

**Total Synthesis of Peniphenones A-D via Biomimetic Reactions
of a Common *o*-Quinone Methide Intermediate**

Justin T. J. Spence and Jonathan H. George*

Department of Chemistry, University of Adelaide, Adelaide, SA 5005, Australia.

Supporting Information

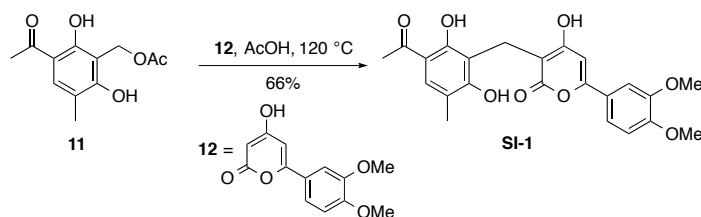
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1. General methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N₂. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (¹H at 600 MHz, ¹³C at 150 MHz) or a 500 MHz spectrometer (¹H at 500 MHz, ¹³C at 125 MHz). Solvents used for spectra were chloroform unless otherwise specified. ¹H chemical shifts are reported in ppm on the δ -scale relative to TMS (δ 0.0) and ¹³C NMR are reported in ppm relative to chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Optical rotations were measured on a modular circular polarimeter.

2. Experimental procedures



Peniphenone B dimethyl ether (SI-1): 2-Methyleneacetoxy-4-methyl-6-acetylresorcinol **11**¹ (48 mg, 0.20 mmol) and pyrone **12**² (50 mg, 0.20 mmol) were dissolved in AcOH (10 mL) in a sealed tube. The tube was flushed with N₂, sealed and the reaction mixture was heated at 120 °C for 16 h. The reaction mixture was then cooled and the precipitate was collected via vacuum filtration, to give peniphenone B dimethyl ether (**SI-1**) (57 mg, 66%) as a brown solid, which was used without further purification.

Data for SI-1: R_f = 0.20 (petroleum ether/ EtOAc, 1:1)

Mp: 158-160 °C

IR (film): 3215, 2940, 1667, 1625, 1568, 1517, 1377, 1274, 1149 cm⁻¹

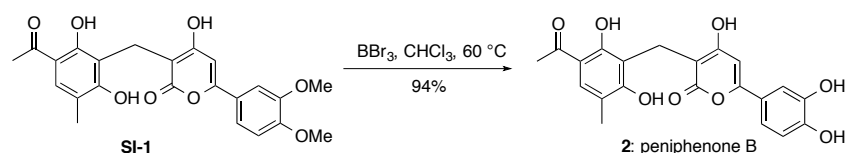
¹H NMR (500 MHz, CDCl₃) δ 10.34 (s, 1H), 9.74 (s, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.28 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.50 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.78 (s, 2H), 2.57 (s, 3H), 2.22 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 203.3, 167.9, 162.0, 159.4, 158.7, 151.7, 149.3, 130.9, 123.4, 119.6, 119.2, 112.5, 112.4, 111.1, 108.2, 102.0, 98.2, 56.13, 56.06, 25.9, 17.5, 16.1.

HRMS (C₂₃H₂₂O₈, ESI): calculated [M-H]⁻ 425.1242, found 425.1245.

¹ Spence, J. T. J.; George, J. H. *Org. Lett.* **2013**, *15*, 3891.

² (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888. (b) Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Mathias, D. S.; Degen, S. J.; Golding, G. M.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 1368.



Peniphenone B (2): To a solution of **SI-1** (58 mg, 0.14 mmol) in CHCl_3 (3 mL) was added BBr_3 (1.0 M in CH_2Cl_2 , 1.36 mL, 1.36 mmol) dropwise and the reaction mixture was heated at reflux for 1.5 h. The reaction mixture was quenched with 1 M HCl (5 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organics were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant solid was recrystallized from acetone to give peniphenone B (**2**) (51 mg, 94%) as a yellow solid.

Data for 2: $R_f = 0.05$ (petroleum ether/ EtOAc, 1:1)

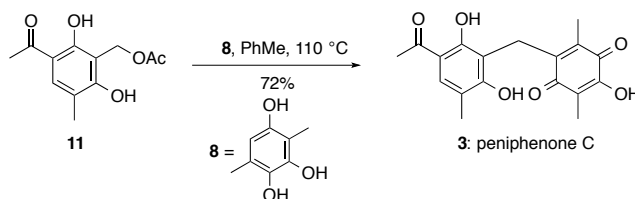
Mp: 255-260 °C

IR (film): 3329, 2924, 1655, 1605, 1555, 1526, 1369, 1289, 1182, 1138 cm^{-1}

^1H NMR (500 MHz, DMSO- d_6) δ 13.10 (s, 1H), 9.65 (s, 1H), 9.40 (s, 1H), 7.55 (s, 1H), 7.14 (d, $J = 2.2$ Hz, 1H), 7.09 (dd, $J = 8.4, 2.2$ Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 1H), 6.52 (s, 1H), 3.68 (s, 2H), 2.53 (s, 3H), 2.11 (s, 3H).

^{13}C NMR (125 MHz, DMSO- d_6) δ 203.1, 167.3, 167.0, 161.3, 160.9, 158.1, 148.6, 145.7, 130.9, 121.7, 117.4, 116.6, 116.1, 112.8, 112.23, 112.18, 100.1, 96.4, 26.3, 16.9, 16.0.

HRMS ($\text{C}_{21}\text{H}_{18}\text{O}_8$, ESI): calculated $[\text{M}+\text{H}]^+ 399.1090$, found 399.1087.



Peniphenone C (3): 2-Methyleneacetoxy-4-methyl-6-acetylresorcinol **11** (100 mg, 0.42 mmol) and 3,6-dimethyl-1,2,4-benzenetriol **8**³ (59 mg, 0.38 mmol) were dissolved in toluene (10 mL) in a sealed tube and heated at 110 °C for 2 h. The reaction mixture was cooled and the solvent was removed *in vacuo*. The resultant residue was purified by flash chromatography (SiO₂, petroleum ether/acetone, 5:1) to give peniphenone C (**3**) (92 mg, 72%) as a bright yellow solid.

Data for 3: R_f = 0.35 (petroleum ether/acetone, 5:1)

Mp: 212-216 °C

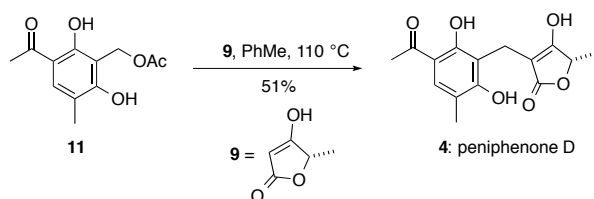
IR (film): 3320, 2926, 1655, 1625, 1603, 1361, 1284, 1253, 1156, 1083 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 13.18 (s, 1H), 9.57 (s, 1H), 7.41 (s, 1H), 3.74 (s, 2H), 2.53 (s, 3H), 2.37 (s, 3H), 2.22 (s, 3H), 1.91 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ 202.7, 191.2, 183.7, 161.8, 161.1, 151.6, 143.4, 139.8, 131.1, 118.4, 116.8, 112.8, 110.6, 26.2, 22.0, 16.1, 12.5, 8.2.

HRMS (C₁₈H₁₈O₆, ESI): calculated [M+H]⁺ 331.1176, found 331.1181.

³ Tyman, J. H. P.; Patel, M. J. *Chem. Res.* **2007**, 298.



Peniphenone D (4): 2-Methyleneacetoxy-4-methyl-6-acetylresorcinol **11** (100 mg, 0.42 mmol) and (*S*)-5-methyl tetronic acid **9**⁴ (144 mg, 1.26 mmol) were dissolved in toluene (10 mL) in a sealed tube. The flask was flushed with N₂, sealed and then the reaction mixture was heated at 110 °C for 16 h. The reaction mixture was concentrated *in vacuo*, then purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 4:1 → 2:1 gradient elution) to give (–)-peniphenone D (**4**) (63 mg, 51 %) as a white solid.

Data for 4: R_f = 0.05 (petroleum ether/EtOAc, 2:1)

[α]_D²⁵ –6.8° (c 1.13, MeOH)

Mp: 175–177 °C

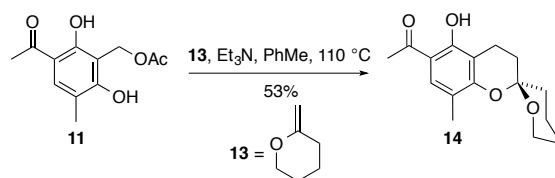
IR (film): 3159, 2916, 2583, 1714, 1655, 1576, 1322, 1233, 1099, 1055, 808 cm^{–1}

¹H NMR (600 MHz, CDCl₃) δ 13.97 (br s, 1H), 8.58 (br s, 1H), 8.24 (br s, 1H), 7.41 (d, *J* = 0.5 Hz, 1H), 4.84 (q, *J* = 6.8 Hz, 1H), 3.48 (d, *J* = 15.1 Hz, 1H), 3.43 (d, *J* = 15.1 Hz, 1H), 2.57 (s, 3H), 2.21 (d, *J* = 0.5 Hz, 3H), 1.46 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃) δ 203.5, 177.2, 175.8, 160.2, 158.8, 130.7, 119.5, 113.3, 112.8, 101.5, 76.2, 26.0, 17.2, 15.9, 14.5.

HRMS (C₁₅H₁₈O₆, ESI): calculated [M–H][–] 291.0874, found 291.0871.

⁴ (a) Fryzuk, M. D.; Bosnich, B. J. *J. Am. Chem. Soc.* **1978**, *100*, 5491. (b) Brandange, S.; Flodman, L.; Norberg, A. *J. Org. Chem.* **1984**, *49*, 927.



Spiroacetal 13: To a solution of 2-methyleneacetoxy-4-methyl-6-acetylresorcinol **11** (50 mg, 0.21 mmol) and 2-methylenetetrahydro-2*H*-pyran **13** (98 mg, 1.00 mmol) in toluene (5 mL) was added Et₃N (0.06 mL, 0.42 mmol). The reaction was heated at 110 °C in a sealed tube for 16 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 10:1) to give **14** (31 mg, 53%) as a pale yellow oil.

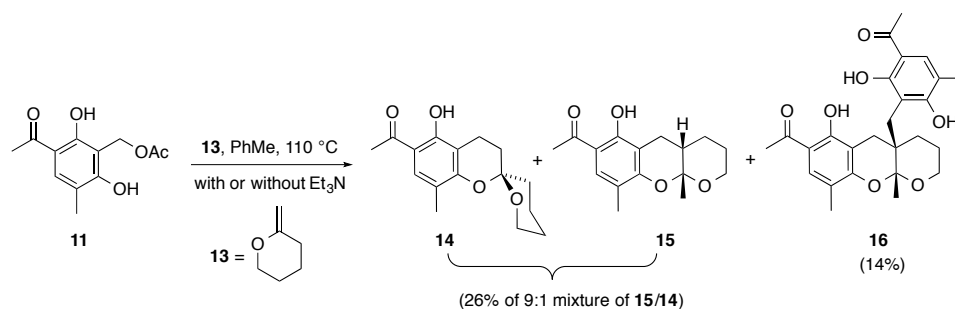
Data for 13: R_f = 0.45 (petroleum ether/EtOAc, 5:1)

IR (film): 2942, 2872, 1619, 1478, 1438, 1369, 1331, 1266, 1230, 1177, 1145, 1070 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 12.84 (s, 1H), 7.36 (s, 1H), 3.72 (td, *J* = 11.8, 2.8 Hz, 1H), 3.65 (dd, *J* = 11.1, 4.7 Hz, 1H), 2.75 – 2.69 (m, 2H), 2.54 (s, 3H), 2.21 (s, 3H), 2.09 – 2.01 (m, 2H), 1.92 (d, *J* = 13.4 Hz, 1H), 1.80 – 1.58 (m, 5H).

¹³C NMR (125 MHz, CDCl₃) δ 202.7, 160.5, 156.9, 129.4, 117.3, 112.7, 110.4, 96.8, 62.2, 34.5, 31.0, 26.2, 25.1, 18.6, 15.4, 15.1.

HRMS (C₁₆H₂₀O₄, ESI): calculated [M+H]⁺ 277.1434, found 277.1440.



Ketals **15 and **16**:** 2-Methyleneacetoxymethyl-4-methyl-6-acetylresorcinol **11** (100 mg, 0.42 mmol) and 2-methylenetetrahydro-2*H*-pyran **13**⁵ (38 mg, 0.38 mmol) were dissolved in toluene (5 mL) and heated at 110 °C in a sealed tube for 16 h. The solvent was removed *in vacuo* and the residue purified by flash chromatography (SiO₂, petroleum ether/EtOAc, 10:1 → 1:1 gradient elution) to give **14** and **15** (28 mg, 26%) as a colourless oil and as a 9:1 inseparable mixture of isomers in favour of **15**. Further elution afforded **16** (13 mg, 14%) as a colourless oil.

Data for **15:** *R*_f = 0.45 (petroleum ether/EtOAc, 5:1)

IR (film): 2931, 1738, 1620, 1478, 1373, 1282, 1232, 1193, 1116, 1074, 997 cm⁻¹

¹H NMR (500 MHz, CDCl₃) δ 12.93 (s, 1H), 7.36 (s, 1H), 3.99 – 3.92 (m, 1H), 3.78 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.83 (dd, *J* = 17.5, 6.5 Hz, 1H), 2.62 (d, *J* = 17.5 Hz, 1H), 2.54 (s, 3H), 2.17 (s, 3H), 2.06 – 1.97 (m, 1H), 1.81 – 1.72 (m, 1H), 1.58–1.54 (m, 2H), 1.41 (s, 3H), 1.38 – 1.27 (m, 1H). **¹³C NMR (125 MHz, CDCl₃)** δ 202.6, 161.3, 158.3, 129.6, 117.2, 112.4, 106.5, 100.9, 62.1, 34.4, 26.2, 25.2, 25.09, 25.07, 25.05, 15.7.

HRMS (C₁₆H₂₀O₄, ESI): calculated [M–H][–] 275.1289, found 275.1278.

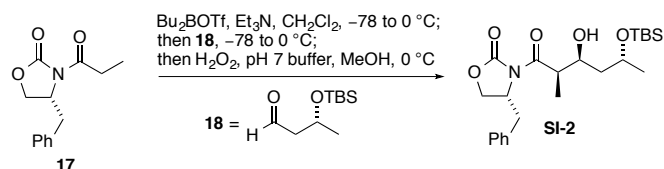
Data for **16:** *R*_f = 0.10 (petroleum ether/EtOAc, 5:1)

IR (film): 3357, 2946, 1626, 1480, 1444, 1380, 1286, 1190, 1114 cm⁻¹

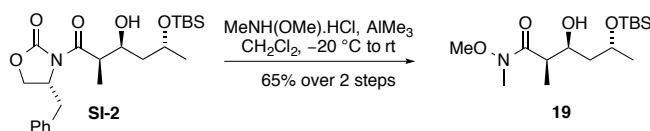
¹H NMR (500 MHz, CDCl₃) 13.07 (s, 1H), 12.88 (s, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 6.04 (br s, 1H), 4.17 (td, *J* = 11.9, 3.3 Hz, 1H), 3.85 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.19 (d, *J* = 14.0 Hz, 1H), 2.95 (d, *J* = 14.9 Hz, 1H), 2.91 (d, *J* = 18.6 Hz, 1H), 2.57 (s, 3H), 2.53 (s, 3H), 2.46 (d, *J* = 17.8 Hz, 1H), 2.42 – 2.28 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.54 (s, 3H), 1.53 – 1.49 (m, 1H), 1.48 – 1.41 (m, 2H). **¹³C NMR (125 MHz, CDCl₃)** δ 202.8, 202.6, 162.7, 161.1, 160.2, 157.4, 131.1, 129.5, 116.8, 114.6, 113.6, 112.51, 112.44, 108.2, 104.5, 62.0, 37.4, 26.9, 26.53, 26.35, 26.2, 22.0, 20.7, 15.78, 15.66.

HRMS (C₂₆H₃₀O₇, ESI): calculated [M–H][–] 453.1919, found 453.1916.

⁵ Cuzzupe, A. N.; Hutton, C. A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.* **2001**, *66*, 2382.



Aldol product SI-2: To a solution of (*R*)-(-)-4-benzyl-3-propionyl-2-oxazolidinone **17** (1.00 g, 4.29 mmol) in CH_2Cl_2 (50 mL) at -78°C was added dibutylboron trifluoromethanesulfonate (1.0 M in CH_2Cl_2 , 6.43 mL, 6.43 mmol) dropwise over 30 min. Et_3N (1.2 mL, 8.6 mmol) was added immediately once the addition was complete and the reaction mixture was stirred at -78°C for 10 min and then warmed to 0°C and stirred for 1 h. The solution was cooled to -78°C and aldehyde **18** (1.30 g, 6.43 mmol) in CH_2Cl_2 (10 mL) was added dropwise and stirred at -78°C for 20 min. The reaction mixture was then warmed to 0°C and stirred for 3 h. pH 7 buffer (5 mL), MeOH (20 mL) and H_2O_2 (30% in H_2O , 10 mL) were added and the mixture stirred at 0°C for 2 h. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 5:1) to give **SI-2** (1.70 g) as a colourless oil that was inseparable from the starting material and was therefore carried through to the next step without further characterization.



Weinreb amide 19: To a solution of *N,O*-dimethylhydroxylamine hydrochloride (1.46 g, 15.0 mmol) in CH_2Cl_2 (100 mL) was added trimethylaluminium (2.0 M in hexane, 7.50 mL, 15.0 mmol) dropwise at 0 °C over 30 min and the mixture was stirred for 1 h. The reaction mixture was cooled to -20 °C and **SI-2** (1.70 g) in CH_2Cl_2 (10 mL) was added dropwise and the reaction was then warmed to room temperature and stirred for 3 h. Saturated sodium potassium tartrate solution (25 mL) was added dropwise (strong effervescence observed) at 0 °C and the mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 5:1 \rightarrow 2:1 gradient elution) to give Weinreb amide **19** (902 mg, 65% over 2 steps) as a colourless oil.

Data for 19: $R_f = 0.15$ (petroleum ether/EtOAc, 2:1)

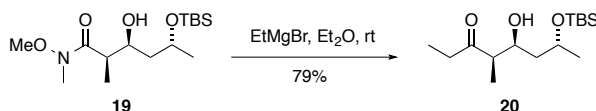
$[\alpha]_D^{25} -21.8$ (c 0.92, CHCl_3)

IR (film): 3472, 2957, 2931, 2857, 1638, 1461, 1381, 1255, 1059, 993, 836 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 4.18 – 4.14 (m, 1H), 4.13 – 4.09 (m, 1H), 4.00 (br s, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.86 (s, 1H), 1.65 (ddd, $J = 13.6, 10.2, 3.1$ Hz, 1H), 1.43 – 1.36 (m, 1H), 1.21 (d, $J = 1.1$ Hz, 3H), 1.19 (d, $J = 2.2$ Hz, 3H), 0.89 (s, 9H), 0.085 (s, 3H), 0.081 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 68.6, 66.5, 61.5, 42.9, 40.2, 32.0, 25.9, 23.7, 18.0, 11.6, -4.5, -4.9.

HRMS ($\text{C}_{15}\text{H}_{33}\text{NO}_4\text{Si}$, ESI): calculated $[\text{M}+\text{H}]^+$ 320.2252, found 320.2244.



Ketone 20: To a solution of Weinreb amide **19** (1.62 g, 5.07 mmol) in Et_2O (100 mL) was added EtMgBr (3.0 M in Et_2O , 5.07 mL, 15.2 mmol) dropwise at room temperature and then the reaction mixture was stirred for 1 h. Further EtMgBr (3.0 M in Et_2O , 2.53 mL, 7.6 mmol) was added at room temperature and the reaction mixture was stirred for a further 3 h before being quenched with saturated aqueous NH_4Cl (100 mL) and then diluted with Et_2O (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/ EtOAc , 8:1) to give **20** (1.15 g, 79 %) as a colourless oil.

Data for 20: $R_f = 0.30$ (petroleum ether/ EtOAc , 5:1)

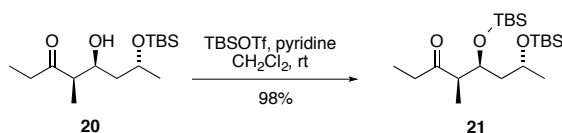
$[\alpha]_D^{25} -21.8$ (c 0.92, CHCl_3)

IR (film): 3491, 2930, 1700, 1463, 1377, 1255, 1066, 1006, 836 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 4.21 – 4.16 (m, 1H), 3.53 (br s, 1H), 2.63 – 2.58 (m, 1H), 2.56 – 2.51 (m, 2H), 1.61 (ddd, $J = 13.8, 10.4, 3.3$ Hz, 1H), 1.37 (ddd, $J = 14.1, 6.2, 1.6$ Hz, 1H), 1.22 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.3$ Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ 215.6, 68.5, 67.0, 51.1, 41.9, 35.5, 25.8, 23.1, 18.0, 11.4, 7.6, -4.5, -5.0.

HRMS ($\text{C}_{15}\text{H}_{32}\text{O}_3\text{Si}$, ESI): calculated $[\text{M}+\text{Na}]^+$ 311.2013, found 311.2019



Ketone 21: To a solution of ketone **20** (250 mg, 0.87 mmol) in CH_2Cl_2 (10 mL) at room temperature was added pyridine (0.07 mL, 0.9 mmol) and TBSOTf (0.22 mL, 0.95 mmol) and the reaction mixture was stirred for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (25 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/ Et_2O , 10:1) to give **21** (343 mg, 98%) as a colourless oil.

Data for 21: $R_f = 0.70$ (petroleum ether/ EtOAc , 5:1)

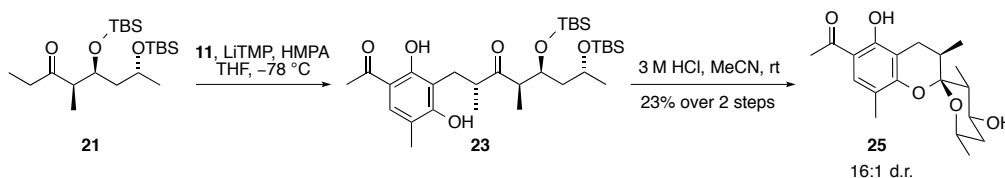
$[\alpha]_D^{25} -39.0$ (c 1.05, CHCl_3)

IR (film): 2956, 2930, 1712, 1473, 1462, 1377, 1253, 1052, 833 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 4.07 – 4.02 (m, 1H), 3.85 (m, 1H), 2.65 – 2.60 (m, 2H), 2.42 (dq, $J = 18.1, 7.2$ Hz, 1H), 1.67 – 1.62 (m, 1H), 1.34 (ddd, $J = 14.0, 6.9, 4.4$ Hz, 1H), 1.16 (d, $J = 6.1$ Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 1.02 (t, $J = 7.3$ Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ 213.2, 71.6, 66.2, 51.7, 45.1, 35.8, 25.90, 25.85, 24.6, 18.07, 18.05, 11.1, 7.5, -2.9, -3.5, -4.24, -4.29.

HRMS ($\text{C}_{21}\text{H}_{46}\text{O}_3\text{Si}_2$, EI): calculated $[\text{M}-\text{CH}_3]^+$ 387.2751, found 387.2757 and calculated $[\text{M}-\text{CH}_2\text{CH}_3]^+$ 373.2594, found 373.2592



Spiroketal 25: To a solution of 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.60 mmol) in THF (10 mL) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (2.5 M in hexanes, 0.64 mL, 1.60 mmol) and the mixture was stirred for 20 min. Ketone **21** (215 mg, 0.53 mmol) in THF (2 mL) was then added dropwise at $-78\text{ }^{\circ}\text{C}$ and the mixture was stirred for a further 20 min. **11** (127 mg, 0.53 mmol) in THF (2 mL) was then added dropwise at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred at this temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl (25 mL) and diluted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was partially purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 50:1 \rightarrow 10:1) to give crude **23** (79.1 mg), which was dissolved in CH_3CN (8 mL) and 3 M HCl (4 mL) was added. The reaction mixture was stirred at room temperature for 16 h, then diluted with H_2O (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 2:1) to give **25** (41.2 mg, 23% over 2 steps) as a colourless oil and as an 16:1 mixture of diastereomers.

Data for 25: $R_f = 0.30$ (petroleum ether/EtOAc, 2:1)

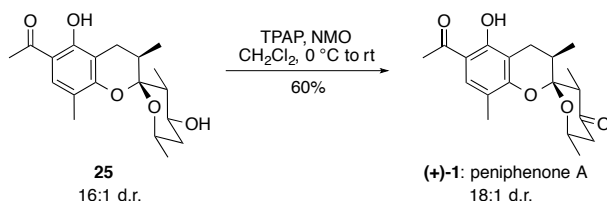
$[\alpha]_D^{25} +63.5$ (c 0.65, CHCl_3)

IR (film): 3392, 2936, 1627, 1478, 1383, 1333, 1281, 1189, 1065, 916 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 12.83 (s, 1H), 7.33 (s, 1H), 4.01 (td, $J = 10.7, 4.6\text{ Hz}$, 1H), 3.71 (dq, $J = 12.4, 6.2, 2.3\text{ Hz}$, 1H), 2.68 (dd, $J = 16.4, 5.5\text{ Hz}$, 1H), 2.54 (s, 3H), 2.44 (dd, $J = 16.4, 12.6\text{ Hz}$, 1H), 2.13 (s, 3H), 2.10 (dd, $J = 12.8, 6.2\text{ Hz}$, 1H), 2.04 (ddd, $J = 12.5, 4.7, 2.4\text{ Hz}$, 1H), 1.76 (dq, $J = 10.0, 6.7\text{ Hz}$, 1H), 1.31 (q, $J = 11.6\text{ Hz}$, 1H), 1.14 (d, $J = 6.7\text{ Hz}$, 3H), 1.11 (d, $J = 6.7\text{ Hz}$, 3H), 1.06 (d, $J = 6.2\text{ Hz}$, 3H).

^{13}C NMR (125 MHz, CDCl_3) 202.7, 160.1, 156.5, 129.2, 116.9, 112.8, 111.3, 102.9, 69.6, 65.5, 42.7, 42.5, 30.5, 26.2, 23.4, 21.4, 15.5, 15.0, 10.6.

HRMS ($\text{C}_{19}\text{H}_{26}\text{O}_5$, ESI): calculate $[\text{M}-\text{H}]^-$ 333.1707, found 333.1711.



Peniphenone A (1): To a solution of **25** (35 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) was added 4 Å molecular sieves, TPAP (1.8 mg, 0.052 mmol) and *N*-methylmorpholine *N*-oxide (13.5 mg, 0.116 mmol) at 0 °C and the reaction was gradually warmed to room temperature and then stirred for 20 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 4:1 → 2:1 gradient elution) to give (+)-peniphenone A (**1**) (20.8 mg, 60%) as a colourless film.

Data for 1: $R_f = 0.25$ (petroleum ether/EtOAc, 5:1)

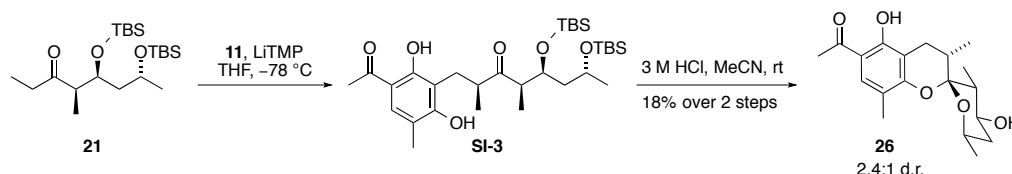
$[\alpha]_D^{25} +85.6$ (c 0.88, MeOH)

IR (film): 2976, 2939, 1725, 1629, 1479. 1455, 1382, 1332, 1278, 1188, 1076, 933 cm^{-1}

^1H NMR (500 MHz, CDCl_3) δ 12.82 (s, 1H), 7.32 (s, 1H), 3.93 (dq, $J = 12.3, 6.2, 3.1$ Hz, 1H), 2.87 (q, $J = 6.8$ Hz, 1H), 2.77 (dd, $J = 16.5, 5.6$ Hz, 1H), 2.54 (s, 3H), 2.53 (dd, $J = 16.5, 3.0$ Hz, 1H), 2.50 (dd, $J = 14.0, 3.0$ Hz, 1H), 2.34 (dd, $J = 13.3, 11.8$ Hz, 1H), 2.09 (dt, $J = 10.1, 6.0$ Hz, 1H), 2.04 (s, 3H), 1.23 (d, $J = 6.8$ Hz, 3H), 1.19 (d, $J = 6.2$ Hz, 3H), 1.14 (d, $J = 6.7$ Hz, 3H).

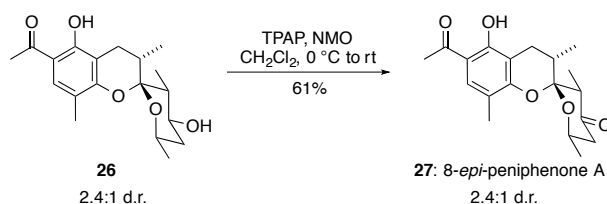
^{13}C NMR (125 MHz, CDCl_3) δ 206.5, 202.9, 160.0, 155.6, 129.5, 117.0, 113.2, 111.1, 105.0, 67.5, 49.2, 48.7, 30.8, 26.3, 23.5, 21.8, 15.2, 15.1, 7.6.

HRMS ($\text{C}_{19}\text{H}_{24}\text{O}_5$, ESI): calculated $[\text{M}-\text{H}]^-$ 331.1551, found 331.1562.



Spiroketal 26: To a solution of 2,2,6,6-tetramethylpiperidine (0.13 mL, 0.74 mmol) in THF (6 mL) at -78°C was added *n*-BuLi (2.5 M in hexanes, 0.30 mL, 0.74 mmol) and the mixture was stirred for 20 min. Ketone **21** (100 mg, 0.25 mmol) in THF (2 mL) was then added dropwise at -78°C and the mixture was stirred for a further 20 min. **11** (60 mg, 0.25 mmol) in THF (2 mL) was then added dropwise at -78°C and the reaction mixture was stirred at this temperature for 5 h. The reaction was quenched with sat. NH_4Cl (25 mL) and diluted with EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 50:1 \rightarrow 10:1) to give crude **SI-3** (39.1 mg), which was dissolved in CH_3CN (2 mL) and 3 M HCl (2 mL) was added. The reaction mixture was stirred at room temperature for 15 min. The reaction was diluted with H_2O (10 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 2:1) to give **26** (15.1 mg, 18% over 2 steps) as a colourless oil as a 2.4:1 mixture of diastereoisomers.

Data for 26: $R_f = 0.30$ (petroleum ether/EtOAc, 2:1)



8-*epi*-Peniphenone A (27): To a solution of spiroketal **26** (15.1 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) was added 4 Å molecular sieves, TPAP (0.8 mg, 0.0023 mmol) and *N*-methylmorpholine *N*-oxide (6.5 mg, 0.054 mmol) at 0 °C and the reaction was gradually warmed to room temperature and then stirred for 16 h. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (SiO_2 , petroleum ether/EtOAc, 4:1 \rightarrow 2:1 gradient elution) to give 8-*epi*-peniphenone A **27** (9.1 mg, 61%) as a colourless film in a 2.4:1 mixture of diastereoisomers.

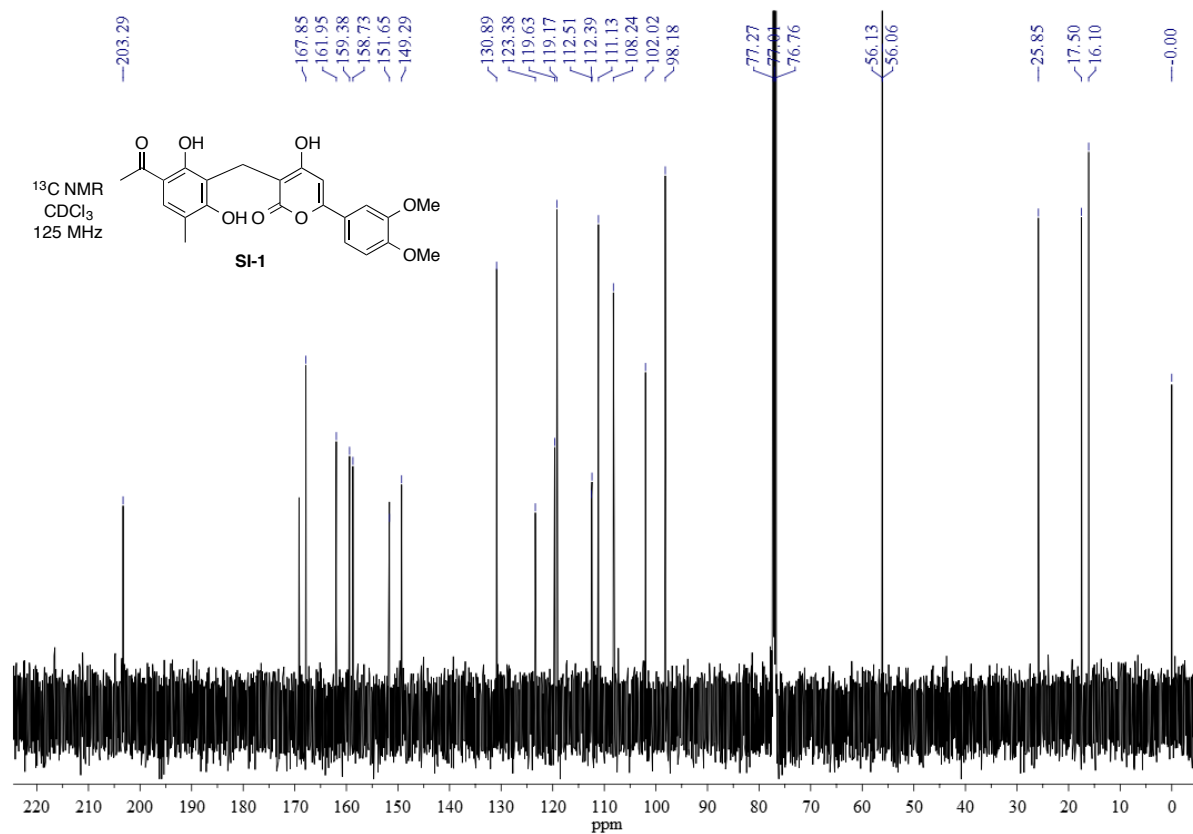
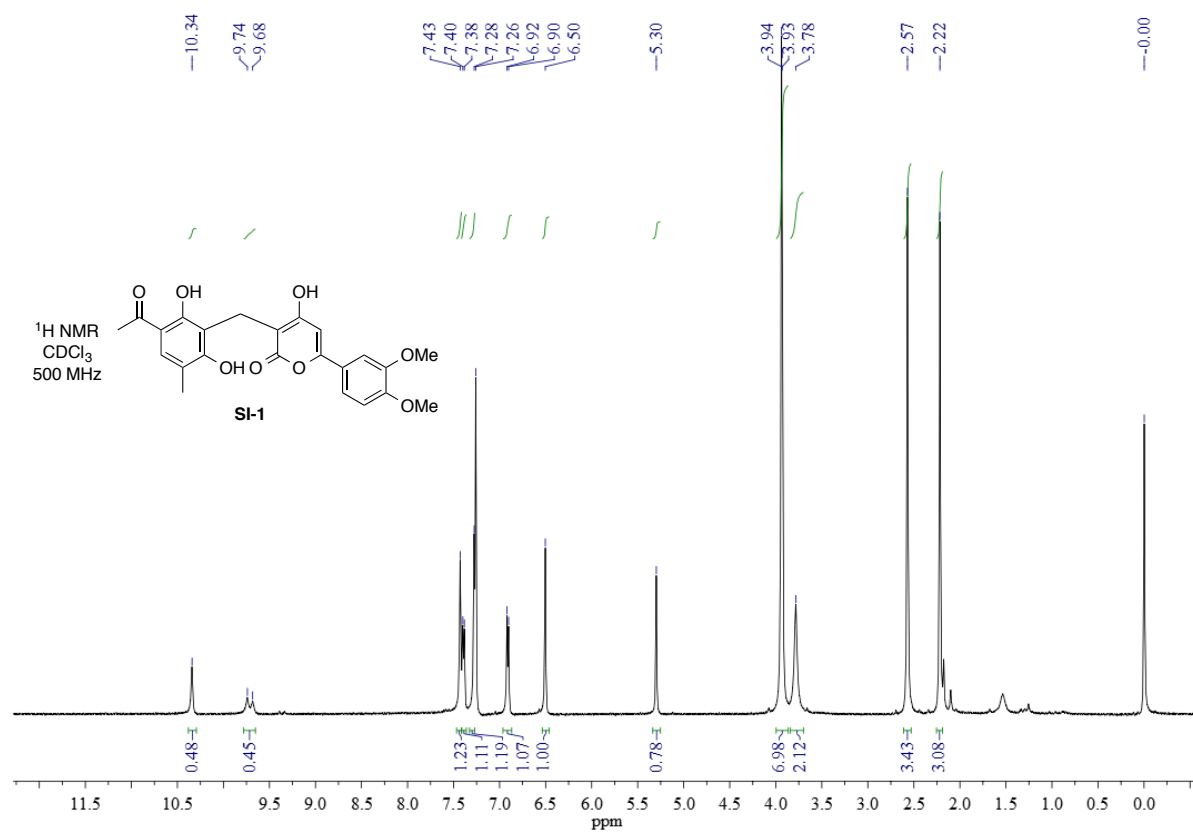
Data for 27: R_f = 0.25 (petroleum ether/EtOAc, 5:1)

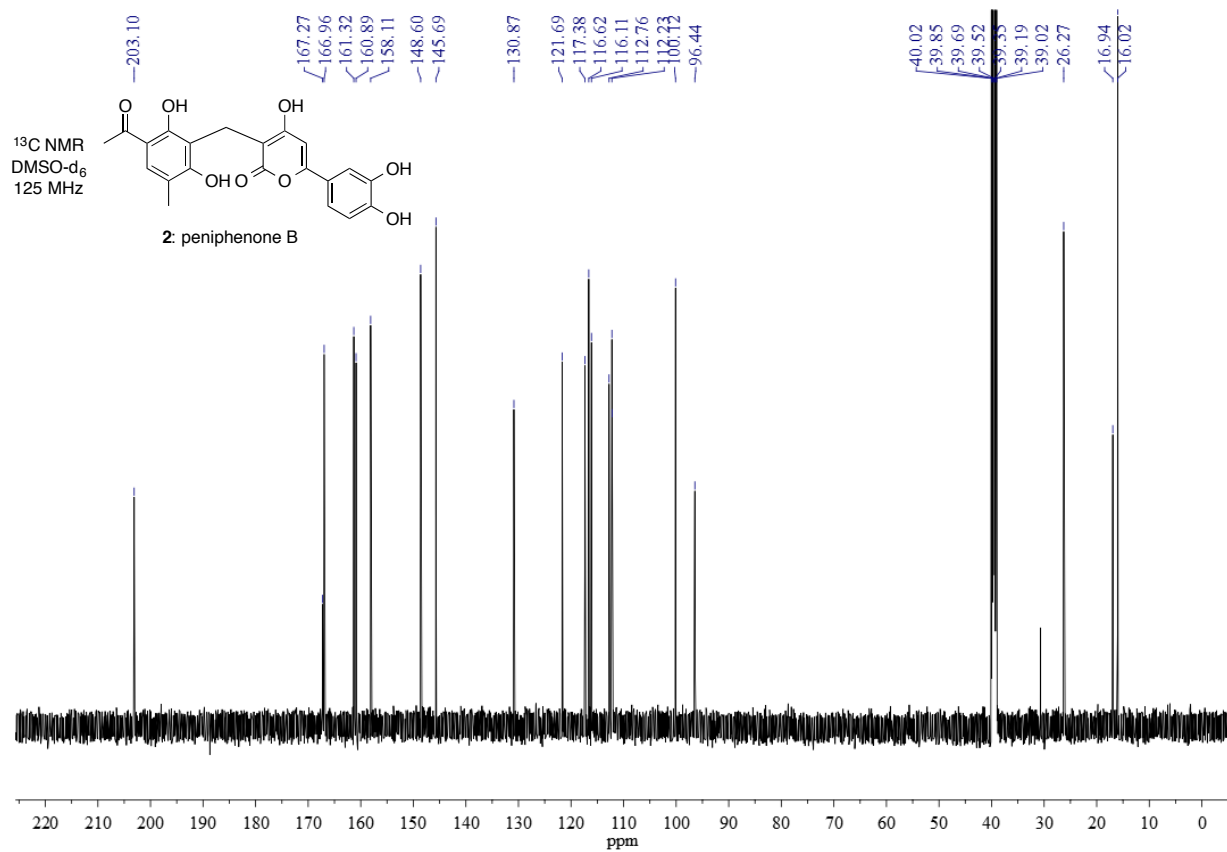
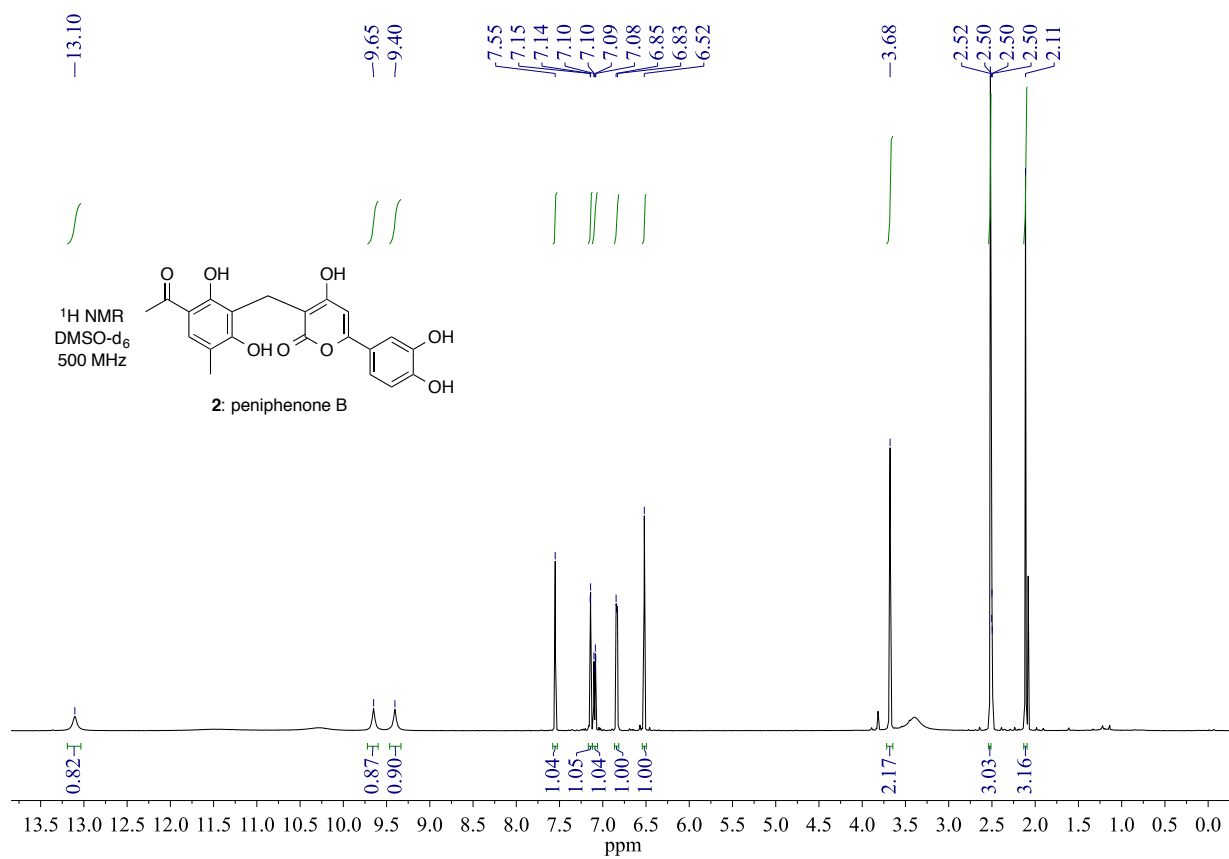
^1H NMR (500 MHz, CDCl_3) δ 12.85 (s, 1H), 7.34 (s, 1H), 4.20 (dq, J = 12.1, 6.1, 2.9 Hz, 1H), 3.07 (dd, J = 16.7, 6.4 Hz, 1H), 2.77 (dd, J = 13.6, 6.3 Hz, 1H), 2.58-2.54 (m, 1H), 2.54 (s, 3H), 2.45 (dd, J = 16.8, 5.7 Hz, 1H), 2.37-2.32 (m, 2H), 2.09 (s, 3H), 1.22 (d, J = 6.4 Hz, 6H), 1.15 (d, J = 7.0 Hz, 3H).

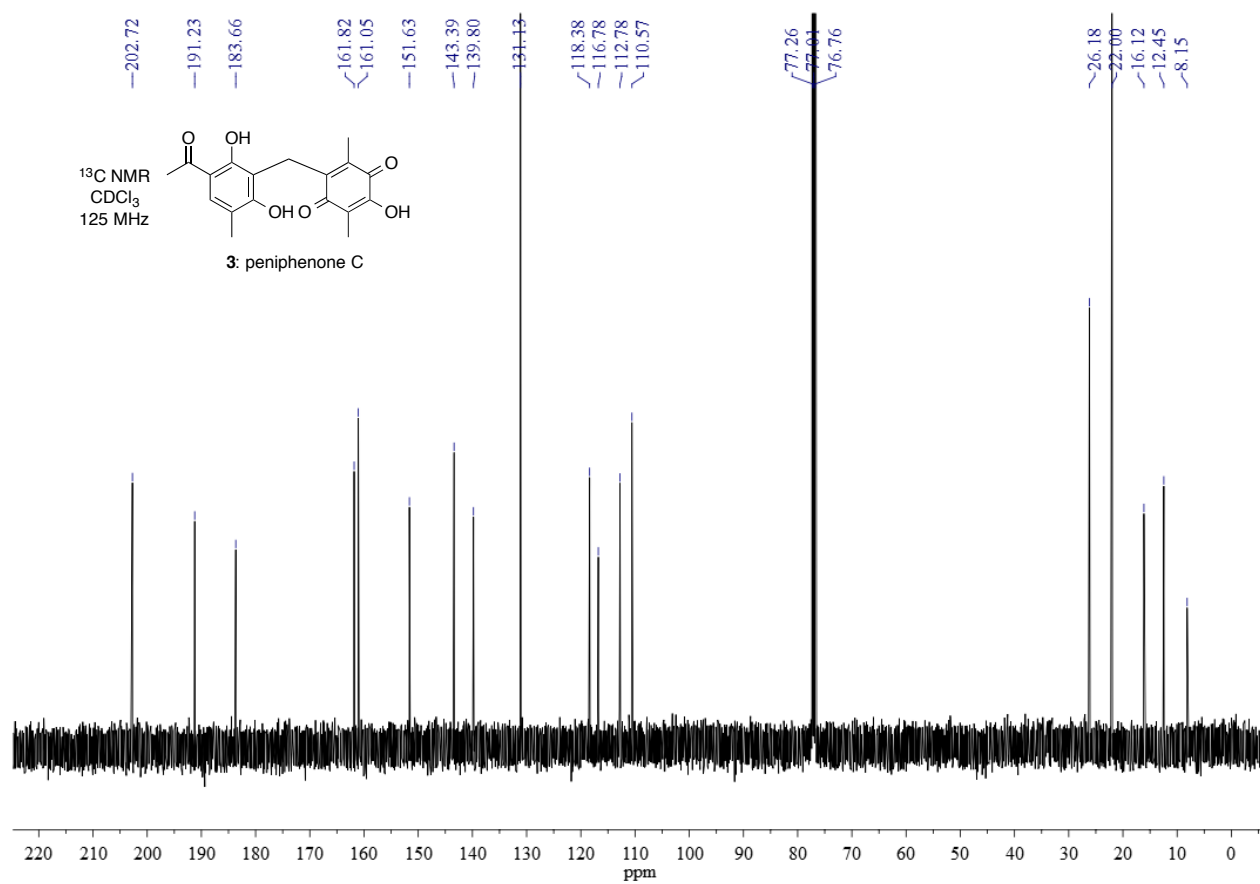
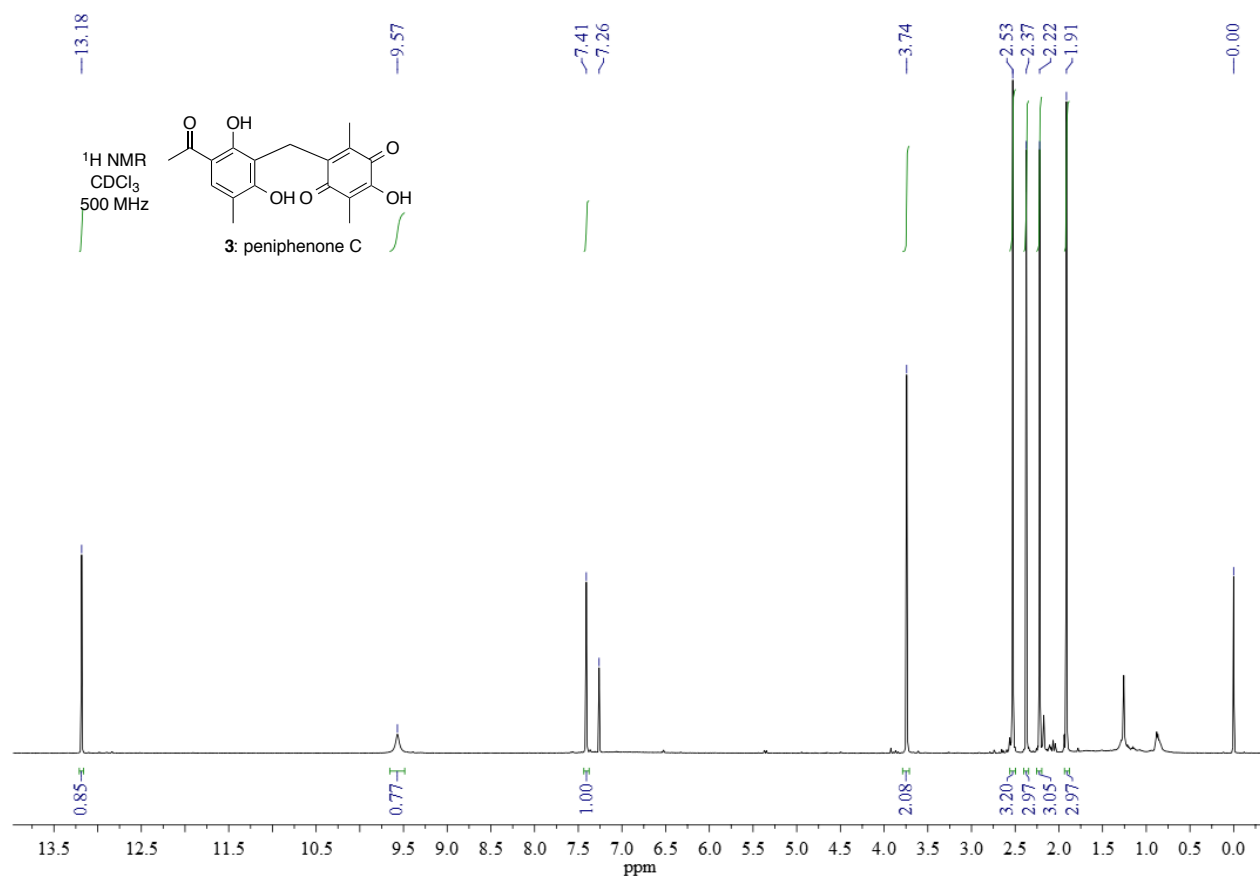
^{13}C NMR (125 MHz, CDCl_3) δ 209.8, 205.5, 163.2, 159.0, 132.2, 119.4, 115.8, 111.8, 107.1, 69.0, 53.6, 50.6, 37.8, 28.9, 28.1, 24.5, 19.3, 18.0, 12.7.

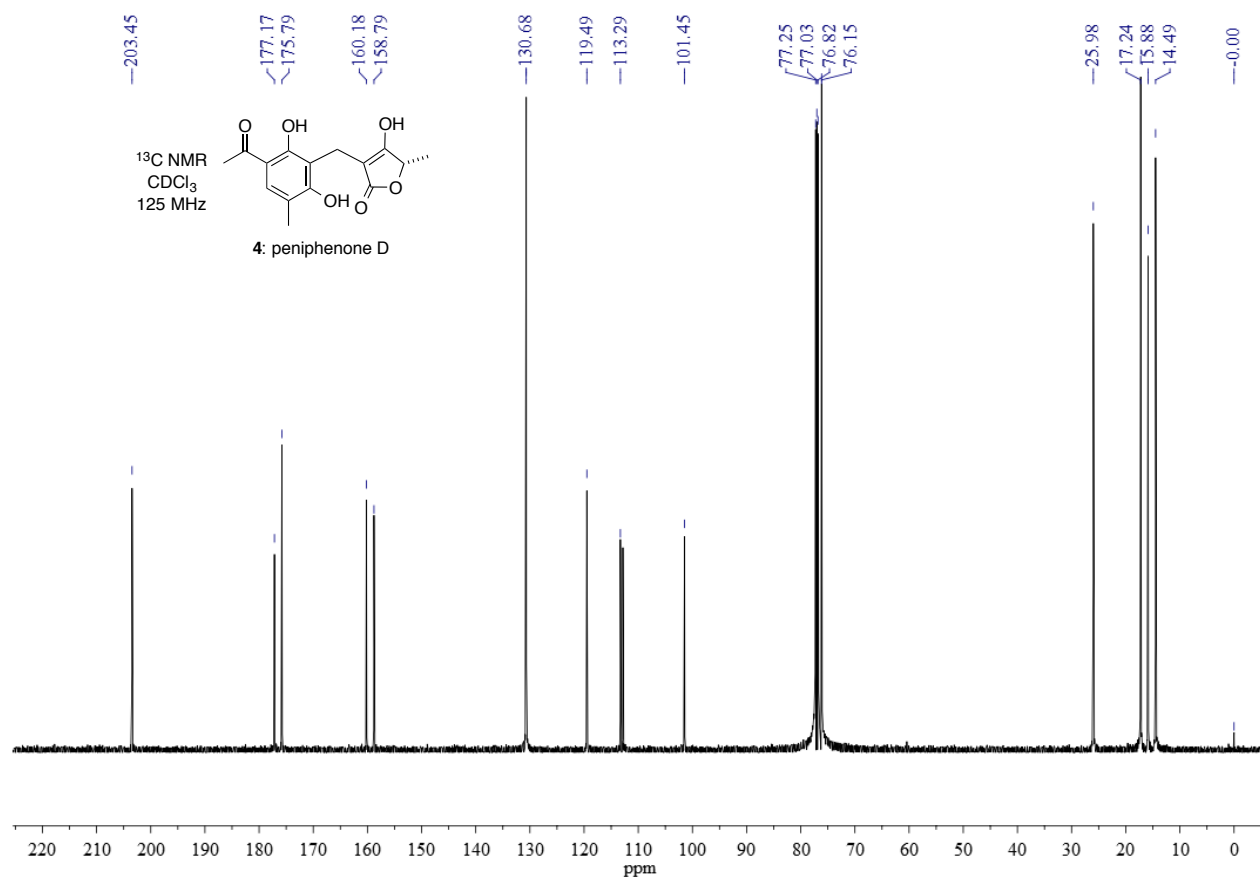
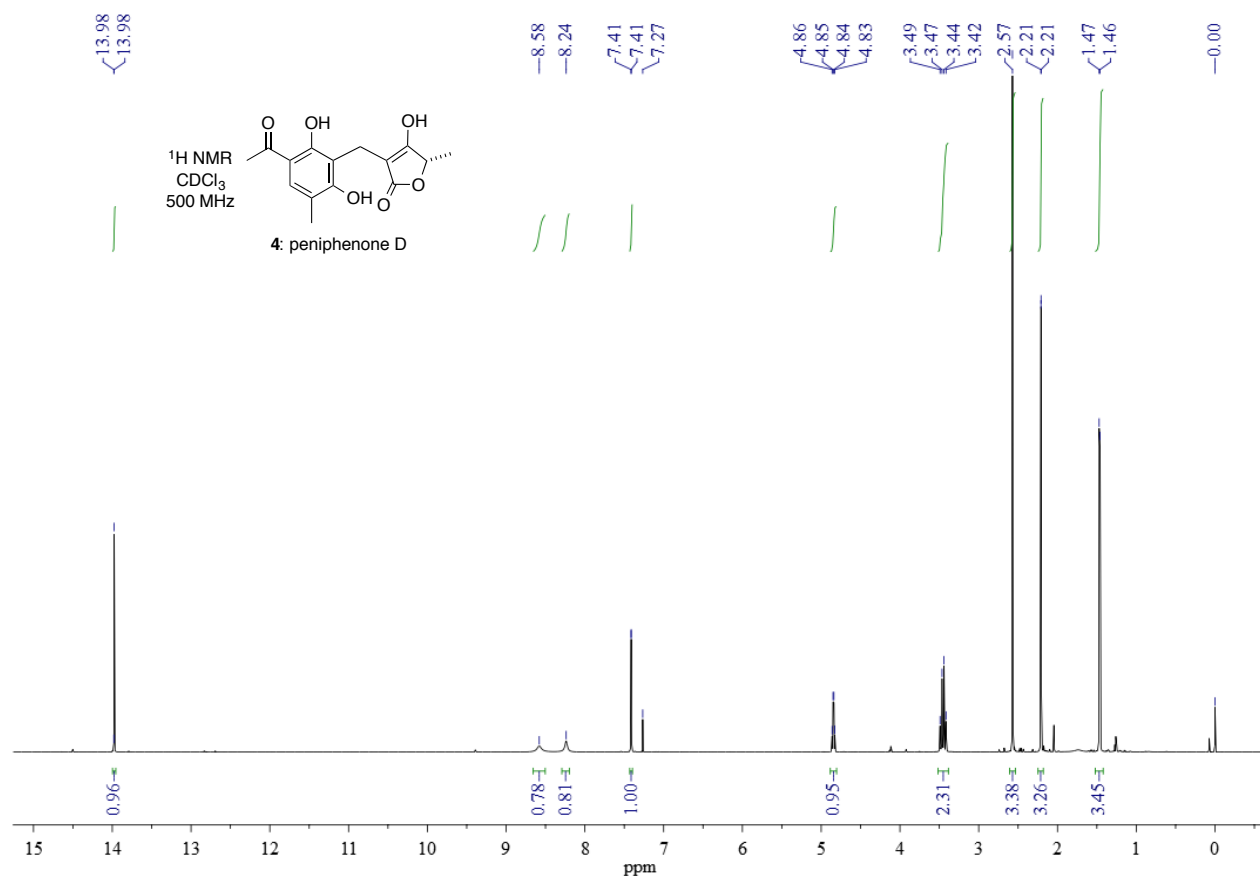
HRMS ($\text{C}_{19}\text{H}_{24}\text{O}_5$, ESI): calculated $[\text{M}-\text{H}]^-$ 331.1551, found 331.1547.

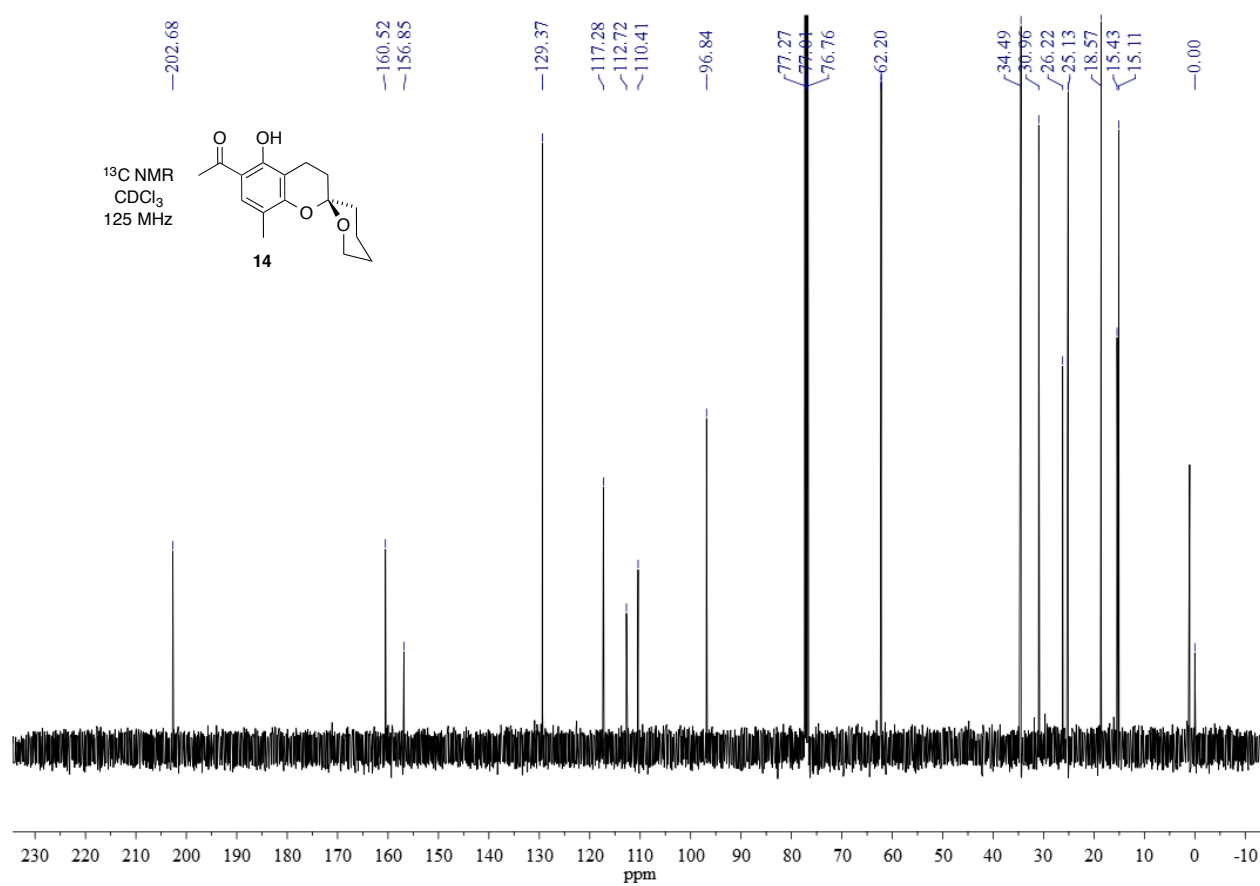
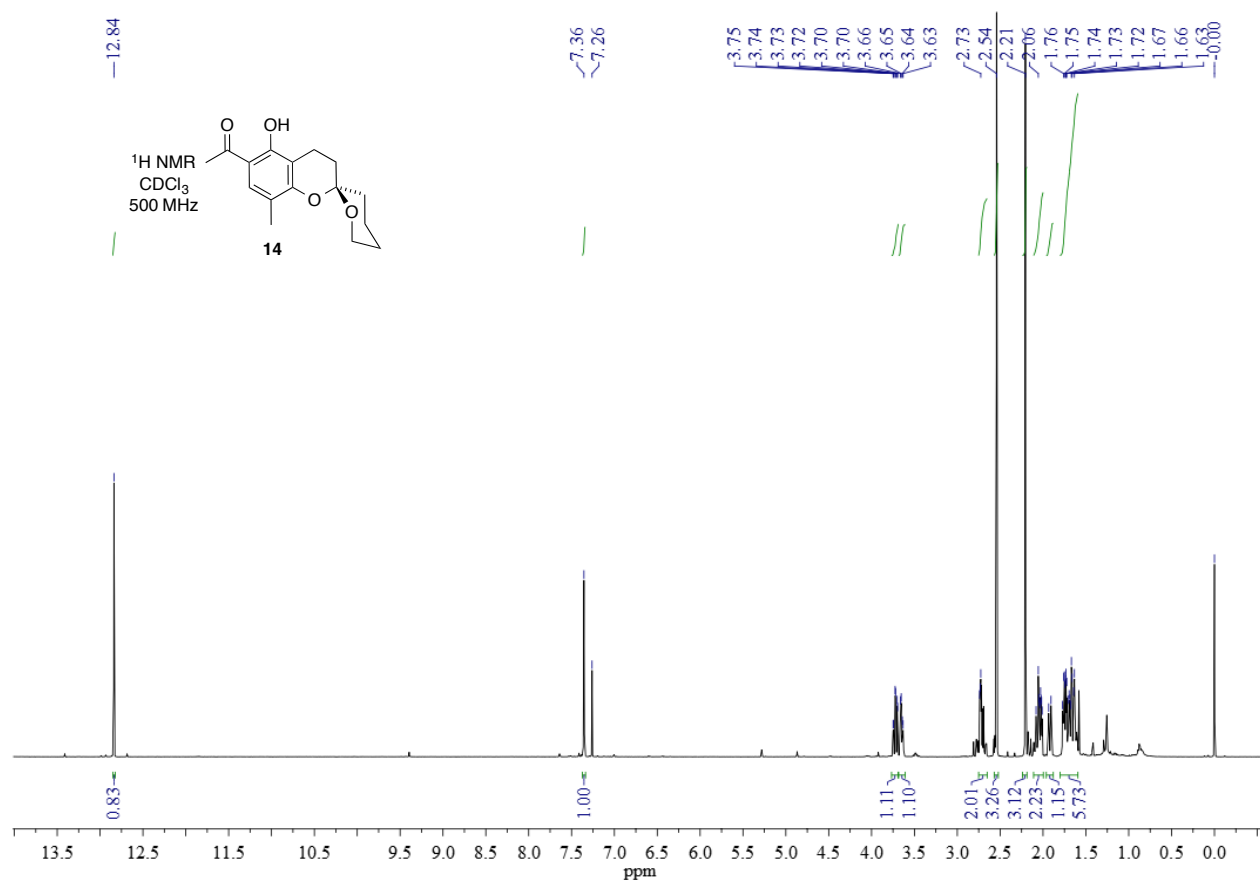
3. ^1H and ^{13}C NMR spectra

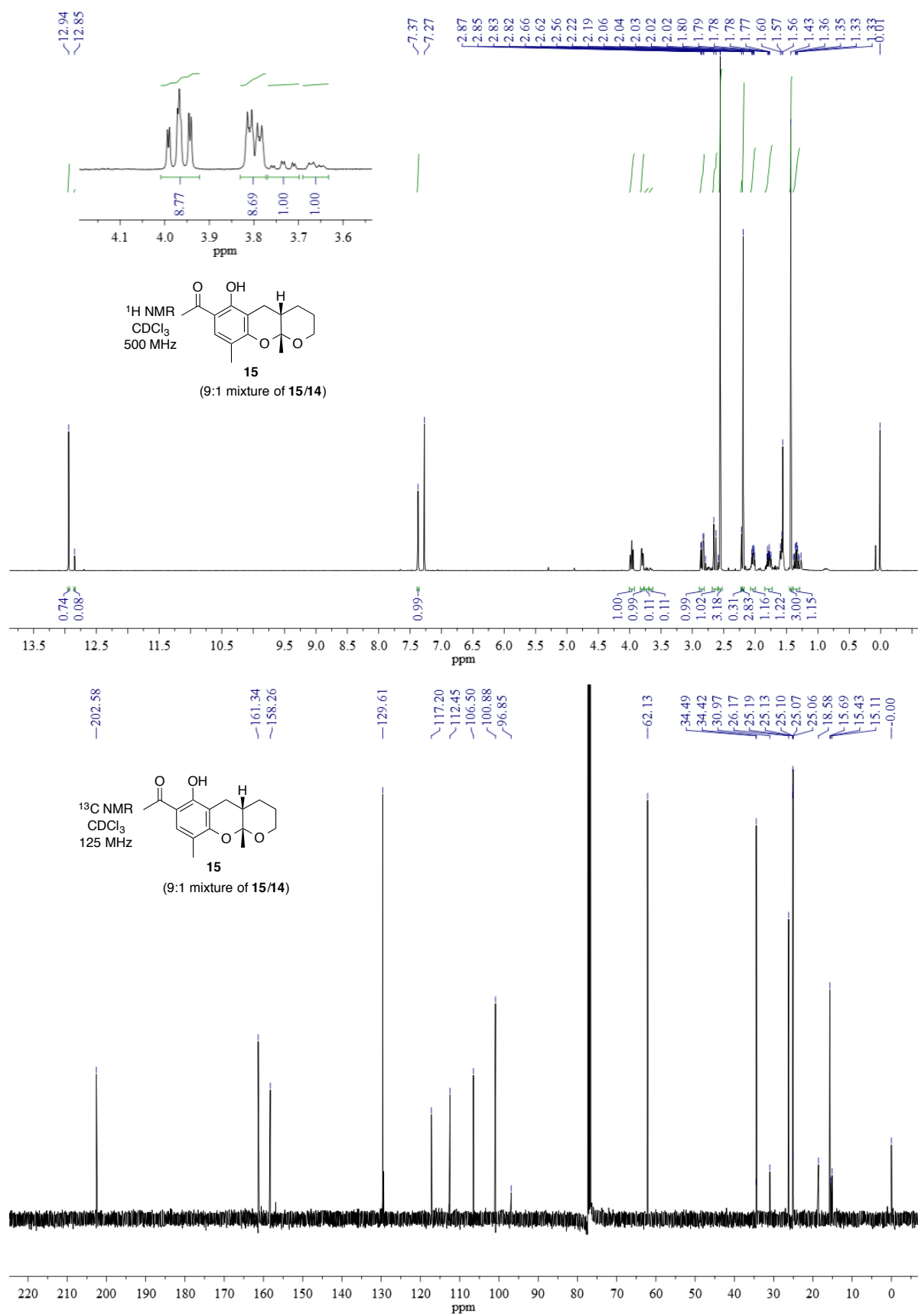


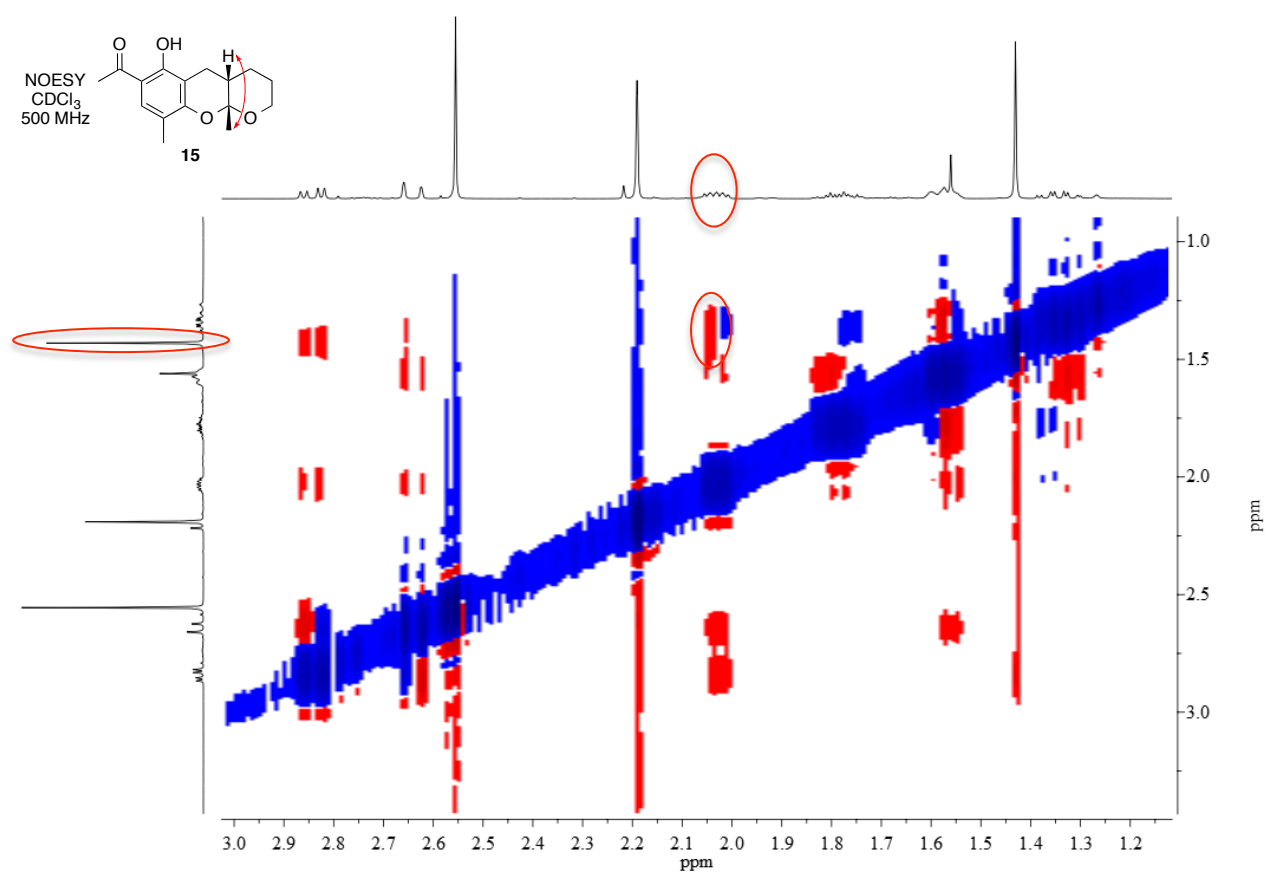
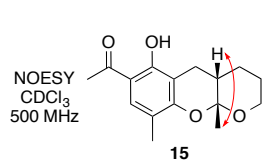
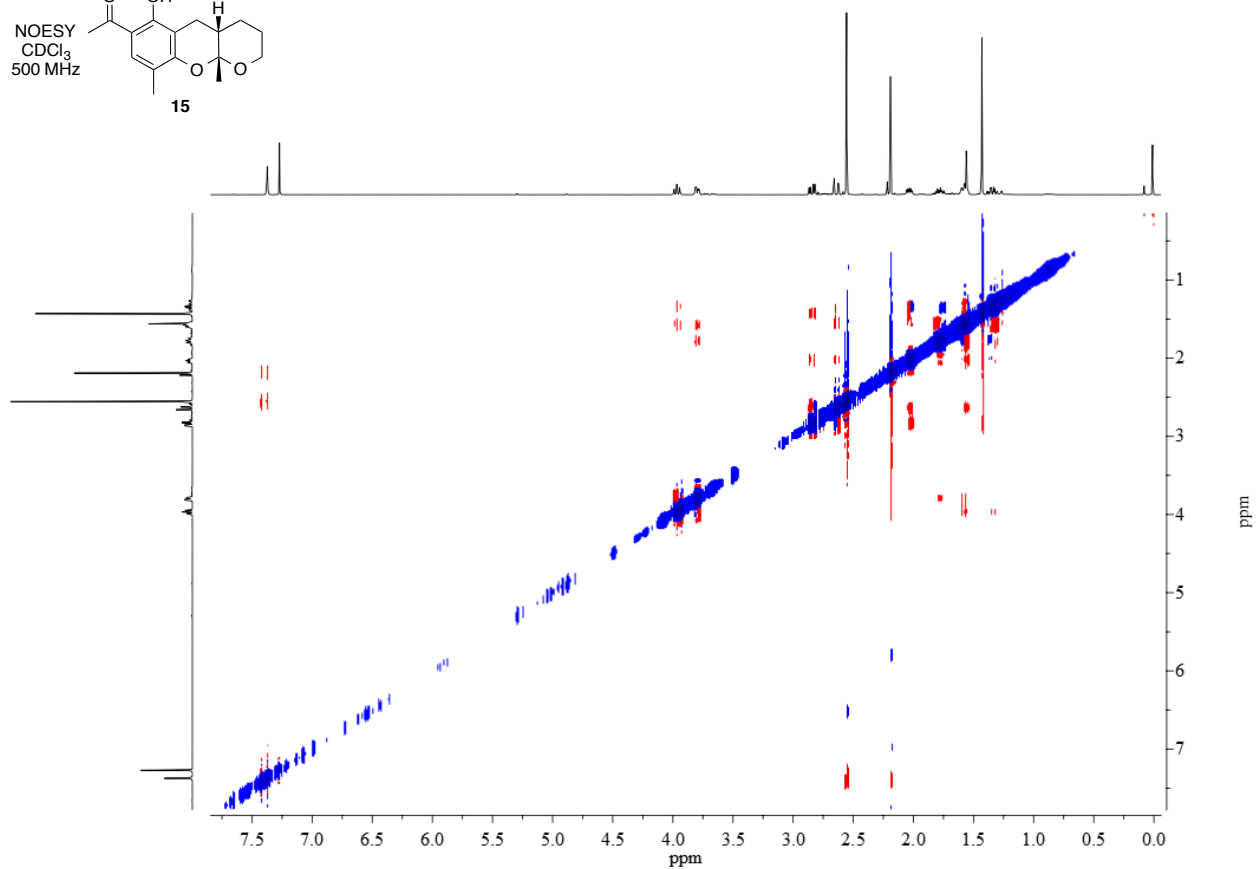
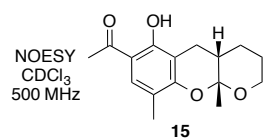


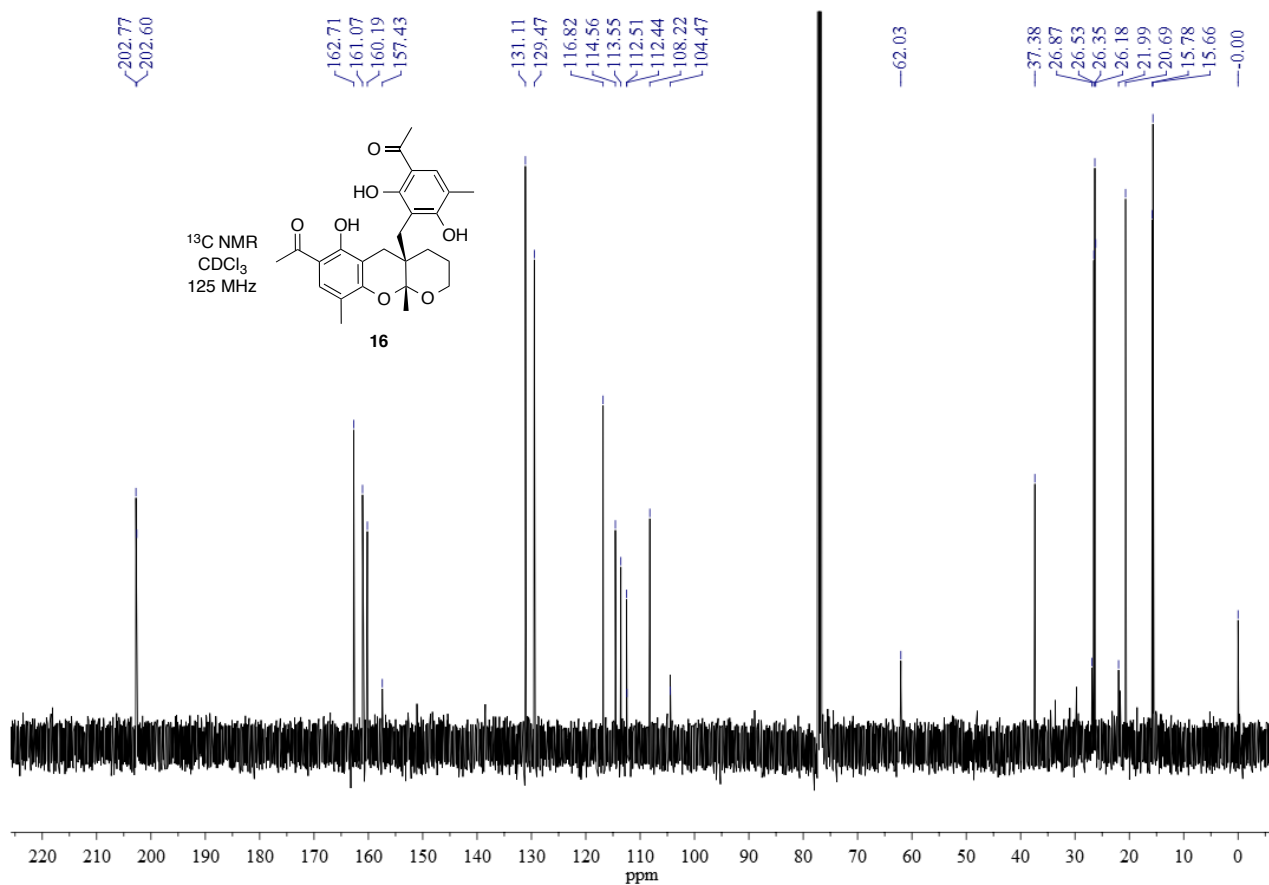
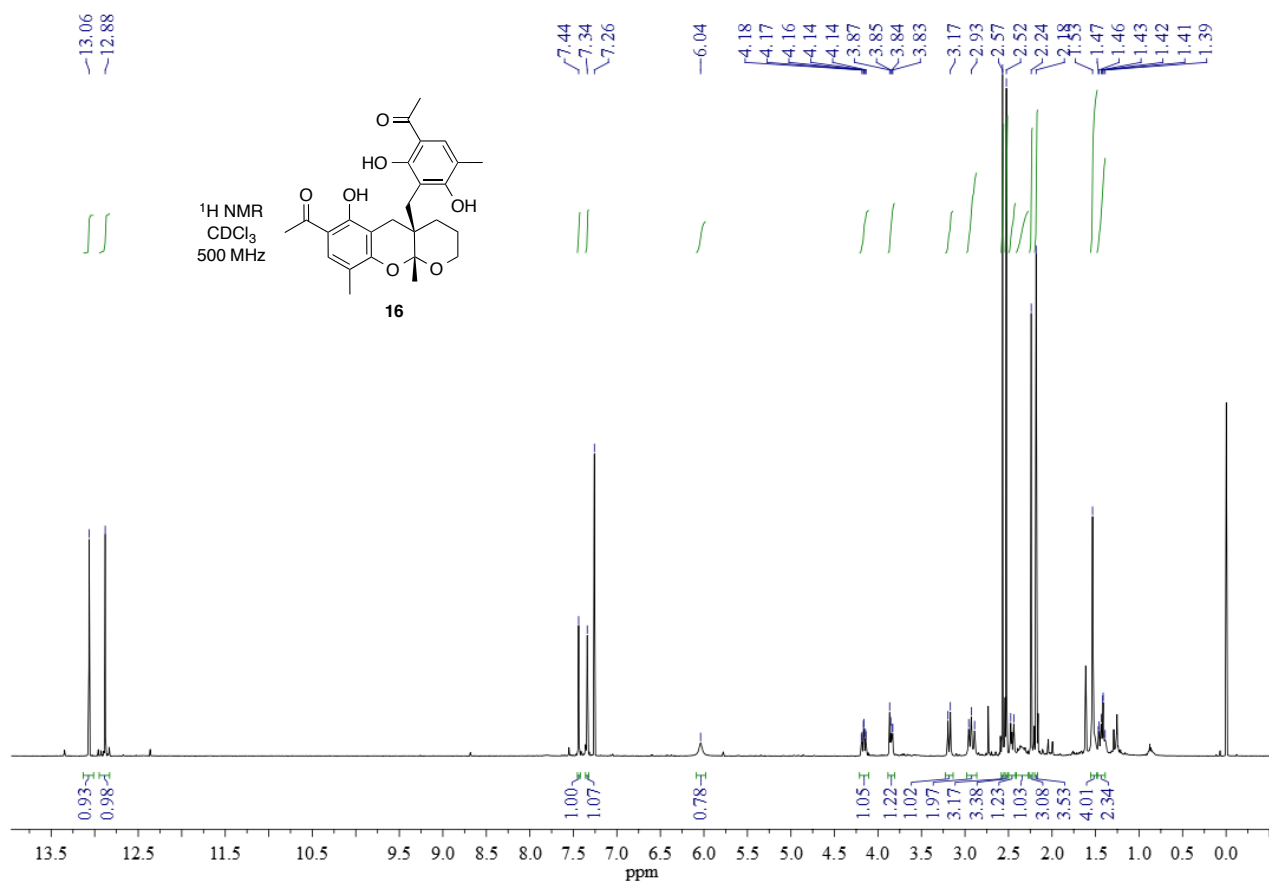


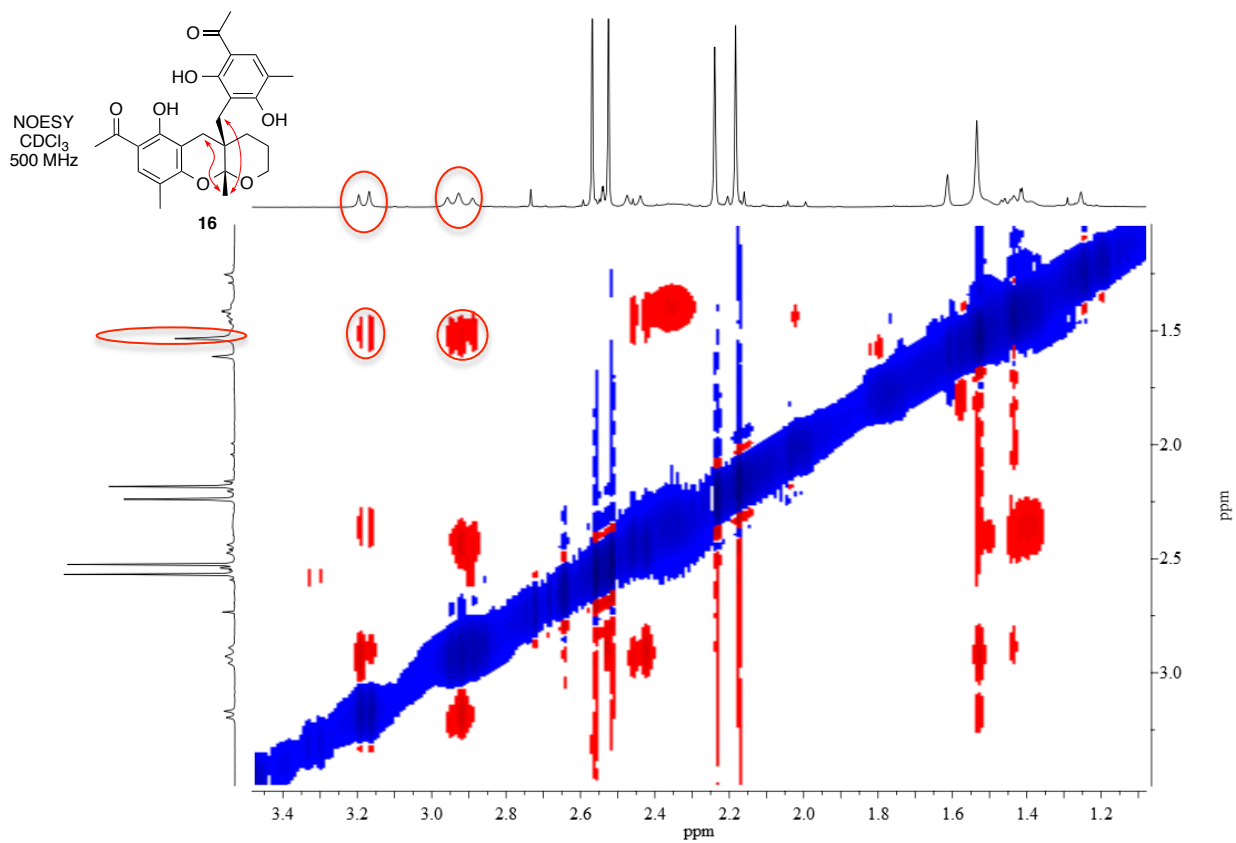
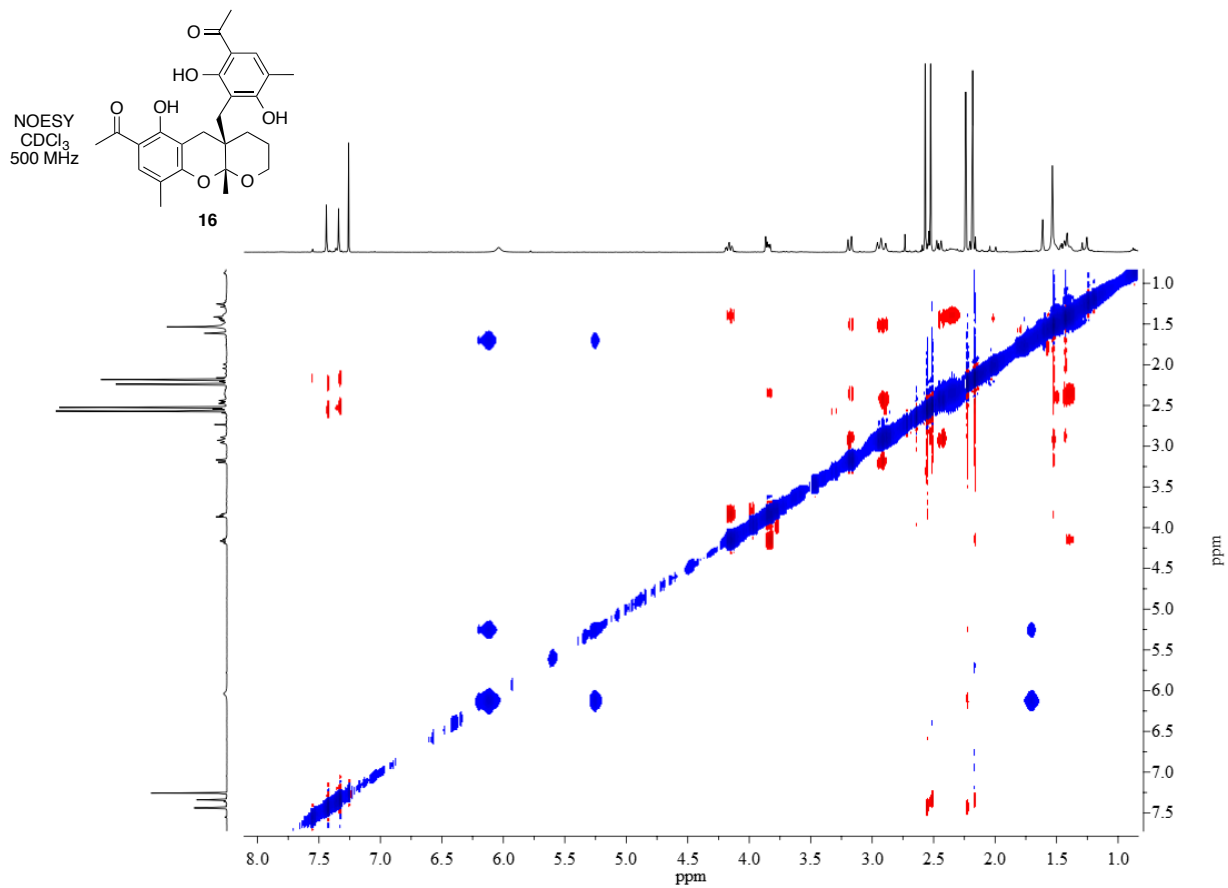


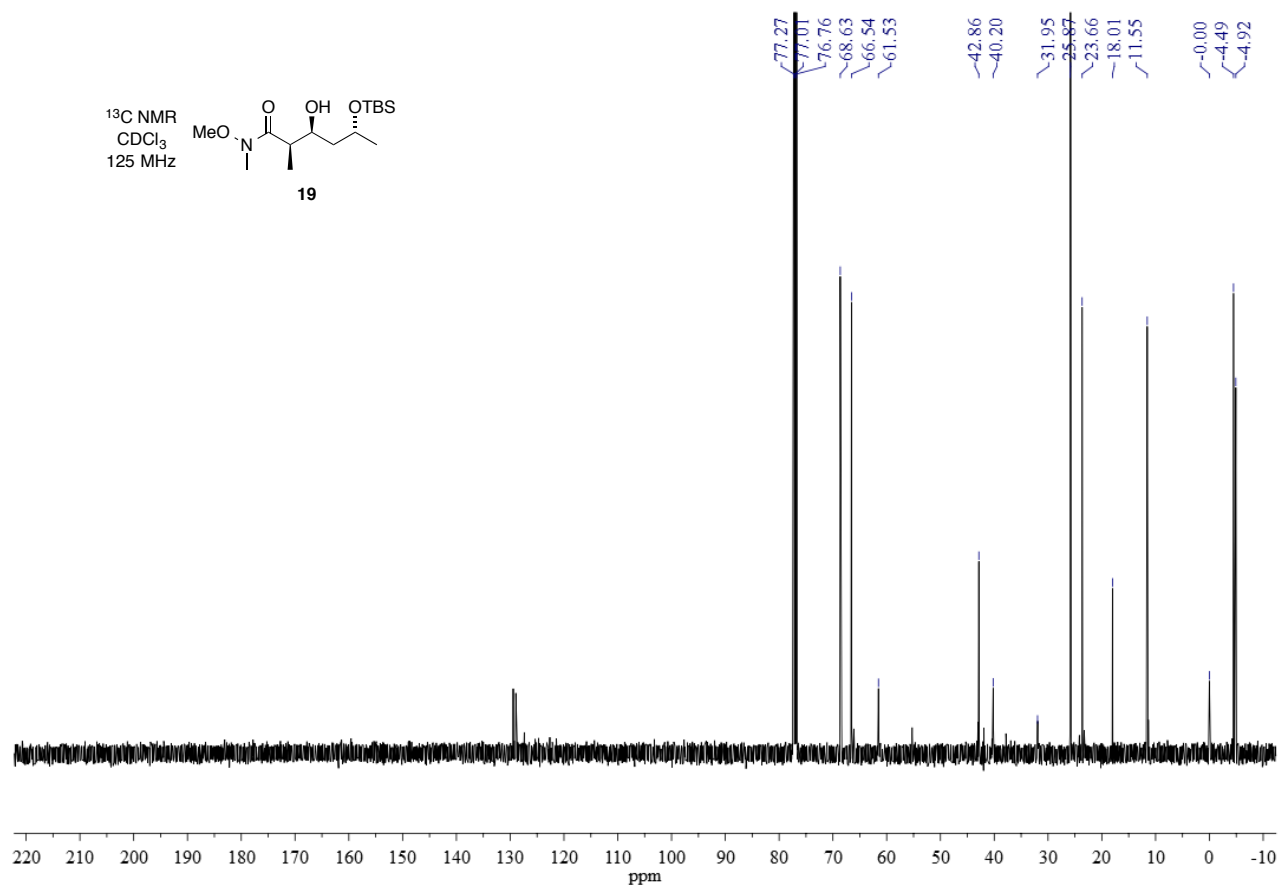
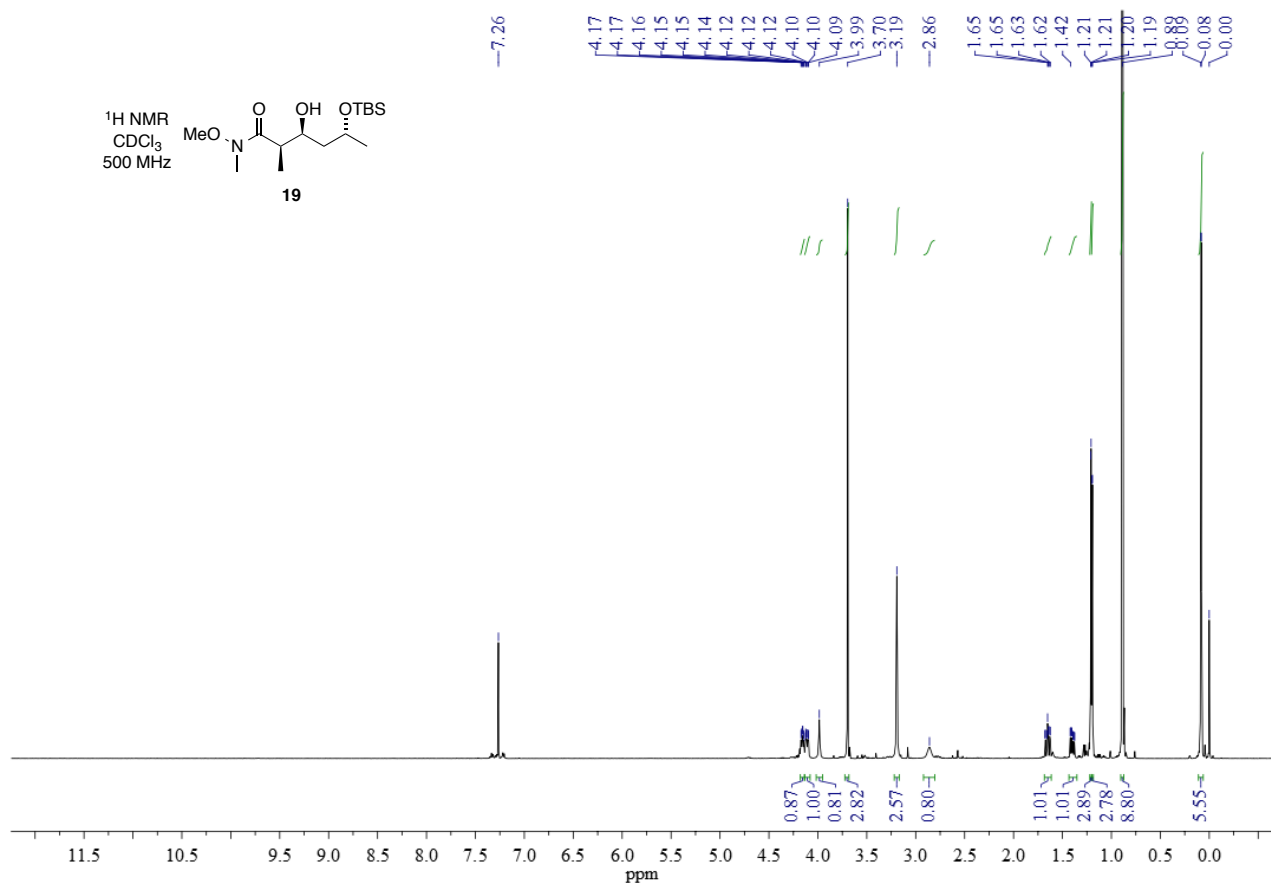


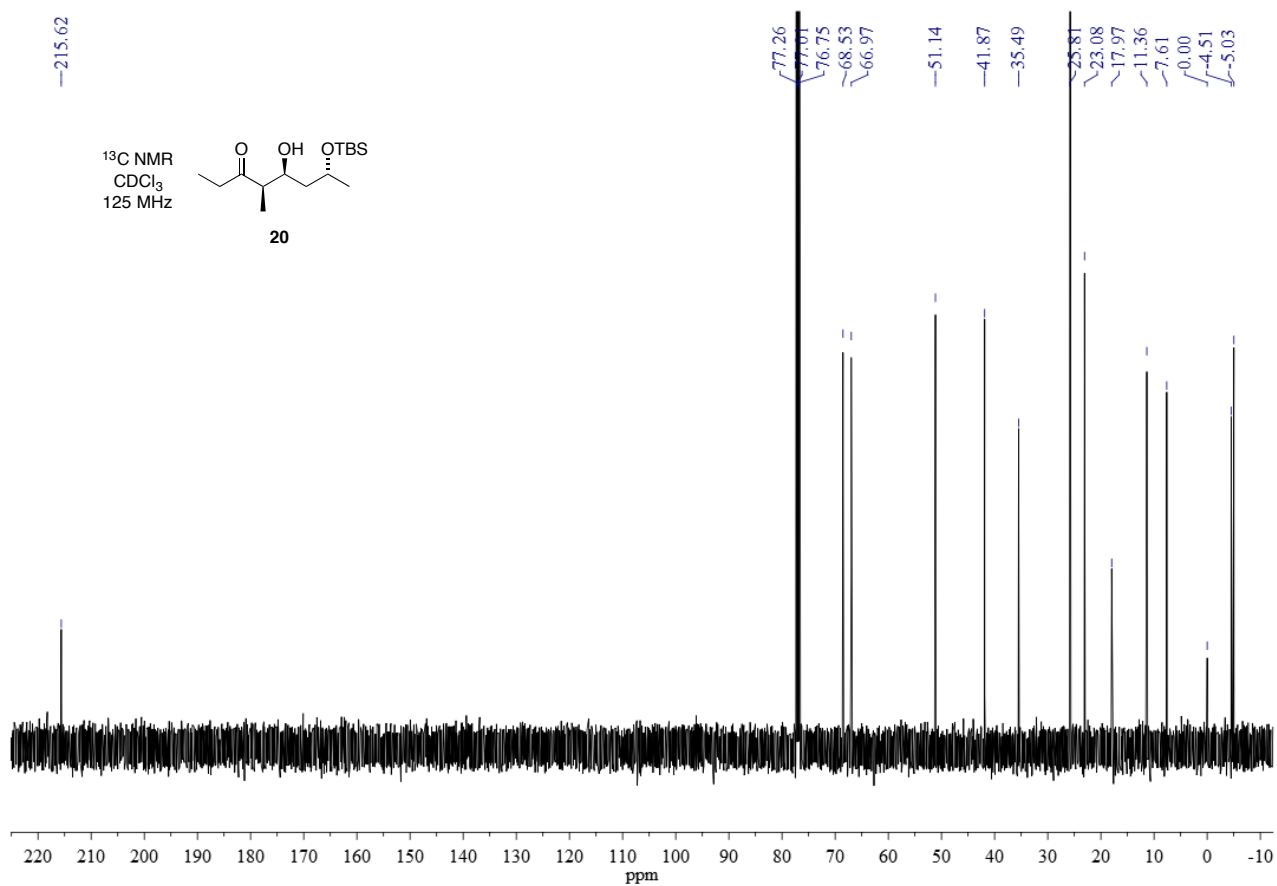
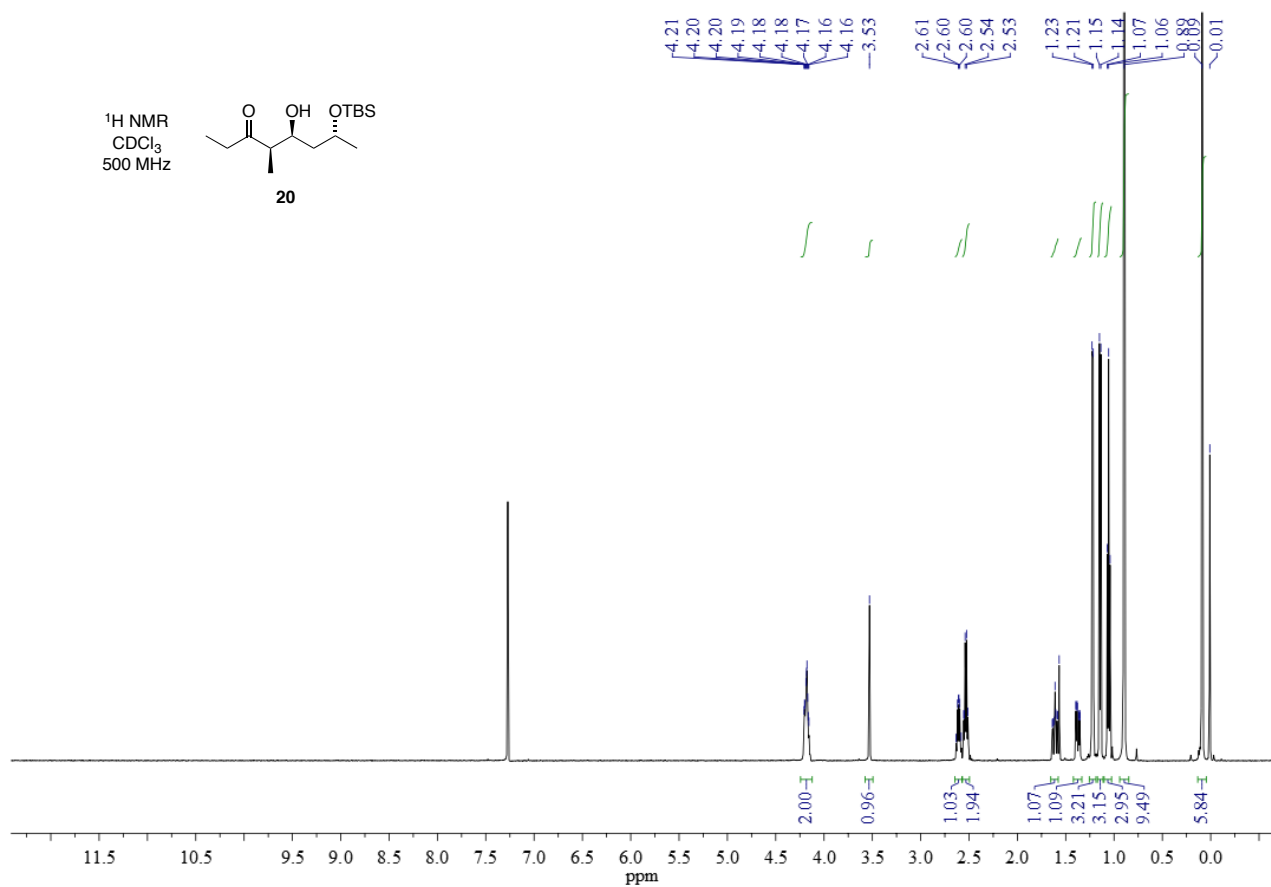


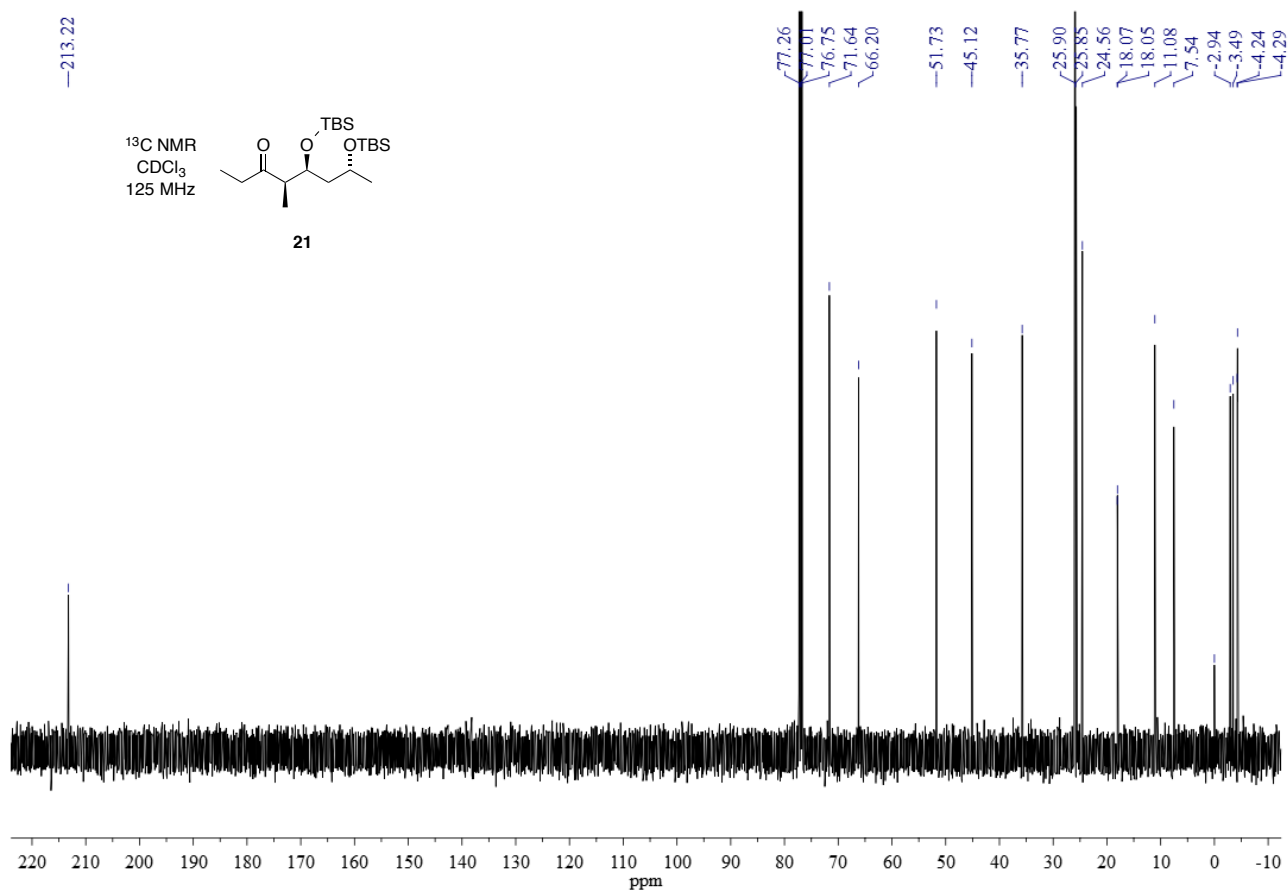
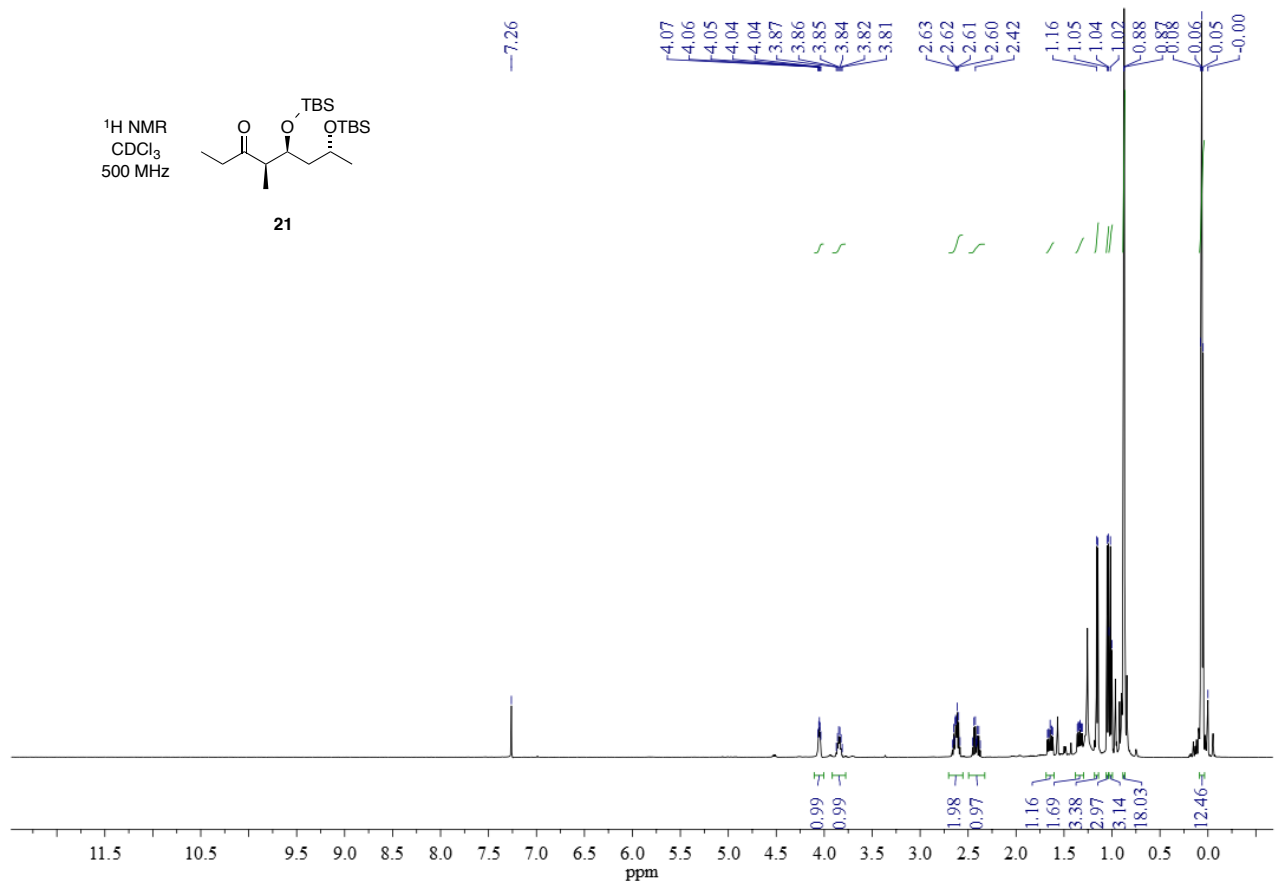


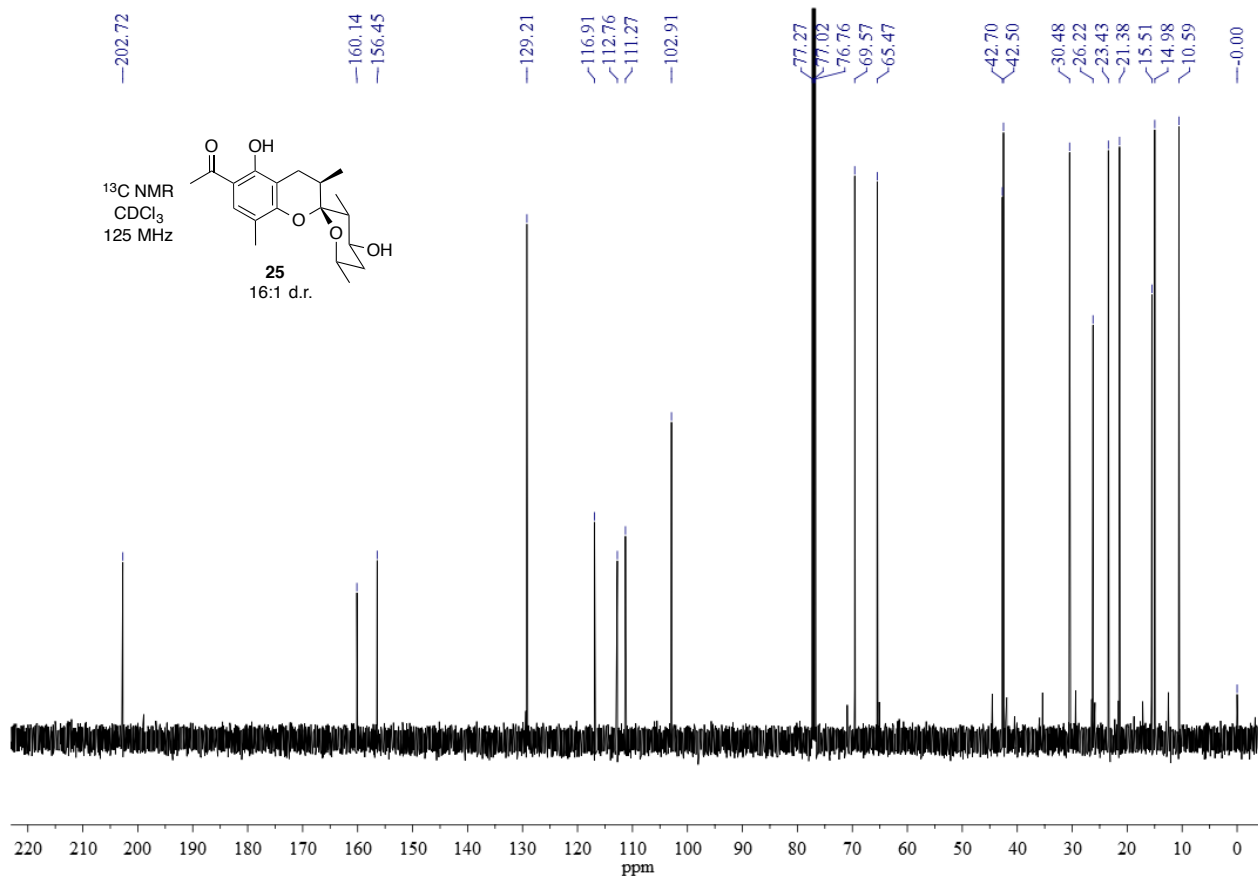
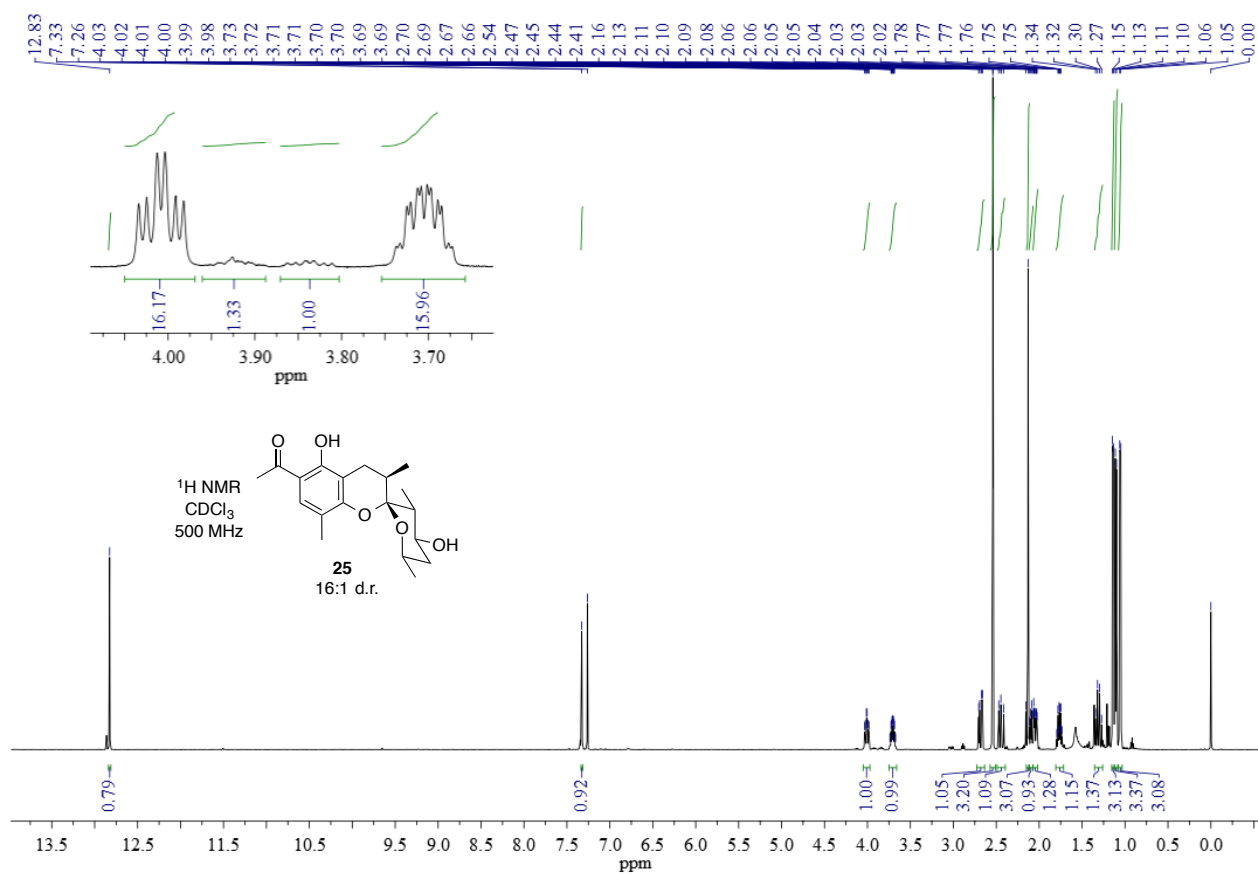


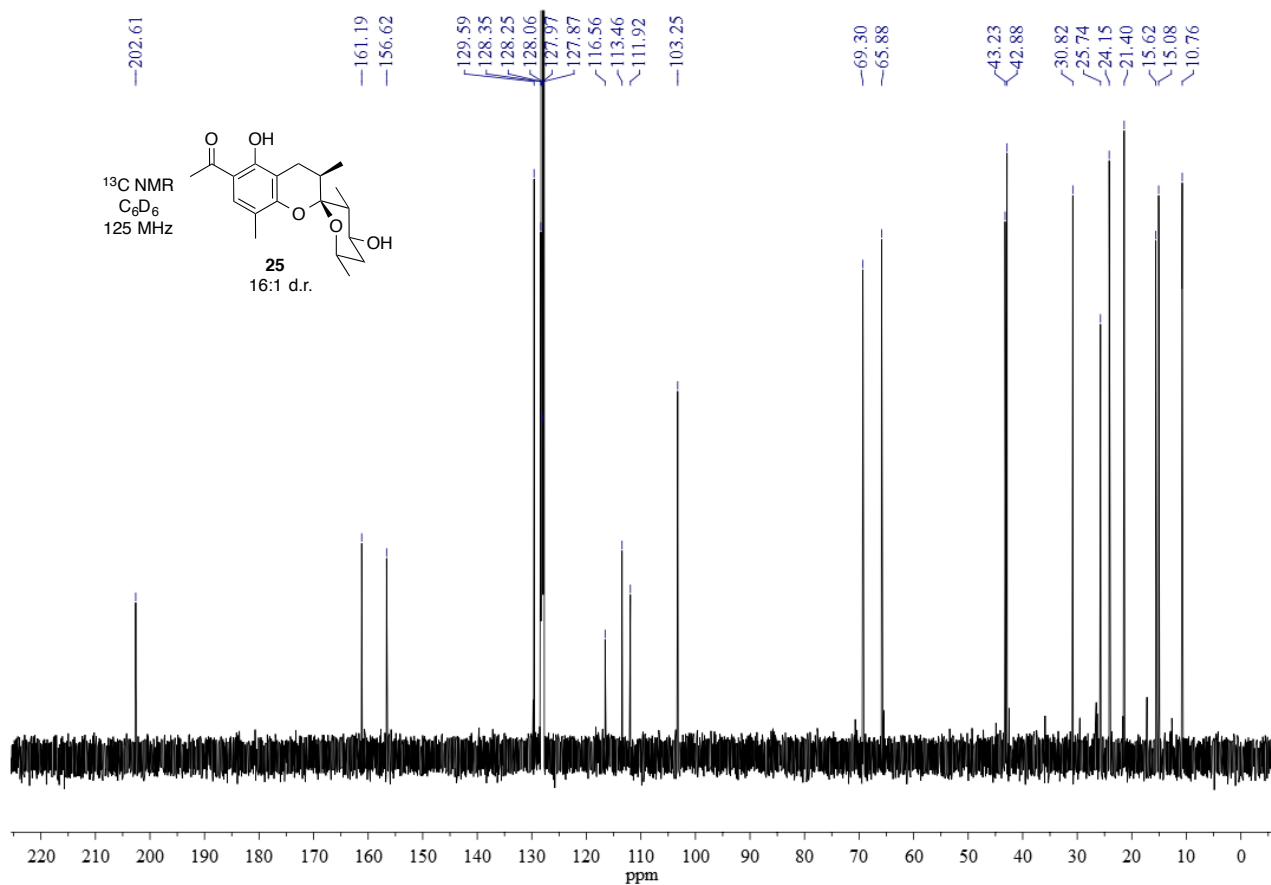
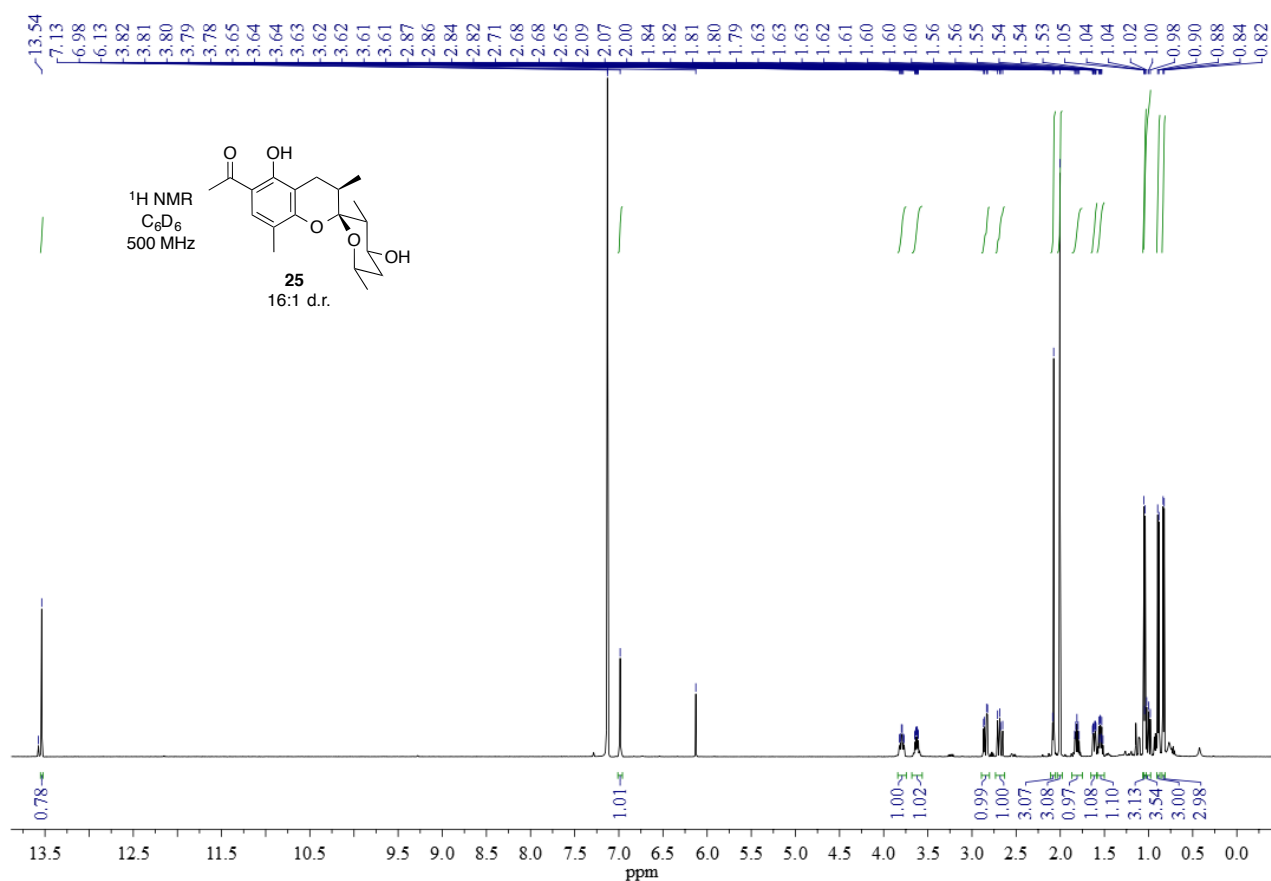


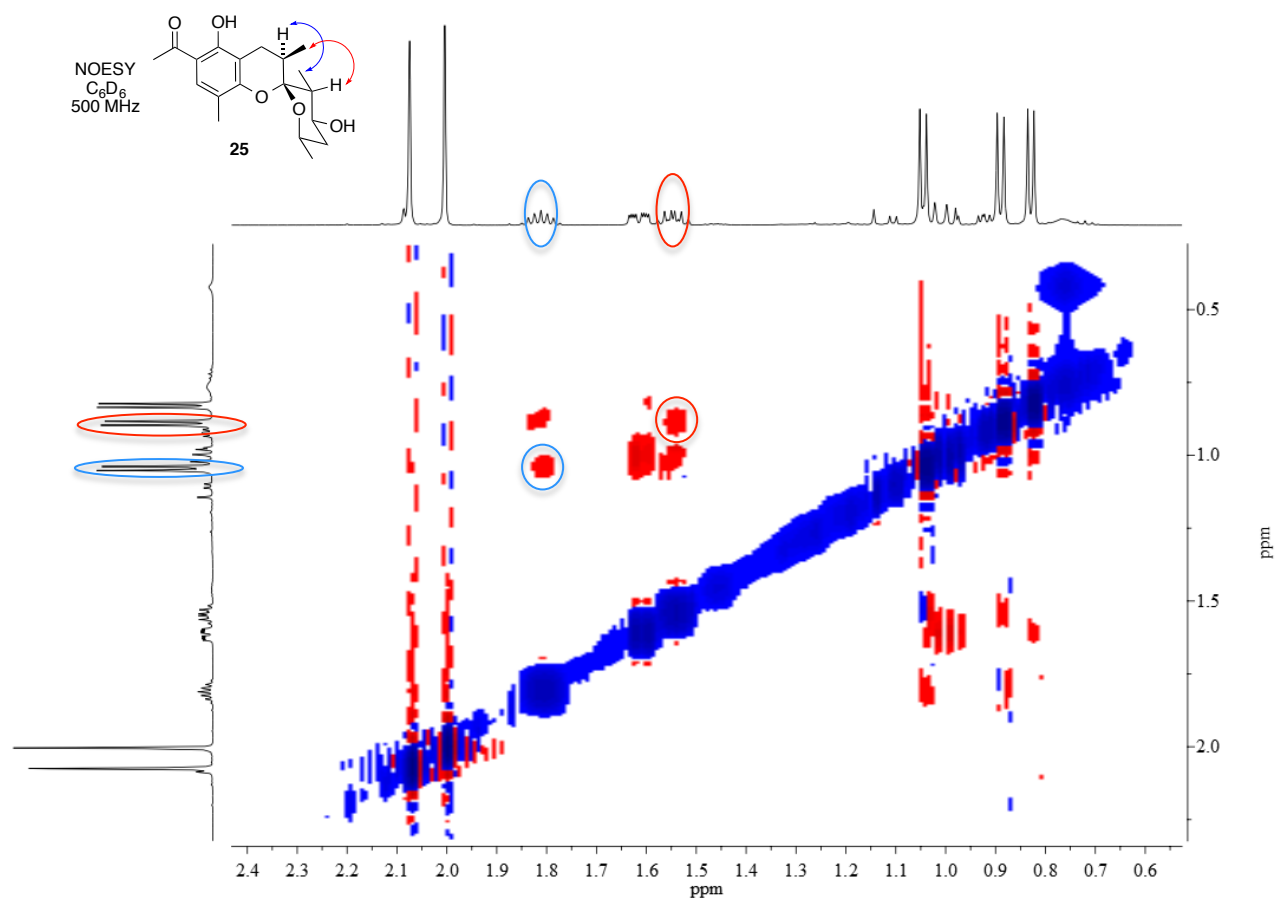
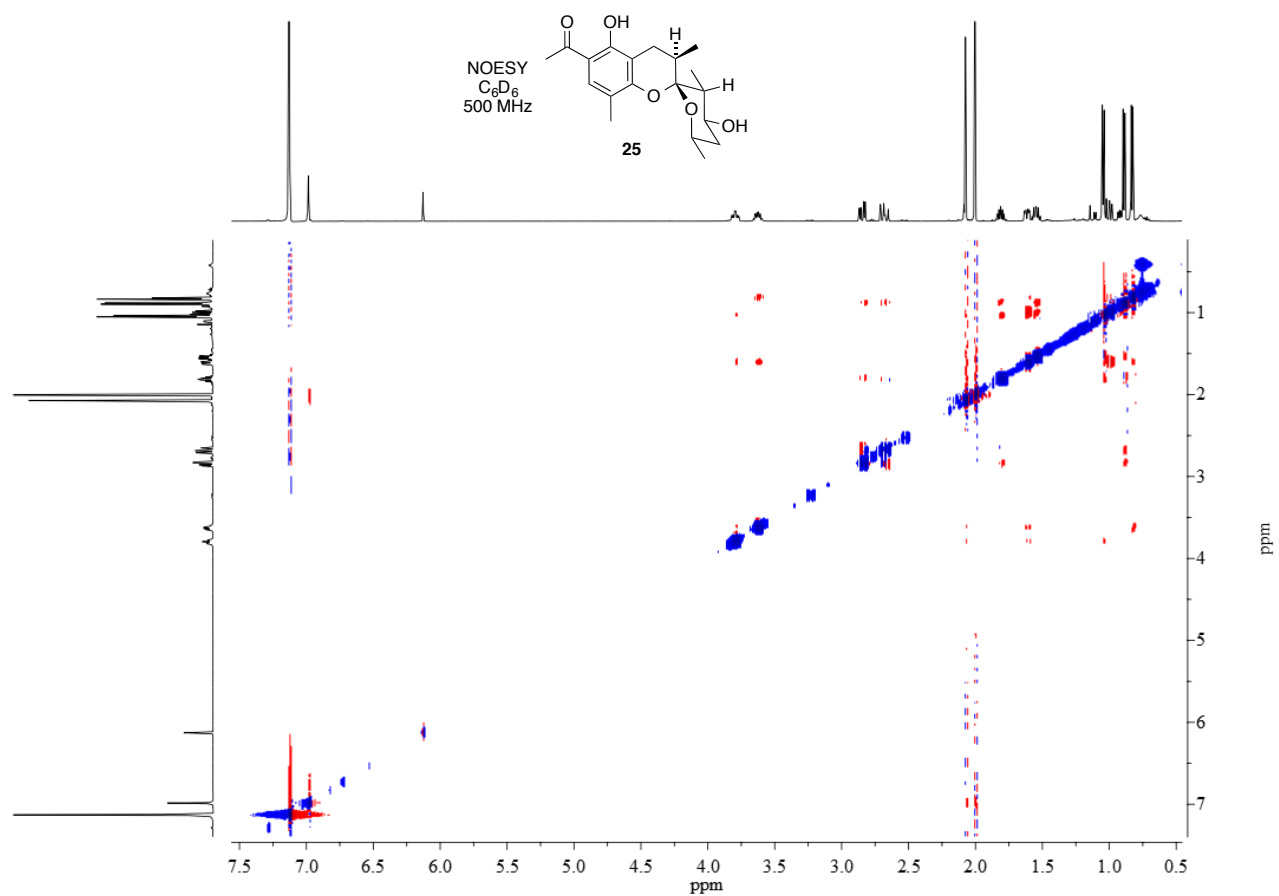


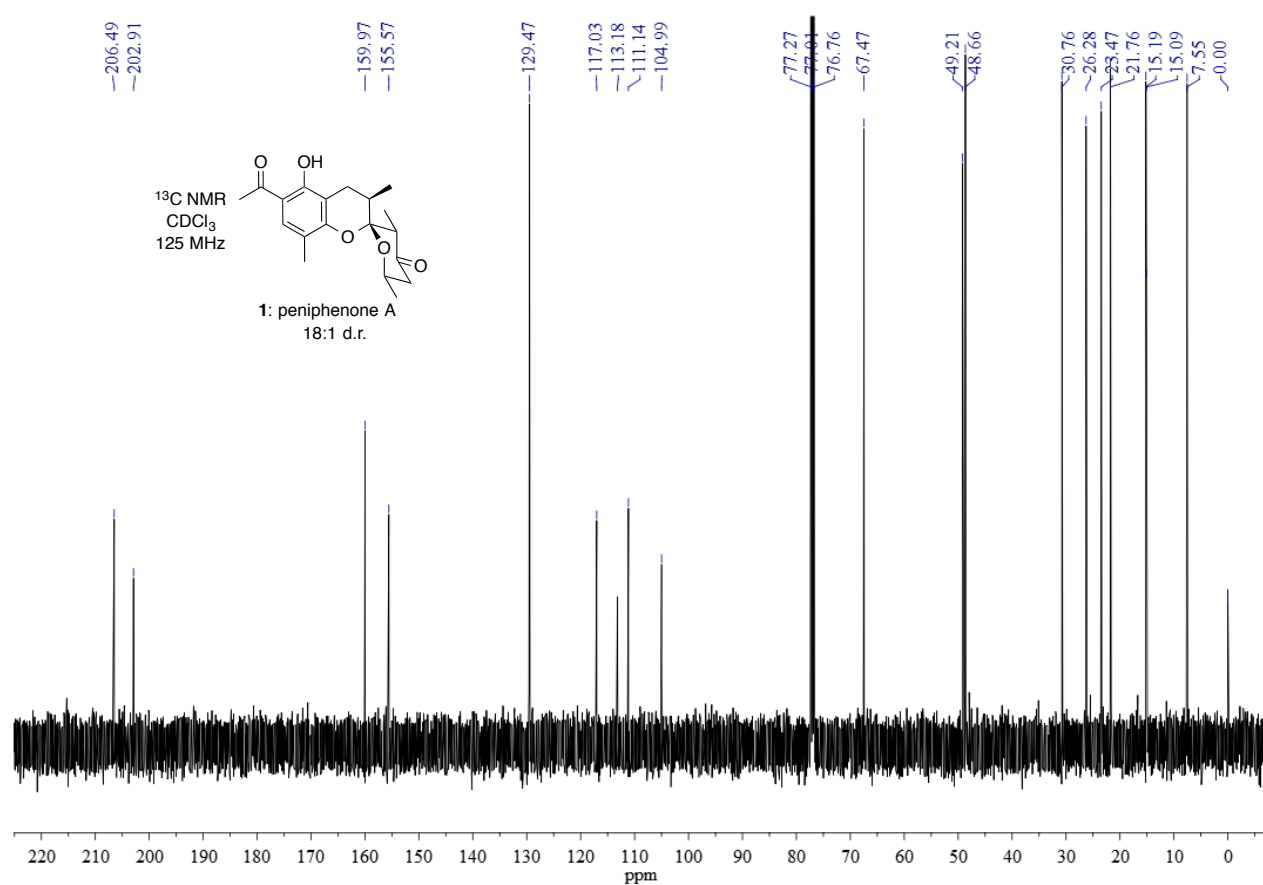
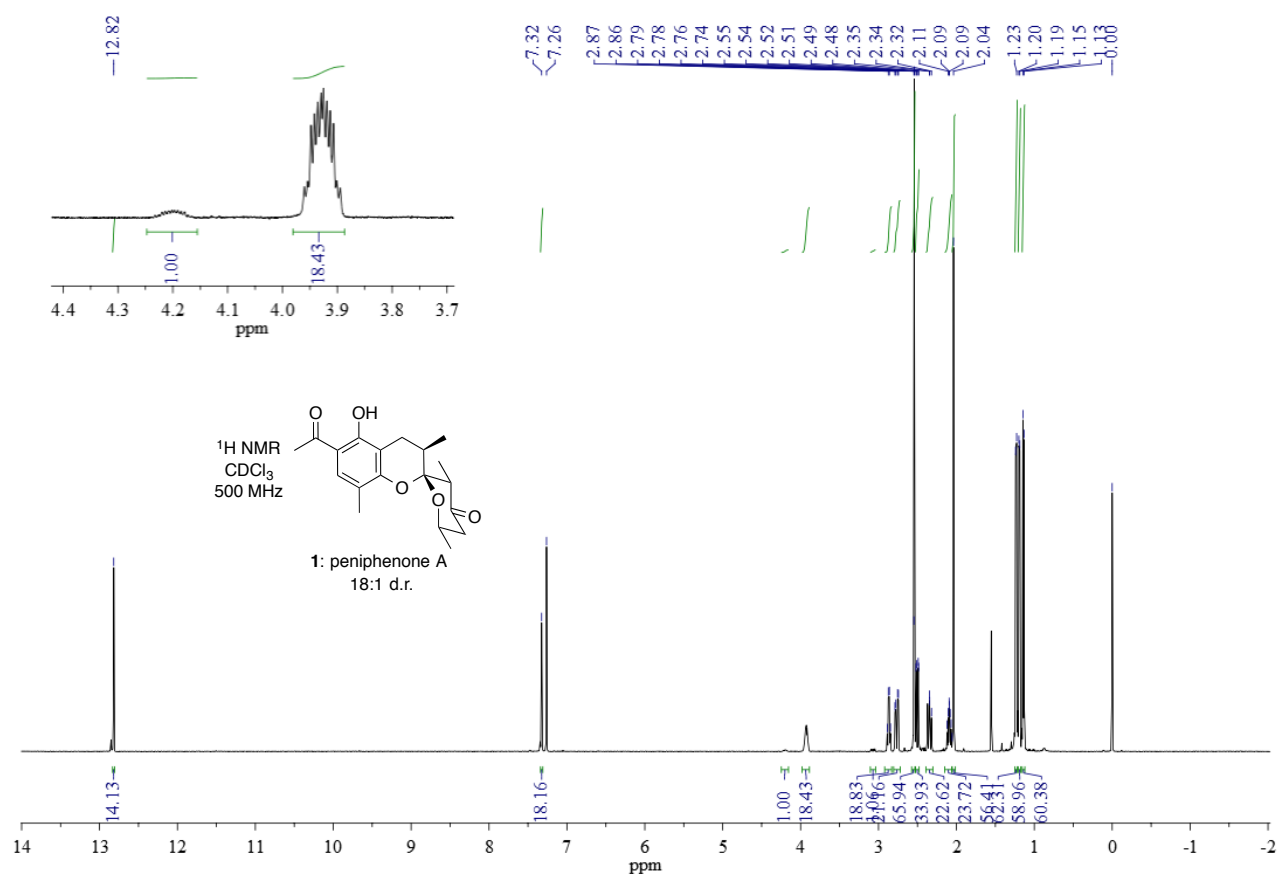


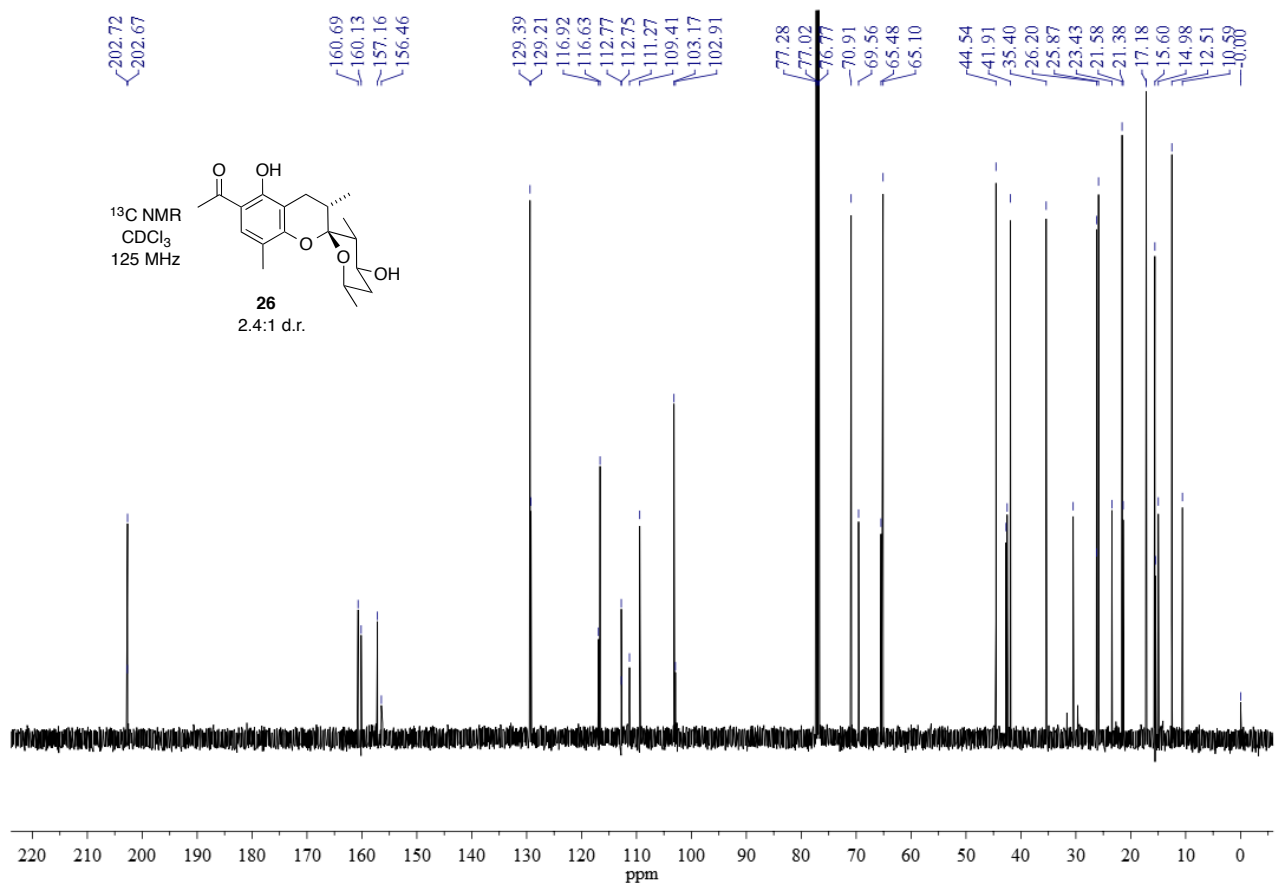
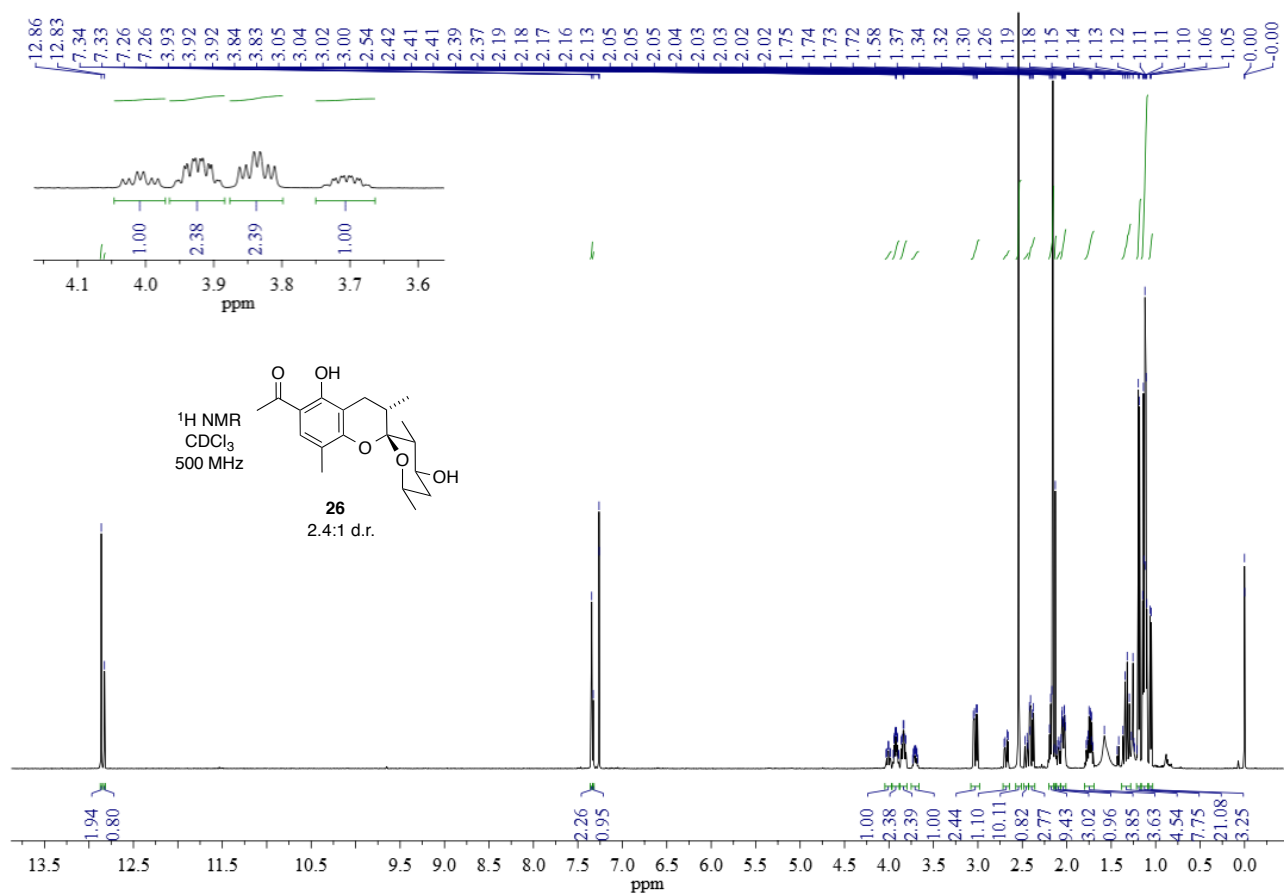


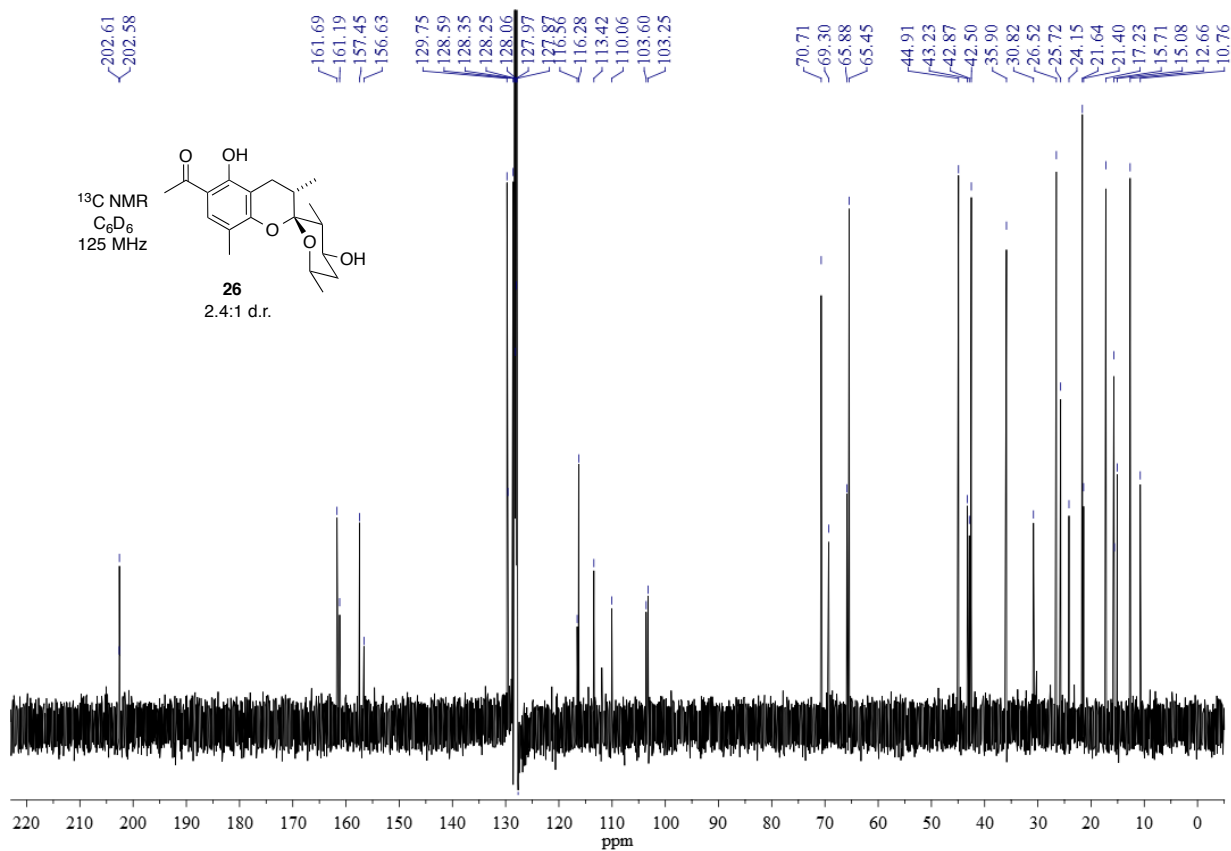
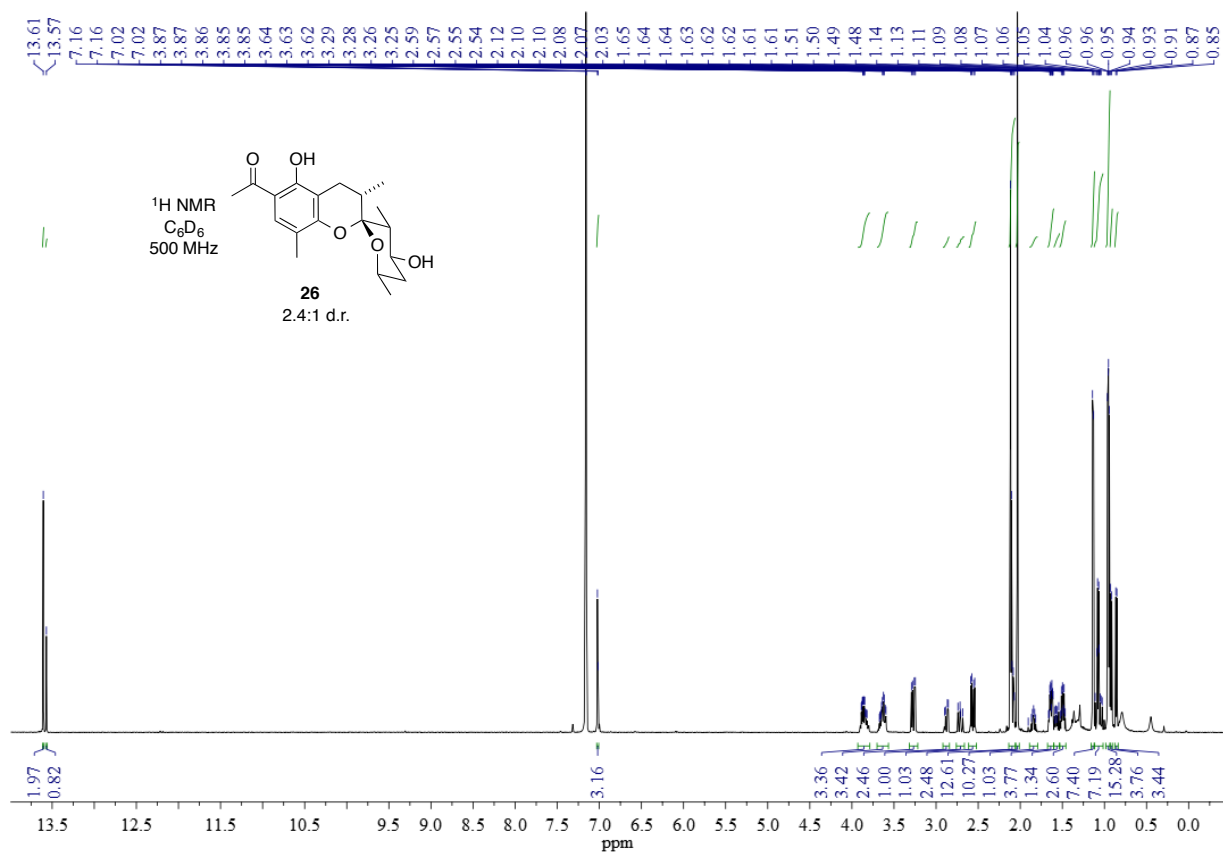


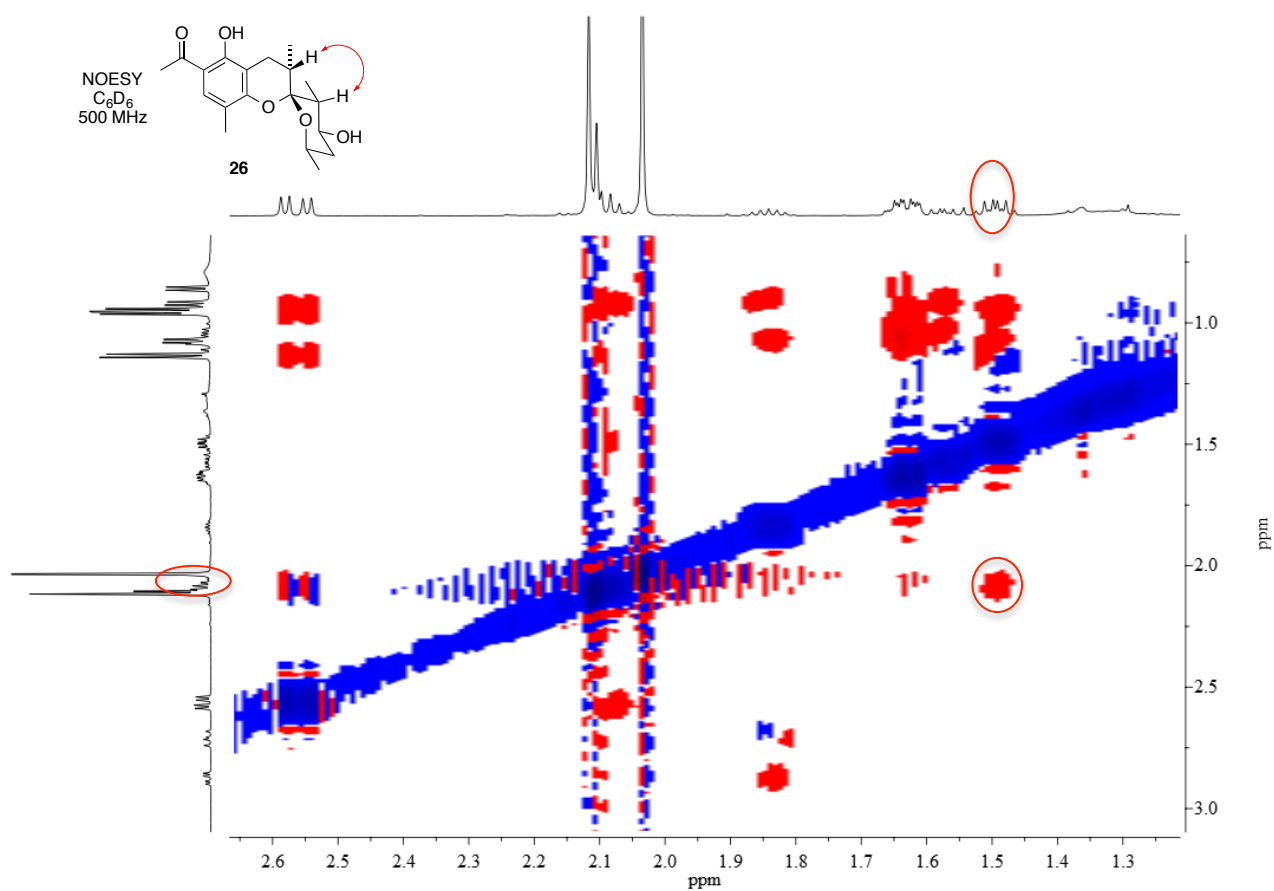
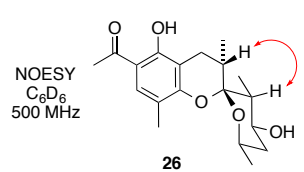
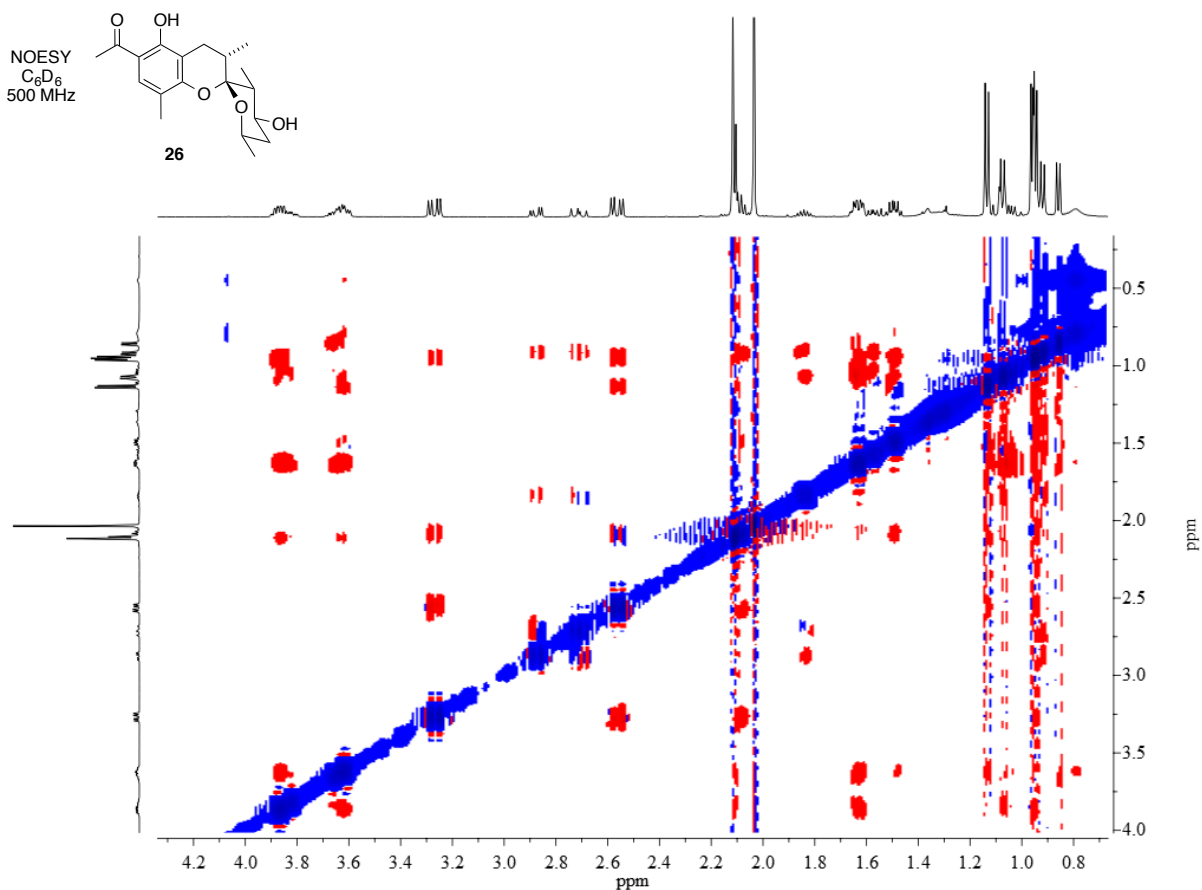
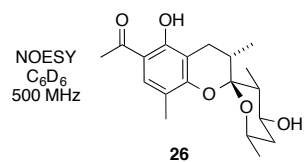


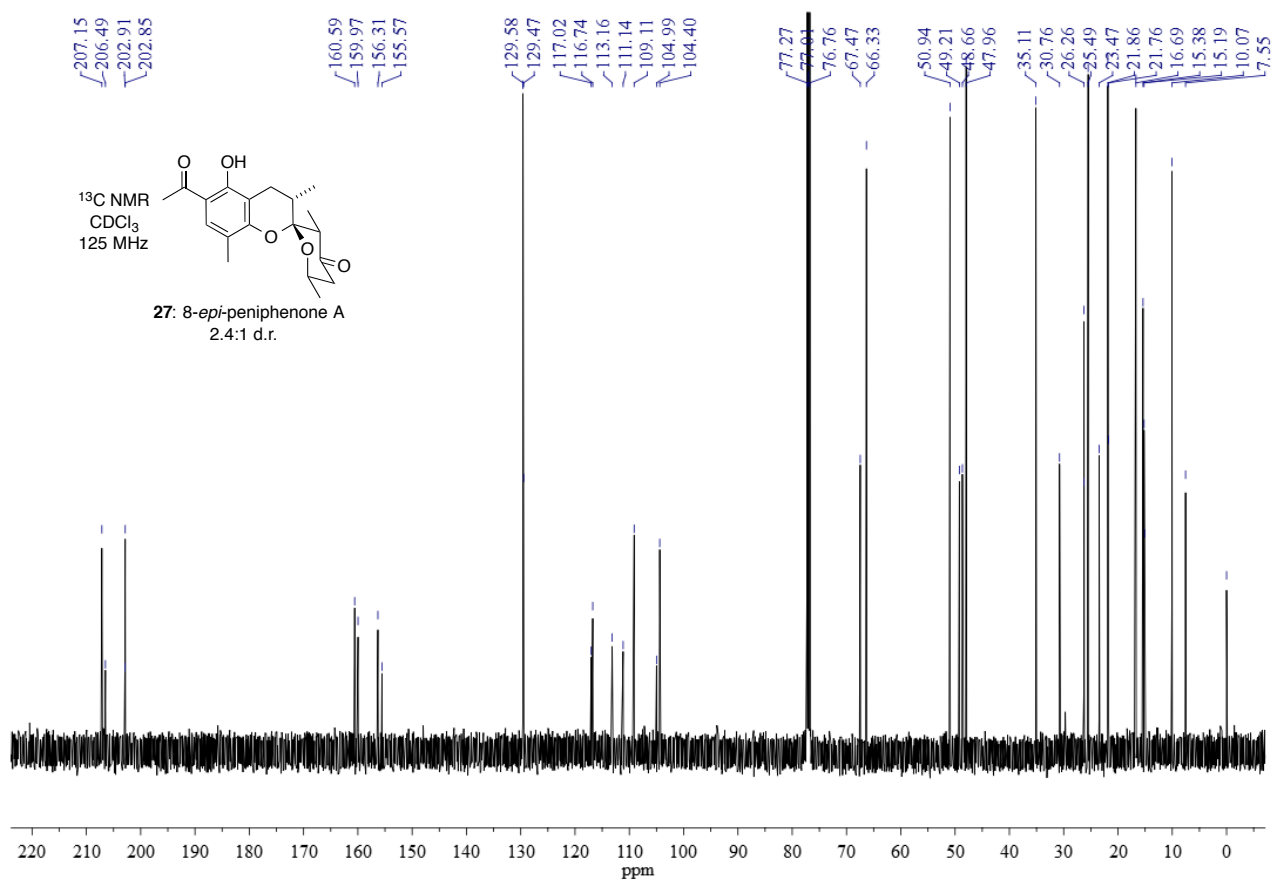
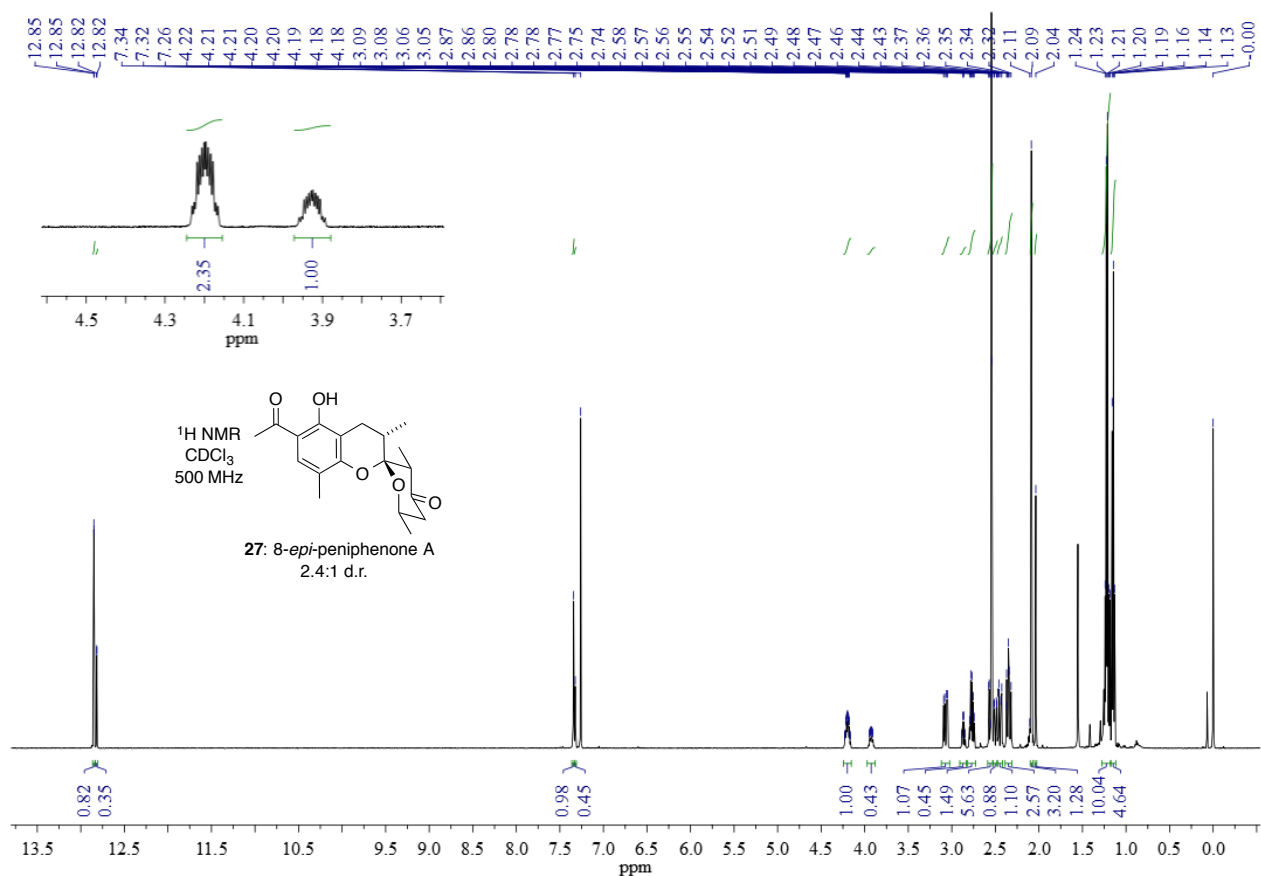












4. Tables of ^1H and ^{13}C NMR data for peniphenones A-D

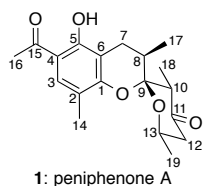


Table 1. Comparison of the ^1H and ^{13}C spectra of natural and synthetic peniphenone A (**1**).⁶

Assignment	Natural sample, ^1H spectrum, CDCl_3 , 400 MHz	Synthetic sample, ^1H spectrum, CDCl_3 , 500 MHz	Natural sample, ^{13}C spectrum, CDCl_3 , 100 MHz	Synthetic sample, ^{13}C spectrum, CDCl_3 , 125 MHz
1			155.6	155.6
2			117.0	117.0
3	7.32 s	7.32	129.5	129.5
4			113.2	113.2
5			160.0	160.0
6			112.2*	111.1*
7a	2.53, dd ($J = 16.6$, 3.1)	2.53, dd ($J = 16.5$, 3.0)	23.5	23.5
7b	2.77, dd ($J = 16.6$, 5.6)	2.77, dd ($J = 16.5$, 5.6)		
8	2.09, m	2.09, dt ($J = 10.1$, 6.0)	30.8	30.8
9			105.0	105.0
10	2.87, qd ($J = 6.7$, 0.8)	2.87, q ($J = 6.8$)	49.2	49.2
11			206.4	206.5
12a	2.34, ddd ($J = 13.8$, 11.3, 0.8)	2.34, dd ($J = 13.3$, 11.8)	48.6	48.7
12b	2.50, dd ($J = 13.8$, 3.1)	2.50, dd ($J = 14.0$, 3.0)		
13	3.93, m	3.93, dqd ($J = 12.3$, 6.2, 3.1)	67.5	67.5
14	2.04, s	2.04, s	15.1	15.1
15				
16	2.54, s	2.54, s	26.2	26.3
17	1.23, d ($J = 6.8$)	1.23, d ($J = 6.8$)	15.2	15.2
18	1.14, d ($J = 6.7$)	1.14, d ($J = 6.7$)	7.5	7.6
19	1.19, d ($J = 6.2$)	1.19, d ($J = 6.2$)	21.7	21.8
OH-5	12.82, br	12.82, br		

*Correction to natural product isolation data.

⁶ Li, H.; Jiang, J.; Liu, Z.; Lin, S.; Xia, G.; Xia, X.; Ding, B.; He, L.; Lu, Y.; She, Z. *J. Nat. Prod.* **2014**, 77, 800.

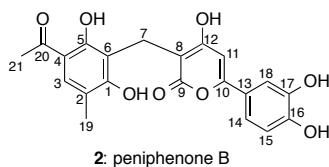


Table 2. Comparison of the ^1H and ^{13}C spectra of natural and synthetic peniphenone B (2).⁶

Assignment	Natural sample, ^1H spectrum, DMSO, 400 MHz	Synthetic sample, ^1H spectrum, DMSO, 500 MHz	Natural sample, ^{13}C spectrum, DMSO, 100 MHz	Synthetic sample, ^{13}C spectrum, DMSO, 125 MHz
1			161.4	161.3
2			116.6	116.6
3	7.52, s	7.55, s	130.6	130.9
4			112.5	112.23
5			160.6	160.9
6			113.2	112.8
7	3.66, s	3.68, s	17.2	16.9
8			100.0	100.1
9			167.0	167.0
10			158.0	158.1
11	6.49, s	6.52, s	97.1	96.4
12			168.4	167.3
13			121.9	121.7
14	7.09, dd ($J = 8.4$, 2.3)	7.09, dd ($J = 8.3$, 2.2)	117.3	117.4
15	6.83, d ($J = 8.4$)	6.84, d ($J = 8.4$)	116.1	116.1
16			148.5	148.6
17			145.7	145.7
18	7.14, d ($J = 2.3$)	7.14, d ($J = 2.2$)	112.3	112.18
19	2.10	2.11, s	16.0	16.0
20			202.6	203.1
21	2.51	2.53, s	26.6	26.3
OH	9.61	9.65, br		
OH	9.37	9.40, br		
OH		13.10, br		

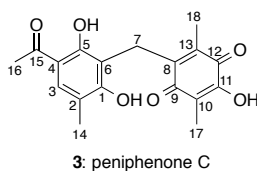


Table 3. Comparison of the ^1H and ^{13}C spectra of natural and synthetic peniphenone C (**3**).⁶

Assignment	Natural sample, ^1H spectrum, CDCl_3 , 400 MHz	Synthetic sample, ^1H spectrum, CDCl_3 , 500 MHz	Natural sample, ^{13}C spectrum, CDCl_3 , 100 MHz	Synthetic sample, ^{13}C spectrum, CDCl_3 , 125 MHz
1			161.1	161.1
2			118.4	118.4
3	7.41, br s	7.41, s	131.1	131.1
4			112.8	112.8
5			161.8	161.8
6			110.6	110.6
7	3.75, s	3.74, s	22.0	22.0
8			143.4	143.4
9			191.2	191.2
10			116.8	116.8
11			151.6	151.6
12			183.7	183.7
13			139.8	139.8
14	2.22, d ($J = 0.4$)	2.22, s	16.1	16.1
15			202.7	202.7
16	2.53, s	2.53, s	26.2	26.2
17	1.92, s	1.91, s	8.1	8.2
18	2.37, s	2.37, s	12.4	12.5
OH-5	13.18, br s	13.18		
OH-1	9.55, br s	9.57		

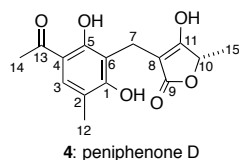


Table 4. Comparison of the ^1H and ^{13}C spectra of natural and synthetic peniphenone D (**4**).⁶

Assignment	Natural sample, ^1H spectrum, CDCl_3 , 400 MHz	Synthetic sample, ^1H spectrum, CDCl_3 , 500 MHz	Natural sample, ^{13}C spectrum, CDCl_3 , 100 MHz	Synthetic sample, ^{13}C spectrum, CDCl_3 , 125 MHz
1			160.2	160.2
2			119.5	119.5
3	7.41, d ($J = 0.4$)	7.41, d ($J = 0.5$)	130.7	130.7
4			113.2	113.3
5			158.8	158.8
6			112.8	112.8
7a	3.42, d ($J = 15.1$)*	3.48, d ($J = 15.1$)*	25.9*	14.5*
7b	3.28, d ($J = 15.1$)*	3.43, d ($J = 15.1$)*		
8			101.5	101.5
9			177.1	177.2
10	4.84, q ($J = 6.8$)	4.84, q ($J = 6.8$)	76.1	76.2
11			175.7	175.8
12	2.21, d ($J = 0.4$)	2.21, s	15.8	15.9
13			203.4	203.5
14	2.57, s	2.57, s	25.9	26.0
15	1.46, d ($J = 6.8$)	1.46, d ($J = 6.8$)	17.2	17.2
OH-5	13.76, br s	13.97		
OH-11	8.55, br s	8.58		
OH-1	8.22, br s	8.24		

*Correction to natural product isolation data.