Synthesis of (±)-Haouamine A

Significance: Isolated from the tunicate Aplidium haouarianum, haouamine A exhibits selective activity against human colon cancer. Haouamine A exists as an inseparable mixture of isomers due to inversion of the nitrogen in the tetrahydropyridine ring. In addition, the highly strained paracyclophane moiety contains a bent aromatic ring.

Comment: Treatment of oxime A with electrophilic bromine source B gave nitrone C after 5-exo-trig cyclization. Reduction of C followed by heating induced ring expansion via aziridinium ion E. Prolonged microwave heating of H induced a pyrene-alkyne Diels–Alder reaction with concomitant loss of CO₂. Subsequent deacetylation gave haouamine A. For an alternative approach based on a 1,3-dipolar cycloaddition strategy, see: J. H. Jeong, S. M. Weinreb Org. Lett. 2006, 8, 2309-2312.