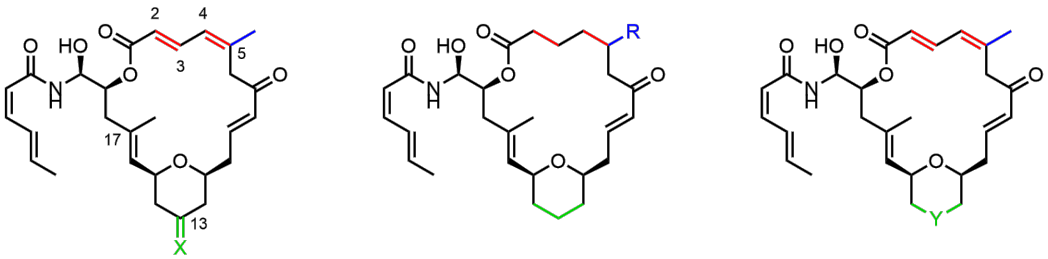
Synthesis of Analogs of (−)-Zampanolide and Structure-Activity Relationship Studies

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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, of the C(5) & C(17) methyl groups[10] and of the atom at position 13. This presentation will describe the synthesis of new analogs of **1**: with a fully saturated C(1) – C(5) domain (**3**), its C(5)-desmethyl variant (**4**)[10] and three analogs where carbon 13 is substituted by either oxygen (**5**) or sulfur (**6**) and its oxidized sulfone analog (**7**). In addition, their binding to microtubules and their cellular activity will be discussed.[10]

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