Access to a Structurally Complex Compound Collection via Ring Distortion of the Alkaloid Sinomenine

*Alfredo Garcia, Bryon S. Drown, and Paul J. Hergenrother**

Roger Adams Laboratory, Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue, Urbana, Illinois 61801, United States

Supporting Information

Table of Contents

1. General Considerations:

Sinomenine was purchased from LKT Laboratories, Inc. as the hydrochloride salt. To obtain the free base, sinomenine hydrochloride was dissolved in a saturated aqueous solution of sodium bicarbonate, extracted with dicloromethane, and concentrated *in vacuo*. Other chemical reagents were purchased from commercial sources and used without further purification. Anhydrous solvents used during these studies were dried after being passed through columns with activated alumina. Flash chromatography was performed using silica gel (230–400 mesh).

Various NMR experiments (including 2-D) were conducted in the NMR facilities at UIUC. ^{1}H NMR and ^{13}C NMR experiments were recorded on Varian Unity spectrometers at 500 MHz and 125 Hz, respectively unless otherwise indicated. Spectra were obtained in the following solvents (reference peaks also included for ^{1}H and ^{13}C NMRs): $CDCl_3$ (^{1}H NMR: 7.26 ppm; ^{13}C NMR: 77.26 ppm), d_6-acetone (^{1}H NMR: 2.05 ppm; ^{13}C NMR: 206.26 ppm), CD_3OD (^{1}H NMR: 3.30 ppm; ^{13}C NMR: 49.00 ppm), d_7-DMF (^{1}H NMR: 2.75 ppm; ^{13}C NMR: 34.90 ppm), D_2O (^{1}H NMR: 4.79 ppm), d_6-DMSO (^{1}H NMR: 2.50 ppm; ^{13}C NMR: 39.52 ppm). NMR experiments were performed at room temperature unless otherwise indicated. Chemical shift values are reported in parts per million (ppm) for all ^{1}H NMR and ^{13}C NMR spectra. ^{1}H NMR multiplicities are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

High–resolution mass spectra were obtained using Waters Q-TOF Ultima ESI and Agilent 6230 ESI TOF LC/MS spectrometers.

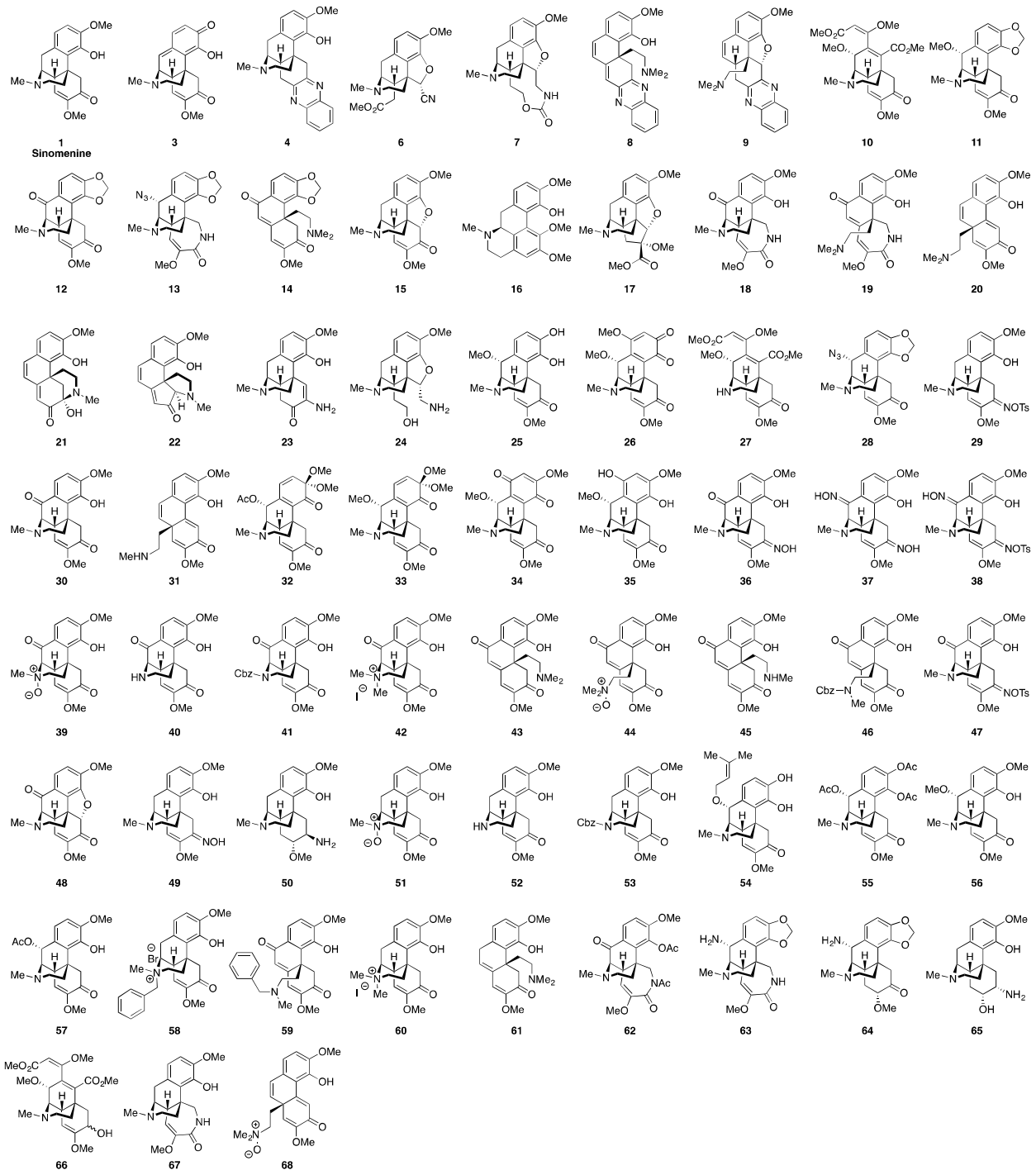
2. Computational Analysis:

The Chembridge Diverset™-CL and Diverset™-EXP compound collections were used for computational analysis (50,000 compounds each; 100,000 compounds total). Structural data was obtained from the Chembridge website.

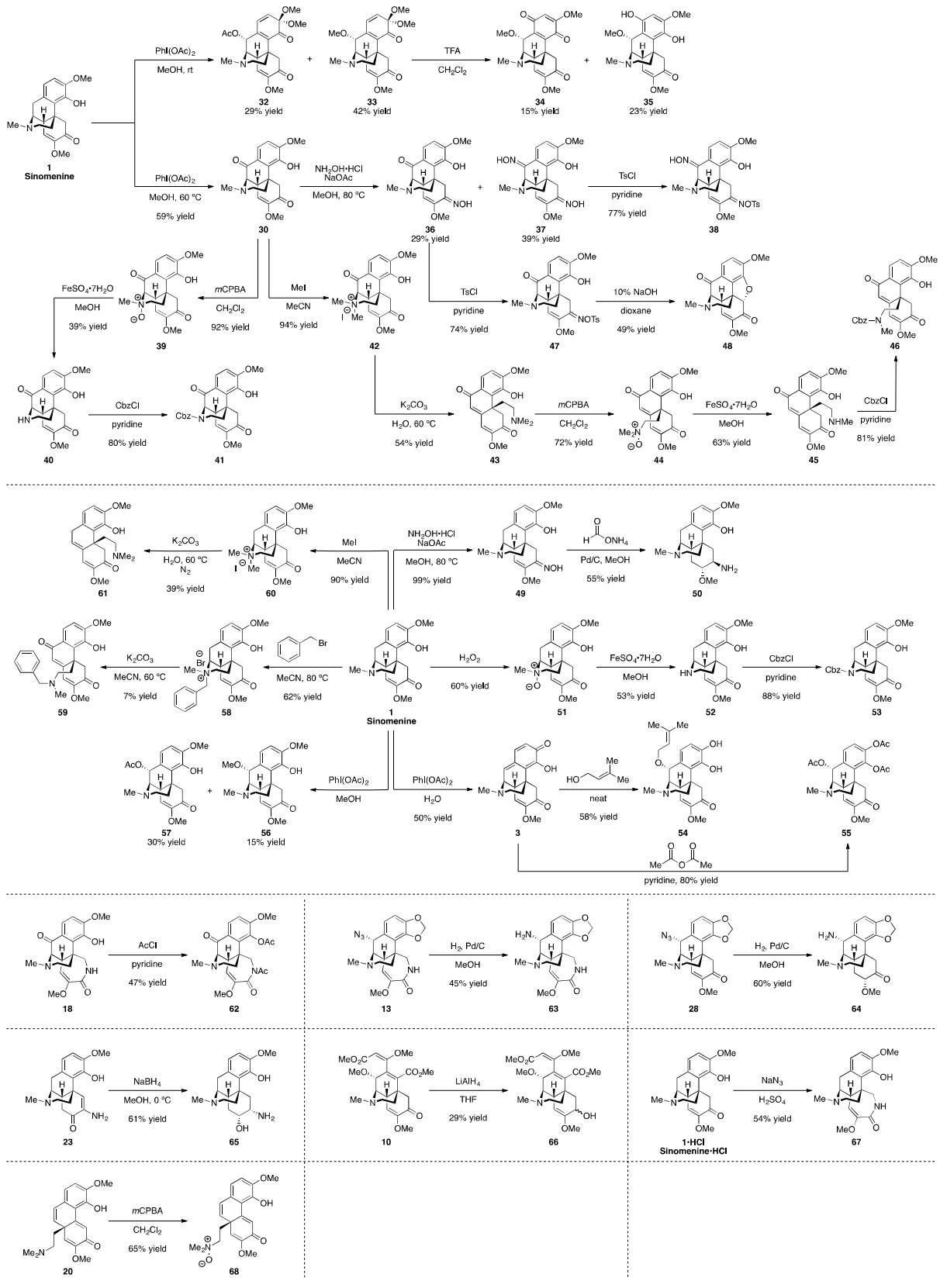
Globularity was calculated by using Maestro version 2.8.013 and MOE 2015.10. Number of stereogenic centers, Fsp^3, Ring Complexity Index (RCI), and Ring Fusion Density (RFD) were calculated using a custom Python program that implements RDKit. Source code is available at https://github.com/HergenrotherLab/ctdTools.

Definitions of Reported Physiochemical Parameters

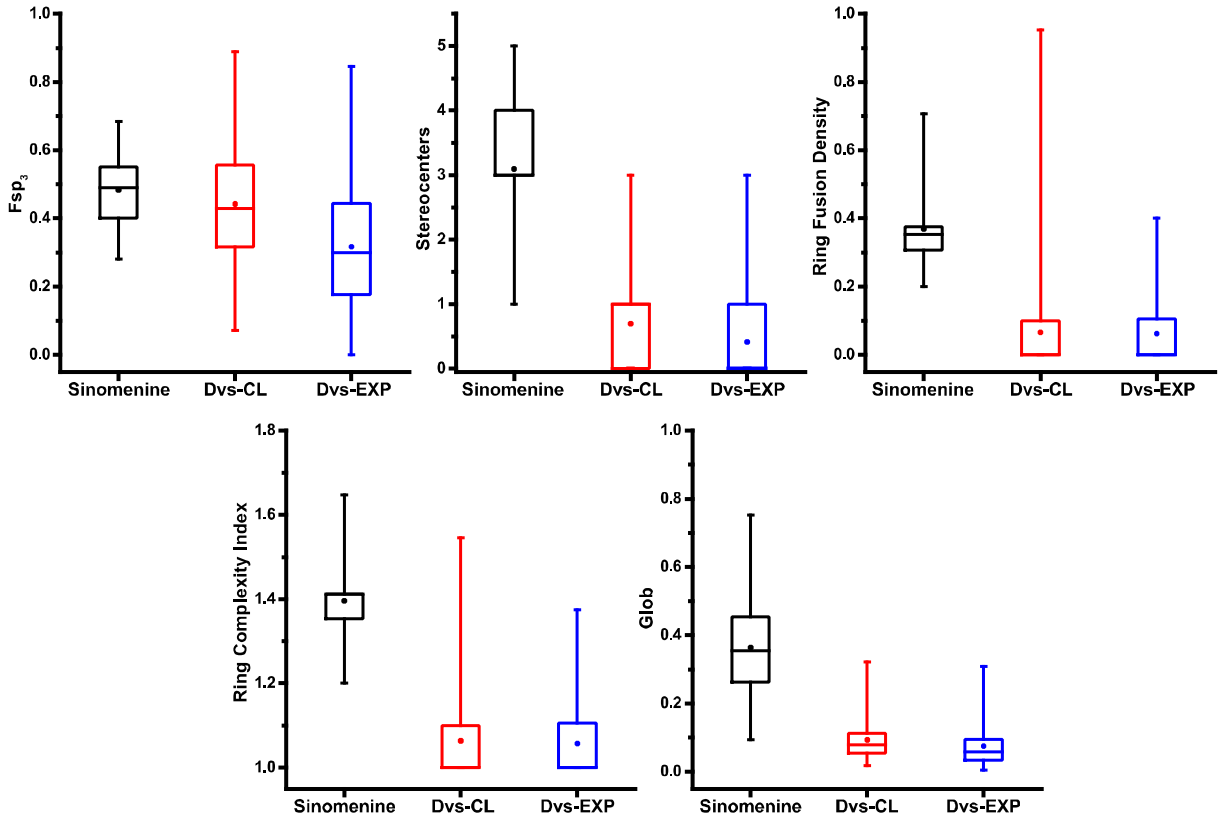
Stereogenic center	Number of sp^3–hybridized stereogenic centers (chiral centers).
Globularity:	Inverse condition number of the covariance matrix of atomic coordinates (a value of 1 indicates a perfect sphere while a value of 0 indicates a two- or one-dimensional object)[1]
Fsp^3	The number of sp^3–hybridized carbons in a compound divided by the sum of the number of sp^3–hybridized and sp^2–hybridized in the compound.[2]
Ring Complexity Index:	$C_R = R/A_R$; where R corresponds to total ring size and A_R is the number of atoms belonging to the ring system.[3]
Ring Fusion Density:	$RF\Delta = 2 \bullet R_B/A_R$; where R_B corresponds to the number of ring bridges in compound. A_R is the number of atoms belonging to the ring systems.[3]



3. **Figure S1.** Sinomenine Compound Collection



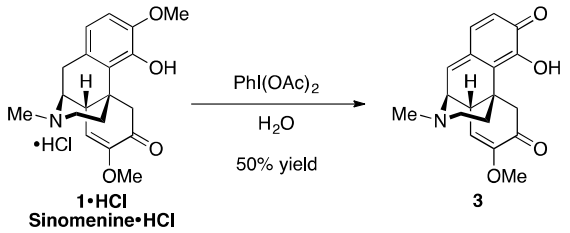
4. **Figure S2.** Synthetic routes to remaining sinomenine compounds.



5. **Figure S3**. Box plots comparing structural complexity of commercial libraries and the 66 sinomenine-derived compounds (including sinomenine) from Figure S1. Box represents quartiles, whiskers represent 1st and 99th percentiles, and dot represents mean. Dvs-CL = Chembridge Diverset™-CL; Dvs-EXP = Diverset™-EXP.

6. Synthesis and Characterization of Sinomenine Compounds:

Compound 3

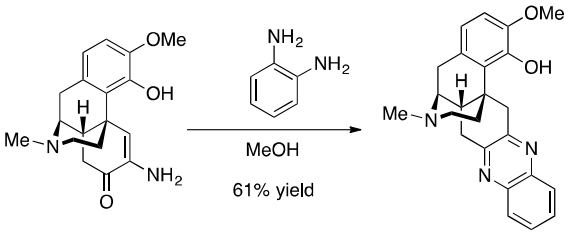


1•HCl
Sinomenine•HCl

3

Procedure: In a vial with a stir bar, **1•HCl** (719.6 mg, 1.967 mmol) was dissolved in water (15 mL). Diacetoxyiodobenzene (771.5 mg, 2.395 mmol) was added to the reaction vial. The reaction mixture was stirred open to air for 1 hour and was then basified with a saturated solution of sodium carbonate. The contents of the vial were poured into a seperatory funnel and were extracted with dichloromethane (4x). The organic layers were combined, dried with sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (9:1 dichloromethane/methanol) to afford known quinone methide **3** (308.7 mg, 50% yield) as an orange solid. Spectral data (^{1}H NMR) was consistent with literature reported values.[4]

Compound 4

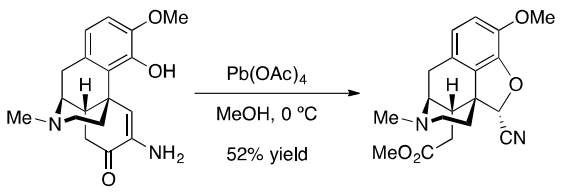


23

4

Procedure: In a vial with a stir bar, **23** (413.9 mg, 1.317 mmol) was dissolved in methanol (10 mL). To this, *o*-phenylenediamine (261.3 mg, 2.417 mmol) was added and was allowed to stir for 15 hours capped under nitrogen. After this time, the reaction mixture was filtered and washed with water to afford the **4** as a white, waxy solid (311.3 mg, 61% yield). Spectral data (^{1}H and ^{13}C NMR) was consistent with literature reported values.[5]

Compound 6



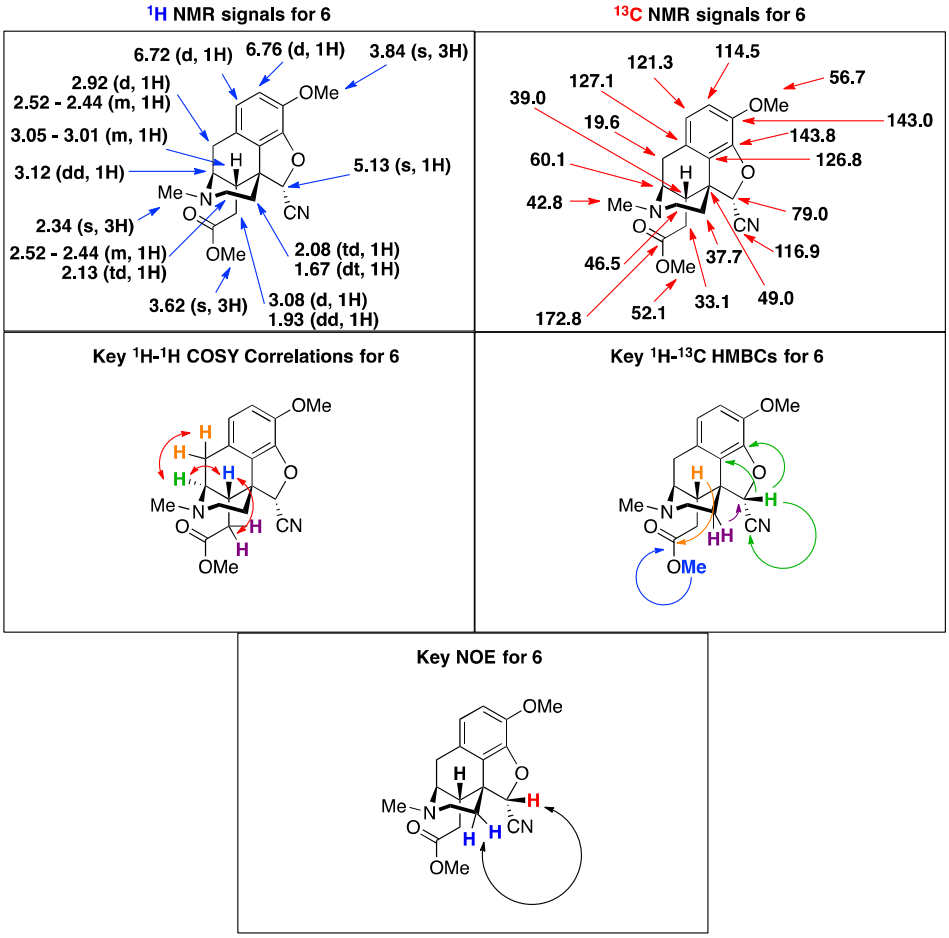
23 **6**

Procedure: In a vial with a stir bar, keto-enamine **23** (82.3 mg, 0.2610 mmol) was dissolved in methanol (6 mL) and was cooled to 0 ºC in an ice/water bath. Lead (IV) tetracetate (410.6 mg, 0.9260 mmol) was added to the vial and the mixture was allowed to stir in a closed vial at 0 ºC under nitrogen. After 40 min, ethylene glycol (2 mL) was added to the reaction along with a saturated solution of sodium bicarbonate. The contents were poured into a seperatory funnel and were extracted with dichloromethane (3x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (15:1 dichloromethane/methanol) to afford **6** (46.5 mg, 52% yield) as a light brown solid.

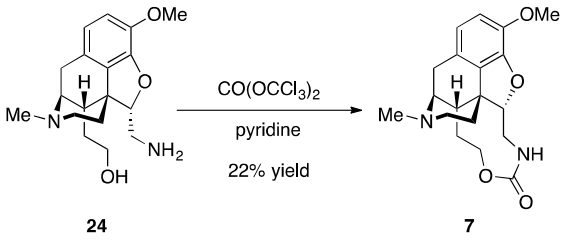
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.76 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 3.12 (dd, *J* = 6.1, 2.9 Hz, 1H), 3.08 (d, *J* = 16.3 Hz, 1H), 3.05–3.01 (m, 1H), 2.92 (d, *J* = 18.8 Hz, 1H), 2.52–2.44 (m, 2H), 2.34 (s, 3H), 2.13 (td, *J* = 12.2, 2.9 Hz, 1H), 2.08 (td, *J* = 12.2, 4.1 Hz, 1H), 1.93 (dd, *J* = 16.4, 8.1 Hz, 1H), 1.67 (dt, *J* = 11.8, 1.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.8, 143.8, 143.0, 127.1, 126.8, 121.3, 116.9, 114.5, 79.0, 60.1, 56.7, 52.1, 49.0, 46.5, 42.8, 39.0, 37.7, 33.1, 19.6.

HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_4$ $[M+H]^+$: 343.1658, found: 343.1651.



Compound 7



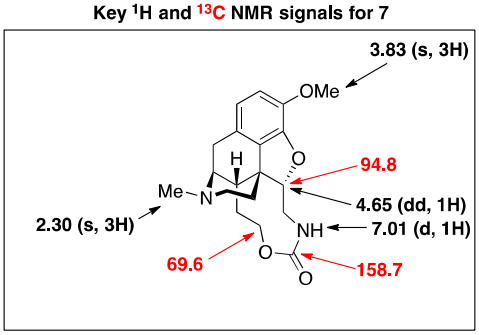
Procedure: In a vial with a stir bar, amino alcohol **24** (14.8 mg, 0.0466 mmol) was dissolved in pyridine (6 mL). The reaction mixture was cooled to 0 ºC in an ice/water bath. After 10 minutes, triphosgene (18.1 mg, 0.0610 mmol) was added to the reaction and the contents of the vial were capped under nitrogen and were stirred for 12 hours. The reaction was diluted with a saturated solution of sodium carbonate and water and was extracted with dichloromethane (3x). The organic layers were combined, dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (9:1 dichloromethane/methanol) to afford carbamate **7** (3.5 mg, 22% yield) as a white solid.

^{1}H NMR (d_7-DMF, 80 ºC, 500 MHz): δ 7.01 (d, J = 9.0 Hz, 1H), 6.79 (d, J = 8.2 Hz, 1H), 6.62

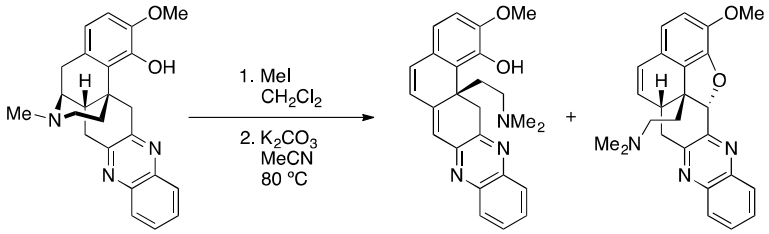
(d, *J* = 8.1 Hz, 1H), 4.65 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.31 (t, *J* = 12.0 Hz, 1H), 4.11–4.03 (m, 1H), 3.99 (dt, *J* = 11.8, 3.0 Hz, 1H), 3.83 (s, 3H), 3.34 (dt, *J* = 14.3, 3.1 Hz, 1H), 3.06–3.02 (m, 1H), 2.85 (d, *J* = 18.9 Hz, 1H), 2.51 (dd, *J* = 18.6, 6.4 Hz, 1H), 2.43 (dt, *J* = 4.5, 3.2 Hz, 1H), 2.37 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.30 (s, 3H), 2.16 (td, *J* = 12.2, 3.3 Hz, 1H), 2.02 (td, *J* = 12.5, 4.9 Hz, 1H), 1.59–1.50 (m, 2H), 1.14 (dt, *J* = 16.2, 2.8 Hz, 1H).

^{13}C NMR (*d*$_7$-DMF, 80 ºC, 125 MHz): δ 158.7, 146.8, 142.4, 130.0, 128.8, 119.2, 114.9, 94.8, 69.6, 63.6, 56.8, 47.8, 46.2, 43.9, 43.1, 43.0, 42.4, 33.4, 19.8.

HRMS(ESI): *m/z* calc. for $C_{19}H_{25}N_2O_4$ $[M+H]^+$: 345.1814, found: 345.1808.



Compounds 8 and 9



4 **8** 3% yield **9** 4% yield

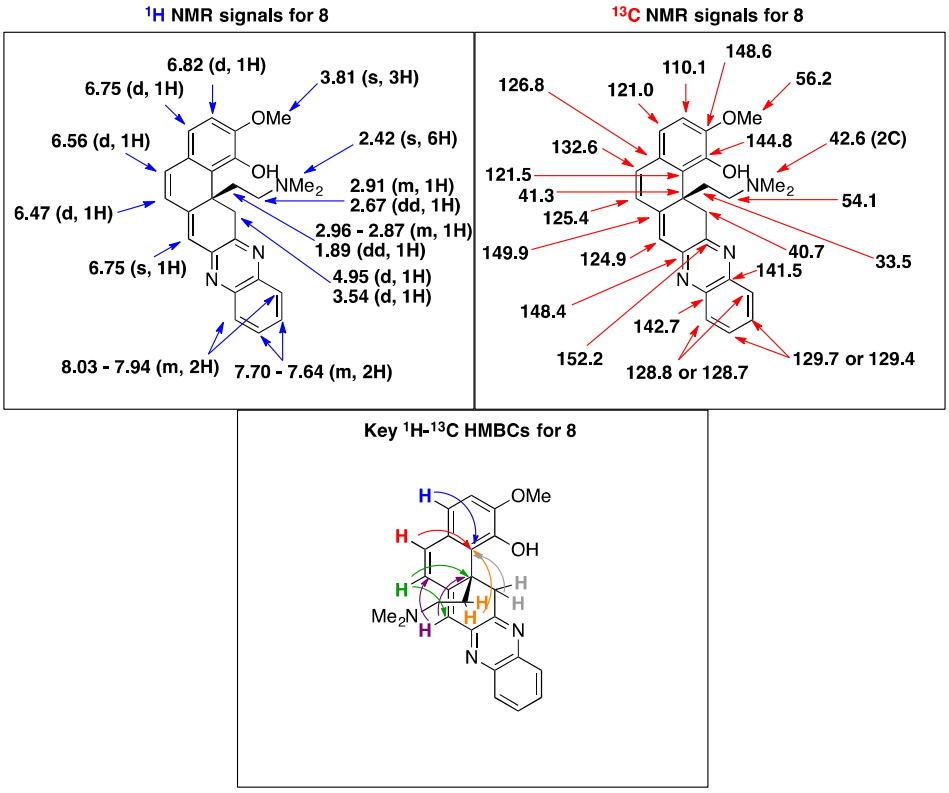
Procedure: In a round-bottom flask, the **4** (489.8 mg, 1.264 mmol) was dissolved in dichloromethane (25 mL). Iodomethane (0.30 mL, 4.819 mmol) was added into the vial and the contents were allowed to stir under a nitrogen atmosphere for 20 hours. After this time, the mixture was diluted with water, and allowed to stir for 30 minutes. The mixture was poured into a round bottom flask and concentrated under reduced pressure. The residue was transferred into a vial and was allowed to dry under a high vacuum. The reaction mixture was used directly for the next reaction. Acetonitrile (10 mL) was added to the solid to form a solution. Potassium carbonate (668.0 mg, 4.833 mmol) was subsequently added and the vial was capped and placed in an 80 ºC oil bath. After 6 hours, the mixture was concentrated under reduced pressure, diluted with water, and extracted with dichloromethane (4x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by column chromatography (15:1dichloromethane/methanol) on silica gel to afford compounds **8** (16.4 mg, 3% yield) and **9** (20.2 mg, 4% yield) as orange solids.

8

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03–7.94 (m, 2H), 7.70–7.64 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 6.56 (d, *J* = 9.5 Hz, 1H), 6.47 (d, *J* = 9.5 Hz, 1H), 4.95 (d, *J* = 17.0 Hz, 1H), 3.81 (s, 3H), 3.54 (d, *J* = 16.7 Hz, 1H), 2.96–2.87 (m, 2H), 2.67 (dd, J = 12.0, 10.3 Hz, 1H), 2.42 (s, 6H), 1.89 (dd, *J* = 12.1, 6.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.2, 149.9, 148.6, 148.4, 144.8, 142.7, 141.5, 132.6, 129.7, 129.4, 128.8, 128.7, 126.8, 125.4, 124.9, 121.5, 121.0, 110.1, 56.2, 54.1, 42.6 (2C), 41.3, 40.7, 33.5.

HRMS(ESI): *m/z* calc. for $C_{25}H_{26}N_3O_2$ $[M+H]^+$: 400.2025, found: 400.2017.

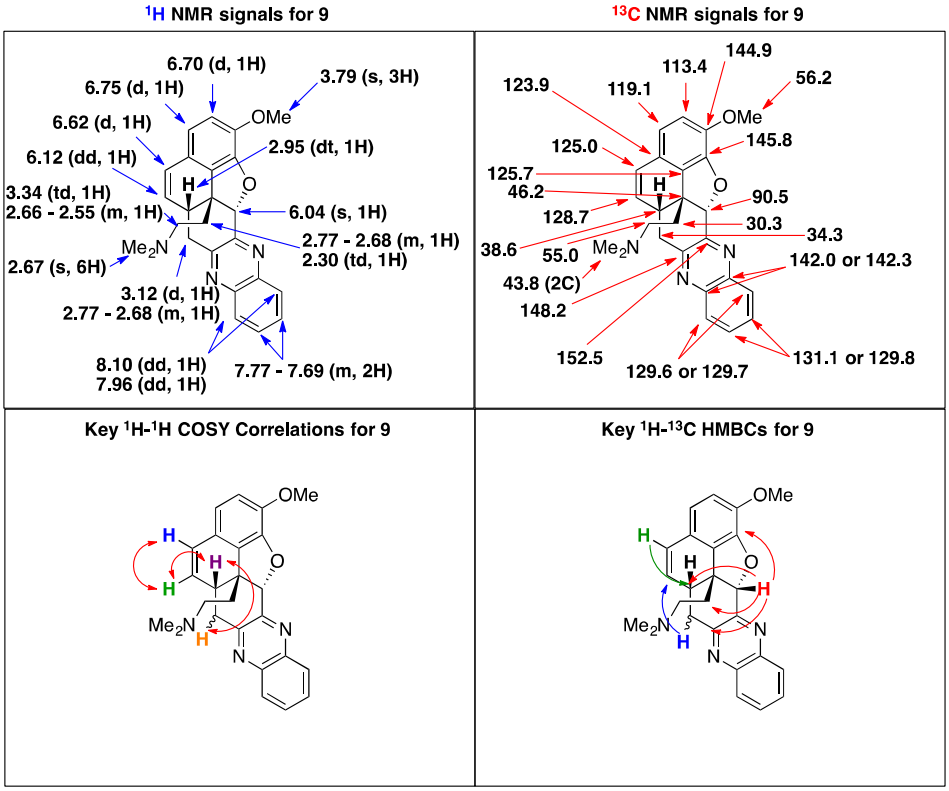


9

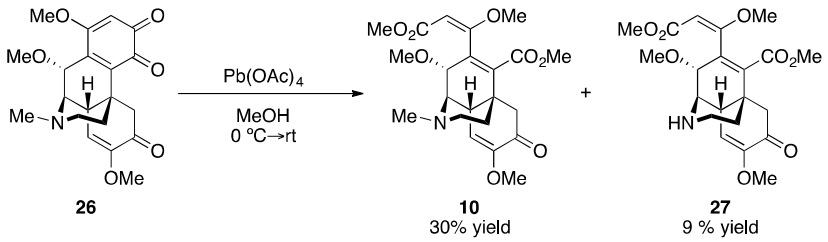
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.77–7.69 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.12 (dd, *J* = 9.2, 6.0 Hz, 1H), 6.04 (s, 1H), 3.79 (s, 3H), 3.34 (td, *J* = 12.6, 4.5 Hz, 1H), 3.12 (dd, *J* = 16.5, 4.6 Hz, 1H), 2.95 (dt, *J* = 12.5, 5.3 Hz, 1H), 2.77–2.68 (m, 2H), 2.67 (s, 6H), 2.66–2.55 (m, 1H), 2.30 (td, *J* = 13.0, 4.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.5, 148.2, 145.8, 144.9, 142.3, 142.0, 131.1, 129.8, 129.7, 129.6, 128.7, 125.7, 125.0, 123.9, 119.1, 113.4, 90.5, 56.2, 55.0, 46.2, 43.8 (2C), 38.6, 34.3, 30.3.

HRMS(ESI): *m/z* calc. for $C_{25}H_{26}N_3O_2$ $[M+H]^+$: 400.2025, found: 400.2019.



Compounds 10 and 27



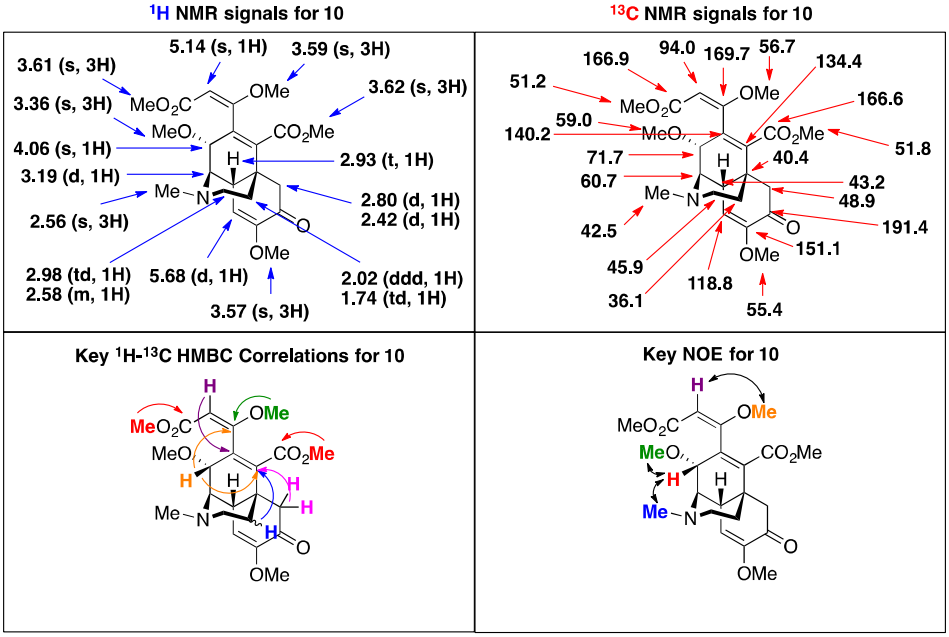
Procedure: In a vial with a stir bar, *o*-quinone **26** (51.8 mg, 0.1387 mmol) was dissolved in methanol (10 mL). The reaction mixture was capped and stirred under N_2. After 5 min, lead(IV) tetracetate (106.2 mg, 0.2395 mmol) was added to the solution. The mixture was stirred for 45 min, quenched with ethylene glycol, and was diluted with saturated sodium bicarbonate. The contents of the vial were extracted with dichloromethane (4x). The organic layers were combined and dried with Na_2SO_4 and were concentrated under reduced pressure. The residue was purified by column chromatography (9:1 dichloromethane/methanol) to yield compounds **10** (17.9 mg, 30% yield) and **27** (5.1 mg, 9% yield) as light yellow solids.

10

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.68 (d, *J* = 2.0 Hz, 1H), 5.14 (s, 1H), 4.06 (s, 1H), 3.62 (s, 3H), 3.61 (s, 3H), 3.59 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H), 3.19 (d, *J* = 2.8 Hz, 1H), 2.98 (td, *J* = 12.2, 2.6 Hz, 1H), 2.93 (t, *J* = 2.1 Hz, 1H), 2.80 (d, *J* = 16.8 Hz, 1H), 2.60–2.56 (m, 1H), 2.56 (s, 3H), 2.42 (d, *J* = 16.8 Hz, 1H), 2.02 (ddd, *J* = 13.3, 2.9, 1.5 Hz, 1H), 1.74 (td, *J* = 12.8, 5.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.4, 169.7, 166.9, 166.6, 151.1,140.2, 134.7, 118.0, 94.0, 71.7, 60.7, 59.0, 56.7, 55.2, 51.8, 51.2, 48.9, 45.9, 43.2, 42.5, 40.4, 36.1.

HRMS(ESI): *m/z* calc. for $C_{22}H_{30}NO_8$ $[M+H]^+$: 436.1971, found: 436.1970.

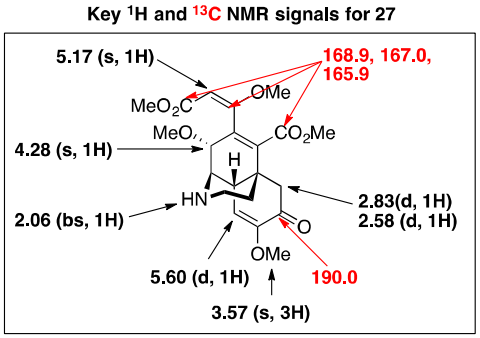


27

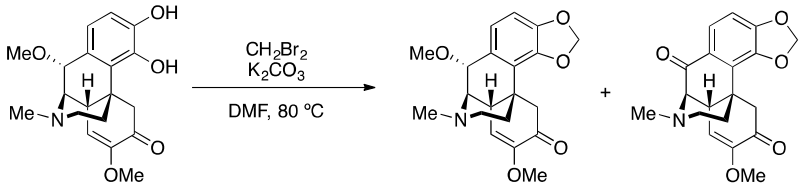
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.60 (d, *J* = 2.1 Hz, 1H), 5.17 (s, 1H), 4.28 (s, 1H), 4.13–4.02 (m, 2H), 3.65 (s, 3H), 3.64 (3H), 3.62 (s, 3H), 3.60 (s, 3H), 3.53 (s, 3H), 3.51–3.47 (m, 1H), 3.32 (dd, *J* = 12.2, 2.5 Hz, 1H), 2.83 (d, *J* = 16.7 Hz, 1H), 2.58 (d, *J* = 16.9, 1H), 2.26 (dd, *J* = 13.3, 2.3 Hz, 1H), 2.10 (td, *J* = 13.6, 3.7 Hz, 1H), 2.06 (bs, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.0, 168.9, 167.0, 165.9, 151.6, 139.1, 134.4, 114.2, 93.9, 75.8, 60.5, 56.9, 55.4, 52.7, 52.1, 51.6, 47.8, 39.9, 39.3, 37.6, 32.9.

HRMS(ESI): *m/z* calc. for $C_{21}H_{28}NO_8$ $[M+H]^+$: 422.1815, found: 422.1814.



Compounds 11 and 12



Procedure: In an oven-dried round bottom flask with a stir bar, the **25** (87 mg, 0.2519 mmol) was dissolved in *N,N*-dimethylformamide (8 mL). Potassium carbonate (202 mg, 1.462 mmol) was added to the mixture along with dibromomethane (0.5 mL, 7.191 mmol). The round bottom flask was attached to a reflux condenser and stirred at 80 ºC for 15 hours. The mixture was poured into a seperatory funnel, diluted with water and was extracted with dicloromethane (4x). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (15:1 dichloromethane/methanol) to yield **11** (24.1 mg, 27% yield) and **12** (6.9 mg, 8% yield) as light yellow solids.

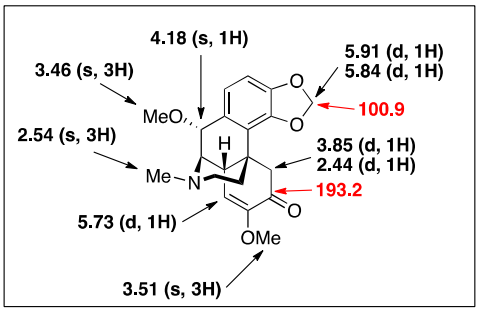
11

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.82 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.91 (d, *J* = 1.2 Hz, 1H), 5.84 (d, *J* = 1.2 Hz, 1H), 5.73 (d, *J* = 1.7 Hz, 1H), 4.18 (s, 1H), 3.85 (d, *J* = 16.0 Hz, 1H), 3.51 (s, 3H), 3.46 (s, 3H), 3.32 (d, *J* = 2.7 Hz, 1H), 3.01 (t, *J* = 2.4 Hz, 1H), 2.54 (s, 3H), 2.49 (ddd, *J* = 12.1, 4.8, 1.3 Hz, 1H), 2.44 (d, *J* = 16.1 Hz, 1H), 2.03 (td, *J* = 12.7, 3.3 Hz, 1H), 1.86 (td, *J* = 12.5, 4.9 Hz, 1H), 1.67 (ddd, *J* = 12.6, 3.2, 1.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.2, 150.6, 147.7, 145.3, 132.0, 123.5, 119.8, 118.0, 107.5, 100.9, 72.0, 59.0, 57.7, 54.9, 48.7, 46.7, 44.0, 43.0, 39.8, 36.9.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_5$ $[M+H]^+$: 358.1654, found: 358.1652.

Key ^{1}H and ^{13}C NMR signals for 11



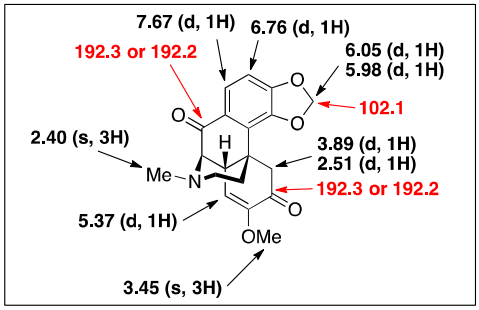
12

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.05 (d, *J* = 1.3 Hz, 1H), 5.98 (d, *J* = 1.3 Hz, 1H), 5.37 (d, *J* = 2.1 Hz, 1H), 3.89 (d, *J* = 16.2 Hz, 1H), 3.45 (s, 3H), 3.33 (d, *J* = 3.3 Hz, 1H), 3.22 (t, *J* = 2.7 Hz, 1H), 2.70 (ddd, *J* = 12.0, 4.7, 2.1 Hz, 1H), 2.51 (d, *J* = 16.2 Hz, 1H), 2.40 (s, 3H), 2.14 (td, *J* = 12.5, 3.4 Hz, 1H), 2.05 (td, *J* = 12.6, 4.5 Hz, 1H), 1.87 (ddd, *J* = 12.5, 3.2, 1.3, 1H).

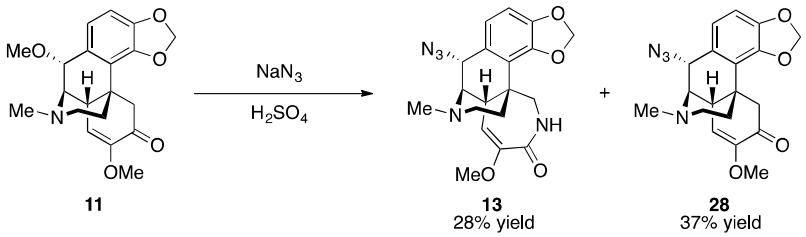
^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.3, 192.2, 153.6, 153.0, 145.7, 130.2, 123.8, 123.1, 113.4, 107.9, 102.1, 67.3, 55.2, 48.8, 47.1, 46.0, 43.4, 40.3, 36.7.

HRMS(ESI): *m/z* calc. for $C_{19}H_{20}NO_5$ $[M+H]^+$: 342.1341, found: 342.1338.

Key ^{1}H and ^{13}C NMR signals for 12



Compounds 13 and 28



Procedure: In a vial with a stir bar, the **11** (84.4 mg, 0.2361 mmol) was added along with sodium azide (96.6 mg, 1.486 mmol). The reaction vial was placed in an ice/water bath. The reaction was acidified with 50% sulfuric acid (5 mL) and stirred vigorously (open to air) for 5 min. After this time, the reaction was allowed to stir at room temperature for 4 hours. The

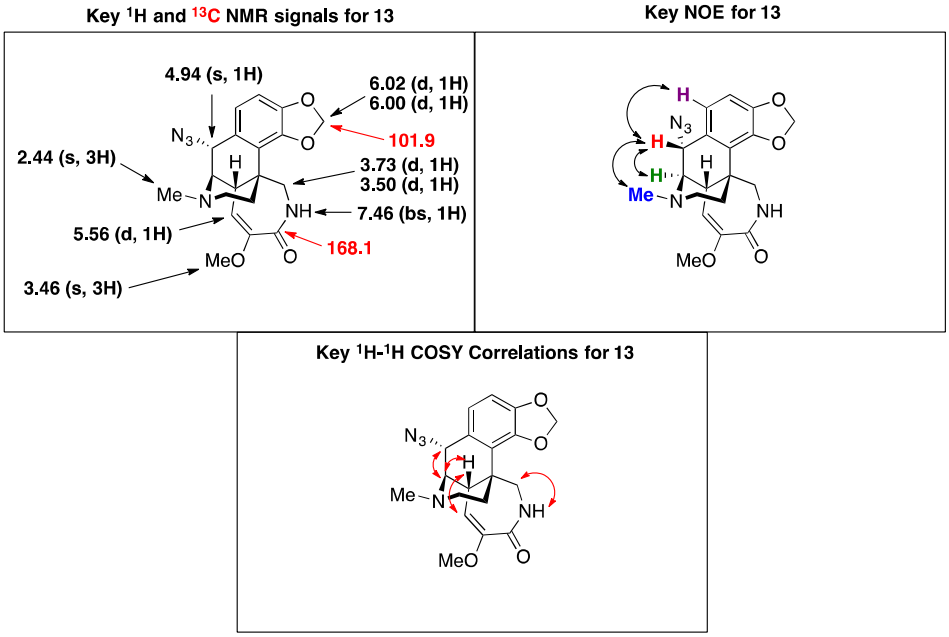
reaction was diluted with water and poured into a seperatory funnel. The mixture was basified with concentrated ammonium hydroxide and was extracted with dichloromethane (3x). The organic layers were combined, dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (15:1 dichloromethane/methanol) to afford and **13** (25.3 mg, 28% yield) and **28** (32.4 mg, 37% yield) as white solids.

13

^{1}H NMR (d_6-acetone, 500 MHz): δ 7.46 (bs, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 1.0 Hz, 1H), 6.00 (d, *J* = 1.1 Hz, 1H), 5.56 (d, *J* = 6.4 Hz, 1H), 4.94 (s, 1H), 3.73 (d, *J* = 14.5, 1H), 3.50 (d, *J* = 14.5, 1H), 3.46 (s, 3H), 3.26 (d, *J* = 1.9 Hz, 1H), 2.75 (dd, *J* = 6.1, 2.5 Hz, 1H), 2.51 (dd, *J* = 11.3, 2.7 Hz, 1H), 2.44 (s, 3H), 2.03–1.92 (m, 2H), 1.47 (d, *J* = 10.7, 1H).

^{13}C NMR (d_6-acetone, 125 MHz): δ 168.1, 151.9, 148.7, 145.9, 129.7, 123.9, 122.4, 108.3, 104.4, 101.9, 61.6, 55.5, 55.0, 50.1, 48.0, 45.4, 42.8, 41.6, 35.1.

HRMS(ESI): *m/z* calc. for $C_{19}H_{22}N_5O_4$ $[M+H]^+$: 384.1672, found: 384.1661.



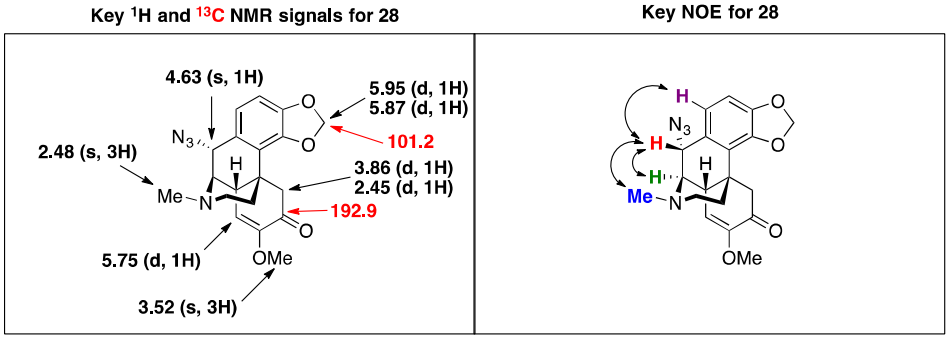
28

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.74 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 4.63 (s, 1H), 3.86 (d, *J* = 16.0 Hz, 1H), 3.52 (s, 3H), 3.22 (d, *J* = 2.9 Hz, 1H), 3.04 (t, *J* = 2.6 Hz, 1H), 2.50 (ddd, *J* = 11.7, 4.9, 1.6 Hz, 1H), 2.48 (s, 3H), 2.45 (d, *J* = 16.1 Hz, 1H), 2.02 (td, *J* = 12.2, 3.4 Hz, 1H), 1.87 (td, *J* = 12.6, 4.9 Hz, 1H), 1.65 (ddd, *J* = 12.9, 3.2, 1.7 Hz, 1H).

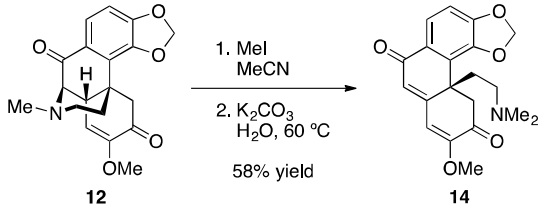
^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.9, 151.1, 148.4, 145.9, 127.6, 123.0, 120.2, 115.5, 107.6,

101.2, 61.7, 54.9, 53.6, 48.4, 46.5, 43.6, 43.0, 39.4, 37.0.

HRMS(ESI): *m/z* calc. for $C_{19}H_{21}N_4O_4$ $[M+H]^+$: 369.1563, found: 369.1551.



Compound 14

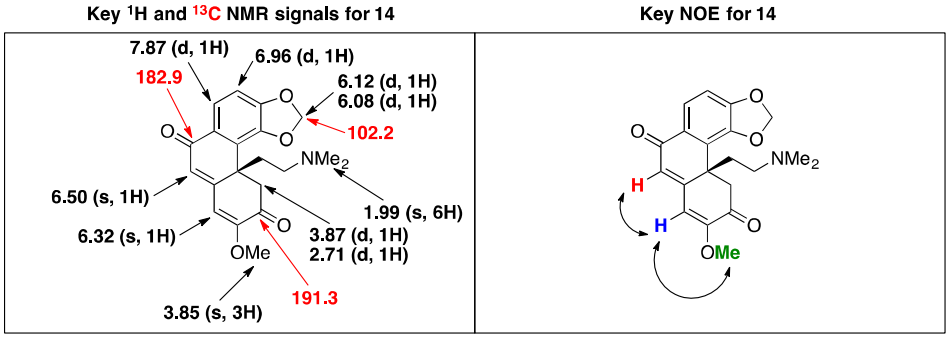


Procedure: In a vial with a stir bar, **12** (6.9 mg, 0.0202 mmol) was dissolved in acetonitrile (4 mL). Iodomethane (0.05 mL, 0.8032 mmol) was added to the reaction mixture and was allowed to stir for 12 hours. Water was added to the reaction and stirred for 30 minutes. The contents of the vial were concentrated under reduced pressure and the crude quaternary ammonium salt was transferred into a separate vial and dissolved in water (12 mL). Potassium carbonate (25.6 mg, 0.1852 mmol) was added to the reaction and was stirred (capped under air) at 60 ºC in an oil bath for 4 hours. The reaction mixture was extracted with dichloromethane (3x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by column chromatography (9:1 dichloromethane/methanol) on silica gel to afford **14** (4.2 mg, 58% yield) as a light yellow solid.

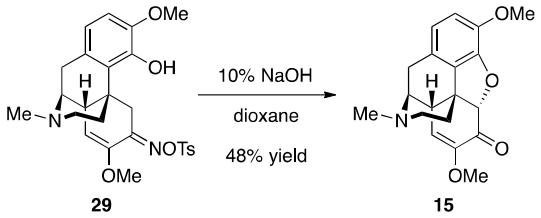
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.50 (s, 1H), 6.32 (s, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 6.08 (d, *J* = 1.3 Hz, 1H), 3.87 (d, *J* = 16.7 Hz, 1H), 3.85 (s, 3H), 2.71 (d, *J* = 16.5 Hz, 1H), 2.35 (ddd, *J* = 13.3, 9.5, 4.5 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.99 (s, 6H), 1.93 (td, *J* = 11.6, 5.5 Hz, 1H), 1.62 (td, *J* = 11.0, 4.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.3, 182.9, 154.1, 153.6, 151.7, 143.8, 127.6, 127.3, 126.7, 123.1, 113.1, 108.9, 102.2, 56.1, 55.3, 47.2, 45.3, 42.7, 36.5. (19 carbons due to symmetry)

HRMS(ESI): *m/z* calc. for $C_{20}H_{22}NO_5$ $[M+H]^+$: 356.1498, found: 356.1497.



Compound 15

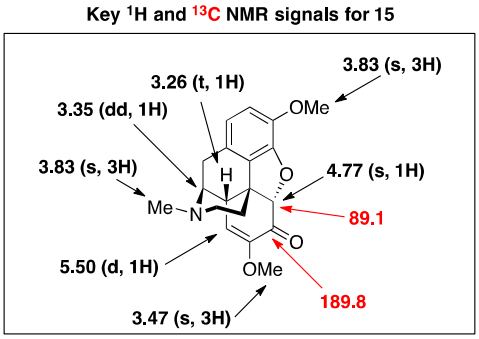


Procedure: In a vial with a stir bar, **29** (771.7 mg, 1.548 mmol) was dissolved in dioxane (8 mL) and 10% NaOH (w/v) (2 mL). The contents of the vial were stirred capped under nitrogen for 8 hours. After this time, the reaction mixture was diluted with water and extracted with dichloromethane (4x). The organic layers were combined, dried over sodium sulfate, filtered, and condensed under reduced pressure. The crude residue was purified by column chromatography (9:1 dichloromethane/methanol) on silica gel to afford **15** (241.8 mg, 48% yield) as a white solid. Crystals suitable for X-ray crystallography were grown by vapor diffusion (inner vial: tetrahydrofuran, outer vial: hexanes).

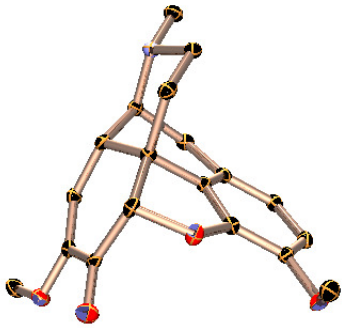
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.65 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 5.50 (d, *J* = 2.3 Hz, 1H), 4.77 (s, 1H), 3.83 (s, 3H), 3.47 (s, 3H), 3.35 (dd, *J* = 5.3, 2.9 Hz, 1H), 3.26 (t, *J* = 2.5 Hz, 1H), 3.09 (d, *J* = 18.1 Hz, 1H), 2.60 (ddd, *J* = 12.2, 5.0, 1.1 Hz, 1H), 2.45 (s, 3H), 2.33 (dd, *J* = 18.2, 5.4 Hz, 1H), 2.28 (td, *J* = 12.2, 3.7 Hz, 1H), 2.04 (td, *J* = 12.0, 4.9 Hz, 1H), 1.81 (ddd, *J* = 12.4, 3.6, 1.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 154.0, 144.9, 142.8, 129.2, 126.1, 120.1, 115.5, 115.3, 89.1, 59.8, 57.2, 55.3, 47.1, 43.3, 43.0, 39.3, 34.0, 20.4.

HRMS(ESI): *m/z* calc. for $C_{19}H_{22}NO_4$ $[M+H]^+$: 328.1549, found: 328.1546.



X-ray Crystallographic Data for 15:



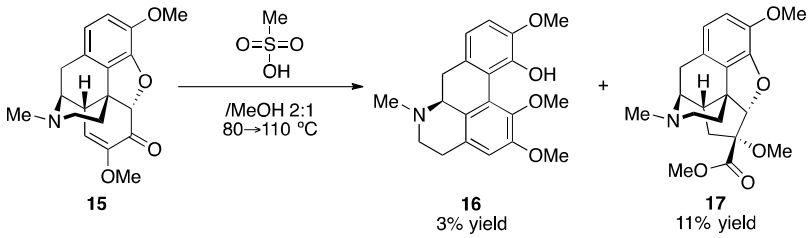
X-ray Crystallographic Data for 15: Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1502193. Copies of the data can be obtained, free of charge, on application to CHGC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

Crystal Data and structure refinement for cd53qsa.

Identification code	cd53qsa	
Empirical formula	$C_{19}H_{21}NO_4$	
Formula weight	327.38	
Temperature	100(2)K	
Wavelength	1.54178 Å	
Crystal System	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.4444(3) Å	α = 90°
	b = 10.0554(4) Å	β = 90°
	c = 18.0941(7) Å	ϒ = 90°
Volume	1536.4(10) $Å^3$	
Z	4	
Density (calculated)	1.415 g/cm^3	
Absorption coefficient	0.810 mm^{-1}	
F(000)	696	

Crystal size	0.318 x 0.182 x 0.06 mm^3
Theta range for data collection	68.373º to 4.888º
Index ranges	-10<=h<=7, -12<=k<=11, -21<=l<=-20
Reflections collected	19334
Independent reflections	2813 [R(int) = 0.0276]
Completeness to theta = 68.373º	99.8 %
Absorption correction	Integration
Max. and min. transmission	0.99975 and 0.99883
Refinement method	Full-matrix least-squares on F2
Data/restraints/parameters	2813 / 0 / 221
Goodness-of-fit on F^2	1.104
Final R indices [I>sigma(I)]	R1 = 0261, wR2 = 0.0647
R indices (all data)	R1 = 0.268, wR2 = 0.0653
Absolute structure (Flack) parameter	0.02(4)
Largest diff. peak and hole	0.194 and -0.188 e. Å-3

Compounds 16 and 17



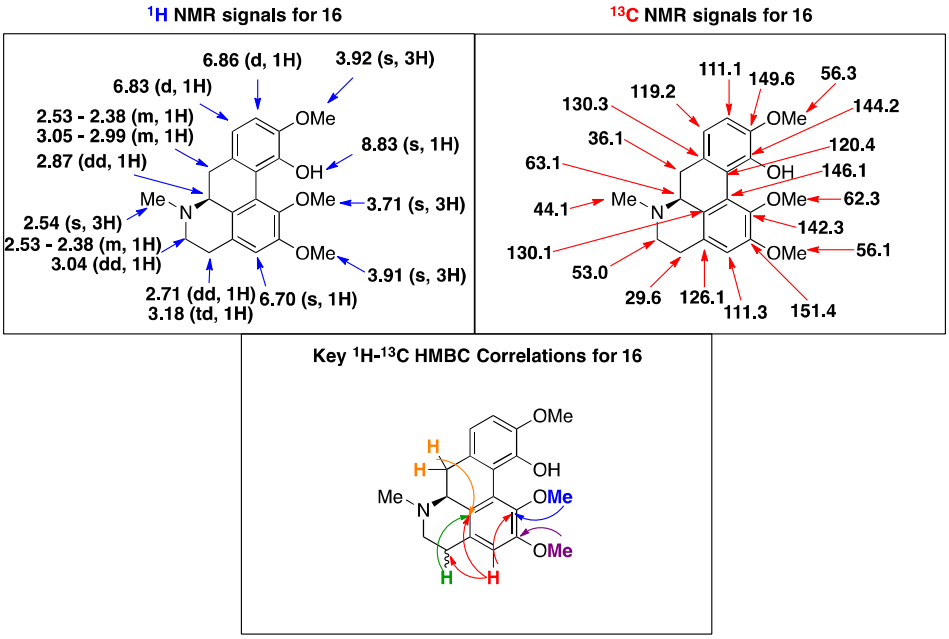
Procedure: In a vial with a stir bar, compound **15** (226.4 mg, 0.6916 mmol) was dissolved in methanol (4 mL). Methanesulfonic acid (2 mL) was added to the vial, which was capped and stirred in an oil bath at 80 ºC. After 10 min, the temperature was raised to 110 ºC and the reaction was stirred for 5 min. The contents were poured into a seperatory funnel along with saturated sodium bicarbonate and water. The mixture was further basified with 30% NH_4OH and was extracted with dichloromethane (4x). The organic layers were combined, dried under Na_2SO_4, and were concentrated under reduced pressure. The crude residue was purified by column chromatography (9:1 dichloromethane/methanol) on silica gel to afford compounds **16** (7.7 mg, 3% yield) and **17** (26.4 mg, 11% yield) as white solids.

16

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.83 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.70 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.71 (s, 3H), 3.18 (td, *J* = 15.0, 5.7 Hz, 1H), 3.04 (dd, *J* = 13.1, 3.5, Hz, 1H), 3.05 - 2.99 (m, 1H), 2.87 (dd, *J* = 15.2, 2.3 Hz, 1H), 2.71 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.54 (s, 3H), 2.53 - 2.38 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.4, 149.6, 146.1, 144.2, 142.3, 130.3, 130.1, 126.1, 120.4, 119.2, 111.3, 111.1, 63.1, 62.3, 56.3, 56.1, 53.0, 44.1, 36.1, 29.6.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_4$ $[M+H]^+$: 342.1705, found: 342.1695.

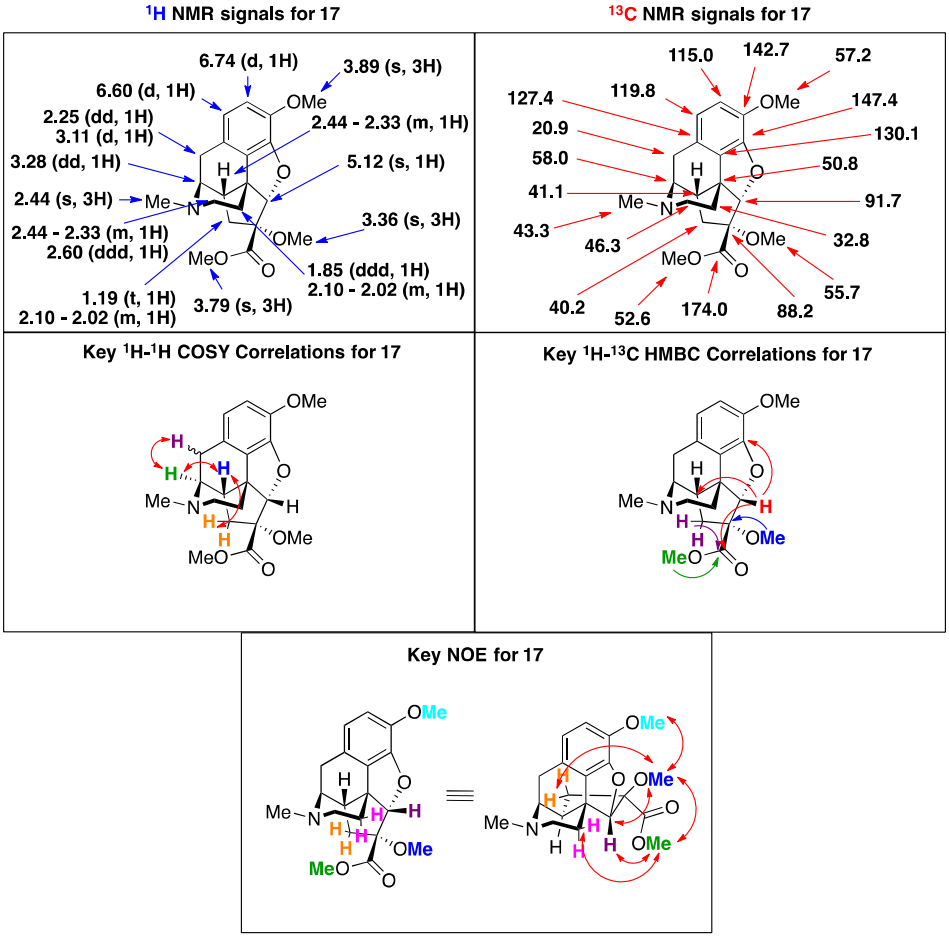


17

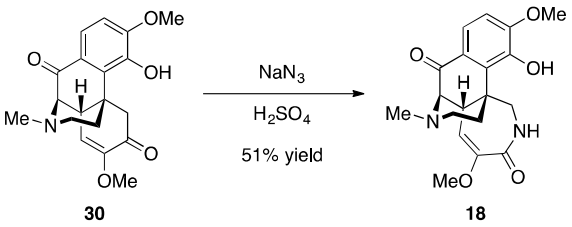
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.74 (d, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.12 (s, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.36 (s, 3H), 3.28 (dd, *J* = 5.9, 2.9 Hz, 1H), 3.11 (d, *J* = 18.7 Hz, 1H), 2.60 (ddd, *J* = 12.1, 5.0, 1.5, 1H), 2.44 (s, 3H), 2.44–2.33 (m, 2H), 2.25 (dd, *J* = 18.8, 6.1 Hz, 1H), 2.10 –2.02 (m, 2H), 1.85 (ddd, *J* = 12.4, 3.7, 1.2 Hz, 1H), 1.19 (t, *J* = 12.8 Hz, 1H).

‘^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.0, 147.4, 142.7, 130.1, 127.4, 119.8, 115.0, 91.7, 88.2, 58.0, 57.2, 55.7, 52.6, 50.8, 46.3, 43.3, 41.1, 40.2, 32.8, 20.9.

HRMS(ESI): *m/z* calc. for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1811, found: 360.1811.



Compound 18

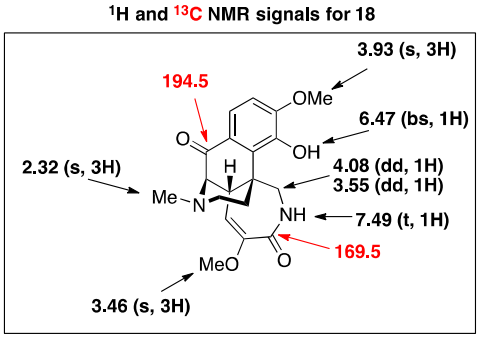


Procedure: In a vial with a stir bar, **30** (342.5 mg, 1.000 mmol) was mixed with sodium azide (475.4 mg, 7.313 mmol). The reaction mixture was placed in an ice water bath (0 ºC). To this, 50% sulfuric acid (8 mL) was added to the vial and the reaction was allowed to stir open to air. After 1 hour, the reaction was stirred at room temperature for 3 hours. The reaction was poured into a seperatory funnel with ice water and was quenched with concentrated ammonium hydroxide. The mixture was extracted with dichloromethane (3x). The organic layers were combined, dried over Na_2SO_4, and were concentrated under reduced pressure. The crude residue was purified by column chromatography (15:1 dichloromethane/methanol) to afford **18** (182.4 mg, 51% yield) as a yellow solid. Starting material **30** (109.5 mg, 32%) was also recovered.

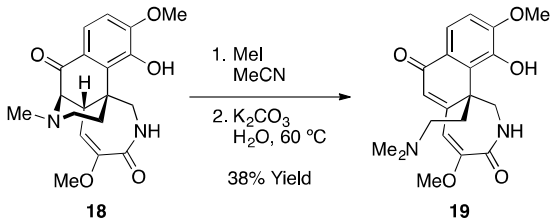
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (d, *J* = 8.6, 1H), 7.49 (t, *J* = 5.2 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.47 (bs, 1H), 4.84 (d, *J* = 6.2 Hz, 1H), 4.08 (dd, *J* = 14.7, 7.0 Hz, 1H), 3.93 (s, 3H), 3.55 (dd, *J* = 14.7, 4.8, 1H), 3.46 (s, 3H), 3.32 (d, *J* = 3.2 Hz, 1H), 3.06 (dd, *J* = 6.3, 3.3 Hz, 1H), 2.71 (ddd, *J* = 11.8, 4.8, 1.6 Hz, 1H), 2.32 (s, 3H), 2.11 (td, *J* = 12.3, 4.8 Hz, 1H), 1.99 (td, *J* = 12.2, 3.3 Hz, 1H), 1.93 (ddd, *J* = 12.0, 3.3, 1.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.5, 169.5, 152.1, 150.9, 143.4, 128.9, 128.7, 119.6, 109.3, 103.8, 67.0, 56.3, 55.7, 50.2, 48.5, 46.3, 43.8, 43.1, 32.9.

HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_5$ $[M+H]^+$: 359.1607, found: 359.1600.



Compound 19

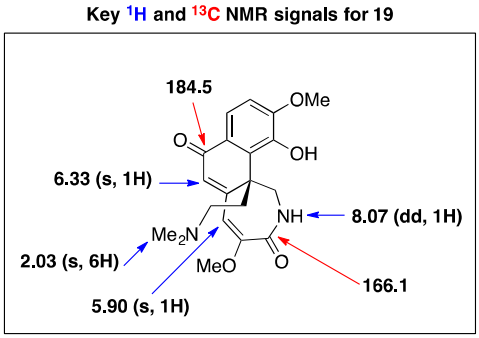


Procedure: In a vial with a stir bar, **18** (69.5 mg, 0.1939 mmol) was dissolved in acetonitrile (16 mL). Iodomethane (1 mL) was added to the reaction and it was allowed to stir for 20 hours. The reaction mixture was diluted with water and stirred for 10 min. The contents of the vial were concentrated under reduced pressure. The crude ammonium salt was used directly by dissolving it in deionized water (12 mL). Potassium carbonate (326.8 mg, 2.365 mmol) was dissolved in the mixture. The vial was capped and stirred in a 60 ºC oil bath for 15 hours. The reaction mixture was poured into water and extracted with dichloromethane (3x). The organic layers were combined, dried over Na_2SO_4, were concentrated under reduced pressure. Compound **19** (27.2 mg, 38% yield) was present as an orange solid and was pure by ^{1}H NMR.

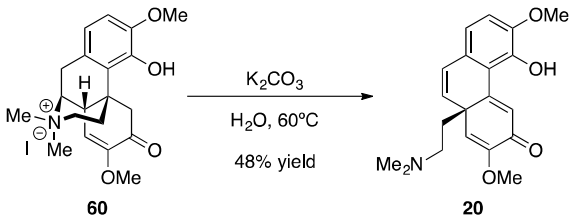
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.33 (s, 1H), 5.90 (s, 1H), 4.31 (dd, *J* = 14.8, 8.1 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.51 (dd, *J* = 14.8, 4.2 Hz, 1H), 3.21 (ddd, *J* = 13.1, 10.9, 6.1 Hz, 1H), 2.09–2.02 (m, 1H), 2.03 (s, 6H), 1.82–1.71 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 184.5, 166.1, 157.5, 151.7, 151.6, 143.9, 130.2, 127.1, 126.6, 118.6, 110.4, 108.1, 56.4, 56.1, 56.0, 46.4, 45.5 (2C), 44.8, 28.5.

HRMS(ESI): *m/z* calc. for $C_{20}H_{25}N_2O_5$ $[M+H]^+$: 373.1763, found: 373.1757.



Compound 20



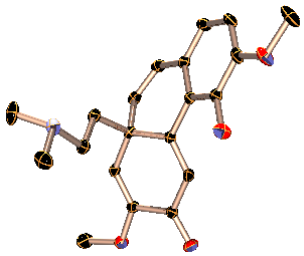
Procedure: In a vial with a stir bar, **60** (130.0 mg, 0.2758 mmol) was dissolved in water (10 mL). Potassium carbonate (182.0 mg, 1.317 mmol) was dissolved in water and the vial was capped and placed in a 60 ºC oil bath. After 20 hours of stirring, the reaction mixture was cooled to room temperature, made less basic with saturated ammonium chloride, and diluted with brine. The reaction mixture was extracted with dichloromethane (4x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified via column chromatography (9:1 dichloromethane/methanol) on silica gel to yield **20** (45 mg, 48% yield) as an orange solid. Crystals suitable for X-ray crystallography were grown by slow evaporation in a capped vial (1:1 dichloromethane/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.94 (s, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.36 (d, J = 9.2 Hz, 1H), 5.91 (d, J = 9.2 Hz, 1H), 5.73 (s, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 2.16–2.09 (m, 2H), 2.12 (s, 6H), 2.00–1.93 (m, 1H), 1.85 (dt, J = 13.4, 7.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 Hz): δ 181.9, 157.8, 152.0, 148.3, 144.2, 131.6, 128.4, 127.0, 126.4, 118.7, 117.9, 117.1, 111.9, 56.3, 55.2, 54.5, 46.4, 45.1 (2C), 38.1.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_4$ $[M+H]^+$: 342.1705, found: 342.1706.

X-ray Crystallographic Data for 20:

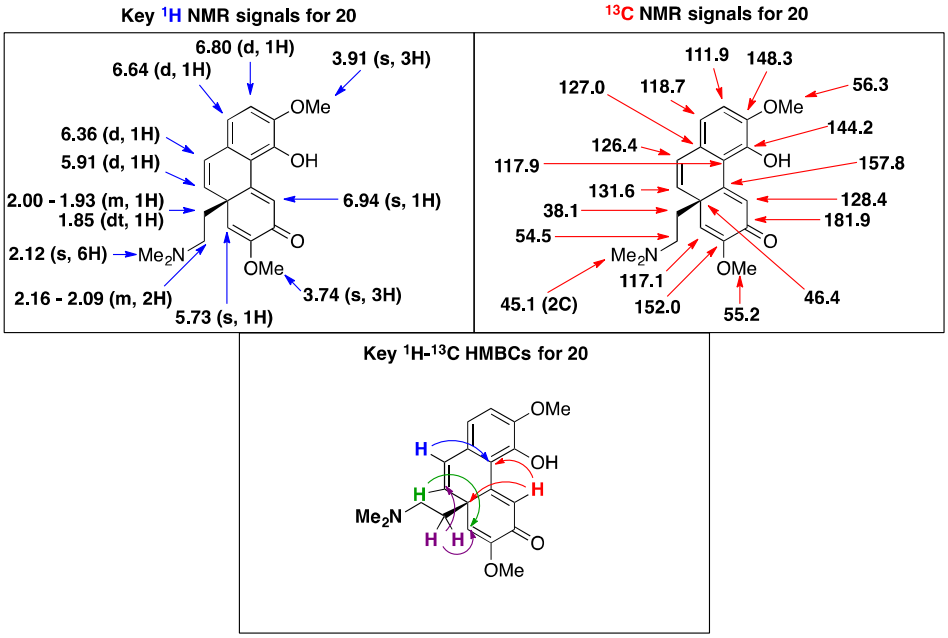


X-ray Crystallographic Data for 20: Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1502194. Copies of the data can be obtained, free of charge, on application to CHGC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).

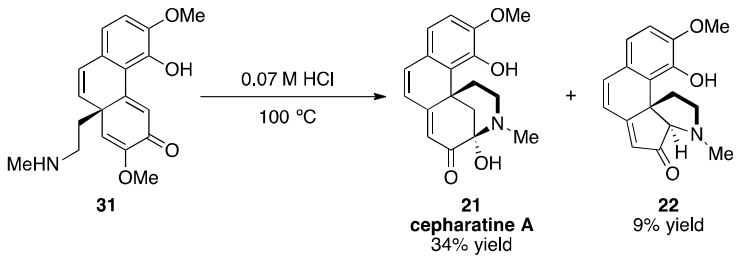
Crystal Data and structure refinement for cd20psa.

Identification code	cd20psa
Empirical formula	$2(C_{20}H_{23}NO_4)$, $3(CH_2Cl_2)$
Formula weight	937.62
Temperature	100(2)K
Wavelength	1.54178 Å
Crystal System	Orthorhombic
Space group	$C22_1$
Unit cell dimensions	a = 18.3635(8) Å α = 90°
	b = 25.2508(11) Å β = 90°
	c = 9.9745(4) Å ϒ = 90°
Volume	4625.1(3) $Å^3$
Z	4
Density (calculated)	1.347 g/cm^3
Absorption coefficient	3.816 mm^{-1}
F(000)	1960
Crystal size	0.409 x 0.305 x 0.166 mm^3
Theta range for data collection	72.368º to 2.975º
Index ranges	-22<=h<=22, -29<=k<=31, -12<=l<=-12
Reflections collected	29417
Independent reflections	4579 [R(int) = 0.0519]t
Completeness to theta = 72.368º	99.8 %
Absorption correction	Integration
Max. and min. transmission	0.97081 and 0.93526
Refinement method	Full-matrix least-squares on F2
Data/restraints/parameters	4579 / 100 / 303
Goodness-of-fit on F^2	1.095
Final R indices [I>sigma(I)]	R1 = 0.0471, wR2 = 0.1.222
R indices (all data)	R1 = 0.0475, wR2 = 0.1226
Absolute structure (Flack) parameter	0.047(10)

Largest diff. peak and hole 0.927 and -0.381 e. Å-3



Compounds 21 and 22



Procedure: In a vial with a stir bar, **31** (9.9 mg, 0.0302 mmol) was dissolved in 0.07 M hydrochloric acid (10 mL) and was capped under N_2. The reaction mixture was stirred in an oil bath at 100 ºC for 4 hours. The contents of the vial were basified with 15% ammonium hydroxide, diluted with water, and were extracted with dichloromethane (3x). The organic layers were combined, dried over sodium sulfate, and were condensed under reduced pressure. The crude residue was purified by column chromatography (15:1 dichloromethane/methanol) on silica gel to afford **21** (**cepharatine A)** (3.2 mg, 34% yield) and **22** (1 mg, 9% yield) as yellow solids. Compound **22** was isolated as a single diastereomer. Spectral data for our synthetic **21** is provided below. Literature values for naturally isolated **21** can be found in the following reference.[6]

21 (cepharatine A)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 9.4 Hz, 1H), 6.29 (d, *J* = 9.4 Hz, 1H), 6.12 (s, 1H), 3.94 (s, 3H), 3.91 (d, *J* = 12.9 Hz, 1H), 2.92–2.85 (m, 1H), 2.73–2.59 (m, 2H), 2.24 (s, 3H), 2.24–2.21 (m, 1H), 1.40–1.35 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.3, 161.6, 148.3, 144.6, 136.2, 125.8, 125.7, 124.3, 123.6, 121.5, 108.9, 83.4, 56.4, 46.8, 44.6, 43.7, 36.4, 31.4.

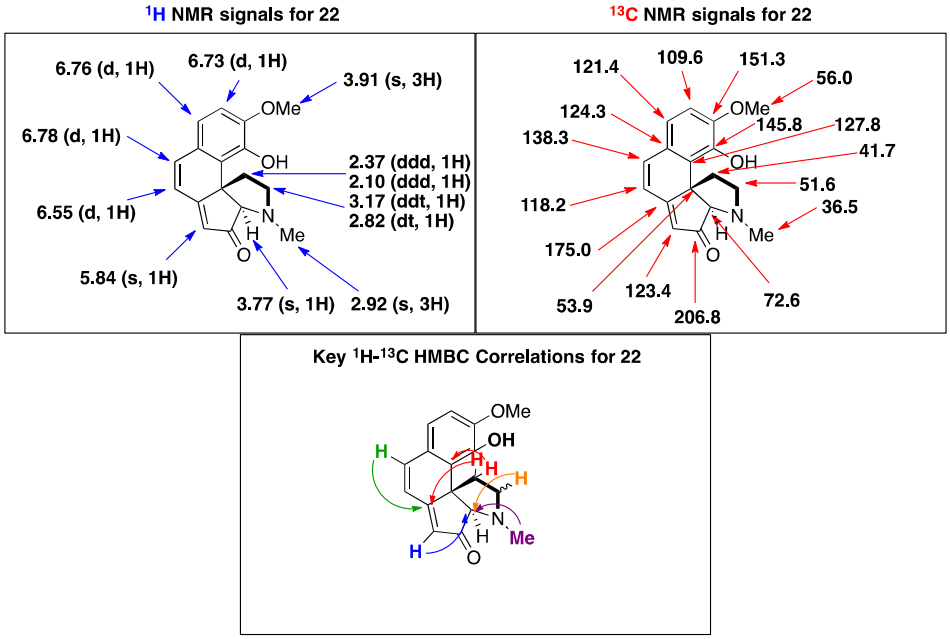
HRMS(ESI): *m/z* calc. for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1392, found: 314.1385.

22

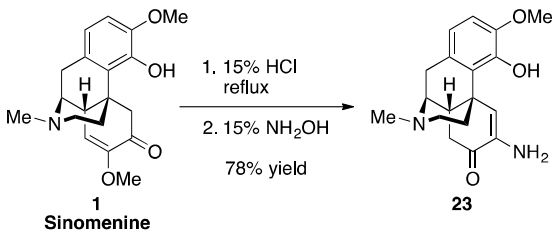
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (d, *J* = 9.5 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 9.4 Hz, 1H), 5.84 (s, 1H), 3.91 (s, 3H), 3.77 (s, 1H), 3.17 (d, *J* = 10.0, 9.3, 1.0 Hz, 1H), 2.92 (s, 3H), 2.82 (dt, *J* = 10.3, 8.1 Hz, 1H), 2.37 (ddd, *J* = 13.4, 7.0, 1.1 Hz, 1H), 2.10 (ddd, *J* = 13.5, 8.1, 8.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 206.8, 175.0, 151.3, 145.8, 138.3, 127.8, 124.3, 123.4, 121.4, 118.2, 109.6, 72.6, 56.0, 53.9, 51.6, 41.7, 36.5.

HRMS(ESI): *m/z* calc. for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287, found: 284.1286.



Compound 23



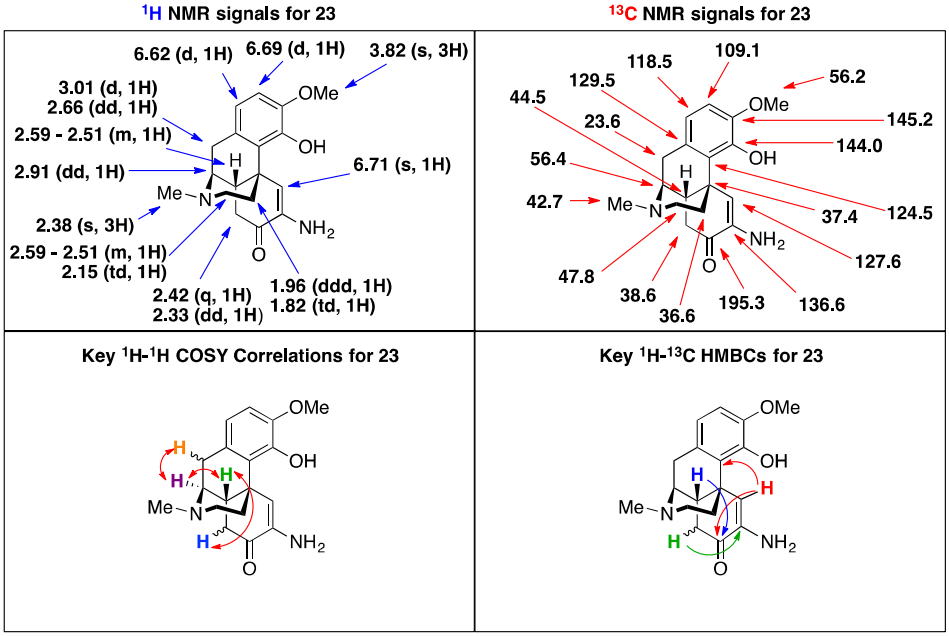
Procedure: In a round bottom flask, **1** (1047.3 mg, 3.179 mmol) was dissolved in 15% HCl (50

mL) and was attached to a reflux condenser. The reaction was stirred in an oil bath at 100 ºC for 12 hours, after which the reaction mixture was diluted with water and basified with concentrated ammonium hydroxide. The contents were extracted with dichloromethane (6x). The organic layers were combined, dried over sodium sulfate, and were concentrated under reduced pressure to yield off-white solid **23** (777.0 mg, 78% yield).

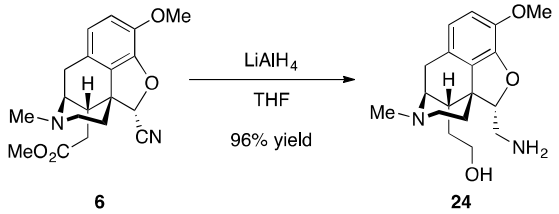
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.71 (s, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.01 (d, *J* = 18.7 Hz, 1H), 2.91 (dd, *J* = 5.8, 3.4 Hz, 1H), 2.66 (dd, *J* = 18.1, 5.6 Hz, 1H), 2.59–2.51 (m, 2H), 2.42 (q, *J* = 16.6 Hz, 1H), 2.38 (s, 3H), 2.33 (dd, *J* = 16.6, 3.6 Hz, 1H), 2.15 (td, *J* = 12.3, 3.2 Hz, 1H), 1.96 (ddd, *J* = 12.5, 3.3, 2.0 Hz, 1H), 1.82 (td, *J* = 12.8, 4.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 Hz): δ 195.3, 145.2, 144.0, 136.6, 129.5, 127.6, 124.5, 118.5, 109.1, 56.4, 56.2, 47.8, 44.5, 42.7, 38.6, 37.4, 36.6, 23.6.

HRMS(ESI): *m/z* calc. for $C_{18}H_{23}N_2O_3$ $[M+H]^+$: 315.1709, found: 315.1704.



Compound 24



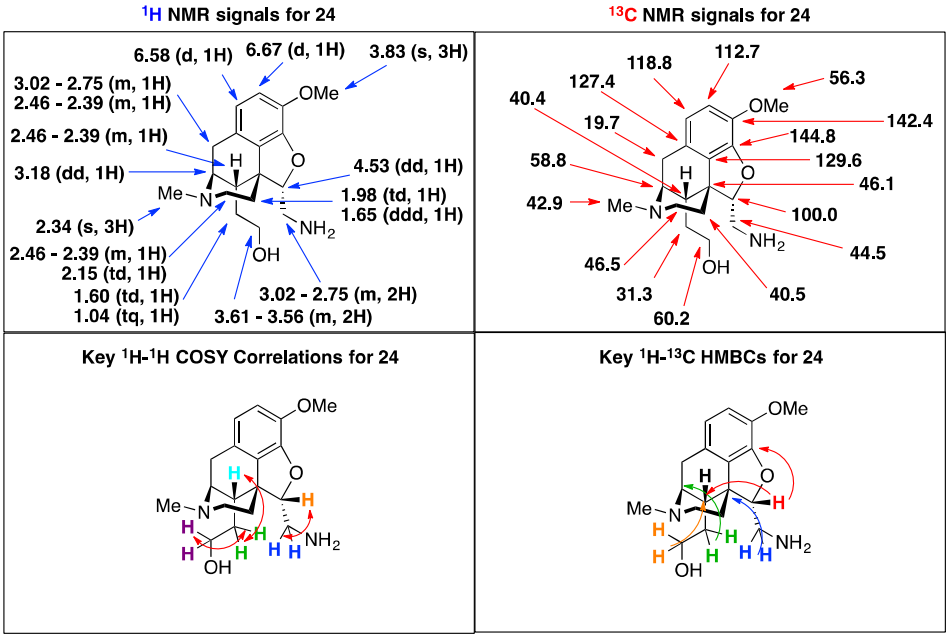
Procedure: In an oven dried round bottom flask, **6** (182.0 mg, 0.5315 mmol) was dissolved in tetrahydrofuran (20 mL) and was cooled to 0 ºC, under nitrogen. After 10 minutes, lithium aluminum hydride (191.3 mg, 5.041 mmol) was slowly added to the reaction vessel and was

allowed to stir at 0 ºC. After 1 hour, water was slowly added to the round bottom flask along with a solution of 10% NaOH. The contents of the flask were stirred for 10 minutes. Sodium sulfate was added and the reaction mixture was filtered through a fritted funnel. The filtrate was concentrated under reduced pressure to afford white solid **24** (163.4 mg, 96% yield).

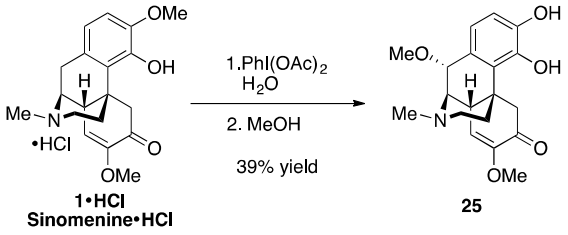
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.67 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 4.53 (dd, *J* = 9.3, 4.0 Hz, 1H), 3.83 (s, 3H), 3.61–3.56 (m, 2H), 3.18 (dd, *J* = 5.9, 2.8 Hz, 1H), 3.02–2.75 (m, 3H), 2.46–2.39 (m, 3H), 2.34 (s, 3H), 2.15 (td, *J* = 12.5, 3.5 Hz, 1H), 1.98 (td, *J* = 12.5, 5.0 Hz, 1H), 1.65 (ddd, *J* = 12.8, 3.3, 1.9 Hz, 1H), 1.60 (td, *J* = 12.2, 7.5, 2.6 Hz, 1H), 1.04 (tq, *J* = 9.8, 5.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.8, 142.4, 129.6, 127.4, 118.8, 112.7, 100.0, 60.2, 58.8, 56.3, 46.5, 46.1, 44.5, 42.9, 40.5, 40.4, 31.3, 19.7.

HRMS(ESI): *m/z* calc. for $C_{18}H_{27}N_2O_3$ $[M+H]^+$: 319.2022, found: 319.2019.



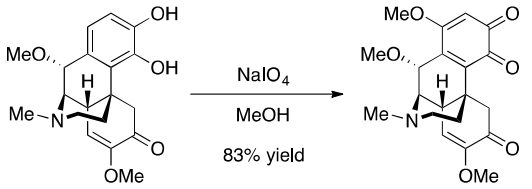
Compound 25



Procedure: In a vial with a stir bar, **sinomenine•HCl** (1034.3 mg, 2.827 mmol) was dissolved in water (15 mL). Diacetoxyiodobenzene (1149.8 mg, 3.570 mmol) was added to the reaction vial. The reaction mixture was stirred open to air for 1 hour and was then basified with a

saturated solution of sodium carbonate. The contents of the vial were poured into a seperatory funnel and were extracted with dichloromethane (4x). The organic layers were combined, dried with sodium sulfate, and were concentrated *in vacuo*. The crude residue was dissolved in methanol (15 mL) and was allowed to stir for 12 hours. The methanol was evaporated *in vacuo*. The crude residue was subsequently purified by flash chromatography on silica gel (9:1 dichloromethane/methanol) to afford known catechol **25** (376.7 mg, 39% yield). Spectral data (^{1}H NMR) was consistent with literature reported values.[4]

Compound 26



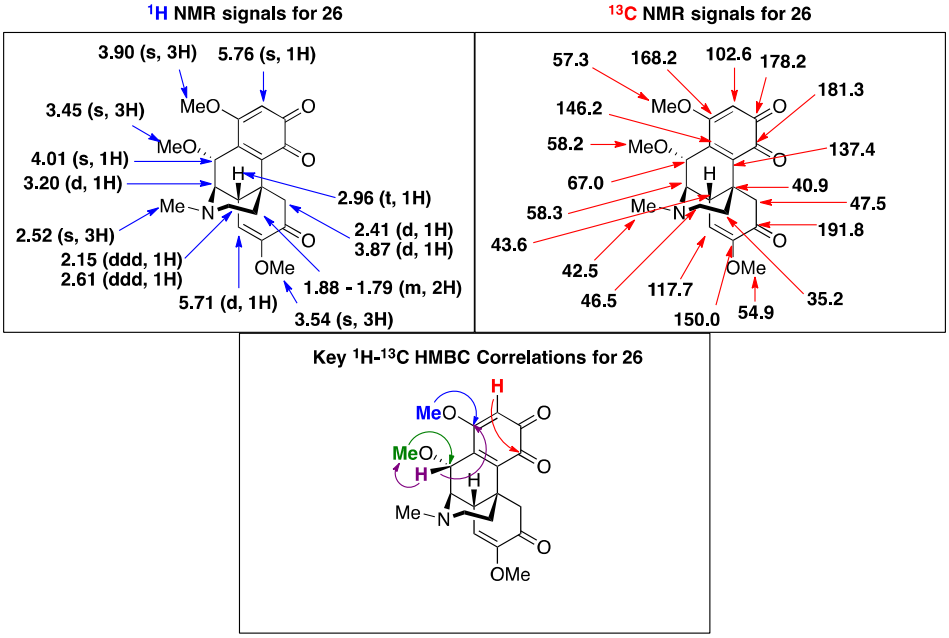
25 **26**

Procedure: In a vial with a stir bar, catechol **25** (132 mg, 0.3822 mmol) was dissolved in methanol (7 mL) and was cooled in an ice/water bath at 0 ºC. Sodium periodate (534 mg, 2.496 mmol) was added to the reaction mixture and was stirred under N_2 for 1 hour. After this time, the reaction was quenched with ethylene glycol (2 mL) and was diluted with saturated sodium bicarbonate. The mixture was poured into a seperatory funnel, diluted with distilled water, and extracted with dichloromethane (3x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography (9:1 dichloromethane/methanol) to afford *o*-quinone **26** (118.1 mg, 83% yield) as an orange solid.

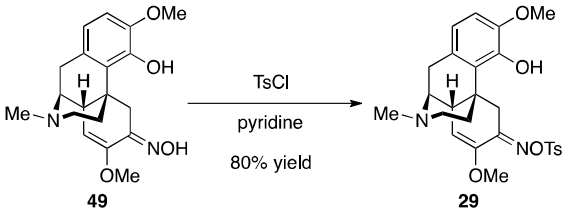
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.76 (s, 1H), 5.71 (d, *J* = 1.7 Hz, 1H), 4.01 (s, 1H), 3.90 (s, 3H), 3.87 (d, *J* = 16.4 Hz, 1H), 3.54 (s, 3H), 3.45 (s, 3H), 3.20 (d, *J* = 2.8, 1H), 2.96 (t, *J* = 2.5 Hz, 1H), 2.61 (ddd, *J* = 12.6, 4.5, 2.1 Hz, 1H), 2.52 (s, 3H), 2.41 (d, *J* = 16.4 Hz, 1H), 2.15 (ddd, *J* = 11.8, 11.2, 5.0 Hz, 1H), 1.88–1.79 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 191.8, 181.3, 178.2, 168.2, 150.0, 146.2, 137.4, 117.7, 102.6, 67.0, 58.3, 58.2, 57.3, 54.9, 47.5, 46.5, 43.6, 42.5, 40.9, 35.2.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_6$ $[M+H]^+$: 374.1604, found: 374.1595.



Compound 29

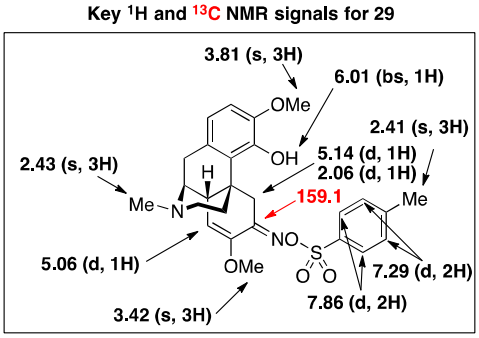


Procedure: In a vial with a stir bar, oxime **49** (274.0 mg, 0.7956 mmol) was dissolved in pyridine (10 mL). Tosyl chloride (322.0 mg, 1.689) was added to the reaction and was stirred for 2.5 hours. After this time, the reaction mixture was evaporated under reduced pressure (azeotroped with toluene) and was purified by flash chromatography (15:1 to 9:1 dichloromethane/methanol) on silica gel to afford tosyl oxime **29** (313.1 mg, 80% yield) as a white solid.

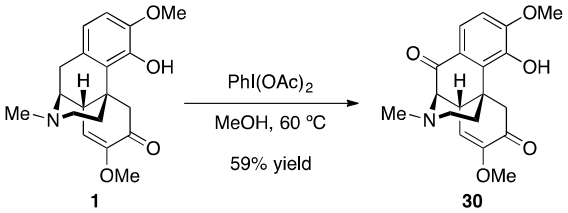
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 6.01 (bs, 1H) 5.14 (d, *J* = 16.2 Hz, 1H), 5.06 (d, *J* = 1.8 Hz, 1H), 3.81 (s, 3H), 3.42 (s, 3H), 3.13 (t, *J* = 3.8 Hz, 1H), 2.94 (d, *J* = 18.2 Hz, 1H), 2.77 (d, *J* = 1.7 Hz, 1H), 2.69 (dd, *J* = 18.2, 5.0 Hz, 1H), 2.57 (dd, *J* = 12.0, 3.1 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.09 (td, *J* = 12.3, 2.9 Hz, 1H), 2.06 (d, *J* = 16.2 Hz, 1H), 1.93 (dt, *J* = 12.6, 2.2 Hz, 1H), 1.79 (td, *J* = 12.9, 4.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 149.6, 145.2, 145.0, 144.8, 133.1, 129.7 (2C), 129.0 (2C), 122.4, 118.3, 109.9, 109.5, 109.3, 57.2, 56.3, 55.1, 47.8, 44.8, 42.8, 37.9, 35.7, 35.6, 24.2, 21.9.

HRMS(ESI): *m/z* calc. for $C_{26}H_{31}N_2O_6S$ $[M+H]^+$: 499.1903, found: 499.1907.

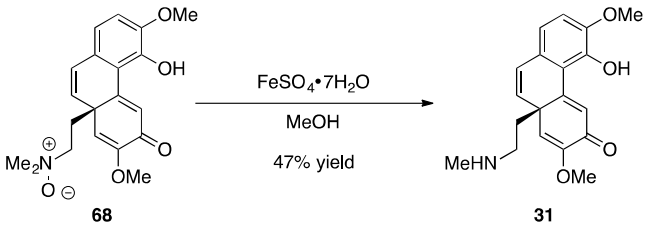


Compound 30



Procedure: In flame-dried round-bottom flask with a stir bar, **1** (725.1 mg, 2.201 mmol) and diacetoxyiodobenzene (1.640 g, 5.090 mmol) were dissolved in methanol (70 mL). The flask was attached to a reflux condenser and stirred at 60 ºC in an oil bath. After 48 hours, the mixture was concentrated under reduced pressure. The crude residue was subsequently purified by column chromatography (9:1 ethyl acetate/methanol) on silica gel to afford **30** (442.4 mg, 59% yield) as a light yellow solid. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature reported values.[4]

Compound 31

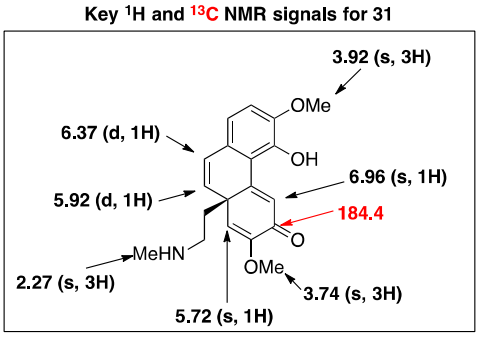


Procedure: In a vial with a stir bar, *N*-oxide **68** (77.2 mg, 0.2160 mmol) was dissolved in methanol (10 mL) and was allowed to cool to 0 ºC in an ice/water bath. After 10 min, iron(II) sulfate heptahydrate (84.1 mg, 0.3024 mmol) was added to the reaction. The mixture was stirred under N_2 at room temperature for 30 min. After this time, the methanol was evaporated under reduced pressure and the crude residue was dissolved in water. The mixture was basified with 15% ammonium hydroxide and it was subsequently concentrated under reduced pressure. Methanol was added to the mixture and filtered through Celite. Next, the mix was filtered through a fritted funnel. The reaction mixture was concentrated under reduced pressure and purified by reverse phase column chromatography to yield orange solid **31** (33.9 mg, 47% yield).

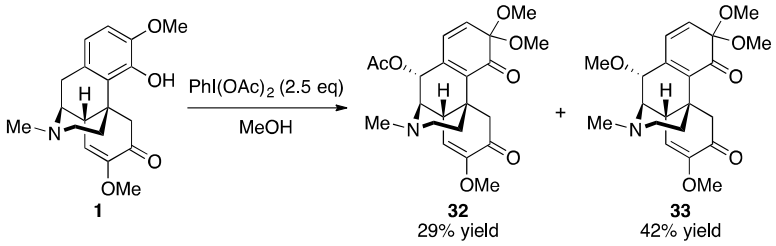
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.96 (s, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.37 (d, *J* = 9.3 Hz, 1H), 5.92 (d, *J* = 9.3 Hz, 1H), 5.72 (s, 1H), 3.92 (s, 3H), 3.74 (s, 3H), 2.48 (dt, *J* = 12.3, 6.1 Hz, 1H), 2.32 (dt, *J* = 12.4, 7.4 Hz, 1H), 2.27 (s, 3H), 2.02 (dt, *J* = 13.6, 5.9 Hz, 1H), 1.83 (dt, *J* = 13.6, 7.2 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 184.4, 160.6, 153.4, 150.8, 147.5, 132.9, 130.6, 129.1, 129.0, 120.7, 120.3, 118.3, 114.5, 57.6, 56.6, 47.8, 47.2, 38.8, 34.5.

HRMS(ESI): *m/z* calc. for $C_{19}H_{22}NO_4$ $[M+H]^+$: 328.1549, found: 328.1545.



Compounds 32 and 33



Procedure: In a vial with a stir bar, **1** (172.5 mg, 0.5237 mmol) was dissolved in methanol (15 mL). To this mixture, diacetoxyiodobenzene (428.5 mg, 1.330 mmol) was added and the reaction was capped and stirred under N_2. The reaction mixture was concentrated under reduced pressure after stirring for 2 hours. The crude residue was purified via column chromatography (9:1 ethyl acetate/methanol) on silica gel to afford masked *o*-quinones **32** (58.6 mg, 29% yield) and **33** (92.2 mg, 42% yield) as yellow and tan solids, respectively.

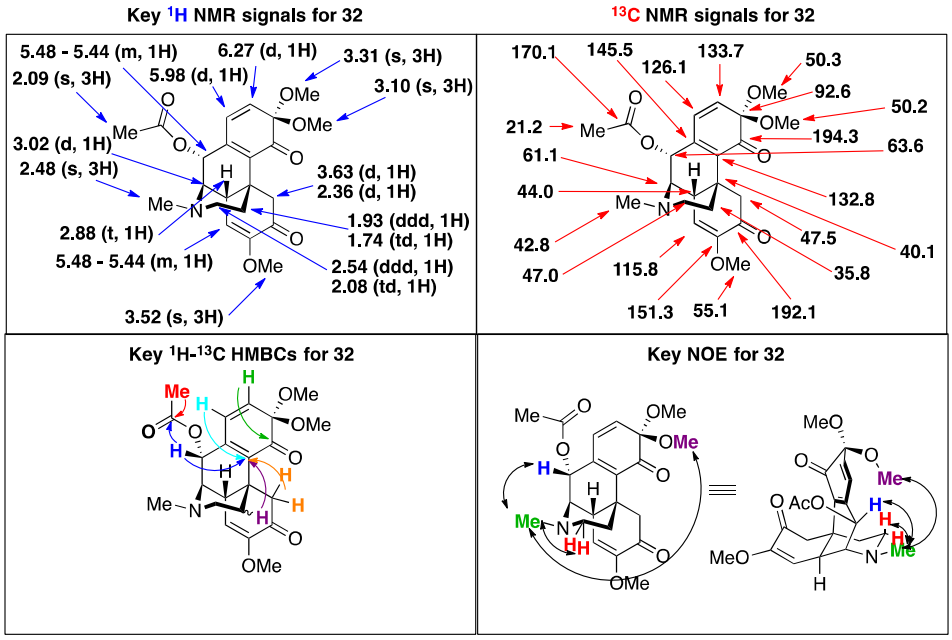
32

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.27 (d, *J* = 10.1 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 5.48–5.44 (m, 2H) 3.63 (d, *J* = 16.3 Hz, 1H), 3.52 (s, 3H), 3.31 (s, 3H), 3.10 (s, 3H), 3.02 (d, *J* = 2.6 Hz, 1H), 2.88 (t, *J* = 2.3 Hz, 1H), 2.54 (ddd, *J* = 12.4, 4.8, 1.4 Hz, 1H), 2.48 (s, 3H), 2.36 (d, *J* = 16.3, Hz, 1H), 2.09 (s, 3H), 2.08 (td, *J* = 12.6, 3.1 Hz, 1H), 1.93 (ddd, *J* = 13.1, 3.1, 1.3 Hz, 1H), 1.74 (td, *J* = 12.8, 4.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.3, 192.1, 170.1, 151.3, 145.5, 133.7, 132.8, 126.1, 115.8,

92.6, 63.6, 61.1, 55.1, 50.3, 50.2, 47.5, 47.0, 44.0, 42.8, 40.1, 35.8, 21.2.

HRMS(ESI): *m/z* calc. for $C_{22}H_{28}NO_7$ $[M+H]^+$: 418.1866, found: 418.1857.

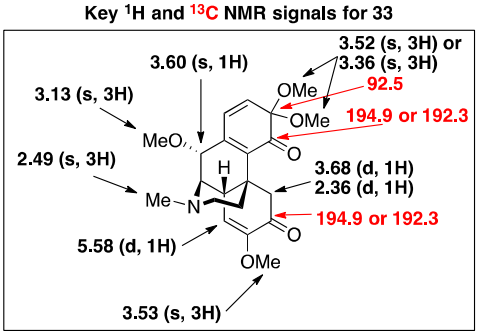


33

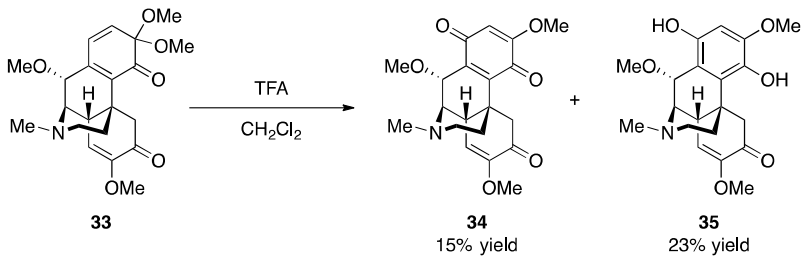
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.30 (d, *J* = 10.1 Hz, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 5.58 (d, *J* = 2.2 Hz, 1H), 3.68 (d, *J* = 16.4 Hz, 1H), 3.60 (s, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 3.36 (s, 3H), 3.20 (d, *J* = 2.6 Hz, 1H), 3.13 (s, 3H), 2.91 (t, *J* = 2.3 Hz, 1H), 2.55 (ddd, *J* = 12.4, 4.9, 1.6 Hz, 1H), 2.49 (s, 3H), 2.36 (d, *J* = 16.4 Hz, 1H), 2.05 (td, *J* = 12.4, 3.1 Hz, 1H), 1.96 (ddd, *J* = 13.2, 3.4, 1.6 Hz, 1H), 1.76 (td, *J* = 12.8, 4.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.9, 192.3, 151.0, 148.0, 132.9, 131.1, 127.0, 117.0, 92.5, 71.7, 58.8, 58.6, 55.2, 50.3, 50.2, 47.6, 46.9, 44.1, 42.4, 40.2, 35.8.

HRMS(ESI): *m/z* calc. for $C_{21}H_{28}NO_6$ $[M+H]^+$: 390.1917, found: 390.1909.



Compounds 34 and 35



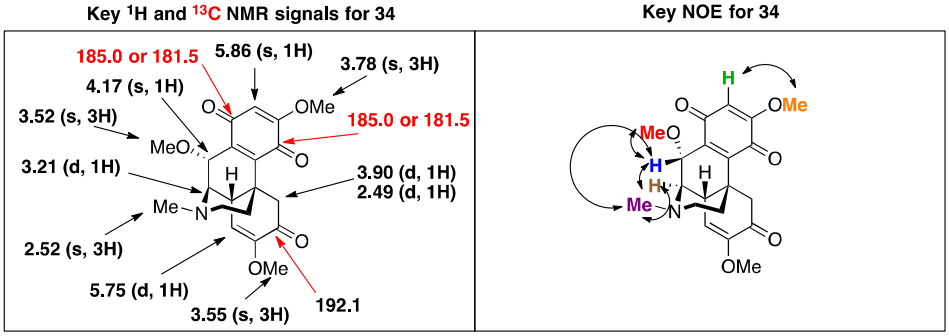
Procedure: In a round bottom flask with a stir bar, **33** (127.7 mg, 0.3050) was dissolved in dichloromethane (12 mL) and cooled to 0 ºC in an ice/water bath. Trifluoroacetic acid (0.5 mL, 6.530 mmol) was added to the reaction mixture. After 1 hour, the reaction was stirred at room temperature. After 1.5 hours, the reaction was quenched with a saturated solution of sodium carbonate and was extracted with dichloromethane (4x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (15:1 dichloromethane/methanol) to afford **34** (16.7 mg, 15% yield) and **35** (26.6 mg, 23% yield) as light yellow and light orange solids, respectively.

34

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.86 (s, 1H), 5.75 (d, *J* = 2.0 Hz, 1H), 4.17 (s, 1H), 3.90 (d, *J* = 16.2 Hz, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 3.21 (d, *J* = 2.9 Hz, 1H), 3.01 (t, *J* = 2.6 Hz, 1H), 2.60 (td, *J* = 2.6 Hz, 1H), 2.52 (s, 3H), 2.49 (d, *J* = 16.3 Hz, 1H), 2.11–2.04 (m, 1H), 1.92–87 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.1, 185.0, 181.5, 159.1, 150.3, 144.8, 139.2, 118.0, 107.2, 66.5, 58.9, 58.6, 56.4, 55.0, 48.1, 46.6, 44.6, 42.6, 41.3, 35.4.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_6$ $[M+H]^+$: 374.1604, found: 374.1598.

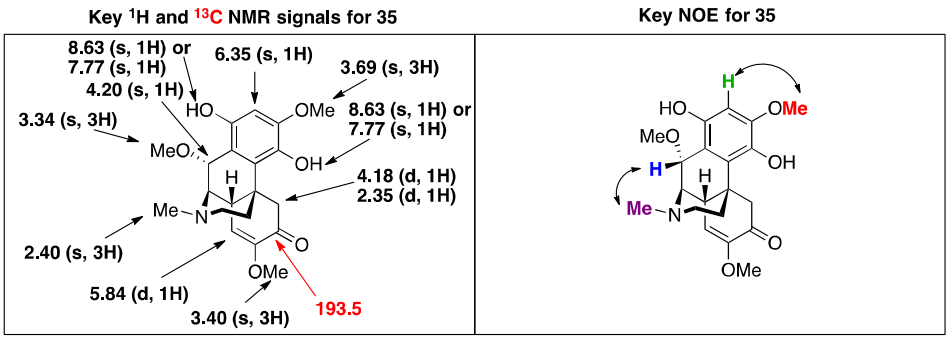


35

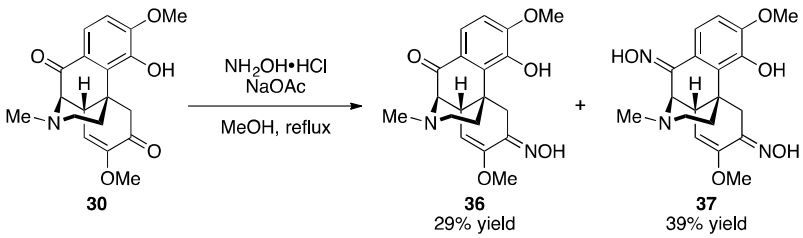
^{1}H NMR (d_6-DMSO, 500 MHz): δ 8.63 (s, 1H), 7.77 (s, 1H), 6.35 (s, 1H), 5.84 (d, *J* = 2.1 Hz, 1H), 4.20 (s, 1H), 4.18 (d, *J* = 16.0 Hz, 1H), 3.69 (s, 3H), 3.40 (s, 3H), 3.34 (s, 3H), 3.20 (d, *J* = 3.0 Hz, 1H), 2.90 (t, *J* = 2.6 Hz, 1H), 2.40 (s, 3H), 2.38–2.34 (m, 1H), 2.35 (d, *J* = 15.5 Hz, 1H), 1.83–1.75 (m, 1H), 1.70–1.65 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.5, 151.4, 149.4, 147.7, 138.4, 121.9, 116.9, 116.1, 99.1, 71.3, 57.0, 56.0, 55.7, 54.9, 49.2, 47.1, 45.0, 42.6, 41.0, 35.7.

HRMS(ESI): *m/z* calc. for $C_{20}H_{26}NO_6$ $[M+H]^+$: 376.1760, found: 376.1749.



Compounds 36 and 37



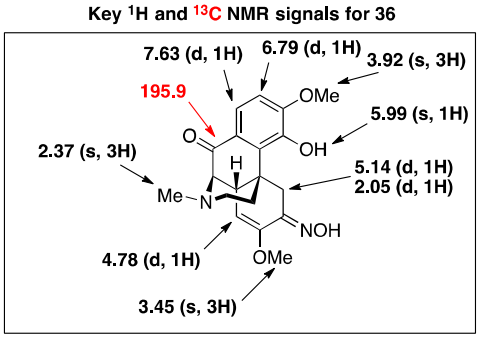
Procedure: In an oven-dried round-bottom flask, **30** (192 mg, 0.5591 mmol), hydroxylamine hydrochloride (264 mg, 3.799 mmol), and sodium acetate (465 mg, 5.669 mmol) were added to methanol (20 mL). The flask was attached to a reflux condenser and stirred at reflux temperature. After 48 hours, the contents of the flask were concentrated under reduced pressure. The residue was dissolved in water and basified with a 15% ammonium hydroxide solution. The reaction mixture was extracted with dichloromethane (6x), dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (15:1 dichloromethane/ methanol) to afford oxime **36** (57.0 mg, 29% yield) and a *bis*-oxime **37** (82.0 mg, 39% yield) as light yellow and tan solids, respectively.

36

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.99 (s, 1H), 5.14 (d, *J* = 16.5 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 3.92 (s, 3H), 3.45 (s, 3H), 3.28 (d, *J* = 3.5 Hz, 1H), 2.97 (dd, *J* = 2.2, 2.0 Hz, 1H), 2.69 (dd, *J* = 12.0, 4.3, 1.7 Hz, 1H), 2.37 (s, 3H), 2.14 (ddd, *J* = 12.6, 3.3, 1.6 Hz, 1H), 2.09–2.03 (m, 1H), 2.05 (d, *J* = 16.6 Hz, 1H), 1.92 (td, *J* = 12.6, 5.0 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 195.9, 154.7, 152.7, 151.5, 146.6, 131.1, 129.0, 120.0, 110.2, 103.6, 68.9, 56.6, 55.2, 49.2, 46.2, 43.5, 39.4, 36.0, 34.4.

HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_5[M+H]^+$: 359.1607, found: 359.1604.

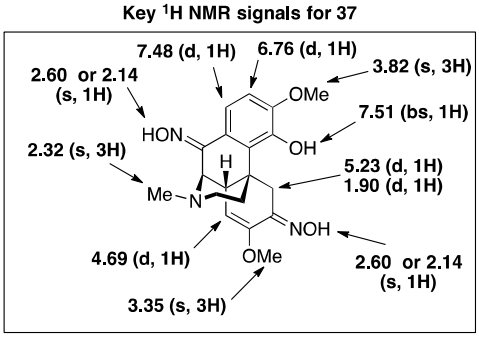


37

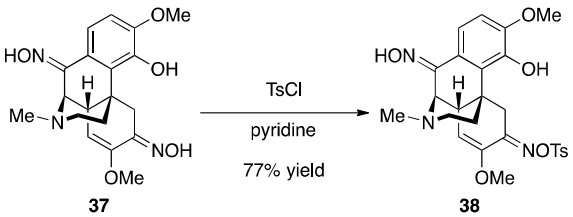
^{1}H NMR (d_6-acetone, 500 MHz): δ 7.51 (bs, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 1H), 5.23 (d, *J* = 16.4 Hz, 1H), 4.69 (d, *J* = 1.8 Hz, 1H), 4.58 (d, *J* = 3.6 Hz, 1H), 3.82 (s, 3H), 3.35 (s, 3H), 2.84 (dd, *J* = 3.9, 1.7 Hz, 1H), 2.60 (s, 1H), 2.53 (d, *J* = 11.6, 4.9, 1.5 Hz, 1H), 2.32 (s, 3H), 2.14 (s, 1H), 2.05–2.01 (m, 1H), 1.97 (td, *J* = 12.0, 3.3 Hz, 1H), 1.90 (d, *J* = 16.5 Hz, 1H), 1.78 (td, *J* = 12.3, 4.8 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 152.4, 151.9, 151.1, 150.1, 146.7, 128.8, 124.8, 115.3, 110.5, 104.1, 56.5, 55.1, 54.5, 49.7, 44.9, 43.7, 38.9, 35.8, 34.2.

HRMS(ESI): *m/z* calc. for $C_{19}H_{24}N_3O_5$ $[M+H]^+$: 374.1716, found: 374.1721.



Compound 38



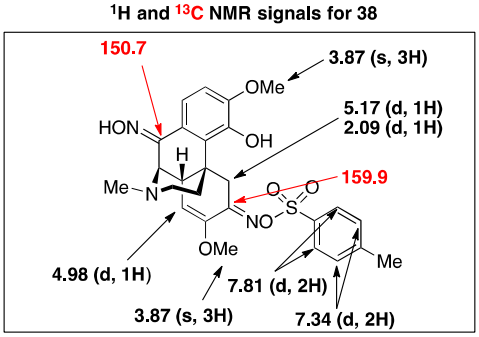
Procedure: In a vial with a stir bar, **37** (20.0 mg, 0.0536 mmol) and 4-toluenesulfonyl chloride (52.6 mg, 0.2759 mmol) were dissolved in pyridine (5 mL) and were stirred under an atmosphere

of N_2. After 4.5 hours, the mixture was transferred to a seperatory funnel and was diluted with water and saturated sodium bicarbonate. The contents were extracted with dichloromethane (3x). The organic layers were combined, dried with sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by flash chromatography (15:1 dichloromethane/methanol) on silica gel to afford **38** (21.7 mg, 77% yield) as a yellow solid.

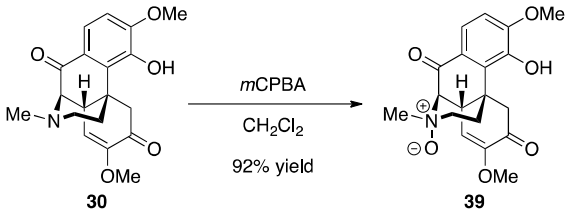
^{1}H NMR (CD_3OD, 500 MHz) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.17 (d, *J* = 16.4 Hz, 1H), 4.98 (d, *J* = 2.2 Hz, 1H), 4.64 (d, *J* = 3.6 Hz, 1H), 3.87 (s, 3H), 3.33 (s, 3H), 2.82 (t, *J* = 2.9 Hz, 1H), 2.59 (dd, *J* = 12.2, 3.9 Hz, 1H), 2.39 (s, 3H), 2.35 (s, 3H), 2.09 (d, *J* = 16.3 Hz, 1H), 2.10 - 2.05 (m, 1H), 2.01 (td, *J* = 12.3, 3.4 Hz, 1H), 1.78 (td, *J* = 12.6, 4.7 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 159.9, 150.7, 150.1, 146.6, 146.5, 134.2, 130.8 (2C), 129.9 (2C), 128.7, 127.0, 123.6, 115.3, 110.8, 109.9, 56.6, 55.4, 54.1, 45.1, 43.7, 39.5, 35.7, 35.4, 30.9, 21.7.

HRMS(ESI): *m/z* calc. for $C_{26}H_{30}N_3O_7S$ $[M+H]^+$: 528.1804, found: 528.1812.



Compound 39



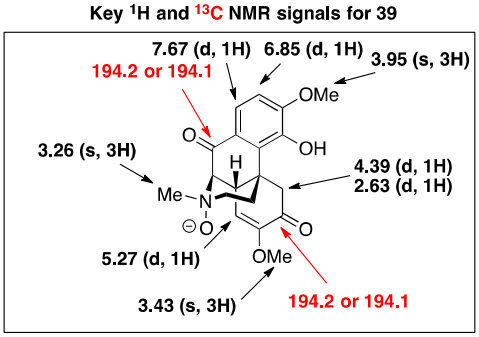
Procedure: In a vial with a stir bar, **30** (171.3 mg, 0.4989 mmol) was dissolved in dichloromethane (12 mL). The reaction was capped, placed under nitrogen and cooled to 0 ºC in an ice/water bath after 15 minutes, *m*-chloroperbenzoic acid (~75%) (210.7 mg, 0.9157 mmol) was slowly added. The reaction was stirred at room temperature for 3.5 hours. The reaction was concentrated under reduced pressure and was purified by silica gel chromatography (9:1 dichloromethane/methanol) to afford **39** (164.4 mg, 92% yield) as a yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 5.27 (d, *J* = 2.1 Hz, 1H), 4.55 (t, *J* = 2.8 Hz, 1H), 4.39 (d, *J* = 15.8 Hz, 1H), 3.95 (s, 3H), 3.84 (d, *J* = 1.8 Hz,

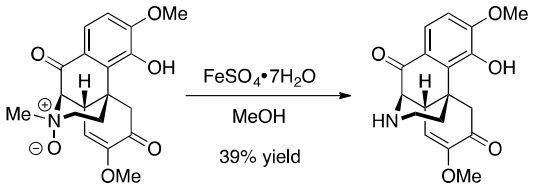
1H), 3.43 (s, 3H), 3.27 (ddd, *J* = 12.4, 2.2, 1.6 Hz, 1H), 3.26 (s, 3H), 3.08 (dt, *J* = 12.8, 3.0 Hz, 1H), 2.85 (td, *J* = 13.1, 4.3 Hz, 1H), 2.63 (d, *J* = 15.8 Hz, 1H), 2.00 (dt, *J* = 13.5, 2.5 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 194.2, 194.1, 152.6, 146.8, 145.7, 125.9, 121.0, 118.6, 114.4, 110.5, 73.1, 60.7, 57.1, 55.5, 54.3, 39.5, 39.4, 31.4, 28.3.

HRMS(ESI): *m/z* calc. for $C_{19}H_{22}NO_6$ $[M+H]^+$: 360.1447, found: 360.1443.



Compound 40

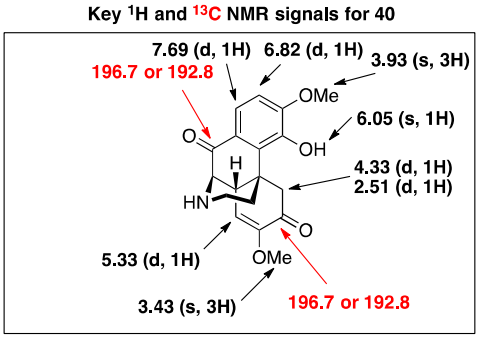


Procedure: In a round bottom flask with a stir bar, **39** (377.0 mg, 1.049 mmol) was dissolved in methanol (24 mL). The reaction mixture was cooled to 0 ºC in an ice/water bath. After 10 min, iron(II) sulfate heptahydrate (535.0 mg, 1.924 mmol) was added slowly to the reaction mixture and was allowed to stir under nitrogen for 2 hours. The contents of the flask were concentrated under reduced pressure. The reaction mixture was subsequently taken up in water and basified with aqueous 15% ammonium hydroxide. An extraction was performed with ethyl acetate (3x) and the organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude mixture was purified via silica gel chromatography (30:1 to 15:1 dichloromethane/methanol) to afford **40** as a yellow solid (107.3 mg, 39% yield).

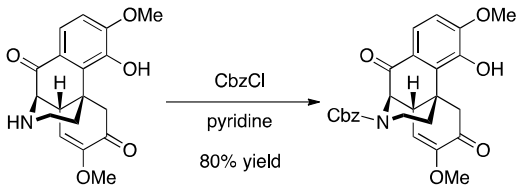
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, *J* = 8.6 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.05 (bs, 1H), 5.33 (dd, *J* = 2.2, 1H), 4.33 (d, *J* = 15.9 Hz, 1H), 3.93 (s, 3H), 3.59 (dd, *J* = 3.3 Hz, 1H), 3.43 (s, 3H), 3.22 (t, *J* = 2.8 Hz, 1H), 2.82 (ddd, *J* = 12.1, 5.0, 1.8 Hz, 1H), 2.58 (td, *J* = 12.5, 3.5 Hz, 1H), 2.51 (d, *J* = 15.9 Hz, 1H), 2.05 (ddd, *J* = 12.9, 3.8, 1.9 Hz, 1H), 1.94 (td, *J* = 12.6, 5.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.7, 192.8, 153.0, 152.5, 144.6, 129.6, 126.9, 119.9, 113.8, 109.0, 60.3, 56.1, 55.0, 49.8, 46.1, 42.4, 38.7, 34.6.

HRMS(ESI): *m/z* calc. for $C_{18}H_{20}NO_5$ $[M+H]^+$: 330.1341, found: 330.1336.



Compound 41



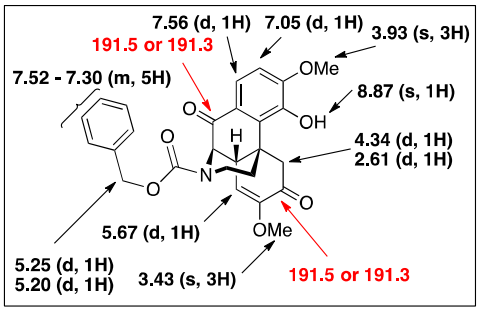
Procedure: In a vial with a stir bar, **40** (107.3 mg, 0.3258 mmol) was dissolved in pyridine (10 mL). The reaction was cooled to 0 ºC in an ice water bath for 10 min. Benzyl chloroformate (0.1 mL, 0.7005 mmol) was added drop wise into the reaction vial. The reaction was capped under N_2 and was stirred for 1.5 hours at room temperature. The reaction was diluted with water, sat. $NaHCO_3$ and was extracted with ethyl acetate (3x). The organic layers were combined, dried over Na_2SO_4, and were concentrated under reduced pressure. The crude residue was purified by column chromatography (15:1 dichloromethane/methanol) on silica gel to afford **41** (121.1 mg, 80% yield) as a white solid.

^{1}H NMR (d_7-DMF, 500 MHz, 80 ºC) δ 8.87 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.52–7.30 (m, 5H), 7.05 (d, *J* = 8.5 Hz, 1H), 5.67 (d, *J* = 2.3 Hz, 1H), 5.25 (d, *J* = 12.7 Hz, 1H), 5.20 (d, *J* = 12.7 Hz, 1H), 5.00 (d, *J* = 3.6 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 4.07 (ddd, *J* = 13.9, 5.5, 1.4 Hz, 1H), 3.93 (s, 3H), 3.43 (s, 3H), 3.31 (dd, *J* = 3.8, 2.2 Hz, 1H), 2.65 (td, *J* = 13.5, 3.5 Hz, 1H), 2.61 (d, *J* = 15.7 Hz, 1H), 2.19 (ddd, *J* = 13.2, 3.6, 1.1 Hz, 1H), 2.01 (td, *J* = 13.1, 5.5 Hz, 1H).

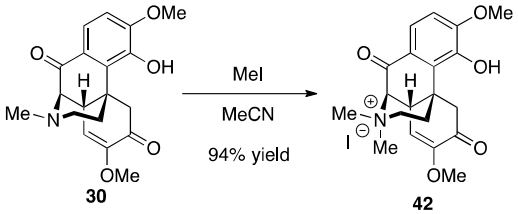
^{13}C NMR (d_7-DMF, 125 MHz, 80 ºC): δ 191.5, 191.3, 155.6, 154.0, 146.0, 137.7, 136.5, 129.3, 128.8, 128.5, 128.2, 128.0, 127.4, 127.0, 119.8, 113.5, 110.5, 69.8, 67.5, 58.7, 56.3, 55.0, 49.1, 45.7, 41.8, 39.3.

HRMS(ESI): *m/z* calc. for $C_{26}H_{26}NO_7$ $[M+H]^+$: 464.1709, found: 464.1710.

Key ^{1}H and ^{13}C NMR signals for 41



Compound 42



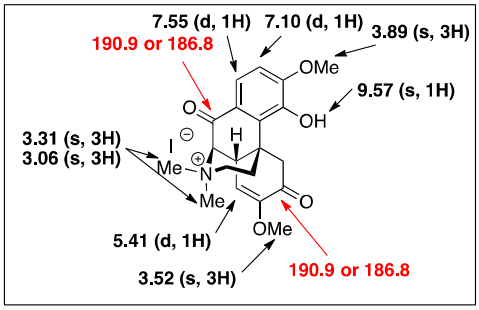
Procedure: In a vial with a stir bar, **30** (58.3 mg, 0.1698 mmol) was dissolved in acetonitrile (10 mL). Iodomethane (0.1 mL, 1.606 mmol) was added drop wise into the vial. The vial was capped and stirred under N_2 for 26 hours. The reaction mixture was diluted with water and was stirred for 30 min. The contents of the vial were concentrated under reduced pressure to yield **42** (80.7 mg, 94% yield) as a yellow solid. No further purification was necessary.

^{1}H NMR (d_6-DMSO, 500 MHz) δ 9.57 (s, 1H), 7.55 (d, J = 8.6, 1H), 7.10 (d, J = 8.7, 1H), 5.41 (d, J = 1.4 Hz, 1H), 4.28 (d, J = 2.6 Hz, 1H), 4.15 (d, J = 15.9 Hz, 1H), 4.12 (t, J = 2.6 Hz, 1H), 3.89 (s, 3H), 3.59–3.52 (m, 1H), 3.54 s, 3H), 3.31 (s, 3H), 3.06 (s, 3H), 3.02–2.94 (m, 2H), 2.59 (td, J = 14.2, 4.2 Hz, 1H), 2.11–2.02 (m, 1H).

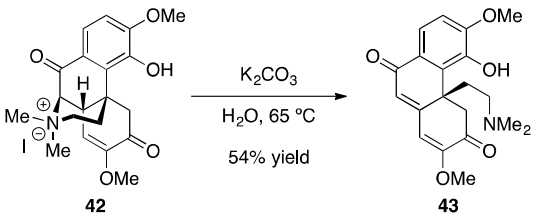
^{13}C NMR (d_6-DMSO, 125 MHz): δ 190.9, 186.8, 171.8, 155.0, 152.9, 145.1, 127.2, 125.7, 121.2, 111.2, 111.0, 72.5, 58.0, 56.6, 55.2, 54.6, 51.1, 46.9, 28.7, 22.9.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_5$ $[M]^+$: 358.1654, found: 358.1650.

Key ^{1}H and ^{13}C NMR signals for 42



Compound 43

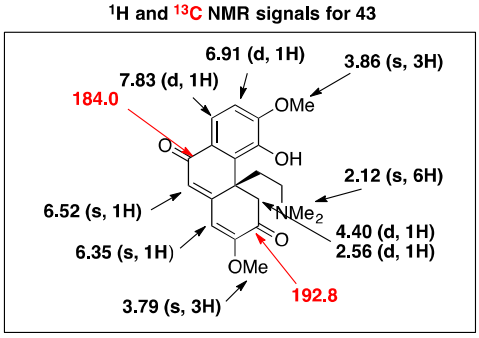


Procedure: In a vial with a stir bar, **42** (100.9 mg 0.2079 mmol) was dissolved in water (10 mL). Potassium carbonate (359.0 mg, 2.597 mmol) was added to the mixture and the vial was capped and placed in an oil bath at 65 ºC. The mixture was stirred for 15 hours. The contents of the vial were poured into a seperatory funnel and diluted with water. The mixture was extracted with dichloromethane (3x). The organic layers were combined, dried with Na_2SO_4, and were concentrated under reduced pressure to afford **43** (40.0 mg, 54% yield) as an orange solid, which was pure by NMR.

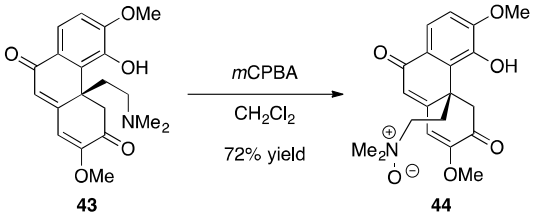
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.52 (s, 1H), 6.35 (s, 1H), 4.40 (d, *J* = 17.0 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 2.93 (td, *J* = 11.8, 3.7 Hz, 1H), 2.56 (d, *J* = 16.8 Hz, 1H), 2.12 (s, 6H), 2.10–2.02 (m, 1H), 2.01–1.93 (m, 1H), 1.75 (td, *J* = 11.4, 3.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.8, 184.0, 155.8, 153.6, 150.9, 144.1, 130.4, 126.9, 126.1, 118.2, 113.3, 109.6, 56.0, 55.8, 55.2, 53.6, 46.3, 44.9, 44.2, 34.0.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_5$ $[M+H]^+$: 358.1654, found: 358.1640.



Compound 44



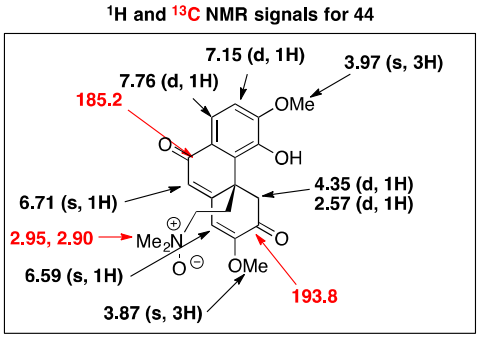
Procedure: In a vial with a stir bar, **43** (129.3 mg, 0.3618 mmol) was dissolved in

dichloromethane (10 mL). The reaction vial was capped and stirred under N_2 at 0 ºC. After 5 min, *m*-chloroperbenzoic acid (267.0 mg, 1.160 mmol) was placed into the vial. The reaction was stirred at room temperature for 1.5 hours and was immediately concentrated under reduced pressure. The crude residue was purified by flash chromatography (9:1 dichloromethane/methanol) on silica gel to afford *N*-oxide **44** (97.2 mg, 72% yield) as a yellow solid.

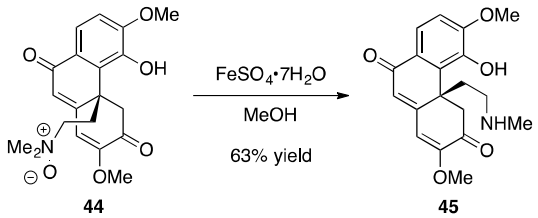
^{1}H NMR (CD_3OD, 500 MHz) δ 7.76 (d, *J* = 8.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 4.35 (d, *J* = 16.7 Hz, 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.27 (td, *J* = 12.4, 4.1 Hz, 1H), 2.95 (s, 3H), 2.90 (s, 3H), 2.84 (td, *J* = 12.0, 4.5 Hz, 1H), 2.57 (d, *J* = 16.5 Hz, 1H), 2.53 (td, *J* = 11.9, 3.9 Hz, 1H), 2.43 (td, *J* = 12.0, 4.5 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 193.8, 185.2, 158.0, 155.0, 153.4, 145.0, 130.9, 128.0, 126.5, 120.7, 115.1, 112.1, 68.4, 59.5, 57.5, 56.9, 56.7, 47.5, 44.9, 44.9.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_6$ $[M+H]^+$: 374.1604 found: 374.1587.



Compound 45



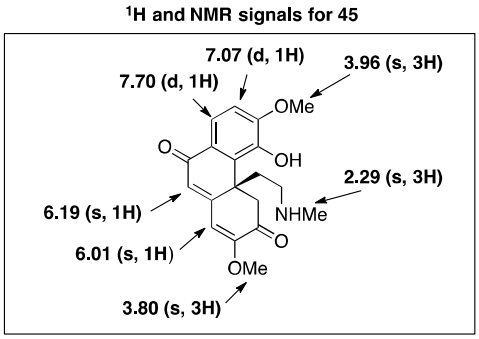
Procedure: In a vial with a stir bar, **44** (55.7 mg, 0.1559 mmol) was dissolved in methanol (7 mL). The vial was capped and stirred in an ice/water bath at 0 ºC. After 5 min, iron sulfate heptahydrate (75.1 mg, 0.2701 mmol) was added to the mixture. The reaction required 1 hour of stirring at room temperature and was diluted with water. The reaction was quenched with 15% ammonium hydroxide and extracted with dichloromethane (4x). The organic layers were combined, dried over sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by flash chromatography (9:1 dichloromethane/methanol) on silica gel to afford **45** (33.9 mg, 63% yield) as a yellow solid.

^{1}H NMR (CD_3OD, 500 MHz) δ 7.70 (d, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.19 (s, 1H),

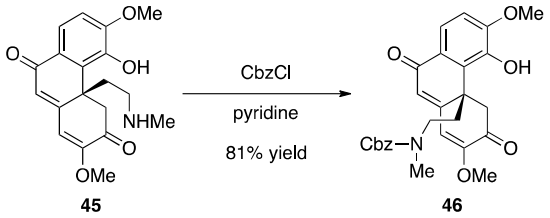
6.01 (s, 1H), 3.97–3.92 (m, 1H), 3.96 (s, 3H), 3.80 (s, 3H), 2.91–2.79 (m, 2H), 3.54 (td, *J* = 13.7, 4.3 Hz, 1H), 2.29 (s, 3H), 2.01–1.96 (m, 1H), 1.26–1.17 (m, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 186.2, 164.8, 160.5, 153.0, 145.2, 133.2, 126.7, 121.6, 119.9, 118.5, 110.9, 104.2, 56.8, 55.7, 50.5, 44.7, 43.9, 37.4, 36.5.

HRMS(ESI): *m/z* calc. for $C_{19}H_{22}NO_5$ $[M+H]^+$: 344.1498, found: 344.1496.



Compound 46



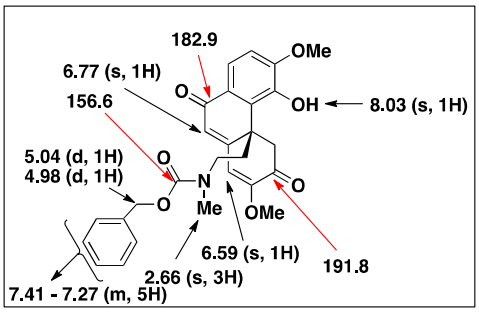
In a vial with a stir bar, **45** (18.9 mg, 0.0550 mmol) was dissolved in pyridine (7 mL) and was cooled to 0 ºC in an ice water bath. After 10 min, benzyl chloroformate (0.03 mL, mmol) was added to the mixture, which was capped and stirred under N_2 at room temperature. After 45 min, the reaction was diluted with saturated sodium bicarbonate and was extracted with ethyl acetate (3x). The organic layers were combined, dried over sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by column chromatography (15:1 dichloromethane/methanol) on silica yield to afford **46** (21.3 mg, 81% yield) as a yellow solid.

^{1}H NMR (d_7-DMF, 500 MHz, 80 ºC): δ 8.03 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.41–7.27 (m, 5H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.77 (s, 1H), 6.59 (s, 1H), 5.04 (d, *J* = 12.7 Hz, 1H), 4.98 (d, *J* = 13.0 Hz, 1H), 4.32 (d, *J* = 16.9 Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 3.13 (s, 1H), 3.04–2.96 (m, 1H), 2.80–2.76 (m, 1H), 2.66 (s, 3H), 2.63–2.55 (m, 1H), 2.12 (dt, *J* = 7.9, 1.6 Hz, 1H).

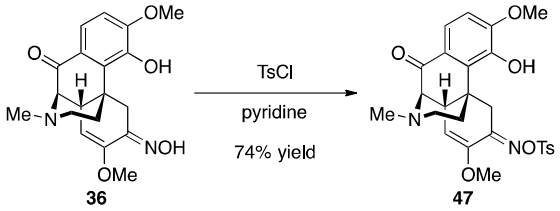
^{13}C NMR (d_7-DMF, 125 MHz, 80 ºC): δ 191.8, 182.9, 156.6, 155.6, 153.9, 151.8, 144.1, 137.8, 131.0, 128.6, 128.3, 127.9, 127.7, 126.8, 126.7, 126.5, 118.8, 114.3, 111.2, 66.5, 63.9, 56.3, 55.9, 47.2, 45.7, 44.4, 44.3.

HRMS(ESI): *m/z* calc. for $C_{27}H_{28}NO_7$ $[M+H]^+$: 478.1866, found: 478.1865.

Key ^{1}H and ^{13}C NMR signals for 46



Compound 47



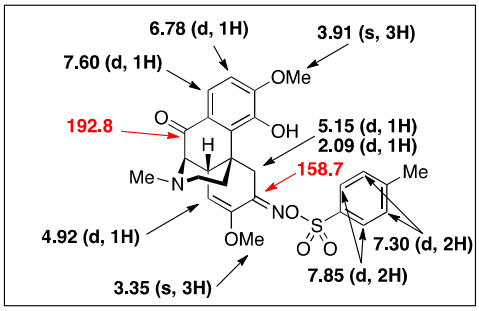
Procedure: In a vial with a stir bar, **36** (38.5 mg, 0.1074 mmol) was dissolved in pyridine (5 mL). Next, 4-toluenesulfonyl chloride (68.1 mg, 0.3572 mmol) was added to the mixture and allowed to stir for 24 hours. The pyridine was blow-dried open to air for a period of 12 hours. The resulting residue was purified by column chromatography (15:1 dichloromethane/methanol) on silica gel to afford tosyl oxime **47** (40.5 mg, 74% yield) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.15 (d, *J* = 16.5 Hz, 1H), 4.92 (d, *J* = 2.2 Hz, 1H), 3.91 (s, 3H), 3.35 (s, 3H), 3.30 (d, *J* = 3.4 Hz, 1H), 2.98 (t, *J* = 2.6 Hz, 1H), 2.74 (dd, *J* = 11.6, 4.8 Hz, 1H), 2.41 (s, 3H), 2.38 (s, 3H), 2.12–2.05 (m, 2H), 2.09 (d, *J* = 16.4 Hz, 1H), 1.93 (td, *J* = 13.5, 5.2 Hz, 1H).

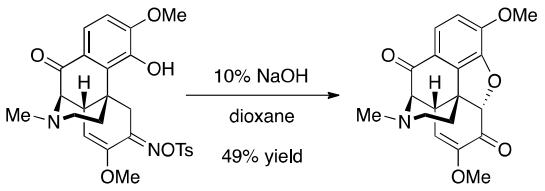
^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.8, 158.7, 152.2, 150.0, 149.8, 145.1, 144.5, 132.7, 129.7 (2C), 129.0 (2C), 126.2, 119.8, 109.1, 107.6, 67.1, 56.3, 55.2, 47.9, 45.5, 43.2, 38.8, 35.8, 34.9, 21.9.

HRMS(ESI): *m/z* calc. for $C_{26}H_{29}N_2O_7S$ $[M+H]^+$: 513.1695, found: 513.1697.

Key ^{1}H and ^{13}C NMR signals for 47



Compound 48



47 48

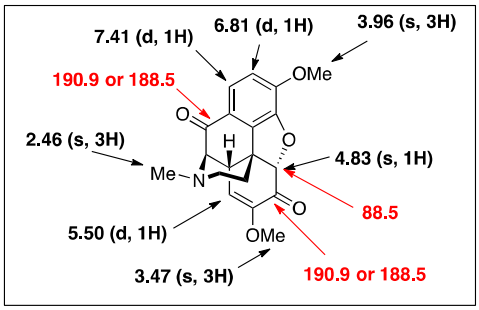
Procedure: In a vial with a stir bar, **47** (40.5 mg, 0.0790 mmol) was dissolved in dioxane (15 mL). Next, 10% NaOH (5 mL) were added to the reaction mixture, which was stirred for 15 hours. The reaction mixture was diluted with water and was extracted with dichloromethane (4x). The organic layers were combined, dried over sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by flash chromatography (9:1 dichloromethane/methanol) on silica gel to afford **48** (13.1 mg, 49% yield) as a yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, *J* = 8.7, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 5.50 (d, *J* = 2.6 Hz, 1H), 4.83 (s, 1H), 3.96 (s, 3H), 3.47 (s, 3H), 3.44 (t, *J* = 2.7 Hz, 1H), 3.35 (d, *J* = 2.8 Hz, 1H), 2.81 (ddd, *J* = 12.4, 5.4, 1.7 Hz, 1H), 2.46 (s, 3H), 2.40 (td, *J* = 12.4, 3.9 Hz, 1H), 2.22 (td, *J* = 11.8, 4.8 Hz, 1H), 2.02 (ddd, *J* = 12.7, 3.9, 1.6 Hz, 1H).

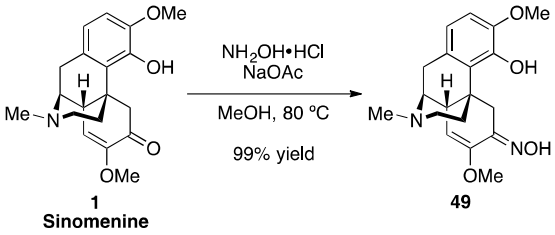
^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.9, 188.5, 153.9, 149.7, 144.7, 137.2, 124.9, 120.1, 115.2, 114.5, 88.5, 69.3, 57.0, 55.4, 47.3, 44.2, 43.5, 42.2, 33.7.

HRMS(ESI): *m/z* calc. for $C_{19}H_{20}NO_5$ $[M+H]^+$: 342.1341, found: 342.1335.

^{1}H and ^{13}C NMR signals for 48



Compound 49

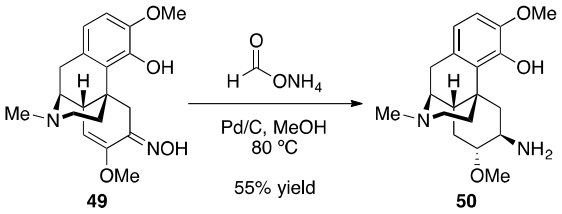


1
Sinomenine

49

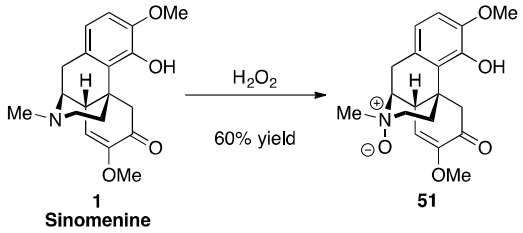
Procedure: In a vial with a stir bar, **1** (120 mg, 0.3667 mmol) was dissolved in methanol (10 mL). Hydroxylamine hydrochloride (173.0 mg, 2.290 mmol) and sodium acetate (294.0 mg, 3.584 mmol) were added to the reaction vial. The vial was capped and stirred in an oil bath at 80 ºC. After 15 hours, the methanol was evaporated under reduced pressure and taken up in water. The contents were basified with 15% ammonium hydroxide. The mixture was poured into a seperatory funnel, diluted with water and extracted with dichloromethane (10x). The organic layers were combined, dried with sodium sulfate, and were condensed under reduced pressure to afford known oxime **49** (123.8 mg, 99% yield) as an off-white solid. Spectral data (^{1}H and ^{13}C NMR) was consistent with literature reported values.[5]

Compound 50



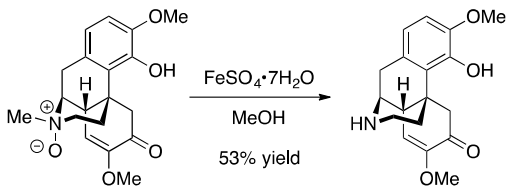
Procedure: In a vial with a stir bar, **49** (89.8 mg, 0.2607 mmol) was dissolved in methanol (7 mL). Ammonium formate (157.3 mg, 2.495 mmol) and 10% palladium on activated charcoal (82.3 mg) were added to the vessel. The vial was capped and stirred at 80 ºC in an oil bath for 2 hours. The mixture was cooled, filtered through Celite, and washed with methanol. The mixture was taken up in water and extracted with dichloromethane (8x). The organic layers were combined, dried with sodium sulfate, concentrated *in vacuo* to afford known primary amine **50** (47.7 mg, 55% yield) as a white solid. Spectral data (^{1}H NMR) was consistent with literature reported values.[5]

Compound 51



Procedure: In a vial with a stir bar, **1** (102.4 mg, 0.3109 mmol) was dissolved in 30% hydrogen peroxide (10 mL). The vial was capped and stirred under N_2 for 3 days. The reaction was diluted in water and was extracted with dichloromethane (20x). The organic layers were combined, dried over Na_2SO_4, and was concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography to afford **51** (64.0 mg, 60% yield) as a white solid. Spectral data (^{1}H NMR) was consistent with literature reported values.[5]

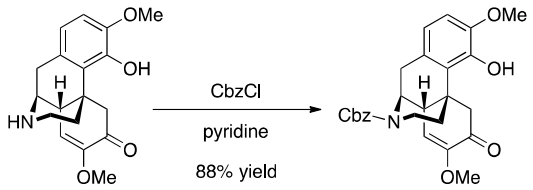
Compound 52



51 52

Procedure: In a vial with a stir bar, **51** (64.0 mg, 0.1855 mmol) was dissolved in methanol (7 mL). Under inert atmosphere, the vial was capped and was cooled to 0 ºC in a water/ice bath. After 10 min, iron sulfate heptahydrate (76.2 mg, 0.2741 mmol) was added to the vial and stirred at 0 ºC for 25 min. After this time, the mixture was stirred at room temperature for 13 min, diluted with water, and quenched with 15% ammonium hydroxide. An extraction was performed with dichloromethane (15x). The organic layers were combined, dried over Na_2SO_4, and were concentrated under reduced pressure. The crude residue was purified by reverse phase column chromatography to afford **52** (31.0 mg, 53% yield) as a white solid. Spectral Data (^{1}H NMR) was consistent with literature reported values.[5]

Compound 53



52 53

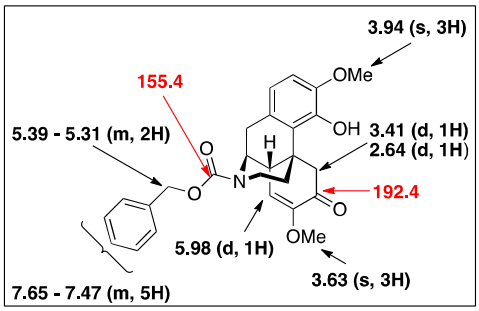
Procedure: In a vial with a stir bar, **52** (31.0 mg, 0.0983 mmol) was dissolved in pyridine (6 mL). The vial was capped under N_2 and cooled to 0 ºC in an ice/water bath. After 10 min, benzyl chloroformate (0.25 mL, 1.751 mmol) was syringed into the solution and was stirred in ice for 15 min. The reaction was allowed to stir at room temperature for 16 hours and was subsequently diluted with saturated sodium bicarbonate and water. The contents were extracted with dicloromethane (3x). The organic layers were combined, dried over Na_2SO_4, and were concentrated under reduced pressure. The crude residue was purified by flash chromatography (15:1 dichloromethane/methanol) to afford **53** (39.0 mg, 88% yield) as a white solid.

^{1}H NMR (d_7-DMF, 80 ºC, 500 MHz) δ 7.65–7.47 (m, 5H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 5.98 (d, *J* = 2.5 Hz, 1H) 5.39–5.31 (m, 2H), 4.90 (t, *J* = 4.6 Hz, 1H), 4.47 (d, *J* = 15.4 Hz, 1H), 4.09 (dd, *J* = 13.5, 5.3 Hz, 1H), 3.94 (s, 3H), 3.63 (s, 3H), 3.41 (dd, *J* = 17.9, 5.2 Hz, 1H), 3.12–3.04 (m, 1H), 2.92 –2.80 (m, 2H), 2.74 (t, *J* = 14.0 Hz, 1H), 2.64 (d, J = 17.9 Hz, 1H), 2.20 –2.15 (m, 1H), 1.94 (td, *J* = 12.9, 5.4 Hz, 1H).

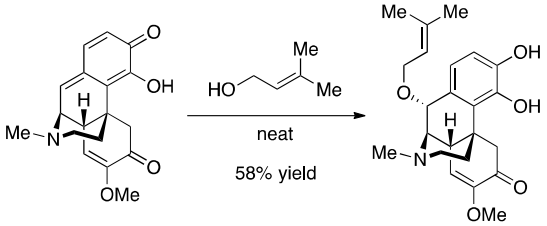
^{13}C NMR (d_7-DMF, 80 ºC, 125 MHz): δ 192.4, 155.8, 155.4, 153.1, 146.7, 146.3, 138.0, 136.5, 129.9, 128.8, 128.2, 128.0, 123.0, 119.1, 115.2, 111.0, 69.8 (2C), 67.0, 56.4, 54.9, 49.9, 48.8, 44.7, 40.8, 39.2.

HRMS(ESI): *m/z* calc. for $C_{26}H_{28}NO_6$ $[M+H]^+$: 450.1917, found: 450.1906.

^{1}H and ^{13}C NMR signals for 53



Compound 54



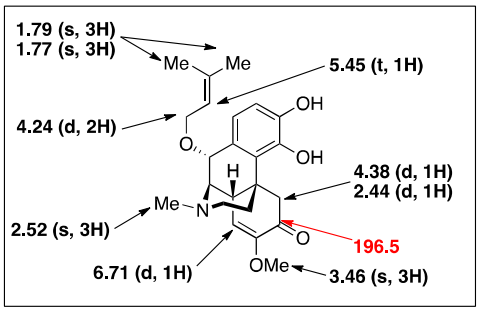
Procedure: In a vial with a stir bar, **3** (308.7 mg, 0.9850 mmol) was dissolved in 3-methylbut-2-en-1-ol (0.4 mL) and was capped and stirred under N_2 for 20 hours. The mixture was directly purified by column chromatography (15:1 dichloromethane/methanol) on silica gel to provide **54** (226.3 mg, 58% yield) as a light orange solid.

^{1}H NMR (CD_3OD, 500 MHz) δ 6.71 (d, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.95 (d, *J* = 2.2 Hz, 1H), 5.45 (t, *J* = 7.0 Hz, 1H), 4.39 (s, 1H), 4.38 (d, (*J* = 15.7 Hz, 1H), 4.24 (d, *J* = 6.9 Hz, 2H), 3.46 (s, 3H), 3.39 (d, *J* = 3.3 Hz, 1H) 3.03 (t, *J* = 3.0 Hz, 1H), 2.53–2.47 (m, 1H), 2.52 (s, 3H), 2.44 (d, *J* = 15.7 Hz, 1H), 2.00 (td, *J* = 12.3, 3.4 Hz, 1H), 1.91 (ddd, *J* = 13.1, 3.5, 1.8 Hz, 1H), 1.82 (td, *J* = 12.7, 4.4 Hz, 1H), 1.79 (s, 3H), 1.77 (s, 3H).

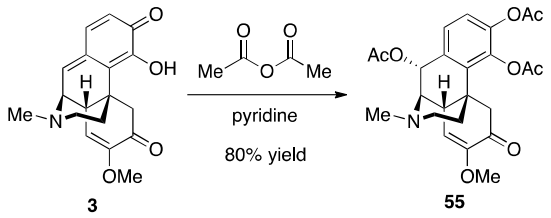
^{13}C NMR (CD_3OD, 125 MHz): δ 196.5, 151.3, 146.1, 145.5, 138.5, 131.9, 123.6, 122.7, 122.3, 120.6, 114.7, 71.1, 67.0, 60.1, 55.0, 49.9, 48.1, 45.9, 42.9, 42.1, 36.5, 26.0, 18.4.

HRMS(ESI): *m/z* calc. for $C_{23}H_{30}NO_5$ $[M+H]^+$: 400.2124, found: 400.2120.

^{1}H and ^{13}C NMR signals for 54

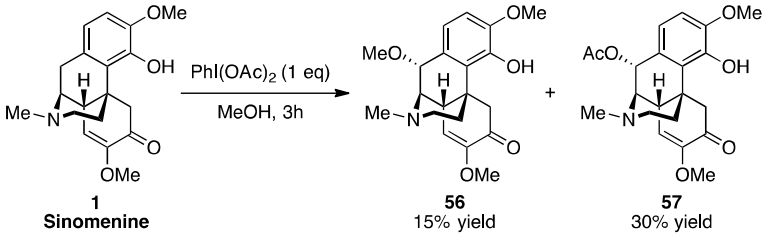


Compound 55



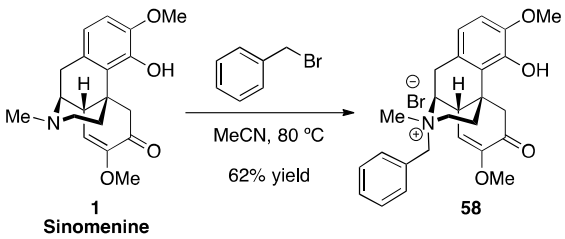
Procedure: In a vial with a stir bar, **3** (202.0 mg, 0.6446 mmol) was dissolved in pyridine (5 mL) and was cooled to 0 ºC in an ice/water bath. Acetic anhydride (3 mL) was added to the vial. The contents were stirred at 0 ºC for 5 min and were allowed to stir at room temperature for 14 hours. The reaction was diluted with saturated sodium bicarbonate and extracted with dichloromethane (4x). The organic layers were combined, dried over sodium sulfate, and were concentrated in vacuo. The crude residue was purified by flash chromatography (15:1 dichloromethane/methanol) to afford **55** (237.0 mg, 80% yield) as a tan solid. Spectral data (^{1}H NMR) was consistent with literature reported values.[4]

Compounds 56 and 57



Procedure: In a vial with a stir bar, **1** (151.7 mg, 0.4605 mmol) was dissolved in methanol (4 mL). Diacetoxyiodobenzene (148.7 mg, 0.4617 mmol) was added to the mixture and was capped under N_2. After 3 hours, the mixture was basified with Na_2SO_4 and was extracted with dichloromethane (4x). The organic layers were combined, dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by column chromatography (9:1 dichloromethane/methanol) on silica gel to yield **56** (25.0 mg, 15% yield) and **57** (53.3 mg, 30% yield) as light yellow solids. Spectral data (^{1}H NMR) was consistent with literature reported values.

Compound 58



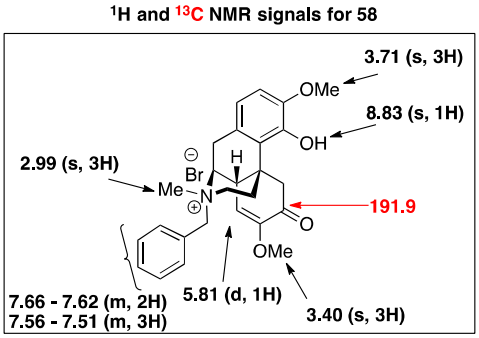
Procedure: In a vial with a stir bar, **1** (283.5 mg, 0.8607 mmol) was dissolved in acetonitrile (5

mL). Benzyl bromide (0.2 mL, 1.684 mmol) was added to the reaction. The vial was capped and stirred in an oil bath at 80 ºC. After 16 hours, contents of the vial were filtered through a fritted funnel and were lightly washed with water to afford **58** (267.9 mg, 62% yield) as a white solid. The chloride salt of this compound is known.[7]

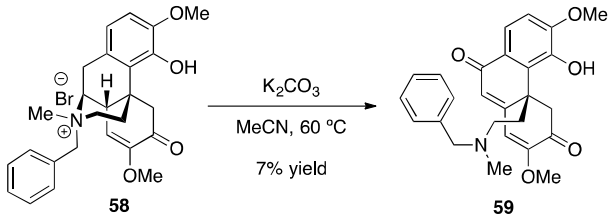
^{1}H NMR (*d*$_6$-DMSO, 500 MHz) δ 8.83 (s, 1H), 7.66–7.62 (m, 2H), 7.56–7.51 (m, 3H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.58 (d, *J* = 8.2 Hz, 1H), 5.81 (d, *J* = 2.3 Hz, 1H) 5.25–5.18 (m, 1H), 5.02–4.94 (m, 1H), 4.25–4.21 (m, 1H), 4.18 (d, *J* = 15.5 Hz, 1H), 3.89–3.84 (m, 1H), 3.71 (s, 3H), 3.40 (s, 3H), 3.37–3.18 (m, 3H), 3.03 (ddd, *J* = 15.3, 8.7, 4.9 Hz, 1H), 2.99 (s, 3H), 2.75–2.59 (m, 2H), 1.87 (d, *J* = 13.1 Hz, 1H).

^{13}C NMR (*d*$_6$-DMSO, 125 MHz): δ 191.9, 151.6, 146.3, 145.0, 133.3 (2C), 130.4, 129.1 (2C), 128.0, 125.8, 121.1, 118.3, 113.0, 110.7, 64.0, 63.0, 55.8 (2C), 54.7 (2C), 49.3, 46.4, 37.4, 29.8, 26.5.

HRMS(ESI): *m/z* calc. for $C_{26}H_{30}NO_4$ $[M]^+$: 420.2175, found: 420.2186.



Compound 59



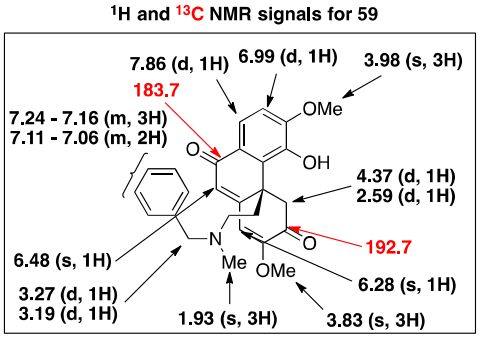
Procedure: In a vial with a stir bar, **58** (143.0 mg, 0.2858 mmol) was dissolved in acetonitrile (10 mL). Potassium carbonate (330.0 mg, 2.388 mmol) was added to the vial, capped under air, and was stirred at 60 ºC in an oil bath. After 16 hours, the contents of the vial were poured into a seperatory funnel and were diluted with water. The mixture was then extracted with ethyl acetate (4x). The organic layers were combined, dried over sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by column chromatography (15:1 dichloromethane/methanol) on silica gel to generate **59** (8.2 mg, 7% yield) as an orange solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.24–7.16 (m, 3H), 7.11–7.06 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.48 (s, 1H), 6.28 (s, 1H), 4.37 (d, *J* = 16.7 Hz, 1H), 3.98 (s, 3H), 3.83

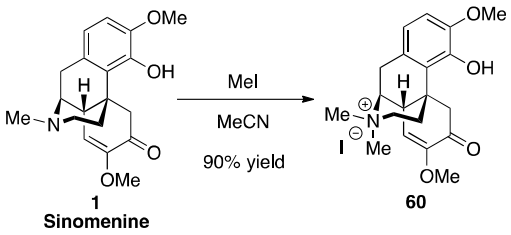
(s, 3H), 3.27 (d, J = 13.1 Hz, 1H), 3.19 (d, J = 13.0 Hz, 1H), 2.91 (ddd, J = 13.4, 11.1, 4.2 Hz, 1H), 2.59 (d, J = 16.6 Hz, 1H) 2.09–1.96 (m, 2H), 1.93 (s, 3H), 1.72–1.64 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 192.7, 183.7, 156.0, 153.5, 150.1, 142.6, 130.3, 129.1 (2C), 128.3 (2C), 127.0, 126.2, 119.8, 113.6, 113.0, 109.9, 98.8, 61.8, 56.4, 56.1, 53.5, 46.8, 44.3, 42.3, 34.3.

HRMS(ESI): *m/z* calc. for $C_{26}H_{28}NO_5$ $[M+H]^+$: 434.1967, found: 434.1955.



Compound 60



1
Sinomenine

60

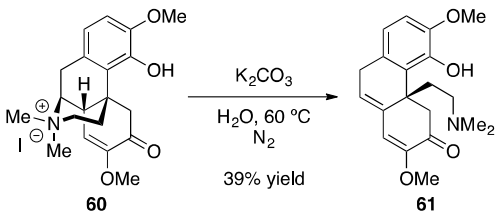
Procedure: In a vial with a stir bar, **1** (208.0 mg, 0.6315 mmol) was dissolved in acetonitrile (15 mL). Iodomethane (0.40 mL, 6.425 mmol) was added and the vial was capped and stirred under N_2. After 20 hours, the mixture was diluted with water, stirred for 30 min, and concentrated under reduced pressure. The crude residue was washed with diethyl ether through a funnel to afford known quaternary ammonium salt **60** (264 mg, 90% yield) as a white solid.[7]

^{1}H NMR (D_2O, 500 MHz): δ 6.69 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 5.83 (d, J = 2.0 Hz, 1H), 4.30 (d, J = 15.9 Hz, 1H), 3.99–3.95 (m, 1H), 3.70–3.67 (m, 1H), 3.68 (s, 3H), 3.46 (s, 3H), 3.39 (s, 3H), 3.38–3.33 (m, 2H), 3.27 (dd, J = 13.7, 3.2 Hz, 1H), 3.19 (s, 3H), 2.88 (td, J = 13.7, 3.4 Hz, 1H), 2.72 (d, J = 16.0 Hz, 1H), 2.27 (td, J = 14.2, 4.2 Hz, 1H), 2.07–1.98 (m, 1H).

^{13}C NMR (d_6-DMSO, 125 MHz): δ 191.6, 151.5, 146.2, 144.9, 125.6, 120.8, 118.3, 113.0, 110.7, 66.8, 56.9, 55.8, 54.6, 53.3, 50.9, 46.4, 39.0, 37.8, 29.9, 26.4.

HRMS(ESI): *m/z* calc. for $C_{20}H_{26}NO_4$ $[M]^+$: 344.1862, found: 344.1852.

Compound 61

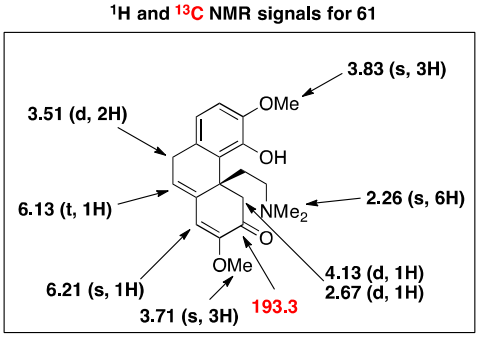


Procedure: In a vial with a stir bar, water (20 mL) was purged with N_2 gas for 24 hours. In a separate vial with a stir bar, **60** (124.5 mg, 0.2557 mmol) and potassium carbonate (312.6 mg, 2.262 mmol) were added. The vial was sealed with a stopper and placed under N_2. The N_2-purged water (12 mL) was syringed into the vial containing the solids. The contents of the vial were purged with N_2 for 5 min. The stopper was carefully replaced with a Teflon vial cap and was sealed with electrical tape. The vial was placed in an oil bath at 60 ºC and was allowed to stir for 8 hours. The vial was removed from heat, cooled to room temperature, and was poured into a seperatory funnel containing water and brine. The mixture was extracted with dichloromethane (4x). The organic layers were combined, dried over Na_2SO_4, and were concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 dichloromethane/methanol) on silica gel to afford **61** (34.5 mg, 39% yield) as an orange solid.

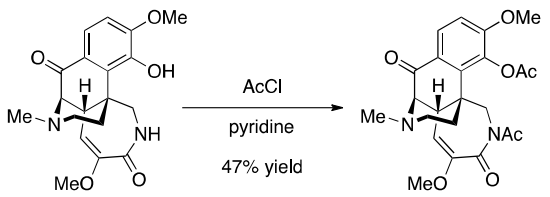
^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.76 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.21 (s, 1H), 6.13 (t, *J* = 4.1 Hz, 1H), 4.13 (d, *J* = 16.8 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.51 (d, *J* = 4.0 Hz, 2H), 2.67 (d, *J* = 16.7 Hz, 1H), 2.56 (td, *J* = 12.1, 4.2 Hz, 1H), 2.43 (td, *J* = 11.8, 4.5 Hz, 1H), 2.26 (s, 6H), 2.16 (td, *J* = 12.1, 4.6 Hz, 1H), 2.02 (td, *J* = 11.8, 4.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.3, 149.7, 145.5, 143.8, 134.6, 127.2, 126.7, 123.2, 119.1, 116.8, 109.9, 56.3, 55.4, 55.3, 48.4, 43.8 (2C), 42.4, 31.2, 30.9.

HRMS(ESI): *m/z* calc. for $C_{20}H_{26}NO_4$ $[M+H]^+$: 344.1862, found: 344.1859.



Compound 62

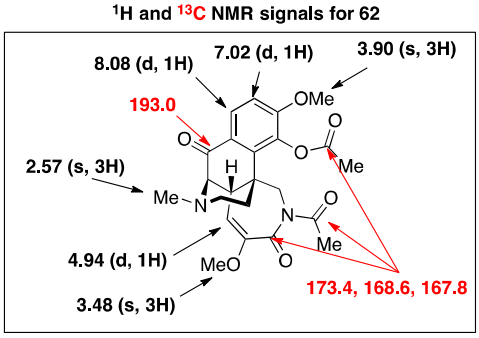


Procedure: In a vial with a stir bar, **18** (105.3 mg, 0.2938 mmol) was dissolved in pyridine (7 mL). The mixture was stirred at 0 ºC in ice/water bath for 5 min. Acetyl chloride (0.3 mL, 4.204 mmol) was added to the reaction and the vial was capped and stirred under N_2 for 10 min. The reaction was then stirred at room temperature for 17 hours. After this time, the mixture was diluted with water and saturated sodium bicarbonate solution and was extracted with dichloromethane (3x). The organic layers were combined, dried over sodium sulfate, and were concentrated under reduced pressure. The crude residue was purified by column chromatography (15:1 dichloromethane/methanol) on silica gel to afford **62** (60.8 mg, 47% yield) as a light orange solid.

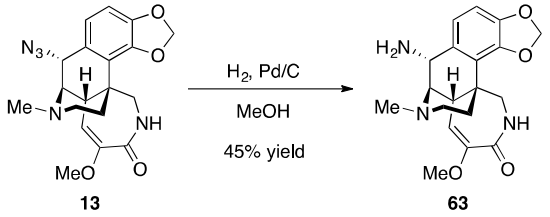
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 5.47–5.39 (m, 1H), 4.94 (d, *J* = 6.6 Hz, 1H), 3.90 (s, 3H), 3.48 (s, 3H), 3.37 (d, *J* = 3.4 Hz, 1H), 3.26–3.17 (m, 1H), 2.95 (dd, *J* = 6.6, 3.3 Hz, 1H), 2.70–2.62 (m, 1H), 2.57 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 2.04–1.89 (m, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 193.0, 173.4, 168.6, 167.8, 157.2, 151.2, 138.0, 136.3, 128.3, 126.2, 111.2, 105.8, 66.2, 56.4, 56.0, 47.9, 45.4, 43.0, 42.5, 34.7, 26.6, 21.4, 21.1.

HRMS(ESI): *m/z* calc. for $C_{23}H_{27}N_2O_7$ $[M+H]^+$: 443.1818, found: 443.1808.



Compound 63

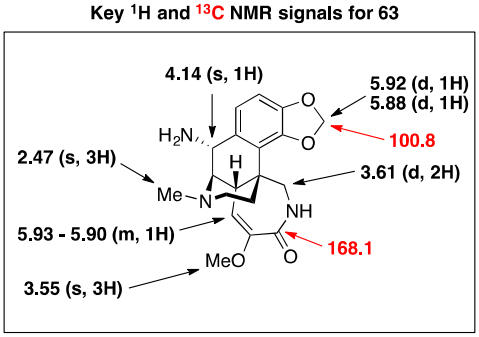


Procedure: In a vial with a stir bar, **13** (14.8 mg, 0.0413 mmol) was dissolved in methanol (6 mL). The mixture was purged with nitrogen for 10 minutes. Palladium on activated charcoal (14.8 mg, 10% w/w) was added to the reaction vial. A balloon of hydrogen was fitted over the vial and the reaction was stirred for 2 hours. The mixture was filtered through Celite, washed with methanol, and concentrated *in vacuo*. The crude residue was purified by C18 chromatography to afford **63** (6.2 mg, 45% yield) as a white solid.

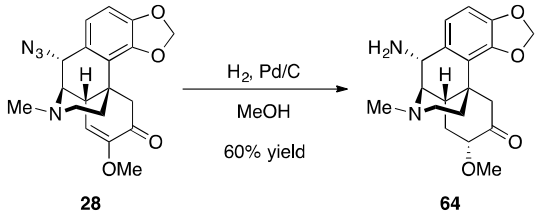
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.87 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.93–5.90 (m, 1H), 5.92 (d, *J* = 1.1 Hz, 1H), 5.88 (d, *J* = 1.0 Hz, 1H), 4.14 (s, 1H), 3.61 (d, *J* = 6.1 Hz, 2H), 3.55 (s, 3H), 3.16 (s, 1H), 2.87 (dd, *J* = 5.4, 2.7 Hz, 1H), 2.52 (dd, *J* = 12.2, 4.1 Hz, 1H), 2.47 (s, 3H), 2.04 (td, *J* = 12.3, 3.1 Hz, 1H), 1.92 (td, *J* = 12.4, 4.5 Hz, 1H), 1.51–1.46 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.1, 148.1, 146.6, 144.4, 135.8, 121.9, 119.9, 108.4, 108.2, 100.8, 64.5, 55.6, 50.0, 47.4, 45.0, 43.2, 42.7, 35.0, 29.9.

HRMS(ESI): *m/z* calc. for $C_{19}H_{24}N_3O_4$ $[M+H]^+$: 358.1767, found: 358.1765.



Compound 64



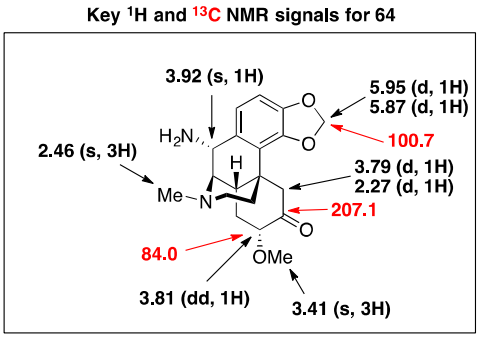
Procedure: In a vial with a stir bar, **28** (32.4 mg, 0.0880 mmol) was dissolved in methanol (10 mL) and purged with nitrogen for 10 minutes. Next, 10% palladium on activated charcoal (30.8 mg) was added to the reaction vial. A balloon of H_2 gas was fitted to the vial and the reaction was stirred for 2 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by C18 chromatography to afford **64** (18.1 mg, 60%) as a white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.90 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 5.95 (d, *J* = 1.5 Hz, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 3.92 (s, 1H), 3.81 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.41 (s, 3H), 2.94 (d, *J* = 2.8 Hz, 1H), 2.46 (s, 3H), 2.42 (ddd, *J* = 12.2, 4.8, 1.6

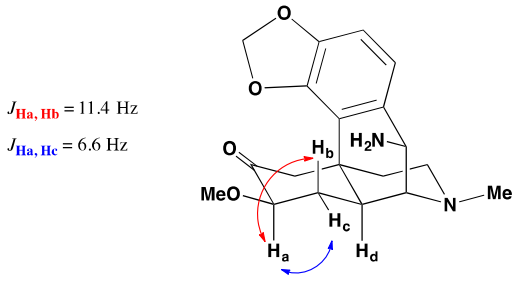
Hz, 1H), 2.34 (dt, *J* = 13.3, 2.9 Hz, 1H), 2.30–2.26 (m, 1H), 2.27 (d, *J* = 13.7 Hz, 1H), 1.97 (td, *J* = 12.3, 3.4 Hz, 1H), 1.81–1.75 (m, 1H), 1.80 (q, *J* = 12.4 Hz, 1H), 1.70 (dt, *J* = 12.8, 2.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.1, 147.1, 145.1, 135.8, 122.1, 119.2, 108.1, 100.7, 84.0, 66.2, 58.3, 48.8, 46.2, 43.9, 43.1, 43.0, 41.9, 39.5, 35.8.

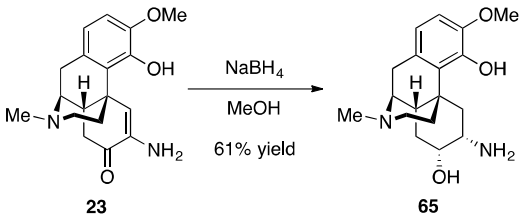
HRMS(ESI): *m/z* calc. for $C_{19}H_{25}N_2O_4$ $[M+H]^+$: 345.1814, found: 345.1811.



Determination of configuration for **64**:



Compound 65

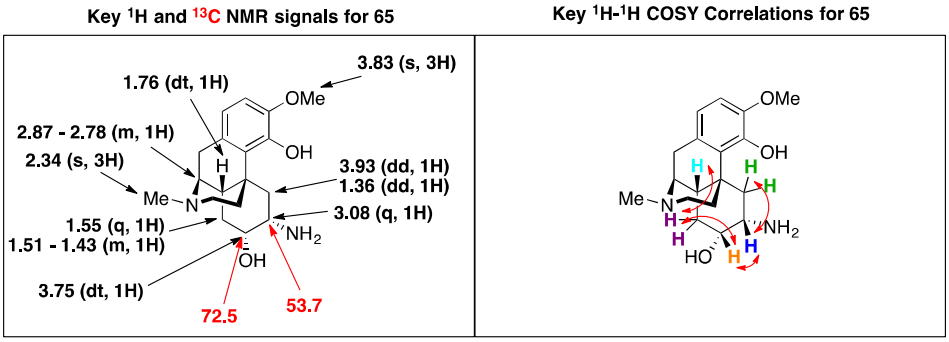


Procedure: In a round bottom flask with a stir bar, **23** (156.2 mg, 0.4968 mmol) was dissolved in methanol (10 mL). The reaction mixture was cooled to –78 ºC in an acetone/dry ice bath. Sodium borohydride (83.7 mg, 2.213 mmol) was added to the reaction mixture. After 1 hour, the reaction temperature was brought up to 0 ºC. After 1 hour, the reaction mixture was diluted with water and concentrated under reduced pressure. The crude mixture was passed through a layer of silica (9:1 dichloromethane/methanol with 1% triethylamine). The organic fractions were concentrated under reduced pressure. The residue was further purified by C18 chromatography to afford amino alcohol **65** (97.2 mg, 61% yield) as a white solid.

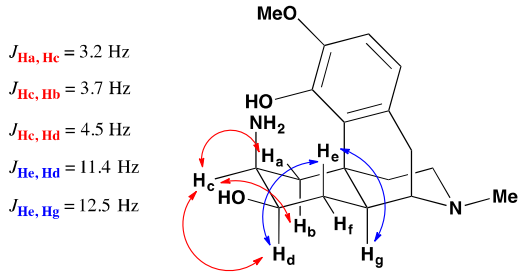
^{1}H NMR (CD_3OD, 500 MHz): δ 6.80 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 3.93 (dd, *J* = 14.6, 3.2 Hz, 1H), 3.83 (s, 3H), 3.75 (dt, *J* = 11.4, 4.5 Hz, 1H), 3.08 (q, *J* = 3.6 Hz, 1H), 2.96 (d, *J* = 17.3 Hz, 1H), 2.87–2.78 (m, 2H), 2.43 (ddd, *J* = 12.1, 4.7, 1.6 Hz, 1H), 2.34 (s, 3H), 1.99 (td, *J* = 12.4, 3.2 Hz, 1H), 1.93 (td, *J* = 13.0, 2.2 Hz, 1H), 1.76 (dt, *J* = 12.4, 2.7 Hz, 1H), 1.55 (q, *J* = 12.4 Hz, 1H), 1.51–1.43 (m, 2H), 1.36 (dd, *J* = 14.6, 3.7 Hz, 1H).

^{13}C NMR (CD_3OD, 125 MHz): δ 147.3, 146.7, 131.3, 126.5, 120.2, 111.0, 72.5, 59.0, 56.8, 53.7, 48.4, 45.6, 42.6, 38.9, 38.6, 36.0, 30.9, 25.2.

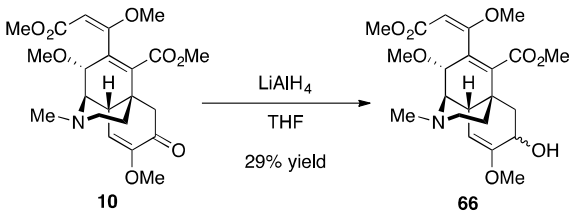
HRMS(ESI): *m/z* calc. for $C_{18}H_{27}N_2O_3$ $[M+H]^+$: 319.2022, found: 319.2008.



Determination of configuration for **65**:



Compound 66



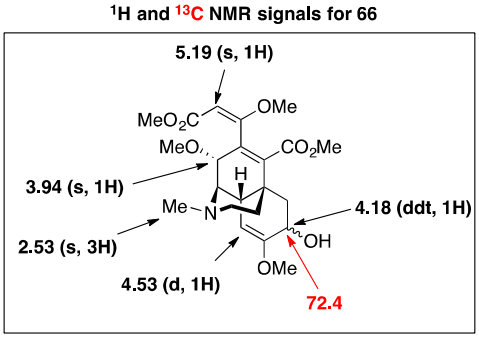
Procedure: In an oven dried round-bottom flask with a stir bar, **10** (19.1 mg, 0.0439 mmol) was dissolved in tetrahydrofuran (6 mL). The contents of the flask were placed on an ice bath and under N_2 atmosphere. After 10 min, lithium aluminum hydride (28.8 mg, 0.7589 mmol) was slowly added to the flask and was allowed to stir at 0 ºC for 1 hour. The reaction was quenched with water and 10% NaOH, placed in an Erlenmeyer flask, and was diluted with ethyl acetate.

Next, sodium sulfate was added to the Erlenmeyer flask to take up any water. The contents were decanted into a round bottom flask and were concentrated *in vacuo*. The crude residue was purified by flash chromatography (15:1 dicloromethane/methanol) on silica gel to afford **66** (5.6 mg, 29% yield) as a tan solid. Compound **66** was isolated as a single diastereomer.

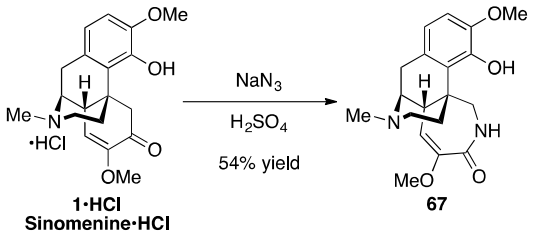
^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.19 (s, 1H), 4.53 (d, *J* = 1.3 Hz, 1H), 4.18 (ddt, *J* = 12.2, 8.6, 4.4 Hz, 1H), 3.94 (s, 1H), 3.68 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 3.51 (s, 3H), 3.35 (s, 3H), 3.06 (d, *J* = 3.2 Hz, 1H), 2.69–2.66 (m, 1H), 2.58 (dd, J = 11.9, 4.7 Hz, 1H), 2.53 (s, 3H), 2.51–2.46 (m, 1H), 2.40 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.14–2.09 (m, 1H), 1.72–1.57 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 168.1, 153.5, 141.0, 134.9, 101.2, 97.3, 94.0, 72.4, 66.0, 61.4, 58.9, 56.5, 54.7, 51.9, 51.1, 46.7, 42.8, 42.4, 40.9, 38.1, 36.1.

HRMS(ESI): *m/z* calc. for $C_{22}H_{32}NO_8$ $[M+H]^+$: 438.2128, found: 438.2123.



Compound 67



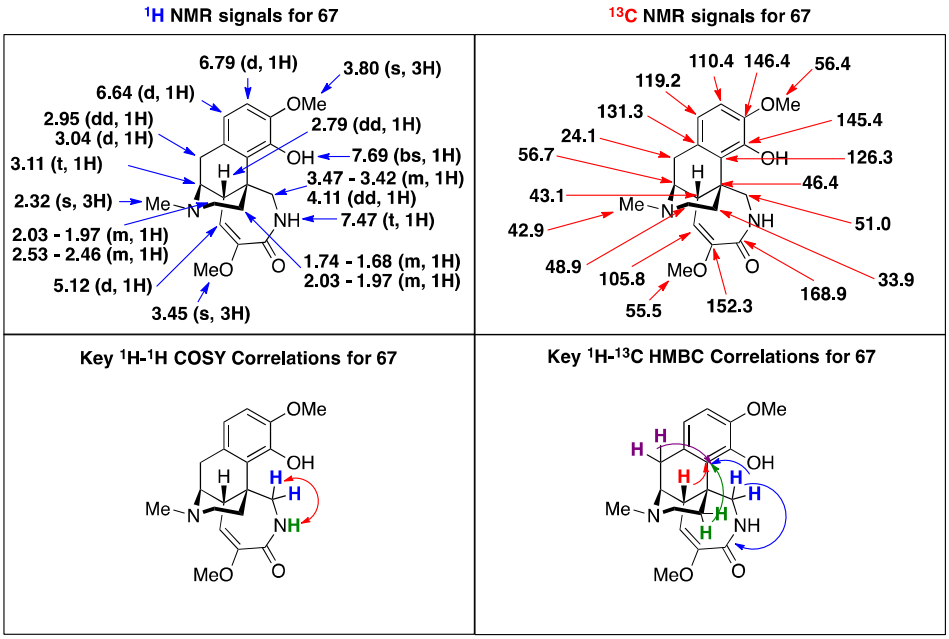
Procedure: In a vial with a stir bar, **1•HCl** (533.4 mg, 1.458 mmol) and sodium azide (454.0 mg, 6.985 mmol) were suspended in 1:1 sulfuric acid/water and were cooled to 0 ºC in an ice bath. After 5 min, the reaction was stirred at room temperature for 6 hours. The reaction was poured into a seperatory funnel containing ice water and was basified with concentrated ammonium hydroxide. An extraction with dichloromethane (5x) was performed. The organic layers were combined, dried over sodium sulfate, and were concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 dichloromethane/methanol) on silica gel to produce lactam **67** (274.1 mg, 54% yield) as a white solid.

^{1}H NMR (d_6-acetone, 500 MHz) δ 7.69 (bs, 1H), 7.47 (t, *J* = 5.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 5.12 (d, *J* = 6.5 Hz, 1H), 4.11 (dd, *J* = 14.5, 7.1 Hz, 1H), 3.80 (s, 3H), 3.45 (s, 3H), 3.47–3.42 (m, 1H), 3.11 (t, *J* = 4.3 Hz, 1H), 3.04 (d, *J* = 18.3 Hz, 1H), 2.95

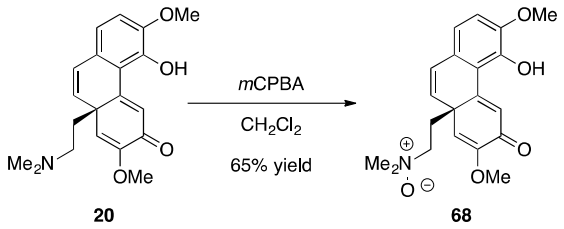
(dd, J = 18.3, 5.4 Hz, 1H), 2.79 (dd, J = 6.4, 3.4 Hz, 1H), 2.53–2.46 (m, 1H), 2.32 (s, 3H), 2.03–1.97 (m, 2H), 1.74–1.68 (m, 1H).

^{13}C NMR (d_6-acetone, 125 MHz): δ 168.9, 152.3, 146.4, 145.4, 131.3, 126.3, 119.2, 110.4, 105.8, 56.7, 56.4, 55.5, 51.0, 48.9, 46.4, 43.1, 42.9, 33.9, 24.1.

HRMS(ESI): *m/z* calc. for $C_{19}H_{25}N_2O_4$ $[M+H]^+$: 345.1814, found: 345.1808.



Compound 68



Procedure: In a vial with a stir bar, **20** (141.9 mg, 0.4156 mmol) was dissolved in dichloromethane (8 mL), capped under nitrogen, and was allowed to cool to 0 ºC in an ice/water bath. After 10 minutes, *m*-chloroperbenzoic acid (126.2 mg, 0.5486 mmol) was added to the vial and stirred at room temperature for 1.5 hours. After this time the dichloromethane was evaporated under reduced pressure. The mixture was immediately purified by column chromatography (9:1 dichloromethane/methanol with 2% triethylamine) on silica gel to afford *N*-oxide **68** (96.2 mg, 65% yield) as an orange solid.

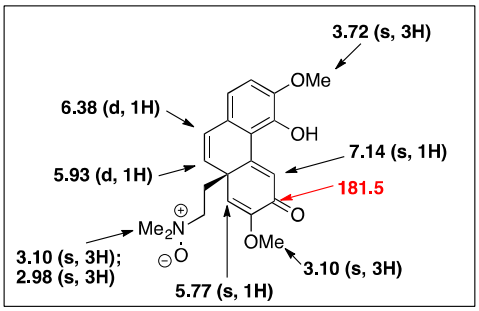
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.14 (s, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 6.38 (d, J = 9.2 Hz, 1H), 5.93 (d, J = 9.2 Hz, 1H), 5.77 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.10 (s, 3H), 3.06–2.97 (m, 2H), 2.98 (s, 3H), 2.51 (ddd, J = 13.0, 10.5, 5.5 Hz, 1H), 2.20 (ddd, J = 13.3,

11.2, 4.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 181.5, 157.3, 151.6, 149.3, 146.6, 130.6, 128.8, 127.1, 126.4, 117.6, 117.0, 116.6, 111.7, 65.9, 58.2, 57.6, 55.6, 55.0, 45.1, 34.5.

HRMS(ESI): *m/z* calc. for $C_{20}H_{24}NO_5$ $[M+H]^+$: 358.1654, found: 358.1648.

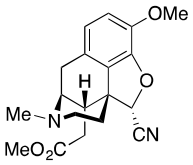
Key ^{1}H and ^{13}C NMR signals for 68



7. References:

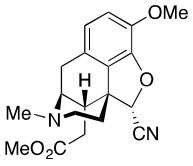
(1) Kuenemann, M. A.; Bourbon L. M. L.; Labbe C. M.; Villoutreix B. O.; Sperandio, O. *J. Chem. Inf. Model.* **2014**, *54*, 3067–3079.
(2) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756.
(3) Todeschini, R.; Consonni, V. *Molecular Descriptors for Chemoinformatics*, Vol. 41; John Wiley & Sons: Hoboken, 2009.
(4) Lou. Y.-T.; Ma, L.-Y.; Wang, M.; Yin, D.; Zhou, T.-T.; Chen, A.-Z.; Ma, Z.; Bian, C.; Wang, S.; Yang, Z.-Y.; Sun, B.; Yao, Z.-J. *Tetrahedron*. **2012**, *68*, 2172–2178.
(5) Teng, P.; Liu, H.-L.; Deng, Z.-S.; Shi, Z.-B.; He, Y.-M.; Feng, L.-L.; Xu, Q.; Li, J.-X. *Bioorg. Med. Chem.* **2011**, *19*, 3096–3104.
(6) He, L.; Zhang, Y.-H.; Guan, H.-Y.; Zhang, J.-X.; Sun, Q.-Y.; Hao, X.-J. *J. Nat. Prod.* **2011**, *74*, 181–184.
(7) Zhang, X.-L.; Zheng, H.-Z.; Jiang, N.-F. Chen, S.; Ouyang, L.-L. *J. Nat. Sci. Hunan Norman Univ*. **2011**. *4*, 59-63.

8. Spectral Data (NMR):



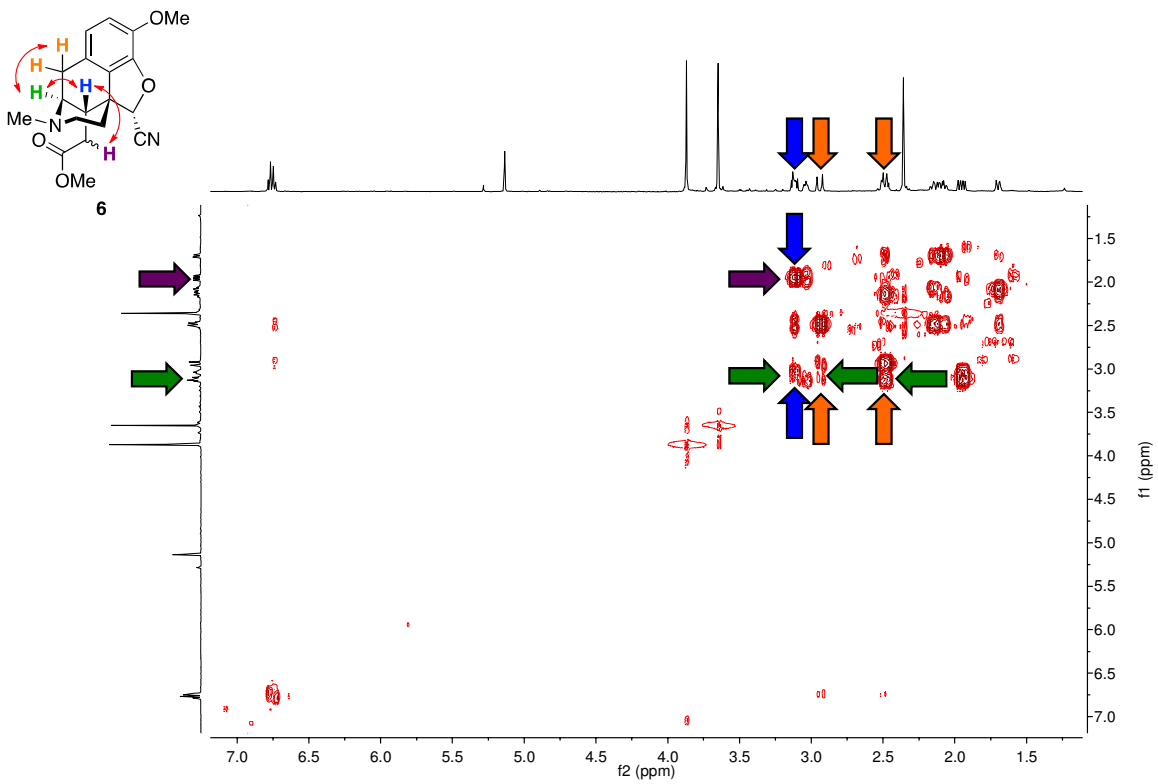
6

^{1}H NMR ($CDCl_3$)

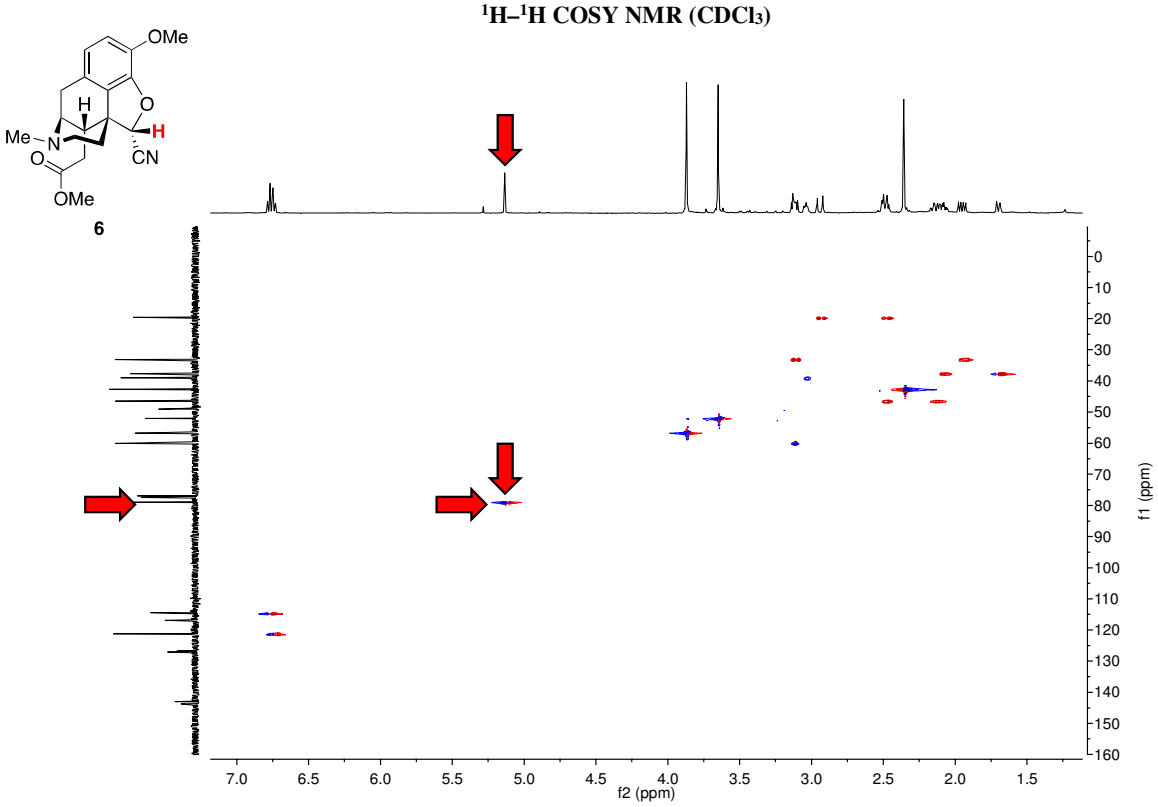


6

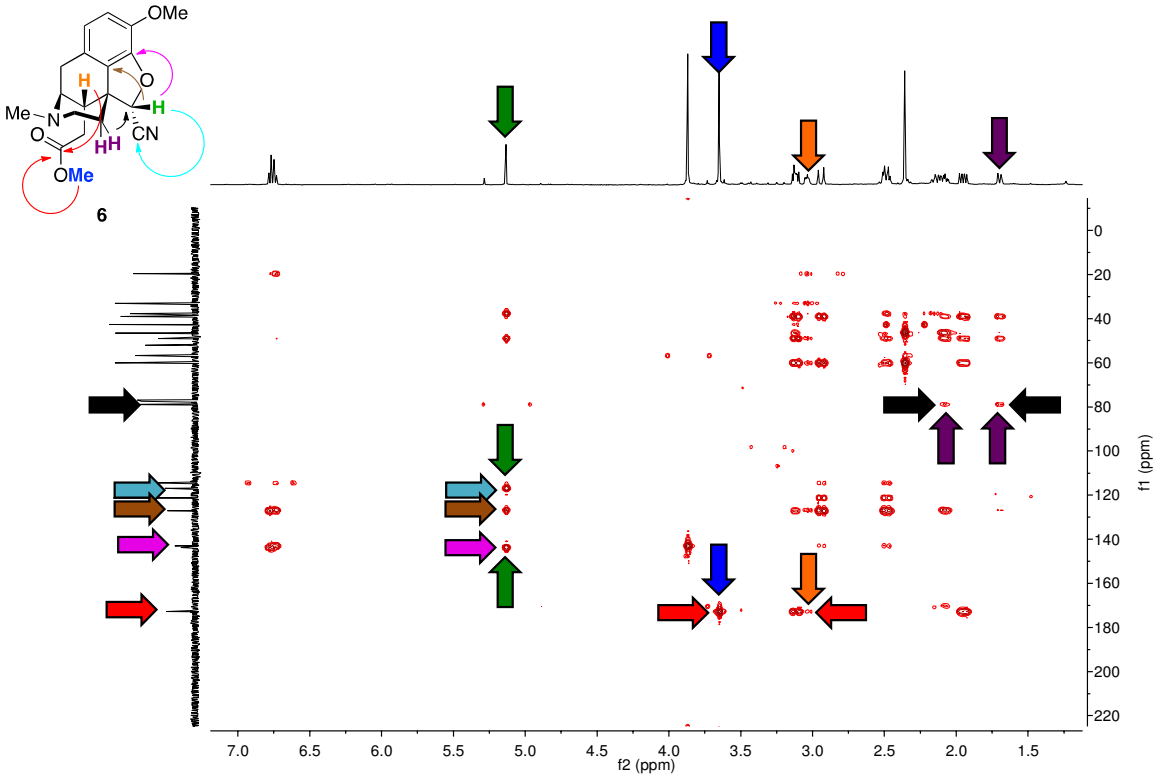
^{13}C NMR ($CDCl_3$)



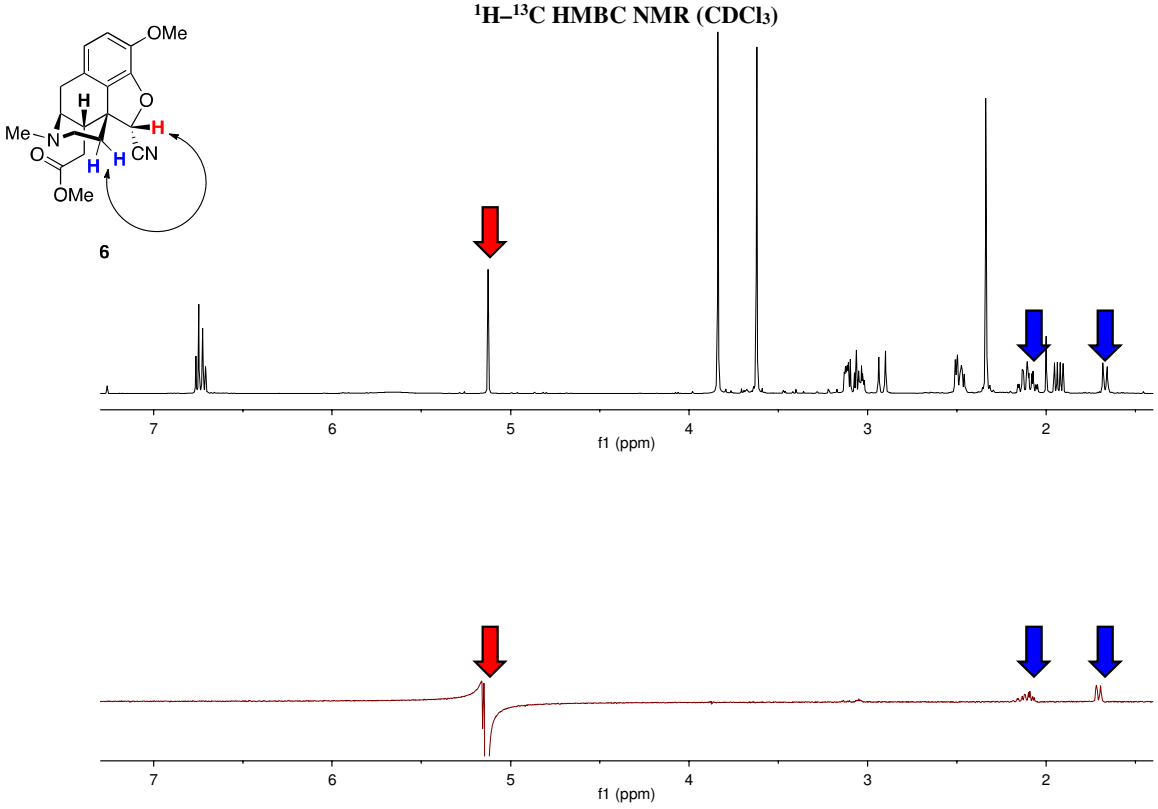
^{1}H–^{1}H COSY NMR ($CDCl_3$)



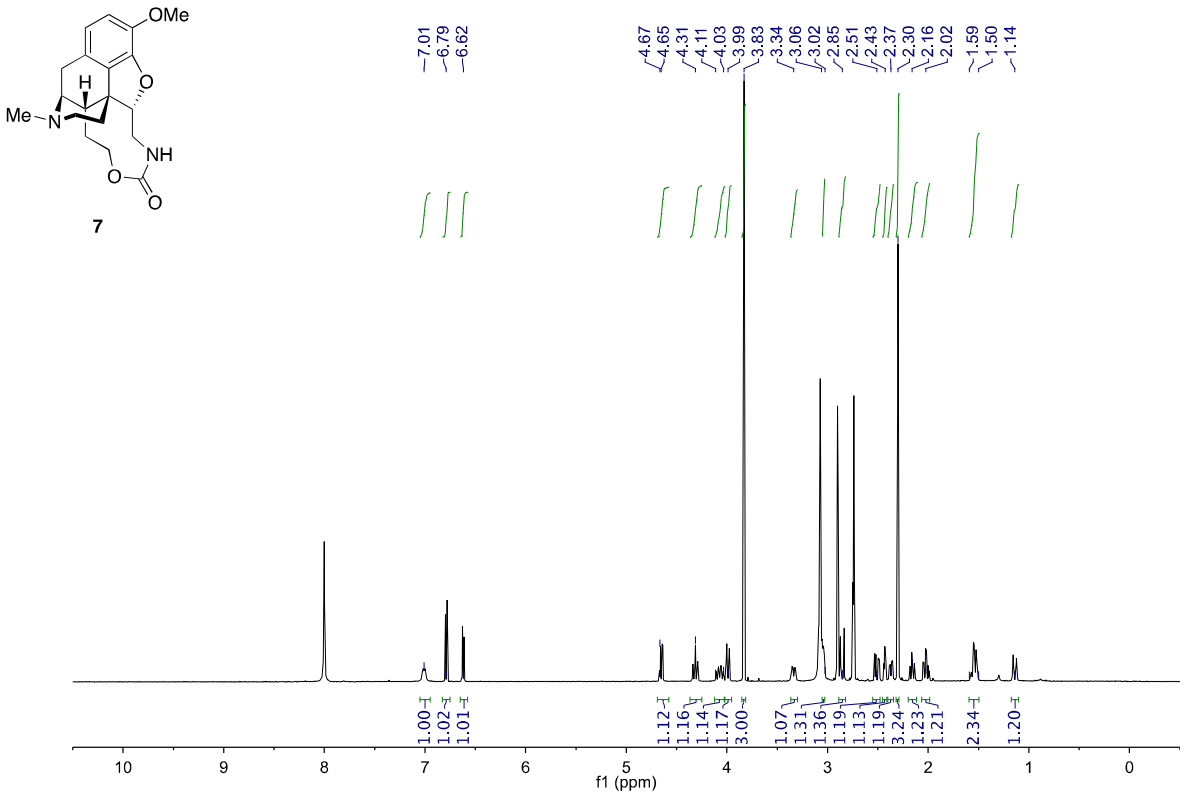
^{1}H–^{13}C HSQC NMR ($CDCl_3$)



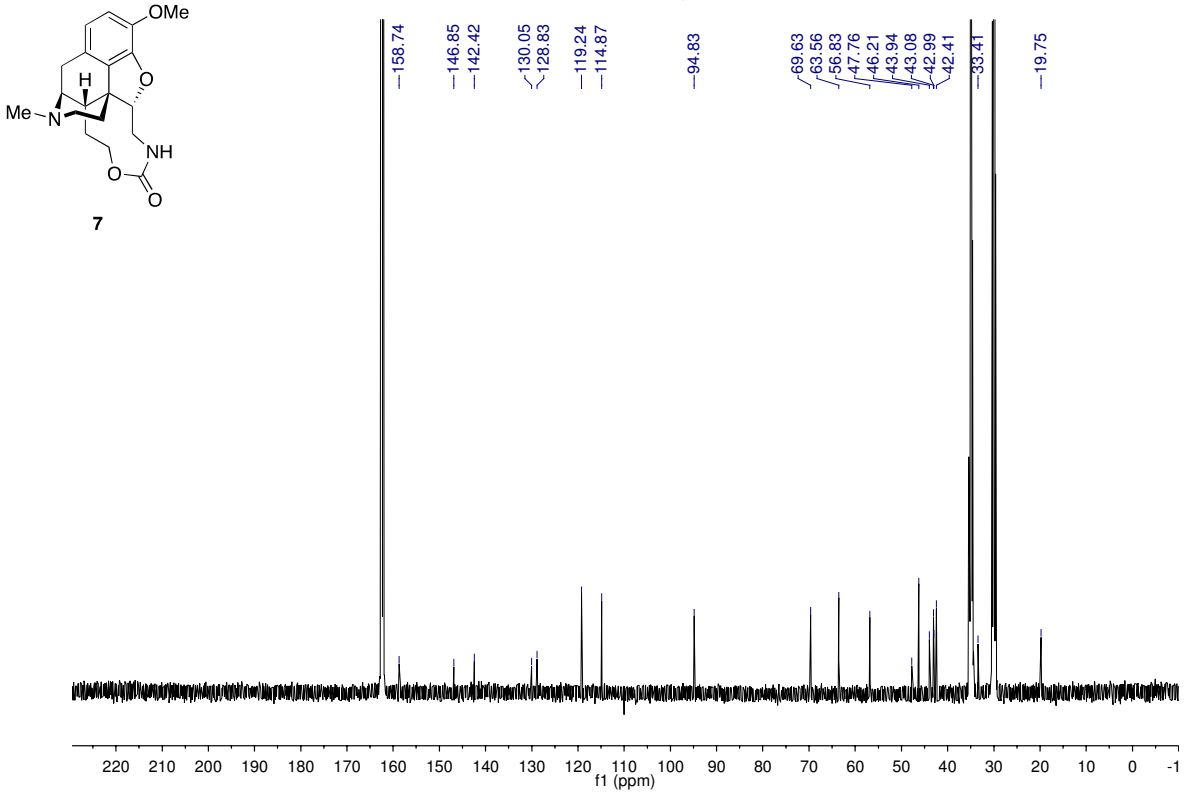
^{1}H–^{13}C HMBC NMR ($CDCl_3$)



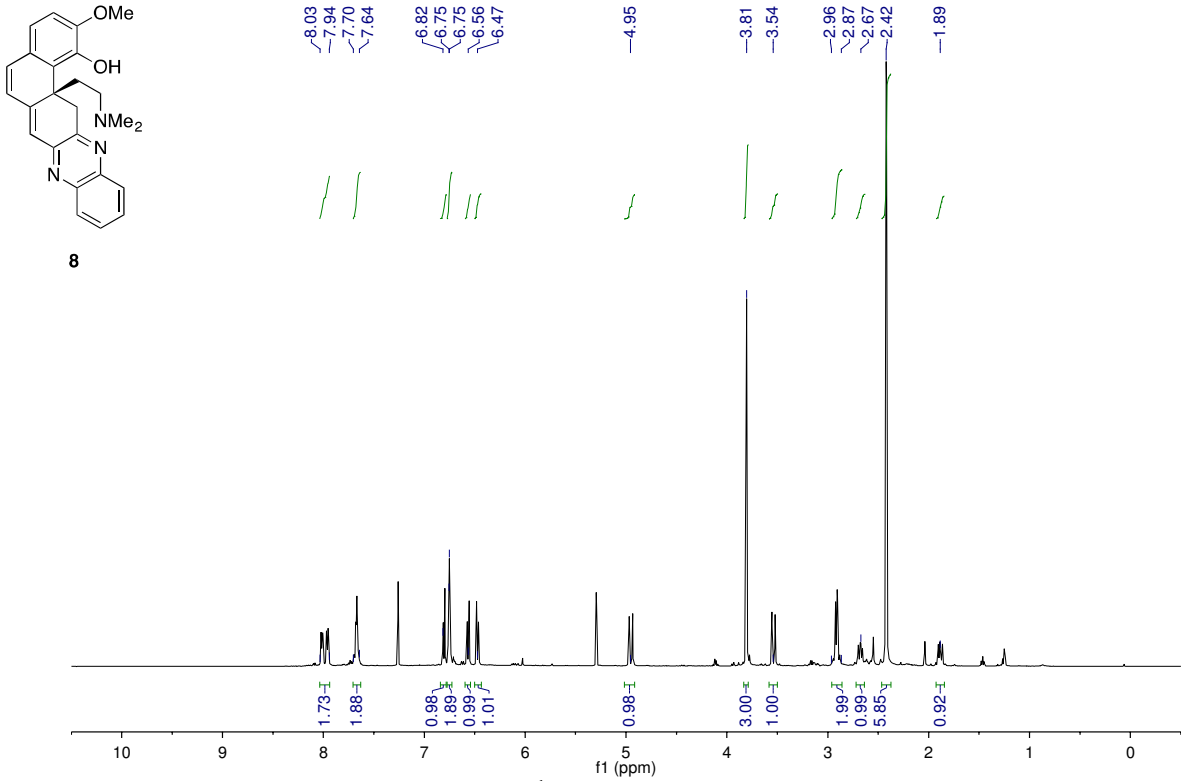
^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)



^{1}H NMR (*d*$_{7}$-DMF, 80 ºC)

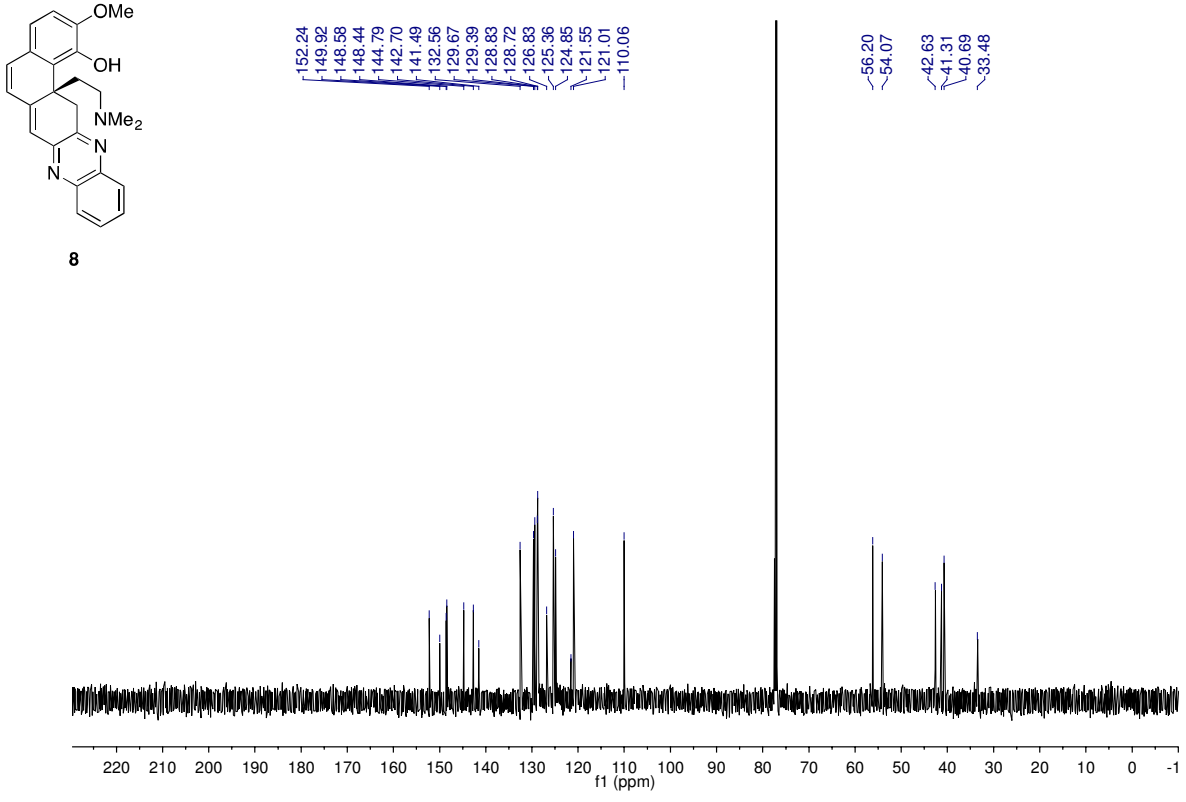


^{13}C NMR (*d*$_{7}$-DMF, 80 ºC)



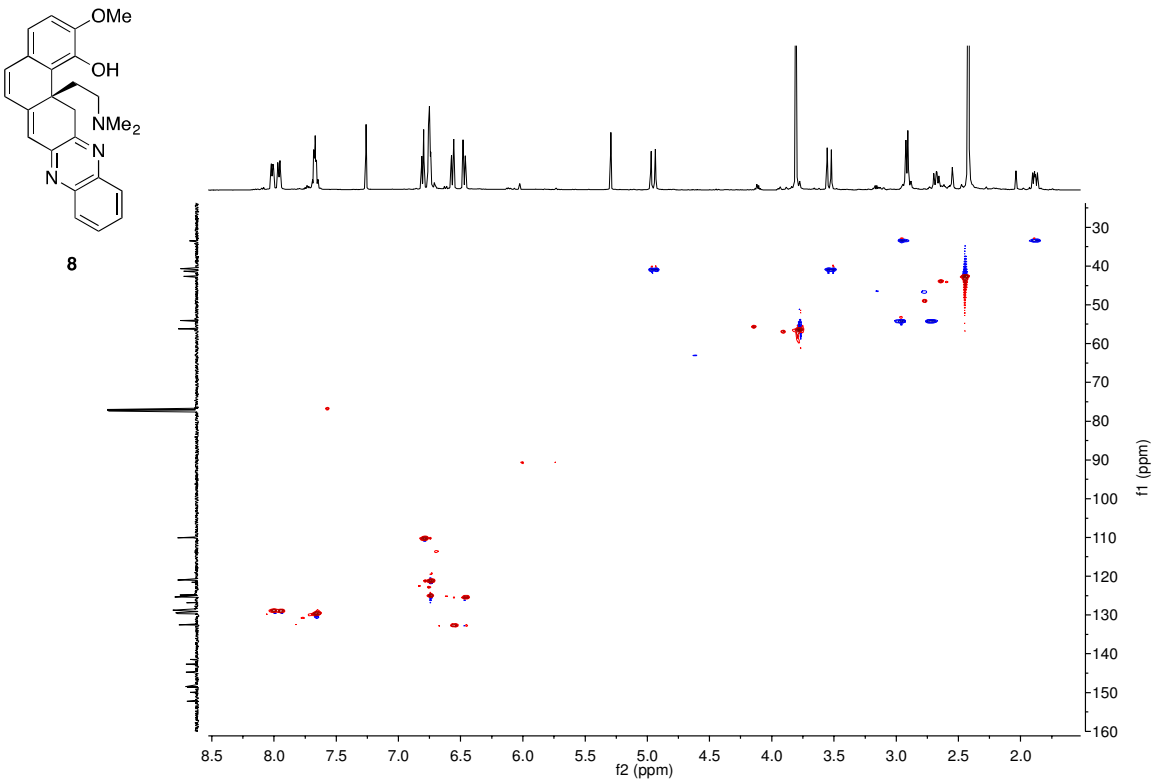
8

^{1}H NMR ($CDCl_3$)

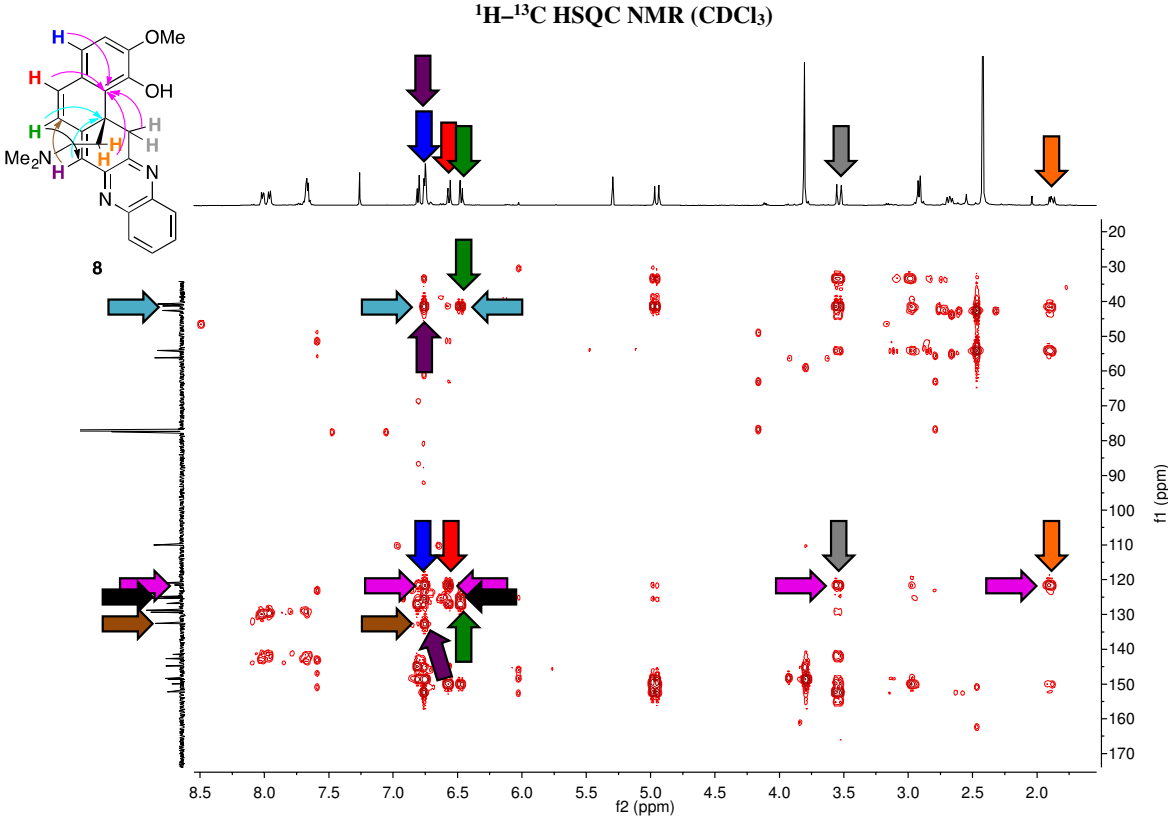


8

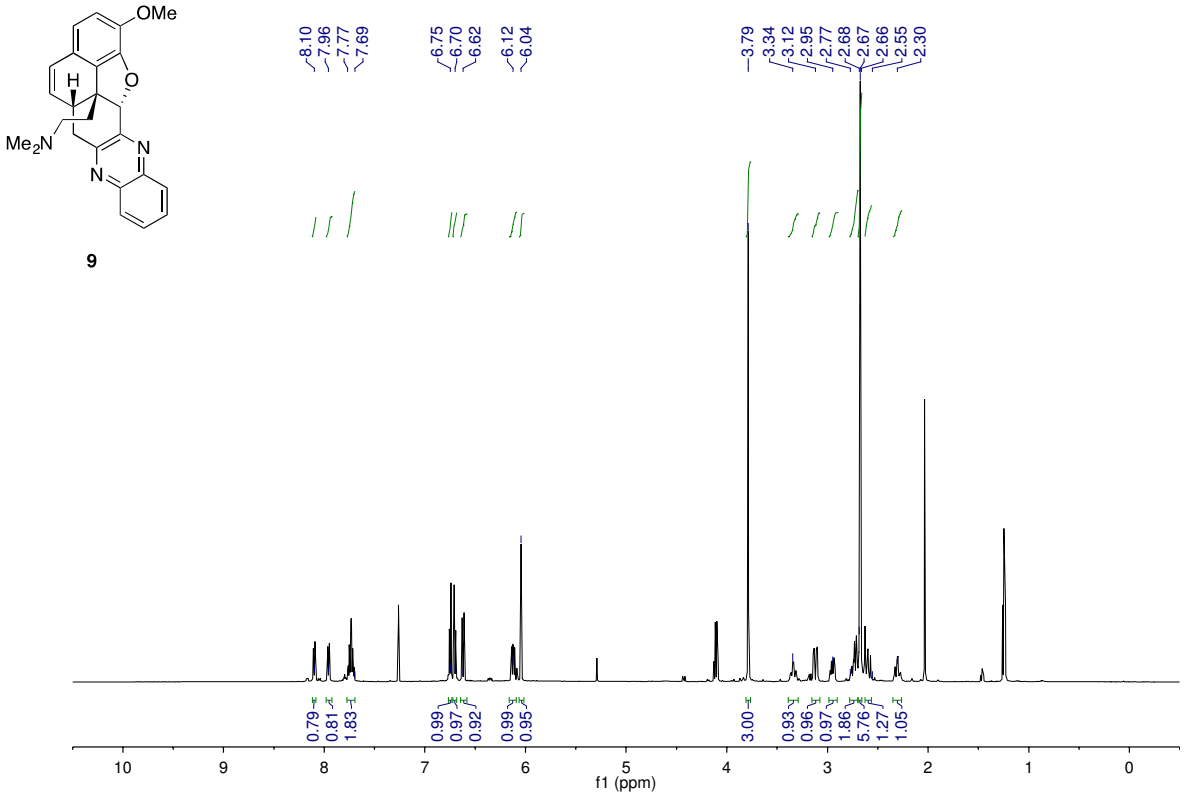
^{13}C NMR ($CDCl_3$)



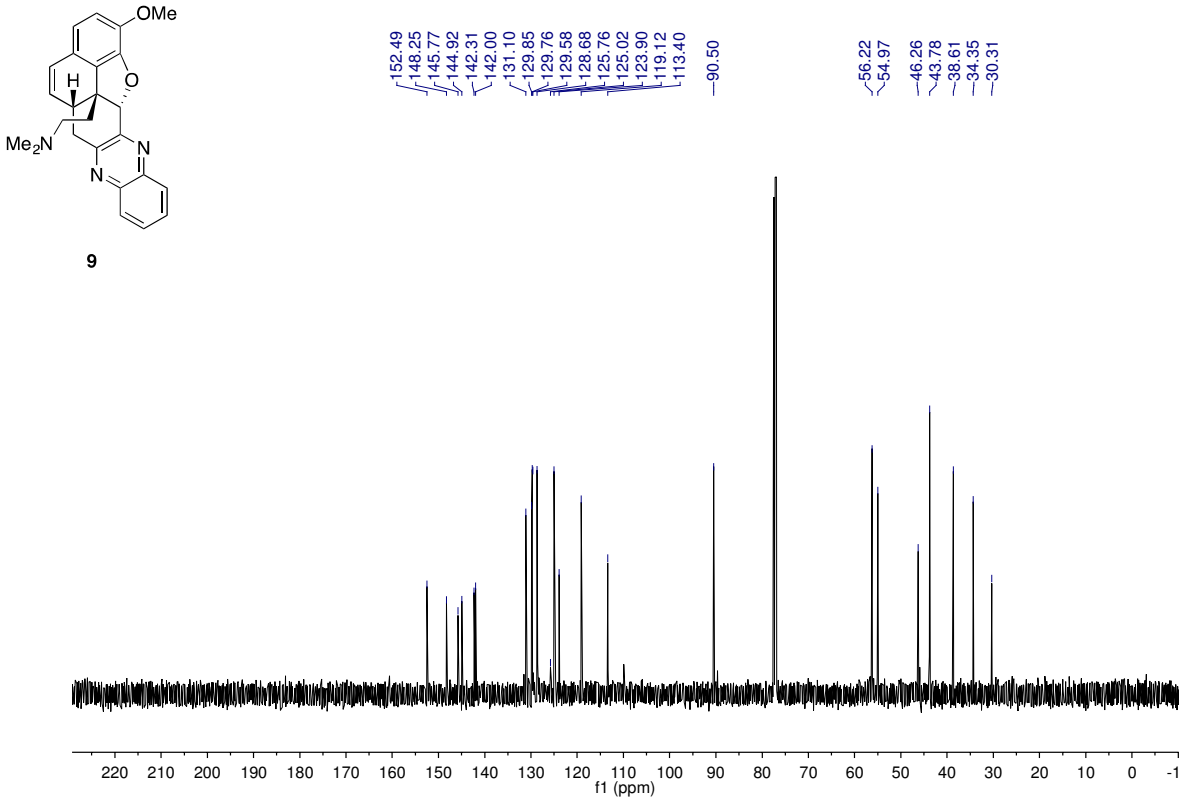
^{1}H–^{13}C HSQC NMR ($CDCl_3$)



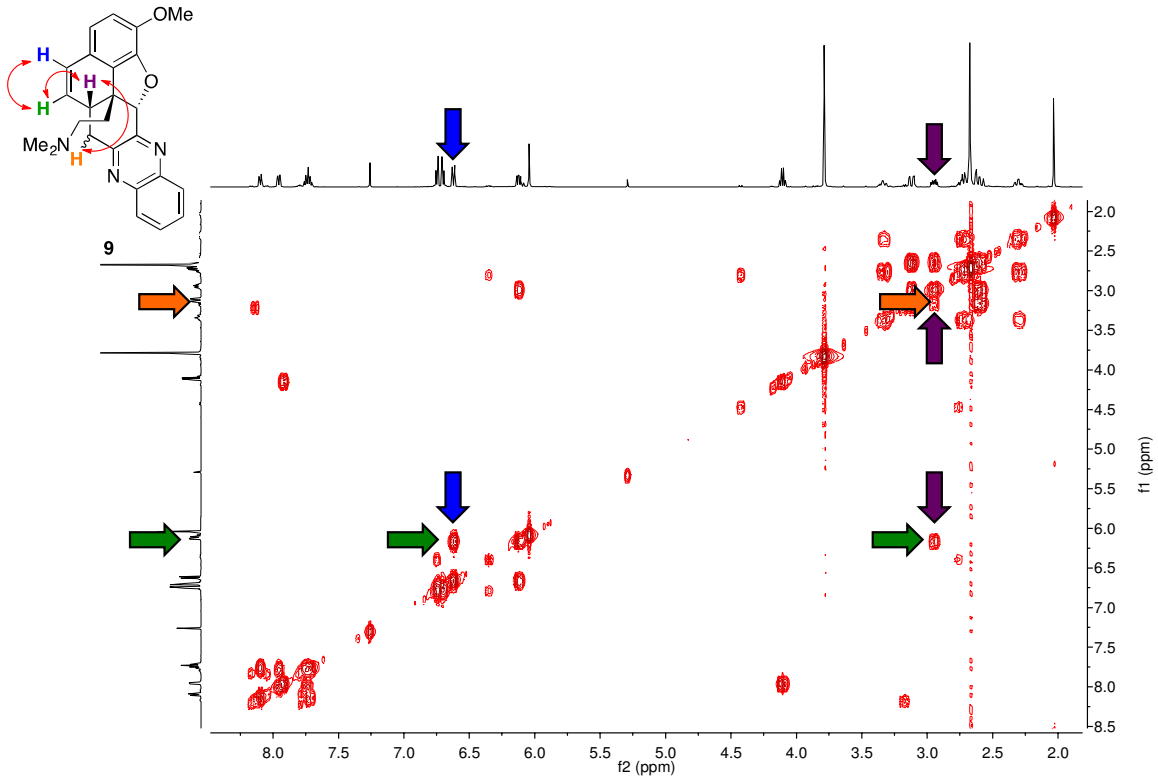
^{1}H–^{13}C HMBC NMR ($CDCl_3$)



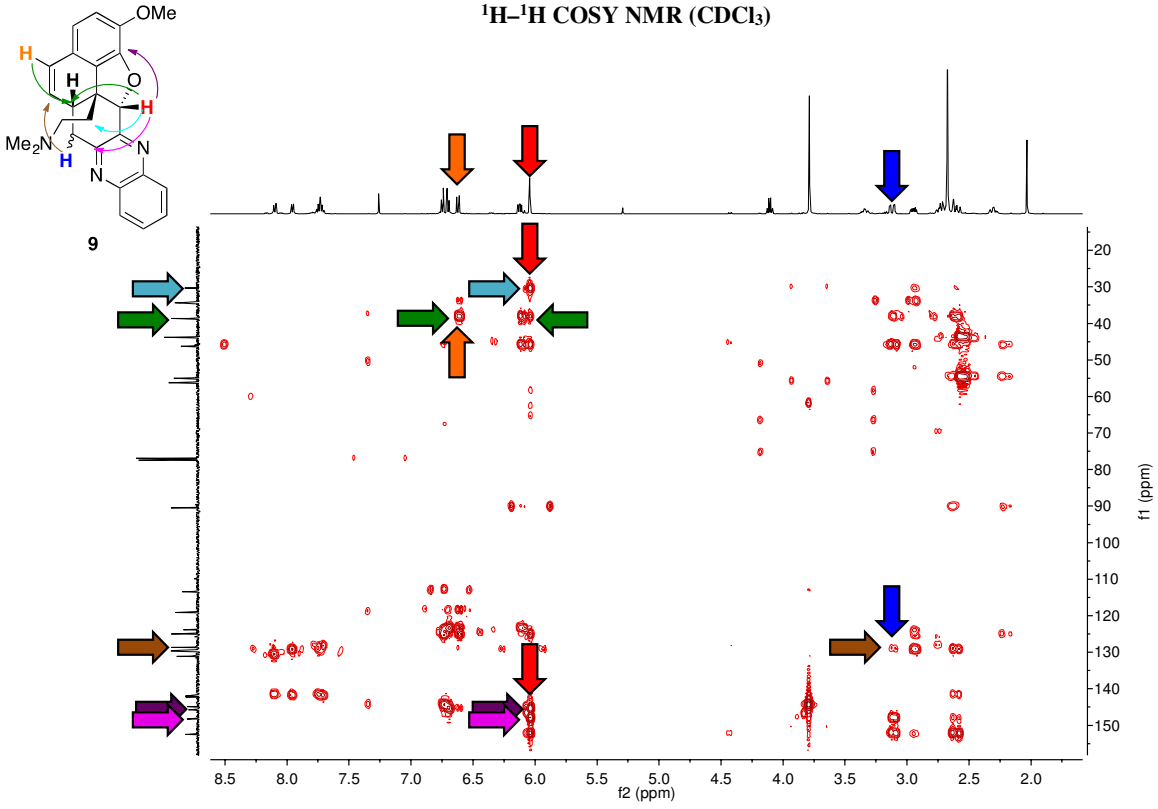
^{1}H NMR ($CDCl_3$)



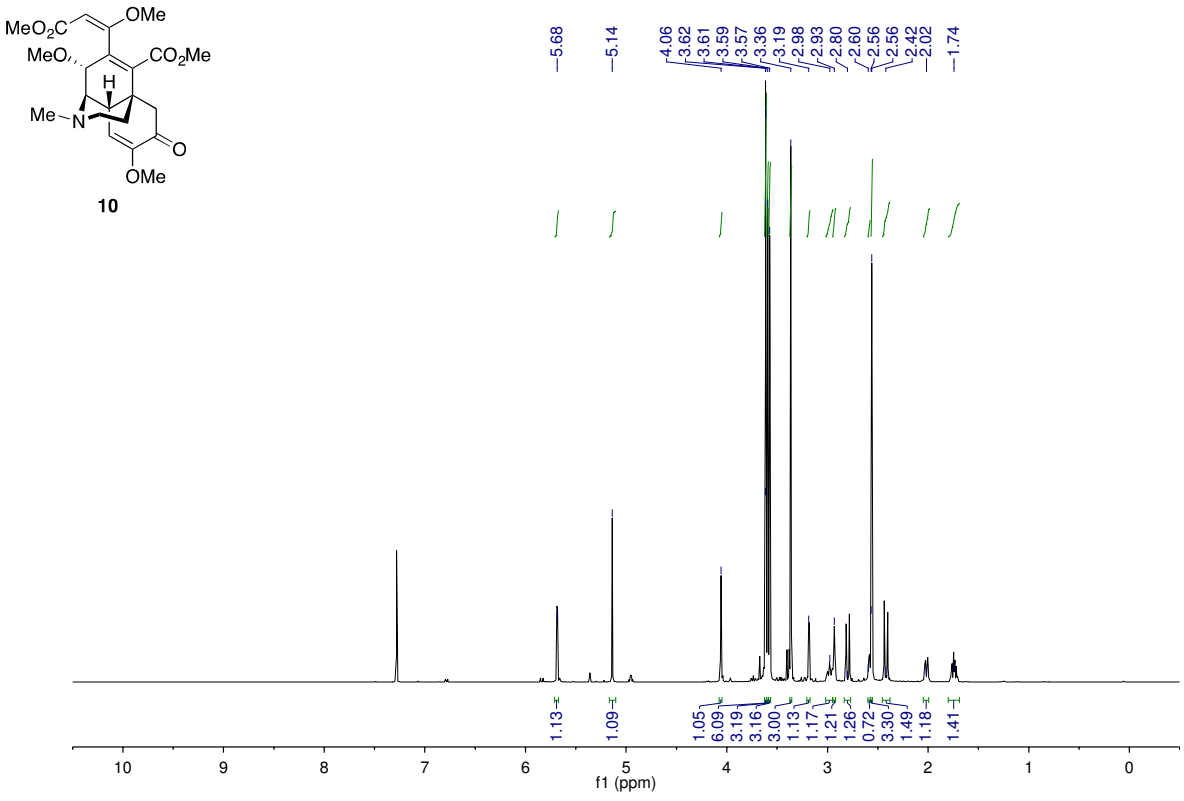
^{13}C NMR ($CDCl_3$)



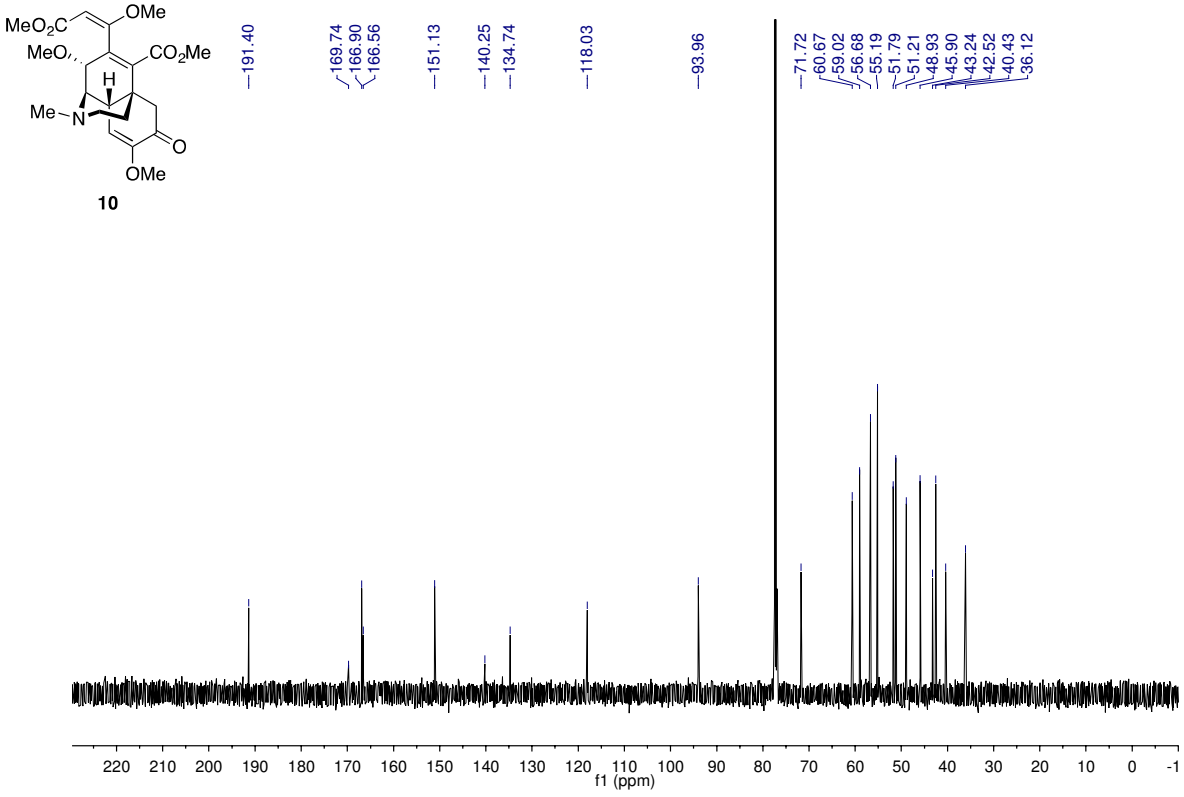
^{1}H–^{1}H COSY NMR ($CDCl_3$)



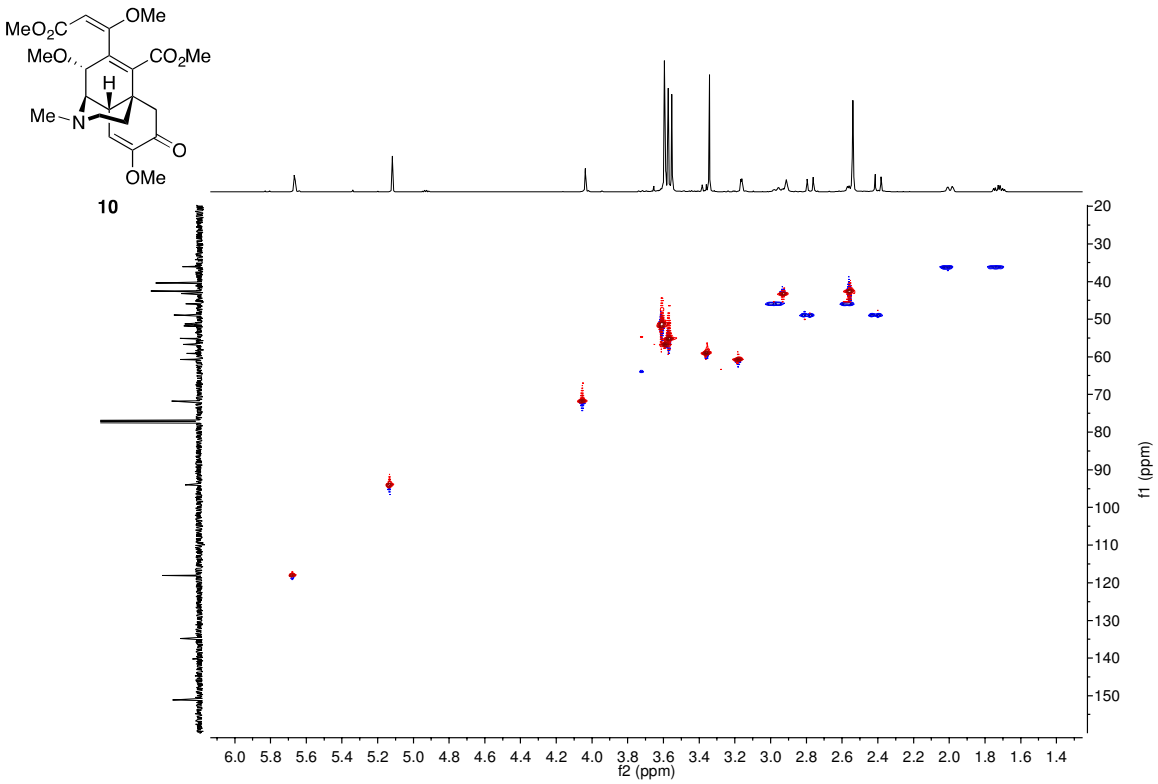
^{1}H–^{13}C HMBC NMR ($CDCl_3$)



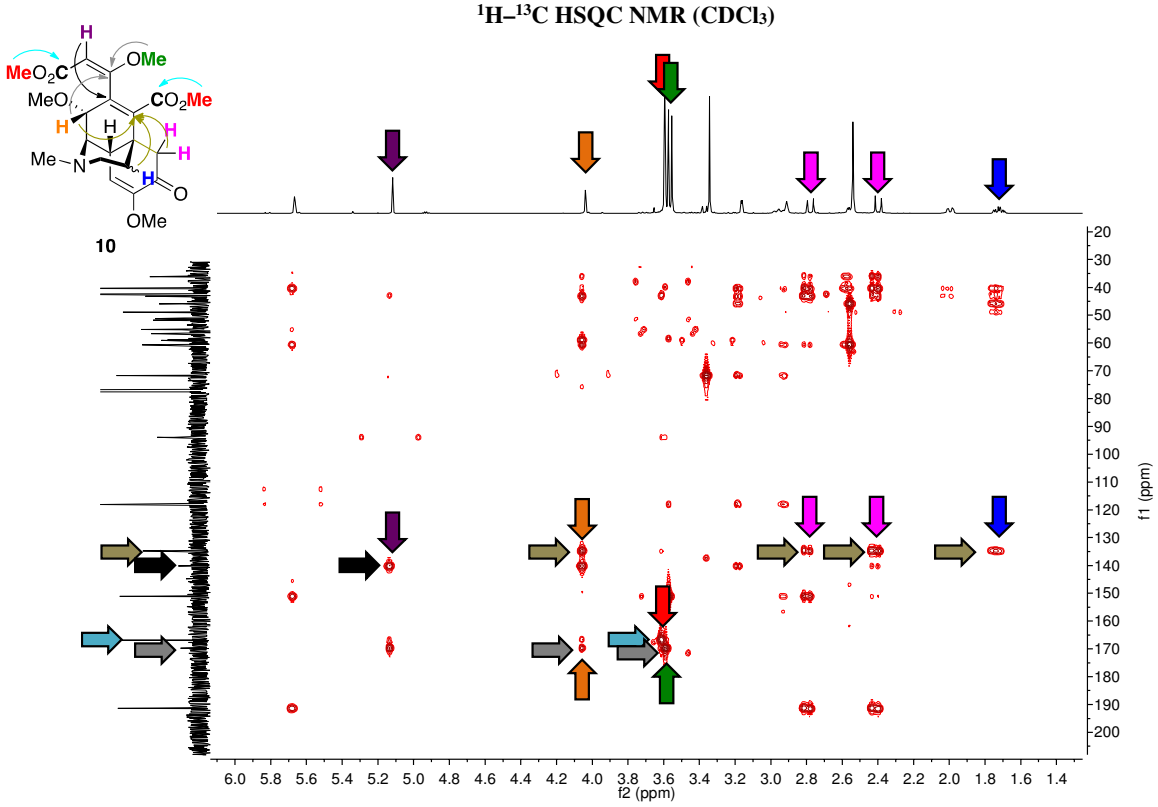
^{1}H NMR ($CDCl_3$)



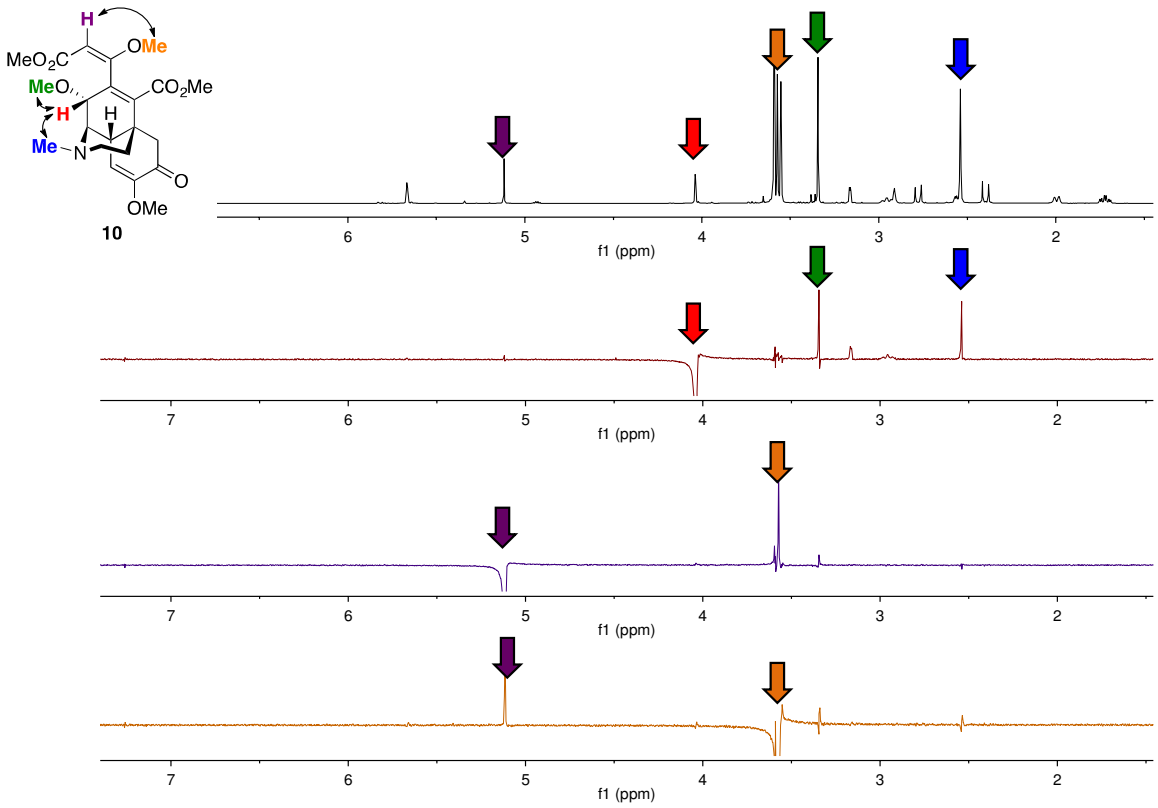
^{13}C NMR ($CDCl_3$)



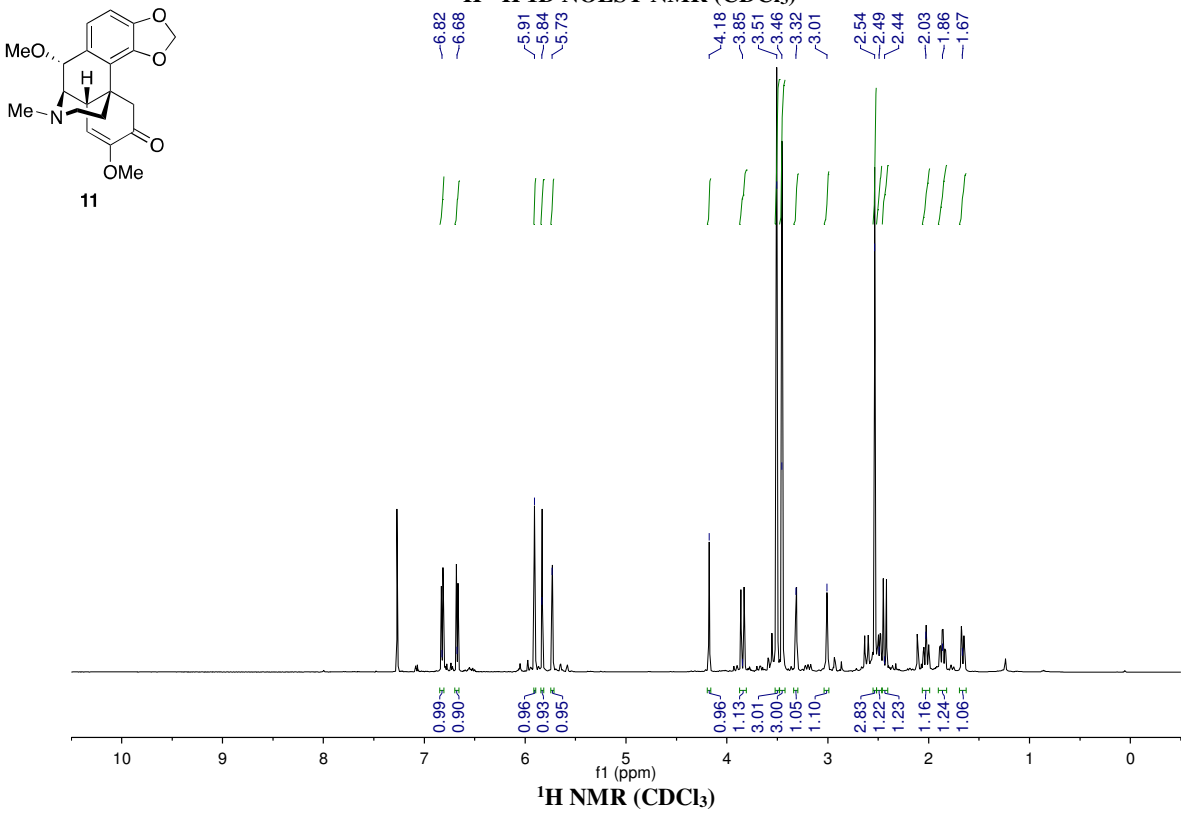
^{1}H–^{13}C HSQC NMR (CDCl$_3$)



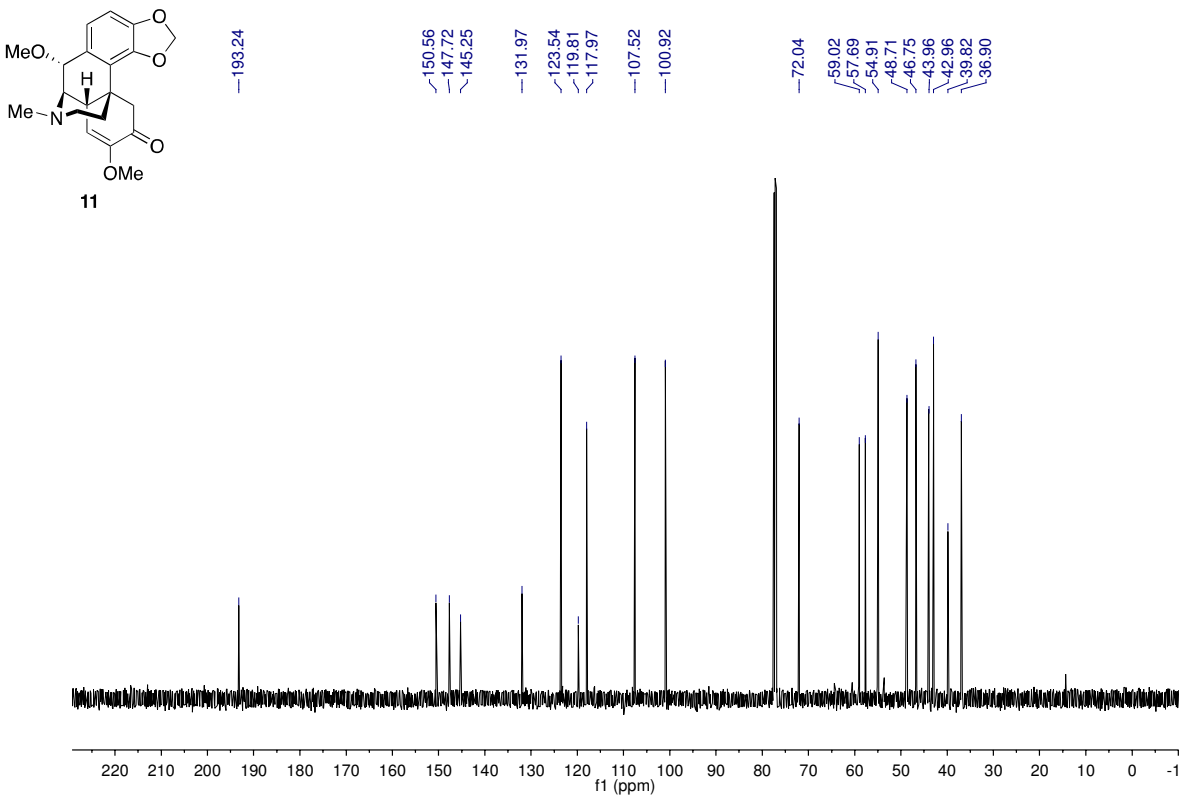
^{1}H – ^{13}C HMBC NMR (CDCl$_3$)



^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)

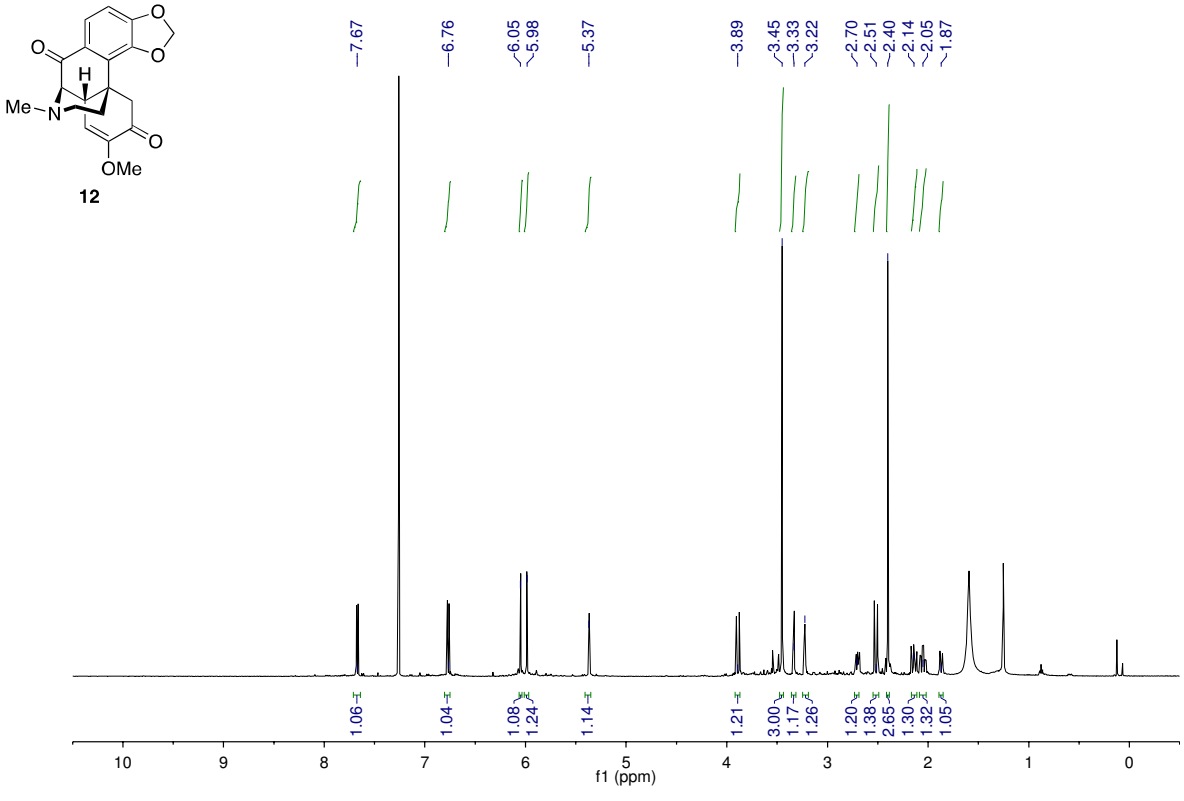


^{1}H NMR ($CDCl_3$)



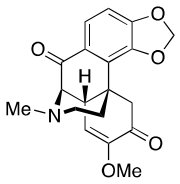
11

^{13}C NMR ($CDCl_3$)



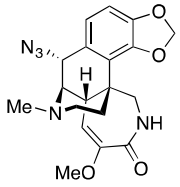
12

^{1}H NMR ($CDCl_3$)



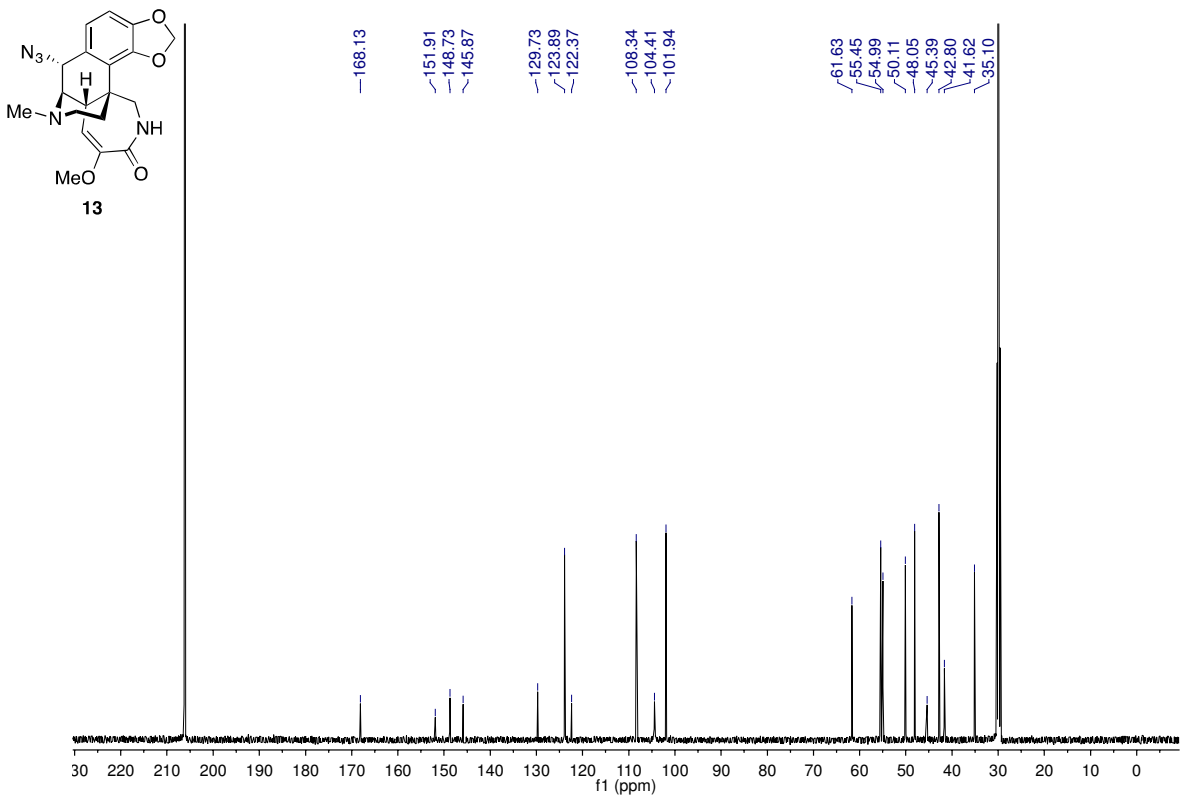
12

^{13}C NMR ($CDCl_3$)

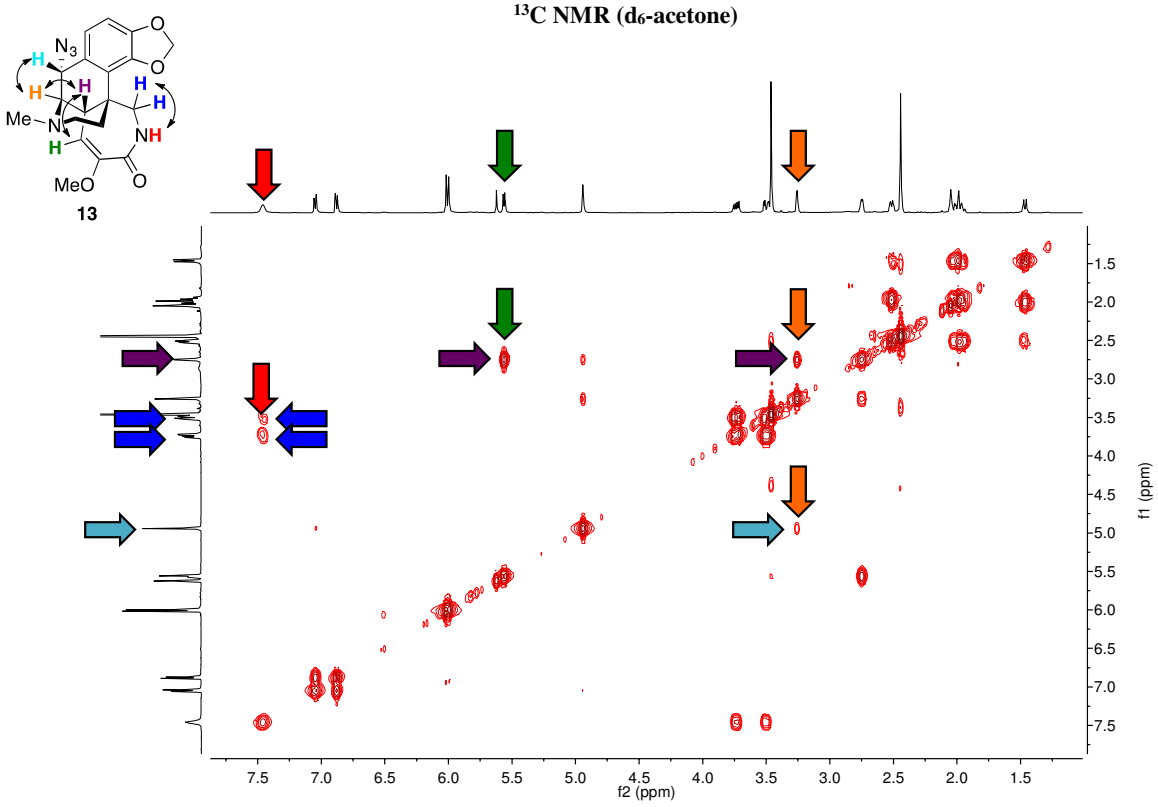


13

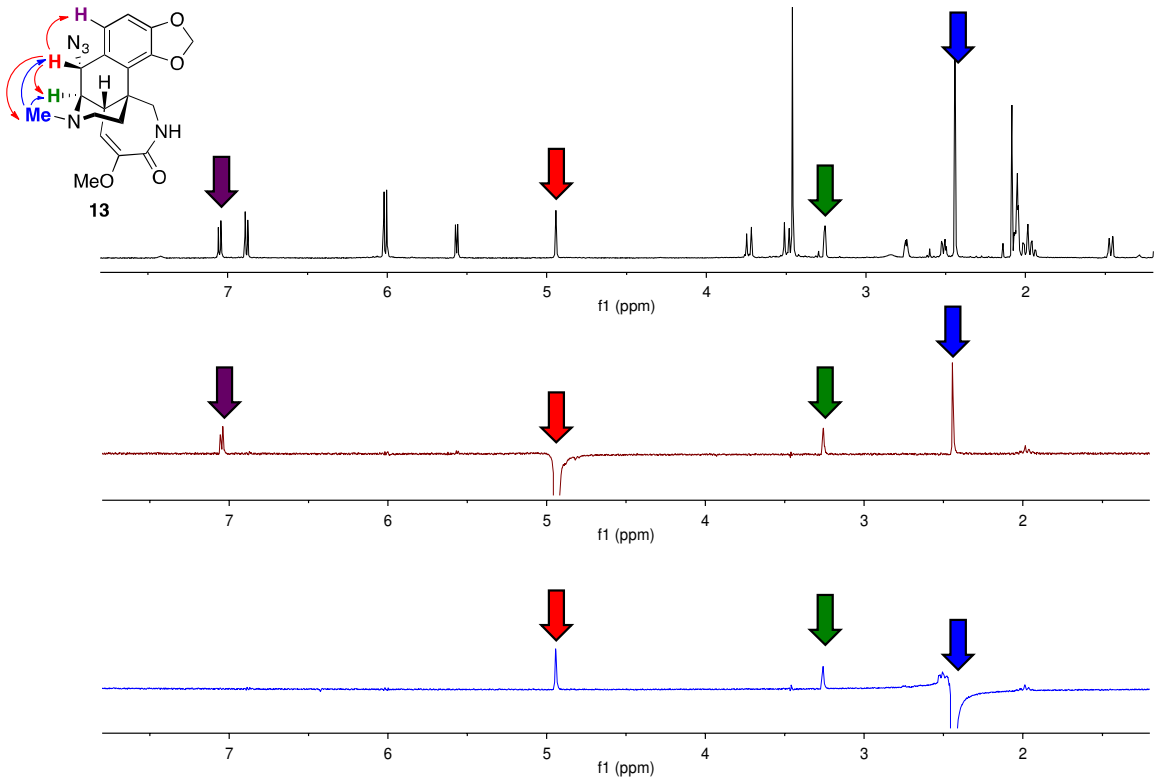
^{1}H NMR (d_6-acetone)



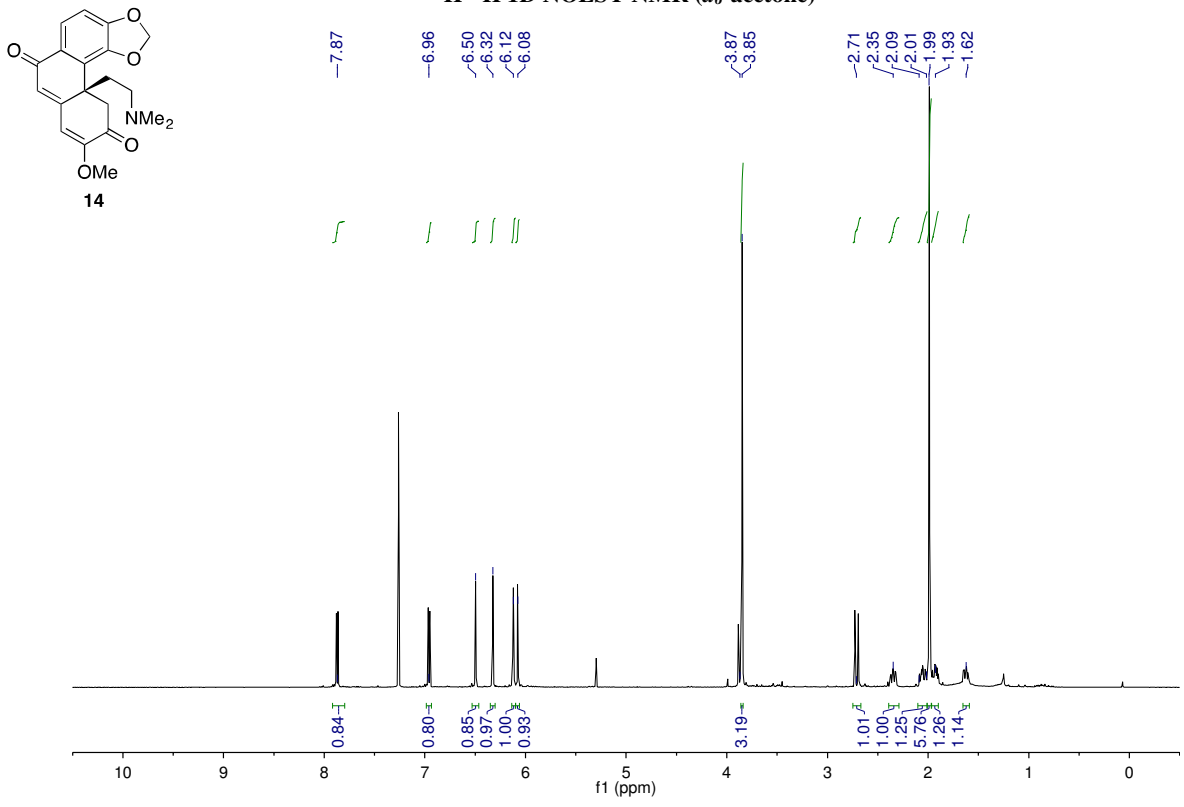
^{13}C NMR (d$_6$-acetone)



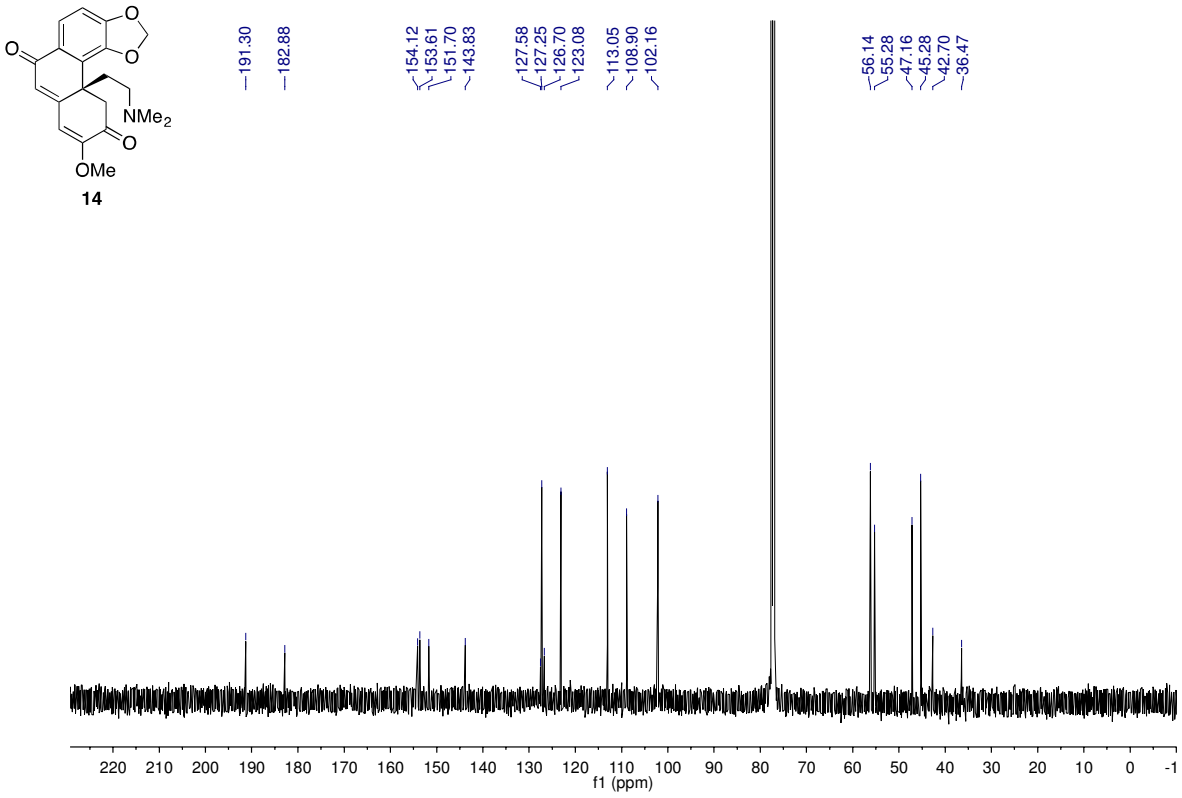
^{1}H – ^{1}H COSY NMR (*d*$_6$-acetone)



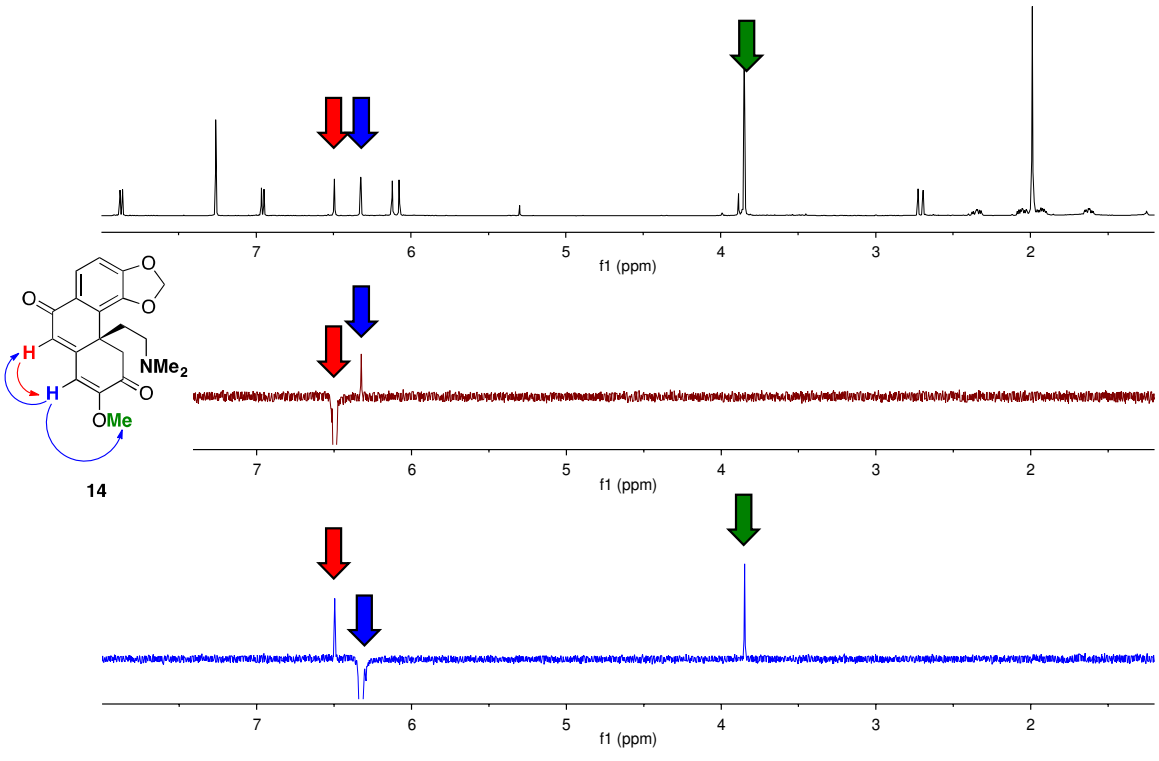
^{1}H–^{1}H 1D NOESY NMR (*d*$_6$-acetone)



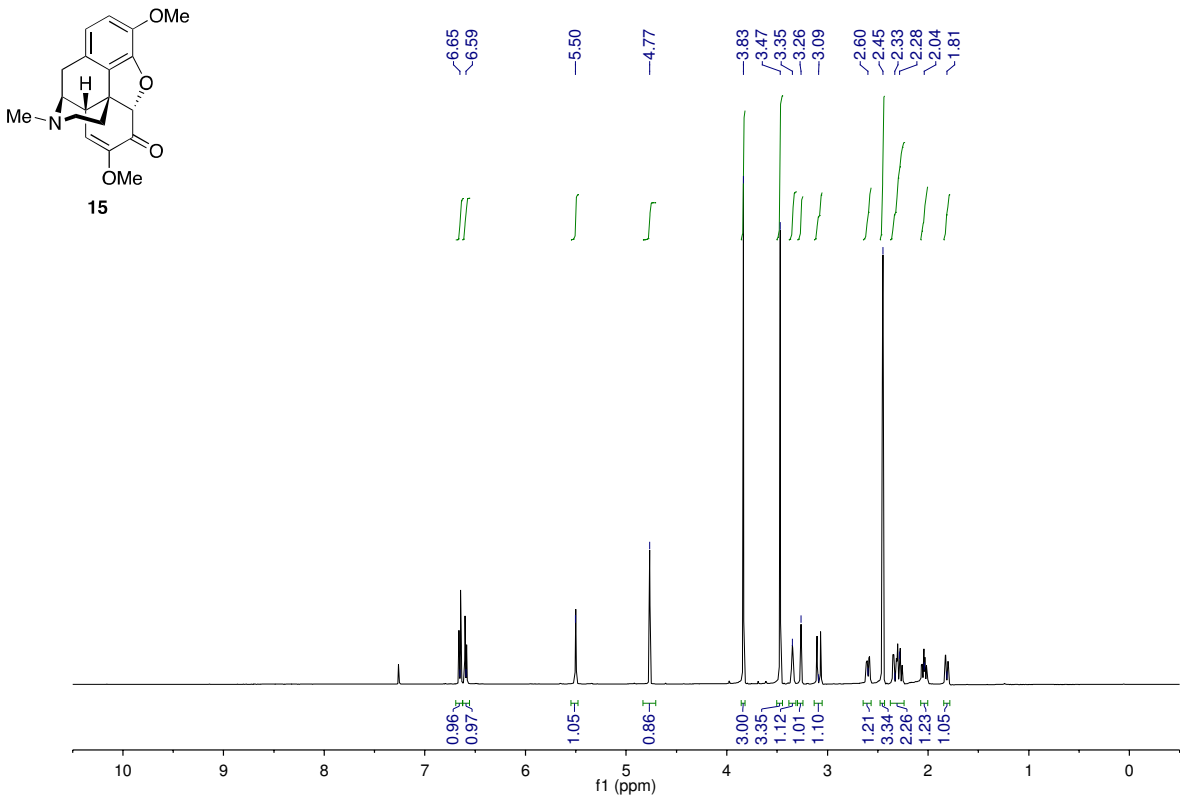
^{1}H NMR (CDCl$_3$)



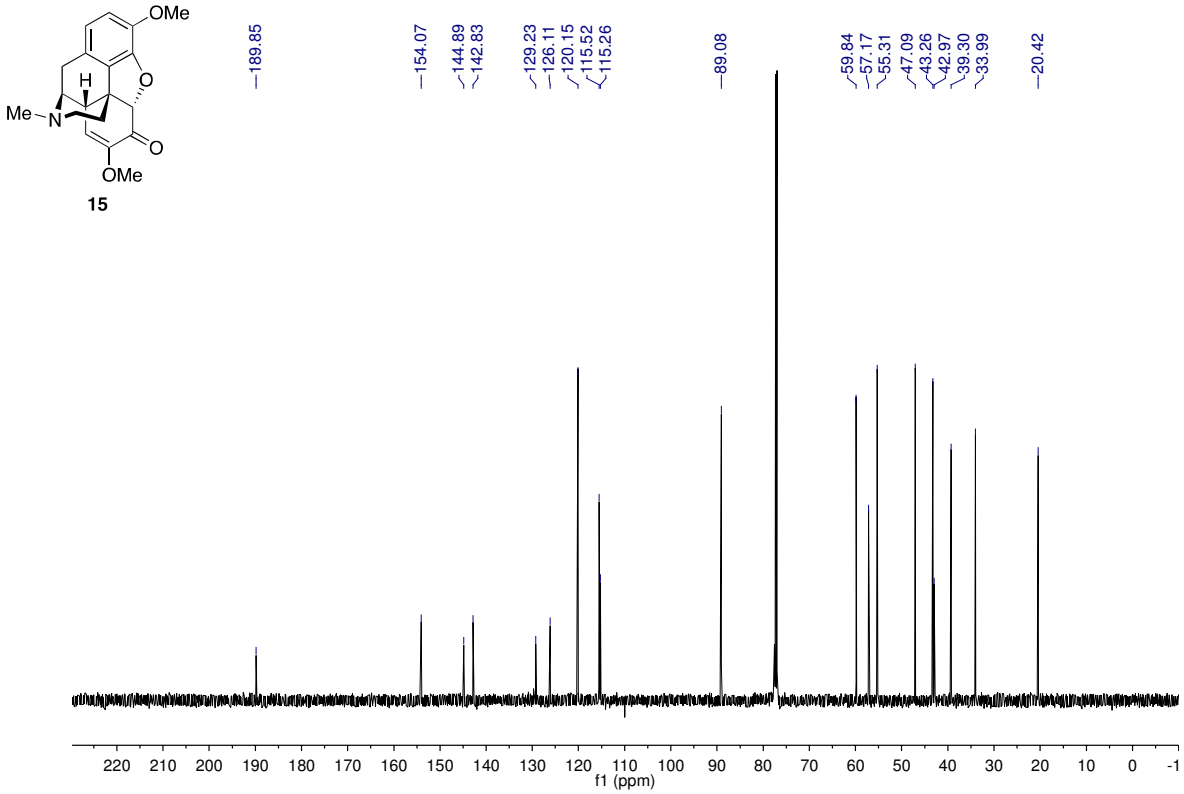
^{13}C NMR ($CDCl_3$)



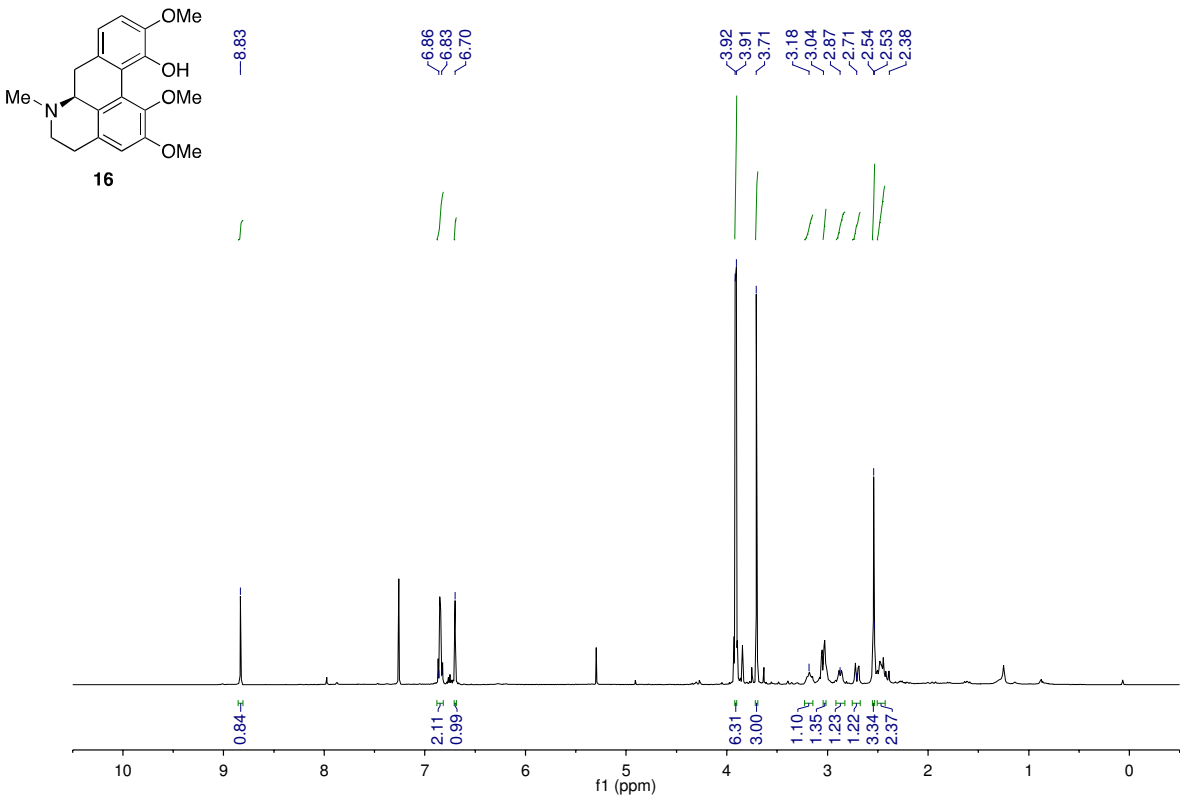
^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)



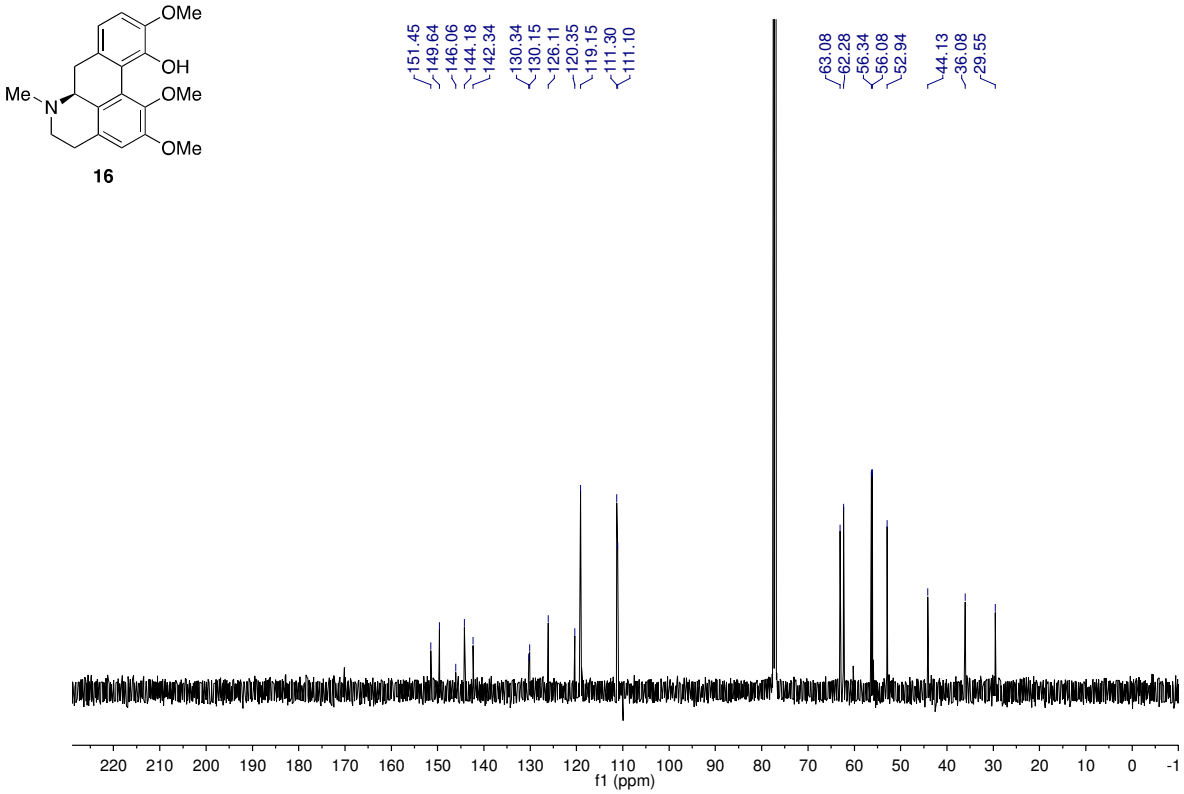
^{1}H NMR ($CDCl_3$)



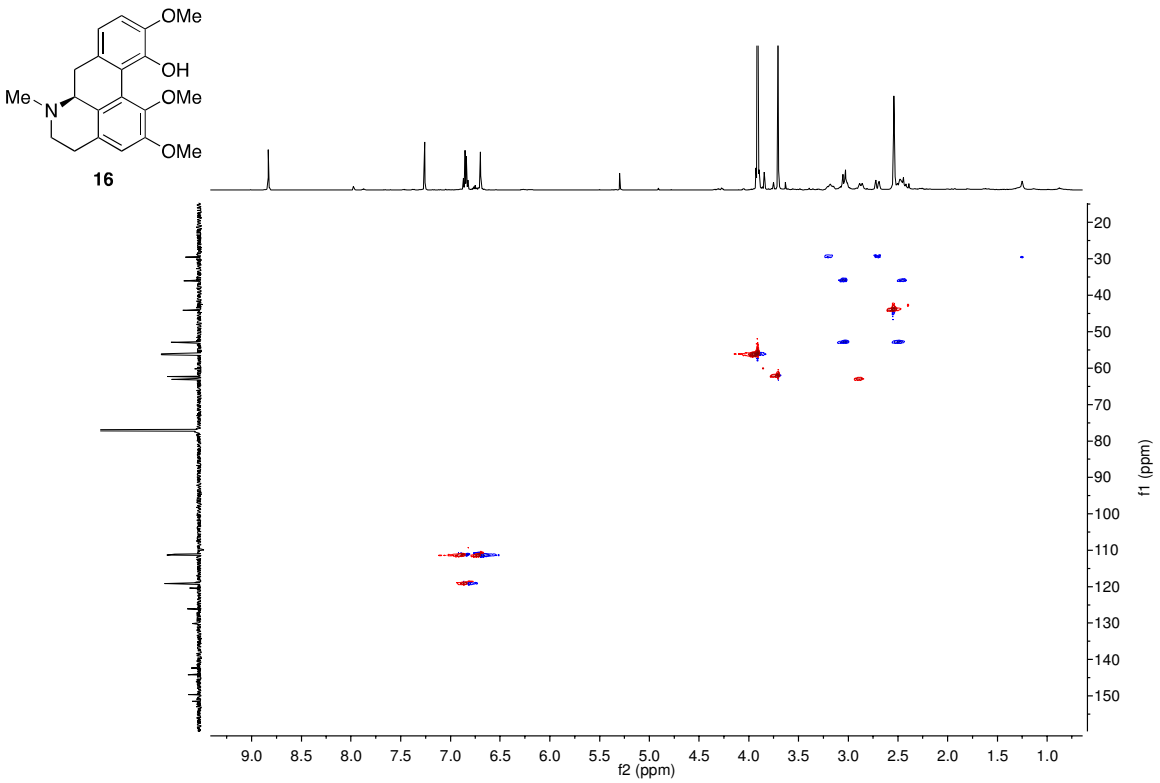
^{13}C NMR ($CDCl_3$)



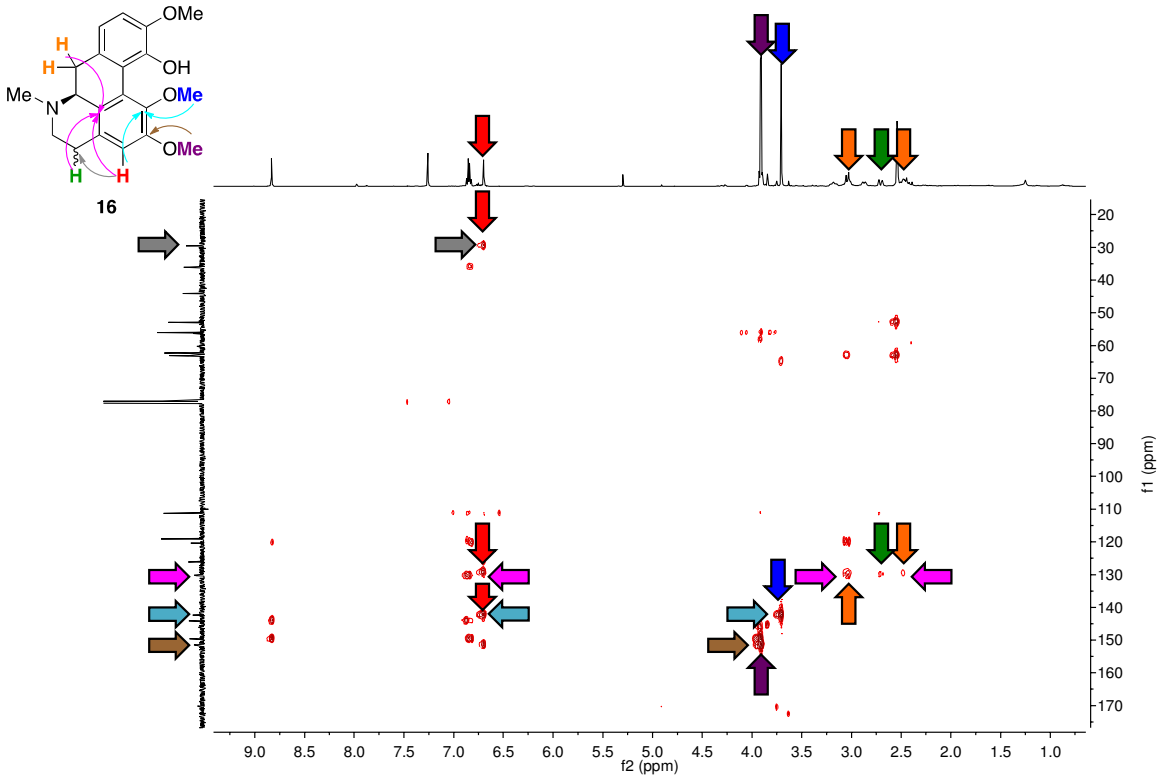
^{1}H NMR ($CDCl_3$)



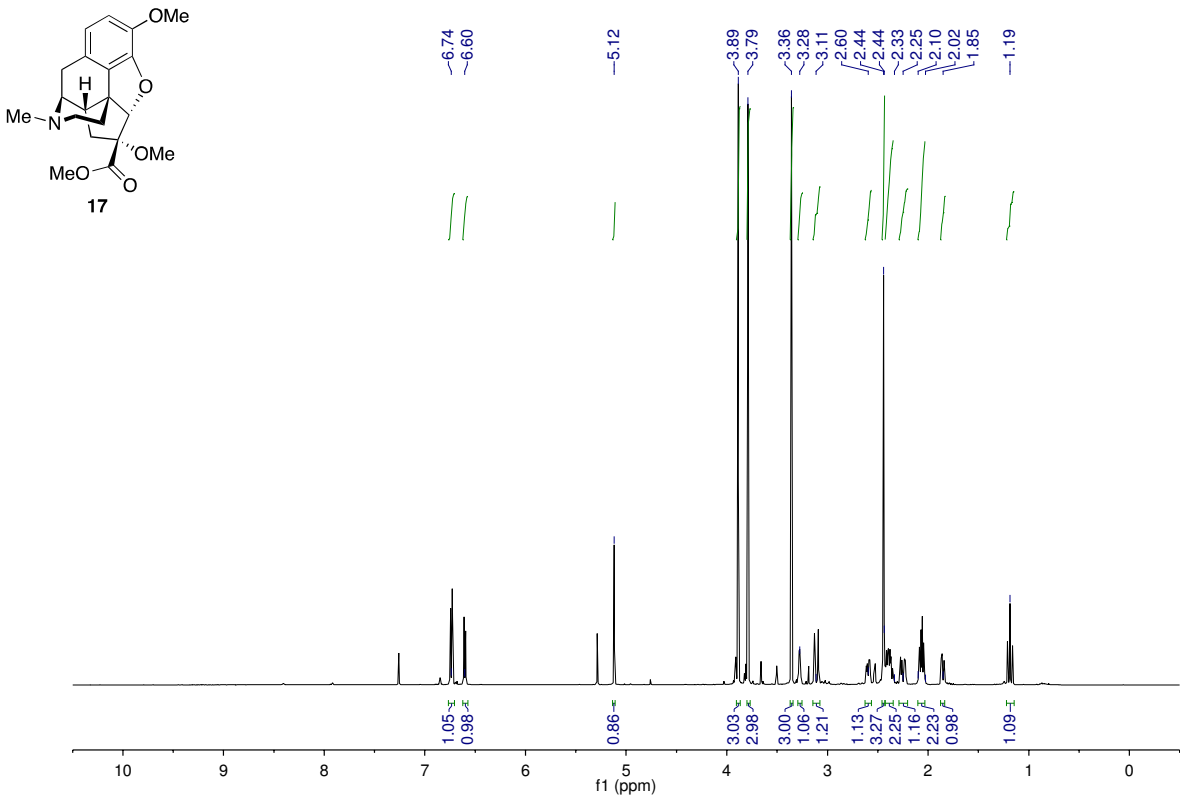
^{13}C NMR ($CDCl_3$)



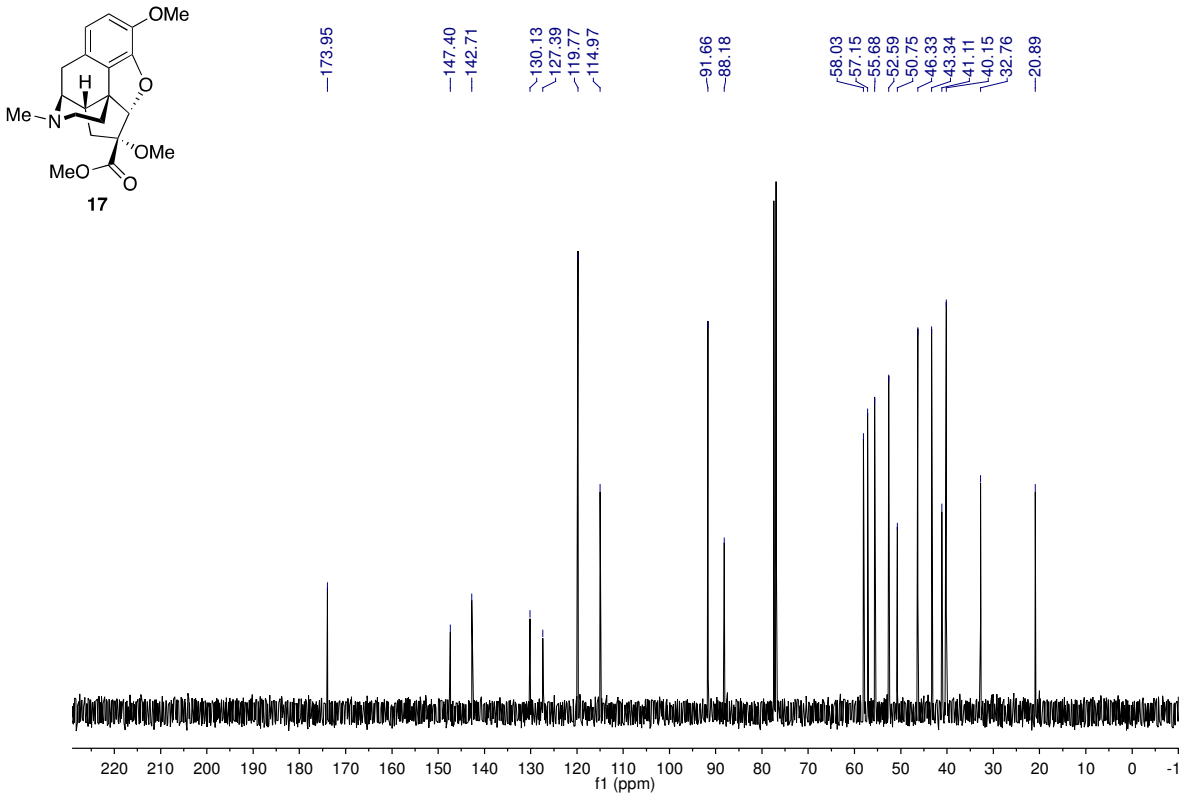
^{1}H – ^{13}C HSQC NMR ($CDCl_3$)



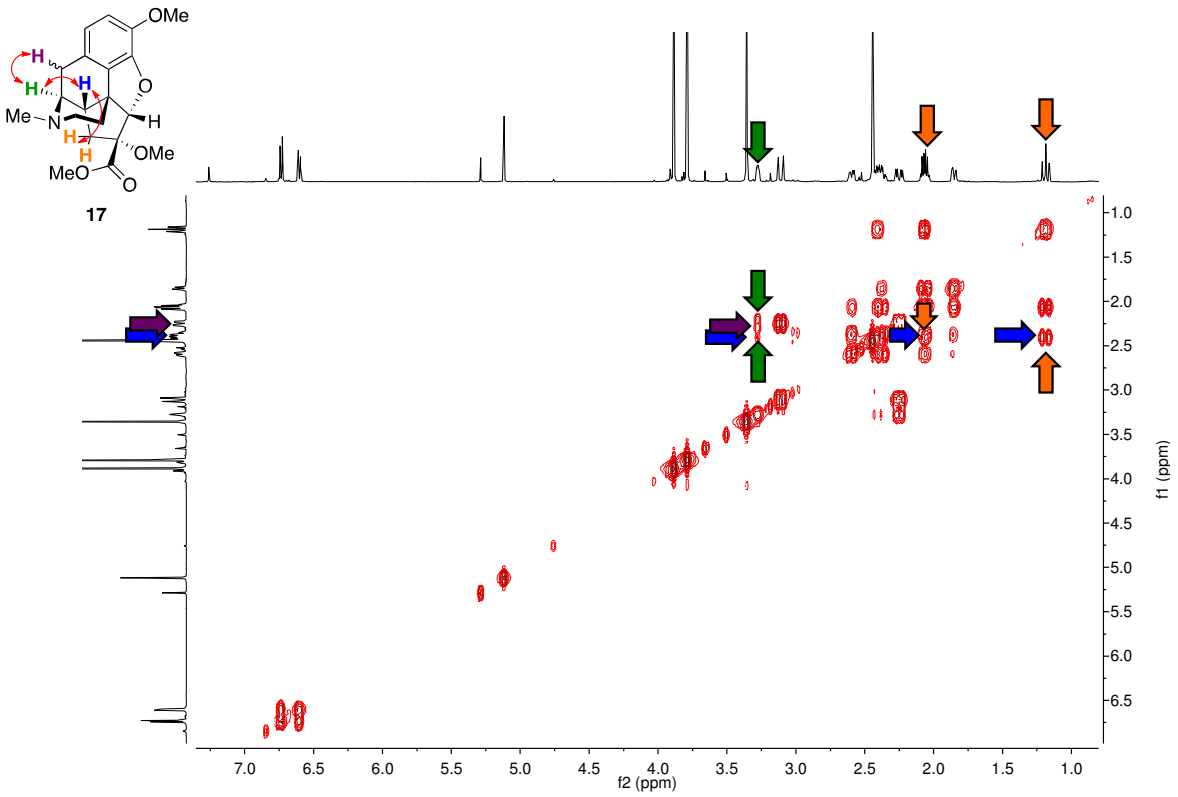
^{1}H – ^{13}C HMBC NMR ($CDCl_3$)



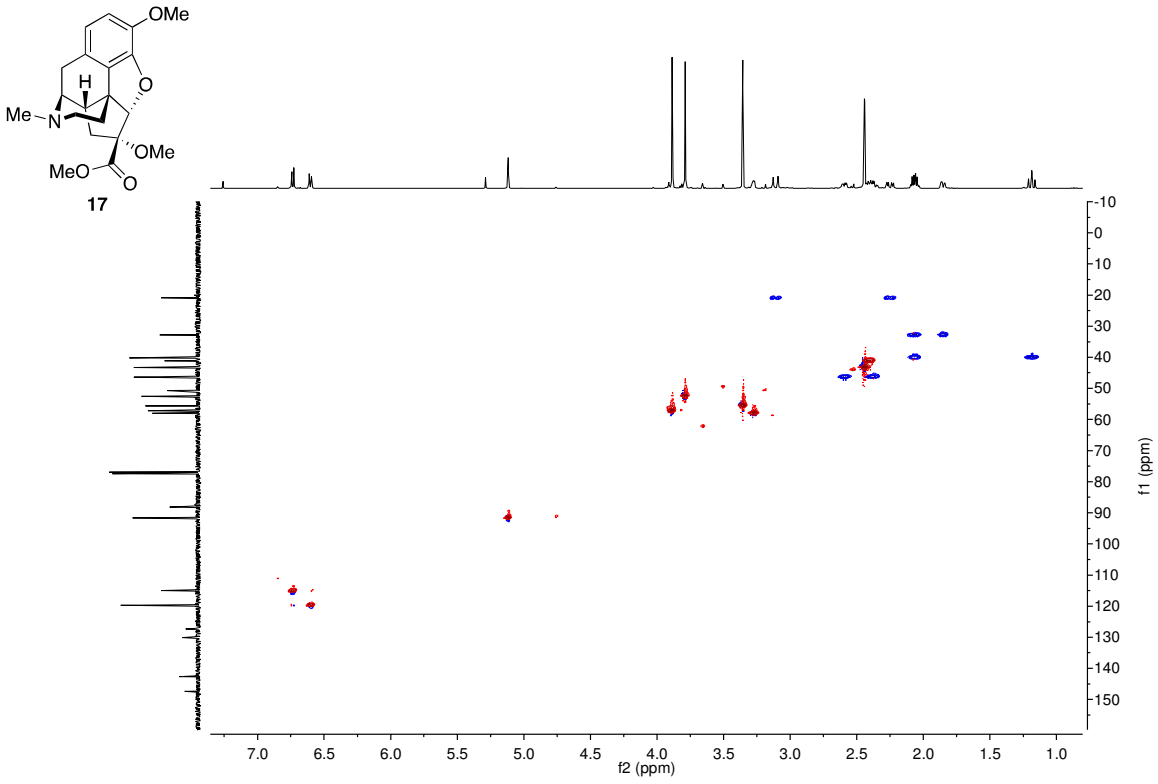
^{1}H NMR ($CDCl_3$)



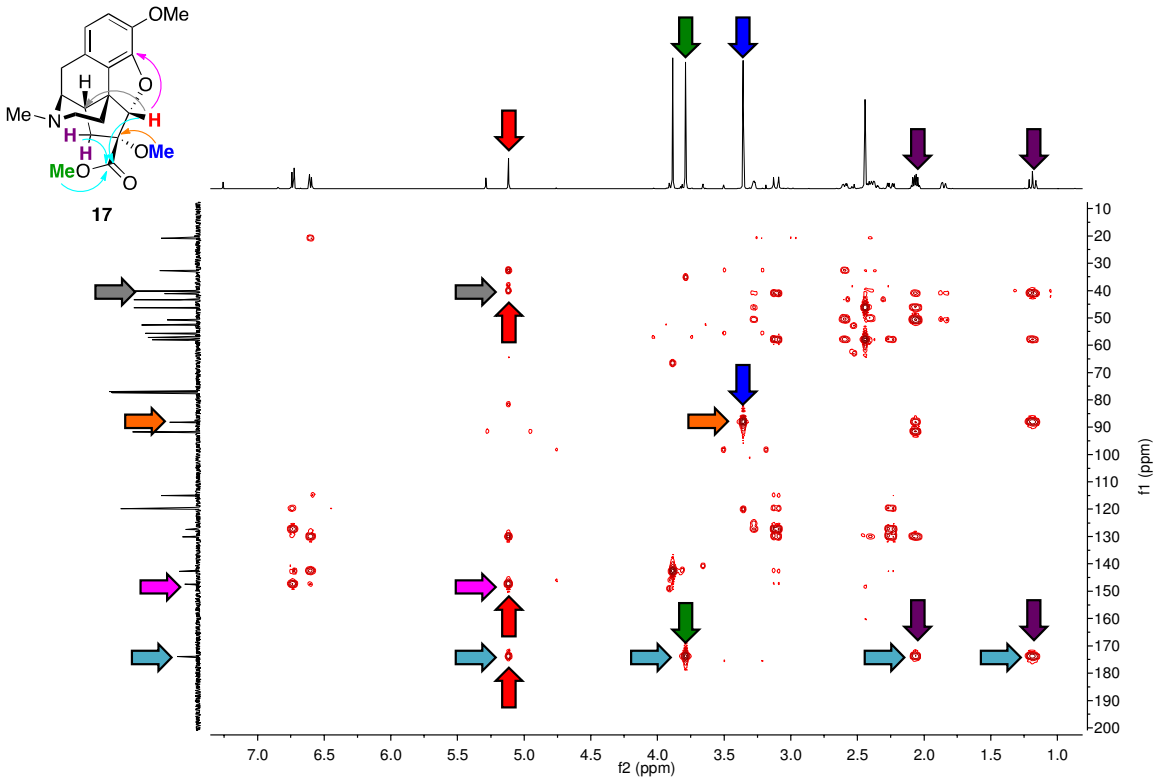
^{13}C NMR ($CDCl_3$)



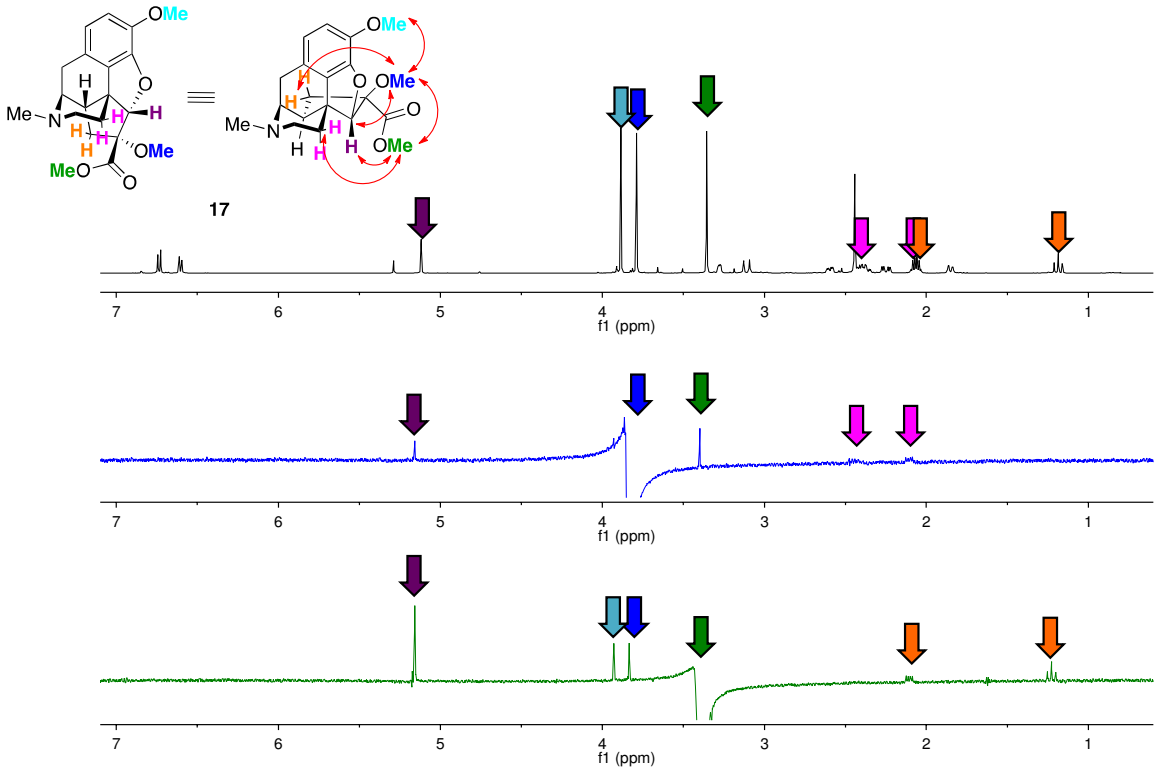
^{1}H–^{1}H COSY NMR ($CDCl_3$)



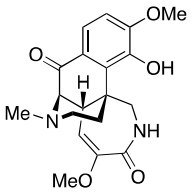
^{1}H–^{13}C HSQC NMR ($CDCl_3$)



^{1}H–^{13}C HMBC NMR ($CDCl_3$)

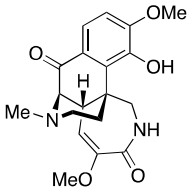


^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)



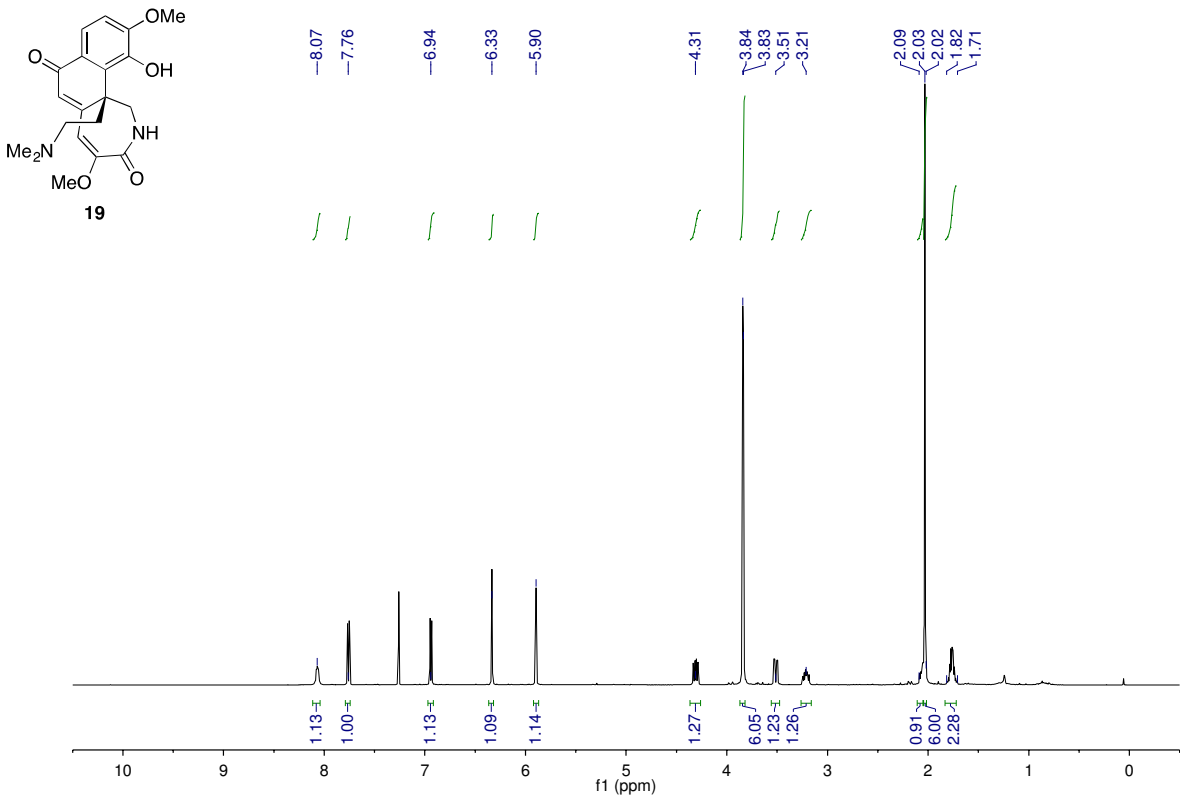
18

^{1}H NMR ($CDCl_3$)

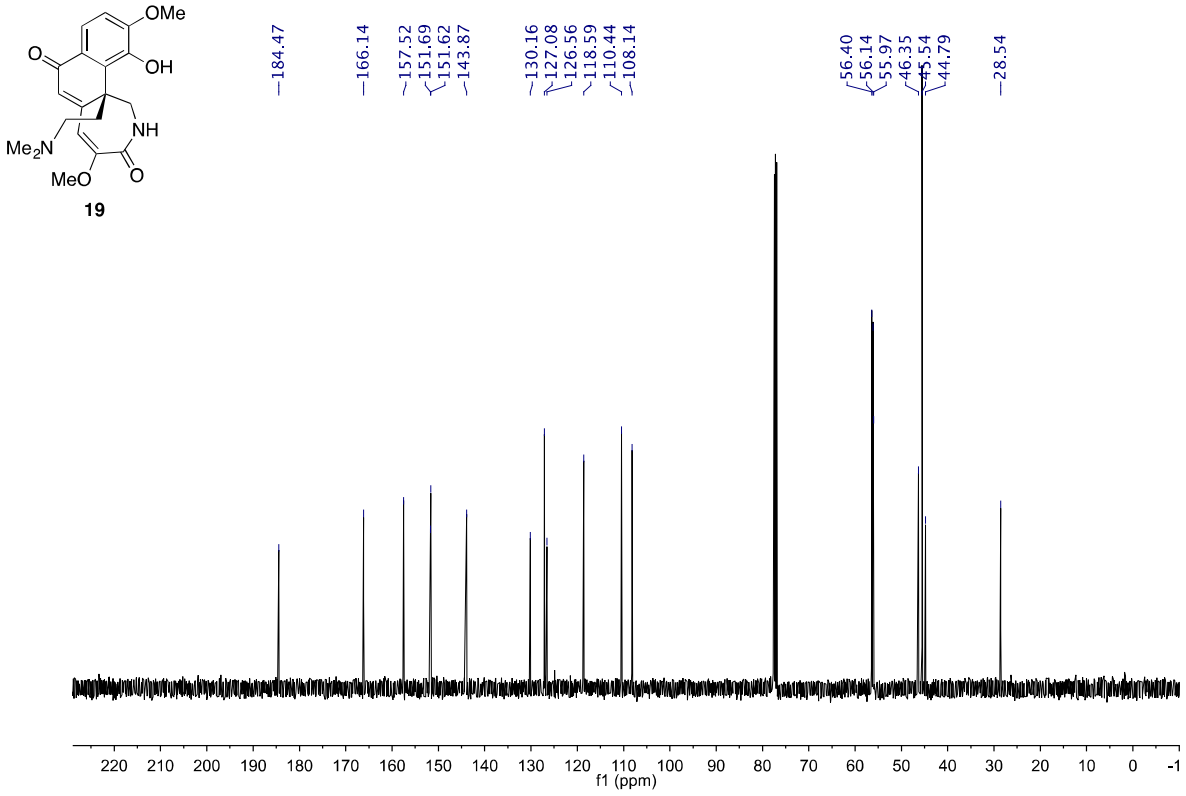


18

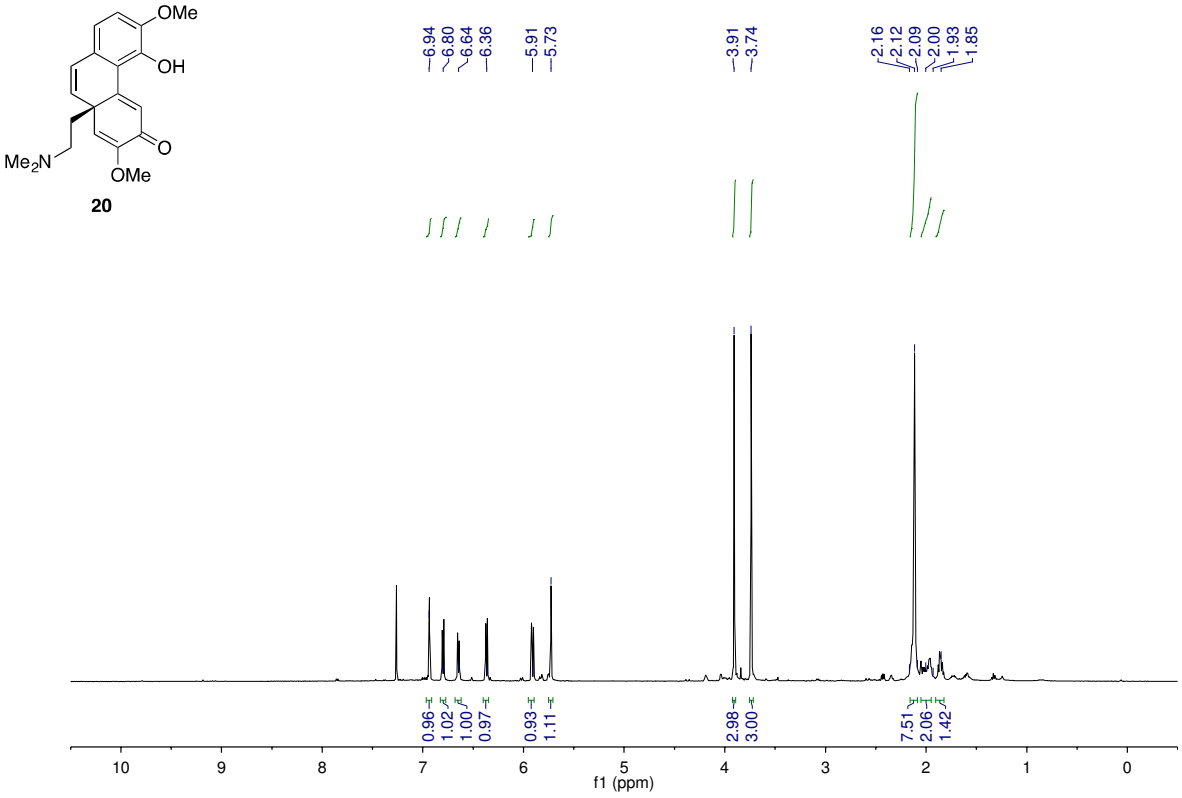
^{13}C NMR ($CDCl_3$)



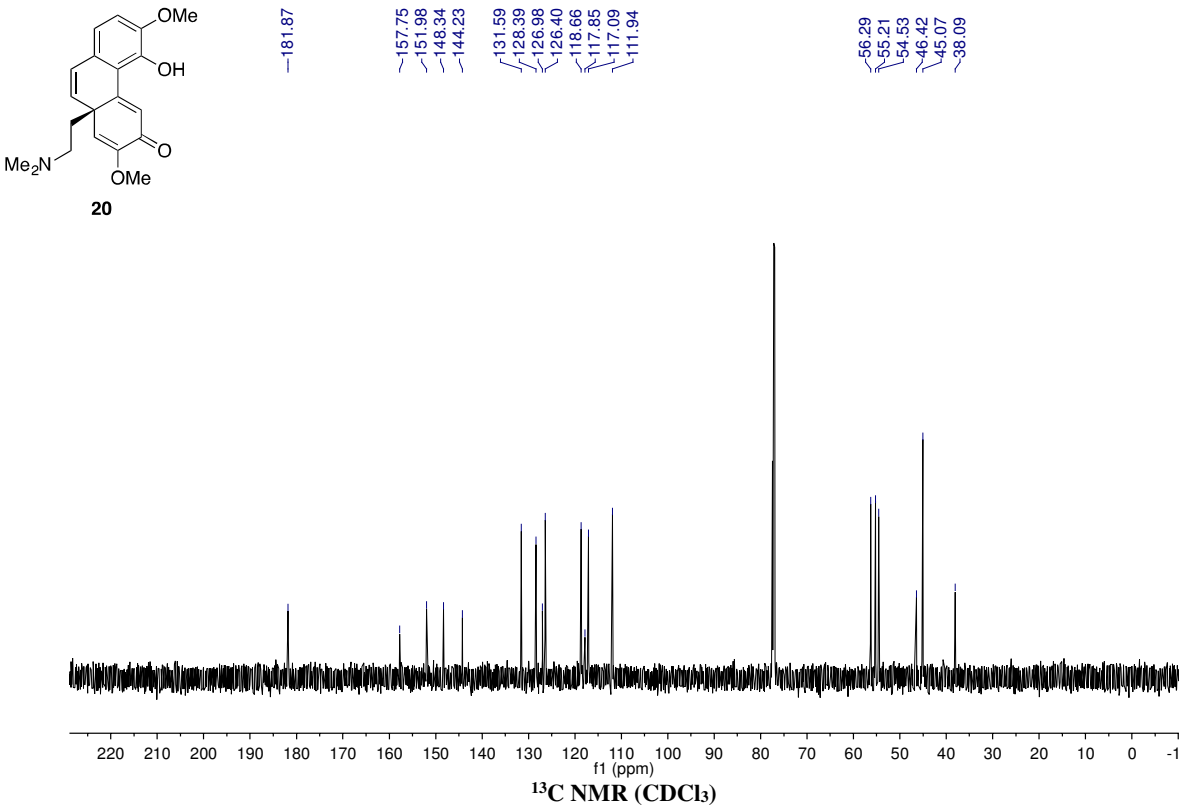
^{1}H NMR ($CDCl_3$)



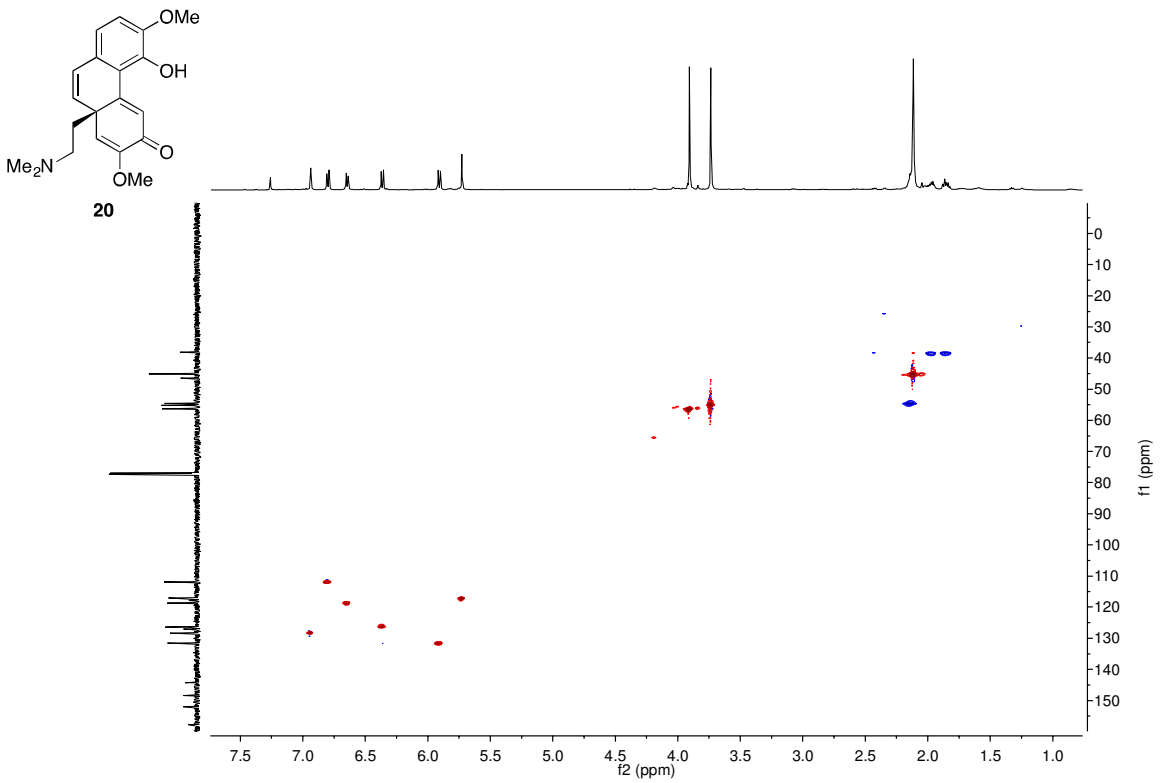
^{13}C NMR ($CDCl_3$)



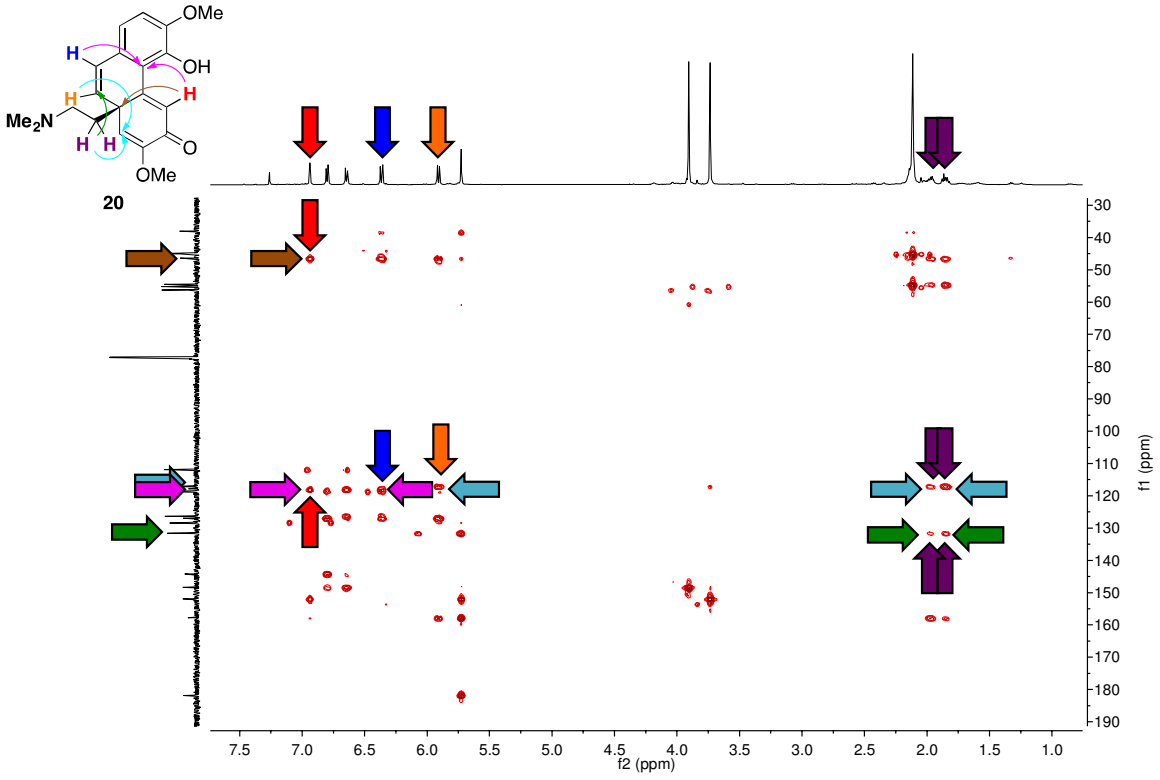
^{1}H NMR ($CDCl_3$)



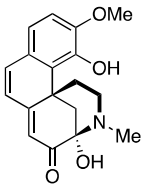
^{13}C NMR ($CDCl_3$)



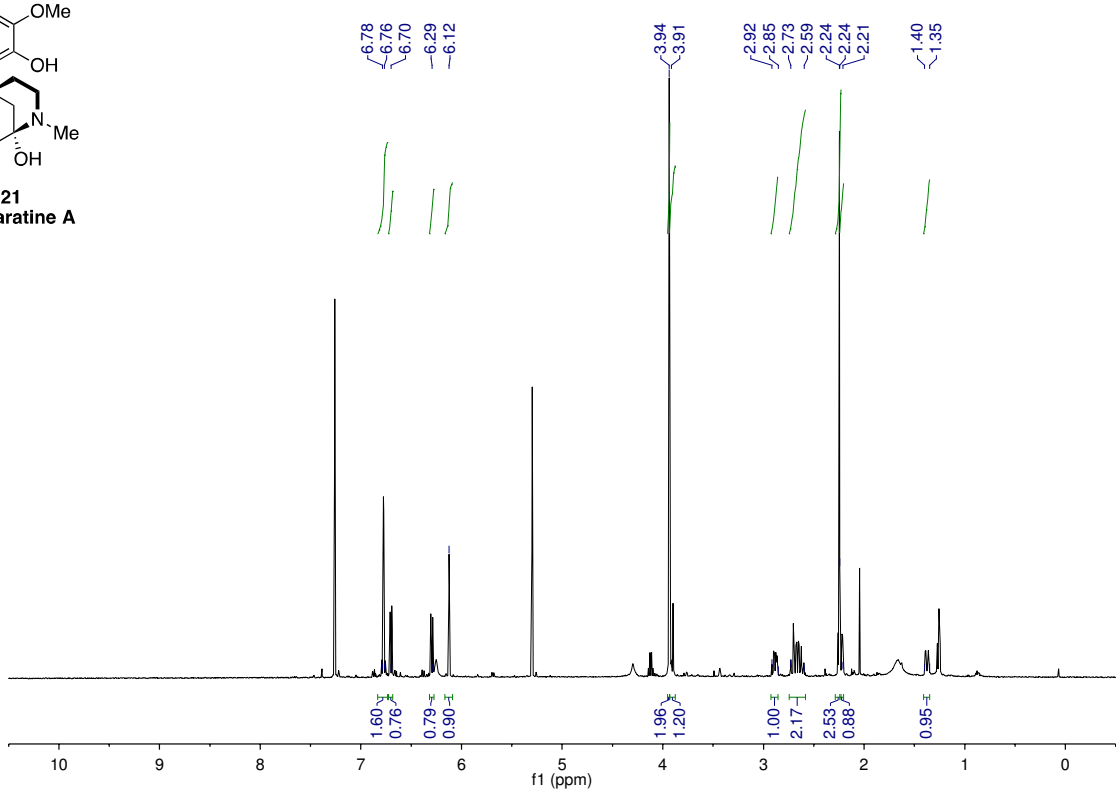
^{1}H–^{13}C HSQC NMR ($CDCl_3$)



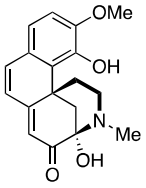
^{1}H–^{13}C HMBC NMR ($CDCl_3$)



21
Cepharatine A

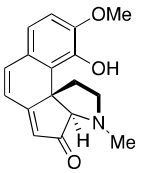


^{1}H NMR ($CDCl_3$)

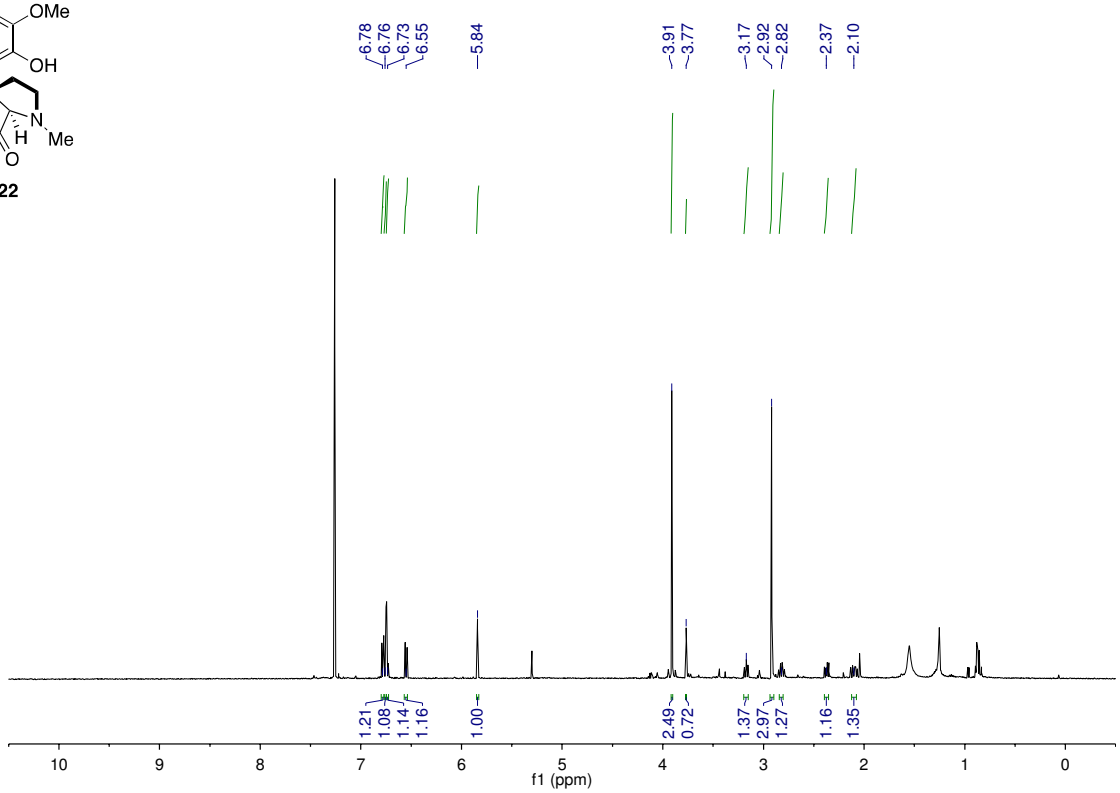


21
Cepharatine A

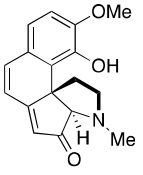
^{13}C NMR ($CDCl_3$)



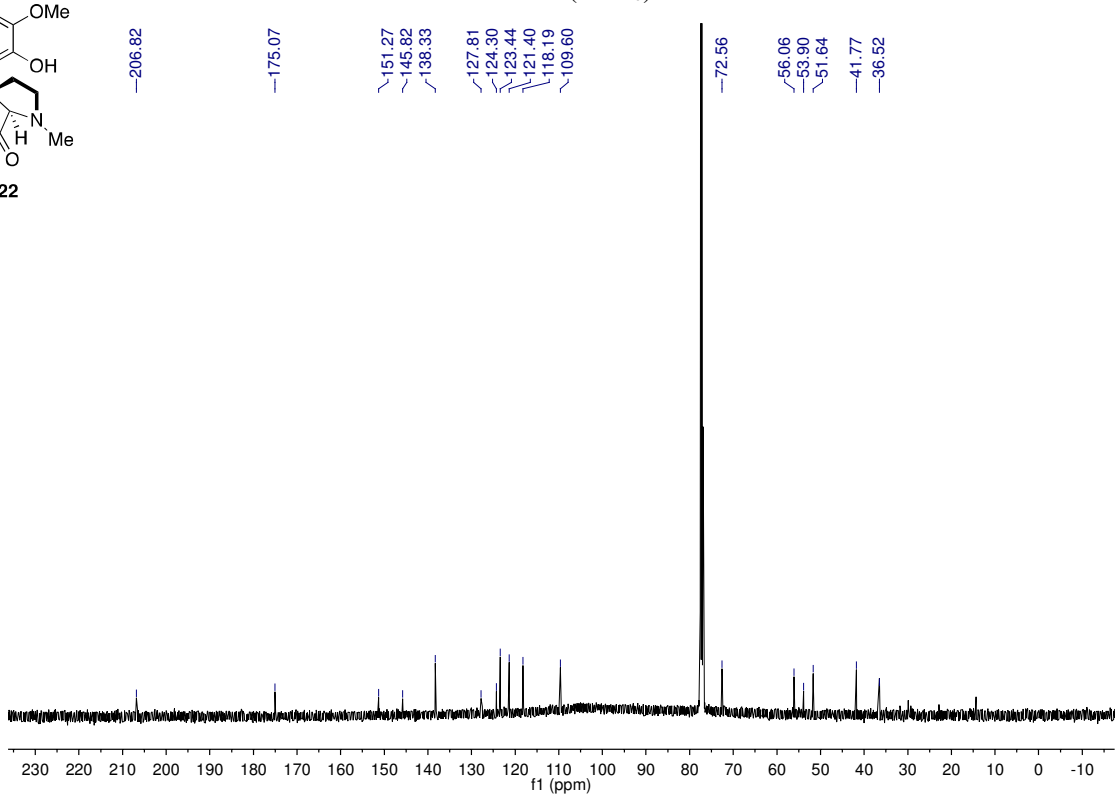
22



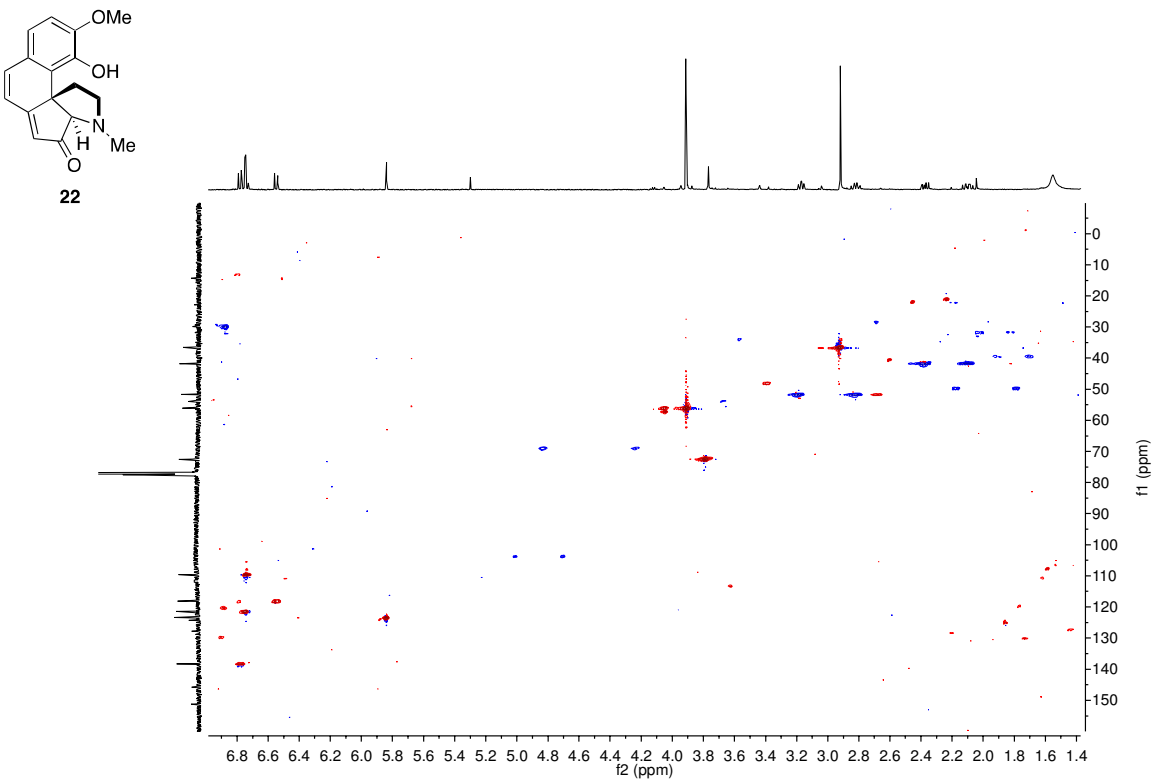
^{1}H NMR ($CDCl_3$)



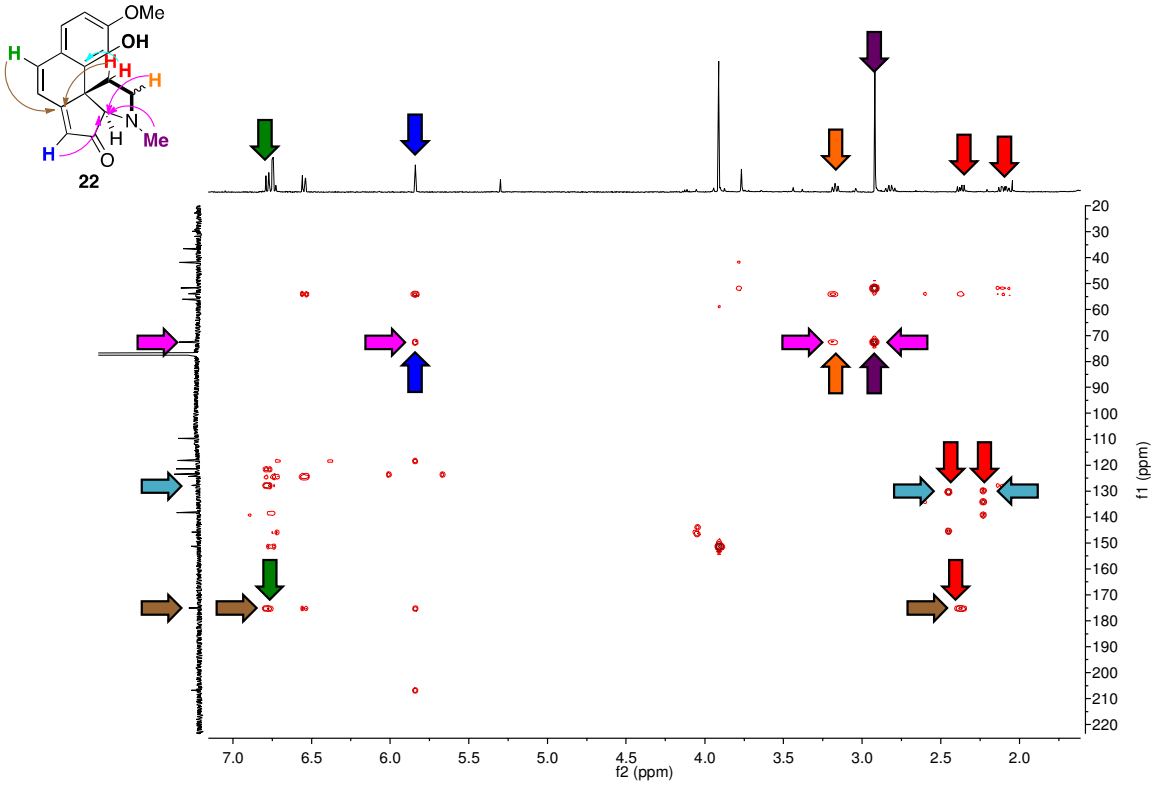
22



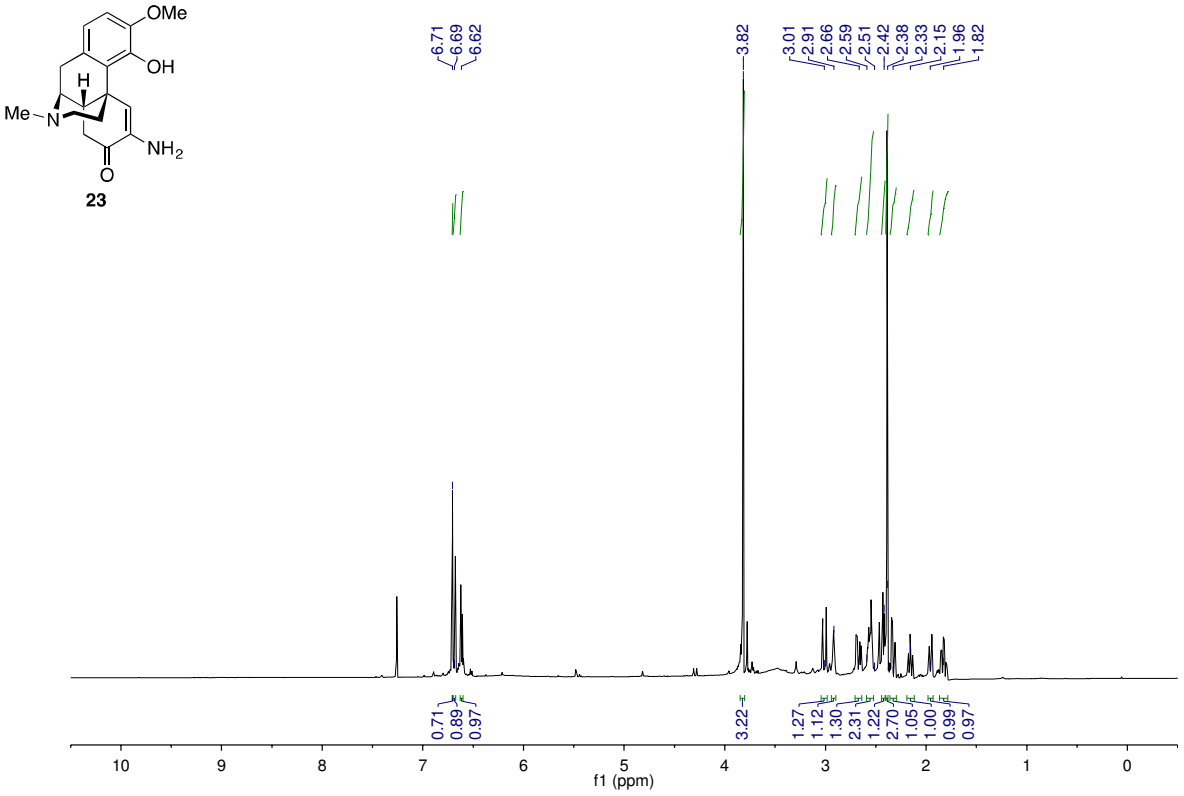
^{13}C NMR ($CDCl_3$)



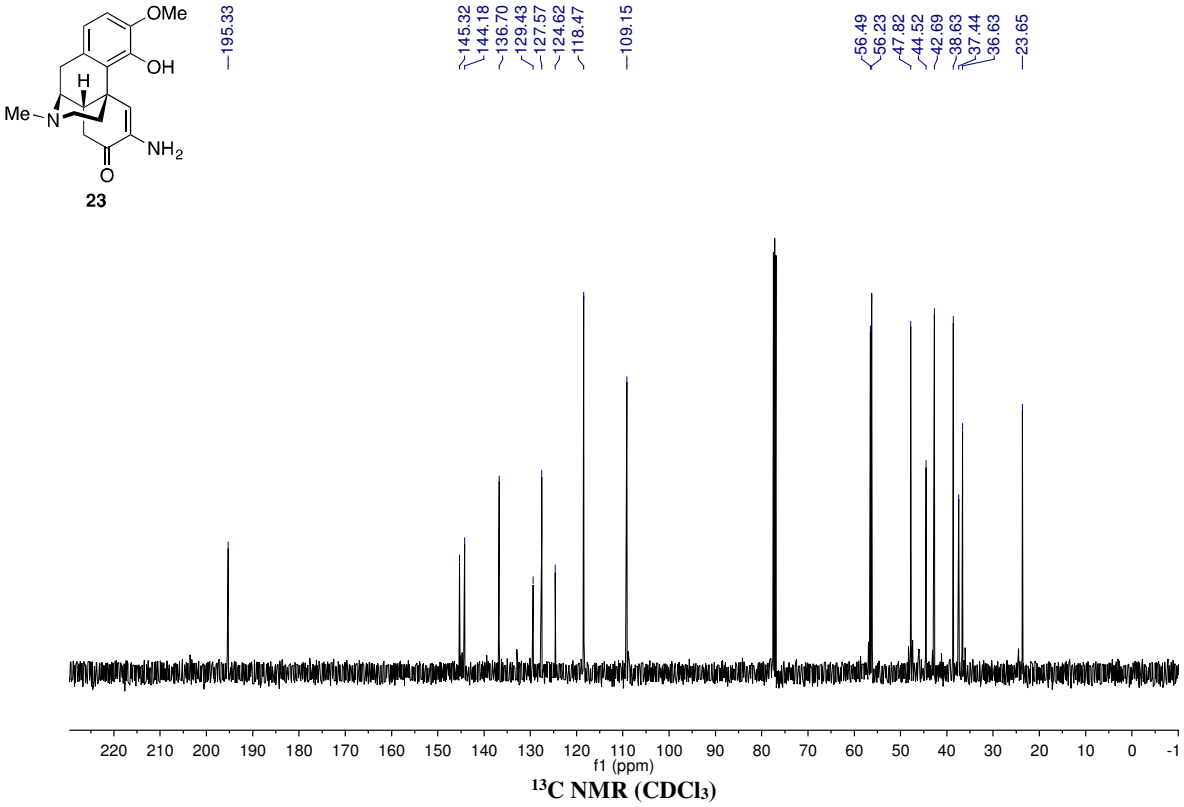
^{1}H–^{13}C HSQC NMR ($CDCl_3$)



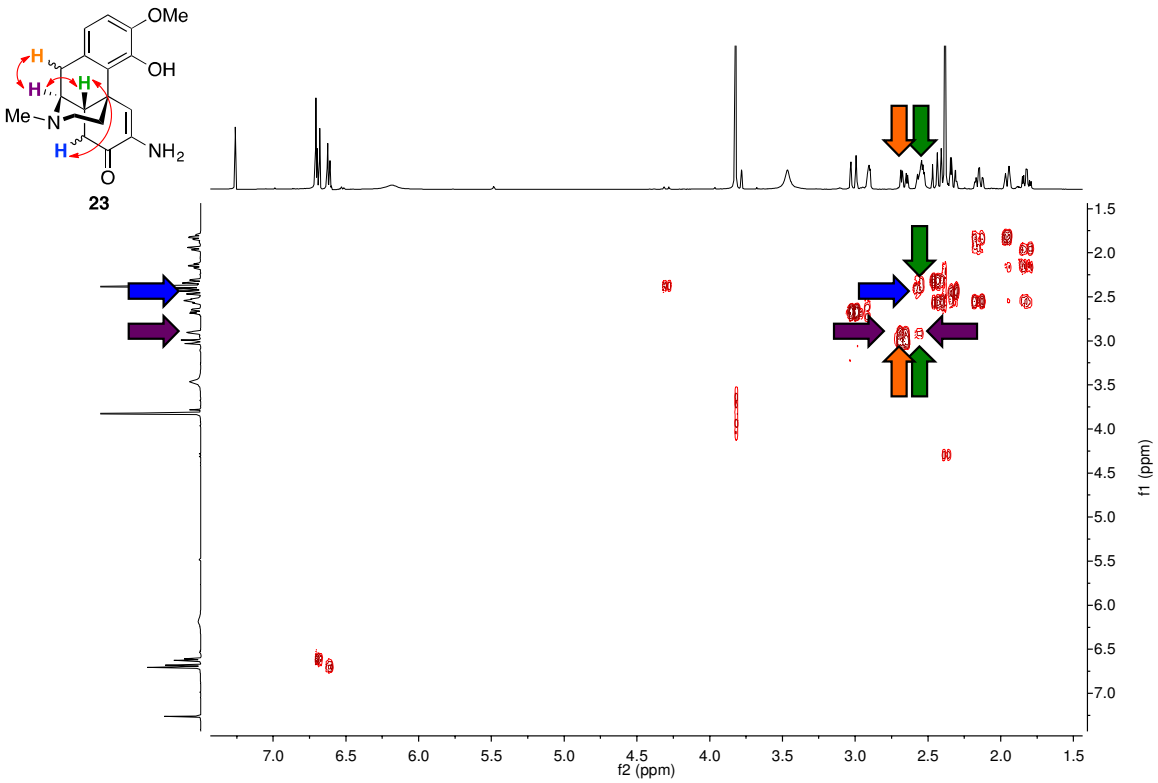
^{1}H–^{13}C HMBC NMR ($CDCl_3$)



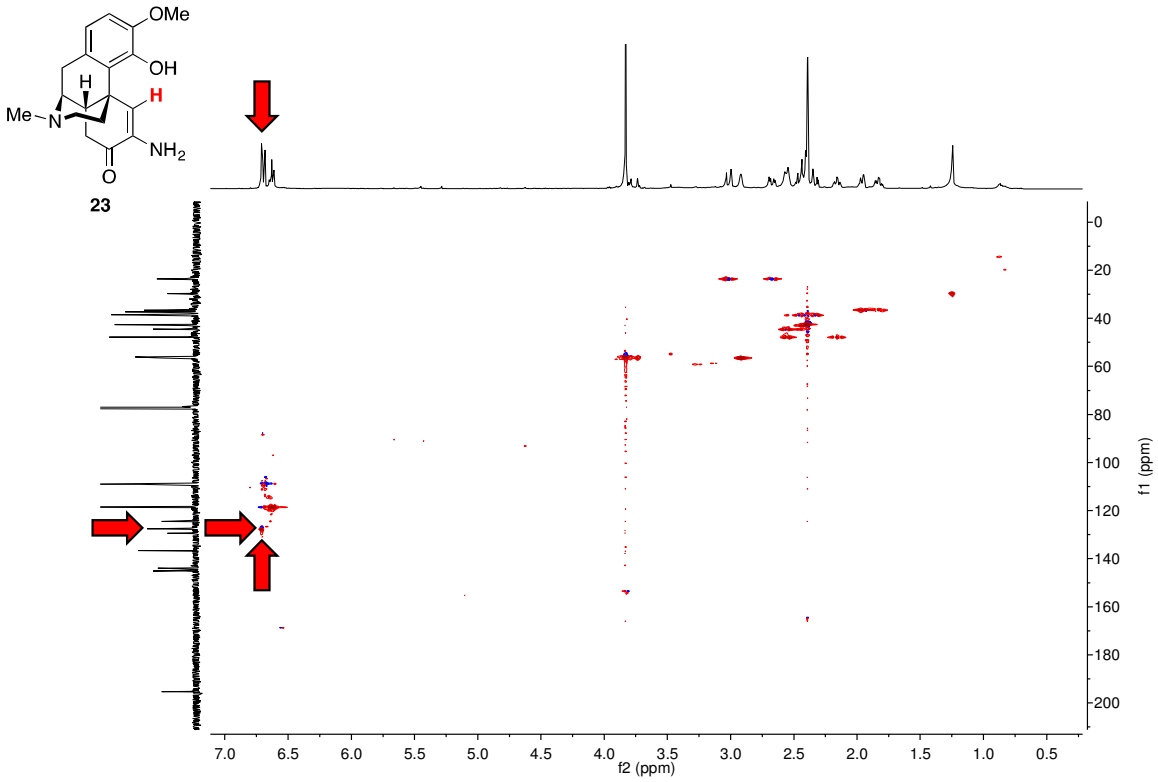
^{1}H NMR ($CDCl_3$)



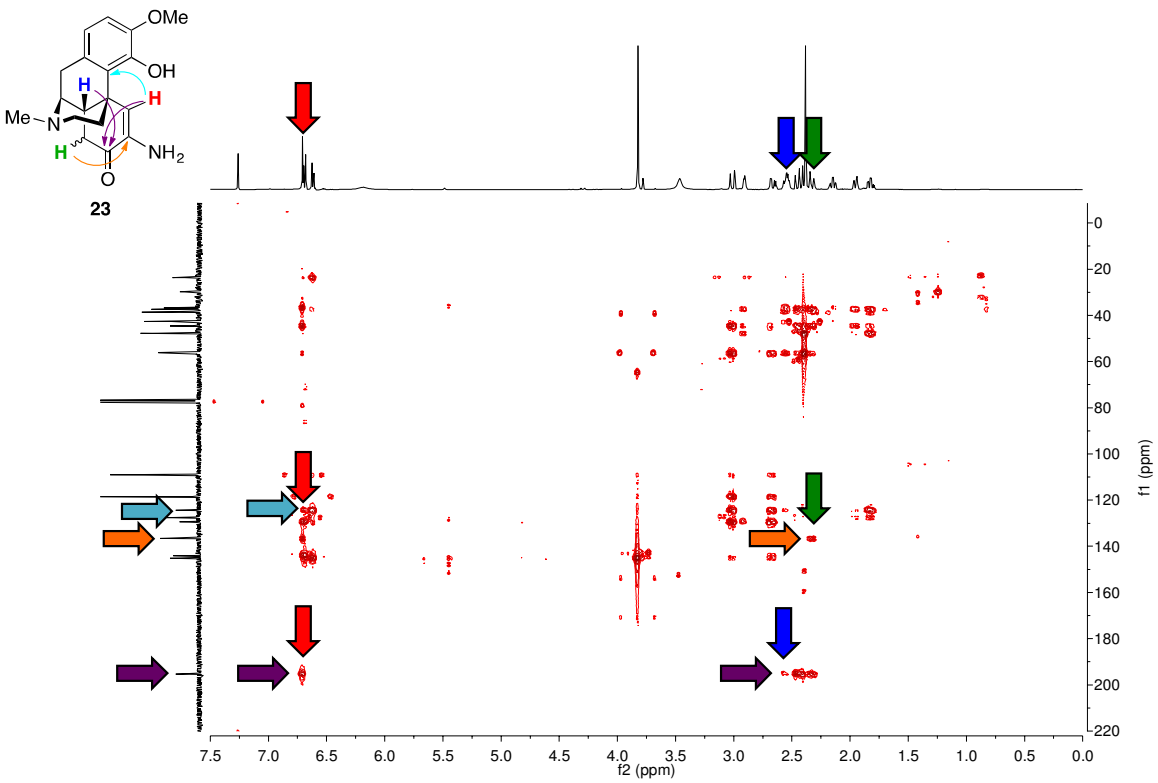
^{13}C NMR ($CDCl_3$)



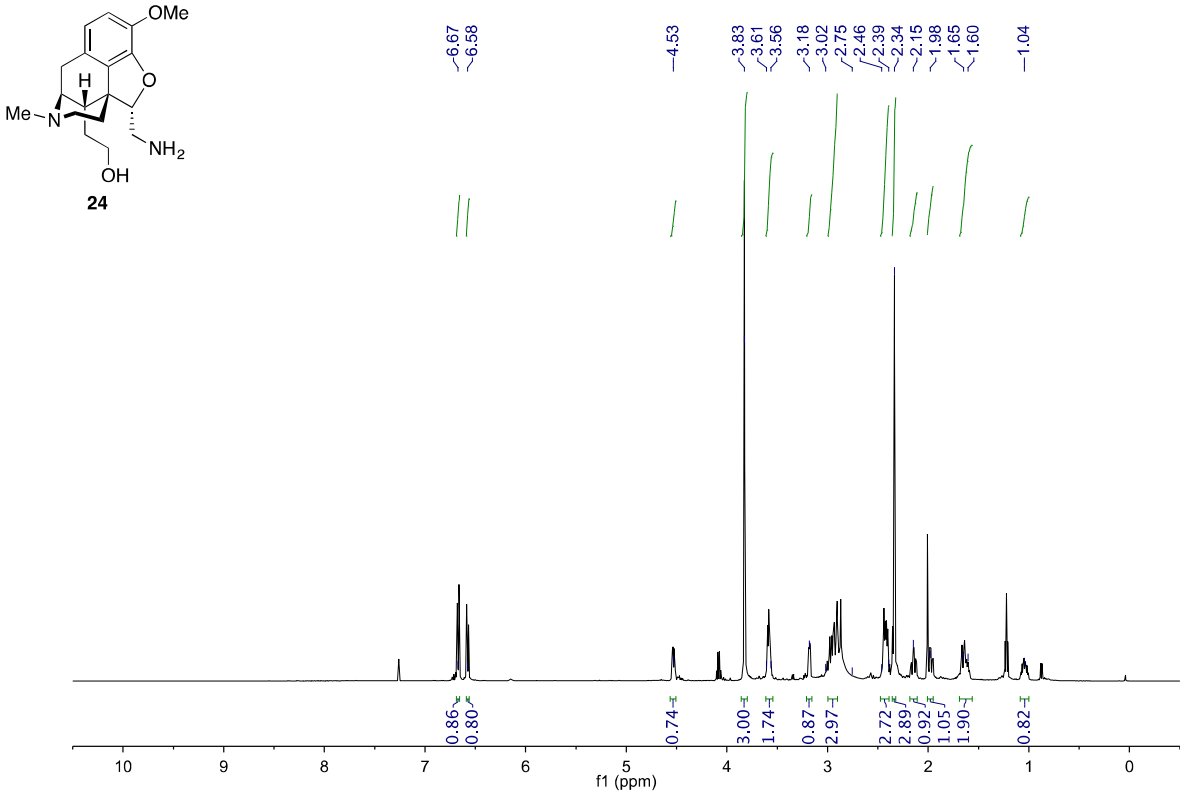
^{1}H – ^{1}H COSY NMR ($CDCl_3$)



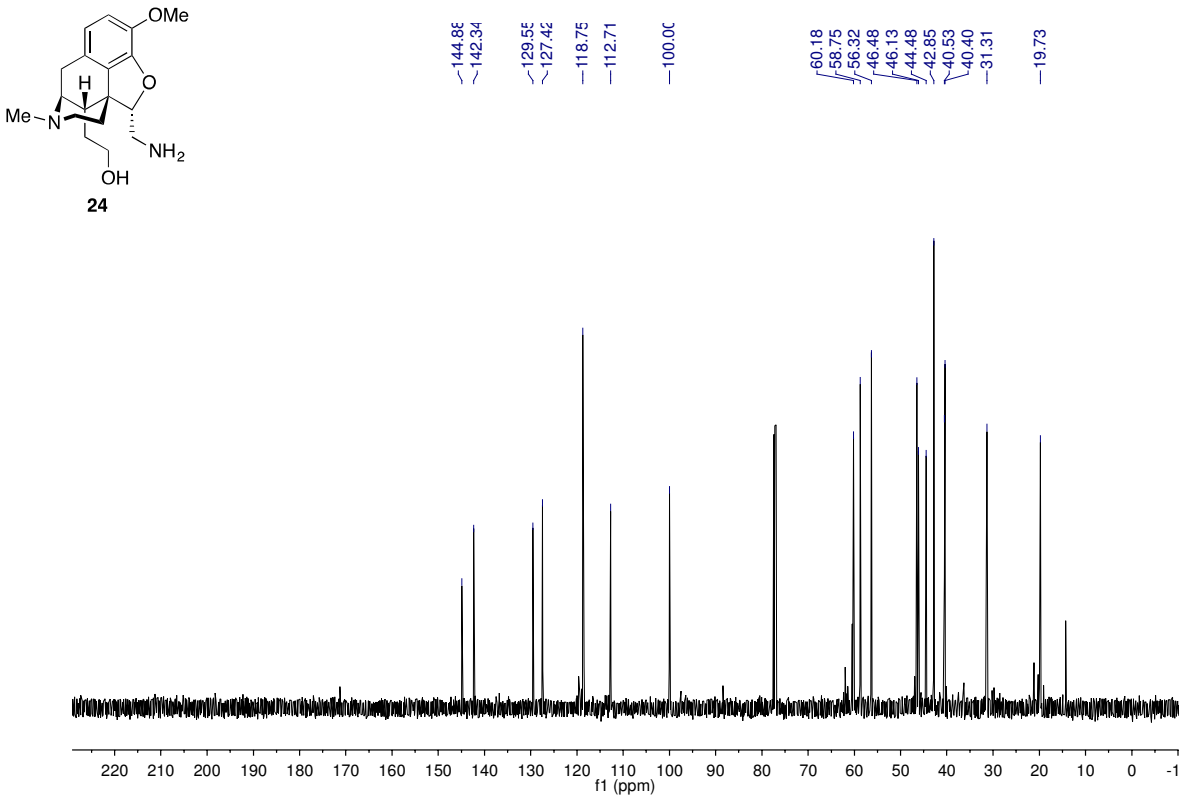
^{1}H – ^{13}C HMQC NMR ($CDCl_3$)



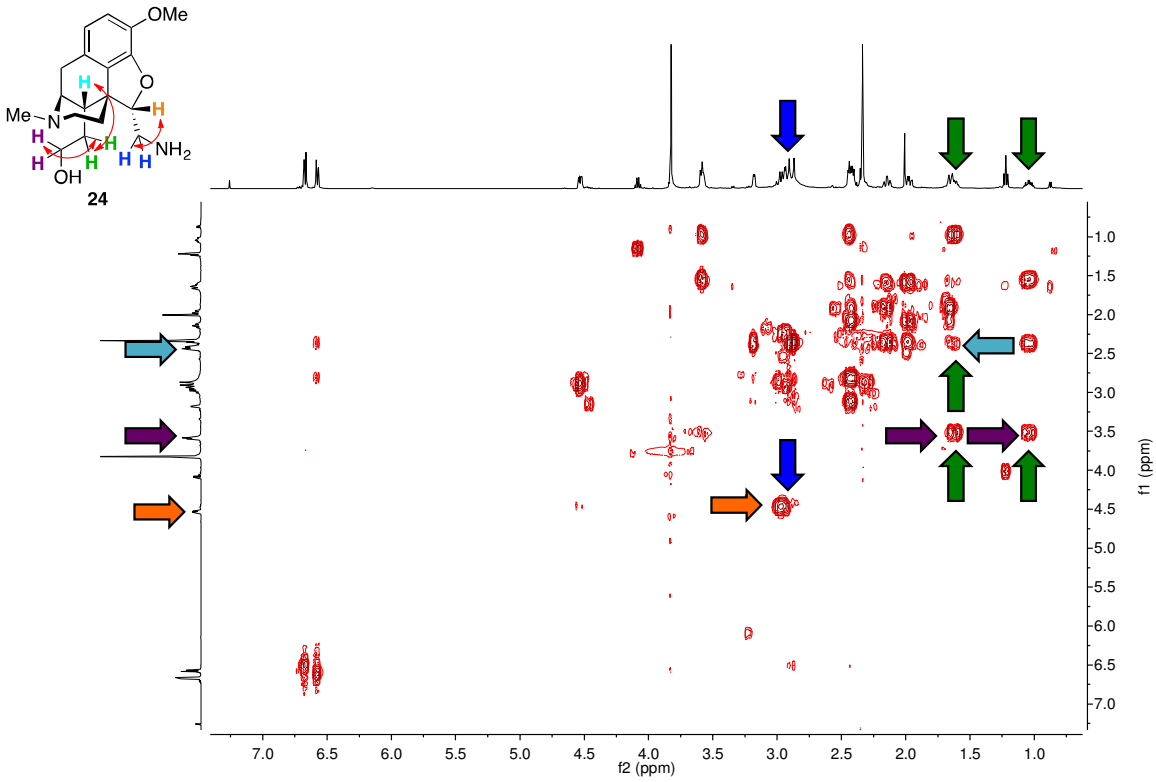
^{1}H – ^{13}C HMBC NMR (CDCl$_3$)



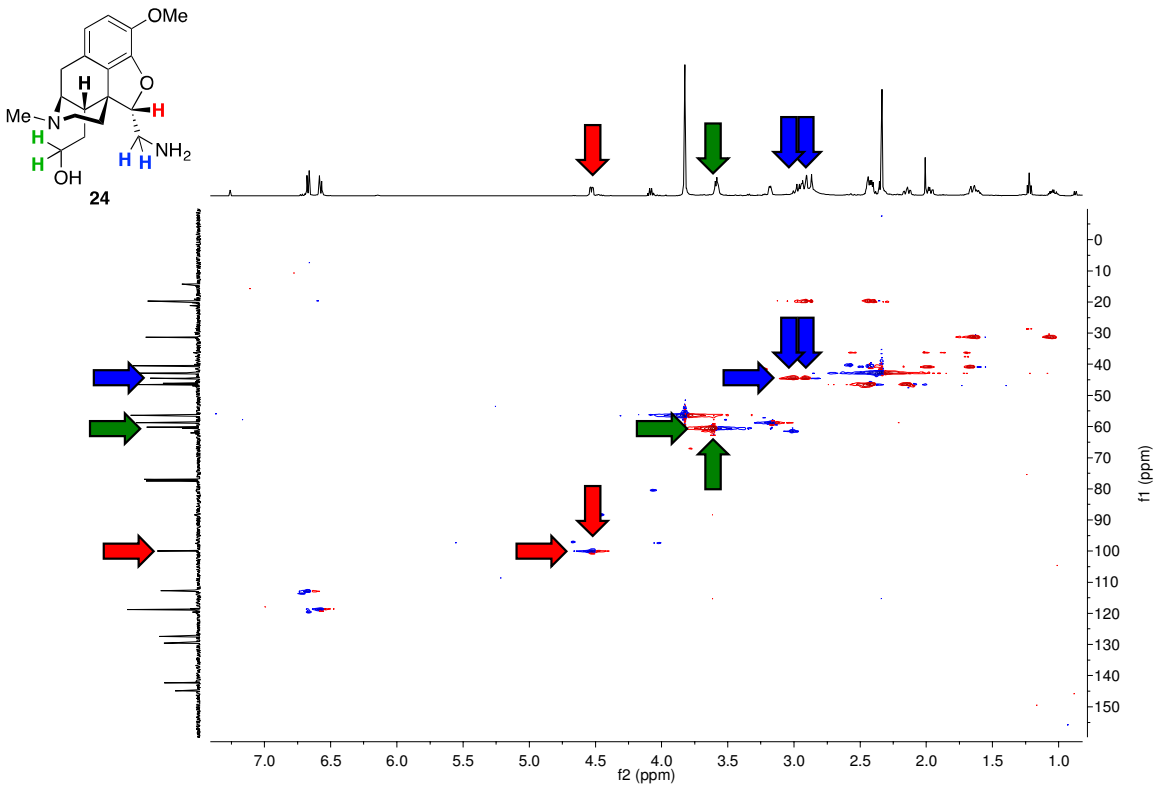
^{1}H NMR (CDCl$_3$)



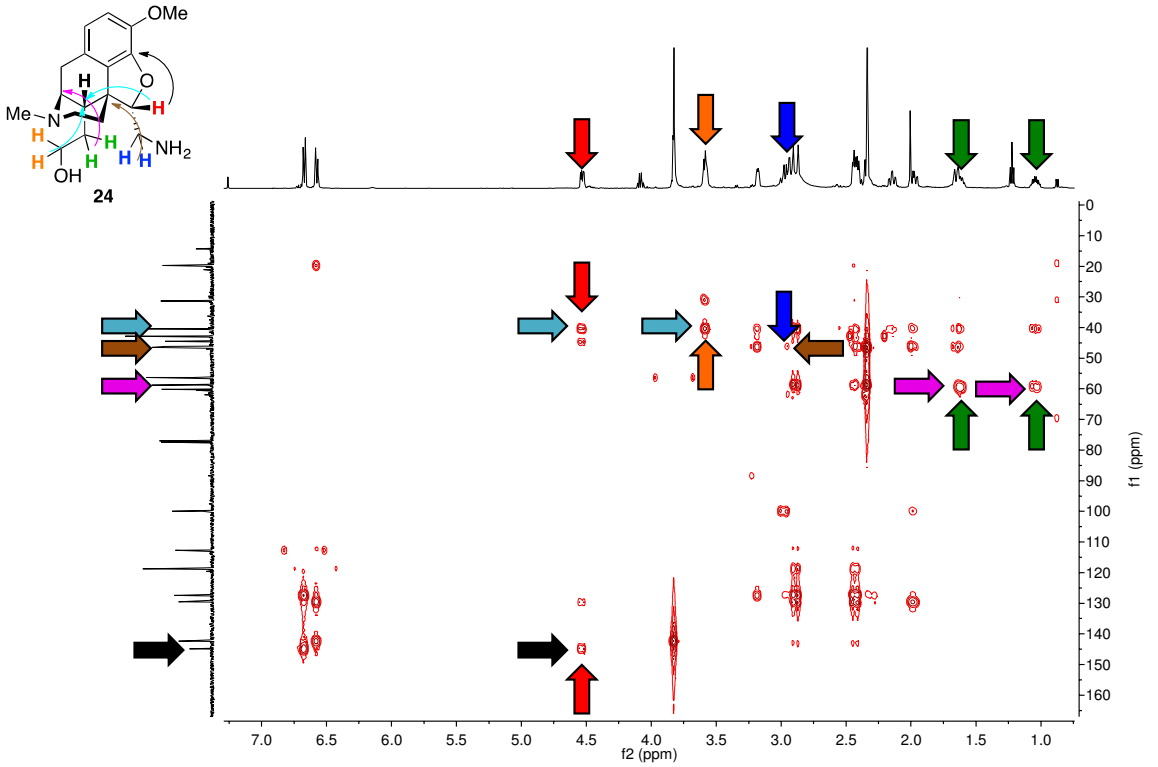
^{13}C NMR ($CDCl_3$)



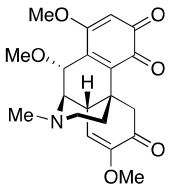
^{1}H–^{1}H COSY NMR ($CDCl_3$)



^{1}H–^{13}C HSQC NMR (CDCl$_3$)

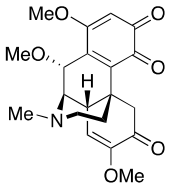


^{1}H–^{13}C HMBC NMR (CDCl$_3$)



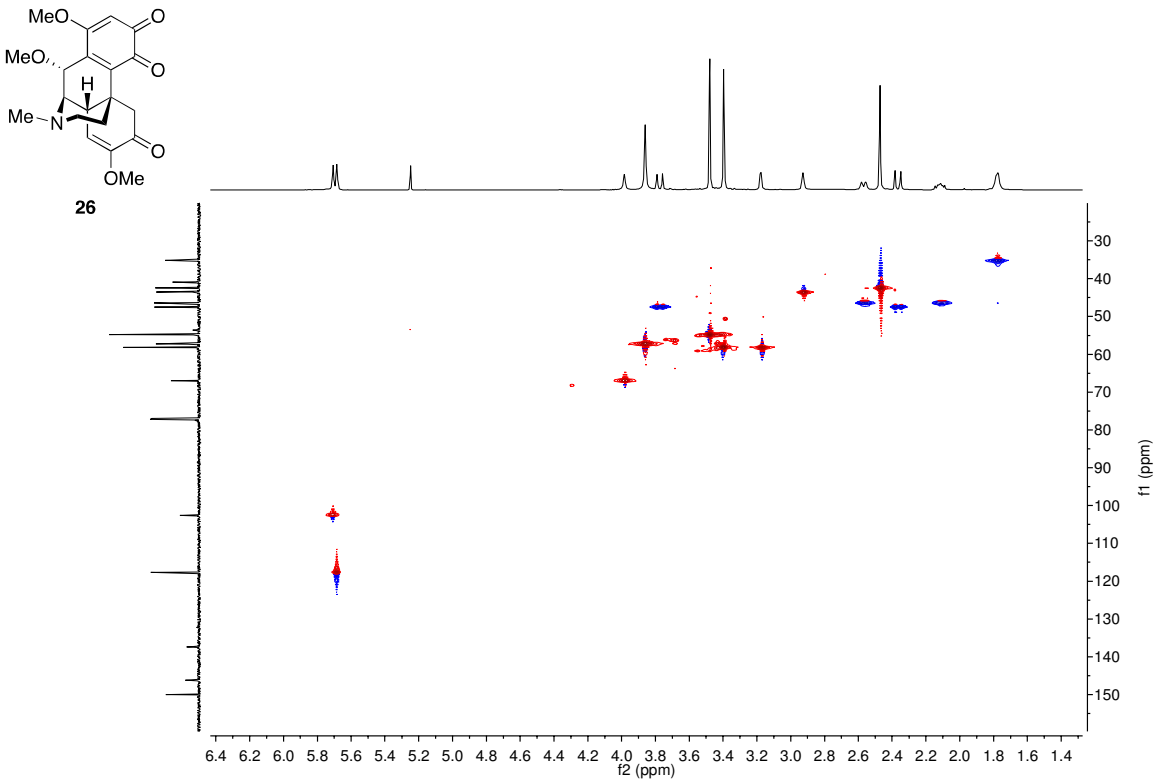
26

^{1}H NMR ($CDCl_3$)

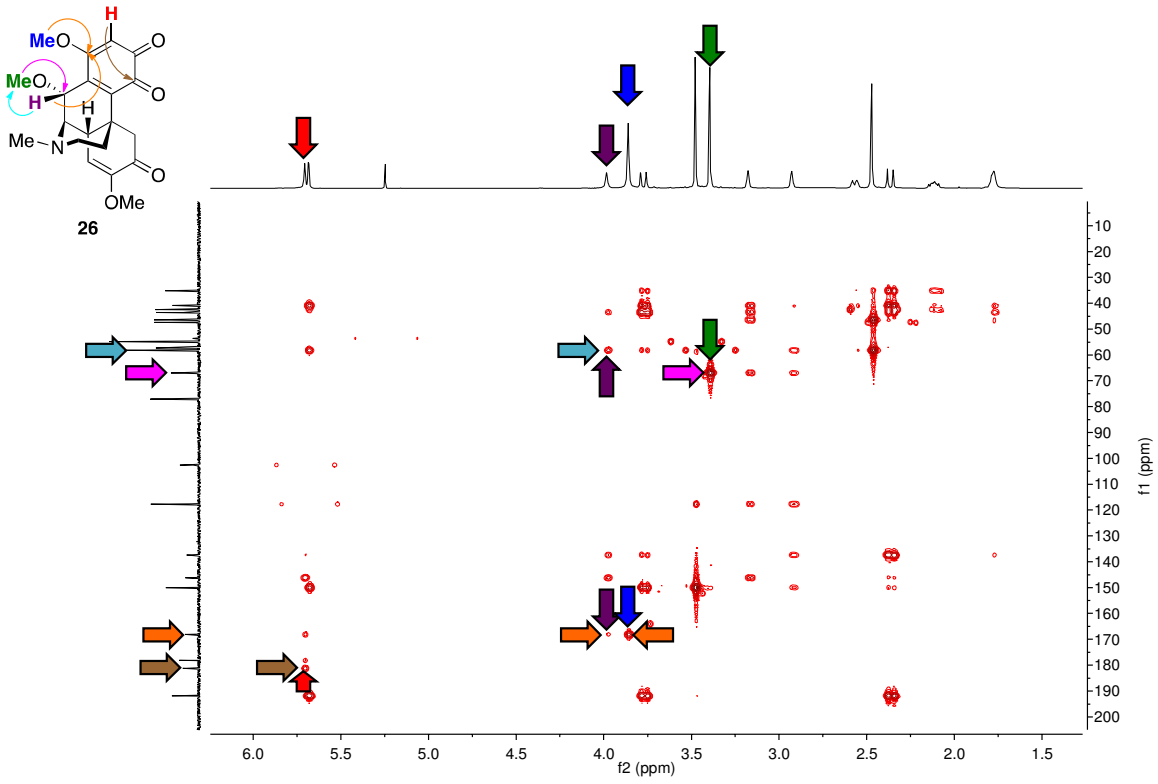


26

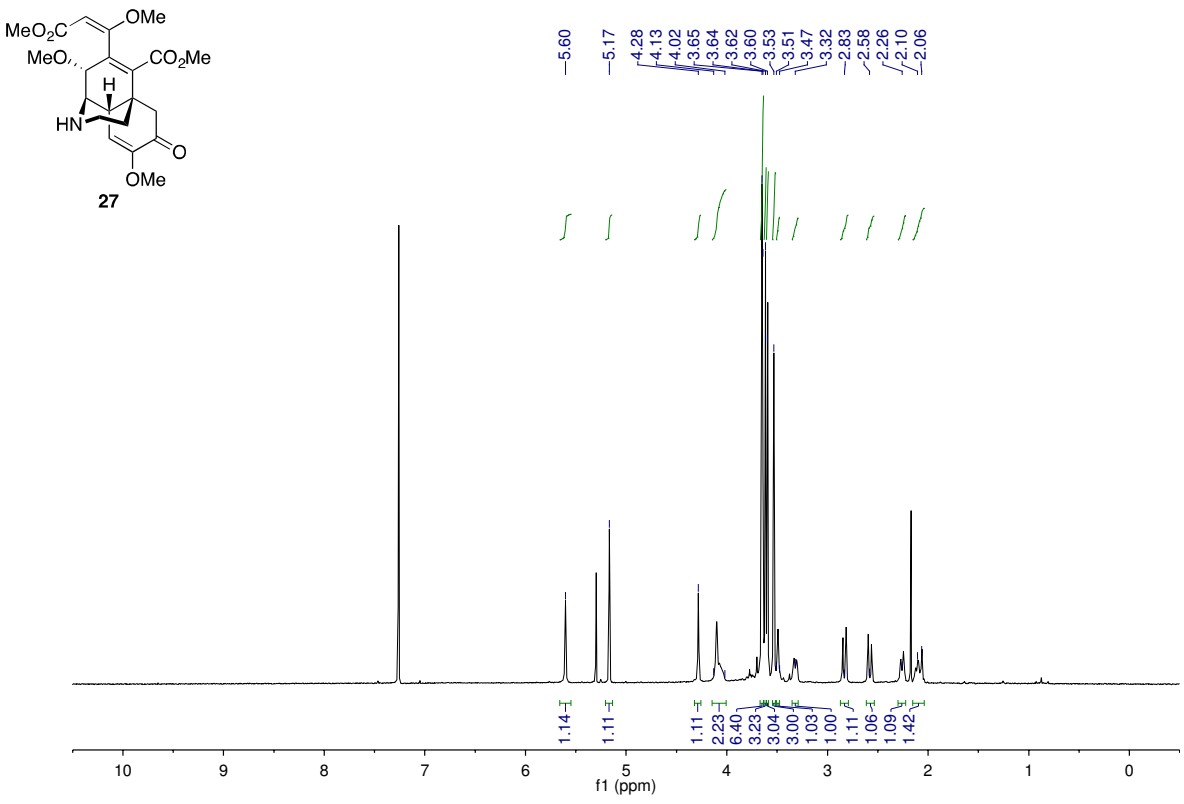
^{13}C NMR ($CDCl_3$)



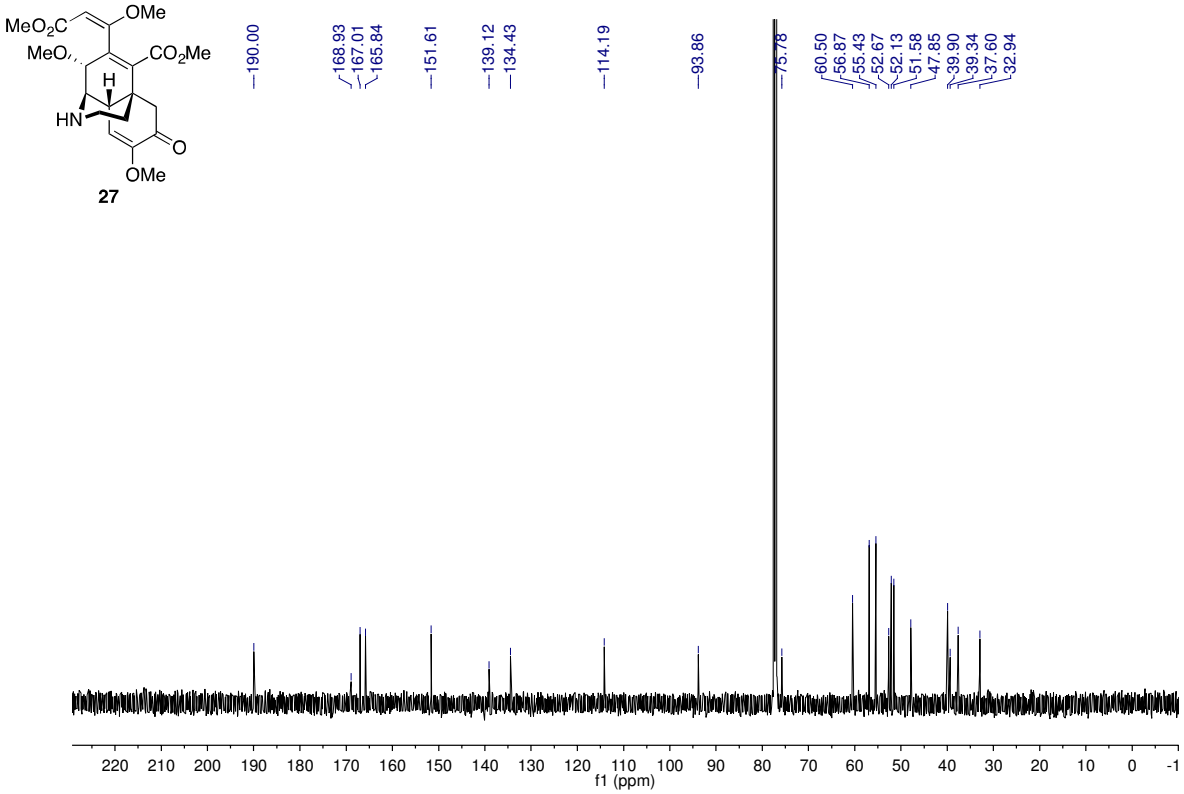
^{1}H–^{13}C HSQC NMR ($CDCl_3$)



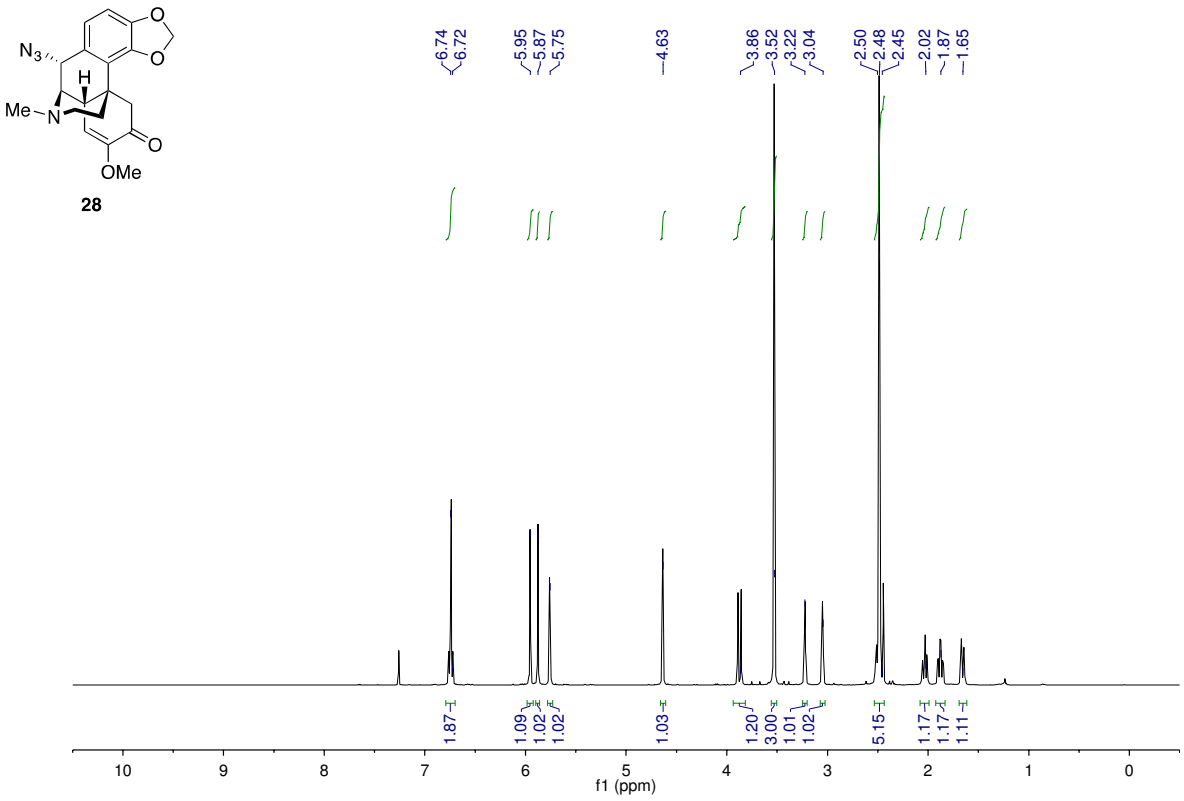
^{1}H–^{13}C HMBC NMR ($CDCl_3$)



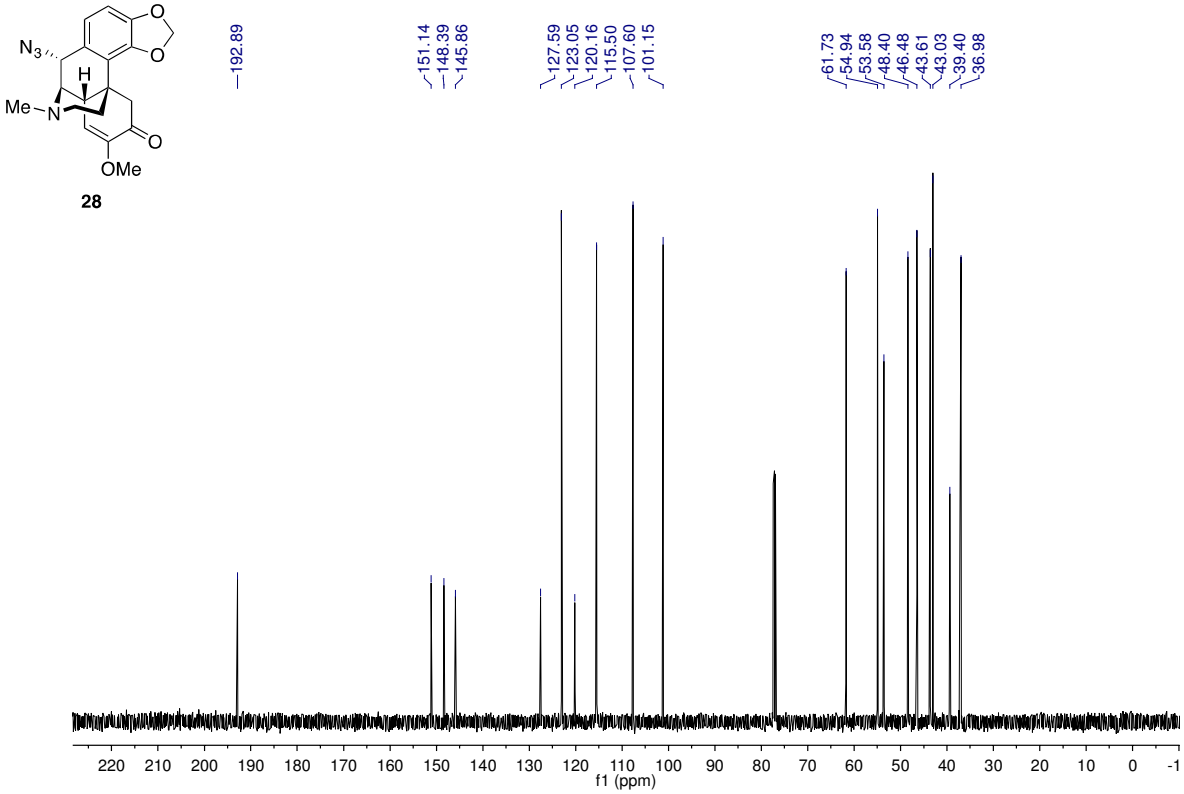
^{1}H NMR ($CDCl_3$)



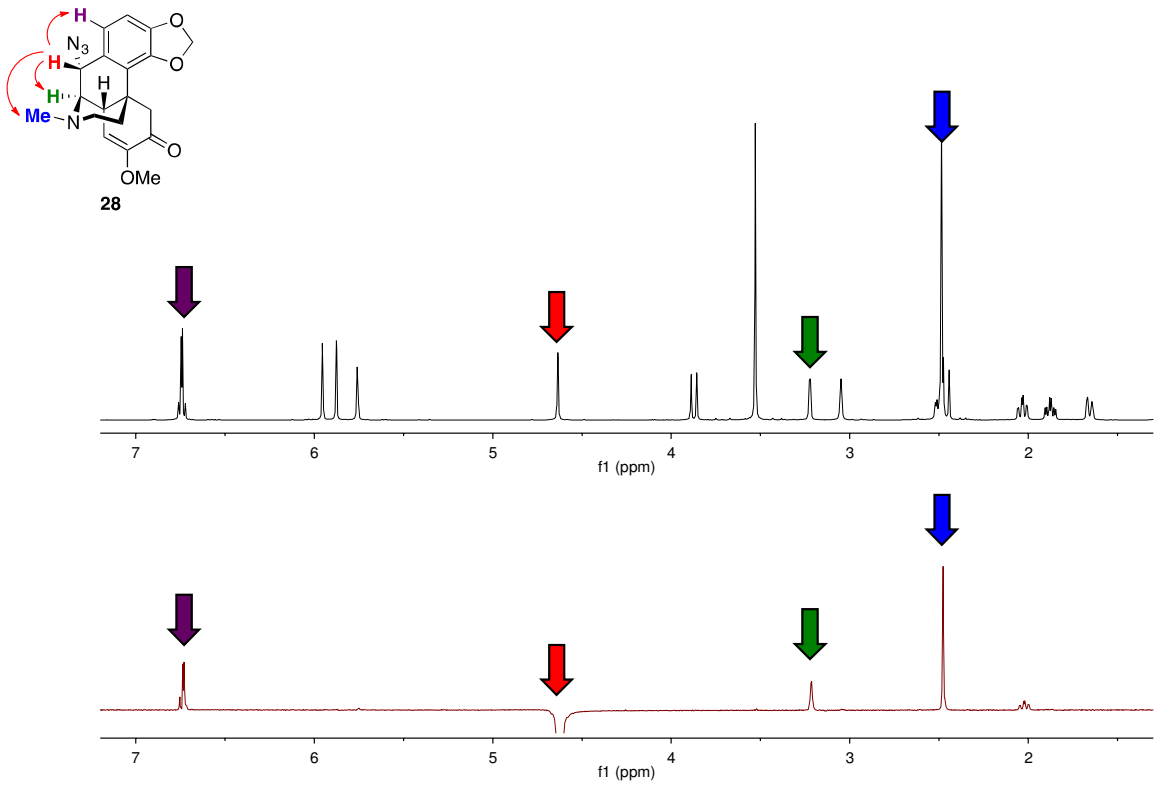
^{13}C NMR ($CDCl_3$)



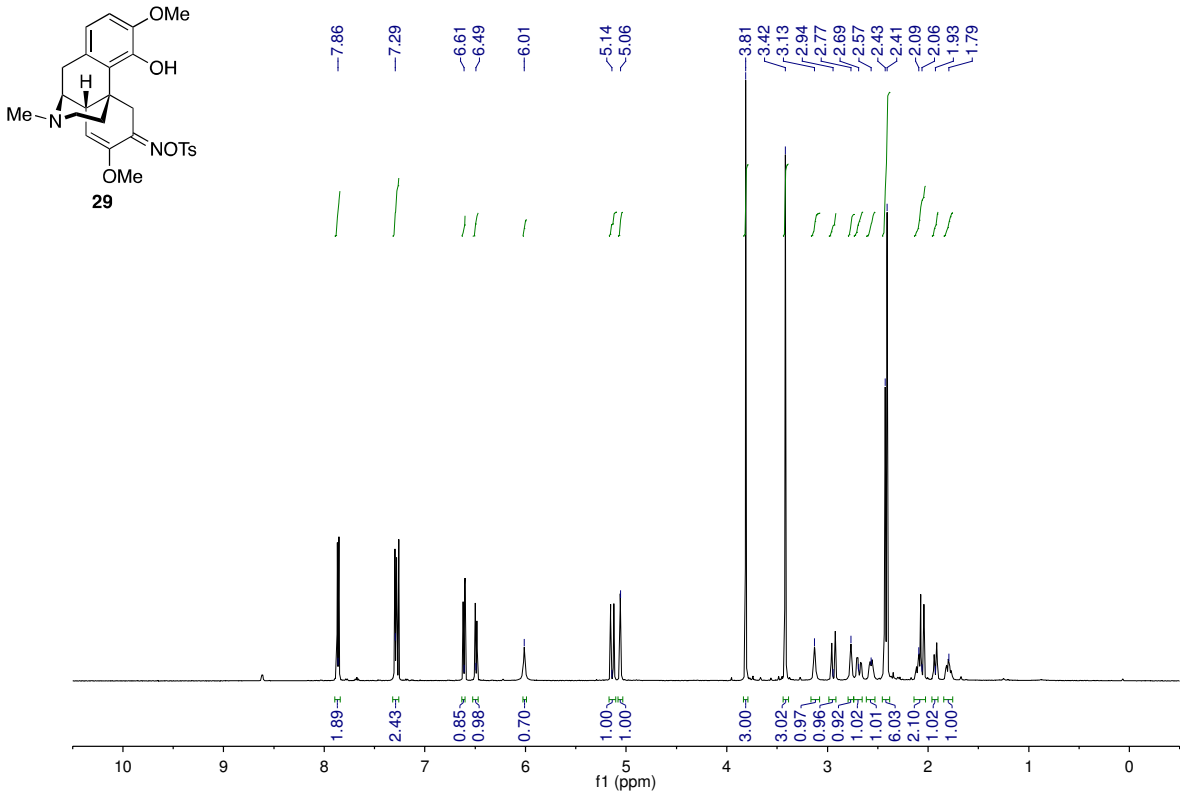
^{1}H NMR ($CDCl_3$)



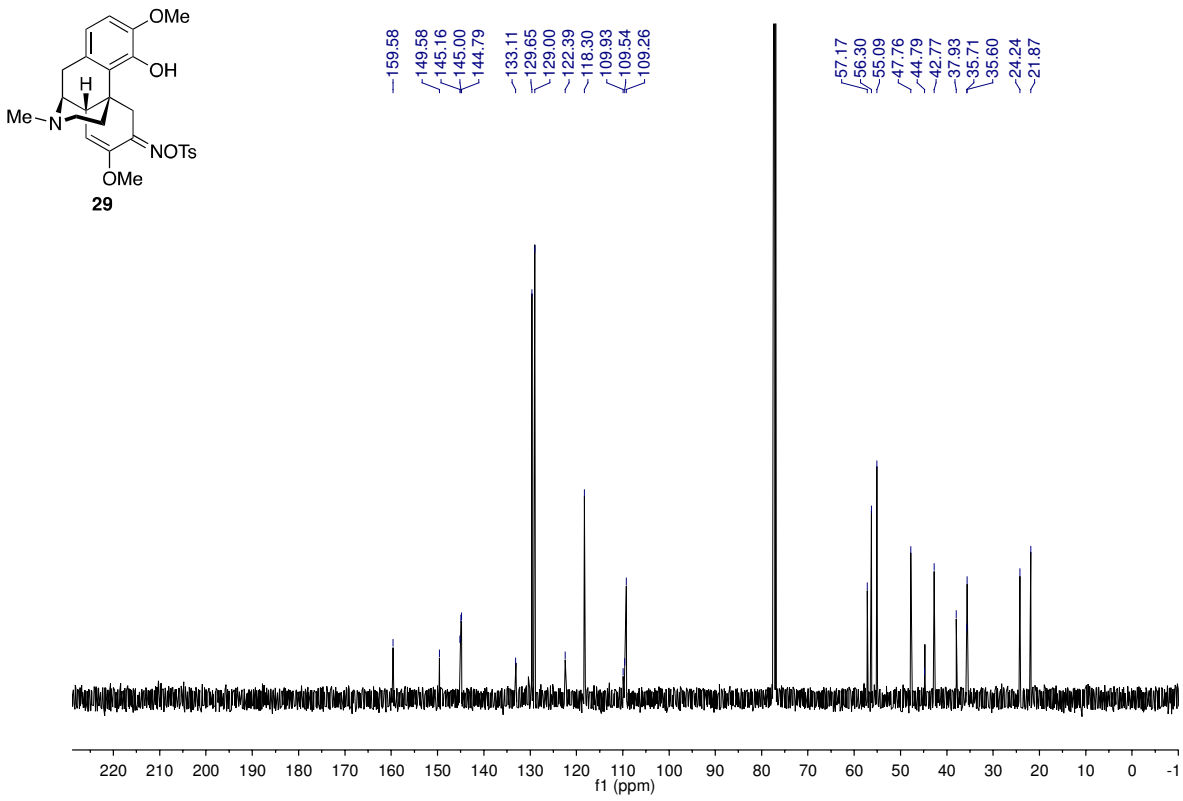
^{13}C NMR ($CDCl_3$)



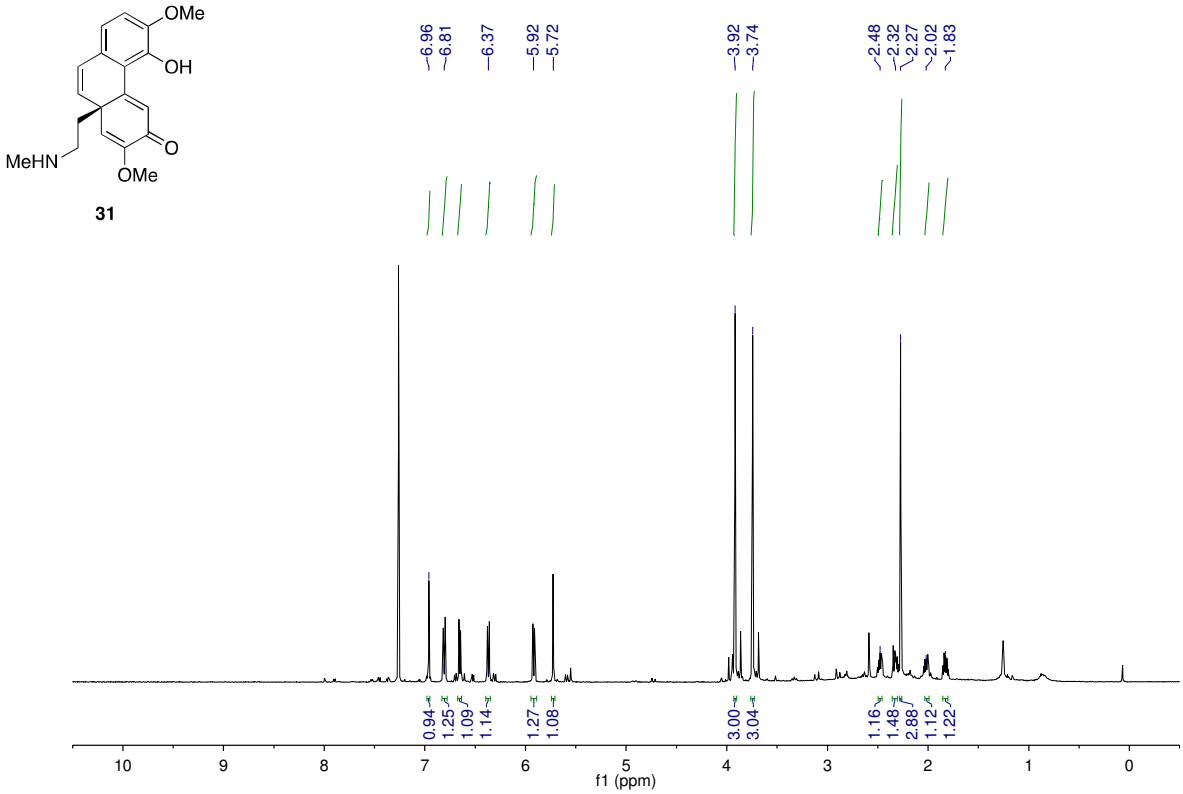
^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)



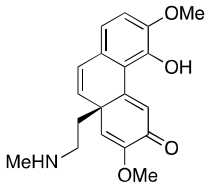
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)

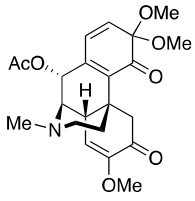


^{1}H NMR ($CDCl_3$)



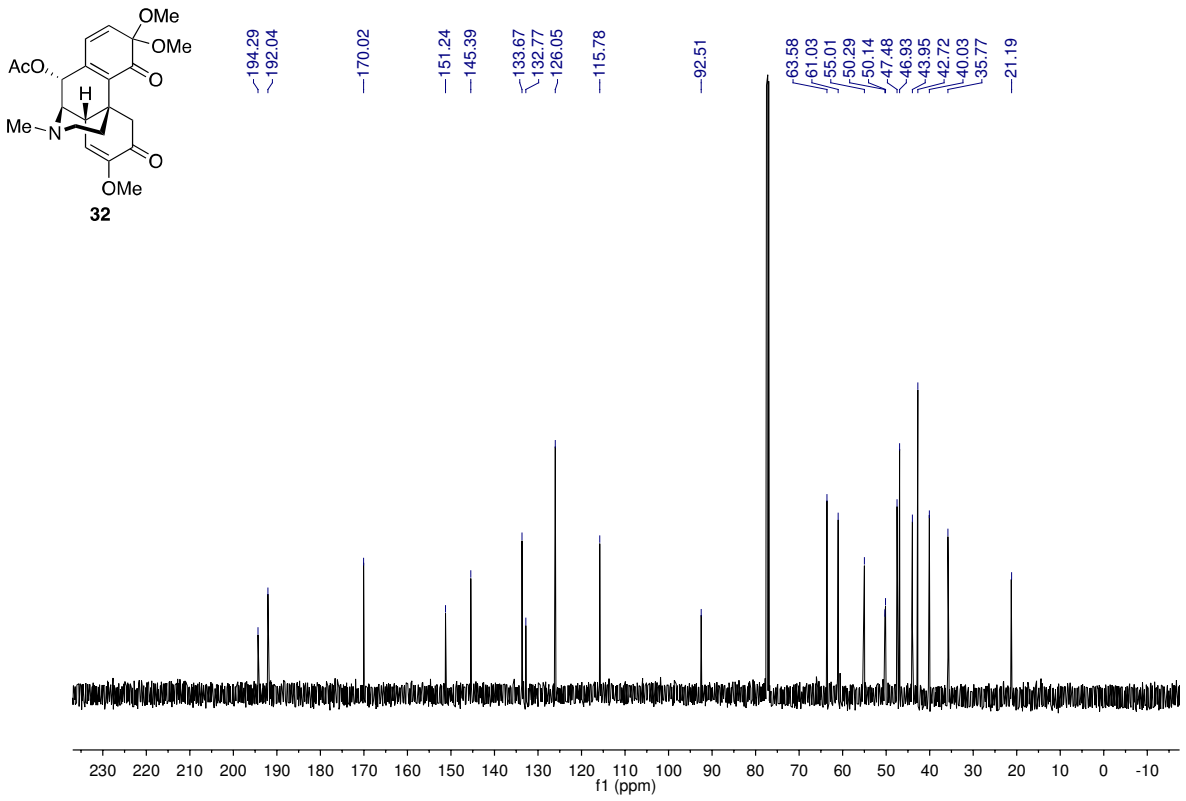
31

^{13}C NMR (CD_3OD)

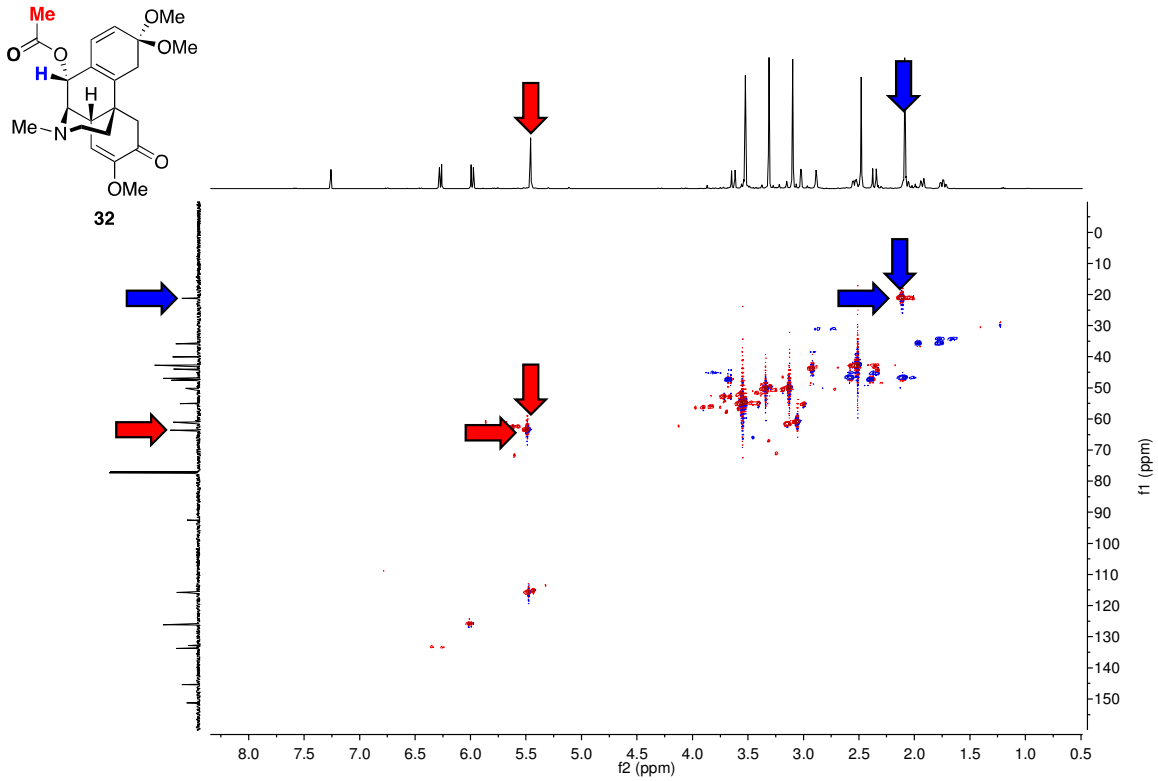


32

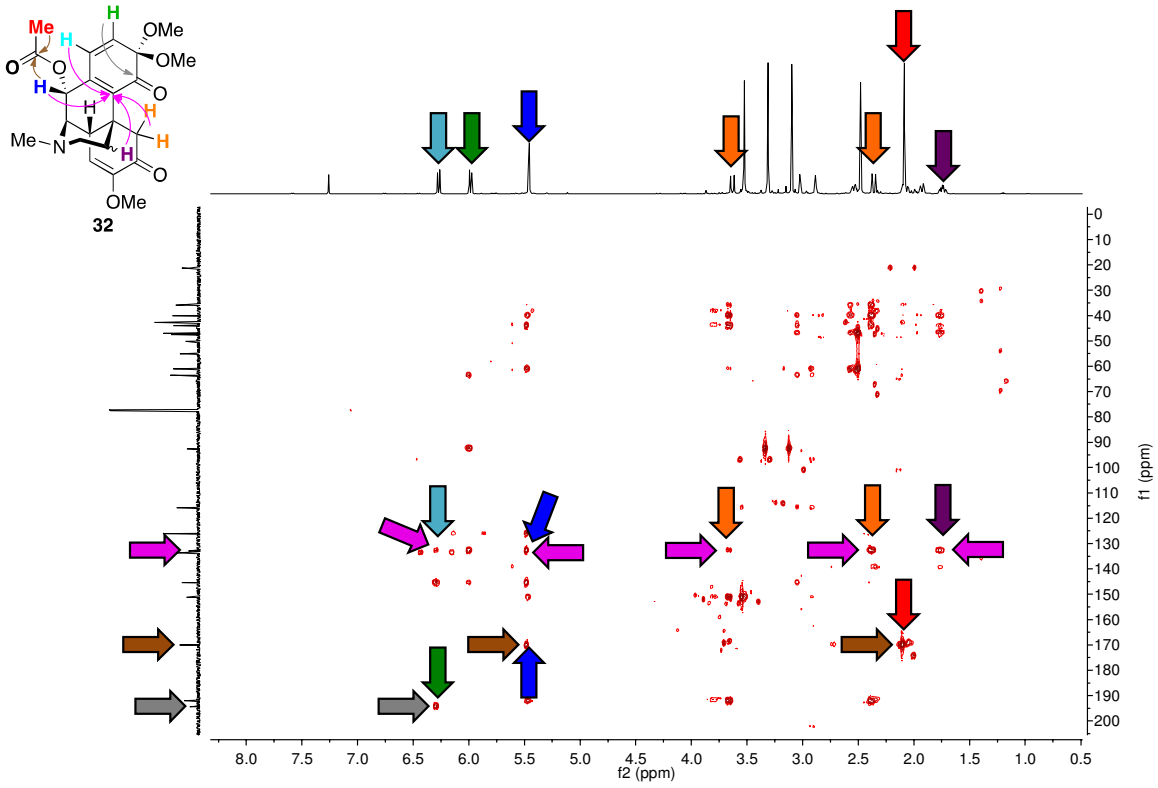
^{1}H NMR ($CDCl_3$)



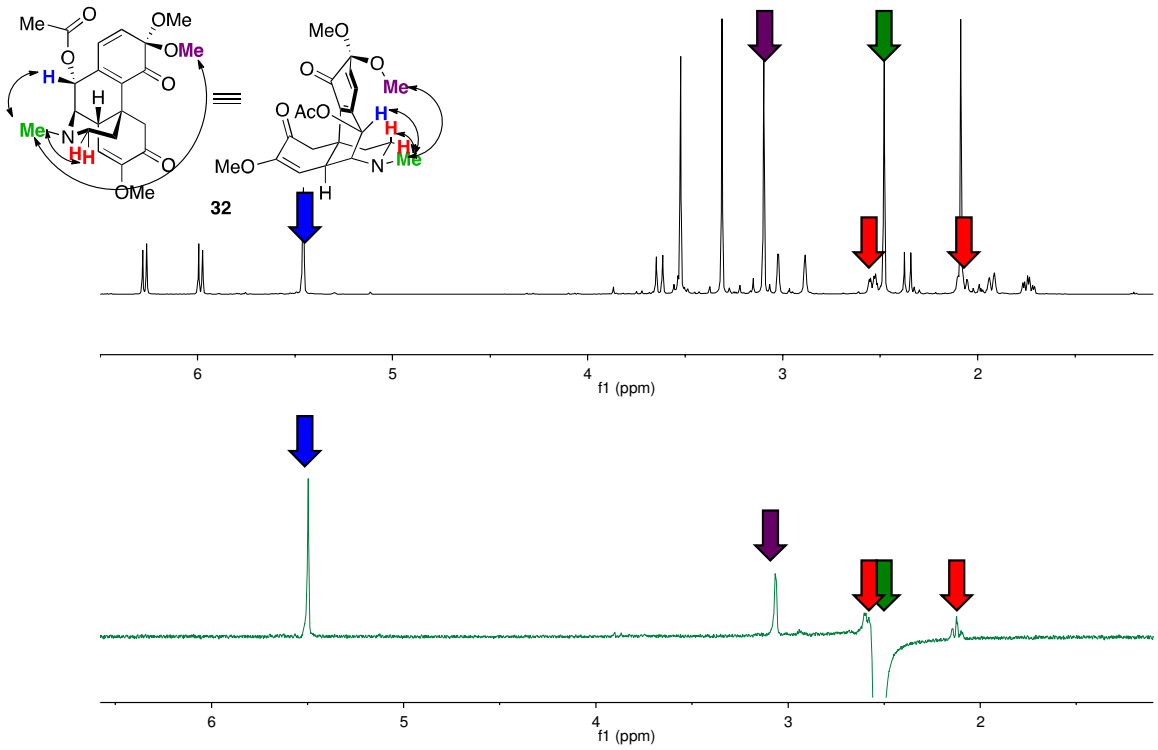
^{13}C NMR ($CDCl_3$)



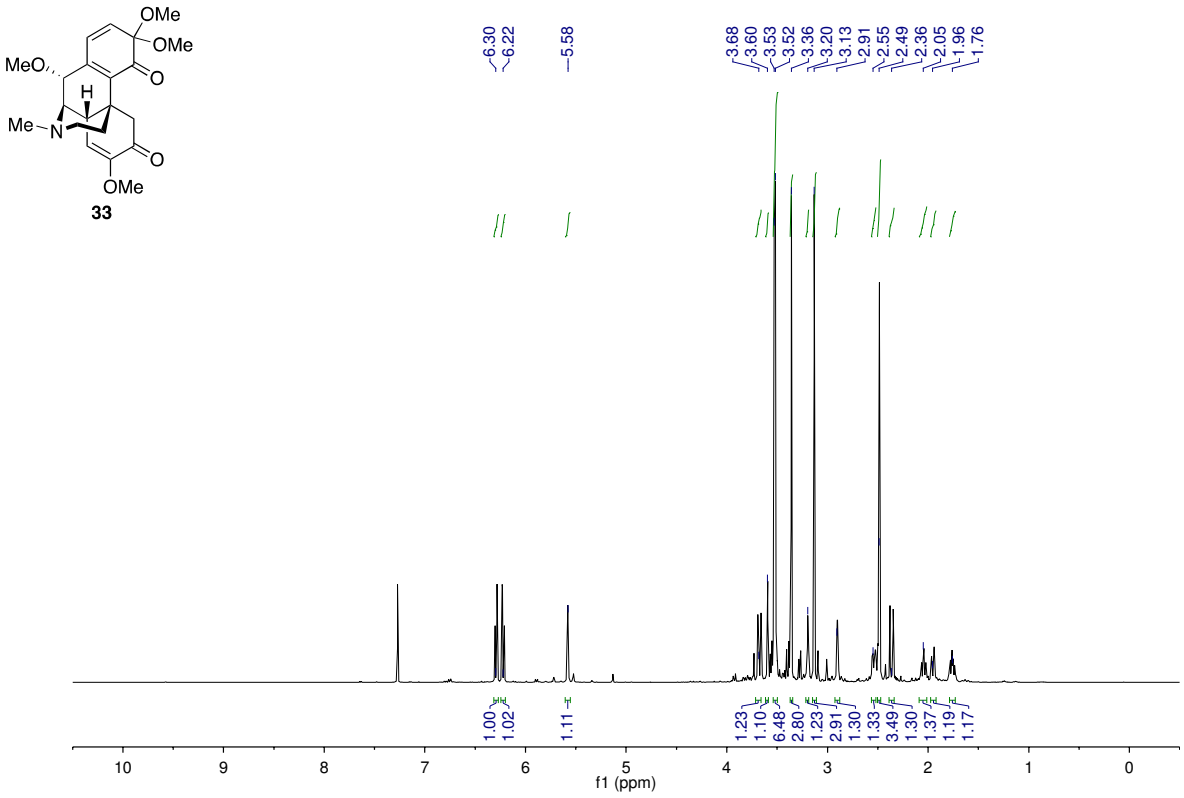
^{1}H–^{13}C HSQC NMR, 600 MHz ($CDCl_3$)



^{1}H–^{13}C HMBC NMR, 600 MHz ($CDCl_3$)

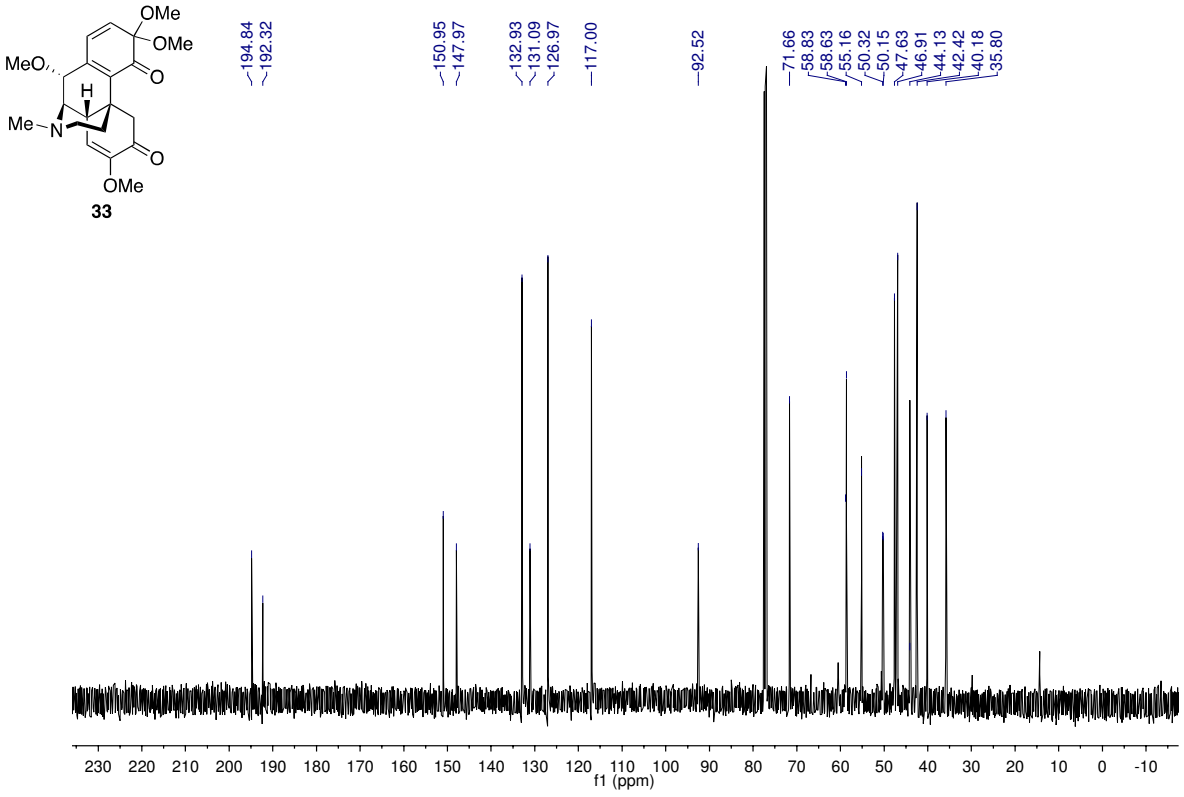


^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)



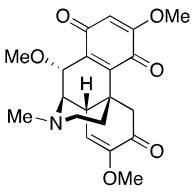
33

^{1}H NMR ($CDCl_3$)



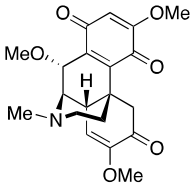
33

^{13}C NMR ($CDCl_3$)



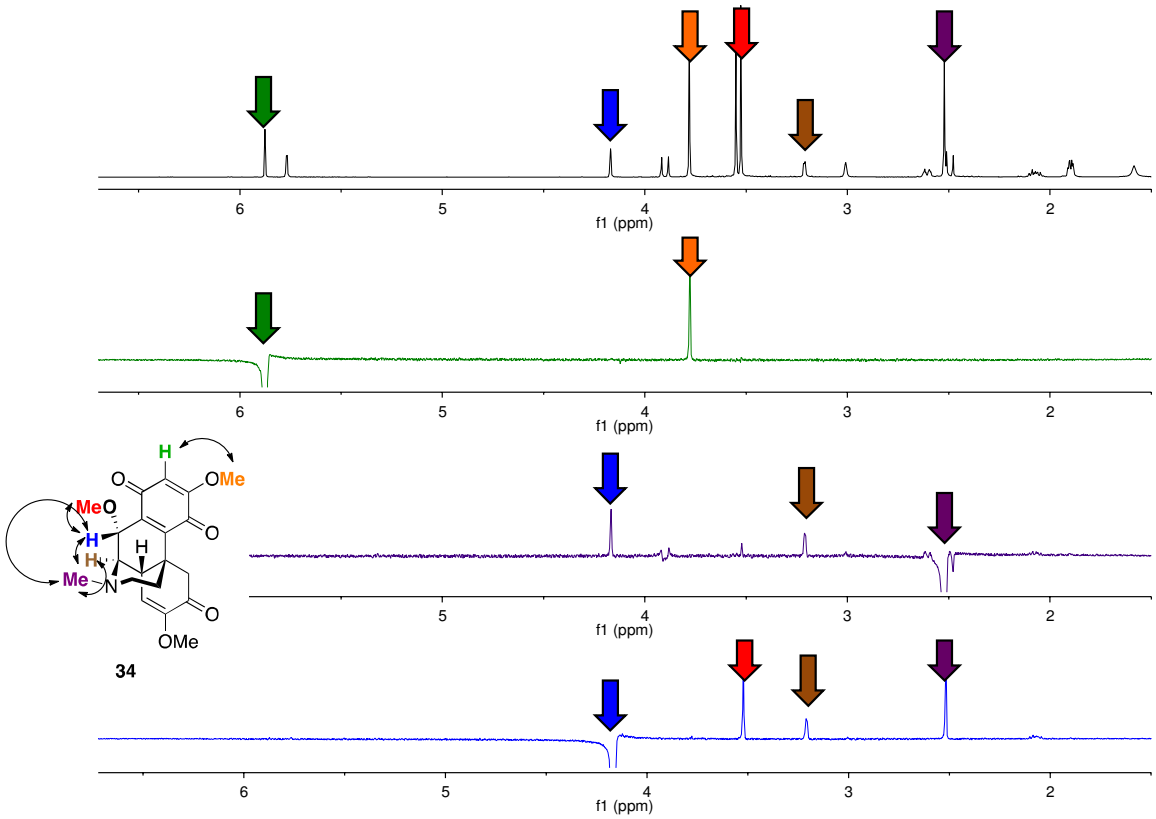
34

^{1}H NMR ($CDCl_3$)

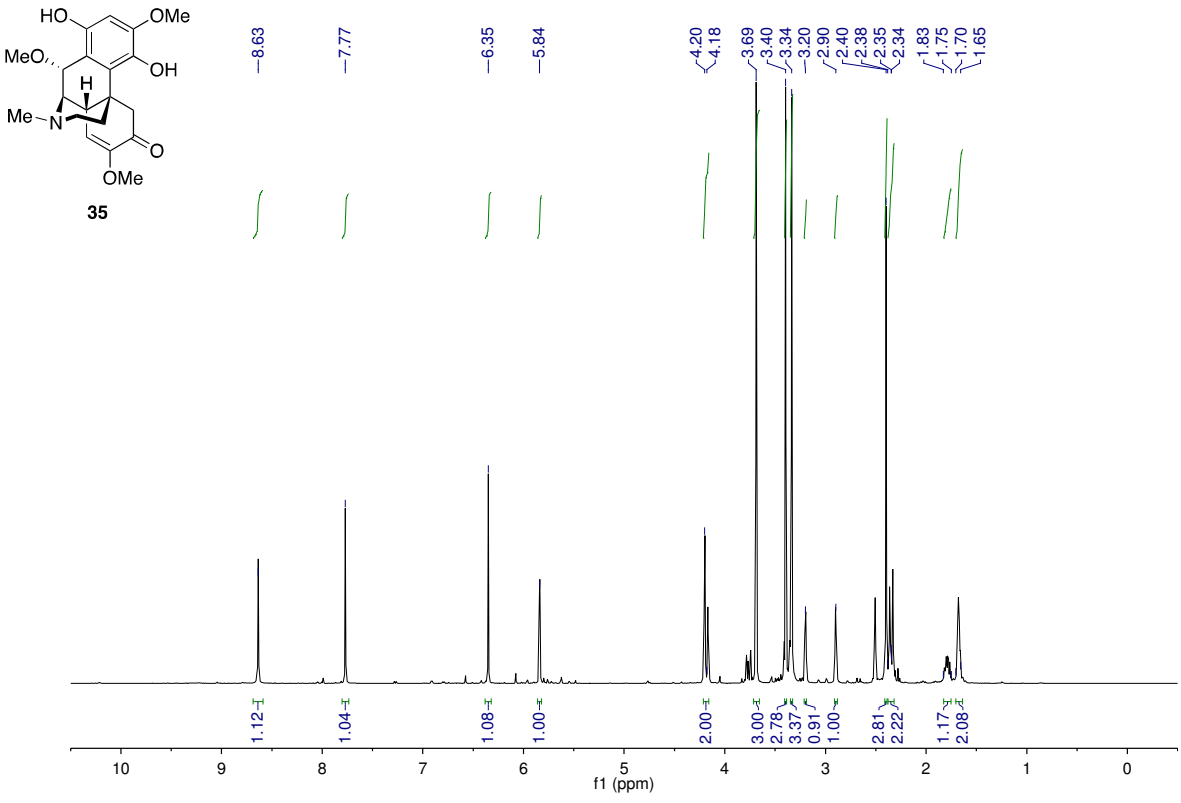


34

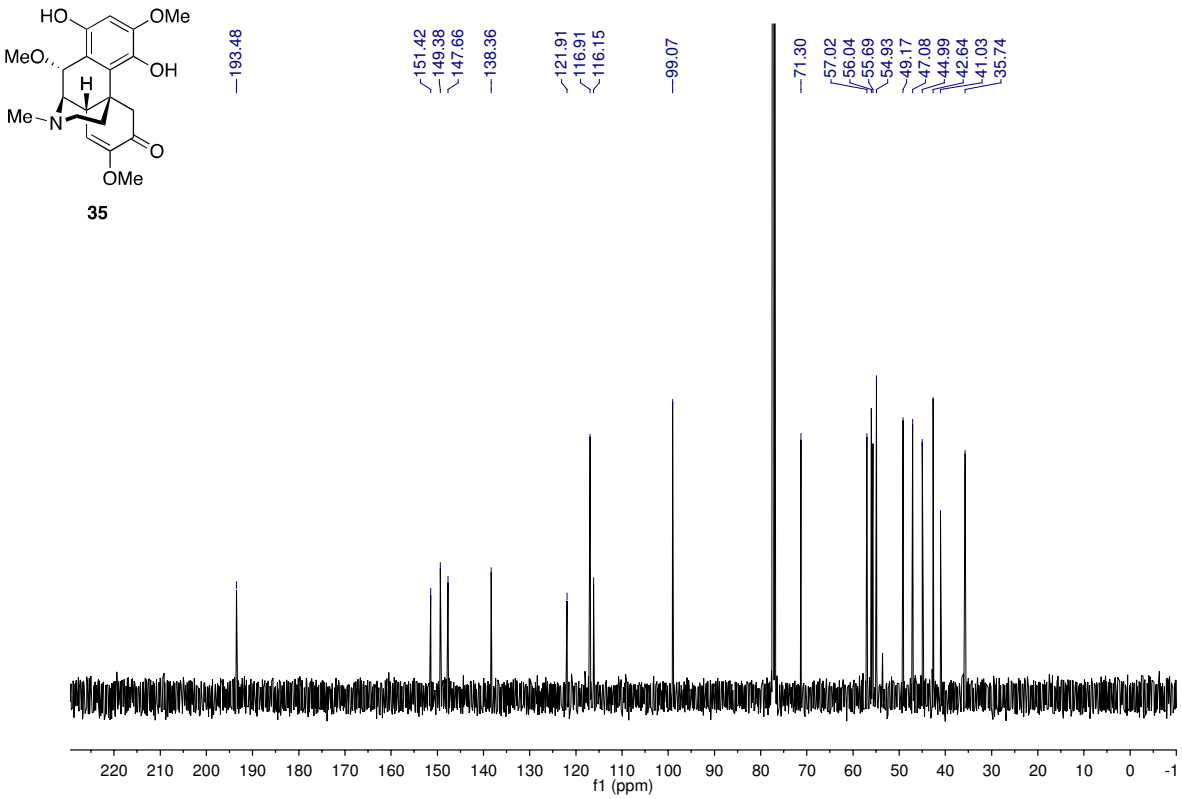
^{13}C NMR ($CDCl_3$)



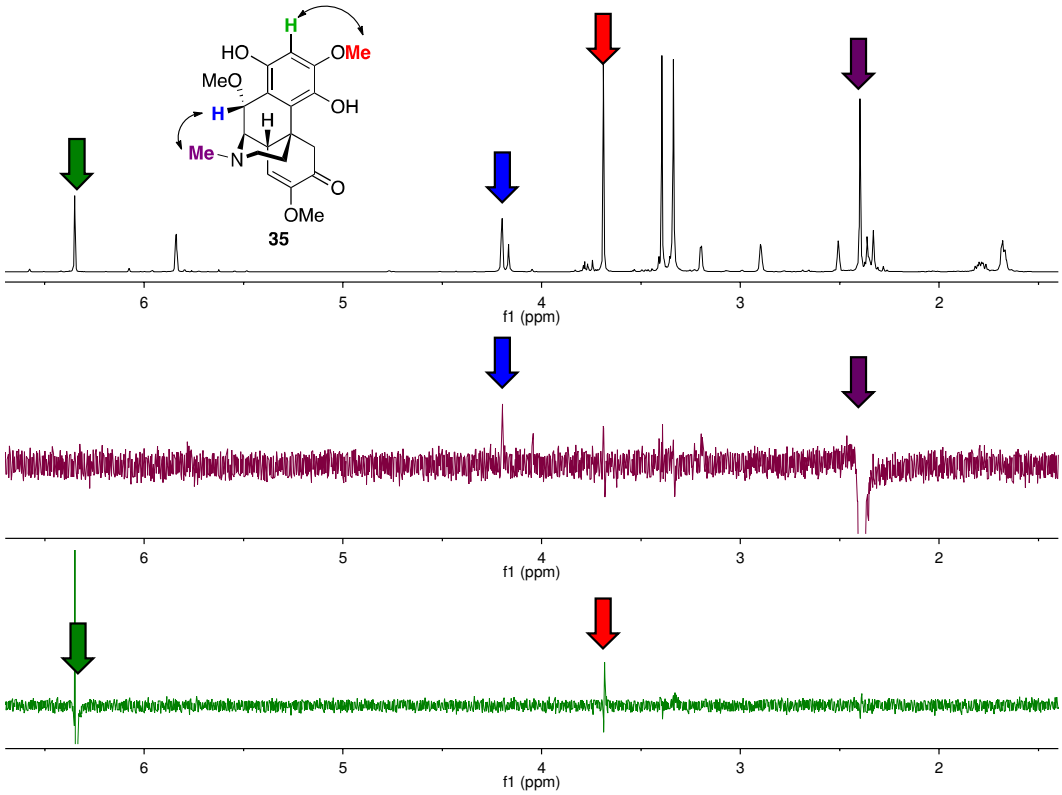
^{1}H–^{1}H 1D NOESY NMR ($CDCl_3$)



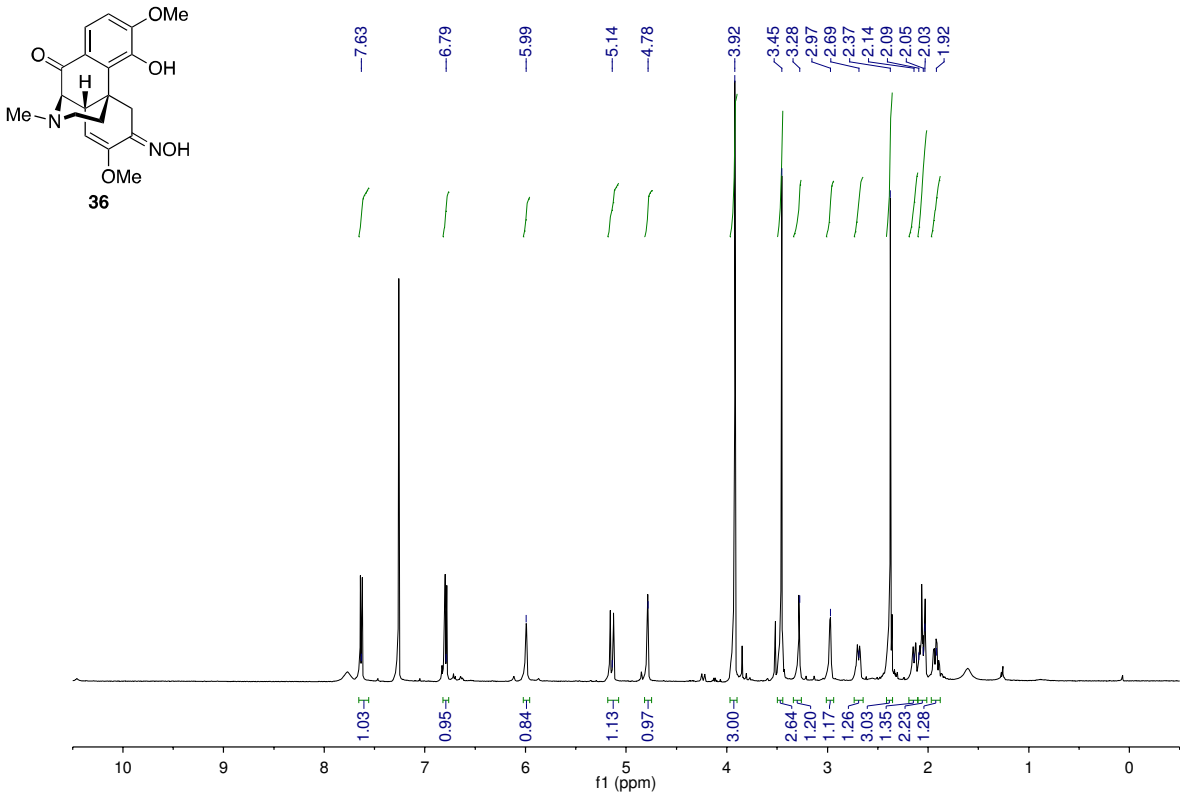
^{1}H NMR (d_6-DMSO)



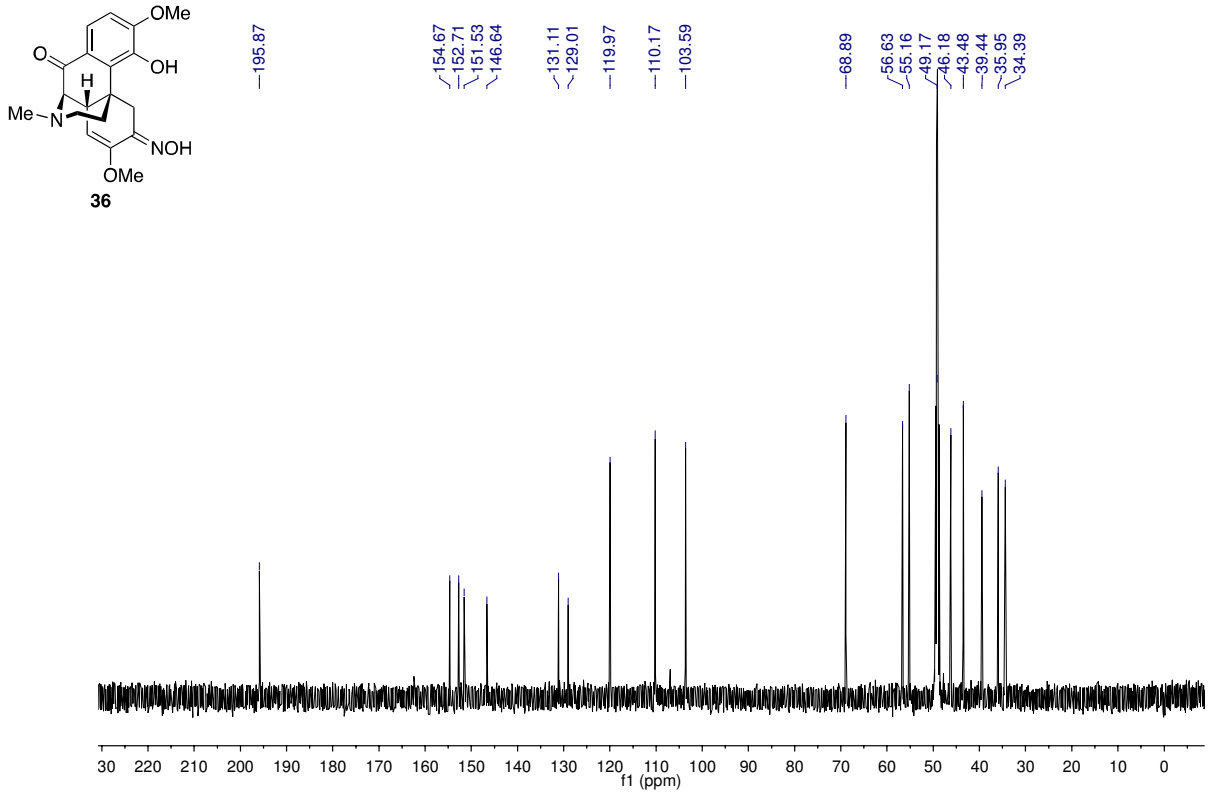
^{13}C NMR ($CDCl_3$)



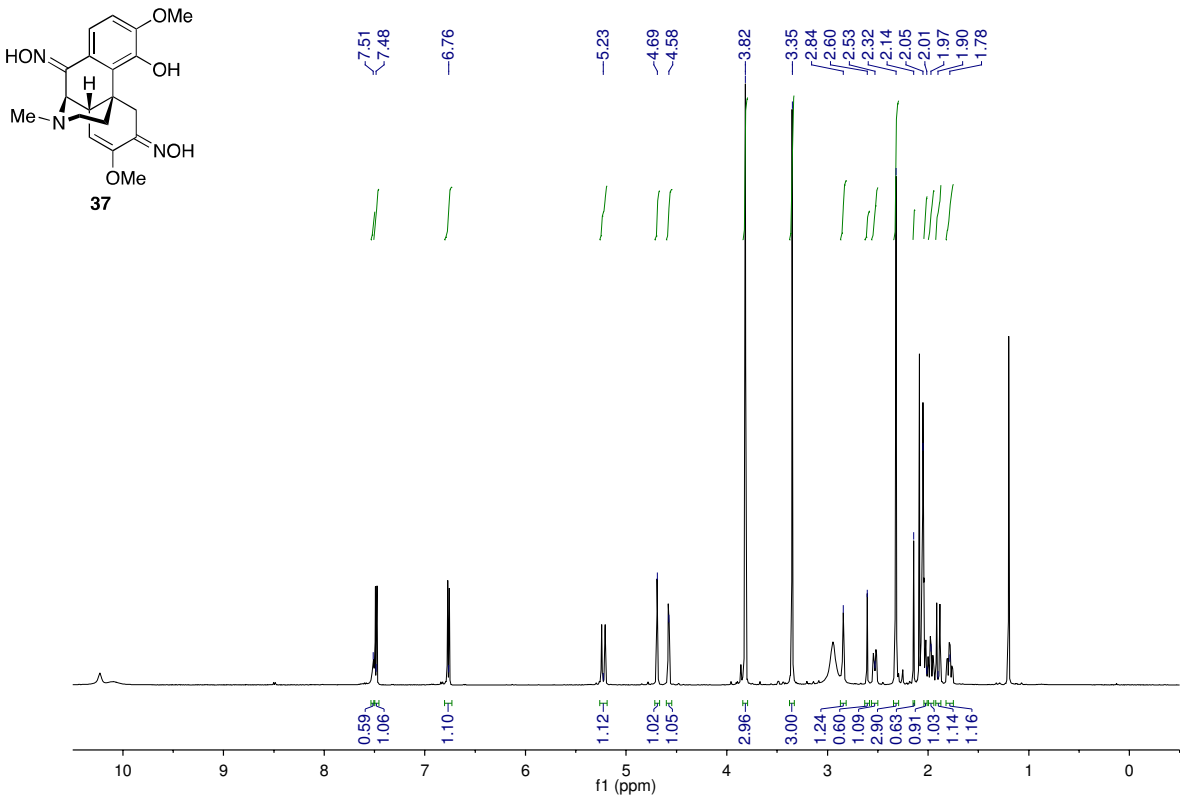
^{1}H–^{1}H 1D NOESY NMR (d_6-DMSO)



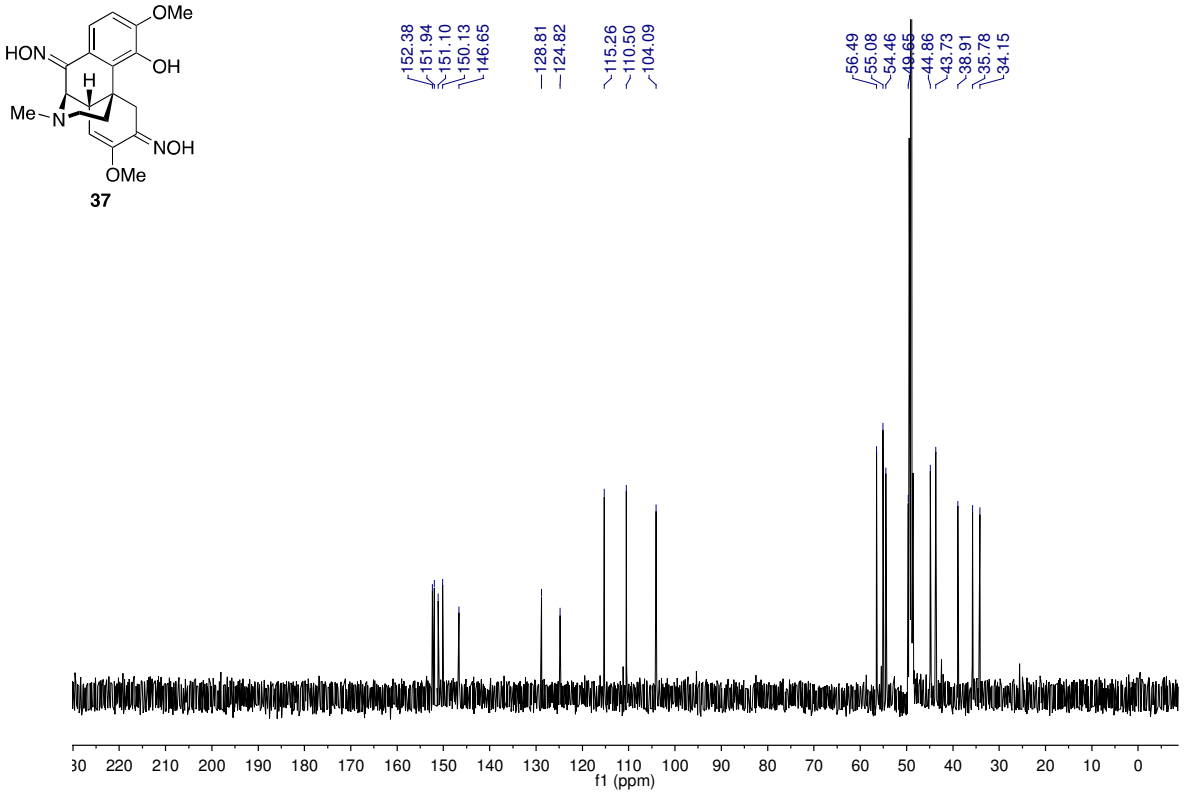
^{1}H NMR ($CDCl_3$)



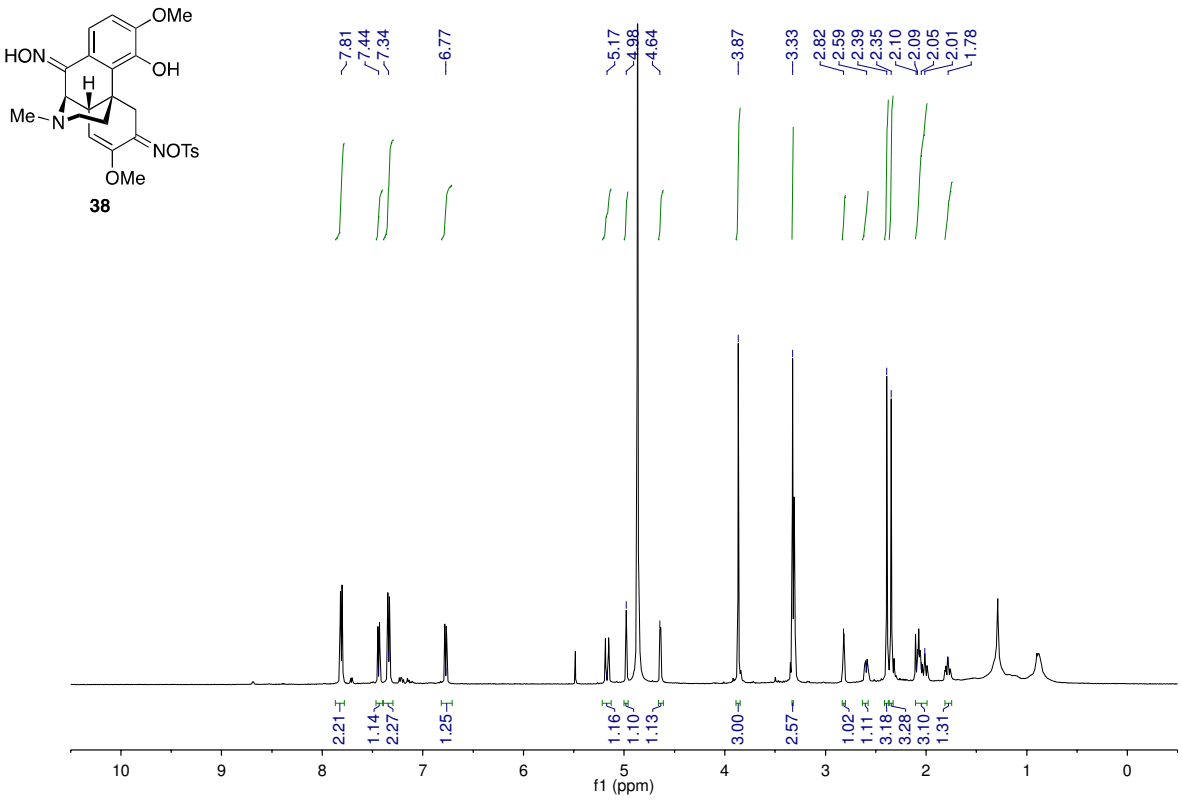
^{13}C NMR (CD_3OD)



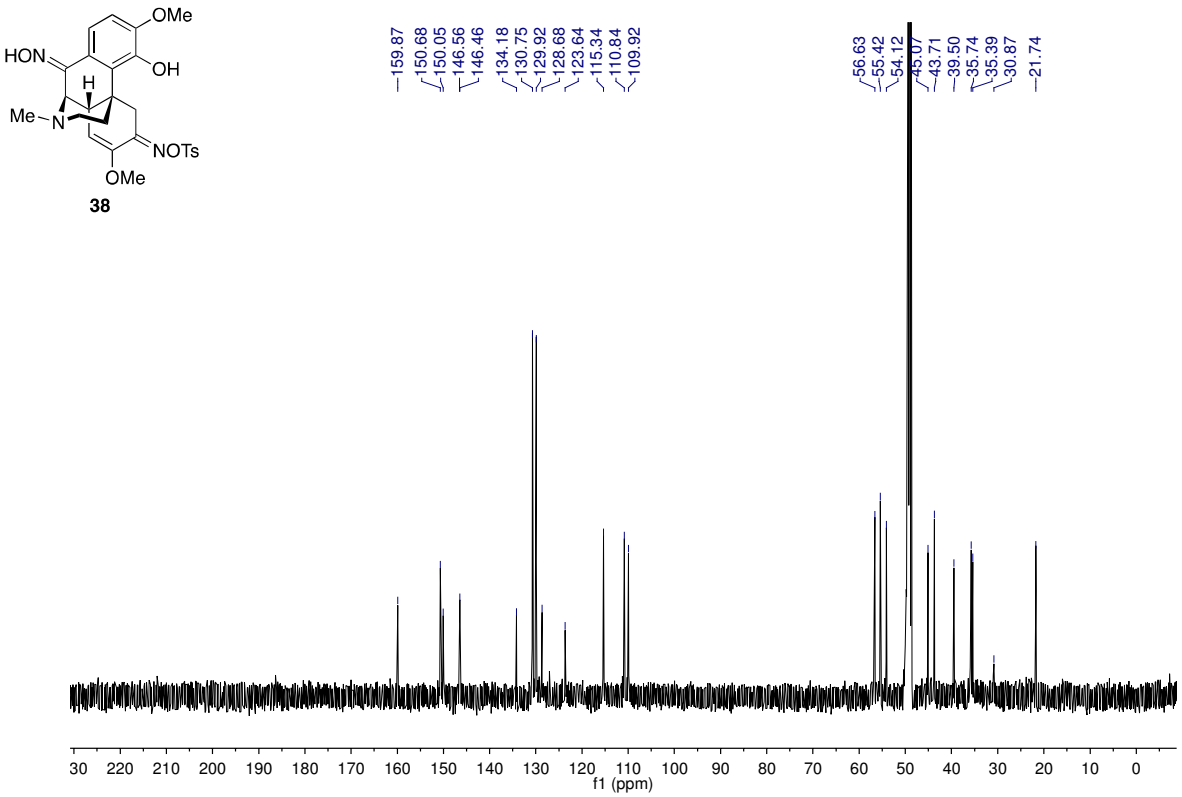
^{1}H NMR (*d*$_6$-acetone)



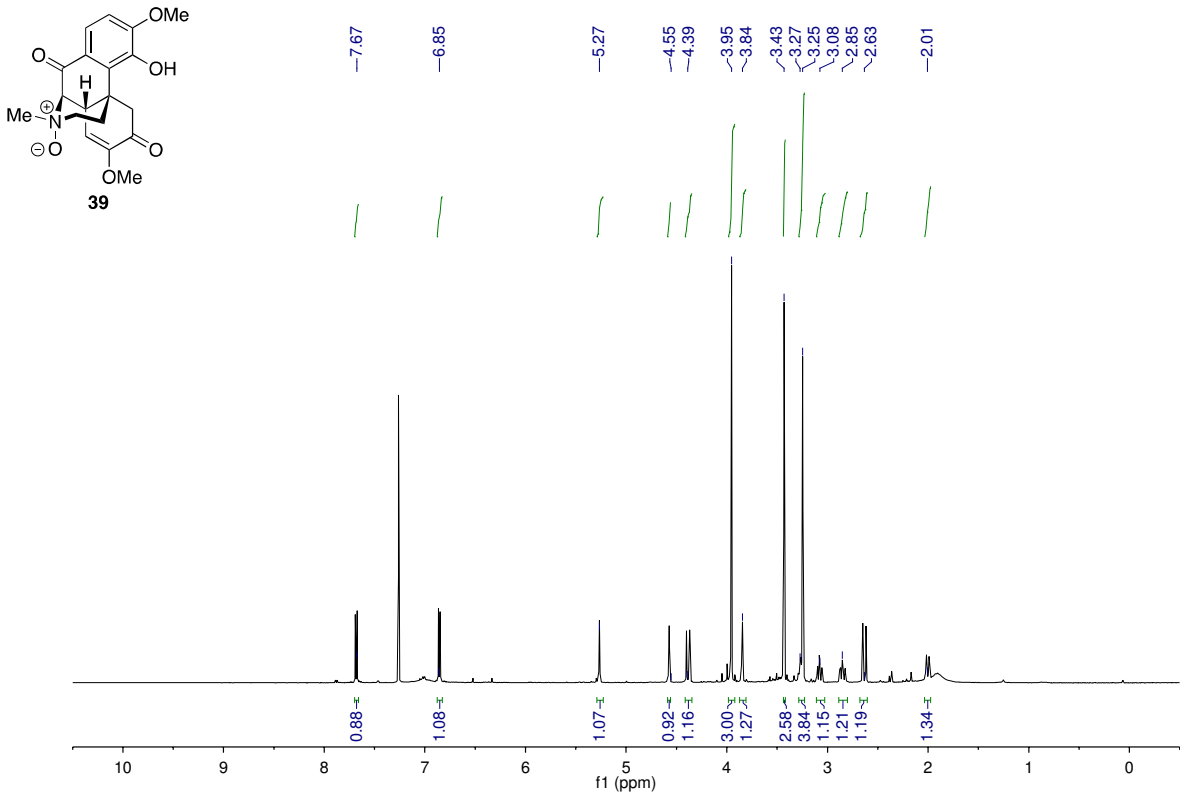
^{13}C NMR (CD_3OD)



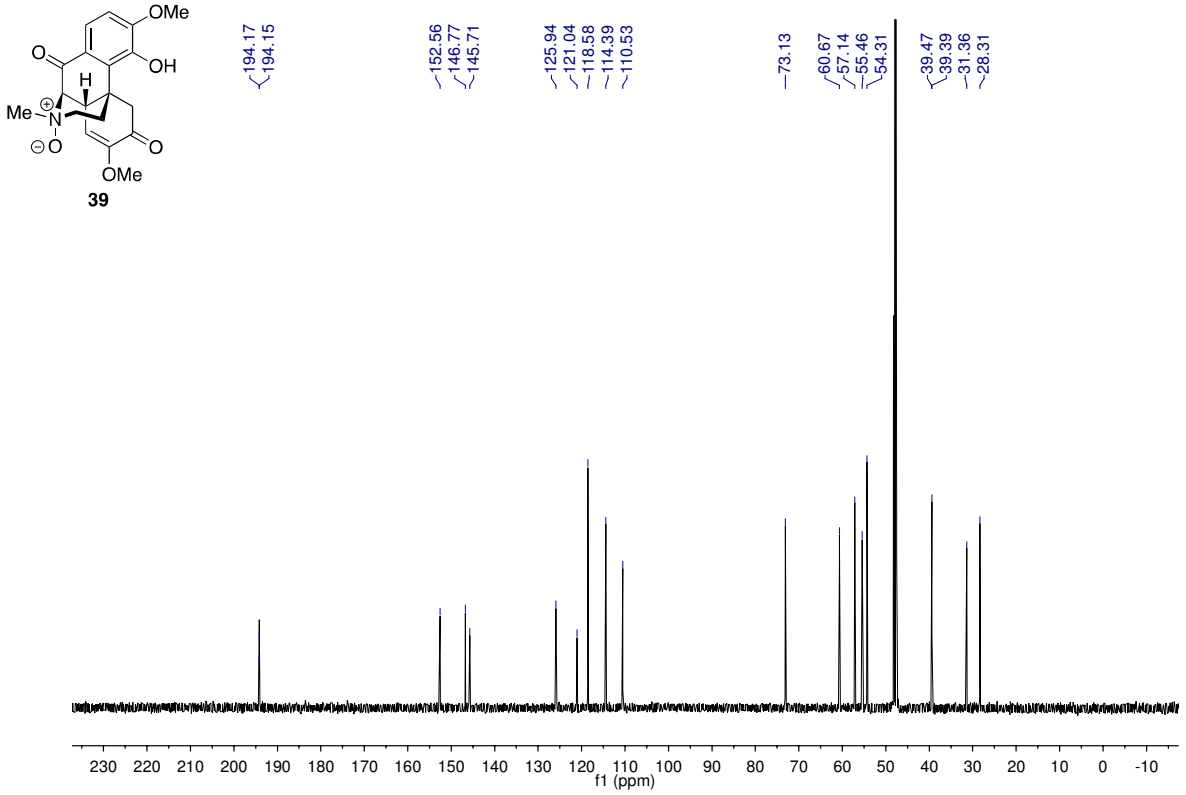
^{1}H NMR (CD_3OD)



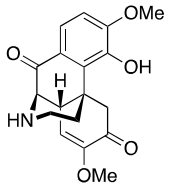
^{13}C NMR (CD_3OD)



^{1}H NMR ($CDCl_3$)

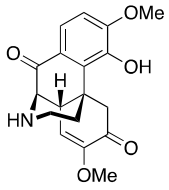


^{13}C NMR (CD_3OD)



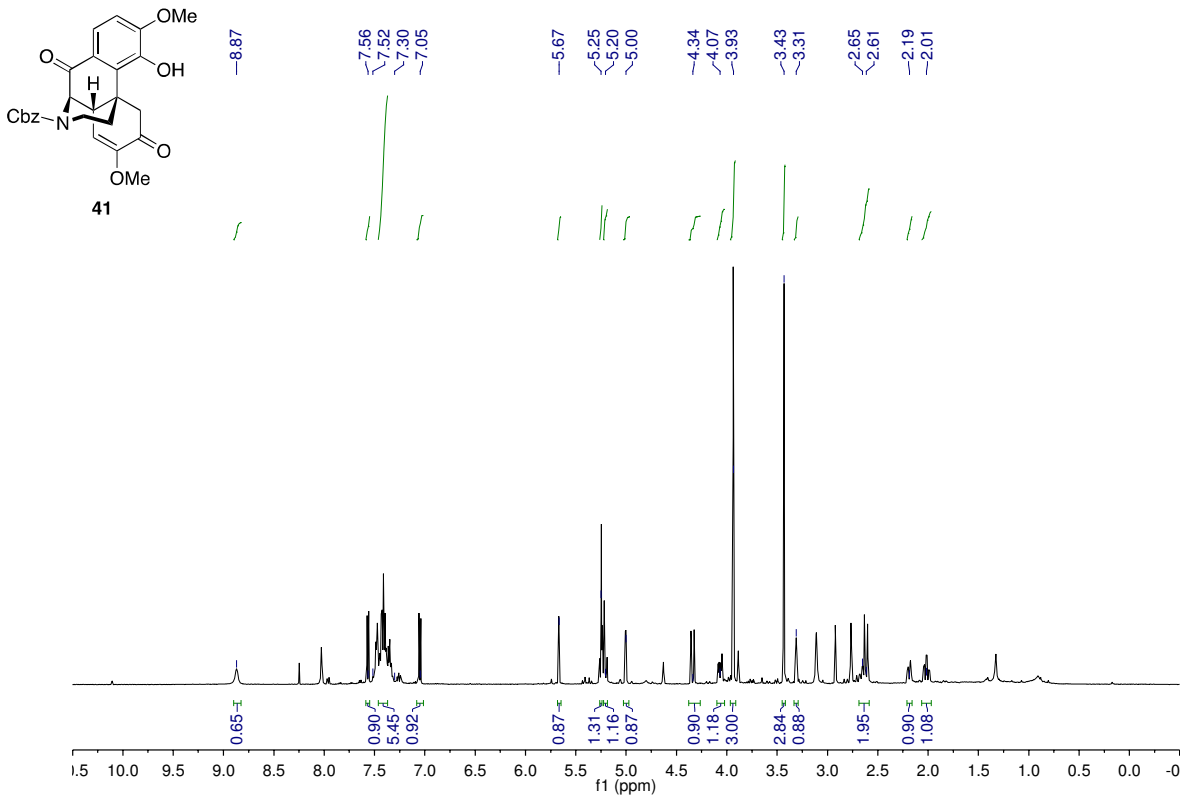
40

^{1}H NMR ($CDCl_3$)

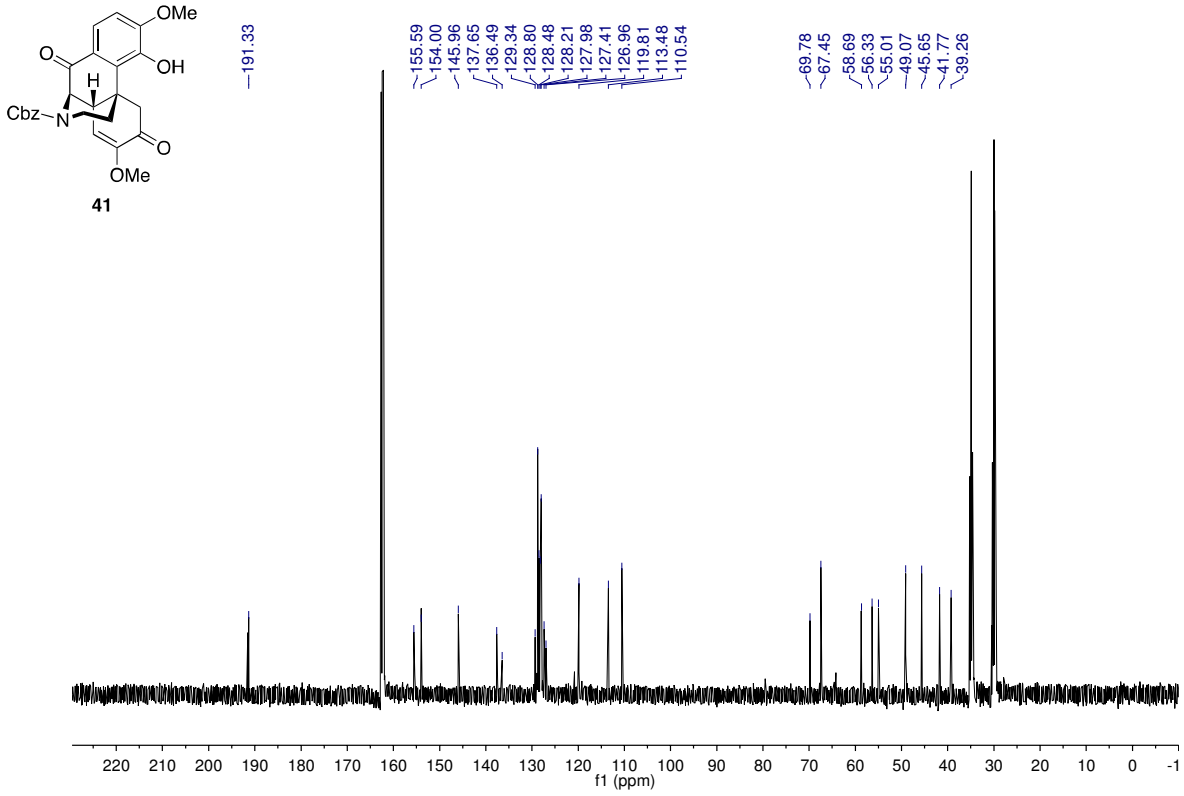


40

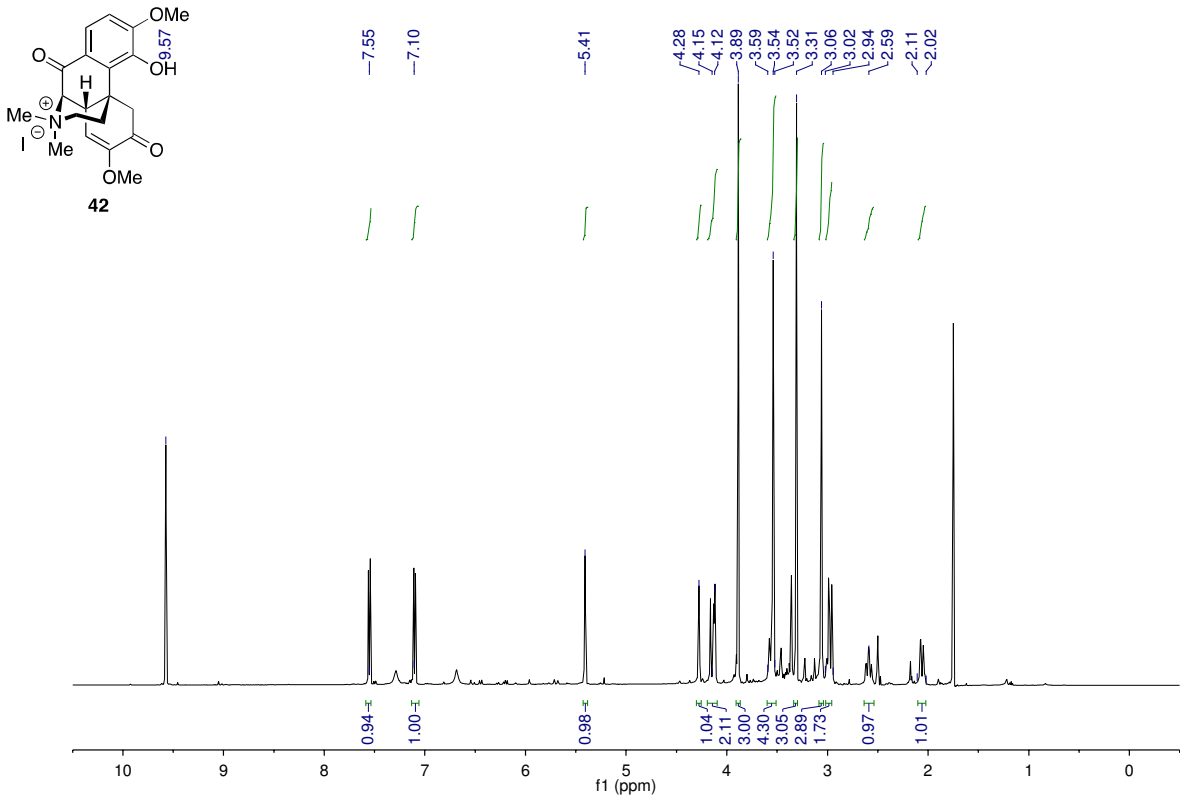
^{13}C NMR ($CDCl_3$)



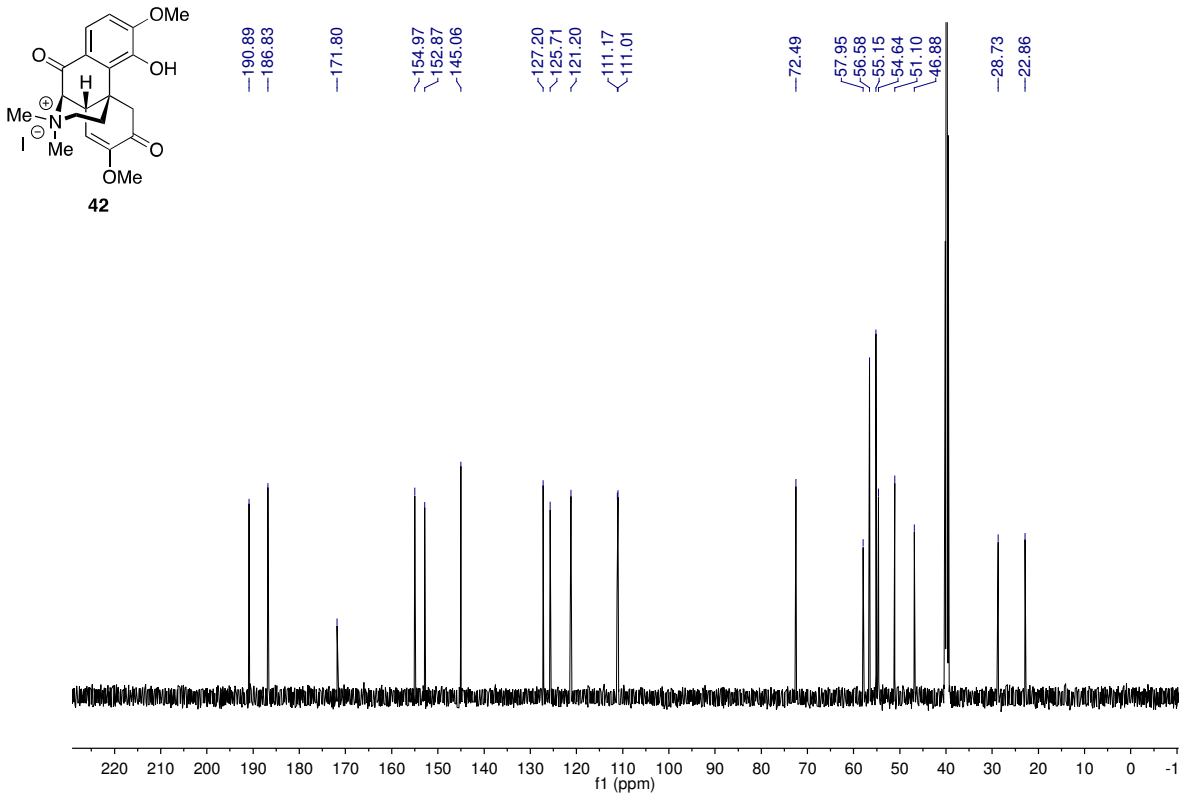
^{1}H NMR (d_7-DMF, 80 ºC)



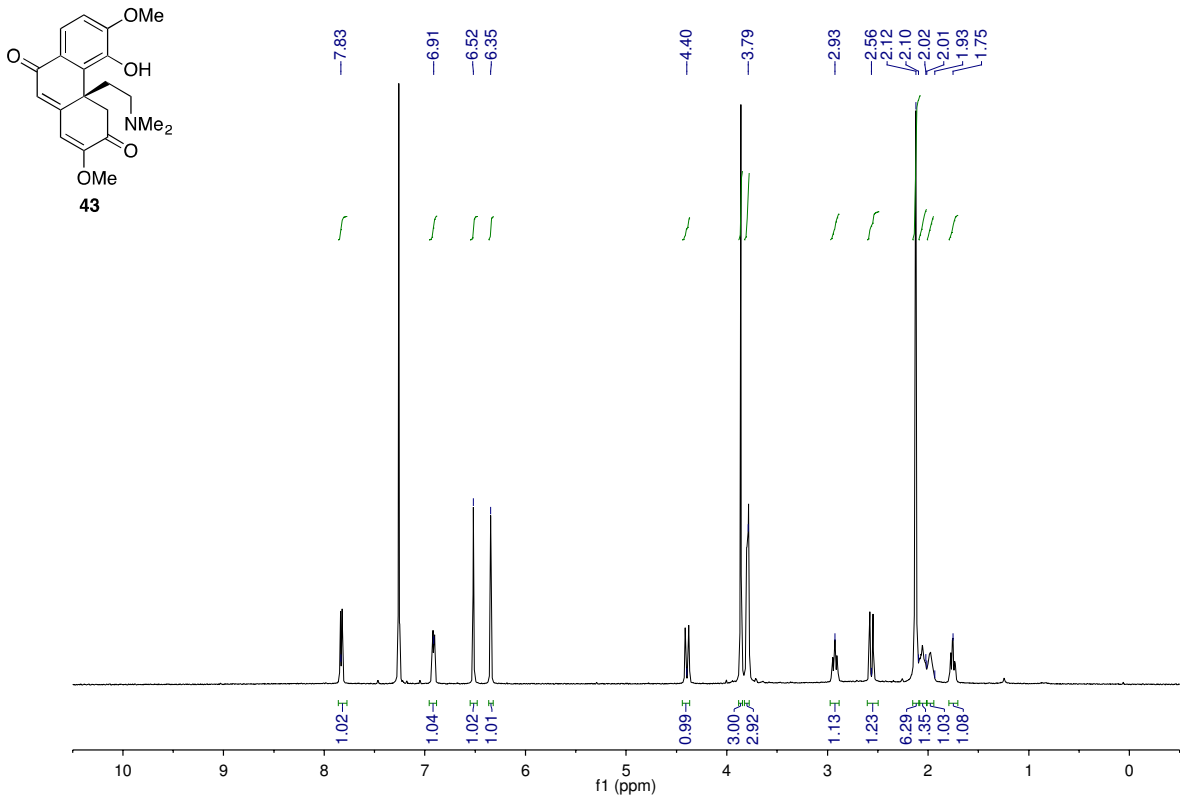
^{13}C NMR (d_7-DMF, 80 ºC)



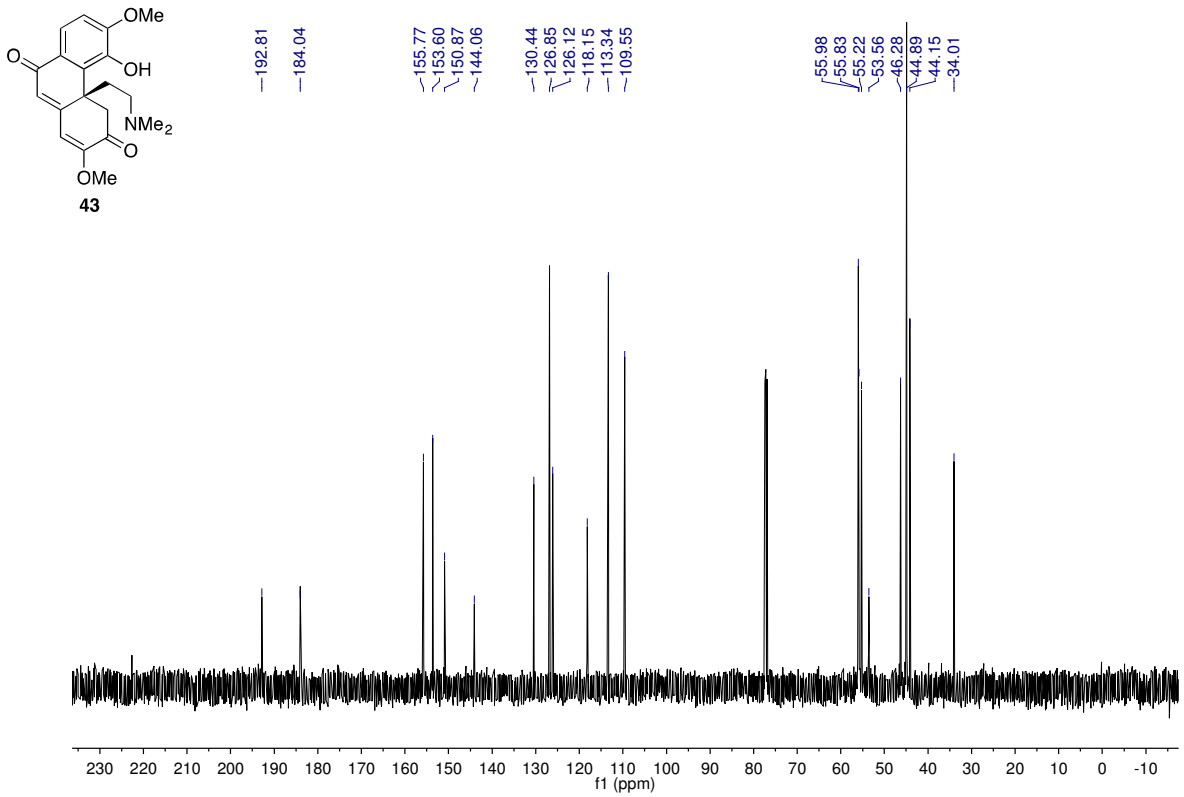
^{1}H NMR (d_6-DMSO)



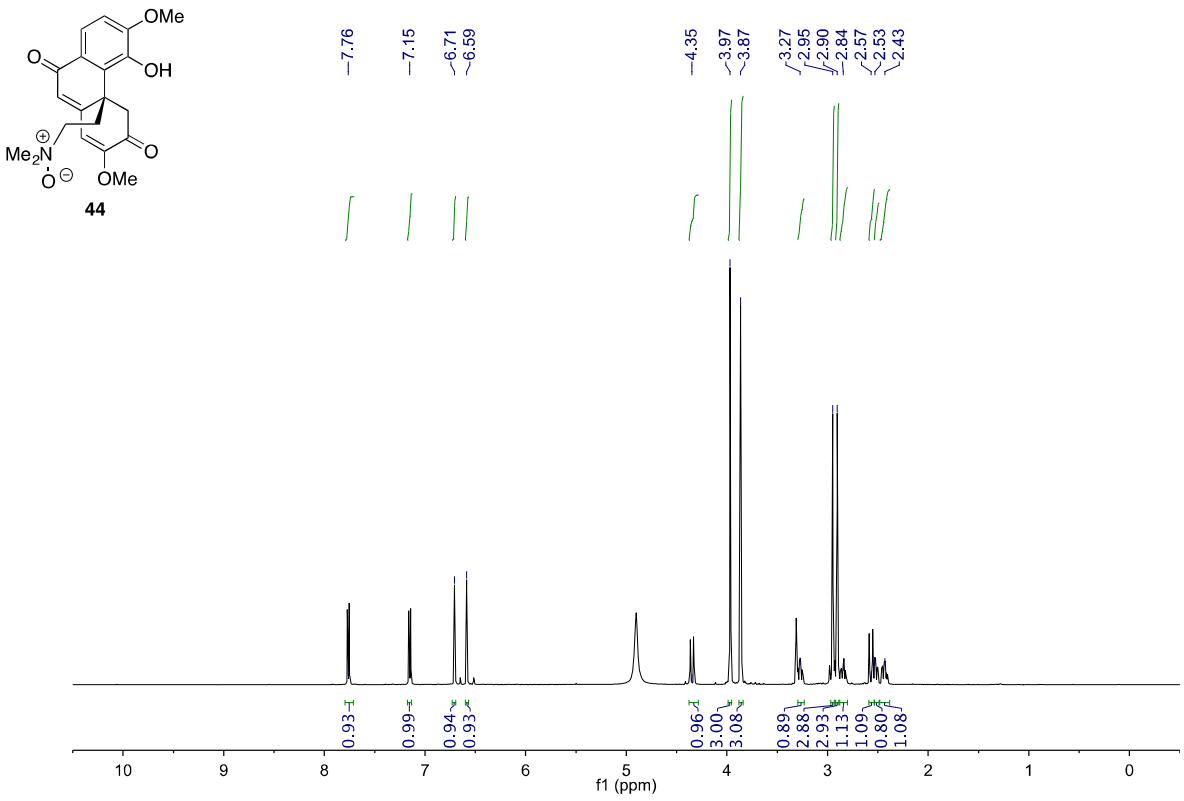
^{13}C NMR (d_6-DMSO)



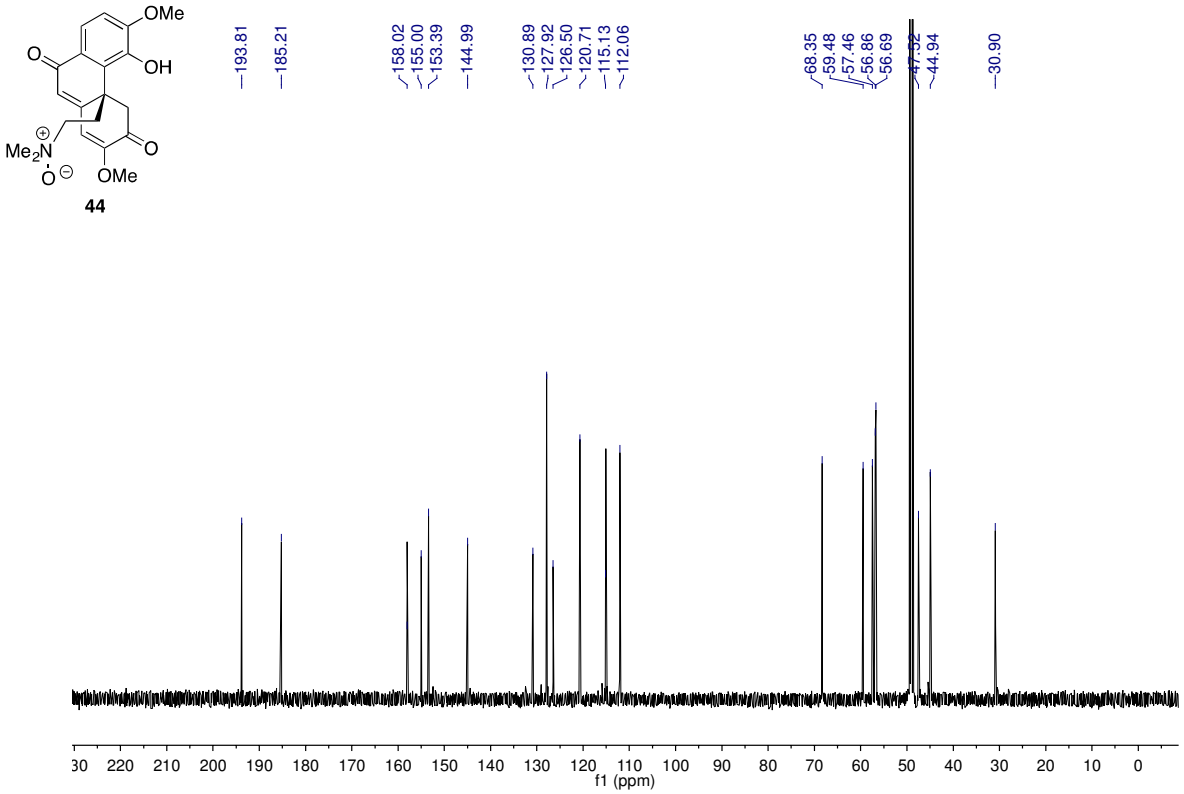
^{1}H NMR ($CDCl_3$)



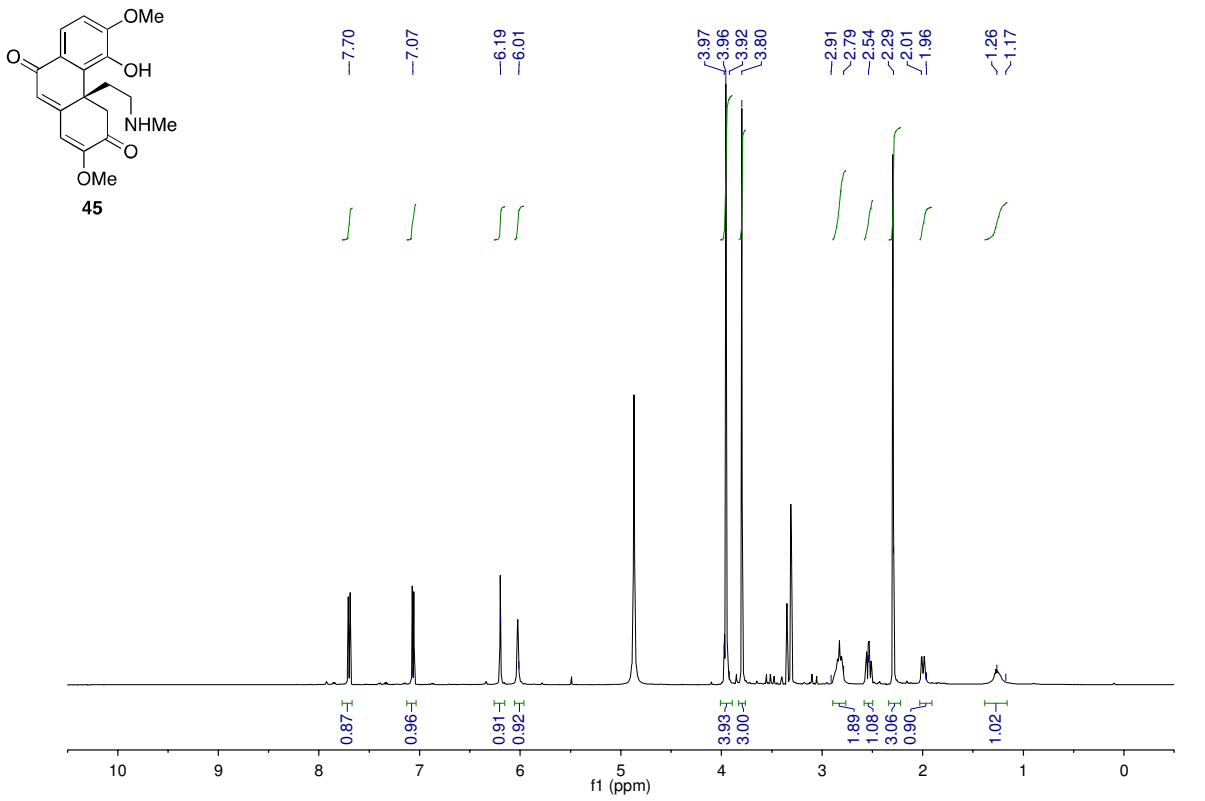
^{13}C NMR ($CDCl_3$)



^{1}H NMR (CD_3OD)

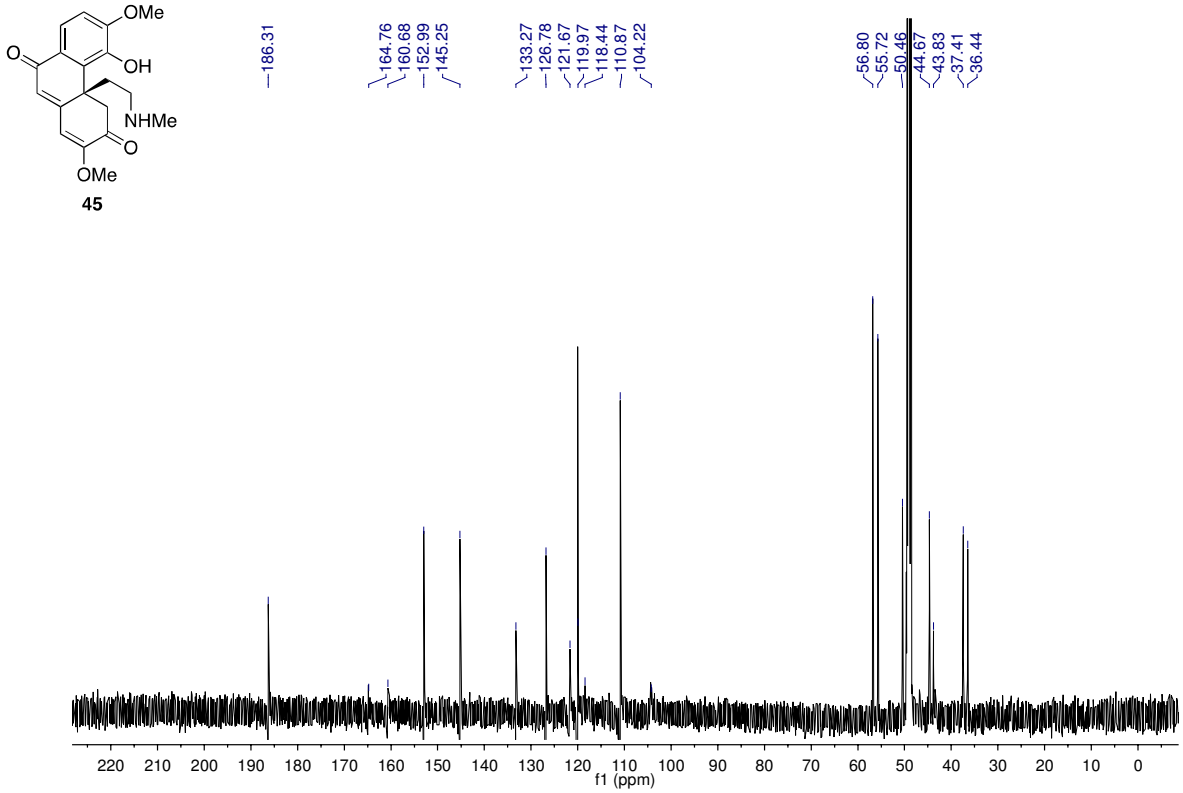


^{13}C NMR (CD_3OD)

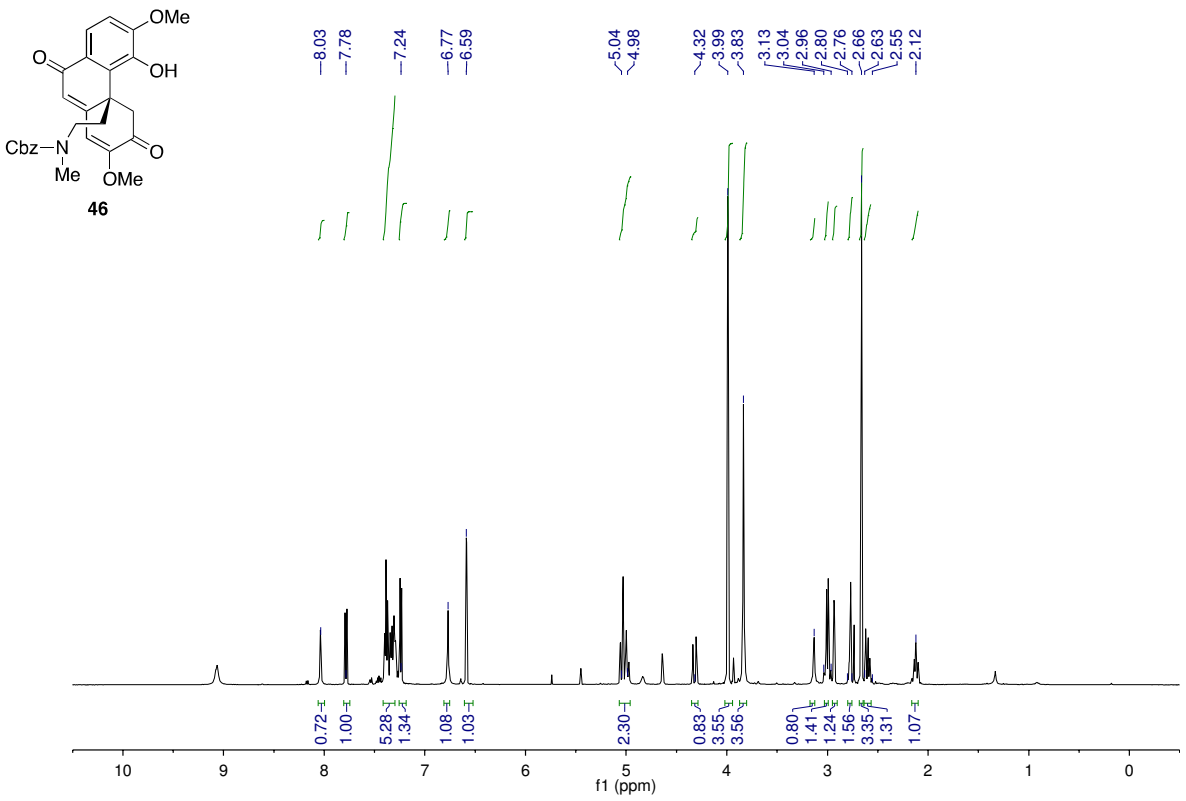


c

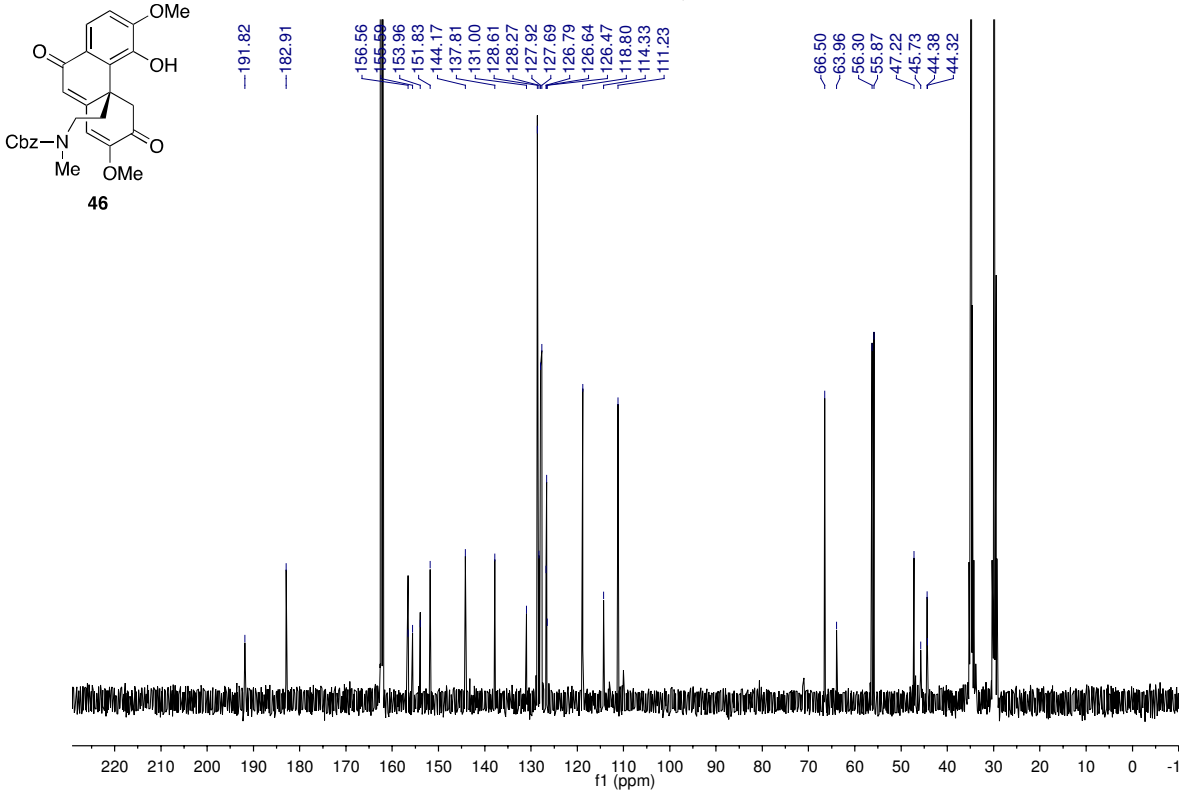
^{1}H NMR (CD_3OD)



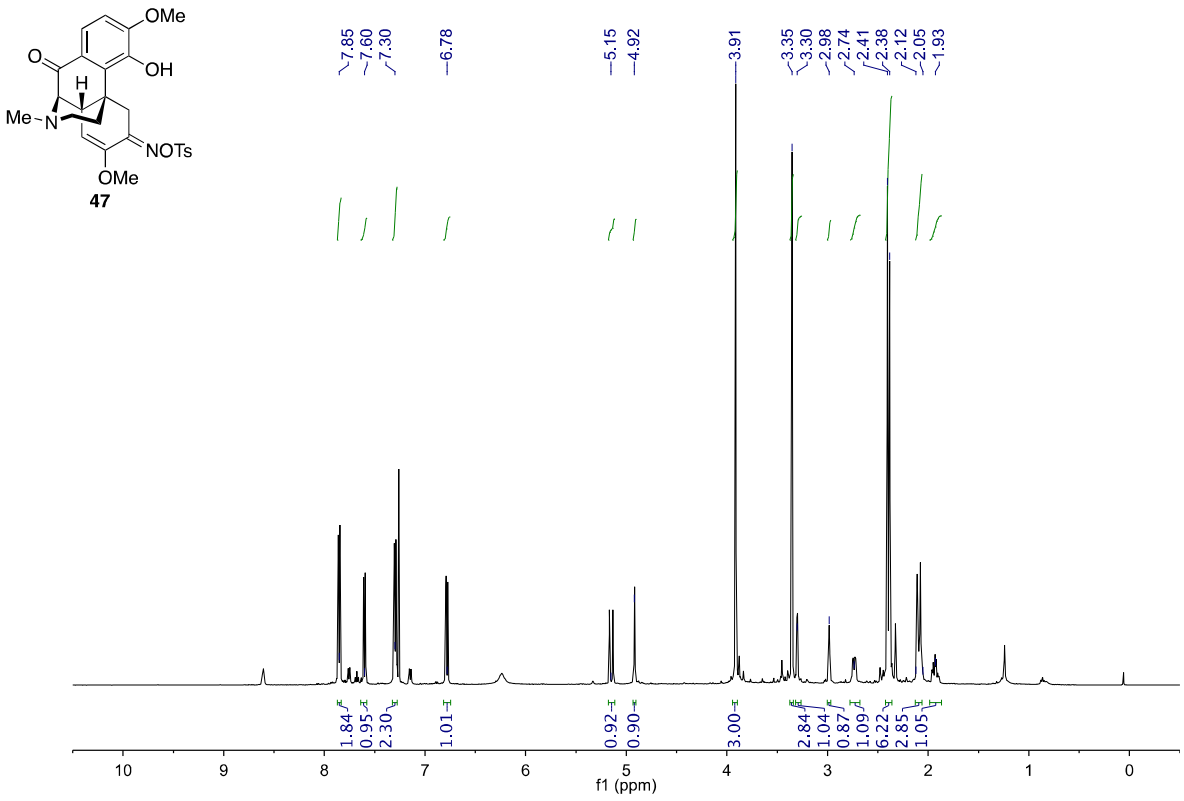
^{13}C NMR (CD_3OD)



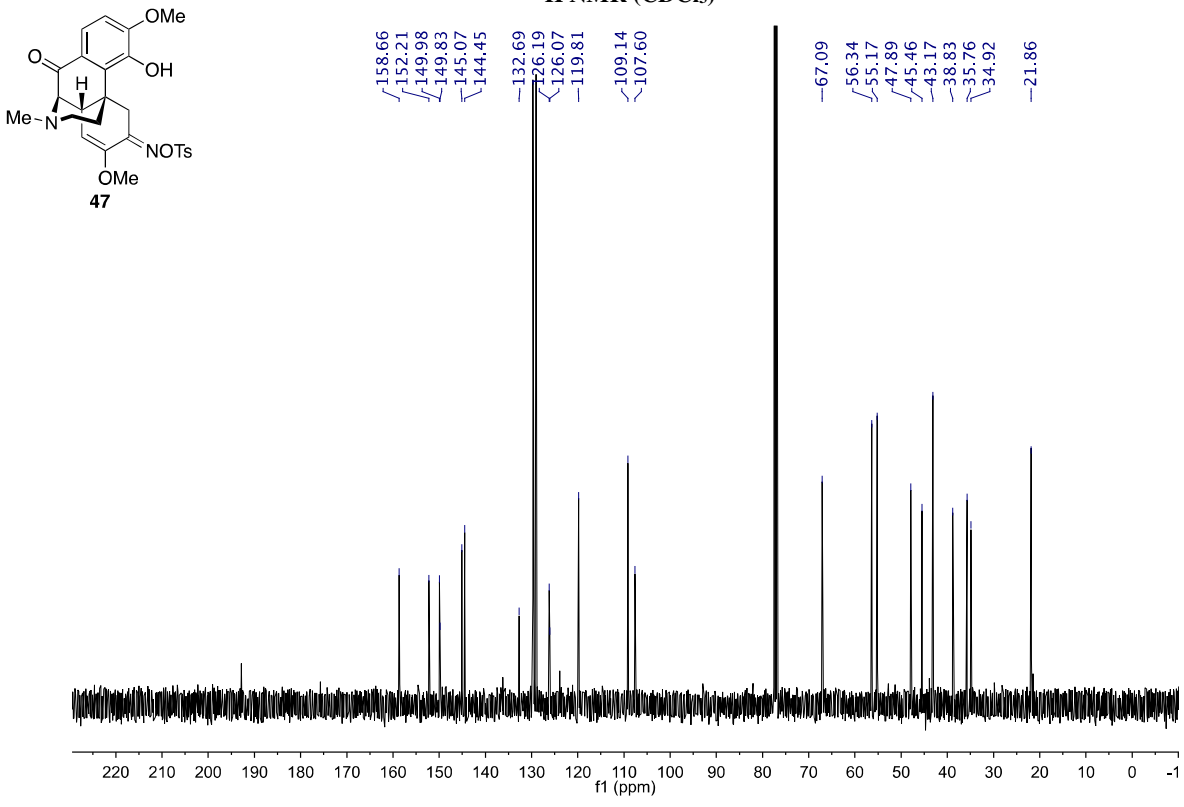
^{1}H NMR (d_7-DMF, 80 °C)



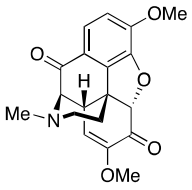
^{13}C NMR (d_7-DMF, 80 °C)



^{1}H NMR ($CDCl_3$)

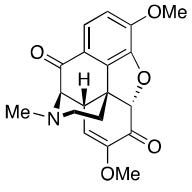


^{13}C NMR ($CDCl_3$)



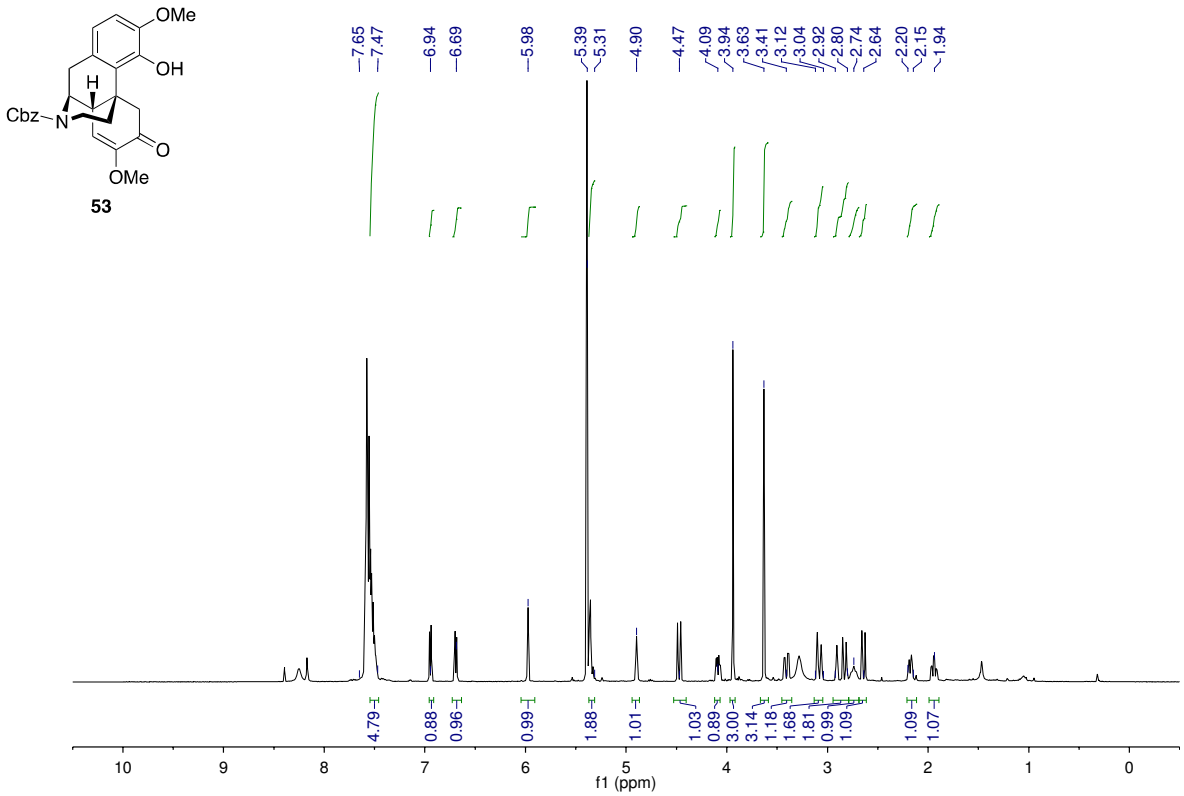
48

^{1}H NMR ($CDCl_3$)

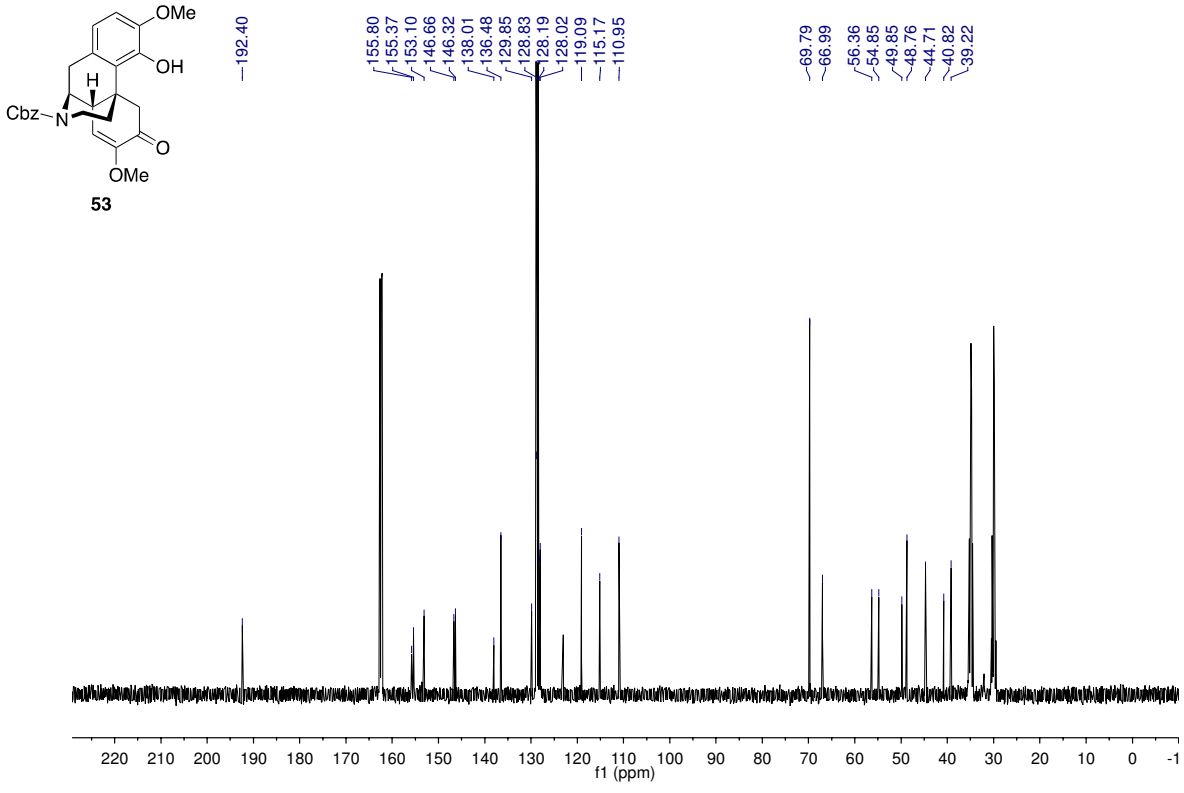


48

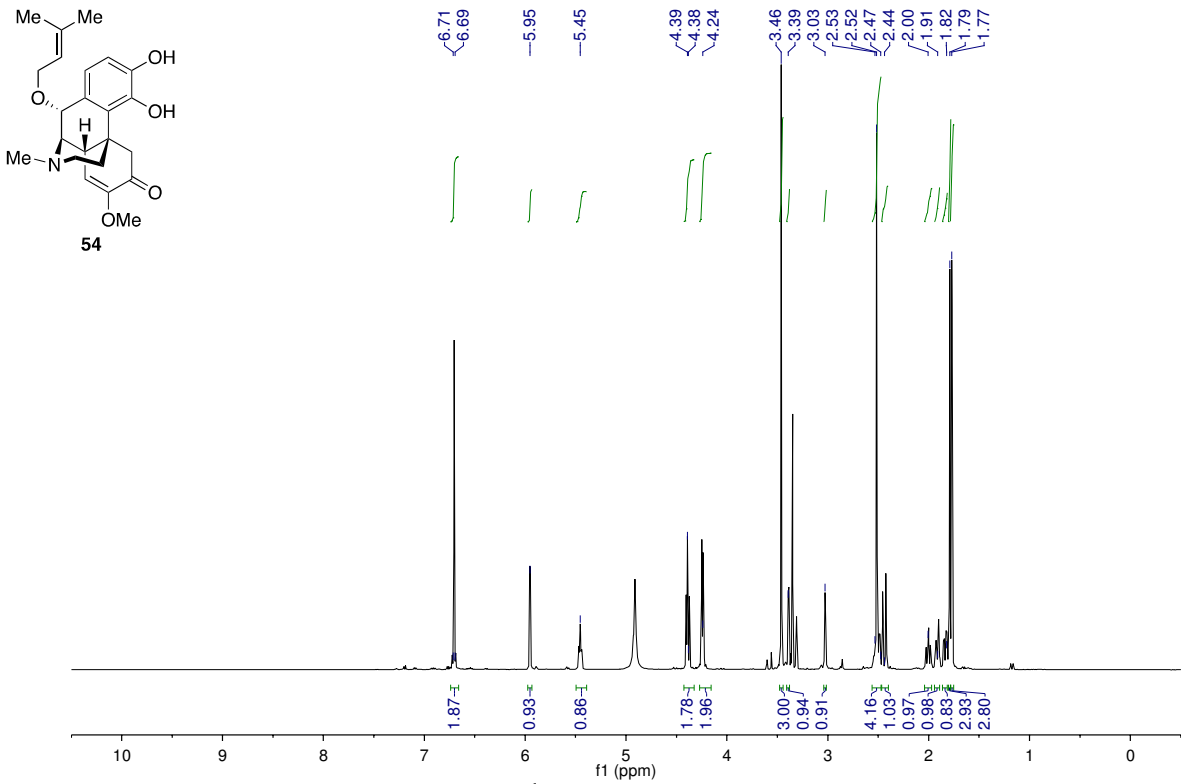
^{13}C NMR ($CDCl_3$)



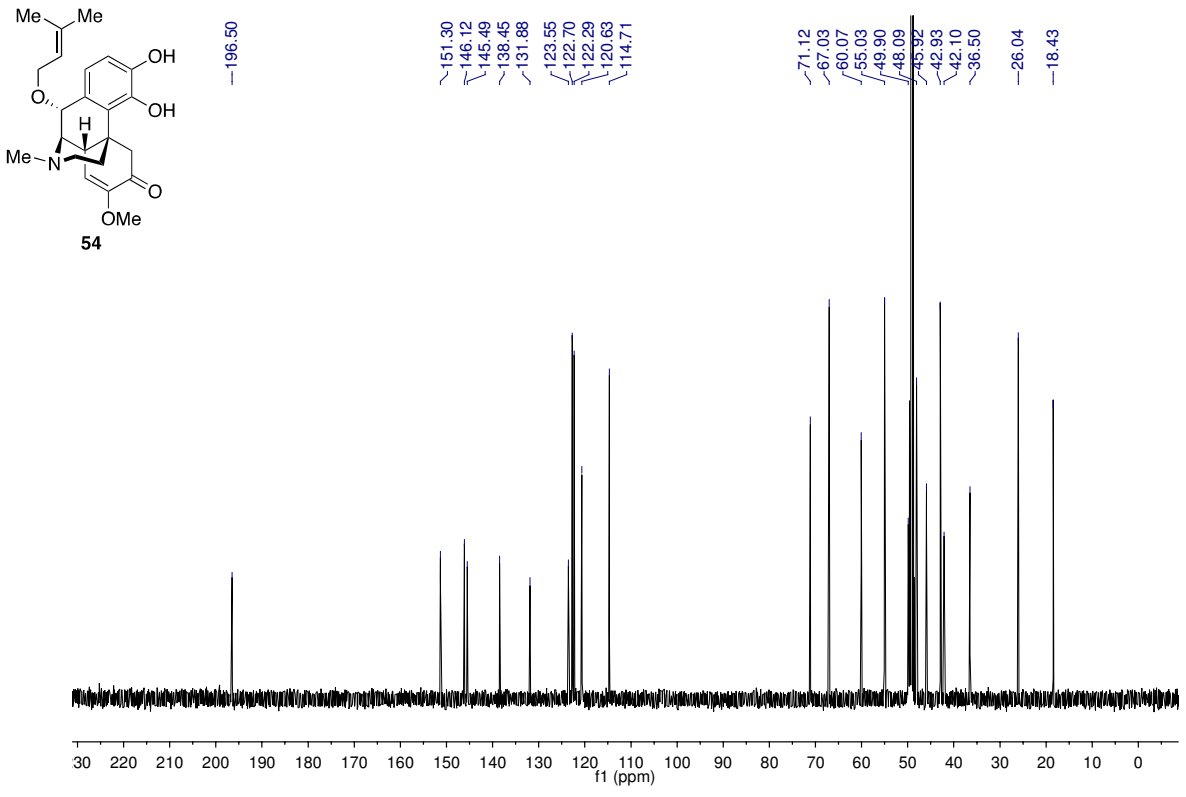
^{1}H NMR (d_7-DMF, 80 ºC)



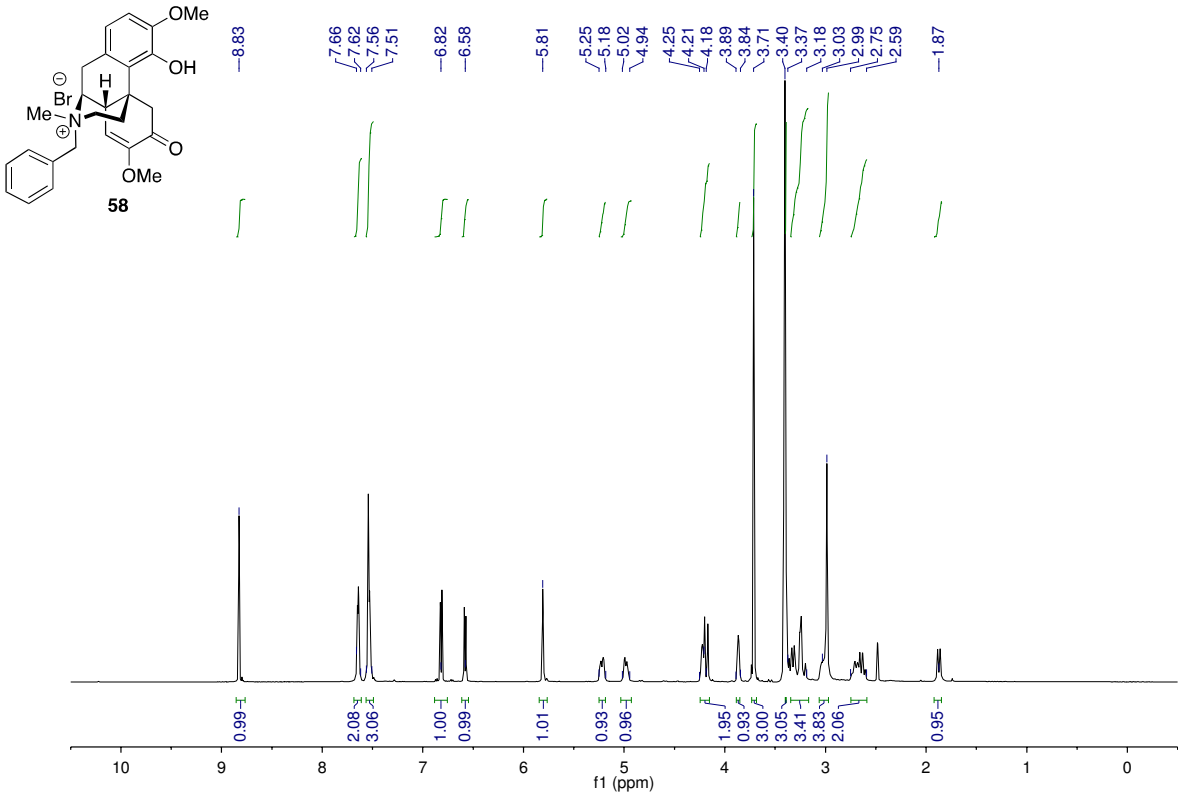
^{13}C NMR (d_7-DMF, 80 ºC)



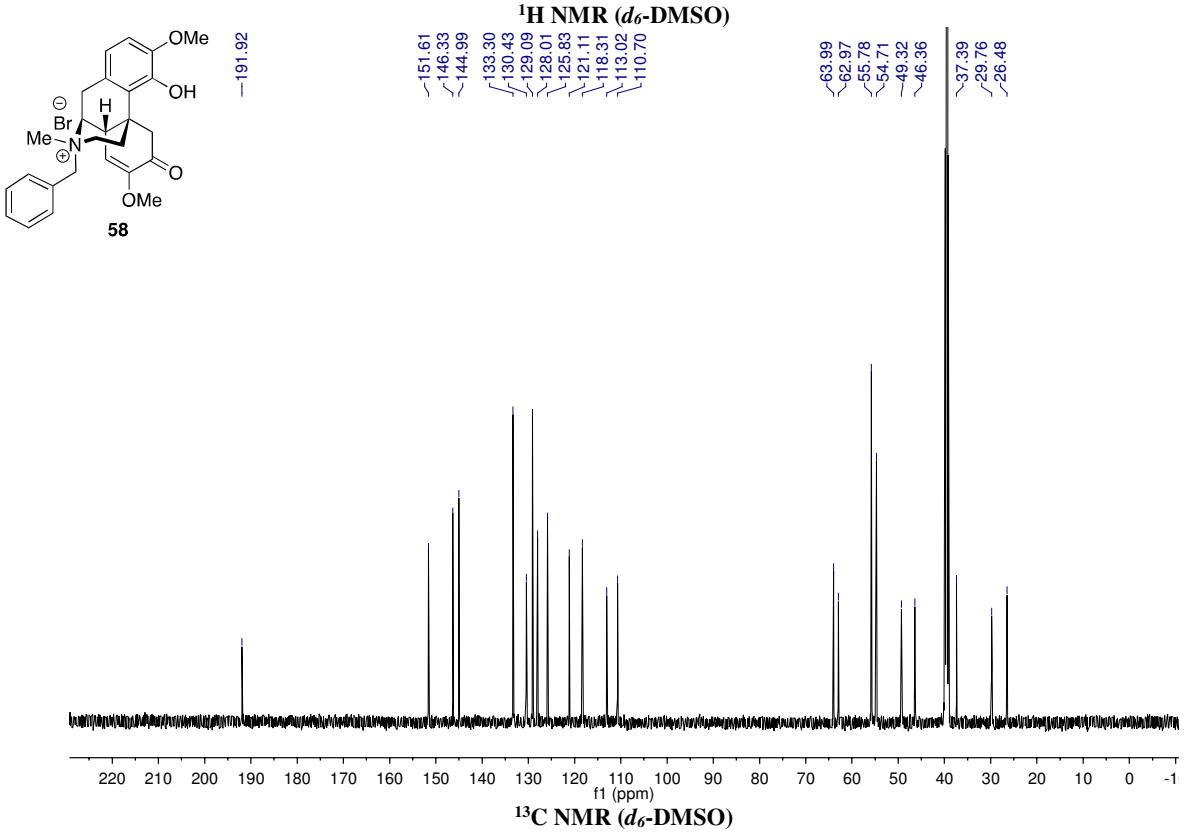
^{1}H NMR (CD_3OD)



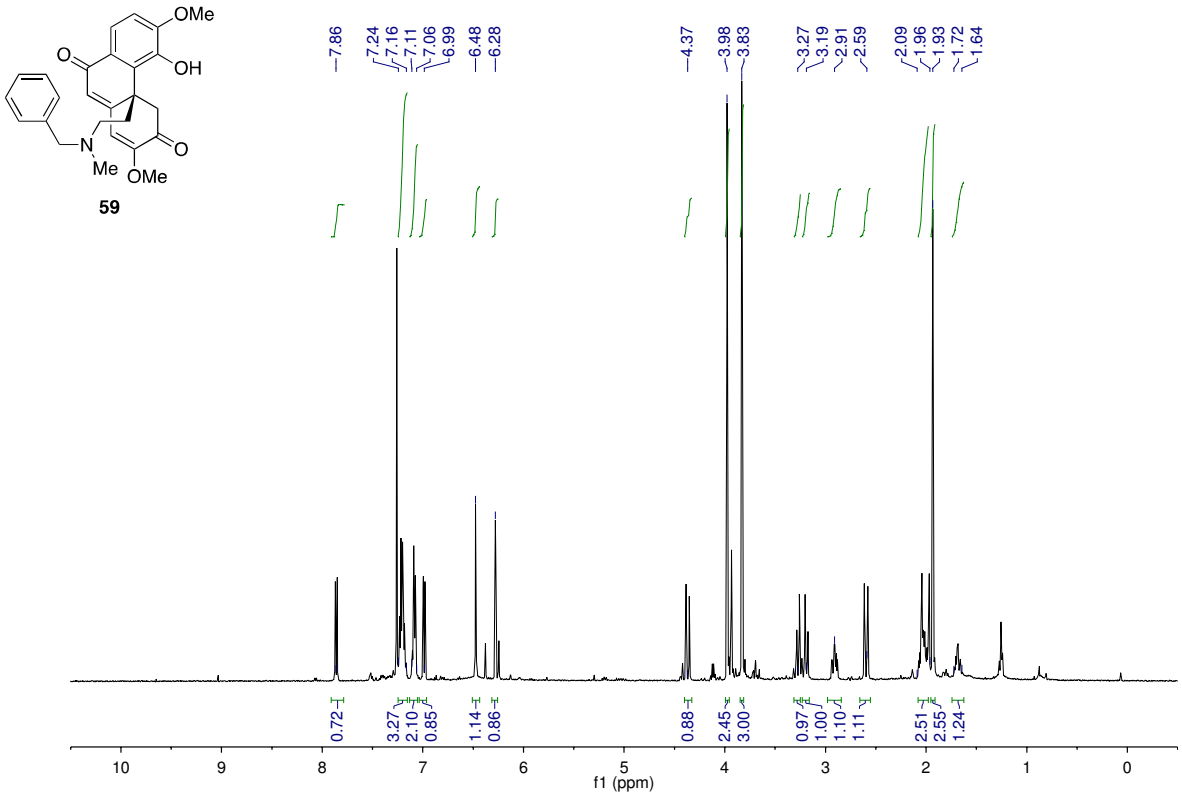
^{13}C NMR (CD_3OD)



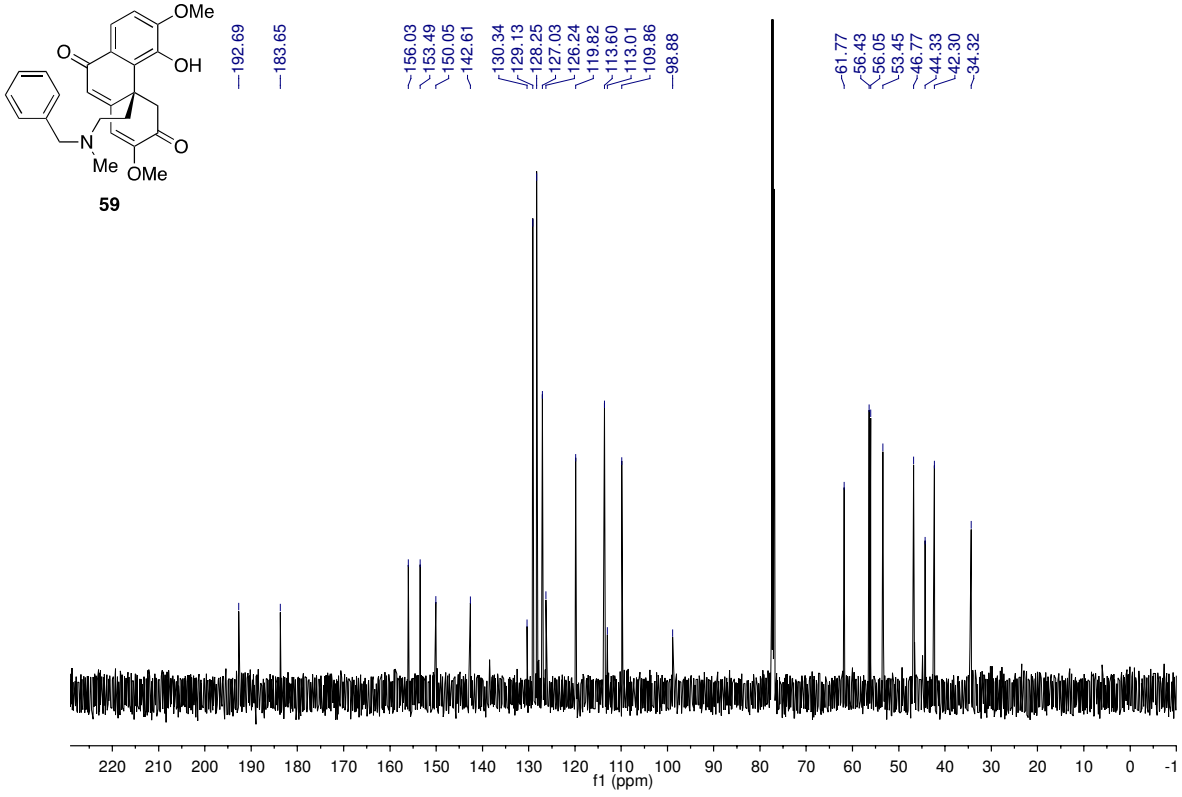
^{1}H NMR (d_6-DMSO)



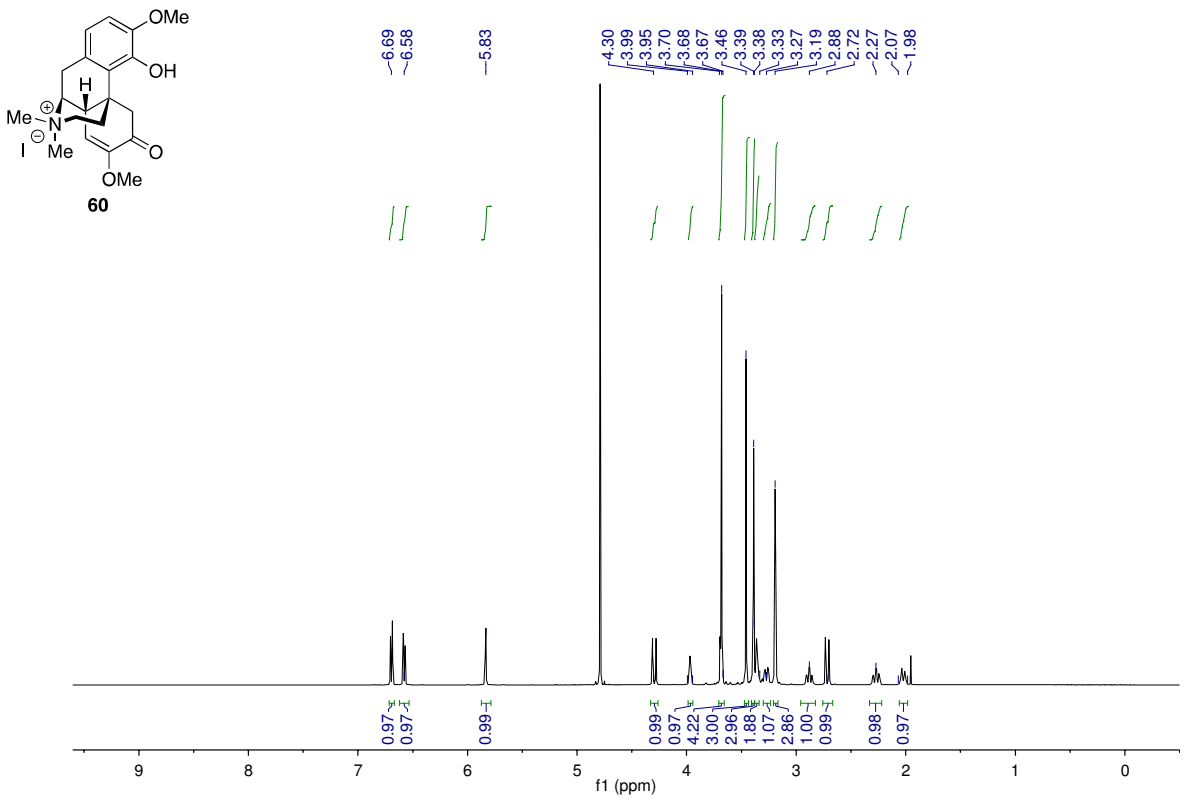
^{13}C NMR (d_6-DMSO)



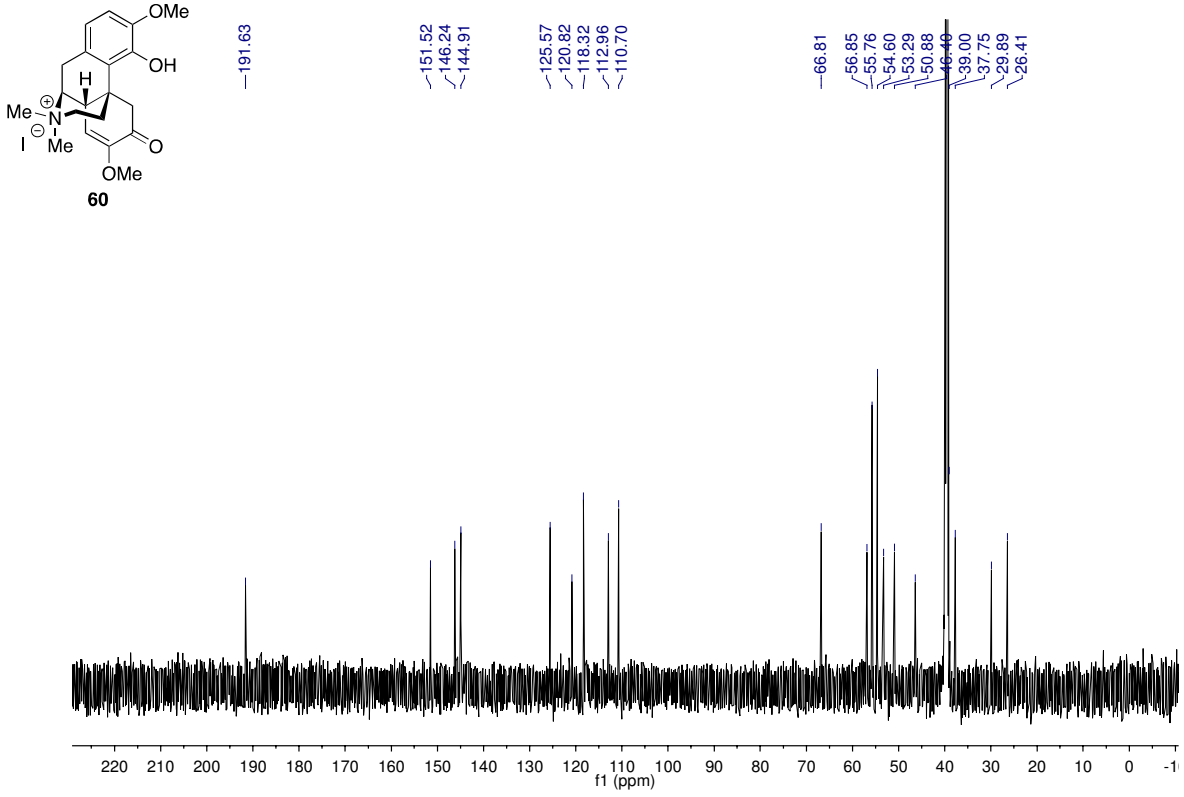
^{1}H NMR ($CDCl_3$)



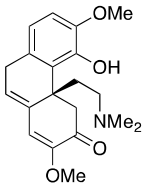
^{13}C NMR ($CDCl_3$)



^{1}H NMR (D_2O)

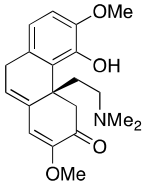


^{13}C NMR (d_6-DMSO)



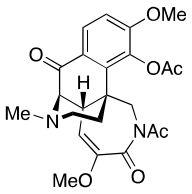
61

^{1}H NMR ($CDCl_3$)



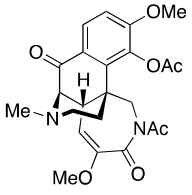
61

^{13}C NMR ($CDCl_3$)



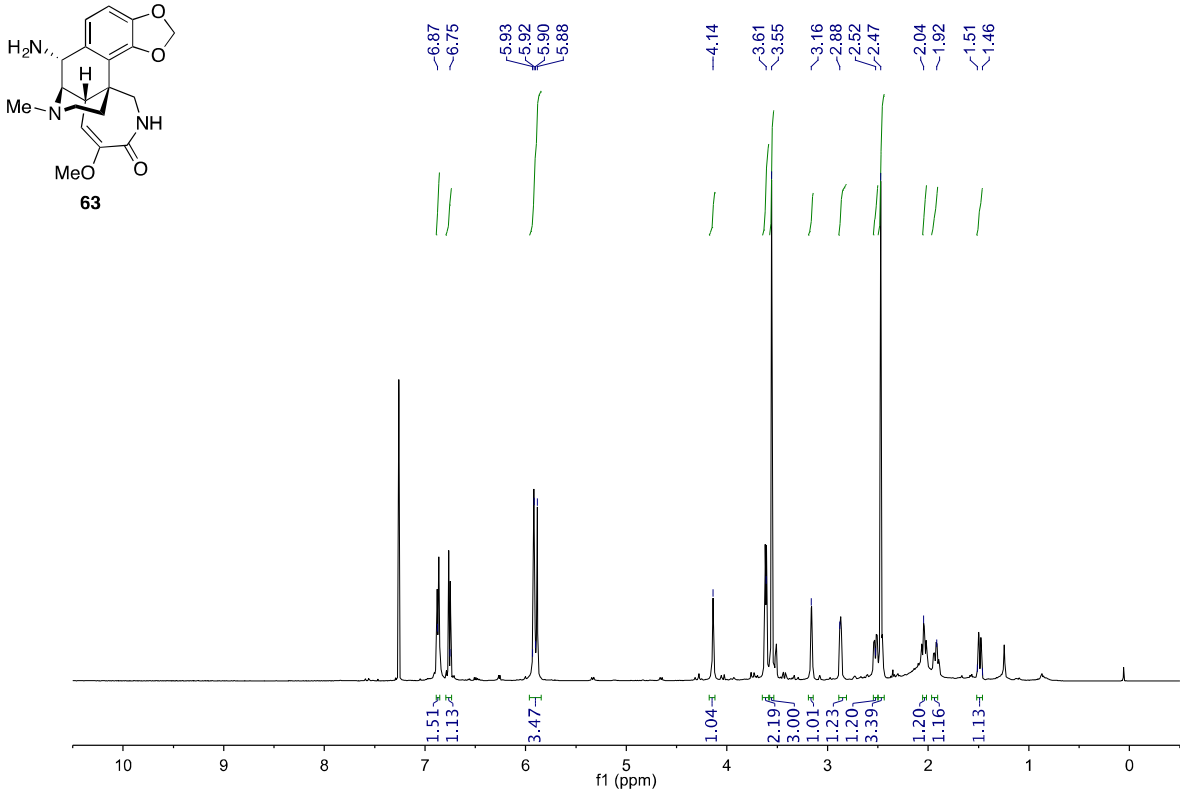
62

^{1}H NMR ($CDCl_3$)

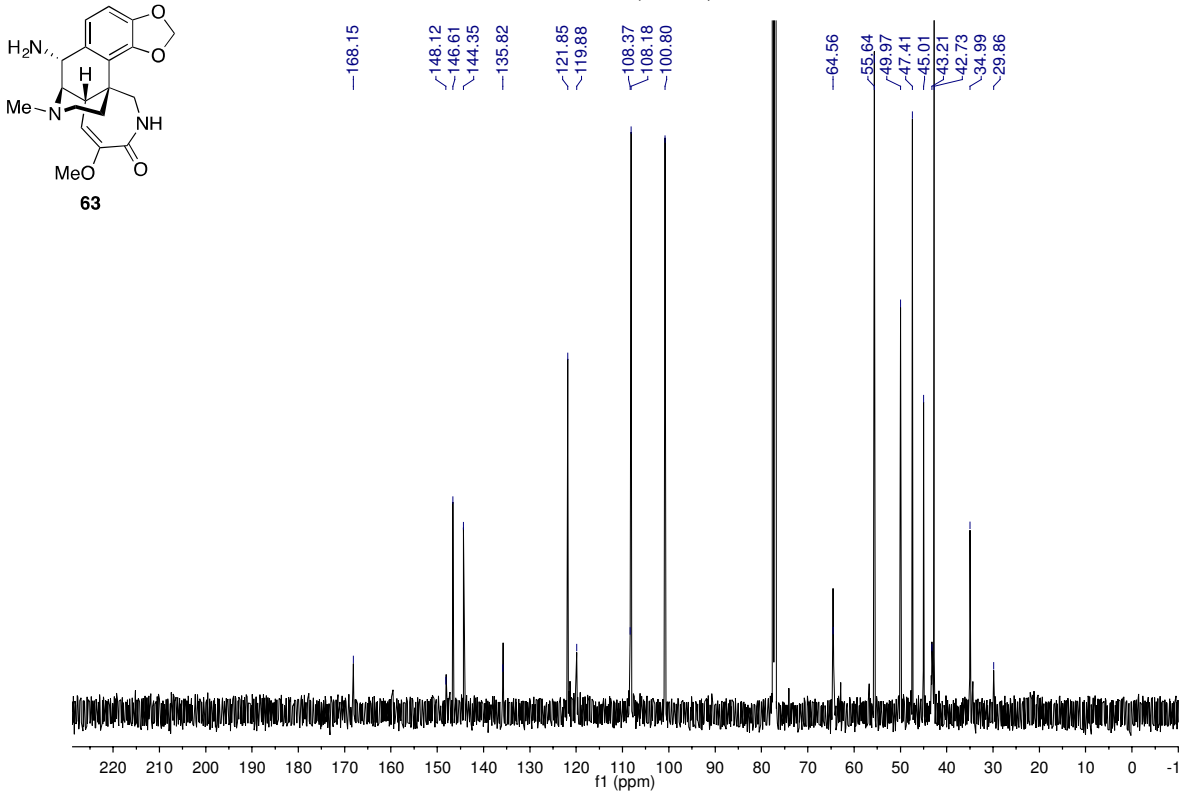


62

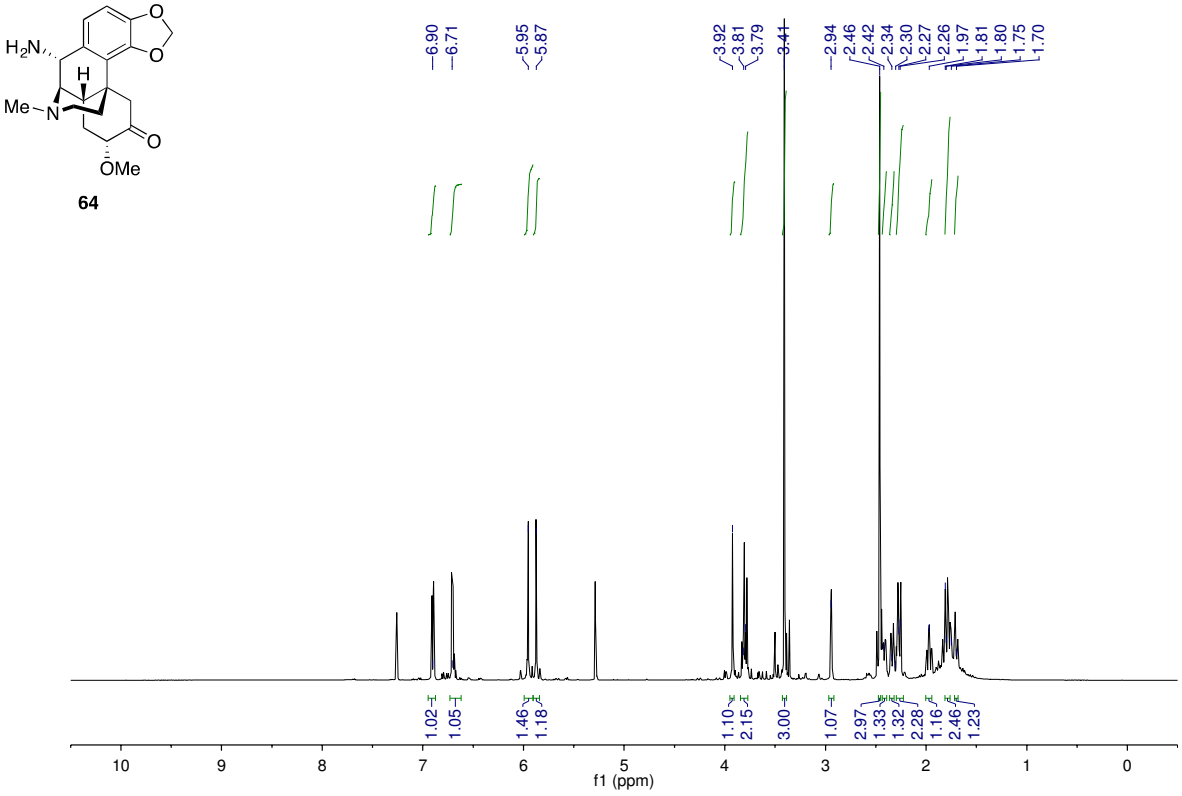
^{13}C NMR ($CDCl_3$)



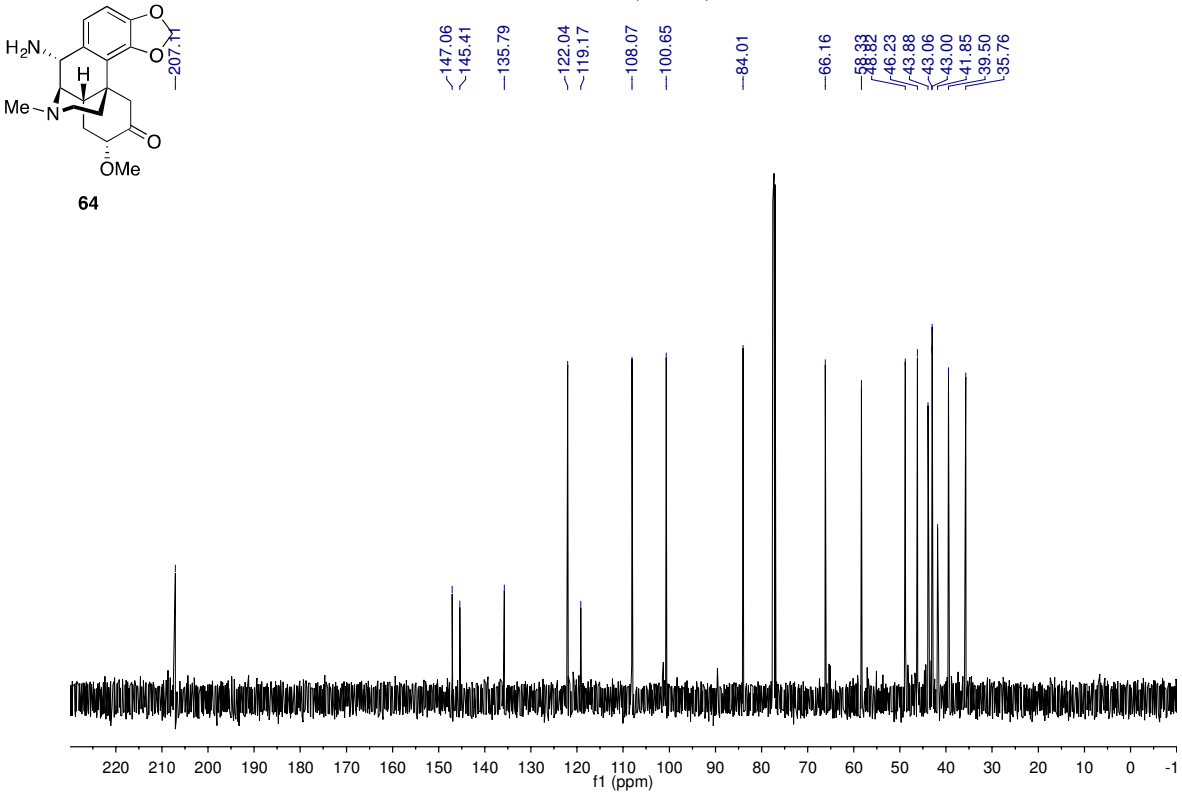
^{1}H NMR ($CDCl_3$)



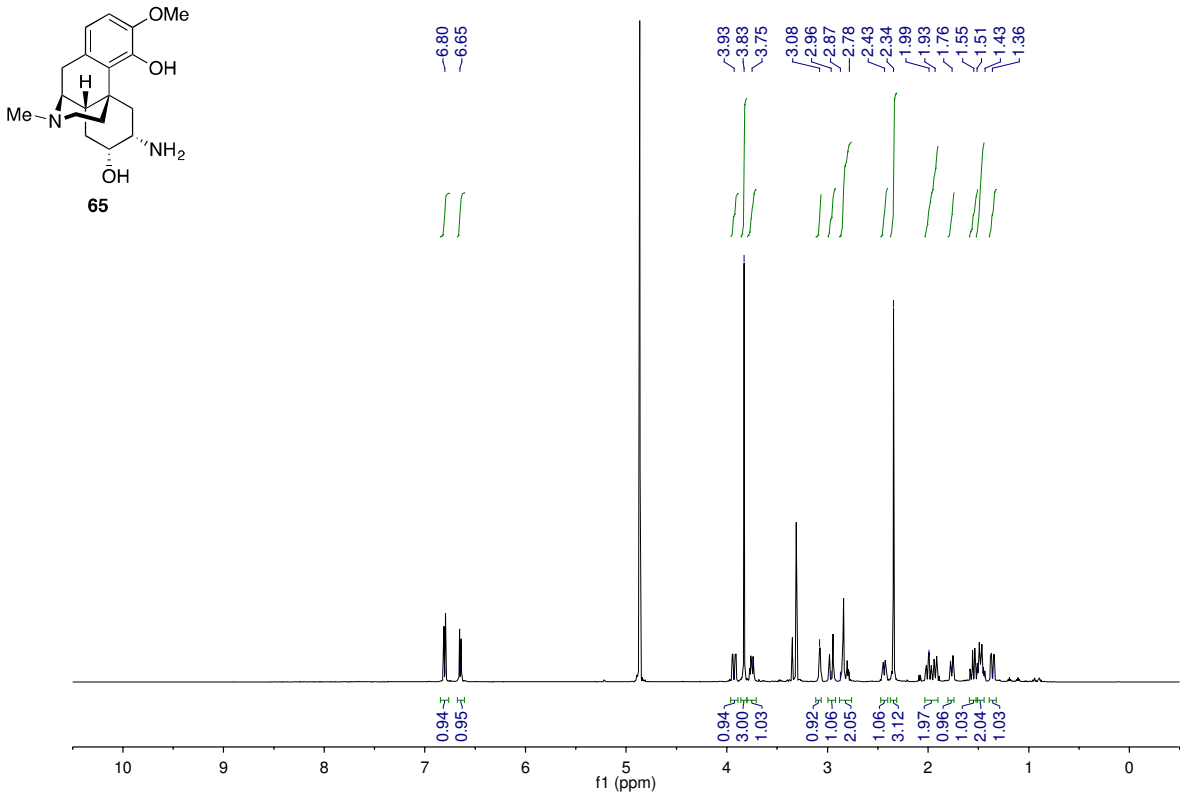
^{13}C NMR ($CDCl_3$)



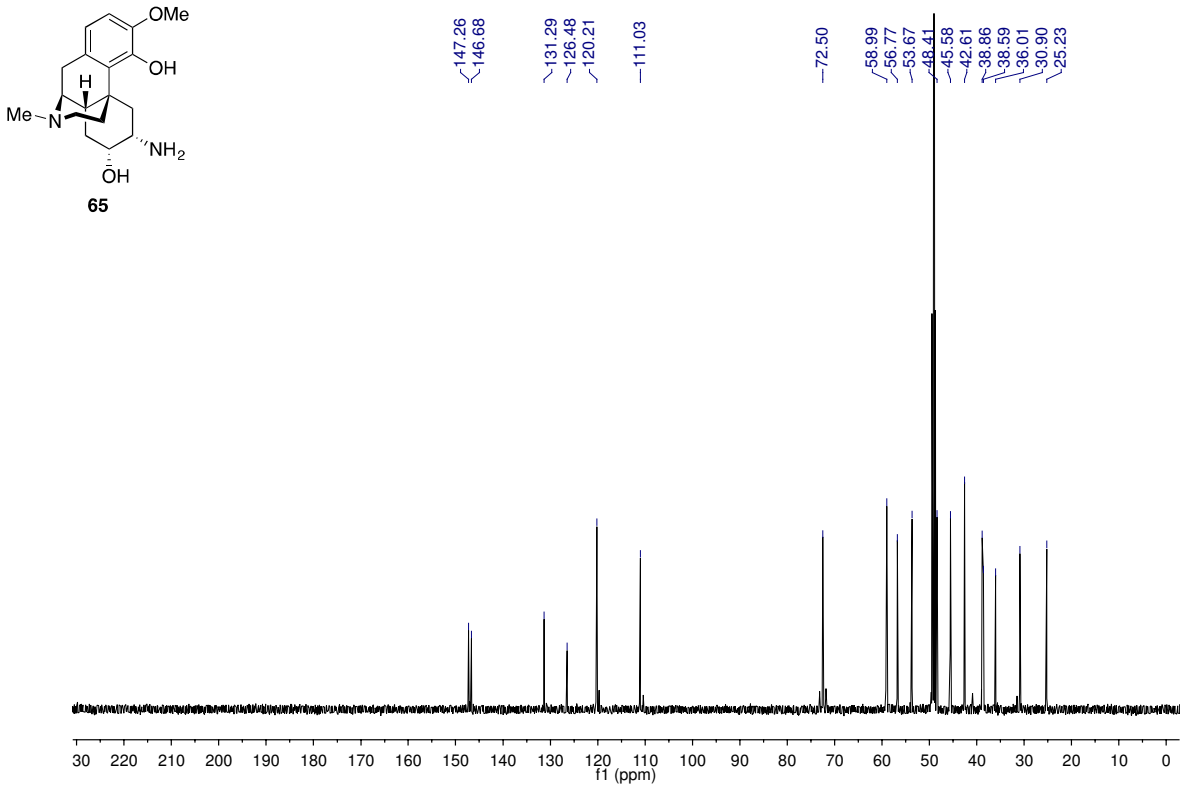
^{1}H NMR ($CDCl_3$)



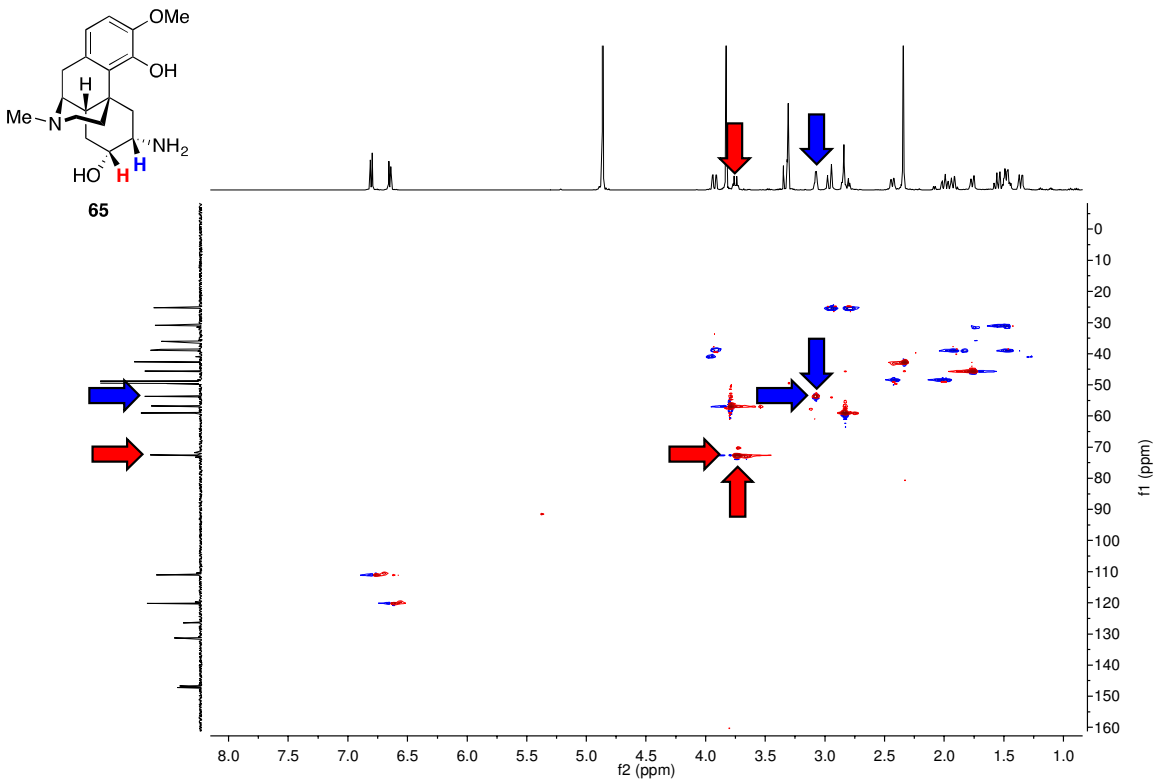
^{13}C NMR ($CDCl_3$)



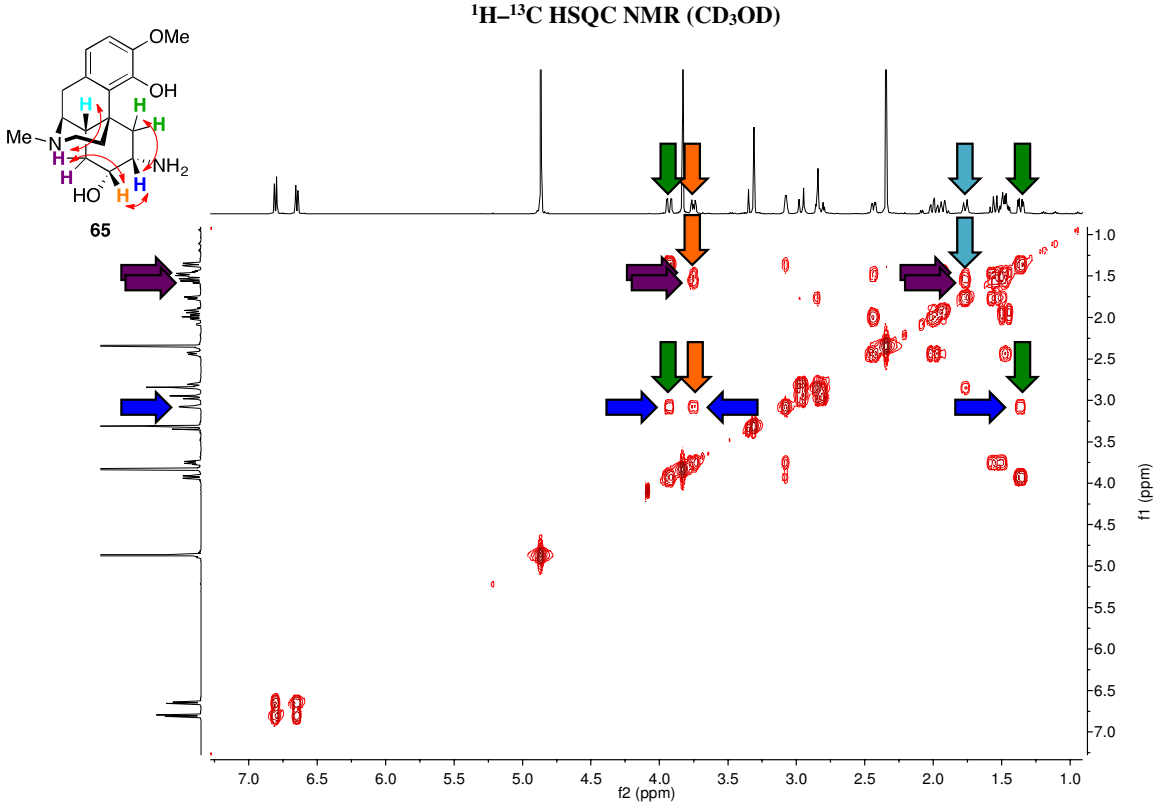
^{1}H NMR (CD_3OD)



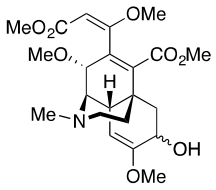
^{13}C NMR (CD_3OD)



^{1}H–^{13}C HSQC NMR (CD$_3$OD)

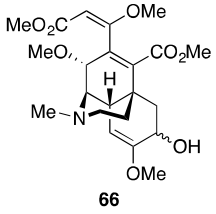


^{1}H–^{1}H COSY NMR (CD$_3$OD)



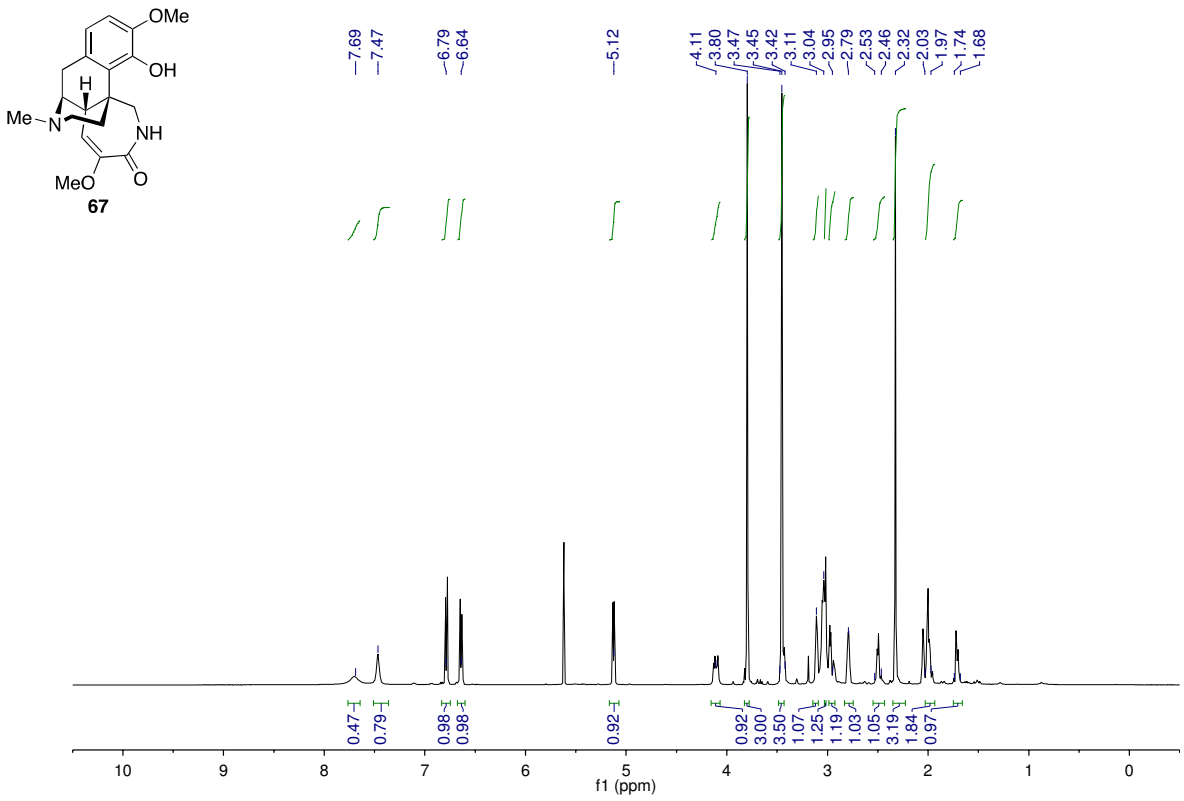
66

^{1}H NMR ($CDCl_3$)

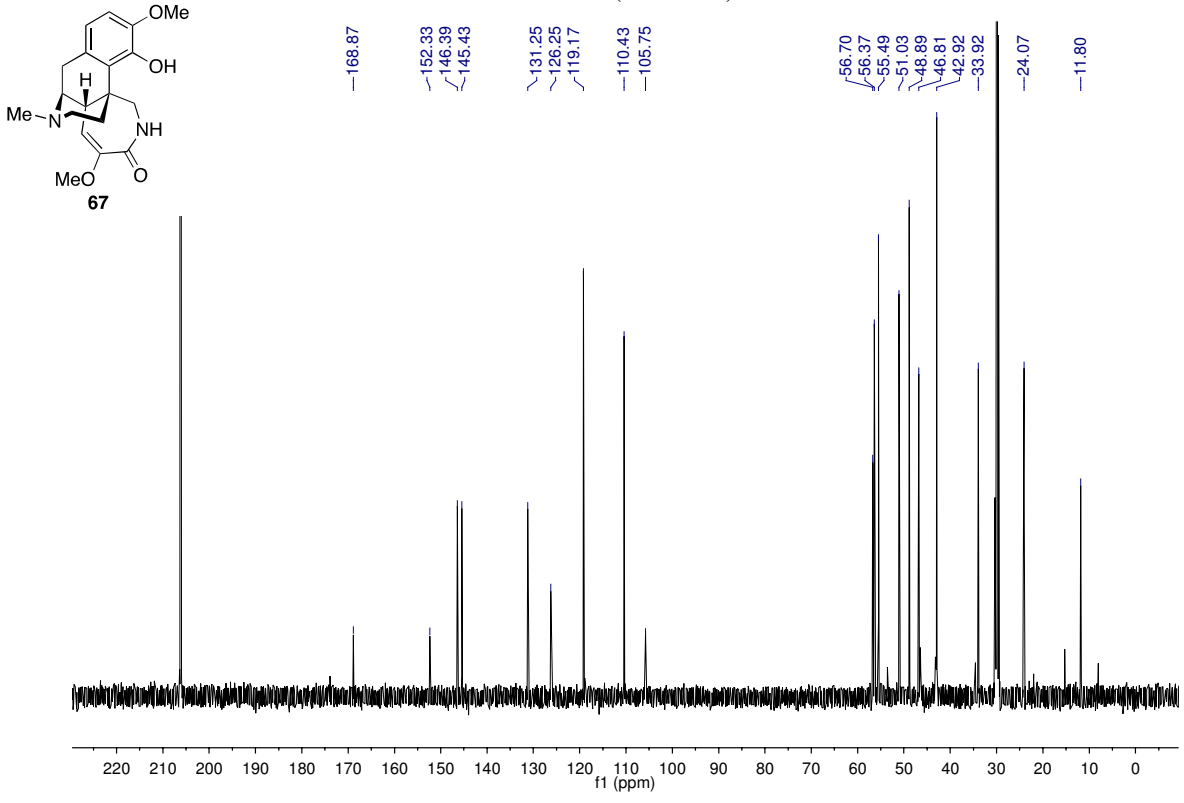


66

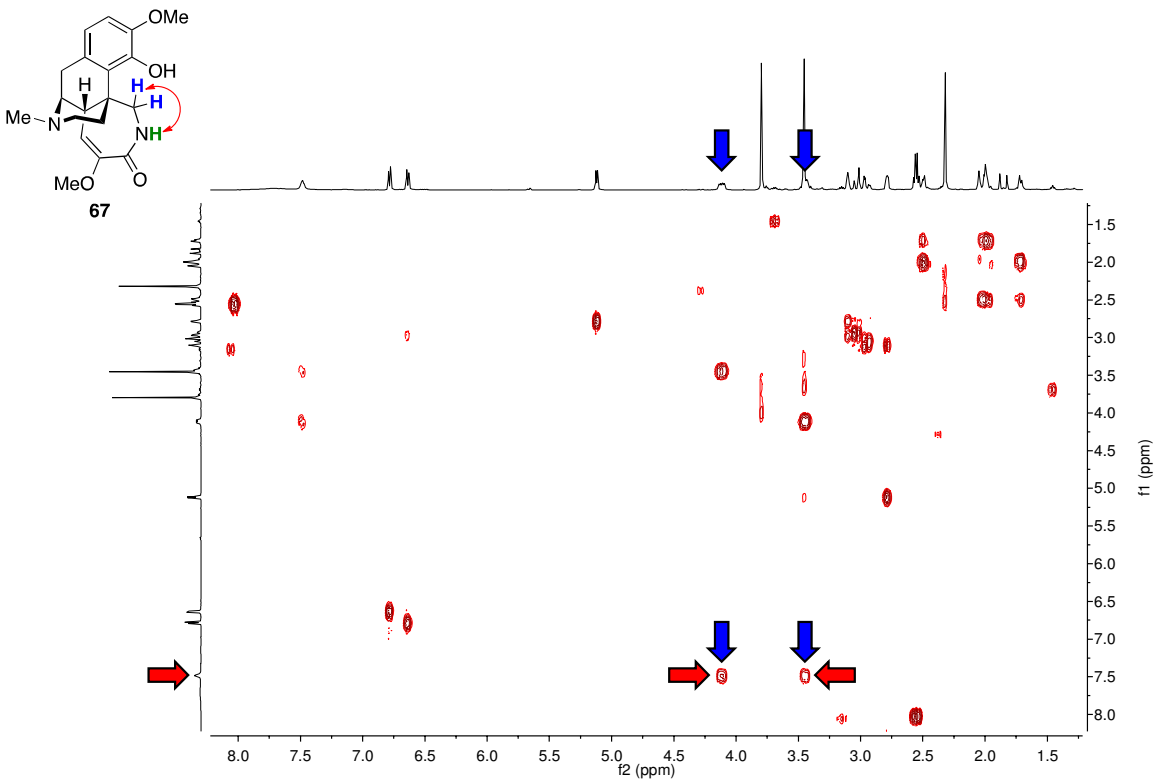
^{13}C NMR ($CDCl_3$)



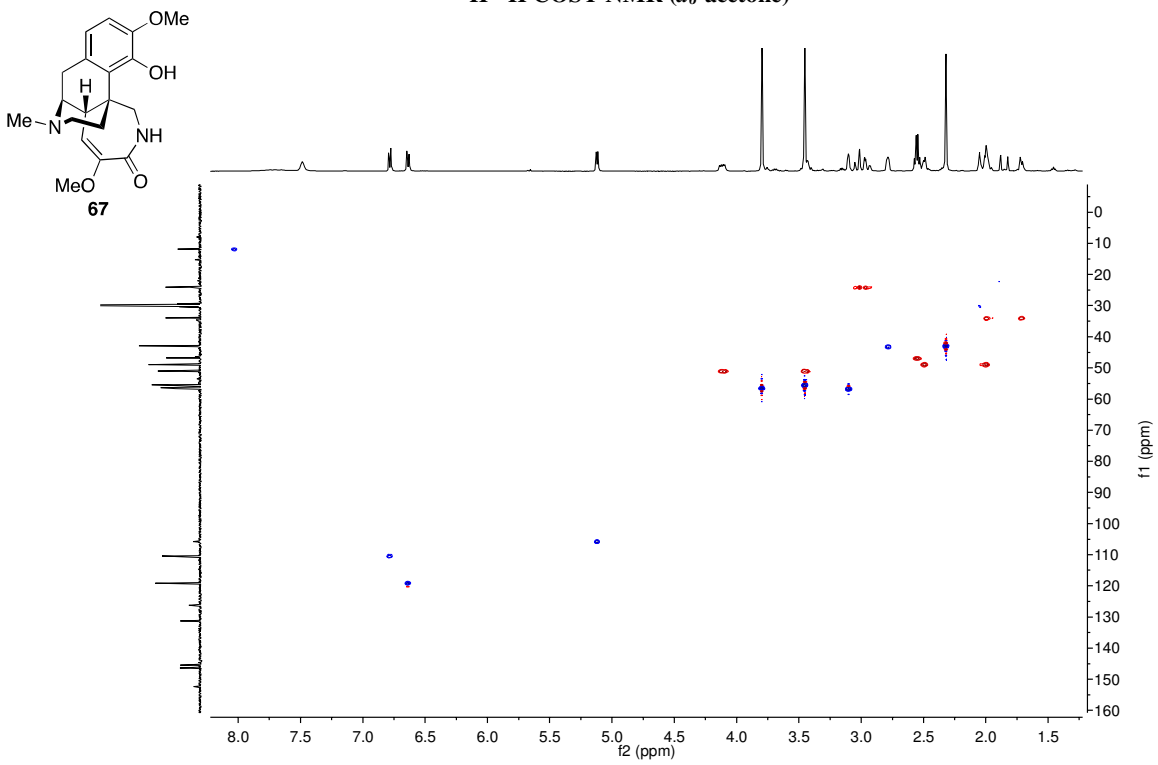
^{1}H NMR (d_6-acetone)



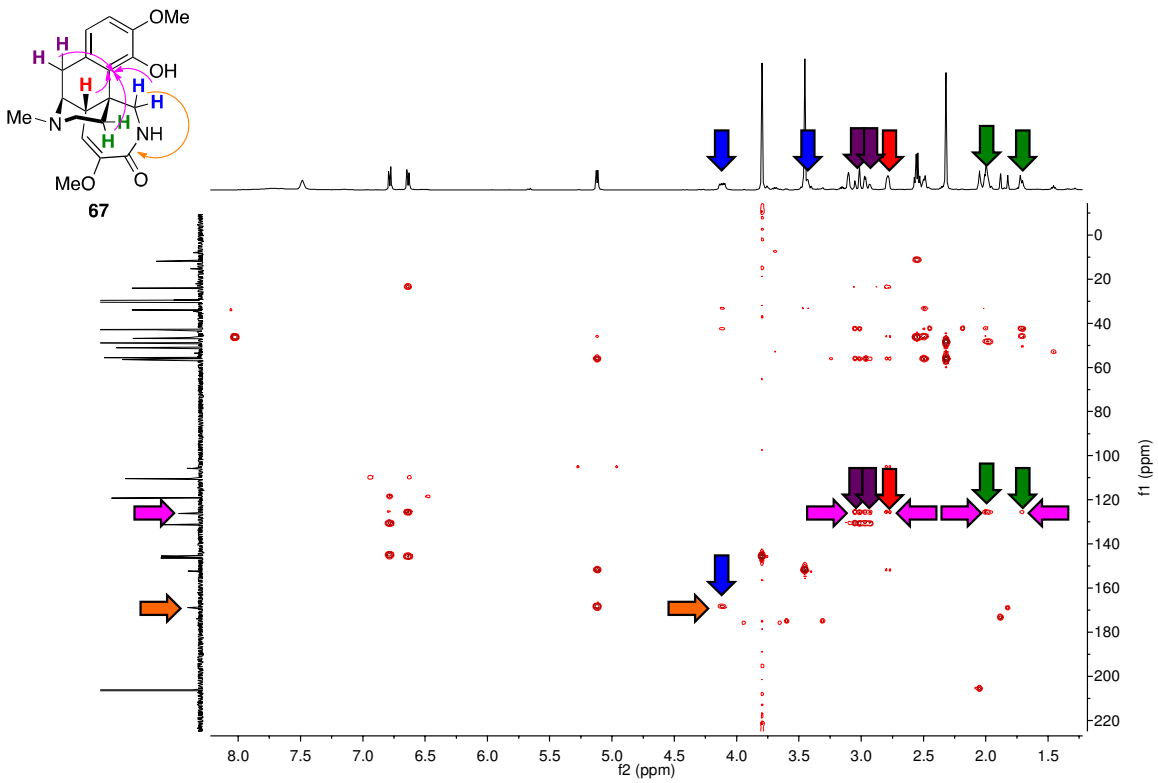
^{13}C NMR (d_6-acetone)



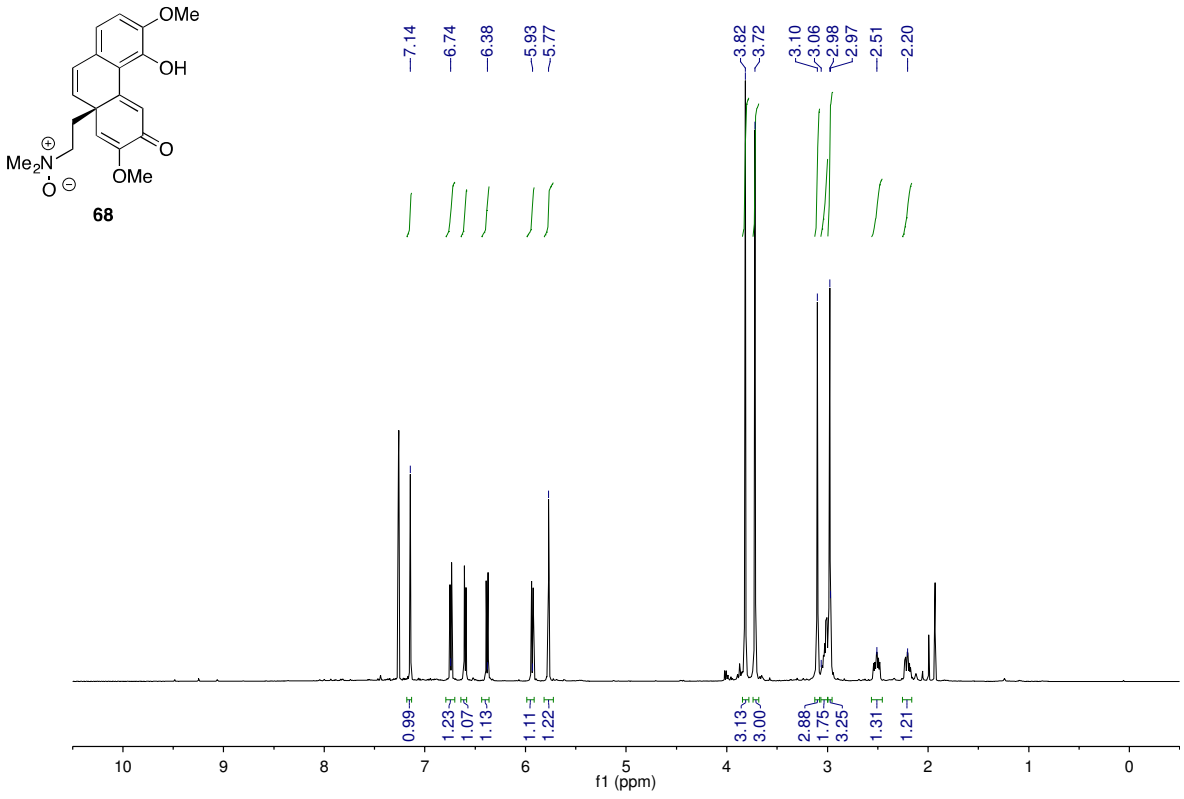
^{1}H–^{1}H COSY NMR (*d*$_{6}$-acetone)



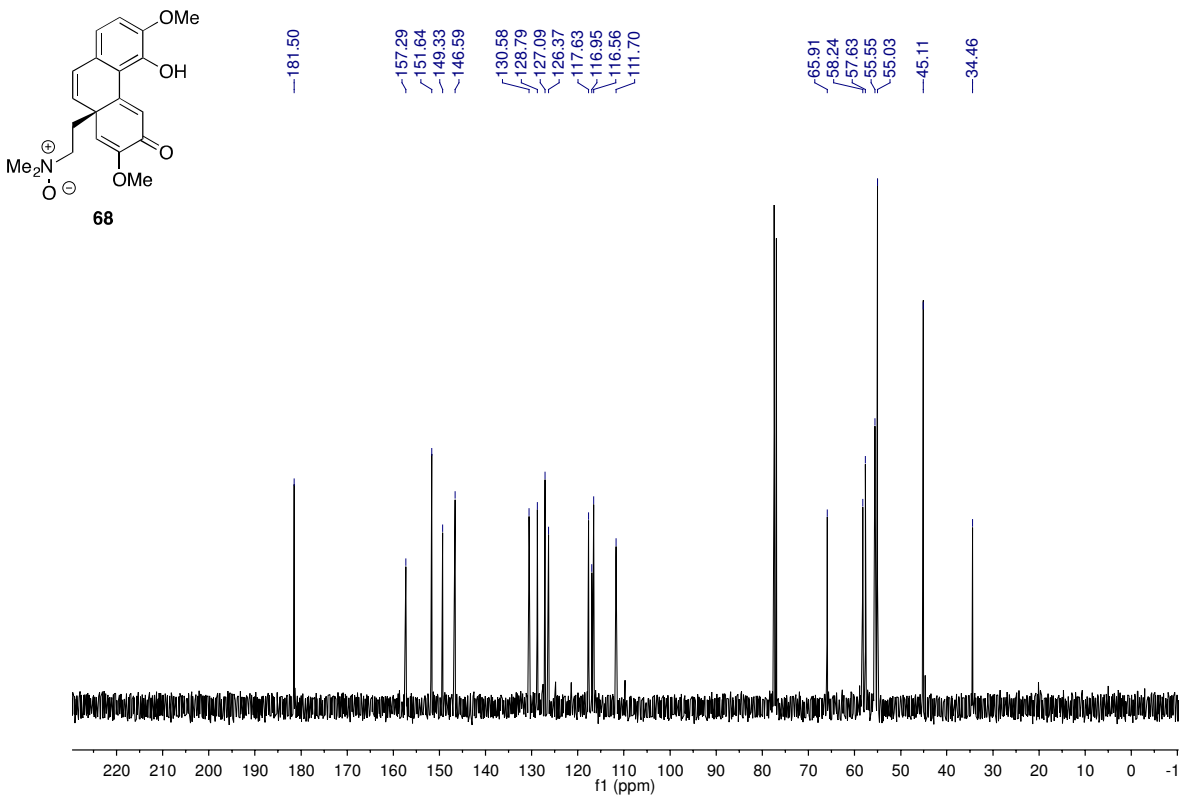
^{1}H–^{13}C HSQC NMR (*d*$_{6}$-acetone)



^{1}H–^{13}C HMBC NMR (*d*$_6$-acetone)



^{1}H NMR (CDCl$_3$)



68

^{13}C NMR ($CDCl_3$)