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Formal Synthesis of Natural Epibatidine and of its Enantiomer: Use of Radical Cyclization in an Enantiospecific Route

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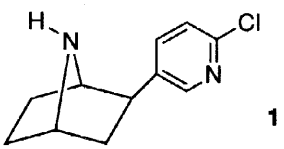
Abstract: (*S*)-Pyroglutamic acid was converted into the (phenylthio)acetylene **14**, which undergoes radical cyclization to the 7-azabicyclo[2.2.1]heptane **15**. Ozonolysis then affords ketone **4**, a synthetic precursor of (-)-epibatidine.

The alkaloid **1**, isolated in very small amounts from the skin of a highly colored Ecuadorian frog (*Epipedobates tricolor*)[1] and given the name *epibatidine*, has attracted attention because of its exceptionally



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powerful analgesic properties[2] — several hundred times greater than those of morphine[1,3] (as judged by animal tests) — and the fact that it acts[1b,3,4] at nicotinic rather than opiate receptors. Although the substance is toxic,[3] it does serve as a lead compound in the development of drugs[5] for pain relief as well as for treatment of disorders whose pathogenesis involves[6] nicotinic receptors. Biological tests[4] have shown that the unnatural enantiomer is about half as potent.

The original samples of **1** were found only in frogs collected in specific habitats; animals reared in captivity were devoid of alkaloids, and further collection in the wild was restricted by the Convention on International Trade in Endangered Species.[1b] Extensive work on the synthesis of *racemic* epibatidine has been reported and, although access to the individual enantiomers can be gained by incorporating a resolution step at an appropriate stage,[7,8,9] the direct preparation of natural (-)-**1** by enantioselective[10] or enantiospecific[10] procedures is now attracting serious attention;[11] the methods developed may prove to be important in medicinal chemistry.

We report a formal synthesis of the natural[8g] enantiomer from a simple derivative of (*S*)-pyroglutamic acid. The route is based on the idea that ketone **4**, from which epibatidine is easily reached,[8g,n] should be accessible by sequential radical cyclization and double bond cleavage along the lines summarized in Scheme 1.

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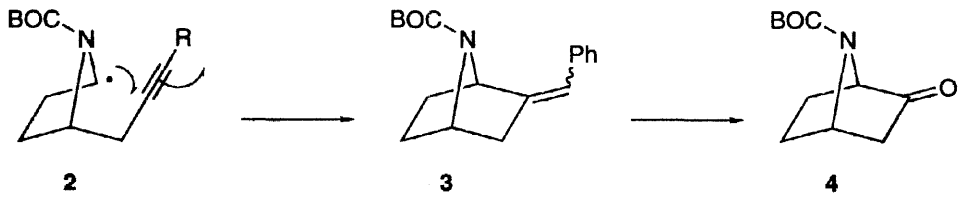
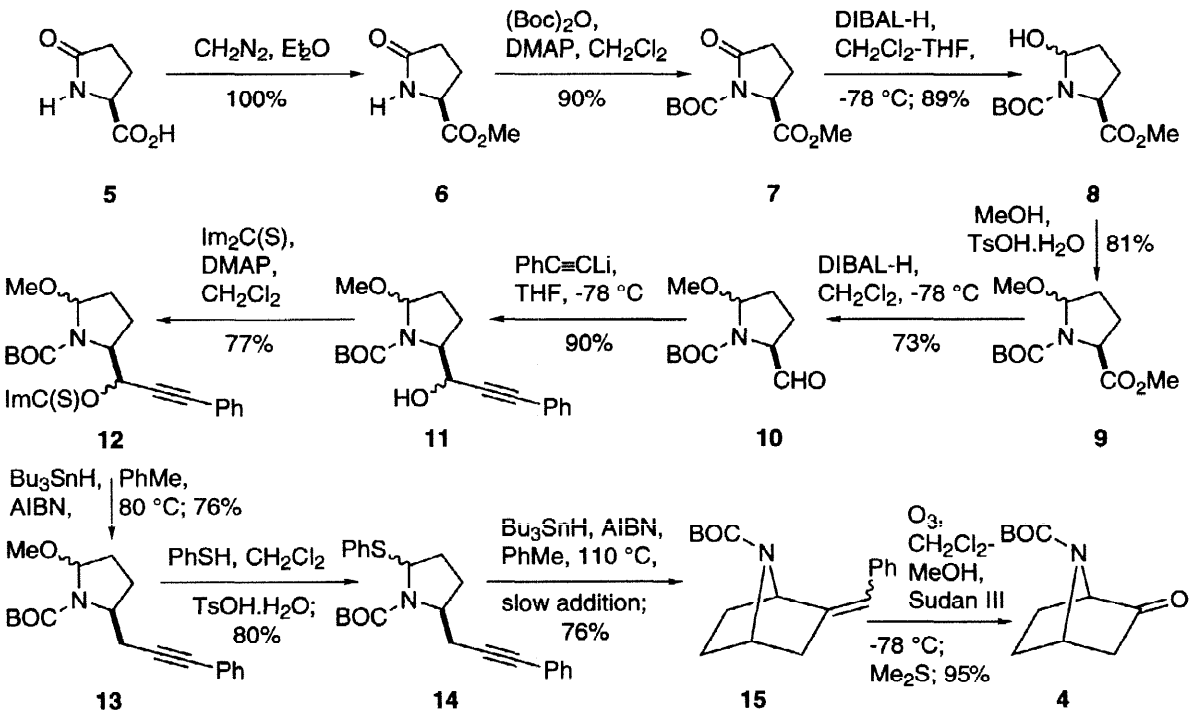


Scheme 1

In order to implement this approach the known ester **9** (Scheme 2) was prepared from (*S*)-pyroglutamic acid (**5**) as shown. The compound is also available by anodic oxidation of methyl 1-(*tert*-butoxycarbonyl)prolinate.[12] Esterification (**5** → **6**,[13] CH_2N_2, 100%), *N*-protection [**6** → **7**,[14] $(Boc)_2O$, 90%], and partial reduction (DIBAL-H, 89%) gave the epimeric alcohols **8**.[15] Replacement of the hydroxy by



Scheme 2

a methoxy group (**8** → **9**,[16] MeOH, $TsOH.H_2O$, 81%) then set the stage for introduction of an acetylenic side chain that would serve as the radical acceptor (*cf.* **2**). The ester group of **9** was converted into an aldehyde (**9** → **10**, DIBAL-H, 73%), and treatment with lithium phenylacetylide then gave (90%) the diastereoisomeric alcohols **11**. Deoxygenation[17] was best[18] accomplished by way of the imidazolyl thionoester **12** (**11** → **12**, Im_2CS, 77%), followed by treatment with Bu_3SnH (**12** → **13**, PhMe, 80 °C, AIBN, 76%). Although the thionoester **12** has the potential to undergo [3,3]-sigmatropic rearrangement[19] [C≡C-C-OC(S)- → -C(O)-S-C=C=C] we did not isolate the allene expected from such a process. One diastereomer of the deoxygenated carbamate **13** is very sensitive to acid hydrolysis (replacement of MeO by OH) but the hydrolysis is easily avoided by omitting the normal acid wash during workup. With **13** in hand, the methoxy group was replaced by a phenylthio group (**13** → **14**, PhSH, TsOH, 80%), and radical cyclization[20] (**14** → **15**), effected by slow addition of Bu_3SnH and AIBN in toluene to a hot (110 °C) solution of **14**, gave the required azabicyclo[2.2.1]-

heptane (76%) as a mixture (*ca* 1:1) of two geometrical isomers. Finally, ozonolysis, monitored by an internal indicator (Sudan III),[21] gave ketone **4** (95%), which was identified by comparison of its spectroscopic properties with the reported values. The compound had $[\alpha]^{26}_{D}$ -75.1 (*c* 1.56, $CHCl_3$).[22]

In exploratory experiments, we protected the hydroxyl of **11** by methylation or acetylation, but encountered difficulties in removing these functions after radical cyclization and double bond cleavage (*cf.* **14** → **15** → **4**).

Ketone **4** is easily converted into (-)-epibatidine[8g,n] and so the synthesis of **4** constitutes a formal synthesis of the natural product. Application of the sequence to (*R*)-pyroglutamic acid [or to methyl (*R*)-1-(*tert*-butoxycarbonyl)prolinate, by way of anodic oxidation[12]] would afford the enantiomer of epibatidine. The present approach involves very simple reactions from the readily accessible protected ester **9**.

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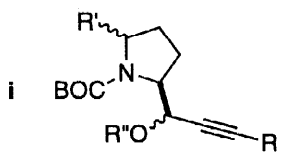

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