Supporting Information

A 9-Step Formal Synthesis of (±)-Morphine

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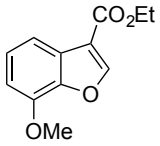
General Information

All reactions were performed under nitrogen or argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All commercial reagents were used without purification, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) analysis. Thin layer chromatography plates were viewed under UV light and stained with potassium permanganate, phosphomolybdic acid or *p*-anisaldehyde staining solution. Yields refer to products isolated after purification, unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AMX 300 MHz or a Bruker AMX 400 MHz instrument. NMR samples were dissolved in chloroform-*d* and chemical shifts are reported in ppm referenced to residual undeuterated solvent. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same Bruker instrument (101 MHz). IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre).

Experimental Procedures

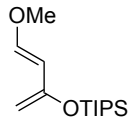


Ethyl 7-methoxy-1-benzofuran-3-carboxylate (4)

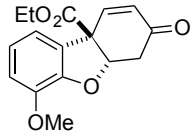
HBF_4•Et_2O (1.32 mL, 9.70 mmol, 10 mol%) was added dropwise to a solution of 2-hydroxy-3-methoxybenzaldehyde **6** (15.0 g, 98.6 mmol, 1 eq.) in dry CH_2Cl_2 (30 mL) at room temperature. A solution of ethyl diazoacetate (87 wt.% solution in CH_2Cl_2, 19 mL, 157.2 mmol, 1.6 eq.) in dry CH_2Cl_2 (120 mL) was added dropwise to the reaction mixture with a dropping funnel as the evolution of N_2 gas permitted. Once gas evolution ceased, the reaction mixture concentrated under reduced pressure. Dry CH_2Cl_2 (10 mL) was added to the resulting mixture and H_2SO_4 (6 mL, 112.6 mmol, 1.1 eq.) was added dropwise at room temperature. After 5 to 10 minutes, the mixture was diluted with CH_2Cl_2 and quenched with solid $NaHCO_3$ (9.5 g). The mixture was then filtered through celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 95/5) to afford pure benzofuran **4** (8.79 g, 40% yield, white amorphous solid).

^{1}H NMR (400 MHz, $CDCl_3$): 8.25 (s, 1H), 7.65 (dd, J = 7.9, 0.9 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 6.87 (dd, J = 7.9, 0.9 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 4.02 (s, 1H), 1.41 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 163.5 (C), 151.0 (CH), 145.6 (C), 145.1 (C), 126.5 (C), 125.1 (CH), 115.2 (C), 114.2

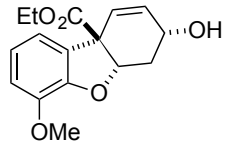
(CH), 107.3 (CH), 60.7 (CH_2), 56.2 (CH_3), 14.5 (CH_3). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 220.0736, found 220.0736. **IR** (neat, cm^{-1}): 1719 (s), 1498 (s), 1276 (vs), 1253 (s), 1233 (s), 1042 (vs), 789 (m), 733 (m).



Methoxy-3-triisopropylsiloxy-1,3-butadiene (5)
To a mixture of 4-methoxy-3-buten-2-one (8 g, 79.9 mmol, 1 eq.) and Et_3N (30 mL, 215.2 mmol, 2.7 eq.) in dry diethyl ether (130 mL) was added dropwise triisopropylsilyl trifluoromethanesulfonate (24 mL, 89.3 mmol, 1.1 eq.) at 0 °C under argon. The resulting mixture was stirred at room temperature. After 15 hours, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed twice with water and twice with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting mixture was diluted with EtOAc and washed again twice with water and twice with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude diene **5** (orange oil) was directly used in the next step without further purification.

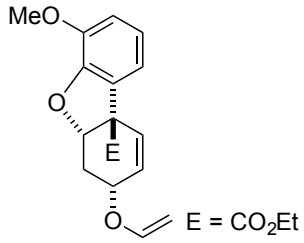


Compound 8
In a reaction flask, a mixture of dienophile **4** (3.18 g, 14.45 mmol, 1 eq.) and diene **5** (7.41 g) was heated at 160 °C under argon. After 16 h, the reaction mixture was cooled down to room temperature and diluted with toluene (270 mL). PTSA•H_2O (1.08 g, 5.78 mmol, 40 mol%), was added and the resulting mixture was stirred under reflux. After 15 hours, the reaction mixture was quenched with 5 wt.% aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude enone **8** (brown oil) was directly used in the next step without further purification



Compound 3
L-selectride (1M in THF, 29 mL, 29.90 mmol, 2 eq.) was added dropwise to a solution of crude enone **8** (14.45 mmol, 1 eq.) in dry THF (95 mL) at – 78 °C, under argon. The resulting mixture was stirred at – 78 °C. After stirring for 90 min, the mixture was treated with saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 7:3) to afford pure enol **3** (2.22 g, 53% yield from benzofuran **7**, yellow oil).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (dd, J = 7.6, 1.2 Hz, 1H), 6.92 (dd, J = 8.1, 7.6 Hz, 1H), 6.82 (dd, J = 8.1, 1.2 Hz, 1H), 6.05 (ddd, J = 10.1, 5.0, 0.8 Hz, 1H), 5.90 (ddd, J = 10.1, 1.0, 1.0 Hz, 1H), 5.42-5.41 (m, 1H), 4.31-4.22 (m, 2H), 4.21-4.15 (m, 1H), 3.87 (s, 3H), 2.66-2.60 (dddd, J = 15.4, 3.7, 2.5,

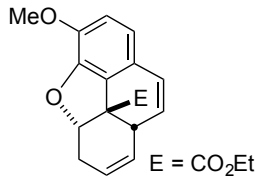
0.8 Hz, 1H), 2.25-2.19 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (C), 146.3 (C), 145.2 (C), 130.7 (C), 129.5 (CH), 126.5 (CH), 122.4 (CH), 116.3 (CH), 112.4 (CH), 83.3 (CH), 62.0 (CH_2), 61.8 (CH), 56.1 (CH_3), 55.1 (C), 31.3 (CH_2), 14.3 (CH_3). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 290.1154, found 290.1184. **IR** (neat, cm^{-1})**:** 3501 (m), 2939 (m), 1726 (s), 1281 (s), 1232 (vs), 1217 (s), 1038 (vs), 727 (vs).



Compound 9

In a dry sealed tube, a mixture of $Pd(TFA)_2$ (36 mg, 0.108 mmol, 0.017 equiv.) and 1,10-phenanthroline (20 mg, 0.111 mmol, 0.017 equiv.) in ethyl vinyl ether (30 mL) was stirred at room temperature for 15 minutes. Et_3N (212 mg, 2.09 mmol, 0.3 eq) and enol **3** (1.90 g, 6.55 mmol, 1 equiv.) in solution in ethyl vinyl ether (35 mL) were added and the reaction mixture was heated at 50 °C under air atmosphere. After stirring for 40 hours, the reaction mixture was filtered through a pad of celite with EtOAc and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 9:1) to afford pure ethyl vinyl ether **9** (1.49 g, 72% yield, colorless oil).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (dd, J = 7.4, 1.4 Hz, 1H), 6.87 (dd, J = 8.1, 7.4 Hz, 1H), 6.80 (dd, J = 8.1, 1.4 Hz, 1H), 6.35 (dd, J = 14.3, 6.7 Hz, 1H), 6.15 (dd, J = 10.1, 1.9 Hz, 1H), 6.02 (dd, J = 10.1, 2.6 Hz, 1H,), 5.57 (dd, J = 8.7, 5.1 Hz, 1H), 4.49-4.43 (m, 1H), 4.27 (dd, J = 14.3, 2.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.07 (dd, J = 6.7, 2.0 Hz, 1H), 3.86 (s, 3H), 2.50-2.43 (m, 1H), 2.15-2.05 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.2 (C), 150.0 (CH), 146.8 (C), 145.3 (C), 129.1 (CH), 129.0 (C), 127.5 (CH), 121.6 (CH), 116.7 (CH), 112.6 (CH), 88.9 (CH_2), 81.6 (CH), 69.1 (CH), 62.1 (CH_2), 56.5 (C), 56.2 (CH_3), 31.8 (CH_2), 14.2 (CH_3). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 316.1311, found 316.1317. **IR** (neat, cm^{-1})**:** 2949 (m), 1734 (vs), 1618 (m), 1495 (s), 1238 (s), 1196 (vs).

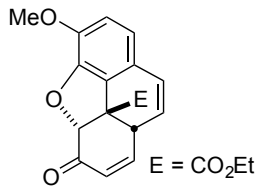


Compound 10

In a dry sealed tube, 2,6-lutidine (16.9 mg, 0.1581 mmol, 1 equiv.) was added to a solution of allyl vinyl ether **9** (50.0 mg, 0.158 mmol, 1 eq.) in dry xylene (2.4 mL). The reaction mixture was stirred at 160 °C under argon. After 24 hours, the reaction mixture was cooled down to room temperature and a solution of PTSA•H_2O (93.0 mg, 0.4901 mmol, 3.1 equiv.) in dry toluene (3.9 mL) was added. The reaction mixture was stirred at 50°C for 16 hours, then diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 95:05 to 9:1) to afford tetracyclic product **10** (28.8 mg, 61% yield, white amorphous solid).

Note: 2,6-lutidine was distilled over calcium hydride prior to use.

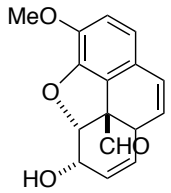
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.48 (dd, J = 9.5, 1.2 Hz, 1H), 5.91 (dd, J = 9.5, 6.1 Hz, 1H), 5.76-5.70 (m, 1H), 5.44 (ddd, J = 10.2, 4.3, 2.4 Hz, 1H), 5.38 (dd, J = 7.5, 3.9 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.54-3.50 (m, 1H), 2.58-2.49 (m, 1H), 2.32-2.25 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.3 (C), 146.6 (C), 145.0 (C), 128.0 (CH), 125.8 (CH), 124.7 (CH), 124.5 (CH), 124.4 (C), 124.4 (C), 117.6 (CH), 113.2 (CH), 86.5 (CH), 61.7 (CH_2), 56.4 (CH_3), 52.9 (C), 36.4 (CH), 29.1 (CH_2), 14.2 (CH_3). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 298.1205, found 298.1190. **IR** (neat, cm^{-1})**:** 2949 (m), 1720 (vs), 1504 (vs), 1456 (s), 1439 (s), 1281 (vs), 1238 (vs).



Compound 11

In a reaction flask, SeO_2 (121 mg, 1.09 mmol, 1 equiv) was added to a solution of the tetracycle **10** (326 mg, 1.09 mmol, 1 equiv) in dry 1,4-dioxane (32.6 mL). The reaction mixture was stirred at 80°C under argon for 90 min. The reaction mixture was then cooled down to room temperature and a solution of Dess-Martin Periodinane (695 mg, 1.64 mmol, 1.5 eq.) in dry dichloromethane (16.3 mL) was added. The mixture was stirred at room temperature for 1 hour, then diluted with EtOAc and quenched with a 5%(w/w) aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was partially purified with a silica gel plug (hexanes/EtOAc 6:4) to afford a dark red sticky solid **11** (233 mg) that was used in the subsequent reaction without additional purification.

Note: The product could not be separated from the Se-based by-products due to its tendency to isomerize.

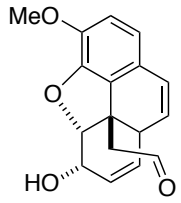


Compound 12

The crude compound **11** (233 mg) was dissolved in dry dichloromethane (2.3 mL) in a flamed-dried reaction flask and the mixture was cooled down to -78°C. A solution of diisobutylaluminum hydride in hexanes (25 wt. %, 2.4 mL) was slowly added over 45 minutes. The resulting mixture was stirred for an additional 30 minutes at -78°C. Upon completion, the reaction mixture was slowly quenched with methanol (0.2 mL over 15 minutes) and then with saturated aqueous NH_4Cl. The biphasic solution was warmed up to room temperature and the organic phase was separated. The aqueous layer was extracted three more times with dichloromethane. The combined organic layers were washed with brine twice, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc, 8:2 to 6:4) to afford the desired product **13** (80 mg, 27% yield over 2 steps from the tetracycle **10**, light yellow solid).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.53 (dd, J = 9.4, 1.0 Hz, 1H), 6.02 (dd, J = 9.4, 6.2 Hz, 1H), 5.84 (dddd, J = 10.2, 3.1, 2.0, 0.9 Hz, 1H), 5.53

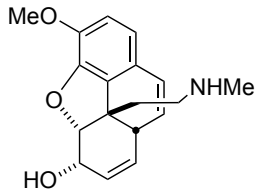
(dd, J = 6.5, 0.9 Hz, 1H), 5.34 (ddd, J = 10.2, 2.6, 2.6 Hz, 1H), 4.26-4.20 (m, 1H), 3.85 (s, 3H), 3.24-3.20 (m, 1H), 2.93 (d, J = 9.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.7 (CH), 147.3 (C), 144.5 (C), 131.8 (CH), 128.1 (CH), 126.6 (CH), 125.9 (CH), 124.3 (C), 121.7 (C), 118.4 (CH), 114.0 (CH), 85.1 (CH), 65.2 (CH), 57.5 (C), 56.3 (CH_3), 33.4 (CH). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 270.0892, found 270.0871. **IR** (neat, cm^{-1}): 3353 (br), 2970 (s), 1379 (m), 1160 (s), 1128 (s), 1108 (s), 951 (vs), 817 (s).



Compound 13

A solution of potassium *tert*-butoxide (135 mg, 1.20 mmol, 4 equiv) in THF (1 mL) was added via cannula to a solution of Ph_3PCH_2OMeCl (431 mg, 1.26 mmol, 4.2 equiv.) in dry THF (2 mL) at 0°C. The solution turned dark red and was allowed to stir at 0°C for 25 minutes. To this reaction flask in then added a solution of the aldehyde **12** (81 mg, 0.30 mmol, 1 equiv.) in THF (1.5 mL) and the reaction mixture was stirred at 0°C for 30 minutes. Upon full consumption of the aldehyde **12**, HCl (12 M, 0.37 mL) was added dropwise and the reaction mixture was stirred at 0°C for another 30 minutes. The reaction was then diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$. The organic phase was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography (hexanes/EtOAc 8:2 to 7:3) to afford the desired product **13** (54 mg, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.74 (t, J = 1.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.54 (dd, J = 9.3, 0.8 Hz, 1H), 5.97 (dd, J = 9.3, 6.5 Hz, 1H), 5.87 (dddd, J = 10.3, 3.1, 2.2, 1.0 Hz, 1H), 5.28 (ddd, J = 10.3, 3.0, 2.2 Hz, 1H), 5.16 (dd, J = 6.5, 1.0 Hz, 1H), 4.56-4.50 (m, 1H), 3.86 (s, 3H), 3.25 (dd, J = 18.4, 1.0 Hz, 1H), 3.04-3.00 (m, 1H), 2.85 (d, J = 18.4 Hz, 1H), 2.76 (d, J = 10.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 201.0 (CH), 146.3 (C), 144.3 (C), 132.8 (CH), 129.2 (CH), 128.0 (C), 127.2 (CH), 125.6 (CH), 123.7 (C), 118.2 (CH), 112.7 (CH), 90.9 (CH), 65.7 (CH), 56.2 (CH_3), 49.5 (CH_2), 43.4 (C), 37.0 (CH). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 284.1049, found 284.1066. **IR** (neat, cm^{-1}): 3462 (br), 2924 (s), 1717 (s), 1507 (vs), 1284 (s), 1272 (s), 1050 (s), 798 (s).



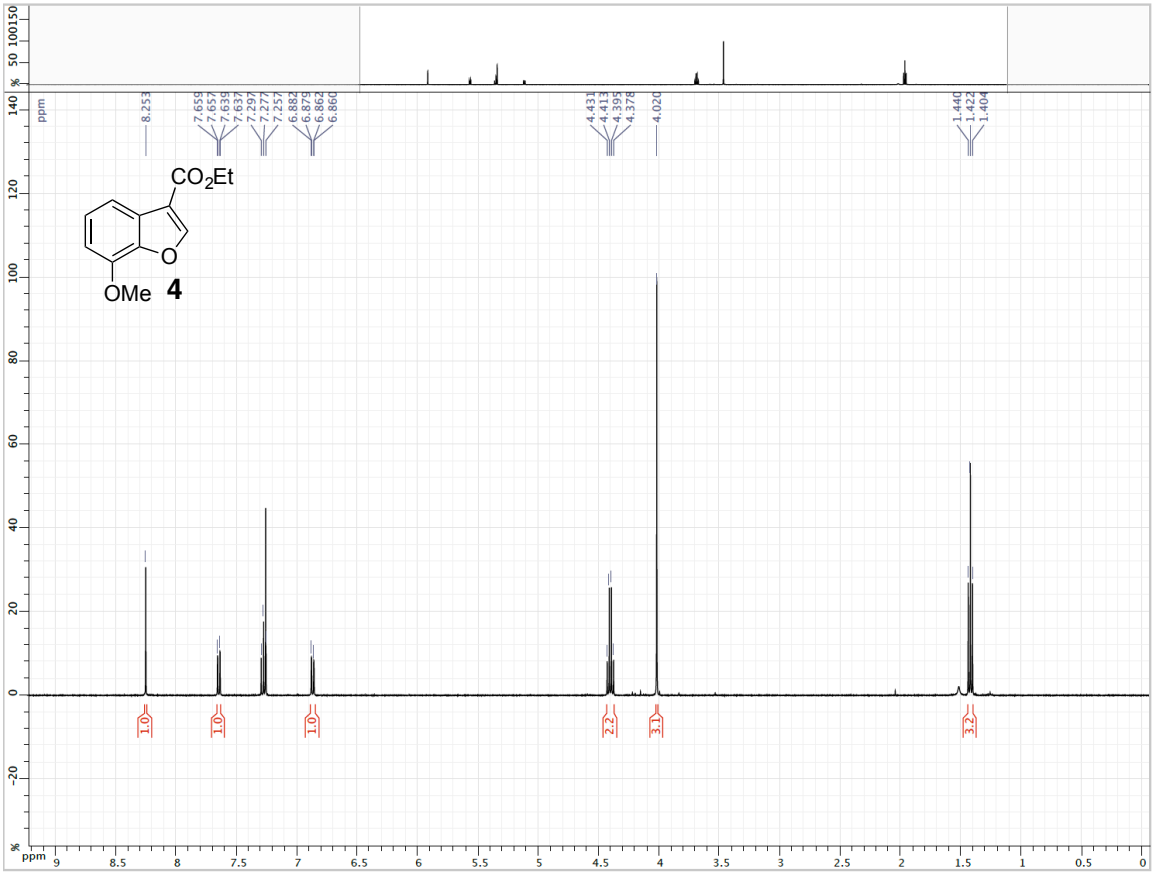
Compound 2

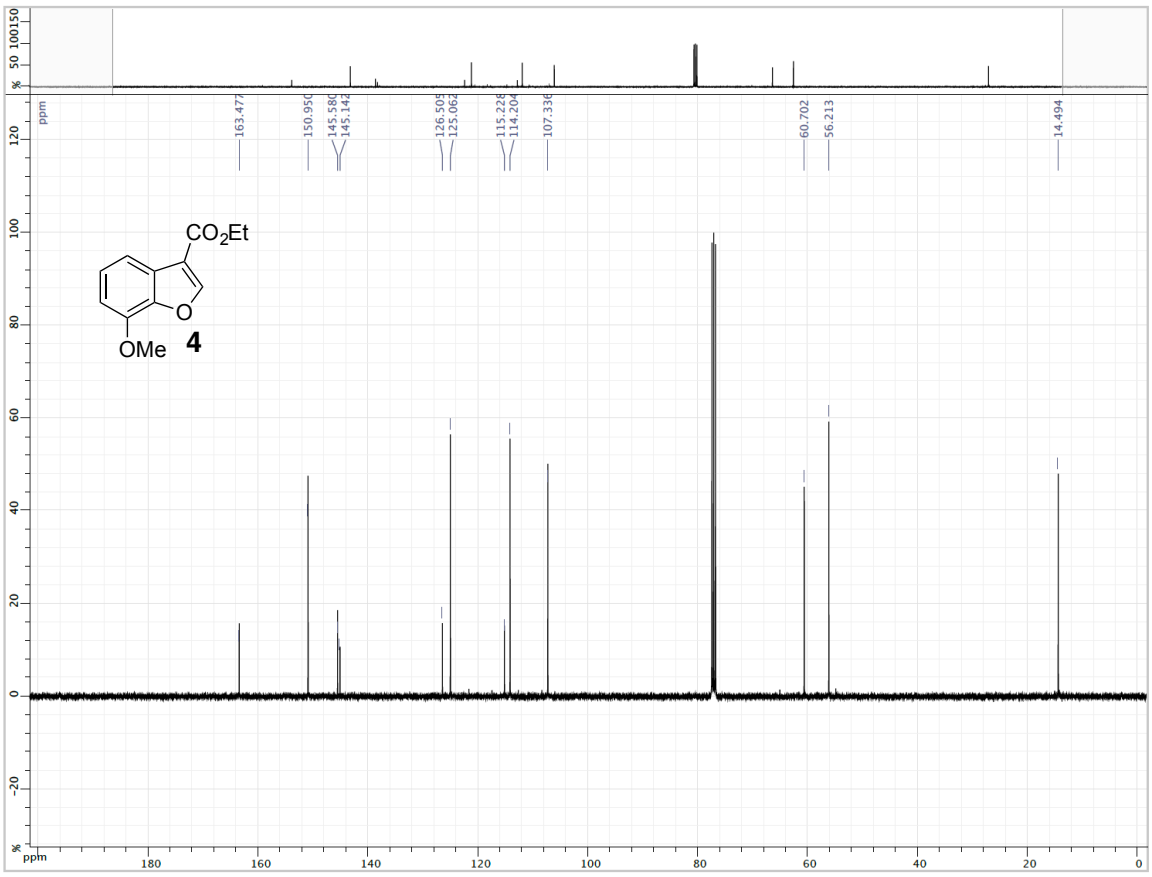
To a solution of the aldehyde **13** (16 mg, 0.07 mmol, 1 eq.) in dry MeOH (4 mL) was added dropwise methylamine (33 wt.% solution in EtOH, 46 µL, 0.44 mmol, 6.5 equiv.) under argon. The reaction mixture was stirred at room temperature under argon. After 2h15, the reaction mixture was cooled to 0 °C and $NaBH_4$ (3.4 mg, 0.09 mmol, 1.3 equiv.) was added in one portion. The resulting mixture was warmed to room temperature. After 50 minutes, the reaction mixture was diluted with CH_2Cl_2 and quenched with water. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude amine was purified by flash chromatography

(MeOH/dichloromethane/ammonium hydroxide 2:8:0 to 2:8:0.1) to afford the secondary amine **2** (18 mg, 88% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 9.3 Hz, 1H), 5.99 (dd, J = 9.3, 6.5 Hz, 1H), 5.82-5.78 (m, 1H), 5.27 (ddd, J = 10.1, 2.3, 2.3 Hz, 1H), 5.15 (dd, J = 6.5, 0.9 Hz, 1H), 4.23-4.20 (m, 1H), 3.84 (s, 3H), 2.82-2.79 (m, 1H), 2.70 (ddd, J = 11.1, 10.9, 5.1 Hz, 1H), 2.42 (ddd, J = 11.1, 10.9, 5.1 Hz, 1H), 2.45-2.38 (br, 1H), 2.35 (s, 3H), 2.18-2.09 (m, 1H), 1.86 (ddd, J = 13.8, 10.9, 5.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$): 146.3 (C), 143.9 (C), 132.2 (CH), 129.3 (CH), 129.2 (C), 127.7 (CH), 125.2 (CH), 123.9 (C), 117.9 (CH), 112.16 (CH), 90.2 (CH), 66.2 (CH), 56.1 (CH_3), 48.0 (CH_2), 45.5 (C), 37.8 (CH), 36.5 (CH_3), 36.0 (CH_2). **HRMS** (EI): m/z calc'd for $C_{12}H_{12}O_4$ [M^+] 299.1521, found 299.1535. **IR** (neat, cm^{-1}): 3332 (br), 2970 (s), 2360 (m), 2343 (m), 1380 (m), 1307 (m), 1161 (s), 1128 (s), 1108 (s), 951 (vs), 817 (s), 677 (s).

^{1}H and ^{13}C NMR spectra

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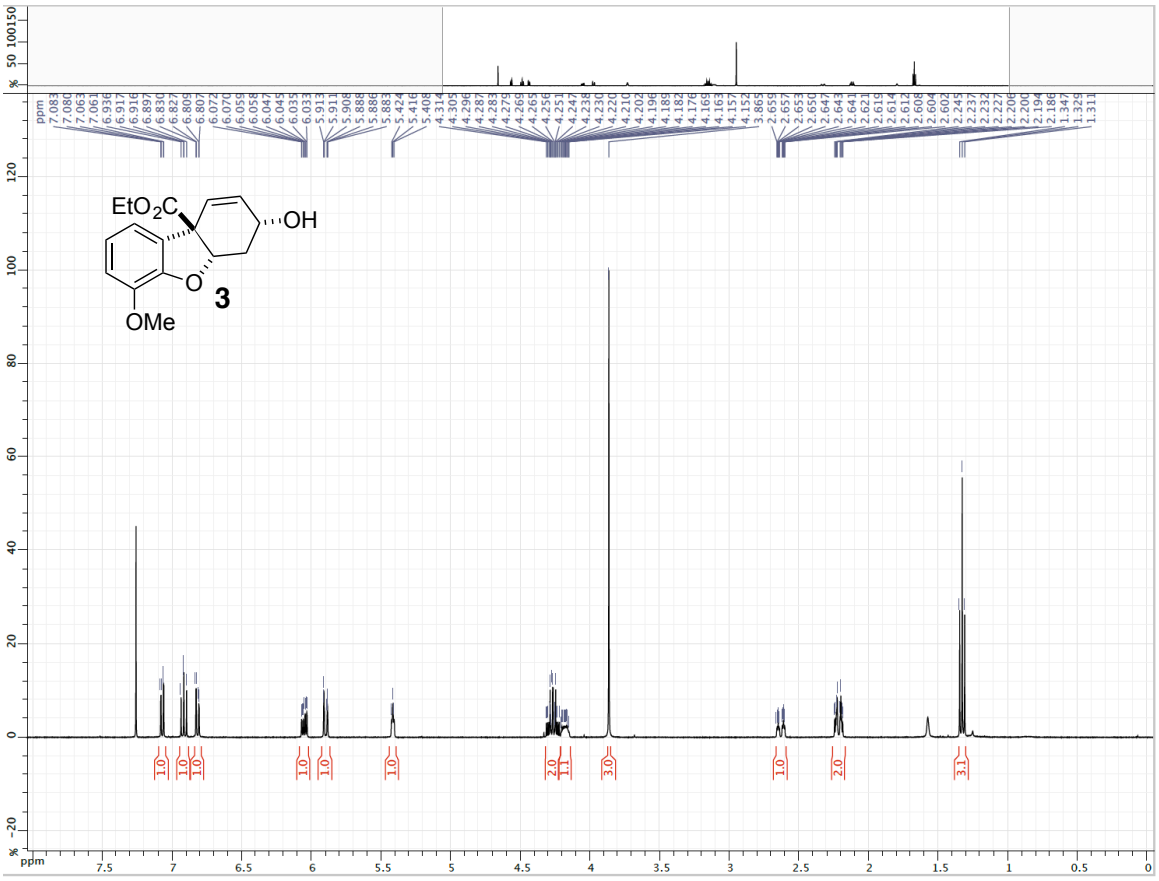
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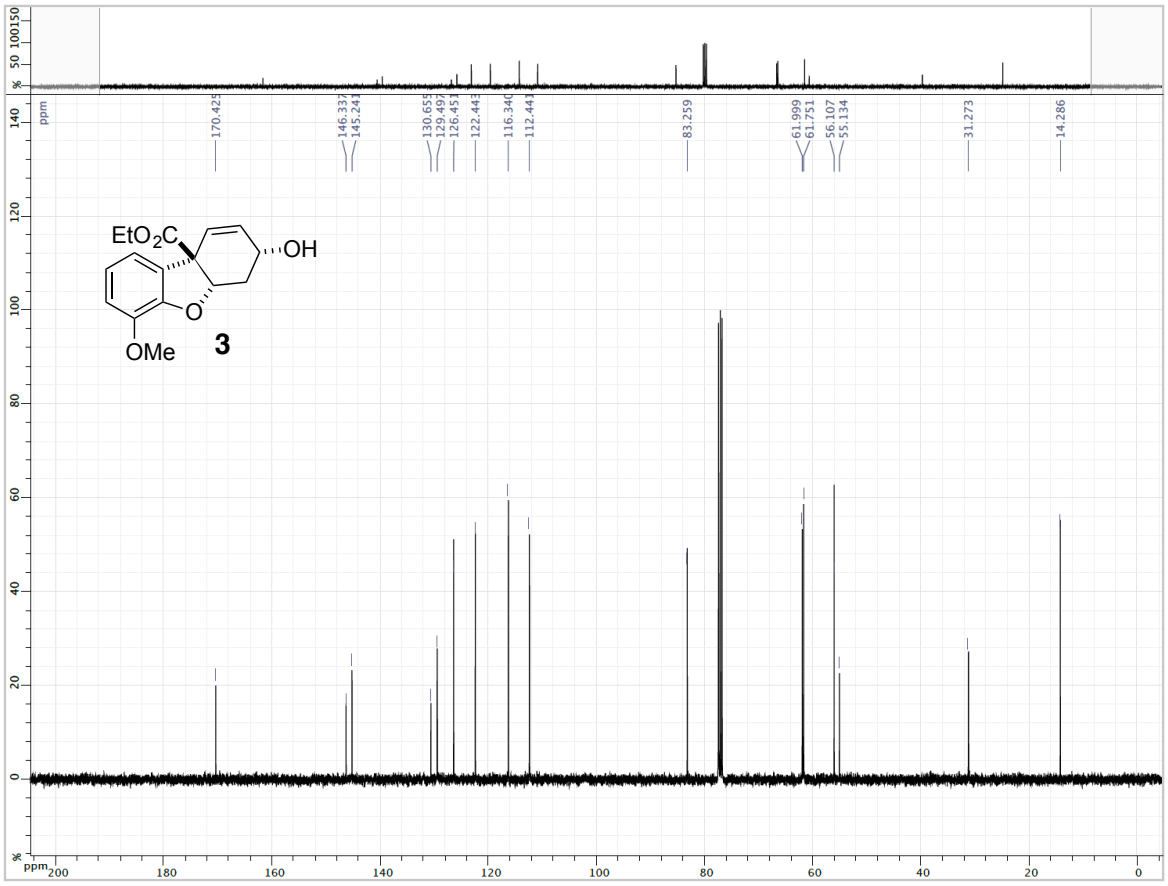
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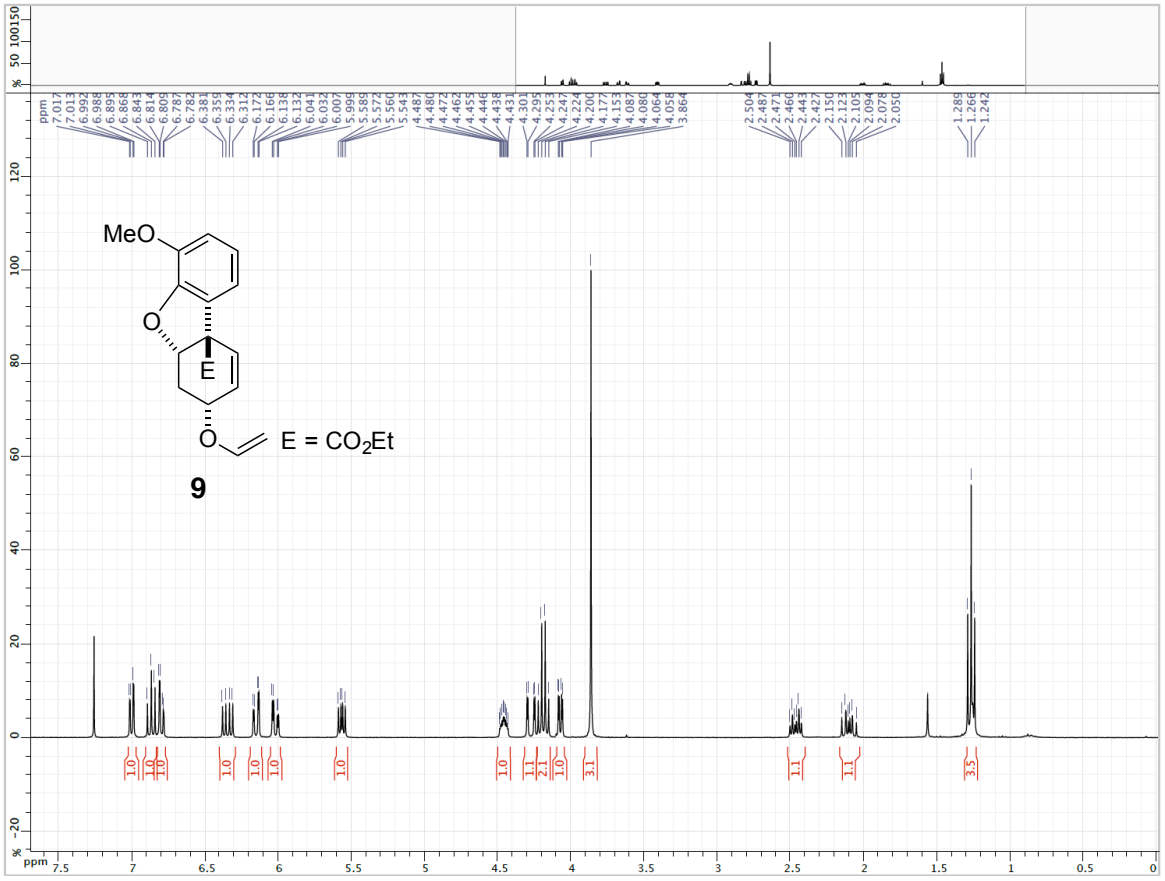
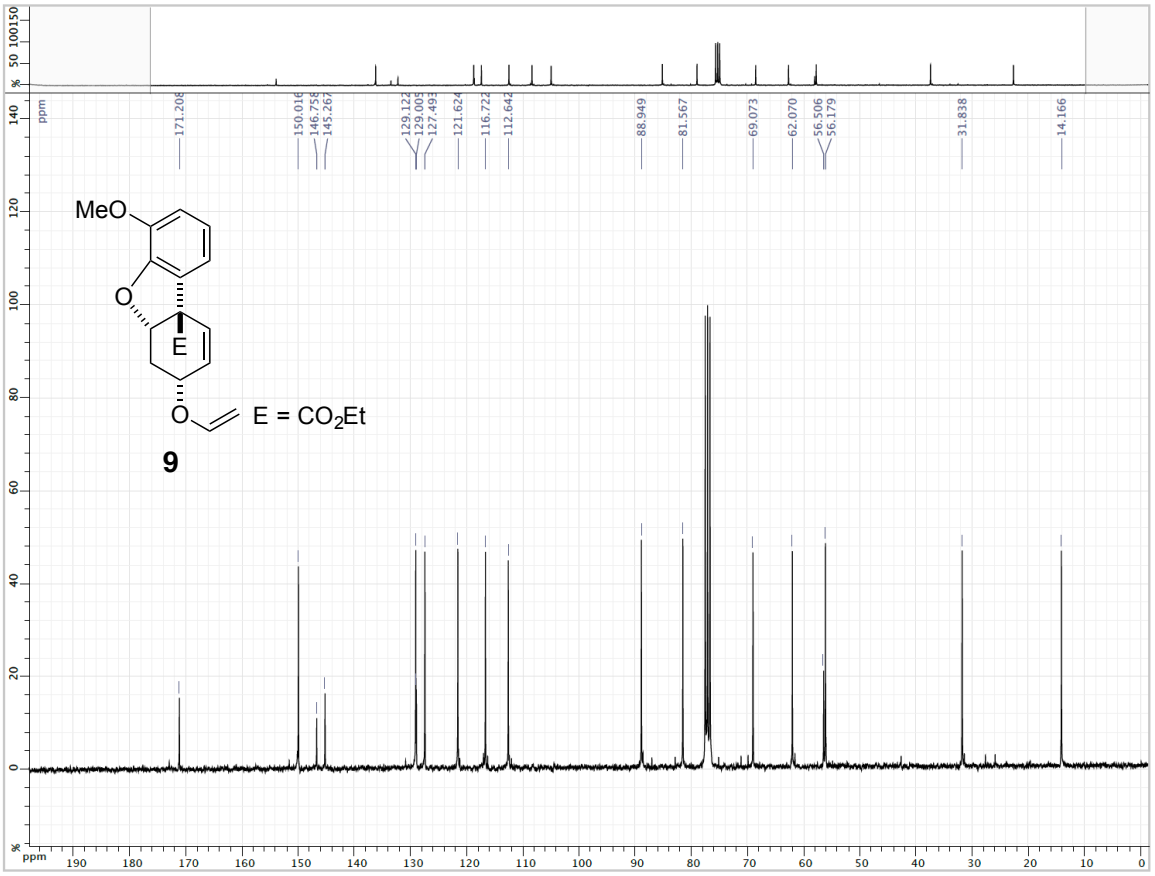
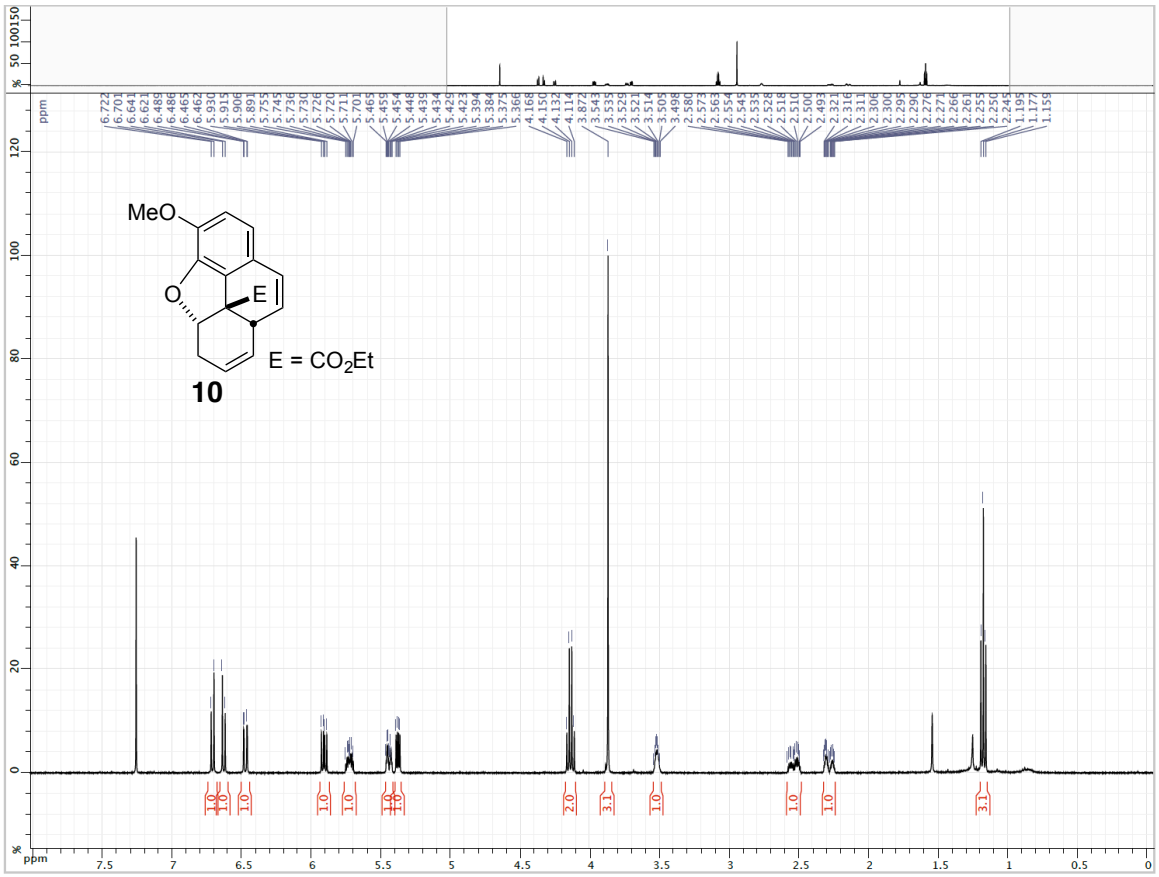
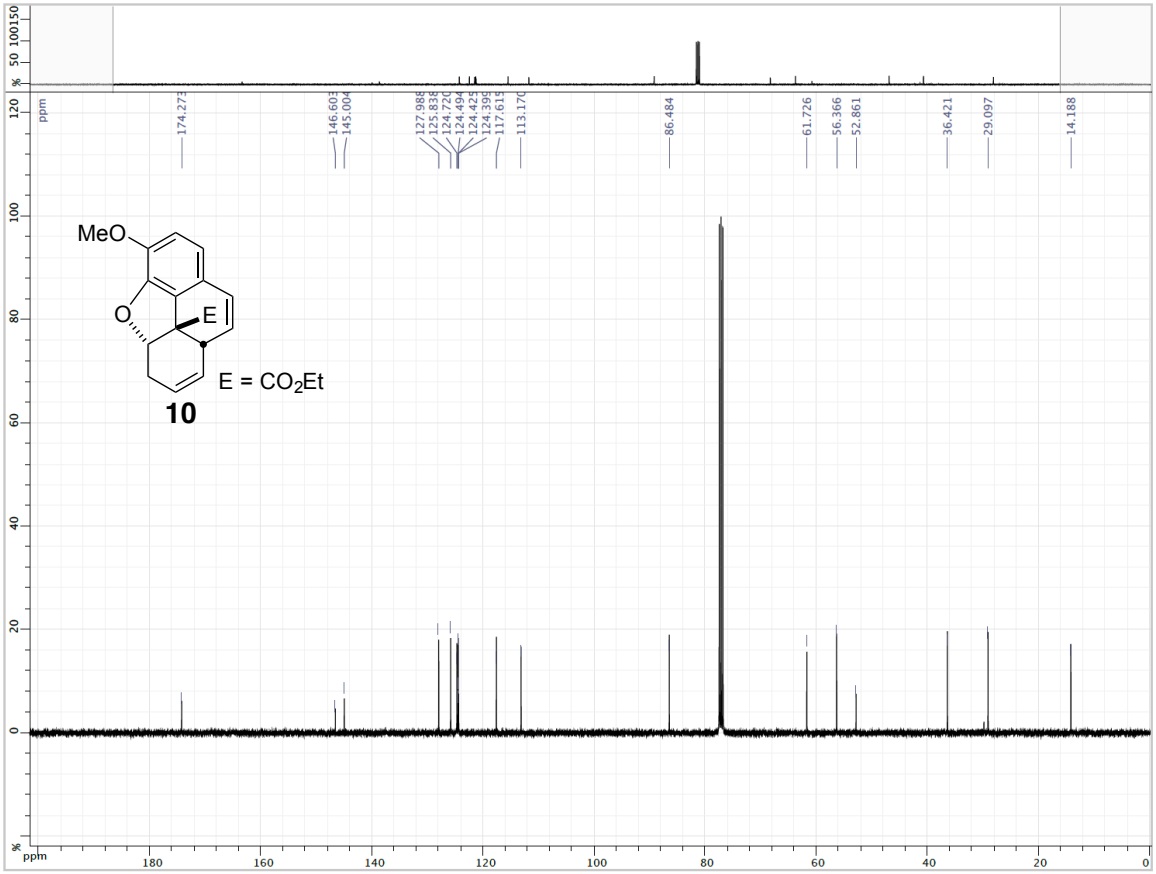
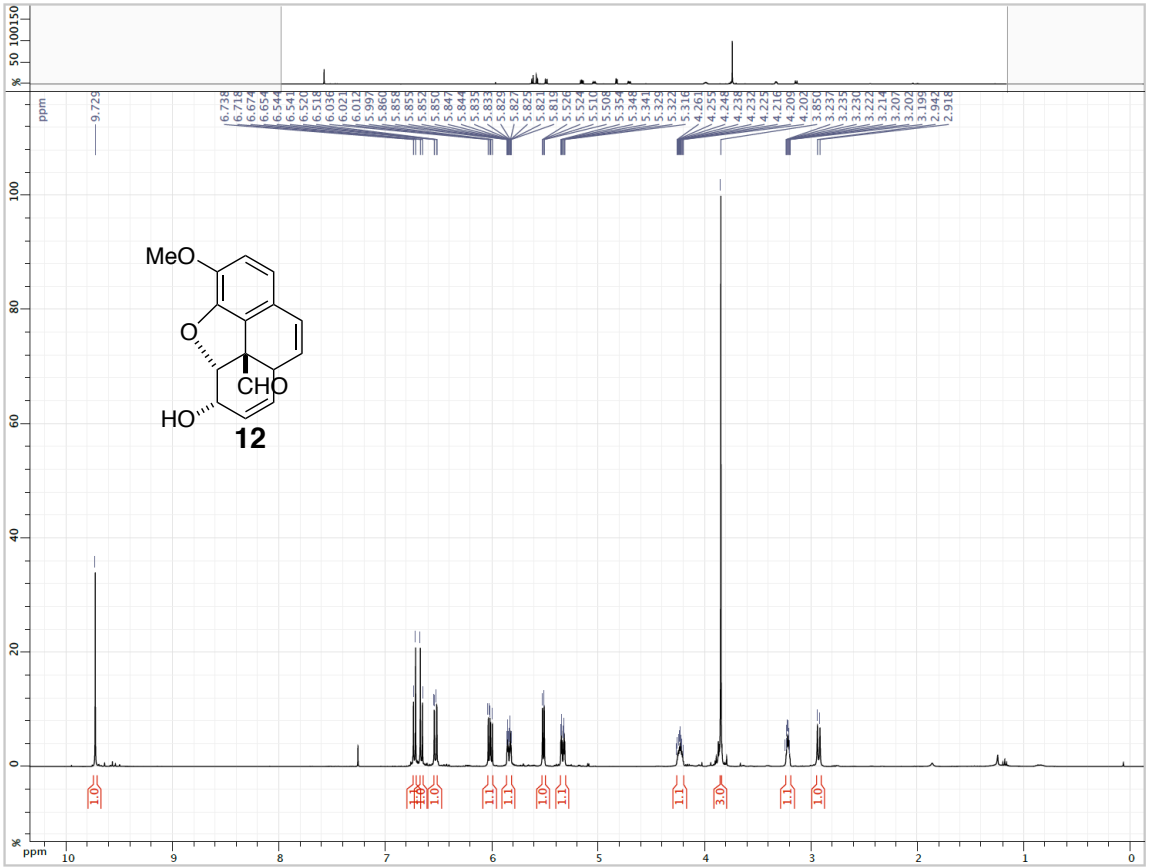
14.286

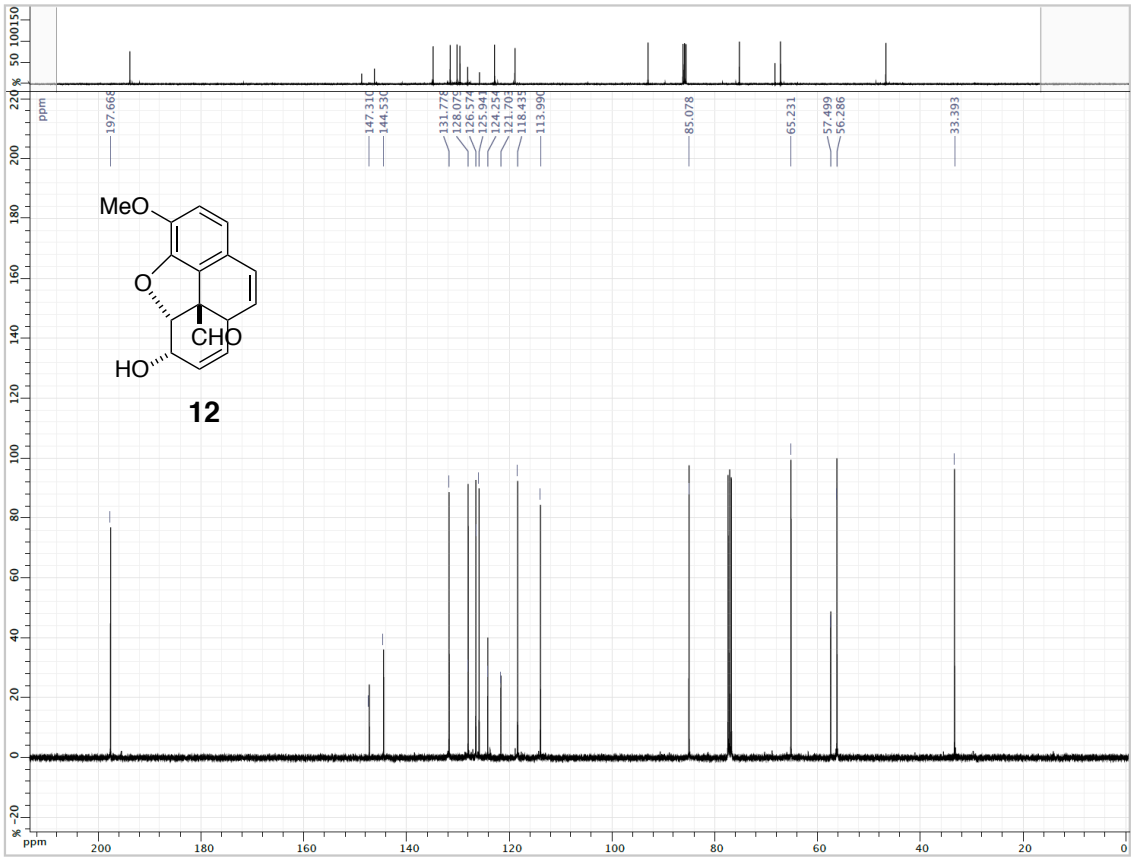

MeO
O
E
O
E = CO2Et
9

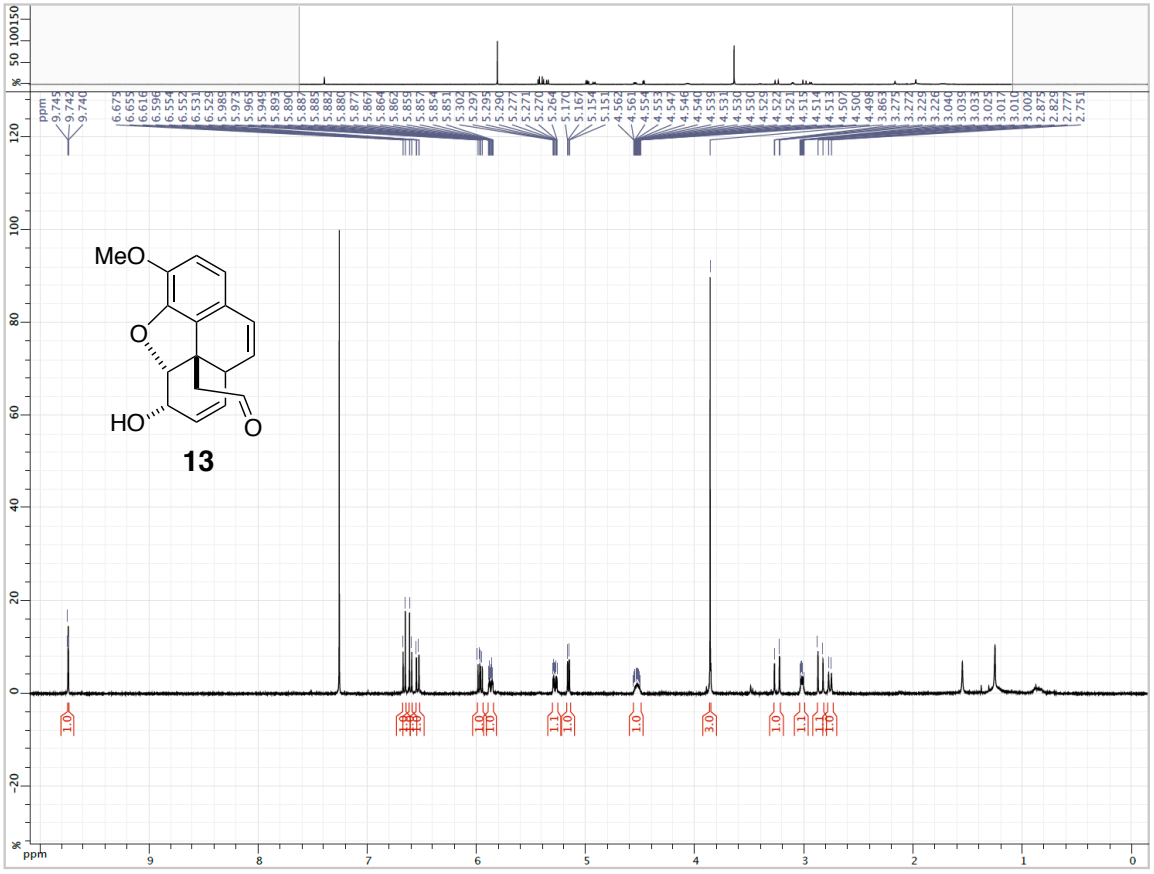

MeO
O
E
O
E = CO2Et
9

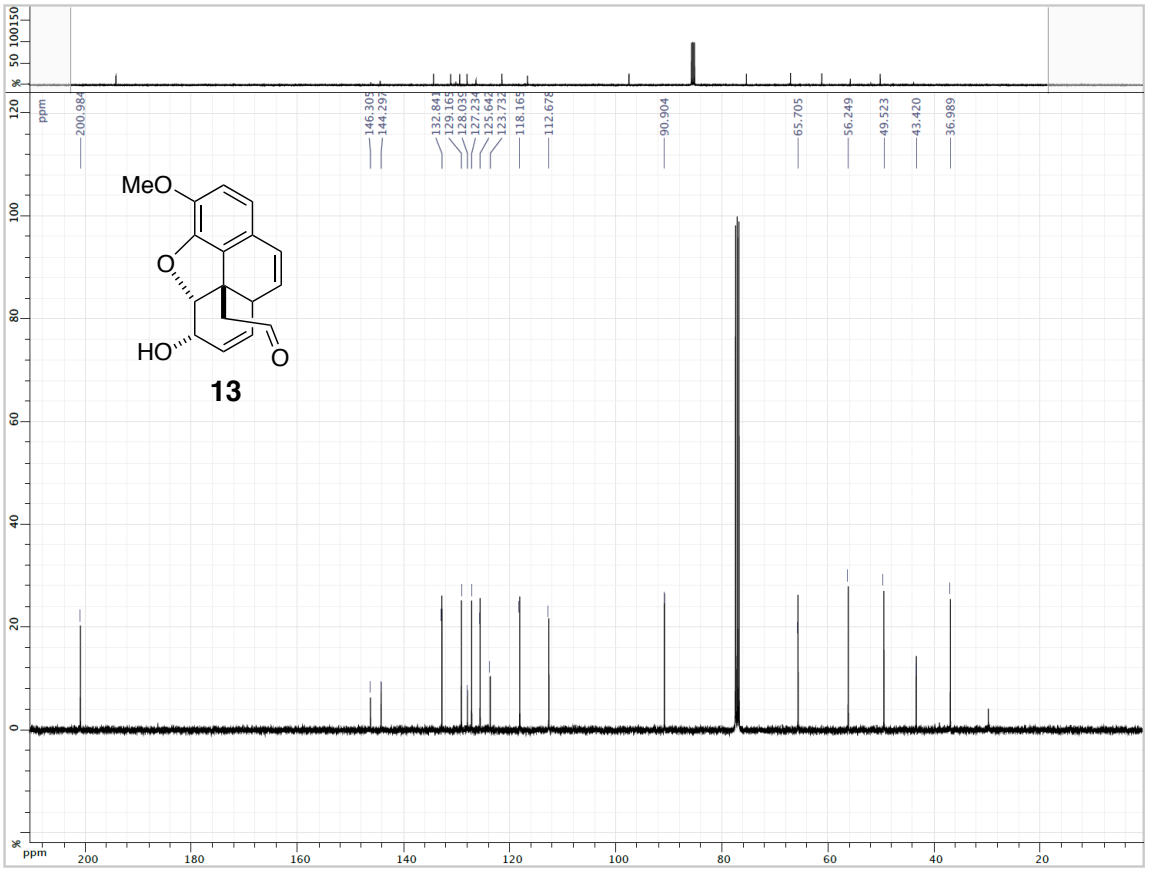

MeO
O
E
E = CO2Et
10

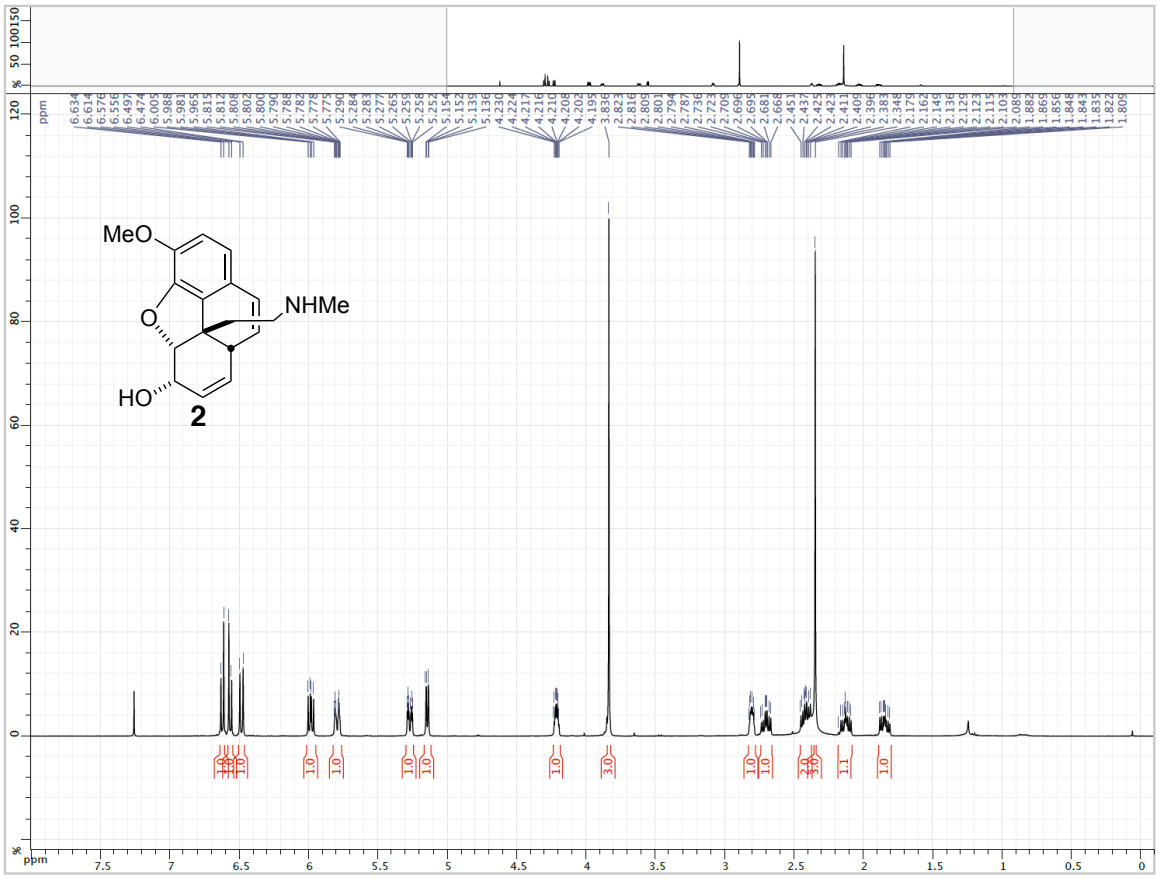

MeO
O
E
E = CO2Et
10

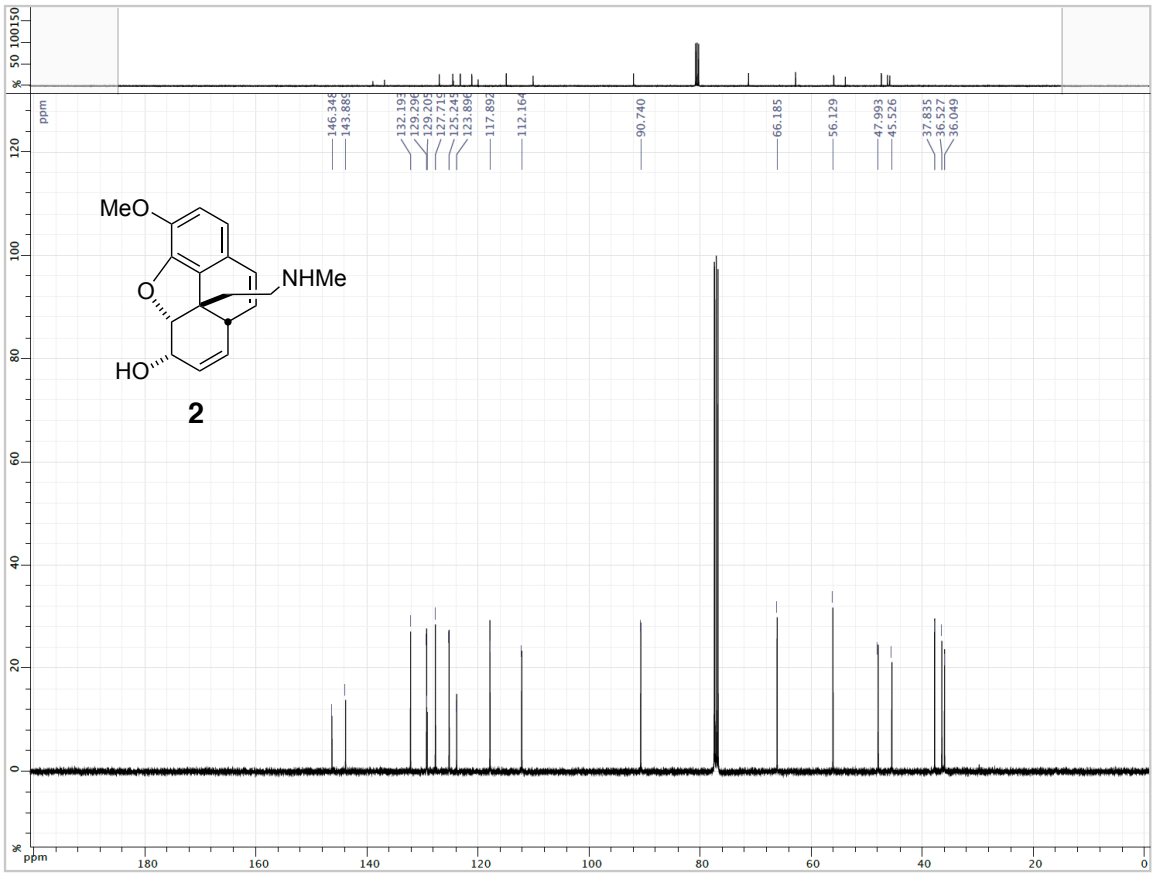

MeO
O
CHO
HO
12


MeO
O
CHO
HO
12


MeO
O
HO
O
13


MeO
O
HO
O
13
200.984
146.305
144.297
132.841
129.165
128.035
127.234
125.642
123.732
118.165
112.678
90.904
65.705
56.249
49.523
43.420
36.989
ppm


MeO
O
NHMe
HO
2
ppm


MeO
O
NHMe
HO
2
146.348
143.885
132.193
129.296
129.205
127.715
125.245
123.896
117.892
112.164
90.740
66.185
56.129
47.993
45.526
37.835
36.527
36.049
ppm