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Asymmetric synthesis of both enantiomers of *syn*-(3-trifluoromethyl)cysteine derivatives

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Dedicated to Professor Richard D. Chambers on the occasion of his 70th birthday.

Abstract

The use of several chiral trifluoromethylated building blocks **1a**, **1b**, **9a** and **9b** was attempted to synthesize of *syn*-(3-trifluoromethyl)-cysteine. A novel and efficient enantioselective synthesis of both enantiomers of *syn*-(3-trifluoromethyl)cysteine derivatives **12a** and **12b** was successfully achieved.

Keywords: Trifluoromethylated compounds; Cysteine; Amino acids; Asymmetric synthesis

1. Introduction

Cysteine is a sulfur-containing amino acid that is distributed widely in proteins, peptides (subtilin, nisin and ancovenin) [1] and antibiotics (griseoviridin, penicillin family) [2]. Many cysteine-containing natural products exhibit important biological activities. Furthermore, synthetic orthogonally protected cyclolanthionines and methylanthionines have been proposed as constrained building blocks for the design of novel peptide mimics [3]. There are also some reports on the synthesis and application of chemically modified cysteines, especially β-substituted cysteines, which show better activities in antibiotics than cysteine itself [4].

Besides being utilized as conformational modifiers in physiologically active proteins and enzymes [5], fluorinated amino acids, especially in an enantiomerically pure form, have been widely used as biochemical probes [6], as inhibitors of enzymes [7], and as antitumor and antibacterial agents [8]. In the past 20 years, there has been a particular interest in trifluoromethylated amino acids because replacement of methyl or other groups with trifluoromethyl group is accompanied by a substantial increase in hydrophobicity, owing to the low polarizability of the fluorine atoms [9]. In addition, due to the strong electron-withdrawing effect of the trifluoromethyl group, the chemical and biological properties of the trifluoromethylated amino acids may differ greatly from those of their non-fluorinated analogues. Introduction of a trifluoromethyl group into cysteine derivatives may bring substantial conformational and physiological changes and provide a useful probe to follow biochemical reactions. However, to the best of our knowledge, no trifluoromethylated cysteine has ever been synthesized to date, which inspired us to pursue an asymmetric synthesis of both enantiomers of *syn*-(3-trifluoromethyl)cysteine.

2. Results and discussion

In our previous study, we conveniently synthesized a class of chiral trifluoromethylated building blocks through

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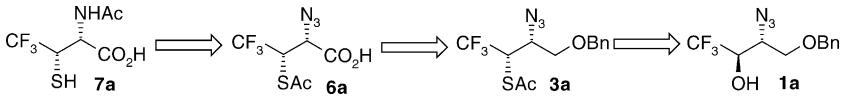
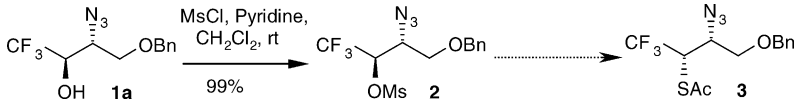


Scheme 1.

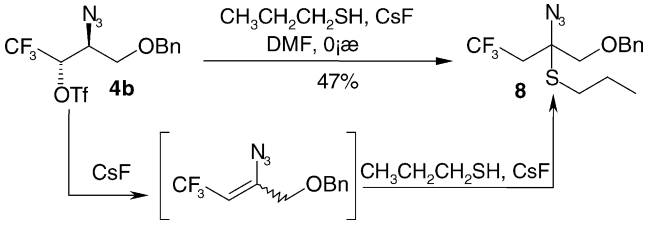


Scheme 2.

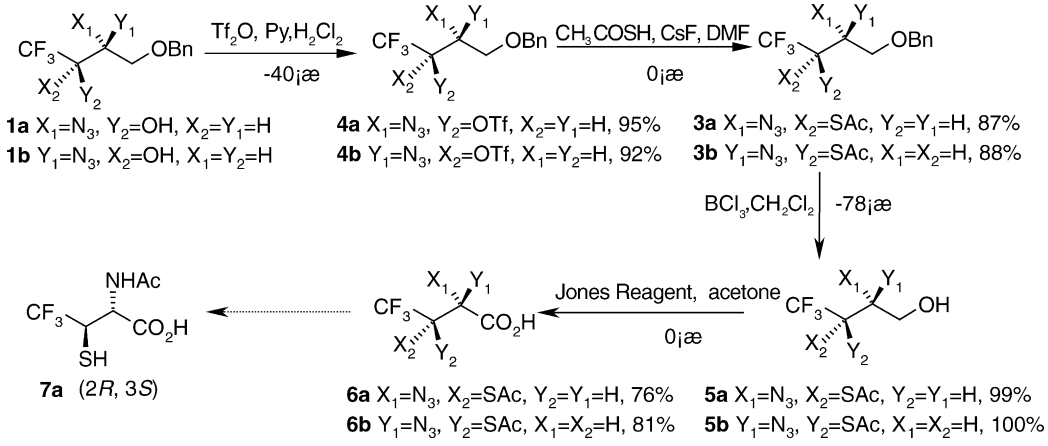
regioselective and stereoselective nucleophilic ring-opening of trifluoromethylated cyclic sulfates [10]. From those chiral building blocks, some trifluoromethylated amino acids (including both enantiomers of *anti*-4,4,4-trifluorothreonine, 2-amino-4,4,4-trifluorobutanoic acid and *syn*-4,4,4-trifluoroisothreonine) were successfully synthesized [10]. Herein, we sought to apply these chiral building blocks to the synthesis of 3-trifluoromethylcysteine. Initially, chiral building blocks **1a** [10a] were chosen as starting materials. The synthetic strategy presented here involved the following steps: introduction of a sulfur atom into the chiral building block **1a**; removal of the benzyl group of **3a** followed by oxidation of the resultant primary alcohol **3a** to the carboxylic acid **6a**; reduction of the azido group to afford the target molecule **7a**. The retrosynthetic analysis of 3-trifluoromethyl-cysteine **7a** is presented in Scheme 1.

Thus, according to our retrosynthetic analysis, trifluoromethylated alcohol **1a** was first treated with methanesulfonyl chloride and pyridine to afford methanesulfonate **2** in 99% yield, which provided a leaving group for the introduction of sulfur atom at C3 of the compound **2** (Scheme 2). However, treatment of methanesulfonate **2** with potassium thioacetate or thioacetic acid/cesium fluoride under various conditions resulted only in recovery of methanesulfonate **2**. The failure to afford the compound **3** should be attributed to the strong electron-withdrawing effect and steric hindrance of trifluoromethyl group, which blocked the S_N2 replacement reaction.

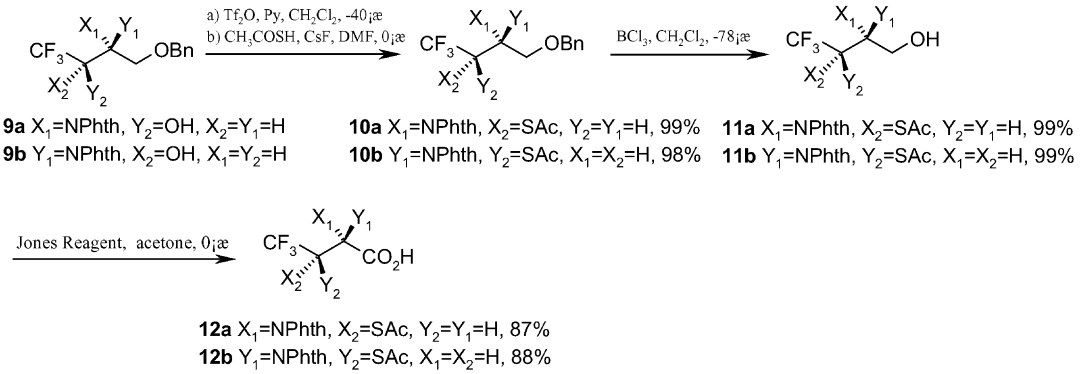
In view of the above failure and corresponding analysis, we envisaged that the trifluoromethanesulfonyl group should probably make the replacement reaction occur because it is a better leaving group than the methanesulfonyl group in S_N2 replacement reaction. Thus exposure of the alcohol **1a** to trifluoromethanesulfonic anhydride and pyridine at −40 °C gave the trifluoromethanesulfate **4a** in 95% yield (Scheme 3). Then, a cesium fluoride mediated S_N2 displacement [11] was carried out on the trifluoromethanesulfate **4a** with thioacetic acid at 0 °C and, the desired intermediate **3a** was provided in 87% yield. Removal of the benzyl group of **3a** was realized with boron trichloride at −78 °C and the alcohol **5a** was isolated in 99% yield. Alcohol **5a** was treated with Jones reagent at



Scheme 4.



Scheme 3.



Scheme 5.

0 °C to give acid **6a** in 76% yield. Many side reactions could take place during the reduction of the azido group of **6a** (intramolecular acyl group migration from sulfur to nitrogen resulted in a sulfhydryl group [12], the sulfhydryl group may then trigger a set of side reactions such as the sulfhydryl group could reduce the azido group and the sulfhydryl group itself could be oxidized). After systematic studies [13], we found that azide **6a** was smoothly reduced in the presence of 1,3-propanedithiol and triethylamine [14] to a single product according to ^{19}F NMR and TLC analysis (this product can be detected only by ^{19}F NMR and TLC in the reaction mixture, and ^{1}H NMR could not give the clear outcome due to the existence of lots of others compounds in the reaction mixture). However, we failed to isolate the resultant product from the reaction mixture because it is extremely unstable. We can provide only both the important precursors of *syn*-(3-trifluoromethyl)cysteine **6a**, **6b** for further use.

To prevent the side reactions induced by the thioacetate group, propanethiol was used as the nucleophile for introducing the sulfur atom (Scheme 4). To our surprise, the unexpected compound **8** was isolated in 47% yield when trifluoromethanesulfonate **4b** was treated with propanethiol and cesium fluoride in DMF at 0 °C. It is evident from the formation of the compound **8** that a cesium fluoride mediated elimination reaction first resulted in the formation of alkene intermediate, which then underwent the Michael addition of propanethiol to give compound **8**.

Finally, an alternative synthetic route was successfully developed (Scheme 5). This started from our reported trifluoromethylated alcohol **9a** [10] and required only a few straightforward steps. Thus, treatment of enantiomerically pure alcohol **9a** with trifluoromethanesulfonic anhydride and pyridine at −40 °C, followed by a cesium fluoride mediated S_N2 displacement of trifluoromethanesulfonate with thiolacetic acid, furnished the intermediate **10a** in almost quantitative yield. Exposure of the compound **10a** in dichloromethane to boron trichloride at −78 °C afforded a primary alcohol **11a** in 99% yield, which underwent Jones oxidation to give the product **12a** in 87% yield. Due to the poor stability of sulfur-containing amino acids and peptides, the protecting groups of amino acid **12a** were not removed unless further synthetic applications were needed. In the same fashion, the other isomer **12b** was also prepared in high yield from the intermediate **9b** in four steps.

3. Conclusions

In summary, we have described our attempts at the synthesis of 3-trifluoromethylcysteine via several different routes. After many arduous efforts, an efficient procedure for enantioselective synthesis of both enantiomers of *syn*-(3-trifluoromethyl)cysteine derivatives **12a**, **12b** starting from our reported chiral trifluoromethylated building blocks was successfully achieved.

4. Experimental

^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer using CCl_3F as external standard, and downfield shifts being designed as negative. Compounds **1a**, **1b**, **9a** and **9b** were prepared according to the reported procedure [10b].

*4.1. (1R, 2R)-Methanesulfonic acid 2-azido-3-benzyloxy-1-trifluoromethyl-propyl ester (**2**)*

To a stirred solution of **1a** (552 mg, 2 mmol) and pyridine (474 mg, 6 mmol) in methylene chloride (5 ml) was added dropwise methanesulfonyl chloride (274 mg, 2.4 mmol) in methylene chloride (2.5 ml) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. Then the solution was washed with brine. The layers were separated. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 15:1) to give 2 (701 mg, 99%). $[\alpha]_D^{20} = +37.0$ (c 0.290, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.37 (m, 5H), 5.15 (qd, J = 6.9, 6.0 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 11.7 Hz, 1H), 3.94–3.99 (m, 1H), 3.88 (dd, J = 10.5, 3.3 Hz, 1H), 3.78 (dd,

J = 10.5, 7.2 Hz, 1H), 3.16 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.52 (d, J = 6.9 Hz); IR (thin film) ν_{max} 3035, 2124, 1498, 1456, 1374, 1184 cm^{-1}; MS (EI) m/z 353 (M^+, <1), 325 (6), 248 (13), 105 (5), 91 (100), 79 (10), 77 (4), 69 (1), 65 (11). Anal. Calcd for $C_{12}H_{14}O_4F_3N_3S$: C, 40.8; H, 4.0; N, 11.9. Found: C, 41.1; H, 3.9; N, 11.9.

4.2. (1R, 2R)-Trifluoro-methanesulfonic acid 2-azido-3-benzyloxy-1-trifluoromethyl-propyl ester (**4a**)

To a stirred solution of **1a** (1.76 g, 6.36 mmol) and pyridine (1.01 g, 12.72 mmol) in methylene chloride (30 ml) at −40 °C was added dropwise trifluoromethanesulfonic anhydride (1.98 g, 7.0 mmol) in methylene chloride (5 ml). The reaction mixture was stirred for 1 h at −40 °C. Then the solution was washed with brine. The layers were separated. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 20:1) to give **4a** (2.44 g, 95%). $[\alpha]_D^{20}$ = +42.6 (c 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.42 (m, 5H), 5.26 (qd, J = 6.3, 5.7 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.00–4.05 (m, 1H), 3.88 (dd, J = 10.5, 3.3 Hz, 1H), 3.78 (dd, J = 10.5, 6.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.39–−73.45 (m, 3F), −73.88 to −73.92 (m, 3F); IR (thin film) ν_{max} 3036, 2127, 1498, 1456, 1427, 1199, 1139 cm^{-1}; MS (EI) m/z 407 (M^+, <1), 378 (100), 302 (100), 148 (41), 105 (30), 91 (100), 79 (27), 77 (42), 69 (97), 65 (99). Anal. Calcd for $C_{12}H_{11}O_4F_3N_3S$: C, 35.4; H, 2.7; N, 10.3. Found: C, 35.3; H, 2.6; N, 10.7.

4.3. (1S, 2S)-Trifluoro-methanesulfonic acid 2-azido-3-benzyloxy-1-trifluoromethyl- propyl ester (**4b**)

This compound was prepared from **1b** in 92% yield by using the same procedure as described for **4a**. $[\alpha]_D^{20}$ = −43.6 (c 1.24, CHCl3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.41 (m, 5H), 5.24 (qd, J = 6.3, 5.7 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 3.99–4.03 (m, 1H), 3.85 (dd, J = 10.5, 3.3 Hz, 1H), 3.75 (dd, J = 10.5, 6.3 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.10 to −73.15 (m, 3F), −73.59 to −73.63 (m, 3F); IR (thin film) ν_{max} 3036, 2127, 1498, 1456, 1427, 1199, 1139 cm^{-1}; MS (EI) m/z 407 (M^+, <1), 378 (67), 302 (28), 148 (7), 105 (4), 91 (100), 79 (2), 77 (3), 69 (10), 65 (10). Anal. Calcd for $C_{12}H_{11}O_4F_3N_3S$: C, 35.4; H, 2.7; N, 10.3. Found: C, 35.3; H, 2.6; N, 10.5.

4.4. (1S, 2R)-Thioacetic acid S-(2-azido-3-benzyloxy-1-trifluoromethyl-propyl) ester (**3a**)

To a stirred solution of thiolacetic acid (0.78 g, 10.25 mmol) in DMF (20 ml) at 0 °C was added anhydrous cesium fluoride (1.56 g, 10.25 mmol). Then a solution of **4a** (1.39 g, 3.42 mmol) in DMF (5 ml) was added and reaction mixture was stirred for 4 h at 0 °C. Then the solution was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 30:1) to give **3a** (1.00 g, 87%). $[\alpha]_D^{20}$ = −17.4 (c 1.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.41 (m, 5H), 4.57 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 11.7 Hz, 1H), 4.49 (qd, J = 9.0, 1.5 Hz, 1H), 4.29 (td, J = 6.9, 1.5 Hz, 1H), 3.60 (dd, J = 9.9, 6.9 Hz, 1H), 3.75 (dd, J = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.67 (d, J = 9.0 Hz); IR (thin film) ν_{max} 2112, 1715, 1498, 1455, 1267, 1176, 1118 cm^{-1}; MS (EI) m/z 305 (M^+-N_2, 2), 304 (5), 105 (4), 91 (100), 77 (3), 69 (<1), 43 (37). HRMS (EI) Calcd for $C_{12}H_{11}O_2F_3N_2S$: 304.05123. Found: 304.05313.

4.5. (1R, 2S)-Thioacetic acid S-(2-azido-3-benzyloxy-1-trifluoromethyl-propyl) ester (**3b**)

This compound was prepared from **4b** in 88% yield by using the same procedure as described for **3a**. $[\alpha]_D^{20}$ = +16.2 (c 1.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.41 (m, 5H), 4.57 (d, J = 11.7 Hz, 1H), 4.51 (d, J = 11.7 Hz, 1H), 4.49 (qd, J = 9.0, 1.5 Hz, 1H), 4.29 (td, J = 6.9, 1.5 Hz, 1H), 3.60 (dd, J = 9.9, 6.9 Hz, 1H), 3.75 (dd, J = 9.9, 6.9 Hz, 1H), 2.42 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.67 (d, J = 9.0 Hz); IR (thin film) ν_{max} 2112, 1708, 1498, 1455, 1267, 1176, 1118 cm^{-1}; MS (EI) m/z 334 (M + 1, <1), 304 (12), 105 (4), 91 (100), 77 (3), 69 (<1), 43 (44). Anal. Calcd for $C_{13}H_{14}O_2F_3N_3S$: C, 46.8; H, 4.2; N, 12.6. Found: C, 46.8; H, 4.3; N, 12.1.

4.6. (1S, 2R)-Thioacetic acid S-(2-azido-3-hydroxy-1-trifluoromethyl-propyl) ester (**5a**)

To a stirred solution of **3a** (839 mg, 2.52 mmol) in anhydrous methylene chloride (50 ml) at −78 °C was added dropwise boron trichloride (5 ml of 1 M solution in methylene chloride, 5 mmol). The reaction mixture was stirred for 2 h at −78 °C. Then methanol (5 ml) was added. The solution was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 5:1) to give **5a** (610 mg, 99%). $[\alpha]_D^{20}$ = −87.3 (c 0.735, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (qd, J = 9.0, 1.8 Hz, 1H), 4.20 (td, J = 7.2, 1.8 Hz, 1H), 3.74 (dd, J = 11.4, 7.2 Hz, 1H), 3.59 (dd, J = 11.4, 7.2 Hz, 1H), 2.47 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.67 (d, J = 9.0 Hz); IR (thin film) υ_{max} 3298, 2926, 2137, 1709, 1273, 1108 cm^{-1}, MS (EI) m/z 244 (M + 1, 2), 200 (2), 174 (7), 69 (2), 43 (100). Anal. Calcd for $C_6H_8O_2F_3N_3S$: C, 29.6; H, 3.3; N, 17.3. Found: C, 29.9; H, 3.1; N, 17.6.

4.7. (1R, 2S)-Thioacetic acid S-(2-azido-3-hydroxy-1-trifluoromethyl-propyl) ester (**5b**)

This compound was prepared **3b** in 100% yield by using the same procedure as described for **5a**. $[\alpha]_D^{20}$ = +86.8 (c

0.685, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (qd, J = 9.0, 1.8 Hz, 1H), 4.20 (td, J = 7.2, 1.8 Hz, 1H), 3.74 (dd, J = 11.4, 7.2 Hz, 1H), 3.59 (dd, J = 11.4 Hz, 7.2 Hz, 1H), 2.47 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −70.67 (d, J = 9.0 Hz); IR (thin film) υ_{max} 3382, 2926, 2137, 1709, 1273, 1108 cm^{-1}, MS (EI) m/z 244 (M + 1, <1), 200 (2), 174 (1), 69 (2), 43 (100). Anal. Calcd for $C_6H_8O_2F_3N_3S$: C, 29.6; H, 3.3; N, 17.3. Found: C, 30.0; H, 3.1; N, 17.5.

4.8. (2R, 3S)-3-Acetylsulfanyl-2-azido-4,4,4-trifluoro-butyric acid (**6a**)

To a mixture of **5a** (0.34 g, 1.4 mmol) in acetone (50 ml) at 0 °C was added Jones reagent (1 M, 10 ml, 10 mmol). The mixture was stirred for 20 min at 0 °C under nitrogen. The reaction was quenched with *iso*-propyl alcohol (5 ml) and then diluted with water (30 ml) and ethyl acetate (30 ml). The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 1:1) to give **6a** (0.36 g, 76%). $[\alpha]_D^{20} = -26.8$ (c 1.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.85(qd, J = 8.4, 2.1 Hz, 1H), 4.80 (d, J = 2.1 Hz, 1H), 2.45 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.96 (d, J = 8.4 Hz); IR (thin film) υ_{max} 3500, 2937, 2127, 1720, 1260, 1118 cm^{-1}, MS (EI) m/z 258 (M + 1, <1), 212 (<1), 69 (3), 43 (100). HRMS (EI) Calcd for $C_5H_5OF_3N_3S$: 212.01055. Found: 212.01231.

4.9. (2S, 3R)-3-Acetylsulfanyl-2-azido-4,4,4-trifluoro-butyric acid (**6b**)

This compound was prepared from **5b** in 81% yield by using the same procedure as described for **6a**. $[\alpha]_D^{20} = +28.2$ (c 1.305, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.85(qd, J = 8.4, 2.1 Hz, 1H), 4.80 (d, J = 2.1 Hz, 1H), 2.45 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.97 (d, J = 8.4 Hz); IR (thin film) υ_{max} 3300, 2937, 2127, 1720, 1260, 1119 cm^{-1}, MS (EI) m/z 258 (M + 1, <1), 212 (<1), 69 (3), 43 (100). HRMS (EI) Calcd for $C_5H_5OF_3N_3S$: 212.01055. Found: 212.01022.

4.10. (2-Azido-4,4,4-trifluoro-2-propylsulfanyl-butoxymethyl)-benzene **8**

This compound was prepared from **4b** in 47% yield by using the same procedure as described for **3a**. Clear oil, ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.43 (m, 5H), 4.66 (d, J = 12.0 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 3.69 (d, J = 9.9 Hz, 1H), 3.64 (d, J = 9.9 Hz, 1H), 2.63–2.84 (m, 4H), 1.58–1.73 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −61.09 (d, J = 10.1 Hz); IR (thin film) υ_{max} 3067, 2967, 2120, 1498, 1456, 1370, 1260, 1139 cm^{-1}; MS (EI) m/z 332 (M + −1, <1), 291 (1), 92 (11), 91 (100), 41 (12). Anal. Calcd for $C_{14}H_{18}OF_3N_3S$: C, 50.4; H, 5.4; N, 12.6. Found: C, 50.7; H, 5.5; N, 12.6.

4.11. (1S, 2R)-Thioacetic acid S-[3-benzyloxy-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-1-trifluoromethyl-propyl] ester (**10a**)

To a stirred solution of **9a** (2.85 g, 7.52 mmol) and pyridine (1.19 g, 15.04 mmol) in methylene chloride (40 ml) at −40 °C was added dropwise trifluoromethanesulfonic anhydride (2.33 g, 8.27 mmol) in methylene chloride (10 ml). The reaction mixture was stirred for 2 h at −40 °C. Then the solution was washed with 2N HCl and brine. The layers were separated. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was used directly without further purification. To a stirred solution of thiolacetic acid (1.72 g, 22.56 mmol) in DMF (40 ml) at 0 °C was added anhydrous cesium fluoride (3.43 g, 22.56 mmol). Then a solution of the crude product in DMF (5 ml) was added and reaction mixture was stirred for 6 h at 0 °C. Then the solution was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 60:1) to give **10a** (3.25 g, 99%). $[\alpha]_D^{20} = -67.8$ (c 0.900, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.91 (m, 2H), 7.74–7.78 (m, 2H), 7.18–7.27 (m, 5H), 5.03–5.11 (m, 1H), 4.93 (qd, J = 9.0, 1.5 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.10 (t, J = 9.0 Hz, 1H), 3.92 (dd, J = 9.0, 6.0 Hz, 1H), 2.37 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.69 (d, J = 9.0 Hz); IR (thin film) υ_{max} 2922, 1781, 1721, 1609, 1497, 1470, 1455, 1389, 1120 cm^{-1}; MS (EI) m/z 438 (M + 1, <1), 437 (M^+, <1), 394 (1), 107 (3), 91 (100) 77 (5), 76 (7), 43 (45). Anal. Calcd for $C_{21}H_{18}O_4F_3NS$: C, 57.7; H, 4.2; N, 3.2. Found: C, 57.6; H, 4.3; N, 3.2.

4.12. (1R, 2S)-Thioacetic acid S-[3-benzyloxy-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-1-trifluoromethyl-propyl] ester (**10b**)

This compound was prepared from **9b** in 98% yield by using the same procedure as described for **10a**. $[\alpha]_D^{20} = +64.1$ (c 1.200, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.91 (m, 2H), 7.73–7.78 (m, 2H), 7.18–7.28 (m, 5H), 5.03–5.11 (m, 1H), 4.91 (qd, J = 9.0, 1.5 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.10 (t, J = 9.0 Hz, 1H), 3.92 (dd, J = 9.0, 6.0 Hz, 1H), 2.36 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.71 (d, J = 9.0 Hz); IR (thin film) υ_{max} 2921, 1781, 1722, 1609, 1498, 1470, 1455, 1374, 1122 cm^{-1}; MS (EI) m/z 437 (M^+, <1), 138 (100), 107 (3), 91 (5), 77 (10), 43 (29). Anal. Calcd for $C_{21}H_{18}O_4F_3NS$: C, 57.7; H, 4.2; N, 3.2. Found: C, 57.3; H, 4.2; N, 3.3.

4.13. (1S, 2R)-Thioacetic acid S-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-hydroxy-1-trifluoromethyl-propyl] ester (**11a**)

To a stirred solution of **10a** (2.99 g, 6.85 mmol) in anhydrous methylene chloride (100 ml) at −78 °C was

added dropwise boron trichloride (13.70 ml of 1 M solution in methylene chloride, 13.70 mmol). The reaction mixture was stirred for 2 h at −78 °C. Then methanol (5 ml) was added. The solution was washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether:ethyl acetate = 4:1) to give **11a** (2.38 g, 99%). $[\alpha]_D^{20} = -63.7$ (c 0.500, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.90 (m, 2H), 7.76–7.80 (m, 2H), 5.05 (qd, J = 8.4, 1.5 Hz, 1H), 4.84–4.91 (m, 1H), 4.19–4.26 (m, 1H), 4.09–4.14 (m, 1H), 2.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.56 (d, J = 8.4 Hz); IR (thin film) υ_{max} 3483, 2928, 1780, 1716, 1614, 1470, 1374, 1126 cm^{-1}; MS (EI) m/z 348 (M + 1, 7), 347 (M^+, 2), 330 (1), 148 (54), 76 (14), 43 (100). Anal. Calcd for $C_{14}H_{12}O_4F_3NS$: C, 48.4; H, 3.5; N, 4.0. Found: C, 49.0; H, 3.6; N, 4.1.

*4.14. (1R, 2S)-Thioacetic acid S-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-hydroxy-1-trifluoromethyl-propyl] ester (**11b**)*

This compound was prepared from **10b** in 99% yield by using the same procedure as described for **11a**. $[\alpha]_D^{20} = +65.0$ (c 0.850, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.89 (m, 2H), 7.76–7.80 (m, 2H), 5.05 (qd, J = 8.4, 1.5 Hz, 1H), 4.84–4.91 (m, 1H), 4.22 (dd, J = 12.0, 7.5 Hz, 1H), 4.11 (dd, J = 12.0, 4.8 Hz, 1H), 2.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.56 (d, J = 8.4 Hz); IR (thin film) υ_{max} 3486, 2950, 1783, 1711, 1611, 1465, 1376, 1132 cm^{-1}; MS (EI) m/z 305 (M-Ac, 1), 148 (33), 76 (17), 45 (100), 43 (84). Anal. Calcd for $C_{14}H_{12}O_4F_3NS$: C, 48.4; H, 3.5; N, 4.0. Found: C, 48.8; H, 3.9; N, 3.7.

*4.15. (2R, 3S)-3-Acetylsulfanyl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4,4,4-trifluoro-butyric acid (**12a**)*

To a mixture of **11a** (0.39 g, 1.1 mmol) in acetone (40 ml) at 0 °C was added Jones reagent (1 M, 9 ml, 9 mmol). The mixture was stirred for 20 min at 0 °C under nitrogen. The reaction was quenched with *iso*-propyl alcohol (4 ml) and then diluted with water (35 ml) and ethyl acetate (35 ml). The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether:-ethyl acetate = 1:1) to give **12a** (345 mg, 87%). $[\alpha]_D^{20} = -54.1$ (c 0.600, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.93 (m, 2H), 7.74–7.82 (m, 2H), 5.69 (d, J = 5.4 Hz, 1H), 5.32 (qd, J = 8.5, 5.4 Hz, 1H), 2.42 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.24 (d, J = 8.5 Hz); IR (thin film) υ_{max} 3519, 2929, 1780, 1725, 1611, 1471, 1386, 1166 cm^{-1}; MS (EI) m/z 362 (M + 1, 3), 361 (M^+, <1), 319 (14), 148 (15), 76 (15), 45 (3), 43 (100). Anal. Calcd for $C_{14}H_{10}O_5F_3NS\cdot(H_2O)_{1/2}$: C, 45.4; H, 3.0; N, 3.8. Found: C, 45.7; H, 3.2; N, 3.7.

*4.16. (2R, 3S)-3-Acetylsulfanyl-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-4,4,4-trifluoro- butyric acid (**12b**)*

This compound was prepared from **11b** in 88% yield by using the same procedure as described for **12a**. $[\alpha]_D^{20} = +56.1$ (c 1.150, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.94 (m, 2H), 7.76–7.82 (m, 2H), 5.70 (d, J = 5.4 Hz, 1H), 5.30 (qd, J = 8.5 Hz, 5.4 Hz, 1H), 2.43 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −69.30 (d, J = 8.5 Hz); IR (thin film) υ_{max} 3522, 2929, 1780, 1724, 1611, 1471, 1386, 1166 cm^{-1}; MS (EI) m/z 319 (20), 148 (23), 76 (25), 45 (6), 43 (100). Anal. Calcd for $C_{14}H_{10}O_5F_3NS\cdot(H_2O)_{1/2}$: C, 45.4; H, 3.0; N, 3.8. Found: C, 45.7; H, 3.1; N, 3.7.

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