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Note

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Catalytic Asymmetric Total Syntheses of (–)-Galanthamine and (–)-Lycoramine

Qing Zhang,[†] Fu-Min Zhang,*[,†] Chang-Sheng Zhang,[†] Si-Zhan Liu,[†] Jin-Miao Tian,[‡] Shao-Hua Wang,[†] Xiao-Ming Zhang[†] and Yong-Qiang Tu*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry & College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

[‡]School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, P. R. China

Correspondence and requests for materials should be addressed to Y.-Q.T. (email: tuyq@lzu.edu.cn; tuyq@sjtu.edu.cn) or to F.-M.Z. (email: zhangfm@lzu.edu.cn).

ABSTRACT

The catalytic asymmetric total syntheses of the biologically important and therapeutically valuable *Amaryllidaceae* alkaloids (–)-galanthamine and (–)-lycoramine have been divergently achieved from commercially available 3-butyn-1-ol. A newly developed spirocyclic pyrrolidine (SPD) catalyzed enantioselective Robinson annulation rapidly constructs the key *cis*-hydrodibenzofuran core bearing an all-carbon quaternary stereocenter of the target molecules with excellent stereoselective control. Additionally, the current asymmetric synthetic strategy provides an alternative approach toward the syntheses of (–)-galanthamine and its analogues.

Galanthamine (**1a**), an *Amaryllidaceae* alkaloid isolated by Proskurnina from the Caucasian snowdrop in 1952, exhibits unique biological and pharmacological characterization[1]. As a competitive and reversible acetylcholinesterase inhibitor, (–)-galanthamine can effectively regulate the expression of nicotinic acetylcholine receptor, so as to achieve the goal of significantly improving memory and cognitive functions of the patients[2]. Consequently, (–)-galanthamine has been approved by the Federal Drug Administration in the USA for the early clinical treatment of Alzheimer's disease (AD) in 2001[3]. Structurally,

galanthamine-type alkaloids contain a strained tetracyclic framework bearing a highly functionalized *cis*-hydrodibenzofuran nucleus which includes a sterically congested all-carbon quaternary stereocenter (Figure 1). As a key structural unit commonly existing in these alkaloids, how to rapidly and efficiently construct such an ABC tricyclic skeleton is a major challenge. Over the past 50 years, extensive synthetic studies towards galanthamine and its analogues[1,4,5] have been carried out, and thus a variety of synthetic strategies[6-11] have also been developed to address the conflict between the increasing clinical demand for (–)-galanthamine and its limited supplies from natural sources. However, catalytic asymmetric total syntheses of (–)-galanthamine are still rather scarce[9-10]. Furthermore, to our best knowledge, no direct and catalytic enantioselective approach to efficiently assemble the crucial *cis*-hydrodibenzofuran core bearing all-carbon quaternary carbon from the racemic precursor in the asymmetric syntheses of (–)-galanthamine has been reported. Therefore, it remains important and challenging to develop an effective and asymmetric synthetic strategy towards the *Amaryllidaceae* alkaloid (–)-galanthamine.

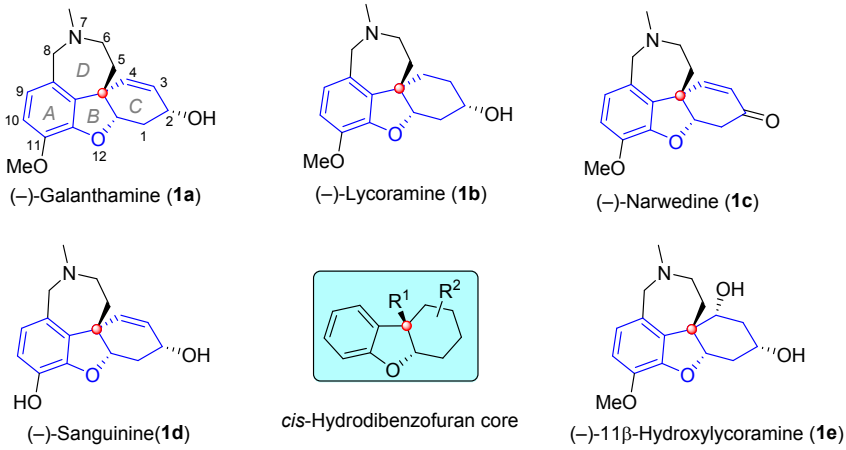
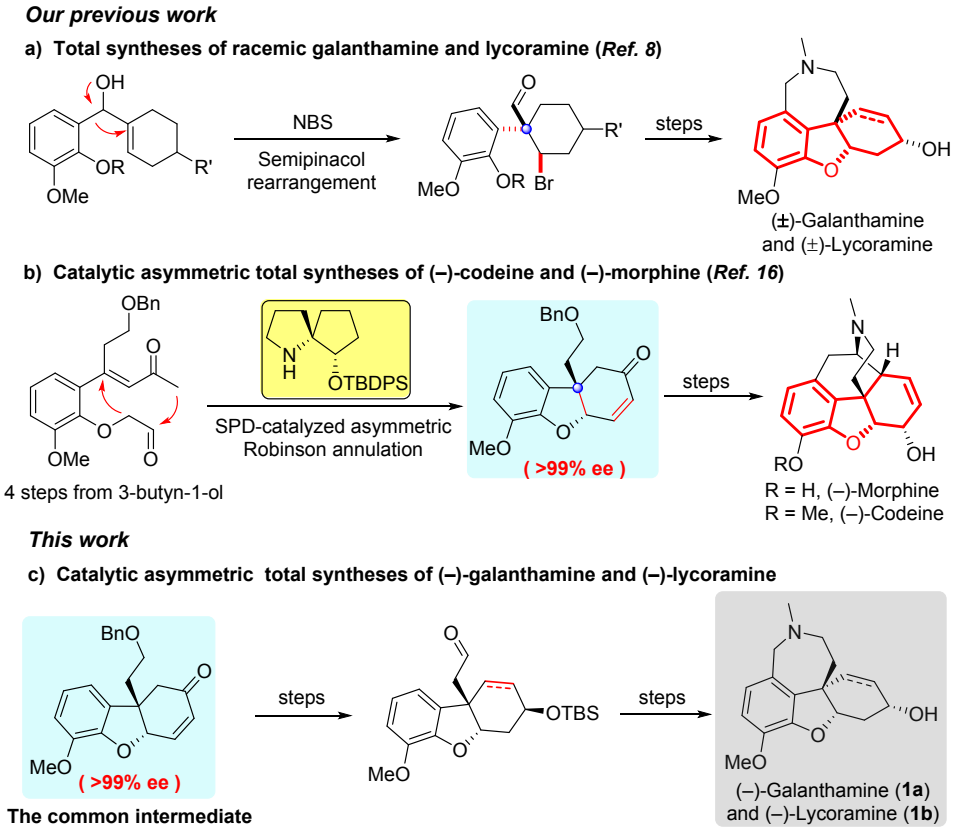


Figure 1. Representative galanthamine-type *Amaryllidaceae* alkaloids

During the past two decades, electrophile-induced semipinacol rearrangement has been extensively investigated in our group[12] for the efficient construction of the quaternary carbon centers and wide application in the total syntheses of bioactive natural products[13]. Particularly, we have accomplished the total syntheses of (±)-galanthamine and (±)-lycoramine using an NBS-mediated semipinacol rearrangement[8] as the key step (Scheme 1a); however, no satisfactory results were obtained in the asymmetric synthesis of (–)-galanthamine based on the enantioselective Michael addition[14]. As a continuation of our ongoing project centered on the exploration of novel chiral ligands or catalysts based on SPD (spirocyclic pyrrolidine) and

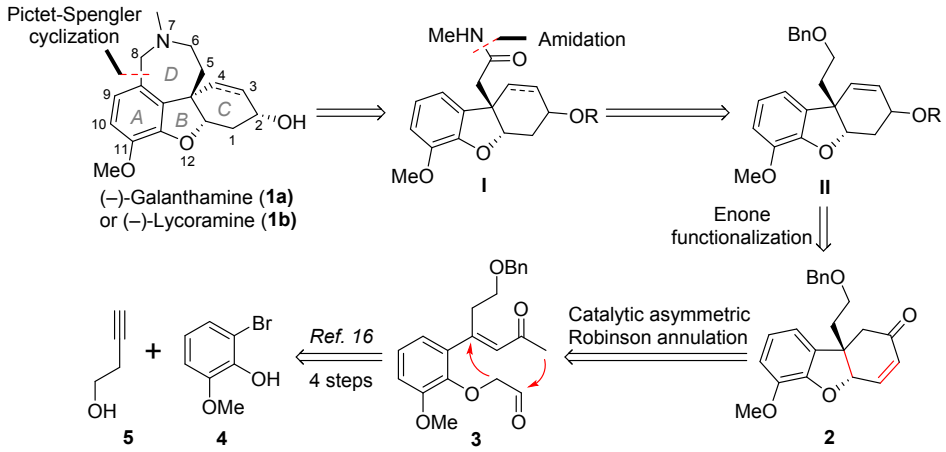
SPA (spirocyclic amide) backbones[15], very recently, we developed a novel SPD-catalyzed enantioselective Robinson annulation to rapidly construct a *cis*-hydrodibenzofuran skeleton and achieved the asymmetric total syntheses of (–)-codeine and (–)-morphine[16] with high efficiency (Scheme 1b). Considering the existence of the common *cis*-hydrodibenzofuran core in these two categories of alkaloids, together with further investigation of the diversity-oriented synthetic application of the SPD-catalyzed Robinson annulation, herein, we present our research results of the asymmetric total syntheses of (–)-galanthamine (**1a**) and (–)-lycoramine (**1b**) (Scheme 1c).



Scheme 1. Studies on the total syntheses of galanthamine and morphine in our group

Our retrosynthetic analysis toward (–)-galanthamine and (–)-lycoramine is outlined in Scheme 2. The D ring of target molecules **1a** and **1b** could be installed by an intramolecular Pictet-Spengler cyclization of intermediate **I**, whereas the amide moiety in **I** would be introduced from the common advanced building block **II** by a subsequent selective debenzylation/oxidation/radical-induced amidation procedure. We expected that intermediate **II** could be prepared via a series of functional group conversions from *α,β*-unsaturated ketone **2**, which can be easily accessible from compound **3** via our newly developed

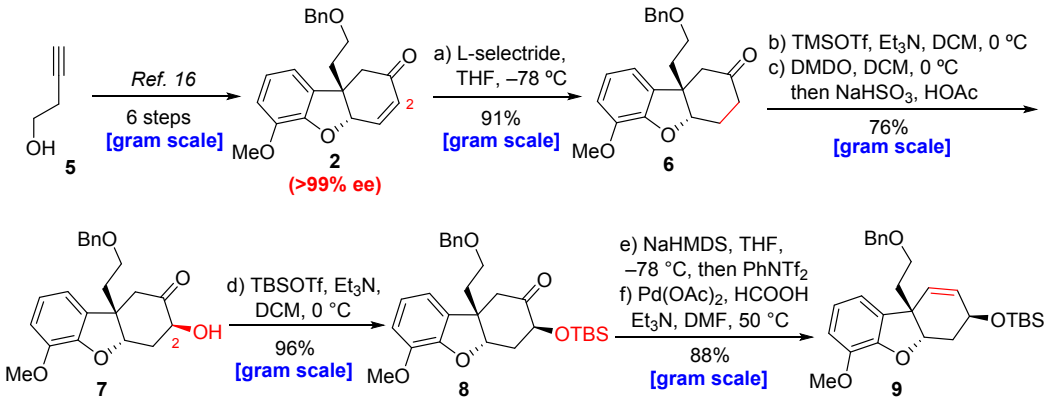
SPD-catalyzed asymmetric Robinson annulation[16] with excellent enantioselectivity (>99% ee). Similarly, following the above-mentioned research results, the enone precursor **3** can also be efficiently synthetized from commercially available **4** and **5** at a gram scale in just four steps.



Scheme 2. Retrosynthetic analysis of (–)-galanthamine and (–)-lycoramine

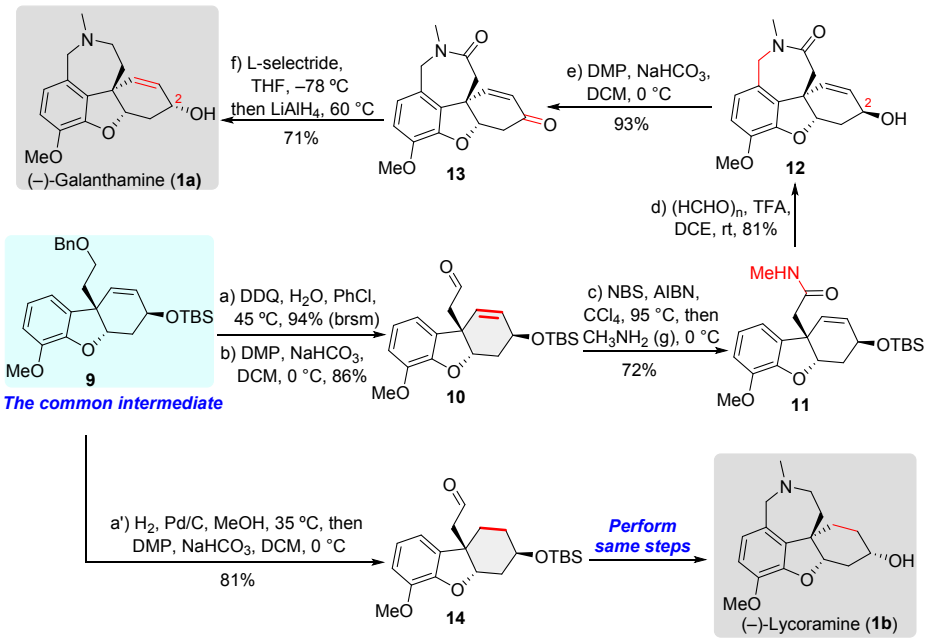
Our synthetic route commenced with the preparation of **9** on a gram scale from the optically pure tricyclic compound **2** (>99% ee), which was readily available from 3-butyn-1-ol **5** through our recently reported six-step protocol featuring a Pd-catalyzed Suzuki coupling reaction and an SPD-catalyzed asymmetric Robinson annulation[16] (Scheme 3). To this end, the first key issue that needed to be addressed was the construction of C2 stereocenter and adjustments of the enone group in compound **2**. According to the classical Rubottom oxidation reaction[17], we successfully achieved the introduction of C2 hydroxyl group through a three-step procedure in high yield. Starting from compound **2**, selective conjugate reduction of the enone with L-selectride afforded ketone **6**, which was able to be efficiently converted into silyl enol ether with TMSOTf and Et_3N in excellent regioselectivity[17c]. In this reaction, attempts to trap the enolate intermediate generated *in situ* by one-pot conjugate reduction/silylation proved to be difficult and no satisfying outcome was achieved. Subsequently, the above crude silylether intermediate was directly treated with dimethyl dioxirane[18] (DMDO), followed by an acid-mediated epoxide cleavage to furnish the α-hydroxy ketone **7** in high diastereoselectivity, whose stereochemical structure was confirmed by NOESY experiments. It is presumed that the epoxidation of the double bond of silyl enol ether could highly selectively proceed on the less-hindered face, leading to deliver the α-hydroxy ketone **7** as a single isomer. Then, under the standard conditions, the protection of the hydroxy group of **7** with TBSOTf produced the

silylether **8** in 96% yield, which was treated with NaHMDS and Tf_2NPh, followed by a Pd-catalyzed reduction reaction[19], giving the desired key building block **9** in 90% yield over two steps. Notably, all of the above-mentioned chemical transformations performed well even on the gram scale.



Scheme 3. Preparation of compound **9** on a gram scale

With ample amounts of key intermediate **9** on hand, then we focused our attentions on the asymmetric total synthesis of the important clinical drug (–)-galanthamine (**1a**) (Scheme 4). Selective debenzylation of **9** with DDQ, followed by Dess-Martin oxidation of the resulting primary alcohol, furnished the aldehyde **10**. The structure of **10** was similar to that of the key intermediate in our previously reported synthesis of (±)-galanthamine[8b]. Therefore, these practical protocols guided our late-stage synthetic steps in the current asymmetric synthesis. The free radical-induced oxidation reaction[8,20] of **10** in the presence of NBS and a catalytic amount of AIBN furnished acyl bromide, without further purification, which was directly reacted with an excess of dry methylamine gas to deliver the desired amide **11** in 72% yield. Subsequently, in order to build the seven-membered *N*-containing heterocycle of **1a**, the Pictet-Spengler reaction[8,21] of **11** with paraformaldehyde and TFA was conducted to readily afford the lactam **12** in 81% yield, in which the TBS protecting group was simultaneously removed under acidic conditions. At this stage, the inversion of the configuration of C2-OH and selective reduction of amide group could furnish the asymmetric total synthesis of (–)-galanthamine. To this end, allylic alcohol **12** was first oxidized with Dess-Martin periodinane to produce enone **13** (Zhou's intermediate[9d,22]), which was then treated subsequently with L-selectride and $LiAlH_4$ in a one-pot procedure to efficiently afford the target molecule (–)-galanthamine (**1a**). All spectroscopic data of our synthetic (–)-galanthamine were in agreement with the ones reported in the literatures[10].



Scheme 4. Catalytic asymmetric total syntheses of (–)-galanthamine (**1a**) and (–)-lycoramine (**1b**)

To further explore the synthetic diversity, our efforts toward the total synthesis of (–)-lycoramine were continued. Starting from the common building block **9**, catalytic hydrogenolysis in the presence of Pd/C resulted in the reduction reaction of the double bond as well as the removal of the benzyl group to provide a primary alcohol, which was directly treated with Dess-Martin periodinane to afford aldehyde **14** in 81% yield. Subsequently, according to the above-mentioned similar synthetic approach toward (–)-galanthamine, a four-step protocol involving radical-mediated amidation[8,20], Pictet-Spengler reaction[8,21], Dess-Martin oxidation, and one-pot reduction reaction smoothly proceeded and afforded (–)-lycoramine (1b) with high efficiency. In addition, the spectral data of synthetic (–)-lycoramine were identical to those of the previous reports[10].

In summary, we have developed a highly efficient and catalytic asymmetric synthetic approach toward (–)-galanthamine and (–)-lycoramine based on an SPD-catalyzed enantioselective Robinson annulation as a key step. Significantly, these results described here not only further exhibit the distinctive superiorities of our SPD catalyst in the construction of the all-carbon quaternary stereocenter but also explore an alternative synthetic methodology for the preparation of the other galanthamine-type alkaloids and their analogues, which could be potentially used for syntheses of a series of lead compounds for pharmaceutical screening.

Additionally, the current study represents the first example of the syntheses of (–)-galanthamine and (–)-lycoramine through direct and catalytic enantioselective construction of the key ABC ring system from the racemic precursor. Efforts toward the asymmetric syntheses of other biologically important natural products based on SPD-catalyzed tandem reactions are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. All moisture or oxygen-sensitive reactions were carried out under argon atmosphere with dry and freshly distilled solvents in oven-dried flasks. Unless otherwise noted, all reagents were analytically pure and used without further purification. All reactions were monitored by thin-layer chromatography (TLC), and the products were purified by flash column chromatography on silica gel (200−300 mesh). NMR spectra were recorded in $CDCl_3$ solution on Bruker AM-400 MHz or Varian Mercury-600 MHz instruments. Chemical shifts (δ) were calibrated by using residual undeuterated solvent $CHCl_3$ (7.26 ppm) or tetramethylsilane (0.00 ppm) as internal references for ^1H NMR and the deuterated solvent $CDCl_3$ (77.0 ppm) as internal standard for ^{13}C NMR. High-resolution mass spectra (HRMS) were measured by the electrospray ionization (ESI) technique on a Fourier-transform ion cyclotron resonance mass analyzer. IR spectra were recorded on a Nicolet FT-170SX spectrometer. Optical rotations were measured with a RUDOLPH A21202-J APTV/GW polarimeter. The compound **2** was readily prepared from commercially available 3-butyn-1-ol **6** through our recently reported six-step protocol[16], and for the more synthetic details, also please see the supporting information.

*(4aS,9bS)-9b-(2-(benzyloxy)ethyl)-6-methoxy-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-2(1H)-one (**6**).* To a stirred solution of **2** (1.00 g, 2.86 mmol, 1 equiv) in dry THF (50 mL) at −78 ºC, L-selectride (2.71 mL, 2.71 mmol, 1 mol/L, 0.95 equiv) was slowly added. After stirring at −78 ºC for 10 min, the reaction mixture was quenched with saturated NH_4Cl solution, and extracted with EtOAc. The combined organic extract was washed with saturated NH_4Cl solution and brine, dried with Na_2SO_4, and concentrated *in vacuum*. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 8:1) to afford product **6** (916 mg, 91%) as a colorless oil. $[\alpha]_D^{25}$ = +40 (c = 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 7.3 Hz, 1H), 6.60 (dd, *J* = 7.5, 1.0 Hz, 1H), 5.17 (t, *J* = 3.5 Hz, 1H), 4.41 (s, 2H), 3.87 (s, 3H), 3.56–3.44 (m, 2H), 2.74 (d, *J* = 15.5 Hz, 1H), 2.64 (d, *J* = 15.5 Hz, 1H), 2.37–2.32 (m, 1H), 2.26–2.22 (m, 2H), 2.19–2.06 (m, 2H), 2.04–1.95 (m, 1H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 210.6, 147.4, 144.0, 137.9, 132.5, 128.4, 127.7, 127.6, 121.7, 115.3, 111.5, 85.8, 73.2, 66.6, 55.8, 48.4, 48.2, 40.8, 33.1, 26.4; HRMS (ESI) calcd for $C_{22}H_{24}O_4Na$ $[M+Na]^+$: 375.1567, found: 375.1561; IR (neat): 2926, 1716, 1619, 1592, 1493, 1460, 1276, 1203, 1094, 734, 700 cm^{-1}; EI MS m/z (%): 91 (100), 161 (20), 217 (38), 261 (9), 352 (64).

(3S,4aS,9bS)-9b-(2-(benzyloxy)ethyl)-3-hydroxy-6-methoxy-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-2(1H)-one (7). To a stirred solution of **6** (1.75 g, 4.97 mmol, 1 equiv) in dry DCM (40 mL) at 0 ºC, Et_3N (2.77 mL, 19.88 mmol, 4 equiv) and TMSOTf (1.62 mL, 8.95 mmol, 1.8 equiv) were added sequentially. The reaction mixture was slowly warmed to room temperature and stirred for 0.5 h. Then, the reaction mixture was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated *in vacuum*. Without purification, the above crude product was dissolved in dry DCM (70 mL) at 0 ºC and the fresh-made DMDO (75 mL, 0.08 mol/L, 5.96 mmol, 1.2 equiv) was added slowly. After stirring at 0 ºC for 15 min, the mixture was quenched with $NaHSO_3$ (783 mg, 7.45 mmol, 1.5 equiv) and HOAc (426 uL, 7.45 mmol, 1.5 equiv). After stirring at 0 ºC for an additional 10 min, the reaction was extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuum*. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 3:1) to afford product **7** (1.39 g, 76% yield) as a colorless oil. $[\alpha]_D^{25}$ = –5 (c = 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 6.86 (t, *J* = 8.0 Hz, 1H), 6.79 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.62 (dd, *J* = 7.4, 1.1 Hz, 1H), 4.97 (t, *J* = 2.8 Hz, 1H), 4.39 (s, 2H), 4.27 (ddd, *J* = 12.8, 6.0, 2.9 Hz, 1H), 3.90 (s, 3H), 3.53–3.45 (m, 2H), 3.26 (d, *J* = 3.0 Hz, 1H), 2.85 (ddd, *J* = 14.7, 6.1, 2.3 Hz, 1H), 2.78 (d, *J* = 16.5 Hz, 1H), 2.68 (d, *J* = 16.4 Hz, 1H), 2.12–1.98 (m, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 210.0, 146.9, 144.6, 137.7, 134.6, 128.4, 127.7, 127.6, 122.0, 114.4, 111.8, 86.1, 73.1, 69.8, 66.2, 55.9, 49.9, 46.7, 38.2, 35.6; HRMS (ESI) calcd for $C_{22}H_{24}O_5Na$ $[M+Na]^+$: 391.1516, found: 391.1513; IR (neat): 3500, 2851, 1715, 1620, 1592, 1493, 1459, 1365, 1267, 1204, 1100, 943, 750, 733 cm^{-1}; EI MS m/z (%): 57 (100), 97 (82), 236 (35), 313 (23), 353 (13), 368 (85).

*(3S,4aS,9bS)-9b-(2-(benzyloxy)ethyl)-3-((tert-butyldimethylsilyl)oxy)-6-methoxy-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-2(1H)-one (**8**).* To a stirred solution of **7** (1.38 g, 3.75 mmol, 1 equiv) in dry DCM (35 mL) at −10 ºC, Et_3N (2.09 mL, 15 mmol, 4 equiv) and TBSOTf (1.29 mL, 5.63 mmol, 1.5 equiv) were added sequentially. The reaction mixture was slowly warmed to room temperature and stirred for 0.5 h. Then, the reaction was quenched with saturated $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuum*. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 20:1) to afford product **8** (1.73 g, 96% yield) as a colorless oil. $[\alpha]_D^{25}$ = –28 (c = 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.85 (t, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 7.3 Hz, 1H), 6.63 (dd, *J* = 7.4, 1.0 Hz, 1H), 4.99 (t, *J* = 3.5 Hz, 1H), 4.39 (s, 2H), 4.23 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.90 (s, 3H), 3.53–3.44 (m, 2H), 2.68 (s, 2H), 2.60 (ddd, *J* = 14.7, 5.5, 3.1 Hz, 1H), 2.31–2.23 (m, 1H), 2.11–1.99 (m, 2H), 0.86 (s, 9H), 0.08 (s, 3H), -0.02 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 207.8, 146.9, 144.5, 137.9, 134.4, 128.4, 127.6, 121.9, 114.7, 111.7, 86.3, 73.1, 71.1, 66.4, 55.9, 49.8, 47.5, 38.3, 36.7, 25.7, 18.3, -4.7, -5.5;

HRMS (ESI) calcd for $C_{28}H_{38}O_5SiNa$ $[M+Na]^+$: 505.2381, found: 505.2373; IR (neat): 2929, 2856, 1732, 1492, 1459, 1257, 1202, 1127, 838, 780, 735 cm^{-1}; EI MS m/z (%): 91 (100), 129 (28), 143 (22), 205 (10), 295 (74), 334 (5), 425 (18).

*(((3S,4aS,9bS)-9b-(2-(benzyloxy)ethyl)-6-methoxy-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-3-yl)oxy)(tert-butyl)dimethylsilane (**9**)*. Under argon atmosphere, to a stirred solution of **8** (1.60 g, 3.32 mmol, 1 equiv) in dry THF (90 mL) at −78 ºC, NaHMDS (2.27 mL, 4.32 mmol, 1.9 mol/L, 1.3 equiv) was slowly added. After stirring at −78 ºC for 50 min, $PhNTf_2$ (1.66 g, 4.65 mmol, 1.4 equiv) was added. Then, the reaction was warmed to room temperature (about 10 min) under argon and stirred for an additional 1 h. The mixture was quenched with saturated NH_4Cl solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuum*. Without purification, the resulting crude product was dissolved in dry DMF (35 mL), and $Pd(OAc)_2$ (74 mg, 0.33 mmol, 0.1 equiv), 1,3-bis(diphenylphosphino)propane (dppp, 165 mg, 0.40 mmol, 0.12 equiv), Et_3N (1.39 mL, 9.96 mmol, 3 equiv) and HCOOH (250 μL, 6.64 mmol, 2 equiv) were added sequentially. After stirring at 60 °C for 1 h, the mixture was quenched with H_2O (1 mL), and extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuum*. The residue was purified by column chromatography on silica gel (petroleum ether : EtOAc = 20:1) to afford product **9** (1.36 g, 88% yield) as a colorless oil. $[\alpha]_D^{25}$ = –60 (c = 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.72 (dd, *J* = 11.5, 7.4 Hz, 2H), 5.74 (d, *J* = 10.2 Hz, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 4.93 (brs, 1H), 4.49–4.47 (m, 1H), 4.45 (d, *J* = 1.0 Hz, 2H), 3.86 (s, 3H), 3.60–3.52 (m, 2H), 2.60–2.53 (m, 1H), 2.17–2.08 (m, 2H), 1.85–1.78 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.9, 144.6, 138.1, 134.8, 132.8, 130.3, 128.3, 127.54, 127.52, 121.3, 115.3, 111.1, 85.8, 73.0, 67.0, 63.0, 55.8, 47.3, 37.5, 33.7, 25.8, 18.1, -4.55, -4.63; HRMS (ESI) calcd for $C_{28}H_{38}O_4SiNa$ $[M+Na]^+$: 489.2432, found: 489.2434; IR (neat): 2929, 2856, 1493, 1459, 1281, 1203, 1090, 876, 837, 776, 733 cm^{-1}; EI MS m/z (%): 91 (100), 199 (20), 331 (6), 466 (16).

*2-((5aS,7S,9aS)-7-((tert-butyldimethylsilyl)oxy)-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)ethan-1-ol (**9-1**)*. To a stirred solution of **9** (470 mg, 1.01 mmol, 1 equiv) in chlorobenzene (45 mL, about 10 mg/mL) at room temperature, DDQ (688 mg, 3.03 mmol, 3 equiv) and H_2O (4.5 mL) were added. Then, the reaction was sealed in argon and stirred at 45 °C for 15 h. After being cooled to room temperature, the reaction mixture was diluted with DCM, quenched with saturated $NaHCO_3$ solution, and extracted with DCM. The combined organic layer was washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated *in vacuum*. The residue was purified by column chromatography on silica gel (petroleum ether : EtOAc = 5:1) to afford product **9-1** (152 mg, 40%) as a colorless oil, together with recovered starting material **9** (255 mg, 54%). $[\alpha]_D^{25}$ = –90 (c = 0.20, CHCl3); ^1H NMR (400 MHz, $CDCl_3$) δ 6.86–6.82 (m, 1H), 6.75–6.71 (m, 2H), 5.81 (dd, *J* = 10.1, 2.4 Hz, 1H), 5.60 (d, *J* = 10.1 Hz, 1H), 5.02 (t, *J* = 4.4 Hz, 1H), 4.46–4.42 (m, 1H), 3.87 (s, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 2.41 (dt, *J* = 10.5, 5.0 Hz, 1H), 2.08–2.00 (m, 2H), 1.95–1.90 (m, 1H), 1.88 (brs, 1H), 0.90 (s, 9H),

0.09 (s, 3H), 0.08 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.7, 144.8, 134.7, 131.9, 130.7, 121.4, 115.2, 111.3, 85.3, 63.3, 59.4, 55.9, 47.6, 40.9, 34.2, 25.8, 18.1, -4.66, -4.71; HRMS (ESI) calcd for $C_{21}H_{32}O_4SiNa$ $[M+Na]^+$: 399.1962, found: 399.1955; IR (neat): 3427, 2927, 2855, 2376, 1619, 1510, 1460, 1281, 1252, 1203, 1088, 875, 837, 776, 733 cm^{-1}; EI MS m/z (%): 199 (11), 214 (29), 244 (64), 331 (8), 376 (3).

*2-((5aS,7S,9aS)-7-((tert-butyldimethylsilyl)oxy)-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)acetaldehyde (**10**).* To a stirred solution of alcohol **9-1** (175 mg, 0.465 mmol, 1 equiv) in dry DCM (20 mL) at 0 ºC, $NaHCO_3$ (195 mg, 2.325 mmol, 5 equiv) and DMP (296 mg, 0.698 mmol, 1.5 equiv) were added. The reaction mixture was slowly warmed to room temperature and stirred for 1 h. Then, the reaction was quenched with saturated NaS_2O_3 solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuum*. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 6:1) to afford product **10** (150 mg, 86% yield) as a colorless oil. $[\alpha]_D^{25}$ = –160 (c = 0.20, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.6 Hz, 1H), 6.86 (t, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 2H), 5.80 (dd, *J* = 10.1, 2.2 Hz, 1H), 5.66 (d, *J* = 10.1 Hz, 1H), 4.88 (t, *J* = 3.8 Hz, 1H), 4.49–4.47 (m, 1H), 3.87 (s, 3H), 2.81 (d, *J* = 2.6 Hz, 2H), 2.53 (dt, *J* = 14.0, 5.0 Hz, 1H), 1.86 (ddd, *J* = 13.9, 9.0, 3.2 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$) δ 200.4, 146.9, 145.0, 133.0, 128.8, 121.9, 115.2, 111.9, 85.3, 62.8, 55.9, 50.9, 46.5, 33.3, 25.8, 18.0, -4.61, -4.65; HRMS (ESI) calcd for $C_{21}H_{30}O_4SiNa$ $[M+Na]^+$: 397.1806, found: 397.1801; IR (neat): 2928, 2855, 2372, 1722, 1492, 1460, 1286, 1252, 1202, 1092, 875, 837, 776 cm^{-1}; EI MS m/z (%): 75 (100), 199 (85), 225 (6), 273 (7), 317 (8), 374 (2).

*2-((5aS,7S,9aS)-7-((tert-butyldimethylsilyl)oxy)-4-methoxy-6,7-dihydrodibenzo[b,d]furan-9a(5aH)-yl)-N-methylacetamide (**11**).* To a stirred solution of **10** (148 mg, 0.396 mmol, 1 equiv) in dry CCl_4 (15 mL), AIBN (3.2 mg, 0.02 mmol, 0.05 equiv) and NBS (85 mg, 0.475 mmol, 1.2 equiv) were added sequentially. The flask was then placed in an oil-bath preheated at 95 °C, and the heterogeneous mixture was stirred for about 10 min. Then the crude reaction mixture was cooled to 0 °C and bubbled by CH_3NH_2 gas, which was freshly prepared *in situ* from $MeNH_2$•HCl and NaOH solid and dried by a basic NaOH drying tower. Keeping on the continuous $MeNH_2$ bubble, the suspension was stirred at room temperature for an additional 10 min. After removal of CCl_4 in *vacuum* at ambient temperature, the residue was rapidly purified by column chromatography on silica gel (petroleum ether : EtOAc = 1:1) to afford the amide **11** (114 mg, 72%) as a white foam. $[\alpha]_D^{25}$ = –117 (c = 0.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.84–6.77 (m, 2H), 6.73 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.73 (dd, *J* = 10.2, 0.9 Hz, 1H), 5.61–5.57 (m, 1H), 5.53 (brs, 1H), 4.98 (t, *J* = 3.2 Hz, 1H), 4.66–4.43 (m, 1H), 3.84 (s, 3H), 2.72 (d, *J* = 4.8 Hz, 3H), 2.65 (d, *J* = 14.1 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.58–2.50 (m, 1H), 1.82 (ddd, *J* = 14.1, 9.4, 3.0 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 146.8, 144.8, 133.9, 133.1, 129.1, 121.6, 115.2, 111.6, 85.4, 63.0, 55.8, 46.8, 44.8, 33.1, 26.3, 25.8, 18.0, -4.6, -4.7; HRMS (ESI) calcd for $C_{22}H_{33}NO_4SiNa$ $[M+Na]^+$:

426.2071, found: 426.2075; IR (neat): 3311, 2954, 2930, 2857, 1739, 1648, 1561, 1493, 1461, 1254, 1204, 1092, 877, 838, 777 cm^{-1}; EI MS m/z (%): 130 (35), 148 (45), 199 (47), 272 (35), 346 (28), 403 (2).

(4aS,6S,8aS)-6-hydroxy-3-methoxy-11-methyl-4a,5,11,12-tetrahydro-6H-benzo[2,3]benzofuro[4,3-cd]azepin-10(9H)-one ***(12)***. To a stirred solution of **11** (102 mg, 0.253 mmol, 1 equiv) in dry DCE (15 mL) at room temperature, paraformaldehyde (30 mg, 1.55 mmol, 4 equiv) and CF_3CO_2H (283 μL, 3.80 mmol, 15 equiv) were added sequentially. The reaction mixture was stirred for 1.5 h. Then, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with DCM. The combined organic phase was washed with brine, and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (DCM : MeOH = 20:1) to afford the product **12** (62 mg, 81%) as a white foam. $[\alpha]_D^{25}$ = –117 (c = 0.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.84 (d, *J* = 10.2 Hz, 1H), 5.45 (dt, *J* = 10.2, 1.8 Hz, 1H), 4.71–4.66 (m, 2H), 4.50 (d, *J* = 15.9 Hz, 1H), 4.23 (d, *J* = 15.9 Hz, 1H), 3.85 (s, 3H), 2.98 (s, 3H), 2.85 (s, 2H), 2.83–2.77 (m, 1H), 2.09 (d, *J* = 6.7 Hz, 1H), 1.84–1.77 (m, 1H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.1, 147.7, 144.6, 131.8, 131.6, 128.9, 125.4, 119.4, 111.7, 87.6, 62.6, 56.1, 52.0, 43.4, 42.8, 35.7, 31.0; HRMS (ESI) calcd for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$: 324.1206, found: 324.1201; IR (neat): 3404, 2922, 1631, 1618, 1433, 1278, 1050, 803, 734 cm^{-1}; EI MS m/z (%): 115 (33), 197 (32), 229 (25), 258 (9), 282 (12), 301 (100).

(4aS,8aS)-3-methoxy-11-methyl-4a,5,11,12-tetrahydro-6H-benzo[2,3]benzofuro[4,3-cd]azepine-6,10(9H)-dione ***(13)***. To a stirred solution of alcohol **12** (31 mg, 0.103 mmol, 1 equiv) in dry DCM (10 mL) at 0 ºC, $NaHCO_3$ (43 mg, 0.515 mmol, 5 equiv) and DMP (65 mg, 0.155 mmol, 1.5 equiv) were added. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. Then the reaction was quenched with saturated NaS_2O_3 solution and extracted with EtOAc. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuum*. The crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 1:2) to afford product **13** (28.5 mg, 93% yield) as a colorless oil. (All spectroscopic data of our synthetic compound **13** were in agreement with the ones reported in the literature[9d].) $[\alpha]_D^{25}$ = –106 (c = 0.30, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.76–6.73 (m, 2H), 6.39 (dd, *J* = 10.2, 2.3 Hz, 1H), 6.06 (d, *J* = 10.2 Hz, 1H), 4.85 (q, *J* = 2.8 Hz, 1H), 4.50 (d, *J* = 16.2 Hz, 1H), 4.41 (d, *J* = 16.2 Hz, 1H), 3.86 (s, 3H), 3.17 (dd, *J* = 17.9, 2.9 Hz, 1H), 3.06 (s, 3H), 3.02 (d, *J* = 13.9 Hz, 1H), 2.96 (d, *J* = 13.8 Hz, 1H), 2.82 (dd, *J* = 17.9, 3.2 Hz, 1H); $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$) δ 193.5, 170.0, 147.8, 145.0, 144.6, 129.9, 127.8, 124.9, 120.2, 112.9, 87.1, 56.3, 52.0, 43.9, 40.7, 36.4, 36.0; HRMS (ESI) calcd for $C_{17}H_{17}NO_4Na$ $[M+Na]^+$: 322.1050, found: 322.1053; IR (neat): 3404, 2924, 2368, 1686, 1639, 1439, 1284, 1164, 1119, 1069, 738 cm^{-1}; EI MS m/z (%): 115 (29), 214 (21), 227 (50), 271 (29), 299 (100).

(–)-galanthamine (1a). To a stirred solution of **13** (25 mg, 0.084 mmol, 1 equiv) in dry THF (6 mL) at −78 ºC, L-selectride (168 μL, 0.168 mmol, 1 mol/L, 2 equiv) was slowly added. After stirring for 10 min, $LiAlH_4$ (29 mg, 0.756 mmol, 9 equiv) at –78 ºC was added slowly. Then, the reaction mixture was stirred at 60 ºC for 2 h. After being cooled to room temperature, the reaction was carefully quenched with NaOH aqueous solution (3mol/L, 4 mL), and extracted with EtOAc. The combined extracts was dried over K_2CO_3, and concentrated *in vacuum*. The residue was purified by column chromatography on silica gel (DCM : MeOH = 15:1) to afford (–)-galanthamine (**1a**) (17 mg, 71%). $[\alpha]_D^{25}$ = –93 (c = 0.30, $CHCl_3$); (lit.[10a]: $[\alpha]_D^{25}$ = –91.3 (c = 1.0, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, *J* = 8.2 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.07–5.99 (m, 2H), 4.62 (s, 1H), 4.15–4.11 (m, 2H), 3.84 (s, 3H), 3.72 (d, *J* = 15.1 Hz, 1H), 3.31 (t, *J* = 13.1 Hz, 1H), 3.08 (d, *J* = 14.6 Hz, 1H), 2.69 (dd, *J* = 15.7, 3.4 Hz, 1H), 2.43 (s, 3H), 2.10 (td, *J* = 13.5, 3.1 Hz, 1H), 2.01 (ddd, *J* = 15.7, 5.0, 2.4 Hz, 1H), 1.61 (dd, *J* = 13.8, 2.3 Hz, 1H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 145.9, 144.3, 133.0, 127.8, 126.6, 122.2, 111.3, 88.7, 62.0, 60.4, 55.9, 53.7, 48.1, 41.7, 33.5, 29.9; HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found: 288.1595; IR (neat): 3369, 2924, 1624, 1593, 1508, 1439, 1282, 1167, 1068, 1047, 921, 731 cm^{-1}; EI MS m/z (%): 115 (53), 128 (31), 174 (40), 216 (41), 244 (31), 270 (15), 286 (100), 287 (81).

*2-((5aS,7R,9aR)-7-((tert-butyldimethylsilyl)oxy)-4-methoxy-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-yl)acetaldehyde (**14**)*. To a stirred solution of **9** (300 mg, 0.64 mmol, 1 equiv) in MeOH (15 mL), Pd/C (30 mg) was added. The reaction was stirred at 35 °C under H_2 atmosphere (1 atm) for 5 h. Then, the reaction mixture was concentrated in *vacuum*, and the dry DCM (20 mL), $NaHCO_3$ (188 mg, 2.24 mmol, 3.5 equiv), and DMP (407 mg, 0.96 mmol, 1.5 equiv) were added sequentially at 0 °C. After stirring at room temperature for 1 h, the mixture was quenched with saturated $Na_2S_2O_3$ solution, and extracted with EtOAc. The combined organic layer was dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether : EtOAc = 10:1) to afford product **14** (195 mg, 81% yield) as a colorless oil. $[\alpha]_D^{25}$ = –33 (c = 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (s, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.79 (t, *J* = 6.6 Hz, 2H), 4.72 (t, *J* = 5.6 Hz, 1H), 4.01 (brs, 1H), 3.87 (s, 3H), 2.71 (dd, *J* = 15.4, 2.7 Hz, 1H), 2.63 (dd, *J* = 15.4, 2.0 Hz, 1H), 2.04–1.93 (m, 3H), 1.89–1.85 (m, 1H), 1.55–1.47 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 201.1, 146.5, 145.4, 134.4, 121.7, 115.1, 111.9, 87.0, 65.9, 55.9, 51.2, 45.9, 35.2, 29.5, 29.3, 25.8, 18.0, -4.8; HRMS (ESI) calcd for $C_{21}H_{32}O_4SiNa$ $[M+Na]^+$: 399.1962, found: 399.1958; IR (neat): 2929, 2856, 1721, 1491, 1456, 1289, 1255, 1098, 1064, 1043, 872, 837, 775 cm^{-1}; EI MS m/z (%): 201 (100), 275 (61), 319 (5), 376 (5).

*2-((5aS,7R,9aR)-7-((tert-butyldimethylsilyl)oxy)-4-methoxy-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-yl)-N-methylacetamide (**15**)*. To a stirred solution of **14** (181 mg, 0.48 mmol, 1 equiv) in dry CCl_4 (18 mL), AIBN (3.9 mg, 0.024 mmol, 0.05 equiv) and NBS (103 mg, 0.58 mmol, 1.2 equiv) were added sequentially. The flask was placed in an oil-bath

preheated at 95 °C, and the heterogeneous mixture was stirred for about 10 min. Then, the reaction mixture was cooled to 0 °C and bubbled with dry CH_3NH_2 gas for 5 min, which was freshly prepared *in situ* from $MeNH_2$•HCl and NaOH solid, and dried with a basic NaOH drying tower. After removal of CCl_4 *in vacuum*, the residue was rapidly purified by column chromatography on silica gel (petroleum ether : EtOAc = 1:1) to afford the product amide **15** (157 mg, 81%) as a white foam. $[\alpha]_D^{25}$ = –23 (c = 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.85–6.82 (m, 1H), 6.79–6.77 (m, 1H), 6.77–6.75 (m, 1H), 5.35 (m, 1H), 4.73 (t, *J* = 5.3 Hz, 1H), 3.98–3.95 (m, 1H), 3.85 (d, *J* = 2.5 Hz, 3H), 2.65 (dd, *J* = 4.8, 2.2 Hz, 3H), 2.51–2.46 (m, 2H), 2.08–2.00 (m, 2H), 1.92–1.91 (m, 1H), 1.82–1.78 (m, 1H), 1.51–1.44 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 170.4, 146.6, 145.2, 135.4, 121.3, 115.2, 111.7, 87.4, 66.0, 55.9, 46.4, 44.4, 35.3, 29.8, 29.3, 26.1, 25.8, 18.0, -4.77, -4.78; HRMS (ESI) calcd for $C_{22}H_{35}NO_4SiNa$ $[M+Na]^+$: 428.2228, found: 428.2223; IR (neat): 3312, 2932, 2857, 1740, 1647, 1491, 1458, 1255, 1096, 1067, 873, 836, 776, 734 cm^{-1}; EI MS m/z (%): 201 (28), 260 (11), 275 (100), 333 (9), 348 (20), 405 (3).

*(4aS,6R,8aR)-6-hydroxy-3-methoxy-11-methyl-4a,5,7,8,11,12-hexahydro-6H-benzo[2,3]benzofuro[4,3-cd]azepin-10(9H)-one (**16**)*. To a stirred solution of **15** (157 mg, 0.388 mmol, 1 equiv) in dry DCE (15 mL), paraformaldehyde (47 mg, 1.55 mmol, 4 equiv) and CF_3CO_2H (434 μL, 5.82 mmol, 15 equiv) were added sequentially at room temperature. The reaction mixture was stirred at ambient temperature for 1.5 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with DCM. The combined organic phase was washed with brine, and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (DCM : MeOH = 20:1) to afford the product **16** (97 mg, 83%) as a white amorphous solid. $[\alpha]_D^{25}$ = –70 (c = 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.46 (brs, 1H), 4.38 (d, *J* = 16.1 Hz, 1H), 4.30 (d, *J* = 16.1 Hz, 1H), 4.10–4.02 (m, 1H), 3.86 (s, 3H), 3.01 (s, 3H), 2.89 (d, *J* = 14.1 Hz, 1H), 2.86 (d, *J* = 14.0 Hz, 1H), 2.68–2.65 (m, 1H), 1.86 (d, *J* = 12.5 Hz, 1H), 1.77 (d, *J* = 14.2 Hz, 1H), 1.70 (ddd, *J* = 14.8, 11.2, 3.6 Hz, 1H), 1.60 (t, *J* = 14.2 Hz, 1H), 1.46 (dd, *J* = 25.2, 12.5 Hz, 1H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 171.9, 146.3, 144.7, 136.3, 124.7, 119.1, 111.5, 90.9, 66.4, 56.1, 52.0, 41.5, 40.2, 36.1, 34.3, 33.4, 30.1; HRMS (ESI) calcd for $C_{17}H_{22}NO_4$ $[M+H]^+$: 304.1543, found: 304.1548; IR (neat): 3394, 2924, 2853, 1738, 1627, 1460, 1377, 1245, 1187, 1081, 970, 739 cm^{-1}; EI MS m/z (%): 70 (100), 188 (36), 230 (43), 231 (35), 303 (79).

*(4aS,8aR)-3-methoxy-11-methyl-4a,5,7,8,11,12-hexahydro-6H-benzo[2,3]benzofuro[4,3-cd]azepine-6,10(9H)-dione (**17**)*. To a stirred solution of alcohol **16** (97 mg, 0.32 mmol, 1 equiv) in dry DCM (10 mL) at 0 ºC, $NaHCO_3$ (134 mg, 1.60 mmol, 5 equiv) and Dess-Martin periodinane (203 mg, 0.48 mmol, 1.5 equiv) were added. The reaction mixture was slowly warmed to room temperature and stirred for 2 h. Then, the reaction was quenched with saturated NaS_2O_3 solution, and extracted with EtOAc. The combined organic layer was washed brine, dried with Na_2SO_4, and concentrated in vacuum. The

crude product was purified by column chromatography on silica gel (petroleum ether : EtOAc = 1:2) to afford product **17** (85 mg, 88% yield) as a colorless oil. (At this point, we had completed the asymmetric formal synthesis of (–)-lycoramine and all spectroscopic data of our synthetic compound **17** were in agreement with the ones reported in the literature[9d].) $[\alpha]_D^{25}$ = –120 (c = 0.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 18.4, 8.2 Hz, 2H), 4.83 (t, J = 3.0 Hz, 1H), 4.42 (dd, J = 25.2, 16.8 Hz, 2H), 3.85 (s, 3H), 3.06–3.02 (m, 1H), 3.02 (s, 3H), 2.99 (d, J = 13.8 Hz, 1H), 2.85 (d, J = 13.8 Hz, 1H), 2.73 (dd, J = 17.6, 2.9 Hz, 1H), 2.39–2.34 (m, 1H), 2.30–2.24 (m, 1H), 2.04–2.01 (m, 2H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 207.3, 171.3, 146.9, 144.5, 132.6, 124.9, 120.0, 112.5, 88.4, 56.3, 52.1, 43.6, 42.3, 39.4, 36.2, 35.8, 32.7; HRMS (ESI) calcd for $C_{17}H_{19}NO_4Na$ $[M+Na]^+$: 324.1206, found: 324.1206; IR (neat): 3399, 2956, 2919, 2851, 1721, 1639, 1509, 1460, 1439, 1285, 1186, 1075, 969 cm^{-1}; EI MS m/z (%): 115 (18), 188 (23), 204 (28), 229 (29), 245 (21), 301 (100).

(–)-lycoramine (1b). To a stirred solution of **17** (23 mg, 0.076 mmol, 1 equiv) in dry THF (6 mL) at −78 ºC, L-selectride (152 μL, 0.152 mmol, 1 mol/L, 2 equiv) was added slowly. After stirring for 10 min, $LiAlH_4$ (26 mg, 0.684 mmol, 9 equiv) at –78 ºC was added slowly. The reaction mixture was stirred at 60 ºC for 2 h. After being cooled to room temperature, the reaction was carefully quenched with NaOH aqueous solution (3 mol/L, 4 mL), and extracted with EtOAc. The combined extract was dried with K_2CO_3, and concentrated *in vacuum*. The residue was purified by column chromatography on silica gel (DCM : MeOH = 15:1) to afford (–)-lycoramine (**1b**) (16 mg, 73%). $[\alpha]_D^{25}$ = –83 (c = 0.35, EtOH) (lit.[10b]: $[\alpha]_D^{22}$ = –89.3 (c = 0.35, EtOH)); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.66 (d, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.38 (s, 1H), 4.09 (s, 1H), 4.05 (d, *J* = 15.0 Hz, 1H), 3.86 (s, 3H), 3.67 (d, *J* = 15.0 Hz, 1H), 3.26 (t, *J* = 13.5 Hz, 1H), 3.08 (d, *J* = 14.3 Hz, 1H), 2.51 (d, *J* = 16.1 Hz, 1H), 2.40 (s, 3H), 2.01–1.95 (m, 1H), 1.93–1.88 (m, 1H), 1.87–1.80 (m, 1H), 1.79–1.75 (m, 1H), 1.74–1.67 (m, 2H), 1.60–1.54 (m, 1H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 146.1, 144.3, 136.2, 127.9, 122.0, 111.0, 89.9, 65.4, 60.2, 55.9, 54.0, 46.7, 41.5, 31.6, 31.1, 27.7, 23.8; HRMS (ESI) calcd for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1751, found: 290.1752; IR (neat): 3360, 2955, 2922, 2851, 1743, 1460, 1377, 1240, 1188, 1082, 969 cm^{-1}; EI MS m/z (%): 115 (14), 187 (8), 202 (10), 232 (8), 288 (100), 289 (67).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXX

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and HPLC chromatograms of compound **2** (PDF)

NMR spectral data comparison of compound **13**, compound **17**, galanthamine (**1a**), and lycoramine (**1b**) (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: tuyq@lzu.edu.cn; tuyq@sjtu.edu.cn.

*E-mail: zhangfm@lzu.edu.cn.

ORCID

Fu-Min Zhang: 0000-0001-5578-1148

Shao-Hua Wang: 0000-0002-4347-8245

Xiao-Ming Zhang: 0000-0002-9294-9672

Yong-Qiang Tu: 0000-0002-9784-4052

Notes

The authors declare no competing financial interest.

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