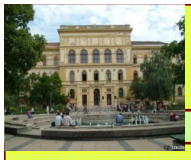

STEREO- AND REGIOSELECTIVE SYNTHESIS OF DIFLUORINATED CYCLIC β-AMINO ACID DERIVATIVES

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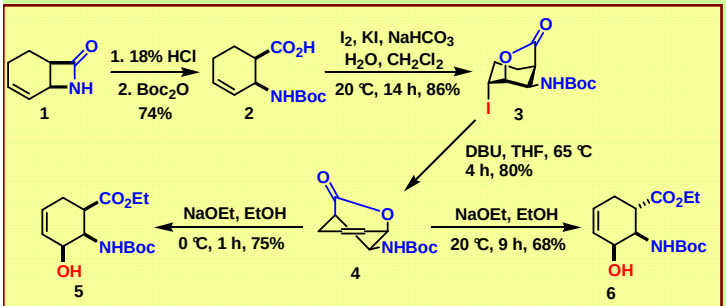
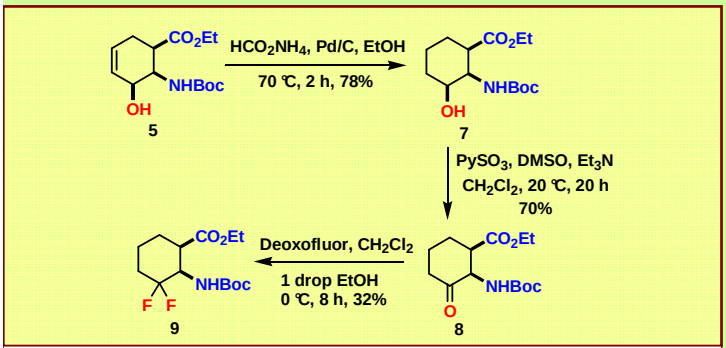
β-Amino acids are components of many natural products and precursors of β-lactams. They are used as building blocks in the synthesis of novel peptides with biological potential.[1] As a consequence of their high importance among pharmaceuticals and drugs the bioactive fluorinated compounds have gained increasing attention last decade.[2] Since only few routes toward the synthesis of fluorinated cyclic β-amino acids have been reported so far,[3] our aim was to develop a novel access for the synthesis of difluorinated cyclic β-amino acids, based on oxo-fluorine interconversion protocol. Starting from bicyclic β-lactams (1 and 13) the key steps of the synthetic route consisted in the stereoselective iodolactonization, lactone opening, oxidation followed by fluorination.



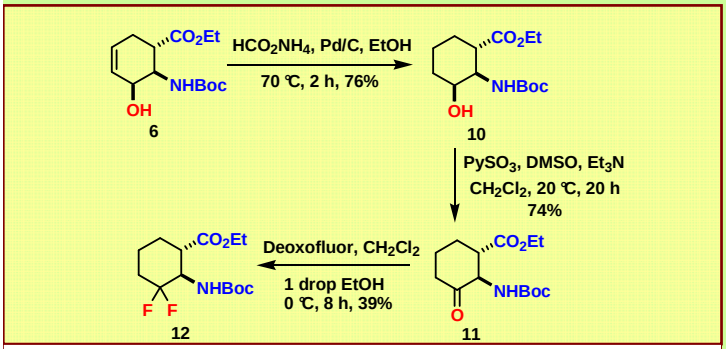
Scheme 1. Synthesis of 3-hydroxylated ethyl 2-aminocyclohexenecarboxylate stereoisomers 5 and 6.

Amino acid 2 derived from lactam 1 by stereo- and regioselective iodolactonization, followed by HI elimination resulted in lactone 4. Lactone opening with NaOEt at 0 °C afforded *all cis* hydroxylated amino ester 5, while at 20 °C amino ester 6, stereoisomer of 5 was formed[4a] (Scheme 1).



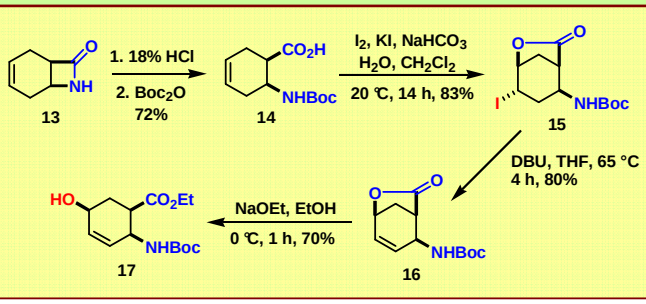
Scheme 2. Sythesis of difluorinated ethyl 2-aminocyclohexanecarboxylate 9.

Hydroxylated amino ester 5 by olefinic bond saturation and hydroxyl group oxidation furnished oxo amino ester 8, which on treatment with Deoxofluor provided difluorinated 2-aminocyclohexenecarboxylate 9 (Scheme 2). Following a similar pathway from 3-hydroxylated β-amino ester 6 3,3-difluoro 2-aminocyclohexanecarboxylate 12, streoisomer of 9 was obtained (Scheme 3).

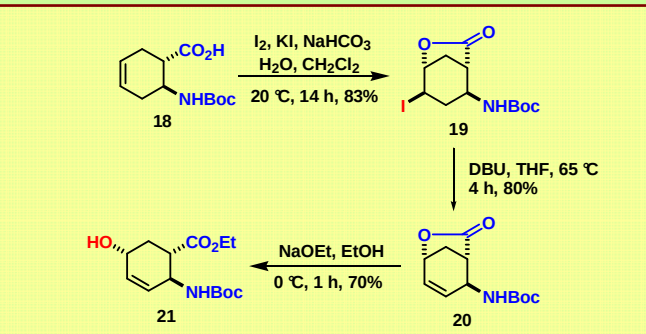


Scheme 3. Sythesis of difluorinated ethyl 2-aminocyclohexanecarboxylate 12.

In order to prepare other difluorinated β-aminocyclohexanecarboxylic acid isomers *cis*-amino acid 14 with a cyclohexene skeleton, derived from bicyclic β-lactam 13 was first subjected to iodolactonization, HI elimination and lactone ring-opening producing 5-hydroxylated 2-aminocyclohexenecarboxylate 17 (Scheme 4). By using similar protocol *trans* amino acid 18 afforded 5-hydroxylated β-amino ester 21, stereoisomer of 17 (Scheme 5).[4b]

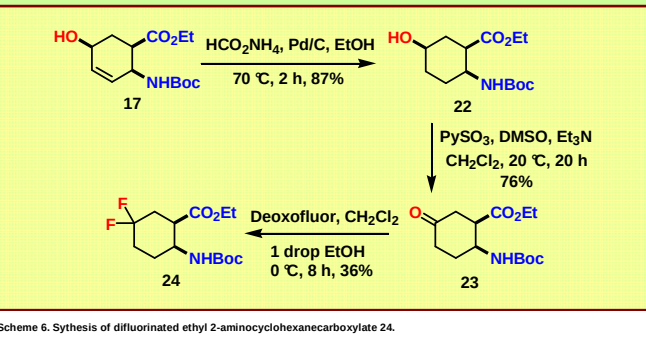


Scheme 4. Synthesis of 5-hydroxylated ethyl 2-aminocyclohexenecarboxylate 17.

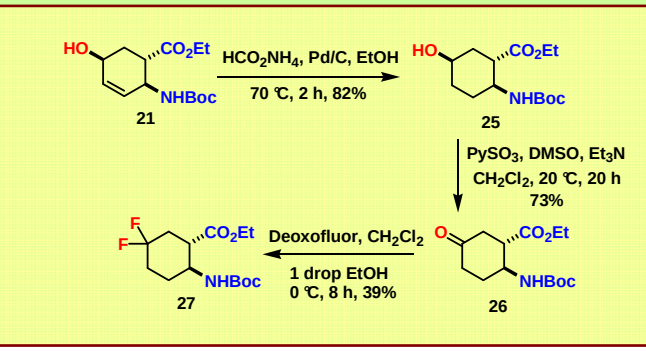


Scheme 5. Synthesis of 5-hydroxylated ethyl 2-aminocyclohexenecarboxylate 21.

Both *cis* and *trans* 5-hydroxylated 2-aminocyclohexenecarboxylate stereoisomers 17 and 21 were next transformed by C-C ring double bond saturation under transfer hydrogenation conditions and oxidation of the hydroxylic function with pyridinium-sulfur trioxide complex to the corresponding oxo β-amino acids 23 and 26 with a cyclohexane framework. On treatment with Deoxofluor oxo esters 23 and 26 furnished the corresponding geminal 5,5-difluorinated 2-aminocyclohexancarboxylate stereoisomers 24 and 27 (Schemes 6 and 7).



Scheme 6. Sythesis of difluorinated ethyl 2-aminocyclohexanecarboxylate 24.



Scheme 7. Sythesis of difluorinated ethyl 2-aminocyclohexanecarboxylate 27.

Summary: Starting from bicyclic β-lactams 1 and 13 difluorinated cyclohexane β-amino ester regio- and stereoisomers have been prepared in six or seven steps. The method was based on stereo- and regioselective hydroxylation, hydroxyl group oxidation and oxo-fluorine interconversion.

[1]. (a) Kiss, L.; Forró, E.; Fülöp, F. *Synthesis of carbocyclic β-amino acids. Amino Acids, Peptides and Proteins in Organic Chemistry*. Vol. 1, Ed. A. B. Hughes, Wiley, Weinheim, 2009, 367. (b) Kiss, L.; Fülöp, F. *Synlett* 2010, 1302. [2]. (a) Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. Chem Soc Rev 2008, *37*, 320. (b) Hagmann W.K. *J Med Chem* 2008, 51, 4359. [3]. (a) Acena, J. L.; Simon-Fuentes, A.; Fustero, S. *Curr Org Chem* 2010, *14*, 928. (b) Fustero, S.; Sanz-Cervera, J. F.; Acena, J. L.; Sanchez-Rosello, M. *Synlett* 2009, 525. [4]. (a) Kiss, L.; Forró, E.; Fustero, S.; Fülöp, F. *Org. Biomol. Chem*. 2011, *9*, 6528. (b) Kiss, L.; Forró, E.; Fustero, S.; Fülöp, F. *Eur. J. Org. Chem*. 2011, 4993.