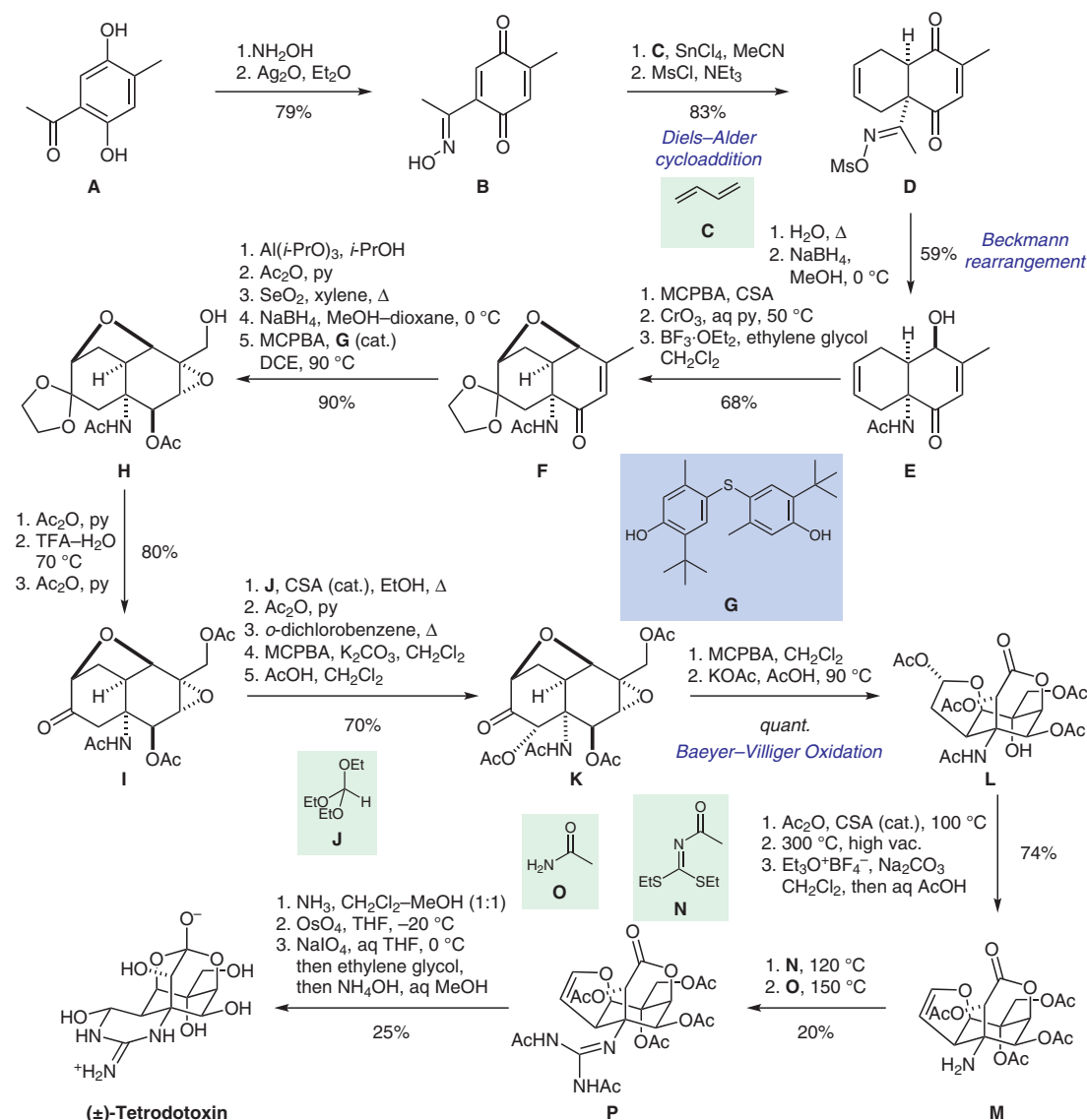


Synthesis of (±)-Tetrodotoxin



Significance: In 1972, Kishi and co-workers disclosed the first total synthesis of (±)-tetrodotoxin, a potent neurotoxin commonly associated with sea food poisoning. Tetrodotoxin has found application in medicinal chemistry as analgesic treatment option in cancer therapy. Kishi describes the complete total synthesis in a series of four publications; the one presented here and *J. Am. Chem. Soc.* **1972**, *94*, 9217, *Tetrahedron Lett.* **1970**, *11*, 5129, and *Tetrahedron Lett.* **1970**, *11*, 5127.

Comment: **D** was accessed by Diels-Alder reaction of **B** with butadiene (**C**). Subsequent Beckmann rearrangement of **D** allowed access to acetamide **E**, which underwent epoxidation and in situ ether-bridge formation. Conversion of **K** into **L** was enabled by Bayer-Villiger oxidation followed by lactone cleavage and in situ epoxide opening.