



## A practical method to access enantiopure $\beta$ -perfluoroalkyl- $\beta$ -amino acids: diastereoselective reduction of cyclic enamino-esters

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### ABSTRACT

A highly practical method to access enantiopure  $\beta$ -perfluoroalkyl- $\beta$ -amino acids was developed, which could be conducted without any expensive reagent, special apparatus/technique, nor tedious chromatographic separation. The condensation of methyl 4,4,4-trifluoro-3-oxobutanoate with (*S*)-2-amino-2-phenylethanol, followed by an intramolecular transesterification, gave an enamino-ester with a seven-membered ring structure. The hydride reduction of the cyclic enamino-ester proceeded with excellent diastereoselectivity (*dr* = 95:5–97:3) to give the corresponding cyclic amino-ester. The major isomer of the cyclic amino-ester was readily separated from the minor one and successfully converted into (*S*)-3-amino-4,4,4-trifluorobutanoic acid (five steps, 38% overall yield, >99% ee). Concerning the key step of this synthesis, the same strategy was applicable to another substrate; the asymmetric hydride reduction of a cyclic enamino-ester with a pentafluoroethyl group also proceeded in excellent diastereoselectivity (*dr* = 96:4).

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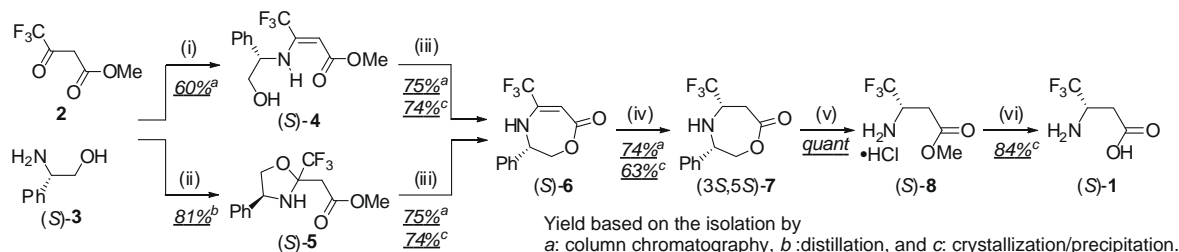
Fluorine-containing amino acids have attracted considerable recent attention, owing to their potential application in widespread scientific fields.<sup>1</sup> To date, several kinds of fluorinated  $\alpha$ - and  $\beta$ -amino acids have been studied, of which the characteristics change dramatically depending on the position of fluorine atom(s). Among them,  $\gamma$ -fluorinated  $\alpha$ -amino acids,  $\delta$ -fluorinated  $\alpha$ -amino acids, and  $\gamma$ -fluorinated  $\beta$ -amino acids should be regarded as exceptionally important classes; they serve as suitable components for peptide-bond formation, because of their stability, tolerance toward racemization, and proper reactivity. Particularly, the incorporation of  $\gamma$ - or  $\delta$ -fluorinated  $\alpha$ -amino acids into peptides has been recognized as a powerful tool to analyze and/or modify the structure and function of peptides and proteins.<sup>1e,g</sup> Likewise,  $\gamma$ -fluorinated  $\beta$ -amino acids also should enlarge the scope of peptide engineering. One of the most promising applications of  $\gamma$ -fluorinated  $\beta$ -amino acids is to incorporate them into the oligomers of  $\beta$ -amino acids ( $\beta$ -peptides);  $\beta$ -peptides have been found to show various intriguing structures and functions, and their partial fluorination would allow us for their further facile manipulation.<sup>2</sup> At present, however, chemistry of  $\gamma$ -fluorinated  $\beta$ -amino acids has not been explored adequately, where even their stereoselective synthesis still remains as a challenging target.<sup>3–6</sup>

Several groups have reported the asymmetric synthesis of  $\beta$ -perfluoroalkyl- $\beta$ -amino acids, which might be classified into the following four categories: (i) the asymmetric reduction of fluorinated enamino-esters,<sup>3</sup> (ii) the asymmetric proton shift reaction

of fluorinated enamino-esters bearing an *N*-benzyl group,<sup>4</sup> (iii) the asymmetric Mannich- or Reformatsky-type reaction of fluorinated aldimines with acetic acid equivalents,<sup>5</sup> and (iv) the resolution of racemates through bio-catalyst approach, chromatography, or crystallization.<sup>6</sup> Taking account of practical utility in terms of accessibility/handling of reagents, synthetic efficiency, and operational convenience, the first strategy is undoubtedly one of the most fascinating approaches. Moreover, the same methodology has been already well investigated for the synthesis of non-fluorinated  $\beta$ -amino acids.<sup>7</sup> In fact, Fustero and his co-workers have developed a highly convenient method based on the hydride reduction of enamino-esters to access various enantio-enriched  $\beta$ -perfluoroalkyl- $\beta$ -amino acids. However, the stereoselectivity achieved in these studies has been limited to an unsatisfactory level (*dr* up to 80:20),<sup>3b</sup> most likely because the perfluoroalkyl group brought unpredictable effects on the property and reactivity of neighboring functional groups.

In previous studies, fluorinated enamino-esters with a relatively simple structure were frequently used as substrates, which possess only one chiral auxiliary on their enamino nitrogen atom or ester oxygen atom. As a result, the enamino-esters can take several kinds of conformations, which would give rise to a number of reaction pathways to make the diastereoselectivity unsatisfactory.<sup>3</sup> To overcome the problem, we designed an enamino-ester with a seven-membered ring structure as a key substrate (**6**, Scheme 1), in which the enamine and ester functional groups are “tethered” by an enantiopure amino alcohol with bifunctional nature. The characteristic cyclic structure would strictly define the conformation around the chiral auxiliary and the

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**Scheme 1.** Synthesis of (*S*)-3-amino-4,4,4-trifluorobutanoic acid ((*S*)-1). Reagents and conditions: (i)  $\text{CH}_3\text{CO}_2\text{H}$  (1 equiv),  $\text{CH}_2\text{Cl}_2$ , reflux, 12 h; (ii)  $\text{CH}_3\text{CO}_2\text{H}$  (3 equiv),  $\text{CHCl}_3$ , reflux, 12 h; (iii)  $\text{SnBr}_4$  (0.3 equiv), *o*-xylene, 130 °C, 4 h; (iv)  $\text{NaBH}_3\text{CN}$  (1.2 equiv),  $\text{HCl}$  (10 equiv),  $\text{CH}_2\text{Cl}_2/\text{dioxane}$  (2:1, v/v),  $-78$  °C to rt, 96 h; (v)  $\text{H}_2$  (1 atm),  $\text{Pd/C}$  (cat),  $\text{HCl}$  (10 equiv),  $\text{MeOH}/\text{dioxane}$  (9:1, v/v), 16 h; (vi)  $\text{HCl}$  aq (3 M), reflux, 12 h, then propylene oxide (excess),  $\text{MeOH}$ , rt.

*E/Z*-isomerism of the enamino part, which would be favorable to achieve the face-selective transformation of the prochiral enamino part. Herein, we report a highly efficient and practical method for the synthesis of enantiopure  $\beta$ -trifluoromethyl- $\beta$ -amino acid via the diastereoselective hydride reduction of an enamino-ester with a cyclic structure (Scheme 1).

Taking account of the easiness in preparation, chirality-induction ability, and easiness in removal, we chose (*S*)-2-amino-2-phenylethanol ((*S*)-phenylglycinol, (*S*)-3) as an auxiliary unit. According to the method established by Soloshonok and his co-workers,<sup>8</sup> the enamino-ester (*S*)-4 was prepared by the condensation of methyl 4,4,4-trifluoro-3-oxobutanoate (2) with (*S*)-3 in acceptable yield (Scheme 1, (i), 60% yield). Owing to the nucleophilicity of the amino unit properly controlled by the coexistence of acetic acid, the aminolysis of the ester group did not take place at all. In addition, among the possible tautomers/stereoisomers (enamine/imine tautomerism with *E/Z* isomerism), the (*Z*)-enamino-ester (*S*)-4 was exclusively generated, most likely owing to the stabilization by intramolecular hydrogen-bonding interaction. Only a problem was the gradual conversion of (*S*)-4 into the oxazolidine (*S*)-5 via the nucleophilic attack of the hydroxy group to the carbon at the  $\beta$ -position of the ester group, which reduced the yield of (*S*)-4 to some extent.<sup>9</sup> Although this side reaction is unfavorable for the synthesis of (*S*)-4, the resultant oxazolidine (*S*)-5 might be regarded as a useful synthetic equivalent of the enamino-ester (*S*)-4, because the oxazolidine unit can be potentially cleaved by the action of acids, etc.<sup>5a,10</sup> and because (*S*)-5 has a relatively low boiling point (150 °C/3 mmHg) suitable for the isolation from a reaction mixture by distillation. Therefore, we re-optimized reaction conditions for the formation of the oxazolidine (*S*)-5, and found that the oxazolidine was selectively obtained by conducting the condensation in the presence of three equivalents of acetic acid (Scheme 1, (ii), 81%).

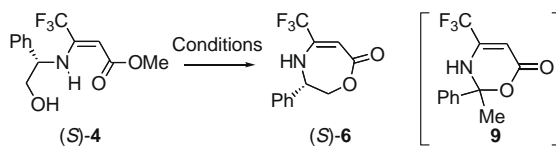
With two kinds of the precursors (*S*)-4 and (*S*)-5 in hand, we attempted intramolecular ester formations, which apparently seemed to proceed smoothly under general transesterification conditions. In fact, Abarbri and his co-workers reported the synthesis of similar cyclic enamino-esters by using a base catalyst, which had a structure almost identical to that of (*S*)-4 except for their side chain residue originated from the amino alcohol component.<sup>11</sup> However, under the same conditions, the enamino-ester (*S*)-4 was quantitatively converted into the oxazolidine (*S*)-5 at the initial stage of the reaction (Table 1, entry 1). In general, perfluoroalkyl groups are known to stabilize neighboring acetals/aminals because of their electron-withdrawing effect.<sup>12</sup> Harsher conditions gave rise to an unexpected rearrangement reaction to afford 9 (entry 2), which was most likely started by the abstraction of the benzylic proton.<sup>13</sup> When a Brønsted acid catalyst was used, the starting material was again converted into the oxazolidine (*S*)-5, and the seven-membered ring formation did not proceed efficiently (entry 3).

Taking account of the time course of product ratios, the ring cleavage of the oxazolidine (*S*)-5 was considered to be the rate-determining step in the present seven-membered ring formation. Therefore, we tested several Lewis acid catalysts, which are generally known to catalyze the cleavage of similar oxazolidine rings (Table 1, entries 4–9).<sup>4a</sup> To our delight, some Lewis acids were found to promote the transformation more efficiently, and exceptionally excellent yield was achieved when  $\text{SnBr}_4$  was used (entries 8 and 9), most likely because of its proper Lewis acidity and oxophilicity. As we expected, essentially the same result was achieved for the seven-membered ring formation from the oxazolidine (*S*)-5 (Scheme 1, (iii), bottom). The reaction catalyzed by  $\text{SnBr}_4$  proceeded so cleanly that the target compound ((*S*)-6) was able to be isolated from a crude mixture only by simple crystallization.

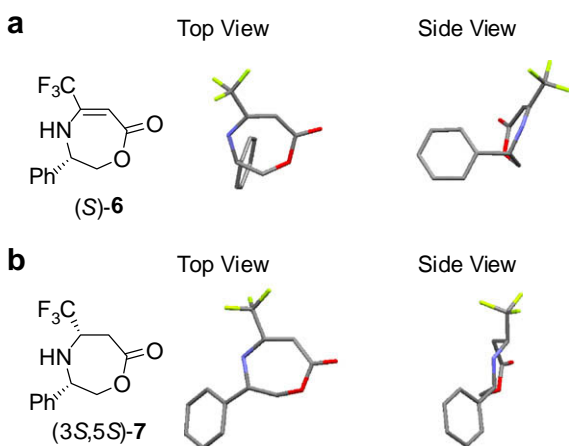
An X-ray crystallographic study on the cyclic enamino-ester (*S*)-6 revealed its intriguing structural characteristics (Fig. 1a).<sup>14</sup> Owing to the ring system of (*S*)-6, the phenyl group at the C(3) was arranged at the axial position of the seven-membered ring. As a result, the phenyl group efficiently covered the *re*-face of the enamino moiety, which was expected to enhance the *si*-face selective transformation of the enamino moiety.

We next performed the key step of the present synthetic route, the diastereoselective reduction of the cyclic enamino-ester (*S*)-6 (Table 2). Unexpectedly, however, (*S*)-6 showed low reactivity under usual reduction conditions, which have been applied for the reduction of a wide range of enamines (entries 1–3).<sup>3,7</sup> We then examined several reductants and additives, and finally found that the combination of  $\text{NaBH}_3\text{CN}/\text{HCl}$  was effective for the conversion of (*S*)-6 into the corresponding amino-ester with a cyclic structure (7, entry 5). For efficient activation of the enamino part of (*S*)-6, the basicity of which is considered to be lower than that of usual enamines because of the electron-withdrawing nature of the trifluoromethyl group, an excess amount of a strong Brønsted acid was essential. As a result, special reductants tolerant to acidic conditions should be employed. The absolute configuration of the major isomer of the cyclic amino-ester 7 was unambiguously determined to be (3*S*,5*S*) by an X-ray crystallographic analysis (Fig. 1b), which is in good agreement with that we anticipated from the structure of its precursor (*S*)-6 (Fig. 1a).<sup>14</sup> Worth noting is the excellent diastereoselectivity achieved here ((3*S*,5*S*)-7:(3*S*,5*R*)-7 = 95:5, entry 5), which is the highest value for the diastereoselective reduction of enamines bearing a fluoroalkyl group, as far as we are aware of. The diastereoselectivity was further improved when the reaction was conducted at  $-78$  °C, as might be expected ((3*S*,5*S*)-7:(3*S*,5*R*)-7 = 97:3, entry 6). Comparing with the results of previous studies,<sup>3</sup> we can clearly deduce that conformational constraint owing to the cyclic structure of (*S*)-6 was a crucial factor for the efficient stereocontrol of the present reduction.

In the context of diastereoisomer separation, additional benefits were brought by the cyclic structure. Owing to the fixation of the direction of dipoles in the cyclic structure, the two

**Table 1**  
Synthesis of the cyclic enamino-ester (S)-6

Entry	Reagent (equiv)	Temp (°C)	Time (h)	Ratio <sup>a</sup> (%)				Isolated yield of (S)-6 (%)
				4	5	6	9	
1 <sup>b</sup>	NaH (2)	100	17	0	88	5	0	—
2 <sup>c</sup>	NaH (2)	130	2	0	23	20	57	—
3 <sup>c</sup>	TsOH·H <sub>2</sub> O (0.1)	144	3	0	97	2	0	—
4 <sup>d</sup>	BF <sub>3</sub> ·OEt <sub>2</sub> (2)	83	8	0	>95	<1	0	—
5 <sup>b</sup>	TiCl <sub>4</sub> (2)	111	6	0	<1	>95	0	36
6 <sup>b</sup>	Ti(OiPr) <sub>4</sub> (2)	111	6	72	20	3	0	—
7 <sup>c</sup>	SnCl <sub>4</sub> (2)	144	4	0	22	78	0	37
8 <sup>c</sup>	SnBr <sub>4</sub> (2)	144	8	0	6	94	0	73
9 <sup>c</sup>	SnBr <sub>4</sub> (0.3)	144	18	0	0	>99	0	75

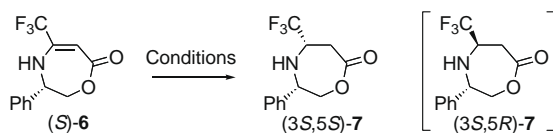
<sup>a</sup> Determined by <sup>19</sup>F NMR.<sup>b</sup> Toluene was used as a solvent.<sup>c</sup> *o*-Xylene was used as a solvent.<sup>d</sup> Dichloroethane was used as a solvent.**Figure 1.** X-ray crystal structure of (a) (S)-6 and (b) (3S,5S)-7. Hydrogen atoms are omitted for clarity.

diastereoisomers exhibited large difference in their polarity (*R<sub>f</sub>* values on a silica gel TLC plate developed with CHCl<sub>3</sub>: 0.37 and 0.20 for (3S,5S)-7 (major) and (3S,5R)-7 (minor), respectively), which

allowed us for the base-line separation of the diastereoisomers by general column chromatography. As a more practical method, the major isomer (3S,5S)-7 was isolated by single-batch crystallization, taking advantage of its high crystallinity (Scheme 1, (iv)).

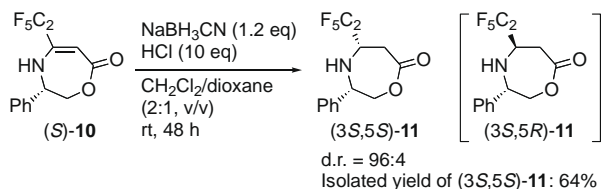
Finally, the diastereopure amino-ester (3S,5S)-7 thus obtained was successfully converted into the target β-trifluoromethyl-β-amino acid **1**, via the hydrogenolysis of the *N*-benzyl methyl, followed by acid-promoted transesterification/hydrolysis (Scheme 1, (v) and (vi)). During the deprotection processes, essentially no racemization took place, which was confirmed by the chiral HPLC analysis of the *N,O*-protected derivative of **1**, as established in a literature.<sup>4e</sup> The absolute configuration of the amino acid was unambiguously deduced to be *S* from that of the cyclic amino-ester determined by an X-ray analysis ((3S,5S)-7). To our surprise, this is the first unambiguous determination of the absolute configuration of the amino acid **1**, based on an X-ray crystallographic analysis.<sup>14,15</sup>

Worth noting is the fact that chromatographic separation was not required throughout the present synthetic route (Scheme 1), which allowed us several-decagram scale preparation of **1**. In fact, we confirmed that the present synthesis can be conducted in a 0.2 mol scale with essentially no decrease in yield nor in enantiopurity. The present synthesis would offer an alternative practical

**Table 2**  
Asymmetric reduction of the cyclic enamino-ester (S)-6

Entry	Reductant (equiv)	Additive (equiv)	Solv.	Conv. <sup>a</sup> (%)	dr <sup>a</sup>	Yield <sup>b</sup> (%)
1 <sup>c</sup>	H <sub>2</sub> /Pd/C (–)	none (–)	MeOH	n.r.	—	—
2 <sup>c</sup>	NaBH <sub>4</sub> (5)	ZnI <sub>2</sub> (3)	CH <sub>2</sub> Cl <sub>2</sub>	n.r.	—	—
3 <sup>c</sup>	NaBH <sub>3</sub> CN (6)	AcOH (35)	CH <sub>2</sub> Cl <sub>2</sub>	n.r.	—	—
4 <sup>c</sup>	NaBH <sub>3</sub> CN (6)	HCl (1)	CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup>	30	90:10	—
5 <sup>c</sup>	NaBH <sub>3</sub> CN (1.2)	HCl (10)	CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup>	>99	95:5	73
6 <sup>d</sup>	NaBH <sub>3</sub> CN (1.2)	HCl (10)	CH <sub>2</sub> Cl <sub>2</sub> <sup>e</sup>	97	97:3	74

<sup>a</sup> Determined by <sup>19</sup>F NMR.<sup>b</sup> Isolated yield of the major isomer ((3S,5S)-7).<sup>c</sup> Reaction was conducted at rt for 48 h.<sup>d</sup> Reaction was conducted at –78 °C to rt for 96 h.<sup>e</sup> Containing 33% (v/v) of dioxane.



**Scheme 2.** Asymmetric reduction of an analogous cyclic enamino-ester having a pentafluoroethyl group ((*S*)-**10**).

synthetic route to enantiopure **1**, which had been limited to the synthesis based on the asymmetric proton shift reaction<sup>4d,e</sup> or the resolution of its racemate.<sup>6b-d</sup>

Considering the fact that 4-fluorinated 3-oxoalkanoates and their equivalents are one of the most easily accessible classes of fluorinated building blocks, the present method would be highly general for the preparation of a wide range of  $\beta$ -fluoroalkyl- $\beta$ -amino acids. As a preliminary study to prove the generality, an analogous cyclic enamino-ester bearing a pentafluoroethyl group in the place of a trifluoromethyl group ((*S*)-**10**) was prepared and employed for the same hydride reduction (Scheme 2).<sup>16</sup> As was expected, the cyclic enamino-ester (*S*)-**10** was converted into the corresponding cyclic amino-ester (3*S*,5*S*)-**11** with excellent diastereoselectivity (dr = 96:4) without any optimization of the reaction conditions. The major isomer could be easily separated from the minor isomer by simple column chromatography, taking advantage of large difference in their polarity. Moreover, the absolute configuration of the major isomer, deduced from <sup>1</sup>H and <sup>19</sup>F NMR studies, was consistent with the case of (*S*)-**6** ((3*S*,5*S*)-isomer), which implies that the face selectivity of the hydride addition was controlled by a common mechanism. In other words, the absolute configuration of the major isomer might be rationally predicted in the present hydride reduction.

In summary, a new synthetic method to access enantiopure  $\beta$ -perfluoroalkyl- $\beta$ -amino acids was established, which could be conducted without any expensive reagent, special apparatus/technique, nor tedious chromatographic separation. Concerning the key asymmetric hydride reduction, prominent reliability of the present method was demonstrated in terms of stereoselectivity, predictability of the stereochemical preference, and easiness in isomer separation. Such a practical and reliable synthetic method would contribute to the further exploration of  $\beta$ -perfluoroalkyl- $\beta$ -amino acids, including their application to de-novo peptide chemistry.

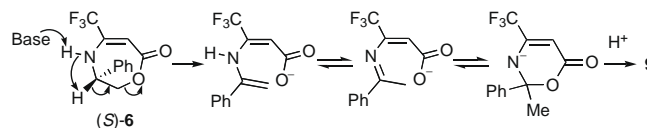
## Supplementary data

Supplementary data (determination of the enantiomeric purity of 3-amino-4,4,4-trifluorobutanoic acid (**1**)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.159.

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- A plausible mechanism for the formation of **9** is as follows: For examples of a related rearrangement reaction, see: (a) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *Mendeleev Commun.* **2006**, *16*, 165; (b) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *J. Fluorine Chem.* **2006**, *127*, 708.



- Crystallographic data for the determination of the absolute configuration of **1** has been limited to one report (Kukhar, V. P.; Soloshonok, V. A.; Švedas, V. K.; Kotik, N. V.; Galaev, I. Y.; Kirilenko, A. G.; Kozlova, E. V. *Bioorgan. Khim.* **1993**, *19*, 474). However, the assignment was based on an X-ray crystal structure of (-)-**1** having neither chiral internal reference nor heavy atom indispensable for the observation of anomalous X-ray scattering. In comparison with the present result, the assignment made by Kukhar et al. was confirmed to be correct.
- As far as we know (*S*)-**6** and (3*S*,5*S*)-**7** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication Numbers CCDC 709483 and CCDC 709484, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
- The cyclic enamino-ester (*S*)-**10** was prepared from an easily available fluorinated building block (ethyl 4,4,5,5,5-pentafluoroethylpent-1-ynoate). See Ref. 11.