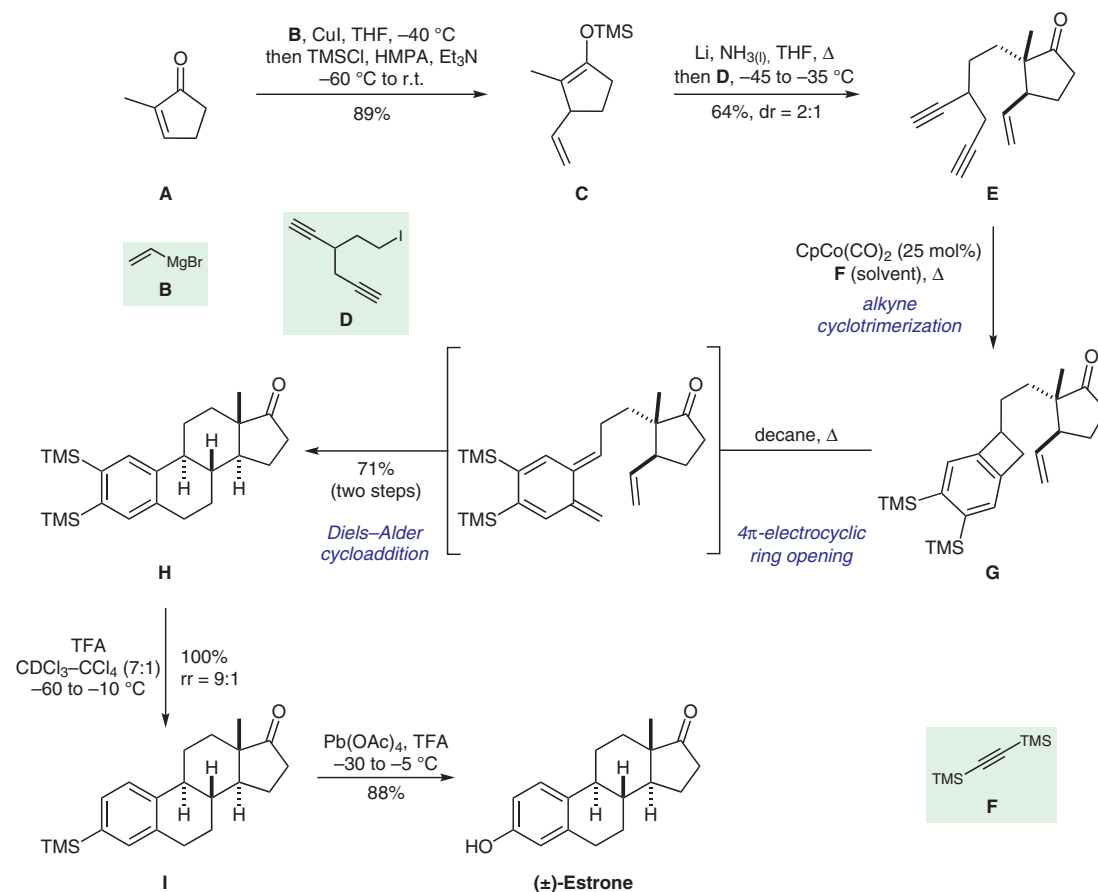


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Transition-Metal-Catalyzed Alkyne Cyclizations. A Cobalt-Mediated Total Synthesis of *dl*-Estrone
J. Am. Chem. Soc. **1980**, *102*, 5253–5261.

Synthesis of (±)-Estrone



Significance: (±)-Estrone, a naturally occurring hormone and agonist of estrogen receptors $\text{ER}\alpha$ and $\text{ER}\beta$, 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 proton and oxidative-desilylation steps culminated in formation of (±)-estrone. Notably the synthesis proceeds in only six steps and 24% overall yield.