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Two-directional synthesis. Part 1: A short formal synthesis of (±)-histrionicotoxin and (±)-histrionicotoxin 235A

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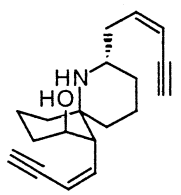
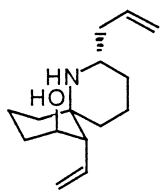
Abstract

The formal synthesis of (±)-histrionicotoxin and (±)-histrionicotoxin 235A using a two-directional strategy has been accomplished. The key feature of the synthesis is a tandem oxime formation/Michael addition/nitrone cycloaddition sequence, which form the azaspiro[5.5]undecane skeleton in two operations from an acyclic symmetrical precursor.

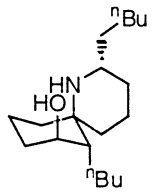
The histrionicotoxins are a family of spirocyclic alkaloids isolated from the skin extracts of the columbian 'poison arrow' frog, *Dendrobates histrionicus*.[1] Histrionicotoxin **1** and its hydrogenation product, the non-natural perhydrohistrionicotoxin **2** are both useful biochemical tools for probing the mechanisms of transsynaptic transmission of neuromuscular impulses.[2] This remarkable biological activity, in combination with the parent compound's low abundance in nature, have prompted considerable synthetic interest over the last few decades, culminating in three syntheses of **1** and numerous syntheses of **2**.[3,4]



Histrionicotoxin **1**



Histrionicotoxin 235A



Perhydrohistrionicotoxin **2**

Herein is reported a short formal synthesis of histrionicotoxin and histrionicotoxin 235A, utilising a tandem Michael addition/[3+2] cycloaddition sequence[5,6] as the key step in a two-directional strategy[7] (Scheme 1).

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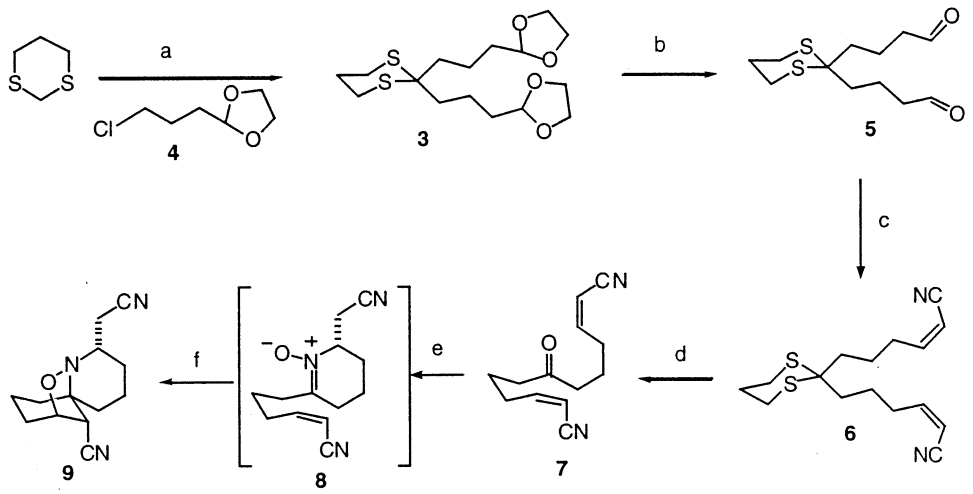

Scheme 1. (a) (i) *n*-BuLi, THF, −25°C, 2 h; (ii) **4**, −78 to 0°C, 16 h; (iii) *n*-BuLi, THF, HMPA, −25°C, 2 h; (iv) **4**, −78 to rt, 24 h, 70%. (b) 1:1 THF/2 M HCl, 100%. (c) Me_3SiCH_2CN, THF, *n*-BuLi, −78°C, 30 min; then **5**, −78°C, 2 h, 73%. (d) NCS, $AgNO_3$, MeCN, H_2O, 15 min, 77%. (e) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, rt, 18 h. (f) Toluene, 160°C, 2 h, 47% from **7**.

1,3-Dithiane was doubly alkylated to give diacetal **3** by successive deprotonation with *n*-butyl lithium followed by treatment with 2-(3′-chloropropyl)-1,3-dioxolane **4**. Two equivalents of HMPA were added after the second addition of *n*-butyl lithium to aid the second deprotonation.[8] Removal of the acetal protecting groups from **3** was achieved in quantitative yield by stirring at room temperature for 24 hours in a 1:1 mixture of THF and 2 M hydrochloric acid. Dialdehyde **5** was converted to dinitrile **6** by use of a double Peterson olefination with trimethylsilylacetonitrile[9] the *Z*,*Z* isomer being isolated in 73% yield, with most of the remaining material being the *Z*,*E* stereoisomer. Removal of the dithiane was achieved in 77% yield using *N*-chlorosuccinimide and silver nitrate in aqueous acetonitrile,[10] to give the symmetrical cyclisation precursor **7**. Treatment of **7** with one equivalent of hydroxylamine hydrochloride and two equivalents of sodium acetate in methanol at room temperature gave nitrone **8** by way of oxime formation and subsequent Michael addition. Crude nitrone **8** was then heated in toluene in a sealed tube at 160°C for 2 hours. Purification gave dinitrile **9** as a single regioisomer in 47% yield over the two steps.

Dinitrile **9** is an advanced intermediate in Holmes' recent synthesis of histrionicotoxin and histrionicotoxin 235A,[4a] thus this represents a formal synthesis of these two alkaloids.[11] Synthesis of dinitrile **9** was achieved in six steps and 18.5% overall yield from 1,3-dithiane. Investigations into the use of this two-directional strategy for the synthesis of related alkaloids are ongoing in these laboratories.

Acknowledgements

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References

1. (a) Witkop, B. *Experientia* **1971**, *27*, 1121. (b) Daly, J. W.; Karle, I.; Meyers, W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 1870. (c) Tokuyama, T.; Venoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta* **1974**, *57*, 2597. (d) Karle, I. *J. Am. Chem. Soc.* **1973**, *95*, 4036.
2. (a) Rapier, C.; Wannacot, S.; Lunt, G. G.; Alberquerque, E. X. *FEBS Lett.* **1987**, *212*, 292. (b) Oliviera, L.; Madison, B. W.; Kapai, H.; Sherby, S. M.; Swanson, K. L.; Edelfraui, M. E.; Alberquerque, E. X. *Eur. J. Pharmacol.* **1987**, *140*, 331. (c) Sobel, A.; Heidmann, T.; Hofler, J.; Changeaux, J. P. *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 510.
3. For reviews, see: (a) Kotera, M. *Bull. Soc. Chim. Fr.* **1989**, 370. (b) Grössinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1983; pp. 139–251. (c) Inubushi, Y.; Ibuka, T. *Heterocycles* **1982**, *17*, 507.
4. For syntheses not covered by reviews, see: (a) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (b) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 5875. (c) Luzzio, F. A.; Fitch, R. W. *J. Org. Chem.* **1999**, *64*, 5485. (d) Tanner, D.; Hagberg, L.; Poulsen, A. *Tetrahedron* **1999**, *55*, 1427. (e) Comins, D. L.; Zhang, Y.; Zheng, X. *Chem. Commun.* **1998**, 2509. (f) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907. (g) Kim, D.; Hong, S. W.; Park, C. W. *Chem. Commun.* **1997**, 2263. (h) Compain, P.; Gore, J.; Vatele, J. M. *Tetrahedron Lett.* **1995**, *36*, 4063. (i) Maezaki, N.; Fukuyama, H.; Yagi, S.; Tanaka, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1835. (j) Zhu, J.; Royer, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1991**, *32*, 2485. (k) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852. For synthetic approaches, see: (l) Comins, D. L.; Zheng, X. *J. Chem. Soc., Chem. Commun.* **1994**, 2681. (m) Parsons, P. J.; Angell, R.; Naylor, A.; Tyrell, E. *J. Chem. Soc., Chem. Commun.* **1993**, 366. (n) Thompson, C. M. *Heterocycles* **1992**, *34*, 979. (o) Venit, J. J.; DiPierro, M.; Magnus, P. *J. Org. Chem.* **1989**, *54*, 4298.
5. (a) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399. (b) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929. (c) Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J. F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991**, *47*, 8297. (d) Grigg, R.; Heaney, F.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4007. (e) Armstrong, P.; Grigg, R.; Heaney, F.; Surerndrakumar, S.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4495. (f) Grigg, R.; Heaney, F.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4477. (g) Grigg, R.; Jordan, M.; Tangthongkum, A.; Einstein, F. W. B.; Jones, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 47.
6. For other approaches to histrionicotoxin utilising nitrone cycloadditions, see references 4(a,m) and Tufariello, J. J.; Trybulski, E. J. *J. Org. Chem.* **1974**, *39*, 3378; Gössinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96.
7. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.
8. If HMPA (2 equiv.) was not added prior to the second addition of alkyl chloride, the yield of the dialkylation was reduced to 37%.
9. (a) Haruta, R.; Ishiguro, M.; Furuta, K.; Mori, A.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1982**, 1093. (b) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.
10. Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
11. Analytical data for selected compounds are as follows. Compound **3**: ^{1}H NMR ($CDCl_3$, 300 MHz) 1.51–1.71 (8H, m), 1.92 (4H, td, $J=7.8$ and 1), 1.94 (2H, m), 2.80 (4H, t, $J=5.7$), 3.82 (4H, m), 3.96 (4H, m), 4.87 (2H, t, $J=4.2$); IR (thin film, cm^{-1}) 1420, 1142; ^{13}C NMR ($CDCl_3$, 75 MHz) 104.5, 65.0, 53.3, 38.1, 33.9, 29.7, 26.1, 18.8; *m/z* (EI) 348 (M^+). Anal. calcd for $C_{16}H_{28}O_4S_2$: C, 55.14; H, 8.10; S, 18.40. Found: C, 54.89; H, 8.05; S, 18.68. Compound **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) 1.62 (4H, m), 1.91 (6H, m), 2.46 (4H, dtd, $J=7.5$, 7.2, 1.2), 2.81 (4H, t, $J=5.7$), 5.38 (2H, td, $J=11.1$, 0.9), 6.50 (2H, dt, $J=11.1$, 7.5); ^{13}C NMR ($CDCl_3$, 67.5 MHz) 156.6, 118.2, 102.7, 54.7, 40.0, 33.9, 31.8, 28.1, 25.2; IR (thin film, cm^{-1}) 2218, 1619; HRMS calcd for $C_{16}H_{26}S_2N_3$ ($M+NH_4$): 324.1568. Found: 324.1562. Compound **7**, ^{1}H NMR ($CDCl_3$, 300 MHz) 1.78 (4H, m), 2.42 (4H, dtd, $J=7.8$, 7.5, 1.2), 2.46 (4H, t, 7.5), 5.36 (2H, dt, $J=10.8$, 1.2), 6.47 (2H, dt, $J=10.8$, 7.8); ^{13}C NMR ($CDCl_3$, 75 MHz) 209.2, 154.3, 118.0, 100.4, 41.7, 31.3, 22.0; IR (thin film, cm^{-1}) 2219, 1708, 1620; HRMS calcd for $C_{13}H_{20}N_3O$ ($M+NH_4$): 234.1606. Found: 234.1602. Compound **9**, ^{1}H NMR ($CDCl_3$, 300 MHz) 1.64–1.96 (10H, m), 2.23 (2H, m), 2.56 (1H, dd, $J=17.2$, 8.3), 2.74 (1H, m), 2.76 (1H, dd, $J=17.2$, 3.3), 3.36 (1H, dd, $J=6.3$, 2.1), 4.73 (1H, ddd, $J=6.3$, 3.3, 2.7); ^{13}C NMR ($CDCl_3$, 67.5 MHz) 117.7, 117.2, 76.1, 65.6, 61.8, 38.3, 35.8, 31.9, 29.4, 27.0, 23.1, 18.7, 17.4; IR (thin film, cm^{-1}) 2240, 1450; HRMS calcd for $C_{13}H_{18}N_3O$ ($M+H^+$): 232.1450. Found: 232.1453.
12. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.