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 NaBH4 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-carboxamyl-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.

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 NaBH4 (Chart 1). The NMR spectra showed ethyl 7α-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 7α-carboxamides 4. The desired compounds 5 were obtained by the debenzylation3) of the corresponding 7α-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 6,7-coupling constant was 12.0 Hz. These observations suggested that 5b would possess the 6α-hydroxyl and the 7β-carboxamyl 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-methylene 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 (R3OH) under the reaction conditions. The novel, strained, and reactive γ-lactone 7 could easily react with the

Reagents and conditions: a) NaH, CO(OE)2, 100 °C, b) NaBH4, MeOH/MeCN, rt., c) N-methylphenethylamine for 4a, allylamine for 4b, DBU, mesitylene, reflux, d) H2, 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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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′ (R1=Me, R4=Et) with DBU in the absence of a primary or secondary amine gave the γ-lactone 7 (R1=Me) in 71% yield. Second, the aminolysis of the isolated γ-lactone 7 (R1=H) with allylamine proceeded at room temperature to give the corresponding carboxamides 5b in 71% yield. Moreover, the reaction of the γ-lactone 7 (R1=H) with MeOH in the presence of NaBH4 for 1 h in accordance with Chadha’s reaction conditions[19] gave the methyl 7β-carboxylate 6 (R1=Me, R4=H) in 54% yield with a trace amount of the reduced product, the tril derivative. On compound 6 (R1=Me, R4=H), the NOE between the 6-proton and the 8β-proton was observed, and the J6,7 coupling constant was 11.5 Hz. Moreover, the chemical shift of the 7-proton of 6 (R1=Me, R4=H) was measured at 2.03—2.13 ppm which was at a higher field than that of the α-methylene proton of the normal ester compound.[9] These observations suggested that 6 (R1=Me, R4=H) 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 3 (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 debenzylization 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 α opioid receptors are predominantly expressed. Of all the synthesized compounds, the 7β-carboxamide 5b showed α opioid receptor antagonistic activities.[15] The detail pharmacological properties of the 7α- and the 7β-carboxamides are now under investigation.

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 NaBH4 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-epoxymorphinans 9 from the same substrate, 7α-carboxylate 3, via the 7α-carboxylic acid were also successful.

Experimental General 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-O-RAPID 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 Silicia NH Silica Gel. All the column chromatographies were carried out using Merck silica Gel Art.9385, Merck silica Gel Art.7734, Fuji Silicia NH Silica Gel. All the experiments were carried out under an argon atmosphere.

Ethyl 3-O-Benzyl-17-(cyclopropylmethyl)-4,5α-epoxy-6α,14β-dihydroxy morphinan-7β-carboxylate (3) Sodium hydride (60% in oil, 1.67 g, 41.8 mmole) 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 mmole) 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 mL 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 mmole) in methanol (10 ml) and acetic acid (20 ml) was added sodium borohydride (154 mg, 4.07 mmole) 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 (CDCl₃, 500 MHz) δ: 0.08—0.18 (2H, m), 0.47—0.58 (2H, m), 0.79—0.88 (1H, m), 1.21 (1H, t, J=7.2 Hz), 1.45 (1H, brd, 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

Reagents and conditions: a) LiOH aq, THF aq, 40°C, b) N-methylphosphonoylamine for 8a, allylamine for 8b, (PPh₃)₃P, N-ethylmorpholine, DME, rt. c) H₂, Pd/C, AcOH, MeOH, rt. for conversion of 8a, d) conc. HCl, AcOH, 80°C for conversion of 8b.
(1H, dd, 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, dd, J = 18.3 Hz), 3.12 (1H, dd, J = 5.6 Hz), 3.13—3.18 (1H, m), 4.08 (1H, dd, 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, dd, J = 6.0 Hz), 5.11 (1H, dd, J = 11.9 Hz), 5.18 (1H, dd, J = 12.1 Hz), 5.20 (1H, brs, 1H, J = 6.2 Hz), 5.2 (1H, dd, J = 8.2 Hz), 6.73 (1H, dd, J = 8.2 Hz), 7.26—7.32 (1H, m), 7.32—7.38 (2H, m), 7.40—7.44 (2H, m).

MS (EI) m/z: Caled for C_{19}H_{21}NO_4: 313.1486. Found: 313.1484.

(6-Epimethyl)-17-(carboxamide) 6α,14β-dihydroxy-3-α-methylphenom-15(3b)-ene (1H, d, 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, d, J = 3.1 Hz), 2.22 (1H, dd, J = 5.1, 12.6 Hz), 2.36 (1H, dd, 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, dd, 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, dd, J = 6.4 Hz), 5.17 (1H, dd, J = 12.1 Hz), 5.23 (1H, dd, J = 12.1 Hz), 6.56 (1H, dd, J = 8.2 Hz), 6.76 (1H, dd, 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: Caled for C_{20}H_{22}NO_4: 362.1560. Found: 362.1563.
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- methylprenylenamine (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 9a. A solution of 9a (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 89 mg (90%).

The residue was chromatographed on silica gel to give 26 mg (71%) of 9b. A solution of 9b (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 97 mg (79%) of 9b. 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 99 mg (87%).

Alcoholysis of γ-Lactone 7 A solution of 7 (R=2-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 26 mg (71%) of 5b.

The reaction was monitored by thin-layer chromatography. After a 60% yield of the isolated product, the reaction mixture was poured into ice-water 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 106 mg (79%) of 8b. A solution of 8b (106 mg, 0.24 mmol) in methanol (5 ml) containing acetic acid (5 µl, 0.08 mmol) was stirred with a 50% solution of propyl phosphoric acid anhydride in DMF (0.3 ml, 0.51 mmol) at 0 °C until the solution became acidic. Ethyl acetate was then added to the solution. The precipitated salt was filtered to give 97 mg (79%) of 8b.