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A FORMAL SYNTHESIS OF (±)-PERHYDROHISTRIONICOTOXIN via α-ACYLIMMONIUM ION-OLEFIN CYCLIZATIONS

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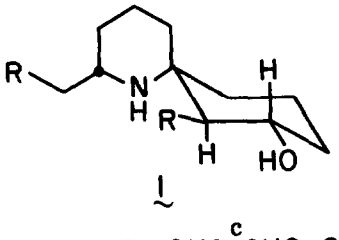
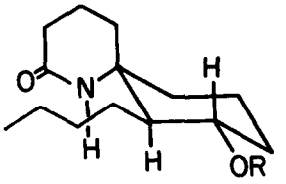
Histrionicotoxin (HTX) (1a),[2] an alkaloid recently isolated from the skin secretions of the Colombian frog Dendrobates histrionicus, has recently attracted considerable interest in relation to its total synthesis.[3] The interest in HTX and perhydrohistrionicotoxin (1b) stems from their unique properties as neurotoxins. It has been shown that both 1a and 1b block post synaptic membrane depolarization while not interfering with acetylcholine binding. It has been postulated that these toxins prevent membrane depolarization by reversible binding to the ion channel.[4]



1

a, R = CHC=CHC≡CH (c)

b, R = n-C_4H_9



2

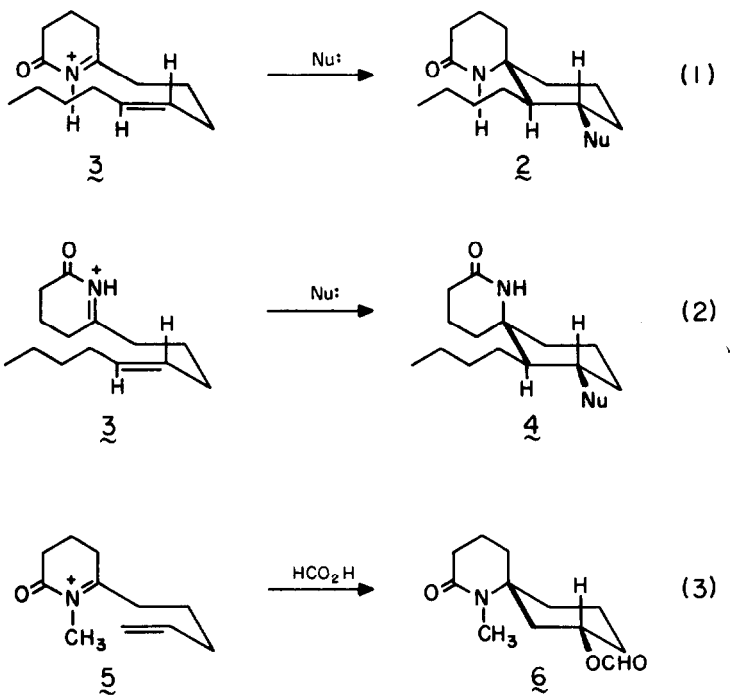
a, R = H

b, R = CH (=O)

Recent studies directed towards the total synthesis of perhydrohistrionicotoxin (PHTX) (1b) have established that spirolactam 2a is a versatile precursor to 1b[3b] In conjunction with our own interest in devising simplified approaches to the synthesis of PHTX analogs we have investigated the olefin cyclization of α-acylimmonium ion 3 which could lead to either the desired spirolactam 2 or its epimer 4 (Scheme I). In spite of the uncertainty associated with the stereochemical outcome of these competitive cyclization modes, a successful ring closure to 2 would insure a considerable improvement in the previously published route to lactam 2.[3] During the course of the present study Speckamp reported the related cyclization of 5 to give 6 in 45% yield.[5] This communication has prompted us to report our own observations on the cyclizations summarized in Scheme I. The requisite precursor

10 was prepared in good overall yield via the route outlined in Scheme II. The Grignard reagent 7b, prepared from alkyl chloride 7a,[6] was added to the iodomagnesium salt of glutarimide (Et_2O, 1 h, reflux).[8] After work-up (sat. aq. NH_4Cl, 0°C) a mixture of hydroxy lactam 8 and keto amide 9, mp 90-91°C, were obtained in 66% yield.[7] In preparative runs this mixture was directly dehydrated in a 75% yield to a 9:1-mixture of enamides 10 and 11 respectively in the presence of a catalytic amount of p-toluenesulfonic acid in refluxing toluene-DMF (50:1, 48 h).

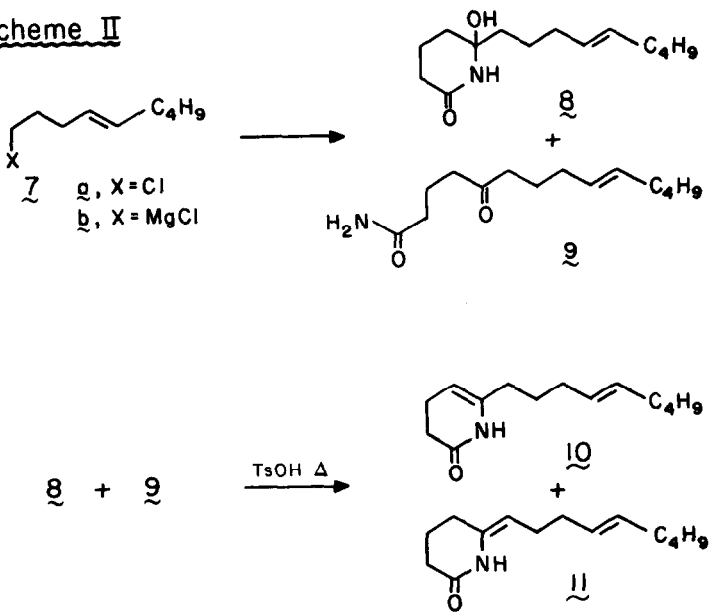
Scheme I



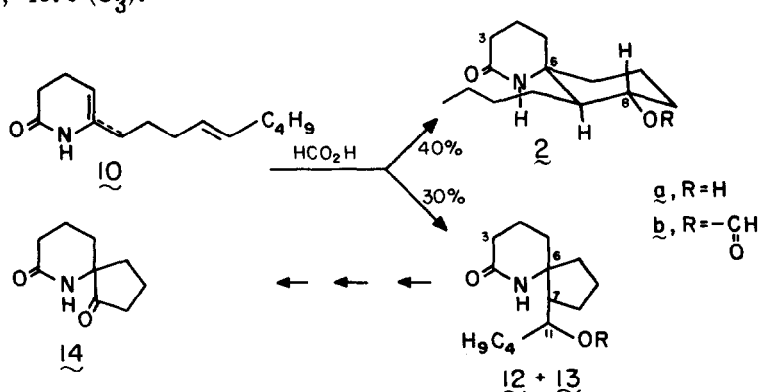
Chromatographic separation of this mixture on Silica Gel (1:1, EtOAc:hexane) afforded the pure enamide isomers 10 and 11: For 10: IR (neat) 3220 (NH), 1687, 1665 cm^{-1} (C=O, C=C); ^1H NMR δ ($CDCl_3$) 4.75 (multiplet, =CH) and for 11: IR (neat) 3220 (NH), 1682, 1665 cm^{-1} (C=O, C=C); ^1H NMR δ ($CDCl_3$) 4.32 (t, J = 6 Hz, C=CH). Upon acid treatment (CF_3CO_2H, $CDCl_3$), each isomer equilibrated via the presumed acylimmonium ion 3 to a 8:1-ratio of 10 and 11.

After exploring a range of cyclization conditions it was found that a 0.1 molar solution of 10 and 11 in anhydrous formic acid (25°C, 32 h) afforded the desired formate 2b, mp 148-149°C, in a 40% yield after chromatography:[7] IR ($CHCl_3$) 1716 (C=O), 1650 cm^{-1} (C=O lactam); ^1H NMR δ ($CDCl_3$) 4.95 (m, 1H, $W^{1/2}$ = 15 Hz, C_8-H), 8.08 (s, 1H, formate); ^{13}C NMR δ ($CDCl_3$), 171.9 (C_2), 160.1 (formate), 73.9 (C_8), 58.5 (C_6), 50.7 (C_7), 36.1 (C_3).

Scheme II



Alcoholysis (MeOH, NaOMe, 25°C, 0.5 h) of formate 2b was carried out in 95% yield to give the beautifully crystalline alcohol 2a: mp 133-134°C; IR ($CHCl_3$), 1623 cm^{-1} (C=O); ^{13}C NMR δ ($CDCl_3$), 171.4 (C_3), 69.7 (C_8), 57.4 (C_6), 49.3 (C_7), 33.1 (C_3), which proved to be identical in all respects to an authentic sample provided by Professor Y. Kishi. Careful chromatographic separation[9] and identification of all reaction products revealed a 10% recovery of enamide 10, a 10% yield of the enamide dimer,[10] and a 30% yield of two separable diastereoisomeric 6,5-spirans (2:1-ratio) shown (vide infra) to possess the general structure 12b. The minor 6,5-spirocyclic formate ester 12b was obtained as an oil while the major isomer 13b was subsequently crystallized: mp 118-120°C; IR ($CHCl_3$), 1708 (formate), 1650 cm^{-1} (lactam C=O); ^1H NMR δ ($CDCl_3$), 5.13 (d, d, J_1 = 5.4 Hz, J_2 = 10.8 Hz, $W^{1/2}$ = 12 Hz, 1H, C_{11}-H), 8.05 (s, 1H, formate); ^{13}C NMR δ ($CDCl_3$), 72.0 (C_2), 160.3 (formate), 7.28 (C_{11}), 64.2 (C_6), 52.2 (C_7), 40.0 (C_3).



Degradation of each spirolactam 12a and 13a afforded the keto lactam 14,[11] thus confirming that both 12a and 12b were diastereosiomers. These results indicate that there are two competing olefin cyclization modes which proceed with nearly equal facility. Nonetheless, in those cyclization modes leading to the 6,6-azaspirane product manifold (Scheme I, eq. 1, 2) the desired ring closure (eq. 1) proceeds with high stereoselectivity to establish three of the four requisite stereocenters for perhydrohistrionicotoxin (1b) in a single step.

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5. H.E. Schoemaker and W.N. Speckamp, Tetrahedron Lett., 1515 (1978).

6. Compound 7a was synthesized from 1-hepten-3-ol in an overall yield of 66% via: a, orthoester Claisen rearrangement; b, lithium aluminum hydride reduction; c, methanesulfonation and sodium chloride displacement.

7. Satisfactory spectral and analytical data were obtained for all new compounds reported.

8. M. Sekiya and Y. Terao, Chem. Pharm. Bull., 19, 391 (1971).

9. Preparative separations were performed on a Waters Prep 500 chromatograph (Silica Gel, EtOAc). Analytical HPLC was carried out with a μ-Poricil (30 cm) column (EtOAc, 6 ml/min). Observed retention volumes: 13b (11.2 ml), 12b (13.1 ml), 2b (14.3 ml).

10. For related dimerizations see: J.B.P.A. Wijnberg, W.N. Speckamp, and J.J.J. de Boer, Tetrahedron Lett., 4077 (1974).

11. IR ($CHCl_3$), 1718 (C=O), 1650 cm^{-1} (C=O lactam); Exact mass calcd. for $C_9H_{13}NO_2$: 167.093. Found: 167.095.

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