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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 C_4 or C_5 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 CITES[7] has restricted the supply of natural material making synthetic routes greater in demand. One formal[8] and three total[9–11] syntheses of histrionicotoxin (HTX) **1** have been reported, the last two of which yielded the naturally occurring (−)-enantiomer.

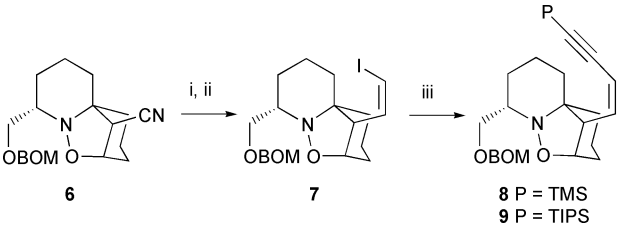
In this paper we report the first total syntheses of (−)-HTX **259A 3**, (−)-HTX **285C 4** and (−)-HTX **285E 5** which are derived from the common tricyclic core **6**.‡ This precursor is obtained in eleven steps (22%) from simple linear precursors by our tandem hydroxylamine alkyne cyclisation–nitrone 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 Wittig[12] reaction with 1.5 eq. of the iodophosphorane ylide [generated at −30 °C from the phosphonium salt with $KN(SiMe_3)_2$] to yield the (*Z*)-iodoalkene **7**. This was readily converted in excellent yield into the (*Z*)-enyne **8** or **9** respectively by Sonogashira ethynylation[13] with either trimethylsilyl- or triisopropylsilylacetylene (Scheme 1).†

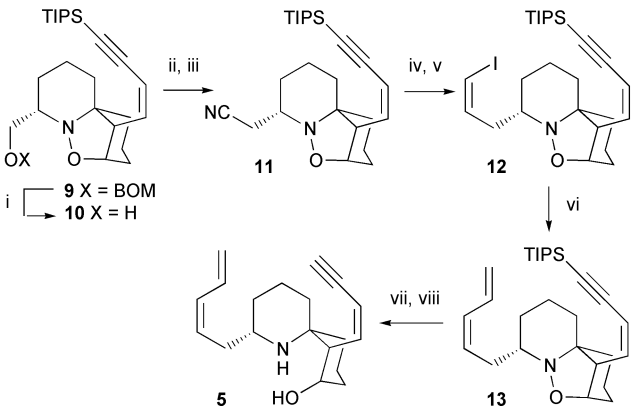
Attention now turned to incorporation of the *C*-2 side chain (Scheme 2). (−)-Histrionicotoxin **285E 5** possesses a (*Z*)-diene moiety, which could be introduced in a two step procedure from the nitrile **11**. Acidic cleavage of the benzyloxymethyl group yielded the crystalline alcohol **10** which was converted *via* the mesylate into the nitrile **11**.§ The (*Z*)-iodoalkene **12** was prepared by the same procedure as described above, and Stille coupling[14] with tributylvinyltin in DMF employing a catalytic quantity of $PdCl_2(MeCN)_2$ 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**, $[\alpha]_D^{27}$ 23.8 (*c* 0.08 in $CHCl_3$) [for **5**·HCl $[\alpha]_D^{27}$ −38.5 (*c* 0.18 in EtOH), lit.[15] $[\alpha]_D^{25}$ −122 (*c* 1.0 in EtOH)],¶ the spectra (^{1}H 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).

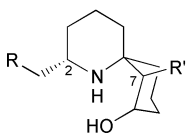
Deprotection of BOM ether **8** followed by IBX oxidation[19] of the resulting alcohol **14** gave the aldehyde **15** in excellent yield. Dropwise addition of a preformed solution of 4-trimethylsilyl-but-3-ynyl magnesium bromide in THF to a solution of the aldehyde in THF cooled to 0 °C yielded a 2:1 mixture of diastereomers **16** which could be readily separated by flash



Scheme 1 Completion of the *C*-7 side chain. *Reagents and conditions*: i, DIBAL-H, toluene, −78 °C, 100%; ii, $KN(TMS)_2$, $[Ph_3PCH_2I]^+I^-$, THF, −78 °C, 82%; iii, $Pd(PPh_3)_4$, CuI, Et_2NH, $Me_3SiC{\equiv}CH$ (for **8**), 95%; $^iPr_3SiC{\equiv}CH$ (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, NEt_3, DMAP, CH_2Cl_2, 97%; iii, NaCN, DMSO, 4 Å MS, 55 °C, 66%; iv, DIBAL-H, toluene, −78 °C, 100%; v, $KN(TMS)_2$, $[Ph_3PCH_2I]^+I^-$, THF, −78 °C, 82%; vi, tributylvinyltin, $PdCl_2(MeCN)_2$, DMF, 80%; vii, Zn, AcOH, 0.5 h, 91%; viii, Bu_4NF (TBAF) THF, 84%.



1; R = (*Z*)-CH=CHC≡CH, R' =(*Z*)-CH=CHC≡CH
2; R = CH=CH$_2$, R' = CH=CH$_2$
3; R = CH=CH$_2$, R' = (*Z*)-CH=CHC≡CH
4; R = CH$_2$CH$_2$C≡CH, R' = (*Z*)-CH=CHC≡CH
5; R = (*Z*)-CH=CHCH=CH$_2$, 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/

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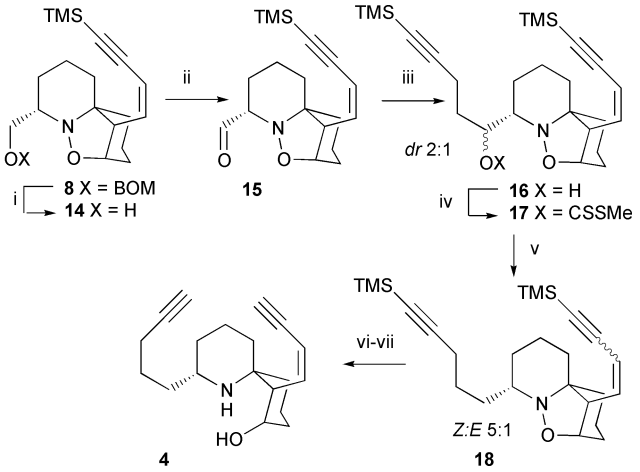
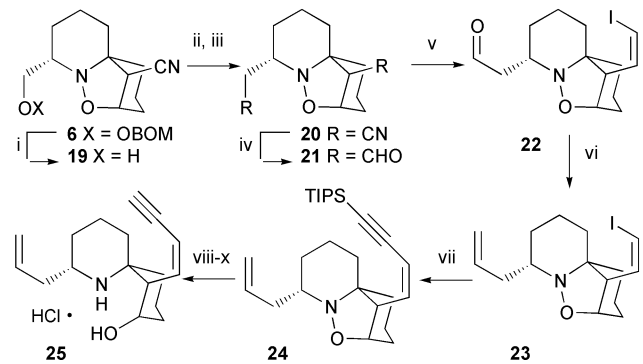


Scheme 3 Completion of the synthesis of (−)-HTX **285C 4**. *Reagents and conditions:* i, Amberlyst-15™, MeOH, 97%; ii, IBX, DMSO, 96%; iii, $TMSC{\equiv}C(CH_2)_2MgBr$, 0 °C, THF, 93%; iv, NaH, 0 °C → rt, 1.5 h; CS_2, 1 h; MeI, 1.5 h, THF, 83%; v, Bu_3SnH, AIBN, benzene, 80 °C, 70%; vi, Zn, AcOH, 30 min, 97%; vii, K_2CO_3, 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**, $[\alpha]_D^{18}$ −43.3 (*c* 0.12 in $CHCl_3$) [for **4**·HCl $[\alpha]_D^{19}$ −44.6 (*c* 0.12 in EtOH), lit.[21] $[\alpha]_D^{25}$ −43.4 (*c* 1.18 in EtOH)], the spectra (^{1}H 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, NEt_3, DMAP, CH_2Cl_2, 100%; iii, NaCN, DMSO, 4 Å MS, 55 °C, 66%; iv, DIBAL-H, toluene, −78 °C, 100%; v, $KN(TMS)_2$, $[Ph_3PCH_2I]^+I^-$, THF, −78 °C, 60%; vi, Cp_2TiMe_2, toluene, 110 °C, 83%; vii, $Pd(PPh_3)_4$, CuI, Et_2NH, $^iPr_3SiC{\equiv}CH$, 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 (dimethyltitanocene)[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), $[\alpha]_D^{25.5}$ −54.0 (*c* 0.2 in EtOH), the spectra (^{1}H, ^{13}C 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–nitrone 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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