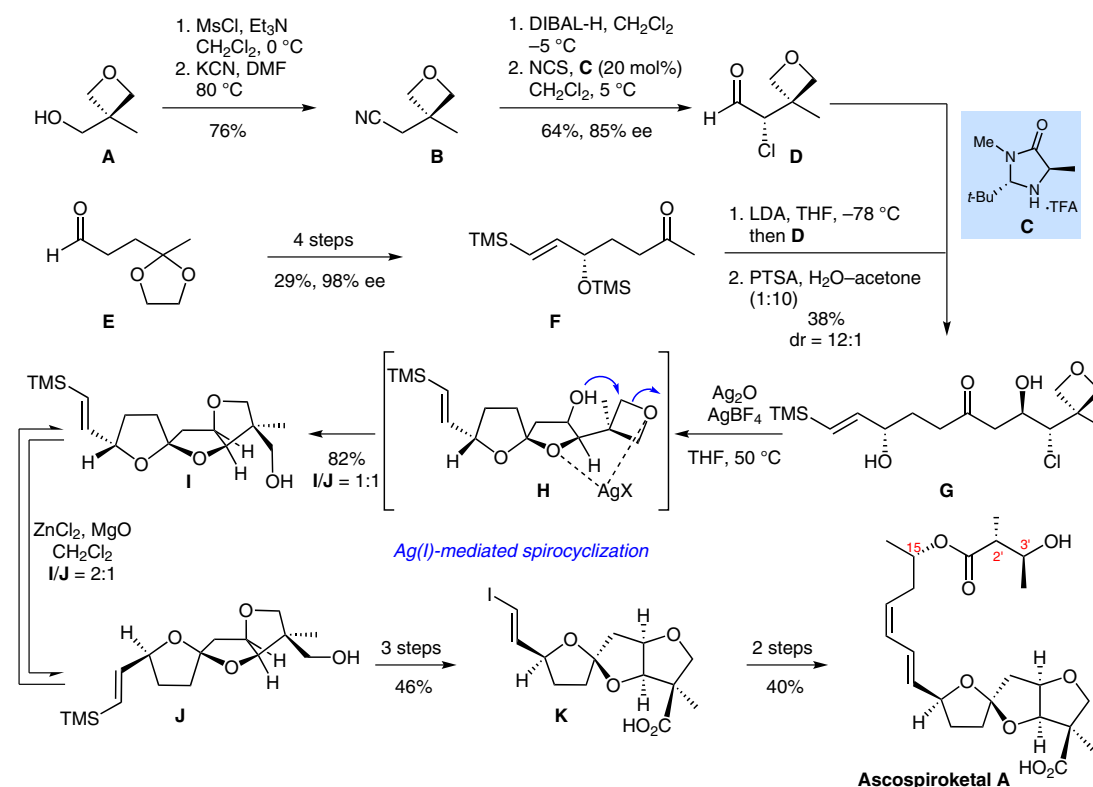


Total Synthesis of Ascospiroketal A



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.