Diastereoselective Synthesis of *S-tert*-Butyl-*β*-(trifluoromethyl)isocysteine

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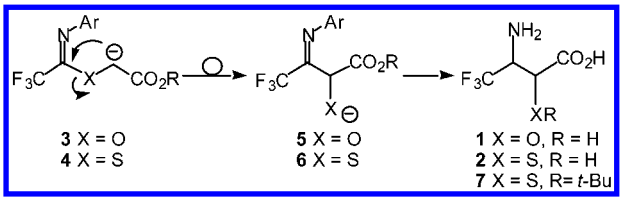
Abstract: Both diastereoisomers of *S-tert*-butyl-*β*-(trifluoromethyl)isocysteine have been synthesized stereoselectively by the sequential reactions of trifluoroacetimidoyl chloride with the lithium enolate of *tert*-butyl α-*tert*-butylthioacetate, followed by the diastereoselective reduction of the imino group with sodium borohydride in the presence of zinc(II) or di(ethylene glycol) dimethyl ether, and finally by the deprotection of N-aryl and *tert*-butyl ester groups.

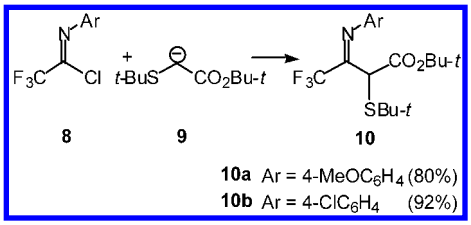
Unnatural and structurally new fluorinated amino acids are current synthetic targets due to their unusual bioactivities. Among them, the chemistry and biological activity of fluorinated *β*-amino acids as antibiotics and/or enzyme inhibitors have gained considerable interest during the last two decades.[1,2] For example, the *β*-(trifluoromethyl)isoserine moiety (**1**) attached to taxol plays an important role in the anticancer activity of its trifluoromethylated taxoid.[3,4] Useful synthetic approaches for α-substituted *β*-amino acids had already been summarized;[5] however, those for fluorinated *β*-amino acids have not yet been well established.

Some amino acid drugs containing a thiol moiety, such as Captopril[6] and its trifluoromethylated analogue,[7] are well-known angiotensin-converting enzyme inhibitors. In connection with this fact and in light of the important biological activity of isoserine (**1**), it is of interest to synthesize the corresponding isocysteine (**2**) and to examine its biological activity. Recently, we have studied the syntheses of **1** and **2** by the Wittig type rearrangements of **3** and **4** (Scheme 1). However, the attempt to transform **4** to **2** was not successful because of the facile desulfurization from the thiolate intermediate **6**,[8] although **3** was transformed to **1** in an excellent yield under the same reaction conditions.[9] To suppress the desulfurization, an appropriate protection of the sulfur moiety would be indispensible. Thus, the strategy of the intermolecular coupling of the enolate of S-protected α-thiohydroxyacetate **9** with trifluoroacetimidoyl chloride **8**[10] would work to construct a synthetic analogue of **6** with the desired isocysteine skeleton,[11] instead of our previous intramolecular rearrangement strategy. In this note, the successful transformation of **8** to *S-tert*-butylisocysteine **7** is described.

Scheme 1



Scheme 2



Imidoyl chloride **8** was coupled with enolate **9** in THF at −40 °C, to provide *β*-imino esters **10** in good yields,[11] as shown in Scheme 2. *β*-Imino ester **10a** exists as an imino form in $CDCl_3$, while *β*-imino ester **10b** in $CDCl_3$ has both imino and enamino forms in equilibrium, as already reported for the related imino ester.[12]

The conversions of the fluorinated *β*-imino ester **10a** into the corresponding *β*-amino acid diastereoisomers *syn*- and *anti*-**11a** can be achieved by stereocontrolled reduction with hydride via the chelated intermediate (Figure 1, *syn*-**11a**) or via the nonchelated Felkin−Anh intermediate (Figure 1, *anti*-**11a**). At first, reduction via zinc(II) chelated conformation was examined. Sodium borohydride reduced **10a** in CH_2Cl_2 very slowly, but the addition of the Lewis acid like zinc(II) ion enhanced the reduction rate dramatically and led to the preferential reduction of the imino moiety, affording the syn product **11a** exclusively[13] along with about 20% of starting imine **10a**. The prolonged reaction resulted in the formation of amino alcohol as a byproduct that arose from further

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(11) Coupling of enolate with trifluoroacetimidoyl chloride.[2b]

(12) Some imino esters are known to exist as an equilibrium mixture of imino and enamino forms. See also ref 2.

(13) Stereocontrolled reduction of *tert*-butyl *β*-imino-*γ*,*γ*,*γ*-trifluoro-α-methylbutanoate was reported by Fustero.[2b]

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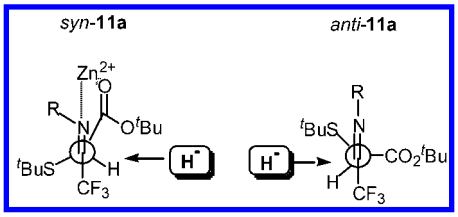
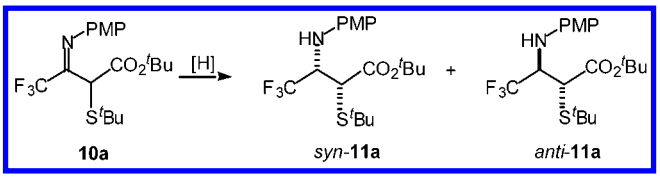


Figure 1.

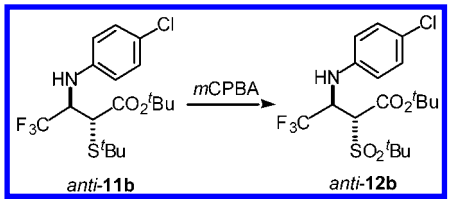
Table 1. Diastereomeric Reduction of 10a with $NaBH_4$ to 11a



entry	solv	additive	temp ()°C	time (h)	yield (%) of **11a** (syn/anti)
1	CH_2Cl_2	$ZnCl_2$	room temp	1	13 (>99/1>)[a]
2	CH_2Cl_2	$ZnBr_2$	room temp	1	70 (>99/1>)[a]
3	CH_2Cl_2	ZnI_2	room temp	1	50 (>99/1>)[a]
4	MeOH		0−room temp	1	80 (25/75)[b]
5	THF	S_8	room temp	3	79 (33/67)[a]
6	THF	CROWN[c]	0−room temp	3	72 (23/77)[a]
7	THF	DGDE[d]	0−room temp	3	81 (11/89)[a]
8	THF	TMDA[e]	0−room temp	3	48 (33/67)[a]

[a] $NaBH_4$ (6 equiv) for **10a**. [b] $NaBH_4$ (30 equiv) for **10a**. [c] Dicyclohexyl-18-crown-6. [d] DGDE = Di(ethylene glycol) dimethyl ether. [e] TMDA = *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine.

Scheme 3



reduction of the ester moiety. Next, *β*-imino ester **10a** was reduced with sodium borohydride in methanol (Table 1, entry 4). Although reduction of **10a** needed an excess amount of sodium borohydride, the anti product **11a** was obtained mainly. Unfortunately, reduction with $NaBH_4$ in THF proceeded very slowly. Thus, $NaBH_2S_3$[14] generated in situ by the reaction of $NaBH_4$ with elemental sulfur was used as an activator of $NaBH_4$. The yield was good, but the stereoselectivity was unsatisfactory (entry 5). Thus, an additive which traps sodium ion to generate naked borohydride anion was examined (entries 6−8). Among the solvents examined, di(ethylene glycol) dimethyl ether (DGDE) was found to give the highest diastereomeric ratio (syn/anti = 11/89), and *anti*-**11a** was isolated in 72% yield from the mixture. Both stereoisomers were separated by column chromatography.

Configurations of the amino acid derivatives *syn*-**11b** and *anti*-**12b**, which were derived by *m*CPBA oxidation of *anti*-**11b** (Scheme 3), were unambiguously confirmed by X-ray crystallographic analysis.[15]

The stereochemical outcome of the reduction of **10a** in the Zn(II)−$NaBH_4$ system to the major diastereoisomer *syn*-**11a** is easily understood on the assumption that hydride attacks the imino carbon from the opposite side of the α-*tert*-butylthio group (Figure 1). Meanwhile, formation of *anti*-**11a** in the presence of Lewis base would be explained by the Felkin−Anh model.

Both of the diastereoisomeric *β*-amino esters *syn*- and *anti*-**11a** could be successively deprotected by first removing the *N*-*p*-methoxyphenyl group by CAN oxidation and then the *tert*-butoxycarbonyl group by acid-catalyzed hydrolysis, affording **13a** and **14a**, respectively, as shown in Scheme 4. In addiiton, deprotection of the *S*-*tert*-butyl group was achieved by a two-step reaction, as shown in Scheme 4. First, the carbon−sulfur bond cleavage of **11a** with *o*-nitrobenzenesulfenyl chloride gave the unsymmetrical disulfide **15a** in 88% yield.[17] Then, sodium borohydride reduction of the disulfide moiety of **15a** provided thiol **16**a as crystals in 63% yield.

Experimental Section

General Methods. Reactions were carried out in anhydrous solvents under an argon atmosphere and in oven-dried glassware. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 200, 50.3, and 188 MHz, respectively. The chemical shifts are reported in *δ* (ppm) values relative to $CDCl_3$ (*δ* 7.26 ppm for ^1H NMR, *δ* 77.0 ppm for ^{13}C NMR) and C_6F_6 (*δ* 0 ppm for ^{19}F NMR). For TLC and column chromatography E. Merck silica gel (Kieselgel 60 F254 and Kieselgel 60, 230−400 mesh) was used. Imidoyl chlorides **8** were prepared according to the methods described in the literature.[10] α-*tert*-Butylthio *tert*-butyl ester **9**[16] was prepared by the triethylamine-catalyzed reaction of *tert*-butyl bromoacetate with *tert*-butyl mercaptan.

Preparation of Fluorinated *β*-Imino α-*tert*-Butylthio Ester 10. *n*-Butyllithium (1.56 M in hexane, 21.4 mL, 33.3 mmol) was added dropwise to a solution of diisopropylamine (4.6 mL, 33.3 mmol) in THF (50 mL) at −78 °C under argon. After the mixture was stirred at this temperature for 15 min and then 0 °C for an additional 15 min, *tert*-butyl α-*tert*-butylthioacetate (**9**; 3.407 g, 16.7 mmol) in THF (5 mL) was added. The resulting mixture was stirred at −40 °C for 3 h and then cooled to −78 °C. Imidoyl chloride **8** (3.967 g, 16.7 mmol) in THF (5 mL) was added and stirred at −78 to 0 °C. After all of the imidoyl chloride was consumed (monitored by TLC), the reaction was quenched by the addition of a saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether (45 mL × 3). The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to furnish the crude product. Purification was carried out as indicated in each case.

***tert*-Butyl 2-(*tert*-Butylthio)-3-[*N*-(4-methoxyphenyl)-imino]-4,4,4-trifluorobutanoate (10a).** Flash chromatography (*n*-hexanes−EtOAc (7:1)) on silica gel gave a yellowish oil (5.411 g, 80%): IR (neat) 1754, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 6.92 (s, 4H), 4.66 (s, 1H), 3.81 (s, 3H), 1.50 (s, 9H), 1.06 (s, 9H); ^{19}F NMR ($CDCl_3$) *δ* 96.4 (s, CF_3). Anal. Calcd for $C_{19}H_{26}F_3NO_3S$: C, 56.28; H, 6.46; N, 3.45. Found: C, 56.21; H, 6.79; N, 3.75.

***tert*-Butyl 2-(*tert*-Butylthio)-3-[*N*-(4-chlorophenyl)imino]-4,4,4-trifluorobutanoate (10b).** Flash chromatography (*n*-hexanes−EtOAc (15:1)) on silica gel gave a yellowish oil (6.300 g, 92%): IR (neat) 1758, 1724, 1670, cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.38 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 1H), 1.50 (s, 9H), 1.09 (s, 9H); ^{19}F NMR ($CDCl_3$) *δ* 96.0 (s, CF_3). Anal. Calcd for $C_{18}H_{23}ClF_3NO_2S$: C, 52.74; H, 5.66; N, 3.42. Found: C, 53.06; H, 5.74; N, 3.81.

Reduction of 10 to *syn*-11. To a solution of anhydrous zinc bromide (0.337 g, 1.5 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C was added the corresponding **10a** (0.203 g, 0.5 mmol) in dry CH_2Cl_2

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(15) Syn and anti configurations of **11a** were determined by comparison of ^1H NMR data with those of *syn*- and *anti*-**11b**, whose structures were determined by X-ray analysis. Detailed ^1H NMR data are shown in Table 2 of the Supporting Information.

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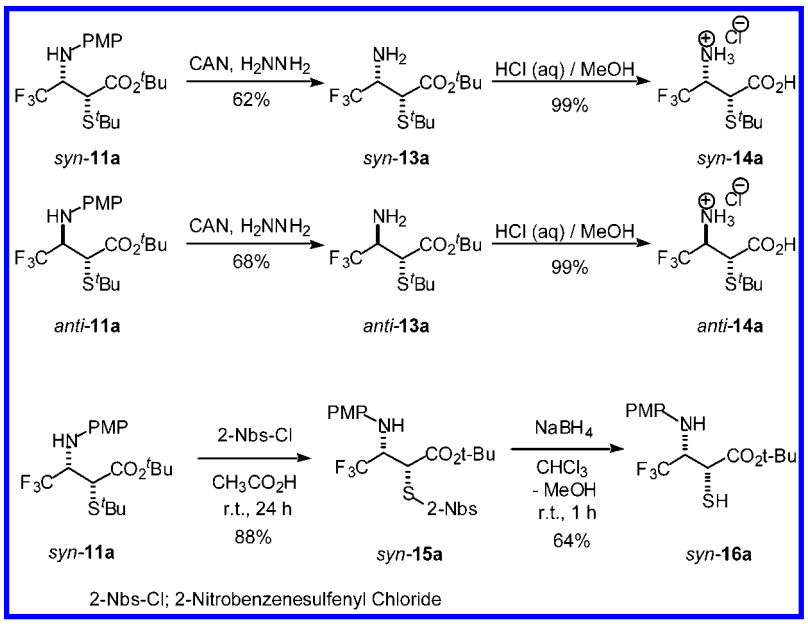
Scheme 4



(1 mL). The resulting mixture was stirred at the same temperature for 1 h, and then sodium borohydride (0.112 g, 3.0 mmol) was added to the mixture at 0 °C, which was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated ammonium chloride, and the aqueous layer was extracted with diethyl ether (25 mL × 3). The organic layers were combined, washed with brine, and dried over magnesium sulfate. After filtration, the solvents were removed under reduced pressure to provide the crude product, which was purified through flash chromatography (*n*-hexanes−EtOAc (10:1)) on silica gel.

***tert*-Butyl 3-[*N*-(4-Methoxyphenyl)amino]-2-*tert*-butylthio-4,4,4-trifluorobutanoate (*syn*-11a).** This compound was obtained as colorless crystals (0.142 g, 70%): mp 58−60 °C; IR (neat) 3424, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79 (d, J = 9.1 Hz, 2H), 6.70 (d, J = 9.1 Hz, 2H), 4.4−4.2 (m, 1H), 3.85−3.75 (m, 1H), 3.75 (s, 3H), 3.53 (d, J = 6.8 Hz, 1H), 1.42 (s, 9H), 1.38 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 88.3 (d, J = 6 Hz, CF_3); MS m/z 407 (11) $[M]^+$, 204 (100), 148 (29), 92 (43), 57 (55). Anal. Calcd for $C_{19}H_{28}F_3NO_3S$: C, 56.00; H, 6.93; N, 3.44. Found: C, 56.02; H, 6.93; N, 3.60.

***tert*-Butyl 3-[*N*-(4-Chlorophenyl)amino]-2-(*tert*-butylthio)-4,4,4-trifluorobutanoate (*syn*-11b).** This compound was obtained as colorless crystals (0.146 g, 71%): mp 100−101 °C; IR (neat) 3408, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 4.5−4.2 (m, 1H), 4.05 (d, J = 9.2 Hz, 1H), 3.53 (d, J = 6.7 Hz, 1H), 1.43 (s, 9H), 1.38 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 88.2 (d, J = 6 Hz, CF_3); MS m/z 413 (2) $[M]^+$, 411 (4) $[M]^+$, 286 (6), 208 (57), 148 (66), 92 (91), 57 (100). Anal. Calcd for $C_{18}H_{25}F_3NO_2S$: C, 52.49; H, 6.12; N, 3.40. Found: C, 52.57; H, 6.34; N, 3.30.

Reduction of 10 to *anti*-11. To a solution of anhydrous sodium borohydride (0.113 g, 3.0 mmol) in dry di(iethylene glycol) dimethyl ether (1 mL), stirred for 30 min at 0 °C, was added the β-imino ester **10a** (0.203 g, 0.5 mmol) in THF (2 mL), and the reaction mixture was stirred at room temperature for 3 h. After almost all the starting material was converted (monitored by TLC), 10 mL of diethyl ether was added and the reaction mixture was quenched with 10 mL of saturated ammonium chloride. The aqueous layer was extracted with diethyl ether (25 mL × 3). The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to furnish the crude product. Purification was carried out as indicated in each case.

***tert*-Butyl 3-[*N*-(4-Methoxyphenyl)amino]-2-(*tert*-butylthio)-4,4,4-trifluorobutanoate (*anti*-11a).** Flash chromatography (*n*-hexanes−EtOAc (15:1)) on silica gel gave a pale yellowish oil (0.147 g, 72%): IR (neat) 3428, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 9.0 Hz, 2H), 5.11 (br, 1H), 4.2−4.0 (m, 1H), 3.75 (s, 3H), 3.57 (d, J = 3.7 Hz, 1H), 1.49 (s, 9H), 1.34 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 88.3 (d, J = 6 Hz, CF_3); MS m/z 407 (3) $[M]^+$, 204 (100), 148 (17), 92 (34), 57 (43). Anal. Calcd for $C_{19}H_{28}F_3NO_3S$: C, 56.00; H, 6.93; N, 3.44. Found: C, 55.66; H, 7.13; N, 3.81.

***tert*-Butyl 3-[*N*-(4-Chlorophenyl)amino]-2-(*tert*-butylthio)-4,4,4-trifluorobutanoate (*anti*-11b).** Flash chromatography (*n*-hexanes−EtOAc (20:1)) on silica gel gave a pale yellowish oil (0.154 g, 75%): IR (neat) 3420, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 5.53 (d, J = 9.2 Hz, 1H), 4.3−4.0 (m, 1H), 3.57 (d, J = 3.6 Hz, 1H), 1.49 (s, 9H), 1.35 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 88.0 (d, J = 7 Hz, CF_3); MS m/z 413 (3) $[M + 2]^+$, 411 (11) $[M]^+$, 282 (14), 208 (60), 148 (54), 92 (98), 57 (100). Anal. Calcd for $C_{18}H_{25}ClF_3NO_2S$: C, 52.49; H, 6.12; N, 3.40. Found: C, 52.24; H, 6.42; N, 3.19.

***tert*-Butyl 3-[*N*-(4-Chlorophenyl)amino]-2-(*tert*-butylsulfonyl)-4,4,4-trifluorobutanoate (*anti*-12b).** To a solution of *m*-chloroperbenzoic acid (0.215 g, 1.25 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added *anti*-**11b** (0.206 g, 0.5 mmol) dissolved in CH_2Cl_2 (2 mL). The resulting mixture was stirred at the same temperature for 3 h and was quenched by the addition of saturated sodium hydrogencarbonate. The aqueous layer was extracted with diethyl ether (25 mL × 3). The organic layers were combined, washed with brine, and dried over magnesium sulfate. After filtration, the solvents were removed under reduced pressure to provide a solid which was purified by recrystallization from $CHCl_3$ to give single crystals of **12b** (0.201 g, 90%): mp 164−166 °C dec; IR (neat) 3408, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 5.85 (d, J = 8.8 Hz, 1H), 4.8−4.5 (m, 1H), 4.31 (d, J = 2.4 Hz, 1H), 1.55 (s, 9H), 1.47 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 87.7 (d, J = 6 Hz, CF_3). Anal. Calcd for $C_{18}H_{25}ClF_3NO_2S$: C, 48.70; H, 5.68; N, 3.16. Found: C, 48.61; H, 6.05; N, 2.95.

Deprotection of the *N*-*p*-Methoxyphenyl Group of 11. A solution of **11a** (0.203 g, 0.5 mmol) in CH_3CN (5 mL) was treated at room temperature with cerium ammonium nitrate (CAN) (0.822 g, 1.5 mmol) dissolved in H_2O (1.7 mL), and the reaction mixture was stirred for 3 h. The aqueous layer was extracted with diethyl ether (25 mL × 3). The organic layers were combined and washed with brine, and then anhydrous hydrazine (0.062 g, 2 mmol) was added. The organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide the crude product mixture, which was purified through flash chromatography (*n*-hexanes−EtOAc (5:1)) on silica gel.

***tert*-Butyl 3-Amino-2-(*tert*-butylthio)-4,4,4-trifluorobutanoate (*syn*-13a).** This compound was obtained as a colorless oil (0.093 g, 62%): IR (neat) 3420, 3380, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8−3.5 (m, 1H), 3.28 (d, J = 8.1 Hz, 1H), 1.70 (brs, 2H), 1.46 (s, 9H), 1.38 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 86.9 (d, J = 6 Hz, CF_3); MS m/z 302 (1) $[M + 1]^+$, 230 (4), 148 (32), 92 (38),

57 (100). Anal. Calcd for $C_{12}H_{22}F_3NO_2S$: C, 47.82; H, 7.36; N, 4.65. Found: C, 48.13; H, 7.75; N, 4.74.

***tert*-Butyl 3-Amino-2-(*tert*-butylthio)-4,4,4-trifluorobutanoate (*anti*-13a).** This compound was obtained as a colorless oil (0.102 g, 68%): IR (neat) 3448, 3356, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6−3.3 (m, 1H), 3.45 (d, J = 1.8 Hz, 1H), 2.04 (br s, 2H), 1.46 (s, 9H), 1.36 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 86.2 (d, J = 7 Hz, CF_3); MS m/z 302 (1) $[M + 1]^+$, 230 (5), 148 (31), 92 (40), 57 (100). Anal. Calcd for $C_{12}H_{22}F_3NO_2S$: C, 47.82; H, 7.36; N, 4.65. Found: C, 47.80; H, 7.53; N, 4.97.

Acid-Catalyzed Hydrolysis of *tert*-Butyl Ester 13a. Concentrated hydrochloric acid (2.0 mL) was added dropwise to a methanol solution of **13**a (0.155 g, 0.5 mmol in MeOH 0.5 mL). The mixture was stirred at room temperature for 12 h. Evaporation of the solvent gave a colorless solid, which was recrystallized from AcOEt.

3-Amino-2-(*tert*-butylthio)-4,4,4-trifluorobutanoic Acid Hydrochloride (*syn*-14a). This compound was obtained as a colorless crystal (0.140 g, 99%): mp 155−157 °C; IR (neat) 3464, 2976, 1724 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.5−4.3 (m, 1H), 3.87 (d, J = 6.9 Hz, 1H), 1.35 (s, 9H); ^{19}F NMR (DMSO-d_6) δ 94.9 (d, J = 6 Hz, CF_3). Anal. Calcd for $C_8H_{15}ClF_3NO_2S$: C, 34.11; H, 5.37; N, 4.97. Found: C, 33.92; H, 5.74; N, 4.57.

3-Amino-2-(*tert*-butylthio)-4,4,4-trifluorobutanoic Acid Hydrochloride (*anti*-14a). This compound was obtained as a colorless crystal (0.1396 g, 99%): mp = 158−160 °C; IR (neat) 2980, 1740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.6−4.4 (m, 1H), 3.96 (d, J = 4.0 Hz, 1H), 1.33 (s, 9H); ^{19}F NMR (DMSO-d_6) δ 94.4 (d, J = 8 Hz, CF_3). Anal. Calcd for $C_8H_{15}ClF_3NO_2S$: C, 34.11; H, 5.37; N, 4.97. Found: C, 33.81; H, 5.59; N, 4.63.

***tert*-Butyl 3-[*N*-(4-Methoxyphenyl)amino]-2-[*S*-[(2-nitrophenyl)sulfenyl]thio]-4,4,4-trifluorobutanoate (*syn*-15a).** To a solution of *syn*-**11** (0.634 g, 1.56 mmol) in CH_3CO_2H (3 mL) at 0 °C was added 2-(nitrophenyl)sulfenyl chloride (2-NpsCl; 0.567 g, 3 mmol). The resulting mixture was stirred at room temperatue for 24 h, and then the solvent was evaporated at room temperature. The crude mixture was purified through flash chromatography (*n*-hexanes−EtOAc (15:1)) on silica gel, affording a yellowish solid as the sole stereoisomer, *syn*-**15a** (0.809 g, 1.34 mmol, 88%): mp 94 °C dec; IR (KBr) 3396, 2988, 1716, 1592, 1570, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39−7.81 (m, 2H), 7.45−7.30 (m, 1H), 7.69−7.53 (m, 1H), 6.88−6.68 (m, 4H), 4.57−4.42 (m, 1H), 3.77 (s, 3H), 3.82−3.68 (m, 2H, CH, NH), 1.37 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 88.4 (d, J = 7 Hz, CF_3). Anal. Calcd for $C_{21}H_{23}F_3N_2O_5S_2$: C, 49.99; H, 4.59; N, 5.55. Found: C, 49.93; H, 4.63; N, 5.82.

***tert*-Butyl 2-Mercapto-3-[*N*-(4-methoxyphenyl)amino]-4,4,4-trifluorobutanoate (*syn*-16a).** To a solution of *syn*-**15a** (0.506 g, 1.0 mmol) in $CHCl_3$ (5 mL) and MeOH (5 mL) was added $NaBH_4$ (0.190 g, 5.0 mmol) at 0 °C. The reaction mixture was stirred for 1 h and quenched with saturated ammonium chloride, and the aqueous layer was extracted with EtOAc (50 mL × 3). The organic layers were combined, washed with brine, and dried over magnesium sulfate. After filtration, the solvents were removed under reduced pressure to provide the crude product, which was purified through flash chromatography (*n*-hexanes−EtOAc (40:1)) on silica gel, affording colorless crystals of *syn*-**16a** (0.224 g, 0.64 mmol, 64%): mp 82.0−82.5 °C; IR (KBr) 3400(NH), 3000, 2968, 2944, 2572(SH), 1722, 1526 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83−6.67 (m, 4H), 4.60−4.37 (m, 1H), 4.15−4.00 (m, 1H), 4.01 (dd, J = 4.4, 6.6 Hz, 1H), 3.74 (s, 3H), 2.21 (d, J = 6.6 Hz, 1H), 1.34 (s, 9H); ^{19}F NMR ($CDCl_3$) δ 88.7 (d, J = 8 Hz, CF_3); MS m/z 351 (8), 295 (10), 204 (100), 57 (25). Anal. Calcd for $C_{15}H_{20}F_3NO_3S$: C, 51.27; H, 5.74; N, 3.99. Found: C, 50.94; H, 5.62; N, 3.62.

X-ray Crystal Data for 11b: $C_{18}H_{25}ClF_3NO_2S$, M_r = 411.91, monoclinic, space group $P2_1/a$ (No. 14), a = 19.760(6) Å, b = 18.375(5) Å, c = 6.007(1) Å, β = 98.32(2)°, V = 2158.0(10) Å^3, Z = 4, D_{calcd} = 1.26(8) g cm^{-3}, R = 0.196 for 5123 observed reflections ($I > 1.60\sigma(I)$) and 235 variable parameters.

X-ray Crystal Data for 12b: $C_{18}H_{25}ClF_3NO_4S$, M_r = 443.91, monoclinic, space group $P2_1/c$ (No. 14), a = 10.342(1) Å, b = 11.594(1) Å, c = 18.668(3) Å, β = 104.235(4)°, V = 2169.6(5) Å^3, Z = 4, D_{calcd} = 1.35(9) g cm^{-3}, R = 0.055 for 3507 observed reflections ($I > 3.00\sigma(I)$) and 353 variable parameters. All measurements were made on a Rigaku RAXIS-IV imaging plate area detector with Mo Kα radiation.

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Supporting Information Available: Detailed X-ray data for compounds **11b** and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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