New Piperidinic Synthons via Ring Contraction. Formal Synthesis of (±)-Perhydrohistrionicotoxin

Pierre DUHAMEL,* Mitsuharu KOTERA, and Thierry MONTEIL
U.A.464 Laboratoire de Chimie Organique,
Faculté des Sciences et des Techniques de Rouen,
76130 Mont Saint Aignan, France
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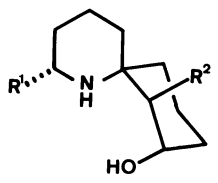
Synopsis. The 2,2-bifunctionalized piperidines **6** and **10** were obtained via ring contraction of the seven-membered heterocyclic enamino aldehyde **5** in nearly quantitative yield. The synthesis of 1-benzyl-1-azaspiro[5.5]undec-7-en-9-one **9** (a formal precursor of perhydrohistrionicotoxin **1b**) in 3 steps from the piperidinedialdehyde monoacetal **6**, is reported.

The histrionicotoxins, a group of unique spiropiperidinol alkaloids isolated from skin extracts of the Colombian poisonous frog "Dendrobates histrionicus," have been the subject of current synthetic investigation because of their important neurophysiological activity.[1] In particular, several successful syntheses of dodecahydro derivative **1b**, commonly named perhydrohistrionicotoxin or H_{12}-HTX, have been reported as have a number of approaches to similar compounds[2-4]. Recently a total synthesis of (±)-histrionicotoxin **1a** ((±)-HTX), the parent alkaloid of this family has been reported[5].



1a R^1 = $-CH_2CH=CH-C\equiv CH$, R^2 = $-CH=CH-C\equiv CH$

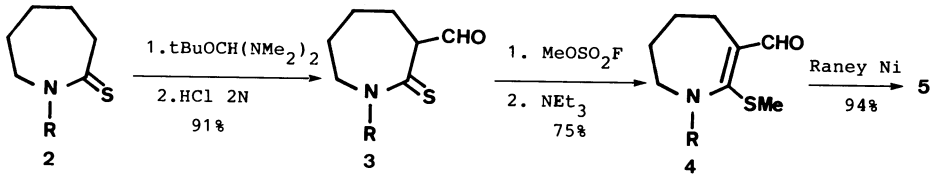
1b R^1 = C_5H_{11}, R^2 = C_4H_9

1c R^1 = $-(CH_2)_3-CH=CH_2$, R^2 = $-(CH_2)_2-CH=CH_2$

1d R^1 = H, R^2 = C_4H_9

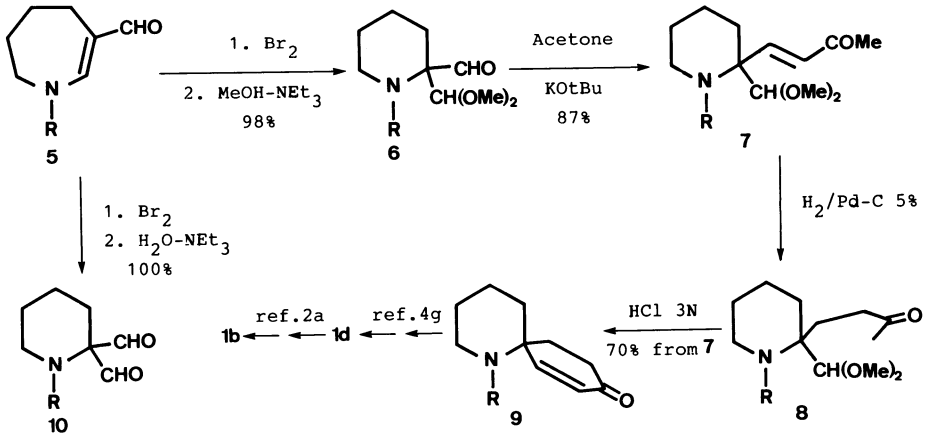
Having developed a new strategy for the preparation of 2,2-bifunctionalized pyrrolidines and piperidines via ring contraction of heterocyclic enamines[6], we sought to further demonstrate its utility by applying it in a synthesis of **9** which is reported to be a flexible synthon for the H_{12}-HTX.[4g] We selected the heterocyclic enamino aldehyde **5**, which is available in 3 steps from the thiolactame **2**,[7] as starting material.

Formylation of **2** was carried out by Bredereck's reagent followed by hydrolysis.[8] Methylation and deprotonation of **3** afford the methylthiotetrahydroazepinecarbaldehyde **4**. Reductive desulfurization of **4** to the enamino aldehyde **5** was accomplished by deactivated Raney nickel (64% overall yield from **2**).



R = Benzyl

Upon treatment with bromine followed by triethylamine-methanol[6], the tetrahydroazepine **5** was easily transformed to the piperidinedicarbaldehyde monoacetal **6** in 98% yield. The same reaction using triethylamine-water lead to the dicarbaldehyde **10** in quantitative yield.



R = Benzyl

This ring contraction affords us a direct and effective method for the synthesis of azaspiranic enone **9**. Thus the monoacetal **6** was condensed with acetone to give the unsaturated keto acetal **7** which was hydrogenated in the presence of 5% Pd-C. The resulting saturated keto acetal **8** was hydrolyzed without isolation and spontaneously cyclized by acid work-up (3 M HCl)[9] to the azaspirannic enone **9** (60% overall yield from **5**). The same enone **9** has been converted by others[4g,2a] into depentyl H_{12}-HTX **1d** and thence H_{12}-HTX **1b**.

Experimental

General Procedure. All melting points are uncorrected. Infrared spectra (IR) were recorded on a Perkin Elmer 337 spectrophotometer and are reported in cm^{-1}. ^1H NMR spectra were taken on a Perkin Elmer R 12. ^{13}C NMR spectra were taken on a Varian CFT20. The chemical shifts (δ values) are given in parts per million relative to TMS as an internal standard in $CDCl_3$ solutions and coupling constants in hertz. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

1-Benzyl-2-thioxohexahydroazepine-3-carbaldehyde 3. A mixture of **2** (35.0 g, 0.16 mol) and *t*-BuOCH(NMe_2)$_2$ (44.3 g, 0.25 mol) was heated at 140 °C for 3 h until most of *t*-BuOH had been removed by distillation. After cooling, the reaction mixture was poured into 2 M HCl (500 ml (1 M=1 mol dm^{-1})) and stirred for 2 h at room temperature. The resulting solid was collected by filtration, washed with cold water and dried on P_2O_5, providing 36.0 g (91%) of **3** which was utilized without further purification: IR (nujol) 1730; ^1H NMR 9.80 (d, J=2 Hz, 1H), 7.35 (s, 5H), 5.44, 5.88 (ABq, J=15 Hz, 2H), 3.5—3.8 (m, 3H), 1.2—2.5 (m, 6H); ^{13}C NMR 202.1, 192.3, 135.2, 128.6, 128.0, 127.7, 60.6, 56.6, 52.4, 27.3, 26.0, 23.6.

1-Benzyl-2-methylthio-4,5,6,7-tetrahydro-1H-azepine-3-carbaldehyde 4. Methyl fluorosulfate (24 g, 0.21 mol) was rapidly added to a solution of **3** (35.6 g, 0.14 mol) in CH_2Cl_2 (350 ml). The mixture was stirred overnight at room temperature. To this mixture, triethylamine (73 g, 0.72 mol) was added slowly with stirring and after 1 h, the dichloromethane was removed in vacuo. The oily residue was continuously extracted with hot hexane. **4** crystallized out on cooling (28.5 g, 75%) and was utilized without further purification: mp 88—89 °C; IR (nujol) 1610, 1510; ^1H NMR 9.92 (s, 1H), 7.30 (s, 5H), 4.73 (s, 2H), 3.15—3.4 (m, 2H), 2.2—2.5 (m, 2H), 2.25 (s, 3H), 1.25—1.6 (m, 4H); ^{13}C NMR 190.2, 168.3, 137.6, 128.7, 127.9, 127.8, 118.7, 56.5, 52.7, 25.1, 24.7, 23.2, 19.1; Anal. ($C_{15}H_{19}NOS$) C, H, N.

1-Benzyl-4,5,6,7-tetrahydro-1*H*-azepine-3-carbaldehyde 5. To about 20 g of W2 Raney nickel previously refluxed in acetone (100 ml) for 2 h was added a solution of **4** (3.9 g, 14.9 mmol) in acetone (30 ml), and the mixture was refluxed for 3 h. After cooling, the solution was decanted and the catalyst was washed six times with acetone. The decanted solution and washings were together filtered and concentrated. The resulting solid was purified by flash chromatography on silica gel with ethyl acetate as the eluant to give 3.0 g (94%) of **5**: Mp 69—70 °C (ethyl acetate); IR (nujol) 1600; ^1H NMR 8.98 (s, 1H), 7.3 (m, 5H), 6.90 (s, 1H), 4.40 (s, 2H), 3.1—3.4 (m, 2H), 2.3—2.6 (m, 2H), 1.5—1.9 (m, 4H); ^{13}C NMR 190.5, 160.3, 136.6, 128.9, 128.1, 127.3, 115.4, 63.1, 52.5, 28.2, 26.2, 23.6; Anal. ($C_{14}H_{17}NO$) C, H, N.

1-Benzyl-2-dimethoxymethylpiperidine-2-carbaldehyde 6. To a suspension of **5** (3.23 g, 15.0 mmol) in anhydrous ether (420 ml) were added at −70 °C 2.6 g (16.2 mmol) of bromine in 25 ml of cold (about −30 °C) anhydrous ether. After completion of the addition, the resulting yellow suspension of the iminium salt was stirred at this temperature for 30 min. To this suspension, a mixture of methanol (12.7 g, 0.39 mol) and triethylamine (4.55 g, 45.0 mmol) was added at −70 °C and the reaction mixture was allowed to warm to room temperature, stirred for 24 h, and filtered. The filtrate was concentrated under reduced pressure, and cold anhydrous ether (50 ml) added to the residue. The triethylamine hydrobromide was filtered and the solvent was evaporated under reduced pressure to give 4.08 g (98%) of **6** which was utilized without further purification. An analytical sample was obtained by flash chromatography on silica gel with petroleum ether/ether (9:1) as the eluant: Mp 38—39 °C (pentane); IR (nujol) 1730; ^1H NMR 9.69 (s, 1H), 7.2—7.6 (m, 5H), 4.72 (s, 1H), 3.93 (s, 2H), 3.59 (s, 6H), 2.6—2.8 (m, 2H), 1.4—2.0 (m, 6H); ^{13}C NMR 201.3, 138.5, 126.0, 125.9, 124.5, 107.1, 67.7, 56.3, 56.0, 53.6, 44.8, 24.5, 23.0, 17.9; Anal. ($C_{16}H_{23}NO_3$) C, H, N.

1-Benzylpiperidine-2,2-dicarbaldehyde 10. To a suspension of the iminium salt (1.0 mmol) in 35 ml of anhydrous ether, prepared from 213 mg of **5** and 0.17 g of bromine as above, was added at −70 °C a mixture of water (38 mg, 2.1 mmol) and triethylamine (0.5 g, 5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The triethylamine hydrobromide was filtered and washed with a solution of triethylamine (0.5 g) in 50 ml of ether. After removal of the solvent, 25 ml of ether were added and the precipitated salt was removed by filtration. The filtrate was concentrated in vacuo to give **10** (220 mg, 100%) as a colorless oil which became discoloured with decomposition on standing at room temperature: IR (neat) 1720; ^1H NMR 9.72 (s, 2H), 7.0—7.4 (m, 5H), 3.80 (s, 2H), 2.5—2.8 (m, 2H), 1.2—1.9 (m, 6H); ^{13}C NMR 202.1, 138.9, 128.3, 128.0, 127.3, 76.2, 58.1, 46.6, 27.6, 24.9, 19.4.

(*E*)-4-(1-Benzyl-2-dimethoxymethylpiperidin-2-yl)-3-buten-2-one 7. To a suspension of *t*-BuOK (2.55 g, 22.7 mmol) in anhydrous THF (50 ml) was rapidly added at −5 °C a solution of acetone (0.95 g, 16.3 mmol) in THF (5 ml). After cooling to −10 °C a solution of **6** (1.25 g, 4, 50 mmol) in THF (10 ml) was added. The reaction mixture was allowed to warm to room temperature, stirred for 1 h and then poured into 2 M HCl (200 ml). After neutralization with Na_2CO_3, the aqueous solution was extracted with ether, dried over Na_2CO_3 and concentrated. The resulting solid was recrystallized from hexane to yield 1.24 g (87%) of **7**: Mp 117—118 °C; IR (nujol) 1670; ^1H NMR 7.2—7.5 (m, 5H), 7.18, 6.45 (ABq, J=17 Hz, 2H), 4.66 (s, 1H), 3.88, 3.71 (ABq, J=15 Hz, 2H), 3.57 (5s, 3H), 3.55 (s, 3H) 2.5—2.7 (m, 2H), 2.23 (s, 3H), 1.4—2.2 (m, 6H); ^{13}C NMR 198.2, 149.6, 140.7, 130.7, 127.7, 127.1, 125.9, 106.8, 64.5, 58.0, 57.2, 55.2, 46.5, 33.1, 26.4, 25.1, 20.3; Anal. ($C_{19}H_{27}NO_3$) C, H, N.

1-Benzyl-1-azaspiro[5.5]undec-7-en-9-one 9. A suspension of 0.22 g of 5% Pd-C in 0.3 M ethanolic KOH (20 ml) was saturated with hydrogen. A solution of enone **7** (1.58 g, 5.0 mmol) in a mixture of 0.3 M ethanolic KOH (20 ml) and ethyl acetate (25 ml) was added and the mixture hydrogenated at room temperature and atmospheric pressure until 1 equiv of hydrogen (120 ml) was absorbed (about 20 min). After filtration of the catalyst, the filtrate was concentrated at reduced pressure to about 20 ml, acidified with 3 M HCl (20 ml), concentrated again to about 20 ml. Then 3 M HCl (30 ml) was added and the mixture refluxed for 16 h. After cooling, the mixture was basified with Na_2CO_3, extracted with ether, dried over Na_2CO_3 and concentrated. The residue was purified by

flash chromatography on silica gel with petroleum ether/ether (1:1) as the eluant to yield 0.89 g (70%): Mp 57—59 °C (methanol–water); IR (neat) 1680; ^{1}H NMR 7.2—7.6 (m, 5H), 6.95 (d, br, J=10 Hz, 1H), 6.03 (d, J=10 Hz, 1H), 3.73, 3.33 (ABq, J=15 Hz, 2H), 2.0—2.8 (m, 6H), 1.3—1.9 (m, 6H); ^{13}C NMR 198.8, 160.1, 139.9, 128.8, 127.9, 127.6, 126.5, 57.3, 55.9, 45.3, 34.3, 32.2, 25.6, 21.0, 20.4; Anal. ($C_{17}H_{21}NO$) C, H, N.

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