Y. SUN, P. CHEN, D. ZHANG, M. BAUNACH, C. HERTWECK, A. LI* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA AND LEIBNIZ INSTITUTE FOR NATURAL PRODUCT RESEARCH AND INFECTION BIOLOGY, JENA, GERMANY)

Bioinspired Total Synthesis of Sespenine

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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 $\bf A$, which is converted into α,β -epoxy ester $\bf B$ in seven steps. Titanium(III)-mediated radical cyclization of $\bf B$ furnishes allylic alcohol $\bf C$, which is oxidized and protected to give enone $\bf D$. Key intermediate $\bf G$ is prepared via 1,4-addition of indole $\bf E$ and Nysted olefination using reagent $\bf F$. Oxidation of $\bf G$ with Oxone affords $\bf H$ 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 $\bf J$, presumably via the intermediacy of $\bf I$. Two additional steps then complete the synthesis of sespenine.

 SYNFACTS Contributors: Erick M. Carreira, Simon Krautwald

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