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Tetrahedron
Tetrahedron 63 (2007) 6977–6989

Total synthesis of Amaryllidaceae alkaloids, (+)-vittatine and (+)-haemanthamine, starting from D-glucose

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Received 5 April 2007; revised 10 May 2007; accepted 10 May 2007
Available online 17 May 2007

This paper is dedicated to the memory of the late Professor Yoshihiko Ito, who passed away on December 23, 2006

Abstract—The stereoselective total synthesis of (+)-vittatine **1** and (+)-haemanthamine **2** starting from D-glucose is described. The cyclohexene ring in **1** was prepared in an optically active form from D-glucose using Ferrier's carbocyclization reaction, and the critical quaternary carbon was stereoselectively generated via chirality transfer by the Claisen rearrangement of cyclohexenol **6**. The hexahydroindole skeleton was effectively constructed by the intramolecular aminomercuration–demercuration of **14**, followed by Chugaev reaction to provide **16**. Finally, Pictet–Spengler reaction completed the first chiral synthesis of (+)-vittatine **1**. On the other hand, the α-hydroxylation of the ester **5** stereoselectively proceeded to give α-hydroxy ester **19**, to which was introduced an amino function to provide **4**. A similar transformation of **4**, as employed in the synthesis of vittatine, furnished (+)-haemanthamine **2**.

1. Introduction

The alkaloids of the Amaryllidaceae family are composed of over 100 structurally interesting bases and have stimulated organic chemists due to their architectural diversity as well as their biological activities.[1] Among them, the crinine-type alkaloids, which have the 5,10b-ethanophenanthridine skeleton as the core structure, represented by haemanthidine, pretazettine, and tazettine, have received considerable attention, since they have been reported to possess antiviral, anticancer, and other interesting activities (Fig. 1).[2] Although a number of synthetic approaches for the crinine-type alkaloids have been developed,[3,4] reports of the chiral syntheses of these natural products are rather limited.[5] Since these alkaloids are expected to show a wide range of biological activities, it is important to establish a chiral and effective synthetic route to these compounds from readily available materials. In this paper, we report the first chiral synthesis of (+)-vittatine[6] **1** and (+)-haemanthamine[7] **2** starting from D-glucose,[8] in which the quaternary carbons in **1** and **2** were stereoselectively generated by Claisen rearrangement, and the hexahydroindole skeleton was effectively constructed by intramolecular aminomercuration–demercuration, followed by Chugaev reaction.

2. Results and discussion

2.1. Retrosynthesis

Our retrosynthetic analysis of (+)-vittatine **1** suggested that hexahydroindole **3** would be a promising intermediate for the total synthesis (Fig. 2). The bicyclic skeleton in **3** was expected to be constructed by the intramolecular aminomercuration[9] of cyclohexene derivative **4**, followed by introduction of the carbon–carbon double bond, exploiting the hydroxy group at C-1 (vittatine numbering). The precursor of **4**, ester **5**, was planned to be stereoselectively prepared by Claisen rearrangement[10] of cyclohexenol derivative **6**. The cyclohexenol **6**, in turn, was envisioned to be synthesized from cyclohexenone **7**, which is the known compound[11] prepared in optically pure form starting from D-glucose utilizing Ferrier's carbocyclization[12] as the key transformation.

On the other hand, if one could introduce a hydroxy group into the α-position of an ester function (C-11, vittatine numbering) in **5** in a stereoselective manner, the resulting product, hydroxyester would be converted into **9**, which is expected to yield haemanthamine **2** via hexahydroindole **8**.

Keywords: Amaryllidaceae alkaloids; Vittatine; Haemanthamine; Claisen rearrangement; Aminomercuration; Chugaev reaction.
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doi:10.1016/j.tet.2007.05.041

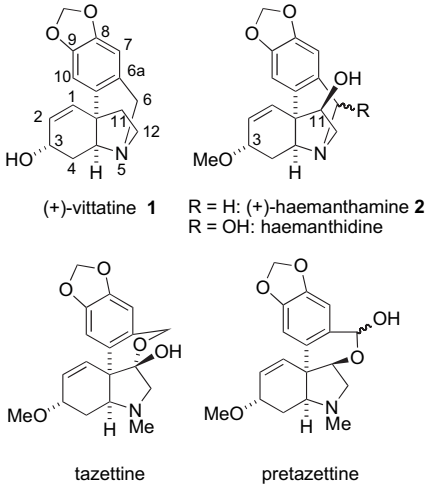
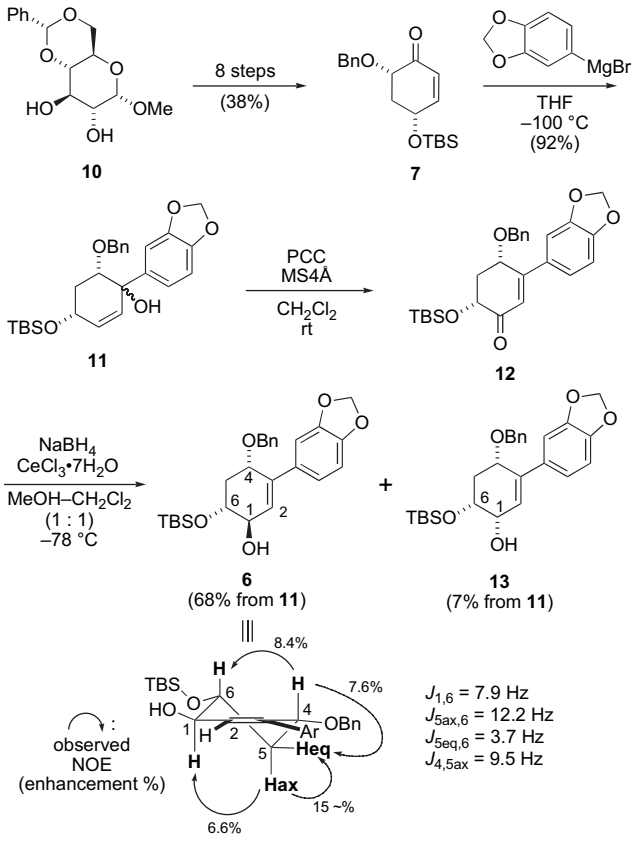


Figure 1. Structures of some representative crinine-type alkaloids.

2.2. Preparation of the common intermediate, ester 5

The synthesis of ester **5** commenced from the known (4*R*,6*S*)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone[11] **7**, prepared from commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **10** utilizing the catalytic Ferrier's carbocyclization[12c] as the key transformation in a total of eight steps with a 38% overall yield (Scheme 1). The reaction of **7** with 3,4-(methylenedioxy)phenylmagnesium bromide at −100 °C gave 1,2-adduct **11** as a diastereomeric mixture (ca. 3:1) in a 92% yield. The oxidation of **11** with PCC in the presence of molecular sieves, 4 Å (MS4Å) afforded cyclohexenone **12**, which was reduced under the conditions of Luche[13] at −78 °C to give cyclohexenol **6** and its epimeric alcohol **13** in 68 and 7% isolated yields from **11**, respectively. The observed coupling constants in **6** ($J_{1,6}$=7.9 Hz) and **13** ($J_{1,6}$=3.7 Hz) as well as the NOE experiments in **6** supported their assigned configurations.



Scheme 1.

With the chiral cyclohexenol **6** in hand, the crucial Claisen rearrangement was then investigated (Scheme 2). The conventional Johnson–Claisen rearrangement[10c,14] of **6** (triethyl orthoacetate and MS4Å in the presence of a catalytic amount of propionic acid in a sealed tube at 130 °C) successfully afforded the rearranged product **5** in a 60% yield along with the recovered starting material **6** (10% yield). However, the reproducibility of the reaction was found to be rather poor, and the yields of the rearranged product **6** sometimes dropped to 35–50% when the reaction was carried out on a larger scale (over 1 mmol scale). After some attempts, it was found that the employment of 2-nitorophenol as the acid catalyst[15] produced an improvement in both the

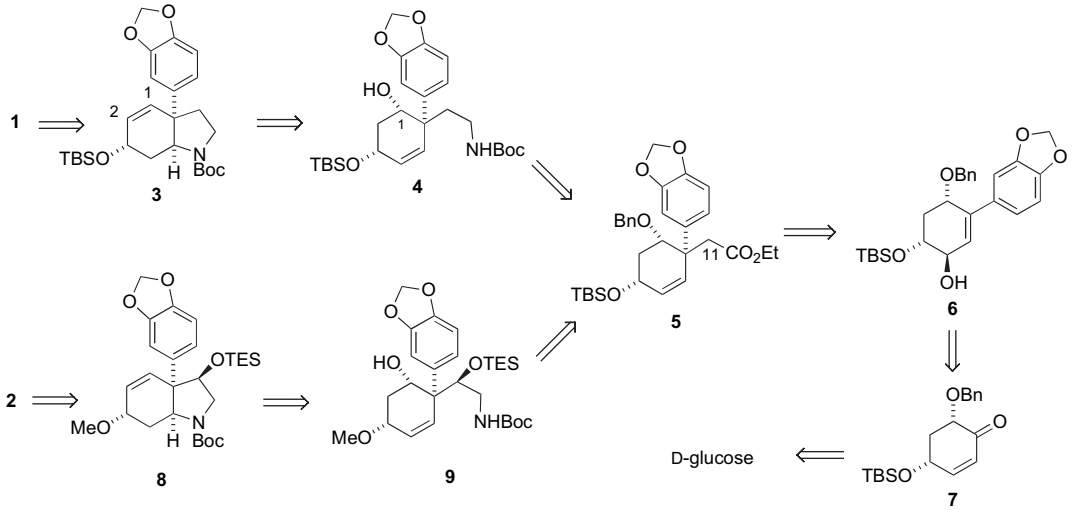
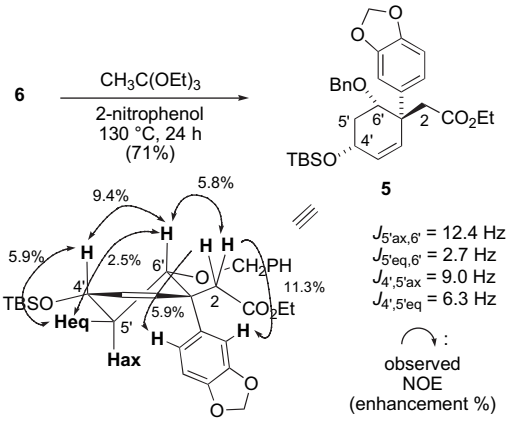


Figure 2. Retrosynthetic analysis of (+)-vittatine **1** and (+)-haemanthamine **2**. TBS=–SiMe$_2$(*t*-Bu), Boc=–C(O)O(*t*-Bu), TES=–SiEt$_3$, and Bn=–CH$_2$Ph.

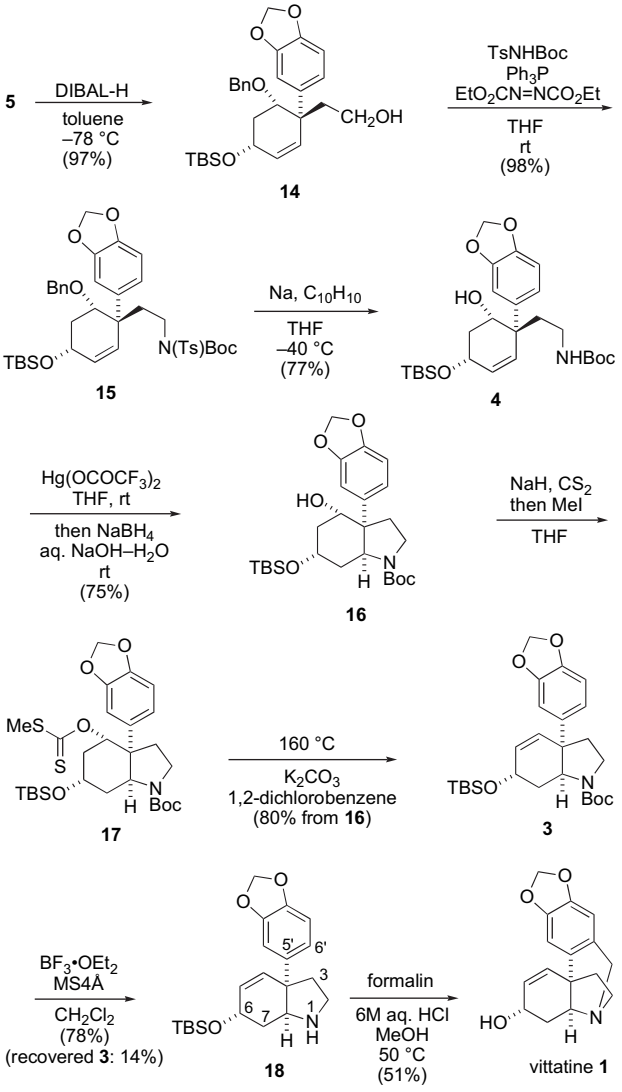
chemical yields and reproducibilities and gave **5** in a 71% yield. The use of 2,4-dinitorophenol,[16] meanwhile resulted in the decomposition of the substrate. The observed coupling constants and NOEs in **5** clearly supported the assigned structure; especially the observed NOE between a methylene group at C-2 and H-6′ clearly revealed that the newly formed quaternary carbon in **5** has an (*S*)-configuration.



Scheme 2.

2.3. Total synthesis of (+)-vittatine

The reduction of the ester function in **5** with DIBAL-H cleanly gave primary alcohol **14** in a 97% yield (Scheme 3), to which was introduced an amino functionality by Mitsunobu amination with NH(Ts)(Boc)[17] as a nucleophile to afford **15** in a 98% yield. The treatment of **15** with Na-naphthalene[18] in THF at −40 °C removed *N*-Ts as well as the *O*-benzyl groups to give **4** in a 77% yield. The construction of the perhydroindole skeleton was successfully achieved by the intramolecular aminomercuration–demercuration of **4** to provide **16** in a 75% yield. Interestingly, the presence of the Boc protecting group was essential for the cyclization; when this reaction was carried out with the corresponding primary amine (with no Boc group), no cyclized product was obtained. Next, the introduction of the requisite carbon–carbon double bond between C-1 and C-2 was investigated. Initially, the hydroxy group in **16** was converted into the sulfonyl esters and the resulting *O*-sulfonyl derivatives (OMs and OTs) were treated with base (DBU or *t*-BuOK). However, under these reaction conditions, only the decomposition of the substrates was observed. To our delight, Chugaev reaction was found to give good results. Thus, the hydroxy group in **16** was transformed into the xanthate ester to afford **17** (97% yield), and this was heated at 160 °C in the presence of potassium carbonate to provide **3** in an 80% yield from **16**. Deprotection of the *N*-Boc group by the action of $BF_3 \cdot OEt_2$ gave **18** (78% yield, starting material **3** was recovered in 14% yield). Finally, the exposure of **18** to the Pictet–Spengler reaction conditions[3b] generated the ethano-bridge between N(1) and C(6′), and induced the deprotection of the *O*-TBS group to furnish (+)-vittatine **1** in a 51% yield. The ^{1}H NMR data were completely identical to those for (−)-crinine [enantiomer of (+)-vittatine] reported by Pearson,[3c] and the physical properties of **1** showed good agreement {mp 205–207 °C; $[\alpha]_D^{22}$ +28 (*c* 0.20, $CHCl_3$)} with those reported for natural (+)-vittatine[6b] {mp 207–208 °C; $[\alpha]_D^{25}$ +26 (*c* 0.50, $CHCl_3$)}.



Scheme 3. Ts=–$SO_2C_6H_4$(*p*-Me).

2.4. Total synthesis of (+)-haemanthamine

Having established the new synthetic pathways to (+)-vittatine **1** from D-glucose, we next turned our attention to the synthesis of (+)-haemanthamine **2**. For this purpose, the introduction of a hydroxy function at C-2 (C-11 in vittatine numbering) of the ester **5** was first investigated. The selected results of the hydroxylation of an enolate derived from **5** with various oxidants[19] are listed in Table 1, which showed that (i) the generation of the ester enolates required a higher (0 °C) temperature, and LiHMDS was the base of choice (entries 1–4), (ii) reaction of the lithium enolate with the (+)-Davis reagent[19b] at 0 °C gave good results and provided the desired **19** in moderate yield (entry 6), and (iii) regardless of types of oxidants, (*R*)-alcohol **19** was obtained as the major product (entries 6, 8, and 9). As a result, the desired product **19** was obtained in a 68% yield based on the recovered starting material, under the conditions noted in entry 6. Although the configuration at C-2′ could not be determined at this stage, the successful

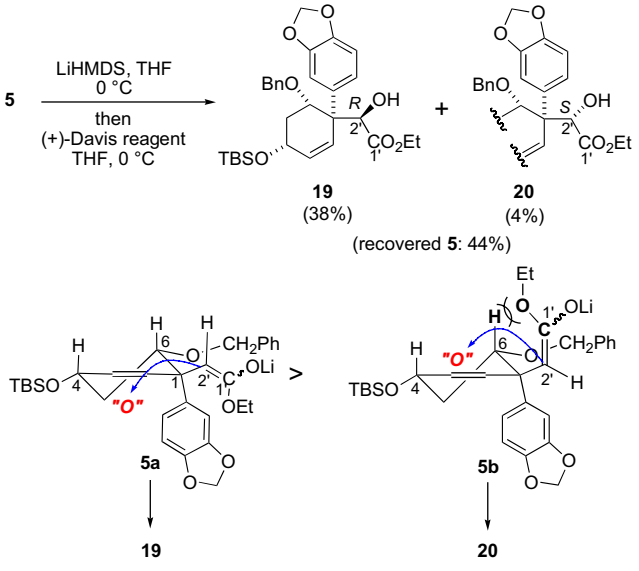
Table 1. Hydroxylation of the enolate of **5**[a]

Entry	Base	Temp 1 (°C)	Oxidant	Temp 2 (°C)	Yield[b] (%)		
					19	**20**	**5**
1	LiHMDS	−78	(+)-DR[c]	−78	0	0	95
2	LiHMDS	0	(+)-DR	−78	16[d]		67
3	NaHMDS	0	(+)-DR	−78	11[d]		65
4	KHMDS	0	(+)-DR	−78	7[d]		84
5	LiHMDS	0	(+)-DR	−40	15	2	66
6	LiHMDS	0	(+)-DR	0	38	4	44
7	NaHMDS	0	(+)-DR	0	12	7	54
8	LiHMDS	0	(−)-DR[e]	0	27	5	52
9	LiHMDS	0	O_2[f]	0	38	9	0

[a] Reaction conditions: compound **5** (1.0 equiv) in THF was treated with base (3.0 equiv) at the temperature shown in Temp 1 for 45 min. To this solution was added a solution of oxidant (1.5 equiv) in THF dropwise at the temperature shown in Temp 2, and the mixture was stirred at Temp 2 for 45 min.
[b] Isolated yield after chromatographic purification.
[c] (+)-Davis reagent: [(1*S*)-(10-camphorsulfonyl)oxaziridine].
[d] Combined yields of **19** and **20**. Compound **19** was the major product but the ratio of **19** to **20** was not determined.
[e] (−)-Davis reagent: [(1*R*)-(10-camphorsulfonyl)oxaziridine].
[f] O_2 gas (excess amount) was introduced to the reaction mixture containing $P(OEt)_3$ (2.0 equiv).

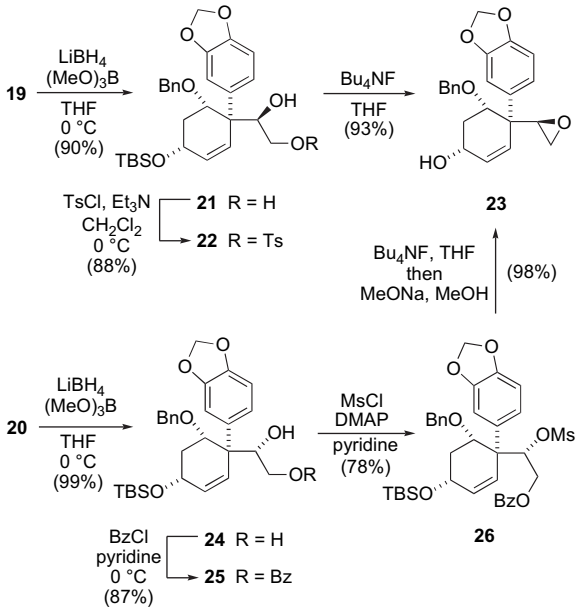
conversion of **19** into haemanthamine **2** (vide infra) unambiguously confirmed the (*R*)-configuration of the newly formed hydroxy group in **19**. The stereoselective formation of (*R*)-alcohol **19** might be accounted for by the steric factor.

In the two plausible transition structures (**5a** and **5b**, Scheme 4) where three of four substituents on a cyclohexene ring are in the equatorial positions, electrophilic attack of the oxidant would occur from the upper face (foreside) of the enolate to give **19** via **5a** and **20** via **5b**, since the lower side (backside) of the enolate is hindered by the benzyloxy group at C-6. In **5b**, there would be non-bonded interactions between an axial hydrogen at C-6 and the enolate oxygen attached to C-1′. Due to the sterically disfavored interactions in **5b**, the transition structure **5a** would become more favored one, thus affording **19** as the major product.



Scheme 4.

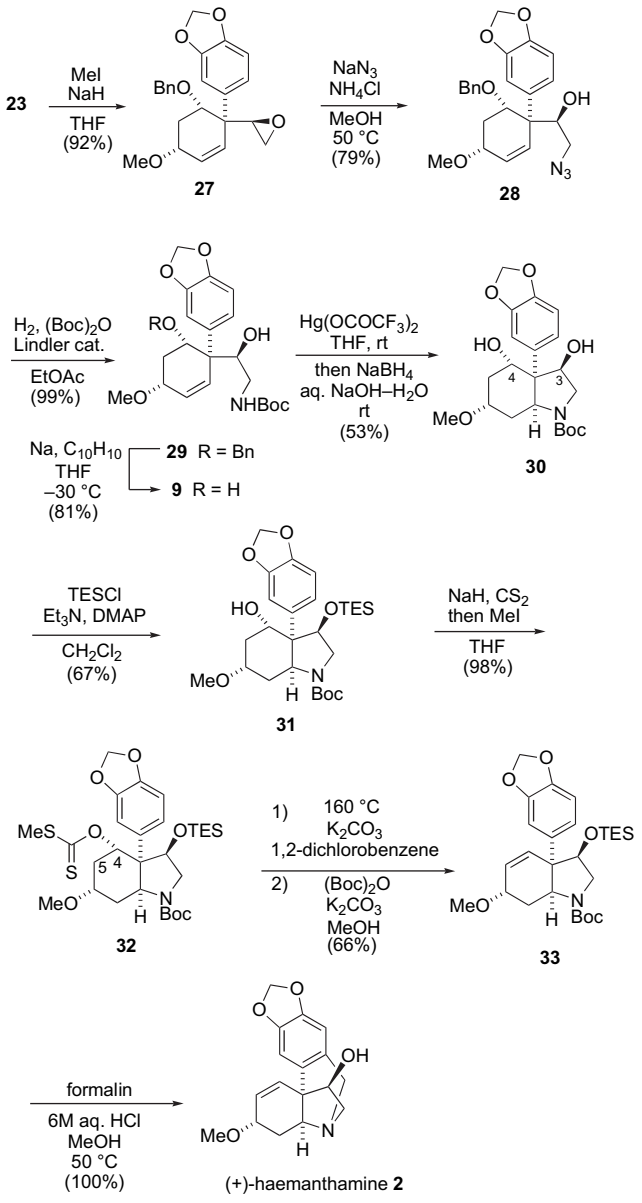
The reduction of the major hydroxy ester **19** with $LiBH_4$ in the presence of $B(OMe)_3$[20] gave diol **21** (90% yield, Scheme 5), whose primary hydroxy group was selectively tosylated to afford **22** in an 88% yield. The treatment of **22** with Bu_4NF deprotected *O*-TBS group as well as induced the intramolecular S_N2 reaction to provide epoxide **23** in a 93% yield (82% from **21**). The minor diastereomer **20** could also be converted into **23**. Reduction of the ester function in **20** and subsequent selective acylation with benzoyl chloride gave benzoate **25** (86% yield from **20**). The remaining alcohol function in **25** was mesylated to afford **26**, whose treatment with Bu_4NF, followed by treatment with MeONa cleanly afforded epoxide **23** in a 76% yield from **25**.



Scheme 5. Bz=–COPh and Ms=–SO_2Me.

With the epoxide **23** possessing the proper functionalities and stereochemistry in hand, the final transformation to **2** was explored. The hydroxy group in **23** was methylated to give **27** (92% yield, Scheme 6), which was reacted with sodium azide to afford primary azide **28** in a 79% yield. Selective hydrogenolysis of the azide function in **28** with the Lindler catalyst in the presence of Boc_2O[21] provided carbamate **29**, whose *O*-benzyl group was removed by the treatment with sodium-naphthalene to give **9** in an 80% yield from **28**. The intramolecular aminomercuration–demercuration of **9** successfully afforded perhydroindole **30** in a 53% yield. The hydroxy group at C-4 in **30** was anticipated to show a lower reactivity than that at C-3 due to the steric congestion. Indeed, the reaction of **30** with TESCl afforded 3-*O*-TES derivative **31** in a 67% isolated yield. To introduce the carbon–carbon double bond between the C-4 and C-5, Chugaev reaction was attempted. Thus, the same reaction sequence as employed for the synthesis of vittatine (xanthate ester formation followed by pyrolysis) was applied to **31** to give, after treatment with Boc_2O and K_2CO_3, hexahydroindole **33** in a 66% yield from **31**. During the pyrolysis of **32**, unexpected deprotection of the *N*-Boc group, which has not been observed in Chugaev reaction of **17**, took place. Protection of a secondary amine group with the Boc group was required for the purification of **33**, since it was difficult

to isolate the amine in pure form from the polar by-products. Finally, Pictet–Spengler reaction of **33** cleanly provided (+)-haemanthamine **2** in a quantitative yield. The ^{1}H and ^{13}C NMR data of the synthetic **2** were fully identical to those of natural (+)-haemanthamine, that had been kindly provided by Professor Takayama, and the physical properties of **2** {mp 199–202 °C; $[\alpha]_D^{25}$ +41 (*c* 0.62, $CHCl_3$)} showed good agreement with those of natural (+)-haemanthamine {mp 200–202 °C; $[\alpha]_D^{24}$ +42 (*c* 0.34, $CHCl_3$)}.[22]



Scheme 6.

3. Conclusion

In this study, a new synthesis route to (+)-vittatine and (+)-haemanthamine starting from D-glucose was established. This synthesis demonstrated that the methodology involving Claisen rearrangement on the chiral cyclohexenol derived from D-glucose by way of the catalytic Ferrier′s carbocyclization is effective for the stereoselective generation of quaternary carbons, and aminomercuration–demercuration followed by Chugaev reaction is a useful reaction sequence for the construction of hexahydroindole skeletons, that are frequently found in Amaryllidaceae alkaloids.

4. Experimental

4.1. 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 and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared (IR) spectra were measured with a JASCO FT/IR-200 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a JEOL Lambda 300 or on a Varian MVX-300 spectrometers for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts are reported as δ values in parts per million. Abbreviations used are: br (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 JEOL Lambda 300 spectrometer for solutions in $CDCl_3$, unless otherwise noted. Chemical shifts are reported as δ values in parts per milion. Mass spectra are measured by a JEOL GC Mate spectrometer with EI (70 eV) or FAB mode. Organic extracts were dried over solid 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) for purification. Preparative TLC (PLC) was performed with Merck PLC plate (Kieselgel 60 F_{254}, 0.5 mm thickness).

4.1.1. Total synthesis of (+)-vittatine.

4.1.1.1. (1*S*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-ol and its (1*R*)-isomer (11). To a solution of (4*R*,6*S*)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone **7**[11] (6.53 g, 19.6 mmol) in THF (320 mL) was slowly added 0.328 mol L^{-1} solution of 3,4-(methylenedioxy)phenylmagnesium bromide in THF (177 mL, 58.1 mmol) at −100 °C under Ar. After being stirred at −100 °C for 1 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution at −100 °C. The mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 200 g, EtOAc/hexanes=1/7 as eluent) to afford first, minor isomer of **11** (2.03 g, 23%) as a colorless syrup: $[\alpha]_D^{23}$ −75 (*c* 0.81, $CHCl_3$); IR (neat) 3530 cm^{-1}; ^{1}H NMR δ 0.12 (6H, s), 0.93 (9H, s), 1.94–2.15 (2H, m), 3.29 (1H, s), 3.58 (1H, dd, *J*=3.4 and 11.0 Hz), 4.28 (1H, d, *J*=11.7 Hz), 4.36 (1H, m), 4.44 (1H, d, *J*=11.7 Hz), 5.64 (1H, dd, *J*=10.0 and 2.0 Hz), 5.87 (1H, br d, *J*=10.0 Hz), 5.97 (2H, s), 6.78 (1H, dd, *J*=0.7 and 7.6 Hz), 6.88 (1H, dd, *J*=2.0 and 7.6 Hz), 6.90 (1H, s), and 7.09–7.30 (5H, m); ^{13}C NMR (75 MHz) δ −4.65, −4.56, 18.2, 25.8, 33.8, 67.1, 71.8, 78.0, 79.3, 101.0, 106.7, 107.7, 119.0, 127.7, 127.8, 128.2, 131.0, 134.2, 137.7, 139.7, 146.5, and 147.5; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{35}O_5Si$ $(M+H)^+$ 455.2254, found 455.2242.

Further elution gave a major isomer of **11** as a colorless syrup (6.10 g, 68%): $[\alpha]_D^{23}$ +144 (*c* 0.23, $CHCl_3$); IR (neat) 3430 cm^{-1}; ^1H NMR (300 MHz) δ 0.00 and 0.02 (each 3H, 2s), 0.82 (9H, s), 1.51 (1H, ddd, *J*=9.5, 12.7, and 12.9 Hz), 2.00 (1H, m), 2.11 (1H, br s), 3.57 (1H, dd, *J*=3.2 and 12.9 Hz), 4.31 (1H, m), 4.68 (2H, s), 5.44 (1H, dd, *J*=1.7 and 10.0 Hz), 5.73 (1H, d, *J*=10.0 Hz), 5.88 (2H, s), 6.72 (1H, d, *J*=8.3 Hz), 6.93 (1H, dd, *J*=1.7 and 8.3 Hz), 7.06 (1H, d, *J*=1.7 Hz), and 7.18–7.28 (5H, m); ^{13}C NMR δ −4.65, −4.56, 18.1, 25.8, 36.0, 68.0, 72.4, 78.0, 80.2, 101.0, 107.2, 109.0, 121.7, 127.52, 127.55, 128.4, 131.6, 132.7, 134.9, 138.7, 146.9, and 147.2; HRMS (FAB) *m/z* calcd for $C_{26}H_{35}O_5Si$ $(M+H)^+$, 455.2254, found 455.2269. Anal. Calcd for $C_{26}H_{34}O_5Si$: C, 68.69; H, 7.54. Found: C, 68.47; H, 7.42.

4.1.1.2. (4*S*,6*R*)-3-(Benzo[1,3]dioxol-5-yl)-4-benzyloxy-6-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-one (12). To a solution of the major isomer of **11** (1.93 g, 4.24 mmol) in CH_2Cl_2 (150 mL) were added pyridinium chlorochromate (3.57 g, 16.5 mmol) and MS4Å (7.5 g), and the reaction mixture was stirred at room temperature for 30 min. Removal of the solvent gave a residue, which was suspended in Et_2O and the insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated to give crude ketone **12** (1.93 g), which was used for next reaction without further purification. The similar treatment of the minor isomer of **11** (0.63 g, 1.39 mmol) also afforded crude **12** (0.62 g). A small amount of **12** was purified by column chromatography (silica gel, EtOAc/hexanes=1/7 as eluent) and used as an analytical sample: mp 131.5–132.5 °C; $[\alpha]_D^{24}$ −142 (*c* 0.78, $CHCl_3$); IR (neat) 1680, 1595 cm^{-1}; ^1H NMR δ 0.08 and 0.19 (each 3H, 2s), 0.92 (9H, s), 2.29 (1H, ddd, *J*=10.2, 13.2, and 13.2 Hz), 2.71 (1H, ddd, *J*=5.1, 5.1, and 13.2 Hz), 4.25 (1H, dd, *J*=5.1 and 13.2 Hz), 4.45 (1H, d, *J*=11.2 Hz), 4.49 (1H, d, *J*=11.2 Hz), 4.91 (1H, br dd, *J*=5.1 and 10.2 Hz), 5.98 (2H, s), 6.15 (1H, br s), 6.79 (1H, d, *J*=8.0 Hz), 6.88 (1H, s), 6.94 (1H, d, *J*=8.0 Hz), 7.13 (2H, m), and 7.23–7.29 (3H, m); ^{13}C NMR δ −5.41, −4.38, 18.5, 25.8, 38.1, 69.5, 72.5, 72.9, 101.4, 107.7, 108.2, 121.7, 125.5, 127.9, 128.1, 128.4, 130.3, 137.1, 147.8, 148.8, 160.1, and 197.6; HRMS (FAB) *m/z* calcd for $C_{26}H_{33}O_5Si$ $(M+H)^+$, 453.2097, found 453.2091. Anal. Calcd for $C_{26}H_{32}O_5Si$: C, 68.99; H, 7.13. Found: C, 68.77; H, 7.10.

4.1.1.3. (1*R*,4*S*,6*R*)-3-(Benzo[1,3]dioxol-5-yl)-4-benzyloxy-6-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-ol (6) and its (1*S*)-isomer (13). To a mixture of crude ketone **12** (2.55 g, 5.63 mmol) in MeOH (50 mL) and CH_2Cl_2 (75 mL) were added $CeCl_3 \cdot 7H_2O$ (3.07 g, 8.24 mmol) and $NaBH_4$ (218 mg, 5.76 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min. The reaction mixture was diluted with H_2O and products were extracted with EtOAc. The organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 120 g, EtOAc/hexanes=1/10 as eluent) to afford **6** (1.87 g, 68% overall yield from **11**) as a colorless syrup: $[\alpha]_D^{19}$ −65 (*c* 0.67, $CHCl_3$); IR (neat) 3440, 1505 cm^{-1}; ^1H NMR δ 0.14 (6H, s), 0.94 (9H, s), 1.89 (1H, ddd, *J*=9.5, 12.2, and 12.2 Hz), 2.29 (1H, br d, *J*=3.4 Hz), 2.39 (1H, ddd, *J*=3.7, 6.1, and 12.2 Hz), 3.64 (1H, ddd, *J*=3.7, 7.9, and 12.2 Hz), 4.28 (1H, m), 4.42 (2H, s), 4.70 (1H, m), 5.84 (1H, br dd, *J*=1.7 and 1.7 Hz), 5.96 (2H, s), 6.74–6.86 (3H, m), 7.10–7.16 (2H, m), and 7.20–7.30 (3H, m); ^{13}C NMR δ −4.6, −4.4, 18.1, 25.8, 36.3, 69.1, 73.3, 73.9, 74.2, 100.9, 107.4, 107.9, 120.4, 127.6, 128.0, 128.2, 128.5, 132.8, 137.9, 140.0, 146.9, and 147.4; HRMS (FAB) *m/z* calcd for $C_{26}H_{35}O_5Si$ $(M+H)^+$, 455.2254, found 455.2259; HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_5Si$, M^+, 454.2176, found 454.2177.

Further elution gave **13** (0.17 g, 7% yield from **11**) as a colorless syrup: $[\alpha]_D^{19}$ −42 (*c* 0.35, $CHCl_3$); IR (neat) 3460–3550, 1505 cm^{-1}; ^1H NMR δ 0.13 and 0.14 (each 3H, 2s), 0.93 (9H, s), 2.08 (1H, m), 2.25 (1H, ddd, *J*=9.8, 11.9, and 11.9 Hz), 2.72 (1H, br d, *J*=1.2 Hz), 3.82 (1H, ddd, *J*=3.7, 3.7, and 11.9 Hz), 4.14 (1H, m), 4.33 and 4.42 (each 1H, 2d, *J*=11.3 Hz), 4.63 (1H, ddd, *J*=1.7, 6.1, and 9.8 Hz), 5.96 (2H, s), 6.05 (1H, dd, *J*=1.7 and 5.9 Hz), 6.77 (1H, d, *J*=8.5 Hz), 6.87–6.91 (2H, m), 7.05–7.09 (2H, m), and 7.20–7.30 (3H, m); ^{13}C NMR δ −4.8, −4.5, 18.1, 25.8, 30.8, 66.3, 68.3, 68.6, 73.1, 101.0, 107.8, 108.0, 120.7, 125.7, 127.5, 127.9, 128.2, 133.0, 138.1, 144.2, 147.1, and 147.4; HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_5Si$, M^+, 454.2176, found 454.2178.

4.1.1.4. [(1*S*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-acetic acid ethyl ester (5). To a solution of **6** (350 mg, 0.768 mmol) in triethyl orthoacetate (48 mL) were added 2-nitorophenol (90.8 mg, 0.656 mmol) and MS4Å (150 mg) under Ar at room temperature. The mixture was stirred at 130 °C for 24 h in a sealed tube. The reaction mixture was filtrated through a pad of Celite and the filtrate was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 20 g, toluene/hexanes=1/1 as eluent) to afford **5** (289.6 mg, 71%) as a colorless syrup: $[\alpha]_D^{22}$ −45 (*c* 0.89, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR δ −0.03 and 0.00 (each 3H, 2s), 0.81 (9H, s), 1.06 (3H, t, *J*=7.0 Hz), 1.34 (1H, ddd, *J*=9.0, 12.4, and 12.4 Hz), 1.92 (1H, ddd, *J*=2.7, 6.3, and 12.4 Hz), 2.74 and 2.81 (each 1H, 2d, *J*=14.4 Hz), 3.64 (1H, dd, *J*=2.7 and 12.4 Hz), 3.91 (2H, q, *J*=7.0 Hz), 4.25 (1H, dd, *J*=6.3 and 9.0 Hz), 4.42 and 4.60 (each 1H, 2d, *J*=11.7 Hz), 5.63 and 5.78 (each 1H, 2d, *J*=10.2 Hz), 5.83 (2H, s), 6.66 (1H, d, *J*=8.0 Hz), 6.84 (1H, dd, *J*=1.7 and 8.0 Hz), 6.94 (1H, d, *J*=1.7 Hz), and 7.15–7.30 (5H, m); ^{13}C NMR δ −4.62, −4.56, 14.1, 18.1, 25.8, 33.1, 42.1, 47.4, 60.0, 68.4, 71.3, 77.5, 100.8, 107.0, 110.3, 123.2, 127.5, 127.6, 128.3, 131.1, 132.8, 134.2, 138.6, 146.1, 146.9, and 171.2; HRMS (FAB) *m/z* calcd for $C_{30}H_{41}O_6Si$ $(M+H)^+$, 525.2672, found 525.2672. Anal. Calcd for $C_{30}H_{40}O_6Si$: C, 68.67; H, 7.68. Found: C, 68.63; H, 7.82.

4.1.1.5. 2-[(1*S*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-ethanol (14). To a solution of **5** (578 mg, 1.10 mmol) in toluene (29 mL) was added diisobutylaluminum hydride (1.0 mol L^{-1} solution in toluene, 2.40 mL, 2.40 mmol) at 0 °C, and the mixture was stirred at 0 °C for 40 min. The mixture was quenched by the addition of H_2O and extracted

with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 15 g, EtOAc/hexanes=1/6 as eluent) to afford **14** (515 mg, 97%) as a colorless syrup: $[\alpha]_D^{22}$ −23 (*c* 0.82, $CHCl_3$); IR (neat) 3375 cm^{-1}; ^1H NMR δ −0.03 and −0.01 (each 3H, 2s), 0.80 (9H, s), 1.31 (1H, dd, *J*=12.5 and 12.5 Hz), 1.92 (2H, m), 2.10 (1H, ddd, *J*=6.1, 8.0, and 14.0 Hz), 3.30–3.44 (3H, m), 4.22 (1H, m), 4.33 and 4.59 (each 1H, d, *J*=11.9 Hz), 5.51 (1H, dd, *J*=1.5 and 10.0 Hz), 5.70 (1H, d, *J*=10.0 Hz), 5.84 (2H, s), 6.65 (1H, d, *J*=7.5 Hz), 6.88 (1H, dd, *J*=1.5 and 7.5 Hz), 6.96 (1H, d, *J*=1.5 Hz), 7.15–7.30 (5H, m); ^{13}C NMR δ −4.57, −4.48, 18.2, 25.9, 33.0, 40.6, 47.6, 59.6, 68.6, 71.1, 77.9, 100.8, 107.0, 110.5, 123.4, 127.6, 127.9, 128.4, 131.7, 132.7, 134.9, 138.6, 146.1, and 147.0; HRMS (FAB) *m/z* calcd for $C_{28}H_{39}O_5Si$ $(M+H)^+$, 483.2567, found 483.2568.

4.1.1.6. *tert*-Butyl 2-[(1*S*,4*R*,6*S*)-1-(benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]ethyl-(4-toluenesulfonyl)carbamate (15). To a solution of **14** (806 mg, 1.67 mmol) in THF (20 mL) under Ar were added *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (681 mg, 2.5 mmol), diethyl azodicarboxylate (527 mg, 3.35 mmol), and triphenyl phosphine (1.32 g, 5.02 mmol) at room temperature. After being stirred for 1 h at room temperature, the reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 40 g, EtOAc/hexanes=1/7 as eluent) to afford **15** (1.21 g, 98%) as a colorless syrup: $[\alpha]_D^{24}$ −27 (*c* 0.85, $CHCl_3$); IR (neat) 1730, 1600 cm^{-1}; ^1H NMR δ 0.08 and 0.10 (each 3H, 2s), 0.91 (9H, s), 1.34 (9H, s), 1.44 (1H, ddd, *J*=9.3, 12.2, and 12.2 Hz), 2.03 (1H, ddd, *J*=2.0, 6.1, and 12.2 Hz), 2.19 (1H, ddd, *J*=4.2, 11.9, and 11.9 Hz), 2.41 (3H, s), 2.55 (1H, ddd, *J*=6.8, 11.9, and 11.9 Hz), 3.53 (1H, dd, *J*=2.0 and 12.2 Hz), 3.64–3.86 (2H, m), 4.35 (1H, dd, *J*=6.1 and 9.3 Hz), 4.58 and 4.71 (each 1H, 2d, *J*=11.7 Hz), 5.75 and 5.88 (each 1H, 2d, *J*=10.5 Hz), 5.92 (2H, d, *J*=2.1 Hz), 6.76 and 6.98 (each 1H, 2d, *J*=8.31 Hz), 7.12 (1H, s), 7.23–7.40 (7H, m), and 7.74 (2H, d, *J*=8.3 Hz); ^{13}C NMR δ −4.66, −4.57, 18.1, 25.8, 27.8, 33.1, 37.3, 43.5, 47.5, 68.5, 71.4, 78.1, 84.0, 100.7, 106.9, 110.6, 123.5, 127.3, 127.6, 127.7, 128.2, 129.1, 130.7, 133.0, 134.0, 137.3, 138.5, 143.9, 146.1, 147.0, and 150.7; HRMS (FAB) *m/z* calcd for $C_{40}H_{54}NO_8SSi$ $(M+H)^+$, 735.3261, found 735.3269.

4.1.1.7. *tert*-Butyl 2-[(1*S*,4*R*,6*S*)-1-(benzo[1,3]dioxol-5-yl)-4-(*tert*-butyldimethylsilyloxy)-6-hydroxy-2-cyclohexen-1-yl]ethylcarbamate (4). A mixture of Na (37.5 mg, 1.63 mmol) and naphthalene (209 mg, 1.63 mmol) in THF (1.5 mL) was sonicated with ultrasound at room temperature for 15 min and the resulting suspension was cooled to −40 °C. To this suspension was added a solution of **15** (20.0 mg, 0.027 mmol) in THF (3.5 mL) at −40 °C via a cannula. The reaction mixture was stirred at −40 °C for 1.5 h, and then quenched with H_2O. The mixture was diluted with EtOAc, washed successively with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 5 g, EtOAc/hexanes=1/4 as eluent) to afford **4** (10.3 mg, 77%) as a colorless syrup: $[\alpha]_D^{22}$ −23 (*c* 0.82, $CHCl_3$); IR (neat) 3400, 1695, 1505, 1490 cm^{-1}; ^1H NMR δ 0.07 and 0.09 (each 3H, 2s), 0.88 (9H, s), 1.42 (9H, s), 1.58 (1H, ddd, *J*=7.8, 10.5, and 12.4 Hz), 1.9–2.2 (2H, m), 2.10 (1H, m), 2.96 (1H, m), 3.08 (1H, m), 3.72 (1H, m), 4.36 (1H, m), 4.48 (1H, br s), 5.74 (1H, d, *J*=10.2 Hz), 5.88 (1H, dd, *J*=2.7 and 10.2 Hz), 5.94 (2H, d, *J*=1.7 Hz), 6.79 (1H, d, *J*=8.3 Hz), 6.86 (1H, dd, *J*=1.4 and 8.3 Hz), and 6.93 (1H, d, *J*=1.4 Hz); ^{13}C NMR δ −4.72, 18.1, 22.6, 25.8, 28.4, 36.6 (2C), 38.0, 48.0, 67.0, 71.4, 79.2, 101.0, 107.8, 109.4, 122.3, 131.1, 132.1, 134.2, 146.3, 147.7, 155.8, and 158.9; HRMS (FAB) *m/z* calcd for $C_{26}H_{42}NO_6Si$ $(M+H)^+$, 492.2781, found 492.2780. Anal. Calcd for $C_{26}H_{41}NO_6Si$: C, 63.51; H, 8.40. Found: C, 63.43; H, 8.44.

4.1.1.8. *tert*-Butyl (3a*R*,4*S*,6*S*,7a*S*)-3a-(benzo[1,3]dioxol-5-yl)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxyoctahydroindole-1-carboxylate (16). A solution of **4** (295 mg, 0.601 mmol) in THF (20 mL) was degassed by freeze–pump–thaw (FPT) cycles, which was added to a solution of $Hg(OCOCF_3)_2$ (462 mg, 1.08 mmol) in THF (10 mL, degassed by FPT cycles) via a cannula at room temperature. After being stirred at room temperature for 22 h, to the mixture was added a solution of $NaBH_4$ (45 mg, 1.20 mmol) and NaOH (48 mg, 1.20 mmol) in MeOH (2.4 mL, degassed by FPT cycles) at room temperature, and the resulting mixture was stirred for 10 min at room temperature. The insoluble material was removed by filtration through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel, 20 g, EtOAc/hexanes=1/5 as eluent) to afford **16** (221 mg, 75%) as a colorless syrup: $[\alpha]_D^{20}$ −17.5 (*c* 0.98, $CHCl_3$); IR (neat) 3490, 1695, 1410 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, at 50 °C) δ 0.12 and 0.16 (each 3H, 2s), 0.90 (9H, s), 1.40–1.60 (1H, m), 1.52 (9H, s), 1.90–2.02 (2H, m), 2.05–2.22 (2H, m), 2.28–2.46 (1H, br s), 2.99 (1H, m), 3.29 (1H, m), 3.76 (1H, br d, *J*=9.5 Hz), 4.18 (1H, br d, *J*=9.5 Hz), 4.27 (1H, br s), 4.67 (1H, m), 5.92 (2H, d, *J*=3.03 Hz), and 6.73–6.85 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz, at 50 °C) δ −5.3, −4.8, 18.0, 25.7, 28.7, 33.9 (br), 34.5, 35.9, 43.0 (br), 53.2, 54.0, 68.7, 72.1, 79.3, 100.9, 107.2, 108.0, 119.3, 138.0, 145.8, 147.9, 154.1, and 160.1; HRMS (FAB) *m/z* calcd for $C_{26}H_{42}NO_6Si$ $(M+H)^+$, 492.2781, found 492.2777.

4.1.1.9. *tert*-Butyl (3a*R*,4*S*,6*S*,7a*S*)-3a-(benzo[1,3]-dioxol-5-yl)-6-(*tert*-butyldimethylsilyloxy)-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (3). To a solution of **16** (210 mg, 0.427 mmol) in THF (9.5 mL) were added sodium hydride (60% in oil, 51.2 mg, 1.28 mmol) and imidazole (2.9 mg, 0.04 mmol) at 0 °C. After being stirred at 0 °C for 30 min, to the mixture were added carbon disulfide (0.194 mL, 3.20 mmol) and methyl iodide (0.053 mL, 0.854 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 18 g, EtOAc/hexanes=1/5 as eluent) to afford xanthate ester **17** (241 mg, 97%) as a colorless syrup: IR (neat) 1695, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, at 45 °C) δ 0.50 and 0.84 (each 3H, 2s), 0.89 (9H, s), 1.46–1.55 (1H, m), 1.49 (9H, s), 1.93–2.31 (5H,

m), 2.29 (3H, s), 3.25–3.45 (2H, m), 4.05 (1H, m), 4.50 (1H, dd, J=5.9 and 5.9 Hz), 5.93 (2H, s), 6.03 (1H, dd, J=5.6 and 5.6 Hz), 6.75 (1H, d, J=8.3 Hz), 6.83 (1H, d, J=8.3 Hz), and 6.86 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz, at 45 °C) δ −4.9 (2C), 18.18, 18.24, 25.9, 28.6, 34.1, 34.3, 35.9, 43.6, 52.0, 57.7 (br), 65.7, 79.7, 81.2, 101.0, 107.8, 108.1, 120.4, 135.4, 146.2, 147.7, 154.5, and 214.9; HRMS (FAB) m/z calcd for $C_{28}H_{44}NO_6S_2Si$ $(M+H)^+$, 582.2379, found 582.2372.

To a solution of the xanthate ester **17** (241 mg) in 1,2-dichlorobenzene (15.5 mL) was added potassium carbonate (85.8 mg, 0.414 mmol), and the mixture was stirred at 160 °C for 16 h under Ar. After cooling, the reaction mixture was diluted with EtOAc, washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 7 g, EtOAc/hexanes=1/7 as eluent) to afford **3** (160 mg, 82%) as a colorless syrup: $[\alpha]_D^{22}$ +99 (c 0.69, $CHCl_3$); IR (neat) 1695, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, at 45 °C) δ 0.09 and 0.10 (each 3H, 2s), 0.91 (9H, s), 1.40–1.55 (10H, m), 1.65 (1H, m), 1.81 (1H, br dd, J=5.1 and 11.7 Hz), 2.32 (1H, m), 3.21 (1H, m), 3.72 (1H, m), 3.93 (1H, br s), 4.28 (1H, br s), 5.48 and 5.91 (each 1H, d, J=10.2 Hz), 5.94 (2H, s), 6.76 (1H, d, J=8.0 Hz), 6.89 (1H, dd, J=1.71 and 8.0 Hz), and 6.95 (1H, d, J=1.71 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, at 45 °C) δ −4.54, 18.2, 26.0, 28.6, 32.4 (br), 36.0 (br), 45.7, 50.7 (br), 62.3, 64.1, 79.4 (br), 101.1, 107.6, 108.0, 120.2, 131.9 (br), 133.0 (br), 137.6, 146.3, and 147.9 (a carbonyl carbon of Boc group could not be detected due to broadening of the signal); HRMS (FAB) m/z calcd for $C_{26}H_{40}NO_5Si$ $(M+H)^+$, 474.2676, found 474.2667. Anal. Calcd for $C_{26}H_{39}NO_5Si$: C, 65.93; H, 8.30. Found: C, 65.98; H, 8.31.

4.1.1.10. (3a*R*,6*S*,7a*S*)-3a-(Benzo[1,3]dioxol-5-yl)-6-(*tert*-butyldimethylsilyloxy)-2,3,3a,6,7,7a-hexahydro-1*H*-indole (18). To a solution of **3** (120 mg, 0.254 mmol) in CH_2Cl_2 (10 mL) were added MS4Å (30 mg) and $BF_3\cdot Et_2O$ (0.0483 mL, 0.381 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with $CHCl_3$, washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 2 g, EtOAc/hexanes=1/7 then MeOH/$CHCl_3$=1/7 as eluents) to afford **18** (77 mg, 78%) as a colorless syrup: $[\alpha]_D^{21}$ +41 (c 0.12, $CHCl_3$); IR (neat) 3300–3400, 1485 cm^{-1}; ^{1}H NMR δ 0.09 and 0.11 (each 3H, 2s), 0.90 (9H, s), 1.65 (1H, ddd, J=3.2, 9.3, and 13.4 Hz), 1.96 (1H, ddd, J=6.6, 6.6, and 13.1 Hz), 2.05 (1H, ddd, J=5.1, 5.1, and 13.4 Hz), 2.40 (1H, ddd, J=7.1, 7.1, and 13.1 Hz), 3.14 (2H, m), 3.42 (1H, m), 4.49 (1H, m, J=5.1 and 9.3 Hz), 5.58 (1H, d, J=10.2 Hz), 5.83 (1H, br d, J=10.2 Hz), 5.94 (2H, s), 6.75 (1H, d, J=8.0 Hz), 6.86 (1H, dd, J=1.71 and 8.0 Hz), and 6.92 (1H, d, J=1.71 Hz); ^{13}C NMR δ −4.56, −4.51, 18.2, 25.9, 32.9, 40.0, 45.6, 49.6, 63.7, 64.6, 101.0, 107.6, 107.8, 120.0, 131.3, 133.1, 139.2, 145.9, and 147.7; HRMS (FAB) m/z calcd for $C_{21}H_{32}NO_3Si$ $(M+H)^+$, 374.2151, found 374.2150. Further elution gave recovered **3** (16.8 mg, 14%).

4.1.1.11. (+)-Vittatine (1). To a solution of **18** (76.7 mg, 0.199 mmol) in MeOH (0.5 mL) was added formaldehyde (37 wt % solution in water, 0.9 mL). After being stirred at room temperature for 5 min, 6 mol L^{-1} aqueous HCl (1.9 mL) was added to the mixture. The resulting mixture was stirred at 50 °C for 15 h, and then made basic with solid potassium carbonate. The products were extracted with $CHCl_3$ and the organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 2 g, MeOH/$CHCl_3$=1/5 as eluent) to give (+)-vittatine (27.3 mg, 51%) as a colorless solid: mp 205–207 °C (lit.[6b] 207–208 °C); $[\alpha]_D^{22}$ +28 (c 0.46, $CHCl_3$) [lit.[6b] $[\alpha]_D^{25}$ +26 (c 0.5, $CHCl_3$)]; IR (neat) 3300, 2900, 1485, 1235, 1040, 935, 750 cm^{-1}; ^{1}H NMR δ 1.75 (1H, ddd, J=3.9, 13.6, and 13.6 Hz), 1.94 (1H, ddd, J=6.1, 10.7, and 12.3 Hz), 2.06 (1H, br d, J=13.6 Hz), 2.20 (1H, ddd, J=4.4, 9.0, and 12.3 Hz), 2.93 (1H, ddd, J=6.1, 9.0, and 13.2 Hz), 3.35–3.50 (2H, m), 3.81 (1H, d, J=16.6 Hz), 4.36 (1H, m), 4.44 (1H, d, J=16.6 Hz), 5.89 and 5.91 (each 1H, 2br s), 5.97 (1H, dd, J=5.1 and 9.9 Hz), 6.49 (1H, s), 6.58 (1H, d, J=9.9 Hz), and 6.85 (1H, s); (in C_5D_5N) δ 1.85 (1H, ddd, J=4.1, 13.4, and 13.4 Hz), 1.95 (1H, ddd, J=5.9, 9.3, and 9.9 Hz), 2.14 (1H, ddd, J=5.1, 8.6, and 9.3 Hz), 2.31 (1H, br d, J=13.4 Hz), 2.88 (1H, ddd, J=5.9, 8.6, and 13.9 Hz), 3.42 (1H, ddd, J=5.1, 9.9, and 13.9 Hz), 3.75–3.85 (1H, m), 3.80 and 4.40 (each 1H, 2d, J=16.8 Hz), 4.54 (1H, m), 5.97 (2H, br s), 6.17 (1H, dd, J=5.4 and 10.0 Hz), 6.51 (1H, s), 6.65 (1H, d, J=10.0 Hz), and 7.05 (1H, s); ^{13}C NMR δ 32.5, 43.8, 44.3, 53.4, 61.9, 63.0, 63.7, 100.8, 102.9, 106.9, 125.4, 127.8, 131.5, 137.9, 145.9, and 146.3; (in C_5D_5N) δ 33.4, 44.3, 44.4, 53.5, 62.2, 63.30, 63.34, 100.8, 103.2, 107.0, 126.7, 129.1, 130.7, 139.0, 145.8, and 146.2; HRMS (FAB) m/z calcd for $C_{16}H_{18}NO_3$ $(M+H)^+$, 272.1287, found 272.1300.

4.1.2. Total synthesis of (+)-haemanthamine.

4.1.2.1. (2*R*)-[(1*R*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-2-hydroxyacetic acid ethyl ester (19) and its (2*S*)-isomer (20). To a solution of **5** (101 mg, 0.192 mmol) in THF (3.0 mL) at 0 °C under Ar was added LiHMDS (1.0 M solution in THF, 0.580 mL, 0.580 mmol), and the mixture was stirred at 0 °C for 45 min. To this solution was added a solution of (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine [(+)-Davis reagent, 66.2 mg, 0.289 mmol] in THF (1.2 mL) at 0 °C via a cannula, and the mixture was stirred at 0 °C for 45 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution at 0 °C. The reaction mixture was diluted with EtOAc and washed with brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 7 g, EtOAc/hexanes=1/15 as eluent) to afford first, starting material **5** (44.8 mg, 44%). Further elution gave **19** (39.1 mg, 38%) as a colorless syrup: $[\alpha]_D^{25}$ −66 (c 0.97, $CHCl_3$); IR (neat) 3500, 1725 cm^{-1}; ^{1}H NMR δ 0.04 and 0.07 (each 3H, 2s), 0.85–0.90 (12H, m), 1.42 (1H, ddd, J=9.9, 12.5, and 12.5 Hz), 2.03 (1H, dddd, J=2.4, 2.4, 6.3, and 12.5 Hz), 2.75 (1H, d, J=8.0 Hz), 3.80–3.99 (2H, m), 4.08 (1H, dd, J=2.4 and 12.5 Hz), 4.34 (1H, dddd, J=1.7, 2.4, 6.3, and 9.9 Hz), 4.59 and 4.72 (each 1H, 2d, J=11.6 Hz), 4.76 (1H, d, J=8.0 Hz), 5.68 (1H, dd, J=1.7 and 10.2 Hz), 5.92 (2H, s), 5.97 (1H, ddd, J=2.4, 2.4, and 10.2 Hz), 6.71 (1H, d, J=8.4 Hz), 6.94 (1H, dd, J=1.8 and 8.4 Hz), 7.14 (1H,

d, J=1.8 Hz), and 7.27–7.42 (5H, m); ^{13}C NMR δ −4.55, −4.62, 13.5, 18.1, 25.8, 33.4, 53.6, 61.0, 68.6, 71.7, 72.9, 75.3, 100.7, 106.8, 111.4, 124.2, 126.8, 127.56, 127.67, 128.3, 131.9, 136.8, 138.5, 146.4, 146.5, and 173.6; HRMS (EI) m/z calcd for $C_{30}H_{40}O_7Si$, M^+, 540.2543, found 540.2544.

Further elution afforded **20** (4.2 mg, 4%) as a colorless syrup: $[\alpha]_D^{23}$ −30 (c 0.65, $CHCl_3$); IR (neat) 3500, 1725 cm^{-1}; ^{1}H NMR δ 0.04 and 0.07 (each 3H, 2s), 0.87 (9H, s), 1.20 (3H, t, J=7.1 Hz), 1.48 (1H, ddd, J=9.9, 12.3, and 12.3 Hz), 2.05 (1H, dddd, J=1.1, 2.7, 6.5, and 12.3 Hz), 2.80 (1H, d, J=4.7 Hz), 4.00 (1H, dd, J=2.7 and 12.3 Hz), 4.11–4.23 (2H, m), 4.27 (1H, dddd, J=1.1, 1.5, 6.5, and 9.9 Hz), 4.50 and 4.67 (each 1H, 2d, J=11.7 Hz), 4.91 (1H, d, J=4.7 Hz), 5.78 (1H, dd, J=1.5 and 10.2 Hz), 5.84 (1H, ddd, J=1.1, 1.1, and 10.2 Hz), 5.94 (2H, s), 6.77 (1H, d, J=8.1 Hz), 6.98 (1H, dd, J=1.8 and 8.1 Hz), 7.13 (1H, d, J=1.8 Hz), and 7.27–7.38 (5H, m); ^{13}C NMR δ −4.5, −4.6, 14.2, 18.2, 25.8, 33.2, 53.7, 61.8, 68.3, 71.1, 73.3, 75.1, 100.9, 107.2, 110.8, 124.0, 127.4, 127.5, 127.6, 128.3, 132.0, 133.8, 138.5, 146.3, 147.0, and 173.1; HRMS (EI) m/z calcd for $C_{30}H_{40}O_7Si$, M^+, 540.2543, found 540.2538.

4.1.2.2. (2*R*)-2-[(1*R*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-2-hydroxyethanol (21). To a solution of **19** (1.06 g, 1.96 mmol) and trimethyl borate (0.262 mL, 2.35 mmol) in THF (32 mL) at 0 °C was added $LiBH_4$ (171 mg, 7.84 mmol). After being stirred at room temperature for 4 h, the reaction mixture was quenched by slow addition of MeOH at 0 °C. The mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 30 g, EtOAc/hexanes=1/3 as eluent) to afford **21** (879 mg, 90%) as a colorless syrup: $[\alpha]_D^{27}$ −109 (c 1.08, $CHCl_3$); IR (neat) 3430 cm^{-1}; ^{1}H NMR δ 0.05 and 0.08 (each 3H, 2s), 0.88 (9H, s), 1.40 (1H, ddd, J=9.9, 12.6, and 12.6 Hz), 1.92 (2H, br s), 2.03 (1H, dddd, J=1.5, 2.7, 6.5, and 12.6 Hz), 3.35–3.39 (2H, m), 3.98 (1H, dd, J=2.7 and 12.6 Hz), 4.30 (1H, dd, J=5.0 and 7.4 Hz), 4.36 (1H, dddd, J=2.0, 2.0, 6.5, and 9.9 Hz), 4.50 and 4.73 (each 1H, 2d, J=11.9 Hz), 5.59 (1H, dd, J=2.0 and 10.0 Hz), 5.91–5.97 (3H, m), 6.74 (1H, d, J=8.4 Hz), 6.90 (1H, dd, J=1.8 and 8.4 Hz), 7.04 (1H, d, J=1.8 Hz), and 7.29–7.40 (5H, m); ^{13}C NMR δ −4.55, −4.61, 18.2, 25.8, 33.0, 52.3, 62.8, 68.5, 71.2, 73.4, 74.2, 100.9, 107.3, 110.5, 123.7, 127.6, 127.8, 128.0, 132.5, 136.0, 138.5, 146.4, and 147.1; HRMS (EI) m/z calcd for $C_{28}H_{38}O_6Si$, M^+, 498.2438, found 498.2445. Anal. Calcd for $C_{28}H_{38}O_6Si$: C, 67.44; H, 7.68. Found: C, 67.15; H, 7.71.

4.1.2.3. (1*R*,4*R*,5*S*)-4-(Benzo[1,3]dioxol-5-yl)-5-benzyloxy-4-[(2*R*)-oxiran-2-yl]-2-cyclohexen-1-ol (23). To a solution of **21** (879 mg, 1.76 mmol) in CH_2Cl_2 (44 mL) at 0 °C was added Et_3N (1.06 mL, 7.05 mmol). After stirring at 0 °C at 10 min, TsCl (672 mg, 3.52 mmol) was slowly added to the reaction mixture at 0 °C. After being stirred at 0 °C for 30 min and then at room temperature for 3.5 h, to the reaction mixture was added 1 mol L^{-1} aqueous HCl solution at 0 °C. The products were extracted with EtOAc, and organic layer was washed successively with 1 mol L^{-1} aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 20 g, EtOAc/hexanes=1/10 as eluent) to afford tosylate **22** (1.013 g, 88%) as a colorless syrup: IR (neat) 3540 cm^{-1}; ^{1}H NMR δ 0.03 and 0.06 (each 3H, 2s), 0.87 (9H, s), 1.33 (1H, ddd, J=9.9, 12.0, and 12.3 Hz), 1.99 (1H, dddd, J=1.4, 2.4, 6.5, and 12.0 Hz), 2.08 (1H, d, J=5.1 Hz), 2.43 (3H, s), 3.84 (2H, m), 3.98 (1H, dd, J=2.4 and 12.3 Hz), 4.33 (1H, dddd, J=2.1, 2.1, 6.5, and 9.9 Hz), 4.41–4.49 (2H, m), 4.68 (1H, d, J=11.9 Hz), 5.42 (1H, dd, J=2.1, and 10.4 Hz), 5.89–5.95 (3H, m), 6.67 (1H, d, J=8.3 Hz), 6.79 (1H, dd, J=1.8 and 8.3 Hz), 6.89 (1H, d, J=1.8 Hz), 7.26–7.42 (7H, m), and 7.65–7.70 (2H, m); ^{13}C NMR δ −4.6, −4.7, 18.3, 21.6, 25.8, 33.0, 52.5, 68.3, 71.3, 72.4, 72.9, 73.8, 100.9, 107.4, 110.2, 123.6, 126.6, 127.8, 127.9, 128.4, 129.8, 131.7, 132.4, 136.4, 138.4, 144.9, 146.6, and 147.2; HRMS (EI) m/z calcd for $C_{35}H_{44}O_8SSi$, M^+, 652.2526, found 652.2529.

To a solution of **22** (1.013 g) in THF (28 mL) was added Bu_4NF (1.0 M solution in THF, 4.94 mL, 4.94 mmol) at 0 °C, and the mixture was stirred at room temperature for 11 h. The mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 15 g, EtOAc/hexanes=2/5 as eluent) to afford **23** (530 mg, 93%, 82% from **21**) as a colorless syrup: $[\alpha]_D^{26}$ +31 (c 0.89, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^{1}H NMR δ 1.98 (1H, ddd, J=5.3, 7.5, and 13.5 Hz), 2.32 (1H, ddd, J=2.1, 5.7, 13.5, and 12.0 Hz), 2.51 (1H, dd, J=3.0 and 4.2 Hz), 2.61 (1H, br s), 2.70 (1H, dd, J=3.9 and 4.2 Hz), 3.43 (1H, dd, J=3.0 and 3.9 Hz), 3.87 (1H, dd, J=2.1 and 7.5 Hz), 4.23 (2H, m), 4.45 (1H, d, J=11.4 Hz), 5.44 (1H, d, J=10.2 Hz), 5.95 and 5.96 (each 1H, 2d, J=1.5 Hz), 6.14 (1H, dd, J=3.8 and 10.2 Hz), 6.79 (1H, d, J=8.4 Hz), 6.90 (1H, dd, J=1.8 and 8.4 Hz), 6.98 (1H, d, J=1.8 Hz), 7.09–7.14 (2H, m), and 7.21–7.32 (3H, m); ^{13}C NMR δ 32.0, 43.2, 47.5, 55.7, 64.7, 72.0, 79.5, 101.0, 107.6, 109.1, 121.5, 125.6, 127.6, 127.7, 128.2, 133.7, 134.8, 137.7, 146.4, and 147.4; HRMS (EI) m/z calcd for $C_{22}H_{22}O_5$, M^+, 366.1467, found 366.1460. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.10; H, 6.09.

4.1.2.4. (2*S*)-2-[(1*R*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-2-hydroxyethanol (24). To a solution of **20** (62.4 mg, 0.115 mmol) and trimethyl borate (0.0193 mL, 0.173 mmol) in THF (2 mL) at 0 °C was added $LiBH_4$ (10.0 mg, 0.462 mmol). After being stirred at room temperature for 3 h, the reaction mixture was quenched by slow addition of MeOH at 0 °C. The mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 1.5 g, EtOAc/toluene=1/4 as eluent) to afford **24** (56.7 mg, 99%) as a colorless syrup: $[\alpha]_D^{28}$ −33 (c 0.99, $CHCl_3$); IR (neat) 3420 cm^{-1}; ^{1}H NMR δ 0.06 and 0.09 (each 3H, 2s), 0.89 (9H, s), 1.38 (1H, ddd, J=9.9, 12.3, and 12.3 Hz), 1.95 (1H, br s), 2.06 (1H, ddd, J=2.6, 6.5, and 12.3 Hz), 3.40 (2H, m), 3.53 (1H, dd, J=2.6 and

12.3 Hz), 4.28 (1H, dddd, *J*=1.8, 1.8, 6.5, and 9.9 Hz), 4.36–4.44 (2H, m), 4.69 (1H, d, *J*=11.7 Hz), 5.75 (1H, dd, *J*=1.8 and 10.5 Hz), 5.85 (1H, dd, *J*=1.8 and 10.5 Hz), 5.96 (2H, s), 6.86 (1H, d, *J*=8.1 Hz), 7.01 (1H, dd, *J*=1.7 and 8.1 Hz), 7.16 (1H, d, *J*=1.7 Hz), and 7.30–7.43 (5H, m); ^{13}C NMR δ −4.5, −4.6, 18.2, 25.8, 32.9, 52.5, 63.3, 68.4, 70.5, 74.2, 74.8, 101.0, 107.6, 110.6, 124.0, 127.9, 128.0, 128.5, 132.5, 133.4, 138.0, 146.5, and 147.5; HRMS (EI) *m/z* calcd for $C_{28}H_{38}O_6Si$, M^+, 498.2438, found 498.2434.

4.1.2.5. (2*S*)-2-[(1*R*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-2-hydroxyethyl benzoate (25). To a solution of **24** (8.1 mg, 0.0162 mmol) in pyridine (0.4 mL) at 0 °C was added benzoyl chloride (0.0028 mL, 0.0244 mmol), and the reaction mixture was stirred at 0 °C for 4.5 h. To the reaction mixture was added aqueous saturated $NaHCO_3$ solution at 0 °C, and the products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 0.5 g, EtOAc/hexanes=1/10 as eluent) to afford **25** (8.5 mg, 87%) as a colorless syrup: $[\alpha]_D^{22}$ −1.5 (*c* 1.12, $CHCl_3$); IR (neat) 3500, 1720 cm^{-1}; ^{1}H NMR δ 0.08 and 0.11 (each 3H, 2s), 0.91 (9H, s), 1.43 (1H, ddd, *J*=10.0, 12.3, and 12.3 Hz), 2.07 (1H, br s), 2.09 (1H, dddd, *J*=1.2, 2.4, 6.3, and 12.3 Hz), 3.71 (1H, dd, *J*=2.4 and 12.3 Hz), 4.12 (1H, dd, *J*=7.8 and 11.4 Hz), 4.23 (1H, dd, *J*=1.2 and 11.4 Hz), 4.34 (1H, dddd, *J*=1.8, 1.8, 6.3, and 10.0 Hz), 4.44 (1H, d, *J*=11.9 Hz), 4.66 (1H, ddd, *J*=1.2, 1.2, and 7.8 Hz), 4.71 (1H, d, *J*=11.9 Hz), 5.82 (1H, dd, *J*=1.8 and 10.5 Hz), 5.91 (1H, ddd, *J*=1.2, 1.8, and 10.5 Hz), 5.96 (2H, s), 6.82 (1H, d, *J*=7.8 Hz), 7.04 (1H, dd, *J*=1.8 and 7.8 Hz), 7.14–7.21 (2H, m), and 7.26–8.07 (9H, m); ^{13}C NMR δ −4.5, −4.6, 18.2, 25.8, 33.0, 52.9, 66.7, 68.3, 70.6, 72.3, 74.9, 101.0, 107.6, 110.7, 124.1, 127.3, 127.8, 127.9, 128.3, 128.4, 129.7, 129.9, 131.8, 133.0, 134.3, 138.0, 146.7, 147.5, and 166.7; HRMS (EI) *m/z* calcd for $C_{35}H_{42}O_7Si$, M^+, 602.2707, found 602.2700.

4.1.2.6. (1*S*)-1-[(1*R*,4*R*,6*S*)-1-(Benzo[1,3]dioxol-5-yl)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexen-1-yl]-2-(benzoyloxy)ethyl methanesulfonate (26). To a solution of **25** (8.5 mg, 0.0141 mmol) in pyridine (0.3 mL) at 0 °C was added methanesulfonyl chloride (0.0044 mL, 0.0564 mmol), and the mixture was stirred at 0 °C for 40 min. To the reaction mixture at 0 °C was added 4-dimethylaminopyridine (1 mg) and the resulting mixture was stirred at room temperature for 28 h. The mixture was diluted with EtOAc and washed successively with 1 mol L^{-1} aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 0.5 g, EtOAc/hexanes=1/15 as eluent) to afford **26** (7.5 mg, 78%) as a colorless syrup: $[\alpha]_D^{26}$ −0.8 (*c* 0.86, $CHCl_3$); IR (neat) 1725, 1360 cm^{-1}; ^{1}H NMR δ 0.06 and 0.09 (each 3H, 2s), 0.89 (9H, s), 1.38 (1H, ddd, *J*=9.9, 12.0, and 12.0 Hz), 2.11 (1H, dd, *J*=6.5 and 12.0 Hz), 2.29 (3H, s), 3.64 (1H, dd, *J*=2.3 and 12.0 Hz), 4.18–4.23 (2H, m), 4.31 (1H, dddd, *J*=1.8, 1.8, 6.5, and 9.9 Hz), 4.46 and 4.74 (each 1H, 2d, *J*=12.2 Hz), 5.69 (1H, dd, *J*=4.1 and 7.1 Hz), 5.83 (1H, dd, *J*=1.8 and 10.4 Hz), 5.92 (1H, br d, *J*=10.4 Hz), 5.96 and 5.97 (each 1H, 2d, J=1.2 Hz), 6.82 (1H, d, *J*=8.1 Hz), 7.11 (1H, dd, *J*=1.8 and 8.1 Hz), and 7.14–8.16 (11H, m); ^{13}C NMR δ −4.6, −4.5, 18.2, 25.8, 33.0, 38.5, 52.2, 64.0, 68.2, 70.5, 74.7, 83.5, 101.1, 107.4, 111.0, 124.1, 126.8, 128.1 (2C), 128.4, 128.6, 129.5, 130.0, 132.6, 133.1, 135.1, 137.5, 146.7, 147.2, and 166.2; HRMS (EI) *m/z* calcd for $C_{36}H_{44}O_9SSi$, M^+, 680.2475, found 680.2485.

4.1.2.7. Conversion of mesylate (26) to epoxide (23). To a solution of **26** (7.5 mg, 0.011 mmol) in THF (0.3 mL) at 0 °C was added Bu_4NF (1.0 M solution in THF, 0.022 mL, 0.022 mmol), and the mixture was stirred at room temperature for 2 h. To the mixture, MeOH (0.3 mL) and MeONa (1.2 mg, 0.022 mmol) were added at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was diluted with $CHCl_3$ and washed successively with 1 mol L^{-1} aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 0.5 g, EtOAc/hexanes=1/2 as eluent) to afford **23** (3.9 mg, 98%) as a colorless syrup. The spectral and physical data were fully identical to those of **23** prepared from **22**.

4.1.2.8. 5-{(1*R*,4*R*,6*S*)-6-Bezyloxy-4-methoxy-1-[(2*R*)-oxiran-2-yl]-2-cyclohexen-1-yl}-benzo[1,3]dioxole (27). To a solution of **23** (83.3 mg, 0.227 mmol) in THF at 0 °C were added sodium hydride (60% in oil, 27.3 mg, 1.14 mmol) and methyl iodide (0.0425 mL, 0.682 mmol), and the mixture was stirred at 0 °C for 5 h. After addition of MeOH (1 mL), the reaction mixture was diluted with EtOAc and washed successively with 1 mol L^{-1} aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, and brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 4 g, EtOAc/hexanes=1/8 as eluent) to afford **27** (79.2 mg, 92%) as a colorless syrup: $[\alpha]_D^{27}$ −94 (*c* 0.89, $CHCl_3$); IR (neat) 3400 cm^{-1}; ^{1}H NMR δ 1.50 (1H, ddd, *J*=10.0, 12.0, and 12.6 Hz), 2.30 (1H, dddd, *J*=1.4, 2.7, 6.3, and 12.0 Hz), 2.64 (1H, dd, *J*=3.2 and 4.4 Hz), 2.77 (1H, dd, *J*=4.1 and 4.4 Hz), 3.38 (3H, s), 3.70 (1H, dd, *J*=3.2 and 4.1 Hz), 3.77 (1H, dd, *J*=2.7 and 12.6 Hz), 3.97 (1H, dddd, *J*=1.4, 2.1, 6.3, and 10.0 Hz), 4.57 and 4.74 (each 1H, 2d, *J*=11.7 Hz), 5.37 (1H, dd, *J*=2.1 and 10.5 Hz), 5.93 (2H, s), 6.04 (1H, ddd, *J*=1.4, 1.4, and 10.5 Hz), 6.75 (1H, d, *J*=8.1 Hz), 6.92 (1H, dd, *J*=1.8 and 8.1 Hz), 7.07 (1H, d, *J*=1.8 Hz), and 7.26–7.40 (5H, m); ^{13}C NMR δ 29.1, 44.0, 48.1, 55.8 (2C), 71.5, 75.6, 77.7, 100.9, 107.3, 110.2, 123.0, 127.47 (2C), 127.52, 128.3, 130.9, 133.1, 138.3, 146.5, and 147.1; HRMS (EI) *m/z* calcd for $C_{23}H_{24}O_5$, M^+, 380.1624, found 380.1625. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.53; H, 6.32.

4.1.2.9. (1*R*)-2-Azido-1-[(1*R*,4*R*,6*S*)-1-(benzo[1,3]-dioxol-5-yl)-6-benzyloxy-4-methoxy-2-cyclohexen-1-yl]-ethanol (28). A mixture of **27** (79.2 mg, 0.208 mmol), NaN_3 (135 mg, 2.08 mmol), and NH_4Cl (111 mg, 2.08 mmol) in MeOH (2.4 mL) was stirred at 50 °C for 48 h. The reaction mixture was diluted with EtOAc and washed with brine, and then dried. Removal of the solvent left a residue, which was purified by column chromatography (silica gel, 3.5 g, EtOAc/hexanes=1/4 as eluent) to afford **28** (70.0 mg,

79%) as a colorless syrup: $[\alpha]_D^{26}$ −37 (*c* 1.01, $CHCl_3$); IR (neat) 3430, 2100 cm^{-1}; ^1H NMR δ 1.34 (1H, ddd, *J*=10.4, 12.0, and 12.6 Hz), 1.75 (1H, d, *J*=6.0 Hz), 2.25 (1H, dddd, *J*=1.4, 2.7, 6.3, and 12.0 Hz), 3.03 (1H, dd, *J*=2.4 and 12.6 Hz), 3.15 (1H, dd, *J*=9.3 and 12.6 Hz), 3.36 (3H, s), 3.95–4.03 (2H, m), 4.30 (1H, ddd, *J*=2.4, 6.0, and 9.3 Hz), 4.46 and 4.76 (each 1H, 2d, *J*=12.2 Hz), 5.68 (1H, dd, *J*=1.5 and 10.5 Hz), 5.94 (2H, s), 6.12 (1H, ddd, *J*=1.4, 1.4, and 10.5 Hz), 6.74 (1H, d, *J*=8.4 Hz), 6.85 (1H, dd, *J*=2.1 and 8.4 Hz), 6.99 (1H, d, *J*=2.1 Hz), and 7.31–7.43 (5H, m); ^{13}C NMR δ 28.9, 52.9, 53.5, 55.7, 71.1, 72.3, 73.8, 76.0, 101.0, 107.5, 110.1, 123.5, 128.0, 128.6, 128.8, 132.1, 132.3, 138.3, 146.6, and 147.4; HRMS (EI) *m/z* calcd for $C_{23}H_{25}N_3O_5$, M^+, 423.1794, found 423.1790.

4.1.2.10. *tert*-Butyl (2*R*)-2-[(1*R*,4*R*,6*S*)-1-(benzo[1,3]-dioxol-5-yl)-6-benzyloxy-4-methoxy-2-cyclohexen-1-yl]-2-hydroxyethylcarbamate (29). A mixture of Lindler catalyst (140 mg) in EtOAc (1.5 mL) was stirred under an atmospheric pressure of H_2 at room temperature for 1 h. To this mixture was added a solution of **28** (70.0 mg, 0.165 mmol) and di-*tert*-butyl dicarbonate (0.0760 mL, 0.331 mmol) in EtOAc (1.5 mL) via a cannula, and the whole mixture was stirred under an atmospheric pressure of H_2 at room temperature for 5 h. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue, which was purified by column chromatography (silica gel, 2.5 g, EtOAc/hexanes=1/2 as eluent) to afford **29** (81.3 mg, 99%) as a colorless syrup: $[\alpha]_D^{25}$ −28 (*c* 1.10, $CHCl_3$); IR (neat) 3390, 1690 cm^{-1}; ^1H NMR δ 1.34 (1H, ddd, *J*=10.5, 12.0, and 12.0 Hz), 1.43 (9H, s), 2.16–2.36 (1H, m), 2.85–3.11 (3H, m), 3.34 (3H, s), 3.99 (1H, dddd, *J*=2.0, 2.0, 6.5, and 9.9 Hz), 4.04 (1H, m), 4.28 (1H, ddd, *J*=2.3, 5.7, and 12.0 Hz), 4.53 (1H, d, *J*=11.7 Hz), 4.70–4.80 (2H, m), 5.75 (1H, br d, *J*=10.4 Hz), 5.92 (2H, s), 6.10 (1H, br d, *J*=10.4 Hz), 6.72 (1H, d, *J*=8.1 Hz), 6.88 (1H, dd, *J*=1.8 and 8.1 Hz), 7.02 (1H, d, *J*=1.8 Hz), and 7.26–7.40 (5H, m); ^{13}C NMR δ 28.3, 29.1, 43.2, 53.2, 55.6, 71.4, 73.6, 74.7, 76.1, 79.8, 100.8, 107.3, 110.3, 123.6, 127.6, 127.7, 128.4, 129.3, 132.1, 132.7, 138.6, 146.4, 147.2, and 157.3; HRMS (EI) *m/z* calcd for $C_{28}H_{35}NO_7$, M^+, 497.2414, found 497.2413. Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09. Found: C, 67.43; H, 7.06.

4.1.2.11. *tert*-Butyl (2*R*)-2-[(1*R*,4*R*,6*S*)-1-(benzo[1,3]-dioxol-5-yl)-4-methoxy-6-hydroxy-2-cyclohexen-1-yl]-2-hydroxyethylcarbamate (9). A mixture of Na (128 mg, 5.58 mmol) and naphthalene (718 mg, 5.58 mmol) in THF (7.0 mL) was sonicated with ultrasound at room temperature for 25 min and the resulting moss green suspension was cooled to −30 °C. To the mixture was added a solution of **29** (111 mg, 0.223 mmol) in THF (4.0 mL) at −30 °C via a cannula. The reaction mixture was stirred at −30 °C for 2 h, and then quenched by slow addition of MeOH, followed by addition of aqueous saturated NH_4Cl solution at −30 °C. After being stirred at room temperature for 10 min, the reaction mixture was diluted with EtOAc, and washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 4 g, EtOAc/toluene=1/4 as eluent) to afford **9** (74.0 mg, 81%) as a colorless syrup: $[\alpha]_D^{23}$ −14 (*c* 1.02, $CHCl_3$); IR (neat) 3420, 1690 cm^{-1}; ^1H NMR δ 1.30–1.48 (1H, m), 1.42 (9H, s), 2.04–2.14 (2H, m), 3.01–3.20 (2H, m), 3.36 (3H, s), 3.61 (1H, br s), 4.01 (1H, dddd, *J*=1.9, 1.9, 6.3, and 9.6 Hz), 4.27 (1H, ddd, *J*=2.7, 9.3, and 12.1 Hz), 4.36 (1H, dd, *J*=5.7 and 11.7 Hz), 4.92 (1H, t, *J*=5.9 Hz), 5.69 (1H, dd, *J*=1.4 and 10.5 Hz), 5.94 and 5.95 (each 1H, 2d, *J*=1.5 Hz), 6.13 (1H, ddd, *J*=1.9, 1.9, and 10.5 Hz), 6.78 (1H, d, *J*=8.4 Hz), 6.90 (1H, dd, *J*=1.4 and 8.4 Hz), and 7.03 (1H, d, *J*=1.4 Hz); ^{13}C NMR δ 28.3, 33.2, 43.4, 53.5, 55.9, 67.4, 74.1, 75.7, 79.9, 101.0, 107.8, 110.0, 123.2, 128.9, 132.1 (2C), 146.6, 147.6, and 157.3; HRMS (FAB) *m/z* calcd for $C_{21}H_{29}NO_7$ $(M+H)^+$, 407.1944, found 407.1944.

4.1.2.12. *tert*-Butyl (2*R*,3a*R*,4*S*,6*S*,7a*S*)-3a-(benzo[1,3]-dioxol-5-yl)-2,4-dihydroxy-6-methoxyoctahydroindole-1-carboxylate (30). A solution of **9** (21.2 mg, 0.0518 mmol) in THF (0.7 mL) was degassed by freeze–pump–thaw (FPT) cycles, which was added to a solution of $Hg(O-COCF_3)_2$ (33.1 mg, 0.0777 mmol) in THF (1.4 mL, degassed by FPT cycles) via a cannula under Ar. After being stirred at room temperature for 120 h, to the mixture was added a solution of $NaBH_4$ (2.8 mg, 0.075 mmol) and NaOH (3.0 mg, 0.075 mmol) in MeOH (0.15 mL, degassed by FPT cycles) at room temperature, and the resulting mixture was stirred for 10 min at room temperature. The insoluble material was removed by filtration through a pad of Celite. The filtrate was partially concentrated and diluted with EtOAc, which was washed with brine, and then dried. Removal of the solvent left a residue, which was purified by preparative TLC (EtOAc/hexanes=1/1) to afford **30** (11.2 mg, 53%) as a colorless syrup: $[\alpha]_D^{22}$ +18 (*c* 1.10, $CHCl_3$); IR (neat) 3430, 1670 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, at 60 °C) δ 1.49 (9H, s), 1.70 (1H, ddd, *J*=7.9, 7.9, and 12.9 Hz), 1.98 (1H, m), 2.22 (1H, ddd, *J*=3.8, 3.8, and 12.9 Hz), 2.36–2.49 (1H, m), 3.19 (1H, dd, *J*=5.0 and 11.6 Hz), 3.34 (3H, s), 3.48 (1H, dd, *J*=6.5 and 11.6 Hz), 3.61 (1H, m), 3.79 (1H, d, *J*=5.7 Hz), 4.25–4.36 (2H, m), 4.43 (1H, ddd, *J*=4.5, 5.0, and 6.5 Hz), 5.74 (1H, d, *J*=4.5 Hz), 6.02 and 6.03 (each 1H, 2d, *J*=0.6 Hz), 6.83 (1H, d, *J*=8.4 Hz), 6.99 (1H, dd, *J*=1.8 and 8.4 Hz), and 7.15 (1H, d, *J*=1.8 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz, at 60 °C) δ 28.1, 30.9, 34.8, 51.9, 54.9, 55.2, 57.4, 67.8, 74.5, 76.9, 78.6, and 79.1 (rotameric pair), 100.6, 107.2, 108.7, 120.6, 136.1, 145.2, 146.8, and 153.6; HRMS (EI) *m/z* calcd for $C_{21}H_{29}NO_7$, M^+, 407.1944, found 407.1950.

Further elution gave the recovered starting material **9** (2.8 mg, 13%).

4.1.2.13. *tert*-Butyl (2*R*,3a*R*,4*S*,6*S*,7a*S*)-3a-(benzo[1,3]-dioxol-5-yl)-4-hydroxy-6-methoxy-2-triethylsilyloxyoctahydroindole-1-carboxylate (31). To a solution of **30** (53.8 mg, 0.131 mmol) in CH_2Cl_2 (5.4 mL) at 0 °C were added Et_3N (0.0494 mL, 0.329 mmol) and *N*,*N*-dimethylaminopyridine (24.1 mg, 0.197 mmol), and the mixture was stirred at 0 °C for 40 min. To this solution, TESCl (0.0662 mL, 0.394 mmol) was added dropwise at 0 °C, and the resulting mixture was stirred at 0 °C for 2.5 h, and then at room temperature for 12 h. To the reaction mixture was added H_2O, and the products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried.

Removal of the solvent left a residue, which was purified by preparative TLC (EtOAc/toluene=1/12) to afford **31** (45.7 mg, 67%) as a colorless syrup: $[\alpha]_D^{24}$ +27 (*c* 1.10, $CHCl_3$); IR (neat) 3510, 1690 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, at 60 °C) δ 0.55–0.65 (6H, m), 0.91 (9H, t, *J*=8.0 Hz), 1.43 (9H, s), 1.77 (1H, ddd, *J*=6.8, 6.8, and 13.2 Hz), 1.99 (1H, m), 2.15 (1H, ddd, *J*=3.9, 3.9, and 13.2 Hz), 2.18–2.27 (1H, m), 3.09 (1H, dd, *J*=3.5 and 11.7 Hz), 3.27 (3H, s), 3.34 (1H, dd, *J*=5.7 and 11.7 Hz), 3.53 (1H, d, *J*=6.0 Hz), 3.56–3.64 (1H, m), 4.22–4.33 (2H, m), 4.51 (1H, dd, *J*=3.5 and 5.7 Hz), 5.96 and 5.97 (each 1H, 2d, *J*=1.1 Hz), 6.82 (1H, d, *J*=8.3 Hz), 6.91 (1H, dd, *J*=1.7 and 8.4 Hz), and 7.10 (1H, d, *J*=1.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz, at 60 °C) δ 4.1, 6.3, 28.1, 30.4, 34.9, 52.5, 55.2, 55.9, 56.5, 67.8, 74.4, 78.7, and 79.1 (rotameric pair), 78.8, 100.7, 107.4, 108.4, 120.5, 135.3, 145.3, 147.0, and 153.5; HRMS (EI) *m*/*z* calcd for $C_{27}H_{43}NO_7Si$, M^+, 521.2809, found 521.2807.

4.1.2.14. *tert*-Butyl (2*R*,3a*R*,6*S*,7a*S*)-3a-(benzo[1,3]dioxol-5-yl)-6-methoxy-2-triethylsilyloxy-2,3,3a,6,7,7a-hexahydro-1*H*-indole-1-carboxylate (33). To a solution of **31** (12.8 mg, 0.0245 mmol) in THF (0.6 mL) was added sodium hydride (60% in oil, 1.8 mg, 0.074 mmol) at 0 °C, and the mixture was stirred at 0 °C for 20 min. To the mixture at 0 °C were added carbon disulfide (0.011 mL, 0.18 mmol), and after being stirred at room temperature for 2 h, methyl iodide (0.0030 mL, 0.048 mmol) was added. The resulting mixture was stirred at room temperature for 5 h. The mixture was diluted with EtOAc, washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 0.5 g, EtOAc/hexanes=1/20 as eluent) to afford xanthate ester **32** (14.8 mg, 98%) as a colorless syrup: IR (neat) 1690 cm^{-1}; ^1H NMR (300 MHz) δ 0.62–0.72 (6H, m), 0.97 (9H, t, *J*=8.0 Hz), 1.45 (9H, s), 2.00–2.15 (m, 2H), 2.10 (3H, s), 2.20–2.30 (1H, m), 2.35–2.46 (1H, m), 3.04 (1H, dd, *J*=1.2 and 12.3 Hz), 3.18 (3H, s), 3.25 (1H, dd, *J*=4.8 and 12.3 Hz), 3.62–3.68 (1H, m), 4.54 (1H, dd, *J*=1.2 and 4.8 Hz), 4.61 (1H, dd, *J*=5.9 and 10.1 Hz), 5.96 and 5.99 (each 1H, 2d, *J*=0.9 Hz), 6.33 (1H, dd, *J*=3.6 and 3.6 Hz), 6.69 (1H, dd, *J*=2.1 and 8.3 Hz), 6.74 (1H, d, *J*=2.1 Hz), and 6.85 (1H, d, *J*=8.1 Hz); HRMS (EI) *m*/*z* calcd for $C_{29}H_{45}NO_7S_2Si$ $(M+H)^+$, 611.2407, found 611.2400.

A mixture of xanthate ester **32** (14.8 mg) and potassium carbonate (5.0 mg, 0.036 mmol) in 1,2-dichlorobenzene (1.0 mL) in a sealed tube was stirred at 160 °C for 12 h. After cooling, the reaction mixture was concentrated to give a residue, which was dissolved in MeOH (0.5 mL). To this solution at room temperature were added potassium carbonate (6.7 mg, 0.0484 mmol) and di-*tert*-butyl dicarbonate (0.0083 mL, 0.036 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc, and washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 0.8 g, EtOAc/hexanes=1/25 as eluent) to afford **33** (8.0 mg, 66%) as a colorless syrup: $[\alpha]_D^{22}$ +67 (*c* 1.00, $CHCl_3$); IR (neat) 1690 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, at 60 °C) δ 0.31–0.51 (6H, m), 0.77 (9H, t, *J*=7.8 Hz), 1.20–1.31 (1H, m), 1.43 (9H, s), 2.50–2.65 (1H, m), 2.85 (1H, m), 3.27 (3H, s), 3.63–3.80 (2H, m), 3.87–3.96 (1H, m), 4.63 (1H, br dd, *J*=7.5 and 7.5 Hz), 5.91 (1H, br d, *J*=10.4 Hz), 5.98 (2H, s), 6.14 (1H, br d, *J*=10.4 Hz), 6.84–6.87 (2H, m), and 7.07 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz, at 60 °C) δ 4.4, 6.1, 26.7 (br), 28.0, 51.7, 53.2 (br), 55.0, 60.7, 71.9, 74.8 (br), 78.6 and 79.0 (rotameric pair), 100.7, 107.3, 107.5, 120.7, 127.9, 130.6, 135.4, 145.8, 147.4, and 153.4; HRMS (EI) *m*/*z* calcd for $C_{27}H_{41}NO_6Si$, M^+, 503.2703, found 507.2722.

4.1.2.15. (+)-Haemanthamine (2). To a solution of **33** (22.7 mg, 0.0451 mmol) in MeOH (1.2 mL) at room temperature was added 6 mol L^{-1} aqueous HCl (2.4 mL), and the mixture was stirred at room temperature for 45 min. To this mixture, formaldehyde (37 wt % solution in water, 1.2 mL) was added, and the reaction mixture was stirred at room temperature for 1 h and then at 50 °C for 21 h. The mixture was washed with Et_2O and then made basic by slow addition of solid potassium carbonate. The products were extracted with $CHCl_3$ and the organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel, 1 g, MeOH/$CHCl_3$=1/60 as eluent) to give (+)-haemanthamine **2** (13.6 mg, 100%) as a crystalline residue: mp 199–202 °C (natural haemanthamine[22] 200–202 °C); $[\alpha]_D^{25}$ +41 (*c* 0.62, $CHCl_3$) [natural haemanthamine[22] $[\alpha]_D^{24}$ +42 (*c* 0.34, $CHCl_3$)]; IR (neat) 3400, 2930, 1510, 1485 cm^{-1}; ^1H NMR δ 1.97–2.06 (2H, m), 2.11 (1H, ddd, *J*=1.8, 5.4, and 13.8 Hz), 3.25 (1H, dd, *J*=3.3 and 14.1 Hz), 3.30–3.43 (2H, m), 3.36 (3H, s), 3.69 (1H, d, *J*=17.1 Hz), 3.86 (1H, ddd, *J*=1.8, 4.0 and 4.7 Hz), 3.98 (1H, dd, *J*=3.3 and 6.7 Hz), 4.32 (1H, d, *J*=17.1 Hz), 5.88 and 5.89 (each 1H, 2br s), 6.36 (1H, dd, *J*=4.7 and 10.2 Hz), 6.43 (1H, d, *J*=10.2 Hz), 6.47 (1H, s), and 6.82 (1H, s); ^{13}C NMR δ 28.2, 50.0, 56.5, 61.3, 62.6, 63.5, 72.7, 80.1, 100.8, 103.3, 106.8, 126.7, 127.3, 131.8, 135.3, 146.1, and 146.4; HRMS (EI) *m*/*z* calcd for $C_{17}H_{19}NO_4$, M^+, 301.1314, found 301.1316.

Acknowledgements

We thank Professor Hiromitsu Takayama (Graduate School of Pharmaceutical Sciences, Chiba University, Chiba, Japan) for a generous gift of natural haemanthamine. We also thank the Ministry of Education, Culture, Sports, Science, and Technology, Japan (Grant-in-Aid for Scientific Research, B15350027 and Grant-in-Aid for the 21st Century COE program 'KEIO LCC') for financial assistance.

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22. These data of natural haemanthamine were measured in our laboratory.