The First Example of the Stereoselective Synthesis of 7β-Carbamoyl-4,5α-epoxymorphinan *via* a Novel and Reactive γ-Lactone

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7β-Carbamoyl-4,5α-epoxymorphinans 5 were stereoselectively synthesized from the 7α-carboxylate intermediate 3 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and amines under reflux conditions in mesitylene *via* a novel and reactive γ-lactone 7. These were the first examples of the stereoselective syntheses of 7β-substituted 4,5α-epoxymorphinans. The mechanism of the reaction process was elucidated as follows: 1) epimerization of 7α-carboxylate 3, 2) intramolecular lactonization of 7β-carboxylate 6, and 3) aminolysis of the resultant γ-lactone 7. The aminolysis of the isolated reactive γ-lactone 7 with allylamine and the alcoholysis with MeOH in the presence of $NaBH_4$ proceeded at room temperature. The γ-lactone 7 can be a useful intermediate for the preparation of 7β-substituted 4,5α-epoxymorphinans that would be potent selective δ opioid receptor ligands. The stereoselective syntheses of the 7α-carbamoyl-4,5α-epoxymorphinans 9 from 7α-carboxylate 3 *via* 7α-carboxylic acid were also successful.

Key words 7β-substituted 4,5α-epoxymorphinan; intramolecular lactonization; γ-lactone; aminolysis

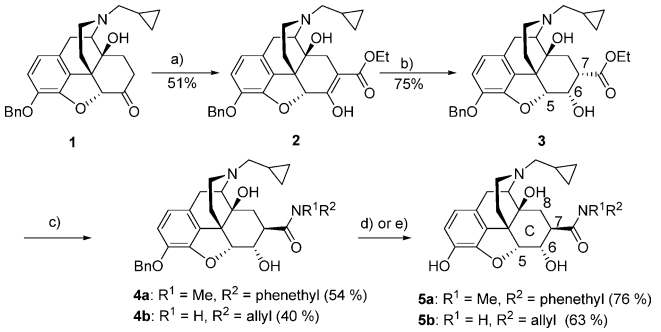
During the course of our research directed toward the development of selective opioid receptor ligands, we focused on the 7β-carbamoyl-4,5α-epoxymorphinans. To the best of our knowledge, though several synthetic methods of 7α-monosubstituted or 7,7-disubstituted 4,5α-epoxymorphinans are known,[3—7)] there were no reports on the stereoselective syntheses of the 7β-substituted derivatives. Portoghese *et al.* reported that thermodynamically less favored 7β-substituted 4,5α-epoxymorphinan detected only by TLC or liquid chromatography/mass spectrometry (LC/MS) could not be isolated.[4)] Herein, we report the first stereoselective synthesis of 7β-carbamoyl-4,5α-epoxymorphinan from 4,5α-epoxymorphinan-7α-carboxylate and its reasonable mechanism, and also report the stereoselective synthesis of 7α-carbamoyl-4,5α-epoxymorphinan from the same substrate.

Results and Discussion

Chemistry Naltrexone 3-*O*-benzyl ether (**1**) was converted to ethyl 7α-carboxylate **3** *via* compound **2** by heating in the presence of sodium hydride in diethyl carbonate as a solvent followed by reduction using $NaBH_4$ (Chart 1). The NMR spectra showed ethyl 7-carboxylate **2** existed in only the enol form.[7)] Compound **3** was refluxed in mesitylene in the presence of DBU and amines to give the 7-carboxamides **4**. The desired compounds **5** were obtained by the debenzylation[8)] of the corresponding 7-carboxamides **4**.

The stereochemistry of compounds **3** and **5** was confirmed by NMR spectral analyses. For compound **3**, a positive nuclear Overhauser effect (NOE) between the 5β-proton and the 7-proton was observed, but not between the 6-proton and 8α-proton. On the other hand, positive NOEs both between the 5β-proton and the 7-proton and between the 6-proton and the 8α-proton were observed on the 6-epimer of compound **3**, which was obtained by the reduction of compound **2** as a by-product. These observations suggested that compound **3** would possess the 6α-hydroxyl and the 7α-ethoxycarbonyl groups. On compound **5b**, a positive NOE between the 6-proton and the 8β-proton was observed, and the $J_{6,7}$ coupling constant was 12.0 Hz. These observations suggested that **5b** would possess the 6α-hydroxyl and the 7β-carbamoyl groups with the boat form of the C-ring. Moreover, the chemical shift of the 7α-proton of **5b** was observed at 1.98—2.06 ppm which was at a higher field than that of the α-methyne proton of the normal carboxamide compound.[9)] The higher chemical shift caused by the shielding effect of the benzene ring supported the stereostructure of **5b** as 6α-hydroxy-7β-carboxamide.[10)]

The mechanism for the conversion of the 7α-carboxylate **3** into the 7β-carboxamide **4** was speculated as follows (Chart 2). In general, the direct aminolysis of esters required a reaction temperature higher than 200 °C or high pressure.[11,12)] Therefore, the direct aminolysis of the 7α-carboxylate **3′** could not occur. On the other hand, a harsh basic condition could deprotonate from the 7 position of the 7α-carboxylate **3′** to reach an equilibrium between the 7α-carboxylate **3′** and the 7β-carboxylate **6**. The resulting 7β-carboxylate **6** (chair) should be converted to the γ-lactone **7**, because the 7β-substituent would be closed to the 14-hydroxyl group in the chair form of the C-ring. Examples of the intramolecular reaction between the 7β- and the 14-substituents have been reported.[7,13,14)] The right shift of the equilibrium would allow the intramolecular formation of the γ-lactone **7** eliminating the alcohol (R^4OH) under the reaction conditions. The novel, strained, and reactive γ-lactone **7** could easily react with the



Reagents and conditions: a) NaH, $CO(OEt)_2$, 100 °C, b) $NaBH_4$, MeOH/MeCN, rt., c) *N*-methylphenethylamine for **4a**, allylamine for **4b**, DBU, mesitylene, reflux, d) H_2, Pd/C, AcOH, MeOH, rt. for conversion of **4a**, e) conc. HCl, AcOH, 80 °C for conversion of **4b**

Chart 1

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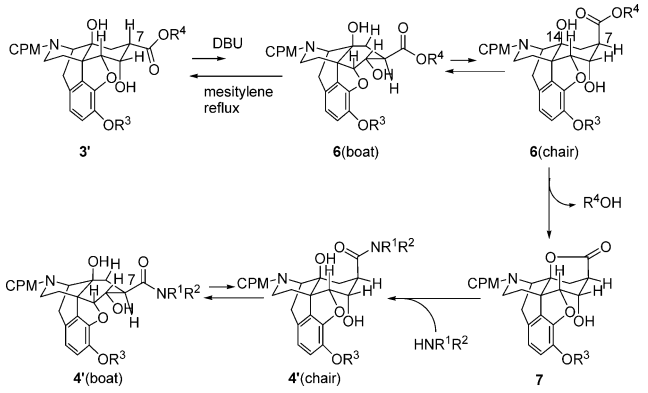


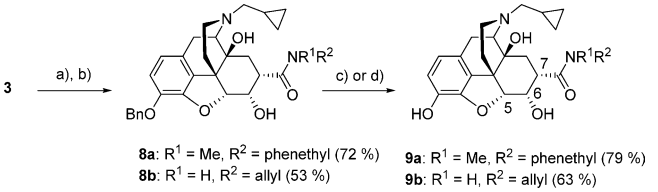
Chart 2. The Speculated Mechanism for the Conversion from 7α-Carboxylate **3**′ to 7β-Carbamoyl-4,5α-epoxymorphinan **4**′

CPM: cyclopropylmethyl.

amine to produce the 7β-carboxamide **4**′. Since the α-proton of the amides is generally less acidic than that of esters, the 7β-carboxamide **4**′ could be obtained without epimerization at the 7 position under the given reaction conditions. This proposed mechanism was confirmed to be reasonable by the following experiments and results. First, the reaction of **3**′ (R^3=Me, R^4=Et) with DBU in the absence of a primary or secondary amine gave the γ-lactone 7 (R^3=Me) in 71% yield. Second, the aminolysis of the isolated γ-lactone **7** (R^3=H) with allylamine proceeded at room temperature to give the corresponding carboxamides **5b** in 71% yield. Moreover, the reaction of the γ-lactone **7** (R^3=Bn) with MeOH in the presence of $NaBH_4$ for 1 h in accordance with Chadha's reaction conditions[15] gave the methyl 7β-carboxylate **6** (R^3=Bn, R^4=Me) in 54% yield with a trace amount of the reduced product, the triol derivative. On compound **6** (R^3=Bn, R^4=Me), the NOE between the 6-proton and the 8β-proton was observed, and the $J_{6,7}$ coupling constant was 11.5 Hz. Moreover, the chemical shift of the 7-proton of **6** (R^3=Bn, R^4=Me) was observed at 2.03—2.13 ppm which was at a higher field than that of the α-methyne proton of the normal ester compound.[9] These observations suggested that **6** (R^3=Bn, R^4=Me) would possess the 6α-hydroxyl and the 7β-methoxycarbonyl groups with the boat form of the C-ring. These observations strongly supported the occurrence of the reactive γ-lactone **7** as an intermediate.

The 7α-carbamoyl-4,5α-epoxymorphinans **9** were also synthesized as the 7-position epimers of compounds **5** (Chart 3). The 7α-carboxylic acid, which was derived by the hydrolysis of ethyl 7α-carboxylate **3**, was condensed with amines using propyl phosphoric acid anhydride[16] to give the 7α-carboxamides **8**. Compounds **8** were converted to the desired compounds **9** by the same debenzylation conditions. The stereochemistry of the 7α-carboxamide **9b** was confirmed by observation of a positive NOE between the 5β-proton and the 7β-proton.

Bioassay The opioid activities of the synthesized compounds were preliminarily evaluated using the mouse vas deference in which the δ opioid receptors are predominantly expressed. Of all the synthesized compounds, the 7β-carboxamide **5b** showed δ opioid receptor antagonistic activities.[17] The detail pharmacological properties of the 7α- and the 7β-carboxamides are now under investigation.



Reagents and conditions: a) LiOH aq, THF aq, 40 °C, b) *N*-methylphenethylamine for **8a**, allylamine for **8b**, $(PrPO_2)_3$, *N*-ethylmorpholine, DMF, rt., c) H_2, Pd/C, AcOH, MeOH, rt. for conversion of **8a**, d) conc. HCl, AcOH, 80 °C for conversion of **8b**

Chart 3

Conclusion

The 7β-carbamoyl-4,5α-epoxymorphinans **5** were stereoselectively synthesized from 7α-carboxylate **3** *via* the novel and reactive γ-lactone **7**. These were the first examples of the stereoselective syntheses of the 7β-substituted morphinans. The mechanism for the reaction process was elucidated. The aminolysis of the isolated reactive γ-lactone **7** with allylamine and the alcoholysis with MeOH in the presence of $NaBH_4$ proceeded at room temperature. The γ-lactone **7** could be a useful intermediate for the preparation of the 7β-substituted 4,5α-epoxymorphinans that would be potent selective δ opioid receptor ligands. The stereoselective syntheses of the 7α-carbamoyl-4,5α-epoxymorphinams **9** from the same substrate, 7α-carboxylate **3**, *via* the 7α-carboxylic acid were also successful.

Experimental

Genaral Nuclear magnetic resonance spectra were recorded on a Varian GEMINI 300 (300 MHz), JEOL JNM-AL 400 (400 MHz), Varian UNITY plus 500 (500 MHz), Varian INOVA 600 (600 MHz) spectrometers, and the chemical shifts are recorded as δ values (ppm) relative to tetramethylsilane (TMS). Infrared (IR) spectra were obtained using a JASCO FT/IR-5000 as KBr pellets or neat. Mass spectra were obtained on a JEOL JMS-D300, JEOL JMS-DX303, VG ZAB-HF, or micromass LCT (HP1100) (A-MS-4) instruments by applying an electric ionization (EI) method, a fast atom bombardment (FAB) ionization method, or an electrospray ionization (ESI) method. Elemental analyses were determined with a Heraeus CHN-ORAPID for carbon, hydrogen, and nitrogen, Yokogawa IC-7000 for sulfur. Elemental analyses were within 0.4% of the theoretical values. The progress of the reaction was determined on Merck silica Gel Art.5715 or Fuji Silycia NH Silica Gel. All the column chromatographies were carried out using Merck Silica Gel Art.9385, Merck Silica Gel Art.7734, Fuji Silycia Silica Gel DM-2010, or Fuji Silycia Silica Gel DM-2035. All the experiments were carried out under an argon atmosphere.

Ethyl 3-*O*-Benzyl-17-(cyclopropylmethyl)-4,5α-epoxy-6α,14β-dihydroxymorphinan-7α-carboxylate (3) Sodium hydride (60% in oil, 1.67 g, 41.8 mmol) was 3 times washed with pentane (10 ml) and suspended in diethyl carbonate (20 ml). To the stirred suspension was added dropwise a solution of 3-*O*-benzyl naltrexone (**1**) (5.65 g, 13.1 mmol) in diethyl carbonate (30 ml). Effervescence was observed. After refluxing for 1 h, the reaction mixture was cooled to room temperature. To the solution was added water at 0 °C, then 1 M hydrochloric acid was added until the solution was acidic. The resulting solution was basified with aqueous ammonia, and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 3.25 g (49%) of **2**. To a stirred solution of **2** (1.0 g, 1.99 mmol) in methanol (10 ml) and acetonitrile (20 ml) was added sodium borohydride (154 mg, 4.07 mmol) at room temperature, and the mixture was stirred for 1 h. The resulting solution was poured into a saturated sodium bicarbonate solution, and then extracted with ethyl acetate. The combined organic layer was washed with brine and dried over magnesium sulfate. After removing the solvent *in vacuo*, the residue was chromatographed on silica gel to give 756 mg (75%) of 3 and 21 mg (2%) of the 6-epimer of **3**. **3**: IR (KBr) cm^{-1}: 3390, 2940, 1736, 1501, 1451, 1251, 1184, 1048, 1000. NMR ($CDCl_3$, 500 MHz) δ: 0.08—0.18 (2H, m), 0.47—0.58 (2H, m), 0.79—0.88 (1H, m), 1.21 (3H, t, *J*=7.2 Hz), 1.45 (1H, br d, *J*=11.6 Hz), 1.72 (1H, dd, *J*=3.1, 13.3 Hz), 1.85 (1H, t, *J*=12.7 Hz), 2.12 (1H, dd, *J*=1.3, 3.0 Hz), 2.12—2.20 (1H, m), 2.22

(1H, dt, J=4.5, 12.1 Hz), 2.36 (1H, dd, J=6.4, 12.5 Hz), 2.39 (1H, dd, J=6.5, 12.5 Hz), 2.61—2.69 (2H, m), 3.03 (1H, d, J=18.3 Hz), 3.12 (1H, d, J=5.6 Hz), 3.13—3.18 (1H, m), 4.08 (1H, dq, J=7.2, 10.8 Hz), 4.13 (1H, dq, J=7.2, 10.8 Hz), 4.52—4.57 (1H, m), 4.67 (1H, d, J=6.0 Hz), 5.11 (1H, d, J=11.9 Hz), 5.18 (1H, d, J=12.1 Hz), 5.20 (1H, br s), 6.56 (1H, d, J=8.2 Hz), 6.73 (1H, d, J=8.2 Hz), 7.26—7.32 (1H, m), 7.32—7.38 (2H, m), 7.40—7.44 (2H, m). HR-MS (EI) m/z Calcd for $C_{30}H_{35}NO_6$: 505.2464. Found: 505.2448.

6-Epimer of **3**: IR (neat) cm^{-1}: 3406, 2932, 2832, 1729, 1499, 1448, 1379, 1278, 1263, 1183, 1046, 913, 729. NMR ($CDCl_3$, 500 MHz) δ: 0.07—0.16 (2H, m), 0.48—0.58 (2H, m), 0.78—0.88 (1H, m), 1.24 (3H, t, J=7.2 Hz), 1.44—1.50 (1H, m), 1.49 (1H, t, J=12.9 Hz), 1.84 (1H, dd, J=2.7, 13.0 Hz), 2.09 (1H, dt, J=3.5, 12.1 Hz), 2.22 (1H, dt, J=5.1, 12.6 Hz), 2.36 (2H, d, J=6.6 Hz), 2.56 (1H, dd, J=5.8, 18.5 Hz), 2.62 (1H, dd, J=4.5, 11.8 Hz), 3.01 (1H, d, J=18.5 Hz), 3.04—3.13 (2H, m), 3.65 (1H, dd, J=6.4, 11.3 Hz), 4.13 (2H, q, J=7.2 Hz), 4.51 (1H, d, J=6.4 Hz), 5.17 (1H, d, J=12.1 Hz), 5.23 (1H, d, J=12.1 Hz), 6.56 (1H, d, J=8.2 Hz), 6.76 (1H, d, J=8.2 Hz), 7.26—7.31 (1H, m), 7.33—7.38 (2H, m), 7.40—7.46 (2H, m). MS (EI) m/z 505.

Ethyl 17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14β-dihydroxy-3-*O*-methylmorphinan-7α-carboxylate (3′: R^3=Me, R^4=Et) The title compound was synthesized by the same procedure described above. IR (KBr) cm^{-1}: 3402, 2942, 2834, 1736, 1638, 1614, 1504, 1443, 1280, 1259, 1184, 1052, 1001. NMR ($CDCl_3$, 300 MHz) δ: 0.07—0.20 (2H, m), 0.48—0.59 (2H, m), 0.77—0.92 (1H, m), 1.21 (3H, t, J=7.1 Hz), 1.42—1.50 (1H, m), 1.73 (1H, dd, J=3.3, 13.4 Hz), 1.86 (1H, dd, J=12.1, 13.2 Hz), 2.11—2.29 (2H, m), 2.32 (1H, dd, J=1.2, 3.2 Hz), 2.36 (1H, dd, J=6.6, 12.9 Hz), 2.39 (1H, dd, J=6.6, 12.9 Hz), 2.58—2.72 (2H, m), 3.05 (1H, d, J=18.4 Hz), 3.11—3.21 (1H, m), 3.14 (1H, d, J=3.3 Hz), 3.85 (3H, s), 4.08 (1H, dq, J=7.1, 10.7 Hz), 4.13 (1H, dq, J=7.1, 10.7 Hz), 4.55—4.61 (1H, m), 4.69 (1H, d, J=6.0 Hz), 5.21 (1H, br s), 6.61 (1H, d, J=8.2 Hz), 6.70 (1H, d, J=8.2 Hz). HR-MS (EI) m/z Calcd for $C_{24}H_{31}NO_6$: 429.2151. Found: 429.2130.

17-(Cyclopropylmethyl)-4,5α-epoxy-3,6α,14β-trihydroxymorphinan-7β-(*N*-methyl-*N*-phenethyl)carboxamide·Methane Sulfonate (5a·CH_3SO_3H) To a stirred solution of **3** (201 mg, 0.4 mmol) in mesitylene (5 ml) were added DBU (0.5 ml, 3.3 mmol) and *N*-methylphenethylamine (1.2 ml, 8.2 mmol), and the mixture was then refluxed for 8.5 h. After cooling to room temperature, the reaction mixture was poured into 1 M hydrochloric acid. The aqueous layer was basified with saturated sodium bicarbonate solution, then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 128 mg (54%) of **4a**. A solution of **4a** (128 mg, 0.22 mmol) in methanol (5 ml) with acetic acid (24 μl, 0.52 mmol) was stirred for 14 h with 10% palladium charcoal (50% wet, 20 mg) under a hydrogen atmosphere (1 atm) at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to half the volume. The resulting solution was poured into a saturated sodium bicarbonate solution, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 82 mg (76%) of **5a**. To a stirred solution of **5a** in methanol was added dropwise methane sulfonic acid at 0 °C until the solution became acidic. Ethyl acetate was then added to the solution. The precipitated salt was filtered to give **5a**·CH_3SO_3H: IR (KBr) cm^{-1}: 3388, 1620, 1504, 1208, 1118, 1058. NMR (DMSO-d_6, 300 MHz) δ: 0.32—0.51 (2H, m), 0.52—0.73 (2H, m), 0.91—1.06 (1H, m), 1.14 (0.7H, dd, J=9.3, 14.8 Hz), 1.48 (0.3H, dd, J=9.5, 15.5 Hz), 1.58—1.72 (1H, m), 1.82 (0.7H, dd, J=8.4, 15.2 Hz), 1.96 (0.3H, dd, J=9.2, 15.0 Hz), 2.26—2.57 (3H, m), 2.30 (3.3H, s), 2.57—2.81 (2H, m), 2.62 (0.9H, s), 2.76 (2.1H, s), 2.83—3.12 (4H, m), 3.22—3.54 (3H, m), 3.78 (0.7H, d, J=6.6 Hz), 3.86 (0.3H, d, J=6.6 Hz), 4.23—4.35 (1H, m), 4.58 (0.7H, d, J=4.1 Hz), 4.60 (0.3H, d, J=4.4 Hz), 6.22 (0.7H, br s), 6.29 (0.3H, br s), 6.56 (0.3H, d, J=8.2 Hz), 6.62 (0.7H, d, J=8.2 Hz), 6.71 (0.3H, d, J=8.0 Hz), 6.80 (0.7H, d, J=8.0 Hz), 6.88—6.96 (1.3H, m), 7.14—7.32 (3.7H, m), 8.74 (1H, br s), 9.21 (0.3H, br s), 9.29 (0.7H, br s). MS (FAB) m/z 505 ($M+H^+$). *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot 1.1MeSO_3H \cdot 0.5H_2O$: C, 60.31; H, 6.74; N, 4.52; S, 5.70. Found: C, 60.07; H, 6.77; N, 4.66; S, 5.57.

17-(Cyclopropylmethyl)-4,5α-epoxy-3,6α,14β-trihydroxymorphinan-7β-(*N*-allyl)carboxamide·Methane Sulfonate (5b·CH_3SO_3H) A stirred solution of **4b** (131 mg, 0.25 mmol), which was synthesized from **3** (313 mg, 0.62 mmol) in 40% yield by the procedure described above, in concentrated hydrochloric acid (2 ml) and acetic acid (4 ml) was heated at 80 °C for 30 min. After cooling to room temperature, the reaction mixture was poured into cooled concentrated aqueous ammonia, then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 69 mg (63%) of **5b**: NMR ($CDCl_3$, 600 MHz) δ: 0.08—0.16 (2H, m), 0.49—0.57 (2H, m), 0.80—0.88 (1H, m), 1.61—1.70 (1H, m), 1.63 (1H, dd, J=5.0, 15.0 Hz), 1.88 (1H, dd, J=8.3, 15.0 Hz), 1.98—2.06 (1H, m), 2.22—2.34 (3H, m), 2.38 (1H, dd, J=6.3, 12.7 Hz), 2.53 (1H, dd, J=6.7, 18.6 Hz), 2.63—2.70 (1H, m), 3.04 (1H, d, J=18.6 Hz), 3.12 (1H, d, J=6.7 Hz), 3.58—3.64 (1H, m), 3.74—3.81 (1H, m), 4.44 (1H, dd, J=4.3, 12.0 Hz), 4.74 (1H, d, J=4.3 Hz), 4.99 (1H, dd, J=1.3, 10.2 Hz), 5.05 (1H, dd, J=1.3, 17.2 Hz), 5.62—5.70 (1H, m), 6.50 (1H, d, J=8.1 Hz), 6.71 (1H, d, J=8.1 Hz), 6.98 (1H, br s). To a stirred solution of **5b** in methanol was added dropwise methane sulfonic acid at 0 °C until the solution became acidic. Ethyl acetate was then added to the solution. The precipitated salt was filtered to give **5b**·CH_3SO_3H: IR (KBr) cm^{-1}: 3394, 1640, 1509, 1320, 1201, 1058. NMR (DMSO-d_6, 300 MHz) δ: 0.31—0.74 (4H, m), 0.91—1.08 (1H, m), 1.48—1.73 (2H, m), 1.86—2.03 (2H, m), 2.30 (3H, s), 2.34—2.50 (1H, m), 2.60—3.10 (4H, m), 3.21—3.70 (3H, m), 3.86 (1H, br d, J=6.6 Hz), 4.31 (1H, dd, J=4.3, 11.1 Hz), 4.56 (1H, d, J=4.4 Hz), 4.94—5.02 (1H, m), 5.05—5.14 (1H, m), 5.71 (1H, tdd, J=5.0, 10.2, 17.2 Hz), 6.22 (1H, br s), 6.54 (1H, d, J=8.1 Hz), 6.70 (1H, d, J=8.1 Hz), 7.94 (1H, br t, J=7.6 Hz), 8.75 (1H, br s), 9.24 (1H, br s). HR-MS (ESI) m/z Calcd for $C_{24}H_{30}N_2O_5$: 427.2233. Found: 427.2267.

3-*O*-Benzyl-17-(cyclopropylmethyl)-4,5α-epoxy-6α-hydroxymorphinan-7β,14β-carbolactone (7: R^3=Bn) To a stirred solution of **3** (300 mg, 0.59 mmol) in mesitylene (10 ml) was added DBU (0.62 ml, 4.1 mmol), and the mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into 1 M hydrochloric acid. The aqueous layer was basified with saturated sodium bicarbonate solution, then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 150 mg (55%) of **7** (R^3=Bn): IR (KBr) cm^{-1}: 3448, 2921, 1774, 1499, 1452, 1191, 1067, 1046, 953. NMR ($CDCl_3$, 300 MHz) δ: 0.08—0.17 (2H, m), 0.48—0.59 (2H, m), 0.85—0.96 (1H, m), 1.53—1.61 (1H, m), 1.85 (1H, dd, J=5.1, 12.2 Hz), 1.99 (1H, d, J=12.5 Hz), 2.27—2.41 (3H, m), 2.48—2.61 (3H, m), 2.72—2.82 (1H, m), 2.94 (1H, t, J=4.6 Hz), 3.23 (1H, d, J=18.3 Hz), 3.66 (1H, d, J=5.6 Hz), 4.40 (1H, dd, J=4.3, 6.5 Hz), 4.63 (1H, d, J=6.8 Hz), 5.13 (1H, d, J=12.0 Hz), 5.21 (1H, d, J=12.0 Hz), 6.66 (1H, d, J=8.3 Hz), 6.82 (1H, d, J=8.3 Hz), 7.30—7.45 (5H, m). HR-MS (EI) m/z Calcd for $C_{28}H_{29}NO_5$: 459.2046. Found: 459.2065.

17-Cyclopropylmethyl-4,5α-epoxy-6α-hydroxy-3-*O*-methylmorphinan-7β,14β-carbolactone (7: R^3=Me) The title compound was synthesized from **3′** (R^3=Me, R^4=Et) by the same procedure described above: IR (KBr) cm^{-1}: 3475, 2938, 1775, 1504, 1452, 1332, 1282, 1264, 1190, 1139. NMR ($CDCl_3$, 300 MHz) δ: 0.09—0.19 (2H, m), 0.48—0.60 (2H, m), 0.86—0.97 (1H, m), 1.55—1.62 (1H, m), 1.86 (1H, dd, J=5.3, 12.2 Hz), 1.99 (1H, d, J=12.0 Hz), 2.32—2.42 (3H, m), 2.52—2.61 (2H, m), 2.75—2.82 (2H, m), 2.96 (1H, t, J=4.6 Hz), 3.24 (1H, d, J=18.6 Hz), 3.67 (1H, d, J=5.4 Hz), 3.88 (3H, s), 4.45 (1H, dd, J=3.9, 6.6 Hz), 4.66 (1H, d, J=7.1 Hz), 6.69 (1H, d, J=8.2 Hz), 6.76 (1H, d, J=8.2 Hz). HR-MS (EI) m/z Calcd for $C_{22}H_{25}NO_5$: 383.1733. Found: 383.1742.

17-Cyclopropylmethyl-4,5α-epoxy-3,6α-dihydroxymorphinan-7β,14β-carbolactone (7: R^3=H) To a stirred solution of **7** (R^3=Me) (742 mg, 2.01 mmol) in dry dichloromethane (20 ml) was added dropwise a 1.0 M solution of boron tribromide in dry dichloromethane (29.0 ml, 29.0 mmol) at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was cooled to 0 °C. To the solution was added cooled saturated sodium bicarbonate solution, then stirred vigorously at 0 °C. The resulting mixture was separated and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 484 mg (68%) of **7** (R^3=H): IR (KBr) cm^{-1}: 3409, 2927, 1775, 1639, 1617, 1503, 1461, 1331, 1234, 1190, 1142, 1064, 1034, 959. NMR ($CDCl_3$, 300 MHz) δ: 0.07—0.20 (2H, m), 0.46—0.62 (2H, m), 0.84—0.98 (1H, m), 1.54 (1H, d, J=9.3 Hz), 1.85 (1H, dd, J=4.9, 12.4 HZ), 2.00 (1H, d, J=12.1 Hz), 2.33—2.44 (3H, m), 2.50—2.63 (2H, m), 2.73—2.84 (1H, m), 2.90—2.96 (1H, m), 3.23 (1H, d, J=18.4 Hz), 3.68 (1H, d, J=5.5 Hz), 4.42 (1H, dd, J=4.0, 6.5 Hz), 4.58—4.64 (1H, m), 6.60 (1H, d, J=8.2 Hz), 6.73 (1H, d, J=8.2 Hz). HR-MS (ESI) m/z Calcd for $C_{21}H_{23}NO_5$: 370.1654. Found: 370.1684.

17-(Cyclopropylmethyl)-4,5α-epoxy-3,6α,14β-trihydroxymorphinan-7α-(*N*-methyl-*N*-phenethyl)carboxamide·Methane Sulfonate (9a·CH_3SO_3H) To a stirred solution of **3** (170 mg, 0.4 mmol) in THF (4.5 ml) and distilled water (1.5 ml) was added 1 M lithium hydroxide solution (0.5 ml), then the mixture was heated at 40 °C for 5.5 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the

residual water was removed by evaporation with benzene. To a solution of the residue in DMF were added *N*-ethylmorpholine (0.36 ml, 2.8 mmol), *N*-methylphenethylamine (0.1 ml, 0.69 mmol), and a 50% solution of propyl phosphoric acid anhydride in DMF (0.3 ml, 0.51 mmol), then the mixture was stirred for 15 h at room temperature. The reaction mixture was poured into saturated sodium bicarbonate solution, then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 144 mg (72%) of **8a**. A solution of **8a** (144 mg, 0.24 mmol) in methanol (5 ml) with acetic acid (50 μl, 0.87 mmol) was stirred for 4.5 h with 10% palladium charcoal (50% wet, 36 mg) under a hydrogen atmosphere (1 atm) at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to half the volume. The resulting solution was poured into saturated sodium bicarbonate solution, then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 97 mg (79%) of **9a**. To a stirred solution of **9a** in methanol was added dropwise methane sulfonic acid at 0 °C until the solution became acidic. Ethyl acetate was then added to the solution. The precipitated salt was filtered to give **9a**·CH_3SO_3H: IR (KBr) cm^{-1}: 3390, 1616, 1502, 1459, 1329, 1211, 1194, 1059, 1042. NMR (DMSO-d_6, 300 MHz) δ: 0.35—0.75 (4H, m), 0.96—1.13 (1H, m), 1.30—1.50 (2H, m), 1.72—1.87 (1H, m), 2.30 (3.3H, s), 2.32—2.56 (2H, m), 2.64—2.75 (1H, m), 2.76—3.12 (5H, m), 2.83 (1.5H, s), 3.00 (1.5H, s), 3.17—3.75 (4H, m), 3.77—3.85 (1H, m), 3.86 (0.5H, d, J=6.0 Hz), 4.23 (0.5H, d, J=6.6 Hz), 4.48 (0.5H, d, J=5.5 Hz), 4.68 (0.5H, d, J=5.5 Hz), 6.11 (1H, br s), 6.48—6.64 (2H, m), 7.15—7.41 (5H, m), 8.77 (1H, br s), 8.96 (1H, br s). MS (free base, EI) m/z 504 (M^+). *Anal.* Calcd for $C_{30}H_{36}N_2O_5 \cdot 1.1MeSO_3H \cdot 0.8H_2O$: C, 59.79; H, 6.78; N, 4.48; S, 5.67. Found: C, 59.67; H, 6.84; N, 4.49; S, 5.78.

17-(Cyclopropylmethyl)-4,5α-epoxy-3,6α,14β-trihydroxymorphinan-7α-(*N*-allyl)carboxamide·Methane Sulfonate (9b·CH_3SO_3H) A stirred solution of **8b** (171 mg, 0.32 mmol), which was synthesized from **3** (319 mg, 0.63 mmol) in 53% yield by the procedure described above, in concentrated hydrochloric acid (2 ml) and acetic acid (4 ml) was heated at 80 °C for 30 min. After cooling to room temperature, the reaction mixture was poured into cooled concentrated aqueous ammonia, then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 87 mg (63%) of **9b**: NMR (free base, $CDCl_3$, 600 MHz) δ: 0.09—0.18 (2H, m), 0.49—0.59 (2H, m), 0.80—0.89 (1H, m), 1.41—1.48 (1H, m), 1.56 (1H, dd, J=2.3, 12.5 Hz), 1.97 (1H, t, J=15.4 Hz), 2.15—2.25 (2H, m), 2.34—2.42 (2H, m), 2.60—2.68 (1H, m), 2.61 (1H, dd, J=5.3, 18.5 Hz), 3.03 (1H, d, J=18.5 Hz), 3.03—3.08 (1H, m), 3.11 (1H, d, J=5.3 Hz), 3.79—3.84 (2H, m), 4.51 (1H, dd, J=1.9, 5.9 Hz), 4.61 (1H, d, J=5.9 Hz), 5.09 (1H, dd, J=1.3, 10.3 Hz), 5.14 (1H, dd, J=1.3, 17.2 Hz), 5.73—5.81 (1H, m), 6.09 (1H, br s), 6.36 (1H, br s), 6.53 (1H, d, J=8.1 Hz), 6.67 (1H, d, J=8.1 Hz). To a stirred solution of **9b** in methanol was added dropwise methane sulfonic acid at 0 °C until the solution became acidic. Ethyl acetate was then added to the solution. The precipitated salt was filtered to give **9b**·CH_3SO_3H: IR (KBr) cm^{-1}: 3370, 1638, 1547, 1506, 1463, 1427, 1329, 1196, 1050. NMR (DMSO-d_6, 300 MHz) δ: 0.35—0.74 (4H, m), 0.96—1.12 (1H, m), 1.37 (1H, br d, J=10.4 Hz), 1.62 (1H, br d, J=11.5 Hz), 1.78 (1H, t, J=12.8 Hz), 2.31—2.55 (2H, m), 2.33 (3.9H, s), 2.74—2.89 (2H, m), 2.95—3.08 (2H, m), 3.25—3.41 (2H, m), 3.59—3.71 (2H, m), 3.77—3.85 (1H, m), 4.31 (1H, dd, J=2.5, 5.5 Hz), 4.59 (1H, d, J=5.8 Hz), 4.96—5.03 (1H, m), 5.07—5.16 (1H, m), 5.74 (1H, tdd, J=4.9, 10.3, 17.2 Hz), 6.06 (1H, br s), 6.52 (1H, d, J=8.2 Hz), 6.61 (1H, d, J=8.2 Hz), 7.74 (1H, br t, J=5.9 Hz), 8.77 (1H, br s). MS (free base, EI) m/z 426 (M^+). *Anal.* Calcd for $C_{24}H_{30}N_2O_5 \cdot 1.3MeSO_3H \cdot 0.5H_2O$: C, 54.22; H, 6.51; N, 5.00; S, 7.44. Found: C, 54.45; H, 6.50; N, 4.95; S, 7.47.

Aminolysis of γ-Lactone 7 To a solution of **7** (R^3=H) (32 mg, 0.09 mmol) in dichloromethane (2 ml) was added allylamine (26 μl, 0.35 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into saturated sodium bicarbonate solution, then extracted with chloroform. The combined organic layer was dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 26 mg (71%) of **5b**.

Alcoholysis of γ-Lactone 7 To a solution of **7** (R^3=Bn) (50 mg, 0.11 mmol) in methanol (5 ml) was added sodium borohydride (9 mg, 0.24 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into saturated sodium bicarbonate solution, then extracted with chloroform/ethanol (3/1). The combined organic layer was dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed on silica gel to give 29 mg (54%) of **6** (R^3=Bn, R^4=Me) with a trace amount of triol derivative. **6** (R^3=Bn, R^4=Me): IR (KBr) cm^{-1}: 3392, 2922, 1741, 1504, 1454, 1282, 1173, 1047. NMR ($CDCl_3$, 400 MHz) δ: 0.08—0.16 (2H, m), 0.49—0.58 (2H, m), 0.77—0.89 (1H, m), 1.57—1.63 (1H, m), 1.71 (1H, dd, J=9.4, 14.8 Hz), 1.89 (1H, dd, J=8.8, 14.6 Hz), 2.03—2.13 (1H, m), 2.20—2.33 (3H, m), 2.38 (1H, dd, J=6.5, 12.6 Hz), 2.40 (1H, d, J=10.0 Hz), 2.57 (1H, dd, J=6.6, 18.3 Hz), 2.60—2.67 (1H, m), 3.04 (1H, d, J=18.3 Hz), 3.12 (1H, d, J=6.6 Hz), 3.68 (3H, s), 4.41 (1H, ddd, J=4.4, 10.0, 11.5 Hz), 4.70 (1H, d, J=4.2 Hz), 4.99 (1H, br s), 5.14 (1H, d, J=12.2 Hz), 5.23 (1H, d, J=12.2 Hz), 6.56 (1H, d, J=8.2 Hz), 6.78 (1H, d, J=8.2 Hz), 7.25—7.46 (5H, m). HR-MS (EI) m/z Calcd for $C_{29}H_{33}NO_6$: 491.2308. Found: 491.2278.

References and Notes

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17) The antagonist activity is expressed as IC_{50} ratio and pA_2. The IC_{50} ratio is calculated from the equation:

IC_{50} ratio = (IC_{50} value of the agonist in the presence of the antagonist)/(IC_{50} value of the agonist in the absence of the antagonist)

The pA_2 is calculated from the equation:

$pA_2 = -\log\{[\text{antagonist}]/(IC_{50}\text{ ratio} - 1)\}$

The assay was performed using morphine as the μ opioid receptor agonist, DPDPE as the δ opioid receptor agonist, and U-50,488H as the κ opioid receptor agonist. The IC_{50} ratio and pA_2 of 7β-carboxiamide **5b** against DPDPE was 5.2 and 8.1, respectively. The IC_{50} ratio against morphine or U-50,488H was not able to be determined because **5b** showed no antagonistic activities against the μ or κ opioid receptors.