P. A. WENDER*, G. B. DREYER (STANFORD UNIVERSITY AND HARVARD UNIVERSITY, CAMBRIDGE, USA)

Synthetic Studies on Arene–Olefin Cycloadditions. 4. Total Synthesis of (±)-Modhephene

J. Am. Chem. Soc. **1982**, *104*, 5805–5807.

Category

Synthesis of Natural Products and Potential Drugs

Key words

(±)-modhephene

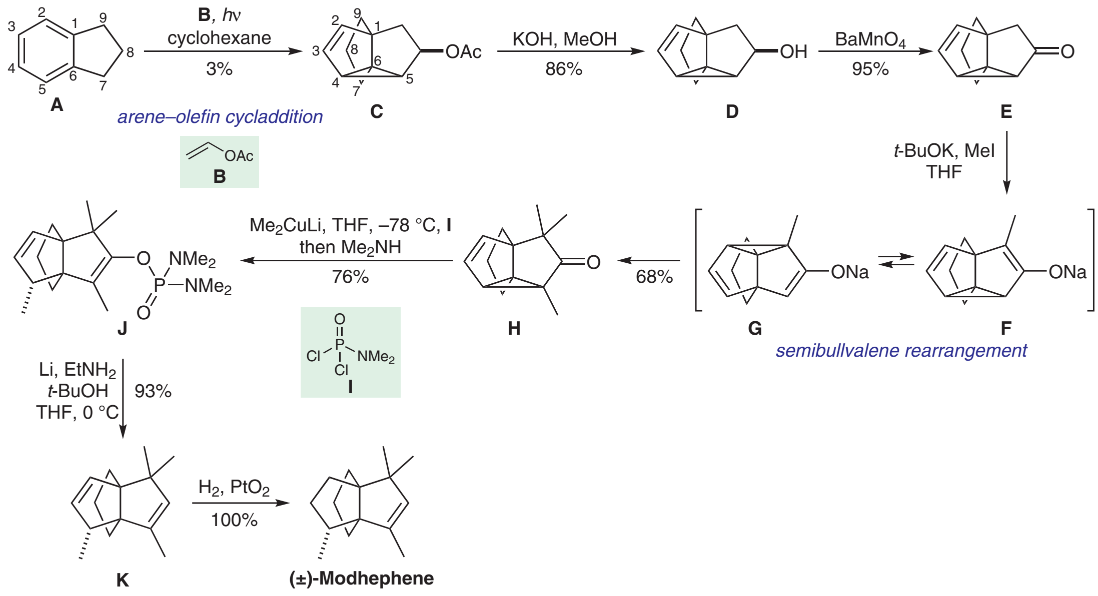
sesquiterpene

arene–olefin cycloaddition

semibullvalene rearrangement

1,5-addition

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** a 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.

SYNFACTS Contributors: Erick M. Carreira, Tobias Sandmeier
Synfacts 2019, 15(12), 1353

DOI: 10.1055/s-0039-1691076; **Reg-No.:** C07019SF

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany