Synthesis of (±)-Modhephene

Significance: (±)-Modhephene is a sesquiterpene that was first isolated in 1978 from the leaves of the rayless goldenrod *Isocoma Wrightii*. It features a unique [3.3.3]propellane core which had not been observed in nature previously. In 1982, Wender and Dreyer reported the highly efficient seven-step synthesis of (±)-modhephene relying on a light-mediated arene–olefin cycloaddition. Additionally, they utilized a semibullvalene rearrangement to install two quaternary carbon centers in one step.

Comment: The synthesis commenced with the light-mediated cycloaddition of indane (A) and vinyl acetate (B) to give propellane C containing five stereocenters, two of which are quaternary, in a single step. Subsequent saponification and oxidation afforded ketone E. Treatment of E with an excess of base and methyl iodide afforded tris-alkylated ketone H. The authors propose that this transformation is enabled through the rapid interconversion of enolates F and G by a semibullvalene rearrangement. The fourth methyl group required for the synthesis of (±)-modhephene was introduced using a copper-mediated 1,5-addition followed by trapping of the transient enolate with phosphoric acid derivative I. Notably, this transformation afforded phosphordiamidate J as a single stereo- and regioisomer. Finally, reductive C–O bond cleavage and subsequent selective hydrogenation of the sterically less hindered double bond afforded (±)-modhephene in 93% yield over two steps.