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Graphical Abstract

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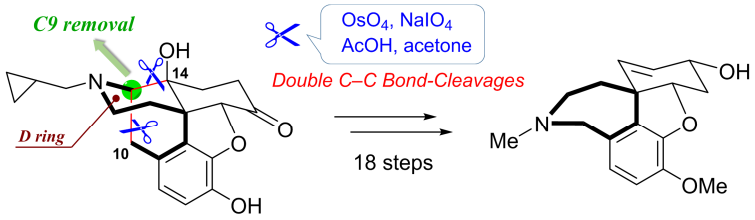

naltrexone (**1**) (–)-galanthamine (**4**)

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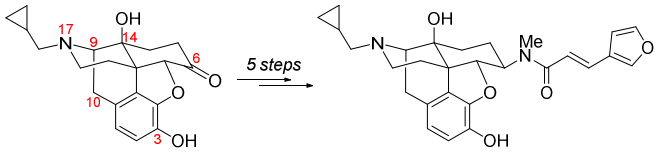
ABSTRACT

(–)-Galanthamine (**4**) was synthesized from naltrexone (**1**) in 18 steps with 3% total yield by overcoming many specific side reactions derived from the 4,5-epoxyymorphinan skeleton. The key features are cleavage of the D-ring by the Hofmann elimination and the following the one-pot C9–C10 and C9–14 bond cleavages concomitant with the C9 removal by the OsO_4–$NaIO_4$ combination reaction. Then, the treatment with zinc powder in acetic acid led to not only removal of the 2,2,2-trichloroethoxycarbonyl (Troc) group, but also reductive amination of the resulting imine to give the desired 7-membered ring.

1. Introduction

Three types of opioid receptors (μ (MOR), δ (DOR), κ (KOR)) are well established not only by pharmacological studies but by molecular biological studies.[1] Narcotic addiction is believed to be derived from MOR type, and therefore KOR and DOR types are promising drug targets for analgesics without addiction.[2] To obtain ideal analgesics without addiction and other side effects derived from the MOR, we have synthesized various kinds of naltrexone derivatives by use of the specific reactivity of the morphinan template and have reported some selective ligands for the KOR[3] and DOR[4] receptors. One of our designed KOR selective agonists, nalfurafine hydrochloride (TRK-820, Scheme 1) prepared *via* 5 steps from the MOR antagonist, naltrexone (**1**),[5] was launched in Japan as an antipruritic for patients undergoing dialysis in 2009 and for patients with hepatic disease in 2015. On the other hand, other KOR agonists, aryl-acetamide derivatives such as U-50488H[6] and U-69593[7] were synthesized and developed (Figure 1). However, all the aryl-acetamide derivatives were eliminated from clinical trials not only as analgesics, but also as antipruritics because of their serious side effects like psychotomimetic and aversive reactions.[8] Notably, nalfurafine has neither aversive nor addictive effects. We postulated that the absence of aversion may derive from the partial structure, the tyrosine moiety in nalfurafine, which is the *N*-terminal structure in the endogenous KOR agonist, dynorphin. The aforementioned aryl-acetamide derivatives have no tyrosine moiety. Focusing on the possible importance of the tyrosine moiety, we utilized naltrexone (**1**) as the starting material to synthesize the nalfurafine. Naltrexone (**1**) is also a medication that reverses the effects of opioids and is used primarily in the management of alcohol and opioid dependence in the USA.[5] The commercially available compound **1** has also been using as a readily available drug-like compound. Therefore, we have utilized **1** as a template to create many novel compounds.[9]



Scheme 1. Nalfurafine (KOR agonist) was synthesized from naltrexone (**1**, MOR antagonist).

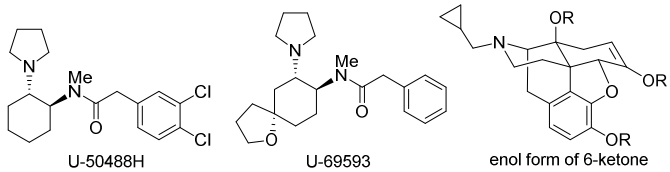


Figure 1. Structures of U-50488H, U-69593, **2** and **3**.

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The specific structural features in naltrexone (**1**), the 4,5-epoxy ring, four sequential asymmetric centers, two hydroxy groups (14-OH and phenolic OH) and a basic nitrogen, have led to many intramolecular interactions resulting in unexpected complex rearrangement reactions. A noteworthy characteristic of the skeleton is the abnormal stability of the enol form of the 6-keto group in **2** (Figure 2).[10] The stability is derived from the rigid and highly strained 4,5-epoxy morphinan skeleton (especially, the 4,5-epoxy ring which plays an important role). Furthermore, the 17-basic nitrogen intramolecularly abstracts the hydrogen in 14-hydroxy group and the resulting hydroxide ion can drag away the 7-axial hydrogen to afford enol form **2**. The compound **2** was acetylated with acetic anhydride/pyridine at room temperature to give triacetates **3**.[10]

We easily synthesized the representative δ and κ receptor selective antagonists (NTI,[11] NTB,[12] TRK-851[13] and nor-BNI[14]) using the stable enol formation (Figure 2). On the other hand, the abnormally strained structure accelerated the undesired cleavage reaction of 4,5-epoxy ring to disturb the reductive removal of the 6-keto-group of **1** in the synthesis of (–)-homogalanthamine.[15] Thus, the abnormal reactivity needed to be effectively controlled to utilize the antagonist as a template. The above-mentioned knowledge of many specific and abnormal reactions derived from the skeleton should help investigators utilize the naltrexone (**1**) as a template. Recently, we have considered the common features between the partial structures of naltrexone (**1**) and the target molecules, (–)-homogalanthamine, mesembrane, and (–)-galanthamine (**4**) (red part of the structures, Figure 2).

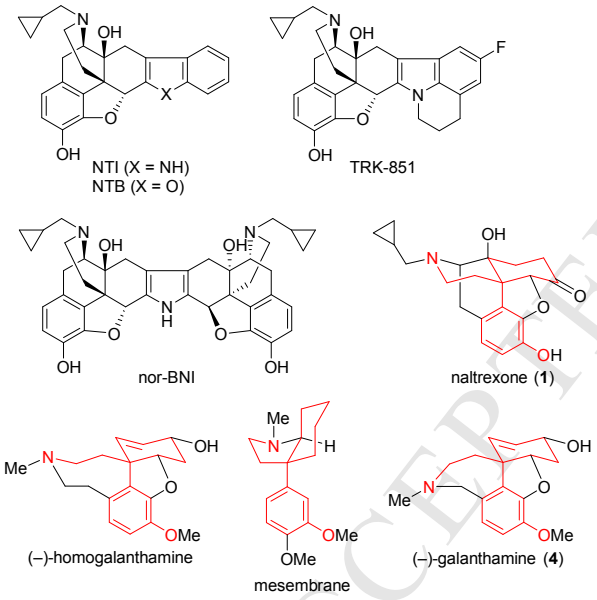
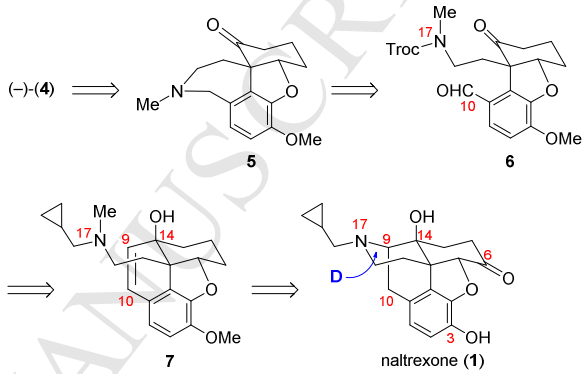


Figure 2. Structures of NTI, NTB, TRK-851 and nor-BNI. The common features between naltrexone (**1**), (–)-homogalanthamine, mesembrane and (–)-galanthamine (**4**).

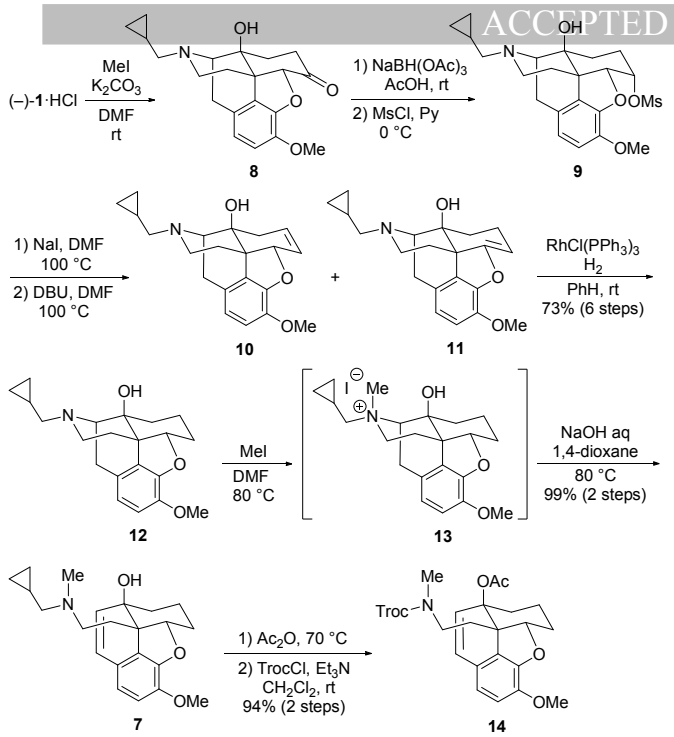
(–)-Galanthamine (**4**),[16] an alkaloid isolated from the Caucasian snowdrop *Galanthus woronowii*, and also from another species of the Amaryllidaceae family, *Lycoris radiata*, is a prescription drug for the treatment of Alzheimer's disease in Europe, the United States and Japan.[17] The mechanism of the anti-Alzheimer's disease effect is derived from the dual action on the cholinergic system, not only inhibiting acetylcholinesterase (AChE) activity but also allosterically modulating the nicotinic acetylcholine receptor.[18] Many reports have described the synthesis of **4**[19] and its derivatives.[20] We were also interested in efficient synthesis of **4** maximizing the similarities with the partial structure of naltrexone (**1**). However, at that time, the lack of a method to remove the carbon (C9) from **1** inevitably led us to synthesize (–)-homogalanthamine[15] instead of (–)-**4**. After reporting the synthesis of (–)-homogalanthamine, we discovered that the C9 removal method cited in the synthesis of mesembrane[21] was applicable to the synthesis of (–)-**4**. In consideration of the key step, we proposed a retrosynthetic pathway of (–)-**4** that differed from that of (–)-homogalanthamine in Scheme 2. The D-ring in **1** can be cleaved by the Hofmann elimination to give an allyl alcohol **7**. A keto-aldehyde **6** would be transformed from **7**, and then, deprotection of the 2,2,2-trichloroethoxycarbonyl (Troc) group of **6** and reductive amination of the resulting imine would lead to ketone **5** with a 7-membered ring. Finally, the ketone group would be converted to the desired allyl alcohol moiety to accomplish synthesis of (–)-**4**. However, again, we encountered the formidable side reactions derived from the reactivity of the naltrexone in the synthesis of (–)-**4** from **1**. We overcame these side reactions and attained the synthesis of (–)-**4**. Herein, we report the two synthetic methods for (–)-**4** from **1**.



Scheme 2. Retrosynthesis of (–)-**4** from naltrexone (**1**).

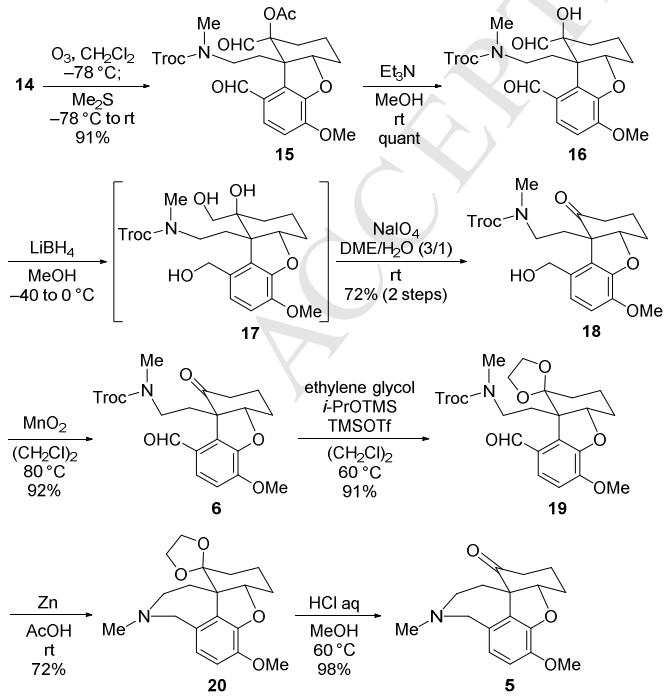
2. Results and discussion

Naltrexone (**1**) was converted to the methyl ether **8** with methyl iodide. It was our bitter experience that the direct removal of the ketone group by either the Clemmensen-type[22] or the Wolff–Kishner reductions[23] led to the cleavage reaction of the 4,5-epoxy ring. Therefore, we applied the longer indirect method as follows: (1) reduction of the ketone with sodium triacetoxy borohydride, (2) mesylation of the resulting α-hydroxy compound with mesyl chloride, and (3) treatment of the mesylate **9** with sodium iodide followed by treatment with DBU to give the isomeric mixtures of double bond **10** and **11**. The obtained mixtures were reduced with Wilkinson's catalyst in benzene to afford a saturated single compound **12** in 73% yield over six steps (Hydrogenation of compound **10** with heterogeneous catalysts like PtO_2 or Pd/C led to the 4,5-epoxy ring opening).[15] The key compound **12** obtained *via* this laborious route was subjected to the Hofmann elimination reaction with methyl iodide followed by treatment with sodium hydroxide to give the 9–17 bond cleaved product **7** in 99% yield in two steps. The resulting allyl alcohol was acetylated with Ac_2O/pyridine followed by treatment with TrocCl to give acetate **14** in 94% yield in two steps (Scheme 3).[21]



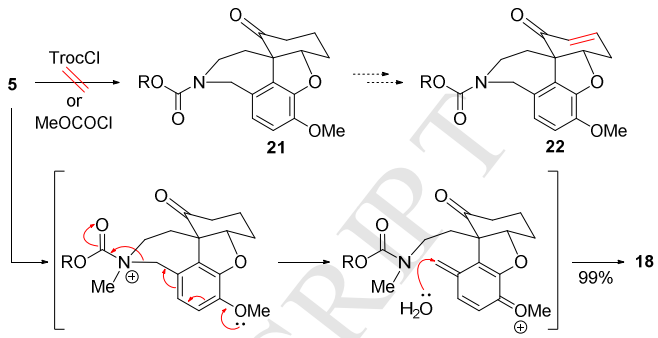
Scheme 3. Synthesis of **14** from (–)-**1**·HCl.

Then, the obtained acetate **14** was subjected to ozonolysis to afford a dialdehyde **15** followed by methanolysis to produce a dialdehyde-alcohol **16** in quantitative yield. The obtained **16** was reduced with $LiBH_4$ in MeOH followed by treatment with $NaIO_4$ to afford a keto-alcohol **18**, in which the one carbon (C9) was removed, *via* an intermediate triol **17** in 72% yield in two steps. The keto-alcohol **18** was oxidized with MnO_2 to give a keto-aldehyde **6** in 92%. The ketone group was treated with ethylene glycol to give an acetal compound **19** in 91%. The deprotection of the Troc group by using a Zn–acetic acid system and the subsequent cyclization of the resulting secondary amine gave **20**. Finally, hydrolysis with HCl aq. gave the important intermediate ketone **5** (Scheme 4).



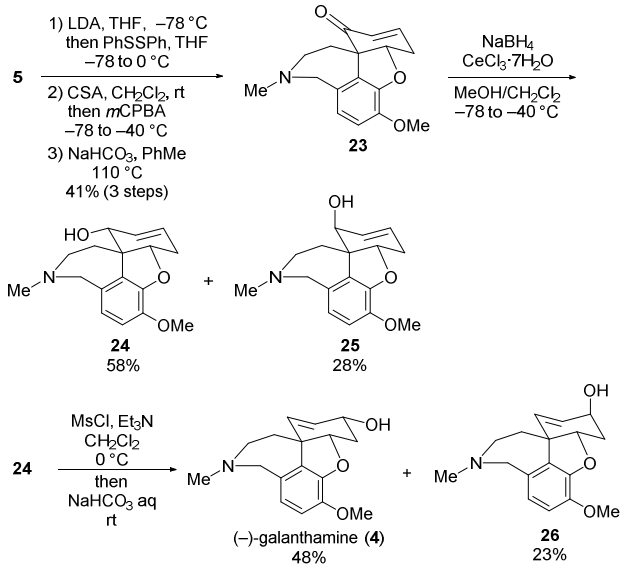
Scheme 4. Synthesis of intermediate **5**.

Next, we attempted to protect the tertiary amine of **5** using TrocCl or methyl chloroformate to obtain the corresponding carbamate **21** because of the protection of the 17-amino group from the oxidation of the sulfide with *m*CPBA in the next step, which is needed for formation of α,β-unsaturated ketone **22** by β-elimination of sulfoxide at the following stage. However, an undesirable ring-cleavage reaction proceeded to give **18**, which was the four-step prior product, in 99% yield (Scheme 5).



Scheme 5. Undesired side reaction of **5**.

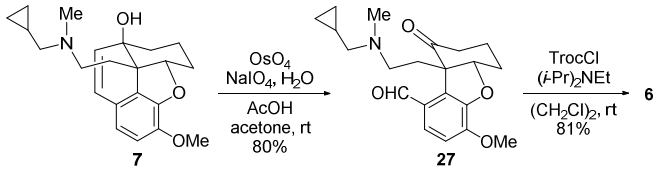
The undesired side reaction led us to protect the 17-amino group with acid in the oxidation of the sulfide instead of performing the amidation. After treatment of **5** with LDA and diphenyl disulfide, we then performed the protection of the tertiary amine by protonation under acidic condition (CSA) followed by *m*CPBA oxidation of the sulfide and the β-elimination of the resulting sulfoxide afforded a desired α,β-unsaturated ketone **23** (Scheme 6). The Luche reduction of **23** gave a diastereomeric mixture of allyl alcohols **24** and **25** (58% and 28% yields, respectively). The structure of the obtained **24** was determined by X-ray crystallographic analysis (see supplementary data). Finally, mesylation of **24** and the following elimination gave (–)-galanthamine (**4**) in 48% and the diastereomer **26** in 23%.[24] The structure of the obtained **4** was determined by X-ray crystallographic analysis (see supplementary data).



Scheme 6. Synthesis of (–)-galanthamine (**4**).

Although we obtained the final objective (–)-**4**, the synthetic steps, especially the removal step of the one carbon at the C9 position was extremely long. Therefore, we earnestly examined the alternative shorter synthetic route. We tried to directly obtain a keto-aldehyde **27** from the Hofmann elimination product **7** (Scheme 7). As we expected, the Lemieux–Johnson oxidation of

7 afforded the desired C9-carbon removal to give **27** in 80%.[25] The cyclopropylmethyl group of **27** was removed with TrocCl to give the compound **6**. The resulting keto-aldehyde **6** was converted to the objective (–)-galanthamine (**4**) *via* the same routes shown in Schemes 4 and 6. As a result, the alternative synthetic pathway succeeded to give the final product (–)-**4** by a five-step shortcut, compared to the previous route.



Scheme 7. Alternative synthesis of **6** from **7**.

3. Conclusion

We have described the specific reactions of naltrexone (**1**) which were sometimes useful and which also sometimes interfered with the pathway to the successful synthesis of (–)-galanthamine (**4**). Especially, we often encountered the cleavage reaction of the 4,5-epoxy ring, the reductive removal of the ketone group at the C6 position, and the reduction of the double bonds in C5–C6 and C6–C7 positions in the case of synthesis of both (–)-homogalanthamine and (–)-**4**. Thus, we had no other choice except the laborious long reaction sequence. Another unexpected side reaction was the azepane ring cleavage reaction which gave compound **18**, which we had prepared four steps earlier in the conversion of **5**. This awkward side reaction was circumvented by the protection of the tertiary amine with acid instead of by urethane formation. Furthermore, we found a five-step shorter synthetic route to obtain the key intermediate, keto-aldehyde **6** which led to the effective synthesis of (–)-**4**.

The description of the above side reactions is expected to be helpful information for medicinal chemists who could use the 4,5-epoxymorphinan skeleton to prepare useful compounds.

4. Experimental section

4.1. General

All melting points were determined on a Yanaco MP melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectral data were obtained with a JEOL JNM-ECS 400 instruments and an Agilent Technologies VXR-400NMR. Chemical shifts are quoted in ppm using tetramethylsilane (δ = 0 ppm) and CD_3OD (δ = 3.31 ppm) as the reference for ^{1}H NMR spectroscopy, $CDCl_3$ (δ = 77.0 ppm) and CD_3OD (δ = 49.0 ppm) for ^{13}C NMR spectroscopy. Mass spectra were measured with a JEOL JMS-T100LP spectrometer. Column chromatography was carried out on silica gel (spherical, neutral, 40–50 µm, Kanto Chemical Co., Japan) and amino silica gel (60µm, Fuji Silysia Chemical Ltd., Japan). Thin layer chromatography (TLC) and preparative TLC were performed on Merck TLC and PLC silica gel 60 F_{254} (0.25 mm and 0.5 mm) plates.

*4.2. (4R,4aS,7aS,12bS)-3-(Cyclopropylmethyl)-9-methoxy-1,2,3,4,5,6,7,7a-octahydro-4aH-4,12-methanobenzofuro[3,2-e]isoquinolin-4a-ol (**12**)*

Compound **12** was synthesized by a modified procedure of the reported method.[15]

To a suspension of naltrexone hydrochloride (30.2 g, 79.9 mmol) in DMF (200 mL) was added K_2CO_3 (27.6 g, 200 mmol) and MeI (5.24 mL, 83.9 mmol), and the mixture was stirred at room temperature under an argon atmosphere. After 11 h, MeI (0.2 mL, 3.20 mmol) was added. After stirring for 13 h, H_2O (600 mL) was added and the mixture was extracted with Et_2O (800, 300, 100, 100 mL). The organic layer was washed with brine and the water layer was extracted with Et_2O (100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (28.8 g, white solid) was used in the next step without further purification. To a stirring solution of the crude product (28.8 g) in AcOH (300 mL) was added $NaBH(OAc)_3$ (25.4 g, 120 mmol), and the mixture was stirred at room temperature under an argon atmosphere. After 0.5 h, acetone (50 mL) was added. After stirring for 2 h, the reaction mixture as concentrated under reduced pressure, and then azeotropically dried with toluene two times to remove the remained AcOH. The residue was basified with H_2O (100 mL) and K_2CO_3 (pH 9). The mixture was poured to H_2O (150 mL) and extracted with $CHCl_3$ (200, 100, 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (27.3 g, white solid) was used in the next step without further purification. The crude product (27.3 g) was dissolved in pyridine (200 mL) and cooled to 0 °C under an argon atmosphere. To the solution was added MsCl (12 mL, 155 mmol), and the mixture was stirred for 0.5 h. The reaction mixture was poured to crushed ice and basified with K_2CO_3 (pH 9–10). The mixture was poured to H_2O (300 mL) and extracted with $CHCl_3$ (400, 200, 100, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (35.9 g, brown amorphous material) was used in the next step without further purification. To a solution of the crude product (35.9 g) in DMF (300 mL) was added NaI (229.7 g, 1.53 mol), and the mixture was stirred at 100 °C for 15 h under an argon atmosphere. Before cooling to room temperature, the hot reaction mixture was poured to H_2O, basified with $NaHCO_3$ and extracted with $CHCl_3$ (600, 300, 150, 100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (35.4 g, brown solid) was used in the next step without further purification. To a solution of the crude product (35.4 g) in DMF (300 mL) was added DBU (44.5 mL, 298 mmol), and the mixture was stirred at 100 °C for 21 h under an argon atmosphere. The reaction mixture was poured to saturated aqueous $NaHCO_3$ solution (300 mL)/H_2O (400 mL) and extracted with Et_2O (400, 200, 200, 100 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (30.6 g, brown amorphous material) was used in the next step without further purification. To a mixture of the crude product (4.96 g) and $RhCl(PPh_3)_3$ (1.34 g, 1.45 mmol) was added degassed benzene (80 mL). The mixture was stirred at room temperature for 40 h under a hydrogen atmosphere, and then concentrated under reduced pressure. The crude residue was purified by column chromatography on amino silica gel (EtOAc/*n*-hexane = 0/1 → 1/4); then silica gel (0–20% (28% NH_3 aq.:MeOH:CPME = 1:9:90)/*n*-hexane) to afford compound **12** (4.01 g, 73% in 6 steps) as a brown oil.

*4.3. (4aS,4a^{1}S,7aR)-4a^1-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-3-methoxy-4a,5,6,7-tetrahydrophenanthro[4,5-bcd]furan-7a(4a^{1}H)-ol (**7**)*

To a solution of compound **12** (1.0 g, 2.93 mmol) in DMF (10 mL) was added MeI (10 mL, 161 mmol), and the mixture was stirred at 80 °C under an argon atmosphere for 72 h. Additional MeI (3.0 mL, 48.2 mmol) was added. After stirring for 24 h, the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in 1,4-dioxane (12 mL), and 1 M aqueous NaOH solution (12 mL) was added. The mixture was stirred for 2 h at 80 °C under an argon atmosphere. The reaction mixture was poured to H_2O (20 mL) and extracted with $CHCl_3$ (50, 30, 20 mL). The organic layer was dried over Na_2SO_4 and

evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (0–2% (28% NH_3 aq./MeOH = 1:9) in $CHCl_3$) to afford compound **7** (1.03 g, 99%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08–0.18 (m, 2H), 0.48–0.59 (m, 2H), 0.82–0.93 (m, 1H), 1.21 (ddd, *J* = 13.6, 13.6, 2.8 Hz, 1H), 1.25–1.39 (m, 2H), 1.47–1.61 (m, 1H), 1.70–1.82 (m, 2H), 1.84–1.95 (m, 1H), 2.15–2.32 (m, 4H), 2.34 (s, 3H), 2.41–2.51 (m, 1H), 3.87 (s, 3H), 4.78 (dd, *J* = 9.6, 8.0 Hz, 1H), 5.68 (d, *J* = 9.2 Hz, 1H), 6.24 (d, *J* = 9.2 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 8.02 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.8, 4.2, 8.4, 15.6, 29.6, 34.2, 36.3, 41.6, 50.3, 52.9, 56.1, 62.2, 73.7, 92.0, 112.2, 117.2, 121.9, 124.1, 131.7, 140.4, 143.8, 145.2. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{22}H_{30}NO_3$: 356.2226; Found: 356.2221.

*4.4. (4aS,4a^{1}S,7aR)-3-methoxy-4a^1-(2-{methyl[(2,2,2-trichloroethoxy)carbonyl]amino}ethyl)-4a,5,6,7-tetrahydrophenanthro[4,5-bcd]furan-7a(4a^{1}H)-yl acetate (**14**)*

A mixture of compound **7** (175 mg, 0.492 mmol) in Ac_2O (1 mL) was stirred at 70 °C for 3 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and the remained Ac_2O was azeotropically removed with toluene. To a solution of the residue in CH_2Cl_2 (2 mL) was added Et_3N (206 μL, 1.48 mmol) and 2,2,2-trichloroethyl chloroformate (136 μL, 0.988 mmol) under cooling with ice-water, and the mixture was stirred at room temperature for 0.5 h. Saturated aqueous $NaHCO_3$ solution (5 mL) was added, and the mixture was extracted with $CHCl_3$ (15, 12, 9 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1/6 → 2/1) to afford compound **14** (241 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19–1.43 (m, 4H), 1.93 (dt, *J* = 12.4, 5.2 Hz, 0.4H), 2.02 (dt, *J* = 12.8, 4.8 Hz, 0.6H), 2.07–2.36 (m, 2H), 2.10 (s, 1.8H), 2.13 (s, 1.2H), 2.76–2.89 (m, 1.6H), 2.81 (s, 1.2H), 2.83 (s, 1.8H), 3.11–3.30 (m, 0.8H), 3.55 (dt, *J* = 13.6, 4.4 Hz, 0.6H), 3.88 (s, 3H), 4.53 (d, *J* = 12.0 Hz, 0.6H), 4.66 (d, *J* = 12.0 Hz, 0.4H), 4.72 (d, *J* = 12.0 Hz, 0.4H), 4.79 (d, *J* = 12.0 HZ, 0.6H), 4.89–4.97 (m, 1H), 6.32 (d, *J* = 10.0 Hz, 1H), 6.46 (d, *J* = 10.0 Hz, 0.6H), 6.49 (d, *J* = 10.0 Hz, 0.4H), 6.63–6.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 22.4, 29.5, 29.6, 30.1, 30.3, 31.6, 31.9, 33.9, 34.9, 45.6, 46.2, 49.1, 56.0, 74.8, 87.5, 88.0, 90.2, 90.6, 95.5, 95.7, 112.66, 112.7, 118.1, 118.3, 122.7, 122.8, 123.9, 124.0, 127.8, 128.2, 129.5, 129.7, 143.9, 145.2, 145.3, 154.0, 154.1, 169.8, 170.1. HRMS–ESI (*m*/*z*): $[M + Na]^+$ Calcd for $C_{23}H_{26}Cl_3NO_6Na$: 540.0723; Found 540.0743.

*4.5. (1S,4aS,9bS)-1,9-diformyl-6-methoxy-9b-(2-{methyl[(2,2,2-trichloroethoxy)carbonyl]amino}ethyl)-1,2,3,4,4a,9b-hexahydrodibenzo[b,d]furan-1-yl acetate (**15**)*

A solution of compound **14** (1.65 g, 3.18 mmol) in CH_2Cl_2 (400 mL) was stirred at –78 °C, and a stream of O_3 was introduced through a pipet for 8 min. The remained O_3 was removed by sparging N_2 gas for 20 min, and cooled Me_2S (–78 °C, 7.0 mL, 95.3 mmol) was added. After sparging N_2 gas for 20 min, the mixture was stirred at room temperature for 3 h, and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane, gradient) to afford compound **15** (1.59 g, 91%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39–1.54 (m, 1H), 1.68–2.42 (m, 7H), 2.21 (s, 3H), 2.93 (s, 1.8H), 2.96 (s, 1.2H), 3.07–3.21 (m, 1H), 3.41–3.60 (m, 1H), 3.98 (s, 3H), 4.58 (d, *J* = 12.0 Hz, 0.6H), 4.69 (d, *J* = 12.0 Hz, 0.4H), 4.75 (d, *J* = 12.0 Hz, 0.4H), 4.90–4.96 (m, 1H), 4.96 (d, *J* = 12.0 Hz, 0.6H), 6.99 (d, *J* = 8.4 Hz, 0.4H), 7.00 (d, *J* = 8.4 Hz, 0.6H), 7.38 (d, *J* = 8.4 Hz, 1H), 9.56 (s, 1H), 9.67 (s, 0.6H), 9.68 (s, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 14.4, 20.7, 20.8, 20.83, 21.2, 21.4, 28.7, 29.3, 34.3, 35.2, 46.1, 46.5, 54.7, 54.73, 56.1, 75.0, 75.02, 87.8, 88.0, 88.5, 95.7, 111.2, 123.7, 124.0, 128.6, 128.7, 131.9, 132.1, 150.2, 150.3, 153.8, 154.2, 169.8, 169.81, 191.7, 191.8, 197.0. HRMS–ESI (*m*/*z*): $[M + Na]^+$ Calcd for $C_{23}H_{26}Cl_3NO_8Na$: 572.0621; Found 572.0635.

*4.6. 2,2,2-trichloroethyl {2-[(5aS,9S,9aS)-1,9-diformyl-9-hydroxy-4-methoxy-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-yl]ethyl}(methyl)carbamate (**16**)*

To a solution of compound **15** (100 mg, 0.182 mmol) in MeOH (2.5 mL) was added Et_3N (35 μL, 0.251 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1/3 → 3/1) to afford compound **16** (93 mg, quant.) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57–1.89 (m, 3H), 1.92–2.16 (m, 3H), 2.37–2.58 (m, 1H), 2.72–3.02 (m, 2H), 2.92 (s, 1.8H), 2.96 (s, 1.2H), 3.39–3.63 (m, 1H), 3.98 (s, 1.8H), 3.99 (s, 1.2H), 4.54–4.73 (m, *J* = 12.0 Hz, 2.4H), 4.85 (d, *J* = 12.0 Hz, 0.6H) 4.88–4.97 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 0.4H), 6.96 (d, *J* = 8.4 Hz, 0.6H), 7.48 (d, *J* = 8.4 Hz, 1H), 9.26 (s, 0.6H), 9.30 (s, 0.4H), 9.93 (s, 0.6H) 9.94 (s, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 16.9, 23.6, 23.64, 26.1, 26.9, 29.3, 29.6, 34.2, 35.0, 45.8, 46.4, 53.6, 56.2, 75.0, 79.1, 79.2, 87.0, 87.1, 95.6, 111.4, 127.4, 128.8, 128.9, 129.2, 129.4, 148.8, 148.9, 150.6, 150.63, 153.7, 154.1, 191.3, 191.4, 201.6, 201.8. HRMS–ESI (*m*/*z*): $[M + Na]^+$ Calcd for $C_{21}H_{24}Cl_3NO_7Na$: 530.0516; Found 530.0531.

*4.7. 2,2,2-trichloroethyl {2-[(5aS,9aS)-1-(hydroxymethyl)-4-methoxy-9-oxo-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-yl]ethyl}(methyl)carbamate (**18**)*

To a stirred solution of compound **16** (245 mg, 0.482 mmol) in MeOH (12 mL) was added $LiBH_4$ (240 mg, 11.0 mmol) at –40 °C. After 0.5 h, the reaction mixture was warmed to 0 °C and stirred for 0.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and the mixture was extracted with $CHCl_3$ (24, 18, 12 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To a solution of the residue in DME/H_2O (3/1, 16 mL) was added $NaIO_4$ (300 mg, 1.40 mmol), and the mixture was stirred at room temperature. After 12 h, H_2O (6 mL) was added and the mixture was extracted with CH_2Cl_2 (15, 12, 7 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/*n*-hexane = 1/3 → 3/1) to afford compound **18** (166 mg, 72%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.89 (m, 2H), 1.97–2.13 (m, 2H), 2.20–2.31 (m, 1H), 2.36–2.57 (m, 3H), 2.85–3.00 (m, 0.5H), 2.93 (s, 1.5H), 2.98 (s, 1.5H), 3.01–3.27 (m, 1H), 3.47–3.59 (m, 0.5H), 3.90 (s, 3H), 4.43–4.74 (m, 3.5H), 4.84 (d, *J* = 12.0 Hz, 0.5H), 5.00–5.10 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 0.5H), 6.85 (d, *J* = 8.4 Hz, 0.5H), 6.89 (d, *J* = 8.4 Hz, 0.5H), 6.95 (d, *J* = 8.4 Hz, 0.5H). One proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 17.6, 28.1, 28.2, 31.3, 32.1, 34.4, 35.0, 38.0, 38.2, 44.9, 45.7, 55.8, 60.7, 60.9, 61.2, 75.0, 88.0, 88.2, 95.4, 95.5, 112.3, 112.6, 123.0, 123.2, 125.1, 125.14, 130.5, 131.0, 143.9, 144.2, 149.1, 153.9, 154.3, 211.2, 211.4. HRMS–

ESI (*m/z*): [M + Na]$^+$ Calcd for $C_{20}H_{24}Cl_3NO_6Na$: 502.0567; Found 502.0562.

*4.8. 2,2,2-Trichloroethyl {2-[(5aS,9aS)-1-formyl-4-methoxy-9-oxo-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-yl]ethyl}(methyl)carbamate (**6**)*

To a solution of compound **18** (150 mg, 0.312 mmol) in 1,2-dichloroethane (5 mL) was added activated MnO_2 (405 mg, 4.66 mmol), and the suspension was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/*n*-hexane = 1/3 → 1/1) to afford compound **6** (138 mg, 92%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73–2.25 (m, 5H), 2.33–2.59 (m, 3H), 2.77–2.89 (m, 1H), 2.91 (s, 1.8H), 2.94 (s, 1.2H), 3.38–3.51 (m, 1H), 3.995 (s, 1.2H), 4.00 (s, 1.8H), 4.56 (d, *J* = 12.0 Hz, 0.6H), 4.66 (d, *J* = 12.0 Hz, 0.4H), 4.70 (d, *J* = 12.0 Hz, 0.4H), 4.79 (d, *J* = 12.0 Hz, 0.6H), 5.06–5.20 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 0.6H), 7.49 (d, *J* = 8.4 Hz, 0.4H), 9.90 (s, 0.6H), 9.94 (s, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 18.5, 28.2, 32.3, 32.8, 34.2, 35.0, 38.0, 44.9, 45.4, 56.2, 60. 9, 61.0, 74.96, 74.99, 90.0, 90.4, 95.5, 95.6, 111.6, 127.2, 127.3, 127.57, 127.6, 127.9, 149.3, 149.4, 150.4, 153.8, 154.1, 189.8, 208.3, 208.6. HRMS–ESI (*m/z*): [M + Na]$^+$ Calcd for $C_{20}H_{22}Cl_3NO_6Na$: 500.0410; Found 500.0412.

*4.9. 2,2,2-Trichloroethyl {2-[(4aS,9bS)-9-formyl-6-methoxy-2,3,4,4a-tetrahydro-9bH-spiro[dibenzo[b,d]furan-1,2'-[1,3]dioxolane]-9b-yl]ethyl}(methyl)carbamate (**19**)*

To a solution of compound **6** (2.96 g, 6.18 mmol) in 1,2-dichloroethane (60 mL) were added ethylene glycol (1.8 mL, 32.3 mmol), isopropoxytrimethylsilane (17 mL, 95.7 mmol) and trimethylsilyl trifluoromethanesulfonate (570 μL, 3.15 mmol). The mixture was stirred at 60 °C for 6 h under an argon atmosphere. The reaction mixture was poured to saturated aqueous $NaHCO_3$ solution (70 mL) and extracted with $CHCl_3$ (60 mL×2). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1/2) to afford compound **19** (2.94 g, 91%) as a colorless oil.

The 4:6 ratio rotamer derived from the carbamate was observed.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51–1.78 (m, 3H), 1.88–2.06 (m, 3H), 2.20–2.42 (m, 1H), 2.55–2.77 (m, 1H), 2.88–3.04 (m, 1H), 2.95 (s, 1.8H), 2.97 (s, 1.2H), 3.14 (dd, *J* = 14.8, 7.2 Hz, 0.4H), 3.21 (dd, *J* = 14.8, 7.2 Hz, 0.6H), 3.42–3.62 (m, 1H), 3.69–3.93 (m, 3H), 3.95 (s, 3H), 4.64 (d, *J* = 12.0 Hz, 0.6H), 4.70 (d, *J* = 12.0 Hz, 0.4H), 4.74 (d, *J* = 12.0 Hz, 0.4H), 4.78–4.91 (m, 1.6H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 0.6H), 7.55 (d, *J* = 8.4 Hz, 0.4H), 10.25 (s, 0.6H), 10.28 (s, 0.4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0, 17.2, 23.4, 23.4, 28.9, 29.1, 29.7, 34. 6, 35.2, 46.2, 46.9, 55.9, 56.2, 56.2, 64.4, 64.5, 64.8, 75.1, 86.9, 87.0, 95.6, 95.6, 110.2, 111.2, 121.8, 122.0, 128.3, 130.6, 131.0, 149.2, 149.8, 154.0, 154.2, 190.4, 190.7. HRMS–ESI (*m/z*): [M + Na]$^+$ Calcd for $C_{22}H_{26}Cl_3NO_7Na$: 544.0673; Found 544.0661.

*4.10. (4aS,8aS)-3-Methoxy-11-methyl-4a,5,6,7,9,10,11,12-octahydrospiro[benzo[2,3]benzofuro[4,3-cd]azepine-8,2'-[1,3]dioxolane] (**20**)*

To a solution of compound **19** (921 mg, 1.76 mmol) in AcOH (15 mL) was added zinc powder (4.6 g, 70.3 mmol), and the mixture was stirred at room temperature for 22 h under an argon atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and adjusted to pH 8 with ammonia solution, and then extracted with $CHCl_3$ (20, 10, 5, 5 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1–7% (28% NH_3 aq.:MeOH = 1:9) in $CHCl_3$) to afford compound **20** (420 mg, 72%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56–1.92 (m, 5H), 1.95–2.09 (m, 1H), 2.09–2.18 (m, 1H), 2.21–2.32 (m, 1H), 2.29 (s, 3H), 2.77–2.91 (m, 1H), 3.09 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.47 (d, *J* = 14.4 Hz, 1H), 3.47–3.58 (m, 1H), 3.70–3.84 (m, 2H), 3.85 (s, 3H), 3.92 (ddd, *J* = 6.8, 6.8, 3.6 Hz, 1H), 4.40 (d, *J* = 14.4 Hz, 1H), 4.40–4.46 (m, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 23.2, 29.3, 29.8, 41.3, 54.5, 54.7, 55.6, 59.4, 63.9, 64.2, 92.7, 110.6, 112.3, 120.9, 130.2, 131.1, 143.6, 148.7. HRMS–ESI (*m/z*): [M + H]$^+$ Calcd for $C_{19}H_{26}NO_4$: 332.1862; Found 332.1862.

*4.11. (4aS,8aS)-3-Methoxy-11-methyl-4a,5,6,7,9,10,11,12-octahydro-8H-benzo[2,3]benzofuro[4,3-cd]azepin-8-one (**5**)*

The mixture of compound **20** (229 mg, 0.690 mmol) in MeOH (3.0 mL) and 2 M HCl (3.0 mL) was stirred at 60 °C for 12 h under an argon atmosphere. The reaction mixture was adjusted to pH 10 with K_2CO_3 and saturated aqueous $NaHCO_3$ solution, and then extracted with $CHCl_3$ (12, 6, 3, 3 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (3–5% (28% NH_3 aq.:MeOH = 1:9) in $CHCl_3$) to afford compound **5** (195 mg, 98%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (ddd, J = 14.4, 2.8, 2.8 Hz, 1H), 1.95–2.27 (m, 4H), 2.32–2.55 (m, 3H), 2.35 (s, 3H), 2.97–3.07 (m, 2H), 3.57 (d, *J* = 14.8 Hz, 1H), 3.85 (s, 3H), 4.42 (d, *J* = 14.8 Hz, 1H), 4.69–4.76 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 25.9, 30.2, 38.4, 41.4, 53.8, 55.8, 61.0, 62.4, 91.7, 111.2, 121.6, 129.9, 132.2, 143.4, 146.9, 211.3. HRMS–ESI (*m/z*): [M + H]$^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1600; Found 288.1599.

*4.12. (4aS,8aS)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8H-benzo[2,3]benzofuro[4,3-cd]azepin-8-one (**23**)*

A solution of compound **5** (195 mg, 0.678 mmol) in THF (4.0 mL) was added to LDA [prepared from freshly distilled diisopropylamine (0.33 mL) and *n*-BuLi (1.6 M in *n*-hexane, 1.27 mL) in THF (4.0 mL)] with stirring at –78 °C under an argon atmosphere. After 0.5 h, a solution of diphenyl disulfide (740 mg, 3.39 mmol) in THF (4.0 mL) was added at –78 °C, and then the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with H_2O (10 mL), and the mixture was extracted with $CHCl_3$ (20, 10 mL, 5 mL×2). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel ($CHCl_3$/*n*-hexane = 9/1 → 0.5–5% (28% NH_3 aq./MeOH = 1:9) in $CHCl_3$) to afford a mixture of α- and β-phenylsulfide. To a solution of α- and β-phenylsulfide in CH_2Cl_2 (5.0 mL) was added (±)-camphor-10-sulfonic acid (103 mg, 0.443 mmol), and the mixture was stirred at room temperature for 10 min under an argon atmosphere. A solution of *m*-CPBA (65%, 118 mg, 0.444 mmol) in CH_2Cl_2 (4.0 mL) was added at −78 °C, and the mixture was stirred at –40 °C for 0.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (5.0 mL). The reaction mixture was poured to saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), and extracted with $CHCl_3$ (20, 10, 5, 3 mL). The organic layer was

washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The mixture of the crude residue and $NaHCO_3$ (112 mg) in toluene (9.0 mL) was stirred at 110 °C for 2 h under an argon atmosphere. Saturated aqueous $NaHCO_3$ solution (10 mL) and H_2O (10 mL) was added, and the mixture was extracted with $CHCl_3$ (12, 6, 3, 3 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel ($CHCl_3$/*n*-hexane = 9/1 → 0–3% (28% NH_3 aq.:MeOH = 1:9) in $CHCl_3$) and PLC ((28% NH_3 aq.:MeOH = 1:9)/$CHCl_3$ = 1/15) to afford compound **23** (79.6 mg, 41%) as a brown amorphous.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.77 (ddd, *J* = 14.0, 3.6, 1.6 Hz, 1H), 2.11–2.24 (m, 1H), 2.41 (s, 3H), 2.79 (dddd, *J* = 20.4, 5.2, 2.8, 2.8 Hz, 1H), 3.01 (ddd, *J* = 13.6, 2.8, 2.8 Hz, 1H), 3.11 (dd, *J* = 20.4, 5.6 Hz, 1H), 3.33–3.47 (m, 1H), 3.61 (d, *J* = 14.8 Hz, 1H), 3.83 (s, 3H), 4.71 (d, *J* = 14.8 Hz, 1H), 4.74–4.79 (m, 1H), 6.12 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.79–6.89 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 29.5, 41.3, 53.3, 55.8, 57.8, 60.7, 88.6, 111.3, 122.0, 129.5, 130.3, 132.3, 143.2, 144.4, 146.8, 197.3. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{17}H_{20}NO_3$: 286.1443; Found 286.1401.

*4.13. (4aS,8R,8aR)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8H-benzo[2,3]benzofuro[4,3-cd]azepin-8-ol (**24**); (4aS,8S,8aR)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8H-benzo[2,3]benzofuro[4,3-cd]azepin-8-ol (**25**)*

To a solution of compound **23** (79.6 mg, 0.277 mmol) in MeOH (2.0 mL) and CH_2Cl_2 (1.0 mL) was added $CeCl_3 \cdot 7\ H_2O$ (314 mg, 0.842 mmol). The mixture was stirred at room temperature for 10 min under an argon atmosphere, and then $NaBH_4$ (21.3 mg, 0.563 mmol) was added at −78 °C. The reaction mixture was stirred at −40 °C for 1 h. The reaction was quenched with acetone (3 mL). After warming to room temperature, the mixture was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and H_2O (10 mL), and extracted with $CHCl_3$ (12, 6 mL, 3 mL×2). The organic layer was washed with brine and dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by PLC ((28% NH_3 aq.:MeOH = 1:9)/$CHCl_3$ = 1/10) to afford compound **24** (46.5 mg, 58%) as a colorless amorphous and compound **25** (22.5 mg, 28%) as a colorless oil. A portion of synthesized compound **24** was recrystallized from Et_2O/*n*-hexane to give colorless prism crystals.

Compound **24**

mp 163–165 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 1.63–1.91 (m, 1H), 2.00–2.11 (m, 1H), 2.29–2.48 (m, 1H), 2.35 (s, 3H), 2.75 (ddd, *J* = 17.6, 5.6, 2.8 Hz, 1H), 2.84–3.05 (m, 1H), 3.24–3.45 (m, 1H), 3.52 (d, *J* = 14.4 Hz, 1H), 3.78 (s, 3H), 4.20–4.46 (m, 2H), 4.57–4.64 (m, 1H), 5.76–5.85 (m, 1H), 5.88–5.96 (m, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H). One proton (OH) was not observed. ^{13}C NMR (100 MHz, CD_3OD): δ 27.4, 36.6, 42.7, 55.1, 56.6, 62.1, 70.0, 90.0, 113.0, 122.6, 125.8, 131.7, 132.7, 133.4, 144.9, 149.8. One carbon was not observed. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1600; Found 288.1594.

Compound **25**

^{1}H NMR (400 MHz, CD_3OD): δ 1.70–1.88 (m, 1H), 2.18 (ddd, *J* = 14.4, 5.6, 2.8 Hz, 1H), 2.34 (s, 3H), 2.53–2.61 (m, 1H), 2.63–2.73 (m, 1H), 2.83–2.95 (m, 1H), 3.25–3.42 (m, 2H), 3.59 (d, *J* = 14.8 Hz, 1H), 3.79 (s, 3H), 4.26 (d, *J* = 14.8 Hz, 1H), 4.29–4.39 (m, 1H), 4.52 (dd, *J* = 4.8, 1.6 Hz, 1H), 5.82–5.92 (m, 1H), 5.94–6.04 (m, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 27.9, 31.7, 43.2, 53.8, 56.2, 56.6, 61.1, 69.0, 90.9, 113.0, 122.5, 128.0, 129.3, 133.0, 135.1, 145.0, 149.4. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1600; Found 288.1600.

*4.14. (4aR,5S,8aR)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8H-benzo[2,3]benzofuro[4,3-cd]azepin-5-ol, (–)-galanthamine (**4**); (4aR,5R,8aR)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8H-benzo[2,3]benzofuro[4,3-cd]azepin-5-ol (**26**)*

To a solution of compound **24** (69 mg, 0.240 mmol) in CH_2Cl_2 (5.0 mL) were added Et_3N (170 μL, 1.22 mmol) and MsCl (60 μL, 0.775 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 0.5 h, and then saturated aqueous $NaHCO_3$ solution (15 mL) was added. After stirring at room temperature for 1.5 h, the reaction mixture was extracted with $CHCl_3$ (30, 20, 10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by PLC ((28% NH_3 aq./MeOH = 1:9)/$CHCl_3$ = 2/25) to afford (–)-galanthamine (**4**) (33.1 mg, 48%) as a colorless solid and compound **26** (15.7 mg, 23%) as a colorless amorphous. A portion of synthesized (–)-galanthamine (**4**) was recrystallized from EtOAc/*n*-hexane to give light yellow needle crystals.

(–)-Galanthamine (**4**)

mp 128–130 °C (lit.26b; mp 128–129 °C). $[\alpha]^{20}_D$ −89.7° (*c* = 0.6, $CHCl_3$) (lit.26b; $[\alpha]^{25}_D$ −93.4° (*c* = 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51–1.64 (m, 1H), 2.01 (ddd, *J* = 16.0, 4.8, 2.8 Hz, 1H), 2.09 (ddd, *J* = 13.2, 13.2, 2.8 Hz, 1H), 2.40 (s, 3H), 2.50 (brs, 1H), 2.62–2.75 (m, 1H), 2.98–3.14 (m, 1H), 3.19–3.33 (m, 1H), 3.68 (d, *J* = 15.2 Hz, 1H), 3.83 (s, 3H), 4.09 (d, *J* = 15.2 Hz, 1H), 4.14 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.56–4.66 (m, 1H), 6.00 (dd, *J* = 10.0, 4.8 Hz, 1H), 6.07 (d, *J* = 10.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 33.7, 42.0, 48.1, 53.8, 55.8, 60.6, 62.0, 88.7, 111.0, 122.0, 126.8, 127.5, 129.3, 132.9, 144.0, 145.7. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1600; Found 288.1595.

All data are in agreement with the literature values.[26]

Compound **26**

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (ddd, *J* = 13.6, 13.6, 1.6 Hz, 1H), 1.72 (ddd, *J* = 13.6, 10.4, 2.4 Hz, 1H), 2.19 (ddd, *J* = 13.2, 13.2, 3.2 Hz, 1H), 2.38 (s, 3H), 2.79 (dddd, *J* = 14.0, 5.6, 4.0, 1.6 Hz, 1H), 2.99–3.12 (m, 1H), 3.20–3.33 (m, 1H), 3.63 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H), 4.07 (d, *J* = 15.2 Hz, 1H), 4.56–4.71 (m, 2H), 5.77–5.86 (m, 1H), 6.08 (ddd, *J* = 10.8, 1.6, 1.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H). One proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.4, 34.3, 42.1, 48.1, 54.0, 55.8, 60.4, 63.3, 88.4, 110.8, 121.5, 126.6, 129.2, 131.5, 132.9, 143.8, 146.6. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3$: 288.1600; Found 288.1590.

*4.15. (5aS,9aS)-9a-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-4-methoxy-9-oxo-5a,6,7,8,9,9a-hexahydrodibenzo[b,d]furan-1-carbaldehyde (**27**)*

To a stirred solution of compound **7** (19.8 mg, 55.7 μmol) in acetone (2.0 mL) and AcOH (0.2 mL) were added a solution of $NaIO_4$ (60.3 mg, 0.282 mmol) in H_2O (2.0 mL) and OsO_4 (2.0 mg/mL in *t*-BuOH, 0.72 mL, 5.66 μmol). The mixture was stirred at room temperature for 60 h under an argon atmosphere. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL) and saturated aqueous $NaHCO_3$ solution (15 mL), and the mixture was extracted with $CHCl_3$ (20, 10, 5 mL). The organic layer was dried over Na_2SO_4 and concentrated under

reduced pressure. The crude product was purified by PLC ((28% NH_3 aq./MeOH = 1:9)/$CHCl_3$ = 1/20) to afford compound **27** (16.0 mg, 80%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (–0.03)–0.10 (m, 2H), 0.39–0.51 (m, 2H), 0.69–0.81 (m, 1H), 1.81–2.36 (m, 9H), 2.24 (s, 3H), 2.37–2.56 (m, 3H), 3.98 (s, 3H), 5.09–5.14 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 10.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 4.6 (two carbons), 6.4, 18.7, 28.0, 30.0, 38.1, 40.3, 51.9, 56.3, 61.0, 61.3, 90.4, 112.0, 126.9, 127.1, 128.6, 149.9, 150.5, 190.8, 208.5. HRMS–ESI (*m*/*z*): $[M + H]^+$ Calcd for $C_{21}H_{28}NO_4$: 358.2018; Found: 358.2015.

*4.16. 2,2,2-Trichloroethyl {2-[(5aS,9aS)-1-formyl-4-methoxy-9-oxo-6,7,8,9-tetrahydrodibenzo[b,d]furan-9a(5aH)-yl]ethyl}(methyl)carbamate (**6**)*

To a solution of compound **27** (12.5 mg, 34.5 μmol) in 1,2-dichloroethane (1.0 mL) were added (*i*-Pr)$_2$NEt (18.3 μL, 0.105 mmol) and 2,2,2-trichloriethyl chloroformate (5.8 μL, 42.1 μmol), and the mixture was stirred at room temperature for 6 h under an argon atmosphere. Additional (*i*-Pr)$_2$NEt (18.3 μL, 0.105 μmol) and 2,2,2-trichloroethyl chloroformate (11.5 μL, 42.1 μmol) were added. After 13 h, additional (*i*-Pr)$_2$NEt (36.5 μL, 0.210 μmol) and 2,2,2-trichloroethyl chloroformate (2.8 μL, 83.5 μmol) were added. Finally, after 3 h, (*i*-Pr)$_2$NEt (18.3 μL, 0.105 μmol) was added. After stirring for 2 h, the reaction mixture was poured to saturated aqueous $NaHCO_3$ solution (5.0 mL) and extracted with $CHCl_3$ (5, 3, 2 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by PLC (EtOAc/*n*-hexane = 1/1) to afford compound **6** (13.6 mg, 81%) as a colorless oil.

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