# COMMENTARY TO HABILITATION THESIS

## SYNTHETICALLY MODIFIED COMPLEX NATURAL PRODUCTS

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Natural products are endowed with diverse bioactivities and have served well as sources of life-saving medicines, particularly for infectious diseases and cancer. The examples of essential antibiotics (e.g., erythromycin, clarithromycin, amoxicillin), antifungal agents (e.g., amphotericin B), anticancer agents (e.g., paclitaxel, docetaxel, campothecin), cholesterol-lowering drugs (e.g., atorvastatin, simvastatin, lovastatin), immunosuppressants (e.g., tacrolimus and cyclosporin A), and antihypertensive agents (e.g., captopril, enalapril) are all based on or inspired by natural products. Likewise, chemical biology – the research field and philosophy about discovering, synthesizing, and manipulating molecules to illuminate life and improve the human condition (definition by David R. Liu) – has benefited tremendously from bioactive natural products. Manipulating the structure of natural products is often necessary to optimize their properties and function, be that in research or medicine. For complex natural products, this remains a considerable challenge.

The presented thesis traces chronologically three research projects performed in my laboratory at Masaryk University since 2013. The first part is devoted to the pseurotin family of fungal natural products characterized by a unique spirocyclic skeleton and diverse biological activities. The second part features a complex natural diterpene forskolin, an iconic molecule to practitioners of natural product synthesis and a common research tool in biology. The third part focuses on a family of potent natural antibiotics, bactobolins, which compromise the function of ribosomes and, thereby, normal protein synthesis. The underlying obstacle we faced within each of these projects has been that of synthetic complexity. In pursuing de novo chemical synthesis, we had to address various challenges ranging from the control of reactivity and stereochemistry, all the way to practical aspects such as overall yield, brevity, flexibility, and scalability of the synthetic route. This thesis features different ideas in synthetic planning driven by the vision of establishing concise and flexible de novo assembly of complex natural products and their analogs. The challenges and successes in implementing these ideas in experimental practice are presented.

The habilitation thesis celebrates the dedicated experimental effort of the talented students I had the pleasure of working with and who made important and original contributions to the individual projects.

**The habilitation procedure at Masaryk University calls for a quantification of the contributions of Jakub Švenda to the key research publications forming the basis of this thesis. Being an inherently simplistic analysis, the indicated percentage values should be understood accordingly. The asterisk (*) denotes the corresponding author.**

**[1]** Facile rearrangements of a vinylogous α-hydroxy-β-dicarbonyl substrate involving an apparent oxirane C–C bond scission. Kučera, R.; Hylse, O.; Babiak, M. and Švenda, J.* *Tetrahedron Lett.* **2015**, *56*, 6171–6173.

*This publication originates from a serendipitous discovery made in my lab regarding an unexpected mode of reactivity. It was carried out experimentally by my students. I supervised and directed the research, wrote ca. 80% of the manuscript, and coordinated the preparation of the experimental section.*

**[2]** Enantioselective synthesis of cephalimysins B and C. Chalupa, D.; Vojáčková, P.; Partl, J.; Pavlovič, D.; Nečas, M.; Švenda, J.* *Org. Lett.* **2017**, *19*, 750−753.

*I helped generate preliminary experimental data for this publication, although most of the experimental work was carried out by my students. I designed the synthetic approach, supervised and directed the research, wrote 80% of the manuscript, and coordinated the preparation of the experimental section.*

**[3]** A concise synthesis of forskolin. Hylse, O.; Maier, L.; Kučera, R.; Perečko, T.; Svobodová, A.; Kubala, L.; Paruch, K.; Švenda, J.* *Angew. Chem. Int. Ed.* **2017**, *56*, 12586–12589.

*This publication is the result of a chemistry-biology collaborative effort. I designed the synthetic approach, supervised and co-directed the chemistry part of the research, led the writing of the manuscript (ca. 70%) with the essential contributions also from my colleagues, and coordinated the preparation of the experimental section by all involved.*

**[4]** Enantioselective conjugate additions of 2-alkoxycarbonyl-3(2*H*)-furanones. Vojáčková, P.; Chalupa, D.; Prieboj, J.; Nečas, M.; Švenda, J.* *Org. Lett.* **2018**, *20*, 7085−7089.

*This publication originates from a discovery made in my lab. I supervised and directed the research, which was experimentally carried out by my students. I led the writing of the manuscript (ca. 80%) and coordinated the preparation of the experimental section.*

**[5]** Natural pseurotins and analogs thereof inhibit activation of B-cells and differentiation into the plasma cells. Vašíček, O.; Fedr, R.; Skoroplyas, S.; Tharra, P. R.; Chalupa, D.; Sklenář, M.; Švenda, J.; Kubala, L.* *Phytomedicine* **2020**, *69*, 153194.

*I supervised and directed the chemistry part of this chemistry-biology collaborative project. I contributed to the writing of the manuscript (ca. 30%) to a minor extent and coordinated the preparation of the experimental section (chemistry part). I'm not a leading author of this publication.*

**[6]** Stereocontrolled synthesis of (−)-bactobolin A. Vojáčková, P.; Michalska, L.; Nečas, M.; Shcherbakov, D.; Böttger, E.; Šponer, J.; Šponer, J.; Švenda, J.* *J. Am. Chem. Soc.* **2020**, *142*, 7306−7311.

*I designed the synthetic approach and supervised and directed the experimental efforts of my students. I wrote ca. 70% of the manuscript with important contributions from my students and coordinated the preparation of the experimental section. The supporting biology experiments were carried out via collaboration, which I helped establish.*

**[7]** Stereocontrolled synthesis of pseurotin $A_2$. Jachak, G.; Tharra, P. R.; Sevelda, P.; Švenda, J.*****, *J. Org. Chem.* **2021**, *86*, 11845–11861.

*I designed the synthetic approach and supervised and directed the experimental efforts of my students and postdocs. I wrote ca. 80% of the manuscript and coordinated the preparation of the experimental section.*

**[8]** Short synthesis of (+)-actinobolin: Simple entry to complex small-molecule inhibitors of protein synthesis. Tharra, P. R.; Mikhaylov, A.; Švejkar, J.; Gysin, M.; Hobbie, S. N.; Švenda, J.*****, *Angew. Chem. Int. Ed.* **2022**, *61*, e202116520.

*I designed the synthetic approach and supervised and directed the experimental efforts of my students and postdocs. I wrote ca. 80% of the manuscript and coordinated the preparation of*

*the experimental section. The supporting biology experiments were carried out via collaboration, which I helped establish.*

**[9]** Convergent assembly of the tricyclic labdane core enables synthesis of diverse forskolin-like molecules. Szczepanik, P. M.; Mikhaylov, A. A.; Hylse, O.; Kučera, R.; Daďová, P.; Nečas, M.; Kubala, L.; Paruch, K.; Švenda, J.*, *Angew. Chem. Int. Ed.* **2023**, *62*, e202213183.

*I designed the synthetic approach and supervised and co-directed the experimental efforts of my students and postdocs. I wrote ca. 80% of the manuscript and coordinated the preparation of the experimental section by my students and colleagues. The biological part was carried out via collaboration.*