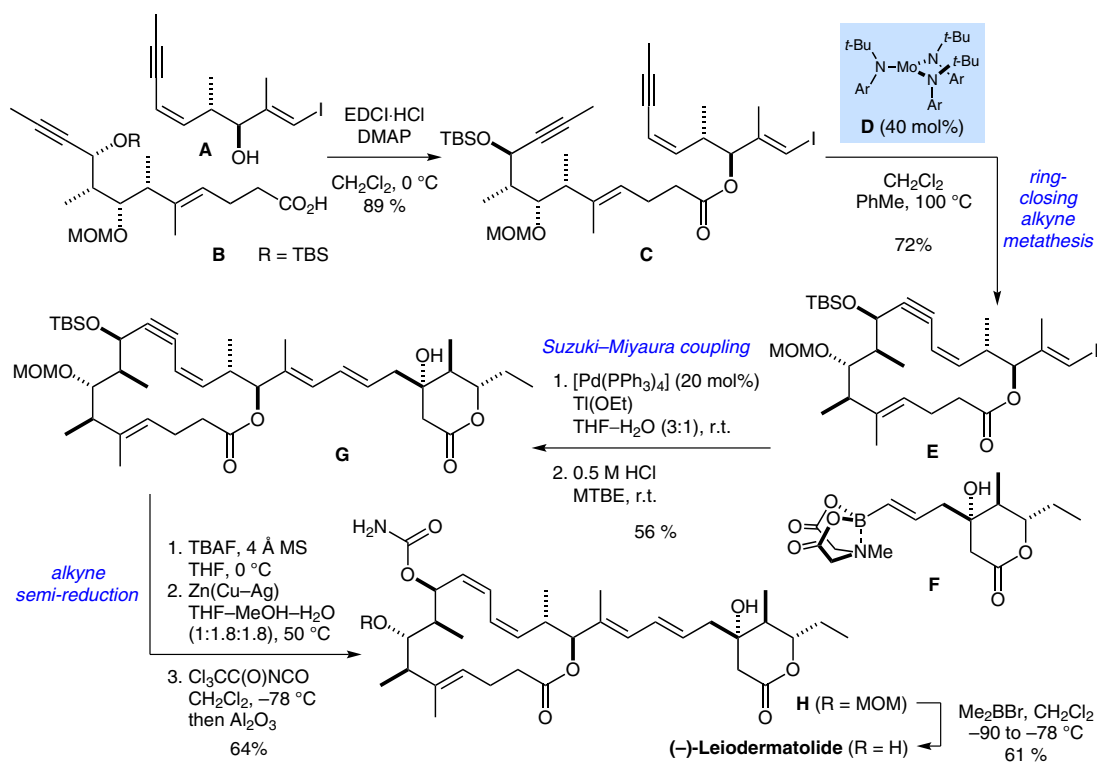


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Divergent Total Synthesis of the Antimitotic Agent Leiodermatolide
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Synthesis of (-)-Leiodermatolide



Significance: Leiodermatolide is an antimitotic macrolide isolated in 2011 from the deep-water sponge *Leiodermatium sp.* that exhibited potent and selective in vitro cytotoxicity against various human cancer cell lines (IC₅₀ < 10 nM). Although the natural product was shown to induce cell cycle arrest at the G2/M transition, it had no effect on purified tubulin, indicating a novel mode of action. In addition to the promising biological activity, leiodermatolide posed an interesting target for synthetic studies, as the segregated stereo-clusters within the macrolactone and the δ-lactone terminus could not be assigned unambiguously.

Comment: In order to address this issue, a strategy was chosen, in which the δ-lactone subunit **F** was merged with macrocycle **E** at a late stage of the synthesis, granting access to either conceivable diastereomer of the target. The assembly commenced with esterification of **A** and **B**, giving diyne **C**, which underwent efficient cyclization using molybdenum complex **D** as a catalyst precursor. Suzuki-Miyaura coupling of vinyl iodide **E** and boronate **F** gave intermediate **G**, which was advanced to leiodermatolide in four further steps, including Zn(Cu-Ag)-mediated enyne semi-reduction to the corresponding *Z,Z*-configured diene. Subtle differences in the ¹H NMR data of the respective isomers allowed for a conclusive stereochemical assignment of the natural product.

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