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An Insight into Substrate-Dependent Fluorination of some Highly Substituted Alicyclic Scaffolds

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The substrate-dependent fluorination of some highly-functionalized cyclopentane derivatives with multiple chiral centers has been investigated. The key steps of the stereocontrolled syntheses are the oxidative cleavage of the ring carbon–carbon double bond of readily available *diexo* or *diendo* norbornene β-amino acid derivatives followed by transformation of the resulted dialdehyde stereoisomers by reduction. Finally, substrate-directable chemodifferentiation of different types of hydroxy groups under fluorination procedures gave various densely functionalized alicyclic derivatives or heterocycles.

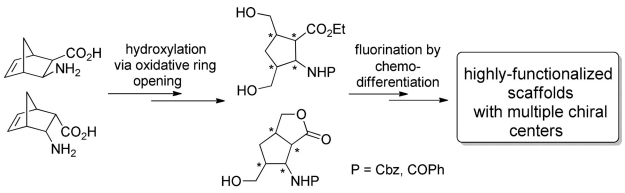
Introduction

As a result of the increasing biomedical relevance of fluorine-containing biomolecules including heterocycles, their syntheses and use as fluorinated building blocks, highly-functionalized alicyclic scaffolds and natural product analogues have received significant interest among medicinal and organic chemists in recent years. The introduction of one or more fluorine atoms into organic moieties may change dramatically their chemical, physical and biological properties. Accordingly, there is a growing interest in the development of selective, efficient routes to access novel fluorinated building blocks.[1]

Among the various fluorinated scaffolds, fluorinated amino acids are of high relevance in pharmaceutical chemistry. A number of fluorinated amino acids are known to be antibacterial, antifungal and antitumoural agents. Furthermore, they are valuable building elements in peptide-based drug research.[2] Noteworthy that cyclic β-amino acids (eg. cispentacin, icofungipen, tilidin, etc.) and their derivatives, less abundant than their α-analogues, have acquired high significance recently both in medicinal chemistry and peptide research.[3] Fluorinated representatives of this class of compounds, consequently, might play a significant role in pharmaceutical research. Relevant information for fluorinated cyclic β-amino acids are found in reference.[4]

Results and Discussion

The aim of the present research was to extend our earlier findings[5] on substrate dependent fluorinations, by investigating the transformation of various hydroxy functionalized cyclopentane β-amino acid derivatives into highly-substituted alicyclic or heterocyclic stereoisomers under fluorination conditions with the intention to explore the chemical behavior of these diversely substituted patterns. The synthetic routes towards various building blocks with multiple chiral stereocenters included stereocontrolled hydroxylation of the ring olefinic bond of the readily available *diexo* or *diendo* norbornene β-amino acids through oxidative ring cleavage and reduction, followed by fluorination of the hydroxylated scaffolds by chemodifferentiation (Scheme 1).



Scheme 1. Schematic route to chemoselective transformation of highly-functionalized cyclopentanes by fluorination.

In order to investigate the fluorination of polyfunctionalized alicyclic scaffolds, first racemic cyclopentane diformyl amino esters (±)-**2a**[6] and (±)-**2b**[5] were synthesized through olefin bond ring cleavage of bicyclic *diexo* amino acid (±)-**1.** These were then transformed into functionalized diol derivatives (±)-**3a** and (±)-**3b** by reducing the formyl group with $NaBH_4$. For the creation of fluoromethylene functions on the skeleton of the *N*-benzoyl- or *N*-Cbz-protected cyclopentane β-amino acid, *bis*-hydroxymethylenic amino esters (±)-**3a** and (±)-**3b** were submitted to monofluorination through hydroxy–fluorine exchange with Deoxofluor.

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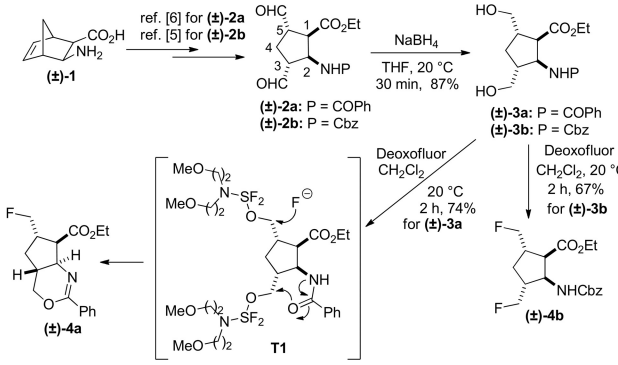
N-Benzoyl-protected amino ester (±)-**3 a** underwent fluorination upon reacting with various amounts of Deoxofluor in CH_2Cl_2 at varied temperatures (-15 °C, 0 °C or 20 °C). The highest yield (74%) was achieved with 2.5 equiv. Deoxofluor at room temperature. However, contrary to the expected amino ester containing two fluormethylene groups, monofluorinated heterocyclic derivative (±)-**4 a** was formed resulting from chemodifferentiation between the two hydroxyl groups. This chemodiscrimination can be explained by the neighboring assistance of the amide group of (±)-**3 a.** It is obvious, that the hydroxy group of the hydroxymethylene function at position 5 underwent the expected fluorination. The other hydroxymethylene moiety in position 3, in turn, after transformation with Deoxofluor into the corresponding leaving group, was involved in cyclization. This took place via the anchimeric effect of the amide function via *O*-nucleophilic intramolecular attack to the corresponding fluorinated intermediate **T-1** leading to oxazine derivative (±)-**4 a** (Scheme 2).



Scheme 2. Fluorination of dihydroxylated ethyl β-aminocyclopentanecarboxylate (±)-**3 a** and (±)-**3 b.**

A different chemical behavior was observed when diol (±)-**3 b** with *N*-Cbz protecting group was subjected to fluorination. When performing the reaction of (±)-**3 b** with Deoxofluor under various conditions (-15 °C, 0 °C or 20 °C), both hydroxyl groups underwent fluorination providing exclusively difluorinated derivative (±)-**4 b** (Scheme 2, Figure 1). Noteworthy that in the reaction with only 1 equiv. of Deoxofluor reagent, difluorinated compound (±)-**4 b** and unreacted material were detected.

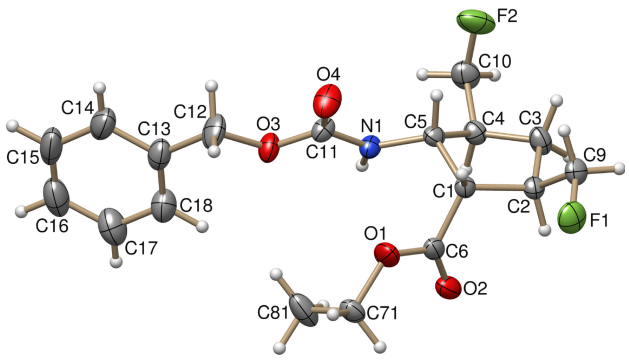
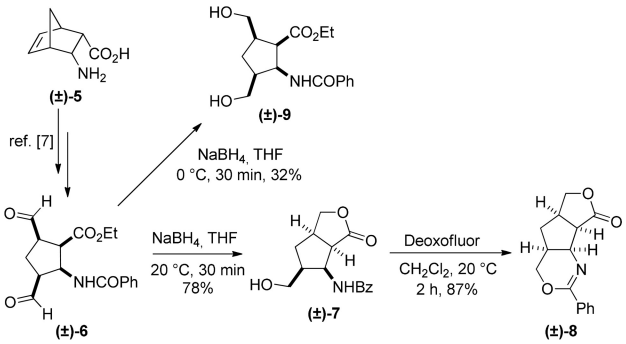


Figure 1. X-ray structure of compound (±)-**4 b.**

Next, *"all-cis"* diformyl amino ester (±)-**6**,[7] accessed from *diendo* norbornene amino acid (±)-**5**, was subjected to reduction with $NaBH_4$ in various solvents (EtOH, THF) (Scheme 3). When the reduction of (±)-**6** was performed in THF



Scheme 3. Fluorination of amino lactone (±)-**7** and dihydroxylated ethyl β-aminocyclopentanecarboxylate (±)-**9.**

at 20 °C, the process resulted in formyl group reduction followed by intramolecular cyclization to amino lactone (±)-**7** as the single product (Scheme 3, Figure 2).

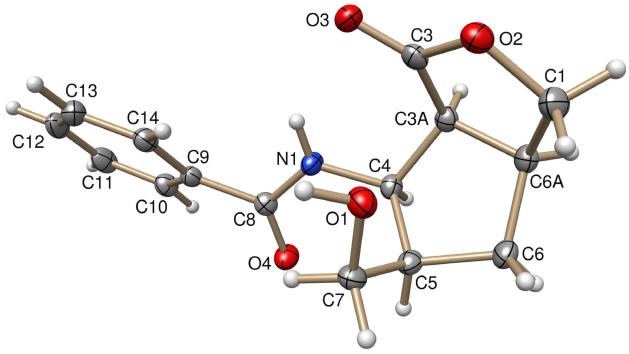


Figure 2. X-ray structure of compound (±)-**7.**

The lactonization during reduction could be prevented by reacting (±)-**6** with $NaBH_4$ at 0 °C for 30 min to have *bis*-hydroxymethyl-substituted amino ester (±)-**9** as the sole product (Scheme 3, Figure 4. However, when running the reduction at 0 °C for a longer time, lactonization also took place to give a significant amount of (±)-**7** alongside (±)-**9.**

Next amino lactone (±)-**7** possessing one hydroxy group was submitted to fluorination with Deoxofluor. However, either at reduced temperature (-15 °C) or at room temperature, intramolecular heterocyclization and concomitant deoxygenation occurred leading to ester (±)-**8** (Scheme 3, Figure 3).

In contrast to the fluorination of dihydroxylated amino ester (±)-**3** (Scheme 2), the *"all-cis"* amino ester (±)-**9** on treatment with Deoxofluor under various conditions did not provide any

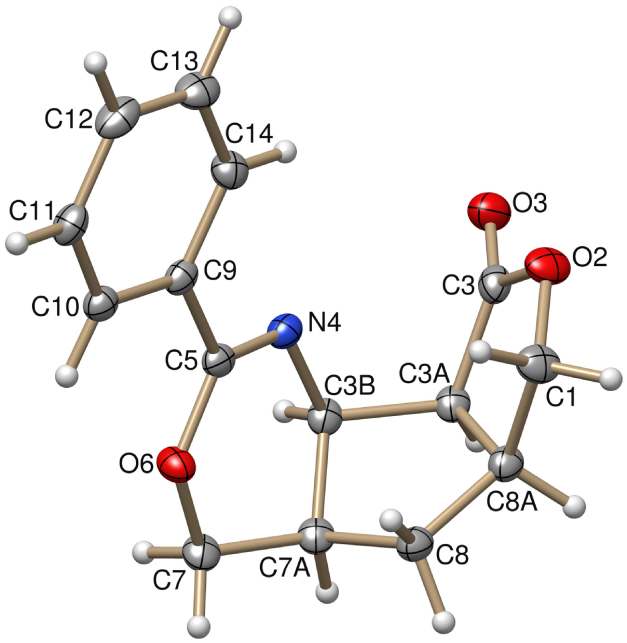


Figure 3. X-ray structure of compound (±)-**8.**.

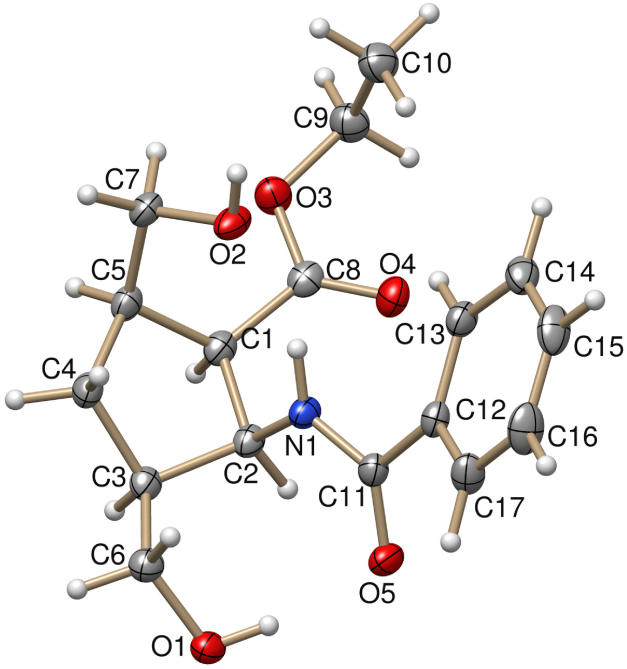
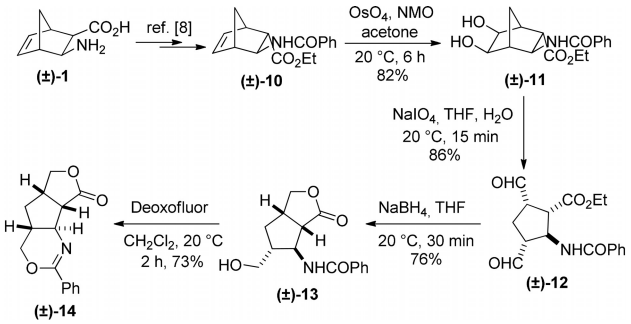


Figure 4. X-ray structure of compound (±)-**9.**

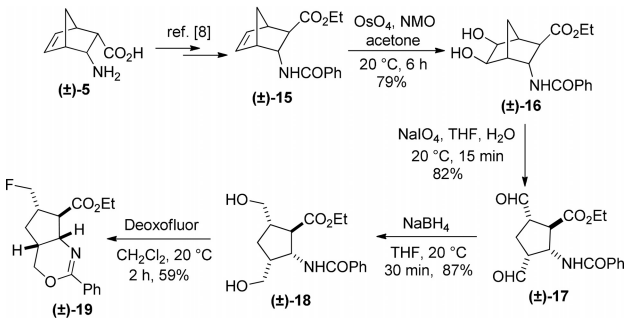
fluorinated product. Rather, only decomposed materials could be detected.

In order to increase the number of stereoisomers of hydroxylated cyclopentanes, *endo,exo* amino ester (±)-**10**,[8] synthesized from *diexo* norbornene amino ester (±)-**1**, was submitted to ring cleavage. First, it was transformed by dihydroxylation into (±)-**11**, followed by oxidative ring opening achieved with $NaIO_4$ affording diformylated cyclopentane amino ester (±)-**12.** Reduction of the aldehyde functions carried out with $NaBH_4$ under varied conditions (THF and EtOH as solvents, 15 °C, 0 °C or 20 °C) furnished exclusively in all cases aminolactone (±)-**13** by cyclization. Deoxofluorination of (±)-**13**, analogously to (±)-**7** resulted in tricyclic compound (±)-**14** a new stereoisomer of (±)-**8** (Scheme 4).



Scheme 4. Fluorination of hydroxylated lactone (±)-**13.**

In continuation of our investigation on the fluorination of hydroxylated cyclopentane stereoisomers, a novel dihydroxylated amino ester (±)-**16** was prepared from *exo,endo* norbornene β-amino ester (±)-**15.** Then oxidative ring cleavage of (±)-**16** afforded diformylated cyclopentane stereoisomer (±)-**17**, which, in turn on treatment with $NaBH_4$, underwent reduction and gave *bis*-hydroxymethylenated derivative (±)-**18** a novel stereoisomer of (±)-**3 a** and (±)-**9** (Scheme 5, Figure 5).



Scheme 5. Fluorination of dihydroxylated ethyl β-aminocyclopentanecarboxylate (±)-**18.**

Fluorination of compound (±)-**18** accomplished with various equivalents of Deoxofluor at different temperatures (-15 °C, 0 °C or 20 °C) provided by intramolecular cyclization through neighboring group participation oxazine derivative (±)-**18**, a novel stereoisomer of (±)-**4 a** as the sole product (Scheme 5).

Conclusions

Starting from readily available *diexo*- or *diendo*-norbornene β-amino acids, selective fluorination of a number of stereo-

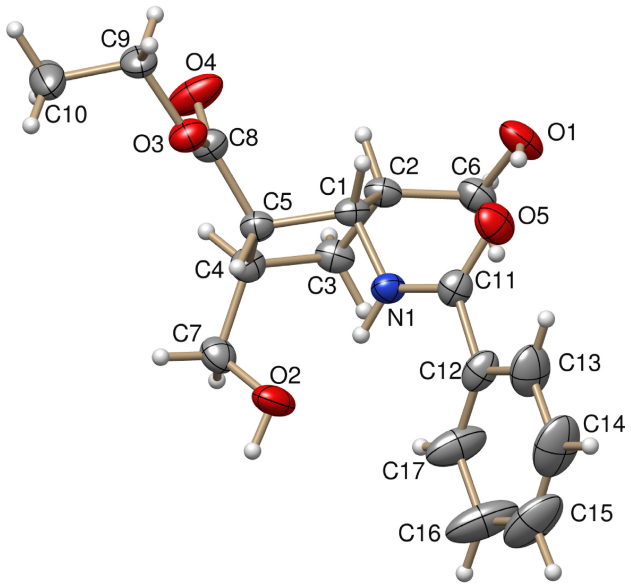


Figure 5. X-ray structure of compound (±)-**18.**

isomers of highly functionalized hydroxylated cyclopentane derivatives with multiple stereogenic centers has been evaluated. Alicyclic scaffolds with varied hydroxylation patterns obtained by oxidative olefinic bond cleavage and reduction were investigated in view of chemoselective monofluorination. The substrate-dependent chemodifferentiation of hydroxy groups under fluorination conditions involved either hydroxy–fluorine exchange or the anchimeric effect of the amide functions and led selectively to novel highly-functionalized molecular entities with multiple stereocenters. The nature of the *N*-protecting group plays a decisive role in the final result of selective fluorination. The prepared building blocks with high chemical diversity might be regarded as interesting heterocyclic or aminolactone scaffolds for further transformations, which are currently investigated in our laboratory.

Supporting Information Summary

General procedure for the synthesis and spectral data of all the synthesized compounds associated with this article will be available as supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amino acids · cyclization · fluorine · heterocycles · lactones

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