dr = 9:91) as a white solid followed by enamine **5** (64 mg, 6%) as a beige solid. **3g**: IR (film) ν_{max} 963, 1060, 1132, 1155, 1181, 2902, 2986 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -73.6 (s, CF_3, minor), -79.6 (s, CF_3, major); NMR ^{1}H (250 MHz, $CDCl_3$) δ major 0.93 (t, *J* =

7.5 Hz, CH_3), 1.10 (t, *J* = 7.0 Hz, CH_3), 1.11 (s, 9H), 1.88 (dq, *J* = 7.5 Hz, *J* = 14.5 Hz, 1H), 2.13 (m, 1H), 3.51 (m, 2H), 3.90 (s, 1H); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ major 7.3, 15.0, 22.3, 24.4, 56.5, 58.0, 89.2 (q, *J* = 28.5 Hz), 123.5 (q, *J* = 288.0 Hz). HRMS (ESI^+): *m*/*z* calcd for $C_{10}H_{20}F_3NaNO_2S$ $[M+Na]^+$ 298.1065, found 298.1055. **5**: mp 107-108°C; $[\alpha]_D^{20}$ +45 (*c* 1.01, $CHCl_3$); IR (film) ν_{max} 1052, 1125, 1179, 1261, 1276, 3125 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -70.1 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.88 (qd, *J* = 2.0 Hz, *J* = 4.5 Hz, 3H), 4.65 (s, 1H), 6.18 (q, *J* = 7.5 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 12.5, 22.4, 57.3, 121.6 (q, *J* = 273.0 Hz), 125.6, 128.4 (q, *J* = 32.5 Hz). HRMS (ESI^+): *m*/*z* calcd for $C_8H_{15}F_3NOS$ $[M+H]^+$ 230.0826, found 230.0820.

(S)-2-methyl-N-(2,2,2-trifluoro-1-(2-methoxyphenyl)ethylidene)propane-2-sulfinamide ***4***. Following the general procedure, 2'-methoxy-2,2,2-trifluoroacetophenone **1d** (1.1 g, 5.39 mmol) reacted with (*S*)-*tert*-butanesulfinamide (*S*)-**2** (784 mg, 6.47 mmol) and $Ti(OEt)_4$ (2.25 mL, 10.68 mmol) in *n*-hexane (20 mL) for 6 days. Purification on silica gel (petroleum ether:Et_2O 2:1 containing 0.1% of Et_3N) afforded imine **4** (1.1 g, 67%) as a yellow oil. IR (film) ν_{max} 1105, 1141, 1199, 1258, 1492, 1600, 1638, 2966 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -71.4 (br s, CF_3); NMR ^1H (250 MHz, $CDCl_3$) δ 1.22 (s, 9H), 3.83 (s, 3H), 6.91 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.38 (m, 1H); NMR ^{13}C (62.9 MHz, $CDCl_3$) δ 22.9, 55.6, 59.0, 110.7, 119.0 (q, *J* = 283.5 Hz), 120.0, 128.2, 132.4, 156.6 (2 quaternary carbons not detected). HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{16}F_3NaNO_2S$ $[M+Na]^+$ 330.0752, found 330.0741.

General procedure for the Reformatsky reaction.

A three-necked flask containing activated Zn (10 equiv) and CuCl (1 equiv) was heated under Ar with a heat gun for 5 min. The flask was allowed to cool to rt, 2-Me-THF 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, alkyl bromoacetate (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 **3** or imine **4** in 2-Me-THF was added and the resulting reaction mixture was stirred at 0°C under Ar (reaction monitored by ^{19}F NMR). The reaction mixture was filtered on a pad of celite (Et_2O). The filtrate was washed with diluted HCl 2%, a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by chromatography on silica gel (petroleum ether:EtOAc).

(S_S,S)-(+)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-phenylbutanoate ***6a*** and *(S_S,R)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-phenylbutanoate* ***6'a***. Following the general procedure, a solution of hemiaminal **3a** (358 mg, 1.11 mmol) in 2-Me-THF (15 mL) was added to a suspension of activated Zn (723 mg, 11.1 mmol), CuCl (110 mg, 1.11 mmol) and ethyl bromoacetate (308 μL, 2.78 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 6h at 0°C. Purification of the residue (dr **6a**: **6'a** = 88:12) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded β-amino ester **6'a** (35 mg, 9%) as a colorless oil, an intermediate fraction containing **6'a** and **6a** (38 mg, 9%), and β-amino ester **6a** (240 mg, 59%) as a colorless oil. **6a**: $[\alpha]_D^{20}$ +80 (c 0.85, $CHCl_3$); IR (film) ν_{max} 1077, 1160, 1178, 1260, 1276, 1729, 2986 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -75.0 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H), 1.29 (s, 9H), 3.24 (d, J = 16.0 Hz, 1H), 3.38 (d, J = 16.0 Hz, 1H), 4.18 (m, 2H), 6.26 (s, 1H), 7.41 (m, 3H), 7.59 (m, 2H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.1, 22.8, 39.1, 57.0, 61.5, 65.0 (q, J = 27.5 Hz), 125.3 (q, J = 286.5 Hz), 128.5, 128.8, 129.5, 133.6, 170.5. HRMS (ESI$^+$): m/z calcd for $C_{16}H_{22}F_3NaNO_3S$ $[M+Na]^+$ 388.1170, found 388.1172. **6'a**: IR (film) ν_{max} 1078, 1180, 1260, 1276, 1734, 2988, 3006 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -73.1 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 3H), 1.33 (s, 9H), 3.42 (d, J = 17.5 Hz, 1H), 3.61 (d, J = 17.5 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 5.14 (s, 1H), 7.39 (m, 3H), 7.52 (d, J = 7.0 Hz, 2H); NMR ^{13}C (125.8 MHz,

$CDCl_3$) δ 14.1, 22.7, 38.4, 57.4, 61.3, 64.9 (q, J = 27.0 Hz), 124.9 (q, J = 286.0 Hz), 127.1, 128.7, 129.2, 136.9, 169.6. HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{22}F_3NaNO_3S$ $[M+Na]^+$ 388.1170, found 388.1166.

(S_S,S)-(+)-Benzyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-phenylbutanoate ***6b*** and *(S_S,R)-Benzyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-phenylbutanoate* ***6'b***. Following the general procedure, a solution of hemiaminal **3a** (321 mg, 0.99 mmol) in 2-Me-THF (15 mL) was added to a suspension of activated Zn (649 mg, 9.92 mmol), CuCl (98 mg, 0.99 mmol) and benzyl bromoacetate (389 µL, 2.48 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 3h at 0°C. Purification of the residue (dr **6b**: **6'b** = 87:13) on silica gel (petroleum ether:EtOAc 6:1 to 2:1) afforded *β*-amino ester **6'b** (47 mg, 11%) as a beige oil, an intermediate fraction containing **6'b** and **6b** (61 mg, 14%), and *β*-amino ester **6b** (245 mg, 58%) as a beige oil. **6b**: $[\alpha]_D^{20}$ +83 (*c* 0.97, $CHCl_3$); IR (film) ν_{max} 1076, 1173, 1260, 1276, 1732, 2962, 2983 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -75.0 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.28 (s, 9H), 3.33 (d, J = 16.0 Hz, 1H), 3.49 (d, J = 16.0 Hz, 1H), 5.16 (s, 2H), 6.20 (s, 1H), 7.34 (m, 5H), 7.40 (m, 3H), 7.60 (m, 2H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 22.6, 39.0, 56.9, 64.9 (q, J = 27.5 Hz), 67.1, 125.2 (q, J = 286.5 Hz), 128.36, 128.39, 128.5, 128.6, 129.4, 133.4, 135.0, 170.0. HRMS (ESI$^+$): *m*/*z* calcd for $C_{21}H_{24}F_3NaNO_3S$ $[M+Na]^+$ 450.1327, found 450.1317. **6'b**: IR (film) ν_{max} 1078, 1160, 1178, 1259, 1275, 1736, 2980 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -73.2 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 3.49 (d, J = 17.5 Hz, 1H), 3.71 (d, J = 17.5 Hz, 1H), 4.99 (d, J = 12.0 Hz, 1H), 5.07 (s, 1H), 5.12 (d, J = 12.0 Hz, 1H), 7.21 (dd, J = 3.0 Hz, J = 6.5 Hz, 2H), 7.32 (m, 3H), 7.36 (m, 3H), 7.49 (m, 2H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 22.6, 38.4, 57.4, 64.9 (q, J = 27.0 Hz), 67.1, 124.9 (q, J = 286.0 Hz), 127.1, 128.5, 128.8, 129.2, 135.2, 136.8, 169.3. HRMS (ESI$^+$): *m*/*z* calcd for $C_{21}H_{24}F_3NaNO_3S$ $[M+Na]^+$ 450.1327, found 450.1312.

(S_S,S)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-phenylbutanoate ***6c*** and *(S_S,R)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-phenylbutanoate* ***6'c***. Following the general procedure, a solution of hemiaminal **3a** (306 mg, 0.95 mmol) in 2-Me-THF (15 mL) was added to a suspension of activated Zn (618 mg, 9.45 mmol), CuCl (94 mg, 0.95 mmol) and *tert*-butyl bromoacetate (347 µL, 2.36 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 5h at 0°C. Purification of the residue (dr **6c**: **6'c** = 93:7) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded *β*-amino ester **6'c** (13 mg, 3%) as a colorless oil, an intermediate fraction containing **6'c** and **6c** (15 mg, 4%), and *β*-amino ester **6c** (241 mg, 65%) as a beige oil. **6c**: $[\alpha]_D^{20}$ +70 (*c* 1.08, $CHCl_3$); IR (film) ν_{max} 1078, 1155, 1260, 1276, 1368, 1723, 2981 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -74.3 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.27 (s, 9H), 1.40 (s, 9H), 3.08 (d, *J* = 15.5 Hz, 1H), 3.26 (d, *J* = 15.5 Hz, 1H), 6.24 (s, 1H), 7.38 (m, 3H), 7.60 (d, *J* = 7.5 Hz, 2H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 22.8, 27.9, 40.6, 57.0, 65.3 (q, *J* = 27.0 Hz), 82.4, 125.4 (q, *J* = 286.5 Hz), 128.4, 128.7, 129.3, 134.1, 169.4. HRMS (ESI^+): *m/z* calcd for $C_{18}H_{26}F_3NaNO_3S$ $[M+Na]^+$ 416.1483, found 416.1471. **6'c**: IR (film) ν_{max} 1077, 1263, 1275, 1726, 2928, 2984 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -72.9 (s, CF_3); NMR ^1H (250 MHz, $CDCl_3$) δ 1.33 (s, 9H), 3.32 (d, *J* = 17.0 Hz, 1H), 3.52 (d, *J* = 17.0 Hz, 1H), 5.12 (s, 1H), 7.39 (m, 3H), 7.53 (m, 2H). HRMS (ESI^+): *m/z* calcd for $C_{18}H_{26}F_3NaNO_3S$ $[M+Na]^+$ 416.1483, found 416.1482.

(S_S,S)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-fluorophenyl)butanoate ***6d*** and *(S_S,R)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-fluorophenyl)butanoate* ***6'd***. Following the general procedure, a solution of hemiaminal **3b** (403 mg, 1.18 mmol) in 2-Me-THF (15 mL) was added to a suspension of activated Zn (772 mg, 11.8 mmol), CuCl (117 mg, 1.18 mmol) and ethyl bromoacetate (327 µL, 2.95 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 5h30 at 0°C. Purification of the residue (dr **6d**: **6'd** = 86:14) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded

an unseparable mixture of *β*-amino esters **6d** and **6'd** (348 mg, 77%) as a pale yellow oil. IR (film) ν_{max} 1078, 1169, 1515, 1729, 2983 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -73.3 (s, CF_3, minor), -75.2 (s, CF_3, major), -112.2 (m, CF, major), -112.9 (m, CF, minor); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.16 (t, *J* = 7.0 Hz, 3H, minor), 1.22 (t, *J* = 7.0 Hz, 3H, major), 1.26 (s, 9H, major), 1.29 (s, 9H, minor), 3.18 (d, *J* = 16.0 Hz, 1H, major), 3.33 (d, *J* = 16.0 Hz, 1H, major), 3.36 (d, *J* = 17.5 Hz, 1H, minor), 3.59 (d, *J* = 17.5 Hz, 1H, minor), 4.06 (m, 2H, minor), 4.15 (m, 2H, major), 5.10 (s, 1H, minor), 6.25 (s, 1H, major), 7.04 (t, *J* = 9.0 Hz, 2H, minor), 7.07 (t, *J* = 8.5 Hz, 2H, major), 7.47 (dd, *J* = 5.0 Hz, *J* = 9.0 Hz, 2H, minor), 7.56 (dd, *J* = 5.0 Hz, 8.5 Hz, 2H, major); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.0 (minor and major), 22.5 (minor), 22.7 (major), 38.2 (minor), 39.1 (major), 57.0 (major), 57.3 (minor), 61.3 (minor), 61.5 (major), 64.5 (q, *J* = 27.5 Hz, minor), 64.6 (q, *J* = 27.5 Hz, major), 115.4 (d, *J* = 22.0 Hz, major), 115.6 (d, *J* = 21.5 Hz, minor), 124.7 (q, *J* = 285.5 Hz, minor), 125.1 (q, *J* = 286.0 Hz, major), 129.0 (d, *J* = 8.5 Hz, minor), 129.3 (d, *J* = 3.5 Hz, major), 130.8 (d, *J* = 8.5 Hz, major), 132.7 (d, *J* = 3.5 Hz, minor), 162.9 (d, *J* = 249.5 Hz, minor), 163.1 (d, *J* = 250.0 Hz, major), 169.4 (minor), 170.2 (major). HRMS (ESI^{+}): *m/z* calcd for $C_{16}H_{21}F_4NaNO_3S$ $[M+Na]^+$ 406.1076, found 406.1080.

(S_S,S)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-fluorophenyl)butanoate ***6e*** and *(S_S,R)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-fluorophenyl)butanoate* ***6'e***. Following the general procedure, a solution of hemiaminal **3b** (378 mg, 1.11 mmol) in 2-Me-THF (15 mL) was added to a suspension of activated Zn (724 mg, 11.1 mmol), CuCl (110 mg, 1.11 mmol) and *tert*-butyl bromoacetate (409 µL, 2.79 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 5h30 at 0°C. Purification of the residue (dr **6e**: **6'e** = 93:7) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded *β*-amino ester **6'e** (8 mg, 2%) as a colorless oil and *β*-amino ester **6e** (305 mg, 67%) as a colorless oil. **6e**: $[\alpha]_D^{20}$ +75 (*c* 0.99, $CHCl_3$); IR (film)

ν_{max} 1079, 1157, 1242, 1369, 1515, 1723, 2981 cm^{-1}; NMR ^{19}F (235 MHz, CDCl$_3$) δ -74.4 (s, CF$_3$), -112.6 (m, CF); NMR ^{1}H (500 MHz, CDCl$_3$) δ 1.27 (s, 9H), 1.40 (s, 9H), 3.05 (d, *J* = 15.5 Hz, 1H), 3.22 (d, *J* = 15.5 Hz, 1H), 6.26 (s, 1H), 7.08 (t, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 5.0 Hz, 8.5 Hz, 2H); NMR ^{13}C (125.8 MHz, CDCl$_3$) δ 22.8, 28.0, 40.7, 57.1, 65.1 (q, *J* = 27.5 Hz), 82.7, 115.4 (d, *J* = 21.5 Hz), 125.3 (q, *J* = 286.5 Hz), 130.0 (d, *J* = 3.5 Hz), 130.9 (d, *J* = 8.5 Hz), 163.1 (d, *J* = 250.0 Hz), 169.3. HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{25}F_4NaNO_3S$ [M+Na]$^+$ 434.1389, found 434.1380. **6'e**: IR (film) ν_{max} 1079, 1158, 1241, 1253, 1512, 1772, 2980 cm^{-1}; NMR ^{19}F (235 MHz, CDCl$_3$) δ -73.1 (s, CF$_3$), -113.1 (m, CF); NMR ^{1}H (250 MHz, CDCl$_3$) δ 1.32 (s, 9H), 1.34 (s, 9H), 3.29 (d, *J* = 17.0 Hz, 1H), 3.53 (d, *J* = 17.0 Hz, 1H), 5.11 (s, 1H), 7.08 (t, *J* = 7.0 Hz, 2H), 7.51 (dd, *J* = 5.0 Hz, *J* = 8.5 Hz, 2H). HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{25}F_4NaNO_3S$ [M+Na]$^+$ 434.1389, found 434.1390.

(S$_S$,S)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-nitrophenyl)butanoate ***6f*** and *(S$_S$,R)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-nitrophenyl)butanoate* ***6'f***. Following the general procedure, a solution of hemiaminal **3c** (247 mg, 0.67 mmol) in 2-Me-THF (8 mL) was added to a suspension of activated Zn (439 mg, 6.71 mmol), CuCl (66 mg, 0.67 mmol) and *tert*-butyl bromoacetate (246 μL, 1.68 mmol) in 2-Me-THF (3 mL). The reaction mixture was stirred 6h at 0°C. Purification of the residue (dr **6f**: **6'f** = 96:4) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded *β*-amino ester **6'f** (9 mg, 3%) as a colorless oil and *β*-amino ester **6f** (233 mg, 79%) as a colorless oil. **6f**: $[\alpha]_D^{20}$ +49 (*c* 1.10, CHCl$_3$); IR (film) ν_{max} 1078, 1159, 1351, 1526, 1722, 2981 cm^{-1}; NMR ^{19}F (235 MHz, CDCl$_3$) δ -73.6 (s, CF$_3$); NMR ^{1}H (500 MHz, CDCl$_3$) δ 1.28 (s, 9H), 1.39 (s, 9H), 3.08 (d, *J* = 16.0 Hz, 1H), 3.25 (d, *J* = 16.0 Hz, 1H), 6.26 (s, 1H), 7.85 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 16.0 Hz, 2H); NMR ^{13}C (125.8 MHz, CDCl$_3$) δ 22.7, 27.9, 40.7, 57.6, 65.7 (q, *J* = 27.5 Hz), 83.2, 123.4, 124.9 (q, *J* =

287.0 Hz), 130.1, 141.6, 148.2, 168.8. HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{25}F_3NaN_2O_5S$ [M+Na]$^+$ 461.1334, found 461.1339. **6'f**: IR (film) ν_{max} 1080, 1161, 1351, 1527, 1723, 2980 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -72.6 (s, CF_3); NMR ^{1}H (250 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.36 (s, 9H), 3.36 (d, *J* = 17.5 Hz, 1H), 3.61 (d, *J* = 17.5 Hz, 1H), 5.16 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 2H), 8.26 (d, *J* = 9.0 Hz, 2H). HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{25}F_3NaN_2O_5S$ [M+Na]$^+$ 461.1334, found 461.1351.

(S$_S$,S)-(+)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(3-methoxyphenyl)butanoate ***6g***. Following the general procedure, a solution of hemiaminal **3d** (226 mg, 0.64 mmol) in 2-Me-THF (10 mL) was added to a suspension of activated Zn (418 mg, 6.40 mmol), CuCl (63 mg, 0.64 mmol) and ethyl bromoacetate (177 µL, 1.60 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 4h30 at 0°C. Purification of the residue (dr **6g**:**6'g** = 90:10) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded *β*-amino ester **6g** (163 mg, 64%) as a colorless oil. $[\alpha]_D^{20}$ +80 (*c* 1.28, $CHCl_3$); IR (film) ν_{max} 1078, 1178, 1258, 1393, 1435, 1587, 1605, 1728, 2962, 2981 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -74.7 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 3H), 1.29 (s, 9H), 3.19 (d, *J* = 16.0 Hz, 1H), 3.36 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 4.18 (m, 2H), 6.22 (s, 1H), 6.93 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.1, 22.9, 39.4, 55.5, 57.1, 61.5, 65.2 (q, *J* = 27.5 Hz), 114.9, 115.3, 120.8, 125.3 (q, *J* = 286.5 Hz), 129.4, 135.2, 159.6, 170.4. HRMS (ESI$^+$): *m*/*z* calcd for $C_{17}H_{24}F_3NaNO_4S$ [M+Na]$^+$ 418.1276, found 418.1286.

(S$_S$,S)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(3-methoxyphenyl)butanoate ***6h*** and *(S$_S$,S)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(3-methoxyphenyl)butanoate* ***6'h***. Following the general procedure, a solution of hemiaminal **3d** (299 mg, 0.85 mmol) in 2-Me-THF (10 mL) was added to a suspension

of activated Zn (553 mg, 8.46 mmol), CuCl (84 mg, 0.85 mmol) and *tert*-butyl bromoacetate (310 μL, 2.11 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 21h at 0°C. Purification of the residue (dr **6h**: **6'h** = 93:7) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded β-amino ester **6'h** (9 mg, 2%) as a colorless oil and β-amino ester **6h** (252 mg, 70%) as a white solid. **6h**: mp 95-97°C; $[\alpha]_D^{20}$ +60 (*c* 1.14, $CHCl_3$); IR (film) ν_{max} 1078, 1155? 1176, 1259, 1368, 1722, 2980 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -73.9 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.40 (s, 9H), 3.04 (d, *J* = 15.5 Hz, 1H), 3.24 (d, *J* = 15.5 Hz, 1H), 3.81 (s, 3H), 6.19 (s, 1H), 6.91 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 7.29 (t, *J* = 8.0 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 22.9, 28.0, 40.9, 55.5, 57.2, 65.6 (q, *J* = 27.0 Hz), 82.5, 114.8, 115.1, 120.7, 125.4 (q, *J* = 286.5 Hz), 129.3, 135.8, 159.5, 169.4. HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{28}F_3NaNO_4S$ $[M+Na]^+$ 446.1589, found 446.1608. An analytical sample of **6h** was crystallized from Et_2O. **6'h**: IR (film) ν_{max} 1154, 1259, 1275, 1725, 2978 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -72.8 (s, CF_3); NMR ^1H (250 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.34 (s, 9H), 3.28 (d, *J* = 17.0 Hz), 3.51 (d, *J* = 17.0 Hz), 3.80 (s, 3H), 5.13 (s, 1H), 6.90 (m, 1H), 7.08 (m, 2H), 7.34 (m, 1H). (ESI$^+$): *m/z* calcd for $C_{19}H_{28}F_3NaNO_4S$ $[M+Na]^+$ 446.1589, found 446.1582.

(S_S,S)-(+)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-methoxyphenyl)butanoate ***6i*** and *(S_S,R)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-methoxyphenyl)butanoate* ***6'i***. Following the general procedure, a solution of hemiaminal **3e** (211 mg, 0.60 mmol) in 2-Me-THF (10 mL) was added to a suspension of activated Zn (391 mg, 5.98 mmol), CuCl (59 mg, 0.60 mmol) and ethyl bromoacetate (166 μL, 1.50 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 4h30 at 0°C. Purification of the residue (dr **6i**: **6'i** = 82:18) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded β-amino ester **6'i** (21 mg, 9%) as an off-white solid, an intermediate fraction

containing **6'i** and **6i** (4 mg, 2%), and *β*-amino ester **6i** (135 mg, 57%) as a colorless oil. **6i**: $[\alpha]_D^{20}$ +100 (*c* 1.21, $CHCl_3$); IR (film) ν_{max} 1077, 1161, 1518, 1728, 2963, 2981, 3245 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -75.4 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 3H), 1.27 (s, 9H), 3.20 (d, *J* = 16.0 Hz, 1H), 3.34 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 4.17 (m, 2H), 6.26 (s, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 2H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.0, 22.8, 39.1, 55.3, 56.8, 61.4, 64.4 (q, *J* = 27.5 Hz), 113.7, 125.1, 125.4 (q, *J* = 286.0 Hz), 130.2, 160.2, 170.6. HRMS (ESI^+): *m/z* calcd for $C_{17}H_{24}F_3NaNO_4S$ $[M+Na]^+$ 418.1276, found 418.1281. **6'i**: mp 123-124°C; IR (film) ν_{max} 1077, 1158, 1180, 1257, 1515, 1732, 2963, 2981 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -73.4 (s, CF_3); NMR ^1H (600 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 1.32 (s, 9H), 3.37 (d, *J* = 17.0 Hz, 1H), 3.57 (d, *J* = 17.0 Hz, 1H), 3.80 (s, 3H), 4.10 (q, *J* = 7.0 Hz, 2H), 5.11 (s, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H); NMR ^{13}C (151.0 MHz, $CDCl_3$) δ 14.1, 22.7, 38.3, 55.4, 57.3, 61.3, 64.5 (q, *J* = 27.0 Hz), 114.0, 125.0 (q, *J* = 286.0 Hz), 128.4, 128.7, 160.0, 169.6. HRMS (ESI^+): *m/z* calcd for $C_{17}H_{25}F_3NO_4S$ $[M+H]^+$ 396.1456, found 396.1448.

(S_S,S)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(4-methoxyphenyl)butanoate ***6j***. Following the general procedure, a solution of hemiaminal **3e** (321 mg, 0.91 mmol) in 2-Me-THF (10 mL) was added to a suspension of activated Zn (594 mg, 9.08 mmol), CuCl (90 mg, 0.91 mmol) and *tert*-butyl bromoacetate (333 μL, 2.27 mmol) in 2-Me-THF (5 mL). The reaction mixture was stirred 21h at 0°C. Purification of the residue (dr **6j**: **6'j** = 90:10) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded *β*-amino ester **6j** (274 mg, 71%) as a white solid. mp 112-114°C; $[\alpha]_D^{20}$ +84 (*c* 1.01, $CHCl_3$); IR (film) ν_{max} 1077, 1154, 1260, 1518, 1723, 2979 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -74.7 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.41 (s, 9H), 3.05 (d, *J* = 15.5 Hz, 1H), 3.22 (d, *J* = 15.5 Hz, 1H), 3.78 (s, 3H), 6.27 (s , 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 2H);

NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 22.8, 27.9, 40.5, 55.2, 56.8, 64.8 (q, J = 27.5 Hz), 82.3, 113.6, 127.0 (q, J = 286.5 Hz), 125.6, 130.1, 160.1, 169.6. HRMS (ESI$^+$): m/z calcd for $C_{19}H_{28}F_3NaNO_4S$ $[M+Na]^+$ 446.1589, found 446.1576.

(S$_S$,R)-(+)-Methyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-methylbutanoate ***6k***. . Following the general procedure, a solution of hemiaminal **3f** (677 mg, 2.59 mmol) in 2-Me-THF (20 mL) was added to a suspension of activated Zn (1.69 g, 25.9 mmol), CuCl (256 mg, 2.59 mmol) and methyl bromoacetate (615 μL, 6.48 mmol) in 2-Me-THF (10 mL). The reaction mixture was stirred 4h at 0°C. Purification of the residue (dr **6k**: **6'k** > 99:1) on silica gel (petroleum ether:EtOAc 4:1 to 3:2) afforded *β*-amino ester **6k** (648 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ +76 (c 0.97, $CHCl_3$); IR (film) ν_{max} 1071, 1170, 1728, 2931, 3265 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -81.0 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.56 (s, 3H), 2.59 (d, J = 15.5 Hz, 1H), 2.66 (d, J = 15.5 Hz, 1H), 3.60 (s, 3H), 5.51 (s, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 19.3, 22.4, 40.1, 52.1, 56.3, 58.9 (q, J = 28.0 Hz), 125.6 (q, J = 285.0 Hz), 170.4. HRMS (ESI$^+$): m/z calcd for $C_{10}H_{18}F_3NaNO_3S$ $[M+Na]^+$ 312.0857, found 312.0865.

(S$_S$,R)-(+)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-methylbutanoate ***6l***. Following the general procedure, a solution of hemiaminal **3f** (838 mg, 3.21 mmol) in 2-Me-THF (25 mL) was added to a suspension of activated Zn (2.10 g, 32.1 mmol), CuCl (318 mg, 3.21 mmol) and ethyl bromoacetate (889 μL, 8.02 mmol) in 2-Me-THF (15 mL). The reaction mixture was stirred 4h30 at 0°C. Purification of the residue (dr **6l**: **6'l** > 99:1) on silica gel (petroleum ether:EtOAc 4:1 to 2:1) afforded *β*-amino ester **6l** (766 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$ +71 (c 1.03, $CHCl_3$); IR (film) ν_{max} 1077, 1170, 1724, 2984, 3263 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -80.9 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.12 (t, J = 7.0 Hz, 3H), 1.53 (s, 3H), 2.55 (d, J = 15.0 Hz, 1H), 2.61 (d, J = 15.0 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 5.55 (s, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 13.8, 19.2,

22.4, 40.3, 56.2, 58.9 (q, *J* = 28.0 Hz), 61.3, 125.6 (q, *J* = 285.0 Hz), 169.9. HRMS (ESI$^+$): *m*/*z* calcd for $C_{11}H_{21}F_3NO_3S$ [M+H]$^+$ 304.1194, found 304.1199.

(S_S,R)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-methylbutanoate ***6m***. Following the general procedure, a solution of hemiaminal **3f** (545 mg, 2.09 mmol) in 2-Me-THF (20 mL) was added to a suspension of activated Zn (1.37 g, 20.9 mmol), CuCl (207 mg, 2.09 mmol) and *tert*-butyl bromoacetate (765 µL, 5.21 mmol) in 2-Me-THF (10 mL). The reaction mixture was stirred 20h at 0°C. Purification of the residue (dr **6m**:**6'm** > 99:1) on silica gel (petroleum ether:EtOAc 6:1 to 4:1) afforded *β*-amino ester **6m** (454 mg, 68%) as a white solid. mp 39-40°C; $[\alpha]_D^{20}$ +66 (*c* 1.10, $CHCl_3$); IR (film) ν_{max} 1070, 1157, 1717, 2871, 3252 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -80.6 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.45 (s, 9H), 1.65 (s, 3H), 2.57 (d, *J* = 15.0 Hz, 1H), 2.62 (d, *J* = 15.0 Hz, 1H), 5.66 (s, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 19.6, 22.7, 28.0, 41.7, 56.5, 59.1 (q, *J* = 28.0 Hz), 82.8, 126.0 (q, *J* = 285.0 Hz), 169.3. HRMS (ESI$^+$): *m*/*z* calcd for $C_{13}H_{24}F_3NaNO_3S$ [M+Na]$^+$ 354.1327, found 354.1321.

(S_S,R)-(+)-Ethyl N-(tert-butanesulfinyl)-3-amino-3-(trifluoromethyl)pentanoate ***6n***. Following the general procedure, a solution of hemiaminal **3g** (179 mg, 0.58 mmol) in 2-Me-THF (8 mL) was added to a suspension of activated Zn (377 mg, 5.76 mmol), CuCl (57 mg, 0.58 mmol) and ethyl bromoacetate (159 µL, 1.44 mmol) in 2-Me-THF (3 mL). The reaction mixture was stirred 4h at 0°C. Purification of the residue (dr **6n**:**6'n** > 99:1) on silica gel (petroleum ether:EtOAc 6:1 to 2:1) afforded *β*-amino ester **6n** (159 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +45 (*c* 1.12, $CHCl_3$); IR (film) ν_{max} 1079, 1171, 1723, 2960, 2983, 3259, 3313 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -77.3 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.5 Hz, 3H), 1.21 (s, 9H), 1.24 (t, *J* = 7.0 Hz, 3H), 2.01 (quint, *J* = 7.5 Hz, 1H), 2.18 (quint, *J* = 7.5 Hz, 1H), 2.63 (d, *J* = 15.0 Hz, 1H), 2.68 (d, *J* = 15.0 Hz), 4.15 (q, *J* = 7.0 Hz, 2H), 5.67 (s, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 7.8, 14.0, 22.6,

26.0, 37.4, 56.9, 61.6, 65.3 (q, J = 26.5 Hz), 126.1 (q, J = 286.5 Hz), 170.6. HRMS (ESI$^+$): m/z calcd for $C_{12}H_{22}F_3NaNO_3S$ [M+Na]$^+$ 340.1170, found 340.1173.

(S$_S$,R)-(+)-tert-Butyl N-(tert-butanesulfinyl)-3-amino-3-(trifluoromethyl)pentanoate ***6o***. Following the general procedure, a solution of hemiaminal **3g** (142 mg, 0.52 mmol) in 2-Me-THF (8 mL) was added to a suspension of activated Zn (338 mg, 5.17 mmol), CuCl (51 mg, 0.52 mmol) and *tert*-butyl bromoacetate (190 μL, 1.29 mmol) in 2-Me-THF (3 mL). The reaction mixture was stirred 4h at 0°C. Purification of the residue (dr **6o**: **6'o** > 99:1) on silica gel (petroleum ether:EtOAc 4:1) afforded *β*-amino ester **6o** (155 mg, 87%) as a white solid. mp 58-59°C; $[\alpha]_D^{20}$ +44 (*c* 1.01, $CHCl_3$); IR (film) ν_{max} 1078, 1157, 1716, 2981, 3251 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -77.2 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.06 (t, J = 7.5 Hz, 3H), 1.19 (s, 9H), 1.40 (s, 9H), 1.97 (quint, J = 7.5 Hz, 1H), 2.15 (quint, J = 7.5 Hz, 1H), 2.49 (d, J = 15.0 Hz, 1H), 2.57 (d, J = 15.0 Hz, 1H), 5.67 (s, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 7.7, 22.6, 26.0, 27.9, 38.1, 56.8, 62.4 (q, J = 26.5 Hz), 82.6, 126.2 (q, J = 286.5 Hz), 169.7. HRMS (ESI$^+$): m/z calcd for $C_{14}H_{26}F_3NaNO_3S$ [M+Na]$^+$ 368.1483, found 368.1484.

(S$_S$,S)-(+)-Ethyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-(2-methoxyphenyl)butanoate ***6p***. Following the general procedure, a solution of imine **4** (342 mg, 1.12 mmol) in 2-Me-THF (20 mL) was added to a suspension of activated Zn (732 mg, 11.2 mmol), CuCl (111 mg, 1.12 mmol) and ethyl bromoacetate (308 μL, 2.78 mmol) in 2-Me-THF (10 mL). The reaction mixture was stirred 24h at 0°C. Purification of the residue (dr **6p**:**6'p** > 99:1) on silica gel (petroleum ether:EtOAc 2:3) afforded the residual imine **4** (255 mg, 74%) as a yellow oil and *β*-amino ester **6p** (60 mg, 14%) as a colorless oil. $[\alpha]_D^{20}$ +94 (*c* 1.07, $CHCl_3$); IR (film) ν_{max} 1026, 1076, 1168, 1255, 1724, 1748, 2929, 2963, 2982, 3301 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -74.2 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.21 (t, J = 7.0 Hz, 3H), 1.22 (s, 9H), 3.20 (d, J = 16.5 Hz, 1H), 3.68 (d, J =

16.5 Hz, 1H), 3.88 (s, 3H), 4.18 (m, 2H), 6.23 (s, 1H), 6.96 (m, 2H), 7.36 (td, *J* = 1.5 Hz, J = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.1, 22.8, 37.1, 55.7, 57.3, 61.1, 65.1 (q, *J* = 27.0 Hz), 112.8, 120.4, 122.7, 125.7 (q, *J* = 288.0 Hz), 129.1, 130.8, 158.0, 169.7. HRMS (ESI$^+$): *m*/*z* calcd for $C_{17}H_{24}F_3NaNO_4S$ $[M+Na]^+$ 418.1276, found 418.1277.

General procedures for the synthesis of 7.

A solution of *β*-amino ester **6** and $LiOH.H_2O$ (2-6 equiv) in a solution of MeOH or EtOH:H_2O (3:1) or THF:H_2O (1:1) was stirred at rt or at reflux. The reaction mixture was then concentrated under reduced pressure. The residue was diluted with AcOEt and acidified with HCl 1M (pH=1). The organic layer was separated and the aqueous layer was extracted thrice with AcOEt. The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to afford *β*-amino acid **7**.

(S_S,R)-(+)-Methyl N-(tert-butanesulfinyl)-3-amino-4,4,4-trifluoro-3-methylbutanoic acid 7. Basic hydrolysis of methyl ester **6k**: A solution of *β*-amino ester **6k** (288 mg, 1.0 mmol) and $LiOH.H_2O$ (84 mg, 1.99 mmol, 2 equiv) in MeOH (2.4 mL) and H_2O (800 μL) was stirred 3h30 at rt to afford *β*-amino acid **7** (274 mg, 99%) as a white cloudy solid. *Basic hydrolysis of ethyl ester* **6l**: A solution of *β*-amino ester **6l** (150 mg, 0.49 mmol) and $LiOH.H_2O$ (41 mg, 0.99 mmol, 2 equiv) in MeOH (1.5 mL) and H_2O (500 μL) was stirred 3h30 at rt to afford *β*-amino acid **7** (124 mg, 92%) as a white cloudy solid. *Basic hydrolysis of tert-butyl ester* **6m**: A solution of *β*-amino ester **6m** (46 mg, 0.145 mmol) and $LiOH.H_2O$ (36 mg, 0.87 mmol, 6 equiv) in THF (400 μL) and H_2O (400 μL) was stirred 14h at reflux to afford *β*-amino acid **7** (31 mg, 78%) as a white cloudy solid. mp 139-140°C; $[\alpha]_D^{20}$ +63 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 1031, 1128, 1713, 2961, 2987, 3000, 3256 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -80.8 (s, CF_3); NMR ^{1}H (500 MHz,

$CDCl_3$) δ 1.25 (s, 9H), 1.68 (s, 3H), 2.67 (d, *J* = 15.5 Hz, 1H), 2.73 (d, *J* = 15.5 Hz, 1H), 5.91 (s, 1H), 10.08 (br s, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 19.3, 22.7, 39.7, 57.3, 59.3 (q, *J* = 28.0 Hz), 125.8 (q, *J* = 284.5 Hz), 171.6. HRMS (ESI^+): *m*/*z* calcd for $C_9H_{16}F_3NaNO_3S$ $[M+Na]^+$ 298.0701, found 298.0708.

General procedure for the coupling reaction of *β*-amino acid 9 with *α*-amino esters hydrochlorides.

A solution of amino acid **7**, *α*-amino ester hydrochloride (2 equiv), EDCI (2.2 equiv), DIEA (4 equiv) and HOBt (2.2 equiv) in DMF was stirred for 24h at rt and under Ar. The reaction mixture was then diluted with CH_2Cl_2, washed with HCl 10%, a saturated aqueous solution of $NaHCO_3$, H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2:MeOH).

(S_S,2S,3'R)-(+)-Methyl 2-[N-(tert-butanesulfinyl)-3'-amino-4',4',4'-trifluoro-3'-methylbutanamido]propanoate ***8a***. Following the general procedure, amino acid **7** (611 mg, 2.22 mmol) reacted with L-alanine methylester hydrochloride (620 mg, 4.44 mmol), EDCI (759 mg, 4.88 mmol), DIEA (1.55 mL, 8.88 mmol) and HOBt (660 mg, 4.88 mmol) in DMF (8 mL). Purification of the residue on silica gel (CH_2Cl_2:MeOH 13:1) afforded dipeptide **8a** (742 mg, 93%) as a brown oil. $[\alpha]_D^{20}$ +50 (*c* 1.10, $CHCl_3$); IR (film) ν_{max} 1055, 1153, 1554, 1661, 1748, 2930, 3263 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -80.4 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.23 (s, 9H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.64 (s, 3H), 2.57 (d, *J* = 14.5 Hz, 1H), 2.62 (d, *J* = 14.5 Hz, 1H), 3.72 (s, 3H), 4.53 (quint, *J* = 7.0 Hz, 1H), 6.11 (s, 1H), 6.94 (d, *J* = 7.0 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 18.1, 19.8, 22.7, 41.9, 48.3, 52.6, 56.5, 59.7 (q, *J* = 28.0 Hz), 125.9 (q, *J* = 285.0 Hz), 168.7, 173.1. HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{23}F_3NaN_2O_4S$ $[M+Na]^+$ 383.1228, found 383.1221.

(S_S,2S,3'R)-(+)-Ethyl 2-[N-(tert-butanesulfinyl)-3'-amino-4',4',4'-trifluoro-3'-methylbutanamido]-3-phenylpropanoate ***8b***. Following the general procedure, amino acid **7**

(81 mg, 0.292 mmol) reacted with L-phenylalanine ethylester hydrochloride (134 mg, 0.585 mmol), EDCI (100 mg, 0.642 mmol), DIEA (203 µL, 1.17 mmol) and HOBt (87 mg, 0.642 mmol) in DMF (1.5 mL). Purification of the residue on silica gel (CH_2Cl_2:MeOH 18:1) afforded dipeptide **8b** (127 mg, 96%) as a beige oil. $[\alpha]_D^{20}$ +80 (*c* 0.98, $CHCl_3$); IR (film) ν_{max} 1054, 1154, 1662, 1741, 2929, 2960, 3264 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -80.2 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.0 Hz, 3H), 1.24 (s, 9H), 1.59 (s, 3H), 2.55 (d, *J* = 15.0 Hz, 1H), 2.58 (d, *J* = 15.0 Hz, 1H), 3.10 (m, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.83 (dd, *J* = 6.5 Hz, *J* = 14.0 Hz, 1H), 6.29 (s, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 2H), 7.25 (m, 3H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.0, 19.7, 22.6, 37.5, 41.3, 53.3, 56.4, 59.6 (q, *J* = 27.5 Hz), 61.6, 125.8 (q, *J* = 285.0 Hz), 127.1, 128.6, 129.2, 135.9, 168.9, 171.2. HRMS (ESI^+): *m/z* calcd for $C_{20}H_{29}F_3NaN_2O_4S$ $[M+Na]^+$ 473.1698, found 473.1711.

General procedure for the deprotection of *N-tert*-butanesulfinyl dipeptides 8.

An alcoholic solution of *N-tert*-butanesulfinyldipeptide **8** reacted with HCl (2N in Et_2O). After 45 min of stirring at rt under Ar, the reaction mixture was concentrated under reduced pressure. The residue was diluted with HCl 2% and washed with Et_2O and *n*-hexane. The aqueous layer was then basified (pH ~ 9) with solid Na_2CO_3 and extracted thrice with AcOEt. The AcOEt layers were combined, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure.

(2S,3'R)-(-)-Methyl 2-(3'-amino-4',4',4'-trifluoro-3'-methylbutanamido)propanoate ***9a***. Reaction of *N-tert*-butanesulfinyl dipeptide **8a** (542 mg, 1.50 mmol) in MeOH (18 mL) with HCl (2N in Et_2O, 9 mL) afforded dipeptide **9a** (314 mg, 82%) as a pale yellow solid. mp 83-84°C $[\alpha]_D^{20}$ -3.5 (*c* 0.98, $CHCl_3$); IR (film) ν_{max} 1170, 1542, 1657, 1743, 3301 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -84.4 (s, CF_3); NMR ^1H (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.38 (d, *J* = 7.5 Hz, 3H), 1.80 (br s, 2H), 2.40 (d, *J* = 15.0 Hz, 1H), 2.47 (d, *J* = 15.0 Hz, 1H), 3.71 (s, 3H), 4.57 (quint, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 6.0 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 18.1,

19.1, 40.5, 47.9, 52.4, 55.5 (q, *J* = 27.5 Hz), 127.1 (q, *J* = 284.5 Hz), 168.8, 173.7. HRMS (ESI$^+$): *m*/*z* calcd for $C_9H_{16}F_3N_2O_3$ [M+H]$^+$ 257.1113, found 257.1105.

(2S,3'R)-(+)-Methyl 2-(3'-amino-4',4',4'-trifluoro-3'-methylbutanamido)-3-phenylpropanoate ***9b***. Reaction of *N*-*tert*-butanesulfinyl dipeptide **8b** (125 mg, 0.278 mmol) in MeOH (3 mL) with HCl (2N in Et_2O, 1.5 mL) afforded dipeptide **9b** (75 mg, 78%) as a pale yellow oil. $[\alpha]_D^{20}$ +23 (*c* 1.23, $CHCl_3$); IR (film) ν_{max} 1170, 1542, 1657, 1739, 2985, 3297 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -84.4 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.38 (s, 3H), 1.85 (br s, 2H), 2.42 (d, *J* = 15.0 Hz, 1H), 2.47 (d, *J* = 15.0 Hz, 1H), 3.11 (dd, *J* = 6.5 Hz, *J* = 14.0 Hz, 1H), 3.18 (dd; *J* = 6.5 Hz, 14.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.91 (q, *J* = 6.5 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.32 (t, *J* = 7.0 Hz, 2H), 8.25 (d, *J* = 7.5 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 14.1, 19.0, 37.9, 40.4, 53.2, 55.4 (q, *J* = 27.5 Hz), 61.5, 127.0 (q, *J* = 284.5 Hz), 127.1, 128.5, 129.3, 136.2, 168.7, 171.8. HRMS (ESI$^+$): *m*/*z* calcd for $C_{16}H_{22}F_3N_2O_3$ [M+H]$^+$ 347.1583, found 347.1584.

(6S,9R,13S)-methyl 1-(9H-fluoren-9-yl)-6,9,13-trimethyl-4,7,11-trioxo-9-(trifluoromethyl)-3-oxa-5,8,12-triazatetradecan-14-oate ***10***. To a solution of freshly prepared L-Fmoc-Alanine chloride[28] (137 mg, 0.415 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) was added at 0°C and under Ar a solution of dipeptide **9a** (97 mg, 0.377 mmol) and DIEA (65 µL, 0.377 mmol, 1 equiv) in CH_2Cl_2 (1 mL). After 5 min of stirring at 0°C and 18h at rt, the reaction mixture was diluted with CH_2Cl_2, washed with diluted citric acid, H_2O, a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue on silica gel (petroleum ether:EtOAc 1:1) afforded tripeptide **10** (181 mg, 87%) as a colorless oil. $[\alpha]_D^{20}$ -1.1 (*c* 1.03, $CHCl_3$); IR (film) ν_{max} 1160, 1532, 1687, 3315 cm^{-1}; NMR ^{19}F (235 MHz, $CDCl_3$) δ -79.5 (s, CF_3); NMR ^{1}H (500 MHz, $CDCl_3$) δ 1.33 (d, *J* = 7.5 Hz, 3H),

1.38 (d, J = 7.0 Hz, 3H), 1.59 (s, 3H), 2.40 (d, J = 13.5 Hz, 1H), 3.89 (s, 4H), 4.20 (t, J = 7.0 Hz, 1H), 4.38 (m, 3H), 4.49 (m, 1H), 5.97 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 7.14 (s, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H); NMR ^{13}C (125.8 MHz, $CDCl_3$) δ 17.5, 17.8, 20.3, 38.0, 47.1, 48.0, 51.1, 52.4, 58.3 (q, J = 29.0 Hz), 67.1, 120.0, 125.0, 125.9 (q, J = 286.0 Hz), 127.0, 127.7, 141.2, 143.6, 143.8, 156.4, 168.2, 173.6. HRMS (ESI$^+$): m/z calcd for $C_{27}H_{30}F_3NaN_3O_6$ $[M+Na]^+$ 572.1984, found 572.1982.

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Supporting Information

Copies of all NMR spectra and X-ray structural data (CIF) of amino ester **6h**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

References and Footnotes

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