TOWARDS THE SYNTHESIS OF LOPHOTOXIN

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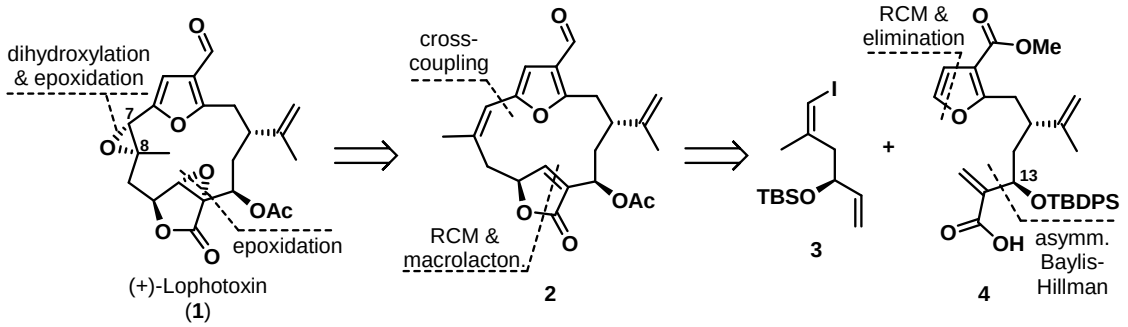
(+)-Lophotoxin (1) was first isolated in 1981 from pacific sea whips (*Lophogorgia*) by FENICAL and co-workers [1]. It is highly toxic and acts as irreversible antagonist of nicotinic acetylcholine receptors [1,2]. Syntheses of other furanocembranoids and fragments (+)-Lophotoxin (1) have been reported. However, a method to install epoxide C-7/8 in the correct configuration within the 14-membered macrocycle, and therefore a synthesis of (+)-Lophotoxin (1), remains elusive.



Our approach is based on dihydroxylation followed by two epoxidation reactions of intermediate 2. Ring-closing metathesis (RCM), macrolactonisation and cross-coupling are the main disconnections leading back to coupling partners 3 and 4. Applying an RCM based furan methodology developed by our group [5], we synthesized fragments 3 and 4 on gram-scale. The stereocenter C-13 is successfully installed by means of an asymmetric BAYLIS-HILLMAN reaction.

[1] W. Fenical, R. K. Okuda, M. M. Bandurraga, P. Culver, R. S. Jacobs, *Science* **1981**, *212*, 1512–1514.

[2] S. N. Abramson, W. Fenical, P. Taylor, *Drug Dev. Res.* **1991**, *24*, 297–312.

[3] N. Toelle, H. Weinstabl, T. Gaich, J. Mulzer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3859–3862.

[4] K. McAulay, J. S. Clark, *Chem. Eur. J.* **2017**, *23*, 9761–9765.

[5] T. J. Donohoe, J. F. Bower, J. A. Basutto, *Nat. Protoc.* **2010**, *5*, 2005-2010.