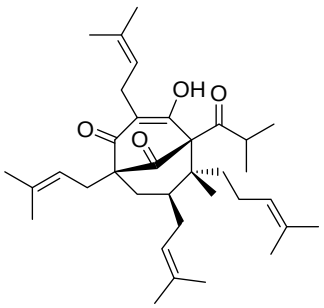
ENANTIOSELECTIVE SYNTHESIS OF HYPERFORIN

Sebastian Frey, Johann Jauch*

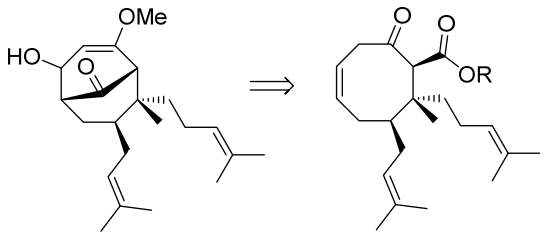
Organic Chemistry II, Saarland University, Saarbrücken, Germany

Polycyclic Polyprenylated Acylphloroglucinols (PPAPs), represented by the most famous molecule in the PPAP family, Hyperforin (**1**), are a group of synthetically challenging natural products exhibiting a broad range of biological activities [1].



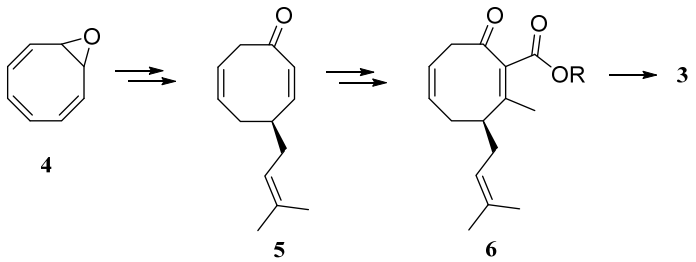
1

In contrast to the present approaches synthesizing the bicyclic PPAP core based on a substituted cyclohexanone derivative [2], our investigation is aimed at building the bicyclo[3.3.1]nonanone by transannular acylation of a highly substituted cyclooctenone **3** via a mixed anhydride [3].



2 **3**

The required β-ketoester **3** is synthesized in only five steps. According to the work of Pineschi *et al.* cyclooctatetraene mono-epoxide (**4**) is opened by copper-catalyzed asymmetric allylic alkylation using prenyl magnesium bromide in presence of a chiral phosphorous ligand [4]. After an [1,5]-H-shift the obtained α,β-unsaturated ketone **5** is further processed into the double activated Michael acceptor **6** via conjugate addition/acylation-cascade followed by recovery of the double bond. Copper-catalyzed diastereoselective conjugate addition of **6** using homoprenyl magnesium bromide or bishomoprenyl zinc provides the desired β-ketoester **3**.



4 **5** **6**

[1] R. Ciochina, R. B. Grossman, *Chem. Rev.* **2006**, *106*, 3963-3986.

[2] X.-W. Yang, R. B. Grossman, G. Xu, *Chem. Rev.* **2018**, *118*, 3508-3558.

[3] S. Schmitt, E. Feidt, D. Hartmann, V. Huch, J. Jauch, *Synlett* **2014**, *25*, 2025-2029.

[4] F. Del Moro, P. Crotti, V. Di Bussolo, F. Macchia, M. Pineschi, *Org. Lett.* **2003**, *5*, 1971-1974.