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An Efficient Total Synthesis of (±)-Lycoramine

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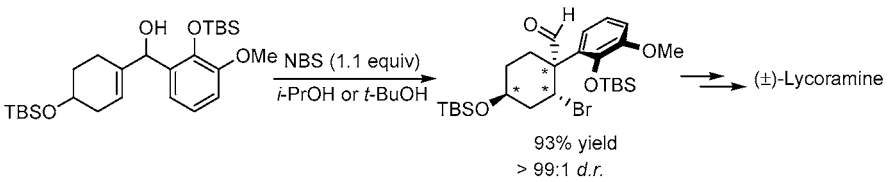
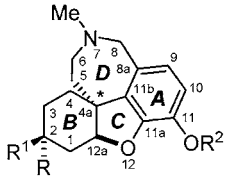
ABSTRACT



A short and unique approach to (±)-lycoramine as one of the galanthamine-type alkaloids has been efficiently developed. The alternative advantage lies in that three stereocenters, including a crucial quaternary carbon center, were constructed with high diasteroselectivity via a key one-step NBS-mediated semipinacol rearrangement of the allylic alcohol.

The galanthamine-type *Amaryllidaceae* alkaloids **1**−**4**[1−4] (Figure 1), which have been attracting much attention of synthetic chemists because of many biologically significant activities and their potential diversity in pharmacology,[5] are structurally featured by four rings A−D and one important spiro quaternary carbon center. As establishment of this sterically congested C_{4a} quaternary carbon is the critical element in the total synthesis of these alkaloids, a number of synthetic efforts have emerged to address this central synthetic challenge since 1960. Up to now, the biomimetic phenolic oxidative coupling[1b,l,2a] photochemical reaction,[1e] radical cyclization,[1j,k] and Heck reaction[1m,2b] have been intramolecularly utilized to create the C_{4a} quaternary carbon. Also, the alkylation[1c,d,f−h] and arylation[1i] have been intermolecularly employed for this synthetic purpose. However,



Lycoramine	**1** (R = H, R^1 = OH, R^2 = Me)
Galanthamine	**2** (R = H, R^1 = OH, R^2 = Me, $\Delta^{3,4}$)
Narwedine	**3** (R, R^1 = O, R^2 = Me, $\Delta^{3,4}$)
Sanguinine	**4** (R = H, R^1 = OH, R^2 = H, $\Delta^{3,4}$)

Figure 1. Representative galanthamine-type alkaloids.

(1) Lycoramine as an Amaryllidaceae alkaloid was first isolated from *Lycoris radiata* by Kondo, Tomimura, and Ishiwata; see: (a) Kondo, H.; Tomimura, K.; Ishiwata, S. *J. Pharm. Soc. Jpn.* **1932**, *52*, 51. For the synthesis of lycoramine, see: (b) Barton, D. H. R. G.; Kirby, W. *J. Chem. Soc.* **1962**, 806. (c) Hazama, N.; Irie, H.; Mizutani, T.; Shingu, T.; Takada, M.; Uyeo, S. *J. Chem. Soc. C* **1968**, 2947. (d) Misaka, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *J. Chem. Soc. C* **1968**, 2954. (e) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065. (f) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1981**, *46*, 3567. (g) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513. (h) Sánchez, I. H.; Soria, J. J.; López, F. J.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157. (i) Ackland, D. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2695. (j) Parker, K. A.; Kim, H.-J. *J. Org. Chem.* **1992**, *57*, 752. (k) Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877. (l) Kita, Y.; Arisawa, M.; Gyoten, M.; Nakajima, M.; Hamada, R.; Tohma, H.; Takada, T. *J. Org. Chem.* **1998**, *63*, 6625. (m) Gras, E.; Guillou, C.; Thal, C. *Tetrahedron Lett.* **1999**, *40*, 9243.

(2) For the synthesis of galanthamine by biomimetic oxidation coupling, see: (a) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659 and references therein. For its synthesis by Heck reaction, see: (b) Trost, B. M.; Tang, W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2795 and references therein.

(3) For the synthesis of narwedine, see refs 1b,f,l and 2b,k and also see: (a) Holton, R. A.; Sibi, M. P.; Murphy, W. S. *J. Am. Chem. Soc.* **1988**, *110*, 314. (b) Chaplin, D. A.; Fraser, N.; Tiffin, P. D. *Tetrahedron Lett.* **1997**, *38*, 7931.

(4) For the synthesis of sanguinine, see ref 1l.

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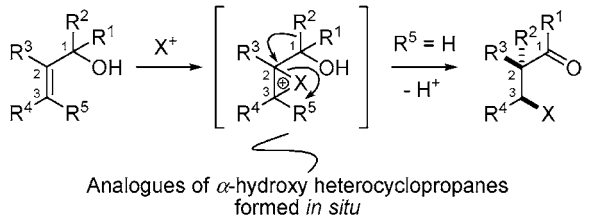
there have been no reports on the application of the semipinacol rearrangement reaction,[6] one of the most important [1,2]-rearrangement reactions in modern organic synthesis, to the stereocontrolled construction of this kind of critical quaternary carbon in **1**−**4**.

From a diversity-oriented synthetic point of view, it is of major importance to further develop an alternative synthetic strategy for these galanthamine-type alkaloids, especially in a concise fashion. During the course of our investigations on the stereoselective construction of 2-quternary 1,3-diheteroatom units[7] starting from α-hydroxy heterocyclopropanes, we recently disclosed an effective synthetic method for the preparation of 2-quaternary 1,3-halogeno carbonyl compounds[8] based on the semipinacol rearrangement of more potentially useful allylic alcohols (Scheme 1). To apply this

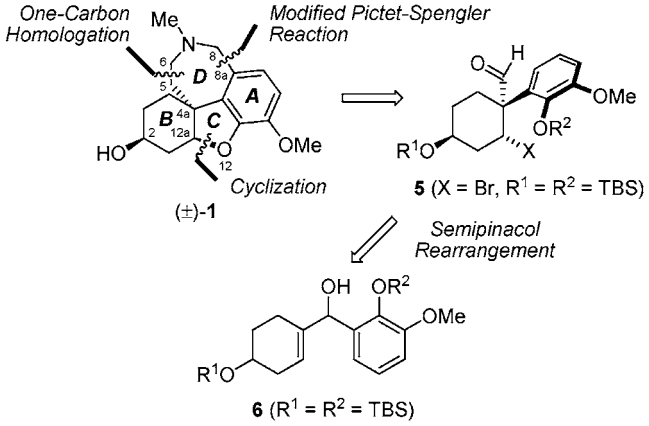
Scheme 1. Semipinacol Rearrangement of Allylic Alcohols



kind of the synthetic methodological concept to the synthesis of galanthamine-type alkaloids, we present preliminary studies toward the total synthesis of (±)-lycoramine **1** as an example of our new synthetic strategy.

Our retrosynthetic considerations on (±)-**1**, as shown in Scheme 2, were focused on establishment of two rings (C

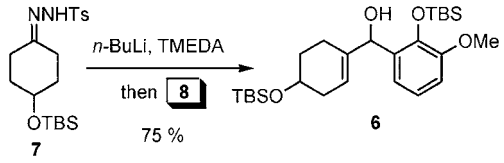
Scheme 2. Retrosynthetic Analysis of (±)-Lycoramine



and D) and three stereocenters (C_2, C_{4a}, and C_{12a}), wherein a 3-fold disconnection of (±)-**1** at the C_5-C_6, C_8-C_{8a}, and $C_{12}-C_{12a}$ junctures was proposed to provide the key synthetic precursor **5**, which is characterized by one 2-quaternary 1,3-diheteroatom unit and three diastereogenic stereocenters. The C_5-C_6 bond was envisaged to arise through the application of one-carbon homologation, whereas the C_8-C_{8a} bond was reserved for a modified Pictet−Spengler reaction.[9] The formation of a $C_{12}-C_{12a}$ bond in the C ring was designed by an S_N2-type intramolecular cyclization. As a key step, the semipinacol rearrangement of the easily available allylic alcohol **6** was elaborately planed to construct the crucial C_{4a} quaternary carbon center in **5** with requisite stereoselectivity.

As demonstrated in Scheme 3, commencing with the

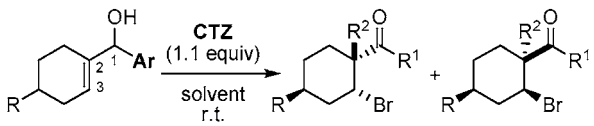
Scheme 3. Preparation of Starting Allylic Alcohol **6**



literature-known hydrazone **7**,[10] the allylic alcohol **6** could be readily afforded as two isomers (approximately 3:2 estimated by GC) in 75% yield through Shapiro reaction of **7** with TBS-protected *o*-vanillin **8**.

In connection with our previous work,[8] **6** was initially subjected to chloramine-T/$ZnBr_2$ condition. As seen in Table 1, when performing in a polar or nonpolar solvent, the

Table 1. Preliminary Studies on the Key Rearrangement of **6**[a]



6 (3:2) **5** (R^1 = H, R^2 = **Ar**) *iso*-**5** (R^1 = H, R^2 = **Ar**)
5a (R^1 = **Ar**, R^2 = H) *iso*-**5a** (R^1 = **Ar**, R^2 = H)

entry	solvent	**5**/*iso*-**5**/(**5a** + *iso*-**5a**)[b]	time (min)	yield[c] (%)
1	CH_3CN	72:11:17	15	43
2	acetone	74:16:10	20	47
3	CH_2Cl_2	60:20:20	15	53
4	*i*-PrOH	68:17:15	30	9

[a] R = OTBS, **Ar** = 2-TBSO-3-MeO-C_6H_3, **CTZ** = chloramine-T/$ZnBr_2$ (1:1). [b] The ratios were estimated by ^1H NMR. [c] Total yield of isolated products **5**/*iso*-**5**/**5a**/*iso*-**5a**.

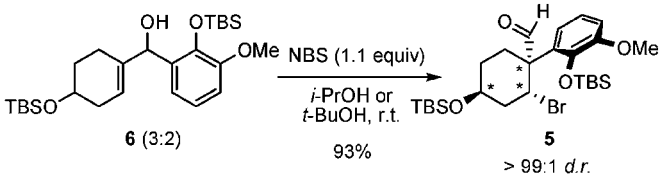
formation of the expected synthetic intermediate **5**,[11] resulting from the migration of the **Ar** group at C_1 position, was observed by NMR spectra analysis of the crude products.

(5) See also ref 1l and references therein.
(6) Coveney, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 777−801.
(7) Hu, X.-D.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Angew. Chem., Int. Ed.* **2004**, *43*, 1702 and references therein.
(8) Wang, B.-M.; Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q.; Chen, W.-M. *Synlett* **2003**, 1497.
(9) For the application of Pictet−Spengler reaction to the formation of benzazepine ring, see ref 1k and also see: (a) Kametani, T.; Terui, T.; Ogino, T.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 874. (b) Wittekind, R. R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8*, 495.
(10) Song, Z.-L.; Wang, B.-M.; Tu, Y.-Q.; Fan, C.-A.; Zhang, S.-Y. *Org. Lett.* **2003**, *5*, 2319.

However, **5** was always contaminated by the undesired diastereoisomer *iso*-**5**. Simultaneously, this rearrangement via the unexpectedly competitive migration of its C_1-hydride also resulted in other hardly purified byproducts, the ketone **5a** and *iso*-**5a**. Possibly this is due to the less unfavorable steric effect of the bulky ortho substituent OTBS in the migratory group C_1-**Ar**. Facing these frustrating results, a new reaction condition must be tentatively investigated in order to conceptually apply this kind of semipinacol rearrangement to the synthesis of the key precursor **5**.

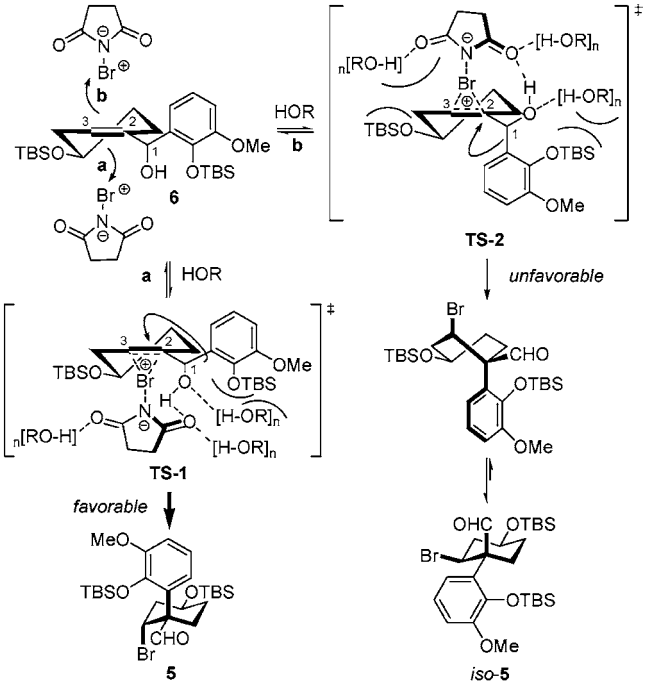
NBS, one of the most important brominating agents, has been widely used to prepare α-bromo carbonyl compounds. As a part of our work on the construction of 2-quaternary 1,3-diheteroatom units through the formation of analogues of α-hydroxy heterocyclicpropanes starting from allylic alcohols (Scheme 1), we found NBS could effectively realize the semipinacol rearrangement of tertiary hydroxy-protected allylic alcohols,[12] leading to a straightforward access to the *β*-bromo carbonyl compound. Although a few of this kind of NBS-promoted rearrangement reactions have been previously examined,[13] only some particular types of substrates such as tertiary hydroxy allylic alcohols with a highly strained cyclobutyl moiety, most of which are functionalized by an electron-rich double bond unit bearing the heteroatom (O, N) substituent,[13b,c] were employed. To our knowledge, however, this type of semipinacol rearrangement of a more general substrate such as the secondary hydroxy allylic alcohol **6** has not been systematically studied in the presence of NBS. Considering these facts above and our preliminary experimental encouragement,[12] detailed investigations on the NBS-promoted rearrangement of **6** were subsequently conducted in various solvents.[14] As shown in Scheme 4,

Scheme 4. NBS-Promoted Semipinacol Rearrangement of **6**



surprisingly the undesired isomers *iso*-**5**, **5a**, and *iso*-**5a** were not observed in this condition. Importantly, the key synthetic precursor **5**[11] with three desired uncontiguous stereocenters, one being a quaternary carbon center, could be afforded with excellent diastereoselectivity and high chemoselectivity in 93% yield, notably wherein the highly diastereoselective amplification was obviously exhibited by the formation of one single diastereoisomer product **5** in this rearrangement of the mixed allylic alcohols **6** with two epimers (2:3).

Scheme 5. Process for the Formation of **5** in the Protic Solvent



On the basis of the above experimental facts, a possible process for the formation of **5** from **6** in the protic solvent was proposed in Scheme 5, wherein the depicted hydrogen bonds[15] among NBS, allylic alcohol **6**, and protic medium not only highly lead to the facial diastereoselectivity of NBS but also, to some extent, increase the driving force of chemoselective migration of the bulky C_1-**Ar**.

After achieving this crucial intermediate **5**, we then investigated the efficient construction of C ring, especially in one step. Initially, some general organic and inorganic bases[16] were employed to realize this desilylation/cyclization transformation, but only very poor yield was obtained. To our surprise, treatment of **5** with 2 equiv of DBU[17] in DMSO at 80 °C for 0.5 h could smoothly and directly lead to the formation of the cyclization product **9** with the anticipated $C_{12}-C_{12a}$ bond of (±)-**1** in 95% yield (Scheme 6). Notably, the dual roles of DBU as a nitrogen organic base in this one-step transformation, the chemoselective desilylation and the stereocontrolled cyclization, have not been reported previously.[18] Interestingly, we further found substoichiometric amounts of DBU could also promote this desilylation/cyclization reaction.[16]

At the beginning of establishing the D ring, the widely applied Wittig reaction was selected to realize carbonyl

(11) For its relative stereochemistry confirmed by 1D NOSEY spectrum of the further cyclization product **9**, see the Supporting Information.

(12) Unpublished result, and see Scheme 1 of the Supporting Information.

(13) (a) Moriarty, K. J.; Shen, C.-C.; Paquette, L. A. *Synlett* **1990**, 263. (b) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. *J. Org. Chem.* **2001**, *66*, 2828. (c) Hurley, P. B.; Dake, G. R. *Synlett* **2003**, 2131.

(14) See Table 1 of the Supporting Information.

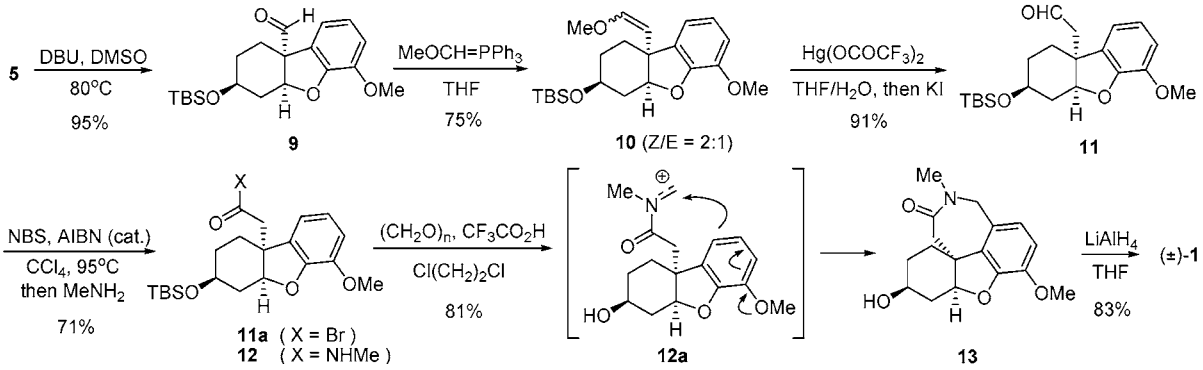
(15) Supported experiments; see Table 2 of the Supporting Information.

(16) See Table 3 of the Supporting Information.

(17) DBU as a hindered organic base is usually used for the dehydrohalogenation of alkyl halides; see: Larock, R. C. In *Comprehensive Organic Transformation*; 2nd ed.; Wiley: New York, 1999; p 258.

(18) Few effectively selective deprotections of phenolic TBS ethers bearing electron-donating group without affecting aliphatic TBS moiety have been reported; see: Oyama, K.-I.; Kondo, T. *Org. Lett.* **2003**, *5*, 209. For a possible mechanism in this DBU-induced transformation, see Scheme 2 of the Supporting Information.

Scheme 6. Construction of C and D Ring



homologation (Scheme 6). Exposure of **9** to the ylide $MeOCH{=}PPh_3$, formed in situ, smoothly gave rise to a mixture of vinyl ethers **10** in 75% yield. However, when the hydrolysis of the vinyl ether moiety of **10** was carried out under the usual acidic condition,[19] a series of more polar uncharacterized byproducts could be found on TLC. Subsequently, a mild neutral condition, $Hg(OAc)_2/THF{-}H_2O$ and KI,[20] was then employed to transform **10** into the aldehyde **11**, but only about 60% conversion was afforded. To our delight, the aldehyde **11** with $C_5{-}C_6$ bond of (±)-**1** could be cleanly generated from **10** in 91% yield in the presence of more electrophilic $Hg(OCOCF_3)_2$ as catalyst followed by addition of excess aqueous potassium iodide.

Furthermore, treatment of **11** with NBS in the presence of a catalytic quantity of AIBN as a radical initiator resulted in the crude acid bromide **11a** through a neutral oxidation reaction,[21] and then the reaction mixture without further purification was directly treated with excess of dry methylamine gas prepared in situ to afford the expected amide **12** in 71% overall yield in one pot. To construct the final $C_8{-}C_{8a}$ bond of (±)-**1**, the modified Pictet−Spengler reaction[1k,10] of **12** and paraformaldehyde with CF_3CO_2H smoothly proceeded via the *N*-acyliminium intermediate **12a** strongly activated by vicinal carbonyl group to expectedly give the lactam **13** in 81% yield, and meantime the quick cleavage of aliphatic TBS ether moiety first took place under this condition. Finally, reduction of **13** with $LiAlH_4$ readily afforded (±)-**1**, which exhibited spectral properties in agreement with previous reports.

In conclusion, we have developed a new strategy for the synthesis of (±)-lycoramine by means of an NBS-promoted highly stereoselective semipinacol rearrangement of allylic alcohol **6** as the key step followed by a novel DBU-induced desilylation/cyclization sequence. The present total synthesis of (±)-**1** proceeds in eight steps and 21% overall yield from easily available hydrazone **7**.

Acknowledgment. We are grateful for the financial support of the NSFC (Nos. 30271488, 20021001, and 203900501).

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

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(19) For example, see: (a) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. (b) Ohtani, M.; Matsuura, T.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1991**, *56*, 2122.

(20) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417.

(21) Markó, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237.