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Synthesis of Fluorinated Piperidine and Azepane β-Amino Acid Derivatives

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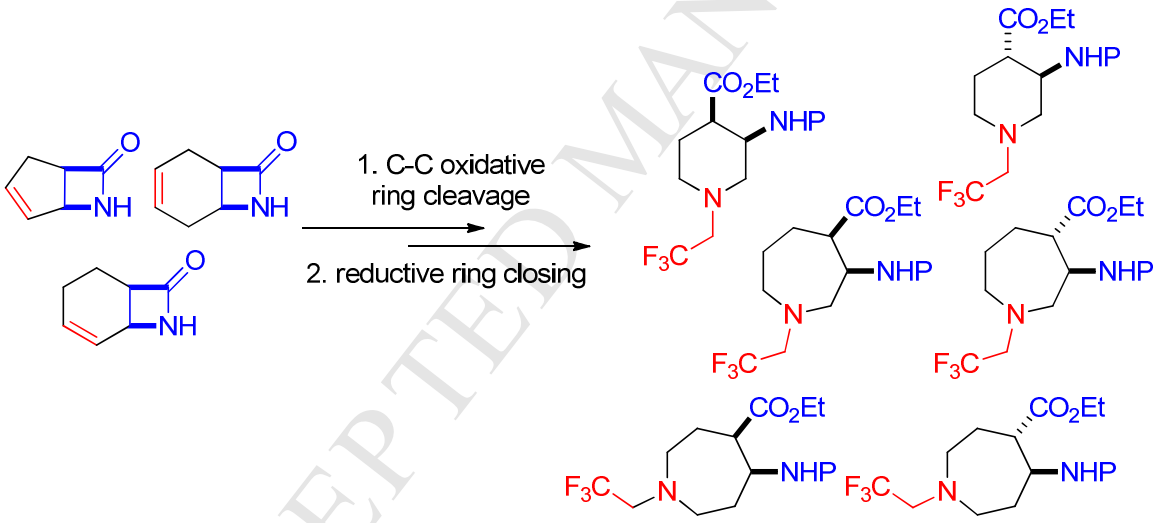
Graphical abstract:



Abstract:

A convenient and robust stereocontrolled procedure has been developed for the synthesis of novel trifluoromethyl-containing piperidine and azepane β-amino ester stereoisomers. The synthesis started from readily available unsaturated bicyclic β-lactams and was based on oxidative cleavage of the ring C=C double bond followed by ring closure of the diformyl intermediates in the presence of 2,2,2-trifluoroethylamine hydrochloride through reductive amination. The synthetic procedure has efficiently been extended towards the synthesis of mono- and difluorinated analogs.

Keywords: stereocontrol, fluorine, azaheterocycle, amino acid, reductive amination, ring closing

Introduction

N-Heterocyclic β-amino acids constitute an important class of derivatives in pharmaceutical and organic chemistry with high biological potential. For example, several piperidine, pyrrolidine or *N*-bridged β-amino acid derivatives exhibit antiviral or antibacterial activities (Figure 1, **1**-**3**).[1]

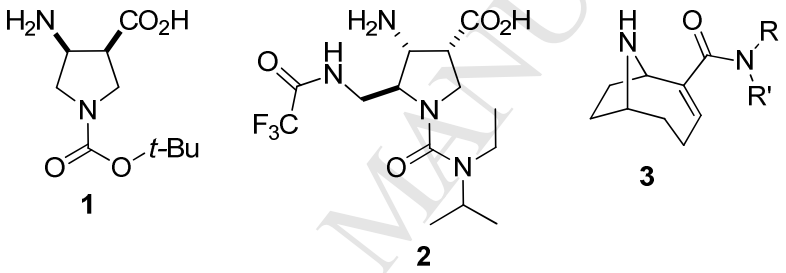


Figure 1. Some *N*-heterocyclic β-amino acids with biological relevance.

Fluorinated molecules have gained increasing attention in the area of pharmaceuticals and agrochemicals over the past decade.[2] Among a significant number of fluorinated biomolecules, a series of fluorine-containing acyclic α- and β-amino acids exhibit antitumoral or antibiotic properties.[3] Molecules containing the β-fluorinated or β-trifluorinated amine units are important scaffolds in medicinal chemistry or agrochemistry.[2a,4] Thus, fluorine-containing pyrrolidines and piperidines, which are present in drugs such as MK-0657, MK-0731 and neceprevir, are of great interest in medicinal chemistry.[5] Fluorine-containing azepanes, in turn, are relatively less reported in the literature. However, because of the important role of various functionalized counterparts in pharmaceutical design, they may receive increasing attention in

the future.[6] Fluorine-containing tetrahydroisoquinoline derivatives, *N*-bridged bicyclic scaffolds and other *N*-fluoroalkylated molecular entities are known to have high biologically relevance.[7] β-Fluoramine or trifluoroamine motifs are also present in various fluorine-containing amino acid derivatives of biological importance (Figure 2).[8]

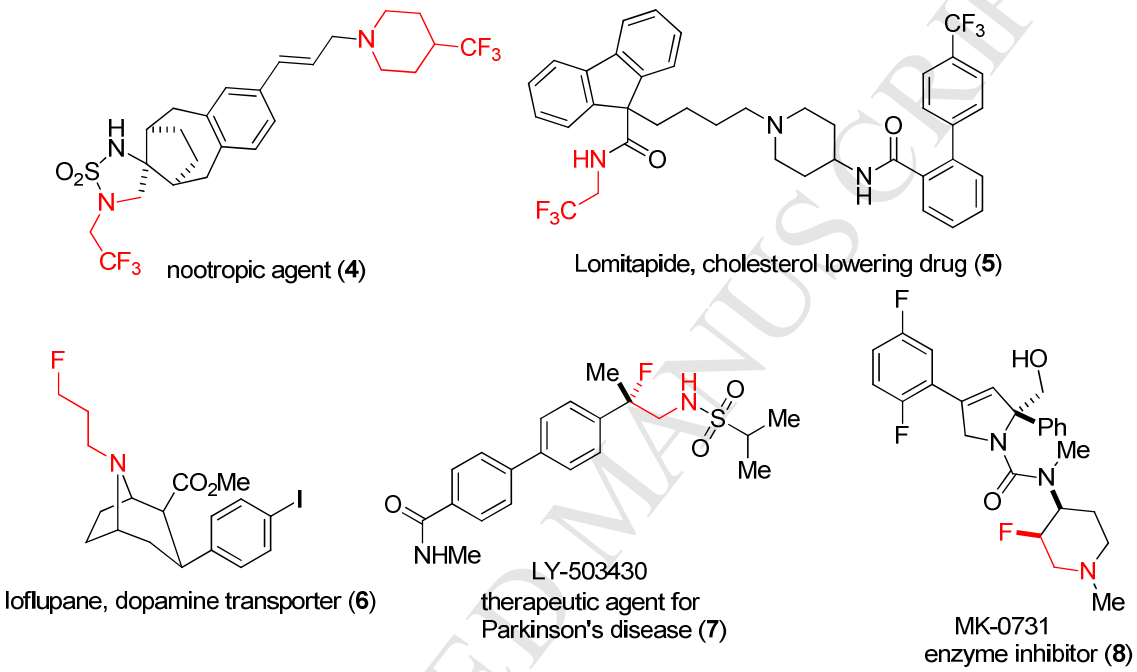


Figure 2. Related molecules with fluoroamine or trifluoroamine element.

Fluorinated saturated *N*-heterocycles are of special interest, since introduction of fluorine into the structure of an azaheterocycle may increase lipophilicity and metabolic stability. In addition, fluorine substitution may reduce basicity thereby providing better bioavailability to a certain molecule.

Results and Discussion

Taking into consideration the high biorelevance of saturated *N*-heterocycles, β-amino acids and organofluorine scaffolds, our present aim was to combine these molecular structures.

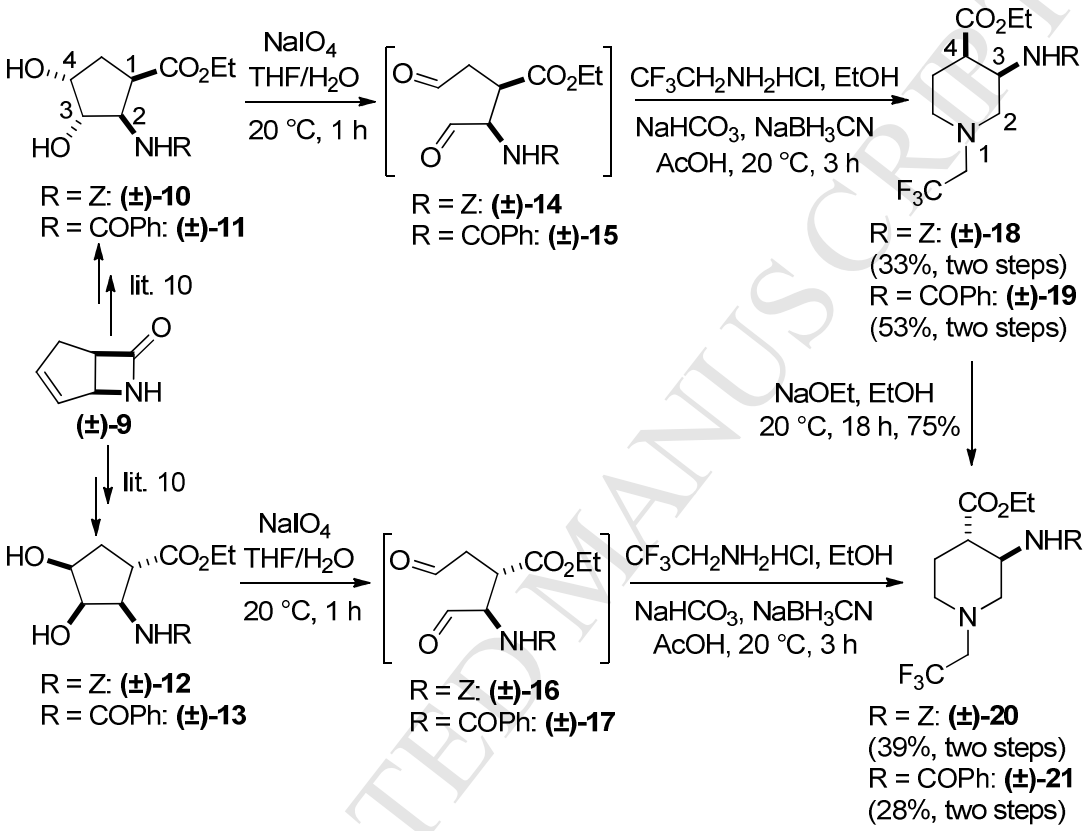
The actual work has been directed towards the stereocontrolled access of novel fluorine-containing six- or seven membered *N*-heterocyclic β-amino acid derivatives.

The synthetic concept included the use of a commercially available reagent, containing the trifluoromethyl group, and was based on the oxidative ring cleavage of unsaturated cyclic β-amino esters, followed through ring closure by reductive amination resulting in ring expansion of the diformyl intermediates.[9]

First, unsaturated bicyclic β-lactam **(±)-9** was transformed to dihydroxylated *cis* amino esters **(±)-10** and **(±)-11** by lactam ring opening with ethanolysis followed by *N*-protection and *cis*-dihydroxylation.[10] The products subjected to oxidative ring cleavage in the presence of $NaIO_4$ in THF/H_2O gave the corresponding open chain diformyl amino esters **(±)-14** and **(±)-15**. These unstable dialdehyde derivatives were further used in the next step without isolation. Upon treatment with the commercially available 2,2,2-trifluoroethylamine hydrochloride in EtOH, in the presence of $NaHCO_3$ and $NaBH_3CN$, ring closure involving reductive amination took place. (Scheme 1).

Since the stereocenters at C-1 and C-2 of amino esters **(±)-10** and **(±)-11** were not affected during the ring expansion procedure, the configuration of the chiral centers in **(±)-18** and **(±)-19** are predetermined by the structure of the starting materials (also assigned on the basis of NMR analysis). Consequently, the *cis* amino ester afforded the corresponding piperidine derivative with the carboxylate and carbamate/amide functions in a *cis* relative arrangement. Analogously, dihydroxylated amino esters **(±)-12** and **(±)-13** (derived from lactam **(±)-9** by ring opening, epimerization at C-1 and *cis*-dihydroxylation)[10] with the ester and the *N*-protected group in a *trans* relationship were submitted to oxidative ring opening with $NaIO_4$. The resulting unstable diformyl intermediates **(±)-16** and **(±)-17** again, without isolation, were reacted with 2,2,2-trifluoroethylamine and $NaBH_3CN$ to afford *trans* trifluoromethylated

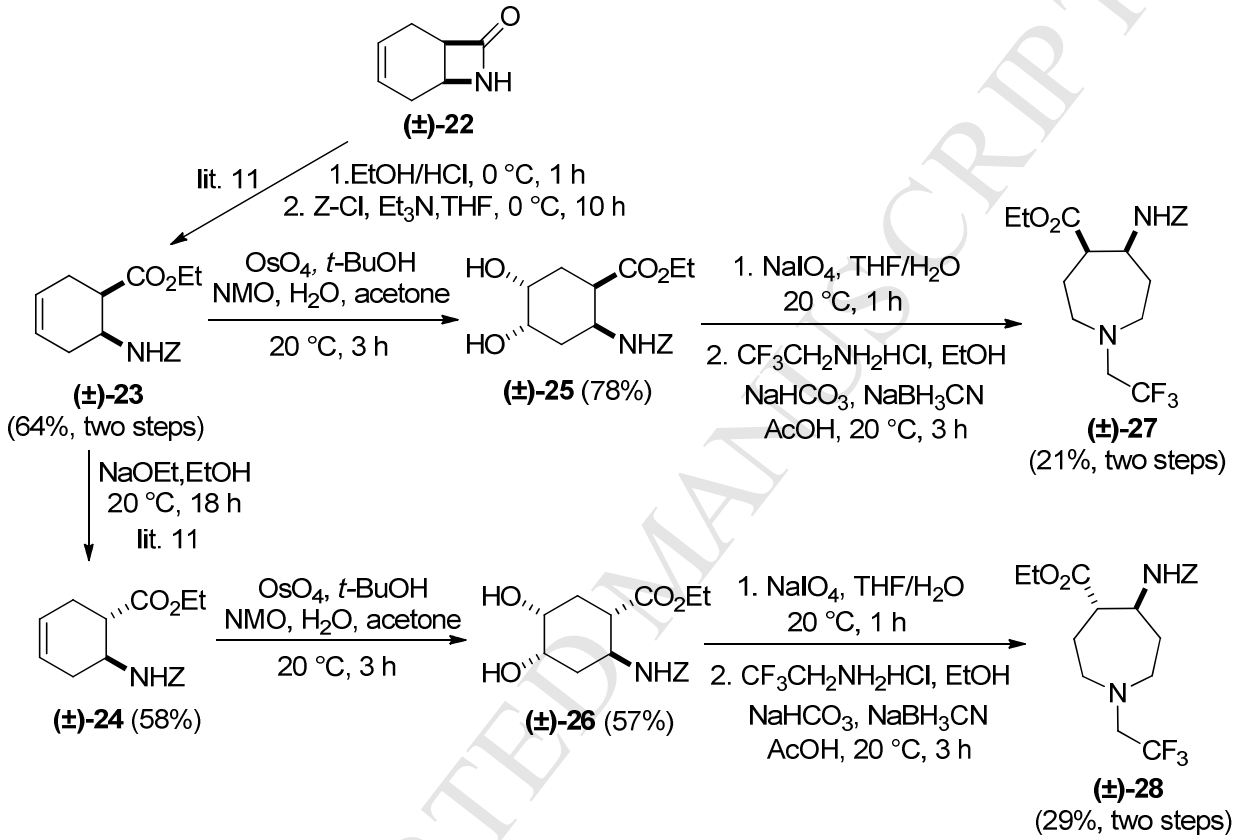
piperidine amino esters **(±)-20** and **(±)-21** (Scheme 1). Amino esters **(±)-20** and **(±)-21** could be accessed on an alternative pathway by epimerization at C-4 of **(±)-18** and **(±)-19** with NaOEt in EtOH with the involvement of the active methine group.



Scheme 1.

The synthetic approach described above was applied towards the synthesis of trifluoromethylated azepane 2-aminocarboxylates. First, *cis* and *trans* 2-aminocyclohex-4-enecarboxylates **(±)-23** and **(±)-24** (derived from bicyclic β-lactam **(±)-22** by azetidinone ring opening with ethanolysis, Z-protection and epimerization)[11] were oxidized with NMO/OsO_4 affording the corresponding vicinal diol derivatives **(±)-25** and **(±)-26** (for similar transformations see, ref. 11c-d). Next, these dihydroxylated esters were converted to *cis* and *trans* amino esters **(±)-27** and **(±)-28** with an azepane ring, which contain the ring *N*-atom at

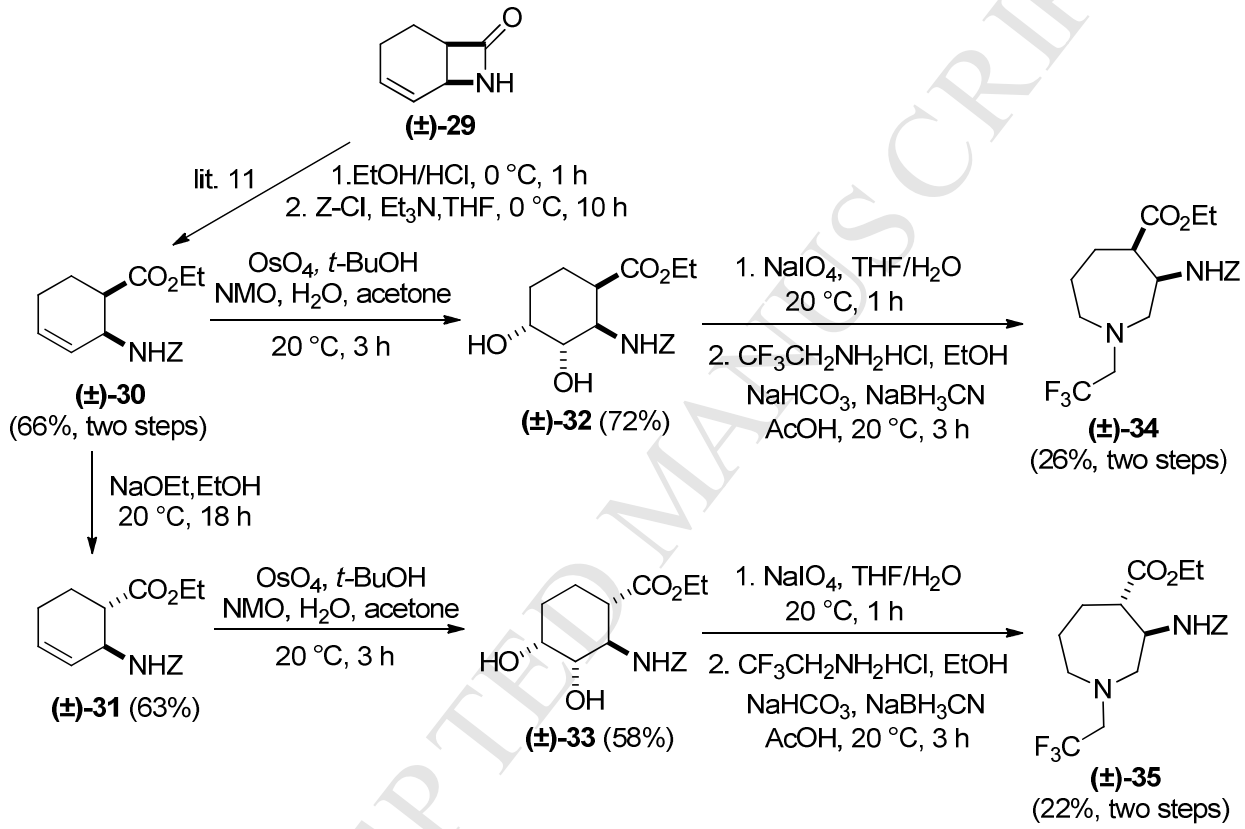
three C-atom distance from the carbamate group (Scheme 2). The corresponding transformations involved oxidative ring cleavage and stereocontrolled ring enlargement through reductive amination with 2,2,2-trifluoroethylamine and $NaBH_3CN$.



Scheme 2.

The synthetic procedure was further extended for the preparation of novel trifluoromethylated azepane derivatives, by starting from bicyclic β-lactam **(±)-29**, a regioisomer of **(±)-22**. Lactam **(±)-29** was converted through lactam ring opening by ethanolysis followed by *N*-Z protection to **(±)-30** and, finally, epimerization to derivative **(±)-31**.[11] Alkene bond dihydroxylation of **(±)-30** and **(±)-31** with NMO and OsO_4 provided vicinal diols **(±)-32** and **(±)-33** (see also ref. 11). Both dihydroxylated amino ester stereoisomers were subjected to

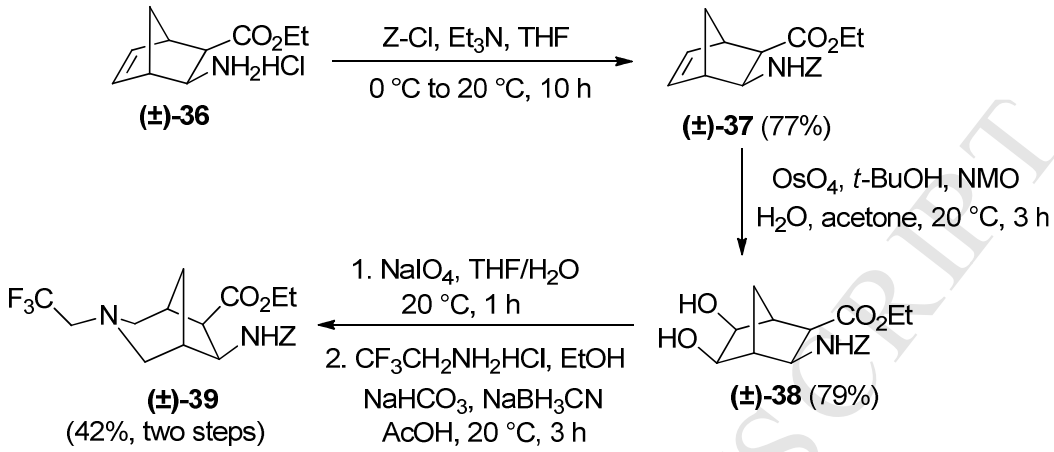
$NaIO_4$ mediated oxidative ring opening followed by reductive ring closing with trifluoroethylamine resulting in *cis* and *trans* azepane amino esters **(±)-34** and **(±)-35** (regioisomers of **(±)-27** and **(±)-28**). In these products, the ring *N*-atom is located at a two C-atom distance from the carbamate group (Scheme 3).



Scheme 3.

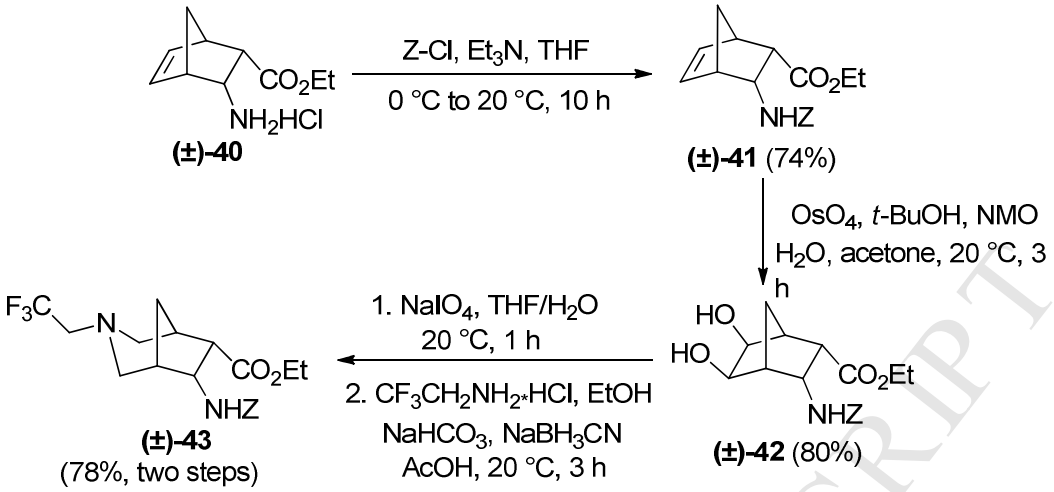
Taking into consideration the high physiological relevance of *N*-bridged bicyclic amino acid derivatives (eg., cocaine, anatoxin-a analogs **3**, etc.), our next aim was the extension of the above described synthetic protocol to the preparation of trifluoromethylated *N*-bicyclic systems. Thus, the readily available *diexo*-norbornene β-amino ester **(±)-36**[9b] was first transformed by *N*-Z protection to **(±)-37** and then dihydroxylation was carried out to form diol derivative **(±)-38**

(see also ref. 9b). Oxidative ring opening of **(±)-38** followed by reductive amination with trifluoroethylamine and $NaBH_3CN$ gave *N*-bicyclic amino ester **(±)-39** (Scheme 4).



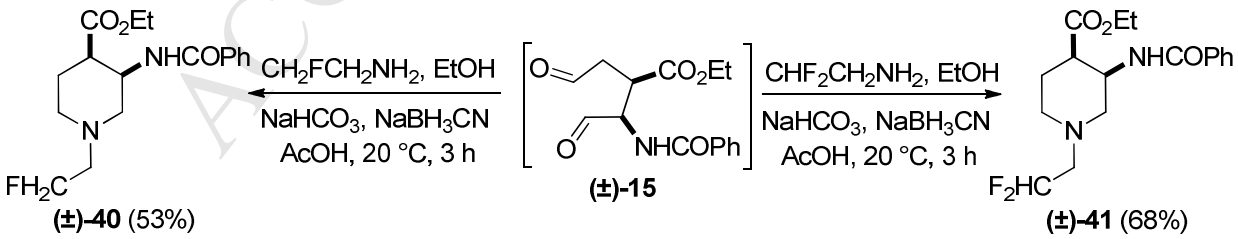
Scheme 4.

The synthesis of the new stereoisomeric *N*-bridged bicyclic β-amino ester containing the trifluoromethyl group could also be accomplished by starting from the *diendo*-norbornene amino ester **(±)-40**.[9b] Following the synthetic approach used as for the *diexo* isomer, *N*-Z-protection of **(±)-40**, dihydroxylation, oxidative ring opening and ring enlargement via reductive amination with trifluoroethylamine led to compound **(±)-43**, a stereoisomer of **(±)-39** (Scheme 5).



Scheme 5.

The synthetic method, based on oxidative carbocyclic ring opening followed by reductive ring closing presented here, could be readily extended to access novel fluorine-containing *N*-heterocyclic β-amino acid derivatives by variation of the fluorine-containing building element. An example consists of the reductive amination either with 2-fluoroethanamine or 2,2-difluoroethanamine. Thus, dialdehyde **(±)-15** (derived from lactam **(±)-9**) on treatment with these commercially available fluoroamines in the presence of $NaHCO_3$ and $NaBH_3CN$ delivered the corresponding monofluorinated and difluorinatedpiperidine β-amino esters **(±)-40** and **(±)-41** (Scheme 6).



Scheme 6.

Conclusions

A convenient and efficient stereocontrolled procedure has been developed for the synthesis of novel trifluoromethyl-containing piperidine and azepane β-amino ester stereoisomers. The protocol is based on the C=C bond oxidative ring cleavage of cyclic β-amino acids, followed by reductive ring closure of diformyl intermediates in the presence of commercially available fluoramine building element 2,2,2-trifluoroethylamine. Since the stereocenters of the starting carbocyclic β-amino acid derivatives are not affected during the synthetic procedure, they will predetermine the configuration of the chiral centers in the products. The synthetic approach has been readily extended towards novel trifluoromethyl *N*-bridged scaffolds and mono- or difluorinated piperidine β-amino acid derivatives.

Experimental

General procedure for the Z-protection of amino esters

To a solution of amino ester hydrochloride (8 mmol) in THF (30 mL), Et_3N (5 mL) was added at 0 °C, followed by the addition of Z-Cl (1 equiv, a 50% solution in toluene). The mixture was stirred for 10 h at 20 °C and then diluted with EtOAc (80 mL). The organic layer was washed with H_2O (3 x 40 mL), dried (Na_2SO_4) and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1), affording the protected amino ester.

General procedure for epimerization of the *cis*-amino esters

To a solution of *cis N*-protected amino ester (3mmol) in EtOH (30 mL), EtONa (1.5 equiv) was added at 0 °C and the mixture was stirred at 20 °C for 18 h. After the addition of H_2O (70 mL), the mixture was extracted with CH_2Cl_2 (3 x 30 mL), the organic layer dried over Na_2SO_4 and

concentrated under vacuo. The crude material was purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) to give the *trans* isomer.

General procedure for dihydroxylation of *N*-protected amino esters

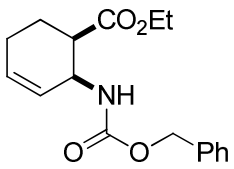
To a solution of *N*-protected β-amino ester (5mmol) and NMO (1.2 equiv) in acetone (30 mL), 0.3 mL of 2% OsO_4 solution in *t*-BuOH was added, and the resulting mixture was stirred for 3 h at room temperature. After completion of the reaction, 90 mL of saturated aqueous Na_2SO_3 solution was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc 1:4).

General procedure for the synthesis of fluorine-containing *N*-heterocyclic amino esters by oxidative ring cleavage followed by ring closure via reductive amination

To a stirred solution of amino ester (2mmol) $NaIO_4$ (1.5 equiv) was added in THF/H_2O (25 mL/2 mL). After stirring for 1 h at 20 °C under an Ar atmosphere, H_2O was added (40 mL). The mixture was then extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried over Na_2SO_4 and the resulting solution containing the dialdehyde derivative was evaporated and the crude product was immediately used for the next reaction without purification. Fluorine-containing ethylamine hydrochloride (2 mmol), $NaHCO_3$ (2 equiv) were added to the solution of the dialdehyde in EtOH (20 mL) and the mixture was stirred at 20 °C for 10 min. Next $NaCNBH_3$ (2mmol) and AcOH (2 drops) were added and stirring was continued for another 4 h at 20 °C. The reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20

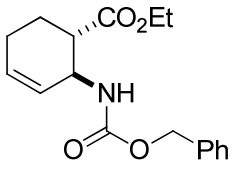
mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Ethyl (1*R,2*S**)-2-(((benzyloxy)carbonyl)amino)cyclohex-3-enecarboxylate (±)-30**



White solid; yield: 66% (980 mg); mp = 56-58 °C; (R_f= 0.36, *n*-hexane/EtOAc 4:1). ^{1}H NMR (DMSO, 400 MHz) δ = 1.08 (t, 3H, CH_3, J = 8.1 Hz), 1.62-2.03 (m, 4H, CH_2), 2.63-2.71 (m, 1H, H-1), 3.92-3.99 (m, 2H, OCH_2), 4.41-4.48 (m, 1H, H-2), 4.96-5.03 (m, 2H, OCH_2), 5.54-5.60 (m, 1H, H-4), 5.77-5.82 (m, 1H, H-3), 7.29-7.40 (m, 6H, Ar-H and N-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 19.9, 24.9, 44.5, 46.6, 60.5, 66.0, 127.1, 128.5, 128.6, 129.1, 130.5, 136.0, 156.3, 173.3. Anal. Calcd for $C_{17}H_{21}NO_4$: C 67.31, H 6.98, N 4.62; found: C 67.01, H 6.61, N 4.29.

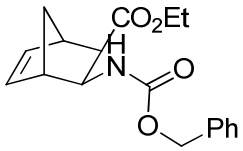
Ethyl (1*S,2*S**)-2-(((benzyloxy)carbonyl)amino)cyclohex-3-enecarboxylate (±)-31**



White solid; yield: 63% (1.46 g).; mp = 52-54 °C; (R_f= 0.33, *n*-hexane/EtOAc 4:1). ^{1}H NMR (DMSO, 400 MHz) δ = 1.18 (t, 3H, CH_3, J = 8.0 Hz), 1.61-1.70 (m, 1H, CH_2), 1.83-1.90 (m, 1H, CH_2), 1.98-2.04 (m, 2H, CH_2), 2.47-2.52 (m, 1H, H-1), 3.97-4.04 (m, 2H, OCH_2), 4.31-4.39 (m, 1H, H-2), 5.01 (s, ,2H, OCH_2), 5.48-5.02 (m, 1H, H-4), 5.73-5.77 (m, 1H, H-3), 7.72-7.86 (m, 5H, Ar-H), 7.94 (brs, 1H, N-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.9, 24.2, 25.1, 45.8,

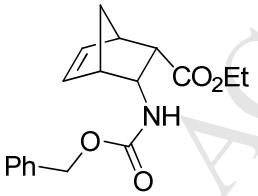
49.4, 60.8, 66.1, 128.5, 128.6, 128.8, 128.9, 129.2, 138.0, 156.5, 174.4. Anal. Calcd for $C_{17}H_{21}NO_4$: C 67.31, H 6.98, N 4.62; found: C 67.02, H 6.64, N 4.92.

Ethyl (1*R,2*R**,3*S**,4*S**)-3-(((benzyloxy)carbonyl)amino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (±)-37**



White solid; yield: 77% (1.94 g); mp 89-90 °C; (R_f = 0.6, *n*-hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.23 (t, 3H, CH_3, J = 7.2 Hz), 1.60-1.66 (m, 1H, CH_2), 1.96-2.01 (m, 1H, CH_2), 2.65-2.70 (m, 1H, H-2), 2.21-2.25 (m, 1H, H-4), 2.99-3.02 (m, 1H, H-1), 3.99-4.18 (m, 3H, OCH_2 and H-3), 5.08 (s, 2H, OCH_2), 5.50 (brs, 1H, N-H), 6.20-6.27 (m, 2H, H-5 and H-6), 7.38-7.48 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 44.8, 45.9, 48.0, 48.2, 54.5, 60.6, 66.2, 128.7, 129.0, 137.7, 137.8, 139.8, 139.9, 156.6, 173.5. Anal. Calcd for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 68.23, H 6.90, N 4.18.

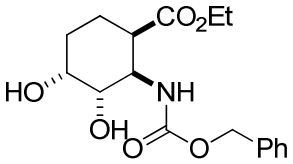
Ethyl (1*R,2*S**,3*R**,4*S**)-3-(((benzyloxy)carbonyl)amino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (±)-41**



Colourless oil; yield: 74% (2.3 g); (R_f = 0.65, *n*-hexane/EtOAc 4:1). ^{1}H NMR (DMSO, 400 MHz) δ = 1.22 (t, 3H, CH_3, J = 7.1 Hz), 1.33-1.38 (m, 1H, CH_2), 1.50-1.55 (m, 1H, CH_2), 3.13-3.18 (m, 2H, H-1 and H-4), 3.21-3.25 (m, 1H, H-2), 4.01-4.13 (m, 2H, OCH_2), 4.56-4.61 (m, 1H, H-3), 5.10 (s, 2H, OCH_2), 5.42 (brs, 1H, N-H), 6.22-6.26 (m, 1H, H-6), 6.44-6.49 (m, 1H,

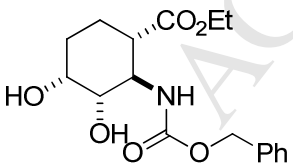
H-5), 7.29-7.37 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 41.0, 46.2, 47.5, 49.5, 55.0, 60.5, 66.2, 128.6, 128.7, 129.1, 133.9, 137.9, 138.9, 156.5, 172.3. MS: (ESI) m/z = 316.1 (M+1). Anal. Calcd for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 68.20, H 6.39, N 4.16.

Ethyl (1*R,2*R**,3*S**,4*R**)-2-(((benzyloxy)carbonyl)amino)-3,4-dihydroxycyclohexane-carboxylate (±)-32**



White solid; yield: 72% (740 mg); mp = 130-132 °C; (R_f= 0.42, *n*-hexane/EtOAc 1:4). ^{1}H NMR (DMSO, 400 MHz) δ =1.10 (t, 3H, CH_3, J = 7.9 Hz), 1.39-1.54 (m, 3H, CH_2), 1.62-1.74 (m, 1H, CH_2), 2.74-2.79 (m, 1H, H-1), 3.51-3.55 (m, 1H, H-4), 3.59-3.63 (m, 1H, H-3), 3.92-4.03 (m, 2H, OCH_2), 4.23-4.29 (m, 1H, H-2), 4.33 (brs, 1H, O-H), 4.84 (brs, 1H, O-H), 4.96-5.04 (m, 2H, OCH_2), 7.19 (brs, 1H, N-H), 7.26-7.41 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.7, 21.4, 27.7, 41.0, 54.3, 60.2, 66.1, 67.2, 71.9, 128.1, 128.5, 128.6, 137.9, 156.6, 173.9. Anal. Calcd for $C_{17}H_{23}NO_6$: C 60.52, H 6.87, N 4.15; found: C 60.18, H 6.48, N 3.85.

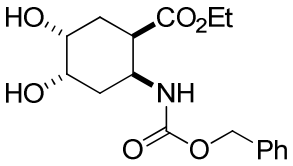
Ethyl (1*S,2*R**,3*S**,4*R**)-2-(((benzyloxy)carbonyl)amino)-3,4-dihydroxycyclohexane-carboxylate (±)-33**



White solid; yield: 58% (850 mg); mp = 102-103 °C (R_f= 0.31, *n*-hexane/EtOAc 1:4). ^{1}H NMR (DMSO, 400 MHz) δ = 1.08 (t, 3H, CH_3, J = 7.9 Hz), 1.29-1.36 (m, 1H, CH_2), 1.41-1.49 (m, 1H, CH_2), 1.58-1.64 (m, 1H, CH_2), 1.72-1.79 (m, 1H, CH_2), 2.37-2.43 (m, 1H, H-1), 3.18-3.24

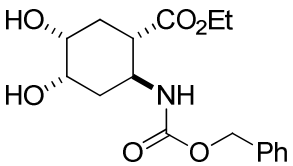
(m, 1H. H-4), 3.78-3.85 (m, 2H, H-2 and H-3), 3.96-4.08 (m, 2H, OCH_2), 4.23 (brs, 1H, O-H), 4.49 (brs, 1H, O-H), 4.97-5.02 (m, 2H, OCH_2), 7.00 (brs, 1H, N-H), 7.32-7.48 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 23.0, 30.4, 48.6, 53.2, 60.5, 65.7, 69.3, 73.9, 128.4, 128.5, 129.1, 138.3, 156.7, 173.9. Anal. Calcd for $C_{17}H_{23}NO_6$: C 60.52, H 6.87, N 4.15; found: C 60.16, H 7.22, N 3.81.

Ethyl (1*R,2*S**,4*S**,5*R**)-2-(((benzyloxy)carbonyl)amino)-4,5-dihydroxycyclohexane-carboxylate (±)-25**



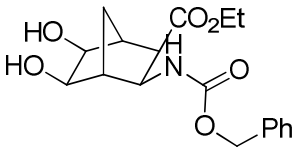
White solid; yield: 78% (1.05 g); mp = 83-85 °C (R_f= 0.33, *n*-hexane/EtOAc 1:4). ^{1}H NMR (DMSO, 400 MHz) δ = 1.03 (t, 3H, CH_3, J = 7.9 Hz), 1.51-1.57 (m, 1H, CH_2), 1.59-1.72 (m, 2H, CH_2), 1.77-1.86 (m, 1H, CH_2), 2.76-2.84 (m, 1H, H-1), 3.59-3.70 (m, 2H, H-4 and H-5), 3.89-4.01 (m, 2H, OCH_2), 4.08-4.14 (m, 1H, H-2), 4.30 (brs, 2H, 2x O-H), 4.96-5.04 (m, 2H, OCH_2), 7.33-7.48 (m, 6H, Ar-H, and N-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 29.3, 34.9, 48.4, 60.5, 66.0, 66.9, 68.2, 69.9, 128.5, 128.6, 129.2, 138.1, 156.5, 173.6. Anal. Calcd for $C_{17}H_{23}NO_6$: C 60.52, H 6.87, N 4.15; found: C 60.15, H 6.51, N 4.41.

Ethyl (1*S,2*S**,4*S**,5*R**)-2-(((benzyloxy)carbonyl)amino)-4,5-dihydroxycyclohexane-carboxylate (±)-26**



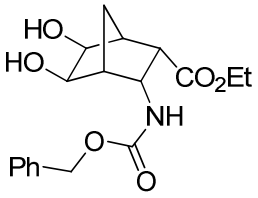
White solid; yield: 57% (750 mg); mp = 102-104 °C (R_f= 0.30, *n*-hexane/EtOAc 1:4). ^{1}H NMR (DMSO, 400 MHz) δ = 1.09 (t, 3H, CH_3, J = 7.9 Hz), 1.45-1.62 (m, 3H, CH_2), 1.71-1.78 (m, 1H, H-1), 2.57-2.65 (m, 1H, H-1), 3.42-3.50 (m, 1H, H-5), 3.55-3.58 (m, 1H, H-4), 3.62-3.69 (m, 1H, H-2), 3.89-4.03 (m, 2H, OCH_2), 4.46 (brs, 1H, O-H), 4.53 (brs, 1H, O-H), 4.98 (s, 2H, OCH_2), 7.73-7.88 (m, 6H, Ar-H and N-H).^{13}C NMR (100 MHz, DMSO): δ = 14.8, 33.5, 35.6, 46.8, 50.5, 61.5. 66.6. 67.5, 70.1, 128.5, 128.6, 129.1, 138.2, 156.1, 174.8.Anal. Calcd for $C_{17}H_{23}NO_6$: C 60.52, H 6.87, N 4.15; found: C 60.18, H 7.20, N 3.88.

Ethyl (1*S,2*R**,3*S**,4*R**,5*R**,6*S**)-3-(((benzyloxy)carbonyl)amino)-5,6-dihydroxybicyclo-[2.2.1]heptane-2-carboxylate (±)-38**



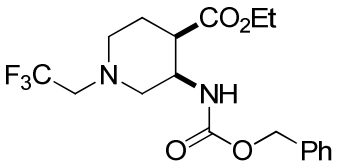
White solid; yield: 79% (1.53 g); mp 85-87 °C; (R_f = 0.4, *n*-hexane/EtOAc 1:4). ^{1}H NMR (DMSO, 400 MHz) δ = 1.11 (t, 3H, CH_3, J = 7.1 Hz), 1.62-1.66 (m, 1H, CH_2), 1.75-1.80 (m, 2H, CH_2 and H-4), 2.18-2.21 (m, 1H, H-1), 2.52-2.56 (m, 1H, H-2), 3.51-3.60 (m, 2H, H-5 and H-6), 3.83-3.94 (m, 3H, OCH_2 and H-3), 4.59 (brs, 2H, O-H), 5.00 (s, 2H, OCH_2), 7.23 (brs, 1H, N-H), 7.32-7.45 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 30.0, 46.3, 49.3, 49.8, 53.5, 60.4, 66.2, 71.9, 72.5, 128.6, 128.7, 129.2, 137.9, 156.4, 172.1. MS: (ESI) m/z = 350.2 (M+1). Anal. Calcd for $C_{18}H_{23}NO_6$: C 61.88, H 6.64, N 4.01; found: C 61.56, H 6.31, N 3.75.

Ethyl (1*S,2*S**,3*R**,4*R**,5*R**,6*S**)-3-(((benzyloxy)carbonyl)amino)-5,6-dihydroxybicyclo-[2.2.1]heptane-2-carboxylate (±)-42**



Colourless oil; yield: 80% (1.24 g); (R_f = 0.45, *n*-hexane/EtOAc 1:4). ^{1}H NMR (DMSO, 400 MHz) δ = 1.15 (t, 3H, CH_3, J = 7.1 Hz), 1.16-1.22 (m, 1H, CH_2), 1.73-1.77 (m, 1H, CH_2), 2.18-2.21 (m, 1H, H-4), 2.22-2.25 (m, 1H, H-1), 2.98-3.03 (m, 1H, H-2), 3.98-4.09 (m, 4H, OCH_2, H-5 and H-6), 4.11-4.16 (m, 1H, H-3), 4.51 (brs, 1H, O-H), 4.58 (brs, 1H, O-H), 5.01 (m, 2H, OCH_2), 7.09 (brs, 1H, N-H), 7.35-7.44 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 31.6, 44.5, 47.7, 49.0, 50.7, 60.7, 66.3, 68.1, 69.4, 128.6, 128.7, 129.2, 137.9, 156.7, 172.4. MS: (ESI) m/z = 350.2 (M+1). Anal. Calcd for $C_{18}H_{23}NO_6$: C 61.88, H 6.64, N 4.01; found: C 61.56, H 6.31, N 3.75.

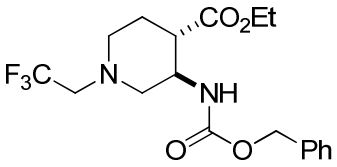
Ethyl (3*R,4*R**)-3-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (±)-18**



Brown oil; yield: 33% (225 mg, two steps). (R_f= 0.43, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.09 (t, 3H, CH_3, J = 7.9 Hz), 1.52-1.59 (m, 1H, CH_2), 1.98-2.08 (m, 1H, CH_2), 2.41-2.50 (m, 1H, H-4), 2.55-2.63 (m, 2H, NCH_2), 2.81-2.88 (m, 2H, NCH_2), 3.12-3.20 (m, 2H, NCH_2CF_3), 3.93-4.02 (m, 2H, OCH_2), 4.10-4.17 (m, 1H, H-3), 4.99-5.10 (m, 2H, OCH_2), 6.88 (brs, 1H, N-H), 7.28-7.46 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 23.9, 43.3, 48.6, 52.3, 57.5 (q, $^2J_{C,F}$= 28.6 Hz, CCF_3), 57.8, 60.3, 66.1, 126.5 ($^1J_{C,F}$ = 284.3 Hz, CF_3), 128.3, 128.5, 131.2, 138.0, 156, 3, 172.8.^{19}F NMR (100 MHz, DMSO): δ = -67.3. MS: (ESI) m/z =

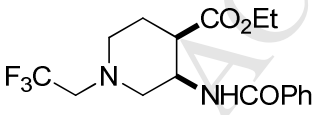
389.6 (M+1). IR (KBr): ν_{max} 1150, 1520, 1710, 2900, 3450. Anal. Calcd for $C_{18}H_{23}F_3N_2O_4$: C 55.67, H 5.97, N 7.21; found: C 55.30, H 6.32, N 6.89.

Ethyl (3*R,4*S**)-3-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (±)-20**



White soli; yield: 39% (302 mg, two steps); mp = 88-89 °C. (R_f= 0.33, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.12 (t, 3H, CH_3, J = 7.9 Hz), 1.51-1.57 (m, 1H, CH_2), 1.72-1.79 (m, 1H, CH_2), 2.17-2.24 (m, 1H, H-4), 2.26-2.31 (m, 2H, NCH_2), 2.87-2.97 (m, 2H, NCH_2), 3.10-3.19 (m, 2H, NCH_2), 3.62-3.69 (m, 1H, H-3), 3.96-4.08 (m, 2H, OCH_2), 4.99 (s, 2H, OCH_2), 7.32-7.48 (m, 6H, Ar-H and N-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 28.7, 46.9, 50.0, 52.6, 57.0 (q, $^2J_{C,F}$= 29.2 Hz, CCF_3),, 58.4, 60.8, 66.1, 127.7 ($^1J_{C,F}$ = 275.5 Hz, CF_3),, 128.5, 128.6, 129.2, 137.9, 156.2, 173.8.^{19}F NMR (100 MHz, DMSO): δ = -67.8. MS: (ESI) m/z = 389.7 (M+1). IR (KBr): ν_{max} 1160, 1510, 1710, 2950, 3300. Anal. Calcd for $C_{18}H_{23}F_3N_2O_4$: C 55.67, H 5.97, N 7.21; found: C 55.31, H 5.69, N 6.87.

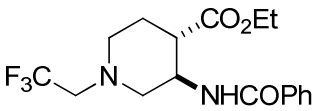
Ethyl (3*R,4*R**)-3-benzamido-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (±)-19**



White-yellowish solid; yield: 53% (389 mg, two steps); mp = 64-67 °C. (R_f= 0.32, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.10 (t, 3H, CH_3, J = 8.1 Hz), 1.58-1.65 (m, 1H, CH_2), 2.07-2.14 (m, 1H, CH_2), 2.50-2.55 (m, 1H, H-4), 2.72-2,77 (m, 2H, NCH_2), 2.88-2.94 (m, 2H, NCH_2), 3.97-4.08 (m, 2H, OCH_2), 4.51-5.54 (m, 1H, H-3). 7.45-7.53 (m, 3H, Ar-

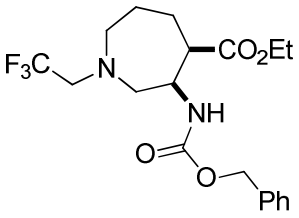
H), 7.68-7.75 (m, 2H, Ar-H), 7.81 (brs, 1H, N-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 25.2, 41.3, 45.8, 52.2, 57.7 (q, $^{2}J_{C,F}$ = 30.3 Hz, CCF_3), 60.8, 125.6 ($^{1}J_{C,F}$ = 281.5 Hz, CF_3), 128.1, 128.4, 129.1, 132.0, 136.7, 166.9, 173.0.^{19}F NMR (100 MHz, DMSO): δ = -67.6. MS: (ESI) m/z = 359.5 (M+1). IR (KBr): ν_{max} 1120, 1510, 1630, 1720, 2330, 3400. Anal. Calcd for $C_{17}H_{21}F_3N_2O_3$: C 56.98, H 5.91, N 7.82; found: C 56.67, H 5.60, N 7.49.

Ethyl (3*R,4*S**)-3-benzamido-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (±)-21**



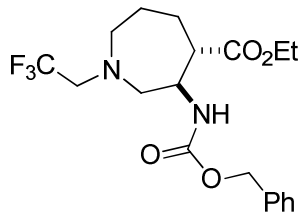
White solid; yield: 28% (203 mg, two steps); mp = 129-132 °C. (R_f= 0.30, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.08 (t, 3H, CH_3, J = 8.1 Hz), 1.59-1.66 (m, 1H, CH_2), 1.88-1.96 (m, 1H, CH_2), 2.39-2.44 (m, 2H, NCH_2), 2.55-2.60 (m, 1H, H-4), 2.93-3.04 (m, 2H, NCH_2), 3.22-3.34 (m, 2H, NCH_2), 3.94-4.04 (m, 2H, OCH_2), 4.21-4.28 (m, 1H, H-3), 7.41-7.51 (m, 3H, Ar-H), 7.77-7.84 (m, 2H, Ar-H), 8.42 (brs, 1H, N-H). ^{13}C NMR (100 MHz, DMSO): δ =14.8, 28.6, 46.6, 48.7, 52.7, 52.2 (q, $^{2}J_{C,F}$= 28.4 Hz, CCF_3), 58.0, 60.8, 128.1, 129.1, 128.8 ($^{1}J_{C,F}$ = 286.5 Hz, CF_3), 132.1, 135.3, 166.7. 173.6. ^{19}F NMR (100 MHz, DMSO): δ = -67.8. MS: (ESI) m/z = 359.3 (M+1). IR (KBr): ν_{max} 1130, 1510, 1650, 1720, 2340, 3400. Anal. Calcd for $C_{17}H_{21}F_3N_2O_3$: C 56.98, H 5.91, N 7.82; found: C 56.64, H 6.29, N 7.50.

Ethyl (3*R,4*R**)-3-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (±)-34**



Colorless oil; yield: 26% (188 mg, two steps). (R_f= 0.30, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.12 (t, 3H, CH_3, J = 8.2 Hz), 1.46-1.52 (m, 1H, CH_2), 1.70-1.85 (m, 3H, CH_2), 2.64-2.73 (m, 2H, H-4 and NCH_2), 2.81-2.87 (m, 1H, NCH_2), 3.07-3.12 (m, 1H, NCH_2), 3.34-3.42 (m, 2H, NCH_2), 3.86-3.98 (m, 2H, OCH_2), 3.99-4.07 (m, 1H, NCH_2), 4.18-4.24 (m, 1H, H-3), 4.87-5.04 (m, 2H, OCH_2), 6.99 (brs, 1H, N-H), 7.37-7.49 (m, 5H, Ar-H).^{13}C NMR (100 MHz, DMSO): δ = 14.8, 24.2, 28.4, 48.8, 52.1, 57.1, 58.4, (q, $^2J_{C,F}$= 29.6 Hz, CCF_3), 58.7, 60.5, 66.1, 127.5 ($^1J_{C,F}$ = 278.5 Hz, CF_3), 128.5, 128.6, 129.1, 134.2, 156.6, 173.9.^{19}F NMR (100 MHz, DMSO): δ = -69.6. MS: (ESI) m/z = 403.4 (M+1). IR (KBr): ν_{max} 1140, 1290, 1530, 1715, 2320, 2950, 3300. Anal. Calcd for $C_{19}H_{25}F_3N_2O_4$: C 56.71, H 6.26, N 6.96; found: C 56.39, H 5.88, N 6.60.

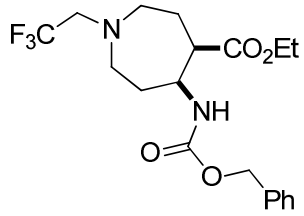
Ethyl (3*R,4*S**)-3-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (±)-35**



Colorless oil; yield: 22% (159 mg, two steps). (R_f= 0.33, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.19 (t, 3H, CH_3, J = 8.2 Hz), 1.47-1.52 (m, 1H, CH_2), 1.66-1.79 (m, 3H, CH_2), 2.48-2.57 (m, 1H, H-4), 2.69-2.90 (m, 4H, NCH_2), 3.38-3.44 (m, 2H, NCH_2), 3.77-3.82 (m, 1H, H-3), 3.98-4.07 (m, 2H, OCH_2), 4.97-5.03 (m, 2H, OCH_2), 7.17 (brs, 1H, N-H), 7.23-7.38 (m, 5H, Ar-H).^{13}C NMR (100 MHz, DMSO): δ = 14.8, 27.0, 27.1, 51.4, 53.7, 54.4, 55.4 (q, $^2J_{C,F}$= 28.3 Hz, CCF_3), 58.4, 60.7, 66.0, 125.8 (q, $^1J_{C,F}$ = 280.5 Hz, CCF_3),128.4, 128.5, 129.1, 138.0, 156.0, 174.9.^{19}F NMR (100 MHz, DMSO): δ = -69.4. MS: (ESI) m/z = 403.5

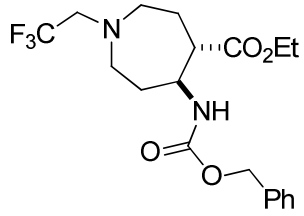
(M+1). IR (KBr): ν_{max} 1160, 1285, 1510, 1710, 2320, 2950, 3300. Anal. Calcd for $C_{19}H_{25}F_3N_2O_4$: C 56.71, H 6.26, N 6.96; found: C 56.35, H 6.50, N 6.61.

Ethyl (4*R,5*S**)-5-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (±)-27**



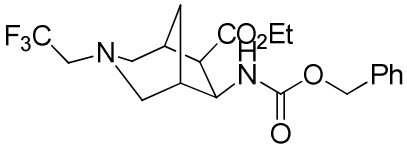
Colorless oil; yield: 21% (147 mg, two steps). (R_f= 0.30, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.20 (t, 3H, CH_3, J = 8.2 Hz), 1.63-1.71 (m, 3H, CH_2), 1.86-1.97 (m, 1H, CH_2), 2.62-2.90 (m, 5H, H-5 and NCH_2), 3.22-3.32 (m, 2H, NCH_2), 3.97-4.04 (m, 2H, OCH_2), 4.10-4.17 (m, 1H, H-4), 4.97-5.03 (m, 2H, OCH_2), 6.93 (brs, 1H, N-H), 7.30-7.47 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 26.7, 33.3, 47.6, 51.3, 51.7, 53.9, 57.6 (q, $^2J_{C,F}$= 29.5 Hz, CCF_3), 60.6, 66.1, 125.8 (q, $^1J_{C,F}$ = 279.5 Hz, CCF_3), 128.2, 128.4, 129.2, 138.0, 156.1, 173.7. ^{19}F NMR (100 MHz, DMSO): δ = -69.5. MS: (ESI) m/z = 403.4 (M+1). IR (KBr): ν_{max} 1110, 1290, 1500, 1720, 2320, 2950, 3450. Anal. Calcd for $C_{19}H_{25}F_3N_2O_4$: C 56.71, H 6.26, N 6.96; found: C 56.40, H 6.53, N 7.31.

Ethyl (4*S,5*S**)-5-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (±)-28**



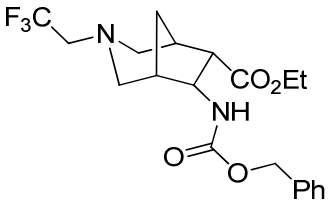
White solid; yield: 29% (207 mg, two steps); mp = 37-40 °C. (R_f= 0.33, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.16 (t, 3H, CH_3, J = 8.2 Hz), 1.66-1.72 (m, 1H, CH_2), 1.74-1.83 (m, 3H, CH_2), 2.54-2.60 (m, 1H, H-5), 2.69-2.74 (m, 2H, NCH_2), 2.77-2.84 (m, 2H, NCH_2), 3.19-3.28 (m, 2H, NCH_2), 3.83-3.90 (m, 1H, H-4), 3.98-4.08 (m, 2H, OCH_2), 4.96-5.01 (m, 2H, OCH_2), 7.30-7.46 (m, 6H, Ar-H and N-H).^{13}C NMR (100 MHz, DMSO): δ = 14.8, 28.6, 34.8, 49.7, 51.7, 53.0, 53.8, 57.4 (q, $^2J_{C,F}$= 29.4 Hz, CCF_3), 60.6, 65.9, 125.8 (q, $^1J_{C,F}$ = 280.3 Hz, CCF_3), 128.5, 128.6, 129.2, 138.1, 156.0, 174.6. ^{19}F NMR (100 MHz, DMSO): δ = -69.0. MS: (ESI) m/z = 403.4 (M+1). IR (KBr): ν_{max} 1110, 1300, 1530, 1710, 2310, 2950, 3300. Anal. Calcd for $C_{19}H_{25}F_3N_2O_4$: C 56.71, H 6.26, N 6.96; found: C 57.02, H 6.52, N 6.63.

Ethyl (1*S,5*S**,6*R**,7*S**)-7-(((benzyloxy)carbonyl)amino)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.2.1]octane-6-carboxylate (±)-39**



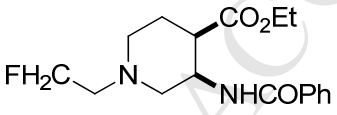
Colorless oil; yield: 42% (298 mg, two steps). (R_f= 0.33, *n*-hexane/EtOAc 4:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.08 (t, 3H, CH_3, J = 8.1 Hz), 1.09-1.18 (m, 2H, CH_2), 1.972.02 (m, 1H, H-1), 2.20-2.25 (m, 1H, H-5), 2.33-2.38 (m, 1H, H-6), 2.59-2.64 (m, 1H, NCH_2), 2.70-2.76 (m, 1H NCH_2), 2.99-3.04 (m, 1H NCH_2), 3.11-3.18 (m, 2H, NCH_2), 3.79-3.99 (m, 3H, NCH_2 and OCH_2), 4.23-4.28 (m, 1H, H-7), 4.99 (s, 2H, OCH_2), 7.80-7.92 (m, 6H, Ar-H amd N-H). ^{13}C NMR (100 MHz, DMsO): δ = 14.8, 35.1, 39.8, 42.1, 53.6, 56.8, 57.0 (q, $^2J_{C,F}$= 29.3 Hz, CCF_3), 58.6, 59.2, 60.3, 66.1, 125.7, (q, $^1J_{C,F}$ = 276.4 Hz, CCF_3), 128.5, 128.7, 129.4, 137.9, 156.2, 173.0.^{19}F NMR (100 MHz, DMSO): δ = -68.1. MS: (ESI) m/z = 415.2 (M+1). IR (KBr): ν_{max} 1180, 1530, 1720, 2940, 3410. Anal. Calcd for $C_{20}H_{25}F_3N_2O_4$: C 57.96, H 6.08, N 6.76; found: C 57.69, H 5.80, N 7.00.

Ethyl (1*S,5*S**,6*S**,7*R**)-7-(((benzyloxy)carbonyl)amino)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.2.1]octane-6-carboxylate (±)-43**



Colorless oil; yield: 78% (548 mg, two steps). (R_f= 0.33, *n*-hexane/EtOAc 4:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.14 (t, 3H, CH_3, J = 8.1 Hz), 1.44-1.50 (m, 1H, CH_2), 1.53-1.57 (m, 1H, CH_2), 2.18-2.22 (m, 1H, H-1), 2.24-2.29 (m, 1H, H-6), 2.41-2.52 (m, 3H, H-6 and NCH_2), 2.78-2.84 (m, 1H, NCH_2), 3.04-3.12 (m, 3H, NCH_2), 3.97-4.06 (m, 2H. OCH_2), 4.40-4.48 (m, 1H, H-7), 5.02 (s, 2H, OCH_2), 6.32 (brs, 1H, N-H), 7.30-7.47 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, DMSO): δ =14.7, 35.2, 37.7, 38.2, 47.1, 52.4, 56.2, 56.3, 56.7, (q, $^2J_{C,F}$= 29.7 Hz, CCF_3), 60.3, 66.5, 125.8 (q, $^1J_{C,F}$ = 279.4 Hz, CCF_3), 128.2, 128.5, 129.1, 138.1, 156.7, 171.4.^{19}F NMR (100 MHz, DMSO): δ = -68.2. MS: (ESI) m/z = 415.4 (M+1). IR (KBr): ν_{max} 1190, 1530, 1720, 2930, 3410. Anal. Calcd for $C_{20}H_{25}F_3N_2O_4$: C 57.96, H 6.08, N 6.76; found: C 58.31, H 5.78, N 7.02.

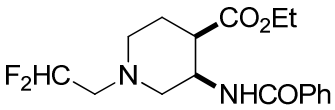
Ethyl (3*R,4*R**)-3-benzamido-1-(2-fluoroethyl)piperidine-4-carboxylate (±)-40**



Colorless oil; yield: 53% (353 mg, two steps). (R_f= 0.20, *n*-hexane/EtOAc 3:1); ^{1}H NMR (DMSO, 400 MHz) δ =1.09 (t, 3H, CH_3, J = 8.0 Hz), 1.60-1.66 (m, 1H, CH_2), 2.04-2.10 (m, 1H, CH_2), 2.18-2.24 (m, 1H, H-4), 2.43-2.50 (m, 1H, NCH_2), 2.59-2.70 (m, 3H, NCH_2), 2.77-2.85 (m, 2H, NCH_2), 3.91-4.04 (m, 2H, OCH_2), 4.50-4.54 (m, 1H, H-3), 4.47-4.59 (dt, 2H, CH_2F, ^1J

= 47.4 Hz, ^2J = 5.45 Hz), 7.47-7.54 (m, 3H, Ar-H), 7.68-7.73 (m, 3H, Ar-H and N-H).^{13}C NMR (100 MHz, DMSO): δ = 14.8, 24.2, 41.0, 46.2, 52.4, 57.7, 58.1 (d, $^2J_{C,F}$= 19.4 Hz, CCH_2F), 60.7, 82.5 (d, $^2J_{C,F}$ = 164.8 Hz, CF_2F), 128.1, 129.1, 132.0, 135.5, 166.8, 173.1.^{19}F NMR (100 MHz, DMSO): δ = -217.1.MS: (ESI) m/z = 323.4 (M+1). IR (KBr): ν_{max} 1310, 1520, 1680, 1720, 2990, 3480. Anal. Calcd for $C_{17}H_{23}FN_2O_3$: C 63.34, H 7.19, N 8.69; found: C 63.01, H 6.84, N 8.99.

Ethyl (3*R,4*R**)-3-benzamido-1-(2,2-difluoroethyl)piperidine-4-carboxylate (±)-41**



Colorless oil; yield: 68% (473 mg, two steps). (R_f= 0.22, *n*-hexane/EtOAc 2:1); ^{1}H NMR (DMSO, 400 MHz) δ = 1.08 (t, 3H, CH_3, J = 8.1 Hz), 1.66-1.73 (m, 1H, CH_2), 2.07-2.13 (m, 1H, CH_2), 2.31-2.38 (m, 1H, H-4), 2.55-2.59 (m, 1H, NCH_2), 2.70-2.97 (m, 5H, NCH_2), 3.96-4.04 (m, 2H, OCH_2), 4.48-4.53 (m, 1H, H-3), 5.96-6.32 (tt, 1H, CHF_2, ^1J = 56.8 Hz, ^2J = 4.9 Hz), 7.46-7.53 (m, 3H, Ar-H), 7.73-7.79 (m, 3H, Ar-H and N-H). ^{13}C NMR (100 MHz, DMSO): δ = 14.8, 24.3, 43.4, 47.0, 52.6, 58.0, 59.7 (t, $^2J_{C,F}$= 26.4 Hz, CCF_2), 61.1, 116.9 (t, $^1J_{C,F}$ = 264.8 Hz, CF_2), 128.1, 128.9, 132.0, 135.6, 166.8, 173.0. ^{19}F NMR (100 MHz, DMSO): δ = -118.6. MS: (ESI) m/z = 341.3 (M+1). IR (KBr): ν_{max} 1280, 1510, 1690, 1715, 2990, 3400. Anal. Calcd for $C_{17}H_{22}F_2N_2O_3$: C 59.99, H 6.51, N 8.23; found: C 59.63, H 6.12, N 7.89.

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