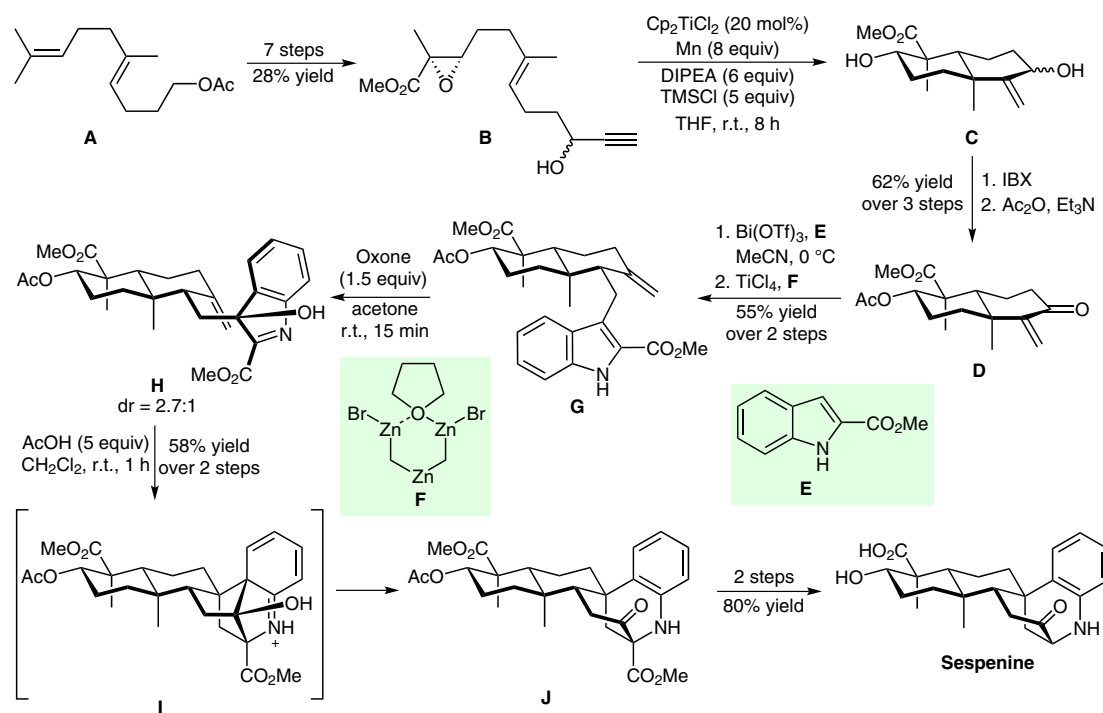


Total Synthesis of Sespentine



Significance: Sespentine is a rare and architecturally complex indole sesquiterpenoid that was isolated from an endophyte in 2011. Biosynthetically, sespentine may be formed from a structurally simpler indole precursor by oxidation of the indole C3 position followed by a cationic cascade involving an aza-Prins/Friedel–Crafts reaction and a subsequent fragmentation. Ang Li and co-workers now report the first total synthesis of sespentine. Their strategy relies on a titanium-mediated radical cascade for quick access to a key intermediate and an elegant implementation of the cationic cascade described above.

Comment: The synthesis commences with acetate **A**, which is converted into α,β -epoxy ester **B** in seven steps. Titanium(III)-mediated radical cyclization of **B** furnishes allylic alcohol **C**, which is oxidized and protected to give enone **D**. Key intermediate **G** is prepared via 1,4-addition of indole **E** and Nysted olefination using reagent **F**. Oxidation of **G** with Oxone affords **H** as a 2.7:1 mixture of epimers. The major and desired product undergoes the crucial sequence of aza-Prins/Friedel–Crafts reaction and fragmentation to give **J**, presumably via the intermediacy of **I**. Two additional steps then complete the synthesis of sespentine.