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Gram-Scale Synthesis of (−)-Epibatidine

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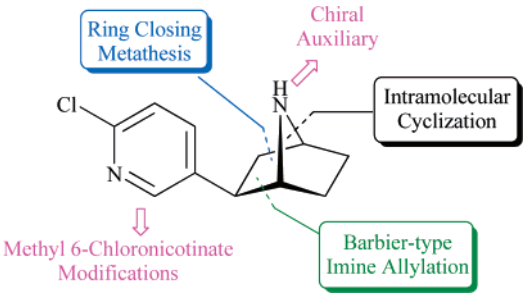
ABSTRACT



A gram-scale approach toward (−)-epibatidine (1, naturally occurring enantiomer), a novel class of amphibian alkaloid, has been developed from readily available starting materials using mild and easily controlled reactions. The entire synthetic route is straightforward and convenient for gram-scale synthesis.

Epibatidine **1**, a novel class of amphibian alkaloid, was first isolated by Daly et al. in a trace amount from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*.[1] The exciting biological properties[2] and unique structure of epibatidine,[3] combined with its scarcity in nature (ca. 1 mg from some 750 frogs), have aroused the interest of synthetic chemists around the world.[4] The fact that the collection of dendrobatid frogs has been prevented by an international treaty enacted in 1984 for the protection of endangered species has also spurred further efforts to prepare needed material in gram scale for further critically important biological investigation.[5] Herein, we communicate a short (12 step) and efficient multigram-scale approach toward the total synthesis of (−)-epibatidine, which could permit extensive pharmacological studies.

Our retrosynthetic analysis for (−)-epibatidine is shown in Scheme 1 where the 7-azabicyclo[2.2.1]heptane ring of **1** was envisioned to arise by an intramolecular nucleophilic cyclization between the amine and the electrophilic bromine-bearing carbon of the intermediate precursor.[6] The latter could have come from the brominated product of the cyclohexenylamine **22**. We planned to utilize ring-closing

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(1) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannel, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.

(2) For some selective reports on the biological activities, see: (a) Heard, N. E.; Turner, J. *J. Org. Chem.* **1995**, *60*, 4302. (b) Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445 and references therein. (c) Damaj, M. I.; Creasy, K. R.; Grove, A. D.; Rosecrans, J. A.; Martin, B. R. *Brain Res.* **1994**, *664*, 34. (d) Decker, M. W.; Bannnon, A. W.; Curzon, P.; Gunther, K. L.; Brioni, J. D.; Holladay, M. W.; Lin, N.-H.; Li, Y.; Daanen, J. F.; Buccafusuco, J. J.; Prendergast, M. A.; Jackson, W. J.; Arneric, S. P. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 247; and references therein.

(3) Fletcher et al. further elucidated the structure: (a) Fletcher, S. R.; Baker, R. B.; Chambers, M. S.; Hobbs, S. C.; Mitchell, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1216. (b) Fletcher, S. R.; Baker, R. B.; 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**, *3*, 1771.

(4) (a) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683. (b) Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485. (c) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C., Jr.; Temesvári-Major, E.; Blaskü, G. *Tetrahedron* **1996**, *52*, 11053. (d) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857. (e) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 4513. (f) Jones, C. D.; Simpkins, N. S.; Giblin, G. M. P. *Tetrahedron Lett.* **1998**, *39*, 1023. (g) Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009.

(5) In 1984, the Convention on International Trade in Endangered Species (CITES) put all the dendrobatid frogs on their Appendix II listing.

(6) Chen, Z.-M.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.

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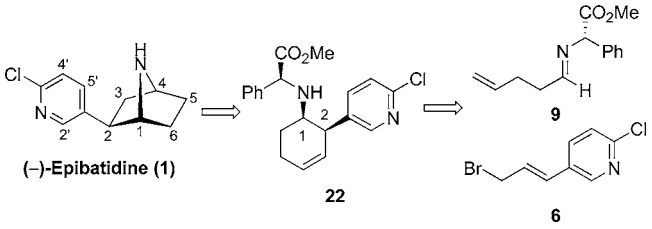
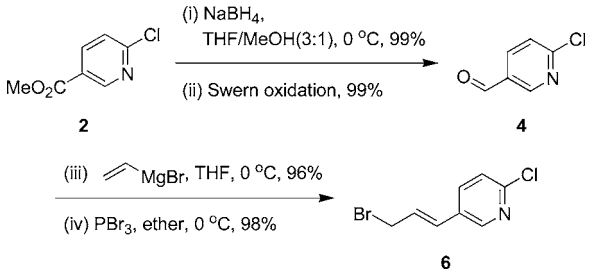
Scheme 1. Retrosynthetic Analysis of (−)-Epibatidine



metathesis (RCM) on the chiral homoallylic amine precursor using the very established Grubbs' catalysts.[7] The homoallylic amine may be prepared by a Barbier-type allylation between the chiral imine **9** and the chloro-nicotinyl bromide **6**.[8] Our experience with imine allylation suggested that the ability to control the stereochemistry at C1 and C2 may be related to the judicious choice of chiral auxiliary used.[9]

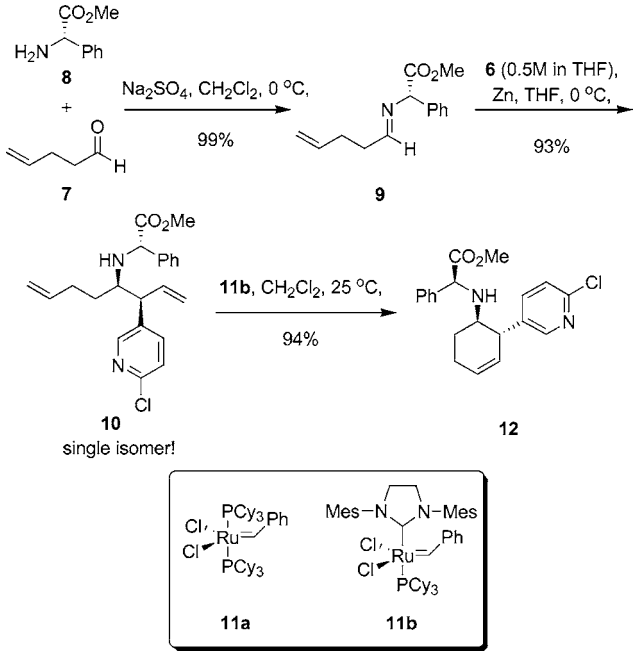
The synthesis commences from the reduction of the commercially available methyl chloro-nicotinate **2**, which then undergoes Swern oxidation to afford the aldehyde **4** (∼100% over two steps). Aldehyde **16** then undergoes a Grignard addition with vinylmagnesium bromide in THF to provide the allylic alcohol **5** in 96% yield, and a further bromination led to the formation of **6** in 98% yield. With a practical synthesis of the chloro-nicotinyl bromide **6** realized (97% yield over four steps), our studies entered into the next synthetic phase (Scheme 2).

Scheme 2. Preparation of Chloro-nicotinyl Bromide **6**[a]



The synthesis of the homoallylic amine **10** began via allylation of the chiral imine **9** (Scheme 3).[10] After the pent-4-enal **7** has successfully condensed with the chiral auxiliary **8** ((*S*)-phenylglycine acid-methyl ester),[11] Zn metal, followed by **6** (0.5 M solution in THF), was introduced. Even though

Scheme 3. Preparation of Key Intermediate **12**[a]



the syn homoallylic amine **10** was isolated in excellent yield as a single isomer (93% yield), it is evident that with trans relative stereochemistry, the late-stage epimerization procedure could be omitted. To base our design on the epimerization in the last step was initially not on the agenda, but efforts to invert the stereochemistry were unsuccessful.[12]

The RCM of **10** catalyzed by the first-generation catalyst **11a** provided the desired product **12** without much success (39%).[13] Gratifyingly, the robust **11b** managed to catalyze the RCM to afford the key cyclohexenylamine intermediate **12** in 94% yield with only 10 mol % loading at ambient temperature (Scheme 3).[14]

Initial attempts for the one-pot synthesis of the 7-azabicyclo-[2.2.1]heptane ring utilizing *N*-bromosuccinimide (NBS) in order to effect an intramolecular cyclization with the secondary amine as a nucleophile proved to be futile.[15] Nevertheless, bromination of **12** in excess $Et_4N^+Br^-$ provided two isomers, **13** and **14**, in admirable yield and moderate selectivity (92%; 66:34). A single-crystal X-ray structure of **13** confirmed that

(7) For a general review, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(8) For a discussion of the mechanism, see: Molle, B. *J. Am. Chem. Soc.* **1982**, *104*, 348175.

(9) (a) Huang, J.-M.; Xu, K.-C.; Loh, T.-P. *Synthesis (Stuttgart)* **2003**, 5, 755. (b) Loh, T.-P.; Huang, J.-M.; Xu, K.-C.; Goh, S.-H.; Vittal, J. J. *Tetrahedron Lett.* **2000**, *41*, 6511. (c) Loh, T.-P.; Wang, R.-B.; Tan, K.-L.; Sim, K.-Y. *Main Group Met. Chem.* **1997**, *20*, 237. (d) Loh, T.-P.; Ho, D. S. C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865.

(10) Lee, C. L. K.; Ling, H. Y.; Loh, T.-P. *J. Org. Chem.* **2004**, *66*, 7787.

(11) For an excellent review, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. For some representative examples, see: (b) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (c) Tanaka, H.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023. (d) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883. (e) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc., Perkins Trans.* **1998**, *1*, 777.

(12) Efforts to afford the anti isomer proved to be futile where (a) different metals (Sn, In, Ga, and Mg) were used; (b) other chiral auxiliaries ((*S*)-valine acid methyl ester and (*R*)-methyl benzylamine) were tried; and (c) catalytic amounts of various Lewis acids were added.

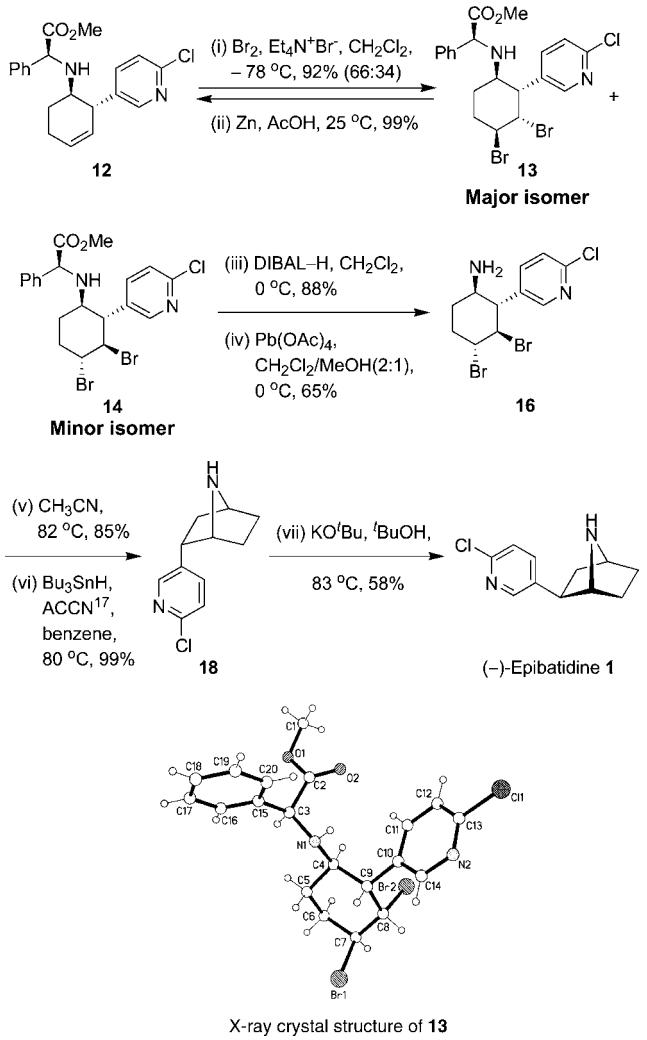
(13) (a) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (b) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847.

(14) For excellent reviews on the RCM with nitrogen-containing compounds, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (b) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959. (c) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.

(15) Corey, E. J.; Loh, T.-P.; Achyutha Rao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600.

the bromination had occurred in the undesired fashion (Scheme 4). To circumvent the impasse in this strategy, the

Scheme 4. Completion of Synthesis



X-ray crystal structure of **13**

major isomer **13** was converted back to **12** quantitatively by stirring the former in Zn and AcOH at ambient temperature. Ultimately, the minor isomer **14** was converted into the primary amine **16** by a two-step deprotection sequence.[16]

Intramolecular cyclization of **16** proceeded by refluxing the latter in CH_3CN, affording 85% (100% convergent yield) of the desired 7-azabicyclo[2.2.1]heptane ring **17** product.[18] The completion of the synthesis required the radical dehalogenation of **17** (100% yield) before the final epimerization of the *endo*-epibatidine **18** (58% yield; 81% convergent yield).[19]

In summary, a short and practical process has been developed for the synthesis of (−)-epibatidine **1** from readily available starting materials using mild and easily controlled reactions. There are several significant features in this synthetic route: (1) the synthesis of (−)-epibatidine requires a total of 12 steps and delivers the alkaloid with a 12% yield over the longest linear sequence; (2) both enantiomers of epibatidine can be obtained by simply switching the chiral auxiliary **8**; (3) the facile method of obtaining enantiomerically pure cyclohexenylamines and the RCM of alkylated amines have been achieved; (4) the bottleneck of the synthesis, the bromination procedure, has been overcome by recycling the undesired **13** to **12** through dehalogenation of the former; and (5) the entire synthetic route is straightforward and convenient for gram-scale synthesis. Continuing efforts in our laboratory have the goal of further refining our synthetic route such that we may attain multigram of epibatidine analogues, thereby aiding meaningful in vivo studies with this intriguing alkaloid.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Initially, **14** was cyclized prior to deprotection. However, deprotection on the reduced product of **14** did not proceed.

(17) ,1′-Azobis(cyclohexanecarbonitrile), a more efficient radical initiator than AIBN; see: Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.

(18) In most cases, more than 10% of the starting material **16** was recovered and could be reused.

(19) Szántay, C. U.S. Patent 5 545 741, 1996; *Tetrahedron* **1996**, *52*, 11053