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Total Synthesis of (−)-Histrionicotoxin 285A and (−)-Perhydrohistrionicotoxin

James M. Macdonald,[†] Helen T. Horsley,[‡] John H. Ryan,[†] Simon Saubern,[†] and Andrew B. Holmes*[,†,§]

CSIRO, Division of Molecular and Health Technologies, Bag 10, Clayton South, Victoria 3169, Australia, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K., and School of Chemistry, Bio21 Institute, University of Melbourne, Parkville, Victoria 3010, Australia

aholmes@unimelb.edu.au

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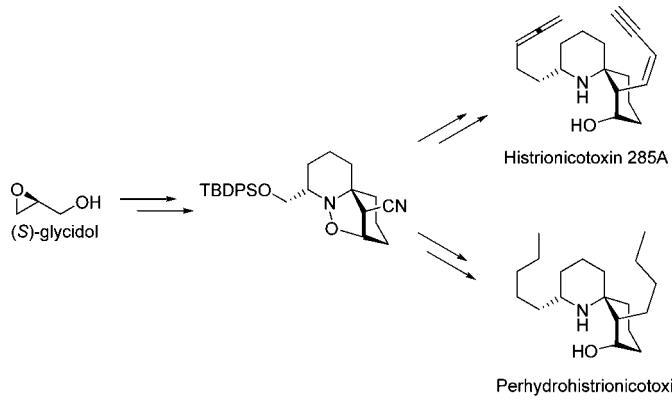
ABSTRACT



Starting from commercially available (*S*)-glycidol, and via a common intermediate, the total synthesis of (−)-histrionicotoxin 285A and (−)-perhydrohistrionicotoxin has been achieved. Key to this synthesis was the efficient construction of a six-membered, chiral, cyclic nitrone.

The histrionicotoxins (HTXs) are a family of spirocyclic piperidine alkaloids isolated in 1971 from the Colombian frog *Dendrobates histrionicus*.[1] Their intriguing molecular architecture coupled with potent inhibition of the nicotinic acetylcholine receptor[2] has made them attractive targets for total synthesis. Most effort has been directed to histrionicotoxin 283A **1** and the unnatural perhydrohistrionicotoxin **2**.[3] In this paper, we report the first synthesis of (−)-HTX 285A **3**, the most abundant[4] and potent[1,2b] alkaloid within this family, containing both a terminal *cis*-enyne and an allene side chain (Figure 1).

We sought a new enantioselective synthetic route, based upon the nitrone dipolar cycloaddition approach,[5] which would necessitate the efficient construction of a six-membered chiral cyclic nitrone. Inspired by the work of Goti[6] and Grigg[7] involving the intramolecular *N*-alkylation of oximes, we reasoned that the required nitrone **15** could be prepared by ring closure of the advanced oxime precursor **14**.

[†] CSIRO.
[‡] University of Cambridge.
[§] University of Melbourne.

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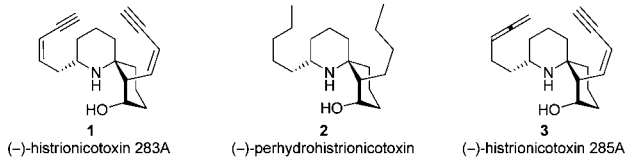


Figure 1. Structures of histrionicotoxins.

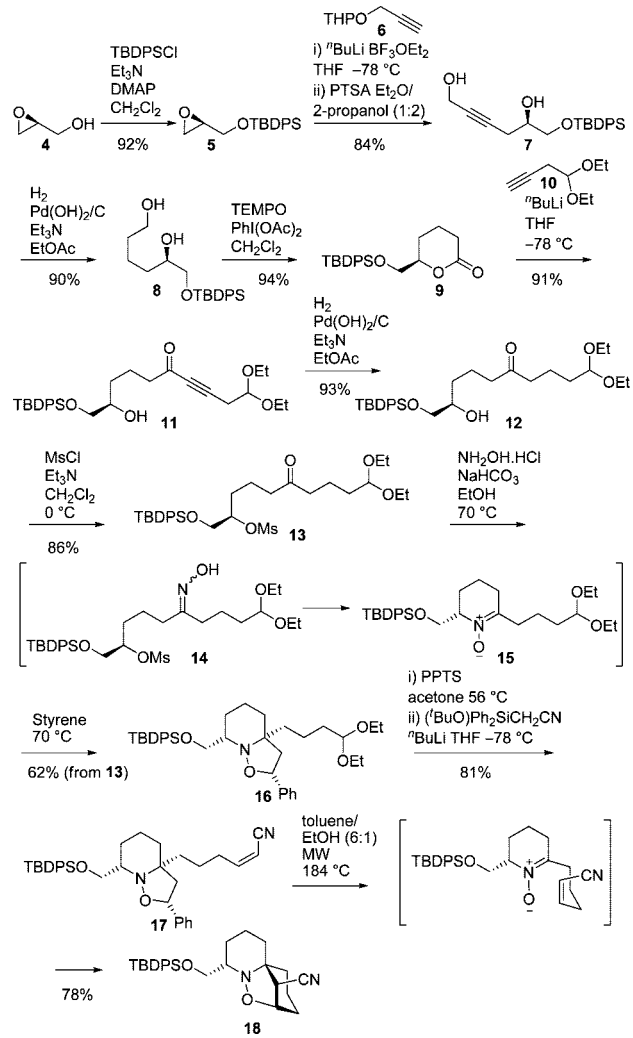
Commercially available *S*-glycidol **4** was transformed into the chiral lactone **9** in five steps (65% overall yield) following the general strategy described by Forsyth[8] (Scheme 1). The lactone **9** was efficiently opened[9] in excellent yield with the lithium acetylide derivative of **10** to give the alkynone **11**, which was catalytically hydrogenated to afford the fully saturated derivative **12**. The keto-alcohol **12** showed no evidence of closure to the corresponding cyclic hemiketal tautomer.

Mesylation of the alcohol **12** gave the mesylate **13**. Treatment of the keto-mesylate **13** with NH_2OH gave the presumed oxime **14** which showed no tendency to cyclize at room temperature. However, following the observation of Py,[10] it was found that simply heating the mesylate **13** in the presence of an excess of NH_2OH in EtOH at 70 °C achieved both the conversion of **13** into the oxime **14** and subsequent intramolecular *N*-alkylation (with inversion of configuration) to give the nitrone **15**. Without purification, the unstable nitrone **15** was immediately protected as its styrene adduct **16**. In this manner, the mesylate **13** was efficiently converted into isoxazolidine **16** in an overall yield of 62%.

Elaboration of the acetal **16** to the *Z*-α,*β*-unsaturated nitrile **17** was achieved by mild transacetalization of **16** to liberate the aldehyde, followed by olefination using the superior, modified Peterson reagent described by Kojima.[11] This latter reaction gave in excess of 95:5 *Z*/*E* selectivity (trace amounts of the *E*-isomer could be chromatographically removed). The nitrile **17** was obtained in 81% yield from acetal **16**. The nitrile **17** was subjected to a microwave (MW) thermally induced 1,3-dipolar cycloreversion (with accompanying extrusion of styrene) followed by an intramolecular cycloaddition process under thermodynamic control to furnish the required (6,6,5)-tricycle **18**.[5]

Thus, the absolute configuration of **18** is determined by *S*-glycidol **4**; the remaining three stereocenters are induced by a diastereoselective dipolar cycloaddition to the *Z*-α,*β*-unsaturated nitrile. This approach produces the core HTX precursor **18** in 13 steps and 19% overall yield from *S*-glycidol **4**.

Scheme 1. Synthesis of Tricycle **18**



With tricycle **18** in hand, we first explored the synthesis of (−)-perhydrohistrionicotoxin **2** (Scheme 2). The silyl protecting group on **18** was removed with AcOH-buffered TBAF[12] (without AcOH slow epimerization of the axial nitrile moiety was observed) to give alcohol **19**. Alcohol **19** was activated as its mesylate and displaced with cyanide to provide the dinitrile **20**. The dinitrile **20** was converted into the dialdehyde followed by Wittig olefination to give exclusively the *Z*,*Z*-dialkene **21**.[13] Owing to the sluggish reactivity of the *N*−*O* bond within **21** toward hydrogenolysis, a direct, one-step reduction to perhydrohistrionicotoxin **2** was abandoned. Instead, the isoxazolidine moiety was selectively reduced under Brandi (SmI_2) conditions,[14] and advantageously, gave rise to a new (albeit unnatural) member of

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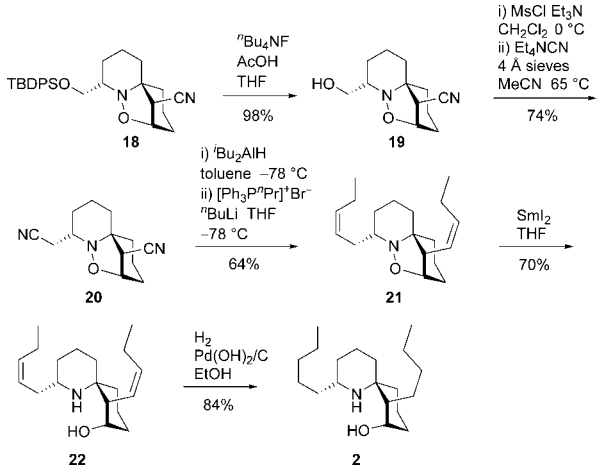
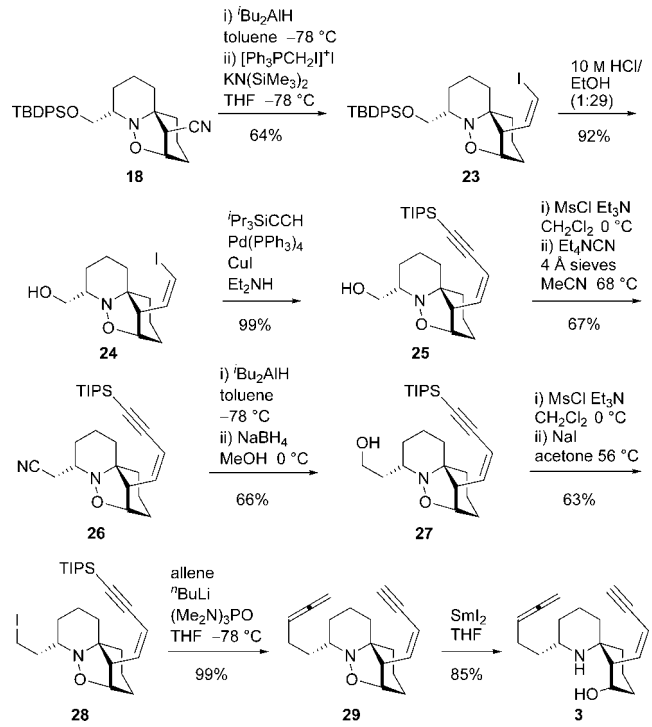
Scheme 2. Synthesis of (−)-Perhydrohistrionicotoxin **2**



Scheme 3. Synthesis of (−)-Histrionicotoxin 285A **3**



the histrionicotoxin family, namely, **22**. Catalytic hydrogenation of dialkene **22** afforded (−)-perhydrohistrionicotoxin **2**. The spectroscopic data including the specific rotation of the hydrochloride salt of (−)-perhydrohistrionicotoxin **2** matched that previously reported.[15,16]

We then investigated the more synthetically challenging histrionicotoxin 285A **3** (Scheme 3). The nitrile **18** was converted into the aldehyde and then olefinated under Stork−Wittig conditions[17] to afford *Z*-vinyl iodide **23**. The silyl-protecting group was cleaved under acidic conditions[18] to provide the alcohol **24**which underwent Sonogashira coupling[19] to give *Z*-enyne **25**. We anticipated introducing the terminal allene moiety by iodide displacement with allenyl lithium. Mesylate activation of the alcohol **25** and cyanide displacement gave the nitrile **26**. A two-step reduction of **26** yielded the primary alcohol **27** which was transformed to the alkyl iodide **28** by mesylation followed by displacement with iodide. The key displacement reaction of iodide **28** with an excess of allenyl lithium in the presence of HMPA was remarkably clean and concomitantly cleaved the triisopropylsilyl protecting group to afford the allene derivative **29** in excellent yield. Finally, SmI_2 cleavage of the N−O bond afforded (−)-histrionicotoxin 285A **3**. The spectroscopic data matched that previously reported.[1,16a,20]

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Supporting Information Available: Experimental procedures and compound characterization for **2**, **3**, **5**, **7**−**9**, **11**−**13**, and **16**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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