R. L. FUNK, K. P. C. VOLLHARDT* (UNIVERSITY OF CALIFORNIA, BERKELEY, USA)

Transition-Metal-Catalyzed Alkyne Cyclizations. A Cobalt-Mediated Total Synthesis of *dl*-Estrone
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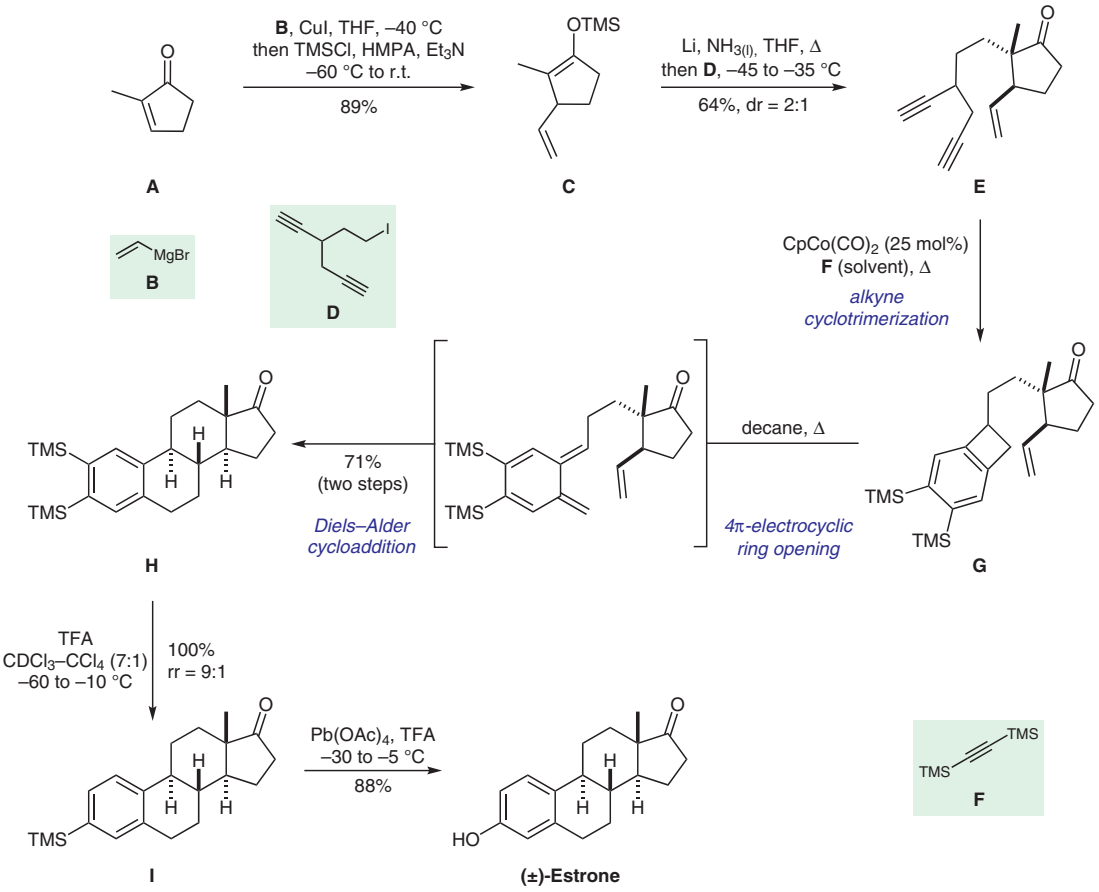
Synthesis of (±)-Estrone



Significance: (±)-Estrone, a naturally occurring hormone and agonist of estrogen receptors ERα and ERβ, was synthesized in 1979 by Funk and Vollhardt. The presented synthesis allows the stereoselective construction of the B and C steroidal rings in a single step through a thermally induced 4π electrocyclic ring opening of a benzocyclobutene, followed by an *exo*-Diels–Alder cycloaddition. Benzocyclobutene **G** was synthesized by cobalt-catalyzed cyclotrimerization of **E** and **F**. The application of this methodology combined with the evolved synthetic strategy allowed rapid access to intermediates en-route to oral contraceptives.

Comment: Vinyl cuprate addition to cyclopentenone **A** and subsequent trapping of the resulting enolate gave silyl enol ether **C** in 89% yield. Formation of the lithium enolate and alkylation with **D** afforded diyne **E**. Importantly, the *trans*-substituted cyclopentanone was formed as the major product. Cobalt-catalyzed cyclotrimerization of **E** with **F** gave benzocyclobutene **G** along with small quantities of tetracycle **H**. Heating **G** in decane afforded **H** in 71% combined yield over two steps. Subsequent proto- and oxidative-desilylation steps culminated in formation of (±)-estrone. Notably the synthesis proceeds in only six steps and 24% overall yield.

SYNFACTS Contributors: Erick M. Carreira, Robert J. Gillespie
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