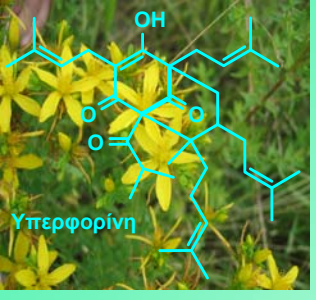

Design and Synthesis of Novel Hyperforin Analogues – Fascinating skeletal rearrangements of polycyclic polyprenylated acylphloroglucinols core

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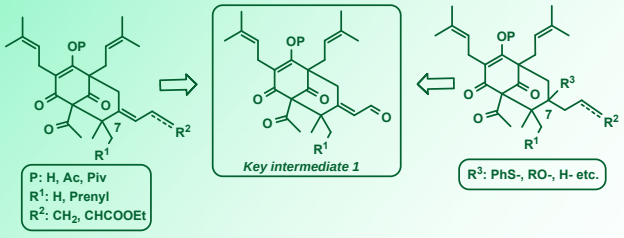
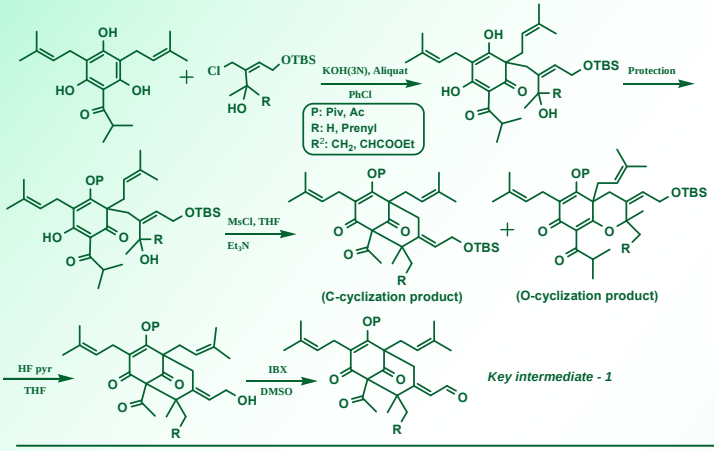
Hyperforin, the most known member of this family, has been isolated from *Hypericum perforatum* (St. Johns's wort), known for its antidepressant and anticancer properties. There is a big interest in synthesizing Hyperforin's analogues in order to improve the molecule's activity.[1,3] Up-to-date analogues showing highest biological activity possess an enol hydroxyl free [3g-i]. Based on this literature background, our efforts focus on the design and synthesis of new analogues with improved properties. In our lab, a new short biomimetic approach has been developed leading to the fully functionalized bicyclic core of type A acylphloroglucinols, including Hyperforin.[2] Based on this strategy we targeted in two classes of compounds possessing either an sp^2- or an sp^3-carbon on C-7, starting from key intermediate **1** (Scheme 1). A general route leading to **1** is depicted on Scheme 2. Approaches to sp^2 C-7 analogues including either Wittig on Ac-**1** (Approach I, Scheme 3) or deprotection after Wittig on Pv-**1** led to no desirable results (Approach II). Thus, approach III was attempted, based on establishing the desirable side chain functionalization before alkylation step. It is interesting that attempting to saturate C-7 of compound **1**, via Michael addition , an unprecedented skeletal rearrangement to a 6,5-bicyclic ring system was observed. Thus, deacetylation of aldehyde Ac-**1**, led to analogue **2**, which after Michael afforded sp^3 C-7 analogue **3** (Scheme 4), whose structure was confirmed by X-ray analysis . Derivatives **4** and **5** were also prepared. Biological activity results obtained from our first derivatives will lead our design to a new generation of hyperforin analogues. Moreover, our efforts focus on the improvement of efficiency of our methodology.

Scheme 1. Retrosynthetic Scheme



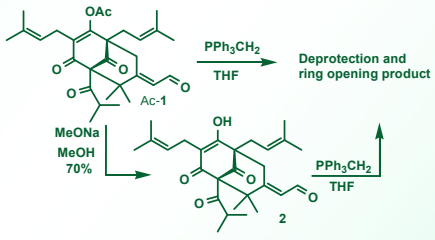
Scheme 2. General synthetic scheme of Hyperforin's analogues



Scheme 3. Attempts to synthesize sp^2 C-7 analogues

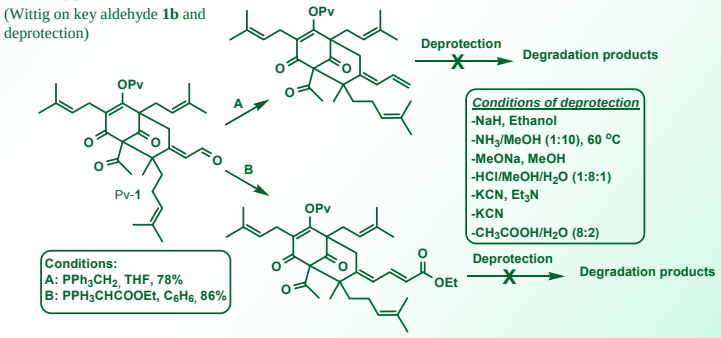
Approach I

(direct Wittig on key aldehyde **1**)

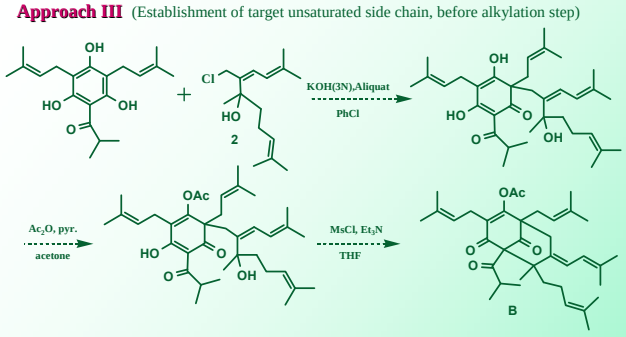


Approach II

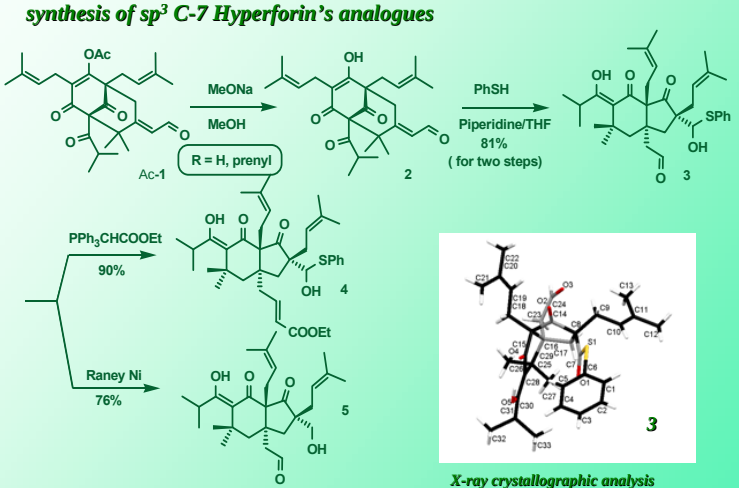
(Wittig on key aldehyde **1b** and deprotection)



Approach III (Establishment of target unsaturated side chain, before alkylation step)



Scheme 4. An interesting skeleton rearrangement observed, attempting synthesis of sp^3 C-7 Hyperforin's analogues



X-ray crystallographic analysis

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