

## Studies on Enantioselective Total Synthesis of (+)-Ophiobolin A

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(+)-Ophiobolin A was first isolated as a metabolite from the culture broth of the pathogenic plant fungus *Ophiobolus Miyabeanus*, and elucidation of its absolute structure identified it as the first naturally occurring sesterterpene. (+)-Ophiobolin A shows a broad spectrum of bioactivity against nematodes, fungi, and bacteria, and recent studies disclosed that (+)-ophiobolin A shows cytotoxicity toward the various cancer cell-lines. (+)-Ophiobolin A possesses eight stereogenic centers on the unique tetracyclic 5-8-5-5 ring system including a spirocyclic ether. The five-membered A-ring incorporates three successive stereogenic centers including a chiral tertiary alcohol and two contiguous stereogenic centers at the *cis*-fused AB-ring junction. The CD-ring is a spirocyclic ether, possessing a total of five stereogenic centers, four of which are successive, as well as a quaternary stereogenic center at the *trans*-fused BC-ring junction. The potent bioactivities as well as the complex structure make (+)-ophiobolin A an attractive synthetic target.

Our synthesis commenced with construction of the challenging spirocyclic CD-ring moiety. After several attempts, the spirocyclic CD-ring moiety possessing the correct C10 and C14 stereochemistry was successfully constructed via a Lewis acid promoted intramolecular Hosomi-Sakurai reaction of the hemiketal, which was prepared by the coupling of the iodide with the lactone in a convergent manner. The CD-ring moiety was assembled with A-ring fragment by Reformatsky-type reaction to provide a  $\beta$ -hydroxyketone, followed by dehydration to afford an  $\alpha,\beta$ -unsaturated ketone. Raney Ni catalyzed hydrogenation of the  $\alpha,\beta$ -unsaturated ketone and subsequent reaction with MeLi provided a tertiary alcohol with high selectivity (C2=35/1, C3=single isomer), establishing all the stereogenic centers in (+)-ophiobolin A. Further studies toward the enantioselective total synthesis of (+)-ophiobolin A is now in progress.