Total Synthesis of Sespenine

Significance: Sespenine is a rare and architecturally complex indole sesquiterpenoid that was isolated from an endophyte in 2011. Biosynthetically, sespenine 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 sespenine. 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 $\alpha,\beta$-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 sespenine.