Stereocontrolled synthesis of functionalized fluorine-containing *N*-heterocycles through oxidative ring opening/ring closure with reductive amination

PhD Thesis

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PUBLICATION LIST

Papers related to the thesis:

I. **Ábrahámi, R. A.**; Kiss, L.; Barrio, P.; Fülöp, F.:
Synthesis of fluorinated piperidine and azepane β-Amino acid derivatives
Tetrahedron **2016**, *72*, 7526-7535.

II. **Ábrahámi, R. A.**:
Fluortartalmú piperidin- és azepánvázas β-aminosavszármazékok szintézisei
Magyar Kémikusok Lapja 2017/4. 106-108.

III. **Ábrahámi, R. A.**; Kiss, L.; Fustero, S.; Fülöp, F.:
Functionalized dialdehydes as promising scaffolds for access to heterocycles and β-amino acids: Synthesis of fluorinated piperidine and azepane derivatives
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IV. **Ábrahámi, R. A.**; Fustero, S.; Fülöp, F.; Kiss, L.:
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V. Kiss, L.; Forró, E.; Orsy Gy.; **Ábrahámi, R. A.**; Fülöp, F.:
Stereo- and Regiocontrolled Syntheses of Exomethylenic Cyclohexane -Amino Acid Derivatives
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Szeged, Hungary, 9. Nov, 2017, oral presentation

List of abbreviations:

ADAR: aza-Diels–Alder reaction

Boc: *tert*-butoxycarbonyl

Cbz: bezyloxycarbonyl

CSI: chlorosulfonyl isocyanate

DPPA: diphenilphosphoryl azide

LAH: lithium aluminium hydride

MAAs: morpholine amino acids

***m*-CPBA:** 3-chloroperbenzoic acid

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

PMP: *p*-methoxyphenyl

SAA: sugar amino acid

TEA: triethylamine

THF: tetrahydrofuran

THIQ: 1,2,3,4-tetrahydroisoquinoline

Tos: *p*-toluenesulfonyl

1. INTRODUCTION AND AIMS

Fluorine-containing organic scaffolds are very rare in nature, but they have received significant interest in many different research fields. The replacement of hydrogen atom by fluorine or a fluorinated group could furnish biomolecules with unique features. The incorporation of fluorine in 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, and this number is expected to increase in years to come [1–3].

Saturated *N*-heterocycles have increasing attention in pharmaceutical and organic chemistry. A large number of nitrogen-containing saturated cyclic amines have been used in clinics as antibiotics, analgesics, antidepressants, anticancer, anti-HIV and anti-HCV agents[4–6]. 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 the ubiquity of nitrogen heterocycles[7–12].

The synthesis of fluorine-containing molecular entities and fluorination are two main research topics 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 cycloalkene derivatives with diverse functionalities. Two different synthetic approaches have been applied to furnish a molecule with fluorine. Direct fluorination means a late-stage exchange by using fluorinating reagents (Figure 1)[2,13–24].

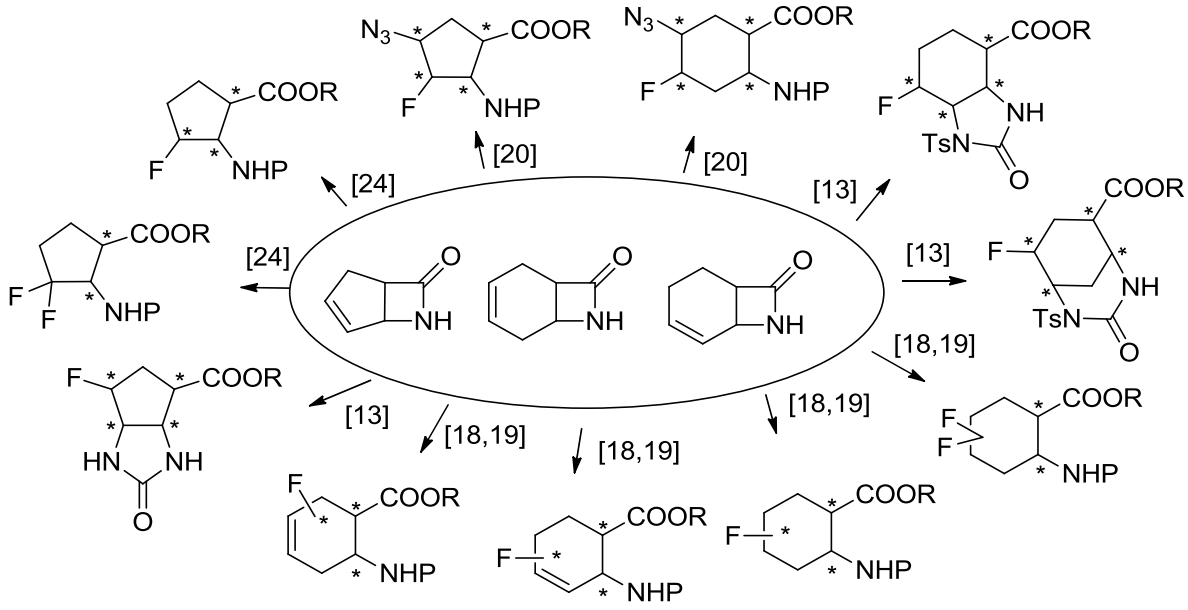


Figure 1. Examples of the fluorination of β-amino acid derivatives

On the other hand, application of fluorinated compounds like fluorine-containing amines could offer a way for the access of fluorine-containing *N*-heterocycles.

Due to the high biorelevance of organofluorine scaffolds and the importance of *N*-heterocyclic compounds, our aim was to develop a novel and efficient stereocontrolled procedure for the access of new fluorine-containing saturated *N*-heterocycles. The introduction of a fluorine atom into the structure of a molecule started with the dihydroxylation of the olefinic bond of various cycloalkane β-amino acids or β-lactams, followed by $NaIO_4$-mediated ring cleavage of the diol intermediate and ring expansion with reductive amination, resulting in novel fluorine-containing *N*-heterocycles (Figure 2).

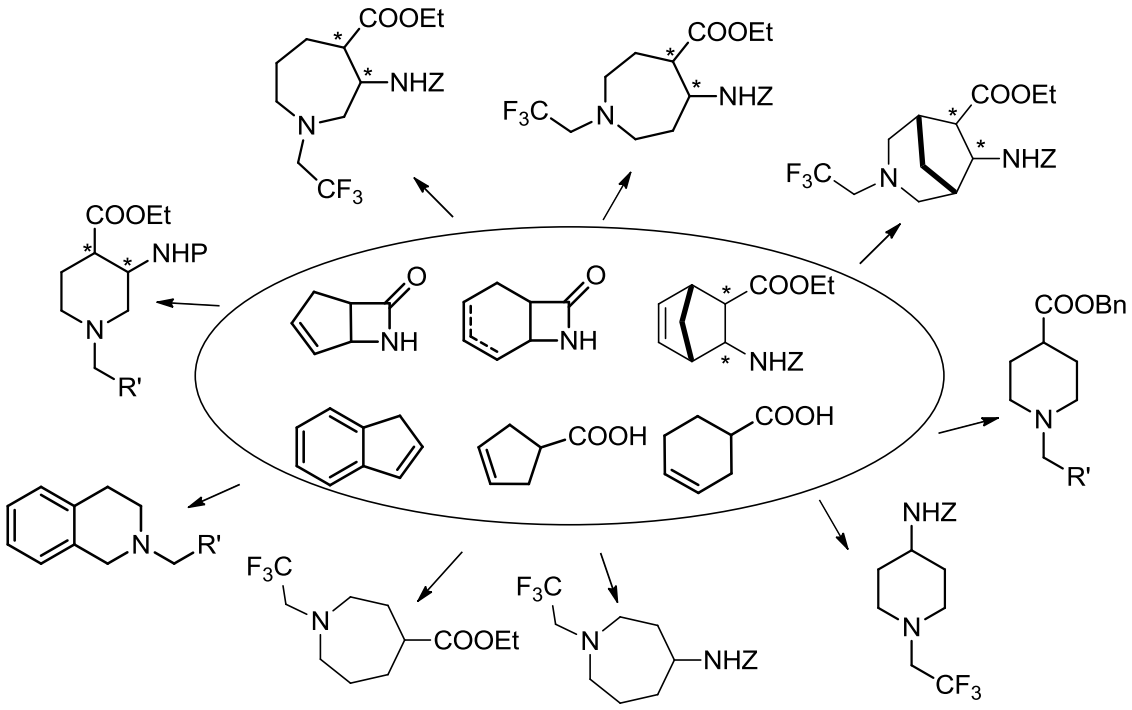


Figure 2. Synthetic processes explored in the present PhD work

2. LITERATURE BACKGROUND

2.1. Importance of fluorination and fluorinated saturated *N*-heterocycles

Fluorinated molecules are very uncommon in nature. Fluorine has rather unique properties and the incorporation of fluorine into the structure of an organic molecule can generate unique changes, which cannot be attained by the use of any other element[2,3]. It has great interest because a large number of fluorine-containing structures are widely applied in different areas like material sciences or medicinal and pharmaceutical chemistry as well as agrochemistry[25–28]. The size of a fluorine atom is very similar to that of hydrogen and fluorine has the highest electronegativity in the periodic table. This could lead to increasing lipophilicity and stability, and could 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 could give special characteristics to the structure with at least one fluorine atom. Due to these unique properties, it is a routine 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 3)[1,2,29–32].

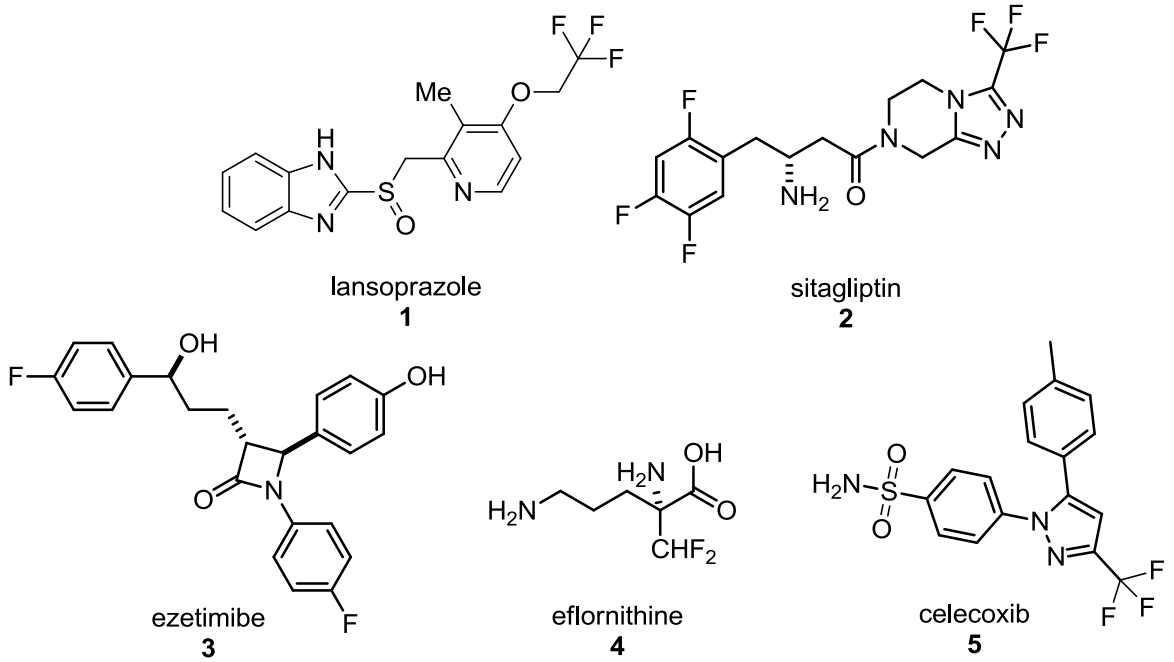


Figure 3. Important representatives of fluorine-containing market leader drugs

Saturated *N*-heterocycles are very prominent building blocks in synthetic bioactive products and medicinal compounds. Five-, six-, and seven-membered rings are the most common structural units. They are increasingly attractive scaffolds in the production of new drugs. Scientists prefer to use saturated building blocks, especially saturated *N*-heterocycles in the development of new pharmaceuticals[4,6]. Figure 4 shows some representative *N*-heterocyclic structures with biological relevance[33–37].

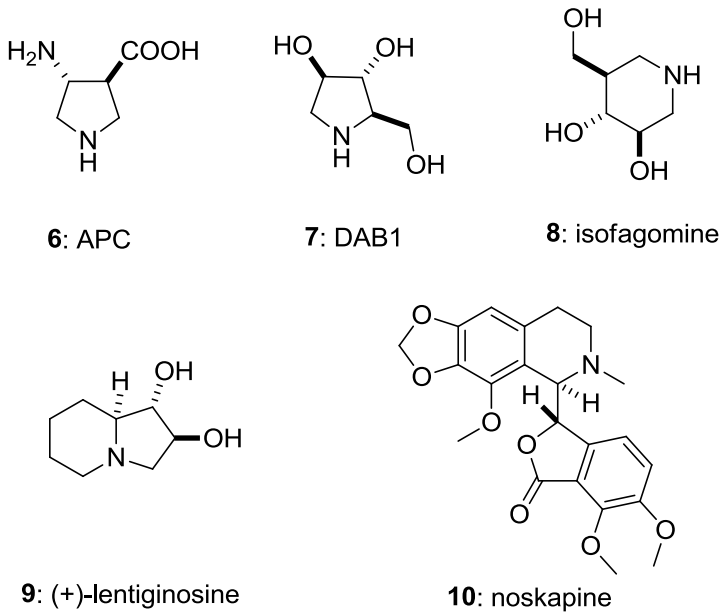


Figure 4: Some *N*-heterocyclic compounds with biological relevance

Among organofluorine compounds of high biorelevance, saturated *N*-heterocyclic scaffolds with fluorine has a special interest. Not surprisingly, the changing of an azaheterocycle motif into a fluorine-containing one may improve the metabolic stability or reduce basicity, thereby providing better bioavailability to a certain molecule. Fluorinated piperidines and their derivatives have shown promising biological activity because of the increased lipophilicity. β-Fluoramine and trifluoroamine moieties are also present in various fluorine-containing derivatives with biological importance (Figure 5)[7,9,10].

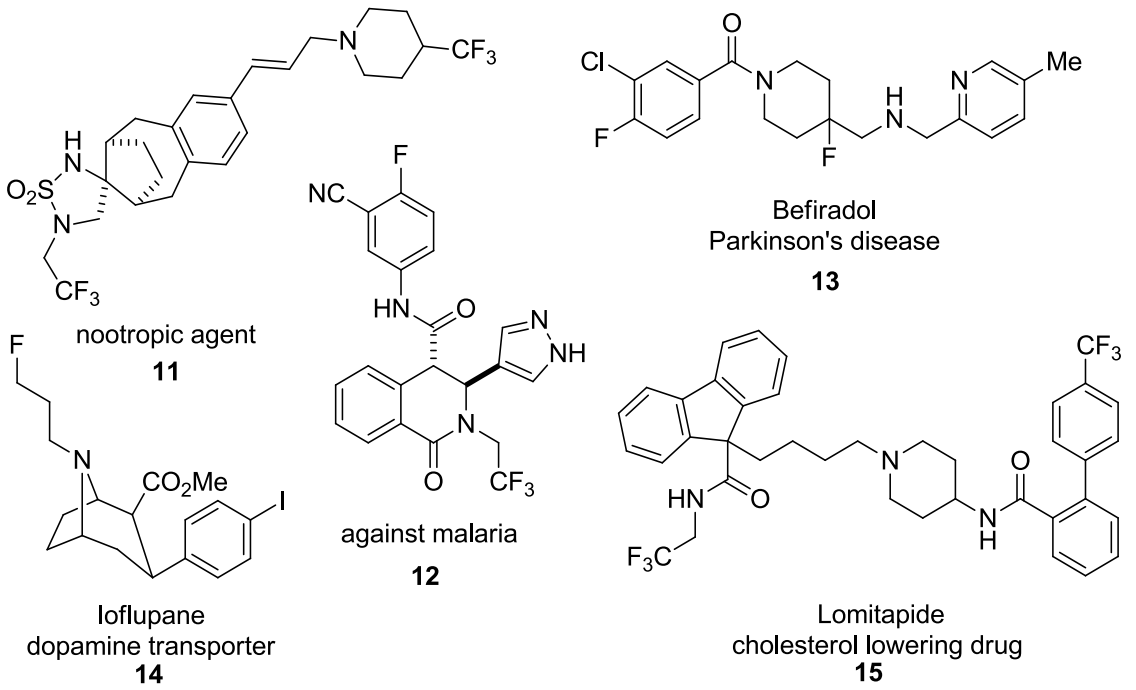


Figure 5. Some biologically important fluorine-containing *N*-heterocyclic derivatives

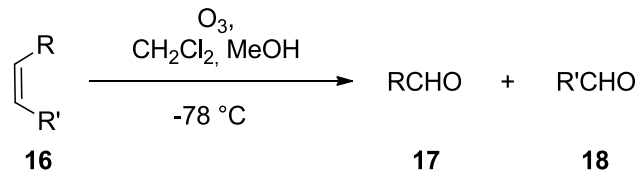
There has been a great interest in fluorine-containing pyrrolidines or piperidines in medicinal chemistry, which are present in various drugs[38]. Although fluorinated azepanes are much less mentioned in the literature, they may receive wide attention in pharmaceutical design in the future[9,39]. It is well-known that fluorine-containing tetrahydroisoquinoline derivatives, *N*-bridged bicyclic scaffolds, and other *N*-fluoroalkylated molecular entities have great biological relevance[40–42].

2.2. Synthesis of saturated *N*-heterocycles from dialdehyde compounds

A large number of synthetic pathways have been developed to obtain azaheterocycles including aziridines, azetidines, pyrrolidines, piperidines or azepanes[43–47]. In organic and pharmaceutical chemistry the creation of novel *N*-heterocycles is a well-explored area. However, due to the increasing interest of these scaffolds, the development of new and efficient protocols for *N*-heterocycles is an enduring challenge in modern chemistry[6].

2.2.1. Oxidative ring opening

The oxidative ring cleavage of olefinic compounds is a widely applied important transformation in organic chemistry to achieve the corresponding carbonyl compounds (aldehydes, ketones or acids). Two main methodologies are known in the literature for oxidative ring opening: either through ozonolysis of alkenes or cleavage of vicinal diols[48-56]. Both are useful methods to prepare carbonyl compounds, which have great interest. A standard pathway to access oxidative ring opening directly is ozonolysis of olefins, illustrated in Scheme 1[51].



Scheme 1. Olefinic bond cleavage by ozonolysis

An alternative pathway involves the oxidation of the olefinic bond resulting in 1,2-diols, which is followed by cleavage with $NaIO_4$ or other oxidizing agents. The dialdehyde produced by the reaction of a *cis*-diol may react further to higher oxidation products. OsO_4 is a commonly used, reliable and widely applied reagent for the oxidation of alkenes into vicinal diol compounds. Since it is toxic and expensive, a catalytic amount is used in the presence of some oxidizing agent[54]. Milas and co-workers were the first to show that the oxidation of alkenes could be catalyzed with osmium tetroxide with the use of hydrogen peroxide[52]. The latter was replaced by some other oxidizing agents like *tert*-butyl hydroperoxide, oxygen, sodium hypochlorite, and amine *N*-oxides[53]. Amine *N*-oxides, such as *N*-methylmorpholine *N*-oxide (NMO), as co-oxidants are able to reoxidize the Os(VI) intermediate species to an Os(VIII) species. Thanks to this property, it is satisfactory to use only a catalytic amount of OsO_4 (Figure 6). The *cis* hydroxylation of olefins with NMO provided better yields than hydrogen peroxide or metal chloride reagents[53].

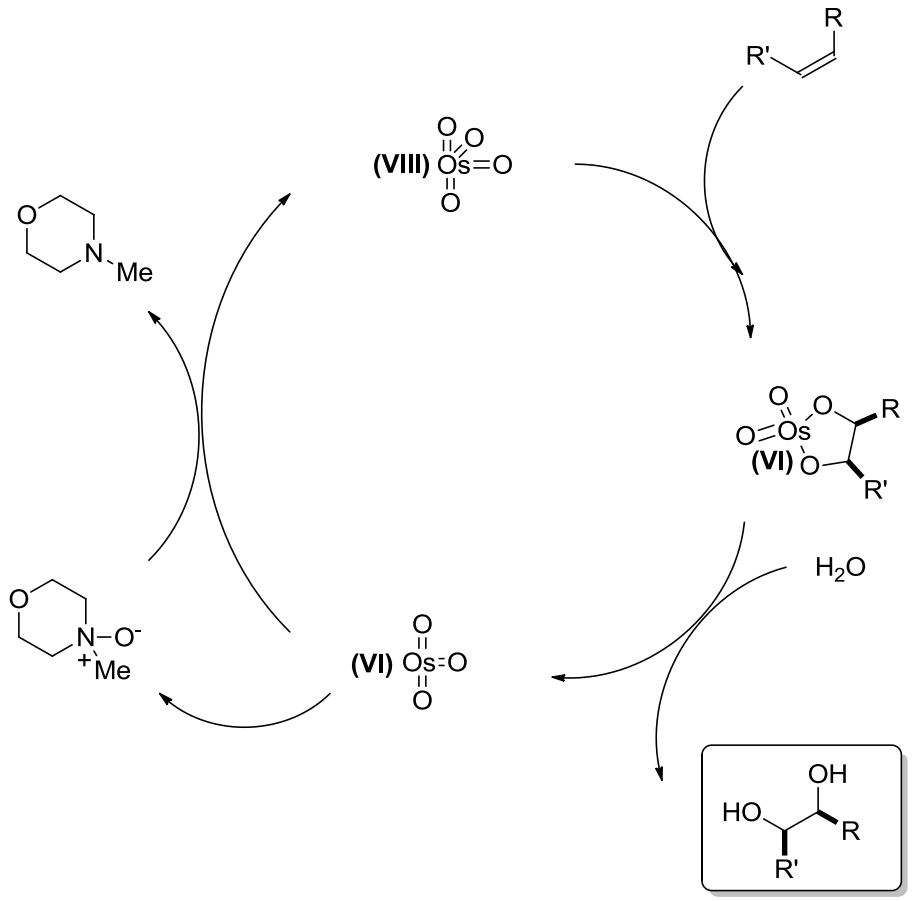
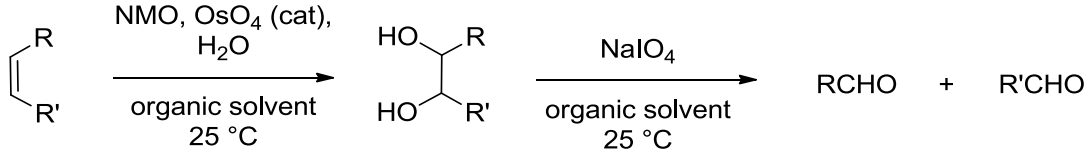


Figure 6. Mechanism of dihydroxylation with NMO/OsO_4

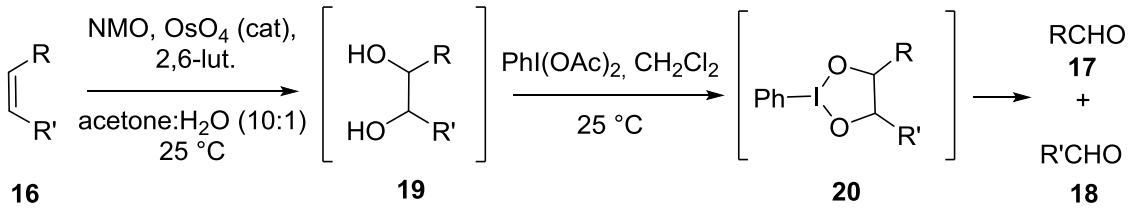
Upjohn and co-workers applied a two-step procedure for the cleavage of the olefinic bond. First OsO_4/NMO produced the vicinal diol intermediate, which underwent further oxidation by the treatment of sodium periodate ($NaIO_4$) giving carbonyl compounds (Scheme 2)[51,54].



Scheme 2. Upjohn dihydroxylation and diol cleavage

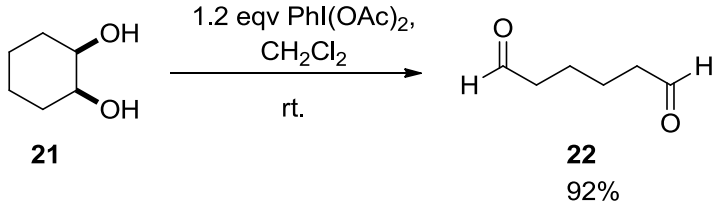
This procedure was improved with the use of oxone with OsO_4 (Borhan and co-workers)[48] or *m*-CPBA, HBF_4 and ArI (Ochiai et *al.*)[55]. However, these processes have limitations because under the strong conditions used both lead to carboxylic acids. Phenyliodiacetate [$PhI(OAc)_2$] is an efficient and selective reagent to cleave 1,2-diol

derivatives providing aldehydes and ketones. This protocol could offer a practical one-pot synthetic method as summarized in Scheme 3[51].



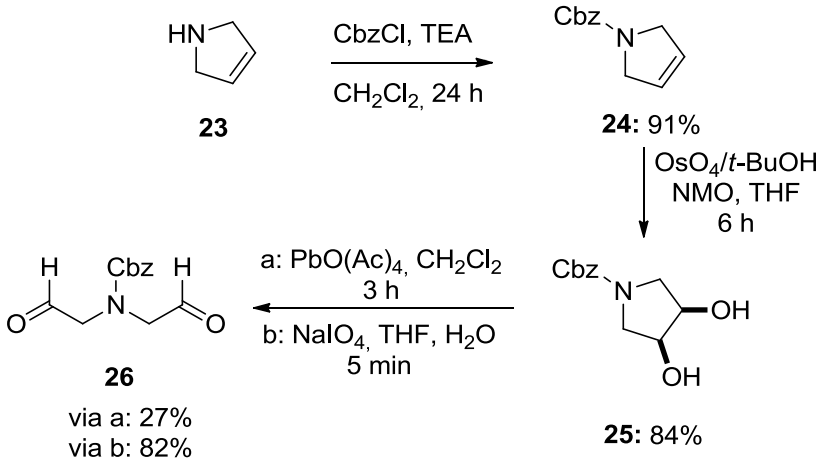
Scheme 3. One-pot cleavage of vicinal diols by $PhI(OAc)_2$

Functionalized dialdehydes are important substrates, which could be transformed into various substituted alicyclic, heterocyclic or polysubstituted products. The synthetic approaches described above provide an opportunity for the ring opening of several cycloalkene derivatives with C–C double bond in the ring, resulting in 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. Scheme 4 shows a representative example of their ring-cleavage protocol[51].



Scheme 4. Synthesis of a linear dialdehyde by oxidative ring cleavage

Fricke et *al*. reported the synthesis of iminodiacetaldehyde derivatives from the corresponding 3,4-dihydroxypyrrolidines. The transformation was based on dihydroxylation followed by an oxidative ring cleavage reaction by the treatment of lead(IV) acetate [$Pb(OAc)_4$] or sodium periodate in aqueous solution (Scheme 5)[56]. The products formed represent promising building blocks, as pharmacologically active agents, especially *N*-heterocyclic diols[56].

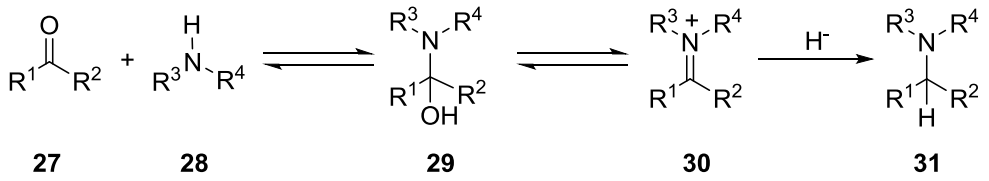


Scheme 5. Synthesis of iminodiacetaldehyde **26**

This oxidation cascade, which involves a dihydroxylation step and oxidative ring cleavage, resulting in aldehydes, ketones, acids or dialdehydes, could supply promising intermediates for the synthesis of pharmacologically valuable scaffolds.

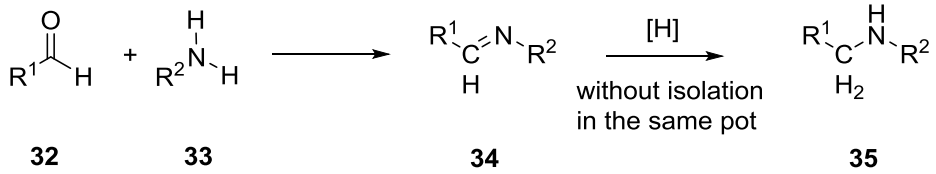
2.2.2. Reductive amination

Since amines represent a large and important class of pharmaceuticals and agrochemicals, the preparation of C–N bonds has a great interest in organic chemistry. There are several methodologies, but reductive amination is the most impressive pathway for the fabrication of a carbon–nitrogen bond in chemical industry[57]. This method, also called reductive alkylation, involves the condensation reaction of a carbonyl compound (aldehydes, ketones) with ammonia, primary or secondary amines in the presence of a reducing agent[58,59]. The first step of the reaction provides a carbinolamine by the condensation of a carbonyl compound and an amine. This intermediate undergoes reversible dehydration to an iminium ion, what is reduced to the amine through an irreversible hydride addition. The pathway is illustrated in Scheme 6[58].



Scheme 6. The reaction mechanism of reductive alkylation/amination

There are two different ways to carry out reductive alkylations. In indirect reductive aminations, the intermediate imines are isolated, and then they undergo reduction in the second step to achieve the corresponding amines. A one-pot reaction is also known, where the imines are not separated; nevertheless, a reducing agent is added and the reaction leads to the required amine compounds. This direct path is preferable as far as efficiency is concerned since it offers an easy access to the amines, which are important products or building blocks (Scheme 7)[59,60].



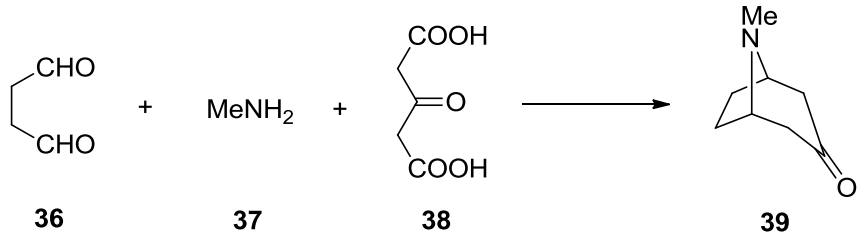
Scheme 7. Pathway of the direct (one pot) reductive amination

Reductive amination of the carbonyl compounds is traditionally carried out with the use of a stoichiometric amount of reducing reagent. The commonly used agents for the reduction of carbon–nitrogen double bonds are metal hydrides like $NaBH_4$, $NaBH_3CN$ or $LiAlH_4$, molecular hydrogen, formates, silanes[57,59]. Sodium cyanoborohydride is a widely-used popular reagent to reduce imines. Due to the electron-withdrawing effect of the cyanide substituent, it can provide mild conditions for the reduction. According to Borch and co-workers, the optimal pH for the reduction is between 5 and 7, and a wide range of solvents could serve as a soluble hydride source[58,61]. The introduction of a nitrogen atom into an alkyl group has great potential in the synthesis of *N*-containing heterocycles or building blocks in pharmaceutical chemistry.

2.2.3. Transformation of linear dialdehydes into *N*-heterocycles

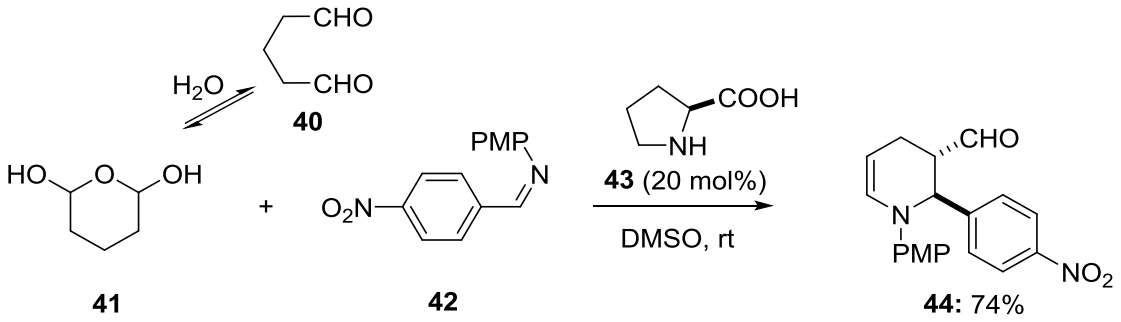
Linear dialdehydes such as succinaldehyde or glutaraldehyde are promising substrates for a number of transformations like aldol, Mannich, Michael and Henry reactions. These dialdehydes are often used for the rapid synthesis of important skeletons with medium-sized carbo- and hetero-cyclic ring systems[62].

In 1917 Sir Robinson applied a novel thinking in his synthetic method and produced tropinone **39** in a one-pot reaction, using succinaldehyde **36**, amine **37** and acetone dicarboxylic acid **38**, presented in Scheme 8[62,63].



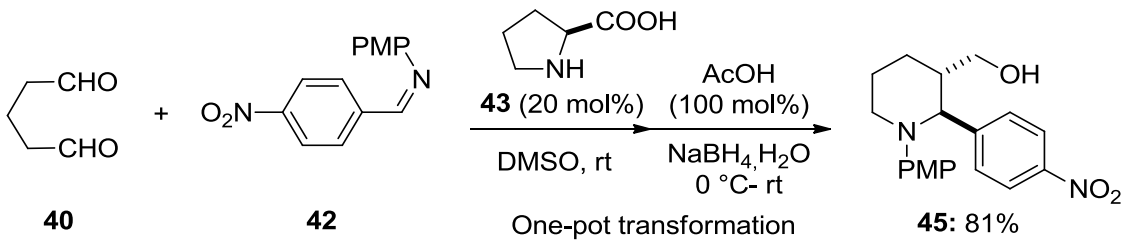
Scheme 8. Total synthesis of tropinone from succinaldehyde

Xu and co-workers reported a diastereo- and enantioselective synthetic method by the application of glutaraldehyde **40** to produce *N*-heterocycles like tetrahydropyridines using amine catalysis. A Mannich-type reaction was developed, which involved **41** formed in intramolecular aqueous cyclization of glutaraldehyde, *N*-PMP aldimine **42** and proline **43** resulting in the corresponding tetrahydropyridine product **44** (Scheme 9)[64].



Scheme 9. Organocatalytic transformation of glutaraldehyde giving optically active tetrahydropyridines

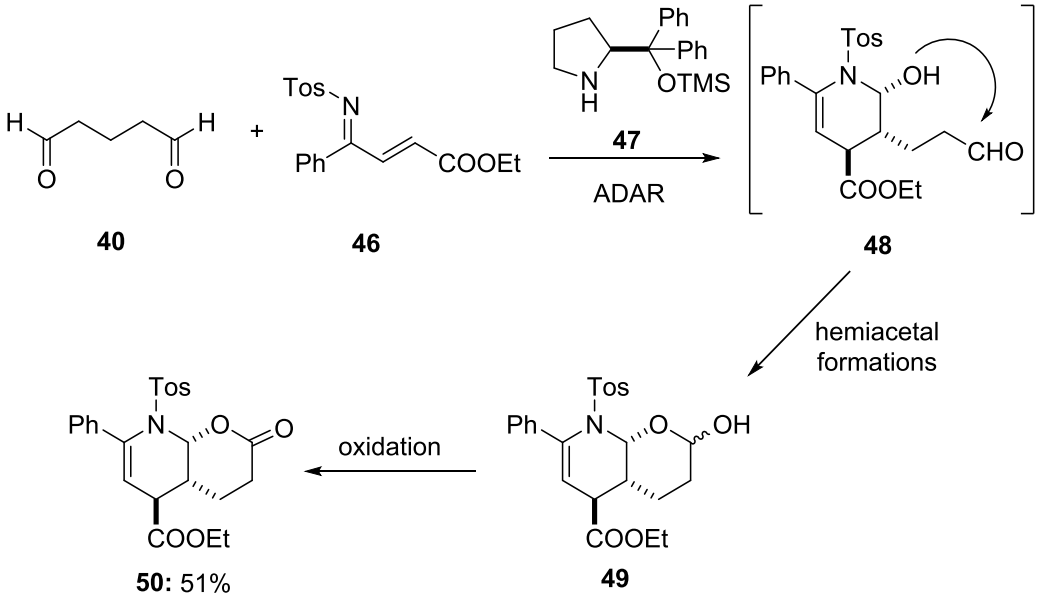
Kumar et *al*. developed an extension of the above-described procedure. Cycloaddition of glutaraldehyde **40** gave asymmetric 2,3-disubstituted piperidine scaffold **45** with reduction in the last step (Scheme 10)[65].



Scheme 10. Cycloaddition for piperidine synthesis

Chen and co-workers published a synthetic method for the synthesis of azaheterocycles starting with aliphatic dialdehyde. The key steps of the synthetic path are

an inverse electron demand aza-Diels–Alder reaction (ADAR) followed by an intramolecular hemiketal formation–oxidation reaction of the widely available *N*-Tos-1-aza-1,3-butadiene **46** and linear dialdehydes (for example glutaraldehyde **40**). This multi-step process results in lactone[2,3-*b*]piperidine derivative **50** (Scheme 11)[66].

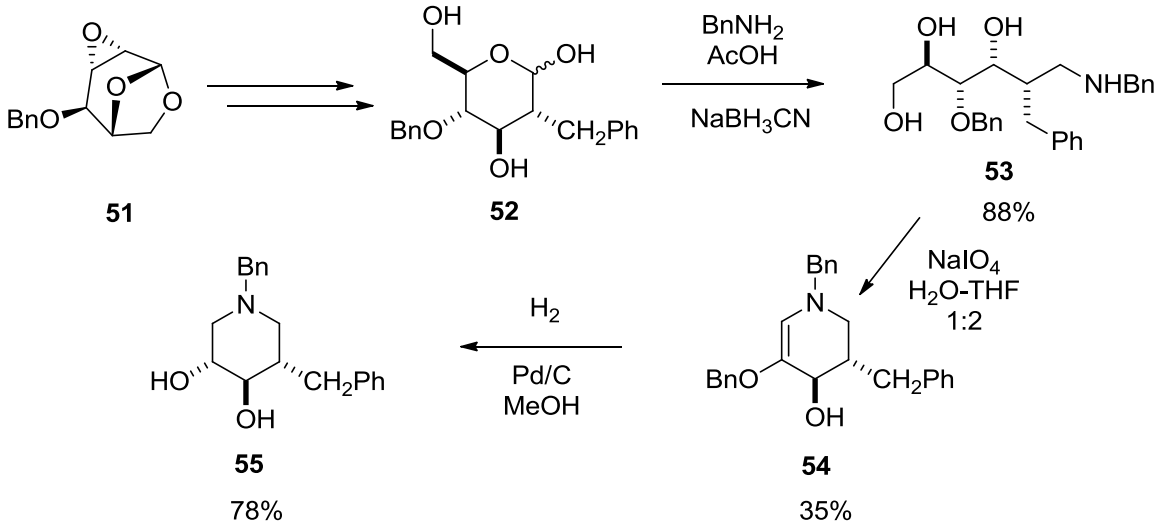


Scheme 11. Synthesis of a lactone[2,3-*b*]piperidine derivative via ADAR

2.2.4. Transformation of dialdehyde derivatives across reductive amination

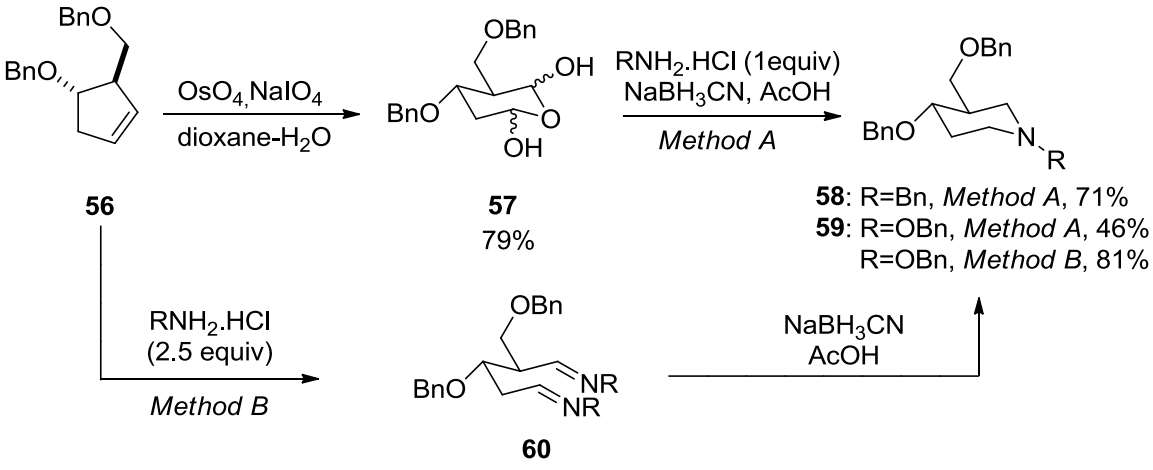
A number of research groups have published methods for the synthesis of *N*-heterocycles by the application of ring closing of linear dialdehydes under reductive amination[34,35,67–76].

Bols and co-workers developed a novel method for the access of isofagomine **8** and substituted hydroxypiperidines. The synthetic route started from epoxide **51**, which is easily accessible from starch. After a two-step transformation, the resulting hemiacetal **52** was submitted to reductive amination by using benzylamine. In the next step, periodate cleavage reaction gave enamine **54**. The reduction of **54** afforded *trans* isomer **55** in 78% yield (Scheme 12)[34].



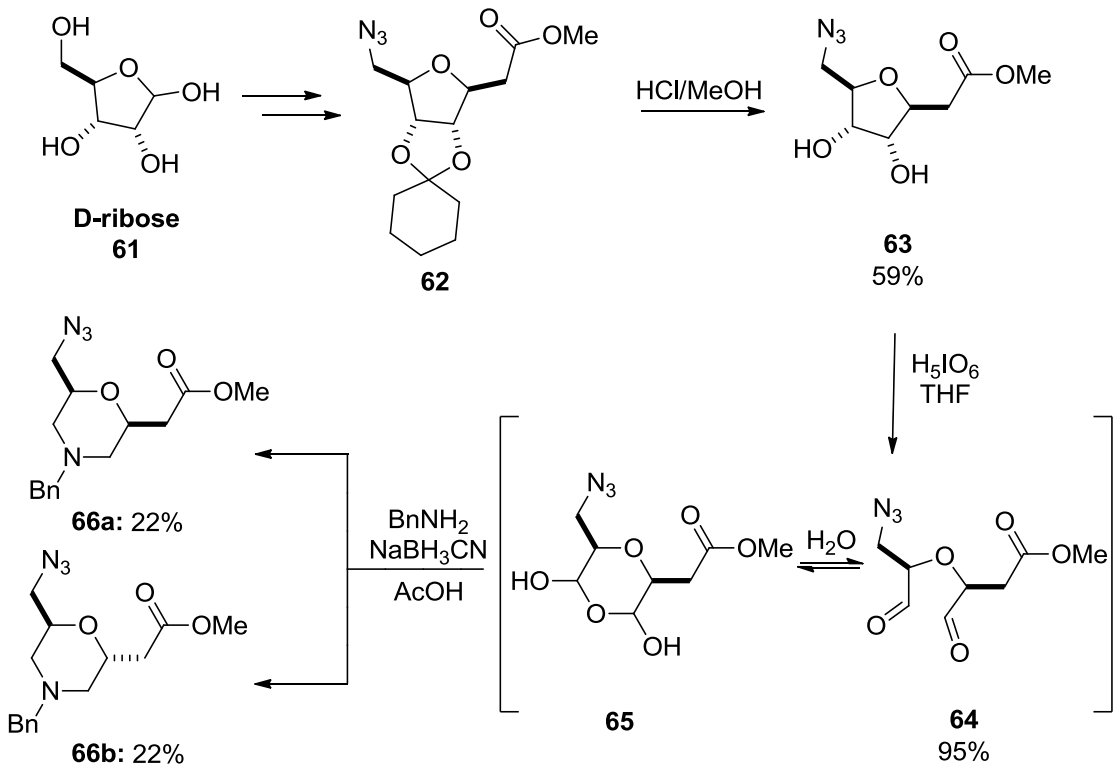
Scheme 12. Synthesis of substituted hydroxypiperidines

Chrick and co-workers developed a novel synthetic method for the access of polyhydroxylated *N*-alkoxypiperidines, which was based on ring closing of 1,5-dialdehydes by double-reductive amination. The oxidative ring opening of olefin **56** was carried out by the classical method with $OsO_4/NaIO_4$ in dioxane and water resulting in cyclic hydrate **57** in diastereomeric forms. In the next step, double-reductive amination using benzylamine similar to the method developed by Bols gave the desired piperidine derivative **58** in a 71% isolated yield. This reaction was extended by using alkoxyamines. Thus, *O*-benzylhydroxylamine was applied for the above-described double-reductive amination affording *N*-alkoxypiperidine **59** in 46% yield. Upon further optimization, the highest yield of **59** was 81% using 2.5 equiv. of alkoxyamine (Scheme 13)[67]. After the optimization of the above method, they focused on the synthesis of more promising dialdehydes to achieve trisubstituted *N*-alkoxypiperidine analogs of isofagomine[67].



Scheme 13. Preparation of *N*-alkoxypiperidines with double-reductive amination

In another study, the synthesis of carbohydrate-derived morpholine amino acids via oxidative cleavage and reductive amination was reported by Grotenberg et *al*. The synthetic route started from commercially available D-ribose **61**, and the key steps of the pathway were glycol cleavage of 1,2-diol **63** (derived from protected SAA **62**) with periodic acid followed by a double-reductive amination of the resulting dialdehyde **64** giving substituted MAA derivatives **66a** and **66b**[68].

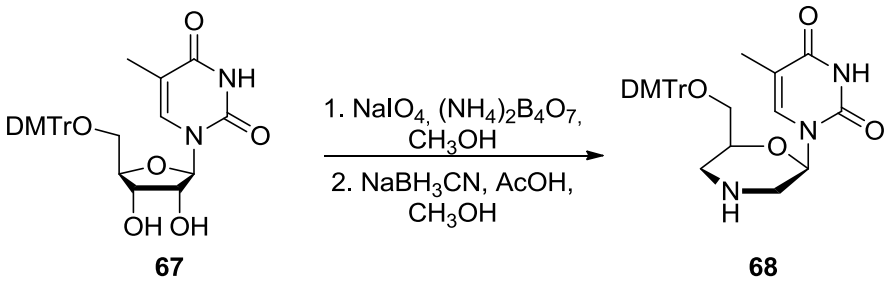


Scheme 14. An example of the synthesis of carbohydrate-derived MAAs

They performed the reductive amination 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 with 22% yield (Scheme 14)[68].

The method, based on oxidative ring cleavage and reductive ring closure, is crucial in the synthesis of morpholine oligomers. The thymine morpholino monomer was prepared from 5'-*O*-dimethoxytrityl ribothymidine **67**, which was submitted to oxidative ring cleavage mediated by sodium periodate followed by reductive amination with ammonium diborate. The dihydroxythymine morpholino monomer intermediate was

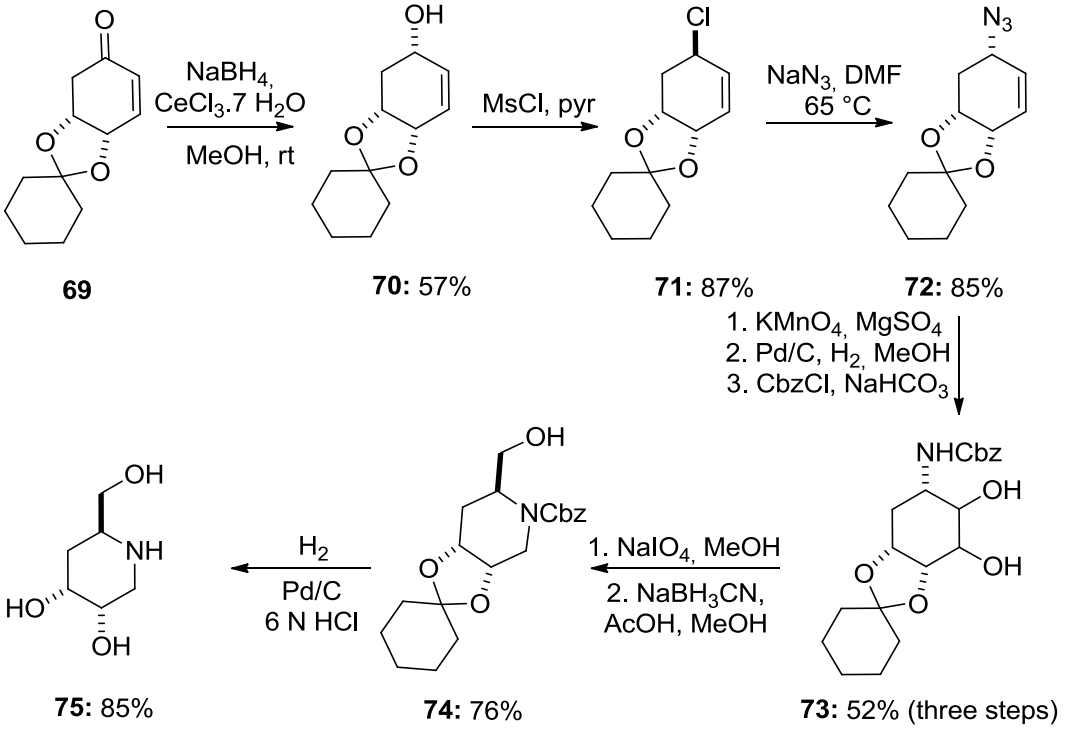
reduced with $NaBH_3CN$ providing the desired product **68** (Scheme 15)[69,70]. The product formed is the key monomer in the design of Eteplirsen (Exondys 51™)[77,78].



67 **68**

Scheme 15 Synthesis of thymine morpholino monomer **68**

Azasugars (polyhydroxylated piperidines) possess high bioactivity. Shih et *al*. reported a synthetic path to achieve new trihydroxypiperidine derivatives from D-(-)-quinic acid in eleven steps starting with enone **69** prepared from D-(-)-quinic acid via a four-step transformation. The main steps of the procedure are oxidative ring opening of the olefinic bond, intramolecular reductive cyclization and deprotection by Pd/C-HCl to provide the required trihydroxy piperidine product **75** (Scheme 16)[71].

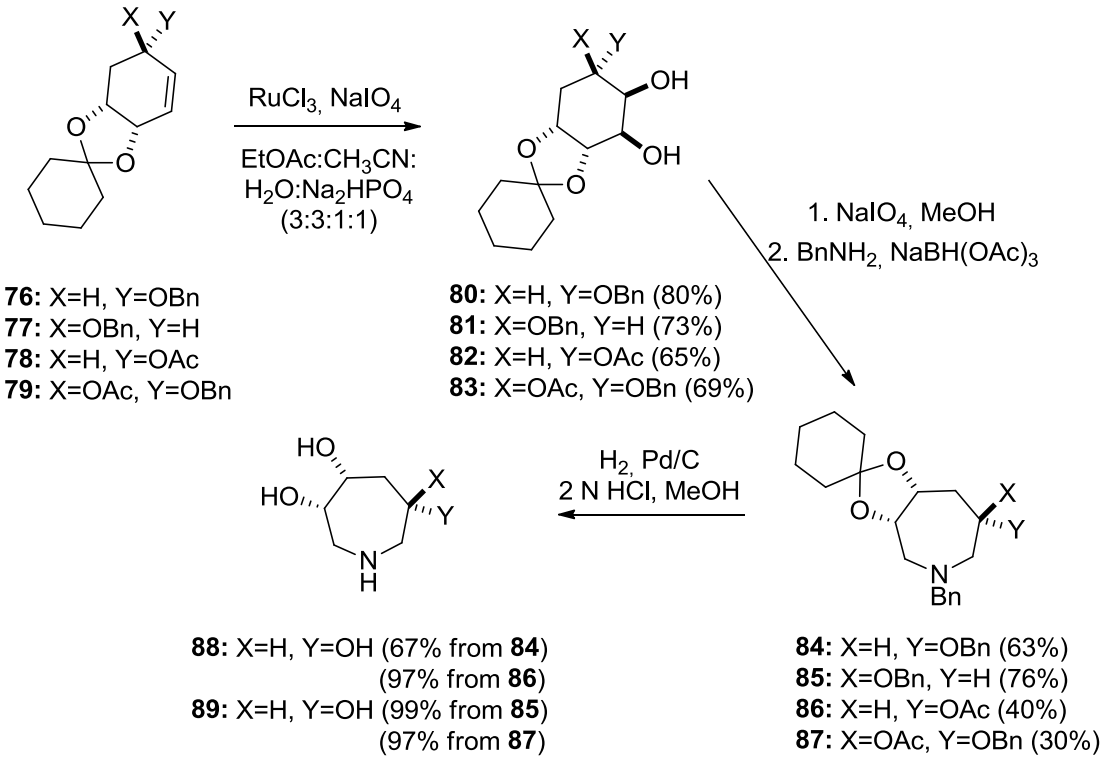


69 **70:** 57% **71:** 87% **72:** 85%

75: 85% **74:** 76% **73:** 52% (three steps)

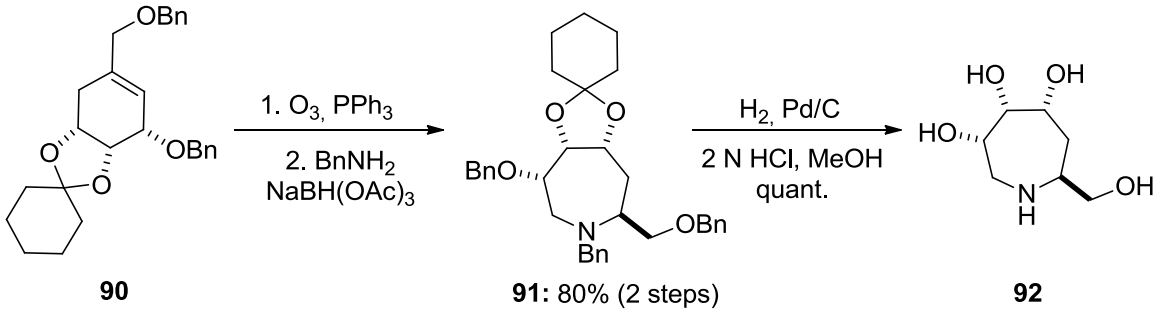
Scheme 16. Synthesis of trihydroxy piperidine scaffold **75**

The preparation of piperidine derivatives is well-known in the literature, though methods to synthesize azepane compounds are less reported. Lin and co-workers developed a novel transformation for the synthesis of tri- and tetrahydroxyazepanes. These hydroxyazepanes are promising glycosidase inhibitors like their five- or six-membered analogs. The reported strategy is based on an oxidative cleavage reaction and subsequent reductive cyclization. The first step was the dihydroxylation of protected 1,4,5-cyclohex-2-ene-triols, which were derived from D-(-)-quinic acid by the treatment of $RuCl_3/NaIO_4$/phosphate puffer (pH 7). The resulting vicinal diols were further reacted via $NaIO_4$-mediated oxidative ring opening to achieve the corresponding diformyl compounds. The reductive cyclization was carried out with benzylamine in the presence of $NaBH(OAc)_3$ as reducing agent (Scheme 17)[72].



Scheme 17. Synthesis of trihydroxyazepanes

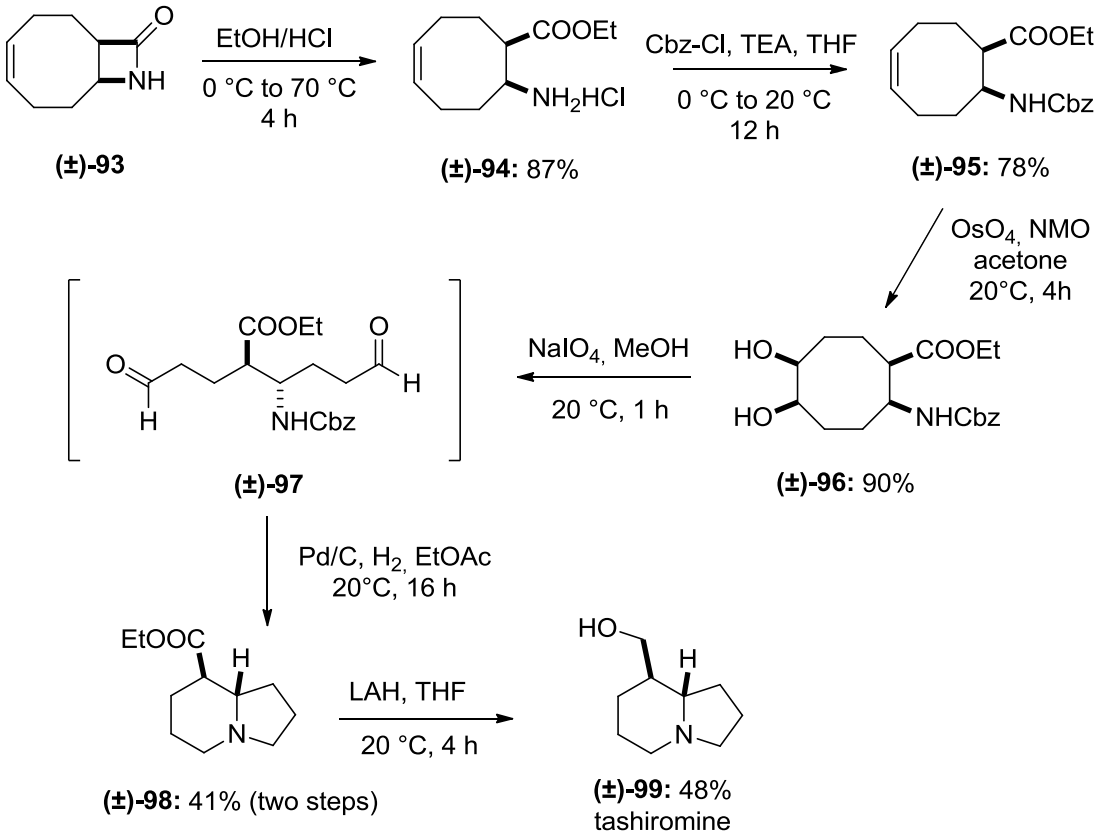
The above-described method was extended and further optimized for the synthesis of 7-hydroxymethyl-3,4,5-trihydroxyazepane. A different route starting from a protected cyclohexenetriol was defined, that includes only three steps: ozonolysis, reductive amination and deprotection (Scheme 18)[72,73].



90 **91:** 80% (2 steps) **92**

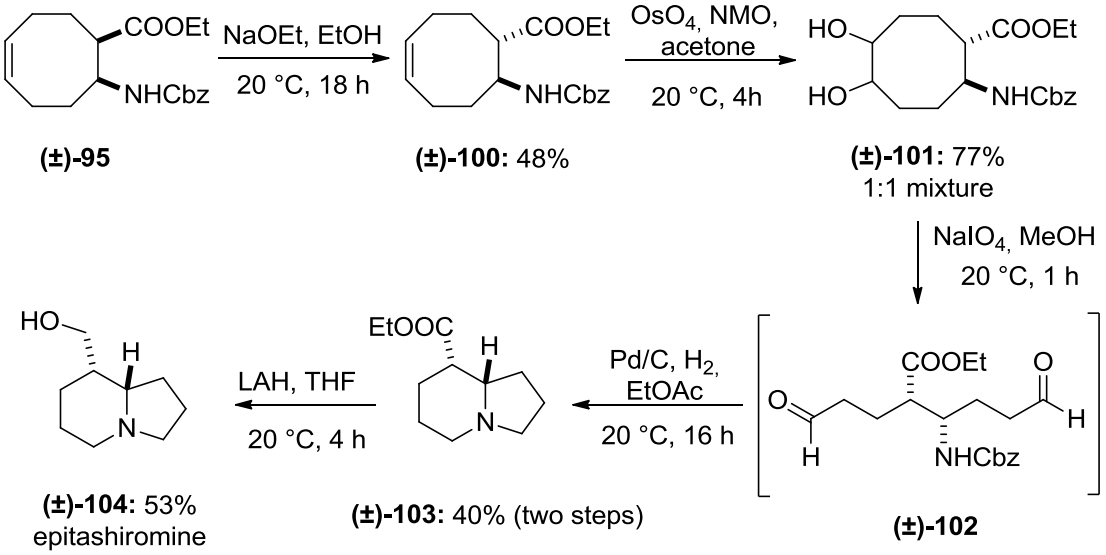
Scheme 18. Synthesis of 7-hydroxymethyl-3,4,5-trihydroxyazepane

The research group of the Institute of Pharmaceutical Chemistry at the University of Szeged has published a novel, stereocontrolled synthesis of tashiromine and epitashiromine alkaloids. Indolizidine alkaloids are very important in medicinal chemistry, because they can 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 **(±)-93**. The procedure was based on the ring opening of the azetidinone skeleton followed by the ring cleavage of the C–C double bond of cyclooctene derivative **(±)-95**. The resulting crude dialdehyde **(±)-97** was subjected to catalytic hydrogenolysis and after *N*-deprotection a reduction via double cyclization gave the desired product **(±)-99** (Scheme 19)[35].



Scheme 19. Synthesis of tashiromine **(±)-99**

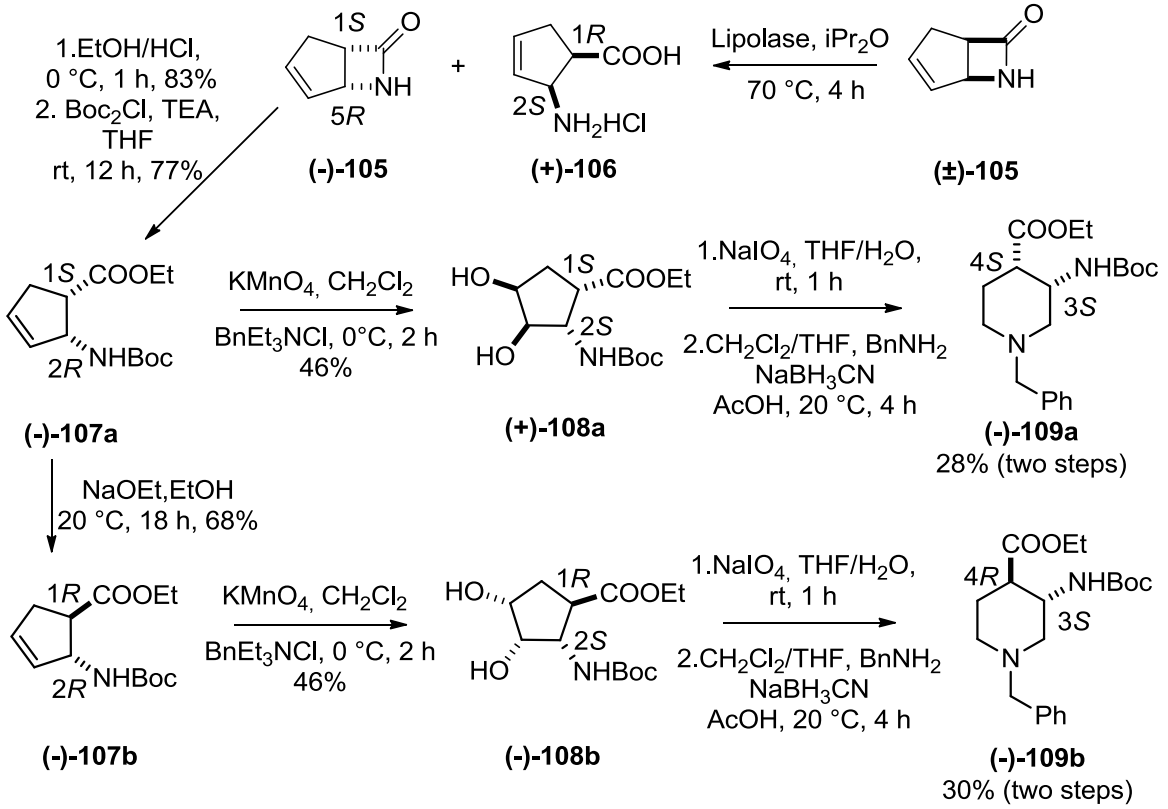
The same method was applied for the synthesis of epitashiromine. The main difference is the epimerization of *cis*-β-aminocyclohexenecarboxylate **(±)-95** giving C-1 epimer *trans* amino ester **(±)-100**. Since the **(±)-101** 1:1 diastereoisomer mixture formed in OsO_4/NMO dihydroxylation could not be isolated, it was further used in the ring-opening oxidation and reductive cyclization steps. After the reduction of the ester with LAH, epitashiromine **(±)-104** could be isolated with 53% yield (Scheme 20)[35].



Scheme 20. Synthesis of epitashiromine **(±)-104**

An efficient stereocontrolled preparation was described for the introduction of a nitrogen atom into a cyclic β-amino acid. The synthesis started from readily available unsaturated bicyclic β-lactams **(±)-105**, **(±)-110** and **(±)-113**. Key steps of the stereocontrolled synthetic path are the oxidative cleavage of the ring C–C double bond and subsequent reductive amination with benzylamine. This method was applied for the synthesis of both racemic and enantiomerically pure forms[74–76].

The preparation of piperidine-4-carboxylate enantiomers started from enantiomerically pure β-lactam **(-)-105**, which was submitted to dihydroxylation mediated by $KMnO_4$. The further reaction path was based on oxidative ring opening of the vicinal diol mediated by $NaIO_4$ followed by ring expansion giving novel β-amino acid scaffolds in enantiomerically pure form (Scheme 21)[74].



Scheme 21. Enantioselective synthesis of piperidine-4-carboxylates

The same transformations were applied for the regio- and stereoisomeric synthesis of azepane amino esters (Figure 7)[75] .

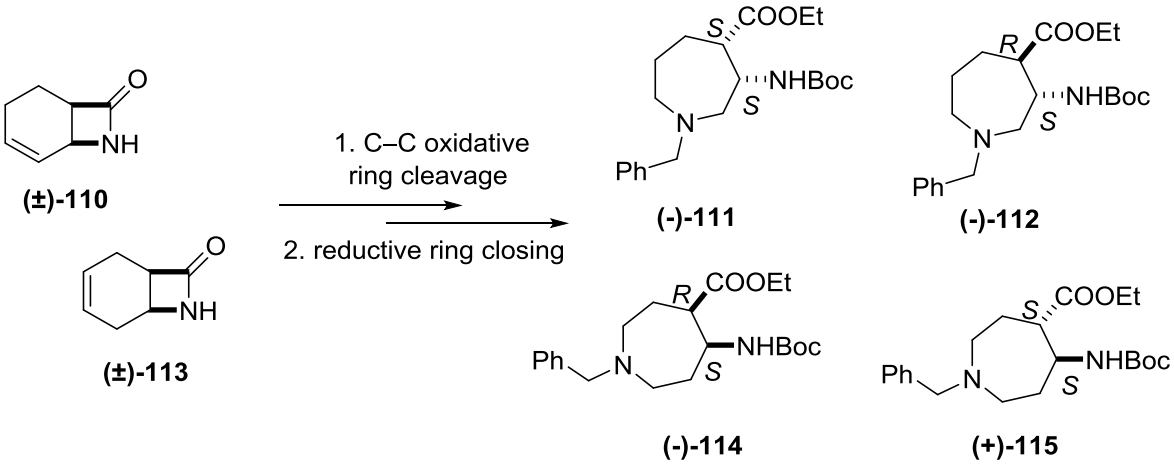
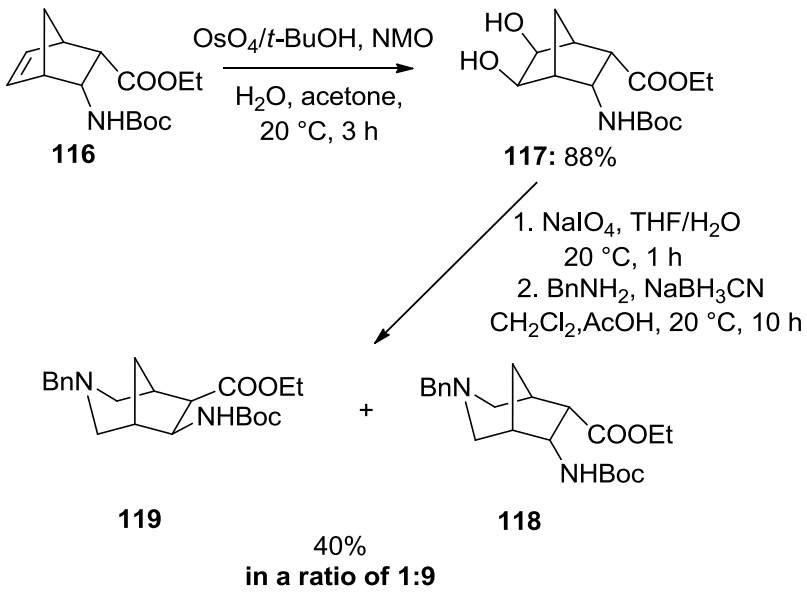


Figure 7. Pathway for the access of regio- and stereoisomeric azepane amino esters

Azabicyclic β-amino esters were obtained from *exo*-norbornene β-lactam with the above-described ring-opening/ring-closing method. Racemic *diendo* norbornane amino ester **116** as starting material provided products **118** and **119** in a ratio of 9:1. The possible

explanation is the keto–enol tautomerism of the diformyl derivatives, which yielded a mixture of *diendo* and *diexo* heterocyclic amino esters (Scheme 22)[76].



Scheme 22. Synthesis of azabicyclic β-amino esters

The synthetic pathway described above was applied for the transformation of *diexo*-*N*-Boc-protected norbornene β-amino ester **120**. The oxidative ring-opening and reductive ring-closure procedure afforded the desired azabicyclic β-amino ester **119 (**Figure 8)[76].

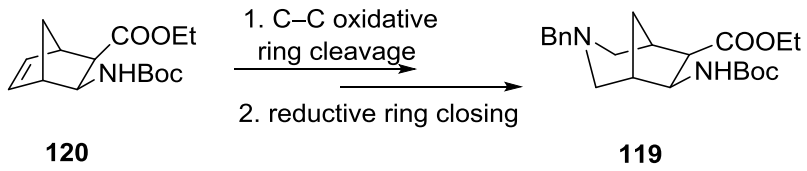


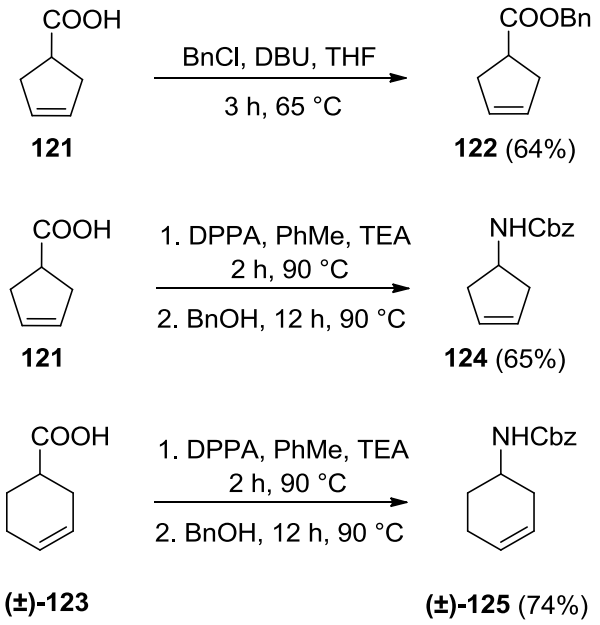
Figure 8. Synthesis of *diexo* azabicyclic β-amino ester

3. RESULTS AND DISCUSSION

Taking into consideration the appropriate biorelevance of saturated *N*-heterocycles and organofluorine scaffolds, our aim was to combine these molecular structures. The actual work was based on the oxidative ring opening of various substituted cycloalkenes and unsaturated cyclic β-amino acid scaffolds. It was followed by cyclization of the diformyl intermediates under reductive amination condition in order to synthesize various *N*-heterocyclic motifs incorporating fluorinated entities. The stereocontrolled synthetic concept included the use of commercially available fluorine-containing amines to achieve novel fluorine-containing piperidine and azepane derivatives and 1,2,3,4-tetrahydroisoquinoline compounds.

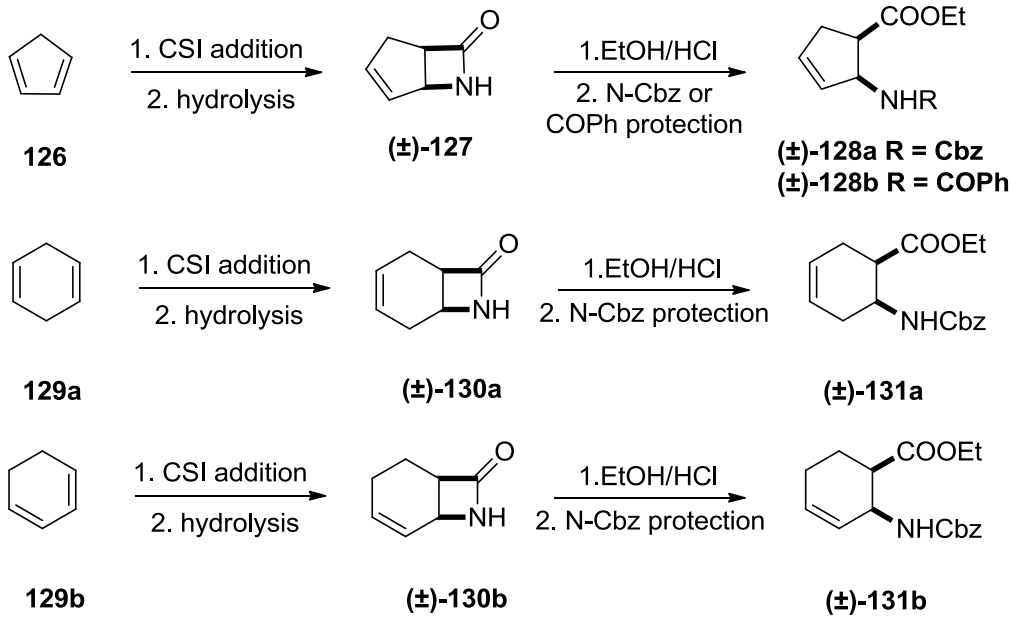
3.1. Synthesis of starting materials

First, our aim was the preparation of five-membered substituted cycloalkenes, namely, a cyclopentene carboxylate and a cyclopenteneamine. Cyclopentenecarboxylic acid benzyl ester **122** was prepared from commercially available cyclopent-3-enecarboxylic acid **121** with benzyl chloride and DBU in THF under reflux. Next, the ester substituent of the cyclopentene ring was changed to a protected amine. Unsaturated acid **121** was converted under Curtius reaction conditions to Cbz-protected amine derivative **124**. The Curtius rearrangement was performed via a known pathway in dry toluene with TEA and diphenylphosphoryl azide (DPPA) in the solution of benzyl alcohol with an overnight reflux. This reaction was also applied for the synthesis of protected cyclohexeneamine **(±)-125** from commercially available cyclohex-3-enecarboxylic acid **(±)-123**[79]. The preparation of five- and six-membered substituted cycloalkenes is presented in Scheme 23.



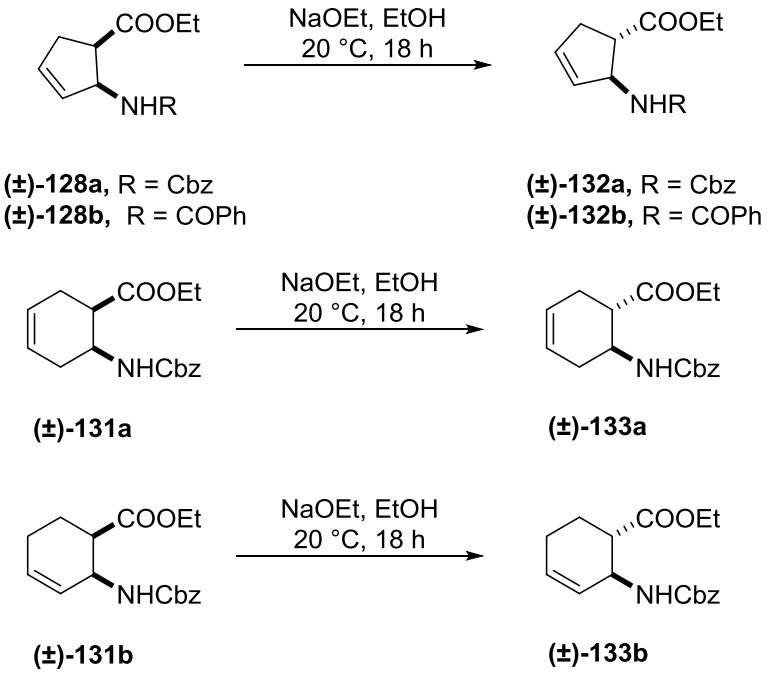
Scheme 23. Preparation of five- and six-membered substituted cycloalkenes

Next, a method described previously was applied for the preparation of unsaturated bicyclic β-lactams **(±)-127** and **(±)-130a,b** as starting materials. Cyclopentadiene **126** and cyclohexadienes **129a,b** were submitted to [2+2] cycloaddition with *N*-chlorosulfonyl isocyanate (CSI) giving the required sulfonamide. Then unsaturated bicyclic β-lactams were obtained by the hydrolysis of the SO_2Cl group with Na_2SO_3[80]. The desired products were recrystallized from diisopropyl ether and further used for lactam ring opening at 0 °C in dry EtOH with HCl/EtOH. The ester hydrochlorides were crystallized with diethyl ether and filtered. This step was followed by *N*-protection with Cbz-Cl and benzoyl chloride. In details, Et_3N was added to a solution of amino ester hydrochloride in THF at 0 °C followed by the addition of Cbz-Cl and stirring the mixture for 10 h at room temperature (Scheme 24)[35]. Benzoyl protection was carried out with benzoyl chloride at 0 °C in toluene, in the presence of $NaHCO_3$ in a 1-h reaction[81]. In both reactions the crude products were purified by column chromatography on silica gel (*n*-hexane/EtOAc) affording Cbz- and COPh-protected β-amino esters (Scheme 24).



Scheme 24. Synthesis of *N*-protected β-aminocyclopentene and β-aminocyclohexene carboxylates

Epimerization at C-1 was also executed with NaOEt in EtOH with the involvement of the active methine group of *cis N*-protected amino esters **(±)-128a,b** and **(±)-131a,b**. The crude materials were purified by column chromatography on silica gel (*n*-hexane/EtOAc) to give *trans* isomers **(±)-132a,b** and **(±)-133a,b** (Scheme 25)[74].



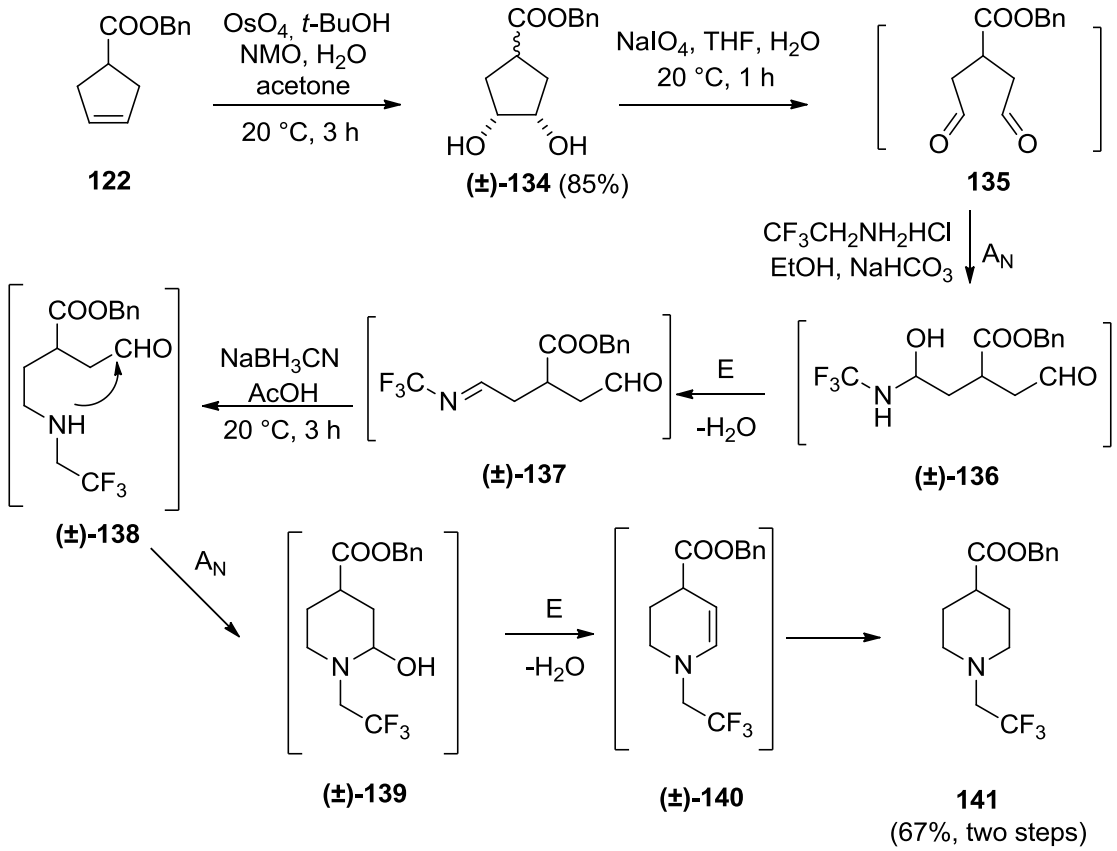
Scheme 25. Epimerization of *cis N*-protected amino esters

3.2. Synthesis of fluorine-containing functionalized piperidine derivatives

The synthetic concept included the preparation of fluorine-containing amines and was based on the oxidative ring cleavage of the above-described unsaturated starting materials and some readily available cycloalkenes, followed by ring closure via reductive amination and ring expansion of the diformyl intermediates.

Synthesis of monosubstituted fluorine-containing piperidines

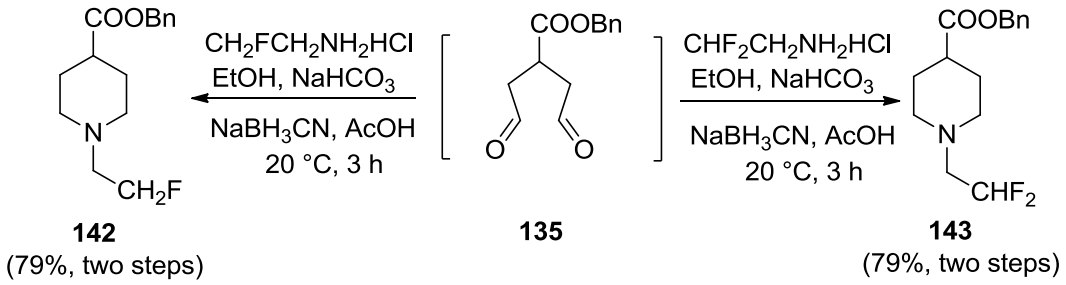
Cyclopentenecarboxylic acid benzyl ester **122** was transformed to the corresponding dialdehyde. First, **122** was oxidized with NMO/OsO_4 providing 1,2-*cis*-diol derivative **(±)-134** as a mixture of stereoisomers in nearly 1:1 ratio. In general, dihydroxylation of substituted cycloalkenes was accomplished using NMO and a catalytic amount of OsO_4 (2%) in *t*-BuOH solution. Both reagents were added to the stirred solution of substituted cycloalkenes in acetone, and the mixture was stirred further for 3 h at room temperature. After completion of the reaction, the mixture was treated with saturated aqueous Na_2SO_3 solution and then extracted with CH_2Cl_2. The crude product was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc). The resulting mixture of stereoisomers could not be separated either by chromatography or by crystallization. However, in the next oxidative ring-cleavage step, the stereocenters disappear and, consequently, the mixture of diastereoisomers could be used further without any problem. The $NaIO_4$-mediated oxidation of this mixture provided the corresponding unstable linear dialdehyde **135**, which was immediately submitted to reductive amination without isolation or purification. The oxidative ring cleavage step was carried out with $NaIO_4$ in THF/H_2O under Ar atmosphere. After stirring for 1 h at 20 °C, H_2O was added until the precipitate dissolved. The mixture was then extracted with CH_2Cl_2 and after solvent evaporation, the dialdehyde product was used in the next step without isolation. Reductive ring closing was performed with commercially available fluorine-containing amine 2,2,2-trifluoroethylamine hydrochloride.



Scheme 26. Synthesis of fluorine-containing piperidine derivative **141** from cyclopentene carboxylate via a diformyl intermediate

Reductive ring expansion was carried out between diformyl intermediate **135** and the above-mentioned fluorine-containing amine, followed by treatment with $NaBH_3CN$ in the presence of $NaHCO_3$ and AcOH in EtOH, resulting in the corresponding trifluoromethylated piperidine derivative **141** (Scheme 26). After a 3-h reaction, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc). A general mechanism of the double-reductive amination is also presented in Scheme 26.

Reductive amination of dialdehydes could be applied by using other fluorine-containing building blocks to achieve other fluorinated piperidines. For this purpose, diformyl derivative **135** was treated with commercially available 2-fluoroethylamine hydrochloride or 2,2-difluoromethylamine hydrochloride followed by reduction yielding, respectively, the corresponding mono- or difluorinated piperidine derivative **(±)-142** and **(±)-143** (Scheme 27).



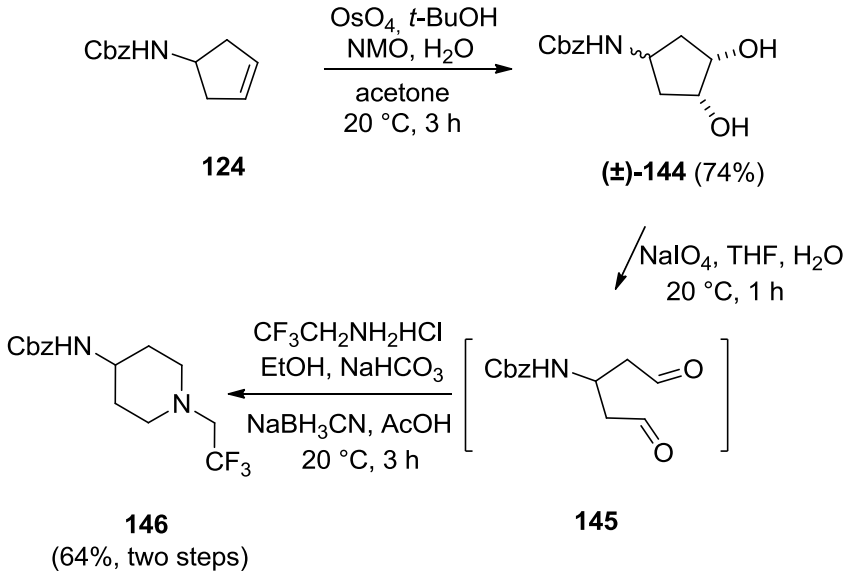
142
(79%, two steps)

135

143
(79%, two steps)

Scheme 27. Synthesis of fluorine-containing piperidine derivatives

Next, Cbz-protected amine **124** (synthesized from commercially available cyclopent-3-enecarboxylic acid **121** with Curtius rearrangement) underwent dihydroxylation furnishing a 1:1 mixture of vicinal diol derivative **(±)-144**, presented in Scheme 28.



124

(±)-144 (74%)

146
(64%, two steps)

145

Scheme 28. Synthesis of functionalized piperidine derivative **146**

Again, this mixture was used in the next step without separation of the diastereomers of **(±)-144** to give dialdehyde **145**. This diformyl intermediate was further used without isolation via double-reductive amination with 2,2,2-trifluoroethylamine in the presence of $NaBH_3CN$ affording trifluoromethylated piperidine **146** with 64% yield (Scheme 28).

Synthesis of fluorine-containing piperidine β-amino esters

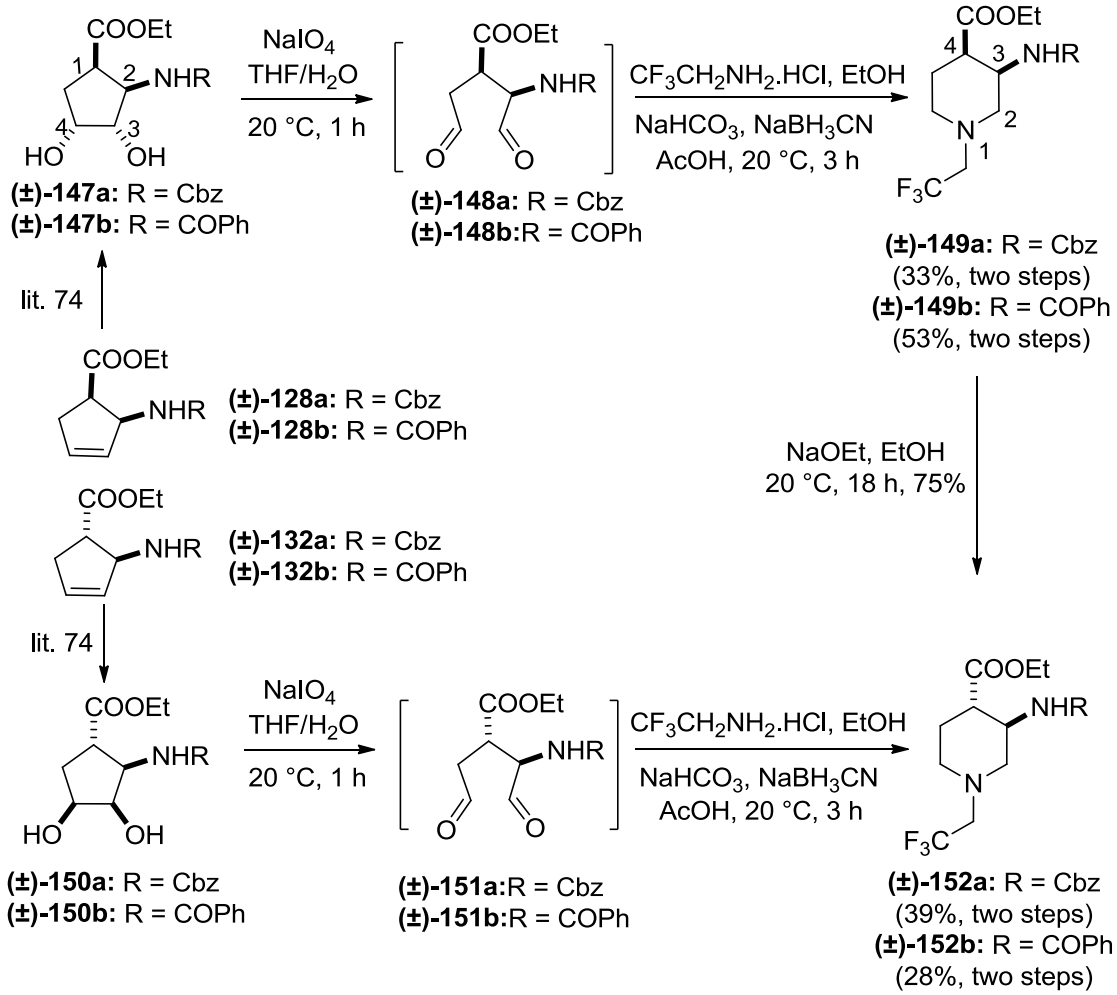
Due to their appreciated biological potential, *N*-heterocyclic β-amino acids are important motifs in pharmaceutical and organic chemistry. A series of fluorine-containing

acyclic α- and β-amino acids exhibit antitumoral or antibiotic properties[43,82–84]. Biomolecules containing β-fluorinated or β-trifluorinated amine units are remarkable scaffolds in medicinal chemistry or agrochemistry[3,11,32,85,86]. Thus, fluorine-containing pyrrolidines and piperidines, which are present in drugs, have great interest in medicinal chemistry[7,38,87–89]. Thanks to these facts, our next goal was to apply the ring-opening/ring-closing protocol to synthesize unsaturated β-amino acid derivatives.

Accordingly, unsaturated β-amino esters **(±)-128a,b** were transformed to dihydroxylated *cis* amino esters **(±)-147a,b** using NMO/OsO_4-mediated dihydroxylation. These were then treated with $NaIO_4$ in THF/H_2O to form the corresponding unstable open-chain dialdehyde amino esters **(±)-148a,b**[74] and then reacted further without isolation. Reductive amination was carried out upon treatment with commercially available 2,2,2-trifluoroethylamine hydrochloride with $NaBH_3CN$ as reducing agent in the presence of $NaHCO_3$ in EtOH. Substituents of the resulting **(±)-149a,b** *cis* β-amino esters are attached to the C-3 and C-4 atoms of the piperidine framework (Scheme 29).

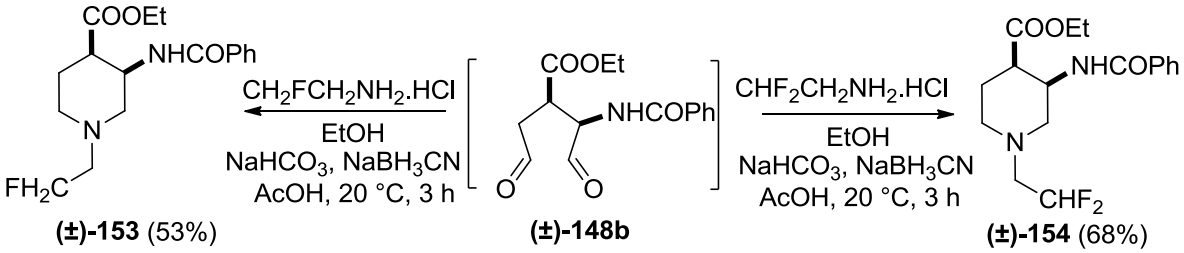
The configuration of the chiral centers in **(±)-149a,b** is predetermined by the structure of the starting materials since the stereocenters at C-1 and C-2 of amino esters **(±)-128a,b** were not affected during the ring expansion procedure. Consequently, the *cis* amino ester afforded the corresponding piperidine derivative with the carboxylate and carbamate/amide functions in a *cis* relative arrangement.

Analogously, dihydroxylated amino esters **(±)-150a,b** with the ester and the *N*-protected group in a *trans* relationship were submitted to $NaIO_4$-mediated oxidative ring opening. The ring-closing procedure of the formed unstable diformyl intermediates **(±)-151a,b** with trifluoroethylamine and $NaBH_3CN$ afforded *trans* trifluoromethylated piperdine amino esters **(±)-152a,b** (Scheme 29). Amino esters **(±)-152a,b** could be accessed on an alternative pathway by epimerization at C-4 of **(±)-149a,b** with NaOEt in EtOH with the involvement of the active methine group[74,90–92].



Scheme 29. Synthesis of trifluoromethylated piperdine β-amino ester frameworks

By the variation of the fluorine-containing building element, the synthetic concept could be readily extended to access novel fluorine-containing *N*-heterocyclic β-amino acid derivatives. A demonstrative example consists of the reductive amination either with 2-fluoroethylmine hydrochloride or 2,2-difluoroethylamine hydrochloride. Thus, dialdehyde **(±)-148b** was submitted to reductive ring expansion on treatment with these commercially available fluoroamines in the presence of $NaHCO_3$ and $NaBH_3CN$, yielding the corresponding monofluorinated and difluorinated piperidine β-amino esters **(±)-153** and **(±)-154** (Scheme 30).



Scheme 30. Synthesis of monofluorinated and difluorinated piperidine β-amino esters **(±)-153** and **(±)-154**

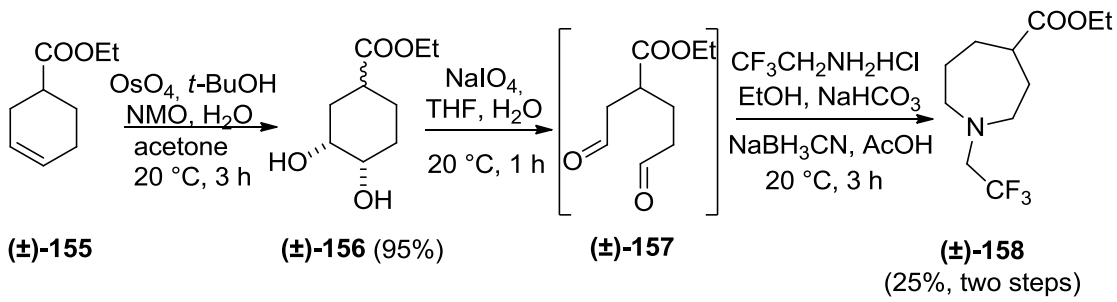
A convenient and efficient stereocontrolled procedure has been demonstrated for the access of different types of fluorinated *N*-heterocycles with piperidine skeleton. The developed procedure is generally applicable and the synthetic path includes an oxidative ring cleavage and a double-reductive amination to achieve substituted piperidine scaffolds with varied substitution patterns.

3.3. Synthesis of fluorine-containing functionalized azepane derivatives

The transformation of dialdehyde substrates could also be applied for the synthesis of seven-membered functionalized *N*-heterocyclic systems. Fluorine-containing azepane motifs are relatively less frequently reported in the literature. However, because of the important role of various functionalized counterparts in pharmaceutical design, they may receive increasing attention in the future[9,39].

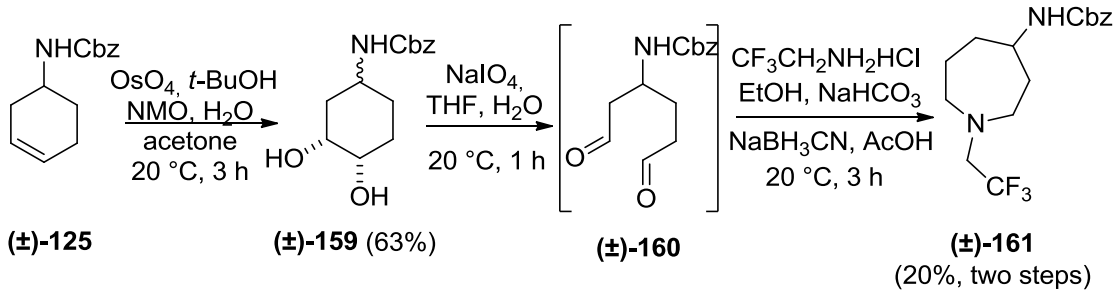
Synthesis of monosubstituted fluorine-containing azepane derivatives

Due to the rising interest of azepane structures, our next aim was the extension of the above-described synthetic technique to the preparation of trifluoromethylated azepane derivatives. For this purpose, we selected the six-membered analogs of the aminocyclopentene ester investigated above. Ethyl cyclohex-3-enecarboxylate **(±)-155**, available on the market, was first submitted to dihydroxylation to form **(±)-156** as a mixture of diol diastereoisomers in a ratio 1:1. Similar to the five-membered analogs, this dihydroxylated diastereoisomer mixture could not be separated and, consequently, it was used further in the next step. Thus, ring opening with $NaIO_4$ afforded the corresponding open-chain dialdehyde **(±)-157**, which was next transformed without isolation on treatment with trifluorinated ethylamine into azepane derivative **(±)-158** (Scheme 31).



Scheme 31. Synthesis of functionalized azepane derivative **(±)-158**

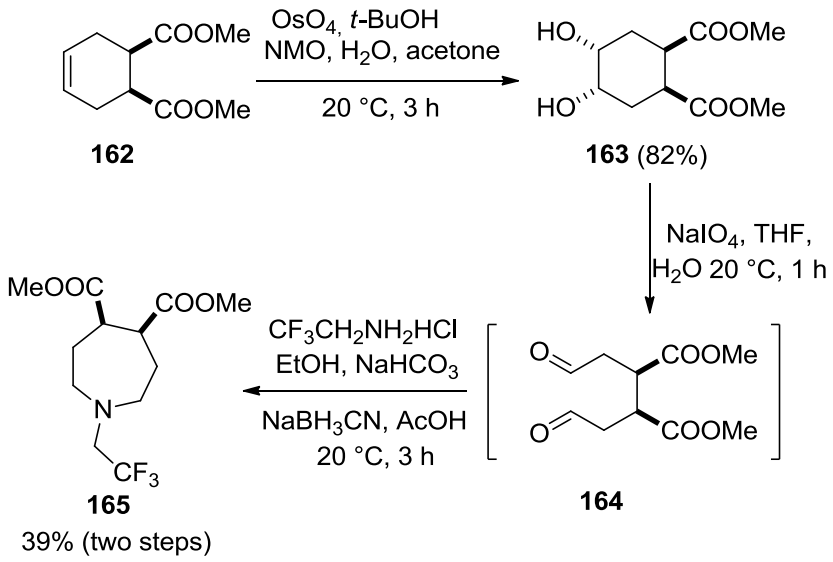
The synthesis of a Cbz-protected amine-substituted fluorinated azepane could be achieved by starting from cyclohexeneamine **(±)-125** synthesized by the Curtius reaction. Dihydroxylation of **(±)-125** led to diol mixture **(±)-159**, which was transformed by oxidative ring cleavage in the presence of $NaIO_4$. Again, the unstable diformyl intermediate **(±)-160** was further used 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 $NaBH_3CN$. The process involved reductive amination and resulted in substituted azepane derivative **(±)-161** containing the desired trifluoromethyl group (Scheme 32). Note that the formation of the seven-membered ring system provides lower yield in comparison with those of the six-membered analogs.



Scheme 32. Synthesis of functionalized azepane derivative **(±)-161**

Synthesis of disubstituted trifluoromethylated azepane derivative

In continuation, our next goal was to synthesize disubstituted trifluoromethylated *N*-heterocyclic derivatives. For this purpose, the olefin bond of commercially available cyclohexene *cis*-diester **162** was transformed with OsO_4/NMO to vicinal diol **163**. Then $NaIO_4$-mediated oxidative ring opening of **163** followed by reductive ring expansion with trifluoroethylamine provided azepane diester **165** via the corresponding dialdehyde motif **164** (Scheme 33).

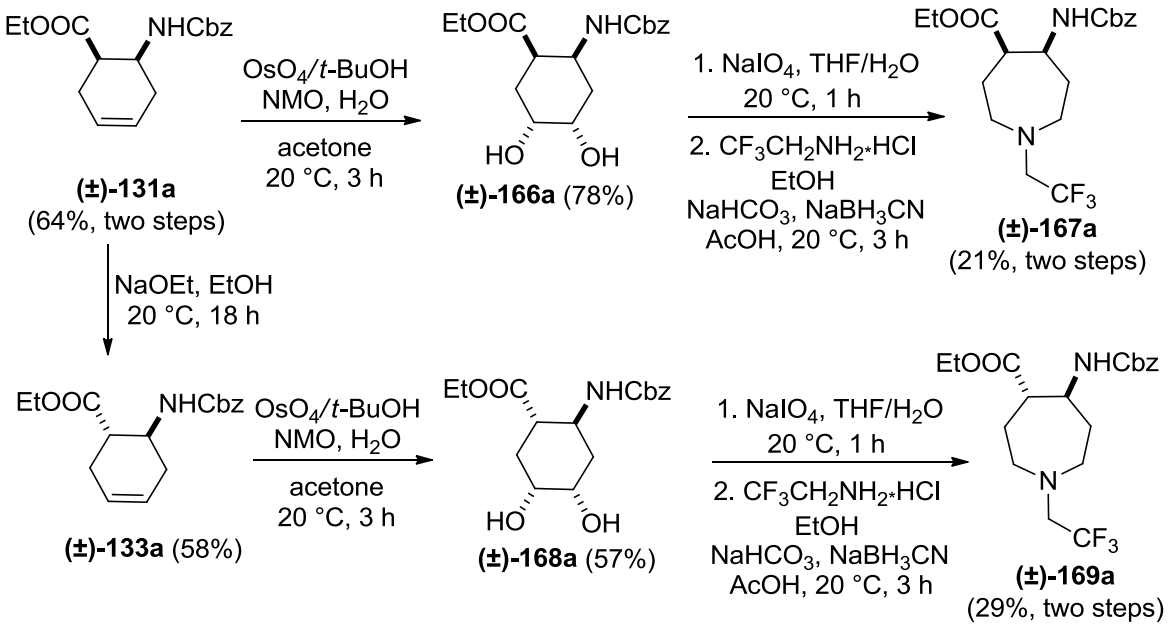


Scheme 33. Synthesis of functionalized azepane derivative **165**

The configuration of the chiral centers in **165** is predetermined by the structure of starting material **162** since the stereocenters were not affected during the ring-expansion procedure.

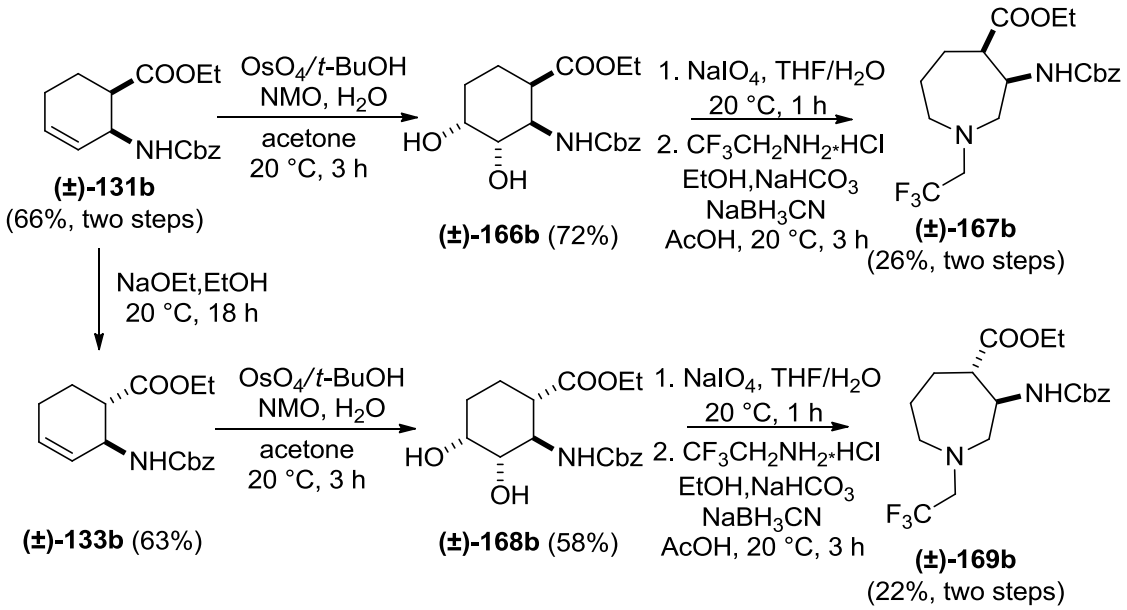
Synthesis of fluorine-containing azepane β-amino esters

The synthetic approach discussed above was then applied for the stereocontrolled synthesis of trifluoromethylated azepane β-aminocarboxylates. First, *cis*- and *trans*-2-aminocyclohex-4-enecarboxylates **(±)-131a** and **(±)-133a** (derived from bicyclic β-lactam) were oxidized with NMO/OsO_4 affording the corresponding vicinal diol derivatives **(±)-166a** and **(±)-168a**. In the next step, these dihydroxylated esters were transformed into *cis* and *trans* amino esters **(±)-167a** and **(±)-169a** bearing an azepane ring. The reaction steps are oxidative ring cleavage and stereocontrolled ring enlargement through reductive amination with 2,2,2-trifluoroethylamine hydrochloride and $NaBH_3CN$. In the trifluoromethylated azepane products, the ring nitrogen atom is in a distance of three carbon atoms from the carbamate group (Scheme 34).



Scheme 34. Synthesis of trifluormethyl-containing azepane β-amino acid stereoisomers

Our next aim was the preparation of the regioisomers of trifluoromethylated azepane derivatives **(±)-167a**, **(±)-169a** starting from bicyclic β-lactam **(±)-130b**, the regioisomer of **(±)-130a**. Lactam **(±)-130b** was converted through lactam ring opening by ethanolysis followed by *N*-Cbz protection yielding **(±)-131b**, which was then subjected to epimerization to give derivative **(±)-133b** (see Schemes 24 and 25). The C–C double bond dihydroxylation of these two compounds with NMO and OsO_4 provided vicinal diols **(±)-166b** and **(±)-168b**. 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 giving *cis* and *trans* azepane amino esters **(±)-167b** and **(±)-169b** [regioisomers of **(±)-167a** and **(±)-169a**]. In these products, the ring nitrogen atom is located at two carbon atom distance from the carbamate group (Scheme 35).



Scheme 35. Preparation of fluorine-containing *cis* and *trans* azepane β-amino esters

Synthesis of fluorine-containing azabicyclic azepane systems

In view of the high physiological relevance of *N*-bridged bicyclic derivatives in synthetic and medicinal chemistry, our next aim was the extension of the described synthetic technique to the preparation of trifluoromethylated *N*-bicyclic systems. *N*-Heterocyclic bicyclic α- and β-amino acids could be key precursors of medicinally important alkaloids such as anatoxin-*a*, epibatidine, epiboxidine and their analogs (Figure 9)[76].

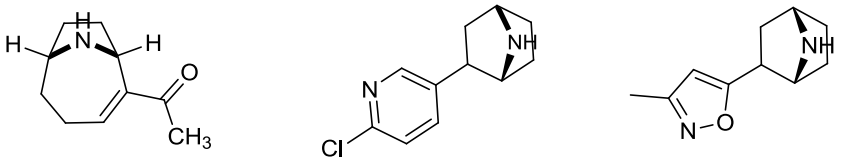
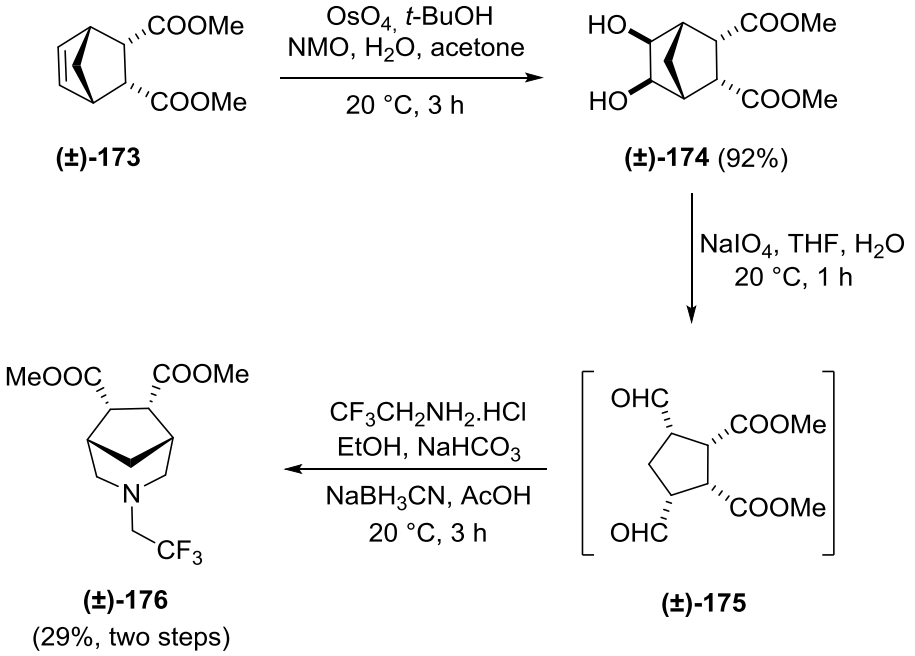


Figure 9. Medicinally important *N*-bicyclic alkaloids

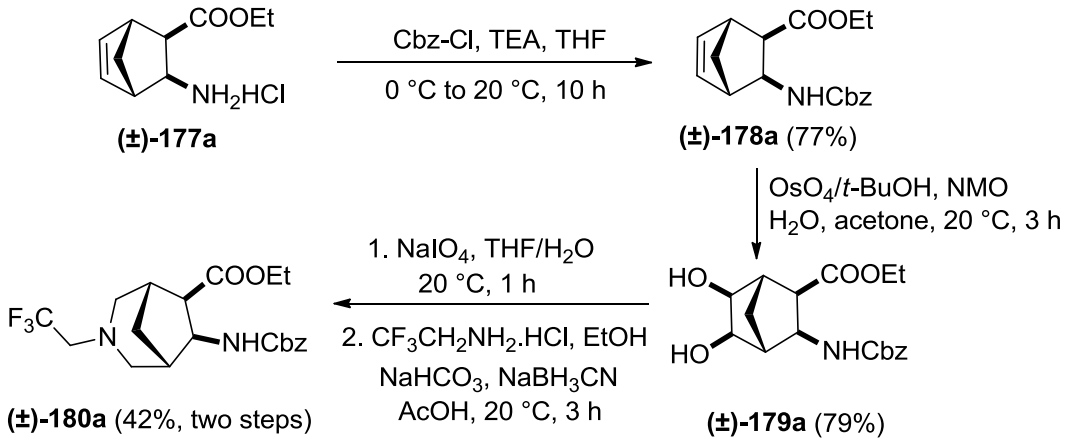
Taking into consideration the high physiological relevance of *N*-bridged bicyclic motifs, the commercially available *diendo* norbornene dicarboxylate **(±)-173** was transformed by dihydroxylation with OsO_4 and NMO to diol derivative **(±)-174**. Subsequent oxidative ring opening gave unstable diformyl intermediate **(±)-175**. Then this dialdehyde was transformed without isolation by reductive amination with trifluoroethylamine hydrochloride in the presence of $NaBH_3CN$ as reducing agent. After the purification of the crude product by column chromatography on silica gel (*n*-

hexane/EtOAc), the desired *N*-bicyclic diester **(±)-176** was isolated in 29% yield. The synthetic approach of *N*-bicyclic diester is shown in Scheme 36.



Scheme 36. Synthesis of trifluoromethyl-containing *N*-bicyclic diester **(±)-176**

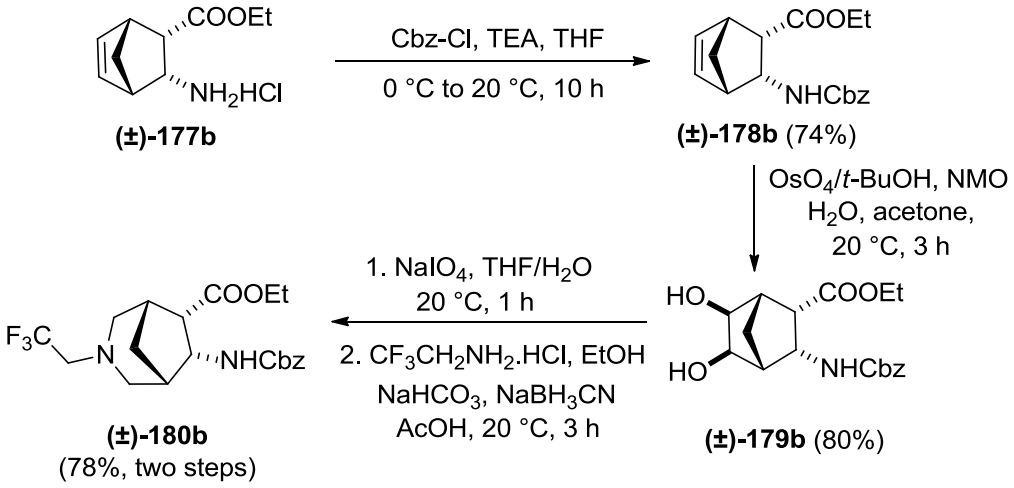
N-Heterocyclic β-amino acids have received wide attention due to their incorporation into the structure of a peptide[76]. Thus, commercially available *diexo* norbornene β-amino ester **(±)-177a** was protected by Cbz-Cl with the general procedure described above to give **(±)-178a**. This *N*-protection was followed by the dihydroxylation step to form the desired diol derivative **(±)-179a** presented in Scheme 37.



Scheme 37. Synthesis of fluorinated *N*-bicyclic β-amino ester **(±)-180a**

In the next step we have accomplished the oxidative ring cleavage of **(±)-179a** followed by reductive amination with trifluoroethylamine hydrochloride and $NaBH_3CN$ in the presence of $NaHCO_3$ and AcOH to have *N*-bicyclic amino ester **(±)-180a** (Scheme 37).

The stereocontrolled synthesis of the new *N*-bridged bicyclic β-amino ester containing the trifluoromethyl group could also be accomplished by starting from *diendo* norbornene amino ester **(±)-177b**. Following the synthetic approach for the *diexo* isomer, *N*-Cbz-protection of **(±)-177b**, dihydroxylation, oxidative ring opening and ring enlargement via reductive amination with trifluoroethylamine hydrochloride led to compound **(±)-180b**, a stereoisomer of **(±)-180a** (Scheme 38).



Scheme 38. Synthesis of fluorinated *N*-bicyclic β-amino ester **(±)-180b**

Here, we investigated a synthetic procedure for the creation of fluorine-containing azepane systems with diverse functionalities. Taking into consideration the availability of a wide variety of cycloalkenes and those of functionalized primary amine building blocks, this convenient methodology might be further applied towards the synthesis of a series of functionalized azepane compounds.

3.4. Synthesis of fluorine-containing 1,2,3,4-tetrahydro-isoquinoline derivatives

The 1,2,3,4-tetrahydroisoquinoline skeleton (THIQ) has high interest, thanks to being an important element of a large number of natural products. Most of them, for

example, alkaloids, exhibit a wide range of therapeutic activities. Several drugs, such as some antidiuretics, antidepressants, hallucinogens and antihypertensive agents, contain a THIQ motif[33,93–98]. Because of these important properties, a large number of synthetic approaches towards the creation of an isoquinoline or THIQ core have been described so far[95,99–106]. The best-known procedures are the Pictet–Spengler, Bischer–Napieralski, and Pomeranz–Fritsch–Bobbit cyclizations, which are widely-applied synthetic techniques to create a number of important isoquinoline alkaloids[99].

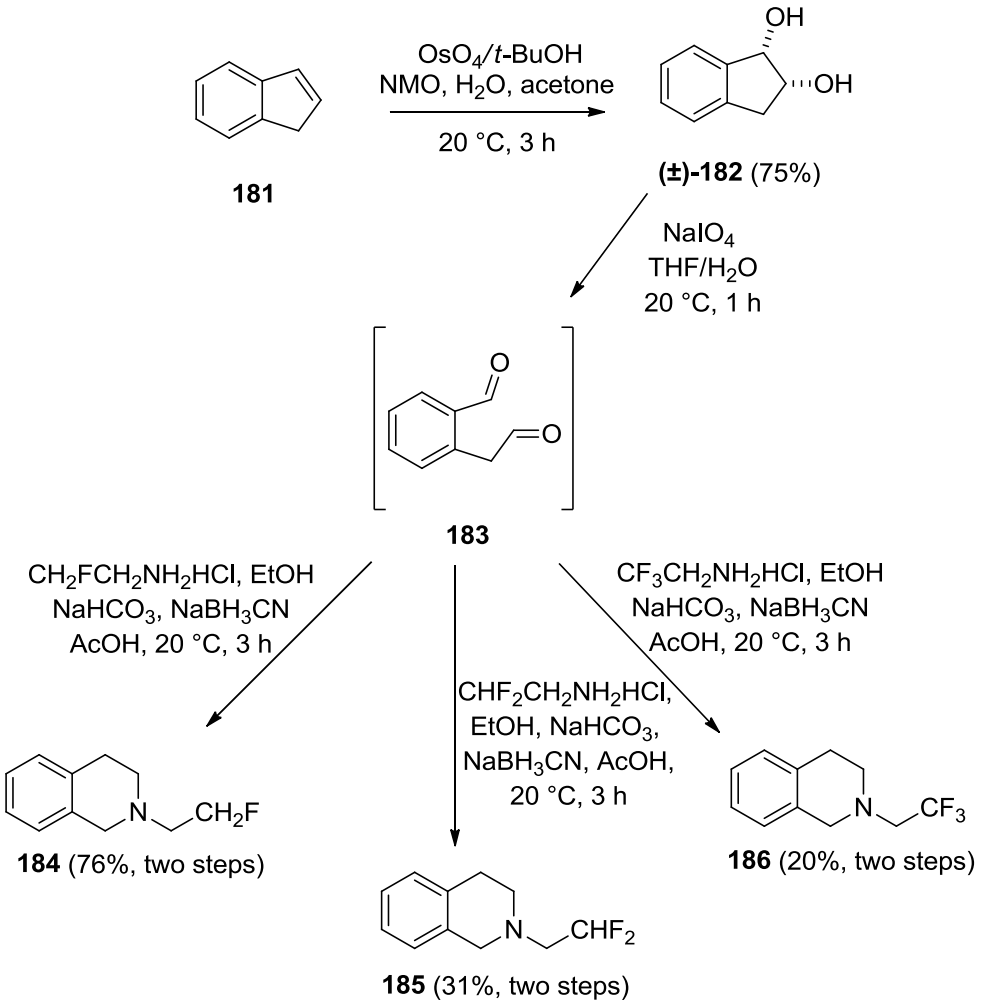
Fluorine-containing tetrahydroisoquinoline or isoquinoline derivatives constitute an important segment of fluorinated molecules either as pharmaceuticals or agrochemicals[107–109]. The synthesis of fluorinated, fluoroalkylated, and fluoroarylated isoquinoline derivatives with precious biological properties continues to be a field of high interest in medicinal and organic chemistry. Several methods for the creation of monofluorinated, trifluoromethylated or fluoroarylated isoquinolines have been developed in recent years[107,108,110–112].

In spite of the fact that there are varied strategies to build the isoquinoline skeleton, the development of new routes are still highly desirable, because these components could be potential pharmaceutical targets.

Taking into consideration the high biological relevance of THIQ alkaloids and the increasing relevance of various organofluorine scaffolds, our goal was to develop a novel and efficient procedure for the access of various fluorinated 1,2,3,4-tetrahydroisoquinoline derivatives. The developed production path was an unknown way in the literature to achieve the desired skeleton. This novel synthetic route was based on the expansion of the transformations described above. It involves oxidative ring opening and subsequent ring closing with reductive amination starting from indene and some substituted indene derivatives. Key steps are C–C double bond oxidative ring cleavage through dihydroxylation/$NaIO_4$-mediated oxidation and subsequent cyclization with primary amines via reductive amination.

First, we started with the transformation of unsubstituted *1-H*-indene **181**. It was oxidized with NMO/OsO_4 and provided the corresponding vicinal diol derivative **(±)-182**. $NaIO_4$-mediated oxidative ring cleavage of this dihydroxylated compound was carried out in THF/H_2O to deliver dialdehyde compound **183**. This unstable diformyl intermediate was further transformed without isolation with various commercially available fluorine-containing primary amines to give the target compounds in two steps. The reductive

amination of **183** with 2-fluoroethylamine, 2,2-difluoroethylamine and 2,2,2-trifluoroethylamine hydrochlorides, in the presence of $NaBH_3CN$ as reducing agent, provided the corresponding mono-, di- or trifluoromethyl tetrahydroisoquinoline derivatives **184–186** in moderate yields [two steps from **(±)-182**, Scheme 39]. As the results show, the yield of the isoquinoline products decreased on increasing the number of fluorine atoms in the final amines.



Scheme 39. Novel synthetic method for the access of 1,2,3,4-tetrahydrisoquinoline compounds

The novel synthetic approach was further extended to synthesize other fluorinated and polyfluorinated tetrahydroisoquinoline scaffolds. Vicinal diol **(±)-182** prepared previously subjected to oxidative ring opening followed by the treatment of the resulting dialdehyde (**183**) with various commercially accessible trifluoromethylated or polyfluorinated amines furnished the corresponding *N*-heterocycles (**187–190**). The novel THIQ scaffolds are summarized in Table 1.

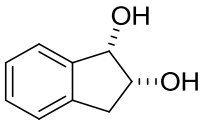
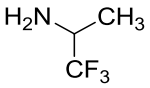
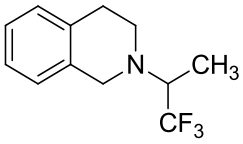
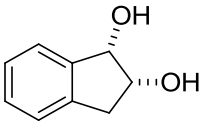
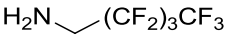
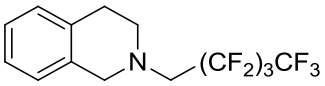
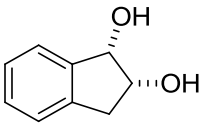
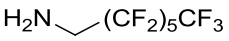
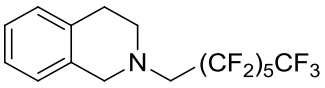
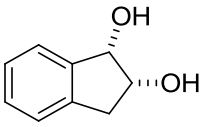
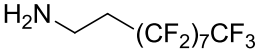
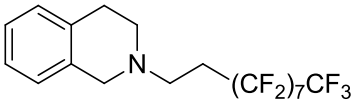
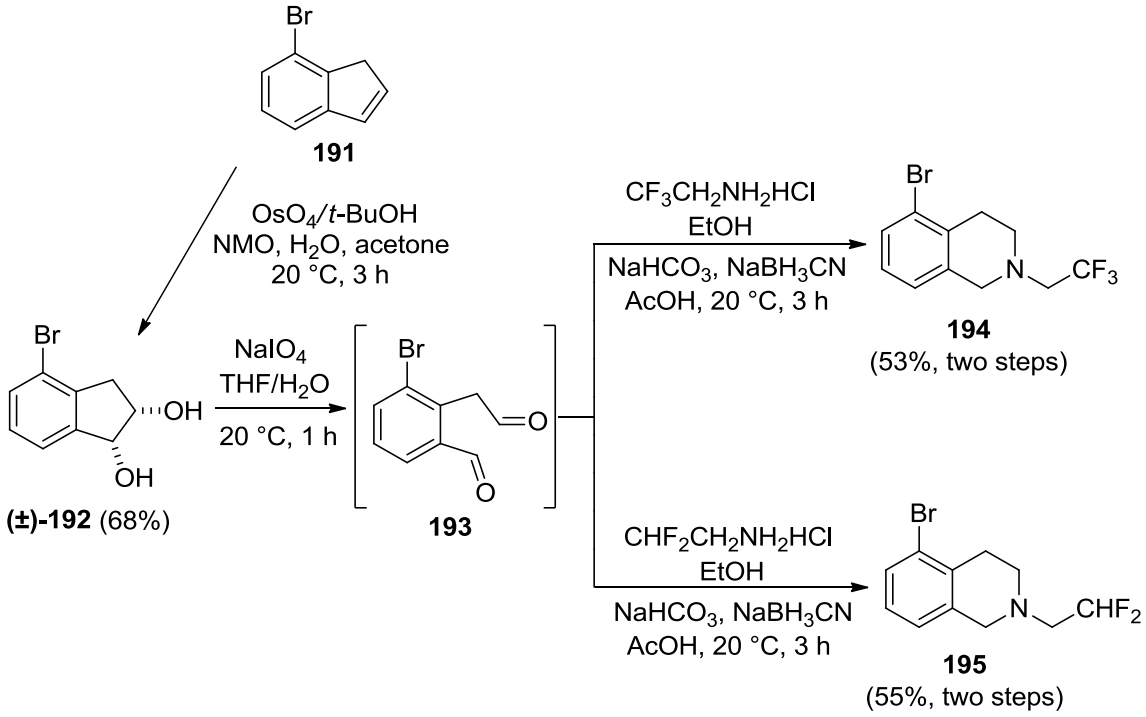
Diol	Fluorinated amine	Product	Yield (%) (two steps)
		 (**187**)	34
		 (**188**)	24
		 (**189**)	53
		 (**190**)	28

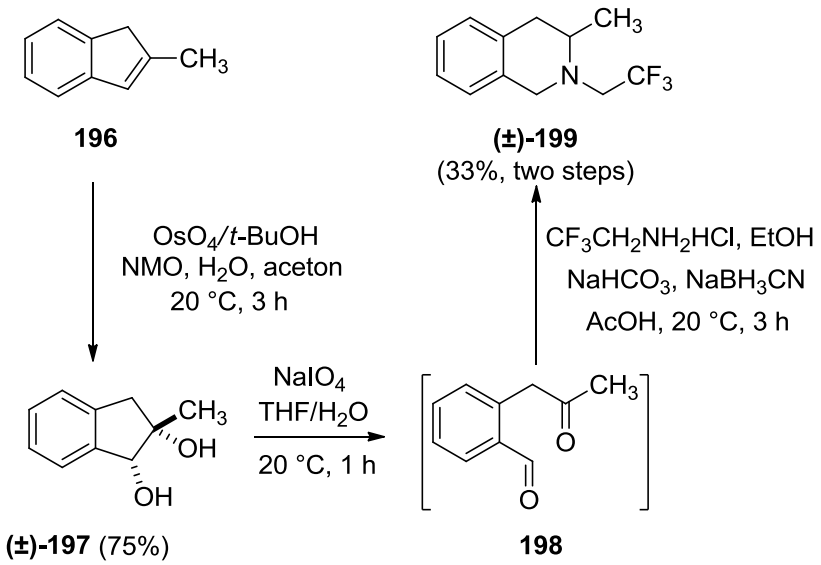
Table 1. Synthesis of novel fluorinated THIQ frameworks **187**–**190.**

In continuation, the synthetic route presented above was further extended by using 1*H*-indene derivatives with substituents attached to the benzene ring of indene. 7-Bromo-1*H*-indene **191** was selected as a model compound. *cis*-Dihydroxylation conducted in the presence of OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) gave the corresponding vicinal diol **(±)-192**. Oxidative ring opening with $NaIO_4$ in THF/H_2O at room temperature, analogously to the unsubstituted derivative, gave unstable diformyl-substituted intermediate **193** in 1 h. Further reaction—reductive ring expansion—without isolation was executed with both 2,2,2-trifluoroethylamine and 2,2-difluoroethylamine under reductive conditions in the presence of $NaBH_3CN$ and $NaHCO_3$ in EtOH at room temperature. Ring formation occurred by double-reductive amination and provided the corresponding trifluorinated or difluorinated tetrahydroisoquinoline derivatives **194** and **195** (Scheme 40).



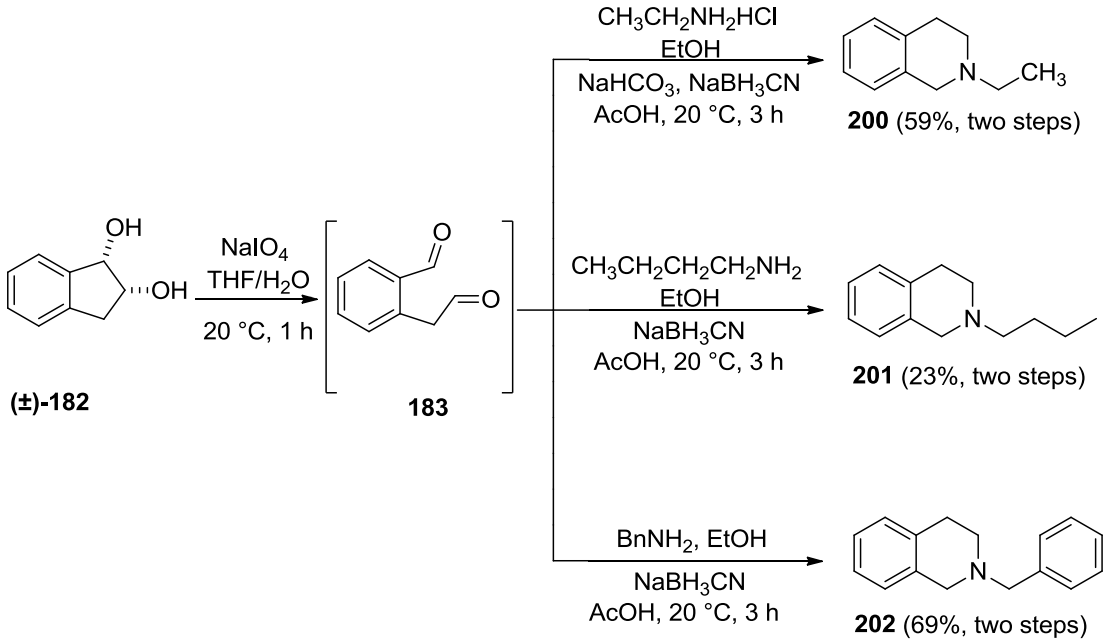
Scheme 40. Preparation of a novel *N*-heterocyclic frameworks from 7-bromo-1*H*-indene via diformyl intermediate **193**

The protocol described above was further extended to the synthesis of the other selected model compound, 2-methyl-1*H*-indene **196**. In this case, the five-membered ring of the indene was substituted. The first step of the generalized synthetic path was the oxidation of the olefinic bond to achieve *cis*-diol **(±)-197**. Subsequent ring cleavage with $NaIO_4$ led to dicarbonyl derivative **198**, which was immediately used after workup in the reductive amination step. Isoquinoline product **(±)-199** was furnished with trifluoroethyamine hydrochloride generating a chiral center. The crude product was purified by means of column chromatography on silica gel (*n*-hexane/EtOAc) to provide a moderate product yield of 33% [two steps from **(±)-197**, Scheme 41].



Scheme 41. Preparation of a novel *N*-heterocyclic framework from 2-methyl-1*H*-indene via dicarbonyl intermediate **198**

Finally, our last goal was to apply this 1,2,3,4-tetrahydroisoquinoline ring-forming synthetic procedure for the access of various non-fluorinated substances, to prove general applicability (Scheme 42).



Scheme 42. Generalization of the developed method

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 upon reacting with diformyl intermediate **183** [derived from diol **(±)-182**] produced the corresponding *N*-substituted tetrahydroisoquinoline products **200–202** through cyclization in moderate yields. After the purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc), the highest yield of 69% was attained with benzylamine [two steps from **(±)-182**] (Scheme 42).

This novel synthetic route could offer an alternative, easy and efficient procedure for the access of THIQ frameworks. Apart from this insight into the presented synthetic approach, other extensions of this method (applying amines with diverse substitution patterns or various indene motifs) could open new ways towards the accesses of various substituted 1,2,3,4-tetrahydroisoquinoline derivatives.

4. SUMMARY

1. A simple strategy was developed for the introduction of a fluorine atom into the structure of varied molecules via dihydroxylation of the olefinic bond, followed by $NaIO_4$-mediated oxidative ring cleavage of the diol intermediate and ring expansion under reductive amination, resulting in novel fluorine-containing *N*-heterocycles.
2. The required starting materials were synthesized by using simple, known literature methods.
   2.1. Five- and six-membered substituted cycloalkenes **122**, **124** and **(±)-125** were prepared from commercially available cyclopent-3-enecarboxylic acid **121** and cyclohex-3-enecarboxylic acid **(±)-123** via the Curtius reaction and esterification (*Scheme 23*)
   2.2. *N*-Protected β-aminocyclopentene carboxylates **(±)-128a,b** and β-aminocyclohexene carboxylates **(±)-131a,b** were prepared and used as starting materials, with two different protecting groups (Cbz and COPh) from readily available unsaturated bicyclic β-lactams **(±)-127** and **(±)-130a,b** (*Scheme 24*)
   2.3. With the epimerization at C-1, the corresponding *trans* β-amino carboxylate isomers **(±)-132a,b** and **(±)-133a,b** were synthetized (*Scheme 25*)
3. Synthesis of fluorine-containing piperidine derivatives
   3.1. The synthetic concept to fluorine-containing **141**, **142**, **143** and **146** molecules included the use of a commercially accessible reagent, a fluorine-containing amine, and was based on the oxidative ring cleavage of the unsaturated five-membered starting materials described above, followed by ring closure by reductive amination and ring expansion of diformyl intermediates (*Scheme 26, Scheme 27, Scheme 28*)
   3.2. Unsaturated β-amino ester **(±)-128a,b** and **(±)-132-a,b** were transformed into β-amino esters with piperidine skeleton [**(±)-149a,b**, **(±)-152a,b**, **(±)-153** and **(±)-154**]. The configuration of the chiral centers in **(±)-149a,b**, **(±)-152a,b**, **(±)-153** and **(±)-154** are predetermined by the structure of the starting materials since the stereocenters of amino esters at C-1 and C-2 were not affected during the ring expansion procedure. Consequently, the *cis* amino ester afforded the corresponding piperidine derivative with the carboxylate and carbamate/amide functions in a *cis* relative arrangement. In the same way, the *trans* amino ester afforded the corresponding piperidine derivative with *trans* relative arrangement of the substituents (*Scheme 29, Scheme 30*)

4. Synthesis of fluorine-containing azepane frameworks.

4.1. Starting materials ethyl cyclohex-3-enecarboxylate **(±)-155** (a commercial product) and cyclohexeneamine **(±)-125** synthesized by the Curtius reaction were further used for the ring-opening step, and the corresponding open-chain dialdehydes were next transformed to the desired substituted azepane derivatives **(±)-158** and **(±)-161** containing the trifluoromethyl group (*Scheme 31, Scheme 32*)

4.2. Disubstituted trifluoromethylated azepane derivative **165** was synthesized from commercially available cyclohexene *cis*-diester **162** (*Scheme 33*)

4.3. The above synthetic approach was applied for the stereocontrolled synthesis of trifluoromethylated azepane β-aminocarboxylate regio- and stereoisomers. Amino esters *cis*-**(±)-167a** and *trans*-**(±)-169a** with an azepane ring were prepared via oxidative ring cleavage and stereocontrolled ring enlargement through reductive amination with 2,2,2-trifluoroethylamine hydrochloride. In the trifluoromethylated azepane products there is a three-carbon-atom distance between the carbamate group and the ring nitrogen atom. The preparation of regioisomers **(±)-167b** and **(±)-169b** of the trifluoromethylated azepane derivatives described above were performed. In these products, the ring nitrogen atom is located at a two-carbon-atom distance from the carbamate group (*Scheme 34*, *Scheme 35*)

4.4. Trifluormethyl-containing *N*-bicyclic diester **(±)-176**, *diexo* and *diendo* β-amino ester frameworks **(±)-180a** and **(±)-180b** were prepared with the developed reaction path (*Scheme 36*, *Scheme 37*, *Scheme 38*)

5. Synthesis of novel 1,2,3,4-tetrahydroisoquinoline scaffolds

5.1. Indene **181** and substituted indene derivatives **191** and **196** as starting materials afforded novel fluorine-containing tetrahydroisoquinoline compounds **184–190, 194, 195** and **(±)-199** (*Scheme 39*, *Scheme 40*, *Scheme 41*, *Table 1*)

5.2. The generalization of the developed pathway was demonstrated by utilizing three different non-fluorinated primary amines. The corresponding *N*-substituted tetrahydroisoquinoline products **200–202** were isolated in moderate yields (*Scheme 42*)

5. ACKNOWLEDGEMENTS

The presented work was carried out in the Institute of Pharmaceutical Chemistry, University of Szeged between 2015 and 2018.

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6. REFERENCES

1. Zhou Y, Wang J, Gu Z, Wang S, Zhu W, Aceña JL, Soloshonok VA, Izawa K, Liu H. *Chem. Rev*. **2016**; *116*: 422–518.
2. Kiss L, Fülöp F. *Chem. Rec*. **2018**; *18*: 266–281.
3. Ojima I, Ed. Fluorine in medicinal chemistry and chemical biology, Wiley-Blackwell: Chichester, U.K, 2009.
4. Vo C-VT, Bode JW. *J. Org. Chem*. **2014**; *79*: 2809–2815.
5. Vo C-VT, Luescher MU, Bode JW. *Nat. Chem*. **2014**; *6*: 310–314.
6. Hameed A, Javed S, Noreen R, Huma T, Iqbal S, Umbreen H, Gulzar T, Farooq T. *Molecules*. **2017**; *22*: 1691.
7. Yan N, Fang Z, Liu Q-Q, Guo X-H, Hu X-G. *Org. Biomol. Chem*. **2016**; *14*: 3469–3475.
8. Walpole C, Liu Z, Lee EE, Yang H, Zhou F, Mackintosh N, Sjogren M, Taylor D, Shen J, Batey RA. *Tetrahedron Lett*. **2012**; *53*: 2942–2947.
9. Patel AR, Liu F. *Tetrahedron*. **2013**; *69*: 744–752.
10. Chernykh A, Tkachenko A, Feskov I, Daniliuc C, Tolmachova N, Volochnyuk D, Radchenko D. *Synlett*. **2016**; *27*: 1824–1827.
11. Hu X-G, Hunter L. *Beilstein J. Org. Chem*. **2013**; *9*: 2696–2708.
12. Han J, Xu B, Hammond GB. *Org. Lett*. **2011**; *13*: 3450–3453.
13. Nonn M, Kiss L, Haukka M, Fustero S, Fülöp F. *Org. Lett*. **2015**; *17*: 1074–1077.
14. Remete A, Nonn M, Fustero S, Fülöp F, Kiss L. *Molecules*. **2016**; *21*: 1493.
15. Kiss L, Petrovszki Á, Vass C, Nonn M, Sillanpää R, Haukka M, Fustero S, Fülöp F. *ChemistrySelect*. **2017**; *2*: 3049–3052.
16. Kiss L, Nonn M, Sillanpää R, Fustero S, Fülöp F. *Beilstein J. Org. Chem*. **2013**; *9*: 1164–1169.
17. Remete AM, Nonn M, Fustero S, Haukka M, Fülöp F, Kiss L. *Beilstein J. Org. Chem*. **2017**; *13*: 2364–2371.
18. Kiss L, Forró E, Fustero S, Fülöp F. *Org. Biomol. Chem*. **2011**; *9*: 6528.
19. Kiss L, Forró E, Fustero S, Fülöp F. *Eur. J. Org. Chem*. **2011**; 4993–5001.
20. Kiss L, Remete AM, Nonn M, Fustero S, Sillanpää R, Fülöp F. *Tetrahedron*. **2016**; *72*: 781–787.

21. Nonn M, Kiss L, Hänninen MM, Sillanpää R, Fülöp F. *Chem. Biodiversity*. **2012**; *9*: 2571–2581.
22. Kiss L, Nonn M, Sillanpää R, Haukka M, Fustero S, Fülöp F. *Chem. Asian J*. **2016**; *11*: 3376–3381.
23. Remete AM, Nonn M, Fustero S, Haukka M, Fülöp F, Kiss L. *Eur. J. Org. Chem*. **2018**; *27*: 3735-3742.
24. Kiss L, Nonn M, Forró E, Sillanpää R, Fustero S, Fülöp F. *Eur. J. Org. Chem*. **2014**; 4070–4076.
25. Dolbier WR. *J. Fluorine Chem*. **2005**; *126*: 157–163.
26. O'Hagan D. *Chem. Soc. Rev.* **2008**; *37*: 308–319.
27. Böhm H-J, Banner D, Bendels S, Kansy M, Kuhn B, Müller K, Obst-Sander U, Stahl M. *ChemBioChem*. **2004**; *5*: 637–643.
28. O'Hagan D. *J. Fluorine Chem*. **2010**; *131*: 1071–1081.
29. Ma J-A, Cahard D. *Chem. Rev*. **2008**; *108*: PR1–PR43.
30. Nie J, Guo H-C, Cahard D, Ma J-A. *Chem. Rev*. **2011**; *111*: 455–529.
31. Cahard D, Xu X, Couve-Bonnaire S, Pannecoucke X. *Chem. Soc. Rev.* **2010**; *39*: 558–568.
32. Wang J, Sánchez-Roselló M, Aceña JL, del Pozo C, Sorochinsky AE, Fustero S, Soloshonok VA, Liu H. *Chem. Rev*. **2014**; *114*: 2432–2506.
33. Singh IP, Shah P. *Expert Opinion on Therapeutic Patents*. **2017**; *27*: 17–36.
34. Lohse A, Bols M. *Tetrahedron*. **1997**; *53*: 6917–6924.
35. Kiss L, Forró E, Fülöp F. *Beilstein J. Org. Chem*. **2015**; *11*: 596–603.
36. Kiss L, Fülöp F. *Chem. Rev*. **2014**; *114*: 1116–1169.
37. Sousa CAD, Rizzo-Aguiar F, Vale MLC, García-Mera X, Caamaño O, Rodríguez-Borges JE. *Tetrahedron Lett*. **2012**; *53*: 1029–1032.
38. Wu L, Chen P, Liu G. *Org. Lett*. **2016**; *18*: 960–963.
39. Beng TK, Wilkerson-Hill SM, Sarpong R. *Org. Lett*. **2014**; *16*: 916–919.
40. Schmitt S, Colloc'h N, Perrio C. *Eur. J. Med. Chem*. **2015**; *90*: 742–750.
41. Riss PJ, Hummerich R, Schloss P. *Org. Biomol. Chem*. **2009**; *7*: 2688.
42. Toyama H, Sato S, Shirakawa H, Komai M, Hashimoto Y, Fujii S. *Bioorg. Med. Chem. Lett*. **2016**; *26*: 1817–1820.
43. Lenz M, Borlinghaus N, Weinmann L, Nestl BM. *World J. Microbiol. Biotechnol*. **2017**; *33:* 199.

44. Singh GS, Sudheesh S, Keroletswe N. *Arkivoc*. **2017**; *2018*: 50–113.
45. Blakemore DC, Castro L, Churcher I, Rees DC, Thomas AW, Wilson DM, Wood A. *Nat. Chem*. **2018**; *10*: 383–394.
46. Jindakun C, Hsieh S-Y, Bode JW. *Org. Lett*. **2018**; *20*: 2071–2075.
47. Singh K, Vellakkaran M, Banerjee D. *Green Chem*. **2018**. DOI: 10.1039/c8gc00318a
48. Travis BR, Narayan RS, Borhan B. *J. Am. Chem. Soc*. **2002**; *124*: 3824–3825.
49. Parida KN, Moorthy JN. *Tetrahedron*. **2014**; *70*: 2280–2285.
50. Gichumbi JM, Omondi B, Friedrich HB. *J. Organomet. Chem*. **2018**; *856*: 56–62.
51. Nicolaou KC, Adsool VA, Hale CRH. *Org. Lett*. **2010**; *12*: 1552–1555.
52. Milas NA, Sussman S. *J. Am. Chem. Soc*. **1936**; *58*: 1302–1304.
53. Schröder M. *Chem. Rev.* **1980**, *80*: 187-213.
54. VanRheenen V., Cha D. Y., Hartley W. M. *Org. Syntheses*. **1978**; *58*: 43.
55. Miyamoto K, Sei Y, Yamaguchi K, Ochiai M. *J. Am. Chem. Soc*. **2009**; *131*: 1382–1383.
56. Fricke Y, Nicole K, Bernhard W. *Synthesis*. **2010**; *5*: 791–796.
57. Petricci E, Santillo N, Castagnolo D, Cini E, Taddei M. *Adv. Synth. Catal*. **2018**; *360*: 2560-2565.
58. Baxter EW, Johnson TRW. *Org. Reactions.* **2002***;* 1-714.
59. De A, Ghosal NC, Mahato S, Santra S, Zyryanov GV, Majee A. *ChemistrySelect*. **2018**; *3*: 4058–4066.
60. Fasano V, Radcliffe JE, Ingleson MJ. *ACS Catal*. **2016**; *6*: 1793–1798.
61. Borch RF. *J. Am. Chem. Soc.* **1971**; 2897-2904.
62. Kumar I, Ramaraju P, Mir NA, Singh A. *Org. Biomol. Chem*. **2015**; *13*: 1280–1293.
63. Robinson R. *J. Chem. Soc, Transactions*. **1917**; *111*: 762–768.
64. Han R, Wang Y, Li Y, Xu P. *Adv. Synth. Catal*. **2008**; *350*: 1474–1478.
65. Kumar I, Ramaraju P, Mir NA, Singh D, Gupta VK, Rajnikant. *Chem. Commun*. **2013**; *49*: 5645.
66. He Z-Q, Han B, Li R, Wu L, Chen Y-C. *Org. Biomol. Chem.*. **2010**; *8*: 755–757.
67. Malik G, Guinchard X, Crich D. *Org. Lett.*. **2012**; *14*: 596–599.
68. Grotenbreg GM, Christina AE, Buizert AEM, van der Marel GA, Overkleeft HS, Overhand M. *J. Org. Chem*. **2004**; *69*: 8331–8339.
69. Paul S, Caruthers MH. *J. Am. Chem. Soc.* **2016**; *138*: 15663–15672.
70. Summerton J, Weller D. *Antisense and Nucleic Acid Drug Dev*. **1997**; *7*: 187–195.

71. Shih T-L, Kuo W-S, Lin Y-L. *Tetrahedron Lett*. **2004**; *45*: 5751–5754.
72. Shih T-L, Yang R-Y, Li S-T, Chiang C-F, Lin C-H. *J. Org. Chem*. **2007**; *72*: 4258–4261.
73. Shih T-L, Liang M-T, Wu K-D, Lin C-H. *Carbohydr. Res*. **2011**; *346*: 183–190.
74. Kiss L, Kazi B, Forró E, Fülöp F. *Tetrahedron Lett*. **2008**; *49*: 339–342.
75. Kazi B, Kiss L, Forró E, Fülöp F. *Tetrahedron Lett*. **2010**; *51*: 82–85.
76. Kazi B, Kiss L, Forró E, Mándity I, Fülöp F. *Arkivoc*. **2010**; *9*: 31-39.
77. Cirak S, Arechavala-Gomeza V, Guglieri M, Feng L, Torelli S, Anthony K, Abbs S, Garralda ME, Bourke J, Wells DJ, Dickson G, Wood MJ, Wilton SD, Straub V, Kole R, Shrewsbury SB, Sewry C, Morgan JE, Bushby K, Muntoni F. *Lancet*. **2011**; *378*: 595–605.
78. Lim KR, Maruyama R, Yokota T. *Drug Des. Devel. Ther*. **2017**; *11*: 533–545.
79. Hameršak Z, Roje M, Avdagić A, Šunjić V. *Tetrahedron: Asymmetry*. **2007**; *18*: 635–644.
80. Benedek G, Palkó M, Wéber E, Martinek TA, Forró E, Fülöp F, *Eur. J. Org. Chem.* **2008**, 3724-3730.
81. Szakonyi Z, Gyónfalvi S, Forró E, Hetényi A, De Kimpe N, Fülöp F. *Eur. J. Org. Chem.* **2005**; 4017–4023.
82. Salwiczek M, Nyakatura EK, Gerling UIM, Ye S, Koksch B. *Chem. Soc. Rev.* **2012**; *41*: 2135–2171.
83. Absalom N, Yamamoto I, O'Hagan D, Hunter L, Chebib M. *Aust. J. Chem*. **2015**; *68*: 23.
84. Vogensen SB, Jørgensen L, Madsen KK, Jurik A, Borkar N, Rosatelli E, Nielsen B, Ecker GF, Schousboe A, Clausen RP. *Bioorg. Med. Chem*. **2015**; *23*: 2480–2488.
85. Jeanmart S, Edmunds AJF, Lamberth C, Pouliot M. *Bioorg. Med. Chem*. **2016**; *24*: 317–341.
86. Kalow JA, Schmitt DE, Doyle AG. *J. Org. Chem*. **2012**; *77*: 4177–4183.
87. Fustero S, Sanz-Cervera J, Aceña J, Sánchez-Roselló M. *Synlett*. **2009**; 525–549.
88. Artamonov O, Slobodyanyuk E, Shishkin O, Komarov I, Mykhailiuk P. *Synthesis*. **2012**; *45*: 225–230.
89. Verniest G, Piron K, Van Hende E, Thuring JW, Macdonald G, Deroose F, De Kimpe N. *Org. Biomol. Chem*. **2010**; *8*: 2509.

90. Kiss L, Forró E, Martinek TA, Bernáth G, De Kimpe N, Fülöp F. *Tetrahedron*. **2008**; *64*: 5036–5043.
91. Cherepanova M, Kiss L, Fülöp F. *Tetrahedron*. **2014**; *70*: 2515–2522.
92. Benedek G, Palkó M, Wéber E, Martinek TA, Forró E, Fülöp F. *Tetrahedron: Asymmetry*. **2009**; *20*: 2220–2225.
93. Forró E, Megyesi R, Paál TA, Fülöp F. *Tetrahedron: Asymmetry*. **2016**; *27*: 1213–1216.
94. Perrey DA, German NA, Gilmour BP, Li J-X, Harris DL, Thomas BF, Zhang Y. *J. Med. Chem.* **2013**; *56*: 6901–6916.
95. Liu W, Liu S, Jin R, Guo H, Zhao J. *Org. Chem. Front*. **2015**; *2*: 288–299.
96. Le VH, Inai M, Williams RM, Kan T. *Nat. Prod. Rep*. **2015**; *32*: 328–347.
97. Santangelo Freel RM, Ogden KK, Strong KL, Khatri A, Chepiga KM, Jensen HS, Traynelis SF, Liotta DC. *J. Med. Chem*. **2013**; *56*: 5351–5381.
98. Dzierszinski F, Coppin A, Mortuaire M, Dewailly E, Slomianny C, Ameisen J-C, DeBels F, Tomavo S. *Antimicrob. Agents Chemother*. **2002**; *46*: 3197–3207.
99. Chrzanowska M, Grajewska A, Rozwadowska MD. *Chem. Rev*. **2016**; *116*: 12369–12465.
100. Balamurugan K, Jeyachandran V, Perumal S, Menéndez JC. *Tetrahedron*. **2011**; *67*: 1432–1437.
101. Hopkins BA, Wolfe JP. *Chem. Sci.* **2014**; *5*: 4840–4844.
102. Awuah E, Capretta A. *J. Org. Chem*. **2010**; *75*: 5627–5634.
103. Si C, Myers AG. *Angew. Chem.* **2011**; *123*: 10593–10597.
104. Jayakumar J, Parthasarathy K, Cheng C-H. *Angew. Chem*. **2012**; *124*: 201–204.
105. Pilgrim BS, Gatland AE, McTernan CT, Procopiou PA, Donohoe TJ. *Org. Lett*. **2013**; *15*: 6190–6193.
106. Stöckigt J, Antonchick AP, Wu F, Waldmann H. *Angew. Chem. Int. Ed*. **2011**; *50*: 8538–8564.
107. Xu T, Liu G. *Org. Lett*. **2012**; *14*: 5416–5419.
108. Kuninobu Y, Nagase M, Kanai M. *Angew. Chem. Int. Ed*. **2015**; *54*: 10263–10266.
109. Liu Q, Wu Y, Chen P, Liu G. *Org. Lett*. **2013**; *15*: 6210–6213.
110. Sloop JC. *J. Chem*. **2017**; 1–15.
111. Mormino MG, Fier PS, Hartwig JF. *Org. Lett*. **2014**; *16*: 1744–1747.
112. Zhang B, Studer A. *Org. Biomol. Chem.* **2014**; *12*: 9895–9898.

ANNEX