STEREOSELECTIVE AND MODULAR ASSEMBLY METHOD FOR DAUCANE, CYATHANE AND TIGLIANE TERPENOID SCAFFOLDS

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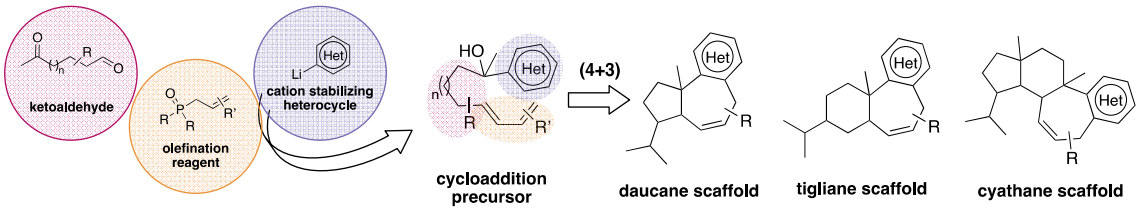
Terpene natural products play an important role in drug discovery and development, since these secondary metabolites are made and tailored by Nature with the purpose to interact with proteins. It has been observed that their intrinsic biological activity is higher than randomly assembled flat molecules.[1] However, terpenes possess an incredibly complex carbon skeleton, where stereochemistry and oxygenations play an important role for the biological activity. Employing total synthesis to obtain these exact natural products for drug discovery and development is a lengthy and laborious task. In our research group we synthesize terpene scaffolds containing a seven-membered ring in a modular, fast and efficient way via a (4+3) cycloaddition between a heterocyclyl cation and a 1,3-diene.[2,3]



In this work, a stereoselective synthetic method is developed for the carbon skeleton found in the common (iso)daucane and tigliane terpene natural products. This method gives access to these scaffolds, wherein the substitution pattern and stereochemistry can be adjusted by simply choosing different starting materials. The different heterocycles do not only create structurally versatile analogues, but also enable the key intramolecular (4+3) cycloaddition with control of stereochemistry and serve as synthetic handles for further derivatization.[4] This strategy was also recently expanded to the enantioselective synthesis of the full cyathane scaffold.

[1] H. van Hattum, H. Waldmann, *J. Am. Chem. Soc.* **2014**, *136*, 11853–11859.

[2] J. M. Winne, S. Catak, M. Waroquier, V. Van Speybroeck, *Angew. Chemie Int. Ed.* **2011**, *50*, 11990–11993.

[3] J. Hullaert, B. Denoo, Mien Christiaens, B. Callebaut, J. M. Winne, *Synlett* **2017**, *28*, 2345–2352.

[4] Mien Christiaens, J. Hullaert, K. Van Hecke, D. Laplace, J. M. Winne, *Chem. - A Eur. J.* **2018**, *24*, 13783–13787.