Review report for PhD. thesis „New Thermal and Oxidative Radical Cyclization Methodology and Application to the Total Synthesis of Bridged Diketopiperazine Alkaloids" submitted by Tynchtyk Amatov, M.Sc.

The thesis submitted by Tynchtyk Amatov deals with new approach towards bridged diketopiperazine alkaloids which are biologically active compounds attracting attention because of their potential application in medicinal chemistry. The main idea of the new synthetic methodology developed within the thesis is application of radical cyclization combined with condensation reactions allowing formation of six-membered and larger rings with controlled stereochemistry at two or three stereogenic centres.

In the introduction part, important literature data about 2,5-diketopiperazine alkaloids are summarized including structure of the main representatives. Then synthetic methodologies having still been used in the synthesis of 2,5-diketopiperazine skeleton are reviewed. The first part is shorter than it is usual in the thesis nevertheless brings sufficient information about the topic to make following text easily understandable. In the chapter Aims of the work, not only aims are clearly specified but this is appropriately combined with the analysis of potential problems.

Next five chapters of the thesis belonging to the results and discussion part clearly describe unique steps leading to new synthetic methodology towards 2,5-diketopiperazine alkaloids. At first, original method for the synthesis of 2,5-diketopiperazine moiety from Boc-protected amino-acid derivatives was improved by implementing silica-gel into the reaction mixture to be applicable also for bridged-alkaloid intermediates. This method was later shown as useful and versatile approach also for the synthesis of compounds with stereogenic centres with the only limitation in double-cyclization of tripeptides affording anthranilate derivatives which is accompanied by epimerization in position 1. As the following radical cyclization based on in-situ oxidation of 2,5-diketopiperazine-enolate was not successful, the author developed completely new approach utilizing persistent TEMPO radical. This cyclization reaction which is crucial for the formation of the carbon-bridge in the alkaloid structure is studied in the next chapter in detail including the effect of protecting group on the diastereoselectivity of cyclization. Further usefulness of the developed synthetic strategy was demonstrated on the synthesis of 8-oxoasperparaline C which was prepared in eleven steps starting from L-proline in good overall yield (approx. 15%). In the next part, applicability of the new cyclization approach was investigated focusing on the effect of alkenyl substituent structure on length of the bridge. Interestingly the character of the alkenyl group, whether it is substituted or not, affects cyclization process being preferably *endo*-trig or *exo*-trig for non-substituted and branched alkenyls, respectively. Cyclization was shown to tolerate heteroatom on alkenyl arm allowing incorporation of oxygen or nitrogen. Finally, interesting trans/cis isomerization of alkoxyamines was described and studied in the last chapter using kinetic methods.

At this point I would like to commend the presented thesis. I really enjoyed reading. The thesis is very well written, I appreciate clear presentation of all experiments both in the Results and Discussion part and in Experimental. Style of the presentation is on high level with Schemes, Figures and other illustrations meeting standard criteria of publishing in the area of organic chemistry. There are minimum typing errors showing author wrote the work also with emphasis on formal aspects. Extend

and choice of the references is appropriate to the scope of the work. Additionally to many standard methods of organic synthesis, author uses broad spectrum of experimental techniques for characterization of the compounds. Beside proton and carbon NMR spectra and mass spectra, many structures are supported by x-ray diffraction analysis which was often the only way to assign the configuration. The data from x-ray analysis were also used to support discussion of cyclization giving evidence on possible conformation of cyclic intermediates (mainly in Chapter 6). Monitoring of isomerization was performed by NMR, the data were analysed by standard physico-chemistry-approach affording thermodynamic data.

There are some issues which should be discussed within the defence:

1. Unexpected formation of product **3.14** is described and discussed on pages 36 and 37. Has been considered intramolecular radical transfer under formation of benzylic radical being trapped with TEMPO formed by previous decomposition of **3.11b**?
2. Several types of radical cyclizations have been observed within the work. Considering size of the cycle formed, from 6- to 9-membered rings are formed. Considering type of cyclizations both *endo*- and *exo*-trig processes were described. Could be given any general conclusion about influence of the structure of alkenyl-2,5-diketopiperazine on the type of cyclization? Can be used this "rule" for prediction of cyclization of other derivatives?

Other comments:

Compounds **2.6** and **2.8** on page 19 are probably racemates. It should be noted in the corresponding Scheme 2.1.

Values of specific rotation should be reported in units of $deg \cdot mL \cdot g^{-1} \cdot dm^{-1}$ or at least deg (°) which is usually used for shortening. No units are given in the text (e.g. page 24).

Configuration of **2.34b** in Scheme 2.11 is the same as for **2.24.a**. It should be the other on carbon 1.

Evaluation:

I would like to conclude that the presented work is at a very high level both from the point of view of the quality of presentation as well as quality of results. High novelty of the work is documented by three publications in the first-class journal - Angewandte Chemie. In all of these publications, Mr. Amatov is the first author. Therefore I strongly recommend **PhD. thesis to be accepted** and doctoral degree to be awarded to author after successful defence.

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