ENANTIO- AND DIASTEREOCONTROLLED SYNTHESIS OF EPIBATIDINE ANALOGUES

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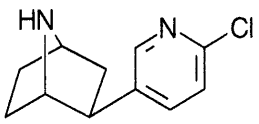
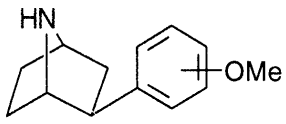
Three structural analogues of a potent non-opiate analgesic alkaloid epibatidine have been synthesized in optically pure forms in enantio- and diastereo-controlled ways using a chiral 2,5-cyclohexadiene-1,4-diol synthon.

KEY WORDS epibatidine; 7-azabicyclo[2.2.1]heptane; epibatidine analogue; enantiocontrolled synthesis

Epibatidine[1] (**1**) is an alkaloid having 7-azabicyclo[2.2.1]heptane framework which has been isolated from the Ecuadoran poison frog, *Epipedobates tricolor*, in 1992. Owing to its remarkable non-opiate analgesic activity, which is more than 200 times greater than that of morphine, a number of total syntheses employing a variety of methodologies have been published since the first racemic synthesis by Broka was disclosed in 1993.[2a] Because we were attracted to its biological activity as well as its unique 7-azabicyclo[2.2.1]heptane structure, we undertook the synthesis of three structural analogues **2a~c** having the methoxybenzene group in place of the chloropyridine moiety of the natural alkaloid **1** in optically pure forms to examine their pharmacological activity and to develop an enantio- and diastereo-controlled route to the natural product itself.



epibatidine (**1**)



2a : 2-MeO
2b : 3-MeO
2c : 4-MeO

Figure 1

The synthesis started with the optically pure tricyclic dienol[3] **4**, which was the chiral equivalent of 2,5-cyclohexadiene-1,4-diol[4] and was obtained efficiently in both enantiomeric forms from a *meso*-symmetric precursor **3** *via* lipase-mediated asymmetrization.[3] Thus, **4** was first transformed into the enone[5] by oxidation with pyridinium dichromate (PDC) in DMF. Reaction of **5** with the cuprate reagent prepared *in situ* from 2-methoxyphenylmagnesium bromide and copper(I) bromide-dimethyl sulfide complex[6] allowed stereoselective 1,4-addition from the *exo*-face to give the ketone **6a**, satisfactorily, as a single product. The same treatments using 3-methoxyphenyl- and 4-methoxyphenylmagnesium

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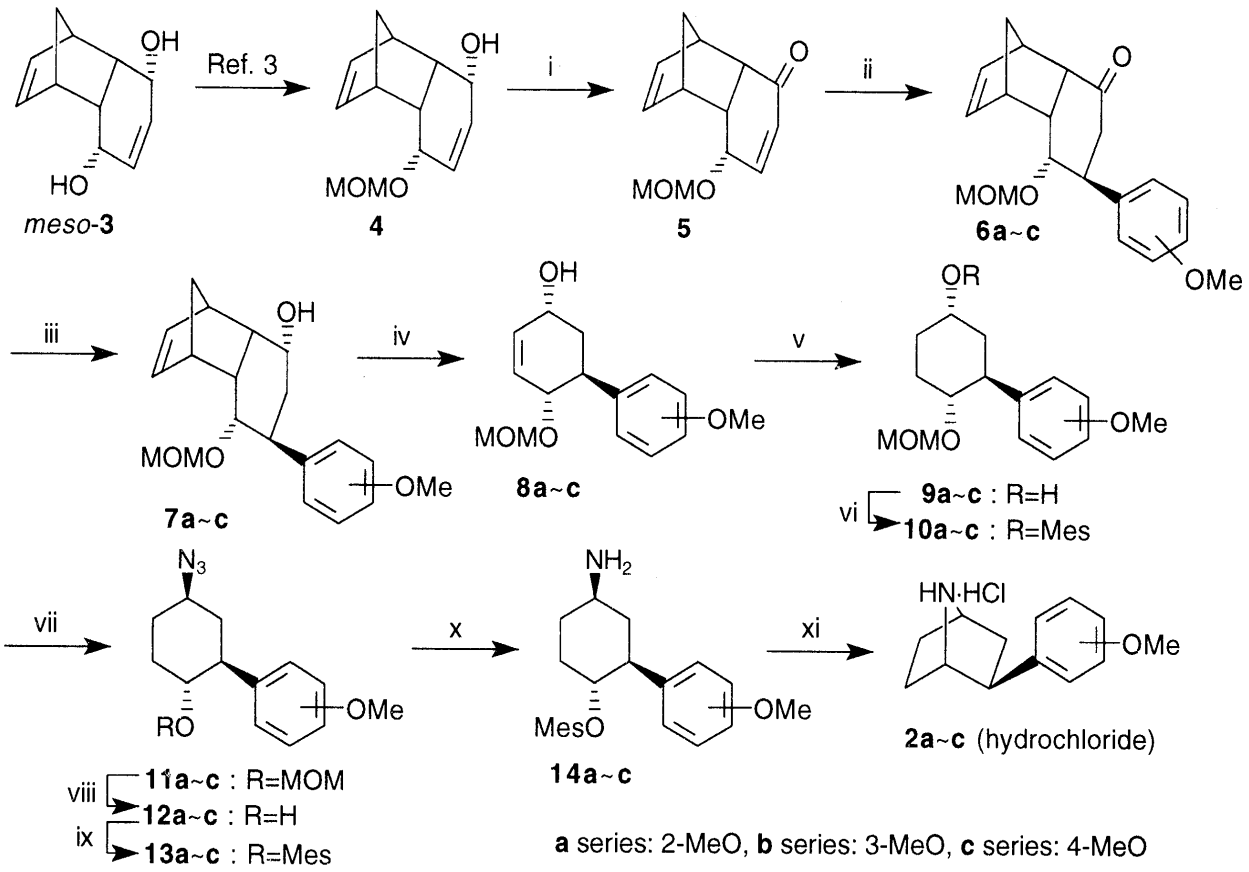

Chart 1

Reagents and conditions: i) PDC, DMF, room temp.: 84%; ii) ArMgBr, CuBr·Me_2S, HMPA, THF, −78 °C: **a** (76%); **b** (60%); **c** (78%); iii) $NaBH_4$, MeOH, −12 °C: **a** (90%); **b** (94%); **c** (90%); iv) diphenyl ether, reflux, 3 h; v) H_2, 10% Pd-C, EtOH, room temp.; vi) MesCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C, 1 h: **a** (56% from **7a**); **b** (57% from **7b**); **c** (50% from **7c**); vii) NaN_3, DMF, 60 °C, 12 h: **a** (76%); **b** (78%); **c** (84%); viii) AcCl (cat.), MeOH, room temp., 12 h; ix) MesCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C, 1 h: **a** (94% from **11a**); **b** (98% from **11b**); **c** (100% from **11c**); x) H_2, 10% Pd-C, EtOH, room temp.; xi) $CHCl_3$, 60 °C, 4 days, then HCl-Et_2O: **a** (54% from **13a**); **b** (65% from **13b**); **c** (54% from **13c**).

bromides afforded the corresponding ketones **6b** and **6c** stereoselectively in comparable yields. Reduction of the ketones **6a~c** with sodium borohydride also occurred selectively from the convex face to give the corresponding *endo*-alcohols **7a~c** in excellent yields, each as a single product. On thermolysis in refluxing diphenyl ether, the alcohols **7a~c** afforded the corresponding cyclohexenols **8a~c**, which were immediately hydrogenated to give the cyclohexanols **9a~c** in satisfactory overall yields. Since the introduction of the amino functionality by the Mitsunobu reaction[7] with phthalimide in the presence of diethyl azodicarboxylate and triphenylphosphine failed, the alcohols were first transformed into the corresponding methanesulfonates **10a~c**, which then were treated with sodium azide in DMF to furnish the azides **11a~c** in satisfactory yields with inversion of the stereochemistry. Removal of the methoxymethyl group followed by methanesulfonylation of the resulting alcohols **12a~c** yielded the corresponding azide-mesylates **13a~c**, each in a comparable overall yield. Finally, catalytic hydrogenation of **13a~c** followed by stirring of the resulting amino-mesylate **14a~c** in warm

chloroform for 4 days[2a] allowed formation of the 7-azabicyclo[2.2.1]heptane framework by intramolecular substitution reaction to give the epibatidine analogues **2a~c** having the methoxyphenyl group in place of the chloropyridine group in natural epibatidine (**1**) as the crystalline hydrochlorides after treatment with ethereal hydrogen chloride.

The merits of the present synthesis are a) high stereocontrolled introduction of the aromatic moiety, b) facile and efficient enantioselective construction of 7-azabicyclo[2.2.1]heptane framework, and c) ready availability of the optically pure starting material utilizable as both enantiomers. Further enantiocontrolled synthesis of epibatidine analogues and epibatidine (**1**) itself based on the present procedure is under investigation.

REFERENCES AND NOTES

1) Spande T. F., Garraffo H. M., Edwards M. W., Yeh H. J. C., Pannell L., Daly J. W., *J. Am. Chem. Soc.*, **114**, 3475 (1992). Although the enantiomeric structure was proposed to the natural product,[2f] the structure (**1**) depicted was used in this text for brevity.
2) a) Broka C. A., *Tetrahedron Lett.*, **34**, 3251 (1993); b) Huang D. F., Shen T. Y., *Tetrahedron Lett.*, **34**, 4477 (1993); c) Fletcher S. R., Baker R., Chambers M. S., Hobbs S. C., Mitchell P. J., *J. Chem. Soc., Chem. Commun.*, **1993**, 1216; d) Corey E. J., Loh T. -P., AchynthaRao S., Daley D. C., Sarshar S., *J. Org. Chem.*, **58**, 5600 (1993); e) Clayton S. C., Regan A. C., *Tetrahedron Lett.*, **34**, 7493 (1993); f) Fletcher S. R., Bayker R., Chambers M. S., Herbert R. H., Hobbs S. C., Thomas S. R., Verrier H. M., Watt A. P., Ball R. G., *J. Org. Chem.*, **59**, 1771 (1994); g) Senokuchi K., Nakai H., Kawamura M., Katsube N., Nonaka S., Sawaragi H., Hamanaka N., *Synlett*, **1994**, 343; h) Okabe K., Natsume M., *Chem. Pharm. Bull.*, **42**, 1432 (1994); i) Szántay C., Kardos-Balogh Z., Moldvai I., Szántay C. Jr., Temesvári-Major E., Blaskó G., *Tetrahedron Lett.*, **35**, 3171 (1994); j) Sestanj K., Melenski E., Jirkovsky I., *ibid.*, **35**, 5417 (1994); k) Ko S. Y., Lerpiniere J., Linney I. D., Wrigglesworth R., *J. Chem. Soc., Chem. Commun.*, **1994**, 1775; l) Pandey G., Bagul T. D., Lakshmaiah G., *Tetrahedron Lett.*, **35**, 7439 (1994); m) Albertini E., Barco A., Benetti S., Risi C. D., Pollini G. P., Romagnoli R., Zanirato V., *ibid.*, **35**, 9297 (1994).
3) a) Takano S., Moriya M., Ogasawara K., *J. Chem. Soc., Chem. Commun.*, **1993**, 614; b) Takano S., Higashi Y., Kamikubo T., Moriya M., Ogasawara K., *Synthesis*, **1993**, 948.
4) Ogasawara K., *Pure & Appl. Chem.*, **66**, 2119 (1994).
5) All new compounds isolated possess satisfactory spectral (IR, ^{1}H NMR, and Mass) and analytical (combustion and high resolution mass) data. Only mp and specific rotation values are described here: **5**: $[\alpha]_D^{31}$ +510° (*c*=0.55, $CHCl_3$). **6a**: mp 87.5-88.0 °C, $[\alpha]_D^{27}$ –47.0° (*c*=0.82, $CHCl_3$); **6b**: $[\alpha]_D^{28}$ –51.0° (*c*=0.42, $CHCl_3$); **6c**: mp 95 °C, $[\alpha]_D^{31}$ –61.3° (*c*=0.98, $CHCl_3$). **7a**: mp 66 °C, $[\alpha]_D^{27}$ –50.3° (*c*=0.47, $CHCl_3$); **7b**: mp 76.0-76.5 °C, $[\alpha]_D^{25}$ –52.7° (*c*=0.48, $CHCl_3$); **7c**: mp 110-111 °C, $[\alpha]_D^{31}$ –64.4° (*c*=0.88, $CHCl_3$). **10a**: $[\alpha]_D^{29}$ –30.0° (*c*=0.50, $CHCl_3$); **10b**: $[\alpha]_D^{29}$ –25.9° (*c*=1.24, $CHCl_3$); **10c**: mp 108-109 °C, $[\alpha]_D^{28}$ –19.5° (*c*=0.50, $CHCl_3$). **11a**: $[\alpha]_D^{27}$ –52.0° (*c*=1.74, $CHCl_3$); **11b**: $[\alpha]_D^{25}$ –33.2° (*c*=1.59, $CHCl_3$); **11c**: mp 64-65 °C, $[\alpha]_D^{28}$ –29.5° (*c*=0.99, $CHCl_3$). **13a**: mp 102-103 °C; $[\alpha]_D^{21}$ –29.1° (*c*=0.81, $CHCl_3$); **13b**: mp 94.5-95.0°, $[\alpha]_D^{27}$ –29.2° (*c*=1.15, $CHCl_3$); **13c**: mp 162.5-163.5°, $[\alpha]_D^{28}$ –19.8° (*c*=0.58, $CHCl_3$). **2a** · hydrochloride: mp 104.5-105.0 °C, $[\alpha]_D^{27}$ –23.6° (*c*=0.91, MeOH); **2b** · hydrochloride: amorphous solid, $[\alpha]_D^{30}$ –27.4° (*c*=2.08, MeOH); **2c** · hydrochloride: mp 210-211 °C, $[\alpha]_D^{26}$ –30.2° (*c*=0.41, MeOH).
6) cf. Takano S., Higashi Y., Kamikubo T., Moriya M., Ogasawara K., *J. Chem. Soc., Chem. Commun.*, **1993**, 788.
7) Mitsunobu O., *Synthesis*, **1981**, 1; Hughes D. L., *Org. Reactions*, **42**, 335 (1992).

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