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A NEW USEFUL CONVERSION METHOD OF NALTREXONE TO 14-DEOXYNALTREXONE

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Abstract – A novel synthetic method of 14-deoxynaltrexone (**2**), a μ-opioid receptor antagonist possessing a new message-structural part of opioid ligands, was established. Naltrexone methyl ether (**5**) was first converted to its acetal (**24**), followed by dehydration with thionyl chloride in pyridine to afford 8,14-dehydroderivative (**26**) of **24**. The resulting unsaturated compound (**26**) was reduced with PtO_2 under hydrogen to give saturated compound (**27**), which was then acid-hydrolyzed to afford the desired 14-deoxynaltrexone (**23**) (3-*O*-methyl of **2**) without degradation of the naltrexone skeleton. The total yield from naltrexone (**1**) to **23** was 86%. Finally, **23** was demethylated to give 14-deoxynaltrexone (**2**) in 85% yield. This method provides a useful reaction route to give various important intermediates as a message part to synthesize selectives ligands for the opioid receptor subtypes.

INTRODUCTION

Opioid receptors are now recognized to possess their multiple populations and have been classified into at least three major types (μ, δ, κ receptors).[1] Many opioid ligands having high selectivity and potency for each opioid receptor type were reported.[2] Furthermore, each receptor type was subdivided into subtypes (μ1, 2, δ1, 2, κ1, 2, 3).[3] Based on the "message-address concept" [4-6], we have designed and synthesized many new selective opioid agonists and antagonists using readily available naltrexone (**1**)[5-10] (μ–receptor

Authors dedicate this paper to Professor Satoshi Omura on the occasion of his 70th birthday.

antagonist) (Figure 1). As shown in Figure 2,[8] a message-structural part (message subsite), which is commonly found in NTI and nor-BNI, is an essential and elicitable moiety for intrinsic activity on opioid

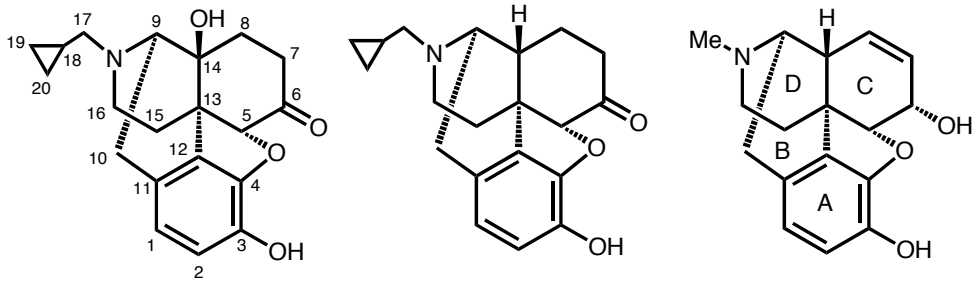

Figure 1

receptors. The other structural part is defined as the address-structural part (address subsite) in the opioid ligand and is a necessary moiety for selectivity on each type of the opioid receptor. The receptor type selectivity of the opioid ligand can be regulated by alteration of the structural size of the address subsite.

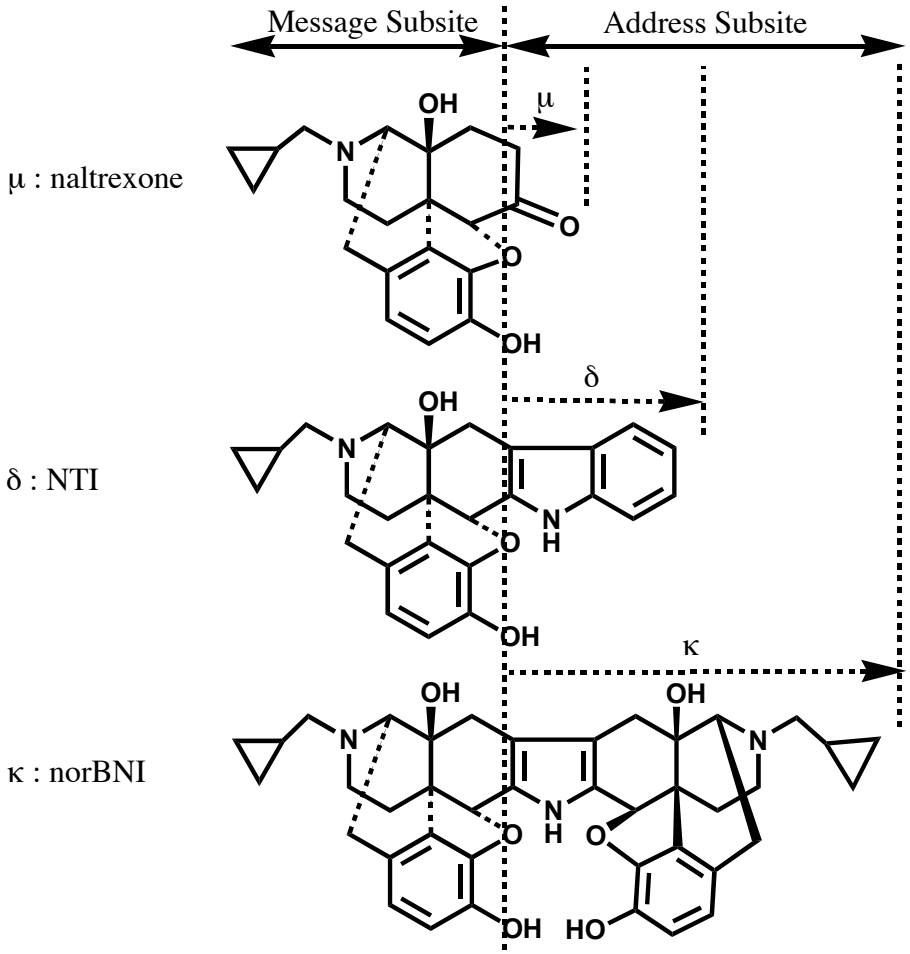

Figure 2 Structural illustration of message and address subsite for μ, δ, and κ receptors in opioid ligand

Although each selective ligand for μ, δ, κ receptor types could be obtained by using the message structural part of **1**, selective ligands for each receptor subtype have not been usually obtained by changing only the address-structure part.

To design and synthesize the subtype selective ligands, we have recently paid much attention to the structure of the message part in **1**. One (Nagase) of the present authors reported that naltrexone (**1**) shows strong antagonist activity for the μ-receptor by fixing the equatorial orientation of the 17-cyclopropylmethyl group of **1** because of the presence of an intramolecular hydrogen bond between a lone pair electron of the 17-nitrogen atom and a hydrogen of the 14-hydroxy group [11] (Figure 3). On the other hand, we also expected that 14-deoxynaltrexone (**2**) (Figure 1) without an intramolecular hydrogen bond would be a useful intermediate not only for design of μ-agonist but also for design of selective ligands for the each receptor subtype.

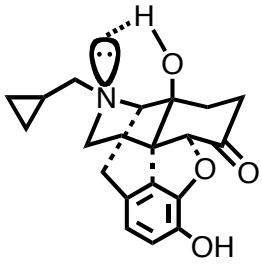

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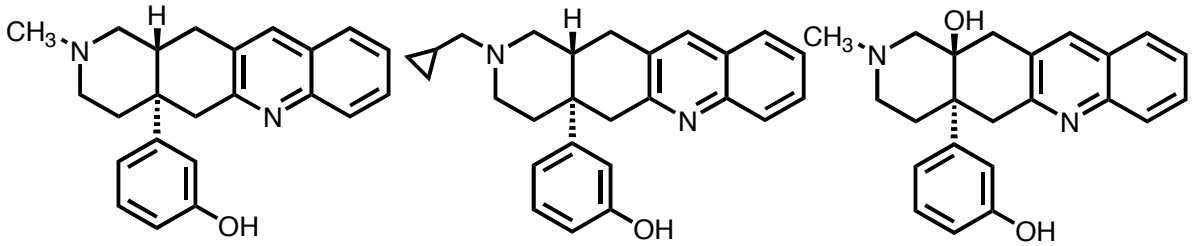
Figure 3

Furthermore, we found that TAN-67 [9] (Figure 4) and compound (**3**) [9] without a hydroxy group at the



TAN-67 **3** **4**

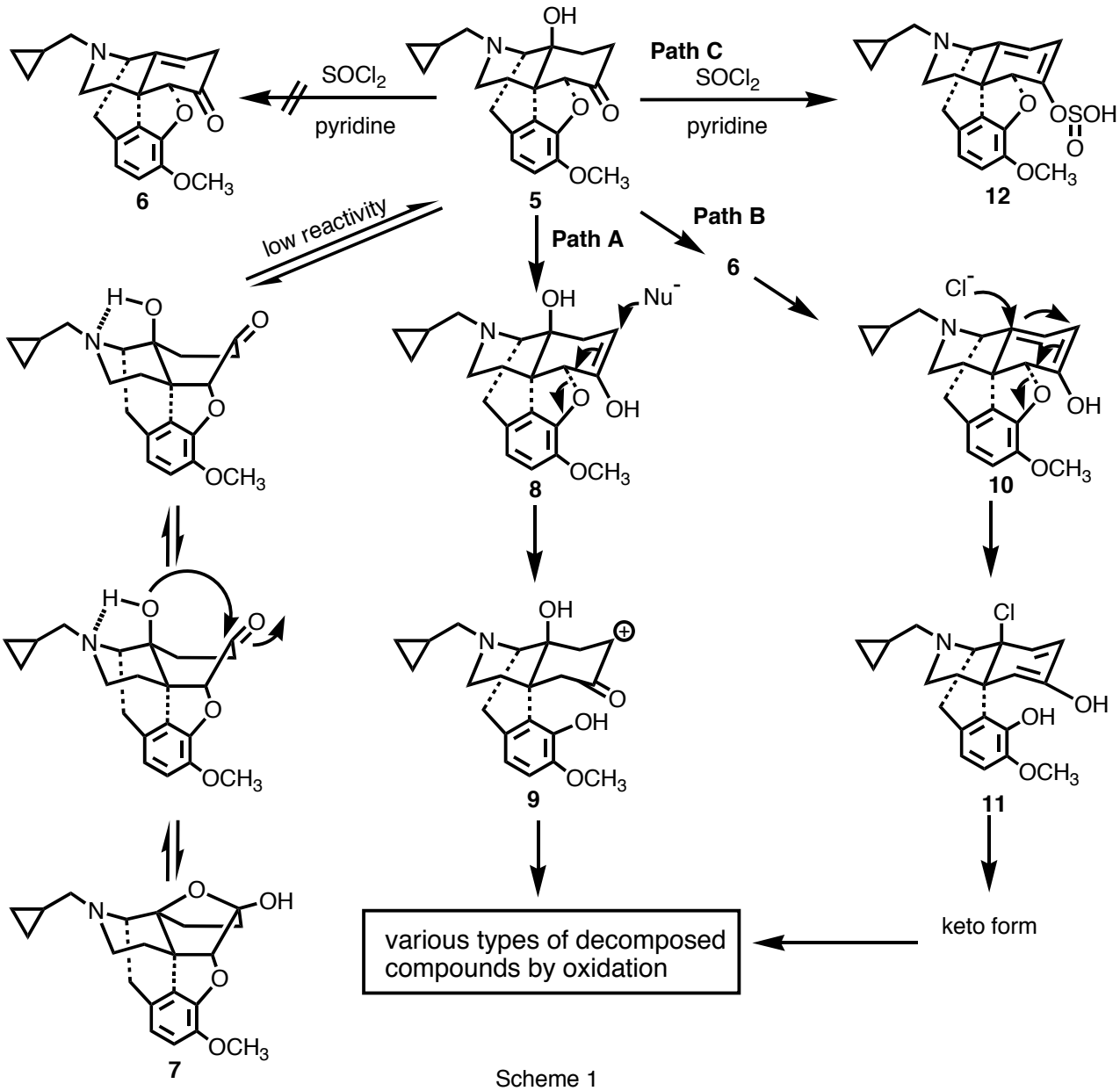
Figure 4

angular position (14-position) were stronger δ-agonists than compound (**4**) with 14-OH (agonist activity: 7 times (TAN-67), 80 times (compound (**3**)) more potent than **4** in MVD (mouse vas deferens test).[12] This result shows that the 14-deoxy compounds were expected to become highly potent agonists. On the basis of the above facts, we have been interested in the removal of 14-OH of naltrexone (**1**) and established a useful synthetic method of 14-deoxynaltrexone.

RESULTS AND DISCUSSION

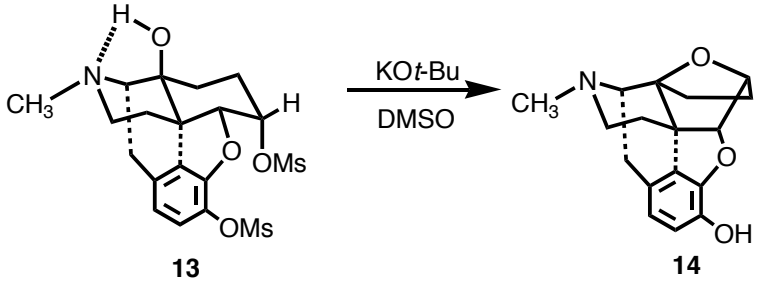
We first examined the dehydration of the 14-hydroxy group of naltrexone methyl ether (**5**) with thionyl chloride in pyridine to give compound (**6**) (Scheme 1). However, this trial did not afford the objective compound (**6**) but afforded only decomposed products and the starting material (**5**) (Scheme 1). This failure may result from formation of a bicyclo[2.2.1]heptane intermediate (**7**) by interaction between the 14-hydroxy group and the 6-keto-group. This postulation of the formation of intermediate (**7**) is supported by formation of 6,14β-epoxide (**14**), which was isolated, from 6α-mesyloxynaltrexol (**13**) [13] by the intramolecular S_N2 reaction of the 14-hydroxy group to the 6α-mesyl group (Scheme 2). [14]

Furthermore, the decomposition of **5** may result from ring-opening of the 4,5-epoxy ring *via* enol form **8** under acid condition and the resulting 4-phenol compound (**9**) would easily be oxidized to give various decomposed compounds (Scheme 1, Path A). Another possible decomposition path to the ring-opening of



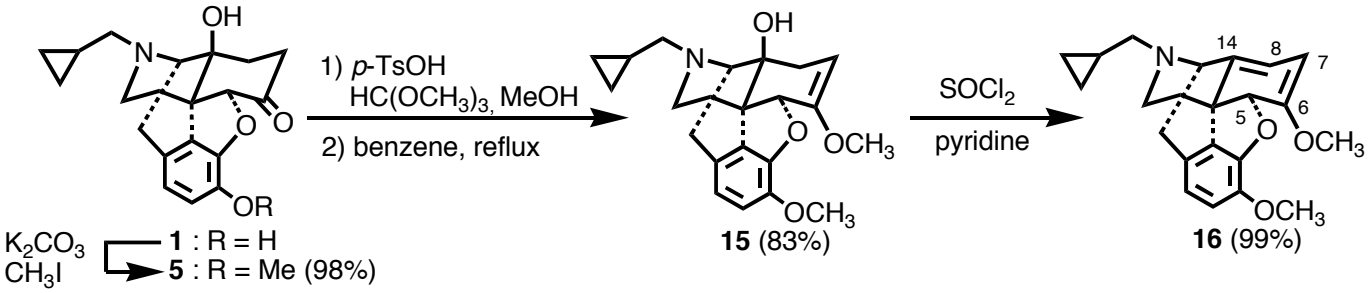
Scheme 1

the 4,5-epoxy ring of **6** were also shown in Scheme 1, Path B. Compound (**5**) was also partly converted to compound (**12**) with thionyl chloride (Scheme 1, Path C). Compound (**12**) could not be isolated, but the structure was confirmed by the existence of a molecular ion peak with sulfur isotope by MS spectroscopy.



Scheme 2

To remove the interaction between 6-carbonyl and the 14-OH group, naltrexone methyl ether (**5**) was converted to enol ether (**15**). The 14-hydoxy group in **15** was easily dehydrated with thionyl chloride in pyridine to afford stable dienol methyl ether (**16**) [15] (Scheme 3).



Scheme 3

Then, the hydrolysis of dienol ether (**16**) was examined. The direct acid hydrolysis of thebaine (**17**) (Figure 5) was reported to give codeine (**18**) in a low yield (5%) under a strong acid condition,[16] but Barber and Rapoport used mercuric acetate as an electrophilic reagent to convert thebaine (**17**) to codeinone in over 90 % yield under a mild condition.[17] We examined Rapoport's method to obtain **23** (Scheme 4).

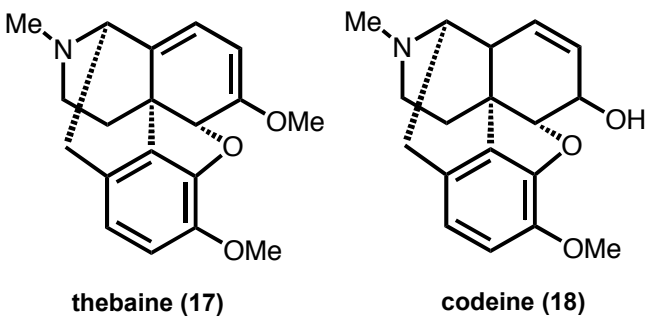
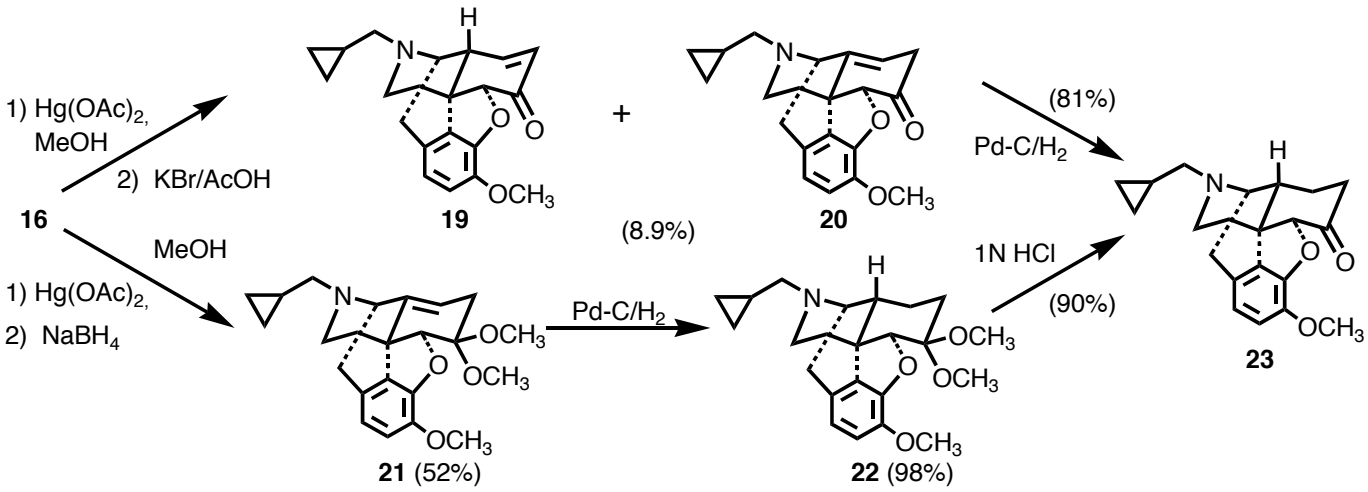


Figure 5

Dienol methyl ether (**16**) was subjected to reaction with ca. 2 mol ratio of mercuric acetate in methanol under reflux, and treated with KBr to afford a mixture of **19** and **20**. The mixture was reduced by catalytic hydrogenation to give **23**. On the other hand, when dienol ether (**16**) was treated with mercuric acetate in methanol under reflux, followed by reduction with $NaBH_4$, dimethyl acetal (**21**) was obtained. The resulting compound (**21**) was reduced by catalytic hydrogenation on Pd-C, followed by acid-hydrolysis to

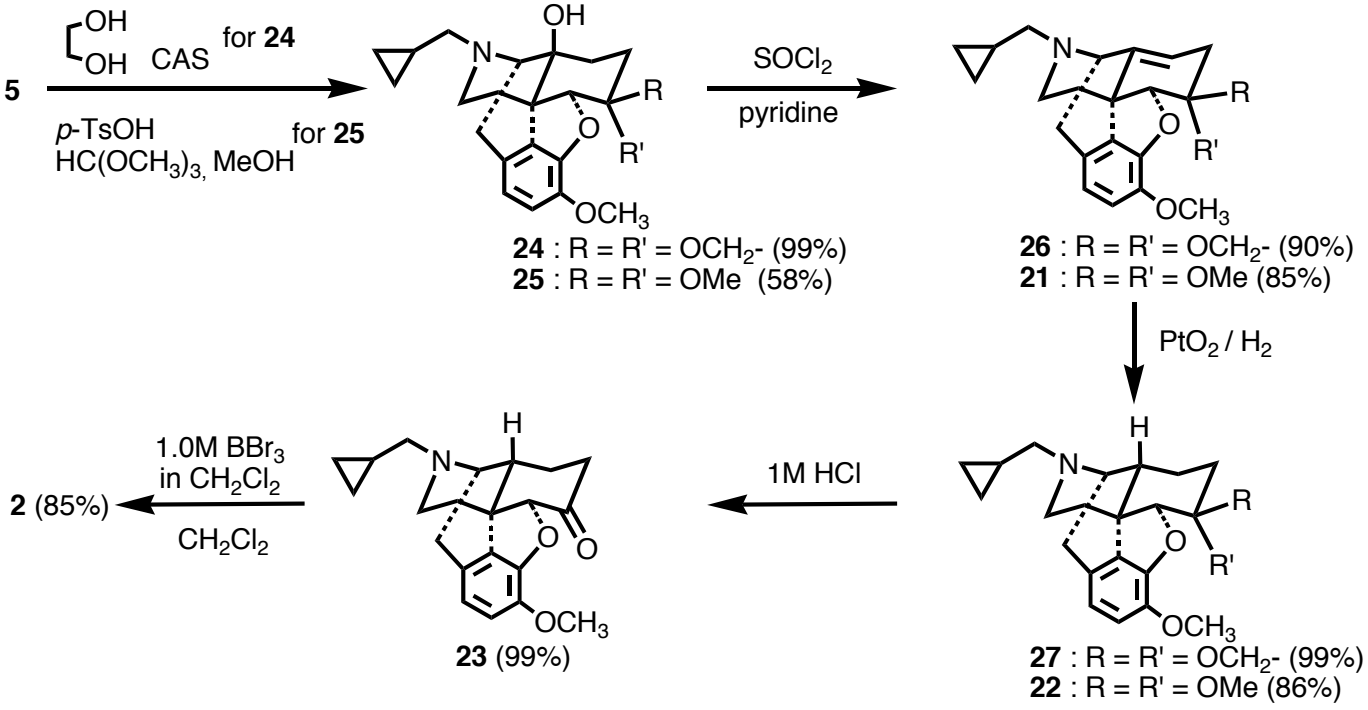


Scheme 4

give **23**. However, both methods did not afford **19**, **20** or **21** in high yield and consequently the total yield of **23** was low.

Because C6, C7, C8, and C14 of dienol ether (**16**) (Scheme 3) are sp^2 carbons and four carbons may exist in the same plane, ring strain of **16** may be much less than that of naltrexone methyl ether (**5**).[10] As hydrolysis of **16** to afford sp^3 carbons may result in compounds (**19**) and (**20**) with strong ring strain, compound (**16**) may resist acid hydrolysis, which might demand strong acid condition for hydrolysis of **16** and cause the decomposition by opening the 4, 5-epoxide ring of **16**. Once the sp^2 carbon in **16** (enol group) was converted to sp^3 carbon (acetal group) by treatment with mercuric acetate to give dimethyl acetal (**21**) followed by reduction of the double bond to afford **22**, the yield of hydrolysis of **22** was improved by inhibiting the ring-opening of the 4, 5-epoxide like the ring-opening of **8**. This fact was supported by the fact that the 14-hydroxy group accelerated enolization of 6-carbonyl.

Based on the above discussion, we adopted a new reaction route as shown in Scheme 5. The 6-carbonyl (sp^2) of naltrexone methyl ether (**5**) was converted to 1, 3-dioxorane (sp^3) (acetal, **24**) with ethylene glycol in 99% yield, which was dehydrated with thionyl chloride in pyridine at room temperature to afford compound (**26**) in 90% yield. The objective dehydration was easily attained by the conversion of carbonyl (sp^2) to acetal (sp^3 carbon). The method also led to removal of the intramolecular interaction between 6-carbonyl and 14-OH. Then, the double bond of acetal (**26**) was reduced with PtO_2 under hydrogen to give the 14-deoxy derivative (**27**) in 99% yield. Finally, the acid hydrolysis of **27** gave 14-deoxy compound (**23**) in 99% yield. The total isolated yield from naltrexone (**1**) to objective compound (**23**) was 86 % in 5 steps. Furthermore, **23** was demethylated with BBr_3 to give the aimed compound (**2**) in 85 % yield.



Scheme 5

Dimethyl acetal protection of 6-carbonyl (**5**) with trimethyl orthoformate was also examined. The yield (ca 60%) of dimethyl acetal (**25**) was lower than that (99%) of **24** because of the formation of methyl enol ether (**15**).

This reaction route is characterized as follows: (1) conversion of 6-carbon (sp^2) of ketone (**5**) to acetal (sp^3) inhibits the decomposition reaction by enolization, (2) the acetal protection of 6-carbonyl also promotes the dehydration of 14-OH by removal of the interaction between 14-OH and 6-carbonyl, (3) use of a toxic reagent such as mercuric acetate was not required, and (4) the procedure is convenient and high yield of the objective product is attained.

Naltrexone (**1**) is the only readily available nonnarcotic 4, 5-epoxymorphinan compound derived from natural product. The naltrexone derivatives possessing 14-OH mainly show antagonist activity because of the equatorial orientation of the cyclopropylmethyl group by the intramolecular hydrogen bond between 14-hydroxyl and the lone pair electron of 17-nitrogen. Design and synthesis of a new message part are important to create subtype selective agonists in the opioid field. The new established route to 14-deoxynaltrexone (**2**) from naltrexone (**1**) by use of an acetal intermediate led to high total yield and will afford wide possibilities to transform various derivatives of readily available naltrexone. Therefore, the present established method can be concluded to be a useful reaction route.

EXPERIMENTAL

Melting points were measured on a YAZAWA BY-10 and are uncorrected. Spectral measurements were recorded on a JMS AX-505HA or a JMS-700MAStation mass spectrometer (for MS), and on a Varian VXR-300, a Unity-Inova-600 spectrometer (for ^{1}H and ^{13}C NMR) in chloroform-*d* ($CDCl_3$). TLC was carried out on a Merck silica gel 60 F_{254}. The spots were visualized under UV light (254 nm) or by charring with molybdophosphoric acid (4% H_2SO_4, 0.85% phosphoric acid, and 0.25% molybdic acid in water). Column chromatography was performed on Silica Gel 60N (spherical, neutral. Kanto Chemical Co., Inc.). Elemental analyses were performed on an MT-5 elemental analyzer (Yanaco). Infrared spectra were recorded using by an FT/IR-460 Plus (JAS.Co.) with KBr.

17-(Cyclopropylmethyl)-4, 5α-epoxy-14-hydroxy-3-methoxy-6-(1,3-dioxolan-2-yl)morphinan (24).

To the solution of **5** (1g, 2.81 mmol) in toluene (80 mL) were added camphor-10-sulfonic acid (980 mg, 4.22 mmol) and ethylene glycol (4 mL, 74.2 mmol), and the whole was stirred under reflux using Dean-Stark apparatus overnight. The $NaHCO_3$ powders were added to the reaction mixture and the solution was concentrated. The residue was dissolved in $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ aqueous and with brine, and dried with Na_2SO_4. The organic layer was concentrated to give a white solid. The solid was crystallized from AcOEt and a white crystal of **24** (1.11 g, 99%) was obtained. **24**: mp 209-210.5 °C; IR (KBr) ν cm^{-1}; 3311, 1617, 1504, 1100-1200; MS (FAB) *m/z*: 400[M+H]$^+$. ^{1}H NMR

($CDCl_3$, 600 MHz) δ: 0.09 (2H, m, H-20), 0.50 (2H, d, H-19), 0.81 (1H, m, H-18), 1.42 (1H, dd, H-8a, *J* = 12.0, 3.0 Hz), 1.49 (1H, m, H-16a), 1.53 (2H, m, H-15), 2.10 (1H, ddd, H-7a, *J* = 12.0, 4.0 Hz), 2.21 (1H, dd, H-8b, *J* = 12.0, 4.0 Hz), 2.24 (1H, m, H-16a), 2.34 (2H, m, H-17), 2.56 (1H, d, H-10a, *J* = 18 Hz), 2.58 (1H, ddd, H-7b, *J* = 12, 3, Hz), 2.99 (1H, d, H-10b, *J* = 18 Hz), 3.05 (1H. m. H-9), 3.76, 3.87, 4.00, 4.17 (each 1H, dd, acetal, *J* = 13,0. 6,0 Hz), 3.84 (3H, s, OMe), 4.54 (1H, s, H-5), 6.56 (1H, d, H-2, *J* = 8.0 Hz), 6.71 (1H, d, H-1, *J* = 8.0 Hz); *Anal*. Calcd for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.10; H, 7.39; N, 3.66.

17-(Cyclopropylmethyl)-4, 5α-epoxy-14-hydroxy-3-methoxy-6-dimethylacetalmorphinan (25).

To the solution of **5** (2g, 5.65 mmol) in MeOH (34 mL) were added trimethyl orthoformate (3.1mL, 28.1 mmol) and *p*-toluenesulfonic acid monohydrate (1.28 g, 6.73 mmol), and the whole was stirred under reflux using Dean-Stark apparatus for 5 h. The $NaHCO_3$ powders were added to the reaction mixture and the solution was concentrated. The residue was dissolved in AcOEt. The organic layer was washed with saturated $NaHCO_3$ aqueous and with brine, and dried with Na_2SO_4. The organic layer was evaporated *in vacuo* and the residue was purified with silica gel column chromatography ($CHCl_3$: MeOH 10: 1) to give **25** (1.21 g, 58 %) as a syrup. **25**: MS (EI) *m/z*: 401$[M]^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.40 (2H, m, H-20), 0.60 (2H, d, H-19), 0.75 (1H, H-18), 1.75 (2H, m, H-15a), 1.95 (1H, m, H-15b), 2.10 (1H, H-7a), 2.45 (2H, H-17), 2.56 (2H, H-7b), 2.80 (1H, H-10a), 2.82 (2H, H-16a), 2.85 (1H, H-16b), 3.75 (1H, m, H-9), 3.30 (3H, s, OMe), 3.55 (3H, s, OMe), 3.85 (3H, s, OMe), 4.65 (1H, s, H-5), 6.65 (1H, d, H-2), 6.75 (1H, d, H-1).

17-(Cyclopropylmethyl)-4, 5α-epoxy-3-methoxy-6-(1,3-dioxolan-2-yl)-8,14-dehydromorphinan (26).

To the solution of **24** (1 g, 2.5 mmol) in pyridine (20 mL) was added thionyl chloride (1.2 mL, 15.9 mmol) at 0°C and the mixture was stirred at rt for 4 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous and extracted with AcOEt (80, 60 and 60 mL). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated to give **26** as a brown crystal (861 mg, 90%). **26**: mp 156-160°C; IR (KBr) ν cm^{-1}; 2942, 1637, 1503, 1100-1200; MS (FAB) *m/z*: 382 $[M+H]^+$. ^1H NMR ($CDCl_3$, 600 MHz) δ: 0.10 (2H, m, H-20), 0.50 (2H, m, H-19), 0.86 (1H, m, H-18), 1.76 (1H, ddd, H-15a, *J* = 12.0, 4.0 Hz), 1.98 (1H, ddd, H-15b, *J* = 12.0, 4.0 Hz), 2.06 (1H, dd, H-7a, *J* = 16.0, 6.5 Hz), 2.40 (2H, m, H-17), 2.43 (1H, dd, H-7b, *J* = 16.0, 2.0 Hz), 2.57 (1H, ddd, H-16a, *J* = 12.0, 4.0 Hz), 2.66 (1H, dd, H-10a, *J* = 18.0, 7.0 Hz), 2.79 (1H, dd, H-16b, *J* = 12.0, 4.0 Hz), 3.10 (1H, d, H-10b, *J* = 18.0 Hz), 3.73, 3.84, 3.86, 4.21 (each 1H, dd, acetal), 3.82 (3H, s, OMe), 3.83 (1H, m, H-9), 4.62 (1H, s, H-5), 5.46 (1H, dd, H-8, *J* = 6.5, 2.0 Hz), 6.55 (1H, d, H-2, *J* = 8.0 Hz), 6.66 (1H, d, H-1, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 3.8 (C-20, 19), 9.3 (C-18), 27.5 (C-10), 32.7 (C-7), 36.0 (C-15), 44.1 (C-16), 46.3 (C-13), 56.7 (OMe), 58.9 (C-9), 59.0 (C-17), 65.3, 66.6 (acetal), 93.1 (C-5), 108.0 (C-6), 113,0 (C-8), 113.6 (C-1), 119.2 (C-2); HRMS calcd. for $[M+H]^+$: 382.2018, found: 382.2011.

17-(Cyclopropylmethyl)-4, 5α-epoxy-3-methoxy-6-dimethylacetal-8,14-dehydromorphinan (21).

Synthesis from **25**: To the solution of **25** (33 mg, 81.2 μmol) in pyridine (1 mL) was added thionyl chloride (37.5 μL, 0.515 mmol) at 0°C and the mixture was stirred at rt for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous and extracted with AcOEt (10, 6 and 4 mL). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated to give **21** as a brown syrup (26 mg, 85%).

Synthesis from **16**: To the solution of **16** (100 mg, 0.285 mmol) in MeOH (2.9 mL) was added 2.9 mL MeOH solution of $(AcO)_2Hg$ (182 mg, 0.57 mmol) and the mixture was stirred under reflux for 2.5 h. After cooling, 3 M NaOH was added under ice-cooling, and the whole was stirred for 0.5 h at rt. $NaBH_4$ (190 mg, 5 mmol) was added to the reaction mixture. The mixture was stirred for 0.5 h and was extracted with $CHCl_3$ (10, 8 and 4 mL). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated *in vacuo*. The residue was purified with silica gel column chromatography ($CHCl_3$: MeOH 20:1) to give **21** (56.6 mg, 52%) as a syrup.

21: IR (film)ν cm^{-1}; 2941, 1605, 1499; MS (EI) *m/z*: 384 $[M+H]^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.15 (2H, m, H-20), 0.55 (2H, m, H-19), 0.80 (1H, m, H-18), 1.75 (1H, ddd, H-15a), 2.00 (1H, ddd, H-15b), 2.35 (1H, dd, H-7a), 2.40 (2H, m, H-17), 2.50 (1H, dd, H-7b), 2.65 (1H, m, H-16a), 2.70 (1H, dd, H-10a), 2.85 (1H, dd, H-16b), 2.90 (3H, s, OMe), 3.15 (1H, d, H-10b), 3.50 (3H, s, OMe), 3.85 (3H, s, OMe), 3.85 (1H, m, H-9), 4.65 (1H, s, H-5), 5.40 (1H, dd, H-8), 6.55 (1H, d, H-2), 6.70 (1H, d, H-1); HRMS calcd. for $[M+H]^+$: 384.2175, found: 384.2176.

17-(Cyclopropylmethyl)-4,5α-epoxy-3-methoxy-6-(1,3-dioxolan-2-yl)morphinan (27).

The solution of **26** (860 mg, 2.26 mmol) in methanol (20 mL) was stirred at rt with PtO_2 (94 mg, 0.414 mmol) under an atmospheric pressure of hydrogen overnight. The reaction mixture was filtered with a celite pad for removing PtO_2 and the organic layer was concentrated to give a solid. The solid was crystallized from MeOH to give **27** (861 mg, 99%). **27**: mp 150-151°C; IR (KBr) ν cm^{-1}; 1615, 1503, 1100-1200; MS (FAB) *m/z*: 384 $[M+H]^+$. ^1H NMR ($CDCl_3$, 600 MHz) δ: 0.12 (2H, m, H-20), 0.50 (2H, d, H-19, *J* = 8.0 Hz), 0.86 (1H, m, H-18), 1.12 (1H, dddd, H-8a, *J* = 12.0, 3.0 Hz), 1.50 (1H, d, H-8b, *J* = 12.0 Hz), 1.53 (1H, dd, H-7a, *J* = 12.0, 4.0 Hz), 1.63 (1H, ddd, H-7b, *J* = 12.0, 4.0, 3.0 Hz), 1.67 (1H, dd, H-15a, *J* = 12.0, 4.0 Hz), 1.91 (1H, m, H-15b), 2.14 (1H, dd, H-16a, *J* = 12.0 Hz), 2.27 (1H, m, H-14), 2.33 (1H, d, H-10a, *J* = 18.0 Hz), 2.38 (1H, m, H-17a), 2.48 (1H, m, H-17b), 2.76 (1H, dd, H-16b), 2.87 (1H, d, H-10b, *J* = 18.0 Hz), 3.40 (1H, m, H-9), 3.76, 3.86, 4.01, 4.16 (each 1H, dd, acetal, *J* = 12.0, 7.0 Hz), 3.84 (3H, s, OMe), 4.46 (1H, s, H-5), 6.57 (1H, d, H-2, *J* = 8.0 Hz), 6.70 (1H, d, H-1, *J* = 8.0Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 3.8 (C-20), 4.0 (C-19), 9.3 (C-18), 20.7 (C-10), 22.4 (C-8), 33.3 (C-7), 36.3 (C-15), 42.8 (C-14), 44.1 (C-13), 45.6 (C-16), 56.5 (OMe), 57.2 (C-9), 59.8(C-17), 64.9, 66.4 (acetal), 94.4 (C-5), 108.6 (C-6), 113.5 (C-1), 118.6 (C-2), 142.2 (C-3), 146.5 (C-4); *Anal*. Calcd for $C_{23}H_{29}NO_4 \cdot 0.5H_2O$: C, 70.38; H, 7.70; N, 3.57. Found: C, 70.38; H, 7.58; N.3.64.

17-(Cyclopropylmethyl)-4,5α-epoxy-3-methoxy-6-dimethylacetalmorphinan (22).

Reaction with PtO_2 : The solution of **21** (20.7 mg, 54 μmol) in methanol (1 mL) was stirred at rt with PtO_2 (30 mg, 0.133 mmol) under an atmospheric pressure of hydrogen overnight. The reaction mixture was filtered with a celite pad for removing PtO_2 and the organic layer was concentrated to give **22** (17.8 mg, 86%) as a syrup.

Reaction with Pd-C: The solution of **21** (4.4 mg, 11.5 μmol) in methanol (0.5 mL) was stirred at rt with 10% Pd-C (16.3 mg) under an atmospheric pressure of hydrogen overnight. The treatment of the reaction mixture was similarly carried out as that with PtO_2 to give **22** (4.3 mg, 98%) as a syrup.

22: IR (film) ν cm^{-1}; 2932, 1605, 1503; MS (FAB) *m/z*: 386 $[M+H]^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.10 (2H, m, H-20), 0.50 (2H, d, H-19), 0.80 (1H, m, H-18), 1.55 (1H, dddd, H-8a), 1.70 (1H, d, H-8b), 1.85 (1H, m, H-7a), 1.90 (1H, m, H-7b), 1.95 (1H, m, H-15a), 2.20 (1H, m, H-15b), 2.40 (1H, m, H-14), 2.45 (1H, m, H-10a), 2.48 (1H, m, H-17a), 2.58 (1H, m, H-17b), 2.75 (1H, dd, H-16b), 2.85 (1H, d, H-10b), 3.25 (3H, s, OMe), 3.30 (3H, s, OMe), 3.40 (1H, m, H-9), 3.85 (3H, s, OMe), 4.45 (1H, s, H-5), 6.55 (1H, d, H-2), 6.70 (1H, d, H-1); HRMS calcd. for $[M+H]^+$: 386.2331, found: 386.2321.

17-(Cyclopropylmethyl)-4,5α-epoxy-3-methoxy-6-oxo-morphinan (23).

Synthesis from **27**: The solution of **27** (50 mg, 0.13 mmol) in 1 M HCl (2 mL) was stirred under reflux for 1.5 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous, and extracted with AcOEt (10 mL). The organic layer was dried with Na_2SO_4, and evaporated *in vacuo*. The residue was purified with silica gel column chromatography ($CHCl_3$: MeOH 10:1) to give **23** (43.7 mg, 99%) as a syrup.

Synthesis from **22**: The solution of **22** (10 mg, 26.7 μmol) in MeOH (0.1 mL) 1 M HCl (2 mL) was stirred at rt for 1.5 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous, and extracted with AcOEt (10, 4 and 3 mL). The organic layer was dried with Na_2SO_4, and evaporated to afford **23** (8.2 mg, 90%) as a syrup.

23: IR (film) ν cm^{-1}; 1727, 1629, 1503; MS (FAB) *m/z*: 340 $[M+H]^+$. ^1H NMR ($CDCl_3$, 600 MHz) δ: 0.10 (2H, m, H-20), 0.50 (2H, d, H-19, *J* = 7.0 Hz), 0.84 (1H, m, H-18), 1.22 (1H, dddd, H-8a, *J* = 12.0, 3.0 Hz), 1.77 (1H, d, H-15a, *J* = 10.0 Hz), 1.80 (1H, dddd, H-8b, *J* = 12.0, 3.0 Hz), 2.06 (1H, dd, H-16a, *J* = 10.0, 8.0 Hz), 2.11 (1H, d, H-15b, *J* = 10.0 Hz), 2.28 (1H, d, H-10a, *J* = 18.0 Hz), 2.33 (1H, m, H-17a), 2.35-2.39 (2H, broad, H-7), 2.46 (1H, dd, H-17b, *J* = 12.0, 6.0 Hz), 2.59 (1H, m, H-14, *J* = 10.0, 4.0 Hz), 2.78 (1H, d, H-16b, *J* = 8.0 Hz), 2.88 (1H, d, H-10b, *J* = 18.0 Hz), 3.44 (1H, m, H-9), 3.86 (3H, s, OMe), 4.62 (1H, s, H-5), 6.57 (1H, d, H-2, *J* = 8.0 Hz), 6.65 (1H, d, H-1, *J* = 8.0 Hz) ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 3.7 (C-20), 3.9 (C-19), 9.4 (C-18), 20.6 (C-10), 25.7 (C-8), 35.5 (C-16), 40 2 (C-7), 42.5 (C-14), 45.2 (C-15), 47.4 (C-13), 56.8 (OMe), 56.9 (C-9), 59.8 (C-17), 91.5 (C-5), 114.5 (C-1), 119.7 (C-2), 142.8 (C-3), 207.9 (C=O); HRMS calcd. for $[M+H]^+$; 340.1913, found: 340.1898.

17-(Cyclopropylmethyl)-4,5α-epoxy-6-oxo-morphinan (2).

To the solution of **23** (35 mg, 0.0876 mmol) in dry CH_2Cl_2 (1.8 mL) was added dropwise a 1.0 M solution of BBr_3 in dry CH_2Cl_2 (0.26 mL, 0.262 mmol) at 0°C under Ar. After stirring for 0.5 h at 0°C, the reaction mixture was quenched with 6% NH_4OH (6 mL) and extracted with $CHCl_3$ (10, 5 and 5 mL). The organic layer was washed with brine (5 mL), dried with Na_2SO_4, and evaporated *in vacuo*. The residue was purified with silica gel column chromatography ($CHCl_3$: MeOH 10:1) to give **2** (24.3 mg, 85 %) as a solid. **2**: IR (KBr) ν cm^{-1}; 1725, 1617, 1507; MS (FAB) *m/z*: 326 $[M+H]^+$. ^1H NMR ($CDCl_3$, 600 MHz) δ: 0.14 (2H, d, H-20, *J* = 4.0 Hz), 0.52 (2H, d, H-19, *J* = 8.0 Hz), 0.93 (1H, m, H-18), 1.22 (1H, m, H-8a), 1.76 (1H, ddd, H-15a, *J* = 12.0, 4.0, 2.0 Hz), 1.83 (1H, dddd, H-8b, *J* = 12.0, 8.0, 4.0 Hz), 2.17 (1H, ddd, H-16a, *J* = 12.0, 11.0, 4.0 Hz), 2.23 (1H, ddd, H-15a, *J* = 12.0, 11.0, 4.0 Hz), 2.35 (1H, d, H-10a, *J* = 18.0 Hz), 2.36 (2H, m, H-7), 2.43 (1H, dd, H-17a, *J* = 13.0, 7.0 Hz), 2.55 (1H, dd, H-17b, *J* = 13.0, 6.0 Hz), 2.75 (1H, m, H-14), 2.89 (1H, d, H-10b, *J* = 18.0 Hz), 2.93 (1H, ddd, H-16b, *J* = 12.0, 4.0 Hz), 3.59 (1H, m, H-9), 4.65 (1H, s, H-5), 6.55 (1H, d, H-2, *J* = 8.0 Hz), 6.68 (1H, d, H-1, *J* = 8.0 Hz) ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 3.9 (C-20), 4.1 (C-19), 8.7 (C-18), 20.6 (C-10), 25.4 (C-8), 34.9 (C-15), 40.1 (C-7), 41.7 (C-14), 45.4 (C-16), 47.3 (C-13), 56.9 (C-9), 59.6 (C-17), 91.3 (C-5), 117.9 (C-1), 120.1 (C-2), 208.9 (C=O); HRMS calcd. for $[M+H]^+$; 326.1756, found: 326.1750.

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