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A Concise Total Synthesis of DL-Histrionicotoxin

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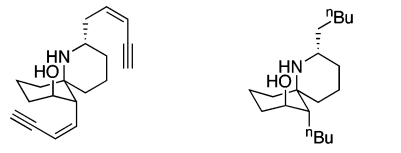
In 1971, Witkop et al. isolated six alkaloids from the skin extracts of 1110 frogs[1] and identified the structure of the major constituent as histrionicotoxin (**1**) by a combination of NMR analysis and X-ray crystal structures of the chloro- and bromohydrates.[2,3]

Both HTX (**1**) and the non-natural perhydrohistrionicotoxin (pHTX, **2**) are noncompetitive inhibitors of the neuromuscular, ganglionic, and central neuronal nicotinic acetylcholine receptors and have become important neurophysiological research tools.[4−9] These compounds have been shown to have extremely low natural abundances (<180 μg per frog). Furthermore, the frogs are now protected under the Convention on International Trade in Endangered Species (CITES agreement). The potent biological activity combined the challenging spirocyclic structure containing a bisenyne side chain, and paucity of material available from the natural source has prompted a multitude of synthetic approaches, the vast majority of which have been aimed at the synthesis of the non-natural perhydrohistrionicotoxin.[10] To date, there have been just three total syntheses of histrionicotoxin itself, by Kishi (38 steps),[11] Stork (18 steps),[12] and most recently by Holmes (24 steps).[13] Herein we report a concise synthesis of (±)-HTX. Previously, we have reported on



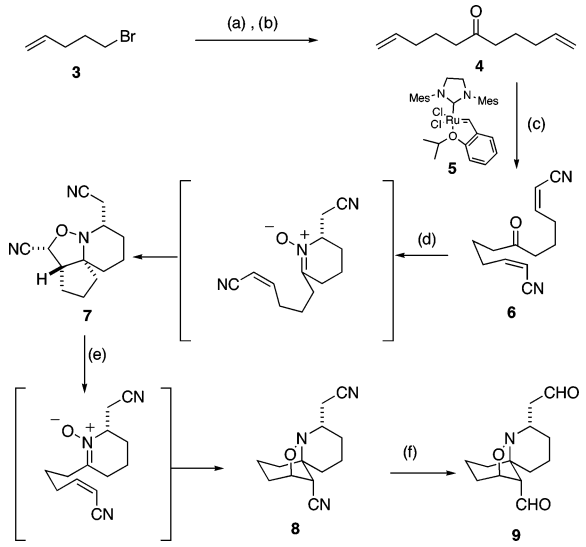
Histrionicotoxin **1** Perhydrohistrionicotoxin **2**

Figure 1. Structures of HTX and pHTX.

the synthesis of dinitrile **8**[14] (Scheme 1) as a precursor to pHTX (**2**).[15] Holmes also used this intermediate to access HTX, and thus this has proved to be a key intermediate for the synthetic entry into this class of compounds.[16] Our original route to **8**, while being relatively short at six steps, was problematic to scale up due to a difficult first dialkylation of dithiane, which produced several unwanted side products, therefore meaning that careful column chromatography was required after the first step of the synthesis in order to obtain clean material in good yield. We have therefore developed a shorter and more efficient route to the dinitrile **8**, using just four or five steps (Scheme 1).

Thus ketodiene **4** is accessed by the addition of pent-5-enylmagnesium bromide to the commercially available nitrile 5-cyano-pent-1-ene (70%)[17] or by the double addition of pent-5-enylmagnesium bromide to ethyl formate followed by oxidation with PCC (82% over two steps). The latter two-step procedure gives better yields and is thus the favored process. A two-directional cross-metathesis reaction, using the Grubbs−Hoveyda catalyst **5**,[18] is then used to homologate the chain to the ketodinitrile **6**. We

Scheme 1 [a]



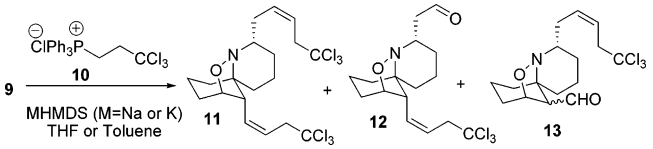
[a] Conditions: (a) Mg, Et_2O, then EtO_2CH, 89%; (b) PCC, CH_2Cl_2, rt, 92%; (c) **5** (30 mol %), acrylonitrile (3 equiv), CH_2Cl_2, 120 °C, microwave, 5 h, 62%; (d) NH_2OH·HCl, NaOAc, MeOH/MeCN, 50 °C, 89%; (e) toluene, 180 °C, sealed tube, 95%; (f) DIBAL, −78 °C, 97%.

have optimized the conversion of **6** into **8** by carrying out a tandem oxime formation/Michael addition/1,4-prototopic shift/[3 + 2]-cycloaddition[15] to form the kinetic product **7**. This is then purified and heated in toluene in a sealed tube at 180 °C for 3 h, in which time the thermodynamically more stable regioisomer, **8**, is formed through a retro-[3 + 2]/[3 + 2]-cycloaddition sequence. In this way, dinitrile was synthesized in five steps and 42% overall yield. Double DIBAL reduction of **8** then gave dialdehyde **9**.

Wittig reaction of dialdehyde **9** with the phosphorane derived from phosphonium chloride **10** was next examined. At low temperatures, the reaction was sluggish in toluene or THF and gave yields in the range of 20−30%. In all the cases, **11** was accompanied by monofunctionalized aldehydes **12** and **13**. While aldehyde **12** can be resubmitted to Wittig conditions to provide additional **11** (∼20%), partially epimerized aldehyde **13** remained unreactive, an observation consistent with Holmes' experiments.[19] A 37% yield of **11** was obtained when NaHMDS/THF was used at −40 °C. The yield was further improved to 59% by conducting the reaction with *freshly purified* dialdehyde **9** (Scheme 2).

As observed previously with various model compounds,[20] hexachloride **11** smoothly reacted with DBU to quantitatively provide

Scheme 2



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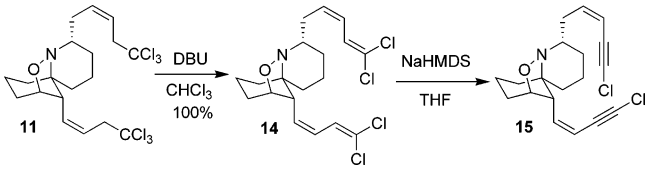
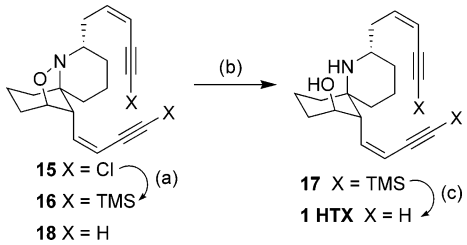
tetrachloride **14**. Low temperature dehydrohalogenation of **14** gave a mixture of starting material and **15**; however, at room temperature, the reaction proceeded to completion to afford a 90% yield of **15** (Scheme 3).

Scheme 3



Completion of (±)-HTX was initially achieved by intersection with Holmes' synthesis.[13] Specifically, treatment of **15** with 4 equiv of *t*-BuLi at −78 °C followed by addition of acid-free TMS−Cl (stored over PVP)[21] gave common intermediate **16**, which Holmes had efficiently converted to **1** in two operations (Scheme 4).[21]

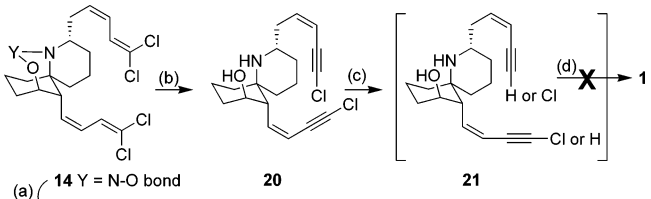
Scheme 4 [a]



[a] Conditions: (a) *t*-BuLi (4 equiv), then TMSCl (13 equiv), THF, −78 °C, 89%; Holmes' Synthesis; (b) Zn−HOAc, 98%; (c) K_2CO_3, MeOH, 94%.

A more optimal conclusion to the synthesis sought a reagent capable of concurrent reduction of the isoxazoline N−O bond along with both the C−Cl bonds of bischloroenyne **15**. Holmes observed 20% over-reduction of the alkynes when **18** was reacted with Zn−HOAc.[19] Similarly, **15** also provided a mixture of products upon treatment with Zn−HOAc or $Mo(CO)_6$.[23] Conducting the Zn−HOAc reaction on earlier intermediate **14** effected cleavage of the N−O bond without over-reduction to give a 70% yield of amino alcohol **19**. Reaction of **19** with NaHMDS/THF gave a 75% yield of bischloroenyne **20**. While simpler substrates successfully underwent *t*-BuLi-mediated transmetalation/protonolysis to generate (*Z*)-1,3-enynes,[20] low temperature transmetalation of **20** with 6 equiv of *t*-BuLi gave monochloride **21** as the major product. Treatment of **20** with >6 equiv of *t*-BuLi resulted in decomposition in preference to forming (±)-HTX (Scheme 5).

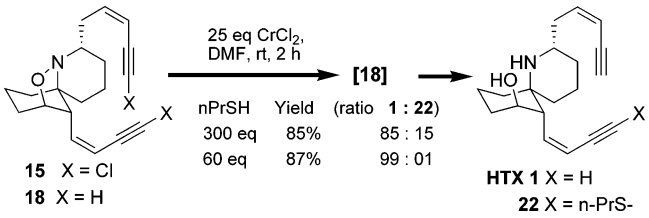
Scheme 5 [a]



[a] Conditions: (a) Zn (25 equiv), HOAc, rt, 3 h, 70%; (b) NaHMDS (14 equiv), THF, 0 °C to rt, 15 min, 75%; (c) *t*-BuLi (6 equiv), THF, −78 °C; (d) 1 equiv of *t*-BuLi THF, −78 °C.

The ideal reagent proved to be $CrCl_2$−*n*PrSH,[24] which Barton demonstrated, wherein the mercaptan serves both as a hydrogen donor and as a ligand, thereby enhancing the reducing power of chromium.[25] When bischloroenyne **15** was reacted with $CrCl_2$ (25 equiv) and *n*-PrSH (300 equiv), smooth reduction ensued and (±)-HTX **1** was obtained in 70% yield along with 15−20% of a

Scheme 6



monothiopropyl alkyne **22** (or the alternative acetylenic sulfide). The reaction was substantially improved by reducing the quantity of *n*-PrSH (60 equiv) to give 87% yield of (±)-HTX **1**, containing only a trace of sulfide **22**. The reaction involves initial reduction of the C−Cl bond since intermediate acetylene **18** was isolated and characterized on one occasion (Scheme 6).

In conclusion, we have synthesized HTX **1** in 10 steps and 19.2% overall yield, or 9 steps and 16.5% yield.

Supporting Information Available: Additional references and experiments, discussion, experimental procedures, and ^1H, ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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