

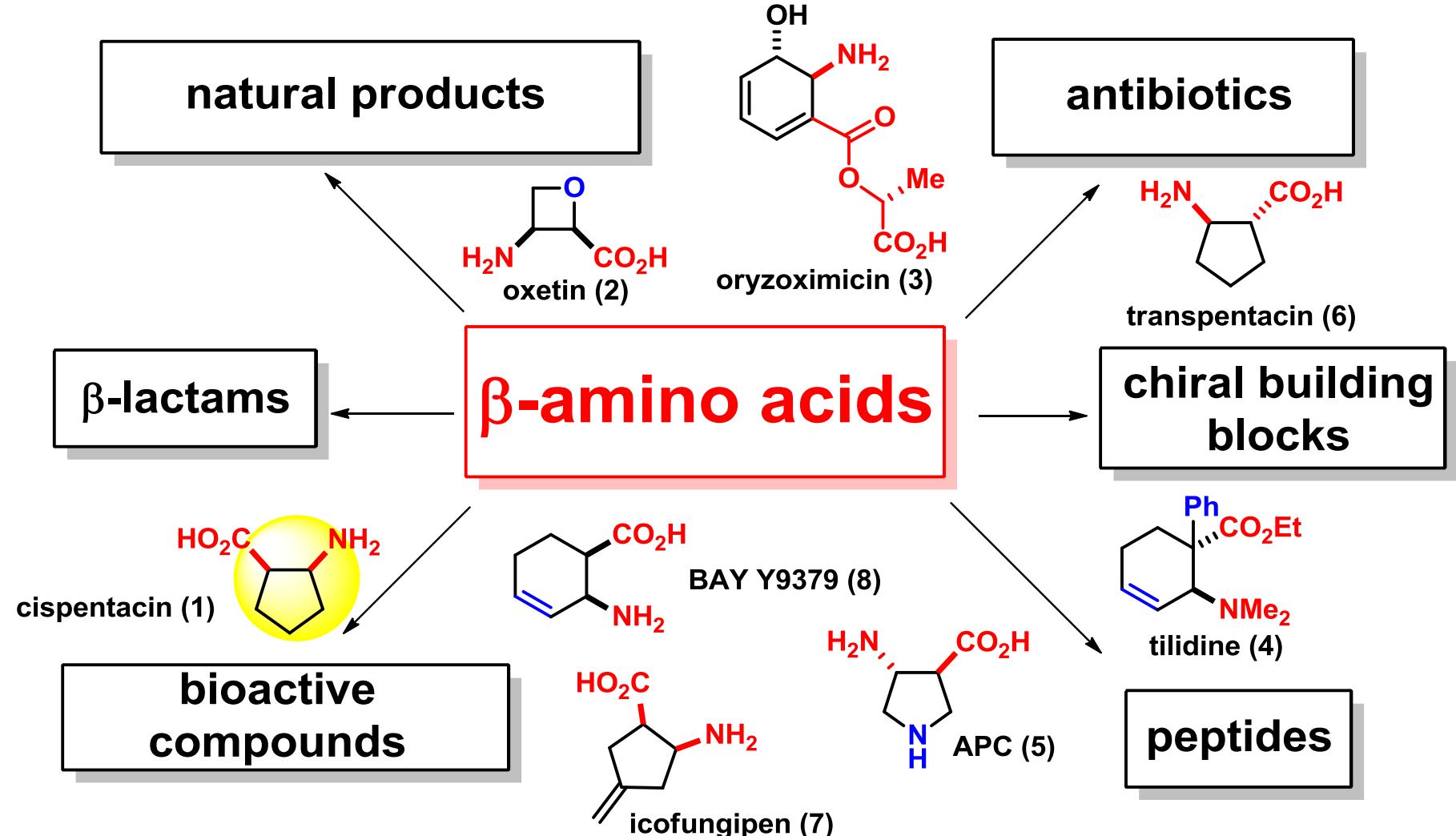


Selective methods for the synthesis of fluorine-containing cyclic β -amino acid derivatives



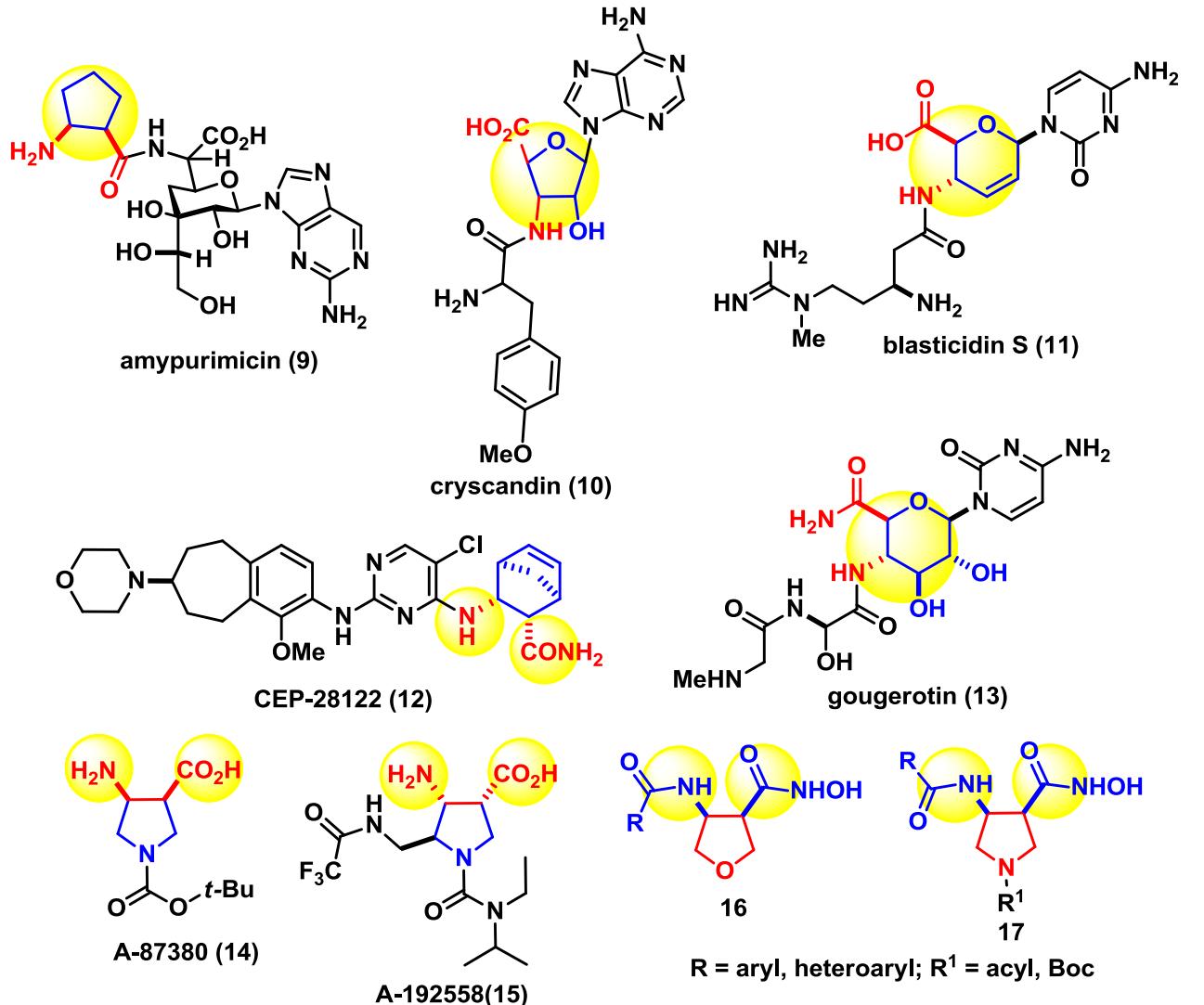
Loránd Kiss, Renáta A. Ábrahámi, Attila M. Remete, Melinda Nonn
University of Szeged, Institute of Pharmaceutical Chemistry, Szeged, Hungary
24th Winter Fluorine Conference, 2019, January 13-18, Clearwater, Florida

Cyclic β -amino acid derivatives

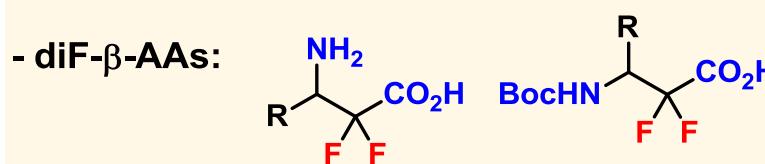
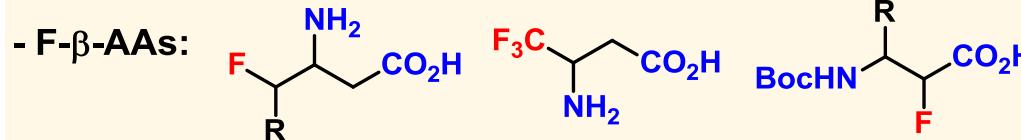
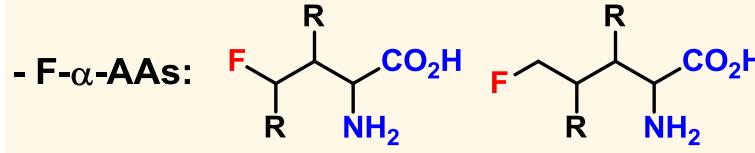


Cyclic β -amino acid derivatives

- antibiotics
- antitumoral agents
- antiviral agents



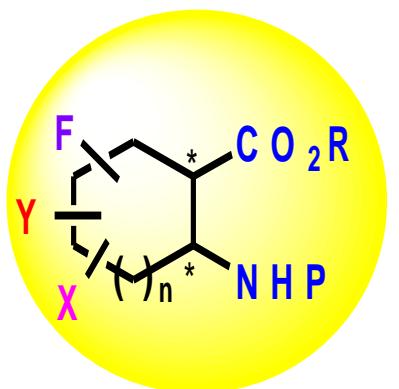
Fluorine-containing amino acids



- bioactive derivatives, antibacterial, antitumoral agents, peptides



*Fluorinations of functionalized alicycles:
a game with molecules and reagents*



- (a) Remete AM, Nonn M, Fustero S, Fülöp F, Kiss L, *Tetrahedron* **2018**, 74, 6367. (b) Mikami K, Fustero S, Sanchez-Rosello M, Acena JL, Soloshonok V, Sorochinsky A, *Synthesis* **2011**, 43, 3045. (c) Acena JL, Sorochinsky A, Soloshonok VA, *Synthesis* **2012**, 44, 1591. (d) Acena JL, Simon-Fuentes A, Fustero S, *Curr. Org. Chem.* **2010**, 14, 928. (e) Qiu XL, Qing FL, *Eur. J. Org. Chem.* **2011**, 3261. (f) Absalom N, Yamamoto I, O'Hagan D, Hunter L, Chebib M, *Aust. J. Chem.* **2015**, 68, 23. (g) Fraser SA, Easton CJ, *Aust. J. Chem.* **2015**, 68, 9.

Synthesis of highly functionalized, fluorine-containing cyclic β -amino acid derivatives

aims: - fluorinated, highly functionalized β -amino acid derivatives
- fluorine-containing three-dimensional small molecules

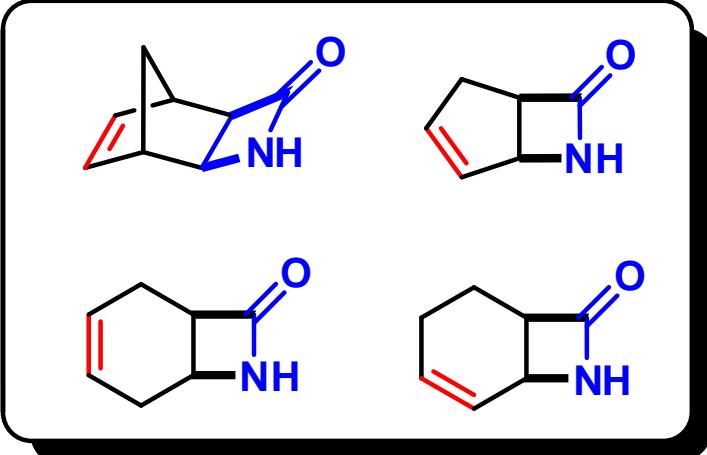
- selective fluorinations:

A. - direct fluorinations:

hydroxy-fluorine/oxo-difluorine exchange („late-stage”)

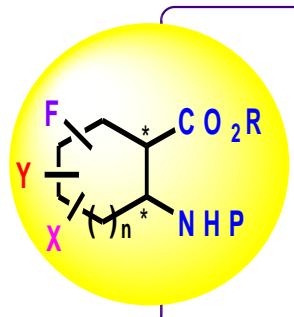
- stereo- and regioselective hydroxylation

B. - fluorine-containing building elements: fluorinated amines



regio- and stereoselective synthetic strategies

stereocontrolled transformations



diversely functionalized,
 β -amino acid derivatives
with multiple stereocenters
multifunctionalized alicyclic
and heterocyclic scaffolds

Methods:

A. hydroxy-fluorine exchange

I. - regio- and stereoselective iodolactonizations

II. - regio- and stereoselective iodooxazine formation

III. - stereoselective epoxidation, regioselective oxirane openings

IV. - stereoselective aziridine formation, regioselective aziridine opening

B: fluorinated amines (building blocks)

V. – transformations following oxidative ring-cleavage

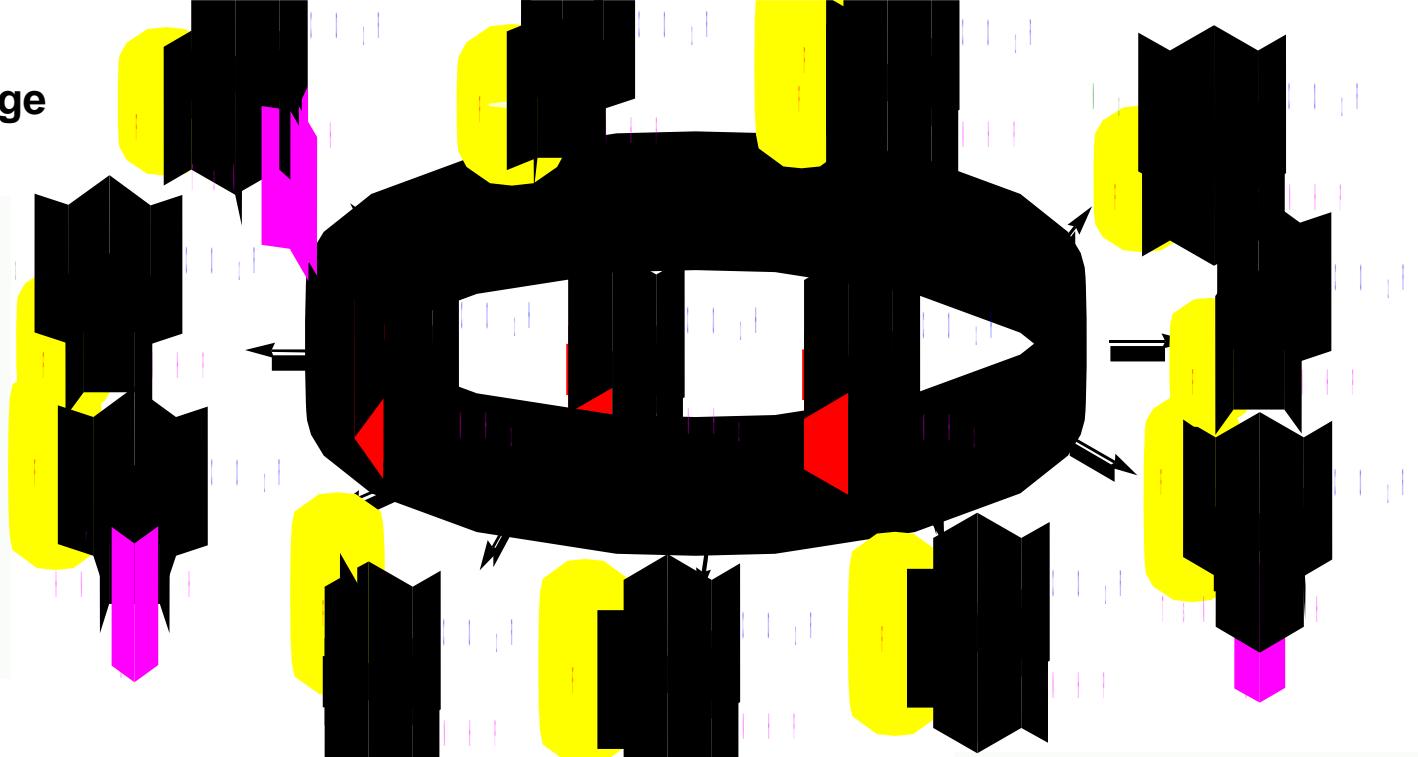
Syntheses of highly functionalized, fluorine-containing cyclic β -amino acid derivatives

Former results:

- hydroxy-fluorine exchange

Investigations:

- regioselectivity
- stereoselectivity
- stereocontrol
- substrate control
- new stereogenic centers
- synthesis of enantiomers
- novel synthetic approaches



diversely functionalized,
 β -amino acid derivatives
with multiple stereogenic centers
polyfunctionalized alicyclic
and heterocyclic building blocks

- diversity-oriented syntheses
- three-dimensional scaffolds with multiple stereocenters
- high chemical diversity
- biological screenings
- peptide synthesis

Synthesis of fluorine-containing cyclic β -amino acid derivatives

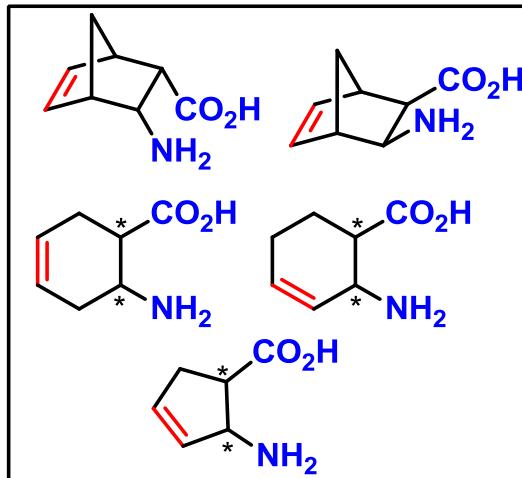
Current presentation:

- fluorinations through ring C=C bond oxidative ring cleavage

- functionalized dialdehydes: useful scaffolds for fluorinated building blocks

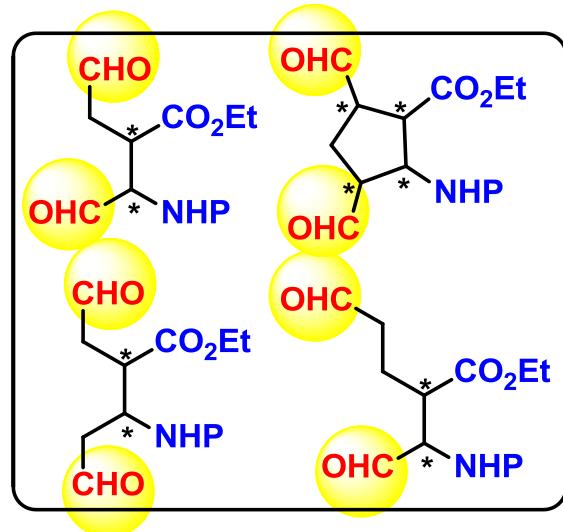
- selective fluorinations:

- direct fluorination: oxo-difluorine exchange (late-stage, nucleophilic)
- fluorine-containing building blocks: fluorinated amines



readily available starting materials

oxidative
ring
opening



valuable functionalized dialdehydes

chemoselective
fluorinations
or
reductive
aminations
with
fluorinated
amines

**fluorine-containing
functionalized
 β -amino acid
derivatives**

**fluorine-containing
functionalized
 N -heterocycles**

**polyfunctionalized scaffolds with
multiple stereogenic centers**

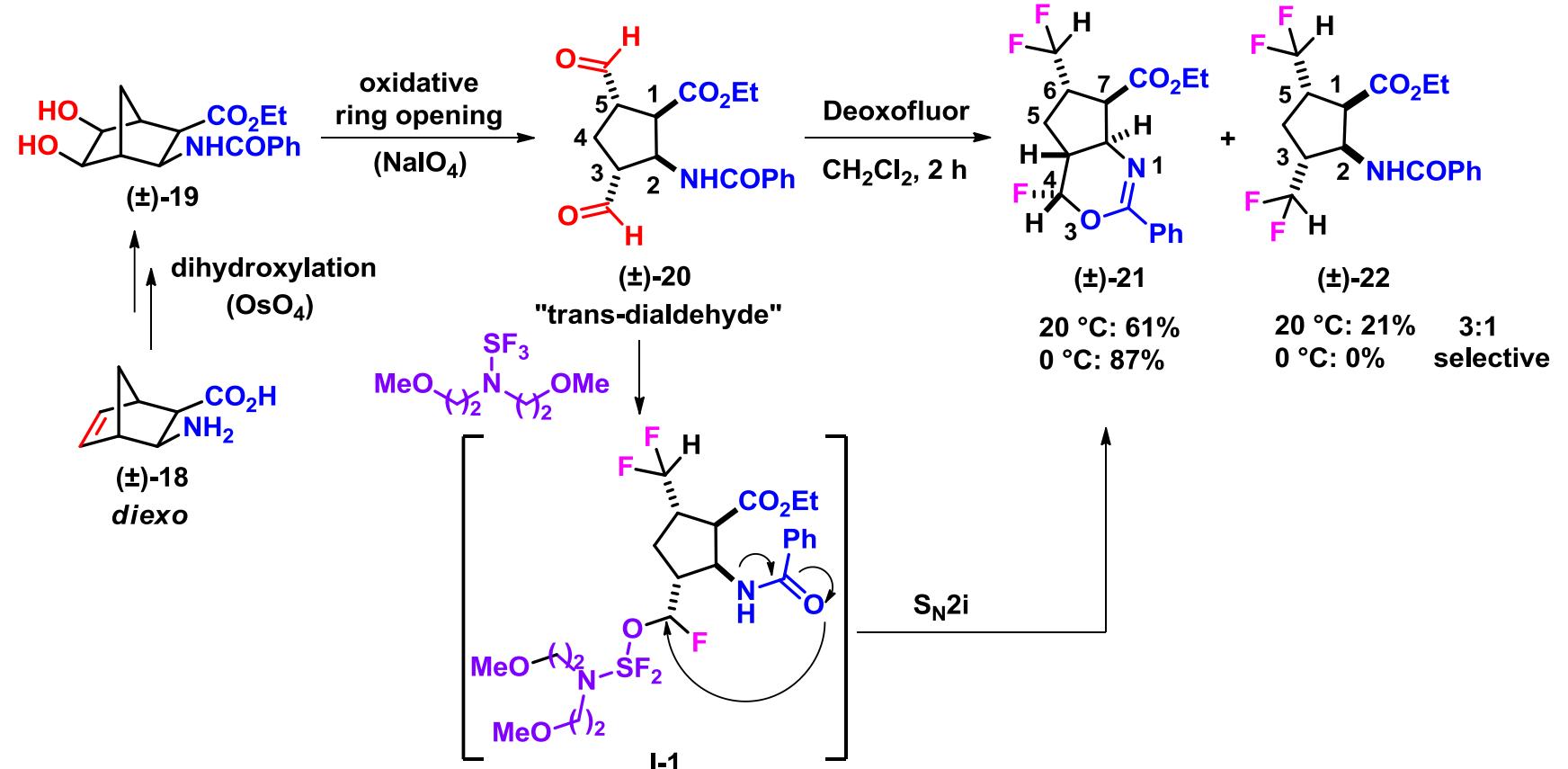
Synthesis of fluorine-containing alicyclic β -amino acid derivatives. Fluorinated cispentacin derivatives

- fluorinations through ring C=C bond oxidative ring cleavage

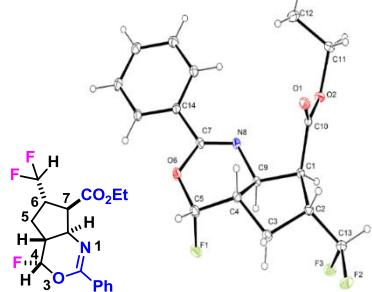
- direct fluorination:
oxo-difluor exchange



- "trans" 3,5-diformyl-substituted ethyl β -aminocyclopentanecarboxylate



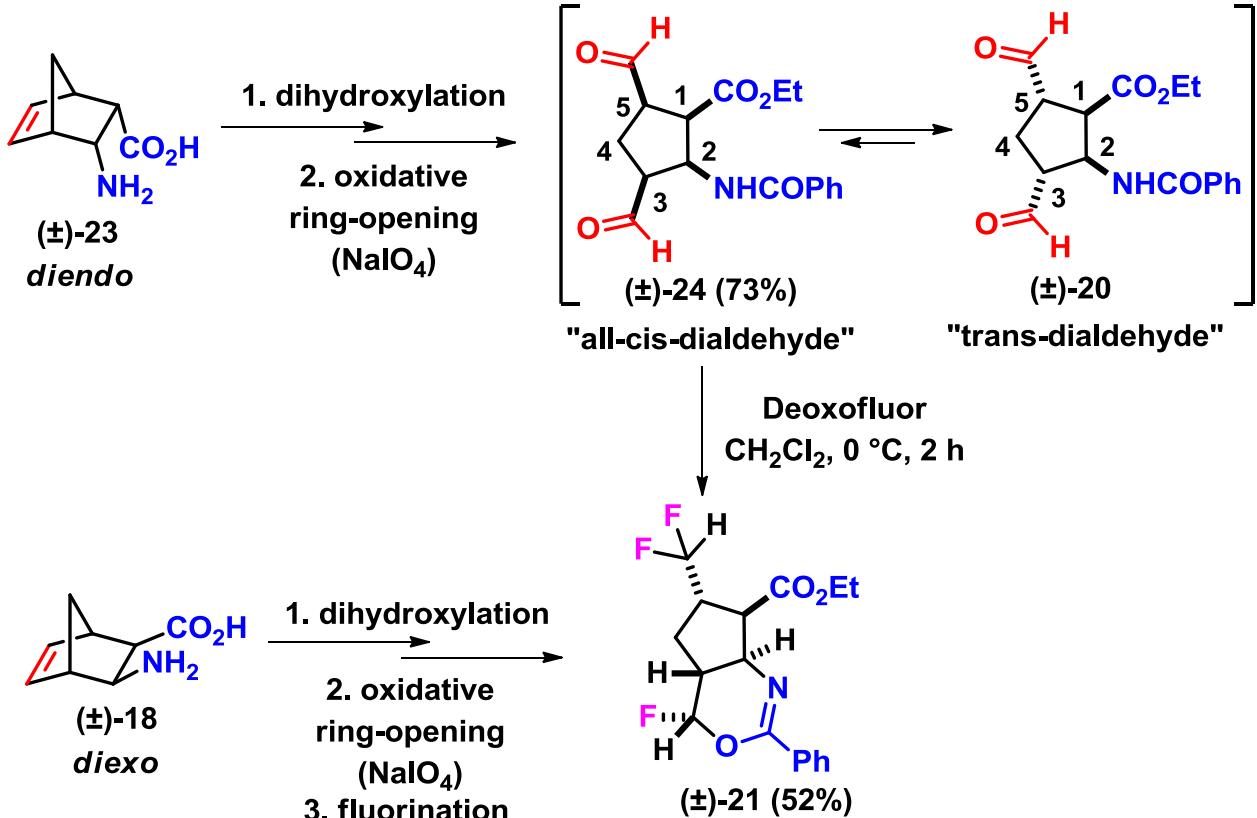
- chemodiscrimination
- substrate dependent fluorinations



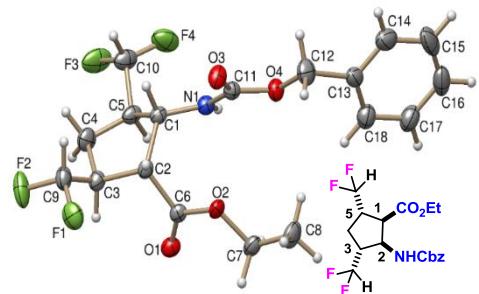
Synthesis of fluorine-containing alicyclic β -amino acid derivatives. Fluorinated cispentacin derivatives

- fluorinations through ring C=C bond oxidative ring cleavage

- “all-cis” 3,5-diformyl-substituted ethyl β -aminocyclopentanecarboxylate



- chemodiscrimination
- substrate directed fluorinations

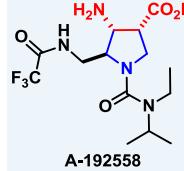
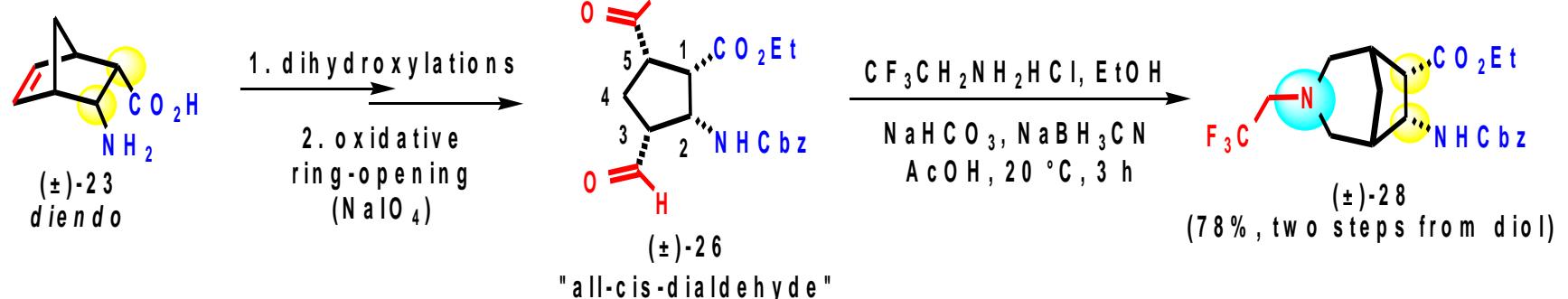
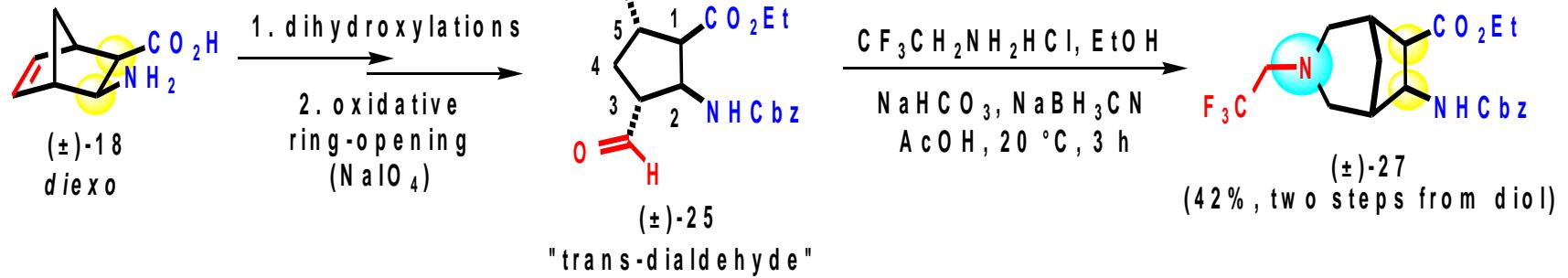


Synthesis of fluorine-containing azaheterocyclic β-amino acid derivatives. Fluorinated azepanes

- fluorinations through ring C=C bond oxidative ring cleavage

- fluorine-containing azepane β-amino esters from “trans” and „all-cis” 3,5-diformyl-substituted ethyl β-aminocyclopentanecarboxylates
- fluorine-containing building blocks: *fluorinated amines*

- stereocontrol



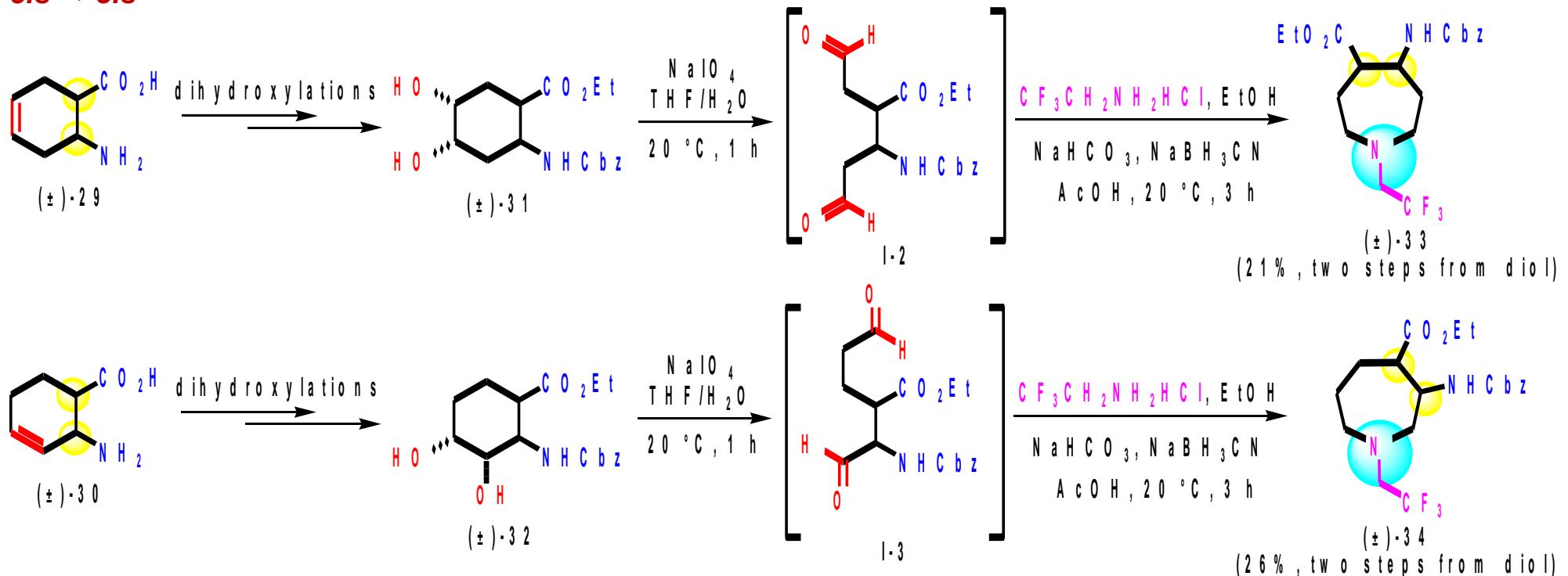
Synthesis of fluorine-containing azaheterocyclic β -amino acid derivatives. Fluorinated azepanes

- fluorinations through ring C=C bond oxidative ring cleavage

- fluorine-containing azepane β -amino esters from cis and trans β -aminocyclohexanecarboxylic acids

- fluorine-containing building blocks: *fluorinated amines*

- stereocontrol: *cis* \rightarrow *cis*



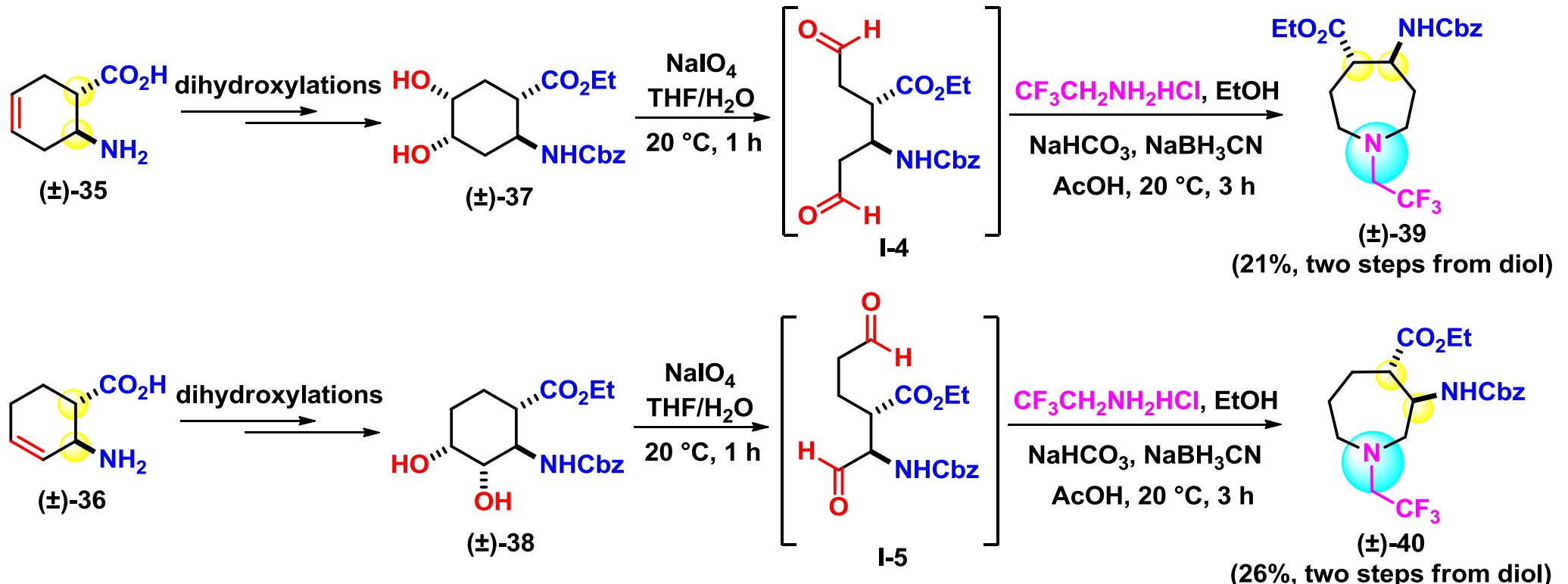
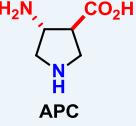
Synthesis of fluorine-containing azaheterocyclic β-amino acid derivatives. Fluorinated azepanes

- fluorinations through ring C=C bond oxidative ring cleavage

- fluorine-containing azepane β-amino esters from cis and trans β-aminocyclohexanecarboxylic acids

- oxidative ring cleavage, reductive ring closing through reductive amination

- stereocontrol: *trans* → *trans*



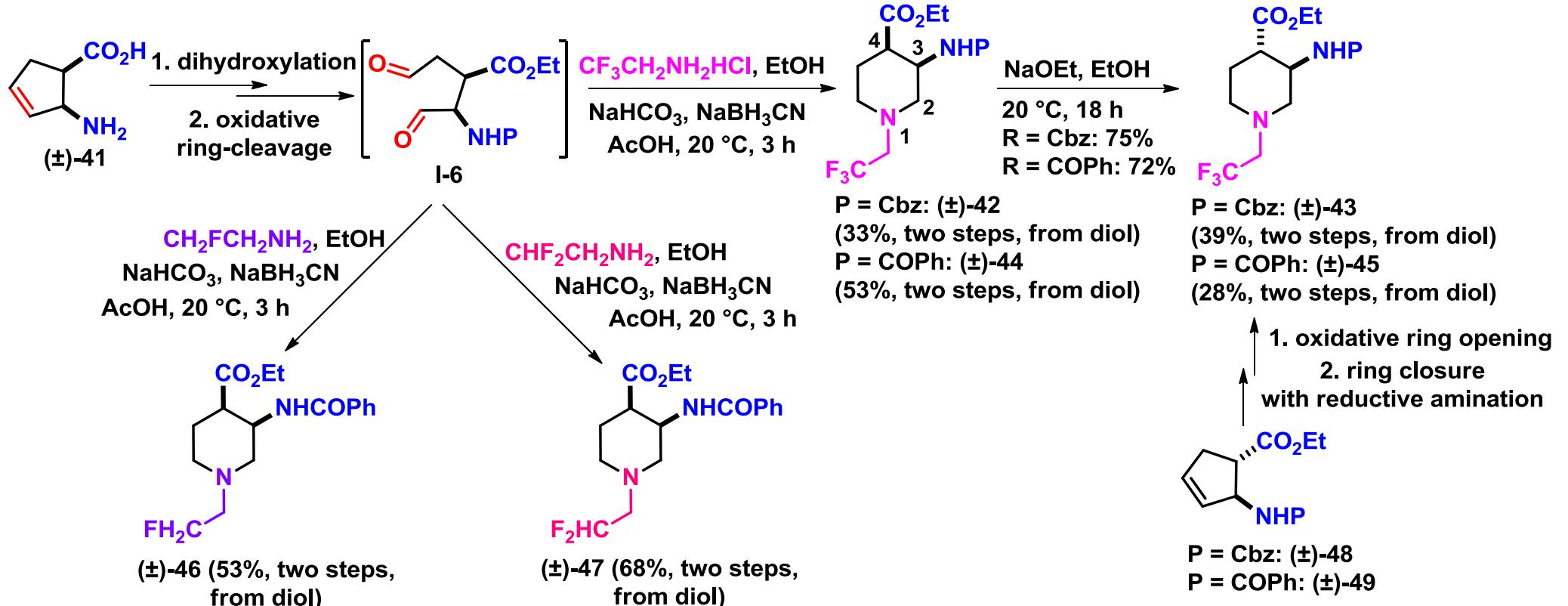
Synthesis of fluorine-containing azaheterocyclic β-amino acid derivatives. Fluorinated piperidines

- fluorinations through ring C=C bond oxidative ring cleavage

- oxidative ring cleavage, reductive ring closing with reductive amination

- stereocontrol: *cis* → *cis*

- stereocontrol: *trans* → *trans*



Synthesis of fluorine-containing cyclic β-amino acid derivatives or functionalized azaheterocycles

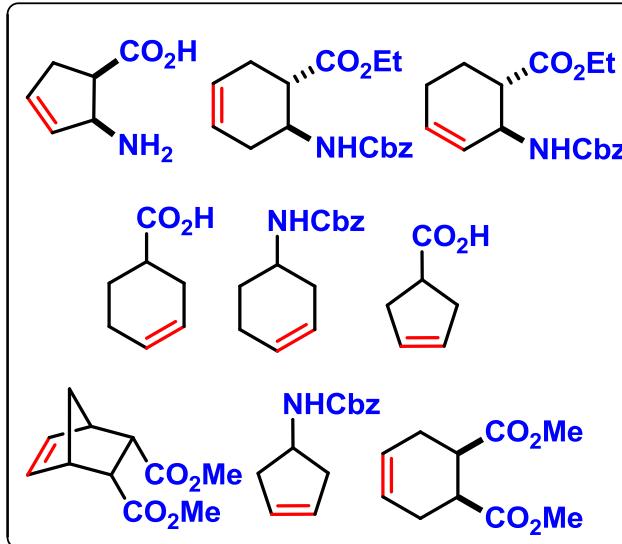
- fluorinations through ring C=C bond oxidative ring cleavage

- synthesis of fluorine-containing functionalized N-heterocycles
- ring expansion

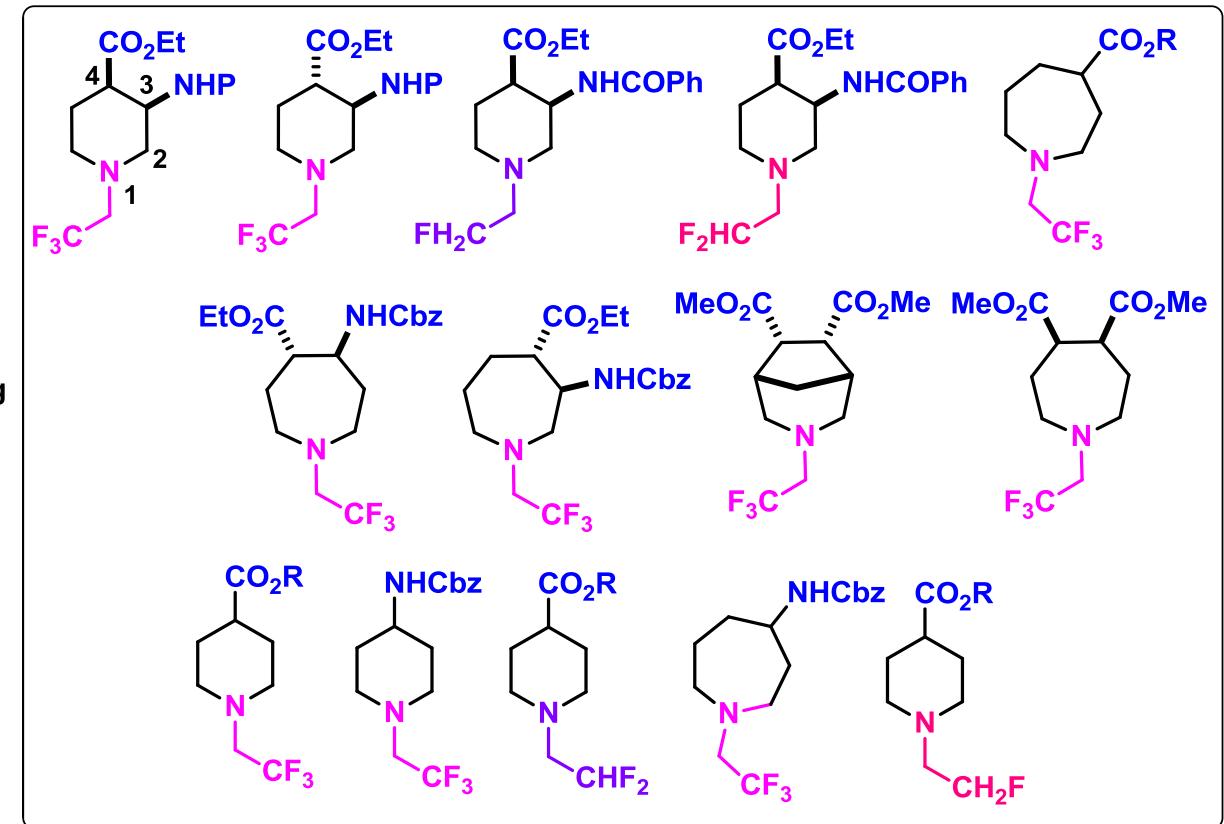
- stereocontrol

- extensions:

substrate scope:



1. oxidative
ring-opening
→
2. reductive
ring-closing



Synthesis of fluorine-containing cyclic functionalized azaheterocycles

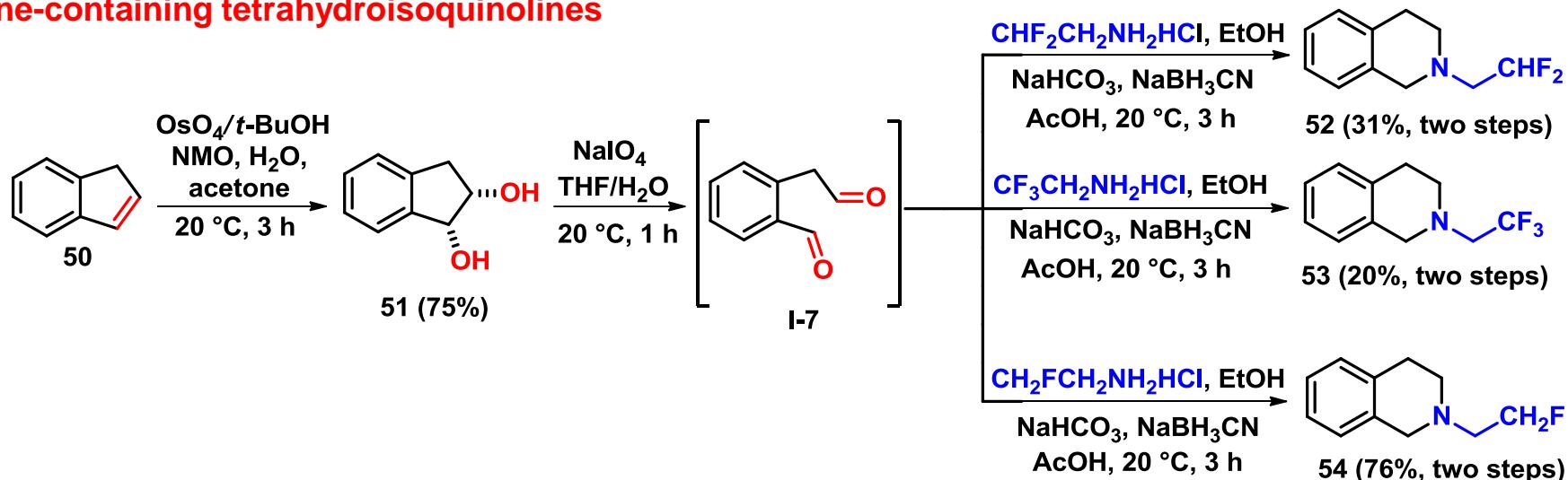
- fluorinations through ring C=C bond oxidative ring cleavage

- synthesis of fluorine-containing functionalized N-heterocycles

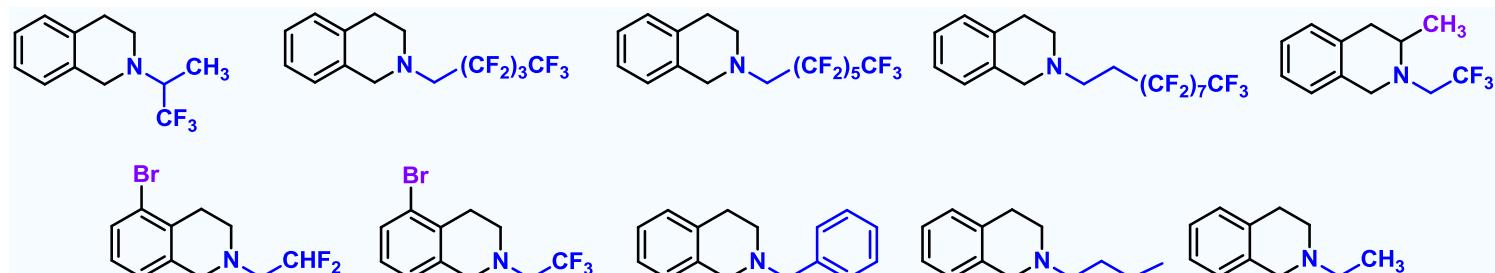
- fluorine-containing building blocks: *fluorinated amines*

- extensions:

- synthesis of fluorine-containing tetrahydroisoquinolines



substrate scope:

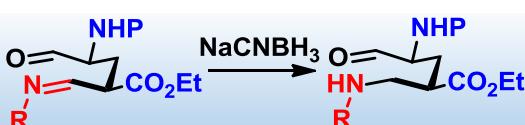
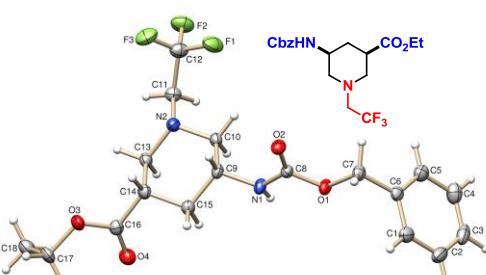
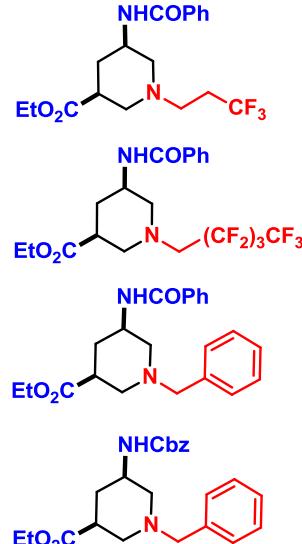
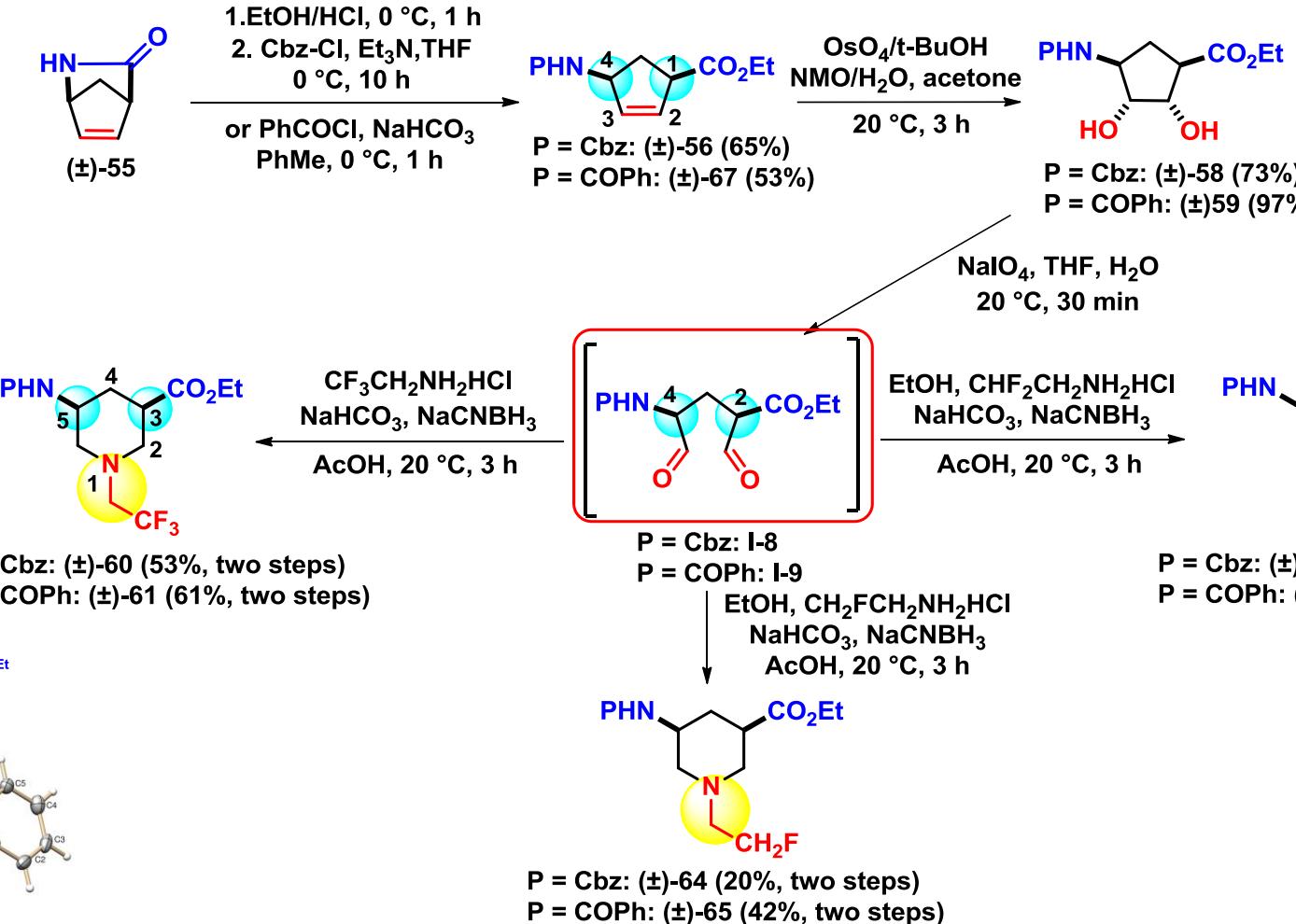


Synthesis of fluorine-containing piperidine γ -amino acid derivatives

- oxidative ring cleavage, reductive ring closing through reductive amination

- β,γ -diamino acid derivatives

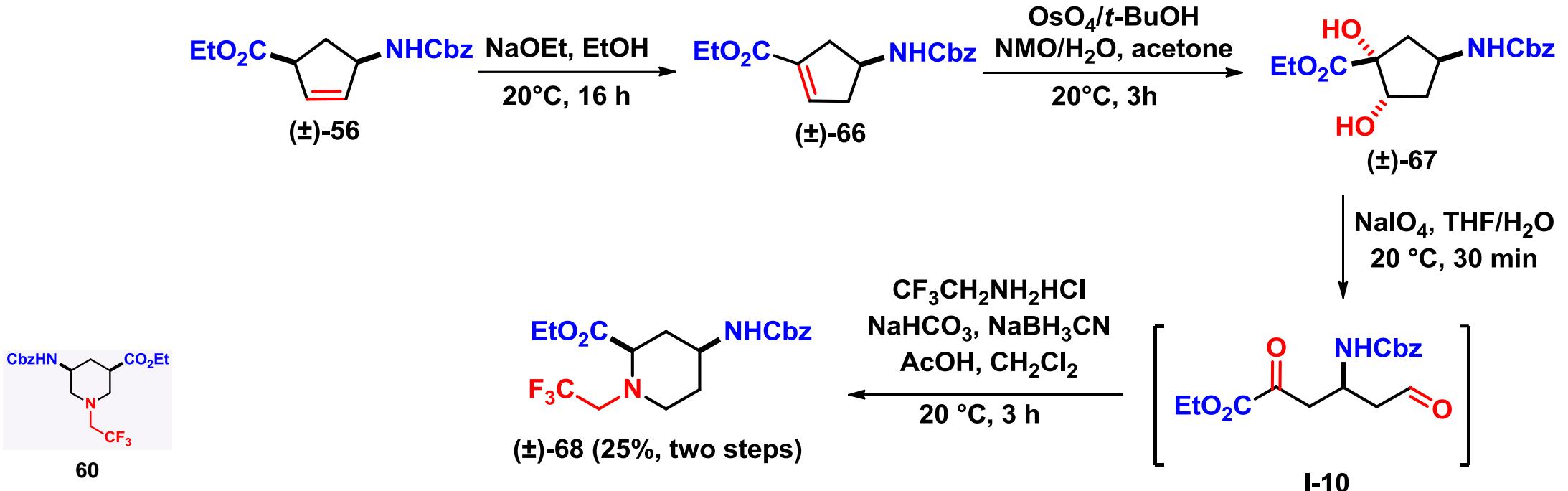
- stereocontrol



Synthesis of fluorine-containing piperidine γ -amino acid derivatives

- oxidative ring cleavage, reductive ring closing through reductive amination

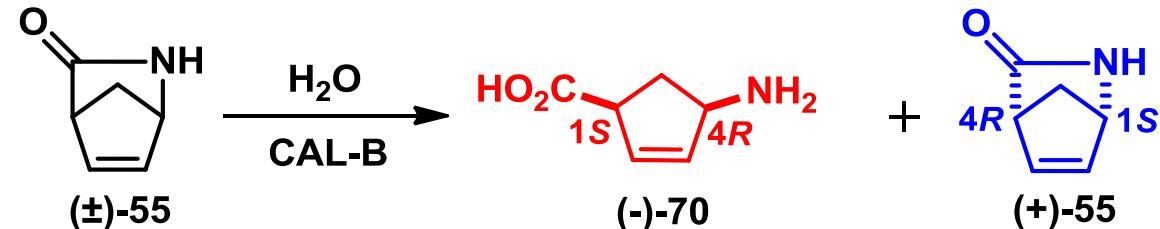
- synthesis of fluorine-containing functionalized *N*-heterocycles



Synthesis of fluorine-containing piperidine γ -amino acid derivatives

- oxidative ring cleavage, reductive ring closing through reductive amination

synthesis of enantiomers



enantioselectivity of hydrolysis of (\pm) -18 (0.05 M substrate in *i*-Pr₂O)

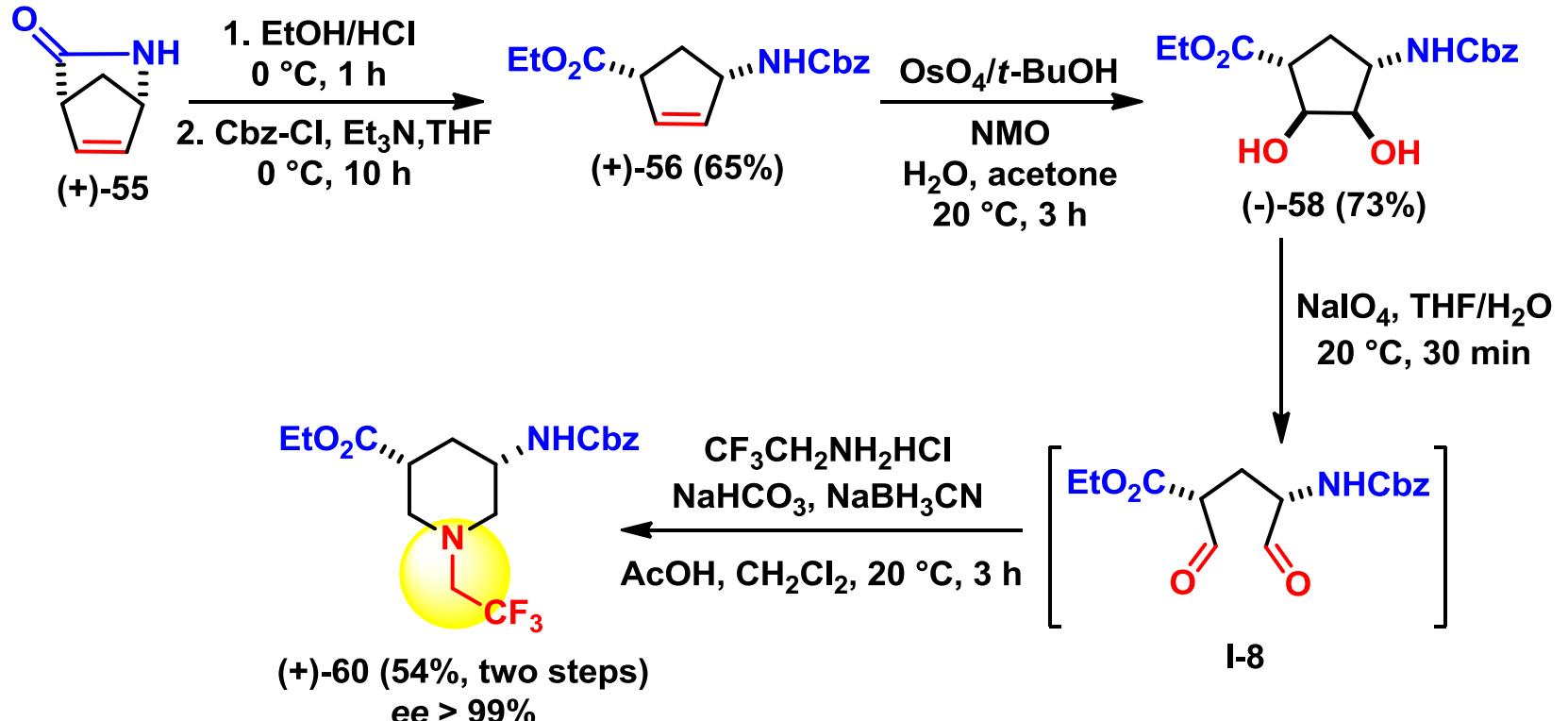
reaction time (min)	Enzyme (30 mg/mL)	temp. (°C)	H ₂ O (equiv.)	ee (%) (GC)
140	CAL-B	60	0.5	>99

Note: similar for various bicyclic β -lactams

Synthesis of fluorine-containing piperidine γ -amino acid derivatives

- oxidative ring cleavage, reductive ring closing through reductive amination

synthesis of enantiomers



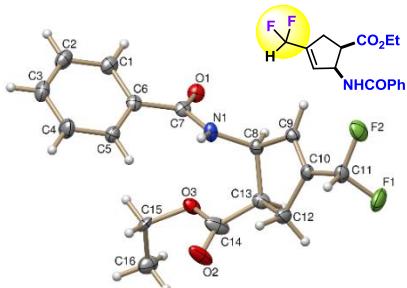
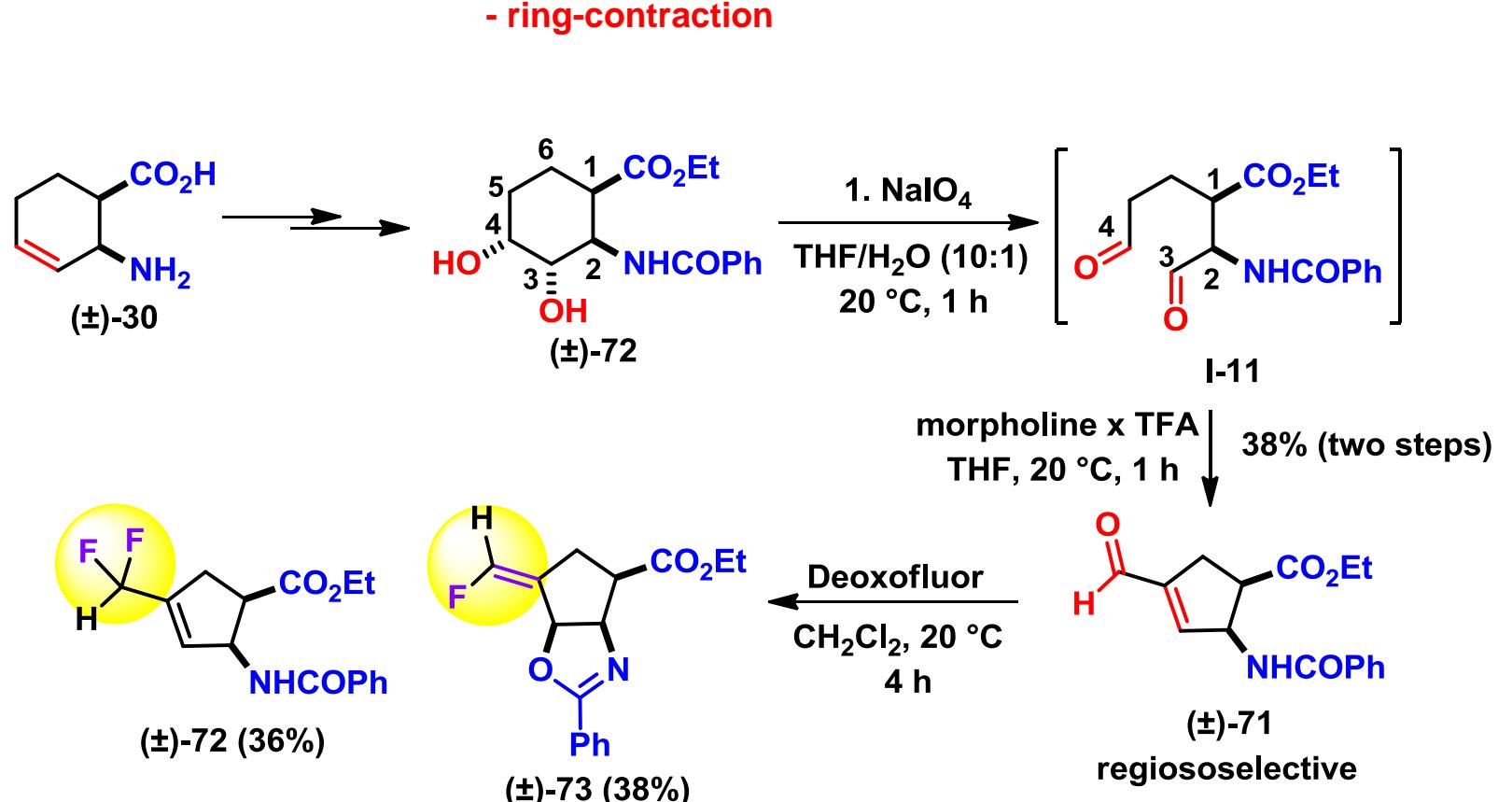
Synthesis of fluorine-containing cyclic β-amino acid derivatives or functionalized heterocycles

- fluorinations following ring C=C bond oxidative ring cleavage
- synthesis of fluorine-containing functionalized heterocycles



formyl-substituted
cyclopentenes

highly-functionalized
fluorinated building blocks

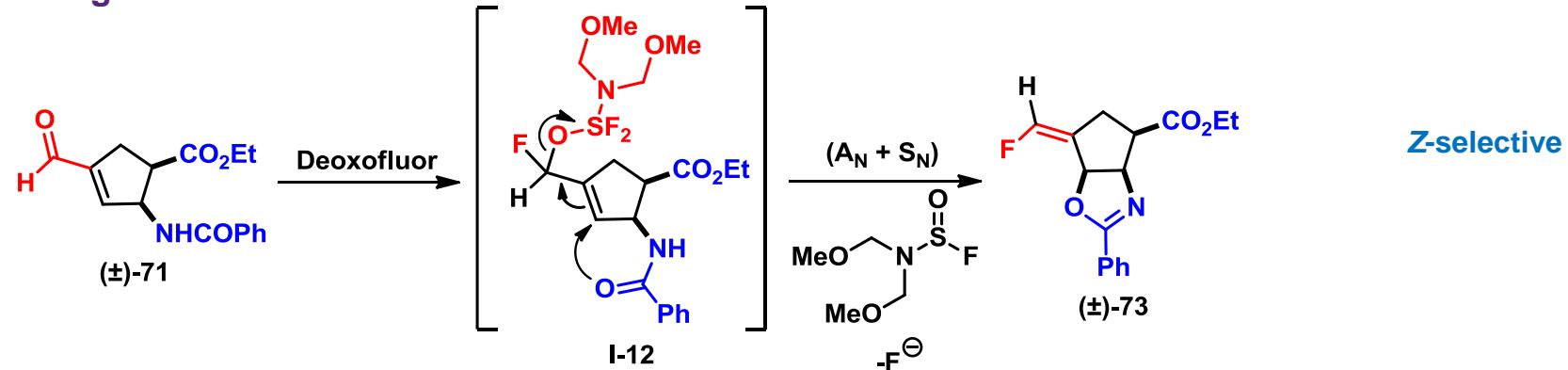


Synthesis of fluorine-containing cyclic β-amino acid derivatives or functionalized heterocycles

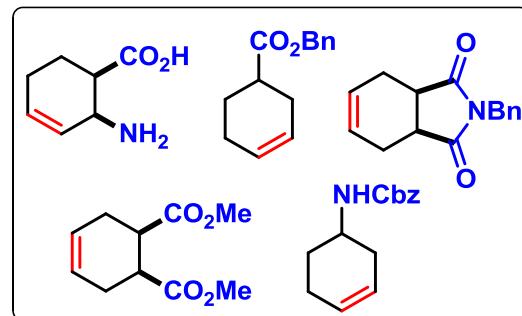
- fluorinations following ring C=C bond oxidative ring cleavage
- synthesis of fluorine-containing functionalized heterocycles



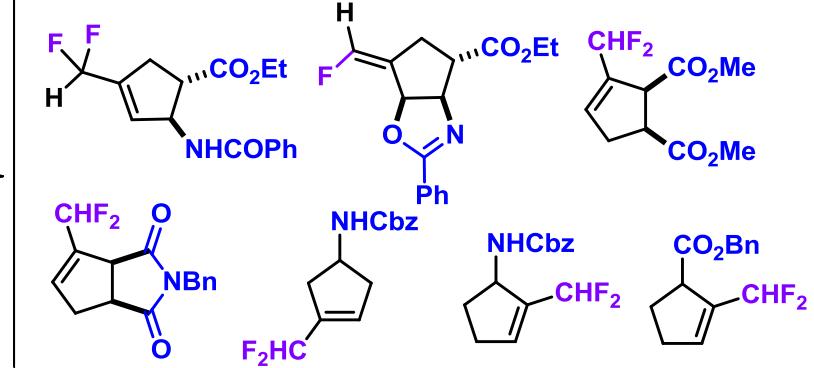
highly-functionalized fluorinated building blocks



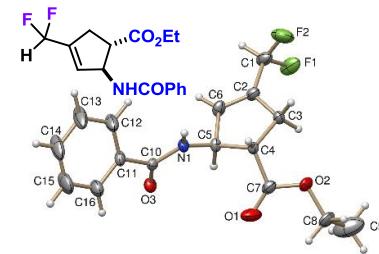
substrate scope:



cheap six-membered materials



valuable five-membered fluorine-containing structures

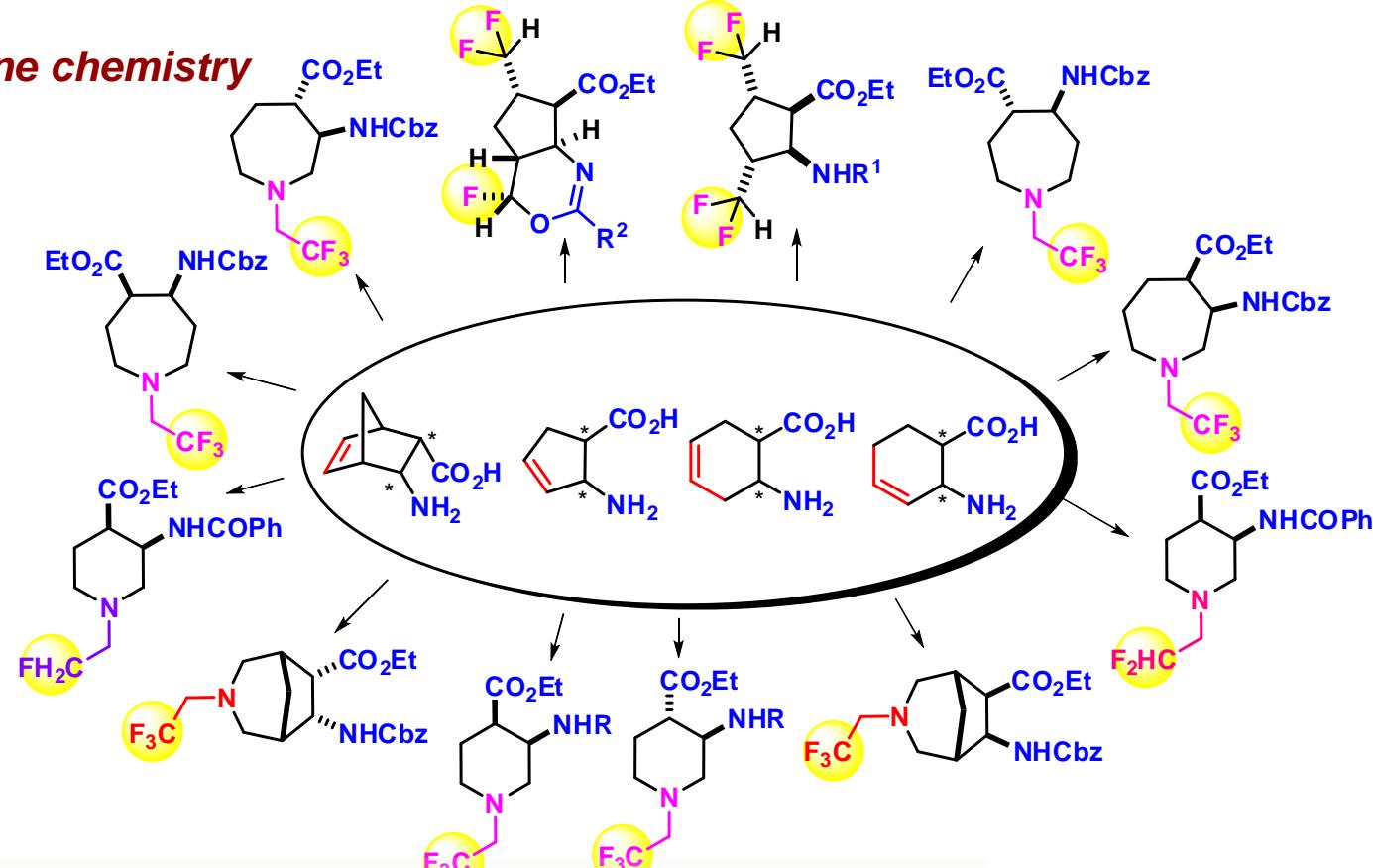
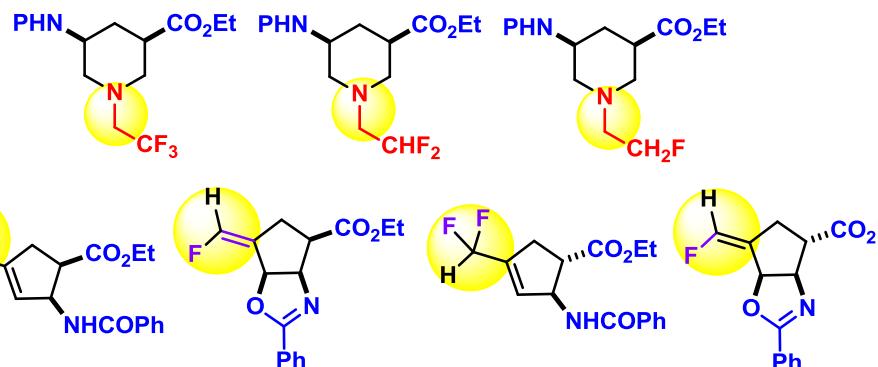
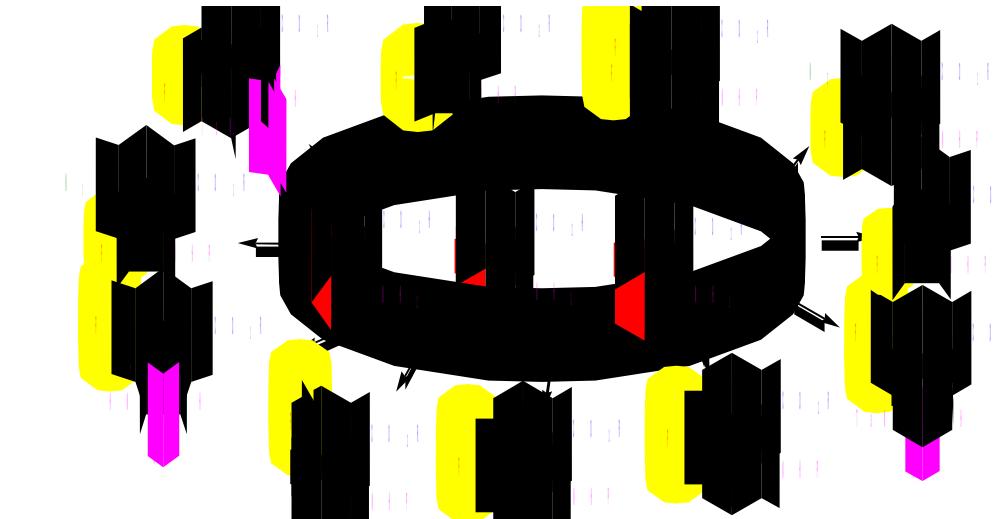


Synthesis of functionalized, fluorine-containing cyclic β -amino acid derivatives

Summary and outlook:

- a combination of β -amino acid chemistry and fluorine chemistry

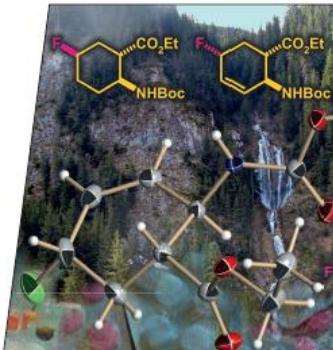
- diversity oriented synthesis



- regio- and stereoselectivity
- stereo- and substrate control
- scaffolds with multiple stereogenic centers
- high chemical diversity
- general applicability
- biological (antifungal or antiviral) evaluations
- synthesis of novel peptides
- highly substituted, three dimensional building blocks in pharmaceutical research

Thank you for your attention!

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Micropreview:
Marcel Mayor et al.
Phenyl-Acetylene Bond Assembly

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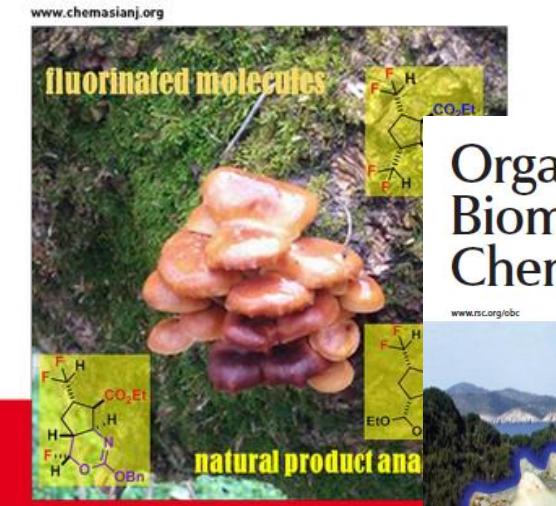
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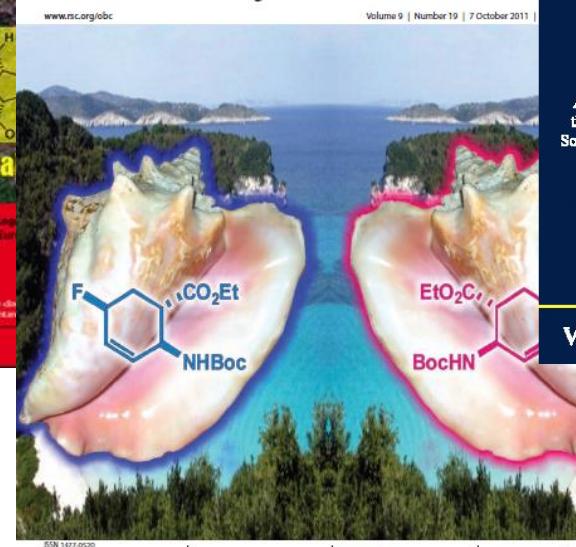
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