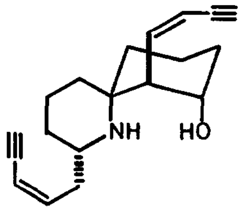
Tetrahedron Letters No. 18, pp 1539 - 1542, 1976. Pergamon Press. Printed in Great Britain.

MODEL STUDIES IN THE HISTRIONICOTOXIN SERIES: A HIGHLY STEREOSELECTIVE SYNTHESIS OF TERMINAL cis ENYNE UNITS.

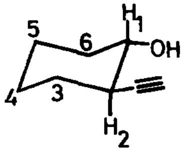
Andrew B. Holmes, Ralph A. Raphael, and Nicholas K. Wellard.
University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

(Received in UK 5 March 1976; accepted for publication 22 March 1976)

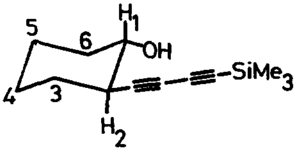
Synthetic interest in histrionicotoxin (1) and its derivatives has been intense.[1] We now wish to report a highly stereoselective synthesis of a terminal cis enyne unit in the model compound (5) which closely resembles the arrangement in the carbocyclic ring of histrionicotoxin itself. In this route the four-carbon chain is sequentially inserted by two acetylenic building blocks, the first (acetylene) being introduced as a nucleophile, and the second (trimethylsilylacetylene) by an oxidative coupling procedure. Inspection of the literature[2] revealed that the catalytic hydrogenation of trimethylsilyl-



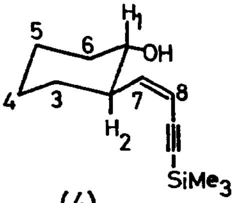
(1)



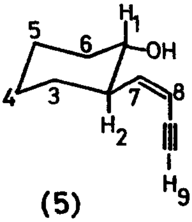
(2)



(3)



(4)



(5)

protected butadiyne derivatives held considerable promise as a potential route to terminal cis enynes. The only previously reported selective synthesis of such compounds involved a non-nucleophilic introduction of the chain and a stepwise elaboration to the desired enyne.[1a]

Treatment of cyclohexene epoxide with lithium acetylide-ethylene diamine complex according to Norton's[3] procedure afforded trans-2-ethynylcyclohexanol(2) in 53% yield. This was oxidatively coupled with a three-fold excess of trimethylsilylacetylene[4] in the presence of the Hay catalyst,[5,6] to give the trimethylsilylbutadiynylcyclohexanol (3),[7] m.p. 91-92.5°, in 57% yield: i.r. ($CHCl_3$) 3590 m (OH), 2230 s (C≡C), 2110 s (Si-C≡C) cm^{-1}; u.v. (C_6H_{12}) 217 nm (ε 400), 229 (600), 241 (900), 254 (1,000), 261 inf. (400), 269 (700). The diyne (3) was hydrogenated (1 atm) in hexane-methanol (20:1) over 5% Pd on $BaSO_4$ containing quinoline until 1.1 mole-equivalent of hydrogen had been consumed. After chromatography of the crude product on silica the only detectable compounds were the starting material (15%) and the silylated cis enyne (4)[7] (65%). The cis enyne was a low melting solid which was shown to be homogenous on various t.l.c. systems and by g.l.c. (4 metre 2% versamid, 175°): i.r. (CCl_4) 3590 w (OH), 2150 m (Si-C≡C) 695 w (cis C=C-H) cm^{-1}; u.v. 231 inf. nm (ε 8,700), 239 (11,600), 249 (9,400). That catalytic reduction of (3) had occurred selectively at the unsilylated triple bond was shown by the disappearance in the i.r. spectrum of (4) of the C≡C band at 2230 cm^{-1}, and the cis stereochemistry of the double bond was clearly confirmed by the 11 Hz coupling constant between the olefinic protons (see Table), and by the presence of an i.r. band at 695 cm^{-1} and the absence of any absorption between 960 and 980 cm^{-1}. Removal of the trimethylsilyl protecting group from (4) using tetra-n-butylammonium fluoride [1a] in anhydrous tetrahydrofuran afforded the cis enyne (5)[7] as a colourless oil in 82% yield: i.r. ($CHCl_3$) 3580 m (OH), 3300 s (C≡C-H), 2090 w (C≡C) cm^{-1}; u.v. 227 nm (ε 8,000).

The n.m.r. spectra of compounds (3), (4), and (5) are summarised in the Table. The extrapolation of this selective cis enyne production to the synthesis of (1) is in hand.[8]

TABLE : N.M.R. SPECTRA OF COMPOUNDS (3), (4) and (5)

Compound	Solvent	δH-1	δH-2	δ H-3, H-4, H-5, H-6	δH-7	δ H-8	δ H-9
(3)	$CDCl_3$	3.31 d of t $J_{1,2} = 9$ Hz $J_{1,6a} = 9$ $J_{1,6e} = 4$	2.13 d of t $J_{2,1} = 9$Hz $J_{2,3a} = 9$ $J_{2,3e} = 4$	0.9-2.0 m	-	-	Me_3Si 0.12 s
(4)	CCl_4	3.25 d of t $J_{1,2} = 9$Hz $J_{1,6a} = 9$ $J_{1,6e} = 4$	2.48 d of q $J_{2,1} = 9$Hz $J_{2,3a} = 9$ $J_{2,3e} = 4$ $J_{2,7} = 9$	1.0-2.2 m	5.77 dd $J_{7,2} = 9$Hz $J_{7,8} = 11$	5.51 d $J_{8,7} = 11$Hz	Me_3Si 0.15 s
(5)	$CDCl_3$	3.35 d of t $J_{1,2} = 9$ Hz $J_{1,6a} = 9$ $J_{1,6e} = 4$	2.63 d of q $J_{2,1} = 9$ Hz $J_{2,3a} = 9$ $J_{2,3e} = 4$ $J_{2,7} = 9$	1.0-2.4 m	5.89 dd $J_{7,2} = 9$Hz $J_{7,8} = 11$	5.56 dd $J_{8,7} = 11$Hz $J_{8,9} = 2$	3.14 d $J_{9,8} = 2$ Hz

References

1. (a) E.J. Corey and R.A. Ruden, Tetrahedron Letters, 1495 (1973);
   (b) J.J. Tufariello and E.J. Trybulski, J. Org. Chem., **39**, 3378 (1974);
   (c) E.J. Corey, J.F. Arnett, and G.N. Widiger, J. Amer. Chem. Soc., **97**, 430 (1975);
   (d) W. Kissing and B. Witkop, Chem. Ber., **108**, 1623 (1975);
   (e) E. Gössinger, R. Imhof, and H. Wehrli, Helv. Chim. Acta, **58**, 96 (1975);
   (f) L.E. Overman, Tetrahedron Letters, 1149 (1975);
   (g) M. Aratani, L.V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura and S. Inoue, J.Org. Chem., **40**, 2009 (1975);
   (h) T. Fukuyama, L.V. Dunkerton, M. Aratani, and Y. Kishi, J. Org. Chem., **40**, 2011 (1975);
   (i) E.J. Corey, M. Petrzilka, and Y. Ueda, Tetrahedron Letters, 4343 (1975);
   (j) E.J. Corey, Y. Ueda, and R.A. Ruden, Tetrahedron Letters, 4347 (1975);
   (k) F.T. Bond, J.E. Stemke, and D.W. Powell, Synthetic Communications, **5**, 427 (1975);

2. B.G. Shakhovskoi, M.D. Stadnichuk, and A.A. Petrov, Zh. Obshch. Khim., **34**, 2625 (1964); J. Gen Chem. USSR, **34**, 2646 (1964).

3. J.R. Norton, K.E. Shenton, and J. Schwartz, Tetrahedron Letters, 51 (1975). We thank Professsor Norton for providing full experimental details of this procedure.

4. U. Krüerke, J. Organomet. Chem., **21**, 83 (1970).

5. A.S. Hay, J. Org. Chem., **27**, 3320 (1962).

6. For the oxidative coupling of silylated acetylenes using the Hay modification of the Glaser procedure, see R. Eastmond, T.R. Johnson, and D.R.M. Walton, Tetrahedron, **28**, 4601 (1972).

7. All new compounds gave satisfactory microanalytical data.

8. We thank the Science Research Council for the award of a studentship to N.K. W.