Opponent's review of Tereza Pavlíčková's dissertation

The presented dissertation is directed to the field of total synthesis of natural substances and their analogues. In general, this is a very demanding field of organic chemistry, requiring not only great expertise, but also experience with various types of chemical transformations under very different conditions. The choice of the topic of the dissertation in this area is always a big challenge with a high degree of risk. Therefore, I admire every student who chooses the topic of their PhD work in this field. The topic of the presented dissertation belongs to the very important areas of organic chemistry, especially with regard to the development of new synthetic methodologies.

The author has specified two main aims of her dissertation:

a) To develop a new enantioselective strategy for the synthesis of A- and J-NeuroPs

b) To develop a unified strategy of synthesis of isoprostanoids with 3-hydroxypentenyl ω-chain and a skipped polyene α-chain

These main goals are then clearly specified by the individual sub-goals and suggested approaches to achieve them. The specification of the planned synthetic approaches is very suitably supplemented by schemes.

The author starts each synthetic pathway development by retrosynthetic analysis. This is always very well suggested and discussed. The intended reactions are very well confronted with literature. The author suggested several possible approaches to get both final structural motives included in the aims of the dissertation and finally tried to apply the successful ones to synthesis of 4-A4-NeuroP, 18-F3t-IsoP and 20-NeuroPs.

In the search for a synthetic approach for the preparation of cyclopentene core of A- and J-NeuroPs, two of the three proposed synthetic strategies proved to be suitable. The author applied a number of chemical reactions involving e.g. double olefin metathesis reaction – one of the modern approach in organic synthesis. The author successfully overcame not only problems of a synthetic nature, but also the instability of some intermediates. She coped very well with the stereochemical issues that accompanied a number of synthetic steps. With the enormous effort she finally synthesized 4(RS)-4-A4-NeuroP 1,4-lactone **103b** and 4-deoxy-$\Delta^{4,6}$-A4-NeuroP **103c** over 21 and 22 steps, respectcivelly.

The strategy suggested for the synthesis of isoprostanoids defined in the aims of the dissertation was finally succesfully used for the first synthesis of rac-18(RS)-18-F3t-IsoP, a metabolite of EPA in 10 reaction steps. The reactions performed in this part of the dissertation, including e.g. enantioselective Mukaiyama reaction, had to be optimized with great care and precision.

I consider the results of the dissertation to be very valuable. From my point of view, they have significantly enriched the portfolio of synthetic approaches and methodologies that can be useful for the preparation of various structural analogues included in natural as well as synthetic compounds.

The dissertation itself is written very clearly without major formal or factual errors. It is then suitably supplemented by a number of clear schedules.

The author has shown great erudition in the field of organic synthesis, from the design of a synthetic strategy through the discussion of reaction mechanisms to the evaluation of the stereochemistry of selected synthetic steps. Scientific results of Tereza Pavlíčková were published in prestigous impacted journals. She is the first author in two articles published in Chemistry - A European Journal and the coauthor of nice paper in ELIFE.

I am fully convinced that the submitted dissertation fully meets the criteria, and that Tereza is more than a suitable candidate for a PhD in organic chemistry. Therefore, I recommend the submitted dissertation for defense.

Questions and comments

1. The optimization of the reaction conditions given in Table 1 seems to me to be somewhat unsystematic. It is difficult to read an influence of individual parameters to the reaction.
2. Scheme 36, page 39: Could the proposed mechanism involve the formation of dihydrofuran moiety instead of intermediate **104-14** and the following subsequent stereoselective addition?
3. There are big differences in the yields of compound **139** (Table 5; items 9-11). The discussion include scale-up trouble and quality of KHMDS. The later one has been fixed by precise determination of its content in the commercial solution to get the results pointed in item 11. Were the data in items 1-10 obtained with the „calibrated" solution of KHMDS?
4. In the studies of CM of cyclopentes **154** (Table 7 p. 57) two catalysts (HG-II a G-II) were used. Author declares higher efficiency of HG-II. As the reaction is also substrate-dependent I would polemicize about this fact. Can you explain this issue with respect of the items in Table 7?
5. The reaction conditions given in item 2, Table 9 (p. 68) do not correspond to the conclusion given in the last sentence before this table ("....a mixture of compounds **83b** and **154** was isolated (entry 2)"). Can you discuss the result of this experiment?

In Olomouc, November 20th, 2020

prof. Jan Hlaváč