SYNTHESIS AND BIOLOGICAL EVALUATION OF DEPUDECIN ANALOGUES

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(-)-Depudecin (**1**) (Figure 1), isolated from the culture broths of the fungus *Alternaria brassicicola*,[1] and later, from the weed pathogen *Nimbya scirpicola*,[2] has been identified as a selective inhibitor of histone deacetylases (HDAC) with an IC_{50} in the low μM range.[3] 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 screening directed towards the identification of antitumour agents with detransforming activity,[4] depudecin was identified as a bioactive metabolite capable of reverting the transformed morphology of tumor cells. This biological activity elicited a great biomedical and biological interest by virtue of its potential as an antitumor agent as well as for further understanding the biological roles of HDACs. Depudecin induced not only morphological changes but also cell cycle arrest and cellular differentiation,[5] and also exhibited remarkable anti-angiogenesis activity.[6] Prompted by its striking biological properties and enticing structure, we decided to initiate a research program directed towards the synthesis of natural depudecin. Our synthetic plan has recently culminated with linear and convergent total syntheses.[7]

Now, we have synthesized an array of depudecin analogues, including truncated and stereoisomeric analogues. With the aim to explore their biological activity, we have performed preliminary biological evaluations, which consisted of the measurement of the antitumor properties of the generated analogues against a panel of various tumor cell lines, including the human promyelocytic leukemia (HL60), human breast adenocarcinoma (MDA-MB-231), human fibrosarcoma (HT1080) and gioblastoma (U87MG), as well as a primary culture of nontransformed bovine aorta endothelial (BAEC) cells, which may indicate a putative antiangiogenic effect.[8] In this communication we report the synthesis and biological activity of an array of depudecin analogues which led us to a structure-activity relationship (SAR) study of this intriguing natural product.

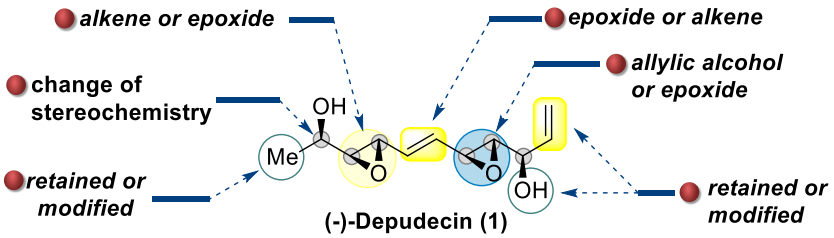

Figure 1. Structure of (-)-Depudecin and Proposed Analogues for SAR study.

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