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

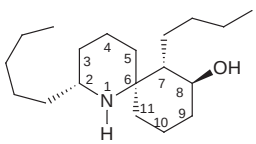
Daniel L. Comins,* Yue-mei Zhang and Xiaoling Zheng

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, USA. E-mail: daniel_comins@ncsu.edu

Received (in Cambridge, UK) 24th September 1998, Accepted 12th October 1998

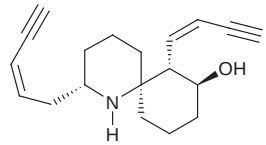
The first chiral auxiliary-mediated asymmetric synthesis of (−)-perhydrohistrionicotoxin is described.

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



1

perhydrohistrionicotoxin



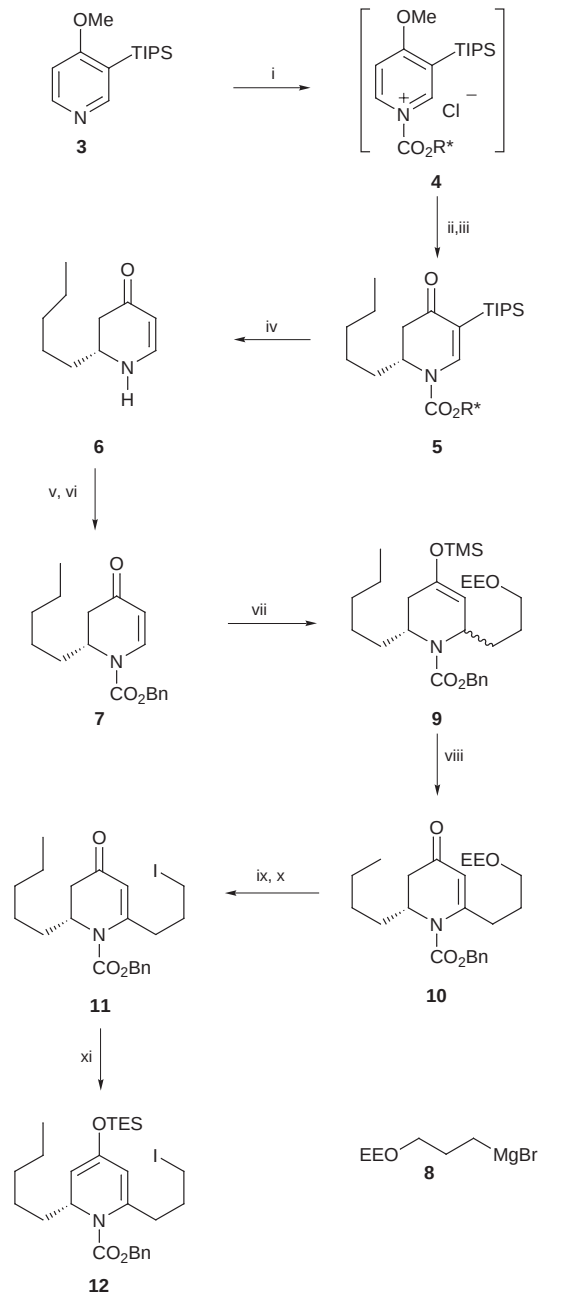
2

histrionicotoxin

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 resolution[7] 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 azaspiroundecane skeleton of **1**.

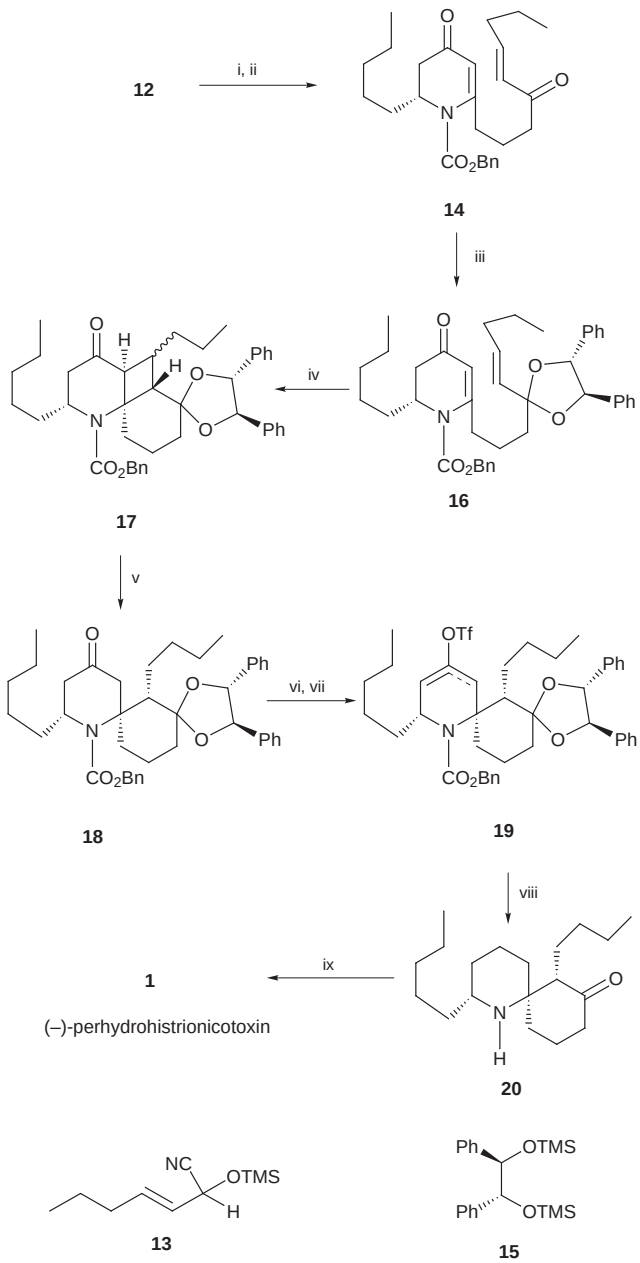
Reaction of enantiopure 1-acylpyridinium salt **4**, prepared *in situ* from 4-methoxy-3-(triisopropylsilyl)pyridine **3**[8] and the chloroformate of (−)-(1*R*,2*S*,4*R*)-2-(α-cumyl)-4-isopropylcyclohexanol (CPC),[9] with *n*-pentylmagnesium bromide in THF–toluene at −78 °C gave the crude dihydropyridone **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; $[\alpha]_D^{23}$ −48.1 (*c* 0.88, $CDCl_3$)]. Treatment of **5** with NaOMe in MeOH followed by aqueous 10% HCl provided dihydropyridone **6** [$[\alpha]_D^{25}$ +353 (*c* 0.18, $CHCl_3$)] in 84% yield, and the chiral auxiliary [(−)-CPC] was recovered in 95% yield. Acylation of **6** with Bu^nLi and $ClCO_2Bn$ gave a 90% yield of enantiopure carbamate **7** [$[\alpha]_D^{23}$ −83.7 (*c* 2.24, $CHCl_3$)]. 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]

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 triethylsily enol ether **12**. The synthesis



Scheme 1 *Reagents and conditions*: i, $ClCO_2R^*$; ii, $C_5H_{11}MgCl$; iii, H_3O^+; iv, NaOMe, MeOH, then 10% HCl, v, Bu^nLi; vi, $ClCO_2Bn$; vii, **8**, CuBr, TMSCl; viii, $Pd(OAc)_2$, MeCN; ix, oxalic acid; x, NIS, PPh_3; 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 SmI_2 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, CH_2Cl_2)] was also in agreement with literature values [$[\alpha]_D^{22}$ −84.1 (*c* 0.024, CH_2Cl_2); $[\alpha]_D^{22}$ −83.1 (*c* 0.0067, CH_2Cl_2)].[6a]



Scheme 2 *Reagents and conditions*: i, **13**, LHMDS, THF; ii, 10% HCl, then 2 M NaOH; iii, **15**, TMSOTf; iv, *hν*, acetone, 5 °C, 16 min; v, SmI_2, THF, DMPU; vi, LHMDS, THF; vii, *N*-(5-chloro-2-pyridyl)triflimide; viii, H_2, $Pd(OH)_2$, Li_2CO_3, EtOH; ix, $LiAl(OBu^t)_3H$.

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 SmI_2-promoted cyclobutane ring opening, which provide the azaspiroundecane skeleton of the alkaloid.

We express appreciation to the National Institutes of Health (Grant GM 34442) and the Petroleum Research Fund (ACS-PRF #28394-AC) for financial support of this research.

Notes and references

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

1 (*a*) D. L. Comins and S. P. Joseph, *Advances in Nitrogen Heterocycles*, ed. C. J. Moody, JAI Press, Greenwich, CT, 1996; vol. 2, pp. 251–294; (*b*) D. L. Comins, S. P. Joseph and X. Chen, *Tetrahedron Lett*., 1995, **36**, 9141; (*c*) D. L. Comins, S. P. Joseph and D. D. Peters, *Tetrahedron Lett*., 1995, **36**, 9449; (*d*) D. L. Comins, S. P. Joseph and Y. Zhang, *Tetrahedron Lett*., 1996, **37**, 793; (*e*) D. L. Comins and L. Guerra-Weltzien, *Tetrahedron Lett*., 1996, **37**, 3807; (*f*) D. L. Comins, X. Chen and S. P. Joseph, *Tetrahedron Lett*., 1996, **37**, 9275; (*g*) D. L. Comins, X. Chen and L. A. Morgan, *J. Org. Chem*., 1997, **62**, 7435; (*h*) D. L. Comins, D. H. LaMunyon and X. Chen, *J. Org. Chem*., 1997, **62**, 8182.

2 D. L. Comins, Y. Lee and P. D. Boyle, *Tetrahedron Lett*., 1998, **39**, 187.

3 P. Guerry and R. Neier, *Chimia*, 1987, **41**, 341; P. Guerry and R. Neier, *J. Chem. Soc., Chem. Commun*., 1989, 1727; P. Guerry, P. Blanco, H. Brodbeck, O. Pasteris and R. Neier, *Helv. Chem. Acta*., 1991, **74**, 163.

4 D. L. Comins and X. Zheng, *J. Chem. Soc., Chem. Commun*., 1994, 2681.

5 J. W. Daly and T. F. Spande, *Alkaloids*: *Chemical and Biological Perspectives*, ed. S. W. Pelletier, Wiley, New York, 1986; vol. 4, ch. 1, pp. 1–274; J. W. Daly, H. M. Garraffo and T. F. Spande, *The Alkaloids*, ed. G. A. Cordell, Academic Press: San Diego, CA, 1993; vol. 43, pp. 185–288.

6 For recent synthetic work and leading references on the histrionicotoxins, see: (*a*) J. D. Winkler and P. M. Hershberger, *J. Am. Chem. Soc*., 1989, **111**, 4852; (*b*) J. J. Venit, M. DiPierro and P. Magnus, *J. Org. Chem*., 1989, **54**, 4298; (*c*) G. Stork and K. Zhao, *J. Am. Chem. Soc*., 1990, **112**, 5875; (*d*) J. Zhu, J. Royer, J.-C. Quirion and H.-P. Husson, *Tetrahedron Lett*., 1991, **32**, 2485; (*e*) C. M. Thompson, *Heterocycles*, 1992, **34**, 979; (*f*) P. Compain, J. Gore and J-M. Vatele, *Tetrahedron Lett*., 1995, **36**, 4063; (*g*) R. W. Fitch and F. A. Luzzio, *Ultrason. Sonochem*., 1997, **4**, 99.

7 K. Takashashi, B. Witkop, A. Brossi, A. M. Maleque and E. X. Albuquerque, *Helv. Chim. Acta*, 1982, **65**, 252.

8 D. L. Comins, S. P. Joseph and R. R. Goehring, *J. Am. Chem. Soc*., 1994, **116**, 4719.

9 D. L. Comins, L. Guerra-Weltzien and J. M. Salvador, *Synlett*, 1994, 972; D. L. Comins and L. Guerra-Weltzien, *Tetrahedron Lett*., 1996, **37**, 3807.

10 C. N. Eid and J. P. Konopelski, *Tetrahedron Lett*., 1991, **32**, 461.

11 For reviews on $A^{1,3}$ strain, see: R. W. Hoffman, *Chem. Rev*., 1989, **89**, 1841; F. Johnson, *Chem. Rev*., 1968, **68**, 375.

12 D. L. Comins and A. Dehghani, *Tetrahedron Lett*., 1992, **33**, 6299; D. L. Comins, A. Dehghani, C. J. Foti and S. P. Joseph, *Org. Synth*. 1996, **74**, 77.

Communication 8/07448H