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 SN2 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 SN2 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 benzoylation afforded (+)-cocaine, to complete one of the first examples of a total synthesis.