

The total synthesis of alkaloids (–)-histrionicotoxin 259A, 285C and 285E†

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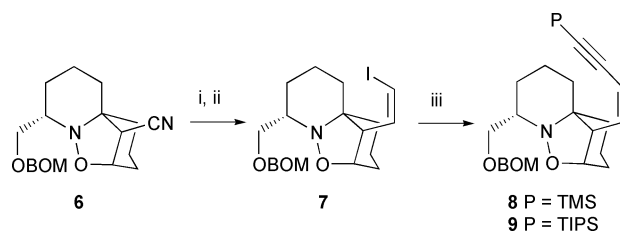
The first total syntheses of three “unsymmetrical” (*i.e.* different terminal groups in the side chains) members of the histrionicotoxin family of alkaloids have been accomplished *via* stepwise introduction of the two side chain moieties onto a common tricyclic core.

The histrionicotoxins are a family of alkaloids isolated from the poison arrow frog *Dendrobates histrionicus* native to the Amazon rain forests of southwestern Colombia. First isolated by Daly, Witkop and co-workers in 1971,¹ they all share a common 1-azaspiro[5.5]undecan-8-ol ring system with unsaturated C₄ or C₅ side chains at both the 2 and 7 positions. The nature and length of the side chains distinguish the different members of the histrionicotoxin family. They have been shown to be potent non-competitive blockers of neuromuscular,^{2,3} ganglionic and central neuronal nicotinic channels,⁴ but as yet, the specific effect of the side chain functionalities on their activity has been the subject of only limited study.^{3,5,6} Protection of *Dendrobates* sp. under Appendix II of CITES⁷ has restricted the supply of natural material making synthetic routes greater in demand. One formal⁸ and three total^{9–11} syntheses of histrionicotoxin (HTX) **1** have been reported, the last two of which yielded the naturally occurring (–)-enantiomer.

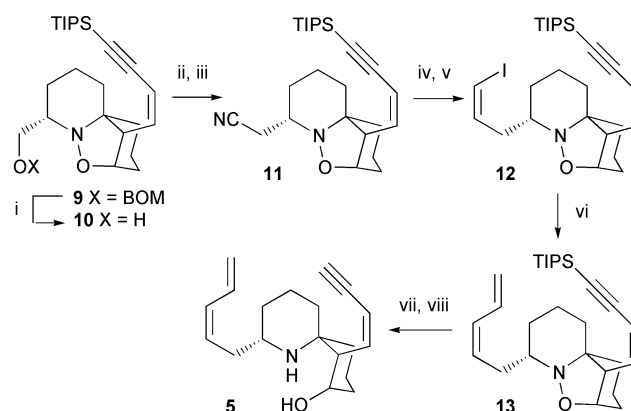
In this paper we report the first total syntheses of (–)-HTX **259A** **3**, (–)-HTX **285C** **4** and (–)-HTX **285E** **5** which are derived from the common tricyclic core **6**.[‡] This precursor is obtained in eleven steps (22%) from simple linear precursors by our tandem hydroxylamine alkyne cyclisation–nitron 1,3-dipolar cycloaddition strategy.¹¹

Both (–)-histrionicotoxin **285C** **4** and (–)-histrionicotoxin **285E** **5** possess a (*Z*)-enyne side chain at the C-7 position. DIBAL-H reduction of the nitrile **6** gave the corresponding aldehyde which underwent the Stork Wittig¹² reaction with 1.5 eq. of the iodophosphorane ylide [generated at –30 °C from the phosphonium salt with KN(SiMe₃)₂] to yield the (*Z*)-iodoalkene **7**. This was readily converted in excellent yield into the (*Z*)-enyne **8** or **9** respectively by Sonogashira ethynylation¹³ with either trimethylsilyl- or triisopropylsilylacetylene (Scheme 1).[†]

Attention now turned to incorporation of the C-2 side chain (Scheme 2). (–)-Histrionicotoxin **285E** **5** possesses a (*Z*)-diene moiety, which could be introduced in a two step procedure from the nitrile **11**. Acidic cleavage of the benzyloxymethyl group yielded the crystalline alcohol **10** which was converted *via* the mesylate into the nitrile **11**.[§] The (*Z*)-iodoalkene **12** was



Scheme 1 Completion of the C-7 side chain. Reagents and conditions: i, DIBAL-H, toluene, –78 °C, 100%; ii, KN(TMS)₂, [Ph₃PCH₂I]⁺I[–], THF, –78 °C, 82%; iii, Pd(PPh₃)₄, CuI, Et₃NH, Me₃SiC≡CH (for **8**), 95%; ^tPr₃SiC≡CH (for **9**), 100%. BOM = benzyloxymethyl.

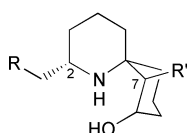


Scheme 2 Completion of the synthesis of (–)-HTX **285E** **5**. Reagents and conditions: i, Amberlyst-15™, MeOH, 84%; ii, methanesulfonyl chloride, NEt₃, DMAP, CH₂Cl₂, 97%; iii, NaCN, DMSO, 4 Å MS, 55 °C, 66%; iv, DIBAL-H, toluene, –78 °C, 100%; v, KN(TMS)₂, [Ph₃PCH₂I]⁺I[–], THF, –78 °C, 82%; vi, tributylvinyltin, PdCl₂(MeCN)₂, DMF, 80%; vii, Zn, AcOH, 0.5 h, 91%; viii, Bu₄NF (TBAF) THF, 84%.

prepared by the same procedure as described above, and Stille coupling¹⁴ with tributylvinyltin in DMF employing a catalytic quantity of PdCl₂(MeCN)₂ afforded the (*Z*)-diene **13**. Reductive N–O bond cleavage of the isoxazolidine **13** with activated zinc dust in acetic acid gave the intermediate amino alcohol which was desilylated with TBAF to yield the natural product **5**, [α]_D²⁷ 23.8 (*c* 0.08 in CHCl₃) [for **5**·HCl [α]_D²⁷ –38.5 (*c* 0.18 in EtOH), lit.¹⁵ [α]_D²⁵ –122 (*c* 1.0 in EtOH)],[¶] the spectra (¹H NMR, IR, *m/z*) of which were identical to those reported for the natural material.^{16–18}

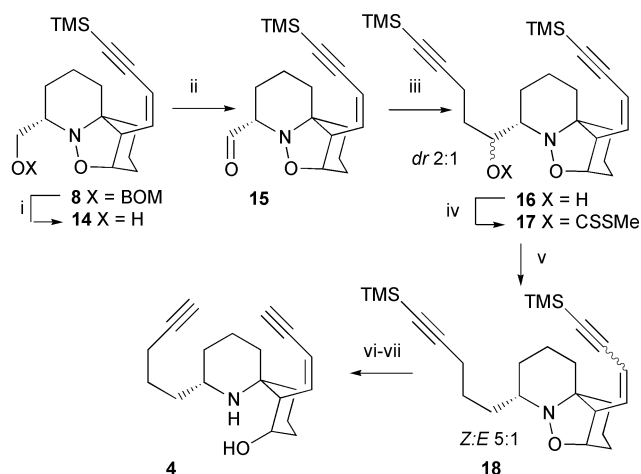
(–)-Histrionicotoxin **285C** **4** contains a terminal pentynyl fragment at the C-2 position and represents a more challenging target. We were unsuccessful in effecting Cu(I)-mediated coupling reactions with a suitably substituted substrate derived from the alcohol **14** and therefore selected a Grignard addition to the aldehyde **15**, followed by deoxygenation (Scheme 3).

Deprotection of BOM ether **8** followed by IBX oxidation¹⁹ of the resulting alcohol **14** gave the aldehyde **15** in excellent yield. Dropwise addition of a preformed solution of 4-trimethylsilylbut-3-ynyl magnesium bromide in THF to a solution of the aldehyde in THF cooled to 0 °C yielded a 2:1 mixture of diastereomers **16** which could be readily separated by flash



- 1; R = (Z)-CH=CHC≡CH, R' = (Z)-CH=CHC≡CH
- 2; R = CH=CH₂, R' = CH=CH₂
- 3; R = CH=CH₂, R' = (Z)-CH=CHC≡CH
- 4; R = CH₂CH₂C≡CH, R' = (Z)-CH=CHC≡CH
- 5; R = (Z)-CH=CHCH=CH₂, R' = (Z)-CH=CHC≡CH

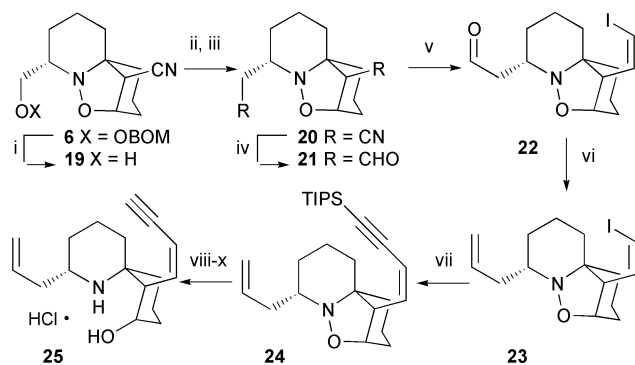
† All new compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data. Electronic supplementary information (ESI) available: experimental procedures for the preparation of compounds **4**, **5**, **13**, **16**, **22** and **25**. See <http://www.rsc.org/suppdata/cc/b1/b111514f/>



Scheme 3 Completion of the synthesis of (–)-HTX **285C 4**. *Reagents and conditions*: i, Amberlyst-15™, MeOH, 97%; ii, IBX, DMSO, 96%; iii, TMS-C≡C(CH₂)₂MgBr, 0 °C, THF, 93%; iv, NaH, 0 °C → rt, 1.5 h; CS₂, 1 h; MeI, 1.5 h, THF, 83%; v, Bu₃SnH, AIBN, benzene, 80 °C, 70%; vi, Zn, AcOH, 30 min, 97%; vii, K₂CO₃, MeOH, overnight, 88%. IBX = *o*-iodoxybenzoic acid.

chromatography. Deoxygenation of each diastereomer using Barton McCombie conditions via the intermediate xanthates **17** in toluene,²⁰ gave the isoxazolidine **18** as a mixture of (*Z*) and (*E*)-enynes. The alkene isomerisation could be minimised to 5:1 (*Z*):(*E*) (70%) using benzene as solvent. Separation of the alkene isomers afforded the required isoxazolidine (*Z*)-**18** for conversion into the natural product. Reductive cleavage of the strained *N*-*O* bond proceeded efficiently to produce bis(trimethylsilyl)histrionicotoxin **285C** which was deprotected to give the natural product **4**, [α]_D¹⁸ –43.3 (*c* 0.12 in CHCl₃) [for **4**·HCl [α]_D¹⁹ –44.6 (*c* 0.12 in EtOH), lit.²¹ [α]_D²⁵ –43.4 (*c* 1.18 in EtOH)], the spectra (¹H NMR, IR, *m/z*) of which were identical to the natural material.^{17,22}

(–)-Histrionicotoxin **259A 3** possesses a simple allyl substituent at the C-2 position which could be introduced by methylenation of a suitable aldehyde. The dinitrile **20** was converted into the relatively unstable dialdehyde **21**¹¹ which underwent regioselective Stork Wittig reaction at the C-7 aldehyde (Scheme 4). This is indeed remarkable since the C-7 aldehyde is apparently the more sterically hindered aldehyde; however, it may be more electron deficient as a result of the two



Scheme 4 The total synthesis of (–)-HTX **259A**·HCl **25**. *Reagents and conditions*: i, Amberlyst-15™, MeOH, 84%; ii, methanesulfonyl chloride, NEt₃, DMAP, CH₂Cl₂, 100%; iii, NaCN, DMSO, 4 Å MS, 55 °C, 66%; iv, DIBAL-H, toluene, –78 °C, 100%; v, KN(TMS)₂, [Ph₃PCH₂I]⁺, THF, –78 °C, 60%; vi, Cp₂TiMe₂, toluene, 110 °C, 83%; vii, Pd(PPh₃)₄, CuI, Et₂NH, ^oPr₃SiC≡CH, 81%; viii, Zn, AcOH, 30 min, 89%; ix, TBAF, THF; x, anhyd. HCl, MeOH, 82% (two steps).

diaxial carbon–heteroatom bonds. Methylenation of the less reactive aldehyde **22** employing the Petasis reagent (dimethylitanocene)²³ completed the allyl side chain **23**. Sonogashira coupling,¹³ followed by *N*-*O* bond cleavage and TBAF deprotection yielded histrionicotoxin (–)-HTX **259A 3**. Owing to its surprising volatility this was immediately converted into the hydrochloride salt **25** in good yield (82%, two steps), [α]_D^{25,5} –54.0 (*c* 0.2 in EtOH), the spectra (¹H, ¹³C NMR and *m/z*) of which were consistent with those of the natural material.^{15,17}

In summary, we have shown that our tandem hydroxylamine cyclisation–nitron cycloaddition route to the histrionicotoxins is highly divergent. Employing this approach followed by selective elaboration of the core molecule **6** afforded (–)-histrionicotoxin **285E 5** in 4.5% overall yield (22 steps), (–)-histrionicotoxin **285C 4** in 6.0% yield (21 steps) and (–)-histrionicotoxin **259A** hydrochloride **25** in 4.5% yield (19 steps). We thank the EPSRC for financial support and provision of the Swansea Mass Spectrometry Service and Novartis for the award of a CASE studentship (to C. J. S).

Notes and references

‡ The BOM derivative was easier to prepare than the corresponding benzyl ether.

§ The triisopropylsilyl protecting group was required to resist desilylation during the forcing conditions required for displacement of the mesylate.

¶ We are unable to explain the discrepancy in the specific rotation of 5·HCl.

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