

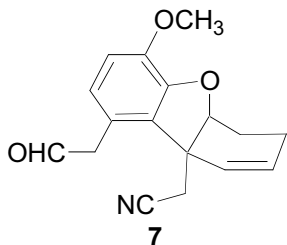
Enantioselective Synthesis of (-)-Codeine and (-)-Morphine

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Supporting Information:

1. Aldehyde 7.



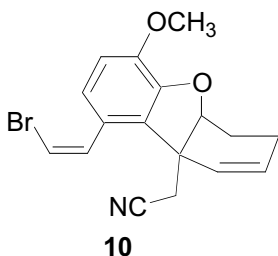
To a solution of aldehyde **8** (110mg, 0.4mmol) in methylene chloride (4ml) was added trimethylsulfonium methyl sulfate (226mg, 1.2mmol) and 50% aqueous NaOH (0.5ml) at 0°C. The reaction mixture was warmed to room temperature and stirred for 3h. Water (10ml) was added to the solution and the organic phase was separated. The aqueous phase was extracted with methylene chloride. The combined organic phase were washed with brine, dried over Na₂SO₄ and concentrated in *vacuo*. Flash column chromatography (25% ethyl acetate in pet ether) on flurosil provided 94mg (81%) of epoxide (dr=1:1).

To a solution of epoxide (94mg, 0.33mmol) from previous step in THF (4ml) was added boron trifluoride etherate (20 μ l, 0.16mmol). The solution was stirred at room temperature for 8h. Saturated sodium carbonate solution (10ml) was added to the reaction mixture. The solution was extracted with ethyl acetate (3x10ml). The combined organic phase was dried over Na₂SO₄ and concentrated in *vacuo*. Flash column chromatography (20%-40% ethyl acetate in pet ether) on flurosil provided 73mg (78%) of aldehyde.

IR (neat) 2926, 2853, 2250, 1723, 1685, 1609, 1573, 1507, 1435, 1285, 1202, 1117, 1046, 1001, 804, 766, 725 cm⁻¹. ¹H NMR (500MHz, C₆D₆) δ 9.34 (t, J=2.5Hz, 1H), 6.40

(d, $J=8.3\text{Hz}$, 1H), 6.27 (d, $J=8.3\text{Hz}$, 1H), 5.50 (ddd, $J=4.0$, 4.0, 10.0Hz, 1H), 5.31 (d, $J=10.0\text{Hz}$, 1H), 4.36 (dd, $J=3.5$, 6.0Hz, 1H), 3.33 (s, 3H), 3.10 (d, $J=2.0\text{Hz}$, 2H), 1.98 (d, $J=17.0\text{Hz}$, 1H), 1.93 (d, $J=17.0\text{Hz}$, 1H), 1.75-1.71 (m, 2H), 1.52-1.48 (m, 2H). ^{13}C NMR (125MHz, C_6D_6) δ 198.01, 148.57, 145.36, 131.43, 130.90, 126.09, 124.07, 120.62, 116.74, 113.42, 85.22, 55.61, 48.20, 46.95, 27.44, 24.12, 19.98. HRMS: Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3(\text{M}^+)$: 283.1208, Found: 283.1210.

2. *cis*-bromoalkene **10**.



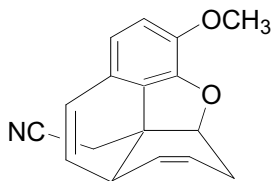
To a solution of carbontetrabromide (585mg, 1.76mmol) and triphenyl phosphine (923mg, 3.52mmol) in methylene chloride (10ml) was added a solution of aldehyde **6** (237mg, 0.88mmol) in methylene chloride (5ml) at 0°C . The reaction mixture was stirred at 0°C for 10min. The solution was filtered through a short silica gel pad and washed with ethyl acetate/pet ether (1:1). The organic solvent was removed in *vacuo*. Flash column chromatography (10-20% ethyl acetate in pet ether) provided 340mg (91%) of gem dibromoalkene.

To a solution of gem dibromo alkene (275mg, 0.647mmol) from previous step and $\text{Pd}(\text{PPh}_3)_4$ (37mg, 0.032mmol) in toluene (7ml) was added a solution Bu_3SnH (565mg, 1.94mmol) in toluene (0.5ml) via syringe pump in 20 min. The reaction was stopped after the addition was completed. Direct flash chromatography (5-20% ethyl acetate in pet ether) provided 197mg (88%) of colorless oil.

$[\alpha]_D = -71.9$ ($c=1.8$, CHCl_3). IR (neat) 3076, 3022, 2930, 2841, 2251, 1619, 1573, 1503, 1423, 1284, 1204, 1115, 1071, 1046, 988, 912, 822, 718 cm^{-1} . ^1H NMR (500MHz, CDCl_3) δ 7.16 (d, $J=7.5\text{Hz}$, 1H), 6.97 (dd, $J=0.5\text{Hz}$, $J=8.5\text{Hz}$, 1H), 6.81 (d, $J=8.5\text{Hz}$, 1H), 6.61 (d, $J=7.5\text{Hz}$, 1H), 6.04 (ddd, $J=10.0$, 5.0, 3.0Hz, 1H), 5.72 (d, $J=10.0\text{Hz}$, 1H), 4.85 (dd, $J=3.5$, 4.0Hz, 1H), 3.90 (s, 3H), 2.88 (d, $J=17\text{Hz}$, 1H), 2.80 (d, $J=17\text{Hz}$, 1H), 2.30-

2.22 (m, 2H), 2.12-1.98 (m, 2H). ^{13}C NMR (125MHz, CDCl_3) δ 146.80, 144.87, 131.18, 129.81, 129.26, 125.19, 124.22, 122.82, 116.72, 111.61, 110.74, 85.57, 55.87, 47.82, 27.22, 23.90, 19.57. HRMS: Calcd for $\text{C}_{17}\text{H}_{16}^{79}\text{BrNO}_2(\text{M}^+)$: 345.0364, Found: 345.0358.

3. Heck cyclization product **14**.

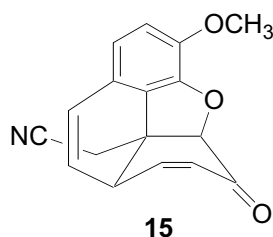


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To a flask (10ml) was added *cis*-bromoalkene **10** (92mg, 0.266mmol), $\text{Pd}(\text{OAc})_2$ (9mg, 0.04mmol), Ag_2CO_3 (221mg, 0.8mmol) and dppp (17mg, 0.04mmol). The flask was evacuated and filled with argon (3x). Degassed toluene (3ml) was added and the resulting suspension was heated at 107°C for 4h. Direct flash chromatography (5-15% ethyl acetate in petroleum ether) gave 46mg (65%) of product and 8mg (9%) recovered starting material.

$[\alpha]_{\text{D}}^{25} = +126.4$ ($c=0.73$, CHCl_3). IR (neat) 3032, 2930, 2840, 2247, 1636, 1578, 1508, 1439, 1282, 1165, 1082, 808 cm^{-1} . ^1H NMR (500MHz, CDCl_3) δ 6.73 (d, $J=8.0\text{Hz}$, 1H), 6.68 (d, $J=8.0\text{Hz}$, 1H), 6.50 (dd, $J=9.5, 1.5\text{Hz}$, 1H), 5.90 (dd, $J=9.5, 5.5\text{Hz}$, 1H), 5.69 (m, 1H), 5.47 (ddd, $J=10.0, 4.5, 2.0\text{Hz}$, 1H), 5.16 (dd, $J=8.0, 4.5\text{Hz}$, 1H), 3.89 (s, 3H), 3.33 (m, 1H), 2.68 (d, $J=17\text{Hz}$, 1H), 2.59 (d, $J=17\text{Hz}$, 1H), 2.65 (m, 1H), 2.22 (m, 1H). ^{13}C NMR (125MHz, CDCl_3) δ 145.51, 144.36, 126.93, 126.84, 124.51, 124.49, 123.70, 122.99, 118.34, 117.61, 113.55, 86.28, 56.33, 43.33, 37.44, 28.81, 25.42. HRMS: Calcd for $\text{C}_{17}\text{H}_{15}\text{NO}_2(\text{M}^+)$: 265.1103, Found: 265.1099.

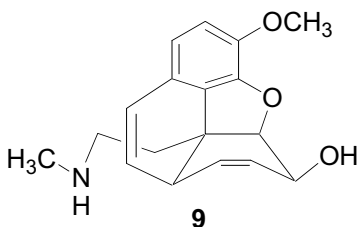
4. Enone **15**.



A flask (5ml) was charged with alkene **14** (24mg, 0.09mmol), finely ground SeO_2 (11mg, 0.09mmol), oven dried quartz sand (50mg) and anhydrous dioxane (1ml). The solution was immersed in a 75°C oil bath. After stirring for 40 min, more selenium dioxide (11mg, 0.09mmol) was added. The solution was stirred for an additional 40min. A solution of Dess-Martin periodinane (115mg, 0.27mmol) in methylene chloride (0.7ml) was added to the above reaction mixture. The resulting solution was stirred at room temperature for 3h. Saturated sodium bicarbonate (5ml) was added and the solution was stirred for additional 30min. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2x10ml). The combined organic solvents were dried over Na_2SO_4 and concentrated in *vacuo*. The resulting slightly yellow oil was purified by flash chromatography (20% to 40% ethyl acetate in petroleum ether) to give 14.6 mg (58%) of the enone.

$[\alpha]_D = -34.4$ ($c=0.8$, CHCl_3). IR (neat) 3040, 2949, 2841, 2243, 1678, 1637, 1506, 1456, 1438, 1279, 1103, 913, 813, 727 cm^{-1} . ^1H NMR (500MHz, CDCl_3) δ 6.75 (s, 2H), 6.68 (dd, $J=9.5$, 1.8Hz, 1H), 6.60 (dd, $J=10.5$, 2.5Hz, 1H), 6.18 (dd, $J=3.0$, 10.5Hz, 1H), 5.91 (dd, $J=6.0$, 9.5Hz, 1H), 5.04 (s, 1H), 3.91 (s, 3H), 3.72 (m, 1H), 2.72 (d, $J=17\text{Hz}$, 1H), 2.65 (d, $J=17\text{Hz}$, 1H). ^{13}C NMR (125MHz, CDCl_3) 192.48, 145.33, 144.48, 144.32, 129.20, 126.42, 124.95, 123.03, 121.34, 119.80, 116.91, 115.20, 86.22, 56.70, 45.09, 37.27, 24.55. HRMS: Calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_3(\text{M}^+)$: 279.0895, Found: 279.0890.

5. amine **9**.



To a cooled solution (-78°C) of enone **15** (20mg, 0.072mmol) in a mixed solvent of Et_2O (0.5ml) and CH_2Cl_2 (0.5ml) was added 0.25ml of DIBAL (1M in hexane). After stirring at -78°C for 2h, the reaction mixture was warmed to 0°C and stirred for additional 1h. To the reaction mixture was added a solution of NH_4Br (20mg, 0.2mmol) in 0.4ml of dry methanol followed by a 2M MeNH_2 solution (0.60ml) in methanol. The cooling bath was removed and the stirring was continued for 2h at room temperature. The mixture was cooled in an ice bath and 48mg (1.27 mmol) of NaBH_4 was added in three portions. The reaction mixture was stirred overnight at room temperature. The excess NaBH_4 was destroyed by addition of HCl (2M). The pH was adjusted to basic ($\text{pH}>12$) using 3N NaOH . The resulting mixture was extracted with chloroform (6x10ml). The combined organic layer was dried over sodium sulfate and concentrated *in vacuo*. Flash column chromatography (5-10% MeOH in CH_2Cl_2 with 5% Et_3N) provided 19mg of amine (89%).

$[\alpha]_{\text{D}} = -118.1$ ($c=0.7$, CHCl_3). IR (neat) 3321, 3031, 2931, 2850, 1636, 1507, 1458, 1271, 1162, 1115, 1088, 799, 731 cm^{-1} . ^1H NMR (500MHz, CDCl_3) δ 6.64 (d, $J=8.0\text{Hz}$, 1H), 6.58 (d, $J=8.0\text{Hz}$, 1H), 6.50 (d, $J=10.0\text{Hz}$, 1H), 6.00 (dd, $J=6.0$, 9.5Hz, 1H), 5.80 (m, 1H), 5.29 (ddd, $J=2.0$, 3.0, 10.0Hz, 1H) 5.17 (dd, $J=1.0$, 6.5Hz, 1H), 4.23 (m, 1H), 3.85 (s, 3H), 2.82 (dd, $J=3.0$, 6.0Hz, 1H), 2.72 (ddd, $J=16.1$, $J=11.1$, 5.1Hz, 1H), 2.44 (ddd, $J=15.5$, 11.1, 5.4Hz, 1H), 2.37 (s, 3H), 2.28 (br, 1H), 2.15 (ddd, $J=16.0$, 10.5, 5.4Hz, 1H), 1.87 (ddd, 15.4, 10.4, 5.1Hz, 1H). ^{13}C NMR (125MHz, CDCl_3) δ 146.16, 143.76, 132.01, 129.15, 128.99, 127.59, 125.11, 123.74, 117.79, 111.99, 90.55, 66.02, 55.98, 47.81, 45.36, 37.69, 36.34, 35.83. HRMS: Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3(\text{M}^+)$: 299.1521, Found: 299.1528.

6. (-)-Codeine **2**.

To a cooled solution (-78°C) of amine **9** (7mg, 0.023mmol) in a mixed solvent of THF (1ml) and diisopropyl amine (0.2ml) was added 90 μl of *n*-BuLi (0.135mmol, 1.5M

in hexane). The reaction mixture was warmed to room temperature and stirred for 6h under the irradiation of a 150W tungsten lamp at a distance of 0.5m. The solution was quenched with aqueous NaHCO₃, dried over Na₂SO₄ and concentrated under *vacuo*. Flash column chromatography (5-10% MeOH in CH₂Cl₂) provided 4mg of codeine (57%).

[α]_D = -133 (c=0.23, EtOH) Lit¹ [α]_D = -137 (c=1.15, EtOH) Lit² [α]_D = +137.5 (c=0.16, EtOH, (+)-codeine). IR (neat) 3366, 2922, 2850, 1673, 1633, 1601, 1501, 1451, 1275, 1116, 1048, 786, 754 cm⁻¹. ¹H NMR (500MHz, CDCl₃) δ 6.67 (d, J=8.0Hz, 1H), 6.58 (d, J=8.0Hz, 1H), 5.72 (ddd, J=1.5, 1.5, 10.0Hz, 1H), 5.29 (ddd, J=2.5, 2.5, 10.0Hz, 1H), 4.91 (dd, J=1.5, 7.0Hz, 1H), 4.19 (m, 1H), 3.85 (s, 3H), 3.44 (br s, 1H), 3.06 (d, J=18.5Hz, 1H), 2.79 (br s, 1H), 2.69 (m, 1H), 2.50 (s, 3H), 2.46 (m, 1H), 2.37 (dd, J=6.0, 18.5Hz, 1H), 2.15 (m, 1H), 1.90 (dd, J=1.5, 12.5Hz, 1H). ¹³C NMR (125MHz, CDCl₃) δ 146.22, 142.36, 133.75, 130.60, 127.52, 126.22, 119.66, 112.93, 91.05, 66.20, 59.09, 56.28, 46.51, 42.75, 42.62, 40.10, 35.16, 20.63. In accordance with literature^{2,3}.

- (1) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, 78, 1380.
- (2) White, J. D.; Hrniciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, 64, 7871.
- (3) Carroll, F. I.; Moreland, C. G.; Brine, G. A.; Kepler, J. A. *J. Org. Chem.* **1976**, 41, 996.