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SYNTHESIS OF ETHYNYLAZASPIROCYCLOUNDECENE: APPROACH TO SIDE CHAIN UNSATURATED HISTRIONICOTOXINS

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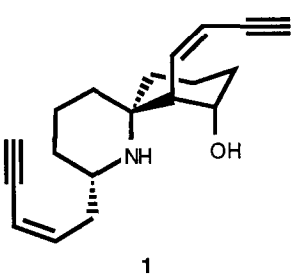
Summary A short synthesis of *N*-benzyl-7-ethynyl-1-azaspirocyclo[5.5]undec-7-ene (**3**) from the spirocyclic ketolactam (**5**) *via* the vinyl iodide (**8**) is described. An unusual allylic rearrangement of the lactam (**9**) occurred during reaction with $LiAlH_4$.

The Colombian frog *Dendrobates histrionicus* is the source of a variety of structurally distinct alkaloids.[1,2] The histrionicotoxins, isolated from the skin extracts of this species, are a family of 1-azaspiro[5.5]undecan-8-ols possessing unsaturated side-chains at the 2- and 7-positions. Interest in these compounds stems from their unusual neurophysiological properties. Both histrionicotoxin (**1**) and the fully reduced derivative (**2**) are potent non-competitive antagonists of acetylcholine.[1-3] The search for synthetic routes to (**1**) and (**2**) has resulted in many interesting approaches and several syntheses of (**2**)[4] as well as Kishi's single route to the more challenging target (**1**).[5] We report a synthesis of the azaspirocyclic enyne (**3**) which formed the basis of our approach to (**1**).



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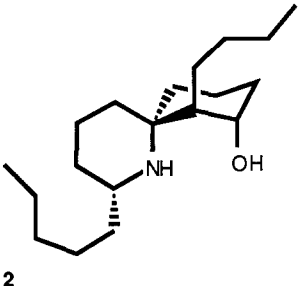
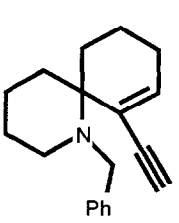


2

The known azaspirocyclic ketolactam (**5**) was prepared either by ruthenium tetroxide-mediated cleavage[6] of the alkene (**4**) or from ethyl cyclohexanone-2-carboxylate by the method of Bond.[7] Treatment of the ketolactam with lithium acetylide in THF at -78 °C gave the acetylenic carbinol (**6**) as a single isomer. This tertiary alcohol



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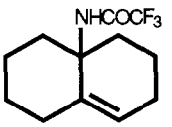

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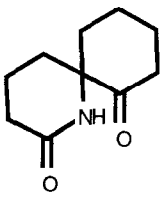
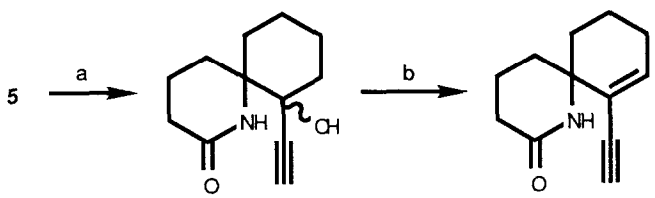


5

was surprisingly resistant to a wide spectrum of dehydrating conditions, the best of which proved to be thionyl chloride in pyridine (Scheme 1) to give (**7**) in 38% yield.

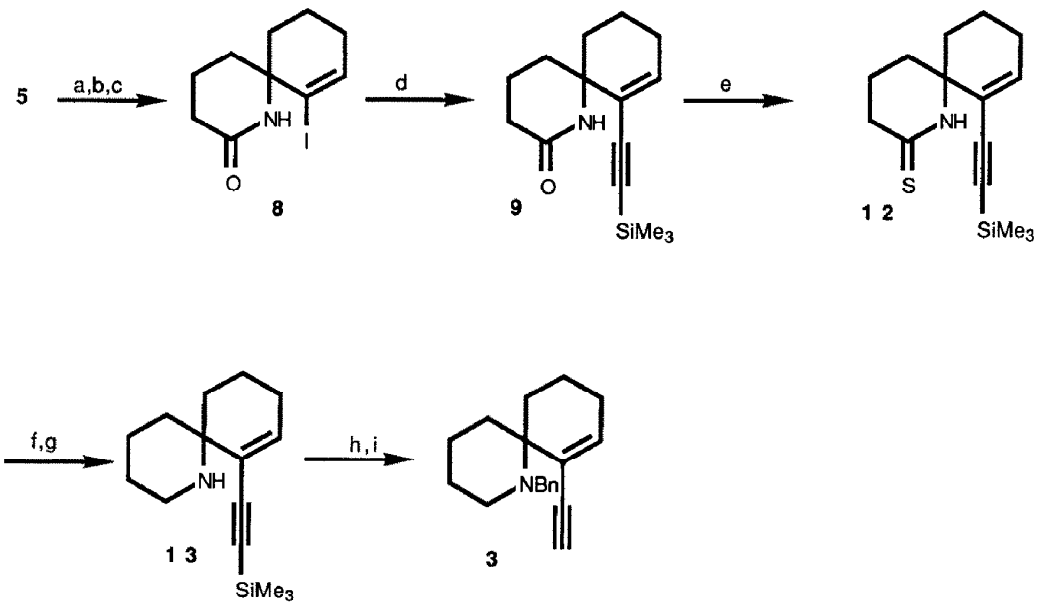


6 7

Reagents: (a) Lithium acetylide, THF, -78 °C to -20 °C (66%); (b) $SOCl_2$, pyridine, 20 °C (38%)

SCHEME 1

A more successful alternative route to this family of compounds is shown in Scheme 2. Treatment of (**5**) with hydrazine gave the corresponding hydrazone (m.p. 113.5-115.5 °C) which was converted into the vinyl iodide (**8**) (m.p. 139-140.5 °C) by oxidation with iodine in the presence of tetramethylguanidine (TMG).[8] Palladium(0)-mediated coupling[9] of (**8**) with ethynyltrimethylsilane gave the enyne (**9**) (m.p. 138.5-140 °C) which could be desilylated to give (**7**) (m.p. 173-174 °C).



SCHEME 2

Reagents: (a) $N_2H_4.H_2O$, 100 °C; (b) I_2, TMG, THF, 20 °C; (c) TMG, 90 °C (65%);
(d) Ethynyltrimethylsilane, $Pd(PPh_3)_4$, CuI, $^nBuNH_2$, benzene (87%);
(e) $(p\text{-}MeOC_6H_4PS_2)_2$, toluene, 100 °C;
(f) $Me_3O^+BF_4^-$, CH_2Cl_2;
(g) $NaBH_4$, MeOH, -78 °C to -20 °C;
(h) Na_2CO_3, MeOH; (i) BnBr, NaI, MeCN, $^iPr_2NEt$ [58% from (9)]

Reduction of the lactam (**9**) with $LiAlH_4$ in refluxing THF gave an unexpected product (**10a**) in which desilylation of the acetylene probably occurred during aqueous work-up. This compound was characterised as the amide (**10b**). The formation of (**10a**) involves reductive allylic rearrangement for which a possible mechanism is shown in Scheme 3. Such allylic rearrangements with $LiAlH_4$ are relatively rare.[10] All attempts to carry out direct reductions of (**9**) or the desilylated compound (**7**) were unsuccessful in complete contrast to the results for $LiAlH_4$ reduction of the mixture of exo- (**11a**) and endocyclic allylic amides (**11b**) where high yields of spirocyclic amine with no rearranged product were observed.[6]

An alternative less direct procedure was then used to reduce the lactam (**9**) under very mild conditions. Treatment of (**9**) with Lawesson's reagent[11] gave the thiolactam (**12**) (m.p. 152-153 °C) which was converted into the corresponding thioimino ether with Meerwein's reagent (20 °C, 2h). Subsequent reduction with $NaBH_4$ in methanol[12] gave the spirocyclic amine (**13**) in high yield and with no evidence of allylic rearrangement. Under these conditions partial desilylation of the enyne occurred. This was taken to completion with Na_2CO_3 in methanol (20 °C, 1h) to give 7-ethynyl-1-azaspirocyclo[5.5]undec-7-ene which was purified as the *N*-benzyl derivative (**3**).[13] In view of the extensive studies on the conversion of the corresponding 7-

butyl compound to perhydrohistrionicotoxin (**2**) which has been in much demand in isotopically labelled form for biological studies,[1,2] the ready availability of compound (**3**) offers a concise approach to highly tritiated perhydrohistrionicotoxin analogues and derivatives.

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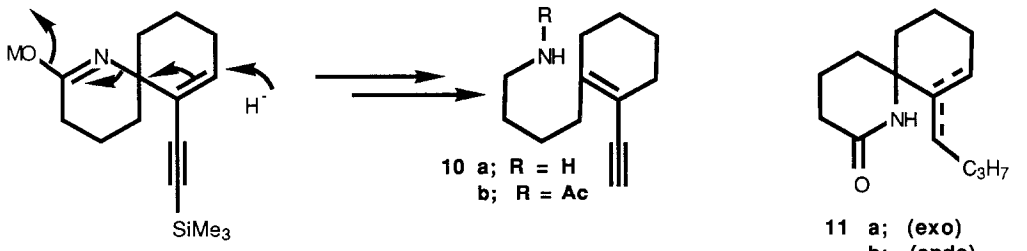

SCHEME 3

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13. All new compounds are racemic and exhibited spectroscopic and analytical data consistent with the proposed structure: (**3**): ^1H δ 7.52-7.14 (5H), 6.35 (1H, t, 4.2Hz), 3.94 & 3.09 (2H, ABq, 13.6 Hz), 2.85 (1H, s), 2.52 & 2.26 (2H, m), 2.11 - 1.47 (12H, m); ^{13}C δ 141.2, 139.7, 129.8, 128.8, 127.8, 126.3, 84.4, 75.9, 55.6, 45.3, 35.0, 26.0, 21.7, 20.3, 19.8; (**9**): ^1H δ 6.24 (1H, t, 4.2 Hz), 5.56 (1H,br s), 2.25 (2H, m), 2.10 (2H, m), 2.07 - 1.6 (8H, m), 0.15 (9H,s); ^{13}C δ 171.9, 138.1, 127.6, 103.7, 95.3, 55.5, 37.2, 33.0, 33.1, 25.5, 18.5, 17.5, -0.12.

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