TOTAL SYNTHESIS OF CALLYSPONGIOLIDE

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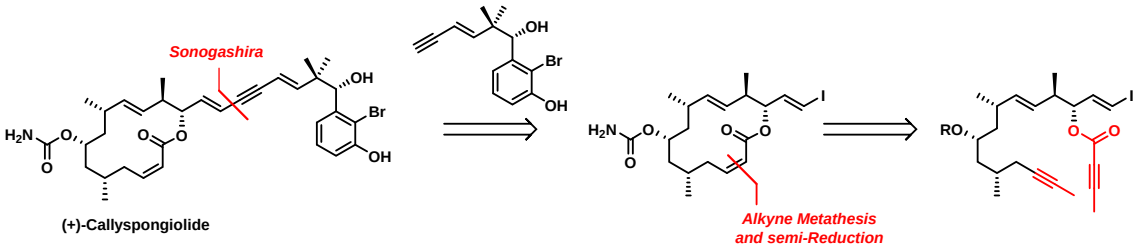
Callyspongiolide was isolated in 2014 from the marine sponge *Callyspongia* sp. The macrolide displays potent cytotoxicity against human lymphocytes and thus represents a potential lead compound for the development of new anticancer agents. A total synthesis of this molecule would not only provide more material for further clinical studies, but also an evaluation of the stereochemical assignment.[1]

Previous approaches towards callyspongiolide, comprising of late-stage *trans*-hydroelementation failed due to steric bias, as such a novel synthetic approach based on ring closing alkyne metathesis (RCAM) of a ynoate derivative was developed.[2] This strategy bore considerable risk as there are only few recorded examples of RCAM on simple ynoates.[3] Highlighting the performance of the latest generation of molybdenum-based catalysts, this total synthesis illustrates the first example of a RCAM on a highly complex ynoate. Another key-step of the devised synthesis was the subsequent *Z*-selective semi-reduction of the resulting ring-internal alkyne. An optimized nickelboride-catalyzed hydrogenation ensured the efficient reduction of the alkyne, tolerating alkene and vinyl iodide functionalities. Finally, *via* Sonogashira reaction the unique enyne side-chain was installed, concluding the efficient total synthesis of (+)-callyspongiolide in 20 steps and 4 % overall yield.



Scheme 1: Retrosynthetic analysis of (+)-callyspongiolide

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[1] C.-D. Pham, R. Hartmann, P. Böhler, B. Stork, S. Wesselborg, W. Lin, D. Lai, P. Proksch, *Org. Lett.* **2014**, *16*, 266-269.

[2] a) B. Wölfl, G. Mata, A. Fürstner, *Chem. Eur. J.* **2019**, *25*, 255-259; b) G. Mata, B. Wölfl, A. Fürstner, *Chem. Eur. J.* **2019**, *25*, 246-254.

[3] a) P. Persich, J. Llaveria, R. Lhermet, T. de Haro, R. Stade, A. Kondoh, A. Fürstner, *Chem. Eur. J.* **2013**, *19*, 13047-13058; b) S. Schaubach, K. Michigami, A. Fürstner, Synthesis **2017**, *49*, 202-208.