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Graphical Abstract

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Stereo-regulated synthesis of peptides containing a *β*-trifluoromethyl-*β*-amino acid

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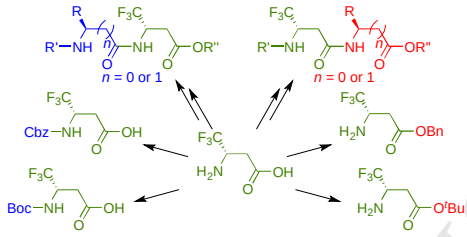

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Stereo-regulated synthesis of peptides containing a β-trifluoromethyl-β-amino acid

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ABSTRACT

For the chemical conversions of a β-trifluoromethyl-β-amino acid ((*S*)-4,4,4-trifluoro-3-aminobutyric acid, **1**), such as the *N*-terminus protection with benzyloxycarbonyl or *tert*-butoxycarbonyl group, the *C*-terminus protection with benzyl or *tert*-butyl group, and peptide elongation at the both termini, highly practical protocols were established. Through these conversions, the stereochemistry of **1** and/or its condensation counterpart was maintained. Because the protocols developed here are indispensable for the application of **1** in peptide engineering, they would expand the utility of **1** and its derivatives.

1. Introduction

The incorporation of fluorinated amino acids into peptides has emerged as a new powerful tool for peptide engineering in the last decade.[1] Owing to the peculiar characteristics of perfluoroalkyl groups, including electron-withdrawing nature, large dipole moment, hyper-hydrophobicity, and lipophobicity,[2] the partial fluorination of peptides often gives rise to significant alterations in the structures, functions, and properties of the resultant peptides.[1a,d] In addition, ^{19}F nucleus is highly NMR sensitive, occurs in 100% natural abundance, and yet rarely exists in biological systems, which allows us to monitor the surrounding environment of the fluorinated positions by NMR.[3] In particular, the incorporation of γ/δ-fluorinated α-amino acids into peptides has been extensively explored.[1]

As another class of fluorinated amino acids, β-perfluoroalkyl-β-amino acids, such as (*S*)-4,4,4-trifluoro-3-aminobutyric acid (**1**), have attracted considerable recent attention.[4] They are expected to possess favorable properties as components of fluorinated peptides, such as chemical stability, tolerance toward racemization, and proper reactivity of the amino/carboxyl groups. Moreover, the incorporation of β-perfluoroalkyl-β-amino acids into peptides would bring significant influence on the structure and properties of the peptides, in which the perfluoroalkyl groups are directly connected to their back bones, unlike peptides derived from other fluorinated amino acids, such as γ/δ-fluorinated α-amino acids. To our wonder, however, studies on the application of β-perfluoroalkyl-β-amino acids to peptide engineering have been surprisingly rare. As far as we know, even the synthesis of peptides containing β-perfluoroalkyl-β-amino acids has been limited to a few examples.[5] Furthermore, only racemates of these fluorinated amino acids were used in these early examples.

For a systematic study on the peptide synthesis using β-perfluoroalkyl-β-amino acids, one of serious obstacles is their hard accessibility, particularly in an enantiopure form. Although several groups have reported the asymmetric synthesis of β-perfluoroalkyl-β-amino acids such as **1**, most of them are not capable of producing enantiopure material in a practical scale.[6–9] Contrary to them, we have recently reported a highly practical method to obtain **1**/its antipode in an enantiopure form, in which the diastereoselective hydride reduction of a cyclic enamino-ester is the key step.[10] Owing to the advantages of this method, including easy access to starting materials, scalability, operational convenience, and high stereoselectivity, a multi-gram quantity of enantiopure **1**/its antipode can be easily produced, which would allow us to explore a new mode of peptide engineering based on **1**. Here we report the first systematic study on peptide formation using **1**, especially focusing on the retention of enantiomeric and diastereomeric purities through the

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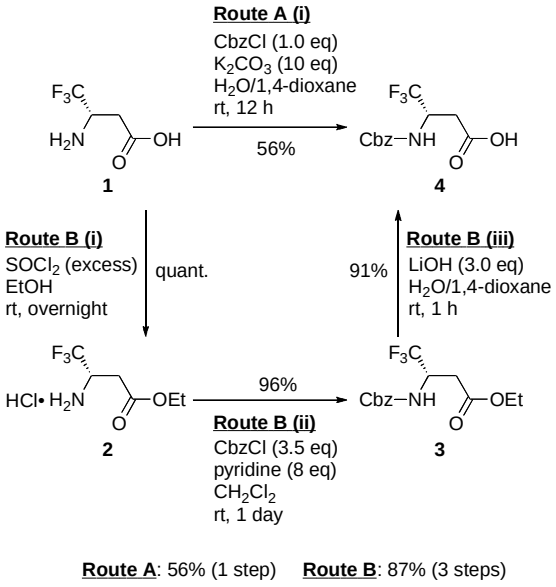
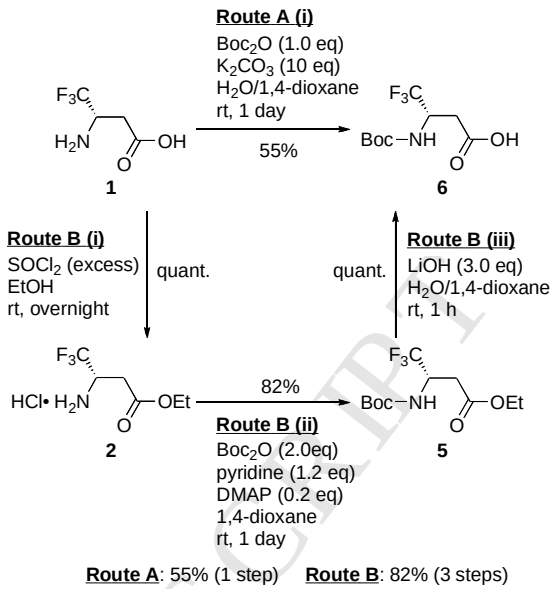


Scheme 1. *N*-Cbz protection of (*S*)-4,4,4-trifluoro-3-aminobutyric acid (**1**).



Scheme 2. *N*-Boc protection of (*S*)-4,4,4-trifluoro-3-aminobutyric acid (**1**).

protection/deprotection/coupling processes, as well as the peculiar reactivity of the amino group in **1**.

2. Results and discussion

2.1. *N*-Protection of 1.

As an indispensable step to incorporate **1** into peptides, we started our work with the protection of the amino group. Taking account of easiness in introduction and deprotection processes, benzyloxycarbonyl (Cbz) and *tert*-butoxycarbonyl (Boc) groups were chosen as the *N*-protecting groups.

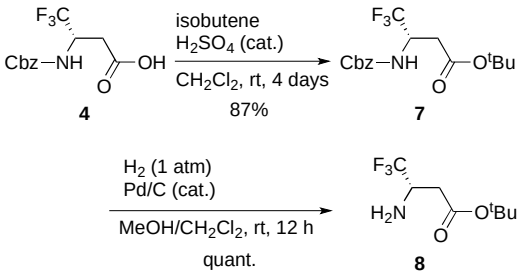
The *N*-Cbz protection of **1** was conducted according to a procedure generally used for various amino acids. For example, **1** was dissolved in an aqueous alkaline solution and then treated with benzyl chloroformate (CbzCl) at rt for 12 h with extensive stirring (Scheme 1, Route A). Although this protocol has been well established and widely used for other amino acids, the target *N*-protected amino acid **4** was obtained only in an unsatisfactory yield (56%), where a considerable amount of **1** unreacted remained. Even the optimization of reaction conditions (amount of CbzCl, pH, *etc*.) could not improve the yield (data not shown).

In the Schotten-Baumann type reactions, *i.e.* the condensation of amines with acyl chlorides in aqueous alkaline media, the amines usually work as predominant nucleophiles to react with acyl chlorides even in the presence of an excess amount of OH^-, owing to the difference in nucleophilicity. Unlike usual amines, the amino group in **1** was considered to exhibit poor nucleophilicity, comparable to or lower than that of OH^-, so that the hydrolysis of CbzCl was likely to proceed mainly. With this consideration in mind, we next examined the *N*-protection in a non-aqueous solution, which involved the following three steps (Scheme 1, Route B): (i) the derivatization of **1** into the corresponding amino ester hydrochloric acid salt **2** to enhance the solubility in an aprotic medium, (ii) the *N*-protection of the amino ester **2** under non-aqueous conditions, and (iii) the hydrolysis of the ester moiety of the resultant *N*-Cbz amino ester **3**. This synthetic route seemed to be so promising, because Soloshonok and co-workers have reported an analogous reaction; the condensation of **2** with 3,5-dinitrobenzoyl chloride proceeded efficiently in dichloromethane by using triethylamine as a base.[7d]

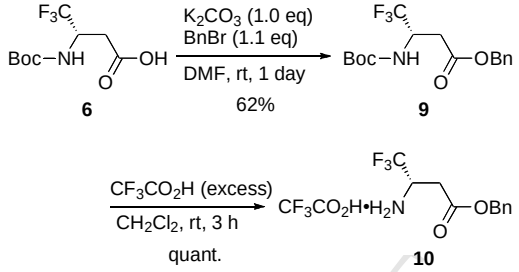
According to the reported procedure,[7d] **1** was quantitatively converted into **2** by treatment with ethanol/thionyl chloride (Scheme 1, Route B (i)). The following *N*-protection was carried out under the conditions similar to those Soloshonok *et al.* have reported, except for using CbzCl in place of phenylacetyl chloride.[9b] Against to our expectation, however, the formation of the target *N*-protected amino ester **3** was sluggish (13%), and several kinds of unidentified byproducts were afforded. Therefore, we surveyed reaction conditions and fortunately found that the yield of **3** could be highly improved by using pyridine in place of triethylamine (Scheme 1, Route B (ii), 96%). The ester part of **3** was readily hydrolyzed by treatment with an aqueous alkaline solution (Scheme 1, Route B (iii), 91%). Thus, the target *N*-protected amino acid **4** was obtained in 87% overall yield from **1** through three steps.

As described above, the choice of the base in the second step of Route B brought an unexpected effect on the yield of **3**. These observations can be elucidated as follows, taking into account of peculiar properties of the amino group in **2**. Firstly, the basicity of the amino group in **2** is comparable to or lower than that of pyridine, so that pyridine was able to work as a proton captor in this reaction system, contrary to the condensation of normal aliphatic amines, where relatively strong base such as tertiary amines are usually necessary to realize satisfactory yield. Secondly, for the acylation of this amino group, specially activated acylating reagents, such as ketenes and acyl pyridiniums, are necessary to compensate the low nucleophilicity of the amino group. In the acylation with acyl chlorides having no hydrogen at the α-position of their carbonyl group, *i.e.* with those incapable of forming ketenes, an N-heteroaromatic system with certain basicity, such as pyridine, 4-(dimethylamino)pyridine, or 1-methylimidazole, would be suitable as a base to efficiently generate activated species. On the other hand, in the reactions of acyl chlorides with a ketene-forming ability, such as the previous report by Soloshonok *et al.*,[9b] a relatively strong base can enhance the acylation.

We also performed the *N*-Boc protection of **1** by the condensation with di-*tert*-butyl dicarbonate (Boc_2O), wherein two synthetic strategies (Scheme 2, Route A and Route B) were again examined. In good agreement with the case of the *N*-Cbz



Scheme 3. *O*-^{t}Bu protection of (*S*)-4,4,4-trifluoro-3-aminobutyric acid (**1**).



Scheme 4. *O*-Bn protection of (*S*)-4,4,4-trifluoro-3-aminobutyric acid (**1**).

protection, the Schotten-Baumann type reaction was found to be unsuitable for the *N*-Boc protection of **1** (Scheme 2, Route A, 55%). Meanwhile, in the alternative route (Scheme 2, Route B), there was some room for optimization. In the second step (*N*-acylation), the protocol widely used for *O*-Boc protection was employed, taking account of the moderate nucleophilicity of the amino group in **1** comparable to the hydroxyl group in usual aliphatic alcohols. For example, the amino ester **2** was treated at rt with Boc_2O (2.0 eq) and pyridine (1.2 eq) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP; 0.2 eq) as an activator of Boc_2O. Although the yield of target *N*-Boc amino ester **5** was again unsatisfactory when the reaction was conducted in dichloromethane (60%, Table S1, entry 1), reaction efficiency was notably enhanced when 1,4-dioxane was used in place of dichloromethane (82%, Table S1, entry 2). Since the increment of reagents brought little effect on the yield of **5** (84%, Table S1, entry 3), we chose the conditions of entry 2 as optimal ones (Scheme 2, Route B (ii)). The hydrolysis of **5** proceeded smoothly to afford the target *N*-Boc protected amino acid **6** in quantitative yield (Scheme 2, Rout B (iii)). Overall, the *N*-Boc protection of **1** was achieved in 82% yield through three steps.

In the transformations shown in Schemes 1 and 2, particularly in the steps under basic/alkaline conditions, the racemization of **1** and its derivatives were anticipated. Fortunately, however, any detectable racemization did not take place in these transformations, which was confirmed by ^{19}F NMR spectroscopy by the aid of chiral NMR shift reagents (Figures S1 and S2).

2.2. *O*-Protection of 1.

It has already been reported that **1** can be readily converted into amino esters by using thionyl chloride and the corresponding alcohols.[7d] Despite its simplicity and reliability, this esterification method requires an excess amount of alcohols and is applicable only to the reaction of primary or secondary alcohols with sufficient volatility and availability in a large scale. Among esters inaccessible with this method, *tert*-butyl (^{t}Bu) and benzyl (Bn) esters of **1** are of special synthetic utility, in terms of orthogonality to other protecting groups in deprotection processes. Therefore, we attempted the synthesis of these two esters, which would expand the scope of the peptide engineering of **1**.

In general, the *O*-^{t}Bu protection of amino acids is conducted by a three-stage synthesis: the *N*-Cbz protection, the *O*-^{t}Bu protection, and the cleavage of the *N*-protecting group. We applied the same strategy for the synthesis of ^{t}Bu ester of **1** (Scheme 3). The introduction of ^{t}Bu group to **4** was conducted according to a general procedure widely employed for the *O*-protection of carboxylic acids. For example, **4** was dissolved in dichloromethane and treated with isobutene in the presence of a catalytic amount of concentrated sulfuric acid. As we expected, the target ^{t}Bu ester **7** was obtained in good yield (87%). In addition, the *N*-protecting group of **7** was smoothly cleaved by hydrogenolysis to afford the target amino acid ^{t}Bu ester **8** in quantitative yield.

The *O*-Bn protection of the carboxyl group in **1** was also achieved by employing a general procedure (Scheme 4). The *N*-Boc amino acid **6** was treated with benzyl bromide and K_2CO_3 in *N*,*N*-dimethylformamide to afford the Bn ester **9** in acceptable yield (62%). The cleavage of the *N*-protecting group was efficiently promoted by trifluoroacetic acid (TFA) to give TFA salt of the target amino acid Bn ester (**10**) in quantitative yield.

As in the case of the *N*-protection, any detectable racemization of **1** and its derivatives again did not take place through the transformations in Schemes 3 and 4, which was confirmed by ^{19}F NMR spectroscopy by the aid of chiral NMR shift reagents (Figures S3 and S4).

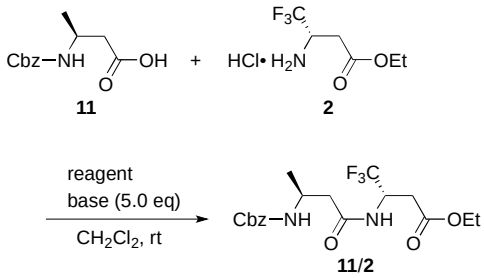
2.3. Incorporation of 1 into peptides: elongation at the *N*-terminus.

With these *N*- and *O*-protected derivatives of **1** in hand, we next attempted the synthesis of peptides incorporating **1**. Particularly, in the peptide elongation at the *N*-terminus of **1**, the low nucleophilicity of the amino group in **1** was an anticipated obstacle, as in the case of the *N*-protection of **1**. In addition, the activation method of the acid component should be carefully chosen, in order to avoid the racemization of the stereogenic centers in the components. Moreover, reaction conditions applicable to solid-state synthesis are more desirable from practical viewpoints.

Firstly, we examined the peptide-bond formation at the *N*-terminus of **1**. As an acid component, *N*-benzyloxycarbonyl-L-*β*-homoalanine (**11**) was chosen, because (i) *β*-amino acids such as **11** can be obtained by the simple homologation of natural amino acids, of which chemistry has been well explored by Seebach *et al.*,[11] and (ii) the *α*-carbon of the carboxyl group in **11** is unsubstituted and is not stereogenic, which is favorable from the viewpoints of the easiness in the activation of the carboxyl group and avoidance of complexity arising from racemization/epimerization.

The condensation of **2** with **11** is summarized in Table 1. As might be anticipated from the low nucleophilicity of the amino group in **2**, usual peptide-forming methods were found to be unsuitable for the present condensation; the usage of 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDC•HCl) and 1-hydroxybenzotriazole (HOBt), as condensing and activating reagents, respectively, afforded the target dipeptide **11**/**2** in unsatisfactory yield (Table 1, entry 1, 41%). Contrary to this, when a guanidinium-type condensing reagent (*O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate [HBTU] or *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate [HATU])

Table 1. *N*-Terminal elongation of the amino ester derived from **1** (**2**) with *N*-benzyloxycarbonyl-L-*β*-homoalanine (**11**).



entry	reagent	base	yield[a)]
1[b)]	EDC•HCl (1.0 eq), HOBt (1.0 eq)	$^{i}Pr_2NEt$	41%
2[b)]	HBTU (1.0 eq)	$^{i}Pr_2NEt$	69%
3[b)]	HATU (1.0 eq)	$^{i}Pr_2NEt$	61%
4[c)]	$(COCl)_2$ (6.0 eq)	Et_3N	64%
5[c)]	$(COCl)_2$ (6.0 eq)	Pyridine	86%

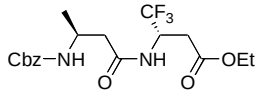
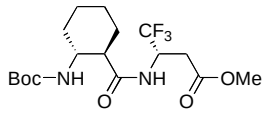
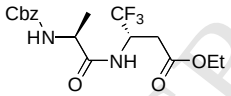
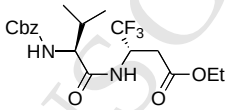
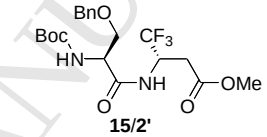
a) Isolated yield. b) **2** and a base were successively added to a mixture of **11** and condensing reagent(s). c) **11** was treated with oxalyl chloride and then reacted with **2** in the presence of a base.

was used, the yield of **11/2** was notably improved (entries 2 and 3, 69 and 61%, respectively), in good agreement with the relative reactivity of intermediates generated from these condensing reagents.[12] In every case, the obtained dipeptides exhibited a set of resonances in ^{1}H and ^{19}F NMR spectra, indicating that the racemization/epimerization of the stereogenic carbons did not occur so that the target dipeptide **11/2** was obtained in a stereopure form (Figure S5).

As an alternative approach for the same condensation, the reaction of **2** with an acyl chloride derived from **11** was examined, taking account of the cost of reagents, atom economy, convenience in isolation, and scalability. According to the reported procedure, **11** was converted into the acyl chloride by treatment with oxalyl chloride. The acyl chloride, obtained as a crude form by removal of volatiles from the reaction mixture, was then mixed with **2** in dichloromethane in the presence of a base to afford the target dipeptide **11/2** in good to excellent yields (Table 1, entries 4 and 5). In good agreement with the case of the *N*-protection of **1**, the yield of **11/2** was significantly influenced by the choice of base. When triethylamine was used as a base, **11**/**2** was obtained in 64% yield (entry 4), which is comparable to those achieved by guanidinium-type condensing reagents (HATU and HBTU). In this case, the condensation was likely to proceed via the generation of a ketene from the acyl chloride. On the other hand, when pyridine was used in place of triethylamine, the yield of **11**/**2** was improved to 86% (entry 5), most likely owing to the activity of the in-situ formed acyl pyridinium. In addition to such good yield, another benefit of this condensation method is the convenience in isolation. Because the reaction mixture contained only hydrophilic and volatile materials except for the target dipeptide, pure **11**/**2** could be isolated by simple washing of the reaction mixture with aqueous acidic and alkaline solutions. Again, the preservation of the stereochemistry of the stereogenic carbons was verified by ^{19}F NMR spectroscopy (data not shown).

Heartened by these results, we next applied these optimized conditions to the condensation with various *β*- or *α*-amino acid derivatives (**12**–**15**), in order to prove the general utility of the *β*-perfluoroalkyl *β*-amino acid **1** in peptide engineering (Table 2).

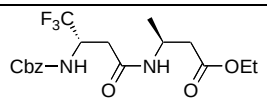
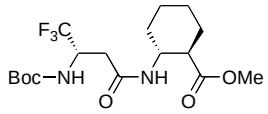
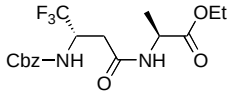
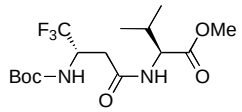
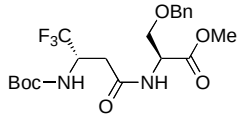
Table 2. *N*-Terminal elongation of the amino esters derived from **1** (**2** and **2'**) with various *β*- or *α*-amino acids (**11**–**15**).

entry	product	reagent	yield[a)]
1	 **11/2**	HBTU (1.0 eq)	69%
2[b)]	 **12/2'**	HBTU (1.0 eq)	9%
3[b)]		HATU (1.0 eq)	65%
4	 **13/2**	HBTU (1.0 eq)	62%
5	 **14/2**	HBTU (1.0 eq)	48%
6[b),c)]	 **15/2'**	HBTU (1.0 eq)	71%
7[b)]		DEPBT (2.0 eq)	73%

a) Isolated yield. b) In place of ethyl ester **2**, methy ester **2'** was used. c) Product was obtained as a mixture of diastereoisomers.

For the condensation with an *N*-protected *β*-amino acid with conformationally constrained structure [(1*R*,2*R*)-2-(*tert*-butoxycarbonylamino)cyclohexane-1-carboxylic acid, **12**], HBTU was not efficient as the condensing reagent (entry 2), while HATU afforded the target dipeptide **12**/**2** in satisfactory yield (entry 3), indicating the effect of steric hindrance around the carbonyl group in **12**. The procedure using HBTU was applicable to the condensation with *N*-protected *α*-amino acids [*N*-benzyloxycarbonyl-L-alanine (**13**) and *N*-benzyloxycarbonyl-L-valine (**14**)] to afford the target dipeptides in acceptable yields (entries 4 and 5). In all cases of entries 2–5, the resultant dipeptides showed a set of signals in ^{1}H and ^{19}F NMR (for ^{19}F NMR, see Figure S7, b–d), suggesting the retention of stereochemistry of stereogenic carbons through the condensation, although the stereogenic carbon in **12**–**14** are located at the *α*-position of the carbonyl group and are generally prone to racemize. Among these dipeptides, **13**/**2** was chosen as a representative to conduct more unambiguous study on stereopurity, where an authentic sample of its diastereoisomer was independently prepared, as in the case of **11**/**2** (Figure S5). Comparison of the diastereoisomers in ^{19}F NMR proved that any detectable racemization/epimerization took place through the formation of **13**/**2** (Figure S6). Only an exception was the condensation with the *N*-protected *α*-amino acid bearing a polar functionality [*O*-benzyl-*N*-(*tert*-butoxycarbonyl)-L-serine (**15**)], where HBTU caused significant stereopurity loss of the target dipeptide **15**/**2** (entry 6). However, by using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT)[13] in place of HBTU, **15**/**2** could be obtained in satisfactory yield (entry 7) in a stereopure form (Figure S7, e).

Table 3. *O*-Terminal elongation of the *N*-protected amino acids derived from **1** (**4** and **6**) with various *β*- or *α*-amino esters (**16**–**20**).

entry	product	yield[a)]
1	 **4/16**	82%
2	 **6/17**	83%
3	 **4/18**	84%
4	 **6/19**	80%
5	 **6/20**	85%

a) Isolated yield.

2.4. Incorporation of 1 into peptides: elongation at the *O*-terminus.

To prove the general utility of the *β*-perfluoroalkyl *β*-amino acid **1** in peptide engineering, the peptide-bond formation at its *O*-terminus was also performed, although this reaction was of little synthetic challenge (Table 3). The condensation of *N*-protected derivatives of **1** (**4** and **6**) with various *β*- or *α*-amino acid esters [L-*β*-homoalanine ethyl ester hydrochloride (**16**), methyl (1*R*,2*R*)-2-aminocyclohexane-1-carboxylate hydrochloride (**17**), L-alanine ethyl ester hydrochloride (**18**), L-valine methyl ester hydrochloride (**19**), and *O*-benzyl-L-serine methyl ester hydrochloride (**20**)] was conducted by applying a common method; the *N*-protected amino acid (**4** or **6**) dissolved in dichloromethane was treated with EDC•HCl (1.0 eq), HOBt (1.0 eq), triethylamine (5.0 eq), and the amino ester (**16**–**20**, 1.0 eq) to afford the target dipeptide in satisfactory yield (entries 1–5). In all cases, a set of signals were observed in ^{1}H and ^{19}F NMR (for ^{19}F NMR, see Figure S10), suggesting the retention of stereochemistry during the condensation. To confirm the retention of stereopurity more unambiguously, **4**/**16** and **4**/**18** were chosen as representatives of dipeptides prepared from an *N*-protected *β*- and *α*-amino acids, respectively. Thus, authentic samples of their diastereoisomers were independently prepared, and the comparison of their ^{19}F NMR spectra clearly excluded the possibility of racemization/epimerization (Figures S8 and S9).

3. Conclusions

The protection, deprotection, and condensation of a *β*-perfluoroalkyl-*β*-amino acid ((*S*)-4,4,4-trifluoro-3-aminobutyric acid, **1**) were systematically studied. For every process, synthetic routes and the reaction conditions were thoroughly optimized, and the preservation of the stereopurity was unambiguously confirmed. In addition, the reactivity of the amino group in **1** toward various acylating reagents was clearly elucidated in terms of its basicity and nucleophilicity. As far as we are aware of, this is the first stereo-regulated synthesis of peptides containing a *β*-perfluoroalkyl-*β*-amino acid. By applying the protection/deprotection/condensation methods established here, various peptides containing **1** could be constructed, which should contribute to the development of novel peptides containing fluoroalkyl-*β*-amino acids.

4. Experimental section

4.1. General

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL model JNM-ECA500 spectrometer operating at 500.16, 125.77, and 470.62 MHz for ^{1}H, ^{13}C, and ^{19}F NMR, respectively. Chemical shifts were determined with respect to an internal ($(CH_3)_4Si$) and an external (C_6F_6) reference for ^{1}H and ^{19}F NMR, respectively. Matrix-assisted laser desorption ionization time-of-flight mass (MALDI-TOF-MS) spectrometry was performed on an Applied Biosystems model Voyager-DE™ STR or a Bruker model MDS SCIEX 4800 MALDI TOF Analyzer using 2,5-dihydroxybenzoic acid (DHB) or *α*-cyano-4-hydroxycinnamic acid (CHCA) as a matrix. Electrospray-ionization TOF-MS (ESI-TOF-MS) spectra were recorded on a JEOL model JMS-T100LC AccuTOF spectrometer on a positive mode. Specific rotation was measured with a JASCO model P-2200 polarimeter.

Materials

(*S*)-4,4,4-Trifluoro-3-aminobutyric acid (**1**),[10] ethyl (*S*)-4,4,4-trifluoro-3-aminobutyrate hydrochloride (**2**),[7d] methyl (*S*)-4,4,4-trifluoro-3-aminobutyrate hydrochloride (**2'**),[7d] *N*-benzyloxycarbonyl-L-*β*-homoalanine (**11**),[14] ethyl (*S*)-3-aminobutyrate hydrochloride (**16**),[14] (1*R*,2*R*)-2-(*tert*-butoxycarbonylamino)cyclohexane-1-carboxylic acid (**12**),[15] and methyl (1*R*,2*R*)-2-aminocyclohexane-1-carboxylate hydrochloride (**17**)[15] were prepared according to the methods in literatures. Dichloromethane was distilled twice successively from P_2O_5 and CaH_2 and stored over activated molecular sieves. Other chemicals were used as received.

4.3. Synthesis of *N*- and *O*-protected derivatives of 1

*4.3.1. Synthesis of **4** (Scheme 1, Route A)*

To a solution of **1** (235 mg, 1.50 mmol) in water/1,4-dioxane (1:2, v/v, 20 mL) were successively added K_2CO_3 (2.07 g, 15 mmol) and benzyl chloroformate (210 *μ*L, 1.50 mmol) at rt. After being stirred at rt for 12 h, the resulting mixture was treated with 1 M aqueous hydrochloric acid until the pH of the mixture became ca. 1 and extracted with ethyl acetate (3 × 30 mL). Organic layers combined were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to dryness to afford **4** as a white solid (245 mg, 0.84 mmol, 56%); mp 145–147 ºC. $[\alpha]_D^{27}$ 2.1 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): *δ* 7.31 (m, 5H), 5.12 (d, 1H, *J* = 12.3 Hz), 5.10 (d, 1H, *J* = 12.3 Hz), 4.71 (m, 1H), 2.78 (dd, 1H, J_1 = 16.6 Hz, J_2 = 4.0 Hz), 2.61 (dd, 1H, J_1 = 16.3 Hz, J_2 = 9.9 Hz) ppm. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): *δ* 172.3, 158.2, 137.9, 129.5, 129.0, 128.7, 126.6 (q, *J* = 279 Hz), 67.9, 51.4 (q, *J* = 31 Hz), 34.0 ppm. ^{19}F NMR (470 MHz, CD_3OD, 25 °C): *δ* –77.9 (d, *J* = 8.1 Hz) ppm. IR (ATR): 3324, 3040, 2986, 2636, 1703, 1536, 1455, 1420, 1368, 1341, 1292, 1246, 1191, 1173, 1126, 1057, 1031, 1005, 971, 935, 864, 779, 736, 695, 645, 575 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 314.06, found 313.98.

*4.3.2. Synthesis of **3** (Scheme 1, Route B)*

To a dichloromethane solution (10 mL) of **2** (336 mg, 1.50 mmol) and pyridine (1.0 mL, 12 mmol) was dropwise added benzyl chloroformate (0.75 mL, 5.3 mmol) at 0 °C. After being allowed to warm to rt and then stirred at the temperature for 1 day, the reaction mixture was concentrated under reduced pressure to dryness, diluted with ethyl acetate (10 mL), and successively washed with 1 M aqueous hydrochloric acid (10 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure to afford **3** as a white solid (464 mg, 1.40 mmol, 96%); mp 84–86 ºC. $[\alpha]_D^{27}$ 15.1 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.36 (m, 5H), 5.51 (d, 1H, J = 9.2 Hz), 5.14 (s, 2H), 4.76 (m, 1H), 4.16 (q, 2H, J = 7.2 Hz), 2.77 (dd, 1H, J_1 = 16.5 Hz, J_2 = 4.9 Hz), 2.62 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 1.24 (t, 3H, J = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, CD_3OD, 55 °C): δ 170.5, 158.2, 137.9, 129.5, 129.1, 128.8, 126.4 (q, J = 281 Hz), 70.7, 68.1, 62.3, 51.5 (q, J = 32 Hz), 34.5, 14.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –79.5 (d, J = 7.2 Hz) ppm. IR (ATR): 3307, 3064, 2997, 2907, 1732, 1702, 1669, 1541, 1457, 1420, 1387, 1365, 1349, 1302, 1284, 1253, 1230, 1182, 1122, 1056, 1024, 969, 912, 884, 838, 779, 747, 735, 698, 659, 623, 577, 530 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 342.09, found 342.00.

*4.3.3. Synthesis of **4** (Scheme 1, Route B)*

To a 1,4-dioxane solution (3 mL) of **3** (306 mg, 1.00 mmol) was added an aqueous solution (3 mL) of $LiOH•H_2O$ (126 mg, 3.00 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred at the temperature for 1 h. The resultant mixture was treated with 3 M aqueous hydrochloric acid (1.5 mL) and extracted with ethyl acetate (3 × 3 mL). Organic layers combined were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to dryness. The resultant residue was dissolved in a mixture of saturated aqueous solution of $NaHCO_3$ (5 mL) and water (5 mL). The aqueous solution was washed with chloroform (3 × 5 mL), treated with 3 M aqueous hydrochloric acid until the pH of the mixture became *ca.* 3, and extracted with ethyl acetate (3 × 5 mL). Organic layers combined were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure to afford **4** as a white solid (266 mg, 0.91 mmol, 91%). Physical properties of this sample thus obtained were essentially identical to those of **4** obtained by Scheme 1, Route A.

*4.3.4. Synthesis of **6** (Scheme 2, Route A)*

To a solution of **1** (235 mg, 1.50 mmol) in water/1,4-dioxane (1:2, v/v, 20 mL) were successively added K_2CO_3 (2.07 g, 15 mmol) and di-*tert*-butyl dicarbonate (330 mg, 1.50 mmol) at 0 °C. After being stirred at rt for 1 day, the resultant mixture was treated with 1 M aqueous hydrochloric acid until the pH of the mixture became *ca.* 2 and extracted with dichloromethane (3 × 30 mL). Organic layers combined were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to dryness to afford **6** as a white solid (210 mg, 0.80 mmol, 55%); mp 109–111 ºC. $[\alpha]_D^{26}$ 10.5 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ 4.64 (m, 1H), 2.73 (dd, 1H, J_1 = 16.5 Hz, J_2 = 4.0 Hz), 2.56 (dd, 1H, J_1 = 16.3 Hz, J_2 = 10.4 Hz), 1.46 (s, 9H) ppm. ^{13}C NMR (125 MHz, CD_3OD, 55 °C): δ 172.3, 157.3, 126.6 (q, J = 282 Hz), 81.1, 50.9 (q, J = 31 Hz), 34.3, 28.6 ppm. ^{19}F NMR (470 MHz, CD_3OD, 25 °C): δ –77.9 (d, J = 8.1 Hz) ppm. IR (ATR): 3354, 2989, 2941, 1692, 1524, 1463, 1434, 1422, 1395, 1371, 1298, 1253, 1228, 1154, 1121, 1087, 1050, 1025, 965, 926, 859, 783, 765, 644, 623, 526 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 280.08, found 280.00.

*4.3.5. Synthesis of **5** (Scheme 2, Route B)*

To a 1,4-dioxane solution (2 mL) of **2** (111 mg, 0.50 mmol) were successively added pyridine (100 μL, 0.60 mmol), 4-(dimethylamino)pyridine (12 mg, 0.10 mmol), and di-*tert*-butyl dicarbonate (219 mg, 1.00 mmol) at rt. The mixture was stirred at the temperature for 1 day. Precipitates generated in the resultant mixture were filtered off, and the filtrate was concentrated under reduced pressure to dryness. The resultant residue was diluted with ethyl acetate (3 mL) and washed with 0.5 M aqueous solution of citric acid (2 × 3 mL), a saturated aqueous solution of $NaHCO_3$ (3 mL), and water (3 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to dryness to afford **5** as a white solid (117 mg, 0.41 mmol, 82%); mp 69–71 ºC. $[\alpha]_D^{27}$ 29.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 5.22 (d, 1H, J = 8.0 Hz), 4.70 (brs, 1H), 4.19 (q, 2H, J = 7.5 Hz), 2.75 (dd, 1H, J_1 = 16.1 Hz, J_2 = 5.2 Hz), 2.58 (dd, 1H, J_1 = 15.8 Hz, J_2 = 7.8 Hz), 1.45 (s, 9H), 1.27 (t, 3H, J = 7.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 169.2, 154.6, 124.7 (q, J = 279 Hz), 80.7, 61.3, 49.4 (q, J = 31 Hz), 33.7, 28.1, 14.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –79.6 (d, J = 7.2 Hz) ppm. IR (ATR): 3331, 2987, 2941, 2909, 2878, 1740, 1694, 1662, 1532, 1461, 1435, 1386, 1371, 1344, 1298, 1249, 1177, 1154, 1123, 1069, 1053, 1027, 919, 876, 850, 787, 753, 723, 700, 654, 635, 587, 527 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 308.11, found 308.05.

*4.3.6. Synthesis of **6** (Scheme 2, Route B)*

The *N*-Boc protected derivative of **1** (**6**) was obtained quantitatively from **5** in the same procedure as that for the synthesis of **4** from **3**. Physical properties of this sample were essentially identical to those of **6** obtained by Scheme 2, Route A.

*4.3.7. Synthesis of **7***

To a mixture of **4** (2.92 g, 10.0 mmol) and concentrated sulfuric acid (0.1 mL) in dichloromethane (50 mL) was added isobutene at 0 °C with stirring until the total volume of the solution became *ca.* 80 mL. The mixture was allowed to warm to rt and stirred at the temperature for 4 days. The resultant mixture was treated with triethylamine (0.26 mL) and concentrated under reduced pressure. The resultant residue was diluted with ethyl acetate (20 mL) and successively washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL) and water (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography eluted with hexane/ethyl acetate (1:1, v/v) to afford **7** as a white solid (3.02 g, 8.7 mmol, 87%); mp 65–67 ºC. $[\alpha]_D^{27}$ 15.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.35 (m, 5H), 5.54 (d, 1H, J = 9.7 Hz), 5.16 (d, 1H, J = 12.3 Hz), 5.12 (d, 1H, J = 12.3 Hz), 4.71 (m, 1H), 2.69 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.6 Hz), 2.58 (dd, 1H, J_1 = 16.1 Hz, J_2 = 8.0 Hz), 1.42 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 168.2, 155.5, 135.8, 128.5, 128.3, 128.2, 124.7 (q, J = 282 Hz), 82.2, 67.4, 50.1 (q, J = 31 Hz), 34.6, 27.8 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –79.5 (d, J = 7.7 Hz) ppm. IR (ATR): 3302, 3075, 2987, 2933, 2898, 1731, 1702, 1673, 1551, 1472, 1458, 1423, 1393, 1370, 1343, 1291, 1248, 1179, 1156, 1127, 1069, 1050, 1029, 1003, 957, 916, 868, 840, 777, 753, 700, 658, 628, 603, 579 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 370.12, found 370.00.

*4.3.8. Synthesis of **8***

To a solution of **7** (416 mg, 1.20 mmol) in methanol/dichloromethane (1:1, v/v, 10 mL) was added 5% Pd/C (416 mg), and the resultant mixture was degassed and purged with hydrogen. After being stirred at rt for 12 h, the catalyst was filtered off through a celite pad, and the solid was washed with a mixture of dichloromethane/methanol (10:1, v/v). The filtrate

and washing were combined and concentrated under reduced pressure to dryness to afford **8** as a white solid (254 mg, quant); mp 132–134 ºC. $[\alpha]_D^{27}$ –19.9 (*c* 0.2, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.71 (brs, 2H), 4.37 (brs, 1H), 2.93 (m, 2H), 1.47 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 167.5, 123.7 (q, J = 281 Hz), 83.1, 50.1 (q, J = 32 Hz), 32.9, 28.0 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –77.4 (brs) ppm. IR (ATR): 3447, 3387, 2955, 2853, 2691, 2528, 1727, 1587, 1528, 1459, 1427, 1387, 1372, 1328, 1285, 1237, 1196, 1137, 1097, 1070, 946, 899, 849, 804, 761, 729, 652, 564, 541 cm^{-1}. ESI-TOF-MS: $[M + Na]^+$ calcd. 236.09, found 236.07.

*4.3.9. Synthesis of **9***

To an *N*,*N*-dimethylformamide solution (100 mL) of **6** (3.85 g, 15.0 mmol) were successively added K_2CO_3 (2.07 g, 15.0 mmol) and benzyl bromide (2.0 mL, 16.5 mmol) at rt. The mixture was stirred at the temperature for 1 day, treated with water (20 mL), and extracted with ethyl acetate (3 × 30 mL). Organic layers combined were successively washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography eluted with hexane/ethyl acetate (2:1, v/v) to afford **9** as a white solid (3.26 g, 9.4 mmol, 62%); mp 65 ºC. $[\alpha]_D^{27}$ 21.6 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.36 (m, 5H), 5.21 (d, 1H, J = 8.5 Hz), 5.15 (s, 2H), 4.73 (brs, 1H), 2.79 (dd, 1H, J_1 = 16.1 Hz, J_2 = 4.6 Hz), 2.65 (dd, 1H, J_1 = 15.7 Hz, J_2 = 7.7 Hz), 1.45 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 169.0, 154.6, 135.1, 128.6, 128.5, 128.4, 124.7 (q, J = 282 Hz), 80.8, 67.2, 49.4 (q, J = 32 Hz), 33.7, 28.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –79.6 (d, J = 7.2 Hz) ppm. IR (ATR): 3341, 3037, 3016, 2979, 2939, 1730, 1697, 1664, 1525, 1460, 1440, 1389, 1373, 1336, 1287, 1248, 1164, 1147, 1121, 1049, 1024, 979, 908, 853, 780, 751, 697, 657, 632, 580 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 370.12, found 370.03.

*4.3.10. Synthesis of **10***

To a dichloromethane solution (10 mL) of **9** (694 mg, 2.00 mmol) was added trifluoroacetic acid (TFA, 10 mL) at rt. After being stirred at rt for 3 h, the resultant mixture was concentrated under reduced pressure to dryness to afford **10** as a white solid (724 mg, quant.); mp 106–109 ºC. $[\alpha]_D^{27}$ 7.7 (*c* 0.2, MeOH). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ 7.38 (m, 5H), 5.24 (d, 1H, J = 12.3 Hz), 5.23 (d, 1H, J = 12.3 Hz), 4.53 (m, 1H), 3.14 (dd, 1H, J_1 = 17.8 Hz, J_2 = 4.0 Hz), 2.89 (dd, 1H, J_1 = 17.8 Hz, J_2 = 9.2 Hz) ppm. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ 169.8, 162.3 (q, J = 36.0 Hz), 136.7, 129.7, 129.6, 129.5, 125.1 (q, J = 279 Hz), 117.8 (q, J = 289 Hz), 68.7, 50.6 (q, J = 32.8 Hz), 32.4 ppm. ^{19}F NMR (470 MHz, CD_3OD, 25 °C): δ –76.4 (d, J = 6.3 Hz), –76.5 ppm. IR (ATR): 3072, 2924, 2853, 2813, 2674, 1750, 1625, 1551, 1500, 1439, 1423, 1390, 1330, 1293, 1255, 1220, 1185, 1165, 1136, 1105, 1075, 1011, 978, 947, 910, 888, 839, 804, 741, 724, 696, 657, 573, 548 cm^{-1}. MALDI-TOF-MS: $[M - CF_3COOH + Na]^+$ calcd. 270.07, found 269.96.

4.4. Synthesis of dipeptides composed of 1

*4.4.1. Synthesis of **11/2** (by using a condensing reagent)*

To a dichloromethane solution (3 mL) of **11** (119 mg, 0.50 mmol) was added HBTU (190 mg, 0.50 mmol) at 0 °C. After being stirred at the temperature for 30 min, the mixture was allowed to warm to rt, and treated with a dichloromethane solution (5 mL) of **2** (111 mg, 0.50 mmol), followed by ^{i}Pr$_2$NEt (0.43 mL, 2.5 mmol). After being stirred at the temperature for 12 h, the resultant mixture was concentrated under reduced pressure to dryness, diluted with ethyl acetate (10 mL), and successively washed with 0.5 M aqueous hydrochloric acid (3 × 3 mL), a saturated aqueous solution of $NaHCO_3$ (3 × 3 mL), and brine (3 × 3 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography eluted with hexane/ethyl acetate (2:1, v/v) to afford **11**/**2** as a white solid (139 mg, 0.34 mmol, 69%). When EDC•HCl/HOBt or HATU was used in place of HBTU, **11**/**2** was obtained in 41% or 61% yield, respectively; mp 177–179 ºC. $[\alpha]_D^{27}$ 14.0 (*c* 0.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.34 (m, 5H), 6.64 (brs, 1H), 5.39 (brs, 1H), 5.09 (s, 2H), 5.03 (m, 1H), 4.15 (q, 2H, J = 7.0 Hz), 4.07 (m, 1H), 2.71 (dd, 1H, J_1 = 16.1 Hz, J_2 = 5.2 Hz), 2.59 (dd, 1H, J_1 = 16.3 Hz, J_2 = 7.2 Hz), 2.48 (m, 2H), 1.26 (d, 3H, J = 5.7 Hz), 1.25 (t, 3H, J = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ 170.4, 169.2, 155.9, 136.6, 128.4, 128.0, 127.9, 124.6 (q, J = 282 Hz), 66.6, 61.4, 47.5 (q, J = 32 Hz), 44.7, 42.5, 33.2, 20.3, 13.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.9 (d, J = 7.7 Hz) ppm. IR (ATR): 3316, 3301, 3067, 2980, 2927, 2853, 1728, 1681, 1660, 1535, 1456, 1427, 1371, 1341, 1309, 1282, 1263, 1203, 1176, 1120, 1065, 1025, 978, 948, 909, 881, 841, 779, 749, 723, 695, 662, 578, 552 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 427.15, found 427.02.

*4.4.2. Synthesis of **11/2** (via the conversion of **11** into acyl chloride)*

To a dichloromethane solution (5 mL) of **11** (142 mg, 0.60 mmol) was added oxalyl chloride (0.26 mL, 3.0 mmol). The mixture was allowed to warm to rt, stirred at the temperature for 3 h, and concentrated under reduced pressure to dryness to give a residue containing the acyl chloride derived from **11**. To the resultant residue were successively added dichloromethane (3 mL), a dichloromethane solution (2 mL) of **2** (111 mg, 0.50 mmol), and pyridine (0.20 mL, 2.5 mmol) at rt. After being stirred at the temperature for 12 h, the resultant mixture was concentrated under reduced pressure, diluted with ethyl acetate (10 mL), and washed with 0.5 M aqueous hydrochloric acid (3 × 3 mL), a saturated aqueous solution of $NaHCO_3$ (3 × 3 mL), and brine (3 × 3 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography eluted with hexane/ethyl acetate (1:1, v/v) to afford **11**/**2** as a white solid (175 mg, 0.43 mmol, 86%). When triethylamine was used in place of pyridine, **11**/**2** was obtained in 64% yield. Physical properties of the product samples were identical to those of **11**/**2** obtained by the method using a condensing reagent [Section 4.4.1. Synthesis of **11**/**2** (by using a condensing reagent)].

*4.4.3. Synthesis of **12/2'***

The dipeptide **12**/**2'** was obtained as a white solid from **12** and **2'** in a procedure similar to the synthesis of **11**/**2**, where HATU was used as a condensing regent (65%); decomp. >220 ºC. $[\alpha]_D^{27}$ –3.6 (*c* 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.76 (d, 1H, J = 8.6 Hz), 5.07 (m, 1H), 4.57 (brs, 1H), 3.72 (s, 3H), 3.52 (m, 1H), 2.74 (dd, 1H, J_1 = 16.0 Hz, J_2 = 5.2 Hz), 2.64 (dd, 1H, J_1 = 16.1 Hz, J_2 = 7.5 Hz), 2.31 (brs, 1H), 2.00 (m, 1H), 1.75 (m, 1H), 1.41 (s, 9H), 1.28 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD (2:1, v/v), 55 °C): δ 175.5, 170.1, 156.5, 125.6 (q, J = 281 Hz), 79.9, 52.4, 51.6, 51.2, 48.0 (q, J = 32 Hz), 33.8, 33.4, 30.0, 28.5, 25.2, 25.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.6 (d, J = 7.6 Hz) ppm. IR (ATR): 3332, 3309, 3216, 3015, 2989, 2937, 2857, 1741, 1678, 1666, 1533, 1440, 1417, 1391, 1356, 1320, 1296, 1278, 1253, 1228, 1175, 1141, 1120, 1074, 1054, 1011, 993, 930, 906, 895, 868, 780, 747, 661, 639, 596, 560 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 419.18, found 413.31.

*4.4.4. Synthesis of **13/2***

The dipeptide **13**/**2** was obtained as a white solid from **13** and **2** in a procedure similar to the synthesis of **11**/**2**, where HBTU was used as a condensing regent (62%); mp 114–116 ºC. $[\alpha]_D^{28}$ 8.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.35 (m, 5H), 6.98 (d, 1H, *J* = 7.5 Hz), 5.24 (m, 1H), 5.12 (s, 2H), 5.00 (m, 1H), 4.26 (m, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 2.73 (m, 1H), 2.62 (dd, 1H, J_1 = 16.1 Hz, J_2 = 7.4 Hz), 1.40 (d, 3H, *J* = 6.9 Hz), 1.25 (t, 3H, *J* = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 172.7, 168.9, 156.0, 136.0, 128.4, 128.1, 127.8, 124.5 (q, *J* = 281 Hz), 66.8, 61.3, 50.3, 47.5 (q, *J* = 32 Hz), 33.2, 18.3, 13.8 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –79.0 (d, *J* = 7.2 Hz) ppm. IR (ATR): 3338, 3092, 3035, 2979, 2934, 1723, 1696, 1682, 1529, 1432, 1369, 1347, 1297, 1264, 1245, 1200, 1175, 1142, 1127, 1117, 1068, 1025, 963, 952, 892, 876, 846, 785, 739, 718, 694, 660, 627, 575, 525 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 413.13, found 413.03.

*4.4.5. Synthesis of **14**/**2***

The dipeptide **14**/**2** was obtained as a white solid from **14** and **2** in a procedure similar to the synthesis of **11**/**2**, where HBTU was used as a condensing reagent (48%); mp 155–156 ºC. $[\alpha]_D^{27}$ 23.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.35 (m, 5H), 6.83 (d, 1H, *J* = 9.7 Hz), 5.33 (d, 1H, *J* = 6.9 Hz), 5.11 (s, 2H), 5.02 (m, 1H), 4.16 (q, 2H, *J* = 7.5 Hz), 4.02 (t, 1H, *J* = 7.5 Hz), 2.73 (dd, 1H, J_1 = 15.5 Hz, J_2 = 4.0 Hz), 2.66 (dd, 1H, J_1 = 16.0 Hz, J_2 = 6.3 Hz), 2.12 (m, 1H), 1.25 (t, 3H, *J* = 6.9 Hz), 0.97 (d, 3H, *J* = 6.3 Hz), 0.93 (d, 3H, *J* = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 171.3, 169.1, 156.4, 136.1, 128.5, 128.2, 127.9, 124.5 (q, *J* = 281 Hz), 67.0, 61.5, 60.3, 47.4 (q, *J* = 32 Hz), 33.1, 31.2, 18.8, 17.7, 13.9 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.7 (d, *J* = 7.7 Hz) ppm. IR (ATR): 3282, 3074, 2974, 2960, 2911, 2874, 1734, 1692, 1666, 1531, 1469, 1456, 1388, 1372, 1340, 1293, 1246, 1229, 1184, 1122, 1072, 1038, 1028, 967, 926, 902, 873, 843, 788, 748, 695, 658, 594, 576 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 441.16, found 441.30.

*4.4.6. Synthesis of **15**/**2***

The dipeptide **15**/**2** was obtained as a transparent oil from **15** and **2** in a procedure similar to the synthesis of **11**/**2**, where DEPBT[13] was used as a condensing reagent (73%); $[\alpha]_D^{25}$ 23.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.32 (m, 5H), 7.22 (d, 1H, *J* = 5.8 Hz), 5.38 (brs, 1H), 5.07 (m, 1H), 4.56 (d, 1H, *J* = 11.5 Hz), 4.53 (d, 1H, *J* = 11.5 Hz), 4.31 (brs, 1H), 3.89 (dd, 1H, J_1 = 9.2 Hz, J_2 = 4.0 Hz), 3.66 (s, 3H), 3.55 (m, 1H), 2.74 (dd, 1H, J_1 = 16.1 Hz, J_2 = 5.2 Hz), 2.61 (dd, 1H, J_1 = 16.3 Hz, J_2 = 7.8 Hz), 1.45 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 170.5, 169.3, 155.4, 137.1, 128.4, 127.9, 127.8, 124.4 (q, *J* = 282 Hz), 80.3, 73.5, 69.5, 53.7, 52.2, 47.5 (q, *J* = 32 Hz), 33.1, 28.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –79.0 (d, *J* = 3.6 Hz) ppm. IR (ATR): 3304, 3032, 2978, 2956, 2930, 2871, 1744, 1712, 1672, 1523, 1496, 1455, 1391, 1366, 1285, 1238, 1168, 1126, 1023, 997, 960, 913, 860, 781, 737, 698, 662, 611, 566 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 471.17, found 471.36.

*4.4.7. Synthesis of **4**/**16***

To a dichloromethane solution (2 mL) of **4** (146 mg, 0.50 mmol) were successively added EDC•HCl (96 mg, 0.50 mmol), HOBt (68 mg, 0.50 mmol), a dichloromethane solution (3 mL) of **16** (84 mg, 0.50 mmol), and triethylamine (0.27 mL, 2.5 mmol) at rt. After being stirred at the temperature for 12 h, the resultant mixture was concentrated to dryness under reduced pressure, diluted with ethyl acetate (15 mL), and successively washed with 0.5 M aqueous hydrochloric acid (3 × 20 mL), a saturated aqueous solution of $NaHCO_3$ (3 × 20 mL), and brine (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography eluted with hexane/ethyl acetate (2:1, v/v) to afford **4**/**16** as a white solid (166 mg, 0.41 mmol, 82%); mp 165–169 ºC. $[\alpha]_D^{27}$ 3.3 (*c* 0.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.34 (m, 5H), 6.37 (d, 1H, *J* = 7.5 Hz), 6.28 (d, 1H, *J* = 8.6 Hz), 5.14 (s, 2H), 4.66 (m, 1H), 4.32 (m, 1H), 4.15 (m, 2H), 2.77 (m, 1H), 2.62 (dd, 1H, J_1 = 15.2 Hz, J_2 = 4.9 Hz), 2.47 (m, 3H), 1.27 (t, 3H, *J* = 7.2 Hz), 1.20 (d, 3H, *J* = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ 171.6, 167.5, 155.7, 136.1, 128.5, 128.2, 128.0, 124.9 (q, *J* = 283 Hz), 67.4, 60.7, 50.7 (q, *J* = 32 Hz), 42.4, 34.7, 29.7, 19.7, 14.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.7 (d, *J* = 7.2 Hz) ppm. IR (ATR): 3298, 3068, 3036, 2988, 2973, 2929, 1723, 1694, 1635, 1543, 1498, 1458, 1439, 1377, 1356, 1308, 1248, 1176, 1149, 1121, 1049, 1032, 936, 912, 875, 854, 824, 774, 752, 697, 670, 649, 610, 580, 564, 521 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 427.15, found 427.02.

*4.4.8. Synthesis of **6**/**17***

The dipeptide **6**/**17** was obtained as a white solid from **6** and **17** in the same procedure for the synthesis of **4**/**16** (83%); decomp. > 200 ºC. $[\alpha]_D^{27}$ 10.7 (*c* 0.3, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 5.96 (d, 1H, *J* = 5.8 Hz), 5.67 (d, 1H, *J* = 5.8 Hz), 4.56 (m, 1H), 3.99 (m, 1H), 2.60 (dd, 1H, J_1 = 15.5 Hz, J_2 = 5.2 Hz), 2.39 (dd, 1H, J_1 = 14.4 Hz, J_2 = 5.2 Hz), 2.39 (td, 1H, J_1 = 12.0 Hz, J_2 = 4.0 Hz), 2.03 (m, 1H), 1.95 (m, 1H), 1.74 (m, 2H), 1.62 (m, 1H), 1.45 (s, 9H), 1.19 (m, 2H) ppm. ^{13}C NMR (125 MHz, CD_3OD, 55 °C): δ 176.0, 169.6, 157.1, 126.8 (q, *J* = 282 Hz), 81.1, 52.3, 51.2, 51.1 (q, *J* = 31 Hz), 50.3, 35.8, 33.1, 29.9, 28.6, 25.7, 25.5 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.9 (d, *J* = 5.4 Hz) ppm. IR (ATR): 3327, 3263, 3062, 2998, 2982, 2966, 2941, 2862, 1735, 1698, 1646, 1542, 1438, 1367, 1308, 1276, 1251, 1208, 1157, 1122, 1051, 1015, 973, 917, 876, 861, 758, 692, 655, 628, 570, 554 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 419.18, found 419.33.

*4.4.9. Synthesis of **4**/**18***

The dipeptide **4**/**18** was obtained as a white solid from **4** and **18** in the same procedure for the synthesis of **4**/**16** (84%); mp 188–191 ºC. $[\alpha]_D^{27}$ –29.9 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD, 25 °C): δ 7.33 (m, 5H), 5.10 (q, 2H, *J* = 7.5 Hz), 4.76 (m, 1H), 4.35 (q, 2H, *J* = 7.3 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 2.69 (dd, 1H, J_1 = 14.9 Hz, J_2 = 4.0 Hz), 2.55 (dd, 1H, J_1 = 15.2 Hz, J_2 = 10.0 Hz), 1.32 (d, 3H, *J* = 6.9 Hz), 1.25 (t, 3H, *J* = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ 174.0, 170.2, 158.0, 138.0, 129.4, 129.1, 128.8, 126.6 (q, *J* = 280 Hz), 68.0, 62.4, 60.3, 51.7 (q, *J* = 32 Hz), 49.7, 35.3, 17.5, 14.4 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.7 (d, *J* = 7.7 Hz) ppm. IR (ATR): 3295, 3068, 3035, 2982, 2929, 2875, 2855, 1735, 1698, 1643, 1542, 1451, 1437, 1377, 1358, 1324, 1305, 1277, 1247, 1228, 1172, 1151, 1119, 1078, 1049, 1030, 979, 937, 915, 878, 864, 827, 755, 738, 696, 639, 606, 580, 565 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 413.13, found 413.26.

*4.4.10. Synthesis of **6**/**19***

The dipeptide **6**/**19** was obtained as a white solid from **6** and **19** in the same procedure for the synthesis of **4**/**16** (80%); mp 179–181 ºC. $[\alpha]_D^{27}$ 40.9 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.19 (d, 1H, *J* = 8.6 Hz), 5.94 (d, 1H, *J* = 9.2 Hz), 4.61 (m, 1H), 4.56 (m, 1H), 3.75 (s, 3H), 2.69 (dd, 1H, J_1 = 15.5 Hz, J_2 = 4.6 Hz), 2.55 (dd, 1H, J_1 = 15.0 Hz, J_2 = 5.1 Hz), 2.17 (m, 1H), 1.44 (s, 9H), 0.94 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ 172.8, 168.7, 154.9, 124.9 (q, *J* = 283 Hz), 80.5, 57.2, 52.3, 49.9 (q, *J* = 31 Hz), 34.4, 31.2, 28.2, 18.8, 17.6 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.8 (d, *J* = 7.2 Hz) ppm. IR (ATR): 3324, 3014, 2980, 2953, 2933, 2878, 1741, 1692, 1652, 1530, 1468,

1435, 1393, 1367, 1310, 1250, 1207, 1180, 1152, 1122, 1055, 1025, 975, 915, 881, 853, 781, 645, 622, 563, 550 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 393.16, found 393.27.

*4.4.11. Synthesis of **6**/**20***

The dipeptide **6**/**20** was obtained as a white solid from **6** and **20** in the same procedure for the synthesis of **4**/**16** (85%); mp 146–148 ºC. $[\alpha]_D^{27}$ 53.7 (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.32 (m, 5H), 6.45 (d, 1H, J = 6.9 Hz), 5.91 (d, 1H, J = 8.6 Hz), 4.73 (dt, 1H, J_1 = 10.9 Hz, J_2 = 2.9 Hz), 4.63 (m, 1H), 4.53 (d, 1H, J = 12.6 Hz), 4.48 (d, 1H, J = 12.0 Hz), 3.91 (dd, 1H, J_1 = 9.8 Hz, J_2 = 2.9 Hz), 3.75 (s, 3H), 3.67 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.9 Hz), 2.69 (dd, 1H, J_1 = 15.5 Hz, J_2 = 4.6 Hz), 2.53 (dd, 1H, J_1 = 14.9 Hz, J_2 = 4.6 Hz), 1.45 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 55 °C): δ 170.4, 168.4, 154.8, 137.4, 128.3, 127.8, 127.6, 125.0 (q, J = 283 Hz), 80.4, 73.3, 69.5, 52.8, 52.3, 49.9, 34.2, 28.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$, 25 °C): δ –78.8 (d, J = 6.8 Hz) ppm. IR (ATR): 3315, 2987, 2942, 2871, 2860, 1740, 1698, 1650, 1532, 1441, 1367, 1340, 1308, 1249, 1232, 1177, 1152, 1120, 1101, 1056, 1028, 984, 920, 882, 853, 782, 736, 697, 672, 635, 612, 580 cm^{-1}. MALDI-TOF-MS: $[M + Na]^+$ calcd. 471.17, found 471.34.

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Supplementary material

Optimization of reaction conditions for the synthesis of **5** and ^{19}F NMR spectra of the derivatives of **1**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/XXXXXXX.

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Supplementary Material

Stereo-regulated synthesis of peptides containing a *β*-trifluoromethyl-*β*-amino acid

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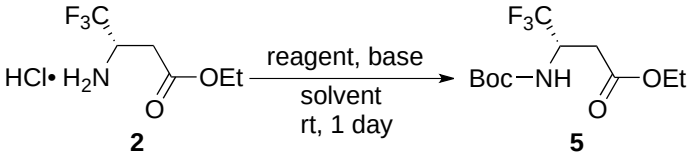
Table of Contents

(i) Optimization of reaction conditions for the synthesis of 5

Table S1. *N*-Boc protection of the amino ester derived from **1** (**2**).



2 **5**

entry	reagent	base	solvent	yield[a)]
1	Boc_2O (2.0 eq), DMAP (0.2 eq)	Pyridine (1.2 eq)	CH_2Cl_2	60%
2	Boc_2O (2.0 eq), DMAP (0.2 eq)	Pyridine (1.2 eq)	1,4-Dioxane	82%
3	Boc_2O (3.5 eq), DMAP (0.2 eq)	Pyridine (8.0 eq)	1,4-Dioxane	84%

a) Isolated yield.

(ii) Determination of the enantiomeric purity of 4 and 6

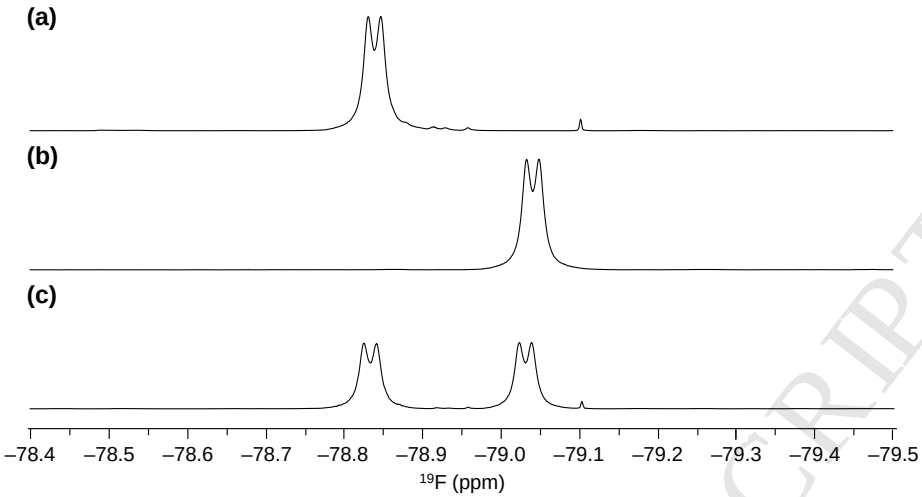


Figure S1. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **4** (10 mM), (b) the antipode of **4** (10 mM), and (c) a mixture of **4** (5 mM) and its antipode (5 mM), where (2*S*,5*S*)-2,5-diphenylpyrrolidine (25 mM) was added as a chiral NMR shift reagent.

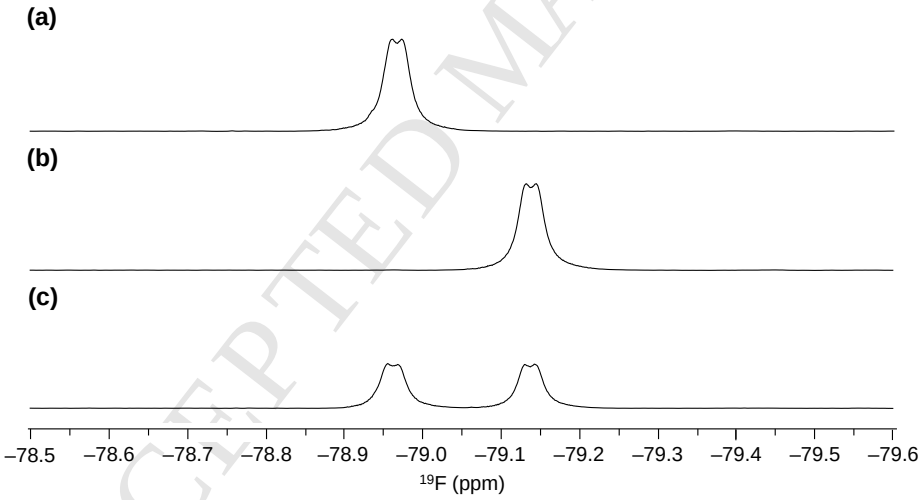


Figure S2. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **6** (10 mM), (b) the antipode of **6** (10 mM), and (c) a mixture of **6** (5 mM) and its antipode (5 mM), where (2*S*,5*S*)-2,5-diphenylpyrrolidine (25 mM) was added as a chiral NMR shift reagent.

(iii) Determination of the enantiomeric purity of 8 and 10

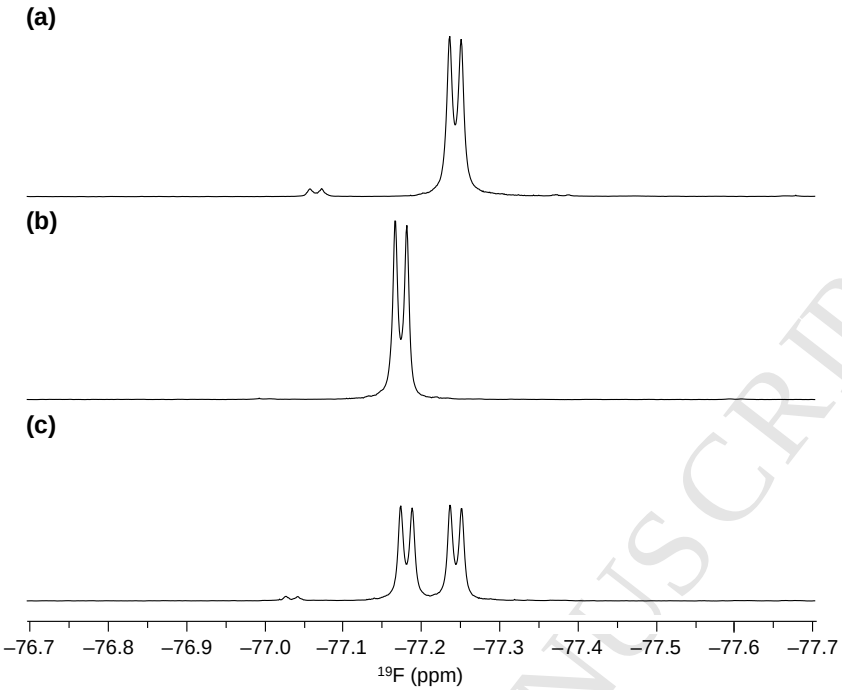


Figure S3. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **8** (10 mM), (b) the antipode of **8** (10 mM), and (c) a mixture of **8** (5 mM) and its antipode (5 mM), where dimethyl L-(+)-tartrate (1.0 M) was added as a chiral NMR shift reagent.

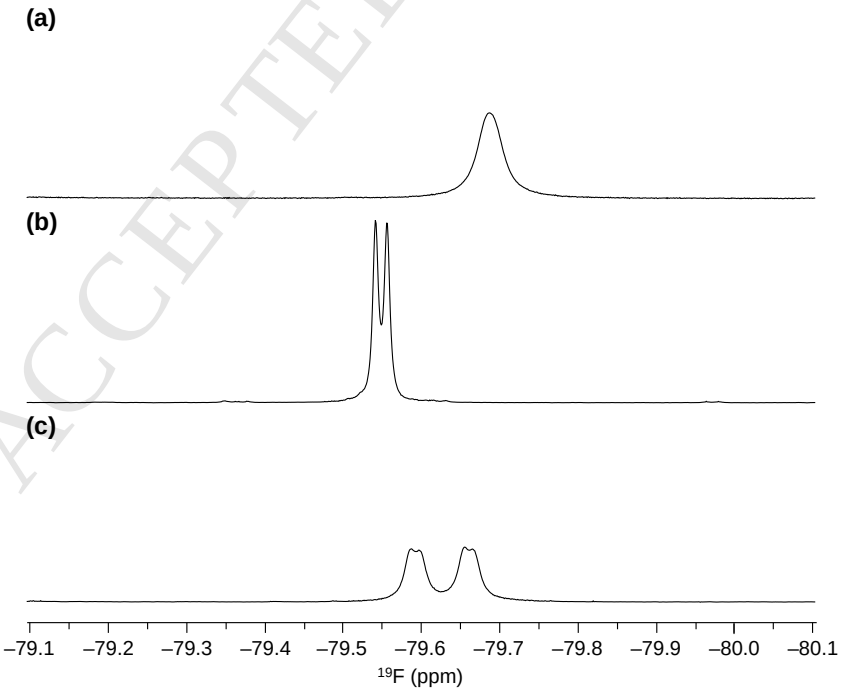


Figure S4. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **10** (10 mM), (b) the antipode of **10** (10 mM), and (c) a mixture of **10** (5 mM) and its antipode (5 mM), where (*S*)-(–)-1,1'-bi-2-naphthol (250 mM) was added as a chiral NMR shift reagent.

(iv) Determination of the diastereomeric purity of 11/2 and 13/2

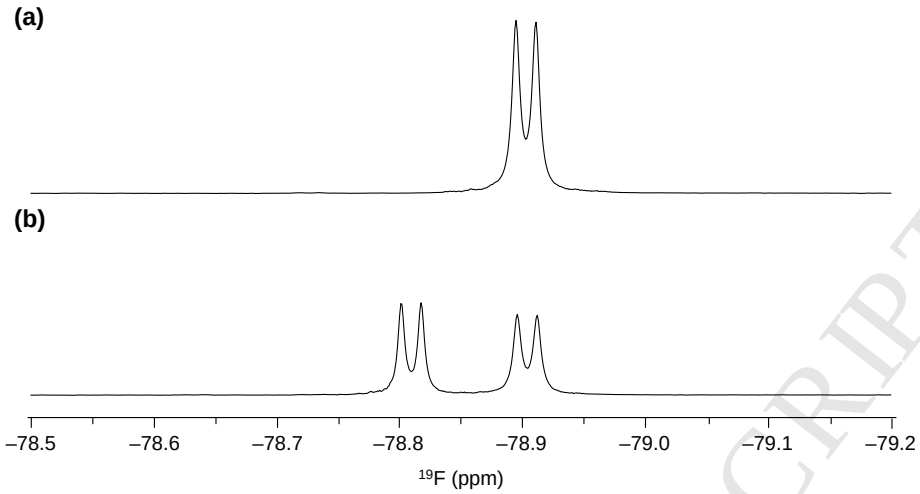


Figure S5. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **11**/**2** (10 mM) and (b) an authentic mixture of **11**/**2** and its diastereoisomer (10 mM in total, prepared from racemic *N*-benzyloxycarbonyl-*β*-homoalanine and **2**).

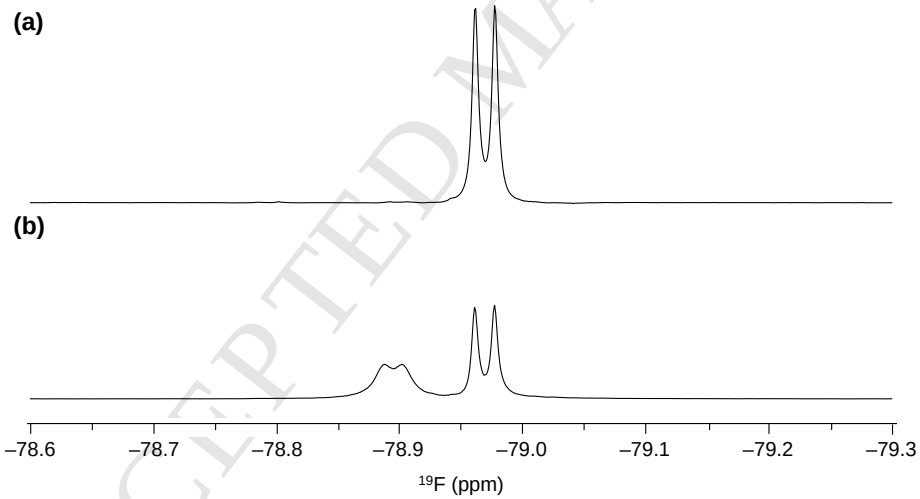


Figure S6. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **13**/**2** (10 mM) and (b) an authentic mixture of **13**/**2** and its diastereoisomer (10 mM in total, prepared from racemic *N*-benzyloxycarbonyl-alanine and **2**).

(v) ^{19}F NMR spectra of 11/2, 12/2', 13/2, 14/2, and 15/2'

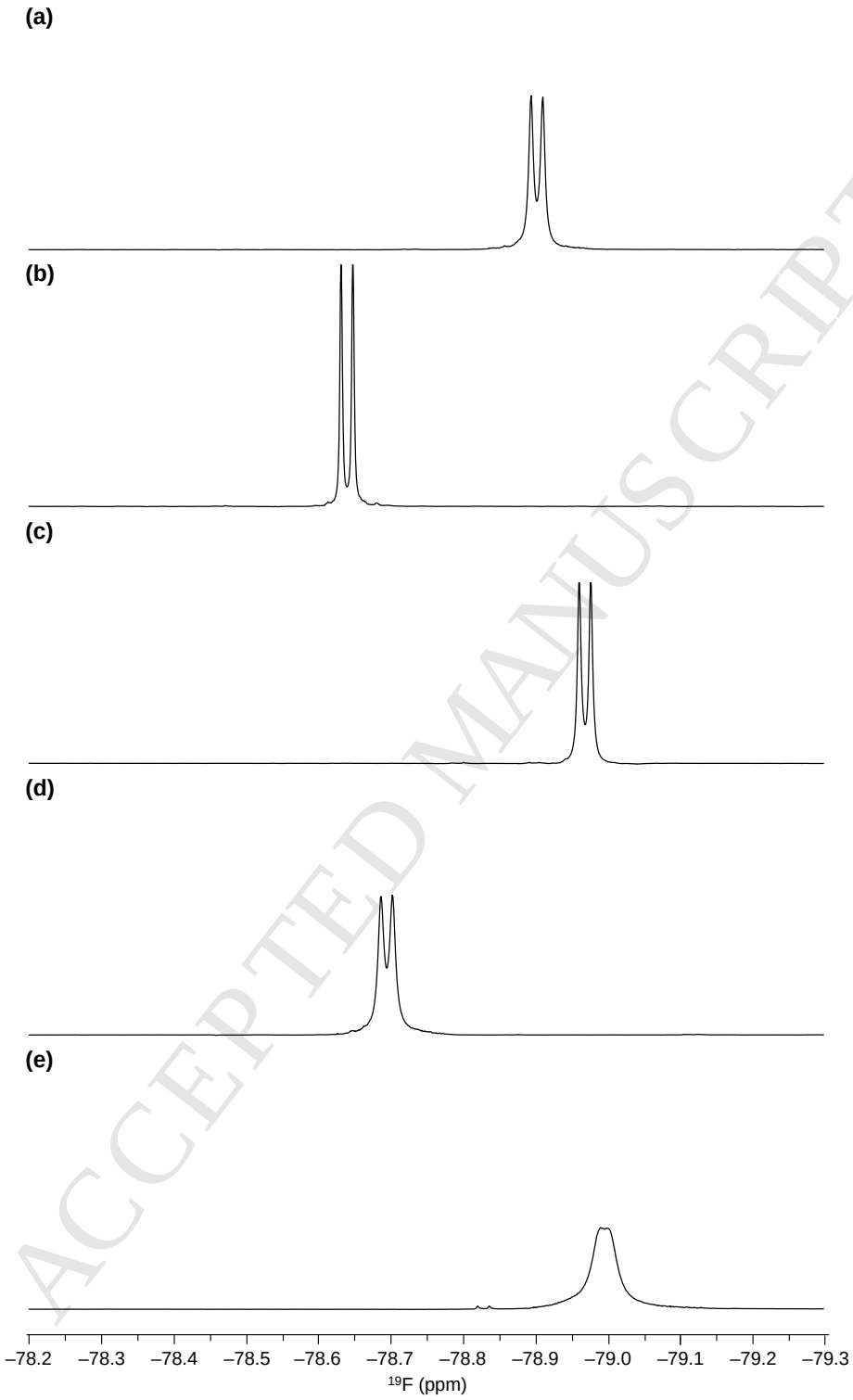


Figure S7. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of dipeptides (10 mM); (a) **11**/**2**, (b) **12**/**2'**, (c) **13**/**2**, (d) **14**/**2**, and (e) **15**/**2'**.

(vi) Determination of the diastereomeric purity of 4/16 and 4/18

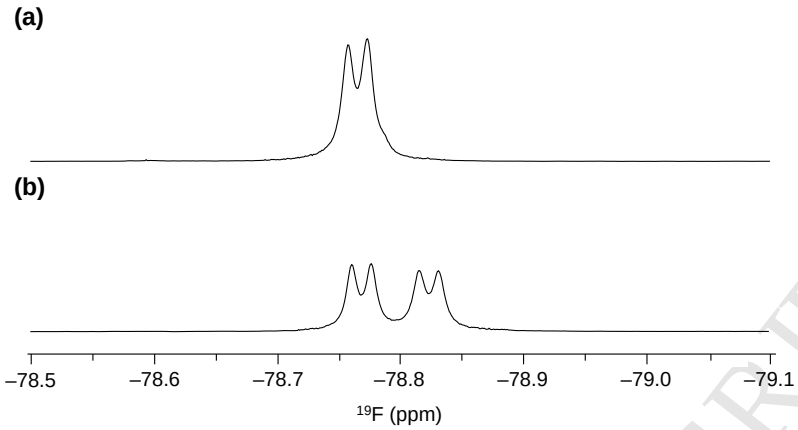


Figure S8. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **4**/**16** (10 mM) and (b) an authentic mixture of **4**/**16** and its diastereoisomer (10 mM in total, prepared from **16** and racemic 3-benzyloxylcarbonylamino-4,4,4,-trifluorobutylic acid).

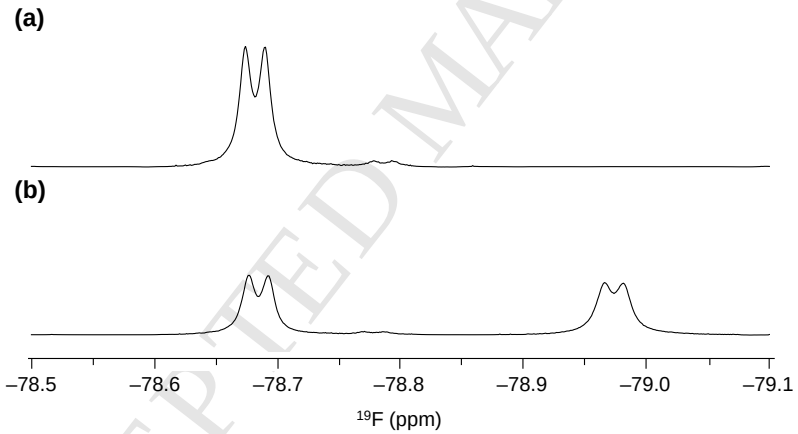


Figure S9. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of (a) **4**/**18** (10 mM) and (b) an authentic mixture of **4**/**18** and its diastereoisomer (10 mM in total, prepared from **18** and racemic 3-benzyloxylcarbonylamino-4,4,4,-trifluorobutylic acid).

(vii) ^{19}F NMR spectra of 4/16, 6/17, 4/18, 6/19, and 6/20

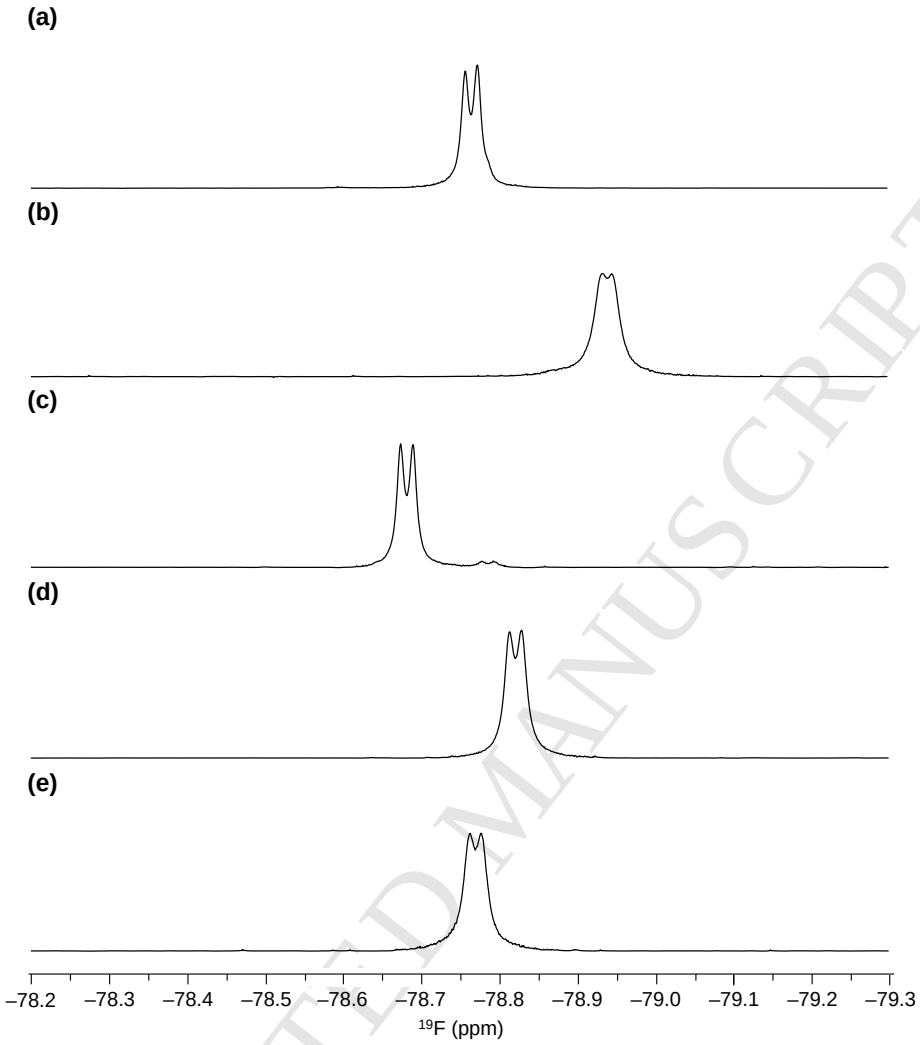


Figure S10. Partial ^{19}F NMR spectra in $CDCl_3$ at 25 °C of dipeptides (10 mM); (a) **4**/**16**, (b) **6**/**17**, (d) **4**/**18**, (d) **6**/**19**, and (e) **6**/**20**.