Total Synthesis of Ascospiroketal A

Significance: Ascospiroketal A was isolated in 2007 from the marine fungus Ascochyta salicorniae. This natural product is characterized by a spiroketal that is part of a fused tricyclic system. While the relative configuration of the spirocyclic core could be elucidated by NOESY spectroscopy, no stereochemical information for the side chain could be obtained. Britton and co-workers present a synthetic strategy, which allowed not only for the efficient construction of the core fragment but also for a late-stage introduction of the contested side chain. Their efforts culminated not only in the first total synthesis of ascospiroketal A but also in the establishment of the C15-C2′-C3′ stereochemistry.

Comment: The synthesis commenced with the preparation of enantioenriched aldehyde D from hydroxyoxetane A. A diastereoselective aldol reaction with ketone F gave cyclization precursor G. Extending a method developed in their laboratory (Org. Lett. 2012, 14, 5844), Britton and co-workers exposed G to a combination of Ag2O and AgBF4. Ketal H is presumed to be formed first, followed by nucleophilic opening of the oxetane, yielding a 1:1 mixture of I and J. The complete diastereoselective oxetane opening might be attributed to the chelation of silver(I). Notably, the undesired isomer I could be epimerized to J. After several isomeric side chains were attached, the authors found that ascospiroketal A possesses the configuration as depicted above.