FRESNO STATE
Chemistry

Chemistry Department Seminar Series

Synthesis Toward a Macrocyclic Ketone Mimic of Zampanolide

by

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Thesis Presentation
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Abstract

(-)-Zampanolide is a medicinally and structurally intriguing macrolide originated from marine sponge. Zampanolide exhibits nanomolar antiproliferative activity against both drug-sensitive and multidrug-resistant cancer cells. However, the natural scarcity and the challenging total synthesis of zampanolide have restricted the supply for in vivo study. We also envision that the lactone moiety of zampanolide is metabolically vulnerable in vivo which has been exemplified by halichondrin B. Therefore, this thesis aims to synthesize a desTHP macrocyclic ketone mimic of zampanolide with a metabolically stable and synthetically simplified structure. Towards this end, two generations of total syntheses have been attempted. In the first-generation synthesis, the crucial carbon bridge C17-C-C1C2 has been constructed through a critical Grignard reaction. A key intermediate C13-C18 branched C17-C-C1-C8 was achieved through a 14-step transformation. The difficulty in forming the ether motif in the first-generation synthesis was overcome in the second-generation synthesis through a Williamson ether synthesis. Fragment C9-C18 was incorporated into Fragment C1-C8 through a critical Grignard reaction. So far, we have achieved a highly advanced key intermediate C9-C18 branched C17-C-C1-C8 (53) via 15 linear steps synthesis (24 steps in total). Only two steps remained to accomplish the core structure of the zampanolide ketone mimic.

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