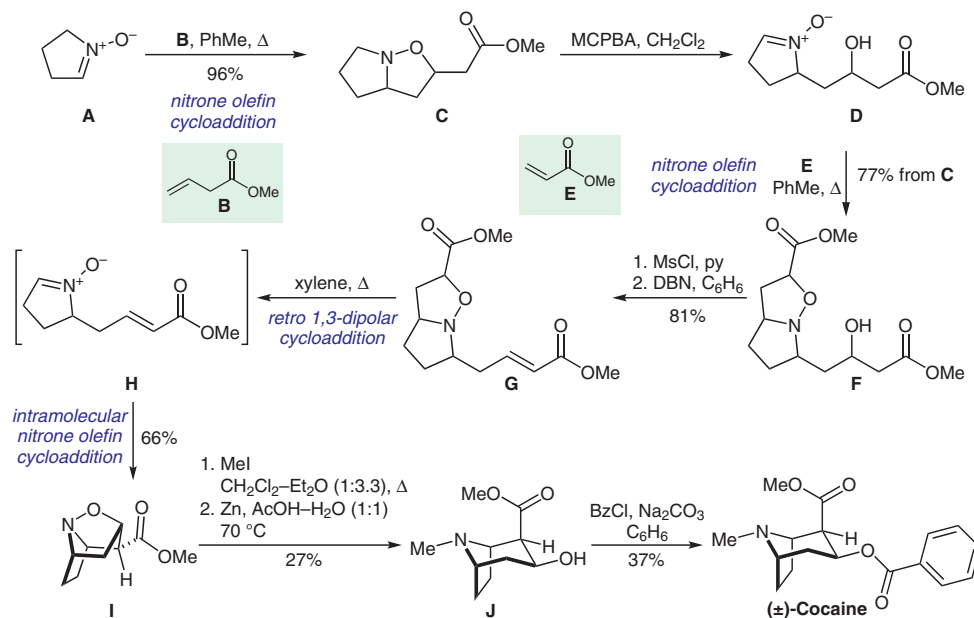


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A Synthesis of *dl*-Cocaine Using Nitron Intermediates*J. Am. Chem. Soc.* **1978**, *100*, 3638–3639.J. J. TUFARIELLO*, G. B. MULLEN, J. J. TEGELER, E. J. TRYBULSKI, S. C. WONG, S. A. ALI
(STATE UNIVERSITY OF NEW YORK AT BUFFALO, USA)Synthesis in the Tropane Class of Alkaloids. Pseudotropine and *dl*-Cocaine*J. Am. Chem. Soc.* **1979**, *101*, 2435–2442.

Synthesis of (±)-Cocaine



Significance: Cocaine is a tropane alkaloid isolated from the *erythroxylum coca* native to South America. It exhibits polypharmacology, including the inhibition of the dopamine transporter protein in the central nervous system. Reduced activity of this transmembrane protein leads to higher concentration of dopamine in the synaptic cleft which activates the brain's reward system and results in feelings of satisfaction and euphoria. Cocaine is used medicinally as a numbing agent for surgical procedures in the mouth or nose; however, it is notorious for its use as a recreational drug worldwide. Cocaine features a bicyclic 8-azabicyclo[3.2.1]octane core with an axial ester substituent. In 1978, Tufariello and co-workers reported the first stereoselective synthesis of cocaine. Previous synthetic approaches were hampered by limited control over the relative stereochemistry of the ester moiety, resulting predominantly in the thermodynamically favored equatorial epimer. Tufariello and co-workers addressed this challenge with a sequence of highly stereoselective nitron-olefin cycloadditions, affording the natural product as a single stereoisomer.

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Comment: The synthesis commenced with the dipolar cycloaddition of nitron **A** and olefin **B**, affording isoxazolidine **C** in 96% yield. Subsequent oxidation and elimination furnished nitron **D** as an inconsequential mixture of stereoisomers. Initial attempts to dehydrate **D** only resulted in the formation of polymeric materials. Thus, the nitron moiety was masked with methyl acrylate via a dipolar cycloaddition. Mesylation and elimination of the secondary alcohol cleanly furnished α,β -unsaturated ester **G**. Heating **G** in toluene initiated a retro 1,3-dipolar cycloaddition releasing methyl acrylate and the resulting intermediate nitron **H** underwent an intramolecular nitron-olefin cycloaddition to afford tricycle **I**. Notably, isoxazolidine **I** was isolated as a single diastereomer in 40% overall yield from **A**. Methylation followed by reductive N-O cleavage gave access to the bicyclic tropane core of cocaine. Finally, benzylation afforded the natural product.