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A General Efficient Strategy for *cis*-3a-Aryloctahydroindole Alkaloids via Stereocontrolled $ZnBr_2$-Catalyzed Rearrangement of 2,3-Aziridino Alcohols

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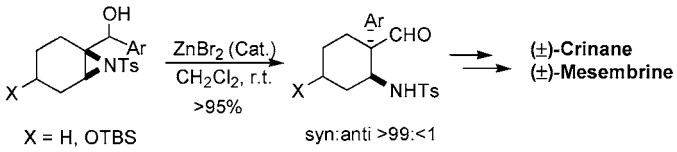
ABSTRACT



A short and general approach to the *cis*-3a-aryloctahydroindole alkaloids has been developed on the basis of a key stereocontrolled $ZnBr_2$-catalyzed rearrangement of 2,3-aziridino alcohols. Two representative members, (±)-crinane and (±)-mesembrine, have been synthesized in 15% and 11% overall yields, respectively.

The *cis*-3a-aryloctahydroindole alkaloids constitute a large class of structurally diverse natural products existing widely in the *Sceletium*[1] and *Amaryllidaceae*[2] alkaloids, such as mesembrine (**2**)[3] and pretazettine (**3**),[4] as well as some nonnatural products, such as crinane (**1**)[5] (Figure 1). As a result of their many biologically significant activities involving antiviral, antitumor, anticholinergic, even anti-HIV effects[6] and their intriguing structures, these alkaloids have been attracting considerable attention of organic chemists

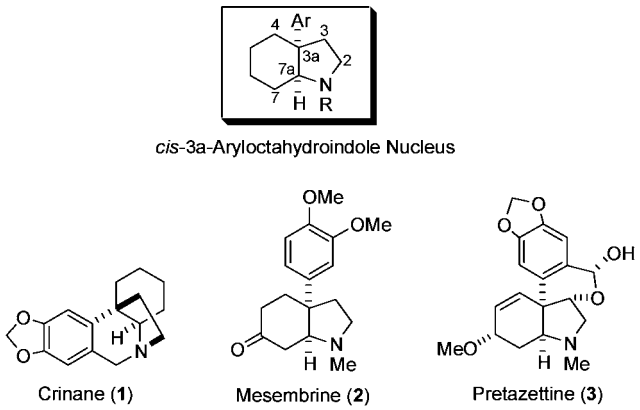


Figure 1. Representative members of *cis*-3a-aryloctahydroindole alkaloids.

(1) Jeffs, P. M. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, 1981; Vol. 19, pp 1−80.

(2) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376. (b) Jeffs, P. M. In *MTP International Review of Science, Alkaloids, Organic Chemistry, Series One*; Hey, D. H., Wiesner, K. F., Eds.; Butterworth: London, 1973; Vol. 9, pp 273−318.

(3) For some previous syntheses of mesembrine, see: (a) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143−147. (b) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673. (c) Ogasawara, K.; Tamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747. (d) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (e) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675.

(4) For some previous syntheses of pretazettine, see: (a) Baldwin, S. W.; Debenham, J. S. *Org. Lett.* **2000**, *2*, 99. (b) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664. (c) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647.

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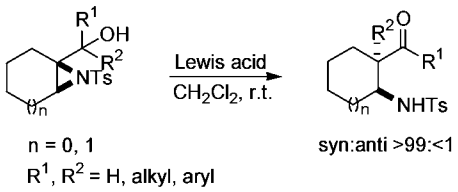
over the years. As a structural feature common to all of these species, the *cis*-3a-aryloctahydroindole nucleus (Figure 1) containing a sterically congested quaternary carbon center located at the hydroindolone bridgehead (C_{3a}) represents a central synthetic challenge, and a number of synthetic efforts have emerged to address this problem.

During the course of our investigation on the stereoselective construction of quaternary carbon centers,[7,8] we recently reported an efficient method to prepare 2-quarternery 1,3-amino carbonyl compounds by Lewis acid promoted highly stereoselective rearrangement of 2,3-aziridino alcohols under fairly mild conditions (Scheme 1).[9] The Mannich bases

Scheme 1

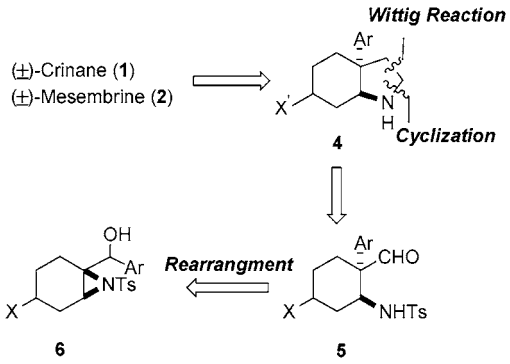


obtained, which are particularly versatile intermediates in the synthesis of numerous pharmaceuticals and natural products, are not accessible by the classical Mannich reaction.[10] More importantly, our further studies have discovered that catalytic amounts (0.1 equiv) of $ZnBr_2$ could also effect this reaction smoothly. Hence, the great potential of this method inspired us to apply it as a key step to accomplish the construction of the *cis*-3a-aryloctahydroindole alkaloids. Herein, the total syntheses of (±)-crinane (**1**) and (±)-mesembrine (**2**) on the basis of this methodology are reported.

Our retrosynthetic analysis is outlined in Scheme 2. We envisioned that both of these two target molecules could be available from the corresponding crucial *cis*-3a-aryloctahydroindole core structures **4** by some facile steps. In turn, **4** might be prepared from 2-aryl 1,3-amino aldehydes **5** through several transformations involving Wittig reaction and reductive cyclization**.** As the key strategy-level step, a $ZnBr_2$-catalyzed rearrangement of 2,3-aziridino alcohols **6** would provide the desired precursors **5** with requisite stereoselectivity.

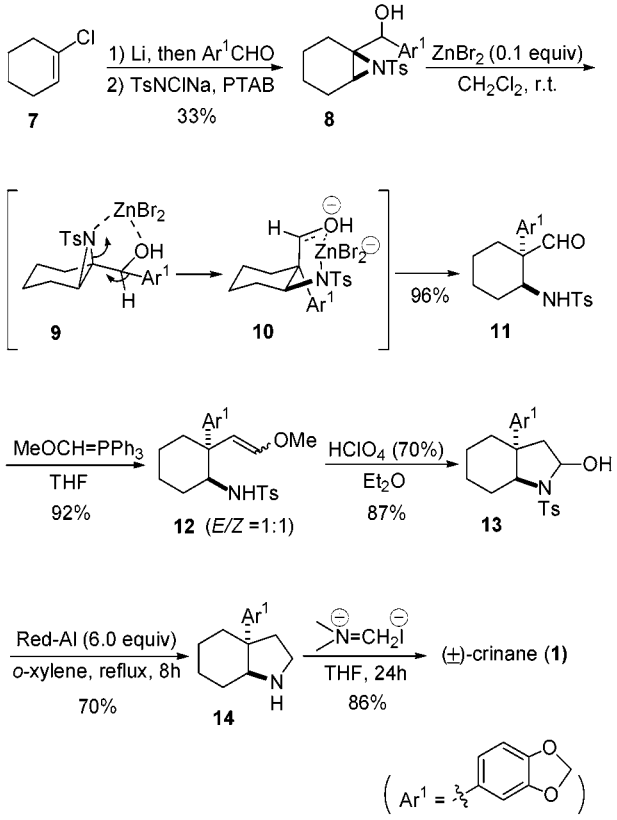
Initially, we selected (±)-crinane (**1**) possessing the basic structural element of interest, although not naturally occur-

Scheme 2. Retrosynthetic Analysis of (±)-Crinane (**1**) and (±)-Mesembrine (**2**)



ring, as an optimal target to test our methodology. According to our reported protocol,[9] the 2,3-aziridino alcohol **8** (Scheme 3) was obtained from cyclohexenyl chloride **7**[11] in 33%

Scheme 3. Total Synthesis of (±)-Crinane (**1**)



overall yield via two steps involving nucleophilic addition and aziridination of the corresponding allylic alcohol by the procedure of Sharpless.[12] With **8** in hand, the key stereoselective rearrangement was investigated. As expected, subjec-

(6) Lin, L. Z.; Hu, S. F.; Chai, H. B.; Pengsuparp, T.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *Phytochemistry* **1995**, *40*, 1295.

(7) For recent reviews on stereoselective construction of a quaternary carbon center, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (c) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

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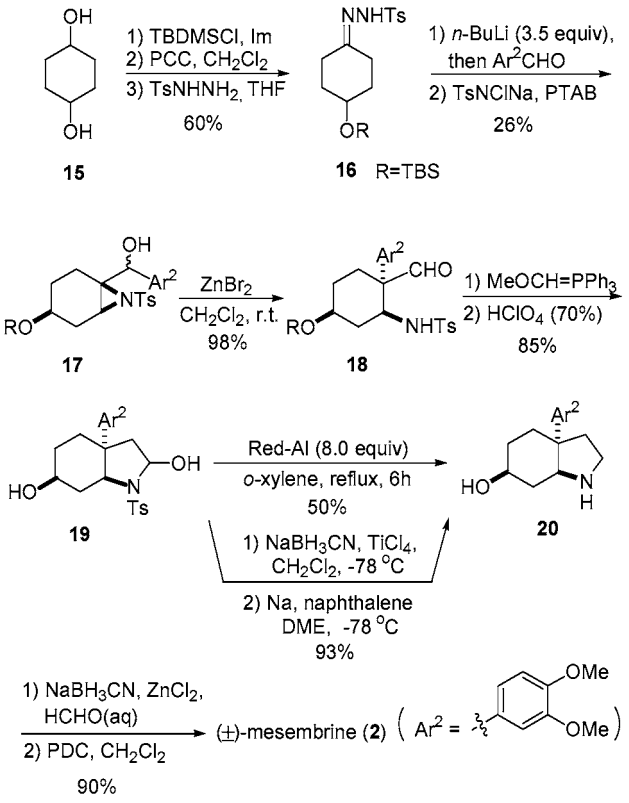
(10) For a general review on Mannich reaction, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(11) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1950**, 2014.

(12) Jeong, J. K.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

Scheme 4. Total Synthesis of (±)-Mesembrine (**2**)



tion of **8** to catalytic amounts of $ZnBr_2$ in dry CH_2Cl_2 at room temperature for 1 h gave rise to **11** as a single diastereoisomer smoothly in 96% yield. The stereochemical assignment of **11** was confirmed by our previously reported results.[9] Meanwhile, the proposed transition state **9** and **10** interpreted effectively the perfect stereocontrol observed in this reaction.

At the beginning of constructing the dihydropyrrole moiety, the Wittig reaction was selected to realize carbonyl homologation. Exposure of **11** to the ylide (4.0 equiv, prepared from methyoxymethyltriphenyl phosphonium chloride[13] and *n*-BuLi in THF) gave a 1:1 *E/Z* mixture of vinyl ethers **12**. When **12** was stirred in Et_2O with several drops of aqueous $HClO_4$ (70%) for 8 h, the unique cyclizing product α-hydroxy sulfonamide **13** was formed and none of the corresponding sulfonamide aldehyde tautomer was detected.[14] When selecting suitable routes for the transformation of **13** to **14**, we first referred to the method reported by Hoshino.[15] To our delight, heating **13** in refluxing *o*-xylene in the presence of excessive sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) for 8 h afforded the desired *cis*-3a-aryloctahydroindole **14** directly in 70% yield. Its spectral properties were in agreement with those previously reported.[5a]

Finally, using the reported Pictet−Spengler cyclization procedure,[5c] treatment of **14** with Eschenmoser's salt at 40 °C in THF for 24 h yielded (±)-crinane (**1**).

The successful synthesis of (±)-crinane encouraged us to apply the strategy above to another more complex target molecule, (±)-mesembrine (**2**), which incorporates a different aryl substituent and oxygenation at C-6. As shown in Scheme 4, the starting point of the synthesis is commercially available cyclohexane-1,4-diol **15**, which was transformed to hydrazone **16** via three steps in 60% overall yield. Then, Shapiro coupling[16] of **16** with 3,4-dimethoxybenzaldehyde followed by aziridination afforded the desired aziridino alcohol **17** as two isomers (2:1) in 26% overall yield. Following the same sequence in the synthesis of (±)-crinane, both isomers of **17** furnished **18**[17] in a single diastereoisomeric form, which then was converted into **19** in 85% overall yield. Treatment of **19** with Red-Al (8.0 equiv) resulted in the amino alcohol **20**, but the extreme condition and moderate yield of 50% led us to develop an alternative improved method. Subjected to $NaBH_3CN$ and $TiCl_4$ in CH_2Cl_2 at −78 °C[18,19] followed by removal of the tosyl group using sodium naphthalenide,[20] **19** was transformed to **20** in 93% overall yield. After *N*-methylation[21] followed by oxidation using PDC, **20** ultimately was converted into (±)-mesembrine (**2**), which has spectral characteristics identical to those reported in the literature.

In summary, we have developed a new and general strategy for the syntheses of *cis*-3a-aryloctahydroindole alkaloids using a $ZnBr_2$-catalyzed highly stereoselective rearrangment of 2,3-aziridino alcohols as the key step, and the total syntheses of (±)-crinane and (±)-mesembrine have been achieved. Application of this methodology to other kinds of more complex alkaloids, especially to enantioselective syntheses of some important molecules, is currently under investigation in our group.

Acknowledgment. This work was supported by NSFC (29972019, 29925205 and QT program), FUKTME of China, the Young Teachers' Fund of Ministry of Education and the Fund of Ministry of Education (99209).

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

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(19) Through the ^1H NMR NOE experiments of the product in this step and the spectral properties of **17**−**20**, the relative configuration of C_{3a}, C_{7a}, C_6 in **17**−**20** could be confirmed. For the detailed analysis, see Supporting Information.
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