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Diversity-Oriented Stereocontrolled Synthesis of Some Piperidine- and Azepane-Based Fluorine-Containing β-Amino Acid Derivatives

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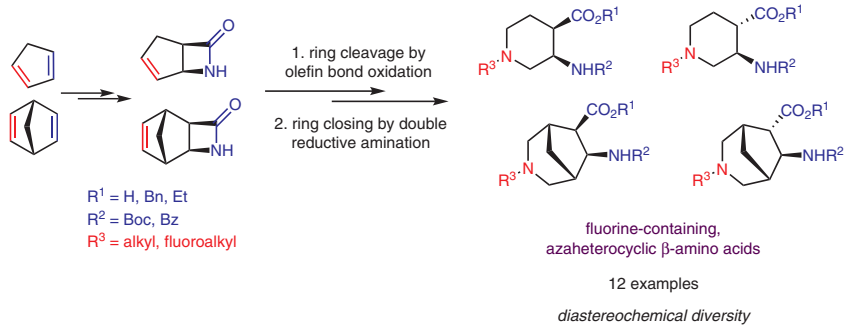

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Abstract Structural diversity-oriented synthesis of some azaheterocyclic β-amino acid derivatives has been accomplished by selective functionalization of readily available cyclodienes. The stereocontrolled synthetic concept was based on the oxidative ring cleavage of unsaturated cyclic β-amino acids derived from cycloalkadiene, followed by ring closing with double reductive amination, which furnished some conformationally restricted β-amino acid derivatives with a piperidine or azepane core.

Key words azaheterocyles, structural diversity, amino acids, stereocontrol, selectivity

Organofluorine compounds have earned increasing interest in the area of drug discovery and agrochemicals during the last years.[1] Among the large number of fluorine-containing scaffolds or fluorinated building elements, some fluorinated amino acid representatives possess antitumoral or antibiotic properties.[2]

Fluorine-containing saturated azaheterocycles occupy an important segment in the area of fluorinated organic molecules, since introduction of one or more fluorine atoms into their skeleton may increase lipophilicity and metabolic stability. Moreover, fluorine atom(s) can reduce basicity, therefore providing better bioavailability to a certain molecule. Molecular entities possessing β-fluorinated or β-trifluorinated amine units are important scaffolds in medicinal chemistry or agrochemistry.[1,3] For example, fluorine-containing piperidine or pyrrolidine derivatives (considered as cyclic fluorinated amine moieties), which are elements in various drugs such as MK-0657 (Rislenemdaz), MK-0731 (**1**) or neceprevir (**6**), are of high relevance in pharmaceutical chemistry.[4] Molecular entities possessing the fluorinated amine part in their structure might receive further relevance in the future, which is due to the importance of some functionalized counterparts in drug design.[5] Fluoroamine or trifluoroamine units are also present in various fluorine-containing amino acid derivatives of biological potential.[6] Figure 1 shows the structures of several illustrative examples of bioactive molecules with fluoroamine unit in their skeleton.

Alicylic and azaheterocyclic β-amino acids and their derivatives are known to be relevant scaffolds in the field of organic and pharmaceutical chemistry and they have attracted high attention over the past two decades due to their relevance of some antibacterial, antifungal, or analgetic molecular entities. Thus, Cispentacin (**10**), Icofungipen (**11**), and Tilidin (**12**) are several representatives of some alicyclic β-amino acids in drug research (Figure 2). These substances are important, since they are known as key elements of various bioactive compounds with antitumoral, antiviral, antibacterial, or cardioprotective properties. As conformationally rigid molecules, these compounds are of high significance for the access of novel types of peptides and, thus, they represent a relevance in the area of biomolecules and drug research.[7] *N*-Heterocyclic β-amino acids and related compounds with biological significance represent a relevant class of derivatives in medicinal chemistry and drug design, for example, **13**–**15**. Some six- or five-membered azaheterocyclic β-amino acid derivatives express antibacterial or antiviral activities (Figure 2).[7]

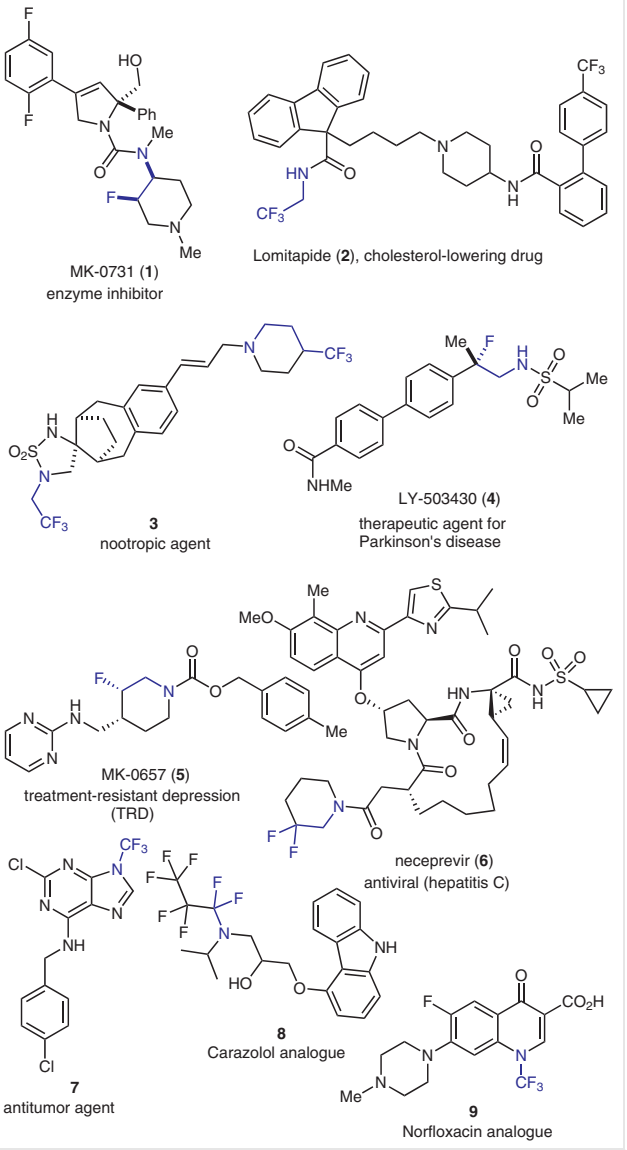


Figure 1 Several bioactive molecules with fluoroamine or trifluoroamine units

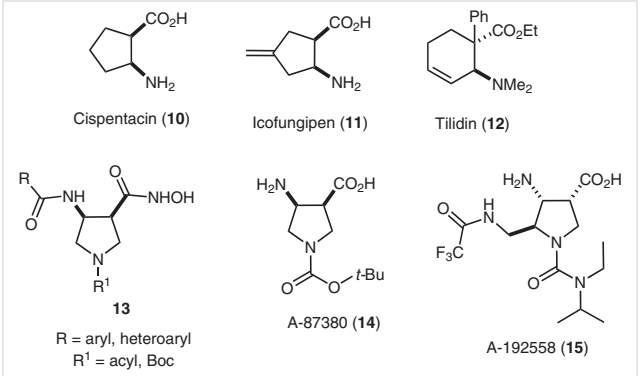


Figure 2 Some alicyclic and azaheterocyclic β-amino acids with biological relevance

A stereocontrolled synthetic protocol was earlier applied by our group for the synthesis of various fluorine-containing piperidine or azepane β-amino acid derivatives. The synthetic protocol involved the application of some commercially available fluorinated or polyfluorinated primary amines and it was based on the oxidative ring cleavage of unsaturated cyclic β-aminocarboxylates through the ring C=C bond, which was followed by ring closing by double reductive amination giving the products across ring expansion of the diformyl intermediates (Figure 3).[8]

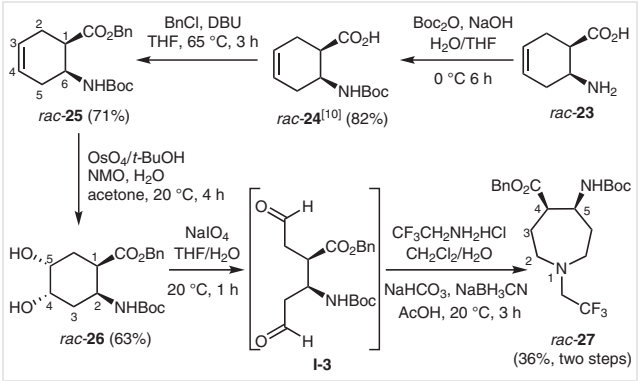
Taking into consideration the high pharmaceutical potential of saturated azaheterocycles, β-amino acids, and organofluorine molecules, our aim was to combine these structural elements and to expand further the chemical space by synthetizing novel molecular structures containing these motifs. This work is intended to offer an insight into the extension of our earlier work.[8] Briefly, we describe stereocontrolled synthesis of fluorine-containing piperidine or azepane β-amino acid derivatives, with focus on the outcome of the olefin bond functionalization/diol formation/oxidative ring cleavage/ring closure by reductive amination synthetic protocol. Our aim was to study substrate effects and to learn the influence of variable experimental reaction conditions.

First, we started the extension of our previous findings with the synthesis of azepane β-amino ethyl esters. Racemic bicyclic β-lactam *rac*-**16** derived from 1,4-cyclohexadiene was converted according to strategies described earlier. Namely, lactam ethanolysis/N-benzoylation/*cis*-dihydroxylation afforded racemic diol stereoisomers *rac*-**18** and *rac*-**21** in which the relative stereochemistry of the ester and amide functions are *cis* in the case of *rac*-**18** and *trans* in the case of *rac*-**21** (Scheme 1).[9] Both dihydroxylated amino esters *rac*-**18** and *rac*-**21** were subjected to oxidative ring cleavage with $NaIO_4$ providing the corresponding diformyl intermediates, which were subsequently transformed without isolation by reaction with 2,2,2-trifluoroethylamine HCl salts, in the presence of $NaHCO_3$ and $NaCNBH_3$ into *cis* and *trans* azepane β-amino esters *rac*-**19** and *rac*-**22** (Scheme 1). Note, that the synthetic pathway proceeded with stereocontrol, that is, the configuration of the stereocenters in the product was predetermined by the structures of the starting cyclohexene esters *rac*-**17** (*cis* isomer) and *rac*-**20** (*trans* isomer). Since the stereocenters at C-1 and C-2 of amino esters *rac*-**18** and *rac*-**21** were not affected during the ring enlargement protocol, the configuration of the chiral centers in *rac*-**19** and *rac*-**22** are predetermined by the stereochemistry of the starting materials (also assigned on the basis of NMR analysis). Accordingly, the *cis* amino ester afforded the corresponding azepane derivative with the carboxylate and carbamate/amide functions in a *cis* relative arrangement,

while the *trans* amino ester gave the related *trans* azepane amino ester.

Since the process described above was highly substrate dependent in view of stereochemistry and structure of the starting compound, our intention was to develop further this synthetic strategy with the analysis of the nature of the ester function. *N*-Boc-protected amino acid *rac*-**24**[10] derived from 1,4-cyclohexadiene was transformed on treatment with BnCl in the presence of DBU into benzyl ester *rac*-**25** (THF, reflux, 3 h). Next, the product subjected to dihydroxylation with the NMO/OsO_4 system stereoselectively provided diol derivative *rac*-**26**, in which the relative configuration of the amide and ester groups is *cis*. The vicinal diol cleavage was performed with $NaIO_4$ in THF and the resulting dialdehyde intermediate gave by reaction with trifluoroethylamine and $NaBH_3CN$, across double reductive amination with conservation of the configuration at chiral centers, the corresponding *cis*-azepane amino ester *rac*-**27** in 36% yield (two steps) (Scheme 2).

The *trans*-stereoisomer of amino ester *rac*-**27** could also be accessed from *trans*-2-aminocyclohexene benzyl ester *rac*-**28**, a stereoisomer of *rac*-**5**. Thus, amino ester *rac*-**28** was prepared from amino acid *rac*-**24** by reaction with BnCl in the presence of DBU in THF at reflux temperature. Contrary to the synthesis of *rac*-**25**, the reaction at prolonged heating after 24 hours provided *trans* amino ester *rac*-**28** through epimerization at C-1. In contrast to the dihydroxylation of ethyl ester *rac*-**21** (with the ester and amide in *trans* arrangement), oxidation under similar conditions of *trans* benzyl ester *rac*-**28** proved to be not selective. It is due

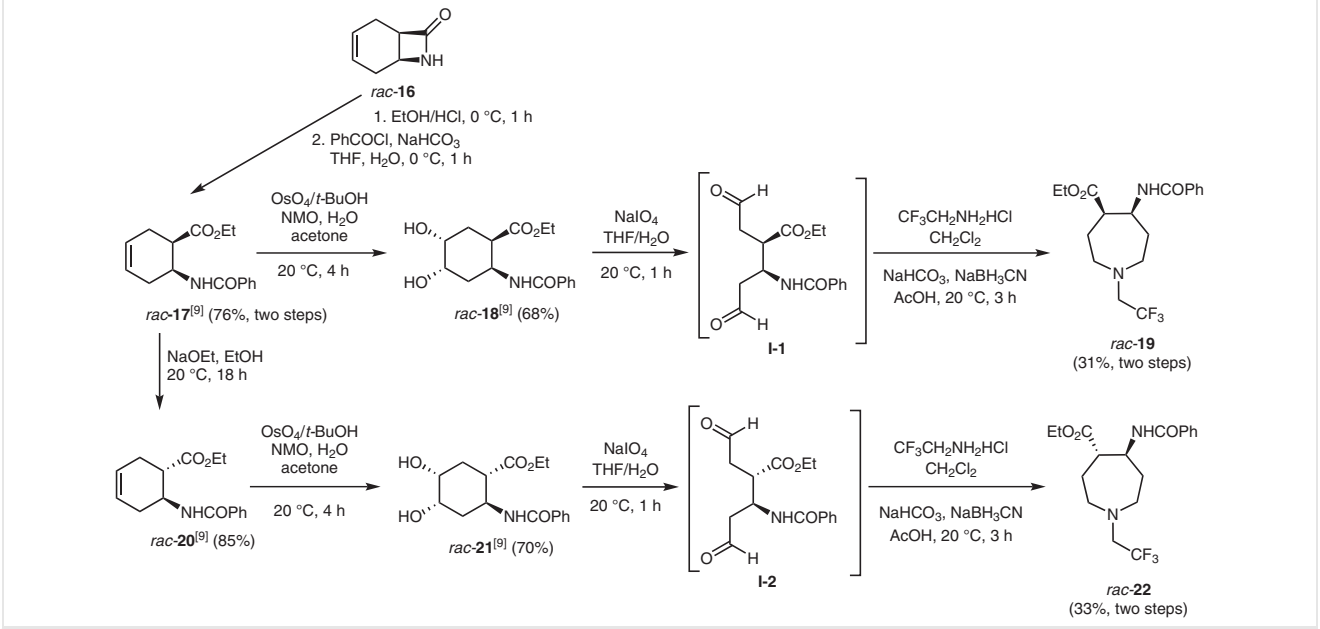


Scheme 2 Stereocontrolled synthesis of azepane β-amino ester *rac*-**27**

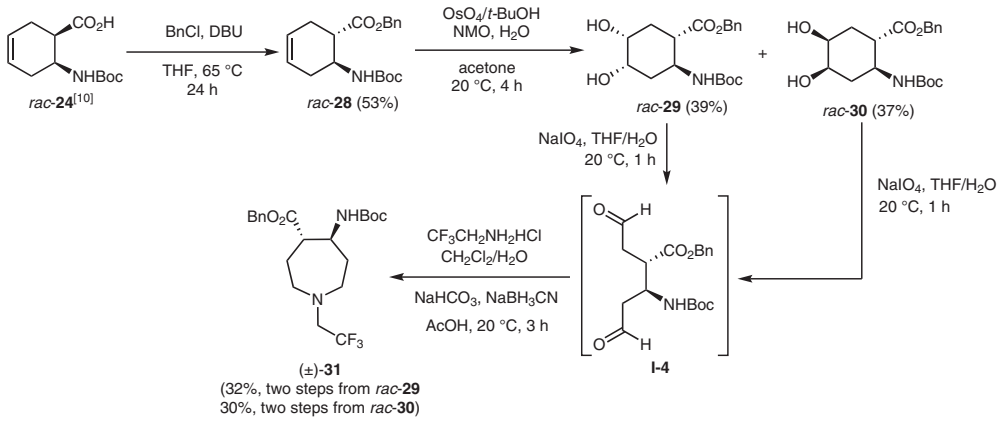
to the bulkier benzyl ester function affording two diol stereoisomers, identified as *rac*-**29** and *rac*-**30** in nearly 1:1 ratio, which were separated by column chromatography.

Dihydroxylated amino ester stereoisomers *rac*-**29** and *rac*-**30** were submitted to $NaIO_4$-mediated oxidative ring cleavage. Diol cleavage in both *rac*-**29** and *rac*-**30** gave dialdehyde **I-4** with the concomitant disappearance of the chiral centers at C-3 and C-4. As a result, after cyclization under reductive amination, both furnished the same azepane derivative *rac*-**31** as the single product (Scheme 3).

Having studied the behavior of benzyl *cis*- and *trans*-cyclohexene 2-aminocarboxylates in the oxidative ring opening/reductive ring closure with ring expansion, which resulted in azepane scaffolds, next we started to evaluate the five-membered analogues in view of the access of piperidine derivatives. First, *cis*-2-aminocyclopentene



Scheme 1 Synthesis of azepane β-amino ester diastereoisomers *rac*-**19** and *rac*-**22**



Scheme 3 Stereocontrolled synthesis of azepane β-amino ester *rac*-**31**

carboxylic acid *rac*-**33** was prepared from the corresponding β-lactam derived from cyclopentadiene through hydrolysis/*N*-Boc protection. Compound *rac*-**33** on treatment with BnCl/DBU system afforded ester *rac*-**34**[11] (THF, reflux, 3 h). Selective OsO_4-catalyzed *cis*-dihydroxylation of the latter led to amino ester *rac*-**35**, in which the steric relationship of the benzyl ester and amide groups was *cis*, while the relative orientation of the two hydroxyl functions was *trans* to the ester and amide groups. Diol *rac*-**35** on treatment with $NaIO_4$ in THF followed by the immediate transformation of the corresponding diformyl intermediate (**I-5**) by ring closing under double reductive amination with trifluoroethylamine yielded, with conservation of the configuration of the stereocenters, piperidine amino ester *rac*-**36** (Scheme 4).

Benzylation of amino acid *rac*-**33** by reaction with BnCl in the presence of DBU (THF, reflux, 22 h) produced *rac*-**37** through epimerization at the active methine moiety to form the corresponding *trans*-amino benzyl ester. Dihydroxylation of *rac*-**37**, again, gave two diol diastereoisomers *rac*-**38** and *rac*-**39** in a non-selective manner in a ratio of about 1:1, which were separated and isolated by column chromatography. Upon treatment with $NaIO_4$, both diol derivatives (*rac*-**38** and *rac*-**39**) underwent ring opening and by reaction with trifluoroethylamine provided the same *trans*-amino ester piperidine skeleton *rac*-**40** (Scheme 5). The transformation occurred through the diformyl intermediate **I-6** resulting in the disappearance of the stereogenic centers at C-3 and C-4.

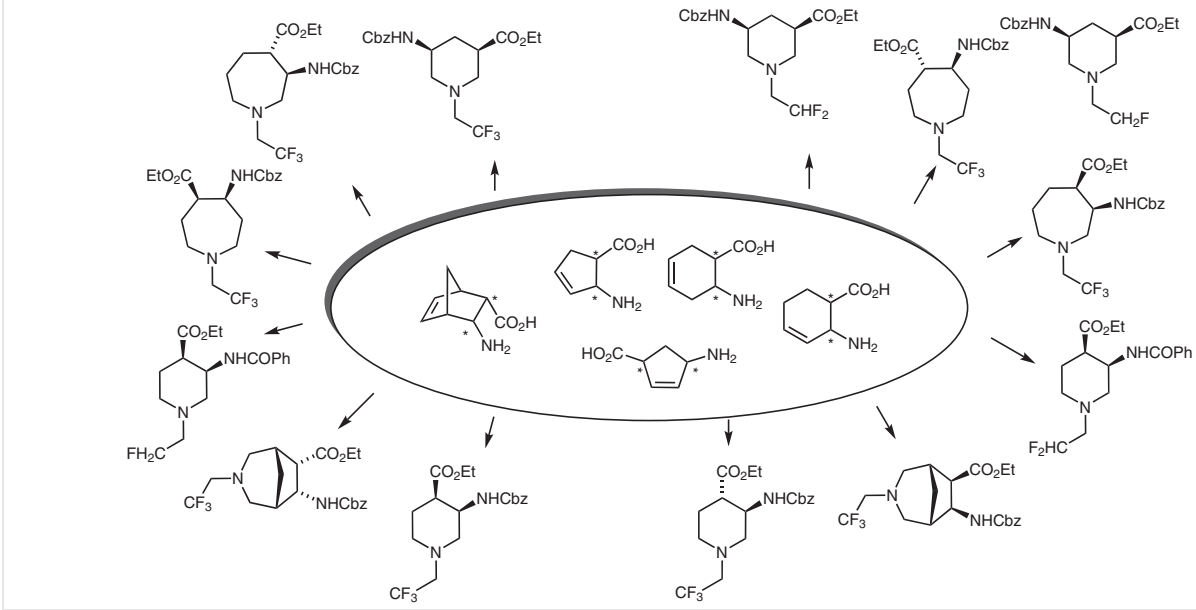
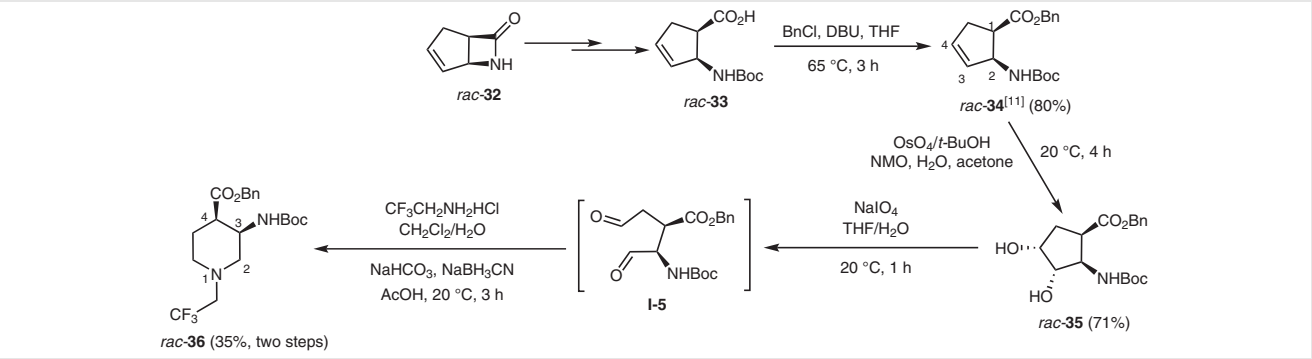
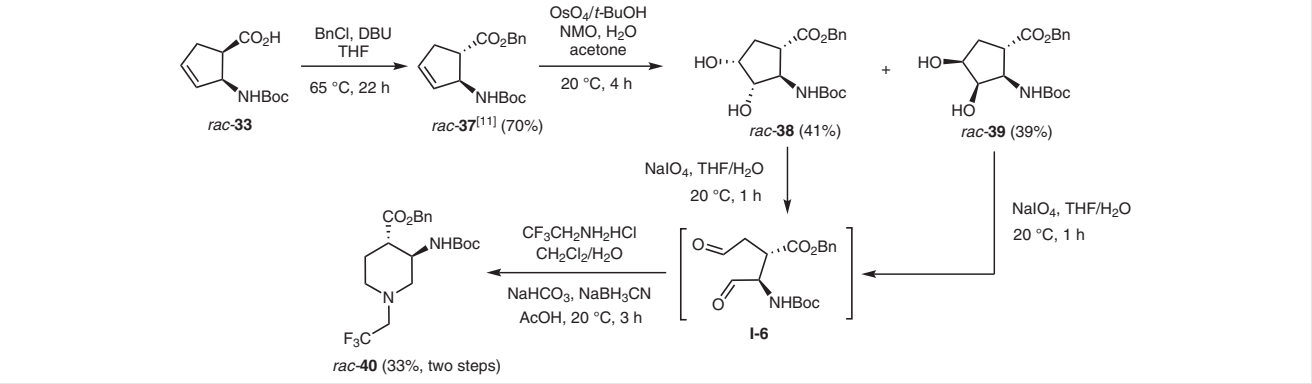


Figure 3 Transformation of some cycloalkene β-amino acids into fluorine-containing N-heterocyclic β-amino esters



Scheme 4 Stereocontrolled synthesis of piperidine β-amino ester *rac*-**36**

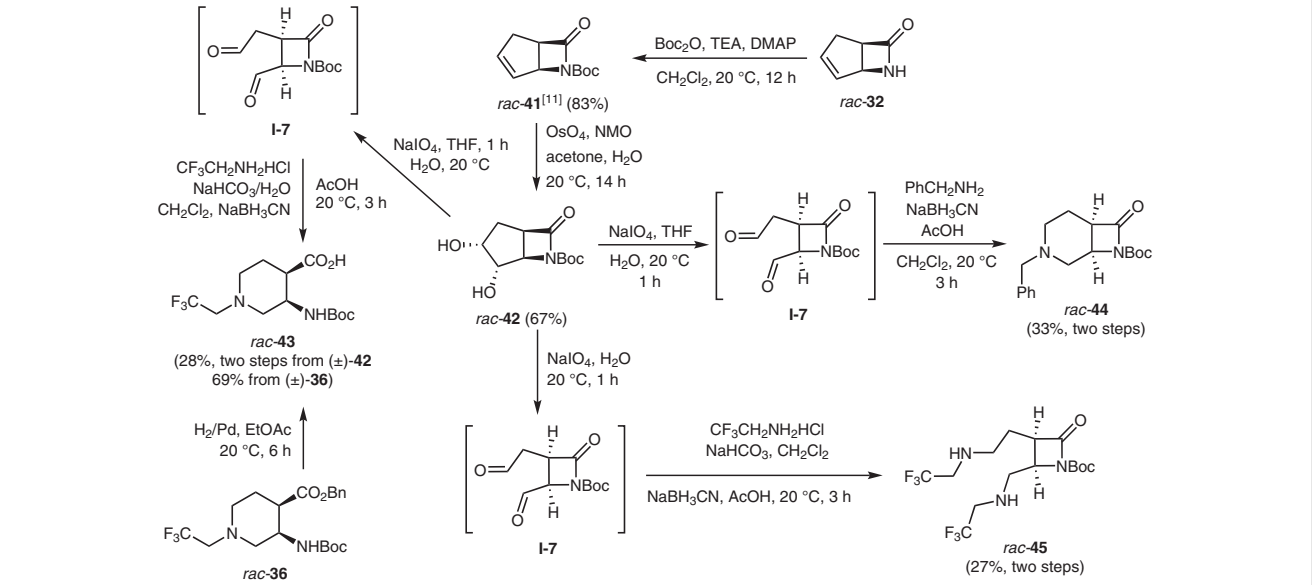


Scheme 5 Stereocontrolled synthesis of piperidine β-amino ester *rac*-**40**

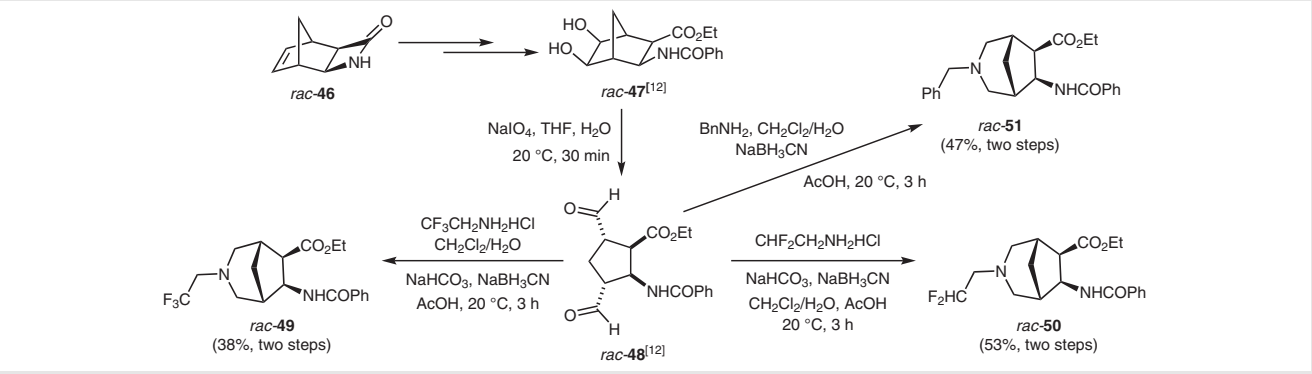
In order to increase the number of novel structures with piperidine core, we selected dihydroxylated β-lactam *rac*-**42** as the starting model compound. The synthesis of *rac*-**42** proceeded selectively, when carried out through OsO_4-catalyzed *cis*-dihydroxylation of *N*-Boc-protected β-lactam *rac*-**41** derived from cyclopentadiene.[11] The outcome of oxidative ring cleavage/reductive ring closing protocol on dihydoxylated bicyclic lactam *rac*-**41** was found to depend on reaction condition. It is in contrast to the transformation of diol amino esters either with six- or five-membered ring described above (see Schemes 3–5). When compound *rac*-**42** was subjected to oxidative ring opening with $NaIO_4$, followed by treatment with trifluoroethylamine HCl salt in the presence of $NaCNBH_3$, cyclization into piperidine with simultaneous lactam ring opening took place giving amino acid *rac*-**43**. It should be noted, that compound *rac*-**43** could be accessed on an alternative route, by hydrogenolysis of benzyl ester *rac*-**36** in the presence of H_2/Pd in EtOAc (Scheme 6).

Next, our study was continued by transforming diol *rac*-**42** under similar conditions, except with the exclusion of water. In this case, no lactam ring formation occurred. However, somewhat surprisingly, instead of cyclization, a simple double reductive amination proceeded and afforded, even with one equivalent of fluorinated amine, the diamino derivative *rac*-**45**. Addition of two equivalents of trifluoroethylamine did not affect significantly the yield of *rac*-**45**. It should be noted, that manipulations of experimental conditions similar to those used in the case of the ring opening/ring closing protocol of diols described above (with or without H_2O, changing the quantity of the fluorinated primary amine, Schemes 2–5) had no influence on the outcome of the reactions. Interestingly, when the cyclization was carried out again with the exclusion of water but with benzylamine as the primary amine, the reaction furnished the desired piperidine-fused lactam framework *rac*-**44** through cyclization and without lactam ring opening (Scheme 6).

Finally, with this latter observation in mind, we proceeded to investigate the behavior of cyclic diformyl amino ester *rac*-**48** (synthesized from β-lactam *rac*-**46** derived from norbornadiene[12]) by cyclization with reductive amination by using different types of amines, namely, 2,2,2-trifluoroethylamine, 2,2-difluoroethylamine, and benzylamine. In all cases, applying the reaction conditions of double reductive amination, cyclization with stereocontrol furnished the corresponding azabicyclic β-amino esters *rac*-**49**, *rac*-**50**, and *rac*-**51**, respectively (Scheme 7, Figure 4). In addition, ester *rac*-**51** was characterized by X-ray crystallographic analysis.[13]



Scheme 6 Transformation of dihydroxylated β-lactam *rac*-**42** across oxidative ring opening/reductive ring closing



Scheme 7 Stereocontrolled synthesis of azabicyclic β-amino esters *rac*-**49**, *rac*-**50**, and *rac*-**51**

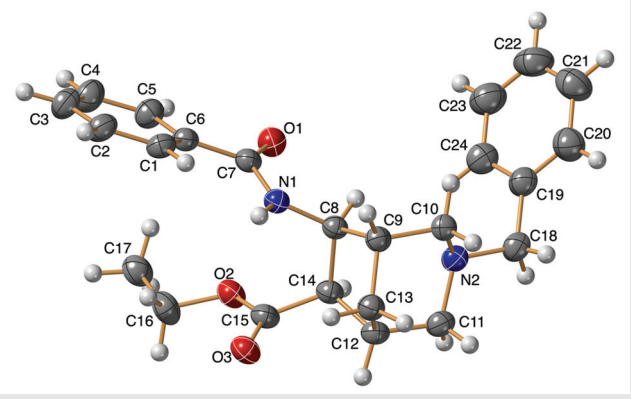


Figure 4 X-ray diffraction analysis of *rac*-**51** (for details, see the Supporting Information)

In conclusion, a simple synthetic procedure with high stereocontrol has been described for the access of novel fluorine-containing six- and seven-membered N-heterocyclic β-amino esters, based on ring olefin bond transformation of some cycloalkene amine esters or lactams. Transformations involved oxidative ring cleavage followed by ring closure with double reductive amination of diformyl intermediates in the presence of commercially available primary fluoroamines and benzylamine. Since the stereocenters of the starting carbocyclic β-amino esters are not affected during the protocol, they will predetermine the configuration of the stereocenters in the corresponding azaheterocyclic products. The outcome of the ring opening/ring closing procedure was studied under various experimental conditions with investigation of the substrate influence. Further experiments in view of extension of the above method towards novel β-lactams as well as for the access of enantiomerically pure substances is ongoing in our laboratory.

General information: Chemicals were purchased from Sigma-Aldrich. Solvents were used as received from the suppliers. Melting points were determined with a Kofler apparatus. Silica gel 60 F254 was purchased from Merck. NMR spectra were acquired at room temperature on a Bruker Avance 400 spectrometer (^{1}H frequency 400.13 MHz; ^{19}F frequency 376.50 MHz, ^{13}C frequency 100.76 MHz) or Bruker Avance Neo spectrometer (^{1}H frequency 500.20 MHz; ^{19}F frequency 470.66 MHz, ^{13}C frequency 125.78 MHz) in $CDCl_3$ or D_6-DMSO solution, using the deuterium signal of the solvent to lock the field. The ^{1}H and ^{13}C chemical shifts are given relative to TMS and ^{19}F to $CFCl_3$ (0.00 ppm).

β-Amino Ester Benzyl Esters; General Procedure

To a solution of amino acid (12 mmol) dissolved in THF (50 mL) were added DBU (2.1 equiv) and benzyl chloride (1 equiv). The mixture was stirred under reflux for the time indicated. Next, the mixture was diluted with EtOAc (80 mL), washed with brine (3 × 70 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Dihydroxylation of N-Protected β-Amino Esters and N-Protected β-Lactams; General Procedure

To a solution of N-protected β-amino ester or N-protected β-lactam (10 mmol) and NMO (1.2 equiv) in acetone (50 mL) was added a 2% OsO_4 solution in *t*-BuOH (0.3 mL) dropwise and the resulting reaction mixture was stirred for 4 h (in the case of amino esters) or 14 h (in the case of lactams) at r.t. After termination of the reaction monitored by TLC, sat. aq Na_2SO_3 (160 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude products were purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Fluorine-Containing N-Heterocyclic β-Amino Esters by Oxidative Ring Cleavage Followed by Ring Closure by Reductive Amination; General Procedure

To a stirred solution of dihydroxylated β-amino ester (3 mmol) was added $NaIO_4$ (1.5 equiv) in THF/H_2O (40 mL/2 mL). After stirring for 30 min at 20 °C under an argon atmosphere, the reaction was quenched by the addition of H_2O (60 mL). The mixture was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried (Na_2SO_4). The resulting solution containing the diformyl intermediate was concentrated to half of its volume and was used without purification in the next reaction step. To the solution of the diformyl derivative were added fluorine-containing amine hydrochloride (1 equiv) and $NaHCO_3$ (2 equiv) and the mixture was stirred at 20 °C for 10 min. After addition of $NaCNBH_3$ (1 equiv) and AcOH (2 drops) stirring was further continued for 3 h at 20 °C. The reaction mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc).

N-Benzylated N-Heterocyclic β-Amino Esters by Oxidative Ring Cleavage Followed by Ring Closure by Reductive Amination; General Procedure

To a stirred solution of dihydroxylated β-amino ester (2 mmol) was added $NaIO_4$ (1.3 equiv) in THF/H_2O (25 mL/1.5 mL). After stirring for 30 min at 20 °C under an argon atmosphere, the reaction was quenched with H_2O (35 mL). The mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were dried (Na_2SO_4). The resulting solution containing the diformyl derivative, concentrated to half of its volume, was used without purification for the next step. To the solution of the dialdehyde intermediate was added benzylamine (1 equiv) and the mixture was stirred at 20 °C for 10 min. After adding $NaCNBH_3$ (1.2 equiv) and AcOH (2 drops) stirring was further continued for 3 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 phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Oxidative Ring Cleavage Followed by Ring Closure by Reductive Amination of Dihydroxylated β-Lactams; Synthesis of *rac*-43; Typical Procedure (Scheme 6)

To a stirred solution of the dihydroxylated β-lactam *rac*-**42** (365 mg, 1.5 mmol) was added $NaIO_4$ (1.3 equiv) in THF/H_2O (15 mL/1 mL). After stirring for 1 h at 20 °C under an argon atmosphere, the reaction was quenched with H_2O (25 mL). The mixture was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried (Na_2SO_4). The resulting solution containing the diformyl derivative **I-7**, concentrated to half of its volume, was used without purification in the next step. To the solution of the dialdehyde intermediate was added trifluoroethylamine HCl salt (1 equiv) and the mixture was stirred at 20 °C for 10 min. After adding $NaCNBH_3$ (1.2 equiv), H_2O (0.5 mL), and AcOH (2 drops), stirring was further continued for 3 h at 20 °C. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Oxidative Ring Cleavage Followed by Ring Closure by Reductive Amination of Dihydroxylated β-Lactams; Synthesis of *rac*-45; Typical Procedure (Scheme 6)

To a stirred solution of the dihydroxylated β-lactam *rac*-**42** (365 mg, 1.5 mmol) was added $NaIO_4$ (1.3 equiv) in THF/H_2O (15 mL/1 mL). After stirring for 1 h at 20 °C under an argon atmosphere, the reaction was quenched with H_2O (25 mL). The mixture was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried (over Na_2SO_4).The resulting solution containing the diformyl derivative **I-7**, concentrated to half of its volume, was used without purification for the next step. To the solution of the dialdehyde intermediate was added trifluoroethylamine HCl salt (1 or 2 equiv), and the mixture was stirred at 20 °C for 10 min. After adding $NaCNBH_3$ (1.2 equiv) and AcOH (2 drops), stirring was further continued for 3 h at 20 °C. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Oxidative Ring Cleavage Followed by Ring Closure by Reductive Amination of Dihydroxylated β-Lactams; Synthesis of *rac*-44; Typical Procedure (Scheme 6)

To a stirred solution of the dihydroxylated β-lactam *rac*-**42** (365 mg, 1.5 mmol) was added $NaIO_4$ (1.3 equiv) in THF/H_2O (15 mL/1 mL). After stirring for 1 h at 20 °C under an argon atmosphere, the reaction was quenched with H_2O (25 mL). The mixture was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases were dried (Na_2SO_4). The resulting solution containing the diformyl derivative **I-**

7, concentrated to half of its volume, was used without purification in the next step. To the solution of the dialdehyde intermediate was added benzylamine (1 equiv), and the mixture was stirred at 20 °C for 10 min. After adding $NaCNBH_3$ (1.2 equiv) and AcOH (2 drops), stirring was further continued for 3 h at 20 °C. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Hydrogenolysis and Cleavage of the *O*-Benzyl Group; General Procedure

To a solution of amino benzyl ester (1 mmol) in EtOAc (25 mL) was added 10% Pd/C (80 mg) and the mixture was stirred under H_2 atmosphere at r.t. for 6 h. Then the solids were filtered off through Celite, the filtrate was concentrated under reduced pressure, and the crude product was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc).

Characterization of the Synthesized New Substances (Schemes 1–6)

tert-Butyl (1*R**,3*R**,4*S**,5*R**)-3,4-Dihydroxy-7-oxo-6-azabicyclo-[3.2.0]heptane-6-carboxylate (*rac*-42)

White solid; yield: 1.63 g (67%); mp 138–140 °C; R_f = 0.40 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.42 (s, 9 H, *t*-C_4H_9), 1.62–1.69 (m, 1 H, CH_2), 1.83–1.90 (m, 1 H, CH_2), 3.43–3.49 (m, 1 H, H-1), 3.92–4.03 (m, 3 H, H-3, H-4, and H-6), 4.80 (br s, 1 H, OH), 4.99 (br s, 1 H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.1, 29.4, 51.0, 59.7, 70.0, 72.0, 82.7, 147.3, 167.6.

HRMS (ESI+): *m*/*z* calcd for $C_{11}H_{17}NO_5Na^+$: 266.1107; found: 266.1006.

Benzyl (1*R**,2*R**,3*S**,4*R**)-2-[(*tert*-Butoxycarbonyl)amino]-3,4-dihydroxycyclopentanecarboxylate (*rac*-35)

White solid; yield: 2.49 g (71%); mp 122–124 °C; R_f = 0.40 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*-C_4H_9), 2.06–2.11 (m, 1 H, CH_2), 2.14–2.19 (m, 1 H, CH_2), 3.38–3.43 (m, 1 H, H-1), 3.94–4.04 (m, 1 H, H-2), 4.18–4.24 (m, 2 H, H-3, and H-4), 5.08 (s, 2 H, OCH_2), 5.52 (br s, 1 H, NH), 7.39–7.47 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 33.7, 41.9, 56.7, 66.9, 70.1, 78.7, 80.4, 128.3, 128.5, 128.7, 135.3, 157.3, 174.1.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{26}NO_6^+$ (M + H)$^+$: 352.1682; found: 352.1763.

Benzyl (1*S**,2*R**,3*S**,4*R**)-2-[(*tert*-Butoxycarbonyl)amino]-3,4-dihydroxycyclopentanecarboxylate (*rac*-38)

White solid; yield: 1.44 g (41%); mp 113–115 °C; R_f = 0.38 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, *t*-C_4H_9), 2.03–2.10 (m, 1 H, CH_2), 2.13–2.18 (m, 1 H, CH_2), 3.36–3.42 (m, 1 H, H-1), 3.92–3.99 (m, 1 H, H-2), 4,.10–4.18 (m, 2 H, H-3, and H-4), 5.03–5.10 (m, 2 H, OCH_2), 5.51 (br s, 1 H, NH), 7.39–7.47 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 33.7, 41.9, 56.8, 67.0, 70.1, 79.2, 80.5, 128.3, 128.6, 128.7, 135.3, 172.0, 174.1.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{25}NO_6$: 351.1682; found: 352.1760.

Benzyl (1*S**,2*R**,3*R**,4*S**)-2-[(*tert*-Butoxycarbonyl)amino]-3,4-dihydroxycyclopentanecarboxylate (*rac*-39)

White solid; yield: 1.37 g (39%); mp 107–108 °C; R_f = 0.36 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.32 (s, 9 H, *t*-C_4H_9), 1.81–1.89 (m, 2 H, CH_2), 2.82–2.87 (m, 1 H, H-1), 3.64–3.69 (m, 1 H, H-2), 3.92–3.99 (m, 2 H, H-3, and H-4), 4.57 (br s, 1 H, OH), 4.64 (br s, 1 H, OH), 5.00–5.09 (m, 2 H, OCH_2), 6.38 (br s, 1 H, NH), 7.36–7.47 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.7, 34.0, 46.5, 55.9, 66.0, 71.6, 73.1, 78.3, 128.0, 128.3, 128.7, 136.7, 172.2, 175.1.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{26}NO_6^+$ (M + H)$^+$: 352.1682; found: 352.1760.

Benzyl (1*R**,6*S**)-6-[(*tert*-Butoxycarbonyl)amino]cyclohex-3-enecarboxylate (*rac*-25)

White solid; yield: 3.46 g (71%); mp 73–75 °C; R_f = 0.36 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *t*-C_4H_9), 2.03–2.09 (m, 1 H, CH_2), 2.30–2.39 (m, 2 H, CH_2), 2.52–2.59 (m, 1 H, CH_2), 2.82–2.89 (m, 1 H, H-1), 4.20–4.28 (m, 1 H, H-6), 5.04 (s, 2 H, OCH_2), 5.62–5.72 (m, 2 H, H-3, and H-4), 7.39–7.48 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 28.3, 30.7, 41.8, 46.3, 66.5, 79.3, 124.8, 124.9, 128.1, 128.2, 128.6, 135.9, 155.3, 173.3.

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{26}NO_4^+$ (M + H)$^+$: 332.17874; found: 332.1866.

Benzyl (1*S**,6*S**)-6-[(*tert*-Butoxycarbonyl)amino]cyclohex-3-enecarboxylate (*rac*-28]

White solid; yield: 3.50 g (53%); mp 76–98 °C; R_f = 0.34 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, *t*-C_4H_9), 1.97–2.06 (m, 1 H, CH_2), 2.31–2.38 (m, 2 H, CH_2), 2.47–2.55 (m, 1 H, CH_2), 2.73–2.80 (m, 1 H, H-1), 4.01–4.10 (m, 1 H, H-6), 4.66 (br s, 1 H, NH), 5.03–5.10 (m, 2 H, OCH_2), 5.58–5.60 (m, 2 H, H-3 and H-4), 7.36–7.46 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.6, 28.4, 31.1, 44.5, 47.3, 66.6, 79.8, 124.3, 124.9, 128.2, 128.3, 128.5, 135.9, 155.0, 173.4.

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{26}NO_4^+$ (M + H)$^+$: 332.17874; found: 332.18677.

Benzyl (1*R**,2*S**,4*S**,5*R**)-2-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydroxycyclohexanecarboxylate (*rac*-26)

White solid; yield: 2.67 g (63%); mp 78–80 °C; R_f = 0.40 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.30 (s, 9 H, *t*-C_4H_9), 1.51–1.56 (m, 1 H, CH_2), 1.66–1.75 (m, 2 H, CH_2), 1.96–2.01 (m, 1 H, CH_2), 2.89–2.97 (m, 1 H, H-1), 3.59–3.68 (m, 2 H, H-2 and H-4), 4.10–4.16 (m, 1 H, H-5), 4.28 (br s, 1 H, OH), 4.36 (br s, 1 H, OH), 4.97–5.03 (m, 2 H, OCH_2), 6.77 (br s, 1 H, NH), 7.30–7.45 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.6, 28.7, 34.2, 40.6, 65.9, 66.1, 66.6, 67.7, 78.4, 128.3, 128.5, 128.7, 136.7, 155.6, 173.3.

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{28}NO_6^+$ (M + H)$^+$: 366.1838; found: 366.1916.

Benzyl (1*S**,2*S**,4*S**,5*R**)-2-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydroxycyclohexanecarboxylate (*rac*-29)

White solid; yield: 1.43 g (39%); mp 140–142 °C; R_f = 0.38 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.32 (s, 9 H, *t*-C_4H_9), 1.48–1.55 (m, 3 H, CH_2), 1.77–1.82 (m, 1 H, CH_2), 2.66–2.73 (m, 1 H, H-1), 3.44–3.49 (m, 1 H, H-2), 3.51–3.57 (m, 1 H, H-4), 3.77–3.83 (m, 1 H, H-5), 4.45 (br s, 1 H, OH), 4.57 (br s, 1 H, OH), 4.99–5.04 (m, 2 H, OCH_2), 6.92 (br s, 1 H, NH), 7.39–7.51 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.7, 39.4, 39.9, 40.4, 42.7, 65.8, 67.0, 69.6, 77.9, 128.0, 128.3, 128.9, 136.8, 155.2, 174.4.

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{28}NO_6^+$ (M + H)$^+$: 366.1838; found: 366.1916.

Benzyl (1*S,2*S**,4*R**,5*S**)-2-[(*tert*-Butoxycarbonyl)amino]-4,5-dihydroxycyclohexanecarboxylate (*rac*-30)**

White solid; yield: 1.35 g (37%); mp 147–149 °C; R_f = 0.36 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.31 (s, 9 H, *t*-C_4H_9), 1.46–1.52 (m, 1 H, CH_2), 1.55–1.60 (m, 1 H, CH_2), 1.78–1.84 (m, 2 H, CH_2), 2.45–2.53 (m, 1 H, H-1), 3.42–3.45 (m, 1 H, H-2), 3.76–3.81 (m, 1 H, H-4), 3.83–3.89 (m, 1 H, H-5), 4.44 (br s, 1 H, OH), 4.51 (br s, 1 H, OH), 5.01 (s, 2 H, OCH_2), 6.72 (br s, 1 H, NH), 7.37–7.48 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 28.7, 30.8, 37.7, 45.9, 47.6, 65.8, 68.5, 69.7, 77.8, 128.0, 128.2, 128.7, 136.8, 155.2, 173.3.

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{28}NO_6^+$ (M + H)$^+$: 366.1838; found: 366.1917.

Ethyl (4*R,5*S**)-5-Benzamido-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (*rac*-19)**

White solid; yield: 346 mg (31%); mp 56–58 °C; R_f = 0.42 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.16 Hz, 3 H, CH_3), 1.84–1.93 (m, 2 H, CH_2), 2.11–2.20 (m, 1 H, CH_2), 2.21–2.30 (m, 1 H, CH_2), 2.81–2.91 (m, 4 H, CH_2NCH_2), 3.02–3.18 (m, 2 H, CH_2CF_3), 3.33–3.43 (m, 1 H, H-4), 4.15 (m, 2 H, OCH_2), 4.66–4.73 (m, 1 H, H-5), 5.66 (br s, 1 H, NH), 7.42–7.52 (m, 3 H, C_6H_5), 7.73–7.77 (m, 2 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 27.9, 31.8, 47.1, 50.1, 52.2, 52.8, 59.3 (q, $^2J_{C,F}$ = 30.3 Hz, CCF_3), 60.7, 125.5 (q, $^1J_{C,F}$ = 279.9 Hz, CF_3), 126.9, 128.5, 131.5, 134.3, 166.6, 173.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.8 (t, *J* = 11.3 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{24}F_3N_2O_3^+$ (M + H)$^+$: 373.1661; found: 373.1748.

Ethyl (4*S,5*S**)-5-Benzamido-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (*rac*-22)**

White solid; yield: 368 mg (33%); mp 62–64 °C; R_f = 0.40 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.13 Hz, 3 H, CH_3), 1.88–1.99 (m, 3 H, CH_2), 2.07–2.14 (m, 1 H, CH_2), 2.81–2.88 (m, 1 H, NCH_2), 2.90–2.96 (m, 3 H, CH_2, NCH_2), 3.05–3.20 (m, 3 H, NCH_2 and CH_2CF_3), 4.12–4.19 (m, 2 H, OCH_2), 4.88–4.95 (m, 1 H, H-5), 7.06–7.11 (m, 1 H, NH), 7.39–7.52 (m, 3 H, C_6H_5), 7.76 (d, *J* = 3.89 Hz, 2 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 28.2, 30.0, 47.6, 49.1, 52.1, 53.2, 59.3 (q, $^2J_{C,F}$ = 30.3 Hz, CCF_3), 60.8, 125.5 (q, $^1J_{C,F}$ = 279.6 Hz, CF_3), 126.9, 128.5, 131.5, 134.3, 166.6, 173.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.9 (t, *J* = 11.5 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{24}F_3N_2O_3^+$ (M + H)$^+$: 373.1661; found: 373.1750.

(3*R,4*R**)-3-[(*tert*-Butoxycarbonyl)amino]-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylic Acid (*rac*-43)**

White solid; yield: 137 mg (28% over 2 steps); mp 100–102 °C; R_f = 0.45 (*n*-hexane/EtOAc 1:2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*-C_4H_9), 2.02–2.11 (m, 1 H, CH_2), 2.21–2.30 (m, 1 H, CH_2), 2.76–2.83 (m, 1 H, H-4), 3.43–3.58 (m, 3 H, CH_2CF_3, H-3), 3.68–3.75 (m, 1 H, OH), 3.81–3.94 (m, 4 H, CH_2NCH_2), 5.59–5.64 (m, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4, 28.3, 43.1, 44.2 (q, $^2J_{C,F}$ = 34.6 Hz, CCF_3), 46.5, 52.7, 63.3, 79.7, 123.9 (q, $^1J_{C,F}$ = 280.9 Hz, CF_3), 156.0, 176.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –69.8 (t, *J* = 10.5 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{22}F_3N_2O_4^+$ (M + H)$^+$: 327.1453; found: 327.1536.

***tert*-Butyl (3*S**,4*S**)-2-Oxo-3-{2-[(2,2,2-trifluoroethyl)amino]ethyl}-4-{[(2,2,2-trifluoroethyl)amino]methyl}azetidine-1-carboxylate (*rac*-45)**

White solid; yield: 164 mg (27% over 2 steps); mp 58–60 °C; R_f = 0.40 (*n*-hexane/EtOAc 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, *t*-C_4H_9), 1.78–1.86 (m, 2 H, CH_2), 2.18–2.26 (m, 1 H, H-3), 2.77–2.85 (m, 1 H, CH_2), 3.02–3.50 (m, 7 H, CH_2), 4.07–4.13 (m, 1 H, H-4), 5.46 (br s, 1 H, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 28.0, 29.7, 43.5, 47.8 (q, $^2J_{C,F}$ = 32.5 Hz, CCF_3), 48.1, 51.0, 51.3, 58.1 (q, $^2J_{C,F}$ = 32.5 Hz, CCF_3), 83.6, 124.2 ($^1J_{C,F}$ = 282.5 Hz, CF_3), 124.4 ($^1J_{C,F}$ = 282.5 Hz, CF_3), 147.8, 170.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.9 (t, *J* = 10.8 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{24}F_6N_3O_3^+$ (M + H)$^+$: 408.1644; found: 408.1725.

***tert*-Butyl (1*R**,6*R**)-3-Benzyl-7-oxo-3,8-diazabicyclo[4.2.0]-octane-8-carboxylate (*rac*-44)**

White solid; yield: 156 mg (33% over 2 steps); mp 57–59 °C; R_f = 0.45 (*n*-hexane/EtOAc 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*-C_4H_9), 1.82–1.89 (m, 1 H, CH_2), 2.16–2.24 (m, 2 H, CH_2), 2.56–2.61 (m, 1 H, H-6), 2.71–2.78 (m, 1 H, CH_2), 3.22–3.33 (m, 2 H, CH_2), 3.52 (d, *J* = 13.15 Hz, 1 H, PhCH_2), 3.61 (d, *J* = 13.15 Hz, 1 H, PhCH_2), 7.33–7.58 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.8, 28.0, 29.7, 43.4, 49.9, 50.0, 52.9, 62.4, 80.3, 127.2, 128.4, 129.0, 132.0, 172.1;

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{25}N_2O_3^+$ (M + H)$^+$: 317.1787; found: 317.1874.

Benzyl (4*R,5*S**)-5-[(*tert*-Butoxycarbonyl)amino]-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (*rac*-27)**

White solid; yield: 464 mg (36% over 2 steps); mp 48–50 °C; R_f = 0.40 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*-C_4H_9), 1.46–1.53 (m, 2 H, CH_2), 1.98–2.08 (m, 2 H, CH_2), 2.46–2.52 (m, 1 H, H-4), 2.69–3.21 (m, 6 H, NCH_2), 4.48–4.53 (m, 1 H, H-5), 4.92 (br s, 1 H, NH), 5.22–5.40 (m, 2 H, OCH_2), 7.39–7.51 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.0, 28.4, 29.7, 44.5, 44.9, 45.4, 56.7 (q, $^2J_{C,F}$ = 31.5 Hz, CCF_3), 57.2, 67.0, 80.3, 124.1, 126.4 ($^1J_{C,F}$ = 280.5 Hz, CF_3), 128.2, 128.6, 135.7, 153.2, 173.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.8.

HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{30}F_3N_2O_4^+$ (M + H)$^+$: 431.2079; found: 431.2171.

Benzyl (4*S,5*S**)-5-[(*tert*-Butoxycarbonyl)amino]-1-(2,2,2-trifluoroethyl)azepane-4-carboxylate (*rac*-31)**

White solid; yield: 413 mg (32% over 2 steps); mp 54–56 °C; R_f = 0.38 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-C_4H_9), 1.42–1.46 (m, 1 H, CH_2), 1.62–1.71 (m, 2 H, CH_2), 1.91–2.02 (m, 1 H, CH_2), 2.18–2.26 (m, 1 H, CH_2), 2.60–3.05 (m, 6 H, NCH_2 and H-4), 4.07–4.12 (m, 1 H, H-5), 5.05–5.12 (m, 2 H, OCH_2), 5.52 (br s, 1 H, NH), 7.39–7.50 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.9, 28.0, 32.4, 46.7, 51.5, 52.0, 52.3, 58.7 (q, $^2J_{C,F}$ = 32.2 Hz, CCF_3), 66.4, 79.2, 125.4 ($^1J_{C,F}$ = 284.15 Hz, CF_3), 128.2, 128.5, 128.7, 135.9, 155.3, 172.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.6.

HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{30}F_3N_2O_4^+$ (M + H)$^+$: 431.2079; found: 431.2111.

Benzyl (3*R,4*R**)-3-[(*tert*-Butoxycarbonyl)amino]-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (*rac*-36)**

White solid; yield: 437 mg (35% ovr 2 steps); mp 54–56 °C; R_f = 0.38 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *t*-C_4H_9), 1.66–1.72 (m, 1 H, CH_2), 1.97–2.04 (m, 1 H, CH_2), 2.45–2.51 (m, 1 H, H-1), 2.53–2.57 (m, 1 H, NCH_2), 2.60–2.66 (m, 1 H, NCH_2), 2.89–2.94 (m, 1 H, NCH_2), 2.98–3.05 (m, 1 H, NCH_2), 4.17–4.22 (m, 1 H, H-2), 4.98–5.04 (m, 2 H, OCH_2), 5.39 (br s, 1 H, NH), 7.39–7.50 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.7, 28.0, 29.7, 47.3, 51.5, 52.0, 58.1 (q, $^2J_{C,F}$ = 29.8 Hz, CCF_3), 67.6, 79.4, 125.6 ($^1J_{C,F}$ = 282.4 Hz, CF_3), 126.9, 127.6, 127.9, 135.9, 155.2, 172.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.9.

HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{28}F_3N_2O_4^+$ (M + H)$^+$: 417.1923; found: 417.2017.

Benzyl (3*R,4*S**)-3-[(*tert*-Butoxycarbonyl)amino]-1-(2,2,2-trifluoroethyl)piperidine-4-carboxylate (*rac*-40)**

White solid; yield: 412 mg (33% over 2 steps); mp 114–116 °C; R_f = 0.35 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-C_4H_9), 1.89–2.00 (m, 2 H, CH_2), 2.39–2.51 (m, 2 H, H-1 and NCH_2), 2.66–2.70 (m, 1 H, NCH_2), 2.89–3.01 (m, 4 H, NCH_2), 4.01–4.07 (m, 1 H, H-2), 4.99 (br s, 1 H, NH), 4.11–4.16 (m, 2 H, OCH_2), 7.30–7.48 (m, 5 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.7, 28.3, 28.9, 46.5, 47.4, 51.4, 57.6, 57.9 (q, $^2J_{C,F}$ = 30.3 Hz, CCF_3), 66.7, 79.6, 123.5 ($^1J_{C,F}$ = 280.5 Hz, CF_3), 128.1, 128.3, 128.5, 139.2, 154.8, 172.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.8.

HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{28}F_3N_2O_4^+$ (M + H)$^+$: 417.1923; found: 417.1638.

Ethyl (1*S,5*S**,6*R**,7*S**)-7-Benzamido-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.2.1]octane-6-carboxylate (*rac*-49)**

White solid; yield: 541 mg (38% over 2 steps); mp 104–106 °C; R_f = 0.42 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.23 (t, *J* = 7.20 Hz, 3 H, CH_3), 1.33–1.39 (m, 1 H, CH_2), 1.98–2.10 (m, 4 H, CH_2, H-1, H-5, and H-6), 2.42–2.47 (m, 1 H, NCH_2), 2.62–2.68 (m, 1 H, NCH_2), 3.02–3.08 (m, 1 H, NCH_2), 3.28–3.33 (m, 1 H, NCH_2), 3.39–3.52 (m, 2 H, NCH_2), 3.99–4.12 (m, 2 H, OCH_2), 4.91–4.99 (m, 1 H, H-7), 7.23–7.50 (m, 3 H, C_6H_5), 7.68–7.76 (m, 2 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 35.1, 41.0, 43.6, 50.7, 54.2, 58.0, 58.4, 60.7, 62.3, 126.8, 127.1, 128.6, 128.8, 128.9, 131.3, 134.6, 136.8, 166.0, 175.5.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –68.8 (t, *J* = 9.2 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{24}F_3N_2O_3^+$ (M + H)$^+$: 385.1661; found: 385.1733.

Ethyl (6*R,7*S**)-7-Benzamido-3-(2,2-difluoroethyl)-3-azabicyclo-[3.2.1]octane-6-carboxylate (*rac*-50)**

White solid; yield: 582 mg (53% over 2 steps); mp 107–109 °C; R_f = 0.80 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.16 Hz, 3 H, CH_3), 1.35–1.42 (m, 1 H, H-8), 2.08–2.15 (m, 1 H, H-8), 2.16–2.21 (m, 1 H, H-2), 2.34–2.41 (m, 2 H, H-4), 2.45–2.50 (m, 1 H, H-2), 2.71–2.88 (m, 3 H, NCH_2, H-1), 3.01–3.08 (m, 1 H, H-5), 3.31–3.38 (m, 1 H, H-6), 4.05–4.15 (m, 2 H, OCH_2), 4.88 (t, *J* = 8.71 Hz, 1 H, H-7), 5.88 (t, *J* = 55.82 Hz, 1 H, CHF_2), 7.38–7.44 (m, 3 H, C_6H_5), 7.46–7.50 (m, 1 H, NH), 7.72–7.76 (m, 2 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 34.4, 40.9, 43.4, 50.3, 54.1, 58.2, 59.3 (t, $^2J_{C,F}$ = 23.6 Hz, $CCHF_2$), 60.9, 126.8, 128.5, 131.4, 134.4, 166.0, 175.4.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –118.2.

HRMS (ESI+): *m*/*z* calcd for $C_{19}H_{24}F_3N_2O_3^+$ (M + H)$^+$: 367.1755; found: 367.1828.

Ethyl (6*R*,7*S*)-7-Benzamido-3-benzyl-3-azabicyclo[3.2.1]octane-6-carboxylate (*rac*-51)

White solid; yield: 553 mg (47% over 2 steps); mp 108–110 °C; R_f = 0.81 (*n*-hexane/EtOAc 3:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.15 Hz, 3 H, CH_3), 1.38–1.43 (m, 2 H, OCH_2), 1.96–2.05 (m, 4 H, CH_2, H-1, and H-5), 2.46–2.49 (m, 1 H, H-7), 2.66–2.72 (m, 1 H, H-6), 2.99–3.05 (m, 1 H, NCH_2), 3.38–3.42 (m, 1 H, NCH_2), 3.44–3.53 (m, 2 H, NCH_2Ph), 4.00–4.12 (m, 2 H, OCH_2), 4.94–4.99 (m, 1 H, NCH_2), 7.24–7.52 (m, 9 H, C_6H_5, NH), 7.79–7.85 (m, 2 H, C_6H_5).

^{13}C NMR (125 MHz, $CDCl_3$): δ =14.3, 35.1, 41.0, 43.6, 50.7, 54.2, 58.0, 58.4, 60.7, 62.3, 126.8, 127.0, 128.3, 128.5, 128.9, 131.3, 134.6, 138.6, 166.0, 175.5.

HRMS (ESI+): *m*/*z* calcd for $C_{24}H_{29}F_3N_2O_3^+$ (M + H)$^+$: 393.2000; found: 393.2190.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706637.

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(13) CCDC 2039976 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures