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A Concise Total Synthesis of DL-Histrionicotoxin

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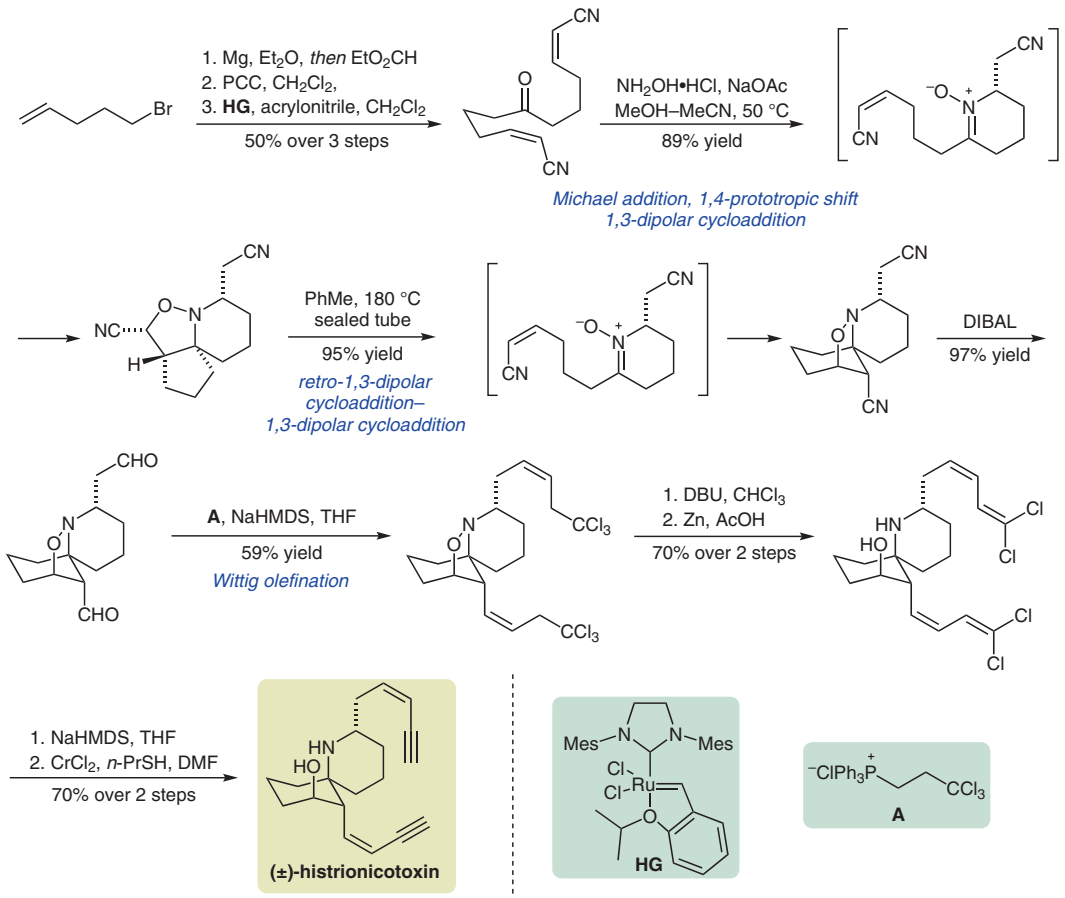
The Hidden Symmetry of (±)-Histrionicotoxin



Significance: Histrionicotoxin (HTX) is a natural product isolated from the skin of poison dart frogs (Dendrobatidae). It is a noncompetitive antagonist of the nicotinic acetylcholine receptor and, when bound, increases the affinity of the receptor for the native agonist acetylcholine while simultaneously stabilizing this desensitized state. Due to its low natural abundance (<180 µg per frog), histrionicotoxin is best produced through total synthesis. A collaborative effort between the Stockman and Fuchs groups delivered (±)-histrionicotoxin in 16.5% overall yield.

Comment: An efficiently synthesized ketodiene underwent double olefin metathesis to afford a ketodinitrile. Key to the synthesis is a tandem Michael addition/1,4-prototropic shift/1,3-dipolar cycloaddition to afford the kinetic product. Heating this product gives the thermodynamically more stable regioisomers via a retro-1,3-dipolar cycloaddition/1,3-dipolar cycloaddition. Reduction followed by double Wittig olefination set the stage for the completion of the synthesis via a chromium-mediated dehalogenation of the bischloroenyne.

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Wittig olefination

1,3-dipolar cycloaddition

bidirectional synthesis