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DESIGN AND SYNTHESIS OF NOVEL OPIOID LIGANDS AND THEIR PHARMACOLOGIES

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Abstract – We describe the recent progress of our investigations in the opioid field in this review, which includes interesting reactions using naltrexone derivatives and pharmacological properties of the synthesized derivatives. Some reactions utilized the characteristic structural features of the morphinan skeleton, and others were applicable to general compounds. Some derivatives were expected to be lead compounds for developing novel ligands selective for the individual opioid receptor types. Triplet drugs consisting of three pharmacophore units in one molecule exhibited interesting pharmacological profiles and would be expected to be a useful tool for clarifying the pharmacology of receptor oligomerization.

CONTENTS

1. **INTRODUCTION**

Opioids are generally classified into three types (μ, δ, and κ types) not only by pharmacological studies but also by molecular biological characterizations,[1] and all receptor types are related to analgesic effects. Narcotic addiction is believed to be derived from the μ receptor type, and therefore δ and κ types are promising drug targets for analgesics without addiction. To obtain ideal analgesics without addiction and other side effects derived from the μ receptor, we have synthesized various kinds of naltrexone derivatives and reported selective ligands for the κ[2] and δ receptors.[3] In 2009, one of our designed κ selective agonists, TRK-820 (nalfurafine (**1**) hydrochloride, Figure 1), was launched in Japan as an antipruritic for patients undergoing dialysis.[2a,b,e] Although many arylacetamide derivatives such as U-50,488H (**2**)[4] and U-69,593 (**3**)[5] (Figure 1) were synthesized and developed as κ agonists, all of these derivatives were eliminated from clinical trials as not only analgesics but as antipruritics because of their serious side effects like psychotomimetic and aversive reactions.[6] On the other hand, nalfurafine (**1**) has neither aversive nor addictive effects.[7] The pharmacological differences between nalfurafine (**1**) and arylacetamide derivatives have been attributed to the differences in their affinities for κ receptor subtypes (κ_1 and κ_3)[8] (arylacetamide derivatives target κ_1[8b,c] and nalfurafine (**1**) targets κ_3[8d–f]).

Although many δ agonists have also been studied as analgesics,[9] antidepressant,[9a,10] and antipollakiuria,[11] no derivatives represented by SNC-80[12] (**4**, Figure 2) have yet been launched, perhaps due to weak activity and/or serious side effects like convulsion[9a,10] and catalepsy.[13] We also synthesized a δ agonist, TAN-67[3a,b,14] (**5**, Figure 2), which showed selective δ agonist activity and analgesic effects without convulsion and catalepsy, but its agonist activity, especially analgesic activity, was weak. Therefore, none

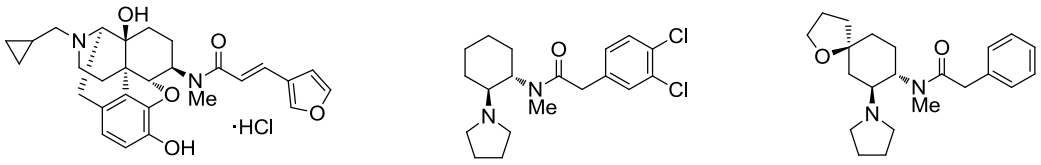


Figure 1. Structures of κ agonists: TRK-820, U-50,488H, and U-69,593

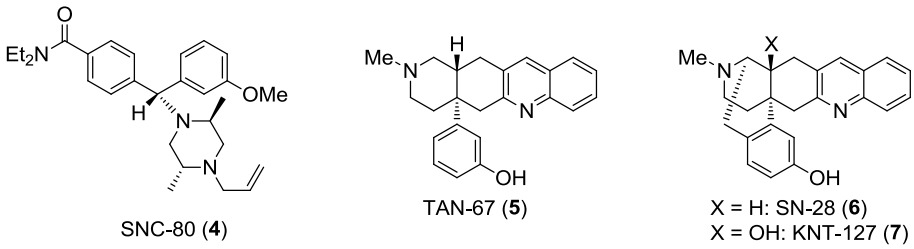


Figure 2. Structures of δ agonists: SNC-80, TAN-67, SN-28, and KNT-127

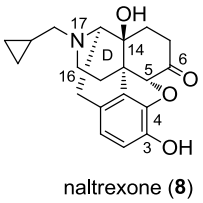


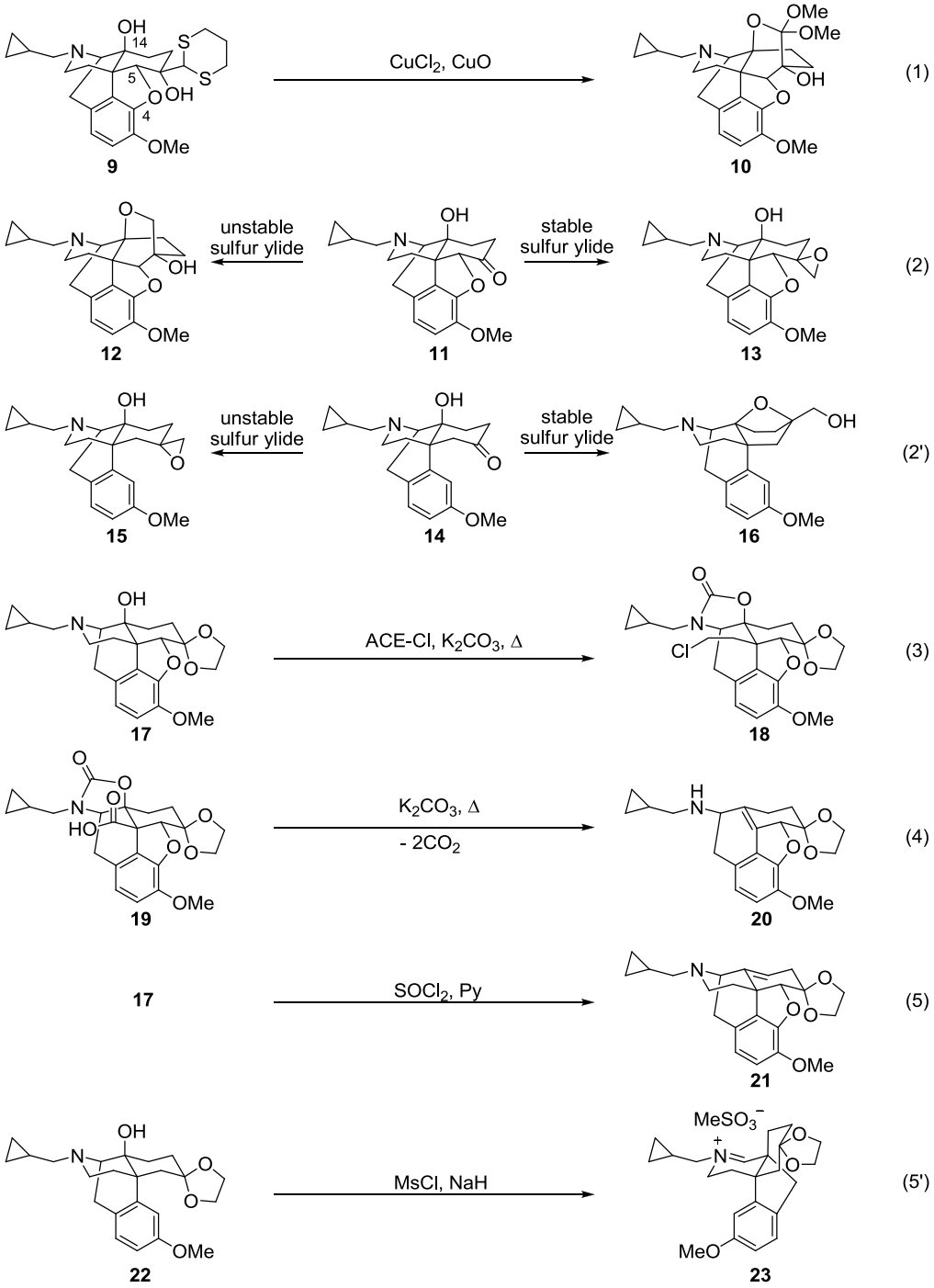
Figure 3. Structure of naltrexone (**8**)

of the *in vivo* pharmacological effects *via* the δ receptor have been sufficiently confirmed except analgesia. Quite recently, we designed and synthesized the potent δ agonists, SN-28 (**6**)[3c] and KNT-127(**7**)[3d,15] (Figure 2). Although subcutaneously injected SN-28 (**6**) showed almost no analgesic activity, s.c. administration of KNT-127 (**7**) showed a 30-fold more potent analgesic activity than did TAN-67 (**5**).[3d] In the course of investigating the design and synthesis of many opioid derivatives, including the aforementioned agonists by using naltrexone (**8**, Figure 3) as a starting material, we found many interesting reactions. Some of them have already been reported in a review article.[16] In the present review, we will describe our recent progress after a brief summary of the previous review.

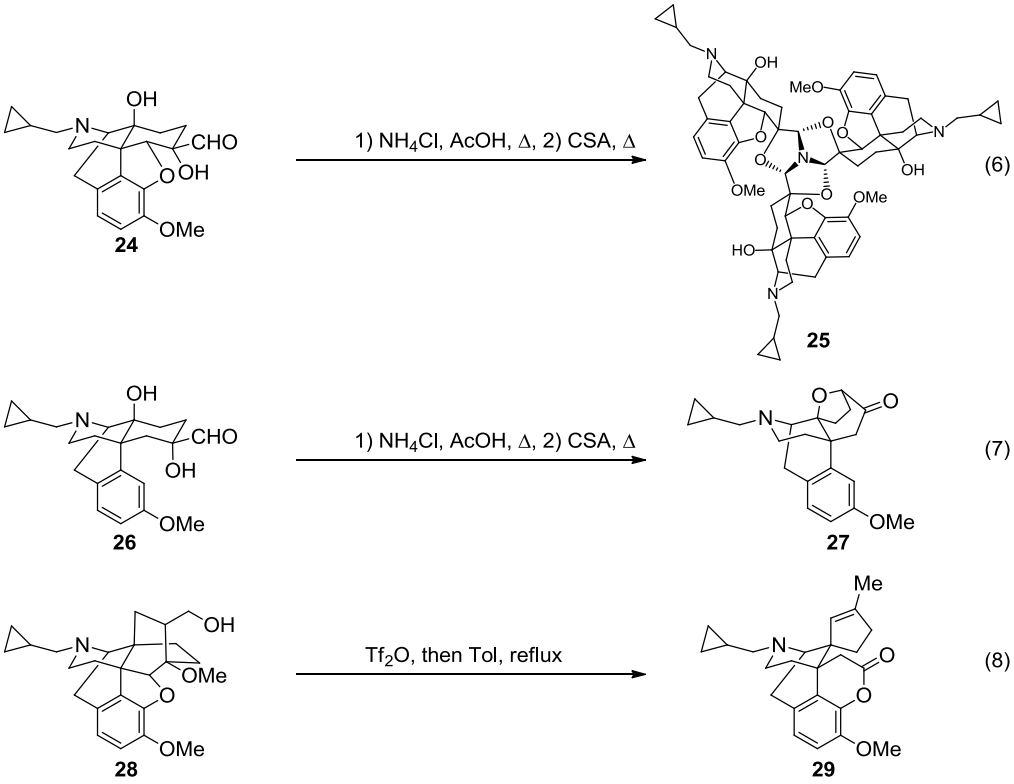
2. BRIEF SUMMARY OF A PREVIOUS REVIEW

The previous review[16] included eight reactions that are summarized in Scheme 1. The 14-OH group plays an essential role in providing the products in the reactions shown by equations (1) – (4), (5') and (7). In

the reactions depicted by equations (2) and (2'), (5) and (5'), and (6) and (7), the presence or absence of the 4,5-epoxy bridge decisively influences the reaction course. The reactions indicated by equations (5'), (7), and (8) are novel rearrangement reactions. Stereoelectronic effects were observed in the reactions shown by (3) and (5'). Novel trimer **25** (equation (6)) was prepared with the anticipation that the compound would elicit unique pharmacological effects and would serve as a useful pharmacological tool.



Scheme 1. Reactions reported by the previous review. ACE-Cl: α-chloroethyl chloroformate, CSA: camphorsulfonic acid



Scheme 1. (Continued)

3. SYNTHESIS OF (–)-HOMOGALANTHAMINE FROM NALTREXONE

(–)-Galanthamine (**30**, Figure 4)[17] was isolated from the Caucasian snowdrop, *Galanthus woronowii*, and also from another species of the Amaryllidaceae family, *Lycoris radiate*. It is an acetylcholinesterase (AChE) inhibitor[18] and a prescription drug for the treatment of Alzheimer's disease in Europe and the United States.[19] There are many reports describing the syntheses of galanthamine (**30**)[20] and its derivatives,[20a] including C-ring,[21] D-ring,[22] quaternary ammonium, and bis-interacted derivatives.[23] However, to the best of our knowledge, the synthesis of (–)-homogalanthamine (**31**, Figure 4) has not yet been reported. We attempted to synthesize (–)-homogalanthamine (**31**) from the μ opioid antagonist naltrexone (**8**)[24] because they share common structural features (Figure 4). We were also interested in whether a transformation from **8** to **31** would impact the pharmacological effects of **31** on either the AChE or the opioid receptors.

We started this synthesis from *O*-methylation of naltrexone (**8**), followed by the reduction of the ketone in **32** with $NaBH(OAc)_3$ in AcOH to give 6α-alcohol **33** (Scheme 2). After the mesylation of **33**, the obtained mesylate **34** was treated with NaI in DMF at 100 ºC, followed by elimination of hydrogen iodide with DBU to afford olefins **35** and **36** in 2 steps with respective yields of 65% and 9%. The resulting olefins were hydrogenated in the presence of Wilkinson's catalyst to give deoxygenated compound **37**

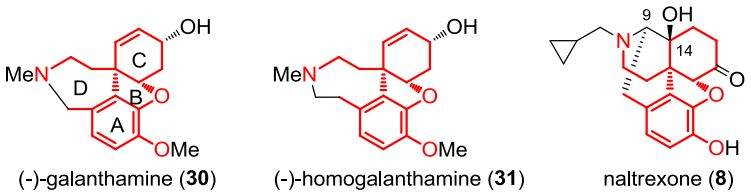
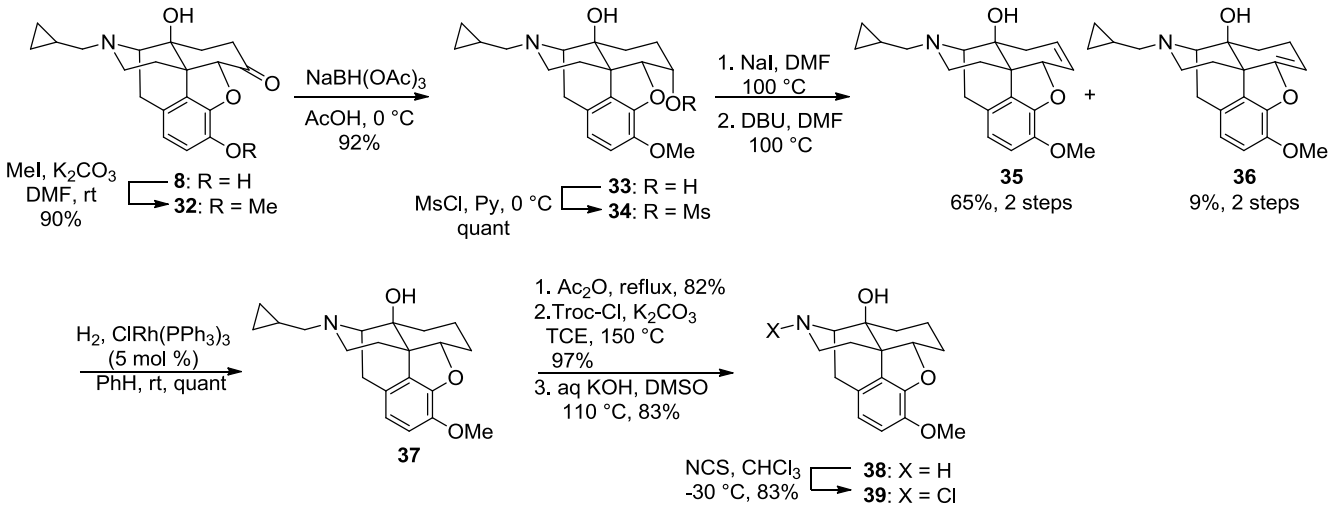


Figure 4. Structures of (–)-galanthamine (**30**), (–)-homogalanthamine (**31**), and naltrexone (**8**). The red lines indicated the common structural features

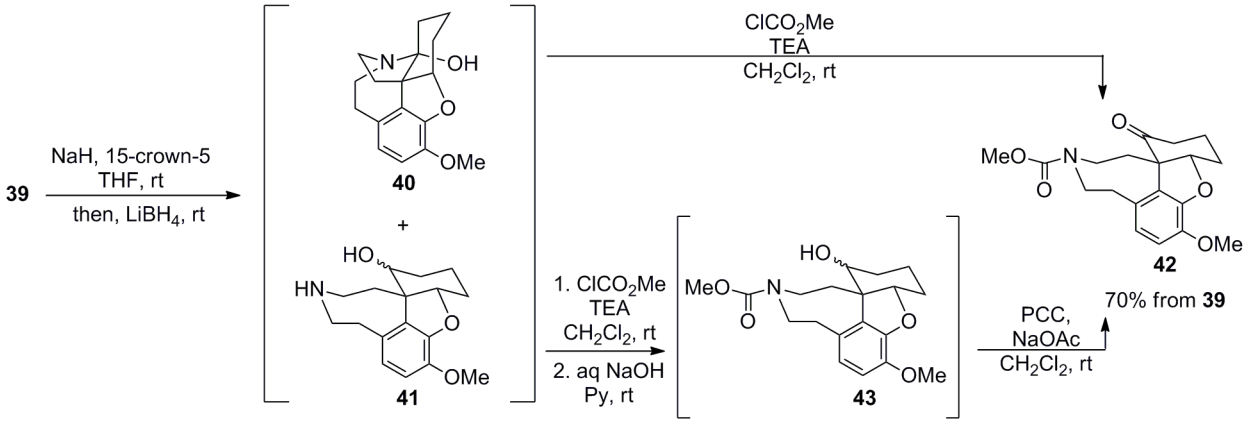


Scheme 2. Synthesis of *N*-chloroamine **39**

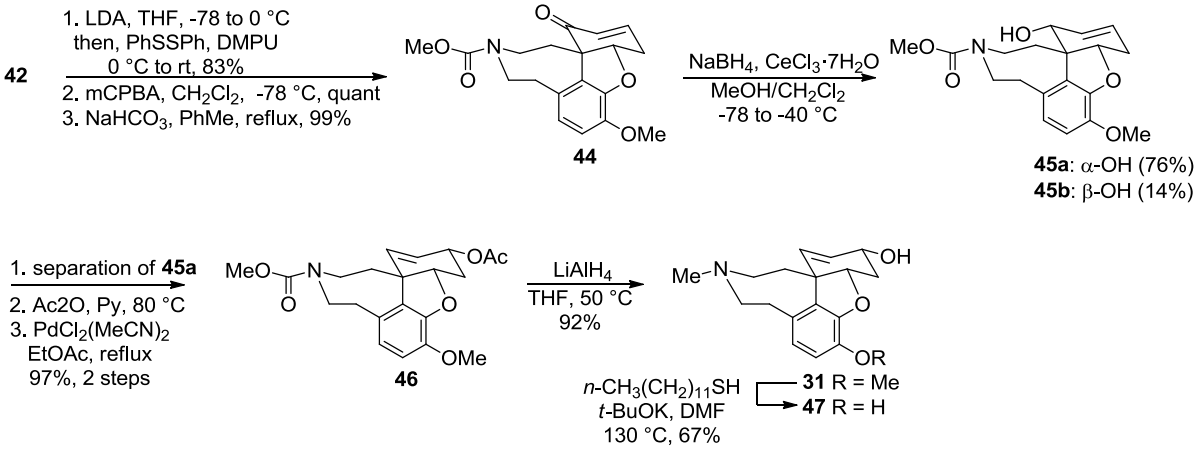
quantitatively. After an acetylation of **37**, a treatment of the obtained acetate with 2,2,2-trichloroethyl chloroformate (Troc-Cl) and K_2CO_3 in 1,1,2,2-tetrachloroethane (TCE) at 150 ºC provided the carbamate, which was hydrolyzed with KOH in DMSO at 110 ºC to give **38**.[3d] The resulting amine **38** was chlorinated with NCS in $CHCl_3$ at -30 ºC to give *N*-chloroamine **39**.[25a,26]

The Grob fragmentation[25] of *N*-chloroamine **39** was a key reaction in our synthesis of (–)-homogalanthamine (**31**) from naltrexone (**8**) (Scheme 3). The Grob fragmentation of **39** under the conditions of NaH in THF proceeded very slowly and the degradation of **39** concomitantly occurred during the reaction. The addition of 15-crown-5 to the reaction mixture effectively facilitated the reaction rate and the fragmentation was complete within five minutes. The Grob fragmentation followed by reduction of the resulting imine with $LiBH_4$ afforded a mixture of hemiaminal **40** and amine **41** in quantitative yield. The mixture was treated with $ClCO_2Me$, which simultaneously opened the five-membered hemiaminal ring in **40** and protected the nitrogen to give ketocarbamate **42**. The treatment **41** with $ClCO_2Me$ and subsequent hydrolysis of the obtained carbonate provided alcohol **43**, which was oxidized with PCC to give ketocarbamate **42** in 4 steps from **39**.

In the final stage of the synthesis (Scheme 4), ketocarbamate **42** reacted with LDA and PhSSPh, followed



Scheme 3. The Grob fragmentation of *N*-chloroamine **39**



Scheme 4. Synthesis of (–)-homogalanthamine (**31**). DMPU: *N*,*N*-dimethyl propylene urea

by mCPBA oxidation and then was heated in the presence of $NaHCO_3$ under reflux in toluene to give α,β-unsaturated ketone **44**. The Luche reduction[27] of **44** at -78 ºC afforded a mixture of desired allylic alcohol **45a** (76%) and its epimer **45b** (14%). After the separation of allylic alcohol mixture **45**, α-isomer **45a** was acetylated and then the $PdCl_2(MeCN)_2$-catalyzed [3.3]sigmatropic rearrangement of the obtained acetate provided rearranged acetate **46** in 97% (2 steps yield).[28] The reduction of the carbamate and acetate moieties in **46** with $LiAlH_4$ gave the objective (–)-homogalanthamine **31**. Demethylation of **31** with dodecanethiol and *t*-BuOK in DMF afforded crystalline phenol derivative **47**, whose structure was confirmed by X-ray crystallography.

(–)-Homogalanthamine (**31**) showed inhibitory activity toward AChE (IC_{50} = 3.0 μM) and its potency was 5-fold less than that of galanthamine (**30**). Interestingly, demethylated compound **47** of (–) homogalanthamine (**31**) did not bind to any of the opioid receptor types at all. This result indicates that the C9–C14 bond (Figure 4) in naltrexone (**8**) is an important structural determinant for binding to all opioid receptor types.

4. A NOVEL REARRANGEMENT REACTION FOR THE SYNTHESIS OF NEW OPIOID LIGAND WITH OXAZATRICYCLODECANE STRUCTURE

4-1. A Novel κ Agonist KNT-63 with Oxabicyclo[2.2.2]octane Skeleton

On the basis of both the detailed structure-activity relationship (SAR) investigations of nalfurafine (**1**) derivatives and their conformational analyses,[29] we developed the working hypothesis for an active conformation of **1** (Figure 5): the C-ring in **1** would assume the boat form to orient the 6-amide side chain toward the upper side of the C-ring when **1** bound to the κ receptor.[2c,d,f] Based on this hypothesis, we designed and synthesized 4,5-epoxymorphinan derivative KNT-63 (Figure 5) with an oxabicyclo[2.2.2]octane skeleton.[2d] KNT-63 showed strong binding affinities for the opioid receptors (K_i (μ) = 0.212 nM, K_i (δ) = 2.73 nM, K_i (κ) = 0.111 nM) in the competitive binding assays and produced a dose-dependent analgesic effect in the mouse acetic acid writhing test. The antinociceptive effect induced by KNT-63 was antagonized by κ antagonist nor-BNI but not by μ antagonist naloxone or δ antagonist NTI, indicating that KNT-63 is a κ agonist.

KNT-63 was prepared from *O*-methyl naltrexone (**32**)[30] as shown by Scheme 5. Intermediates **48** were prepared using the Darzens condensation. After a separation, 6'α-isomer **48a** was treated with aniline in the presence of strong base (*n*-BuLi or NaH) under reflux in THF to give **49** with the oxabicyclo[2.2.2]octane skeleton in 60% yield. Finally, *O*-demethylation of **49** with BBr_3 afforded KNT-63.[2d]

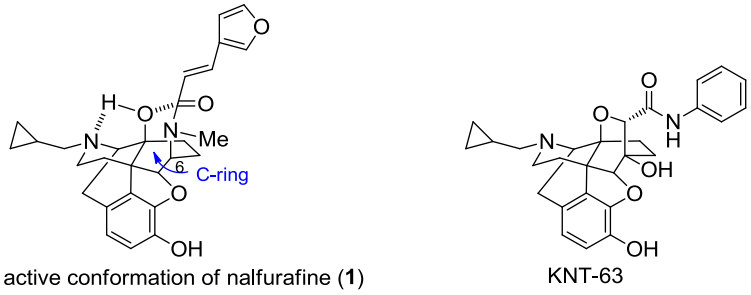
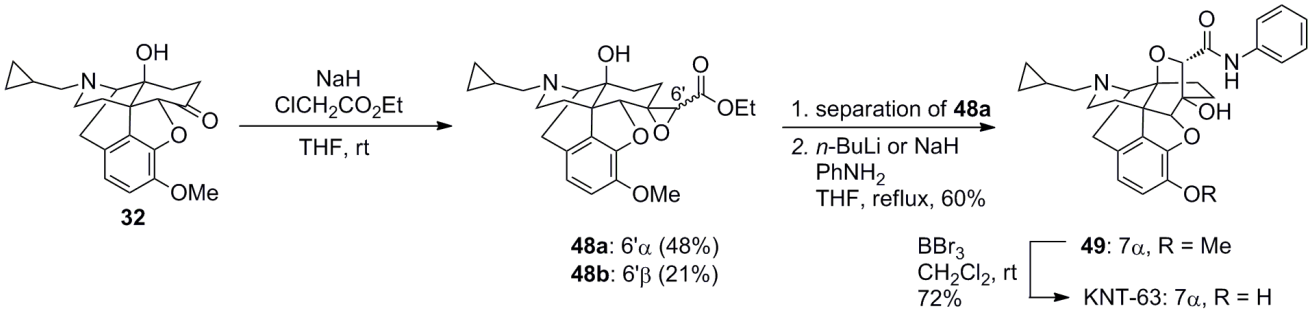


Figure 5. Active conformation of nalfurafine (**1**) and structure of KNT-63

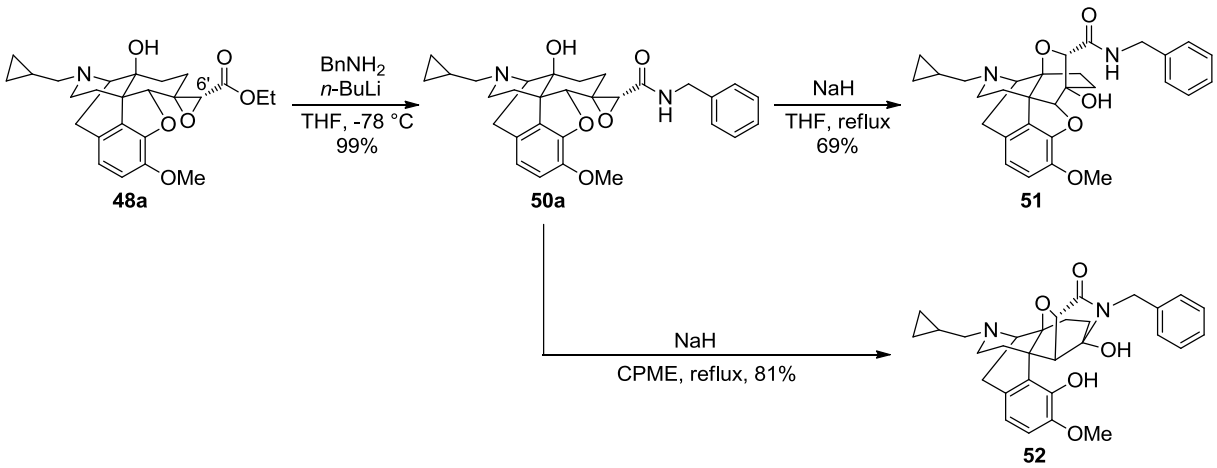


Scheme 5. Synthesis of KNT-63

4-2. Rearrangement Reaction of 4,5-Epoxymorphinan Derivatives with Carbamoylepoxy Rings

Although *N*-phenyl amide **49** was directly prepared from 4,5-epoxymorphinan with ethoxycarbonylepoxy ring **48a** (Scheme 5), the analogues with various amide *N*-substituents were synthesized from **48** *via* 4,5-epoxymorphinan with the carbamoylepoxy ring (*e.g.*, **50a** in Scheme 6). Scheme 6 illustrates an example of *N*-benzyl derivative synthesis. Contrary to the case of aniline, ester-amide exchange reaction with a lithium amide, which was prepared from a more nucleophilic alkyl amine, smoothly proceeded at -78 ºC to enable isolation of carbamate **50a**. The treatment of **50a** in the presence of NaH under reflux in THF (bp: 66 ºC) provided intramolecular cyclization to give oxabicyclo[2.2.2]octane derivative **51** in 69% yield. For the purpose of improving the yield of **51**, we attempted to carry out the intramolecular cyclization reaction at higher reaction temperature. Surprisingly, the reaction under the cyclopentyl methyl ether (CPME, bp: 106 ºC) reflux conditions did afford novel oxazatricyclodecane structure **52** in 81% yield without objective compound **51**.[31] The structure of **52**[32] was confirmed by NOESY experiments and X-ray crystallography. Compound **52** exhibited moderate binding affinities for the opioid receptor types (K_i (μ) = 47.7 nM, K_i (δ) = 174.6 nM, and K_i (κ) = 248.1 nM),[33a] indicating that compound **52** may be a lead compound for the development of novel opioid ligands.

We examined the progress of the rearrangement reaction under various reaction conditions. The treatment



Scheme 6. The rearrangement reaction providing oxazatricyclodecane structure **52**

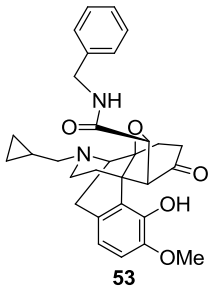
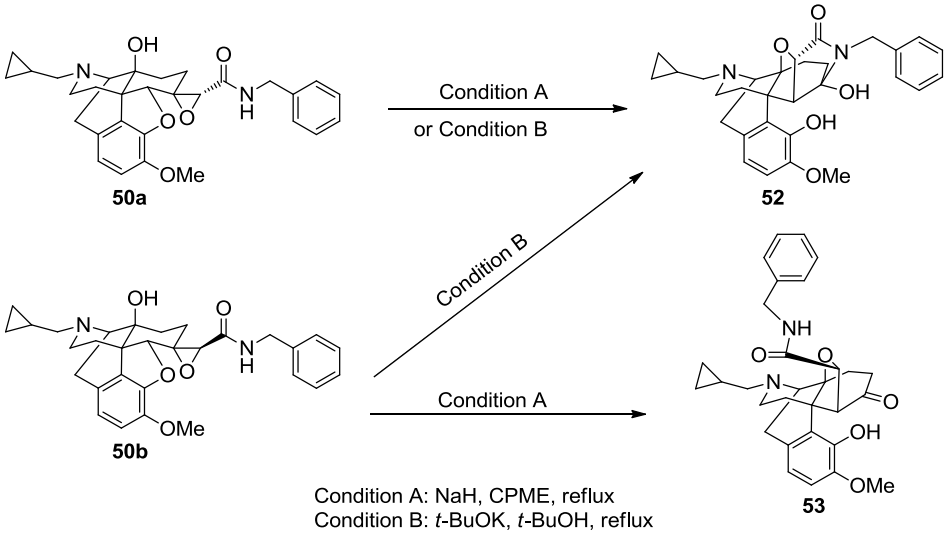


Figure 6. Structure of epimer **53**

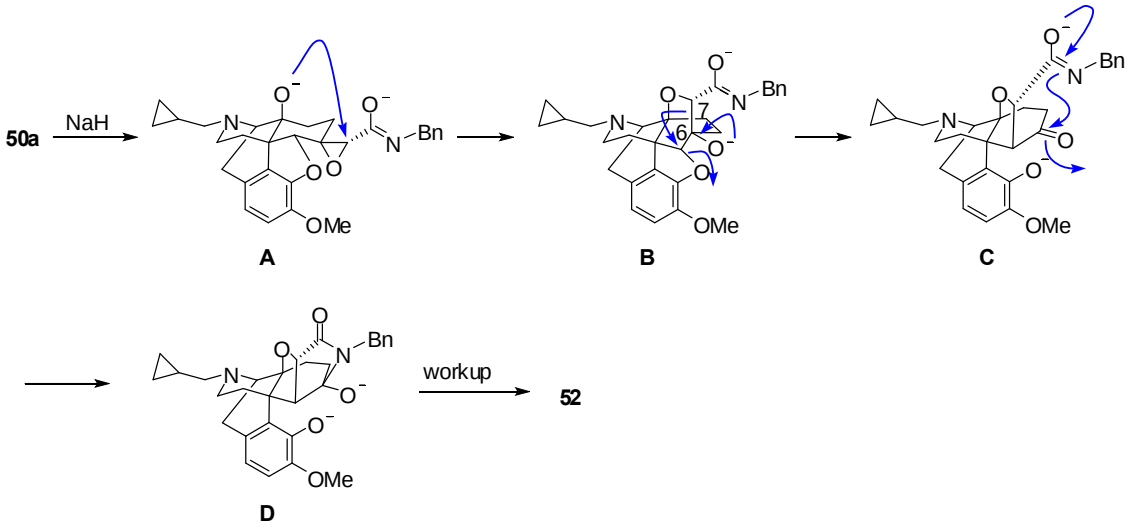


Scheme 7. The treatment of **50a** or **50b** under the reaction conditions A and B

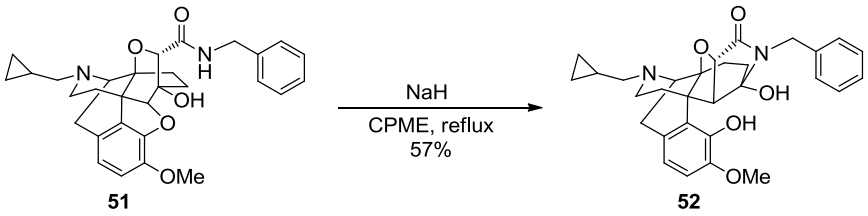
of the solution of **50a** in CPME with NaH at 60 ºC provided only compound **51** in 84% yield and compound **50a** was recovered in 11% yield. This result indicated that the reaction temperature was an important factor in facilitating the rearrangement and that the oxabicyclo[2.2.2]octane derivative **51** could be an intermediate that could provide rearrangement compound **52**. The reaction of **50a** with *t*-BuOK in *t*-BuOH under reflux conditions also afforded **52** in 93%. It is worth noting that in spite of the strong basic reaction conditions no epimer **53** (Figure 6) was isolated in any of these reactions.

We examined the rearrangement reaction using amide **50b**, the epimer of amide **50a**, under both reaction conditions (condition A: NaH, CPME, reflux; condition B: *t*-BuOK, *t*-BuOH, reflux). Interestingly, each of the two reaction conditions afforded different products. Compound **53** was obtained in 91% yield under the condition A, whereas condition B provided rearrangement compound **52** in 89% yield. The results suggested that an epimerization occurred under condition B, but not under condition A. As mentioned above, amide **50a** was converted into compound **52** under both reaction conditions (Scheme 7).

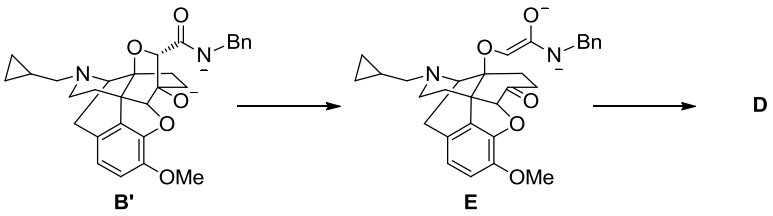
On the basis of the obtained results, we proposed a mechanism for the rearrangement reaction (Scheme 8). In the case of reaction conditions A, the irreversible deprotonation of **50a** would proceed to give dianion **A**. The intramolecular cyclization would occurs through attack by the resulting alkoxide in **A** at the α-carbon of the amide group to provide oxabicyclo[2.2.2]octane intermediate **B**. The reaction would stop at this stage at a relatively low reaction temperature (*e.g.*, a THF refluxing temperature). When the reaction temperature was sufficiently high (*e.g.*, at the CPME or *t*-BuOH refluxing temperature), the rearrangement reaction would proceed. The alkoxide in **B** would facilitate a 1,2-shift of the C6–C7 bond with cleavage of the 4,5-epoxy bridge to give the intermediate ketone **C**. The amide and ketone moieties in **C** were located so close to each other that the subsequent cyclization could occur smoothly to afford



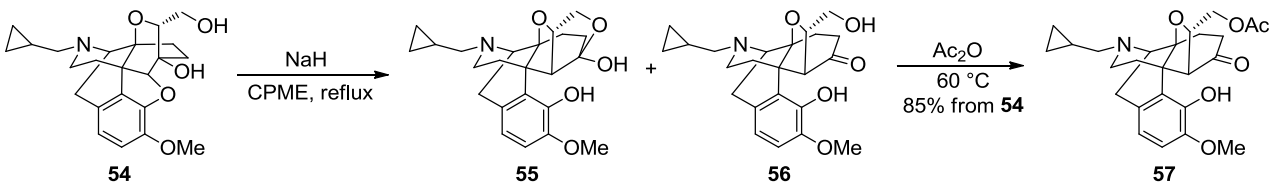
Scheme 8. Proposed mechanism of the rearrangement reaction



Scheme 9. The reaction of **51** under the reaction condition A



Scheme 10. Alternative possible mechanism of the rearrangement reaction



Scheme 11. The reaction of **53** under the reaction condition A

the rearrangement product **52**. The dianion species prepared under the irreversible deprotonation conditions may prevent further deprotonation of the α-proton of the amide group. Therefore, no epimerization could be observed. On the other hand, the reversible deprotonation by *t*-BuOK in *t*-BuOH

could permit deprotonation of the α-proton of the amide group. As a result, the epimerization could proceed to eventually give convergent product **52**, regardless of the configuration of the amide group in **50a** or **50b**. Oxabicyclo[2.2.2]octane intermediate **B** was a key intermediate in the proposed mechanism. Indeed, the treatment of oxabicyclo[2.2.2]octane **51** under the rearrangement reaction conditions provided the rearrangement product **52** (Scheme 9). Although we proposed that the rearrangement from **B** to **C** would proceed by a 1,2-shift, a mechanism *via* amide enolate **E** (Scheme 10) could not be ruled out. However, the treatment of compound **54** with a hydroxymethyl group instead of an electron withdrawing amide group under the rearrangement reaction conditions gave a mixture of the corresponding rearrangement product **55** and ketone **56**, acetylation of which provided compound **57** (Scheme 11). The result supports our proposed mechanism including a 1,2-shift.

5. INVESTIGATION OF THE BECKETT–CASY MODEL

5-1. Beckett–Casy Model

Beckett and Casy proposed a model for the interaction between the opioid receptor and a ligand like morphine.[34] According to the Beckett–Casy model, (–)-morphine can bind the opioid receptor site by use of three pharmacophoric interactions; ionic, π–π (aromatic ring) interactions, and hydrogen bonding. Furthermore, the C15–C16 bond (green line) projecting in front of and to the side of the plane consisting of the A-ring and the basic nitrogen in morphine is proposed to fit into the receptor cavity moiety in this model (Figure 7). Because many structural skeletons have been applied to the Beckett–Casy model, the credibility of the Beckett–Casy model has been under discussion for a long time and a decisive conclusion has not yet been reached. Therefore, we attempted to synthesize 16,17-*seco*-naltrexone derivatives **58** (Figure 7) by use of C16–N17 bond cleavage reaction (Scheme 1, equation (3)) to investigate the Beckett–Casy model.[35]

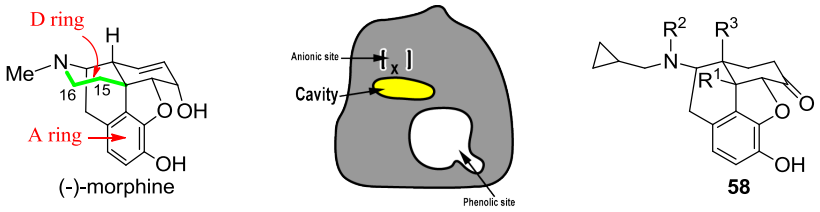


Figure 7. (–)-Morphine, the Beckett–Casy binding model of the receptor, and 16,17-*seco*-naltrexone derivatives **58**. Reprinted from ref. 35 with permission from Elsevier. Copyright (2010)

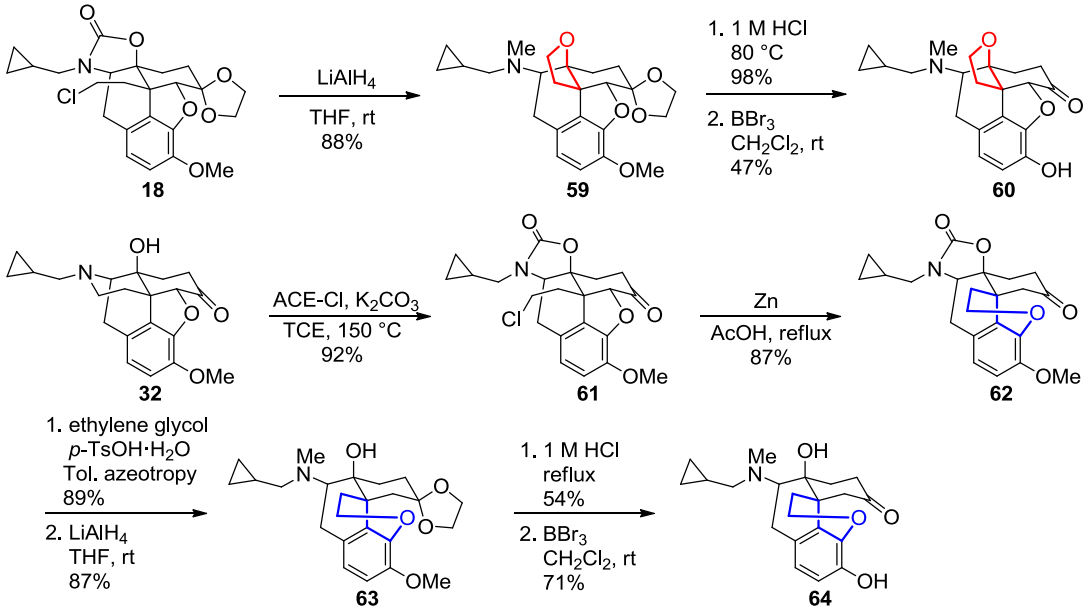
5-2. Synthesis of 16,17-*seco*-Naltrexone Derivatives and Their Binding Profiles for Opioid Receptor Types

The reduction of the oxazolidinone ring in chloride **18**,[36] prepared from naltrexone derivative **17** (equation (3) in Scheme 1), with $LiAlH_4$ provided tetrahydrofuran derivative **59**. Compound **59** was hydrolyzed and subsequently demethylated with BBr_3 to afford **60** (Scheme 12). The preparation of another cyclic compound, dihydropyran derivative **64** commenced with naltrexone methyl ether (**32**) (Scheme 12). Compound **61** obtained by the C16–N17 cleavage reaction of **32** was reduced with Zn in AcOH to give dihydropyran derivative **62** in 87% yield. The keto group in **62** was protected with the acetal, followed by reduction with $LiAlH_4$ to provide amine **63**. Deacetalyzation of **63** with 1 M HCl was followed by subsequent demethylation with BBr_3 to afford **64**.

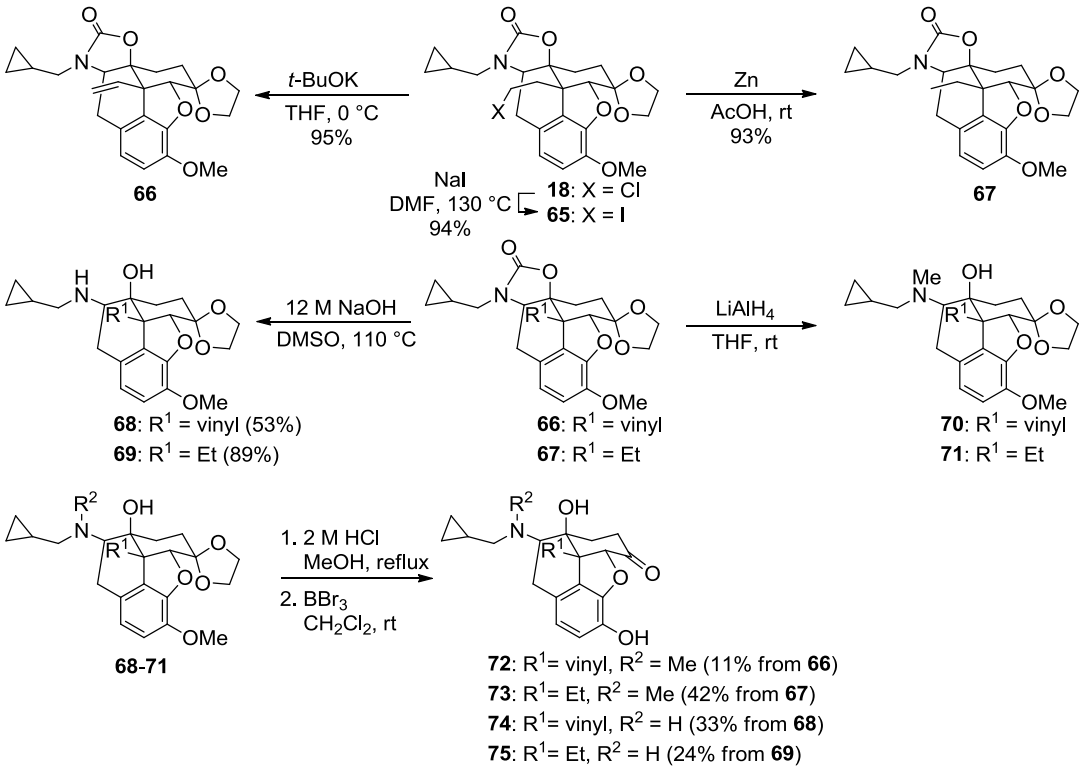
The other 16,17-*seco*-naltrexone derivatives were also synthesized from oxazolidinone **18** (Schemes 13 and 14). After exchange reaction of chloride **18** into iodide **65**, the treatment of **65** with *t*-BuOK gave vinyl derivative **66**, whereas the reduction of **65** with Zn in AcOH provided ethyl derivative **67** (Scheme 13). Compounds **66** and **67** were converted into compounds **68** and **69** by basic hydrolysis or into **70** and **71** by reduction with $LiAlH_4$. The objective 16,17-*seco*-naltrexone derivatives **72**–**75** were obtained by appropriate deprotections of compounds **68**–**71** (Scheme 13).

Triazole derivative **77** was prepared by 1,3-dipolar cycloaddition of azide **76** with 2,5-norbornadiene,[37] which was derived from chloride **18** (Scheme 14). Triazole **77** was converted into the objective derivative **78** *via* the methods similar to those shown by Scheme 13.

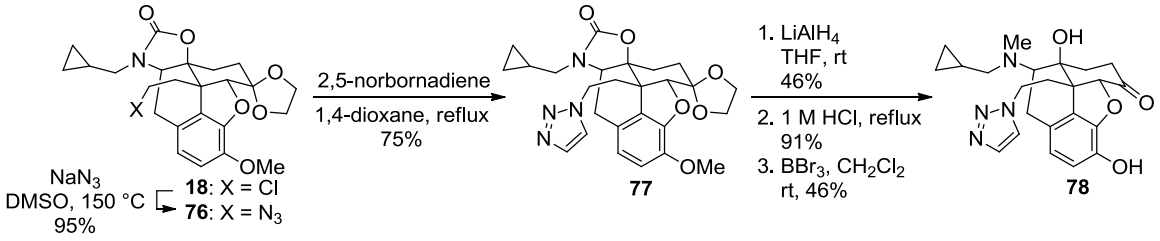
Table 1 shows the results of the opioid receptor binding assays[33b] of the synthesized compounds. The



Scheme 12. Synthesis of cyclic derivatives **60** and **64**



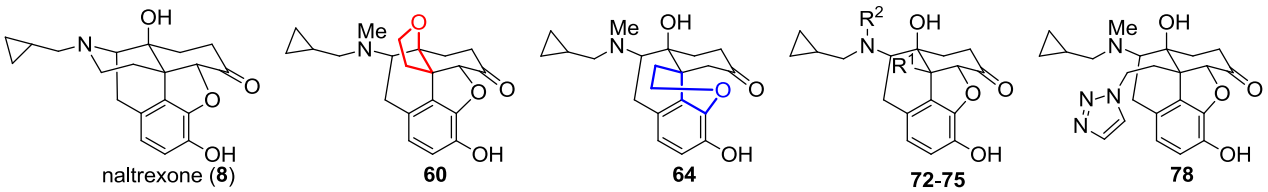
Scheme 13. Synthesis of 16,17-*seco*-naltrexone derivatives **72**–**75**



Scheme 14. Synthesis of 16,17-*seco*-naltrexone derivative **78**

binding affinities of all the compounds for the all opioid receptor types were much weaker than that of naltrexone (**8**). Especially, compounds **64**, **73**, and **78** were scarcely bound to any of the three receptor types. Meanwhile, compounds **60**, **72**, **74**, and **75** showed moderate binding affinity. In **64**, the dihydropyran ring projecting in front of and to the lower side of the molecule may prevent the molecule from binding to the receptor. The orientation of the triazole ring in **78** in front of and to the lower side of the molecule may provide severe steric hindrance. On the other hand, the tetrahydrofuran ring in **60** sticks out to the upper side of the molecule, which may not severely disturb the binding of the molecule to the receptor. The modest binding affinity of **73** to only the κ receptor may result from less steric hindrance caused by the Et group as compared to triazole in **78**. In contrast to the *N*-Me derivative **73**, **75** without the *N*-Me group showed satisfactory K_i values for all the three receptor types. Probably, the Me group of **73** forces the Et substituent to the lower side of the molecule to increase the steric hindrance. Likewise,

Table 1. Binding affinities of 16,17-*seco*-naltrexone derivatives for the opioid receptor types[33b]



Compound	R^1	R^2	K_i (μ) (nM)	K_i (κ) (nM)	K_i (δ) (nM)
naltrexone (**8**)	–	–	0.335	0.373	44.2
60	–	–	24	43.2	ND [a]
64	–	–	ND [a]	ND [a]	ND [a]
75	Et	H	26.3	24.1	275
73	Et	Me	ND [a]	77.6	ND [a]
74	vinyl	H	8.6	4.73	193
72	vinyl	Me	26.4	39.7	200
78	–	–	ND [a]	ND [a]	ND [a]

[a] ND: The K_i value was not determined because the IC_{50} value was over 1,000 nM.
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74 lacking the *N*-Me group showed higher affinity than that of corresponding *N*-Me derivative **72**. The observation that **72** or **74** with vinyl substituents showed stronger binding affinities than did **73** or **75** may stem from the sterically smaller vinyl group compared to the Et group. In naltrexone (**8**), the C15–C16 ethylene unit forming the D ring appears to just fit into the cavity to result in excellent affinity. These results may support the idea of the existence of a cavity structure as proposed in the Beckett–Casy model. However, it is necessary to examine the binding of the molecules without the C15–C16 bond, the 15-16 nornaltrexone derivatives **79** (Figure 8).

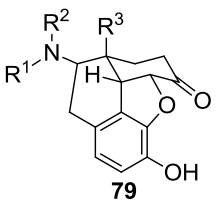


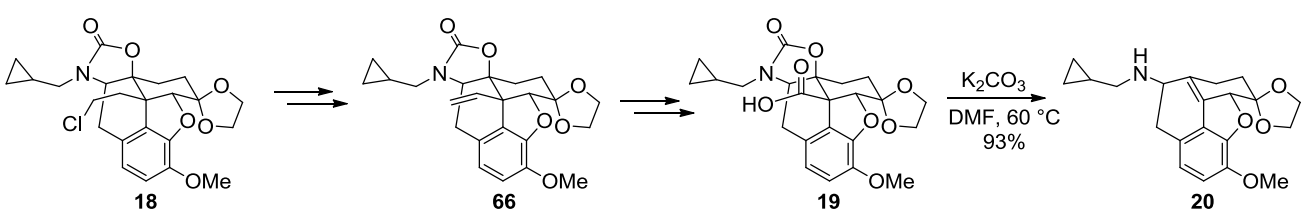
Figure 8. Structure of 15-16 nornaltrexone derivatives **79**

5-3. Synthesis of 15-16 Nornaltrexone Derivatives and Their Binding Profiles for Opioid Receptor Types

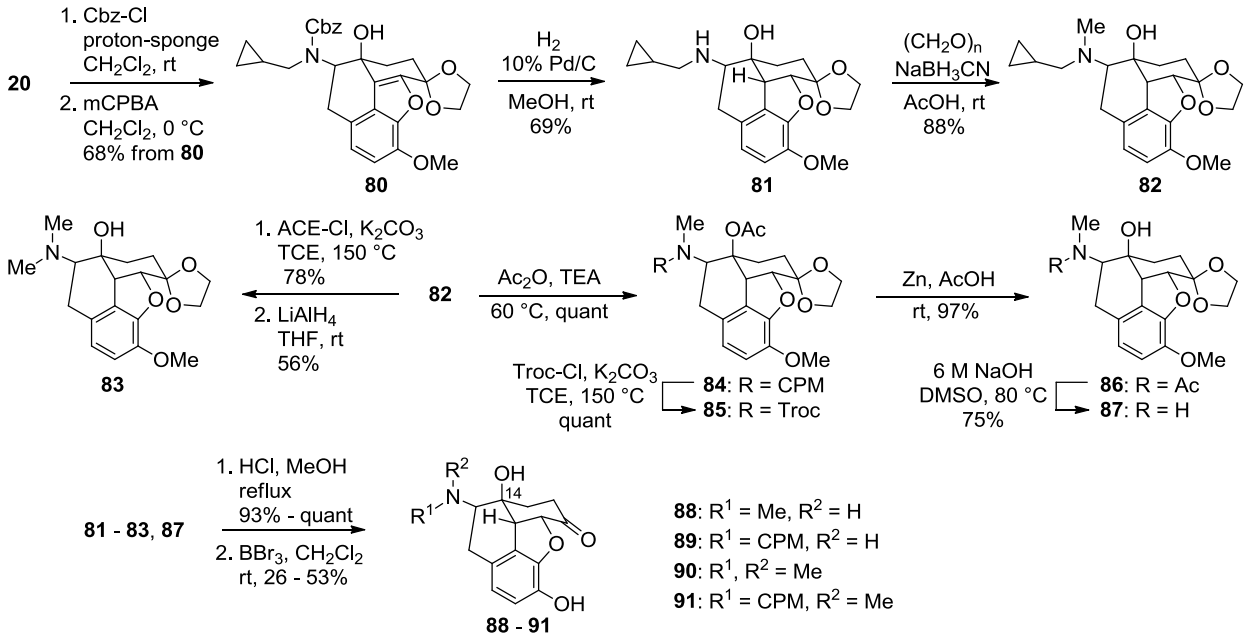
With the C16–N17 bond-cleaved compound **18** in hand, removal of the two carbon unit from **18** should provide the objective 15-16 nornaltrexone derivatives **79**.[38] This goal was achieved by a series of reactions (Scheme 15) including the double carboxylation reaction[39] (Scheme 1, equation (4)) as a key reaction.

The synthesis of 15-16 nor-14-OH-naltrexone derivatives **88**–**91** commenced with compound **20** obtained by the double decarboxylation reaction (Scheme 16). The secondary amino group in **20** was protected by a Cbz group followed by oxidation with mCPBA to give allylic alcohol **80** in 68% yield *via* epoxide ring opening reaction. Catalytic hydrogenation of **80** provided saturated compound **81**. The stereochemistries of compounds **80** and **81** were determined by 2D NMR experiments of their corresponding acetamide derivatives. Secondary amine **81** was converted into tertiary amine **82** by reductive methylation. After the treatment of **82** with α-chloroethyl chloroformate (ACE-Cl),[36] the obtained oxazolidinone was reduced with $LiAlH_4$ to afford **83**. The acetate **84** obtained by acetylation of **82** was treated with Troc-Cl to provide compound **85** because the cyclopropylmethyl (CPM) group was selectively replaced with the Troc group.[36] Deprotection of the Troc group in compound **85** with Zn in AcOH facilitated concomitant migration of Ac group from the 14-OH group to the 17-nitrogen to give acetamide **86** in 97% yield, which was hydrolyzed to provide **87**. The acetal of each compound **81**–**83** and **87** was hydrolyzed, and then demethylated with BBr_3 to afford the objective 15-16 nor-14-OH-naltrexone derivatives **88**–**91**, respectively. Similarly, the corresponding 15-16 nor-14-H-naltrexone derivatives **97**–**100** were also synthesized from **20** as shown by Scheme 17. At first, catalytic hydrogenation of **20** gave saturated compound **92**. The stereochemistries of compound **92** were determined by 2D NMR experiments. The conversion of **92** into the objective compounds **97**–**100** was carried out by the manner similar to that shown by Scheme 16.

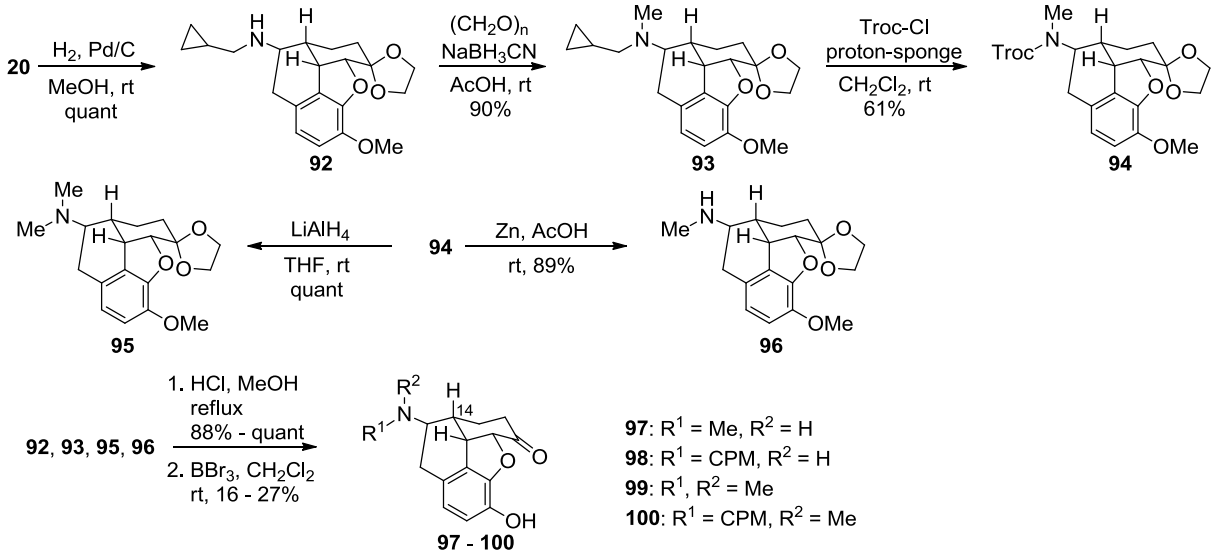
Tethered compounds **104** and **105** were synthesized from compound **81** (Scheme 18). Treatment of **81** with chloroacetyl chloride and subsequent reaction with NaH gave the lactam, which was reduced with $LiAlH_4$ to give compound **101**. According to the methods mentioned above, *N*-CPM derivative **101** was converted into *N*-Me derivative **103**. The appropriate deprotections of **101** and **103** provided the objective



Scheme 15. Synthesis of **20** using double decarboxylation reaction as a key reaction



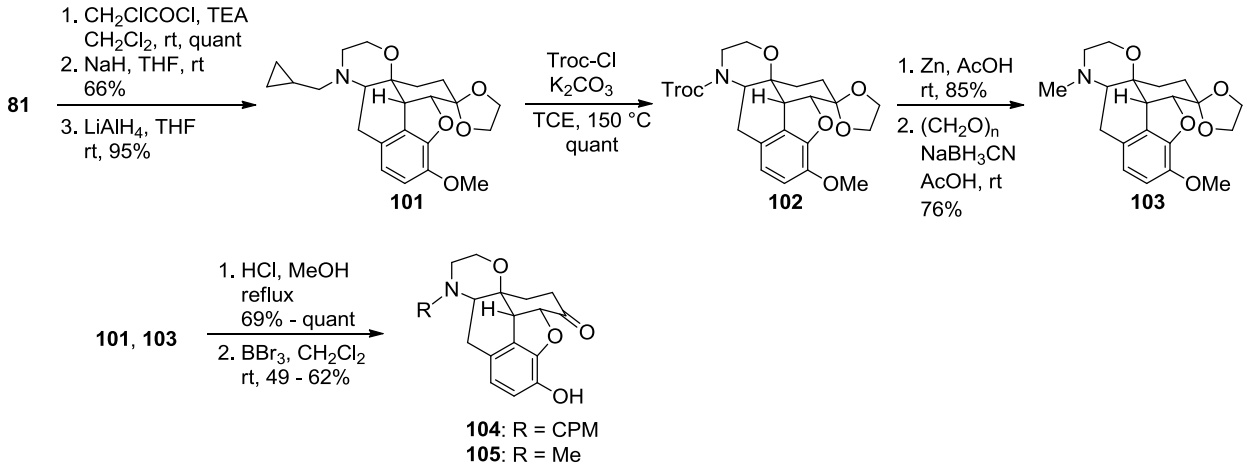
Scheme 16. Synthesis of 15-16 nor-14-OH-naltrexone derivatives **88**–**91**



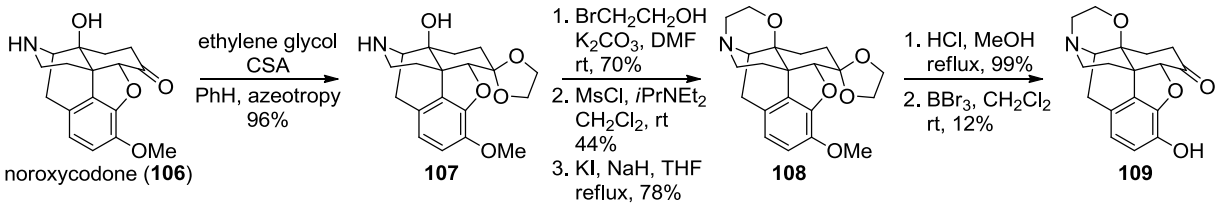
Scheme 17. Synthesis of 15-16 nor-14-H-naltrexone derivatives **97**–**100**

tethered derivatives **104** and **105**, respectively. Another tethered compound was also prepared as shown by Scheme 19. After acetalization of noroxycodone (**106**), compound **107** was treated with 2-bromoethanol and subsequently with MsCl to give the mesylate, of which cyclization proceeded in the presence of KI and NaH to afford **108**. The appropriate deprotections of **108** gave the objective compound **109**.

The binding affinities of the synthesized 15-16 nornaltrexone derivatives to the opioid receptor types were evaluated by the competitive binding assays[33b] (Table 2). The tertiary amines **90**, **91**, **99**, and **100**



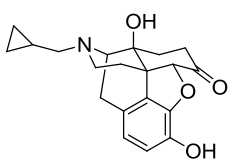
Scheme 18. Synthesis of the tethered compounds **104** and **105**

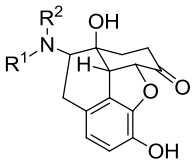


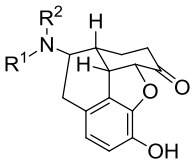
Scheme 19. Synthesis of the tethered compound **109**

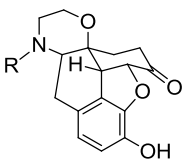
showed higher affinities for the μ receptor than did the corresponding secondary amines **88**, **89**, **97**, and **98**, respectively, suggesting that the higher electron density on the 17-nitrogen in the tertiary amines favored stronger binding to the opioid receptor than for the secondary amines. Furthermore, the compounds **89**, **91**, **98**, and **100** with the 17-CPM group showed stronger affinities than the corresponding **88**, **90**, **97**, and **99** with the Me group, respectively, which may be due to stronger electron releasing effects by the CPM group.[36] However, the binding affinities of the compounds **88**–**91** and **97**–**100** were three to 500-fold lower than naltrexone (**8**). These results seem to support the idea of the existence of the cavity described in the Beckett–Casy model. However, the affinities of 14-OH derivatives **88**–**91** were stronger than those of 14-H derivatives **97**–**100**. The C9–N17 bond of 15-16 nornaltrexone derivatives **88**–**91** and **97**–**100** can freely rotate around the axis, whereas the rotation at that site was prevented in naltrexone (**8**) by the fixed C16–N17 bond (Figure 9). Moreover, in comparing the structures of 14-OH derivatives **88**–**91** with 14-H derivatives **97**–**100**, the hydrogen bonds between the 17-nitrogen and the 14-OH groups[40] in the 14-OH derivatives **88**–**91** could restrict the free rotation of the C9–N17 bond (Figure 9). As a result, the formation of the hydrogen bond may decrease the population of those rotamers with hardly any binding to the receptor, leading to an overall increase in binding affinities for the 14-OH derivatives **88**–**91** as compared to the corresponding 14-H derivatives **97**–**100**. The C9–N17 bond in the tethered compounds **104**, **105**, and **109** cannot freely rotate due to the ethylene bridge between the 17-

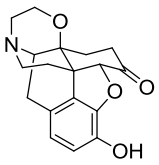
Table 2. Binding affinities of 15-16 nornaltrexone derivatives for the opioid receptor types[33b]


naltrexone (**8**)


88 - 91


97 - 100


104, **105**


109

Compound	R^1 or R	R^2	K_i (μ) (nM)	K_i (κ) (nM)	K_i (δ) (nM)
naltrexone (**8**)	–	–	0.335	0.373	44.2
88	Me	H	118	ND [a]	ND [a]
89	CPM	H	24.7	68.4	ND [a]
90	Me	Me	8.95	ND [a]	ND [a]
91	CPM	Me	1.17	5.1	55.2
97	Me	H	164	ND [a]	ND [a]
98	CPM	H	30.3	32.2	ND [a]
99	Me	Me	50.9	ND [a]	ND [a]
100	CPM	Me	3.36	8.81	272
104	CPM	–	294	ND [a]	ND [a]
105	Me	–	ND [a]	ND [a]	ND [a]
109	–	–	86	72.6	ND [a]

[a] ND: The K_i value was not determined because the IC_{50} value was over 1,000 nM.
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nitrogen and 14-OH group. So, these compounds would be expected to display improved binding affinities. However, contrary to our expectation, compounds **104** and **105** were hardly bound to the opioid receptors at all. Moreover, the other tethered compound **109** bound to the opioid receptor, but its affinity was very weak in spite of the presence of the C15–C16 ethylene unit.

It is difficult to explain these outcomes by only the existence of the cavity and/or by the steric hindrance arising from some rotamers. Therefore, we focused on the ionic interaction between the 17-nitrogen and a receptor site. In general, the ion–ion interaction between the ligand and the receptor is the most important pharmacophore,[41] which led us to the alternative hypothesis that the orientation of the lone electron pair on the 17-nitrogen may play an important role when a ligand interacts with the opioid receptor. Figure 9 illustrates the orientations of the lone electron pairs in compounds **8**, **88**–**91**, **97**–**100**, **104**, **105**, and **109**. In naltrexone (**8**), both the C15–C16 bond in the D-ring and the hydrogen bonding between 17-nitrogen and the 14-OH group can tightly lock the orientation of the lone electron pair on the17-nitrogen in the axial orientation. Therefore, its affinity for the opioid receptor would be strongest. The hydrogen bond

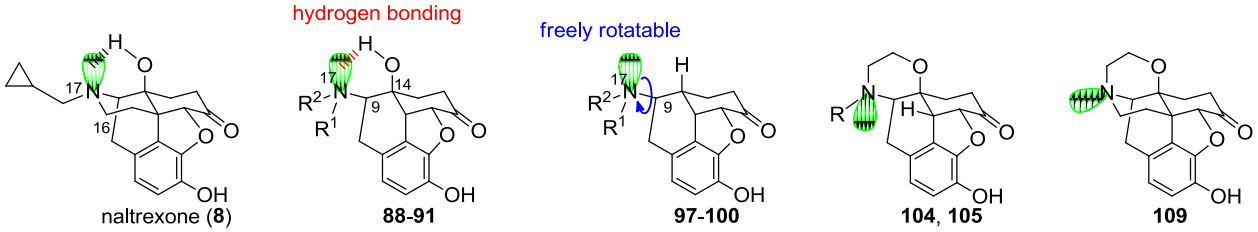


Figure 9. Structures of compounds **8**, **88**–**91**, **97**–**100**, **104**, **105**, and **109**, and their lone electron pairs

between the 17-nitrogen and 14-OH group in **88**–**91** would tend to direct the lone electron pairs in an axial direction in clear contrast to the compounds **97**–**100** which lack the 14-OH group. In summary, the difference of orientational tendency would influence the binding affinities: 14-OH derivatives **88**–**91** showed higher affinities than the corresponding 14-H derivatives **97**–**100**. The lone electron pair of tethered compound **109** would be restricted to the equatorial position by an ethylene bridge. As a result, **109** would show weaker affinity than 14-OH derivatives **88**–**91**, which have the lone electron pair located in the axial position, despite the fact that the compound **109** has the C15–C16 ethylene moiety. On the other hand, the lone electron pairs in compounds **104** and **105**, which exhibited almost no binding affinities, were predicted to protrude in front of the plane consisting of the 17-nitrogen and the phenol ring. The above discussion would argue against a role for the cavity of the Beckett–Casy model and support the idea the the C15–C16 bond in the D-ring may play a role in fixing the lone electron pair on the 17-nitrogen in the desired axial orientation. However, the possibility cannot be ruled out that a steric hindrance arising from the ethylene moiety in tethered compounds **104**, **105**, and **109** may decrease the binding abilities of these compounds. The confirmation of our hypothesis requires compounds without steric hindrance, whose lone electron pairs either do or do not project toward the desired axial orientation.

5-4. Synthesis of Naltrexone Derivatives with Contracted or Expanded D-Rings and Their Binding Profiles for Opioid Receptor Types

We designed naltrexone derivatives **110** and **111** with contracted and expanded D-rings to confirm our hypothesis: the desired axial orientation of the lone electron pair on the 17-nitrogen is important for binding to the opioid receptor. Although both compounds would have lone electron pairs with the axial orientation, they would project in opposite direction from each other (Figure 10).[42]

Synthesis of naltrexone derivative **110** with contracted D-ring commenced with compound **66** (Scheme 20). Ozonolysis of compound **66** and subsequent reduction with $NaBH_4$, followed by hydrolysis provided compound **112**. The hydroxy group was converted into the chloride by the Appel[43] reaction and the cyclization reaction concomitantly proseeded to give the compound **113** with a contracted D-ring. The

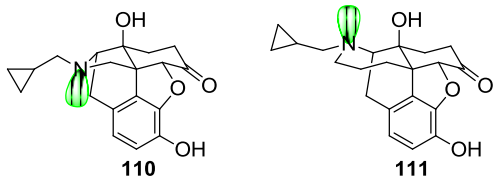
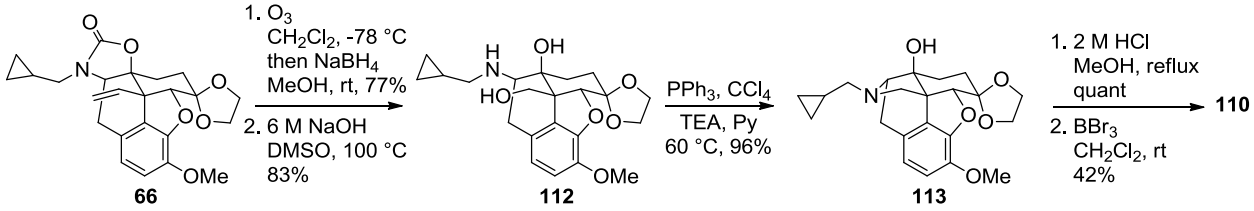
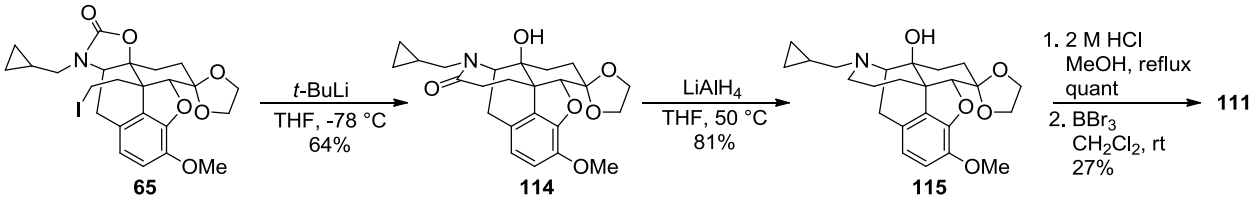


Figure 10. Structures of naltrexone derivatives **110** and **111** with contracted and expanded D-ring and their lone electron pairs



Scheme 20. Synthesis of naltrexone derivative with contracted D-ring **110**



Scheme 21. Synthesis of naltrexone derivative with expanded D-ring **111**

appropriate deprotections of **113** afforded the objective compound **110**. On the other hand, the expansion of the D-ring was achieved by one step reaction in 64% yield *via* halogen–lithium exchange reaction of iodide **65** with *t*-BuLi (Scheme 21). The amide moiety of the obtained compound **114** with an expanded D-ring was reduced with $LiAlH_4$ to give compound **115**. The objective compound **111** was obtained by the consequtive deprotections of **115**.

Compound **111** with an expanded D-ring bound to the μ receptor with affinity (K_i (μ) = 0.41 nM, K_i (κ) = 0.373 nM, K_i (δ) = 44.2 nM) comparable to naltrexone (**8**) (K_i (μ) = 0.335 nM, K_i (κ) = 2.09 nM, K_i (δ) =10.35 nM), whereas compound **110** with a contracted D-ring showed almost no binding affinities for any of the opioid receptors (K_i > 1,000 nM).[33b]

Morphinan **116** and benzomorphan derivatives **117** with a contracted D-ring and benzomorphan dervative **118** with an expanded D-ring were synthesized in racemic form and their antinociceptive effects were evaluated.[44] Compound **116** showed neither agonistic nor antagonistic activities,[45a,b] while compound **117**, which lacked the C-ring, exhibited a 36-fold weaker analgesic effect than morphine.[44c] The antinociceptive effect of compound **118** was as potent as morphine.[44d] According to the X-ray

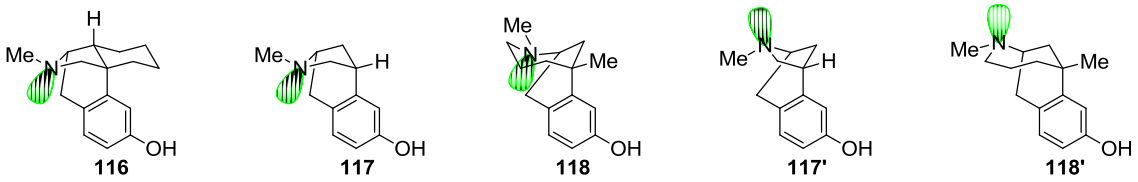


Figure 11. Structures of morphinan and benzomorphan derivatives **116** and **117** with a contracted D-ring and benzomorphan derivative **118** with an expanded D-ring. Structures **117'** and **118'** indicate possible conformers with the alternative quasi-chair form in the D-rings

crystallographic analyses of these compounds, all the compounds possessed the lone electron pair on the 17-nitrogen in the axial position orienting toward the same side as the phenol ring. However, Itai and co-workers made an interesting mention about the conformation of compound **118**: although the X-ray crystallographic analysis showed that the D-ring[46] of **118** was in the quasi-chair conformation and that the lone electron pair projected toward the same side as the phenol ring, the D-ring could flip to adopt the alternative quasi-chair form **118'** in which the lone electron pair would take on the axial position orienting toward the opposite site to the phenol ring[45c,d] (Figure 11). This proposed flip of the D-ring can explain the strong analgesic activity of **118**: because the seven-membered ring in **118** is so flexible, it could easily adopt another quasi-chair form **118'** having its lone electron pair in the axial direction, *i.e.*, at the site opposite to the phenol ring, and thus the conformer **118'** would bind to the opioid recptor to produce a strong antinociception. A comparison of the structures between **116** and **117** reveals that the structure of **116** may be particularly rigid due to an additional ring, the C-ring, that would permit it to adopt only the conformation exhibited by X-ray analysis. As a result, compound **116** would show no opioid activities. On the other hand, the lack of an additional ring in compound **117** would make this compound somewhat more flexible, allowing the D-ring of **117** to flip to alternative conformation **117'** with axial lone electron pair protruding toward the opposite site to the phenol ring. The weak analgesic effect induced by **117** may result from the alternative conformer **117'**. These experimental results and discussions are consistent with our working hypothesis: the desired axial orientation of the lone electron pair on the 17-nitrogen plays an important role in the ligand's binding ability to the opioid receptor.

We further investigated the conformations of compounds **110** and **111** by both the conformational analyses using the Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS) 2.1 program[47] and by NOE experiments in D_2O. These analyses and experiments also support our working hypothesis. These results, taken together, permit us to conclude that the axial orientation of the lone electron pair on the 17-nitrogen would provide sufficient binding abilities to the opioid receptor and that the C15–C16 ethylene moiety in the morphine structure would contribute to fixation of this lone electron pair in the optimum axial direction. Thus, effective binding of these compounds with the opioid receptor

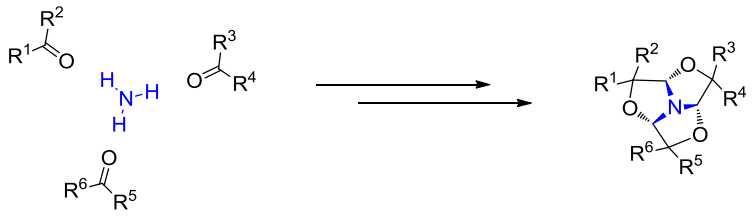
would be mediated primarily by the axial orientation of the lone electron pair on 17-nitrogen rather than *via* interaction with the putative cavity in the Beckett–Casy model. Although the interaction between 17-nitrogen and the opioid receptor was generally believed to be a non-directional ionic interaction, the directional property was supported by our conclusion. Therefore, the interaction would be the directionally enforced ionic interaction which was reinforced by the directional hydrogen bond.[48,49]

6. SYNTHESIS OF TRIPLET DRUGS WITH 1,3,5-TRIOXAZATRIQUINANE SKELETONS AND THEIR PHARMACOLOGIES

Twin drugs, which possess two pharmacophore units in a single molecule, have been described in numerous domains of medicinal chemistry. Symmetrical twin drugs can simultaneously interact with the symmetrical binding sites of a protein to induce increased activity. In contrast, nonsymmetrical twin drugs bind to the individual relevant binding sites to provide dual action.[50] Another application of symmetrical or nonsymmetrical twin drugs is tools for investigation of G-protein-coupled receptor (GPCR) dimers/oligomers phenomena.[51] However, twin drugs can only play one role, either to increase activity or to provide dual action. Moreover, twin drugs can be applied to only investigations of the GPCR dimers. Triplet drugs with three pharmacophore units could open the door for more versatile investigations. Nonsymmetrical triplet drugs having two identical moieties and one different part could exhibit both increased pharmacological action and dual action. Two of the same moieties may bind the same receptor sites simultaneously while the third part may interact with a different receptor or enzyme. Moreover, triplet drugs would enable us to investigate GPCR oligomers. We have reported the synthesis of novel triplet **25** with 1,3,5-trioxazatriquinane skeleton from α-hydroxyaldehydes (Scheme 1, equation (6)), which could be derived from ketones.[30c] In this reaction, nitrogen plays an important role in the construction of the novel skeleton. As nitrogen serves as the central atom to gather three identical or nonidentical ketones to form a 1,3,5-trioxazatriquinane skeleton, it acts in a manner analogous to a three-pronged clamp; we termed this phenomenon a "nitrogen clamp" (Scheme 22). To investigate SAR of triplet drugs with morphinan units, we synthesized various triplets including symmetrical and nonsymmetrical triplets, and a capped homotriplet. A symmetrical or nonsymmetrical triplet is composed of three identical or different pharmacophores, respectively, whereas a capped homotriplet has two identical pharmacophore units and an epoxymethano group (cap structure) (Figure 12).

6-1. New Synthetic Method of the Key Intermediate α-Hydroxyaldehyde

The reported synthesis of a triplet is shown in Scheme 23. The method includes nucleophilic addition of lithiated dithiane to the ketone **119** and subsequent acetal exchange reaction and hydrolysis. In this



Scheme 22. Schematic illustration of a "nitrogen clamp"

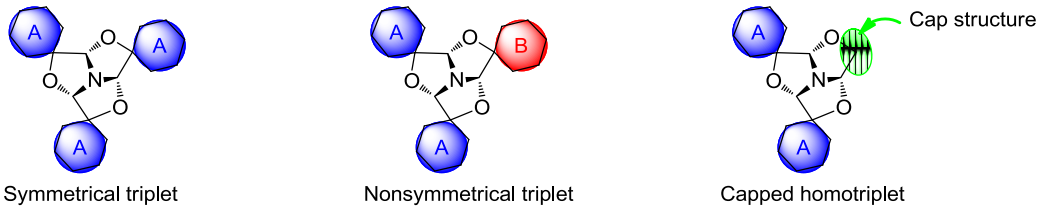


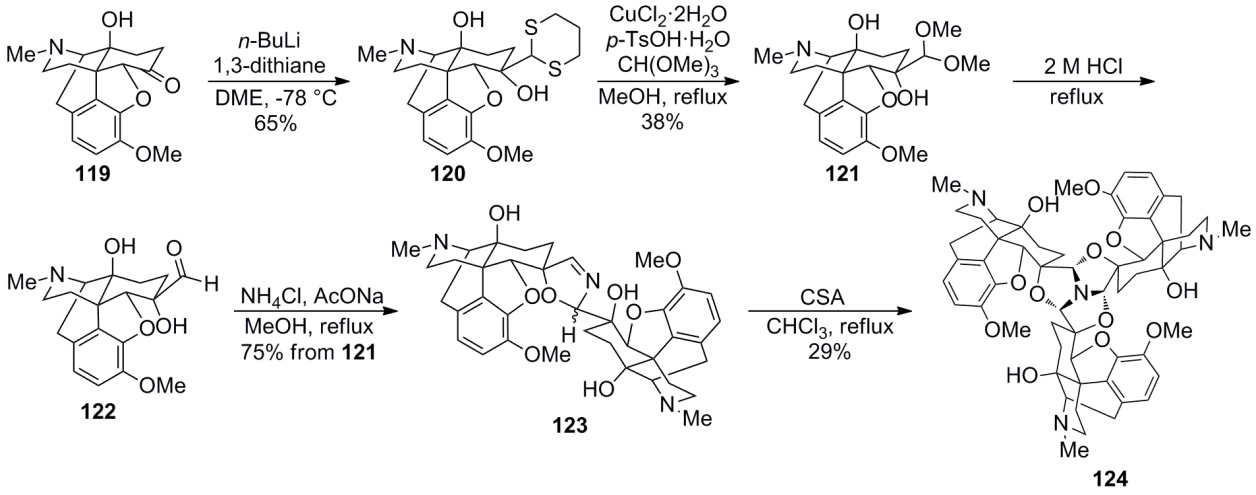
Figure 12. Symmetrical and nonsymmetrical triplet and capped homotriplet

synthesis, the preparation of the key intermediate α-hydroxyaldehyde **122** requires the use of air- and moisture-sensitive *n*-BuLi and malodorous 1,3-dithiane. Moreover, the reaction must be carried out at low reaction temperature (-78 ºC). Therefore, we sought reaction conditions that were more practical and concise to develop a new synthetic method using *p*-toluenesulfonylmethyl isocyanide (Tos-MIC).[52] The treatment of ketone **125** with TosMIC at rt in the presence of K_2CO_3 gave tosyloxazoline intermediate **126**, followed by hydrolysis of **126** with 2 M HCl to provide a mixture of a α-hydroxyaldehyde **127** and hemiacetal dimer **128**. The reaction of the resulting mixture with NH_4Cl in MeOH in the presence of AcONa gave the intermediate oxazoline dimers **129** in 64% from **125** (Scheme 24). Thus, the new method improved the yield of the intermediate oxazolidine dimer **129**.

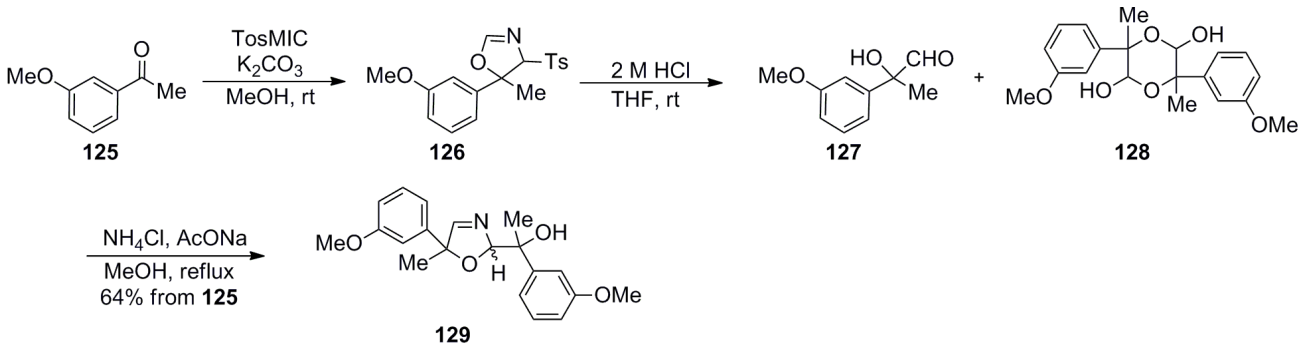
6-2. Synthesis of Symmetrical and Nonsymmetrical Triplet Drugs with Morphinan Skeletons and Their Pharmacologies

According to the method indicated by Scheme 23 (previous method), oxycodone (**119**), naltrexone methyl ether (**32**), and 14-dehydroxynaltrexone methyl ether (**130**) were converted into the corresponding symmetrical triplets **124**, **131**, and **132**, which were treated with BBr_3 to give the respective phenolic hydroxy derivatives **133**–**135** (Scheme 25).[53]

It is noteworthy that an oxazoline dimer like **123** (Scheme 23) could be isolated, because the oxazoline dimer enabled the effective synthesis of nonsymmetrical triplets. The example of synthesizing triplet **137** with two *N*-CPM and one *N*-Me substituents is shown in Scheme 26. The oxazoline dimer **136** with the *N*-CPM groups was treated with α-hydroxyaldehyde **122** with the *N*-Me group in the presence of



Scheme 23. Previous synthesis of triplet **124**

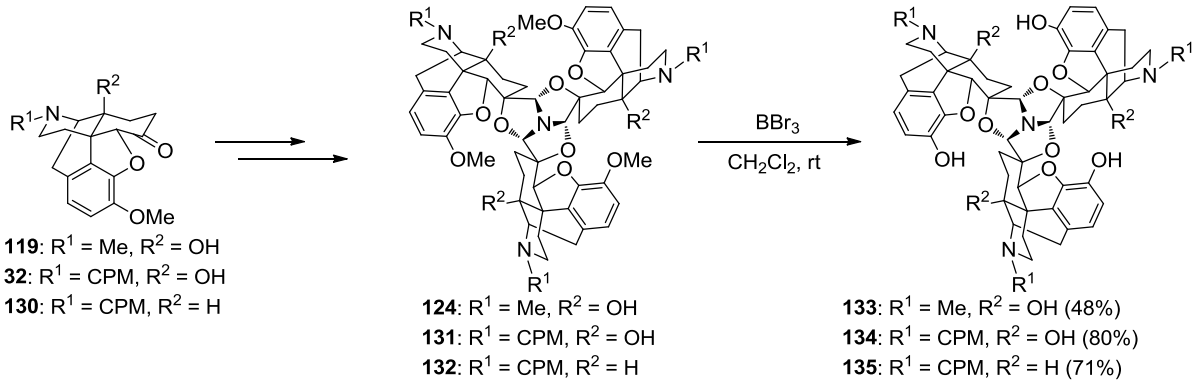


Scheme 24. New synthesis of the intermediate oxazoline dimer **129**

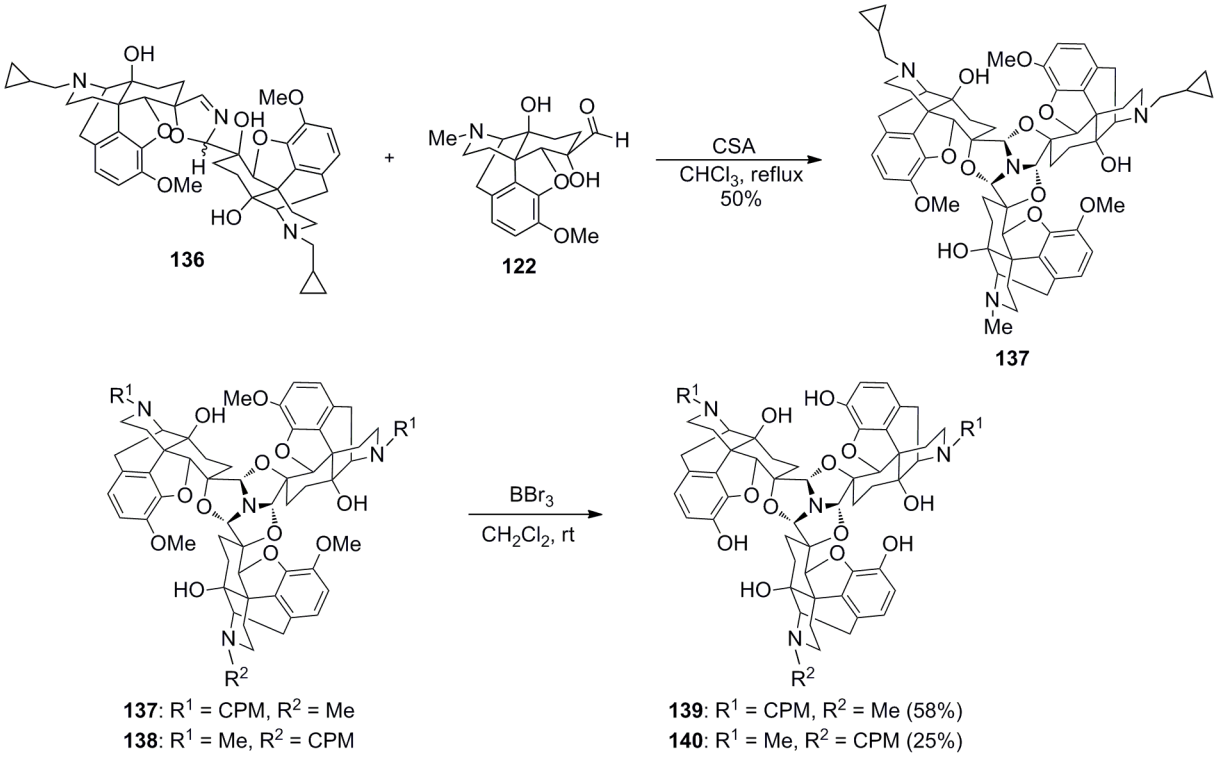
camphorsulfonic acid (CSA) to provide nonsymmetrical triplet **137** in 50% yield. By the same manner, another nonsymmetrical triplet **138** was also prepared. The obtained nonsymmetrical triplets **137** and **138** were demethylated with BBr_3 to give the corresponding phenolic hydroxy derivatives **139** and **140** (Scheme 26).

The binding affinities of the synthesized triplet drugs for the opioid receptor types were shown in Table 3.[33b] The symmetrical triplet **133** with three *N*-Me groups bound most strongly to the μ receptor among the three types. Although its K_i value for the μ receptor was larger than that of naltrexone (**8**), the selectivity of **133** for the μ receptor over the κ receptor was higher than that of naltrexone (**8**). With an increase in the number of *N*-CPM groups, the selectivity for the κ receptor increased; the order of increasing κ selectivity was **133** < **140** < **139** < **134**. These results were in good agreement with reports that the *N*-Me group contributed to the μ selectivity, while the *N*-CPM group favored the κ selectivity.[2b,54] The 14-dehydroxy symmetrical triplet **135** with three *N*-CPM groups had lower affinity for the κ receptor than the corresponding 14-OH triplet **134**, which was consistent with our previous reports.[2b]

Subcutaneous administration of **133**, which showed the highest selectivity and affinity for the μ receptor,



Scheme 25. Synthesis of symmetrical triplet drugs **133**–**135**



Scheme 26. Synthesis of nonsymmetrical triplets **139** and **140**

induced dose-dependent antinociceptive effects in the acetic acid writhing test.[2b] This effect could be antagonized with the μ antagonist naloxone (Figure 13). The antinociception of **133** (ED_{50} = 0.034 μmol/kg) was 56-fold higher than that of morphine (ED_{50} = 1.9 μmol/kg).[55] The strong activity of **133** might result from its simultaneous occupancy of three μ opioid receptors. It is noteworthy that **133** did show profound analgesic effects despite its lacking drug-like properties as a central nervous system drug, *e.g.*, an extremely large molecular weight (MW = 957) and numerous nitrogen and oxygen atoms (the sum of the nitrogen and oxygen atoms in **133** is over six).[56] It is not clear why a triplet drug with these

Table 3. Binding affinities of symmetrical and nonsymmetrical triplet drugs for the opioid receptor types[33b]

Compound	K_i (μ) (nM)	K_i (δ) (nM)	K_i (κ) (nM)	Selectivity	
				κ/μ	δ/μ
morphine	1.98	325	54.3	27.4	164
naltrexone (**8**)	0.335	20.7	0.373	1.1	61.8
133	1.05	38.6	16.1	15.3	36.8
140	1.85	23.5	10.9	5.9	12.7
139	3.98	24.6	10.1	2.5	6.2
134	22.2	122	22.1	1.0	5.5
135	22.3	53.7	43.2	1.9	2.4

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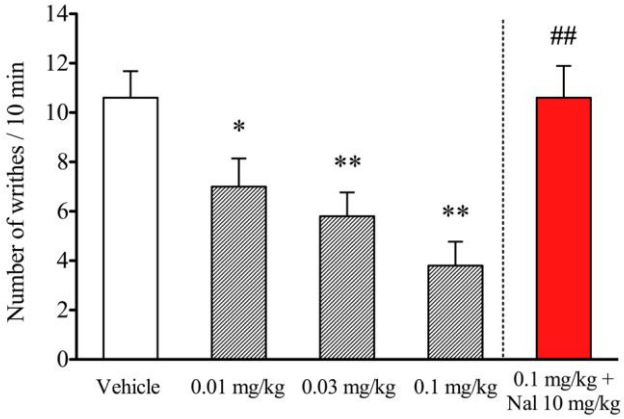


Figure 13. Antinociceptive effect of **133** (hatched bars) and effect of naloxone (Nal, red) on the antinociception induced by **133** (0.1 mg/kg) in the mouse acetic acid writhing test.[2b] The statistical significance of differences between the groups was assessed with one-way ANOVA followed by Newman-Kenuls test. *$p < 0.05$ and **$p < 0.01$ versus saline treated mice. ##$p < 0.01$ versus mice treated with **133** (0.1 mg/kg, sc). Reprinted from ref. 53 with permission from Elsevier. Copyright (2011)

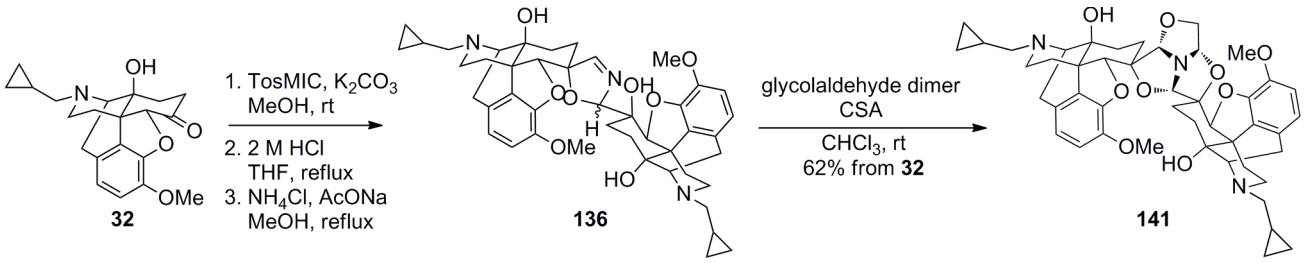
properties showed strong antinociception, but certain transporters may help the absorption and/or penetration of the triplet into the brain.

6-3. Synthesis of Capped Homotriplet Drugs with Morphinan Skeletons and Their Pharmacologies

To compare with pharmacological effects induced by triplet drugs, capped triplets, which have two pharmacophore units and the epoxymethano structure (cap structure), would serve as useful reference

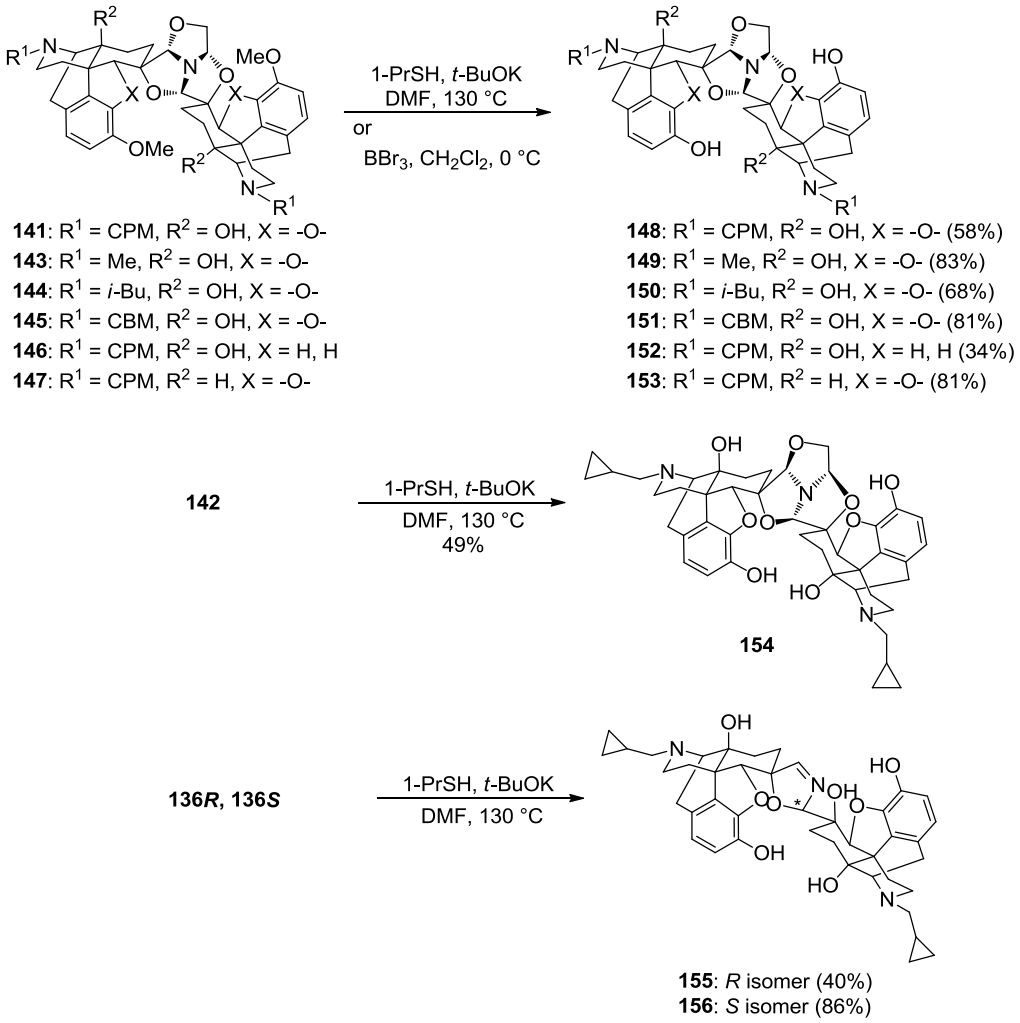
compounds (Figure 12). We expected the capped triplet to be a useful tool to investigate the phenomenon of GPCR dimerization. Therefore, we attempted to synthesize capped homotriplet **141** using a new method (Scheme 27).[52] Other capped triplets **143**–**147** (Scheme 29) were synthesized from the corresponding ketones by the same manner. In the reaction shown by Scheme 27, the kinetically controlled oxazoline dimer **136*R*** with *R*-configuration at the *-position (Scheme 28) was reported to be epimerized into the thermodynamically controlled oxazoline dimer **136*S*** with *S*-configuration during the reaction to provide the 1,3,5-trioxazatriquinone skeleton structure with *S*-configuration at all methyne positions.[30c] It is intersting that the isolated *R*-oxazoline dimer **136*R*** with TMSOTf instead of CSA afforded capped homotriplet **142** with *R*-configuration at all methyne positions (#-positions) (Scheme 28). The configurations of the 1,3,5-trioxazatriquinane skeleton moieties in capped homotriplets **141** and **142** were determined by 2D-NMR experiments. Thus obtained capped homotriplets **141**–**147**[57] and oxazoline dimers **136*R*** and **136*S*** were demethylated to give phenolic hydroxy derivatives **148**–**156** (Scheme 29).

The binding affinities of the synthesized capped homotriplets and oxazoline dimers for the opioid receptor types are shown in Table 4.[33a] Capped homotriplets **150** and **154** bound to the opioid receptors, but their affinities were much lower compared to the other test compounds. Both the weak electron donating ability and steric hindrance of *N*-*i*-Bu groups in **150** may disturb its binding to the opioid receptors. Even though the Me group is a weaker electron donor than the *i*-Bu group, the affinities of **149** with *N*-Me groups were higher than those of **150**. These results may stem from low steric hindrance of the Me group in comparison to the *i*-Bu group. Contrary to the low affinity of **154**, its stereoisomer **148** showed sufficient affinity for the opioid receptor types. The difference of affinities between the two



Scheme 27. Synthesis of capped homotriplet **141** using the new method

Scheme 28. Synthesis of capped homotriplet **142** from kinetically controlled oxazolidine dimer **136*R***



Scheme 29. *O*-Demethylation of capped homotriplets **141**–**147** and oxazoline dimers **136**. CBM: cyclobutylmethyl

stereoisomers may be due to the different configurations of the trioxazatriquinane skeletons in the two isomers. The absence of the 4,5-epoxy bridge (compound **152**) or the angular OH group (compound **153**) had almost no influence on their affinities. Interestingly, the capped homotriplet **148** showed μ selectivity, whereas its precursor, the oxazoline dimer **156**, exhibited κ selectivity. The superimposition of **148** or **156** onto the selective κ antagonist nor-BNI provided a clue to explain the difference of the receptor type selectivities between **148** and **156**. The two 4,5-epoxymorphinan units in **156** occupied a relative spatial location similar to that of nor-BNI, while the same units of **148** were located in a different position (Figure 14). To the best of our knowledge, **149** showed the highest selectivity for the μ receptor over the κ receptor among any of the reported non-peptidic ligands.[58] Therefore, **149** is expected to be a useful tool for the investigation of pharmacologies *via* the μ receptor.

Capped homotriplet **149** dose-dependently produced antinociception in the acetic acid writhing test[2b] (Figure 15 (A)) and its effect was significantly reduced by the μ antagonist naloxone (Figure 15 (B)). The

Table 4. Binding affinities of capped homotriplet and oxazoline dimer drugs for the opioid receptor types[33a]

Compound	K_i (μ) (nM)	K_i (δ) (nM)	K_i (κ) (nM)	Selectivity	
				κ/μ	δ/μ
naltrexone (**8**)	0.265	12.27	0.702	2.64	46.23
148	0.480	16.15	2.752	5.73	33.62
149	2.093	52.86	337.4	161.2	25.26
150	25.27	> 1,000	118.7	4.70	–
151	2.600	49.96	176.1	67.73	19.22
152	0.771	5.979	8.670	11.25	7.76
153	0.719	7.797	6.355	8.84	10.85
154	38.22	> 1,000	247.2	6.47	–
155	1.031	39.62	1.656	1.61	38.43
156	1.900	53.74	1.164	0.61	28.28

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potency of the analgesic effect induced by **149** (ED_{50} = 0.18 μmol/kg) was 11-fold more potent than that of morphine (ED_{50} = 1.9 μmol/kg), but about five fold less potent than that of symmetrical triplet **133** (ED_{50} = 0.034 μmol/kg).[53] It is interesting that the increment of morphinan units exerted non-linearly increasing effects of antinociception. These phenomena would result from the features of symmetrical twin and triplet drugs mentioned above.

7. SYNTHESIS OF PROPELLANE DERIVATIVES WITH AFFINITIES FOR OPIOID RECEPTORS

The receptor type selectivity is generally influenced by the 17-substituents; 17-Me and 17-CPM derivatives tend to bind preferably to the μ and the κ receptors, respectively. Indeed, morphine and oxymorphone (**157**) with the 17-Me group showed high selectivity for the μ receptor, whereas naltrexone (**8**) with the 17-CPM substituent bound to the κ receptor with a smaller K_i value than did oxymorphone, the corresponding derivative with a 17-Me group (**157**) (Figure 16). A similar tendency was observed in the selective κ agonist, nalfurafine (**1**, Figure 1) and the selective κ antagonist, nor-BNI, which have 17-CPM substituents; the conversion of the 17-substituent from CPM into a Me group in nalfurafine (**1**) significantly lowered the κ selectivity,[2b,2e] whereas the 17-Me derivative of nor-BNI showed full agonistic

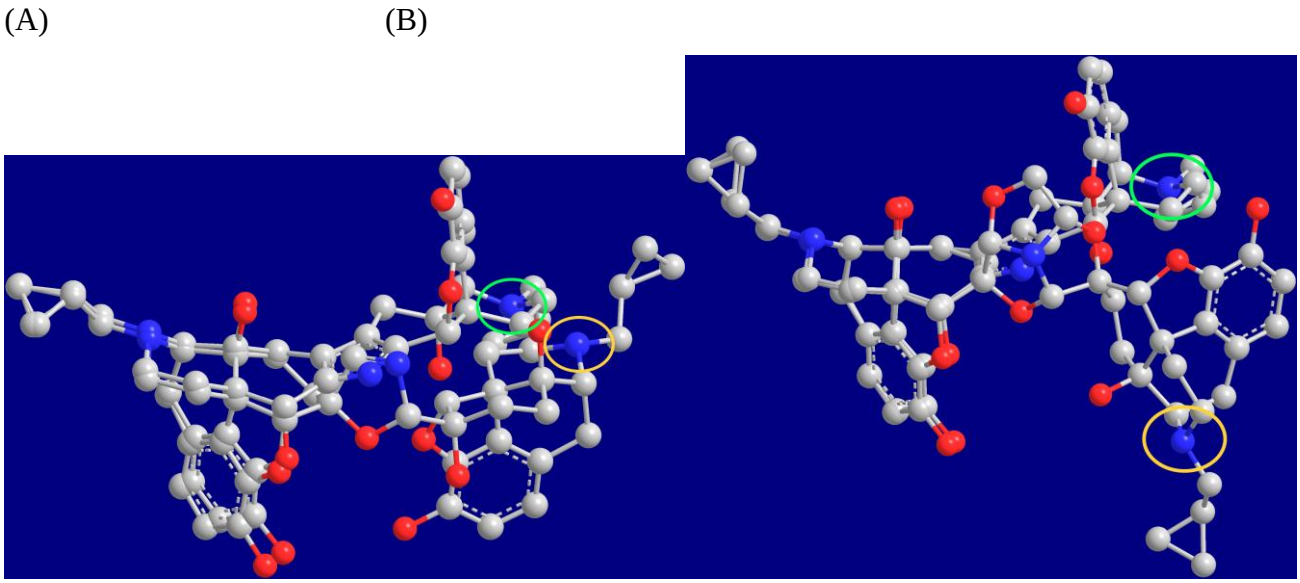


Figure 14. Superimposition of the 3D-alignment of nor-BNI onto that of **156** (A) or **148** (B). The 17'-nitrogen, which was reported to exert κ selectivity,[59] and the corresponding nitrogen in **156** or **148** are indicated by green and yellow circles, respectively. Reprinted from ref. 52 with permission from Elsevier. Copyright (2011)

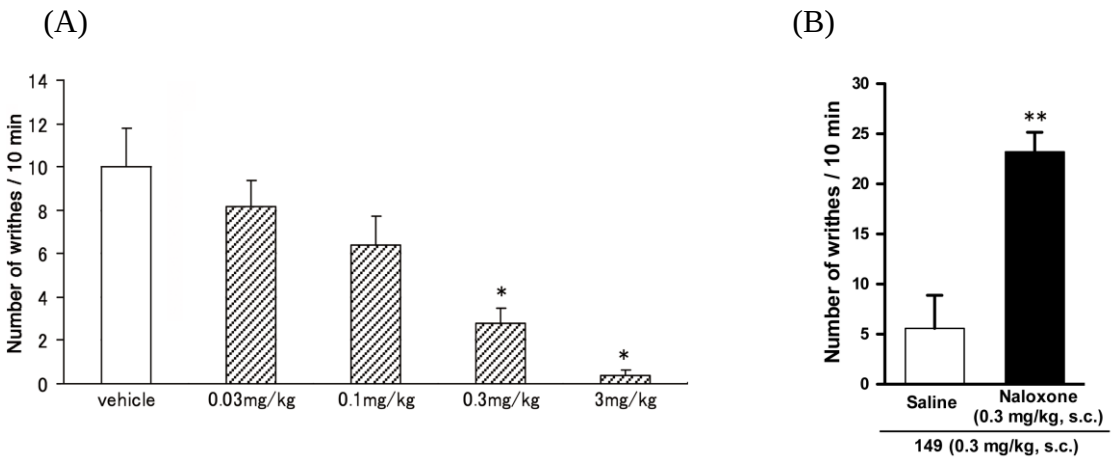


Figure 15. Analgesic effects induced by **149** (A) and effects of naloxone on the antinociception induced by **149** (B) in the mouse acetic acid writhing test.[2b] The statistical significance of differences between the groups was assessed with one-tailed nonparametric Williams' test (A) or Student's *t*-test (B). **p* < 0.025 and ***p* <0.01 versus saline treated mice. Reprinted from ref. 52 with permission from Elsevier. Copyright (2011)

activity for the μ receptor.[60]

Taking into account the tendencies mentioned above, a careful observation of the relationship between receptor type selectivities and the presence or absence of the 4,5-epoxy ring in the compounds depicted in Figure 16 provided an interesting correlation: The morphinan derivatives **8** and **158** with a 4,5-epoxy ring

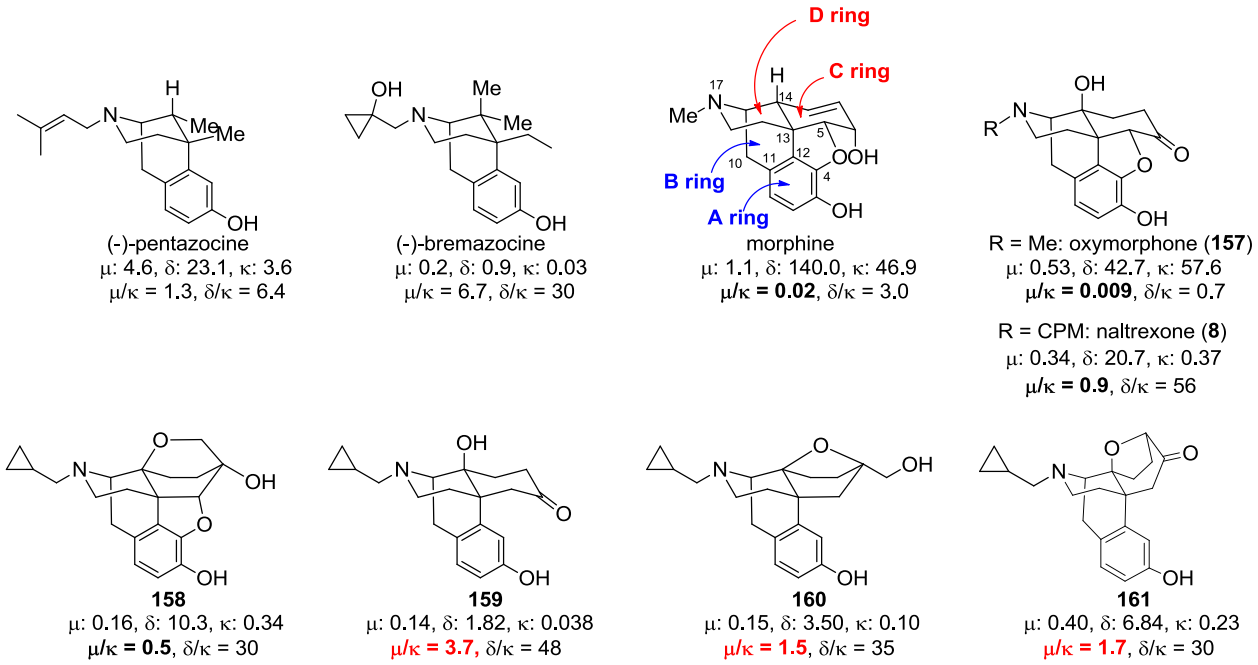


Figure 16. Structures of compounds **8**, **157**–**161**, (–)-pentazocine, (–)-bremazocine, and morphine, and their opioid receptor type selectivity. K_i Values (nM) and selectivities (K_i ratio) are indicated. Reprinted from ref. 54 with permission from Elsevier. Copyright (2011)

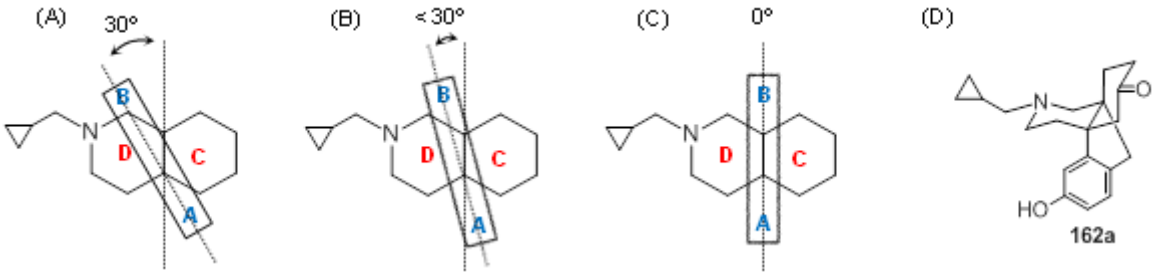


Figure 17. Pattern diagrams of the relationship between the A, B rings and the C, D rings, and the structure of propellane derivative **162a**. The numerical values indicate the torsion angle C11–C12–C13–C14 for (A) 4,5-epoxymorphinans, (B) morphinans without a 4,5-epoxy ring or benzomorphans, and (C) propellane derivatives **162a**. (D) The structure of **162a**. Reprinted from ref. 54 with permission from Elsevier. Copyright (2011)

showed rather lower κ selectivity (μ/κ) despite having 17-CPM groups, while the derivatives **159**–**161** without the 4,5-epoxy ring tended to show higher κ selectivity (Figure 16).[58e] The benzomorphan derivatives like (–)-pentazocine and (–)-bremazocine, which showed κ selectivity, also have no 4,5-epoxy ring. This tendency led us to propose that, with respect to the 17-CPM derivatives, the position of the plane composed of the A and B rings, which can be defined by the torsion angle C11–C12–C13–C14, would influence the receptor type selectivity and that a decrease in the torsion angle could improve the κ

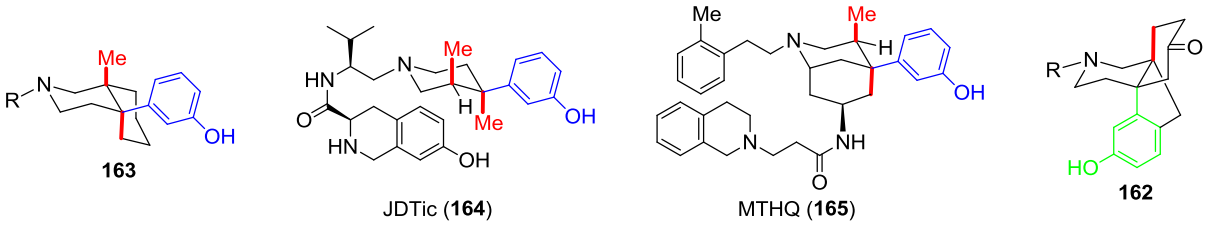
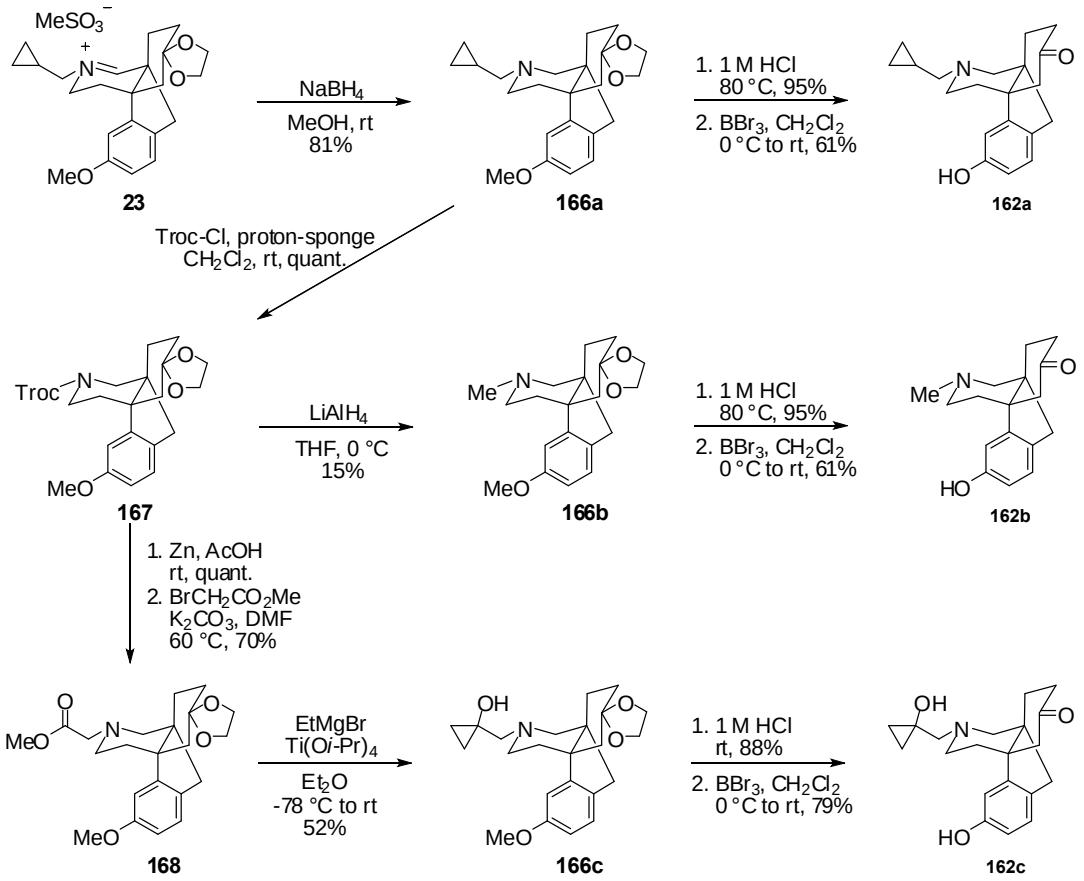


Figure 18. Structures of compounds **162**–**165**. The axial Me (alkylene) groups, equatorial 3-hydroxyphenyl groups, or axial 3-hydroxyphenyl group are indicated by red, blue, or green color, respectively

selectivity. The torsion angles C11–C12–C13–C14 in 4,5-epoxymorphinans are approximately 30º (Figure 17(A)) and are fixed by both the 4,5-epoxy ring and the 10-methylene bridge. These compounds like **8** and **158** prefer to bind the μ receptor. On the other hand, in morphinan derivatives lacking the 4,5-epoxy ring or in the benzomorphans, the torsion angle C11–C12–C13–C14 could be less than 30º (Figure 17(B)) because the plane comprised of the A and B rings was not fixed as tightly, permitting rotation around the C12–C13 axis. These compounds tend to show κ selectivity. This working hypothesis led us to the propellane derivatives **162a** whose A and B rings are fixed and the torsion angle C11–C12–C13–C14[61] is about 0º (Figure 17(C)). The structure in the solid state of propellane derivative **162b** (Scheme 30), which was prepared from the extremely stable iminium ion **23** (Scheme 1, equation (5')), was confirmed by X-ray crystallographic analysis.[62]

Additionally, Carroll and colleagues recently reported that *N*-substituted *cis*-4a-(3-hydroxyphenyl)-8a-methyloctahydroisoquinolines **163** was an opioid antagonist.[63a] According to Carroll *et al.*, JDTic (**164**)[63b] or MTHQ (**165**),[63c] which were κ antagonists belonging to this chemical class, had the 3-hydroxyphenyl group in the equatorial position and a *trans*-3,4-dimethyl structure, and these structural features would play an essential role in antagonist activity regardless of the nitrogen substituents (Figure 18). From this point of view, the propellane derivatives **162** have two structural features: an axial alkylene group corresponding to the axial 3-Me group in **163** and the 3-hydroxyphenyl group fixed in the axial conformation by a methylene bridge (Figure 18). Therefore, the propellane derivatives **162** were very interesting compounds from two viewpoints: 1) the decrease in torsion angles C11–C12–C13–C14 would improve the κ selectivity and 2) the validation of Carroll's proposal that both the equatorial 3-hydroxyphenyl conformation and the *trans*-3,4-dimethyl structure in the series of derivatives of **163** would exert the antagonist activity.[54]

For the synthesis of objective propellane derivatives **162** (Scheme 30), the extremely stable iminium **23** (Scheme 1, equation (5')) was reduced with $NaBH_4$ to give the saturated propellane **166a**. After exchange of *N*-CPM substituent into the *N*-Troc group, the reduction of the obtained carbamate **167** with $LiAlH_4$



Scheme 30. Synthesis of propellane derivatives **162**

provided *N*-Me derivative **166b**. *N*-((1-Hydroxycyclopropyl)methyl) derivative **166c** was prepared by the treatment of compound **168** with EtMgBr in the presence of Ti(O*i*-Pr)$_4$ (Kulinkovich reaction)[64] in 52% yield. Compound **168** was obtained from carbamate **167** by deprotection of the Troc group and subsequent alkylation. Thus prepared propellane derivatives **166** were appropriately deprotected to afford the objective phenolic hydroxy derivatives **162**.

Table 5 exhibited the binding affinities of prepared propellanes **162** (Table 5).[33b] Both **162a** with the *N*-CPM group and **162c** with the *N*-((1-hydroxycyclopropyl)methyl) substituent displayed high selectivity for the κ receptor. Their selectivities for the κ receptor over the μ receptor (**162a**: μ/κ= 3.3, **162c**: μ/κ = 3.6) were higher than those of the representative κ agonist nalfurafine (μ/κ = 2.5) and (–)-pentazocine (μ/κ = 1.3). These results support our conjecture that a decrease in the torsion angle C11–C12–C13–C14 in morphinan-related derivatives with the *N*-CPM substituent would improve the κ selectivity. Propellane derivatives **162a** and **162c** displayed lower binding affinities for all receptor types than did nalfurafine (**1**) and (–)-pentazocine. This result may be due to the *cis*-fused C and D rings. Contrary to the *trans*-fused decahydroisoquinoline derivatives, the *cis*-fused derivatives showed very weak analgesic effects.[66] In contrast to **162a** and **162c**, **162b** with an *N*-Me group showed high binding affinity for the μ receptor, but

Table 5. Binding affinities of propellane derivatives **162** for the opioid receptor types[33b]

Compound	K_i (μ) (nM)	K_i (δ) (nM)	K_i (κ) (nM)	Selectivity	
				μ/κ	δ/κ
nalfurafine (**1**)[a]	0.58	96.5	0.23	2.5	420
(–)-pentazocine	4.6	23.1	3.6	1.3	6.4
162a	58.2	448	17.4	3.3	26
162b	3.6	441	255	0.02	2.0
162c	77.7	500	21.7	3.6	23

[a] See references and notes 2g and references cited therein.

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its affinity for the κ receptor decreased. This result was consistent with the feature of *N*-Me derivatives mentioned above, *i.e.*, preference for the μ receptor.

N-CPM-Derivative **162a** produced antinociceptive effects in the mouse acetic acid writhing test.[2b] The analgesic effect by **162a** was as potent as that by morphine (ED_{50} = 0.86 mg/kg, s.c.). The antinociception of **162a** was mainly antagonized by κ antagonist nor-BNI and partly by μ antagonist naloxone (Figure 19). This result indicates that **162a** was a somewhat selective κ agonist and is also consistent with our working hypothesis. Moreover, the result suggests that the elicitation of antagonist activity requires the equatorial 3-hydroxy group, not the axial methyl (alkylene) group.

The 6-keto group in the C-ring of propellane **162a** could exist in a more elevated position compared to the 6-keto group in naltrexone (**8**). Therefore, the introduction of an amide side chain at the 6- or 7-position[61] would be more effective for improving the κ selectivity because the amide side chain introduced into the propellane skeleton would be expected to locate in a position similar to that of the amide side chain in the active conformation of nalfurafine (**1**)[2c,d,f] (Figure 20). Therefore, we next synthesized propellane derivatives with an amide side chain in the 6- or 7-position to improve the κ selectivity.[67]

The propellane derivatives **175** and **176** with a 6-amide side chain were prepared from **166a** (Scheme 31). After reductive amination of **166a** with benzylmethylamine, hydrogenolysis of the obtained tertiary amines **169** and **170** gave secondary amines **171** and **172**, respectively. Amines **171** and **172** were acylated with the corresponding acyl chlorides, followed by *O*-demethylation to afford the respective propellane derivatives **175** and **176**.

The preparation of propellane derivatives **185** and **186** with a 7-amide side chain also commenced with **166a** (Scheme 32). The methoxycarbonyl group was introduced at the 7-position by the reaction of **166a** with $CO(OMe)_2$ in the presence of NaH. The obtained β-ketoesters **178** and **179** were converted into α,β-

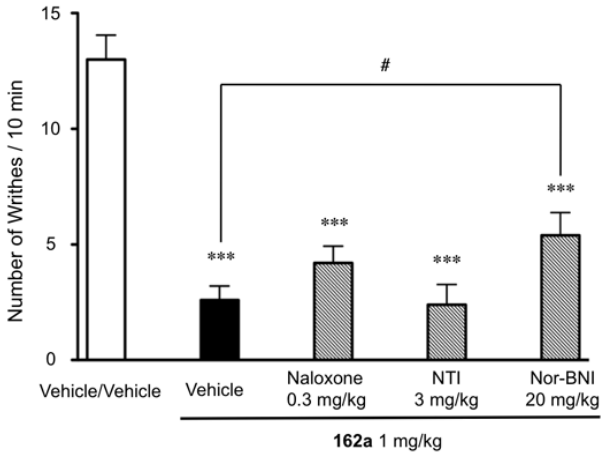


Figure 19. Effects of opioid receptor antagonists on the antinociception induced by **162a** in the mouse acetic acid writhing test.[2b] Naloxone, NTI, and nor-BNI are selective antagonists for the μ, δ, and κ receptors, respectively. The statistical significance of differences between the groups was assessed with one-way ANOVA followed by Newman-Kenuls test. ***p < 0.001 versus vehicle/vehicle group. #p < 0.05 versus vehicle/**162a** group. Reprinted from ref. 54 with permission from Elsevier. Copyright (2011)

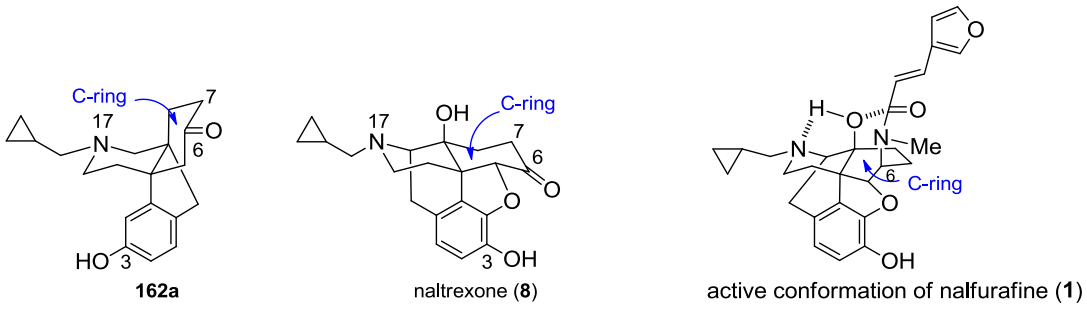
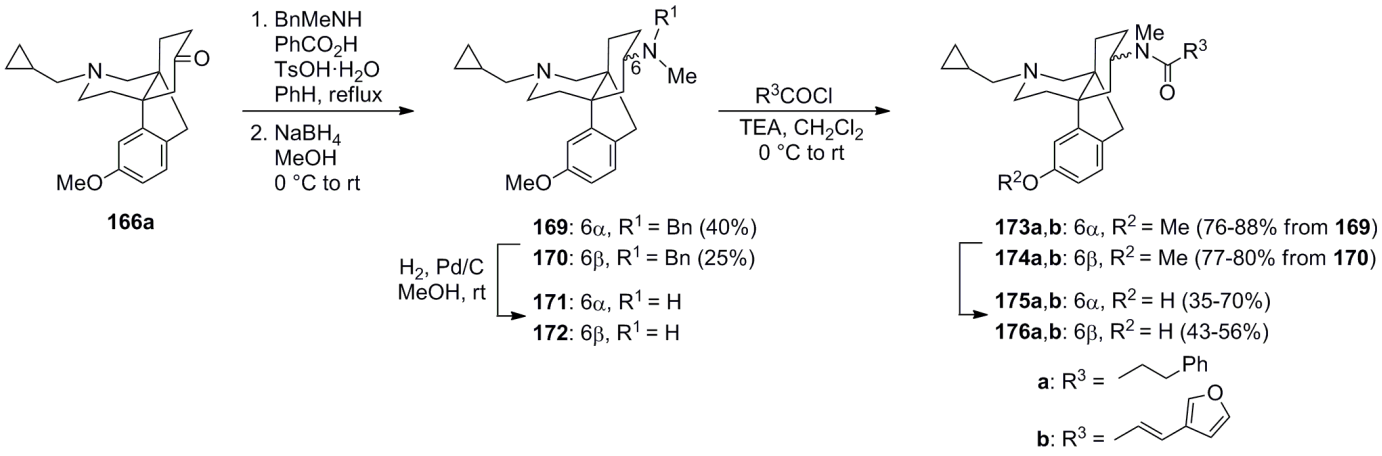
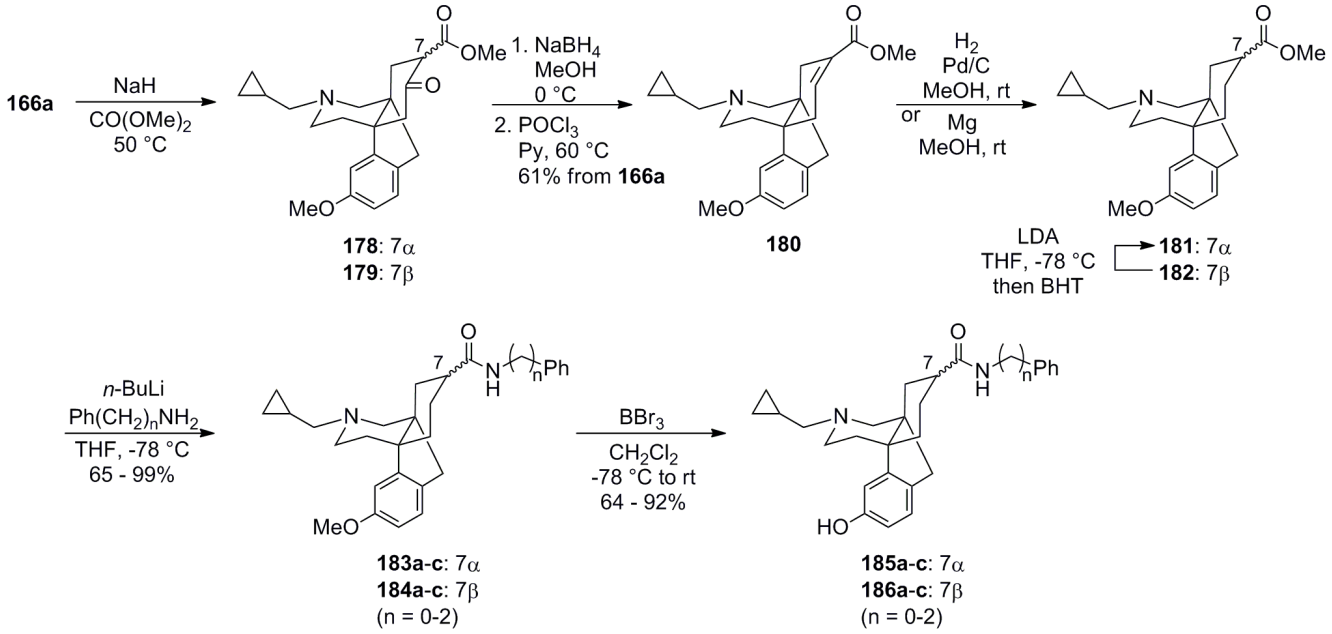


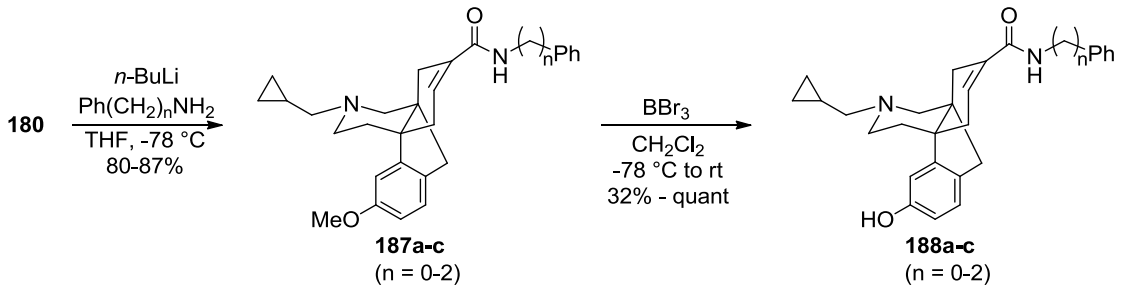
Figure 20. Comparison of structures between propellane **162a** and naltrexone (**8**), and active conformation of nalfurafine (**1**)



Scheme 31. Synthesis of propellane derivatives **175** and **176** with a 6-amide side chain



Scheme 32. Synthesis of propellane derivatives **185** and **186** with a 7-amide side chain. BHT: 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene)



Scheme 33. Synthesis of propellane derivatives **188** with α,β-unsaturaed amide moiety

unsaturated ester **180** by the reduction with $NaBH_4$ and subsequent dehydration with $POCl_3$. The hydrogenation of **180** provided saturated 7-esters **181** (α-isomer) and **182** (β-isomer) in 5% and 77% yield, respectively. The attempted epimerization of major product **182** with LDA gave α-isomer **181** in 24% yield with recovery of **182** in 65%. The alternative synthesis of 7-esters **181** and **182** was carried out by reduction of **180** with Mg[68] in respective yield of 30% and 53%. The obtained esters **181** and **182** were converted into the respective 7-amides **183** and **184** by the ester–amide exchange reaction with the appropriate lithium amide. The objective propellane derivatives **185** and **186** were obtained by the *O*-demethylation of **183** and **184**, respectively.

The propellane derivatives **188** with the α,β-unsaturated amide moiety were derived from α,β-unsaturated ester **180** by the ester–amide exchange reaction and subsequent *O*-demethylation (Scheme 33).

The binding affinities of the synthesized propellane derivatives for the opioid receptors are shown in Table 6. All the 6-amide derivatives **175** and **176** bound to all three receptor types with smaller K_i values than propellane **162a** lacking the amide side chain. Compound **176b** showed improved κ selectivity over the μ receptor compared to nalfurafine (**1**) and propellane **162a**. Interestingly, 6β-isomers **176** were more κ selective over the μ receptor than the corresponding 6α-isomers **175**. This result may be caused by the orientation of the 6β-amide side chain toward the upper side of the C-ring. Meanwhile, the 7-amide derivatives **185**, **186**, and **188** showed lower affinities than the 6-amide derivatives **175** and **176**. Especially, the affinities of 7β-isomers **186** were low and **186b** hardly bound to the δ and κ receptors. On the other hand, 7α-isomers **185** and α,β-unsaturated amides **188** interacted with the three receptor types with somewhat higher affinities compared to the β-isomers **186**. The α,β-unsaturated amides **188** showed μ selectivity, whereas the α-isomers **185** except for **185c** exhibited κ selectivity. The κ selectivities of **185a** and **185b** were higher than those of nalfurafine (**1**) and 6β-amide **176b**. The different orientation of the amide side chain may provide these outcomes (Figure 21). The amide side chain of **185** may be able to locate in a direction that enhances binding to the κ receptor, whereas that of **188** cannot. However, it is difficult to explain the extreme decrease in the affinities of the 7β-isomer **186** by an unfavorable orientation of the amide side chain, *i.e.*, the side chain is incapable of functioning as the κ address. Therefore, we postulated that the flexible 7β-side chain could locate over the 17-nitrogen to interfere with the ionic interaction between the 17-nitrogen and the opioid receptor. The ionic interaction of the 17-nitrogen is one of the three important interactions between ligand and opioid receptor: the other two interactions are a π–π interaction with the phenol ring and a hydrogen bond with the phenolic hydroxy group. Figure 22 depicts the results of conformational analyses of three 7-amides **185b**, **186b**, and **188b** using CAMDAS 2.1 program.[47] The benzene ring of the 7β-amide side chain in **186b** located over the 17-nitrogen and almost completely shields the lone electron pair of the 17-nitrogen (Figure 22 (C)). On the other hand, the side chain in 7α-amide **185b** would not shield the lone electron pair of 17-nitrogen (Figure 22 (A)). The shielding effect of the side chain in the α,β-unsaturated amide **188b** would be insufficient (Figure 22 (B)). The results of conformational analyses supported our hypothesis and indicated that the ionic interaction between the 17-nitrogen and the opioid receptor would be especially important among the three known ligand–receptor interactions in opioid action.[34a,69]

Table 6. Binding affinities of propellane derivatives **162a**, **175**, **176**, **185**, **186**, and **188** for the opioid receptor types[33a]

compound	K_i (μ) (nM)	K_i (δ) (nM)	K_i (κ) (nM)	Selectivity	
				μ/κ	δ/κ
nalfurafine (**1**)[a]	0.431	51.3	0.178	2.42	288
162a[b]	58.2	448	17.4	3.34	25.7
175a	1.23	44.3	7.10	0.17	6.24
175b	2.20	35.0	0.83	2.65	42.2
176a	31.9	65.2	16.4	1.95	3.98
176b	12.2	121	3.43	3.56	35.3
185a	79.7	282	13.4	5.95	21.0
185b	106	>1,000	19.2	5.52	–[c]
185c	54.1	>1,000	169	0.32	–[c]
186a	80.8	207	108	0.75	1.92
186b	112	>1,000	>1,000	–[d]	–[d]
186c	453	>1,000	641	0.71	–[c]
188a	12.4	192	46.7	0.27	4.11
188b	33.9	298	72.7	0.47	4.10
188c	35.9	412	253	0.14	1.63

[a] See references and notes 2g and references cited therein.
[b] Ref. 54.
[c] Selectivity was not calculated because the K_i value for the δ receptor was over 1,000 nM.
[d] Selectivity was not calculated because the K_i value for the κ receptor was over 1,000 nM.
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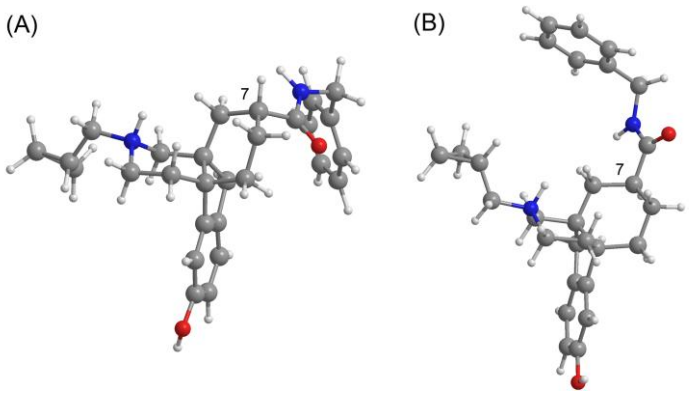

Figure 21. Comparison of 3D-alignments of 7α-amide **185b** (A) and 7β-amide **186b** (B). Reprinted from ref. 67 with permission from Elsevier. Copyright (2012)

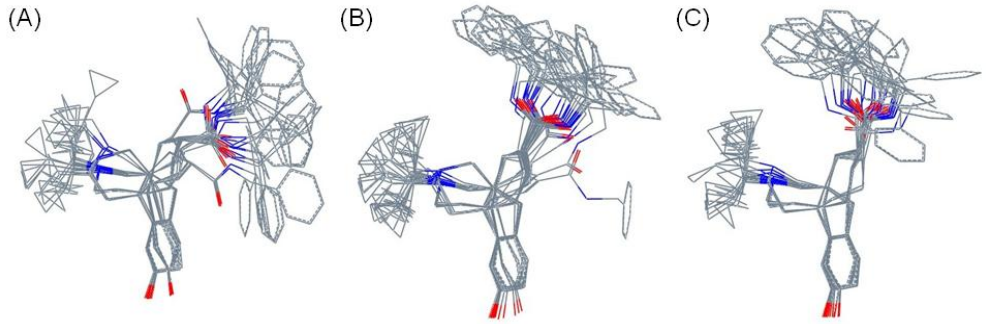

Figure 22. Results of conformational analyses of (A) 7α-amide **185b**, (B) α,β-unsaturated amide **188b**, and (C) 7β-amide **186b**. Structures within 10 kcal/mol of the most stable conformer were collected. Reprinted from ref. 67 with permission from Elsevier. Copyright (2012)

8. CONCLUDING REMARKS

In this review, we have described the recent progress of our investigations, including interesting reactions using naltrexone derivatives and the pharmacological properties of the synthesized derivatives. A key reaction in the (–)-homogalanthamine synthesis was the Grob fragmentation, in which the observed stereoelectronic effect due to characteristic structure of naltrexone (**8**) was utilized. Novel derivatives with oxazatricyclodecane or propellane skeletons would be useful as lead compounds for novel opioid ligands exhibiting receptor type selectivities. The investigation of the Beckett–Casy model suggested that the interaction between the 17-nitrogen and the opioid receptor would be not a simple ionic but an enforced ionic interaction with directional properties. Triplet drugs have promising features. Symmetrical triplets with 17-Me groups described in this review showed increased agonistic activities. Nonsymmetrical triplet drugs would exhibit dual or triple pharmacological actions. Moreover, these triplets are expected to be useful tools for investigating the phenomena of GPCR dimerization and/or oligomerization. We are now vigorously pursuing the synthesis of new derivatives and the utilization of the obtained derivatives.

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33. (a) Binding assays was carried out in duplicate (κ: cerebellum of guinea pig, μ and δ: whole brain without cerebellum of mouse). [^{3}H] DAMGO, [^{3}H] DPDPE, and [^{3}H] U-69,593 were used as a selective ligand for the μ, δ, and κ receptor, respectively; (b) Binding assay was carried out in duplicate using homogenate of guinea pig brain (κ: cerebellum, μ and δ: forebrain). [^{3}H] DAMGO, [^{3}H] NTI, and [^{3}H] U-69,593 were used as a selective ligand for the μ, δ, and κ receptor, respectively.
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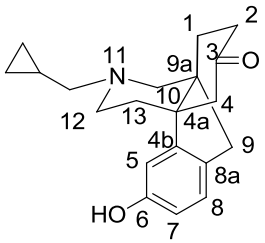

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