

## The First Total Synthesis of Cocaine

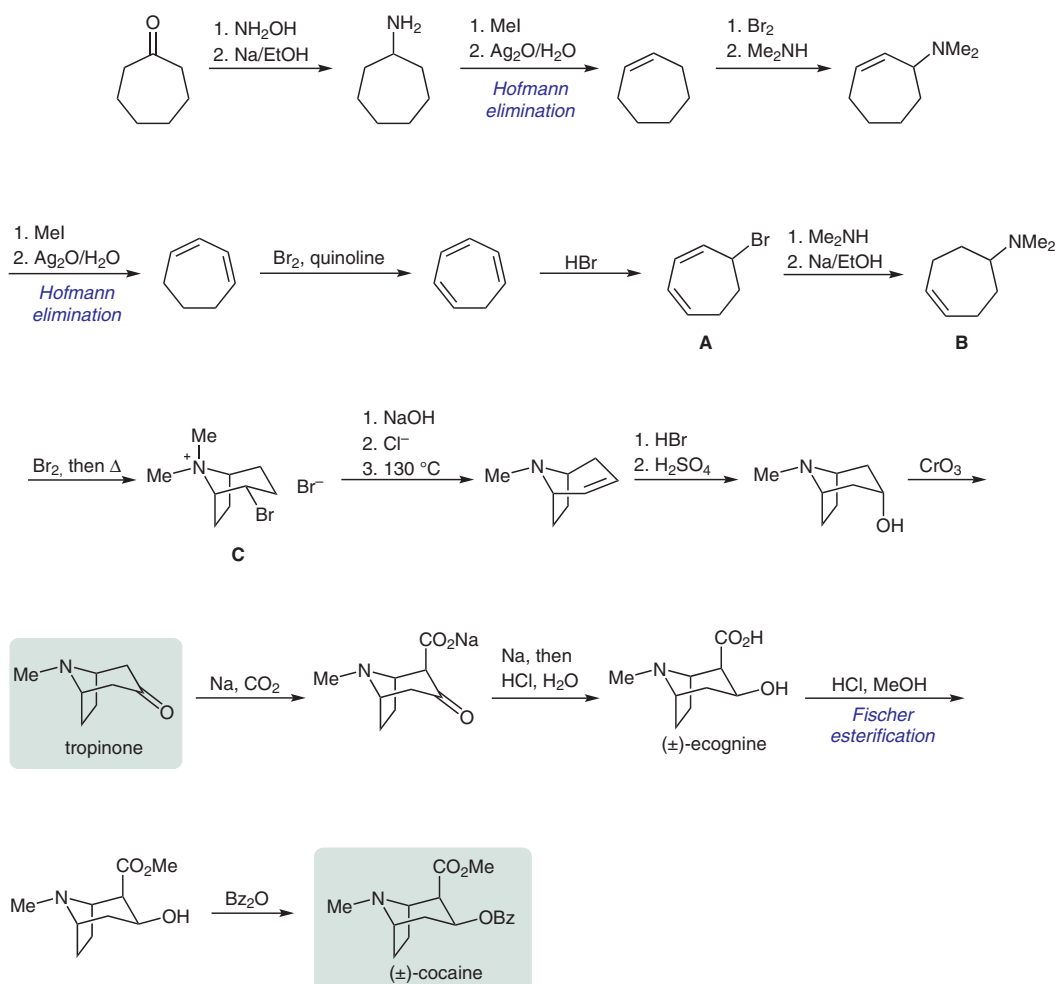
Category

Chemistry in  
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Key words

cocaine  
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Hofmann  
elimination

Synfact  
Classic



**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  $\text{S}_{\text{N}}2$  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  $\text{S}_{\text{N}}2$  reaction was achieved upon exposure to  $\text{Br}_2$  and the resulting salt **C** was further manipulated to complete the synthesis of tropinone. Finally, an  $\alpha$ -carboxylation, dissolving metal reduction, Fischer esterification, and a benzylation afforded (±)-cocaine, to complete one of the first examples of a total synthesis.