Prague, November 25, 2019

Subject: PhD Thesis Report

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Reviewer: Jiří Míšek, Ph.D.

Thesis Title: Asymmetric Tandem Lithium Amide Conjugate Addition/Radical Reactions and Their Application in the Total Synthesis of Natural Products.

The submitted thesis deals with the development of a robust synthestic methodology for the asymmetric construction of β-amino-α-hydroxy carboxylic acids and various N-heterocyclic compounds. The principal strategy is based on the tandem conjugate addition/radical functionalization that can be iterated to obtain a plethora of structurally complex molecular scaffold. The products of the reactions would be surely interesting from the medicinal chemistry point of view as they allow to display different functional groups in a defined three-dimensional manner.

The thesis is split into six classical sections. Introduction covers the past approaches to the desired scaffolds as well as the relevant previous results from the group. Aims of the thesis are clearly stated followed by the section of Results and discussion that is split into several subsections. The author first validated the tandem approach on the asymmetric synthesis of β-amino-α-hydroxy carboxylic acid derivatives that are building blocks found in a variety of biologically active compounds including commercial drugs. After a thorough optimization of the reaction conditions a small library of β-amino-α-hydroxy carboxylic acid derivatives was prepared in moderate to good yields, excellent enantioselectivities and good to excellent diastereoselectivities. The removal of protecting/directing groups was also worked out and the entire protocol was utilized for the total asymmetric synthesis of biologically active compounds or their fragments (cytoxazone, perthamide C and largamide H). This tandem methodology was further extended by radical cyclization step in order to prepare complex pentasubstituted pyrrolidines and pyrrolidine-based bicyclic and spirocyclic derivatives. These desired derivatives were also successfully prepared in asymmetric fashion in moderate to good yields and generally good degree of distereoselectivity. As the products of these reactions are stereochemically complex molecules I appreciate the discussion of the stereochemistry assignment and reprints of the 2D NOE NMR spectra in this section.

The next section of the thesis is the bulky experimental part followed by Conclusions that are to the point and the final References.

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Overall, this thesis represents an important contribution to the field of expedient asymmetric synthesis of β-amino-α-hydroxy carboxylic acids and stereochemically complex pyrrolidines. The author proved that she can conduct a high level research, interpret the results with the erudition and write about it. I particularly appreciate the proposed mechanistic rational of the observed results of the reactions that are provided with an obvious thorough literature knowledge and deep insight of the problem.

Thus, I have no reservation to recommend this thesis for the defense.

Questions:

1. On the page 28 Scheme 3.1.3 it is shown that using bulkier substituent on the lithium amide leads to a lower diastereoselectivity of the final product of the tandem reaction. Can you explain this observation?
2. The stereochemical assignment of compound **3-85** was not fully disclosed as the NOE experiment along with lactonization reaction indicates *trans* configuration at the C3-C3a bond that is in contradiction with *cis* configuration in other derivatives confirmed by X-ray crystallography. Can you comment on this?
3. Can you put in perspective your method of asymmetric synthesis of β-amino-α-hydroxy carboxylic acids with the already known ones in terms of substrate scope, yield and stereoselectivity?

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