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Stereocontrolled Synthesis of Functionalized Azaheterocycles from Carbocycles through Oxidative Ring Opening/Reductive Ring Closing Protocols

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Abstract: Fluorine-containing organic scaffolds are of significant interest in medicinal chemistry. The incorporation of fluorine into biomolecules can lead to remarkable changes in their physical, chemical, and biological properties. There are already many drugs on the market, which contain at least one fluorine atom. Saturated functionalized azaheterocycles as bioactive substances have gained increasing attention in pharmaceutical chemistry. Due to the high biorelevance of organofluorine molecules and the importance of *N*-heterocyclic compounds, selective stereocontrolled procedures to the access of new fluorine-containing saturated *N*-heterocycles are considered to be a hot research topic. This account summarizes the synthesis of functionalized and fluorine-containing saturated azaheterocycles starting from functionalized cycloalkenes and based on oxidative ring cleavage of diol intermediates followed by ring expansion with reductive amination.

Keywords: azaheterocycles, functionalization, oxidative ring opening, ring closing, reductive amination

1. Introduction

1.1. Importance of Functionalized Saturated Azaheterocycles and Fluorinated Saturated *N*-heterocycles

Saturated azaheterocycles have gained increasing attention in medicinal and organic chemistry. A large number of nitrogen-containing saturated cyclic compounds are known as antibiotics, analgesics, antidepressants, anticancer, anti-HIV, and anti-HCV agents.[1–3] According to the medicinal chemistry literature, there are two main fields of interest with respect to the structures of the present drug candidates: the popularity of organofluorine scaffolds and of azaheterocycles.[4–9] Saturated *N*-heterocycles are building blocks in synthetic bioactive products and medicinal compounds. Five-, six-, and seven-membered frameworks are the most common structural units. In the development of new pharmaceuticals three-dimensional, functionalized scaffolds with saturated building blocks, especially saturated *N*-heterocycles, are used preferably.[1–3] Figure 1 shows some representative *N*-heterocyclic structures with biological relevance.[10–14]

Fluorine-containing organic molecules (except only a few representatives) are practically absent in nature, but they have received significant interest in drug research. The replacement of a hydrogen atom or a functional group by fluorine or a fluorinated group could furnish biomolecules with unique biological features. The incorporation of fluorine in biomolecules can lead to remarkable changes in their physical, chemical, and pharmaceutical properties. There are already many drugs on the market, which contain at least one fluorine atom, and this number is expected to increase in years to come.[15–17] Application of fluorinated compounds like fluorine-containing amines could offer a route to the access of fluorine-containing azaheterocycles.

Due to the high biorelevance of organofluorine scaffolds and the importance of *N*-heterocyclic compounds, develop-

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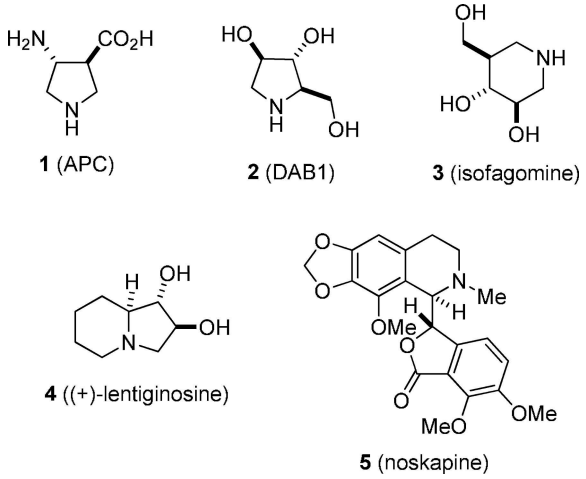

Figure 1. Some bioactive functionalized *N*-heterocyclic compounds.

ment of novel and efficient stereocontrolled procedures to the access of new fluorine-containing saturated *N*-heterocycles is a topic of high interest in synthetic organic chemistry. The introduction of one or more fluorine atoms into molecules may be achieved by starting from various functionalized cycloalkenes. The transformations involved are oxidative ring cleavage (olefin bond dihydoxylation, oxidative ring cleavage of the diol intermediate) followed by ring expansion with reductive amination, resulting in novel fluorine-containing *N*-heterocycles.

Fluorine and the C–F bond have rather unique properties and the incorporation of fluorine into a molecule may generate unique changes, which cannot be attained by the use of any other element.[16,17] It has great impact because a large number of fluorine-containing substances are widely applied in various areas like material sciences or medicinal and pharmaceutical chemistry as well as agrochemistry.[18–21] The size of the fluorine atom is very similar to that of hydrogen and fluorine has the highest electronegativity. This could lead to increasing lipophilicity and stability, and might furnish resistance to metabolic transformations. The van der Waals radius of fluorine is more similar to that of oxygen and the carbon–fluorine bond length is comparable but weaker than the carbon–oxygen bond. Hydrogen-bonding interactions may provide special characteristics to the structure with at least one fluorine atom. Due to these unique properties, it is a general aim in drug design to furnish a biomolecule with fluorine or fluorinated groups. There are an increasing number of drugs on the market, which contain at least one fluorine atom (Figure 2).[16,17,22–25]

Among organofluorine compounds of significant biorelevance, saturated *N*-heterocyclic scaffolds with fluorine are of special interest. Not surprisingly, the changing of an azaheterocycle motif into a fluorine-containing one can improve the metabolic stability or reduce basicity, thereby providing better bioavailability to a certain molecule. Fluorinated piperidines and their derivatives exhibit promising biological activity because of increased lipophilicity. β-Fluoroamine and trifluoroamine moieties are also present in various fluorine-containing derivatives with biological relevance (Figure 3).[4–7]

There has been a great interest in fluorine-containing pyrrolidines or piperidines in pharmaceutical chemistry, which are elements of various drugs.[26] Although fluorinated azepanes are much less studied, they may also have wide attention in pharmaceutical design in the future.[6,27] It is well known that fluorine-containing tetrahydroisoquinoline derivatives, *N*-bridged bicyclic frameworks, and other *N*-fluoroalkylated molecular structures have great biological importance.[28–30]

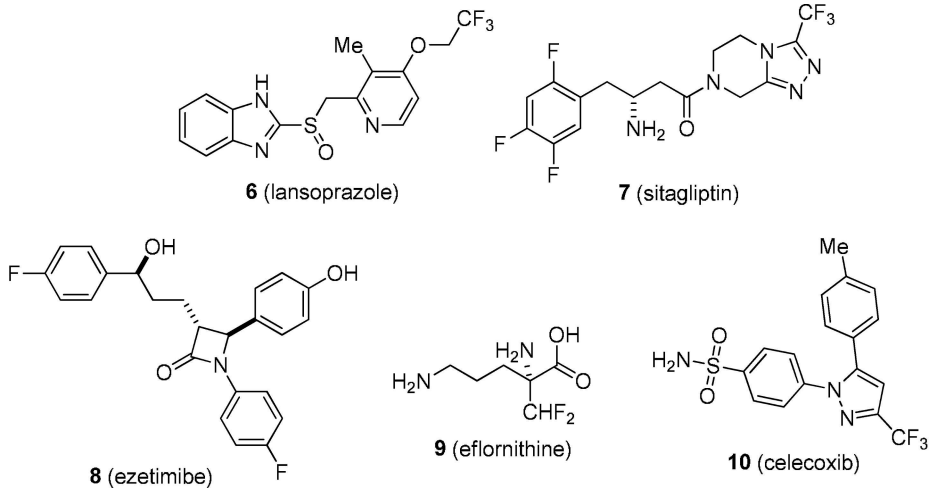

Figure 2. Several important representatives of fluorine-containing market leader drugs.

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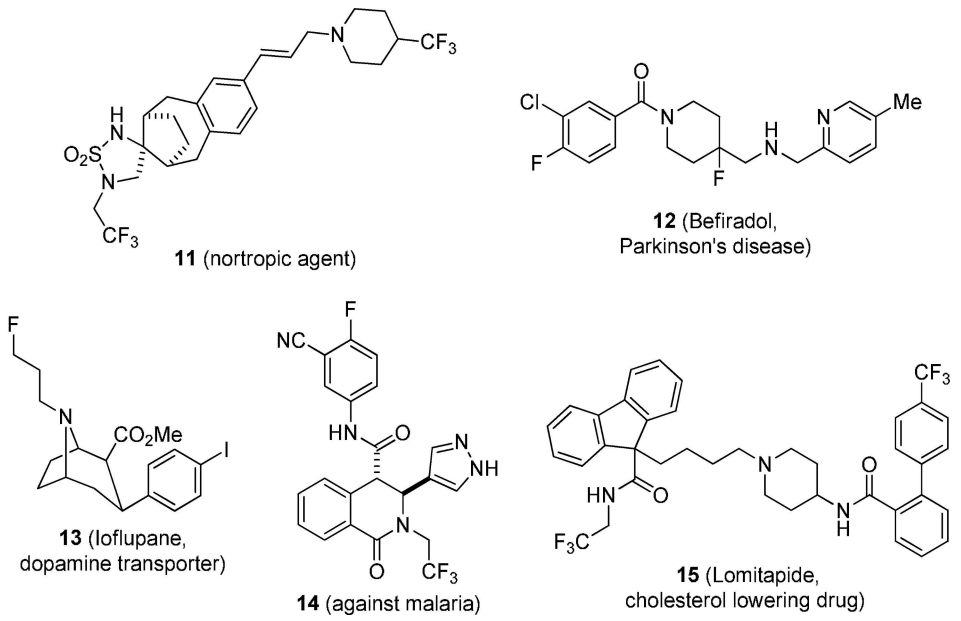

Figure 3. Fluorine-containing azaheterocyclic derivatives of biological importance.

2. Synthesis of Saturated *N*-heterocycles from Dialdehyde Compounds

A large number of synthetic methodologies have been developed to the access of azaheterocycles including aziridines, azetidines, pyrrolidines, piperidines or azepanes.[31–35] In organic and pharmaceutical chemistry, the creation of novel saturated *N*-heterocycles is a field explored deeply. However, due to the increasing importance of these scaffolds, the development of novel, efficient, cost effective, selective, and stereocontrolled protocols for these derivatives is a continuous challenge in modern chemistry.[3a]

A simple and convenient method to obtain saturated azaheterocycles is based on the transformation of cycloalkene derivatives across oxidative ring opening, followed by reductive amination of the diformyl intermediates.[3b]

The oxidative ring cleavage through the olefin bond of unsaturated compounds is a widely applied, effective transformation in organic chemistry to afford the corresponding carbonyl compounds. There are two main methodologies in the literature for oxidative ring opening: either through ozonolysis of alkenes or cleavage of vicinal diols.[36–41] Both are useful methods to prepare synthetically valuable dialdehydes or diketones.[39] The Upjohn method is a two-step procedure for the cleavage of the C–C double bond. First OsO_4/NMO produces the vicinal diol intermediate, which undergoes further oxidation by the treatment of sodium periodate ($NaIO_4$) giving carbonyl compounds.[39] This procedure was modified with the use of oxone in combination with OsO_4 (Borhan and co-workers)[36a] or *m*-CPBA, HBF_4 and ArI (Ochiai et al.).[40] However, these procedures have limitations, because of the forcing conditions used. Phenyliododiacetate [$PhI(OAc)_2$] is an efficient and selective reagent to cleave vicinal diol derivatives providing aldehydes and ketones.[39]

Functionalized dialdehydes are valuable substrates, which might be transformed into various substituted alicyclic, heterocyclic or polysubstituted derivatives. The oxidative synthetic approaches described above offer an opportunity for the ring opening of several cycloalkene derivatives resulting in the corresponding diformyl compounds. Nicolaou and co-workers applied the ring-opening method for several cyclic 1,2-diol derivatives by $PhI(OAc)_2$ in good yields.[39] Fricke et al. reported the synthesis of iminodiacetaldehyde derivatives from the corresponding 3,4-dihydroxypyrrolidines. The transformation was based on diol production followed by oxidative ring cleavage on treatment with $Pb(OAc)_4$ or $NaIO_4$ in aqueous solution (Scheme 1).[41]

Since scaffolds possessing amino groups represent a large and important class of pharmaceuticals and agrochemicals, the creation of a C–N bonds has a great interest in organic chemistry. There are several methodologies, but reductive amination is the most impressive pathway for the formation of a carbon–nitrogen bond in chemical industry.[42] This method, also named reductive alkylation, involves the condensation of a carbonyl compound with ammonia, primary or secondary amines in the presence of a reducing agent.[43–45] The introduction of a nitrogen atom into an organic molecule has

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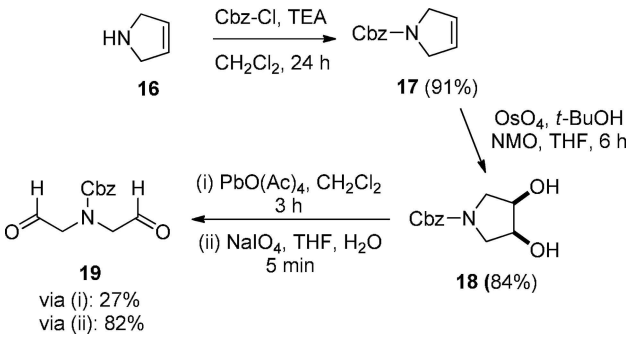
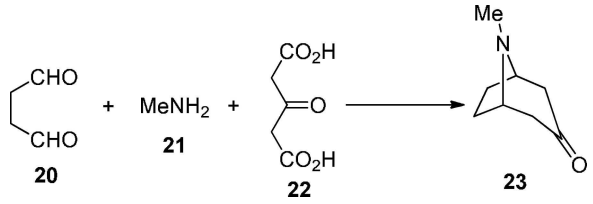


Scheme 1. Synthesis of iminodiacetaldehyde **19**.



Scheme 2. Synthesis of tropinone from succinaldehyde.

great potential in the synthesis of azaheterocycles or building blocks in medicinal chemistry.

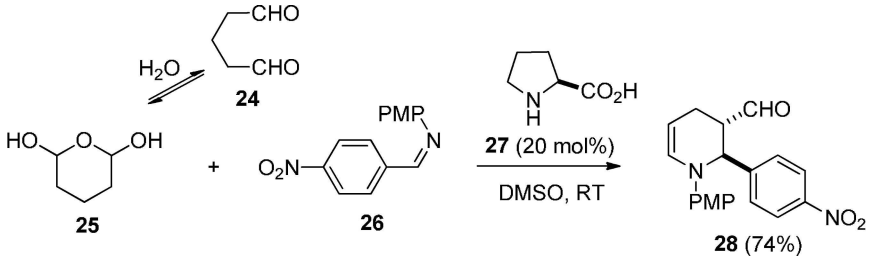
2.1. Transformation of Linear Dialdehydes into *N*-heterocycles

Linear dialdehydes such as succinaldehyde or glutaraldehyde are useful substrates for a number of transformations such as aldol, Mannich, Michael and Henry reactions. These dialdehydes are often used for the rapid synthesis of frameworks with medium-sized carbo- and hetero-cyclic ring systems.[3b] A century ago Sir Robert Robinson applied a novel thinking in the synthetic method and produced tropinone **23** in a one-pot reaction by using succinaldehyde (**20**), primary amine (**21**), and acetone dicarboxylic acid (**22**) (Scheme 2).[3b]

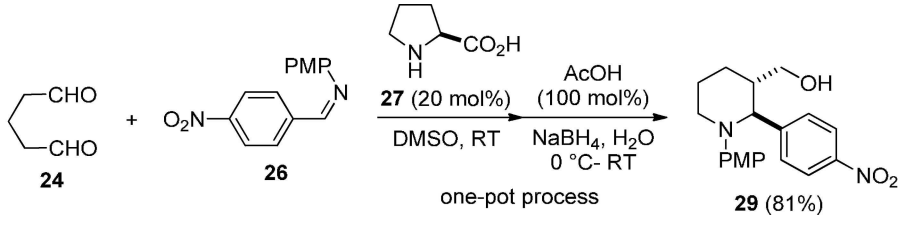
Xu and co-workers reported a diastereo- and enantioselective synthetic protocol by the application of glutaraldehyde (**24**) to produce *N*-heterocycles such as tetrahydropyridines by using primary amine catalysis. A Mannich-type reaction was developed, which gave **25** in an intramolecular aqueous cyclization of glutaraldehyde, *N*-PMP aldimine **26** and proline (**27**) providing the corresponding tetrahydropyridine derivative **28** (Scheme 3).[46]

Kumar et al. reported an extension of the above-described procedure. Cycloaddition of glutaraldehyde (**24**) furnished asymmetric 2,3-disubstituted piperidine framework (**29**) with reduction in the last step (Scheme 4).[47]

Chen and co-workers described a synthetic pathway for the preparation of azaheterocycles starting from aliphatic dialdehydes. The key steps of the synthetic procedure are an inverse electron demand aza-Diels-Alder reaction (ADAR) followed by an intramolecular hemiketal formation/oxidation reaction of the *N*-Tos-1-aza-1,3-butadiene (**30**) and linear dialdehydes



Scheme 3. Organocatalytic transformation of glutaraldehyde into optically active tetrahydropyridine.



Scheme 4. Functionalized piperidine synthesis through cycloaddition.

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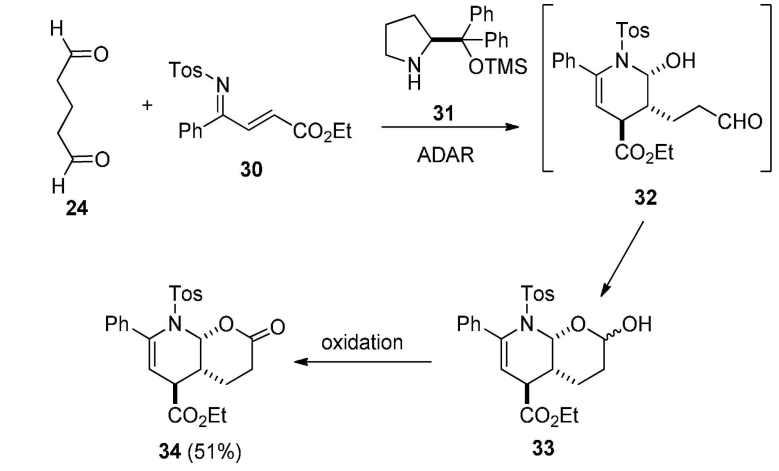
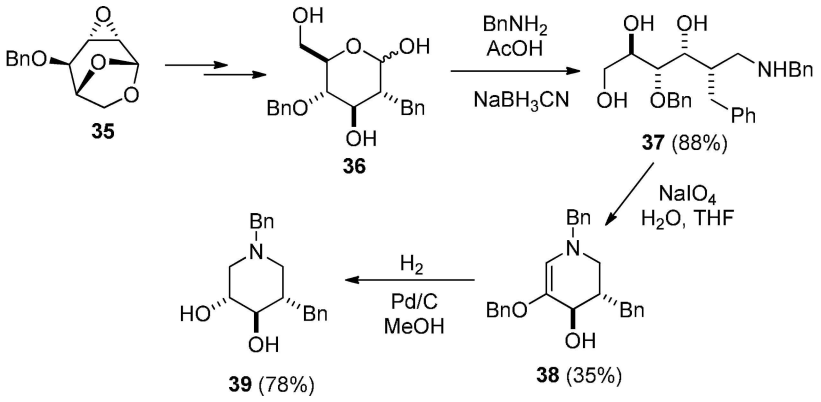


Scheme 5. Synthesis of a lactone[2,3-*b*]piperidine product via ADAR.



Scheme 6. Synthesis of substituted hydroxypiperidine derivative.

(eg. glutaraldehyde). This multi-step process yielded lactone [2,3-*b*]piperidine derivative **34** (Scheme 5).[48]

2.2. Transformation of Dialdehyde Derivatives into Functionalized Azaheterocycles across Reductive Amination

A number of methods was published for the synthesis of *N*-heterocycles by the application of ring closing of linear dialdehydes under reductive amination.[11,12,49–57]

Bols and co-workers developed a new method for the synthesis of substituted hydroxypiperidines. The synthetic process started from epoxide **35** affording hemiacetal **36** in a two-step transformation. This was then submitted to reductive amination with benzylamine. In the final steps, cleavage by periodate gave enamine **38**, which underwent hydrogenation to deliver *trans* isomer **39** (Scheme 6).[11]

Chrick and co-workers developed a novel synthetic protocol to the access of polyhydroxylated *N*-alkoxypiperidines based on ring closing of dialdehydes by double-reductive amination. The oxidative ring opening of olefin **40** was carried out with $OsO_4/NaIO_4$ in dioxane and water resulting in cyclic hydrate **41** in diastereomeric forms. In the following step, double-reductive amination with benzylamine afforded the desired piperidine derivative **42**. This reaction was extended by using alkoxyamines. Thus, *O*-benzylhydroxylamine was used for the above-described double-reductive amination giving *N*-alkoxypiperidine **43**. The highest yield of **43** was attained by using 2.5 equiv. of alkoxyamine (Scheme 7).[49] After the optimization of this method, the synthesis of trisubstituted *N*-alkoxypiperidine analogs of isofagomine was achieved.[49]

In another study, the synthesis of carbohydrate-derived morpholine amino acids via oxidative cleavage and reductive amination was described by Grotenberg et al. The synthetic route started from commercial D-ribose **45**, and the key step of

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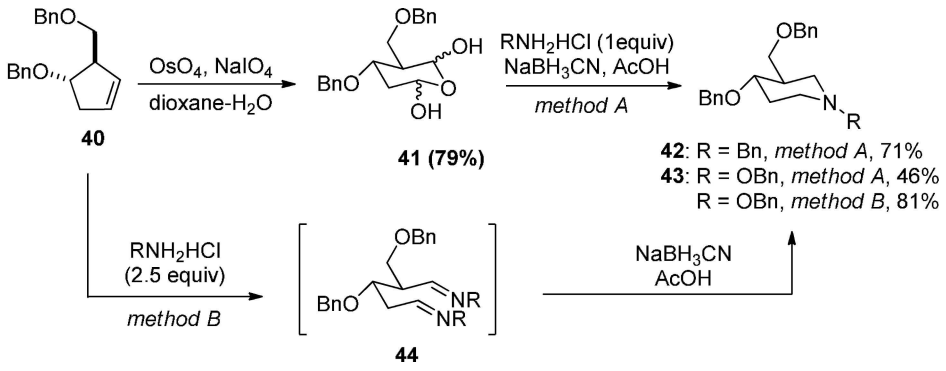
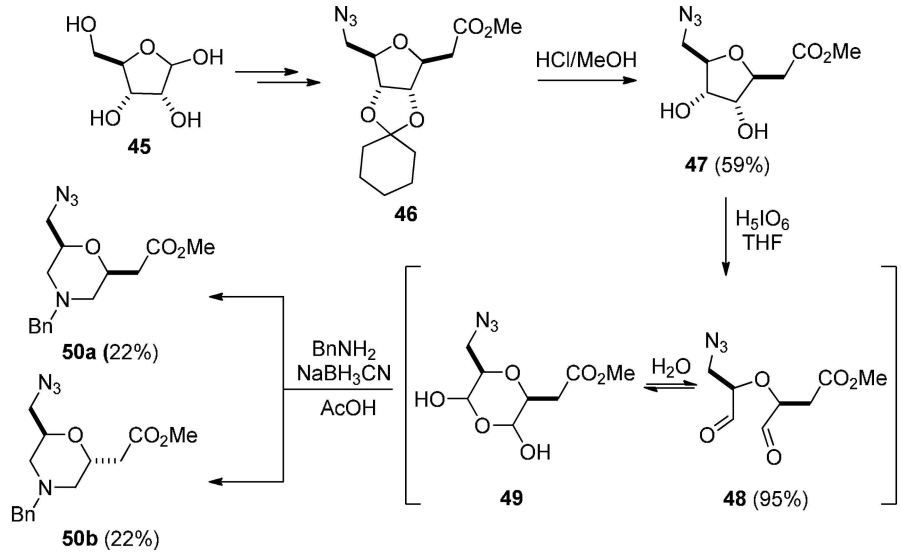


Scheme 7. Preparation of substituted piperidines with double-reductive amination.



Scheme 8. Synthesis of carbohydrate-derived morpholino amino acid derivatives.

the pathway were glycol cleavage of vicinal diol derivative **47** (derived from protected sugar amino acid derivative **46**) with HIO_4. Double-reductive amination of the formed dialdehyde **48** furnished substituted morpholine amino acid derivatives **50 a** and **50 b**.[50a]

Reductive aminations were accomplished directly with different amines including benzylamine at pH 5 (acidified with AcOH) in the presence of $NaBH_3CN$ as reducing agent. After purification, both diastereomeric morpholines were isolated in 22% yield (Scheme 8).[50b] Herczegh and co-workers applied the oxidative C–C cleavage/cyclization protocol to provide various so-called "tricyclanos" regarded as conformationally constrained nucleoside analogues with a new heterotricycle.[50b]

The method, based on oxidative ring cleavage and reductive ring closure, is the key step in the synthesis of morpholine oligomers. The thymine morpholino monomer (**52**) was prepared from 5′-*O*-dimethoxytrityl ribothymidine **51** through oxidative ring cleavage with $NaIO_4$ followed by reductive amination with ammonium diborate. The formed dihydroxythymine morpholino monomer intermediate was reduced with $NaBH_3CN$ providing **52** (Scheme 9).[51] The product formed is the key monomer in the design of Eteplirsen.[58,59]

Azasugars (polyhydroxylated piperidines) exhibit significant bioactivities. Shih et al. reported a synthetic procedure to accomplish the synthesis of novel trihydroxypiperidine derivatives starting with enone **53** synthetized from D-(−)-quinic acid. The main steps of the procedure are oxidative ring cleavage of the ring olefinic bond, intramolecular reductive cyclization of the formed dialdehyde, and deprotection by Pd/C/HCl leading to the required trihydroxy piperidine product **59** (Scheme 10).[52]

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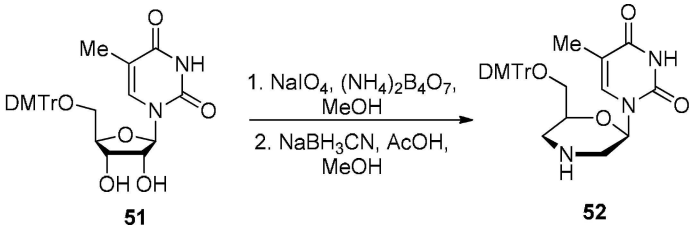
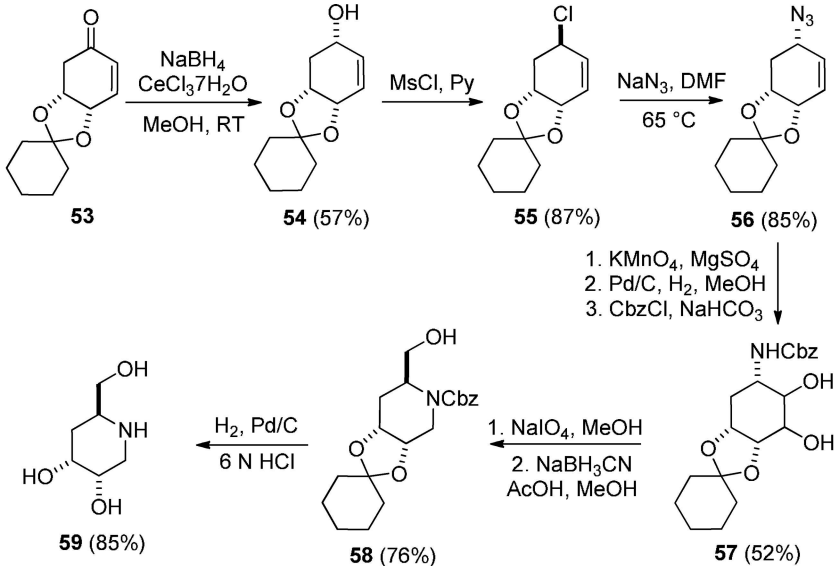


51 52

Scheme 9. Synthesis of thymine morpholino derivative **52**.



53 **54** (57%) **55** (87%) **56** (85%)

57 (52%) **58** (76%) **59** (85%)

Scheme 10. Synthesis of trihydroxy piperidine structure **59**.

The synthesis of functionalized piperidine derivatives is well-documented in the literature, whereas methods to synthesize azepane compounds are much less reported. Lin and co-workers described a new transformation for the synthesis of tri- and tetra-hydroxyazepanes. Hydroxyazepanes are promising glycosidase inhibitors analogously to their five- or six-membered analogs. The reported strategy is based on an oxidative cleavage reaction and subsequent reductive cyclization.

In the first step, protected 1,4,5-cyclohex-2-ene-triols derived from D-(−)-quinic acid underwent dihydroxylation by the treatment of $RuCl_3/NaIO_4$. The resulting vicinal diols (**64**–**67**) were further transformed via $NaIO_4$-mediated oxidative ring opening to afford the corresponding diformyl compounds (**68**–**71**). The reductive cyclization was performed with benzylamine in the presence of $NaBH(OAc)_3$ as the reducing agent (Scheme 11).[53]

This method was extended and further optimized for the preparation of 7-hydroxymethyl-3,4,5-trihydroxyazepane (**76**). The route, starting from a protected cyclohexenetriol, included only three steps: ozonolysis, reductive amination, and deprotection (Scheme 12).[72,73]

Robinson et al. developed an effective synthesis of a series of novel analogs of the antibacterial agent gemmacin B with a bridged azepane framework (**81**). The key steps are oxidative ring opening/ring closing through reductive amination (Scheme 13).[60]

A novel and efficient stereocontrolled procedure for the synthesis of tashiromine and epitashiromine alkaloids started from cyclooctene-based β-lactam and involved an intramolecular double reductive amination step of the diformyl intermediates. Indolizidine alkaloids are highly important in pharmaceutical chemistry, because they exhibit a wide range of therapeutic activities such as anticancer, antimetastatic or antitumor effects. The strategy for the synthesis of tashiromine and epitashiromine alkaloids started from bicyclic β-lactam **(±)-82** and was based on the ring opening of the azetidinone skeleton followed by the ring cleavage of the olefin double bond of cyclooctene derivative **(±)-84**. The resulting crude dialdehyde **(±)-86** was submitted to catalytic hydrogenolysis

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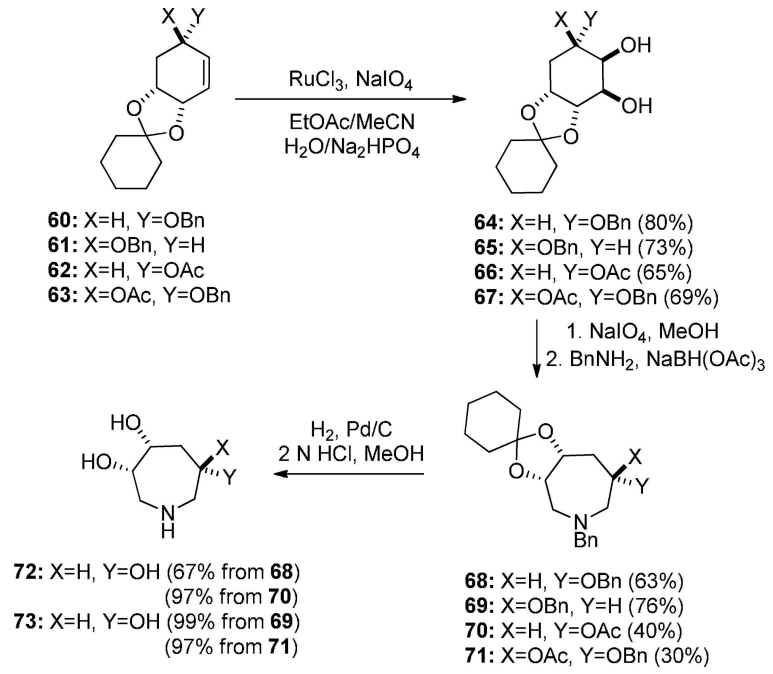
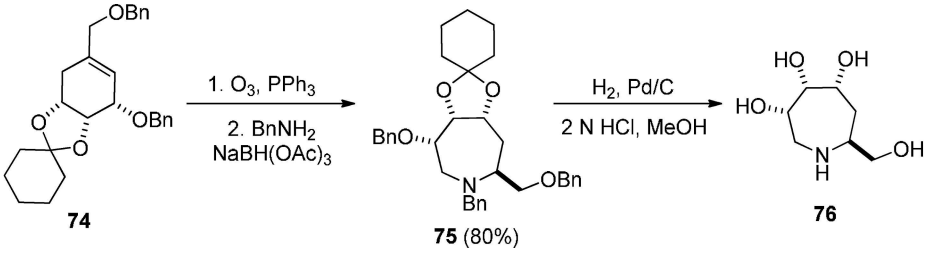


Scheme 11. Synthesis of trihydroxylated azepanes **72** and **73**.



Scheme 12. Synthesis of 7-hydroxymethyl-3,4,5-trihydroxyazepane.

and after *N*-deprotection a reduction via double intramolecular cyclization gave the desired alkaloid **(±)-88** (Scheme 14).[12]

The same method was successfully applied for the synthesis of epitashiromine, a stereoisomers of tashiromine. The main difference is the epimerization with NaOEt of *cis*-β-amino-cyclohexenecarboxylate **(±)-84** giving its C-1 epimer *trans* amino ester **(±)-89**. The 1 : 1 diastereoisomer mixture formed in OsO_4/NMO dihydroxylation of **(±)-89** could not be purified and next it was used in the ring-opening oxidation and reductive cyclization steps. After the reduction of the ester with $LiAlH_4$, epitashiromine **(±)-93** was isolated (Scheme 15).[12]

Note, that the protocol is stereocontrolled, that is, in both cases the configuration of the stereocenters of the starting *cis* and *trans* esters **(±)-84** and **(±)-89** were conserved furnishing the corresponding alkaloid epimers (**(±)-88** and **(±)-93**).

An efficient stereocontrolled preparation was reported for the introduction of a nitrogen atom into a cyclic β-amino acid. The syntheses started from the readily available unsaturated bicyclic β-lactams **(±)-94**, **(±)-99**, and **(±)-100**. Key steps of the stereocontrolled synthetic pathways are the oxidative cleavage of the ring olefin bond and subsequent reductive amination with benzylamine. This method was applied for the synthesis of both the racemic and enantiomerically pure forms.[55–57]

The preparation of piperidine β-amino ester enantiomers started from enantiomerically pure β-lactam **(−)-94** (obtained by enzymatic resolution of the racemate), which was submitted to dihydroxylation with $KMnO_4$. The next reaction step was based on oxidative ring opening of the vicinal diol (**97a**,**b**) mediated by $NaIO_4$ followed by ring expansion giving novel *cis*- and *trans*-β-aminocarboxylate scaffolds in enantiomerically pure form (Scheme 16).[55]

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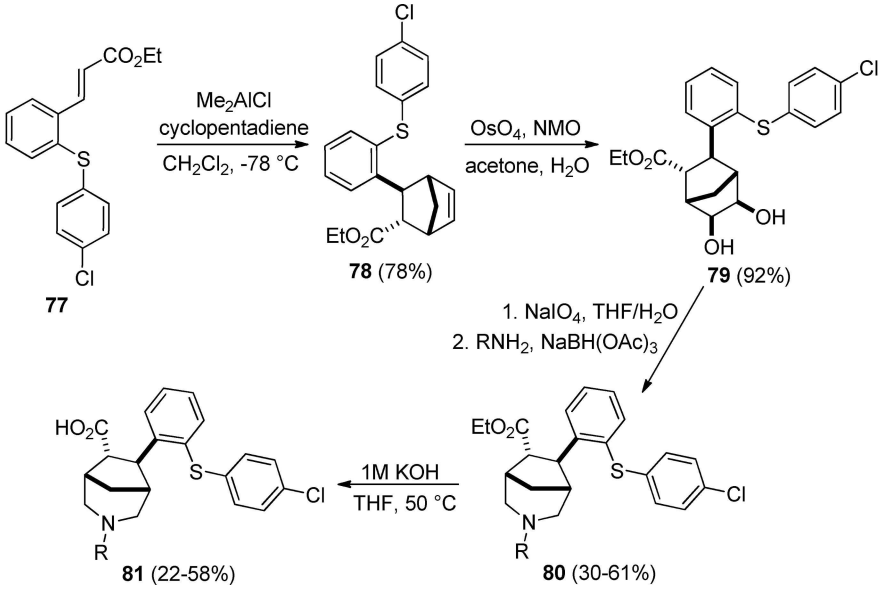
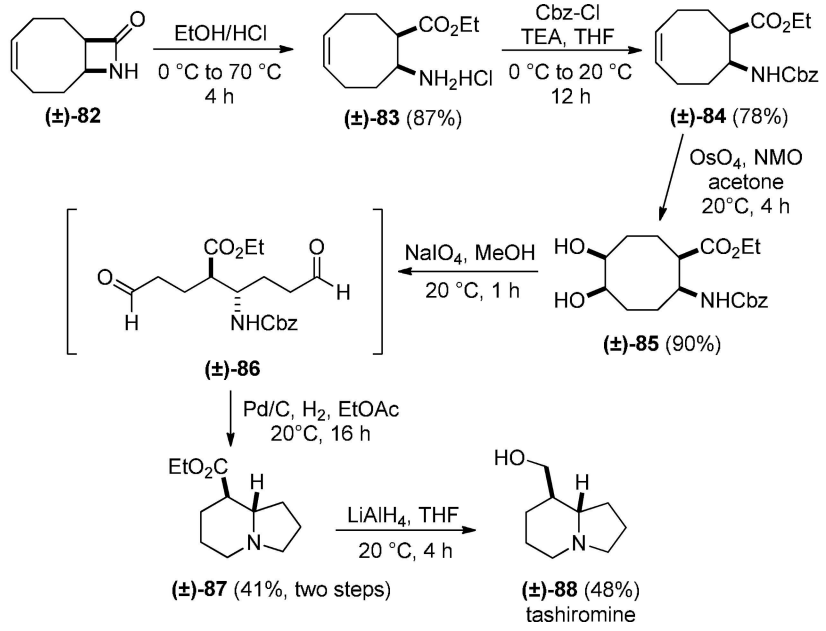


Scheme 13. Synthesis of racemic gemmacin analogs.



Scheme 14. Synthesis of racemic tashiromine **(±)-88**.

Similar transformations were applied for the regio- and stereoisomeric synthesis of azepane β-amino esters (Scheme 17).[56]

Azabicyclic β-amino esters were synthetized starting from *diendo*- and *diexo*-norbornene β-amino acids with the above-described ring-opening/ring-closure protocol. Racemic *diendo* norbornane amino ester **105** as starting material provided azaheterocyclic products **107** and **108** in a ratio of 1 : 9. The possible explanation for the formation of the isomeric mixture is the keto–enol tautomerism of the diformyl derivatives, which yielded a mixture of *diendo* and *diexo* azaheterocyclic amino esters (Scheme 18).[57]

In a similar way, the synthetic pathway described above was applied for the transformation of *diexo-N*-Boc-protected norbornene β-amino ester **109**. The oxidative ring-opening

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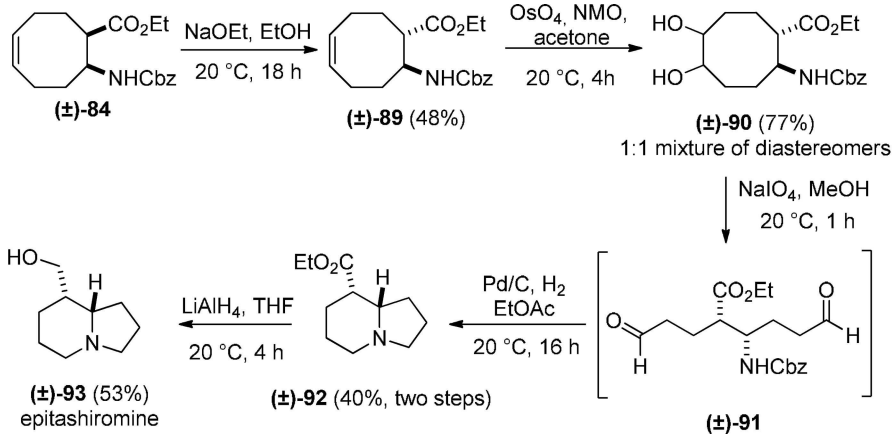
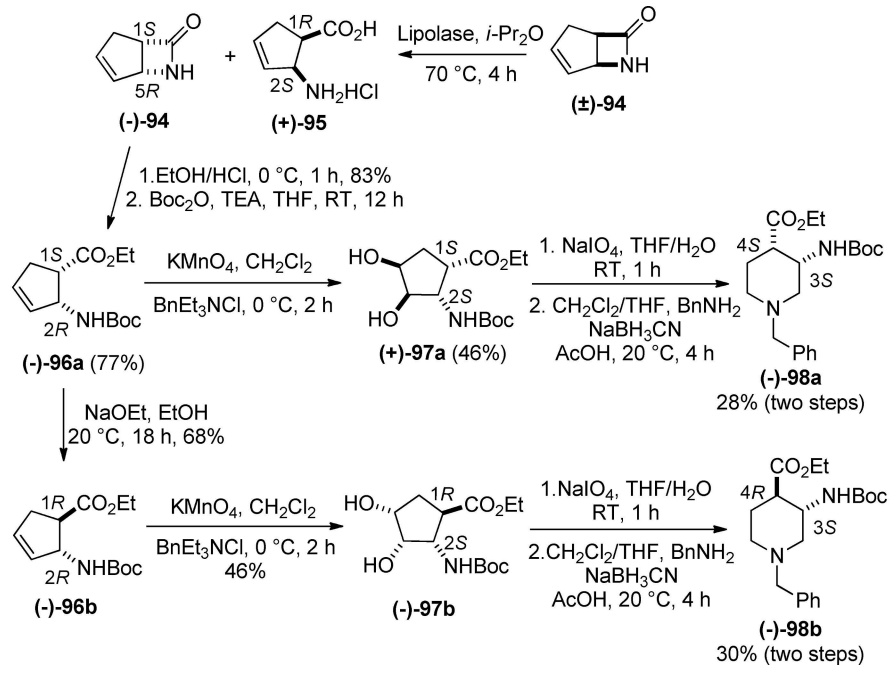


Scheme 15. Synthesis of racemic epitashiromine (±)-**93**.



Scheme 16. Synthesis of piperidine-4-carboxylates in enantiomerically pure form.

and reductive ring-closure methods provided azabicyclic β-amino ester **107** (Scheme 19).[57]

3. Synthesis of Fluorine-containing Azaheterocycles

Taking into consideration of the high biorelevance of saturated *N*-heterocycles[1–9] and organofluorine molecules,[15–17] the combination of these molecular structures is a hot topic in synthetic and medicinal chemistry. The synthetic methods based on the oxidative ring opening of various substituted cycloalkenes and unsaturated cyclic β-amino acid scaffolds followed by cyclization of the diformyl intermediates under reductive amination condition furnishes various *N*-heterocyclic motifs incorporating fluorinated entities. The stereocontrolled synthetic concept uses some fluorine-containing amines to construct novel fluorine-containing azaheterocyclic compounds.

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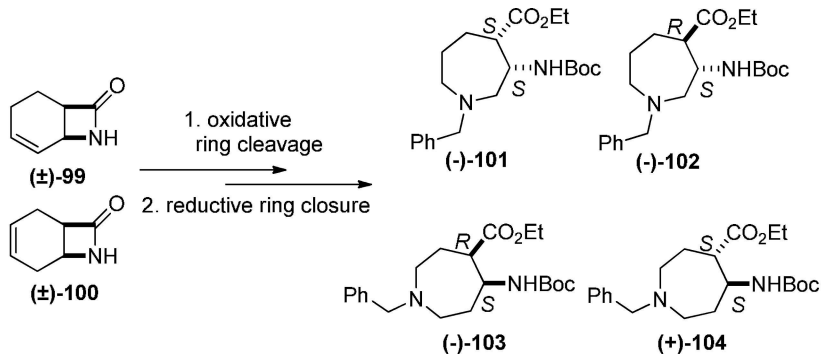
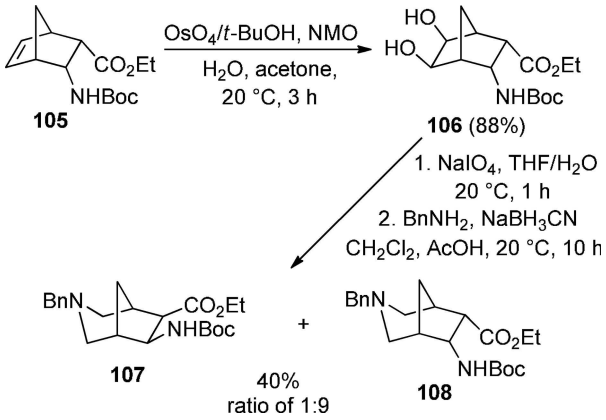
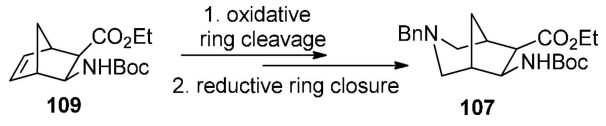


Scheme 17. Pathway to the access of regio- and stereoisomeric azepane amino esters.



Scheme 18. Synthesis of bridged azabicyclic β-amino ester stereoisomers **107** and **108**.



Scheme 19. Synthesis of *diexo* azabicyclic β-amino ester **107**.

3.1. Synthesis of Fluorine-containing Functionalized Piperidine Derivatives

The synthetic concept is based on the oxidative ring cleavage of functionalized cycloalkenes, followed by ring closure via reductive amination and, finally, ring expansion of the diformyl intermediates.

3.1.1. Synthesis of Monosubstituted Fluorine-containing Piperidines

Cyclopentenecarboxylic acid benzyl ester **110** was oxidized with NMO/OsO_4 yielding 1,2-*cis*-diol derivative **(±)-111** as a mixture of diastereoisomers in nearly 1 : 1 ratio. However, in the next oxidative ring-cleavage step, the stereocenters disappear and, accordingly, the mixture of diastereoisomers could be used in the next step without any difficulty. The oxidation of this mixture mediated by $NaIO_4$ furnished the corresponding unstable linear dialdehyde **112**, which was immediately subjected to reductive amination. The oxidative ring cleavage step was carried out with $NaIO_4$ in THF/H_2O. Reductive ring closure was accomplished with commercially available fluorine-containing amine 2,2,2-trifluoroethylamine hydrochloride (Scheme 20).[61]

Reductive ring expansion was performed with diformyl intermediate **112** and fluorine-containing amine and subsequent treatment with $NaBH_3CN$ in the presence of $NaHCO_3$ and AcOH in EtOH, resulting in the corresponding trifluoromethylated piperidine derivative **117** (Scheme 20).[61]

The synthetic approach could be applied by using other fluorine-containing building blocks to accomplish the synthesis of other fluorine-containing piperidines. Diformyl derivative **112** was treated with commercially available hydrochloride salts of 2-fluoroethylamine or 2,2-difluoromethylamine followed by reduction providing the corresponding mono- or difluorinated piperidine derivatives **(±)-118** and **(±)-119** (Scheme 21).[61]

Cbz-protected amine **120** (synthesized from commercially available cyclopent-3-enecarboxylic acid through Curtius rearrangement) underwent dihydroxylation giving a 1 : 1 mixture of vicinal diol derivatives **(±)-121**. This mixture was used in the next step without separation of the diastereomers to yield dialdehyde **122**. Then it was used further without isolation via double-reductive amination with 2,2,2-trifluoroethylamine in the presence of $NaBH_3CN$ providing trifluoromethylated piperidine **123** (Scheme 22).[61]

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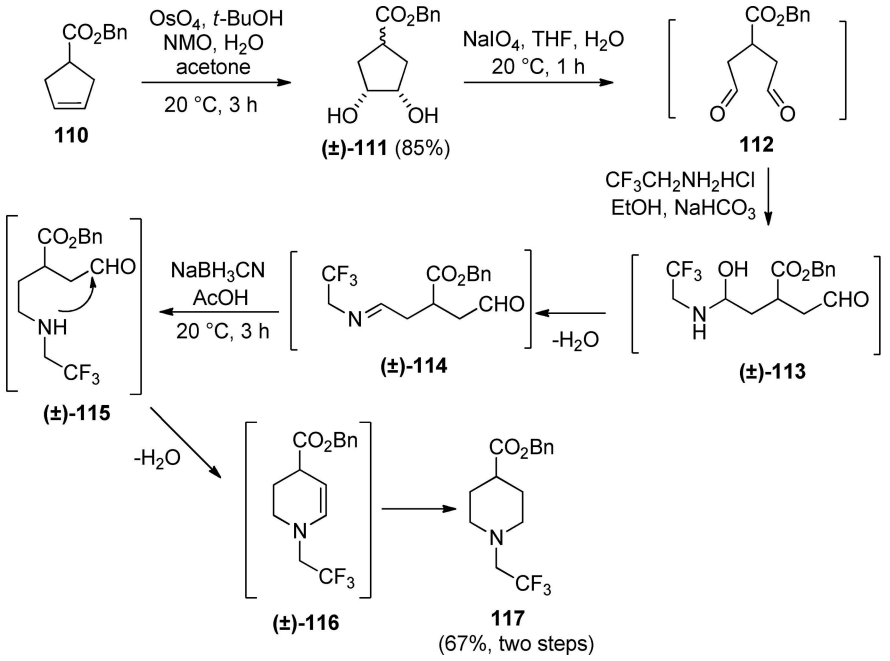
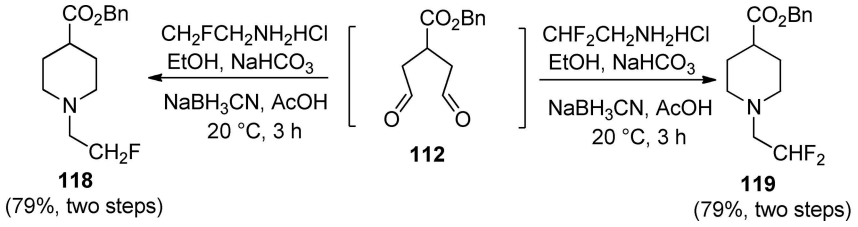
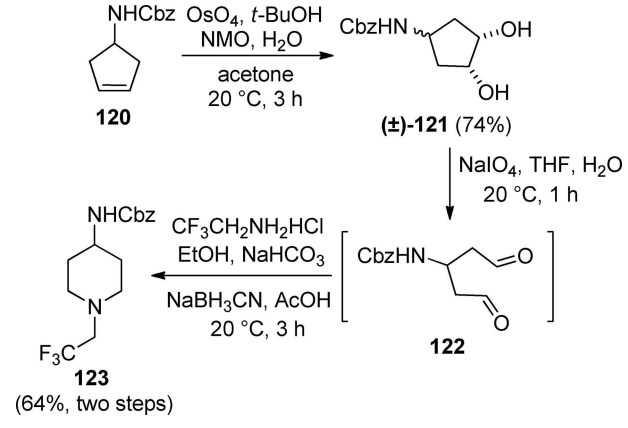


Scheme 20. Synthesis of fluorine-containing piperidine derivative **117** from benzyl cyclopentenecarboxylate.



Scheme 21. Synthesis of fluorine-containing piperidine derivatives.



Scheme 22. Synthesis of functionalized piperidine derivative **123**.

3.1.2. Synthesis of Fluorine-containing Piperidine β-amino Esters

Due to their high biological potential, *N*-heterocyclic β-amino acids are important motifs in pharmaceutical and organic chemistry.[13] A number of fluorine-containing acyclic α- and β-amino acids exhibit antitumoral or antibiotic properties.[31a,62–64] Biomolecules containing β-fluorinated or β-trifluorinated amine moieties are remarkable scaffolds in medicinal chemistry or agrochemistry.[8,25,65,66] Thus, fluorine-containing pyrrolidines and piperidines, which are present in drug molecules, have enormous interest in medicinal chemistry.[26,67–69] The application of the ring-opening/ring-closing protocol has gained importance for the synthesis of unsaturated β-amino acid derivatives as well.

Cyclopentene *cis*-β-amino esters **(±)-124a,b** were converted to dihydroxylated *cis* amino esters **(±)-126a,b** by NMO/OsO_4-mediated dihydroxylation. These were then

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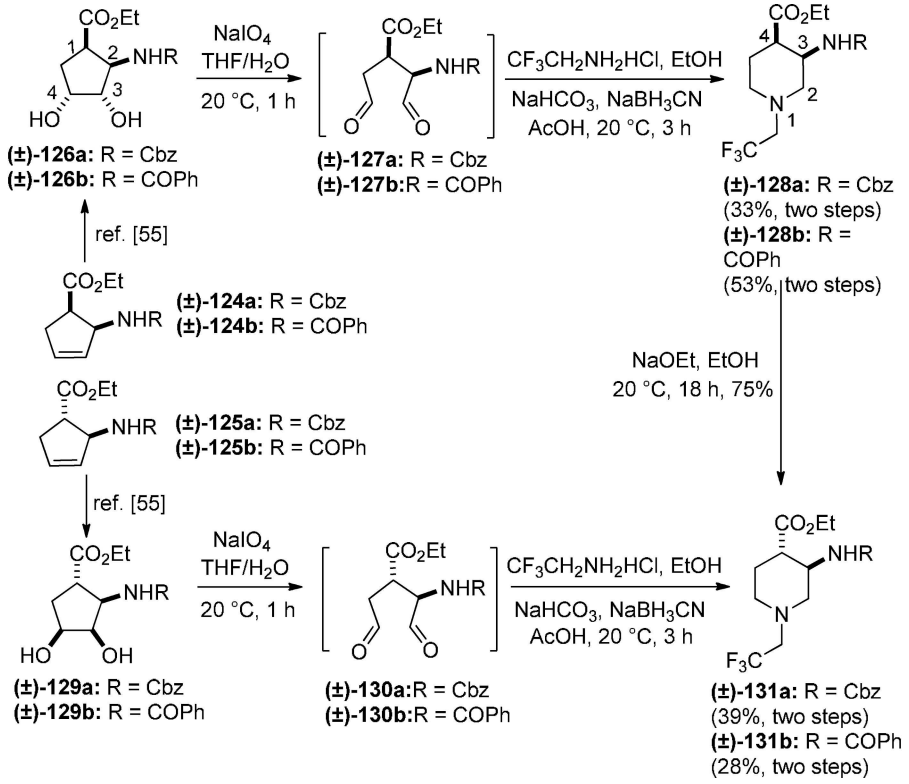

Scheme 23. Synthesis of trifluoromethylated piperdine *cis*- and *trans*-β-amino ester frameworks.

reacted with $NaIO_4$ in THF/H_2O to form the corresponding unstable open-chain dialdehyde amino esters **(±)-127a,b**.[55] Reductive amination was achieved upon treatment with commercially available 2,2,2-trifluoroethylamine hydrochloride with $NaBH_3CN$ as reducing agent in the presence of $NaHCO_3$ in EtOH. The substituents of the resulting **(±)-128a,b** β-amino esters are bonded to the C-3 and C-4 atoms of the piperidine framework in *cis* relationship (Scheme 23).[70]

The configuration of the chiral centers in **(±)-128a,b** is predetermined by the structure of the starting materials, since the C-1 and C-2 stereocenters of amino esters **(±)-124a,b** were not affected during the ring expansion procedure. Consequently, the *cis* amino ester gave the corresponding piperidine derivative with the carboxylate and carbamate/amide functions in a *cis* relative steric arrangement.[70]

Analogously, dihydroxylated amino esters **(±)-129a,b** with the ester and the *N*-protected group in a *trans* relationship were subjected to $NaIO_4$-mediated oxidative ring cleavage. The ring-closing procedure of the formed unstable diformyl intermediates **(±)-130a,b** with trifluoroethylamine and $NaBH_3CN$ afforded *trans* trifluoromethylated piperdine amino esters **(±)-131a,b** (Scheme 23). Amino esters **(±)-131a,b** were accessed via an alternative pathway by epimerization at C-4 of **(±)-128a,b** with NaOEt in EtOH with the involvement of the active methine group.[55,71–73]

By the variation of the starting fluorine-containing amine, the synthetic concept could be readily extended to prepare novel fluorine-containing piperidine β-amino acid derivatives. An illustrative example is reductive amination either with 2-fluoroethylamine hydrochloride or 2,2-difluoroethylamine hydrochloride. Thus, dialdehyde **(±)-127b** was subjecteded to reductive ring expansion on treatment with the above-mentioned commercially available fluoroamines in the presence of $NaHCO_3$ and $NaBH_3CN$, providing the corresponding monofluorinated and difluorinated piperidine β-amino esters **(±)-132** and **(±)-133** (Scheme 24).[70]

3.2. Synthesis of Fluorine-containing Functionalized Azepane Derivatives

The transformation of dialdehyde substrates could also be applied for the construction of seven-membered functionalized azaheterocyclic systems. Fluorine-containing azepane motifs are described relatively less frequently in the literature than their six-membered analogs. However, due to the important role of various functionalized counterparts in drug design, they may receive increasing attention in the future.[6,27]

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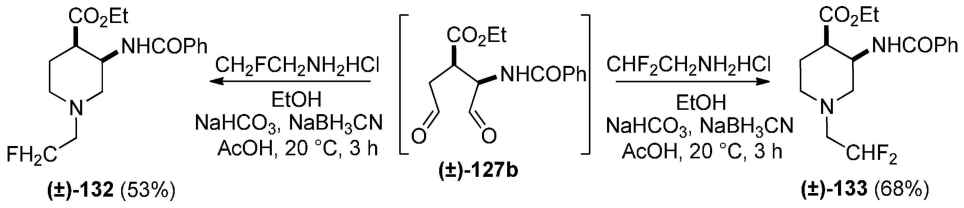
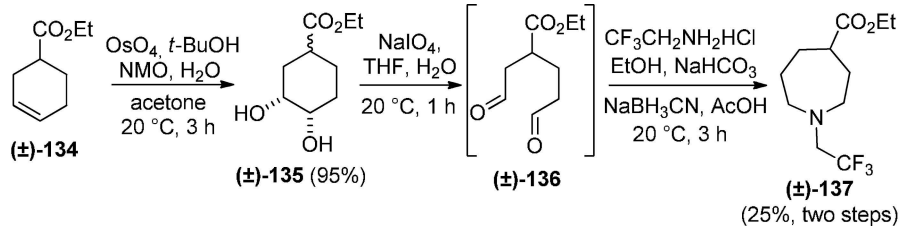
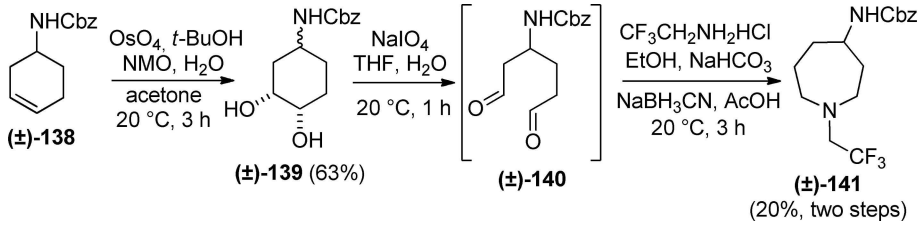


Scheme 24. Synthesis of monofluorinated and difluorinated piperidine β-amino esters **(±)-132** and **(±)-133**.



Scheme 25. Synthesis of fluorine-containing azepane derivative **(±)-137**.



Scheme 26. Synthesis of fluorine-containing azepane derivative **(±)-141**.

3.2.1. Synthesis of Monosubstituted Fluorine-containing Azepane Derivatives

Because of the increasing importance of azepane structures, the oxidative ring opening/reductive amination protocol was also extended to the preparation of trifluoromethylated azepane derivatives. Ethyl cyclohex-3-enecarboxylate **(±)-134**, a commercially available product, was first submitted to dihydroxylation to yield **(±)-135** as a mixture of diol diastereoisomers in a 1 : 1 ratio. This dihydroxylated diastereoisomer mixture could not be separated and, consequently, it was used further in the next step. Thus, ring opening with $NaIO_4$ gave the corresponding open-chain dialdehyde **(±)-136**, which was next converted on treatment with trifluorinated ethylamine into azepane derivative **(±)-137** (Scheme 25).[61]

The synthesis of a Cbz-protected fluorine-containing azepane could be accomplished by starting from cyclohexeneamine **(±)-138** prepared by the Curtius reaction. Dihydroxylation of **(±)-138** afforded diol mixture **(±)-139**, which was further converted by oxidative ring cleavage in the presence of $NaIO_4$. The unstable diformyl intermediate **(±)-140** was subjected to ring closure without isolation. The ring closure was carried out by treatment with 2,2,2-trifluroethylamine hydrochloride in EtOH, in the presence of $NaHCO_3$ and $NaBH_3CN$ and resulted in substituted azepane derivative **(±)-141** (Scheme 26). Note, that the formation of the seven-membered framework provided lower yield in comparison with those of the six-membered analogs.

3.2.2. Synthesis of Disubstituted Trifluoromethylated Azepane Derivative

Commercially available cyclohexene *cis*-diester **142** was transformed by dihydroxylation with OsO_4/NMO furnishing vicinal diol **143**. Then $NaIO_4$-mediated oxidative ring opening of **143** followed by reductive ring expansion with trifluoroethylamine gave azepane diester **145** via the corresponding dialdehyde intermediate **144** (Scheme 27).[61]

The configuration of the chiral centers in **145** is predetermined by the structure of starting material **142**, since the stereocenters were not affected during the ring-expansion procedure.

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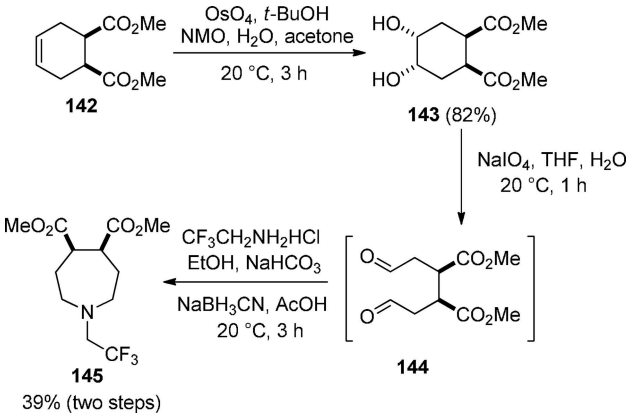


Scheme 27. Synthesis of functionalized azepane derivative **145**.

3.2.3. Synthesis of Fluorine-containing Azepane β-amino Esters

The synthetic method was applied for the stereocontrolled synthesis of trifluoromethylated azepane β-aminocarboxylates. Thus, *cis*- and *trans*-2-aminocyclohex-4-enecarboxylates **(±)-146** and **(±)-149** (derived from bicyclic β-lactam) were oxidized with NMO/OsO_4 yielding the corresponding vicinal diol derivatives **(±)-147** and **(±)-150**. In the forthcoming step, these dihydroxylated esters were transformed into *cis* and *trans* amino esters **(±)-148** and **(±)-151** possessing an azepane ring. The reaction steps are oxidative ring opening and stereocontrolled ring enlargement through reductive amination with 2,2,2-trifluoroethylamine hydrochloride and $NaBH_3CN$. In the trifluoromethylated azepane compounds, the ring nitrogen atom is in a distance of three carbon atoms from the carbamate group (Scheme 28).[70]

The preparation of the regioisomers of trifluoromethylated azepane derivatives **(±)-148** and **(±)-151** was also achieved. *N*-Cbz protected ester **(±)-152** subjected to epimerization gave derivative **(±)-155**. Dihydroxylation of the C–C double bond of these two compounds with NMO and OsO_4 provided vicinal diols **(±)-153** and **(±)-156**. In the next step, both dihydroxylated β-amino ester stereoisomers were subjected to oxidative ring opening mediated by $NaIO_4$ followed by reductive ring expansion with trifluoroethylamine hydrochloride furnishing *cis* and *trans* azepane amino esters **(±)-154** and **(±)-157** [regioisomers of **(±)-148** and **(±)-151**]. In these products, the ring nitrogen atom is located at two carbon atom distance from the carbamate group (Scheme 29).[70]

3.2.4. Synthesis of Fluorine-containing Azabicyclic Azepane Systems

Trifluoromethylated azabicyclic systems are of the high physiological importance in medicinal chemistry. *N*-Heterocyclic bicyclic α- and β-amino acids are key precursors of medicinally important alkaloids, such as anatoxin-*a*, epibatidine, epiboxidine, and their analogs (Figure 4).[57]

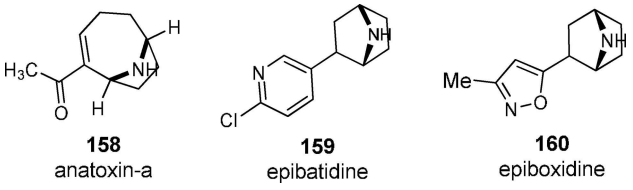
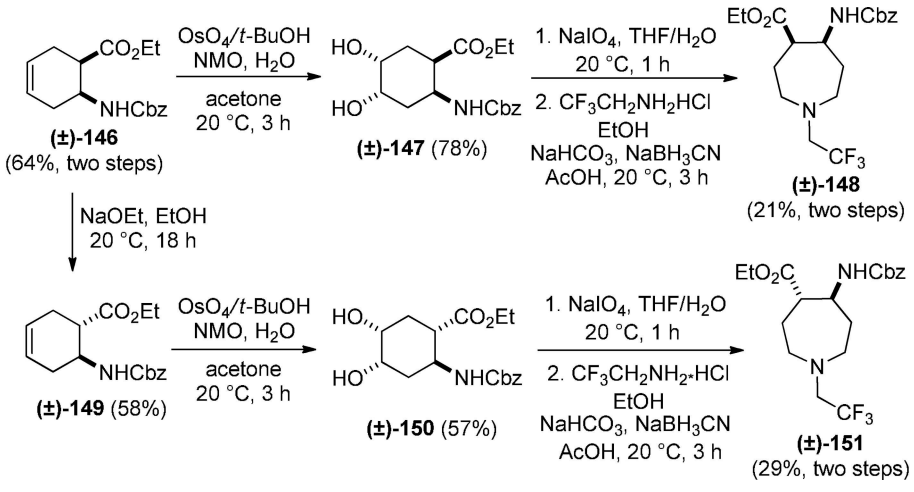


Figure 4. Medicinally important azabicyclic alkaloids.



Scheme 28. Synthesis of azepane β-amino acid stereoisomers bearing a trifluormethyl group.

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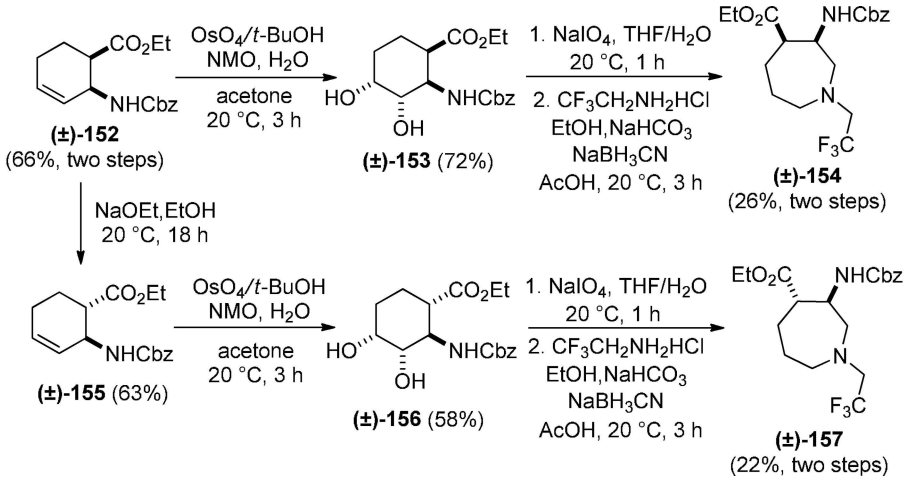
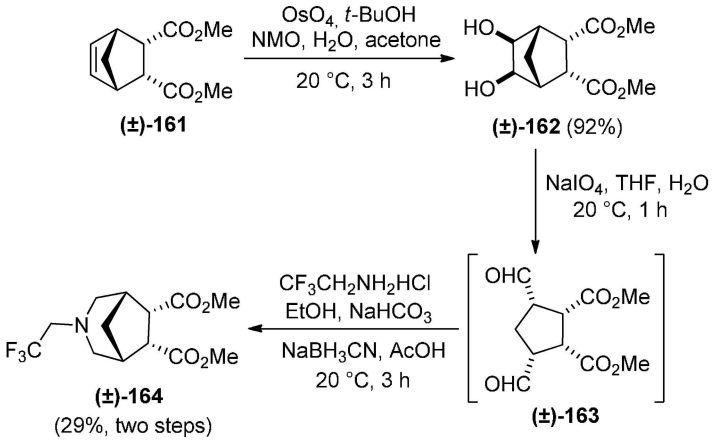


Scheme 29. Synthesis of fluorine-containing *cis* and *trans* azepane β-amino esters.



Scheme 30. Synthesis of trifluoromethyl-containing azabicyclic diester **(±)-164**.

The commercially available *diendo* norbornene dicarboxylate **(±)-161** was transformed by dihydroxylation with OsO_4 and NMO to diol derivative **(±)-162**. Subsequent oxidative ring cleavage afforded unstable diformyl intermediate **(±)-163**. The dialdehyde was transformed by reductive amination with trifluoroethylamine hydrochloride in the presence of $NaBH_3CN$ as reducing agent yielding *N*-bicyclic diester **(±)-164** (Scheme 30).[61]

N-Heterocyclic β-amino acids have gained wide attention because of their incorporation into peptide structures.[13] Commercially available *diexo* norbornene β-amino ester **(±)-165** was protected by Cbz–Cl to give **(±)-166** followed by the dihydroxylation step to form diol derivative **(±)-167** (Scheme 31).

The oxidative ring cleavage of **(±)-167** followed by reductive amination with trifluoroethylamine hydrochloride and $NaBH_3CN$ in the presence of $NaHCO_3$ and AcOH provided *N*-bicyclic amino ester **(±)-168** (Scheme 31).

The stereocontrolled synthesis of the new azabridged bicyclic β-amino ester containing the trifluoromethyl group was also performed starting from *diendo* norbornene amino ester **(±)-169**. Analogous to the synthetic approach for the *diexo* isomer, *N*-Cbz-protection of **(±)-169**, dihydroxylation, oxidative ring opening and ring enlargement across reductive amination with trifluoroethylamine hydrochloride led to compound **(±)-172**, a stereoisomer of **(±)-168** (Scheme 32).

Taking into consideration the availability of a wide range of cycloalkenes and those of functionalized primary amine building blocks, the above-described convenient method might be further applied towards the access of a series of functionalized azepane products.

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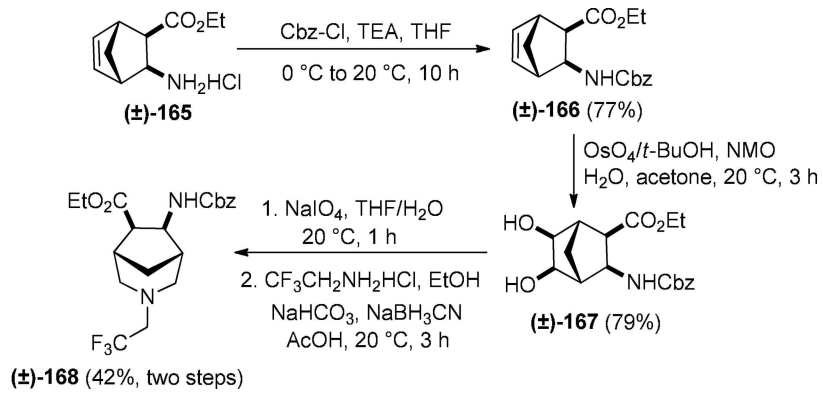
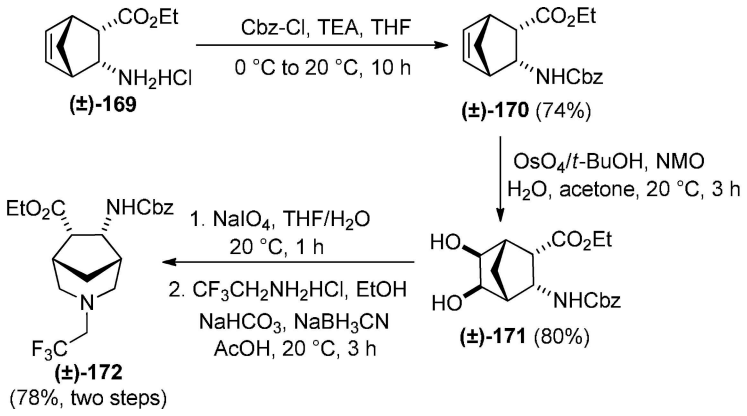


Scheme 31. Synthesis of fluorinated *N*-bicyclic β-amino ester **(±)-168**.



Scheme 32. Synthesis of fluorinated *N*-bicyclic β-amino ester **(±)-172**.

3.3. Synthesis of Fluorine-containing 1,2,3,4-tetrahydro-isoquinoline Derivatives

The 1,2,3,4-tetrahydroisoquinoline skeleton (THIQ) has main interest, because it is an important framework of a large number of natural products. Most of them, for example, alkaloids, exhibit a set of therapeutic activities. Several drugs, such as some antidiuretics, antidepressants, hallucinogens and antihypertensive agents, contain a THIQ motif.[74–79] Because of these relevant properties, many synthetic approaches towards the creation of an isoquinoline or THIQ core have been described so far.[80–87] The well-known procedures are the Pictet-Spengler, Bischer-Napieralski, and Pomeranz-Fritsch-Bobbit cyclizations, which are widely-applied synthetic methodologies to create a number of important isoquinoline alkaloids.[80]

Fluorine-containing tetrahydroisoquinoline or isoquinoline derivatives constitute an important area of fluorinated molecules either as pharmaceuticals or agrochemicals.[88–90] The preparation of fluorinated, fluoroalkylated, and fluoroarylated isoquinoline derivatives with valuable biological properties continues to be an area of high interest in medicinal chemistry. Several methods for the creation of monofluorinated, trifluoromethylated or fluoroarylated isoquinolines have been developed in recent years.[88,89,91–93]

A novel and effective procedure for the synthesis of various fluorinated 1,2,3,4-tetrahydroisoquinoline compounds has been recently reported.[94] The developed production route was a novel possibility to achieve the desired skeleton. The synthetic path was based on further extension of the transformations described above. It involves oxidative ring opening and subsequent ring closing under reductive amination conditions starting from indene and some substituted indene derivatives. Key steps are oxidative ring cleavage of the olefin bond through dihydroxylation/$NaIO_4$-mediated oxidation and subsequent ring closing with primary amines via reductive amination. Unsubstituted 1*H*-indene **173** oxidized with NMO/OsO_4 furnished the corresponding vicinal diol derivative **(±)-174**. $NaIO_4$-mediated oxidative ring opening of this dihydroxylated compound afforded dialdehyde **175**. This diformyl intermediate was further transformed with some

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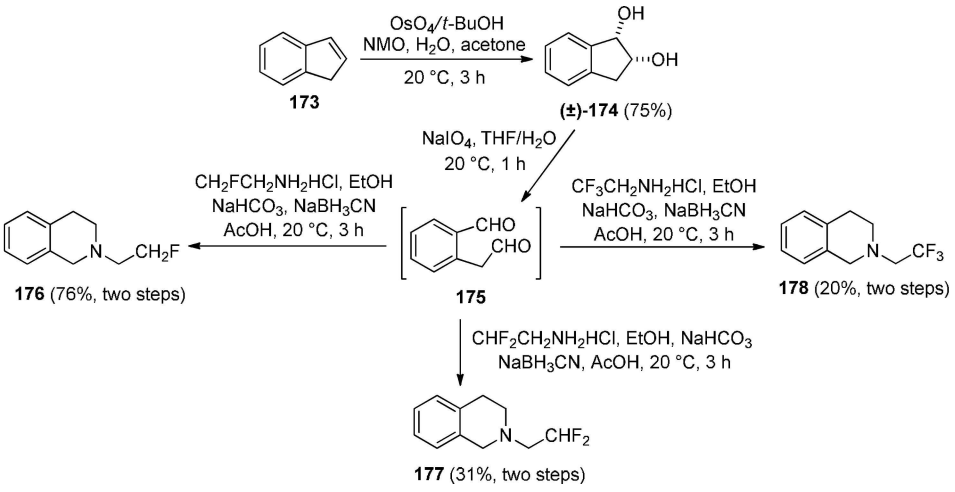
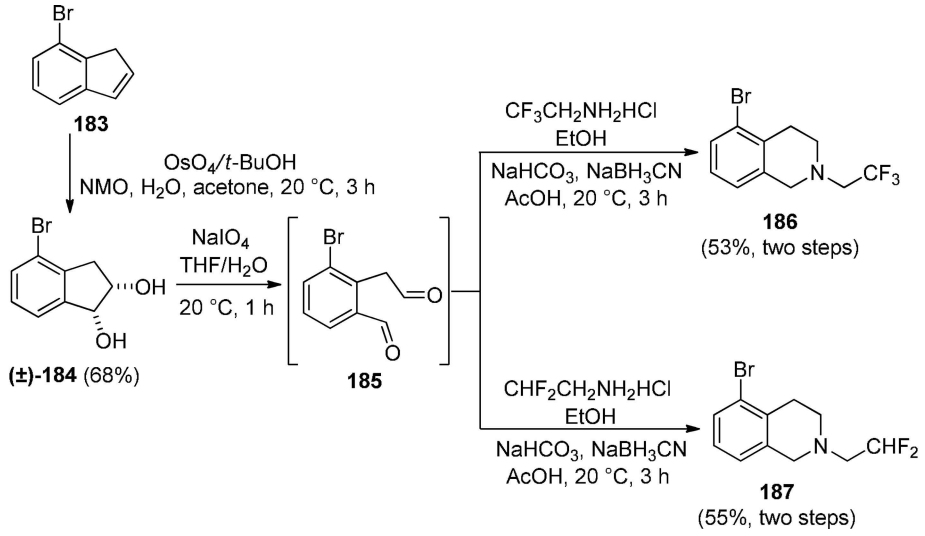


Scheme 33. Novel synthetic method for the preparation of 1,2,3,4-tetrahydrisoquinoline compounds.



Scheme 34. Synthesis of *N*-heterocyclic frameworks from 7-bromo-1*H*-indene.

commercially available fluorine-containing primary amines to provide the target compounds in two steps.

The reductive amination of **175** with 2-fluoroethylamine, 2,2-difluoroethylamine, and 2,2,2-trifluoroethylamine hydrochlorides, in the presence of $NaBH_3CN$, yielded the corresponding mono-, di- or trifluoromethyl tetrahydroisoquinoline derivatives **176**–**178** (Scheme 33). The yield of the isoquinoline derivatives decreased with the increasing number of fluorine atoms in the amine molecules.

The synthetic approach could be extended to synthesize other fluorinated and polyfluorinated tetrahydroisoquinoline products. Vicinal diol **(±)-174** subjected to oxidative ring cleavage followed by treating the resulting dialdehyde (**175**) with various commercially available trifluoromethylated or polyfluorinated amines provided the corresponding azaheterocycles (**179**–**182**) (Table 1).[94]

A procedure was described by using a 1*H*-indene derivative with substituent attached to the benzene moiety. 7-Bromo-1*H*-indene **183** in the presence of OsO_4 and NMO gave the corresponding vicinal diol **(±)-184**. Oxidative ring opening with $NaIO_4$ gave unstable diformyl-substituted intermediate **185**. Further reaction (reductive ring expansion) without isolation with both 2,2,2-trifluoroethylamine and 2,2-difluoroethylamine under reductive conditions provided the corresponding trifluorinated or difluorinated tetrahydroisoquinoline derivatives **186** and **187** (Scheme 34).

The protocol was further extended for another selected model compound, 2-methyl-1*H*-indene **188** with a substituent

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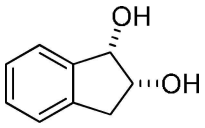
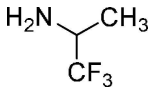
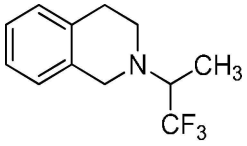
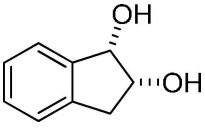
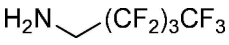
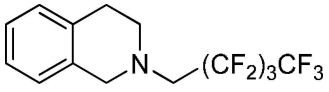
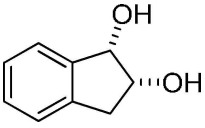
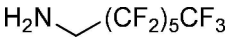
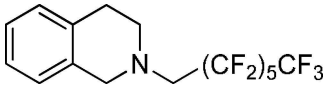
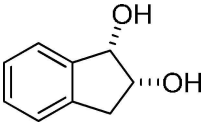
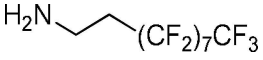
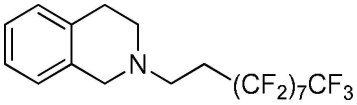
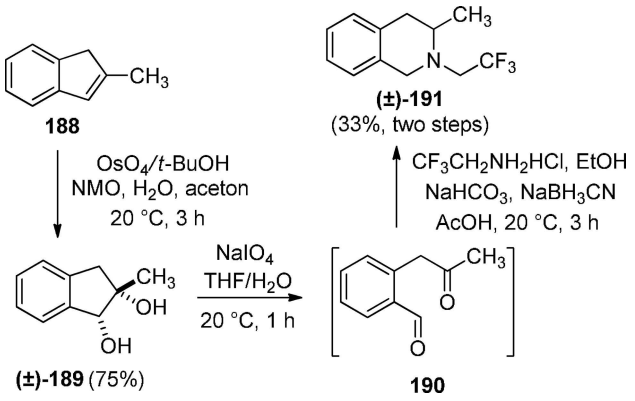
Table 1. Synthesis of fluorinated THIQ compound **179–182**.

Diol	Fluorine-containing amine	Product	Yield (%) (two steps)
		 (**179**)	34
		 (**180**)	24
		 (**181**)	53
		 (**182**)	28

at the five-membered ring of indene. Ring cleavage of diol **189** led to dicarbonyl derivative **190**, which then underwent reductive amination. Isoquinoline product **(±)-191** was created with trifluoroethyamine hydrochloride generating a chiral center (Scheme 35).[94]



Scheme 35. Synthesis of *N*-heterocyclic framework **(±)-191** from 2-methyl-1*H*-indene.

The generalization and extension of the developed pathway was demonstrated by utilizing three different primary amines: ethylamine (as the nonfluorinated counterpart of the mono-, di- or trifluoroethylamines used earlier), butylamine (as an alkylamine), and benzylamine (as an arylalkylamine). These amines produced the corresponding *N*-substituted tetrahydroisoquinoline products. The above novel synthetic route offers an alternative, simple and efficient procedure to the access of THIQ frameworks[94] as well as other saturated azaheterocycles such as γ-lactam[95] or more recently γ-amino acid derivatives.[96]

4. Summary and Outlook

Simple, efficient, cost-effective synthetic methods are of main interest for the creation of molecular libraries in drug research. Oxidative ring opening of substituted cycloalkenes and ring closing under reductive amination provide valuable three-dimensional functionalized azaheterocycles. Readily available functionalized cyclic olefins as starting materials are easily transformed to valuable substituted dialdehydes. These can be reacted further to access various types of substituted or fluorine-containing highly functionalized fluorinated regio- and stereoisomers of azaheterocycles as polysubstituted building blocks with multiple chiral centers with high chemical diversity. The protocol involves stereocontrolled synthetic methodologies, based on oxidative ring opening and fluorination of the diformyl intermediates either by using various

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primary alkylamines or fluorine-containing amines. The synthesized derivatives might be considered to be promising scaffolds for drug design. They may also function as building blocks in the synthesis of peptide research.

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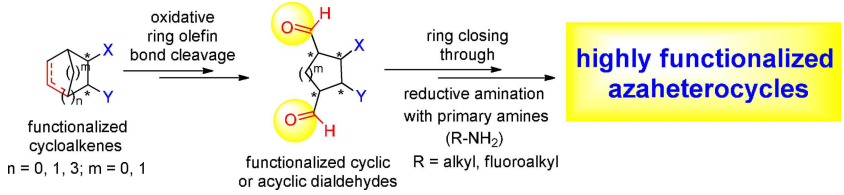

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Because of the high biorelevance of organofluorine molecules and the importance of *N*-heterocyclic compounds, selective stereocontrolled synthetic methodologies to the access of new fluorine-containing saturated azaheterocycles are considered to be a hot topic of research. This account summarizes the synthesis of functionalized and fluorine-containing saturated azaheterocyclic derivatives starting from functionalized cycloalkenes and based on oxidative ring opening of diol intermediates followed by ring expansion under reductive amination.