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Total Synthesis of (±)-Galanthamine‡

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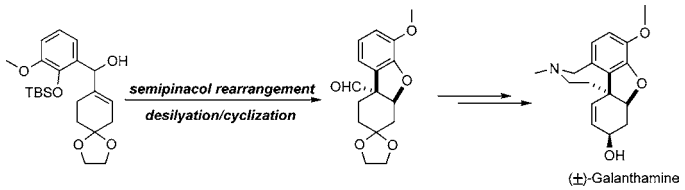
ABSTRACT



A practical and efficient total synthesis of (±)-galanthamine was achieved from commercially available materials through a novel approach, in which the construction of its core structure and the special allylic alcohol group were based on a successive semipinacol rearrangement/desilyation/cyclization and Saegusa−Ito oxidation, respectively.

Galanthamine (**1**),[1] the parent member of the galanthamine-type *Amaryllidaceae* alkaloids, is a centrally acting competitive and reversible inhibitor of acetylcholinesterase (Ache), which significantly enhances cognitive functions of patients suffering from Alzheimer's disease and was first approved in Austria and most recently in the rest of Europe and in the United States for the treatment of Alzheimer's disease.[2] To date, several elegant total syntheses of **1** were developed,[3] in which the key transformations involved the construction of two units: (i) the universal tricyclic benzofuran core A with a sterically congested quaternary carbon, which was shared by galanthamine-type and morphine-type alkaloids (Figure 1), and (ii) the special C3 allylic alcohol moiety, which is essential for its anticholinesterase activity.[4] In constructing the universal skeleton, many synthetic strategies, such as biomimetic phenolic oxidative coupling,[3a−n] photochemical reaction,[5] radical cyclization,[6] intramolecular Heck reaction,[3o−r] semipinacol rearrangement,[7] intermolecular alkylation,[8] and arylation,[9] had been utilized. However, the successful introduction of the allylic alcohol moiety only relied on two protocols, biomimetic oxidative bisphenol

‡ The new approach to galanthamine is under application for the Chinese Patent (No. 200610041682.6).

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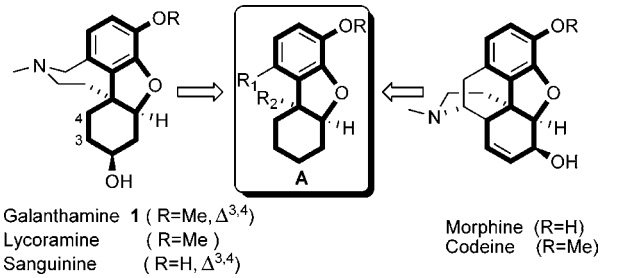


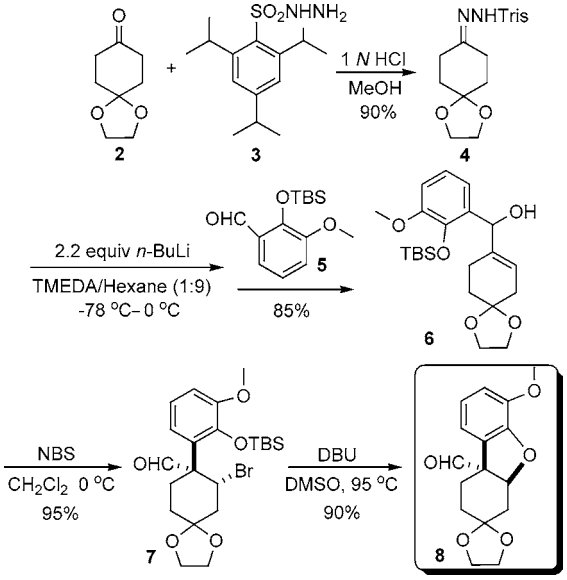
Figure 1. Representative galanthamine-type and morphine-type alkaloids.

coupling and intramolecular Heck reaction. Because of the outstanding biological activity but the limited supplies of **1**,[10] other practical and efficient synthetic approaches to **1** are still desirable.

On the basis of our preliminary efficient strategy, the combination of the bromonium ion promoted semipinacol rearrangement of allylic alcohol, and the desilyation/cyclization to the universal tricyclic benzofuran core A developed in the total synthesis of Lycoramine,[7] we established successfully the allylic alcohol group of **1** by a key Saegusa−Ito oxidation[11] and accomplished its total synthesis.

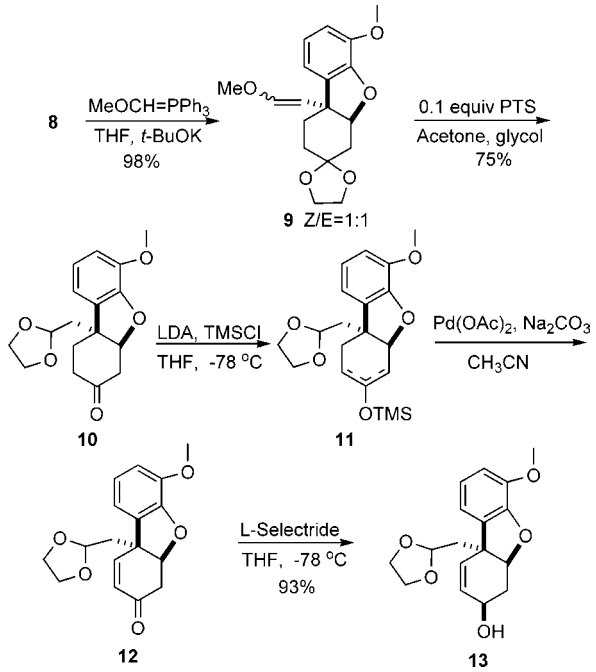
Starting from the construction of the key core A, namely, the corresponding intermediate **8** (Scheme 1), we prepared the allylic alcohol **6** in 85% yield first through the modified Shapiro reaction[12] of hydrazone **4**, obtained in 90% yield from commercially available materials **2** and **3**, with TBS-protected *o*-vanillin **5**. Because of our study on the construction of quarternary carbon with semipinacol rearrangement,[13] the aldehyde **7**, structurally featuring a sterically congested quaternary carbon, was obtained readily in 95% yield by treating **6** with NBS in CH_2Cl_2 at 0 °C. Then, the intramolecular cyclization of **7** proceeded under DBU/DMSO at 95 °C, and the important aldehyde **8** was obtained in 90% yield.

Scheme 1. Construction of Tricyclic Benzofuran **8**



Once we had established the core structure of the galanthamine, we turned our attention to the introduction of its C3 allylic alcohol group. As demonstrated in Scheme 2, the

Scheme 2. Synthesis of Allylic Alcohol **13**



carbonyl homologation of **8** was realized by a widely applied Wittig reaction and smoothly gave rise to a mixture of vinyl ethers **9** in 98% yield. When the hydrolysis of the glycol protection moiety of **9** was carried out under the usual acidic condition, it was very interesting that an unexpected intramolecular exchange of the glycol protection proceeded and ketone **10** was obtained but in poor yield. To our delight,

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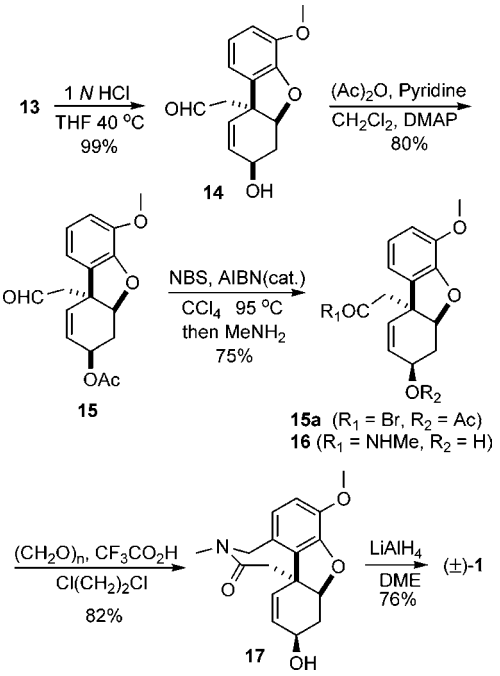
this transformation can be improved by the addition of glycol, and **10** was obtained in 75% yield under the best result.

The efficient and elegant transformation of the protecting group built a firm basis for the introduction of the C3−C4 double bond of **1**. Following the regular operation of Saegusa−Ito oxidation,[11] **10** was transformed into the corresponding silyl enol ether **11** and was directly oxidized by $Pd(OAc)_2$ in acetonitrile. However, the expected enone **12** was not obtained. To our delight, through the protocol of P. A. Grieco by the addition of Na_2CO_3, the enone **12** was obtained in 63.5% yield over two steps reclaiming **10** in 17% yield. The introduction of the C3−C4 double bond, which was vital and had been accomplished with a $(phSeO)_2O$ oxidation in 50% yield in the total synthesis of **1** reported by the C. Guillou group,[3p] was achieved in 76.5% yield based on the consumed ketone **10**. Then, enone **12** was reduced with L-selectride to give **13** in 93% yield.

At the end, we are now in a position to apply the experience gained from our studies to the synthesis of Lycoramine. As shown in Scheme 3, after simple hydrolysis and the protection operations of **13**, aldehyde **15** was obtained in 80% yield. Treatment of **15** with NBS in the presence of a catalytic quantity of AIBN as a radical initiator resulted in the crude acid bromide **15a**,[7,14] and then, without further purification, the reaction mixture was directly treated with an excess of dry methylamine gas prepared in situ (in the meantime, the cleavage of the acetyl ester moiety took place under this condition) to afford the expected amide **16** in 75% overall yield in one pot. To construct the final cycle of **1**, the Pictet−Spengler reaction of **16** with *para*-formaldehyde smoothly proceeded and gave the known lactam **17**[3p] in 82% yield. Finally, reduction of **17** with $LiAlH_4$ readily afforded (±)-**1**.

In summary, a practical and efficient total synthesis of (±)-galanthamine **1** was achieved in 13 steps from the commercially available **2** and **3** in an overall yield of 12% through a novel approach, in which the construction of the universal core structure and the successful introduction of its special allylic alcohol succeeded from a successive semipinacol rearrangement/desilyation/cyclization and the modified Saegusa−Ito oxidation, respectively. Further work on the asymmetric establishment of the universal basic skeleton and the synthesis of morphine is underway in our laboratory.

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



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

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