A Novel Approach to the Histrionicotoxin Framework

Philip J. Parsons,*[a] Richard Angell,[a] Alan Naylor[b] and Elizabeth Tyrell[c]

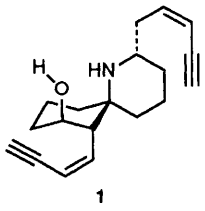
[a] *Department of Chemistry, University of Reading, Whiteknights, PO Box 224, Reading RG6 2AD, UK*
[b] *Glaxo Group Research Ltd., Ware, Hertfordshire, UK*
[c] *Department of Pharmacy, The Cockroft Building, Brighton Polytechnic, Brighton, Sussex, UK*

A tandem Michael addition–nitrone cyclisation sequence has been used to construct the histrionicotoxin skeleton.

Histrionicotoxin **1** was first isolated from the Columbian tree frog *Dendrobates histrionicus* by Daly *et al.* in 1971.[1] In common with other alkaloids (batrachotoxins, gephyrotoxins, pumiliotoxins[2]) isolated from the skin secretions of these frogs, the histrionicotoxins display neurological activity, interfering with the binding of acetylcholine to its protein bound receptor at the junction between a neuron and a muscle cell.[3]

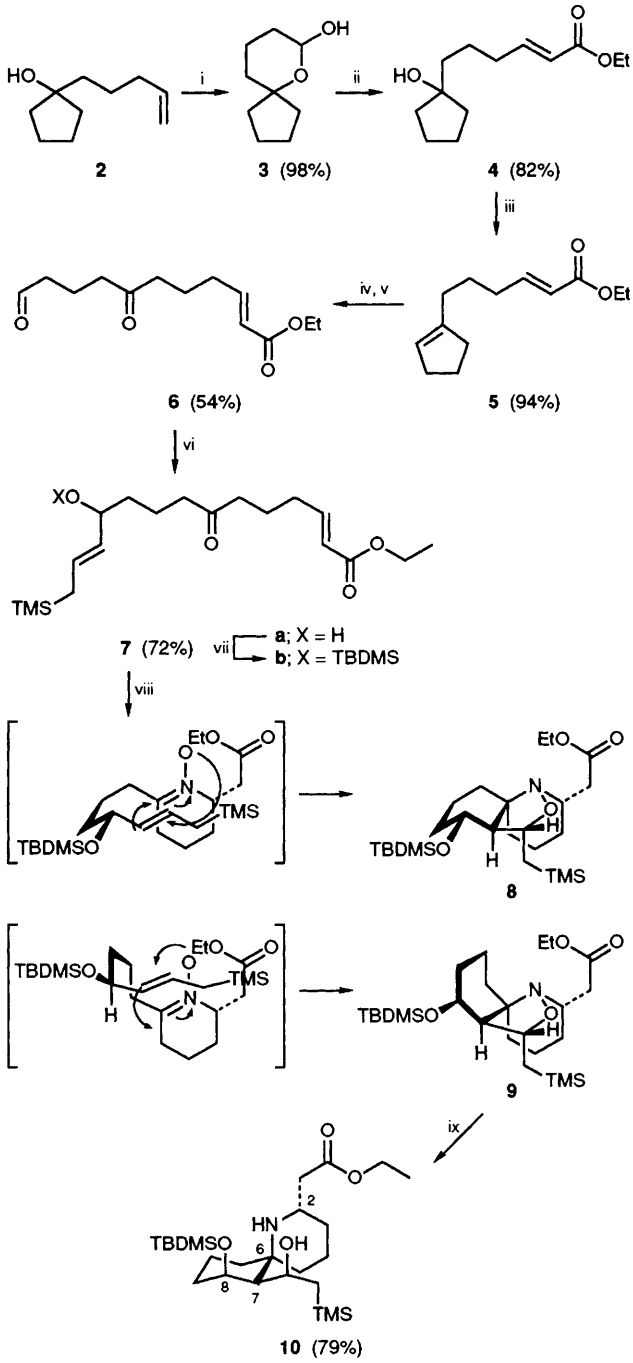
Our approach to histrionicotoxin **1** relies on a tandem Michael addition–nitrone cyclisation sequence. Treatment of cyclopentanone with the Grignard reagent derived from 1-bromopent-4-ene gave the alcohol **2** quantitatively (Scheme 1). Ozonolysis of **2** in DCM (CH_2Cl_2) followed by reductive work-up with triphenylphosphine gave lactol **3**, which was treated with ethoxycarbonylmethylenetriphenylphosphorane to yield the acrylic ester **4**. Elimination of the alcohol was achieved with phosphorus oxychloride in pyridine to give alkene **5**, which was smoothly converted to the keto-aldehyde **6** by epoxidation followed by periodate cleavage. A chromium mediated addition[4] of 3-bromoallyltrimethylsilane[5] to **6** furnished our cyclisation precursor in high yield. The alcohol was protected as the TBDMS (*tert*-butyldimethylsilyl) ether under standard reaction conditions. When the ester **7b** was committed to our cyclisation conditions two cyclised products were obtained in equal quantities in 52% overall yield. Cycloaddition of the intermediate nitrone took place by way of a 'boat-like', rather than a 'chair-like' transition state, to produce isoxazolidines **8** and **9**† [relative stereochemistries were confirmed by NOE (nuclear Overhauser effect) spectroscopic studies]. The nitrogen–oxygen bond was reductively cleaved to yield hydroxy-amine **10**.

Compound **10** has the correct relative stereochemistry at centres 2, 6 and 8 to be taken through to histrionicotoxin, while we expect to be able to isomerise centre 7 to the correct stereochemistry once the side chain has been developed to the aldehyde.



1

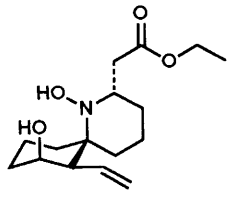
This cyclisation is reminiscent of work by Tufariello and Trybulski[6] but relies on the addition of an oxime nitrogen to an electron-deficient double bond followed by cycloaddition



Scheme 1 *Reagents and conditions*: i, (*a*) O_3, DCM, −78 °C; (*b*) PPh_3; ii, Ph_3PCHCO_2Et, DCM, room temp.; iii, $POCl_3$, pyridine, reflux; iv, m-chloroperbenzoic acid, DCM; v, H_5IO_6, tetrahydrofuran–H_2O; vi, 3-bromoallyltrimethylsilane, $CrCl_2$, $NiCl_2$ (cat), DMF (dimethylformamide); vii, TBDMSCl, DMF, dimethylaminopyridine (cat), imidazole; viii, NH_2OH·HCl, NaOAc, toluene, H_2O, sealed tube, 150 °C; ix, H_2, Pd, EtOH, 40 psi, (TMS = trimethylsilyl).

† *Spectroscopic data* for **8**: IR υ_{max}/cm^{-1} (DCM solution cell) 1727s (C=O), 1278s, 840s (Si–C). δ_H (400 MHz, $CDCl_3$) 0.00 (15H, s), 0.85 (9H, s), 0.95 (1H, dd, *J* 15, 3 Hz), 1.05 (1H, dd, *J* 11, 15 Hz), 1.18 (1H, m), 1.22 (3H, t, *J* 7 Hz), 1.30–1.45 (4H, m), 1.55–1.60 (2H, m), 1.75–1.85 (3H, m), 2.20 (1H, bs), 2.50 (1H, bs, *J* 9.0 Hz), 2.75 (1H, bd, *J* 10 Hz), 3.10 (1H, dd, *J* 15, 2 Hz), 3.25 (1H, m), 3.85 (1H, bt, *J* 9Hz), 3.95 (1H, apparent q, *J* 2.4 Hz), 4.15 (2H, dq, *J* 7, 1.6Hz). δ_C (100.614MHz) −5.24, −5.02, 14.17, 16.62, 17.79, 19.17, 25.64, 27.02, 29.20, 29.60, 31.26, 32.03, 35.93, 39.82, 55.17, 31.26, 32.03, 35.93, 39.82, 55.17, 60.03, 60.07, 67.32, 80.48, 172.54.

For **9**; IR υ_{max}/cm^{-1} (DCM solution cell) 1727s (C=O), 1278s, 840s (Si–C). δ_H (400 MHz, $CDCl_3$) 0.00 (5H, s), 0.85 (10H, bs), 0.95 (1H, dd, *J* 15, 12 Hz), 1.22(3H, t, *J* 7 Hz), 1.20–1.85 (12H, m), 2.05–2.20 (2H, m), 2.65 (1H, dd, *J* 9, 5 Hz), 3.15 (1H, dd, *J* 16, 2 Hz), 3.25–3.35 (1H, br m), 3.85 (1H, dt, *J* 5, 12 Hz), 4.30 (1H, br m), 4.10(2H, q, *J* 7 Hz).



11

to an allylic trimethylsilane to successfully direct the cycloaddition,[7] in contrast to the acrylic ester employed by Tufariello and Trybulski. Work in the 1960s demonstrated the reaction of oximes with electron-poor double bonds[8] and has been the subject of a thorough investigation in recent years by Grigg and coworkers[9] and ourselves.[10]

Cyclisation of the parent alcohol **7a** under similar conditions gave the hydroxylamine **11** (40%), produced by a consecutive Michael addition, cycloaddition fragmentation sequence. Compound **11** compares with azaspirocycle **10** and arises from an *in situ* fragmentation of the intermediate isoxazolidine. This compound is also under investigation in our new approach to the histrionicotoxins and related compounds.

Received, 21st October 1992; Com. 2/05628C

References

1 J. W. Daly, I. L. Karle, C. W. Myers, T. Tokuyama, J. A. Waters and B. Witkop, *Proc. Natl. Acad. Sci. USA*, 1971, **68**, 1870. For the only total syntheses of histrionicotoxin to date see Y. Kishi, S. C. Carey and M. Aratani, *Tetrahedron Lett.*, 1985, **26**, 5887; G. Stork and K. Zhao, *J. Am. Chem. Soc.*, 1990, **112**, 5875.

2 B. Witkop and E. Gossinger, *The Alkaloids*, Academic Press, 1983, 168.

3 J. Elliot and M. A. Raftery, *Biochemistry*, 1979, **18**, 1968; E. X. Albuquerque and D. M. Feigl, *Biochem. Pharmacol.*, 1985, **34**, 3037; J. W. Daly and T. Lovenberg, *Neurochem. Res.*, 1986, **11**, 1609.

4 Y. Kishi, H. Jin, J. Uenishi and W. J. Christ, *J. Am. Chem. Soc.*, 1986, **108**, 5644.

5 K. Itoh, H. Nishiyama and S. Narimalsu, *Tetrahedron Lett.*, 1981, **22**, 5289.

6 J. J. Tufariello and E. J. Trybulski, *J. Org. Chem.*, 1974, **39**, 3378.

7 A. Hosomi, H. Shoji and H. Sakurai, *Chem. Lett.*, 1985, 1049.

8 K. Moriota, N. M. Obayshi and M. Ochiai, *Tetrahedron*, 1967, **23**, 2641; A. Lablanche-Combier and M. L. Villaume, *Tetrahedron*, 1968, **24**, 6951; E. Winterfeldt, W. Krohn and H-V. Stracke, *Chem. Ber.*, 1969, **102**, 2346.

9 R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4477; P. Armstrong, R. Grigg, F. Heaney, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4495, and references cited therein.

10 E. Tyrell, PhD Thesis, University of Southampton, 1989; C. P. Till, PhD Thesis, University of Southampton, 1982.