PhD thesis

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

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2019

University of Szeged
Doctoral School of Pharmaceutical Sciences

Educational programme: Pharmaceutical Chemistry and Drugs Research
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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.

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. 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.

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.

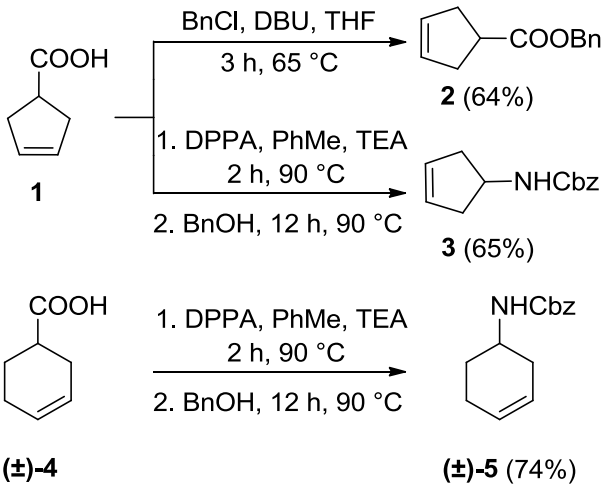
2. Methods

The synthesized compounds were separated and purified by column chromatography on silica gel. The newly prepared compounds were characterized by NMR spectroscopy, mass spectrometry, melting point measurement and elemental analysis.

3. Results and discussion

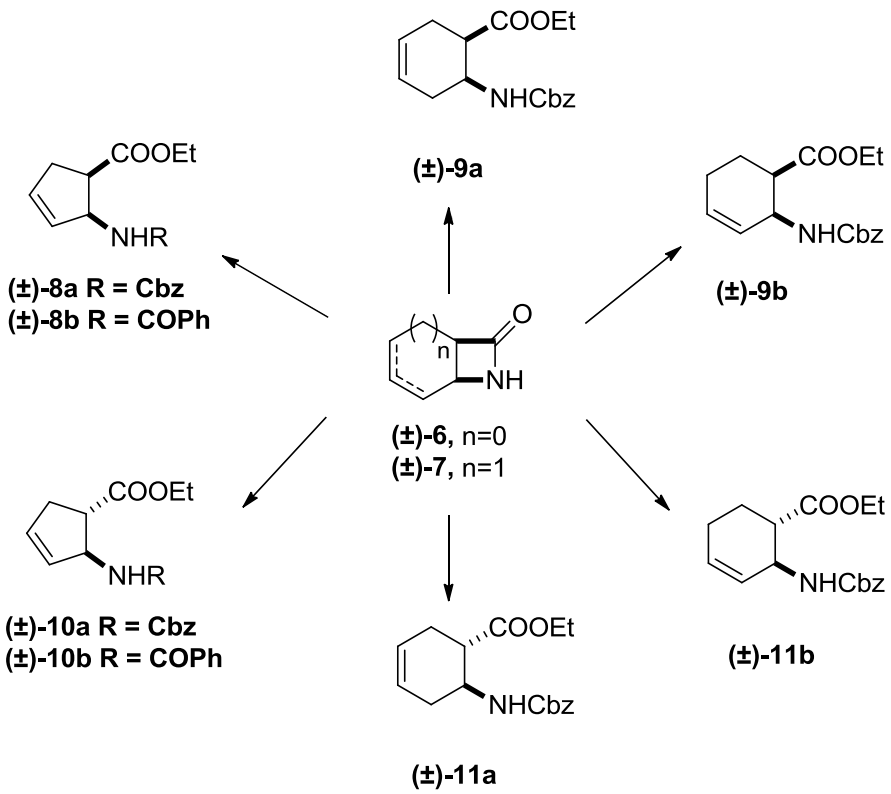
3.1. Synthesis of starting materials

The required starting materials were synthesized by using simple, known literature methods. Five- and six-membered substituted cycloalkenes **2**, **3** and **(±)-5** were prepared from commercially available cyclopent-3-enecarboxylic acid **1** and cyclohex-3-enecarboxylic acid **(±)-4** via the Curtius reaction and esterification (*Scheme 1*)



Scheme 1. Preparation of five- and six-membered substituted cycloalkenes

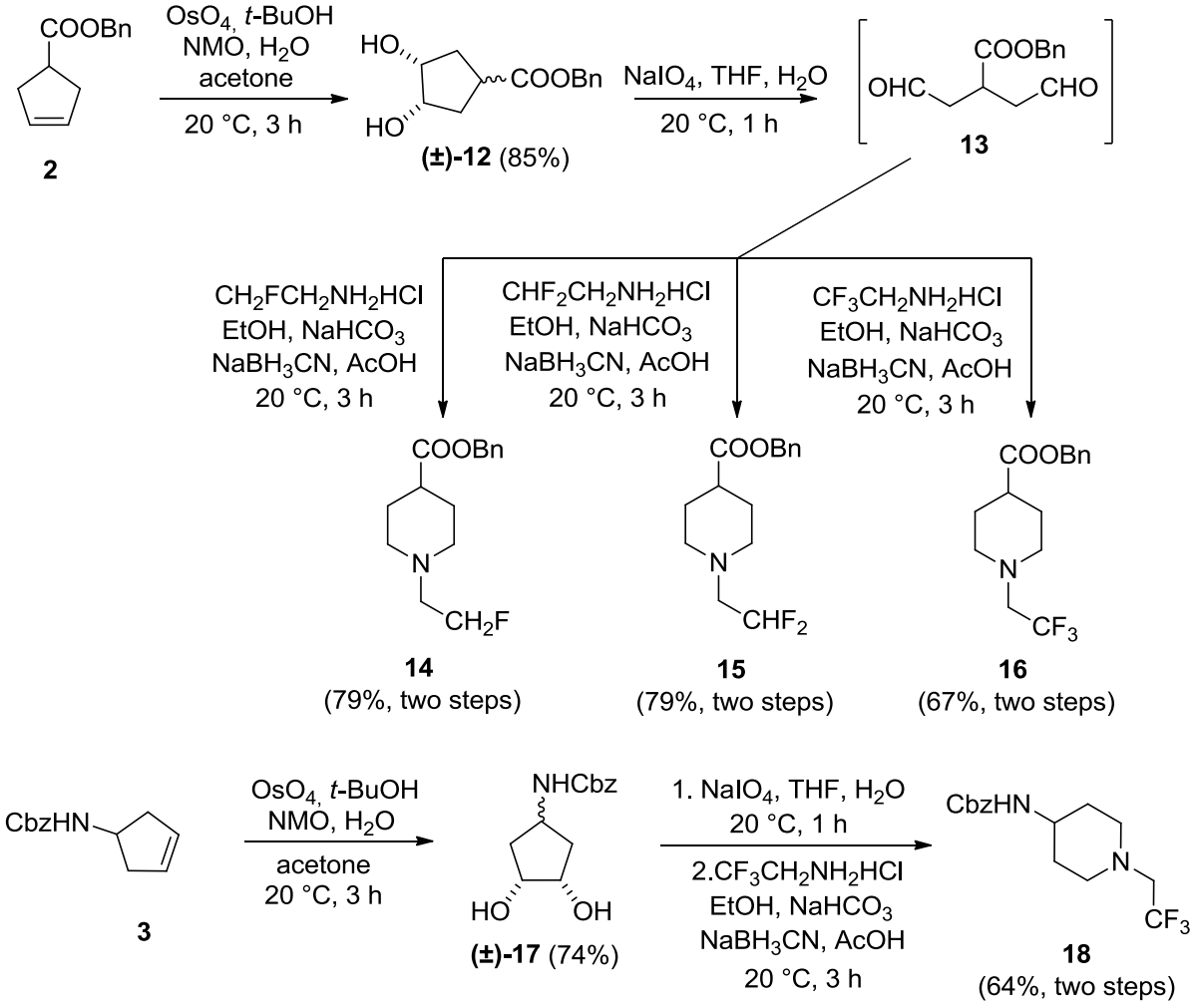
N-Protected *cis* β-aminocyclopentene carboxylates **(±)-8a,b** and *cis* β-aminocyclohexene carboxylates **(±)-9a,b** were prepared and used as starting materials, with two different protecting groups (Cbz and COPh) from readily available unsaturated bicyclic β-lactams **(±)-6** and **(±)-7**. With the epimerization at C-1, the corresponding *trans* β-amino carboxylate isomers **(±)-10a,b** and **(±)-11a,b** were synthetized (*Scheme 2*).



Scheme 2. Synthesis of *N*-protected β-aminocyclopentene and β-aminocyclohexene carboxylates

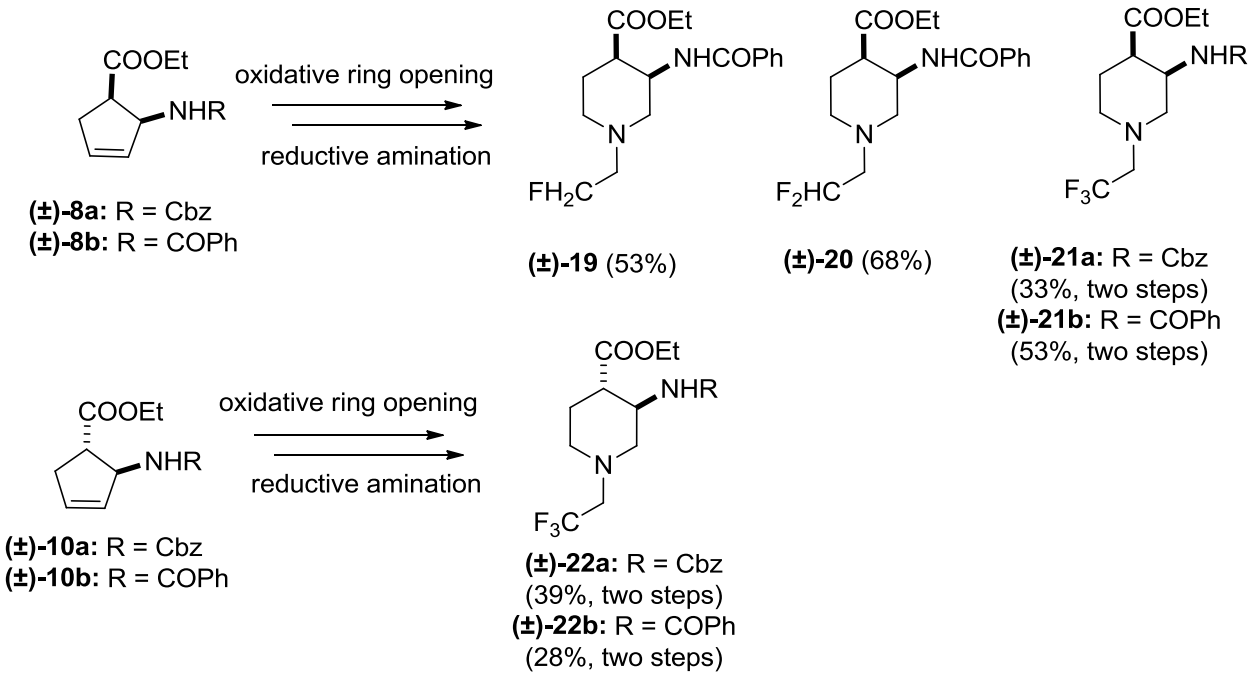
3.2. Synthesis of fluorine-containing piperidine derivatives

The synthetic concept to fluorine-containing **14**, **15**, **16** and **18** 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 3*).



Scheme 3. Synthesis of functionalized piperidine derivatives

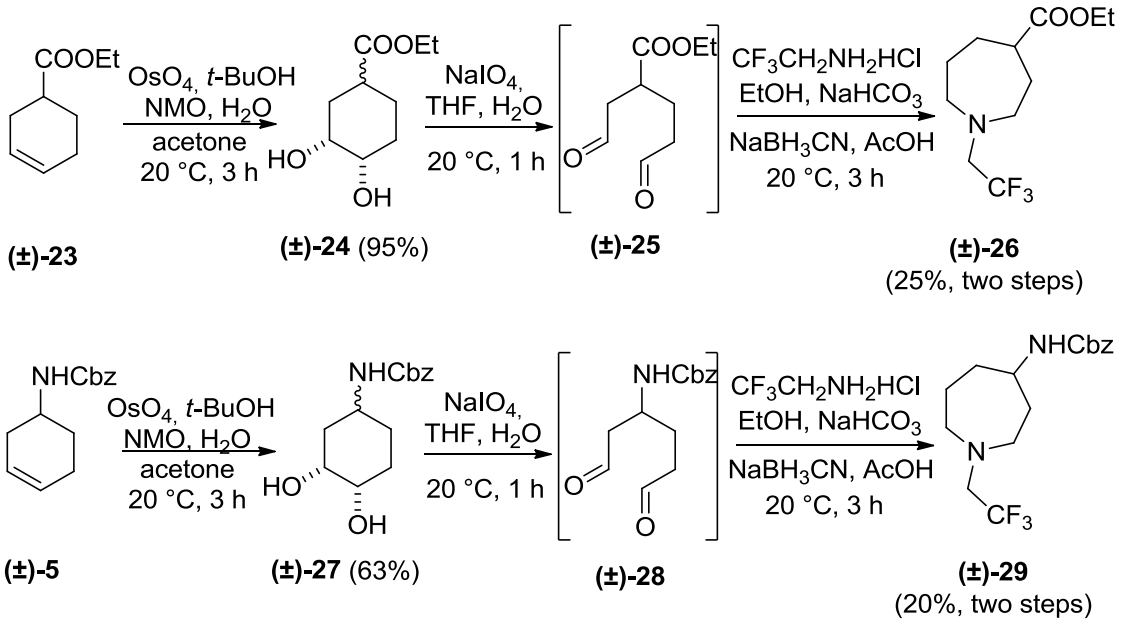
Unsaturated β-amino ester **(±)-8a,b** and **(±)-10-a,b** were transformed into β-amino esters with piperidine skeleton [**(±)-19, (±)-20, (±)-21a,b**, and**(±)-22a,b**]. The configurations of the chiral centers in **(±)-19, (±)-20, (±)-21a,b**, and **(±)-22a,b** are predetermined by the structure of 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 (*Scheme 4).*



Scheme 4. Synthesis of fluorinated piperidine β-amino esters

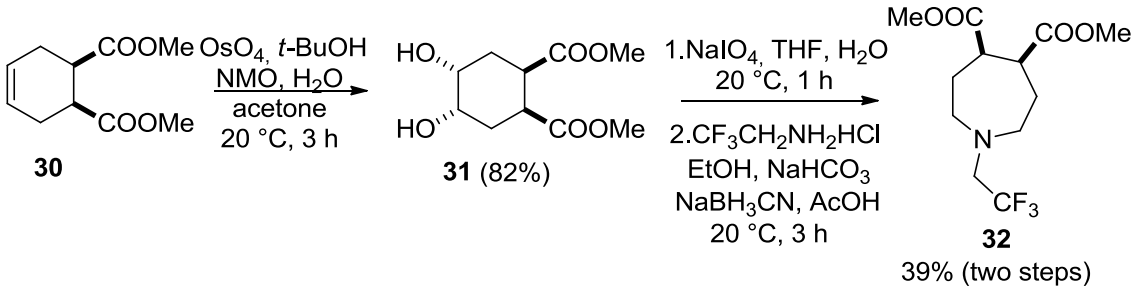
3.3. Synthesis of fluorine-containing azepane frameworks

Starting materials ethyl cyclohex-3-enecarboxylate **(±)-23** (a commercial product) and cyclohexeneamine **(±)-5** 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 **(±)-26** and **(±)-29** containing the trifluoromethyl group (*Scheme 5*).



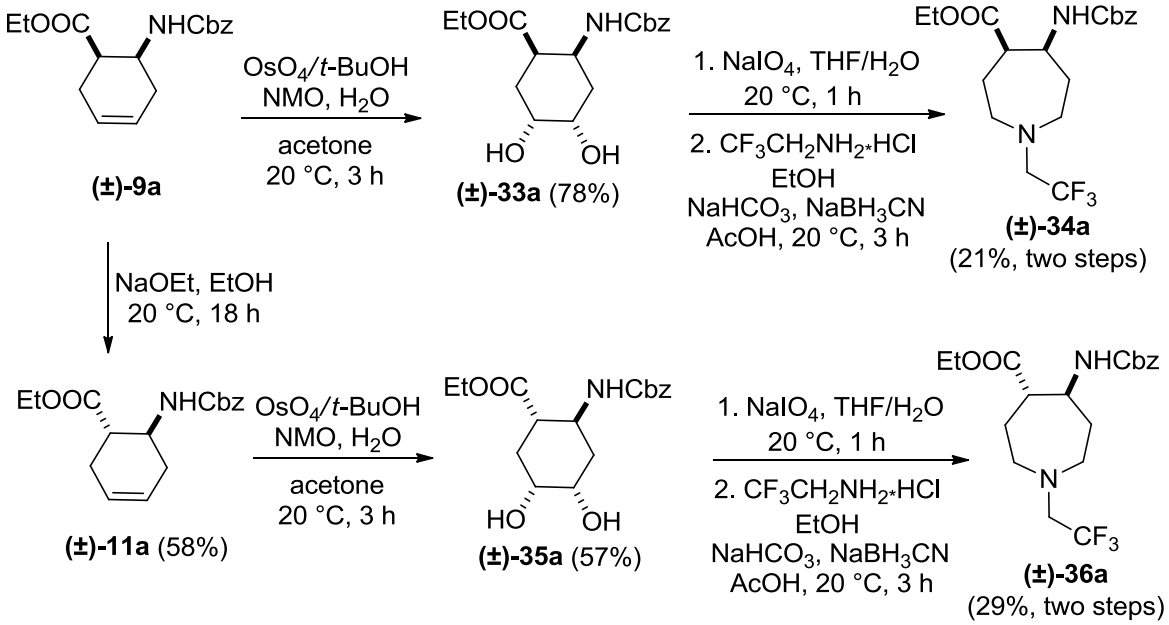
Scheme 5. Synthesis of functionalized azepane derivatives

Disubstituted trifluoromethylated azepane derivative **32** was synthesized from commercially available cyclohexene *cis*-diester **30** (*Scheme 6*).



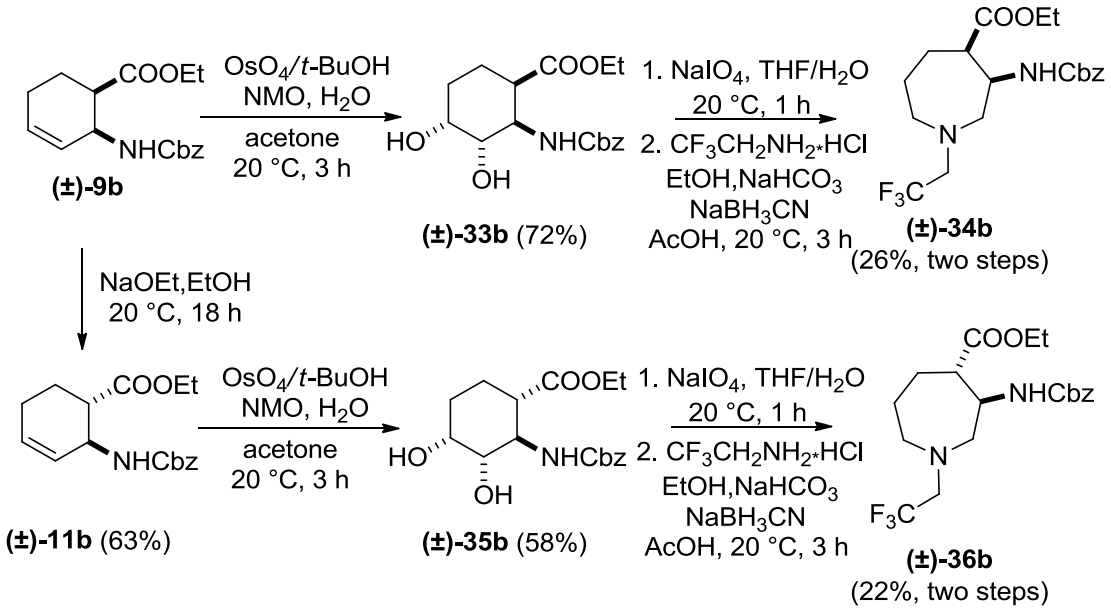
Scheme 6. Synthesis of disubstituted trifluoromethylated azepane derivative

The above synthetic approach was applied for the stereocontrolled synthesis of trifluoromethylated azepane β-aminocarboxylate regio- and stereoisomers. Amino esters *cis*-**(±)-34a** and *trans*-**(±)-36a** 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 (*Scheme 7*).



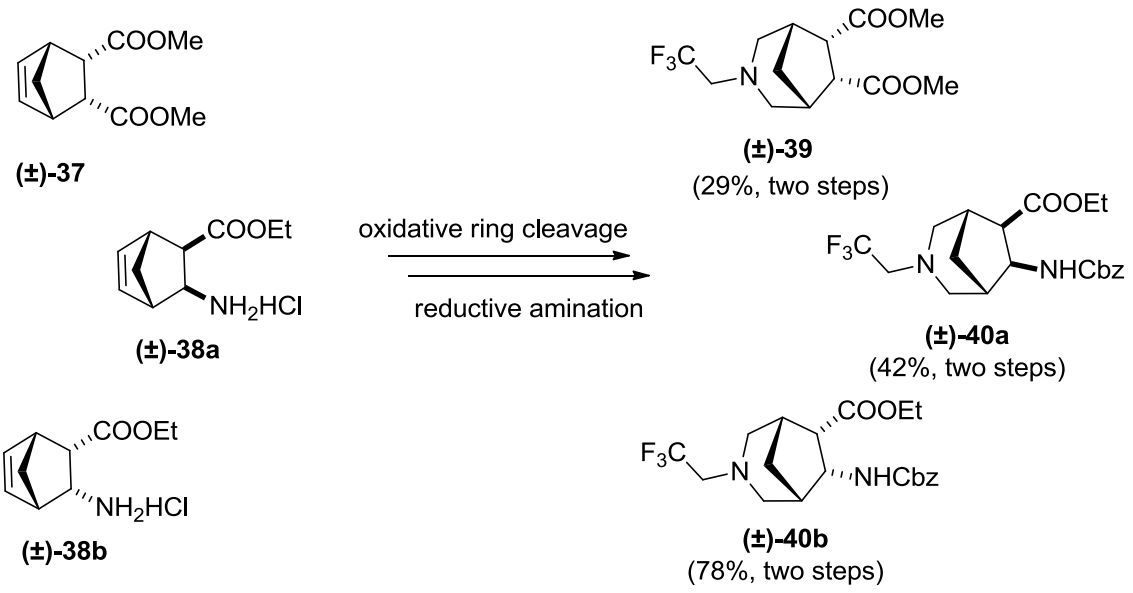
Scheme 7. Preparation of fluorine-containing *cis* and *trans* azepane β-amino esters

The preparation of regioisomers **(±)-34b** and **(±)-36b** 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 8*).



Scheme 8. Preparation of trifluoromethylated *cis* and *trans* azepane β-amino esters

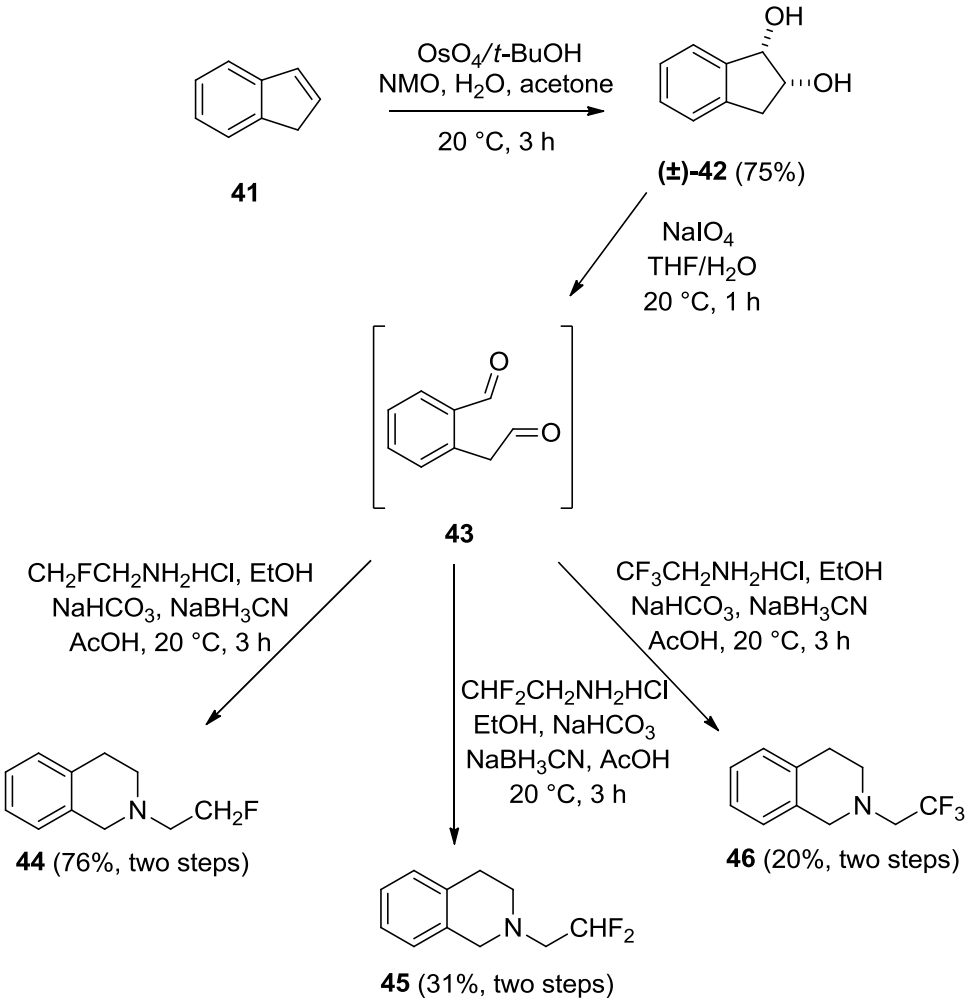
Trifluormethyl-containing *N*-bicyclic diester **(±)-39**, *diexo* and *diendo* β-amino ester frameworks **(±)-40a** and **(±)-40b** were prepared with the developed reaction path (*Scheme 9*).



Scheme 9. Synthesis of fluorine-containing azabicyclic azepane systems

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

Indene **41** as starting material afforded novel fluorine-containing tetrahydroisoquinoline compounds **44, 45, 46** (*Scheme 10*).



Scheme 10. 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 **(±)-42** prepared previously, was subjected to oxidative ring opening followed by the treatment of the resulting dialdehyde (**43**) with various commercially accessible trifluoromethylated or polyfluorinated amines furnished the corresponding *N*-heterocycles (**47–50**) (*Table 1*).

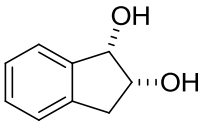
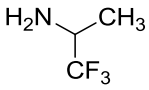
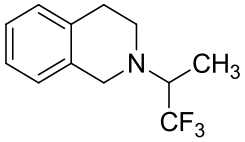
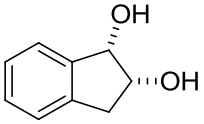
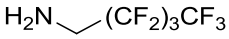
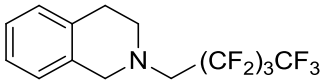
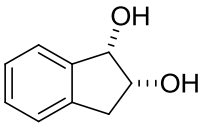
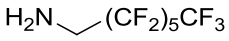
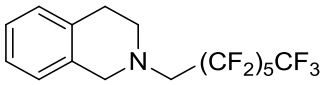
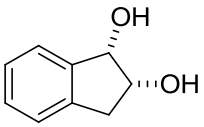
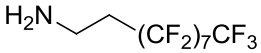
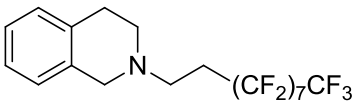
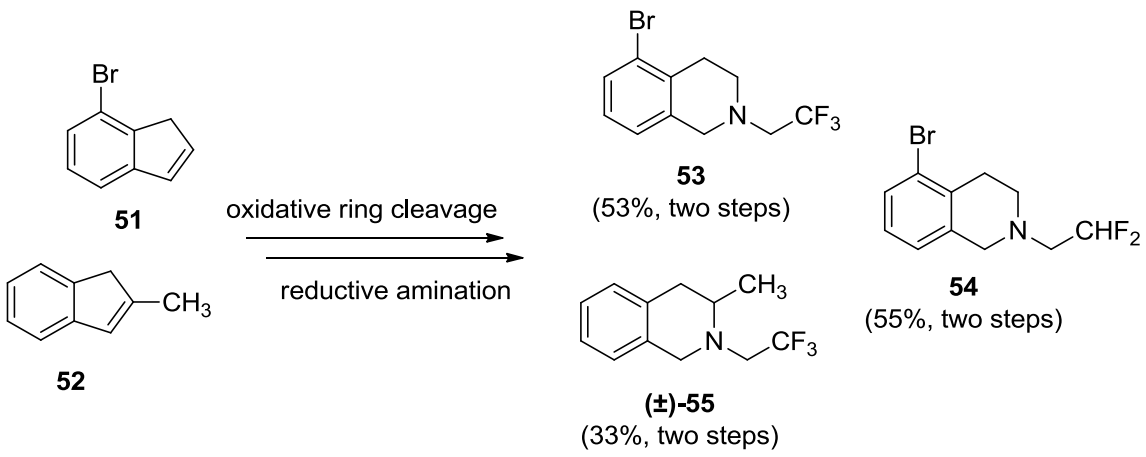
Starting compound	Fluorinated amine	Product	Yield (%) (two steps)
		 (**47**)	34
		 (**48**)	24
		 (**49**)	53
		 (**50**)	28

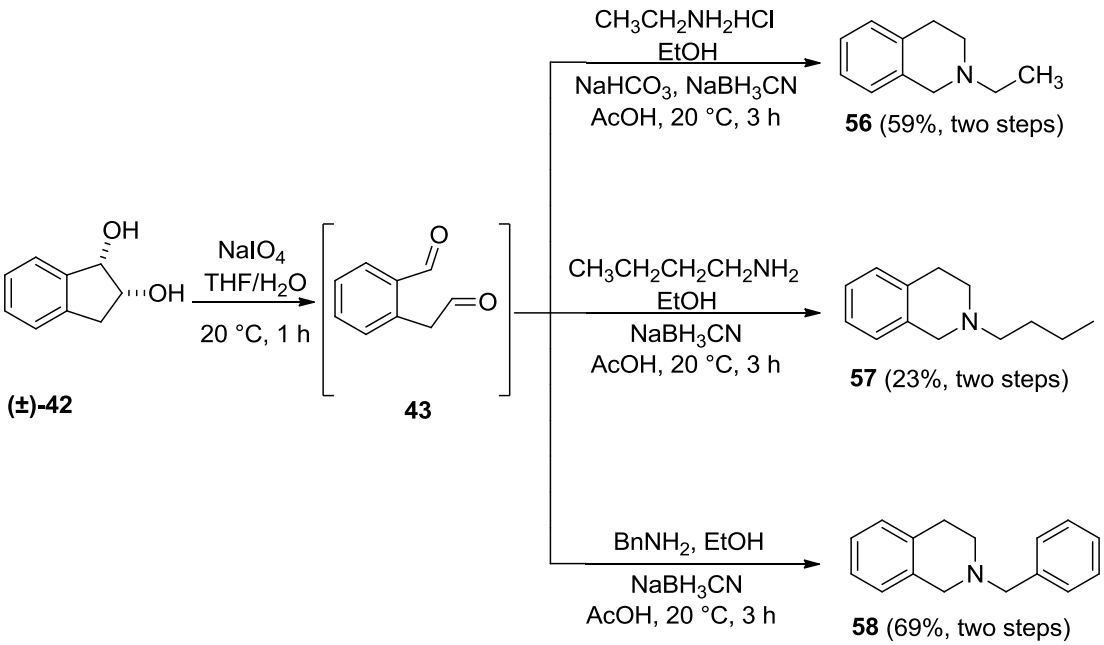
Table 1 Synthesis of novel fluorinated THIQ frameworks **47–50**

The synthetic route presented above was further extended by using 7-bromo-1*H*-indene (**51**) and 2-methyl-1*H*-indene (**52**) (*Scheme 11*).



Scheme 11. Synthesis of novel fluorinated THIQ frameworks

The generalization of the developed pathway was demonstrated by utilizing three different non-fluorinated primary amines. The corresponding *N*-substituted tetrahydroisoquinoline products **56-58** were isolated in moderate yields (*Scheme 12*).



Scheme 12. Generalization of the developed method

List of publications and lectures

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
Synthesis **2017**, *49*, 1206–1213.

IV. **Ábrahámi, R. A.**; Fustero, S.; Fülöp, F.; Kiss, L.:
A de novo synthetic access route to 1,2,3,4-tetrahydroisoquinoline derivatives
Synlett, **2018**, *29*, 2066-2070.

Other publications:

V. Kiss, L.; Forró, E.; Orsy Gy.; **Ábrahámi, R. A.**; Fülöp, F.:
Stereo- and Regiocontrolled Syntheses of Exomethylenic Cyclohexane -Amino Acid Derivatives
Molecules **2015**, *20*, 21094-21102.

Conference lectures

VI. **Ábrahámi, R. A.**:
Fluortartalmú piperidin és azepánvázas β-aminosavszármazékok szintézisei
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány és a SZAB Szerves és Gyógyszerkémiai Munkabizottsága 15. tudományos előadóülés
Szeged, Hungary, 12 May, 2016, oral presentation

VII. **Ábrahámi, R.A.**; Kiss, L.; Fülöp, F.:
Fluortartalmú piperidin és azepánvázas β-aminosavszármazékok szintézisei
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
Balatonszemes, Hungary, 18-20 May, 2016, oral presentation

VIII. Kiss, L.; **Ábrahámi. R. A.**; Fustero, S.; Fülöp, F.:
Synthesis of Trifluoromethylated Piperidine and Azepane β-Amino Acid Derivatives
Bremen FluorineDays 2016
Bremen, Germany, 7-3 July, 2016, Abstr.: P05, poster presentation

IX. **Ábrahámi. R. A.**; Kiss, L.; Fustero, S.; Fülöp, F.:
Synthesis of trifluormethylated piperidine and azepane derivatives
8th Central European Conference „Chemistry towards Biology"
Brno, Czech Republic, 28th Aug– 1st Sept, 2016, Abstr.: P-01, poster presentation

X. **Ábrahámi, R. A.**; Kiss, L.; Fustero, S., Fülöp, F.:
Trifluormetilcsoportot tartalmazó piperidin és azepánvázas vegyületek szintézise
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '16
Herceghalom, Hungary, 15-16 Sept, 2016, oral presentation.

XI. **Ábrahámi, R. A.**:
Trifluormetilcsoportot tartalmazó piperidin és azepánvázas β-aminosavszármazékok szintézisei
Clauder Ottó Emlékverseny
Budapest, Hungary, 20-21 Oct, 2016, oral presentation

XII. **Ábrahámi, R. A.**; Kiss, L.; Fülöp, F.:
Fluortartalmú, funkcionalizált *N*-heterociklusok sztereokontrollált szintézisei
Alkaloid- és Flavonoidkémiai Munkabizottság Ülése
Mátrafüred, Hungary, 6-7 Apr, 2017, oral presentation

XIII. **Ábrahámi, R. A.**; Kiss, L.; Fülöp, F.:
Új sztereokontrollált szintézisutak fluortartalmú *N*-heterociklusok előállítására
Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
Balatonszemes, Hungary, 15-17 May, 2017, oral presentation

XIV. Kiss, L.; **Ábrahámi**, **R. A.**; Fülöp F.:
Functionalized dialdehydes: promising scaffolds for the access of fluorinated heterocycles and highly functionalized β-amino acids
XVII. International Conference on Heterocycles in Bioorganic Chemistry
Galway, Ireland, 28-31 May, 2017, oral presentation

XV. **Ábrahámi, R. A.**; Kiss, L.; Fülöp, F.:
Új sztereokontrollált szintézisutak fluorozott *N*-heterociklusok előállítására
Vegyészkonferencia
Hajdúszoboszló, Hungary, 19-21 June, 2017, Abstr.: P-01, poster presentation

XVI. **Ábrahámi, R. A.**; Fülöp, F.; Kiss, L.:
Új szintézisút fluorozott 1,2,3,4-tetrahidroizokinolinvázas vegyületek előállítására
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium '17
Szeged, Hungary, 11-12 Sept, 2017, oral presentation

XVII. **Ábrahámi, R. A.**; Fülöp, F.; Kiss, L.:
Novel synthesis of fluorinated 1,2,3,4- tetrahydroisoquinoline derivatives
7th BBBB International Conference on Pharmaceutical Sciences
Balatonfüred, Hungary, 5-7 Oct, 2017, Abstr.: P1F-4, poster presentation

XVIII. **Ábrahámi, R. A.**:
Új, trifluormetilcsoportot tartalmazó piperidin- és azepánvázas vegyületek szintézisei
Magyar Tudomány Ünnepe- 2016/2017 évi UNKP program támogatását elnyert hallgatók eredményei
Szeged, Hungary, 9. Nov, 2017, oral presentation