Synthesis of Analogs of (–)-Zampanolide & Structure-Activity Relationship Studies

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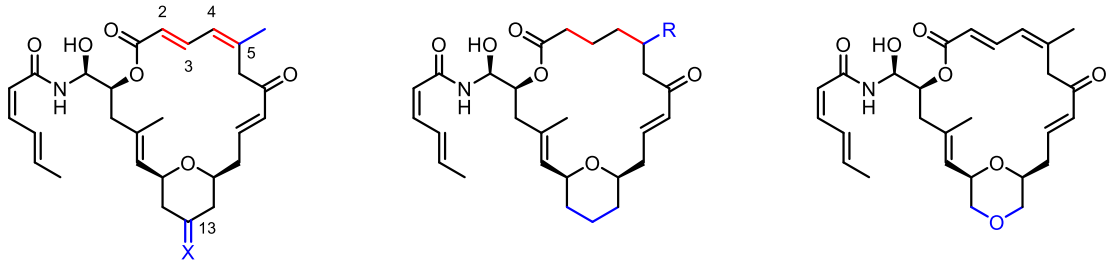
(–)-Zampanolide (**1**) is a complex marine macrolide that was first isolated from the sponge *Fasciospongia rimosa* in 1996 by *Tanaka* & *Higa* and found to exhibit nanomolar *in vitro* antiproliferative activity against a range of human cancer cell lines.[1]



The compound was subsequently shown to be a microtubule-stabilizing agent which, as the only potent microtubule stabilizer known, binds to β-tubulin in a covalent fashion.[2] (–)-Zampanolide (**1**) has been the target of several total synthesis campaigns,[3-7] including a synthesis developed in our own laboratory that is based on macrocycle formation by intramolecular HWE reaction.[8]

Our group has recently reported the fully stereoselective total synthesis of C(13)-desmethylene-(–)-zampanolide (**2**).[9] C(13)-Desmethylene-(–)-zampanolide (**2**) was found to be at least equipotent with natural **1**. Therefore, it has served as a more readily accessible template for SAR studies that aimed to address the importance of the various double bonds in the macrolactone ring and of the C(5) and C(17) methyl groups. This presentation will describe the synthesis of a new analog of **1** with a fully saturated C(1)–C(5) domain (**3**) and itsC(5)-desmethyl variant (**4**), their binding to microtubules and their cellular activity. In addition, the synthesis and biological characterization of the dioxane analog (**5**) will be discussed.

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