Stereocontrolled Total Synthesis of (+)- and (−)-Epibatidine

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Summary: The stereocontrolled total synthesis of the novel analgesic agent (−)-epibatidine (1) and its enantiomer starting with 6-chloropyridine-3-carboxaldehyde (2) has been carried out by way of intermediates 3–10.

Epibatidine (1, or mirror image) was isolated by Daly and co-workers at the National Institutes of Health from extracts of the skin of the poisonous frog *Epipedobates tricolor* (*ca.* 1 mg from 750 frogs) and found to have potent analgesic activity.[1] In two assays epibatidine was found to be 200–500 times as potent as morphine, although binding studies with an opioid receptor preparation showed almost 9000 times weaker binding for 1 in comparison with [^{3}H]-dihydromorphine.[1] Because of the intriguing biological activity of epibatidine, the interesting chemical structure, and the scarcity of epibatidine in nature, we have developed a simple, efficient, and stereocontrolled synthesis which is reported herein. Three very recent papers describe different synthetic approaches to the epibatidine structure.[2-4] Because the absolute configuration of epibatidine had not been determined, the synthesis described herein was developed to provide both possible enantiomers.

6-Chloropyridine-3-carboxaldehyde (2)[5] was converted stereospecifically to the (*Z*)-α,β-unsaturated ester 3 using the Still–Gennari reagent[6] under the conditions shown in Scheme I (temperatures shown are in °C). Thermal Diels–Alder addition of 1,3-butadiene to 3 occurred at 190 °C to give a single adduct, the *cis* ester 4, cleanly and in high yield. Saponification of 4 afforded quantitatively the corresponding carboxylic acid 5, which was transformed to the acyl azide. Curtius rearrangement of the azide in the presence of 2-(trimethylsilyl)ethanol gave the *cis* carbamate 6 in high yield.[7] Treatment of 6 with tetra-*n*-butylammonium fluoride in THF at reflux resulted in carbamate cleavage to form the corresponding primary amine which was acylated with trifluoroacetic anhydride to give the *cis* trifluoroacetamide 7. This amide underwent stereospecific bromination at −78 °C with Br_2 in the presence of a bromide ion source to form a single dibromide (8) almost quantitatively. This highly specific reaction can be understood in terms of kinetically-favored formation of the bromonium ion with *cis* CF_3CONH (axial) and bromine substituents followed by diaxial opening of that bromonium ion by bromide ion attack. The excess of bromide ion, which enhances trapping of the kinetically favored *cis* bromonium ion, is essential to selective formation of 8 relative to the other possible diastereomeric *trans* dibromide (not shown).

The 7-azabicyclo[2.2.1]heptane ring system of epibatidine was formed by base-promoted internal nucleophilic displacement which transformed dibromide 8 cleanly into the bridged monobromide 9. Sequential debromination of 9 to form 10 with tri-*n*-butyltin hydride and deacylation of 10 with methanolic methoxide provided (±)-epibatidine in excellent yield.

The two enantiomerically pure epibatidines were prepared by a simple modification of the above approach. The enantiomeric *N*-(trifluoroacetyl)epibatidines 10 were easily separated by HPLC using a Daicel OD column (Chiral Technologies, Exton, PA; both analytical and preparative-scale columns were used). Using 10% isopropyl alcohol in hexane containing 0.1% Et_2NH for elution, the *levo* enantiomer eluted at 15 min, $[\alpha]^{23}_D$ −32° (c = 0.5, $CHCl_3$), and the *dextro* enantiomer eluted at 20 min, $[\alpha]^{23}_D$ +32° (c = 0.5, $CHCl_3$). The *levo* and *dextro* enantiomers of the trifluoroacetamide 10 upon treatment with methanolic sodium methoxide generated *dextro* and *levo* enantiomers of epibatidine, $[\alpha]^{23}_D$ +5° and −5° (c = 0.35, $CHCl_3$), respectively. Reaction of this product with acetic anhydride afforded the *N*-acetyl derivative, the ^{1}H NMR spectrum of which was identical with that reported for *N*-acetylepibatidine.[1a]

The separation of enantiomers could also be accomplished easily at the stage of the trifluoroacetamides 7; retention times of 10.6 min (*dextro*) and 16.7 min (*levo*) were found for a Daicel AS column using 7.5% isopropyl alcohol in hexane for elution. The enantiomers of 7 showed equal and opposite $[\alpha]^{23}_D$ values of 114° (c = 1.6, $CHCl_3$). The dextrorotatory enantiomer was shown to have the absolute configuration shown in 7 by conversion to the dextrorotatory dibromide 8,[8] the structure and absolute stereochemistry of which were proven by a single-crystal X-ray crystallographic determination.[9] Cyclization of the (+)-dibromide 8 afforded the bridged monobromide 9, $[\alpha]^{23}_D$ +20° (c = 0.5, $CHCl_3$), which upon debromination gave *dextro N*-(trifluoroacetyl)epibatidine (10), $[\alpha]^{23}_D$ +32 (c = 0.5, $CHCl_3$). Deacylation of (+)-10 gave (−)-epi-

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(1) (a) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475. (b) See also: Lenz, G. R.; Evans, S. M. *Chemtracts Org. Chem.* **1992**, 332.

(2) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251.

(3) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477.

(4) Chen, H. Y.; Huang, D. F.; Gonzalez, J.; Shen, T. Y.; Harman, W. D. *Abstr. 205th Natl. Mtg. Am. Chem. Soc.* **1993**, ORG, 347.

(5) Prepared from 6-chloropyridine-3-carboxylic acid (Aldrich Co.) by reduction to the corresponding primary alcohol ($LiAlH_4$, THF, 0 °C, 2 h, 60%) followed by oxidation (pyridinium chlorochromate, CH_2Cl_2, 23 °C, 2 h, 88%).

(6) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

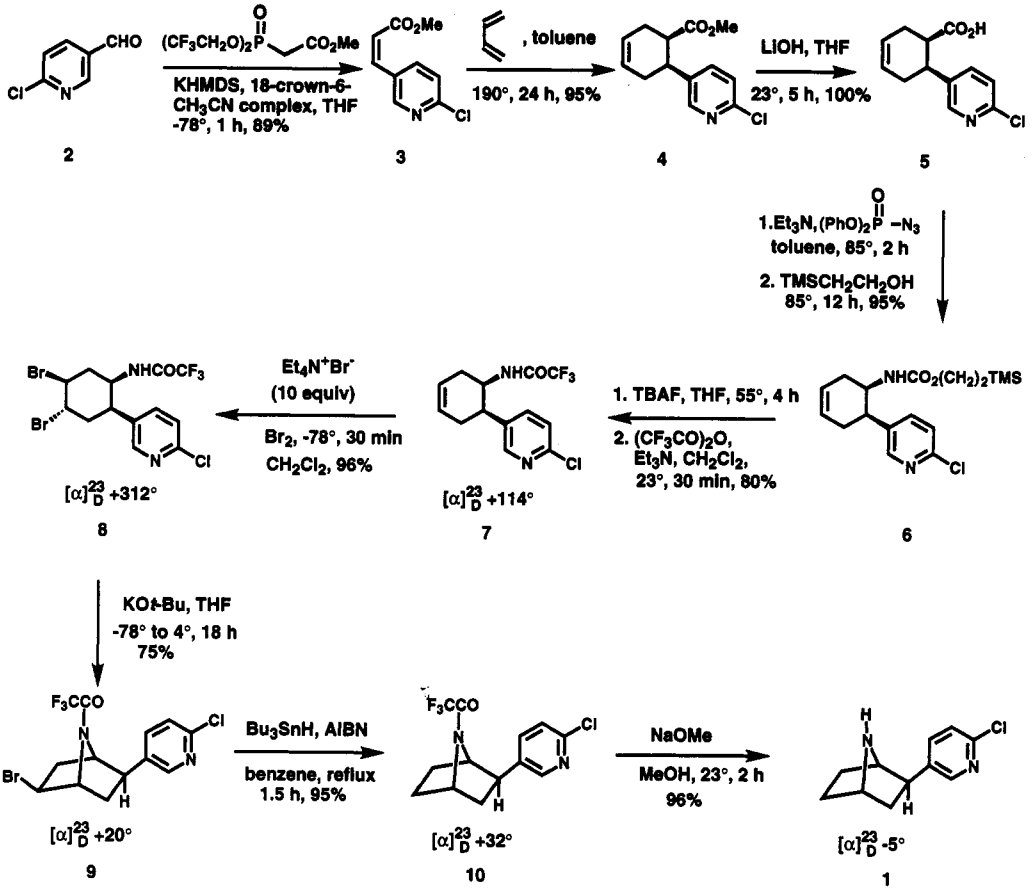
(7) Capson, T. L.; Poulter, D. C. *Tetrahedron Lett.* **1984**, *25*, 3515.

(8) Dibromide 8, $[\alpha]^{23}_D$ +312° (c = 0.25, $CHCl_3$), and its enantiomer, $[\alpha]^{23}_D$ −315° (c = 0.3, $CHCl_3$) were separated using a Daicel OD column with 5% isopropyl alcohol in hexane for elution, retention times 26.8 and 29.2 min, respectively. In the crystal 8 adopts a chair conformation with Br and CF_3CONH substituents all axial.

(9) The authors have deposited atomic coordinates for structure 8 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

0022-3263/93/1958-5600$04.00/0

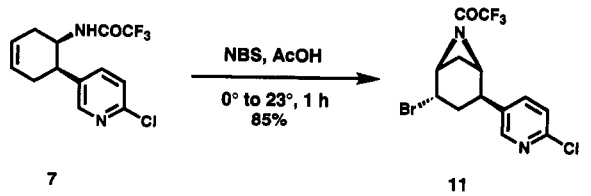
Scheme I



batidine, $[\alpha]^{23}_D$ −5°, which can be assigned the absolute configuration shown in **1**.

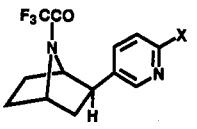
Preliminary bioassays of the levorotatory form of epibatidine (**1**) and the dextrorotatory enantiomer which have been carried out by Dr. John Daly and the NIH group suggest that these enantiomers have comparable analgesic activity. Unfortunately, toxicity can be detected at *ca.* five-fold higher concentration. We have noticed that exposure to very low levels of **1** and the enantiomer (for example when eluting a few mg from a TLC plate) in ambient air caused nasal irritation and congestion in both individuals (T.-P.L. and S.A.) who have worked with these substances. Toxicity of (±)-**1** has also been reported by Dr. Broka at Syntex Corp.[2]

The unsaturated amide **7** also can serve as a useful intermediate for the synthesis of azabicyclo[3.1.1]heptane analogs of epibatidine. Reaction of **7** with *N*-bromosuccinimide in acetic acid at 0–23 °C for 1 h afforded directly the azabicyclo[3.1.1]heptane derivative **11**. This interesting result indicates that the bromonium ion with bromine and amide functions *trans* may be favored in acetic acid as solvent and that, in the absence of bromide ion, the amide nitrogen can participate as a nucleophile under these conditions.[10]

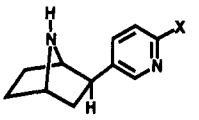


7 **11**

N-(Trifluoroacetyl)epibatidine **10**, and also its enantiomer, have also been used to synthesize the epibatidine derivatives **15**–**17** (and enantiomers) for biological evaluation. Treatment of **10** with sodium iodide (20 equiv)



12, X = I
13, X = H
14, X = Me



15, X = I
16, X = H
17, X = Me

and acetyl chloride (7 equiv) in propionitrile at 120 °C for 10 h resulted in formation of **12** (84%), mp 102–102.5 °C, $[\alpha]^{23}_D$ +29° (*c* = 0.6, $CHCl_3$). Deiodination of **12** to form **13** (96%) could be effected by heating at 80° in benzene with tri-*n*-butyltin hydride; $[\alpha]^{23}_D$ +40° (*c* = 1.3, $CHCl_3$), colorless oil. Alternatively, **13** could be formed directly from **10** in 95% yield by conducting the above described NaI–AcCl reaction at 130 °C for 48 h. Reaction of the iodopyridine **12** with 3.5 equiv of MeZnCl (from MeLi and

(10) One reason for the differing reaction pathways in the bromination of the unsaturated trifluoroacetamide **7** in CH_2Cl_2 and HOAc might be the following. In CH_2Cl_2, the relatively acidic NH group of the trifluoroacetamide function assists in the formation of the *cis* bromonium ion by hydrogen bonding to the terminal bromine of the *cis* Br_2–olefin π-complex and facilitating Br–Br cleavage. In acetic acid as solvent the trifluoroacetamide might provide acceleration as a nucleophile which selectively captures the *trans* bromonium ion. Such nucleophilic behavior could arise if there is a small concentration of **7** hydrogen bonded through NH to acetate ion. The use of NBS in the reaction to form **11** serves to minimize the bromide ion concentration and the formation of dibromide.

$ZnCl_2$) in THF–ether in the presence of 0.1 equiv of $(Ph_3P)_4$-Pd at 0–23 °C for 3 h resulted in the replacement of iodine by methyl to form 14 (98%), $[\alpha]^{23}_D$ +28° (c = 0.7, $CHCl_3$), oil. Deacylation of the trifluoroacetamides 12–14 (NaOMe–MeOH as shown in Scheme I) afforded the epibatidine analogs 15–17 in high yield. The enantiomers of 15–17 were prepared similarly.

In summary, we have synthesized the *dextro* and *levo* forms of epibatidine and have assigned absolute configuration. The absolute configuration of the natural epibatidine cannot be assigned at this time because of the unavailability of reference material and chirochromatographic/optical data.[11]

Supplementary Material Available: Experimental data for the reactions and compounds described herein (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) This research was assisted financially by a grant from the National Science Foundation. We are grateful to Dr. John Daly and his group for bioactivity data.