Supporting Information

Total Synthesis of (±)-Morphine

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Technical notes

Nuclear magnetic resonance (^1H NMR (400 MHz), ^{13}C NMR (100 MHz)) spectra were determined on a JEOL-LA400 instrument unless otherwise noted. Chemical shifts for ^1H NMR are reported in parts per million downfield from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR were reported in ppm relative to the center line of a triplet at 77.0 ppm for deuteriochloroform.

Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}).

Mass spectra (MS) were obtained on a JEOL JMS-GCmate at 70 eV, unless otherwise noted, using direct probe insertion at temperature of 30 to 300 °C. High resolution mass spectra were obtained under similar conditions. Fast atom bombardment (FAB) mass spectra were obtained with polyethylene glycol (PEG) as the matrix.

Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₅₄. Preparative TLC separations were made on Merck precoated analytical plates, 0.50 mm thick, silica gel 60 F₂₅₄. Compounds were eluted from the adsorbent with 10% methanol in chloroform.

Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh).

Reagents and solvents were commercial grades. All solvents were used after being dried over molecular sieves 3A or 4A. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

1-Methoxy-2-(methoxymethoxy)-4-(dimethoxymethyl)benzene (**26**)

To a stirred solution of isovanillin (**7**) (29.2 g, 192 mmol) in dichloromethane (500 ml) were added *N,N*-diisopropylethylamine (49.1 ml, 288 mmol) and chloromethyl methyl ether (21.9 ml, 288 mmol) at 0 °C, then the reaction mixture was allowed to warm to room temperature. After stirring for 1 hour, saturated aqueous ammonium chloride was added and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was dissolved in methanol (380 ml), and to the solution were added trimethyl orthoformate (31.5 ml, 288 mmol) and 10-camphorsulfonic acid (45.0 mg, 0.192 mmol) at 0 °C. After stirring at 0 °C for 100 minutes, pulverized potassium carbonate (100 mg) was added and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 20/80) to give **26** (44.5 g, 96% in 2 steps) as a colorless oil.

IR (film, cm⁻¹) 2951, 2831, 1514, 1263, 1157, 1132, 1101, 1078, 1053, 1007

¹H NMR (400 MHz, CDCl₃) δ: 7.25 (1H, d, *J* = 1.8 Hz), 7.08 (1H, dd, *J* = 9.2 Hz, 1.8 Hz), 6.89 (1H, d, *J* = 9.2 Hz), 5.33 (1H, s), 5.24 (2H, s), 3.89 (3H, s), 3.52 (3H, s), 3.32 (6H, s)

¹³C NMR (100 MHz, CDCl₃) δ: 149.7, 146.1, 130.8, 120.7, 114.8, 111.1, 102.8, 95.4, 56.2, 55.8, 52.6 (2C)

HRMS (FAB) Calcd for C₁₂H₁₈O₅ 242.1154 (M⁺), Found 242.1150

2- Iodo-4-methoxy-3-(methoxymethoxy)-1-(dimethoxymethyl)benzene (**9**)

To a stirred solution of **26** (44.5 g, 184 mmol) in diethyl ether (700 ml) was dropped 2.15 M *n*-butyllithium in hexane (128 ml, 276 mmol) over 40 minutes at $0\text{ }^\circ\text{C}$. After stirring at $0\text{ }^\circ\text{C}$ for 10 minutes, to the reaction mixture was added a solution of iodine (74.7 g, 294 mmol) in tetrahydrofuran (60 ml) over 40 minutes at $0\text{ }^\circ\text{C}$. After stirring at $0\text{ }^\circ\text{C}$ for 10 minutes, the reaction was quenched with water. After saturated aqueous sodium sulfite was added, the mixture was allowed to warm to room temperature and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 7/93 – 10/90) to give **8** (51.0 g, 75%) as a yellow oil.

IR (film, cm^{-1}): 2937, 2829, 1587, 1479, 1294, 1159, 1109, 1076, 1056, 1028, 966

^1H NMR (400 MHz, CDCl_3) δ : 7.29 (1H, d, $J = 9.2\text{ Hz}$), 6.91 (1H, d, $J = 9.2\text{ Hz}$), 5.40 (1H, s), 5.16 (2H, s), 3.86 (3H, s), 3.69 (3H, s), 3.38 (6H, s)

^{13}C NMR (100 MHz, CDCl_3) δ : 152.4, 145.5, 132.7, 123.6, 111.8, 106.8, 98.7, 97.2, 58.4, 56.0, 54.0 (2C)

HRMS (FAB) Calcd for $\text{C}_{12}\text{H}_{17}\text{IO}_5$ 368.0121 (M^+), Found 368.0132

2-Iodo-4-methoxy-3-(methoxymethoxy)benzaldehyde (**26**)

To a stirred solution of **8** (51.0 g, 139 mmol) in tetrahydrofuran (250 ml) were added water (100 ml) and acetic acid (200 ml) at 0 °C, then the reaction mixture was allowed to warm to room temperature. After stirring for 3 hours, the solvent was evaporated under reduced pressure. The crude product was rinsed with hexane to give **9** (39.5 g, 89%) as a white solid.

mp: 93.0-94.0 °C

IR (film, cm⁻¹): 1682, 1575, 1479, 1274, 1249, 1021, 904, 773

¹H NMR (400 MHz, CDCl₃) δ: 10.04 (1H, s), 7.73 (1H, d, *J* = 8.7 Hz), 6.98 (1H, d, *J* = 8.7 Hz), 5.20 (2H, s), 3.94 (3H, s), 3.70 (3H, s)

¹³C NMR (100 MHz, CDCl₃) δ: 195.8, 157.8, 146.4, 129.7, 128.0, 112.5, 101.2, 99.5, 59.2, 56.9

Anal. Calcd for C₁₀H₁₁IO₄: C, 37.29; H, 3.44; N, 0; Found: C, 37.08; H, 3.58; N, 0

2-Iodo-4-methoxy-3-(methoxymethoxy)-1-(2-methoxyvinyl)benzene (**10**)

To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (36.7 g, 107 mmol) in tetrahydrofuran (350 ml) was added 0.99 M sodium bis(trimethylsilyl)amide in tetrahydrofuran (108 ml, 107 mmol) over 50 minutes at 0 °C. After stirring at 0 °C for 10 minutes, to the reaction mixture was added a solution of **9** (32.8 g, 102 mmol) in tetrahydrofuran (135 ml) over 1 hour at 0 °C. After stirring at 0 °C for 10 minutes, the reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched with saturated aqueous ammonium chloride (50 ml) and the solvent was evaporated under reduced pressure. The residue was diluted with diethyl ether, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 25/75) to give **10** (34.0 g, 95%) as a white solid. The product was the mixture of *E* and *Z* (70:30).

E

¹H NMR (400 MHz, CDCl₃) δ: 7.04 (1H, d, *J* = 8.2 Hz), 6.83 (1H, d, *J* = 8.2 Hz), 6.77 (1H, d, *J* = 12.8 Hz), 5.99 (1H, d, *J* = 12.8 Hz), 5.16 (2H, s), 3.83 (3H, s), 3.72 (3H, s), 3.68 (3H, s)

¹³C NMR (100 MHz, CDCl₃) δ: 150.1, 149.4, 145.8, 133.6, 120.9, 112.8, 109.6, 98.9, 98.6, 58.5, 56.5, 56.2

Z

¹H NMR (400 MHz, CDCl₃) δ: 7.73 (1H, d, *J* = 8.2 Hz), 6.87 (1H, d, *J* = 8.2 Hz), 6.16 (1H, d, *J* = 7.3 Hz), 5.50 (1H, d, *J* = 7.3 Hz), 5.14 (2H, s), 3.84 (3H, s), 3.75 (3H, s), 3.68 (3H, s)

¹³C NMR (100 MHz, CDCl₃) δ: 150.0, 147.8, 145.4, 132.1, 125.3, 112.3, 109.2, 98.8, 98.6, 60.6, 58.4, 56.1

Anal. Calcd for C₁₂H₁₅IO₄: C, 41.10; H, 4.39; N, 0; Found: C, 41.16; H, 4.32; N, 0

2-Iodo-6-methoxy-3-(2,2-dimethoxyethyl)phenol (**11**)

To a stirred solution of **10** (42.0 g, 120 mmol) in methanol (500 ml) was added acetyl chloride (4.3 ml, 60.0 mmol) at room temperature. After stirring at 40 °C for 1 hour, pulverized potassium carbonate (8.30 g, 60.0 mmol) was added and the solvent was evaporated under reduced pressure. The residue was diluted with diethyl ether, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was rinsed with hexane to give **11** (39.0 g, 96%) as white crystals.

mp: 90.0-91.3 °C

IR (film, cm^{-1}): 3374, 2937, 2835, 1599, 1483, 1281, 1119, 1034, 804

^1H NMR (400 MHz, CDCl_3) δ : 6.85 (1H, d, $J = 8.4$ Hz), 6.78 (1H, d, $J = 8.4$ Hz), 6.19 (1H, s), 4.58 (1H, t, $J = 5.5$ Hz), 3.89 (3H, s), 3.36 (6H, s), 3.04 (2H, d, $J = 5.5$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ : 145.4, 144.4, 132.5, 122.1, 110.2, 104.3, 88.7, 56.3, 54.0 (2C), 43.4

Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{IO}_4$: C, 39.07; H, 4.41; N, 0; Found: C, 39.07; H, 4.47; N, 0

3-(*tert*-Butyldimethylsilyloxymethyl)-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexenol (12**)**

To a stirred solution of **11** (35.0 g, 104 mmol) and epoxide **6** (28.6 g, 119 mmol) in acetonitrile (280 ml) were added tris(dibenzylideneacetone)dipalladium(0) (948 mg, 1.04 mmol) and tri-2-furylphosphine (961 mg, 4.14 mmol) at room temperature. After stirring for 20 minutes, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 20/80) to give **12** (52.8 g, 91%) as a yellow oil.

IR (film, cm^{-1}): 3421, 2933, 2856, 2360, 1587, 1473, 1265, 1119, 1072, 1030, 839

^1H NMR (400 MHz, CDCl_3) δ : 6.99 (1H, d, $J = 8.2$ Hz), 6.83 (1H, d, $J = 8.2$ Hz), 6.03 (1H, s), 4.88 (1H, s), 4.57 (1H, t, $J = 5.5$ Hz), 4.48 (1H, d, $J = 14.7$ Hz), 4.33 (1H, d, $J = 14.7$ Hz), 4.25 (1H, br), 3.82 (3H, s), 3.36 (3H, s), 3.35 (3H, s), 3.06 (2H, d, $J = 5.5$ Hz), 2.16-2.01 (2H, m), 1.91-1.88 (1H, m), 1.57-1.53 (1H, m), 0.92 (9H, s), 0.069 (3H, s), 0.065 (3H, s)

^{13}C NMR (100 MHz, CDCl_3) δ : 150.2, 146.5, 139.6, 132.8, 127.1, 125.7, 112.0, 104.1, 100.9, 74.9, 66.8, 63.6, 55.5, 54.0, 53.8, 44.1, 28.8, 26.0, 25.9 (3C), 18.3, -5.4 (2C)

HRMS (FAB) Calcd for $\text{C}_{24}\text{H}_{39}\text{IO}_6\text{Si}$ 578.1561 (M^+), Found 578.1571

3-(*tert*-Butyldimethylsilyloxymethyl)-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexen-1-yl 4-nitrobenzoate (27**)**

To a stirred solution of **12** (25.5 g, 44.0 mmol), *p*-nitrobenzoic acid (8.46 g, 50.6 mmol) and triphenylphosphine (15.0 g, 57.2 mmol) in toluene (200 ml) and tetrahydrofuran (40 ml) was dropped 2.2 M diethyl azodicarboxylate in toluene (24.0 ml, 52.8 mmol) over 80 minutes at 0 °C, then the reaction mixture was allowed to warm to room temperature. After stirring for 20 minutes, the solvent was evaporated under reduced pressure. The residue was diluted with diethyl ether (50 ml) and hexane (50 ml), and then filtered to remove triphenylphosphine oxide. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 17/83) to give **27** (28.7 g, 90%) as a yellow foam.

IR (film, cm^{-1}): 2933, 2857, 2360, 1720, 1529, 1473, 1344, 1269, 1119

^1H NMR (400 MHz, CDCl_3) δ : 8.28 (2H, d, $J = 9.2$ Hz), 8.19 (2H, d, $J = 9.2$ Hz), 7.01 (1H, d, $J = 8.2$ Hz), 6.85 (1H, d, $J = 8.2$ Hz), 6.11 (1H, s), 5.70 (1H, s), 5.06 (1H, s), 4.58 (1H, t, $J = 5.5$ Hz), 4.53 (1H, d, $J = 14.7$ Hz), 4.36 (1H, d, $J = 14.7$ Hz), 3.85 (3H, s), 3.36 (3H, s), 3.35 (3H, s), 3.07 (2H, d, $J = 5.5$ Hz), 2.64–2.55 (1H, m), 2.05–2.00 (1H, m), 1.91–1.84 (2H, m), 0.91 (9H, s), 0.07 (3H, s), 0.06 (3H, s)

^{13}C NMR (100 MHz, CDCl_3) δ : 164.2, 150.4, 150.3, 146.0, 143.5, 136.1, 133.0, 130.7 (2C), 125.9, 123.4 (2C), 121.3, 112.1, 104.2, 100.9, 74.4, 69.4, 63.8, 55.6, 54.0, 53.8, 44.1, 25.9 (3C), 25.3, 24.9, 18.4, -5.3, -5.4

HRMS (FAB) Calcd for $\text{C}_{31}\text{H}_{42}\text{INO}_9\text{Si}$ 727.1674 (M^+), Found 727.1690

4-[3-(2,2-Dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-3-hydroxymethyl-2-cyclohexen-1-yl 4-nitrobenzoate (13**)**

To a stirred solution of **27** (1.01 g, 1.39 mmol) in methanol (10 ml) was added 10-camphorsulfonic acid (16.1 mg, 0.0695 mmol) at room temperature. After stirring for 80 minutes, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 40/60) to give **13** (802 mg, 94%) as a yellow foam.

IR (film, cm^{-1}): 3454, 2939, 2835, 2360, 1720, 1527, 1475, 1344, 1271, 1119, 1024

^1H NMR (400 MHz, CDCl_3) δ : 8.28 (2H, d, $J = 9.2$ Hz), 8.19 (2H, d, $J = 9.2$ Hz), 7.06 (1H, d, $J = 8.2$ Hz), 6.89 (1H, d, $J = 8.2$ Hz), 6.07 (1H, s), 5.69 (1H, s), 5.16-5.14 (1H, m), 4.58 (1H, t, $J = 5.5$ Hz), 4.49 (1H, d, $J = 13.6$ Hz), 4.33 (1H, d, $J = 13.6$ Hz), 3.89 (3H, s), 3.37 (3H, s), 3.36 (3H, s), 3.10-3.07 (2H, m), 2.60-2.52 (1H, m), 2.18-2.10 (1H, m), 1.97-1.79 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ : 163.8, 150.0, 149.8, 145.3, 143.0, 135.5, 132.8, 130.4 (2C), 126.0, 123.3, 123.1 (2C), 111.8, 103.8, 100.9, 75.1, 69.2, 63.8, 55.5, 53.7, 53.5, 43.7, 25.3, 25.0

Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{INO}_9$: C, 48.95; H, 4.60; N, 2.28; Found: C, 48.88; H, 4.65; N, 2.15

**3-Cyanomethyl-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexen-1-yl
4-nitrobenzoate (**14**)**

To a stirred solution of **13** (20.9 g, 34.1 mmol), acetone cyanohydrin (6.92 ml, 68.2 mmol) and triphenylphosphine (11.6 g, 44.2 mmol) in toluene (200 ml) was dropped 2.2 M diethyl azodicarboxylate in toluene (18.6 ml, 40.9 mmol) over 1 hour at 0 °C, then the reaction mixture was allowed to warm to room temperature. After stirring for 40 minutes, the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (20 ml) and hexane (30 ml), and then filtered to remove triphenylphosphine oxide. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography (dichloromethane only, ethyl acetate/hexane = 25/75 – 33/67, dichloromethane only) to give **14** (22.0 g) containing impurities. Further purification was not done at this stage.

IR (film, cm^{-1}): 2941, 2833, 2252, 1722, 1527, 1475, 1346, 1271, 1119, 1026, 918, 721

^1H NMR (400 MHz, CDCl_3) δ : 8.28 (2H, d, $J = 9.2$ Hz), 8.20 (2H, d, $J = 9.2$ Hz), 7.06 (1H, d, $J = 8.2$ Hz), 6.89 (1H, d, $J = 8.2$ Hz), 6.25 (1H, d, $J = 2.7$ Hz), 5.70 (1H, s), 5.04 (1H, s), 4.58 (1H, t, $J = 5.5$ Hz), 3.90 (3H, s), 3.63-3.52 (2H, m), 3.37 (3H, s), 3.36 (3H, s), 3.12-3.03 (2H, m), 2.62-2.55 (1H, m), 2.13-2.05 (1H, m), 1.95-1.88 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ : 164.0, 150.5, 150.1, 145.3, 135.0, 134.3, 133.1, 130.7 (2C), 127.5, 126.5, 123.5 (2C), 117.4, 112.0, 104.1, 100.8, 75.1, 68.7, 55.6, 54.0, 53.7, 44.0, 25.1, 24.9, 22.4

HRMS (FAB) Calcd for $\text{C}_{26}\text{H}_{27}\text{INO}_8$ 622.0812 (M^+), Found 622.0811

**3-Cyanomethyl-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexenol
(28)**

To a stirred solution of crude **14** (22.0 g) in diethyl ether (200 ml) and methanol (10.0 ml) was dropped 2.0 M lithium borohydride in tetrahydrofuran (20.5 ml, 40.9 mmol) over 20 minutes at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 40 minutes. Saturated aqueous ammonium chloride was added to the solution and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 40/60 – 60/40) to give **28** (15.3 g, 95% in 2 steps) as a colorless oil.

IR (film, cm^{-1}): 3449, 2936, 2835, 2250, 1589, 1476, 1268, 1119, 1066, 1027

^1H NMR (400 MHz, CDCl_3) δ : 7.03 (1H, d, $J = 8.2$ Hz), 6.86 (1H, d, $J = 8.2$ Hz), 6.14 (1H, s), 4.94 (1H, s), 4.57 (1H, t, $J = 5.5$ Hz), 4.39 (1H, s), 3.87 (3H, s), 3.52 (2H, s), 3.36 (3H, s), 3.35 (3H, s), 3.07-3.04 (2H, m), 2.38-2.28 (1H, m), 1.95-1.84 (2H, m), 1.63-1.55 (1H, m)

^{13}C NMR (100 MHz, CDCl_3) δ : 150.2, 145.5, 132.9, 132.0, 131.2, 126.3, 117.8, 111.9, 104.1, 100.0, 76.2, 65.0, 55.6, 54.1, 53.8, 44.0, 28.9, 25.4, 22.0

HRMS (FAB) Calcd for $\text{C}_{19}\text{H}_{24}\text{INO}_5$ 473.0699 (M^+), Found 473.0698

***tert*-Butyl[3-cyanomethyl-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexenoxymethyl]dimethylsilane (**15**)**

To a stirred solution of **28** (12.8 g, 27.0 mmol) and imidazole (2.21 g, 32.5 mmol) in *N,N*-dimethylformamide (67.5 ml) was added *t*-butyldimethylchlorosilane (4.89 g, 32.5 mmol) at room temperature, then the reaction mixture was stirred for 1 hour. Water was added to the solution and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was rinsed with hexane and filtered to collect **15** (13.5 g) as white crystals. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography (diethyl ether/hexane = 20/80 – 75/25) to give **15** (1.70 g) as white crystals. Finally, 15.2 g of **15** was obtained in 96% yield.

mp: 106.5-107.5 °C

IR (film, cm⁻¹): 2952, 2894, 2856, 2250, 1589, 1475, 1265, 1120, 1072, 1022, 837, 804

¹H NMR (400 MHz, CDCl₃) δ: 7.01 (1H, d, *J* = 8.2 Hz), 6.85 (1H, d, *J* = 8.2 Hz), 6.00 (1H, s), 4.94 (1H, s), 4.56 (1H, t, *J* = 5.5 Hz), 4.36 (1H, s), 3.85 (3H, s), 3.54 (1H, d, *J* = 19.2 Hz), 3.45 (1H, d, *J* = 19.2 Hz), 3.35 (3H, s), 3.34 (3H, s), 3.08-3.02 (2H, m), 2.21-2.16 (1H, m), 1.92-1.89 (2H, m), 1.57-1.49 (1H, m), 0.89 (9H, s), 0.10 (3H, s), 0.09 (3H, s)

¹³C NMR (100 MHz, CDCl₃) δ: 150.2, 145.6, 132.9 (2C), 130.0, 126.2, 117.8, 111.9, 104.2, 101.0, 76.8, 65.9, 55.6, 54.0, 53.8, 44.0, 29.8, 25.9, 25.8 (3C), 21.8, 18.1, -4.6, -4.7

Anal. Calcd for C₂₅H₃₈INO₅Si: C, 51.10; H, 6.52; N, 2.38; Found: C, 51.03; H, 6.39; N, 2.36

***tert*-Butyldimethyl[3-[2-methoxycarbonylaminoethyl]-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexenoxy]silane (**16**)**

To a stirred solution of **15** (1.64 g, 2.79 mmol) in dichloromethane (30.0 ml) was dropped 0.99 M diisobutylaluminium hydride in toluene (3.67 ml, 3.63 mmol) over 10 minutes at $-78\text{ }^\circ\text{C}$, and the reaction mixture was stirred for 2 hours. Sodium borohydride (317 mg, 8.37 mmol) and methanol (10.0 ml) were added to the solution, then the reaction mixture was allowed to warm to room temperature and stirred for 40 minutes. Pulverized potassium carbonate (463 mg, 3.35 mmol) and methyl chloroformate (259 μl , 3.35 mmol) were added and the reaction mixture was stirred for 30 minutes. 30% aqueous potassium sodium (+)-tartrate (30.0 ml) was added to the mixture, and it was stirred for 1 hour, then extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 25/75) to give **16** (1.71 g, 94%) as a white foam.

IR (film, cm^{-1}): 3352, 2950, 2856, 1724, 1475, 1255, 1120, 1072, 1026, 835, 775

^1H NMR (400 MHz, CDCl_3) δ : 6.94 (1H, d, $J = 8.2\text{ Hz}$), 6.79 (1H, d, $J = 8.2\text{ Hz}$), 5.57 (1H, s), 5.08 (1H, s), 5.02 (1H, s), 4.51 (1H, t, $J = 5.5\text{ Hz}$), 4.26 (1H, s), 3.78 (3H, s), 3.59 (2H, s), 3.43-3.37 (2H, m), 3.31 (3H, s), 3.29 (3H, s), 3.06-2.96 (2H, m), 2.62-2.52 (2H, m), 2.40-2.32 (1H, m), 2.13-2.05 (1H, m), 1.80-1.72 (2H, m), 1.47-1.40 (1H, m), 0.85 (9H, s), 0.05 (3H, s), 0.04 (3H, s)

^{13}C NMR (100 MHz, CDCl_3) δ : 156.9, 150.2, 145.4, 136.7, 132.7, 131.5, 125.6, 111.9, 104.1, 101.1, 77.3, 66.1, 55.5, 53.9, 53.6, 51.7, 44.0, 39.6, 33.6, 29.8, 25.7 (3C), 25.4, 18.0, -4.8 (2C)

HRMS (FAB) Calcd for $\text{C}_{27}\text{H}_{44}\text{INO}_7\text{Si}$ 649.1932 (M^+), Found 649.1935

1-(2,2-Dimethoxyethyl)-4-methoxy-5aH-6,7,9-trihydrodibenzofuran-8-one-9a-yl-1-methoxycarbonylaminoethane (17**)**

To a stirred solution of **16** (1.65 g, 2.54 mmol), tri-*o*-tolylphosphine (155 mg, 0.508 mmol) and triethylamine (0.704 ml, 5.08 mmol) in acetonitrile (17.0 ml) was added tris(dibenzylideneacetone)dipalladium(0) (116 mg, 0.127 mmol) at room temperature, then the reaction mixture was refluxed for 1 hour. The reaction mixture was allowed to cool to room temperature and 1.0 M tetrabutylammonium fluoride in tetrahydrofuran (3.05 ml, 3.05 mmol) was added. After stirring for 90 minutes, saturated aqueous ammonium chloride was added to the mixture and it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 25/75 – 100/0) to give **17** (897 mg, 87%) as a pale yellow foam.

IR (film, cm^{-1}): 3327, 2941, 2837, 1716, 1541, 1506, 1435, 1344, 1281, 1169, 1120, 1068, 733
 ^1H NMR (400 MHz, CDCl_3) δ : 6.77-6.70 (2H, m), 4.96 (1H, s), 4.62-4.52 (2H, m), 3.85 (3H, s), 3.62 (3H, s), 3.39 (3H, s), 3.34 (3H, s), 3.30-3.20 (1H, m), 2.92 (1H, d, $J = 15.6$ Hz), 2.90-2.80 (3H, m), 2.65 (1H, d, $J = 15.6$ Hz), 2.40-2.14 (5H, m), 1.93-1.83 (1H, m)
 ^{13}C NMR (100 MHz, CDCl_3) δ : 210.0, 156.8, 147.8, 142.6, 127.9, 125.8, 122.8, 111.9, 105.5, 84.7, 55.7, 54.5, 53.6, 51.9, 49.4, 48.2, 40.1, 37.0, 34.4, 33.1, 26.4
 HRMS (FAB) Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_7$ 407.1944 (M^+), Found 407.1952

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-8-one (**18**)

To a stirred solution of **17** (555 mg, 1.36 mmol) in methanol (10.0 ml) was added acetyl chloride (969 μ l, 13.6 mmol) at room temperature, then the reaction mixture was refluxed for 12 hours. It was allowed to cool to room temperature, acetyl chloride (969 μ l, 13.6 mmol) was added and it was refluxed for another 12 hours. It was allowed to cool to room temperature, diluted with toluene, and evaporated under reduced pressure to remove methanol. The organic layer was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 50/50) to give **18** (440 mg, 94%) as a white foam.

mp: 126-128 $^{\circ}$ C

IR (film, cm^{-1}): 2949, 1709, 1504, 1448, 1405, 1313, 1263, 1130, 920, 730

^1H NMR (400 MHz, CDCl_3) δ : 6.75 (1H, d, J = 8.2 Hz), 6.58 (1H, d, J = 8.2 Hz), 5.42-5.34 (minor amide rotamer)(0.40 1H, br), 5.29-5.21 (major amide rotamer)(0.60 1H, br), 4.90 (1H, s), 4.16-4.06 (major amide rotamer)(0.60 1H, d, J = 13.8 Hz), 4.02-3.92 (minor amide rotamer)(0.40 1H, d, J = 13.8 Hz), 3.87 (3H, s), 3.74 (3H, s), 3.20-2.70 (2H, m), 2.72 (1H, s), 2.64 (1H, d, J = 18.3 Hz), 2.35-2.04 (3H, m), 1.95-1.75 (3H, m)

^{13}C NMR (100 MHz, CDCl_3) (major amide rotamer) δ : 207.6, 155.4, 146.5, 141.6, 128.0, 126.4, 119.8, 114.1, 88.1, 56.2, 52.6, 50.8, 47.7, 42.8, 37.0, 35.8, 33.4, 29.0, 26.7 (minor amide rotamer) δ : 207.0, 155.3, 146.5, 141.6, 128.0, 126.6, 119.8, 114.1, 88.1, 56.2, 52.6, 50.6, 47.6, 42.9, 37.1, 36.1, 33.4, 28.9, 26.7

HRMS (FAB) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_5$ 343.1420 (M^+), Found 343.1430

8-membered hemiaminal intermediate (19)

IR (film, cm^{-1}) 2947, 2837, 1704, 1624, 1585, 1508, 1438, 1404, 1342, 1277, 1082

^1H NMR (400 MHz, CDCl_3) δ : 6.67 (0.5 1H, d, $J = 8.0$ Hz), 6.64 (0.5 1H, d, $J = 8.0$ Hz), 6.62 (0.5 1H, d, $J = 8.0$ Hz), 6.57 (0.5 1H, d, $J = 8.0$ Hz), 5.41 (0.5 1H, dd, $J = 10.5, 5.3$ Hz), 5.21 (0.5 1H, dd, $J = 10.3, 5.7$ Hz), 3.84 (3H, s), 3.61 (0.5 3H, s), 3.60-3.55 (0.5 1H, m), 3.53 (0.5 3H, s), 3.49-3.44 (0.5 1H, m), 3.40-3.33 (1H, m), 3.24 (0.5 3H, s), 3.21 (0.5 3H, s), 3.10-3.05 (1H, m), 2.97-2.73 (3H, m), 2.49 (0.5 1H, t, $J = 12.6$ Hz), 2.37-2.20 (4H+0.5 1H, m), 1.72-1.65 (1H, m)

^{13}C NMR (100 MHz, CDCl_3) δ : 209.8, 209.6, 157.3, 156.5, 147.8, 147.5, 143.4, 143.3, 129.7, 129.4, 125.4, 125.3, 123.5, 123.1, 111.6, 111.4, 88.8, 88.7, 87.7, 87.5, 55.9, 55.7, 55.1, 54.7, 52.7, 52.5, 49.4, 49.3, 44.8, 44.5, 42.8, 41.7, 36.6, 36.4, 36.1, 35.9, 33.5, 33.4, 26.7, 26.6

HRMS (FAB) Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_6$ 375.1682 (M^+), Found 375.1697

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-6-en-8-one (**21**)

To a stirred solution of **18** (3.03 g, 8.82 mmol) and chlorotrimethylsilane (1.34 ml, 10.6 mmol) in tetrahydrofuran (50.0 ml) was added 1.00 M lithium bis(trimethylsilyl)amide in tetrahydrofuran (12.4 ml, 12.4 mmol) over 5 minutes at 0 °C. After stirring for 40 minutes, saturated aqueous ammonium chloride was added to the mixture and it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was dissolved in acetonitrile (50.0 ml), and to the solution was added palladium acetate (2.97 g, 13.2 mmol) at room temperature. After stirring for 2 hours, saturated aqueous sodium hydrogen carbonate was added to the mixture and it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 40/60 – 60/40) to give **21** (2.78 g, 92% in 2 steps) as a white foam.

mp: 122-124 °C

IR (film, cm^{-1}): 2951, 1697, 1504, 1446, 1277, 910, 764

^1H NMR (400 MHz, CDCl_3) δ : 6.76 (1H, d, $J = 8.2$ Hz), 6.65-6.56 (2H, m), 6.00 (1H, d, $J = 10.1$ Hz), 5.42-5.19 (2H, m), 4.15-4.10 (major amide rotamer)(0.60 1H, m), 4.05-3.97 (minor amide rotamer)(0.40 1H, m), 3.86 (3H, s), 3.76 (major amide rotamer)(0.60 3H, s), 3.73 (minor amide rotamer)(0.40 3H, s), 3.15-3.00 (1H, m), 2.90-2.80 (1H, m), 2.67 (1H, d, $J = 18.3$ Hz), 1.96-1.80 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) (major amide rotamer) δ : 194.6, 155.3, 142.8, 142.5, 140.2, 131.3, 127.8, 125.8, 120.0, 114.2, 84.8, 56.1, 52.5, 48.7, 46.8, 42.8, 37.3, 33.2, 28.7 (minor amide rotamer) δ : 194.3, 155.4, 142.8, 142.5, 139.8, 131.4, 127.8, 126.0, 120.0, 114.2, 84.8, 56.1, 52.5, 48.7, 46.7, 42.9, 37.4, 33.5, 28.5

HRMS (FAB) Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_5$ 342.1341 ($\text{M}+1^+$), Found 342.1338

4,5-Epoxy-6,7-epoxy-3-methoxy-17-methoxycarbonylmorphinan-8-one (**22**)

To a stirred solution of **21** (600 mg, 1.76 mmol) in acetonitrile (12.0 ml) were added 30% aqueous hydroperoxide (897 μl , 8.79 mmol) and 5% aqueous sodium hydroxide (3.52 ml, 4.39 mmol) at 0 $^{\circ}\text{C}$. After stirring for 15 minutes, saturated aqueous ammonium chloride was added to the mixture and it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was rinsed with ethyl acetate/hexane (15/85) to give **22** (572 mg, 91%) as white crystals.

mp: 189-192 $^{\circ}\text{C}$

IR (film, cm^{-1}): 2951, 1699, 1506, 1448, 1315, 1279, 1132, 1053, 798, 733

^1H NMR (400 MHz, CDCl_3) δ : 6.78 (1H, d, $J = 8.2$ Hz), 6.65 (1H, d, $J = 8.2$ Hz), 5.17-4.96 (2H, m), 4.07 (major amide rotamer)(0.55 1H, d, $J = 13.7$ Hz), 3.93 (minor amide rotamer)(0.45 1H, d, $J = 13.7$ Hz), 3.88 (3H, s), 3.74 (major amide rotamer)(0.55 3H, s), 3.71 (minor amide rotamer)(0.45 3H, s), 3.61 (1H, s), 3.31-3.19 (1H, m), 3.18-3.11 (2H, m), 2.85-2.70 (1H, m), 2.63 (1H, d, $J = 18.3$ Hz), 2.05-1.94 (1H, m), 1.84-1.73 (1H, m)

^{13}C NMR (100 MHz, CDCl_3) (major amide rotamer) δ : 202.3, 155.0, 144.1, 142.3, 126.5, 125.5, 120.3, 114.3, 83.8, 58.1, 56.0, 54.8, 52.6, 47.2, 46.5, 45.8, 36.9, 35.0, 29.1 (minor amide rotamer) δ : 202.0, 155.2, 144.1, 142.3, 126.7, 125.5, 120.3, 114.3, 83.8, 58.1, 56.0, 54.8, 52.5, 47.2, 46.3, 45.7, 37.0, 35.3, 28.9

HRMS (FAB) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_6$ 358.1290 ($\text{M}+1^+$), Found 358.1280

4,5-Epoxy-6,7-epoxy-3-methoxy-17-methoxycarbonylmorphinan-8-ol (**23**)

To a stirred solution of **22** (572 mg, 1.60 mmol) in methanol (5.0 ml) and dichloromethane (5.0 ml) was added sodium borohydride in tetrahydrofuran (60.6 mg, 1.60 mmol) at $0\text{ }^\circ\text{C}$. After stirring for 20 minutes, saturated aqueous ammonium chloride was added to the mixture and it was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was rinsed with diethyl ether/hexane (50/50) to give **23** (521 mg, 91%) as white crystals.

mp: $182\text{--}185\text{ }^\circ\text{C}$

IR (film, cm^{-1}): 3440, 2933, 1680, 1506, 1452, 1408, 1327, 1275, 1128, 1057, 918, 800, 733

^1H NMR (400 MHz, CDCl_3) δ : 6.80 (1H, d, $J = 8.2\text{ Hz}$), 6.69 (1H, d, $J = 8.2\text{ Hz}$), 5.00–4.81 (2H, m), 4.31–4.23 (1H, m), 4.08–3.88 (4H, m), 3.75 (minor amide rotamer)(0.40 3H, s), 3.71 (major amide rotamer)(0.60 3H, s), 3.39–3.28 (2H, m), 3.22–3.18 (1H, m), 2.98–2.81 (1H, m), 2.70 (1H, d, $J = 18.3\text{ Hz}$), 2.17 (1H, s), 1.80–1.61 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) (major amide rotamer) δ : 155.3, 144.6, 142.3, 128.2, 127.5, 119.4, 113.5, 84.9, 64.9, 56.0, 54.6, 52.5, 50.9, 49.9, 38.7, 38.1, 37.6, 37.4, 31.7 (minor amide rotamer) δ : 154.9, 144.6, 142.4, 128.0, 127.5, 119.5, 113.7, 84.9, 65.4, 56.1, 54.5, 52.6, 50.9, 50.1, 38.7, 38.2, 37.3, 37.2, 31.9

HRMS (FAB) Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_6$ 360.1447 ($\text{M}+1^+$), Found 360.1457

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-7-en-6-ol (**23**)

To a stirred solution of **23** (40.0 mg, 0.111 mmol) in 1,2-dichloroethane (1.0 ml) were added *N,N*-dimethylaminopyridine (16.3 mg, 0.134 mmol) and 1,1'-thiocarbonyldiimidazole (44.1 mg, 0.223 mmol) at room temperature, then the reaction mixture was refluxed for 15 hours at 60 °C. It was allowed to cool to room temperature, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane only, twice) to give thioimidazolide (48.3 mg) containing impurities. The product was dissolved in tetrahydrofuran (1.0 ml), and to the cloudy solution were added tributyltin hydride (89.8 μ l, 0.334 mmol) and 1.02 M triethylborane in hexane (109 μ l, 0.111 mmol) at room temperature. The mixture turned clear, and it was stirred for 3 hours. Half saturated aqueous potassium fluoride was added to the mixture and stirred for 2 hours, then it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 50/50 – 60/40) to give **24** (18.3 mg, 48% in 2 steps) as a white foam.

IR (film, cm⁻¹): 3417, 2952, 1680, 1606, 1504, 1450, 1327, 1275, 1028, 796, 731

¹H NMR (400 MHz, CDCl₃) δ : 6.70 (1H, d, *J* = 8.0 Hz), 6.57 (1H, d, *J* = 8.0 Hz), 6.05-6.00 (1H, m), 5.68-5.60 (1H, m), 4.85-4.75 (2H, m), 4.27 (1H, s), 4.12 (minor amide rotamer)(0.40 1H, dd, *J* = 13.7 Hz, 4.6 Hz), 3.97 (major amide rotamer)(0.60 1H, dd, *J* = 13.7 Hz, 4.6 Hz), 3.85 (3H, s), 3.76 (minor amide rotamer)(0.40 3H, s), 3.73 (major amide rotamer)(0.60 3H, s), 3.01-2.80 (3H, m), 2.75 (1H, d, *J* = 18.3 Hz), 2.03-1.84 (2H, m)

¹³C NMR (100 MHz, CDCl₃) (major amide rotamer) δ : 155.9, 145.7, 142.3, 131.8, 131.7, 129.3, 125.8, 119.2, 113.2, 94.0, 67.7, 56.2, 52.7, 50.3, 44.2, 38.9, 38.0, 35.3, 28.9 (minor amide rotamer) δ : 155.6, 145.7, 142.3, 131.8, 131.6, 129.3, 125.6, 119.2, 113.2, 94.1, 67.7, 56.2, 52.8, 50.6, 44.2, 39.1, 38.0, 35.1, 29.2

HRMS (FAB) Calcd for C₁₉H₂₁NO₅ 343.1420 (M⁺), Found 343.1421

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-7-en-6-one (29)

To a stirred solution of **24** (45.0 mg, 0.131 mmol) in dichloromethane (1.5 ml) was added Dess-Martin periodinane (72.3 mg, 0.170 mmol) at room temperature. After stirring for 30 minutes, saturated aqueous sodium hydrogen carbonate was added to the mixture and it was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by PTLC (ethyl acetate/hexane = 67/33) to give **29** (42.8 mg, 96%) as a white foam.

IR (film, cm^{-1}): 2952, 1684, 1504, 1446, 1406, 1321, 1273, 1234, 731

^1H NMR (400 MHz, CDCl_3) δ : 6.72 (1H, d, $J = 8.2$ Hz), 6.68-6.61 (2H, m), 6.14 (1H, dd, $J = 10.1$ Hz, 2.8 Hz), 5.07-5.01 (major amide rotamer)(0.60 1H, br), 4.91-4.85 (minor amide rotamer)(0.40 1H, br), 4.70 (1H, s), 4.18-4.11 (minor amide rotamer)(0.40 1H, m), 4.04-3.97 (major amide rotamer)(0.60 1H, m), 3.87 (3H, s), 3.78 (minor amide rotamer)(0.40 3H, s), 3.74 (major amide rotamer)(0.60 3H, s), 3.07-3.04 (1H, m), 2.96-2.80 (3H, m), 2.03-1.87 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) (major amide rotamer) δ : 194.0, 155.9, 147.1, 144.9, 142.8, 133.2, 127.8, 124.6, 120.5, 115.1, 87.7, 56.7, 52.9, 50.4, 43.5, 40.3, 38.1, 33.5, 29.1 (minor amide rotamer) δ : 194.0, 155.4, 146.8, 144.9, 142.8, 133.3, 127.8, 124.4, 120.5, 115.1, 87.7, 56.7, 53.0, 50.7, 43.4, 40.4, 38.1, 33.3, 29.4

HRMS (FAB) Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_5$ 341.1263 (M^+), Found 341.1274

Codeine (25)

To a stirred solution of **29** (31.0 mg, 0.0908 mmol) in tetrahydrofuran (2.0 ml) was added lithium aluminum hydride (17.2 mg, 0.454 mmol) at room temperature, then the reaction mixture was refluxed for 40 minutes. It was allowed to cool to 0 °C, then methanol (0.2 ml) and sodium sulfate decahydrate (250 mg) was added. The mixture was diluted with dichloromethane and stirred for 3 hours. It was filtered, and evaporated under reduced pressure. The crude product was purified by PTLC (chloroform/methanol = 90/10) to give codeine (**25**) (22.0 mg, 81%) as white crystals.

mp: 144-146 °C (recrystallized with MeOH/H₂O)

IR (film, cm⁻¹): 3386, 2931, 2839, 1633, 1602, 1502, 1450, 1279, 1255, 1120, 1055, 787, 731

¹H NMR (400 MHz, CDCl₃) δ: 6.67 (1H, d, *J* = 8.2 Hz), 6.57 (1H, d, *J* = 8.2 Hz), 5.71 (1H, ddd, *J* = 9.8 Hz, 1.4 Hz, 1.4 Hz), 5.30 (1H, ddd, *J* = 9.8 Hz, 2.5 Hz, 2.5 Hz), 4.90 (1H, dd, *J* = 6.6 Hz, 1.2 Hz), 4.21-4.15 (1H, m), 3.85 (3H, s), 3.38-3.32 (1H, m), 3.05 (1H, d, *J* = 18.7 Hz), 2.70-2.65 (1H, m), 2.59 (1H, dd, *J* = 12.4 Hz, 4.0 Hz), 2.44 (3H, s), 2.40 (1H, dd, *J* = 12.4, 3.6 Hz), 2.30 (1H, dd, *J* = 18.7 Hz, 6.4 Hz), 2.06 (1H, dt, *J* = 12.4, 5.0 Hz), 1.88 (1H, d, *J* = 10.8 Hz)

¹³C NMR (100 MHz, CDCl₃) δ: 146.2, 142.1, 133.4, 130.9, 128.2, 127.0, 119.5, 112.7, 91.3, 66.3, 58.8, 56.2, 46.4, 43.0, 42.9, 40.7, 35.7, 20.3

HRMS (FAB) Calcd for C₁₈H₂₁NO₃ 299.1521 (M⁺), Found 299.1532

Morphine (1)

To a stirred solution of **25** (24.0 mg, 0.0802 mmol) in dichloromethane (2.0 ml) was added 1.0 M boron tribromide in dichloromethane (481 μl , 0.481 mmol) at room temperature. After stirring for 30 minutes, 10% aqueous ammonia was added to the mixture at 0 °C and it was extracted with dichloromethane/ethanol (90/10). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was crystallized from methanol/chloroform/diethyl ether to give **1** (17.0 mg, 74%) as white crystals.

mp: 202-206 °C (decomp.)

IR (film, cm^{-1}): 3357, 2929, 2850, 1635, 1614, 1504, 1458, 1250, 1120, 787, 731

^1H NMR (400 MHz, CDCl_3) δ : 6.63 (1H, d, $J = 8.2$ Hz), 6.59 (1H, d, $J = 8.2$ Hz), 5.64 (1H, d, $J = 9.8$ Hz), 5.27-5.23 (1H, m), 4.86 (1H, d, $J = 6.4$ Hz), 4.20-4.17 (1H, m), 3.43-3.40 (1H, m), 3.02 (1H, d, $J = 18.7$ Hz), 2.75-2.69 (1H, m), 2.67 (1H, dd, $J = 12.0$ Hz, 4.4 Hz), 2.49-2.42 (1H, m), 2.46 (3H, s), 2.33 (1H, dd, $J = 18.7$ Hz, 6.4 Hz), 2.11 (1H, dt, $J = 12.6$ Hz, 4.8 Hz), 1.87 (1H, d, $J = 11.4$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ : 145.9, 138.7, 133.0, 130.5, 128.1, 125.6, 119.9, 117.5, 91.2, 66.5, 58.9, 46.4, 42.9, 42.8, 40.2, 35.1, 20.6

HRMS (FAB) Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}_3$ 285.1365 (M^+), Found 285.1367

26

7.2637
7.2362
7.2316
7.0918
7.0873
7.0712
7.0666
6.9039
6.8810

5.3298
5.2450

3.8885

3.5241

3.3202

0.0000

S24

7.3026
7.2820
7.2683
6.9246
6.9039

5.3985
5.1625

3.8541
3.6914
3.3775

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S25

PPM

0.00 0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50 8.00 8.50 9.00 9.50 10.00 10.50 11.00

27
R = *p*-nitrobenzoyl

13
R = *p*-nitrobenzoyl

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6.0401
6.0263
6.0149
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5.3199
5.6968
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5.7214
5.7248
5.7283
6.5645
6.5851
6.6550
6.6751

7.2633

S44

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1.8798
2.0706
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