Alkaloids

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Catalytic Asymmetric Total Synthesis of (−)-Galanthamine and (−)-Lycoramine**

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Dedicated to Professor Jieping Zhu on the occasion of his 50th birthday

Abstract: *The catalytic asymmetric total syntheses of (−)-galanthamine (**1**) and (−)-lycoramine (**2**) have been achieved by using a conceptually new strategy featuring two metal-catalyzed reactions as the key steps. A new method for the construction of 3,4-fused benzofurans has been developed through a palladium-catalyzed intramolecular Larock annulation reaction, which was successfully applied to the construction of the ABD tricyclic skeleton of **1** and **2**. To achieve the asymmetric synthesis of **1** and **2**, a Sc^{III}/N,N′-dioxide complex was used to catalyze the enantioselective conjugate addition of 3-alkyl-substituted benzofuranone to methyl vinyl ketone for the construction of a chiral quaternary carbon center.*

The 3,4-fused (dihydro)benzofuran skeleton, in which the 3-position of the (dihydro)benzofuran is bridged to the 4-position, represents the key structural motif of a diverse group of natural products which exhibit a wide range of biological activities (Figure 1). These natural products include the medicinally important galanthamine-type *Amaryllidaceae* alkaloids and the *Opium* alkaloids, which could serve as ideal model compounds for the development of new synthetic methods and strategies.[1]

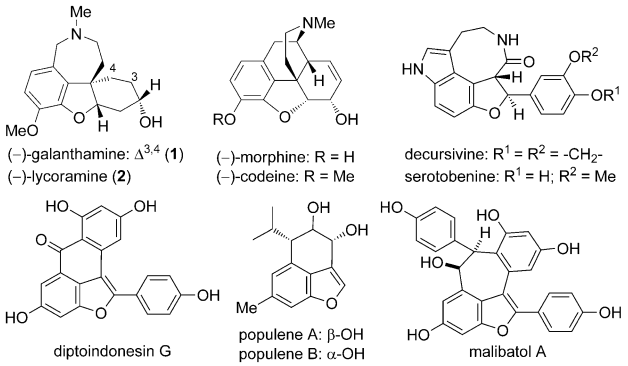
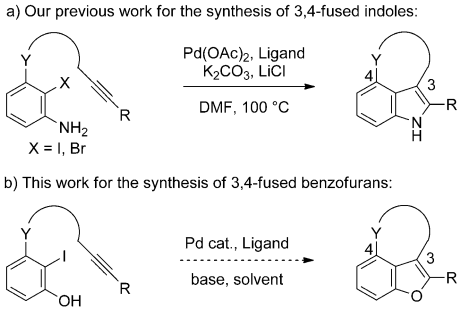


Figure 1. Representative 3,4-fused (dihydro)benzofuran natural products.

As a continuation of our ongoing projects focused on the total synthesis of 3,4-fused indole alkaloids,[2] we have recently developed a general and convenient strategy for the construction of 3,4-fused indoles by an intramolecular Larock indolization reaction (Scheme 1 a).[3] Considering the structural similarity of 3,4-fused benzofurans with 3,4-fused indoles, we were curious whether the palladium-catalyzed intramolecular Larock annulation could be applied to the preparation of 3,4-fused benzofurans (Scheme 1 b). If this idea could be realized, then we would have opportunity to explore a new strategy for the synthesis of (−)-galanthamine (**1**) and (−)-lycoramine (**2**).



Scheme 1. Synthesis of 3,4-fused indoles and 3,4-fused benzofurans by an intramolecular Larock annulation.

(−)-Galanthamine (**1**), a representative member of the *Amaryllidaceae* alkaloids, has been clinically used for the treatment of Alzheimer's disease and other memory impairments.[4] (−)-Lycoramine (**2**) has a similar, albeit less potent activity as an acetylcholinesterase inhibitor and an allosteric potentiating ligand.[5] Because of the high cost of its isolation and the limited natural sources, a number of total syntheses of **1** have been reported.[6–16] According to the strategy for the formation of the ring system, these syntheses can be divided into two categories: 1) synthesis proceeding from AC ring→ADC ring→ABCD ring (Scheme 2, path a),[6–8] and it mainly involves intramolecular phenolic oxidative coupling followed by intramolecular oxa-Michael addition to form the benzofuran B ring, and 2) synthesis proceeding from the AC(AB) ring→ABC ring→ABCD ring (Scheme 2, path b),[9–16] in which the formation of the bridged seven-membered D ring is placed at the late stage of the synthesis. To our knowledge, no synthesis from the ABD ring→ABCD ring (Scheme 2, path c) has been reported.

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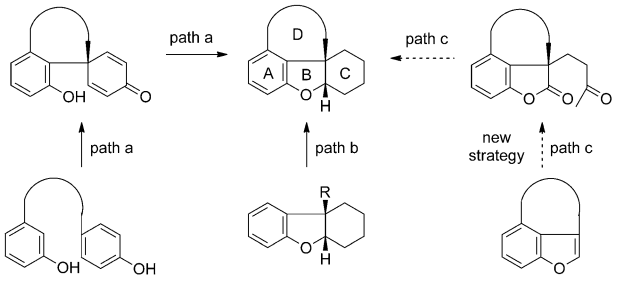
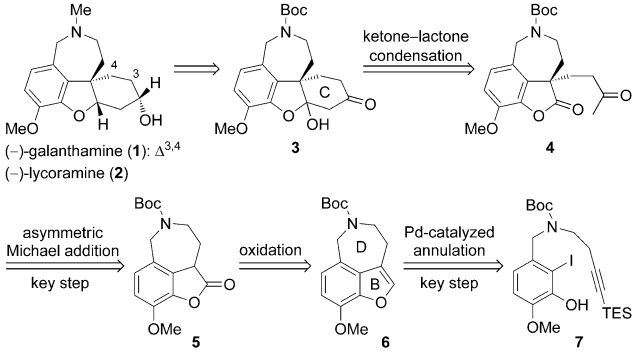


Scheme 2. Strategies for the synthesis of galanthamine (**1**).

Structurally, galanthamine-type alkaloids contain a chiral all-carbon quaternary center, and the enantioselective construction of this sterically congested quaternary center[17] is the critical step in the total synthesis of these alkaloids. Although numerous asymmetric total syntheses of these alkaloids have been reported,[7–16] only the groups of Trost,[9,15] and Fan,[13] as well as that of Zhou and Xie,[14] have recently achieved catalytic asymmetric synthesis of galanthamine (**1**) and related alkaloids.

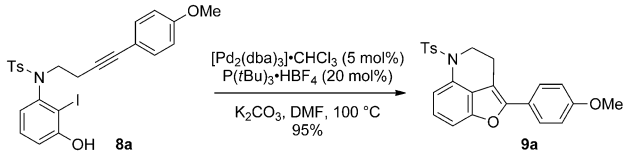
To explore a new strategy for the effective construction of polycyclic ring systems and a new method for the catalytic asymmetric establishment of the crucial chiral all-carbon quaternary stereocenter, a retrosynthetic analysis of **1** and **2** is outlined in Scheme 3. We envisioned that both **1** and **2** could



Scheme 3. Retrosynthetic analysis for **1** and **2**. Boc = *tert*-butoxycarbonyl, TES = triethylsilyl.

be derived from the same advanced intermediate **3**. The tetracyclic compound **3** could be generated from the tricyclic compound **4** by intramolecular ketone–lactone condensation. In turn, **4** could be accessed from **5** by key catalytic asymmetric Michael addition with methyl vinyl ketone (MVK). The benzofuranone **5** should be readily prepared by oxidation of 3,4-fused benzofunan **6**, which could be derived from **7** by a novel palladium-catalyzed annulation reaction.

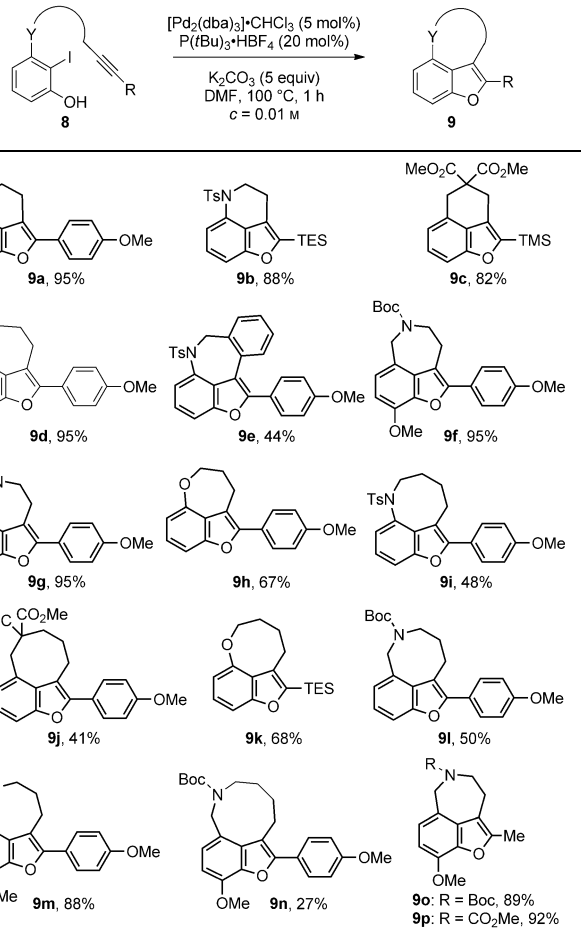
We firstly examined the feasibility of our strategy for the synthesis of 3,4-fused benzofuran by an intramolecular Larock annulation reaction (Scheme 4).[18,19] A variety of reaction conditions were screened and we found that under the reaction conditions of $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%) and



Scheme 4. Realization of the intramolecular Larock annulation reaction. dba = dibenzylideneacetone, Ts = 4-toluenesulfonyl, DMF = *N*,*N*-dimethylformamide.

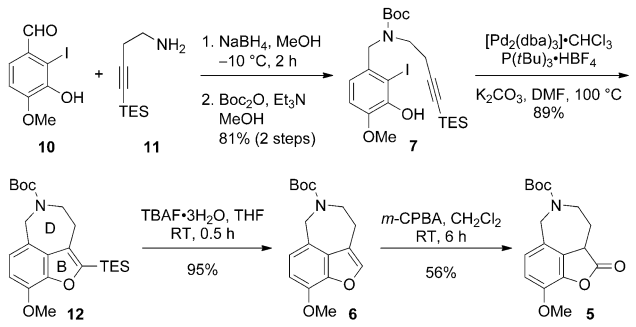
$P(t\mathrm{Bu})_3\cdot HBF_4$ (20 mol%) at 100 °C, the desired product **9a** was obtained in 95% yield (see the Supporting Information).[20] The substrate scope of this reaction was subsequently examined. The transformation was found to be quite general, and a variety of 3,4-fused benzofurans containing either carbon, oxygen, or nitrogen tethers were obtained in reasonable yields (Table 1).

Table 1: Synthesis of 3,4-fused benzofurans.[a]



[a] Yields are those of the isolated products. TMS = trimethylsilyl.

We then set out to apply this method to the assembly of the ABD ring system of **1** and **2** (Scheme 5). Reductive coupling of the known aldehyde **10**[9c] and amine **11**,[3a] and subsequent protection with Boc_2O provided **7** in 81% yield. Treatment of **7** under our aforementioned reaction conditions



Scheme 5. Construction of ring B/D in the tricyclic synthon. *m*-CPBA = *meta*-chloroperoxybenzoic acid, TBAF = tetra-*n*-butylammonium fluoride.

successfully afforded the 3,4-fused benzofuran **12** in 89% yield. Removal of the TES group in **12** with TBAF (95%), and subsequent oxidation with *m*-CPBA, afforded **5** in 56% yield.

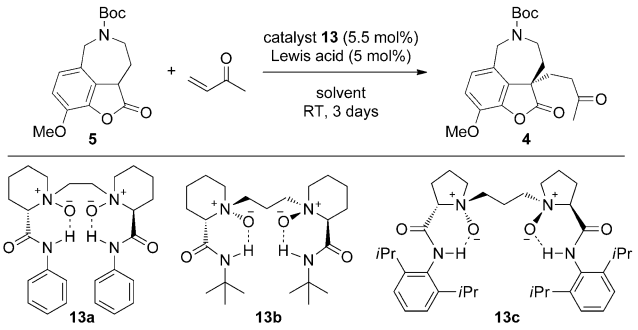
After successful construction of the ABD ring system, we turned our attention to the construction of the chiral all-carbon quaternary stereocenter in **1** and **2**. Although a few catalytic enantioselective conjugate additions of 3-substituted benzofuranones were reported,[21] to the best of our knowledge, the catalytic enantioselective conjugate addition of 3-alkyl-substituted benzofuranone to MVK has not been reported.

Initially, various amine-thiourea or urea bifunctional organocatalysts were screened for the conjugate addition of **5** to MVK. However, the highest enantioselectivity obtained was 55% *ee* (see the Supporting Information). These results prompted us to investigate alternative catalytic reaction systems. Inspired by the recent work of Feng and co-workers,[22] we turned our attention to examining an asymmetric Michael addition using the chiral metal/*N*,*N*′-dioxide complexes. As described in Table 2, we initially investigated the Michael addition, in CH_2Cl_2 at room temperature, catalyzed by $Yb(OTf)_3$/**13** complexes (entries 1–3). But only $Yb(OTf)_3$/**13c** gave the desired product **4** in 10% yield with 42% *ee* (entry 3). When the solvent was changed to ethanol, **4** was obtained in higher yield (33%) with similar *ee* value (entry 4). However, when $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$ at room temperature, the reaction proceeded smoothly to afford **4** in 85% yield with 93% *ee* (entry 5). Additionally, when the reaction was run at 10 °C, **4** was obtained in 85% yield with 94% *ee* (entry 6). Under the aforementioned reaction conditions, conjugate additions of several 3-alkyl-substituted benzofuranones to MVK were investigated. The results showed that both the yield and the *ee* values were excellent (Table 3).

With **4** in hand, we proceeded with the total synthesis of **1** (Scheme 6). Treatment of **4** with LDA yielded the cyclization product **3** in 95% yield. Subsequent direct reduction of the **3** with Et_3SiH provided the β-alcohol **16** in 73% yield and α-alcohol **17** in 12% yield, with the simultaneous reduction of ketone and removal of the Boc group.[23] Selective protection of the amine in **16** and **17** with methyl chloroformate and subsequent oxidiation with Dess–Martin periodinane provided the known ketone **18**, the key intermediate in Fan's total synthesis of **1**, in 75% yield over three steps. The physical properties (^1H and ^{13}C NMR spectra, MS data, and $[\alpha]_D$) of **18** are consistent with those described in the literature.[13] Treatment of **18** with TMSOTf and Et_3N provided the corresponding silyl enol ether, which was oxidized under Saegusa conditions to give the enone **19** in 67% yield. Finally, **19** was readily converted into **1** in a two-step sequence.[13]

After completion of the synthesis of **1**, we turned our attention to the synthesis of **2** (Scheme 7). Considering the lower yield in the conversion of **3** into **17** (Scheme 6), we tried to develop a more efficient approach. Thus, stereoselective reduction of **3** with L-selectride gave the sole α-alcohol **20** in 91% yield. Reduction of **20** with Et_3SiH provided **17** in 88% yield. Reaction of **17** and formaldehyde under standard reaction conditions [$NaBH_4$, $NaBH_3CN$ or $NaBH(OAc)_3$] gave **2** in only 30–40% yield. Methylation of **17** under

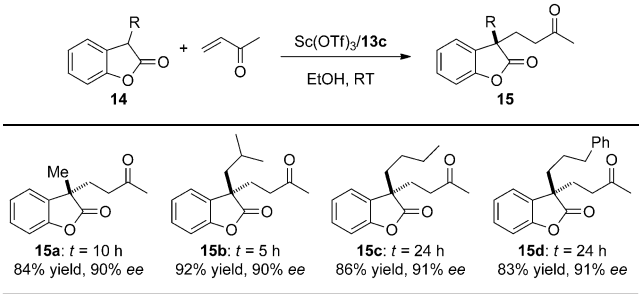
Table 2: Michael addition catalyzed by Lewis acid/*N*,*N*′-dioxide complexes.[a]



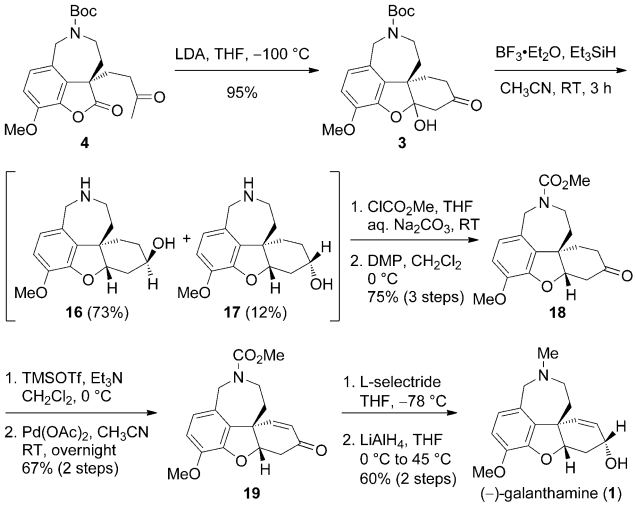
Entry	Lewis acid	Ligand	Solvent	Yield [%][b]	*ee* [%][c]
1	$Yb(OTf)_3$	**13a**	CH_2Cl_2	n.r.	–
2	$Yb(OTf)_3$	**13b**	CH_2Cl_2	n.r.	–
3	$Yb(OTf)_3$	**13c**	CH_2Cl_2	10	42
4	$Yb(OTf)_3$	**13c**	EtOH	33	38
5	$Sc(OTf)_3$	**13c**	EtOH	85	93
6[d]	$Sc(OTf)_3$	**13c**	EtOH	85	94

[a] Reaction conditions: **5** (0.1 mmol), MVK (0.15 mmol), solvent (0.3 mL). [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] The reaction was run at 10 °C. n.r. = no reaction, Tf = trifluoromethanesulfonyl.

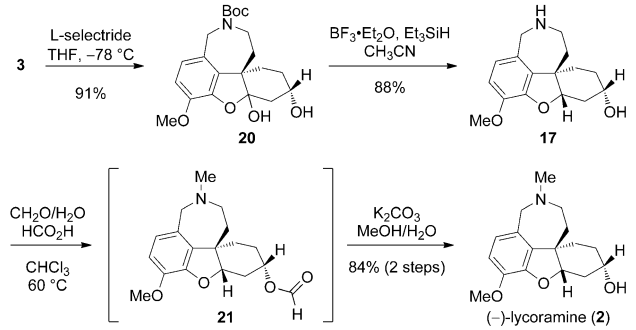
Table 3: Substrate scope of the asymmetric Michael reaction.[a]



[a] Reaction conditions: **14** (0.1 mmol), MVK (0.15 mmol), EtOH (0.3 mL). Yields are those of the isolated products. Enantiomeric excess was determined by HPLC using a chiral stationary phase.



Scheme 6. Synthesis of **1**. DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, THF = tetrahydrofuran.



Scheme 7. Synthesis of **2**.

Eschweiler–Clarke conditions (HCO_2H, HCHO, reflux)[24] and subsequent treatment of the resulting product with K_2CO_3/MeOH/H_2O afforded **2** in 84% yield over two steps.

In summary, an asymmetric total synthesis of both (−)-galanthamine (**1**) and (−)-lycoramine (**2**) have been achieved based on a conceptually new strategy by employing two metal-catalyzed reactions. A new method for the construction of 3,4-fused tricyclic benzofurans, the core structure of a variety of bioactive important natural products, has been developed using a palladium-catalyzed intramolecular Larock annulation reaction. In addition, a Sc^{III}/*N*,*N*′-dioxide complex catalyzed the enantioselective conjugate addition reaction of 3-alkyl-substituted benzofuranone to MVK for the construction of a quaternary carbon center was developed for the first time.

Keywords: alkaloids · asymmetric catalysis · natural products · palladium · total synthesis

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