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STEREOCONTROLLED SYNTHESIS OF THE HISTRIONICOTOXIN RING SYSTEM

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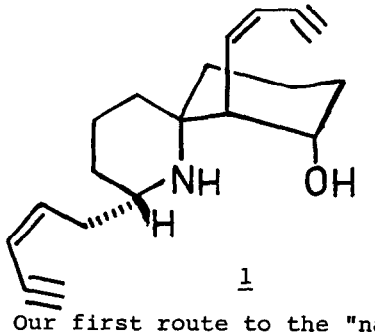
Abstract. Two simple, efficient and stereocontrolled routes to the cis-azaspiro-[5.5]-undecan-8-ol skeleton of the histrionicotoxin alkaloids are described.

Histrionicotoxin, 1, is an unusual alkaloid isolated[1,2] from extracts of the skin of the Colombian "poison arrow" frog species Dendrobates histrionicus. This biologically active compound and its congeners both natural and non-natural, eg. the perhydro-derivative 2, have proved to be remarkably useful probes in the study of neurophysiological ion transport[4k] while the intriguing molecular structure and very low natural abundance of such toxins have inspired widespread synthetic activity[3,4] ever since the pioneering work of Corey[3a] and Kishi[3b]. The recent renewal of synthetic and pharmacological interest[4k] in simpler analogues such as 3 prompts us to disclose two efficient routes to this azaspirocycloundecanol skeleton common to the histrionicotoxin alkaloid family.



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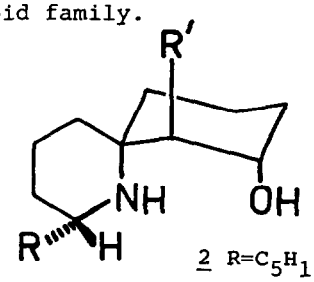
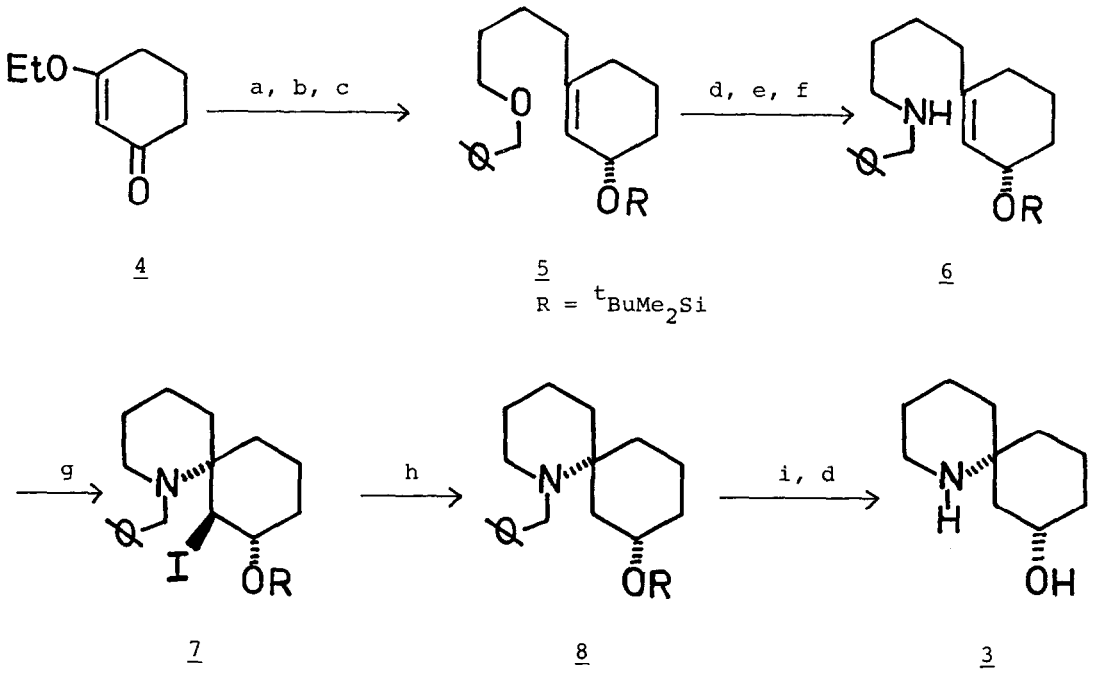


2 R=C_5H_{11}, R'=C_4H_9

3 R=R'=H

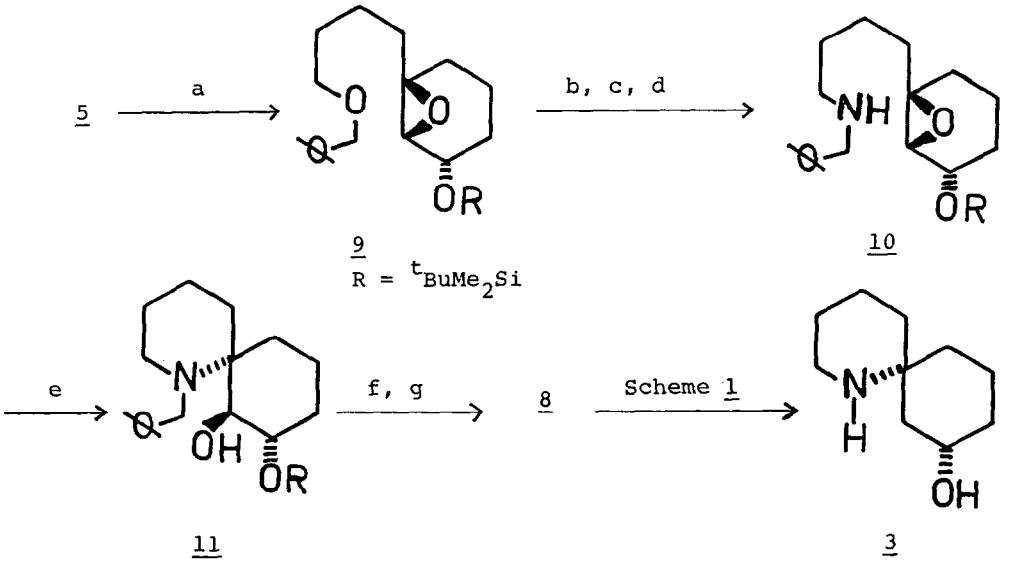
Our first route to the "naked histrionicotoxin" 3 (Scheme 1) bears some resemblance to recent work on 2 by Godleski[4d,4e] and Carruthers[4g]. Thus, the vinylogous ester 4[5] provided, after Grignard reaction[6] and acidic work-up, the appropriate 3-substituted enone in excellent yield. Subsequent DIBAL reduction was followed by silylation to 5 which was then efficiently debenzylated and the resultant primary alcohol tosylated. Displacement of



Scheme 1. (a) $BnO(CH_2)_4MgBr$, THF, then H^+/H_2O, 85% yield (b) DIBAL, CH_2Cl_2, 97% (c) TBDMSCl, imidazole, DMF, 98% (d) H_2, $Pd(OH)_2/C$, EtOH, 100% (e) TsCl, pyridine, 93% (f) $BnNH_2$, cat. NaI, DMSO, 85% (g) I_2, CH_2Cl_2, 90% (h) $NaBH_3CN$, HMPA, 73% or $(Bu)_3SnH$, C_6H_6, 80% (i) Bu_4NF, THF then (d), 82% from 8.

the tosyl group by benzylamine in the presence of NaI furnished amine 6 which upon exposure to 1.5 equiv. of I_2 in CH_2Cl_2 smoothly yielded the desired azaspirocycle 7 as a single diastereomer in 90% yield[7]. That the required regio- and stereochemistry had indeed been obtained was shown unambiguously by the 270 MHz ^1H NMR spectrum, the silyl ether, iodo and amino substituents on the cyclohexane ring all adopting equatorial positions and the proton adjacent to iodine appearing as a doublet (J_{axax} = 10 Hz) at δ 4.27. The diastereotopic benzylic protons of 7 (a sharp singlet in the spectrum of 6) appear as a well-separated AB-system[4g] (J = 13.5 Hz) at δ 3.89 and 2.83. Iodide 7 was transformed in 66% yield to the known[4k] 3 by reductive deiodination, desilylation and debenzylation. The desired azaspirocyclic alcohol is thus readily available in quantity from the simple starting material 4 (38% overall yield for ten steps).

Scheme 2 shows a complementary route to 3, the key spirocyclisation step in this case being an efficient regiospecific intramolecular ring-



Scheme 2. (a) mCPBA, $CH_2Cl_2/NaHCO_3$ aq., 87%, trans:cis 9:1 (b) H_2,$Pd(OH)_2/C$ EtOH, 100% (c) TsCl, pyridine, 95% (d) $BnNH_2$, cat. NaI, DMSO, 82% (e) toluene, reflux, 100% (f) MeLi then MsCl, Et_2O, 95% (g) $LiAlH_4$, THF, 76%.

opening[8] of the amino-epoxide 10. Epoxidation of the protected allylic alcohol 5 yielded an easily separable 9:1 mixture of epoxides, the major component being the expected[9] and desired trans-isomer 9 which was isolated in 80% yield after flash chromatography. Debenzylation, tosylation and amination as before proceeded efficiently to 10 which upon prolonged reflux in dilute toluene solution cyclised cleanly to the azaspirocyclic alcohol 11, a quantitative yield of chromatographically homogeneous and NMR-spectroscopically pure material being realised. The stereochemical assignment again rests on the high-field ^1H NMR spectrum, in particular the -CHOH doublet (J = 9 Hz) at δ 3.55 and the benzylic AB-type doublets (J = 14 Hz) at 4.14 and 2.95. Mesylation of 11 was followed by immediate LAH reduction, the resultant material being in all respects identical to 8 prepared as described in Scheme 1. Treatment of the mesylate with a slight excess of NaI in warm acetone yielded iodide 7 exclusively, overall substitution occurring either via double S_N2-type inversion[10] or possibly via an aziridinium species. The reaction sequence depicted in Scheme 2 thus delivers the desired 3 in twelve straightforward steps, the overall yield being a satisfying 30% based on 4.

In conclusion, two efficient and stereocontrolled routes to the histrionicotoxin analogue 3 have been developed; the use of similar

methodology and the elaboration of intermediates such as 7 and 11 to higher histrionicotoxins such as 2, the biological activity of which is fully comparable to that of 1,[1,2] will be described in the full paper[11].

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