Application of nucleophilic fluorinating reagents for the synthesis and transformations of cyclic β-amino acid derivatives

PhD Thesis

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II. **Remete, A. M.**:
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List of abbreviations:

AIBN: azobisisobutyronitrile, $[Me_2C(CN)]_2N_2$

CDI: 1,1'-carbonyldiimidazole

Chloramine-T: *N*-chloro 4-methylbenzenesulfonamide, sodium salt

DAST: diethylaminosulfur trifluoride, Et_2NSF_3

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

DCC: dicyclohexyl carbodiimide

DCE: 1,2-dichloroethane

DEAD: diethyl azodicarboxylate, $EtO_2C\text{-}N{=}N\text{-}CO_2Et$

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

DMAP: 4-dimethylaminopyridine

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

FluoLead: 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride

HOBt: *N*-hydroxybenzotriazole

LDA: lithium diisopropylamide, LiN^iPr_2

L-Selectride: lithium tri-*sec*-butyl(hydrido)borate, $LiB(^sBu)_3H$

MCPBA: 3-chloroperbenzoic acid

Morph-DAST: morpholinosulfur trifluoride

MOST: morpholinosulfur trifluoride

MW: microwave heating

NBS: *N*-bromosuccinimide

NCS: *N*-chlorosuccinimide

NMO: *N*-methylmorpholine-*N*-oxide (4-methylmorpholine-*N*-oxide)

Selectfluor: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

TEMPO: (2,2,6,6-tetramethyl-piperidyl-1-yl)oxyl

TFA: trifluoroacetic acid, CF_3CO_2H

XtalFluor-E: diethylaminodifluorosulfinium tetrafluoroborate, $[Et_2N{=}SF_2][BF_4]$

XtalFluor-M: morpholinodifluorosulfinium tetrafluoroborate

1. INTRODUCTION AND AIMS

Fluorination has become a highly important topic in recent decades, because incorporation of the highly electronegative F atom can greatly influence key pharmaceutical parameters like metabolism, lipophilicity and bioavailability.[1-6] Thanks to the isosterism of F, H and OH, fluorination can leave conformation of the molecule unchanged unless stereoelectronic effects of fluorine requires otherwise.[1-8] Thanks to their advantageous properties, fluorinated drug molecules have become common[9] with their current ratio within newly approved drugs is about 20-25%.[5]

Cyclic amino acids are of high importance in pharmaceutical chemistry. Conformational restrictions resulting from their cyclic nature make them promising building blocks of new bioactive peptides.[10-12] Numerous natural or synthetic cyclic amino acid derivatives, including approved drugs, show relevant biological activity.[13-22]

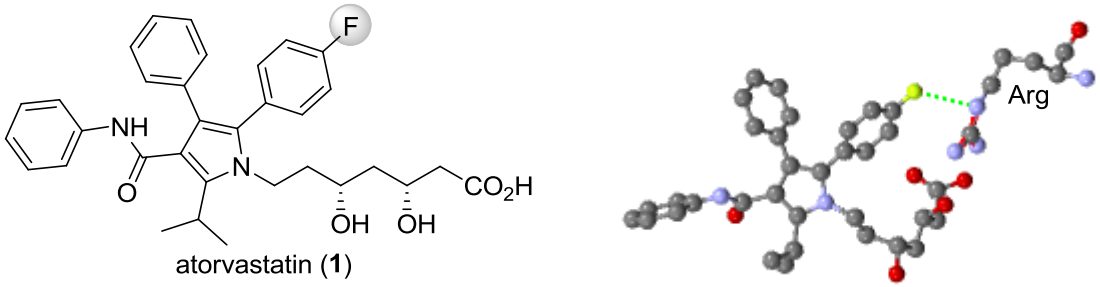
Because of the importance of fluorination, fluorinated cyclic amino acid derivatives also gained attention.[23,24] However, within these compounds, fluorinated cyclic β-amino acids received less interest. Because the synthesis of highly functionalized cyclic β-amino acids is amongst the main research topics at the Institute of Pharmaceutical Chemistry at the University of Szeged, the synthesis of fluorine-containing members of this compound family became an important aim. With the help of nucleophilic fluorinating reagents, preparation of a high number of such derivatives was accomplished.[25-34]

The present PhD work focused on the synthesis of various types of fluorinated functionalized cyclic β-amino acid derivatives. The aim of the research was to obtain such compounds through new synthetic pathways starting from selectively epoxidated or dihydroxylated cyclic β-amino acid derivatives, utilizing deoxyfluorinating reagents. High emphasis was placed on substrate dependence (including neighboring group effects), selectivity, and chemodifferentiation between functional groups.

2. LITERATURE BACKGROUND

2.1. Importance of fluorination and of fluorinated cyclic amino acids

Incorporation of fluorine attracted increasing attention in the last decades, because of the advantages originating from the unique properties of the F atom and the C–F bond. For example, thanks to the high electronegativity of fluorine, C–F bonds are polar (while C–H bonds are non-polar), enabling dipole–dipole and dipole–charge interactions, which can enhance protein binding.[1-6,35] A good example for this effect is the drug atorvastatin (*Scheme 1*).[1,5,35] At the same time, since the C–F bond is relatively nonpolarizable, it is only a weak hydrogen bond acceptor[2,6] and, as a result, solvation by water is not too effective. The overall result of these effects is polar hydrophobicity, which influences lipophilicity, a key molecular parameter in medicinal chemistry.[1-6] The high electronegativity of F also influences pK_a values of nearby functional groups,[1-6] which together with polar hydrophobicity can substantially affect bioavailability, another key parameter.[4,5,6]

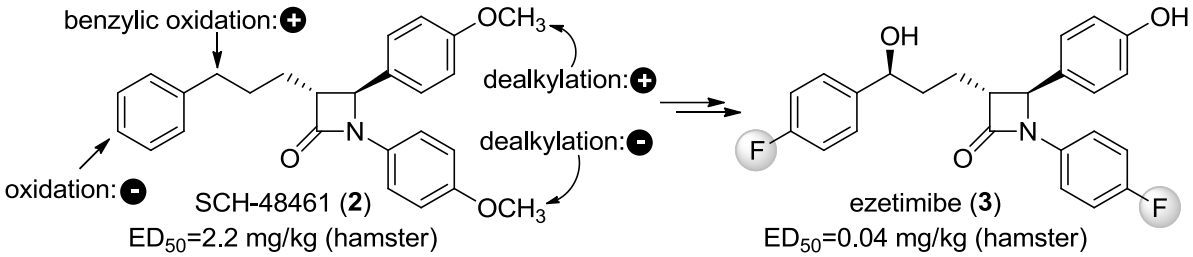


Scheme 1. The drug atorvastatin blocks cholesterol synthesis by inhibiting HMG-CoA reductase. The F atom increases binding of atorvastatin through an electrostatic $C–F^{\delta-}\cdots N^{\delta+}$ interaction.

Fluorine is considered to be isosteric with H and OH, so fluorination often leaves the conformation of the molecule intact, although stereoelectronic effects of F can overrule this.[1-6] Importantly, the greater strength of C–F bonds compared to that of the C–H bonds can increase metabolic stability[1-6] as shown for the drug ezetimibe on *Scheme 2*.[6] As an overall result, fluorinated drug molecules became common[9] and in the 2000s, their ratio within newly approved drugs started to increase.[5] Incorporation of ^{18}F ($t_{1/2}$ = 110 min) to produce radiopharmaceuticals is also an emerging area.[1,2,36]

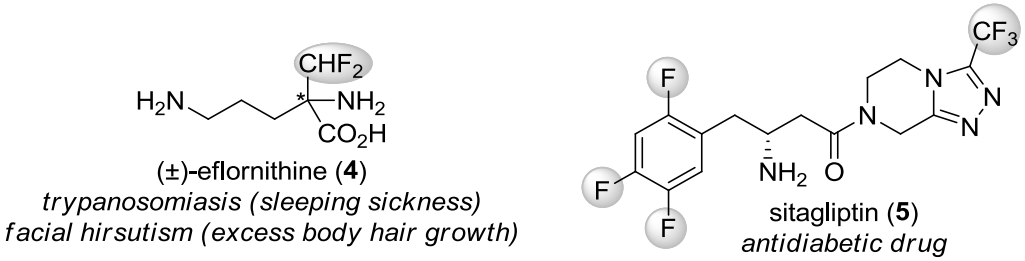
The increasing popularity of fluorinated molecules resulted in significant development of fluorination techniques in the last decades.[3] Currently, both electrophilic and nucleophilic fluorine

sources as well as fluorinated building blocks are available at affordable prices. Nevertheless, fluorination is still challenging,[3] especially in the case of highly functionalized scaffolds.



Scheme 2. Fluorination prevents unwanted metabolic changes in the case of ezetimibe, another cholesterol-lowering medication

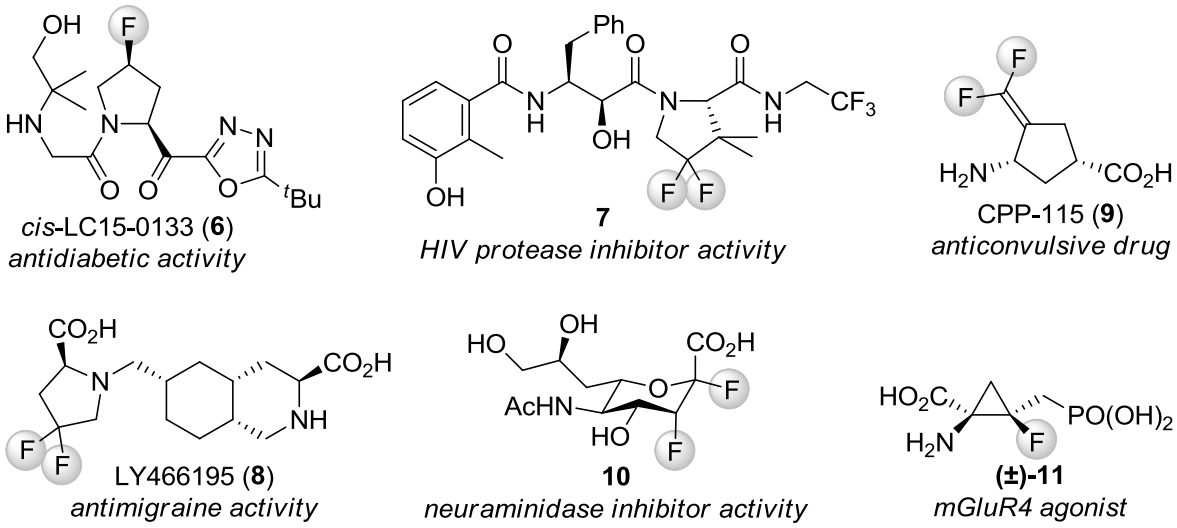
Amino acids have an enormous importance in pharmaceutical chemistry thanks to their versatility, bioactivity and structural diversity. Because of the importance of fluorination, fluorinated amino acid derivatives also gained increasing attention.[1,7,8,23,24,37] These compounds can often be incorporated into proteins without structural changes, enabling investigation of protein structures with ^{19}F-NMR and study of enzyme mechanisms.[1,37] The latter can be achieved with fluorinated amino acid substrates too.[1,8] Research of peptide-based drugs could also benefit from fluorinated amino acids, because of the conformational changes and restrictions caused by stereoelectronic effects of fluorine.[7,8] Most attention was directed toward acyclic α- and β-amino acids[23,24] resulting in a high number of bioactive compounds[38-45] and two fluorinated amino acid drugs[46-48] (*Scheme 3*).



Scheme 3. Fluorinated amino acid drugs

Although they received less attention, cyclic amino acids also proved their worth for pharmaceutical chemistry. Synthesis of fluorinated proline derivatives as starting materials of syntheses or as conformationally restricted proline analogues to study conformational effects was a popular research topic.[14,49-51] Such moieties can also be found in dipeptidyl peptidase IV inhibitor (potential antidiabetic) *cis*-LC15-0133 (**6**),[14] second generation HIV protease

inhibitor **7**[15] and antimigraine compound LY466195 (**8**), [16] which is currently undergoing Phase II trials (*Scheme 4*).[52] CPP-115 (**9**), a difluorinated analogue of cyclic γ-amino acid anticonvulsant drug vigabatrin, shows an effectivity two orders of magnitude higher than its parent compund, and markedly reduced off-target activities. It was granted orphan drug designation by the FDA for the treatment of infantile spasms.[22] Fluorinated sialic acid analogues, like **10**, are sialidase (neuraminidase) inhibitors possessing potential antiviral activity.[53-55] In the case of α-amino acid mGluR4 agonist **(±)-11**, fluorination increased binding affinity nearly sevenfold.[56]



Scheme 4. Bioactive fluorinated cyclic amino acid derivatives

As shown above, amongst fluorinated cyclic amino acid derivatives, β-amino compounds were somewhat ignored. It raised the interest in the Institute of Pharmaceutical Chemistry, and a high number of such derivatives were synthesized from unsaturated bicyclic β-lactams.[25-34] Usually, the first step was regio- and stereo-selective introduction of a hydroxy group followed by either hydroxy–fluorine exchange or oxidation into keto derivatives and subsequent carbonyl→difluoromethylene transformation.[25-29,31,33] A new aziridine ring-opening method with XtalFluor-E was developed too.[30]

2.2. Evolution of deoxyfluorinating reagents

Deoxyfluorination is a subtype of nucleophilic fluorination, where incorporation of fluorine and oxygen removal happens simultaneously. The history of sulfur fluoride deoxyfluorinating agents started in 1958 with the discovery that SF_4, the parent compound of this reagent family,

is capable of transforming carbonyl and carboxyl groups into difluoromethylene and trifluoromethyl groups, respectively.[57] In 1960, its ability to exchange the hydroxy group to fluorine was also reported.[58] Unfortunately, SF_4 a toxic and corrosive gas under standard conditions is difficult to handle. This fact together with the specialized equipment requirements of its use (autoclave, elevated temperature or fluoropolymer vessel, liquid HF solution)[2,3] resulted in intensive research for better alternatives.

2.2.1. DAST, MOST

Dialkylaminosulfur trifluorides were the next generation of deoxyfluorinating reagents. Their ability to perform C=O → CF_2 and OH → F transformations were reported in 1973[59] and 1975,[60] respectively. In contrast with SF_4, OH → F exchange works even at -78 °C, and C=O → CF_2 transformation can usually be performed at room temperature (although sometimes temperatures up to 80-85 °C are required).[2,60] Their handling is also easier: they are liquid at room temperature and can be used in ordinary glassware.[2,59] These advantages allowed the widespread use of the easily accessible diethylaminosulfur trifluoride or DAST (*Scheme 5*) for deoxyfluorination.[61] Unfortunately, DAST is thermally unstable: heating above ~90 °C results in explosion.[61,62] This not only greatly limits large-scale applications of DAST, but also makes it unsuited for CO_2H → CF_3 transformation, which requires prolonged heating close to the decomposition temperature of the reagent.[63]

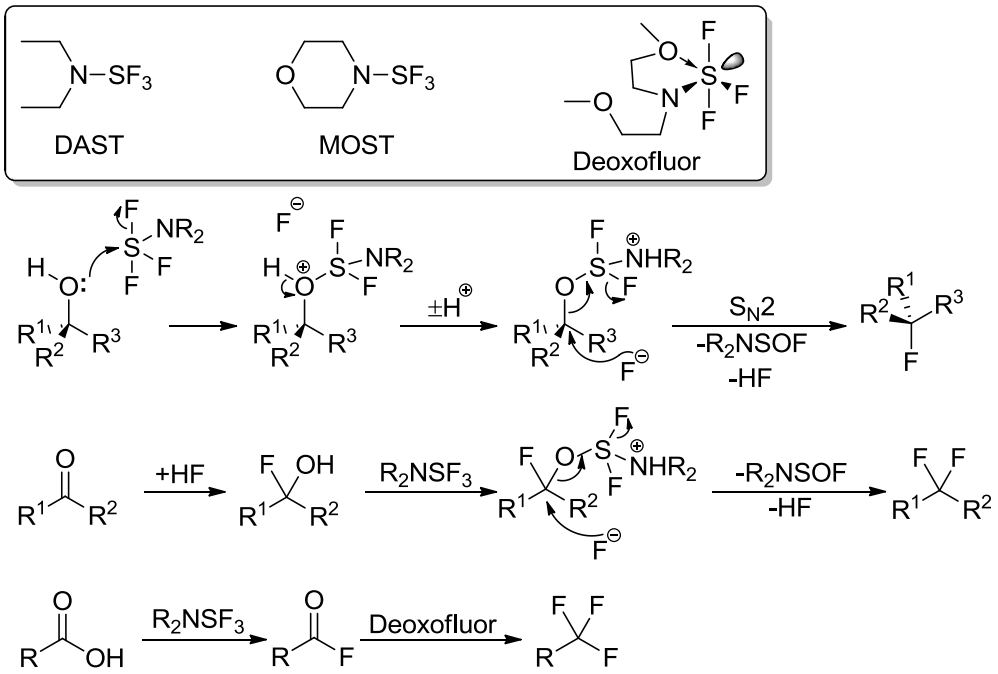
In order to develop better reagents, the thermal stability of dialkylaminosulfur trifluorides was studied in 1989 with the finding that their decomposition is a two-step process. At first, slow disproportion of R_2NSF_3 to SF_4 and $(R_2N)_2SF_2$ takes place at approximately 90 °C. The resulting bis(dialkylamino)sulfur difluorides are explosive and they trigger detonation of the whole mixture when their concentration is sufficiently high. Changing the R groups has no effect on the disproportion temperature, but greatly influences its rate. Morpholinosulfur trifluoride (Morph-DAST or MOST, *Scheme 5*) and other R_2NSF_3 compounds derived from six-membered cyclic amines showed increased thermal stability, making them a safer alternative of DAST.[61]

2.2.2. Deoxofluor

In 1999, further research resulted in a new, even safer reagent, Deoxofluor or bis(2-methoxyethyl)aminosulfur trifluoride. It is more suited for use on a larger, practical scale because, compared to DAST, its decomposition is much slower and produces less heat. It can

even safely transform a carboxyl group into a CF_3 moiety despite the necessary heating of the acyl fluoride at 85-90 °C in Deoxofluor as solvent for prolonged time. The reason of this enhanced thermal stability is coordination of an ether oxygen atom of the side chain to the electron-deficient sulfur center, which results in kinetic stabilization.[62]

Despite these developments, R_2NSF_3 reagents still have some disadvantages. All of them are moisture sensitive similar to SF_4 and although their synthesis is easy (SF_4 is reacted with R_2NSiMe_3 in apolar organic solvent), the crude product had to be purified through vacuum distillation, which is dangerous, requires extensive safety measures and increases the final cost of the reagent.[64] Mechanisms of deoxyfluorinations with dialkylaminosulfur trifluorides are shown on *Scheme 5*.[2,64,65] Most OH → F exchanges proceed through an S_N2 pathway,[2] although substrates capable of producing stabilized carbocations favor an S_N1 mechanism.[3]

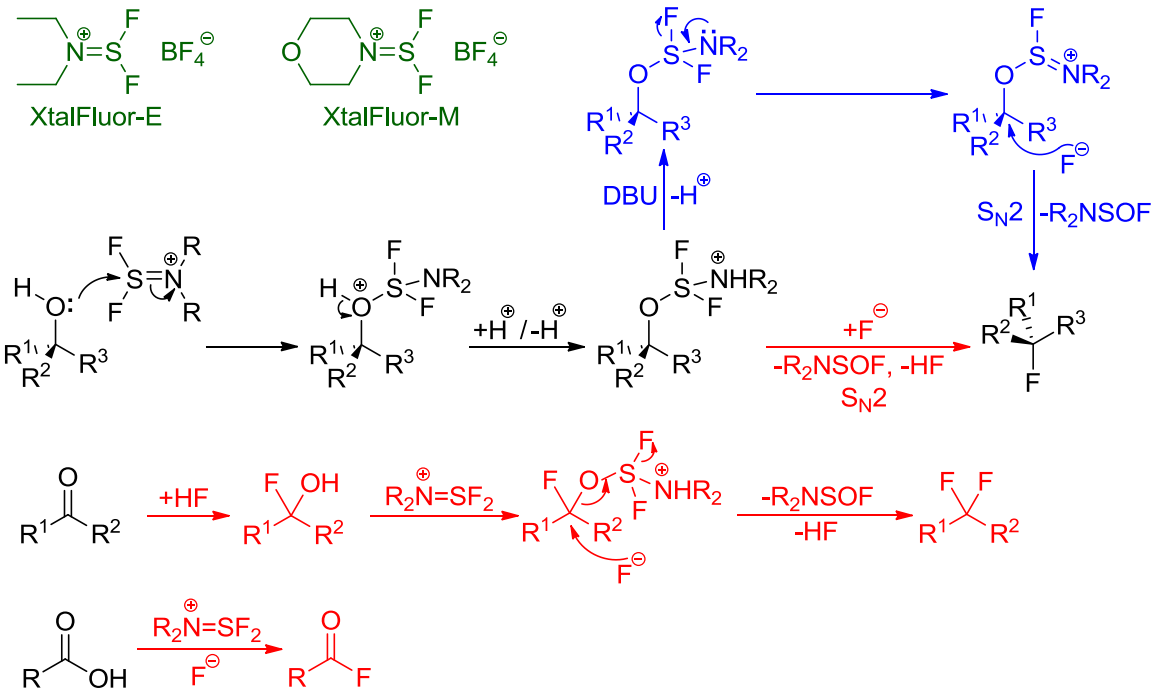


Scheme 5. Mechanisms of deoxyfluorinations with dialkylaminosulfur trifluorides

2.2.3. XtalFluor reagents

The ability of aminodifluorosulfinium salts to induce effective deoxyfluorination of alcohols and oxo compounds in the presence of exogenous fluoride source was discovered in 2009[66] followed by a more detailed publication in 2010.[64] Currently, diethylaminodifluorosulfinium tetrafluoroborate (XtalFluor-E) and morpholinodifluorosulfinium tetrafluoroborate (XtalFluor-M) are commercially available.[64]

In contrast with previous deoxyfluorinating reagents, XtalFluors do not liberate fluoride ion when they transform the hydroxy group into a good leaving group, which explains the need for exogenous fluoride sources, although bases like DBU can also induce release of fluoride ion and completion of the reaction with alcohols. XtalFluor reagents are easy-to-handle solid compounds with multiple advantages: decreased moisture sensitivity (they can be handled under open atmosphere for short times), better selectivity (less elimination side products) and much higher decomposition temperature (making their use safer). From a manufacturing point of view, they can be synthesized in high quality and yield from crude DAST or MOST, eliminating the need for vacuum distillation of these dialkylaminosulfur trifluorides. Because XtalFluors crystallize out of this reaction mixture, a simple filtration is satisfactory for their isolation. DBU or $Et_3N{\cdot}3HF$, which are required in excess for successful deoxyfluorination, are cheap and $Et_3N{\cdot}3HF$ can be handled in standard borosilicate glassware up to 150 °C without etching. However, XtalFluor reagents convert carboxylic acids only to acyl fluorides. The mechanisms of deoxyfluorinations with these salts are shown on *Scheme 6*.[64]



Scheme 6. Mechanisms of deoxyfluorinations with XtalFluor reagents. Red pathways require external fluoride source, blue pathway requires DBU

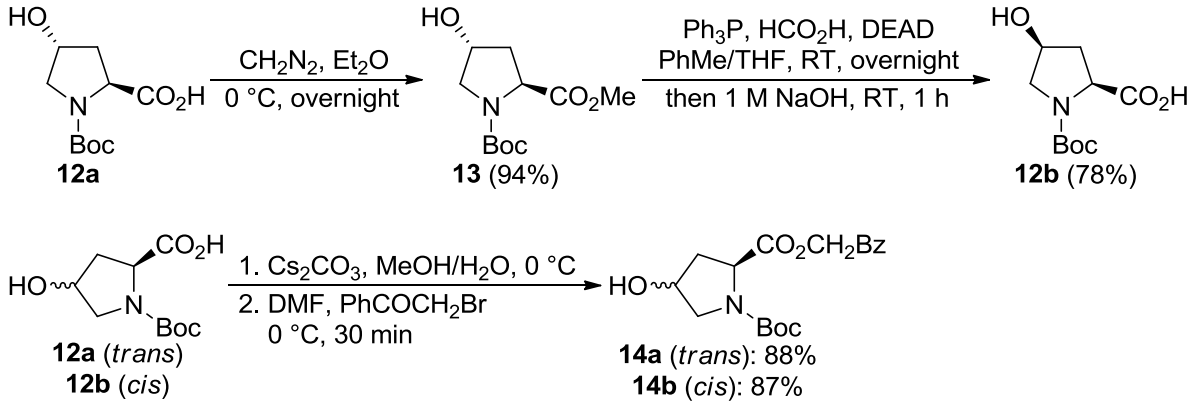
2.2.4. Other nucleophilic fluorinating reagents

In 2010, discovery of new fluorinating reagent 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride or FluoLead was reported. The new reagent is an easy-to-handle solid, which has thermal stability comparable to XtalFluor reagents. It also shows remarkable resistance to hydrolysis; for example, it can be handled under open atmosphere. FluoLead can transform OH into F and C=O into CF_2 at room temperature or slightly below (the second transformation requires excess pyridine·9HF). It can even transform COOH into CF_3 at elevated temperature (with excess pyridine·9HF, 50 °C is sufficient, whereas 100 °C is required without its use).[67]

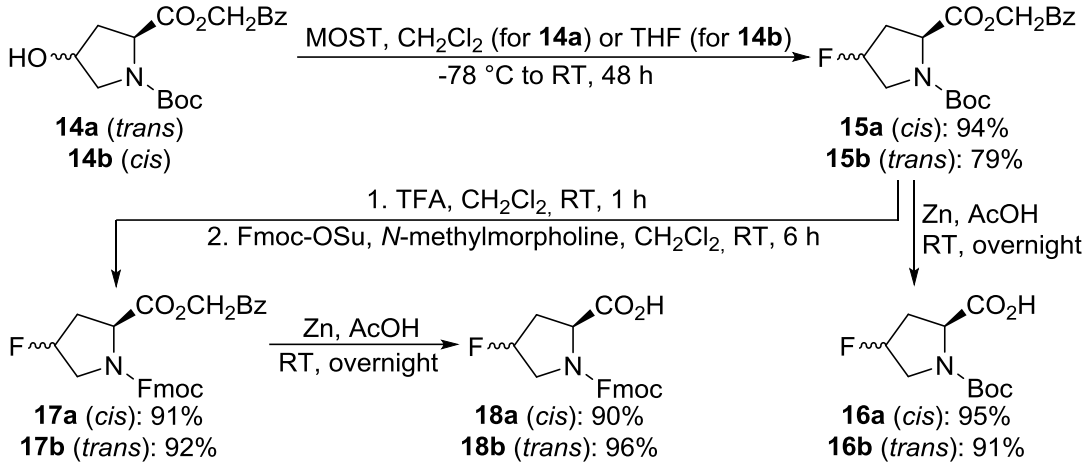
2.3. Synthesis of representative fluorinated cyclic amino acid derivatives through late-stage deoxyfluorinations

2.3.1. Cyclic α-amino acid derivatives

Fluorination of proline derivatives imposes conformational restrictions on the molecule. Such fluorine-containing amino acids are useful for the study of conformational effects in peptides.[14,49-51] In order to facilitate access to Boc- and Fmoc-protected (2*S*,4*S*)-4-fluoroprolines, which can be used for solid-state peptide synthesis, Kobayashi and co-workers synthesized *N*-Boc-protected 4-fluoroproline phenacyl esters **15a,b**. The phenacyl ester moiety of these compounds is stable during acidolytic Boc, but deprotection can be performed with Zn/AcOH without harming the Boc and Fmoc groups (*Scheme 7 and 8*).[50]

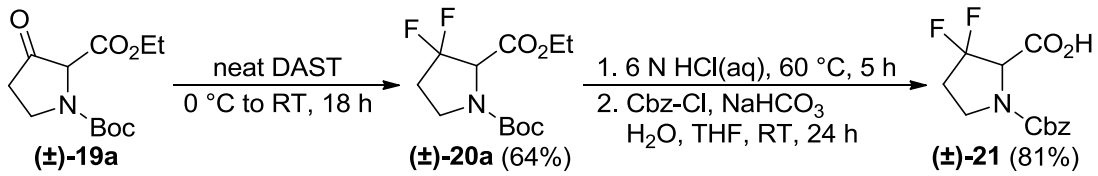


Scheme 7. Synthesis of *N*-Boc-protected (2*S*,4*R*)- and (2*S*,4*S*)-4-hydroxyproline phenacyl esters from cheap, commercially available *N*-Boc-protected (2*S*,4*R*)-4-hydroxyproline



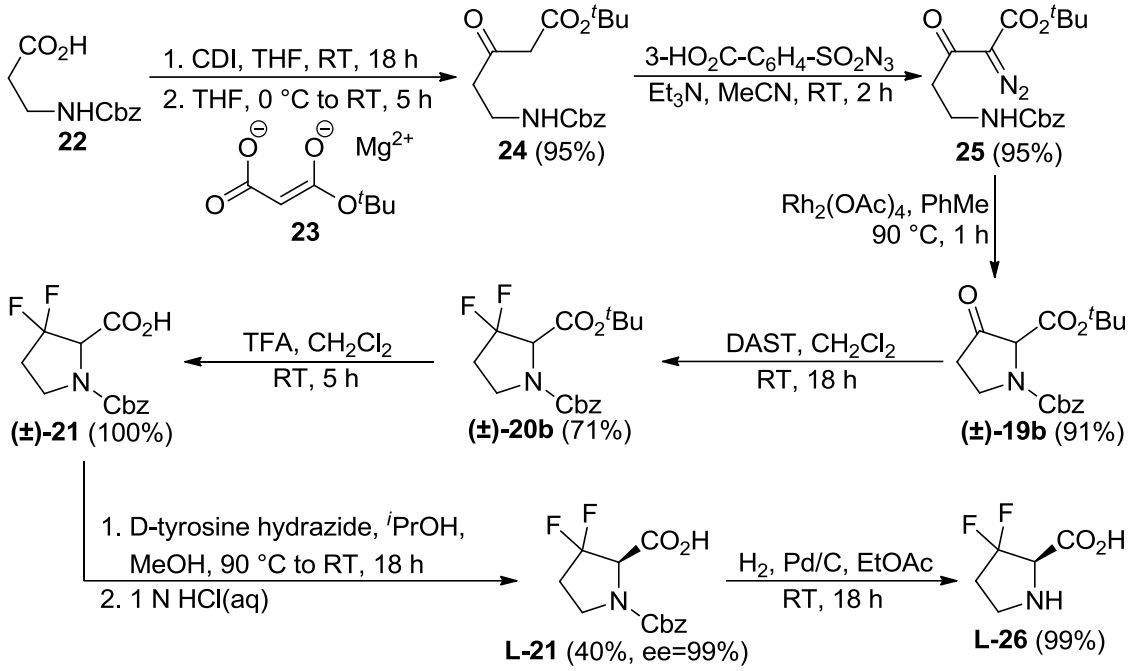
Scheme 8. Synthesis of (2*S*,4*S*)- and (2*S*,4*R*)-4-fluoroproline derivatives **16a,b** and **18a,b** suitable for solid-state peptide synthesis

Doebelin *et al.* aimed to develop a new, scalable and fast synthetic route to enantiomerically pure 3,3-difluoroproline. Fluorination of the commercially available 3-oxoproline derivative **(±)-19a** required neat DAST, because the conversion was not satisfying under normal conditions. Subsequent protecting group exchange provided racemic 3,3-difluoroproline derivative **(±)-21** (*Scheme 9*).[68]



Scheme 9. Synthesis of racemic *N*-Cbz-protected 3,3-difluoroproline

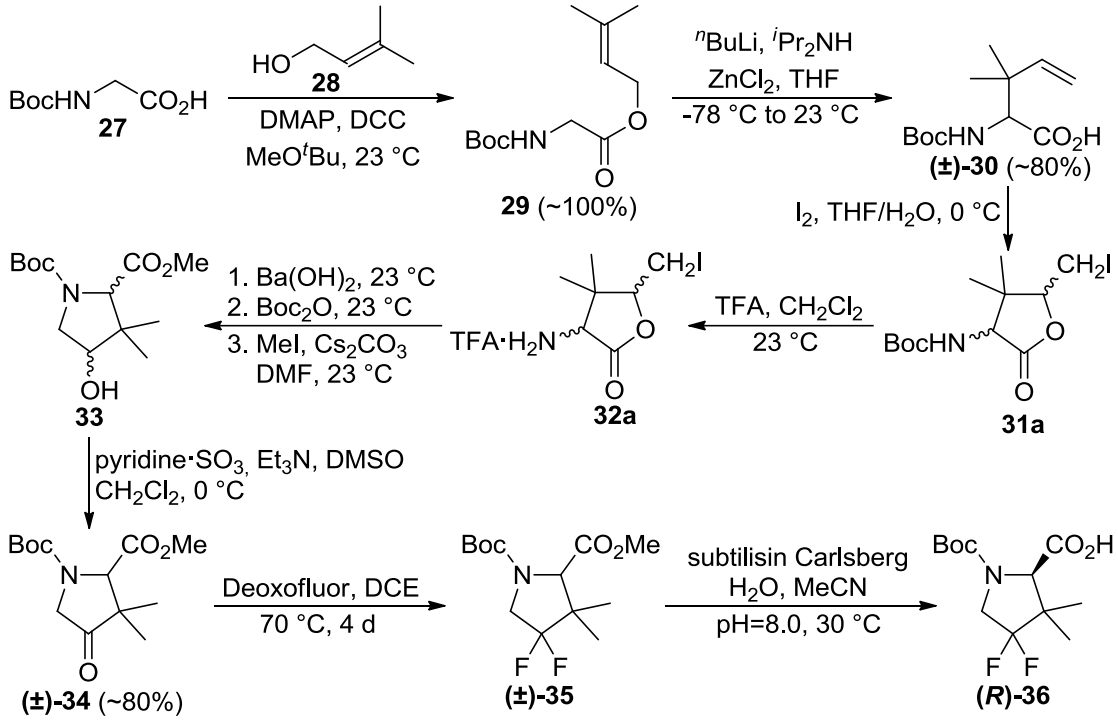
To improve and scale up this synthesis, 3-oxoproline derivative **(±)-19b** was synthesized by carboxylic activation of protected β-alanine **22** with 1,1'-carbonyldiimidazole, reaction with magnesium enolate **23** (prepared from *tert*-butyl hydrogen malonate with ^{i}PrMgBr), diazo transfer to the obtained β-oxo ester **24** from 3-(azidosulfonyl)benzoic acid, and finally Rh-catalyzed carbene insertion into the N–H bond. Deoxyfluorination of the obtained **(±)-19b** went smoothly, and after ester hydrolysis, resolution of the resulting **(±)-21** with D-tyrosine hydrazide produced enantiomerically pure **L-21** in 40% yield, which was deprotected with hydrogenolysis almost quantitatively (*Scheme 10*). Resolution of **(±)-21** or the mother liquor left after removal of **L-21** with L-tyrosine hydrazide analogously gave **D-21** in 40% yield and 99% ee.[68]



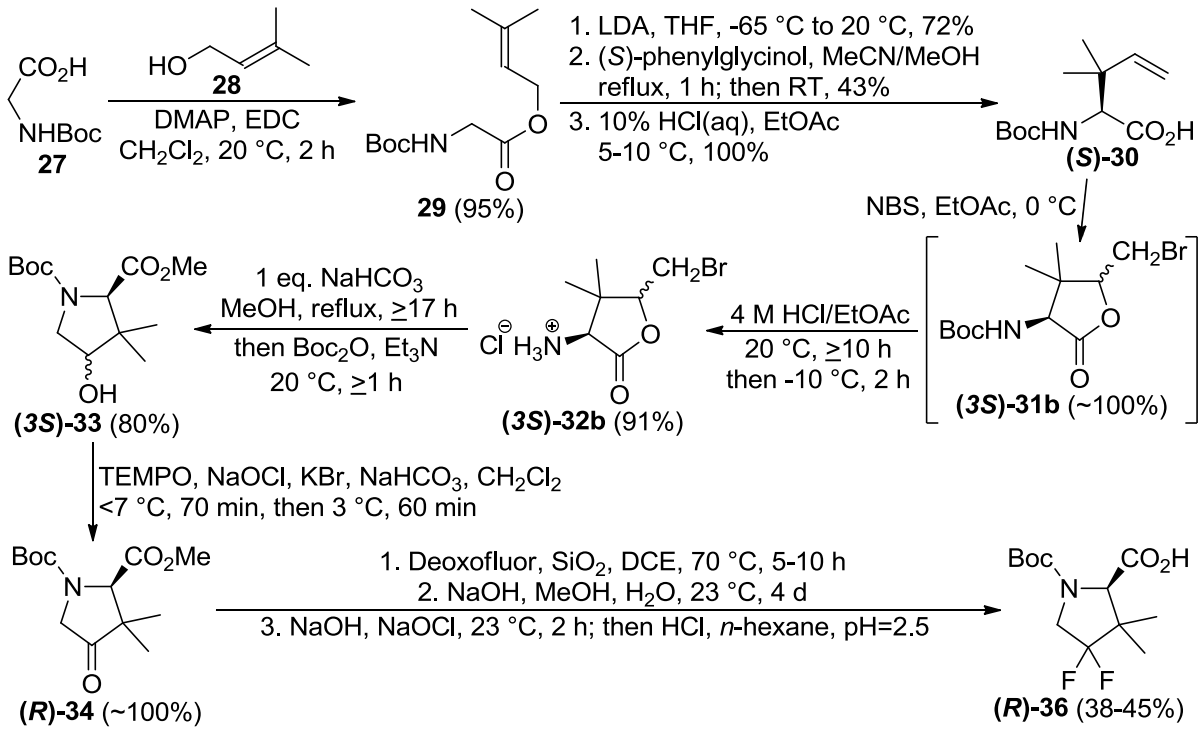
Scheme 10. Synthesis of enantiomerically pure 3,3-difluoro-L-proline

Rossi *et al.* improved the synthesis of 4,4-difluoro-3,3-dimethylproline derivative **(*R*)-36**, which is an intermediate for the synthesis of HIV protease inhibitors such as compound **7** (see *Scheme 4*). The original process (*Scheme 11*) had multiple drawbacks, including low productivity and the use of large quantities of solvents and reagents, which hindered scale-up. In addition, the enzyme used for the resolution was no longer commercially available and the overall yield was a mere 1.5%. Changing the coupling agent in the first step from DCC to EDC resulted in a water-soluble urea byproduct, eliminating the need for filtration. Surprisingly, the next step (Ireland–Claisen rearrangement) worked well even without the original $ZnCl_2$ additive reducing waste issues. The resulting **(±)-30** was resolved through (*S*)-phenylglycinol salts. Halolactonization was accomplished with NBS rather than using the more expensive iodine. Deprotection of the amine group was performed with cheap HCl/EtOAc instead of TFA. To avoid epimerization, equimolar amount of base was used for the rearrangement of **(3*S*)-32b** to **(3*S*)-33**. The original oxidation procedure required expensive pyridine·SO_3 and produced stoichiometric amounts of toxic Me_2S gas, while TEMPO and cheap bleach was utilized in the improved process. Fluorination time was successfully reduced from 4 days to 5-10 h in the silica-catalyzed process. To avoid chromatographic purification, unreacted **(*R*)-34** was removed with selective hydrolysis after fluorination, and then treatment of the remaining material with NaOH and bleach hydrolyzed the ester groups and oxidatively decomposed the fluorovinyl by-

product. Upon acidification of this reaction mixture, pure **(*R*)-36** was precipitated (*Scheme 12*).[69]



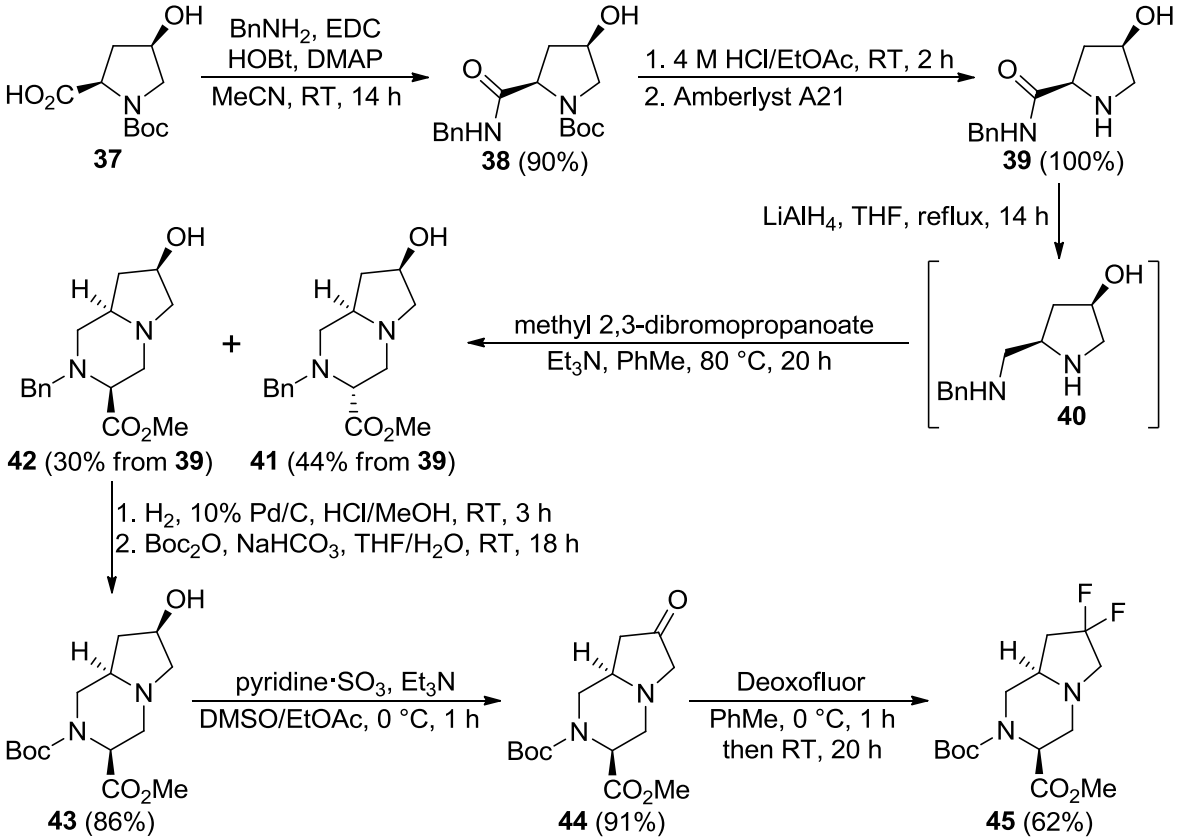
Scheme 11. The original synthetic pathway towards **(*R*)-36**



Scheme 12. The improved synthetic pathway towards **(*R*)-36**

To sum up, toxic and hazardous reagents were avoided as much as possible, the overall yield increased to 4.5% and the calculated sum of all materials needed to produce 1 kg **(*R*)-36** decreased to 2 t from 7 t.[69]

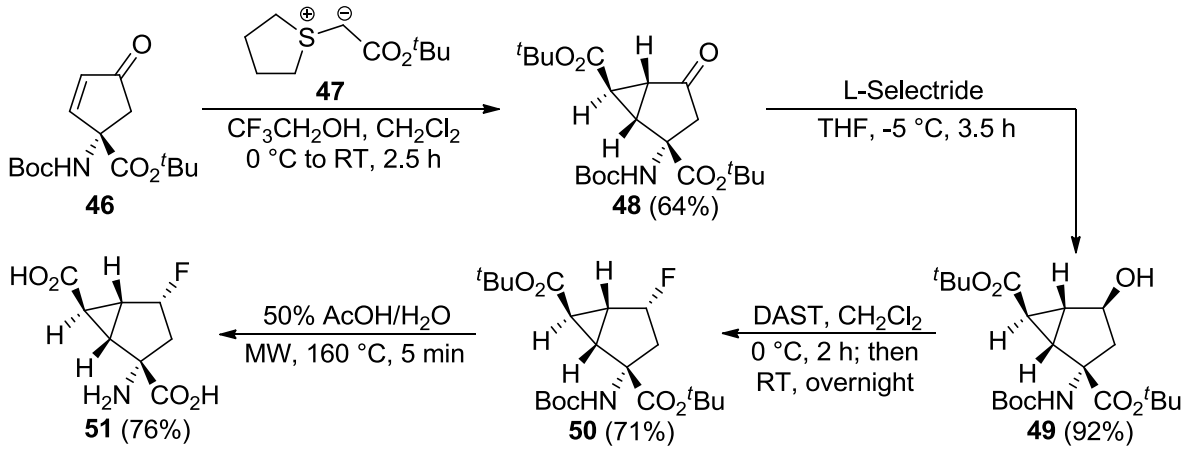
Ishikawa and co-workers synthesized fluorinated octahydropyrrolo[1,2-*a*]pyrazine derivative **45**, which served as a building block for inhibitor of apoptosis protein (IAP) antagonists. The first step of the synthesis was coupling of *N*-Boc-protected *cis*-4-hydroxy-D-proline and benzylamine followed by *N*-deprotection. Reduction of the resulting amide **39** gave 1,2-diamine intermediate **40**, which was reacted with methyl 2,3-dibromopropanoate to construct the heterocyclic skeleton. Subsequent exchange of Bn with Boc, oxidation and deoxyfluorination provided compound **45** (*Scheme 13*).[70]



Scheme 13. Synthesis of fluorinated octahydropyrrolo[1,2-*a*]pyrazinecarboxylic ester **45**

Monn *et al.* synthesized multiple 4-substituted 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylates, including a fluorinated one, as potential metabotropic glutamate 2/3 receptor agonists. The synthesis started with stereoselective cyclopropanation of enone **46** with sulfur

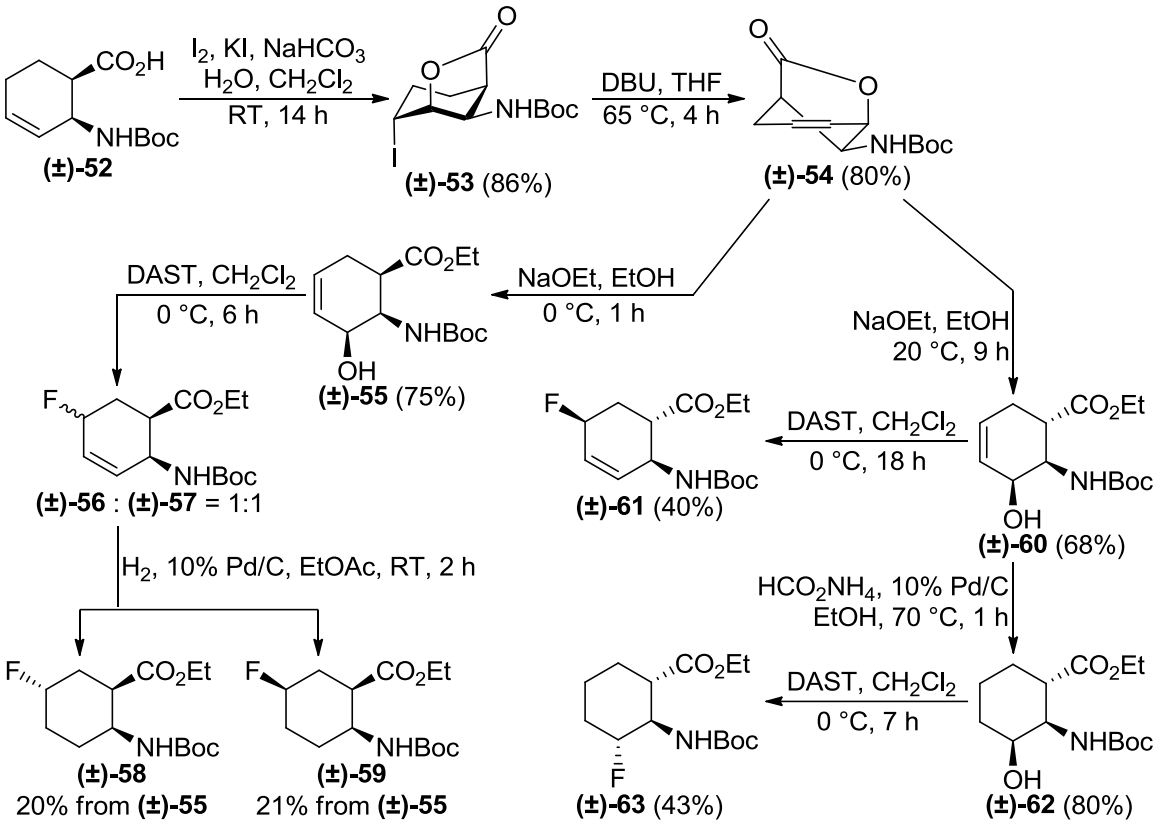
ylide **47**, followed by diastereoselective reduction of the carbonyl group, hydroxy–fluorine exchange and deprotection (*Scheme 14*).[71]



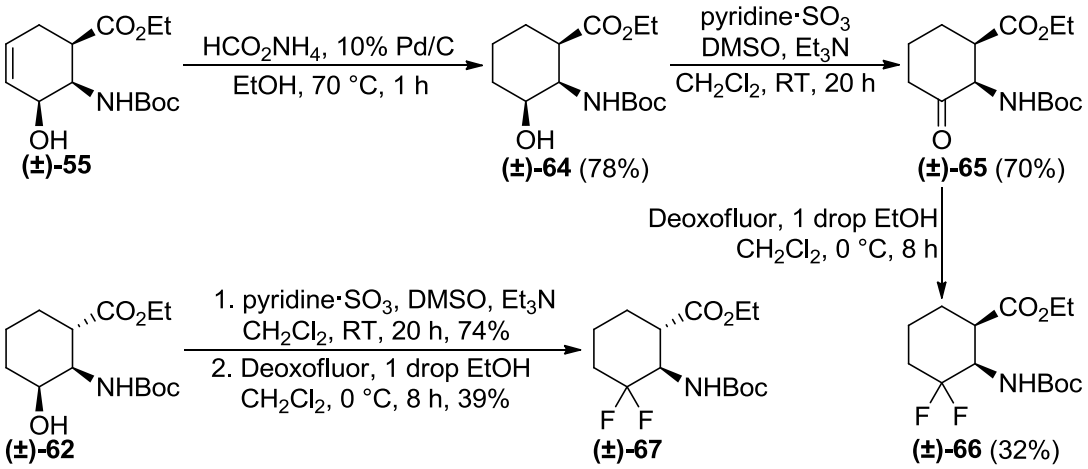
Scheme 14. Synthesis of 4-fluoro-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid **51**

2.3.2. Cyclic β-amino acid derivatives

In order to prepare regio- and stereo-selectively hydroxylated β-amino acid derivatives with cyclohexane or cyclohexene skeleton as substrates for subsequent fluorination, Kiss *et al.* performed regio- and stereo-selective iodolactionization of *N*-Boc-protected *cis*-2-aminocyclohex-3-enecarboxylic acid **(±)-52**, followed by HI elimination to obtain unsaturated lactone **(±)-54**. The outcome of its reaction with ethoxyde depended on the conditions: in a short reaction at 0 °C, only lactam ring opening occurred affording allylic alcohol **(±)-55**. Increasing the reaction time and performing the reaction at 20 °C, however, resulted in diastereomeric allylic alcohol **(±)-60** through epimerization of the primary product at C-1. Both allylic alcohols can be saturated with catalytic hydrogenation. From these four alcohols, fluorinated β-amino acid derivatives were obtained through either hydroxy→fluorine exchange (*Scheme 15*) or oxidation followed by transformation of the carbonyl group to difluoromethylene moiety (*Scheme 16*). Interestingly, thanks to their allylic structure, both **(±)-55** and **(±)-60** reacted through S_N2' pathway, but in a different manner. Compound **(±)-55** produced a product mixture, which was only separable after saturation, ultimately resulting in fluorinated compounds **(±)-58** and **(±)-59**. In contrast, **(±)-60** gave a single product. Enantiomerically pure fluorinated β-amino acid derivatives **(+)-58**, **(+)-59** and **(+)-63** were also prepared from enantiopure **(+)-52**, which was obtained by enzymatic resolution.[25]



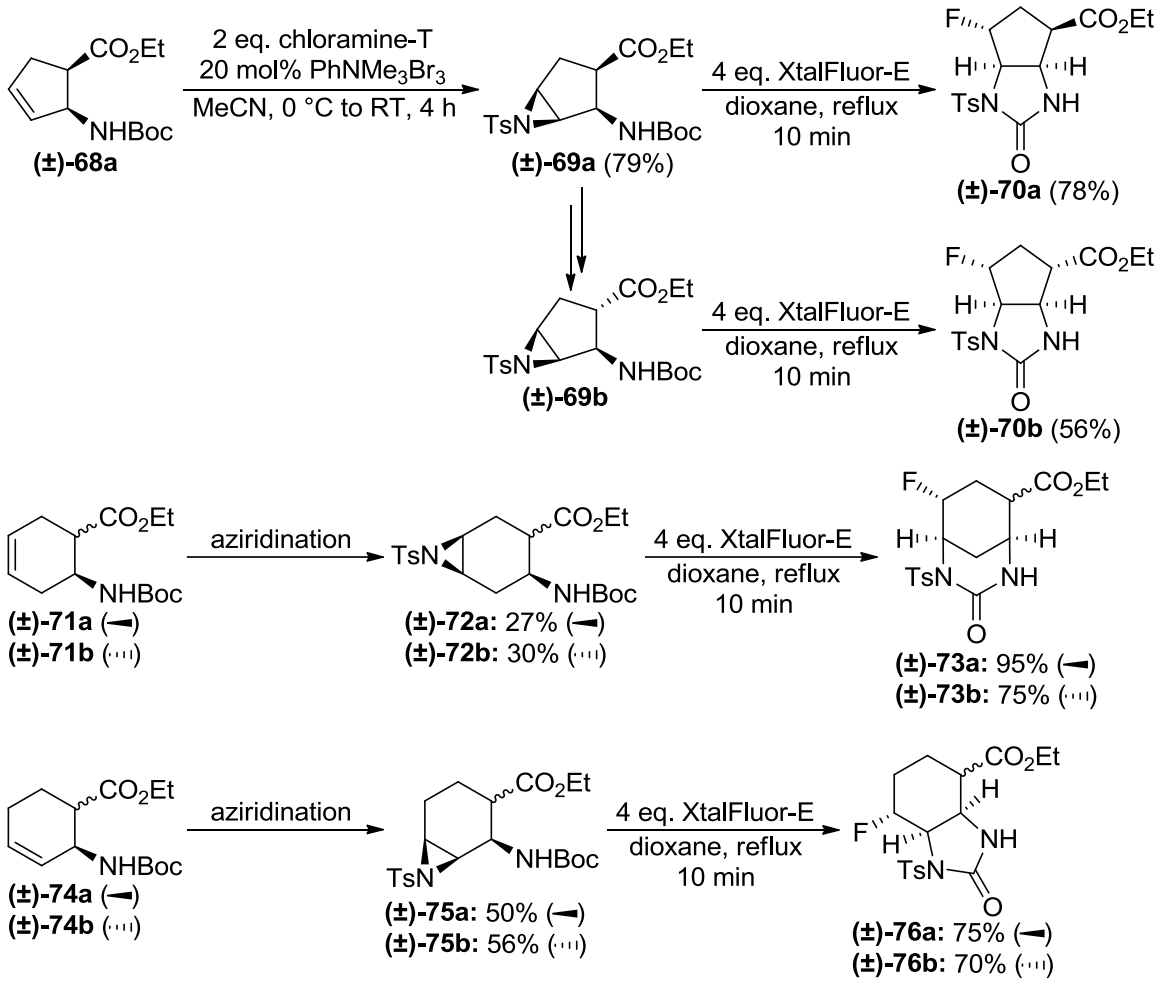
Scheme 15. Synthesis of monofluorinated β-amino acid derivatives from *N*-Boc-protected *cis*-2-aminocyclohex-3-enecarboxylic acid. Separation of **(±)-56** and **(±)-57** was not successful.



Scheme 16. Synthesis of 3,3-difluoro-2-aminocyclohexanecarboxylic acid derivatives

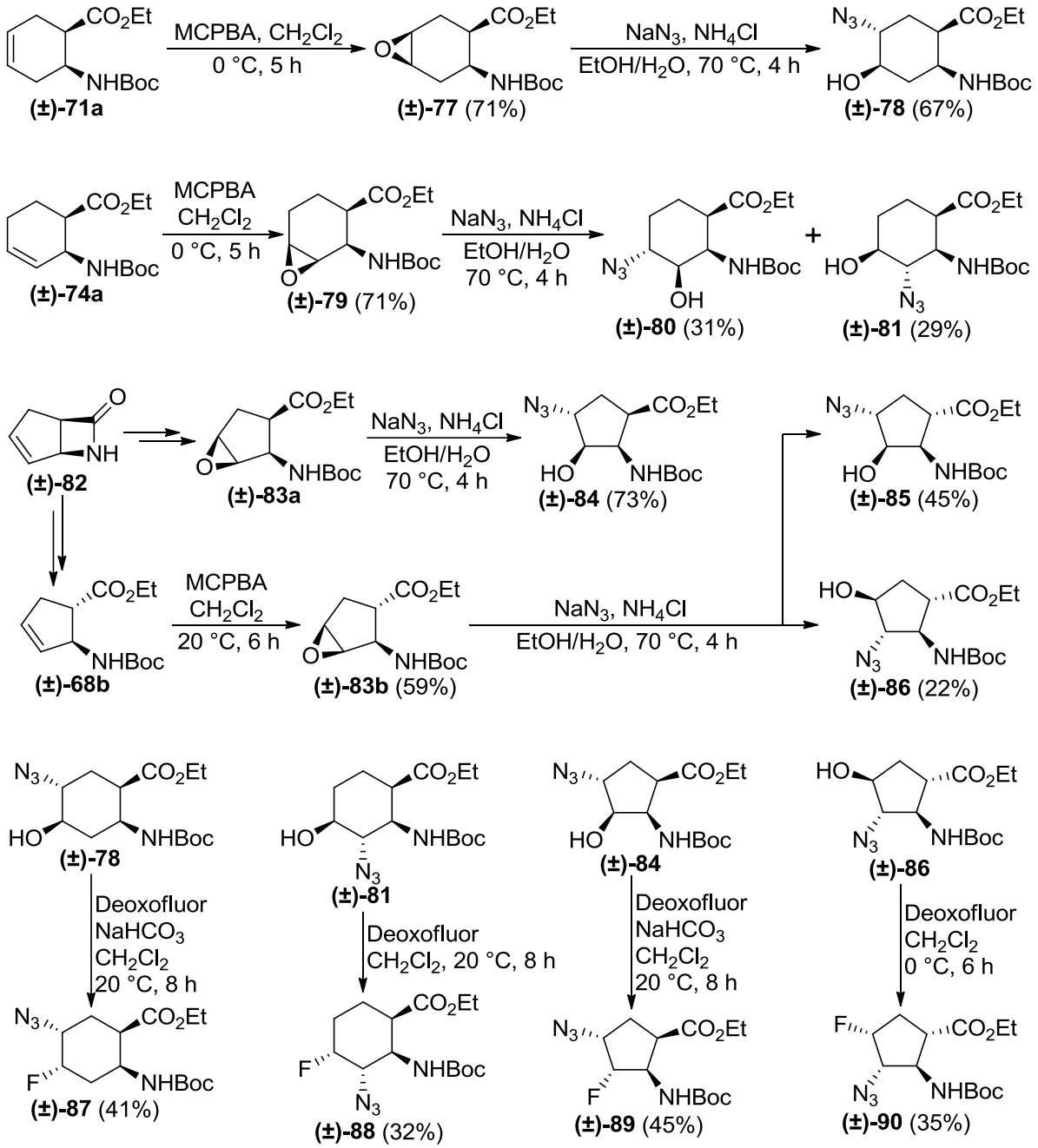
Nonn *et al.* developed a new method for the ring opening of *N*-tosylaziridines with fluoride utilizing the XtalFluor-E reagent. The aziridines were obtained by stereoselective direct aziridination of unsaturated compounds. Both reactions were usually fast and effective

enabling the synthesis of fluorinated β-amino acid derivatives (*Scheme 17*) and other fluorinated cyclic amino acid derivatives (see *Scheme 22*).[30]



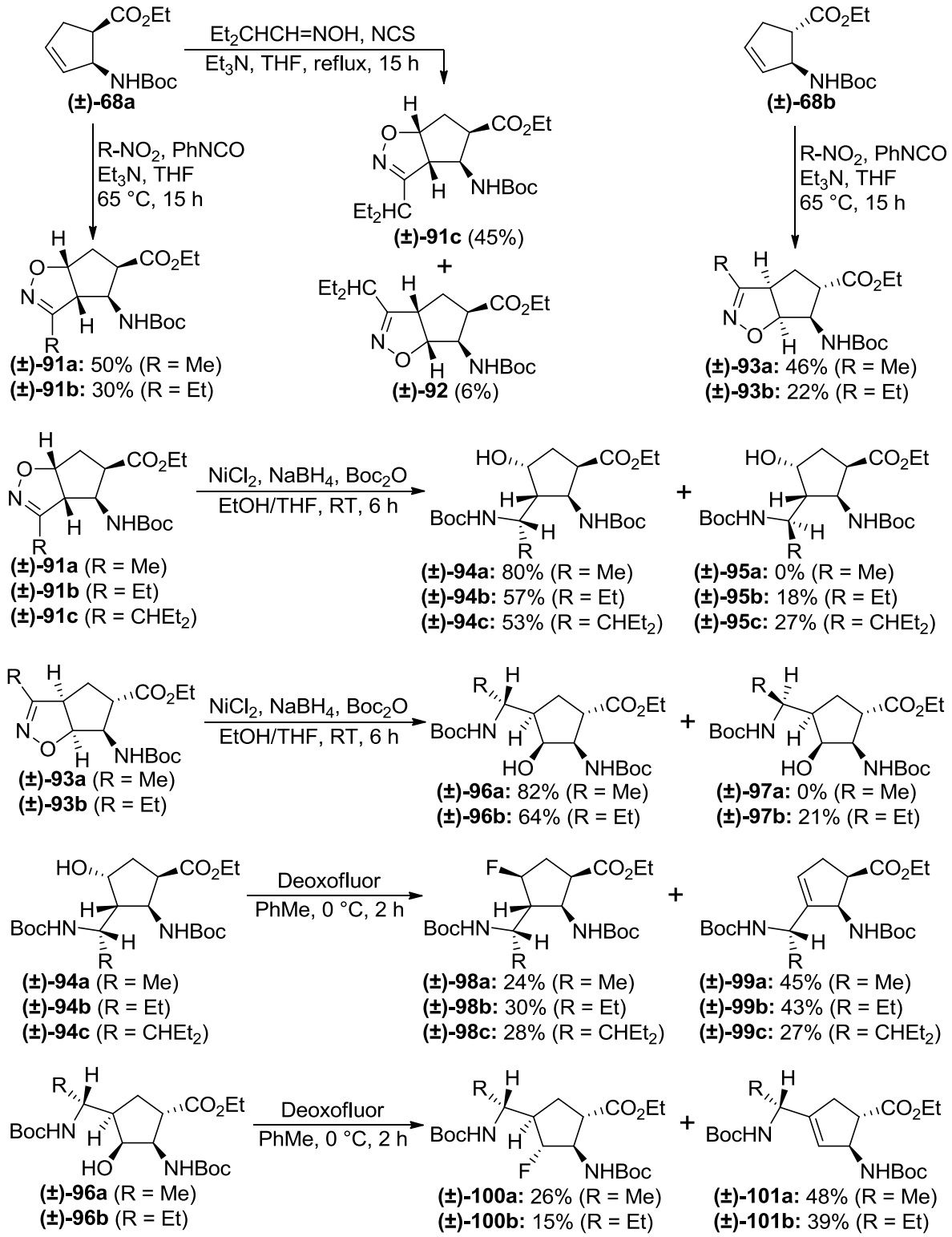
Scheme 17. Synthesis of fluorinated β-amino acid derivatives by aziridine ring opening with XtalFluor-E. All aziridinations were performed under the same conditions.

Kiss *et al.* synthesized numerous functionalized fluorine-containing β-amino acid derivatives. The first step was stereoselective epoxidation of β-aminocycloalkenecarboxylic acid derivatives: hydrogen bonding with the NHBoc group directs the percarboxylic acid to one side of the ring resulting in *cis* arrangement of oxirane and NHBoc moieties relative to each other. Product oxiranes were then subjected to ring opening with azide to give azidoalcohols **(±)-78**, **(±)-80**, **(±)-81**, **(±)-84**, **(±)-85** and **(±)-86**.[72] Deoxyfluorination of **(±)-78**, **(±)-81**, **(±)-84** and **(±)-86** were successful (*Scheme 18*). The reaction of **(±)-80** with Deoxofluor gave only an elimination product, while **(±)-85** did not react. Cyanoalcohols obtained by ring opening of the epoxides with Et_2AlCN yielded only elimination products with Deoxofluor.[31]



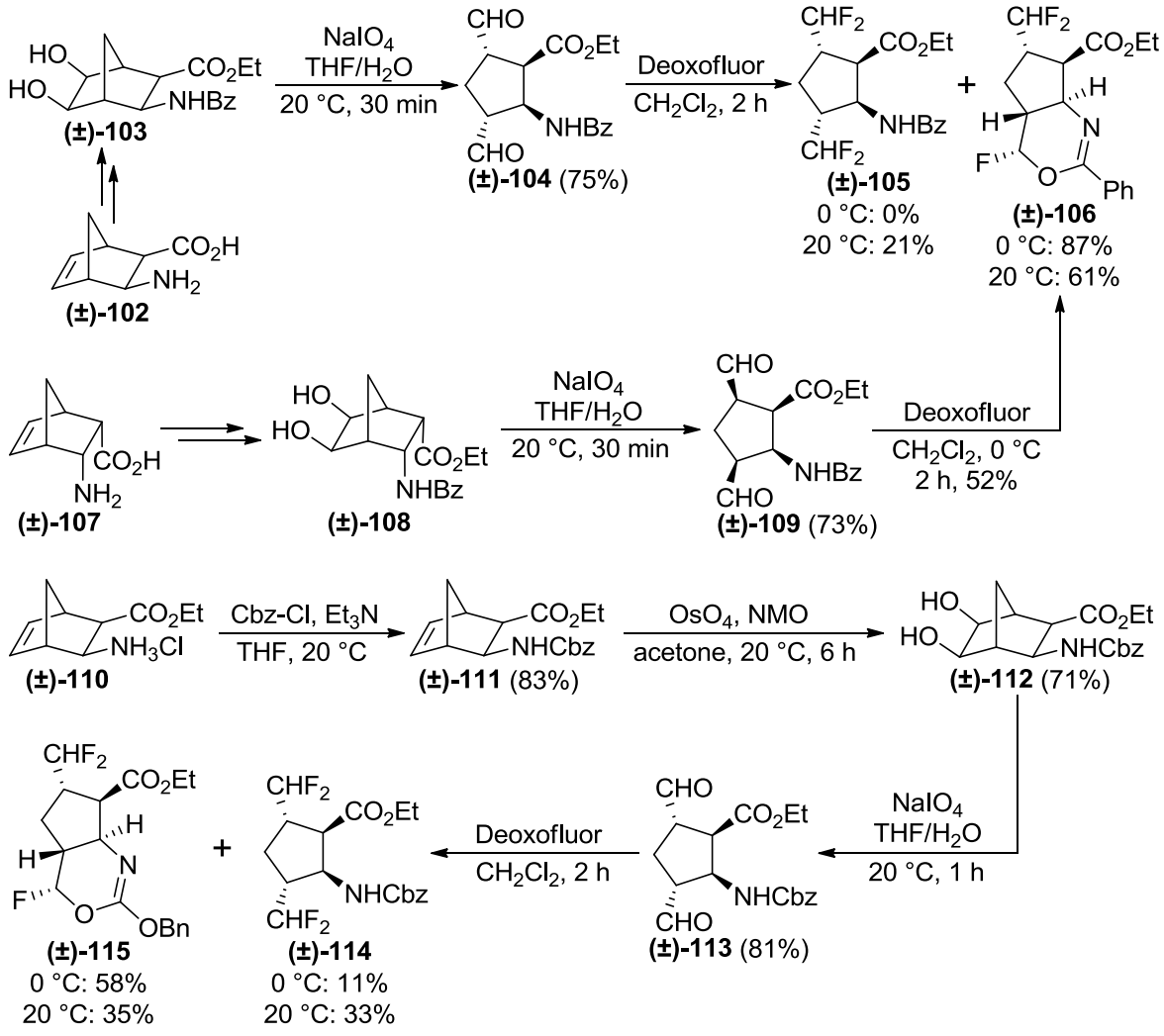
Scheme 18. Synthesis of fluorine-containing functionalized β-amino acid derivatives through stereoselective epoxidation, regioselective oxirane ring opening and fluorination

Nonn *et al.* synthesized multifunctional β-amino acid derivatives **(±)-94a-c** and **(±)-96a,b** by nitrile oxide [3+2] dipolar cycloaddition to protected 2-aminocyclopent-3-enecarboxylates and subsequent reductive opening of their heterocycle.[27,73,74] These hydroxy-containing derivatives underwent deoxyfluorination yielding fluorine-containing derivatives and elimination products (*Scheme 19*).[27]



Scheme 19. Synthesis of fluorinated β-amino acid derivatives through isoxazole-fused β-amino acid derivatives

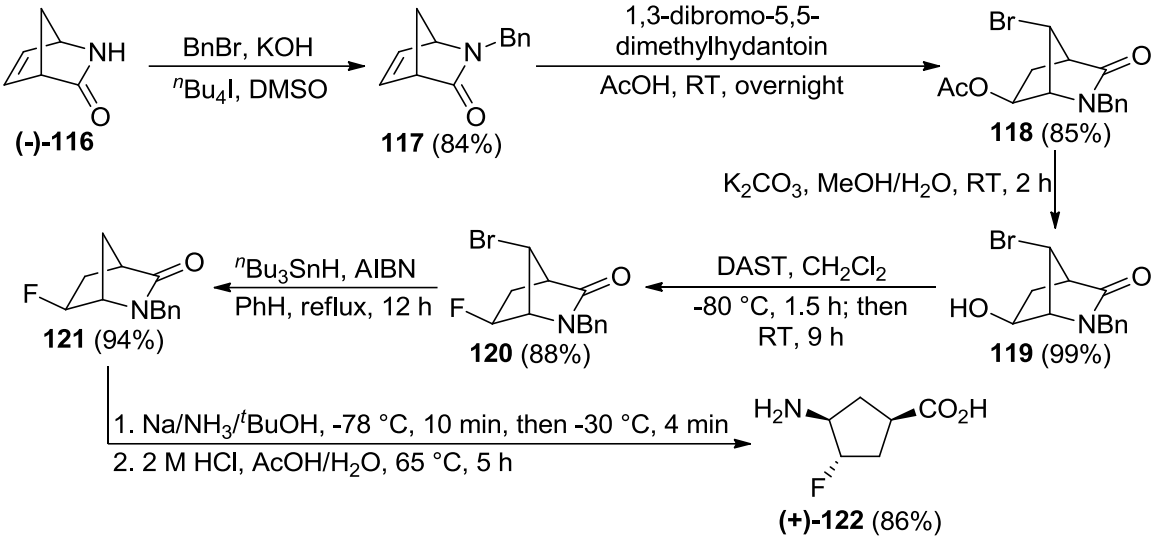
Kiss *et al.* synthesized difluoromethyl-containing β-amino acids too. Dihydroxylated compounds **(±)-103**, **(±)-108** and **(±)-112** (prepared from norbornene β-amino acids) underwent oxidative ring opening with $NaIO_4$. Of the resulting dialdehydes, reaction of **(±)-104** with Deoxofluor gave two products in a temperature-dependent manner. At 0 °C, **(±)-106** was formed exclusively with the 5-formyl group transformed into CHF_2, while the 3-formyl group underwent cyclization with the amide group. At 20 °C, another product [**(±)-105**] was formed too with both formyl groups transformed into CHF_2 groups. Interestingly, reaction of **(±)-109** with Deoxofluor also afforded **(±)-106** suggesting that basic fluoride ions cause isomerization at C-3 and C-5 before fluorination can take place. Dialdehyde **(±)-113** behaved similarly to **(±)-104** (*Scheme 20*).[32]



Scheme 20. Synthesis of CHF_2-containing β-amino acids by fluorination of dialdehydes

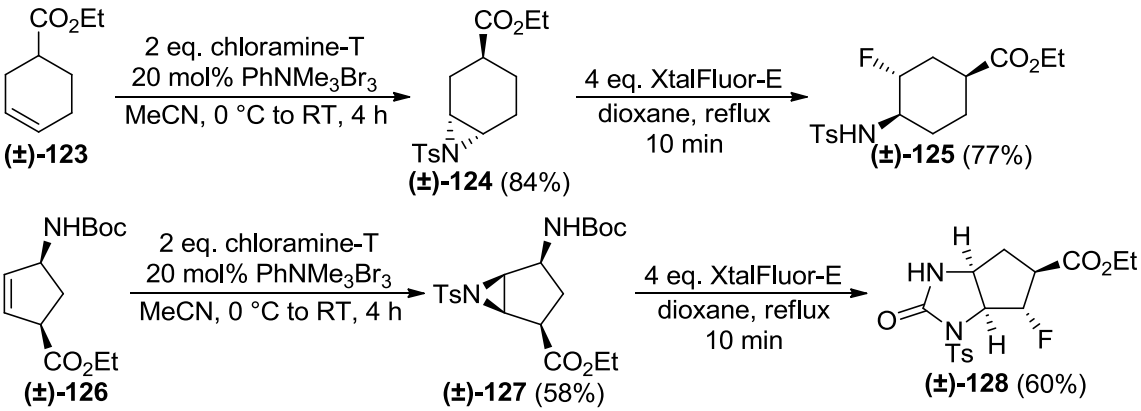
2.3.3. Cyclic γ- and δ-amino acid derivatives

Silverman and co-workers reported the synthesis of several fluorinated 3-aminocyclopentane carboxylic acids as the analogues of GABA aminotransferase inhibitors. For example, in order to synthesize (1*R*,3*S*,4*S*)-3-amino-4-fluorocyclopentanecarboxylic acid **(+)-122**, *N*-benzyl-protected (-)-enantiomer of Vince lactam was reacted with a Br^+ source in AcOH, which induced rearrangement to **118**. After acetate hydrolysis, fluorination, reductive debromination, reductive debenzylation and subsequent lactam hydrolysis resulted in free acid **(+)-122** (*Scheme 21*).[75]



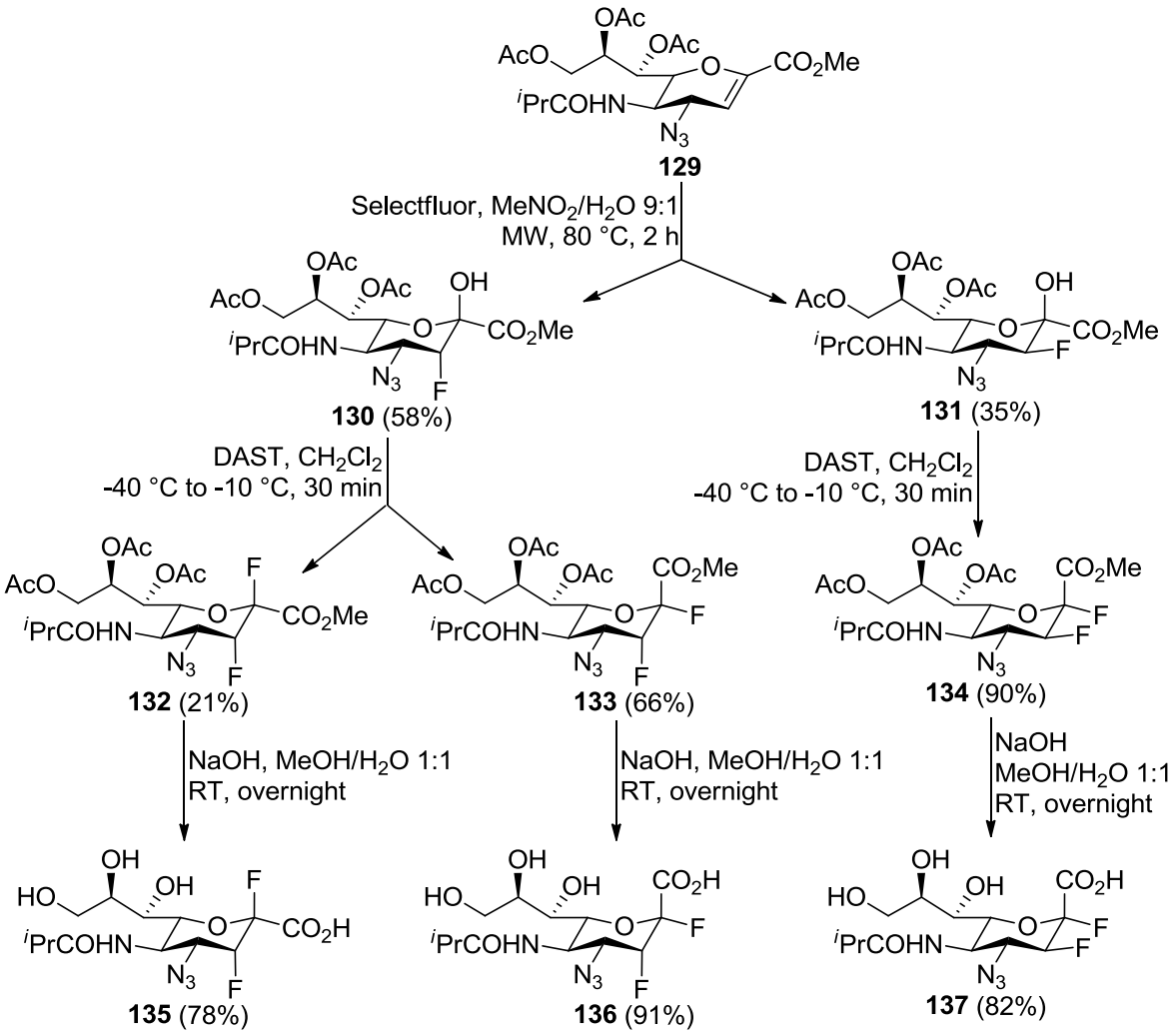
Scheme 21. Synthesis of a fluorinated cyclic GABA aminotransferase inhibitor analogue

Nonn *et al.* used their aziridine ring-opening method (see *Scheme 17*) to synthesize a number of fluorinated cyclic γ- and δ-amino acids (*Scheme 22*).[30]



Scheme 22. Synthesis of fluorinated cyclic amino acids from aziridines

Dirr *et al.* synthesized multiple 2,3-difluorosialic acid analogues to study the mechanism of human parainfluenza virus type 3 haemagglutin-neuraminidase. The first fluorine atom was introduced by reacting unsaturated **129** with electrophilic fluorinating agent Selectfluor in the presence of water. The OH group formed during this process was then exchanged to fluorine with DAST. Finally, both the *O*-acetyl groups and the methyl ester were hydrolyzed to obtain analogues **135-137** (*Scheme 23*).[55]



Scheme 23. Synthesis of 2,3-difluorosialic acid analogues[55]

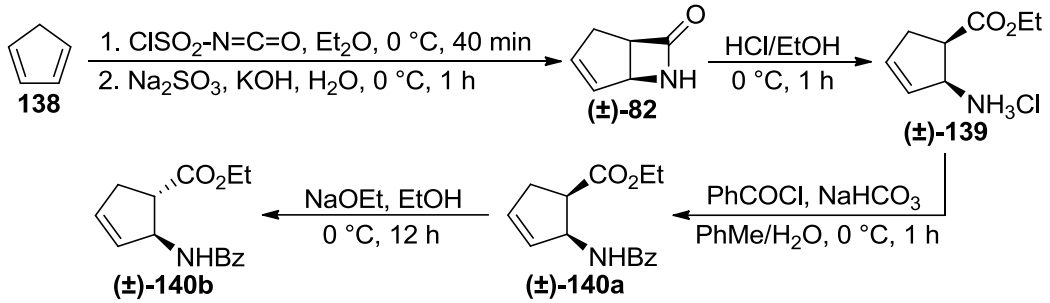
3. RESULTS AND DISCUSSION

3.1. Fluorinations through substrate-dependent oxirane opening

Oxirane ring opening with nucleophiles is a powerful tool to incorporate a wide range of functional groups into organic molecules,[31,72,76-80] including fluorine atom.[3,81-83] However, despite the high number of reported methods, achieving regio- and stereo-selectivity during ring opening of oxiranes (especially highly functionalized or bicyclic ones) with fluoride is still challenging.[84-93] Inspired by the successful aziridine ring-opening method utilizing XtalFluor-E,[30] we aimed at developing new oxirane ring-opening methods with nucleophilic fluorinating agents Deoxofluor and XtalFluor-E, and the application of these methods for the synthesis of fluorine-containing β-amino acids.

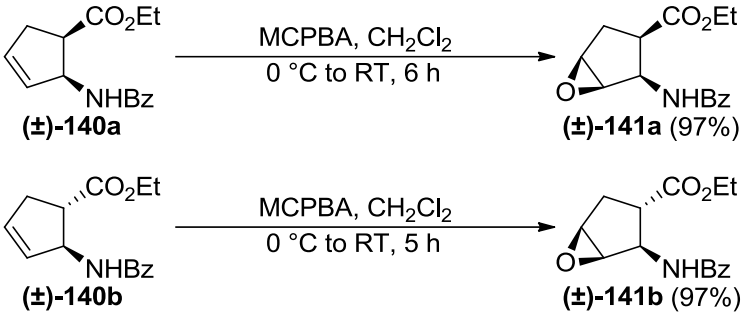
3.1.1. Synthesis of epoxy amino esters

According to our goal, mainly protected epoxy β-amino esters were chosen as substrates. Synthesis of oxiranes **(±)-141a,b** with a cyclopentane skeleton started with [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) with cyclopentadiene,[94] which is thermally allowed thanks to the cumulated π-system of CSI and its regioselectivity is the result of electronic effects. After removal of the *N*-SO_2Cl group with basic aqueous sulfite, ring opening of the obtained β-lactam **(±)-82** with HCl/EtOH resulted in amino ester hydrochloride **(±)-139**,[94] which precipitates of the reaction mixture in pure form. Subsequent benzoylation[95] gave *cis*-β-amino ester **(±)-140a**, which can be epimerized to its *trans* isomer[94] through its enolate (*Scheme 24*).



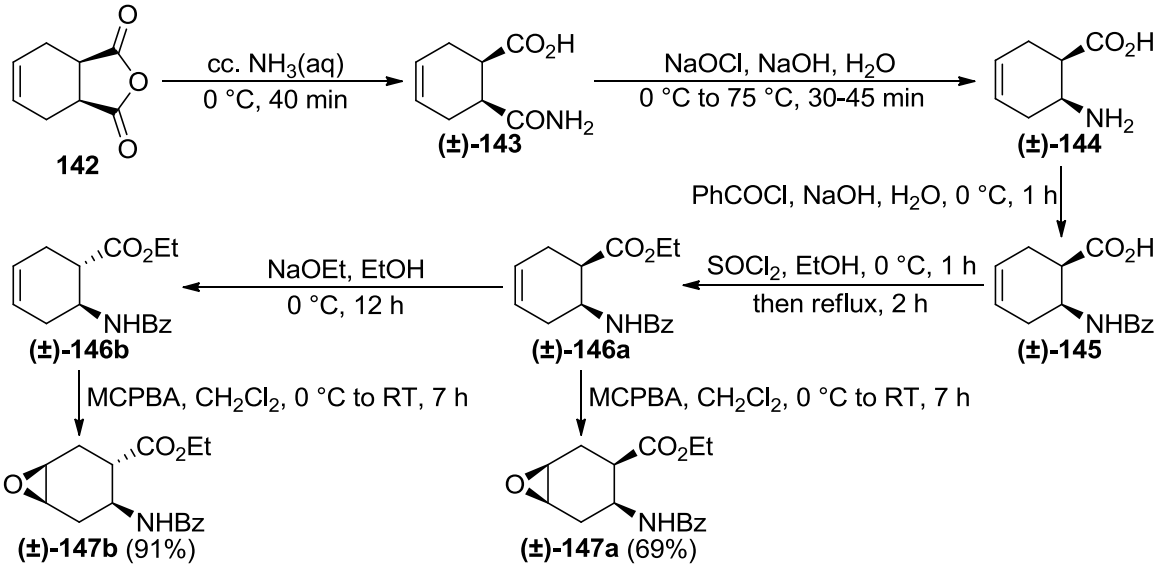
Scheme 24. Synthesis of β-amino esters **(±)-140a,b**

Epoxidation of these unsaturated β-amino esters was stereoselective: the oxirane ring formed in *cis* arrangement relative to the protected amino group (*Scheme 25)*. This directing effect of the NHBz group is the result of hydrogen bonding with the percarboxylic acid.[31,96]



Scheme 25. Stereoselective epoxidation of β-amino esters with cyclopentene skeleton

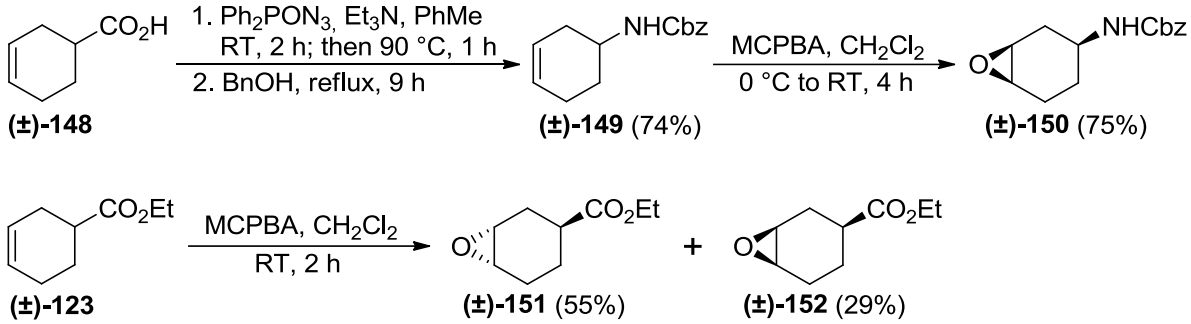
The key intermediate to synthesize oxiranes **(±)-147a,b** with a cyclohexane skeleton is β-amino ester **(±)-146a**. Although this compound can be obtained from cyclohexa-1,4-diene by CSI addition, hydrolysis of the *N*-SO_2Cl group, lactam ring opening[97] and *N*-benzoylation[95] (analogously to the preparation of **(±)-140a** on *Scheme 24*), a more economic pathway is preferred. Treatment of cheap *cis*-tetrahydrophthalic anhydride **142** with aqueous NH_3, followed by Hoffmann degradation of the resulting monoamide, gives *cis*-2-amino-cyclohex-4-enecarboxylic acid **(±)-144**,[98] which can be transformed into β-amino ester **(±)-146a** by benzoylation[95] and esterification.[94] Epimerization of compound **(±)-146a** results in its *trans* isomer **(±)-146b**.[99] Epoxidations of both compounds were stereoselective (*Scheme 26*).[97,100]



Scheme 26. Synthesis of epoxy β-amino esters with cyclohexane skeleton

Some simpler oxiranes were also synthesized in order to study the effects of the ester and protected amine moieties individually. Similarly to the case of β-amino esters, reaction of *N*-Cbz-protected cyclohex-3-eneamine **(±)-149** (obtained from cyclohex-3-enecarboxylic acid

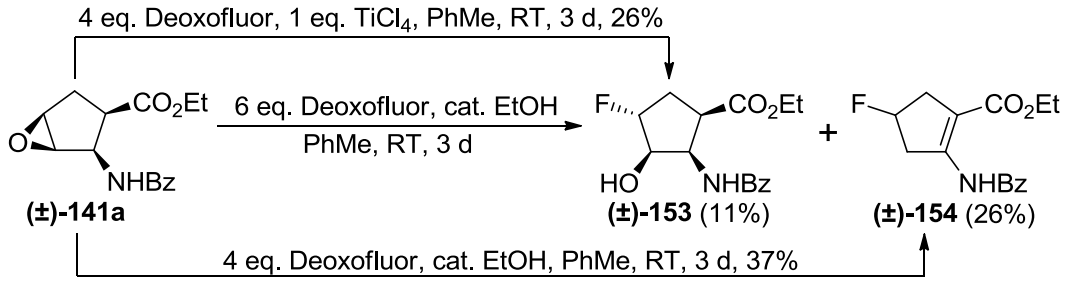
by Curtius rearrangement[101]) with MCPBA was highly stereoselective. In contrast, epoxidation of ethyl cyclohex-3-enecarboxylate **(±)-123** resulted in a 1.9 : 1 mixture of *trans* and *cis* epoxides **(±)-151** and **(±)-152**. Because the hydrogen-bonding directing effect is absent in this molecule, selectivity is controlled by steric effects, which are less effective and prefer the *trans* product (*Scheme 27*).



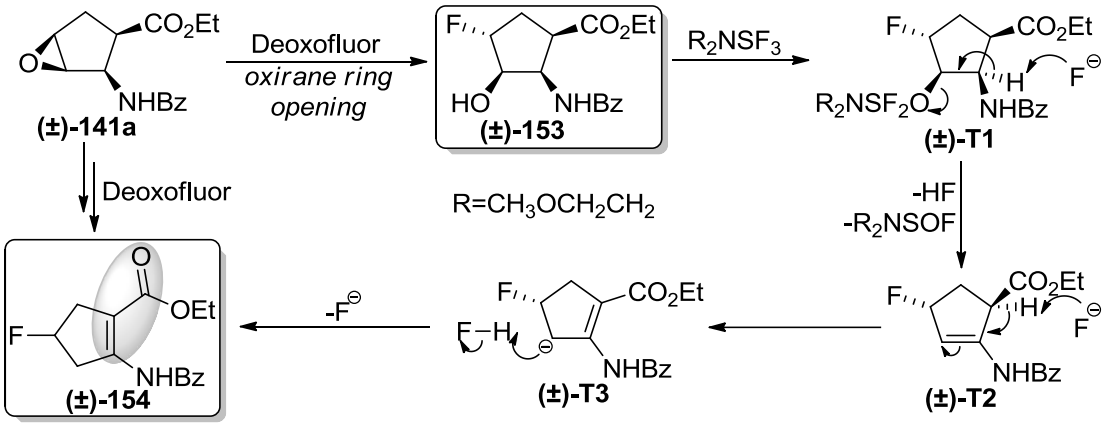
Scheme 27. Synthesis of monofunctional bicyclic oxiranes

3.1.2. Fluorination reactions

First, reactions of compound **(±)-141a** were studied with Deoxofluor. To facilitate the process, electrophilic activation of the epoxide ring was attempted. Initially, catalytic amount of EtOH was added to the reaction mixtures to produce some HF, which can protonate the oxirane oxygen atom. The use of anhydrous PhMe gave better results than anhydrous CH_2Cl_2. After some optimization, we found that with 6 eq. Deoxofluor two products, fluorohydrin **(±)-153** and fluorine-containing unsaturated product **(±)-154**, were formed. With 4 eq. of Deoxofluor, only product **(±)-154** was obtained, albeit in better yield. Other agents for electrophilic activation were also tested ($ZnCl_2$, LiBr, $AlCl_3$, $BF_3{\cdot}OEt_2$ etc.) and $TiCl_4$ was the most effective. In its presence, fluorohydrin **(±)-153** was obtained in 26% yield (*Scheme 28*). Possibly, oxirane ring opening first gives fluorohydrin **(±)-153**. This is corroborated by the regioselectivity of the ring opening of the analogous epoxide **(±)-83a** with azide ion (*Scheme 18*). Then, transformation of the hydroxy group into a good leaving group followed by elimination and isomerization resulted in fluorinated β-amino ester **(±)-154**. The driving force of the isomerization is the formation of a conjugated π-system, and it proceeds through enolate intermediate **(±)-T3** with an extended mesomeric structure (*Scheme 29*).

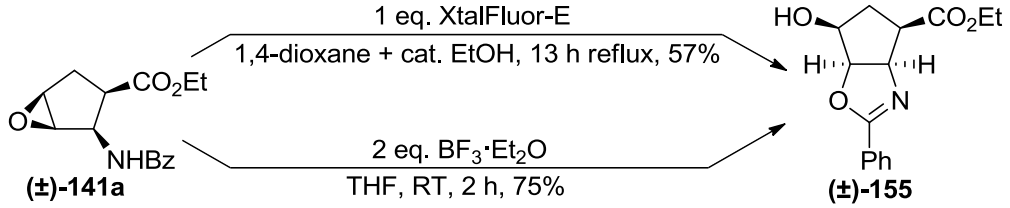


Scheme 28. Reactions of oxirane **(±)-141a** with Deoxofluor

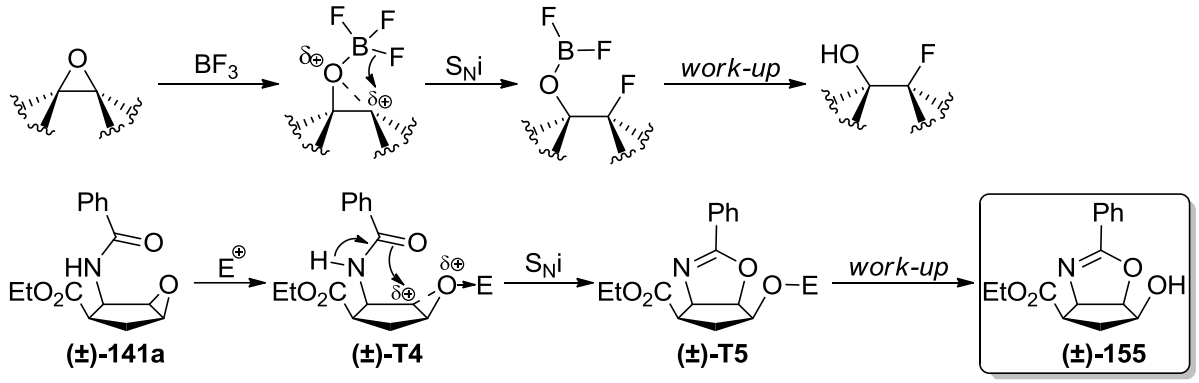


Scheme 29. Formation mechanism of **(±)-153** and **(±)-154**. The conjugated π-system of **(±)-154** is highlighted.

During our experiments with Deoxofluor–Lewis acid systems, the reaction of **(±)-141a** with only $BF_3 \cdot OEt_2$ was tested too, because BF_3 can open epoxides to form *syn*-fluorohydrins.[87] The result was heterocycle **(±)-155** thanks to participation of the protected amino group. Applying a slightly modified version of the conditions of the *N*-tosylaziridine ring opening developed in the Institute of Pharmaceutical Chemistry on oxirane **(±)-141a** resulted in the formation of the same heterocyclic product (*Scheme 30*). Taking into account the mechanism of *syn*-fluorohydrin formation, a plausible mechanistic explanation for the formation of oxazoline **(±)-155** is shown in *Scheme 31*.

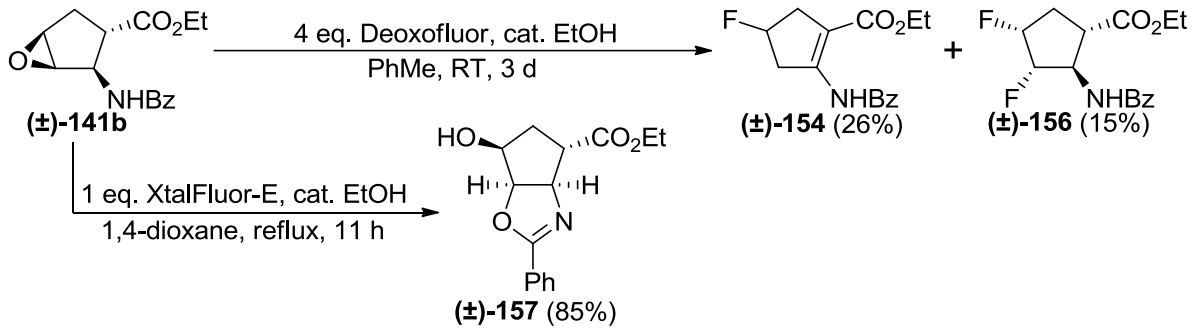


Scheme 30. Reaction of epoxide **(±)-141a** with XtalFluor-E and $BF_3 \cdot OEt_2$

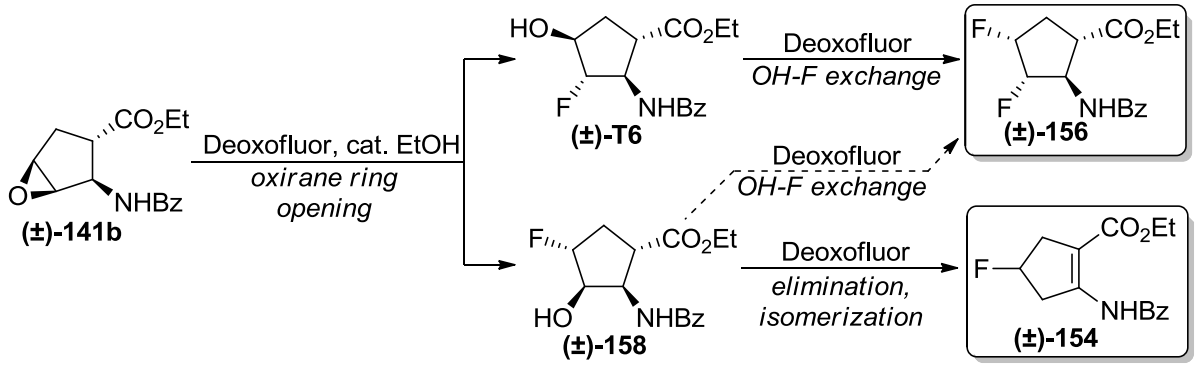


Scheme 31. Formation mechanism of **(±)-155** compared to the mechanism of *syn*-fluorohydrin formation from oxiranes with BF_3 (E^+ = $Et_2N{=}SF_2^+$ or BF_3)

We continued our work on diastereomeric epoxide **(±)-141b**. Reaction with Deoxofluor in the presence of catalytic amount of EtOH gave both unsaturated derivative **(±)-154** and difluorinated product **(±)-156**. Reaction with XtalFluor-E yielded heterocyclic derivative **(±)-158** similarly to the formation of **(±)-155** (*Scheme 32*). Noteworthy that opening of analogous epoxide **(±)-83b** with N_3^- is not regioselective (*Scheme 18*), which provides some insight into the mechanisms of the reactions of **(±)-141b** with Deoxofluor (*Scheme 33*).

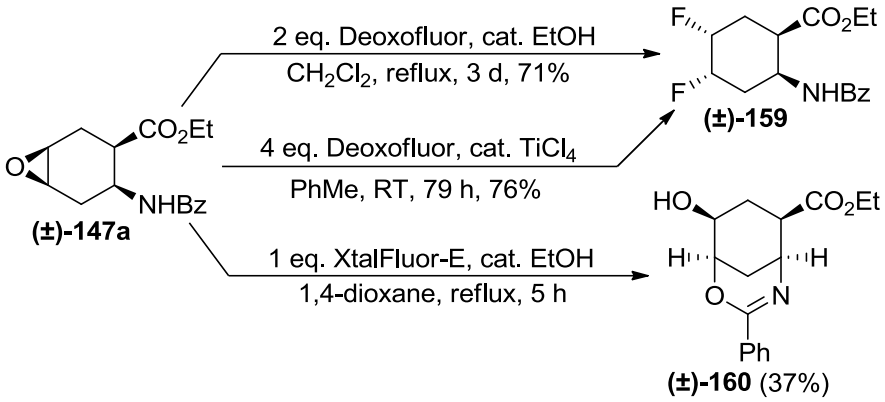


Scheme 32. Fluorinations of epoxide **(±)-141b**



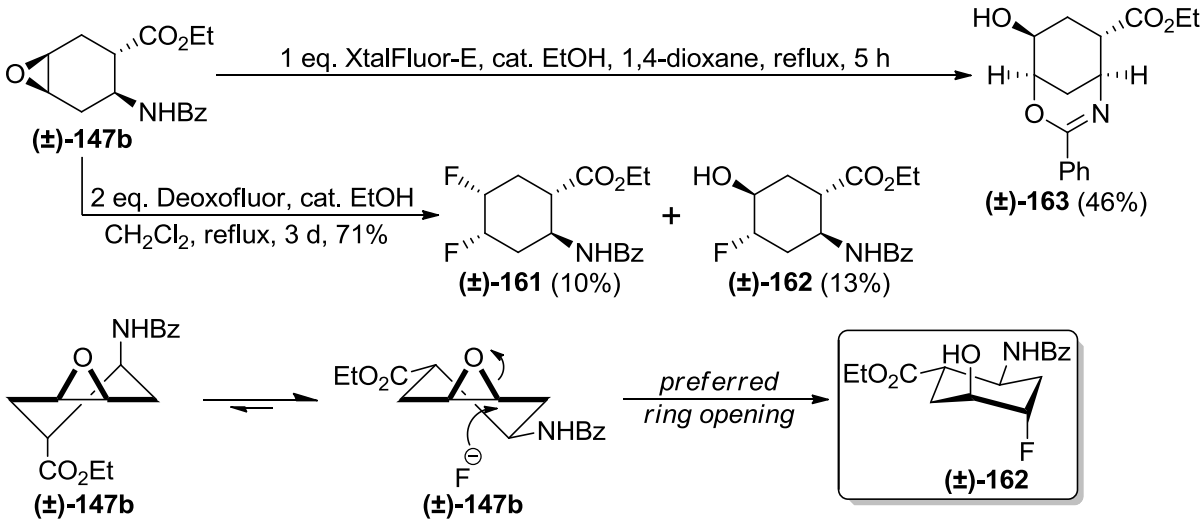
Scheme 33. Possible pathways of the reaction of **(±)-141b** with Deoxofluor

Reaction of epoxide **(±)-147a** with Deoxofluor in the presence of EtOH was the most effective in refluxing CH_2Cl_2, where difluorinated product **(±)-159** was obtained in 71% yield. The use of $TiCl_4$ instead of EtOH improved the yield to 76%. Treatment of epoxide **(±)-147a** with XtalFluor-E furnished cyclized product **(±)-160** (*Scheme 34*).



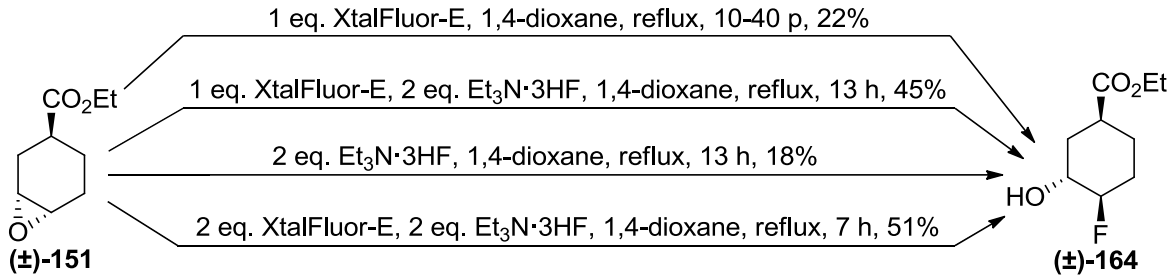
Scheme 34. Reactions of epoxide **(±)-147a** with nucleophilic fluorinating reagents

Interestingly, reacting epimeric compound **(±)-147b** with Deoxofluor was much less effective. In the presence of EtOH, products **(±)-161** and **(±)-162** were obtained in low yields, while Deoxofluor used together with $TiCl_4$ yielded no identifiable products. In the case of epoxycyclohexanes, pseudoequatorial substituents and nucleophilic ring opening directly to chair conformation are preferred explaining the formation of fluorohydrin **(±)-162**. The reaction of oxirane **(±)-147b** with XtalFluor-E gave cyclized **(±)-163** (*Scheme 35*).

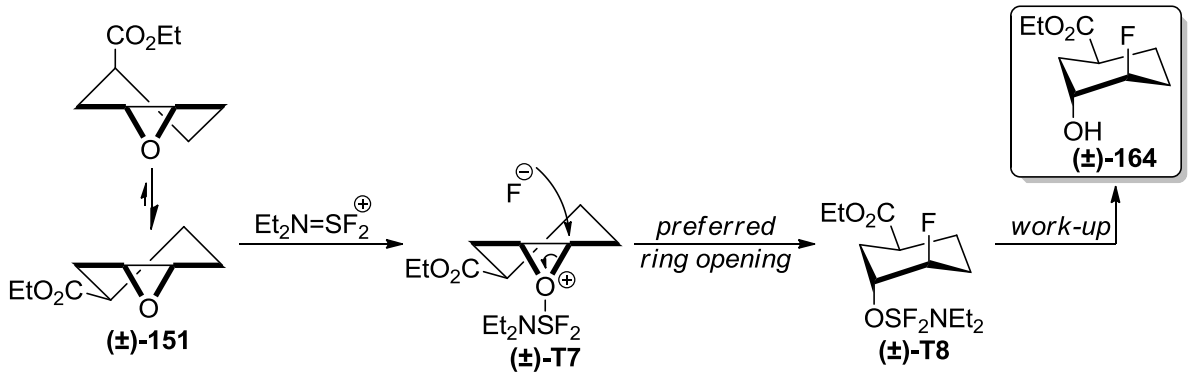


Scheme 35. Reactions of epoxide **(±)-147b** with nucleophilic fluorinating reagents and the reason of selective formation of fluorohydrin **(±)-162**

We continued our work on monofunctionalized epoxides. The reaction of *trans*-epoxycyclohexanecarboxylate **(±)-151** with Deoxofluor did not give any identifiable products. Applying a slightly modified version of the protocol used for *N*-tosylaziridines, ring opening brought about quick decomposition, but fluorohydrin **(±)-164** was isolated in 22% yield from the complex reaction mixture. When we tried to improve the yield by addition of $Et_3N{\cdot}3HF$, complete consumption of the starting material required much longer time, but TLC showed clearer reaction and the yield was much higher. Because $Et_3N{\cdot}3HF$ can induce oxirane ring opening too,[86] the previous experiment was repeated without XtalFluor-E giving product **(±)-164** in 18% yield along with 72% unreacted starting material (*Scheme 36*). This suggested that the presence of XtalFluor-E greatly accelerates oxirane ring opening with $Et_3N{\cdot}3HF$ probably through electrophilic activation of the substrate (*Scheme 37*). Doubling the amount of XtalFluor-E indeed resulted in yield enhancement and shortened reaction time (*Scheme 36*).

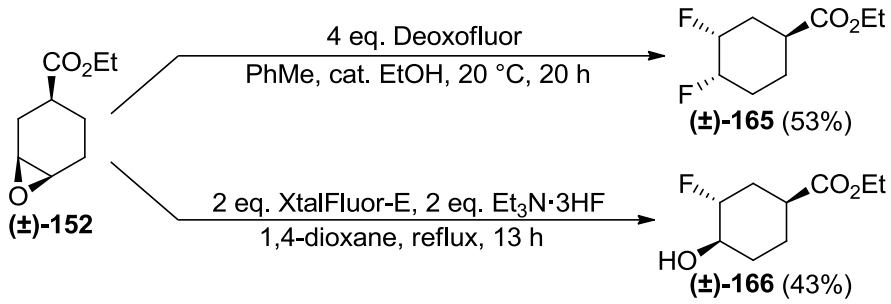


Scheme 36. Selective ring opening of epoxide **(±)-151** with nucleophilic fluorinating reagents

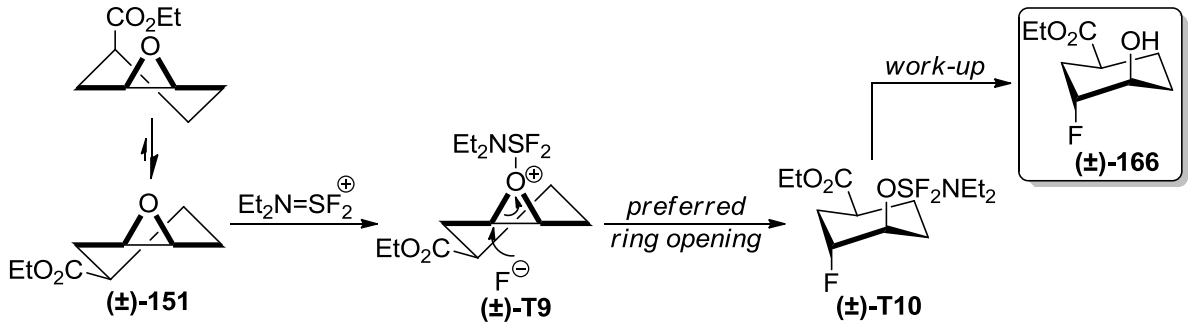


Scheme 37. Possible role of XtalFluor-E in the ring opening of **(±)-151**

In contrast with its *trans* isomer, reaction of *cis*-epoxycyclohexanecarboxylate **(±)-152** with Deoxofluor yielded difluorinated derivative **(±)-165**. However, with XtalFluor-E and $Et_3N{\cdot}3HF$, oxirane **(±)-152** reacted similarly to its *trans* isomer (*Scheme 38 and 39*).

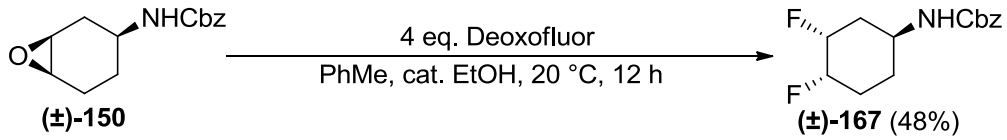


Scheme 38. Ring opening of epoxide **(±)-152** with nucleophilic fluorinating reagents



Scheme 39. Mechanism of stereo- and regio-selective formation of fluorohydrin **(±)-166**

Reaction of protected epoxyaminocyclohexane **(±)-150** with Deoxofluor resulted in difluorinated derivative **(±)-167**, similarly to the case of **(±)-152**. Reaction with XtalFluor-E, however, did not afford any identifiable product (*Scheme 40*).



Scheme 40. Ring opening of epoxide **(±)-150** with Deoxofluor

3.2. Chemoselective substrate-directed fluorinations of functionalized diol derivatives

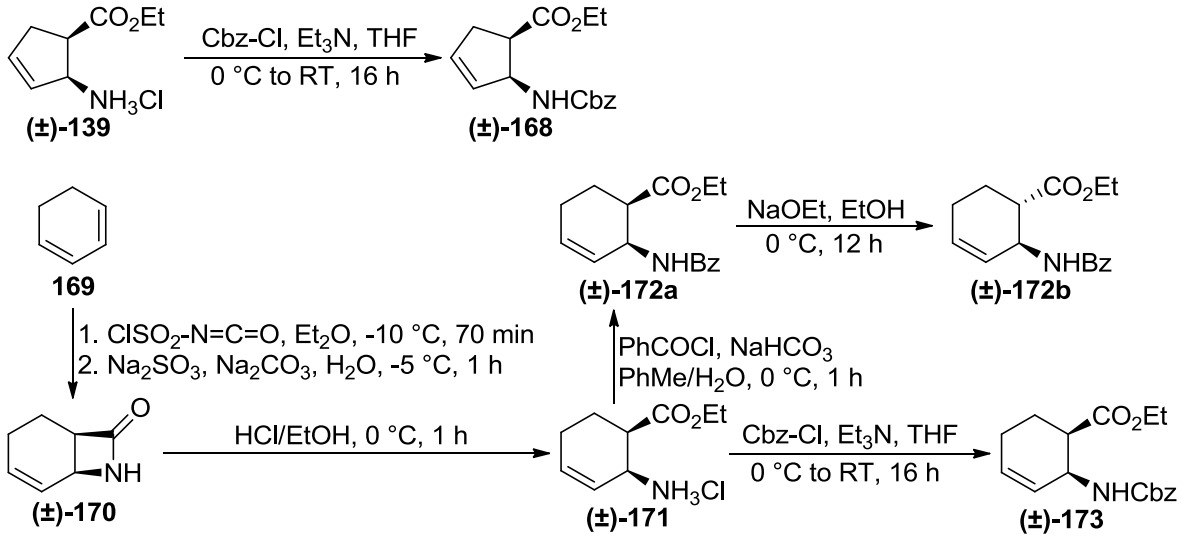
Hydroxy–fluorine exchange is a commonly used and seemingly simple approach for nucleophilic fluorination. However, in the case of highly-functionalized frameworks, stereo- and regio-selectivity issues together with substrate influence can be quite challenging.[33,102,103] In the case of functionalized cyclic vicinal *syn*-diols, which are easily available from functionalized cycloalkenes by *syn*-dihydroxylation, the presence of two OH groups together with the possibility of neighboring group participation could result in a wide variety of reactions

including ring-closing to a heterocycle, fluorination and dehydration. Depending on the conditions, for example, changing the amount of fluorinating reagent and the stereochemistry of the substrate, different combinations of these reactions can occur, further increasing diversity.

With these in mind, our aim was to study the reactions of functionalized cyclic vicinal *syn*-diols with Deoxofluor focusing on the chemodiscrimination between the hydroxy groups and substrate dependence. Assuming that our experiments will lead to new fluorine-containing β-amino acid derivatives, mostly dihydroxylated β-amino acid derivatives were selected as substrates. One equivalent of Deoxofluor was used to probe reactivity differences between OH groups, while four equivalents were used to facilitate transformation of all reactive moieties.

3.2.1. Synthesis of diols

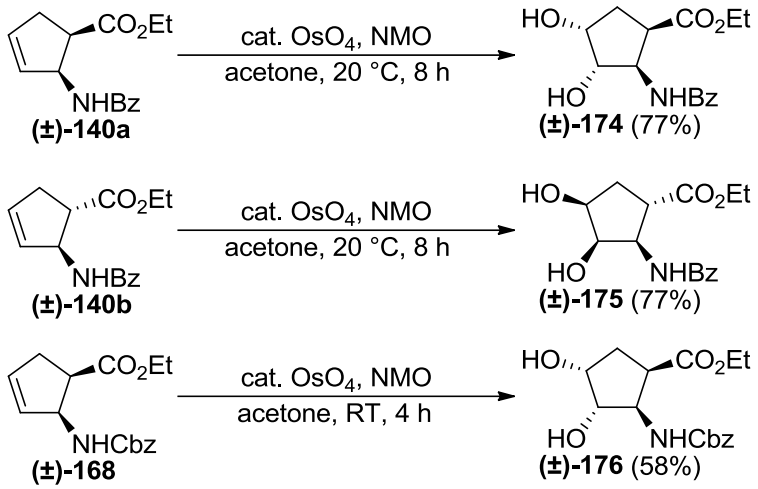
Our work was started with the synthesis of unsaturated β-amino esters followed by their dihydroxylation. Compounds **(±)-140a,b** and **(±)-146a,b** were synthesized according to *Scheme 24* and *Scheme 26*, respectively. The synthesis of **(±)-168**, a relative of **(±)-140a** with *N*-Cbz instead of *N*-Bz protection, was achieved by the reaction of amino ester hydrochloride **(±)-139** with Cbz-Cl.[96] β-Amino esters **(±)-172a,b**[99,104] and **(±)-173**[105] were obtained from cyclohexa-1,3-diene similar to the synthesis of **(±)-140a,b** and **(±)-168** (*Scheme 41).*



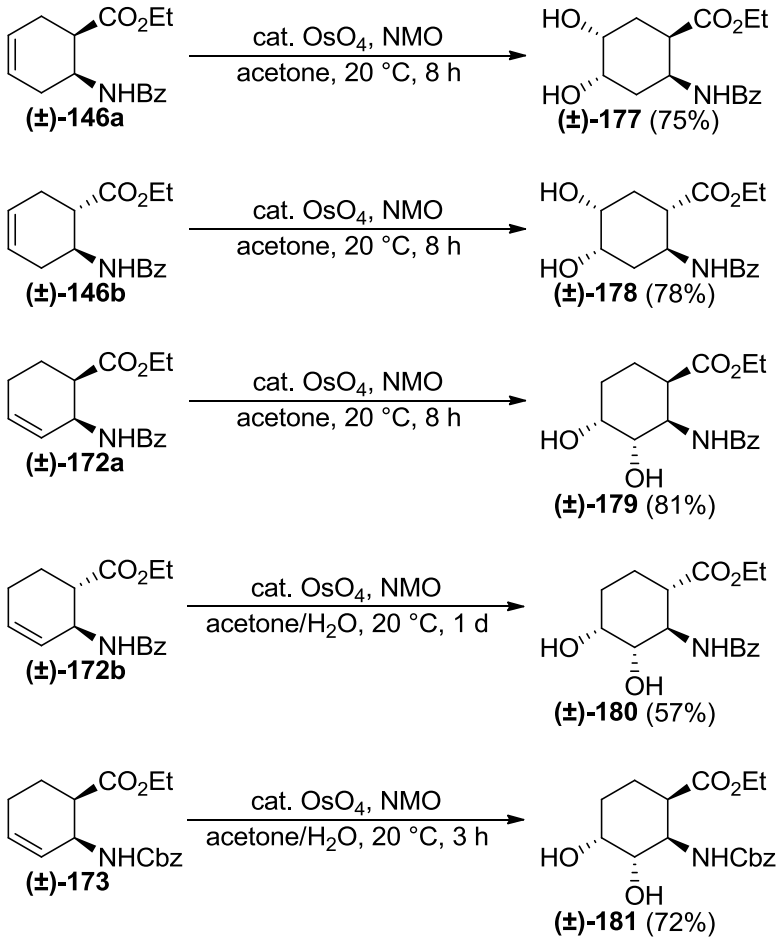
Scheme 41. Synthesis of unsaturated β-amino esters **(±)-168**, **(±)-172a,b** and **(±)-173**

syn-Dihydroxylation of the obtained β-amino esters was performed with catalytic amount of OsO_4 in the presence of excess co-oxidant *N*-methylmorpholine-*N*-oxide (NMO). The

reactions proceeded smoothly and resulted in only a single product in each case (*Scheme 42 and 43*).[94,99,105-107] This stereoselectivity is mainly caused by steric hindrance.

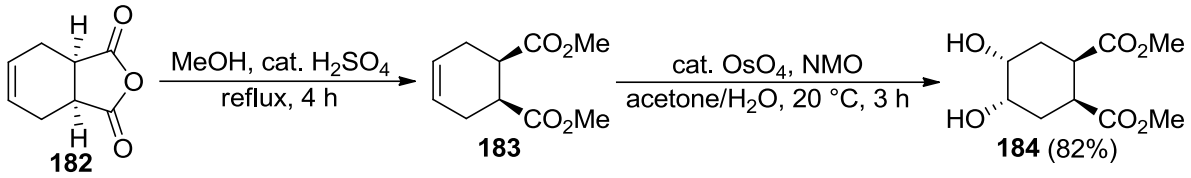


Scheme 42. Synthesis of dihydroxylated cyclopentane β-amino acid derivatives



Scheme 43. Synthesis of dihydroxylated cyclohexane β-amino acid derivatives

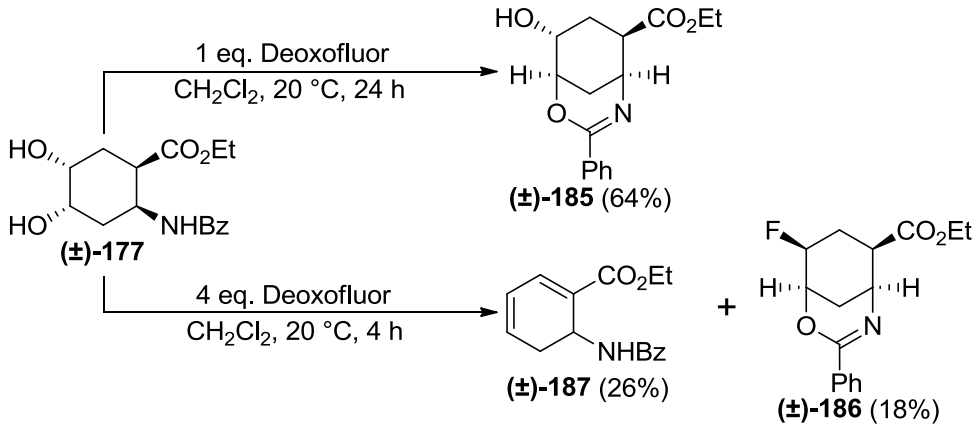
To widen the substrate scope and avoid interference of the protected amino group, dimethyl *cis*-cyclohex-4-ene-1,2-dicarboxylate **183** (obtained by refluxing *cis*-tetrahydrophthalic anhydride in MeOH in the presence of H_2SO_4) was dihydroxylated with the OsO_4/NMO system, resulting in the stereoselective formation of compound **184** (*Scheme 44*).[101]



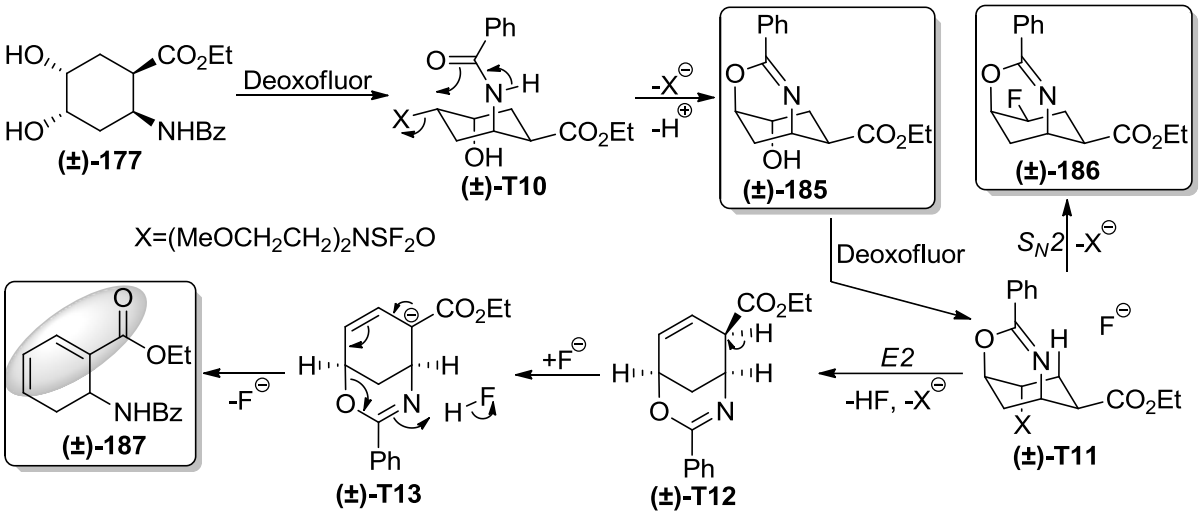
Scheme 44. Synthesis of dihydroxylated diester **184**

3.2.2. Fluorination reactions

We started our studies with diol **(±)-177** by transforming it with equimolar amount of Deoxofluor to cyclized product **(±)-185**. This suggests that only the OH group at C-4 was transformed into a good leaving group, and it was displaced by intramolecular nucleophilic attack of the amide oxygen instead of fluoride. The use of 4 equivalents of reagent resulted in two products: fluorinated oxazine **(±)-186** and unsaturated β-amino ester **(±)-187** (*Scheme 45*). Possibly, after formation of **(±)-185**, the unreacted OH group is transformed into a good leaving group by the excess reagent resulting in **(±)-T11**. Because fluoride ions are not only nucleophilic, but have basic character as well, S_N2 and E2 competes with each other resulting in the formation of compounds **(±)-186** and **(±)-T12**, respectively. Then, E1cb elimination from **(±)-T12** gives highly conjugated product **(±)-187** (*Scheme 46*). Strangely, epimeric diol **(±)-178** did not react with Deoxofluor under similar conditions.

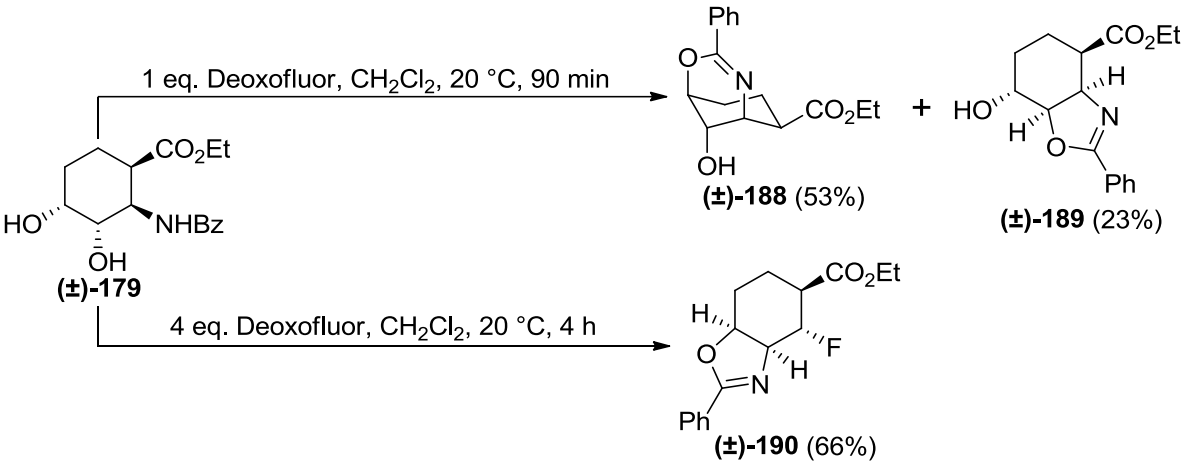


Scheme 45. Fluorination of 4,5-dihydroxy-2-aminocyclohexanecarboxylate **(±)-177**

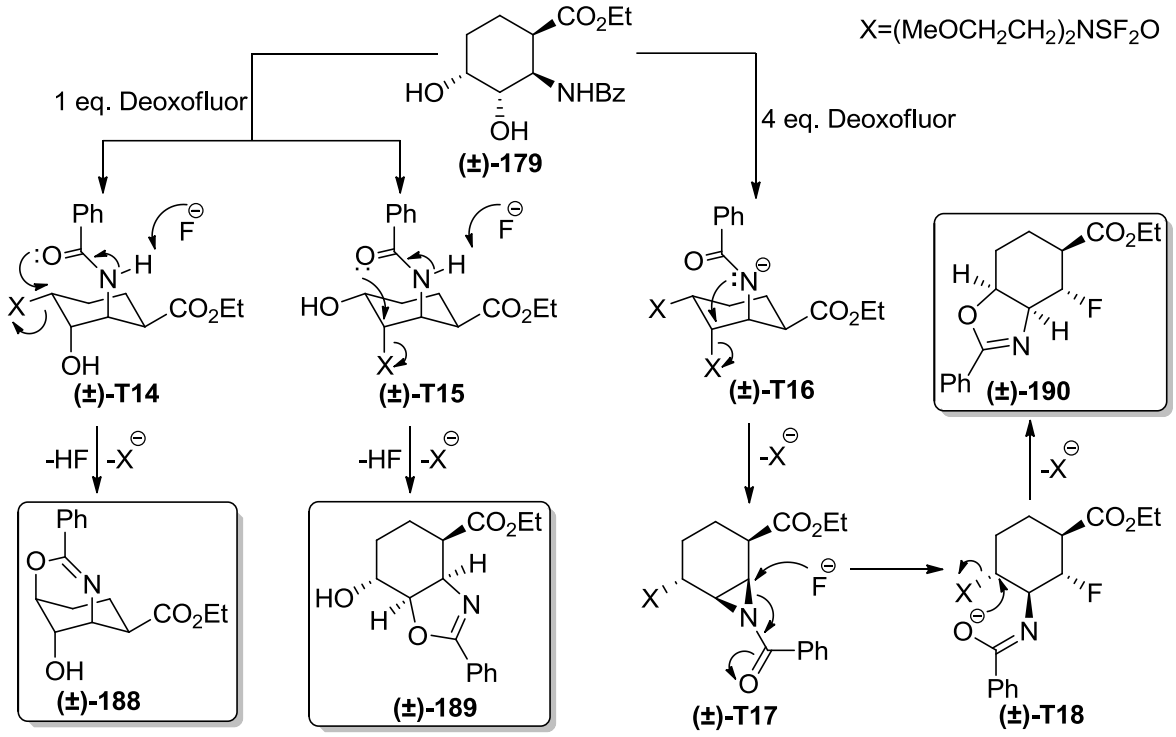


Scheme 46. Formation mechanisms of the products shown on *Scheme 45*. The conjugated system in product **(±)-187** is highlighted.

Fluorination of 3,4-dihydroxy-2-aminocyclohexanecarboxylic acid derivative **(±)-179** was inspected next. With 1 eq. reagent, two cyclized products were formed: **(±)-188** with a six-membered heterocycle and **(±)-189** with a five-membered one indicating that the two OH groups have similar reactivity. To our surprise, reaction with excess Deoxofluor resulted in fluorinated amino acid derivative **(±)-190** with the nitrogen atom in γ position to CO_2Et (*Scheme 47*). This reaction starts with the transformation of both OH groups into a good leaving group and deprotonation of the amide group by the basic F^- ions. Then, aziridine **(±)-T17** is formed by nucleophilic attack of the anionic nitrogen to the neighboring leaving group. Ring opening of **(±)-T17** with fluoride followed by closure of a heterocycle gives product **(±)-190** (*Scheme 48*).

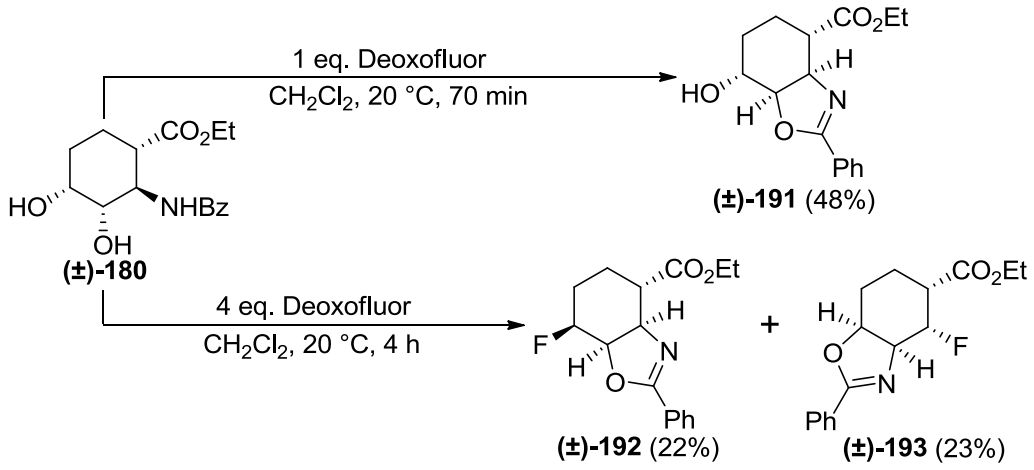


Scheme 47. Reaction of dihydroxylated β-amino acid derivative **(±)-179** with Deoxofluor



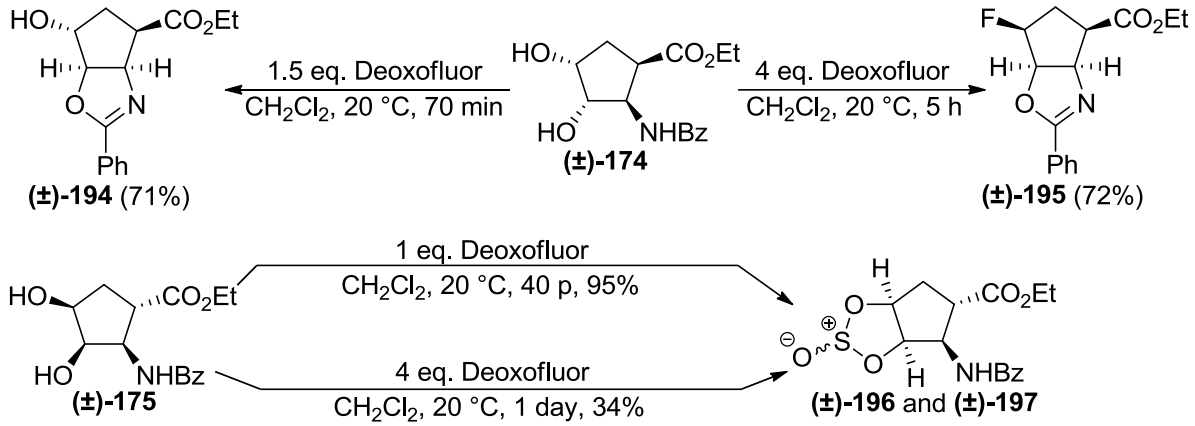
Scheme 48. Mechanisms of transformations shown on *Scheme 47*

Interestingly, when C-1 epimeric diol **(±)-180** was subjected to 1 eq. Deoxofluor, **(±)-191** the only single cyclized product was obtained, epimer of **(±)-189** (*Scheme 48)*. This indicates that the OH group at C-3 is more reactive. However, the use of 4 eq. reagent resulted in two fluorine-containing heterocyclic products (*Scheme 49*). β-Amino acid derivative **(±)-192** was formed by deoxyfluorination of **(±)-191**, while γ-amino acid derivative **(±)-193** was formed by rearrangement through an aziridine similarly to **(±)-190** (*Scheme 48)*.



Scheme 49. Reactions of diol **(±)-180** with Deoxofluor

We continued our studies on diol **(±)-174**. With limited amount of Deoxofluor, cyclized product **(±)-194** was formed (see formation of **(±)-189** on *Scheme 48*). This suggests that the C-3 OH group is more reactive. The use of excess reagent resulted in fluorinated oxazoline **(±)-195**. In contrast, reaction of stereoisomeric diol **(±)-175** with either 1 or 4 equivalents of Deoxofluor resulted in a diastereomeric mixture of cyclic sulfites (*Scheme 50*).

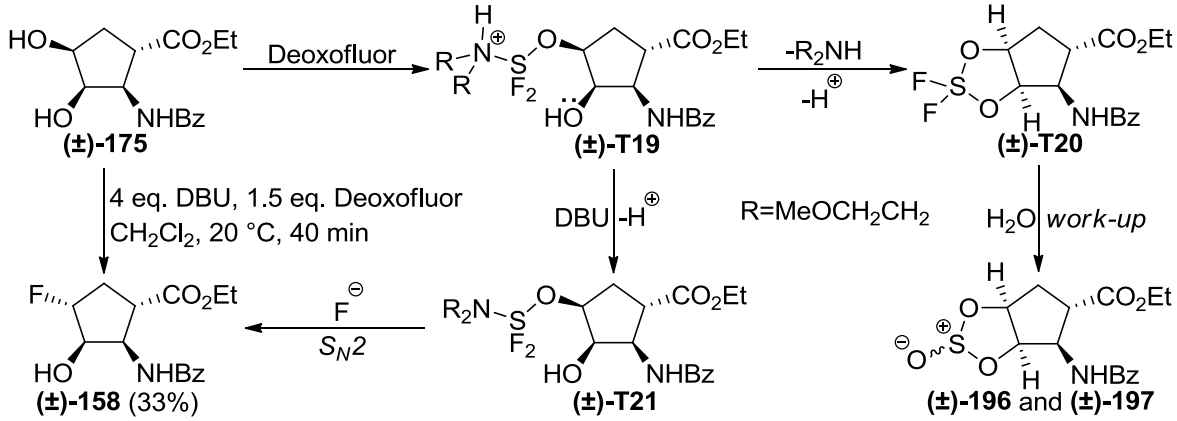


Scheme 50. Fluorinations of stereoisomeric diols **(±)-174** and **(±)-175**

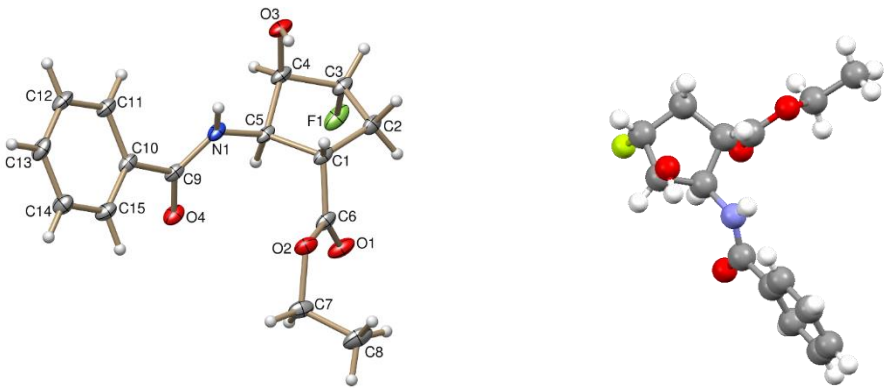
To investigate the effect of the *N*-protecting group, Cbz-containing derivatives **(±)-176** and **(±)-181** were subjected to Deoxofluor. Unfortunately, our attempts only provided unidentifiable mixtures of products. Treatment of diester **184** with Deoxofluor gave similar results.

Sulfite formation was a serious problem during the development of XtalFluor reagents, because they transform the OH group into cation $OSF_2NR_2H^+$ instead of OSF_2NR_2 and their BF_4^- counteranion is not effective as fluoride donor. Without F^- ions, the OH of another substrate molecule can act as the nucleophile. Then it displaces either the whole $OSF_2NR_2H^+$ group or its NR_2H moiety resulting in ether and sulfite by-products. As a result, deoxyfluorinations of alcohols with XtalFluor reagents require an additive to work as required. Usually, external fluoride ions, such as $Et_3N{\cdot}3HF$, are introduced to compete with the nucleophilic attack of the substrate. In addition, DBU works as well, because deprotonation of the nitrogen atom transforms acceptable leaving group NR_2H into bad leaving group NR_2^- and enables liberation of F^- ions from the intermediate (see *Scheme 6*).[64] Taking these into account, deoxyfluorination of diol **(±)-175** was attempted in the presence of DBU. To our delight, cyclic

sulfite formation was suppressed and fluorohydrin **(±)-158** was obtained in 33% yield (*Scheme 51*). Its structure was proven by single-crystal X-ray diffraction (*Scheme 52*).

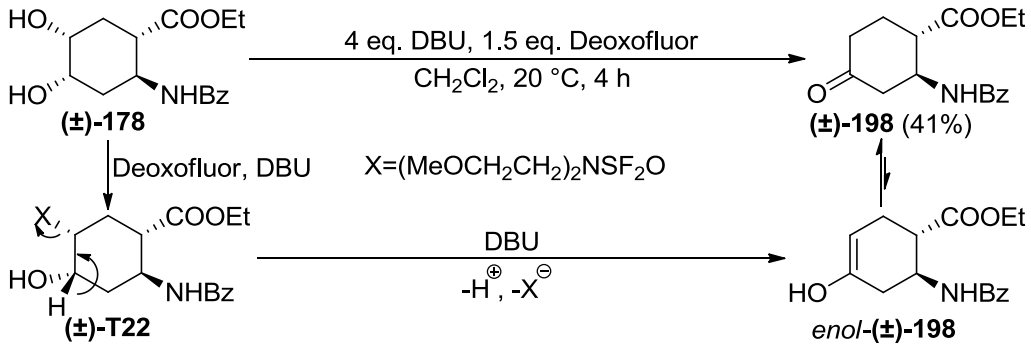


Scheme 51. Reactions of diol **(±)-174** with Deoxofluor in the absence or presence of DBU

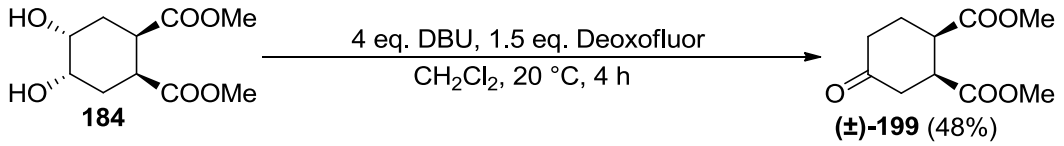


Scheme 52. Two different views of X-ray structure of molecule **(±)-158**

The new conditions were first applied to diols **(±)-178** and **184**, which underwent dehydration to oxo compounds **(±)-198** and **(±)-199** (*Scheme 53 and 54*).

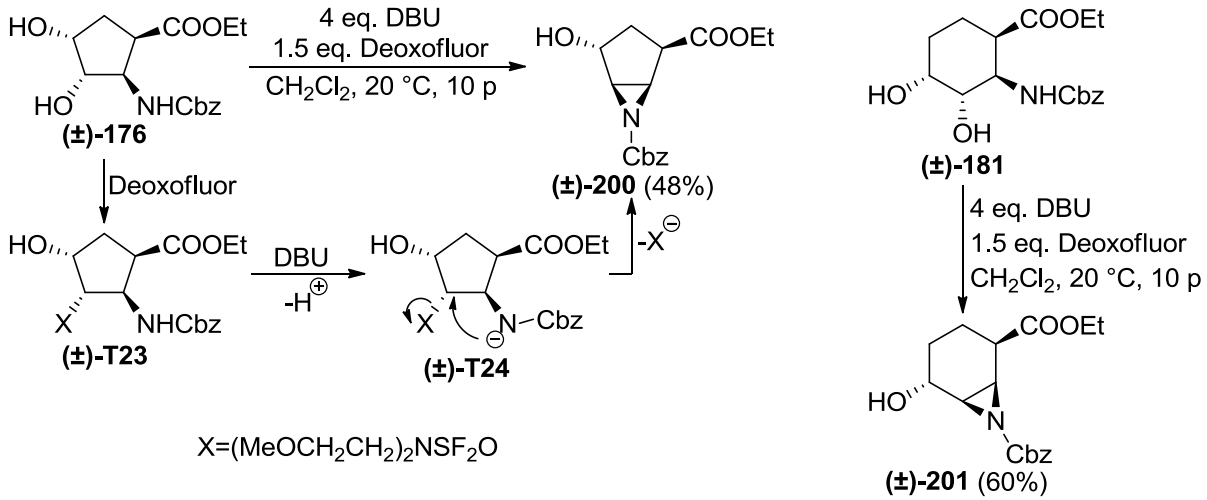


Scheme 53. Reaction of diol **(±)-178** with Deoxofluor in the presence of DBU



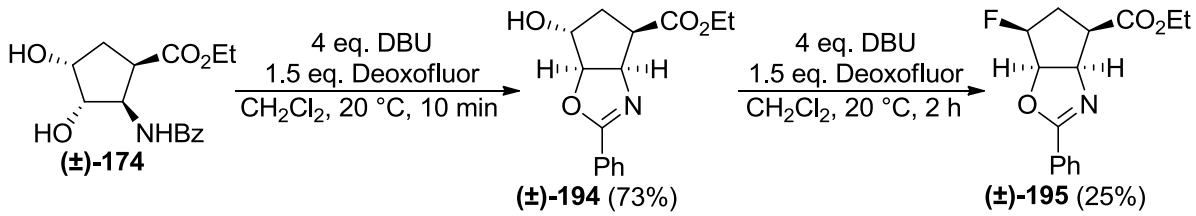
Scheme 54. Reaction of diol **184** with Deoxofluor in the presence of DBU

Treatment of *N*-Cbz-protected β-amino esters **(±)-176** and **(±)-181** with Deoxofluor and DBU resulted in aziridines **(±)-200** and **(±)-201** (*Scheme 55*), similarly to the formation of amino acid derivatives **(±)-190** (*Scheme 48*) and **(±)-193** (*Scheme 49*).



Scheme 55. Reactions of diols **(±)-176** and **(±)-181** with Deoxofluor and DBU

Performing the reaction of 3,4-dihydroxy-β-amino ester **(±)-174** with Deoxofluor in the presence of DBU produced oxazoline **(±)-194** in a somewhat higher yield than without DBU with the reaction time shortened considerably. Fluorination of isolated **(±)-194** in the presence of DBU produced fluorinated derivative **(±)-195** in 25% yield (*Scheme 56*).



Scheme 56. Reaction of β-amino ester **(±)-174** with Deoxofluor in the presence of DBU

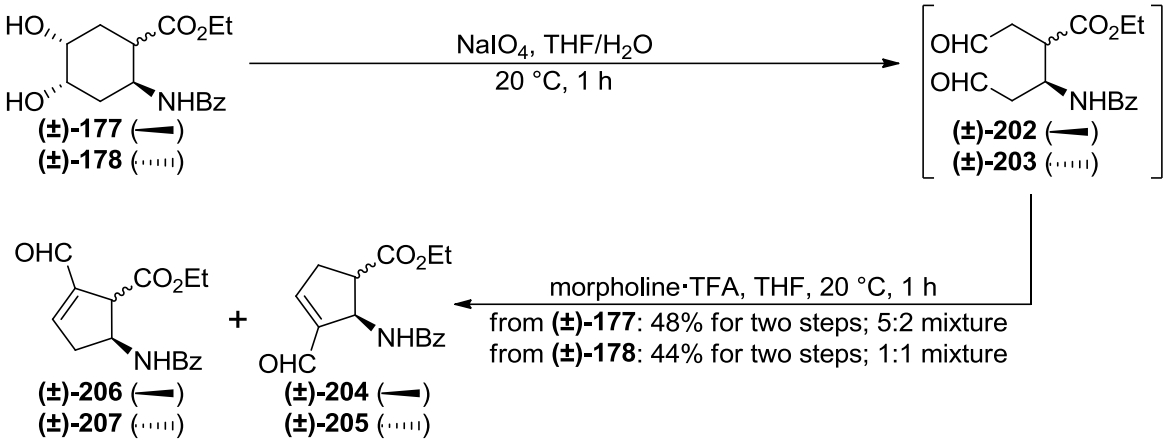
3.3. Transformation of functionalized diol derivatives through ring opening/ring contraction and substrate-dependent fluorinations

Dihydroxylated compounds are versatile starting materials. After their direct fluorinations accomplished, we became interested in developing other synthetic pathways towards fluorine-containing molecules, e.g. β-amino esters, functionalized cycloalkenes, from these diols. Oxidative ring opening to dialdehydes, in particular, caught our attention. Previous research demonstrated that although acyclic dialdehydes are unstable and cannot be isolated, but they can be reacted in Wittig reaction [99,106] and their reductive amination effectively yields *N*-heterocyclic compounds.[108,109] Extension of the reductive amination method to fluorinated amines enabled the synthesis of fluorine-containing β-amino acid derivatives and related compounds.[101,105]

In contrast with reductive amination, which results in *ring expansion*, intramolecular aldol condensation of acyclic dialdehydes would result in cyclic α,β-unsaturated aldehydes through *ring contraction*. Deoxyfluorination of a formyl group normally yields a difluoromethyl moiety. In contrast, previous experiences with cyclic dialdehydes (see *Scheme 20*) showed that neighboring group participation can lead to quite different outcomes. (Cyclic dialdehydes were obtained by oxidative ring opening of bicyclic diols, and showed increased stability compared to their acyclic counterparts, enabling their isolation.)[32] As a result, we decided to synthesize α,β-unsaturated aldehydes from dihydroxylated β-amino acid derivatives and investigate the substrate dependence of their fluorination. Because transformation of cyclopentanediols in this manner would require closure of a strained four-membered ring and compounds with seven-membered ring are expensive, only cyclohexanediols were chosen as starting materials.

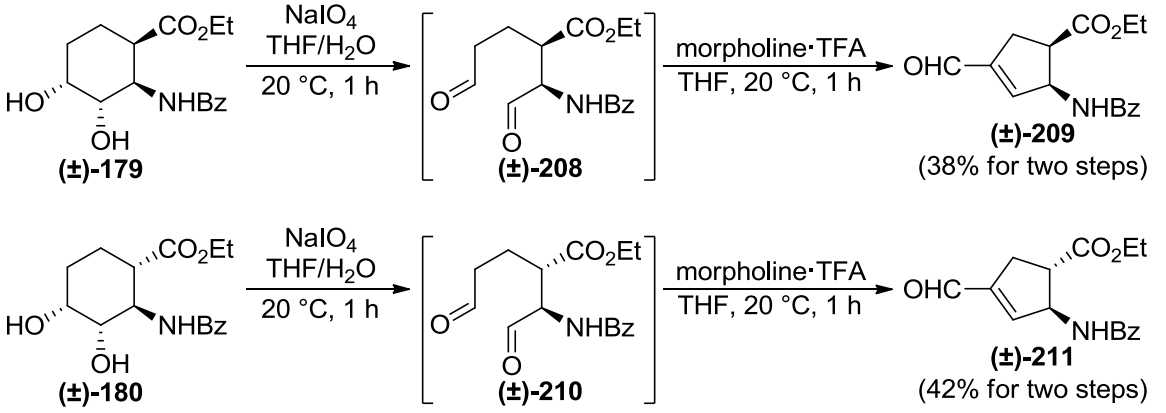
3.3.1. Synthesis of formyl-substituted cyclic β-amino esters

Our first substrates were 4,5-dihydroxy-β-amino esters **(±)-177** and **(±)-178** synthesized according to *Scheme 43*. Oxidative ring opening was achieved with periodate, and the aldol reaction was facilitated by mildly acidic morpholinium trifluoroacetate. In the case of both compounds, the result was the formation of both possible unsaturated aldehydes. Unfortunately, separation of these aldehyde mixtures failed (*Scheme 57*).

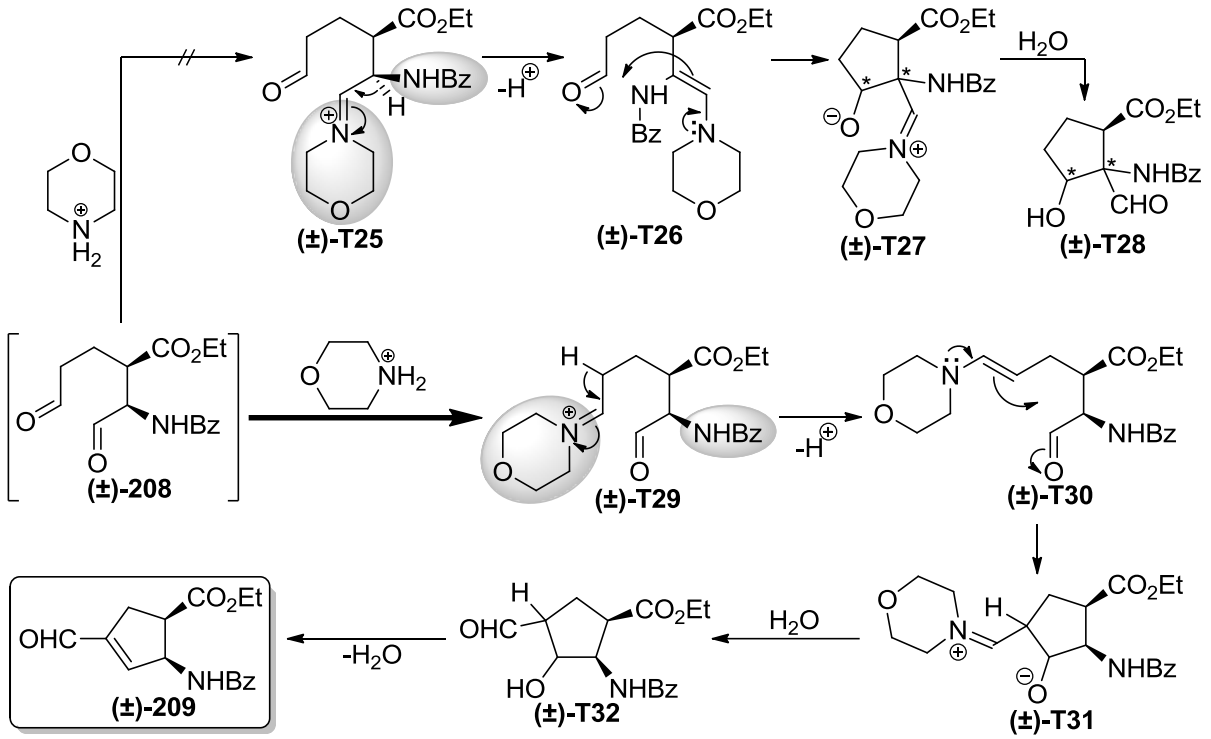


Scheme 57. Ring opening/ring contraction of diols **(±)-177** and **(±)-178**

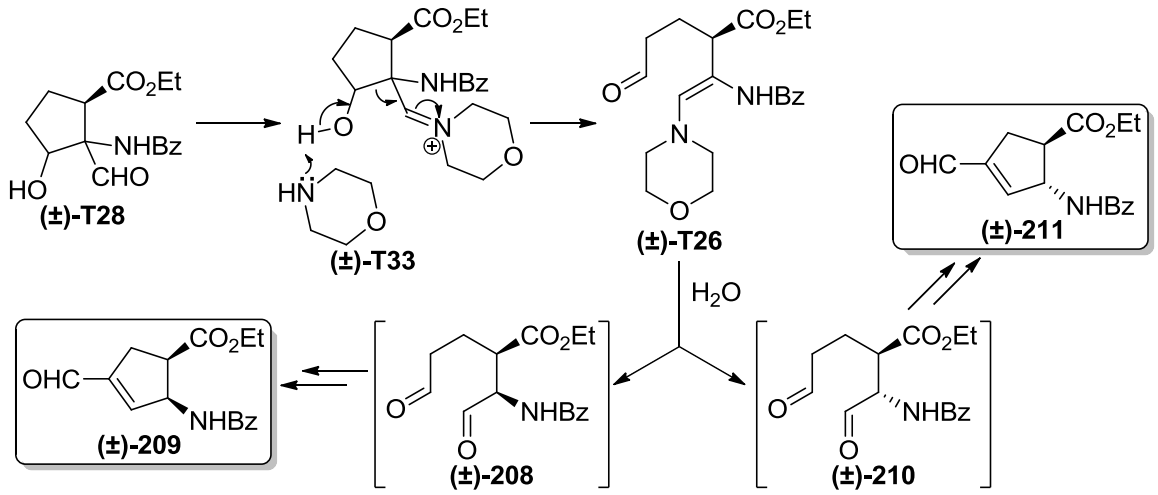
The transformation of 3,4-dihydroxy-β-amino esters **(±)-179** and **(±)-180** (also synthesized according to *Scheme 43*) was different forming an unsaturated aldehyde as a single product (*Scheme 58*). As shown in details for the formation of **(±)-209**, the large morpholinium cation can be assumed to react preferably with the sterically less hindered formyl group resulting in enamine **(±)-T30** through an iminium ion. **(±)-T30** then undergoes cyclization and the hydrolysis of the iminium ion moiety followed by dehydration via E1cb mechanism affords conjugated product **(±)-209** (*Scheme 59*). Cyclization of the other possible enamine **(±)-T26** would result in stereoisomers of compound **(±)-T28**, which cannot be dehydrated via E1cb mechanism. Retro-aldol reaction of **(±)-T28** stereoisomers would produce both **(±)-209** and **(±)-211** (*Scheme 60*). Because compounds **(±)-209** or **(±)-T28** were not detected in the reaction mixture, formation of enamine **(±)-T26** can be excluded.



Scheme 58. Ring opening/ring contraction of diols **(±)-179** and **(±)-180**



Scheme 59. Interpretation of selective formation of unsaturated aldehyde **(±)-209**

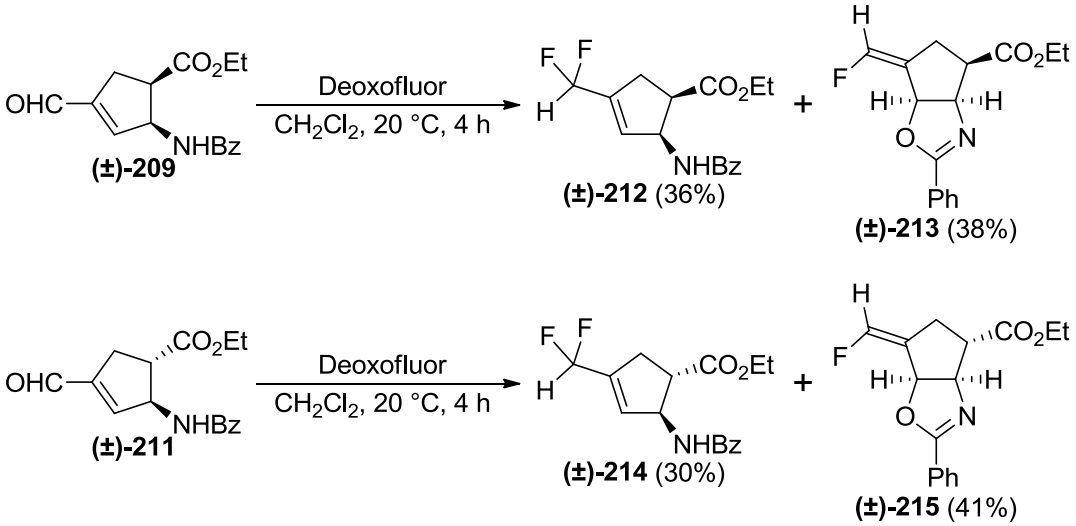


Scheme 60. Hypothetical retro-aldol reaction of compound **(±)-T28** showing the formation of a mixture of **(±)-209** and **(±)-211**

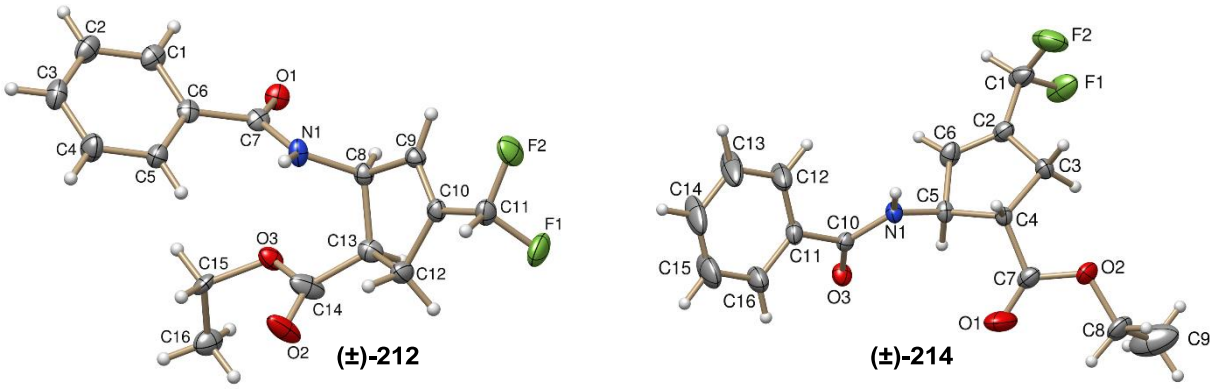
3.3.2. Fluorination reactions

In the reaction of aldehyde **(±)-209** with DAST or Deoxofluor, two products were formed: the expected CHF_2-containing β-amino acid derivative **(±)-212** and fluorovinyl-containing compound **(±)-213**. Interestingly, the reaction conditions (temperature, type or amount of the

nucleophilic fluorinating agent) did not affect significantly the yields or the ratio of the products. Fluorination of aldehyde **(±)-211** produced similar results (*Scheme 61*). Structures of difluoromethyl-substituted derivatives **(±)-212** and **(±)-214** were confirmed by single-crystal X-ray diffraction (*Scheme 62*), while stereochemistry of **(±)-213** and **(±)-215** was determined on the basis of 2D NMR data. It is worth to note that the fluorovinyl group can effectively mimic the amide group,[110] and many bioactive molecules (for example, HIV protease inhibitors) contain this moiety.[111,112]



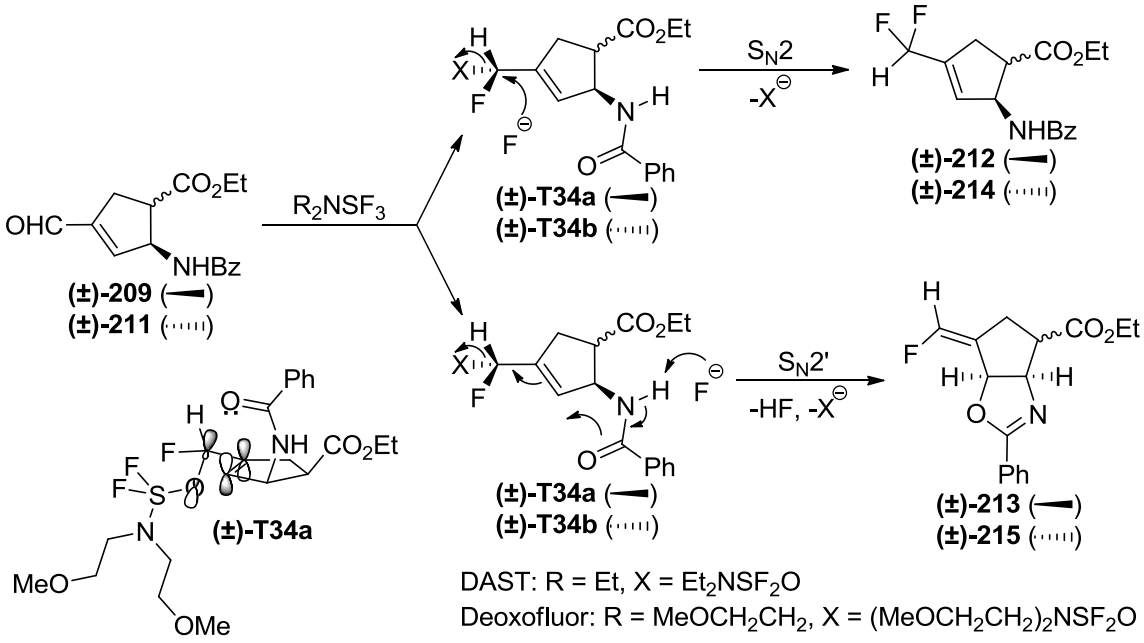
Scheme 61. Fluorinations of aldehydes **(±)-209** and **(±)-211**



Scheme 62. X-ray structure of CHF_2-substituted derivatives **(±)-212** and **(±)-214**

The outcomes of these reactions are originating from the structure of their intermediate: the good leaving group in intermediates **(±)-T34a,b** is in allylic position. As a result, it can be displaced by either via an S_N2 mechanism resulting in products **(±)-212** and **(±)-214** or by S_N2' mechanism involving the attack on the other end of the allylic system. Because the amide oxygen

is in perfect position for the latter, its attack completely suppresses S_N2' by fluoride and results in products **(±)-213** and **(±)-215**. Because the S_N2' reaction requires the *p* orbitals of the C=C bond to be parallel with the carbon leaving group bond, and the large leaving group should point away from other substituents (*Scheme 63*), the observed stereochemistry can be partially explained.

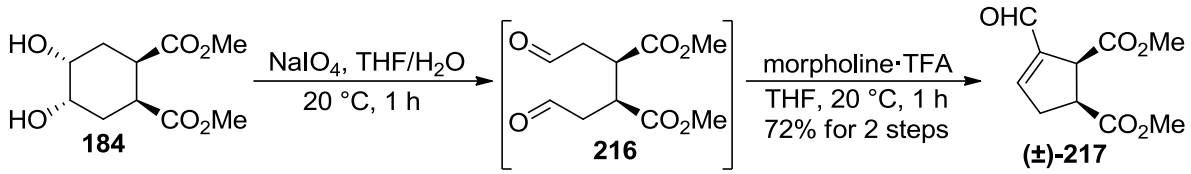


Scheme 63. Fluorination mechanisms of aldehydes **(±)-209** and **(±)-211** together with S_N2' reactive conformation of intermediate **(±)-T34a**

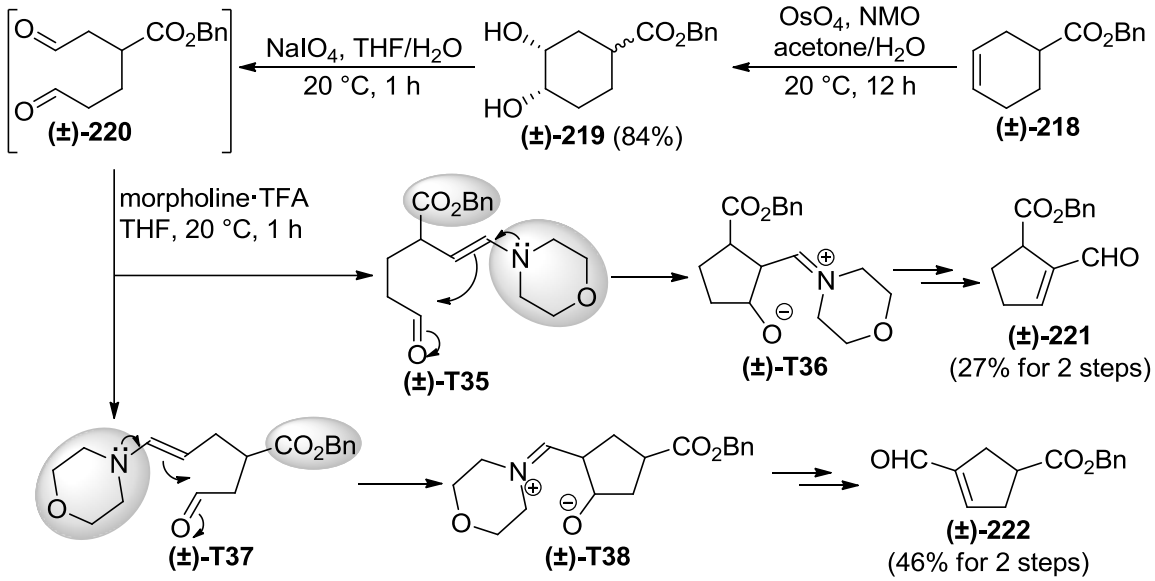
3.3.3. Extension of the method

After finishing fluorinations of α,β-unsaturated aldehydes derived from β-amino acid derivatives, we aimed to extend this strategy to other functionalized cyclohexanediols with special emphasis on the fluorination conditions. Because of its symmetric structure, diol **184** (synthesized according to *Scheme 44*[101]) provided a single unsaturated aldehyde (*Scheme 64*). In contrast, transformation of diastereomeric mixture **(±)-219** obtained by dihydroxylation of ester **(±)-218** resulted in two hardly separable aldehydes in 1.7:1 ratio. The main product was formed from intermediate **(±)-T37** where the large benzyl ester and enamine moieties are further from each other (*Scheme 65*). Dihydroxylation of *N*-Cbz-protected cyclohex-3-eneamine **(±)-149** gave diastereomeric diol mixture **(±)-223**[101] which, upon treatment with $NaIO_4$ followed by morpholine·TFA, yielded another hardly separable aldehyde mixture, but with a 1:1 product ratio. Possibly, an intramolecular hydrogen bond compensates for the steric crowding in intermediate

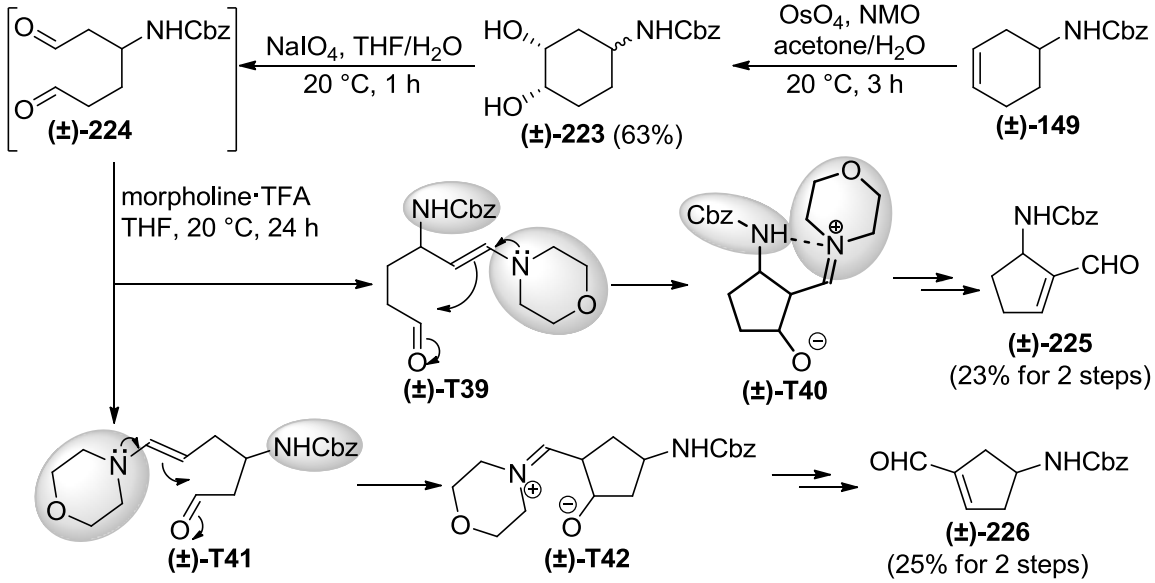
(±)-T40 (*Scheme 66*). To further extend our strategy, bicyclic aldehyde **(±)-229** was synthesized from *N*-benzyl-*cis*-tetrahydrophthalimide **227** by stereoselective dihydroxylation, oxidative ring opening and intramolecular aldol reaction (*Scheme 67*).



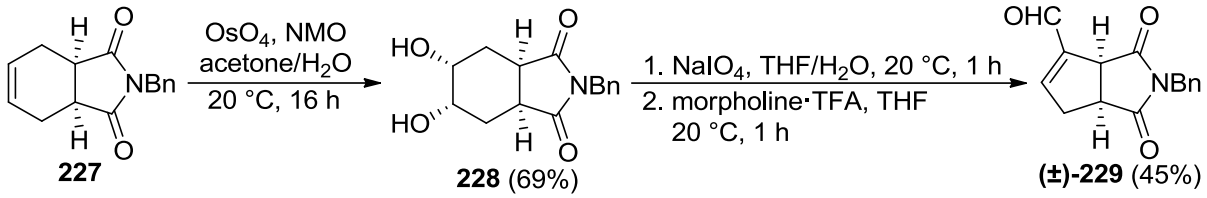
Scheme 64. Transformation of diol **184** into unsaturated aldehyde **(±)-217**



Scheme 65. Synthesis of unsaturated aldehydes **(±)-221** and **(±)-222** with a CO_2Bn function



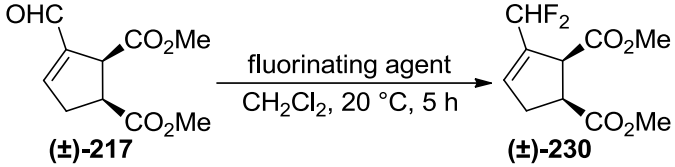
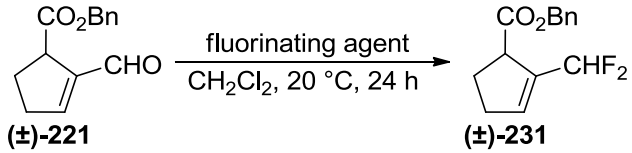
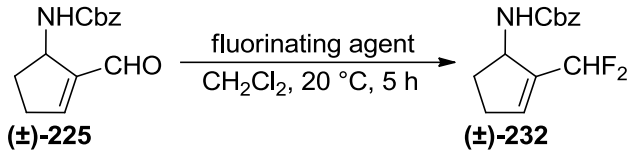
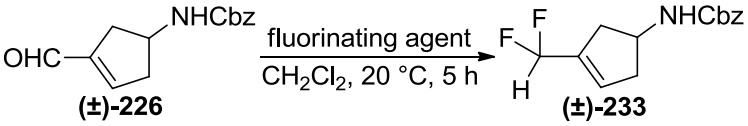
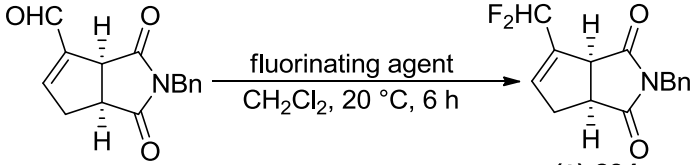
Scheme 66. Synthesis of unsaturated aldehydes **(±)-225** and **(±)-226** with an NHCbz function



Scheme 67. Synthesis of bicyclic unsaturated aldehyde **(±)-229**

Fluorinations of these aldehydes are summarized in *Table 1*. Every reaction was performed in CH_2Cl_2 at 20 °C. Four different conditions were used: 2.2 equivalents DAST, 4 equivalents DAST, 2.2 equivalents Deoxofluor, or 4 equivalents Deoxofluor.

Table 1. Reactions of unsaturated aldehydes with nucleophilic fluorinating reagents. Conditions resulting in the best yield for each reaction are highlighted.

Reaction	Fluorinating reagent		Yield
	Name	Amount	
	Deoxofluor	2.2 eq.	36%
	Deoxofluor	4 eq.	38%
	DAST	2.2 eq.	38%
	DAST	4 eq.	46%
	Deoxofluor	2.2 eq.	23%
	Deoxofluor	4 eq.	29%
	DAST	2.2 eq.	21%
	DAST	4 eq.	40%
	Deoxofluor	2.2 eq.	31%
	Deoxofluor	4 eq.	30%
	DAST	2.2 eq.	41%
	DAST	4 eq.	46%
	Deoxofluor	2.2 eq.	20%
	Deoxofluor	2.2 eq.	58%
	Deoxofluor	4 eq.	59%
	DAST	2.2 eq.	60%
	DAST	4 eq.	61%

Treatment of aldehyde **(±)-217** with DAST or Deoxofluor resulted in the expected difluoromethyl-containing **(±)-230** as the sole product. Increasing the amount of reagent from 2.2 to 4 equivalents and use of DAST instead of Deoxofluor improved the yield.

In the case of CO_2Bn-containing aldehydes, fluorination of minor isomer **(±)-221** yielded the expected CHF_2-containing **(±)-231** as a single product. Again, 4 equivalents of DAST gave the best yield under the studied conditions. Unfortunately, fluorination of major isomer **(±)-222** resulted in decomposition under every experimental conditions tested.

Deoxyfluorinations of NHCbz-containing aldehydes afforded only the expected CHF_2-containing products. In contrast to reactions of **(±)-209** and **(±)-211** (*Scheme 61*), cyclization was not observed. Fluorination of aldehyde **(±)-225** was studied thoroughly and similarly to the case of **(±)-217** and **(±)-221**, the highest yield was achieved with 4 equivalents of DAST. In the case of compound **(±)-226**, only one condition was tested.

Reactions of bicyclic compound **(±)-229** with nucleophilic fluorinating reagents occurred smoothly. Interestingly, changing the fluorinating agent or its quantity did not significantly affect the yield of the resulting difluoromethyl-containing product.

4. SUMMARY

- New methods were developed for the ring opening of oxiranes with fluoride utilizing nucleophilic fluorinating reagents XtalFluor-E and Deoxofluor as F^- sources (*Section 3.1*). [Remete *et al.*, *Molecules* **2016**, *21*, 1493]
- When only one fluorine atom was incorporated (*Scheme 28*, *Scheme 32*, *Scheme 35 and 36*, *Scheme 38*), the oxiranes clearly showed their usual ring opening regioselectivity, which can be rationalized easily in the case of epoxicyclohexanes (*Scheme 35*, *Scheme 37*, *Scheme 39*).
- In the case of β-amino ester epoxides, treatment with XtalFluor-E always lead to cyclization thanks to the participation of the neighboring protected amino group (*Scheme 30-32*, *Scheme 34 and 35*). Applying Deoxofluor gave fluorine-containing products in a highly substrate dependent manner (*Scheme 28 and 29*, *Scheme 32-35*).[Remete *et al.*, *Molecules* **2016**, *21*, 1493]
- In the case of monofunctionalized oxiranes, neighboring group participation was absent. By using XtalFluor-E and $Et_3N{\cdot}3HF$ together, effective fluoride ring opening was achieved for these substrates yielding fluorohydrins (*Scheme 36-39*) with the exception of NHCbz-substituted epoxicyclohexane **(±)-150**. Deoxofluor, however, transformed these substrates into vicinally difluorinated derivatives (*Scheme 38*, *Scheme 40*) except *trans*-epoxicyclohexanecarboxylate **(±)-151**.[Remete *et al.*, *Fluorine Notes*, Volume #4 (113), July - August **2017**]
- To synthesize new fluorinated β-amino acid derivatives, fluorinations of dihydroxylated β-amino esters were attempted. The reactions were highly substrate dependent and showed both chemodiscrimination of the two OH groups in multiple cases and neighboring group participation (*Section 3.2*).[Remete *et al.*, *Beilstein J. Org. Chem.* **2017**, *13*, 2364]
- The reaction of dihydroxylated β-amino esters **(±)-174** and **(±)-177** with equimolar Deoxofluor resulted only in cyclization. When excess reagent was used, these heterocyclic products were fluorinated further (*Scheme 45 and 46*, *Scheme 50*), accompanied by elimination when the starting material was β-amino ester **(±)-177**.[Remete *et al.*, *Beilstein J. Org. Chem.* **2017**, *13*, 2364]
- Treatment of 3,4-dihydroxy-2-aminocyclohexanecarboxylate **(±)-179** with 1 eq. Deoxofluor resulted in two cyclized products: an oxazoline and an oxazine. Surprisingly, the use of 4 eq. Deoxofluor produced a fluorine-containing γ-amino ester through an aziridine intermediate (*Scheme 47 and 48*). Reactions of epimeric diol **(±)-180** were slightly different: equimolar reagent provided a single oxazoline, while excess reagent produced both a fluorinated γ- and a fluorinated β-amino acid derivative (*Scheme 49*).[Remete *et al.*, *Beilstein J. Org. Chem.* **2017**, *13*, 2364]

- Unfortunately, fluorination of several diols failed. Within *N*-Bz-protected β-amino esters, **(±)-175** produced only cyclic sulfites with Deoxofluor, while **(±)-178** did not even react. *N*-Cbz-protected β-amino esters **(±)-176** and **(±)-181** produced unidentifiable mixtures of products with Deoxofluor, similarly to diester **184**.[Remete *et al., Beilstein J. Org. Chem.* **2017**, *13*, 2364]
- Addition of DBU suppresses cyclic sulfite formation during fluorination of dihydroxylated β-amino ester **(±)-175** enabling fluorohydrin formation (*Scheme 50 and 51*). This new condition was applied to the other diols listed in the previous point: diols **(±)-178** and **(±)-184** were dehydrated into ketoesters (*Scheme 53 and 54*), while *N*-Cbz-protected β-amino esters **(±)-176** and **(±)-181** were cyclized into aziridines (*Scheme 55*).[Remete *et al., Beilstein J. Org. Chem.* **2017**, *13*, 2364]
- From dihydroxylated β-amino esters, another synthetic pathway was developed towards fluorinated β-amino acid derivatives. It was based on oxidative ring opening of these functionalized vicinal cycloalkanediols into dialdehydes with $NaIO_4$ followed by cyclization through intramolecular aldol condensation and fluorination. This method was later extended to other functionalized vicinal cyclohexanediols (*Section 3.3*).[Remete *et al., Eur. J. Org. Chem.* **2018**, 3735]
- In the case of dialdehydes **(±)-202** and **(±)-203** obtained from 4,5-dihydroxy-β-amino esters, aldol condensation yielded inseparable aldehyde mixtures (*Scheme 57*). In contrast, the less symmetric structure of dialdehydes **(±)-208** and **(±)-210**, obtained from 3,4-dihydroxy-β-amino esters, enabled chemodifferentiation of their CHO groups resulting in α,β-unsaturated aldehydes **(±)-209** and **(±)-211** as the single products (*Scheme 58-60*). Fluorination of these aldehydes produced cyclized products and the desired CHF_2-containing products in similar amounts, because of neighboring group participation (*Scheme 61-63*).[Remete *et al., Eur. J. Org. Chem.* **2018**, 3735]
- Dihydroxycyclohexanedicarboxylate **184** and bicyclic diol **228** afforded only a single unsaturated aldehyde each attributed to their plane of symmetry (*Scheme 64, Scheme 67*). From asymmetric diol mixtures **(±)-219** and **(±)-223** hardly separable aldehyde mixtures were obtained (*Scheme 65 and 66*). Fluorination of these aldehydes (*Table 1*) produced the desired CHF_2-containing products in all cases with the exception of **(±)-222**. Of the investigated conditions, usually 4 eq. DAST gave the best yield.[Remete *et al., Eur. J. Org. Chem.* **2018**, 3735]
- Most cyclizations resulted in kinetically and thermodynamically favored five- or six-membered rings. However, in the cases of 3,4-hydroxy-2-amino esters, *N*-Cbz-protected **(±)-176** and **(±)-181** were cyclized into aziridines (*Scheme 55*), while reactions of *N*-Bz-protected **(±)-179** and **(±)-180** involved aziridine intermediates (*Scheme 48*).[Remete *et al., Beilstein J. Org. Chem.* **2017**, *13*, 2364]

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ANNEX