Supporting Information

Novel Synthesis of Orthoester Derivative of 4,5-Epoxymorphinan

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**General Methods.** Melting points were measured on a Yazawa BY-10 melting point apparatus. Infrared (IR) spectra were measured on a JASCO FT/IR-460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-300 spectrometer operating at 300 MHz for $^1$H NMR and 75.5 MHz for $^{13}$C NMR. Chemical shifts were reported as δ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were measured on a JMS-AX505HA or JMS-700 MStation instruments by applying a fast atom bombardment (FAB) ionization method. Elemental analyses were measured by Yanako MT-5 instrument. The progress of the reaction was determined on Merck Silica Gel Art. 5715. Column chromatographies were carried out using Kanto Silica Gel 60N (63–210 μm). Preparative TLC was performed using Merck Silica Gel Art. 5744.

17-((Cyclopropylmethyl)-4,5α-epoxy-6α,14-dihydroxy-3-methoxy-6β-(1’,3’-dithia-2’-yl)-morphinan (5). n-BuLi in hexane (1.54 mol/L, 5.85 mL, 9.01 mmol) was added dropwise to a solution of 1,3-dithiane (1.20 g, 10.0 mmol) in THF (29 mL) at −78 °C and the mixture was stirred at −40 °C for 2 h under Ar atmosphere. A solution of naltrexone methyl ether$^1$ (0.705 g, 1.98 mmol) in THF (1.8 mL) was added to the mixture. After 3 h at −60 °C, the reaction mixture was poured into ice water (50 mL), and 2 mol/L HCl was added until the solution became acidic. The solution was separated, and the aqueous layer was washed with ether (50 mL x 2). The combined ether layer was extracted with 2 mol/L HCl (10 mL) and water (10 mL). All aqueous layer was combined, neutralized with NaOH, and adjusted using NaHCO$_3$ at pH 8.3. The suspension was extracted with CHCl$_3$ (100 mL, 50 mL x 2), and washed with brine (50 mL). The CHCl$_3$ layer was dried over Na$_2$SO$_4$ and evaporated in vacuo. The residue (1.01 g) was dissolved in anhydrous MeOH (10 mL), and NaBH$_4$ (0.501 g) was added to the solution. The mixture was stirred at room temperature for 1 h, and evaporated in vacuo. CHCl$_3$ (50 mL) and a saturated solution of NaHCO$_3$ (30 mL) were added to the residue, the solution was shaken and separated. The aqueous layer was extracted with CHCl$_3$ (50 mL x 2), and the combined CHCl$_3$ layer was washed with

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brine (50 mL). The CHCl₃ layer was dried over Na₂SO₄ and evaporated in vacuo, which was purified by silica gel column chromatography (CHCl₃/MeOH/NH₄OH = 100/1/0.1) to afford 5 as a white solid. The product was recrystallized from MeOH to give 5 (0.808 g, 85%) as a colorless prism: mp 151–153 °C; IR (KBr) νmax 3567, 2921, 2827, 1605, 1497, 1439, 1344, 1284, 1256, 1201, 1164, 1094, 1047, 1016 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ: 0.07–0.13 (2H, m), 0.47–0.54 (2H, m), 0.74–0.89 (1H, m), 1.41 (1H, dt, J = 3.0, 13.5 Hz), 1.41 (1H, ddd, J = 1.0, 4.0, 12.5 Hz), 1.58 (1H, dt, J = 3.0, 13.5 Hz), 1.72 (1H, dt, J = 3.0, 13.5 Hz), 2.13 (1H, dt, J = 4.0, 12.0 Hz), 2.27 (1H, ddd, J = 5.0, 12.0, 12.5 Hz), 2.31 (1H, ddd, J = 1.0, 6.5, 13.0 Hz), 2.37 (1H, ddd, J = 1.0, 6.5, 13.0 Hz), 2.56 (1H, dd, J = 6.0, 18.5 Hz), 2.57–2.63 (2H, m), 2.62 (1H, ddd, J = 1.0, 5.0, 12.0 Hz), 2.83 (1H, dt, J = 3.0, 14.5 Hz), 2.85–2.95 (4H, m), 3.00 (1H, d, J = 18.5 Hz), 3.05 (1H, d, J = 6.0 Hz), 3.86 (3H, s), 4.32 (1H, s), 4.94 (1H, s), 6.58 (1H, d, J = 8.0 Hz), 6.68 (1H, d, J = 8.0 Hz); MS (FAB) m/z 476 [M+H]+; HRMS (FAB) m/z calcd for C₂₅H₃₄NO₄S₂ [M+H]+: 476.1929. Found: 476.1914. Anal. Calcd for C₂₃H₃₃NO₄S₂: C, 63.13; H, 6.99; N, 2.94. Found: C, 63.05; H, 6.92; N, 3.06.

**General Procedure for Acetal Exchange Reaction.** Under the reaction conditions in Table 1 and 2, anhydrous MeOH was added to a solution of CuCl₂, CuO and 5 in trimethyl orthoformate, and the mixture was stirred under Ar atmosphere. The reaction mixture was filtered with Celite, and the filtrate was evaporated. CHCl₃ (20 mL), a saturated solution of NaHCO₃ (20 mL), and EDTA·4Na (the same equivalent of CuCl₂) were added to the residue, and the mixture was sonicated at room temperature for 10 min. The mixture was extracted with CHCl₃ (20 mL x 2, 10 mL), and the combined CHCl₃ layer was washed with a saturated solution of NaHCO₃ (20 mL x 2), brine (20 mL). The CHCl₃ layer was dried over Na₂SO₄ and evaporated in vacuo, which was separated by silica gel column chromatography (saturated NH₄OH/CHCl₃) to afford 6–11.

**17-(Cyclopropylmethyl)-4,5α-epoxy-6α-hydroxy-3,7,7-trimethoxy-8-oxa-6,14-endoethanomorphinan (6).** Compound 6 was isolated as an amorphous substance: IR (film) νmax 3433, 2949, 1598, 1500, 1442, 1325, 1257, 1028 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ: 0.07–0.12 (2H, m), 0.45–0.51 (2H, m), 0.76–0.94 (1H, m), 0.83 (1H, dt, J = 4.0, 12.0 Hz),
1.46 (1H, ddd, $J = 1.0, 6.0, 13.0$ Hz), 1.50 (1H, ddd, $J = 1.0, 6.0, 13.0$ Hz), 1.59 (1H, ddd, $J = 1.0, 5.0, 12.0$ Hz), 1.63 (1H, ddd, $J = 2.0, 7.0, 16.0$ Hz), 2.26 (1H, dd, $J = 7.0, 12.0$ Hz), 2.36 (1H, dd, $J = 7.0, 18.5$ Hz), 2.41 (1H, dd, $J = 5.0, 16.0$ Hz), 2.45 (1H, dt, $J = 4.0, 12.0$ Hz), 2.57 (1H, dd, $J = 5.0, 12.0$ Hz), 2.72 (1H, ddd, $J = 5.0, 12.0$ Hz), 3.17 (1H, d, $J = 18.5$ Hz), 2.26 (1H, dd, $J = 7.0, 12.0$ Hz), 2.36 (1H, dd, $J = 7.0, 18.5$ Hz), 2.41 (1H, ddd, $J = 1.0, 5.0, 12.0$ Hz), 2.45 (1H, dt, $J = 4.0, 12.0$ Hz), 2.57 (1H, dd, $J = 5.0, 12.0$ Hz), 2.72 (1H, ddd, $J = 5.0, 12.0$ Hz), 3.17 (1H, d, $J = 18.5$ Hz), 3.41 (1H, d, $J = 7.0$ Hz), 3.50 (3H, s), 3.52 (3H, s), 3.86 (3H, s), 4.65 (1H, d, $J = 2.0$ Hz), 6.53 (1H, d, $J = 8.0$ Hz), 6.69 (1H, d, $J = 8.0$ Hz); $^{13}$C NMR (CDCl$_3$, 75.5 MHz) δ: 3.2, 4.1, 9.0, 20.4, 26.1, 28.8, 32.3, 42.9, 46.1, 50.1, 51.5, 56.6, 57.7, 59.5, 76.2, 76.3, 91.3, 113.7, 114.3, 119.8, 128.0, 133.0, 142.1, 147.4; MS (FAB) m/z 430 [M+H]$^+$; HRMS (FAB) m/z calcd for C$_{24}$H$_{32}$NO$_6$ [M+H]$^+$: 430.2230. Found: 430.2225.

17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14-dihydroxy-3-methoxy-6β-dimethoxy-methylmorphinan (7). Compound 7 was isolated as a white solid, which was recrystallized from ether to afford 7 as a colorless prism: mp 133–135 °C; IR (KBr) $\nu_{\text{max}}$ 3558, 3349, 2916, 2830, 1638, 1607, 1505, 1449, 1398, 1335, 1281, 1189, 1163, 1075, 1055 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ: 0.10–0.18 (2H, m), 0.49–0.56 (2H, m), 0.80–0.90 (1H, m), 1.40 (1H, ddd, $J = 3.0, 5.0, 13.5$ Hz), 1.43 (1H, ddd, $J = 1.0, 4.0, 12.5$ Hz), 1.52 (1H, ddd, $J = 3.0, 3.5, 14.5$ Hz), 1.59 (1H, ddd, $J = 3.5, 13.5, 14.5$ Hz), 2.15 (1H, dt, $J = 4.0, 12.0$ Hz), 2.17 (1H, dt, $J = 5.0, 14.5$ Hz), 2.21 (1H, ddd, $J = 5.0, 12.0, 12.5$ Hz), 2.26–2.42 (4H, m), 2.60 (1H, ddd, $J = 6.0, 18.5$ Hz), 2.61 (1H, ddd, $J = 1.0, 5.0, 12.0$ Hz), 3.02 (1H, d, $J = 18.5$ Hz), 3.04–3.10 (1H, m), 3.57 (3H, s), 3.59 (3H, s), 3.86 (3H, s), 4.03 (1H, s), 4.77 (1H, s), 6.58 (1H, d, $J = 8.0$ Hz), 6.70 (1H, d, $J = 8.0$ Hz); MS (FAB) m/z 432 [M+H]$^+$; HRMS (FAB) m/z calcd for C$_{24}$H$_{34}$NO$_6$ [M+H]$^+$: 432.2386. Found: 432.2372.

17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14-dihydroxy-3-methoxy-6β-methoxy-carbonylmorphinan (8). Compound 8 was isolated as a white solid, which was recrystallized from AcOEt–ether to afford 8 as a colorless prism: mp 142–144 °C; IR (KBr) $\nu_{\text{max}}$ 3511, 3309, 2925, 1734, 1607, 1500, 1437, 1327, 1258, 1214, 1162, 1099, 1052, 1016 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ: 0.03–0.09 (2H, m), 0.43–0.50 (2H, m), 0.71–0.84 (1H, m), 1.35 (1H, ddd, $J = 1.0, 4.0, 12.5$ Hz), 1.39 (1H, ddd, $J = 3.0, 5.0, 13.5$ Hz), 1.60 (1H, ddd, $J = 3.5, 13.5, 14.5$ Hz), 1.61 (1H, ddd, $J = 3.0, 3.5, 14.5$ Hz), 2.09 (1H, dt, $J = 4.0, 12.0$ Hz), 2.24 (1H, ddd, $J = 5.0, 12.0, 12.5$ Hz), 2.33 (2H, ddd, $J = 1.0, 6.5, 13.5$ Hz), 2.38 (1H, dt, $J = 5.0, 14.5$ Hz), 2.55 (1H, dd, $J = 6.0, 18.5$ Hz), 2.58 (1H, ddd, $J = 1.0, 5.0, 12.0$ Hz), 2.08 (1H, dd, $J = 1.0, 6.0, 13.0$ Hz).
2.97 (1H, d, J = 18.5 Hz), 3.02 (1H, d, J = 6.0 Hz), 3.76 (3H, s), 3.79 (3H, s), 4.79 (1H, s), 6.54 (1H, d, J = 8.0 Hz), 6.65 (1H, d, J = 8.0 Hz); MS (FAB) m/z 416 [M+H]+; HRMS (FAB) m/z calcd for C_{23}H_{30}NO_{6} [M+H]+: 416.2073. Found: 416.2067. Anal. Calcd for C_{23}H_{29}NO_{6}: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.27; H, 6.95; N, 3.37.

17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14-dihydroxy-3-methoxy-6β-trimethoxy-methylmorphinan (9). Compound 9 was isolated as an amorphous substance: 'H NMR (CDCl₃, 300 MHz) δ: 0.05–0.14 (2H, m), 0.48–0.56 (2H, m), 0.79–0.92 (1H, m), 0.87 (1H, ddd, J = 1.0, 4.0, 12.5 Hz), 1.42 (1H, ddd, J = 3.0, 5.0, 13.5 Hz), 1.52 (1H, dt, J = 3.0, 13.5 Hz), 1.63 (1H, dt, J = 3.0, 13.5 Hz), 2.16 (1H, dt, J = 5.0, 13.5 Hz), 2.16 (1H, ddd, J = 5.0, 12.0, 12.5 Hz), 2.23 (1H, dt, J = 4.0, 12.0 Hz), 2.33 (1H, ddd, J = 1.0, 6.0, 13.0 Hz), 2.38 (1H, ddd, J = 1.0, 6.0, 13.0 Hz), 2.63 (1H, ddd, J = 1.0, 5.0, 12.0 Hz), 2.70 (1H, dd, J = 7.0, 18.5 Hz), 2.80 (1H, d, J = 7.0 Hz), 3.00 (1H, d, J = 18.5 Hz), 3.04 (3H, d, J = 2.0 Hz), 3.46 (6H, s), 3.86 (3H, s), 4.94 (1H, s), 6.56 (1H, d, J = 8.0 Hz), 6.69 (1H, d, J = 8.0 Hz); MS (FAB) m/z 484 [M+Na]+; HRMS (FAB) m/z calcd for C_{25}H_{35}NO_{7}Na [M+Na]+: 484.2311. Found: 484.2300.

17-(Cyclopropylmethyl)-4,5α-epoxy-6α,14-dihydroxy-3-methoxy-6β-dimethoxyepoxy-methylmorphinan (10). Compound 10 was isolated as an oil: IR (film) ν_max 3443, 2946, 2837, 1634, 1502, 1455, 1345, 1259, 1237, 1144, 1045 cm⁻¹; 'H NMR (CDCl₃, 300 MHz) δ: 0.37–0.55 (2H, m), 0.77–0.89 (1H, m), 1.45 (1H, ddd, J = 1.0, 7.0, 12.5 Hz), 1.58 (1H, ddd, J = 3.0, 3.5, 12.5 Hz), 1.60 (1H, ddd, J = 3.5, 12.5, 13.5 Hz), 1.63 (1H, ddd, J = 3.0, 6.0, 13.5 Hz), 1.73 (1H, ddd, J = 1.0, 6.5, 13.0 Hz), 1.74 (1H, ddd, J = 1.0, 6.5, 13.0 Hz), 2.14 (1H, dt, J = 7.0, 12.5 Hz), 2.26 (1H, dt, J = 5.5, 12.5 Hz), 2.66 (1H, dt, J = 6.0, 12.5 Hz), 2.68 (1H, ddd, J = 1.0, 5.5, 12.5 Hz), 2.77 (1H, d, J = 15.5 Hz), 2.99 (1H, ddd, J = 1.0, 4.0, 15.5 Hz), 3.14 (1H, d, J = 4.0 Hz), 3.41 (3H, s), 3.48 (3H, s), 3.84 (3H, s), 4.42 (1H, s), 6.69 (1H, d, J = 8.0 Hz), 6.75 (1H, dd, J = 1.0, 8.0 Hz); MS (FAB) m/z 430 [M+H]+; HRMS (FAB) m/z calcd for C_{24}H_{32}NO_{6} [M+H]+: 430.2230. Found: 430.2231.

17-(Cyclopropylmethyl)-4,5α-epoxy-6α-hydroxy-3-methoxy-8-oxa-7-(1',3'-dithia-2'-yl)-6,14-endoethanomorphinan (11). Compound 11 was isolated as an amorphous substance: IR (KBr) ν_max 2911, 1598, 1495, 1448, 1325, 1255, 1206, 1157, 1095, 1070
cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\): 0.10–0.23 (2H, m), 0.48–0.54 (2H, m), 0.80–0.95 (1H, m), 0.89 (1H, dt, \(J = 4.0, 12.0\) Hz), 1.57 (1H, ddd, \(J = 1.0, 6.0, 13.0\) Hz), 1.60 (1H, ddd, \(J = 1.0, 6.0, 13.0\) Hz), 1.88 (1H, ddd, \(J = 1.0, 5.0, 12.0\) Hz), 1.90 (1H, ddd, \(J = 2.0, 7.0, 16.0\) Hz), 2.32 (1H, dd, \(J = 7.0, 12.0\) Hz), 2.47 (1H, dt, \(J = 4.0, 12.0\) Hz), 2.53 (1H, dd, \(J = 7.0, 18.5\) Hz), 2.59 (1H, dd, \(J = 5.0, 12.0\) Hz), 2.75 (1H, ddd, \(J = 1.0, 5.0, 12.0\) Hz), 2.80 (1H, dd, \(J = 5.0, 16.0\) Hz), 2.84–2.97 (4H, m), 3.16 (1H, d, \(J = 18.5\) Hz), 3.37 (1H, d, \(J = 7.0\) Hz), 3.41–3.54 (2H, m), 3.88 (3H, s), 5.00 (1H, d, \(J = 2.0\) Hz), 6.55 (1H, d, \(J = 8.0\) Hz), 6.71 (1H, d, \(J = 8.0\) Hz); MS (FAB) m/z 474 [M+H]\(^+\); HRMS (FAB) m/z calcd for C\(_{25}\)H\(_{32}\)NO\(_3\)S\(_2\) [M+H]\(^+\): 474.1773. Found: 474.1780.

**Hydrolysis of 6.** A solution of 6 (442 mg, 1.03 mmol) in 67% AcOH (30 mL) was stirred at 80 °C for 4 h. The solution was evaporated in vacuo, and the residue was coevaporated with toluene (100 mL x 2) and CHCl\(_3\) (50 mL x 2) to afford 8 (411 mg, 96%) as an amorphous substance. \(^1\)H NMR and mass spectra matched the previously reported data.

17-(Cyclopropylmethyl)-4,5\(\alpha\)-epoxy-6\(\alpha\)-hydroxy-3,7-dimethoxy-8-oxa-6,14-endo-ethanomorphinan (14). Aluminium chloride (185 mg, 1.39 mmol) was added to a solution of 6 (129 mg, 0.300 mmol), borane-trimethylamine (200 mg, 2.73 mmol), molecular sieves 4A (300 mg) in anhydrous THF (5 mL) at –40 °C. The mixture was stirred at –40 °C for 1 h at room temperature for 40 min under Ar atmosphere. Ammonia water (0.5 mL) and AcOEt (2 mL) was added to the mixture, and the mixture was stirred for 15 min. A saturated solution of NaHCO\(_3\) (15 mL) was added to the mixture, and the mixture was extracted with CHCl\(_3\) (15 mL x 2). The combined CHCl\(_3\) layer was washed with a saturated solution of NaHCO\(_3\) (15 mL x 2) and brine (15 mL x 2). The CHCl\(_3\) layer was dried over Na\(_2\)SO\(_4\) and evaporated in vacuo, which was purified by preparative TLC (saturated NH\(_4\)OH–CHCl\(_3\)) to afford 14 (82.1 mg, 69%) as an oil: IR (film) \(\nu_{\text{max}}\) 3419, 2930, 1626, 1501, 1450, 1259, 1100 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\): 0.10–0.18 (2H, m), 0.48–0.66 (2H, m), 0.82–0.94 (1H, m), 0.87 (1H, dt, \(J = 3.0, 13.0\) Hz), 1.58 (2H, ddd, \(J = 1.0, 6.0, 13.0\) Hz), 1.66 (1H, ddd, \(J = 1.0, 5.0, 13.0\) Hz), 1.74 (1H, ddd, \(J = 2.0, 8.0, 16.0\) Hz), 2.03 (1H, dd, \(J = 8.0, 12.0\) Hz), 2.22 (1H, dd, \(J = 6.0, 18.5\) Hz), 2.33 (1H, dd, \(J = 5.0, 16.0\) Hz),
2.42 (1H, dt, $J = 3.0$, 12.0 Hz), 2.61 (1H, dd, $J = 5.0$, 12.0 Hz), 2.85 (1H, ddd, $J = 1.0$, 5.0, 12.0 Hz), 3.18 (0.2H, d, $J = 18.5$ Hz), 3.21 (0.8H, d, $J = 18.5$ Hz), 3.34 (1H, d, $J = 6.0$ Hz), 3.57 (2.4H, s), 3.59 (0.6H, s), 3.87 (2.4H, s), 3.88 (0.6H, s), 4.45 (0.2H, d, $J = 2.0$ Hz), 4.74 (0.8H, d, $J = 2.0$ Hz), 4.80 (0.8H, s), 4.81 (0.2H, s), 6.55 (0.8H, d, $J = 8.0$ Hz), 6.56 (0.2H, d, $J = 8.0$ Hz), 6.71 (0.8H, d, $J = 8.0$ Hz), 6.72 (0.8H, d, $J = 8.0$ Hz); MS (FAB) m/z 400 [M+H]$^+$; HRMS (FAB) m/z calcd for C$_{23}$H$_{30}$NO$_5$ [M+H]$^+$: 400.2124. Found: 400.2120.
$^1$H NMR Spectrum of 5
$^1$H NMR Spectrum of 6
$^{13}$C NMR Spectrum of 6
$^1$H NMR Spectrum of 7
$^1$H NMR Spectrum of 8
$^1$H NMR Spectrum of 9
$^1$H NMR Spectrum of 10
\(^1\)H NMR Spectrum of II
$^1$H NMR Spectrum of 14