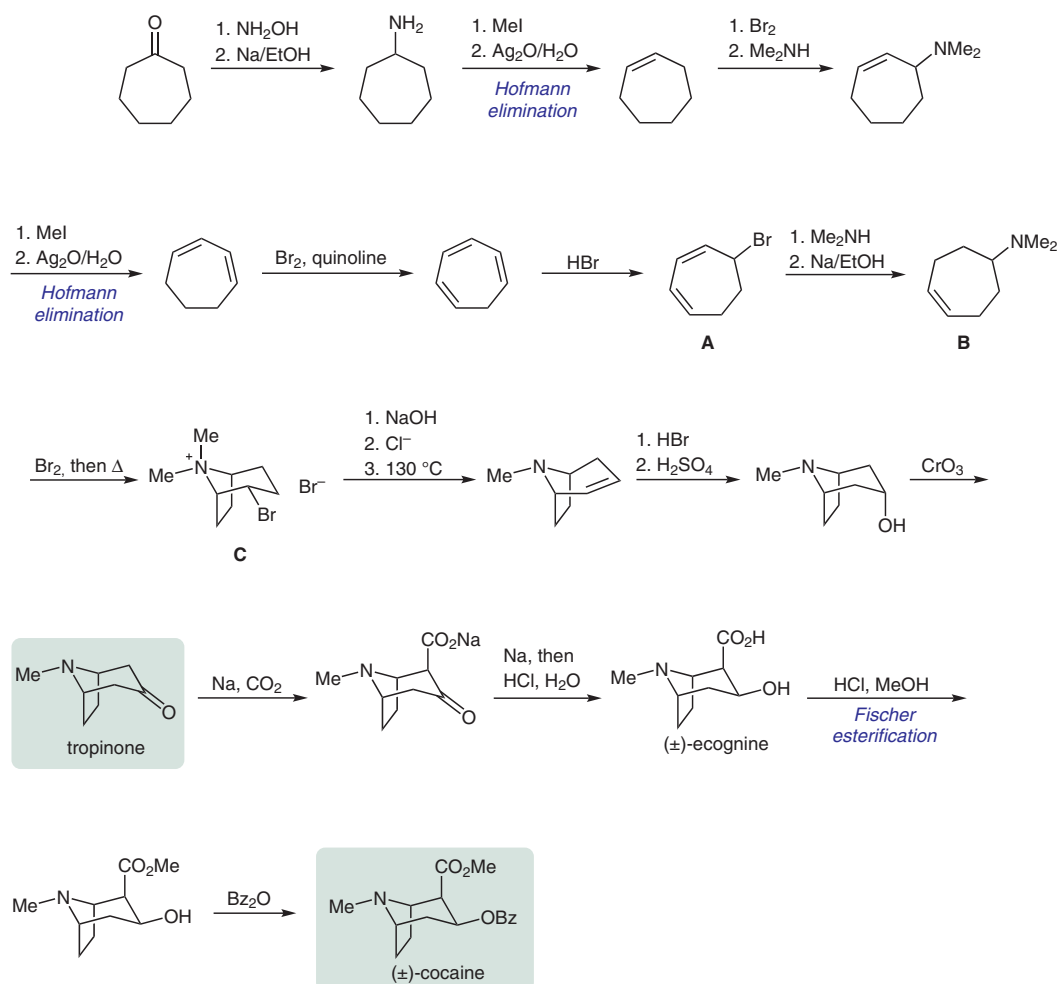


The First Total Synthesis of Cocaine



Significance: In 1901, Richard Willstätter and Adolf Bode reported one of the first *vollständige Synthese* (complete or total synthesis) of a complex natural product. In this seminal work, the authors began their synthesis from cycloheptanone and, in 23 linear steps, completed the synthesis of (±)-cocaine. The key step is a bromination followed by an intramolecular transannular S_N2 to form the tropane skeleton (*Chem. Ber.* **1901**, 34, 129).

Comment: Cycloheptanone was elaborated to allylic bromide **A**, which was reductively aminated to afford the precursor **B** to the tropane skeleton. The key intramolecular transannular S_N2 reaction was achieved upon exposure to Br₂ and the resulting salt **C** was further manipulated to complete the synthesis of tropinone. Finally, an α-carboxylation, dissolving metal reduction, Fischer esterification, and a benzylation afforded (±)-cocaine, to complete one of the first examples of a total synthesis.