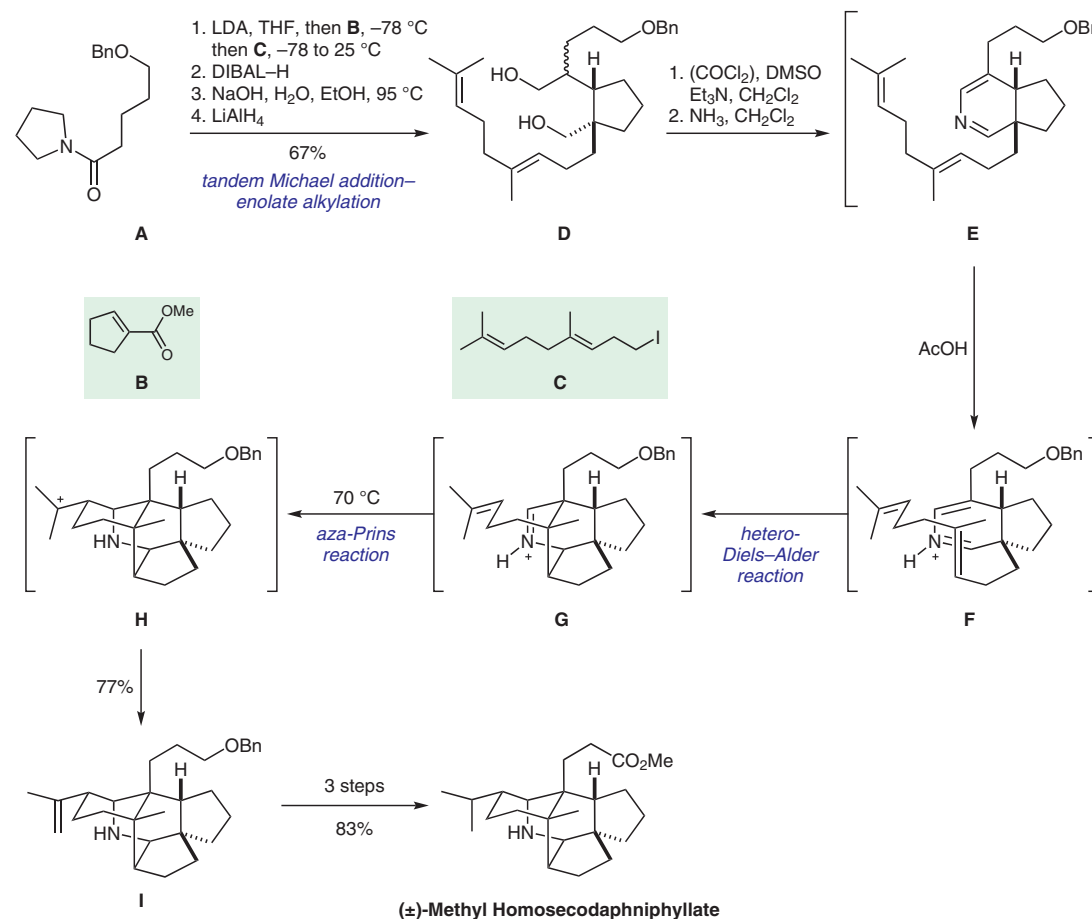


Total Synthesis of (±)-Methyl Homosecodaphniphyllate



Significance: A truly inspiring contribution to the development of tandem cyclization and bioinspired synthesis was made by Heathcock and co-workers in 1988. In this classic communication, the authors provide a striking example of an intramolecular hetero-Diels–Alder reaction and aza-Prins cyclization in the same pot and under mild conditions. The total synthesis proceeds in high yield and selectivity en route to (±)-methyl homosecodaphniphyllate, which ultimately proved accessible in only nine steps and 44% overall yield from simple precursors **A**, **B**, and **C**.

Comment: The authors commence their elegant route with a tandem Michael addition–enolate alkylation sequence followed by functional group interconversion, thereby obtaining diol **D** in high yield and selectivity. Condensation of the corresponding dialdehyde with ammonia afforded aza-diene **E** in two steps. Hetero-Diels–Alder reaction and aza-Prins cyclization afforded pentacyclic unsaturated amine **I** in a single operation. This advanced intermediate was converted into the target structure in three additional steps.