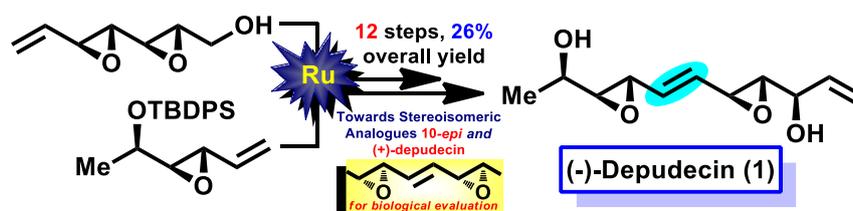


# Total Synthesis of Depudecin and Analogues via an Olefin Cross-Metathesis Based Strategy

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(-)-Depudecin (**1**), isolated from the culture broths of the fungus *Alternaria brassicicola* [1], has been identified as a selective inhibitor of histone deacetylases (HDAC) with an IC<sub>50</sub> in the low  $\mu\text{M}$  range. In contrast to representative HDAC inhibitors, depudecin represents a unique inhibitor of these enzymes by virtue of its molecular structure, featuring the presence of two oxirane rings separated by a *trans* double bond. Originally discovered as part of a biological screen directed towards the identification of antitumour agents with detransforming activity [2], depudecin was identified as a bioactive metabolite capable of reverting the transformed morphology of tumor cells. Depudecin induced cell cycle arrest and cellular differentiation [3], and also exhibited anti-angiogenesis activity [4]. Prompted by its striking biological properties and enticing structure, we decided to initiate a research program directed towards the synthesis of natural depudecin which has recently culminated with a linear total synthesis [5]. In order to develop an improved access to natural depudecin and analogues for further biological screenings, we explored a synthetic alternative as a shorter and more convergent approach. In this communication we report a new total synthesis of the natural product (-)-depudecin. A key feature of the synthesis is the utilization of an olefin cross-metathesis strategy, which provides for an efficient and improved access to natural depudecin. This strategy was applied to the preparation of the 10-*epi* and (+)-depudecin, which represent interesting stereoisomeric analogues for SAR studies.



**Scheme 1.** Structure of (-)-Depudecin and Olefin Cross-Metathesis Strategy.

**Acknowledgments:** I.C.-S. thanks the Ministerio de Educación, Cultura y Deporte for a predoctoral fellowship (FPU Programme).

Literature:

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