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

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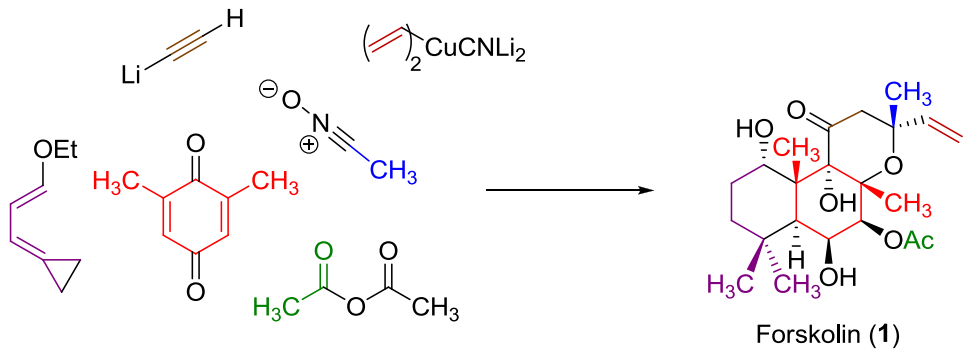
Forskolin (**1**) is a highly oxidized and structurally complex labdane diterpene with important biological effects. Best described is the ability of forskolin to activate membranous adenylyl cyclases (ACs) – enzymes that catalyze conversion of ATP to cAMP.[1] As many clinically used drugs act by indirect 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.[2]

Majority of known forskolin analogs was made semisynthetically.[3] 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.



Forskolin (**1**)

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

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[2] (a) S. Pierre, T. Eschenhagen, G. Geisslinger, K. Scholich, *Nat. Rev. Drug Discov.* **2009**, *8*, 321–335. (b) B. Pavan, C. Biondi, A. Dalpiaz, *Drug. Disc. Today* **2009**, 14, 982–991.

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