Total Synthesis of (+)-Cavicularin

Significance: (+)-Cavicularin, isolated from the liverwort Cavicularia densa, is a chiral cyclophane natural product. Because of its unusual molecular structure, several total syntheses have been reported to date. Zhao and Beaudry report a conceptionally different approach, which relies on an intramolecular enantioselective pyrone Diels–Alder reaction with subsequent CO₂ extrusion to generate the aromatic A ring of the natural product.

Comment: The synthesis commences with a remarkably selective one-pot three-component Suzuki cross-coupling of dibromide B and boronic esters A and C. Coupling product D was further advanced to α-hydroxy pyrone E. In the presence of cinchona alkaloid F, this material underwent the desired Diels–Alder reaction to yield intermediate G, which immediately eliminated CO₂ and phenylsulfinic acid to generate H as a single regioisomer. Finally, reduction and protecting group removal yielded (+)-cavicularin in 7.3% overall yield.