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Concise synthesis of enantiopure (*S*)- and (*R*)-α-trifluoromethyl aspartic acid and α-trifluoromethyl serine from chiral trifluoromethyl oxazolidines (Fox) via a Strecker-type reaction

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ABSTRACT

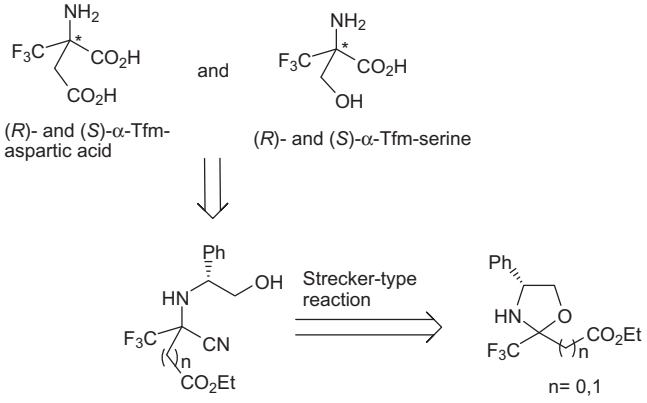
A concise synthesis of enantiopure (*S*)- and (*R*)-α-Tfm-aspartic acid and α-Tfm-serine is reported. The key step involves a Strecker-type reaction on chiral CF_3-oxazolidines (Fox) derived from ethyl 4,4,4-trifluoroacetoacetate (ETFAA) or ethyl trifluoropyruvate.

1. Introduction

α-Trifluoromethyl α-amino acids have attracted considerable interest as natural α-amino acids analogues, owing to the unique properties imparted by the Tfm group, such as high electronegativity, electron density, steric hindrance, and a hydrophobic character.[1] Thus, the presence of the Tfm group produces significant changes in the physical, chemical, and biological properties of the molecules that render α-trifluoromethyl α-amino acids as very attractive for the design of biologically active molecules, particularly peptides.[2] However, despite their promising potency, the preparation of α-trifluoromethyl α-amino acids in enantiopure form involving convenient and scalable experimental procedures remains a challenge and thus, limits systematic investigation of their biomedicinal and structural features.[3]

In previous contributions from our group, we have already reported several approaches for the stereoselective syntheses of various linear and cyclic α-trifluoromethyl α-amino acids starting from chiral CF_3-oxazolidines (Fox) or imines derived from ethyl trifluoropyruvate, trifluoromethyl ketones or fluoral.[4] In parallel, we have also developed new methodologies allowing their incorporation into peptides.[5]

As an extension of our investigations, we are now focusing our attention on the stereoselective synthesis of various side chain functionalized α-trifluoromethyl α-amino acids such as α-Tfm-aspartic acid and α-Tfm-serine. Despite their potential interest, there have been very few reported procedures for the stereoselective synthesis of these amino acids in enantiopure form. Although several syntheses of racemic α-Tfm-aspartic acid and derivatives are reported in the literature,[6] to the best of our knowledge the only one preparation in the asymmetric series was reported by Zanda et al.[7] The synthesis of both enantiomers of α-Tfm-serine has also been reported.[8] These two stereoselective methodologies are based on the use of chiral sulfinimines and sulfoxides. In order to provide a convenient and straightforward access to both (*S*)- and (*R*)-α-trifluoromethyl aspartic acid and α-trifluoromethyl serine, we herein report another strategy based on highly functionalized fluorinated oxazolidines (Fox). This approach involves the commonly used (*R*)-phenylglycinol chiral inducer and the commercially available fluorinated building blocks ethyl 4,4,4-trifluoroacetoacetate (ETFAA) and ethyl trifluoropyruvate as starting materials. We have designed a straightforward approach that involves Strecker-type reactions in order to introduce cyano groups as precursors of carboxylic acid groups to synthesize the target amino acids (Scheme 1).



Scheme 1. The strategy.

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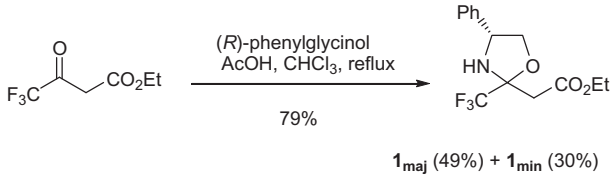
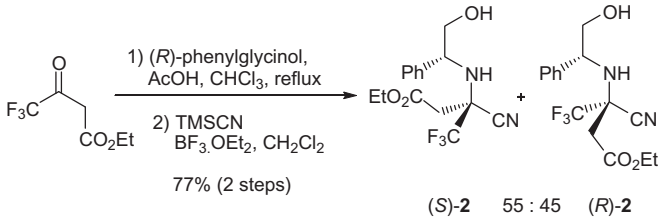
2. Results and discussion

The synthesis of the ethyl trifluoroacetoacetate (ETFAA) -based oxazolidine **1** (Scheme 2) was not trivial because of the presence of acidic protons at the α-position of the ester function. The acid catalyzed condensation of ETFAA with (*R*)-phenylglycinol gave the corresponding oxazolidines **1** as well as the formation of 10–20% of an enamine side product.[9] This enamine is in thermodynamic equilibrium with the oxazolidine **1** under acidic conditions. During the course of our work, Saigo et al.[9] reported the selective formation of oxazolidines **1** versus the enamine using 3 equiv of glacial acetic acid. Following their procedure, the oxazolidines **1** were obtained in 79% yield as two isolated diastereomers (Scheme 2).[10]



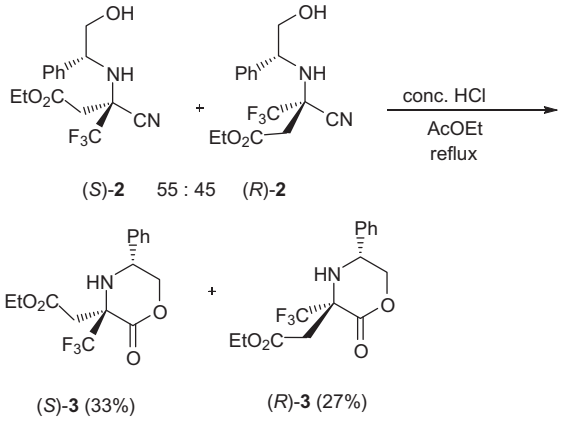
Scheme 2. Synthesis of ethyl trifluoroacetoacetate-based oxazolidine **1**.

As we have already mentioned in previous reports,[4a,b,5] the isolation of diastereomerically pure oxazolidines is not necessary because the introduction of the cyano group through the Strecker-type reaction involves the same iminium intermediate from both oxazolidines. Therefore, the Strecker-type reaction was performed from the crude diastereomeric mixture of oxazolidines **1** obtained from ETFAA and (*R*)-phenylglycinol. This transformation was achieved according to our previously described conditions using TMSCN under $BF_3{\cdot}OEt_2$ activation.[4a,b,5] The two aminonitriles (*S*)-**2** and (*R*)-**2** were obtained on a 5 g scale in good yield (77% from ETFAA) as an inseparable 55:45 diastereomeric mixture (Scheme 3). This very low diastereoselectivity can be due to the addition of TMSCN to a mixture of *E*- and *Z*-iminium or to an enamine intermediate.



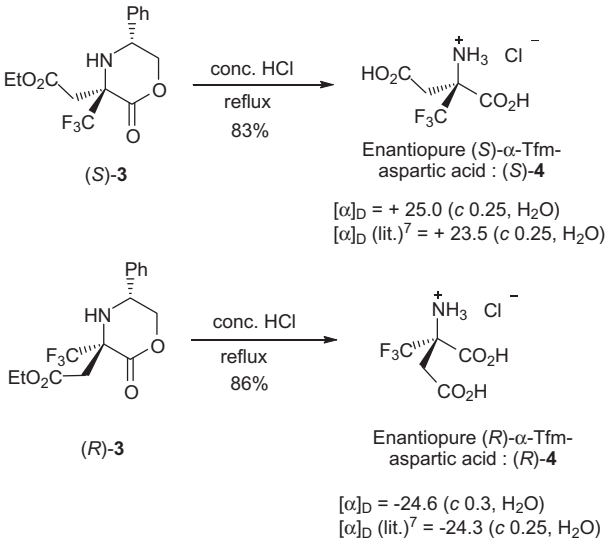
Scheme 3. Synthesis of amino nitriles **2**.

The next steps for the synthesis of enantiopure α-Tfm-aspartic acid required the efficient separation of the two diastereoisomers and the hydrolysis of the cyano group into a carboxylic acid group. We envisioned that these two operations could be achieved according to a previously described strategy relying on the formation of intermediate morpholinones.[4c,e] Several acidic conditions were tested resulting in the formation of six and seven membered rings mixtures. The use of concentrated HCl solution in AcOEt[11] was the best condition found for the selective formation of the morpholinones (*S*)-**3** and (*R*)-**3** (Scheme 4). Due to the cyclic structure of the morpholinones, their separation was possible after silica gel chromatography to give (*S*)-**3** and (*R*)-**3** in 33% and 27% isolated yields, respectively (Scheme 4).



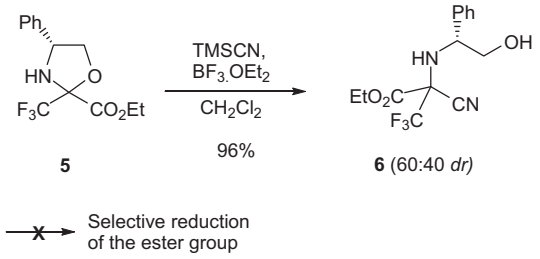
Scheme 4. Syntheses of morpholinones **3**.

Starting from the pure isolated morpholinone (*S*)-**3** and (*R*)-**3,** the enantiopure (*S*)- and (*R*)-α-trifluoromethyl aspartic acid hydrochlorides (*S*)-**4** and (*R*)-**4**[12] were very conveniently obtained in 83% and 86% yield, respectively, after acidic treatment (Scheme 5). The hydrolysis of the two ester functions and the removal of the phenylethanol moiety occurred at the same time by treatment with concentrated HCl at reflux.



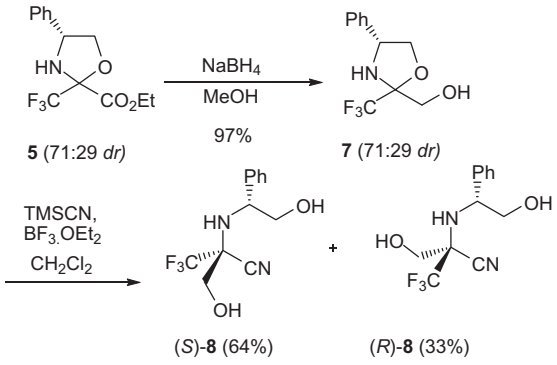
Scheme 5. Synthesis of both enantiomers of the α-Tfm-aspartic acid **4**.

The synthesis of both enantiomers of α-Tfm-serine was then anticipated through the same three step strategy involving a Strecker-type reaction on a trifluoropyruvate-based oxazolidine followed by a selective ester reduction and the simultaneous acidic hydrolysis of the nitrile and removal of the phenylethanol side chain. The $BF_3{\cdot}Et_2O$ promoted Strecker-type reaction performed on the chiral ethyl trifluoropyruvate-based CF_3-oxazolidine **5** (7.31 g scale)[13] gave the corresponding *gem*-cyanoester **6** in high yield (96%) with moderate diastereoselectivity[14] (Scheme 6). At this stage, all attempts at the chemoselective reduction of the ester group of the *gem*-cyanoester **6** into a hydroxyl group leading to an α-Tfm-serine precursor were unsuccessful, despite that such reductions being reported in the literature in the non-fluorinated series (Scheme 6).[15]



Scheme 6. Synthesis of α-Tfm-*gem*-cyanoester **6**.

We next decided to reverse the order of the reactions and reduce the ester group of the oxazolidine **5** before performing the Strecker-type reaction. We recently reported that the use of $LiAlH_4$ as a reducing agent to achieve the reduction of the ester group of **5** was accompanied with the ring opening of the oxazolidine.[16] Due to the enhanced electrophilicity of the ester moiety due to the electron withdrawing effect of the trifluoromethyl group, we hypothesized that the use of a mild reducing reagent should be sufficient enough to carry out the chemoselective reduction of the ester group and avoid the side ring opening reaction. Indeed, the ester group of the oxazolidine **5** (71:29 dr) was chemoselectively reduced with $NaBH_4$ to afford the expected 2-hydroxymethyl oxazolidine **7** (71:29 dr) in 90% yield (Scheme 7). These oxazolidines could be separated by silica gel chromatography but as previously demonstrated this operation is not required for the next step. The Stecker-type reaction was then performed on the diastereomeric mixture of **7** under the usual conditions. At this point, the two amino nitriles diastereomers **8** were very conveniently separated by silica gel chromatography[17] to give (*S*)-**8** and (*R*)-**8** in 64% and 33% isolated yield, respectively (Scheme 7).

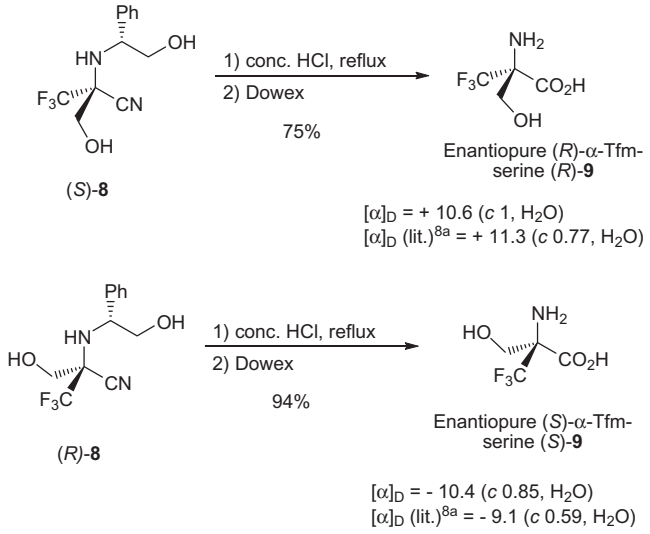


Scheme 7. Chemoselective reduction of oxazolidine **5** and Strecker-type reaction.

The enantiopure (*R*)-α-Tfm-serine (*R*)-**9** was obtained in 75% yield after concentrated HCl treatment of the diastereomerically pure (*S*)-**8** aminonitrile and Dowex purification (Scheme 8). The clean removal of the phenylethanol side chain and the hydrolysis of the nitrile group occurred at the same time. Following the same procedure, enantiopure (*S*)-α-Tfm-serine (*S*)-**9** was obtained in 94% yield from the diastereomerically pure (*R*)-**8**. The specific rotations of (*R*)-**9** and (*S*)-**9** were consistent with those reported in the literature.[8a]

3. Conclusion

In conclusion we have demonstrated that the Strecker-type reaction from chiral fluorinated oxazolidines (Fox) derived from (*R*)-phenylglycinol provides an expedient and convenient access to enantiopure side chain functionalized α-trifluoromethyl α-amino acids such as α-Tfm-aspartic acid and α-trifluoromethyl serine.



Scheme 8. Synthesis of both enantiomers of α-Tfm-serine **9**.

4. Experimental

4.1. General

Unless otherwise mentioned, all the reagents were purchased from commercial source. All glassware was dried in an oven at 150 °C prior to use. Ether and THF were distilled under nitrogen from sodium/benzophenone prior to use. CH_2Cl_2 was distilled under nitrogen from CaH_2 prior to use. ^1H NMR (400.00 MHz), ^{13}C NMR (100.50 MHz) and ^{19}F NMR (376.20 MHz) were measured on a JEOL ECX400 spectrometer. Chemical shifts of ^1H NMR are expressed in parts per million downfield from tetramethylsilane ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR are expressed in parts per million downfield from $CDCl_3$ as internal standard ($\delta = 77.0$). Chemical shifts of ^{19}F NMR are expressed in parts per million downfield from C_6F_6 as an internal standard ($\delta = -164.9$). Coupling constants are reported in Hertz. Column chromatography was performed on SDS 60A, (40–63 μm) silica gel, employing a mixture of the specified solvent as eluent. Thin-layer chromatography (TLC) was performed on Merck silica gel (Merck 60 PF_{254}) plates. Silica TLC plates were visualized under UV light, by a 10% solution of phosphomolybdic acid in ethanol followed by heating. Gas chromatography (CPV) was performed on HP 5890 II (detector with ionization of flame) and with a polydimethylsiloxane column HP ultra I (25 m × 3.2 mm × 0.52 μm thickness of layer). Mass spectra (MS) were obtained on a GC/MS apparatus HP 5973 MSD with an HP 6890 Series GC. Ionization was obtained by electronic impact (EI 70 eV). Infrared spectra (IR) were obtained by Fourier-transformation on BRÜCKER TENSOR 27, wavenumbers are given in cm^{-1}. Elemental analyses were performed on Perkin–Elmer CHN 2400. Optical rotations were determined using a JASCO P1010 polarimeter. HRMS analyses were performed on a Jeol JMS-GC Mate II. Melting points were obtained on a Büchi apparatus and are uncorrected.

4.2. (4*R*)-2-Carboethoxymethyl-2-trifluoromethyl-4-phenyl-1,3-oxazolidines 1

To a solution of ethyl 4,4,4-trifluoroacetoacetate (3.63 g, 19.7 mmol, 1 equiv) and glacial acetic acid (3.5 mL, 61.1 mmol, 3.1 equiv) in $CHCl_3$ (60 mL) was added (*R*)-phenylglycinol (3.14 g, 22.9 mmol, 1.2 equiv) and the mixture was refluxed for 12 h. The mixture was cooled down to room temperature and carefully

neutralized with a saturated solution of $NaHCO_3$ and the reaction mixture was stirred for 1 h. The mixture was extracted with DCM (3×20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, and evaporated under vacuum. The crude product could be used without further purification in the next step or purified by silica gel chromatography (80:20 cyclohexane/ethyl acetate) to give $\mathbf{1_{maj}}$ (2.89 g, 49%) and $\mathbf{1_{min}}$ (1.77 g, 30%) as pure isolated compounds.

Major diastereomer $\mathbf{1_{maj}}$: yellow oil; $R_f = 0.53$ (80:20 cyclohexane/ethyl acetate); $[\alpha]_D^{27} = -20.0$ (c 1.4, CH_2Cl_2); IR (neat): 3338, 2938, 2898, 1727, 1469, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, $^3J = 6.9$ Hz); 2.84 (d, 1H, $^2J = 15.1$ Hz); 3.04 (d, 1H, $^2J = 15.1$ Hz); 3.69 (t, 1H, $J = 7.5$ Hz); 3.89 (d, 1H, $^3J = 10.5$ Hz); 4.22 (dq, 1H, $^3J = 6.9$ Hz, $^2J = 13.9$ Hz); 4.25 (dq, 1H, $^3J = 6.9$ Hz, $^2J = 13.9$ Hz); 4.32 (t, 1H, $J = 7.5$ Hz); 4.55 (ddd, 1H, $^3J = 10.5$ Hz, $^3J = 7.5$ Hz, $^3J = 7.5$ Hz); 7.30–7.49 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 14.0, 35.5, 61.5, 62.7, 74.6, 95.1 (q, $^2J_{C-F} = 30.7$ Hz), 124.0 (q, $^1J_{C-F} = 287.5$ Hz), 127.3, 128.4, 129.0, 137.0, 169.5, ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −85.9 (s); HRMS (EI) calcd for $C_{14}H_{16}F_3NO_3$ 303.1082, found 303.1082.

Minor diastereomer $\mathbf{1_{min}}$: yellow oil; $R_f = 0.26$ (80:20 cyclohexane/ethyl acetate); IR (neat): 3338, 2938, 2898, 1727, 1469, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, $^3J = 7.3$ Hz); 2.83 (d, 1H, $^2J = 14.6$ Hz); 2.88 (d, 1H, $^2J = 14.6$ Hz); 3.67 (br s, 1H); 3.81 (t, 1H, $^3J = 8.9$ Hz); 4.23 (q, 2H, $^3J = 6.9$ Hz); 4.36 (t, 1H, $^3J = 8.9$ Hz); 4.72 (br s, 1H); 7.28–7.44 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 14.1, 37.6, 61.1, 61.4, 75.2, 93.3 (q, $^2J_{C-F} = 30.7$ Hz), 124.3 (q, $^1J_{C-F} = 288.5$ Hz), 126.8, 127.8, 128.5, 139.3, 168.8; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −85.8 (s); HRMS (EI) calcd for $C_{14}H_{16}F_3NO_3$ 303.1082; found 303.1082.

4.3. Ethyl (3*S*)-3-cyano-4,4,4-trifluoro-3-[(1*R*)-2-hydroxy-1-phenylethylamino]butanoate (*S*)-2 and ethyl (3*R*)-3-cyano-4,4,4-trifluoro-3-[(1*R*)-2-hydroxy-1-phénylethylamino]butanoate (*R*)-2

To a solution of ethyl 4,4,4-trifluoroacetoacetate (3.63 g, 19.7 mmol, 1 equiv) and glacial acetic acid (3.5 mL, 61.1 mmol, 3.1 equiv) in $CHCl_3$ (60 mL) was added (*R*)-phenylglycinol (3.14 g, 22.9 mmol, 1.2 equiv). The mixture was refluxed for 12 h. The mixture was cooled down to room temperature and carefully neutralized with a saturated solution of $NaHCO_3$ and the reaction mixture was stirred for 1 h. The mixture was then extracted with DCM (3×20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude mixture of oxazolidines **1** (6.06 g) was used in the next step without further purification. To a solution of the crude mixture of oxazolidines **1** (6.06 g) in DCM (60 mL) at room temperature under an argon atmosphere were added dropwise trimethylsilyl cyanide (3.7 mL, 29.5 mmol, 1.5 equiv) and $BF_3{\cdot}OEt_2$ (3.75 mL, 29.5 mmol, 1.5 equiv). The mixture was stirred until consumption of the starting material (20 h). The mixture was carefully neutralized with a saturated solution of K_2CO_3 and the reaction mixture was stirred for 1 h, until no gas evolution was observed. Then the mixture was extracted with DCM (3×20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product was purified by silica gel chromatography (90:10 cyclohexane/ethyl acetate) to give a 55:45 diastereomeric mixture of aminonitriles (*S*)-**2** and (*R*)-**2** (5 g, 15.13 mmol, 77%).

Compound (*S*)-**2**: yellow oil; $R_f = 0.46$ (80:20 cyclohexane/ethyl acetate), IR (neat): 3456, 3374, 2938, 2930, 2160, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, $J = 7.3$ Hz), 1.93 (t, 1H, $J = 6.4$ Hz), 2.86 (d, 1H, $J = 16.5$ Hz), 3.03 (d, 1H, $J = 16.5$ Hz), 3.38 (br s, 1H), 3.55 (ddd, 1H, $J = 11.6$, 6.4, 6.4 Hz), 3.85 (ddd, 1H, $J = 11.6$, 6.4, 4.1 Hz), 4.14–4.21 (m, 2H); 4.24 (dd, 1H, $^3J = 6.4$, 6.4 Hz), 7.15–7.33 (m, 5H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.9, 37.7, 60.6 (q, $J = 30.7$ Hz), 61.9, 62.4, 67.1, 114.3, 122.3 (q, $J = 286.7$ Hz), 126.9, 127.5, 128.3, 139.9, 167.8. ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −79.5 (s).

Compound (*R*)-**2**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, 3H, $J = 7.3$ Hz), 1.98 (t, 1H, $J = 5.5$ Hz), 2.70 (d, 1H, $J = 15.6$ Hz), 2.80 (d, 1H, $J = 15.6$ Hz), 3.38 (br s, 1H), 3.46–3.54 (m, 1H), 3.61–3.68 (m, 1H), 4.08 (dq, 1H, $J = 7.3$, 2.4 Hz), 4.12–4.20 (m, 1H), 4.24 (dd, 1H, $J = 7.8$, 7.8 Hz), 7.18–7.35 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.7, 38.0, 59.4 (q, $J = 28.8$ Hz), 61.4, 62.2, 67.0, 113.8, 122.9 (q, $J = 286.6$ Hz), 127.3, 128.3, 128.7, 138.8, 167.2. ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −79.4 (s); HRMS (EI) calcd for $C_{15}H_{17}F_3N_2O_3$ 330.1191; found 330.1194.

4.4. (3*S*,5*R*)-3-Carboethoxymethyl-3-trifluoromethyl-5-phenylmorpholin-2-one (*S*)-3 and (3*R*,5*R*)-3-carboethoxymethyl-3-trifluoromethyl-5-phenylmorpholin-2-one (*R*)-3

To a solution of a 55:45 diastereomeric mixture of aminonitriles (*S*)-**2** and (*R*)-**2** (6.46 g, 19.6 mmol, 1 equiv) in AcOEt (200 mL) was added 22.4 mL of HCl concd (270 mmol, 14 equiv) at room temperature then the mixture was refluxed for 24 h. The reaction was monitored by TLC (80:20 cyclohexane/ethyl acetate eluent). The reaction was cooled down to room temperature and carefully neutralized with a saturated solution of K_2CO_3 and extracted with AcOEt (3×60 mL), dried over $MgSO_4$ and evaporated under vacuum. A fraction of the crude material (1.65 g) was then purified by silica gel chromatography with an elution gradient (95:5–90:10 cyclohexane/ethyl acetate) to give (*S*)-**3** (0.55 g, 33%) and (*R*)-**3** (0.45 g, 27%) as pure isolated compounds.

Compound (*S*)-**3**: white solid; mp 94 °C; $[\alpha]_D^{21} = +55.3$ (c 1.3, CH_2Cl_2); $R_f = 0.19$ (85:15 cyclohexane/ethyl acetate); IR (neat): 3335, 2963, 2951, 2956, 2155, 1741, 1454, 1309, 1212, 1162, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, $^3J = 7.1$ Hz), 2.33 (br s, 1H), 2.60 (d, 1H, $^2J = 16.2$ Hz), 3.39 (d, 1H, $^2J = 16.2$ Hz), 4.14–4.24 (m, 2H), 4.26 (dd, 1H, $^3J = 3.0$ Hz, $^2J = 10.2$ Hz), 4.44 (dd, 1H, ^{2} $J = 10.2$ Hz $^3J = 11.0$ Hz), 4.52 (dd, 1H, $^3J = 11.0$ Hz, $^3J = 3.0$ Hz), 7.28–7.32 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 14.1, 40.3, 52.9, 61.6, 63.4 (q, $^3J_{C-F} = 25.9$ Hz), 74.2, 124.9 (q, $^1J_{C-F} = 291.4$ Hz), 127.2, 128.9, 129.1, 136.6, 163.8, 168.9. ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −76.9 (s). HRMS (EI) calcd for $C_{15}H_{16}F_3NO_4$ 331.1031, found 331.1038.

Compound (*R*)-**3**: white solid; mp 126 °C; $[\alpha]_D^{21} = -24$ (c 0.5, $CHCl_3$); $R_f = 0.14$ (85:15 cyclohexane/ethyl acetate), IR (neat): 3362, 3000, 2160, 1740, 1727, 1297, 1253, 1204, 1179, 1032, 766, 703, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, $^3J = 7.1$ Hz), 2.12 (br s, 1H), 2.71 (d, 1H, $^2J = 17.2$ Hz), 3.55 (d, $^2J = 17.2$ Hz), 4.15–4.25 (m, 2H); 4.34 (dd, 1H, $^3J = 2.8$ Hz, $^2J = 10.8$ Hz), 4.41 (dd, 1H, $^2J = 10.8$ Hz, $^3J = 10.8$ Hz), 4.80 (d, 1H, $^3J = 10.8$ Hz), 7.33–7.49 (m, 5H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 14.0, 39.8, 54.6, 61.7, 63.6 (q, $^3J_{C-F} = 26.8$ Hz), 74.0, 124.1 (q, $^1J_{C-F} = 284.7$ Hz), 127.3, 128.8, 137.3, 164.8, 169.3. ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −80.6 (s). HRMS (EI) calcd for $C_{15}H_{16}F_3NO_4$ 331.1031, found 331.1032.

4.5. (*S*)-α-Trifluoromethylaspartic acid hydrochloride (*S*)-4 and (*R*)-α-trifluoromethylaspartic acid hydrochloride (*R*)-4

The morpholinone (*S*)-**3** (0.226 g, 0.68 mmol) was dissolved in concentrated HCl (10 mL). The heterogeneous solution was refluxed for 12 h. The acidic aqueous phase was washed with Et_2O (2×10 mL) and evaporated under vacuum to give analytically pure (*S*)-**4** (0.118 g, 83%).

Spectroscopic data of (*S*)-**4** are in accordance with the literature[7] reported data: white solid; $[\alpha]_D^{21} = +25$ (c 0.25, H_2O); ^1H NMR (400 MHz, D_2O) δ 3.01 (d, 1H, $J = 18.1$ Hz), 3.35 (d, 1H, $J = 18.1$ Hz). ^{13}C NMR (100.3 MHz, D_2O) δ 34.3, 62.8 (q, $J = 28.8$ Hz, C–CF_3),

122.4 (q, J = 283.7, CF_3), 165.6, 171.5. ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 34.3, 62.8 (q, J = 28.8 Hz, C–CF_3), 122.4 (q, J = 283.7, CF_3), 165.6, 171.5. ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −78.4 (s).

Following the same procedure, the enantiomer (*R*)-**4** (0.119 g, 86%) was obtained from the morpholinone (*R*)-**3** (0.220 g, 0.66 mmol). (*R*)-**4**: $[\alpha]_D^{25} = -24.6$ (*c* 0.3, H_2O). The other spectroscopic data of (*R*)-**4** were similar to those of (*S*)-**4**.

4.6. Ethyl 2-[(1*R*)-2-hydroxy-1-phenylethylamino]-2-cyano-2-trifluoromethylacetate 6

To a solution of oxazolidine **5** (7.313 g, 25.3 mmol, 1.0 equiv) in dichloromethane (85 mL) at 0 °C under an argon atmosphere were successively added TMSCN (5.08 mL, 37.95 mmol, 1.5 equiv) and $BF_3{\cdot}Et_2O$ (4.48 mL, 37.95 mmol, 1.5 equiv). After stirring at room temperature overnight, the mixture was poured into a saturated $NaHCO_3$ aqueous solution (250 mL) and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed successively with water (2 × 20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (85:15 cyclohexane/ethyl acetate) to afford 7.65 g (96%) of aminonitrile **6** as a 60:40 mixture of diastereomers. Starting from the oxazolidine **5** (7.12 g, 24.6 mmol, 1.0 equiv), the reaction was performed in similar manner and the two diastereomers were separated by flash chromatography (85:15 cyclohexane/ethyl acetate) to afford 4.67 g (47%) of the major diastereomer $\mathbf{6_{maj}}$ and 3.11 g (32%) of the minor diastereomer $\mathbf{6_{min}}$.

$\mathbf{6_{maj}}$: yellow solid; mp 77 °C; R_f = 0.37 (80:20 cyclohexane/ethyl acetate); $[\alpha]_D^{25} = -72.6$ (*c* 0.98, $CHCl_3$); IR (neat): 3562, 3336, 2359, 1739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.1 Hz, 3H), 2.30 (s, 1H), 3.11 (d, J = 7.4 Hz, 1H), 3.45–3.95 (m, 4H), 4.13 (dt, J = 7.7, 4.7 Hz, 1H), 7.10–7.40 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.3, 62.0, 64.8, 65.6 (q, J = 31.3 Hz), 66.3, 111.2, 121.2 (q, J = 287.2 Hz), 127.8, 128.5, 128.6, 137.4, 161.6; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −77.6 (s). Anal. Calcd for $C_{14}H_{15}F_3N_2O_3$ (316.27): C, 53.17; H, 4.78; N, 8.86. Found: C, 53.51; H, 5.00; N, 8.89.

$\mathbf{6_{min}}$: yellow solid; mp 46 °C; R_f = 0.21 (80:20 cyclohexane/ethyl acetate); $[\alpha]_D^{26} = -96.1$ (*c* 1.09, $CHCl_3$); IR (neat): 3562, 3336, 2359, 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 2.20 (s, 1H), 3.20 (s, 1H), 3.50 (dd, J = 11.3, 8.6 Hz, 1H), 3.60 (dd, J = 11.3, 4.1 Hz, 1H), 4.00 (dd, J = 8.6, 4.1 Hz, 1H), 4.20–4.45 (m, 2H), 7.10–7.45 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.7, 61.7, 65.2, 65.4 (q, J = 31.3 Hz), 67.0, 111.2, 121.0 (q, J = 287.7 Hz), 127.2, 128.2, 128.6, 138.5, 162.2; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −77.3 (s). Anal. Calcd for $C_{14}H_{15}F_3N_2O_3$ (316.27): C, 53.17; H, 4.78; N, 8.86. Found: C, 53.08; H, 4.70; N, 8.98.

4.7. (4*R*)-2-Hydroxymethyl-2-trifluoromethyl-4-phenyl-1,3-oxazolidine 7

To a 71:29 dr mixture of oxazolidine **5** (9.45 g, 32.7 mmol, 1.0 equiv) in methanol (142 mL) under an argon atmosphere at 0 °C was added $NaBH_4$ (1.24 g, 32.7 mmol, 1.0 equiv). The reaction was stirred for 1 h at room temperature, and then quenched with saturated NH_4Cl aqueous solution (100 mL). Methanol was removed under reduced pressure and the corresponding aqueous solution was taken up with ethyl acetate (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. After filtration through a short pad of silica gel, the reduced oxazolidine **7** was obtained as a 71:29 diastereoisomeric mixture. Precipitation in pentane followed by filtration gave the pure major diastereomer $\mathbf{7_{maj}}$ (5.50 g, 68%) as a white solid and the pure minor diastereomer $\mathbf{7_{min}}$ (2.35 g, 29%) was obtained as a colorless oil after evaporation of the filtrate.

$\mathbf{7_{maj}}$: white solid; mp 156 °C; R_f = 0.40 (80:20 cyclohexane/ethyl acetate); $[\alpha]_D^{21} = +0.3$ (*c* 1.0, CH_3OH); IR (neat): 3277 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (dd, J = 7.4, 6.6 Hz, 1H), 3.79 (d, J = 12.1 Hz, 1H), 4.00 (d, J = 12.1 Hz, 1H), 4.42 (t, J = 7.4 Hz, 1H), 4.61 (dd, J = 7.4, 6.6 Hz, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 60.5, 62.2, 75.0, 96.5 (q, J = 31.3 Hz), 124.0 (q, J = 287.2 Hz), 126.8, 128.5, 129.0, 137.8; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −84.0 (s). Anal. Calcd for $C_{11}H_{12}F_3NO_2$ (247.21): C, 53.44; H, 4.89; N, 5.67. Found: C, 53.44; H, 5.13; N, 5.62.

$\mathbf{7_{min}}$: colorless oil; R_f = 0.27 (80:20 cyclohexane/ethyl acetate); $[\alpha]_D^{21} = -36$ (*c* 1.0, CH_3OH); IR (neat): 3227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, J = 12.4 Hz, 1H), 3.86 (dd, J = 9.5, 8.0 Hz, 1H), 3.91 (d, J = 12.4 Hz, 1H), 4.44 (dd, J = 8.0, 7.3 Hz, 1H), 4.71 (dd, J = 9.5, 7.3 Hz, 1H), 7.25–7.50 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 61.9, 62.0, 76.7, 94.9 (q, J = 29.7 Hz), 124.0 (q, J = 288.5 Hz), 126.9, 128.5, 129.1, 139.0; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −83.8 (s). Anal. Calcd for $C_{11}H_{12}F_3NO_2$ (247.21): C, 53.44; H, 4.89; N, 5.67. Found: C, 53.50; H, 4.94; N, 5.62.

4.8. 2-Trifluoro-3-hydroxy-2-[(1*R*)-2-hydroxy-1-phenyl-amino] propanenitrile 8

To a 71:29 dr mixture of hydroxymethyl oxazolidines **7** (2.0 g, 8.1 mmol, 1.0 equiv) in dichloromethane (25 mL) at 0 °C under an argon atmosphere were successively added TMSCN (1.1 mL, 8.1 mmol, 1.0 equiv) and $BF_3{\cdot}OEt_2$ (1.0 mL, 8.1 mmol, 1.0 equiv). The corresponding mixture was stirred at room temperature for 30 min and three other additions of TMSCN (0.5 mL, 4 mmol, 0.5 equiv each) and $BF_3{\cdot}OEt_2$ (0.53 mL, 4 mmol, 0.5 equiv each) were successively achieved in 30 min intervals. The reaction mixture was stirred at room temperature overnight, poured into a saturated $NaHCO_3$ aqueous solution (100 mL) and stirred vigorously for 1 h. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (80:20 cyclohexane/ethyl acetate) gave 1.03 g (46%) of a pure fraction of the (*S*)-**8**, 510 mg (23%) of a mixture of both diastereomer and 630 mg (28%) of a pure fraction of the minor diastereomer (*R*)-**8**.

Compound (*S*)-**8**: white solid; mp 59 °C; R_f = 0.41 (60:40 cyclohexane/ethyl acetate); $[\alpha]_D^{21} = -77.4$ (*c* 1.0, $CHCl_3$); IR (neat): 3228, 3198, 2350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (br s, 3H), 3.52 (dd, J = 12.2, 8.8 Hz, 1H), 3.75 (m, 3H), 4.15 (dd, J = 8.8, 4.3 Hz, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 61.1, 62.3, 63.7 (q, J = 28.7 Hz), 66.9, 114.2, 125.0 (q, J = 285.6 Hz), 127.1, 128.6, 129.1, 139.1; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −77.63 (s). Anal. Calcd for $C_{12}H_{13}F_3N_2O_2$ (274.24): C, 52.56; H, 4.78; N, 10.21. Found: C, 52.38; H, 4.69; N, 10.21.

Compound (*R*)-**8**: white solid; mp 78 °C; R_f = 0.32 (60:40 cyclohexane/ethyl acetate); $[\alpha]_D^{21} = -83.3$ (*c* 1.0, $CHCl_3$); IR (neat): 3345, 3250, 2350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (br s, 3H), 3.60 (dd, J = 11.2, 8.7 Hz, 1H), 3.86 (dd, J = 11.2, 4.0 Hz, 1H), 3.93 (d, J = 11.7 Hz, 1H), 4.17 (d, J = 11.7 Hz, 1H), 4.20 (dd, J = 8.7, 4.0 Hz, 1H), 7.27–7.39 (m, 5H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 61.5, 62.7, 64.7 (q, J = 34.5 Hz), 67.3, 99.9, 122.0 (q, J = 268.4 Hz), 127.0, 128.0, 128.7, 139.5; ^{19}F NMR (376.2 MHz, $CDCl_3$) δ −77.56 (s). Anal. Calcd for $C_{12}H_{13}F_3N_2O_2$ (274.24): C, 52.56; H, 4.78; N, 10.21. Found: C, 52.38; H, 5.04; N, 9.87.

4.9. (*R*)-α-Trifluoromethylserine (*R*)-9

A solution of aminonitrile (*S*)-**8** (1.46 g, 5.3 mmol, 1.0 equiv) in concentrated HCl (38 mL) was heated at reflux overnight, and then

concentrated under reduced pressure. The crude mixture was washed with diethyl ether to give, after filtration, the (*R*)-(α)-trifluoromethylserine hydrochloride as a white solid. mp degradation over 200 °C; $[\alpha]_D^{21} = -2.5$ (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.04 (d, *J* = 11.7 Hz, 1H), 4.19 (d, *J* = 11.7 Hz, 1H); ^{13}C NMR (100.5 MHz, CD_3OD) δ 65.7, 78.0 (q, *J* = 32.6 Hz), 125.5 (q, *J* = 283.7 Hz), 164.0; ^{19}F NMR (376.2 MHz, CD_3OD) δ −75.0 (s); HRMS (EI): $C_4H_7ClF_3NO_3$: 209.0067; found: 209.0069.

The crude hydrochloride ammonium salt of (*R*)-(α)-trifluoromethylserine was then loaded onto DOWEX 50W8-400 resin to afford 636 mg (75%) of the pure (*R*)-α-Tfm-serine (*R*)-**9**. White solid; mp degradation over 200 °C; R_f = 0.70 (50:50 dichloromethane/methanol); $[\alpha]_D^{23} = +10.6$ (*c* 1, H_2O); {lit. $[\alpha]_D^{20} = +11.3$ (*c* 0.77, H_2O)};[8a] ^{1}H NMR (400 MHz, D_2O) δ 3.00 (br s, 3H); ^{13}C NMR (100.5 MHz, D_2O) δ 59.7, 66.4 (q, *J* = 25.9 Hz), 122.8 (q, *J* = 283.6 Hz), 165.8; ^{19}F NMR (376.2 MHz, D_2O) δ −75.2 (s).

4.10. (*S*)-α-Trifluoromethylserine (*S*)-9

A solution of aminonitrile (*R*)-**8** (935 mg, 3.4 mmol, 1.0 equiv) in concentrated HCl (24 mL) was warmed to reflux overnight, then concentrated under reduced pressure. The crude hydrochloride ammonium salt of (α)-trifluoromethylserine was then washed with diethyl ether and then loaded onto DOWEX 50W8-400 to afford 544 mg (94%) of the pure (*S*)-α-Tfm-serine (*S*)-**9**. $[\alpha]_D^{28} = -10.4$ (*c* 0.85, H_2O); {lit. $[\alpha]_D^{20} = -9.1$ (*c* 0.59, H_2O)}.[3] The other spectroscopic data of (*S*)-**9** were similar to those of (*R*)-**9**.

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