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 (IC$_{50}$ < 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 vinyliodide 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 $^{1}$H NMR data of the respective isomers allowed for a conclusive stereochemical assignment of the natural product.