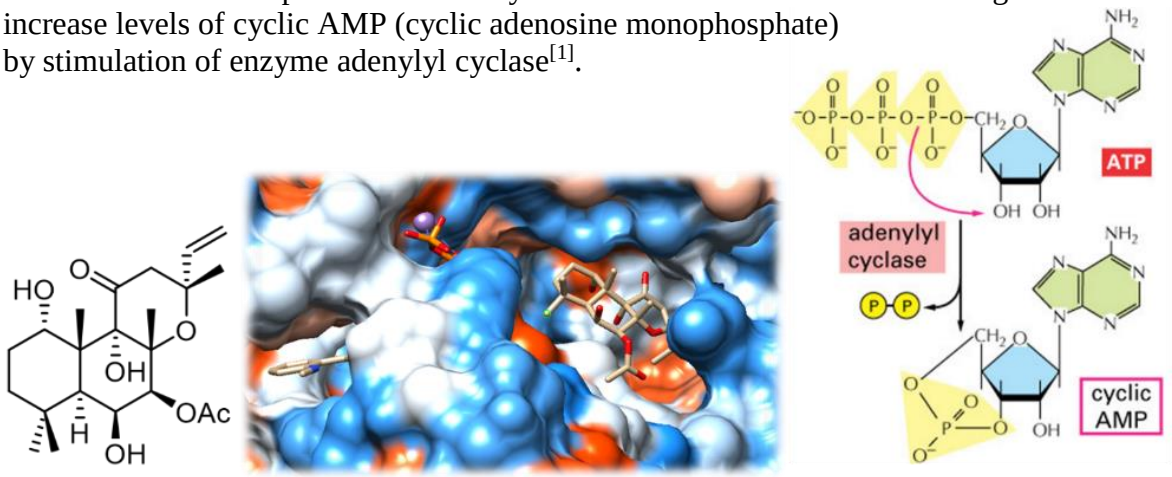
A flexible synthetic strategy enabling preparation of novel forskolin analogues

Paweł Marcin Szczepanik [a, b]; Andrey Mikhaylov [a, b]; Jakub Švenda*, [a, b]

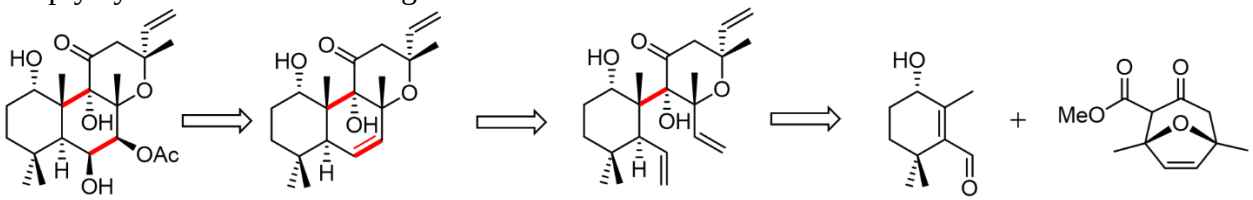
[a] *Masaryk University, Faculty of Science, Department of Chemistry, Kamenice 5/A8, 623 00 Brno, Czech Republic*
[b] *International Clinical Research Center, St. Anne's University Hospital Brno, Pekařská 53, 656 91 Brno, Czech Republic*
**svenda@chemi.muni.cz*

Forskolin is a natural product commonly used in biomedical research as a reagent to increase levels of cyclic AMP (cyclic adenosine monophosphate) by stimulation of enzyme adenylyl cyclase[1].



Forskolin | **Forskolin bound inside adenylyl cyclase** | **Biochemical transformation**

Aim of our work is to develop a flexible synthetic route that would enable preparation of novel forskolin analogues not accessible by semisynthesis or published fully synthetic approaches.[2-6]. Structure of forskolin presents a considerable challenge for synthesis, because of high level of oxidation, dense substitution and rich stereochemistry. Using a convergent approach (strategic bonds in red), we would like to flexibly alter the structure of this natural product at novel positions simply by choice of the building blocks.



Ring closing *metathesis* | **Michael addition**

Literature

[1] Sadana, R.; Dessauer C. W. Physiological Roles for G Protein-Regulated Adenylyl Cyclase Isoforms: Insights from Knockout and Overexpression Studies *Neurosignals* **2009**, 17, 5–22.
[2] Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. A Synthetic Route to Forskolin *J. Am. Chem. Soc.* **1987**, 109 (26), 8115–8116.
[3] Hashimoto, S.; Sakata, S.; Sonegawa, M.; Ikegami, S. A Total Synthesis of (±)-Forskolin *J. Am. Chem. Soc.* **1988**, 110 (11), 3670–3672.
[4] Corey, E. J.; Jardine, P. da S.; Rohloff, J. C. Total Synthesis of (±)-Forskolin *J. Am.Chem. Soc.* **1988**, 110 (11), 3672–3673.
[5] Delpech, B.; Calvo, D.; Lett, R. Total Synthesis of Forskolin — Part I *Tetrahedron Lett.* **1996**, 37 (7), 1015–1018.
[6] Hylse, O.; Maier, L.; Kučera, R.; Perečko, T.; Svobodová, A.; Kubala, L.; Paruch, K.; Švenda, J. A Concise Synthesis of Forskolin *Angew.Chem. Int. Ed.* **2017**, 56 (41), 12586–12589.