

Photochemical reactions of chiral 2,3-dihydro-4(1*H*)-pyridones: asymmetric synthesis of (–)-perhydrohistrionicotoxin

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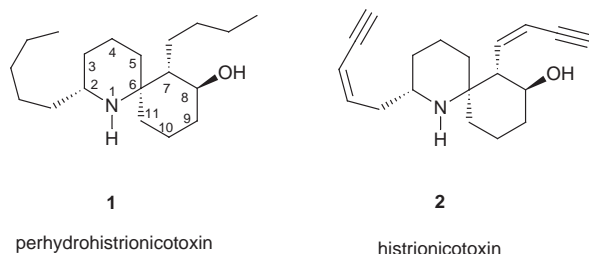
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The first chiral auxiliary-mediated asymmetric synthesis of (–)-perhydrohistrionicotoxin is described.

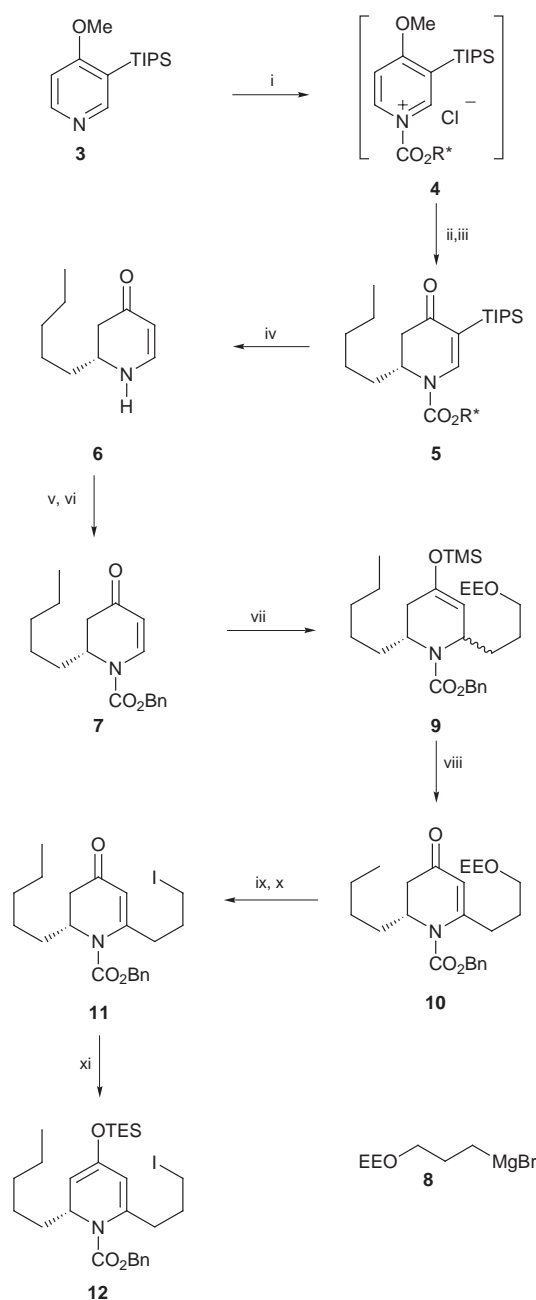
In an effort to expand the utility of chiral 2,3-dihydro-4(1*H*)-pyridones as synthetic building blocks,¹ we are exploring their annulation using intramolecular [2+2] photocycloaddition reactions.² As was first demonstrated by Neier,³ novel ring systems can be prepared from dihydropyridones using this approach. We were able to demonstrate through model studies that the skeleton of perhydrohistrionicotoxin **1** was accessible using this strategy.⁴ Histrionicotoxin **2** is one of the biologically active alkaloids found in the skin secretions of the neotropical frog *Dendrobates histrionicus*.⁵ Alkaloids **1** and **2** have been used in

The acetal was hydrolyzed and the resulting alcohol was converted to iodide **11** in high yield (84%). The C-4 carbonyl of **11** was protected as the triethylsilyl enol ether **12**. The synthesis



studies of the mechanisms involved in transsynaptic transmission of neuromuscular impulses. The biological activity and novel structure of these alkaloids have stimulated numerous synthetic studies.⁶ Several racemic and two enantioselective syntheses of **1** have been published. In addition, one asymmetric route to histrionicotoxin **2** has been reported.^{6c} The enantioselective routes used enantiopure intermediates prepared by resolution⁷ or derived from L-glutamic acid.^{6a} Here we report a novel asymmetric synthesis of **1** using a photochemical conversion of an enantiopure 2,3-dihydro-4(1*H*)-pyridone as a key step. The enantiopure dihydropyridone was prepared by an efficient chiral auxiliary-mediated asymmetric synthesis.¹ The synthetic plan called for a stereoselective intramolecular [2+2] cycloaddition of an enantiopure dihydropyridone to set the stereochemistry at C-6 and C-7, and a subsequent cyclobutane ring opening to provide the azaspiroindecane skeleton of **1**.

Reaction of enantiopure 1-acylpyridinium salt **4**, prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine **3**⁸ and the chloroformate of (–)-(1*R*,2*S*,4*R*)-2-(α-cumyl)-4-isopropylcyclohexanol (CPC),⁹ with *n*-pentylmagnesium bromide in THF–toluene at –78 °C gave the crude dihydropyridone **5** in 95% yield and 90% de (Scheme 1). Purification by radial PLC (silica gel, EtOAc–hexanes) afforded a 91% yield of pure **5** [mp 75–78 °C; [α]_D²³ –48.1 (c 0.88, CHCl₃)]. Treatment of **5** with NaOMe in MeOH followed by aqueous 10% HCl provided dihydropyridone **6** [[α]_D²⁵ +353 (c 0.18, CHCl₃)] in 84% yield, and the chiral auxiliary [(–)-CPC] was recovered in 95% yield. Acylation of **6** with BuⁿLi and ClCO₂Bn gave a 90% yield of enantiopure carbamate **7** [[α]_D²³ –83.7 (c 2.24, CHCl₃)]. A side chain was introduced at C-6 of **7** through a 1,4-addition and oxidation sequence. In the presence of TMSCl, copper-mediated conjugate addition of Grignard reagent **8** to **7** provided silyl enol ether **9**. Oxidation of crude **9** with Pd(OAc)₂ gave dihydropyridone **10** in 92% overall yield for the two steps.^{1c}



Scheme 1 Reagents and conditions: i, ClCO₂R*; ii, C₅H₁₁MgCl; iii, H₃O⁺; iv, NaOMe, MeOH, then 10% HCl; v, BuⁿLi; vi, ClCO₂Bn; vii, **8**, CuBr, TMSCl; viii, Pd(OAc)₂, MeCN; ix, oxalic acid; x, NIS, PPh₃; xi, NaHMDS, TESCl.

was continued (Scheme 2) by treatment of crude **12** with the anion of **13**, prepared from the corresponding commercially available aldehyde, to give enone **14** in 94% yield. Protection of the ketone carbonyl using enantiopure bis-TMS ether **15**¹⁰ provided ketal **16** (87%). Since the C-2 substituent of **16** is axial, due to A^{1,3} strain,¹¹ photocyclization was anticipated to be highly stereoselective for the less hindered olefin face. On photolysis in acetone (460 W Hanovia Hg lamp, 16 min, 5 °C), **16** gave a 79% yield of cycloadduct **17** as the sole isolated product. The (*R,R*)-hydrobenzoin ketal of **16** is important for high facial selectivity, for the corresponding ethylene ketal gave only a 7:1 mixture of photoadducts. At this stage of the synthesis, installation of three stereogenic centers with the correct relative and absolute stereochemistry needed for the construction of **1** had been achieved. Treatment of **17** with SmI₂ in THF and DMPU effected cyclobutane ring opening to give spirocyclic ketone **18** in 70% yield, which was converted to a mixture of vinyl triflates **19** (90%) using LiHMDS and *N*-(5-chloro-2-pyridyl)triflimide.¹² Catalytic hydrogenation of this mixture effected vinyl triflate reduction, cleavage of the ketal, and removal of the Z group to provide the known amino ketone **20**^{6a} in 81% yield. The synthesis of (–)-perhydrohistrionicotoxin **1** was completed by reduction of **20** with LiAl(OBu^t)₃H according to the procedure of Winkler.^{6a} Our synthetic **1** exhibited spectral data in agreement with reported data of authentic material.^{5,6} The optical rotation [$[\alpha]_D$ –83.8 (*c* 0.2, CH₂Cl₂)] was also in agreement with literature values [$[\alpha]_D$ ²² –84.1 (*c* 0.024, CH₂Cl₂); [$[\alpha]_D$ ²² –83.1 (*c* 0.0067, CH₂Cl₂)].^{6a}

In summary, the first chiral auxiliary-mediated asymmetric synthesis of (–)-perhydrohistrionicotoxin was accomplished in 15 steps (14% overall yield) with a high degree of stereoselectivity. Key steps include a highly stereoselective intramolecular [2+2] photocyclization of dihydropyridone **16** and a SmI₂-promoted cyclobutane ring opening, which provide the azaspirodecane skeleton of the alkaloid.

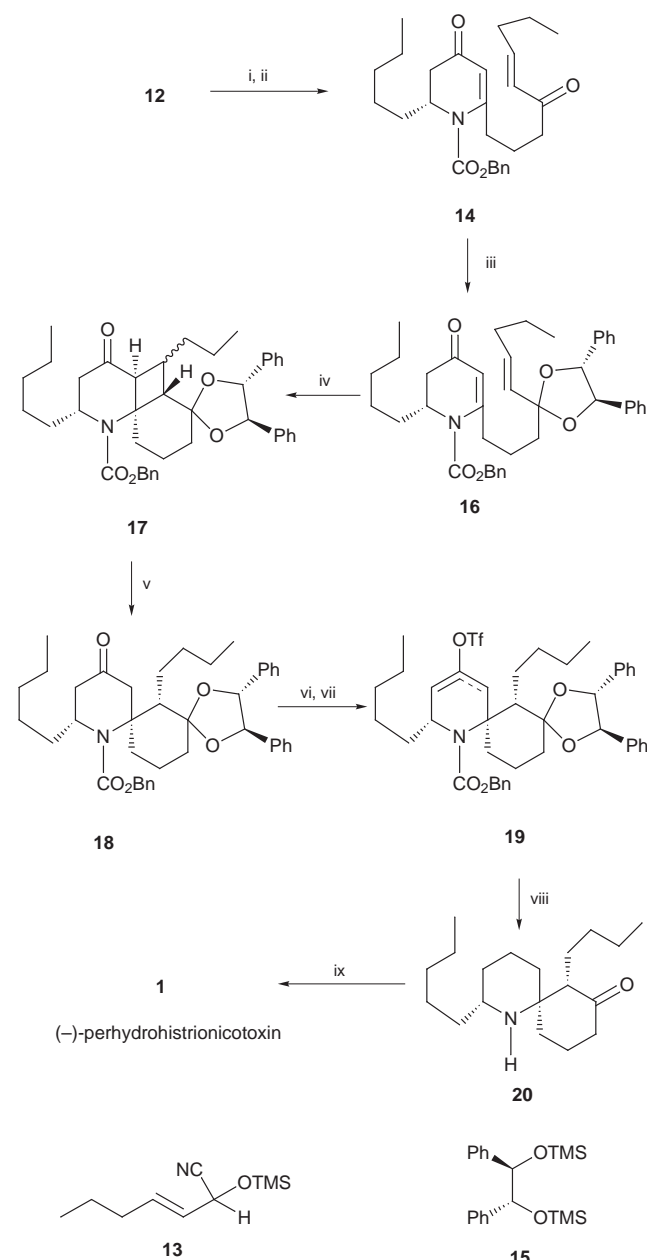
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† Satisfactory IR, ¹H and ¹³C NMR spectra, HRMS or microanalyses were obtained for all compounds described.

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Scheme 2 Reagents and conditions: i, **13**, LiHMDS, THF; ii, 10% HCl, then 2 M NaOH; iii, **15**, TMSOTf; iv, hv, acetone, 5 °C, 16 min; v, SmI₂, THF, DMPU; vi, LiHMDS, THF; vii, *N*-(5-chloro-2-pyridyl)triflimide; viii, H₂, Pd(OH)₂, Li₂CO₃, EtOH; ix, LiAl(OBu^t)₃H.