SYNTHESIS THROUGH SUBSTRATE-DEPENDENCE OF SOME FLUORINATED HIGHLY SUBSTITUTED ALICYCLIC SCAFFOLDS

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β-Amino acids and their highly functionalized derivatives are regarded as to be interesting scaffolds in medicinal chemistry. Several cyclic β-amino acid derivatives, such as cispentacin, tilidin, oxetin or icofungipen exhibit interesting biological properties (Figure 1) [1]. Fluorinated organic molecules have generated an increasing impact in drug research thanks to their changed metabolic and lipophilic properties. Apart from the large number of fluorine-containing drugs, some fluorinated α- and acyclic β-amino acids are known as antitumoural agents or antibiotics [2-7].

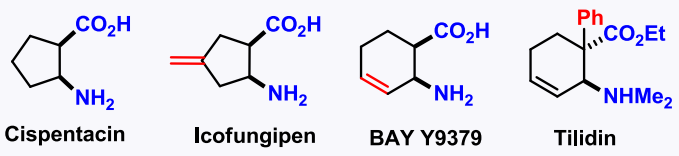
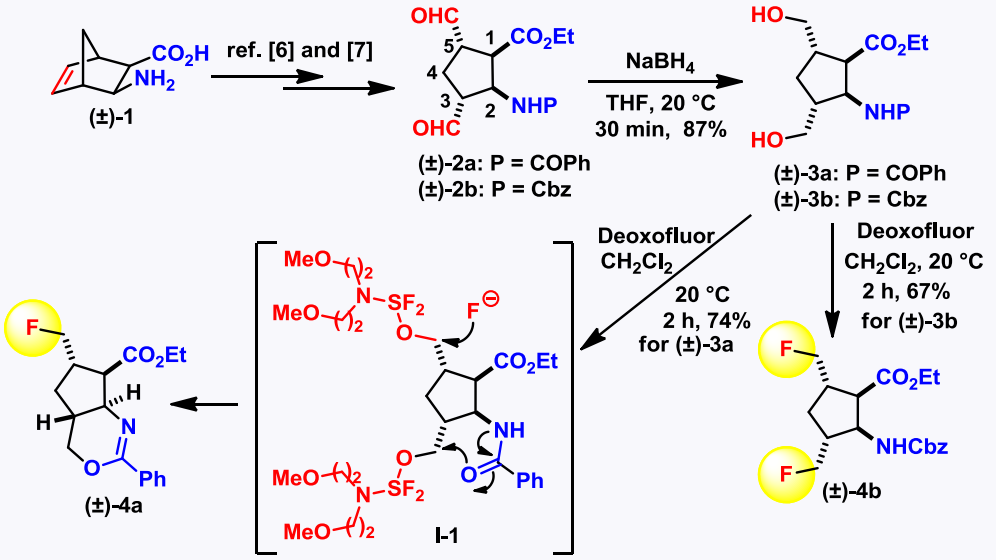


Figure 1.

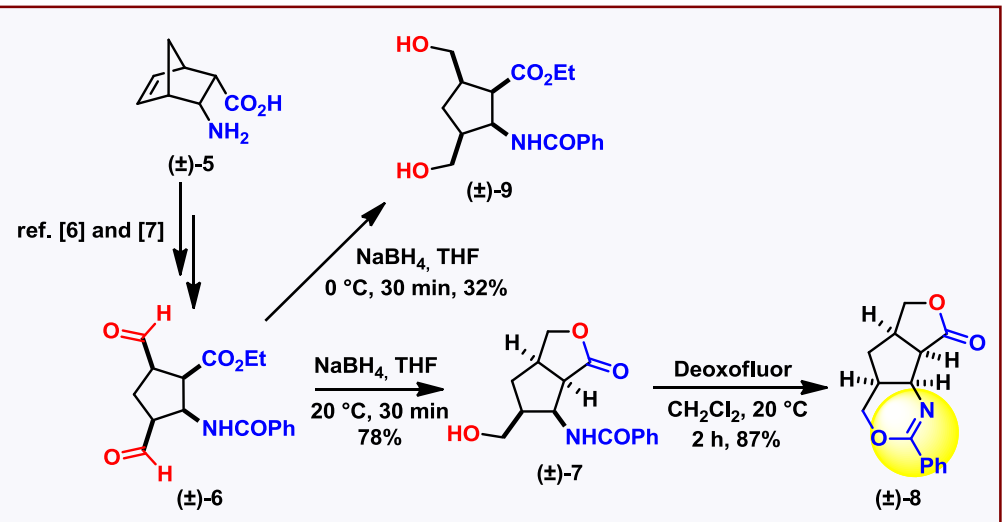
The aim of the research was to explore the substrate dependent fluorinations of various highly functionalized alicycles. Transformation of some hydroxy functionalized cyclopentane β-amino acid derivatives into highly-substituted alicyclic or heterocyclic stereoisomers under fluorination conditions with the intention to investigate the chemical behavior of these diversely substituted patterns has been performed.

In order to investigate the fluorination of polyfunctionalized alicyclic scaffolds, first racemic cyclopentane diformyl amino esters (±)-2a and (±)-2b were prepared through olefin bond ring cleavage of bicyclic *diexo* amino acid (±)-1. These were then converted into functionalized diol derivatives (±)-3a and (±)-3b by reduction of the formyl group. For the creation of fluoromethylene functions on the skeleton of the *N*-protected cyclopentane β-amino acid, bis-hydroxymethylenic amino esters (±)-3a and (±)-3b were submitted to fluorination with Deoxofluor.



Scheme 1.

N-Benzoyl-protected amino ester (±)-3a upon reacting with Deoxofluor, monofluorinated heterocyclic derivative (±)-4a was formed resulting from chemodifferentiation between the two hydroxyl groups. The reaction took place via the anchimeric effect of the amide function via *O*-nucleophilic intramolecular attack to the corresponding fluorinated intermediate I-1 leading to oxazine derivative (±)-4a (Scheme 1).



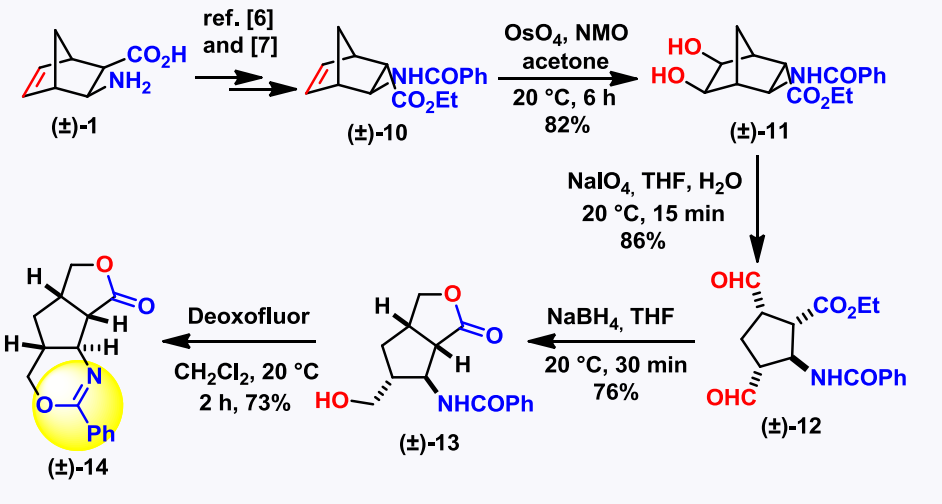
Scheme 2.

When diol (±)-3b with *N*-Cbz protecting group was subjected to fluorination both hydroxyl groups underwent fluorination providing exclusively difluorinated derivative (±)-4b through the hydroxy-fluorine exchange (Scheme 1).

Next, "*all-cis*" diformyl amino ester (±)- prepared from *diendo* norbornene amino acid (±)-5, was subjected to reduction and resulted in formyl group reduction followed by intramolecular cyclization to amino lactone (±)-7 as the single product (Scheme 2). The lactonization could be prevented by reacting (±)-6 with $NaBH_4$ at 0 °C for 30 min to have amino ester (±)-9 as the sole product (Scheme 2).

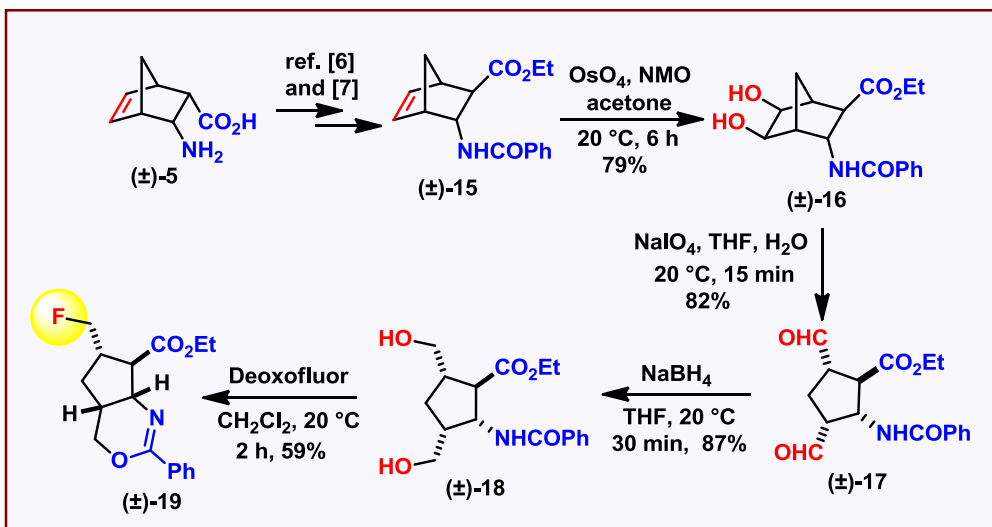
Next amino lactone (±)-7 possessing one hydroxy group was submitted to fluorination with Deoxofluor when intramolecular heterocyclization and concomitant deoxygenation occurred leading tocompound (±)-8 (Scheme 2). Contrary to the fluorination of dihydroxylated amino ester (±)-3 (Scheme 1), the "*all-cis*" amino ester (±)-9 on treatment with Deoxofluor under various conditions did not provide any fluorinated product.

In order to increase the number of stereoisomers of hydroxylated cyclopentanes, endo,exo amino ester (±)-10, 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 affording diformylated cyclopentane amino ester (±)-12. Reduction of the aldehyde functions furnished exclusively aminolactone (±)-13. Deoxofluorination of (±)-13, analogously to (±)-7 resulted in tricyclic compound (±)-14 a new stereoisomer of (±)-8 (Scheme 3).



Scheme 3.

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 $NaBH_4$, sufferred reduction and gave *bis*-hydroxymethylenated derivative (±)-18 a novel stereoisomer of (±)-3a and (±)-9 (Scheme 4). 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 (±)-4a as the sole product (Scheme 4).



Scheme 4.

Summary:

Starting from readily available *diexo-* or *diendo*-norbornene β-amino acids, selective fluorination of a number of stereoisomers of highly functionalized hydroxylated cyclopentane derivatives with multiple stereogenic centers has been evaluated. 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.

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