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FORMAL SYNTHESIS OF (±)-PERHYDROHISTRIONICOTOXIN

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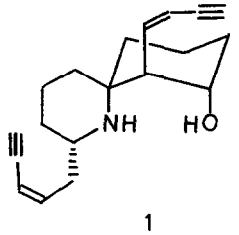
Summary: The syntheses of 1-benzyl-7-butyl-1-azaspirocyclo[5.5]undec-7-ene **(14)** [a formal precursor of perhydrohistrionicotoxin **(2)**] and the thermodynamically preferred exocyclic isomer **(13)** in six steps from the readily available N-benzyloxycarbonyl-10-amino-$\Delta^{1,9}$-octalin **(5)** are reported.

The alkaloids of neotropical poison frogs (Dendrobatidae) have provided a rich source of structural variation and biological activity.[1-6,13] In particular, histrionicotoxin **(1)** and a number of reduced derivatives, including the non naturally occurring perhydrohistrionicotoxin **(2)**, have been the subject of numerous synthetic investigations.[1,3,5,7-12] Both **(1)** and **(2)** block the passage of potassium and sodium ions in a number of different systems. The enantiomer of **(2)** shows similar activity, and the desamyl-derivative **(3)** exhibits parallel but less potent properties.

We now report a short synthesis of the azaspirocycle **(14)** which represents a formal synthesis of **(3)** and **(2)**. The nitrosyl chloride adduct of octalin **(4)** serves as the starting material for the azaspirocycloundecane system. This is converted by a modification of known procedures into the urethane **(5)** (Scheme 1). Ozonolysis[18] of the urethane **(5)** gave under the work-up conditions the azaspirocyclic enamide **(6)** which upon catalytic reduction yielded the saturated derivative **(7)** (Scheme 2). Removal of the benzyloxycarbonyl group with iodotrimethylsilane gave the amino-ketone **(8)** which could be converted into the N-benzyl derivative **(9)** [54% from **(6)**]. The carbonyl groups of both compounds **(7)** and **(9)** were severely hindered to attack by most carbon nucleophiles, and were either rapidly enolised or reduced even in the presence of the recently described organotitanium[19] and organozirconium[20] reagents which have been reported suitable for nucleophilic attack on readily enolisable carbonyl groups. Eventually, a modest yield of the isomeric alcohols **(10)** was obtained by repetitive addition of n-butyl-lithium to the amino-ketone **(8)**, followed by quenching with methanol.[21]



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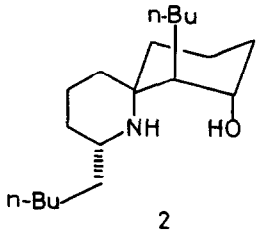

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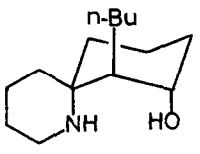

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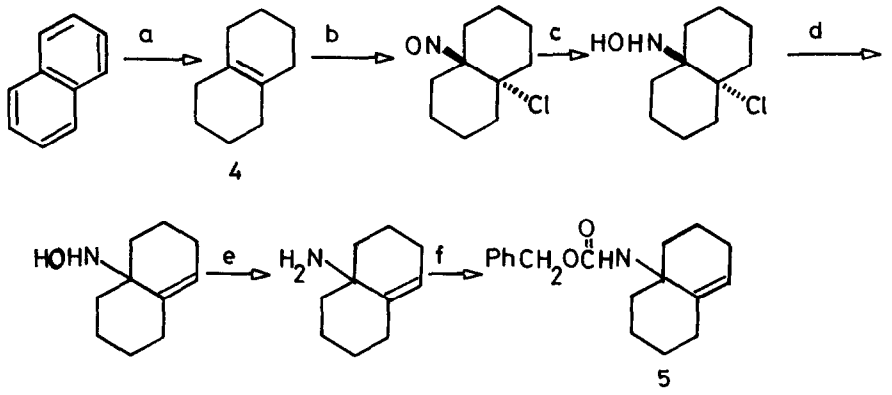
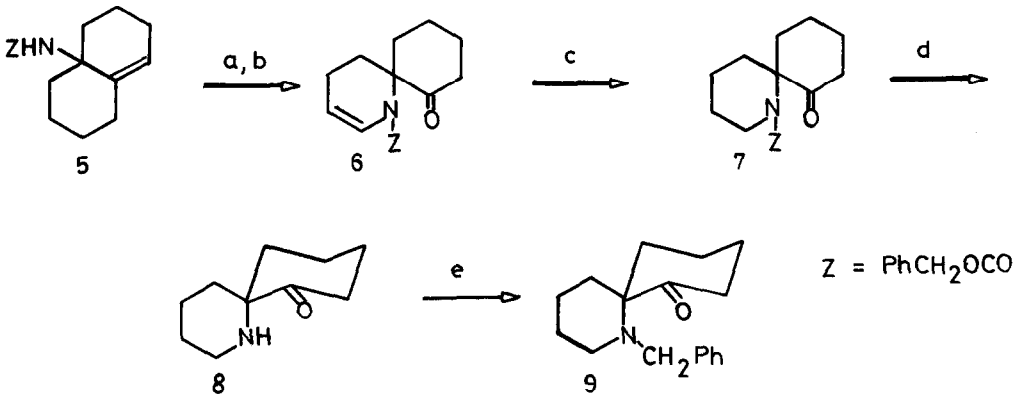


Reagents: (a) Li, $EtNH_2$-Me_2NH[14](63%), (b) iso-amyl nitrite-HCl[15] (70%), (c) H_2-Pt(98%)-see Ref 16, (d) NaOMe-MeOH, RT (90%), (e) Al-Hg, THF-H_2O, reflux (100%)-see Ref 17, (f) $PhCH_2OCOCl$ (99%).

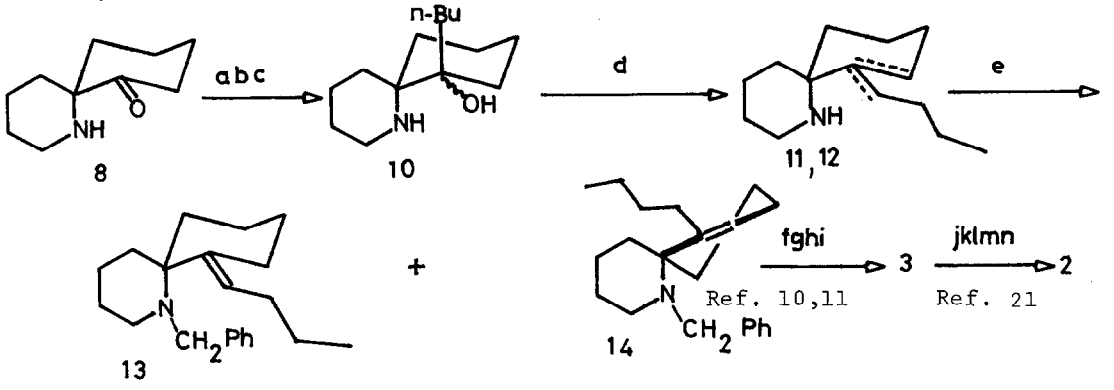
SCHEME 1



Reagents: (a) O_3, CH_2Cl_2, -78 °C, (b) Me_2S (43-72%), (c) H_2-PtO_2, EtOH (95%), (d) Me_3SiI, CH_3CN, 16h, RT (85%), (e) $PhCH_2Br$, K_2CO_3, THF, 4-5d, RT (55%)

SCHEME 2

Dehydration of the alcohols **(10)** gave a 4:1 mixture of exocyclic **(11)** and endocyclic **(12)** azaspirocyclic alkenes, identified as the corresponding N-benzyl derivatives **(13)** and **(14)**. These compounds could be obtained from **(7)** in a five step sequence in 26% yield. The endocyclic alkene **(14)** was identical in all respects to an authentic sample which has been converted by others[10,11] into **(3)** and thence **(2)**.[21,22]



Reagents: (a) n-BuLi, (b) MeOH, (c) Repeat five times (25%), (d) $KHSO_4$, 170 °C (53%), (e) $PhCH_2Br$, KI, $(i\text{-}Pr)_2NEt$, CH_3CN (35%), (f) BH_3, (g) $Me_3N^+\text{-}O^-$, (h) Acetylation, (i) H_2, Pd-C, (j) t-$BuSiMe_2Cl$, (k) NBS, (l) KOt-Am, (m) $C_5H_{11}Li$, (n) n-Bu_4NF

The well known thermodynamic preference for endocyclic double bonds in six-membered rings[21,23] would indicate that the mixture of **(13)** and **(14)** could be equilibrated in favour of **(14)**. However, all attempts at base-catalysed isomerisation were unsuccessful. Ultimately it was found that stoichiometric quantities of rhodium trichloride in refluxing ethanol converted the endocyclic N-benzyl alkene **(14)** to the exocyclic debenzylated[24] amino-alkene **(11)**. We conclude that the usual thermodynamic preference for endocyclic double bonds is overcome in this special case by the $A_{1,2}$-strain[25] present in **(14)**.

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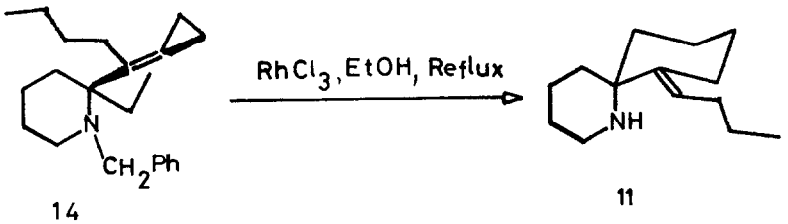

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