Synthesis of (−)-Histrionicotoxin by a Tandem Process

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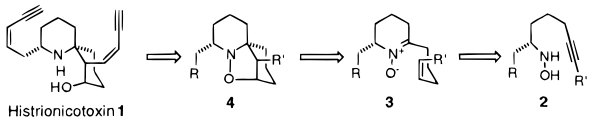
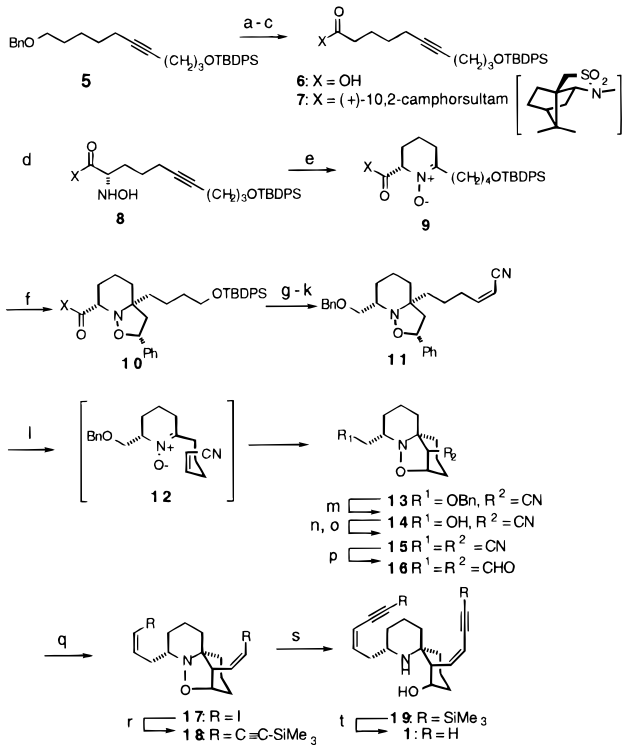
(−)-Histrionicotoxin **1** (HTX), the archetype of a group of spiropiperidine-containing alkaloids from the brightly colored poison-arrow frog *Dendrobates histrionicus*, was isolated and characterized by Daly, Witkop, and co-workers.[1] HTX and its analogues have generated considerable pharmacological interest as noncompetitive inhibitors of the nicotinic acetylcholine receptors and as probes to study neuromuscular signal transmission,[2,3] but an ever-diminishing supply of the natural material demands that total synthesis provide an alternative source. Indeed, a number of syntheses of the simpler perhydrohistrionicotoxin have now been reported,[4] but only two successful syntheses of the unsaturated parent molecule have been published,[5,6] the latter being enantioselective.

Scheme 1. Retrosynthetic Analysis of Histrionicotoxin 1



We report a new synthesis of (−)-HTX **1** using a sequence of intramolecular pericyclic processes (Scheme 1); first, a hydroxylamine−alkyne cyclization[7,8] of **2** is used to prepare the nitrone **3** which is intercepted by an intramolecular [3 + 2] cycloaddition to afford **4**, the core ring system of HTX **1**. Thus, in a single step the sole stereocenter in **2** directs formation of the three new chiral centers in the product. The dipolar cycloaddition approach has been explored previously on a number of occasions,[9−11] but all attempts at its implementation using a variety of substituted olefins and nitrones have invariably given the alternative regioisomer.[12−16]

Scheme 2. Synthesis of Histrionicotoxin 1[a]



[a] (a) BCl_3·DMS, CH_2Cl_2, 97%; (b) Jones reagent, acetone, 98%; (c) NEt_3, pivaloyl chloride, 0 °C then (1*R*)−(+)-10,2-camphorsultam, *n*-BuLi, THF, −78 °C, 84%; (d) $NaN(TMS)_2$, 1-chloro-1-nitrosocyclohexane, THF, then HCl (aq), 70%; (e) toluene, 80 °C, 6 h; (f) styrene, 75 °C, 85% (2 steps); (g) $LiAlH_4$, THF, 0 °C; (h) NaH, BnBr, THF, 90% (2 steps); (i) HF, CH_3CN, 91%; (j) TPAP, NMO, 4 Å sieves, 98%; (k) Me_3SiCH_2CN, *n*-BuLi, THF, −78 °C, $B(O^iPr)_3$, 87% (*E*:*Z* 10:90 increasing to 8:92 with HMPA); (l) toluene, sealed tube, 190 °C, 3.5 h, 80%; (m) BCl_3·DMS, CH_2Cl_2, 99%; (n) methanesulfonyl chloride, NEt_3, DMAP, CH_2Cl_2, 100%; (o) NaCN, DMSO, 4 Å sieves, 55 °C, 85%; (p) DIBAL-H, toluene, −78 °C, 100%; (q) $KN(TMS)_2$, $[Ph_3PCH_2I]^+I^-$, THF, −78 °C, 95%; (r) $Pd(PPh_3)_4$, CuI, Et_2NH, $Me_3Si-C\equiv CH$, 92%; (s) Zn, AcOH, 30 min, 98%; (t) K_2CO_3, MeOH, 94%.

This has been attributed to unfavorable steric constraints in the transition state. In this work the required regiocontrol in the intramolecular [3 + 2] cycloaddition has in part been realized by the use of an α,β-unsaturated nitrile.

The acetylenic diol **5** was prepared by reaction of 1-benzyloxy-5-iodopentane[17] and the lithio derivative of 5-*tert*-butyldiphenylsilyloxy-1-pentyne (Scheme 2).[18] Debenzylation,[19] oxidation of the resulting alcohol to the acid **6**, and incorporation of (*1R*)-(+)-2,10-camphorsultam via a mixed anhydride method afforded the acyl sultam **7**. Oppolzer's methodology[20] was then exploited to introduce a hydroxylamine group diastereoselectively. Thus, reaction of the sodium enolate derived from **7** with 1-chloro-1-nitrosocyclohexane followed by mineral acid hydrolysis afforded the hydroxylamine **8** as a single diastereomer. The intramolecular

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hydroxylamine−alkyne cyclization[7,8] then gave the nitrone **9** which was immediately masked by styrene cycloaddition, affording the isoxazolidine **10** as a single regio- and diastereomer.[21] Reductive removal of the chiral auxiliary[22] and benzylation of the resulting alcohol followed by desilylation and oxidation afforded an aldehyde which was converted into the (*Z*)-α,*β*-unsaturated nitrile **11** by Yamamoto's[23] version of the Petersen olefination.

After considerable experimentation it was found that the adduct **11**, when heated at 190 °C in toluene in a sealed tube for 3.5 h, lost styrene and formed the required dipolar cycloadduct **13** in consistently high yield (78−82%). The almost exclusive formation of a single regioisomer (established by NMR spectroscopy and the X-ray structure of a later intermediate) through the presumed intermediacy of the nitrone **12** is a remarkable outcome. First, three new chiral centers necessary for the natural product have been created with extraordinary efficiency, and second, the regiochemistry is contrary to that observed with a number of closely related examples.[9,10,12−16]

The result is difficult to explain but may be a consequence of a different pathway not involving the nitrone **12** directly.[24] This is under investigation.

The (*Z*)-enyne side chains were elaborated using Stork's iodophosphorane to prepare *cis*-iodo-alkenes.[6] Conversion of **14** via the mesylate into the crystalline bis-nitrile **15** allowed the side chains to be processed in parallel. DIBAL-H reduction of the nitrile groups gave the corresponding bis-aldehyde **16** quantitatively; this was converted in a modified Stork−Wittig procedure[25] into the bis-iodoalkene **17** and thence to the bis-enyne **18**, using a Pd(0)/Cu(I)-mediated coupling[26] with (trimethylsilyl)-acetylene.[27]

Reduction of the strained N−O bond using activated zinc dust in glacial acetic acid[28] proceeded efficiently to afford bis-(trimethylsilyl)-HTX **19** which was deprotected to give the natural product $[\alpha]^{20}_{D}$ −112° (*c*, 0.34, EtOH), the spectra (^{1}H and ^{13}C NMR) of which were identical to those reported in the data.[1,6] On storage at −15 °C crystals (mp 75−76 °C) slowly formed that were suitable for X-ray analysis, which served to confirm the structure of the synthetic histrionicotoxin (Figure 1).[29]

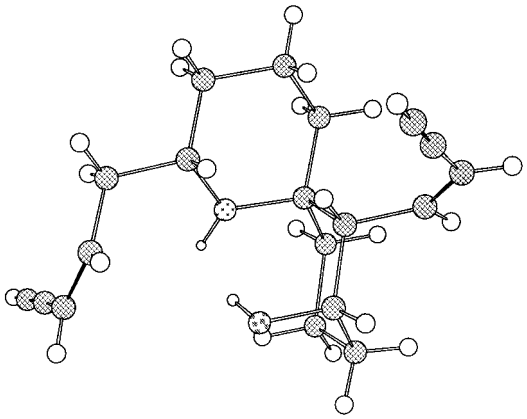
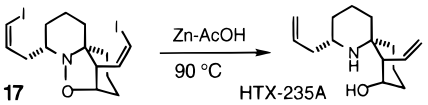


Figure 1. The X-ray structure (Chem 3D representation) of synthetic (−)-histrionicotoxin **1**.

Scheme 3



In summary an enantioselective synthesis of (−)-HTX from 5-TBDPSO-1-pentyne in 16% overall yield is described using an intramolecular [3 + 2] cycloaddition to construct the core ring system. Furthermore, conversion of **17** into the bis-vinyl derivative, HTX-235A (Scheme 3), demonstrates the potential of this intermediate to serve as a common precursor of the other members of the HTX family and to offer a realistic alternative source for these biologically important natural products.

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Supporting Information Available: Experimental procedures for the synthesis and characterization of **10**, **11**, **13**, **14**, **18**, **19**, **1**, HTX-235A; details of the *X*-ray structure determination, tables of atomic coordinates, isotropic displacement parameters, anisotropic displacement parameters, bond lengths, and bond angles for (−)-HTX **1** (these data have been deposited with the Cambridge Crystallographic Database (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Cleavage of the N−O bond in the presence of the desilylated enynes was accompanied by reduction of the acetylenic groups to give a mixture of HTX, dihydro-HTX, neodihydro-HTX, and tetrahydro-HTX.

(29) Crystallographic details for **1**. Crystal system monoclinic; space group $P2_1$; colorless crystal; a = 9.593(5) Å, b = 7.815(5) Å, c = 11.342(5) Å; α = 90°, β = 99.47(4)°, γ = 90°; Z = 2; final R indices [$I > 2\sigma(I)$] R1 = 0.0453, wR2 = 0.0783; R indices (all data) R1 = 0.0680, wR2 = 0.0864; GOF on F^2 = 0.837.