ORGANIC LETTERS

1999
Vol. 1, No. 9
1439−1441

Synthesis and Stereochemical Assignment of *exo*- and *endo*-7-Methyl-7-azabicyclo[2.2.1]heptan-2-ol

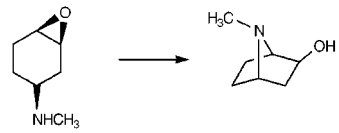
K. C. V. Ramanaiah,[†] Naiju Zhu,[‡] Cheryl Klein-Stevens,[‡] and Mark L. Trudell*,[†]

Departments of Chemistry, University of New Orleans, New Orleans, Louisiana 70148, and Xavier University of Louisiana, New Orleans, Louisiana 70125

mtrudell@uno.edu

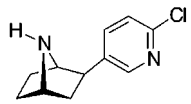
Received August 27, 1999

ABSTRACT



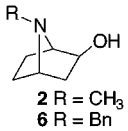
The syntheses of both the *exo* and *endo* stereoisomers of 7-methyl-7-azabicyclo[2.2.1]heptan-2-ol were achieved in straightforward fashion. Alternatively, the intramolecular cyclization of *syn*-4-*N*-methylaminocyclohexane 1,2-epoxide was found to give *exo*-7-methyl-7-azabicyclo-[2.2.1]heptan-2-ol as the sole product. The stereochemistry of the *exo* isomer was unequivocally confirmed by X-ray crystallography.

Since the discovery of the novel alkaloid epibatidine (**1**) isolated from the skin of the Ecuadorian poison dart frog *Epipedobates tricolor*,[1] a number of synthetic studies directed toward the total synthesis of **1** have been reported.[2] From these studies, a variety of methods have been established for the construction of the novel 7-azabicyclo[2.2.1]heptane ring system. More recently, due to the antinociceptive activity of **1**, studies have focused on the synthesis and structure−activity relationships of analogues of **1**.[3,4]

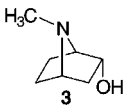


epibatidine (**1**)

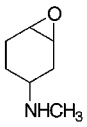
As part of an ongoing study in our laboratories directed toward the synthesis of novel analgesic agents based on the structure of **1**,[4a,5] *exo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol (**2**) and *endo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol (**3**) were identified as important synthetic intermediates.



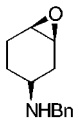
2 R = CH_3
6 R = Bn



3



4



5

During the course of the syntheses of **2** and **3**, conflicting reports in the literature describing the intramolecular cyclization of 4-alkylamino epoxides and the stereochemistry

[†] University of New Orleans.
[‡] Xavier University of Louisiana.

(1) 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.

(2) For a recent review on the synthesis of epibatidine, see: Szántay, C.; Kardos-Balogh, Z.; Szántay, C., Jr. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1995; Vol. 46, p 95.

(3) For a review on the synthesis of the 7-azabicyclo[2.2.1]heptane ring system, see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.

(4) (a) Zhang, C.; Gyermek, L.; Trudell, M. L. *Tetrahedron Lett.* **1997**, *38*, 5619. (b) Wright, E.; Gallagher, T.; Sharples, C. G. V.; Wonnacott, S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2867. (c) Malpass, J. R.; Cox, C. D. *Tetrahedron Lett.* **1999**, *40*, 1419. (d) Krow, G. R.; Cheung, O. H.; Hu, A.; Huang, Q.; Hutchinson, J.; Liu, N.; Nguyen, K. T.; Ulrich, S.; Yuan, J.; Xiao, Y.; Wypij, D. M.; Zuo, F.; Carroll, P. J. *Tetrahedron* **1999**, *55*, 7747. (e) Olivo, H. F.; Colby, D. A.; Hemenway, M. S. *J. Org. Chem.* **1999**, *64*, 4966.

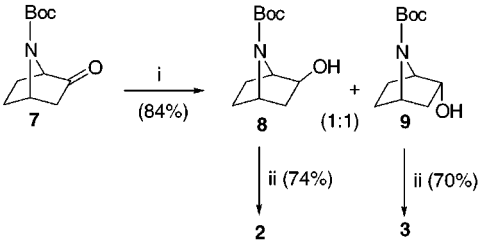
(5) Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189.

10.1021/ol990989y CCC: $18.00
Published on Web 09/25/1999

of the corresponding 7-azabicyclo[2.2.1]heptan-2-ols were revealed.[6−8] In an earlier report by Pfister et al.,[5] it was claimed that epoxide **4** was converted into the *endo* isomer **3**. This procedure was also recently used to prepare **3** as an intermediate in a synthesis of **1**.[7] However, in a recent report using identical reaction conditions, Fletcher et al.[6] described the conversion of the *N*-benzyl derivative **5** into the *exo* isomer **6**. Although rare, the *syn* attack of the *N*-benzylamino group on the epoxide was unequivocally established as the net reaction pathway for the formation of **6**. The difference in the stereochemical outcome between the *N*-methyl and *N*-benzyl systems was intriguing and prompted a further investigation of this cyclization reaction.

Initially, the 7-methyl-7-azabicyclo[2.2.1]heptan-2-ols **2** and **3** were prepared by an alternative method. As illustrated in Scheme 1, the ketone **7**[5] was hydrogenated over Adam's

Scheme 1



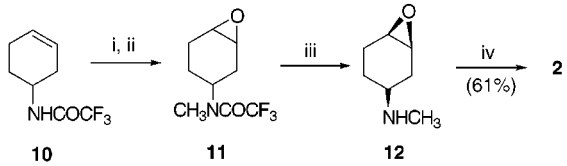
Reagents: (i) H_2, PtO_2, CH_3OH. (ii) $LiAlH_4$, THF, reflux.

catalyst in anhydrous methanol to afford the 7-Boc-7-azabicyclo[2.2.1]heptan-2-ols (**8**:**9**, 1:1) in 84% yield. The isomeric mixture was separated by column chromatography, and the isomers **8**[8] and **9**[8] were then independently converted with $LiAlH_4$ into the corresponding *N*-methyl analogues **2** and **3**.[9]

The two stereoisomers were easily distinguished by ^1H and ^{13}C NMR. Most notably, the chemical shift of the 2βH (δ 4.34 ppm) of **3** was significantly shifted downfield due the proximity of the lone pair of electrons on the nitrogen atom, while the 2αH of **2** was more upfield (δ 3.62 ppm). In addition, the stereochemistry of *exo* isomer **2** was unequivocally established by X-ray crystallographic analysis of the corresponding oxalate salt.[10] Upon comparison of the NMR data originally reported for **3** by Pfister et al.,[6] it was apparent that the original stereochemical assignment was incorrect and the actual product was the *exo* isomer **2**.

With both stereoisomers in hand, attention focused on the intramolecular cyclization reaction to unequivocally establish the stereochemical outcome of the cyclization reaction of the *N*-methyl analogue. A mixture of the epoxides **11** (3:1, *syn:anti*) was prepared in fashion similar to that previously described for *N*-trifluoroacetoamidocyclohex-3-ene (**10**) (Scheme 2).[7] Mixture **11** was then treated with potassium

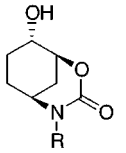
Scheme 2



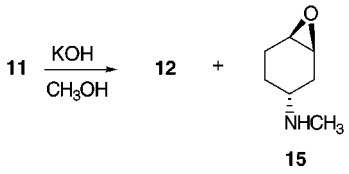
Reagents: (i) NaH, CH_3I, DMF. (ii) *m*-CPBA, CH_2Cl_2. (iii) K_2CO_3, CH_3OH. (iv) NMP, K_2CO_3,160 °C, 3 days.

carbonate to remove the trifluoroacetyl protecting group. Although it was not noted in the original work,[7] this afforded *syn*-*N*-methylamino epoxide **12** as the sole product.

Subsequently, epoxide **12** was heated at 160 °C in *N*-methylpyrrolidone/potassium carbonate for 72 h and then allowed to cool to room temperature over 12 h. After workup, a single product was obtained which corresponded to *exo* isomer **2**[7] (61% yield). This result also confirms the stereochemistry of epoxide **12**, since only *syn* isomer **11** can afford *exo* isomer **2**. The yield of **2** was diminished if the heating period exceeded 72 h. After this time the formation of side products became apparent by TLC and the yield of **2** decreased. It is believed that long exposure to high temperatures results in thermal decomposition of the bicyclic amine.



13 R = CH_3
14 R = Bn



It is noteworthy that a single diastereoisomer (**12**) was obtained from the hydrolysis reaction of **11**. It is believed

(6) Fletcher, S. R.; Baker, 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.* **1994**, *59*, 1771.

(7) Senokuchi, K.; Nakai, H.; Kawamura, M.; Katsube, N.; Nonaka, S.; Sawaragi, H.; Hamanaka, N. *Synlett* **1994**, 343.

(8) Pfister, J. R.; Wymann, W. E.; Weissberg, R. M.; Strosberg, A. M. *J. Pharm. Sci.* **1985**, *74*, 208.

(9) (a) Data for **2**: ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (dd, J = 7.2, 2.1 Hz, 1H), 3.21 (br s, OH), 3.19 (d, J = 2.7 Hz, 1H), 3.10 (d, J = 3 Hz, 1H), 2.25 (s, 3H), 1.71 (m, 3H), 1.55 (m, 1H), 1.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.0, 68.3, 60.0, 43.4, 34.2, 24.3, 21.2. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10. 30; N, 11.01. Found: C, 66.00; H, 10. 20; N, 10.91. (b) Data for **3**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (t, J = 5.2 Hz, 1H), 3.25 (t, J = 4.4 Hz, 1H), 3.19 (t, J = 4.8 Hz, 1H), 2.99 (br s, OH), 2.28 (s, 3H), 2.13 (m, 2H), 1.88 (m, 1H), 1.67 (m, 1H), 1.47 (m, 1H), 0.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.3, 66.3, 62.7, 39.7, 34.6, 26.5, 17.5. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10. 30; N, 11.01. Found: C, 66.31; H, 10. 50; N, 11.11.

(10) X-ray data for **2**·1.5$(CO_2H)_2$ is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.: $(C_7H_{13}NO)_2$·$(C_2H_2O_4)_3$; $P21/n$; Z = 4; a = 13.361(4) Å; b = 6.819(9) Å; c = 26.713(6) Å; β = 94.46°.

that the during the course of the reaction, the *anti* isomer of **11** was converted into carbamate **13** in fashion similar to that which was reported for the *N*-benzyl system (**14**).[8]

However, *N*-methyl derivative **13** presumably was less stable than **14** and hence decomposed during the reaction to afford water-soluble intractable compounds. As a result only *syn* isomer **12** was isolated from the reaction mixture. Alternatively, if the mixture of epoxides **11** was treated with methanolic potassium hydroxide, a mixture of *syn* and *anti* epoxides **12**:**15** (3:1) was obtained.

In summary, the stereochemical assignments of the important intermediates, 7-methyl-7-azabicyclo[2.2.1]-heptan-2-ols **2** and **3**, have been unequivocally established. Moreover, it is apparent that the intramolecular cyclization of *syn*-4-(*N*-methylamino)cyclohexane 1,2-epoxide (**12**) in *N*-methylpyrrolidone/potassium carbonate proceeds via a *syn*-addition mechanism to afford only the corresponding *exo*-7-methyl-7-azabicyclo[2.2.1]heptan-2-ol (**2**) in good yield. These results are in agreement with previously reported results in the *N*-benzyl system and resolves the inconsistency in the literature.

Acknowledgment. This work was supported by a grant from the National Institute on Drug Abuse.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**, **3**, **12**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990989Y