Application of reductive amination for the stereocontrolled synthesis of functionalized azaheterocycles

Ph.D. Thesis

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PUBLICATION LIST

Papers related to the thesis:

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Eur. J. Org Chem. **2019**, 2202-2211.

II. **L. Ouchakour,** M. Nonn, L. Kiss:
Stereocontrolled synthesis of *N*-heterocyclic fluorine-containing β-amino acid derivatives
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III. **L. Ouchakour,** M. Nonn, M. D'hooghe, L. Kiss:
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Stereocontrolled Synthesis of Functionalized Azaheterocycles from Carbocycles through Oxidative Ring Opening/Reductive Ring Closing Protocols
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VII. **L. Ouchakour,** F. Fülöp, L. Kiss:
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Mátrafüred, Hungary, 11-12 Apr, 2019, oral presentation

List of abbreviations:

Boc: *tert*-butyloxycarbonyl

Cbz: benzyloxycarbonyl

CSI: chlorosulfonyl isocyanate, $ClSO_2NCO$

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

Deoxofluor: bis(2-methoxyethyl)aminosulfur trifluoride, $(MeOCH_2CH_2)_2NSF_3$

NMO: *N*-methylmorpholine *N*-oxide

THF: tetrahydrofuran

THIQ: 1,2,3,4-tetrahydroisoquinoline

1. INTRODUCTION AND AIMS

The chemistry of functionalized azaheterocycles has become a highly important topic in recent decades. These compounds are widely distributed in nature and are essential to life in various ways. For instance, alkaloids, antibiotics, amino acids, vitamins, and a large number of synthetic drugs contain azaheterocyclic ring systems.[1-3] The ring size as well as the nature and stereochemical features of the substituents present in these heterocycles play a fundamental role in assessing their biological activity.[4] Furthermore, a large number of pharmacologically active natural and synthetic *N*-heterocyles are in regular clinical use. They have been utilized as antibiotics, analgesics, and antidepressants as well as anticancer, anti-HIV, and anti-HCV agents.[5-8]

Fluorinated organic compounds are of particular interest in the fields of functional materials science, pharmaceuticals, and agrochemicals,[9-11] due to the unique characteristics of the fluorine atom, which can alter the properties of organofluorines.[12] The fluorine atom is undoubtedly one of the elements that has recently attracted high research interest in several aspects of chemistry. The incorporation of the fluorine atom or a certain fluorinated moiety into organic compounds has become a powerful tool to discover new chemical entities possessing unique physical, chemical, and biological properties in comparison to those of their nonfluorinated parent compounds.[13-15] Recently, it has been estimated that about 30% of the newly approved drugs contain fluorine atoms.[16-19]

In view of the importance of fluorination, fluorinated azaheterocyles have received much attention. Therefore, the synthesis of such molecular entities became an important research topic in the Institute of Pharmaceutical Chemistry at the University of Szeged. The research is focused on the incorporation of fluorine into cyclic β-amino acids and some functionalized cycloalkene derivatives using two common approaches. The first method applies late-stage exchange of hydroxy or oxo functions by using various nucleophilic fluorinating reagents such as diethylaminosulfur trifluoride (DAST) or Deoxofluor (a direct fluorination approach). The other method is based on the application of fluorine-containing building blocks such as fluorinated amines *(Figure 1*).[20-26]

The present PhD work focuses on the synthesis of various types of fluorinated functionalized azaheterocycles. The aim of the research was to further extend and improve an efficient stereocontrolled procedure to the access of new fluorine-containing saturated *N*-heterocycles. The key step of this procedure is reductive amination of dialdehydes using

fluorinated amines. The required dialdehydes were obtained from various cycloalkenes in two pathways. The first approach starts with the OsO_4-mediated dihydroxylation of the olefinic bond of cycloalkenes, followed by oxidative cleavage of the diol intermediate using $NaIO_4$. In order to improve atom economy, reduce wastes, and avoid the use of toxic heavy metal compounds, a second, "greener" approach has been developed. It uses ozonolysis reaction (treatment with ozone, then reductive workup with dimethyl sulfide) to convert functionalized alkenes into the corresponding carbonyl compounds in a single step.

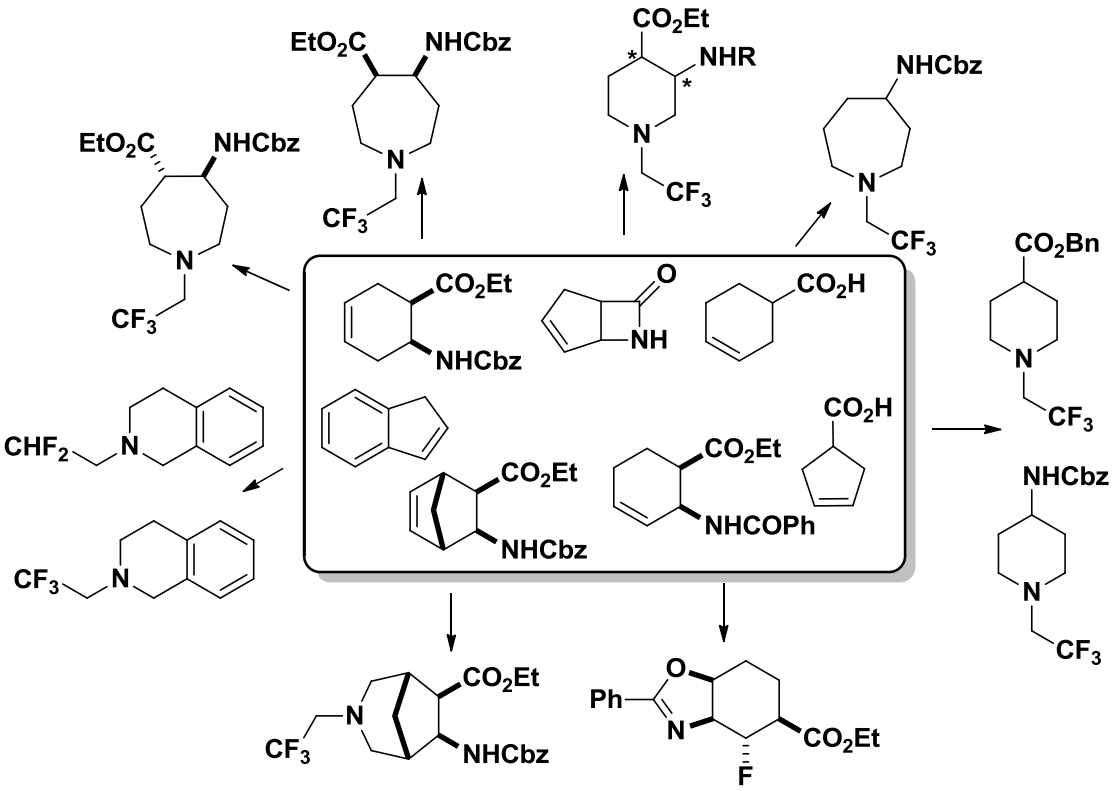


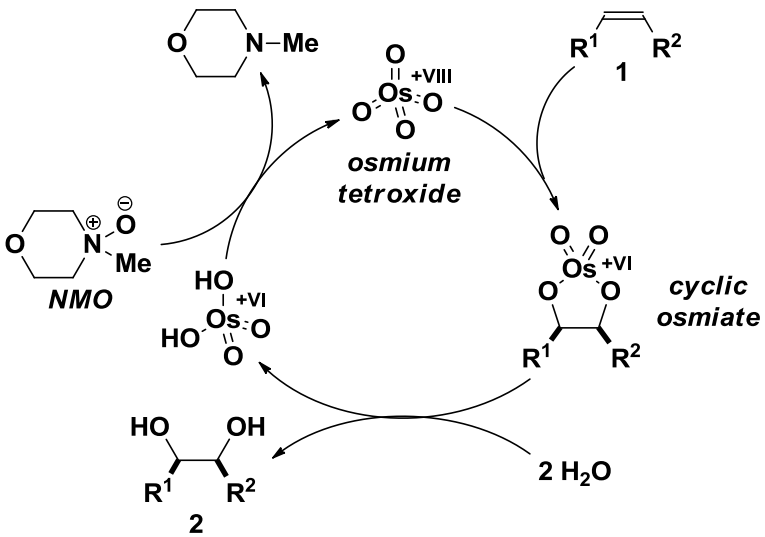
Figure 1. Examples of the synthesis of fluorine-containing *N*-heterocycles

2. LITERATURE BACKGROUND

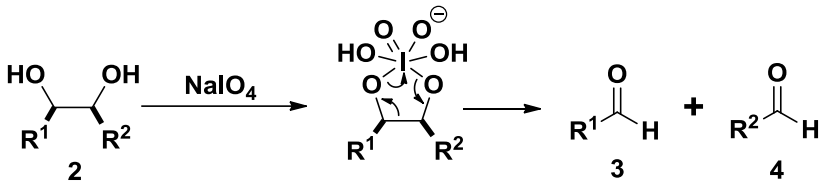
2.1. Olefin bond transformation by oxidative ring cleavage/ring closure through reductive amination protocols

Oxidative cleavage of olefins is one of the paramount reactions developed in organic chemistry used to synthesize the corresponding carbonyl compounds. Many oxidative pathways discussed in the literature can be summarized into two main methodologies: either transformation of olefins into 1,2-diols followed by cleavage of the C–C bond with an oxidant or ozonolysis of the C–C ring double bond. Both are useful transformations to prepare synthetically valuable dialdehydes. The most common methods employed to carry out these operations are the Upjohn method, the Lemieux–von Rudloff oxidation, and the ozonolysis reaction.[27,28]

The Upjohn method is a two-step procedure for the cleavage of the C–C double bond. The first step is dihydroxylation with OsO_4/NMO. This system, which was discovered by Van Rheenen and co-workers,[29] is known as the most efficient catalytic dihydroxylation reaction and, in general, provides vicinal diols in high yields. The reaction is performed in aqueous acetone. OsO_4, the active dihydroxylating agent, is present in a catalytic amount, and a stoichiometric amount of *N*-methylmorpholine *N*-oxide (NMO) co-oxidant is applied to reoxidize the formed osmium(VI) to osmium(VIII) (*Scheme 1*). The second step, the oxidation of vicinal *cis*-diols by $NaIO_4$, is well-known to give the corresponding dicarbonyl products (*Scheme 2*).

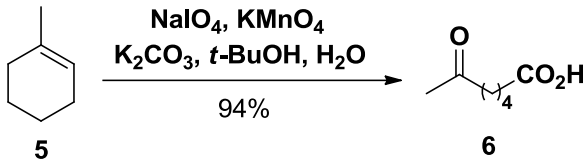


Scheme 1. Dihydroxylation of olefins with NMO/OsO_4



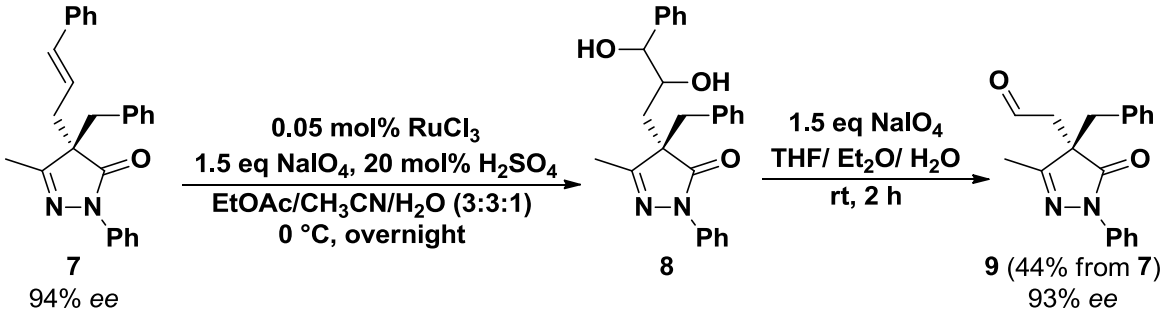
Scheme 2. Vicinal diol cleavage with sodium periodate

Lemieux and von Rudloff reported another oxidative cleavage of C–C double bonds using catalytic amounts of $KMnO_4$ in the presence of $NaIO_4$. The process starts with permanganate-mediated *syn*-dihydroxylation. The formed diol undergoes periodate-mediated oxidative cleavage to oxo compounds. Finally, the newly formed formyl groups are oxidized by permanganate to give the corresponding carboxylic acid (*Scheme 3*), and then $NaIO_4$ oxidizes back the Mn(V) byproduct to Mn(VII).[30]



Scheme 3. Oxidative cleavage of the double bond with $NaIO_4/KMnO_4$

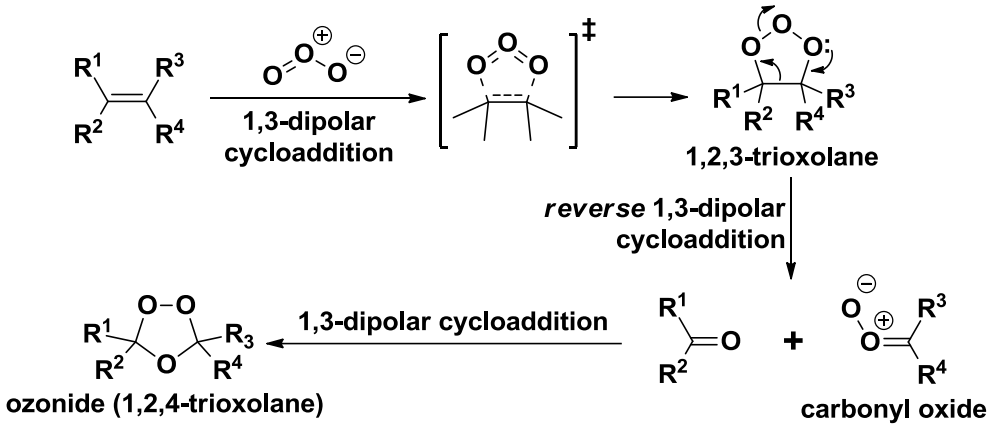
An alternative pathway, developed by Sharpless and co-workers, is based on the $NaIO_4/RuCl_3$ system.[31] Zhong-Lin Tao and co-workers[32] applied the above procedure for the synthesis of pyrazol-5-one derivatives. At first, $RuCl_3$ is oxidized by $NaIO_4$ to RuO_4, then the resulting tetroxide converts the alkene into a vicinal diol in the presence of sulfuric acid in a solvent mixture. The Ru(VI) byproduct is oxidized back to RuO_4 by $NaIO_4$. In the next step, $NaIO_4$-mediated oxidative ring cleavage of **8** furnishes aldehyde **9** (*Scheme 4*).



Scheme 4. Transformation of the double bond to a formyl group with $RuCl_3/NaIO_4$

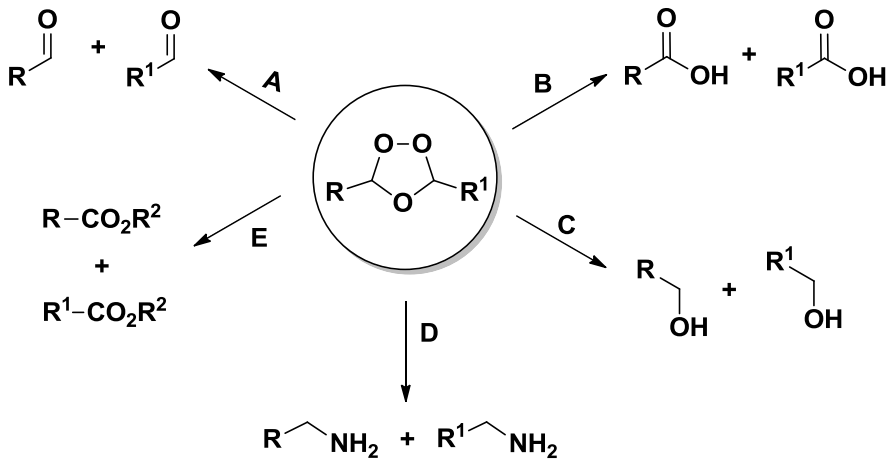
Since the classical work of Schönbein,[33] organic chemists have assumed that ozone reacts with a double bond of an unsaturated compound to form a pair of carbonyl compounds,

which is basically referred to as "Harries ozonolysis" for Carl Dietrich Harries.[34]. Since that time, ozonolysis chemistry has been used extensively in academic research and industrial environments. More recently, ozonolysis has become one of the most important transformations in organic chemistry and it has been used in the multistep synthesis of natural products and steroids.[35,36] Extensive investigation of the mechanism of alkene ozonolysis has confirmed the basic pathway originally proposed by Criegee,[37] which involves three steps (*Scheme 5*). The first step is a 1,3-dipolar cycloaddition between the alkene and ozone, leading to the formation of an unstable intermediate. This spontaneously decomposes via a cycloreversion process to a carbonyl oxide (also called the Criegee intermediate) and a stable carbonyl compound, which can react again in a 1,3-dipolar cycloaddition to give a 1,2,4-trioxolane what is traditionally described as an ozonide (*Scheme 5*).



Scheme 5. Formation of ozonides

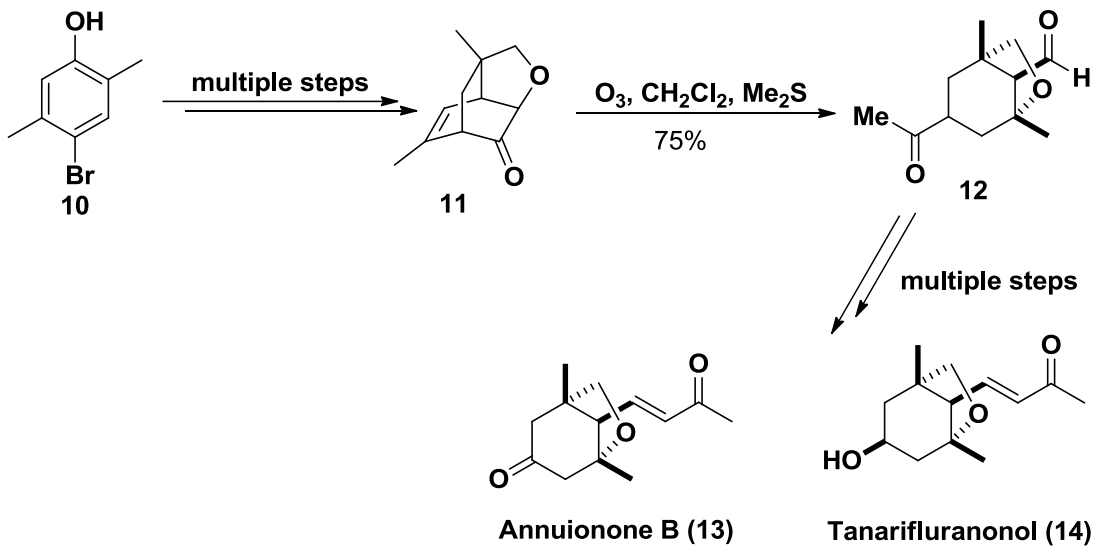
The decomposition of ozonides to give a number of different functional products can be carried out using a variety of reagents (*Scheme 6*).



Scheme 6. Decomposition of ozonides

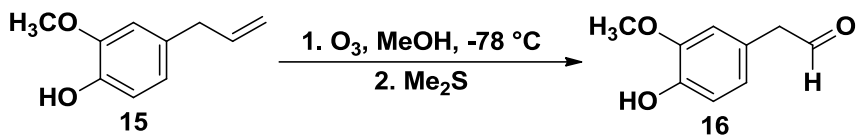
Commonly, mild reducing agents such as dimethyl sulfide,[38] triphenylphosphine or zinc/acetic acid[39] are employed to produce aldehydes (*Pathway A*). Ozonides can also be oxidized with oxygen, peroxyacids or H_2O_2[40] to give carboxylic acids (*Pathway B*). Treatment with reducing agents such as $LiAlH_4$[41] or $NaBH_4$[42] yields alcohols (*Pathway C*). Hydrogenation in the presence of ammonia gives the corresponding amines (*Pathway D*),[43] whereas treatment with alcohol (R^2-OH) and anhydrous HCl affords the corresponding esters (*Pathway E*)[44] (*Scheme 6*).

Shiao *et al*.[45] improved the synthesis of Annuionone B (**13)** and Tanarifuranonol (**14**) from bromo-substituted phenol **10**. A crucial step in the synthesis of these compounds involved the ozonolysis of tricyclic alkene **11** in the presence of Me_2S in CH_2Cl_2 at –78 °C to give carbonyl compound **12** which possesses the necessary 6-oxabicyclo[3.2.1]octane skeleton present in natural products **13** and **14** (*Scheme 7*).[46,47]



Scheme 7. Synthesis of Annuionone B and Tanarifuranonol

Branan and co-workers described a convenient ozonolysis experiment. In this process, the alkene motif of eugenol (**15**) reacts with ozone in MeOH at –78 °C to give an ozonide intermediate, which is reduced to aldehyde **16** using dimethyl sulfide (*Scheme 8*).[48]



Scheme 8. Ozonolysis of eugenol

2.2. Synthesis of saturated azaheterocycles via ring-closing double reductive amination

Saturated heterocyclic compounds are of great importance in medicinal chemistry, biochemistry, and material science. They are attractive scaffolds in the development of new pharmaceuticals.[49] Amongst heterocycles, five-, six-, and seven-membered azaheterocyclic compounds are the most common structural units. A large number of nitrogen-containing saturated cyclic compounds are also attractive building blocks employed to construct other molecules of medicinal or biological interest.[50] Furthermore, azaheterocyclic structures have found widespread clinical uses,[51] albeit, the majority of the pharmacologically active compounds are mainly found in nature. They are common structural units in marketed drugs and in medicinal chemistry targets in the drug discovery processes. They have been utilized as antibiotics, analgesics, antidepressants, anticancer agents, anti-HIV agents, and anti-HCV agents (*Figure 2*).[52-56]

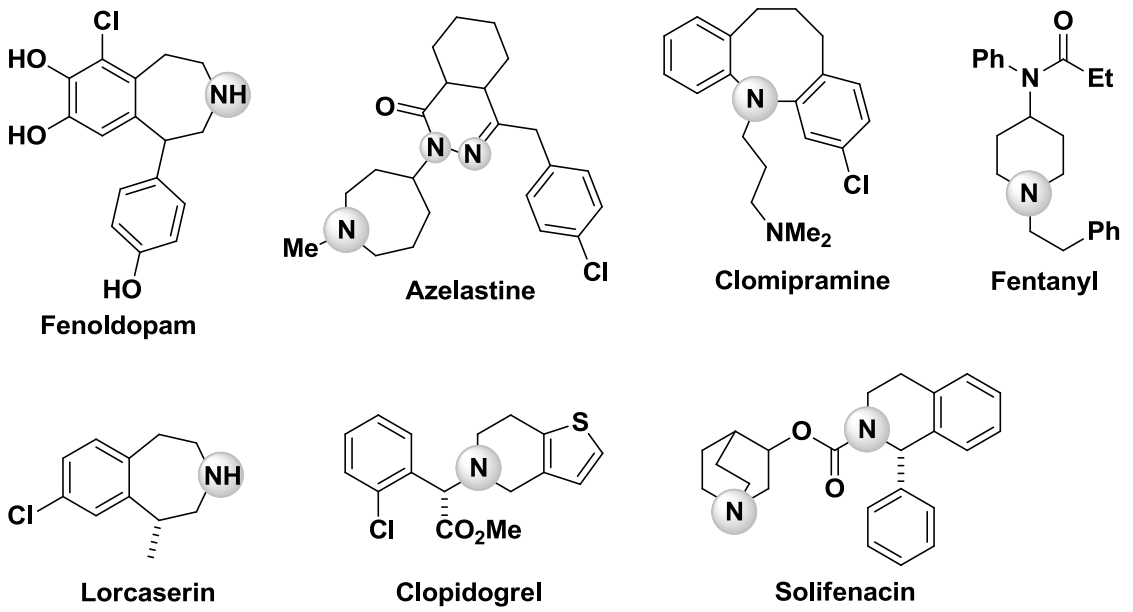
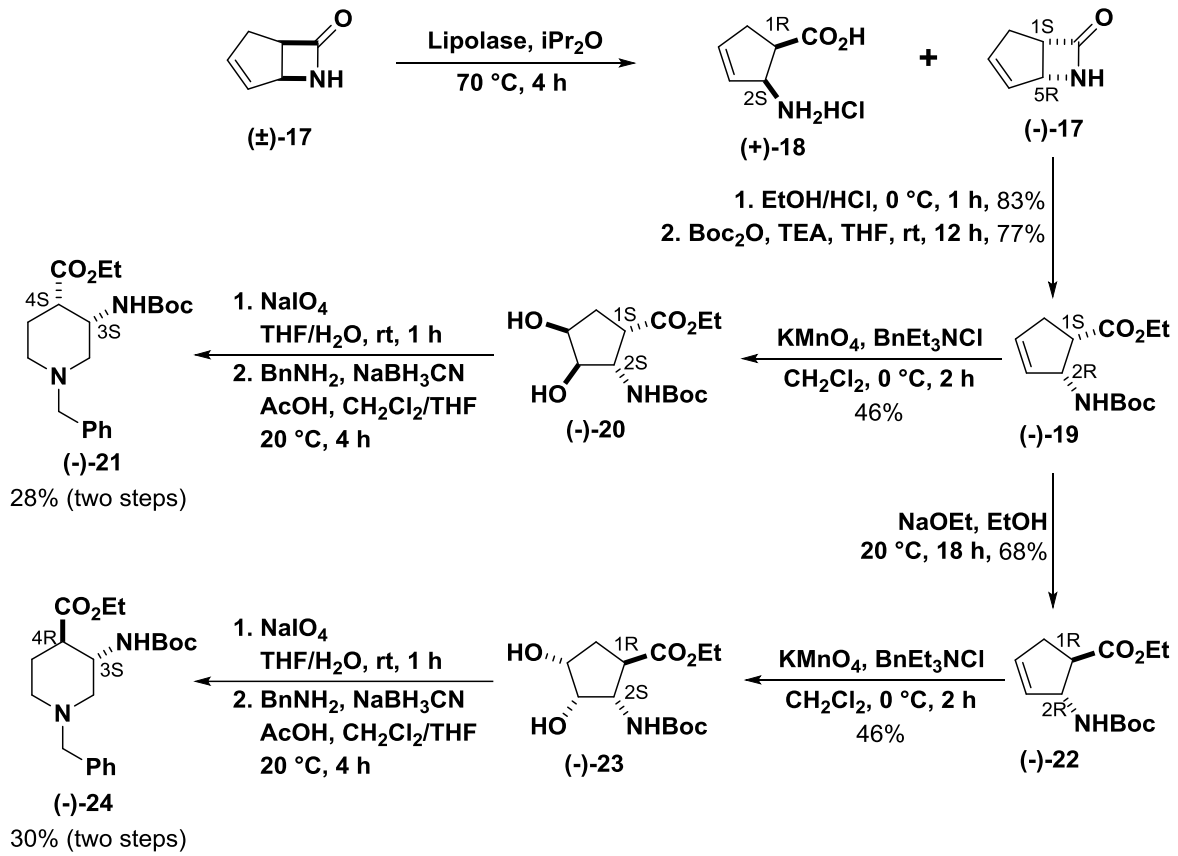


Figure 2. Pharmacologically active compounds based on azaheterocycles

Due to these significant biological activities and structural importance, numerous methods have been developed for their assembly over the past decades.[57] One of the most efficient, useful, and versatile methods to construct saturated azaheterocycles of different ring sizes is ring closure by reductive amination of nitrogen-containing acyclic precursors with appropriate functionalizations.[58]

2.2.1. Synthesis of β-amino acid derivatives by oxidative ring opening/reductive amination protocol

It is already well known that amino acids are relevant structural motifs in a wide variety of biologically active compounds. Thus, the development of synthetic routes towards these compounds is of high practical importance, yet remains methodologically challenging.[59] In particular, β-amino acids[60] are fundamental building blocks for β-lactams, an important class of antibiotics.[61, 62] Indeed, they emerged as privileged scaffolds for the construction of more complex molecular architectures such as biologically active molecules, peptidomimetics, and foldamers.[63] Furthermore, β-amino acids are precursors of β-peptides, which have displayed a high tendency to form stable secondary structures. Finally, β-amino acids are extensively used as chiral starting materials, auxiliaries, and catalysts in organic synthesis.[64]

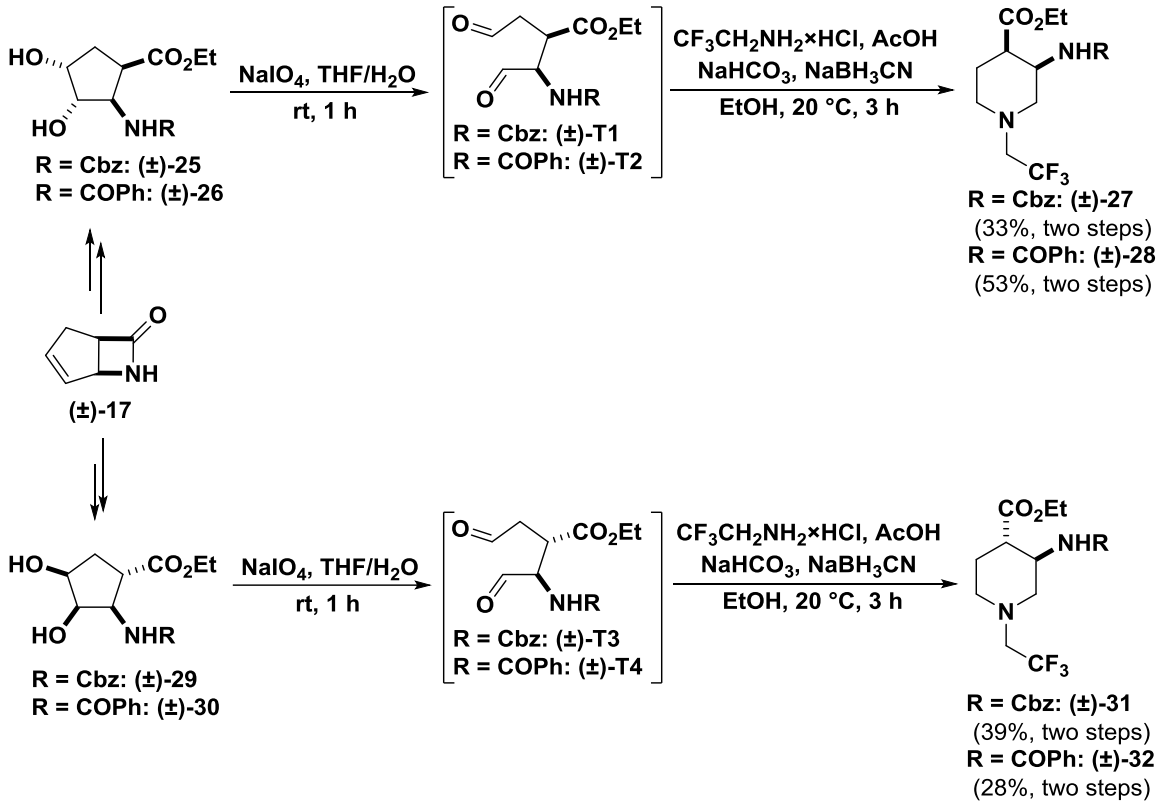


Scheme 9. Enantioselective synthesis of piperidine-4-carboxylates

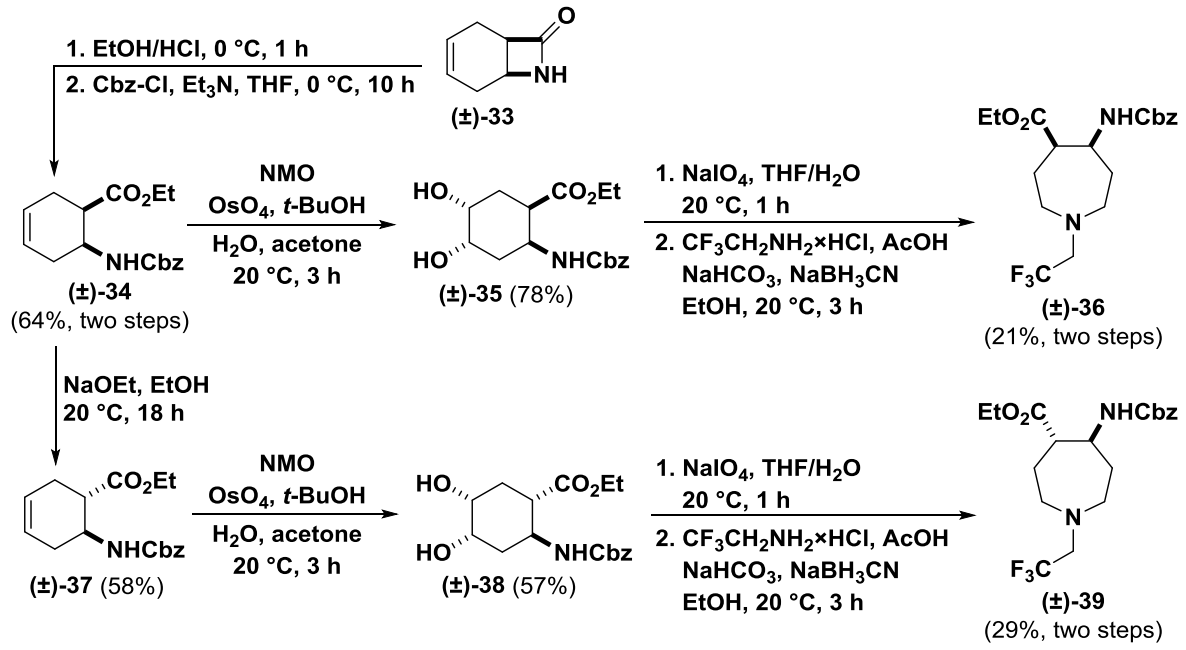
Due to the high biorelevance of organofluorine scaffolds and the importance of *N*-heterocyclic compounds, mentioned above, the research group of the Institute of Pharmaceutical Chemistry has developed a novel route for the introduction a nitrogen atom into the ring of saturated cyclic β-amino acids. The stereocontrolled synthetic route of piperidine-4-

carboxylate enantiomers started from readily available unsaturated bicyclic β-lactam **(±)-17**. Compound **(±)-17** was submitted to enzymatic ring opening in the presence of CAL-B and provided enantiomerically pure β-amino acid **(+)-18** together with unreacted β-lactam enantiomer **(–)-17**. Compound **(–)-17** was transformed into amino ester hydrochloride followed by *N*-protection. Dihydroxylation was carried out with $KMnO_4$ under phase transfer conditions. The next step, $NaIO_4$-mediated oxidative ring opening of the vicinal diols followed by ring expansion via reductive amination, gave novel enantiomerically pure β-amino acid scaffolds **(–)-21** and **(–)-24** (*Scheme 9*).[65]

The above synthetic route was extended for the stereocontrolled synthesis of trifluoromethylated piperidine β-amino esters. Thus, cyclopentene *cis*- and *trans*-β-amino esters were transformed into the corresponding dihydroxylated derivatives with NMO/OsO_4. These were then submitted to oxidative ring opening with $NaIO_4$, followed by ring closure via reductive amination of the diformyl intermediates using trifluoroethylamine to obtain analogues **(±)-27**, **(±)-28**, **(±)-31**, and **(±)-32** (*Scheme 10*).[66]

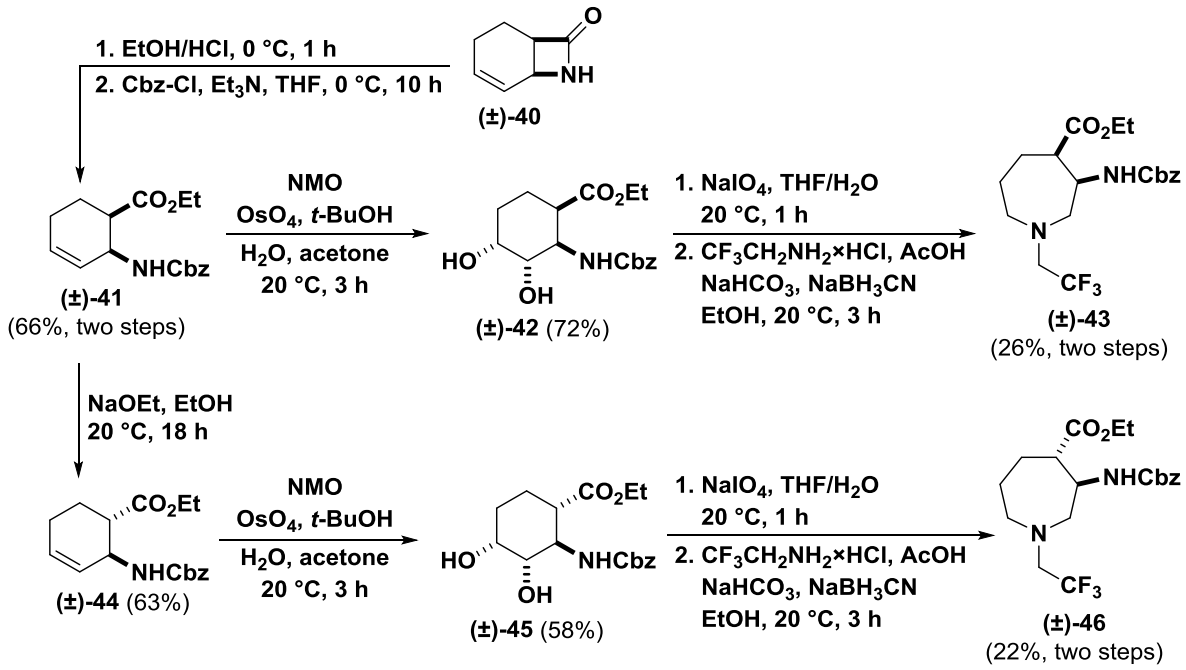


Scheme 10. Synthesis of trifluoromethylated piperidine β-amino ester stereoisomers



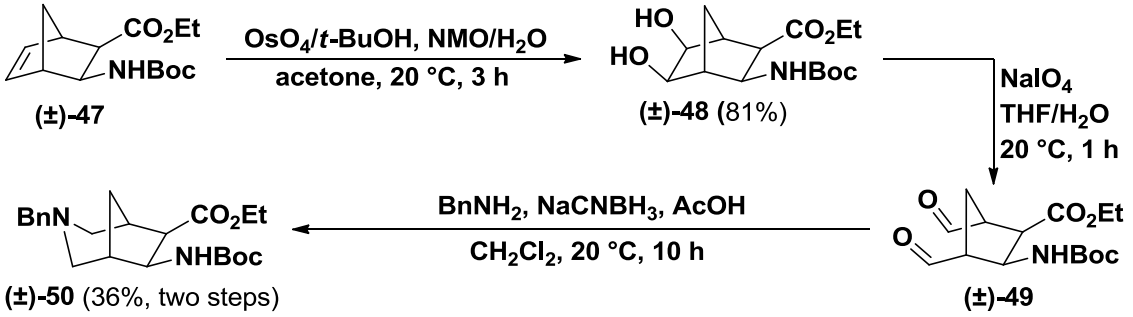
Scheme 11. Synthesis of trifluoromethylated azepane β-amino ester stereoisomers

Bicyclic β-lactam **(±)-33** was transformed in a similar manner. First, it was converted to *cis*- and *trans*-2-aminocyclohex-4-enecarboxylates **(±)-34** and **(±)-47**, which were dihydroxylated with NMO/OsO_4. The resulting **(±)-35** and **(±)-38** diols were subjected to oxidative ring opening with $NaIO_4$. Subsequent reductive amination with trifluoroethylamine yielded azepane β-amino esters **(±)-36** and **(±)-39** (*Scheme 11*).[66] Regioisomeric trifluoromethylated azepane β-amino esters **(±)-43** and **(±)-46** were prepared in an analogous way (*Scheme 12*).[66]



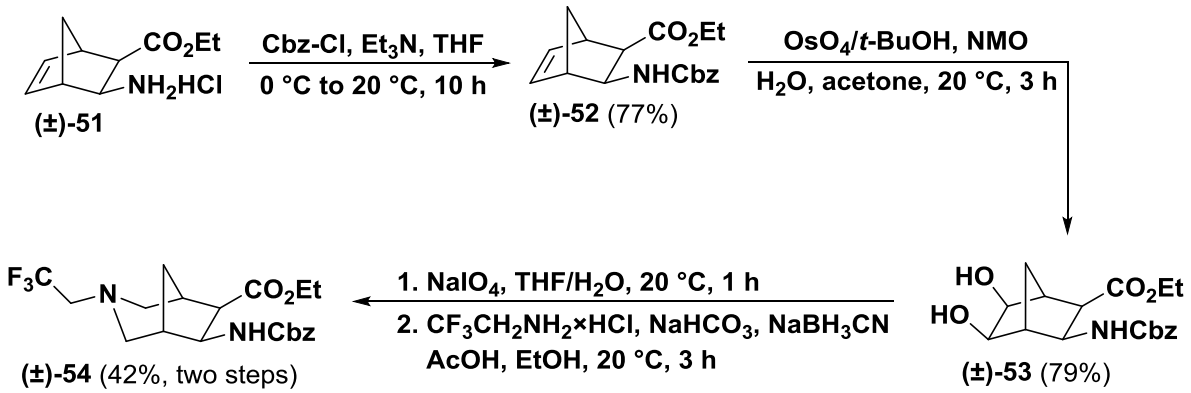
Scheme 12. Synthesis of regioisomeric trifluoromethylated azepane β-amino esters

In further studies, azabicyclic β-amino esters were synthesized starting from *diexo-N*-Boc-protected norbornene amino ester **(±)-47**. The described synthetic pathway utilized oxidative ring-opening and reductive ring-closure methods (*Scheme 13*).[67]



Scheme 13. Synthesis of racemic azabicyclic β-amino ester

In a similar way, the stereocontrolled synthesis of new trifluoromethyl-containing *N*-bridged bicyclic β-amino ester **(±)-54** was also performed starting from readily available *diexo*-norbornene β-amino ester **(±)-52** (*Scheme 14*).[66]



Scheme 14. Synthesis of trifluoromethylated *N*-bicyclic β-amino ester

2.2.2. Synthesis of tetrahydroisoquinoline derivatives through oxidative ring opening/reductive amination protocol

1,2,3,4-Tetrahydroisoquinoline (THIQ) represents one of the most prevalent "privileged heterocylic scaffolds". It is commonly found in a number of naturally occurring alkaloids and possesses a wide range of therapeutic activities including antitumor, antibacterial, antiviral, anticoagulant, anti-inflammatory, anti-Alzheimer, and anticonvulsant activity *(Figure 3*).[68, 69] A number of bioactive small molecules bearing THIQ skeletons as potential therapeutic agents for treatment of diverse diseases, such as cancer, AIDS, Parkinson's disease, etc. have shown

incredible development.[70] Besides, THIQ-containing molecules have shown growing interest in organic synthesis, notably, applications in asymmetric catalysis as chiral scaffolds.[71] Because of these relevant properties, many synthetic approaches towards the creation of an isoquinoline or THIQ core have been described so far. Traditional methods such as the Pictet–Spengler reaction and the Bischler–Napieralski cyclization/reduction sequence were successfully demonstrated and continue to show their power in the synthesis of isoquinoline alkaloid frameworks.[72]

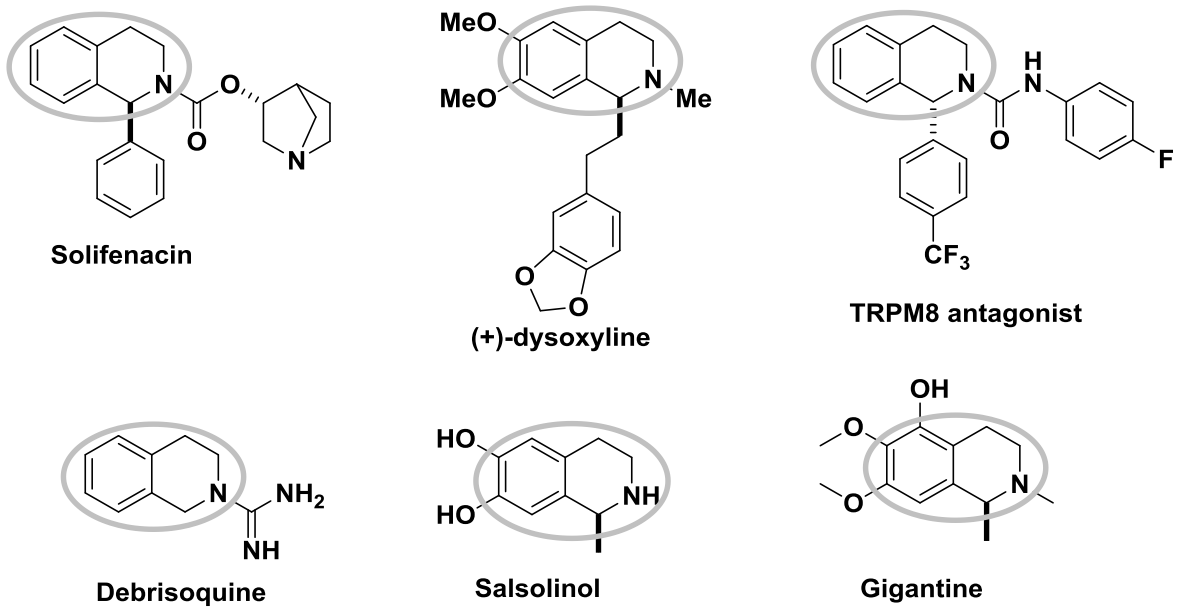
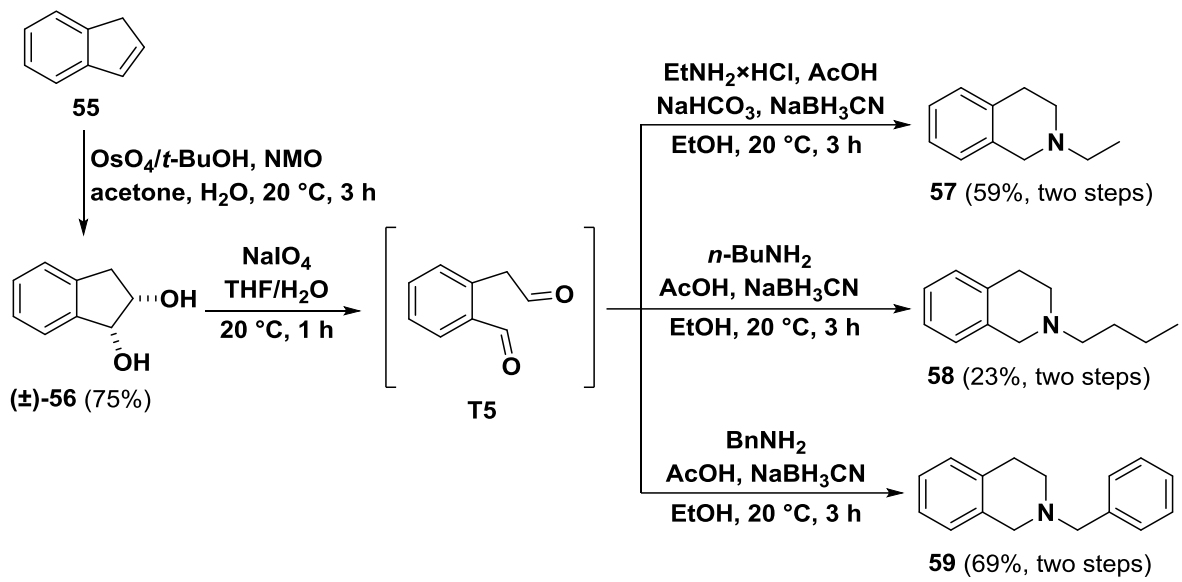


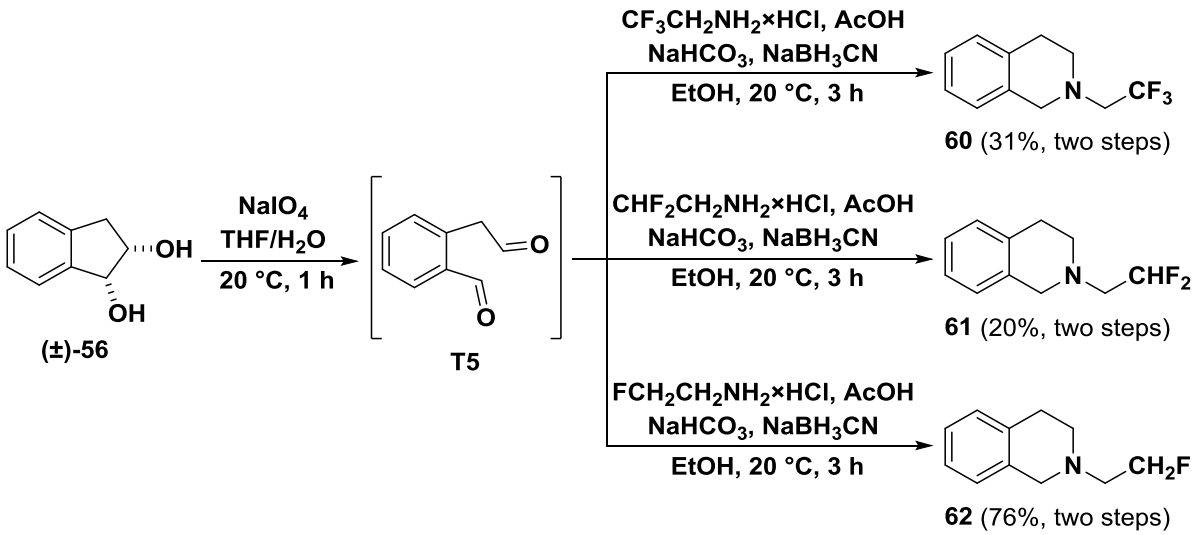
Figure 3. Some biologically active isoquinoline derivatives

Recently, the research group of the Institute of Pharmaceutical Chemistry at the University of Szeged has developed a novel and effective procedure for the construction of the 1,2,3,4-tetrahydroisoquinoline framework possessing various functions.[73] The synthetic strategy involved oxidative ring opening and subsequent ring closing under reductive amination conditions starting from indene and some substituted indene derivatives.

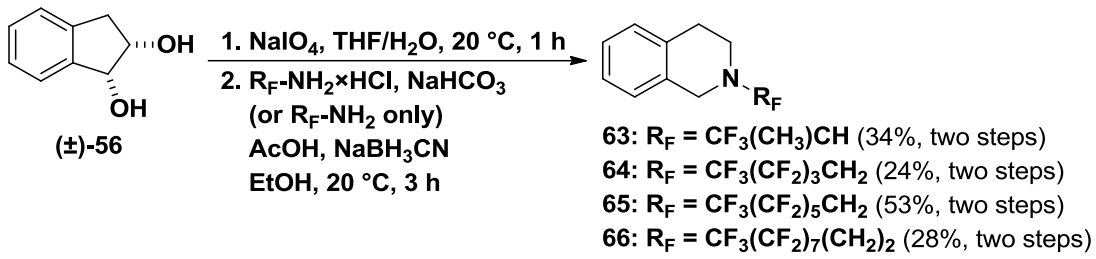
Initially, 1*H*-indene was oxidized with NMO/OsO_4 giving the corresponding vicinal diol derivatives **(±)-56**. Next, oxidation with $NaIO_4$ provided the corresponding unstable dialdehyde intermediate **T5**, which was submitted without isolation to a reductive ring-closure step using different primary amines to form the desired *N*-substituted tetrahydroisoquinoline derivatives (*Scheme 15*).[73] Additionally, the synthetic approach was extended to synthesize fluorinated and polyfluorinated tetrahydroisoquinoline products (*Scheme 16, 17*).[73]



Scheme 15. Synthesis of tetrahydroisoquinoline derivatives



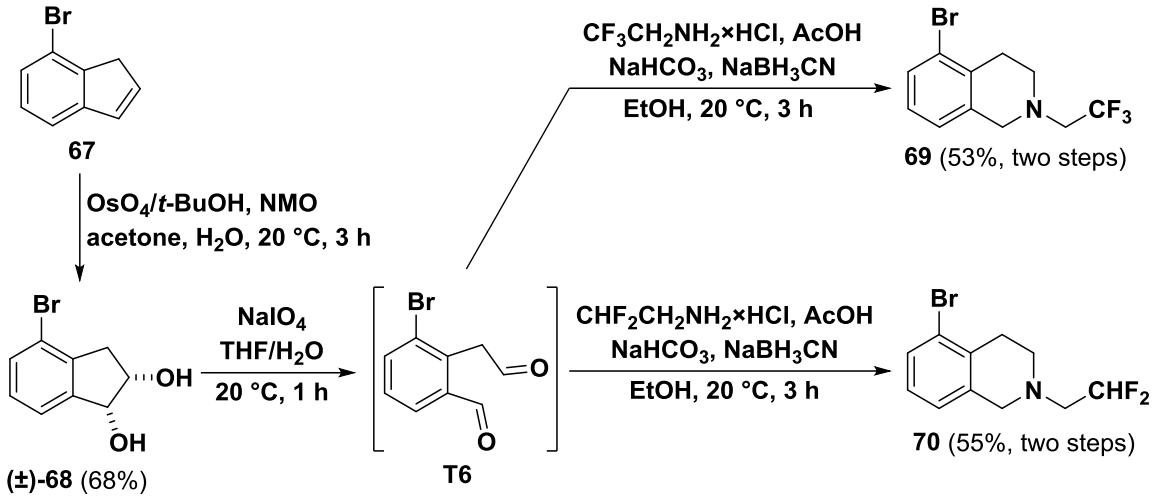
Scheme 16. Synthesis of tetrahydroisoquinoline derivatives with fluorinated ethyl groups



Scheme 17. Synthesis of other polyfluorinated tetrahydroisoquinolines

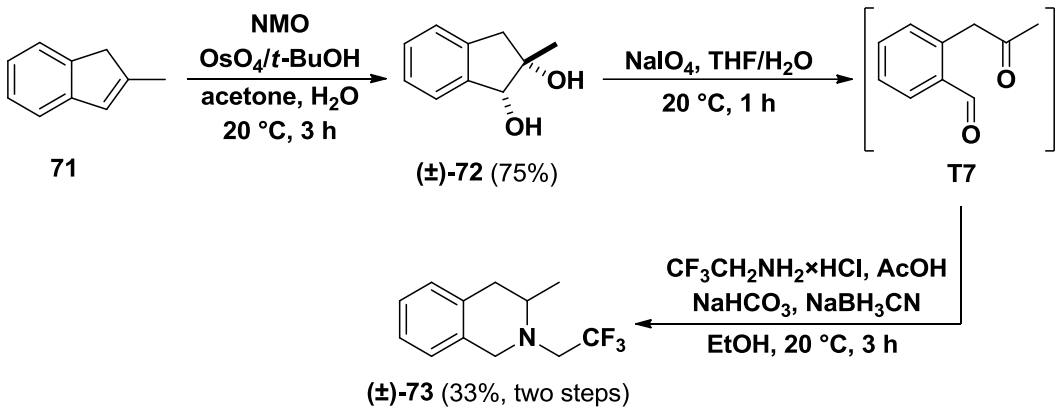
In continuation, the experiments were performed using indene derivatives with substituents on the benzene ring. 7-Bromo-1*H*-indene **67** was subjected to dihydroxylation in the presence of NMO/OsO_4. Vicinal diol **(±)-68** submitted to oxidative ring cleavage led to

dialdehyde **T6**, which then underwent reductive amination with 2,2,2-trifluoroethylamine and 2,2-difluoroethylamine to provide the corresponding trifluorinated and difluorinated tetrahydroisoquinoline derivatives **69** and **70** (*Scheme 18*).[73]



Scheme 18. Synthesis of *N*-heterocycles frameworks from 7-bromo-1*H*-indene

The protocol was further extended to 2-methyl-1*H*-indene **71**. After dihydroxylation with NMO/OsO_4, oxidative ring opening followed by reductive ring closure with trifluoroethylamine provided isoquinoline derivative **(±)-73** (*Scheme 19*).[73]



Scheme 19. Synthesis of *N*-heterocyclic frameworks from 2-methyl-1*H*-indene

2.3. Importance of fluorine-containing azaheterocycles in pharmaceutical research

Fluorine is one of the most abundant elements on earth; however, it occurs extremely rarely in biological compounds. Nevertheless, the introduction of fluorine atoms or fluorine-

containing groups into the structure of an organic molecule has attracted growing attention in recent decades, thanks to the possible advantages originating from the unique properties of the fluorine atom and the carbon–fluorine bond. For instance, the replacement of a C–H bond with a C–F bond in biologically active compounds frequently introduces beneficial properties such as higher metabolic stability.[74] Interestingly, although the very high electronegativity of fluorine relative to carbon imparts a strong dipole moment to the C–F bond, this motif is hydrophobic. As a result, fluorination usually slightly increases lipophilicity. This affects binding affinity to target proteins and increases membrane permeability.[75] As such, fluorine chemistry has played an increasingly important role within pharmaceuticals, agrochemicals, and in materials science. Indeed, more than 20% of pharmaceuticals and 35% of agrochemicals on the market contain at least one fluorine atom.[76,77]

Fluorinated organic compounds are interesting to organic chemists, because they have found a wide range of applications in pharmaceuticals, medicine, agrochemicals, and materials science. The efforts of researchers are directed to find new synthetic strategies for fluorine incorporation into organic molecules and to demonstrate the unique ability of fluorine to modulate their structural, physical, and biological properties.[78] In particular, for making such fluorinated target molecules, either fluorine-containing building blocks are used or fluorinated functional groups are introduced with the help of selective fluorinating or fluoroalkylating reagents. Recent surveys suggest that approximately 25% of all newly approved small-molecule drugs contain fluorine. This increasing prevalence has been driven by a deeper understanding and sophistication by the medicinal chemist community in applying fluorination to drug candidates to address many of the commonly encountered challenges in drug design.

Despite their interesting properties, only a few naturally occurring fluorine-containing organic compounds have been discovered to date. As such, almost all known organic fluorine-containing compounds are synthetic products. Consequently, the development of efficient and practical methodologies to introduce fluorine atoms into important organic molecules is highly desirable. On the other hand, fluorine-containing compounds constitute over 50% of blockbuster drugs, generating some profound excitement in the organic chemistry community.[79] In fact, the medicinal applications of new organic compounds have always been a major driving force behind the development of organic methodologies.

It is evident that fluorine plays a significant role in medicinal chemistry, chemical biology, and drug discovery. It is hardly surprising, that a large number of fluorine-containing compounds have been approved for medical and agricultural use. In this regard, numerous fluorine-containing agents have been approved by the US Food and Drug Administration

(FDA) for medical use, which clearly demonstrates the importance of fluorine in drug discovery and development. *Figure 4* shows the most recent developments on the market of fluorinated drugs approved by the FDA in 2018 and 2019.[80-81]

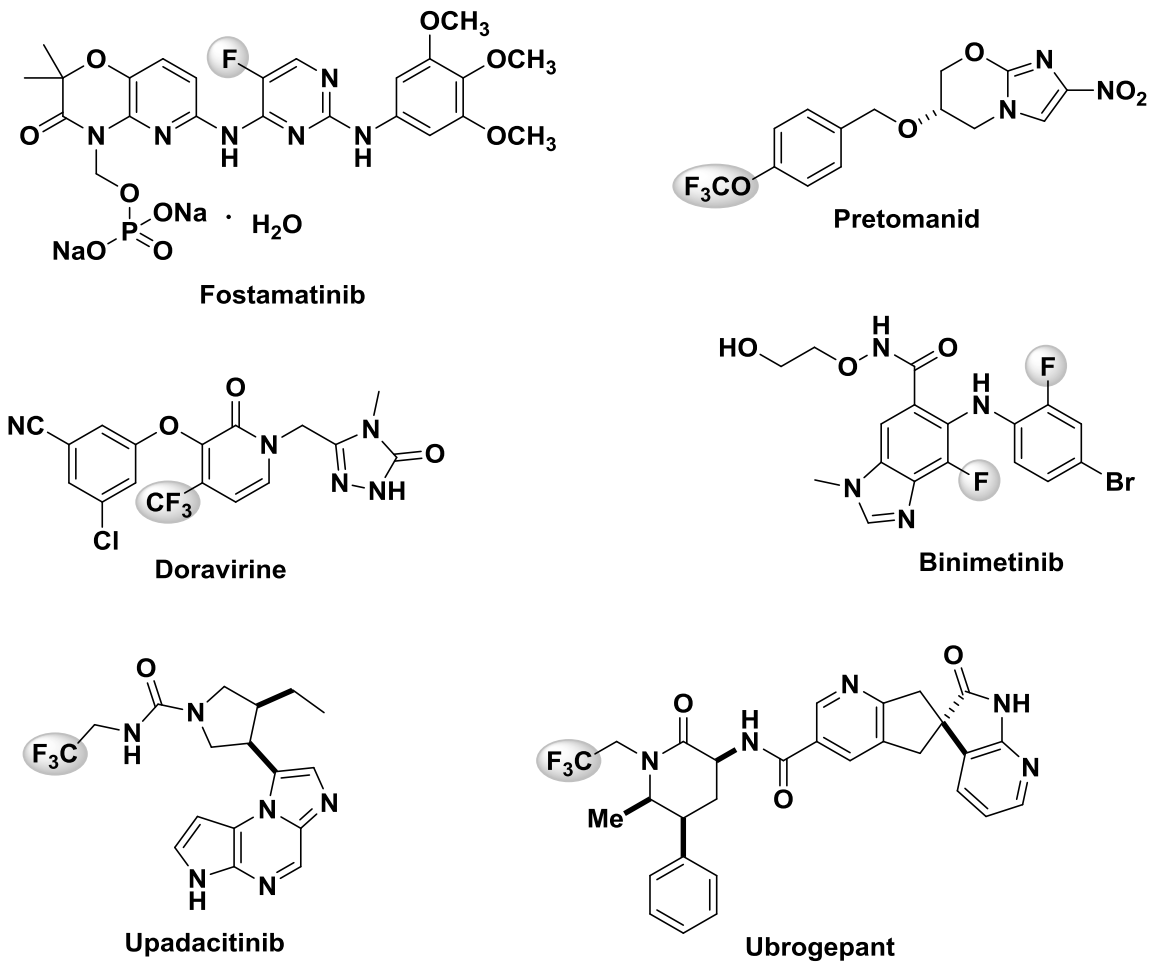


Figure 4. Structures of a few new fluorine-containing drugs

Fluorine-containing saturated *N*-heterocycles are of special significance, since introduction of one or more fluorine atoms into the skeleton of an azaheterocycle leads to dramatic changes in the physical and chemical properties of molecules. These changes can be rationally exploited for the benefit of diverse fields such as medicinal chemistry and organocatalysis.

3. RESULTS AND DISCUSSION

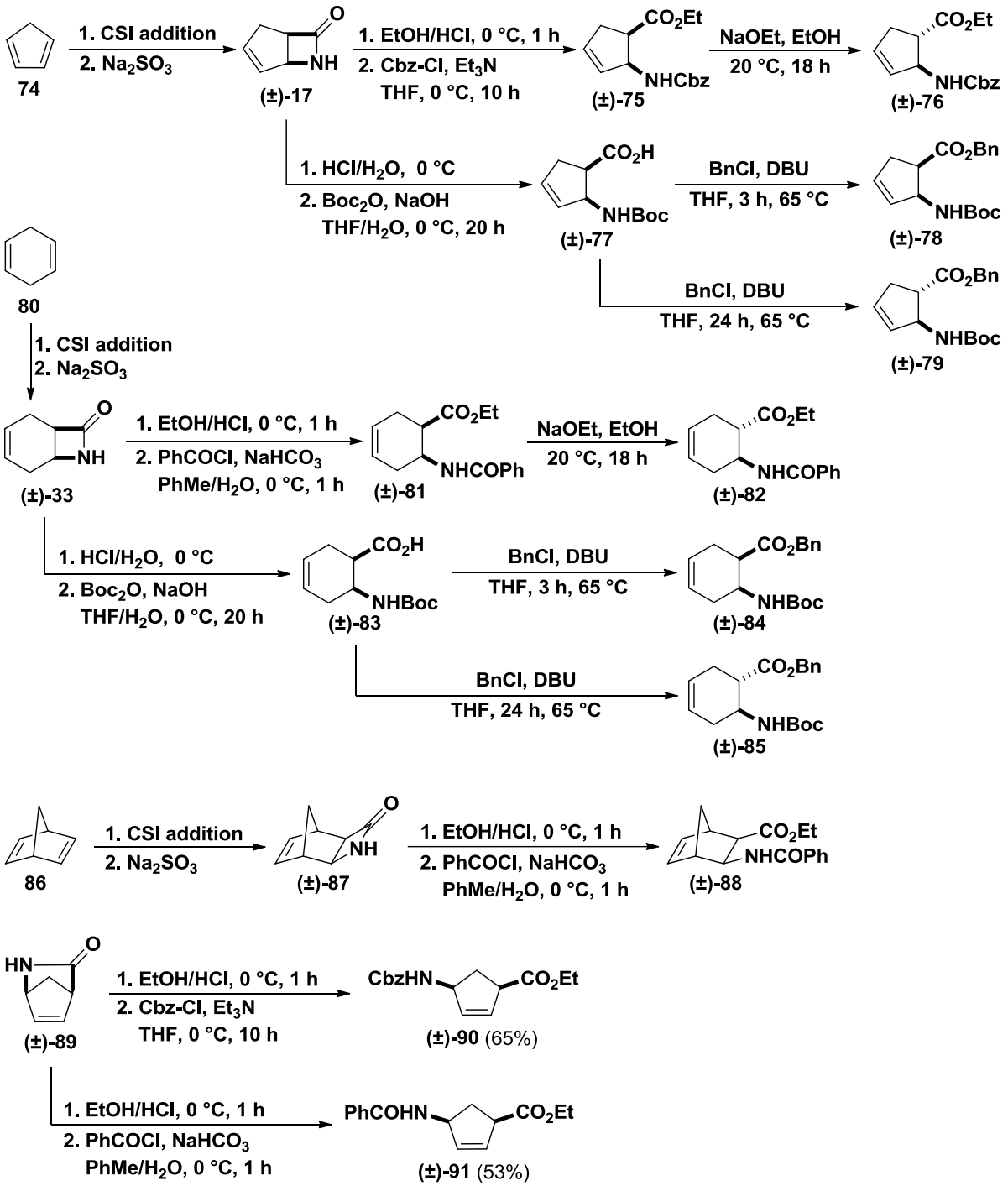
Oxidative ring opening of alkenes and reductive amination of the formed dialdehydes with various amines are widely used methods for the creation of azaheterocycles. As a result of the considerable importance of functionalized saturated azaheterocycles and fluorinated organic molecules, herein we aimed to combine these structural elements and to expand further the chemical space by synthetizing novel molecular structures containing these motifs. The first step of our synthetic approach was the oxidative ring opening of unsaturated cyclic β- and γ-amino acid derivatives, dihydronaphthalenes, and various other substituted cycloalkenes through their ring C=C bond. The subsequent reductive amination step was achieved by using commercially available fluorine-containing amines to obtain novel fluorine-containing azaheterocycles.

3.1. Synthesis of azaheterocyclic amino acid derivatives with a piperidine or azepane framework through oxidative ring opening/reductive amination

3.1.1. Synthesis of starting materials

According to our goal, protected β- and γ-amino esters and lactams were selected as model substrates. The preparation of *N*-protected β-aminocyclopentene- and β-aminocyclohexenecarboxylates started with [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) with cyclopentadiene and cyclohexadiene, followed by treatment of the formed *N*-chlorosulfonyl lactams with basic aqueous sulfite to remove the *N*-SO_2Cl group and obtain the key intermediate β-lactams.[82] On the one hand, opening of their heteroring with HCl/EtOH gave *cis* amino ester hydrochlorides, which were *N*-protected using benzoyl chloride or Cbz-Cl.[83-85] Epimerization of the resulting *cis*-β-amino esters with NaOEt in EtOH yielded *trans*-β-amino esters. On the other hand, hydrolysis of β-lactams resulted in *cis*-β-amino acids, which were subjected to *N*-Boc protection. When these *N*-Boc-protected *cis*-β-amino acids were treated with BnCl in the presence of DBU, the result depended on the reaction time. Namely, a 3-h reflux in THF led to *cis*-β-amino benzyl esters, while increasing the reaction time to 24 h allowed base-promoted epimerization and formation of *trans*-β-amino benzyl esters.[86] Norbornadiene **86** was also subjected to CSI addition, treatment with sulfite, ethanolysis, and *N*-benzoylation, yielding norbornene β-amino ester

(±)-88. Finally, applying the above synthetic protocols on Vince lactam **(±)-89** afforded COPh- and Cbz- protected *cis*-γ-amino ethyl esters too (*Scheme 20*).[85]



Scheme 20. Synthesis of *N*-protected β- and γ-amino ester starting model compounds

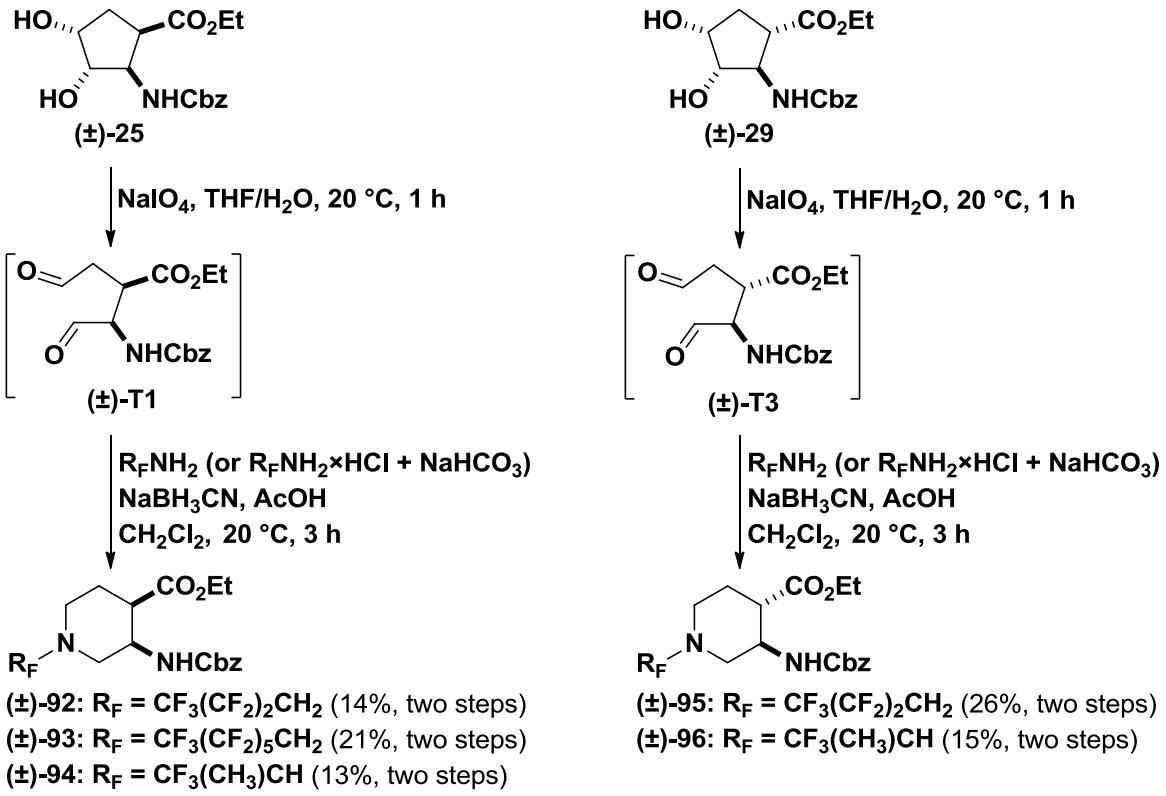
3.1.2. Synthesis of fluorine-containing piperidine β-amino esters

It is well known, that β-amino acids have attracted particular attention on account of their occurrence in natural products such as alkaloids and antibiotic, as well as intermediates

for preparing β-lactams antibiotics, agrochemical target molecules and their utilization in the development of drugs and biomolecular structures. They also gained significant interest due to their remarkable pharmaceutical uses and their antifungal activities.[23]

Cyclic β-amino acids are considered to be relevant compounds in the field of synthetic and medicinal chemistry and they have exerted increasing interest over the past two decades due to their relevance as antifungal, antibacterial or analgetic small molecules.[87]

Azaheterocyclic β-amino acids, which express high biological relevance, represent important motifs in both medicinal and organic chemistry. Furthermore, a number of fluorine-containing β-amino acids exhibit antitumoral or antibiotic properties. Thus, several fluorine-containing piperidines and pyrrolidines, which are present in drug molecules, have enormous interest in medicinal chemistry. The application of the ring-opening/ring-closing protocol has gained importance for the synthesis of unsaturated β-amino acid derivatives as well.[87,88,89]

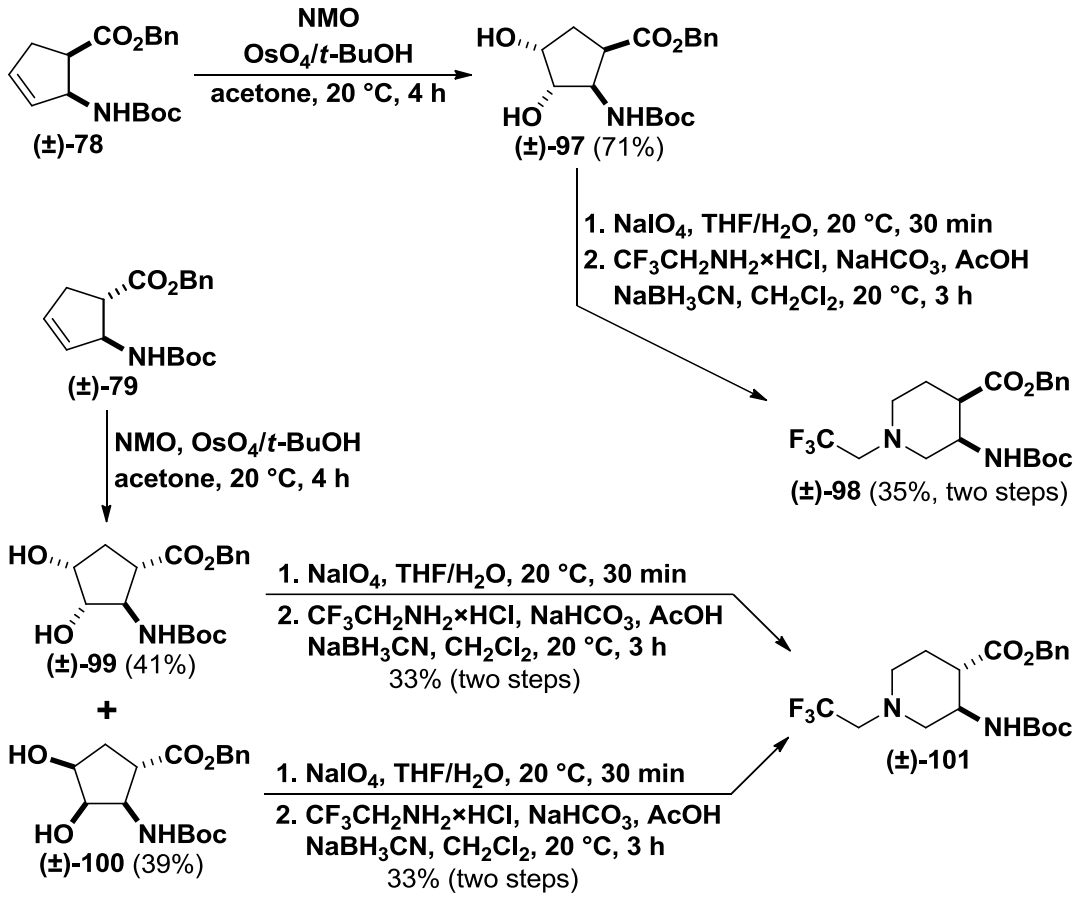


Scheme 21. Synthesis of piperidine *cis*- and *trans*-β-amino esters

Our primary aim was to combine β-amino acids and organofluorine molecular entities to synthesize novel molecular structures. The synthetic approach was based on the oxidative ring cleavage of unsaturated cyclic β-amino esters through the ring olefin bond (dihydroxylation with OsO_4/NMO, then treatment with $NaIO_4$). First, compound **(±)-25** was prepared by dihydroxylation of *cis* amino ester **(±)-75**. Oxidative ring cleavage of diol **(±)-25**

with $NaIO_4$ provided the corresponding diformyl intermediate, which was further submitted to double reductive amination with various fluorine-containing amines in the presence of $NaCNBH_3$ to form the corresponding fluorinated piperidine *cis*-β-amino esters **(±)-92**, **(±)-93** and **(±)-94**. Similarly, transformation of diol **(±)-29** [obtained by dihydroxylation of *trans* amino ester **(±)-76**] led to compounds **(±)-95** and **(±)-96** (*Scheme 21*).[88]

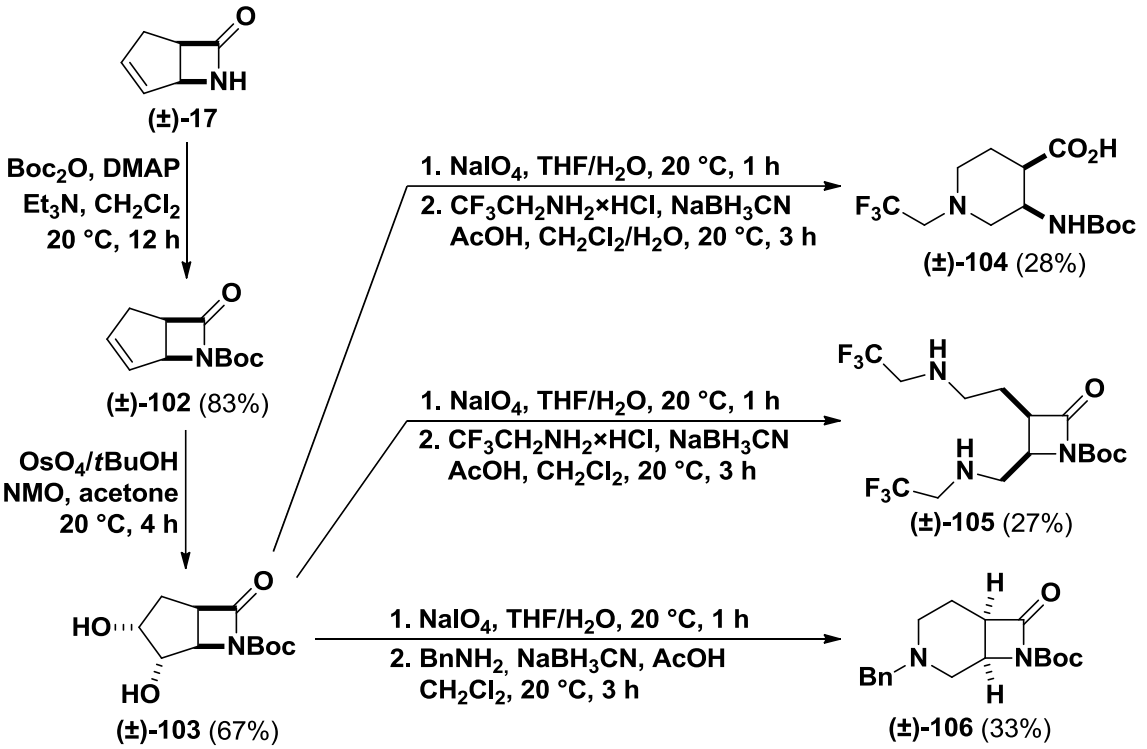
Furthermore, in order to extend the synthetic route towards orthogonally protected piperidine β-amino esters, diols **(±)-97**, **(±)-99**, and **(±)-100** were prepared. The vicinal diol cleavage of these diols was performed with $NaIO_4$ in THF and the resulting dialdehyde intermediates gave, in reaction with trifluorethylamine and $NaBH_3CN$ across double reductive amination, the corresponding piperidine *cis*-and *trans*-β-amino benzyl esters **(±)-98** and **(±)-101** (*Scheme 22*).[89]



Scheme 22. Synthesis of piperidine *cis*- and *trans*-β-amino esters

In order to increase the number of novel structures with piperidine core, we selected dihydroxylated bicyclic β-lactam **(±)-103** [accessible from compound **(±)-17** via *N*-Boc protection and dihydroxylation] as another starting model compound. Noteworthy, the outcome of oxidative ring-cleavage/reductive ring-closing protocol on **(±)-103** depended on the reaction

conditions. Thus, when oxidative ring opening of diol **(±)-103** with $NaIO_4$ was followed by treatment with trifluoroethylamine and $NaCNBH_3$ in CH_2Cl_2/H_2O biphasic mixture, cyclization into a scaffold containing a piperidine framework with simultaneous lactam ring opening took place and gave amino acid **(±)-104**. Performing the second step (reductive amination) under anhydrous conditions (pure CH_2Cl_2 solvent) proceeded without lactam ring opening. However, somewhat surprisingly, instead of cyclization, a simple double reductive amination took place and afforded diamino derivative **(±)-105**. Under the same anhydrous conditions, but with benzylamine instead of $CF_3CH_2NH_2$, the expected cyclization occurred and afforded the desired piperidine-fused lactam framework **(±)-106** (*Scheme 23*).[89]



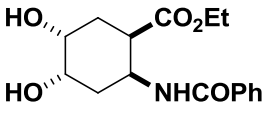
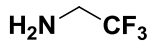
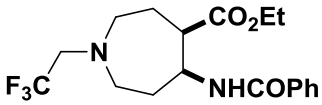
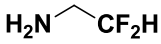
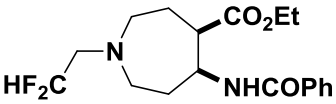
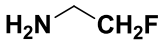
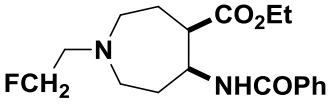
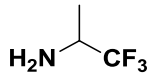
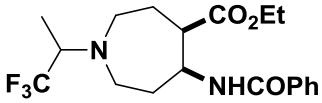
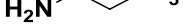
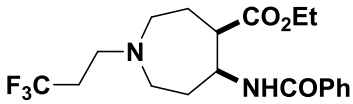
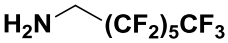
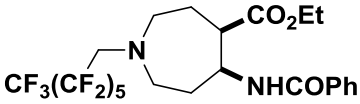
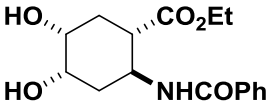
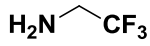
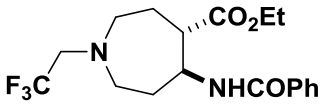
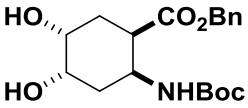
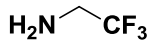
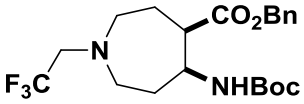
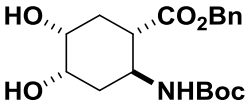
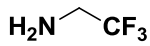
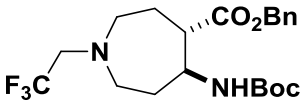
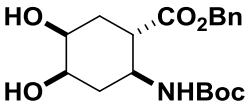
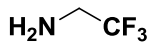
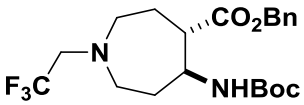
Scheme 23. Transformations of dihydroxylated bicyclic β-lactam (±)-**103**

3.1.3. Synthesis of fluorine-containing azepane β-amino esters

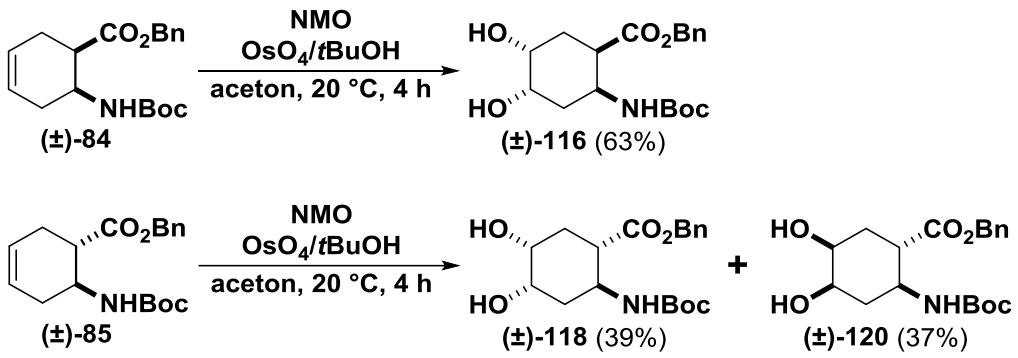
Seven-membered heterocycles are found in various biologically active natural products and medicinally important compounds. Among them, azepane is a structural motif of several alkaloids, and a vast array of methods have been developed for their synthesis.[87]

Due to the importance of azepanes in medicinal chemistry, we were interested in the possibility to modulate the properties of these compounds by introducing fluorinated groups. Therefore, the synthetic procedure presented above was further extended to the efficient access of fluorinated azepane β-aminocarboxylic esters (*Table 1*).

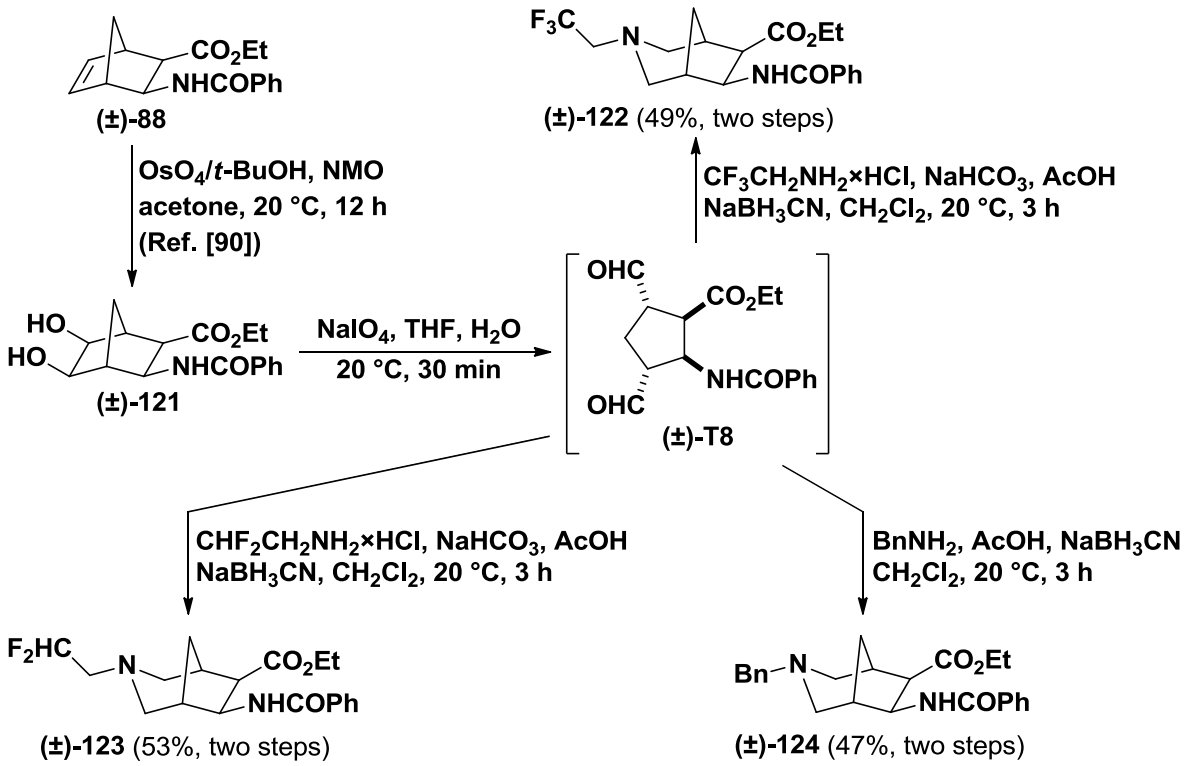
Table 1. Synthesis of azepane *cis*- and *trans*-β-amino esters. First step: $NaIO_4$, THF/H_2O, 20 °C, 30 min. Second step: R_F-NH_2 (or R_F-NH_2×HCl and $NaHCO_3$), $NaBH_3CN$, AcOH, CH_2Cl_2, 20 °C, 3 h.

Substrate	*R_F-NH_2*	*Product and yield for two steps*
 **(±)-107**		 **(±)-108** (31%)
		 **(±)-109** (15%)
		 **(±)-110** (12%)
		 **(±)-111** (27%)
		 **(±)-112** (38%)
		 **(±)-113** (27%)
 **(±)-114**		 **(±)-115** (33%)
 **(±)-116**		 **(±)-117** (36%)
 **(±)-118**		 **(±)-119** (32%)
 **(±)-120**		 **(±)-119** (30%)

In order to achieve this goal, dihydroxylated cyclohexene β-amino esters were subjected to oxidative ring cleavage and ring expansion. The latter step involved reductive amination with commercially available fluorinated or perfluorinated primary amines (*Table 1*) in the presence of $NaCNBH_3$ and AcOH. The process was stereocontrolled, that is the stereochemistry of the starting compound (*cis* or *trans*) was retained in the product azepane amino esters.[88,89] Substrates **(±)-107** and **(±)-114** were already known,[26] while diols **(±)-116**, **(±)-118**, and **(±)-120** were obtained by dihydroxylation of benzyl esters **(±)-84** and **(±)-85** (*Scheme 24*).[89]



Scheme 24. Dihydroxylation of benzyl esters **(±)-84** and **(±)-85**



Scheme 25. Synthesis of various bridged azepane β-amino esters

In view of the high physiological relevance of *N*-bridged bicyclic derivatives in synthetic and medicinal chemistry,[67] we also aimed to synthesize *N*-bridged bicyclic β-amino

acids. In order to achieve this goal, norbornene β-amino ester **(±)-88** was dihydroxylated with NMO/OsO_4.[90] Oxidative ring opening of the obtained diol derivative **(±)-121** led to dialdehyde **(±)-T8**, which was immediately subjected to cyclization via double reductive amination. The use of 2,2,2-trifluoroethylamine, 2,2-difluoroethylamine, and benzylamine led to the corresponding azabicyclic β-amino esters **(±)-122**, **(±)-123**, and **(±)-124**, respectively (*Scheme 25*).[89]

3.1.4. Synthesis of fluorine-containing piperidine γ-amino esters

As a privileged group of structural scaffolds, γ-amino acids are frequently found in a variety of natural products and biologically active compounds.[91] They are versatile and powerful building blocks due to their unique structural properties derived from the additional carbon atoms between the carboxyl and amino groups. Therefore, because of the range of side-chains, the preparation of a large variety of derivatives of these compounds is possible. On the other hand, cyclic γ-amino acids are of particular interest in foldamer synthesis, because of their conformational restrictions, such as the orientation of the carboxyl and amino groups. Representatives of this class of compounds include some acyclic and alicyclic γ-amino acid derivatives, which are of considerable importance in drug research, *e.g.*, as antiepileptic, antihyperalgesic, and anxiolytic agents.[92]

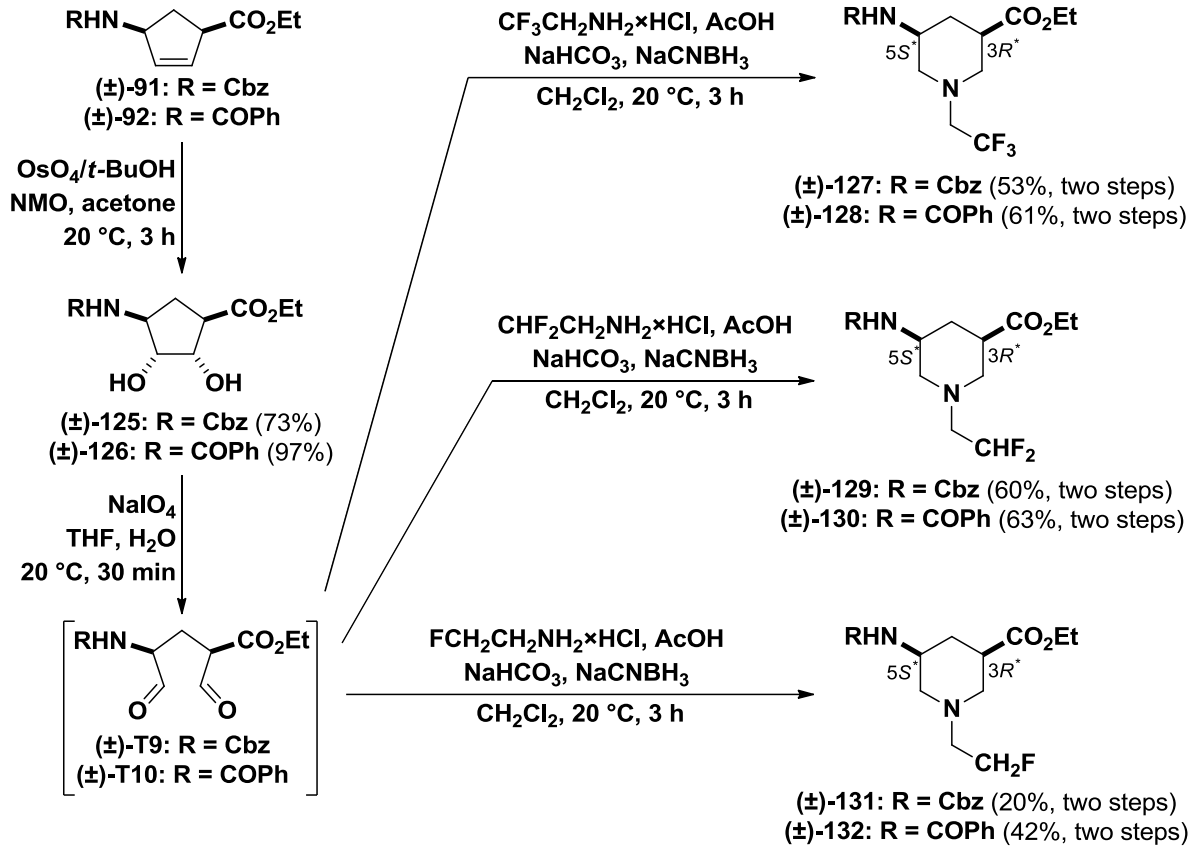
Vince lactam, one of the most valuable building blocks, was the starting material for the access of bioactive carbasugars and amino acid carbasugars. Furthermore, it is used as a synthetic precursor of some blockbuster antiviral drugs.[93,94]

Taking into account the importance of fluorinated organic molecules in medicinal chemistry and the increasing impact of fluorine-containing biomolecules in drug research, an ever-increasing number of fluorination methodologies have emerged during the past decade to access versatile fluorine-containing molecular entities. Especially, fluorinated amino acids have received considerable attention, because in most cases they exhibit better bioactivities than their non-fluorinated counterparts.[87] Fluorine-containing amino acids have found widespread medical and bioorganic applications, such as their use as enzyme inhibitors. Moreover, fluorine-containing amino acid drugs can also have a profound effect on drug absorption and extent of drug metabolism. At the same time, fluorine-containing amino acids have also been widely used as components of modified peptides and proteins. Additionally, some fluorine-containing cyclic γ-amino acids possess relevant biological properties.

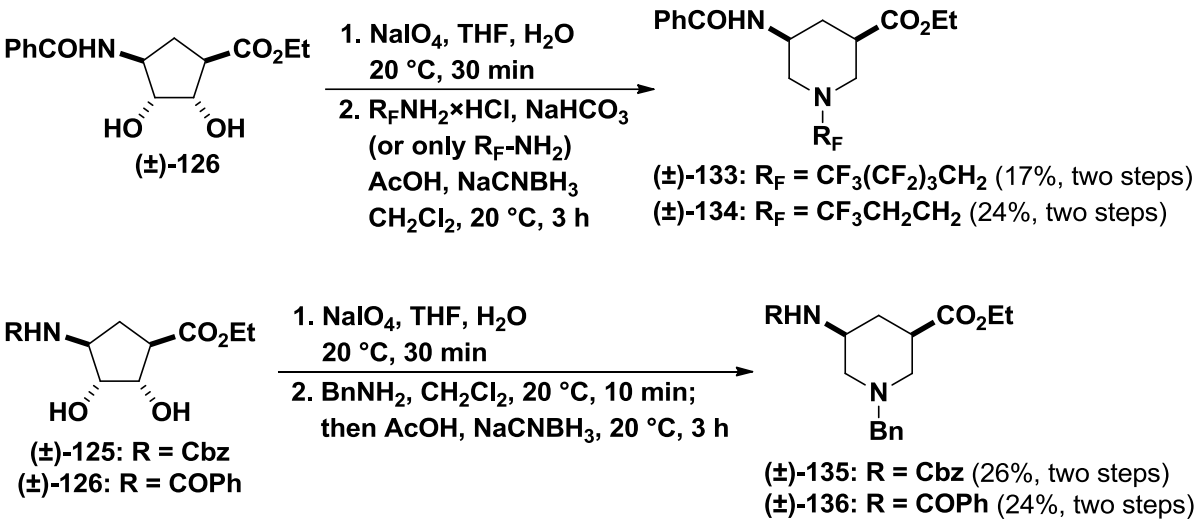
We have an ongoing interest in the development of synthetic protocols towards the access of novel fluorinated piperidine γ-amino acid derivatives. This is due to the importance of applications of both γ-amino acids and organofluorine derivatives in the pharmaceutical industry and organic synthesis. Therefore, we carried out oxidative ring cleavage of bicyclic Vince lactam at its C=C bond followed by double reductive amination through ring closing with various fluorine-containing amines.[85]

In the first step of our primary synthetic work, we carried out dihydroxylation of cyclopentene γ-amino esters **(±)-90** and **(±)-91**, derived from Vince lactam, with NMO and a catalytic amount of OsO_4. In the product diols **(±)-125** and **(±)-126** the hydroxyl groups are on one side of the ring, while the ester and carbamate functions are on the other side. In continuation, both **(±)-125** and **(±)-126** were submitted to a one-pot two-step transformation. Oxidative ring opening of diols **(±)-125** and **(±)-126** led to the corresponding unstable dialdehyde derivatives **(±)-T9** and **(±)-T10** which, in turn, were immediately transformed further after work-up of the oxidative ring-cleavage step. The reductive amination steps were performed by the addition of the hydrochloride salt of mono-, di- or trifluoroethylamine in the presence of $NaHCO_3$ in a CH_2Cl_2/THF solvent mixture, followed by the addition of $NaCNBH_3$ and AcOH at room temperature after 10 min. This order of addition of the reagents proved to be essential in these reactions. In all cases, reductive amination took place with ring expansion providing the corresponding racemic piperidine γ-amino esters: trifluorinated compounds **(±)-127** and **(±)-128**, difluorinated compounds **(±)-129** and **(±)-130**, and monofluorinated compounds **(±)-131** and **(±)-132** (*Scheme 26*). The structure of ester **(±)-127** was confirmed by single crystal X-ray diffraction.[85] Noteworthy, the synthetic protocol proceeded with stereocontrol, that is the configurations of the chiral centers in all products were predetermined by the configuration of the stereocenters of the starting Vince lactam **(±)-89.**

The synthetic approach was further extended to synthesize other novel functionalized piperidines. Thus, 2,2,3,3,4,4,5,5,5-nonafluoropentanamine, 3,3,3-trifluoropropylamine, and benzylamine were used as amine sources in the ring-closing step with dialdehydes **(±)-T9** and **(±)-T10**. The addition of $NaCNBH_3$ in THF/CH_2Cl_2 after 10 min provided the corresponding γ-amino esters through double reductive amination (*Scheme 27).*[85]



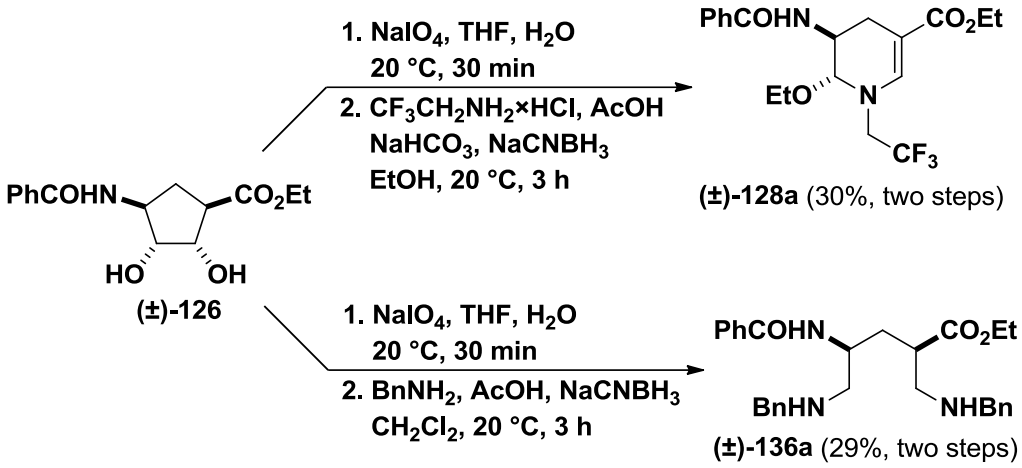
Scheme 26. Synthesis of tri-, di-, and monofluorinated piperidine γ-amino acid derivatives



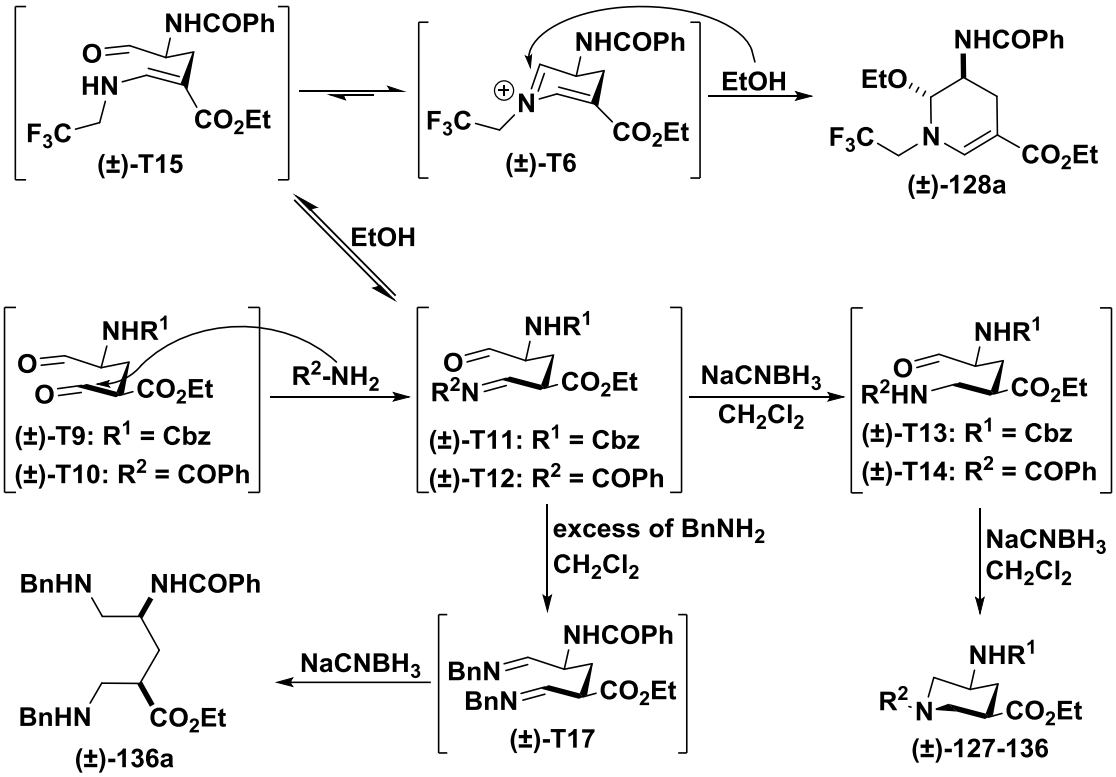
Scheme 27. Synthesis of further piperidine γ-amino esters

Selection of the appropriate solvent was important. For example, when the ring closure of **(±)-T10** with trifluoroethylamine was carried out in EtOH as solvent, adduct **(±)-128a** was formed through the nucleophilic attack of EtOH (*Scheme 28*), rather than piperidine derivative **(±)-128** observed earlier (see *Scheme 26*). The order and timing of addition of the reagents were essential too. When $NaCNBH_3$ was added immediately to the mixture of dialdehyde and amine,

the ring closure did not occur and diamino derivative **(±)-136a** was obtained (*Scheme 28*) instead of piperidine **(±)-136** (see *Scheme 27*).[85]



Scheme 28. Effects of changing the conditions of the reductive amination step

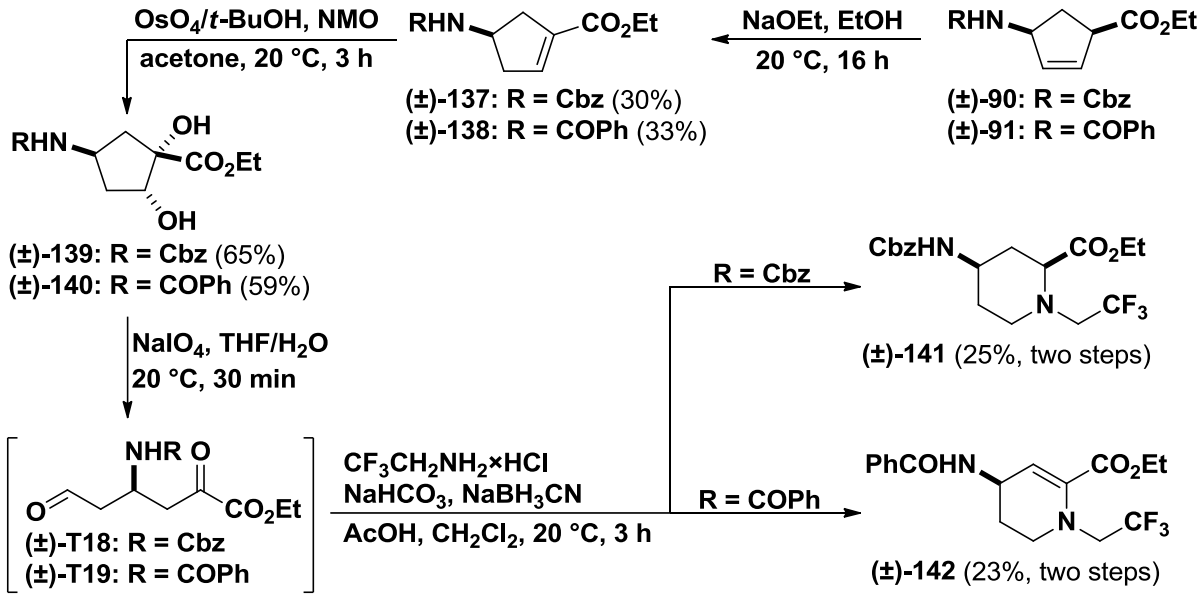


Scheme 29. Formation mechanism of **(±)-127–136, (±)-128a** and **(±)-136a**

Note that dialdehyde intermediates **(±)-T9** and **(±)-T10** possess active hydrogens in the α position to the formyl moiety (one of these is in the α position to the ester group too). Fortunately, enolization of these chirality centers (which would result in racemization of the affected positions and formation of *trans* disubstituted piperidine products) did not take place. Because ring closure of intermediates **(±)-T13** and **(±)-T14** takes place via a six-membered

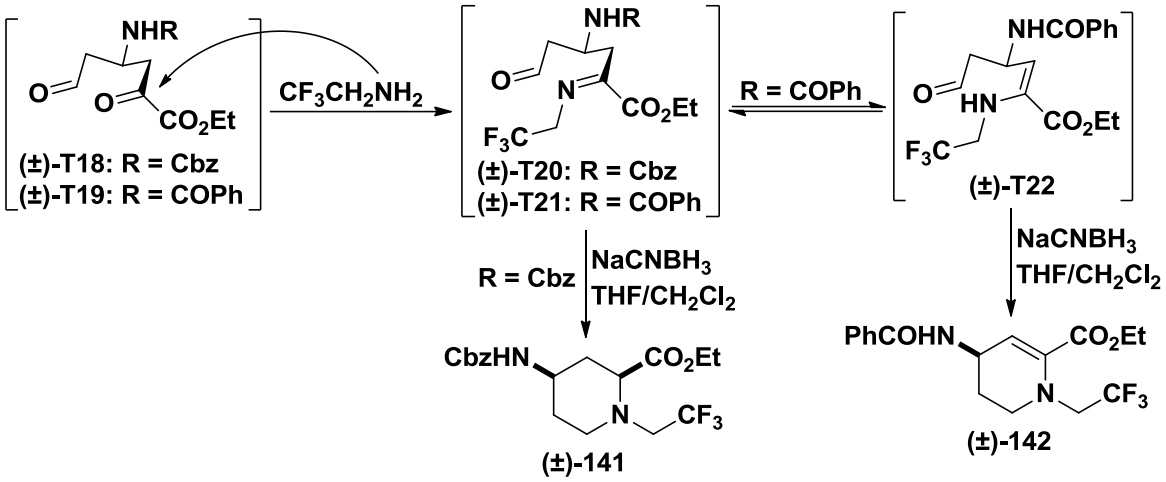
cyclic transition state, where the diequatorial arrangement of the ester and amino groups is preferred (*Scheme 29*), conservation of the *cis* relative stereochemistry can be accounted for.[85]

To increase the number of piperidine amino ester isomers, the synthesis of compound **(±)-141** and its *N*-benzoylated analogue was attempted. First, reaction of **(±)-90** and **(±)-91** with NaOEt resulted in ring double bond migration, because deprotonation of their active methyne group resulted in a carbanion stabilized by conjugation, whose reprotonation favored the formation of products **(±)-137** and **(±)-138** with a conjugated π system. *cis*-Dihydroxylation conducted in the presence of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) gave the corresponding vicinal diols **(±)-139** and **(±)-140**. Subsequent ring cleavage with $NaIO_4$ in THF/H_2O led to dicarbonyl intermediates **(±)-T18** and **(±)-T19** which, without isolation, were immediately submitted to the reductive amination step with trifluoroethylamine leading to **(±)-141** and **(±)-142** (*Scheme 30*).[85]



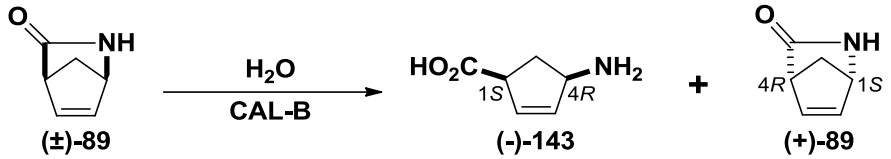
Scheme 30. Synthesis of fluorine-containing piperidine derivatives (±)-**134** and (±)-**135**

The initial step, the attack of the amine, takes place most probably at the carbon atom of the α-oxo group, leading to imines **(±)-T20** and **(±)-T21** with a conjugated system. In the case of *N*-Cbz-protected **(±)-T20**, reduction and subsequent ring closure through a second reductive amination step furnishes the expected piperidine amino ester **(±)-141**, a regioisomer of **(±)-127**. Interestingly, in the case of *N*-Bz-protected **(±)-T21**, under the same experimental conditions, tetrahydropyridine derivative **(±)-142** is formed. It is surmised, that this transformation involves enamine intermediate **(±)-T22** (*Scheme 31*).[85]



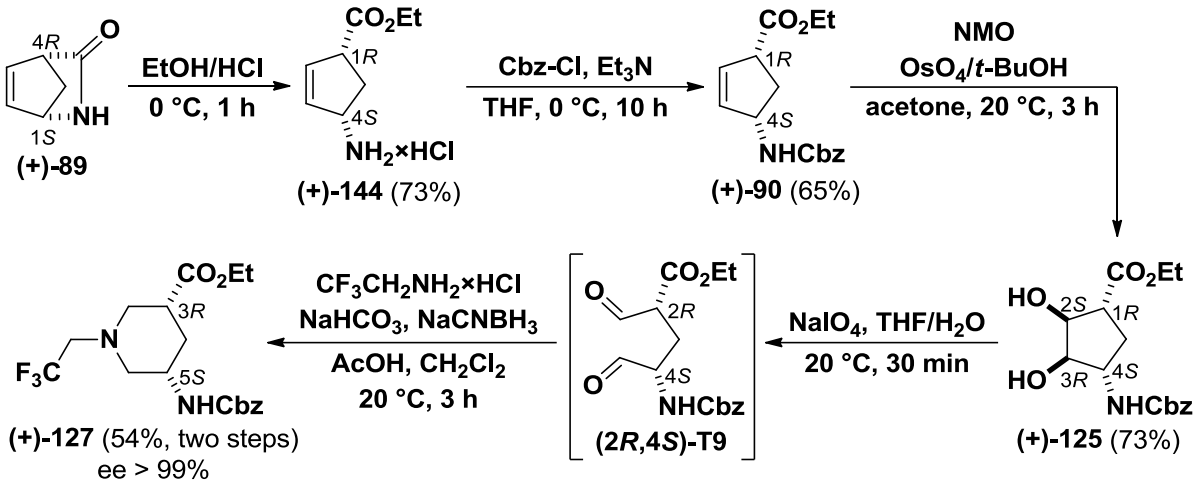
Scheme 31. Mechanisms for the formation of the products (±)-**141** and (±)-**142**

It should be noted, that the synthetic protocol presented above was utilized only to the access of racemates. However, our next goal was to prepare enantiomerically pure piperidine γ-amino esters. Accordingly, we selected and planned to transform enantiopure γ-lactam **(+)-89** as starting material. Since the configurations of the stereogenic centers during the synthetic process were not affected, the enantiopure starting material is expected to produce the corresponding enantiomeric target substances. Optically pure (+)-**89** was obtained according to our earlier literature procedure, which was based on lactam ring opening through hydrolysis of racemic (±)-**89** catalyzed by *Candida antarctica* lipase-B (*Scheme 32*).[95]

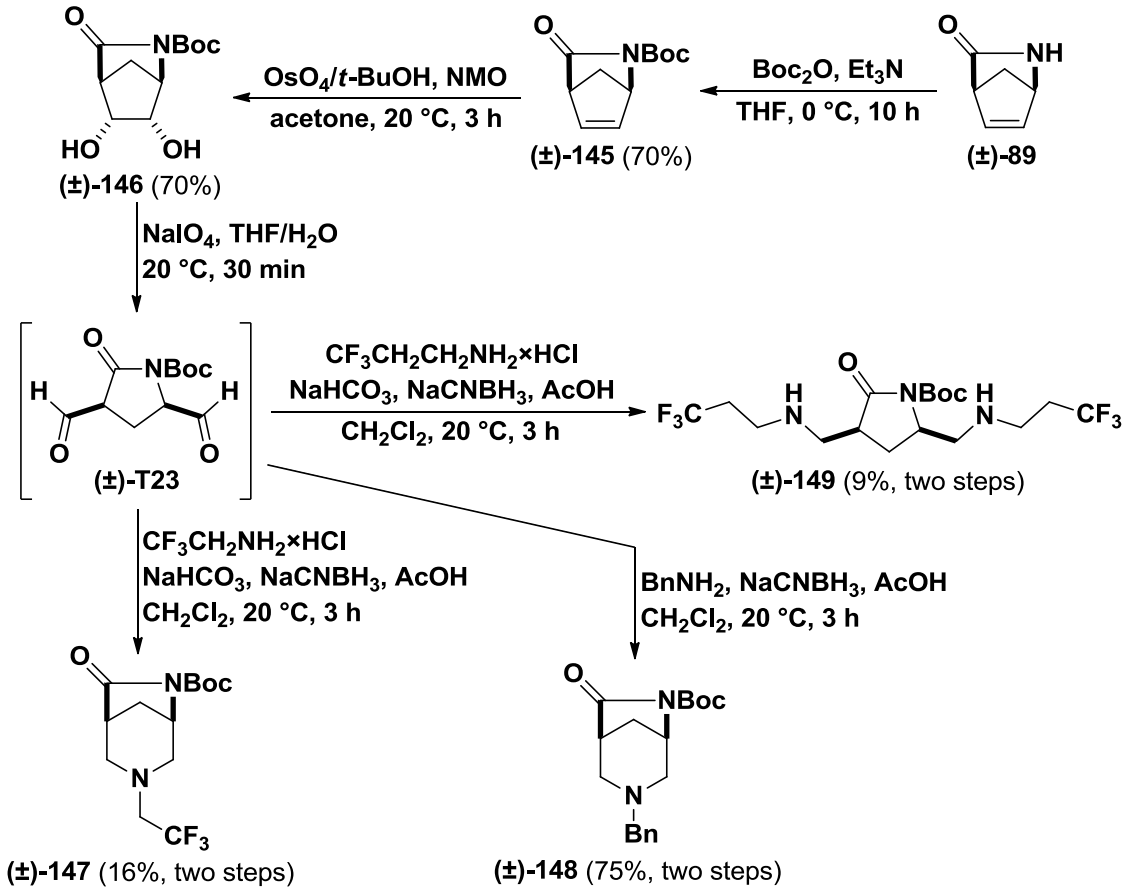


Scheme 32. Synthesis of enantiomerically pure γ-lactam (+)-**89**

Pursuing the protocol described above for the racemates, herein, our work started with enantiomerically pure lactam **(+)-89**, which was converted to amino ester with EtOH/HCl and Cbz-Cl. The C=C bond dihydroxylation of **(+)-90** with NMO and a catalytic amount of OsO_4 provided vicinal diol **(+)-125**. $NaIO_4$-mediated oxidative ring cleavage of this dihydroxylated compound was carried out in THF/H_2O to deliver dialdehyde **(2*R*,4*S*)-T9**, which was further transformed without isolation into enantiomerically pure γ-amino ester **(+)-127** by reductive amination with trifluoroethylamine. Compound **(+)-127** was isolated with an *ee* of >99% (determined by means of HPLC, Chiralpak IA column, *Scheme 33*).[85]



Scheme 33. Synthesis of enantiomerically pure fluorine-containing γ-amino ester **(+)-127**



Scheme 34. Synthesis of piperidine-fused γ-lactams **(±)-147** and **(±)-148** and monocyclic γ-lactam **(±)-149**

Ultimately, we decided to further extend the synthetic methodology for the access of novel fluorine-containing bicyclic lactam derivatives. Thus, racemic *N*-Boc-protected Vince lactam **(±)-145** upon oxidation provided the corresponding vicinal diol derivative **(±)-146**. $NaIO_4$-mediated oxidative ring cleavage of this dihydroxylated compound yielded diformyl-

substituted pyrrolidinone intermediate **(±)-T23**. This unstable intermediate was immediately subjected to reductive amination. The reaction with trifluoroethylamine or benzylamine led to the desired cyclized azabicyclic compounds **(±)-147** and **(±)-148**. In contrast, the process with 3,3,3-trifluoropropylamine under the same reaction conditions afforded diamino lactam **(±)-149** (*Scheme 34*).[85]

3.2. Synthesis of functionalized benzazepines through reductive amination

Benzannulated heterocycles are key structural motifs in various biologically active molecules, including different kinds of natural products, pharmaceuticals, and agrochemicals. Among these pivotal heterocycles, benzo-fused azepines are a unique family of seven-membered azaheterocycles.[96] Benzazepine derivatives have been known since the beginning of the 20th century. Studies published over the last two decades have greatly expanded the information on pharmacology of benzazepines. They are widely found in numerous bioactive molecules, natural products, and pharmaceuticals. This is due to their chemotherapeutic properties and interesting biological activities. *Figure* 5 shows some typical examples, such as capsazepine (competitive antagonist of TRPV1), Fenoldopam (antihypertensive agent), tolvaptan (competitive vasopressin receptor antagonist), halobenzazepine (D1 receptor antagonist), galanthamine (acetylcholinesterase inhibitor), and some serotonin 5-HT_{2C} receptor agonists.[97]

Considering the relevance of the topic as well as related important properties, the development of efficient methods to construct benzazepine skeleton is of great practical importance. Accordingly, various synthetic methods have been reported, including Beckmann or Schmidt rearrangements, transition-metal-catalyzed coupling, or ring closure metathesis.[98]

As mentioned earlier, the incorporation of fluoro atom(s) into these seven-membered azaheterocycles has generated increasing interest in pharmaceutical research. Up to date, however, there is only a limited number of examples of fluorine-containing bioactive benzazepines described in the literature. The structure of several representatives of this group of bioactive products is shown in Figure 5.[96,97,99]

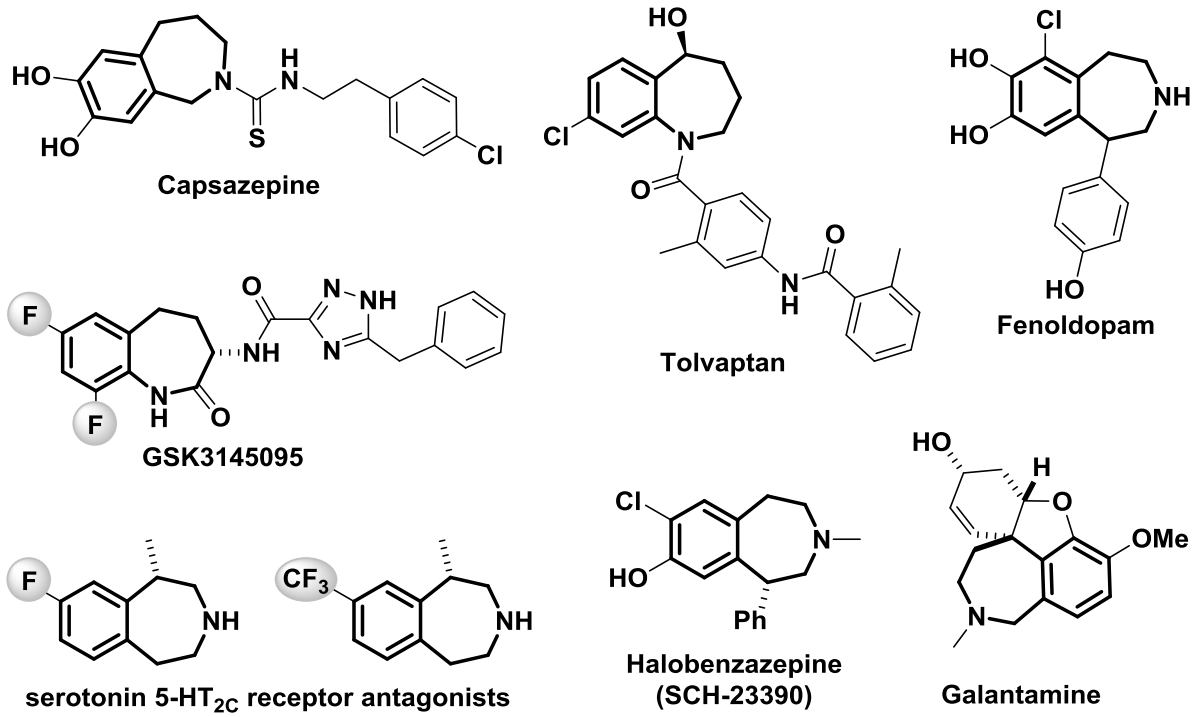
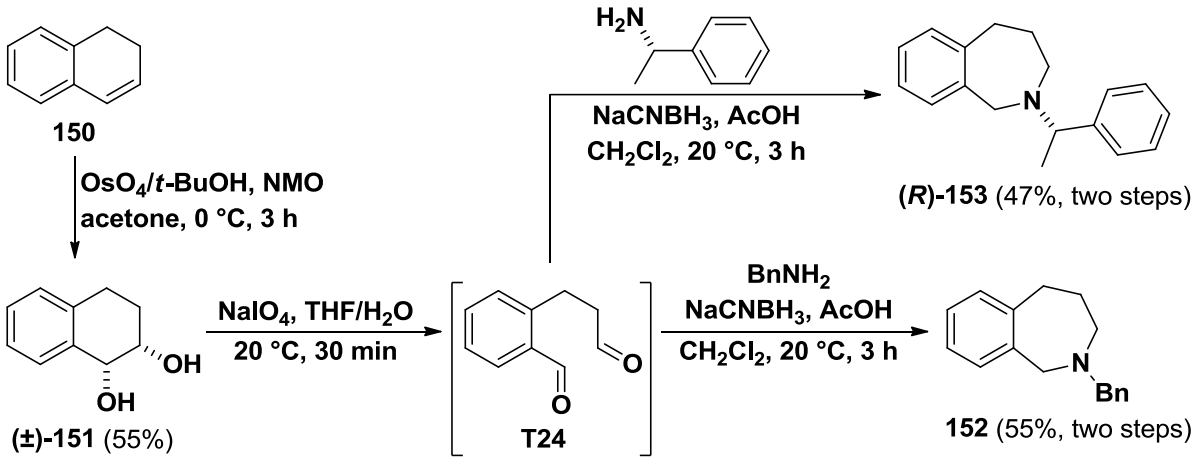


Figure 5. Representative pharmacologically interesting substances containing benzazepine moiety

3.2.1. Synthesis of benzo[*c*]azepines

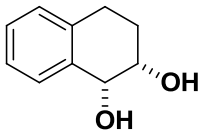
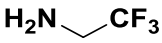
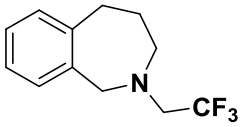
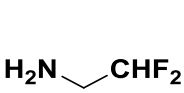
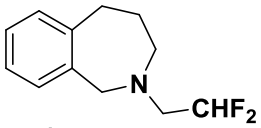
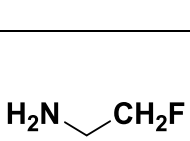
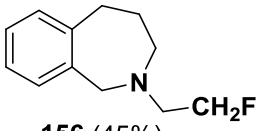
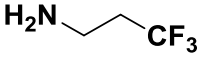
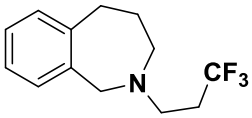
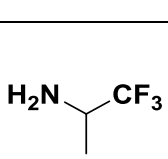
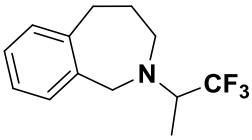
Therefore, our aim was to develop new synthetic strategies towards these structures, which represent a significant challenge in synthetic organic chemistry. We have elaborated a novel synthetic approach for the synthesis of different types of benzazepines (mainly *N*-fluoroalkylated ones), which involves ring expansion of 1,2-dihydronaphthalene or 1,4-dihydronaphthalene via oxidative ring opening and subsequent ring closing with double reductive amination. Construction of the desired heterocyclic skeleton in this way was unknown in the literature.[99]

Our synthetic method for the creation of benzazepine ring systems began with dihydroxylation of 1,2-dihydronaphthalene **150** with NMO/OsO_4 in acetone at room temperature, which provided the corresponding *cis*-diol derivative **(±)-151**. Next, vicinal diol **(±)-151** was subjected to oxidative ring opening with $NaIO_4$ in a THF/H_2O solvent to deliver unstable diformyl intermediate **T24**. Then, the latter intermediate was submitted to double reductive amination with benzylamine and $NaBH_3CN$ in CH_2Cl_2 at room temperature for 3 h to give the corresponding benzazepine product **152** in 55% yield in two steps. Replacing benzylamine with (*R*)-α-methylbenzylamine resulted in product **(*R*)-153**, demonstrating that synthesis of enantiopure compounds is possible too (*Scheme 35*).[99]



Scheme 35. Novel synthetic method for the access of benzazepine derivatives.

Table 2. Synthesis of novel fluorinated benzo[*c*]azepine frameworks **154–157** and **(±)-158**. First step: $NaIO_4$, THF/H_2O, 20 °C, 30 min. Second step: R_F-NH_2×HCl, $NaHCO_3$, AcOH, $NaBH_3CN$, CH_2Cl_2, 20 °C, 3 h.

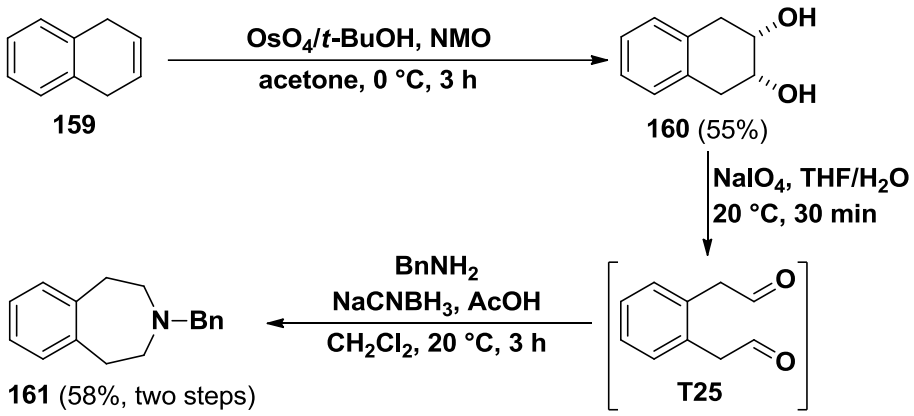
Starting compound	*R_F-NH_2*	*Product and yield for two steps*
 (±)-151		 **154** (51%)
		 **155** (26%)
		 **156** (45%)
		 **157** (25%)
		 **(±)-158** (43%)

It is well known, that incorporation of fluorine atoms into the structure of an organic scaffold, especially in the skeleton of azaheterocycles, will significantly affect basic

characteristics; therefore, we extended the protocol described above towards the preparation of novel benzazepine derivatives using different fluorinated primary amines. In all cases, the reductive amination involved cyclization and provided the corresponding fluorine-containing benzo[*c*]azepines in moderate to good yields (*Table 2*).[99]

3.2.2. Synthesis of benzo[*d*]azepines

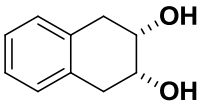
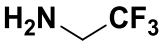
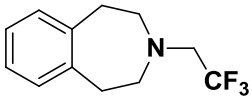
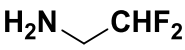
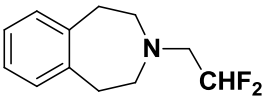
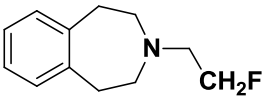
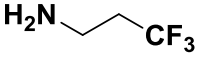
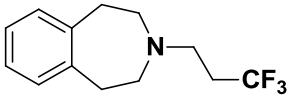
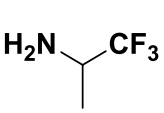
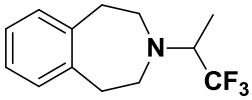
In order to increase the number of benzazepine derivatives, the synthetic route presented above was further extended by targeting structural isomers. Hence, 1,4-dihydronaphthalene **159**, a regioisomer of **150**, was selected as a model compound. *cis*-Dihydroxylation conducted with NMO/OsO_4 gave the corresponding vicinal diol **160**, which subsequently underwent oxidative ring opening upon treatment with $NaIO_4$ to furnish diformyl intermediate **T25**. This unstable dialdehyde intermediate was used without isolation in the subsequent double reductive amination step. Treatment of **T25** with benzylamine in the presence of $NaBH_3CN$ as reducing agent yielded the desired benzo[*d*]azepine derivative **161** via cyclization (*Scheme 36*).[99]



Scheme 36. Extension of the method to the synthesis of benzo[*d*]azepine **161**

After the viability of the synthetic pathway was confirmed, analogous reactions were performed with fluorinated primary amines instead of benzylamine. The desired products [**162–165** and **(±)-166**] were isolated in moderate yields (*Table 3*).[99]

Table 3. Synthesis of fluorine-containing benzo[*d*]azepine derivatives **162–165** and **(±)-166**. First step: $NaIO_4$, THF/H_2O, 20 °C, 30 min. Second step: R_F-NH_2×HCl, $NaHCO_3$, AcOH, $NaBH_3CN$, CH_2Cl_2, 20 °C, 3 h.

Starting compound	*R_F-NH_2*	*Product and yield for two steps*
 **160**		 **162** (45%)
		 **163** (26%)
		 **164** (25%)
		 **165** (36%)
		 **(±)-166** (30%)

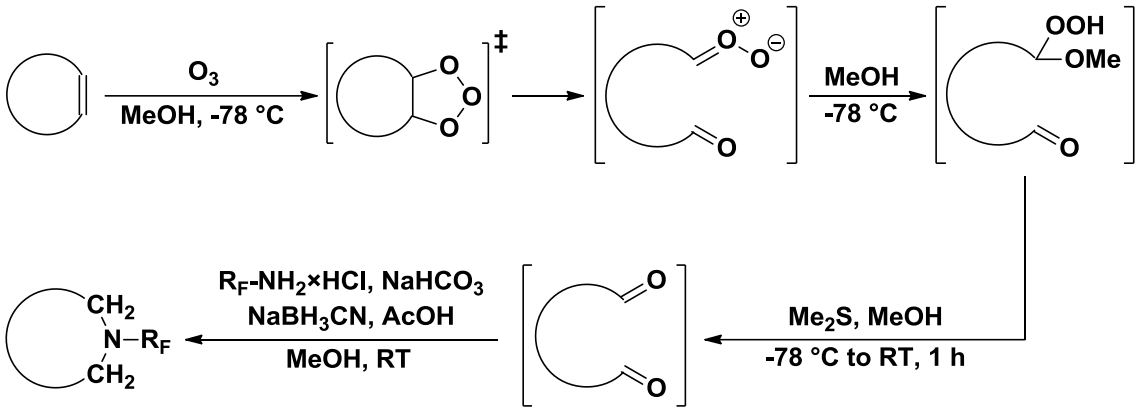
3.3. Synthesis of various *N*-heterocycles via ozonolysis/reductive amination

The scientific strategies and practical aspects of green and sustainable chemistry (development of economical, eco-friendly methodologies, prevention of pollution, energy efficiency, utilization of renewable materials, reduced toxicity, prevention of waste, less hazardous transformations, usage of green and safe solvents, improving atom economy) became more and more important during the last decades. There is an increasing demand in synthetic organic chemistry to develop novel chemical methods or improve existing literature procedures by taking into consideration the above-mentioned factors. Common solutions to these challenges are effective catalytic procedures (which have high atom economy), one-pot processes (which involve less purification steps, thereby reducing wastes and saving time), and use of environmentally benign solvents or neat conditions.[100-103]

The ozonolysis of alkenes is a widely used and environmentally sustainable oxidative transformation to generate oxygenated compounds.[35,36,38] Although ozone is unstable, it can

be generated easily from air or oxygen using electric current ("ozone generator").[36,48] As shown on *Schemes 5 and 6*, ozonolysis involves normal and reverse 1,3-dipolar cycloaddition steps and it can provide a wide range of products, depending on the workup of the ozonide intermediate.[37-44]

From our viewpoint, mild reductive treatments were the most interesting, because they result in the formation of oxo compounds.[38-39] We realized that replacing the dihydroxylation (OsO_4/NMO) and diol cleavage ($NaIO_4$) steps used previously with a single ozonolysis step (with appropriate reductive workup) would be highly advantageous. First of all, it would eliminate the need for the toxic and expensive OsO_4. It would also decrease production of organic (*N*-methylmorpholine) and inorganic (Os compounds and $NaIO_3$) wastes. Furthermore, it would greatly reduce solvent usage by removing the need for chromatographic purification. (The original synthetic pathway required purification of the diol intermediate with column chromatography before diol cleavage.) Finally, it would shorten the synthesis, which may result in enhancement of the overall yield.



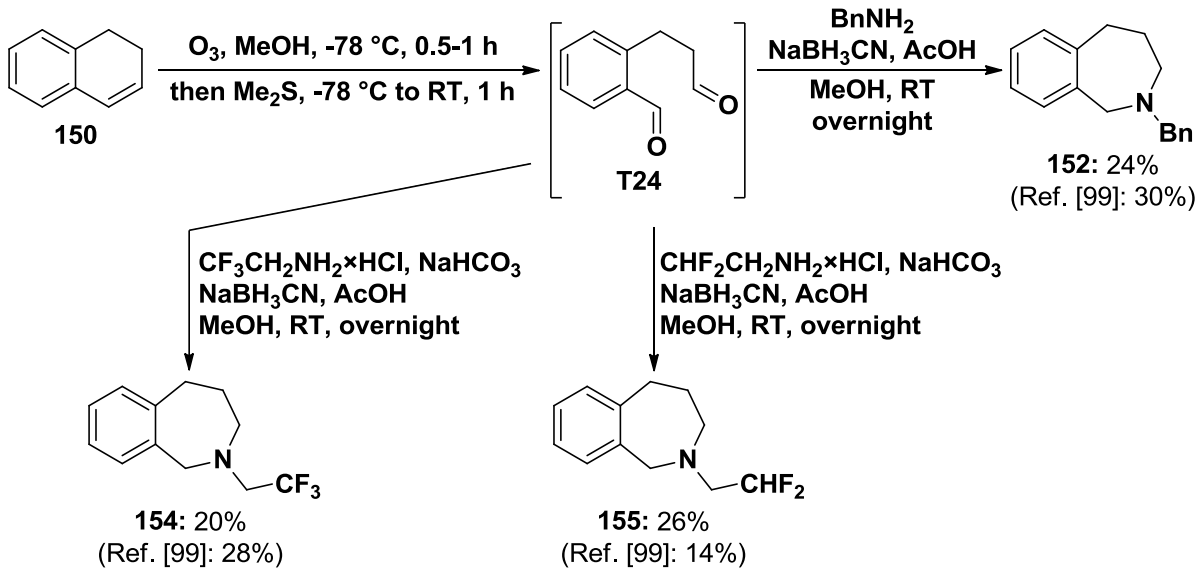
Scheme 37. The greener, improved synthetic pathway towards *N*-heterocycles

Therefore, we aimed to modify and improve our oxidative ring opening/reductive amination protocol by using ozonolysis to transform the starting olefins to dioxo compounds. We performed the ozonolysis step at –78 °C for 0.5–1 h in methanol as solvent. Under these conditions the carbonyl oxide intermediate reacts with the solvent (not with the oxo compound) and alkoxy hydroperoxides are formed instead of ozonides. This is beneficial, because alkoxy hydroperoxides are less hazardous and can be reduced more easily than ozonides.[36] Then, the cooling bath was removed, a large excess of dimethyl sulfide[38] (0.5 ml) was added to the reaction mixture and the system was stirred for 1 h while it was allowed to warm up to room temperature. This kind of reductive workup was chosen, because reaction of Me_2S with alkoxy hydroperoxides is less exothermic than analogous reactions with other commonly used mild

reducing agents.[36] Subjecting the solution of obtained methanolic dioxo compounds to reductive amination [2 equiv fluorinated amine hydrochloride and 2 equiv $NaHCO_3$ (or 2 equiv $BnNH_2$), RT, 10 min, then 1 equiv $NaBH_3CN$ and 2 drops of AcOH, RT, overnight] gave azaheterocycles in a telescoped synthetic pathway (*Scheme 37*). Note that chromatographic purification was necessary only in the final step of the synthesis.[104]

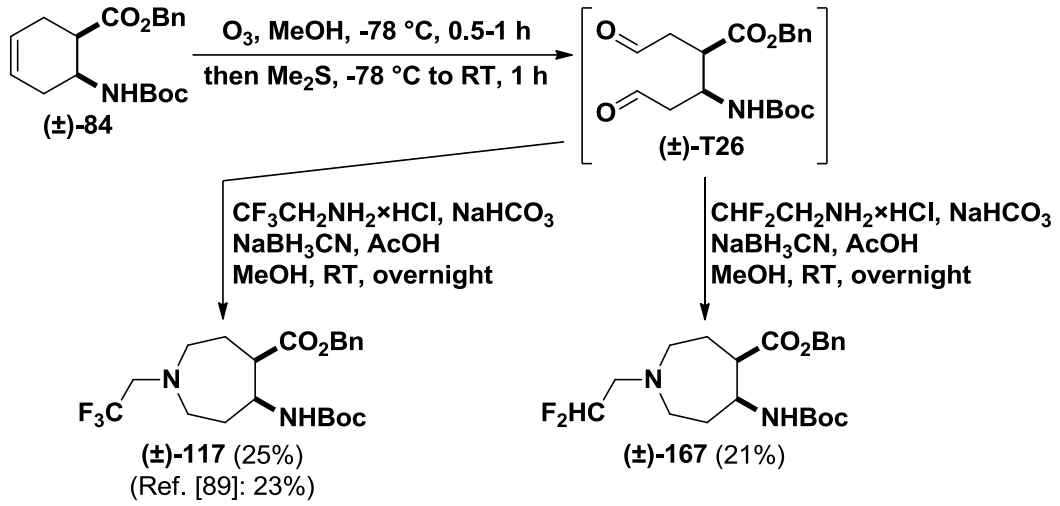
3.3.1. Synthesis of compounds with an azepane ring

First, we applied our new approach for the preparation of some benzo[*c*]azepines, which we synthesized recently.[99] Ozonolysis of 1,2-dihydronaphthalene went smoothly, and treatment of the resulting methanolic dialdehyde solution with various amines yielded the desired benzazepines. By comparing the obtained yields with overall yields achieved in the previous method,[99] we decided that the new pathway is worth further study (*Scheme 38*).[104]

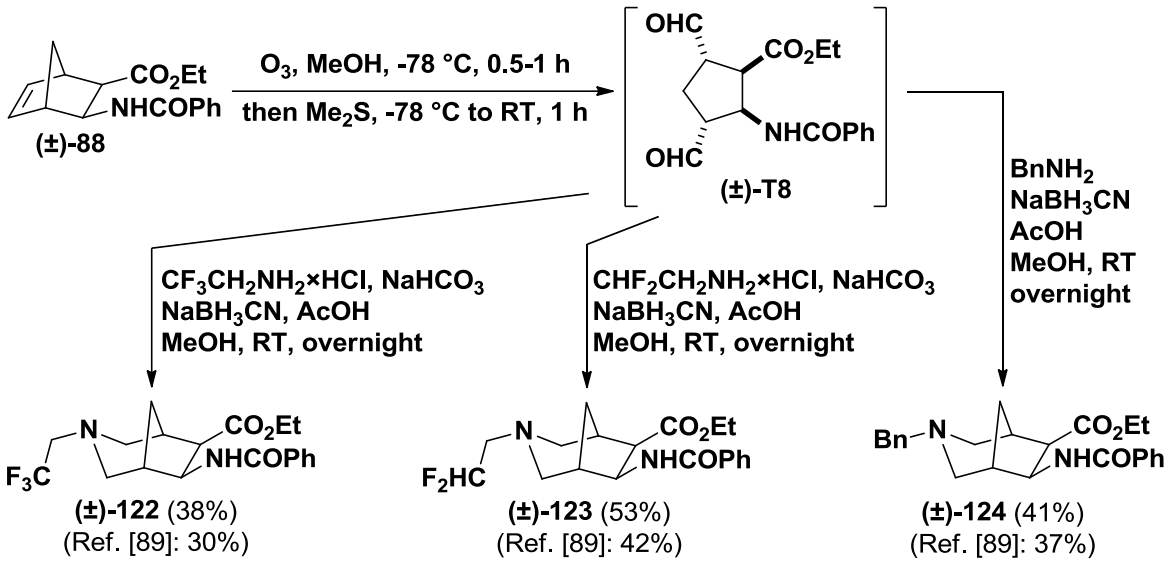


Scheme 38. Synthesis of benzo[*c*]azepines through ozonolysis/reductive amination

We continued our work with the synthesis of azepane β-amino esters. First, the synthesis of monocyclic products was attempted. Compound **(±)-117**[89] was obtained in slightly higher overall yield than found previously, and **(±)-167** a new difluorinated derivative was also synthesized (*Scheme 39*).[104] Then, bridged azepane β-amino esters were prepared with ozonolysis/reductive amination of norbornene β-amino ester **(±)-88** (*Scheme 40*).[104] In this case, all three products were obtained in better overall yields than those utilizing the previous method.[89]



Scheme 39. Synthesis of orthogonally protected azepane β-amino esters

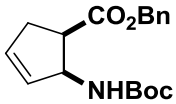
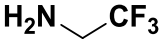
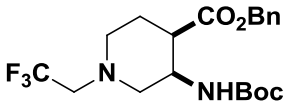
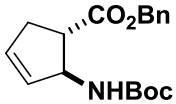
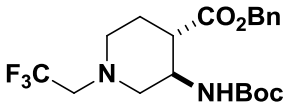
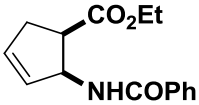
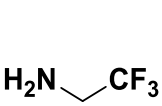
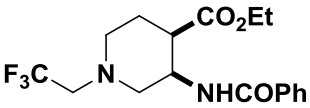
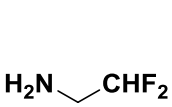
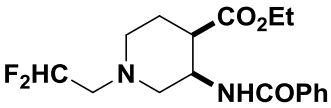
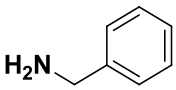
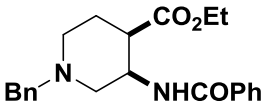


Scheme 40. Synthesis of bridged azepane β-amino esters

3.3.2. Synthesis of piperidine β-amino acids and piperidine-fused β-lactams

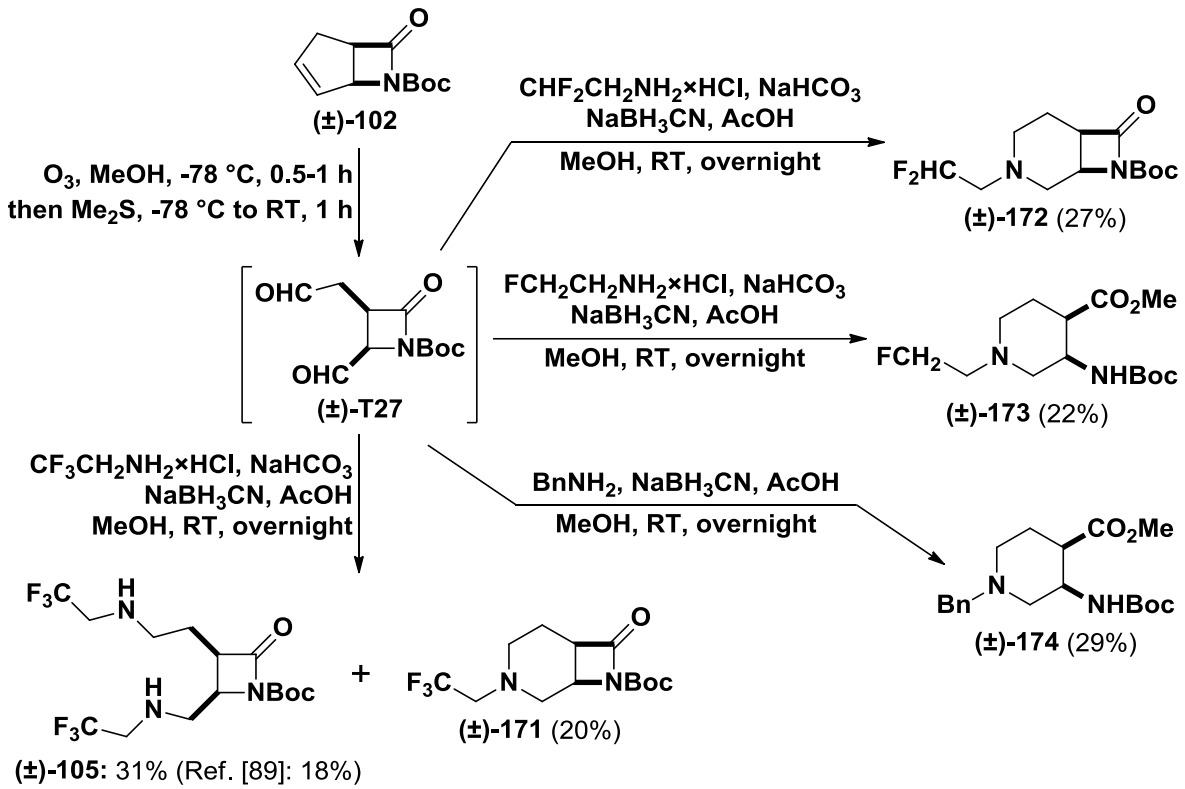
Since our new method demonstrated its superiority in the synthesis of azepanes (*Scheme 38–40*), we investigated its applicability for the preparation of β-amino acids and β-lactams with a piperidine ring. First, known fluorinated piperidine β-amino esters **(±)-98**, **(±)-101**, **(±)-28**, and **(±)-169** were synthesized from readily accessible cyclopentene β-amino esters **(±)-78**[86], **(±)-79**[86], and **(±)-168**[105] (*Table 4*). In most cases, the ozonolysis method was more effective. New piperidine β-amino ester **(±)-170** was synthesized too (*Table 4*).[104]

Table 4. Synthesis of piperidine β-amino esters. Reaction conditions: O_3, MeOH, –78 °C, 0.5–1 h; then addition of Me_2S, –78 °C to RT, 1 h, then addition of $BnNH_2$ (or $CF_3CH_2NH_2 \times HCl$ and $NaHCO_3$), AcOH, and $NaBH_3CN$, RT, overnight.

Starting compound	*Amine*	*Product and yield*
 **(±)-78**		 **(±)-98** (40%) (Ref. [89]: 25%)
 **(±)-79**		 **(±)-101** (22%) (Ref. [89]: 26%)
 **(±)-168**		 **(±)-28** (71%) (Ref. [105], Ref. [66]: 45%)
		 **(±)-169** (40%) (Ref. [105], Ref. [66]: 58%)
		 **(±)-170** (40%)

We also attempted the transformation of *N*-Boc-protected β-lactam **(±)-102**, which was a poor substrate in the previous dihydroxylation/diol cleavage/reductive amination protocol.[89] The result was highly dependent on the amine used (*Scheme 41*). With 2,2,2-trifluoroethylamine, two products were formed: the known monocyclic diamino lactam **(±)-105** and the desired piperidine-fused lactam **(±)-171**. Note that compound **(±)-171** was previously inaccessible. With 2,2-difluoroethylamine, the desired piperidine-fused lactam **(±)-172** was formed as the sole product. With 2-fluoroethylamine and benzylamine, however, reductive cyclization of intermediate **(±)-T27** was accompanied with methanolysis of the lactam ring to produce β-amino esters **(±)-173** and **(±)-174**. It can be assumed, that strong acidic or basic conditions promote methanolysis of the sensitive β-lactam ring. It is expected, that careful fine-tuning of the conditions (especially the acidity of the mixture) may enable suppression of

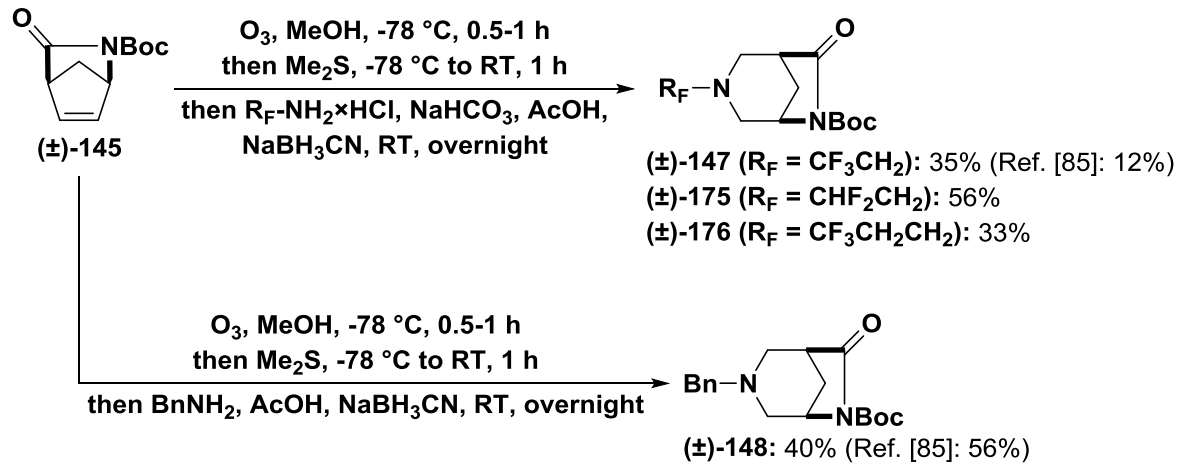
methanolysis. We can also conclude that the ozonolysis/reductive amination protocol is more versatile than the three-step method used previously.[104]



Scheme 41. Ozonolysis/reductive amination of β-lactam **(±)-102**

3.3.3. Synthesis of γ-lactams with a piperidine ring

Taking into account that γ-lactams are much less prone to ring opening than β-lactams, it was reasonable to assume that methanolysis of their lactam motif would not happen during our ozonolysis/reductive amination procedure.

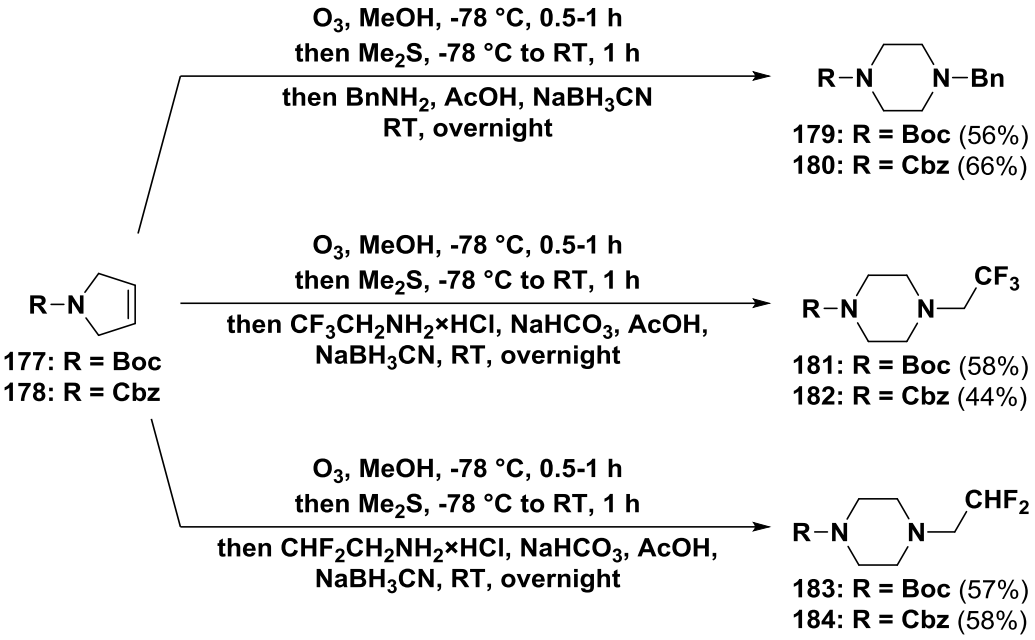


Scheme 42. Synthesis of γ-lactams condensed with a piperidine ring

Indeed, ozonolysis of lactam **(±)-145** and reductive amination of the formed **(±)-T23** (see *Scheme 34*) with benzylamine and various fluorinated amines were successful and provided the expected bridged bicyclic lactams. Compounds **(±)-147** and **(±)-148** are known compounds, while **(±)-175** and **(±)-176** are new fluorine-containing γ-lactams (*Scheme 42*).[104]

3.3.4. Synthesis of other *N*-heterocycles

Based on the above positive experiences with the new synthetic strategy, it was extended for the synthesis of other *N*-heterocyclic compounds too. First, *N*-protected 3-pyrroline derivatives **177** and **178** were subjected to ozonolysis/reductive amination. The reactions with both benzylamine and fluorinated amines were successful, and the expected piperazine derivatives formed in medium to good yields (*Scheme 43*).[104]



Scheme 43. Synthesis of piperazines via ozonolysis/reductive amination

4. SUMMARY

- A simple approach was applied for the stereocontrolled synthesis of functionalized azaheterocycles. First, various substituted unsaturated cyclic compounds were subjected to oxidative ring opening (OsO_4-mediated dihydroxylation followed by $NaIO_4$-mediated cleavage of the resulting diol). Then, the formed diformyl intermediates were subjected to ring closure via reductive amination. The overall outcome of the process is ring expansion.
- Amongst the required starting materials, β- and γ-amino esters were synthesized from readily available unsaturated bicyclic β- and γ-lactams **(±)-17**, **(±)-33**, **(±)-87**, and **(±)-89** using simple, known literature methods. The primary products were *cis* amino esters: *N*-Cbz-protected ethyl esters [**(±)-75**, **(±)-90**], *N*-benzoylated ethyl esters [**(±)-81**, **(±)-88**, **(±)-91**] or *N*-Boc-protected benzyl esters [**(±)-78**, **(±)-84**]. Epimerization of monocyclic *cis*-β-amino esters led to *trans*-β-amino esters **(±)-76**, **(±)-79**, **(±)-82**, and **(±)-85** (*Scheme 20*).
- The synthetic route to fluorine-containing *cis* and *trans* piperidine β-amino esters started with oxidative ring cleavage of unsaturated *cis*- and *trans*-β-aminocyclopentenecarboxylates. Reductive amination of the formed dialdehyde intermediates with fluorinated amines resulted in the desired *N*-Cbz-protected ethyl esters [**(±)-92**, **(±)-93**, **(±)-94**, **(±)-95**, and **(±)-96**, *Scheme 21*] and *N*-Boc-protected benzyl esters [**(±)-98** and **(±)-101,** *Scheme 22*]. The synthesis of compounds **(±)-104**, **(±)-105**, and **(±)-106** started from bicyclic β-lactam **(±)-103** through oxidative ring-cleavage/reductive ring-closing protocol (*Scheme 23*).
- The above synthetic approach was applied for the stereocontrolled synthesis of fluorine-containing azepane β-amino esters **(±)-108–113**, **(±)-115**, **(±)-117**, and **(±)-119** (*Table 1*) from various dihydroxylated cyclohexene β-amino esters. Bridged azepane β-amino esters **(±)-122**, **(±)-123**, and **(±)-124** were prepared similarly from diol **(±)-121** (*Scheme 25*).
- Unsaturated γ-amino esters were transformed into *cis*-γ-amino esters **(±)-127–136**, **(±)-128a**, and **(±)-136a** with piperidine skeleton via oxidative ring opening and stereocontrolled ring expansion through reductive amination with various fluorine-containing amines and benzylamine (*Schemes 26–28)*. The synthesis of regioisomeric trifluoromethyl-containing piperidine *cis*-γ-amino esters **(±)-141** and **(±)-142** was also accomplished (*Scheme 30*).
- Optically pure γ-lactam **(+)-89** was obtained by a literature protocol (enantioselective hydrolysis of racemic **(±)-89** catalyzed by *Candida antarctica* lipase-B, see *Scheme 32*). Using the already established synthetic pathway, lactam **(+)-89** was transformed into enantiomerically pure fluorine-containing piperidine γ-amino ester **(+)-127** (*Scheme 33*).

- The synthetic methodology was further extended for the access of novel fluorine-containing γ-lactam derivatives. Subjecting *N*-Boc-protected Vince lactam **(±)-145** to ring cleavage followed by double reductive amination with $CF_3CH_2NH_2$, $BnNH_2$ or $CF_3CH_2CH_2NH_2$ yielded piperidine-fused γ-lactams **(±)-147** and **(±)-148** as well as monocyclic γ-lactam **(±)-149** (*Scheme 34*).
- The protocol described above was extended towards the preparation of novel benzo[*c*]azepine and benzo[*d*]azepine derivatives. Oxidative ring cleavage of dihydronaphthalenes and subsequent cyclization via double reductive amination with $BnNH_2$ or different fluorine-containing amines provided the corresponding benzazepines **152**, **(*R*)-153**, **154–157**, **(±)-158**, **161–165**, and **(±)-166** (*Scheme 35, Table 2, Scheme 36, Table 3)*.
- In order to improve the synthetic methods described above, oxidative ring cleavage was performed in a single step by ozonolysis and workup with Me_2S. Subjecting the resulting diformyl intermediate to reductive amination without isolation allowed a telescoped synthetic pathway towards azaheterocycles (*Scheme 37*). This one-pot two-step approach is shorter and greener than the previous method, because it no longer needs toxic and expensive OsO_4, produces much less inorganic and organic wastes, and involves less chromatographic purification steps.
- The new synthetic strategy was applied for the synthesis of various known or new *N*-heterocyclic compounds, including benzo[*c*]azepines [*Scheme 38*, known products: **152**, **154**, **155**], monocyclic azepane β-amino esters [*Scheme 39*, known product: **(±)-117**, new product: **(±)-167**], bridged azepane β-amino esters [*Scheme 40*, known products: **(±)-122**, **(±)-123**, **(±)-124**], piperidine β-amino esters [*Table 4*, known products: **(±)-28**, **(±)-98**, **(±)-101**, and **(±)-169**, new product: **(±)-170**], piperidine-fused γ-lactams [*Scheme 42*, known compounds: **(±)-147** and **(±)-148**, new products: **(±)-175** and **(±)-176**], and piperazines [*Scheme 43*, **179–184**].
- The ozonolysis/reductive amination method was generally more versatile and it usually provided better yields. However, during the transformation of *N*-Boc-protected β-lactam **102**, the expected piperidine-fused β-lactams were obtained only with $CF_3CH_2NH_2$ and $CHF_2CH_2NH_2$ (and in the former case, monocyclic diamino lactam **(±)-105** was also formed). With $BnNH_2$ and $FCH_2CH_2NH_2$, reductive amination was accompanied with lactam methanolysis and new β-amino methyl esters **(±)-173** and **(±)-174** were formed. Therefore, acidity of the reaction mixture during reductive amination must be fine-tuned.

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ANNEX

I.

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Reductive Amination

Stereocontrolled Synthesis of Fluorine-Containing Piperidine γ-Amino Acid Derivatives

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Abstract: An efficient synthetic approach for the construction of fluorine-containing piperidine γ-amino acid derivatives has been developed. The synthetic concept was based on oxidative ring opening of an unsaturated bicyclic γ-lactam (Vince-lactam) through its ring C=C bond, followed by double reductive amination of the diformyl intermediate performed with various fluoroalkylamines. The method has been extended towards the access of alkylated and perfluoroalkylated substances and for γ-lactam derivatives. The transformations proceeded with stereocontrol: the configuration of the stereocenters in the products were predetermined by the configuration of the chiral centers of the starting γ-lactam. The method could be extended for the access to enantiopure piperidine γ-amino esters.

Introduction

Although less abundant than their α-analogs, γ-amino acids are considered to be an important family of compounds in medicinal chemistry. Representatives of this class of compounds include some acyclic derivatives, such as the neurotransmitter GABA (γ-aminobutyric acid), (*R*)-Baclofen the agonist of the $GABA_C$ receptor, (*S*)-Vigabatrin an inhibitor of GABA-T or (*S*)-Pregabalin an antiepileptic, antihyperalgesic agent (Figure 1).[1]

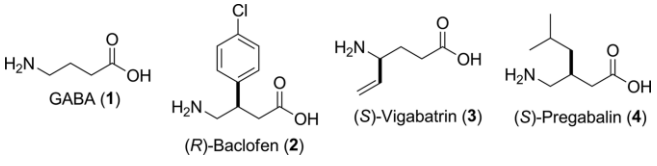

Figure 1. Some bioactive acyclic γ-amino acids.

Alicyclic γ-amino acids are conformationally rigid analogs of their acylic counterparts, some of them are known as $GABA_A$ or $GABA_C$ receptors, while Gabapentin is a drug commercialized for the treatment of cerebral disorder diseases (Figure 2).[1] Furthermore, cyclic γ-amino acids as conformationally restricted structures are key building elements in the synthesis of pharmaceutically relevant α/γ-, β/γ- or γ/γ-peptides.[2]

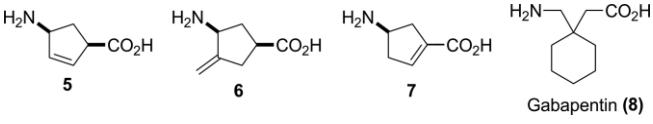

Figure 2. Structures of several biologically relevant alicyclic γ-amino acids.

As a result of the considerable importance of fluorinated organic molecules in medicinal chemistry and the increasing impact of fluorine-containing biomolecules in drug research, an ever-increasing number of fluorination methodologies have emerged during the past decade for the access of versatile fluorine-containing molecular entities. Among them, fluorinated amino acids are of significant importance in drug research since they might exhibit more efficient biological activities than their non-fluorinated counterparts.[3] Some fluorine-containing cyclic γ-amino acid representatives (Figure 3) possess relevant biological properties; e.g. they are potential inactivators of γ-aminobutyric acid aminotransferase (GABA-AT) (Figure 3).[4]

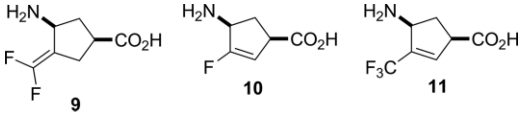

Figure 3. Biologically interesting alicyclic fluorine-containing γ-amino acids.

The antiviral drug Peramivir[5] contains a functionalized cyclopentane γ-amino acid motif whose synthesis starts from bicyclic γ-lactam 2-azabicyclo[2.2.1]hept-5-ene-3-one (Vince lactam, **(±)-15**).[6] Vince lactam, a valuable building block, is the starting material for the access of bioactive carbasugars and amino acid carbasugars. Furthermore, it is the precursor in the synthesis of some blockbuster drugs such as of carbovir, abacavir or entecavir.[7]

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Some heterocyclic α-amino acid derivatives with a piperidine moiety possess various biological properties. For example, Remifentanil and Carfentanil with a piperidine 4-amino-4-carboxylate framework are anesthetics, while AZD5363 is an antitumoral agent (Figure 4).[1h,1i,8] Apart from this, some five- and six-membered azacyclic β-amino acids, possessing both the ring *N*-atom and an extracyclic amino group in their structures, as small molecular entities exhibit antiviral activities or they are key components of bioactive substances with complex structures with antitumoral or antibacterial properties.[9]

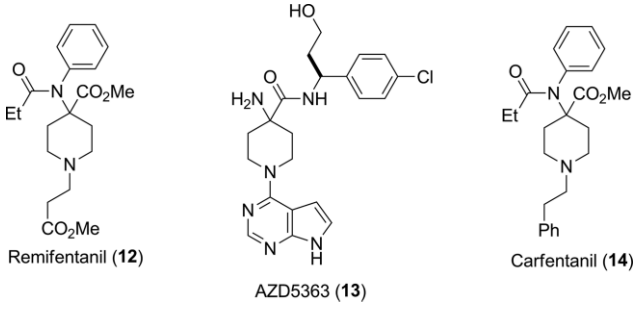


Figure 4. Some bioactive α-amino acid derivatives with a piperidine core.

In view of the high biological potential of both organofluorine derivatives and γ-amino acids, we have planned to develop a synthetic protocol towards the access of novel fluorinated piperidine γ-amino acid derivatives.

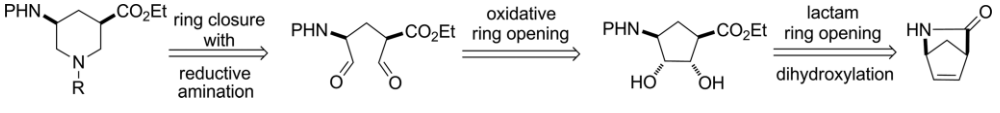
Our synthetic strategy was based on the application of an oxidative ring-opening/reductive ring-closure protocol.[9c,10] Specifically, we carried out oxidative ring cleavage via the C-C double bond of bicyclic Vince lactam (Scheme 1) followed by double reductive amination through ring closing with various fluorine-containing amines.

Results and Discussion

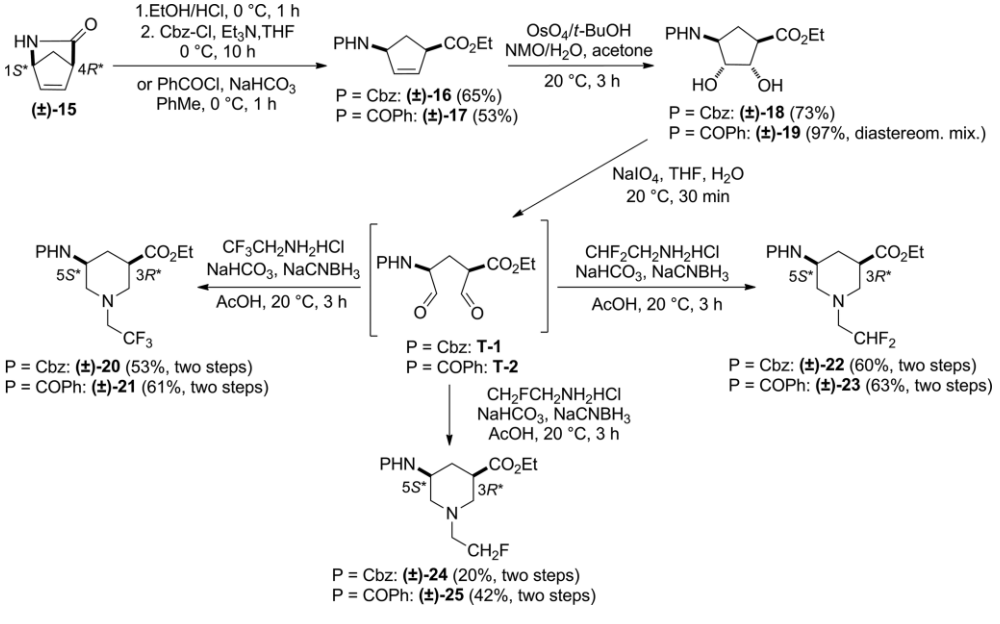
Racemic Vince lactam **(±)-15** was first subjected to acid-catalyzed heteroring opening with ethanolysis followed by Cbz or benzoyl protection of the amino group to have the corresponding cyclopentene γ-amino esters **(±)-16** and **(±)-17**.

Next, these compounds were oxidized with NMO and a catalytic amount of OsO_4. While *cis*-dihydroxylation of Cbz-protected ester **(±)-16** diastereoselectively produced diol **(±)-18** (with the hydroxy groups, the ester and carbamate functions in *trans* relationship), benzoyl-protected derivative **(±)-17** furnished a mixture of diols [*cis*/*trans* **(±)-19**] in nearly 1:1 ratio.

In continuation, both **(±)-18** and diastereomeric mixture **(±)-19** were submitted to a one-pot transformation, which included oxidative ring cleavage with $NaIO_4$ followed by double reductive amination with fluorine-containing amines. Oxidative ring opening of diols **(±)-18** and **(±)-19** led to the corresponding unstable dialdehyde derivatives **T-1** and **T-2** which, in turn, were immediately transformed further after work-up of the oxidative ring-cleavage step. The reductive amination steps were performed by the addition of the fluorine-containing amine HCl salts (mono-, di- or trifluoroethylamines) in the presence of $NaHCO_3$ in a CH_2Cl_2/THF solvent mixture followed by the addition of $NaCNBH_3$ at room temperature, after 10 min in the presence of AcOH (see Experimental). This order of addition of the reagents proved to be essential in these reactions. In all cases, reductive aminations took place with ring expansion



Scheme 1.



Scheme 2.

providing the corresponding racemic trifluorinated [**(±)-20** and **(±)-21**], difluorinated [**(±)-22** and **(±)-23**], and monofluorinated piperidine γ-amino esters [**(±)-24** and **(±)-25**] (Scheme 2, Figure 5).

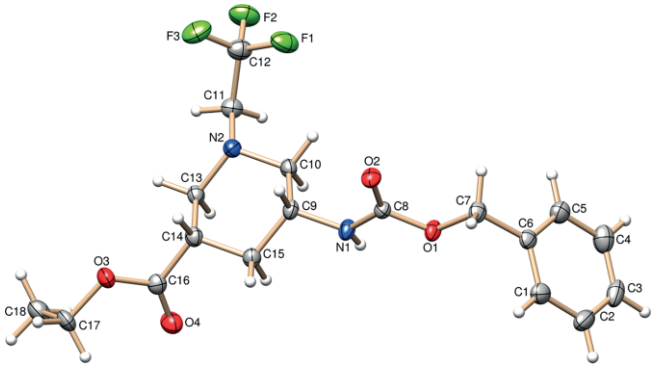
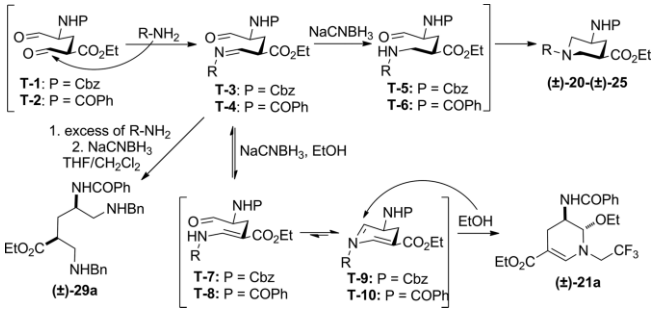


Figure 5. X-ray structure of compound **(±)-20**.

Noteworthy, the synthetic protocol proceeded with stereocontrol, that is the configurations of the chiral centers in all products were predetermined by the configuration of the stereocenters of starting lactam **(±)-15**.

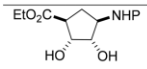
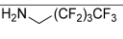
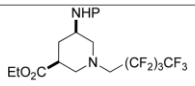
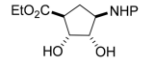
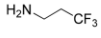
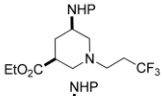
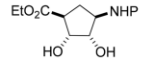
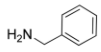
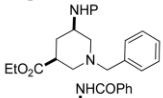
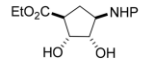
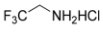
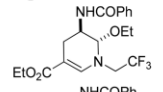
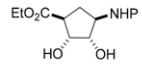
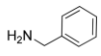
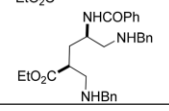
Note, that the dialdehyde intermediates (**T-1** and **T-2**) possess active hydrogens in the α position to the formyl moieties. Fortunately, the possible enolization, which would lead through the cyclization process to inversion of configuration with the piperidine ring containing the ester and protected amine in *trans* relationship, did not take place. The preferred diequatorial arrangement of both the ester and amino groups might be responsible for the conservation of the relative stereochemistry that is the formation of products bearing the two groups in *cis* relative arrangement (see structures **T-5** and **T-6**, Scheme 3).



Scheme 3.

Next we planned to extend the synthetic protocol based on oxidative cleavage/ring closure for the access of other novel functionalized piperidines. Thus, nonafluoropentanamine, trifluoropropylamine and benzylamine were used as amine sources in the ring-closing step with dialdehydes **T-1** or **T-2**. The addition of $NaCNBH_3$ in THF/CH_2Cl_2 after 10 min provided the corresponding γ-amino esters **(±)-26**, **(±)-27**, **(±)-28** and **(±)-29** through double reductive amination (Table 1). Note that the ring closure of **T-2** with trifluoroethylamine was carried out in EtOH as solvent, adduct **(±)-21a** was formed through the nucleophilic attack of EtOH (Table 1), rather than piperidine derivative **(±)-21** observed earlier. As mentioned, the order and timing of addition of the reagents were essential. When $NaCNBH_3$ was added immediately to the mixture of dialdehyde and amine, the ring closure did not occur; instead, the corresponding diamino derivative **(±)-29a** was obtained (Table 1).

Table 1. Synthesis of piperidine derivatives **(±)-21a**, **(±)-26**-**(±)-28**, **(±)-29a**. Reaction conditions: $NaCNBH_3$, CH_2Cl_2, 20 °C (see experimental part).

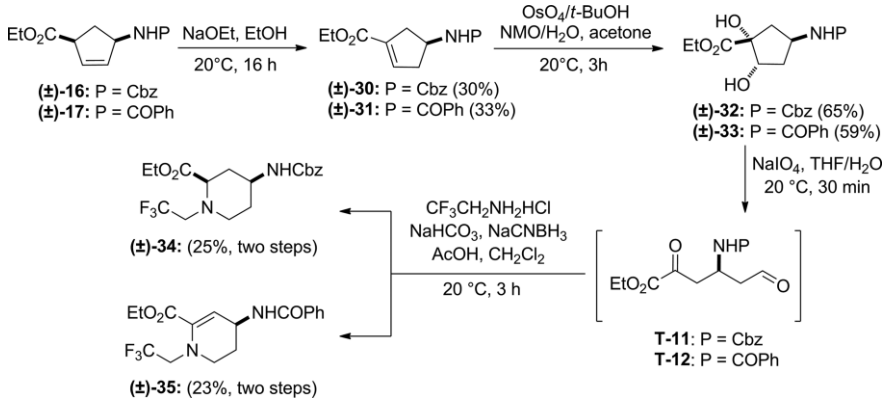
Amino ester	Amines	Product	Yield (two steps)
			P: COPh, 17%, **(±)-26**
			P: COPh, 24%, **(±)-27**
			P: Cbz, 26%, **(±)-28** P: COPh, 24%, **(±)-29**
			P: COPh, 30%, **(±)-21a**
			P: COPh, 29%, **(±)-29a**

In continuation, we designed the synthesis of novel piperidine γ-amino ester derivatives. In order to increase the number of six-membered *N*-heterocyclic γ-amino ester isomers, first the isomerization of the ring double bond in **(±)-16/(±)-17** was accomplished. Compounds **(±)-16/(±)-17** underwent ring double bond migration through the deprotonation of the active H in the presence of NaOEt leading via isomerization to unsaturated esters **(±)-30** and **(±)-31**. Diol derivatives **(±)-32** and **(±)-33**, obtained by OsO_4-catalyzed *cis*-stereoselective dihydroxylation of **(±)-30** and **(±)-31** (determined by the NMR analysis of the crude mixture), were next subjected to oxidative ring opening with $NaIO_4$ in THF/H_2O (Scheme 4).

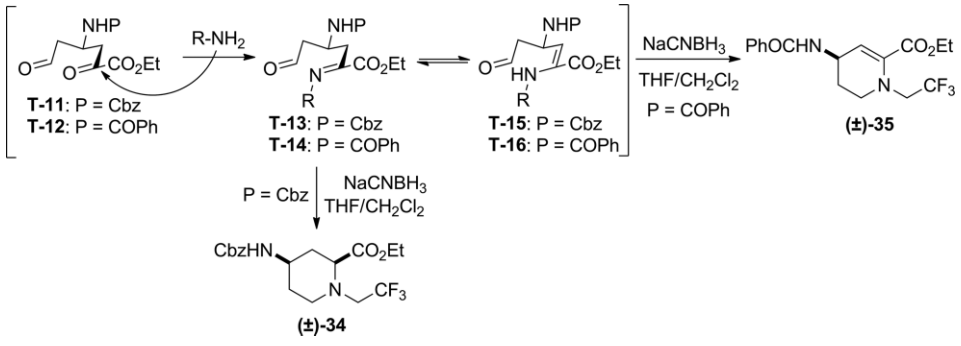
The resulting dicarbonyl intermediates **T-11/T-12** were immediately submitted to the reaction with trifluoroethylamine without isolation. In the first step, most probably, the attack of the amine takes place at the α-oxo group (which leads to an enamine with a conjugated system).

The reductive amination/ring-closure step of **T-11** (Cbz protecting group) furnished the expected piperidine amino ester **(±)-34** a regioisomer of **(±)-20**. Interestingly, benzoyl-protected amino ester **T-12**, under the same experimental conditions, gave tetrahydropyridine derivative **(±)-35**. It is surmised, that this transformation involves an enamine intermediate (Scheme 4 and Scheme 5).

The synthetic protocol presented above was utilized only for the access of racemates. Our next goal was to prepare enantiomerically pure piperidine γ-amino esters. Accordingly, we selected and planned to transform enantiopure γ-lactam **(+)-15** as starting material. Since the configurations of the stereogenic centers during the synthetic process were not affected, the enantiopure starting material is expected to produce the corresponding enantiomeric target substances. Optically pure **(+)-15** was obtained according to our earlier literature procedure,

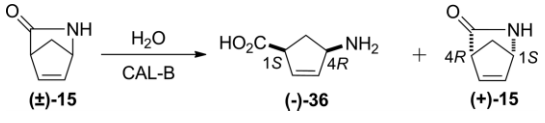


Scheme 4.



Scheme 5.

which was based on lactam ring opening through hydrolysis of racemic **(±)-15** catalyzed by *Candida antarctica* lipase-B (Scheme 6).[11]

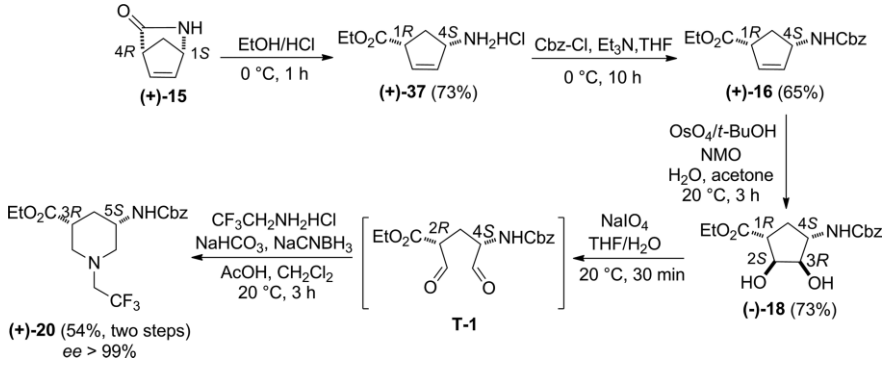


Scheme 6.

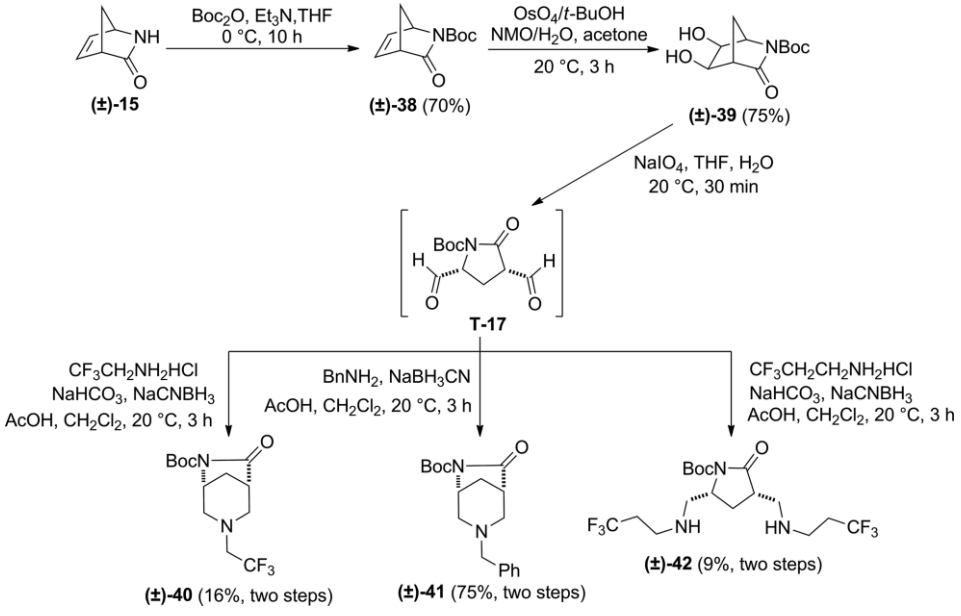
An illustrative example for the synthesis of a piperidine γ-amino ester enantiomer is depicted on Scheme 7. Following the reaction sequences described above for the racemates, enantiomerically pure lactam **(+)-15** was converted via amino ester **(+)-16** and diol **(-)-18** into enantiomerically pure γ-amino ester **(+)-20** isolated with an *ee* of >99 % (determined by means of HPLC, Chiralpak IA column, Scheme 7).

Finally, we decided to further extend the synthetic methodology for the access of novel fluorine-containing bicyclic lactams. Correspondingly, racemic *N*-Boc-protected Vince lactam **(±)-38** was transformed into the corresponding diol derivative **(±)-39**.[12]

Oxidative ring opening of vicinal diol **(±)-39** gave diformyl-substituted pyrrolidinone intermediate **T-17**. Similar to the other dialdehydes, this intermediate is unstable and, therefore, it was immediately subjected to reductive amination. The reaction with trifluoroethylamine or benzylamine led to the desired cyclized azabicyclic compounds **(±)-40** and **(±)-41**. In contrast, the process with trifluoropropylamine under the same reaction



Scheme 7.



Scheme 8.

conditions, even at variation of the amount of amine afforded only diamino compound **(±)-42** (Scheme 8).

Conclusions

An effective synthetic method for the synthesis of novel fluorine-containing piperidine γ-amino acid derivatives has been developed. The synthetic strategy, as novel method for the construction of functionalized saturated *N*-heterocycles, was based on oxidative ring opening of unsaturated bicyclic γ-lactam (Vince-lactam) through its ring olefin bond, followed by reductive ring closure with ring expansion, through reductive amination of the diformyl intermediate performed with various fluoroalkylamines. The novel compounds thus prepared may be regarded as valuable orthogonally-protected β,γ-diaminocarboxylate building scaffolds in synthetic organic and peptide chemistry. Further studies with respect to the transformation of the diformyl intermediates formed in oxidative ring cleavage in view of the synthesis of other novel heterocycles as well as preparation of amino acids from the synthesized *N*-protected esters are currently being carried out in our group.

Experimental Section

General procedure for Cbz protection of γ-amino esters

To a stirred solution of γ-amino ester hydrochloride (8 mmol) in THF (50 mL), Et_3N (3 equiv) was added at 0 °C followed by the addition of Cbz-Cl (1 equiv). 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 (3×40 mL), dried with 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) giving the Cbz-protected γ-amino ester.

General procedure for benzoyl protection of γ-amino esters

To a stirred solution of γ-amino ester hydrochloride (8 mmol) benzoyl chloride (1 equiv) was added in toluene (50 mL), water (30 mL) and $NaHCO_3$ (3 equiv) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. The residue was taken up in EtOAc (80 mL) and washed with water (3×40 mL). The organic layer was dried with Na_2SO_4 and concentrated under vacuoo. The crude material was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to give the benzoyl-protected γ-amino ester.

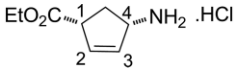
General procedure for dihydroxylation of *N*-protected amino esters

To a solution of *N*-protected β-amino ester (5 mmol) 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 the termination of the reaction, 90 mL of saturated aqueous Na_2SO_3 solution was added and the reaction mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried with 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).

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

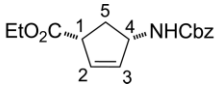
To a stirred solution of dihydroxylated γ-amino ester (2 mmol) or dihydroxylated γ-lactam (2 mmol) $NaIO_4$ (1.5 equiv) was added in THF/H_2O (25 mL/2 mL). After stirring for 30 min at 20 °C under an Ar atmosphere, the reaction was quenched with H_2O (40 mL). The mixture was then extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried with Na_2SO_4. The resulting solution containing the dialdehyde derivative, concentrated to half of its volume, was used without purification for the next reaction. To the solution of the dialdehyde were added fluorine-containing amine hydrochloride (1 equiv) and $NaHCO_3$ (2 equiv) or benzylamine (1 equiv), and the mixture was stirred at 20 °C for 10 min. After adding $NaCNBH_3$ (1 equiv) and AcOH (2 drops) stirring was contin-

ued for another 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 layers were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).



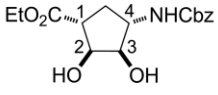
(1*R*,4*S*)-Ethyl 4-aminocyclopent-2-enecarboxylate hydrochloride (+)-37[11]

White solid, mp: 133–135 °C; yield: 73 % (1.9 g); $[\alpha]_D^{20}$ = +178 (*c* = 0.15, CH_2Cl_2); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.21 (t, *J* = 7.05 Hz, 3 H, CH_3), 1.93 (dt, *J* = 13.66 Hz, *J* = 6.84 Hz, 1 H, H-5), 2.55 (dt, *J* = 13.63 Hz, *J* = 8.45 Hz, 1 H, H-5), 3.65–3.71 (m, 1 H, H-1), 4.08–4.15 (m, 2 H, CH_2CH_3), 4.15–4.21 (m, 1 H, H-4), 5.86–5.90 (m, 1 H, H-2), 6.06–6.10 (m, 1 H, H-3), 8.27 (brs, 3 H, NH); ^{13}C-NMR (126 MHz, [D$_6$]DMSO) δ = 14.6, 31.6, 49.6, 55.7, 61.0, 130.8, 134.9, 172.4; Anal. Calcd for $C_8H_{14}ClNO_2$: C, 50.13; H, 7.36; Cl, 18.50; N, 7.31; found C, 50.11; H, 7.34; Cl, 18.53; N, 7.30.



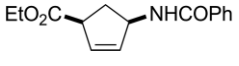
(1*R*,4*S*)-Ethyl 4-(((benzyloxy)carbonyl)amino)cyclopent-2-enecarboxylate, (+)-16

White solid, mp: 55–58 °C; yield: 68 % (1.6 g); R_f = 0.51 (*n*-hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ = +47 (*c* = 0.15, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.00 Hz, 3 H, CH_3), 1.90 (dt, *J* = 13.97 Hz, *J* = 3.59 Hz, 1 H, H-5), 2.49 (dt, *J* = 14.09 Hz, *J* = 8.35 Hz, 1 H, H-5), 3.43–3.50 (m, 1 H, H-1), 4.09–4.20 (m, 2 H, CH_2CH_3), 4.80–4.89 (m, 1 H, H-4), 5.09 (s, 2 H, OCH_2), 5.21 (brs, 1 H, NH), 5.89 (s, 2 H, H-2 and H-3), 7.27–7.41 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.2, 34.5, 49.4, 56.3, 61.1, 66.6, 128.0, 128.1, 128.5, 131.7, 134.5, 136.6, 155.6, 174.4; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84; found C, 66.40; H, 6.63; N, 4.83.



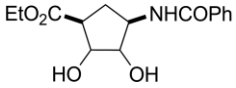
(1*R*,2*S*,3*R*,4*S*)-Ethyl 4-(((benzyloxy)carbonyl)amino)-2,3-dihydroxycyclopentanecarboxylate, (-)-18

White solid, mp: 74–76 °C; yield: 92 % (1.4 g); R_f = 0.30 (*n*-hexane/EtOAc, 1:4); $[\alpha]_D^{20}$ = –29 (*c* = 0.3, $CHCl_3$); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.18 (t, *J* = 7.00 Hz, 3 H, CH_3), 1.46 (dt, *J* = 13.07 Hz, *J* = 8.92 Hz, 1 H, H-5), 2.17 (dt, *J* = 12.99 Hz, *J* = 8.57 Hz, 1 H, H-5),2.59–2.67 (m, 1 H, H-1), 3.57–3.63 (m 1 H, H-2), 3.67–3.77 (m, 1 H, H-4), 3.94–3.99 (m, 1 H, H-3), 4.03–4.09 (m, 2 H, CH_2CH_3), 4.73 (d, *J* = 5.60, 1 H, OH), 4.86 (d, *J* = 5.80, 1 H, OH), 5.00 (s, 2 H, OCH_2), 7.27–7.41 (m, 6 H, NH, Ar-H); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 14.6, 31.0, 47.9, 55.9, 60.5, 65.6, 73.6, 76.0, 128.2, 128.3, 128.8, 137.6, 156.2, 172.3; Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33; found C, 59.45; H, 6.54; N, 4.32.



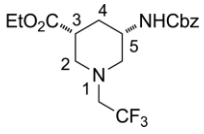
(1*S,4*R**)-Ethyl 4-benzamidocyclopent-2-enecarboxylate, (±)-17**

White solid, mp: 73–75 °C; yield: 66 % (2.3 g); R_f = 0.58 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.10 Hz, 3 H, CH_3), 1.99–2.06 (m, 1 H, H-5), 2.50 (dt, *J* = 14.06 Hz, *J* = 8.27 Hz, 1 H, H-5),3.51–3.58 (m, 1 H, H-1), 4.15–4.23 (m, 2 H, CH_2CH_3), 5.26–5.33 (m, 1 H, H-4), 5.93–5.98 (m, 1 H, H-2), 6.01–6.06 (m, 1 H, H-3), 6.92 (br s, 1 H, NH), 7.38–7.85 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.2, 34.5, 49.6, 54.5, 61.3, 127.0, 128.5, 131.4, 132.0, 134.4, 134.6, 166.2, 175.3; Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; found C, 69.49; H, 6.60; N, 5.41.



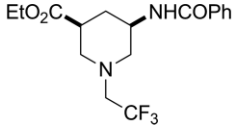
(1*S,2*R**,3*S**,4*R**)-Ethyl 4-benzamido-2,3-dihydroxycyclopentanecarboxylate, (±)-19**

White solid, mp: 93–95 °C; yield: 97 % (2.5 g); R_f = 0.28 (*n*-hexane/EtOAc, 1:4). Benzoyl-protected γ- amino carboxylate dihydroxylation furnished a mixture of diol derivatives which was used in the next step without separation of the components.



(3*R*,5*S*)-Ethyl 5-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylate, (+)-20

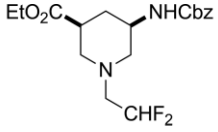
The *ee* values for the enantiomers were recorded by HPLC [Chiralpak IA column (4.6 mm×250 mm)]. Eluent: *n*-hexane/*i*PrOH (98:2), flow rate: 0.5 mL min^{-1}, 208 nm; retention times (min) for (3*R*,5*S*)-**(+)-17**: 66.84, for (3*S*,5*R*)- **(-)-17**: 71.84. White solid, mp: 39–42 °C; yield: 54 % (396 mg); R_f = 0.32 (*n*-hexane/EtOAc, 1:1); $[\alpha]_D^{20}$ = +5 (*c* = 0.165, EtOH), *ee* = 99 %; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.10 Hz, 3 H, CH_3), 1.43–1.50 (m, 1 H, H-4), 2.16 (d, *J* = 12.40 Hz, 1 H, H-4), 2.29–2.40 (m, 1 H, H-3), 2.61–2.73 (m, 2 H, H-2), 2.97–3.13 (m, 4 H, H-6 and CH_2CF_3), 3.71–3.82 (m, 1 H, H-5), 4.08–4.18 (m, 2 H, CH_2), 4.92 (brs. 1 H, NH), 5.09 (s, 2 H, OCH_2), 7.29–7.41 (m, 5 H, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.5, 32.4, 40.9, 47.3, 54.7, 55.7, 58.3 (q, $^2J_{C,F}$ = 26.7 Hz, CCF_3), 61.2, 67.2, 124.5 ($^1J_{C,F}$ = 235.0 Hz, CF_3), 128.6, 128.9, 136.8, 156.1, 183.2; ^{19}F NMR (471 MHz, [D$_6$]DMSO): δ = –67.8 (t, *J* = 10.3 Hz). MS: (ESI) *m/z* = 389.2 (M + 1); Anal. Calcd for $C_{18}H_{23}F_3N_2O_4$: C, 55.67; H, 5.97; N, 7.21; found C, 55.64; H, 5.96; N, 7.20.



(3*S,5*R**)-Ethyl 5-benzamido-1-(2,2,2-trifluoroethyl)piperidine-3-carboxylate, (±)-21**

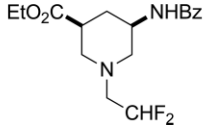
White solid, mp: 67–69 °C; yield: 61 % (514 mg); R_f = 0.45 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, [D$_6$]DMSO): δ = 1.19 (t, *J* = 7.20 Hz, 3 H, CH_3), 1.43–1.56 (m, 1 H, H-4), 2.06–2.13 (m, 1 H, H-4), 2.26 (t, *J* = 10.7 Hz, 1 H, H-2), 2.37 (t, *J* = 11.2 Hz, 1 H, H-2), 2.63–2.72 (m, 1 H, H-3), 3.05 (dd, *J* = 10.86 Hz, *J* = 3.86 Hz, 1 H, H-6), 3.13 (dd, *J* = 11.40 Hz, *J* = 3.36 Hz, 1 H, H-6), 3.32 (q, *J* = 10.22 Hz, 2 H, CH_2CF_3), 3.92–4.02 (m, 1 H, H-5), 4.04–4.13 (q, *J* = 7.04 Hz, 2 H, CH_2), 7.41–7.86 (m, 5 H, Ar-H), 8.27 (brs. 1 H, NH); ^{13}C-NMR (100 MHz, [D$_6$]DMSO): δ = 14.9, 32.8, 41.4, 46.3, 55.2, 57.1 (q, $^2J_{C,F}$ = 22.0 Hz, CCF_3), 58.2, 61.0, 122.8 ($^1J_{C,F}$ = 284.0 Hz, CF_3), 128.1, 129.1, 132.1,

135.3, 166.7, 173.4; ^{19}F-NMR (376 MHz, [D$_6$]DMSO): δ = –67.7 (t, J = 10.2 Hz); MS: (ESI) m/z = 359.3 (M + 1); Anal. Calcd for $C_{17}H_{21}F_3N_2O_3$: C, 56.98; H, 5.91; N, 7.82; found C, 56.96; H, 5.90; N, 7.81.



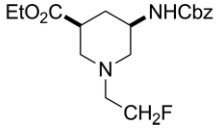
(3*S,5*R**)-Ethyl 5-(((benzyloxy)carbonyl)amino)-1-(2,2-difluoroethyl)piperidine-3-carboxylate, (±)-22**

Colorless oil; yield: 42 % (191 mg); R_f = 0.74 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.22–1.25 (m, 3 H, CH_3), 1.55–1.65 (m, 2 H, H-4), 2.38–2.46 (m, 1 H, H-2), 2.52 (d, J = 11.44 Hz, 1 H, H-2), 2.67–2.81 (m, 4 H, H-6, NCH_2), 3.02–3.09 (m, 1 H, H-3), 3.96–4.03 (m, 1 H, H-5), 4.09–4.16 (m, 2 H, CH_2CH_3), 5.05–5.16 (m, 2 H, OCH_2), 5.39 (br.s., 1 H, NH), 5.66–5.98 (tt, 1 H, CHF_2, ^1J = 55.67 Hz, ^2J = 4.37 Hz), 7.29–7.43 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.2, 31.0, 37.9, 45.4, 55.6, 58.2, 58.7 (t, $^2J_{C,F}$ = 24.6 Hz, $CCHF_2$), 60.7, 66.8, 115.3 (t, $^1J_{C,F}$ = 242.6 Hz, CHF_2), 128.2, 128.3, 128.6, 136.4, 155.4, 173.3; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = –119.0; MS: (ESI) m/z = 371.3 (M + 1); Anal. Calcd for $C_{18}H_{24}F_2N_2O_4$: C, 58.37; H, 6.53; N, 7.56; found C, 58.35; H, 6.54; N, 7.55.



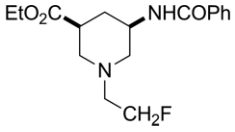
(3*S,5*R**)-Ethyl 5-benzamido-1-(2,2-difluoroethyl)piperidine-3-carboxylate, (±)-23**

White solid, mp: 104–107 °C; yield: 63 % (301 mg); R_f = 0.51 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.16 Hz, 3 H, CH_3), 1.87–1.99 (m, 1 H, H-4), 2.03–2.12 (m, 1 H, H-4), 2.57–2.66 (m, 1 H, H-3), 2.70–2.96 (m, 6 H, H-2, H-6, NCH_2), 4.00–4.20 (m, 2 H, CH_2CH_3), 4.21–4.30 (m, 1 H, H-5), 5.69–6.00 (tt, 1 H, CHF_2, ^1J = 55.98 Hz, ^2J = 4.15 Hz), 7.05 (brs. 1 H, NH), 7.36–7.89 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 30.7, 39.8, 45.1, 55.1, 58.7, 59.5 (t, $^2J_{C,F}$ = 25.4 Hz, $CCHF_2$), 61.0, 115.6 (t, $^1J_{C,F}$ = 242.6 Hz, CHF_2), 126.9, 128.5, 131.5, 134.3, 166.5, 174.4; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = –118.9; MS: (ESI) m/z = 341.3 (M + 1); Anal. Calcd for $C_{17}H_{22}F_2N_2O_3$: C, 59.99; H, 6.51; N, 8.23; found C, 59.97; H, 6.50; N, 8.24.



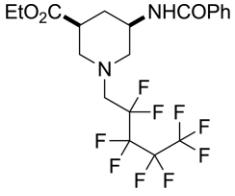
(3*S,5*R**)-Ethyl 5-(((benzyloxy)carbonyl)amino)-1-(2-fluoroethyl)piperidine-3-carboxylate, (±)-24**

White solid, mp: 41–43 °C; yield: 20 % (126 mg); R_f = 0.56 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, [D$_6$]DMSO): δ = 1.18 (t, J = 6.8 Hz, 3 H, CH_3), 1.45–1.56 (m, 1 H, H-4), 1.82–1.94 (m, 1 H, H-4), 2.10–2.21 (m, 1 H, H-2), 2.38–2.47 (m, 1 H, H-2), 2.54–2.72 (m, 3 H, H-3, CH_2-CH_2F), 2.76–2.86 (m, 2 H, H-6), 3.67–3.78 (m, 1 H, H-5), 3.98–4.14 (m, 2 H, CH_2), 4.38–4.59 (dt, 2 H, CH_2F, ^1J = 47.85 Hz, ^2J = 4.94 Hz), 5.02 (s, 2 H, OCH_2), 7.10 (brs. 1 H, NH), 7.27–7.40 (m, 5 H, Ar-H); ^{13}C-NMR (100 MHz, [D$_6$]DMSO): δ = 14.9, 31.2, 39.1, 45.9, 55.2, 58.1 (d, $^2J_{C,F}$ = 19.5 Hz, CCH_2F), 59.1, 60.7, 66.1, 82.9 (d, $^1J_{C,F}$ = 163.7 Hz, CH_2F), 128.4, 128.6, 129.2, 138.0, 156.3, 173.8; ^{19}F-NMR (376 MHz, [D$_6$]DMSO): δ = –216.7. MS: (ESI) m/z = 353.3 (M + 1); Anal. Calcd for $C_{18}H_{25}FN_2O_4$: C, 61.35; H, 7.15; N, 7.95; found C, 61.33; H, 7.14; N, 7.94.



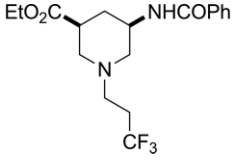
(3*S,5*R**)-Ethyl 5-benzamido-1-(2-fluoroethyl)piperidine-3-carboxylate, (±)-25**

White solid, mp: 56–58 °C; yield: 42 % (134 mg); R_f = 0.51 (*n*-hexane/EtOAc, 1:6); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.40 Hz, 3 H, CH_3), 1.57–1.69 (m, 1 H, H-4), 1.82–1.95 (m, 1 H, H-4), 2.07–2.16 (m, 1 H, H-2), 2.42–2.54 (m, 1 H, H-2), 2.68–2.94 (m, 5 H, H-3, CH_2-CH_2F, H-6), 4.01–4.21 (m, 2 H, CH_2), 4.23–4.31 (m, 1 H, H-5), 4.46–4.69 (m, 2 H, CH_2F), 6.97 (brs. 1 H, NH), 7.40–7.84 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 30.8, 39.9, 45.3, 54.9, 57.0 (d, $^2J_{C,F}$ = 20.0 Hz, CCH_2F), 58.4, 60.9, 82.1 (d, $^1J_{C,F}$ = 140.0 Hz, CH_2F), 126.9, 128.5, 131.4, 134.5, 166.5, 174.4; ^{19}F-NMR (471 MHz, [D$_6$]DMSO): δ = –218.2; MS: (ESI) m/z = 322.37 (M + 1); Anal. Calcd for $C_{17}H_{23}FN_2O_3$: C, 63.34; H, 7.19; N, 8.69; found C, 63.32; H, 7.18; N, 8.68.



(3*S,5*R**)-Ethyl 5-benzamido-1-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)piperidine-3-carboxylate, (±)-26**

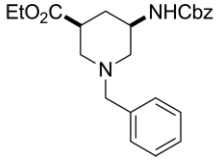
Colorless oil; yield: 17 % (176 mg); R_f = 0.31 (*n*-hexane/EtOAc, 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.30 Hz, 3 H, CH_3), 1.63 (td, J = 13.26 Hz, J = 2.98 Hz, 1 H, H-4), 2.32–2.38 (m, 1 H, H-4), 2.57–2.64 (m, 1 H, H-3), 2.72–3.27 (m, 6 H, H-2, CH_2CF_2, H-6), 4.06–4.14 (m, 2 H, CH_2), 4.41–4.48 (m, 1 H, H-5), 6.93 (brs. 1 H, NH), 7.40–7.82 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 30.6, 38.1, 44.4, 56.1, 57.0 (t, $^2J_{C,F}$ = 23.3 Hz, $CCHF_2$), 58.6, 60.8, 117.3–124.4 (m, 4C, $(CF_2)_3CF_3$) 126.8, 128.6, 131.6, 134.2, 166.3, 173.0; ^{19}F-NMR (471 MHz, [D$_6$]DMSO): δ = –80.9 (t, J = 9.58 Hz), –115.8, –123.4, –126.1; MS: (ESI) m/z = 509.41 (M + 1); Anal. Calcd for $C_{20}H_{21}F_9N_2O_3$: C, 47.25; H, 4.16; N, 5.51; found C, 47.24; H, 4.15; N, 5.50.



(3*S,5*R**)-Ethyl 5-benzamido-1-(3,3,3-trifluoropropyl)piperidine-3-carboxylate, (±)-27**

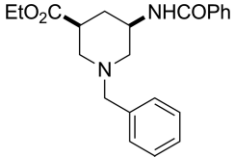
White solid, mp: 113–115 °C; yield: 24 % (128 mg); R_f = 0.52 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, [D$_6$]DMSO): δ = 1.19 (t, J = 6.8 Hz, 3 H, CH_3), 1.43–1.56 (m, 1 H, H-4), 1.85–2.04 (m, 2 H, H-2), 2.05–2.13 (m, 1 H, H-4), 2.36–2.49 (m, 2 H, CH_2CF_3), 2.57–2.71 (m, 3 H, H-3, NCH_2), 2.94–3.09 (m, 2 H, H-6), 3.92–4.02 (m, 1 H, H-5), 4.08 (q, J = 7.07 Hz, 2 H, CH_2), 7.41–7.88 (m, 5 H, Ar-H), 8.26 (brs. 1 H, NH); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 14.5, 30.9 (q, $^2J_{C,F}$ = 26.5 Hz,

CCF_3) 32.8, 41.0, 46.0, 50.3, 54.5, 57.5, 60.6, 127.7 (q, $^1J_{C,F}$ = 277.20 Hz, CF_3), 127.8, 128.7, 131.7, 134.8 166.2, 173.1; ^{19}F-NMR (471 MHz, [D_6]DMSO): δ = –63.5 (t, J = 11.70 Hz). MS: (ESI) m/z = 373.4 (M + 1); Anal. Calcd for $C_{18}H_{23}F_3N_2O_3$: C, 58.06; H, 6.23; N, 7.52; found C, 58.04; H, 6.21; N, 7.50.



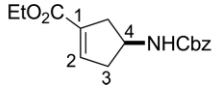
(3*S,5*R**)-Ethyl 1-benzyl-5-(((benzyloxy)carbonyl)amino)piperidine-3-carboxylate, (±)-28**

Yellow solid, mp: 74–77 °C; yield: 26 % (127 mg); R_f = 0.30 (*n*-hexane/EtOAc, 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.2 Hz, 3 H, CH_3), 1.54–1.64 (m, 1 H, H-4), 2.09–2.19 (m, 2 H, H-2), 2.21–2.29 (m, 1 H, H-4), 2.66–2.77 (m, 2 H, H-6), 2.96–3.05 (m, 1 H, H-3), 3.44–3.54 (m, 2 H, NCH_2), 3.96–4.01 (m, 1 H, H-5), 4.04–4.14 (m, 2 H, CH_2CH_3), 5.02–5.16 (m, 2 H, OCH_2), 4.56 (brs. 1 H, NH), 7.22–7.40 (m, 10 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.2, 31.6, 37.9, 45.5, 54.9, 57.3, 60.5, 62.8, 66.7, 127.3, 127.8, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 136.5, 137.6, 155.4, 173.7; MS: (ESI) m/z = 397.2 (M + 1); Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07; found C, 69.65; H, 7.11; N, 7.08.



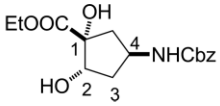
(3*S,5*R**)-Ethyl 5-benzamido-1-benzylpiperidine-3-carboxylate, (±)-29**

White solid, mp: 106–109 °C; yield: 21 % (110 mg); R_f = 0.51 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 1.16 (t, J = 7.2 Hz, 3 H, CH_3), 1.42–1.55 (m, 1 H, H-4), 1.86 (t, J = 10.58 Hz, 1 H, H-2), 1.94 (t, J = 11.12 Hz, 1 H, H-2), 2.05–2.13 (m, 1 H, H-4), 2.60–2.72 (m, 1 H, H-3), 2.89–3.04 (m, 2 H, H-6), 3.56 (s, 2 H, NCH_2), 3.94–4.10 (m, 3 H, H-5, CH_2CH_3), 7.21–7.87 (m, 10 H, Ar-H), 8.25 (brs. 1 H, NH); ^{13}C-NMR (126 MHz, [D_6]DMSO): δ = 14.5, 32.9, 41.1, 46.1, 54.6, 57.7, 60.6, 62.1, 127.5, 127.7, 128.7, 129.2, 131.7, 134.8, 138.4, 166.2, 173.2; MS: (ESI) m/z = 367.2 (M + 1); Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64; found C, 72.09; H, 7.14; N, 7.65."/>



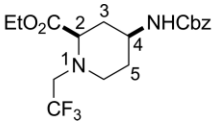
(*S)-Ethyl 4-(((benzyloxy)carbonyl)amino)cyclopent-1-enecarboxylate, (±)-30**

Colorless oil; yield: 30 % (0.5 g); R_f = 0.46 (*n*-hexane/acetone, 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.07 Hz, 3 H, CH_3), 2.36–2.50 (m, 2 H, H-3, H-5), 2.87–3.03 (m, 2 H, H-3, H-5), 4.19 (q, J = 7.13 Hz, 2 H, CH_2CH_3), 4.38–4.47 (m, 1 H, H-4), 4.98 (br s, 1 H, NH), 5.08 (s, 2 H, OCH_2), 6.67–6.73 (m, 1 H, H-2), 7.29–7.39 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.3, 39.1, 41.1, 50.7, 60.4, 60.7, 128.1, 128.2, 128.6, 134.8, 136.4, 140.7, 155.8, 164.2; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84; found C, 66.40; H, 6.63; N, 4.86.



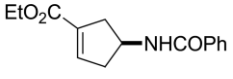
(1*R,2*S**,4*S**)-Ethyl 4-(((benzyloxy)carbonyl)amino)-1,2-dihydroxycyclopentanecarboxylate, (±)-32**

White solid, mp: 78–80 °C; yield: 65 % (450 mg); R_f = 0.47 (*n*-hexane/EtOAc, 1:2); ^{1}H-NMR (500 MHz, [D_6]DMSO): δ = 1.19 (t, J = 7.03 Hz, 3 H, CH_3), 1.72–1.79 (m, 1 H, H-3), 1.85–1.93 (m, 2 H, H-3, H-5), 2.03 (dd, J = 13.23 Hz, J = 7.78 Hz, 1 H, H-5), 4.03–4.14 (m, 3 H, CH_2CH_3, H-4), 4.26–4.34 (m, 1 H, H-2), 4.87 (s, 1 H, OH), 4.93 (d, J = 7.1, 1 H, OH), 4.99 (s, 2 H, OCH_2), 7.03–7.38 (m, 5 H, Ar-H), 7.42 (brs. 1 H, NH); ^{13}C-NMR (126 MHz, [D_6]DMSO): δ = 14.6, 38.6, 42.8, 48.0, 60.9, 65.6, 75.4, 81.2, 128.3, 128.8, 137.7, 156.0, 174.6; Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33; found C, 59.41; H, 6.56; N, 4.30.



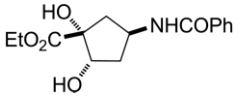
(2*R,4*S**)-Ethyl 4-(((benzyloxy)carbonyl)amino)-1-(2,2,2-trifluoroethyl)piperidine-2-carboxylate, (±)-33**

White solid, mp: 83–85 °C; yield: 25 % (140 mg); R_f = 0.65 (*n*-hexane/EtOAc, 4:1); ^{1}H-NMR (500 MHz, [D_6]DMSO): δ = 1.24 (t, J = 7.16 Hz, 3 H, CH_3), 1.54–1.65 (m, 1 H, H-5), 1.82–1.98 (m, 2 H, H-5, H-3), 2.12–2.22 (m, 1 H, H-3), 2.62–2.72 (m, 1 H, H-6), 3.10–3.26 (m, 3 H, H-6, CH_2CF_3), 3.40–3.47 (m, 1 H, H-2). 3.69–3.80 (m, 1 H, H-4), 4.08–4.22 (m, 2 H, CH_2CH_3), 4.84 (brs. 1 H, NH), 5.02–5.13 (m, 2 H, OCH_2), 7.29–7.40 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, [D_6]DMSO): δ = 14.1, 31.1, 34.6, 45.7, 48.8, 55.6 (q, $^2J_{C,F}$ = 30.5 Hz, CCF_3), 61.1, 61.6, 66.7, 125.5 (q, $^1J_{C,F}$ = 284.7 Hz, CF_3), 128.2, 128.6, 136.3, 155.5, 172.8; ^{19}F-NMR (471 MHz, [D_6]DMSO): δ = –69.3; MS: (ESI) m/z = 389.56 (M + 1); Anal. Calcd for $C_{18}H_{23}F_3N_2O_4$: C, 55.67; H, 5.97; N, 7.21; found C, 55.64; H, 5.98; N, 7.20.



(*S)-Ethyl 4-benzamidocyclopent-1-enecarboxylate, (±)-31**

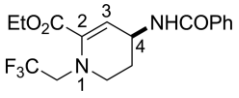
Colorless oil; yield: 33 % (363 mg); R_f = 0.19 (*n*-hexane/acetone, 4:1); ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 1.23 (t, J = 7.20 Hz, 3 H, CH_3), 2.52–2.64 (m, 2 H, H-3, H-5), 2.83–2.96 (m, 2 H, H-3, H-5), 4.14 (q, J = 7.10 Hz, 2 H, CH_2CH_3), 4.56–4.66 (m, 1 H, H-4), 6.69–6.74 (m, 1 H, H-2), 7.40–7.91 (m, 5 H, Ar-H), 8.54 (brs. 1 H, NH); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.7, 38.5, 40.6, 49.3, 60.3, 127.8, 128.6, 131.6, 134.6, 134.9, 142.1, 164.5, 166.5; Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; found C, 69.51; H, 6.59; N, 5.38.



(1*R,2*S**,4*S**)-Ethyl 4-benzamido-1,2-dihydroxycyclopentanecarboxylate, (±)-33**

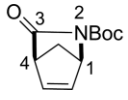
White solid, mp: 87–89 °C; yield: 59 % (248 mg); R_f = 0.16 (*n*-hexane/EtOAc, 1:4); ^{1}H-NMR (400 MHz, [D_6]DMSO): δ = 1.21 (t, J = 7.20 Hz, 3 H, CH_3), 1.86–2.02 (m, 2 H, H-5), 2.03–2.12 (m, 2 H, H-3), 4.12 (q, J = 7.20 Hz 2 H, CH_2CH_3), 4.37–4.56 (m, 1 H, H-2), 4.46–4.55 (m,

1 H, H-4), 4.85 (s, 1 H, OH), 4.90 (d, J = 7.1, 1 H, OH), 7.41–7.88 (m, 5 H, Ar-H), 8.46 (brs. 1 H, NH); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 14.6, 38.4, 42.5, 46.7, 60.9, 75.7, 81.4, 127.7, 128.6, 131.5, 135.0, 166.1, 174.7; Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78; found C, 61.39; H, 6.54; N, 4.76.



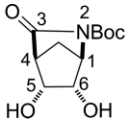
(*S)-Ethyl 4-benzamido-1-(2,2,2-trifluoroethyl)-1,4,5,6-tetrahydropyridine-2-carboxylate, (±)-35**

White solid, mp: 83–85 °C; yield: 23 % (143 mg); R_f = 0.21 (*n*-hexane/EtOAc, 3:1); ^{1}H-NMR (400 MHz, [D$_6$]DMSO): δ = 1.22 (t, J = 7.30 Hz, 3 H, CH$_3$), 1.74–1.85 (m, 1 H, H-5), 1.86–1.95 (m, 1 H, H-5), 3.29–3.33 (m, 2 H, H-6), 3.91–4.10 (m, 2 H, CH$_2$CF$_3$). 4.17 (q, J = 7.01 Hz, 2 H, *CH*$_2$CH$_3$), 4.60–4.68 (m, 1 H, H-4), 5.64 (d, J = 3.56 Hz, 1 H, H-3), 7.31–7.91 (m, 5 H, Ar-H), 8.49 (brs. 1 H, NH); ^{13}C-NMR (100 MHz, [D$_6$]DMSO): δ = 14.8, 28.8, 43.1, 48.0, 51.9 (q, $^2J_{C,F}$ = 33.3 Hz, CCF$_3$), 61.7, 114.2, 126.5 (q, $^1J_{C,F}$ = 273.0 Hz, CF$_3$), 128.3, 129.0, 132.0, 135.2, 137.9, 164.6, 166.6; ^{19}F-NMR (376 MHz, [D$_6$]DMSO): δ = –68.5 (t, J = 9.5 Hz); MS: (ESI) m/z = 379.41 (M + 23); Anal. Calcd for $C_{17}H_{19}F_3N_2O_3$: C, 57.30; H, 5.37; N, 7.86; found C, 57.27; H, 5.39; N, 7.84.



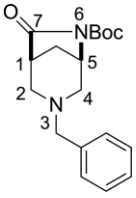
(1*R,4*S**)-*tert*-Butyl 3-oxo-2-azabicyclo[2.2.1]hept-5-ene-2-carboxylate, (±)-38[11]**

White solid, mp: 56–58 °C; yield: 70 % (1.3 g); R_f = 0.40 (*n*-hexane/EtOAc, 2:1); ^{1}H-NMR (500 MHz, CDCl$_3$): δ = 1.50 (s, 9 H, CH$_3$), 2.12–2.18 (m, 1 H, CH$_2$), 2.32–2.38 (m, 1 H, CH$_2$), 3.36–3.42 (m, 1 H, H-4), 4.93–4.99 (m, 1 H, H-1), 6.64–6.68 (m, 1 H, H-5), 6.88–6.92 (m, 1 H, H-6); ^{13}C-NMR (126 MHz, CDCl$_3$): δ = 28.1, 54.5, 55.0, 62.4, 82.6, 138.2, 140.0, 150.4, 176.3; Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69; found C, 63.12; H, 7.21; N, 6.72.



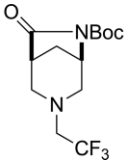
(1*R,4*S**,5*R**,6*S**)-*tert*-Butyl 5,6-dihydroxy-3-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate, (±)-39[12]**

White solid, mp: 155–157 °C; yield: 75 % (0.9 g); R_f = 0.27 (*n*-hexane/EtOAc, 1:2); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.52 (s, 9 H, CH$_3$), 1.95–2.04 (m, 1 H, CH$_2$), 2.06–2.12 (m, 1 H, CH$_2$), 2.78–2.82 (m, 1 H, H-4), 4.09–4.17 (m, 1 H, H-5), 4.24–4.30 (m, 1 H, H-6), 4.32–4.38 (m, 1 H, H-1); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 28.1, 31.7, 53.9, 62.4, 68.2, 70.5, 82.4, 149.1, 172.6; Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76; found C, 54.35; H, 7.02; N, 5.77.



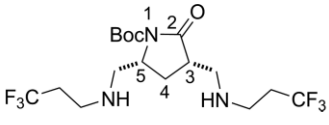
(1*S,5*R**)-*tert*-Butyl 3-benzyl-7-oxo-3,6-diazabicyclo[3.2.1]octane-6-carboxylate, (±)-40**

Yellow solid, mp: 84–86 °C; yield: 75 % (590 mg); R_f = 0.40 (*n*-hexane/EtOAc, 4:1); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.40 (s, 9 H, CH$_3$), 1.57–1.61 (m, 1 H, H-8), 2.09–2.20 (m, 2 H, H-2), 2.37 (d, J = 10.20 Hz, 1 H, H-8), 2.48–2.50 (m, 1 H, H-1), 2.95 (dd, J = 10.70 Hz, J = 2.75 Hz, 1 H, H-4), 3.00 (dd, J = 10.05 Hz, J = 3.49 Hz, 1 H, H-4), 3.46–3.73 (dd, ^1J = 94 Hz, ^2J = 13 Hz, 2 H, NCH$_2$), 4.13–4.17 (m, 1 H, H-5), 7.16–7.31 (m, 5 H, Ar-H); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 28.1, 33.5, 42.5, 46.1, 52.0, 54.1, 54.6, 60.5, 81.6, 127.4, 128.6, 138.5, 149.6, 174.6; MS: (ESI) m/z = 317.76 (M + 1); Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85; found C, 68.30; H, 7.67; N, 8.83.



(1*S,5*R**)-*tert*-Butyl 7-oxo-3-(2,2,2-trifluoroethyl)-3,6-diazabicyclo[3.2.1]octane-6-carboxylate, (±)-41**

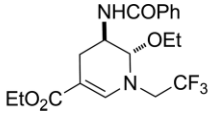
Colorless oil; yield: 16 % (120 mg); R_f = 0.51 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (500 MHz, CDCl$_3$): δ = 1.53 (s, 9 H, CH$_3$), 1.61–1.65 (m, 1 H, H-8), 2.21–2.28 (m, 1 H, H-8), 2.56–2.61 (m, 1 H, H-1), 2.82 (d, J = 11.08 Hz, 1 H, H-2), 2.90 (d, J = 10.41 Hz, 1 H, H-2), 3.04–3.26 (m, 4 H, H-4, NCH$_2$), 4.26–4.31 (m, 1 H, H-5); ^{13}C-NMR (126 MHz, CDCl$_3$): δ = 28.0, 33.1, 42.6, 52.3, 53.2, 54.4, 56.9 (q, $^2J_{C,F}$ = 30.7 Hz, CCF$_3$), 82.9, 125.8 ($^1J_{C,F}$ = 285.8 Hz, CF$_3$), 149.6, 174.5; ^{19}F-NMR (471 MHz, CDCl$_3$): δ = –68.2 (t, J = 9.4 Hz); MS: (ESI) m/z = 331.74 (M + 23); Anal. Calcd for $C_{13}H_{19}F_3N_2O_3$: C, 50.65; H, 6.21; N, 9.09; found C, 50.68; H, 6.20; F, 18.48; N, 9.07.



(3*R,5*S**)-*tert*-Butyl 2-oxo-3,5-bis(((3,3,3-trifluoropropyl)amino)methyl)pyrrolidine-1-carboxylate, (±)-42**

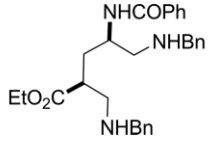
Colorless oil; yield: 9 % (70 mg); R_f = 0.31 (*n*-hexane/EtOAc, 1:1); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.43 (s, 9 H, CH$_3$), 1.57–1.62 (m, 1 H, H-4), 2.07–2.15 (m, 1 H, H-4), 2.24 (d, J = 10.75 Hz, 1 H, CH$_2$CF$_3$), 2.31–2.36 (m, 1 H, CH$_2$CF$_3$), 2.35–2.45 (m, 2 H, CH$_2$CF$_3$), 2.45–2.49 (m, 1 H, H-3), 2.52–2.60 (m, 2 H, NH*CH*$_2$), 2.61–2.69 (m, 2 H, NH*CH*$_2$), 2.70–2.77 (m, 2 H, NH*CH*$_2$), 2.92–3.08 (m, 2 H, NH*CH*$_2$), 4.18–4.23 (m, 1 H, H-5), 6.17–6.28 (brs. 2 H, NH); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 28.1, 30.0 and 30.2 and 30.4 and 30.6 (q, $^2J_{C,F}$ = 26.5 Hz, CCF$_3$), 31.72 and 31.94 and 32.17 and 32.40 (q, $^2J_{C,F}$ = 28.5 Hz, CCF$_3$), 33.4, 39.2 and 39.3 (q, $^3J_{C,F}$ = 4.1 Hz, CCH$_2$CF$_3$), 42.3, 49.1 and 49.2 (q, $^3J_{C,F}$ = 3.7 Hz, CCH$_2$CF$_3$), 52.0, 53.3, 54.5, 81.7, 125.4 and 127.6 ($^1J_{C,F}$ = 279.7 Hz, CF$_3$), 126.5 ($^1J_{C,F}$ = 279.7 Hz, CF$_3$), 149.5, 174.3; ^{19}F-NMR (471 MHz, [D$_6$]DMSO): δ = –63.4 (t, J = 11.8 Hz), –64.4 (t, J = 11.8 Hz);

Anal. Calcd for $C_{17}H_{27}F_6N_3O_3$: C, 46.89; H, 6.25; N, 9.65; found C, 46.92; H, 6.23; F, 26.19; N, 9.67.



(5*R,6*S**)-Ethyl 5-benzamido-6-ethoxy-1-(3,3,3-trifluoropropyl)-1,4,5,6-tetrahydropyridine-3-carboxylate, (±)-21a**

White solid, mp: 199–200 °C; yield: 30 % (0.11 g); R_f = 0.30 (*n*-hexane/EtOAc, 1:2); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.10 (t, *J* = 7.20 Hz, 3 H, CH_3), 1.23 (t, *J* = 7.22 Hz, 3 H, CH_3), 2.39–2.48 (m, 2 H, CH_2), 3.52–3.61 (m, 2 H, OCH_2), 3.95–4.01 (m, 1 H, H-5), 4.11–4.18 (m, 2 H, OCH_2), 4.20–4.26 (m, 1 H, CH_2CF_3), 4.30–4.37 (m, 1 H, CH_2CF_3), 4.78–4.81 (m, 1 H, H-6), 7.28 (s, H-2), 7.45–7.56 (m, 3 H, Ar-H), 7.88–8.00 (m, 2 H, Ar-H), 8.40 (brs, 1 H, N-H); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 15.0, 15.8, 21.8, 48.2, 53.6 (q, $^2J_{C,F}$ = 31.5 Hz, CCF_3), 59.4, 64.8, 85.4, 99.0, 125.2 (q, $^1J_{C,F}$ = 281.4 Hz, CF_3), 127.9, 128.7, 131.8, 134.6, 142.7, 166.7, 166.9; ^{19}F-NMR (471 MHz, [D$_6$]DMSO): δ = –72.2 Hz; Anal. Calcd for $C_{20}H_{25}F_3N_2O_4$: C, 57.96; H, 6.08; N, 6.76; found C, 57.65; H, 6.32; N, 6.99;



(2*S,4*R**)-Ethyl 4-benzamido-5-(phenylamino)-2-((phenylamino)methyl)pentanoate, (±)-29a**

White solid, mp:110–112 °C; yield: 29 % (0.12 g); R_f = 0.33 (*n*-hexane/EtOAc, 1:2); ^{1}H-NMR (500 MHz, [D$_6$]DMSO): δ = 1.15 (t, *J* = 7.20 Hz, 3 H, CH_3), 1.47–1.53 (m, 1 H, CH_2), 1.82–1.98 (m, 2 H, CH_2 and H-2), 2.04–2.10 (1 H, NCH_2), 2.76–2.83 (m, 1 H, NCH_2), 2.83–3.02 (m, 2 H, NCH_2), 3.53–3.57 (m, 2 H, CH_2Ph), 3.68–3.76 (m, 2 H, CH_2Ph), 3.92–4.07 (m, 3 H, H-4 and OCH_2), 6.41 (brs, 2 H, NH), 7.30–7.53 (m, 13 H), 7.78–7.82 (m, 2 H, Ar-H), 8.43 (brs, NH); ^{13}C-NMR (126 MHz, [D$_6$]DMSO): δ = 14.5, 32.8, 41.1, 46.1, 50.1, 54.6, 57.7, 60.6, 52.1, 127.7, 127.8, 128.3, 128.6, 128.7, 128.8, 129.0, 129.1, 129.3, 131.6, 134.8, 136.4, 138.3, 166.2, 173.2; Anal. Calcd for $C_{27}H_{31}N_3O_3$: C, 72.78; H, 7.01; N, 9.43; found C, 72.50; H, 6.75; N, 9.08.

Acknowledgments

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Keywords: Amino acids · Piperidines · Ring closing · Reductive amination · Fluorine

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Stereocontrolled synthesis of *N*-heterocyclic fluorine-containing β-amino acid derivatives

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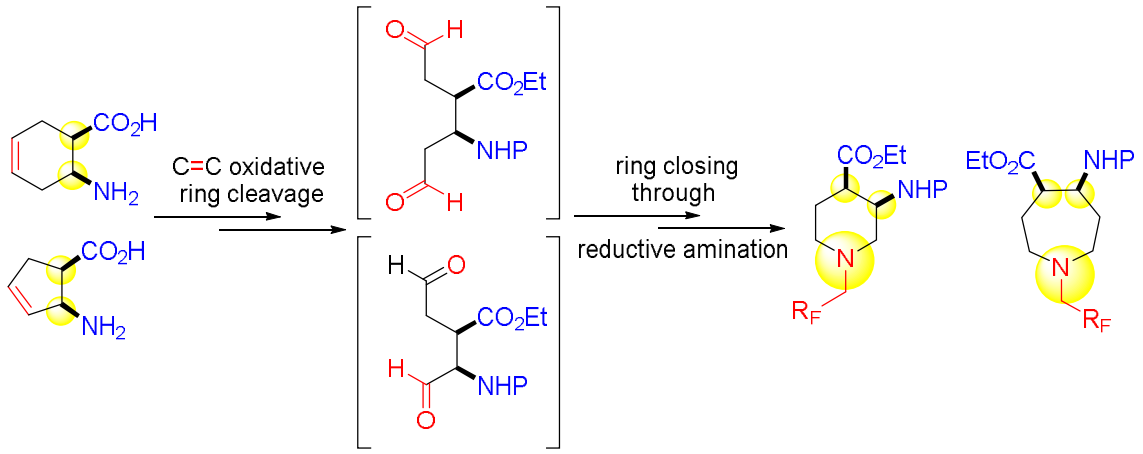
Graphical abstract:



Abstract:

A stereocontrolled procedure is reported for the access of various fluorine-containing piperidine and azepane β-amino esters. The synthetic protocol starts from readily available unsaturated cycloalkene β-amino acids and is based on oxidative cleavage of the ring olefin bond followed by ring closing of the diformyl intermediates in the presence of some fluorine-containing amines across reductive amination.

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

Introduction

Cyclic β-amino acids are considered to be novel compounds in the field of synthetic and medicinal chemistry and they have exerted increasing interest during the past twenty years because of the importance of some antifungal, antibacterial or analgetic small molecules. For example, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin, **1**), (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid (icofungipen, **2**), BAY Y9379 (**3**), (2*R*,3*S*)-3-aminooxetane-2-carboxylic acid (oxetin, **4**) or tilidin (**5**) are a few of some highly functionalized derivatives in drug research (Figure 1, **1**-**5**). These compounds are of high significance because they are key elements of various bioactive products with antitumoral, antibacterial, antiviral and cardioprotective activities. As conformationally restricted building blocks, these small molecules are of appreciable importance for the synthesis of peptides and, accordingly, they exert a considerable impact in the fields of biomolecules and drug design.[1]

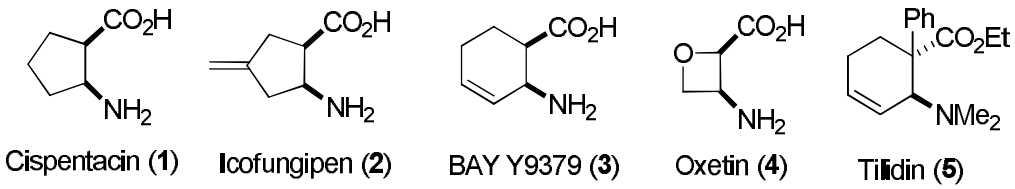


Figure 1. Some small cyclic β-amino acids with pharmaceutical relevance.

Azaheterocyclic β-amino acids, which express high biological relevance, represent an important class of compounds in both medicinal and organic chemistry. Thus, several piperidine and pyrrolidine β-amino acid derivatives exhibit antiviral or antibacterial activities (Figure 2, **6**-**8**).[1]

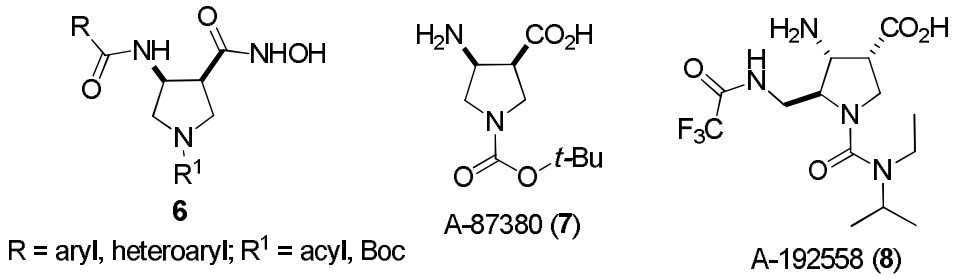


Figure 2. Some azaheterocyclic β-amino acids with biological importance.

Organofluorine compounds have generated increasing attention in the field of pharmaceuticals and agrochemicals over the last decade.[2] Among the ever-increasing number of fluorine-containing biomolecules or building blocks, a number of fluorinated open-chain α-, β- or γ-amino acids exhibit antitumoral or antibiotic properties.[3]

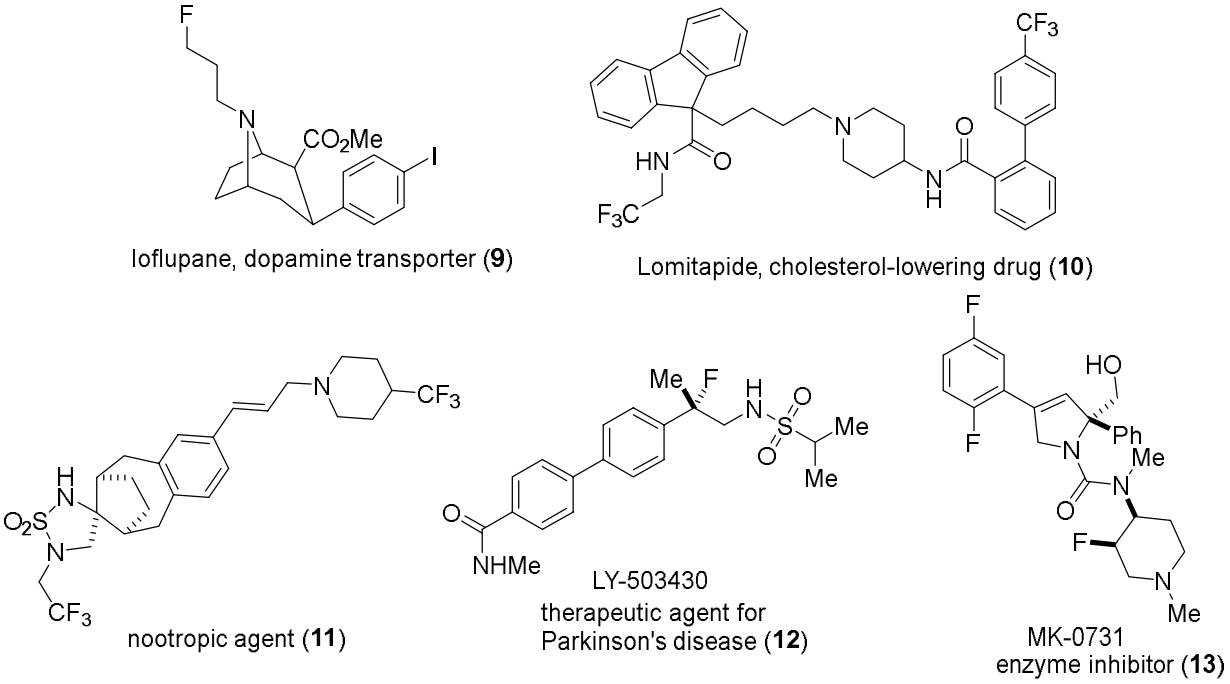


Figure 3. Several molecules with fluoroamine or trifluoroamine units.

Molecules containing β-fluorinated or β-trifluorinated amine moieties are important entities in pharmaceutical chemistry or agrochemistry.[2,4] Accordingly, fluorine-containing five- or six-membered azaheterocycles, which are components in drugs such as MK-0657, MK-0731 or neceprevir, are of high importance in medicinal chemistry.[5] However, fluorine-containing seven-membered *N*-heterocycles are relatively less abundant in the literature.

Despite of this, they might gain high relevance in the future, which is due to the important role of some functionalized counterparts in drug research.[6] Fluorine-containing tetrahydroisoquinoline derivatives and other types of *N*-fluoroalkylated molecular scaffolds are known to possess important biologically properties.[7] β-Fluoroamine or β-trifluoroamine units are also present in versatile fluorine-containing amino acid derivatives of biological relevance (Figure 3, **9-13**).[8]

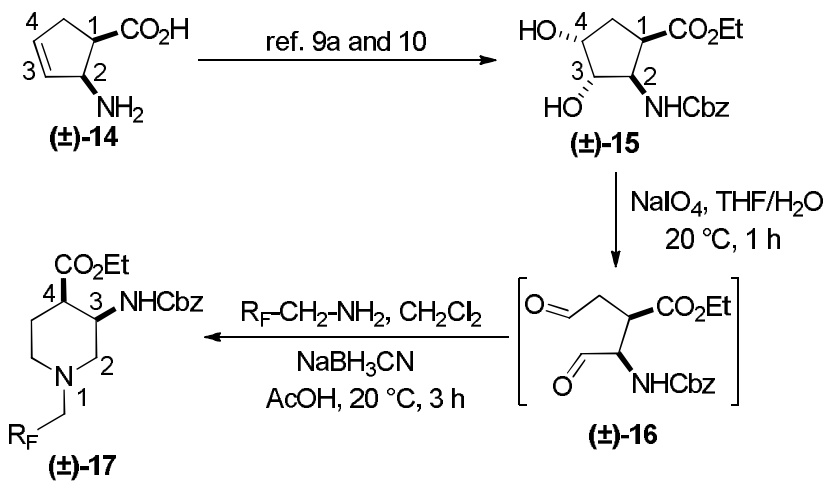
Fluorine-containing saturated *N*-heterocycles are of special significance, since introduction of one or more fluorine atoms into the skeleton of an azaheterocycle can increase lipophilicity and metabolic stability. Moreover, fluorine substitution may reduce basicity and, accordingly, it provides better bioavailability to a certain molecule. Moreover, perfluorocarbons are characterized by biological inertness, however they exhibit intense hydrophobic and lipophilic effects.

Results and Discussion

Because of the high biological importance of saturated azaheterocycles, our current ai was to combine β-amino acid and organofluorine molecular entities and synthesize novel molecular structures. This manuscript is intended to offer an insight into the extension of our earlier work[9a] based on stereocontrolled synthesis of fluorine-containing piperidine or azepane β-amino acid derivatives. The synthetic approach included the use of some commercially available fluorinated or polyfluorinated primary amines and was based on the oxidative ring cleavage of unsaturated cyclic β-amino esters through the ring olefin bond (through vicinal diol). It is followed by ring closing by double reductive amination giving the products across ring expansion of the diformyl intermediates.[9]

Cyclopentene *cis*-β-amino acid **(±)-14** was first converted by esterification according to the route described earlier[10], followed by *N*-protection and *cis*-dihydroxylation with the OsO_4/NMO system to the corresponding dihydroxylated *cis* amino ester **(±)-15**. This diol was submitted to oxidative ring opening with $NaIO_4$ in THF/H_2O affording the corresponding acylic diformyl amino ester **(±)-16**. This relatively unstable dialdehyde derivative was further used in the forthcoming step without isolation. Thus **(±)-16** was subjected to double-reductive amination with various commercially available fluorinated primary amines such as 2,2,3,3,4,4,5,5,5-nonafluoropentan-1-amine, 2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptan-1-amine and 1,1,1-trifluoropropan-2-amine. The reaction was induced with $NaBH_3CN$ in the presence of CH_2Cl_2. Ring closing involves

reductive amination and gives the corresponding fluorinated or perfluorinated *cis* β-amino esters with a piperidine ring system (**(±)-17a-c**) (Scheme 1).



Scheme 1. Synthesis of fluorinated piperidine *cis*-β-amino esters.

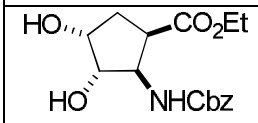
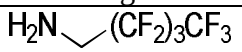
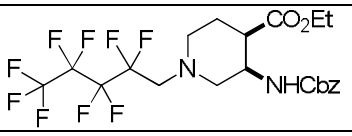
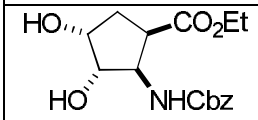
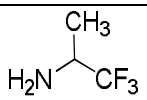
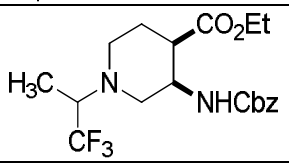
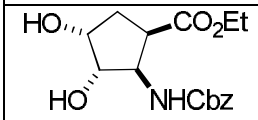
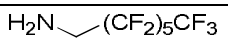
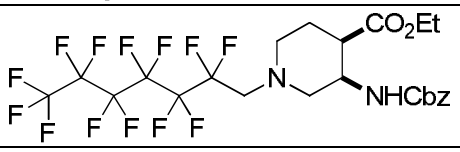
amino ester	fluorine-containing amine	product	yield (two steps)
			13%, **(±)-17a**
			14%, **(±)-17b**
			21%, **(±)-17c**

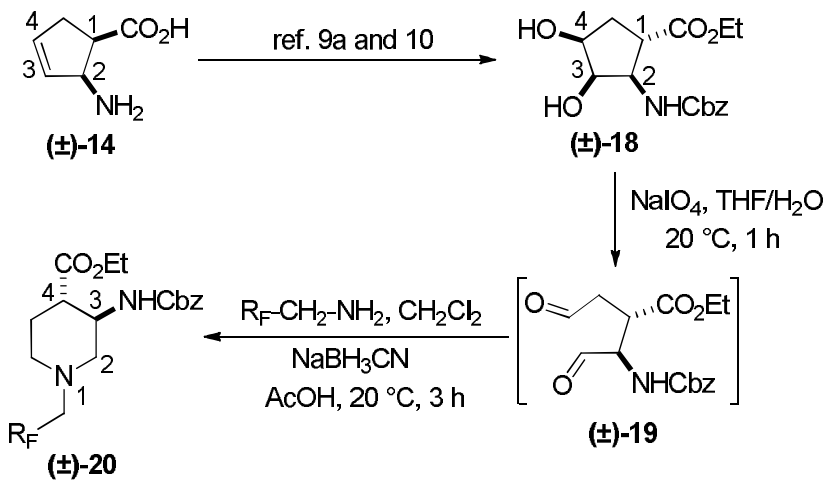
Table 1. Synthesis of piperidine cis-β-amino esters **17a-c**.

Since the configuration of the stereocenters at C-1 and C-2 of amino esters (±)-**14** and (±)-**15** were not affected during the ring closing procedure, the integrity of the configuration of the chiral centers in **(±)-17a-c** was conserved, that is configurations are predetermined by the structure of the starting materials.

Accordingly, *cis* amino ester provided the corresponding piperidine derivative with the carboxylate and carbamate functions at C-3 and C-4 in a *cis* relative arrangement (Scheme 1, Table

1). Noteworthy, that the cyclization reaction performed with 1,1,1-trifluoropropan-2-amine as the amine source containing a chiral center yielded only a single piperidine compound (**(±)-17b**).

In continuation, *cis* isomer **(±)-15** was converted to cyclopentene *trans*-β-amino acid **(±)-18**[9a,10] in an analogous way. Namely, compound **(±)-15** with the ester and the carbamate groups in a *trans* relationship was subjected to oxidative ring opening with $NaIO_4$.



Scheme 2. Synthesis of fluorinated piperidine *trans*-β-amino esters.

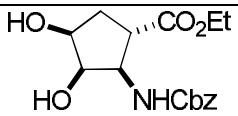
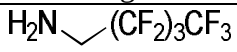
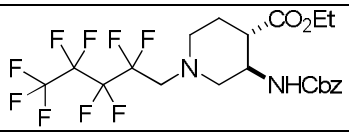
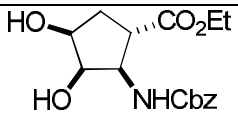
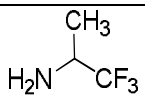
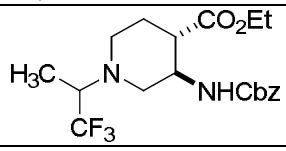
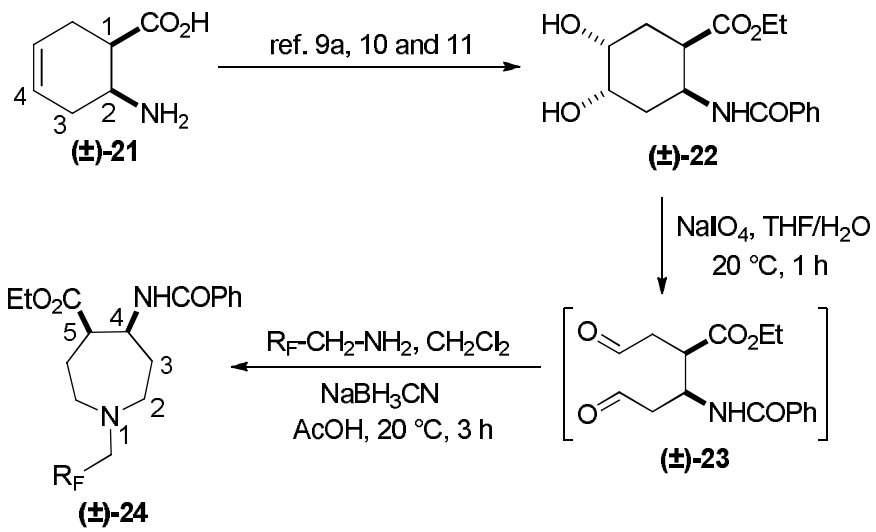
amino ester	fluorine-containing amine	product	yield (two steps)
			15%, **(±)-20a**
			26%, **(±)-20b**

Table 2. Synthesis of piperidine *trans*-β-amino esters **20a-b**.

The formed instable dialdehyde intermediate **(±)-19** was treated with fluorinated amines and $NaBH_3CN$ in CH_2Cl_2 without isolation furnishing fluorinated piperdine *trans* amino esters **(±)-20a,b** (Scheme 2, Table 2). Note, contrary to its cis counterpart compound **(±)-20a** proved to be unstable. Again, the reaction took place with stereocontrol with the conservation of the configuration of the chiral centers C-1 and C-2 of **(±)-18** corresponding to C-3 and C-4 in products **(±)-20a,b** (Scheme 2, Table 2).

The synthetic procedure presented above was further extended to the efficient access of fluorinated azepane β-aminocarboxylic esters. For example, *cis*-β-aminocyclohex-4-enecarboxylates **(±)-21** undergoing esterification, *N*-benzoylation and *cis*-dihydroxylation with NMO/OsO_4[9a,11] resulted in the corresponding vicinal *cis* diol derivatives **(±)-22**. Subsequently, this dihydroxylated ester was transformed via oxidative ring cleavage and ring expansion. The latter step involved reductive amination with commercially available fluorinated or perfluorinated primary amines (see Table 3) in the presence of $NaBH_3CN$. The process proceeds through stereocontrol affording the corresponding *cis* azepane amino esters **(±)-24a-e** (Scheme 3).
Thus, applying the oxidative ring opening/ring closure with reductive amination protocol, a series of mono-, di- or trifluorinated as well as perfluorinated seven-membered *N*-heterocyclic *cis* amino esters could be accessed.



Scheme 3. Synthesis of fluorinated azepane β-amino esters.

Conclusions

A simple stereocontrolled synthetic route has been developed for the preparation of novel fluorine-containing six- and seven-membered *N*-heterocyclic β-amino esters, based on olefin bond oxidative ring cleavage of cyclopentene and cyclohexene β-amino acids, followed by ring closing with double reductive amination of diformyl intermediates in the presence of commercially available primary fluoroamines. Since the stereocenters of the starting carbocyclic β-amino esters

are not affected during the process, they will predetermine the configuration of the chiral centers in the azaheterocyclic products.

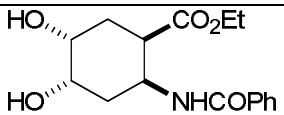
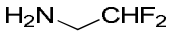
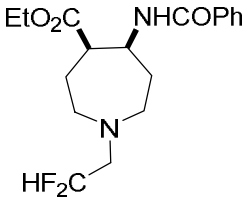
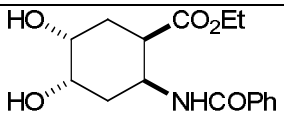
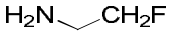
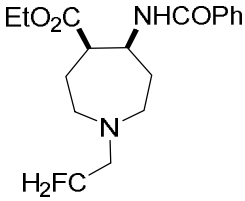
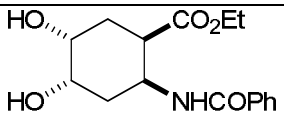
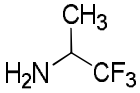
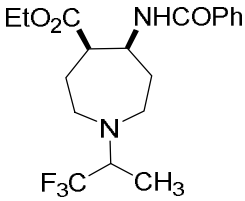
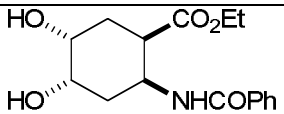
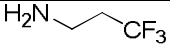
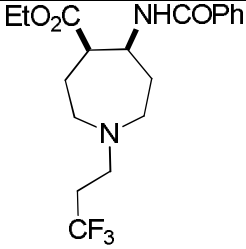
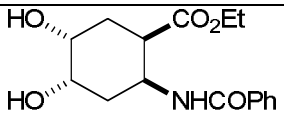
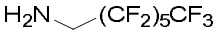
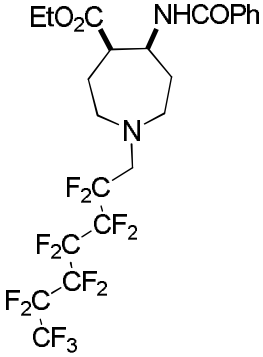
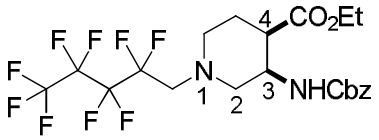
amino ester	fluorine-containing amine	product	yield (two steps)
			15%, **(±)-24a**
			12%, **(±)-24b**
			27%, **(±)-24c**
			38%, **(±)-24d**
			27%, **(±)-24e**

Table 3. Synthesis of azepane β-amino esters **24a-e**.

Experimental Section

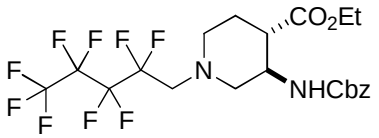
General procedure for the synthesis of fluorine-containing *N*-heterocyclic β-amino esters by oxidative ring cleavage followed by reductive amination

To a stirred solution of β-amino ester (2 mmol) $NaIO_4$ (1.5 equiv) was added in THF/H_2O (25 mL/2 mL). After stirring for 1 h at 20 °C under argon atmosphere, H_2O was added (40 mL). Then the mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined extract was dried over Na_2SO_4. The crude dialdehyde product was immediately used for reductive amination without purification. Fluorinated or polyfluorinated amines (1 equiv) were added to the solution in CH_2Cl_2 (30 mL) and the mixture was stirred at 20 °C for 10 minutes. Next $NaBH_3CN$ (1 equiv) and AcOH (2 drops) were added and stirring was continued for another 4 h at 20 °C. Then the reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).



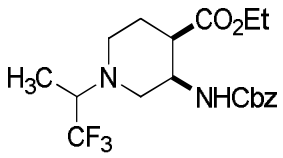
(3*R,4*R**)-Ethyl 3-(((benzyloxy)carbonyl)amino)-1-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-piperidine-4-carboxylate,** (±)-**17a**

Yellow oil; yield: 13% (126 mg); R_f = 0.75 (*n*-hexane/acetone 4:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3H, CH_3), 1.73-1.80 (m, 1H, H-5), 1.93-2.05 (m, 1H, H-5), 2.45-2.55 (m, 2H, H-2, H-6), 2.67-2.72 (m, 1H, H-4), 2.88-2.94 (m, 2H, H-2, H-6), 3.06 (t, *J* = 16.1 Hz, 2H, NCH_2), 4.05-4.15 (m, 2H, CH_2CH_3) 4.28-4.34 (m, 1H, H-3), 5.07 (s, 2H, OCH_2), 5.56 (brs, 1H, N-H), 7.28-7.39 (m, 5H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 23.8, 43.6, 47.8, 52.9, 56.7 (t, $^2J_{C,F}$ = 22.5 Hz, $C(CF_2)_5$), 58.8, 60.9, 66.7, 107.6-120.8 (m, 4 C, $(CF_2)_5CF_3$), 127.9, 128.0, 128.5, 136.6, 155.6, 172.4; ^{19}F-NMR (471 MHz, $CDCl_3$): *δ* = -80.9 (t, *J* = 9.4 Hz), -115.8, -124.1, -126.2. MS: (ESI) m/z = 539.73 (M+1).



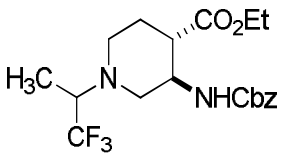
(3*R,4*S**)-Ethyl 3-(((benzyloxy)carbonyl)amino)-1-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-piperidine-4-carboxylate,** (±)-**20a**

Yellow oil; yield: 15% (210 mg); R_f = 0.41 (*n*-hexane/EtOAc 4:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 3H, CH_3), 1.70-2.04 (m, 2H, H-5), 2.41-3.17 (m, 6H, H-2, H-6, NCH_2), 4.07-4.21 (m, 3H, CH_2CH_3, H-4), 5.10 (s, 2H, OCH_2), 5.21-5.34 (m, 1H, H-3), 7.28-7.47 (m, 6H, Ar-H, N-H); ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -80.9 (t, *J* = 7.5 Hz), -115.8, -124.1, -126.1.



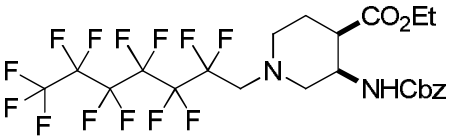
(3*R,4*R**)-Ethyl 3-(((benzyloxy)carbonyl)amino)-1-(1,1,1-trifluoropropan-2-yl)piperidine-4-carboxylate,** (±)-**17b**

Yellow oil; yield: 14% (111 mg); R_f = 0.24 (*n*-hexane/EtOAc 4:1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.08-1.19 (m, 6H, CH_3), 1.53-1.62 (m, 1H, H-5), 1.82-1.98 (m, 1H, H-5), 2.53-2.95 (m, 4H, H-2, H-6), 3.35-3.51 (m, 1H, H-4), 3.88-4.03 (m, 2H, CH_2CH_3), 4.03-4.27 (m, 2H, H-3, NCH), 4.95-5.08 (m, 2H, OCH_2), 6.79 (brs, 1H, N-H), 7.29-7.41 (m, 5H, Ar-H), ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.7, 14.8, 24.2, 44.2, 48.6, 49.7, 52.9, 59.5, 60.0 (q, $^2J_{C,F}$ = 23.3 Hz, CCF_3), 60.6, 66.0, 117.7, 128.4, 128.6, 129.1, 138.2, 151.9, 172.8; ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -70.1 (t, *J* = 11.3 Hz); MS: (ESI) m/z = 403.41 (M+1).



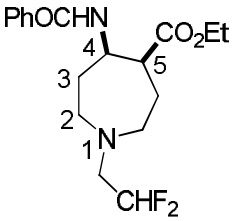
(3*R,4*S**)-Ethyl 3-(((benzyloxy)carbonyl)amino)-1-(1,1,1-trifluoropropan-2-yl)piperidine-4-carboxylate,** (±)-**20b**

Colorless oil; yield: 26% (300 mg); R_f = 0.48 (*n*-hexane/EtOAc 1:4); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.17-1.27 (m, 6H, CH_3), 1.83-1.96 (m, 2H, H-5), 2.35-2.88 (m, 4H, H-2, H-6), 2.99-3.02 (m, 2H, H-4, NCH), 3.97-4.08 (m, 1H, H-3), 4.10-4.20 (m, 2H, CH_2CH_3), 5.09 (m, 2H, OCH_2), 5.16 (brs, 1H, N-H), 7.28-7.40 (m, 5H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 10.5, 14.2, 26.2, 45.3, 46.3, 48.9, 52.2, 60.5 (q, $^2J_{C,F}$ = 26.9 Hz, CCF_3), 60.8, 66.8, 125.7 (q, $^1J_{C,F}$ =288.5 Hz, CF_3) , 128.2, 128.5, 136.4, 155.4, 172.7; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = -71.4.



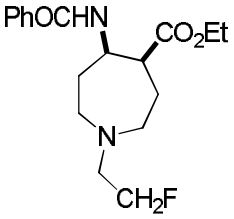
(3*R,4*R**)-Ethyl 3-(((benzyloxy)carbonyl)amino)-1-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)piperidine-4-carboxylate,** (±)**-17c**

Yellow oil; yield: 21% (125 mg); R_f = 0.58 (*n*-hexane/EtOAc 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3H, CH_3), 1.74-1.83 (m, 1H, H-5), 1.93-2.04 (m, 1H, H-5), 2.45-2.56 (m, 2H, H-2, H-6), 2.67-2.74 (m, 1H, H-4), 2.88-2.97 (m, 2H, H-2, H-6), 3.07 (t, *J* = 15.5 Hz, 2H, N-CH_2), 4.06-4.14 (m, 2H, CH_2CH_3) 4.29-4.37 (m, 1H, H-3), 5.07 (s, 2H, OCH_2), 5.57 (brs, 1H, N-H), 7.27-7.39 (m, 5H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 23.8, 43.6, 47.8, 52.9, 56.7 (t, $^2J_{C,F}$ = 22.0 Hz, $C(CF_2)_5$), 58.0, 60.9, 66.7, 108.1-119.5 (m, 6 C, $(CF_2)_5CF_3$), 127.9, 128.1, 128.5, 136.5, 155.7, 172.4; ^{19}F-NMR (471 MHz, $CDCl_3$): *δ* = -80.8 (t, *J* = 9.4 Hz), -115.4, -122.0, -122.8, -123.0, -126.1; MS: (ESI) m/z = 639.27 (M+1).



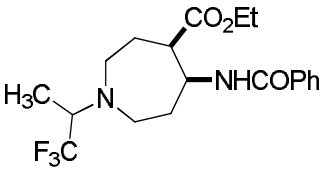
Ethyl (4*S, 5*S**)-5-benzamido-1-(2,2-difluoroethyl)azepane-4-carboxylate, (±)-24a**

Colorless oil; yield: 15% (90 mg); R_f =0.48 (*n*-hexane/EtOAc 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.24-1.28 (m, 5H, CH_3, H-6), 1.82-1.94 (m, 2H, H-3), 2.08-2.29 (m, 2H, H-2), 2.73-2.83 (m, 3H, H-7, H-4), 2.84-2.94 (m, 3H, CH_2CHF_2, H-5), 4.12-4.23 (m, 2H, CH_2), 4.65-4.76 (brs. 1H, NH), 5.60-6.25 (tt, 1H, CHF_2, ^1J = 56.17 Hz, ^2J = 54.76 Hz) 7.39-7.84 (m, 5H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 27.9, 29.7, 31.9, 47.1, 48.2 (t, $^2J_{C,F}$ = 25.3 Hz, $CCHF_2$), 50.0, 52.3, 52.8, 60.4, 60.6, 60.7, 60.8, 115.4 (t, $^1J_{C,F}$ = 241.2 Hz, CHF_2), 126.9, 127.2, 128.5, 128.6, 131.4, 134.5, 166.4, 173.4; ^{19}F-NMR (471 MHz, $CDCl_3$): *δ* = -123.9 Hz; MS: (ESI) m/z = 355.88 (M+1).



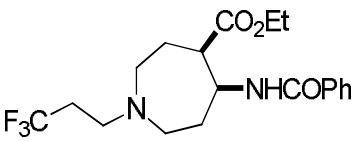
Ethyl (4*S,5*S**)-5-benzamido-1-(2-fluoroethyl)azepane-4-carboxylate, (±)-24b**

Colorless oil; yield: 12% (80 mg); R_f =0.5 (*n*-hexane/EtOAc 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.23-1.25 (m, 3H, CH_3), 1.26-1.28 (m, 2H, H-3), 1.84-1.93 (m, 2H, H-6), 2.13-2.27 (m, 2H, H-2), 2.65-2.75 (m, 2H, H-7), 2.79-2.93 (m, 3H, H-4, CH_2-CH_2F), 4.08-4.19 (m, 2H, CH_2CH_3), 4.41-4.57 (dt, 2H, CH_2F, ^1J = 48.49 Hz, ^2J = 27.01 Hz), 4.78-4.86 (m, 1H, H-5), 7.38-7.50 (m, 3H, Ar-H), 7.63-7.70 (brs. 1H, NH), 7.74-7.82 (m, 5H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 28.1, 29.7, 31.5, 47.9, 49.6, 51.7, 51.9, 58.5 (d, $^2J_{C,F}$ = 19.3 Hz, CCH_2F), 60.7, 81.9 (d $^1J_{C,F}$ = 168.9 Hz, CH_2F), 126.9, 127.6, 128.4, 128.7, 131.3, 134.6, 166.3, 173.4; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = -216.3 Hz; MS: (ESI) m/z = 337.57 (M+1).



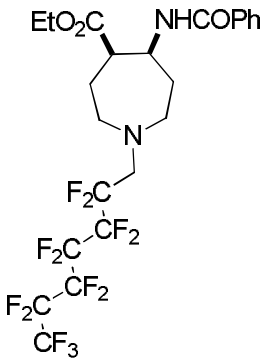
Ethyl (4*R, 5*S**)-5-benzamido-1-(1,1,1-trifluoropropan-2-yl)azepane-4-carboxylate, (±)-24c**

Colorless oil, yield: 27% (100mg); R_f = 0.51 (*n*-hexane/EtOAc, 6:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.17-1.22 (d, 3H, CH_3), 1.28 (t, *J* = 7.08 Hz, 3H, CH_3), 1.81-1.90 (m, 2H, H-6, H-3), 1.98-2.09 (m, 1H, H-6), 2.26-2.37 (m, 1H, H-3), 2.65-2.91 (m, 4H, H-2, H-7), 2.91-3.00 (m, 1H, H-4), 3.12-3.25 (m, 1H, H-5), 4.11-4.24 (m, 2H, CH_2), 4.46-4.58 (m, 1H, NCH), 7.38-7.45 (t, 3H, Ar-H); 7.46-7.51 (brs. 1H, NH), 7.70-7.81 (d, 2H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 10.0, 14.1, 27.9, 32.7, 45.9, 47.2, 48.5, 50.9, 60.5, 60.8 (q, $^2J_{C,F}$ = 27.0 Hz, CCF_3), 126.9, 127.8 ($^1J_{C,F}$ = 285 Hz, CF_3),, 128.5, 131.3, 134.6, 166.2, 173.2; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = -72.7 Hz; MS: (ESI) m/z = 387.62 (M+1).



(4*R, 5*S**)-Ethyl 5-benzamido-1-(3,3,3-trifluoropropyl)azepane-4-carboxylate, (±)-24d**

Colorless oil, yield: 38% (240mg); R_f = 0.35 (*n*-hexane/EtOAc, 6:1); ^{1}H-NMR (500MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3H, CH_3), 1.82-1.93 (m, 2H, H-6, H-3), 2.03-2.16 (m, 1H, H-6), 2.17-2.30 (m, 3H, H-3, CH_2CF_3), 2.51-2.61 (m, 2H, H-2), 2.66-2.79 (m, 4H, H-7, NCH_2), 2.79-2.88 (m, 1H, H-4), 4.09-4.22 (m, 2H, OCH_2), 4.62-4.74 (m, 1H, H-5), 7.40-7.43 (brs. 1H, NH), 7.43-7.77 (m, 5H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 27.7, 31.9, 32. (q, $^2J_{C,F}$ = 26.8 Hz, CCF_3), 47.1, 50.1, 51.0, 51.3 (d, $^3J_{C,F}$ = 2.7 Hz, $CCCF_3$), 51.6, 60.6, 126.4 (q, $^1J_{C,F}$ =277.0 Hz, CF_3), 126.9, 128.5, 131.4, 134.6, 166.4, 173.4; ^{19}F-NMR (471 MHz, $CDCl_3$): δ = -64.9 Hz; MS: (ESI) m/z = 387.61 (M+1).



(4*R,5*S**)-Ethyl 5-benzamido-1-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluorohepty)azepane-4-carboxylate, (±)-24e**

Colorless oil; yield: 27% (200 mg); R_f = 0.28 (*n*-hexane/EtOAc 2:1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.16 Hz, 3H, CH_3), 1.84-1.93 (m, 2H, H-3, H-6), 2.10-2.34 (m, 2H, H-3, H-6), 2.77-2.87 (m, 2H, H-2), 2.87-2.92 (m, 1H, H-4), 2.92-2.98 (m, 2H, H-7), 3.09-3.29 (m, 2H, CH_2CF_2), 4.12-4.20 (m, 2H, CH_2), 4.61-4.74 (m, 1H, H-5), 7.33-7.44 (m, 3H, Ar-H), 7.45-7.54 (brs. 1H, NH), 7.74-7.81 (m, 2H, Ar-H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 14.1, 27.9, 32.0, 46.9, 50.1, 52.7, 53.4, 57.6 (t, $^2J_{C,F}$ = 20.5 Hz, $CCHF_2$), 60.6, 111.0-121.2 (m, 6C, $(CF_2)_5CF_3$), 126.9, 128.4, 131.3, 134.5, 166.47, 173.1; ^{19}F-NMR (471 MHz, DMSO-d_6): δ = -81.1 (t, *J* = 9.94 Hz), -117.3, -122.0, -122.8, -123.5, -126.1; MS: (ESI) m/z = 624 (M+1).

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Supporting Information

Stereocontrolled synthesis of *N*-heterocyclic fluorine-containing β-amino acid derivatives

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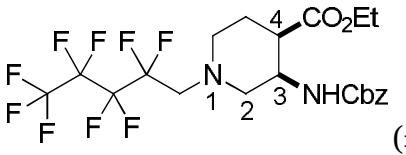
http://www2.pharm.u-szeged.hu/gyki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F F F
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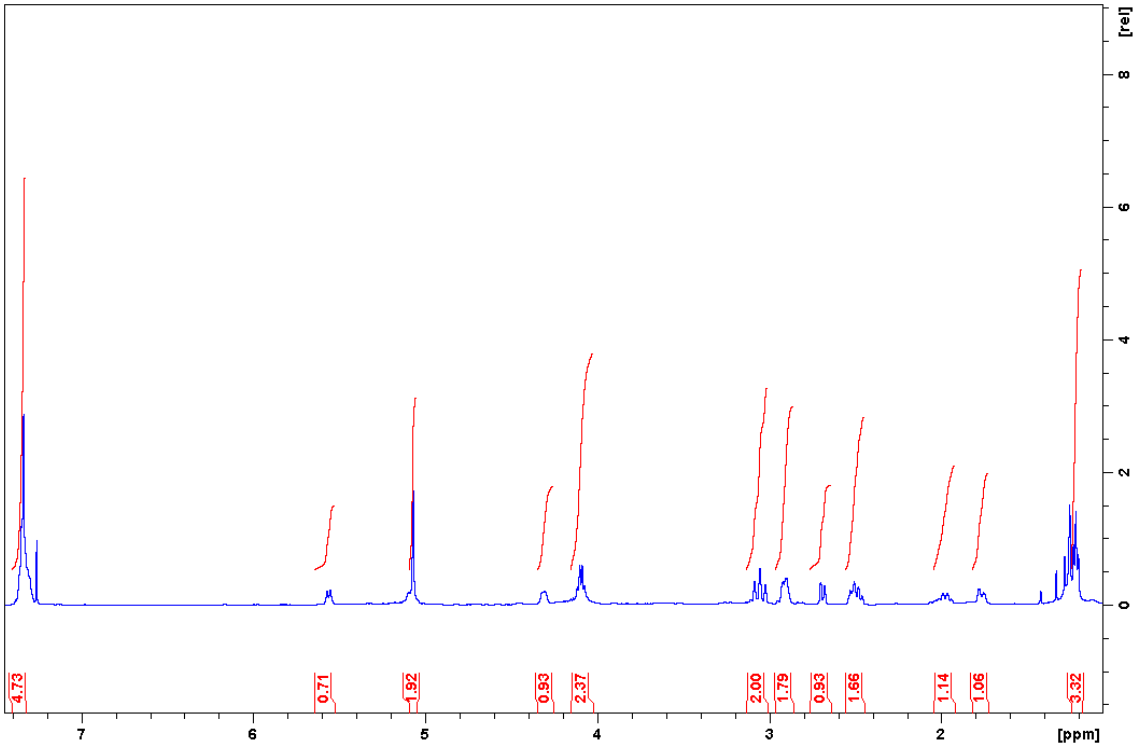
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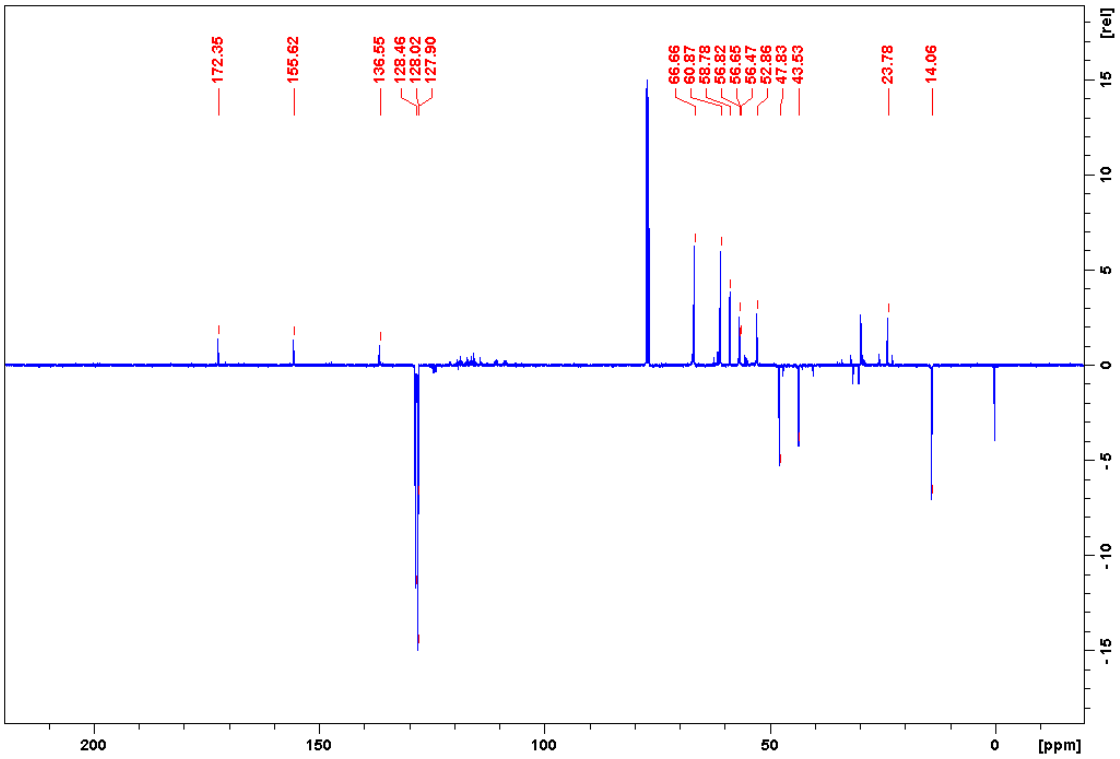
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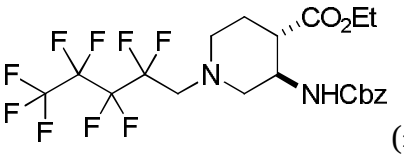
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F
F F F

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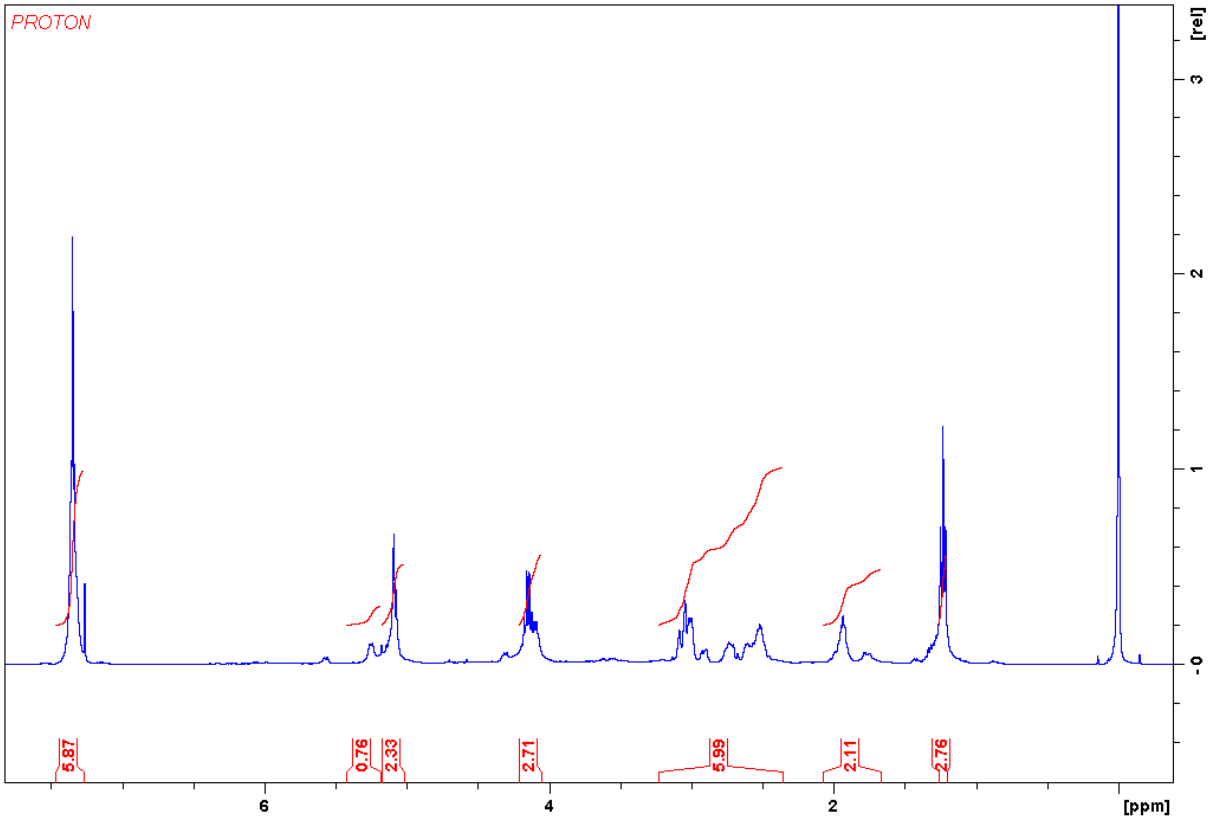
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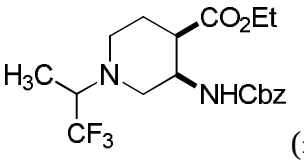
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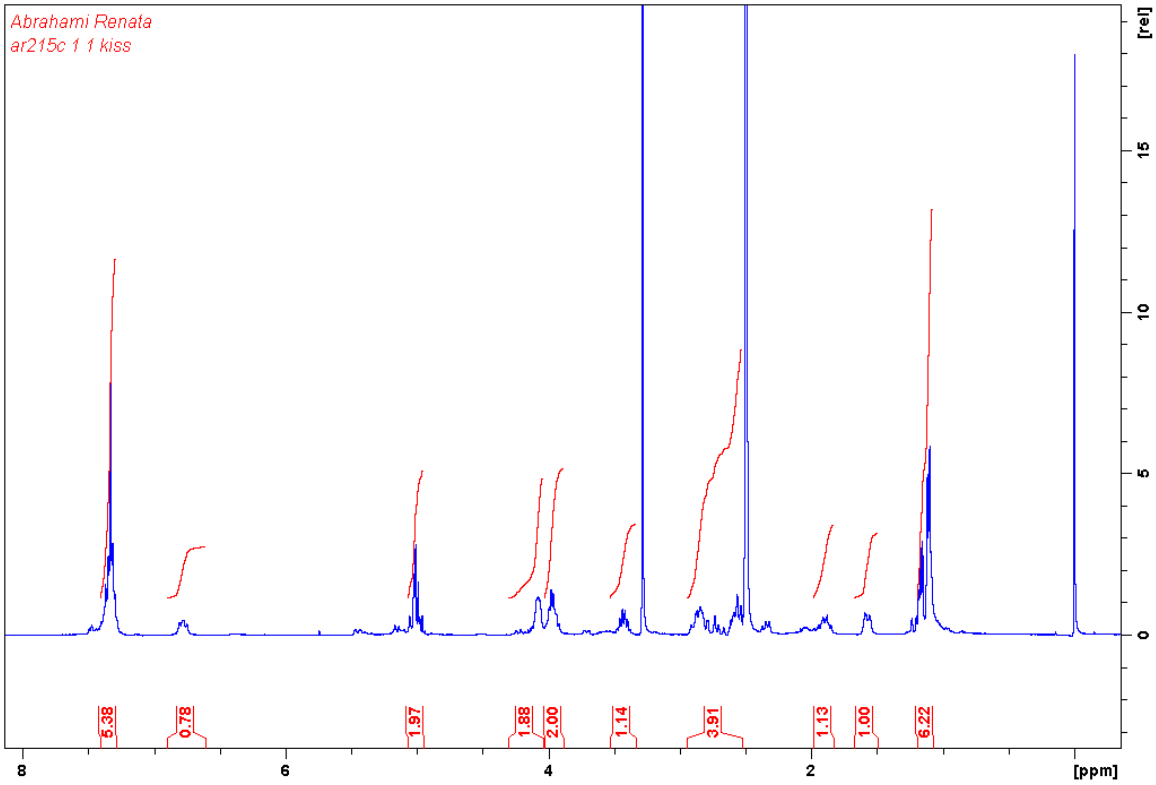
N
NHCbz
CF3

(±)-**17b**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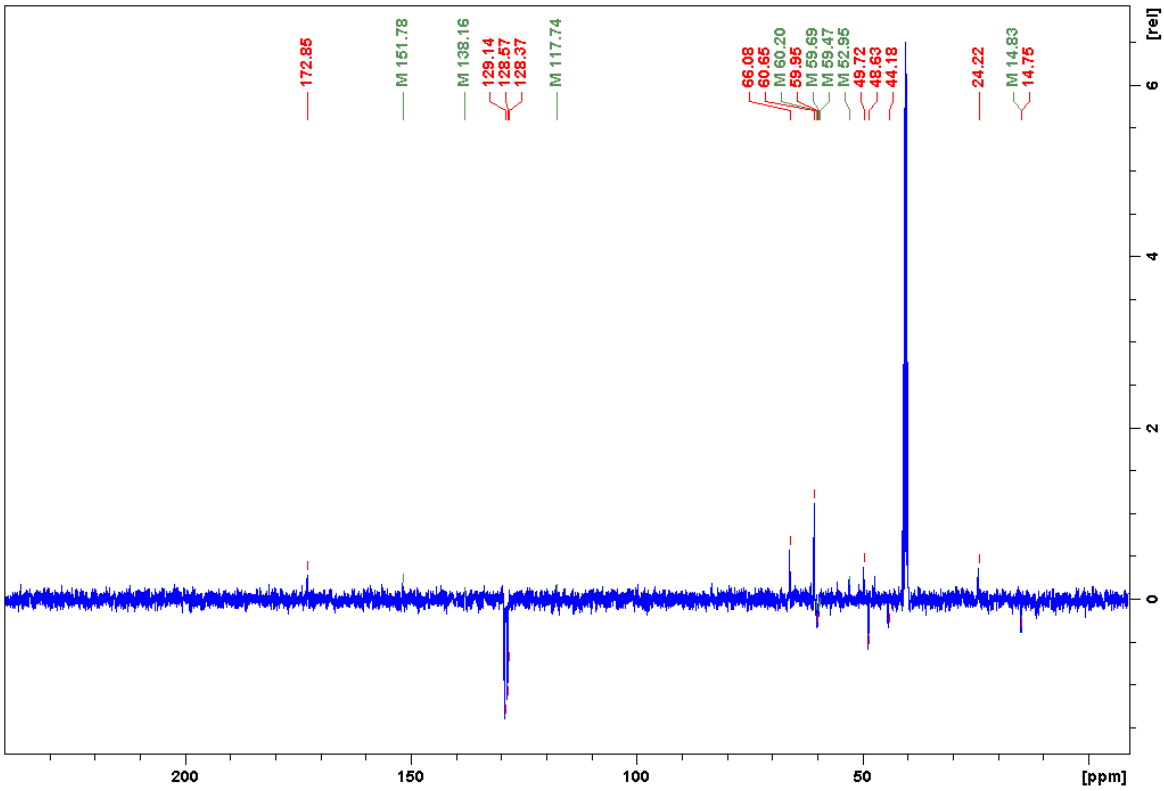
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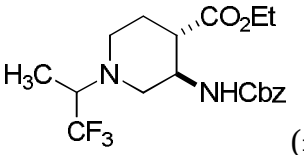
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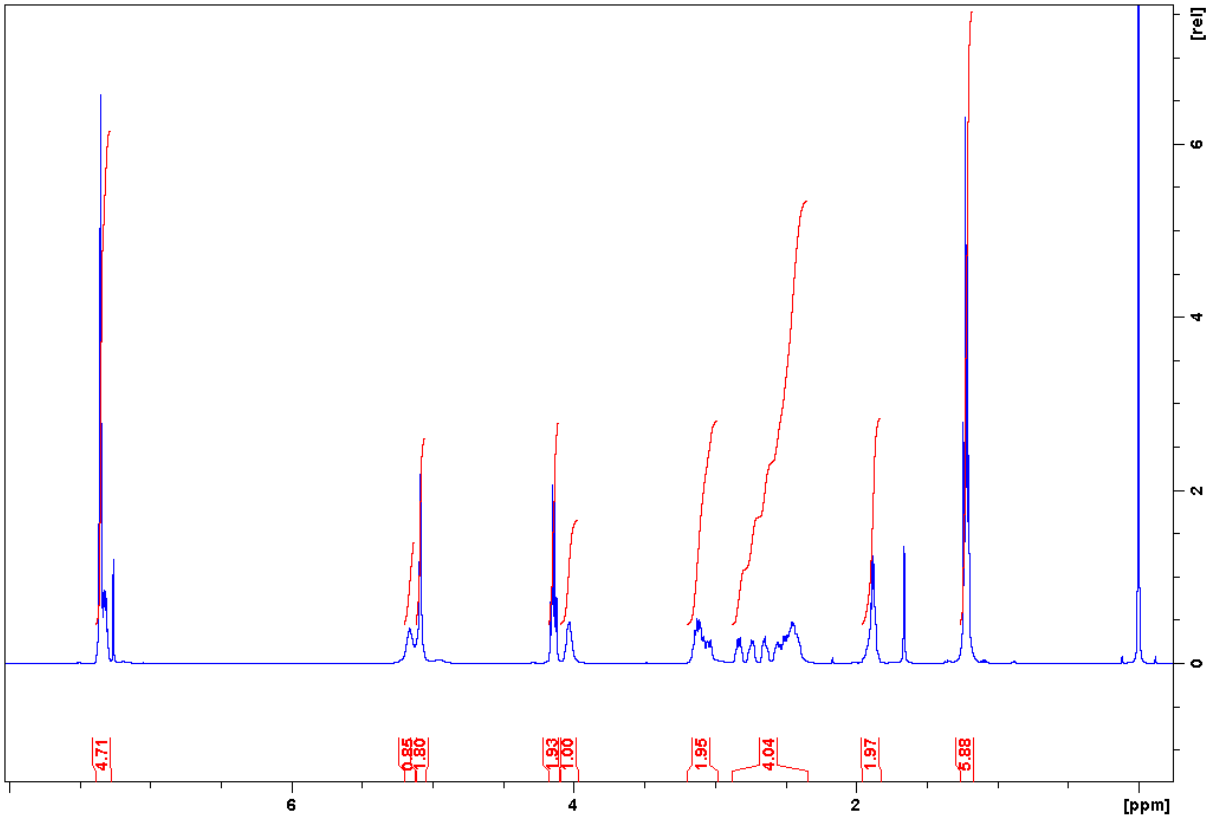
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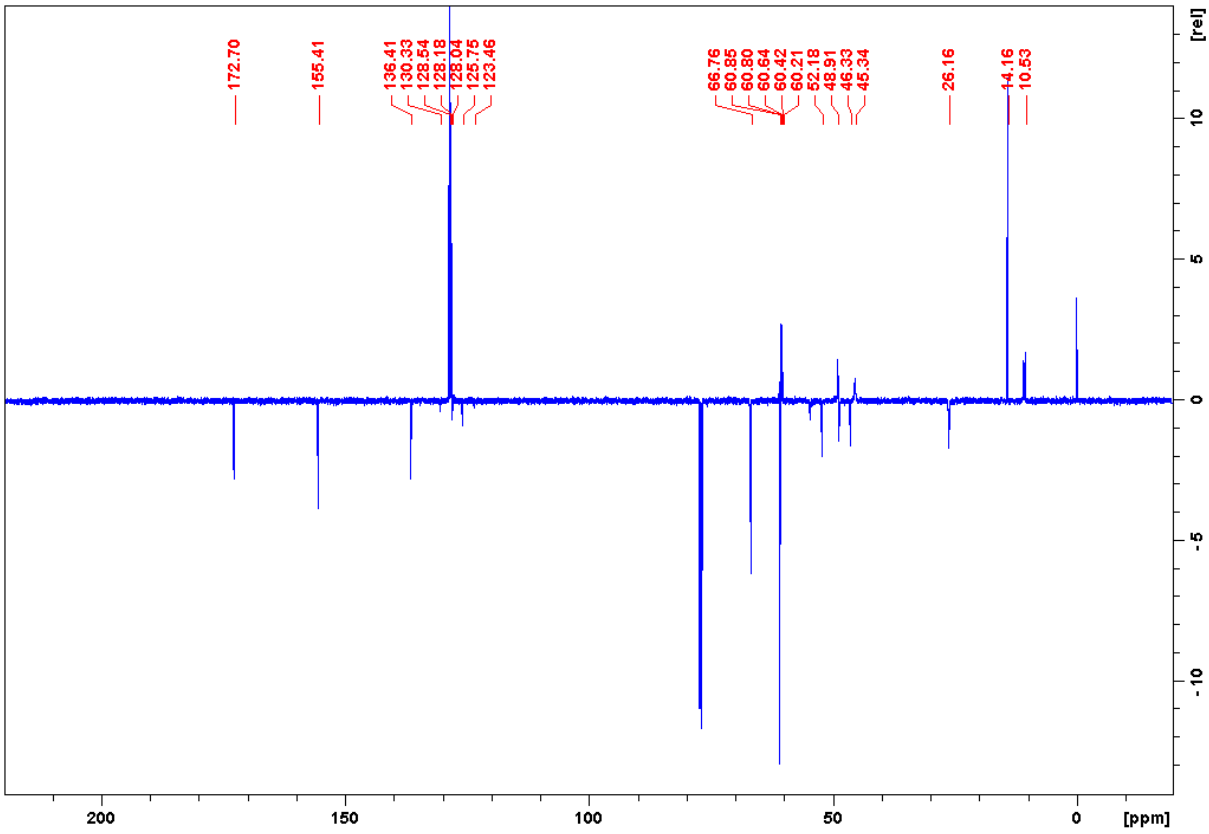
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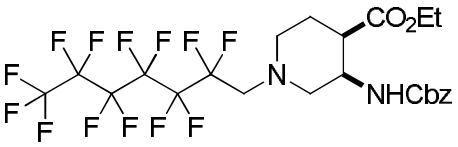
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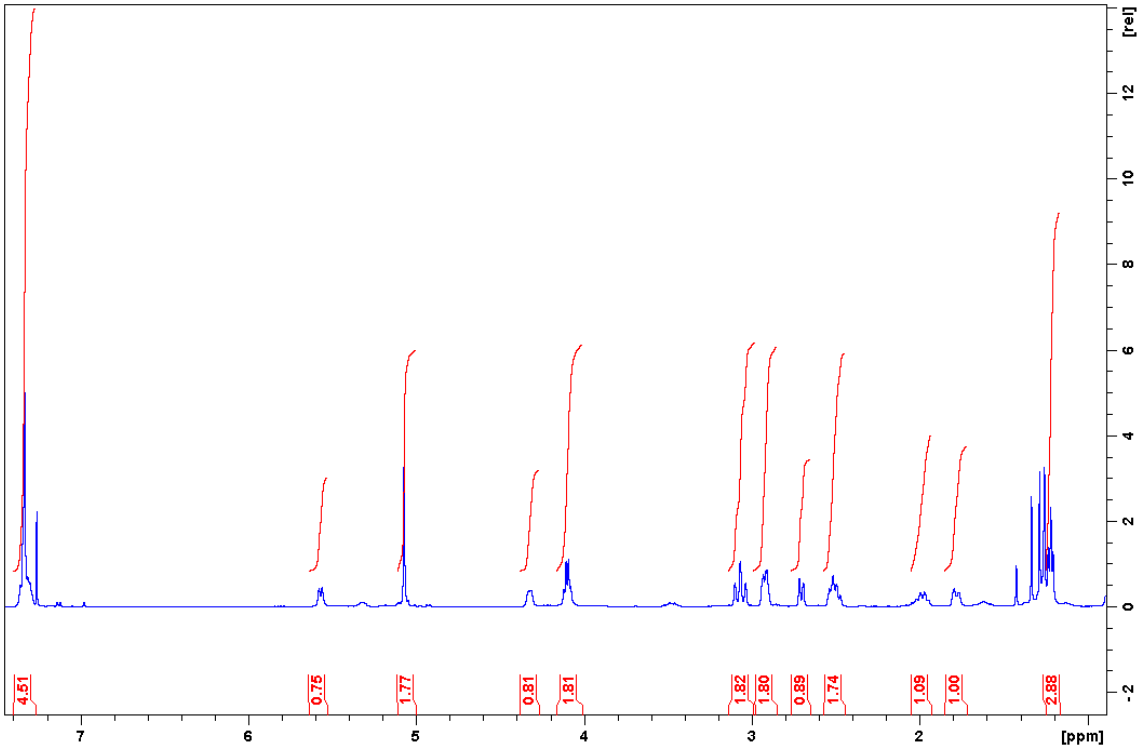
N
F F F F F F
F
F
F F F F F

(±)-**17c**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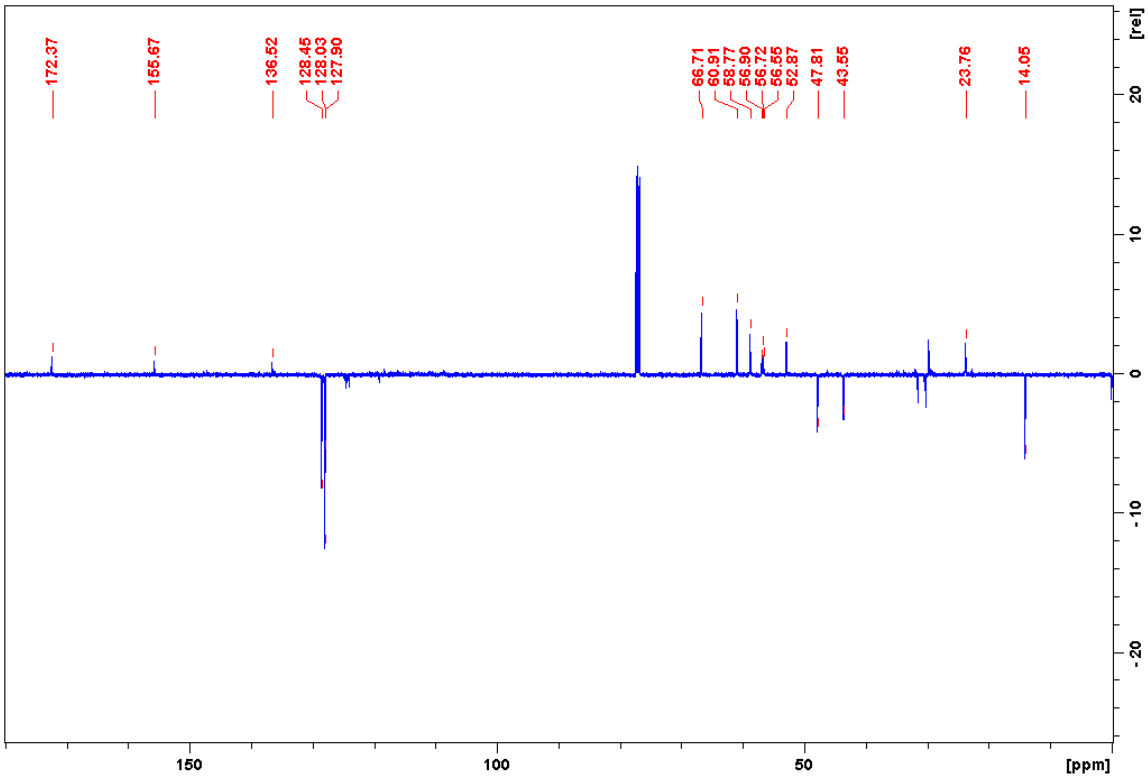
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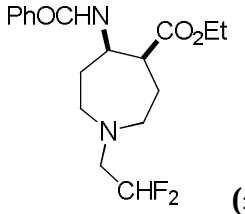
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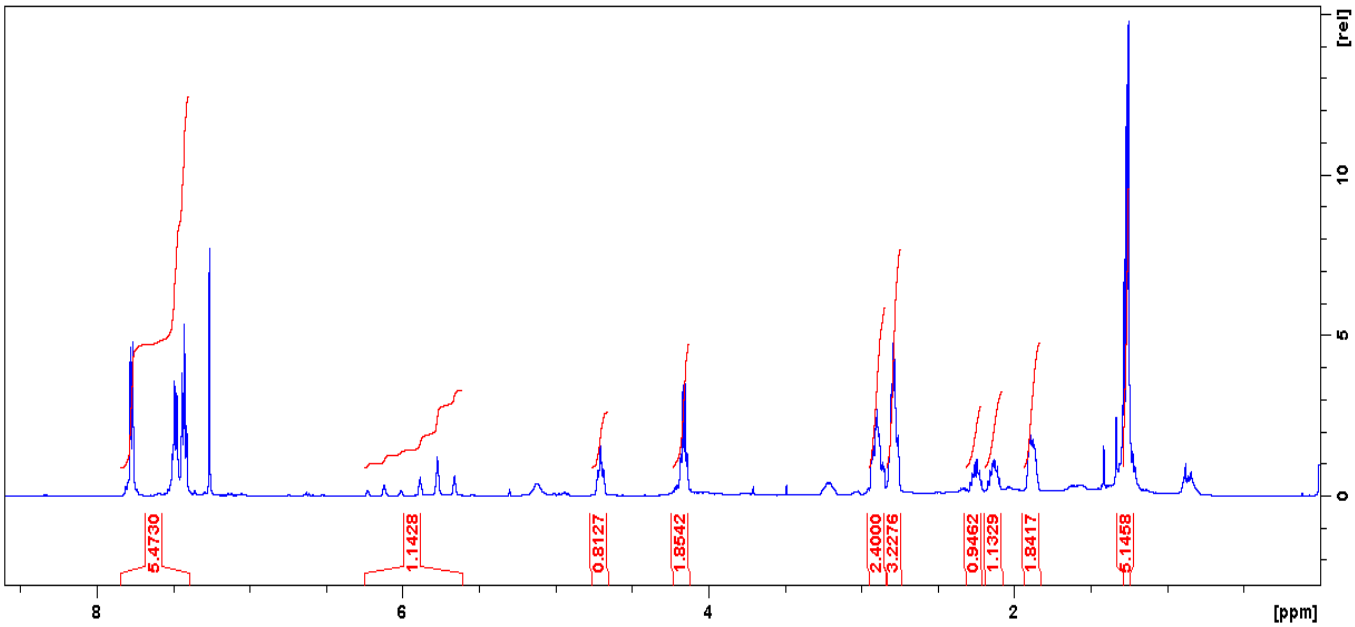
(±)-24a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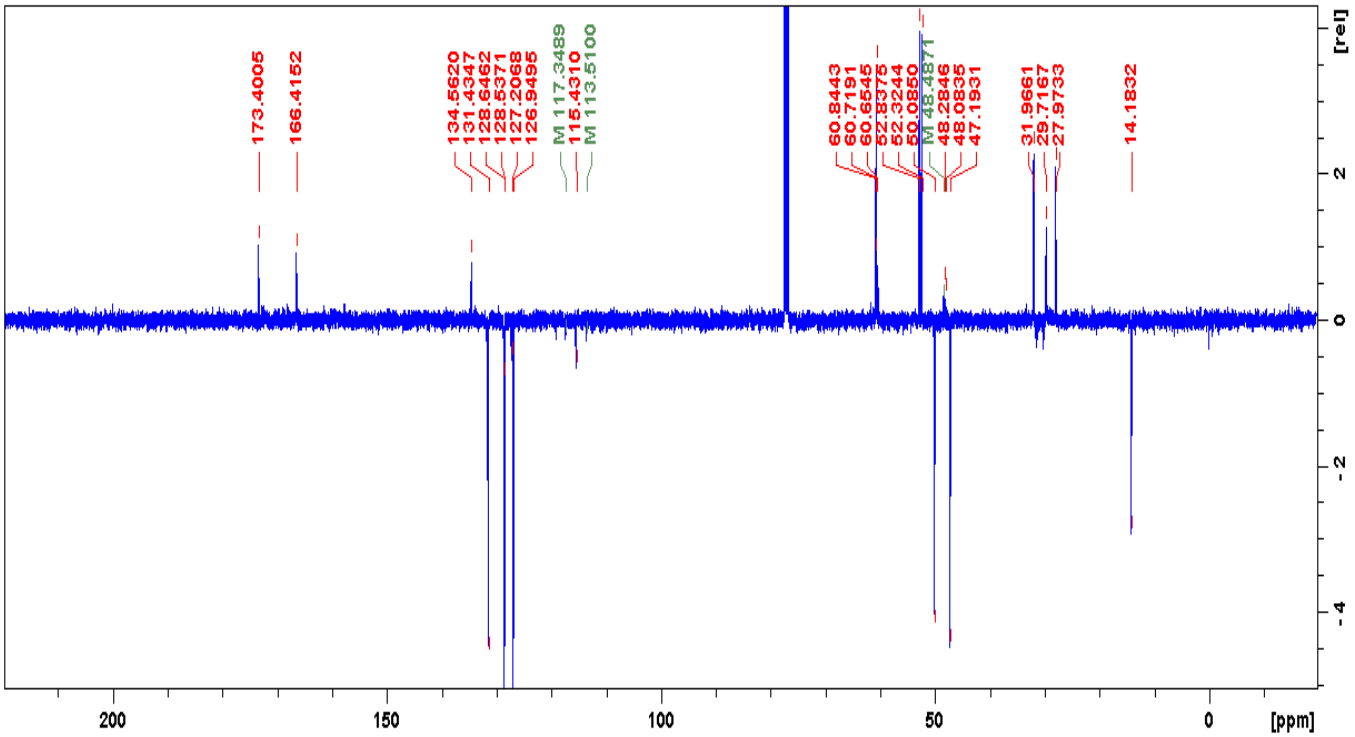
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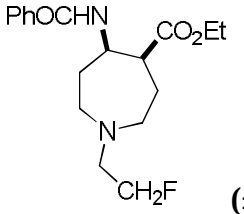
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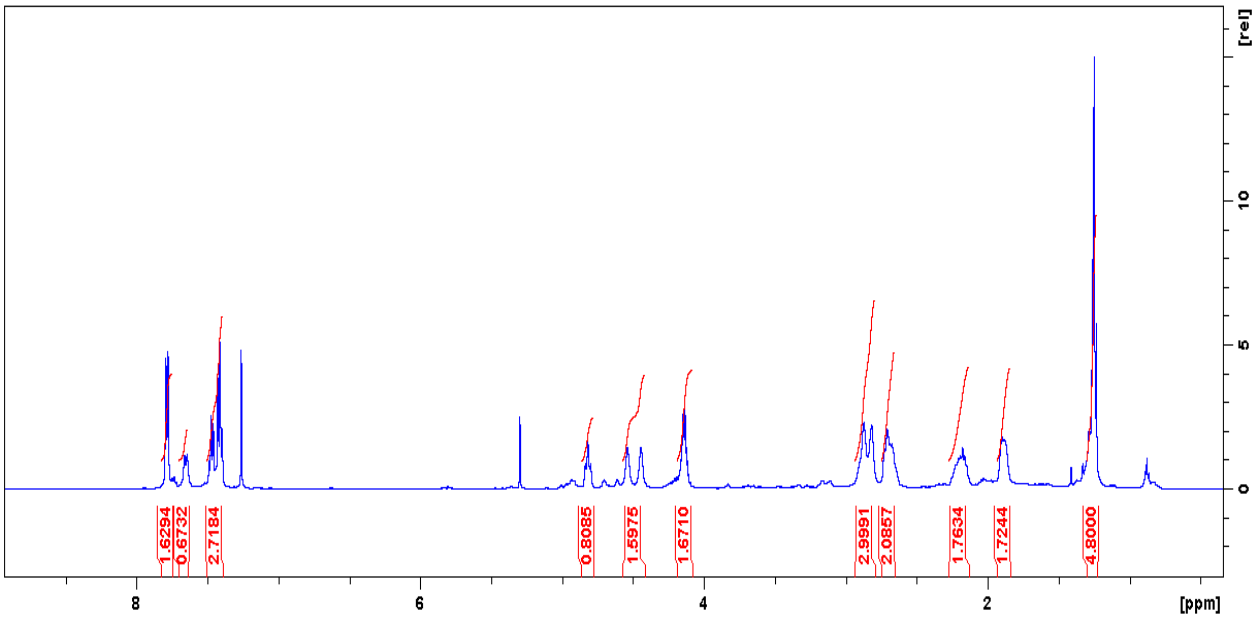
N
CH2F

(±)-24b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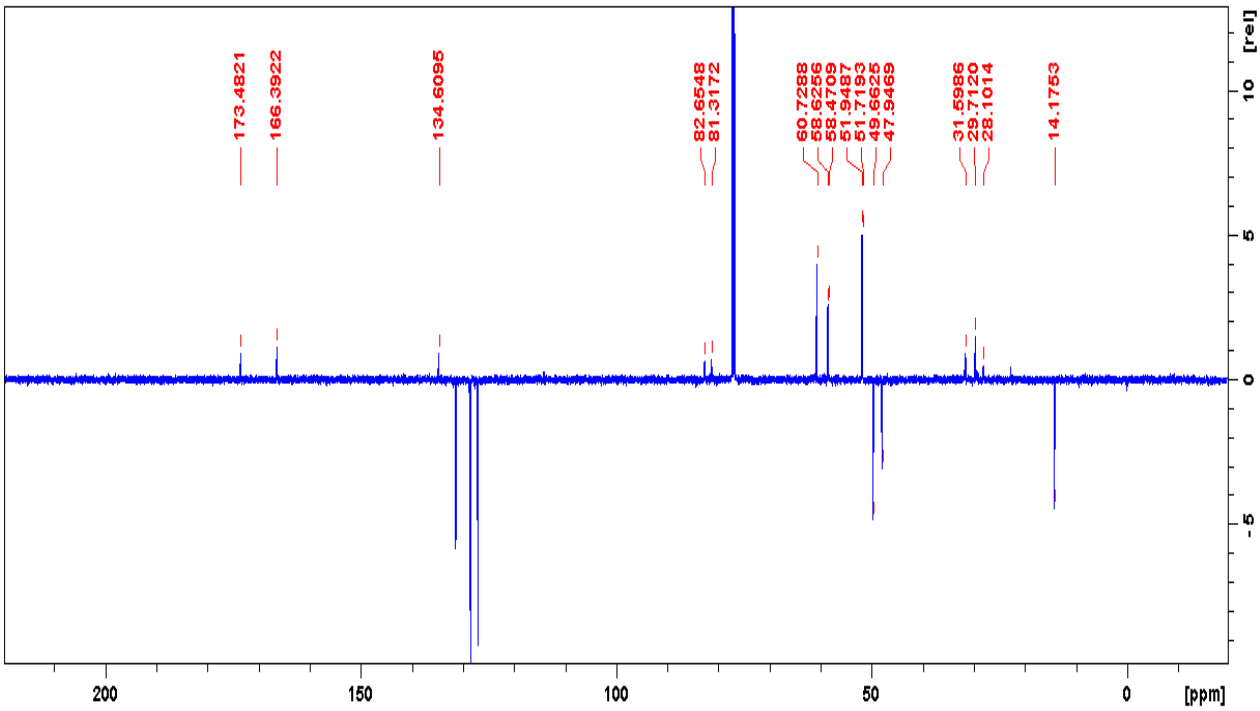
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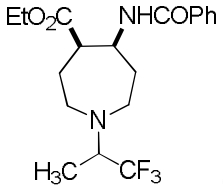
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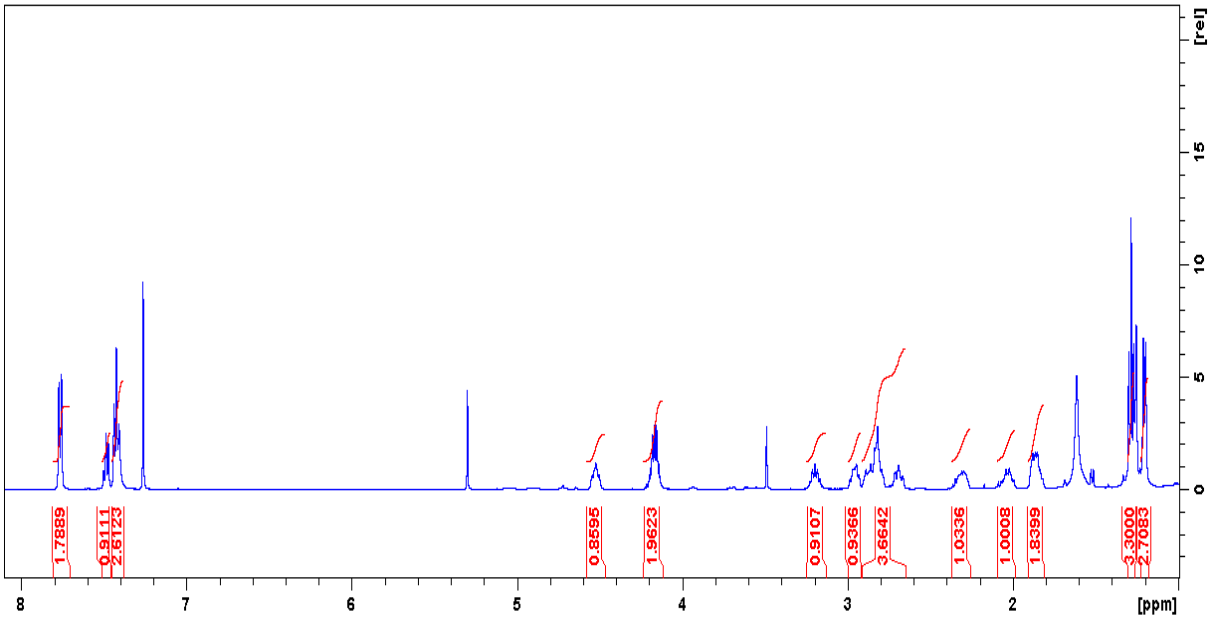
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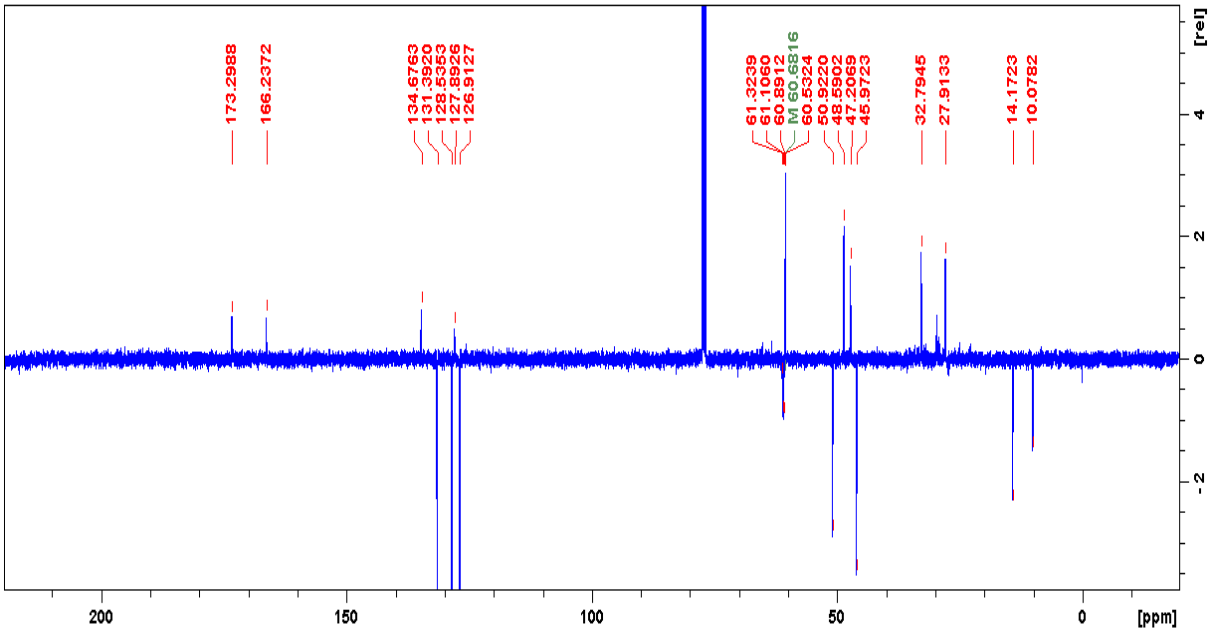
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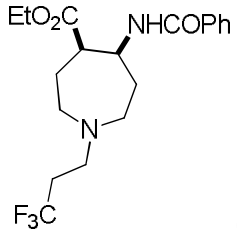
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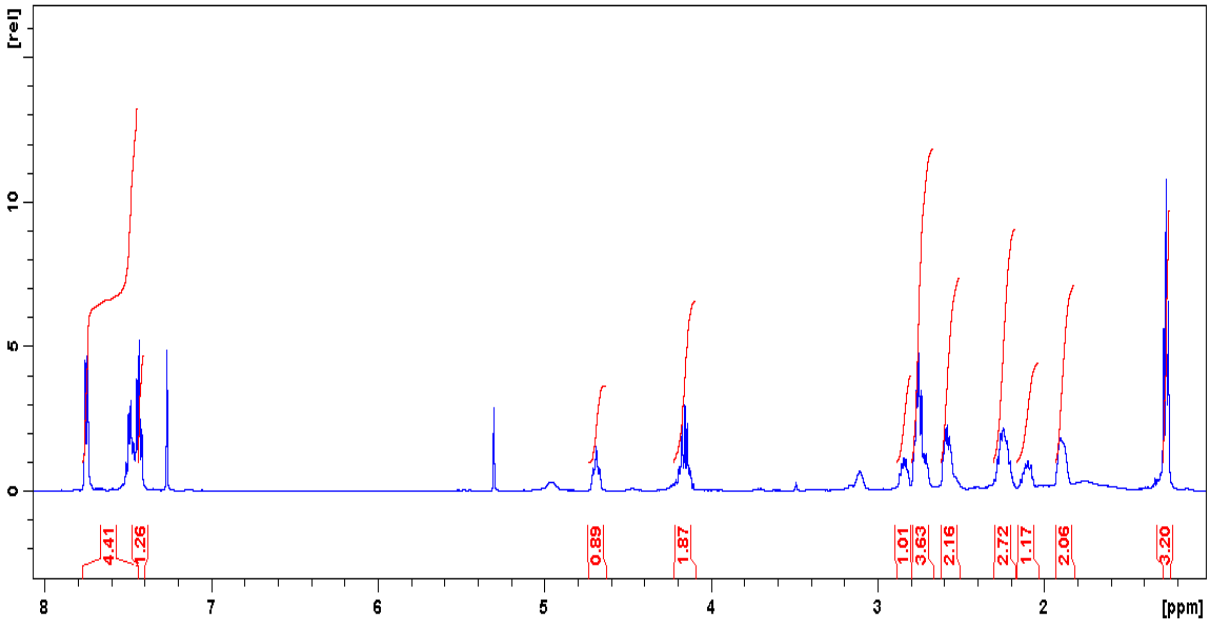
(±)-24d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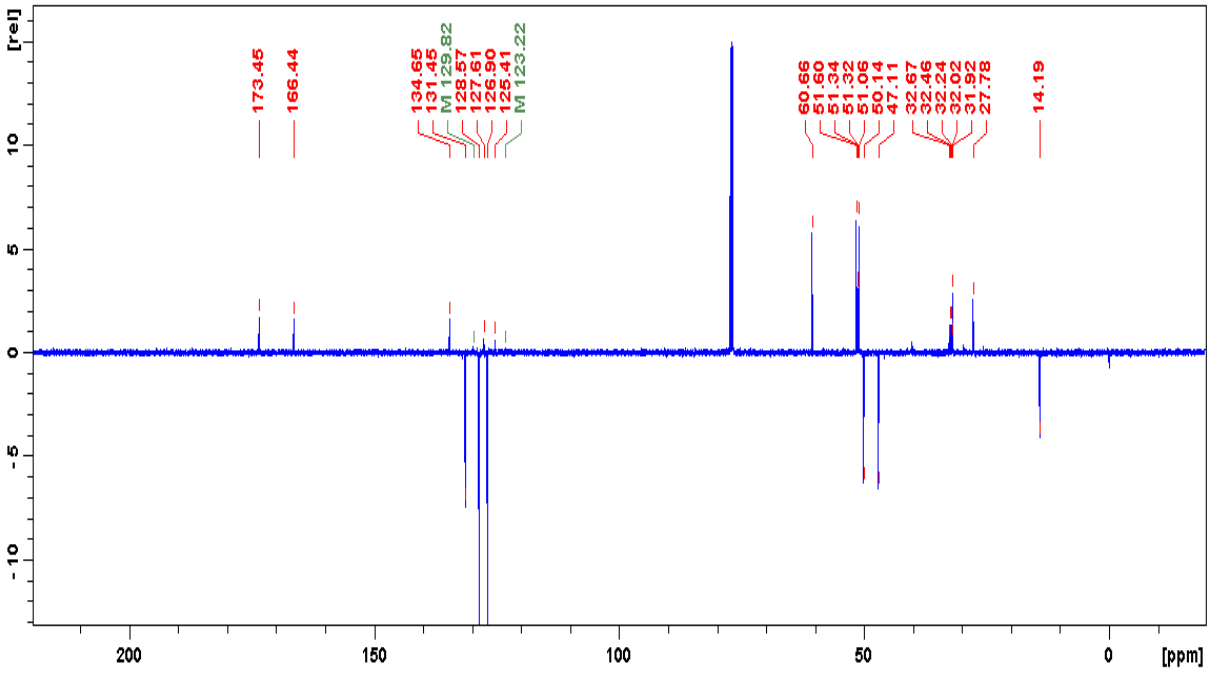
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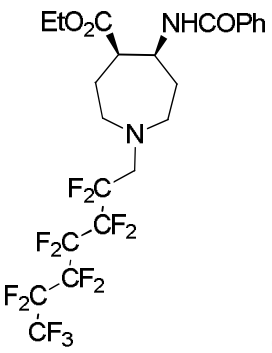
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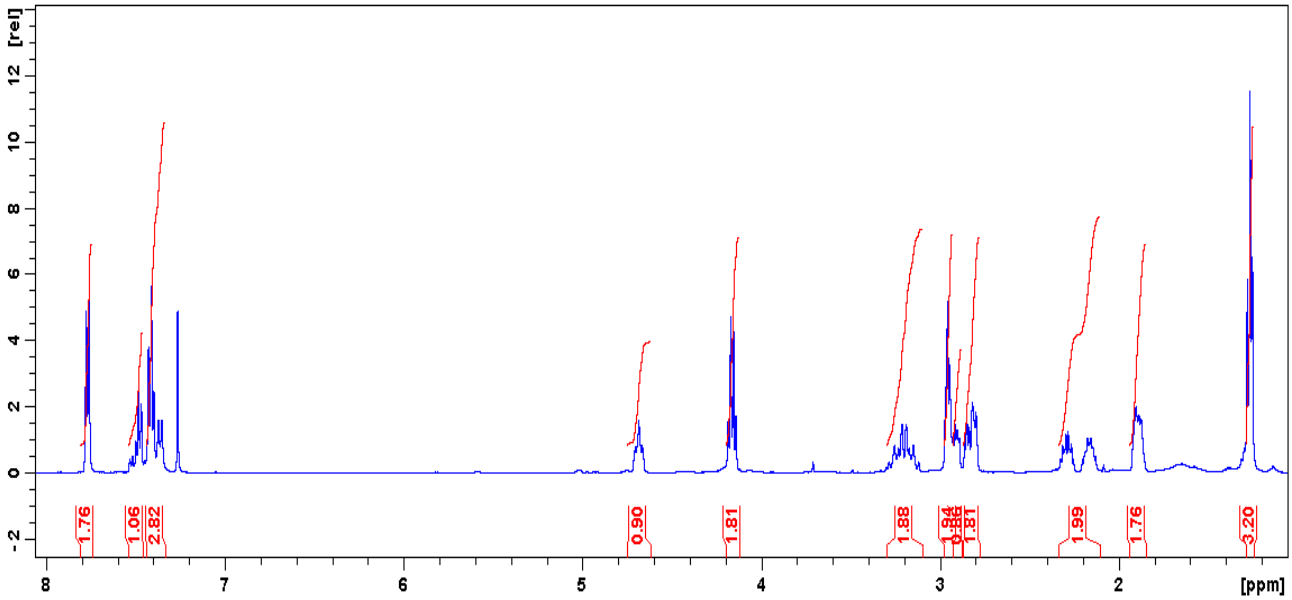
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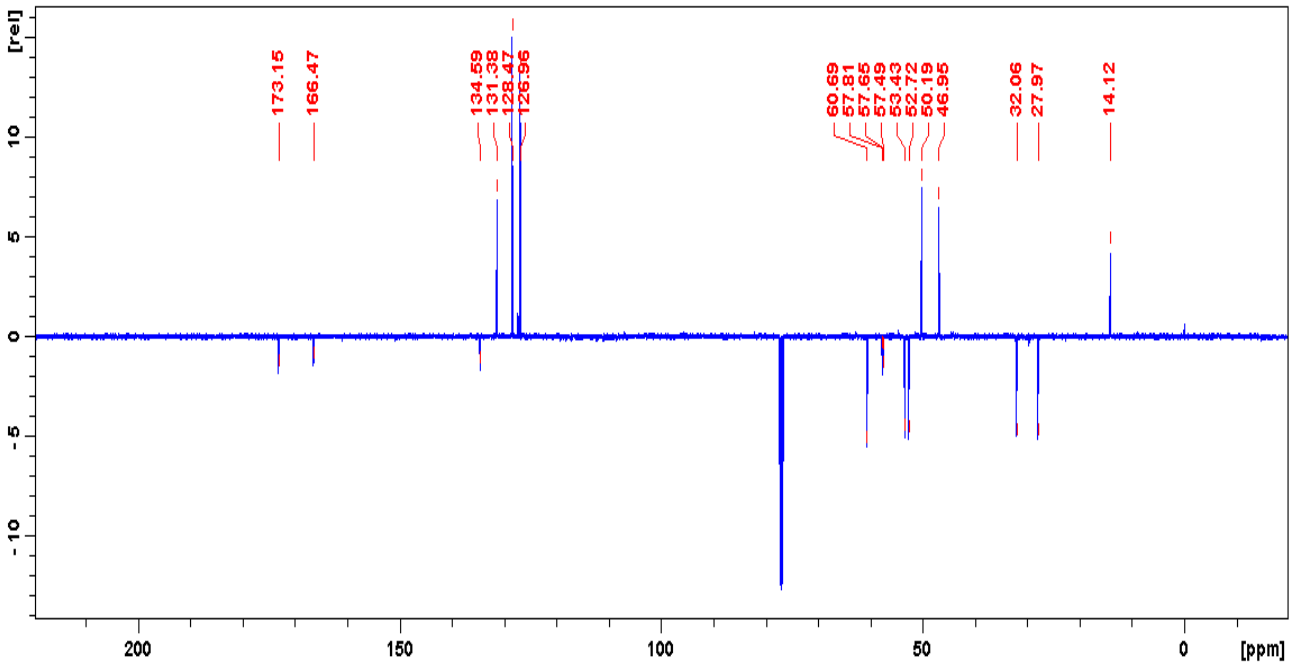
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[ppm]

III.

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A *de novo* synthetic method to the access of *N*-substituted benzazepines

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Ring closing

ABSTRACT

A novel, convenient procedure has been described for the construction of fluorine-containing benzazepines. The synthetic protocol starting from readily available dihydronaphthalene regioisomers is based on oxidative ring olefin bond cleavage followed by ring closure of the diformyl intermediates in the presence of some fluorine-containing primary amines across double reductive amination. The applicability of the developed synthetic method was demonstrated by the synthesis of 13 benzazepine compounds isolated in 22–35 % overall yields.

1. Introduction

Functionalized azepanes constitute important components of several biologically relevant natural and non-natural products with interesting pharmaceutical properties. Some representatives of this class of azaheterocycles are known as antiviral agents, glycosidase inhibitors, anticancer agents or antidiabetics [1–5]. Therefore, in view of their medicinal relevance, an increasing number of synthetic methods have been described in recent years for the construction of highly substituted azepane derivatives [6–10]. Fluorine chemistry has become a rapidly expanding research area during the last 10–15 years. Because of the high impact of organofluorine molecules in drug research (approximately 25 % of the drugs introduced in the market contain at least one fluorine atom) and agrochemistry, the synthesis of fluorinated organic scaffolds has been recognized to be a hot topic in synthetic organic chemistry over the past decades [11–13]. This high interest is based on the general understanding that the presence of fluorine atom(s) can influence biological property, metabolic stability, acid–base character, and lipophilicity [14–20]. Functionalized azepanes are important frameworks in small drug molecular design. Accordingly, the incorporation of F atom(s) in these seven-membered azaheterocycles has generated increasing interest in pharmaceutical research.

Benzo-fused azepines (benzazepines) including their functionalized derivatives form a relevant subclass in the area of azaheterocyclic compounds. Many representatives of these compounds, some of them found in various commercial drugs, are known to possess important biological properties. The structures of some representative drugs with a benzazepine core are presented on Fig. 1.

For example, Lorcaserin (**1**) [21] is a drug used in the treatment of obesity, Ivabradine (**2**) [15] and Zatebradine (**3**) [22] are cardioprotective drugs (hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker), Benazepril (**4**) [23] is known as angiotensin-converting enzyme (ACE) inhibitor, Fedovapagon (**5**) [23] possesses antidiuretic properties, while Fenoldopam (Corlopam) (**6**) [24] is a D1-like receptor agonist (Fig. 1).

Despite the fact that a relatively large number of functionalized azepanes, fluorine-containing azepines, and various benzazepines with biological properties are known, there are only a very limited number of examples of fluorine-containing bioactive benzazepines available in the literature. The structure of several representatives of this group of bioactive products is collected in Fig. 2 (structures **7**–**12**) [25–27].

Considering the potential biological importance of fluorine-containing benzazepines on the one hand and the limited number of literature reports on these scaffolds on the other hand, the development of new synthetic strategies towards these structures represents a relevant challenge in synthetic organic chemistry. Within that framework, the main objective of this research involved the preparation of different types of fluorine-containing benzazepines via a convenient new approach.

2. Results and discussion

The synthetic concept towards the construction of benzazepine scaffolds was based on our earlier findings regarding the synthesis of

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E-mail address: kiss.lorand@pharm.u-szeged.hu (L. Kiss).

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Available online 27 January 2020

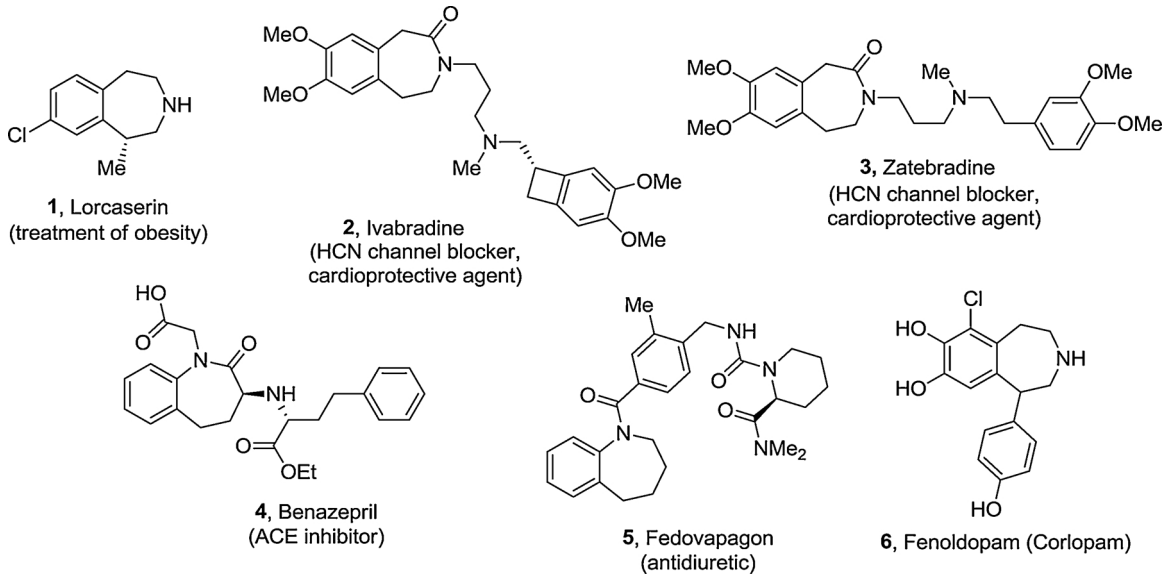


Fig. 1. Structures of some bioactive benzazepine derivatives.

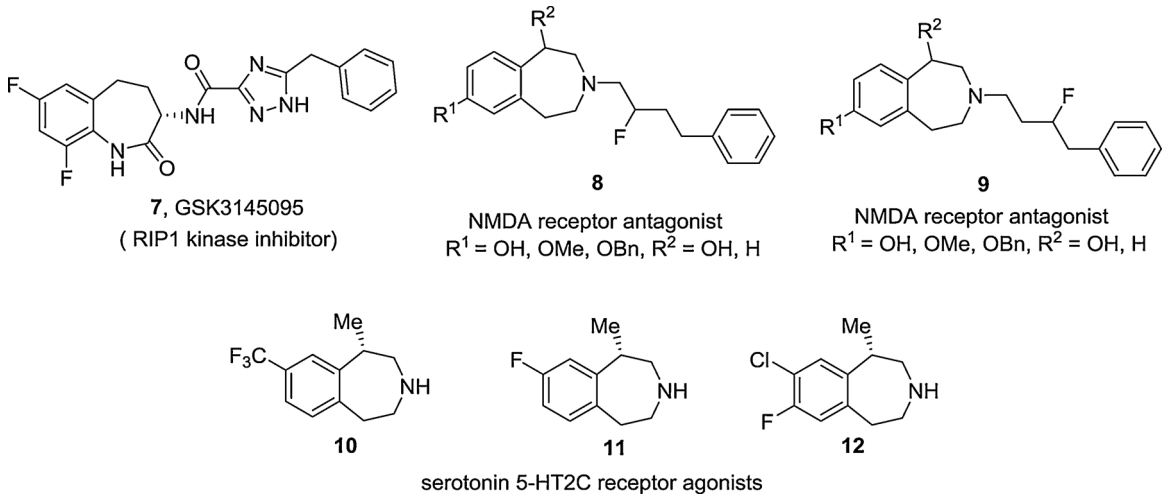


Fig. 2. Several fluorine-containing benzazepines with biological activities.

functionalized, saturated azaheterocyclic substances. This protocol involved the oxidative cleavage of the ring olefin bond of substituted cycloalkenes, followed by ring closing of the diformyl intermediates mediated by double reductive amination with various primary amines [28–30].

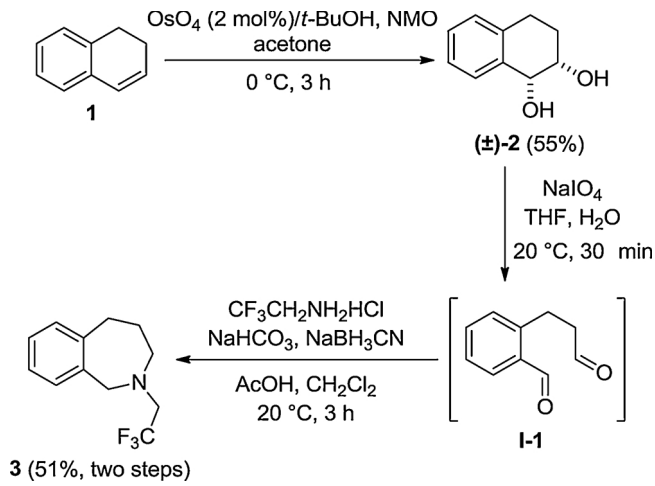
Our synthetic strategy for the creation of the benzazepine ring system started with the dihydroxylation of the ring CC— double bond of 1,2-dihydronaphthalene (**1**) with OsO_4 (2 mol%)/NMO in acetone at room temperature, which provided the corresponding *cis*-diol derivative **(±)-2** [31]. Vicinal diol **(±)-2** was next subjected to oxidative CC— ring cleavage with $NaIO_4$ in a THF/H_2O solvent system giving an unstable diformyl intermediate (**I-1**), which was then used further without isolation. It is well known that fluorine atoms incorporated into the structure of an organic scaffold, especially in the skeleton of an azaheterocycles, will significantly affect basic characteristics. Therefore, we intended to carry out the construction of the benzazepine skeleton by ring closing of dialdehyde intermediate **I-1** using various fluorine-containing primary amines. First we selected trifluoroethylamine as the amine component.

Thus, dialdehyde **I-1** resulting from the ring opening of diol **(±)-2** was submitted to double reductive amination with 2,2,2-trifluoroethylamine hydrochloride in the presence of $NaHCO_3$ and reducing agent in CH_2Cl_2 at room temperature. After investigating various reducing agents such as $NaBH_4$, $NaBH(OAc)_3$ and $NaBH_3CN$, while the first two provided the desired product in low yields (12 % and 18 %), the reaction in the presence of the latter reagent, after 3 h, yielded the corresponding trifluoromethyl-containing benzazepine **3** in moderate yield (55 %, two steps) (Scheme 1) confirming the feasibility of the proposed synthetic strategy.

In continuation, we extended the protocol described above towards the preparation of other benzazepines derivatives. Thus, diol **(±)-2** was submitted to $NaIO_4$-mediated ring opening followed by subsequent treatment of diformyl intermediate **I-1** with four different fluorine-containing primary amines: 2-fluoroethylamine, 2,2-difluoroethylamine, 3,3,3-trifluoropropylamine, and 1,1,1-trifluoropropan-2-amine. The reductive amination with the involvement of cyclization provided the corresponding fluorine-containing benzazepines **4–7** (Table 1).

Obviously, this procedure could be applied for the access of non-fluorinated derivatives as well. When benzylamine or (*R*)-methylbenzylamine its methyl-substituted counterpart was reacted, the corresponding benzazepines **8** and **9** could be isolated in moderate yields (two steps, 47 % and 55 %) (Table 1).

Next, we intended to further extend the synthetic methodology and



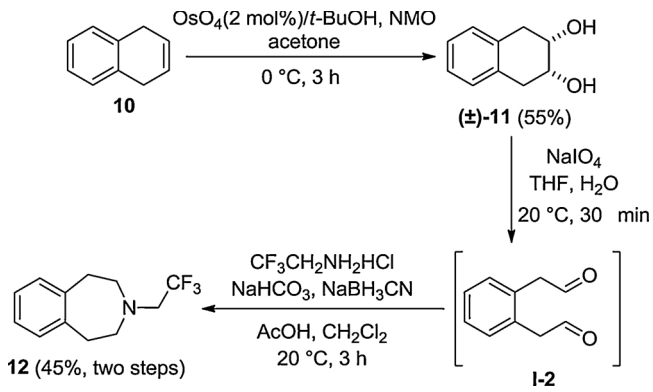
Scheme 1. Synthesis of benzazepine **3** containing a trifluoromethyl group.

Table 1
Synthesized benzazepane derivatives **4–9** from diol **(±)-2**.

fluorine-containing amine	product	yield (two steps); compound number
H_2N CH_2F	FH_2C	45 %, (**4**)
H_2N CHF_2	F_2HC	26%, (**5**)
H_2N CF_3	CF_3	25 %, (**6**)
H_2N CF_3 Me	Me F_3C	43%, (**7**)
H_2N		55 %, (**8**)
NH_2 Ph Me	CH_3 Ph	47 %, (**9**)

increase the number of benzazepine derivatives by targeting structural isomers. Accordingly, 1,4-dihydronaphthalene (**10**) a regioisomer of **1** was subjected to the same oxidative ring opening. First compound **10** under OsO_4-mediated dihydroxylation conditions yielded the corresponding diol **(±)-11**,[8] which subsequently underwent ring opening upon treatment with $NaIO_4$ to furnish diformyl intermediate **I-2** (Scheme 2) (Table 2).

Similar to Scheme 1, dialdehyde **I-2** was used in the forthcoming step without isolation. Thus on treatment with 2,2,2-trifluoroethylamine in the presence of $NaBH_3CN$, double reductive amination afforded by cyclization the desired benzazepine derivative **12** containing the trifluoromethyl group. This product is a regioisomer of **3** (45 %, two steps) (Scheme 2).



Scheme 2. Synthesis of benzazepine **12** containing a trifluoromethyl group.

Table 2
Synthesized benzazepane derivatives **13–17** diol **(±)-11**.

fluorine-containing amine	product	yield (two steps); compound number
H_2N CH_2F	CH_2F	25 %, (**13**)
H_2N CHF_2	CHF_2	26%, (**14**)
H_2N CF_3	CF_3	36%, (**15**)
H_2N CF_3 Me	Me CF_3	30%, (**16**)
H_2N		58%, (**17**)

Finally, diformyl intermediate **I-2** derived from diol **11** was treated with the fluorinated primary amines 2-fluoroethylamine, 2,2-difluoroethylamine, 3,3,3-trifluoropropylamine, 1,1,1-trifluoropropan-2-amine and benzylamine under reductive condition, in the presence of $NaBH_3CN$, to deliver the corresponding opposite regioisomers **13–17** in moderate yield (Scheme 2).

3. Conclusions

In this paper we described a novel route for the construction of 2-benzazepine and 3-benzazepine ring systems starting from dihydronaphthalene regioisomers, providing a convenient access to both tetrahydrobenzo[*c*]azepine and tetrahydrobenzo[*d*]azepine regioisomers. The key steps of the synthetic procedure are (i) oxidative olefin bond cleavage of dihydronaphthalenes followed by (ii) cyclization resulting in a formal ring expansion under reductive amination with various primary amines. In view of the importance of organofluorine scaffolds, we applied fluorinated amines for the ring-closing step, which yielded various fluorine-containing benzazepines. Further extensions of the described procedure regarding the access of functionalized benzazepines are currently being studied in our laboratory.

4. Experimental

4.1. General procedure for dihydroxylation of dihydronaphthalene

To a solution of 1,2-dihydronaphthalene or 1,4-dihydronaphthalene (2 mmol) in acetone (30 mL) was added NMO (1.5 equiv) at 0 °C with stirring, followed by addition of a solution of 2 % OsO_4 in *t*-butyl

alcohol (0.3 mL). Next the resulting mixture was stirred for 3 h at room temperature. After termination of the reaction (monitored by TLC) 10 mL of saturated aqueous Na_2SO_3 solution was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 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 or *n*-hexane/acetone).

4.2. General procedure for the synthesis of fluorine-containing benzazepine derivative by oxidative ring cleavage followed by ring closure by reductive amination

To a stirred solution of dihydroxylated tetrahydronaphthalene (2 mmol) $NaIO_4$ (1.5 equiv) was added in THF/H_2O (25 mL/2 mL). After stirring for 30 min at 20 °C under Ar atmosphere, H_2O was added (40 mL). The mixture was then extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4. The resulting solution containing the dialdehyde derivative concentrated to half of its volume was used without purification for the next reaction.

To the solution of the dialdehyde was added fluorine-containing amine hydrochloride (1 equiv) and $NaHCO_3$ (2 equiv) or benzylamine or methylbenzylamine (1 equiv, without $NaHCO_3$). Then the mixture was stirred at 20 °C for 10 min and, after adding $NaBH_3CN$ (1 equiv) and AcOH (2 drops), stirring was continued for another 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 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 or *n*-hexane/acetone).

Characterization and ^1H NMR and ^{13}C NMR spectra of the synthetized compounds are available in the Supporting Information.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2020.109466.

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IV.

Synthesis M. Nonn et al. Paper

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

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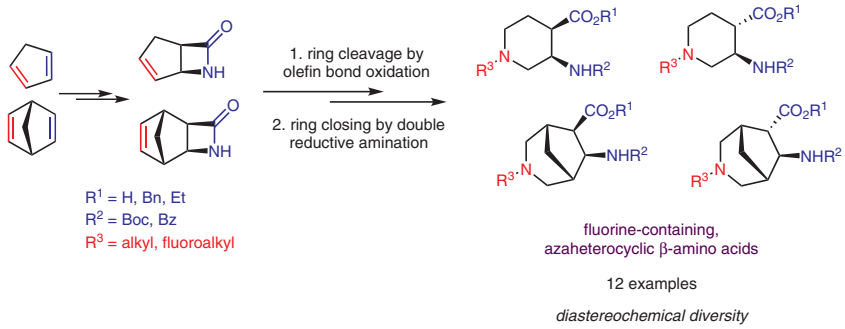

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Abstract Structural diversity-oriented synthesis of some azaheterocyclic β-amino acid derivatives has been accomplished by selective functionalization of readily available cyclodienes. The stereocontrolled synthetic concept was based on the oxidative 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]

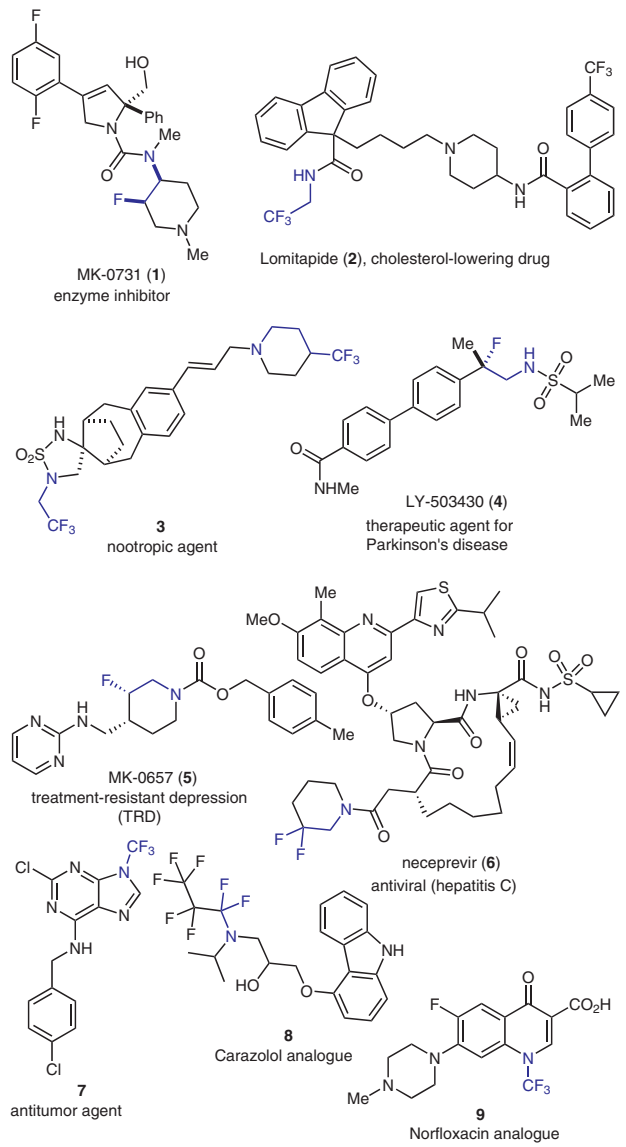


Figure 1 Several bioactive molecules with fluoroamine or trifluoroamine units

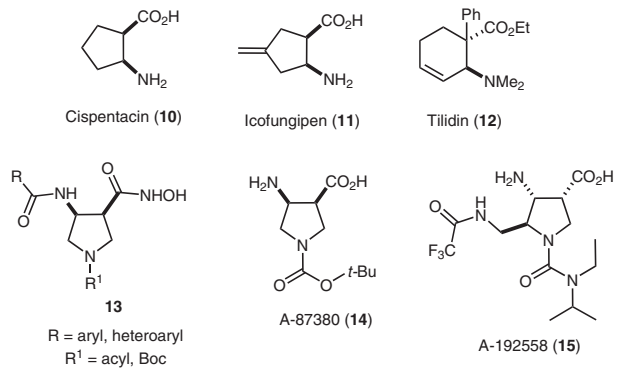


Figure 2 Some alicyclic and azaheterocyclic β-amino acids with biological relevance

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]

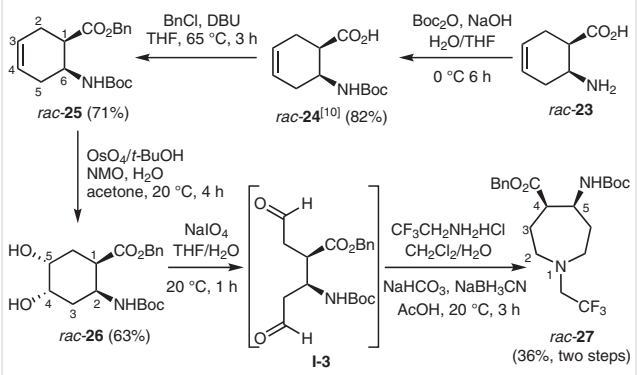
Taking into consideration the high pharmaceutical potential of saturated azaheterocycles, β-amino acids, and organofluorine molecules, our aim was to combine these structural elements and to expand further the chemical space by synthetizing novel molecular structures containing these motifs. This work 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

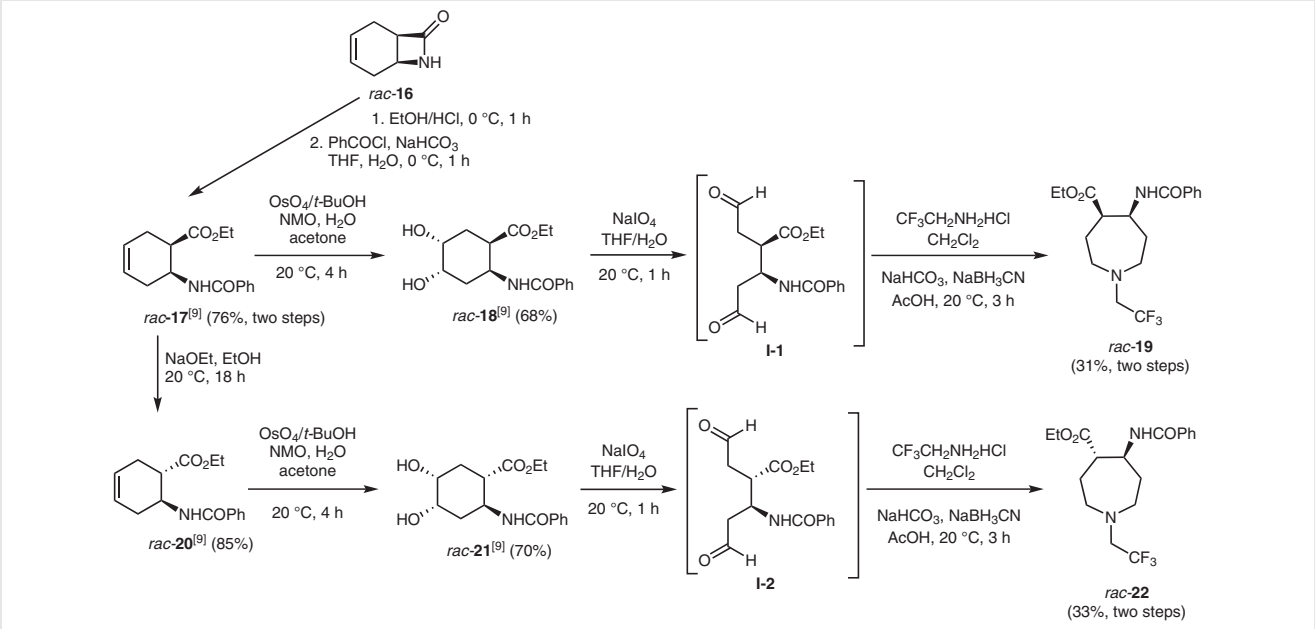


Scheme 2 Stereocontrolled synthesis of azepane β-amino ester *rac*-**27**

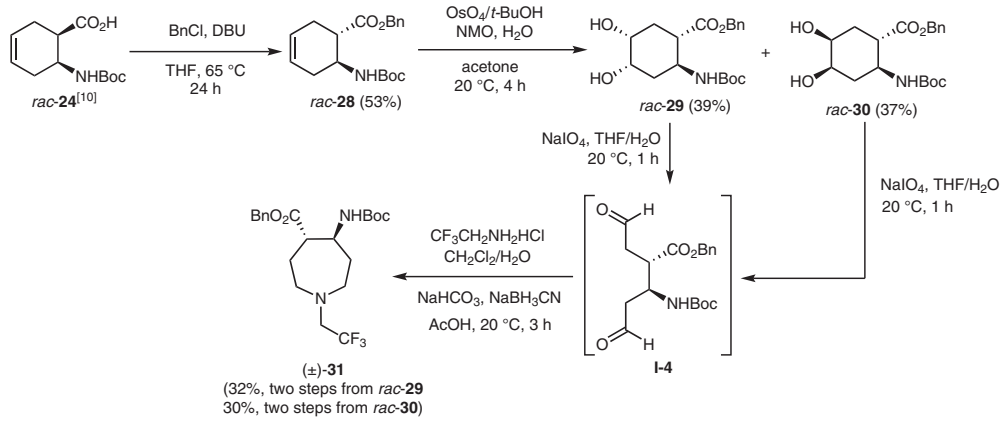
to the bulkier benzyl ester function affording two diol stereoisomers, identified as *rac*-**29** and *rac*-**30** in nearly 1:1 ratio, which were separated by column chromatography.

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.

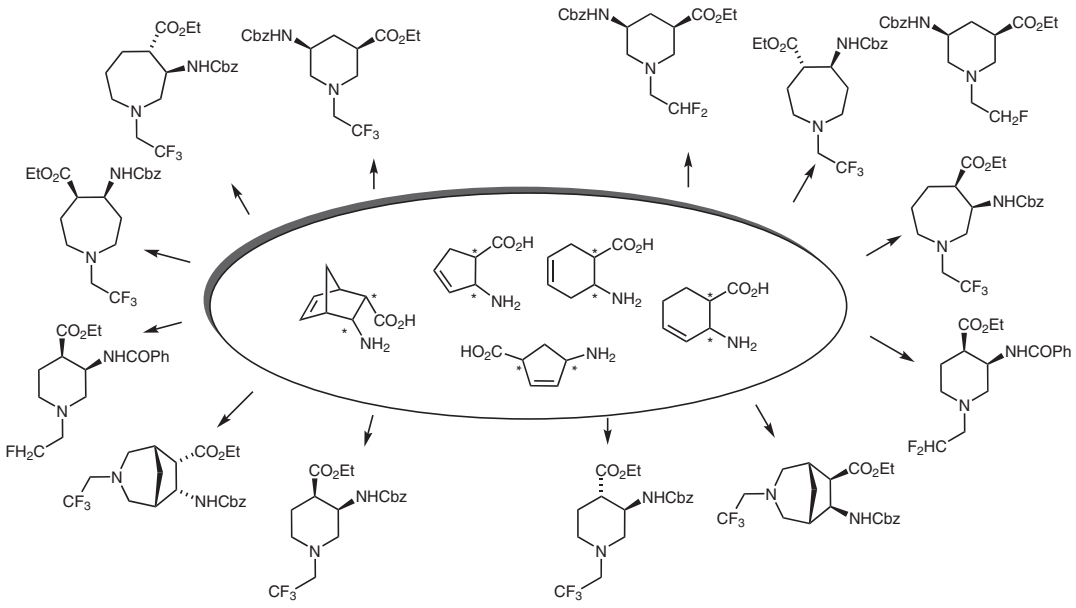
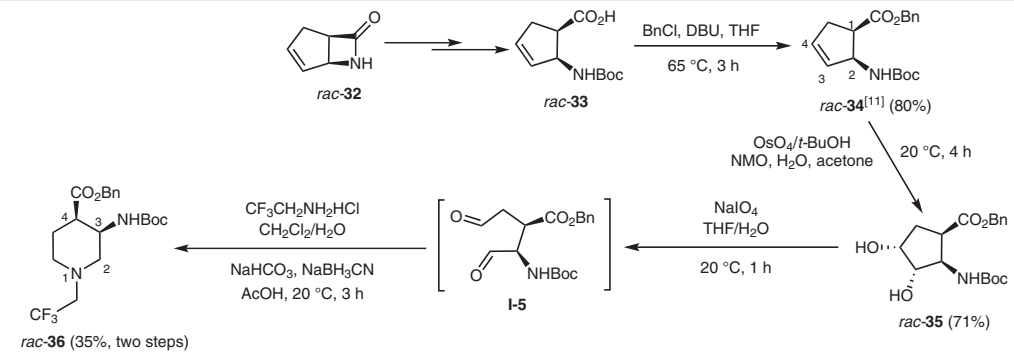
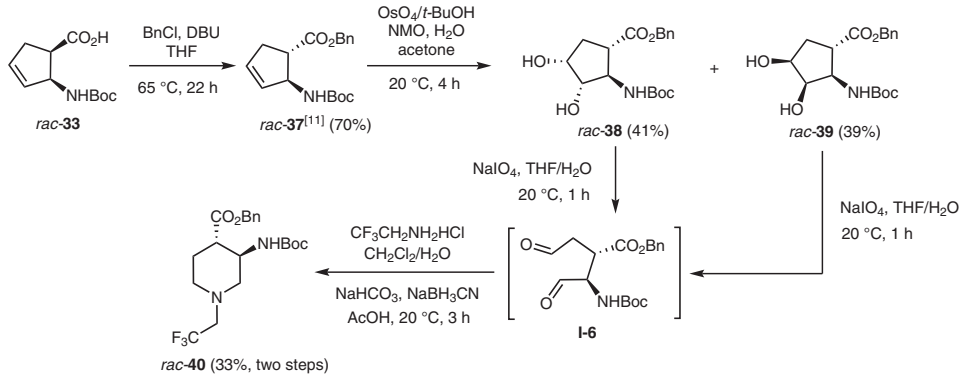


Figure 3 Transformation of some cycloalkene β-amino acids into fluorine-containing N-heterocyclic β-amino esters



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

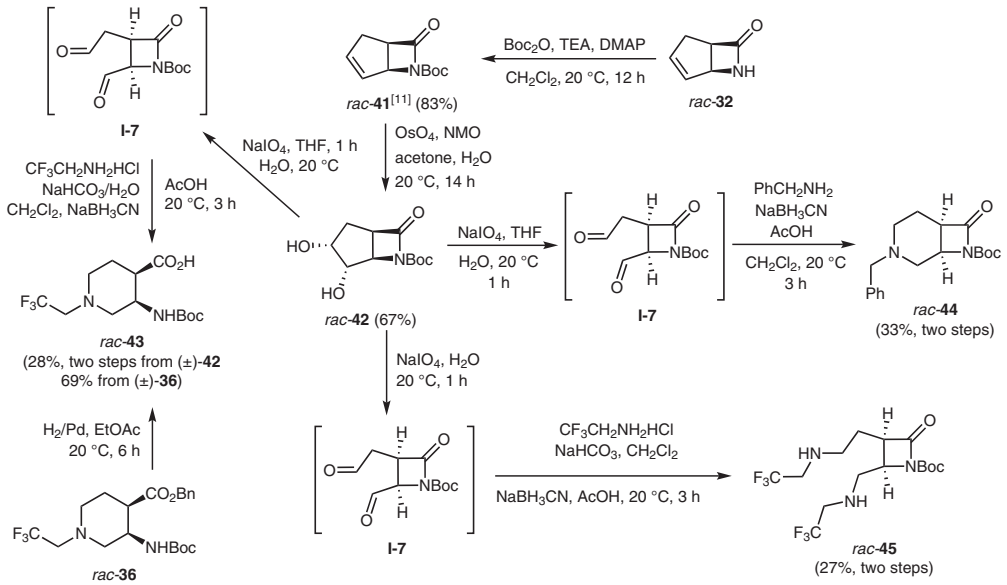


Scheme 5 Stereocontrolled synthesis of piperidine β-amino ester *rac*-**40**

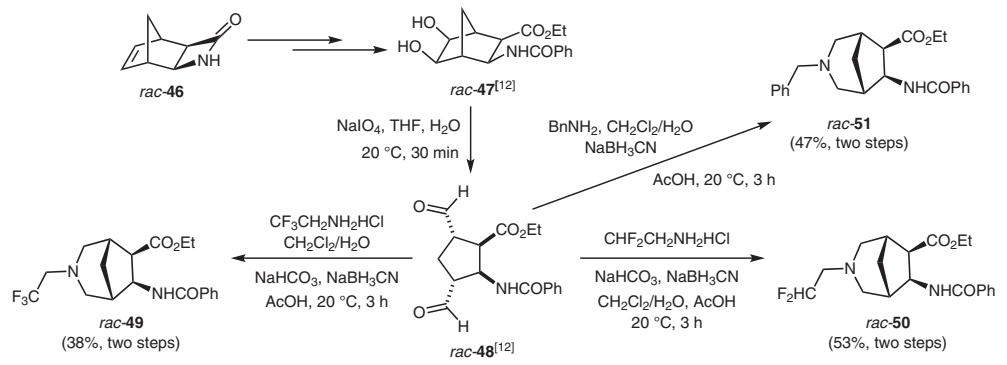
In order to increase the number of novel structures with piperidine core, we selected dihydroxylated β-lactam *rac*-**42** as the starting model compound. The synthesis of *rac*-**42** proceeded selectively, when carried out through OsO_4-catalyzed *cis*-dihydroxylation of *N*-Boc-protected β-lactam *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**

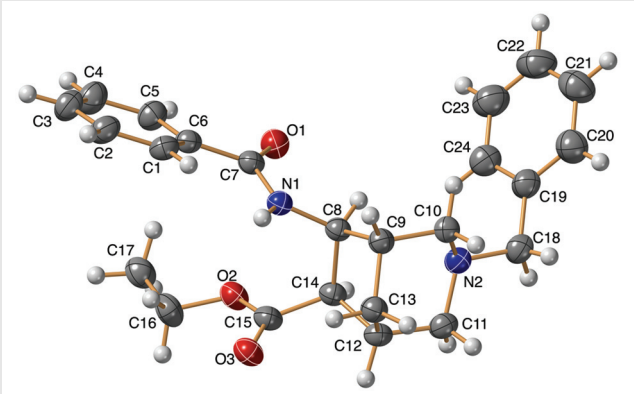


Figure 4 X-ray diffraction analysis of *rac*-**51** (for details, see the Supporting Information)

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