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A facile aminocyclization for the synthesis of pyrrolidine and piperidine derivatives†

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Bromination of an isolated double bond followed by aminocyclization furnishes a highly stereoselective protocol for the intramolecular formation of pyrrolidine and piperidine ring containing subunits that are presented in numerous biologically active natural products.

Nitrogen heterocycles, especially pyrrolidine and piperidine containing sub-structures, are presented in a large class of biologically active natural products.[1] Selected examples are Dysinosin A,[2] Lycorine,[3] Stenine[4] and Lepadin B[5] as shown in Fig. 1. Those ring systems are also found in numerous therapeutic agents.[6] Synthesis of the core heterocyclic center has been an evergreen topic of the synthetic community since the early 1980s. Efforts towards this field have generated numerous synthetic methodologies.[7] Recent progresses can be found in the intramolecular hydrovinylation carried out by Johannsen,[8] synthesis of 2,5,6-trisubstituted piperidines by Padwa,[9] radical cyclization by Zard,[10] amidation of γ-iodoolefin by Komatsu,[11] a Mitsunobu-promoted intramolecular displacement of allylic alcohol by Banwell[12] and transition metal catalyzed amidation of double bonds by Livinghouse,[13] Stahl[14] and McDonald.[15] Here we report a new method for the synthesis of the core hexahydroindole and octahydroquinoline ring system presented in numerous natural products.

In the course of developing an efficient but flexible strategy towards the total synthesis of Lycorine and its analogues, a general method for the synthesis of the *N*-heterocyclic core center was needed by our group (see Scheme 1).

It was envisaged that intramolecular haloamidation of the double bond might be an ideal method to serve our purpose, since the halogen can be further manipulated to a double bond as required by Lycorine. However, on careful analysis of the literature there are few examples for intramolecular haloamidation of isolated double bonds forming hexahydroindole and octahydroquinoline ring systems.[16] Development of a general method for the synthesis of the core heterocyclic ring system, intermediate **1**, was thus initiated.

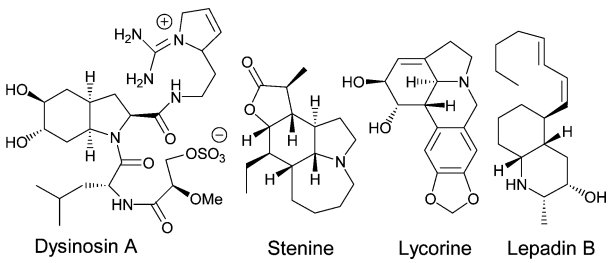
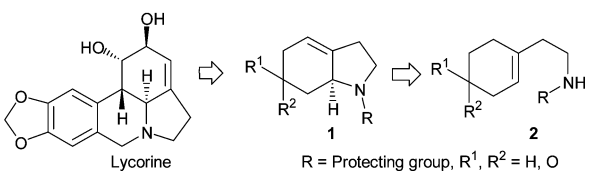


Fig. 1 Examples of pyrrolidine and piperidine containing natural products.

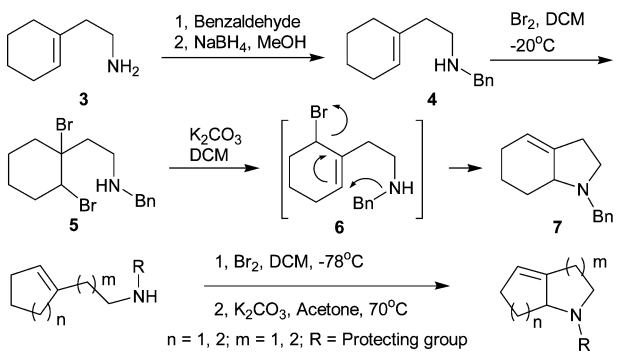


Scheme 1 Retrosynthetic analysis of Lycorine.

Treatment of commercially available cyclohexenylethylamine with benzaldehyde followed by reduction with $NaBH_4$ afforded intermediate **4**. Following the iodoamidation procedure reported in the literature,[16a] we did not get the desired iodocyclization product, but a complex mixture instead. Variation of solvent (DCM, THF, acetone, DMF), temperature as well as reagents (NBS, NIS) for haloamidation were fruitless, complex mixtures were obtained in all cases. To our delight, the target reaction was finally realized when bromine was employed. Treatment of intermediate **4** with bromine at −20 °C in dichloromethane followed by reflux in the presence of K_2CO_3 provided the desired hexahydroindole **7** in good yield. The process combined two reactions in one pot. In the initial stage, dibromide **5**, which could be isolated by flash chromatography, was formed by addition of bromine. By treatment with base, the hexahydroindole **7** was obtained; likely through an allylic bromide intermediate (**6**) as depicted in Scheme 2. A number of secondary amines were thus prepared and aminocyclizations were carried out. The results are summarized in Table 1 (entries 1 to 6). We also tested different protecting groups in the amino side. It was found that amides as well as sulfonamides could not undergo this process to afford the desired cyclization product. Free amines such as **3** are less effective, possibly due to relatively poor nucleophilicity of the primary amino group.

The protocol described herein is flexible; it could be extended to prepare the octahydroquinoline as well as hexahydro-1*H*-pyridine ring systems (entries 7, 8 and 9). Although the aminocyclization could be carried out in dichloromethane, better yields are generally obtained by using higher boiling point solvents such as THF, acetone or DMF. In principle, for entries 5 to 9, four stereoisomers (2^n, *RS*, *RR*, *SR* and *SS*) were expected. In our cases, however, only one unassigned diastereoisomer (*RS* and *SR* or *RR* and *SS*) were isolated.[17]

In order to further confirm the diastereoselectivity observed for entries 5 to 9 in Table 1, chiral secondary amines such as **8**,



Scheme 2 Formation of the pyrrolidine and piperidine ring system.

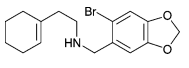
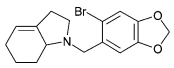
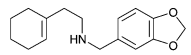
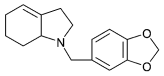
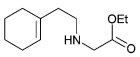
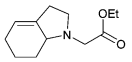
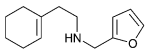
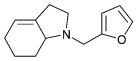
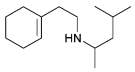
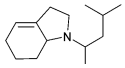
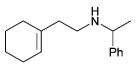
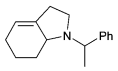
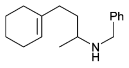
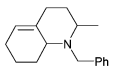
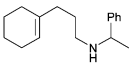
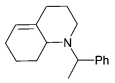
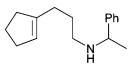
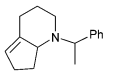
† Electronic supplementary information (ESI) available: experimental details and characterization data. See http://www.rsc.org/suppdata/cc/b3/b304157c/

DOI: 10.1039/b304157c

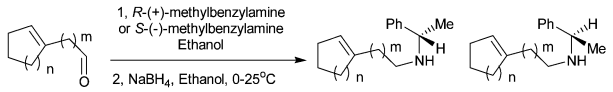
9, **10** and **11** were thus prepared by the procedure shown in Scheme 3 and similar aminocyclizations were conducted.

To our delight, only one diastereoisomer was obtained in those reactions carried out with chiral secondary amines (see Table 2). For entries 1 and 2 in Table 2, the products obtained have identical retention time in HPLC (Agilent Extend C_8-column, $CH_3CN : H_2O = 60 : 40$) as well as identical spectra of NMR but with opposite optical rotation.[18] The results observed further supported our speculation that an allylic bromide intermediate such as **6** in Scheme 2 might exist. Direct displacement of the secondary bromo-group in dibromides such as compound **5** would be less likely to afford high diastereoselectivity.

Table 1 Aminocyclization to form pyrrolidine and piperidine rings[a]

Entry	Secondary amine	Product	Yield (%)
1			78
2			75[b]
3			75
4			65
5			70
6			71
7			76
8			85[b]
9			73

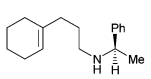
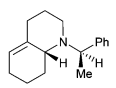
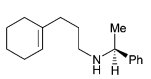
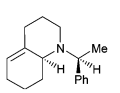
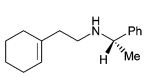
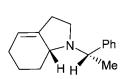
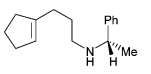
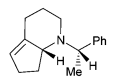
[a] For reaction conditions see ESI. Yields represent isolated yield based on secondary amines. All products were confirmed by GC-MS, ^{1}H-NMR and ^{13}C-NMR. [b] The structure was further confirmed by H–H COSY and C–H COSY.



8(*R*) and **9**(*S*) : n = 2, m = 2; **10**(*S*) : n =2, m =1; **11**(*S*) : n =1, m =2

Scheme 3 Procedure for the formation of chiral secondary amines.

Table 2 Aminocyclization to form chiral pyrrolidine and piperidine ring systems[a]

Entry	Secondary amine	Product[b]	Yield (%)
1			74
2			83
3			71
4			74

[a] For reaction conditions see ESI. Yields represent isolated yield. [b] Absolute configuration is not determined.

In summary, we have developed an easy to use, efficient yet flexible procedure for the formation of pyrrolidine and piperidine ring containing compounds. The bromination followed by aminocyclization furnishes a general protocol for the intramolecular haloamidation of an isolated double bond. It is noteworthy that a double bond was concomitantly formed upon the cyclization which is very useful for further manipulation. Application of this process towards the total syntheses of Lepadin B and Lycorine is currently underway in our laboratory.

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15 J.-S. Ryu, T. J. Marks and F. E. McDonald, *Org. Lett.*, 2001, **3**, 3091.
16 To the best of our knowledge, only one paper has dealt with iodocyclization of homoallylic sulfonamides to form a pyrrolidine ring system: (*a*) A. D. Jones, D. W. Knight and D. E. Hibbs, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1182. Other examples were mainly focused on intramolecular haloamidation of 3-acetyloxybut-1-enylamines or *N*-protected 3-hydroxy-4-pentenalamine and 4-hydroxy-5-hexenylamines as described in: (*b*) W. S. Lee, K. C. Jang, J. H. Kim and K. H. Park, *Chem. Commun.*, 1999, 251; (*c*) Y. Tamaru, S. Kawamura, T. Bando, K. Tanaka, M. Hojo and Z. Yoshida, *J. Org. Chem.*, 1988, **53**, 5491.
17 Although a trace spot in TLC well above the spot of the main product was suspected to be the other diastereoisomer, however, no product corresponding to this trace spot was isolated by flash chromatography.
18 Optical rotations were recorded on HORIBA SEPA-300 at 24 ° C. For entry 1 in Table 2: 1-[1-(*R*)phenylethyl]-1,2,3,4,6,7,8,8*a*-octahydroquinoline: $[\alpha]_D = -23.67°$ (c = 0.0017 g mL^{-1}, $CHCl_3$); For entry 2 in Table 2: 1-[1-(*S*)phenylethyl]-1,2,3,4,6,7,8,8*a*-octahydroquinoline: $[\alpha]_D = +26.79°$ (c = 0.0028 g mL^{-1}, $CHCl_3$).