Fully synthetic route to forskolin and development of strategies for analog preparation

Ondřej Hylse and Jakub Švenda

Department of Chemistry, Faculty of Science, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic.

Forskolin (1) is a highly oxidized and structurally complex labdane diterpene with important biological effects. Best described is the ability of forskolin to activate membranous adenylyl cyclases (ACs) – enzymes that catalyze conversion of ATP to cAMP. As many clinically used drugs act by indirect stimulation of ACs, there has been a great interest in forskolin for biomedical applications. Adenylyl cyclases are known to exist in nine isoforms and forskolin activates most of them (AC1–AC8). As there are not many isoform-selective activators or inhibitors of ACs, we were wondering if modification of the forskolin skeleton could provide isoform-selective modulators of ACs.

Majority of known forskolin analogs was made semisynthetically. To enable structural modifications at unprecedented sites of forskolin, other approaches are necessary. Densely grouped array of quaternary carbons and stereocenters present a considerable synthetic challenge. We have recently completed the shortest fully synthetic route to forskolin, which is scalable and allowed us to prepare hundred miligram quantities of this natural product.

Initial studies into analog preparation will be discussed as well as preliminary studies on the completely new and promising convergent synthesis of forskolin analogs.

