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TOTAL SYNTHESIS OF (±)-MORPHINE

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Abstract – The morphinan skeleton was effectively synthesized by an intramolecular Mannich-type reaction. Further transformation led to the total synthesis of morphine.

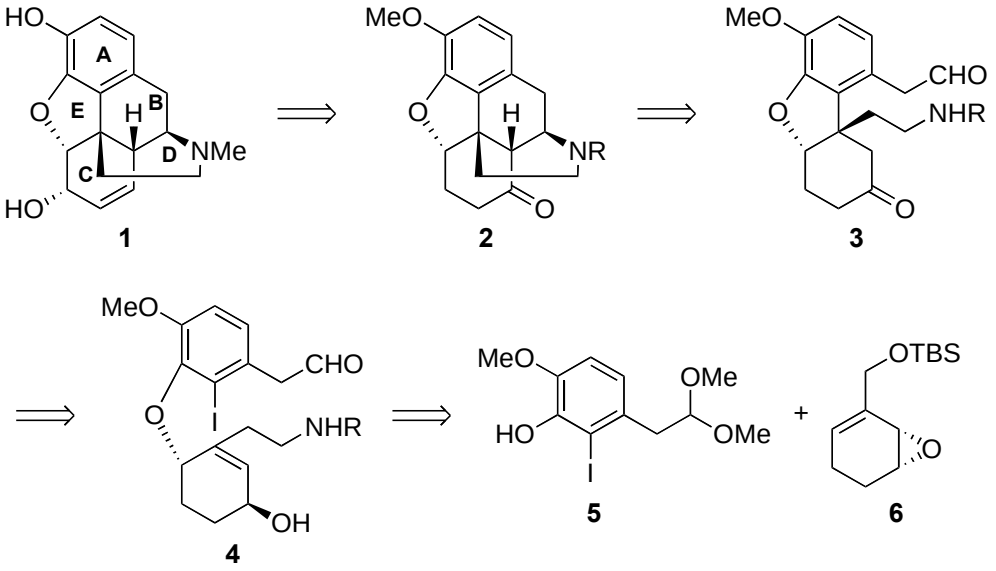
INTRODUCTION

Morphine (**1**) is a fascinating compound, which has been used as an efficient analgesic and is indispensable in treating pain associated with cancer. Although morphine is strictly controlled by authorities due to its addictive nature, its structure is quite attractive from a synthetic point of view. Its complicated pentacyclic skeleton, which includes a quaternary carbon center, has stimulated extensive synthetic efforts. Hence, a number of synthetic studies as well as the total syntheses of morphine have been reported.[1] Among them, the Pd-mediated total synthesis reported recently by Trost and co-workers seems quite versatile.[1f,g,2] However, in our efforts to develop a novel, non-addictive morphine-type drug, we have investigated the efficient total synthesis of (±)-morphine which involves the unique construction of the morphinan skeleton.

RESULTS AND DISCUSSION

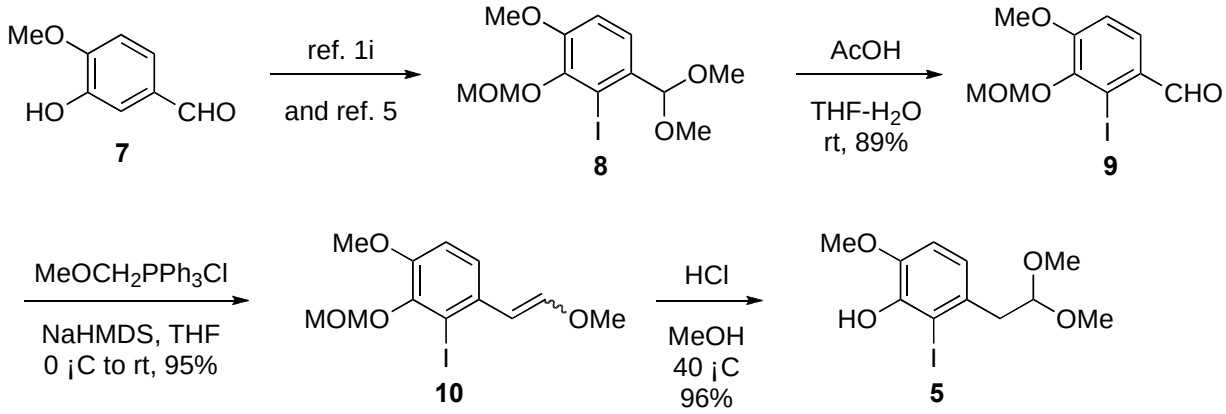
Scheme 1 shows our retrosynthetic analysis. Morphine could be derived from ketone intermediate **2**, which in turn could be prepared from ketoaldehyde **3** by either a successive aldol-Michael protocol or

a Mannich-type reaction (vide infra). Ketoaldehyde **3** could be obtained via an intramolecular Heck reaction[1f,g,2] of **4**, which could be prepared from phenol **5** and epoxide **6**[3] using Tsuji-Trost coupling.[4]



Scheme 1. Retrosynthetic Analysis

Our synthesis commenced with the conversion of isovanillin (**7**) into iodide **8** according to a known procedure (Scheme 2).[1i,5] Acidic hydrolysis of the acetal and subsequent Wittig olefination gave the enol ether **10**, which upon treatment with methanolic HCl furnished phenol **5**.

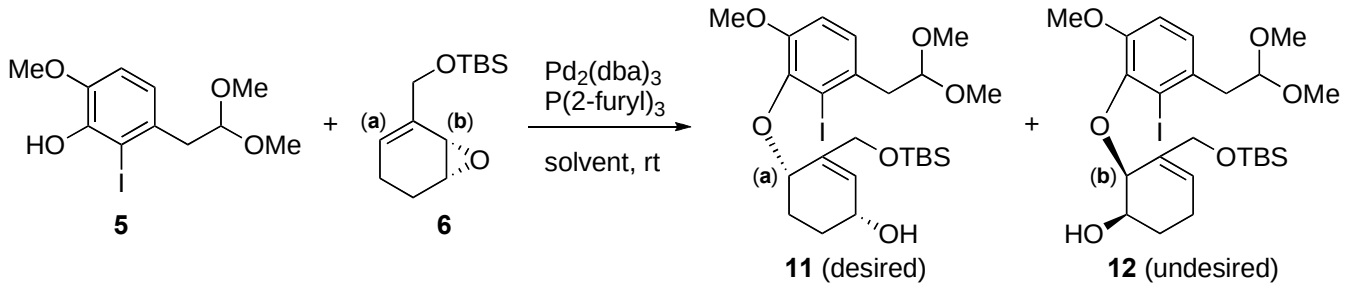


Scheme 2. Conversion of Isovanillin

Tsuji-Trost reaction[4] was used to condense A ring **5** and C ring **6**. As shown in Table 1, this Pd-mediated coupling reaction of phenol **5** and epoxide **6** had an interesting solvent effect. A higher selectivity for desired ether **11**, which resulted from the reaction at (**a**) of **6**, was obtained upon employing a polar solvent, such as acetonitrile or *N*,*N*-dimethylformamide (entries 3 and 4) instead of toluene or tetrahydrofuran (entries 1 and 2). Hence, Tsuji-Trost reaction of **5** and **6** in acetonitrile, which is suitable

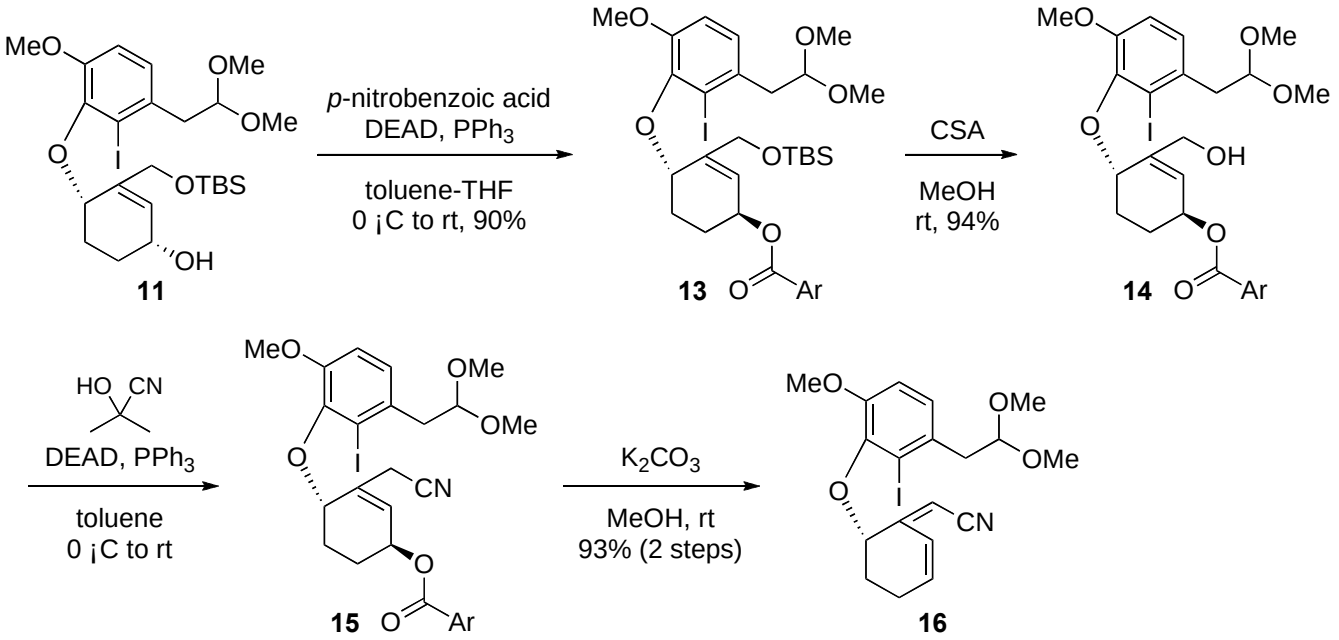
for a scaled up reaction, provided desired **11** in 91% yield in a completely regio- and stereoselective manner.

Table 1. Tsuji-Trost Reaction with Phenol **5** and Epoxide **6**



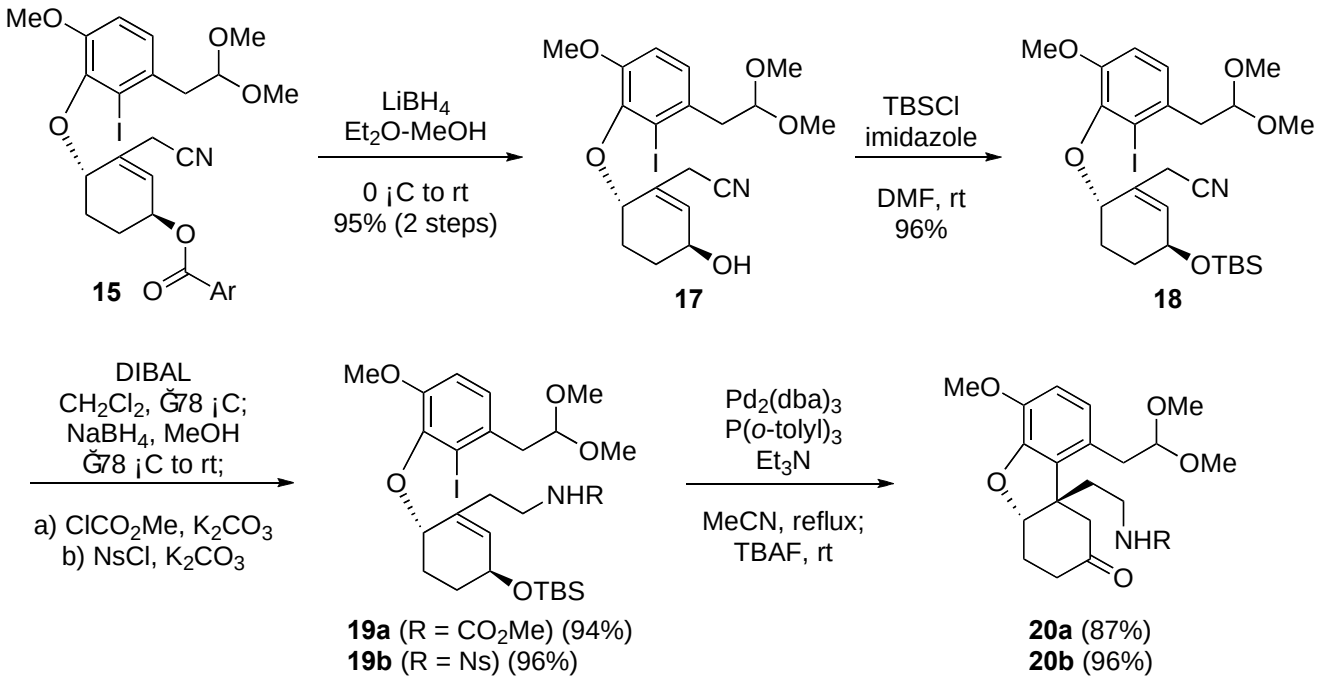
entry	solvent	yield (**11** : **12**) (%)
1	toluene	64 : 30
2	THF	71 : 18
3	DMF	91 : trace
4	MeCN	91 : trace

We then focused on the functionalities of the C ring (Scheme 3). After inversion of the hydroxyl group of **11** under Mitsunobu conditions,[6] the *t*-butyldimethylsilyl (TBS) group was removed to give alcohol **14**. The alcohol was then converted to nitrile **15** using a Mitsunobu reaction.[7] Attempts to cleave the *p*-nitrobenzoate of **15** under basic conditions provided unsaturated nitrile **16** as a single isomer (*E* or *Z* was not determined).



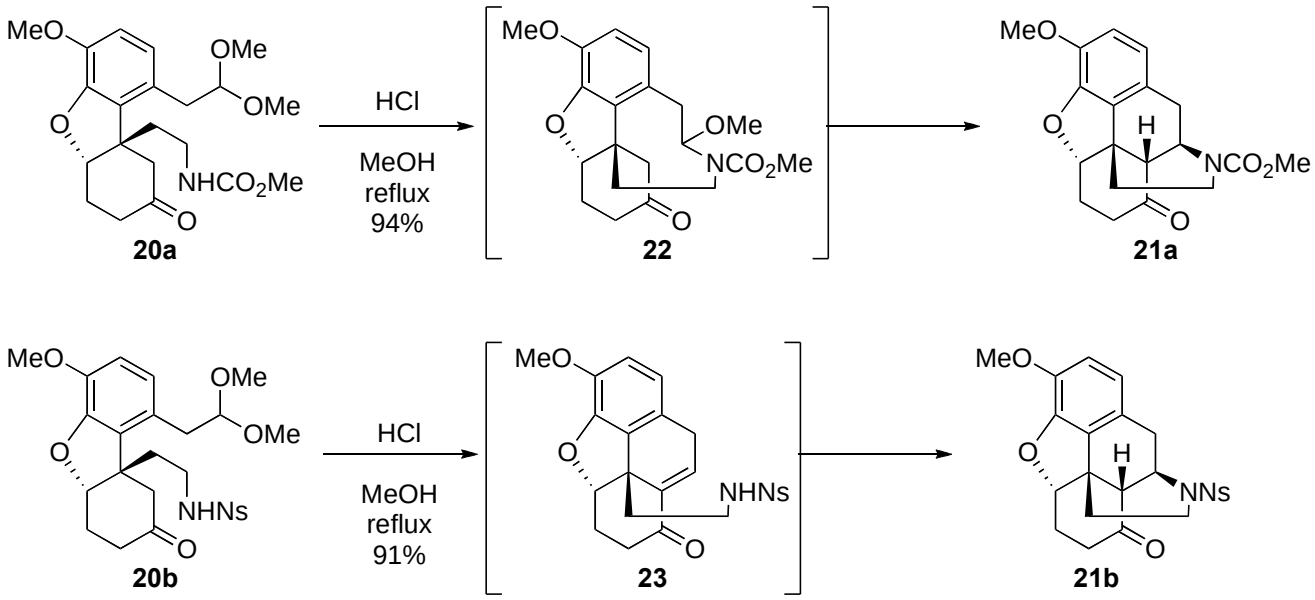
Scheme 3. Functionalities of the C Ring

Treatment with lithium borohydride affected the cleavage of the *p*-nitrobenzoate (Scheme 4). The resulting alcohol was protected as TBS ether **18**. To suppress the reductive cleavage of the aromatic iodide, the nitrile was initially reduced with diisobutylaluminum hydride (DIBAL) at –78 °C, and methanol and sodium borohydride were subsequently added to give the desired amine, which was isolated as corresponding methyl carbonate **19a** and 2-nitrobenzenesulfonamide (Ns amide) **19b**. The crucial intramolecular Heck reaction of **19** proceeded smoothly in refluxing acetonitrile to give a silyl enol ether, which upon treatment with tetrabutylammonium fluoride (TBAF) furnished ketone **20**.



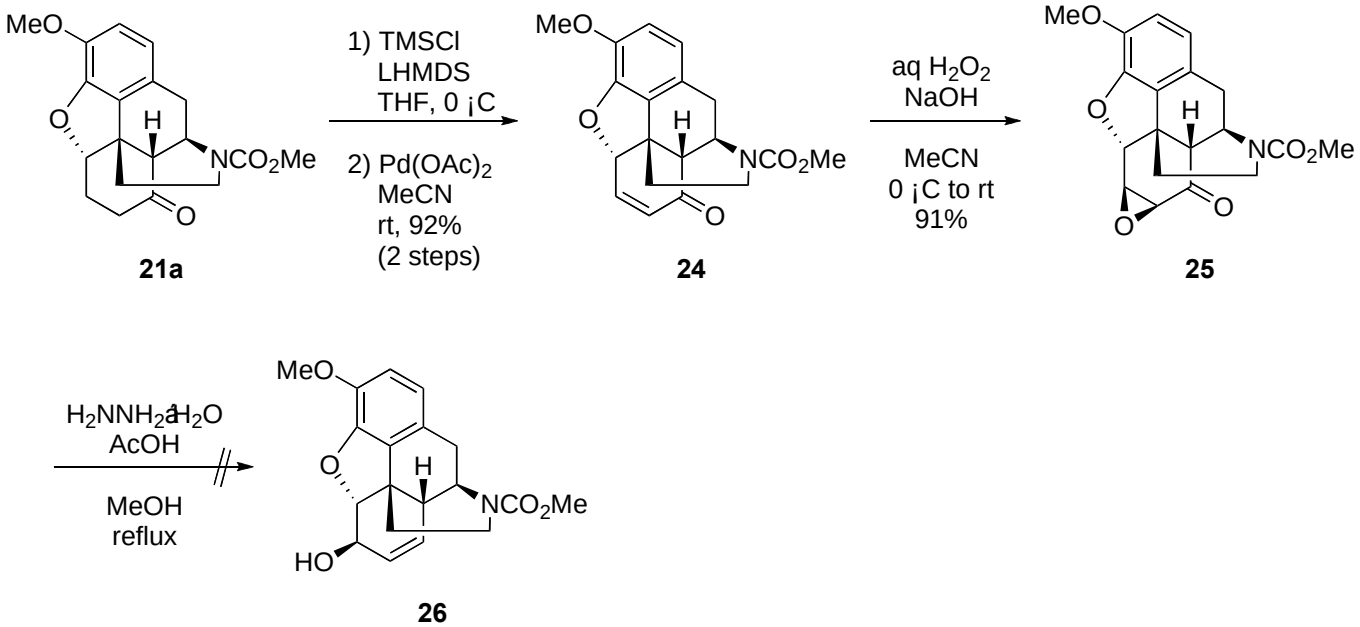
Scheme 4. Construction of the E Ring

With requisite ketone **20** in hand, we then focused on constructing the B and D rings as shown in Scheme 5. To our surprise, acidic hydrolysis conditions for dimethylacetal of **20** provided double cyclization product **21**. Upon treatment of **20** in refluxing methanolic HCl, the desired tandem cyclization reaction proceeded smoothly to give desired **21** in excellent yield as the sole product. Even if different amide **20a** and **20b** was employed, the reaction gave the desired product **21a** or **21b**, respectively. However, the reaction intermediates were completely different. In the reaction of **20a,** which was protected with a methoxycarbonyl group, eight-membered hemiaminal **22** could also be isolated by terminating the reaction after a short time. On the other hand, similar treatment with **20b** produced enone **23**. These results suggest that in the case of **20a**, the reaction proceeds via an intramolecular Mannich-type reaction, while the reaction of **20b** proceeds via an aldol condensation-Michael reaction.



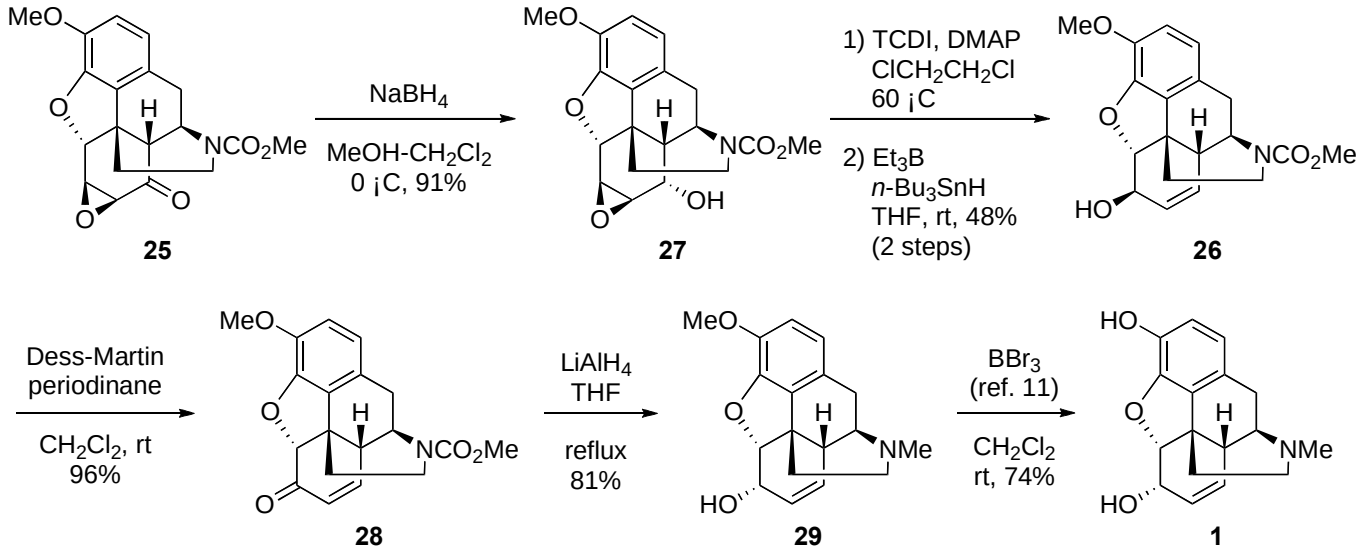
Scheme 5. Construction of the B and D Rings

The next task in the synthesis of **1** was to change the oxidation state at the C ring. After conversion to the sillyl enol ether from ketone **21a**, a Pd-mediated Ito-Saegusa reaction[8] provided the enone **24** (Scheme 6). Upon treatment of **24** with H_2O_2 under basic conditions, the β-selective epoxidation reaction proceeded smoothly to furnish epoxyketone **25** as a single isomer. Although we initially tested the Wharton reaction[9] of **25** to obtain allylic alcohol **26**, the reaction of **25** and hydrazine in acidic conditions did not proceed, even upon refluxing. Thus, we then investigated a radical fragmentation of epoxyalcohol **27** derived from **25**.



Scheme 6. Attempted Wharton Reaction

Reduction of ketone **25** gave the epoxyalcohol **27** as the sole isomer (Scheme 7). **27** was converted to the thiocarbamate, and subsequent exposure to radical conditions[10] using 2,2'-azobis(isobutyronitrile) (AIBN) and tributyltin hydride only led to the decomposition of the thiocarbamate under reflux conditions. However, switching from AIBN to triethylborane induced the epoxide opening at room temperature, and provided allylic alcohol **26**. The resulting alcohol was inverted by a two-step oxidation-reduction sequence where the methyl carbamate was reduced with lithium aluminum hydride to afford codeine (**29**).[1h] Finally, the methyl ether was cleaved according to a literature procedure to furnish morphine (**1**).[11]



Scheme 7. Total Synthesis of Morphine

In summary, we successfully synthesized morphine using an intramolecular Mannich-type reaction to construct the B and D rings. The substrate for this critical reaction was efficiently prepared by taking advantage of two types of palladium-catalyzed reactions. Further studies on a more efficient and enantioselective total synthesis of morphine are currently underway, and our results will be reported in due course.

EXPERIMENTAL

General. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were determined on a JEOL-LA400 instrument. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (δ) in deuterochloroform as the internal standard, while coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm relative to the centerline of a triplet at 77.0 ppm for deuterochloroform ($CDCl_3$). Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Infrared spectra (IR), which are reported in

wavenumbers (cm^{-1}), were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrometer. Mass spectra (MS) were obtained on a JEOL JMS-GCmate MS-DIP20 with polyethylene glycol as the matrix. 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% MeOH in $CHCl_3$. Flash column chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (40-100 mesh). All non-aqueous reactions were carried out in oven-dried glass apparatuses under a slight positive pressure of argon. All solvents were dried over molecular sieves 3A or 4A before use. All other reagents were commercially available, and used without further purification, unless otherwise specified.

2-Iodo-4-methoxy-3-(methoxymethoxy)benzaldehyde (9).

Water (100 mL) and acetic acid (200 mL) were added at 0 °C to a stirred solution of **8** (51.0 g, 139 mmol) in THF (250 mL). Then the reaction mixture was warmed to rt. After stirring for 3 h, 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 157.8, 146.4, 129.7, 128.0, 112.5, 101.2, 99.5, 59.2, 56.9. Anal. Calcd for $C_{10}H_{11}IO_4$: 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).

0.99 M Sodium bis(trimethylsilyl)amide in THF (108 mL, 107 mmol) was added over 50 min at 0 °C to a stirred solution of (methoxymethyl)triphenylphosphonium chloride (36.7 g, 107 mmol) in THF (350 mL). After stirring at 0 °C for 10 min, a solution of **9** (32.8 g, 102 mmol) in THF (135 mL) was added to the reaction mixture over 1 h at 0 °C. After stirring at 0 °C for 10 min, the reaction mixture was warmed to rt, and was subsequently stirred for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the solvent was evaporated under reduced pressure. The residue was diluted with Et_2O, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane = 25/75) to give **10** (34.0 g, 95%) as a white solid. The product was a mixture of *E* and *Z* (70:30) isomers. Anal. Calcd for $C_{12}H_{15}IO_4$: C, 41.10; H, 4.39; N, 0. Found: C, 41.16; H, 4.32; N, 0. *E*: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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*: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

2-Iodo-6-methoxy-3-(2,2-dimetoxyethyl)phenol (5).

Acetyl chloride (4.3 mL, 60.0 mmol) was added at rt to a stirred solution of **10** (42.0 g, 120 mmol) in MeOH (500 mL). After stirring at 40 °C for 1 h, pulverized K_2CO_3 (8.30 g, 60.0 mmol) was added, and the solvent was evaporated under reduced pressure. The residue was diluted with Et_2O, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was rinsed with hexane to give **5** (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; ^{1}H 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 $C_{11}H_{15}IO_4$: 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).

Tris(dibenzylideneacetone)dipalladium(0) (948 mg, 1.04 mmol) and tri-2-furylphosphine (961 mg, 4.14 mmol) were added at rt to a stirred solution of **5** (35.0 g, 104 mmol) and **6** (28.6 g, 119 mmol) in MeCN (280 mL). After stirring for 20 min, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/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; ^{1}H 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 $C_{24}H_{39}IO_6Si$: 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 (13).

2.2 M Diethyl azodicarboxylate in toluene (24.0 mL, 52.8 mmol) was added dropwise over 80 min at 0 °C to a stirred solution of **11** (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 THF (40 mL). The reaction mixture was warmed to rt. After stirring for 20 min, the solvent was evaporated under reduced pressure. The residue was diluted with Et_2O (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 (EtOAc/hexane = 17/83) to give **13** (28.7 g, 90%) as a yellow foam. IR (film, cm^{-1}) 2933, 2857, 2360, 1720,

1529, 1473, 1344, 1269, 1119; ^{1}H 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 $C_{31}H_{42}INO_9Si$: 727.1674 (M^+). Found: 727.1690.

4-[3-(2,2-Dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-3-hydroxymethyl-2-cyclohexen-1-yl 4-nitrobenzoate (14).

10-Camphorsulfonic acid (16.1 mg, 0.0695 mmol) was added at rt to a stirred solution of **13** (1.01 g, 1.39 mmol) in MeOH (10 mL). After stirring for 80 min, the reaction mixture was diluted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 40/60) to give **14** (802 mg, 94%) as a yellow foam. IR (film, cm^{-1}) 3454, 2939, 2835, 2360, 1720, 1527, 1475, 1344, 1271, 1119, 1024; ^{1}H 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 $C_{25}H_{28}INO_9$: 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 (15).

2.2 M Diethyl azodicarboxylate in toluene (18.6 mL, 40.9 mmol) was added dropwise over 1 h at 0 °C to a stirred solution of **14** (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). Then the reaction mixture was warmed to rt. After stirring for 40 min, the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (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 (CH_2Cl_2 only, EtOAc/hexane = 25/75 – 33/67, CH_2Cl_2 only) to give **15** (22.0 g), which contained impurities. The product was not further purified at this stage. IR (film, cm^{-1}) 2941, 2833, 2252, 1722, 1527, 1475, 1346, 1271, 1119, 1026, 918, 721; ^{1}H 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 $C_{26}H_{27}INO_8$: 622.0812 (M^+). Found: 622.0811.

3-Cyanomethyl-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexenol (17).

2.0 M Lithium borohydride in THF (20.5 mL, 40.9 mmol) was added dropwise over 20 min at 0 °C to a stirred solution of crude **15** (22.0 g) in Et_2O (200 mL) and MeOH (10.0 mL). The reaction mixture was warmed to rt and stirred for 40 min. Saturated aqueous NH_4Cl was added to the solution, and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 40/60 – 60/40) to give **17** (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; ^{1}H 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 $C_{19}H_{24}INO_5$: 473.0699 (M^+). Found: 473.0698.

***tert*-Butyldimethyl[3-cyanomethyl-4-[3-(2,2-dimethoxyethyl)-2-iodo-6-methoxy]phenoxy-2-cyclohexenoxy]silane (18).**

t-Butyldimethylchlorosilane (4.89 g, 32.5 mmol) was added at rt to a stirred solution of **17** (12.8 g, 27.0 mmol) and imidazole (2.21 g, 32.5 mmol) in DMF (67.5 mL), and then the reaction mixture was stirred for 1 h. Water was then added to the solution, and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was rinsed with hexane and filtered to collect **18** (13.5 g) as white crystals. The filtrate was evaporated under reduced pressure and purified by silica gel column chromatography (Et_2O/hexane = 20/80 – 25/75) to give **18** (1.70 g) as white crystals. Finally, 15.2 g of **18** 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{38}INO_5Si$: 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 (19a).**

0.99 M Diisobutylaluminium hydride in toluene (3.67 mL, 3.63 mmol) was added dropwise over 10 min at -78 °C to a stirred solution of **18** (1.64 g, 2.79 mmol) in CH_2Cl_2 (30.0 mL), and then the reaction mixture was stirred for 2 h. Sodium borohydride (317 mg, 8.37 mmol) and MeOH (10.0 mL) were added to the solution. The reaction mixture was warmed to rt, and was subsequently stirred for 40 min. Pulverized K_2CO_3 (463 mg, 3.35 mmol) and methyl chloroformate (259 μL, 3.35 mmol) were added, and the reaction mixture was stirred for 30 min. 30% Aqueous potassium sodium (+)-tartrate (30.0 mL) was added to the mixture. The reaction mixture was stirred for 1 h, and then extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 25/75) to give **19a** (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 Hz), 6.79 (1H, d, *J* = 8.2 Hz), 5.57 (1H, s), 5.08 (1H, s), 5.02 (1H, s), 4.51 (1H, t, *J* = 5.5 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 $C_{27}H_{44}INO_7Si$: 649.1932 (M^+). Found: 649.1935.

1-(2,2-Dimethoxyethyl)-4-methoxy-9a-(2-methoxycarbonylaminoethyl)-5a,6,7,9-tetrahydrodibenzo-furan-8-one (20a).

Tris(dibenzylideneacetone)dipalladium(0) (116 mg, 0.127 mmol) was added at rt to a stirred solution of **19a** (1.65 g, 2.54 mmol), tri-*o*-tolylphosphine (155 mg, 0.508 mmol), and triethylamine (704 μL, 5.08 mmol) in MeCN (17.0 mL). Then the reaction mixture was refluxed for 1 h, cooled to rt and 1.0 M tetrabutylammonium fluoride in THF (3.05 mL, 3.05 mmol) was added. After stirring for 90 min, saturated aqueous NH_4Cl was added to the mixture, which was subsequently extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 25/75 – 100/0) to give **20a** (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 $C_{21}H_{29}NO_7$: 407.1944

(M^+). Found: 407.1952.

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-8-one (21a).

Acetyl chloride (969 μL, 13.6 mmol) was added at rt to a stirred solution of **20a** (555 mg, 1.36 mmol) in MeOH (10.0 mL), and then the reaction mixture was refluxed for 12 h. It was cooled to rt, and acetyl chloride (969 μL, 13.6 mmol) was added. Then the reaction mixture was refluxed for another 12 h, and cooled to rt, diluted with toluene, and evaporated under reduced pressure to remove MeOH. The organic layer was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 50/50) to give **21a** (440 mg, 94%) as a white foam. mp 126-128 °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), 4.11 (major amide rotamer) (0.60 1H, d, *J* = 13.8 Hz), 3.96 (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 $C_{19}H_{21}NO_5$: 343.1420 (M^+). Found: 343.1430.

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-6-en-8-one (24).

1.00 M Lithium bis(trimethylsilyl)amide in THF (12.4 mL, 12.4 mmol) was added over 5 min at 0 °C to a stirred solution of **21a** (3.03 g, 8.82 mmol) and chlorotrimethylsilane (1.34 mL, 10.6 mmol) in THF (50.0 mL). After stirring for 40 min, saturated aqueous NH_4Cl was added to the mixture, which was subsequently extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was dissolved in MeCN (50.0 mL), and palladium acetate (2.97 g, 13.2 mmol) was added to the solution at rt. After stirring for 2 h, saturated aqueous $NaHCO_3$ was added to the mixture, which was subsequently extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 40/60 – 60/40) to give **24** (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 $C_{19}H_{19}NO_5$: 342.1341 (M^++H). Found: 342.1338.

4,5-Epoxy-6,7-epoxy-3-methoxy-17-methoxycarbonylmorphinan-8-one (25).

30% Aqueous H_2O_2 (897 μL, 8.79 mmol) and 5% aqueous sodium hydroxide (3.52 mL, 4.39 mmol) were added at 0 °C to a stirred solution of **24** (600 mg, 1.76 mmol) in MeCN (12.0 mL). After stirring for 15 min, saturated aqueous NH_4Cl was added to the mixture, which was subsequently extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was rinsed with EtOAc/hexane (15/85) to give **25** (572 mg, 91%) as white crystals. mp 189-192 °C; IR (film, cm^{-1}) 2951, 1699, 1506, 1448, 1315, 1279, 1132, 1053, 798, 733; ^{1}H 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 $C_{19}H_{20}NO_6$: 358.1290 (M^++H). Found: 358.1280.

4,5-Epoxy-6,7-epoxy-3-methoxy-17-methoxycarbonylmorphinan-8-ol (27).

Sodium borohydride (60.6 mg, 1.60 mmol) was added at 0 °C to a stirred solution of **25** (572 mg, 1.60 mmol) in MeOH (5.0 mL) and CH_2Cl_2 (5.0 mL). After stirring for 20 min, saturated aqueous NH_4Cl was added to the mixture, which was subsequently extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was rinsed with Et_2O/hexane (50/50) to give **27** (521 mg, 91%) as white crystals. mp 182-185 °C; IR (film, cm^{-1}) 3440, 2933, 1680, 1506, 1452, 1408, 1327, 1275, 1128, 1057, 918, 800, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.80 (1H, d, *J* = 8.2 Hz), 6.69 (1H, d, *J* = 8.2 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 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 $C_{19}H_{21}NO_6$: 360.1447 (M^++H). Found: 360.1457.

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-7-en-6-ol (26).

N,*N*-Dimethylaminopyridine (16.3 mg, 0.134 mmol) and 1,1'-thiocarbonyldiimidazole (44.1 mg, 0.223

mmol) were added at rt to a stirred solution of **27** (40.0 mg, 0.111 mmol) in 1,2-dichloroethane (1.0 mL). The reaction mixture was heated for 15 h at 60 °C, cooled to rt, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (CH_2Cl_2 only, twice) to give thioimidazolide (48.3 mg), which contained impurities. The product was dissolved in THF (1.0 mL), and to the cloudy solution were added tributylthin hydride (89.8 μL, 0.334 mmol) and 1.02 M triethylborane in hexane (109 μL, 0.111 mmol) at rt. The mixture turned clear, and was stirred for 3 h. Half saturated aqueous potassium fluoride was added to the mixture, stirred for 2 h, and subsequently extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane = 50/50 – 60/40) to give **26** (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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) (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 $C_{19}H_{21}NO_5$: 343.1420 (M^+). Found: 343.1421.

4,5-Epoxy-3-methoxy-17-methoxycarbonylmorphinan-7-en-6-one (28).

Dess-Martin periodinane (72.3 mg, 0.170 mmol) was added at rt to a stirred solution of **26** (45.0 mg, 0.131 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 30 min, saturated aqueous $NaHCO_3$ was added to the mixture, which was subsequently extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by PTLC (EtOAc/hexane = 67/33) to give **28** (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 $C_{19}H_{19}NO_5$: 341.1263 (M^+). Found: 341.1274.

Codeine (29).

Lithium aluminum hydride (17.2 mg, 0.454 mmol) was added at rt to a stirred solution of **28** (31.0 mg, 0.0908 mmol) in THF (2.0 mL). The reaction mixture was refluxed for 40 min, and subsequently cooled to 0 °C. Then MeOH (0.2 mL) and sodium sulfate decahydrate (250 mg) were added. The mixture was diluted with CH_2Cl_2, stirred for 3 h, filtered, and evaporated under reduced pressure. The crude product was purified by PTLC ($CHCl_3$/MeOH = 90/10) to give codeine (**29**) (22.0 mg, 81%) as white crystals. mp 144-146 °C (recrystallized with MeOH/H_2O); IR (film, cm^{-1}) 3386, 2931, 2839, 1633, 1602, 1502, 1450, 1279, 1255, 1120, 1055, 787, 731; ^1H NMR (400 MHz, $CDCl_3$) 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 Hz, 3.6 Hz), 2.30 (1H, dd, *J* = 18.7 Hz, 6.4 Hz), 2.06 (1H, dt, *J* = 12.4 Hz, 5.0 Hz), 1.88 (1H, d, *J* = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{21}NO_3$: 299.1521 (M^+). Found: 299.1532.

Morphine (1).

1.0 M Boron tribromide in CH_2Cl_2 (481 μL, 0.481 mmol) was added at rt to a stirred solution of **29** (24.0 mg, 0.0802 mmol) in CH_2Cl_2 (2.0 mL). After stirring for 30 min, 10% aqueous ammonia was added to the mixture at 0 °C, which was subsequently extracted with CH_2Cl_2/EtOH (90/10). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under a reduced pressure. The crude product was crystallized from MeOH/$CHCl_3$/Et_2O to give morphine (**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 $C_{17}H_{19}NO_3$: 285.1365 (M^+). Found: 285.1367.

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