A Novel Approach to the Perhydrohistrionicotoxin Ring System

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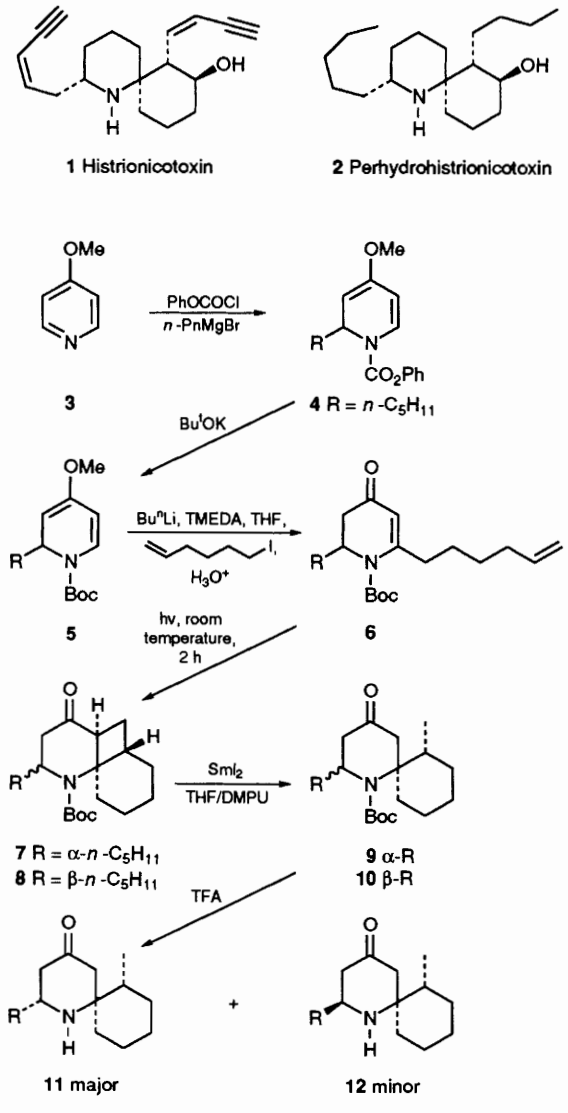
An approach to the skeleton of perhydrohistrionicotoxin *via* an intramolecular photocycloaddition of a 2,3-dihydro-4-pyridone and a SmI_2-mediated cyclobutane ring opening is described.

Histrionicotoxin **1** is one of the physiologically active alkaloids found in the skin secretions of the neotropical frog *Dendrobates histrionicus*.[1] Both **1** and perhydrohistrionicotoxin **2** have been used in studies of the mechanisms involved in transsynaptic transmission of neuromuscular impulses. The unique biological activity of these alkaloids has stimulated considerable synthetic interest.[1,2] Here we report a novel approach to the skeleton of **2** using an intramolecular photocycloaddition of a 2-alkyl-2,3-dihydro-4-pyridone[2] and a SmI_2-mediated cyclobutane ring opening as the key steps.

Addition of phenyl chloroformate to 4-methoxypyridine **3** in THF at −23 °C forms a 1-acylpyridinium salt *in situ*, which on treatment with *n*-pentylmagnesium bromide provides 2-alkyl-1,2-dihydropyridine **4** (Scheme 1).[3] Without purification, **4** was treated with Bu^{t}OK in THF to give *N*-Boc derivative **5** in 95% overall yield (silica gel, 1% Et_3N–hexane). Lithiation at C-6, alkylation with 6-iodohex-1-ene, and acidic workup provided 2,3-dihydro-4-pyridone **6** in 65% yield.[3b] On photolysis in acetone (460 W Hanovia Hg lamp, 2 h, room temp.),[4] **6** gave an 80% yield of tricyclic ketones **7** and **8** in a ratio of 5.9 : 1. Without separation, the mixture of diastereomers was carried through the next two steps. Treatment with SmI_2 in THF–DMPU effected regioselective cyclobutane ring opening to give spirocyclic ketones **9** and **10** in 68% yield. Although SmI_2 has been used to cleave α-ketocyclopropanes,[5] this is the first example of an analogous cyclobutane ring opening. The *N*-Boc groups were cleaved using trifluoroacetic acid providing the crude piperidones which were separated by radial plc (silica gel, 20% EtOAc–hexane) to give **11** and **12** in 62 and 15% yields, respectively. The relative stereochemistry of both isomers (**11** and **12**) was confirmed by single-crystal X-ray analysis of their hydrochloride salts (Fig. 1).† The spirocyclic ketone **11**, prepared in six steps from 4-methoxypyridine, has the skeleton and proper relative stereochemistry of perhydrohistrionicotoxin.‡ Dihydropyridones, *i.e.* **6**, can be prepared enantiopure from homochiral 1-acylpyridinium salts.[6] An asymmetric synthesis of perhydrohistrionicotoxin using the above strategy is underway in our laboratories.



Scheme 1

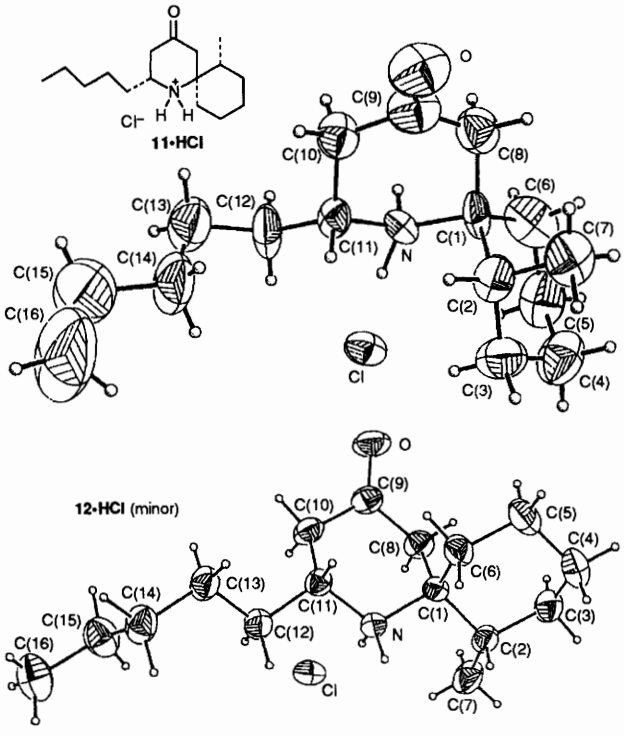


Fig. 1 Crystal structures of **11**·HCl and **12**·HCl

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Footnotes

† Crystals of **11**·HCl, mp 161–162 °C, and **12**·HCl, mp 171–172 °C, suitable for diffraction were grown from ethanol at room temperature.

Crystal data: **11**·HCl, $C_{16}H_{29}NO$·HCl, M = 287.96, crystal size 0.40

× 0.20 × 0.06 mm, monoclinic, space group $P2_1/c$, a = 11.08(2), b = 11.52(2), c = 13.33(2) Å, β = 95.59(6)° U = 1693(5) Å, Z = 4, D_c = 1.13 g cm^{-3}, λ(Mo-Kα) = 0.71073 Å, F(000) = 632, ω scan, scan speed 4–29.3° min^{-1}, 3 ≤ 2θ ≤ 42°, hkl −11 to 11, 0–10, 0–13, 1820 unique reflections with 759 observed [$I \geq 4\sigma(I)$], μ = 2.2 cm^{-1}, R = 0.081, R_w = 0.11, S = 1.0, max. shift/σ = 0.03, 185 variables, ρ(max., min.) = 0.38, −0.31 e Å^{-3}.

12·HCl, $C_{16}H_{29}NO$·HCl, M = 287.96, crystal size 0.50 × 0.20 × 0.12 mm, monoclinic, space group $C2/c$, a = 24.287(17), b = 8.544(7), c = 17.001(15) Å, β = 111.67(5)°, U = 3278(5) Å^3, Z = 8, D_c = 1.16 g cm^{-3}, λ(Mo-Kα) = 0.71073 Å, F(000) = 1264, ω scan, scan speed 4–29.3° min^{-1}, 3 ≤ 2θ ≤ 55°, hkl, −30 to 29, 0–11, 0–21, 3767 unique reflections with 2527 observed, μ = 2.2 cm^{-1}, R = 0.046, R_w = 0.057, S = 1.4, max. shift/σ = 0.12, 289 variables, ρ(max., min.) = 0.46, −0.20 e Å^{-3}.

Atomic coordinates, bond lengths and angles, and thermal parameters have been desposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ Satisfactory IR, ^{1}H and ^{13}C NMR, HRMS and microanalyses were obtained for all compounds described.

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