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Exploiting morph-DAST mediated ring-expansion of substituted cyclic β-amino alcohols for the preparation of cyclic fluorinated amino acids. Synthesis of 5-fluoromethylproline and 5-fluoropipecolic acid

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ABSTRACT

The synthesis of proline analogues bearing a fluorine-containing substituent at the fifth position of the pyrrolidine ring, racemic *trans*- and *cis*-5-fluoromethyl prolines, was performed. The key step of the synthesis is a transformation of the CH_2OH-group into the CH_2F-one using morpholinosulfur trifluoride. During the synthesis, an efficient procedure to prepare *trans*- and *cis*-5-fluoropipecolic acids was elaborated.

1. Introduction

4-Fluoroprolines and large molecules containing them have gained widespread popularity in the last decades. For example, they were used in the applications, such as biochemical probes, enzyme inhibitors, and enzyme substrates.[1] In particular, they were shown to control cis–trans isomerization of the amide bonds, which is closely related to biologically relevant processes, primarily to protein folding and unfolding.[2] Moreover, proline analogues bearing fluoro-containing substituents at the position 4 of the pyrrolidine ring became very popular within the drug discovery programs (Fig. 1).[3] In part, this is due to a number of the well-documented and well-elaborated synthetic protocols toward such compounds.[4]

Practical applications of prolines with fluorinated substituents at the positions 2[8] and 3[9] of the pyrrolidine ring, however, received much less development, since the first synthetic approaches to these compounds appeared in the literature only recently.

In contrast to the other isomers, chemistry of prolines with fluorine-containing substituents at the position 5 of the pyrrolidine ring attracted almost no attention so far. In only 2010 Brigaud et al. described the synthesis of 5-trifluoromethylpseudoprolines and studied their conformational behavior.[10] Hence, the development

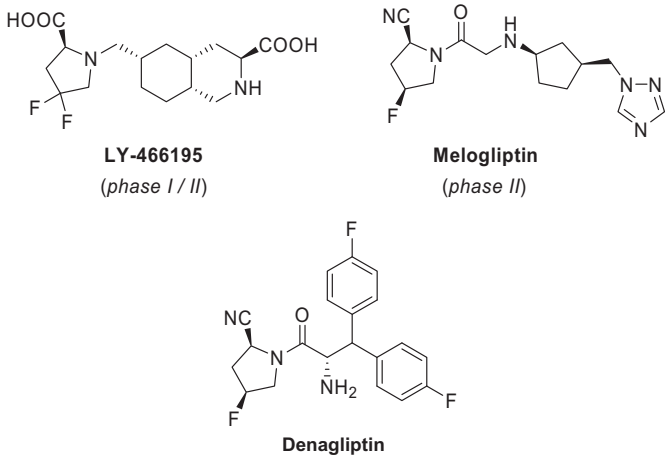

Fig. 1. Some representative pharmacologically relevant derivatives 4-fluoroprolines: LY-466195 (antimigraine, *Eli Lilly*, phase I/II),[5] Melogliptin (dipeptidyl aminopeptidase IV inhibitor, *Glenmark Pharmaceuticals*, phase II),[6] Denagliptin (dipeptidyl aminopeptidase IV inhibitor, *GlaxoSmithKline*).[7]

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of synthetic methodologies for a facile and practical preparation of the prolines, containing fluorinated substituents at the position 5 of the pyrrolidine ring is still a challenge. Our interest in such compounds was additionally stimulated by recent work on the application of fluorinated prolines as the solid state ^{19}F NMR labels to study the membrane active peptides.[11] In this strategy, the both enantiomerically pure and racemic ^{19}F-amino acids are used.[12] In this context, the original aim of this work was to develop a reliable synthetic strategy toward prolines having a common fluorine-containing substituent—CH_2F—at the fifth position: *trans*-(**1a**) and *cis*-5-fluoromethyl prolines (**1b**, Fig. 2).[13]

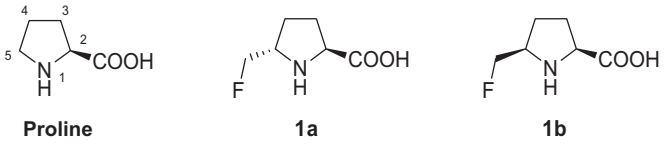
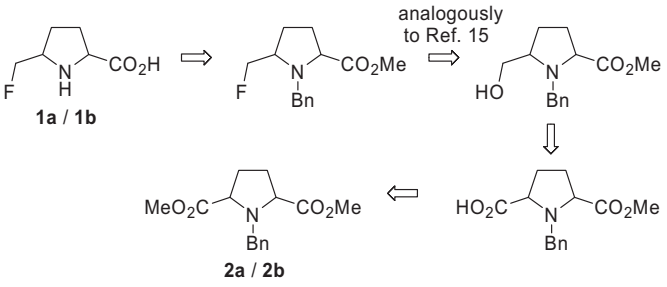


Fig. 2. Proline and its fluorinated analogues: *trans*-5-fluoromethyl proline (**1a**) and *cis*-5-fluoromethyl proline (**1b**).

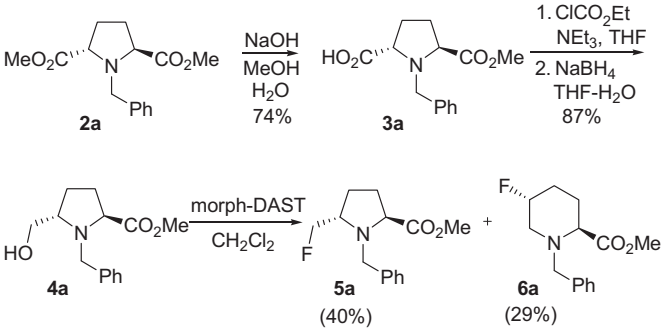
2. Results and discussion

Our retrosynthetic approach to the both **1a** and **1b** was based on *trans*- and *cis*-*N*-benzyl-2,5-dicarbomethoxy pyrrolidines **2a** and **2b** as the starting materials (Scheme 1). The key step of the synthesis—the transformation of the CH_2OH-group into CH_2F-one—was expected to be performed with readily available morpholinosulfur trifluoride (morph-DAST, $O(CH_2CH_2)_2NSF_3$)[14] analogously to the reported literature procedures.[15]



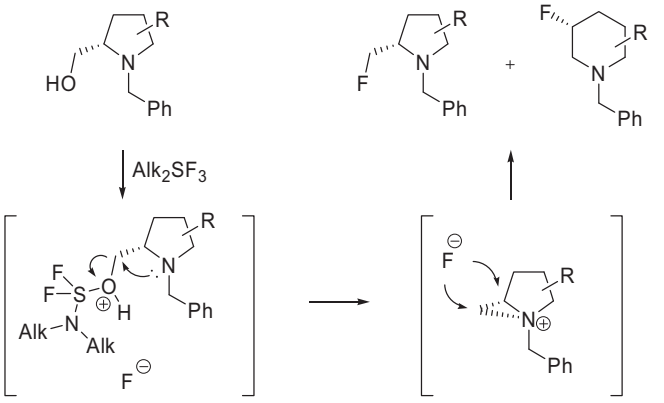
Scheme 1. Retrosynthetic approach to amino acids **1a**, **1b**.

The compounds **2a**/**2b** were readily prepared from dimethyl hexanedioate via a two-step literature protocol.[16] Hydrolysis of *trans*-isomer **2a** with 1 equiv of NaOH in methanol/water mixture at room temperature provided *trans*-monoacid **3a** in a reasonable yield of 74% (Scheme 2).[17]



Scheme 2. Synthesis of compounds **5a**, **6a**.

Next, compound **3a** was treated with EtOCOCl in tetrahydrofuran in the presence of NEt_3 as a base, and the formed activated intermediate was reduced with $NaBH_4$ to give smoothly the corresponding *trans*-alcohol **4a**.[18] The key step of the synthesis—the reaction of hydroxymethyl group in **4a** with $O(CH_2CH_2)_2NSF_3$—unexpectedly resulted in a formation of two compounds: the target pyrrolidine **5a** (40% yield) and the side product **6a** (29% yield). The mixture of compounds **5a**/**6a** was successfully separated by flash column chromatography. After careful revision of the literature,[19] it became clear, that the reaction proceeded via the well-documented formation of the cationic aziridine intermediate (Scheme 3), which underwent ring-opening by a fluorine-anion to give either 2-fluoromethylpyrrolidine derivative or the corresponding 3-fluoropiperidine.

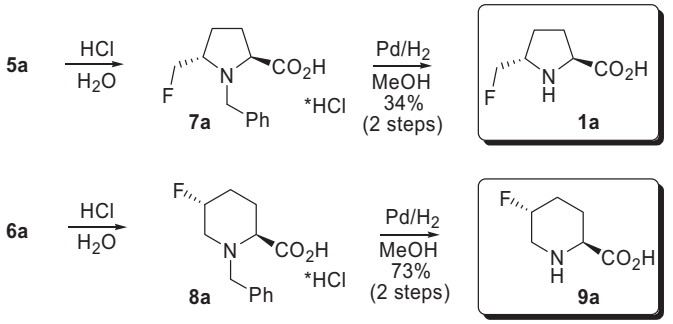


Scheme 3. A mechanism of the reaction of substituted prolinols with DAST-analogues according to Ref. 19.

Indeed, ring-expansion of cyclic β-amino alcohols induced by DAST or DAST-analogues was comprehensively described in the literature before.[19,20] Despite the great potential of this transformation, however, to the very best of our knowledge, it did not find any practical application in the synthesis of 3-fluoropyrrolidine- and 3-fluoropiperidine-containing building blocks so far. Hence, by isolating compound **6a**, we realized that the given reaction could serve as a powerful tool for the preparation of novel fluorinated cyclic amino acids. In particular, it became evident that along with the target amino acid **1a**, the synthesis of *trans*-5-fluoropipecolic acid could be accomplished as well.

Notably, according to the literature data[19] the reaction of various substituted *N*-benzylprolinols with dialkylaminosufhur trifluorides always leads to the corresponding *N*-benzyl-3-fluoropiperidines as the major reaction products. In our hands, however, the rearranged piperidine **6a** was formed as a minor compound. The reason behind that is not clear in full, but definitely, the structure of the corresponding substituent has a valuable impact on the ratio of the reaction products.

Acidic hydrolysis of the CO_2Me group in **5a** provided *N*-benzyl acid **7a**·HCl (Scheme 4). Hydrogenation of pyrrolidine **7a**·HCl using 10% palladium on charcoal as the catalyst followed by a cation-



Scheme 4. Synthesis of *trans*-5-fluoromethyl proline (**1a**) and *trans*-5-fluoropipecolic acid (**9a**).

exchange chromatography on CU-2 resin accomplished the synthesis of the target *trans*-5-fluoromethyl proline (**1a**). Alternatively, *trans*-5-fluoropipecolic acid (**9a**) was conveniently obtained from piperidine **6a** in 73% overall yield. The synthesis of amino acid **9a** was previously described in the literature.[21] However, in stark contrast to our method, the published procedure can scarcely be considered as a practical method for the preparation of **9a**, as the last synthetic step was performed in only 6% yield.[21]

3. Conclusion

In summary, we have performed the synthesis of racemic *trans*-(**1a**) and *cis*-5-fluoromethyl prolines (**1b**). During the synthesis we found an effective strategy for the preparation of cyclic fluorinated amino acids: morph-DAST mediated ring-expansion of the correspondingly substituted cyclic β-amino alcohols. In particular, synthesis of racemic *trans*-(**9a**) and novel *cis*-5-fluoropipecolic acids

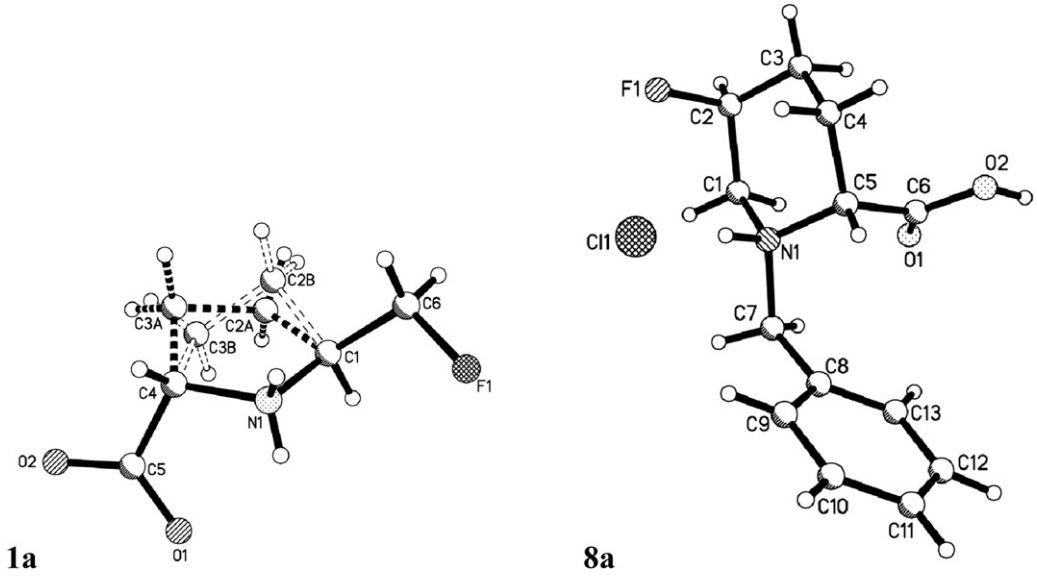


Fig. 3. X-ray crystal structures of the compounds **1a** and **8a**. In crystalline state compound **1a** exists in two conformations.

The structures of the compounds **1a** and **8a** were confirmed by an X-ray diffractional study (Fig. 3).

Contrary to the *trans*-isomer **2a**, hydrolysis of the *cis*-isomer **2b** with 1 equiv of NaOH in MeOH/H_2O did not provide the corresponding monoacid **3b**. Instead, a mixture of the starting compound **2b** and diacid **10** was formed. Presumably, the free COOH group in *cis*-compound **3b** accelerated the saponification of the neighboring carboxymethyl group by an intramolecular interaction.[16b] Therefore, *cis*-monoacid **3b** was prepared from *cis*-diester **2b** by a three-step procedure following the modified literature protocols. First, compound **2b** was treated with 3 equiv of NaOH in water to give after standard work up diacid **10** in 70% yield (Scheme 5).[22] Next, diacid **10** was heated at 100 °C for 10 min with an excess of Ac_2O to afford anhydride **11**.[23] Finally, *cis*-monoacid **3b** was obtained by dissolving compound **11** in absolute MeOH and evaporating the obtained solution.[24] Activation of the carboxyl group in **3b** using EtOCOCl/NEt_3 in THF followed by a reduction of the formed intermediate with $NaBH_4$ at 0 °C gave *cis*-alcohol **4b** in 51% total yield from diacid **10**. Next, alcohol **4b**[25] was reacted with $O(CH_2CH_2)_2NSF_3$ in CH_2Cl_2. Still, the formation of two products—*cis*-pyrrolidine **5b** (44% yield) and *cis*-piperidine **6b** (20% yield)—was observed. The isomers were separated by flash column chromatography. Hydrolysis of the carboxymethyl group in pyrrolidine **5b** using aq HCl gave acid **7b**·HCl. Hydrogenation of the benzyl group in **7b** using 10% Pd/C as the catalyst, followed by a cation-exchange chromatography on CU-2 resin furnished the target *cis*-5-fluoromethyl proline (**1b**). Analogously, the novel amino acid—*cis*-5-fluoropipecolic acid (**9b**)—was prepared from piperidine **6b** in 80% overall yield.

The structures of the compounds **7b** and **9b** were proven by an X-ray diffraction study (Fig. 4).

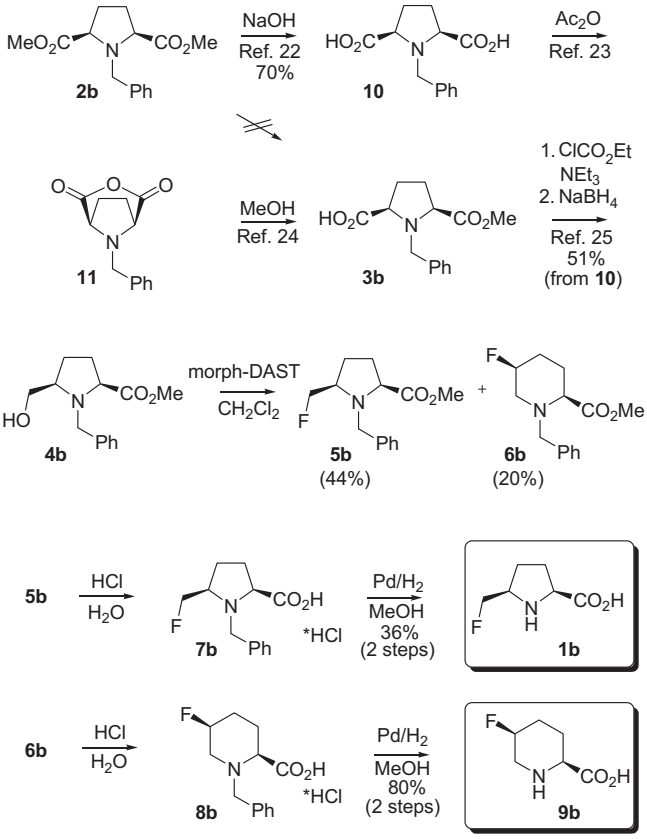
(**9b**) was elaborated. We hope that the discovered strategy will find wide applications in the synthesis of novel 3-fluoropyrrolidine-, 3-fluoropiperidine-, etc.-containing amino acids.

4. Experimental section

4.1. General

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer at 499.9 MHz, 124.9 MHz, and 470.3 MHz, respectively. Chemical shifts are reported in parts per million downfield from TMS (^1H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument by chemical ionization (CI).

*4.1.1. rel-(2S,5S)-1-(Phenylmethyl)-2,5-pyrrolidinedicarboxylic acid, mono-methyl ester (**3a**).* NaOH (0.93 M solution) in water (66.5 mL, 61.9 mmol) was added to a solution of the compound **2a** (17.1 g, 61.9 mmol) in MeOH (80 mL) upon stirring over a period of 30 min. The reaction mixture was stirred for additional 24 h at room temperature. The solvent was evaporated in vacuum and water (200 mL) was added to the residue. The solution was washed with EtOAc (3×50 mL). 12 N aq HCl was added to the water phase to adjust pH value to 5.4. The reaction mixture was extracted with EtOAc (3×100 mL). The combined organic phase was dried over Na_2SO_4, and evaporated in vacuum to give pure **3a** (12.0 g, 45.6 mmol, 74% yield). Yellowish oil. ^1H NMR (500 MHz; DMSO-d_6; Me_4Si), δ: 12.39 (1H, br s, O*H*), 7.29 (5H, m, Ph), 3.93 (1H, d, ^2J(H, H)=13.5 Hz, NC*H*HPh), 3.71 (1H, d, ^2J(H, H)=13.5 Hz, NCH*H*Ph), 3.66 (1H, m, C*H*), 3.59 (4H, m, C*H*+OCH_3), 2.18 (2H, m, CH_2), 1.84 (2H, m,



Scheme 5. Synthesis of *cis*-5-fluoromethyl proline (**1b**) and *cis*-5-fluoropipecolic acid (**9b**).

1 h, water was added, and the mixture was extracted three times with EtOAc (3×100 mL). The organic layer was washed with water (2×100 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give crude product **4a** (2.3 g, 0.009 mmol, 87% yield) as a yellowish oil. The compound was used in the next step without additional purification. ^{1}H NMR (500 MHz; DMSO-d_6; Me_4Si), δ: 7.26 (5H, m, Ph), 4.46 (1H, br s, O*H*), 4.02 (1H, d, ^2J(H, H)=13.5 Hz, NC*H*HPh), 3.67 (1H, d, ^2J(H, H)=13.5 Hz, NCH*H*Ph), 3.58 (3H, s, OCH_3), 3.47 (1H, d, J=7.0, NC*H*CO_2Me), 3.41 (1H, m, NCHC*H*HOH), 3.27 (1H, m, NCHCH*H*OH), 3.17 (1H, br s, NC*H*CH_2OH), 2.01 (2H, m, 3-CH_2), 1.70 (2H, m, 4-CH_2). ^{13}C NMR (125 MHz; DMSO-d_6; Me_4Si), δ: 174.4 (s, CO_2Me), 139.2 (s, quat-*C*, Ph), 128.7 (s, *C*H, Ph), 128.7 (s, *C*H, Ph), 127.5 (s, *C*H, Ph), 63.7 (s, NCHCO_2Me), 62.3 (s, NCHCH_2OH), 53.0 (s, NCH_2Ph), 51.3 (s, OCH_3), 28.8 (s, 3-CH_2), 27.1 (s, 4-CH_2). MS (m/z): 249 (M^+).

*4.1.3. rel-(2S,5S)-5-(Fluoromethyl)-1-(phenylmethyl)-proline, methyl ester (**5a**). 4.1.3.1. rel-(2S,5R)-5-Fluoro-1-(phenylmethyl)-2-piperidine-carboxylic acid, methyl ester (**6a**).* A solution of **4a** (3.55 g, 14.3 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C under argon. Morpho-DAST (2.74 g, 15.7 mmol, 1.1 equiv) was added at once upon stirring. The reaction mixture was allowed to warm to a room temperature and was stirred for 72 h. Thereafter, a saturated solution of $NaHCO_3$ in water (100 mL) was added. The organic layer was separated and the water phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to give the mixture **5a**/**6a** as a yellowish oil. The isomers were separated by flash column chromatography using hexane/EtOAc=18/1 as an eluent. Elution afforded isomer **5a** first (1.43 g, 5.7 mmol, 40%) as a colorless oil. R_f=0.60 (hexane/EtOAc=6/1). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 7.31 (5H, m, Ph), 4.30 (2H, dd, J=48.0, 3.5 Hz, CH_2F), 4.05 (1H, d, ^2J(H, H)=13.5 Hz, NC*H*HPh), 3.85 (1H, d, ^2J(H, H)=13.5 Hz, NCH*H*Ph), 3.69 (4H, br s, OCH_3+NC*H*CH_2F), 2.25 (1H, m, C*H*H), 2.14 (1H, m, CH*H*), 1.78 (2H, m, CH_2). ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si), δ: 174.0 (s, CO_2Me), 139.5 (s, quat-*C*, Ph), 128.5 (s, *C*H, Ph), 128.3 (s, *C*H, Ph), 127.1 (s, *C*H, Ph), 85.5 (d, ^1J(C, F)=170.0 Hz, *C*H_2F), 63.7 (s, *C*HCO_2Me), 61.1 (d, ^2J(C, F)=21.3 Hz, *C*HCH_2F), 53.8 (s, NCH_2Ph), 51.2 (s, OCH_3), 28.3 (s, 3-CH_2), 26.2 (d, ^3J(C, F)=5.0 Hz, 4-CH_2). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −229.50 (td, J(F, H)=45.2, 18.9 Hz, CH_2F). MS (m/z): 251 (M^+). Anal. calcd for $C_{14}H_{18}FNO_2$: C, 66.91; H, 7.22; N, 5.57. Found: C, 67.00; H, 7.47; N, 5.40. Further elution gave isomer **6a** (1.02 g, 4.1 mmol, 29%) as a colorless oil. R_f=0.55 (hexane/EtOAc=6/1). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 7.29 (5H, m, Ph), 4.71 (1H, d, ^2J(H, F)=48.0 Hz, C*H*F), 3.84 (1H, d, ^2J(H, H)=14.0 Hz, NC*H*HPh), 3.75 (s, OCH_3), 3.64 (1H, d, ^2J(H, H)=14.0 Hz, NCH*H*Ph), 3.37 (1H, t, ^3J(H, H)=5.0 Hz, NC*H*CO_2Me), 3.25 (1H, ddd, J=28.5, 12.0, 2.0 Hz, NC*H*H),

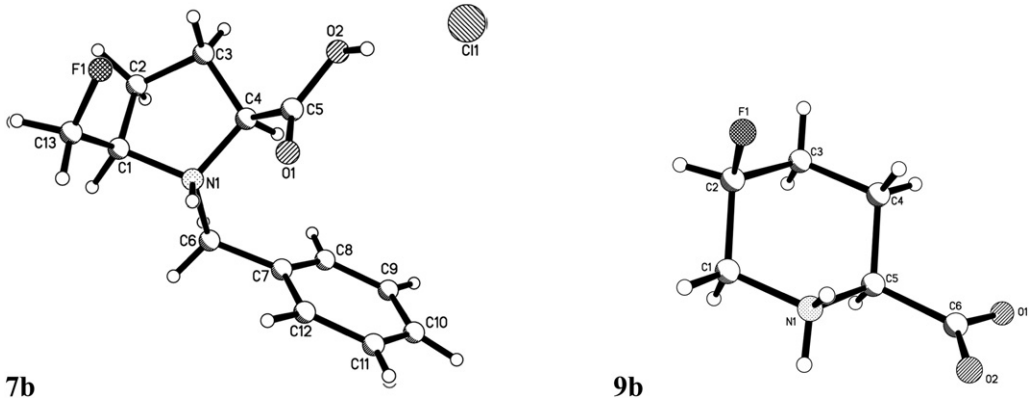


Fig. 4. X-ray crystal structures of the compounds **7b** and **9b**.

2.60 (1H, td, *J*=11.5, 5.5 Hz, NCH*H*), 2.19 (1H, m, C*H*H), 1.84 (3H, m, CH*H*+C*H*$_2$). ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si), δ: 173.2 (s, *C*O$_2$Me), 137.8 (s, quat-*C*, Ph), 129.1 (s, *C*H, Ph), 128.5 (s, *C*H, Ph), 127.4 (s, *C*H, Ph), 87.4 (d, ^1J(C, F)=171.0 Hz, *C*HF), 61.7 (s, *C*HCO$_2$Me), 59.9 (s, NCH$_2$Ph), 52.8 (d, ^2J(C, F)=23.0 Hz, *C*H$_2$CHF), 51.7 (s, OCH$_3$), 27.4 (d, ^2J (C, F)=20.0 Hz, 4-*C*H$_2$), 24.5 (d, ^3J(C, F)=5.0 Hz, 3-*C*H$_2$). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −188.43 (m, CH*F*). MS (*m*/*z*): 251 (M^+). Anal. calcd for $C_{14}H_{18}FNO_2$: C, 66.91; H, 7.22; N, 5.57. Found: C, 67.11; H, 7.41; N, 5.76.

*4.1.4. rel-(2S,5S)-5-(Fluoromethyl)-1-(phenylmethyl)-proline, hydrochloride (**7a**).* A suspension of **5a** (200 mg, 0.8 mmol) in 6 M aq HCl (10 mL) was heated at reflux for 3 h. The solution was evaporated in vacuum to give crude **7a**·HCl as a brown oil, which solidifies upon standing. The compound was used in the next step without additional purification. ^{1}H NMR (500 MHz; D_2O; Me_4Si), δ: 7.40 (5H, m, Ph), 4.97 (0.5H, d, *J*=12.0 Hz, C*H*HF), 4.85–4.75 (1.5H, m, C*H*HF+CH*H*F), 4.62 (1H, d, ^2J(H, H)=12.5 Hz, NC*H*HPh), 4.37 (1H, d, ^2J(H, H)=12.5 Hz, NCH*H*Ph), 4.28 (2H, m, C*H*CO$_2$H+NC*H*CH$_2$F), 2.46 (1H, m, C*H*H), 2.25 (1H, m, CH*H*), 2.09 (2H, m, CH$_2$). ^{13}C NMR (125 MHz; D_2O; Me_4Si), δ: 171.5 (s, *C*O$_2$H), 130.8 (s, *C*H, Ph), 130.4 (s, *C*H, Ph), 129.5 (s, *C*H, Ph), 129.3 (s, quat-*C*, Ph), 80.0 (d, ^1J(C, F)=170.0 Hz, *C*H$_2$F), 66.3 (d, ^2J(C, F)=17.5 Hz, *C*HCH$_2$F), 66.0 (s, *C*HCO$_2$H), 55.8 (s, NCH$_2$Ph), 27.4 (s, 3-*C*H$_2$), 24.7 (d, ^3J(C, F)=4.5 Hz, 4-*C*H$_2$). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −1.46 (td, *J*(F, H)=49.0, 22.6 Hz, CH$_2$*F*). Anal. calcd for $C_{13}H_{17}ClFNO_2$: C, 57.04; H, 6.26; N, 5.12. Found: C, 57.33; H, 6.51; N, 5.41.

*4.1.5. rel-(2S,5S)-5-(Fluoromethyl)-proline (**1a**).* All amount of **7a**·HCl obtained in the previous step was dissolved in MeOH (10 mL) and was hydrogenated at room temperature at 60 atm for 12 h using 10% palladium on charcoal (10 mg) as the catalyst. The solution was filtered, and the filtrate was evaporated in vacuum to give the residue, which was purified by cation-exchange chromatography on CU-2 resin. Elution with water and then with aq NH_3 (10%) afforded **1a** (40 mg, 34% yield after two steps from **5a**). ^{1}H NMR (400 MHz; D_2O; Me_4Si), δ: 4.95–4.75 (0.5H, the signal is hidden under the signal of solvent, C*H*HF), 4.67 (0.5H+0.5H, m, C*H*HF+CH*H*F), 4.17 (1H, t, ^3J(H, H)=8.0 Hz, C*H*CO$_2$H), 4.55 (0.5H, dd, *J*=11.2, 6.4 Hz, C*H*HF), 4.09 (1H, m, NC*H*CH$_2$F), 2.41 (1H, m, 4-C*H*H), 2.17 (1H, m, 4-CH*H*), 2.05 (1H, dt, *J*=20.6, 8.0 Hz, 3-C*H*H), 1.91 (1H, dt, *J*=20.6, 8.0 Hz, 3-CH*H*). ^{13}C NMR (125 MHz; D_2O; Me_4Si), δ: 174.1 (s, *C*O$_2$H), 81.2 (d, ^1J(C, F)=167.5 Hz, *C*H$_2$F), 62.0 (s, *C*HCO$_2$H), 59.8 (d, ^2J(C, F)=18.8 Hz, *C*HCH$_2$F), 28.7 (s, 3-*C*H$_2$), 25.3 (d, ^3J(C, F)=6.3 Hz, 4-*C*H$_2$). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −226.28 (td, *J*(F, H)=49.0, 22.6 Hz, CH$_2$*F*). MS (*m*/*z*): 147 (M^+). Anal. calcd for $C_6H_{10}FNO_2$: C, 48.97; H, 6.85; N, 9.52. Found: C, 48.71; H, 6.50; N, 9.81. Crystals suitable for X-ray crystallographic analysis were obtained by a slow evaporation of a diluted solution of **1a** in water.

*4.1.6. rel-(2S,5R)-5-Fluoro-1-(phenylmethyl)-2-piperidinecarboxylic acid, hydrochloride (**8a**).* A suspension of **6a** (100 mg, 0.8 mmol) in 6 M aq HCl (7 mL) was heated at reflux for 3 h. The solution was evaporated under vacuum to give crude **8a**·HCl as a white solid. The compound was used in the next step without additional purification. ^{1}H NMR (400 MHz; DMSO-d_6; Me_4Si), δ: 7.59 (2H, s, Ph), 7.46 (3H, s, Ph), 5.05 (1H, d, ^2J(H, F)=46.8 Hz, C*H*F), 4.52 (1H, d, ^2J (H, H)=12.8 Hz, NC*H*HPh), 4.38 (1H, d, ^2J(H, H)=12.8 Hz, NCH*H*Ph), 4.07 (1H, br s, NC*H*CO$_2$H), 3.55 (1H, br s, NC*H*H), 3.20 (1H, br s, NCH*H*), 2.34 (1H, m, C*H*H), 1.92 (3H, m, CH*H*+C*H*$_2$). ^{13}C NMR (100 MHz; CD_3OD; Me_4Si), δ: 167.3 (s, *C*O$_2$H), 129.6 (s, *C*H, Ph), 128.6 (s, *C*H, Ph), 127.5 (s, *C*H, Ph), 126.9 (s, quat-*C*, Ph), 81.4 (d, ^1J(C, F)=172.5 Hz, *C*HF), 57.9 (s, *C*HCO$_2$Me), 57.7 (s, NCH$_2$Ph), 49.5 (d, ^2J (C, F)=25.0 Hz, *C*H$_2$CHF), 23.4 (br s, 4-*C*H$_2$), 19.8 (s, 3-*C*H$_2$). ^{19}F NMR (377 MHz; DMSO-d_6; C_6F_6), δ: −182.34 (m, CH*F*). Anal. calcd for $C_{13}H_{17}ClFNO_2$: C, 57.04; H, 6.26; N, 5.12. Found: C, 57.21; H, 6.57; N, 5.43. Crystals suitable for X-ray crystallographic analysis were obtained by a slow evaporation of a diluted solution of **8a**·HCl in MeOH.

*4.1.7. rel-(2S,5R)-5-Fluoro-2-piperidinecarboxylic acid (**9a**).* All amount of **8a**·HCl obtained in the previous step was dissolved in MeOH (7 mL) and was hydrogenated at room temperature at 60 atm for 12 h using 10% palladium on charcoal (10 mg) as the catalyst. The solution was filtered, and the filtrate was evaporated in vacuum to give the residue, which was purified by cation-exchange chromatography on CU-2 resin. Elution with water and then with aq NH_3 (10%) afforded **9a** (43 mg, 73% yield after two steps from **6a**) as a colorless solid. ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 5.02 (1H, dm, ^2J(H, F)=45.6 Hz, C*H*F), 3.95 (1H, t, ^3J(H, H)=5.0 Hz, NC*H*CO$_2$H), 3.61 (1H, ddd, *J*=31.6, 13.6, 2.0 Hz, NC*H*H), 3.37 (1H, m, NCH*H*), 2.25 (1H, m, C*H*H), 2.05 (2H, m, C*H*$_2$), 1.74 (1H, m, CH*H*). ^{13}C NMR (125 MHz; D_2O; Me_4Si), δ: 172.8 (s, *C*O$_2$H), 85.1 (d, ^1J(C, F)=167.5 Hz, *C*HF), 56.2 (s, *C*HCO$_2$H), 44.2 (d, ^2J(C, F)=23.8 Hz, NC*H*$_2$CHF), 24.9 (d, ^2J(C, F)=20.0 Hz, 4-*C*H$_2$), 20.0 (d, ^3J(C, F)=5.0 Hz, 3-*C*H$_2$). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −188.80 (m, CH*F*). MS (*m*/*z*): 147 (M^+). Anal. calcd for $C_6H_{10}FNO_2$: C, 48.97; H, 6.85; N, 9.52. Found: C, 48.62; H, 6.47; N, 9.87.

*4.1.8. rel-(2S,5R)-1-(Phenylmethyl)-2,5-pyrrolidinedicarboxylic acid (**10**).* We used a slightly modified procedure to that reported previously in Ref 15. The authors hydrolyzed the mixture **2a**/**2b** with NaOH to provide diacid **10** in 68% yield.

NaOH (0.93 M solution) in water (66.5 mL, 61.9 mmol) was added to a solution of the compound **2b** (5.7 g, 20.6 mmol) in MeOH (80 mL) upon stirring over a period of 30 min. The reaction mixture was stirred for additional 24 h at room temperature. The solvent was evaporated in vacuum and water (50 mL) was added to the residue. The solution was washed with EtOAc (3×50 mL). 12 M aq HCl was added to the water phase to adjust pH value to 2.0. The reaction mixture was left in refrigerator at 0 °C for 12 h. The precipitate was filtered off and dried on air to give pure **10** (3.6 g, 14.2 mmol, 70% yield).

*4.1.9. rel-(2S,5R)-1-(Phenylmethyl)-2,5-pyrrolidinedicarboxylic acid, mono-merthyl ester (**3b**).* The synthesis of **11** was performed from **10** according to Ref 23. Compound **3b** was obtained from **11** according to Ref 24.

*4.1.10. rel-(2S,5R)-5-(Hydroxymethyl)-1-(phenylmethyl)-2-pyrrolidinecarbo-xylic acid (**4b**).* Compound **4b** has been prepared from **3b** following the Ref 25. Compound **4b** was obtained in 51% overall yield from diacid **10**.

*4.1.11. rel-(2S,5R)-5-(Fluoromethyl)-1-(phenylmethyl)-proline, methyl ester (**5b**). 4.1.11.1. rel-(2S,5S)-5-Fluoro-1-(phenylmethyl)-2-piperidinecarboxylic acid, methyl ester (**6b**).* A solution of **4b** (1.76 g, 10.0 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C under argon atmosphere. Morpho-DAST (2.74 g, 11.1 mmol, 1.1 equiv) was added at once upon stirring. The reaction mixture was allowed to warm to a room temperature and was stirred for 72 h. Thereafter, a saturated solution of $NaHCO_3$ in water (80 mL) was added. The organic layer was separated and the water phase was extracted with CH_2Cl_2 (2×40 mL). The combined organic phases were dried over Na_2SO_4, and evaporated under vacuum to give the mixture **5b**/**6b** as a yellowish oil. The isomers were separated by flash column chromatography using hexane/EtOAc=15/1 as an eluent. Elution afforded **6b** first (0.51 g, 2.0 mmol, 20%) as colorless oil. R_f=0.30 (hexane/EtOAc=15/1). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 7.32 (5H, m, Ph), 4.62 (1H, d, ^2J(H, F)=48.5 Hz, C*H*F), 3.87 (1H, d, ^2J(H, H)=10.8 Hz, NC*H*HPh), 3.77 (s, OC*H*$_3$), 3.74 (1H, d, ^2J(H, H)=10.8 Hz, NCH*H*Ph), 3.37 (1H, dd, ^3J(H, H)=7.5, 5.0 Hz, NC*H*CO$_2$Me), 3.25 (1H, dt, *J*=11.0,

7.0 Hz, NC*H*H), 2.76 (1H, td, *J*=11.0, 2.0 Hz, NCH*H*), 2.16 (1H, ddd, *J*=20.5, 8.5, 3.5 Hz, C*H*H), 1.93 (1H, m, CH*H*), 1.84 (1H, m, C*H*H), 1.73 (1H, m, CH*H*). ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si), δ: 173.1 (s, *C*O_2Me), 138.1 (s, quat-*C*, Ph), 128.8 (s, *C*H, Ph), 128.3 (s, *C*H, Ph), 127.3 (s, *C*H, Ph), 87.2 (d, ^1J(C, F)=172.5 Hz, *C*HF), 60.6 (s, *C*HCO$_2$Me), 59.6 (s, NCH_2Ph), 52.1 (d, ^2J(C, F)=23.8 Hz, *C*H_2CHF), 51.4 (s, OCH_3), 27.7 (d, ^2J(C, F)=20.0 Hz, 4-*C*H_2), 25.4 (d, ^3J(C, F)=8.8 Hz, 3-*C*H_2). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −186.57 (dm, ^2J(F, H)=49.0 Hz, CH*F*). MS (*m*/*z*): 251 (M^+). Anal. calcd for $C_{14}H_{18}FNO_2$: C, 66.91; H, 7.22; N, 5.57. Found: C, 67.21; H, 7.20; N, 5.31. Further elution gave isomer **5b** (1.10 g, 4.4 mmol, 44%) as a colorless oil. R_f=0.25 (hexane/EtOAc=15/1). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 7.31 (5H, m, Ph), 4.31–4.14 (2H, dddd, *J*=47.5, 22.5, 8.5, 5.5 Hz, CH_2F), 3.92 (2H, s, NCH_2Ph), 3.58 (3H, s, OCH_3), 3.48 (1H, t, ^3J(H, H)=8.0 Hz, NC*H*CO$_2$Me), 3.20 (1H, m, NC*H*CH$_2$F), 2.07 (1H, m, C*H*H), 1.96 (2H, m, CH_2), 1.81 (1H, m, CH*H*). ^{13}C NMR (125 MHz; $CDCl_3$; Me_4Si), δ: 174.5 (s, *C*O_2Me), 138.3 (s, quat-*C*, Ph), 129.3 (s, *C*H, Ph), 128.2 (s, *C*H, Ph), 127.3 (s, *C*H, Ph), 86.3 (d, ^1J(C, F)=170.0 Hz, *C*H_2F), 66.7 (s, *C*HCO$_2$Me), 63.1 (d, ^2J(C, F)=22.5 Hz, *C*HCH$_2$F), 58.7 (s, NCH_2Ph), 51.7 (s, OCH_3), 28.6 (s, 3-*C*H_2), 27.2 (d, ^3J(C, F)=3.8 Hz, 4-*C*H_2). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −224.57 (td, *J*(F, H)=45.2, 11.3 Hz, CH$_2$*F*). MS (*m*/*z*): 251 (M^+). Anal. calcd for $C_{14}H_{18}FNO_2$: C, 66.91; H, 7.22; N, 5.57. Found: C, 66.69; H, 6.88; N, 5.31.

*4.1.12. rel-(2S,5R)-5-(Fluoromethyl)-1-(phenylmethyl)-proline hydrochloride (**7b**).* A suspension of **5b** (200 mg, 0.8 mmol) in 6 M aq HCl (10 mL) was heated at reflux for 3 h. The solution was evaporated in vacuum to give crude **7b**·HCl as a brown solid. The compound was used in the next step without additional purification. ^{1}H NMR (500 MHz; D_2O; Me_4Si), δ: 7.46 (5H, m, Ph), 4.77–4.68 (2H, m, CH_2F), 4.65 (1H, d, ^2J(H, H)=13.0 Hz, NC*H*HPh), 4.44 (1H, d, ^2J(H, H)=13.0 Hz, NCH*H*Ph), 4.29 (1H, dd, *J*=9.0, 5.5 Hz, C*H*CO$_2$H), 4.10 (1H, m, NC*H*CH$_2$F), 2.38 (1H, m, C*H*H), 2.22 (1H, m, CH*H*), 2.11 (1H, m, C*H*H), 1.90 (1H, m, CH*H*). ^{13}C NMR (125 MHz; D_2O; Me_4Si), δ: 171.4 (s, *C*O_2H), 131.3 (s, *C*H, Ph), 130.5 (s, *C*H, Ph), 129.5 (s, *C*H, Ph), 128.8 (s, quat-*C*, Ph), 80.7 (d, ^1J(C, F)=170.0 Hz, *C*H_2F), 68.3 (d, ^2J(C, F)=17.5 Hz, *C*HCH$_2$F), 67.7 (s, *C*HCO$_2$H), 58.7 (s, NCH_2Ph), 27.5 (s, 3-*C*H_2), 24.7 (d, ^3J(C, F)=6.3 Hz, 4-*C*H_2). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −225.87 (td, *J*(F, H)=49.0, 22.6 Hz, CH$_2$*F*). Anal. calcd for $C_{13}H_{17}ClFNO_2$: C, 57.04; H, 6.26; N, 5.12. Found: C, 56.82; H, 6.02; N, 5.20. Crystals of **7b**·HCl, suitable for X-ray diffractional study, were obtained by a slow evaporation of a diluted solution of **7b**·HCl in MeOH.

*4.1.13. rel-(2S,5R)-5-(Fluoromethyl)-proline (**1b**).* All amount of **7b**·HCl obtained in the previous step was dissolved in MeOH (10 mL) and was hydrogenated at room temperature at 60 atm for 12 h using 10% palladium on charcoal (10 mg) as the catalyst. The solution was filtered, and the filtrate was evaporated in vacuum to give the residue, which was purified by cation-exchange chromatography on CU-2 resin. Elution with water and then with aq NH_3 (10%) afforded **1b** (42 mg, 36% yield after two steps from **5b**). ^{1}H NMR (500 MHz; D_2O; Me_4Si), δ: 4.76 (0.5H, dd, *J*=11.0, 3.0 Hz, C*H*HF), 4.73–4.61 (0.5H+0.5H, the signals are hidden within the signal of solvent, C*H*HF+CH*H*F), 4.55 (0.5H+0.5H, dd, *J*=11.0, 6.5 Hz, C*H*HF+CH*H*F), 4.13 (1H, dd, *J*=8.5, 4.5 Hz, C*H*CO$_2$H), 3.94 (1H, m, NC*H*CH$_2$F), 2.26 (1H, m, C*H*H), 2.10 (2H, m, CH_2), 1.71 (1H, m, C*H*H). ^{13}C NMR (125 MHz; D_2O; Me_4Si), δ: 174.2 (s, *C*O_2H), 81.5 (d, ^1J(C, F)=168.8 Hz, *C*H_2F), 61.8 (s, *C*HCO$_2$H), 60.3 (d, ^2J(C, F)=18.8 Hz, *C*HCH$_2$F), 28.4 (s, 3-*C*H_2), 24.6 (d, ^3J(C, F)=6.3 Hz, 4-*C*H_2). ^{19}F NMR (377 MHz; D_2O; $CFCl_3$), δ: −224.67 (td, *J*(F, H)=45.2, 18.9 Hz, CH$_2$*F*). MS (*m*/*z*): 147 (M^+). Anal. calcd for $C_6H_{10}FNO_2$: C, 48.97; H, 6.85; N, 9.52. Found: C, 49.21; H, 6.46; N, 9.55.

*4.1.14. rel-(2S,5R)-5-Fluoro-1-(phenylmethyl)-2-piperidinecarboxylic acid, hydrochloride (**8b**).* A suspension of **6b** (100 mg, 0.8 mmol) in 6 M aq HCl (7 mL) was heated at reflux for 3 h. The solution was evaporated in vacuum to give crude **8b**·HCl as a white solid. The compound was used in the next step without additional purification. ^{1}H NMR (400 MHz; DMSO-d_6; Me_4Si), δ: 7.48 (5H, s, Ph), 5.03 (1H, d, ^2J(H, F)=44.8 Hz, C*H*F), 4.53 (1H, d, ^2J(H, H)=13.2 Hz, NC*H*HPh), 4.30 (1H, d, ^2J(H, H)=13.2 Hz, NCH*H*Ph), 3.92 (1H, br s, NC*H*CO$_2$H), 3.68 (1H, t, *J*=10.4 Hz, NC*H*H), 3.20 (1H, t, *J*=40.0, 10.4 Hz, NCH*H*), 2.18 (3H, m, C*H*H+CH_2), 1.78 (1H, m, CH*H*). ^{13}C NMR (100 MHz; DMSO-d_6; Me_4Si), δ: 171.3 (s, *C*O_2H), 132.0 (s, *C*H, Ph), 130.6 (s, *C*H, Ph), 129.3 (s, *C*H, Ph), 127.3 (s, quat-*C*, Ph), 84.7 (d, ^1J(C, F)=170.0 Hz, *C*HF), 63.9 (s, *C*HCO$_2$Me), 59.9 (s, NCH_2Ph), 53.1 (br s, NCH_2CHF), 25.5 (d, ^2J(C, F)=17.0 Hz, 4-*C*H_2), 22.6 (s, 3-*C*H_2). ^{19}F NMR (377 MHz; DMSO-d_6; $CFCl_3$), δ: −187.12 (m, CH*F*). Anal. calcd for $C_{13}H_{17}ClFNO_2$: C, 57.04; H, 6.26; N, 5.12. Found: C, 57.10; H, 6.35; N, 5.01.

*4.1.15. rel-(2S,5S)-5-Fluoro-2-piperidinecarboxylic acid (**9b**).* All amount of **8b**·HCl obtained in the previous step was dissolved in MeOH (7 mL) and was hydrogenated at room temperature at 60 atm for 12 h using 10% palladium on charcoal (10 mg) as the catalyst. The solution was filtered, and the filtrate was evaporated in vacuum to give the residue, which was purified by cation-exchange chromatography on CU-2 resin. Elution with water and then with aq NH_3 (10%) afforded **9b** (47 mg, 80% yield after two steps from **6a**). ^{1}H NMR (500 MHz; $CDCl_3$; Me_4Si), δ: 5.02 (1H, d, ^2J(H, F)=45.5 Hz, C*H*F), 3.57 (2H, m, NC*H*H+NC*H*CO$_2$H), 3.19 (1H, dd, *J*=40.6, 14.5 Hz, NCH*H*), 2.14 (2H, m, CH_2), 1.79 (2H, m, CH_2). ^{13}C NMR (125 MHz; D_2O; Me_4Si), δ: 173.7 (s, *C*O_2H), 85.0 (d, ^1J(C, F)=168.8 Hz, *C*HF), 58.4 (s, *C*HCO$_2$H), 46.3 (d, ^2J(C, F)=21.1 Hz, NCH_2CH$_2$F), 26.8 (d, ^2J(C, F)=20.0 Hz, 4-*C*H_2), 21.0 (s, 3-*C*H_2). ^{19}F NMR (377 MHz; $CDCl_3$; $CFCl_3$), δ: −226.28 (dtm, *J*(F, H)=33.9, 41.5 Hz, CH*F*). MS (*m*/*z*): 147 (M^+). Anal. calcd for $C_6H_{10}FNO_2$: C, 48.97; H, 6.85; N, 9.52. Found: C, 48.59; H, 6.63; N, 9.35. Crystals of **9b**, suitable for X-ray directional study, were obtained by a slow evaporation of a diluted solution of **9b** in water.

Supplementary data

Crystallographic data for the compounds **1a**, **8a**, **7b**, **9b**, structure description and full spectroscopic data for all new compounds. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.082.

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