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# SYNTHESIS OF EPIBATIDINE

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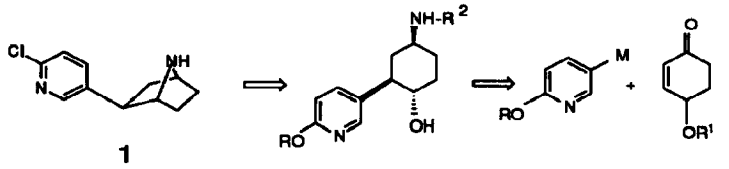
**Abstract:** A total synthesis of racemic epibatidine, a natural product with analgesic activity, is described. Distinctly different from the previously published routes it starts from simple, known precursors, to provide the alkaloid in six steps.

Epibatidine (**1**), one of the numerous alkaloids isolated from the skin of poisonous frog Epipedobates tricolor, is pharmacologically interesting for its strong analgesic action apparently effected by a non-opioid mechanism.[1]

The scarcity of the natural material has prompted us to investigate a synthetic approach that would secure a supply of **1** and its derivatives in quantities sufficient for the biological testing. Our strategy was to close the nitrogen bridge of the 7-azabicyclo[2.2.1]heptane ring after the rest of the skeleton had been assembled (including an easily convertible precursor of the chloropyridine moiety) as shown in the retrosynthetic scheme:

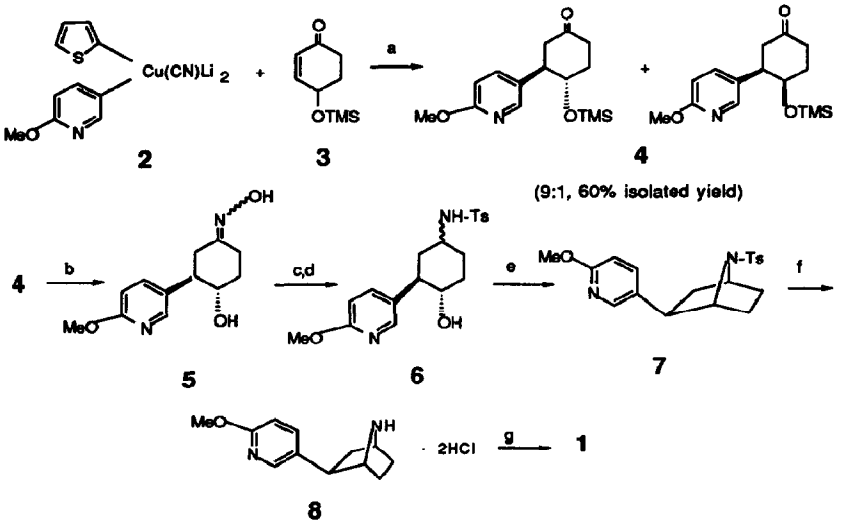



**1**

Several total syntheses of epibatidine which are conceptually different from our own, have been published so far.[1-4] Two of them[2,3] use Diels-Alder type reactions to construct the molecular framework with subsequent removal of activating groups (initially needed to achieve a reasonable rate of cycloaddition). The first published synthesis[2a] employed the diene addition at a very early stage and required 16 steps for completion. In the second synthesis,[3] the entire system was assembled in one step but it suffered from an unfavorable ratio of the stereoisomers (endo/exo 2:1) as a result of an unavoidable double bond reduction at the critical stereocenter. The third synthesis[4] used a 7-azabicyclo[2.2.1]heptane derivative as a starting material and then introduced the chloropyridine substituent. This process also produced the exo isomer as a minor component only (1:4 ratio). An epimerisation step was then needed for an apparently successful endo to exo conversion.[16]

We have employed known 2-methoxy-5-lithiopyridine[5a] and 4-hydroxy-2-cyclohexenone[6] as starting materials. The lithiopyridine was converted to a "higher order" lithiocuprate **2** and the hydroxyl of the hydroxyketone was protected with trimethylsilyl group (**3**). The essential requirement for the successful preparation of **2** and conjugate addition of **2** to **3** was to prepare 2-methoxy-5-lithiopyridine in diethyl ether as all attempts to work with tetrahydrofuran failed.[5b] That problem might have thwarted the conjugate addition in an attempt to shorten the first mentioned, published synthesis.[2b]

We obtained the ketone **4** after a column chromatography on silica gel in 60% yield as 9:1 (trans/cis) mixture of isomers.[7] The proper stereochemistry for two out of three centers was thus introduced in the first step. The ketone **4** was then converted to its oxime **5** ( 70%, crude, mixture of syn- and anti-)[8] which furnished a mixture of tosylamino-isomers **6** upon reduction with Ni/Al alloy and tosylation[9] in 60% yield. Without separation of the resulting stereoisomers (1:1 ratio), the mixture was subjected to Mitsunobu conditions (DEAD, $PPh_3$) giving the fully assembled ring system **7**[10] in 88% yield (based on the correct isomer). Removal of the tosyl group with sodium amalgam and conversion to dihydrochloride **8**[11] (40%) followed by the transformation of methoxy group to the chloro- substituent with $POCl_3$ /$PCl_5$ completed the synthesis of racemic **1**.[12]




a) -35°>20°, $Et_2O$/THF, $NH_4Cl$; b) $NH_2OH.HCl$, NaOAc, MeOH; c) Ni/Al, NaOH, EtOH; d) TsCl , $NaHCO_3$, THF/$H_2O$; e) DEAD, $PPh_3$, THF; f) Na/Hg, $Na_2HPO_4$, $Et_2O$/HCl; g) $POCl_3$/$PCl_5$, $Et_2O$/HCl.

Yields of the last step were erratic and seemingly dependent on conditions of the work-up.[15] The best yield obtained in one case was 40% (crude) by heating **8** at 105-110° for 3.5 days with 10 molar equivalents of pentachloride and enough $POCl_3$ to dissolve the starting material (after five days no **1** could be isolated).

The merits of the synthesis are two crucial steps: a) successful preparation of the pyridyl lithiocuprate **2** and conjugate addition to the ketone **3**; b) novel method to prepare 7-azabicyclo[2.2.1]heptane ring system by Mitsunobu reaction of 4-tosylaminocyclohexanols (reported so far only in formation of monocyclic systems from acyclic tosylaminoalcohols[13].

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**References and notes**

1. Spande,T.F. et al. *J. Am. Chem. Soc.* **1992,** *114,* 3475.

2. a)Broka,C.A. *Tetrahedron Letters* **1993,** *34,* 3251; b) ibid. Ref. 8. (the problem could have also arisen if a "higher order" cyanocuprate was not employed in the conjugate addition).

3. Huang,D.F. and Shen,T.Y. *Tetrahedron Letters* **1993,** *34,* 4477 and references herein.

4. Fletcher,S.R. et al. *J. Chem. Soc., Chem. Commun.* **1993,** 1216.

5. a) Kompis, I. et al. *Eur. J. Med. Chem.* **1977,** *12,* 531; b) In order to avoid possible solubility problems by mixing solvents an attempt was made at first to prepare 2-methoxy-5-lithiopyridine in THF since the thiophene lithiocyanocuprate, necessary for the complex formation was commercially available as a THF solution. However, it was established later that once the lithiopyridine had been prepared in ether as an insoluble precipitate, the addition of thiophene lithiocuprate- THF solution led to formation of desired **2** (the presence of THF had obviously no negative effect at that stage); Bell, A.S. et al. *Synthesis* **1987,** 843, claim a successful preparation of several lithiopyridines in THF.

6. Danishefsky,S.J. and Simoneau, B. *J. Am. Chem. Soc.* **1989,** *111,* 2599.

7. **4:** MS (EI) m/z 293 ($M^+$), 278, 265. $^1H$ NMR ($CDCl_3$) δ 8,00 (d, 1H, J=2.5 Hz), 7.40 (dd, 1H, J=2.5 Hz, 8.5 Hz), 6.72 (d, 1H, J=8.5 Hz), 3.91 (m, 4H), 3.02 (td, J=14.7 Hz, 3 Hz, 1H), 2.65-2.40 (m, 4H), 2.06 (m, 1H), 1.85 (m, 1H), -0.1 (s, 9H).

8. **5:** MS (DEI) m/z 236

9. **6:** MS (FAB) m/z 375 $(M-H)^-$. $^1H$ NMR showed duplex chemical shifts of several characteristic protons designating a presence of two stereoisomers. HPLC revealed a 1:1 mixture of isomers.

10. **7:** MS (EI) m/z 358 $(M^+)$. $^1H$ NMR ($CDCl_3$) δ 7.90 (d, J=2.5, 1H), 7.78 (d, J=8.3, 2H), 7.52 (dd, J=2.5, 8.7, 1H), 7.28 (d, J=8.3, 2H), 6.59 (d, J=8.7, 1H), 4.32 (t, J=4, 1H), 4.05 (d, J=3.5, 1H), 3.88 (s, 3H), 2.76 (dd, J=9, 5, 1H), 2.42 (s, 3H), 1.94 (dd, J=9, 12, 1H), 1.86-1.74 (broad, 3H), 1.52 (m, 2H).

11. **8:** MS (EI) m/z 204 $(M^+)$. $^1H$ NMR (DMSO) δ 8.95 (br, 1H), 8.40 (br, 1H), 8.14 (d, J=2.7, 1H), 7.72 (dd, J=2.7, 8.5, 1H), 6.81 (d, J=8.5, 1H), 4.36 (br, 1H), 4.22 (br, 1H), 3.83 (s, 3H), 3.24 (m, 1H), 2.25 (m, 1H), 1.95-1.79 (br, 4H), 1.72-1.66 (br, 1H).

12. **1** (oxalate): MS (EI) m/z 208 $(M^+)$. $^1H$ NMR (DMSO) δ 8.40 (d, J=2.4, 1H), 7.84 (dd,J=8.3, 2.6, 1H) 7.48 (d, J=8.1, 1H), 4.40 (s, 1H), 4.20 (s, 1H), 3.30 (dd,J=9.4, 6.0, 1H), 2.27 (dd, J= 9.4, 12.9, 1H), 1.95-1.60 (m, 5H).

13. Henry,J.R. et al. *Tetrahedron Letters* **1989,** *30,* 5709

14. After completion of this work a stereocontrolled synthesis of optically active epibatidine by E. J. Corey et al.(*J. Org. Chem.* **1993,** *58,* 5600) and a short elegant synthesis of racemic **1** by S. C. Clayton and A. C. Regan (*Tetrahedron Lett.* **1993,** *34,* 7493) have been published both also distinctly different from our own.

15. The excess of $POCl_3$ was evaporated, conc. HCl added to the residue, the mixture heated to boiling point, cooled, alkalized (pH~10) and extracted with ether.

16. Note added in proof: Szantay, C. et al. *Tetrahedron Letters* **1994,** *35,* 3171, described a new synthesis of epibatidine which also relied on the epimerisation in the last step.

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