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The Interaction of *N*-(*tert*-butylsulfinyl)imine of Trifluoropyruvate with Diazomethane as a Convenient Synthetic Approach to Enantiomeric Trifluoromethylamino Acids

Abstract
The interaction of enantiomerically pure *N*-*tert*-butylsulfinyl imines of trifluoropyruvate with diazomethane has been studied. It has been shown that there is the [3+2]-cycloaddition at the initial step with the formation of diastereomeric trifluoromethyltriazoline carboxylates in the ratio of 5.6:1. Treating the triazoline carboxylates with trifluoroacetic acid yielded optically pure aziridine carboxylates, which were subsequently converted into their corresponding acids. When subjected to hydrochloric acid in an ethereal solution, trifluoromethylaziridines underwent ring-opening and the sulfinyl group removal, producing α-chloromethylamino acids. The study also demonstrates the potential use of these aziridinecarboxylic acids in the peptide synthesis.
***Keywords*:** amino acids; trifluoromethyl; diazomethane; enantiomeric; *tert*-butylsulfinyl; imine

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Взаємодія *N*-(трет-бутилсульфініл)іміну трифторопірувату з діазометаном як зручний синтетичний підхід до енантіомерних трифторометиламінокислот

Анотація
Досліджено взаємодію енантіомерно чистих *N*-трет-бутилсульфініліміні трифторопірувату з діазометаном. З'ясовано, що на першому етапі відбувається [3+2]-циклоприєднання з утворенням діастереомерних трифторометилтриазолінкарбоксилатів у співвідношенні 5.6:1. Енантіомерно чисті триазоліни було виділено в індивідуальному стані методом перекристалізації. Дія трифтороцтової кислоти на триазолінкарбоксилати приводить до утворення оптично чистих азиридинкарбоксилатів, які були перетворені на відповідні кислоти. В ефірному розчині хлоридної кислоти трифторометилазиридини зазнають розкриття циклу, що супроводжується видаленням сульфінільної групи та приводить до утворення α-хлорометиламінокислот. Продемонстровано можливість застосування азиридинкарбонових кислот у пептидному синтезі.
Ключові слова: амінокислоти; трифторометил; діазометан; енантіомерний; трет-бутилсульфініл; імін

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■ Introduction

α-Amino acids are fundamental to life, not only serving as the structural components of proteins, but also as crucial precursors for other biologically important molecules, including hormones, neurotransmitters, and purines. Consequently, numerous methods for the synthesis of both natural and unnatural α-amino acids have been developed. They allow the creation of new drugs, functional materials, and protein analogs for scientific research. The site-selective introduction of fluorine-containing groups into amino acids allows for the targeted modification of their structure, thereby altering specific physicochemical and/or biological properties [1–7]. Therefore, introducing fluorine into an amino acid is an effective strategy for protecting peptide bonds from enzymatic cleavage, which significantly increases the stability of peptides and proteins in biological systems. Trifluoropyruvate imines contain an oxidized trifluoroalanine fragment, which allows for their reductive functionalization at the azomethine bond. This provides an efficient route to acyclic and heterocyclic derivatives of trifluoromethyl substituted amino acids (CF_3-α-AAs) [8–12].

A prime example of heterocyclization of trifluoropyruvate imines **I** is their interaction with diazomethane, which proceeds *via* the [3+2]-cycloaddition scheme and leads to triazolines **II**, which further transformation provided the first known examples of water-soluble 2-(trifluoromethyl)aziridine-2-carboxylic acids **III** [13–15] (**Figure 1**). This transformation is important since triazoline and aziridine rings can be considered as "built-in" heterocyclic prodrugs due to their chemical reactivity and propensity for ring opening [16].

At the same time, stereochemical aspects are an integral part of the chemistry of α-amino acids since their optical antipodes interact differently with the active sites of receptors, leading to different, and sometimes even opposite, biological activities towards target molecules. Therefore, the synthesis of compounds containing a chiral stereocenter in optically pure form remains an important task. So, imines **I** with a stereo-directing *N*-phenylethyl group were among those investigated in their reaction with diazomethane (**Figure 1**). They were shown to form a mixture of two diastereomeric triazolines **II** in the ratio of 4.5:1, which could be separated chromatographically [15].

Recently, a preparative method for the synthesis of *N*-*tert*-butylsulfinyl imines of trifluoropyruvate **1** has been developed, and it has been shown that this type of imines are convenient substrates for the preparation of enantiomerically pure CF_3-α-AAs derivatives [10]. However, the reaction between *N*-sulfinyl imine **1** and diazomethane has not been previously studied. At the same time, they have significant advantages over *N*-phenylethyl analogs [15], namely a relatively higher reactivity towards nucleophilic agents and the possibility of removing the sulfinyl group from the nitrogen atom after carrying out the necessary transformations. The latter factor is particularly important as it will allow the production of compounds with a *free* amino group, which will significantly expand the scope of the products in synthetic practice.

This work reports the results of the study on the interaction between *N*-*tert*-butylsulfinyl imines of trifluoropyruvate **1** and diazomethane. The subsequent transformations of the resulting products are explored as a pathway to enantiomerically pure CF_3-α-AA derivatives.

■ Results and discussion

It has been found that (S_S)-*N*-*tert*-butylsulfinyl imine of trifluoropyruvate (S_S)-**1** reacts with diazomethane similarly to other fluorinated imines, giving at the first stage the products of the [3+2]-cycloaddition – triazolines (S,S_S)-**2**/(R,S_S)-**2** isolated as a mixture of diastereomers in the ratio of 5.6:1 with the total yield of 99% (**Scheme 1**). Note that the cycloaddition for *N*-sulfinyl imine **1** occurs much faster, completing in minutes, compared to *N*-phenylethyl imine **II** under similar conditions, which takes five days [15]. The reaction progress is easily monitored by ^{19}F NMR spectroscopy, the $sp^2 \rightarrow sp^3$ rehybridization of the imino carbon atom causes a shift in the trifluoromethyl group signal from -71 ppm to -73.5 ppm (minor diastereomer) and -74.3 ppm (major diastereomer). While the diastereoselectivity of the

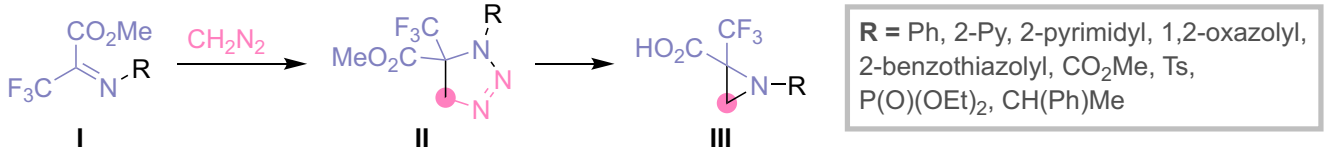

Figure 1. The interaction of trifluoropyruvate imines **I** with diazomethane

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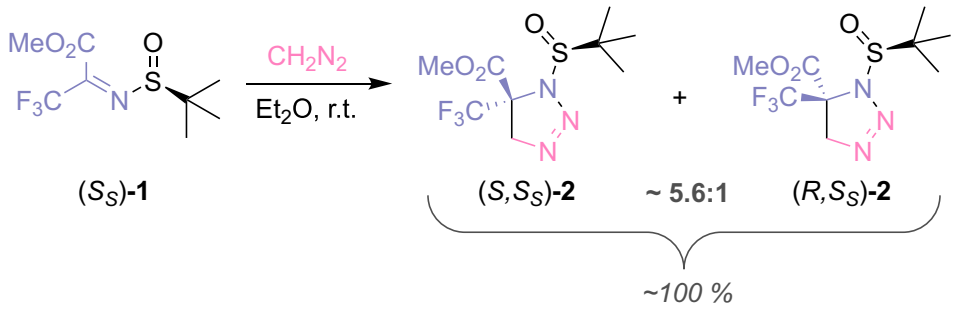


Scheme 1. The cycloaddition of diazomethane to the enantiomeric trifluoropyruvate imine (S_S)-**1**

process typically depends on temperature, the ratio of diastereomers (S,S_S)-**2**/(R,S_S)-**2** in this reaction remains unchanged, even when the temperature is lowered to -78°C.

Triazolines **2** are stable compounds that can be stored long-term without losing their chemical or optical purity. The major diastereomer (S,S_S)-**2** was easily isolated in the yield of 40% in an optically pure form by the trituration with the MTBE/hexane mixture (1:1).

The X-ray diffraction analysis of the single crystal confirmed the (*S*)-configuration of the newly created stereocenter in the major triazoline (S,S_S)-**2**, which was formed from the (S_S)-imine **1** (**Figure 2**). The partially unsaturated nature of the triazole ring caused a slightly pyramidal configuration of the N1 atom (the sum of bond angles centered at this atom is 352.1°). The *tert*-butylsulfinyl substituent was found in the *cis*-conformation to the carboxylate group (the C4–C2–N1–S1 torsion angle is -43.3(8)°) and is turned in such a way that the S1=O1 bond is orthogonal to the C2–N1 endocyclic bond (the C2–N1–S1–O1 torsion angle is 91.6(6)°). The planar carboxylate group is rotated in relation to the triazole ring by -67.9(9)° (the N1–C2–C4–O2 torsion angle).

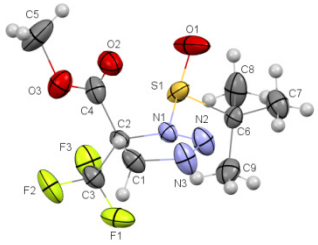
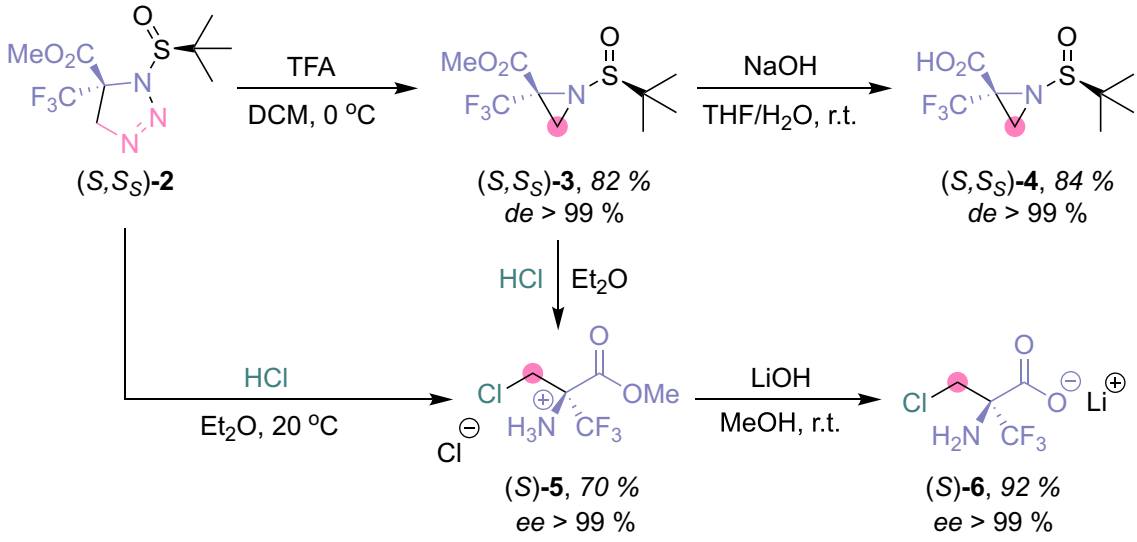


Figure 2. The molecular structure of triazolinecarboxylate (S,S_S)-**2**. Thermal ellipsoids of non-hydrogen atoms are shown at 50 % probability level

Using reaction conditions identical to **Scheme 1**, we obtained diastereomers (R,R_S)-**2** and (S,R_S)-**2** (5.6:1) by reacting diazomethane with the imine of trifluoropyruvate **1** in the (R_S)-configuration.

The acid catalysis with trifluoroacetic acid (0.1 equiv., 0 °C, DCM) caused triazoline (S,S_S)-**2** to undergo the denitrogenation, leading to the quantitative formation of aziridine carboxylate (S,S_S)-**3**, isolated in the yield of 82% (**Scheme 2**). It is worth noting that the ethyl ester of aziridinecarboxylic acid **3** was previously prepared from the corresponding trifluoropyruvate imine using the aza-Corey-Chaykovsky reaction [17]. In contrast to our findings, this approach produced



Scheme 2. The synthesis of aziridine carboxylic acid (S,S_S)-**4** and polyfluorinated chloroethylamino acid derivatives (*S*)-**5**, (*S*)-**6**

the compound in only milligram quantities and with a modest 24% yield.

The sequential treatment of aziridine carboxylate (S,S_S)-**3** with NaOH and diluted acid converted it to aziridine carboxylic acid (S,S_S)-**4** with the yield of 84%. Mild conditions for converting triazoline **2** → aziridine carboxylate **3** → aziridine carboxylic acid **4** allow to avoid opening of the three-membered ring and preserve the protecting sulfinyl group on the nitrogen atom. Additionally, NMR data shows the presence of only one stereoisomer of the aziridines **3**, **4** formed, indicating that the optical purity of the reaction products is preserved. Since the chiral carbon atom is not involved in the **2** → **3** transformation, the stereocenter's configuration in aziridines (S,S_S)-**3**, **4** is maintained.

In the ethereal solution of hydrochloric acid at room temperature, aziridine (S,S_S)-**3** undergoes ring opening, accompanied by removal of the sulfinyl group. As a result, a chloromethyl derivative of trifluoroalanine (*S*)-**5** is formed, isolated in the optically pure form as hydrochloride. Compound (*S*)-**5** can be also obtained directly from triazoline (S,S_S)-**3** by the action of hydrochloric acid on the latter.

It should be noted that the hydrolysis of esters containing several electron-withdrawing substituents near the quaternary carbon atom is often accompanied by the decarboxylation. This process can be either secondary or dominant, depending on the environment around the carbon atom. The decarboxylation can be avoided by obtaining amino acid (*S*)-**6** as a water-soluble lithium salt.

The trifluoromethyl-substituted aziridine-2-carboxylic acid (S,S_S)-**4** (CF_3-Azy) synthesized can be used in the peptide synthesis primarily as a unique electrophilic building block for the late-stage, site-selective chemical modification of peptides. Its highly strained three-membered aziridine ring provides an active anchor for the attachment of various complex molecules, while the trifluoromethyl group can be served as a specific ^{19}F NMR label. The possibility of their use in the peptide synthesis was demonstrated in the **Scheme 3**. For this purpose, compound (S,S_S)-**4** was converted *in situ* to the corresponding anhydride using oxalyl chloride, and the resulting intermediate was subsequently reacted with the (*R*)-phenylglycine methyl ester to give dipeptide (R,S,S_S)-**7**. Notably, the aziridine ring remains intact under these conditions, but undergoes opening with the removal of the sulfinyl group upon treatment with hydrochloric acid in dioxane, forming dipeptide (*R,S*)-**8**, which contains a free amino group and can thus be involved in the further peptide chain extension.

Conclusions

The reaction of *N-tert*-butylsulfinyl imines of trifluoropyruvate and diazomethane leads to the quantitative formation of [3+2]-cycloaddition products, triazolines, in the ratio of 5.6:1. Upon the acid catalysis, the major (S,S_S)-triazoline is converted to enantiomeric aziridine carboxylate (S,S_S)-**3**, which after the reaction with NaOH gives optically pure (S,S_S)- aziridine carboxylic acid. The latter is involved to the peptide synthesis.

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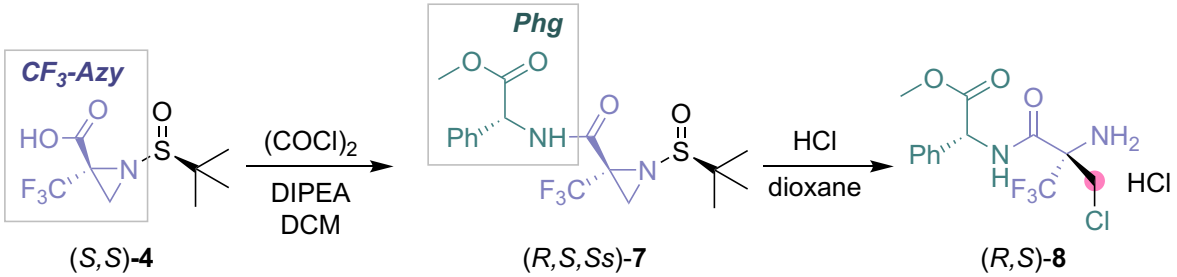
Experimental part

NMR spectra were recorded on a Bruker Avance DRX 600 spectrometer with operating frequencies of 600 MHz (^1H), 150.8 MHz (^{13}C), and 470 MHz (^{19}F); a Bruker Avance DRX 500 spectrometer with operating frequencies of 499.9 MHz (^1H), 125.6 MHz (^{13}C), and 376.5 MHz (^{19}F); a Varian Unity Plus 400 instrument with operating frequencies of 400 MHz (^1H), 100 MHz (^{13}C) and 376.5 MHz (^{19}F); a Mercury Varian Unity Plus 300



Scheme 3. An example of the use of aziridine carboxylic acid (S,S_S)-**4** in the peptide synthesis

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instrument with operating frequencies of 300 MHz (^{1}H) and 76 MHz (^{13}C); a Mercury VX 200 Varian instrument with operating frequency of 188 MHz (^{19}F). Chemical shifts were reported relative to the internal TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) standards. The optical rotation was measured on an Anton Paar MCP 300 polarimeter (the sample cell path length – 100 mm, the wavelength – 589 nm). The solvents were dried according to the standard procedures. The starting materials were purchased from Enamine Ltd. Melting points were uncorrected. TLC was performed using Kieselgel Merck 60 silica gel (400–630 mesh) as the stationary phase. The elemental analysis was performed in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

Methyl *(S)*-1-((*S*)-tert-butylsulfinyl)-5-(trifluoromethyl)-4,5-dihydro-1H-1,2,3-triazole-5-carboxylate ((S,S_S)-**2**)

A cooled solution of diazomethane (41.8 mmol) in diethyl ether (250 mL) was added dropwise to the solution of (*S*)-*N-tert*-butylsulfinyl imine of trifluoropyruvate (*S*)-**1** (5.4 g, 20.9 mmol) in diethyl ether (50 mL) at room temperature. The reaction mixture was kept at r.t. for 2 h. ^{19}F NMR spectra showed the formation of the diastereomeric mixture of triazolinecarboxylates (S,S_S)-**2**/(R,S_S)-**2** (5.6:1). The solvent was evaporated to give product (S,S_S)-**2**/(R,S_S)-**2** (6.2 g, ~100%), which was triturated with the mixture of MTBE/hexane (1:1), a white solid was filtrated to obtain the major diastereomer (S,S_S)-**2**.

A white solid. Yield – 2.52 g (40%). M. p. = 90–100°C (dec.). $[\alpha]_D^{20}$ = +533.59 (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_9H_{14}F_3N_3O_3S$, %: C 35.87, H 4.84, N 13.94. Found, %: C 36.05, H 4.79, N 14.10. ^{1}H NMR (301.5 MHz, $CDCl_3$), δ, ppm: 1.47 (9H, s, *t*Bu), 3.93 (3H, s, CH_3O), 4.80 (1H, d, $^2J_{HH}$ = 18 Hz, CH_2), 5.13 (1H, d, $^2J_{HH}$ = 18 Hz, CH_2). ^{13}C NMR (125.6 MHz, $CDCl_3$), δ, ppm: 23.49 ($C(\underline{C}H_3)_3$), 53.94 (CH_2), 61.76 ($\underline{C}(CH_3)_3$), 67.00 (q, $^2J_{CF}$ = 30 Hz, $\underline{C}CF_3$), 75.58 (CH_3O), 122.2 (q, $^1J_{CF}$ = 282 Hz, CF_3), 163.7 (C=O). ^{19}F NMR (188.1 MHz, $CDCl_3$), δ, ppm: -72.9.

The X-ray experimental part

The colorless crystals of compound (S,S_S)-**2** ($C_9H_{14}N_3O_3S$) are trigonal. At 173 K $a = b$ = 10.1183(3), c = 11.3463(4) Å, V = 1006.00(7) Å^3, M_r = 301.29, Z = 3, space group $P3_2$, d_{calc}= 1.492 g/cm^3, m(MoK_a) = 0.285 mm^{-1}, F(000) = 468. Intensities of 10656 reflections (2351 independent, R_{int}=0.0360) were measured on a Bruker APEX II diffractometer (graphite monochromated MoK_a radiation, a CCD detector, φ- and ω-scaning, $2\Theta_{max}$ = 50°). The structure was solved by the direct method using the OLEX2 [18] package with SHELXT [19] and SHELXL modules [20]. Positions of the hydrogen atoms were located from electron density difference maps and refined using the "riding" model with U_{iso} = nU_{eq} (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in the anisotropic approximation for non-hydrogen atoms using 2351 reflections was converged to wR_2 = 0.1459 (R_1 = 0.0580 for 2099 reflections with $F > 4\sigma(F)$, S = 1.046). The final atomic coordinates, and crystallographic data for molecule (S,S_S)-**2** were deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2497351).

Methyl (*S*)-1-((S)-tert-butylsulfinyl)-2-(trifluoromethyl)aziridine-2-carboxylate ((S,S_S)-**3**)

Trifluoroacetic acid (0.094 g, 0.063 mL, 0.83 mmol) was added to the solution of triazolinecarboxylate (S,S_S)-**2** (2.5 g, 8.3 mmol) in DCM (20 mL) at 0 °C. The reaction mixture was kept at r.t. for 4 h, washed with the saturated aqueous solution of $NaHCO_3$, the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a pure aziridine carboxylate (S,S_S)-**3**.

A white solid. Yield – 1.87 g (82%). M. p. = 65–67 °C. $[\alpha]_D^{20}$= -238.62 (*c* 1, $CHCl_3$). Anal. Calcd for $C_9H_{14}F_3NO_3S$, %: C 39.55, H 5.16, N 5.12. Found, %: C 39.37, H 5.20, N 4.88. ^{1}H NMR (301.5 MHz, $CDCl_3$), δ, ppm: 1.24 (9H, s, *t*Bu), 2.44 (1H, s, CH_2), 3.14 (1H, s, CH_2), 3.85 (3H, s, CH_3O). ^{13}C NMR (150.8 MHz, $CDCl_3$), δ, ppm: 22.17 ($C(\underline{C}H_3)_3$), 26.93 (CH_2), 44.0 (q, $^2J_{CF}$ = 38 Hz, $\underline{C}CF_3$), 53.69 (CH_3O), 58.16 ($C(\underline{C}H_3)_3$), 121.6 (q, $^1J_{CF}$ = 276 Hz, $\underline{C}F_3$), 162.8 (C=O). ^{19}F NMR (188.1 MHz, $CDCl_3$), δ, ppm: -71.0.

(*S*)-1-((*S*)-tert-butylsulfinyl)-2-(trifluoromethyl)aziridine-2-carboxylic acid ((S,S_S)-**4**)

Aziridine carboxylate (S,S_S)-**3** (1.8 g, 6.6 mmol) was added to a stirred solution of NaOH (0.52 g, 13 mmol) in THF (10 mL) and water (10 mL). The resulting reaction mixture was left at r.t. overnight. The organic solvent was removed in *vacuo*, the resulting water solution was washed with dichloromethane (5 mL) and acidified to pH 2-3 with the saturated sodium hydrogen sulfate solution. The solution was extracted with DCM (3×15 mL), dried over Na_2SO_4, the solvent was evaporated under reduced pressure to give a pure aziridine carboxylic acid (S,S_S)-**4**.

A white solid. Yield – 1.5 g (84%). M. p. = 115–120 °C (dec.). $[\alpha]_D^{20}$ = -192.51 (*c* 1, $CHCl_3$). Anal. Calcd. for $C_8H_{12}F_3NO_3S$, %: C 37.06, H 4.66, N 5.40. Found, %: C 37.38, H 4.59, N 5.49. ^{1}H NMR (301.5 MHz, $CDCl_3$), *δ*, ppm: 1.30 (9H, s, *t*Bu), 2.48 (1H, s, CH_2), 3.22 (1H, s, CH_2), 8.79 (1H, s, COOH). ^{13}C NMR (75.8 MHz, $CDCl_3$), *δ*, ppm: 22.33 ($C(\underline{C}H_3)_3$), 27.75 (CH_2), 44.39 (q, $^2J_{CF}$ = 37 Hz, $\underline{C}CF_3$), 58.94 ($C(\underline{C}H_3)_3$), 121.69 (q, $^1J_{CF}$ = 277 Hz, $\underline{C}F_3$), 162.84 (C=O). ^{19}F NMR (188.1 MHz, $CDCl_3$), *δ*, ppm: -72.0.

Methyl (*S*)-2-amino-2-(chloromethyl)-3,3,3-trifluoropropanoate hydrochloride ((*S*)-**5**)

A dioxane solution of hydrogen chloride (10 mL) was added to the stirred solution of (*S*,S_S)-**3** (1.86 g, 6.8 mmol) in MeOH (100 mL) at 0 °C. The reaction mixture was allowed to warm up to r.t. and was kept for 6 h. The solvent was removed under reduced pressure; the residue was triturated with hexane and filtered to give compound (*S*)-**5**.

A white solid. Yield – 1.15 g (70%). M. p. = 154–156 °C. $[\alpha]_D^{20}$ = -0.37 (*c* 0.5, MeOH). Anal. Calcd for $C_5H_8Cl_2F_3NO_2$, %: C 24.81, H 3.33, Cl 29.29, N 5.78. Found, %: C 24.72, H 3.47, Cl 29.77, N 5.67. ^{1}H NMR (301.5 MHz, DMSO-d_6), *δ*, ppm: 3.85 (3H, s, CH_3O), 4.0 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH_2), 4.2 (1H, d, $^2J_{HH}$ = 12.1 Hz, CH_2), 5.87 (2H, s, NH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6), *δ*, ppm: 42.73 ($(\underline{C}H)_2$), 55.26 (CH_3O), 65.62 (q, $^2J_{CF}$=28 Hz, $\underline{C}CF_3$), 122.68 (q, $^1J_{CF}$ = 286 Hz, $\underline{C}F_3$), 164.01 (C=O). ^{19}F NMR (188.1 MHz, DMSO-d_6), *δ*, ppm -72.4.

Lithium (*S*)-2-amino-2-(chloromethyl)-3,3,3-trifluoropropanoate ((*S*)-**6**)

Lithium hydroxide (0.04 g, 1.6 mmol) was added to the solution of compound (*S*)-**5** (0.2 g, 0.8 mmol) in methanol (10 mL). The mixture was stirred at r.t. for 16 h. The precipitate formed was filtered off, the solution was evaporated under reduced pressure to obtain a white crystalline residue (S)-**6**.

White crystals. Yield – 0.15 g (92%). M. p. = 160 °C (dec.). Anal. Calcd for $C_4H_4ClF_3LiNO_2$, %: C 24.32, H 2.04, Cl 17.95, N 7.09. Found, %: C 24.06, H 2.23, Cl 18.33, N 6.78. ^{1}H NMR (301.5 MHz, DMSO-d_6), *δ*, ppm: 4.11–4.24 (2H, m, CH_2), 5.12 (2H, s, NH_2). ^{13}C NMR (100.6 MHz, DMSO-d_6), *δ*, ppm: 44.56 (CH_2Cl), 66.46 (q, $^2J_{CF}$ = 30 Hz, $\underline{C}CF_3$), 124.83 (q, $^1J_{CF}$ = 280 Hz, $\underline{C}F_3$), 165.83 (C=O). ^{19}F NMR (188.1 MHz, DMSO-d_6), *δ*, ppm: -69.84.

Methyl (*R*)-2-((*S*)-1-((*S*)-tert-butylsulfinyl)-2-(trifluoromethyl)aziridine-2-carboxamido)-2-phenylacetate ((*R*,*S*,S_S)-**7**)

Oxalyl chloride (0.42 g, 3.2 mmol) was added to the stirring solution of aziridine carboxylic acid (*S*,S_S)-**4** (0.28 g, 1.08 mmol) and DIPEA (0.7 g, 5.4 mmol) in DCM (5 mL) at 0 °C. The reaction mixture was allowed to warm up to r.t. and stirred for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in DCM (5 mL) and added dropwise to the stirring mixture of (*R*)-phenylglycine methylester hydrochloride (0.217 g, 1.08 mmol) and DIPEA (0.42 g, 3.2 mmol) in DCM (5 mL) at 0 °C. The reaction mixture was allowed to warm up to room temperature and was stirred for 24 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc, 1:1, Rf = 0.6) to give a compound (*R*,*S*,S_S)-**7**.

A white solid. Yield – 135 mg (30%). M. p. = 138–140 °C. $[\alpha]_D^{20}$ = -292.3 (*c* 0.25, DCM). Anal. Calcd for $C_{17}H_{21}F_3N_2O_4S$, %: C 50.24, H 5.21, N 6.89. Found, %: C 50.32, H 5.17, N 6.83. ^{1}H NMR (301.5 MHz, $CDCl_3$), *δ*, ppm: 1.23 (9H, s, *t*Bu), 2.40 (1H, s, CH_2), 3.12 (1H, s, CH_2), 3.72 (3H, s, CH_3O), 5.55 (1H, d, $^2J_{HH}$ = 6.8 Hz, CH), 7.29–7.41 (6H, m, Ph+NH). ^{13}C NMR (150.8 MHz, $CDCl_3$), *δ*, ppm: 22.27 ($C(\underline{C}H_3)_3$), 30.48 (CH_2), 44.55 (q, $^2J_{CF}$ = 30 Hz, $\underline{C}CF_3$), 52.87 (CH_3O), 56.10 (CHPh) 59.38 ($\underline{C}(CH_3)_3$), 121.72 (q, $^1J_{CF}$ = 281 Hz, CF_3), 127.53 (C_{Ar}), 128.56 (C_{Ar}), 128.85 (C_{Ar}), 135.87 (C_{Ar}), 163.81 ((C=O)NH), 171.64 (COOMe). ^{19}F NMR (188.1 MHz, $CDCl_3$), *δ*, ppm: -71.5 ppm.

Methyl (*R*)-2-((*S*)-2-amino-2-(chloromethyl)-3,3,3-trifluoropropanamido)-2-phenylacetate hydrochloride ((*R*,*S*)-**8**)

A dioxane solution of hydrogen chloride (2 mL) was added to the dipeptide (*R*,*S*,S_S)-**7** (85 mg, 0.21 mmol) in dioxane (2 mL) at 0 °C. The reaction mixture was allowed to warm up to r.t. and kept for 2 h. The solvent was removed under reduced pressure. The residue was triturated with hexane and filtered to give compound (*R*,*S*)-**8**.

A white solid. Yield – 60 mg (85%). M. p. = 160 °C. Anal. Calcd for $C_{13}H_{15}Cl_2F_3N_2O_3$, %: C 41.61, H 4.02, Cl 18.90, N 7.46. Found, %: C 41.45, H 4.15, Cl 18.72, N 7.59. ^{1}H NMR (301.5 MHz, DMSO-d_6), *δ*, ppm: 3.91 (1H, d, $^2J_{HH}$ = 11.8 Hz, CH_2), 4.20 (1H, d, $^2J_{HH}$ = 11.8 Hz, CH_2), 5.48 (1H, d, $^2J_{HH}$ = 6.7 Hz, CH), 7.29–7.46 (5H, m, Ph), 8.87 (2H, br s, NH_2). ^{13}C NMR (150.8 MHz, DMSO-d_6), *δ*, ppm: 47.48 (CH_2), 52.81 (CH_3O), 56.10 (CHPh), 68.43 (q, $^2J_{CF}$ = 32 Hz, $\underline{C}CF_3$), 123.72 (q, $^1J_{CF}$ = 279 Hz, $\underline{C}F_3$), 128.53 (C_{Ar}), 129.56 (C_{Ar}), 129.85 (C_{Ar}), 136.38 (C_{Ar}), 167.45 ((C=O)NH), 171.45 (COOMe). ^{19}F NMR (188.1 MHz, DMSO-d_6), *δ*, ppm: -73.0.

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