Supporting Information

A Unified Strategy for the Syntheses of the Isoquinolinium Alkaloids Berberine, Coptisine, and Jatrorrhizine

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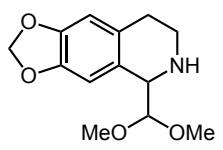
1. General Information

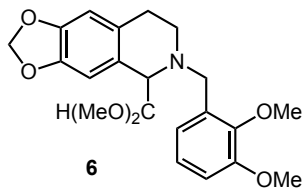
Reactions were run in oven-dried glassware under argon atmosphere and stirred magnetically. Methanol and dichloromethane were purified by passing the solvent through activated alumina using a solvent purification system. Purification of products was carried out by flash chromatography using silica gel (230-400 Mesh, Grade 60). Reactions were monitored by Thin Layer Chromatography (TLC) (silica gel 60 F_{254}) and visualized using UV or $KMnO_4$, phosphomolybdic acid (PMA) and ceric ammonium molybdate (CAM) stain solutions. ^1H NMR and ^{13}C NMR were recorded at room temperature in a Bruker 400 or Bruker 500 instrument. Chemical shifts are reported in ppm and referenced with respect to residual protic solvents: chloroform at 7.26 ppm, DMSO at 2.50 ppm, and methanol at 3.31 ppm (^1H NMR); and the carbon resonances of the solvent: chloroform at 77.16 ppm, DMSO at 39.52 ppm, and methanol at 49.0 ppm (^{13}C NMR). The following abbreviations were used to refer to multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quadruplet, m = multiplet. Infrared spectra were recorded using a Shimadzu FTIR-8400S spectrometer. Mass spectra were obtained on a Micromass LCT Premier quadrupole and time-of-flight tandem mass analyzer.

2. Synthesis of Precursors and Targets



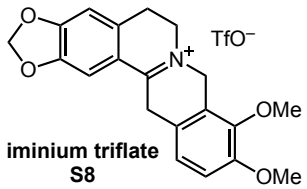
5ab

5-(Dimethoxymethyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (5ab): To a 100 mL round bottom flask was added 3,4-(methylenedioxy)phenethylamine **2ab** (826 mg, 5 mmol) followed by dichloromethane (25 mL). A 2,2-dimethoxyacetaldehyde solution (60 wt.% in water, 2.3 mL, 15 mmol, 3 equiv) was then added, followed by addition of $MgSO_4$ (13 g $MgSO_4$ / 1 g amine). The mixture was stirred under air at room temperature for 2 h. $MgSO_4$ was filtered through celite and the organic collection was transferred into a new 100 mL RBF and concentrated to ~25 mL. Trifluoroacetic acid (11.1 mL, 145 mmol, 29 equiv) was added and the reaction stirred at room temperature for 2 h. The reaction mixture was extracted with 40 mL water. The organic phase was extracted with water (2 x 40 mL). The combined aqueous extracts were basified with 3 M NaOH and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (3-5% methanol / dichloromethane) afforded **5ab** as a brown oil (865 mg, yield 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.55 (d, J = 1.0 Hz, 1H), 5.88 (s, 2H), 4.41 (d, J = 6.0 Hz, 1H), 3.91 (d, J = 5.9 Hz, 1H), 3.433 (s, 3H), 3.427 (s, 3H), 3.17 (m, 1H), 2.92 (m, 1H), 2.71 (m, 2H), 2.20 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 145.6, 129.5, 127.6, 108.8, 108.2, 107.4, 100.7, 57.0, 56.1, 55.2, 40.9, 30.2. FTIR (film) 3349, 2902, 1484, 1205, 1152, 1039 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{13}H_{18}NO_4]^+$ 252.1236, found 252.1248.



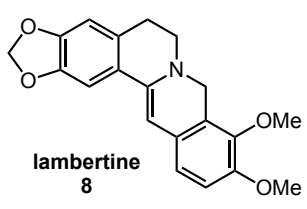
6

6-(2,3-Dimethoxybenzyl)-5-(dimethoxymethyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (6): To a 100 mL round bottom flask was added isoquinoline **5ab** (1.73 g, 6.89 mmol), 2,3-dimethoxybenzaldehyde (1.26 g, 7.58 mmol, 1.1 equiv) methanol (17 mL) and acetic acid (0.80 mL, 13.78 mmol, 2 equiv). Sodium triacetoxyborohydride (1.9 g, 8.96 mmol, 1.3 equiv) was then added slowly. The flask was capped with a needle to relieve gas pressure and the needle was removed after ~30 min. After 23 h a second portion of sodium triacetoxyborohydride (292 mg, 1.38 mmol, 0.2 equiv) was added and the reaction ran for 2 h more. The reaction was basified (*p*H~8) with 3 M NaOH and then concentrated to remove most methanol. The mixture was diluted with water (10 mL) extracted with dichloromethane (3 x 20 mol). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Column chromatography (15-30% ethyl acetate in hexanes) afforded product **6** as a yellow oil (2.19 g, yield 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, J = 7.8, 1.7 Hz, 1H), 7.03 (t, J = 7.9 Hz, 1H), 6.82 (m, 1H), 6.80 (s, 1H), 6.57 (s, 1H), 5.89 (dd, J = 7.8, 1.5 Hz, 2H), 4.39 (d, J = 5.0 Hz, 1H), 3.86 (s, 3H), 3.84 (d, overlapped, 1H), 3.77 (s, 3H), 3.75 (d, overlapped, 1 H), 3.70 (d, J = 5.1 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 3.24 (ddd, J = 12.6, 9.4, 5.0 Hz, 1H), 2.91–2.77 (m, 2H), 2.51 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 147.9, 146.3, 145.4, 133.5, 129.2, 126.7, 123.9, 122.5, 111.1, 110.1, 108.3, 107.9, 100.6, 62.7, 60.9, 56.8, 55.9, 53.7, 52.2, 45.0 , 25.1; FTIR (film) 2933, 2829, 1481, 1208, 1153, 1072 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{22}H_{28}NO_6]^+$ 402.1917, found 402,1892.



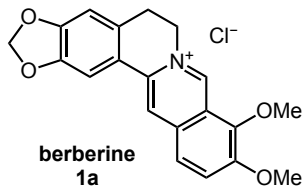
iminium triflate
S8

9,10-Dimethoxy-5,6,8,13-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolino[3,2-*a*]isoquinolin-7-ium triflate (S8): To a 25 mL round bottom flask was added a magnetic stirbar and amine **6** (200 mg, 0.498 mmol, 1 equiv). The flask was evacuated / backfilled with Ar (3 cycles), then dichloromethane (10 mL) was added. The solution was cooled to 0 ºC and triflic acid (88 µL, 0.1 mmol, 2 equiv) was added dropwise. After 10 minutes the cold bath was removed and the reaction stirred at room temperature for 2 h. The reaction was then cooled back to 0 ºC. A yellow solid precipitated overnight. The solid was filtered, washed with dichloromethane, and dried under vacuum to afford iminium **S8** (133 mg, 55%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 7.15 (d, *overlapped*, 1H), 7.14 (s, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.25 (s, 2H), 5.10 (t, J = 4.0 Hz, 2H), 4.58 (d, J = 4.1 Hz, 2H), 4.14 – 4.06 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.11 (t, J = 7.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.7, 153.9, 151.1, 147.4, 143.9, 135.4, 122.6, 121.4, 120.7 (q, J = 322.9 Hz, CF_3), 119.5, 119.3, 113.5, 108.6, 108.4, 103.1, 60.3, 56.0, 52.3, 51.1, 31.5, 25.1; ^{19}F NMR (376 MHz, DMSO-d_6) δ -77.8; HRMS (ESI) *m/z* calcd for $[C_{20}H_{20}NO_4]^+$ 338.1392, found 338.1405.



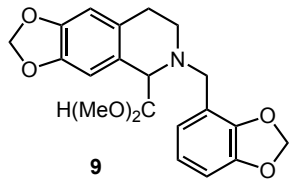
lambertine
8

Lambertine (8):[1] To a dry 25 mL round bottom flask was added a magnetic stirbar and amine **6** (219 mg, 0.523 mmol, 1 equiv). The flask was evacuated / backfilled with Ar (3 cycles), then dichloromethane (10.5 mL) was added. The solution was cooled to 0 ºC and triflic acid (0.14 mL, 1.569 mmol, 3 equiv) was added dropwise. After 5 minutes, the cold bath was removed and the reaction stirred at room temperature. After 50 minutes the reaction was opened to air, diluted with dichloromethane (40 mL), and transferred to a separatory funnel. The solution was washed with saturated $NaHCO_{3\ (aq)}$ (2 x 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. Due to instability, compound **8** was not further purified. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.73 (d, *J* = 1.7 Hz, 2H), 6.58 (s, 1H), 5.95 (s, 1H), 5.94 (s, 2H), 4.32 (s, 2H), 3.84 (s, 6H), 3.13 (t, *J* = 5.9 Hz, 2H), 2.87 (t, *J* = 5.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.4, 146.8, 144.7, 141.8, 128.9, 128.7, 124.7, 122.3, 119.0, 111.6, 108.0, 103.9, 101.1, 96.5, 60.9, 56.1, 49.5, 49.2, 30.0. HRMS (ESI) *m/z* calcd for $[C_{20}H_{20}NO_4]^+$ 338.1392, found 338.1399. The spectral data is in accord with published values.[2]



berberine
1a

Berberine (1a): To a round bottom flask was added a magnetic stirbar and compound **6** (97.3 mg, 0.243 mmol). The flask was evacuated / backfilled with Ar (3 cycles), then dichloromethane (5 mL) was added, followed by triflic acid (65 µL, 0.729 mmol, 3 equiv). After 1.5 h the reaction was opened to air, diluted with dichloromethane (40 mL), and transferred to a separatory funnel. The solution was washed with saturated $NaHCO_{3\ (aq)}$ (2 x 10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to give the crude **lambertine (8)**, which was immediately submitted to oxidation. Potassium acetate (29.74 mg, 0.303 mmol, 1.25 equiv) was added to the flask containing **8**, along with ethanol (10 mL). A solution of iodine (61.5 mg, 0.243 mmol, 1 equiv) in ethanol (10 mL) was then added dropwise with vigorous stirring. After 1 h, 10% $Na_2S_2O_3$ (10 mL) was added and the mixture concentrated to remove ethanol. Water (5 mL) and 20% $NaOH_{\ (aq)}$ (5 mL) were added to the resulting residue and swirled for ~5 minutes. The mixture was extracted with dichloromethane (4 x 30 mL). The combined organic extracts were extracted with 1 M HCl (9 mL) and water (5 x 20 mL). The combined aqueous extracts were collected and concentrated to afford **1a** as a yellow solid (88.9 mg, yield 99%), mp = 204-206. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 8.95 (s, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 7.80 (s, 1H), 7.09 (s, 1H), 6.17 (s, 2H), 4.94 (t, *J* = 6.3 Hz, 2H), 4.09 (s, 3H), 4.07 (s, 3H), 3.21 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.4, 149.8, 147.7, 145.5, 143.7, 137.5, 133.0, 130.7, 126.8, 123.5, 121.4, 120.5, 120.2, 108.4, 105.4, 102.1, 61.9, 57.1, 55.2, 26.3; FTIR (film) 3212, 2983, 2910, 1601, 1506, 1365, 1243, 1205, 1037 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{20}H_{18}NO_4]^+$ 336.1230, found 336.1249. The spectral data is in accord with published values.[3]



9

6-(Benzo[d][1,3]dioxol-4-ylmethyl)-5-(dimethoxymethyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (9): Following the procedure for the preparation of **6**, to **5ab** (1g, 3.98 mmol), 1,3-benzodioxole-4-carbaldehyde (0.66 g, 4.38 mmol, 1.1 equiv), methanol (10 mL), acetic acid (0.46 mL, 7.96 mmol, 2.0 equiv), sodium triacetoxyborohydride (1.10 g, 5.17 mmol, 1.3 equiv), and a second portion of sodium triacetoxyborohydride after 17 h (0.25 g, 1.2 mmol, 0.3 equiv) afforded, after workup and column chromatography (first column, 20-25% ethyl acetate / hexanes; second column, 10% acetone / hexanes), compound **9** (869 mg, yield 57%) as a white solid, mp = 90–91 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.82 – 6.71 (m, 3H), 6.56 (s, 1H), 5.92 (s, 2H), 5.90 (d, *J* = 1.4 Hz, 1H), 5.89 (d, *J* = 1.5 Hz, 1H), 4.37 (d, *J* = 5.3 Hz, 1H), 3.80 – 3.70 (m, 2H), 3.68 (d, *J* = 5.2 Hz, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 3.31 – 3.23 (m, 1H), 2.91 – 2.79 (m, 2H), 2.53 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 146.4, 146.3, 145.4, 128.9, 126.5, 123.4, 121.5, 120.8, 110.1, 108.3, 107.7, 107.5, 100.8, 100.7, 62.4, 56.8, 53.5, 52.1, 45.1, 24.9. FTIR (film) 2931, 1481, 1154, 1069 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{21}H_{24}NO_6]^+$ 386.1604, found 386.1609.

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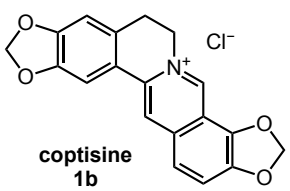
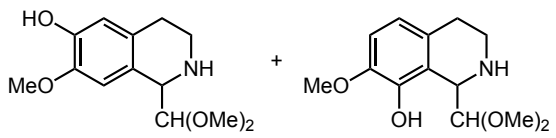
[1] Chatterjee, R.; Maiti, P. C. *J. Indian Chem. Soc.* **1955**, *32*, 609–610.
[2] Zhou, S.; Tong, R. *Chem. Eur. J.* **2016**, *22*, 7084–7089.
[3] Blaskó, G.; Cordell, G. A.; Bhamarapravati, S.; Beecher, C. W. W. *Heterocycles* **1988**, *27*, 911–916.



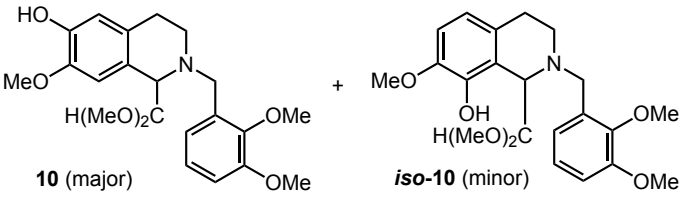
coptisine
1b

Coptisine (1b): To a round bottom flask was added a magnetic stirbar, compound **9** (100 mg, 0.259 mmol), and dichloromethane (5.2 mL). The flask was then flushed with argon for ~5 min. The solution was cooled to 0 ºC and triflic acid (69 µL, 0.78 mmol, 3.0 equiv) was added dropwise. After 5 min, the ice bath was removed and the reaction stirred at room temperature for 1.5 h. The reaction mixture was then diluted with dichloromethane (~20 mL) and washed with sodium bicarbonate (2 x 5 mL). The organic phase was dried over Na_2SO_4 and concentrated to give the crude enamine, which was immediately submitted to the oxidation step. A stirbar and potassium acetate (31.8 mg, 0.324 mmol, 1.25 equiv) were added to the flask containing the crude enamine along with ethanol (8.1 mL). A solution of iodine (65.74 mg, 0.259 mmol, 1.0 equiv) in ethanol (0.5 mL) was then added dropwise to the reaction mixture with vigorous stirring. After 1 h, $Na_2S_2O_{3\,(aq)}$ (10% w/w, 2 mL) was added to the reaction mixture to reduce excess iodine. The solution was then concentrated to remove ethanol. Water (5 mL) and 20% $NaOH_{(aq)}$ (5 mL) were added to the resulting residue and swirled for ~5 minutes. The solution was extracted with dichloromethane (6 x 10 mL). The combined organic extracts were extracted with 1 M HCl (9 mL) and water (6 x 20 mL). The aqueous layers were combined and concentrated to afford **1b** as an orange solid (91 mg, yield ~99%). Mp = 240 ºC (decomp.); ^{1}H NMR (500 MHz, CD_3OD) δ 9.73 (s, 1H), 8.75 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.66 (s, 1H), 6.97 (s, 1H), 6.47 (s, 2H), 6.11 (s, 2H), 4.89 (m, 2H), 3.26 (t, *J* = 6.4 Hz, 2H). 13C NMR ^{13}C NMR (126 MHz, CD_3OD) δ 152.2, 150.0, 149.3, 145.8, 145.3, 139.0, 134.5, 131.8, 123.1, 122.5, 122.3, 122.0, 113.7, 109.4, 106.5, 106.2, 103.7, 57.2, 28.1. FTIR (film) 2910, 1606, 1504, 1056 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{19}H_{14}NO_4]^+$ 320.0923, found 320.0920. The spectral data is in accord with published values.[4]



5c (major) ***iso*-5c** (minor)

1-(Dimethoxymethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-6-ol (5c) and 1-(dimethoxymethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-8-ol (iso-5c): Phenethylamine **2c** (393 mg, 2.35 mmol) was added to a 50 mL pear-shaped flask. A solution of 2,2-dimethoxyacetaldehyde (60 wt.% in water, 1.06 mL, 7.05 mmol, 3.0 equiv) was extracted with dichloromethane (2 x 1 mL). The combined organic phases were dried over Na_2SO_4, and then filtered into the flask containing amine **2c**. Dichloromethane (3 mL) was added to the flask and the mixture stirred at room temperature. After 30 min, the reaction was cooled to 0 ºC and trifluoroacetic acid (2.70 mL, 35.25 mmol, 15 equiv) was added dropwise. After 1 h, 3 M $NaOH_{(aq)}$ was added until neutral *p*H. The mixture was then extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Column chromatography (10% methanol / dichloromethane) afforded a mixture of **5c** and **iso-5c** (6.7:1.0 ratio) as a thick golden brown oil (489 mg, yield 82%). Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.66 (s, 1H), 4.51 (d, *J* = 5.6 Hz, 1H), 4.25 (d, *J* = 5.6 Hz, 1H), 3.85 (s, 3H), 3.46 (s, 3H), 3.43 (s, 3H), 3.37 (m, 1H), 3.15 (m, 1H), 2.83 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.4, 145.2, 127.4, 122.2, 114.7, 110.2, 106.3, 56.4, 56.1, 55.9, 55.9, 40.4, 27.2; Minor isomer : ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (m, 1H), 6.69 (m, 1H), 4.95 (d, *J* = 3.3 Hz, 1H), 4.73 (d, *J* = 3.3 Hz, 1H), 3.87 (s, 3H), 3.61 – 3.54 (m, 1H), 3.53 (s, 3H), 3.29 (s, 3H), 3.23 (m, 1H), 2.95 (m, 1H), 2.87 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 162.7, 142.7, 120.1, 110.7, 104.1, 57.0, 56.6, 56.3, 52.8, 40.3, 26.4 (note: one carbon could not be located due to overlap); FTIR (film) 3384, 1674, 1151 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{13}H_{20}NO_4]^+$ 254.1392, found 254.1394.

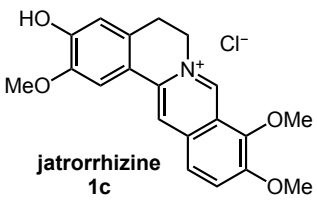


10 (major) ***iso*-10** (minor)

2-(2,3-dimethoxybenzyl)-1-(dimethoxy me thyl)-7-methoxy-1,2,3,4-tetrahydroiso qui nolin-6-ol (10c) 2-(2,3-dimethoxybenzyl)-1-(dimethoxymethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinolin-8-ol (*iso*-10c): To a 50 mL round bottom flask was added 2,3-dimethoxybenzaldehyde (618 mg, 3.72 mmol, 1.93 equiv), a mixture of **5c** and ***iso*-5c** (6.7:1.0 ratio, 489 mg, 1.93 mmol), and 1,2-dichloroethane (8.4 mL).

[4] Jung, H. A.; Yoon, N. Y.; Bae, H. J.; Min, B.-S.; Choi, J. S. *Arch. Pharm. Res.* **2008**, *31*, 1405–1412.

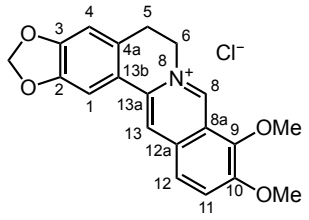
Sodium triacetoxyborohydride (1.187 g, 5.6 mmol, 2.9 equiv) was added and the reaction stirred at room temperature for 3 h. Saturated $NaHCO_{3\ (aq)}$ (17 mL) was added to the mixture and then extracted with dichloromethane (3 x 20 mL). The organic collection was dried over $MgSO_4$ and concentrated. ^{1}H NMR analysis showed a mixture of **10** and ***iso*-10c** (3.4:1.0 ratio). Column chromatography (0-3% methanol / dichloromethane – first column and 5-20% acetonitrile / dichloromethane – second column) afforded a mixture of **10** and ***iso*-10c** as a thick yellow oil (465 mg, yield 60%, 3.3:1.0 ratio). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (m, 1H), 7.04 (m, 1H), 6.87 – 6.77 (m, 2H), 6.65 (s, 1H), 5.48 (s, 1H), 4.39 (d, J = 5.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H), 3.70 (d, J = 5.6 Hz, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 3.22 (m, 1H), 2.95 – 2.79 (m, 2H), 2.59 – 2.43 (m, 1H). (Note: benzylic protons and one methoxy group hidden under signals at ~3.86). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 147.9, 144.5, 144.4, 133.6, 128.7, 125.0, 123.9, 122.5, 114.0, 112.50, 110.9, 107.7, 62.6, 60.9, 56.9, 56.1, 55.8, 53.6, 52.1, 44.9, 24.1. Minor isomer: (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.00 – 7.06 (m, 2H), 6.87 – 6.77 (m, 2H), 6.70 (m, 1H), 4.65 (d, J = 5.7 Hz, 1H), 4.08 (d, 5.6 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.42 (s, 3H), 3.36 (s, 3H), 3.22 (m, 1H), 2.95 – 2.79 (m, 2H), 2.59 – 2.43 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.9, 148.0, 147.0, 144.3, 133.1, 128.6, 123.8, 122.6, 121.7, 120.5, 111.4, 111.1, 107.9, 67.2, 58.6, 56.9, 55.9, 52.9, 51.9, 44.2, 23.5. (Note: one carbon hidden under major isomer signal). FTIR (film) 3374, 1635, 1206, 1150 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{22}H_{30}NO_6]^+$404.2073, found 404.2077.



jatrorrhizine
1c

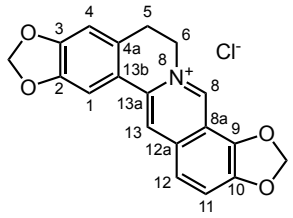
Jatrorrhizine (1c): To a 50 mL round bottom flask was added compound **10** (375 mg, 0.93 mmol), dichloromethane (18.6 mL), and a magnetic stirbar. The flask was then flushed with argon for ~5 min. The solution was cooled to 0 ºC and triflic acid (247 µL, 2.79 mmol, 3.0 equiv) was added dropwise. After 5 min, the ice bath was removed and the reaction ran for 45 min. The mixture was diluted with dichloromethane (50 mL) and washed with sodium bicarbonate (2x). The organic layers were then dried over Na_2SO_4 and concentrated to a crude enamine that was immediately submitted to oxidation. Potassium acetate (114 mg, 1.16 mmol, 1.25 equiv) was added to the flask containing crude enamine, along with ethanol (25 mL). A solution of iodine (236 mg, 0.93 mmol, 1.0 equiv) in ethanol (6 mL) was then added dropwise with vigorous stirring. After 1 h, $Na_2S_2O_{3\ (aq)}$ (10% w/w, 6 mL) was added. The mixture was then filtered through celite, rinsed with methanol, and the filtrate was concentrated. Column chromatography (2-16% methanol / dichloromethane – first column and 0-10% methanol / dichloromethane – second column) followed by purification through an ion exchange column (Dowex 50W XS H form, 200-400 mesh using methanol/water and flushing with 3M HCl/methanol (1:1), then 6M HCl/methanol (6:1), and 15% methanol / chloroform – third column) afforded **1c** (141 mg, yield 41%) as an orange solid. mp = 201-203 ºC; ^{1}H NMR (500 MHz, CD_3OD) δ 9.74 (s, 1H), 8.77 (s, 1H), 8.11 (d, J = 9.1 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.67 (s, 1H), 6.87 (s, 1H), 4.91 (m, 2H), 4.21 (s, 3H), 4.11 (s, 3H), 4.03 (s, 3H), 3.21 (t, J = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, MeOD) δ 152.0, 151.8, 149.7, 146.2, 145.7, 140.3, 135.5, 130.3, 128.1, 124.4, 123.2, 120.9, 119.4, 115.9, 110.0, 62.5, 57.7, 57.4, 56.9, 27.7. FTIR (film) 3355, 2943, 1604, 1510, 1361, 1109 cm^{-1}. HRMS (ESI) *m/z* calcd for $[C_{20}H_{20}NO_4]^+$ 338.1392, found 338.1393. The spectral data is in accord with published values.[4]

3. NMR Comparison Tables



berberine
1a

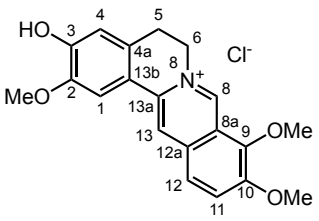
Atom	^{1}H NMR (natural)[3] DMSO-d_6 δ multiplicity (*J* in Hz)	^{1}H NMR (synthetic) DMSO-d_6 δ multiplicity (*J* in Hz)	^{13}C NMR (natural)[3] DMSO-d_6 δ	^{13}C NMR (synthetic) DMSO-d_6 δ
1	7.79 s	7.80 s	105.4	105.4
2	-	-	147.6	147.7
3	-	-	149.8	149.8
4	7.09 s	7.09 s	108.4	108.4
4a	-	-	130.6	130.7
5	3.22 t (6.2)	3.21 t (6.4)	26.4	26.3
6	4.95 t (6.3)	4.93 t (6.3)	55.2	55.2
8	9.91 s	9.90 s	145.4	145.5
8a	-	-	121.4	121.4
9	-	-	143.6	143.7
10	-	-	150.4	150.4
11	8.20 d (9.1)	8.21 d (9.1)	126.7	126.8
12	8.01 d (9.1)	8.00 d (9.1)	123.5	123.5
12a	-	-	132.9	133.0
13	8.96 s	8.95 s	120.2	120.2
13a	-	-	137.4	137.5
13b	-	-	120.4	120.5
OCH_2O	6.17 s	6.17 s	102.1	102.1
9-OCH_3	4.10 s	4.09	62.0	61.9
10-OCH_3	4.07 s	4.07	57.1	57.1



coptisine
1b

Atom	^{1}H NMR (natural)[4] CD_3OD δ multiplicity (*J* in Hz)	^{1}H NMR (synthetic) CD_3OD δ multiplicity (*J* in Hz)	^{13}C NMR (natural)[4] CD_3OD δ	^{13}C NMR (synthetic) CD_3OD δ
1	7.63 s	7.66 s	105.3	106.5
2	-	-	148.1	149.3
3	-	-	148.8	150.0
4	6.84 s	6.97 s	108.2	109.4
4a	-	-	130.6	131.8
5	3.23 m	3.26 t (6.4)	27.0	28.1
6	4.89 m	4.89 m	56.0	57.2
8	9.71 s	9.73 s	144.6	145.8
8a	-	-	112.5	113.7
9	-	-	144.1	145.3
10	-	-	151.0	152.2
11	7.87 d (8.0)	7.89 d (8.7)	120.7	122.0
12	7.83 d (8.0)	7.87 d (8.8)	121.9	123.1
12a	-	-	133.2	134.5
13	8.71 s	8.75 s	120.7	122.7
13a	-	-	137.8	139.0
13b	-	-	121.6	122.5
2,3-OCH_2O	6.09 s	6.11 s	105.0	106.2
9,10-OCH_2O	6.45 s	6.47 s	102.5	103.7

Note: Although all resonances in the ^{13}C NMR spectrum of synthetic coptisine are shifted from that of natural coptisine,[4] the consistent difference (~1.2 ppm) led us to believe these differences are due to the lack of reference in the reported spectrum of natural coptisine.

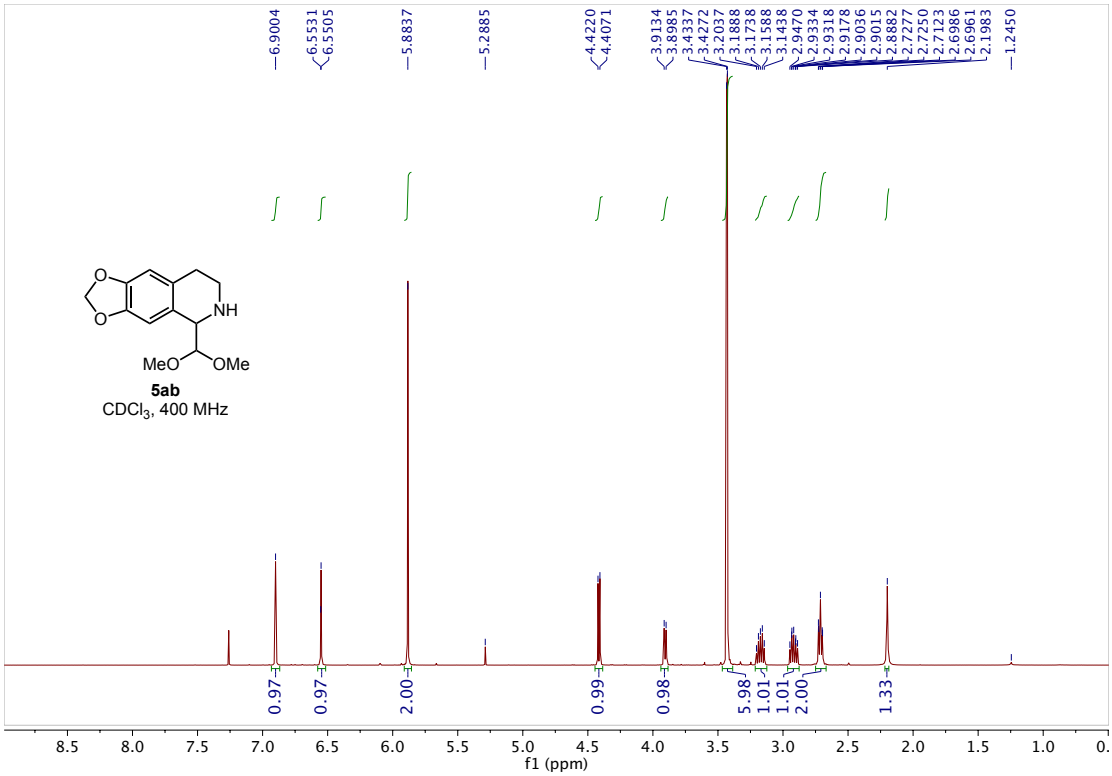


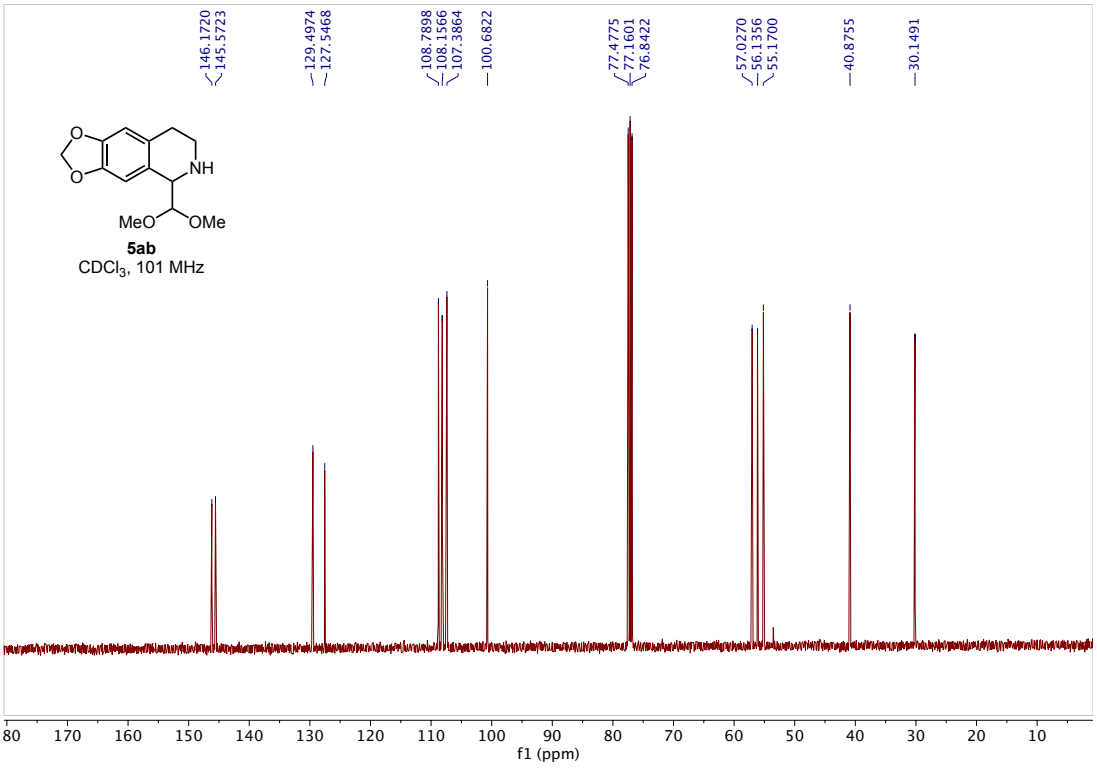
jatrorrhizine
1c

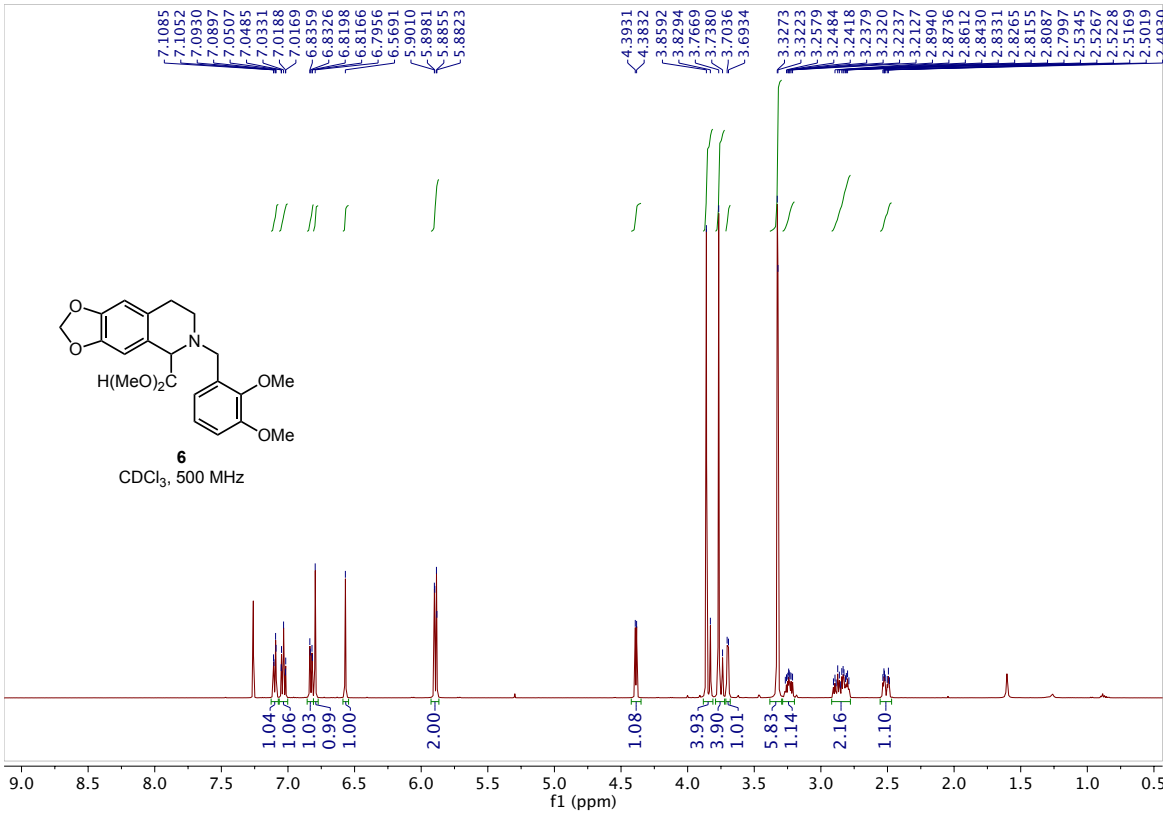
Atom	^{1}H NMR (natural)[4] CD_3OD δ multiplicity (*J* in Hz)	^{1}H NMR (synthetic) CD_3OD δ multiplicity (*J* in Hz)	^{13}C NMR (natural)[4] CD_3OD δ	^{13}C NMR (synthetic) CD_3OD δ
1	7.63 s	7.67 s	108.8	110.0
2	-	-	150.5	151.8
3	-	-	148.4	149.7
4	6.84 s	6.87 s	114.7	115.9
4a	-	-	129.1	130.3
5	3.18 m	3.21 t (6.4)	26.4	27.7
6	4.48 m	4.91 m	56.2	56.9
8	9.71 s	9.74 s	145.0	146.2
8a	-	-	118.2	119.4
9	-	-	150.6	152.0
10	-	-	144.5	145.7
11	8.08 d (8.0)	8.11 d (9.1)	123.1	124.4
12	7.97 d (8.0)	8.00 d (9.1)	126.8	128.1
12a	-	-	134.2	135.5
13	8.74 s	8.77 s	119.7	120.9
13a	-	-	139.1	140.3
13b	-	-	122.0	123.2
2-OMe	4.00 s	4.03 s	56.4	57.4
9-OMe	4.18 s	4.21 s	61.3	62.5
10-OMe	4.09 s	4.11 s	55.7	55.7

Note: Although all resonances in the ^{13}C NMR spectrum of synthetic jatrorrhizine are shifted from that of natural jatrorrhizine,[4] the consistent difference (~1.2 ppm) led us to believe these differences are due to the lack of reference in the reported spectrum of natural jatrorrhizine.

4. Copies of ^{1}H, ^{13}C, and ^{19}F NMR Spectra



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7.0169
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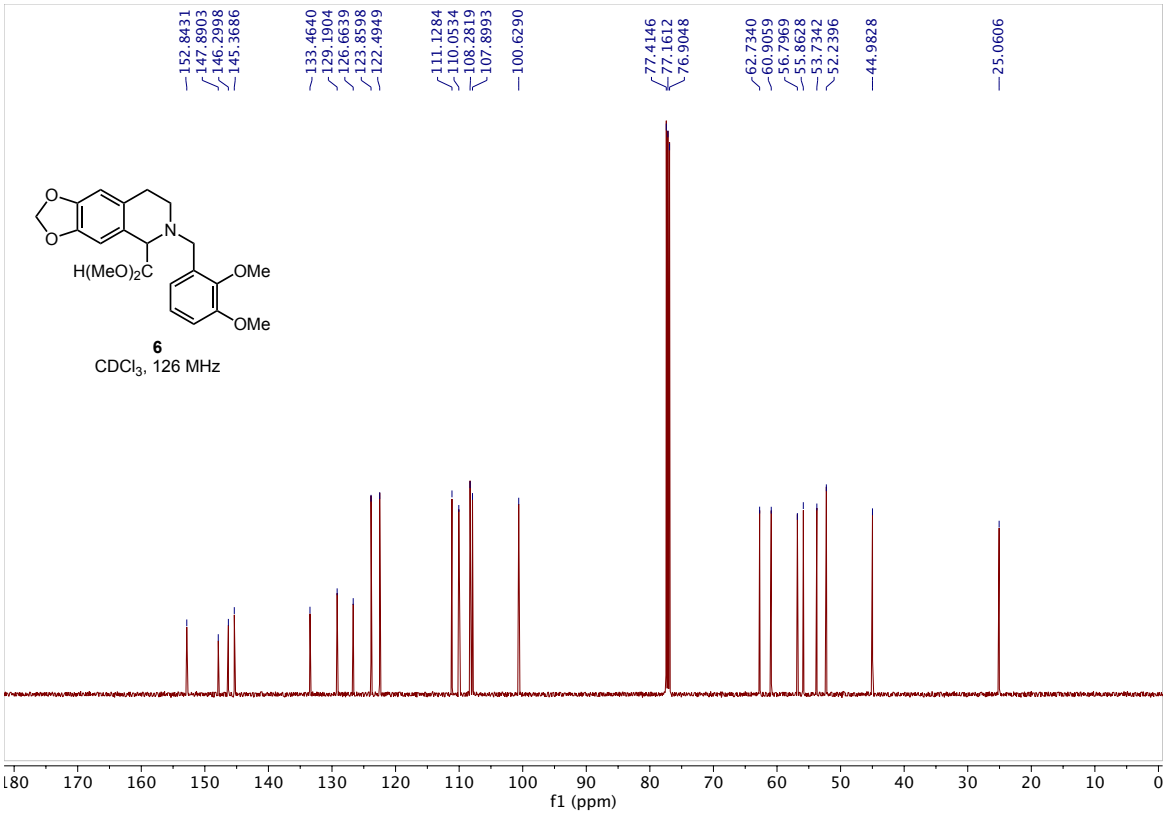
6.8326
6.8198
6.8166
6.7956
5.9010
5.8981
5.8855
5.8823
4.3931
4.3832
3.8592
3.8294
3.7669
3.7380
3.7036
3.6934
3.3273
3.3223
3.2579
3.2484
3.2418
3.2379
3.2320
3.2237
3.2127
2.8940
2.8736
2.8612
2.8430
2.8331
2.8265
2.8155
2.8087
2.7997
2.5345
2.5267
2.5228
2.5169
2.5019
O
O
N
H(MeO)2C
OMe
OMe
6
CDCl3, 500 MHz
1.04
1.06
1.03
0.99
1.00
2.00
1.08
3.93
3.90
1.01
5.83
1.14
2.16
1.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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146.2998
145.3686
133.4640
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126.6639
123.8598
122.4949
111.1284
110.0534
108.2819
107.8993
100.6290
77.4146
77.1612
76.9048
62.7340
60.9059
56.7969
55.8628
53.7342
52.2396
44.9828
25.0606
O
O
N
H(MeO)2C
OMe
OMe
6
CDCl3, 126 MHz
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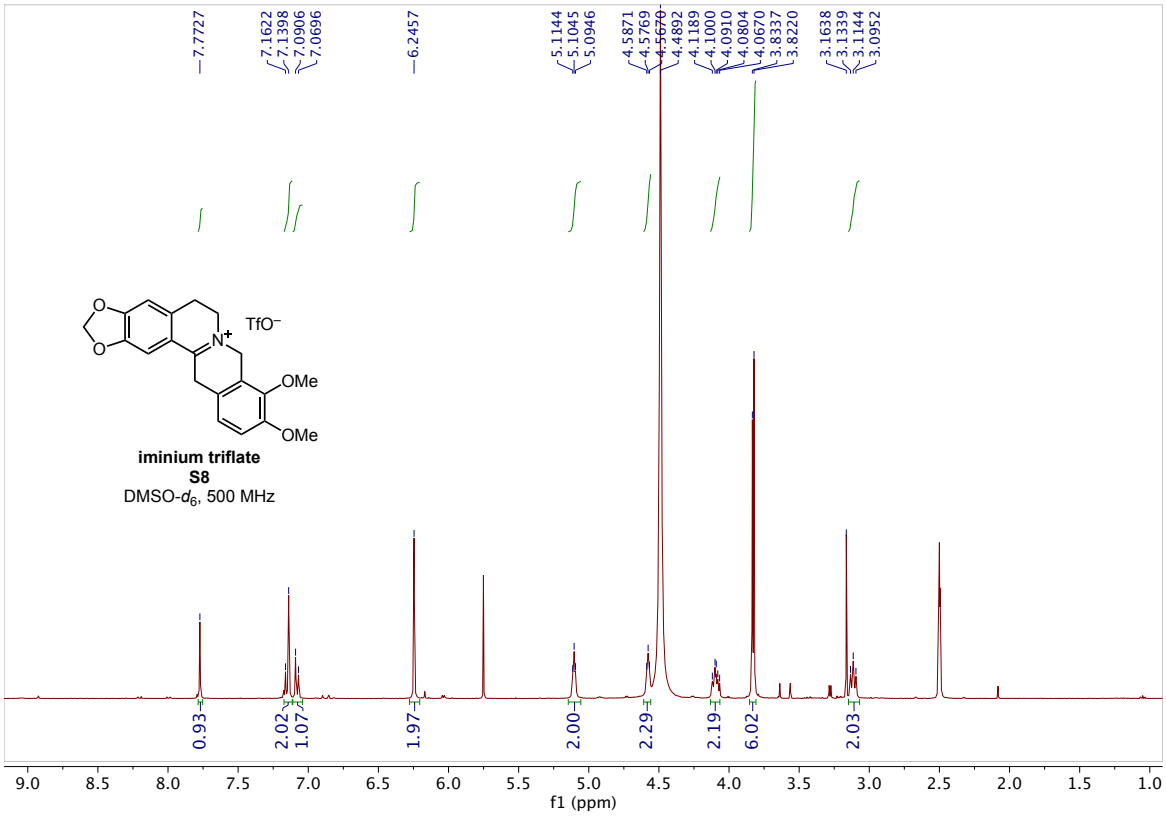
f1 (ppm)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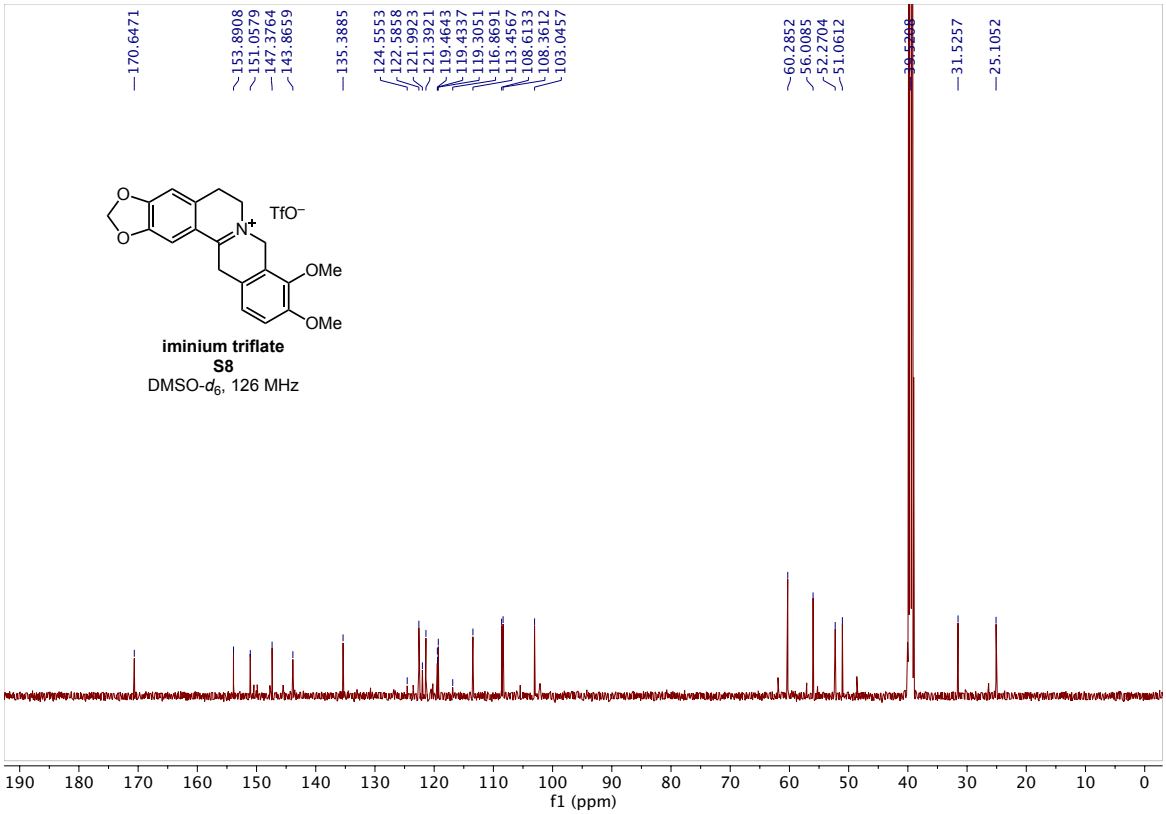
7.0696
6.2457
5.1144
5.1045
5.0946
4.5871
4.5769
4.5670
4.4892
4.1189
4.1000
4.0910
4.0804
4.0670
3.8337
3.8220
3.1638
3.1339
3.1144
3.0952
O
O
N+
TfO−
OMe
OMe
iminium triflate
S8
DMSO-d6, 500 MHz
0.93
2.02
1.07
1.97
2.00
2.29
2.19
6.02
2.03
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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143.8659
135.3885
124.5553
122.5858
121.9923
121.3921
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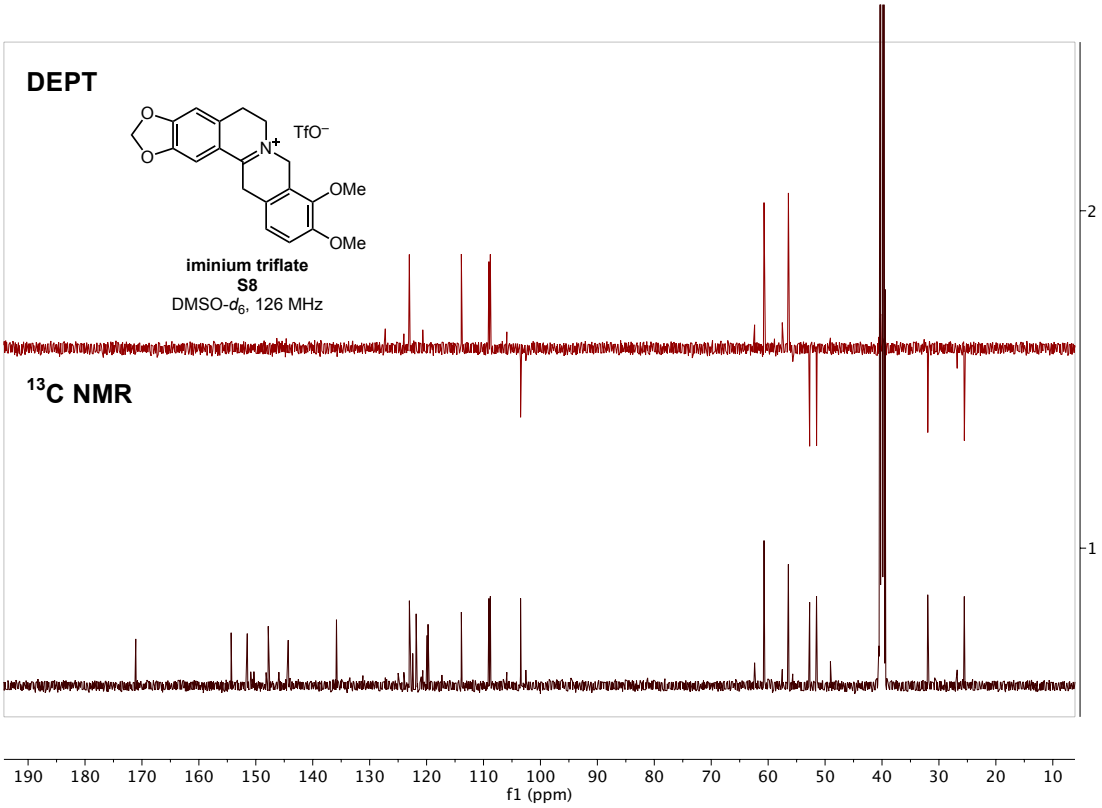
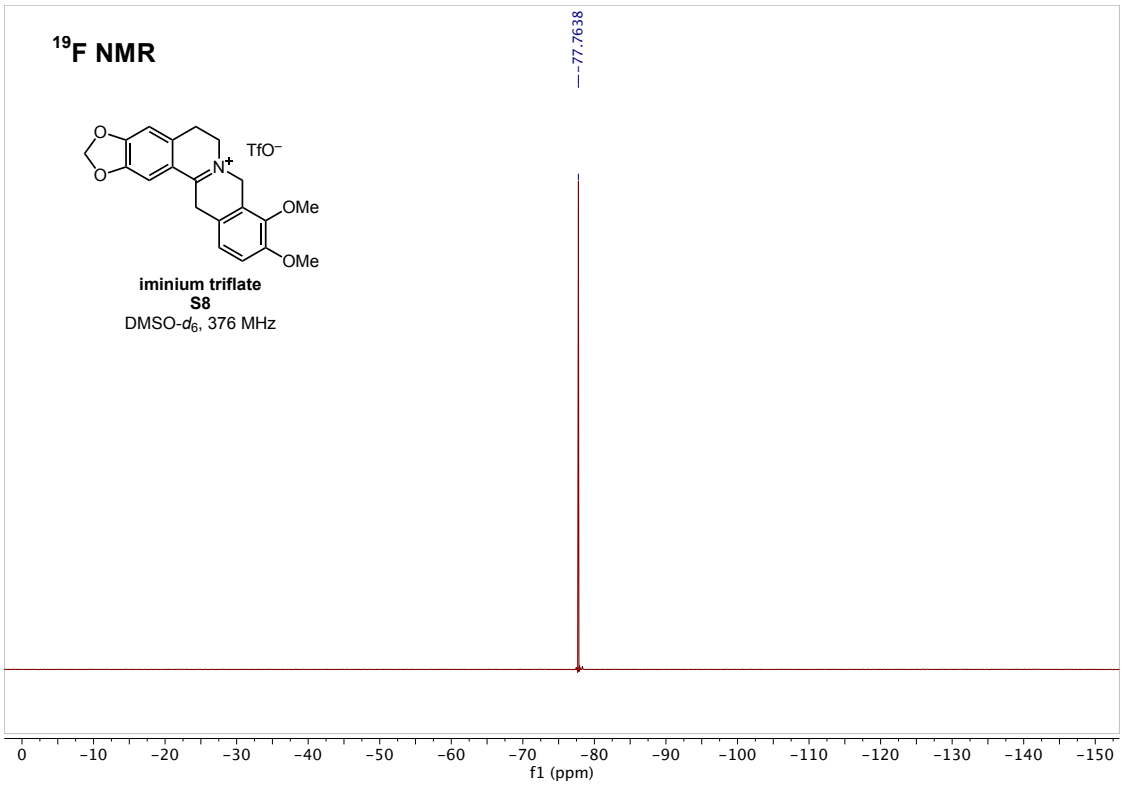
119.4337
119.3051
116.8691
113.4567
108.6133
108.3612
103.0457
60.2852
56.0085
52.2704
51.0612
39.5308
31.5257
25.1052
TfO⁻
OMe
OMe
iminium triflate
S8
DMSO-d_6, 126 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


DEPT
TfO⁻
OMe
OMe
iminium triflate
S8
DMSO-d_6, 126 MHz
^{13}C NMR
2
1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


19F NMR
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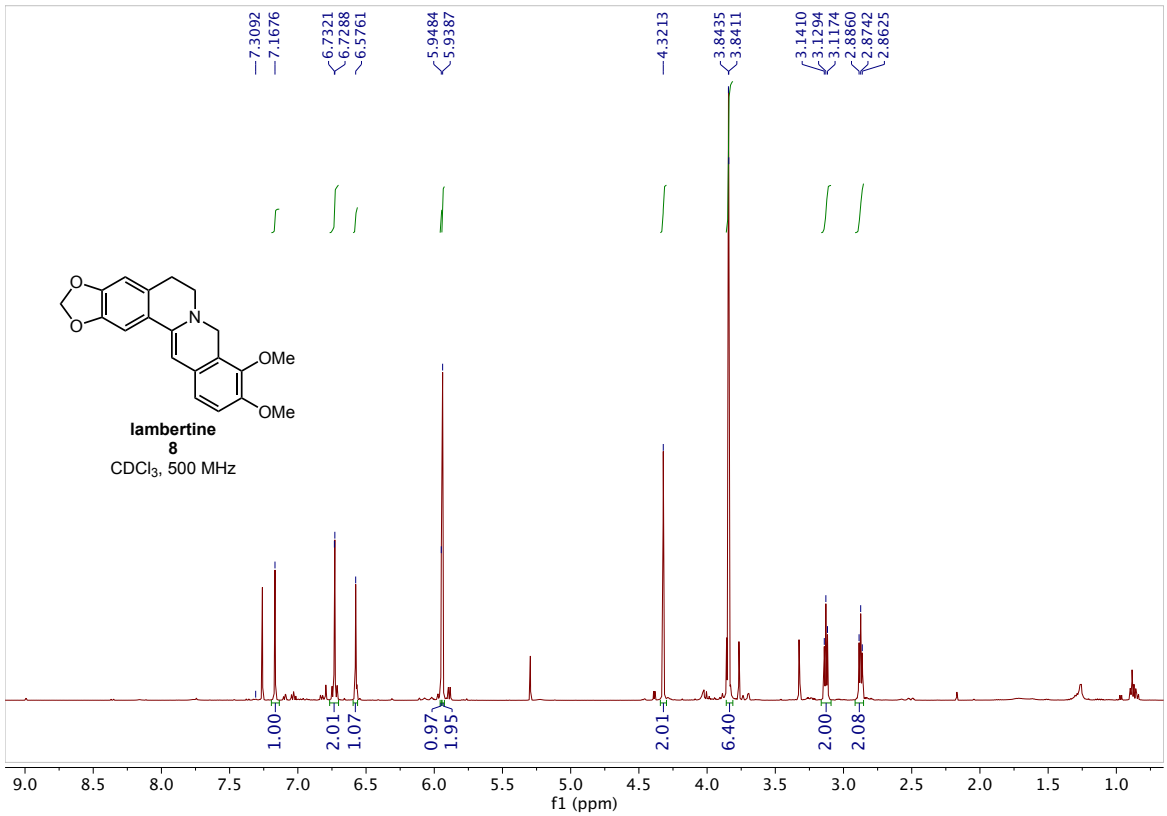
TfO⁻
OMe
OMe
iminium triflate
S8
DMSO-d6, 376 MHz
0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150
f1 (ppm)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6.5761
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5.9387
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3.8435
3.8411
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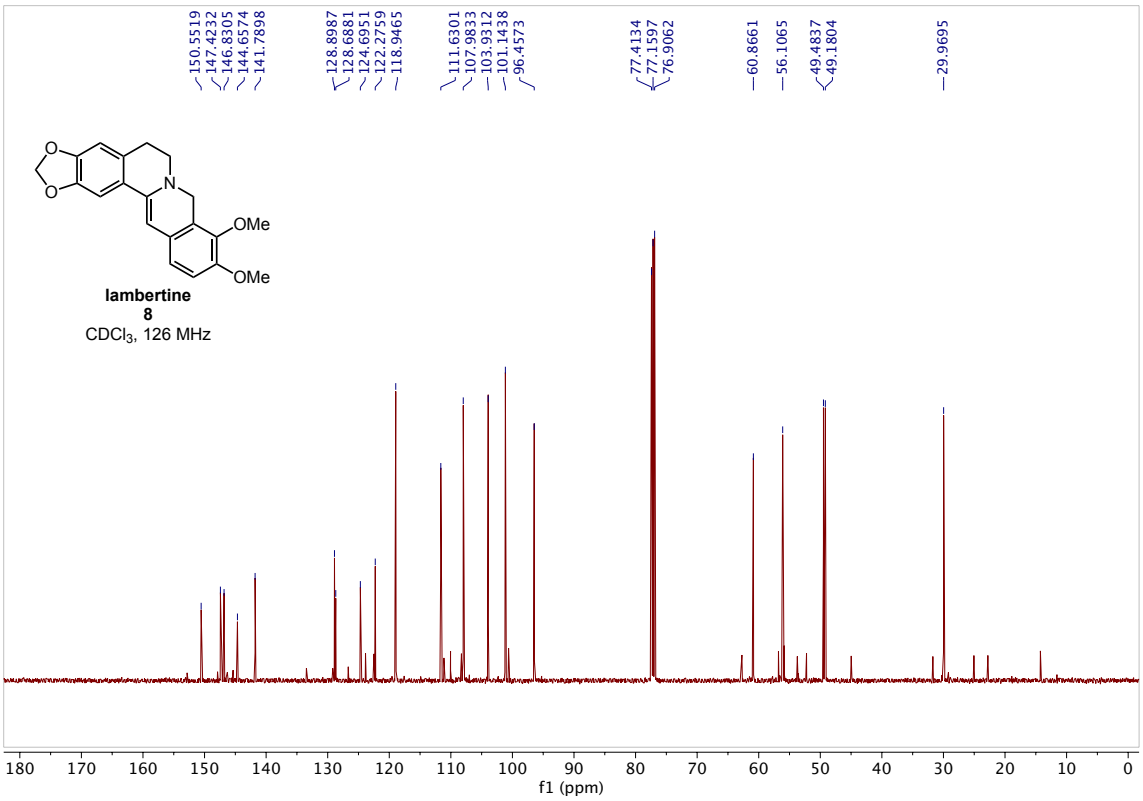
3.1294
3.1174
2.8860
2.8742
2.8625
OMe
OMe
lambertine
8
CDCl3, 500 MHz
1.00
2.01
1.07
0.97
1.95
2.01
6.40
2.00
2.08
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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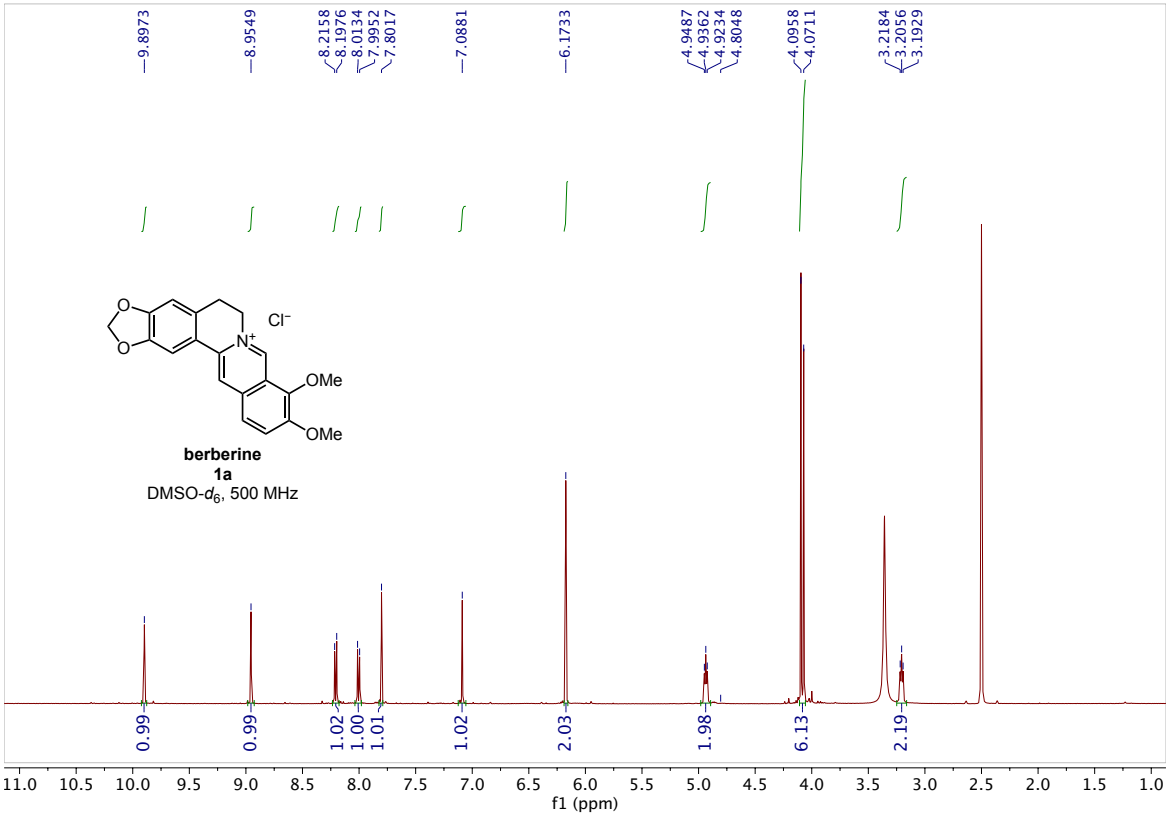
111.6301
107.9833
103.9312
101.1438
96.4573
77.4134
77.1597
76.9062
60.8661
56.1065
49.4837
49.1804
29.9695
O
O
N
OMe
OMe
lambertine
8
CDCl3, 126 MHz
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.2158
8.1976
8.0134
7.9952
7.8017
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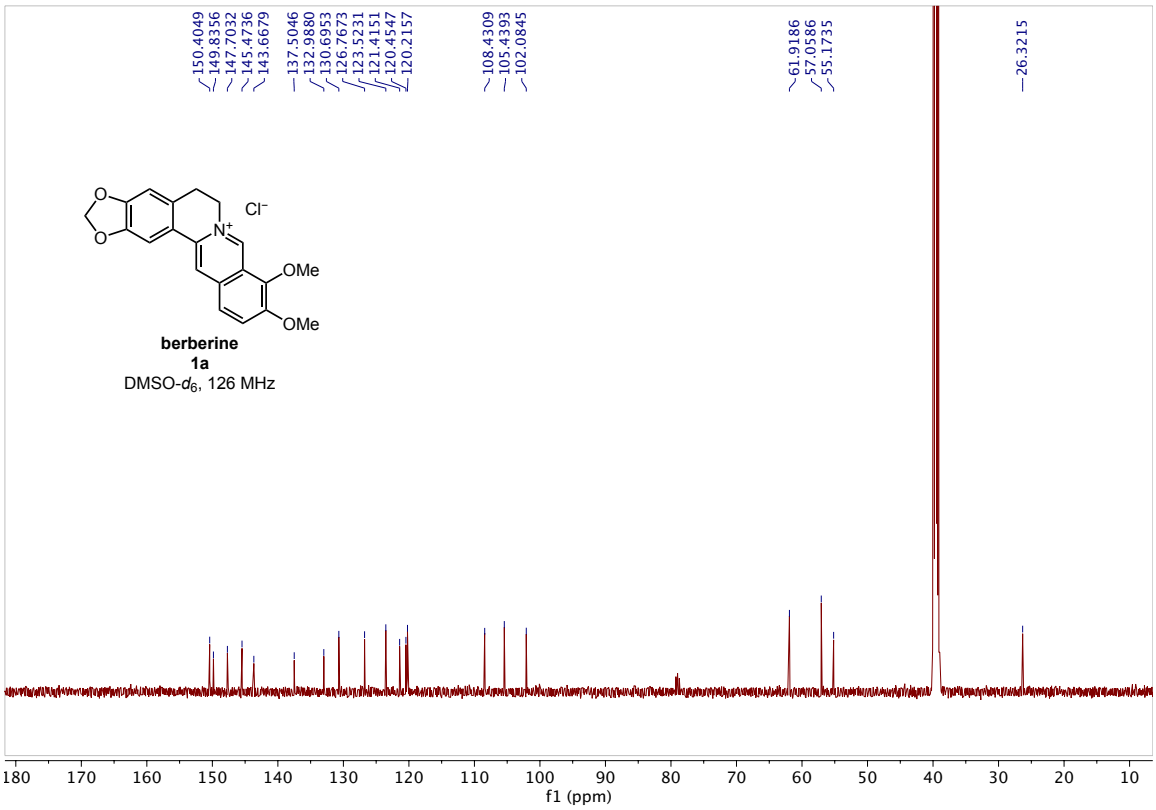
6.1733
4.9487
4.9362
4.9234
4.8048
4.0958
4.0711
3.2184
3.2056
3.1929
O
O
N+
Cl−
OMe
OMe
berberine
1a
DMSO-d6, 500 MHz
0.99
0.99
1.02
1.00
1.01
1.02
2.03
1.98
6.13
2.19
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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143.6679
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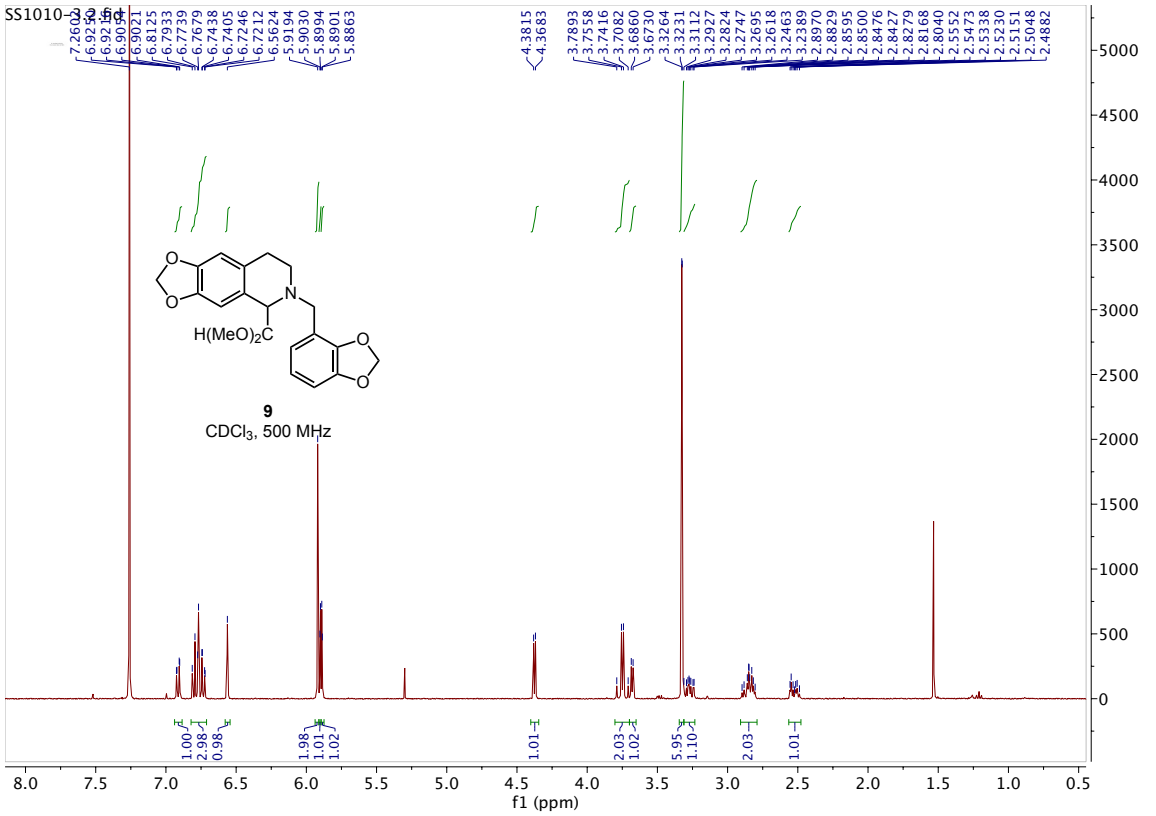
132.9880
130.6953
126.7673
123.5231
121.4151
120.4547
120.2157
108.4309
105.4393
102.0845
61.9186
57.0586
55.1735
26.3215
Cl⁻
N⁺
OMe
OMe
berberine
1a
DMSO-d6, 126 MHz
f1 (ppm)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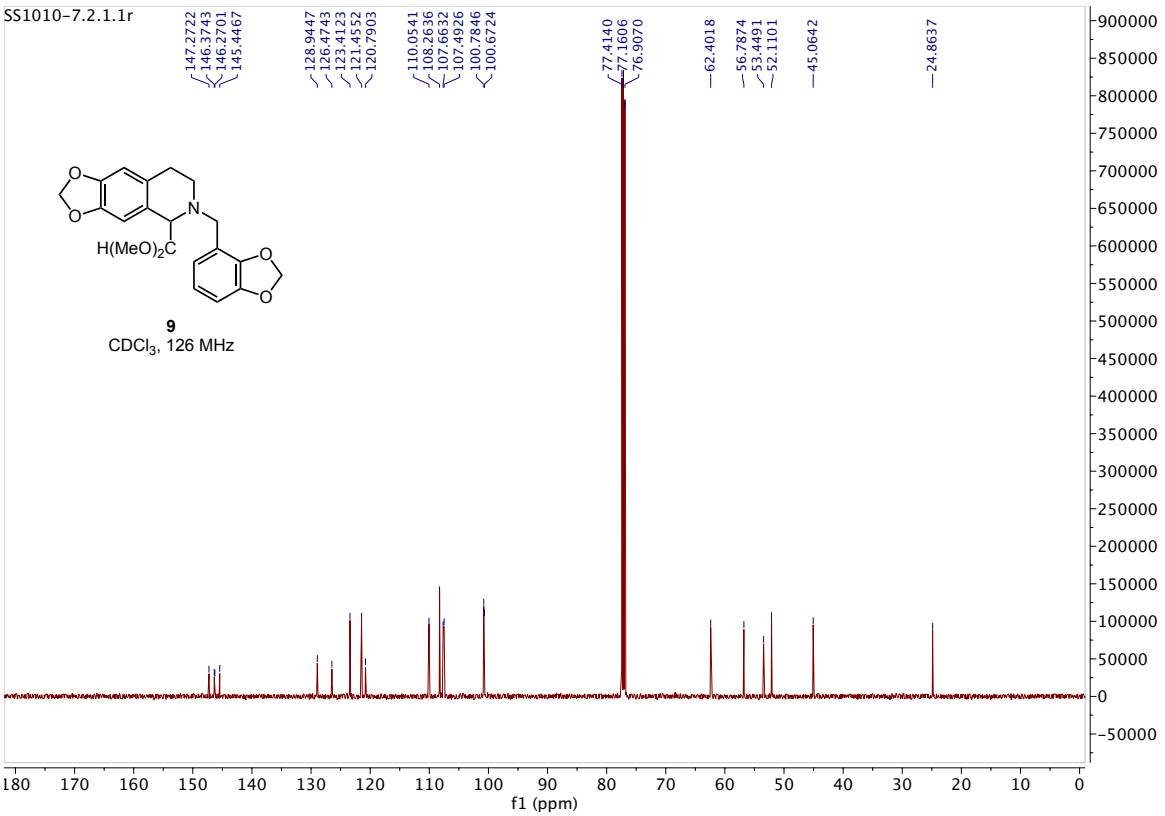
9
CDCl3, 500 MHz
f1 (ppm)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107.6632
107.4926
100.7846
100.6724
77.4140
77.1606
76.9070
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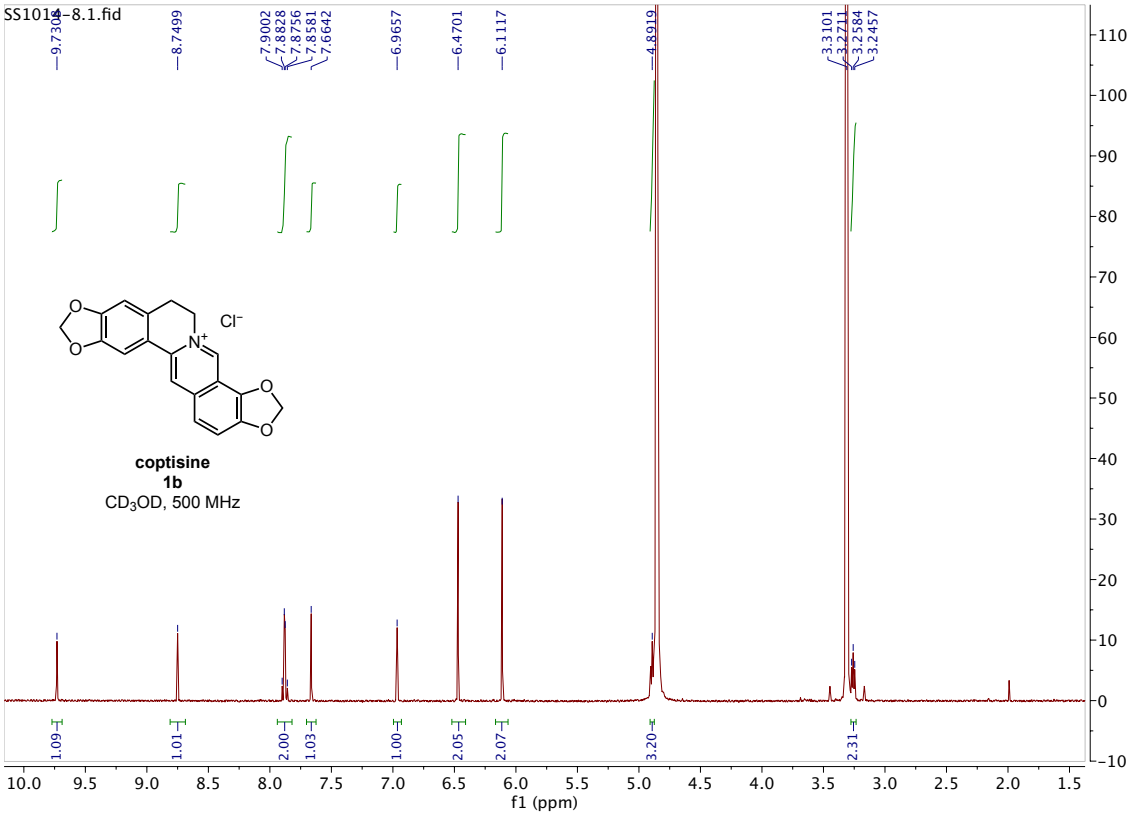
H(MeO)2C
9
CDCl3, 126 MHz
f1 (ppm)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7.8756
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6.9657
6.4701
6.1117
4.8919
3.3101
3.2771
3.2584
3.2457
Cl⁻
coptisine
1b
CD3OD, 500 MHz
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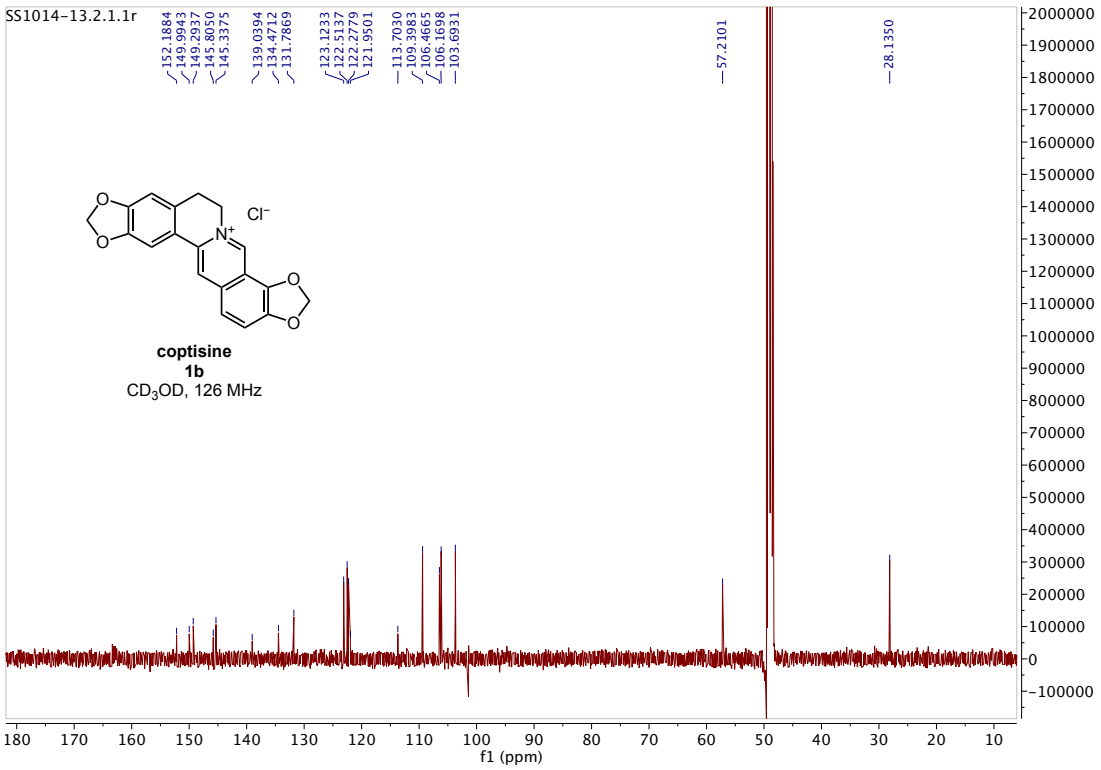
1.01
2.00
1.03
1.00
2.05
2.07
3.20
2.31
f1 (ppm)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113.7030
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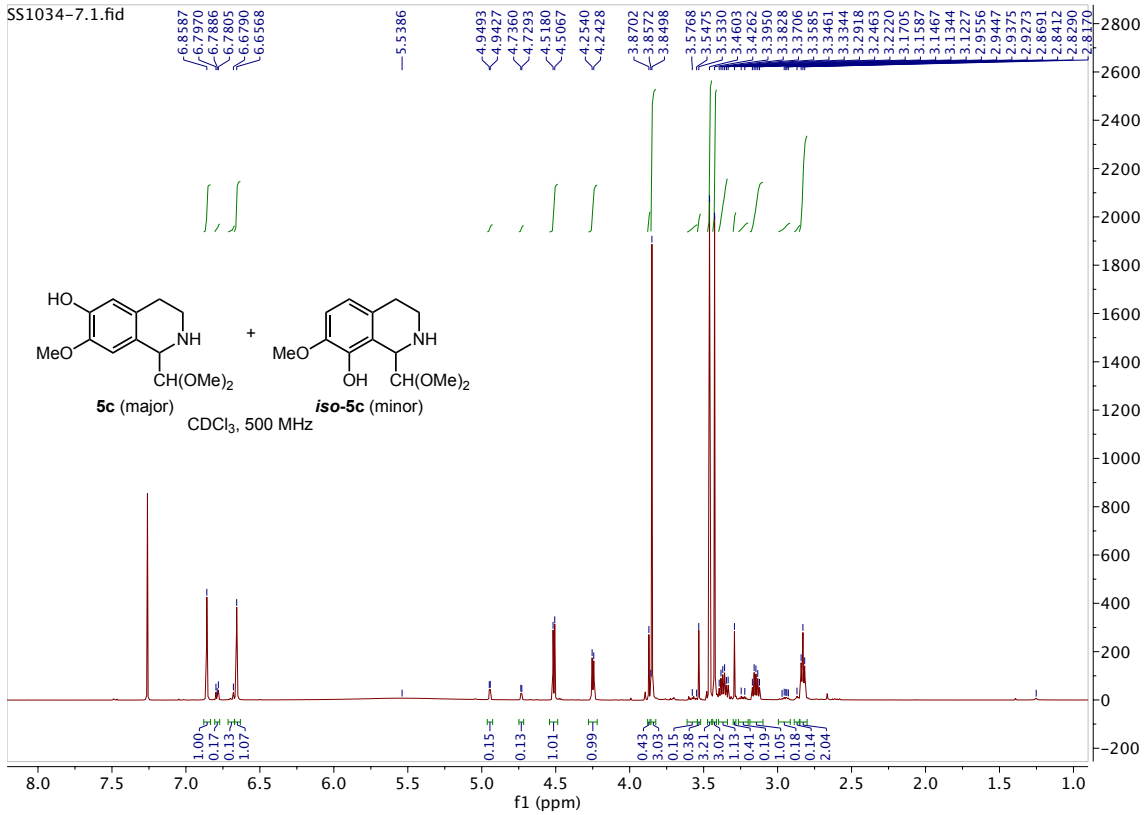
Cl⁻
coptisine
1b
CD3OD, 126 MHz
f1 (ppm)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3.1587
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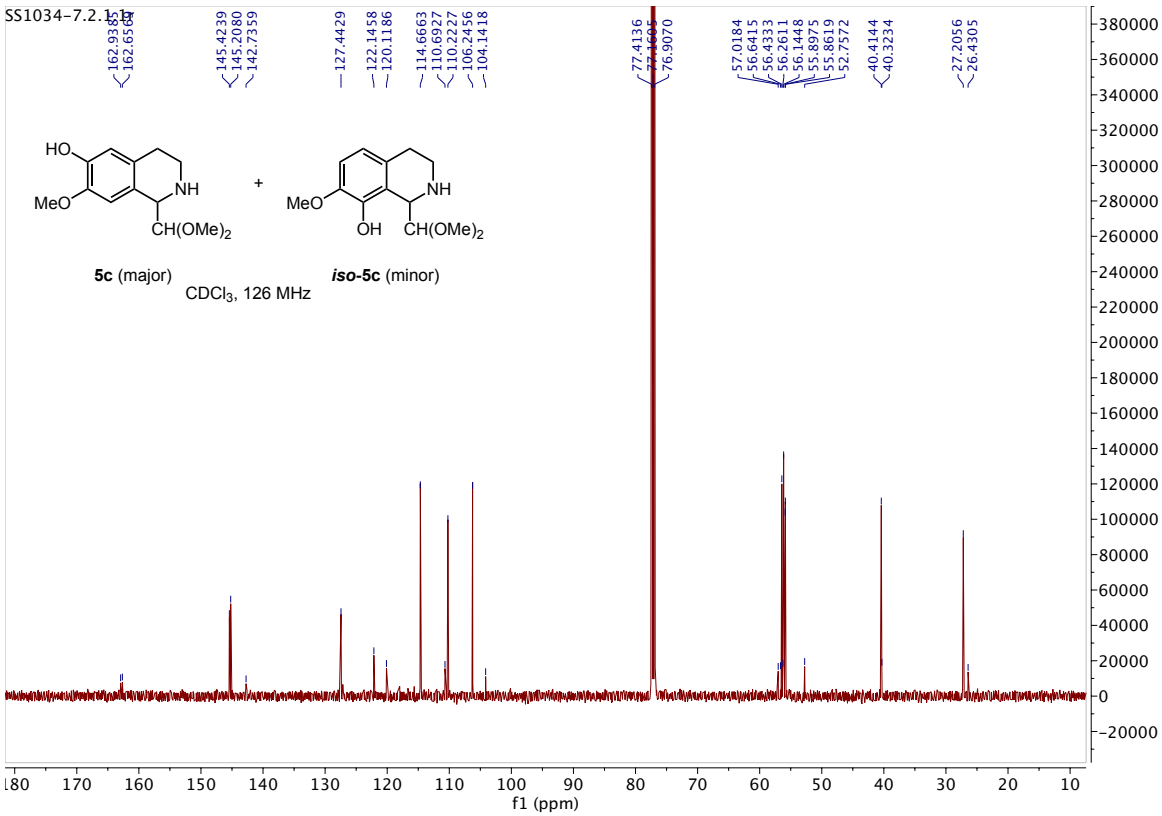
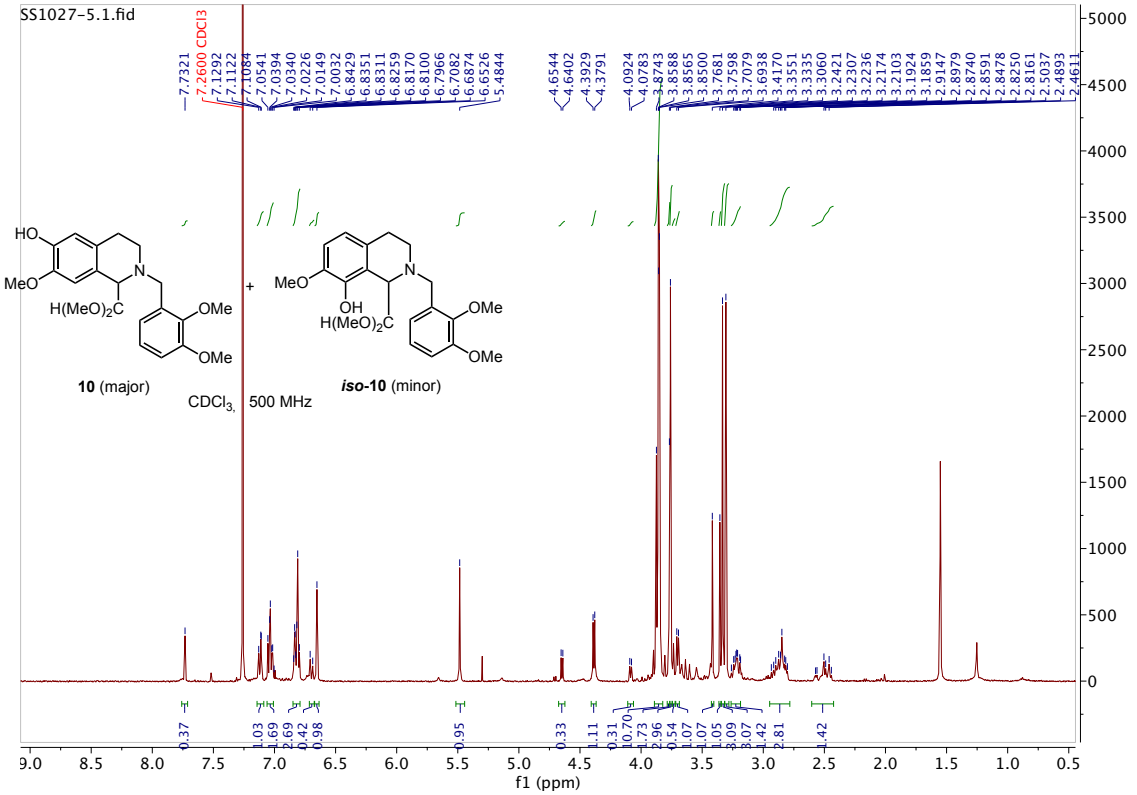
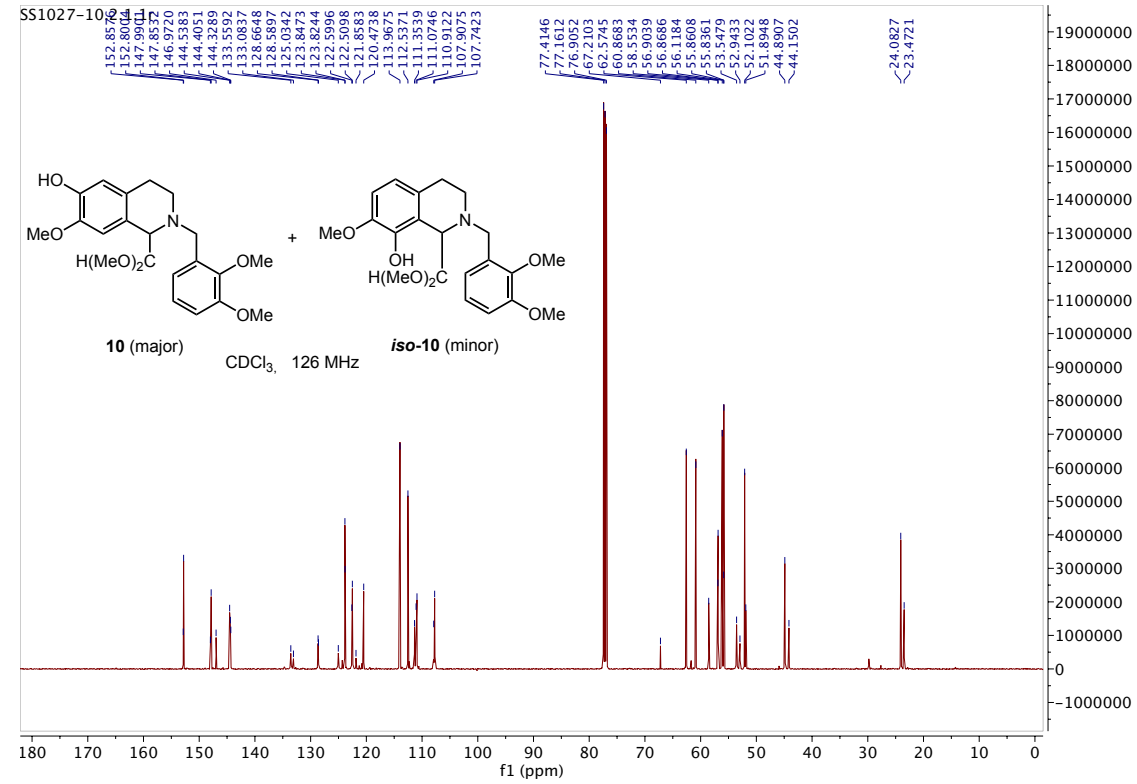
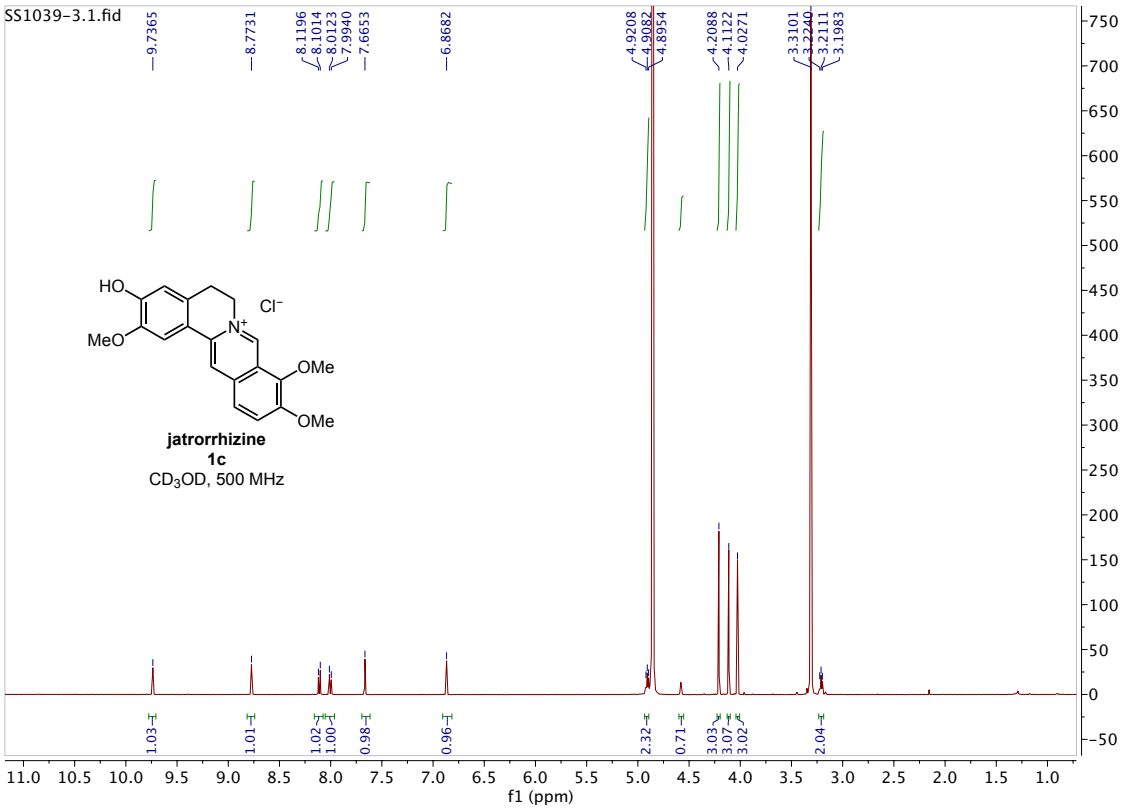
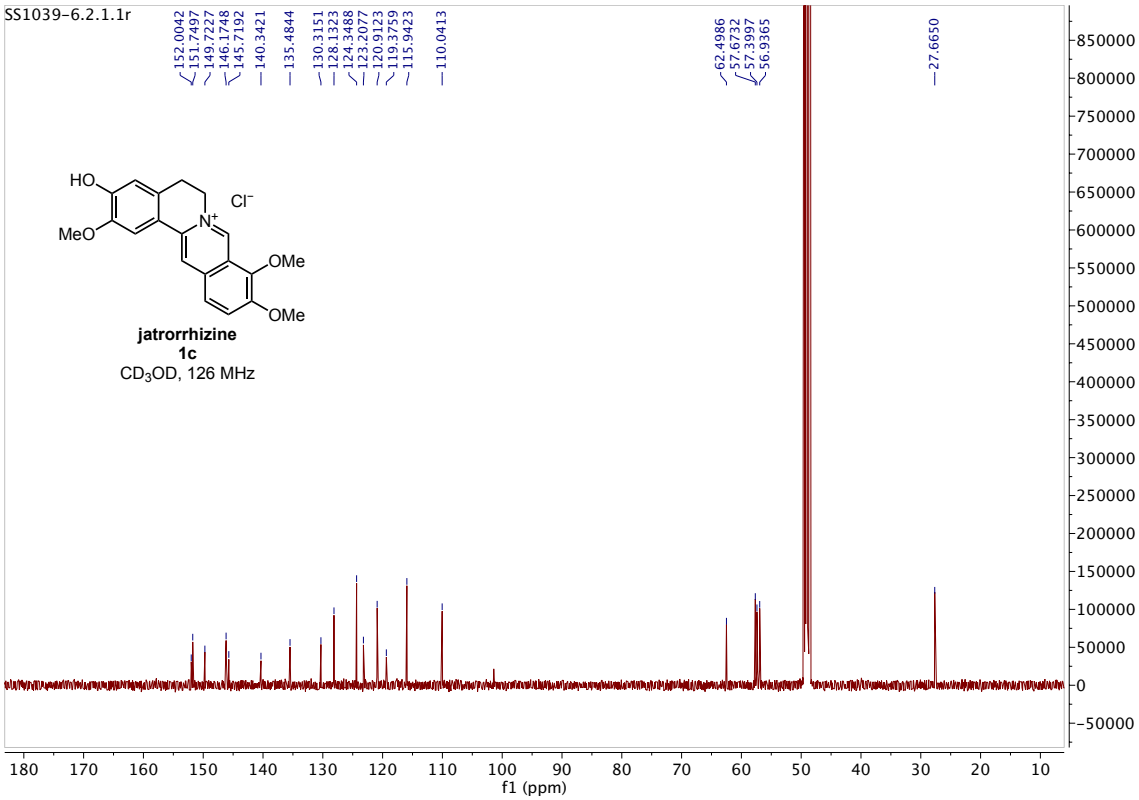
3.1344
3.1227
2.9556
2.9447
2.9375
2.9273
2.8691
2.8412
2.8290
2.8170
HO
MeO
NH
CH(OMe)2
5c (major)
MeO
OH
NH
CH(OMe)2
iso-5c (minor)
CDCl3, 500 MHz
1.00
0.17
0.13
1.07
0.15
0.13
1.01
0.99
0.43
3.03
0.15
0.38
3.21
3.02
1.13
0.41
0.19
1.05
0.18
0.14
2.04
f1 (ppm)


SS1034-7.2.1.13
162.9380
162.6568
145.4239
145.2080
142.7359
127.4429
122.1458
120.1186
114.6663
110.6927
110.2227
106.2456
104.1418
77.4136
77.1605
76.9070
57.0184
56.6415
56.4333
56.2611
56.1448
55.8975
55.8619
52.7572
40.4144
40.3234
27.2056
26.4305
HO
MeO
NH
CH(OMe)2
+
MeO
OH
NH
CH(OMe)2
5c (major)
iso-5c (minor)
CDCl3, 126 MHz
f1 (ppm)


SS1027-5.1.fid
HO
MeO
H(MeO)2C
OMe
OMe
10 (major)
+
MeO
OH
H(MeO)2C
OMe
OMe
iso-10 (minor)
CDCl3, 500 MHz
f1 (ppm)


SS1027-10.fid
HO
MeO
H(MeO)2C
OMe
OMe
10 (major)
+
MeO
OH
H(MeO)2C
OMe
OMe
iso-10 (minor)
CDCl3, 126 MHz
f1 (ppm)


SS1039-3.1.fid
9.7365
8.7731
8.1196
8.1014
8.0123
7.9940
7.6653
6.8682
4.9208
4.9082
4.8954
4.2088
4.1122
4.0271
3.3101
3.2240
3.2111
3.1983
HO
MeO
Cl⁻
N+
OMe
OMe
jatrorrhizine
1c
CD3OD, 500 MHz
1.03
1.01
1.02
1.00
0.98
0.96
2.32
0.71
3.03
3.07
3.02
2.04
f1 (ppm)


SS1039-6.2.1.1r
152.0042
151.7497
149.7227
146.1748
145.7192
140.3421
135.4844
130.3151
128.1323
124.3488
123.2077
120.9123
119.3759
115.9423
110.0413
62.4986
57.6732
57.3997
56.9365
27.6650
HO
MeO
Cl⁻
N+
OMe
OMe
jatrorrhizine
1c
CD3OD, 126 MHz
f1 (ppm)