A Desymmetrization-Based Approach to Morphinans:
Application in the Total Synthesis of Oxycodone

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Supporting Information Available

I) Experimental Procedures and Physical Data for Compounds
II) Abbreviations
III) References
IV) $^1$H and $^{13}$C NMR Spectra for Compounds

I) Experimental Procedures and Physical Data for Compounds

General Procedures. Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), diethyl ether (Et$_2$O), methylene chloride (CH$_2$Cl$_2$) and toluene were dried and distilled according to the standard protocols. Benzene and acetonitrile (CH$_3$CN) were purchased in anhydrous form and used without further purification. Acetone, ethyl acetate (EtOAc), Et$_2$O, CH$_2$Cl$_2$, hexanes and water were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F–254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, anisaldehyde or potassium permanganate, and
heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on an Agilent 400-MR DD2 Magnetic Resonance System or Varian/Oxford As-500 instrument and calibrated using residue undeuterated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Thermo Scientific Nicolet 6700 spectrometer and IRTracer-100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker (compact) Ultra High Resolution ESI Q-TOF mass spectrometer. Optical rotation ([α]) was recorded on a Jasco P-1030 polarimeter.

Biaryl Phenol 1

(i) To a stirred solution of phosphonium salt 4\textsuperscript{[1]} (dried over P\textsubscript{2}O\textsubscript{5} under vacuum overnight, 19.8 g, 36.7 mmol) in THF (350 mL) at 0 °C was added NaH (3.06 g, 128 mmol). The resulting mixture was stirred for 2 h before a solution of benzaldehyde 3\textsuperscript{[2]} (8.77 g, 31.9 mmol) in THF (50 mL) was added. The resulting mixture was warmed to room temperature and stirred for 4 h before it was cooled to 0 °C and quenched with water (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 6:1) afforded an inconsequential geometric mixture of stilbene 1a (12.3 g, 85%) as an amorphous yellow solid. 1a: \( R_f \) = 0.45, 0.52 (silica gel, hexanes:EtOAc 3:1).
(ii) To a stirred solution of stilbene 1a (14.5 g, 31.8 mmol) in EtOAc/MeOH (4:1, 320 mL) at room temperature was added Pd/C (10% wt/wt, 1.70 g, 1.60 mmol). The resulting mixture was evacuated and filled with hydrogen (3 ×) and stirred under an atmosphere of H₂ (balloon) for 1 h. The resulting mixture was filtered through Celite® and eluted with EtOAc (3 × 80 mL), and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded biaryl phenol 1 (8.19 g, 70%) as an amorphous white solid. 1: Rf = 0.27 (silica gel, hexanes:EtOAc 2:1); IR (film) νmax 3690, 3054, 2987, 1421, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.04 (d, J = 7.2 Hz, 2H), 6.84 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 7.3 Hz, 2H), 5.17 (s, 2H), 4.73 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 2.95–2.91 (m, 2H), 2.81–2.77 ppm (m, 2H); ¹³C NMR (101 MHz, CDCl₃): δ 153.7, 151.4, 143.3, 134.2, 133.8, 129.6, 125.2, 120.1, 115.1, 111.2, 98.6, 58.0, 56.1, 38.4, 35.4 ppm; HRMS calcd. For C₁₇H₁₉BrO₄ Na⁺ [M + Na]⁺ 389.0359, found 389.0361.

**Dienone 5**

To a stirred solution of phenol 1 (6.30 g, 17.2 mmol) in MeCN/H₂O (1:1, 170 mL) at 0 °C was added PIDA (6.63 g, 20.6 mmol). The resulting mixture was stirred for 2 h before it was warmed to room temperature and quenched with Na₂S₂O₃ (50 mL, sat. aq.) and water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 80 mL), the
combined organic layer was washed with NaHCO$_3$ (100 mL, sat. aq.), brine (100 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:E$_{t}$OAc 4:1) afforded dienone 5 (4.34 g, 66%) as an orange amorphous solid. 5: $R_f$ = 0.30 (silica gel, hexanes:E$_{t}$OAc 1:1); IR (film) $\nu_{max}$ 3583, 3152, 2985, 1671, 733 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.88 (d, $J$ = 10.4 Hz, 3H), 6.77 (d, $J$ = 8.6 Hz, 1H), 6.24 (d, $J$ = 10.3 Hz, 2H), 5.13 (s, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 2.69–2.65 (m, 2H), 2.08 (br s, 1H), 2.04–1.99 ppm (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 185.4, 151.7, 150.5, 143.5, 133.2, 128.7, 124.9, 120.1, 111.4, 98.6, 69.8, 58.1, 56.1, 40.0, 30.4 ppm; HRMS calcd. For C$_{17}$H$_{19}$BrO$_5$ Na$^+$ [M + Na]$^+$ 405.0308, found 405.0312.

**Tricyclic Dienone 6**

To a stirred solution of dienone 5 (2.80 g, 7.30 mmol) in toluene (80.0 mL) at room temperature was added K$_2$CO$_3$ (3.03 g, 21.9 mmol), Pd(OAc)$_2$ (0.26 g, 1.16 mmol) and PPh$_3$ (0.61 g, 2.32 mmol). The resulting mixture was warmed to 110 °C and stirred for 24 h before it was cooled to room temperature and diluted with water (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL), the combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:E$_{t}$OAc 4:1) afforded tricyclic dienone 6 (1.77 g, 80%) as an amorphous yellow solid. 6: $R_f$ = 0.32 (silica gel, hexanes:E$_{t}$OAc 1:1); IR (film) $\nu_{max}$ 3585, 3154, 2940, 1660, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.95 (d, $J$ = 8.4 Hz, 1H), 6.92 (d, $J$ = 8.4 Hz, 1H), 6.90 (s, 1H), 6.87 (d, $J$ = 11.0 Hz, 1H), 6.24 (d, $J$ = 10.0 Hz, 1H), 4.96 (s, 2H), 3.84 (s, 3H), 3.38 (s, 3H), 3.21–3.12 (m, 1H), 2.90 (dd, $J$ = 17.1, 7.6 Hz, 1H), 2.49 (s, 1H), 2.28 (dd, $J$ = 13.9, 7.0 Hz, 1H), 1.83–1.79 ppm (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 186.3, 153.0, 151.1, 150.8,
145.2, 130.3, 127.6, 127.4, 126.7, 124.3, 113.9, 99.6, 66.9, 57.9, 56.1, 34.3, 24.2 ppm; HRMS calcd. For C_{17}H_{18}O_{5}Na^{+} [M + Na]^{+} 325.1046, found 325.1047.

Table 1: Asymmetric Heck Reaction Studies of Dienone 5:

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<tr>
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<td>Pd(OAc)$_2$, K$_2$CO$_3$, L1, Toluene, 110 °C, 48 h</td>
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<td>3</td>
<td>Pd(OAc)$_2$, Cy$_2$MeN, L2, CHCl$_3$, 80 °C, 48 h</td>
<td>(no reaction)</td>
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<tr>
<td>4</td>
<td>Pd(OAc)$_2$, K$_2$CO$_3$, L2, Toluene, 110 °C, 48 h</td>
<td>6.2% ee</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$, Cy$_2$MeN, L3, CHCl$_3$, 80 °C, 48 h</td>
<td>(no reaction)</td>
</tr>
</tbody>
</table>

- standard condition: Pd(OAc)$_2$ (0.15 equiv.), K$_2$CO$_3$ (3.0 equiv.), PPh$_3$/L1/L2/L3 (0.3 equiv.)
- enantiomeric excess (% ee) determined by chiral HPLC analysis

![Chemical structures](image-url)
Chiral HPLC (CHIRALCEL OD-H, flow rate: 1 mL/min, gradient hexanes:isopropanol 1:0 → 4:1) Chromatographs of Dienone 6 Obtained from (a) Racemic (Table 1, Entry 1); and (b) Asymmetric (Table 1, Entries 2 and 4) Conditions:

(a)  
Table 1, Entry 1:

(b)  
Table 1, Entry 2:

Table 1, Entry 4:
Attempted Preparation of Optically Active Hydroxy Enone 8 via Asymmetric 1,4-Reduction of Dienone 5

To a stirred solution of (R,R)-Ph-BPE (14.4 mg, 28 µmol) and CuI (5.4 mg, 28 µmol) in THF (3.0 mL) at −78 °C was added DIBAL-H (1.0 M in hexane, 0.57 mL, 0.57 mmol), HMPA (0.30 mL, 1.72 mmol) and a solution of dienone 5 (109 mg, 0.28 mmol) in THF (2.0 mL) via cannula. The resulting mixture was warmed to −50 °C and stirred for 36 h before it was quenched with sodium potassium tartrate (10 mL, sat. aq.) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. ¹H NMR and thin-layer-chromatography analysis of the crude reaction mixture indicated only starting material 5 was present.

Tricyclic Enone 7

To a stirred solution of tricyclic dienone 6 in benzene (1.77 g, 5.85 mmol) at room temperature was added RhCl(PPh₃)₃ (0.27 g, 0.29 mmol). The resulting mixture was evacuated and filled with argon (3 ×) followed by hydrogen (3 ×), and stirred under an atmosphere of H₂ (balloon) for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic enone 7 (1.39 g,
78%) as an amorphous brown solid. 7: \( R_f = 0.31 \) (silica gel, hexane:EtOAc 1:1); IR (film) \( \nu_{\text{max}} \) 3586, 3054, 2830, 1713, 1662, 714 cm\(^{-1}\); \(^1\)H NMR (499 MHz, CDCl\(_3\)): \( \delta \) 6.94 (d, \( J = 8.0 \) Hz, 1H), 6.91 (d, \( J = 8.7 \) Hz, 1H), 6.70 (s, 1H), 4.98 (q, \( J = 7.2 \) Hz, 2H), 3.85 (s, 3H), 3.43 (s, 3H), 2.90–2.84 (m, 2H), 2.62–2.58 (m, 1H), 2.48–2.44 (m, 1H), 2.44 (s, 1H), 2.23–2.15 (m, 2H), 2.15–2.10 (m, 1H), 1.94–1.90 ppm (m, 1H); \(^1\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) 200.1, 152.5, 151.1, 145.6, 132.7, 128.2, 127.8, 123.5, 113.8, 99.5, 68.8, 58.0, 56.1, 38.0, 35.8, 33.6, 26.1 ppm; HRMS calcd. For C\(_{17}\)H\(_{20}\)O\(_5\)Na\(^+\) [M + Na\(^+\)] 327.1203, found 327.1204.

### Hydroxy enone 8

(i) To a stirred solution of dienone 5 (248 mg, 0.65 mmol) in toluene at room temperature was added RhCl(PPh\(_3\))\(_3\) (29.9 mg, 32 \( \mu \)mol) and triethylsilane (0.2 mL, 1.25 mmol). The resulting mixture was warmed to 50 °C and stirred for 10 h before it was cooled to room temperature and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 6:1) afforded silyl enol ether 5a (200 mg, 62%) and recovered dienone (5, 40 mg, 16%) as an amorphous brown solids. 5a: \( R_f = 0.68 \) (silica gel, hexane:EtOAc 1:1).

5a: \(^1\)H NMR (400 MHz, CDCl\(_3\))
(ii) To a stirred solution silyl of enol ether 5a (200 mg, 0.40 mmol) in THF (5.0 mL) at 0 °C was added TBAF (1.0 M in THF, 0.71 mL, 0.71 mmol). The resulting mixture was warmed to room temperature and stirred for 4 h before it was quenched with NH4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na2SO4) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded hydroxy enone 8 (105 mg, 68%) as an amorphous yellow solid. 8: Rf = 0.35 (silica gel, hexanes:EtOAc 1:1); IR (film) νmax 2850, 1680, 1490, 1270, 1030 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 6.95 (d, J = 8.3 Hz, 1H), 6.81 (t, J = 8.3 Hz, 2H), 5.93 (d, J = 10.1 Hz, 1H), 5.14 (s, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 2.93–2.79 (m, 2H), 2.68–2.61 (m, 1H), 2.51–2.43 (m, 1H), 2.29–2.24 (m, 1H), 2.15–2.08 (m, 1H), 1.96–1.87 ppm (m, 2H); 13C NMR (101 MHz, CDCl3): δ 198.8, 153.5, 151.6, 143.5, 133.8, 128.7, 124.9, 120.0, 111.5, 98.6, 70.3, 58.1, 56.1, 40.2, 34.9, 34.5, 30.2 ppm; HRMS calcd. For C17H21BrO5Na+ [M + Na]⁺ 407.0465, found 407.0469.

Peroxyquinol 26

To a stirred solution of biaryl phenol 1 (565 mg, 1.54 mmol) in CHCl₃ (30.0 mL) at room temperature was added TPP (47.6 mg, 77 µmol). The resulting mixture was exposed to 27W household lamp and stirred for 5 d under an atmosphere of oxygen (balloon) before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded peroxyquinol 26 (284 mg, 46%) as an yellow amorphous solid. 26: Rf = 0.25 (silica gel, hexanes:EtOAc 2:1); IR (film) νmax 2950, 1680, 1490, 1270, 1040 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 8.10 (s, 1H), 6.94 (d, J = 10.2 Hz, 2H), 6.86 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.39 (d, J = 10.2 Hz, 2H), 5.13 (s, 2H), 3.80 (s, 3H), 3.63 (s,
3H), 2.67–2.63 (m, 2H), 1.98–1.93 ppm (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 185.3, 151.8, 148.1, 143.5, 132.8, 131.6, 125.0, 120.0, 111.4, 98.6, 81.3, 58.1, 56.1, 36.1, 30.2 ppm; HRMS calcd. For C$_{17}$H$_{19}$BrO$_6$Na$^+$ [M + Na]$^+$ 421.0257, found 421.0260.

1,2,4-Trioxane 27 (absolute stereochemistry arbitrarily shown)

To a stirred solution of peroxyquinol 26 (90 mg, 0.23 mmol) in 1,2-dichloroethane (1.1 mL) at room temperature was added (R)-TRIP (8.5 mg, 11 µmol), isobutyraldehyde (26 µL, 0.28 mmol) and 4Å MS (30.0 mg). The resulting mixture was warmed to 45 °C and stirred for 21 h before it was cooled to room temperature and diluted with water (5 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 5 mL), the combined organic layer was washed with water (15 mL), brine (15 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded 1,2,4-trioxane 27 (70 mg, 66%) as an amorphous yellow solid. 27: $R_f$ = 0.67 (silica gel, hexanes:EtOAc 2:1); [α]$_D^{25}$ = −116 (c = 1.0, CHCl$_3$); IR (film) $\nu_{\text{max}}$ 2980, 1685, 1485, 1265, 1040 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 6.96 (dd, $J$ = 10.5, 2.7 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 6.12 (d, $J$ = 10.5 Hz, 1H), 5.13 (s, 2H), 5.03 (d, $J$ = 5.2 Hz, 1H), 4.26 (s, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 2.91 (td, $J$ = 12.8, 4.9 Hz, 1H), 2.76 (td, $J$ = 12.8, 4.9 Hz, 1H), 2.75–2.70 (m, 2H), 2.00 (td, $J$ = 12.8, 4.9 Hz, 1H), 1.89 (td, $J$ = 12.8, 4.9 Hz, 1H), 1.83–1.75 (m, 1H), 0.89 ppm (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 195.2, 151.8, 150.2, 143.6, 133.1, 130.0, 125.0, 119.9, 111.5, 107.1, 98.6, 79.6, 75.0, 58.1, 56.1, 40.8, 36.0, 30.9, 29.4, 16.7, 16.7 ppm; HRMS calcd. For C$_{21}$H$_{27}$BrO$_7$Na$^+$ [M + Na]$^+$ 493.0832, found 493.0835.
1,2,4-Trioxane 27 (Racemic)

To a stirred solution of peroxyninol 26 (24 mg, 60 µmol) in 1,2-dichloroethane (1.0 mL) at room temperature was added diphenylphosphinic acid (3.9 mg, 18 µmol) and isobutyraldehyde (11 µL, 0.12 mmol). The resulting mixture was warmed to 45 °C and stirred for 21 h before it was cooled to room temperature and diluted with water (3 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 5 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded 1,2,4-trioxane 27 (ca. 3:1 diastereoisomeric ratio by $^1$H NMR, 17 mg, 60%) as an amorphous yellow solid.

Chiral HPLC (CHIRALPAK 1A, flow rate: 1.0 mL/min, gradient hexanes:isopropanol 4:1)

Chromatographs of (a) Racemic Hydroxy 1,2,4-Trioxane 27; and (b) Optically Active 1,2,4-Trioxane 27 (95:5 er):

(a)

(b)
(i) To a stirred solution of 1,2,4-trioxane 27 (37.0 mg, 78 µmol) in EtOAc (3.0 mL) at room temperature was added Rh/Al (5.0 mg) and PtO₂ (5.0 mg, 22 µmol). The resulting mixture was evacuated and filled with argon (3 ×) followed by hydrogen (3 ×), and stirred under an atmosphere of H₂ (balloon) for 3 h before it was filtered through Celite® and eluted with EtOAc (3 × 5 mL). The resulting filtrate was concentrated under reduced pressure to afford ketone 27a as an amorphous yellow solid, which was used directly in the subsequent step without further purification.

27a: ¹H NMR (400 MHz, CDCl₃, crude)
(ii) To a stirred solution of crude residue (obtained above) in CH₂Cl₂ (3.0 mL) at room temperature was added DBU (30 μL, 0.20 mmol). The resulting mixture was warmed to 45 °C and stirred for 4 h before it was cooled to room temperature and diluted with water (5 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded enone (-)-8 (13.0 mg, 43% over two steps) as an amorphous yellow solid. All physical characteristics are identical to those obtained from racemic hydroxy enone 5. \([\alpha]_{D}^{24} = -39\ (c = 0.1, \text{CHCl}_3)\).

**Chiral HPLC** (CHIRALCEL OJ-H, flow rate: 0.8 mL/min, gradient hexanes:isopropanol 1:0→4:1) Chromatographs of (a) Racemic Hydroxy Enone 8; and (b) Optically Active Hydroxy Enone 8 (95:5 er):

(a)

(b)
Hydroxy Enone 7

To a stirred solution of hydroxy enone (-)-8 (12.0 mg, 31 µmol) in DMSO (0.8 mL) at room temperature was added Na₂CO₃ (9.9 mg, 93 µmol) and X-Phos (5.9 mg, 12 µmol). The resulting mixture was stirred for 15 min before the addition of tBu₃PH•BF₄ (7.2 mg, 25 µmol) and Pd(PPh₃)₂Cl₂ (4.4 mg, 6.3 µmol). The resulting mixture was warmed to 100 °C and stirred for 40 h before it was cooled to room temperature and diluted with water (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 3 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded tricyclic enone (-)-7 (6.5 mg, 69%) as an amorphous yellow solid. All physical characteristics of hydroxy enone (-)-7 are identical to those obtained from RhCl(PPh₃)₃ catalyzed hydrogenation of hydroxy dienone 6. \( [\alpha]_{D}^{25} = -109 \) (c = 0.1, CHCl₃).
**Chiral HPLC** (ChiralPak1A, flow rate: 0.8 mL/min, gradient hexanes:isopropanol 1:0→4:1)

Chromatographs of (a) Racemic; and (b) Optically Active Hydroxy Enone 7 (95:5 er):  

(a)  

(b)  

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Tetracycle 11

(i) To a stirred solution of hydroxy enone 7 (1.5 g, 4.93 mmol) in CH$_2$Cl$_2$ (50 mL) at −20 °C was added ethyl vinyl ether (1.89 mL, 19.7 mmol) followed by NIS (3.32 g, 14.8 mmol). The resulting mixture was stirred for 1 h before additional ethyl vinyl ether (1.89 mL, 19.7 mmol)
and NIS (3.32 g, 14.8 mmol) were added. The resulting mixture was warmed to room temperature and stirred for 12 h before it was quenched with Na₂S₂O₃ (80 mL, sat. aq.) and water (100 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 80 mL), the combined organic layer was washed with water (150 mL), brine (150 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH₂Cl₂→CH₂Cl₂:Et₂O 1:0→8:1) afforded iodide 9 (mixture of diastereoisomers, as an amorphous yellow solid. 9: R₉ = 0.45, 0.52 (silica gel, hexanes:EtOAc 3:1).

(ii) Method 1: nBu₃SnH/Et₃B Condition:

To a stirred solution of iodide 9 (obtained above) in benzene (300 mL) at room temperature was added nBu₃SnH (1.77 mL, 6.58 mmol), Et₃B (1.0 M in hexane, 6.58 mL, 6.58 mmol) and small amount of air (via an empty syringe filled with air). The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 5:1) afforded tetracycle 11 (mixture of diastereoisomers, 1.15 g, 62% over two steps) as an amorphous yellow solid. 11: R₉ = 0.39, 0.43 (silica gel, hexanes:EtOAc 3:1); IR (film) νmax 3050, 2987, 1714, 1550, 715 cm⁻¹; ¹H NMR (499 MHz, CDCl₃, mixture of isomers): δ 6.81–6.74 (m, 2H), 5.23 (d, J = 4.5 Hz, 1H), 5.13 (d, J = 5.0 Hz, 0.4H), 5.10 (d, J = 4.5 Hz, 0.3H), 5.09 (d, J = 4.5 Hz, 0.3H), 5.03 (d, J = 4.8 Hz, 1H), 3.80 (s, 3H), 3.77–3.71 (m, 1H), 3.63 (s, 2.2H), 3.63 (s, 0.8H), 3.54 (d, J = 16.1 Hz, 0.4H), 3.44–3.36 (m, 1H), 3.19 (d, J = 13.8 Hz, 0.6H), 2.93 (dd, J = 14.7, 6.4 Hz, 1H), 2.83 (td, J = 14.7, 4.4 Hz, 1H), 2.76 (td, J = 14.5, 4.7 Hz, 1H), 2.70–2.61 (m, 1H), 2.57 (d, J = 13.8 Hz, 1H), 2.54–2.46 (m, 0.4H), 2.47 (d, J = 16.3 Hz, 0.6H), 2.39–2.30 (m, 1H), 2.30–2.22 (m, 1H), 2.22–2.12 (m, 1H), 2.05–1.96 (m, 1H), 1.96–1.87 (m, 1H), 1.18 (t, J = 7.0 Hz, 1.2H), 1.13 ppm (t, J = 7.0 Hz, 1.8H); ¹³C NMR (101 MHz, CDCl₃, mixture of isomers): δ 213.2, 211.4, 150.6, 145.0, 144.8, 136.5, 136.0, 128.2, 127.9, 123.8, 123.6, 111.2, 111.1, 103.2, 102.7, 99.0, 99.0, 83.4, 63.3, 63.1, 57.8, 57.7, 55.9, 50.5, 50.3, 49.4, 48.6, 47.7, 46.3, 35.3, 35.0, 34.0, 33.5, 32.2, 30.1, 27.7, 26.7, 15.2, 15.0 ppm; HRMS calced. For C₂₁H₂₈O₆Na⁺ [M + Na]⁺ 399.1778, found 399.1778.

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(ii) **Method 2: Photoredox Condition:**

To a stirred solution of iodide 9 (40 mg, 80 μmol) in acetonitrile (4.0 mL) at room temperature was added [Ir(ppy)₂(dtbbpy)]PF₆ (2.2 mg, 2.0 μmol) and iPr₂NEt (0.14 mL, 0.8 mmol). The resulting mixture was exposed to 12W household lamp and stirred for 36 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 5:1) afforded tetracycle 11 (mixture of diastereoisomers, 17.1 mg, 57%) as an amorphous yellow solid. All physical data of tetracycle 11 are identical to those obtained from the nBu₃SnH/Et₃B mediated cyclization of iodide 9.

**Phenolic Lactone 12**

To a stirred solution of tetracyclic acetal 11 (2.50 g, 6.64 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added mCPBA (70–75%, 2.98 g, 12.1 mmol) and boron trifluoride diethyl etherate complex (1.64 mL, 13.3 mmol). The resulting mixture was stirred for 1 h before it was quenched with Na₂S₂O₃ (30 mL, sat. aq.) and water (30 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL), the combined organic layer was washed with NaHCO₃ (100 mL, sat. aq.), brine (100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded phenolic lactone 12 (1.51 mg, 75%) as an amorphous yellow solid. 12: Rₜ = 0.28 (silica gel, hexanes:EtOAc 1:1); IR (film) νmax 3095, 2831, 1776, 1719, 767 cm⁻¹; ¹H NMR (499 MHz, CDCl₃): δ 6.75 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 5.99 (s, 1H), 3.87 (s, 3H), 3.32 (d, J = 15.0 Hz, 1H), 3.11 (d, J = 19.7 Hz, 1H), 3.06 (d, J = 19.7 Hz, 1H), 2.95–2.88 (m, 1H), 2.86–2.80 (m, 1H), 2.78 (d, J = 15.8 Hz, 1H), 2.55–2.46 (m, 1H), 2.45–2.23 (m, 4H), 2.11–2.04 ppm (m, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 209.8, 175.0, 145.4, 143.6, 127.5, 125.5, 119.6, 109.8, 85.4, 56.2, 46.5, 45.3, 42.1, 35.4, 32.7, 32.1, 25.6 ppm; HRMS calcd. For C₁₇H₁₈O₅Na⁺ [M + Na]^+ 325.1046, found 325.1047.
To a stirred solution of phenolic ketone 12 (95.0 mg, 0.31 mmol) in CH₂Cl₂ (3.0 mL) at room temperature was added a solution of pyridinium tribromide (111 mg, 0.35 mmol) in acetic acid (10.2 mL) dropwise. The resulting mixture was stirred for 30 min before it was diluted with toluene and concentrated under reduced pressure. The resulting residue was redissolved in CH₂Cl₂ (5.0 mL) and water (5.0 mL), extracted with CH₂Cl₂ (3 × 15 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford a crude residue, which was used directly in the subsequent step without further purification.

To a stirred solution of crude residue (obtained above) in MeCN (5.0 mL) at room temperature was added LiBr (164 mg, 1.89 mmol) and Et₃N (70 μL, 0.50 mmol). The resulting mixture was warmed to 60 °C and stirred for 10 min before it was cooled to room temperature and quenched with NH₄Cl (5 mL, sat. aq.) and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded pentacycle 13 (60 mg, 64% over two steps) as an amorphous yellow solid. 13: Rᵣ = 0.30 (silica gel, hexanes:EtOAc 1:1); IR (film) ʋ_max 3111, 2985, 1790, 1604, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.77 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 4.93 (s, 1H), 3.90 (s, 3H), 3.18 (d, J = 18.8 Hz, 1H), 2.95 (dt, J = 16.8, 5.6 Hz, 1H), 2.89 (d, J = 19.0 Hz, 1H), 2.80 (td, J = 13.4, 4.5 Hz, 1H), 2.69–2.57 (m, 1H), 2.51 (dt, J = 14.8, 4.2 Hz, 1H), 2.30 (dt, J = 14.5, 4.1 Hz, 1H), 2.25–2.15 (m, 1H), 2.10–2.02 (m, 1H), 1.98 ppm (td, J = 13.5, 3.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 204.4, 174.0, 146.5, 143.2, 125.5, 124.5, 121.3, 115.5, 91.8, 84.9, 56.7, 54.3, 43.6, 33.8, 33.3, 31.5, 24.3 ppm; HRMS calcd. For C₁₇H₁₆O₅Na⁺ [M + Na]⁺ 323.0890, found 323.0893.
Dioxolane 14

To a stirred solution of pentacyclic ketone 13 (60.0 mg, 0.20 mmol) in CH$_2$Cl$_2$/ethylene glycol (1:1, 2.0 mL) at room temperature was added TMSCl (0.12 mL, 0.95 mmol). The resulting mixture was stirred for 7 h before it was quenched with NaHCO$_3$ (10 mL, sat. aq.). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 15 mL), the combined organic layer was washed with water (40 mL), brine (40 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded dioxolane 14 (52.0 mg, 76%) as an amorphous yellow solid. 14: $R_f = 0.50$ (silica gel, hexanes:EtOAc 1:1); IR (film) $\nu_{max}$ 2950, 1770, 1500, 1450, 1270 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.77 (d, $J = 8.1$ Hz, 1H), 6.67 (d, $J = 8.1$ Hz, 1H), 4.61 (s, 1H), 4.21–4.19 (m, 1H), 3.87–3.82 (m, 2H), 3.87 (s, 3H), 3.80–3.73 (m, 1H), 2.96 (d, $J = 18.6$ Hz, 1H), 2.94–2.85 (m, 1H), 2.76 (d, $J = 18.6$ Hz, 1H), 2.73–2.62 (m, 1H), 2.25–1.99 (m, 3H), 1.94–1.74 (m, 2H), 1.62–1.46 ppm (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 174.6, 147.5, 142.5, 127.6, 124.7, 120.2, 114.7, 106.8, 94.6, 85.7, 66.7, 65.2, 56.7, 50.6, 44.8, 34.4, 28.5, 27.9, 24.7 ppm; HRMS calcd. For C$_{19}$H$_{20}$O$_6$Na$^+$ [M + Na]$^+$ 367.1152, found 367.1154.

Amide 15

To a stirred solution of lactone 14 (80.0 mg, 0.23 mmol) in MeOH/CH$_2$Cl$_2$ (6:1, 3.5 mL) at room temperature was added MeNH$_2$ (40% aq., 0.23 mL, 2.7 mmol). The resulting mixture
was stirred for 12 h before it was concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 1:1) afforded amide 15 (75.0 mg, 86%) as a white amorphous solid. 15: Rf = 0.13 (silica gel, hexanes:EtOAc 1:1); IR (film) νmax 3250, 2930, 1640, 1510, 1440 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.76 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 5.68 (br s, 1H), 4.75 (s, 1H), 4.15–4.12 (m, 1H), 3.90–3.81 (m, 2H), 3.86 (s, 3H), 3.75–3.72 (m, 1H), 2.97 (d, J = 15.7 Hz, 1H), 2.89–2.78 (m, 4H), 2.64–2.62 (m, 1H), 2.30 (d, J = 15.6 Hz, 1H), 2.13–2.06 (m, 2H), 1.87 (dd, J = 14.5, 7.1 Hz, 1H), 1.56–1.53 (m, 2H), 1.43 ppm (dt, J = 17.4, 3.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 173.3, 146.1, 142.3, 132.2, 124.7, 119.9, 113.6, 108.5, 93.0, 71.1, 66.3, 64.8, 56.3, 51.1, 44.2, 33.8, 30.6, 28.2, 26.7, 24.9 ppm; HRMS calcd. For C₂₀H₂₅NO₆Na⁺ [M + Na]⁺ 398.1574, found 398.1577.

**Tosyl Amide 16**

(i) To a stirred solution of amide 15 (52.0 mg, 0.14 mmol) in THF (1.5 mL) at 0 °C was added LiAlH₄ (52.6 mg, 1.39 mmol). The resulting mixture was warmed to reflux and stirred for 12 h before it was cooled to 0 °C and slowly quenched with sodium potassium tartrate (3 mL, sat. aq.) and water (3 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL), the combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure afforded crude amine 20, which was used directly in the subsequent step without further purification.
To a stirred solution of crude amine 20 (obtained above) in CH$_2$Cl$_2$ (2.5 mL) at room temperature was added TsCl (35.7 mg, 0.19 mmol) and Et$_3$N (50 μL, 0.36 mmol). The resulting mixture was stirred for 4 h before it was quenched with H$_2$O (3 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 3 mL), the combined organic layer was washed with water (10 mL), brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded tosylamide 16 (47 mg, 66% over two steps) as an amorphous yellow solid. 16: $R_f$ = 0.28 (silica gel, hexanes:EtOAc 1:1); IR (film) $\nu_{\max}$ 3500, 2950, 1530, 1340, 1160 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J$ = 7.7 Hz, 2H), 7.24 (d, $J$ = 7.7 Hz, 2H), 6.74 (d, $J$ = 8.2 Hz, 1H), 6.60 (d, $J$ = 8.1 Hz, 1H), 4.60 (s, 1H), 4.16–4.12 (m, 1H), 3.97 (dd, $J$ = 13.0, 6.5 Hz, 1H), 3.88 (dd, $J$ = 13.0, 6.4 Hz, 1H), 3.85–3.74 (m, 1H), 3.83 (s, 3H), 3.32 (td, $J$ = 13.0, 4.7 Hz, 1H), 2.90 (dd, $J$ = 17.8, 8.2 Hz, 1H), 2.80 (td, $J$ = 12.8, 4.6 Hz, 1H), 2.70–2.58 (m, 1H), 2.66 (s, 3H), 2.39 (s, 3H), 2.30–2.10 (m, 2H), 1.93 (td, $J$ = 13.1, 4.2 Hz, 1H), 1.81 (td, $J$ = 12.7, 4.6 Hz, 1H), 1.77–1.68 (m, 1H), 1.68–1.58 (m, 1H), 1.54–1.47 (m, 1H), 1.47–1.36 ppm (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 146.7, 143.1, 141.9, 134.8, 130.3, 129.6, 127.3, 124.7, 120.2, 114.2, 108.0, 92.2, 72.8, 66.1, 65.0, 56.6, 50.7, 47.3, 35.5, 35.3, 33.6, 31.8, 27.4, 24.5, 21.5 ppm; HRMS calcd. For C$_{27}$H$_{33}$NO$_7$SNa$^+$ [M + Na]$^+$ 538.1870, found 538.1872.
Styrene 17

To a stirred solution of tosyl amide 16 (66.0 mg, 0.13 mmol) in carbon tetrachloride (freshly distilled, 20.0 mL) at room temperature was added benzoyl peroxide (freshly recrystallized, 6.2 mg, 26 μmol) and N-bromosuccinimide (24.1 mg, 0.14 mmol). The resulting mixture was warmed to reflux and stirred for 45 min before it was cooled to room temperature and added Et₃N (0.3 mL, 2.15 mmol). The resulting mixture was warmed to reflux and stirred for 10 min before it was cooled to room temperature. The resulting mixture was washed with NaHCO₃ (15 mL, sat. aq.), Na₂S₂O₃ (15 mL, sat. aq.), brine (15 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded alkene 17 (46 mg, 70%) as an amorphous solid. 17: Rₛ = 0.30 (silica gel, hexanes:EtOAc 1:1); IR (film) νₘₐₓ 3320, 2920, 1640, 1280, 1180 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, J = 7.7 Hz, 2H), 7.24 (d, J = 7.7 Hz, 2H), 6.68 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.25 (d, J = 9.5 Hz, 1H), 5.57 (d, J = 9.5 Hz, 1H), 4.60 (s, 1H), 4.19–4.16 (m, 1H), 4.06–3.96 (m, 1H), 3.92–3.76 (m, 2H), 3.86 (s, 3H), 3.11–2.96 (m, 2H), 2.67–2.60 (m, 1H), 2.60 (s, 3H), 2.39 (s, 3H), 2.11 (td, J = 12.9, 5.6 Hz, 1H), 1.98 (td, J = 12.1, 5.2 Hz, 1H), 1.87 (td, J = 11.5, 5.5 Hz, 1H), 1.74–1.68 (m, 2H), 1.46 ppm (dt, J = 13.2, 3.2 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 146.1, 144.1, 143.1, 136.4, 134.8, 129.6, 128.3, 127.3, 123.8, 122.6, 118.0, 113.0, 108.1, 94.5, 75.3, 66.5, 65.0, 56.3, 50.8, 46.7, 35.1, 33.5, 33.4, 26.8, 21.5 ppm; HRMS calcd. For C₂₂H₃₁NO₇SNa⁺ [M + Na]⁺ 536.1713, found 536.1716.
Styrene Amide 19

(i) To a stirred solution of dioxolane 14 (220 mg, 0.64 mmol) in carbon tetrachloride (freshly distilled, 91 mL) at room temperature was added benzylo peroxide (freshly recrystallized, 15 mg, 62 µmol) and N-bromosuccinimide (123 mg, 0.69 mmol). The resulting mixture was warmed to reflux and stirred for 45 min before it was cooled to room temperature and added Et₃N (0.5 mL, 3.58 mmol). The resulting mixture was warmed to reflux and stirred for 10 min before it was cooled to room temperature. The resulting mixture was washed with NaHCO₃ (50 mL, sat. aq.), Na₂S₂O₃ (50 mL, sat. aq.), brine (50 mL), dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 4:1) afforded mixture of styrene 18 and vinyl bromide 18a (18:18a ca. 5:1, 140 mg, 64%) as an amorphous solid.

18:18a: ¹H NMR (400 MHz, CDCl₃, crude)

(ii) To a stirred solution of mixture of styrene 18 and 18a (18 mg, 40 µmol) in MeOH/CH₂Cl₂ (6:1, 0.7 mL) at room temperature was added MeNH₂ (40% aq., 0.1 mL, 1.16 mmol). The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure.
Flash column chromatography (silica gel, hexanes:EtOAc 1:1) afforded styrene amide 19 (18 mg, 92%) as an amorphous solid. 19: Rf = 0.14 (silica gel, hexanes:EtOAc 1:1); 1H NMR (400 MHz, CDCl3): δ 6.69 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.16 (d, J = 9.6 Hz, 1H), 6.04 (s, 1H), 5.61 (d, J = 9.6 Hz, 1H), 5.23 (br s, 1H), 4.65 (s, 1H), 4.19–4.16 (m, 1H), 3.99–3.91 (m, 1H), 3.90–3.82 (m, 1H), 3.84 (s, 3H), 3.82–3.79 (m, 1H), 2.69 (d, J = 4.8 Hz, 3H), 2.56 (s, 2H), 1.97 (t, J = 13.7 Hz, 1H), 1.83 (d, J = 14.1 Hz, 1H), 1.58 (t, J = 13.7 Hz, 1H), 1.45 ppm (d, J = 13.4 Hz, 1H); 13C NMR (101 MHz, CDCl3): δ 173.4, 145.7, 144.1, 138.6, 129.0, 123.1, 121.4, 117.3, 113.1, 108.2, 95.3, 74.2, 66.5, 64.9, 56.2, 52.5, 43.4, 32.7, 27.0, 26.8 ppm.

Tosyl Amide 16

(i) To a stirred solution of styrene amide 19 (18.0 mg, 48 µmol) in THF (1.0 mL) at 0 °C was added LiAlH4 (15.1 mg, 0.40 mmol). The resulting mixture was warmed to reflux and stirred for 12 h before it was cooled to 0 °C and slowly quenched with sodium potassium tartrate (3 mL, sat. aq.) and water (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layer was dried (Na2SO4) and concentrated under reduced pressure afforded crude amine 20 (11.0 mg, 63%), which was used directly in the subsequent step.
(ii) To a stirred solution of crude amine 20 (obtained above) in CH$_2$Cl$_2$ (1.0 mL) at room temperature was added TsCl (8.80 mg, 46 μmol) and Et$_3$N (60 μL, 0.43 mmol). The resulting mixture was stirred for 3 h before it was quenched with H$_2$O (3 mL). The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 3 mL), the combined organic layer was washed with water (8 mL), brine (8 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 3:1) afforded tosyl amide 16 (12 mg, 76%) as an amorphous yellow solid. All physical properties of tosyl amide 16 are identical to those obtained from amide 15.

**Diol 21**

![Diol 21](image)

To a stirred solution of lactones 18 and 18a (12.0 mg, 35 μmol) in THF (3.0 mL) at 0 °C was added LiAlH$_4$ (11 mg, 0.29 mmol). The resulting mixture was warmed to 50 °C and stirred for 5 h before it was cooled to 0 °C and slowly quenched with sodium potassium tartrate (3 mL, sat. aq.) and water (3 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layer was dried (Na$_2$SO$_4$) and
concentrated under reduced pressure. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded diol 21 (6.2 mg, 51%) as an amorphous solid. 21: Rf = 0.50 (silica gel, hexanes:EtOAc 1:1); IR (film) νmax 3756, 3692, 3056, 2990, 1424 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.69 (d, J = 8.1 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.24 (d, J = 9.6 Hz, 1H), 5.66 (d, J = 9.6 Hz, 1H), 4.60 (s, 1H), 4.31 (br s, 1H), 4.21–4.17 (m, 1H), 4.05–3.97 (m, 1H), 3.93–3.83 (m, 1H), 3.86 (s, 1H), 3.84–3.78 (m, 1H), 3.69–3.50 (m, 2H), 2.25–2.16 (m, 1H), 2.07 (br s, 1H), 1.91 (td, J = 13.6, 2.6 Hz, 1H), 1.84–1.77 (m, 2H), 1.64 (td, J = 14.1, 2.2 Hz, 1H), 1.43 ppm (dt, J = 13.3, 2.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 146.2, 144.2, 137.9, 129.3, 123.5, 122.9, 117.5, 112.9, 108.3, 96.4, 73.8, 66.5, 65.0, 58.5, 56.3, 51.3, 38.8, 33.1, 27.0 ppm; HRMS calcd. For C₁₉H₂₂O₆Na⁺ [M + Na]⁺ 369.1309, found 369.1310.

**Oxycodone (2)**

(i) To a stirred solution liquid ammonia (10 mL), THF (1.0 mL) and tBuOH (0.1 mL) at –78 °C was added lithium metal (finely-cut, 30 mg) in small portions. The resulting solution was stirred for 15 min before a solution of alkene 17 (37.0 mg, 72 µmol) in THF (3.0 mL) was added via a cannula. The resulting mixture was stirred for 10 min before it was quenched with NaHCO₃ (10 mL, sat. aq.) and MeOH (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL), the combined organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH₂Cl₂:MeOH:NH₄OH 94:2:1) afforded oxycodone ethylene ketal (2a, 18.0 mg, 70%) as an amorphous clear solid. 2a: Rf = 0.39 (silica gel, EtOAc:MeOH 1:2); IR (film) νmax 2940, 1735, 1505, 1380, 1250 cm⁻¹; ¹H NMR (499 MHz, CDCl₃): δ 6.75 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.57 (s, 1H), 4.20 (dd, J = 12.6, 6.9 Hz, 1H), 4.03 (dd, J = 13.2, 6.6 Hz, 1H), 3.91 (dd, J = 13.2, 6.6 Hz, 1H), 3.88 (s, 3H), 3.79 (dd, J = 12.3, 6.5 Hz, 1H), 3.13 (d, J = 18.3
Hz, 1H), 2.81 (d, J = 5.0 Hz, 1H), 2.57 (dd, J = 16.9, 6.0 Hz, 1H), 2.49–2.38 (m, 1H), 2.39 (s, 3H), 2.32–2.12 (m, 3H), 1.62–1.49 (m, 3H), 1.45 ppm (dd, J = 12.4, 2.6 Hz, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 146.3, 142.3, 130.8, 124.9, 118.1, 114.0, 108.9, 93.8, 70.0, 66.4, 64.9, 56.6, 47.4, 45.6, 42.6, 31.0, 29.1, 28.8, 22.0 ppm; HRMS calcd. For C\(_{20}\)H\(_{26}\)NO\(_5\)\(^+\) [M + H]\(^+\) 360.1805, found 360.1807.

(ii) To a stirred solution of oxycodone ethylene ketal (2a, 6.7 mg, 18 \(\mu\)mol) in THF (1.0 mL) at room temperature was added HCl (2.0 N aq., 0.1 mL). The resulting mixture was warmed to 80 °C stirred for 12 h before it was cooled to 0 °C quenched with NaHCO\(_3\) (5 mL). The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 \(\times\) 8 mL), the combined organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure. Flash column chromatography (silica gel, CH\(_2\)Cl\(_2\):MeOH:NH\(_4\)OH 94:2:1) afforded oxycodone (2, 3.6 mg, 61%) as a clear amorphous solid. 2: \(R_f\) = 0.39 (silica gel, EtOAc:MeOH 1:2); IR (film) \(\nu_{\text{max}}\) 2910, 1740, 1460, 1275, 1060 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.68 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 4.64 (s, 1H), 3.88 (s, 3H), 3.14 (d, J = 18.6 Hz, 1H), 3.00 (td, J = 14.4, 5.0 Hz, 1H), 2.86 (d, J = 5.7 Hz, 1H), 2.54 (dd, J = 18.5, 5.9 Hz, 1H), 2.50–2.32 (m, 2H), 2.37 (s, 3H), 2.28 (dt, J = 14.2, 2.8 Hz, 1H), 2.19–2.11 (m, 1H), 1.90–1.79 (m, 1H), 1.65–1.54 ppm (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 208.5, 145.0, 142.9, 129.3, 124.8, 119.4, 114.8, 90.4, 70.3, 64.6, 56.8, 50.2, 45.2, 42.7, 36.1, 31.4, 30.5, 21.9 ppm; HRMS calcd. For C\(_{18}\)H\(_{22}\)NO\(_4\)\(^+\) [M + H]\(^+\) 316.1543, found 316.1546.
$^1$H and 13C NMR (CDCl$_3$, ppm) Comparison for Synthetic Oxycodone (2)

<table>
<thead>
<tr>
<th>Fukuyama$^{[3]}$ ($^1$H, 400 MHz, ppm)</th>
<th>This work ($^1$H, 400 MHz, ppm)</th>
<th>Fukuyama$^{[3]}$ ($^{13}$C, 100 MHz, ppm)</th>
<th>This work ($^{13}$C, 101 MHz, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.70 (d, $J = 8.1$ Hz, 1H)</td>
<td>6.68 (d, $J = 8.2$ Hz, 1H)</td>
<td>208.7</td>
<td>208.5</td>
</tr>
<tr>
<td>6.63 (d, $J = 8.1$ Hz, 1H)</td>
<td>6.61 (d, $J = 8.2$ Hz, 1H)</td>
<td>145.2</td>
<td>145.0</td>
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<tr>
<td>4.66 (s, 1H)</td>
<td>4.64 (s, 1H)</td>
<td>143.1</td>
<td>142.9</td>
</tr>
<tr>
<td>3.90 (s, 3H)</td>
<td>3.88 (s, 3H)</td>
<td>129.5</td>
<td>129.3</td>
</tr>
<tr>
<td>3.16 (d, $J = 18.6$ Hz, 1H)</td>
<td>3.14 (d, $J = 18.6$ Hz, 1H)</td>
<td>125.0</td>
<td>124.8</td>
</tr>
<tr>
<td>3.02 (dd, $J = 14.4$, 14.3, 5.1, Hz, 1H)</td>
<td>3.00 (dd, $J = 14.4$, 5.0 Hz, 1H)</td>
<td>119.6</td>
<td>119.4</td>
</tr>
<tr>
<td>2.88 (d, $J = 5.8$ Hz, 1H),</td>
<td>2.86 (d, $J = 5.7$ Hz, 1H)</td>
<td>115.1</td>
<td>114.8</td>
</tr>
<tr>
<td>2.57 (dd, $J = 18.6$, 5.8 Hz, 1H)</td>
<td>2.54 (dd, $J = 18.5$, 5.9 Hz, 1H)</td>
<td>90.5</td>
<td>90.4</td>
</tr>
<tr>
<td>2.50–2.34 (m, 2H)</td>
<td>2.50–2.32 (m, 2H)</td>
<td>70.5</td>
<td>70.3</td>
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<tr>
<td>2.41 (s, 3H)</td>
<td>2.37 (s, 3H)</td>
<td>64.8</td>
<td>64.6</td>
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<tr>
<td>2.30 (dd, $J = 14.4$, 3.3, 3.1 Hz, 1H)</td>
<td>2.28 (dt, $J = 14.2$, 2.8 Hz, 1H)</td>
<td>57.0</td>
<td>56.8</td>
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<tr>
<td>2.22–2.13 (m, 1H)</td>
<td>2.19–2.11 (m, 1H)</td>
<td>50.4</td>
<td>50.2</td>
</tr>
<tr>
<td>1.87 (ddd, $J = 13.8$, 5.1, 3.1 Hz, 1H)</td>
<td>1.90–1.79 (m, 1H)</td>
<td>45.4</td>
<td>45.2</td>
</tr>
<tr>
<td>1.64 (ddd, $J = 14.3$, 13.8, 3.3 Hz, 1H)</td>
<td>1.65–1.54 ppm (m, 2H)</td>
<td>42.9</td>
<td>42.7</td>
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<tr>
<td>1.60–1.54 (m, 1H)</td>
<td></td>
<td>36.3</td>
<td>36.1</td>
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<td></td>
<td>31.6</td>
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<td>30.7</td>
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<tr>
<td></td>
<td></td>
<td>22.1</td>
<td>21.9</td>
</tr>
</tbody>
</table>
II) Abbreviations

Bn = benzyl

\textit{m}CPBA = \textit{meta}-chloroperoxy benzoic acid

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DIABAL-H = diisobutylaluminium hydride

HMPA = hexamethylphosphoramide

\[ \text{[Ir(ppy)}_2\text{(dtbbpy)}]\text{PF}_6 = \]

\[ [4,4’-\text{Bis}(1,1-\text{dimethylethyl})-2,2’-\text{bipyridine-}N1,N1’\text{bis}[2-\text{(2-pyridinyl-N)phenyl-C}]\text{iridium(III)}] \] hexafluorophosphate

MOM = methoxymethyl

MS = molecular sieves

NBS = \textit{N}-bromosuccinimide

NIS = \textit{N}-iodosuccinimide

\((R,R)-\text{Ph-BPE} = (-)-1,2-\text{Bis}[(2R,5R)-2,5-\text{diphenylphospholano}]\text{ethane}\)

PIDA = (diacetoxyiodo)benzene

\(\text{PyH-Br}_3\) = pyridinium tribromide

TBAF = tetra-n-butylammonium fluoride

TMSCl = trimethylsilyl chloride

TPP = 5,10,15,20-Tetraphenyl-21\textit{H},23\textit{H}-porphine

\(\text{(R)-TRIP} = (R)-3,3’-\text{bis}(2,4,6-\text{triisopropylphenyl})-1,1’-\text{binaphthyl}-2,2’-\text{diylhydrogenphosphate}\)

\(\text{Ts} = p\text{-toluenesulfonyl}\)

\(\text{TsCl} = p\text{-toluenesulfonyl chloride}\)

X-Phos = 2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

III) References


Manuscript reference 3:

IV) $^1$H and $^{13}$C NMR Spectra for Compounds

$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
(-)-27

^1H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (499 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
^1H NMR (499 MHz, CDCl₃)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (101 MHz, CDCl$_3$)