Unique reactions of naltrexone derivatives and their application to the synthesis of galanthamine

Takahiro Okada

February 2019

Unique reactions of naltrexone derivatives and their application to the synthesis of galanthamine

Takahiro Okada

Doctoral Program in Chemistry

Submitted to the Graduate School of
Pure and Applied Sciences
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in
Science

at the
University of Tsukuba

Table of contents

List of Abbreviation

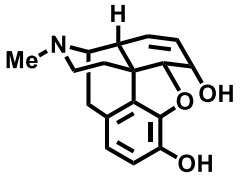
Ac	acetyl
aq.	aqueous
Arg	arginine
Asn	asparagine
Asp	aspartic acid
β-FNA	β-funaltrexamine
BNTX	7-benzylidene naltrexone
CPME	cyclopentyl methyl ether
CSA	(±)-camphor-10-sulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N,N*-diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
DOR	δ opioid receptor
ESI	electrospray ionization
Et	ethyl
EU	European Union
Gln	glutamine
Gly	glycine
HR-MS	high-resolution mass spectrometry
Ile	isoleucine
i-Pr	isopropyl
IR	infrared
KOR	κ opioid receptor
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Leu	leucine
Lys	lysine

m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Met	methionine
MOR	μ opioid receptor
mp	melting point
Ms	methanesulfonyl
n-Bu	normal butyl
N.D.	not detected
NMR	nuclear magnetic resonance
nor-BNI	nor-binaltorphimine
NTB	naltriben
NTI	naltrindole
OX_1R	orexin 1 receptor
Ph	phenyl
Phe	phenylalanine
PLC	preparative thin layer chromatography
Pro	proline
quant.	quantitative
rt	room temperature
t-Bu	tertiary butyl
Tf	triflyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Troc	2,2,2-trichloroethoxycarbonyl
Trp	tryptophan
Ts	tosyl
Tyr	tyrosine
US	United States

Chapter 1. General Introduction

1.1 History of opioids

Opium is a substance derived from the poppy (*Papaver Somniferum*), which has long been used for pain relief and to induce sleep.[1] However, since opium has serious side effects including dependence, many researchers have attempted to separate these undesirable actions. In 1803, Sertürner isolated an alkaloid from opium and named it morphine (**1**)[2] after Morpheus, the god of dreaming in Greek mythology (Figure 1). Various compounds exhibiting analgesic activity, including morphine (**1**), that were isolated from opium were collectively called "opiates", which indicated that they were obtained from opium. In the mid-1970s, endogenous peptides exhibiting morphine-like effects were discovered, which did not originate from opium, and therefore "opiate" ceased to be recognized as an exact term. Currently, all compounds having a morphine-like pharmacological action including endogenous peptides, synthetic drugs, and semi-synthetic drugs are known as "opioids", meaning morphine-like substances.

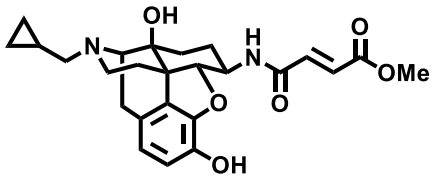


Morphine (**1**)
MOR agonist

Figure 1. The structure of morphine (**1**)

The structure of morphine (**1**) was proposed in 1925 by Gulland and Robinson[3] and determined in 1927 by Schöpf *et al.*[4] Although many researchers attempted to separate the analgesic effect from the drug dependence potential by chemically modifying morphine (**1**), these attempts were unsuccessful. Since two pentapeptide enkephalins (Met-enkephalin and Leu-enkephalin) were isolated from pig brain in 1976,[5] over 20 types of endogenous opioid peptides including β-endorphin[6], dynorphin[7], and endomorphin[8] were reported. Many such peptide derivatives were synthesized at that time, as these endogenous peptides were not expected to induce dependence. However, these attempts also failed, as even the endogenous peptides induced dependence. In 1976, Martin *et al.* proposed three types of opioid receptors known as μ, κ, and σ.[9] However, in a subsequent study, it was recognized that the σ receptor was different from opioid receptors, and the three receptors were alternatively named μ, κ, and δ (MOR, KOR, and DOR, respectively).[10] In 1984, Portoghese *et al.* reported that mice pretreated with irreversible MOR antagonist β-FNA (**2**) showed analgesic effect without dependence

potential despite administration of morphine (**1**) (Figure 2).[11] This result revealed that the morphine-like side effects typified by drug dependence were derived from MOR. Thus, DOR or KOR were expected to become targets for developing potent analgesics without dependence potential and many medicinal chemists began to develop DOR or KOR agonists.



β-FNA (**2**)
irreversible MOR antagonist

Figure 2. The structure of β-FNA (**2**)

U-50488H (**3**) was reported as a highly selective non-peptidic KOR agonist developed by researchers at Upjohn Company (Figure 3).[12] Subsequently, over 100 research groups worldwide continued to design and synthesize its derivatives to develop KOR agonists. As expected, these drugs showed high KOR selectivity and analgesic action without dependence potential; many pharmaceutical companies then conducted clinical trials of the U-50488H (**3**) derivatives. However, these compounds induced severe drug aversion (psychotomimetic effects such as visual and auditory hallucinations), which were opposite effects to drug dependence, and these U-50488H (**3**) derivatives were dropped in early clinical trials.[13] However, in the early 1990s, Nagase *et al.* focused on a partial structure, the *N*-terminal Tyr-Gly moiety in endogenous opioid peptides, designing and synthesizing nalfurafine (**4**) containing the Tyr-Gly moiety in a skeleton derived from naltrexone (**5**), which exhibited highly selective and potent KOR agonist activity (Figure 3).[14] This was the first KOR agonist inducing neither drug dependence nor aversion, and the key to its success was the presence of a Tyr-Gly moiety in the agonist structure unlike other groups' compounds. However, nalfurafine (**4**) was withdrawn from its application to post-operative pain, despite its strong analgesic effect. Nalfurafine (**4**) showed a strong sedative effect at the same dose as that for the analgesic effect in the clinical trials. Finally, nalfurafine (**4**) was released to the market for application to intractable pruritus in kidney dialysis patients in 2009, and to severe itching in liver disease patients in 2015.

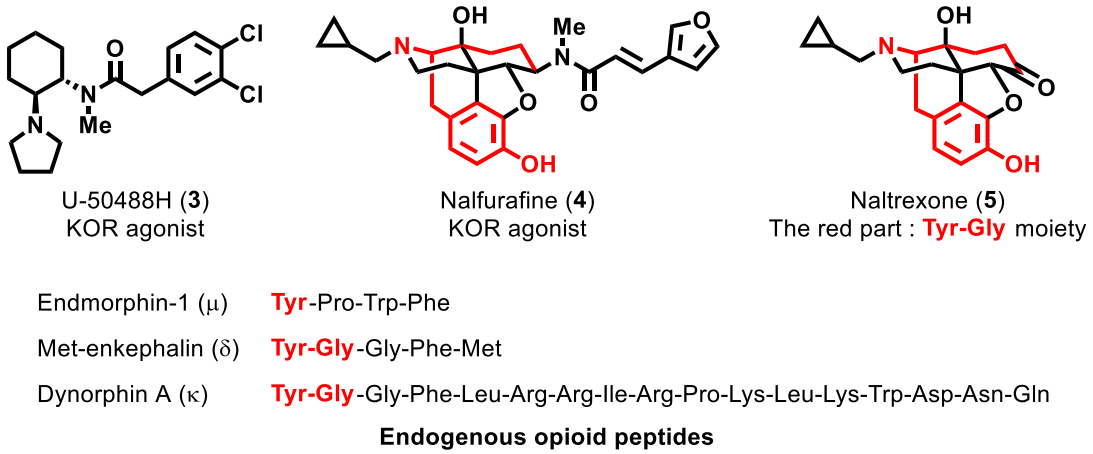


Figure 3. The structures of U-50488H (**3**), nalfurafine (**4**), naltrexone (**5**), and representative endogenous opioid peptides

Nagase *et al.* employed the two concepts of "message–address"[15] and "accessory site"[16] in the design of nalfurafine (**4**). Portoghese *et al.* applied the "message–address concept" to synthesizing NTI (**6**)[17] and nor-BNI (**7**)[18], which were selective non-peptidic opioid antagonists (Figure 4). In this concept, the "message" site is an essential structural moiety that binds with the receptor and exhibits activity, and the "address" site is a structural part involved in receptor selectivity. Moreover, the length of the "address" site determines the opioid receptor-type selectivity.

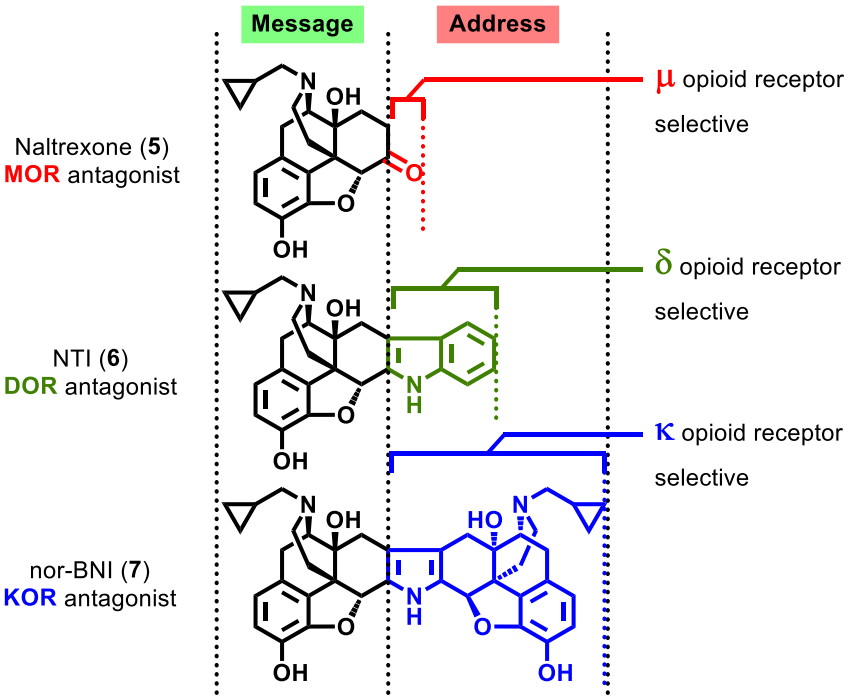


Figure 4. Message–address concept and the structures of MOR, DOR, and KOR-selective antagonists

The “accessory site” concept was based on the different structural features of the agonist and antagonist (Figure 5).[16] Generally, after the agonist is bound to the target receptor, the receptor changes the shape to induce the effect. However, when the antagonist is bound to the receptor, the receptor does not change the shape but only disturbs the binding of the agonist. Additionally, the structures of the agonist tend to be smaller than those of the antagonist with additional lipophilic moieties. The additional lipophilic parts are termed “accessory sites”, which are usually hydrophobic and sterically bulky to hinder agonist binding. The antagonists could be designed by adding the “accessory sites” to the corresponding agonists, and the agonists could be designed by removing the “accessory sites” from the corresponding antagonists.

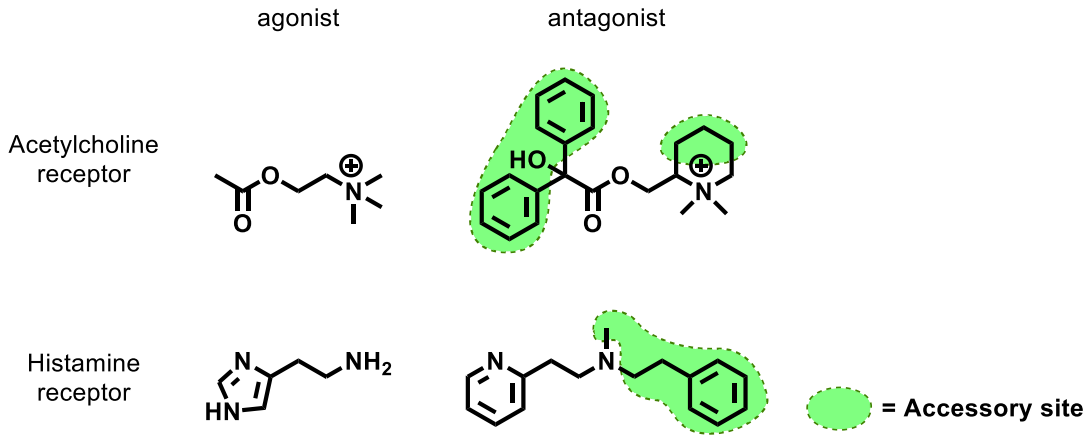


Figure 5. Typical examples of structural differences between agonists and antagonists and the “accessory sites”

Based on the “accessory site” concept, Nagase *et al.* synthesized the KOR agonist nalfurafine (**4**) by removing the lipophilic “accessory sites” from the KOR antagonist nor-BNI (**7**) (Figure 6).[14]

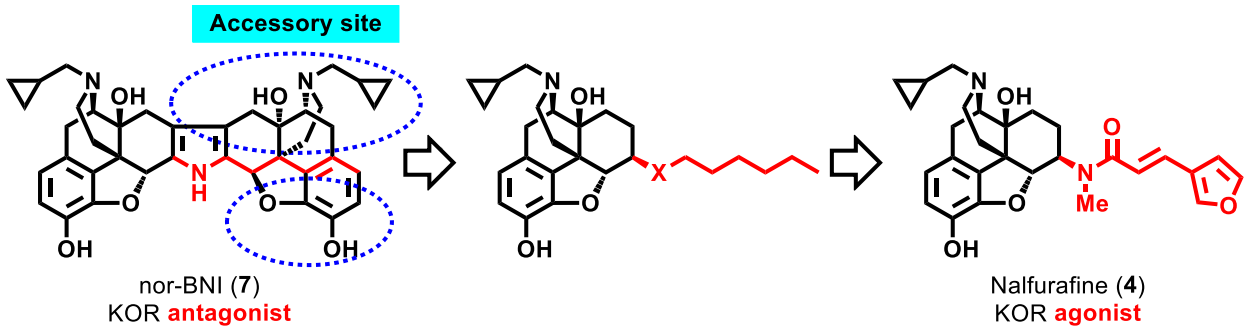


Figure 6. Design of nalfurafine (**4**) by using the “accessory site” concept

The DOR agonist was also energetically developed worldwide with a focus on two leading compounds, SNC-80 (**8**)[19] and TAN-67 (**9**)[20] (Figure 7). SNC-80 (**8**) was developed by the National Institutes of Health, and TAN-67 (**9**) was developed by Nagase *et al*. Both compounds were expected to become analgesics without dependence potential. Although neither agonist appeared addicting, SNC-80 (**8**) induced strong convulsion and catalepsy in mice, and its development was ceased due to this side effect in early clinical trials. However, TAN-67 (**9**) induced neither convulsions nor catalepsy, though its blood brain barrier permeation was insufficient. Subsequently, an improved ligand, KNT-127 (**10**)[21] was designed and synthesized in 2010; this exhibited higher permeation through the blood brain barrier, and its DOR agonistic activity was 80 times more potent than TAN-67 (**9**) (Figure 7). Currently, a further improved derivative, NC-2800 is under development as an antidepressant and anxiolytic in a non-clinical study.

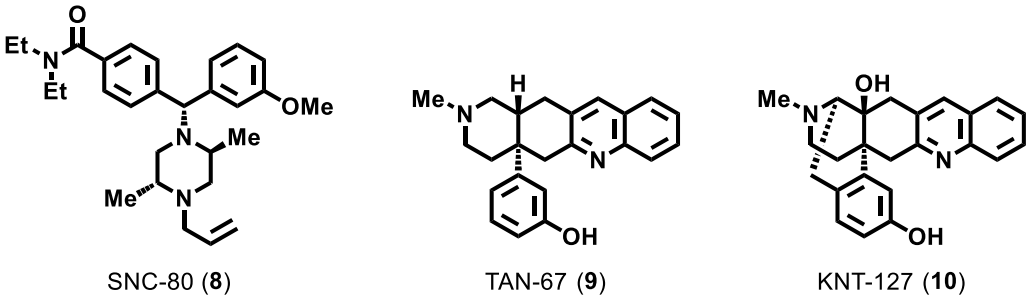
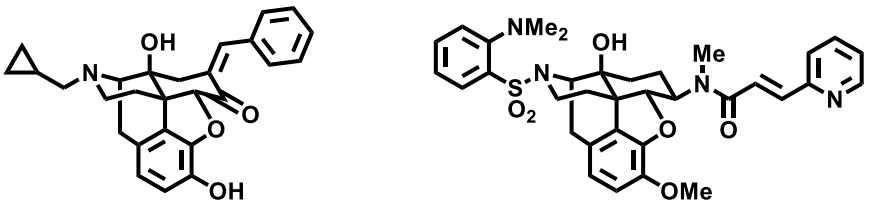


Figure 7. The structures of representative DOR-selective agonists

1.2 Application studies on morphinan skeleton

As described above, Nagase *et al*. focused on the morphinan skeleton, which possesses a useful Tyr-Gly partial structure at message sites for opioid receptors, and designed and synthesized several DOR and KOR-selective ligands by using the commercially available naltrexone (**5**) as a starting material. Additionally, as opioid receptors showed various pharmacological activities including analgesic, the type-selective agonists were expected to form various useful drugs if their dependence potential was removed. During the studies, Nagase *et al.* also found that DOR antagonist BNTX (**11**) exhibited antiprotozoal activity,[22] and nalfurafine (**4**) showed an antagonistic action against the orexin 1 receptor (OX_1R) in recent years[23] (Figure 8). By modifying the nalfurafine (**4**) structure, Nagase *et al.* synthesized the more potent and water soluble OX_1R antagonist YNT-1310 (**12**),[24] which attenuated withdrawal syndrome in morphine-dependent mice (Figure 8). As suggested by these studies, morphinan derivatives were expected to function not only as analgesics through opioid receptors but also as various drugs targeting for other receptors, and therefore Nagase *et al.* used the morphinan skeleton as a template for drug design and discovery.

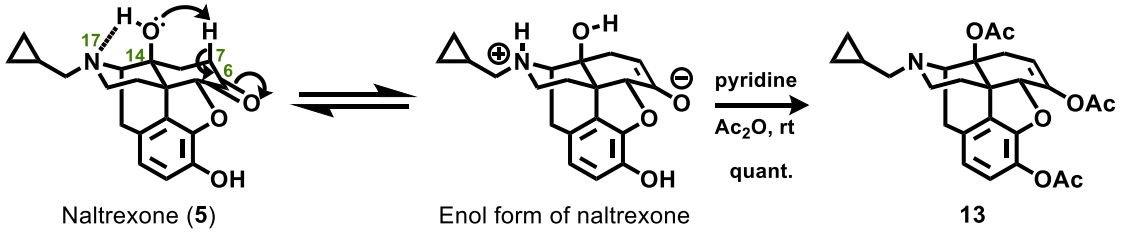


BNTX (**11**)
Antiprotozoal activity

YNT-1310 (**12**)
OX_1R antagonistic activity

Figure 8. The structures of morphinan derivatives BNTX (**11**) and YNT-1310 (**12**)

As mentioned above, naltrexone (**5**) is a useful starting material and template; however, researchers sometimes encounter abnormal reactions originating from its characteristic 4,5-epoxy morphinan skeleton. Naltrexone (**5**) contains four sequential asymmetric centers and active functional groups including a 4,5-epoxy ring, two hydroxyl groups at the 3- and 14-positions, 17-basic nitrogen, and 6-ketone. As these functional groups are rigidly located on positions that can cause intramolecular interactions, this sometimes leads to unexpected and complex degradation products.[25] For instance, acetylation of the 14-hydroxy group in naltrexone (**5**) with acetic anhydride/pyridine at room temperature yielded unusual triacetate **13** (Scheme 1).[26] The high tendency for enolization of the 6-ketone in naltrexone (**5**) activates the 7-axial hydrogen by the effects of neighboring group participation by the 17-basic nitrogen and 14-hydroxyl group, resulting in acetylation of the 14-hydroxy and 6-enolate groups shown in Scheme 1. By applying the abnormal enolization reaction, Nagase *et al.* readily synthesized the pyrrole, benzofuran, and indole rings in DOR and KOR antagonists including NTI (**6**),[14] NTB (**14**),[27] TRK-851 (**15**),[28] and nor-BNI (**7**)[18] in high yield (Figure 9).



Scheme 1. The intramolecular interaction and acetylation of naltrexone (**5**)

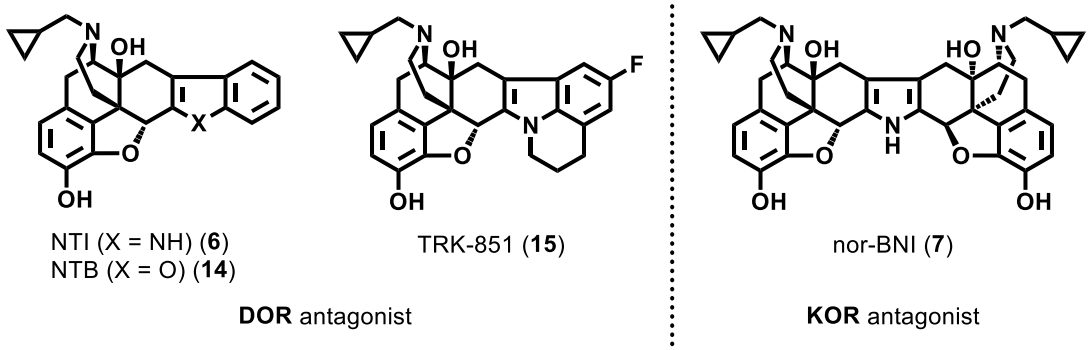


Figure 9. The structures of representative antagonists for DOR or KOR derived from naltrexone (**5**)

However, the 4,5-epoxy ring was extremely easily cleaved due to the strong ring strain, and the cleavage reactions were often encountered in reducing 6-ketone to the methylene group in synthesizing homogalanthamine (**16**).[29] At Nagase laboratory, it was reported that many abnormal reactions were observed during the transformation of naltrexone (**5**), and these were controlled to afford novel compounds.[25] Some examples of the conversion of naltrexone (**5**) are illustrated in Figure 10 (compounds **17** to **22**).

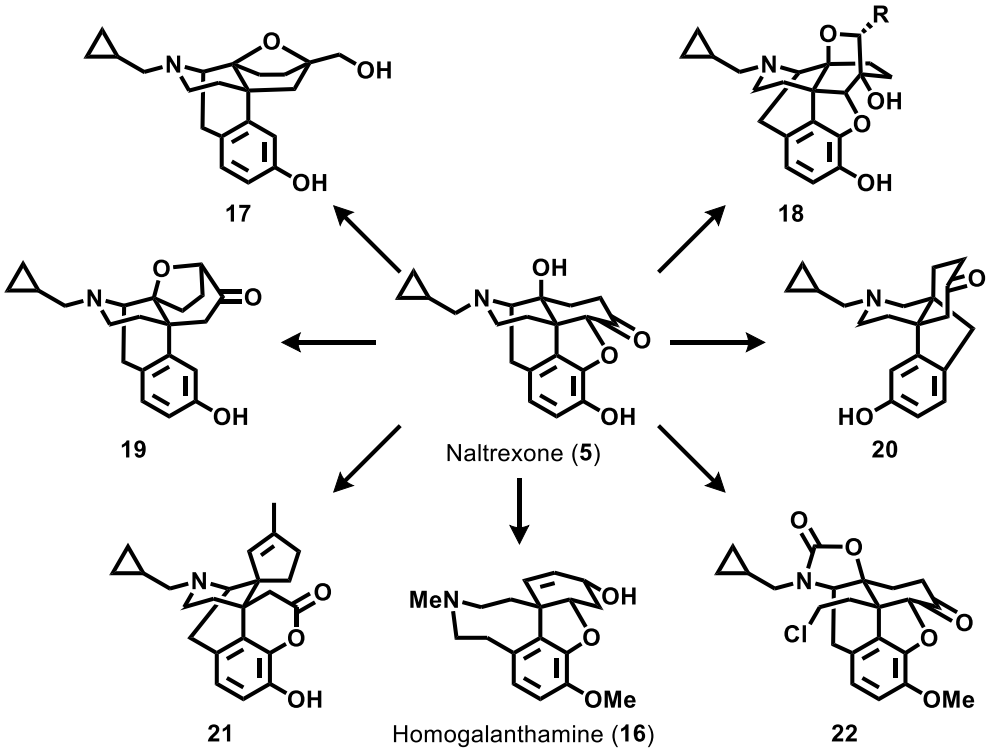


Figure 10. Some examples of the novel compounds obtained by the abnormal reactions of naltrexone (**5**)

Particularly, the conversion of naltrexone (**5**) into spiro compound **21**[30] was cited in the leading textbook on organic reaction mechanisms (The Art of Problem Solving in Organic Chemistry, second ed., 2014, Wiley), because product **21** was obtained *via* multiple steps and its structure was extremely complex as determined by 2D NMR. When researchers have neither much experience nor knowledge of a number of specific abnormal reactions of the morphinan skeleton, they may encounter complex reaction products that cannot be isolated and whose structures are difficult to determine when naltrexone (**5**) is used as a template. Nagase *et al.* expected the reaction examples described in their previous papers, and this doctoral thesis will greatly assist researchers who utilize the morphinan skeleton for the first time.

Nagase *et al.* also synthesized natural physiologically active substances and their analogs, paying attention to common structural features between the morphinan skeleton and the natural products and attempting to convert naltrexone (**5**) to the natural products, mesembrane (**23**)[31] and homogalanthamine (**16**),[29] which possesses one extra carbon atom compared with the natural alkaloid galanthamine (**24**) (Figure 11).

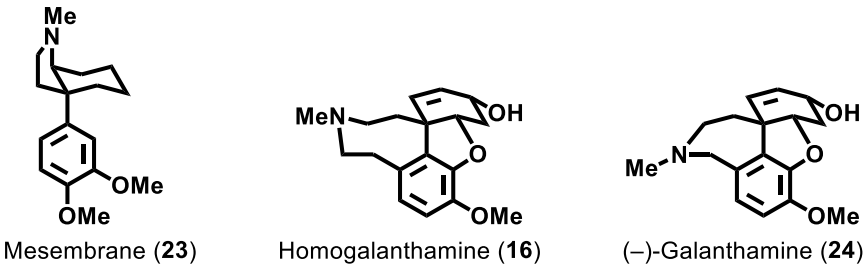
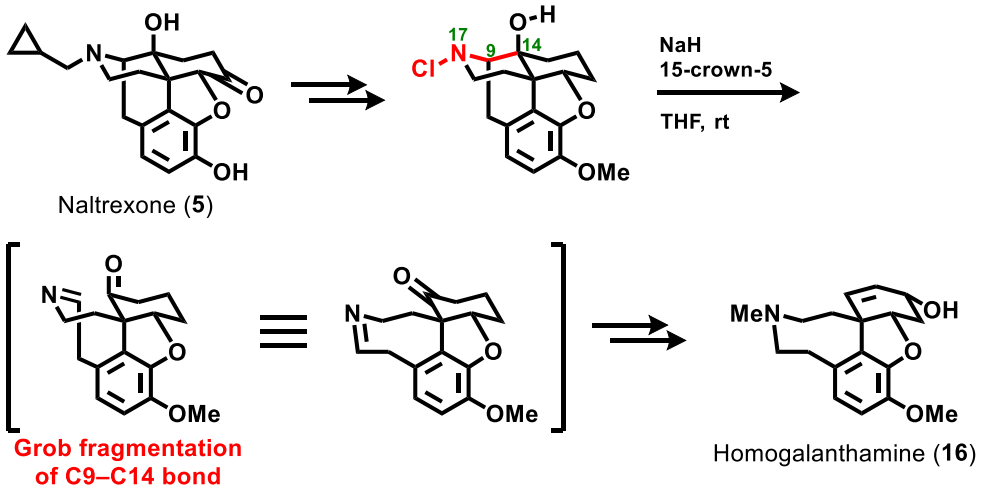


Figure 11. The structures of mesembrane (**23**), homogalanthamine (**16**), and galanthamine (**24**)

Homogalanthamine (**16**) contains the same number of carbon atoms as naltrexone (**5**). Thus, Nagase *et al.* could synthesize homogalanthamine (**16**) from naltrexone *via* Grob fragmentation.[32] In this reaction, the C9–C14 bond was oriented antiperiplanar to the N17–Cl bond by the rigid morphinan skeleton (Scheme 2). In this synthesis, Nagase *et al.* also encountered many abnormal reactions derived from the morphinan skeleton.



Scheme 2. Synthesis of homogalanthamine (**16**) from naltrexone (**5**) *via* Grob fragmentation

However, because the skeleton of galanthamine (**24**) contains one less carbon than that of naltrexone (**5**), one carbon atom must be removed from the morphinan skeleton to synthesize galanthamine (**24**). However, during the homogalanthamine (**16**) synthesis, Nagase *et al.* had no means to remove this carbon. Subsequently, they discovered a method for removing one carbon from the morphinan skeleton in their synthetic study on mesembrane (**23**).[31]

Chapter 2 describes the synthesis of galanthamine (**24**) *via* a new synthetic route that removes one carbon from the morphinan skeleton.

Chapter 3 describes a novel retro-ene reaction of an intermediate during the synthesis of mesembrane (**23**).

Chapter 2. Synthesis of Galanthamine from Naltrexone

2.1 Background of galanthamine

Galanthamine (**24**) is an alkaloid isolated from the Caucasian snowdrop plant (*Galanthus woronowii*), which belongs to the Amaryllidaceae family.[33] Galanthamine (**24**) inhibits acetylcholinesterase and functions as a positive allosteric modulator of nicotinic acetylcholine receptors, consequently enhancing the effect of acetylcholine in the central nervous system.[34] Thus, it has been clinically used to treat Alzheimer's disease in the US, EU, and Japan.[35]

As described in the previous chapter, Nagase *et al.* successfully exploited the unique reactivity of the morphinan skeleton to develop various useful ligands and discovered many novel reactions unique to the skeleton. The author began the synthesis of galanthamine (**24**), which has a skeleton with one less carbon than naltrexone (**5**), by using the recently discovered method for removing one carbon from **5**.

2.2 Retrosynthetic analysis of galanthamine

Galanthamine (**24**) has three rings in common with naltrexone (**5**); these rings are termed A, C, and E-rings in naltrexone (**5**). Additionally, as mentioned above, **24** has one less carbon in its structure than naltrexone (**5**). Thus, the author attempted to synthesize galanthamine (**24**) by employing a C9 carbon removal method with seven-membered ring construction *via* C10–N17 bond formation (Figure 12).

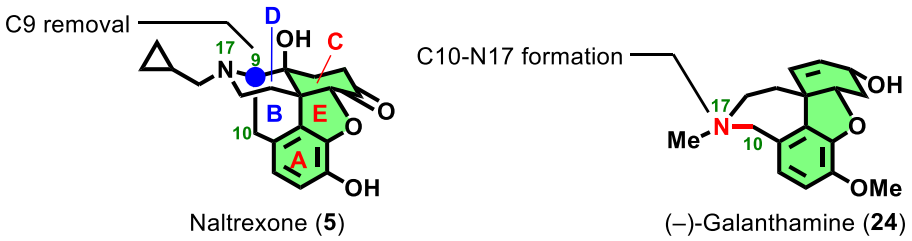
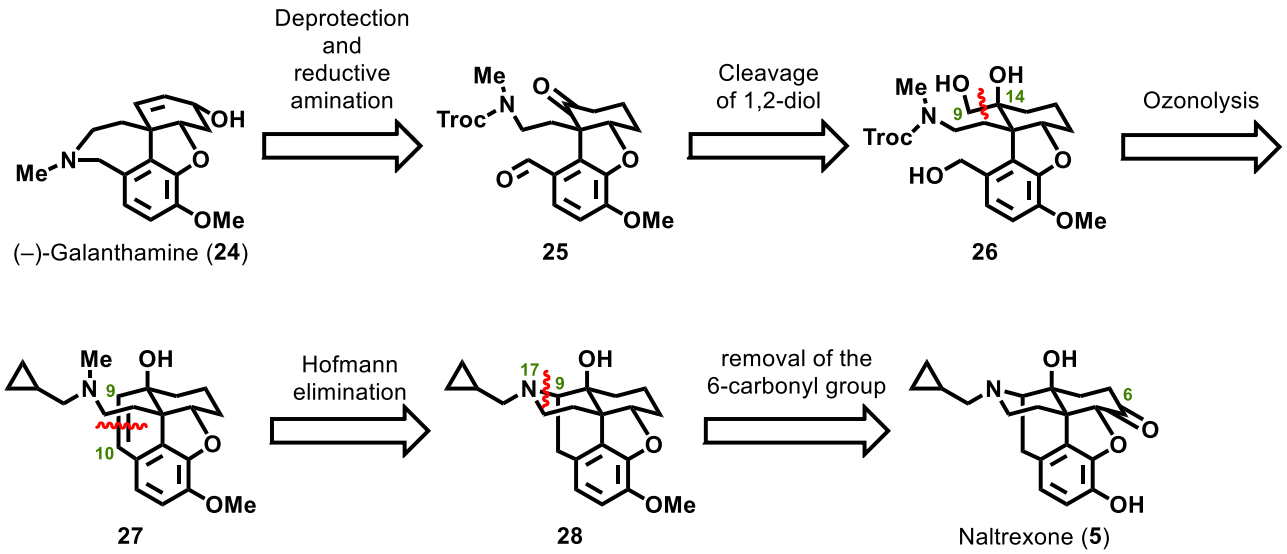


Figure 12. Common structure (green moieties) between naltrexone (**5**) and galanthamine (**24**)

The retrosynthetic analysis of **24** was shown in Scheme 3. The seven-membered ring of **24** could be constructed by reductive amination of keto-aldehyde **25**, which could be synthesized by the C9 carbon removal *via* oxidative cleavage of the vicinal diol moiety at the C9–C14 position in triol **26**. Triol **26** was obtained by cleavage of the C9–C10 double bond *via* ozonolysis of allyl alcohol **27**, which could be obtained from methyl ether **28** by Hofmann elimination of the C9–N17 bond. Compound **28** could be obtained from naltrexone (**5**) by employing the previously reported method.[28]

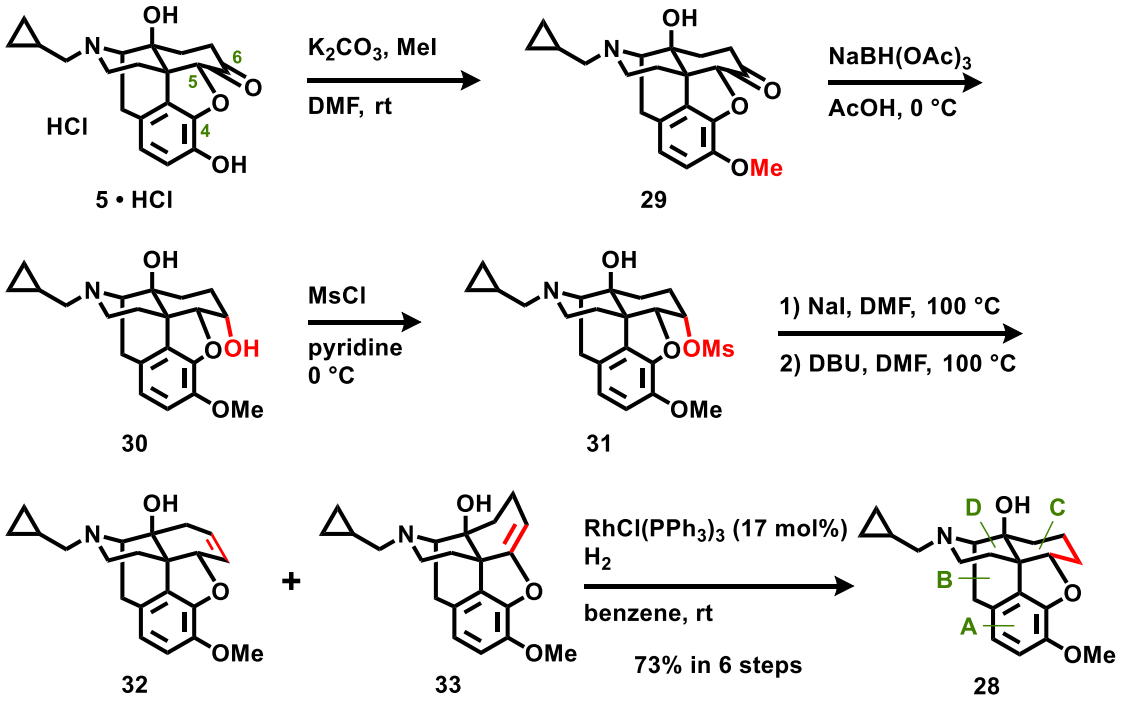


Scheme 3. The retrosynthetic analysis of (−)-galanthamine (**24**) from naltrexone (**5**)

2.3 Synthesis of galanthamine

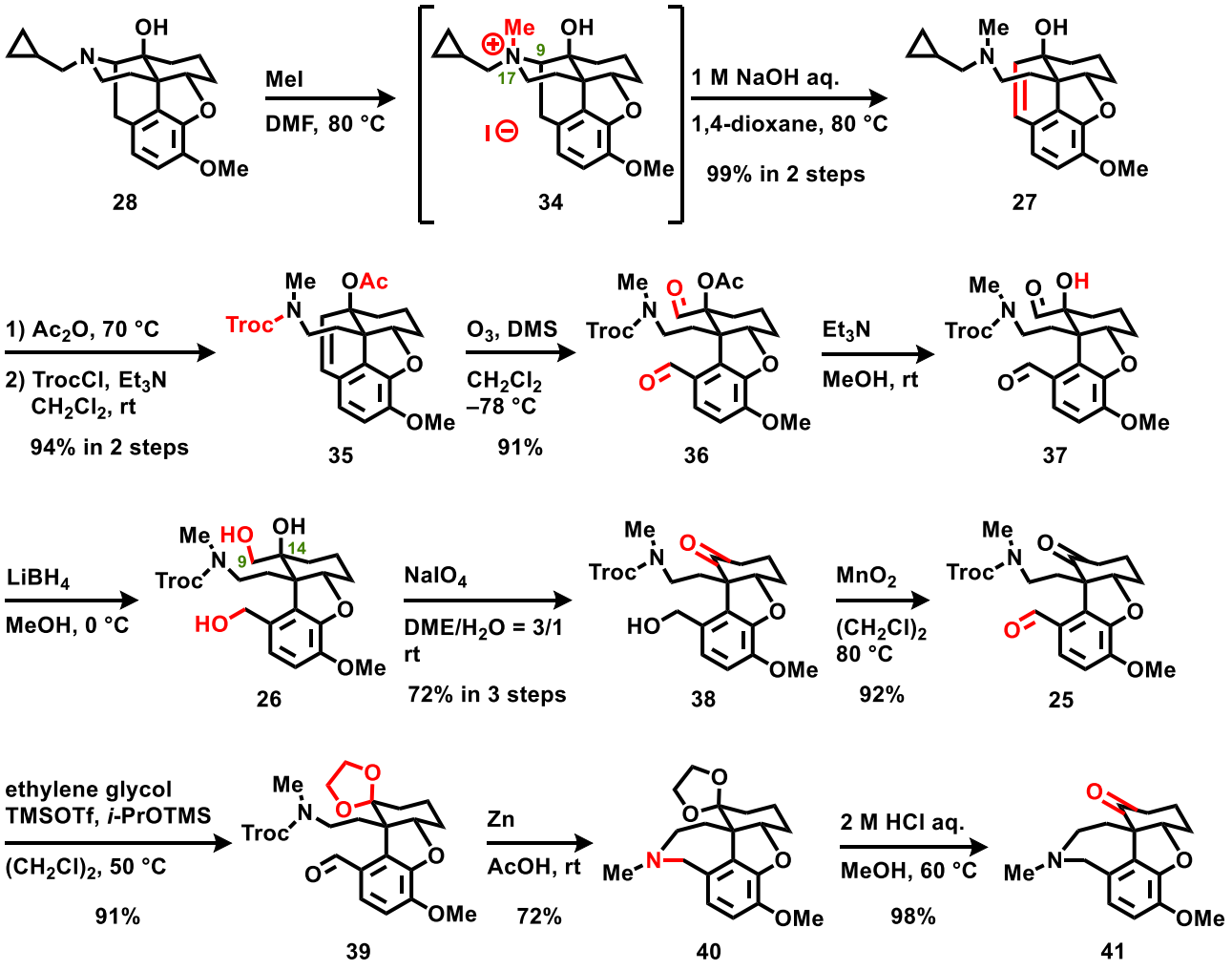
The author attempted to reduce the ketone at the C6-position in naltrexone (**5**) to a methylene group. As previously reported for the synthesis of homogalanthamine (**16**), the direct reduction of the carbonyl group to a methylene group (Wolff–Kishner reduction,[36] Clemmensen reduction, or thioacetal desulfurization using Raney nickel) led to cleavage of the 4,5-epoxy ring. Thus, in this synthesis, the author attempted to remove the ketone *via* the following multi-step process developed by Nagase's group (Scheme 4).[29]

Naltrexone hydrochloride (**5**·HCl) was converted to methyl ether **29** by methylating the phenolic hydroxy group. Diastereoselective reduction of the ketone in methyl ether **29** using $NaBH(OAc)_3$ afforded alcohol **30**, which was mesylated with MsCl to afford mesylate **31**. A substitution reaction of the mesyl group in **31** with NaI, followed by treatment with DBU provided a mixture of olefins **32** and **33**. As the 4,5-epoxy ring of olefin **32** was also cleaved by hydrogenation using heterogeneous catalysts such as Pd/C and Pt_2O,[29] the author reduced the double bonds in the mixture of **32** and **33** with homogenous Wilkinson's catalyst to afford **28**. The high chemical reactivity of the 4,5-epoxy ring in the 4,5-epoxymorphinan skeleton appears to originate from the intrinsic strong ring strain derived from the A, B, C, and D-rings as well as the strong ring strain derived from the 4,5-epoxy ring.



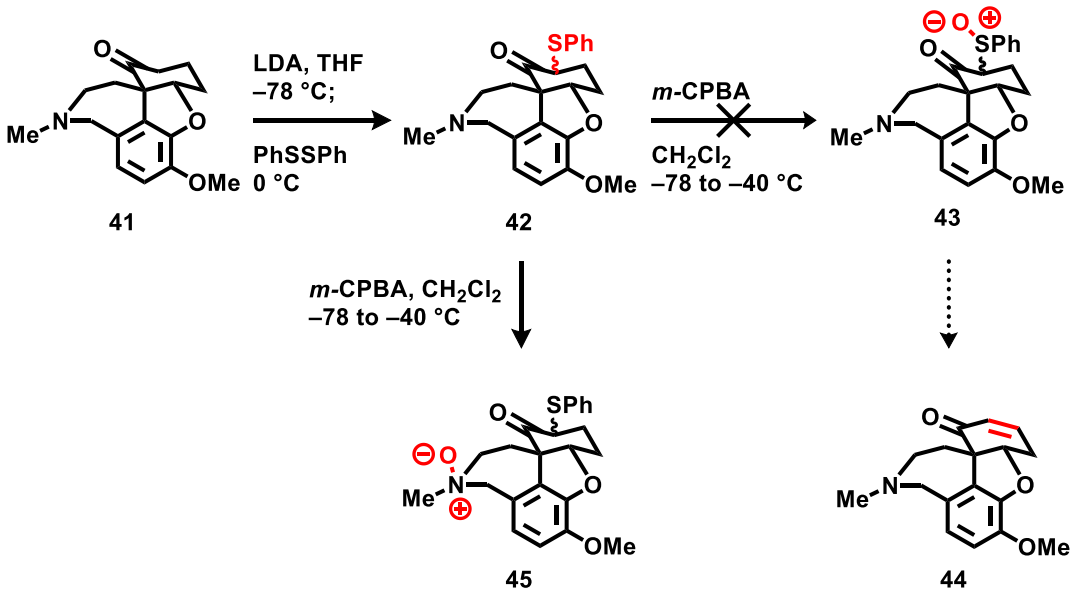
Scheme 4. Synthesis of **28** from **5**·HCl

After methylating the basic nitrogen at the 17-position in **28**, the C9–N17 bond in methiodide **34** was cleaved by Hofmann elimination to afford allyl alcohol **27** in high yield (Scheme 5). Acetylation of the tert-hydroxy group in **27** followed by decyclopropylmethylation with TrocCl gave acetate **35**.[37] The compound **35** was converted to dialdehyde **36** by ozonolysis and deprotection of the acetyl group to give dialdehyde-alcohol **37**. The compound **37** was reduced with $LiBH_4$ in MeOH to afford triol **26**. Oxidative cleavage of the C9–C14 bond in **26** with $NaIO_4$ resulted in the C9 carbon removal. The benzyl alcohol of obtained keto-alcohol **38** was oxidized with MnO_2 to afford keto-aldehyde **25**. After acetalization of the ketone group of **25** by employing Kurihara's procedure,[38] treating obtained aldehyde **39** with Zn in AcOH provided seven-membered compound **40**, possessing the basic skeleton of galanthamine (**24**). In this reaction, the Troc group was initially removed and the resulting *sec*-amine reacted with aldehyde to form iminium, which was subsequently reduced. The acetal group in **40** was deprotected to afford ketone **41**.

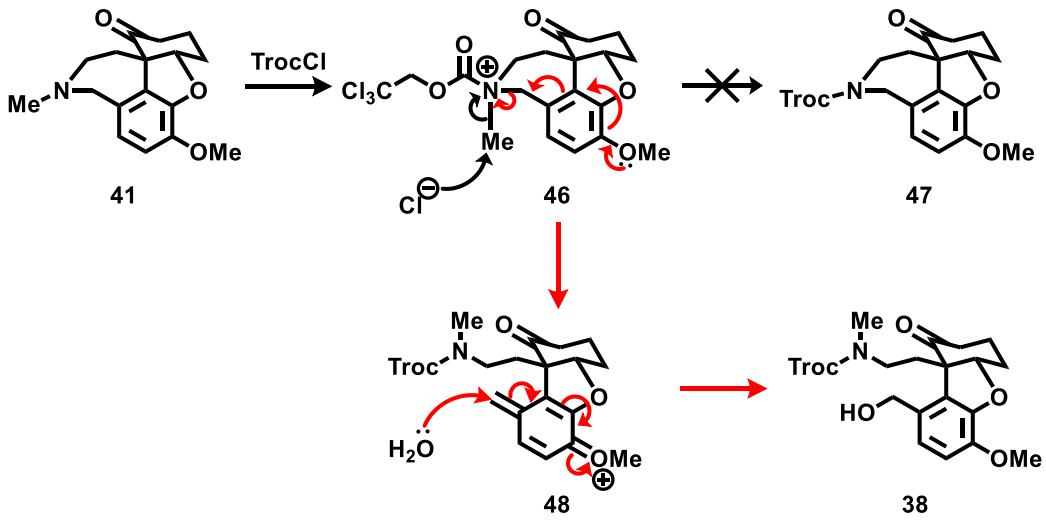


Scheme 5. Synthesis **41** from **28** *via* one-carbon removal

The author then examined the conversion of the ketone group in **41** to an α,β-unsaturated ketone group. However, after reacting **41** with PhSSPh, oxidation of the resulting phenyl sulfide **42** with *m*-CPBA produced undesired *N*-oxide **45**, rather than sulfoxide **43** leading to α,β-unsaturated ketone **44** (Scheme 6). The susceptibility to oxidation of the basic nitrogen in **41** led to an attempt to protect the amino group with a Troc group. However, the attempt to protect the nitrogen led to keto-alcohol **38** which was the compound obtained four steps before and not target carbamate **47** (Scheme 7). The proposed reaction mechanism was shown in Scheme 7. In this way, as unexpected reactions often occur with the morphinan skeleton, researchers using morphinan derivatives should study the reactivity of the skeleton.

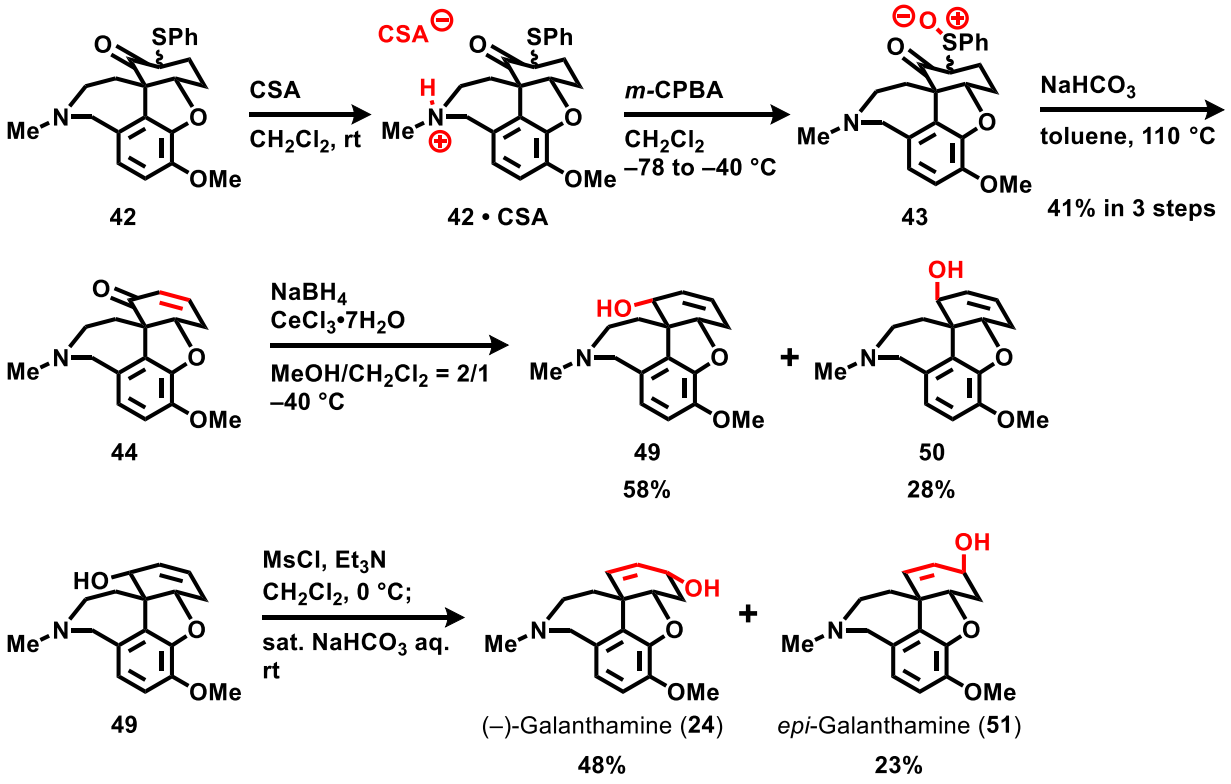


Scheme 6. Examination of the selective sulfide oxidation in the presence of basic nitrogen



Scheme 7. Unexpected seven-membered ring cleavage reaction of **41** to give **38**

The author subsequently attempted to protect the basic nitrogen by protonation with acid. After examining several acids, desired phenyl sulfoxide **43** was successfully obtained by protonation of the nitrogen in **42** with CSA, followed by treatment with *m*-CPBA. Desired α,β-unsaturated ketone **44** was then obtained by treating **43** with $NaHCO_3$ under toluene reflux condition. The resulting **44** was reduced with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ to afford allyl alcohols **49** and **50** in 58% and 28% yields, respectively. The stereochemistry of alcohol **49** was verified by X-ray crystallography (Figure 13). Finally, allyl alcohol **49** was converted to (−)-galanthamine (**24**) and its diastereomer **51** in 48% and 23% yields by mesylation of the allyl alcohol and treatment with saturated aqueous $NaHCO_3$ solution, as reported by Trost's group[39] (Scheme 8).



Scheme 8. Synthesis of (−)-galanthamine (**24**)

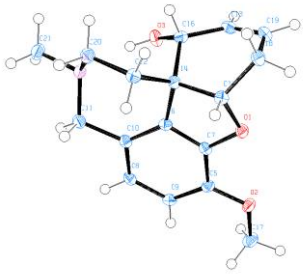
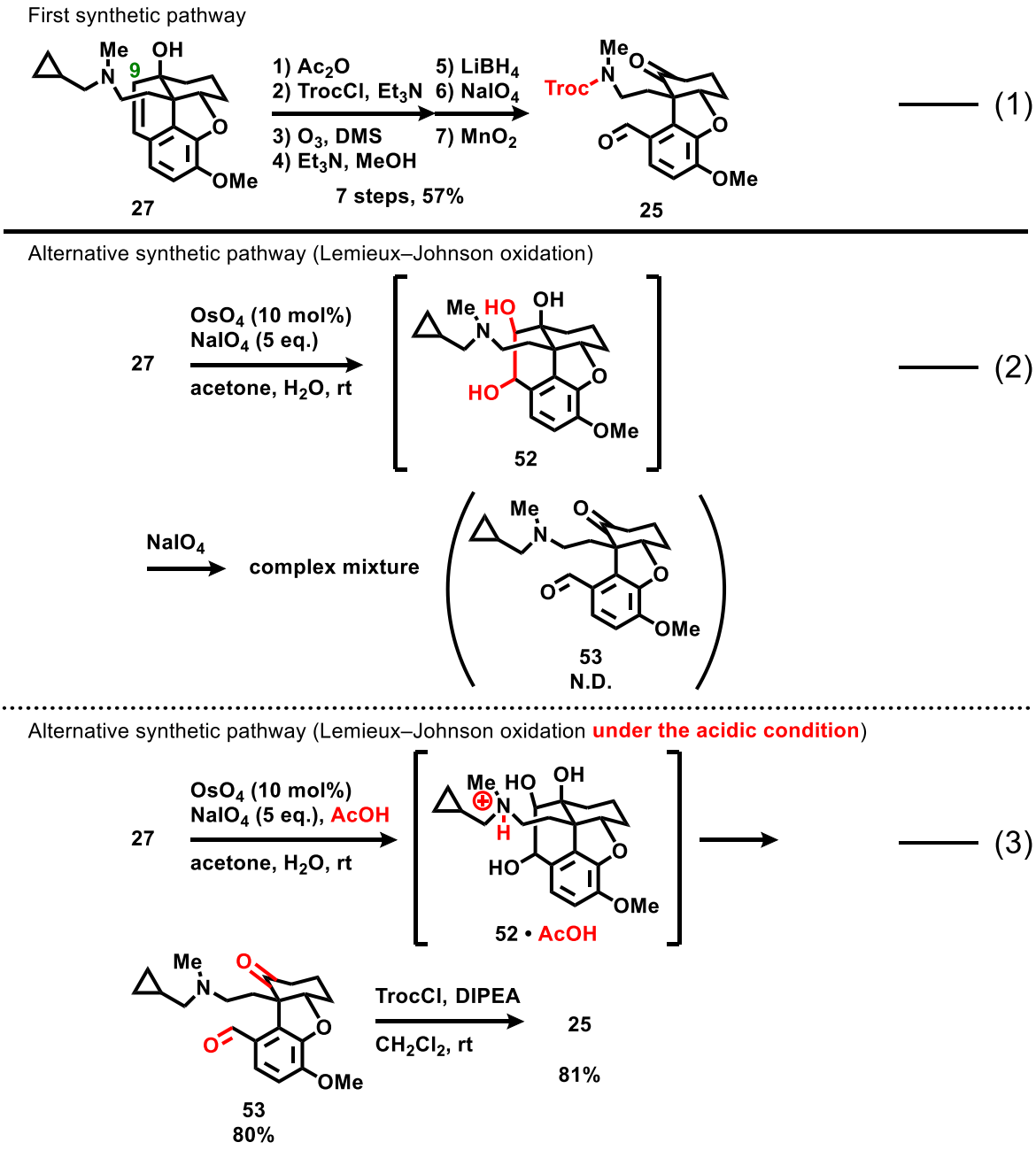


Figure 13. ORTEP view of **49**

2.4 Discovery of the effective one-carbon removal method

In the above-mentioned synthesis of galanthamine (**24**), seven steps, including two oxidative cleavage reactions, were needed to remove the C9 carbon during the conversion of **27** to **25** (Scheme 9, (1)). The author attempted to find a more effective one-carbon removal method for synthesizing galanthamine (**24**) by focusing on the allyl alcohol structural moiety in **27**. The author attempted to convert allyl alcohol **27** to triol **52** with OsO_4 followed by oxidative cleavage of the triol with $NaIO_4$ to remove the one carbon, but this reaction afforded only a complex mixture (Scheme 9, (2)).[40] This result indicated that the basic nitrogen in **27** was oxidized under these conditions, leading to a complex mixture. Thus, protection of the basic nitrogen was attempted using acid. As expected, target keto-aldehyde **53** without the C9 carbon was obtained *via* Lemieux–Johnson oxidation under acidic conditions with AcOH (Scheme 9, (3)). The resulting **53** was converted to **25** with TrocCl. The five-step shorter alternative synthetic pathway was then completed to convert **27** to **25** in 65% yield, compared to the previous route, which gave 57% yield. Obtained keto-aldehyde **25** was converted to galanthamine (**24**) in the same manner.



Scheme 9. Proposed synthetic pathway to **25** from **27**

2.5 Conclusion

In conclusion, the author synthesized galanthamine (**24**) from naltrexone (**5**) as a practical example of morphinan skeleton conversion with a focus on the common structure between the starting material and final product. During this synthesis, characteristic side reactions of the morphinan skeleton, such as cleavage of the 4,5-epoxy ring and the seven-membered ring, were avoided. Hofmann elimination, two oxidative cleavages for the C9 carbon removal, and reductive amination to construct the seven-membered ring were the key reactions. Protonation of the basic nitrogen with acid was a useful protective method, which enabled Lemieux–Johnson oxidation. This reaction saved five steps in the C9 carbon removal (Figure 14). The author hopes that the specific reactivity of the morphinan skeleton and the new carbon removal reaction reported in this thesis will be useful to medicinal chemists employing morphinan derivatives in the future.

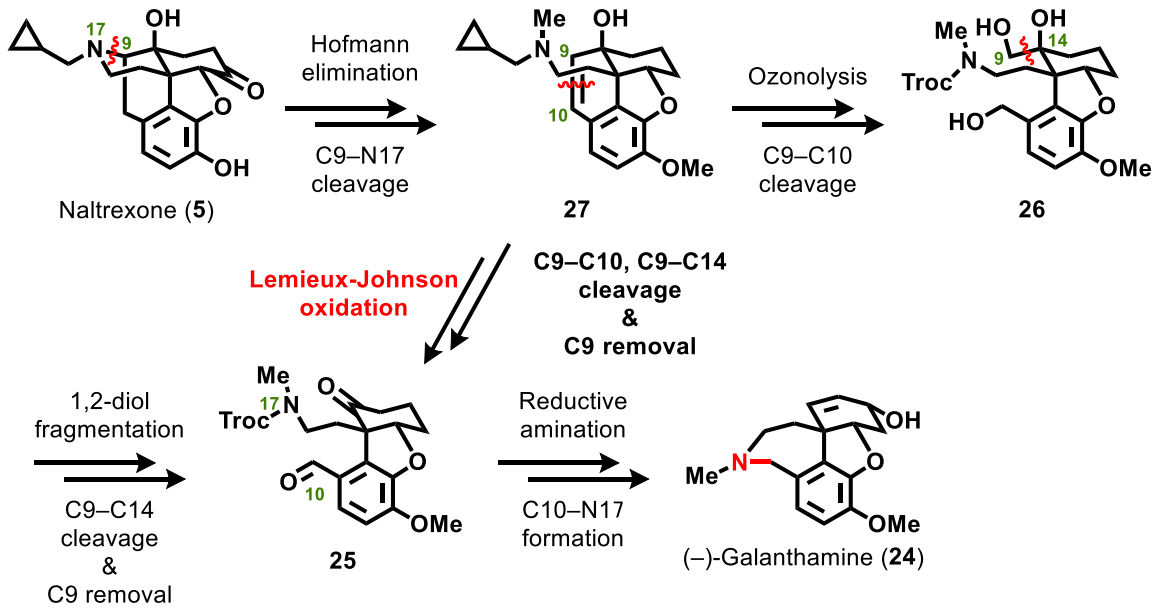
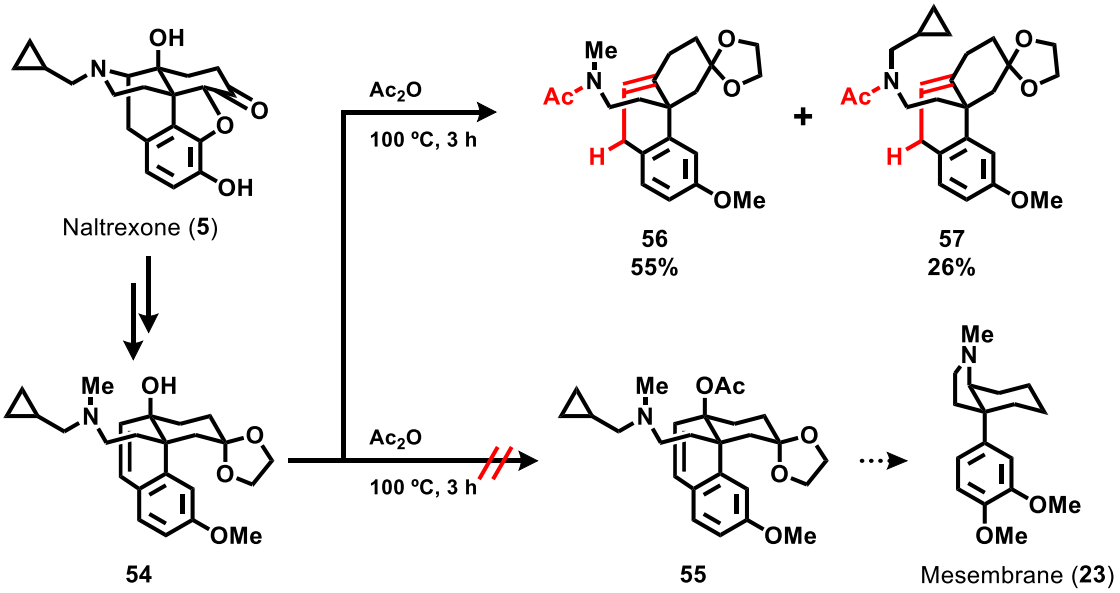


Figure 14. Summary of the synthesis of galanthamine (**24**) from naltrexone hydrochloride (**5**·HCl)

Chapter 3. Novel Retro-Ene Reaction in Morphinan Derivatives

3.1 Discovery of a novel retro-ene reaction

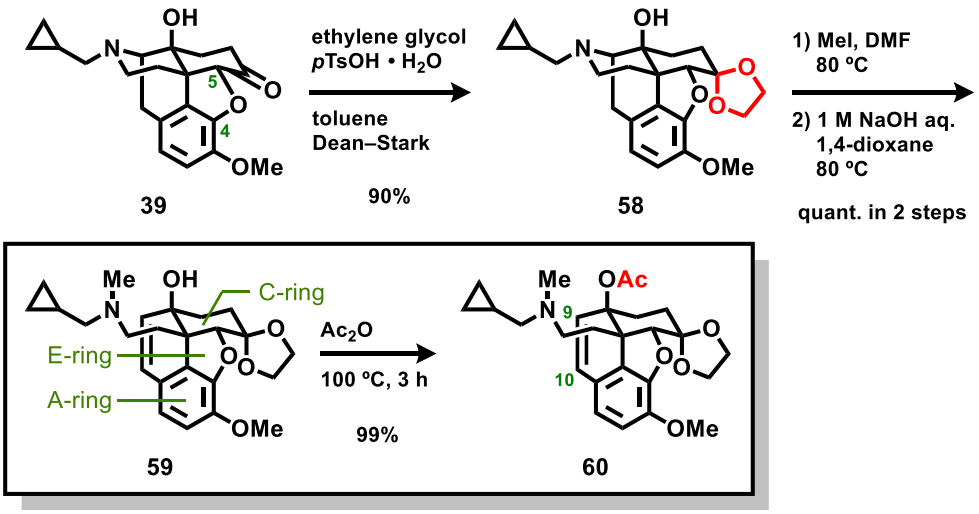
During a study on synthesizing the biologically active natural product mesembrane (**23**) from naltrexone (**5**), acetylation of allyl alcohol **54** (acetic anhydride, 100 °C) afforded unexpected acetamides **56** and **57** in 55% and 26% yields, respectively, but not target acetylated product **55** (Scheme 10). The author was interested in this specific reaction of the morphinan skeleton and investigated the reaction mechanism.



Scheme 10. Discovery of abnormal amidation reaction of morphinan derivative **54**

3.2 Studies of the scope of the reaction substrate and discovery of the key intermediate

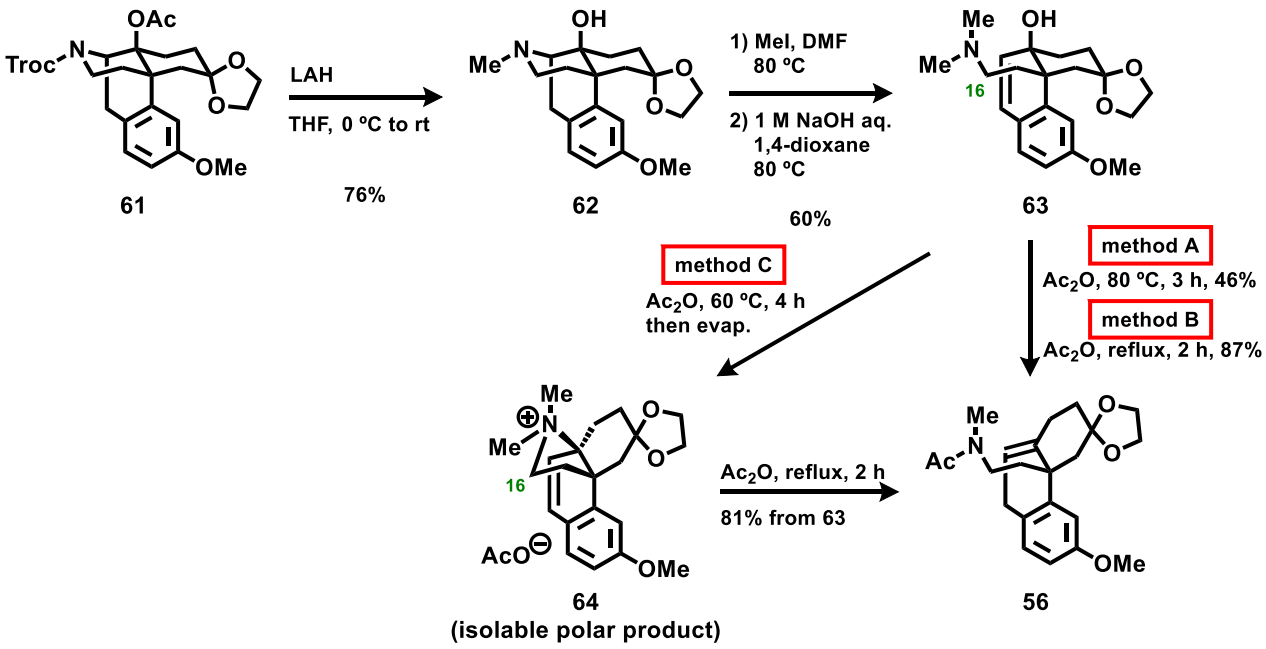
Initially, the author investigated whether the characteristic reaction occurred in the presence of the E-ring (4,5-epoxy ring) of the morphinan skeleton. The 4,5-epoxymorphinan derivative **59**, corresponding to allyl alcohol **54** without the E-ring, was synthesized as follows. Based on a known procedure,[41] naltrexone methyl ether (**39**) was acetalized to afford compound **58** in 90% yield; subsequently, Hofmann elimination of **58** afforded target allyl alcohol derivative **59** in quantitative yield. Reaction of 4,5-epoxymorphinan derivative **59** with acetic anhydride under the same conditions as for **54** afforded acetylation product **60** in 99% yield, unlike the reaction of morphinan derivative **54**. The E-ring is known to play an important role in fixing the A-ring rotation to bind with the C-ring in morphinan derivatives.[42] Thus, removal of the *tert*-acetate of 4,5-epoxymorphinan **60** would be difficult because the E-ring fixed the conformation by preventing the A-ring rotation and disturbed the conjugation between the C9–C10 double bond and the A-ring. However, the A-ring in morphinan **55** can rotate to the position conjugating with the C9–C10 double bond, which could accelerate removal of the *tert*-acetate.



Scheme 11. Synthesis of 4,5-epoxymorphinan **59** and its acetylation reaction

Reaction substrate **54** with two types of alkyl side chains on the nitrogen atom afforded a mixture of products **56** and **57**. To facilitate elucidation of the reaction mechanism, the author prepared allyl alcohol derivative **63** with an *N*,*N*-dimethylamino group. Initially, known Troc-protected compound **61**[21] was converted to *N*-methyl derivative **62** using $LiAlH_4$ (Scheme 12). Hofmann elimination of **62** afforded target allyl alcohol derivative **63**. Allyl alcohol derivative **63** was expectedly converted into acetamide **56** with acetic anhydride as a single

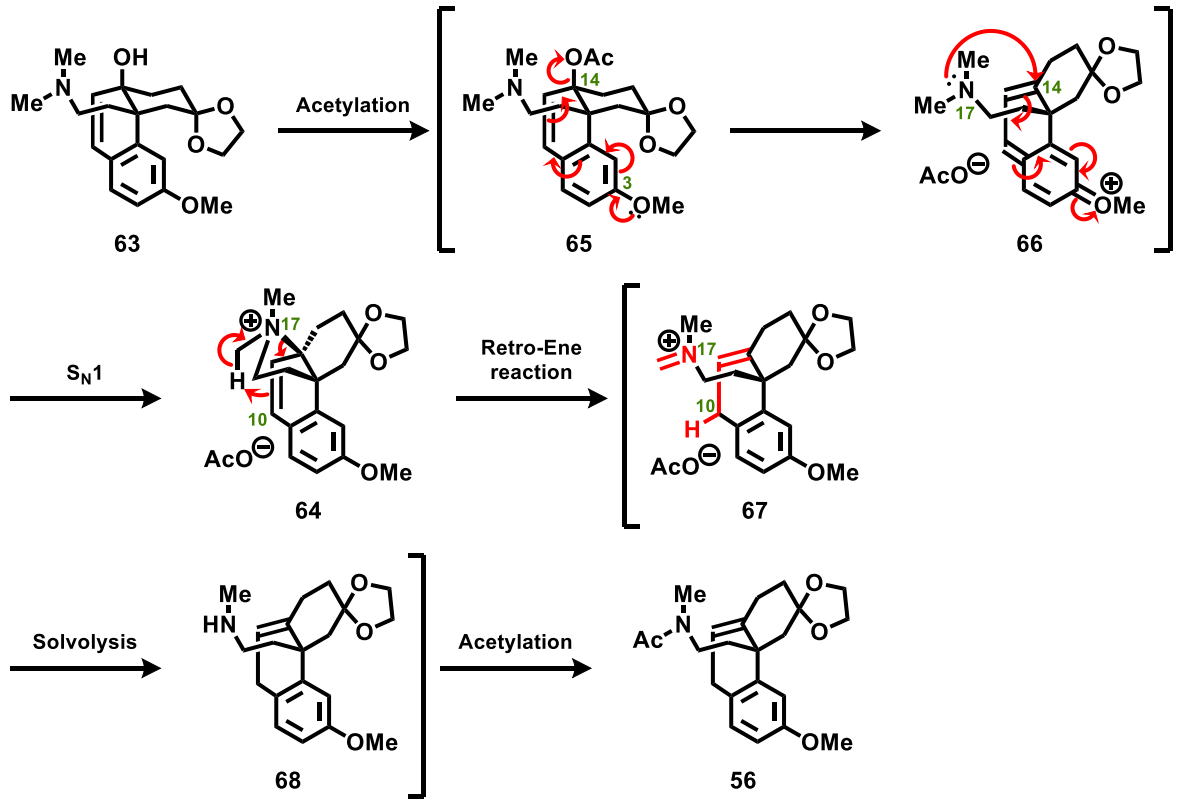
product at 80 °C in 46% yield (method A) (Scheme 12). The reflux condition in acetic anhydride over 2 hours afforded desired compound **56** in 87% yield (method B). On the other hand, when the reaction was performed at 60 °C for 4 hours, followed by removal of acetic anhydride in vacuo (method C), a highly polar compound was mainly detected in the reaction system by TLC. The ^{1}H NMR and ^{13}C NMR spectra of the isolated polar product revealed two non-equivalent methyl groups (2.70 and 3.09 ppm) and downfield shifts of both protons at the C16 position and at the *N*-methyl groups (2.06, 2.53 → 3.77 ppm and 2.22 → 2.70, 3.09 ppm). Finally, 1D and 2D NMR spectroscopy confirmed the compound to be quaternary ammonium salt **64** with a [4.4.3]propellane skeleton. Furthermore, obtained compound **64** was easily transformed into **56** in 81% yield from **63** under acetic anhydride reflux condition for 2 hours. These results confirmed that ammonium salt **64** was the key intermediate in this unprecedented reaction.



Scheme 12. Reactions of morphinan **63** with the *N*,*N*-dimethylamino group and of isolated ammonium salt **64** with acetic anhydride

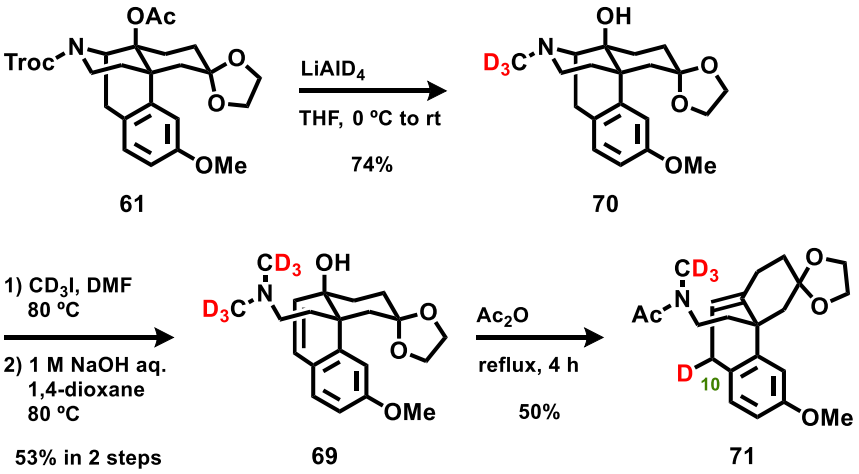
3.3 Proposed reaction mechanism and verification experiment using a deuterated compound

Based on these investigations, a proposed reaction mechanism was shown in Scheme 13. After acetylating the *tert*-allyl alcohol in **63** with acetic anhydride to afford acetate **65**, the acetoxy group at the C14 position of **65** was easily removed *via* the intramolecular nucleophilic electron-donating effect of the methoxy group at the C3 position to generate oxonium intermediate **66**, followed by addition of the basic nitrogen at the 17-position to the C14-position to afford quaternary ammonium salt **64**. By a thermal retro-ene-type reaction, ammonium salt **64** was converted to iminium intermediate **67**. Solvolysis of resulting iminium **67** afforded secondary amine **68**, which was acetylated to afford acetamide **56**. The lower reactivity of compound **63** with a dimethylamino group compared to compound **54** with cyclopropylmethylamino and methyl groups would originate from the higher electron donating ability of the cyclopropylmethyl group compared to that of the methyl group.[43]



Scheme 13. Proposed reaction mechanism *via* quaternary ammonium salt intermediate **64**

To confirm the proposed mechanism of the retro-ene reaction, the reaction was performed using *N*,*N*-deuterated dimethylamino derivative **69** (Scheme 14). Deuterated substrate **69** was obtained from Troc-protected compound **61** by employing the procedure for synthesizing allyl alcohol **63** (Scheme 12) with the corresponding deuterated reagents. Compound **61** was reduced with lithium aluminum deuteride to afford deuterated methyl amine **70** followed by Hofmann elimination using CD_3I, which gave allyl alcohol **69**. This was converted to acetamide **71**, which was deuterated at the C10-position under reflux in acetic anhydride over 4 hours, although the reaction of the deuterated **69** was relatively slow compared to that of **63**.[44] This result verified the proposed reaction mechanism described above.



Scheme 14. Deuteration study to clarify the reaction mechanism

3.4 Conclusion

In conclusion, the author discovered a novel retro-ene reaction of [4.4.3]propellane intermediate **64** containing a quaternary ammonium linkage, which was achieved by nucleophilic addition of the basic nitrogen at the 17-position to the C14-position, and also confirmed the reaction mechanism by employing deuterated derivative **69** (Figure 15).

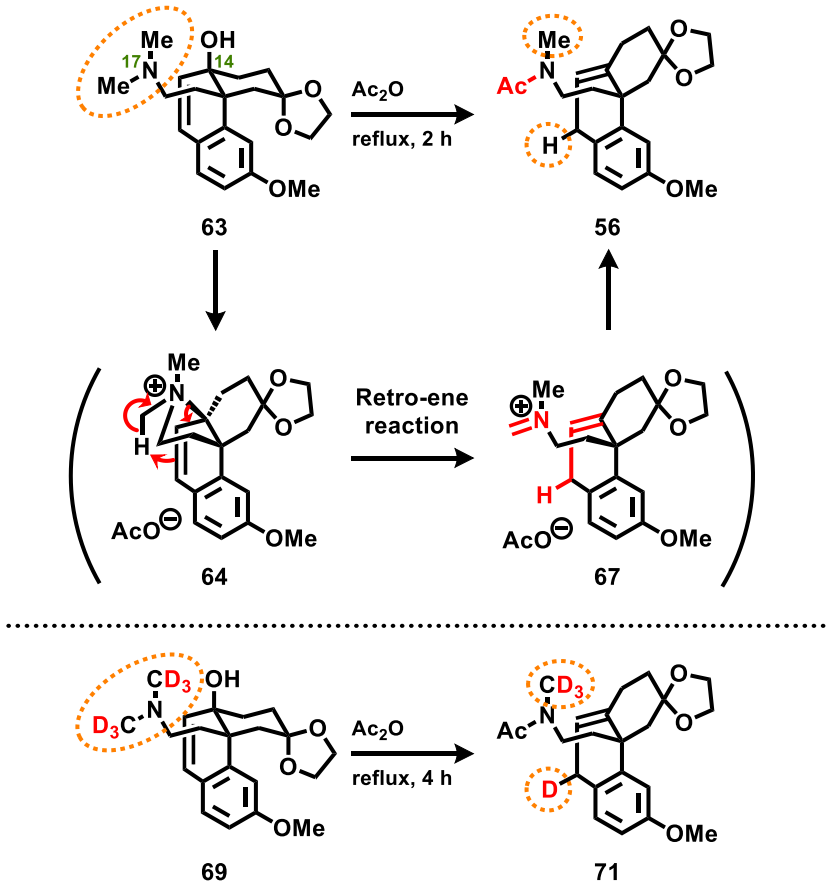


Figure 15. The mechanism of the novel retro-ene reaction *via* quaternary ammonium intermediate **64**

Chapter 4. Conclusion

In this doctoral thesis, the characteristic reactions of morphinan derivatives, which are useful for medicinal chemistry, were studied by employing commercially available naltrexone as a starting material.

The first research topic addressed the C9 carbon removal of the morphinan skeleton and Lemieux–Johnson oxidation of 4,5-epoxymorphinan bearing a basic amino group under acidic condition.

The second topic covers a novel retro-ene reaction *via* a [4.4.3]propellane skeleton intermediate containing a quaternary ammonium salt under acetic anhydride reflux condition. The author accidently discovered that reacting the morphinan derivative with acetic anhydride at 100 °C afforded unexpected acetoamides rather than simple acetylated morphinan during the synthesis of mesembrane from naltrexone. The reaction mechanism was clarified by using deuterated substrates and isolating the [4.4.3]propellane intermediate. Further experiments using the deuterated morphinan derivative clarified the mechanism by confirming rearrangement to the expected position of deuterium in the methyl group.

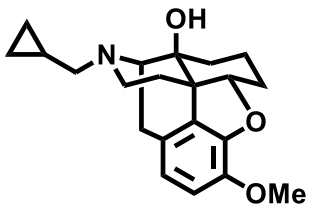
This information should be useful to medicinal chemists interested in synthesizing bioactive morphinan alkaloids.

Experimental section

General

Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} plates (0.25 mm). Preparative TLC (PLC) was accomplished by using Merck Kieselgel 60 F_{254} plates (0.5 mm). Column chromatography was carried out on silica gel (spherical, neutral, 40–50 μm, Kanto Chemical Co.) or amino silica gel (60 μm, Fuji Silysia Chemical Ltd.). All melting points were determined on a Yanaco MP melting point (mp) apparatus and were uncorrected. Infrared spectra were recorded with a JASCO FT/IR 4100 spectrophotometer. ^{1}H and ^{13}C NMR spectral data were obtained with JEOL JNM-ECS 400 instruments and an Agilent Technologies VXR-400NMR. Chemical shifts are quoted in ppm using tetramethylsilane (δ= 0 ppm) or CD_3OD (δ = 3.31 ppm) as the reference for ^{1}H NMR spectroscopy, and $CDCl_3$ (δ = 77.0 ppm) or CD_3OD (δ = 49.0 ppm) or C_6D_6 (δ = 128.0 ppm) for ^{13}C NMR spectroscopy. High-resolution mass spectra were measured with a JEOL JMS-T100LP spectrometer. Elemental analysis was performed with a YANACO CHN-CODER JM-10 model analyzer. The reactions were performed under an argon atmosphere unless otherwise noted. NH_3 aq. is 28% aqueous ammonia solution.

(4*R*,4a*S*,7a*S*,12b*S*)-3-(Cyclopropylmethyl)-9-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-4a-ol (**28**)



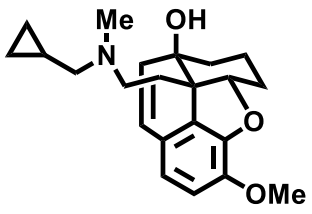
28

Compound **28** was synthesized by a modified procedure of the reported method, and the spectral data were also reported.[28]

A mixture of naltrexone hydrochloride (30.2 g, 79.9 mmol), K_2CO_3 (27.6 g, 200 mmol) and MeI (5.24 mL, 83.9 mmol) in DMF (200 mL) was stirred at room temperature for 11 h, and additional MeI (0.2 mL, 3.20 mmol) was added. The mixture was stirred for 13 h, and H_2O (600 mL) was added. The mixture was extracted with Et_2O (800, 300, 100, and 100 mL). The organic layer was washed with brine, and the aqueous 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 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 for 0.5 h. The reaction was quenched with acetone (50 mL). After being stirred for 2 h, the reaction mixture was concentrated under reduced pressure, and then azeotropically dried with toluene twice. To the residue was added H_2O (100 mL), and basified with K_2CO_3 (pH 9). The mixture was poured to H_2O (150 mL) and extracted with $CHCl_3$ (200, 100, and 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. To a solution of the crude product (27.3 g) in pyridine (200 mL) was added MsCl (12 mL, 155 mmol) at 0 °C, 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, and 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. A mixture of the crude product (35.9 g) and NaI (229.7 g, 1.53 mol) in DMF (300 mL) was stirred at 100 °C for 15 h. The hot reaction mixture was poured to H_2O, basified with $NaHCO_3$, and extracted with $CHCl_3$ (600, 300, 150, and 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. A mixture of the crude product (35.4 g) and DBU (44.5 mL, 298 mmol) in DMF (300 mL) was stirred at 100 °C for 21 h. 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, and 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. A mixture of the crude product (4.96 g) and $RhCl(PPh_3)_3$ (1.34 g, 1.45 mmol) in degassed benzene (80 mL) 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%NH_3 aq./MeOH/CPME = 1/9/90) in *n*-hexane) to afford compound **28** (4.01 g, 73% in 6 steps) as a brown oil.

(4a*S*,4a^1*S*,7a*R*)-4a^1-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-3-methoxy-4a,5,6,7-tetrahydrophenanthro[4,5-*bcd*]furan-7a(4a^1*H*)-ol (**27**)



27

A mixture of compound **28** (1.0 g, 2.93 mmol) and MeI (10 mL, 161 mmol) in DMF (10 mL) was stirred at 80 °C for 72 h, and additional MeI (3.0 mL, 48.2 mmol) was added. After being stirred 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 at 80 °C for 2 h, and then poured to H_2O (20 mL), and extracted with $CHCl_3$ (50, 30, and 20 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 (0→2% (NH_3 aq./MeOH = 1/9) in $CHCl_3$) to afford compound **27** (1.03 g, 99%) as a colorless oil.

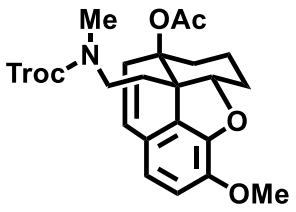
IR (neat): 1505, 1282 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 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 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{30}NO_3$: 356.2226. Found: 356.2221.

(4a*S*,4a^1*S*,7a*R*)-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 (**35**)



35

A solution of compound **27** (175 mg, 0.492 mmol) in Ac_2O (1.0 mL) was stirred at 70 °C for 3 h. 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 (2.0 mL) was added Et_3N (206 μL, 1.48 mmol) and 2,2,2-trichloroethyl chloroformate (136 μL, 0.988 mmol) at 0 °C, and the mixture was stirred at room temperature for 0.5 h. To the mixture was added saturated aqueous $NaHCO_3$ solution (5 mL), and the mixture was extracted with $CHCl_3$ (15, 12, and 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 **35** (241 mg, 94%) as a colorless oil.

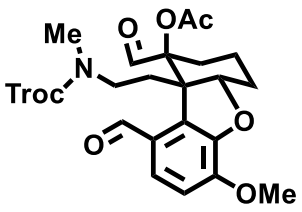
IR (neat): 1720, 1507, 1244 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 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, $CDCl_3$, mixture of rotamers): δ (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{23}H_{26}Cl_3NO_6Na$: 540.0723. Found: 540.0743.

(1*S*,4a*S*,9b*S*)-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 (**36**)



36

A solution of compound **35** (1.65 g, 3.18 mmol) in CH_2Cl_2 (400 mL) was stirred at −78 °C, and O_3 was introduced for 8 min. The remained O_3 was removed by sparging N_2 for 20 min, and cold Me_2S (−78 °C, 7.0 mL, 95.3 mmol) was added. After sparging N_2 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 **36** (1.59 g, 91%) as a colorless oil.

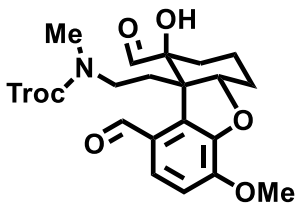
IR (neat): 1722, 1688, 1282 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 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, $CDCl_3$, mixture of rotamers): δ (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{23}H_{26}Cl_3NO_8Na$: 572.0621. Found: 572.0635.

2,2,2-Trichloroethyl {2-[(5a*S*,9*S*,9a*S*)-1,9-diformyl-9-hydroxy-4-methoxy-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}(methyl)carbamate (**37**)



37

A mixture of compound **36** (100 mg, 0.182 mmol) and Et_3N (35 μL, 0.251 mmol) in MeOH (2.5 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1/3 → 3/1) to afford compound **37** (93 mg, quant.) as a colorless oil.

IR (neat): 3442, 1716, 1683, 1604, 1285 cm^{-1}.

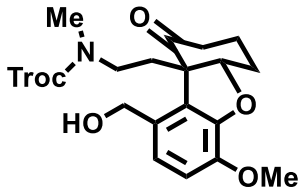
^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 1.57−1.89 (m, 3H), 1.92–2.16 (m, 3H), 2.37–2.58 (m, 1H), 2.72–3.02 (m, 2H), 2.92 (s, 1.8H), 2.96 (s, 1.2H), 3.39–3.63 (m, 1H), 3.98 (s, 1.8H), 3.99 (s, 1.2H), 4.54–4.73 (m, *J* = 12.0 Hz, 2.4H), 4.85 (d, *J* = 12.0 Hz, 0.6H) 4.88–4.97 (m, 1H), 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, $CDCl_3$, mixture of rotamers): δ (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{21}H_{24}Cl_3NO_7Na$: 530.0516. Found: 530.0531.

.

2,2,2-Trichloroethyl {2-[(5a*S*,9a*S*)-1-(hydroxymethyl)-4-methoxy-9-oxo-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}(methyl)carbamate (**38**)



38

To a stirred solution of compound **37** (245 mg, 0.482 mmol) in MeOH (12 mL) was added $LiBH_4$ (240 mg, 11.0 mmol) at −40 °C. After additional 0.5 h, the reaction mixture was warmed to 0 °C, and then 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, and 12 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. A mixture of the residue and $NaIO_4$ (300 mg, 1.40 mmol) in DME/H_2O (3/1) (16 mL) was stirred at room temperature for 12 h, and then H_2O (6 mL) was added. The mixture was extracted with CH_2Cl_2 (15, 12, and 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 **38** (166 mg, 72%) as a colorless oil.

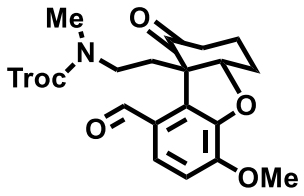
IR (neat): 3466, 1711, 1507, 1280 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 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, $CDCl_3$, mixture of rotamers): δ (ppm) 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.

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

2,2,2-Trichloroethyl {2-[(5a*S*,9a*S*)-1-formyl-4-methoxy-9-oxo-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}(methyl)carbamate (**25**)



25

To a solution A mixture of compound **38** (150 mg, 0.312 mmol) and activated MnO_2 (405 mg, 4.66 mmol) in 1,2-dichloroethane (5.0 mL) was stirred at 80 ° C for 12 h. 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 **25** (138 mg, 92%) as a colorless oil.

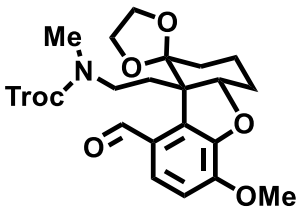
IR (neat): 1715, 1688, 1605, 1286 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 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, $CDCl_3$, mixture of rotamers): δ (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{22}Cl_3NO_6Na$: 500.0410. Found: 500.0412.

2,2,2-Trichloroethyl {2-[(4a*S*,9b*S*)-9-formyl-6-methoxy-2,3,4,4a-tetrahydro-9b*H*-spiro[dibenzo[*b*,*d*]furan-1,2′-[1,3]dioxolane]-9b-yl]ethyl}(methyl)carbamate (**39**)



39

A mixture of compound **25** (2.96 g, 6.18 mmol), ethylene glycol (1.8 mL, 32.3 mmol), isopropoxytrimethylsilane (17 mL, 95.7 mmol) and trimethylsilyl trifluoromethanesulfonate (570 μL, 3.15 mmol) in 1,2-dichloroethane (60 mL) was stirred at 60 ° C for 6 h. 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 concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane = 1/2) to afford compound **39** (2.94 g, 91%) as a colorless oil.

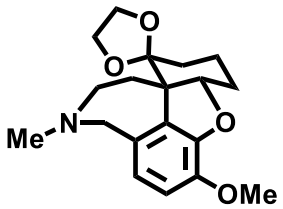
IR (neat): 1725, 1715, 1604, 1503 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 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, $CDCl_3$, mixture of rotamers): δ (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{26}Cl_3NO_7Na$: 544.0673. Found: 544.0661.

(4a*S*,8a*S*)-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] (**40**)



40

A mixture of compound **39** (921 mg, 1.76 mmol) and zinc powder (4.6 g, 70.3 mmol) in AcOH (15 mL) was stirred at room temperature for 22 h. 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 NH_3 aq., and then extracted with $CHCl_3$ (20, 10, 5, and 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% (NH_3 aq./MeOH = 1/9) in $CHCl_3$) to afford compound **40** (420 mg, 72%) as a yellow oil.

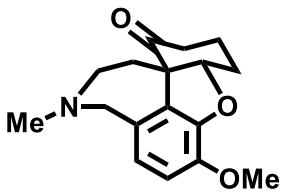
IR (neat): 1506, 1277 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 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 (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+H]^+$ Calcd for $C_{19}H_{26}NO_4$: 332.1862. Found: 332.1862.

(4a*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,6,7,9,10,11,12-octahydro-8*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-8-one (**41**)



41

A mixture of compound **40** (229 mg, 0.690 mmol) and 2 M HCl (3.0 mL) in MeOH (3.0 mL) was stirred at 60 °C for 12 h. The reaction mixture was adjusted to pH 10 with saturated aqueous $NaHCO_3$ solution and K_2CO_3, and then extracted with $CHCl_3$ (12, 6, 3, and 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% (NH_3 aq./MeOH = 1/9) in $CHCl_3$) to afford compound **41** (195 mg, 98%) as a colorless oil.

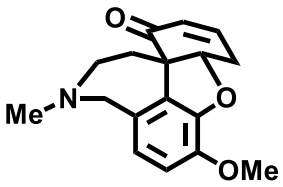
IR (neat): 1706, 1508, 1271 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 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 (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1599.

(4a*S*,8a*S*)-3-Methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-8-one (**44**)



44

A solution of compound **41** (195 mg, 0.678 mmol) in THF (4.0 mL) was added to LDA solution [prepared from freshly distilled diisopropylamine (0.33 mL, 2.35 mmol) and *n*-BuLi (1.6 M in *n*-hexane, 1.27 mL, 2.03 mmol) in THF (4.0 mL)] with stirring at −78 °C. 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 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, 5, and 5 mL). 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% (NH_3 aq./MeOH = 1/9) in $CHCl_3$]) to afford a mixture of α- and β-phenylsulfide. A mixture of the phenylsulfide and (±)-camphor-10-sulfonic acid (103 mg, 0.443 mmol) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 10 min. 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 mL). The reaction mixture was poured to saturated aqueous $NaHCO_3$ solution (10 mL), and then brine (10 mL), and extracted with $CHCl_3$ (20, 10, 5, and 3 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. A mixture of the crude residue and $NaHCO_3$ (112 mg) in toluene (9.0 mL) was stirred at 110 °C for 2 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ solution (10 mL) / H_2O (10 mL) was added, and the mixture was extracted with $CHCl_3$ (12, 6, 3, and 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% (NH_3 aq./MeOH = 1/9) in $CHCl_3$), and PLC ((NH_3 aq./MeOH = 1/9):$CHCl_3$ = 1:15) to afford compound **44** (79.6 mg, 41%) as a brown amorphous.

IR (KBr): 1660, 1510, 1280 cm^{-1}.

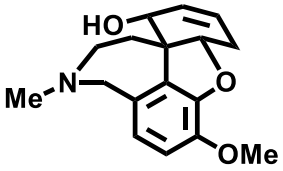
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.77 (ddd, *J* = 14.0, 3.6, 1.6 Hz, 1H), 2.11–2.24 (m, 1H), 2.41 (s, 3H), 2.79 (dddd, *J* = 20.4, 5.2, 2.8, 2.8 Hz, 1H), 3.01 (ddd, *J* = 13.6, 2.8, 2.8 Hz, 1H), 3.11 (dd, *J* = 20.4, 5.6 Hz,

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).

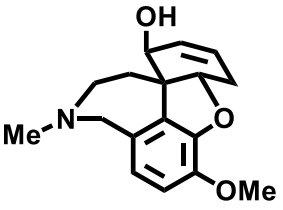
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 26.2, 29.5, 41.3, 53.3, 55.8, 57.8, 60.7, 88.6, 111.3, 122.0, 129.5, 130.3, 132.3, 143.2, 144.4, 146.8, 197.3.

HR-MS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{20}NO_3$: 286.1443. Found: 286.1401.

(4a*S*,8*R*,8a*R*)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-8-ol (**49**) and (4a*S*,8*S*,8a*R*)-3-methoxy-11-methyl-4a,5,9,10,11,12-hexahydro-8*H*-benzo[2,3]benzofuro[4,3-*cd*]azepin-8-ol (**49**)



49



50

A mixture of compound **44** (79.6 mg, 0.277 mmol) and $CeCl_3 \cdot 7H_2O$ (314 mg, 0.842 mmol) in MeOH/CH_2Cl_2 (2.0 mL/1.0 mL) was stirred at room temperature for 10 min, 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). The mixture was poured to aqueous $NaHCO_3$ solution (10 mL) / H_2O (10 mL), and extracted with $CHCl_3$ (12, 6, 3, and 3 mL). The organic layer was washed with brine, and dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by PLC ((NH_3 aq./MeOH = 1/9):$CHCl_3$ = 1:10) to afford compounds **49** (46.5 mg, 58%) as a colorless amorphous and **50** (22.5 mg, 28%) as a colorless oil. A portion of synthesized compound **49** was recrystallized from Et_2O/*n*-hexane to give colorless prism crystals.

Compound **49**

mp 163–165 °C.

IR (KBr): 3422, 1510, 1282 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ (ppm) 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 (ppm) 27.4, 36.6, 42.7, 49.7, 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.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1594.

Compound **50**

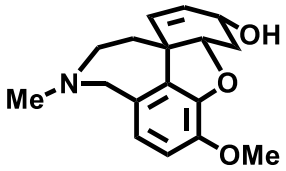
IR (neat): 3356, 1506, 1280 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 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, 1H), 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). One proton (OH) was not observed.

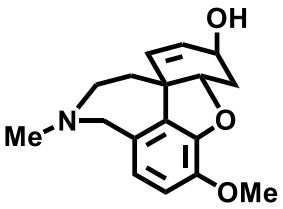
^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 27.9, 31.7, 43.2, 53.8, 56.2, 56.6, 61.1, 69.0, 90.9, 113.0, 122.5, 128.0, 129.3, 133.0, 135.1, 145.0, 149.4.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1600.

(–)-Galanthamine (**24**) and *epi*-galanthamine (**51**)



(–)-Galanthamine (**24**)



51

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. The mixture was stirred at the same temperature for 0.5 h, and then saturated aqueous $NaHCO_3$ solution (15 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h, and then extracted with $CHCl_3$ (30, 20, and 10 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by PLC ((NH_3 aq./MeOH = 1/9):$CHCl_3$ = 2:25) to afford (−)-galanthamine (**24**) (33.1 mg, 48%) as a colorless solid and compound **51** (15.7 mg, 23%) as a colorless amorphous. A portion of synthesized (−)-galanthamine (**24**) was recrystallized from EtOAc/*n*-hexane to give light yellow needle crystals.

(−)-Galanthamine (**24**)

mp 128–130 °C (lit.45; mp 128–129 °C).

$[\alpha]_D^{20}$ −89.7 (c = 0.6, $CHCl_3$) (lit.45; $[\alpha]_D^{20}$ −93.4 (c = 1, $CHCl_3$)).

IR (KBr): 3549, 3376, 1507, 1282 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 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 (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1595.

Compound **51**

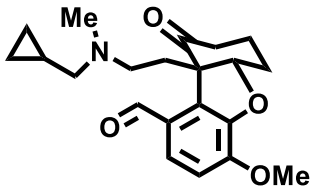
IR (film): 3323, 1506, 1278 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 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 (ppm) 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.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1590.

(5a*S*,9a*S*)-9a-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-4-methoxy-9-oxo-5a,6,7,8,9,9a-hexahydrodibenzo[*b*,*d*]furan-1-carbaldehyde (**53**)



53

To a stirred solution of compound **27** (19.8 mg, 55.7 mmol) in acetone/AcOH (2.0 mL/0.2 mL) were added $NaIO_4$ (60.3 mg, 0.282 mmol) in H_2O (2.0 mL) and OsO_4 in *t*-BuOH (2 mg/mL, 0.72 mL, 5.66 mmol), and the mixture was stirred at room temperature for 60 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL) / saturated aqueous $NaHCO_3$ solution (15 mL), and the mixture was extracted with $CHCl_3$ (20, 10, and 5 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by PLC ((NH_3 aq./MeOH = 1/9):$CHCl_3$ = 1:20) to afford compound **53** (16.0 mg, 80%) as a brown oil.

IR (neat): 1706, 1684, 1604, 1286 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) (−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).

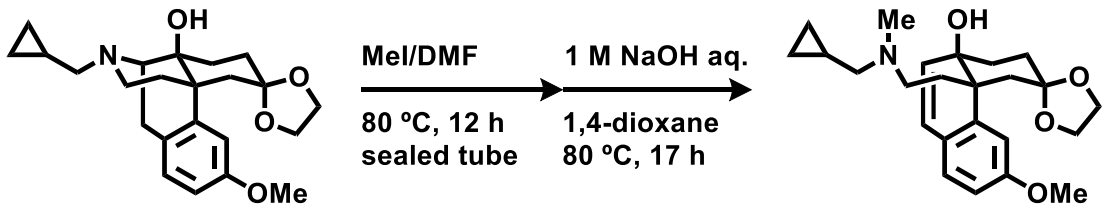
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 4.6 (×2), 6.4, 18.7, 28.0, 30.0, 38.1, 40.3, 51.9, 56.3, 61.0, 61.3, 90.4, 112.0, 126.9, 127.1, 128.6, 149.9, 150.5, 190.8, 208.5.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{28}NO_4$: 358.2018. Found: 358.2015.

2,2,2-Trichloroethyl {2-[(5a*S*,9a*S*)-1-formyl-4-methoxy-9-oxo-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-9a(5a*H*)-yl]ethyl}(methyl)carbamate (**25**)

A mixture of compound **53** (12.5 mg, 34.5 mmol), (*i*-Pr)$_2$NEt (18.3 μL, 0.105 mmol) and 2,2,2-trichloriethyl chloroformate (5.8 μL, 42.1 μmol) in 1,2-dichloroethane (1.0 mL) was stirred at room temperature for 6 h, and then additional (*i*-Pr)$_2$NEt (18.3 μL, 0.105 mmol) and 2,2,2-trichloroethyl chloroformate (5.8 μL, 42.1 μmol) were added. After 13 h, additional (*i*-Pr)$_2$NEt (36.5 μL, 0.210 mmol) and 2,2,2-trichloroethyl chloroformate (11.5 μL, 83.5 μmol) were added. After 3 h, (*i*-Pr)$_2$NEt (18.3 μL, 0.105 mmol) was added. The mixture was stirred for 2 h, and then poured to saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with $CHCl_3$ (5, 3, and 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 **25** (13.6 mg, 81%) as a colorless oil.

(4a*R*,10a*R*)-4a-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-6-methoxy-1,2,4,4a-tetrahydro-10a*H*-spiro[phenanthrene-3,2′-[1,3]dioxolan]-10a-ol (**54**)



72 **54**

A mixture of compound **72**[46] (0.401g, 1.04 mmol) and MeI (2.5 mL, 40.2 mmol) in DMF (2.5 mL) was stirred at 80 °C in a sealed tube for 12 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude residue was dissolved in 1,4-dioxane (5.0 mL), and 1 M aqueous NaOH solution (5.0 mL, 5.00 mmol) was added. After being stirred at 80 °C for 17 h, and the mixture was extracted with $CHCl_3$ (20, 15, and 5 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 (0→10% (NH_3 aq./MeOH = 1/9) in $CHCl_3$) to afford compound **54** (406 mg, 98%) as a colorless oil.

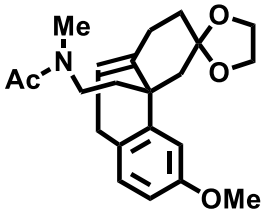
IR (neat): 3401, 1606, 1275 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.06–0.20 (m, 2H), 0.47–0.61 (m, 2H), 0.83–0.95 (m, 1H), 1.28–1.45 (m, 1H), 1.48–1.58 (m, 1H), 1.58–1.73 (m, 2H), 1.98–2.24 (m, 5H), 2.24–2.42 (m, 2H), 2.30 (s, 3H), 2.66 (dd, *J* = 12.1, 12.1 Hz, 1H), 3.80 (s, 3H), 3.75–4.02 (m, 4H), 5.78 (d, *J* = 9.6 Hz, 1H), 6.30 (d, *J* = 9.6 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H). One proton (OH) was not observed.

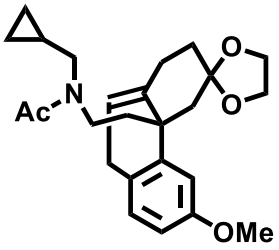
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 3.8, 4.2, 8.0, 30.3, 32.5, 36.3, 36.9, 40.7, 48.1, 52.3, 55.2, 61.7, 63.7, 64.3, 71.1, 109.4, 110.1, 113.2, 124.9, 125.4, 128.0, 136.0, 144.9, 158.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{34}NO_4$: 400.2488. Found: 400.2470.

(*S*)-*N*-{2-[6-Methoxy-1,9-dihydro-2*H*-spiro[phenanthrene-3,2′-[1,3]dioxolan]-4a(4*H*)-yl]ethyl}-*N*-methylacetamide (**56**) and (*S*)-*N*-(cyclopropylmethyl)-*N*-{2-[6-methoxy-1,9-dihydro-2*H*-spiro[phenanthrene-3,2′-[1,3]dioxolan]-4a(4*H*)-yl]ethyl}acetamide (**57**)



56



57

1) Retro-ene reaction of compound **54**

A solution of compound **54** (0.10 g, 0.250 mmol) in Ac_2O (2.6 mL) was stirred at 100 °C for 3 h, then cooled to room temperateure, and concentrated under reduced pressure. The crude product was purified by PLC (*n*-hexane:THF = 1:1) to afford compounds **56** (51.0 mg, 55%) as a colorless oil and **57** (26.8 mg, 26%) as a colorless oil.

2) Retro-ene reaction of compound **63**

A solution of compound **63** (50.7 mg, 0.140 mmol) in Ac_2O (2.0 mL, 21.2 mmol) was stirred under reflux for 2 h, then cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by PLC (*n*-hexane:THF= 3:2, twice) to afford compound **56** (45.5 mg, 87%) as a colorless oil.

Compound **56**

IR (neat): 1644, 1504, 1274 cm^{-1}.

^1H NMR (400 MHz, C_6D_6, mixture of rotamers): δ (ppm) 1.51–1.77 (m, 1.4H), 1.54 (s, 1.2H), 1.66 (s, 1.8H) , 1.78–1.91 (m, 1H), 1.92–2.13 (m, 2H), 2.17 (ddd, *J* = 13.7, 4.4, 2.5 Hz, 0.4H), 2.36 (dd, *J* = 13.7, 2.3 Hz, 0.6H), 2.42–2.58 (m, 2H), 2.65–2.77 (m, 0.6H), 2.67 (s, 1.8H), 2.81–3.08 (m, 1H), 3.03 (ddd, *J* = 13.3, 11.9, 4.6 Hz, 0.4H), 3.08–3.30 (m, 2H), 3.25–3.72 (m, 4.6H), 3.33 (s, 1.8H), 3.41 (s, 1.2H), 5.50–5.55 (m, 0.6H), 5.61–5.65 (m, 0.4H), 6.66–6.76 (m, 1H), 6.81–6.91 (m, 1.6H), 7.06 (d, *J* = 2.3 Hz, 0.4H).

^{13}C NMR (100 MHz, C_6D_6, mixture of rotamers): δ (ppm) 20.6, 21.5, 29.5, 29.6, 30.3, 30.4, 32.9, 35.3, 36.2, 36.3, 36.8, 38.1, 41.5, 41.8, 44.5, 47.2, 48.5, 49.2, 54.8, 63.6, 63.8, 64.9, 64.9, 109.0, 109.3, 110.5, 110.9, 112.4, 112.7, 120.4, 120.7, 125.2, 125.6, 129.2, 129.3, 136.5, 137.1, 142.6, 143.1, 159.1, 159.2, 168.8, 168.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{29}NO_4Na$: 394.1994. Found: 394.1978.

Compound **57**

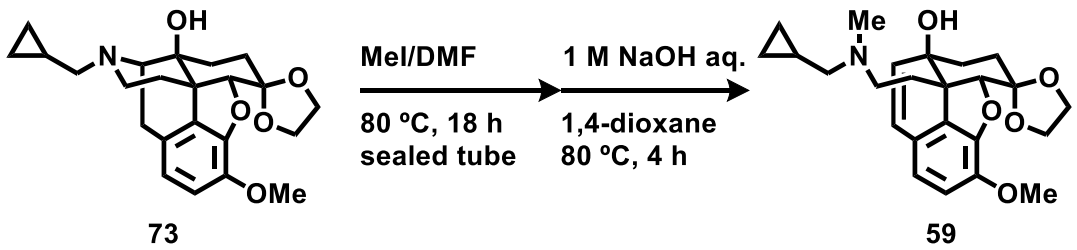
IR (neat): 1643, 1504, 1272 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) (–0.24)– 0.10 (m, 2H), 0.28–0.45 (m, 2H), 0.61–0.81 (m, 1H), 1.55 (ddd, *J* = 14.0, 13.1, 4.6 Hz, 1H), 1.65–1.94 (m, 3.4H), 1.81 (s, 1.8H), 2.01 (s, 1.2H), 2.22–2.36 (m, 2H), 2.41–2.59 (m, 1H), 2.59–2. 90 (m, 2.4H), 2.92– 3.05 (m, 1.6H), 3.15 (dd, *J* = 14.0, 6.6 Hz, 0.6H), 3.28–3.39 (m, 2H), 3.87–4.12 (m, 4H), 3.787 (s, 1.8H), 3.793 (s, 1.2H), 5.77–5.85 (m, 1H), 6.71–6.85 (m, 2H), 7.00 (d, *J* = 8.5 Hz, 0.4H), 7.03 (d, *J* = 8.5 Hz, 0.6H).

^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers): δ (ppm) 3.2, 3.3, 3.5, 3.6, 9.6, 10.1, 20.9, 21.7, 29.2, 29.9, 30.0, 35.6, 36.6, 38.2, 41.2, 41.4, 42.2, 44.6, 47.5, 48.0, 49.3, 52.9, 55.3, 63.6, 63.8, 64.8, 108.8, 109.0, 110.2, 110.4, 112.1, 112.3, 120.0, 120.6, 125.2, 125.4, 128.8, 129.0, 135.8, 136.5, 142.0, 142.5, 158.3, 158.4, 169.5, 170.2.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{25}H_{33}NO_4Na$: 434.2307. Found: 434.2297.

(3a*R*,3a^1*S*,9a*R*)-3a^1-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-5-methoxy-1,2,3a,3a^1-tetrahydro-9a*H*-spiro[phenanthro[4,5-*bcd*]furan-3,2′-[1,3]dioxolan]-9a-ol (**59**)



73 **59**

A mixture of compound **73**[41] (0.302 g, 0.760 mmol) and MeI (2.0 mL, 32.1 mmol) in DMF (2.0 mL) was stirred at 80 °C in a sealed tube for 18 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude residue was dissolved in 1,4-dioxane (3.0 mL), and 1 M aqueous NaOH solution (3.0 mL, 3.00 mmol) was added. The mixture was stirred at 80 °C for 4 h, then cooled to room temperature, and extracted with $CHCl_3$ (20, 10, and 5 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 (0→10% (NH_3 aq./MeOH=1/9) in $CHCl_3$) to afford compound **59** (326 mg, 100%) as a colorless solid.

mp: 129.8–131.1 °C.

IR (KBr): 3421, 1501, 1269 cm^{-1}.

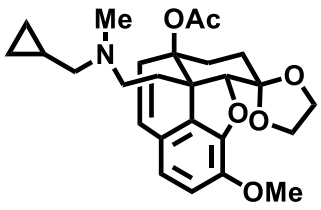
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.08–0.20 (m, 2H), 0.49–0.59 (m, 2H), 0.81–0.94 (m, 1H), 1.43 (ddd, *J* = 13.3, 3.9, 2.5 Hz, 1H), 1.61 (ddd, *J* = 14.0, 14.0, 2.3 Hz, 1H), 1.68–1.84 (m, 2H), 1.89–2.04 (m, 2H), 2.22 (dd, *J* = 13.5, 7.6 Hz, 1H), 2.29 (dd, *J* = 6.4, 2.3 Hz, 2H), 2.34 (s, 3H), 2.48 (dd, *J* = 13.5, 9.8 Hz, 1H), 3.83 (ddd, *J* = 6.9, 6.9, 5.0 Hz, 1H), 3.88 (s, 3H), 3.90 (ddd, *J* = 6.9, 6.9, 6.9 Hz, 1H), 4.03 (ddd, *J* = 6.9, 6.9, 6.9 Hz, 1H), 4.22 (ddd, *J* = 6.9, 6.9, 5.0 Hz, 1H), 4.62 (s, 1H), 5.68 (d, *J* = 9.6 Hz, 1H), 6.24 (d, *J* = 9.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 3.8, 4.2, 8.4, 27.2, 33.2, 35.3, 41.6, 52.1, 52.6, 56.3, 62.3, 64.9, 66.5, 72.6, 96.4, 108.6, 112.6, 117.3, 122.3, 123.5, 131.0, 139.7, 144.0, 146.0.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{24}H_{32}NO_5$: 414.2281. Found: 414.2263.

Elemental Analysis: Anal Calcd for $C_{24}H_{32}NO_5 \cdot 0.18CHCl_3$: C, 68.98; H, 7.94; N, 3.33, Found: C, 69.33; H, 7.58; N, 3.46.

(3a*R*,3a^1*S*,9a*R*)-3a^1-{2-[(Cyclopropylmethyl)(methyl)amino]ethyl}-5-methoxy-1,2,3a,3a^1-tetrahydro-9a*H*-spiro[phenanthro[4,5-*bcd*]furan-3,2′-[1,3]dioxolan]-9a-yl acetate (**60**)



60

A solution of compound **59** (49.7 mg, 0.120 mmol) in Ac_2O (2.0 mL, 21.2 mmol) was stirred at 100 °C for 3 h, then cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by PLC [*n*-hexane/EtOAc/MeOH/NH_3 aq. = 50/100/9/1] to afford acetate **60** (54.4 mg, 99%) as a brown oil.

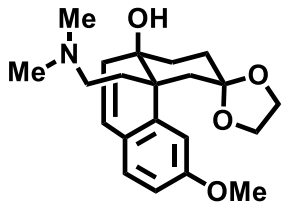
IR (neat): 1732, 1506 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) (–0.07)–0.08 (m, 2H), 0.35–0.49 (m, 2H), 0.67–0.79 (m, 1H), 1.39–1.52 (m, 1H), 1.59–1.71 (m, 2H), 1.94 (ddd, *J* = 12.5, 12.5, 4,4 Hz, 1H), 2.06–2.27 (m, 4H), 2.10 (s, 3H), 2.20 (s, 3H), 2.47 (ddd, *J* = 12.5, 12.5, 4.4 Hz, 1H), 2.81–2.93 (m, 1H), 3.85 (ddd, *J* = 6.4, 6.4, 5.0 Hz, 1H), 3.89 (s, 3H), 3.91 (ddd, *J* = 6.9, 6.4, 6.4 Hz, 1H), 4.07 (ddd, *J* = 6.9, 6.4, 6.4 Hz, 1H), 4.23 (ddd, *J* = 6.9, 6.9, 5.0 Hz, 1H), 4.73 (s, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 6.44 (d, *J* = 9.8 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 3.7, 3.8, 8.7, 22.4, 27.0, 27.4, 32.5, 42.4, 51.6, 53.0, 56.3, 62.7, 65.0, 66.6, 87.0, 95.4, 107.9, 112.9, 117.9, 122.4, 124.3, 127.9, 128.9, 144.1, 146.2, 170.1.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{26}H_{34}NO_6$: 456.2386. Found: 456.2376.

(4a*R*,10a*R*)-4a-[2-(Dimethylamino)ethyl]-6-methoxy-1,2,4,4a-tetrahydro-10a*H*-spiro[phenanthrene-3,2′-[1,3]dioxolan]-10a-ol (**63**)



63

A mixture of compound **62** (0.656 g, 1.90 mmol) and MeI (3.0 mL, 48.2 mmol) in DMF (3.0 mL) was stirred at 80 °C in a sealed tube for 16 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude residue was dissolved in 1,4-dioxane (10 mL), and 1 M aqueous NaOH solution (10 mL, 10.0 mmol) was added. The mixture was stirred for 4 h at 80 °C, then cooled to room temperature, and was extracted with $CHCl_3$ (30, 20, and 10 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 (0→10% (NH_3 aq./MeOH = 1/9) in $CHCl_3$) to afford compound **63** (413 mg, 60%) as a colorless solid.

mp 121.5–122.3 °C.

IR (KBr): 1607, 1487, 1277 cm^{-1}.

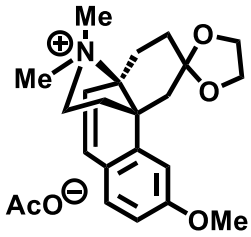
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.33–1.74 (m, 4H), 1.92–2.12 (m, 4H), 2.17–2.35 (m, 1H), 2.23 (s, 6H), 2.54 (dd, *J* = 12.1, 12.1 Hz, 1H), 3.80 (s, 3H), 3.84–4.02 (m, 4H), 5.77 (d, *J* = 9.6 Hz, 1H), 6.31 (d, *J* = 9.6 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.93 (d, *J* = 2.8 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H). One proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 30.4, 32.6, 36.5, 37.1, 44.2 (two carbons), 47.9, 54.3, 55.2, 63.8, 64.3, 71.1, 109.4, 110.1, 113.2, 125.0, 125.4, 128.1, 135.7, 144.7, 158.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{30}NO_4$: 360.2175. Found: 360.2176.

Elemental Analysis: Anal Calcd for $C_{21}H_{30}NO_4 \cdot 0.5H_2O$: C, 68.45; H, 8.21; N, 3.80, Found: C, 68.28; H, 7.86; N, 4.03.

Retro-ene reaction of compound **63** *via* **64**



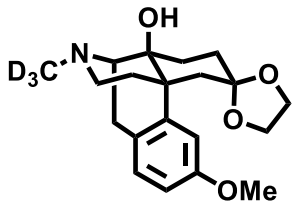
64

A mixture of compound **63** (31.3 mg, 0.090 mmol) in Ac_2O (2.00 mL, 21.2 mmol) was stirred at 60 °C for 4 h, then cooled to room temperature, and concentrated under reduced pressure to afford **64** as a crude product.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.33 (d, *J* = 14.7 Hz, 1H), 1.58 (ddd, *J* = 13.8, 13.8, 3.4 Hz, 1H), 1.79 (ddd, *J* = 13.2, 6.5, 3.3 Hz, 1H), 1.86 (dd, *J* = 14.7, 3.2 Hz, 1H), 1.92 (s, 3H), 2.10 (ddd, *J* = 12.8, 3.4, 3.4 Hz, 1H), 2.31 (ddd, *J* = 13.4, 13.4, 3.4 Hz, 1H), 2.71 (s, 3H), 2.78 (ddd, *J* = 14.7, 9.2, 7.3 Hz, 1H), 3.10 (s, 3H), 3.24 (ddd, *J* = 14.2, 10.5, 5.0 Hz, 1H), 3.66–3.86 (m, 4H), 3.78 (s, 3H), 3.86–4.00 (m, 2H), 5.55 (d, *J* = 9.6 Hz, 1H), 6.70 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 7.07 (d, *J* = 9.6 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H).

The crude product **64** was dissolved in Ac_2O (2.0 mL, 21.2 mmol), and stirred under reflux for 2 h. The mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by PLC (*n*-hexane:THF = 2:3) to afford compound **56** (26.3 mg, 81%).

(4b′*R*,8a′*S*,9′*R*)-3′-Methoxy-11′-(methyl-d_3)-7′,8′,9′,10′-tetrahydro-5′*H*,8a′*H*-spiro[[1,3]dioxolane-2,6′-[9,4b](epiminoethano)phenanthren]-8a′-ol (**70**)



70

To a suspension of $LiAlD_4$ (536 mg, 12.8 mmol) in THF (6.0 mL) was added a solution of **61** (703 mg, 1.28 mmol) in THF (6.0 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous potassium sodium tartrate solution (30 mL), and the mixture was extracted with $CHCl_3$ (30, 20, and 10 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 (0→10% (NH_3 aq./MeOH = 1/9] in $CHCl_3$} to afford compound **70** (331 mg, 74%) as a colorless solid.

mp 172.3–174.1 °C.

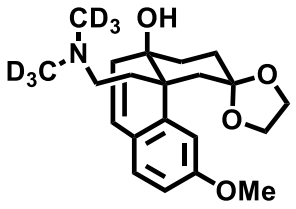
IR (KBr): 3418, 2243, 1614, 1497, 1270 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ (ppm) 0.89–1.00 (m, 1H), 1.54 (ddd, *J* = 12.4, 4.1, 2.3 Hz, 1H), 1.68–1.77 (m, 1H), 1.89–2.03 (m, 4H), 2.34 (dd, *J* = 14.2, 2.3 Hz, 1H), 2.41–2.50 (m, 2H), 2.51 (dd, *J* = 17.9, 5.5 Hz, 1H), 2.71 (ddd, *J* = 13.7, 12.8, 4.6 Hz, 1H), 2.80 (d, *J* = 17.9 Hz, 1H), 3.33–3.42 (m, 1H), 3.45 (s, 3H), 3.47–3.55 (m, 2H), 3.56–3.63 (m, 1H), 6.69 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 2.8 Hz, 1H).

^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 24.2, 30.5, 31.4, 37.8, 38.4, 41.5 (sept, *J* = 20.6 Hz), 42.1, 45.7, 54.8, 63.1, 63.7, 64.3, 68.9, 109.4, 111.7, 113.0, 127.4, 127.9, 142.7, 158.0.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{25}D_3NO_4$: 349.2207. Found: 349.2205.

(4a*R*,10a*R*)-4a-{2-[Bis(methyl-d_3)amino]ethyl}-6-methoxy1,2,4,4a-tetrahydro-10a*H*-spiro[phenanthrene-3,2'-[1,3]dioxolan]-10a-ol (**69**)



69

A mixture of **70** (0.308 g, 0.880 mmol) and CD_3I (2.0 mL, 31.5 mmol) in DMF (2.0 mL) was stirred at 80 °C in a sealed tube for 14 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude residue was dissolved in 1,4-dioxane (6.0 mL), and 1 M aqueous NaOH solution (6.0 mL, 6.00 mmol) was added. The mixture was stirred at 80 °C for 6 h, then cooled to room temperature, and extracted with $CHCl_3$ (40, 20, and 10 mL). The organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (0→10% (NH_3 aq./MeOH = 1/9] in $CHCl_3$) to afford compound **69** (172 mg, 53%) as a colorless oil.

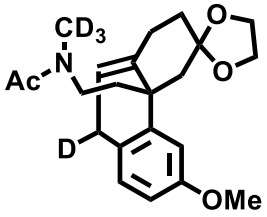
IR (neat): 3367, 2192, 2048, 1606, 1489, 1276 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32–1.73 (m, 4H), 1.94–2.13 (m, 3H), 1.96 (ddd, *J* = 15.8, 11.5, 1.4 Hz, 1H), 2.25 (d, *J* = 14.2 Hz, 1H), 2.52 (ddd, *J* = 12.8, 11.9, 0.9 Hz, 1H), 3.79 (s, 3H), 3.82–4.00 (m, 4H), 5.76 (d, *J* = 9.6 Hz, 1H), 6.30 (d, *J* = 9.6 Hz, 1H), 6.67 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 30.3, 32.5, 36.5, 37.0, 43.2 (sept, *J* = 19.7 Hz, ×2), 47.9, 54.1, 55.1, 63.7, 64.3, 71.0, 109.3, 110.0, 113.2, 124.9, 125.4, 128.1, 135.7, 144.7, 158.3.

HR-MS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{21}H_{24}D_6NO_4$: 366.2551. Found: 366.2543.

N-{2-[(4a*S*)-6-Methoxy-1,9-dihydro-2*H*-spiro[phenanthrene-3,2′-[1,3]dioxolan]-4a(4*H*)-yl-9-*d*]ethyl}-*N*-(methyl-d_3)acetamide (**71**)



71

A solution of **69** (49.1 mg, 0.130 mmol) in Ac_2O (2.0 mL, 21.2 mmol) was stirred under reflux for 4 h, then cooled to room temperature, and concentrated under reduced pressure. The crude residue was purified by PLC (CH_2Cl_2:MeOH = 3:1) to afford compound **71** (25.0 mg, 50%) as a colorless oil.

IR (neat): 2278, 2074, 1644, 1504, 1274 cm^{-1}.

^1H NMR (400 MHz, C_6D_6, mixture of rotamers): δ (ppm) 1.54 (s, 1.2H), 1.51–1.76 (m, 1.4H), 1.66 (s, 1.8H), 1.78–1.91 (m, 1H), 1.91–2.13 (m, 2H), 2.07 (ddd, *J* = 13.7, 4.6, 2.8 Hz, 0.4H), 2.36 (dd, *J* = 13.7, 2.3 Hz, 0.6H), 2.42–2.58 (m, 2H), 2.65–2.76 (m, 0.6H), 2.81–3.08 (m, 1.4H), 3.07–3.18 (m, 1H), 3.25–3.72 (m, 4.6H), 3.33 (s, 1.8H), 3.41 (s, 1.2H), 5.53 (dd, *J* = 4.6 1.4 Hz, 0.6H), 5.63 (dd, *J* = 4.6 1.4 Hz, 0.4H), 6.66–6.76 (m, 1H), 6.81–6.91 (m, 1.6H), 7.06 (d, *J* = 2.3 Hz, 0.4H).

^{13}C NMR (100 MHz, C_6D_6, mixture of rotamers): δ (ppm) 20.6, 21.5, 29.1 (t, *J* = 19.2 Hz), 29.2 (t, *J* = 19.2 Hz), 30.3, 30.4, 32.2 (sept, *J* = 21.1 Hz), 34.5 (sept, *J* = 21.1 Hz), 36.2, 36.3, 36.8, 38.1, 41.5, 41.8, 44.4, 47.1, 48.6, 49.3, 54.8, 63.6, 63.8, 64.9, 64.91, 109.0, 109.3, 110.5, 110.9, 112.4, 112.7, 120.4, 120.6, 125.2, 125.6, 129.2, 136.5, 137.2, 142.6, 143.1, 159.1, 159.2, 168.8, 168.9.

HR-MS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{25}D_4NO_4Na$: 398.2245. Found: 398.2259.

Table 1. Crystal data and structure refinement for compound **49**

Compound	**49**
CCDC number	1493066
Molecular formula	C17H21NO3
Formula weight	287.36
Temperature (K)	93
Wavelength (Å)	1.54187
Crystal size (mm^3)	0.232 × 0.225 × 0.170
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a/b/c (Å)	6.25838(14)/14.0249(3)/16.6165(4)
α/β/γ (°)	90/90/90
Volume (Å)	1458.48(6)
Z	4
Density (calculated) (g/cm^3)	1.309
F (000)	616.00
Index ranges	–7<=h<=7, –16<=k<=16, –20<=l<=19
Reflections collected	15886
Independent reflections	2667
R (int)	0.0266
Completeness to theta	67.687 °, 100%
Refinement method	Full-matrix least-squares on F^2
No. Observations (All reflections)	2667
No. Variables	191
Reflection/Parameter Ratio	13.96
Residuals: R1 [$I > 2.00\ \sigma\ (I)$]	0.0286
Residuals: R (All reflections)	0.0293
Residuals: wR2 (All reflections)	0.0759
Goodness-of-fit	1.042
Absolute structure parameter	0.08 (4)
Max. and min. peak in Final Diff. Map ($e^-/Å^3$)	–0.19 / 0.23

References and notes

1. (a) Brownstein, M. J. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5391–5393.
   (b) Martin, B. In *Opium: A History*; Simon & Schuster, Ltd.: London, 1996.
2. Sertürner, F. W. *Trommsdorf's J. Pharmazie* **1805**, *13*, 234–241.
3. (a) Gulland, J. M.; Robinson, R. *J. Chem. Soc.* **1923**, 980–998.
   (b) Gulland, J. M.; Robinson, R. *Mem. Proc. Manchester Lit. Phil. Soc.* **1925**, *69*, 79–86.
4. Schöpf, C. *Justus Liebigs Ann. Chem.* **1927**, *452*, 211–267.
5. Hughes, J.; Smith, T. W.; Kosterlitz, H. W.; Forthergrill, L. A.; Morgan, B. A.; Morris, H. R. *Nature* **1976**, *258*, 577–579.
6. (a) Li, C. H.; Chung, D. *Proc. Natl. Acad. Sci. USA* **1976**, *73*, 1145–1148.
   (b) Bradbury, A. F.; Smyth, D. G.; Snell, C. R.; Birdsall, N. J. M.; Hulme, E. C. *Nature* **1976**, *260*, 793–795.
7. Goldstein, A.; Tachibana, S.; Lowney, L. I.; Hunkapiller, M.; Hood, L. *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 6666–6670.
8. Zadine, J.; Hackler, L.; Ge, J.-G.; Chen, C.; Liu-chen, L.-Y. *Nature* **1997**, *386*, 499–502.
9. Gilbert, P. E.; Martin, W. R. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 66–82.
10. Load, J. A. H.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. *Nature* **1977**, *267*, 495–499.
11. DeLander, G. E.; Portoghese, P. S.; Takemori, A. E. *J. Pharmacol. Exp. Ther.* **1984**, *231*, 91–96.
12. (a) Piercey, M. F.; Lahti, R. A.; Schroeder, L. A.; Einspahr, F. J.; Barsuhn, C. *Life Sci.* **1982**, *31*, 1197–1200.
    (b) Lahti, R. A.; Von Voigtlander, P. F.; Barshun, C. *Life Sci.* **1982**, *31*, 2257–2260.
    (c) Szmuszkovicz, J.; Von Voigtlander, P. F. *J. Med. Chem* **1982**, *25*, 1125–1126.
    (d) Von Voigtlander, P. F.; Lahti, R. A.; Ludens, J. H. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 7–12.
13. (a) Tang, A. H.; Collins, R. J. *Psychopharmacology (Berl)* **1985**, *85*, 309–314.
    (b) Mucha, R. F.; Hertz, A. *Psychopharmacology* **1985**, *86*, 274–280.
    (c) Millan, M. J. *Trends Pharmacol. Sci.* **1990**, *11*, 70–76.
14. Nagase, H.; Hayakawa, J.; Kawamura, K.; Kawai, K.; Takezawa, Y.; Matsuura, H.; Tajima, C.; Endo, T. *Chem. Pharm. Bull.* **1998**, *46*, 366–369.
15. (a) Portoghese, P. S. *Trends Pharmacol. Sci.* **1989**, *10*, 230–235.
    (b) Portoghese, P. S. *J. Med. Chem.* **1991**, *34*, 1757–1762.
16. Nogrady, T. In *Medicinal Chemistry A Biochemical Approach*; Oxford University Press: New York, 1985; pp 68–69.
17. (a) Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281–282.
    (b) Portoghese, P. S.; Sultana, M.; Takemori, A. E. *Eur. J. Pharmacol.* **1988**, *146*, 185–186.
    (c) Portoghese, P. S.; Sultana, M.; Takemori, A. E. *J. Med. Chem.* **1990**, *33*, 1714–1720.
18. (a) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. *J. Med. Chem.* **1987**, *30*, 238–239.
    (b) Portoghese, P. S.; Nagase, H.; Lipkowski, A. W.; Larson, D. L.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 836–841.
19. Calderpm, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125–2128.
20. (a) Nagase, H.; Wakita, H.; Kawai, K.; Endo, T.; Matsumoto, O. JP04275288, **1992**.
    (b) Nagase, H.; Kawai, K.; Hayakawa, J.; Wakita, H.; Mizusuna, A.; Matsuura, H.; Tajima, C.; Takezawa, Y.; Endoh, T. *Chem. Pharm. Bull*. **1998**, *46*, 1695–1702.
    (c) Nagase, H.; Yajima, Y.; Fujii, H.; Kawamura, K.; Narita, M.; Kamei, J.; Suzuki, T. *Life Sci*. **2001**, *46*, 2227–2231.
21. Nagase, H.; Nemoto, T.; Matsubara, A.; Saito, M.; Yamamoto, N.; Osa, Y.; Hirayama, S.; Nakajima, M.; Nakao, K.; Mochizuki, H.; Fujii, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6302–6305.
22. (a) Miyata, Y.; Fujii, H.; Uenohara, Y.; Kobayashi, S.; Takeuchi, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5174–5176.
    (b) Miyata, Y.; Fujii, H.; Osa, Y.; Kobayashi, S.; Takeuchi, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4710–4712.
    (c) Kutsumura, N.; Nakajima, R.; Koyama, Y.; Miyata, Y.; Saitoh, T.; Yamamoto, N.; Iwata, S.; Fujii, H.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4890–4892.

23. Saitoh, T.; Yamamoto, N.; Nakajima, R.; Irukayama, Y.; Ogawa, Y.; Tominaga, H., Ishikawa, Y.; Yanagisawa, M.; Nagase, H. Abstracts of Papers, The 32nd Medicinal Chemistry Symposium, Kobe, Japan, Nov 26−28, 2014; The Pharmaceutical Society of Japan, Division of Medicinal Chemistry: Tokyo, 2014; 1P-11.
24. Nagase, H.; Yamamoto, N.; Yata, M.; Ohrui, S.; Okada, T.; Saitoh, T.; Kutsumura, N.; Nagumo, Y.; Irukayama-Tomobe, Y.; Ishikawa, Y.; Ogawa, Y.; Hirayama, S.; Kuroda, D.; Watanabe, Y.; Gouda, H.; Yanagisawa, M. *J. Med. Chem.* **2017**, *60*, 1018–1040.
25. (a) Nagase, H.; Fujii, H. *Top. Curr. Chem.* **2011**, *299*, 29–62.
(b) Nagase, H.; Fujii, H. *Heterocycles* **2012**, *85*, 1821–1867.
(c) Kutsumura, N.; Nagase, H. *J. Synth. Org. Chem. Jpn.* **2018**, *76*, 914–921.
26. Nagase, H.; Abe, A.; Portoghese, P. S. *J. Org. Chem.* **1989**, *54*, 4120–4125.
27. Portoghese, P. S.; Nagase, H.; Maloney Huss, K. E.; Lin, C-E.; Takemori, A. E. *J. Med. Chem.* **1991**, *34*, 1715–1720.
28. Sakami, S.; Kawai, K.; Maeda, M.; Aoki, T.; Fujii, H.; Ohno, H.; Ito, T.; Saitoh, A.; Nakao, K.; Izumimoto, N.; Matsuura, H.; Endo, T.; Ueno, S.; Natsume, K.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 7956–7967.
29. Yamamoto, N.; Fujii, H.; Imaide, S.; Hirayama, S.; Nemoto, T.; Inokoshi, J.; Tomoda, H.; Nagase, H. *J. Org. Chem.* **2011**, *76*, 2257–2260.30.
30. Fujii, H.; Watanabe, Y.; Osa, Y.; Nemoto, T.; Sato, N.; Nagase, H. *Tetrahedron* **2009**, *65*, 4808–4813.
31. Konoura, K.; Fujii, H.; Imaide, S.; Gouda, H.; Hirayama, S.; Hirono, S.; Nagase, H. *Bioorg. Med. Chem.* **2015**, *23*, 439–448.
32. (a) Franck, R. D.; Johnson, W. S. *Tetrahedron Lett.* **1963**, *9*, 545–547.
(b) Grob, C. A.; Schiess, P. W. *Angew. Chem. Int. Ed.* **1967**, *6*, 1–15.
(c) Yoshimitsu, T.; Yanagiya, M.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 5215–5218.
(d) Prantz, K.; Mulzer, J. *Chem. Rev*. **2010**, *110*, 3741–3766.
33. Proskurnina, N. F.; Yakoleva, A. P. *J. Gen. Chem. U.S.S.R.* **1952**, *22*, 1899–1902.
34. Lilienfeld, S.; *CNS Drug Rev.* **2002**, *8*, 159–176.
35. (a) Sramek, J. J.; Frackiewicz, E. J.; Cutler, N. R. *Expert Opin. Invest. Drugs* **2000**, *9*, 2393–2402.
(b) Heinrich, M.; Teoh, H. L. *J. Ethnopharmacol*. **2004**, *92*, 147–162.
36. Smith, D. H., Jr. US4478840, **1984**.
37. Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, *15*, 1325–1327.
38. Kurihara, M.; Hakamata, W. *J. Org. Chem.* **2003**, *68*, 3413–3415.
39. Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785–14803.
40. Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.
41. Osa, Y.; Ida, Y.; Yano, Y.; Furuhata, K.; Nagase, H. *Heterocycles* **2006**, *69*, 271–282.
42. Nagase, H.; Osa, Y.; Nemoto, T.; Fujii, H.; Imai, M.; Nakamura, T.; Kanemasa, T.; Kato, A.; Gouda, H.; Hirono, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2792–2795.
43. (a) Silver, M. S.; Caserio, M. C.; Rice, H. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 3671–3678.
(b) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69–95.
(c) Fujii, H.; Imaide, S.; Watanabe, A.; Nemoto, T.; Nagase, H. *Tetrahedron Lett.* **2008**, *49*, 6293–6296.
44. (a) Wiberg, K. B. *Chem. Rev.* **1955**, *55*, 713–743.
(b) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, 111, 4857–4963.
45. Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463–5465.
46. Nagase, H.; Yamamoto, N.; Nemoto, T.; Yoza, K.; Kamiya, K.; Hirono, S.; Momen, S.; Izumimoto, N.; Hirono, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2792–2795.

Acknowledgment

Above all, I would like to express my profound gratitude to Professor Hiroshi Nagase for his polite guidance and continuous support of my Ph.D. study and related research. He gave me the opportunity to learn medicinal chemistry and organic chemistry. His considerable encouragement and valuable advice helped me in all the time and lead to better results. I am proud to learn and research under his tutelage to date.

I would like to sincerely thank Dr. Naoshi Yamamoto for his detailed support especially in the synthesis of galanthamine. And I feel sincere gratitude to Dr. Noriki Kutsumura for his tremendous support especially in the studies of novel retro-ene reaction. I also thank Dr. Satomi Imaide who pioneered the synthesis of galanthamine and discovered the novel retro-ene reaction and Yukimasa Harada who developed the preceding study for the synthesis of galanthamine.

Thanks go to Drs. Tsuyoshi Saitoh and Yasuyuki Nagumo for instructing me in organic chemistry and pharmacology, respectively. I am grateful to Professor Hideaki Fujii for educating me when I was at Kitasato University. I feel gratitude to Dr. Ryo Nakajima for giving me useful advice of not only the study, but also the career and so on. I would like to sincerely thank Drs. Shuji Ioka, and Tomoya Sugai for stimulating me to work hard.

I would like to sincerely thank student members of the Nagase group, Sayaka Ohrui, Yan Zhang, Naoto Hosokawa, Ryuichiro Ohsita, Yasuaki Koyama, Kazunori Seki, Masahiro Yata, Jumpei Horiuchi, Yuko Suzuki, Keita Iio, Kenta Maeda, Tsubasa Hino, Mao Amezawa, and Akihisa Tokuda, for the friendly and intellectually stimulating laboratory atmosphere. I am grateful for the administrative support provided by the secretary of Nagase group, Ms. Naoko Yamada.

List of publications

(1) Yamamoto, N.; Okada, T.; Harada, Y.; Kutsumura, N.; Imaide, S.; Saitoh, T.; Fujii, H.; Nagase, H. "The application of a specific morphinan template to the synthesis of galanthamine" *Tetrahedron* **2017**, *73*, 5751–5758.

(2) Kutsumura, N.; Okada, T.; Imaide, S.; Fujii, H.; Nagase, H. "Acetic Anhydride Mediated Retro-Ene Reaction via a [4.4.3]Propellane Skeleton Intermediate Containing a Quaternary Ammonium Linkage" *Synthesis* **2018**, *50*, 4263–4269.