Synthesis of (–)-Longeracinphyllin A

Significance: Alkaloid natural products isolated from leaves and roots of the Daphniphyllum genus of plants are widely used in Chinese herbal medicine. The first and asymmetric total synthesis of (–)-longeracinphyllin A, a member of this structurally complex family of natural products, was accomplished by Li and co-workers. The significance of the approach chosen by the authors lies in the rapid construction of intermediate D and assembly of structurally advanced tetracycle F in large quantities. This enables elegant completion of the highly challenging target by [3+2] cycloaddition in just 21 synthetic steps.

Comment: Borrowing from their previously established route for a related natural product (Nat. Chem. 2013, 5, 679), the authors gained expedient entry to the core of the target from abundant precursor C by silver-catalyzed 6-exo-dig cyclization, intramolecular conjugate addition, and asymmetric olefin hydrogenation. Acquisition of enone G proved crucial as this electron-deficient substrate was found to undergo diphosphine-promoted [3+2] cycloaddition with allenoate H, while other olefins would not react. The pentacyclic lactam I was carried on forward to render (–)-longeracinphyllin A.