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TOTAL SYNTHESIS OF (+)- AND (–)-GALANTHAMINE

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This paper is dedicated to Professor Dr. Albert Eschenmoser on occasion of his 85th birthday.

Abstract – The stereoselective total synthesis of (+)-galanthamine [(+)-**1**], an antipode of the natural product, and (–)-galanthamine [(–)-**1**] starting from D-glucose is described. The cyclohexene unit in (+)-**1** was prepared in an optically active form from D-glucose using Ferrier's carbocyclization reaction, and the benzylic quaternary carbon was stereoselectively generated via chirality transfer by Johnson- or Eschenmoser-Claisen rearrangement. The dibenzofuran skeleton was effectively constructed by the bromonium ion-mediated intramolecular dealkylating etherification. After the introduction of a carbon-carbon double bond, the Pictet-Spengler type cyclization, followed by reduction of an amide function afforded (+)-**1**. Starting from D-glucose, (–)-galanthamine [(–)-**1**] was also totally synthesized.

INTRODUCTION

(–)-Galanthamine [(–)-**1**], an alkaloid isolated from some species of the *Amaryllidaceae* family,[1,2] has been reported to be a centrally acting acetylcholinesterase inhibitor[3] and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine.[4] On the basis of these biological activities, (–)-galanthamine was developed as a medicine for Alzheimer's disease and has been clinically used in Europe and the USA.[2c,3b] Its important and significant biological activity as well as its interesting structure have naturally received considerable attention from the synthetic community, and several synthetic approaches to **1** have been reported to date.[2,5,6] A number of successful total syntheses of galanthamine, employing the biomimetic oxidative bisphenol coupling,[2,5a,6a] intramolecular Heck reaction,[2,5b,6b,6d,6e,6f] semipinacol rearrangement,[5c] double Michael-Claisen reaction cascade of acetone derivatives with acrylates,[5d] and intramolecular *para*-alkylation of a phenol derivative,[5e] for construction of the characteristic tetracyclic skeleton possessing a benzylic quaternary carbon, have appeared, however, reports of the chiral syntheses of **1** are rather limited.[6] Due to the scarce supplies of galanthamine from natural sources[7] and the necessity for preparing structural analogues for the development of more potent drugs, it is still important to establish a chiral and effective synthetic route to the alkaloid from readily available materials. In this paper, we report a stereoselective total synthesis of (+)-galanthamine [(+)-**1**] and its natural enantiomer (–)-**1** starting from D-glucose.[8]

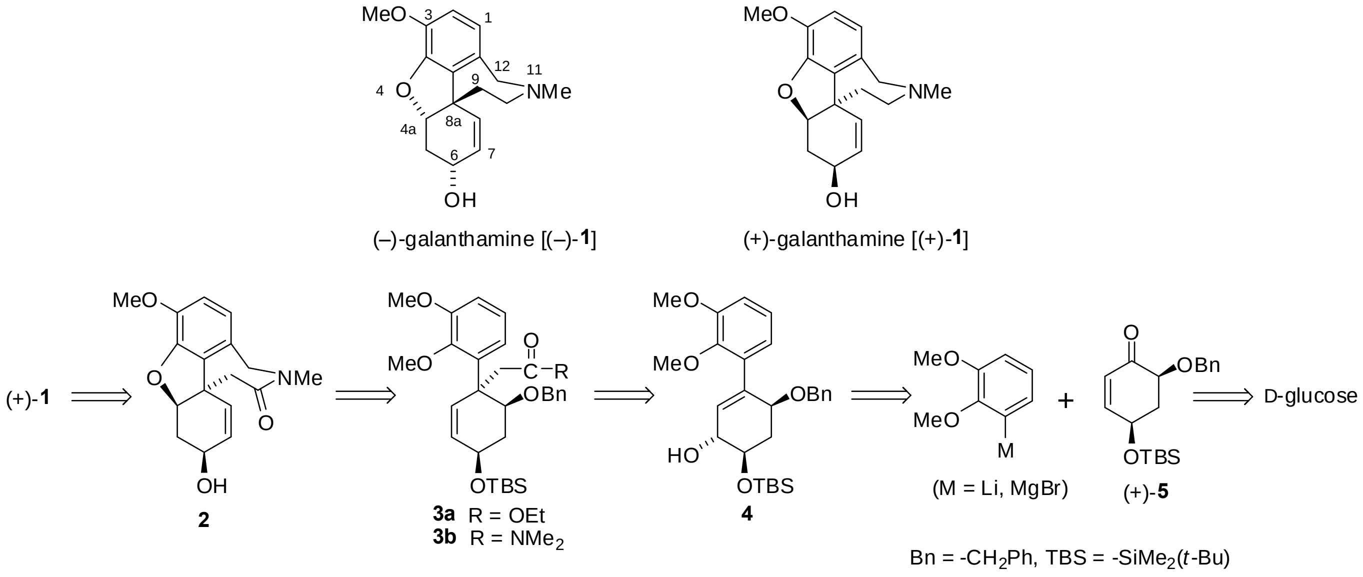
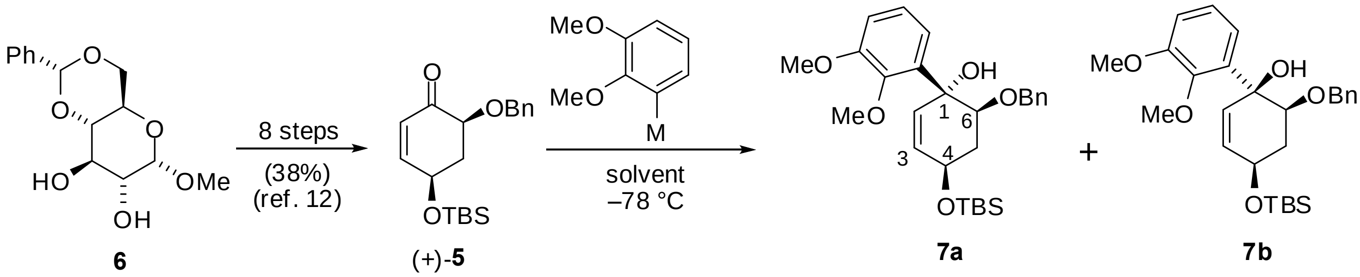


Figure 1. Structures of galanthamine and its retrosynthetic analysis.

RESULTS AND DISCUSSION

Our earlier reports of the total synthesis of (+)-vittatine and (+)-haemanthamine, *Amaryllidaceae* alkaloids possessing the hexahydroindole skeleton with a 1,3-dioxolane ring at *m*- and *p*-positions in the phenyl group as the core structure, starting from D-glucose revealed that the methodology involving Claisen rearrangement on the chiral cyclohexenol derived from carbohydrates is effective for the stereoselective generation of quaternary carbons.[9] Taking the successful synthesis of vittatine and haemanthamine into accounts, our retrosynthetic analysis for (+)-galanthamine (+)-**1** suggested that the tetracyclic lactam **2**, which had been utilized in the synthesis of racemic galanthamine by Guillou,[5b] would be a suitable intermediate for the total synthesis (Figure 1). The dibenzofuran skeleton in **2** was expected to be constructed by the bromonium ion-mediated intramolecular dealkylating etherification[10] of cyclohexene **3** possessing phenolic ether functions at *o*- and *m*-positions, whose crucial quaternary carbon preparation was planned using the Claisen rearrangement[9,11] of cyclohexenol derivative **4**. The cyclohexenol **4**, in turn, was envisioned to be synthesized by the coupling reaction of an aryl metal species with cyclohexenone (+)-**5**, which is a known compound[12] and has been prepared in the optically pure form starting from D-glucose by way of the Ferrier's carbocyclization.[13] Since the enantiomeric cyclohexenone (–)-**5** could also be synthesized from D-glucose,[12] the synthetic way to (+)-galanthamine would be readily applicable to the synthesis of a natural enantiomer of galanthamine.

The treatment of (4*R*,6*S*)-6-benzyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclohexenone[12] (+)-**5**, prepared from commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **6** utilizing the catalytic Ferrier's carbocyclization[13c] as the key transformation in a total of 8 steps with 38% overall yield, with 2,3-dimethoxyphenylmagnesium bromide at –78 °C gave 1,2-adducts **7** in 85% yield as a diastereomeric mixture (**7a** : **7b** = 4 : 1) (Scheme 1). The configuration of C-1 in **7a** was assigned by the observed NOE between H-6 and OH at C-1. When cyclohexenone (+)-**5** was reacted with 2,3-dimethoxyphenyllithium in the presence of TMEDA, compound **7** was obtained in 60% yield with a reverse stereoselectivity (**7a** : **7b** = 1 : 3).



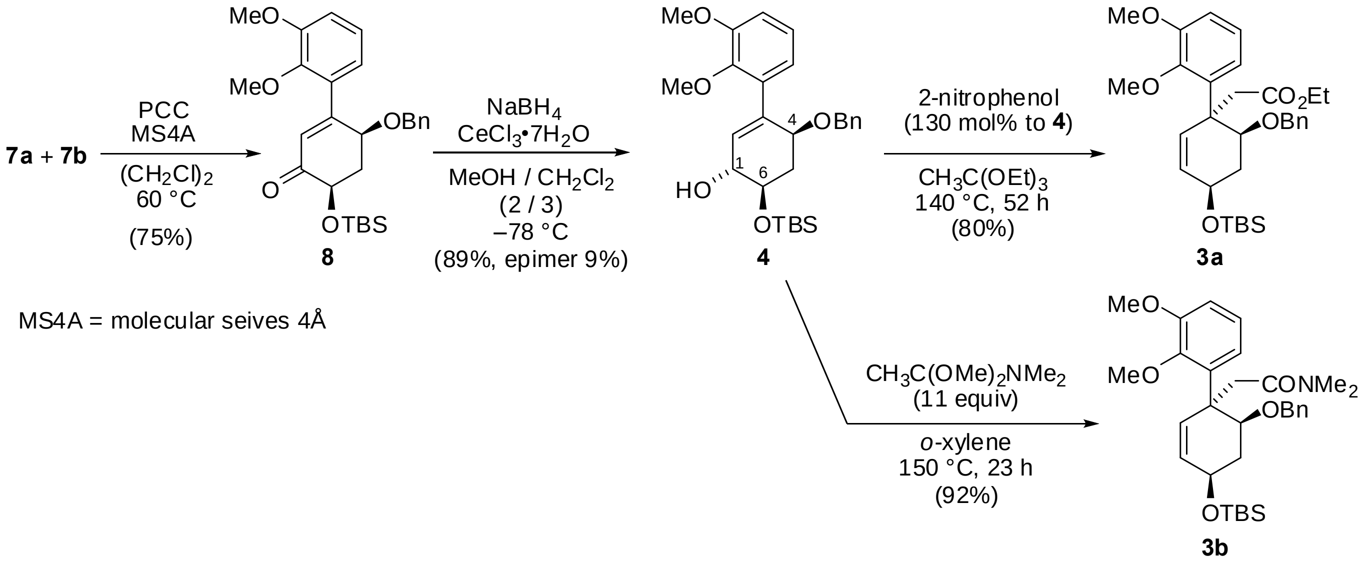
M	solvent	additive	yield (%)	**7a** / **7b**
MgBr	THF	--	85	4/1
Li	Et_2O	TMEDA	60	1/3

TMEDA = *N*,*N*,*N'N'*-tetramethylethylenediamine

Scheme 1

The oxidation of a mixture of **7a** and **7b** (4 : 1) with pyridinium chlorochromate (PCC) in the presence of molecular sieves 4A (MS4A) afforded cyclohexenone **8** in 75% yield,[14] which was reduced under the conditions of Luche[15] at –78 °C to give cyclohexenol **4** and its C-1 epimer in 89 and 9% isolated yields, respectively (Scheme 2). The observed coupling constants in **4** ($J_{1,6}$ = 7.8 Hz) and its C-1 epimer ($J_{1,6}$ = 4.1 Hz) supported their assigned configurations. With cyclohexenol **4** possessing the desired stereochemistry in hand, the crucial Claisen rearrangement was next investigated. Johnson-Claisen rearrangement[16] of **4** in triethyl orthoacetate in the presence of 2-nitrophenol[9b,17] in a sealed tube at 140 °C for 52 h successfully afforded the rearranged product **3a** in 80% yield. It is important to note that the

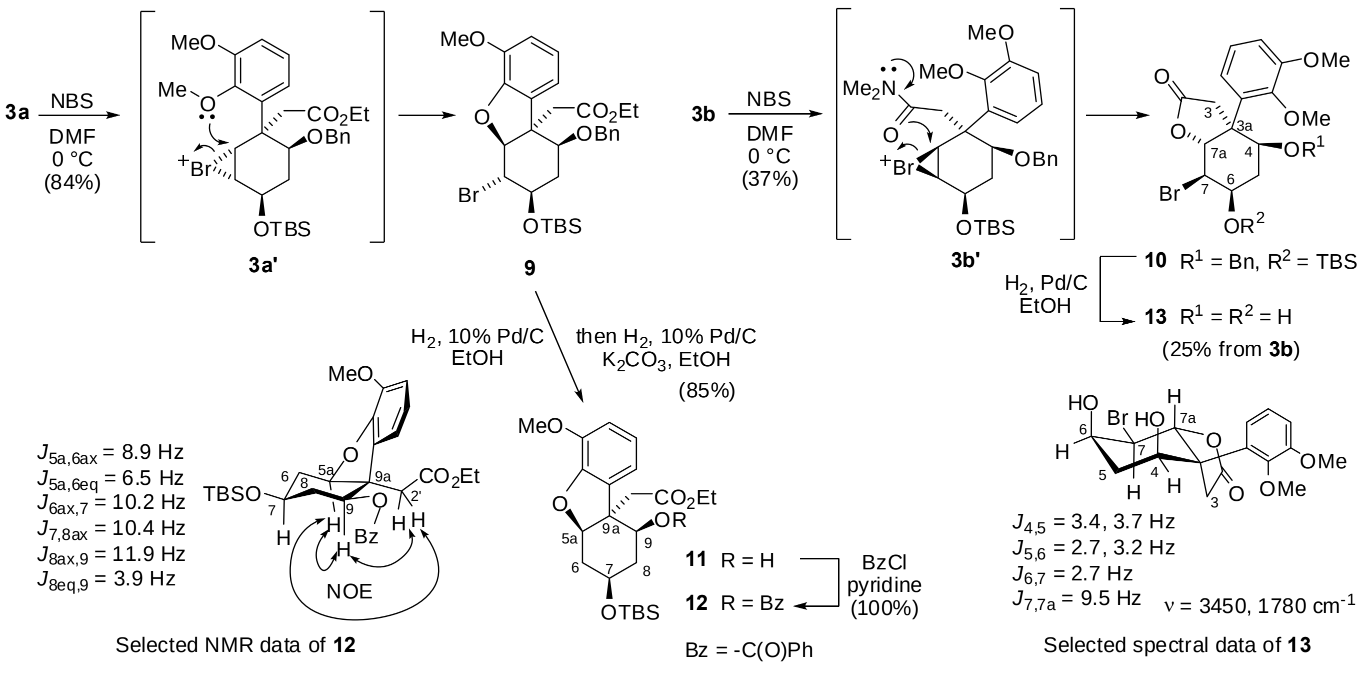
Johnson-Claisen rearrangement of **4**, possessing an *o*-methoxy substituent in the phenyl group, proceeded in a high yield when 2-nitrophenol was employed as the acid catalyst. It has been reported that the conventional Johnson-Claisen rearrangement (using propionic acid as the catalyst) of the simple cyclohexenol systems similar to **4** resulted in the very poor yields of the rearranged products, probably due to the acid sensitivity of the substrates and the steric congestion at the reaction center caused by the presence of the *o*-methoxy substituent in the phenyl group.[10,11b,18] Indeed, the Johnson-Claisen rearrangements of **4** in the presence of propionic acid (10 ~ 130 mol% to **4**) at 140 °C gave **3** in less than 40% yields, and the formation of a significant amount of unidentified by-products was observed. The acidity of 2-nitrophenol (pK_a = 7.04) would be appropriate for the Johnson-Claisen rearrangement of **4**; its weaker acidity than that of propionic acid (pK_a = 4.62) suppressed the decomposition of the acid-labile substrate but could catalyze the formation of a ketene acetal. On the other hand, Eschenmoser-Claisen rearrangement[19] of **4** (*N*,*N*-dimethylacetamide dimethyl acetal in *o*-xylene in a sealed tube at 150 °C) cleanly afforded **3b** in an excellent yield (92%).



MS4A = molecular seives 4Å

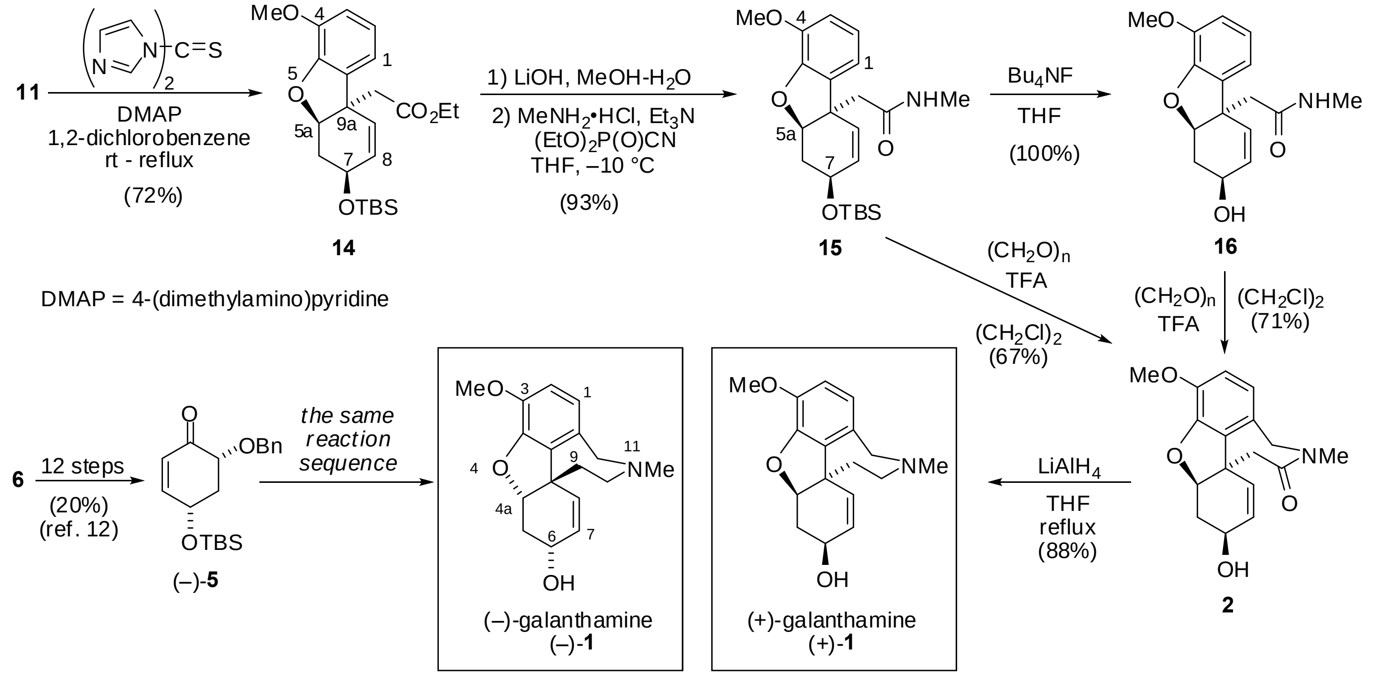
Scheme 2

Next, we turned out attention to construct the dibenzofuran skeleton from **3a** and **3b**. The treatment of **3a** with *N*-bromosuccinimide (NBS) in DMF induced the intramolecular dealkylating etherification via a bromonium ion intermediate[10] **3a'** to give bromo-dibenzofuran derivative **9** as a single product in 84% yield (Scheme 3). Similar reaction of **3b** with NBS, however, afforded no dibenzofuran product and resulted in the formation of many unidentified products. Among them, γ-lactone **10** was isolated in 37% yield. It is known that the formation of a cyclic bromonium ion intermediate in the congested alkene systems is a reversible step, and the subsequent nucleophilic opening of the bromonium ion is a rate-determining one.[10,20] The carbonyl group in amide **3b** is more nucleophilic than the phenolic ether oxygen, thus providing lactone **10** via the epimeric cyclic bromonium ion intermediate **3b'**. Hydrogenolysis of **9** in the presence of Pd on carbon and potassium carbonate in EtOH under atmospheric pressure of H_2 caused the debromination as well as the deprotection of the *O*-benzyl group to provide **11**. However, under these basic conditions, the de-*O*-benzylation process was found to be very sluggish, and resulted in the low yield of **11** (less than 40%). In contrast, under similar hydrogenolytic conditions without potassium carbonate, deprotection of the *O*-benzyl group smoothly proceeded, but the debromination process became slow. After some attempts, it was found that the two-steps in a one-pot reaction gave satisfactory results. Thus, deprotection of the *O*-benzyl group in **9** under neutral conditions (Pd on carbon, atmospheric pressure of H_2 in EtOH) was first carried out. After completion of the de-*O*-benzylation (TLC monitoring), potassium carbonate was added to the reaction mixture and the hydrogenolysis of the C-Br bond was further continued in the same reaction vessel to give **11** in 85% yield. The structure of **11** was confirmed by NMR analyses of the derived benzoate **12**; the observed large coupling constants ($J_{5a,6ax}$, $J_{6ax,7}$, $J_{7,8ax}$ and $J_{8ax,9}$) revealed that the substituents at C-5a, C-7 and C-9 are all in the equatorial positions, and NOE experiments (correlations between H-5a and C-2'methylene, and H-9 and C-2' methylene) clearly assigned the stereochemistry of the quaternary carbon at C-9a as *R*. Hydrogenolysis of **10** in the absence of potassium carbonate similarly removed the *O*-benzyl group, and under the reaction conditions, the *O*-TBS group was also detached to give bromo-diol **13** (25% yield from **3b**). The IR spectrum of **13** suggested the presence of hydroxy and γ-lactone groups, and the ^{1}H NMR analysis assigned the structure of **13** as depicted in Scheme 3.



Scheme 3

To introduce the requisite carbon-carbon double bond, compound **11** was treated with (thiocarbonyl)diimidazole and DMAP in dichlorobenzene at 180 °C[21] to afford **14** in 72% yield (Scheme 4). Hydrolysis of the ethyl ester function in **14**, followed by condensation with methylamine under the conditions of Shioiri,[22] provided amide **15** in 93% yield. The Pictet-Spengler type reaction of **15** with paraformaldehyde in the presence of TFA[5b,5c] generated the methano-bridge between the amide nitrogen and C-1, and induced the deprotection of the *O*-TBS group to give tetracyclic lactam **2**, which is known as the intermediate for the synthesis of racemic galanthamine reported by the Guillou[5b] and Tu[5c] in 67% yield. However, the reproducibility of the reaction was found to be rather poor, and the yields of **2** sometimes dropped to 20-40%. Fortunately, it was found when the same reaction conditions were applied to allylic alcohol **16**, compound **2** was obtained in better yields with good reproducibility. Removal of the *O*-TBS group in **15** afforded the known alcohol **16**,[5c] whose reaction with paraformaldehyde and TFA provided **2** in 71% overall yield from **15**. Finally, reduction of **2** with $LiAlH_4$ cleanly afforded (+)-galanthamine [(+)-**1**] in 88% yield. The ^1H and ^{13}C NMR data of the synthetic **1** were totally identical with those of natural (–)-galanthamine and the $[\alpha]_D$ value of the synthetic compound {$[\alpha]_D^{24}$ +112 (*c* 0.50, EtOH): lit.,[1c] $[\alpha]_D^{20}$ –118.8 (*c* 1.378, EtOH)} confirmed its unnatural absolute configuration. Thus, total synthesis of (+)-galanthamine starting from D-glucose has been accomplished. Starting from the enantiomeric cyclohexenone (–)-**5**[12] obtained from **6** in 12 step reactions, (–)-galanthamine [(–)-**1**] {$[\alpha]_D^{23}$ –112 (*c* 0.19, EtOH)} was also totally synthesized via the same reaction sequence.



Scheme 4

CONCLUSIONS

In summary, a new and non-biomimetic synthetic route to optically active galanthamine starting from D-glucose has been established. This synthesis, required 12 steps with a 13.6% overall yield from (+)-**5** (20 steps, 5.2% overall yield from commercially available **6**) for the synthesis of (+)-galanthamine, and 24 steps with 2.7% overall yield from **6** for the synthesis of (–)-galanthamine, demonstrated that the methodology involving the Claisen rearrangement on chiral cyclohexenol derived from D-glucose is effective for the chiral and stereoselective synthesis of galanthamine-type alkaloids. It was shown that the Eschenmoser-Claisen rearrangement is a powerful method for the construction of the sterically hindered quaternary carbon. The effectiveness of 2-nitrophenol as the acid catalyst for the Johnson-Claisen rearrangement is particularly noteworthy. It was also revealed that the intramolecular dealkylating etherification using NBS is a useful procedure for the construction of benzofuran skeletons that are commonly found in galanthamine-type as well as morphine-type biologically significant alkaloids.

EXPERIMENTAL

General. Melting points were determined on a Mitamura-Riken micro hot stage and were not corrected. Optical rotations were recorded using a sodium lamp (589 nm) with a JASCO DIP-370 instrument with 1 dm tube. Infrared (IR) spectra were measured with a JASCO FT/IR-200 spectrometer with a KBr cell. ^{1}H NMR spectra were recorded at 300 MHz on a Varian MVX-300 spectrometer for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts are reported as δ values in ppm. Abbreviations used are: b (broad peak), s (singlet), d (doublet), t (triplet), q (quartet) and m (complex multiplet). ^{13}C NMR spectra were recorded at 75 MHz on a Varian MVX-300 spectrometer for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts are reported as δ values in ppm. Mass spectra are measured by a JEOL GC Mate spectrometer with EI (70 eV) or FAB (glycerol matrix) mode. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Column chromatography was carried out with silica gel (Merck Kieselgel 60 F_{254}, 230-400 mesh). Preparative TLC was performed with Merck PLC plate (Kieselgel 60 F_{254}, 0.5 mm thickness).

(1*R*,4*R*,6*S*)-6-Benzyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-1-(2,3-dimethoxyphenyl)-2-cyclohexen-1-ol (7a) and Its (1*S*)-Epimer (7b). *Preparation with Grignard reagent*: To a solution of (+)-**5** (42.0 mg, 0.126 mmol) in THF (2.1 mL) under argon at –78 ºC was added 2,3-dimethoxyphenylmagnesium bromide (0.5 M solution in THF, 0.80 mL, 0.40 mmol). After being stirred at –78 ºC for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution at –78 ºC and the products were extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (3 g, toluene then EtOAc/toluene = 1/100 as an eluent) to afford **7a** (40.3 mg, 68%) as a colorless oil: $[\alpha]_D^{28}$ +3.4 (*c* 1.54, $CHCl_3$); IR (neat) ν_{max} = 3440, 2950, 2930, 2880, 2860, 1470, 1260, 1070 cm^{-1}; ^{1}H NMR δ 7.34–7.22 (5H, m), 7.02 (1H, dd, *J* = 8.1 and 7.8 Hz), 6.94 (1H, dd, *J* = 7.8 and 1.8 Hz), 6.89 (1H, dd, *J* = 8.1 and 1.8 Hz), 6.62 (1H, s), 5.81 (1H, ddd, *J* = 10.1, 1.7 and 0.9 Hz), 5.61 (1H, dd, *J* = 10.1 and 1.8 Hz), 4.67 and 4.62 (each 1H, 2d, *J* = 12.3 Hz), 4.37 (1H, dddd, *J* = 9.1, 6.3, 1.8 and 1.7 Hz), 3.85 and 3.84 (each 3H, 2s), 3.74 (1H, dd, *J* = 12.6 and 3.2 Hz), 2.09 (1H, dddd, *J* = 12.6, 6.3, 3.2 and 0.9 Hz), 1.59 (1H, ddd, *J* = 12.6, 12.6 and 9.1 Hz), 0.90 (9H, s), 0.09 and 0.06 (each 3H, 2s); ^{13}C NMR δ 152.6, 148.9, 138.5, 132.4, 132.3, 131.9, 128.2, 128.0, 127.5, 123.1, 122.7, 112.4, 82.4, 79.1, 71.7, 67.8, 61.5, 55.9, 34.6, 25.9, 18.2, –4.57, –4.64; HRMS (FAB) *m/z* calcd for $C_{27}H_{39}O_5Si$ $(M+H)^+$ 471.2567, found 471.2571. Anal. Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14%. Found: C, 68.60; H, 8.04%. Further elution gave **7b** (10.1 mg, 17%) as a colorless oil: $[\alpha]_D^{20}$ +111 (*c* 1.04, $CHCl_3$); IR (neat) ν_{max} = 3520, 2950, 2930, 2860, 1470, 1270, 1090 cm^{-1}; ^{1}H NMR δ 7.16–7.24 (4H, m), 7.07 (1H, dd, *J* = 8.0 and 8.0 Hz), 6.98–7.04 (2H, m), 6.90 (1H, dd, *J* = 8.0 and 1.5 Hz), 5.86 (1H, ddd, *J* = 10.0, 2.0 and 1.2 Hz), 5.66 (1H, dd, *J* = 10.0 and 2.2 Hz), 4.40 (1H, dddd, *J* = 10.1, 5.3, 2.2 and 2.0 Hz), 4.32 and 4.13 (each 1H, 2d, *J* = 11.7 Hz), 4.06 (1H, dd, *J* = 12.0 and 3.9 Hz), 3.92 (1H bs), 3.87 and 3.73 (each 3H, 2s), 2.11 (1H, dddd, *J* = 12.0, 5.3, 3.9 and 1.2 Hz), 1.98 (1H, ddd, *J* = 12.0, 12.0 and 10.1 Hz), 0.92 (9H, s), 0.11 and 0.10 (each 3H, 2s); ^{13}C NMR δ 152.9, 146.4, 139.0, 138.0, 133.6, 130.9, 128.1, 127.6, 127.5, 123.4, 119.5, 111.8, 78.5, 72.5, 72.2, 68.2, 60.5, 55.8, 35.0, 25.8, 18.2, –4.68, –4.67; HRMS (FAB) *m/z* calcd for $C_{27}H_{39}O_5Si$ $(M+H)^+$ 471.2567, found 471.2561. Anal. Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14%. Found: C, 68.62; H, 8.23%.

Preparation with aryllithium reagent: To a solution of 1,2-dimthoxybenzene (1.23 g, 8.90 mmol) in Et_2O (8.6 mL) at 0 ºC under Ar were added TMEDA (1.34 mL, 8.90 mmol) and *n*-BuLi (1.52 M hexane solution, 5.86 mL, 8.90 mmol). After being stirred at 0 °C for 45 min, the resultant yellow suspension was cooled to ‑78 ºC. To this mixture at ‑78 ºC under Ar was added a solution of (+)-**5** (296.1 mg, 0.891 mmol) in Et_2O (1.5 mL) dropwise through a cannula. After being stirred at –78 °C for 30 min, the mixture was quenched with saturated aqueous NH_4Cl solution at ‑78 ºC and the products were extracted with EtOAc. The extract was washed successively with saturated aqueous NH_4Cl aqueous solution and saturated aqueous $NaHCO_3$ solution, and then dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (15 g, EtOAc/toluene = 1/100 → 1/50 → 1/2 as an eluent) to afford **7a** (61.1 mg, 15%), **7b** (188.5 mg, 45%), and recovered starting material (+)-**5** (80.1 mg, 27% recovery).

(4*S*,6*R*)-4-Benzyloxy-6-[(*tert*-butyldimethylsilyl)oxy]-3-(2,3-dimethoxyphenyl)-2-cyclohexen-1-one (8). To a solution of a diastereomeric mixture of **7a** and **7b** (**7a** : **7b** = 4:1, 679.0 mg, 1.443 mmol) in 1,2-dichloroethane (34 mL) at rt were added activated MS4A (679 mg) and PCC (1.24 g, 5.77 mmol), and the mixture was stirred at 60 ºC for 1 h. Silica gel (10 g) was added to the reaction mixture and the resulting mixture was stirred vigorously at rt for 5 min. The mixture was diluted with Et_2O and the insoluble material was removed by filtration through a pad of silica gel. The filtrate was concentrated to give a residue, which was purified by column chromatography (20 g, EtOAc/toluene = 1/50 as an eluent) to afford **8** (504.9 mg, 75%) as a colorless oil: $[\alpha]_D^{29}$ −125 (*c* 1.34, $CHCl_3$); IR (neat) ν_{max} = 2950, 2930, 2860, 1690, 1470, 1270, 1160, 1110 cm^{-1}; ^1H NMR δ 7.23–7.16 (3H, m), 7.08 (1H, dd, *J* = 8.1 and 7.7 Hz), 7.01–6.92 (3H, m), 6.80 (1H, dd, *J* = 7.7 and 1.5 Hz), 6.09 (1H, d, *J* = 2.2 Hz), 5.03 (1H, ddd, *J* = 10.7, 5.0 and 2.2 Hz), 4.47 (2H, s), 4.32 (1H, dd, *J* = 13.2 and 5.0 Hz), 3.90 and 3.81 (each 3H, 2s), 2.65 (1H, ddd, *J* = 11.8, 5.0 and 5.0 Hz), 2.24 (1H, ddd, *J* = 13.2, 11.8 and 10.7 Hz), 0.95 (9H, s), 0.22 and 0.12 (each 3H, 2s); ^{13}C NMR δ 198.0, 162.2, 152.4, 146.1, 137.9, 132.1, 128.1, 127.6, 127.5, 127.4, 124.2, 121.5, 113.2, 74.8, 72.9, 71.1, 60.9, 56.0, 39.7, 25.8, 18.5, −4.3, −5.4; HRMS (FAB) *m/z* calcd for $C_{27}H_{37}O_5Si$ $(M+H)^+$ 469.2410, found 469.2411. Anal. Calcd for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74%. Found: C, 68.97; H, 7.87%.

(1*R*,4*S*,6*R*)-4-Benzyloxy-6-[(*tert*-butyldimethylsilyl)oxy]-3-(2,3-dimethoxyphenyl)-2-cyclohexen-1-ol (4) and Its (1*S*)-Epimer. To a solution of **8** (13.3 mg, 0.0284 mmol) in MeOH (0.2 mL) and CH_2Cl_2 (0.3 mL) was added cerium chloride heptahydrate (15.9 mg, 0.0427 mmol) at rt. After being stirred for 1 h, the reaction mixture was cooled to −78 ºC. To the mixture was added $NaBH_4$ (1.1 mg, 0.029 mmol) at −78 ºC, and the resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was quenched with water at −78 ºC and the products were extracted with EtOAc. The extract was washed with brine and then dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (1 g, EtOAc/toluene = 1/100 as an eluent) to afford **4** (11.9 mg, 89%) as a colorless oil: $[\alpha]_D^{28}$ −82 (*c* 0.84, $CHCl_3$); IR (neat) ν_{max} =3450, 2960, 2930, 2890, 2860, 1580, 1470, 1260, 1100 cm^{-1}; ^1H NMR δ 7.22–7.14 (3H, m), 7.02 (1H, dd, *J* = 8.0 and 7.7 Hz), 7.00–6.93 (2H, m), 6.89 (1H, dd, *J* = 8.0 and 1.4 Hz), 6.81 (1H, dd, *J* = 7.7 and 1.4 Hz), 5.73 (1H, dd, *J* = 2.1 and 2.0 Hz), 4.83 (1H, dddd, *J* = 10.0, 5.9, 2.1 and 2.0 Hz), 4.39 and 4.33 (each 1H, 2d, *J* =11.3 Hz), 4.28 (1H, ddd, *J* = 7.8, 2.0 and 2.0 Hz), 3.88 and 3.78 (each 3H, 2s), 3.71 (1H, ddd, *J* = 12.2, 7.8 and 3.4 Hz), 2.28 (1H, ddd, *J* = 12.2, 5.9 and 3.4 Hz), 2.22 (1H, bs), 1.82 (1H, ddd, *J* = 12.2, 12.2 and 10.0 Hz), 0.93 (9H, s), 0.14 and 0.13 (each 3H, 2s); ^{13}C NMR δ 152.5, 146.6, 140.6, 138.6, 134.4, 129.7, 128.0, 127.6, 127.2, 123.9, 122.6, 111.8, 75.6, 74.3, 73.6, 70.9, 60.6, 55.9, 37.5, 25.8, 18.1, −4.3, −4.5; HRMS (FAB) *m/z* calcd for $C_{27}H_{39}O_5Si$ $(M+H)^+$ 471.2567, found 471.2572. Anal. Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14%. Found: C, 68.62; H, 8.08%. Further elution afford the 1-epimer of **4** (1.2 mg, 9%) as a colorless oil: $[\alpha]_D^{21}$ −37 (*c* 0.64, $CHCl_3$); IR (neat) ν_{max} = 3540, 2960, 2930, 2880, 2860, 1580,1470, 1260, 1230, 1090 cm^{-1}; ^1H NMR δ 7.21−7.11 (3H, m), 7.02 (1H, dd, *J* = 8.3 and 7.1 Hz), 6.96–6.85 (4H, m), 5.94 (1H, dd, *J* = 5.1 and 1.9 Hz), 4.71 (1H, dddd, *J* = 10.2, 6.0, 1.9 and 0.6 Hz), 4.36 (2H, s), 4.13 (1H, dddd, *J* = 5.0, 4.1, 1.0 and 0.6 Hz), 3.88 (1H, ddd, *J* = 11.6, 4.1 and 4.1 Hz), 3.87 and 3.79 (each 3H, 2s), 2.77 (1H, bs), 2.13 (1H, ddd, *J* = 11.6, 11.6 and 10.2 Hz), 2.00 (1H, dddd, *J* = 11.6, 6.0, 4.1 and 1.0 Hz), 0.93 (9H, s), 0.14 (6H, s); ^{13}C NMR δ 152.3, 146.6, 144.4, 138.7, 134.3, 127.9, 127.5, 127.09, 127.06, 123.9, 122.7, 112.0, 74.8, 69.9, 68.8, 66.2, 60.6, 56.0, 31.9, 25.8, 18.1, –4.4, –4.8; HRMS (FAB) *m/z* calcd for $C_{27}H_{39}O_5Si$ $(M+H)^+$ 471.2567, found 471.2569.

(1*S*,4*R*,6*S*)-6-Benzyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-1-(2,3-dimethoxyphenyl)-2-cyclohexene-1-acetic Acid Ethyl Ester (3a). To a solution of **4** (71.7 mg, 0.152 mmol) in triethyl orthoacetate (10 mL) was added 2-nitrophenol (27.6 mg, 0.198 mmol) at rt. This mixture in a sealed tube filled with Ar was heated at 140 ºC for 52 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, and then dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (4.5 g, EtOAc/hexane = 1/30) to afford **3a** (65.9 mg, 80%) as a colorless oil: $[\alpha]_D^{26}$ –7.2 (*c* 0.38, $CHCl_3$); IR (neat) ν_{max} = 2960, 2940, 2860, 1730, 1580, 1470, 1260, 1230, 1100 cm^{-1}; ^{1}H NMR δ 7.35–7.21 (6H, m), 6.95 (1H, dd, *J* = 8.0 and 8.0 Hz), 6.83 (1H, dd, *J* = 8.0 and 1.4 Hz), 6.03 (1H, dd, *J* = 10.2 and 1.7 Hz), 5.66 (1H, ddd, *J* = 10.2, 1.5 and 1.0 Hz), 4.66 and 4.53 (each 1H, 2d, *J* = 11.7 Hz), 4.30 (1H, dddd, *J* = 9.3, 6.8, 1.7 and 1.5 Hz), 4.00 (2H, q, *J* = 7.1 Hz), 3.83 (1H, dd, *J* = 12.2 and 2.7 Hz), 3.82 and 3.75 (each 3H, 2s), 3.26 and 3.03 (each 1H, 2d, *J* = 14.9 Hz), 2.06 (1H, dddd, *J* = 12.2, 6.8 Hz, 2.7 and 1.0 Hz), 1.83 (1H, ddd, *J* = 12.2, 12.2 and 9.3 Hz), 1.13 (3H, t, *J* = 7.1 Hz), 0.87 (9H, s), 0.05 and 0.03 (each 3H, 2s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 153.2, 149.5, 138.7, 134.2, 133.0, 130.4, 128.1, 127.9, 127.4, 124.1, 122.1, 111.6, 78.6, 71.7, 68.2, 60.3, 59.8, 55.8, 48.2, 42.4, 33.2, 25.9, 18.2, 14.1, –4.5, –4.6; LRMS (EI) *m/z* 540 (M^+, 5%), 483 (4), 406 (41), 402 (15), 175 (31), 115 (19), 91 (77), 75 (100); HRMS (EI) *m/z* calcd for $C_{31}H_{44}O_6Si$ (M^+) 540.2907, found 540.2908. Anal. Calcd for $C_{31}H_{44}O_6Si$: C, 68.85; H, 8.20%. Found: C, 68.74; H, 8.19%.

2-[(1*S*,4*R*,6*S*)-6-Benzyloxy-4-[(*tert*-butyldimethylsilyl)oxy]-1-(2,3-dimethoxyphenyl)-2-cyclohexene-1-yl]-*N*,*N*-dimethylacetamide (3b). To a solution of **4** (112.2 mg, 0.2384 mmol) in *o*-xylene (11.2 mL) was added *N*,*N*-dimethylacetamide dimethyl acetal (0.350 mL, 2.66 mmol) at rt. This mixture in a sealed tube filled with Ar was heated at 150 ºC for 23 h. The reaction mixture was concentrated to give a residue, which was purified by column chromatography (5 g, EtOAc/toluene = 1/3) to afford **3b** (118.3 mg, 92%) as a colorless oil: $[\alpha]_D^{26}$ +5.8 (*c* 0.60, $CHCl_3$); IR (neat) ν_{max} = 2930, 2960, 2860, 1650, 1470, 1260, 1100 cm^{-1}; ^{1}H NMR δ 7.46 (1H, dd, *J* = 8.0 and 1.5 Hz), 7.38–7.21 (5H, m), 6.97 (1H, dd, *J* = 8.0 and 8.0 Hz), 6.81 (1H, dd, *J* = 8.0 and 1.5 Hz), 6.21 (1H, dd, *J* = 10.2 and 1.7 Hz), 5.61 (1H, ddd, *J* = 10.2, 2.0 and 1.2 Hz), 4.71 and 4.50 (each 1H, 2d, *J* = 12.1 Hz), 4.40 (1H, dddd, *J* = 9.5, 6.3, 2.0 and 1.7 Hz), 4.08 (1H, dd, *J* = 12.2 and 2.4 Hz), 3.83 and 3.78 (each 3H, 2s), 3.40 and 2.74 (each 1H, 2d, *J* = 15.6 Hz), 2.92 and 2.86 (each 3H, 2s), 2.15 (1H, dddd, *J* = 12.2, 6.3, 2.4 and 1.2 Hz), 1.96 (1H, ddd, *J* = 12.2, 12.2 and 9.5 Hz), 0.86 (9H, s), 0.044 and 0.035 (each 3H, 2s); ^{13}C NMR δ 171.4, 153.2, 148.9, 139.0, 136.0, 133.9, 129.8, 128.2, 127.9, 127.3, 123.7, 122.5, 111.0, 78.4, 71.4, 68.7, 60.3, 55.7, 48.7, 39.2, 37.6, 35.3, 33.4, 25.9, 18.2, –4.5, –4.6; LRMS (EI) *m/z* 539 (M^+, 15.4%), 508 (59.2), 448 (66.0), 405 (100), 333 (69.2), 316 (43.0), 199 (59.9); HRMS (EI) *m/z* calcd for $C_{31}H_{45}NO_5Si$ (M^+) 539.3067, found 539.3065.

(5a*S*,6*R*,7*R*,9*S*,9a*S*)-9-Benzyloxy-6-bromo-7-[(*tert*-butyldimethylsilyl)oxy]-6,7,8,9-tetrahydro-4-methoxy-9a(5a*H*)-dibenzofuranacetic Acid Ethyl Ester (9). To a solution of **3a** (66.3 mg, 0.123 mmol) in DMF (4.3 mL) was added NBS (43.6 mg, 0.245 mmol) at 0 ºC. After being stirred at 0 °C for 12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at 0 ºC and the products were extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and then dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (3 g, EtOAc/toluene = 1/100 as an eluent) to afford **9** (62.3 mg, 84%) as a colorless oil: $[\alpha]_D^{26}$ +26 (*c* 1.78, $CHCl_3$); IR (neat) ν_{max} = 2960, 2930, 2860, 1730, 1640, 1590, 1490, 1460, 1260, 1200, 1140, 1090 cm^{-1}; ^1H NMR δ 7.44–7.28 (5H, m), 7.22 (1H, dd, *J* = 6.8 and 1.4 Hz), 6.82–6.76 (2H, m), 5.18 (1H, d, *J* = 7.6 Hz), 4.71 and 4.52 (each 1H, 2d, *J* = 11.6 Hz), 4.19–4.00 (3H, m), 3.87 (3H, s), 3.76–3.62 (2H, m), 2.89 and 2.48 (each 1H, 2d, *J* = 16.1 Hz), 2.27 (1H, ddd, *J* = 12.7, 3.4 and 3.4 Hz), 1.53 (1H, m), 1.22 (3H, t, *J* = 7.2 Hz), 0.86 (9H, s), 0.13 and 0.07 (each 3H, 2s); ^{13}C NMR δ 171.0, 146.6, 145.9, 138.1, 132.0, 128.5, 127.81, 127.78, 122.3, 118.8, 113.2, 90.2, 75.4, 72.1, 69.8, 60.5, 60.1, 56.3, 54.5, 39.7, 36.3, 25.7, 18.0, 14.1, –4.4, –4.5; LRMS (EI) *m/z* 606 [M^+ (^{81}Br), 4%], 604 [M^+ (^{79}Br), 4], 549 (4), 547 (4), 531 (4), 529 (3), 337 (42), 247 (93), 91 (100), 73 (39); HRMS (EI) *m/z* calcd for $C_{30}H_{41}{}^{79}BrO_6Si$ (M^+) 604.1856, found 604.1857.

(5a*R*,7*R*,9*S*,9a*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7,8,9-tetrahydro-9-hydroxy-4-methoxy-9a(5a*H*)-dibenzofurnacetic Acid Ethyl Ester (11). To a solution of **9** (27.0 mg, 0.0447 mmol) in EtOH (1.5 mL) was added 10 % Pd on carbon (12 mg) and the mixture was stirred under an atmospheric pressure of H_2 at rt for 1 h. After confirming the disappearance of **9** by TLC analysis, potassium carbonate (6.2 mg, 0.045 mmol) was added to the mixture and the resulting mixture was further stirred under an atmospheric pressure of H_2 at rt for 1 h. The reaction mixture was filtrated through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by column chromatography (1.5 g, EtOAc/toluene = 1/30 as an eluent) to afford **11** (16.6 mg, 85%) as a colorless oil: $[\alpha]_D^{23}$ +44 (*c* 0.56, $CHCl_3$); IR (neat) ν_{max} = 3530, 2950, 2940, 2860, 1730, 1620, 1590, 1490, 1450, 1260, 1190, 1180, 1120 cm^{-1}; ^1H NMR δ 7.15 (1H, dd, *J* = 7.0 and 2.0 Hz), 6.83 (1H, dd, *J* = 8.1 and 7.0 Hz), 6.78 (1H, dd, *J* = 8.1 and 2.0 Hz), 4.75 (1H, dd, *J* = 8.6 and 6.4 Hz), 4.06 (3H, m), 3.86 (3H, s), 3.75 (1H, dddd, *J* = 9.8, 9.8, 4.7 and 4.4 Hz), 3.47 (1H, d, *J* = 4.4 Hz), 2.90 and 2.59 (each 1H, 2d, *J* = 14.8 Hz), 2.23 (1H, dddd, *J* = 12.7, 6.4, 4.7 and 1.7 Hz), 2.04 (1H, dddd, *J* = 10.7, 4.4, 4.4 and 1.7 Hz), 1.73-1.52 (2H, m), 1.16 (3H, t, *J* = 7.1 Hz), 0.83 (9H, s), 0.033 and 0.025 (each 3H, 2s); ^{13}C NMR δ 172.2, 147.2, 145.6, 131.2, 121.6, 118.5, 112.3, 85.5, 71.2, 65.1, 60.9, 56.0, 52.7, 42.3, 39.6, 37.5, 25.7, 18.0, 14.0, –4.8 (2C); LRMS (EI) *m/z* 436 (M^+, 26%), 379 (32), 287 (61), 241 (85), 235 (78), 234 (89), 213 (100), 199 (66), 161 (76), 75 (63), 73 (56); HRMS

(EI) *m/z* calcd for $C_{23}H_{36}O_6Si$ (M^+) 436.2281, found 436.2280. Anal. Calcd for $C_{23}H_{36}O_6Si$: C, 63.27; H, 8.31%. Found: C, 62.98; H, 8.25%.

(5a*R*,7*R*,9*S*,9a*R*)-9-Benzoyloxy-7-[(*tert*-butyldimethylsilyl)oxy]-6,7,8,9-tetrahydro-4-methoxy-9a(5a*H*)-dibenzofurnacetic Acid Ethyl Ester (12). To a solution of **11** (7.5 mg, 0.017 mmol) in pyridine (0.5 mL) were added benzoyl chloride (3.0 μL, 0.026 mmol) and DMAP (0.2 mg, 2 μmol) at rt. After being stirred at rt for 27 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the products were extracted with Et_2O. The extract was washed with brine and then dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (0.5 g, EtOAc/hexane = 1/50 as an eluent) to afford **12** (11.3 mg, 100%) as a colorless oil: $[\alpha]_D^{23}$ −38 (*c* 0.42, $CHCl_3$); IR (neat) ν_{max} = 2950, 2930, 2860, 1730, 1490, 1455, 1270, 1095 cm^{-1}; ^1H NMR δ 8.11 (2H, m), 7.63 (1H, m), 7.52 (2H, m), 7.27 (1H, dd, *J* = 7.5 and 1.0 Hz), 6.92 (1H, dd, *J* = 7.5 and 8.0 Hz), 6.83 (1H, dd, *J* = 8.0 and 1.0 Hz), 5.55 (1H, dd, *J* = 11.9 and 3.9 Hz), 5.23 (1H, dd, *J* = 9.0 and 6.4 Hz), 4.10-4.00 (2H, m), 3.88 (3H, s), 3.94 - 3.82 (1H, m), 2.67 and 2.57 (each 1H, 2d, *J* = 15.3 Hz), 2.37 (1H, dddd, *J* = 13.4, 6.4, 4.9 and 1.7 Hz), 2.24 (1H, dddd, *J* = 11.9, 4.6, 3.9 and 1.7 Hz), 1.69 (1H, ddd, *J* = 11.9, 11.9 and 10.5 Hz), 1.61 (1H, ddd, *J* = 13.4, 10.2 and 9.0 Hz), 1.19 (3H, t, *J* = 7.1 Hz), 0.82 (9H, s), 0.05 and 0.03 (each 3H, 2s); ^{13}C NMR δ 170.7, 165.9, 147.2, 145.9, 133.2, 131.4, 130.7, 129.6, 128.6, 121.8, 117.7, 112.2, 84.1, 72.0, 64.6, 60.6, 55.9, 52.3, 40.1, 38.1, 37.1, 25.7, 17.9, 13.9, –4.78, –4.81; LRMS (EI) *m/z* 540 (M^+, 5%), 483 (18), 343 (35), 241 (35), 179 (32), 105 (100), 77 (38); HRMS (EI) *m/z* calcd for $C_{30}H_{40}O_7Si$ (M^+) 540.2543, found 540.2539.

(3a*S*,4*S*,6*R*,7*R*,7a*R*)-7-Bromo-3a-(2,3-dimethoxyphenyl)-4,6-dihydroxy-hexahydro-2(3*H*)-benzofuranone (13). To a solution of **3b** (29.1 mg, 0.0539 mmol) in DMF (3.5 mL) was added NBS (18.2 mg, 0.102 mmol) at 0 ºC and the mixture was stirred at rt. After being stirred for 3 h, NBS (18.2 mg, 0.102 mmol) was added at 0 ºC and mixture was further stirred at rt for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at 0 ºC and the products were extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and then dried. Removal of the solvent left a residue, which was purified by column chromatography (1.5 g, EtOAc/toluene = 1/100 as an eluent) and further purified by preparative TLC (EtOAc/toluene =1/5) to afford **10** (11.8 mg, 37%) as a colorless oil. Compound **10** (11.8 mg, 0.199 mmol) was dissolved in EtOH (2 mL). To the mixture was added 10 % Pd on carbon (8 mg) and the mixture was stirred under an atmospheric pressure of H_2 at rt for 2 h. The mixture was filtrated through a pad of Celite and the filtrate was concentrated to give a residue, which was purified by column chromatography (1 g, EtOAc/toluene = 1/1 as an eluent) to afford **13** (5.3 mg, 25% from **3b**) as an amorphous solid: $[\alpha]_D^{24}$ −14 (*c* 0.27, $CHCl_3$); IR (neat) ν_{max} = 3450, 1780, 1470, 1270 cm^{-1}; ^1H NMR δ 7.07 (1H, dd, *J* = 8.5 and 8.3 Hz), 6.95 (1H, dd, *J* = 8.3 and 1.5 Hz), 6.90 (1H, dd, *J* = 8.5 and 1.5 Hz), 5.54 (1H, d, *J* = 9.5 Hz), 4.89 (1H, dd, *J* = 3.7 and 3.4 Hz), 4.34

(1H, ddd, *J* = 3.2, 2.7 and 2.7 Hz), 4.15 (1H, dd, *J* = 9.5 and 2.7 Hz), 3.95 and 3.87 (each 3H, 2s), 2.95 and 2.76 (each 1H, 2d, *J* = 17.3 Hz), 2.57 (1H, ddd, *J* = 15.6, 3.7 and 3.2 Hz), 2.15 (1H, ddd, *J* = 15.6, 3.4 and 2.7 Hz); ^{13}C NMR δ 173.7, 153.4, 147.5, 131.6, 123.8, 119.5, 113.3, 81.9, 71.1, 68.9, 60.4, 57.9, 55.8, 55.1, 38.4, 32.3; LRMS (EI) *m/z* 388 [M$^+$ (^{81}Br), 9%], 386 [M$^+$(^{79}Br), 9], 356 (92), 354 (100), 289 (10), 243 (31), 189 (53), 77 (47); HRMS (EI) *m/z* calcd for $C_{16}H_{19}{}^{79}BrO_6$ (M$^+$) 386.0365, found 386.0369.

(5a*R*,7*S*,9a*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7-dihydro-4-methoxy-9a(5a*H*)-dibenzofuranacetic Acid Ethyl Ester (14) To a solution of **11** (12.4 mg, 0.0284 mmol) in 1,2-dichlorobenzene (2.0 mL) were added thiocarbonyldiimidazole (20.2 mg, 0.113 mmol) and DMAP (0.4 mg, 0.3 μmol). The reaction mixture was heated at reflux temperature. After being refluxed for 6 h, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution. The products were extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$ solution and then dried. Removal of the solvent left a residue, which was purified by column chromatography (1 g, EtOAc/hexane = 1/10 as an eluent) to afford **14** (8.6 mg, 72%) as a colorless oil: $[\alpha]_D^{28}$ –22 (*c* 0.80, $CHCl_3$); IR (neat) ν_{max} = 2960, 2930, 2860, 1730, 1620, 1590, 1500, 1460, 1260, 1200, 1100 cm^{-1}; ^{1}H NMR δ 6.88–6.71 (3H, m), 5.93 (1H, dd, *J* = 10.0 and 2.0 Hz), 5.82 (1H, ddd, *J* = 10.0, 1.8 and 1.2 Hz), 5.24 (1H, dd, *J* = 11.6 and 5.6 Hz), 4.35 (1H, dddd, *J* = 10.2, 4.4, 2.0 and 1.8 Hz), 4.08 (2H, q, *J* = 7.1 Hz), 3.87 (3H, s), 2.62 and 2.54 (each 1H, 2d, *J* = 14.6 Hz), 2.33 (1H, dddd, *J* = 11.6, 5.6, 4.4 and 1.2 Hz), 1.70 (1H, ddd, *J* = 11.6, 11.6 and 10.2 Hz), 1.21 (3H, t, *J* = 7.1 Hz), 0.85 (9H, s), 0.060 and 0.055 (each 3H, 2s); ^{13}C NMR δ 170.4, 145.8, 145.3, 134.6, 133.1, 126.8, 121.5, 115.4, 111.6, 84.4, 65.2, 60.4, 55.9, 48.3, 44.7, 37.0, 25.7, 18.0, 14.2, –4.6, –4.8; LRMS (EI) *m/z* 418 (M$^+$, 8%), 361 (23), 343 (66), 297 (42), 269 (66), 254 (72), 181 (50), 75 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{34}O_5Si$ (M$^+$) 418.2176, found 418.2173. Anal. Calcd for $C_{23}H_{34}O_5Si$: C, 65.99; H, 8.19%. Found: C, 65.81; H, 8.22%.

(5a*R*,7*S*,9a*R*)-7-[(*tert*-Butyldimethylsilyl)oxy]-6,7-dihydro-4-methoxy-*N*-methyl-9a(5a*H*)-dibenzofuranacetamide (15). To a solution of **14** (7.6 mg, 0.018 mmol) in EtOH (0.4 mL) and water (0.1 mL) was added lithium hydroxide monohydrate (0.9 mg, 0.02 mmol) at rt. After being stirred at rt for 20 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution at 0 ºC and the products were extracted with Et_2O. The extract was washed with brine and then dried. Removal of the solvent gave a carboxylic acid as a syrup, which was used for the next reaction without further purification. To a solution of a crude carboxylic acid in DMF (0.4 mL) were added methylammonium chloride (6.1 mg, 0.091 mmol), diethyl cyanophosphonate (0.027 mL, 0.18 mmol) and Et_3N (0.025 mL, 0.18 mmol) at –10 ºC. After being stirred at –10 ºC for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the products were extracted with EtOAc. The extract was washed with brine and then dried. The organic solvent was concentrated to give a residue, which was purified by column chromatography (0.5 g, EtOAc/hexane = 1/1) to afford **15** (6.8 mg, 93% for 2 steps) as a crystalline residue: mp 58–60 ºC; $[\alpha]_D^{24}$ –3.5 (*c* 0.98, $CHCl_3$); IR (KBr disk) ν_{max} = 3310, 2950, 2930, 2860, 1650, 1490, 1260, 1090 cm^{-1}; ^{1}H NMR δ 6.83 (1H, dd, *J* = 8.0 and 7.3 Hz), 6.74 (1H, dd, *J* = 8.0 and 1.5 Hz), 6.71 (1H, dd, *J* = 7.3 and 1.5 Hz), 5.99 (1H, dd, *J* = 10.1 and 2.0 Hz), 5.82 (1H, ddd, *J* = 10.1, 1.9 and 1.2 Hz), 5.19 (1H, dd, *J* = 11.6 and 2.0 Hz), 5.18 (1H, bs,), 4.37 (1H, dddd, *J* = 10.4, 4.9, 2.0 and 1.9 Hz), 3.86 (3H, s), 2.69 (3H, d, *J* = 4.9 Hz), 2.48 and 2.34 (each 1H, 2d, *J* = 13.8 Hz), 2.31 (1H, dddd, *J* = 11.7, 4.9, 2.0 and 1.2 Hz), 1.69 (1H, ddd, *J* = 11.7, 11.6 and 10.4 Hz), 0.84 (9H, s), 0.054 and 0.047 (each 3H, 2s); ^{13}C NMR δ 170.0, 145.9, 145.4, 134.2, 133.3, 127.1, 121.4, 115.4, 111.7, 84.9, 65.2, 56.0, 48.4, 47.0, 36.9, 26.2, 25.7, 18.0, –4.6, –4.8; LRMS (EI) *m/z* 403 (M^+, 9%), 346 (42), 328 (100), 75 (45), 73 (40); HRMS (EI) *m/z* calcd for $C_{22}H_{33}NO_4Si$ (M^+) 403.2179, found 403.2165.

(5a*R*,7*S*,9a*R*)-6,7-Dihydro-7-hydroxy-4-methoxy-*N*-methyl-9a(5a*H*)-dibenzofuranacetamide (16). To a solution of **15** (7.6 mg, 0.019 mmol) in THF (0.4 mL) was added TBAF (1.0 M THF solution, 0.038 mL, 0.038 mmol) at rt and the mixture was stirred at 40 ºC for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and the products were extracted with EtOAc. The extract was washed with brine and then dried. Removal of the solvent left a residue, which was purified by column chromatography (0.3 g, EtOAc as an eluent) to afford **16** (5.8 mg, 100%) as a colorless oil: $[\alpha]_D^{24}$ –13 (*c* 0.58, $CHCl_3$); IR (neat) ν_{max} = 3310, 3100, 3000, 2940, 2840, 1650, 1490, 1460, 1280, 1070 cm^{-1}; ^{1}H NMR δ 6.90 (1H, dd, *J* = 7.8 and 7.8 Hz), 6.80 (1H, dd, *J* = 7.8 and 1.2 Hz), 6.78 (1H, dd, *J* = 7.8 and 1.2 Hz), 5.98 (1H, ddd, *J* = 10.1, 4.6 and 0.5 Hz), 5.73 (1H, ddd, *J* = 10.1, 1.0 and 1.0 Hz), 5.47 (1H, bs), 5.08 (1H, dd, *J* = 4.1 and 3.2 Hz), 4.20 (1H, m), 3.86 (3H, s), 2.74 (3H, d, *J* = 4.9 Hz), 2.61 and 2.57 (each 1H, 2d, *J* = 14.9 Hz), 2.43 (1H, dddd, *J* = 14.7, 4.1, 4.1 and 1.0 Hz), 2.22 (1H, ddd, *J* = 14.7, 4.9 and 3.2 Hz), 2.18 (1H, d, *J* = 9.7 Hz); ^{13}C NMR δ 169.6, 145.9, 145.2, 133.9, 129.6, 129.2, 122.2, 114.9, 111.9, 86.2, 62.4, 55.9, 47.3, 44.5, 31.9, 26.3; LRMS (EI) *m/z* 289 (M^+, 34%), 216 (100), 201 (33), 199 (42), 103 (39); HRMS (EI) *m/z* calcd for $C_{16}H_{19}NO_4$ (M^+) 289.1314, found 289.1311.

(4a*R*,6*S*,8a*R*)-4a,5,11,12-Tetrahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]-benzazepin-10(9*H*)-one (2). To a solution of **16** (3.9 mg, 0.014 mmol) in 1,2-dichloroethane (1.2 mL) were added paraformaldehyde (1.6 mg, 0.054 mmol) and TFA (0.02 mL) at rt. After being stirred at rt for 2.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution at 0 ºC and the products were extracted with $CHCl_3$. The extract was washed with brine and then dried. Removal of the solvent left a residue, which was purified by column chromatography (0.5 g, MeOH/$CHCl_3$ = 1/200) to afford **2** (2.9 mg, 71%) as a crystalline residue: mp 213–214 ºC; $[\alpha]_D^{25}$ +115 (*c* 0.63, $CHCl_3$); IR (KBr disk) ν_{max} = 3450, 2930, 1650, 1640, 1510, 1440, 1280, 1060 cm^{-1}; ^{1}H NMR δ 6.70 (2H, s), 6.03 (1H, ddd, *J* = 10.1, 5.1 and 1.4 Hz), 5.49 (1H, d, *J* = 10.1 Hz), 4.74 (1H, dd, *J* = 2.0 and 1.7 Hz), 4.47 and 4.35 (each 1H, 2d, *J* = 16.1 Hz) 4.22 – 4.09 (1H, m), 3.85 and 3.02 (each 3H, 2s), 2.82 and 2.75 (each 1H, 2d, *J* = 13.7 Hz), 2.68 (1H, dddd, *J* = 15.8, 3.9, 1.7 and 1.4 Hz), 2.48 (1H, d, *J* = 11.5 Hz), 2.12 (1H, ddd, *J* =

15.8 Hz, 5.4 and 2.0 Hz); ^{13}C NMR δ 170.9, 146.6, 144.8, 132.1, 128.3 (2C), 125.1, 120.0, 111.9, 88.3, 61.5, 56.1, 52.0, 43.3, 41.6, 35.9, 29.2; LRMS (EI) *m/z* 302 [(M+H)$^+$, 9%], 301 (M$^+$, 100), 283 (24), 230 (21), 224 (23), 211 (21), 181 (19), 165 (25), 115 (36), 91 (22), 77 (24); HRMS (EI) *m/z* calcd for $C_{17}H_{19}NO_4$ (M$^+$) 301.1314, found 301.1317. Anal. Calcd for $C_{17}H_{19}NO_4 \cdot 1/2H_2O$: C, 65.79; H, 6.50; N, 4.51%. Found: C, 65.46; H, 6.37; N, 4.50%.

The similar treatment of compound **15** (3.5 mg, 0.0087 mmol) also provided **2** (1.8 mg, 67%).

(+)-Galanthamine [(+)-1]. To a solution of **2** (9.4 mg, 0.031 mmol) in THF (1.5 mL) under Ar at 0 ºC was added $LiAlH_4$ (2.0 M solution in THF, 0.062 mL, 0.124 mmol) and the mixture was stirred at reflux temperature for 3 h. The reaction mixture was quenched with 3 mol/L aqueous NaOH solution at 0 ºC and the products were extracted with CH_2Cl_2. The extract was washed with brine and then dried over sodium carbonate. The organic solvent was concentrated to give a residue, which was purified by column chromatography (0.5 g, MeOH/$CHCl_3$ = 1/20) to afford (+)-**1** (7.9 mg, 88%) as a crystalline residue: mp 124–125 ºC (lit.,[1c] mp 125–126 °C); $[\alpha]_D^{23}$ +112 (*c* 0.50, EtOH); IR (KBr disk) ν_{max} = 3360, 2920, 1620, 1590, 1510, 1440, 1280, 1050 cm^{-1}; ^{1}H NMR δ 6.66 (1H, d, *J* = 8.3 Hz), 6.62 (1H, d, *J* = 8.3 Hz), 6.06 (1H, dd, *J* = 10.3 and 1.2 Hz), 6.00 (1H, ddd, *J* = 10.3, 4.9 and 1.3 Hz), 4.61 (1H, bs), 4.14 (1H, dd, *J* = 4.9 and 4.9 Hz), 4.08 (1H, d, *J* = 15.1 Hz), 3.83 (3H, s), 3.68 (1H, d, *J* = 15.1 Hz), 3.26 (1H, ddd, *J* = 14.6, 13.0 and 1.7 Hz), 3.05 (1H, ddd, *J* = 14.6, 3.9 and 3.2 Hz), 2.68 (1H, dddd, *J* = 15.6, 3.2, 1.5 and 1.3 Hz), 2.40 (3H, s), 2.08 (1H, ddd, *J* = 13.7, 13.0 and 3.2 Hz), 2.00 (1H, ddd, *J* = 15.6, 4.9 and 2.4 Hz), 1.57 (1H, ddd, *J* = 13.7, 3.9 and 1.7 Hz); ^{13}C NMR δ 145.8, 144.2, 133.0, 128.5, 127.7, 126.7, 122.2, 111.2, 88.7, 62.0, 60.4, 55.9, 53.7, 48.1, 41.8, 33.6, 29.9; LRMS (EI) *m/z* 288 ((M+H)$^+$, 18%), 287 (M$^+$, 100), 286 (84), 269 (14), 230 (20), 174 (19); HRMS (EI) *m/z* calcd for $C_{17}H_{19}NO_4$ (M$^+$) 287.1521, found 287.1521.

Synthesis of (–)-Galanthamine [(–)-1] from (–)-5. Starting from (–)-**5**,[12] (–)-galanthamine [(–)-**1**] was synthesized by the same procedure as described for the preparation of (+)-**1** from (+)-**5**. *ent*-**7a**: $[\alpha]_D^{21}$ –4.6 (*c* 1.40, $CHCl_3$). *ent*-**7b**: $[\alpha]_D^{21}$ –116 (*c* 1.16, $CHCl_3$). *ent*-**8**: $[\alpha]_D^{24}$ +120 (*c* 1.12, $CHCl_3$). *ent*-**4**: $[\alpha]_D^{24}$ +84 (*c* 1.28, $CHCl_3$). *ent*-**3a**: $[\alpha]_D^{24}$ +8.0 (*c* 0.76, $CHCl_3$). *ent*-**9**: $[\alpha]_D^{24}$ –27 (*c* 0.92, $CHCl_3$). *ent*-**11**: $[\alpha]_D^{24}$ –48 (*c* 0.76, $CHCl_3$). *ent*-**14**: $[\alpha]_D^{24}$ +21 (*c* 1.11, $CHCl_3$). *ent*-**15**: $[\alpha]_D^{24}$ +3.2 (*c* 1.69, $CHCl_3$). *ent*-**16**: $[\alpha]_D^{26}$ +11 (*c* 1.11, $CHCl_3$). *ent*-**2**: $[\alpha]_D^{24}$ –110 (*c* 0.45, $CHCl_3$). (–)-**1**: $[\alpha]_D^{23}$ –112 (*c* 0.19, EtOH) {lit.,[1c] $[\alpha]_D^{20}$ –118.8 (*c* 1.378, EtOH)}.

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