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Concise access to enantiopure (*S*)- and (*R*)-α-trifluoromethyl pyroglutamic acids from ethyl trifluoropyruvate-based chiral CF_3-oxazolidines (Fox)

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ABSTRACT

A straightforward synthesis of enantiopure (*S*)- and (*R*)-α-Tfm-pyroglutamic acid is reported. The strategy is based on the use of a chiral CF_3-hydroxymorpholinone intermediate conveniently obtained from ethyl trifluoropyruvate-based chiral CF_3-oxazolidines (Fox). The key step is an oxidative cyclization followed by a reductive cleavage of the (*R*)-phenylglycinol chiral auxiliary.

1. Introduction

Conformationally constrained cyclic amino acids have recently gained considerable interest because of their ability to control the conformation of peptides for structure–activity relationships investigations as well as for the design of peptidomimetics [1]. In particular, incorporation of a proline unit is known to restrict the amino acyl-proline *cis*/*trans* isomerization [2], to limit the protein folding and consequently to modulate the biological activity of peptides. Among the numerous proline derivatives reported in the literature, fluorinated proline-type amino acids have received increasing attention [3]. This is particularly due to the unique physical and biological properties induced by the introduction of fluorinated groups in peptides and peptidomimetics [4]. However, their use in peptide chemistry remains very limited due to the difficulty to prepare them efficiently, particularly in their enantiopure form. Pyroglutamic acid derivatives were also reported to be efficient tools for the control of the peptidyl bond geometry [5]. Although several examples of fluorine containing pyroglutamic derivatives are reported in the literature [6], the preparation of α-Tfm-pyroglutamic acids in enantiopure form has never been reported [7].

In the course of our studies, we recently reported several approaches for the stereoselective synthesis of α- and β-trifluoromethyl amino acids (Tfm AAs) starting from chiral CF_3-oxazolidines (Fox) or imines [8]. Among them, we developed an efficient route for the synthesis of (*S*)- and (*R*)-α-Tfm proline based on the use of the key chiral CF_3-hydroxymorpholinone **2** (Scheme 1) [9]. This compound was conveniently prepared in a few step from the oxazolidines **1** derived from ethyl trifluoropyruvate.

We present here another feature of the use of the CF_3-hydromorpholinone **2**. This versatile intermediate proved to be also highly valuable for the synthesis of α-Tfm-pyroglutamic acids in enantiopure form.

2. Results and discussion

The preparation of the starting CF_3-hydroxymorpholinone **2** was based on our reported procedure [9]. In addition, the first step involving the formation of oxazolidines **1** from ethyl trifluoropyruvate and (*R*)-phenylglycinol was significantly improved. We observed that the yield of the direct condensation was not entirely reproducible (65–90%) [10]. This was probably due to both bis-nucleophilic reactivity of (*R*)-phenylglycinol and bis-electrophilic reactivity of ethyl trifluoropyruvate. In order to increase the

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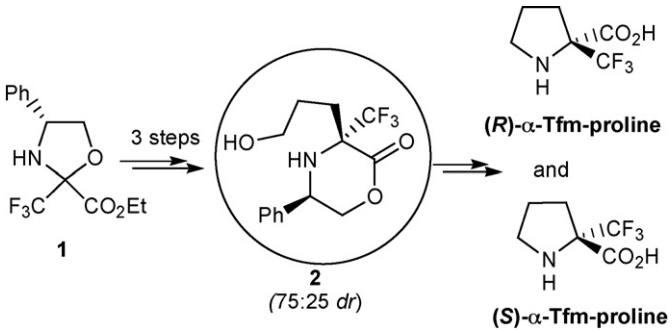
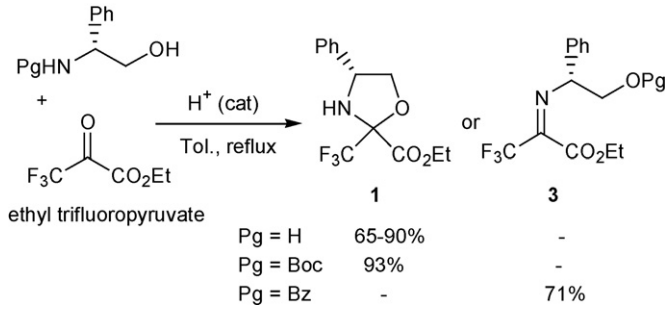


Scheme 1.

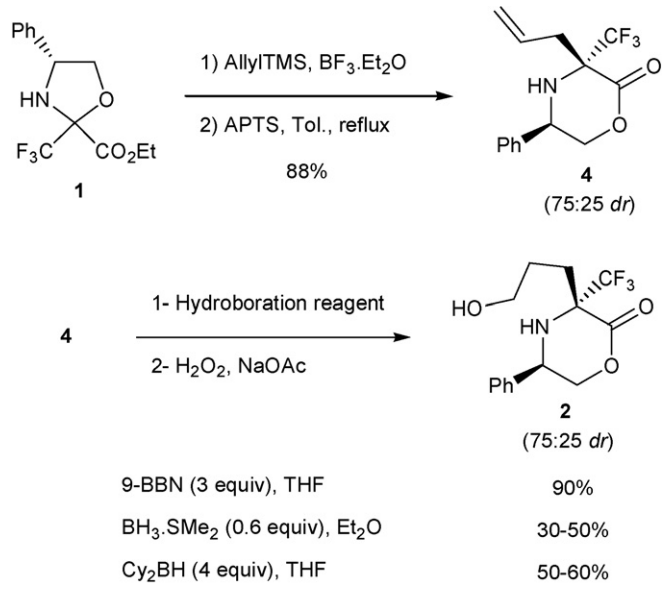


Scheme 2.

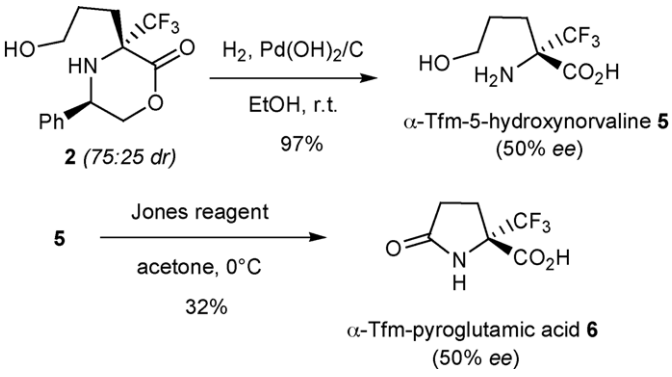
selectivity of the oxazolidine **1** formation, we designed to use a *N*-protected (*R*)-phenylglycinol which would give an intermediate ethyl trifluoropyruvate hemiacetal. After removal of the protecting group, the cyclization of the hemiacetals would lead to the expected oxazolidines. We were pleased to observe that the reaction of the *N*-Boc (*R*)-phenylglycinol under acidic catalysis (0.1 equiv. PPTS) gave directly the oxazolidines **1** (75:25 diastereomeric mixture) in a completely reproducible high yield (93%) (Scheme 2). Intriguingly, when reaction was performed starting from the *N*-Bz phenylglycinol, the only corresponding *O*-Bz imine **3** was isolated in 71% yield. We postulate that in both cases, there is a protecting group transfer from the amino to the hydroxyl group of the (*R*)-phenylglycinol in the acidic reaction conditions. The free amino group would then react selectively with the carbonyl group of the ethyl trifluoropyruvate to give an imine intermediate. The reaction stopped at the imine stage **3** when the stable benzoyle protecting group was used. However, with the Boc protecting group, the acidic mediated smooth removal of the Boc group should undergo a selective intramolecular cyclization of the resulting hydroxyimine into oxazolidines **1**.

The CF_3-hydroxymorpholinone **2** was then obtained as a non-separable 75:25 diastereomeric mixture following our previously reported three-step allylation/lactonisation/hydroboration sequence from oxazolidines **1** (Scheme 3) [9]. The hydroboration reaction of **4** was performed in high yield (90%) using 9-BBN. Lowest yield were achieved using $BH_3{\cdot}SMe_2$ or dicyclohexylborane (30–60%).

As an explorary study, the synthesis of the α-Tfm-pyroglutamic acid **6** from the 75:25 diastereomeric mixture of the hydroxymorpholinone **2** was investigated. The target compound was obtained by the following sequence involving the removal of the chiral auxiliary followed by the oxidation of the hydroxyl group into the corresponding acid and the ring closure by lactamization (Scheme 4). The hydrogenolysis of the hydroxymorpholinone **2** catalyzed by Pearlman's catalyst led to the new α-Tfm-5-hydroxynorvaline **5** in 97% yield. Finally, the expected α-Tfm-



Scheme 3.

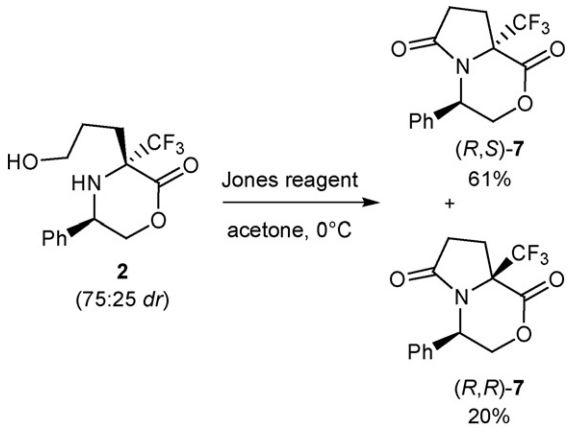


Scheme 4.

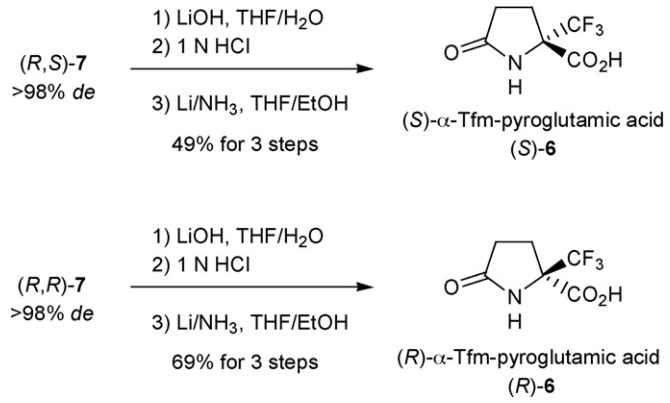
pyroglutamic acid **6** (50% *ee*) was obtained by oxidative cyclization using Jones reagent in 32% non-optimized yield. The direct cyclization of the intermediate amino acid is in accordance with the observation of Burger et al. [7] since they reported in the racemic series that α-Tfm-glutamic acid gave rise to spontaneous cyclization into α-Tfm-pyroglutamic acid.

The main drawback of this synthetic pathway is that it supposes an efficient separation of both diastereomers of the CF_3-hydroxymorpholinone **2** in order to obtained enantiopure α-Tfm-pyroglutamic acids. As the chromatographic separation of both diastereomers of **2** is difficult, we anticipated that the separation of the bicyclic lactams resulting from oxidative cyclization of **2** would be more convenient [11]. Hence the diastereomeric mixture of **2** was subjected to oxidation using the convenient Jones reagent to give the corresponding bicyclic lactams **7** in high yield (Scheme 5) [12].

As expected, at this stage, both diastereomers of the bicyclic lactams **7** were very easily separated by silica gel chromatography to afford (*R*,*S*)-**7** in 61% isolated yield and (*R*,*R*)-**7** in 20% isolated yield (Scheme 5) [13]. Moreover, we were pleased to observe that both diastereomers could also be very conveniently separated by selective crystallization and filtration. Indeed, (*R*,*S*)-**7** is a white solid poorly soluble in diethyl ether, whereas (*R*,*R*)-**7** is an oil completely soluble in this solvent. This very efficient and convenient separation of both diastereomers will provide an easy



Scheme 5.



Scheme 6.

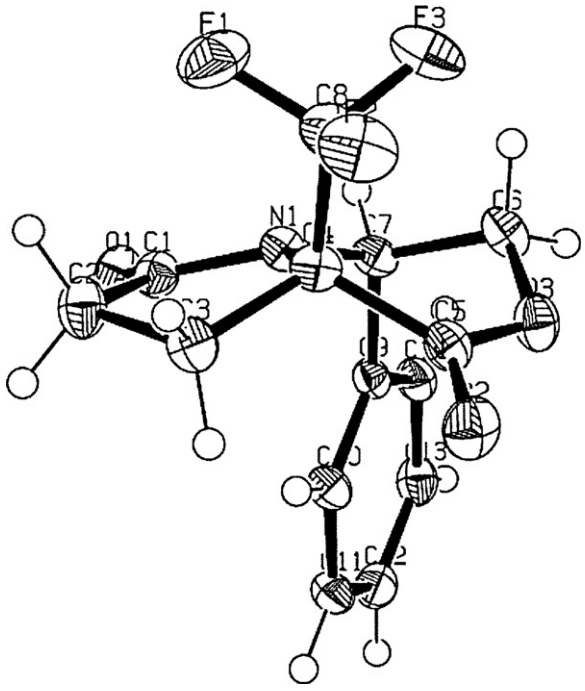


Fig. 1. ORTEP view of (*R*,*S*)-**7**.

access to enantiopure derivatives of **7** in large scale. The (*R*,*S*) configuration assignment of the major diastereomer of **7**, was confirmed by single crystal X-ray analysis (Fig. 1) [14].

The removal of the (*R*)-phenylglycinol chiral auxiliary was then considered. In accordance with the observations reported by Ma et al. [15], all attempts to cleave the *N*-benzylic bond of the diastereomerically pure (*R*,*S*)-**7** by Pd/C or $Pd(OH)_2/C$ catalyzed hydrogenolysis under acidic or neutral conditions failed. However, the removal of the chiral auxiliary was suitably achieved in a three-step procedure involving the saponification of the lactone ring by LiOH, acidification with 1N HCl followed by a reductive cleavage of the benzylic bond using lithium in liquid ammonia [15,16]. Following this procedure, enantiopure (*S*)-α-Tfm-pyroglutamic acid (*S*)-**6** was obtained in 49% yield from (*R*,*S*)-**7**. The enantiopurity (>98% *ee*) of (*S*)-**6** was confirm by its derivatization into the corresponding diastereomerically pure (*S*)-1-phenylethylamide. In a similar manner, (*R*)-α-Tfm-pyroglutamic acid (*R*)-**6** was obtained in enantiopure form in 69% yield from (*R*,*S*)-**7** (Scheme 6).

3. Conclusion

In conclusion, we have successfully developed a concise synthesis of both enantiomers of the highly constrained α-Tfm-pyroglutamic acid in enantiopure form from a highly versatile chiral CF_3-hydroxymorpholinone intermediate. Further investigations about synthetic applications of this conformationally constrained cyclic amino acid are underway and will be reported in due course.

4. Experimental

General: Unless otherwise mentioned, all the reagents were purchased from commercial source. THF was distilled under nitrogen from sodium/benzophenone 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 400 spectrometer. Chemical shifts of ^1H NMR were expressed in parts per million downfield from tetramethylsilane ($\delta = 0$) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as internal standard ($\delta = 77.0$). Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from C_6F_6 as internal standard ($\delta = -164.9$). Coupling constants are reported in hertz. Column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm), employing mixture of 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. 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 by the CNRS analysis central service. Optical rotations are reported as their specific rotations determined using a JASCO DIP-370 polarimeter. Melting points were obtained on a Büchi apparatus and are uncorrected.

4.1. (4R)-2-Ethoxycarbonyl-2-trifluoromethyl-4-phenyl-1,3-oxazolidine (1) [9]

To a stirred solution of 5.14 g of (*R*)-*N*-Boc-phenylglycinol (21.7 mmol, 1.0 equiv.) in 200 mL of toluene at room temperature were added 1.09 g of pyridinium *p*-toluenesulfonate (4.34 mmol, 0.2 equiv.) and 3.17 mL of ethyl trifluoropyruvate (23.8 mmol, 1.1 equiv.). The mixture was stirred for 1 h at room temperature, warmed to 140 °C with a Dean–Stark apparatus for 20 h, and then

cooled to 0 °C with an ice-bath. The resulting mixture was filtered and toluene was evaporated. Purification by flash chromatography (95:5 cyclohexane/ethyl acetate) gave 5.80 g (93%) of **1** (75:25 diastereomeric mixture).

4.2. (E)-1-Ethoxycarbonyl-2,2,2-trifluoroethylidene (1R)-2-benzoyloxy-1-phenylethylamine (3)

To a stirred solution of 200 mg of (*R*)-*N*-Bz-phenylglycinol (0.83 mmol, 1.0 equiv.) in 10 mL of toluene at room temperature, were added 23 mg of *p*-toluenesulfonic acid (0.12 mmol, 0.15 equiv.) and 110 μL of ethyl trifluoropyruvate (0.83 mmol, 1.0 equiv.). The mixture was warmed to 140 °C with a Dean–Stark apparatus for 20 h, and then cooled to 0 °C with an ice-bath. The resulting mixture was filtered and toluene was evaporated. Purification by flash chromatography (9:1 cyclohexane/ethyl acetate) gave 229 mg of imine **3** (71%). Colorless oil; $[\alpha]_D^{20}$ −3.05 (*c* 2.1, $CHCl_3$); IR (neat): 2987, 1742, 1684, 1452, 1272, 713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.30 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.50 (dd, *J* = 11.1, 9.3 Hz, 1H), 4.74 (dd, *J* = 11.1, 3.8 Hz, 1H), 5.33 (dd, *J* = 9.3, 3.8 Hz, 1H), 7.37–7.47 (m, 8H), 8.02–7.99 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 13.8, 62.9, 66.3, 67.8, 118.1 (q, *J* = 279.0 Hz), 127.3, 128.4, 128.6, 128.9, 129.6, 133.2, 136.8, 150.2 (q, *J* = 36.4 Hz), 158.4, 166.0; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ = −72.9 (s); MS (EI) *m*/*z* 393 [M+·], 271; 243, 198, 105 (100), 77; Anal. Calcd for $C_{20}H_{18}F_3NO_4$: C, 61.07; H, 4.61; N, 3.56. Found: C, 61.01; H, 5.01; N, 3.45.

4.3. α-Trifluoromethyl-5-hydroxynorvaline (5)

To a 75:25 diastereomeric mixture of hydroxymorpholinone **2** (207 mg, 0.68 mmol) in EtOH (20 mL) was added 380 mg of 20% $Pd(OH)_2/C$. The reaction was stirred for 48 h under 1 bar atmosphere pressure of hydrogen. The resulting mixture was filtered and evaporated under reduced pressure. The crude mixture was taken up with ether and water. The aqueous phase was washed with ether and evaporated to afford 133 mg of **5** (97%) as white solid. ^1H NMR (400 MHz, D_2O): δ = 1.21–1.33 (m, 1H), 1.34–1.49 (m, 1H), 1.80 (ddd, *J* = 16.7, 11.9, 5.0 Hz, 1H), 2.03 (ddd, *J* = 16.7, 11.9, 4.6 Hz, 1H), 3.39 (td, *J* = 6.0, 2.8 Hz, 2H); ^{13}C NMR (100.5 MHz, D_2O): δ = 27.7, 29.4, 63.1, 68.2 (q, *J* = 26.8 Hz), 125.9 (q, *J* = 283.7 Hz), 169.3; ^{19}F NMR (376.2 MHz, D_2O): δ = −76.2.

4.4. 8a-Trifluoromethyl-4-phenyltetrahydropyrrolo[2,1-c][1,4]oxazine-1,6-dione (7)

To a stirred solution of 263 mg of a 75:25 diastereomeric mixture of alcohol **2** (0.87 mmol, 1.0 equiv.) in 2.8 mL of acetone was added dropwise at 0 °C 634 μL of solution of Jones reagent (2.74 M in 3.2:1 H_2O/H_2SO_4 solution, 1.7 mmol, 2.0 equiv.). After 20 min at 0 °C, 250 μL of solution of Jones reagent was added once more and the reaction mixture was stirred for another 20 min at 0 °C. Finally, isopropanol was added until color turned green and the resulting solution was diluted in 50 mL of diethyl ether and 25 mL of water. The layers were separated and the aqueous phase was extracted with AcOEt (3 mL × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography (9:1 cyclohexane/ethyl acetate) gave 157 mg (61%) of the diastereomer (*R*,*S*)-**7** as a white solid and 53 mg (20%) of the diastereomer (*R*,*R*)-**7** as a colorless oil. (*R*,*S*)-**7**: white solid; m.p.: 189–190 °C; R_f = 0.41 (7:3 cyclohexane/ethyl acetate); $[\alpha]_D^{25}$ −124.4 (*c* 0.26, $CHCl_3$); IR (neat): 2360, 1763, 1725, 1226, 1172, 1151, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34–2.48 (m, 1H), 2.60–2.74 (m, 2H), 2.86–2.98 (m, 1H), 4.40 (dd, *J* = 11.5, 1.4 Hz, 1H), 5.05 (dd, *J* = 11.5, 4.1 Hz, 1H), 5.07 (dd, *J* = 4.1, 1.4 Hz, 1H), 7.04–7.08 (m, 2H), 7.27–7.40 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 28.6, 29.2, 53.0, 66.6 (q, *J* = 29.7 Hz), 71.4, 124.3 (q, *J* = 288.9 Hz), 125.6, 128.5, 129.2, 138.2, 165.3, 174.8; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ = −76.67 (s); MS (EI) *m*/*z* 299 [M+·], 230, 212, 104 (100), 91; Anal. Calcd for $C_{14}H_{12}F_3NO_3$: C, 56.12; H, 4.04; N, 4.68. Found: C, 56.03; H, 4.06; N, 4.61. (*R*,*R*)-**7**: colorless oil; R_f = 0.29 (7:3 cyclohexane/ethyl acetate); $[\alpha]_D^{25}$ −1.6 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (ddd, *J* = 16.0, 9.2, 1.4 Hz, 1H), 2.60–2.78 (m, 2H), 2.87–2.92 (m, 1H), 4.49 (t, *J* = 12.8 Hz, 1H), 4.59 (ddd, *J* = 12.8, 6.9, 1.4 Hz, 1H), 5.04 (dd, *J* = 12.8, 6.9 Hz, 1H), 7.26–7.30 (m, 2H), 7.32–7.45 (m, 3H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 28.7, 28.8, 53.7, 66.3 (q, *J* = 30.1 Hz), 68.8, 124.2 (q, *J* = 284.9 Hz), 127.2, 128.5, 129.1, 134.8, 165.7, 176.6; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ = −76.75 (s); MS (EI) *m*/*z* 299 [M+·], 230, 212, 104 (100).

4.5. (S)-α-Trifluoromethylpyroglutamic acid ((S)-6)

To a solution of pure bicyclic diastereomer (*R*,*S*)-**7** (372 mg, 1.04 mmol) in THF (6.3 mL) was slowly added at 0 °C, a 1 M aqueous solution of LiOH (1.25 mL, 1.25 mmol, 1.2 equiv.). The resulting mixture was vigorously stirred at 0 °C for 2 h, and then diluted with ether (10 mL). The layers were separated and the organic layer was washed with water (2× 10 mL). The combined aqueous layers were then acidified with 1N HCl until pH 2, extracted with EtOAc (3× 10 mL), dried over Na_2SO_4 and concentrated to give 380 mg of crude acid directly used in the next step without further purification.

A solution of the above acid (1.04 mmol) in anhydrous THF (25 mL) and absolute ethanol (2.5 mL) was added to an oven dried three-neck round bottom flask charged with argon. The flask was cooled to −40 °C bath, liquid NH_3 (approximately 150 mL) was condensed using an acetone/liquid nitrogen cold trap flask. Fresh polished lithium flakes were added to the reactants at −40 °C until the deep blue color was kept for 5 min. The reaction was quenched by the addition of NH_4Cl powder (2.7 g), and the reaction was left in the hood until almost all the NH_3 evaporated. The reaction mixture was then diluted with EtOAc (15 mL) and water (15 mL). The aqueous layer was washed with EtOAc (2× 20 mL), acidified with 1N HCl until pH 2 and extracted with EtOAc (3× 20 mL). The combined organic layers were evaporated to afford 100 mg of pure (*S*)-**6** (49%). White solid; m.p.: 143–144 °C; $[\alpha]_D^{22}$ −12.6 (*c* 2.2, MeOH); IR (neat): 3139, 3049, 1670, 1402, 1155 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 2.35–2.55 (m, 4H); ^1H NMR (400 MHz, D_2O): δ = 2.20–2.40 (m, 4H); ^{13}C NMR (100.5 MHz, CD_3OD): δ = 26.9; 30.3; 69.0; 126.2 (q, *J* = 283.6 Hz), 170.2, 180.3; ^{13}C NMR (100.5 MHz, D_2O): δ = 25.3, 29.0, 67.8 (q, *J* = 28.8 Hz), 124.2 (q, *J* = 283.6 Hz), 170.4, 181.3; ^{19}F NMR (376.2 MHz, D_2O): δ −79.0 (s); MS (EI) *m*/*z* 152 (M+–CO_2H) (100); Anal. Calcd for $C_6H_6F_3NO_3$: C, 36.56; H, 3.07; N, 7.11. Found: C, 36.93; H, 3.10; N, 6.97.

4.6. (R)-α-Trifluoromethylpyroglutamic acid ((R)-6)

According to the procedure described for (*S*)-**6**, starting from (*R*,*R*)-**7** (551 mg, 1.84 mmol) in THF (11 mL) and 1 M aqueous solution of LiOH (2.21 mL, 2.21 mmol, 1.2 equiv.), crude acid (451 mg) was obtained. This acid was directly used in the next reductive debenzylation step without further purification to afford 222 mg of pure (*R*)-**6** (69%). White solid; $[\alpha]_D^{25}$ +11.7 (*c* 2.2, MeOH). The spectral data of (*R*)-**6** were identical to those of (*S*)-**6**.

4.7. (S,S)-5-oxo-2-trifluoromethylpyrrolidine-2-carboxylic acid (1-phenyl)ethylamide ((S,S)-8)

To a solution of (*S*)-phenylethylamine (69 μL, 0.53 mmol, 1.5 equiv.) in DMF (1.5 mL) was successively added at 0 °C Et_3N (203 μL, 1.45 mmol, 4.1 equiv.), HOBt (72 mg, 0.53 mmol, 1.5 equiv.), EDCI (102 mg, 0.53 mmol, 1.5 equiv.) and pure (*S*)-**6** (70 mg, 0.36 mmol) in DMF (1 mL). The resulting mixture was stirred at 0 °C for 20 min and then at room temperature overnight. Then, the reaction mixture was diluted with AcOEt (20 mL) and washed with 1N HCl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2× 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ solution (10 mL) and water (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The ^1H and ^{19}F NMR analysis of the crude mixture confirmed that one single diastereomer was obtained. Purification by flash chromatography (1:1 cyclohexane/ethyl acetate) gave 43 mg (51%) of the diastereomer (*S*,*S*)-**8** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.9 Hz, 3H), 2.17 (ddd, *J* = 14.5, 9.2, 4.8 Hz, 1H), 2.30–2.40 (m, 1H), 2.40–2.55 (m, 2H), 5.10 (dq, *J* = 7.8, 6.9 Hz, 1H), 7.20–7.35 (m, 5H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.4, 26.0, 29.0, 49.7, 67.5 (q, *J* = 28.8 Hz); 124.6 (q, *J* = 285.6 Hz), 126.1, 127.6, 128.6, 142.3, 165.3, 178.6; ^{19}F NMR (376.2 MHz, $CDCl_3$): δ −80.1 (s).

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Appendix A. X-ray crystallographic study

Data were collected at 150.0(1)K on a Nonius Kappa CCD diffractometer using a Mo Kα (λ = 0.71070 Å) X-ray source and a graphite monochromator. All data were measured using phi and omega scans. The crystal structures were solved using SIR 9744 and Shelxl-97. CCDC-695212 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) + 44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk

Compound: (*R*,*S*)-8a-Trifluoromethyl-4-phenyltetrahydropyrrolo[2,1-*c*][1,4]oxazine-1,6-dione.

Molecular formula	$C_{14}H_{12}F_3NO_3$
Molecular weight	299.25
Crystal habit	Block colorless
Crystal dimensions (mm)	0.20 × 0.18 × 0.18
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	7.8210(10)
b (Å)	7.5940(10)
c (Å)	10.6570(10)
α (°)	90.00
β (°)	93.4520(10)
γ (°)	90.00
V (Å^3)	631.80(13)
Z	2
d (g cm^{-3})	1.573
F (0 0 0)	308
μ (cm^{-1})	0.139
Absorption corrections	Multi-scan; 0.9727 min, 0.9754 max
Diffractometer	KappaCCD
X-ray source	Mo Kα
λ (Å)	0.71069
Monochromator	Graphite
T (K)	150.0(1)
Scan mode	Phi and omega scans
Maximum θ	27.48
H K L ranges	−10 10; −9 9; −13 13
Reflections measured	2790
Unique data	2790
Rint	0.0000
Reflections used	2680
Criterion	$I > 2\sigma I$
Refinement type	Fsqd
Hydrogen atoms	Mixed
Parameters refined	191
Reflections/parameter	14
wR2	0.0932
R1	0.0322
Flack's parameter	−0.1(5)
Weights *a*, *b*	0.0590, 0.0754
GoF	1.053
Difference peak/hole (*e* Å^{-3})	0.194(0.048)/−0.179(0.048)

References

[1] For recent entries, see:
(a) P.K. Mikhailiuk, S. Afonin, A.N. Chernega, E.B. Rusanov, M.O. Platonov, G.G. Dubinina, M. Berditsch, A.S. Ulrich, I.V. Komarov, Angew. Chem. Int. Ed. 45 (2006) 5659–5661;
(b) B.C.J. van Esseveldt, P.W.H. Vervoort, F.L. van Delft, F.P.J.T. Rutjes, J. Org. Chem. 70 (2005) 1791–1795 (and references therein);
(c) C.L. Jenkins, G. Lin, J. Duo, D. Rapolu, I.A. Guzei, R.T. Raines, G.R. Krow, J. Org. Chem. 69 (2004) 8565–8573 (and references therein);
(d) P. Karoyan, S. Sagan, O. Lequin, J. Quancard, S. Lavielle, G. Chassaing, Targets Heterocycl. Syst. 8 (2004) 216–273;
(e) J.R. Del Valle, M. Goodman, J. Org. Chem. 68 (2003) 3921–3933 (and references therein);
(f) J. Zhang, W. Wang, C. Xiong, V.J. Hruby, Tetrahedron Lett. 44 (2003) 1413–1415.
[2] (a) L. Moroder, C. Renner, J.J. Lopez, M. Mutter, G. Tuchscherer, in: C. Dugave (Ed.), *Cis–trans* Isomerization in Biochemistry, Wiley–VCH, Weinheim, Germany, 2006;
(b) A. Flores-Ortega, A.I. Jiménez, C. Cativiela, C. Nussinov, R. Aleman, J. Casanovas, J. Org. Chem. 73 (2008) 3418–3427 (and references therein);
(c) C. Dugave, L. Demange, Chem. Rev. 103 (2003) 2475–2532.
[3] (a) T. Kitamoto, T. Ozawa, M. Abe, S. Marubayashi, T. Yamazaki, J. Fluorine Chem. 129 (2008) 286–293;
(b) Y. Guo, K. Fujiwara, H. Amii, K. Uneyama, J. Org. Chem. 72 (2007) 8523–8526 (and references therein);
(c) U.E.W. Lange, D. Baucke, W. Hornberger, H. Mack, W. Seitz, H.W. Höffken, Bioorg. Med. Chem. Lett. 16 (2006) 2648–2653;
(d) W. Kim, R.A. McMillan, J.P. Snyder, V.P. Conticello, J. Am. Chem. Soc. 127 (2005) 18121–18132;
(e) W. Kim, K.I. Hardcastle, V.P. Conticello, Angew. Chem. Int. Ed. 45 (2006) 8141–8145.
[4] (a) V.P Kukhar, V.A Soloshonok, Fluorine Containing Amino Acids, Synthesis and Properties, Wiley,, New York, 1995 (and references cited therein);
(b) X.-L. Qui, W.-D. Meng, F.-L. Qing, Tetrahedron 60 (2004) 6711–6745;
(c) M. Molteni, C. Pesenti, M. Sani, A. Volonterio, M. Zanda, J. Fluorine Chem. 125 (2004) 1735–1743.
[5] (a) G. Luppi, D. Lanci, V. Trigari, M. Garavelli, A. Garelli, C. Tomasini, J. Org. Chem. 68 (2003) 1982–1993 (and references therein);
(b) C. Tomasini, M. Villa, Tetrahedron Lett. 42 (2001) 5211–5214.
[6] For literature concerning fluorinated pyroglutamic acids, see:
(a) F.-L. Qing, X.-L. Qiu, Synthesis of fluorinated prolines and pyroglutamic acids, in: V.A. Soloshonok (Ed.), Fluorine Containing Synthons, American Chemical Society, Washington, DC, 2005 , p. 562 (and references therein);
(b) X.-L. Qiu, W.-D. Meng, F.-L. Qing, Tetrahedron 60 (2004) 5201–5206;
(c) X.-L. Qiu, W.-D. Meng, F.-L. Qing, J. Org. Chem. 68 (2003) 3614–3617;
(d) V.A. Soloshonok, C. Cai, V.J. Hruby, L. Van Meervelt, N. Mischenko, Tetrahedron 55 (1999) 12031–12044;
(e) V.A. Soloshonok, C. Cai, V.J. Hruby, L. Van Meervelt, Tetrahedron 55 (1999) 12045–12058;
(f) V.A. Soloshonok, D.V. Avilov, V.P. Kukhar, L. Van Meervelt, N. Mischenko, Tetrahedron Lett. 38 (1997) 4903–4904;
(g) D. Gestmann, A.J. Laurent, E.G. Laurent, J. Fluorine Chem. 80 (1996) 27–30.
[7] α-Tfm-pyroglutamic acid has only been reported in the racemic series: B. Koksch, D. Ullmann, H.-D. Jakubke, K. Burger, J. Fluorine Chem. 80 (1996) 53–57.
[8] (a) F. Huguenot, T. Brigaud, J. Org. Chem. 71 (2006) 7075–7078;
(b) F. Huguenot, T. Brigaud, J. Org. Chem. 71 (2006) 2159–2162;
(c) N. Lebouvier, C. Laroche, F. Huguenot, T. Brigaud, Tetrahedron Lett. 43 (2002) 2827–2830;
(d) T. Brigaud, G. Chaume, J. Pytkowicz, F. Huguenot, Chim. Oggi Chem. Today 25 (2007) 8–10.

[9] G. Chaume, M.-C. Van severen, S. Marinkovic, T. Brigaud, Org. Lett. 8 (2006) 6123–6126.
[10] The formation of similar oxazolidines has already been reported in the non-fluorinated series:
(a) C. Agami, F. Couty, B. Prince, O. Venier, Tetrahedron Lett. 37 (1993) 7061–7062;
(b) L.M. Harwood, K.J. Vines, M.G.B. Drew, Synlett (1996) 1051–1053.
[11] In our previous report (Ref. 9) we observed that the chromatographic separation of both diastereomers of similar bicyclic CF3-morpholinones was very easy.
[12] The synthesis of similar bicyclic lactams has also been reported in the non fluorinated series by an alternative strategy:
L.M. Harwood, G. Hamblett, A.I. Jimenez-Dias, D.J. Watkin, Synlett (1997) 935–938.
[13] R_f of (*R*,*S*)-7 = 0.41 (7:3 cyclohexane/ethyl acetate) and Rf of (*R*,*R*)-7 = 0.29 (7:3 cyclohexane/ethyl acetate).
[14] Crystallographic data (excluding structure factors) for compound (*R*,*S*)-7 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 695212. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44 1223 336033 or email: deposit@ccdc.cam.ac.uk.
[15] G. Tang, H. Tian, D. Ma, Tetrahedron 60 (2004) 10547–10552.
[16] D. Ma, G. Tang, H. Tian, G. Zou, Tetrahedron Lett. 40 (1999) 5753–5756.