ENANTIOSELECTIVE SYNTHESIS OF HYPERFORIN

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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].

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].

The required β-ketoester 3 is synthesized in only five steps. According to the work of Pineschi et al. cyclooctatetraene monoepoxide (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.