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Supporting Information

Total Synthesis Establishes the Biosynthetic Pathway to the Naphterpin and Marinone Natural Products

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Supporting Information

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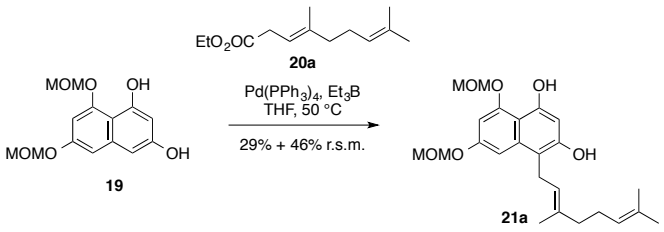
1. General methods

All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel F_{254}. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate or $KMnO_4$ stain followed by heating. All R_f values were measured to the nearest 0.05. Flash column chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a Reichart Thermovar Kofler microscope apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR spectra were recorded using a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). Solvent used for spectra were $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C NMR are reported in ppm relative to $CDCl_3$ (δ 77.00). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (quin) quintet, (sext) sextet, (hept) heptet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high-resolution mass spectra were recorded on an ESI-TOF mass spectrometer.

2. Experimental procedures

Synthesis of 7-demethylnaphterpin



A solution of **19**[1] (7.50 g, 26.7 mmol), ethyl geranyl carbonate (**20a**) (9.06 g, 40.0 mmol) and $Pd(PPh_3)_4$ (1.56 g, 1.35 mmol) in THF (100 mL) was degassed. Et_3B (1.0 M in THF, 40.0 mL, 40.0 mmol) was then added and the resultant mixture was stirred at 50 °C for 2 h. The mixture was cooled, quenched with *sat*. NH_4Cl solution (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine (100 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol/EtOAc 5:1 → 3:1) to yield **21a** (3.28 g, 29%) as a brown gum along with recovered starting material (3.46 g, 46%).

Data for 21a:

R_f = 0.20 (3:1, petrol/EtOAc)

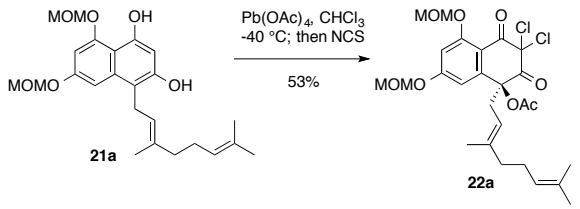
IR (neat): 3378, 2915, 1622, 1602, 1378, 1287, 1138, 1019, 990, 909, 816 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.24 (s, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.40 (s, 1H), 5.41 (s, 2H), 5.25 (s, 2H), 5.21 (t, *J* = 6.7 Hz, 1H), 5.06 (t, *J* = 6.8 Hz, 1H), 3.59 (d, J = 6.6 Hz, 1H), 3.58 (s, 3H), 3.52 (s, 3H), 2.13 – 1.99 (m, 4H), 1.88 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 155.6, 155.3, 154.0, 153.3, 137.1, 136.7, 131.7, 124.0, 122.6, 109.7, 107.4, 101.1, 100.5, 98.8, 95.8, 94.6, 56.9, 56.1, 39.7, 26.6, 25.6, 24.5, 17.7, 16.3.

HRMS (ESI): calculated for $C_{24}H_{33}O_6$ 417.2277 $[M+H]^+$, found 417.2268.

[1] Compound **19** was prepared according to: Z. D. Miles, S. Diethelm, H. P. Pepper, D. M. Huang, J. H. George, B. S. Moore, *Nat. Chem*. **2017**, *9*, 1235.



To a solution of **21a** (234 mg, 0.576 mmol) in $CHCl_3$ (8 mL) at −40 °C was added $Pb(OAc)_4$ (268 mg, 0.604 mmol) in small portions. The mixture was stirred at −40 °C for 5 min before NCS (147 mg, 1.04 mmol) was added portion wise. The mixture was stirred at −40 °C for a further 20 min before $Na_2S_2O_3$ (20 mg) was added. The mixture was warmed to rt, filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol/EtOAc 5:1) to yield **22a** (166 mg, 53%) as a yellow oil.

Data for 22a:

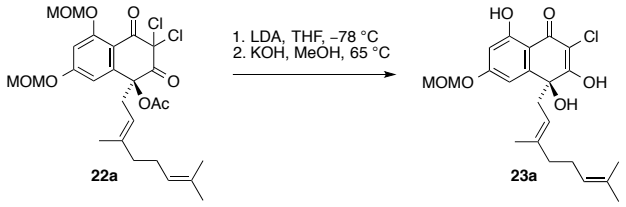
R_f = 0.20 (3:1, petrol/EtOAc)

IR (neat): 2917, 1753, 1719, 1599, 1324, 1225, 1147, 1019, 972, 924 cm^{-1}

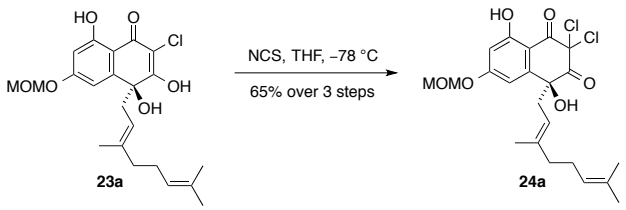
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.90 (d, *J* = 2.2 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.23 (d, *J* = 7.0 Hz, 1H), 5.20 (d, *J* = 7.0 Hz, 1H), 5.02 (t, *J* = 6.8 Hz, 1H), 4.92 (t, *J* = 7.3 Hz, 1H), 3.53 (s, 3H), 3.48 (s, 3H), 2.96 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.73 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.14 (s, 3H), 2.04 – 1.90 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.41 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 190.7, 178.5, 169.2, 162.8, 159.8, 143.4, 141.9, 131.7, 123.8, 113.7, 113.6, 105.4, 104.0, 94.9, 94.4, 82.1, 81.4, 56.7, 56.6, 40.4, 39.8, 26.0, 25.7, 20.4, 17.6, 16.3.

HRMS (ESI): calculated for $C_{26}H_{33}Cl_2O_8$ 543.1552 $[M+H]^+$, found 543.1554.



To a solution of **22a** (2.35 g, 4.32 mmol) in THF (70 mL), was added LDA (2.0 M in THF, 6.49 mL, 13.0 mmol) at −78 ºC. The mixture was stirred at −78 ºC for 30 min. The mixture was quenched with 0.5 M HCl (80 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant yellow oil was dissolved in MeOH (60 mL), and KOH (970 mg, 17.3 mmol) was added at rt. The mixture was heated at reflux for 2 h before cooling to rt. 1 M HCl (80 mL) was added and the mixture was stirred at rt for 10 min before extracting with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **23a** as a brown oil which was used in the next step without further purification.



To a solution of **23a** (crude from previous step, <4.32 mmol) in THF (50 mL) was added NCS (519 mg, 3.89 mmol) at −78 ºC. The reaction mixture was stirred at −78 ºC for 25 min. The mixture was warmed to rt, quenched with $Na_2S_2O_3$ (50 mg), filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (7:1, petrol/EtOAc) to give **24a** (1.29 g, 65% over 3 steps) as an orange oil.

Data for 24a:

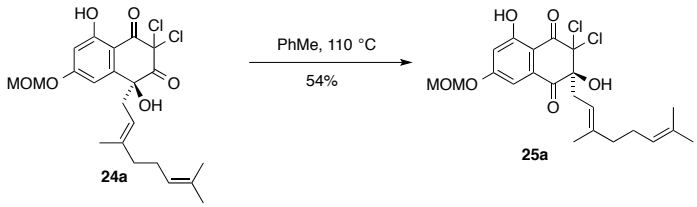
R_f = 0.35 (4:1, petrol/EtOAc)

IR (neat): 3478, 2969, 2916, 1747, 1619, 1571, 1444, 1375, 1289, 1253, 1148 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.61 (s, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 5.05 (t, *J* = 6.6 Hz, 1H), 4.99 (t, *J* = 7.1 Hz, 1H), 3.84 (s, 1H), 3.48 (s, 3H), 2.71 (dd, *J* = 14.6, 8.8 Hz, 1H), 2.62 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.10 – 1.99 (m, 4H), 1.70 (s, 3H), 1.59 (s, 3H), 1.50 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.9, 186.3, 166.3, 166.1, 145.0, 143.3, 131.9, 123.7, 115.0, 107.3, 105.8, 103.1, 94.1, 79.5, 77.8, 56.6, 45.4, 39.7, 26.1, 25.6, 17.6, 16.4.

HRMS (ESI): calculated for $C_{22}H_{27}Cl_2O_6$ 457.1185 $[M+H]^+$, found 457.1170.



A solution of **24a** (1.50 g, 3.28 mmol) in PhMe (150 mL) was stirred at 110 ºC for 20 h. The mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to give **25a** (802 mg, 54%) as a yellow oil.

Data for 25a:

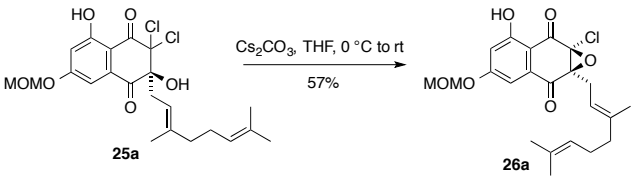
R_f = 0.55 (3:2, petrol/EtOAc)

IR (neat): 3478, 2969, 2916, 1748, 1619, 1571, 1487, 1375, 1289, 1253, 1148 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ11.43 (s, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 5.29 (d, *J* = 7.0 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 5.00 (t, *J* = 6.7 Hz, 1H), 4.88 (t, *J* = 7.9 Hz, 1H), 4.43 (s, 1H), 3.49 (s, 3H), 2.80 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.35 (dd, *J* = 14.2, 9.1 Hz, 1H), 2.00 – 1.85 (m, 4H), 1.70 (s, 3H), 1.58 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 187.1, 165.5, 164.6, 141.4, 133.3, 131.8, 123.6, 115.0, 109.6, 109.1, 108.0, 94.3, 90.4, 85.7, 56.7, 39.7, 36.3, 26.2, 25.6, 17.7, 16.0.

HRMS (ESI): calculated for $C_{22}H_{27}Cl_2O_6$ 457.1185 $[M+H]^+$, found 457.1176.



To a solution of **25a** (532 mg, 1.16 mmol) in THF (40 mL) was added Cs_2CO_3 (1.14 g, 3.49 mmol) at 0 ºC. The reaction was stirred at 0 ºC for 1 h. The mixture was then warmed to rt and stirred for a further 1.5 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to give **26a** (277 mg, 57%) as a yellow oil.

Data for 26a:

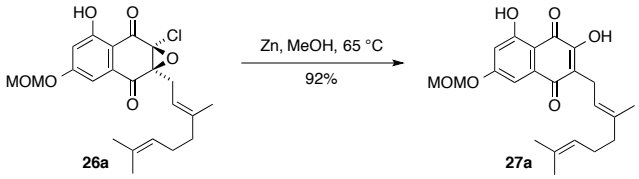
R_f = 0.50 (3:2, petrol/EtOAc)

IR (neat): 3108, 2967, 2923, 1699, 1664, 1609, 1488, 1380, 1280, 1146 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.47 (s, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 5.26 (d, *J* = 6.9 Hz, 1H), 5.24 (d, *J* = 6.9 Hz, 1H), 5.19 (t, *J* = 6.7 Hz, 1H), 5.03 (t, *J* = 6.9 Hz, 1H), 3.47 (s, 3H), 3.36 (dd, *J* = 14.6, 7.7 Hz, 1H), 2.67 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.10 – 1.99 (m, 4H), 1.78 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 187.33, 187.32, 164.9, 164.9, 164.4, 140.5, 133.5, 131.5, 123.9, 115.1, 109.9, 109.3, 107.9, 94.2, 80.9, 67.8, 56.6, 39.8, 26.4, 26.0, 25.6, 17.6, 16.6.

HRMS (ESI): calculated for $C_{22}H_{24}ClO_6$ 419.1261 $[M-H]^-$, found 419.1273.



To a solution of **26a** (560 mg, 1.33 mmol) in MeOH (50 mL) was added Zn powder (174 mg, 2.66 mmol) at rt. The reaction was stirred at 65 ºC for 15 min. The mixture was cooled to rt, quenched with saturated NH_4Cl solution (40 mL) and stirred for a further 10 min before extraction with EtOAc (3 × 30 mL). The combined organic extracts were washed sequentially with saturated NH_4Cl solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1 → 1:1, petrol/EtOAc gradient elution) to give **27a** (474 mg, 92%) as an orange solid.

Data for 27a:

R_f = 0.75 (2:1, petrol/EtOAc)

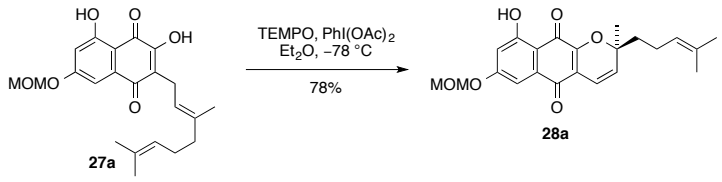
Mp = 114 - 116 °C

IR (neat): 3364, 2923, 1645, 1621, 1605, 1487, 1313, 1237, 1146 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.21 (s, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 5.26 (s, 2H), 5.17 (t, *J* = 7.0 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 3.48 (s, 3H), 3.27 (d, *J* = 7.3 Hz, 2H), 2.09 – 1.93 (m, 4H), 1.77 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 183.3, 182.9, 164.7, 163.7, 152.7, 137.3, 134.5, 131.4, 124.2, 123.8, 119.3, 110.0, 108.0, 107.1, 94.1, 56.6, 39.7, 26.6, 25.6, 22.5, 17.6, 16.2.

HRMS (ESI): calculated for $C_{22}H_{27}O_6$ 387.1808 $[M+H]^+$, found 387.1795.



To a solution of **27a** (452 mg, 1.17 mmol) in Et_2O (40 mL) was added $PhI(OAc)_2$ (416 mg, 1.29 mmol) and TEMPO (219 mg, 1.40 mmol) at −78 ºC. The reaction was stirred at −78 ºC for 1 h. The mixture was then warmed to rt and stirred overnight. The mixture was filtered through SiO_2, washing with Et_2O and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (9:1, petrol/EtOAc) to give **28a** (353 mg, 78%) as a red oil.

Data for 28a:

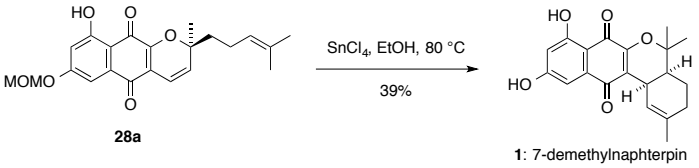
R_f = 0.50 (4:1, petrol/EtOAc)

IR (neat): 3363, 2970, 2925, 1646, 1621, 1573, 1487, 1387, 1378, 1315, 1237, 1147 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.06 (s, 1H), 7.26 (d, *J* = 2.5 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H), 5.64 (d, *J* = 10.1 Hz, 1H), 5.26 (s, 2H), 5.09 (t, *J* = 7.1 Hz, 1H), 3.49 (s, 3H), 2.19 – 2.05 (m, 2H), 1.95 (ddd, *J* = 14.3, 10.0, 6.5 Hz, 1H), 1.69 (ddd, *J* = 14.2, 10.3, 5.7 Hz, 1H), 1.63 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 182.8, 180.6, 164.1, 163.8, 153.0, 133.3, 132.3, 129.4, 123.3, 117.6, 115.9, 109.7, 109.1, 107.8, 94.1, 83.4, 56.5, 41.6, 27.5, 25.6, 22.6, 17.7.

HRMS (ESI): calculated for $C_{22}H_{25}O_6$ 385.1651 $[M+H]^+$, found 385.1643.



To a solution of **28a** (20 mg, 0.059 mmol) in EtOH was added $SnCl_4$ (3 drops) at rt. The reaction was stirred at 80 ºC for 1.5 h. The mixture was cooled to rt, quenched with 1 M HCl solution (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to give a 4:1 mixture of 7-demethylnaphterpin **1** to an unknown impurity (16 mg, 77%). Recrystallisation from EtOAc gave 7-demethylnaphterpin **1** (8 mg, 39% overall yield) as an orange solid.

Data for 1:

R_f = 0.60 (1:1, petrol/EtOAc)

Mp = 255 - 257 ºC

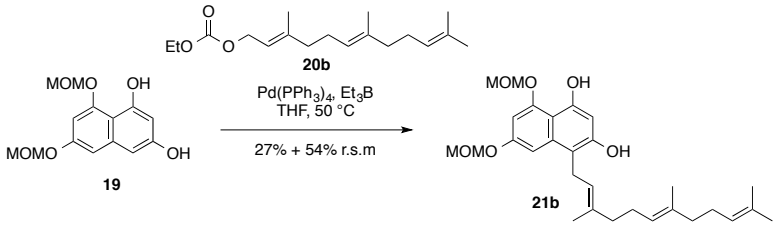
IR (neat): 3344, 2921, 1625, 1600, 1572, 1458, 1335, 1285, 1220, 1159, 1126 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.91 (s, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.89 (s, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 6.03 (d, *J* = 4.0 Hz, 1H), 3.49 (s, 1H), 2.02 – 1.95 (m, 2H), 1.93 (m, 1H), 1.77 (ddd, *J* = 12.1, 6.1, 2.8 Hz, 1H), 1.67 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.33 – 1.28 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 184.0, 183.0, 164.4, 163.4, 153.2, 136.2, 134.8, 123.7, 119.9, 108.7, 108.6, 107.3, 80.8, 39.7, 31.1, 29.7, 25.6, 25.0, 23.6, 20.4.

HRMS (ESI): calculated for $C_{20}H_{19}O_5$ 339.1232 $[M-H]^-$, found 339.1238.

Synthesis of debromomarinone



A solution of **19** (12.0 g, 42.8 mmol), ethyl farnesyl carbonate **20b** (12.7 g, 42.8 mmol) and $Pd(PPh_3)_4$ (2.48 g, 2.15 mmol) in THF (125 mL) was degassed. Et_3B (1.0 M in THF, 65.0 mL, 65.0 mmol) was then added at the resultant mixture was stirred at 50 ºC for 2 h. The mixture was cooled, quenched with *sat.* NH_4Cl solution (150 mL) and extracted with Et_2O (2 x 100). The combined organics were washed with brine (200 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 5:1 → 3:1 gradient elution) to give **21b** (5.64 g, 27%) as brown oil along with recovered starting material (6.49 g, 54%).

Data for 21b:

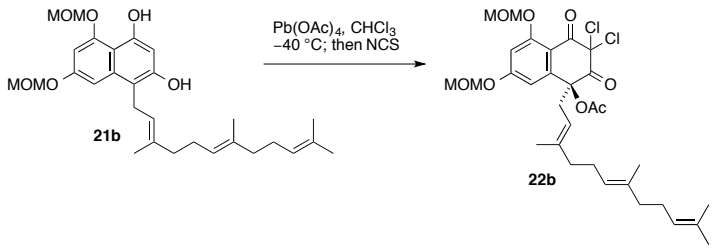
R_f = 0.25 (3:1, petrol/EtOAc)

IR (neat): 3373, 2913, 1623, 1378, 1287, 1138, 1022, 910, 832 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H), 7.09 (d, *J* = 2.1 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.45 (s, 1H), 6.08 (s, 1H), 5.40 (s, 2H), 5.27 (s, 2H), 5.23 (t, *J* = 6.1 Hz, 1H), 5.11 (t, *J* = 6.6 Hz, 1H), 5.09 (t, *J* = 7.0 Hz, 1H), 3.61 (d, *J* = 6.8 Hz, 2H), 3.57 (s, 3H), 3.54 (s, 3H), 2.14 – 1.94 (m, 8H), 1.90 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 155.2, 153.7, 153.1, 136.8, 136.0, 135.0, 131.1, 124.4, 124.1, 123.1, 110.4, 107.2, 101.2, 100.5, 98.7, 95.7, 94.5, 56.8, 56.1, 39.7, 39.7, 26.7, 26.6, 25.7, 24.3, 17.6, 16.3, 16.0.

HRMS (ESI): calculated for $C_{29}H_{40}O_6Na$ 507.2717 $[M+Na]^+$, found 507.2721.



To a solution of **21b** (11.0 g, 22.7 mmol) in $CHCl_3$ (150 mL) was addded $Pb(OAc)_4$ (10.6 g, 23.8 mmol) portion wise at – 20 ºC. The mixture was stirred at – 20 ºC for 5 min before NCS (5.76 g, 43.4 mmol) was added portion wise at – 20 ºC. The mixture was stirred at – 20 ºC for a further 20 min before $Na_2S_2O_3$ (100 mg) was added. The mixture was warmed to rt, filtered through a short pad of SiO2 and concentrated *in \vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to give **22b** as a yellow oil (8.70 g, 63%).

Data for 22b:

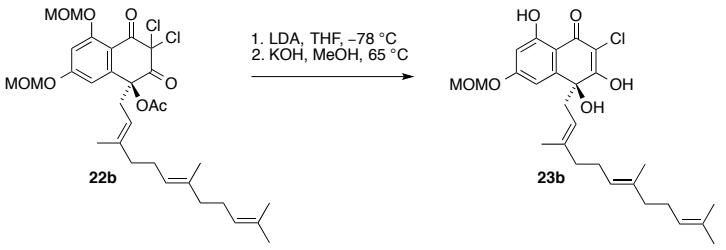
R_f = 0.20 (3:1, petrol/EtOAc)

IR (neat): 2915, 1753, 1719, 1600, 1324, 1225, 1147, 1019, 973 cm^{-1}.

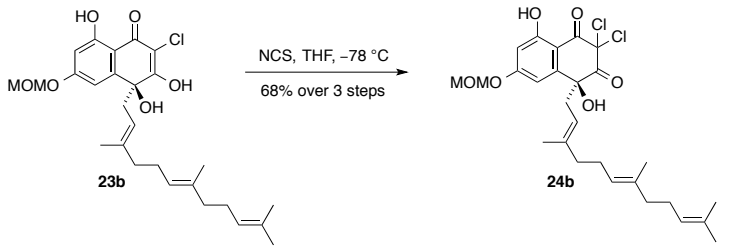
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 6.9 Hz, 1H), 5.23 (d, *J* = 7.0 Hz, 1H), 5.20 (d, *J* = 7.0 Hz, 1H), 5.07 (t, *J* = 6.1 Hz, 1H), 5.05 (t, *J* = 6.9 Hz, 1H), 4.92 (t, *J* = 7.8 Hz, 1H), 3.53 (s, 3H), 3.48 (s, 3H), 2.96 (dd, *J* = 14.2, 8.1 Hz, 1H), 2.72 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.14 (s, 3H), 2.08 – 1.89 (m, 8H), 1.67 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 178.6, 169.3, 162.9, 159.9, 143.6, 142.1, 135.5, 131.5, 124.5, 123.9, 113.8, 113.8, 105.5, 104.2, 95.1, 94.5, 82.3, 81.6, 56.8, 56.7, 40.5, 40.0, 39.8, 26.9, 26.2, 25.8, 20.6, 17.8, 16.5, 16.1.

HRMS (ESI): calculated for $C_{31}H_{40}Cl_2O_8Na$ 633.1992 $[M+Na]^+$, found 633.1987.



To a solution of **22b** (11.2 g, 18.3 mmol) in THF (150 mL), was added LDA (2.0 M in THF, 27.5 mL, 54.9 mmol) at −78 ºC. The mixture was stirred at −78 ºC for 30 min. The mixture was quenched with 1 M HCl (150 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant yellow oil was dissolved in MeOH (150 mL), and KOH (4.11 g, 73.2 mmol) was added at rt. The mixture was heated at reflux for 2 h before cooling to rt. 1 M HCl (150 mL) was added and the mixture was stirred at rt for 10 min before extracting with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **23b** as a brown oil which was used in the next step without further purification.



To a solution of **23b** (crude from previous step, <18.3 mmol) in THF (100 mL) at −78 ºC was added NCS (2.44 mg, 18.3 mmol). The reaction mixture was stirred at −78 ºC for 25 min. The mixture was warmed to rt, quenched with $Na_2S_2O_3$ (100 mg), filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (8:1, petrol/EtOAc) to give **24b** as an orange oil (6.50 g, 68% over 3 steps).

Data for 24b:

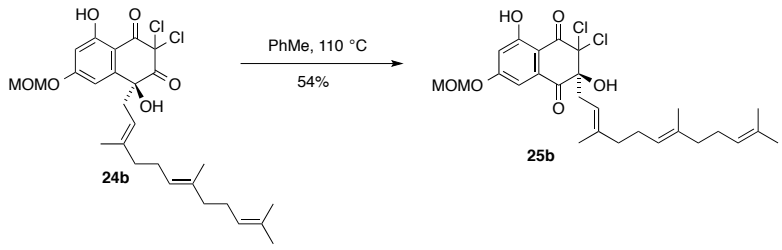
R_f = 0.40 (3:1, petrol/EtOAc)

IR (neat): 3388, 2923, 1748, 1622, 1452, 1105, 1163, 857, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.62 (s, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.25 (d, *J* = 6.8 Hz, 1H), 5.09 (t, *J* = 6.6 Hz, 1H), 5.08 (t, *J* = 6.8 Hz, 2H), 5.01 (t, *J* = 7.5 Hz, 2H), 3.77 (s, 1H), 3.49 (s, 3H), 2.73 (dd, *J* = 14.7, 8.8 Hz, 1H), 2.63 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.11 – 1.98 (m, 8H), 1.68 (s, 3H), 1.61 (s, 6H), 1.52 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.2, 186.6, 166.5, 166.4, 145.2, 143.7, 135.9, 131.5, 124.5, 123.7, 115.1, 107.6, 106.1, 103.4, 94.4, 79.7, 78.0, 56.9, 45.7, 40.0, 39.8, 26.9, 26.4, 25.9, 17.8, 16.8, 16.2.

HRMS (ESI): calculated for $C_{27}H_{33}Cl_2O_6$ 523.1660 $[M-H]^-$, found 523.1658.



A solution of **24b** (1.07 g, 2.04 mmol) in PhMe (120 mL) was stirred at 110 ºC for 16 h. The mixture was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to give **25b** as a yellow oil (574 mg, 54%).

Data for 25b:

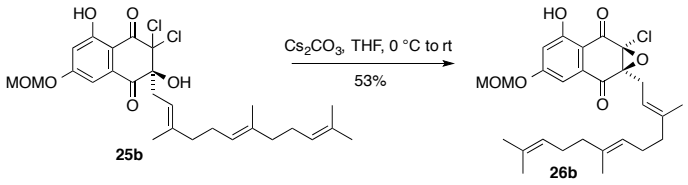
R_f = 0.45 (3:1, petrol/EtOAc)

IR (neat): 3380, 2917, 1712, 1656, 1614, 1580, 1349, 1248, 1096, 810 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.44 (s, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 5.30 (d, *J* = 6.9 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 5.09 (t, *J* = 7.1 Hz, 1H), 5.03 (t, *J* = 6.8 Hz, 1H), 4.89 (t, *J* = 7.8 Hz, 1H), 4.44 (s, 1H), 3.49 (s, 3H), 2.80 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.36 (dd, *J* = 14.5, 8.8 Hz, 1H), 2.10 – 1.86 (m, 8H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.81, 187.21, 165.61, 164.73, 141.61, 135.59, 133.46, 131.44, 124.43, 123.65, 115.14, 109.78, 109.28, 109.24, 108.17, 94.47, 90.60, 85.81, 56.84, 39.83, 39.80, 26.85, 26.38, 25.82, 17.81, 16.17, 16.11.

HRMS (ESI): calculated for $C_{27}H_{34}Cl_2O_6Na$ 547.1625 $[M+Na]^+$, found 547.1607.



To a solution of **25b** (576 mg, 1.10 mmol) in THF (30 mL) was added Cs_2CO_3 (1.07 g, 3.29 mmol) at 0 ºC. The reaction was stirred at 0 ºC for 1.5 h. The mixture was then warmed to rt and stirred for a further 1.5 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (9:1, petrol/EtOAc) to give **26b** (286 mg, 53%) as a yellow oil.

Data for 26b:

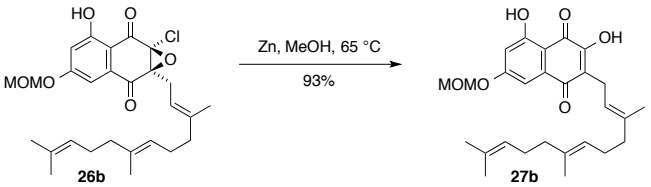
R_f = 0.50 (3:1, petrol/EtOAc)

IR (neat): 2915, 1703, 1662, 1612, 1375, 1148, 1076, 1019, 950, 826 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.46 (s, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 5.26 (d, *J* = 6.9 Hz, 1H), 5.24 (d, *J* = 6.9 Hz, 1H), 5.19 (t, *J* = 6.9 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 5.03 (t, *J* = 7.0 Hz, 1H), 3.47 (s, 3H), 3.35 (dd, *J* = 14.6, 7.7 Hz, 1H), 2.67 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.13 – 1.86 (m, 8H), 1.78 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 187.50, 187.47, 165.1, 164.6, 140.7, 135.3, 133.6, 131.4, 124.4, 123.9, 115.3, 110.1, 109.5, 108.1, 94.4, 81.1, 68.0, 56.8, 39.9, 39.8, 26.9, 26.4, 26.2, 25.8, 17.8, 16.8, 16.2.

HRMS (ESI): calculated for $C_{27}H_{33}Cl_2O_6$ 523.1660 $[M+Cl]^+$, found 523.1666



To a solution of **26b** (190 mg, 0.389 mmol) in MeOH (8 mL) was added Zn powder (50 mg, 0.76 mmol) at rt. The reaction was stirred at 65 ºC for 15 min. The mixture was cooled to rt, quenched with 1 M HCl solution (20 mL) and stirred for a further 10 min before extraction with EtOAc (3 × 10 mL). The combined organic extracts were washed sequentially with 1 M HCl (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (6:1 petrol/EtOAc) to give **27b** (163 mg, 93%) as a yellow solid.

Data for 27b:

R_f = 0.35 (3:1, petrol/EtOAc)

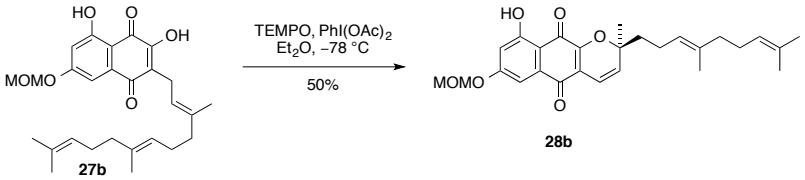
Mp: 96 - 101 °C

IR (neat): 3368, 3123, 2918, 1646, 1620, 1606, 1571, 1486, 1314, 1238, 1146, 1081, 952, 756, 639 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.21 (s, 1H), 7.35 (s, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 2.3 Hz, 1H), 5.26 (s, 2H), 5.18 (t, *J* = 6.8 Hz, 1H), 5.06 (t, *J* = 7.0 Hz, 1H), 5.04 (t, *J* = 8.5 Hz, 1H), 3.48 (s, 3H), 3.27 (d, *J* = 7.4 Hz, 2H), 2.10 – 1.88 (m, 8H), 1.78 (s, 3H), 1.66 (s, 3H), 1.56 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 183.5, 183.0, 164.8, 163.9, 152.9, 137.5, 135.1, 134.7, 131.3, 124.5, 124.1, 124.0, 119.5, 110.1, 108.2, 107.3, 94.3, 56.7, 39.8, 39.8, 26.9, 26.6, 25.8, 22.7, 17.8, 16.4, 16.1.

HRMS (ESI): calculated for $C_{27}H_{35}O_6$ 455.2428 $[M+H]^+$, found 455.2429.



To a solution of **27b** (163 mg, 0.359 mmol) in Et_2O (10 mL) was added $PhI(OAc)_2$ (126 mg, 0.394 mmol) and TEMPO (67 mg, 0.43 mmol) at −78 ºC. The reaction was stirred at −78 ºC for 1 h. The mixture was then warmed to rt and stirred for a further 16 h. The mixture was filtered through SiO_2, washing with Et_2O and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (10:1, petrol/EtOAc) to give **28b** (81 mg, 50%) as a red oil.

Data for 28b:

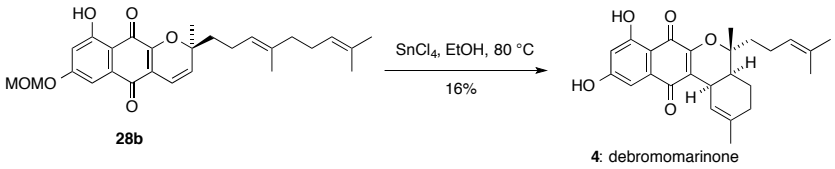
R_f = 0.45 (3:1, petrol/EtOAc)

IR (neat): 2916, 1646, 1620, 1573, 1377, 1316, 1224, 1146, 940, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.05 (s, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H), 5.65 (d, *J* = 10.1 Hz, 1H), 5.25 (s, 2H), 5.10 (t, *J* = 6.8 Hz, 1H), 5.06 (t, *J* = 6.9 Hz, 1H), 3.48 (s, 3H), 2.17 – 2.11 (m, 2H), 2.07 – 1.90 (m, 5H), 1.74 – 1.68 (m, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 182.8, 180.6, 164.1, 163.8, 153.0, 136.0, 133.3, 131.4, 129.5, 124.2, 123.1, 117.7, 115.9, 109.7, 109.2, 107.9, 94.1, 83.4, 56.5, 41.6, 39.6, 27.5, 26.6, 25.7, 22.5, 17.6, 16.0.

HRMS (ESI): calculated for $C_{27}H_{33}O_6$ 453.2272 $[M+H]^+$, found 453.2277.



To a solution of **28b** (81 mg, 0.18 mmol) in EtOH (8 mL) was added $SnCl_4$ (3 drops) at rt. The reaction was stirred at 80 ºC for 3 h. The mixture was cooled to rt, quenched with 1 M HCl solution (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to give debromomarinone **4** (12 mg, 16%) as an orange solid.

Data for 4:

R_f = 0.30 (3:1, petrol/EtOAc)

Mp: 83 – 88 °C

IR (neat): 3296, 2923, 1630, 1586, 1324, 1221, 1160, 1007, 768 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.90 (s, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.03 (d, *J* = 4.3 Hz, 1H), 5.02 (t, *J* = 7.0 Hz, 1H), 3.46 (t, *J* = 5.9 Hz, 1H), 2.10 – 1.89 (m, 5H), 1.89 (dddd, *J* = 12.0, 5.8, 3.0 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H), 1.38 – 1.30 (m, 1H).

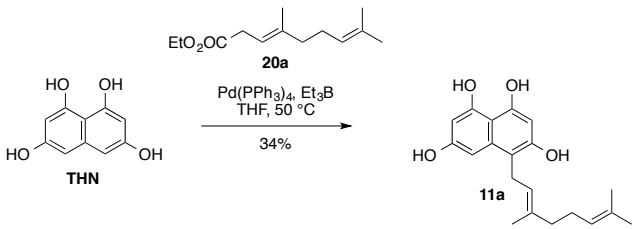
^{13}C NMR (125 MHz, $CDCl_3$): δ 184.3, 183.0, 164.6, 163.9, 153.4, 136.4, 134.9, 132.6, 124.1, 123.3, 120.1, 109.0, 108.7, 107.5, 83.3, 37.5, 36.9, 31.0, 29.9, 25.7, 23.7, 22.8, 22.4, 20.4, 17.8.

^{1}H NMR (500 MHz, CD_3OD): δ 6.96 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.01 (d, *J* = 5.0 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 3.41 (t, *J* = 5.9 Hz, 2H), 2.14 – 1.92 (m, 5H), 1.90 (ddd, *J* = 11.7, 6.1, 2.8 Hz, 1H), 1.70 – 1.60 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.33 – 1.25 (m, 2H).

^{13}C NMR (125 MHz, CD_3OD): δ 184.8, 183.9, 167.0, 165.6, 154.2, 136.9, 136.1, 132.9, 124.9, 124.8, 121.4, 109.6, 108.8, 107.3, 83.9, 39.0, 37.6, 32.2, 30.6, 25.8, 23.7, 23.2, 22.6, 21.4, 17.6.

HRMS (ESI): calculated for $C_{25}H_{29}O_5$ 409.2010 $[M+H]^+$, found 409.2017

Synthesis of biosynthetic intermediates



A solution of THN[2] (318 mg, 1.66 mmol), ethyl geranyl carbonate (**20a**) (250 mg, 1.10 mmol) and $Pd(PPh_3)_4$ (64 mg, 0.055 mmol) in THF (4 mL) was degassed. Et_3B (1.0 M in THF, 1.66 mL, 1.66 mmol) was then added and the resultant mixture was stirred at 50 °C for 2 days under an Ar atmosphere. The mixture was cooled, quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated using cold hexanes, and further purified via silica flash chromatography under an Ar atmosphere (4:1 petrol/EtOAc, 1.25% AcOH), to yield **11a** (124 mg, 34%) as a light brown powder.

Data for 11a:

R_f = 0.45 (1:1 petrol/EtOAc, 1.25% AcOH)

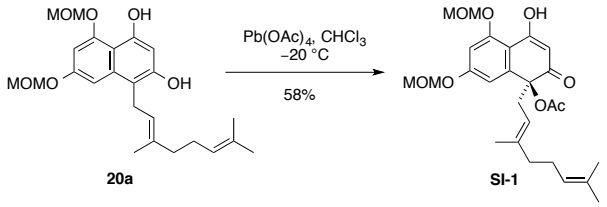
IR (EtOAc cast): 3391 (br), 2974, 2922, 1623, 1528, 1480, 1377, 1295, 1213, 1158 cm^{-1}

^{1}H NMR (600 MHz, d_6-DMSO): δ 10.64 (s 1H), 9.11 (s, 1H), 8.96 (s, 1H), 8.32 (s, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.00 (s, 1H), 5.90 (d, *J* = 1.9 Hz, 1H), 5.08-5.01 (m, 2H), 3.31 (d, *J* = 6.5 Hz, 2H), 2.02-1.96 (m, 2H), 1.92-1.88 (m, 2H), 1.77 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H).

^{13}C NMR (150 MHz, d_6-DMSO): δ 157.4, 154.1, 153.8, 151.5, 135.9, 133.0, 130.7, 129.2, 124.4, 124.2, 110.0, 107.0, 106.7, 96.6, 40.1, 26.3, 25.5, 23.4, 17.6, 16.2.

HRMS (ESI): calculated for $C_{20}H_{23}O_4$ 327.1602 $[M-H]^-$, found 327.1603.

[2] THN prepared according to: M. Pittelkow, U. Boas, J. B. Christensen, *Org. Lett.* **2006**, *8*, 5817.



To a solution of **20a** (2.05 g, 5.04 mmol) in $CHCl_3$ (40 mL) was added $Pb(OAc)_4$ (2.35 g, 5.30 mmol) portion-wise at -20 °C. The mixture was stirred at -20 °C for 5 min before slowly warming to rt. The mixture was filtered through a short pad of SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (petrol/EtOAc, 2:1) to yield **SI-1** (1.40 g, 58%) as a yellow oil.

Data for SI-1:

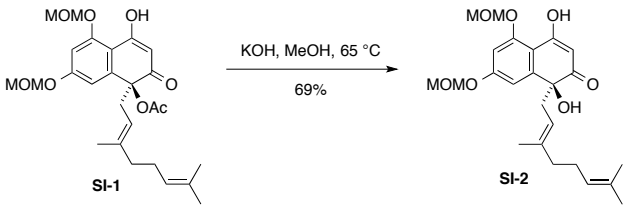
R_f = 0.20 (1:1 petrol/EtOAc)

IR (neat): 3316, 2919, 1744, 1634, 1600, 1232, 1149, 1016, 966 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 5.66 (s, 1H), 5.36 (s, 2H), 5.19 (d, *J* = 7.0 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 5.04 (t, *J* = 6.8 Hz, 1H), 4.92 (t, *J* = 7.4 Hz, 1H), 3.56 (s, 3H), 3.47 (s, 3H), 2.69 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.60 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.13 (s, 3H), 1.98 – 1.85 (m, 4H), 1.67 (s, 3H), 1.57 (s, 3H), 1.31 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 195.1, 169.2, 167.6, 159.9, 155.6, 147.0, 140.8, 131.5, 124.0, 115.0, 109.5, 107.9, 103.0, 102.2, 96.4, 94.3, 81.8, 57.2, 56.4, 40.9, 39.9, 26.8, 25.6, 21.0, 17.6, 15.9.

HRMS (ESI): calculated for $C_{26}H_{35}O_8$ 475.2332 $[M+H]^+$, found 475.2331.



To a solution of **SI-1** (1.40 g, 2.95 mmol) in MeOH (40 mL) was added KOH (662 mg, 11.8 mmol). The mixture was heated at reflux for 2 h. The mixture was cooled, quenched with 0.5 M HCl (50 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol/EtOAc, 2:1) to yield **SI-2** (888 mg, 69%) as a yellow oil.

Data for SI-2:

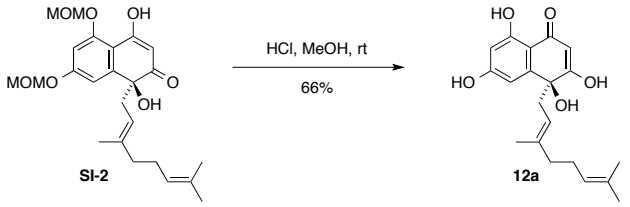
R_f = 0.35 (1:1 petrol/EtOAc)

IR (neat): 3440, 3313, 1629, 1597, 1425, 1147, 1015, 964 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 5.57 (s, 1H), 5.38 (s, 2H), 5.26 (d, *J* = 5.8 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.07 (t, *J* = 7.6 Hz, 1H), 5.01 (t, *J* = 7.8 Hz, 1H), 4.02 (s, 1H), 3.56 (s, 3H), 3.49 (s, 3H), 2.51 – 2.41 (m, 2H), 2.07 – 1.90 (m, 4H), 1.68 (s, 3H), 1.59 (s, 3H), 1.35 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 204.1, 200.7, 188.8, 168.7, 162.7, 160.1, 159.0, 155.6, 148.8, 148.6, 140.7, 140.3, 131.8, 131.4, 124.1, 123.7, 116.8, 116.4, 109.1, 108.2, 105.9, 103.7, 102.1, 100.0, 96.3, 95.2, 94.2, 94.1, 80.4, 78.9, 57.2, 56.6, 56.5, 56.4, 50.6, 45.8, 43.0, 39.9, 39.7, 26.8, 26.3, 25.6, 25.6, 17.7, 17.6, 16.3, 15.9.

HRMS (ESI): calculated for $C_{34}H_{31}O_7$ 431.2075 $[M-H]^-$, found 431.2081.



To a solution of **SI-2** (98 mg, 0.23 mmol) in MeOH (4 mL) was added 32% HCl (0.4 mL). The mixture was stirred at rt for 16 h. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol /EtOAc, 2:1) to yield pure **12a (**52 mg, 66%) as a brown solid.

Data for 12a:

R_f = 0.05 (1:1 petrol/EtOAc)

Mp: 100 – 104 °C

IR (neat): 3254, 2915, 1590, 1231, 1157, 1007 cm^{-1}

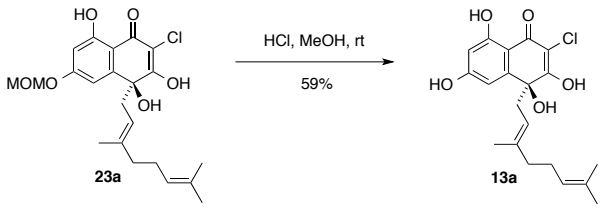
major tautomer

^{1}H-NMR (500 MHz, acetone-d_6) δ 13.24 (s, 1H), 12.53 (s, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 5.55 (s, 1H), 4.98 (t, *J* = 6.7 Hz, 1H), 4.69 (t, *J* = 7.4 Hz, 1H), 2.91 (dd, *J* = 13.1, 8.2 Hz, 1H), 2.55 (dd, *J* = 13.1, 7.4 Hz, 1H), 1.91 – 1.78 (m, 4H), 1.62 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H).

all peaks

^{13}C-NMR (125 MHz, acetone-d_6) δ 192.7, 178.4, 166.1, 165.4, 151.2, 142.3, 133.6, 126.7, 120.0, 119.8, 119.5, 111.0, 108.7, 107.7, 107.4, 105.3, 104.7, 104.4, 104.1, 76.1, 52.6, 46.2, 45.4, 45.2, 42.4, 29.2, 29.0, 27.5, 19.5, 18.2, 17.9.

HRMS (ESI): calculated for $C_{20}H_{23}O_5$ 343.1551 $[M-H]^-$, found 343.1161.



To a solution of **23a** (326 mg, 0.698 mmol) in MeOH (8 mL), was added 32% HCl (0.8 mL). The mixture was stirred at rt for 16 h. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated with cold CH_2Cl_2 to yield **13a** (163 mg, 59%) as an off white solid.

Data for 13a:

R_f = 0.05 (6:1 CH_2Cl_2/MeOH)

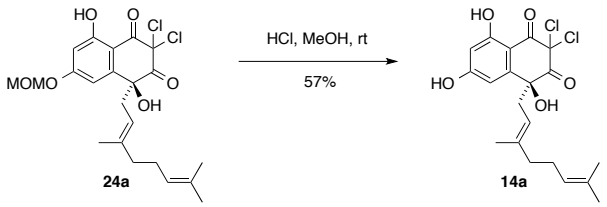
Mp: 172 − 175 °C

IR (neat): 3340, 3159, 2925, 1645, 1604, 1587, 1455, 1323, 1206, 1147, 1009, 829 cm^{-1}.

^{1}H-NMR (500 MHz, d_6-acetone): δ 13.02 (s, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.27 (d, *J* = 2.3 Hz, 1H), 4.99 (t, *J* = 6.9 Hz, 1H), 4.62 (t, *J* = 7.5 Hz, 1H), 2.94 (dd, *J* = 13.1, 8.6 Hz, 1H), 2.52 (dd, *J* = 13.1, 7.4 Hz, 1H), 1.93 – 1.75 (m, 4H), 1.62 (s, 3H), 1.54 (s, 3H), 1.38 (s, 3H).

^{13}C-NMR (125 MHz, d_6-acetone): δ 183.7, 164.0, 163.7, 148.1, 141.4, 131.8, 124.9, 118.0, 117.2, 108.6, 105.9, 102.6, 76.3, 44.4, 40.6, 27.5, 25.7, 17.6, 16.0.

HRMS (ESI): calculated for $C_{20}H_{22}ClO_5$ 377.1161 $[M-H]^-$, found 377.1170.



To a solution of **24a** (110 mg, 0.24 mmol) in MeOH (4 mL), was added 32% HCl (0.4 mL) at rt. The mixture was stirred at rt for 24 h. The mixture was diluted with brine (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (9:1 → 4:1, petrol/EtOAc gradient elution) to yield **14a** (57 mg, 57%) as a pale yellow oil.

Data for 14a:

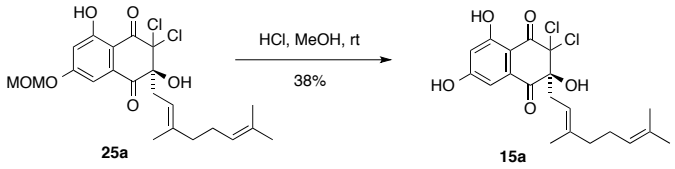
R_f = 0.20 (petrol/EtOAc, 3:1)

IR (neat): 3376, 2918, 1748, 1621, 1585, 1453, 1309, 1258, 1164, 856 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ 11.70 (s, 1H), 6.95 (s, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 5.07 (t, *J* = 6.5 Hz, 1H), 5.00 (t, J = 7.0 Hz, 1H), 3.86 (s, 1H), 2.73 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.65 (dd, *J* = 14.6, 6.1 Hz, 1H), 2.15 – 2.01 (m, 4H), 1.72 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ 193.9, 186.2, 166.6, 166.0, 145.7, 143.7, 132.2, 123.7, 115.0, 106.9, 105.4, 103.4, 79.5, 77.9, 45.5, 39.8, 26.2, 25.7, 17.7, 16.5

HRMS (ESI): calculated for $C_{20}H_{23}Cl_2O_5$ 413.0923 $[M+H]^+$, found 413.0898.



To a solution of **25a** (230 mg, 0.503 mmol) in MeOH (10 mL), was added 32% HCl (1.0 mL) at rt. The mixture was stirred at rt for 40 h. The mixture was diluted with brine (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (9:1, petrol/EtOAc) to yield **15a** (79 mg, 38%) as an orange oil.

Data for 15a:

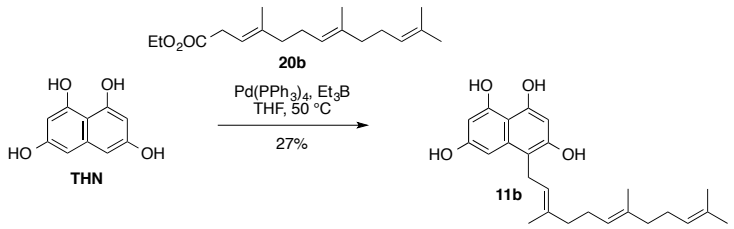
R_f = 0.30 (petrol/EtOAc, 3:1)

IR (neat): 3377, 2919, 1712, 1656, 1613, 1580, 1350, 1248, 1172, 1095, 810 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ 11.46 (s, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.64 (s, 1H), 6.56 (s, 1H), 5.00 (t, *J* = 6.7 Hz, 1H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.44 (s, 1H), 2.81 (dd, *J* = 14.5, 6.2 Hz, 1H), 2.37 (dd, *J* = 14.2, 8.5 Hz, 1H), 2.03 – 1.83 (m, 4H), 1.70 (s, 3H), 1.59 (s, 3H), 1.24 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 193.7, 186.9, 165.7, 163.9, 141.6, 133.7, 131.9, 123.6, 114.9, 109.4, 108.5, 107.7, 90.4, 85.7, 39.7, 36.3, 26.2, 25.7, 17.7, 16.1.

HRMS (ESI): calculated for $C_{20}H_{23}Cl_2O_5$ 413.0923 $[M+H]^+$, found 413.0914.



A solution of THN (220 mg, 1.14 mmol), ethyl farnesyl carbonate (**20b**) (336 mg, 1.14 mmol) and $Pd(PPh_3)_4$ (69 mg, 0.057 mmol) in THF (10 mL) was degassed. Et_3B (1.0 M in THF, 1.71 mL, 1.71 mmol) was then added and the resultant mixture was stirred at 50 °C for 18 h under an Ar atmosphere. The mixture was cooled, quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified via silica flash chromatography under an Ar atmosphere (5:1 → 2:1 petrol/EtOAc, 1.25% AcOH), to yield **11b** (122 mg, 27%) as a brown oil.

Data for 11b:

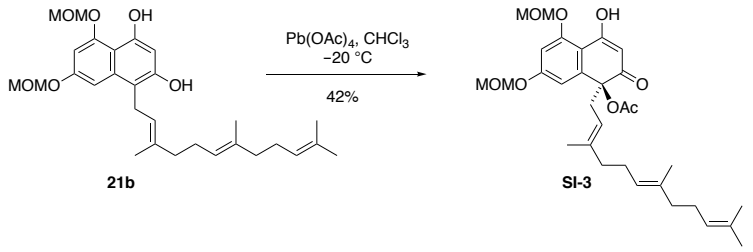
R_f = 0.45 (1:1, petrol/EtOAc, 1.25% AcOH)

IR (neat): 3337 (br), 2973, 1607, 1377, 1273, 1088, 1046, 879 cm^{-1}.

^{1}H NMR (600 MHz, d_6-DMSO): **δ** 9.09 (s, 1H), 8.95 (s, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 6.01 (s, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.10 – 5.02 (m, 3H), 3.33 (d, *J* = 6.7 Hz, 2H), 2.04 – 1.93 (m, 4H), 1.93 – 1.86 (m, 4H), 1.78 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H), 1.53 (s, 3H).

^{13}C NMR (150 MHz, d_6-DMSO): **δ** 157.4, 154.1, 153.8, 151.5, 135.9, 134.3, 133.0, 130.6, 124.4, 124.2, 124.0, 107.1, 106.9, 96.7, 96.6, 95.8, 26.4, 26.2, 25.6, 17.6, 16.2, 15.8.

HRMS (ESI): calculated for $C_{25}H_{32}O_4H$ 379.2379 $[M+H]^+$, found 379.2371.



To a solution of **21b** (660 mg, 1.36 mmol) in $CHCl_3$ (20 mL) was added $Pb(OAc)_4$ (634mg, 1.43 mmol) at −20 °C. The mixture was stirred at −20 °C for 5 min. The mixture was filtered through SiO_2 and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (2:1, petrol/EtOAc) to yield **SI-3** (309 mg, 42%) as a yellow oil.

Data for SI-3:

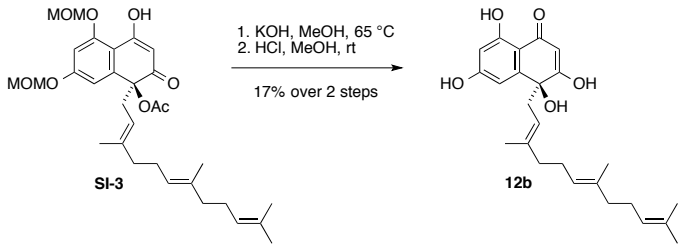
R_f = 0.10 (petrol/EtOAc, 1:1)

IR (neat): 3320, 2917, 1745, 1635, 1601, 1427, 1233, 1149, 1017, 967 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 5.66 (s, 1H), 5.36 (s, 2H), 5.17 (s, 2H), 5.07 (t, *J* = 6.9 Hz, 1H), 5.05 (t, *J* = 7.3 Hz, 1H), 4.93 (t, *J* = 7.7 Hz, 1H), 3.56 (s, 3H), 3.46 (s, 3H), 2.68 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.60 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.12 (s, 3H), 2.07 – 1.86 (m, 8H), 1.67 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.31 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 195.2, 169.3, 167.8, 160.1, 155.7, 147.1, 141.1, 135.3, 131.4, 124.4, 124.1, 115.1, 109.6, 108.0, 103.1, 102.3, 96.5, 94.4, 81.9, 57.4, 56.5, 41.0, 40.1, 39.8, 27.0, 26.9, 25.8, 21.1, 17.8, 16.1, 16.0.

HRMS (ESI): calculated for $C_{31}H_{43}O_8$ 543.2953 $[M+H]^+$, found 543.2959.



To a solution of **SI-3** (263 mg, 0.485 mmol) in MeOH (10 mL) was added KOH (109 mg, 1.94 mg) at rt. The mixture was heated at 65 °C for 4 h. The mixture was cooled, quenched with 1 M HCl (20 mL) and extracted with EtOAc (3 x10 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (8 mL), 32% HCl (0.8 mL) was added and the mixture was stirred at rt for 16 h. The mixture was diluted with 1 M HCl (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated with cold CH_2Cl_2 to yield **12b** (33 mg, 17%) as a pale brown solid.

Data for 12b:

R_f = 0.15 (CH_2Cl_2/MeOH, 20:1)

Mp = 122 -126 °C

IR (neat): 3176, 2916, 1589, 1452, 1376, 1160, 1115, 1007, 851 cm^{-1}

major tautomer

^{1}H-NMR (500 MHz, $CDCl_3$): δ 13.23 (s, 1H), 9.86 (s, 2H), 9.12 (s, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 1H), 5.55 (s, 1H), 5.07 (t, *J* = 6.8 Hz, 1H), 5.02 (t, *J* = 6.6 Hz, 1H), 4.70 (t, *J* = 7.6 Hz, 1H), 2.91 (dd, *J* = 13.2, 8.3 Hz, 1H), 2.55 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.11 – 1.78 (m, 8H), 1.64 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.40 (s, 3H).

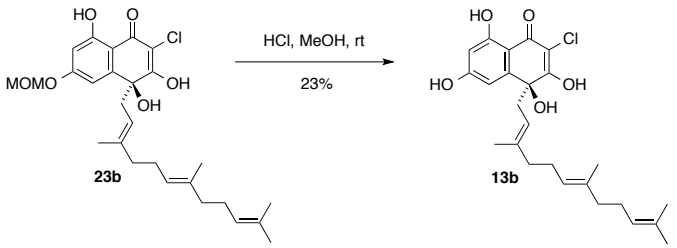
minor tautomer

^{1}H-NMR (500 MHz, $CDCl_3$): δ 12.53 (s, 1H), 9.86 (s, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.17 (t, *J* = 7.6 Hz, 1H), 5.10 (t, *J* = 6.8 Hz, 1H), 5.08 (t, *J* = 6.6 Hz, 1H), 4.08 (d, *J* = 19.4 Hz, 1H), 3.48 (d, *J* = 19.3 Hz, 1H), 2.72 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.64 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.11 – 1.78 (m, 8H), 1.65 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H).

all peaks

^{13}C-NMR (125 MHz, $CDCl_3$): δ 204.0, 197.0, 190.9, 176.6, 166.4, 166.0, 164.3, 163.6, 150.6, 149.4, 140.8, 140.7, 135.8, 135.6, 131.6, 131.5, 125.2, 125.2, 124.9, 124.8, 124.8, 118.0, 117.7, 109.2, 106.9, 105.9, 103.5, 102.6, 102.3, 81.0, 74.4, 50.8, 43.6, 43.4, 40.6, 40.6, 40.4, 40.4, 32.7, 27.5, 27.4, 27.2, 25.8, 25.3, 17.8, 17.7, 16.4, 16.2, 16.1, 16.0.

HRMS (ESI): calculated for $C_{25}H_{33}O_5$ 413.2328 $[M+H]^+$, found 413.2323.



To a solution of **23b** (333 mg, 0.745 mmol) in MeOH (12 mL), was added 32% HCl (1.2 mL) at rt. The mixture was stirred at rt for 16 h. The mixture was diluted with 1 M HCl (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated with cold CH_2Cl_2 to yield **13b** (76 mg, 23%) as a pale brown solid.

Data for 13b:

R_f = 0.05 (CH_2Cl_2/MeOH, 10:1)

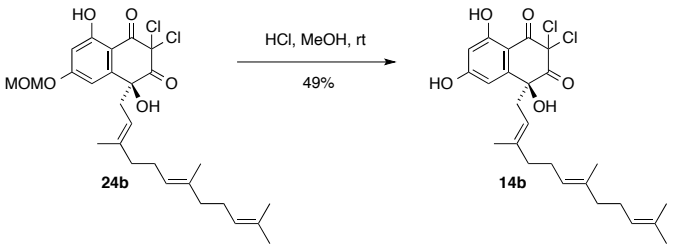
Mp = 162 – 164 °C

IR (neat): 3347, 3159, 2922, 1638, 1587, 1456, 1148, 1008, 830 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ 12.78 (s, 1H), 9.46 (s, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 5.48 (s, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 5.02 (t, *J* = 6.9 Hz, 1H), 4.60 (t, *J* = 7.7 Hz, 1H), 2.97 (dd, *J* = 13.0, 8.6 Hz, 1H), 2.55 (dd, *J* = 13.0, 8.6 Hz, 1H), 2.06 – 1.79 (m, 8H), 1.64 (s, 3H), 1.58 (s, 3H), 1.56 (s, 3H), 1.40 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 184.0, 170.5, 164.2, 164.1, 148.2, 141.9, 135.7, 131.5, 125.2, 124.8, 124.8, 116.9, 108.5, 106.0, 102.8, 76.1, 44.1, 40.6, 40.4, 27.5, 27.4, 25.8, 17.7, 16.2, 16.0.

HRMS (ESI): calculated for $C_{25}H_{32}ClO_5$ 447.1933 $[M+H]^+$, found 447.1930.



To a solution of **24b** (196 mg, 0.373 mmol) in MeOH (6 mL), was added 32% HCl (0.6 mL) at rt. The mixture was stirred at rt for 24 h. The mixture was diluted with 1 M HCl (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to yield **14b** (88 mg, 49%) as a yellow oil.

Data for 14b:

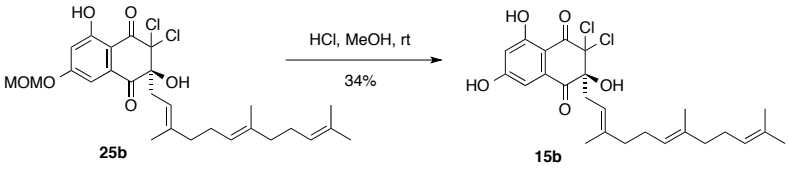
R_f = 0.15 (petrol/EtOAc, 3:1)

IR (neat): 3388, 2923, 2854, 1748, 1622, 1452, 1163, 857, 732 cm^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ 11.69 (s, 1H), 7.26 (s, 1H), 6.83 (d, *J* = 2.3 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 5.09 (t, *J* = 6.8 Hz, 1H), 5.08 (t, *J* = 6.8 Hz, 1H), 5.01 (t, *J* = 7.7 Hz, 1H), 3.90 (s, 1H), 2.74 (dd, *J* = 14.7, 8.8 Hz, 1H), 2.65 (dd, *J* = 14.7, 6.1 Hz, 1H), 2.14 – 1.96 (m, 8H), 1.67 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.26 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 194.1, 186.3, 166.7, 166.1, 145.8, 144.0, 135.9, 131.6, 124.4, 123.7, 114.9, 107.1, 105.6, 103.6, 79.8, 78.0, 45.6, 40.0, 39.8, 26.9, 26.4, 25.8, 17.8, 16.7, 16.2.

HRMS (ESI): calculated for $C_{25}H_{29}Cl_2O_5$ 479.1398 $[M-H]^-$, found 479.1394.



To a solution of **25b** (295 mg, 0.561 mmol) in MeOH (10 mL), was added 32% HCl (1.0 mL) at rt. The mixture was stirred at rt for 24 h. The mixture was diluted with 1 M HCl (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (4:1, petrol/EtOAc) to yield **15b** (83 mg, 31%) as an orange oil along with recovered starting material (101 mg, 34%).

Data for 15b:

R_f = 0.20 (petrol/EtOAc, 3:1)

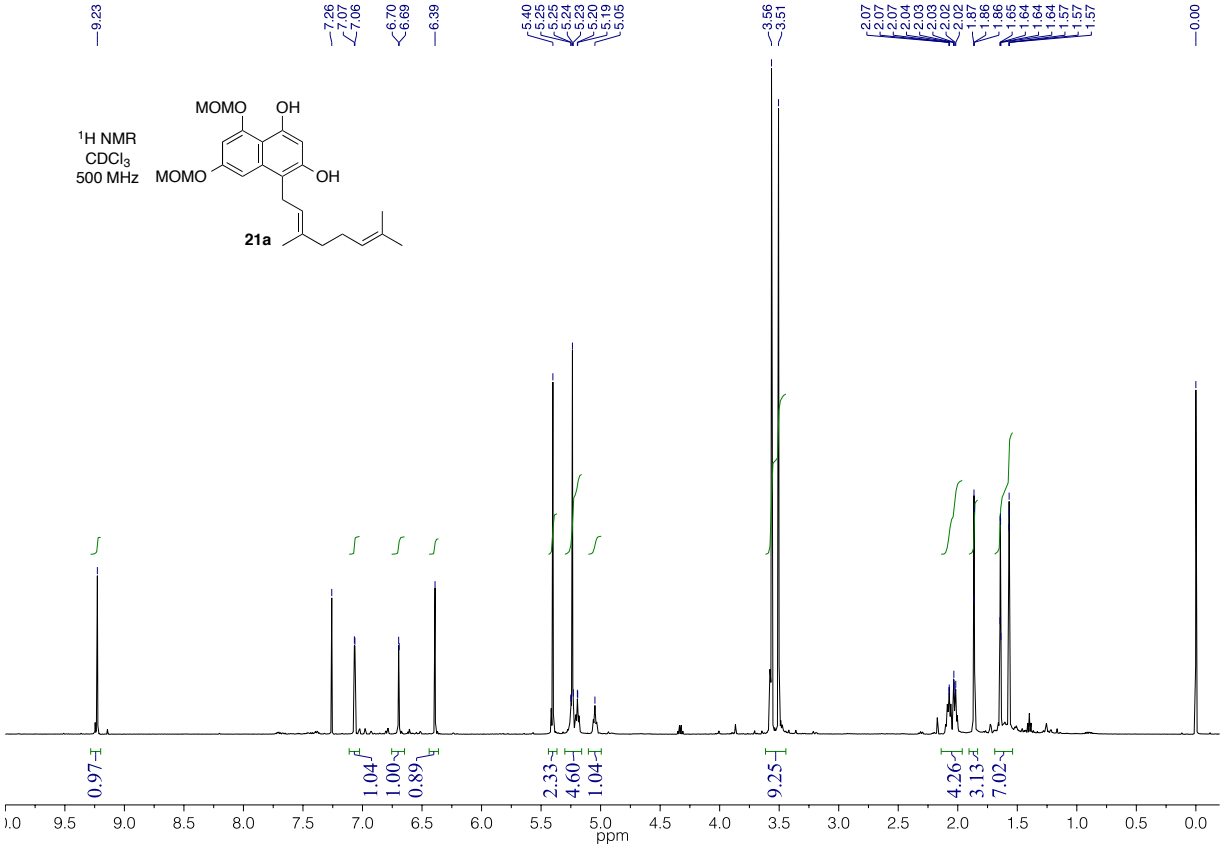
IR (neat): 3380, 2917, 1712, 1656, 1614, 1580, 1349, 1248, 1168, 1095, 810 cm^{-1}

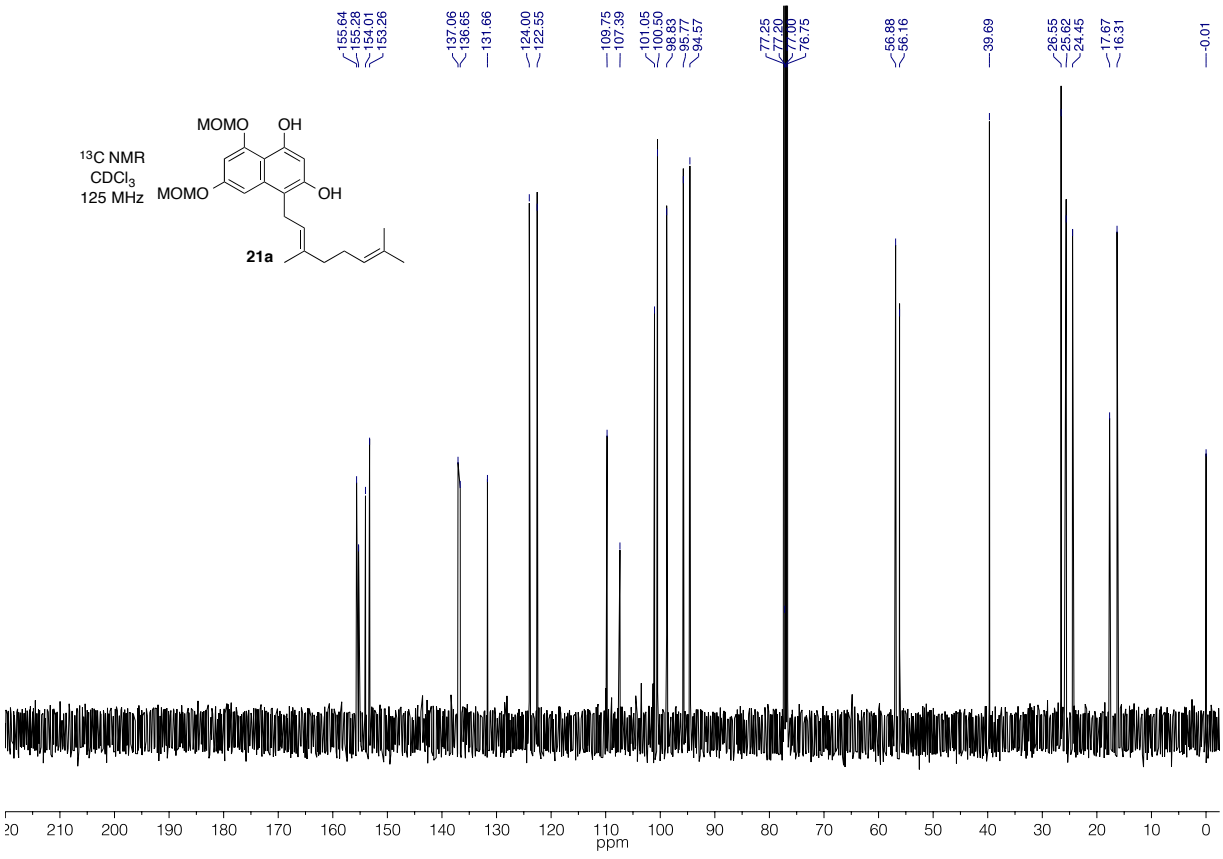
^{1}H-NMR (500 MHz, $CDCl_3$): δ 11.45 (s, 1H), 7.09 (s, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 5.10 (t, *J* = 7.0 Hz, 1H), 5.02 (t, *J* = 6.4 Hz, 1H), 4.88 (t, *J* = 7.4 Hz, 1H), 4.47 (s, 1H), 2.81 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.37 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.16 (s, 1H), 2.09 – 1.88 (m, 8H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.25 (s, 3H).

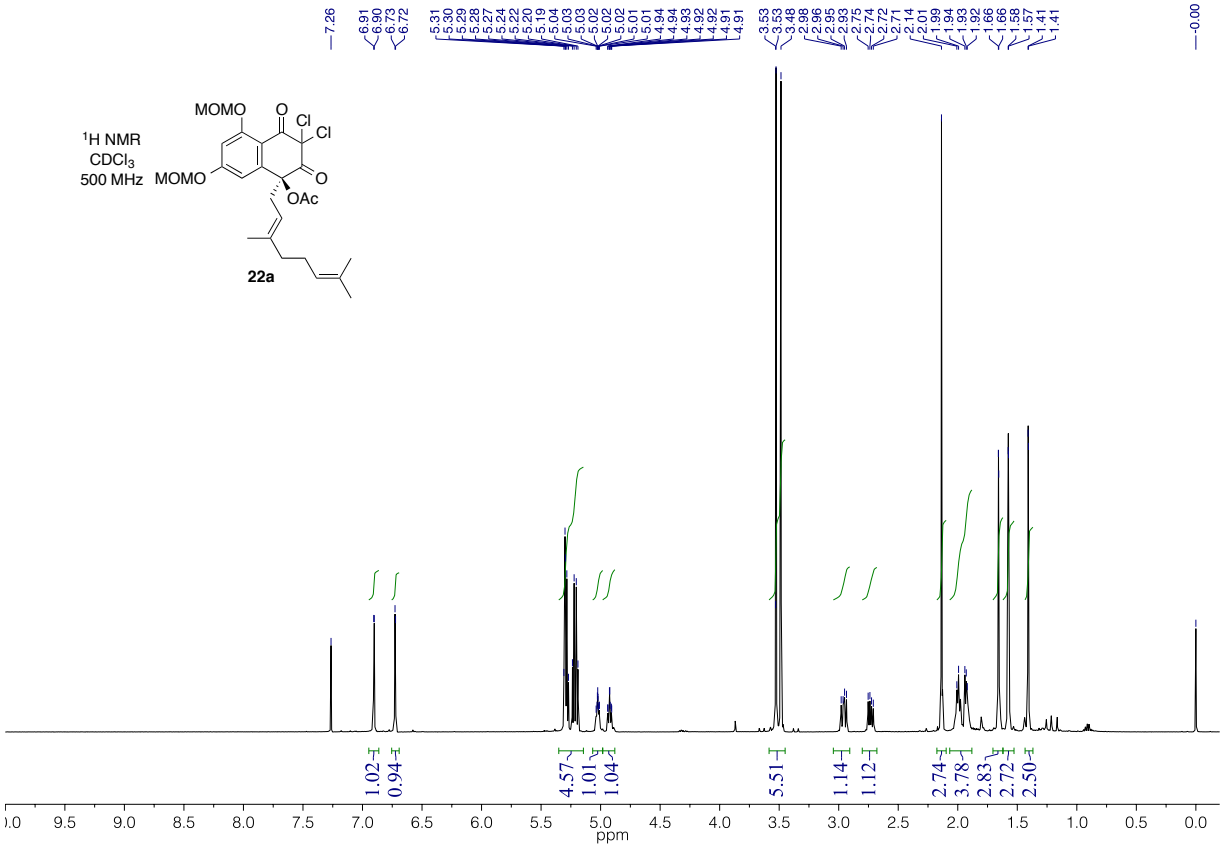
^{13}C-NMR (125 MHz, $CDCl_3$): δ 193.9, 187.0, 165.9, 164.3, 141.8, 135.7, 133.8, 131.7, 124.5, 123.6, 115.0, 109.6, 108.7, 107.7, 90.6, 85.9, 39.8, 36.5, 26.9, 26.4, 25.8, 17.8, 16.3, 16.1.

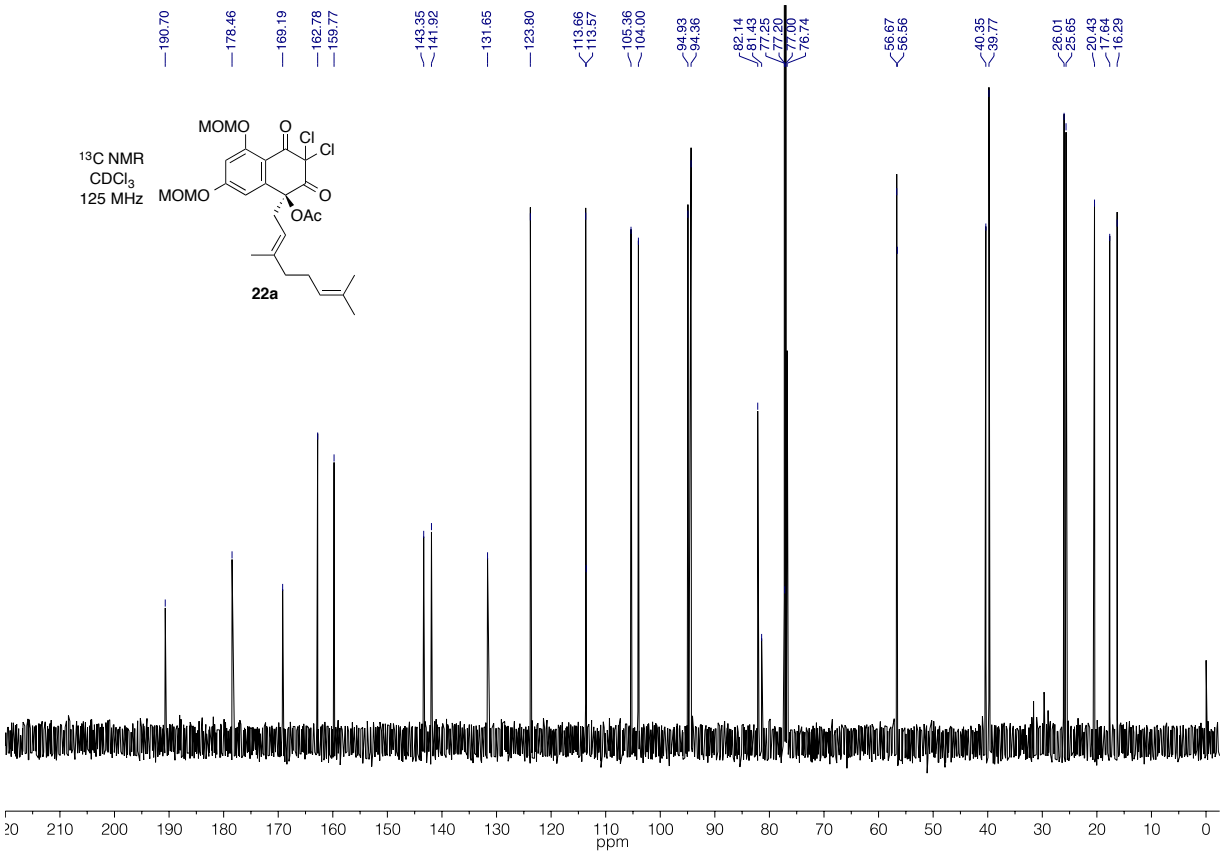
HRMS (ESI): calculated for $C_{25}H_{31}Cl_2O_5$ 481.1543 $[M+H]^+$, found 481.1538.

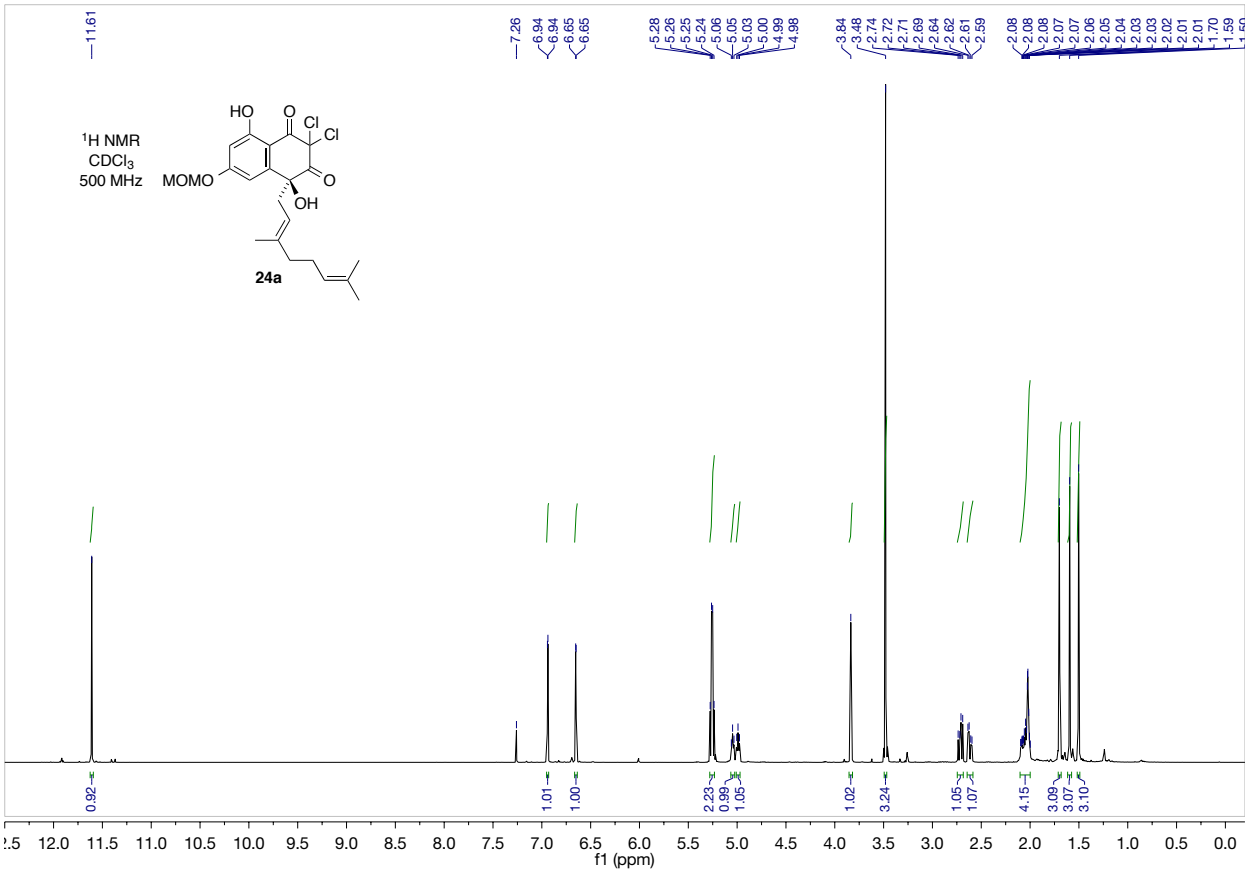
3. NMR spectra

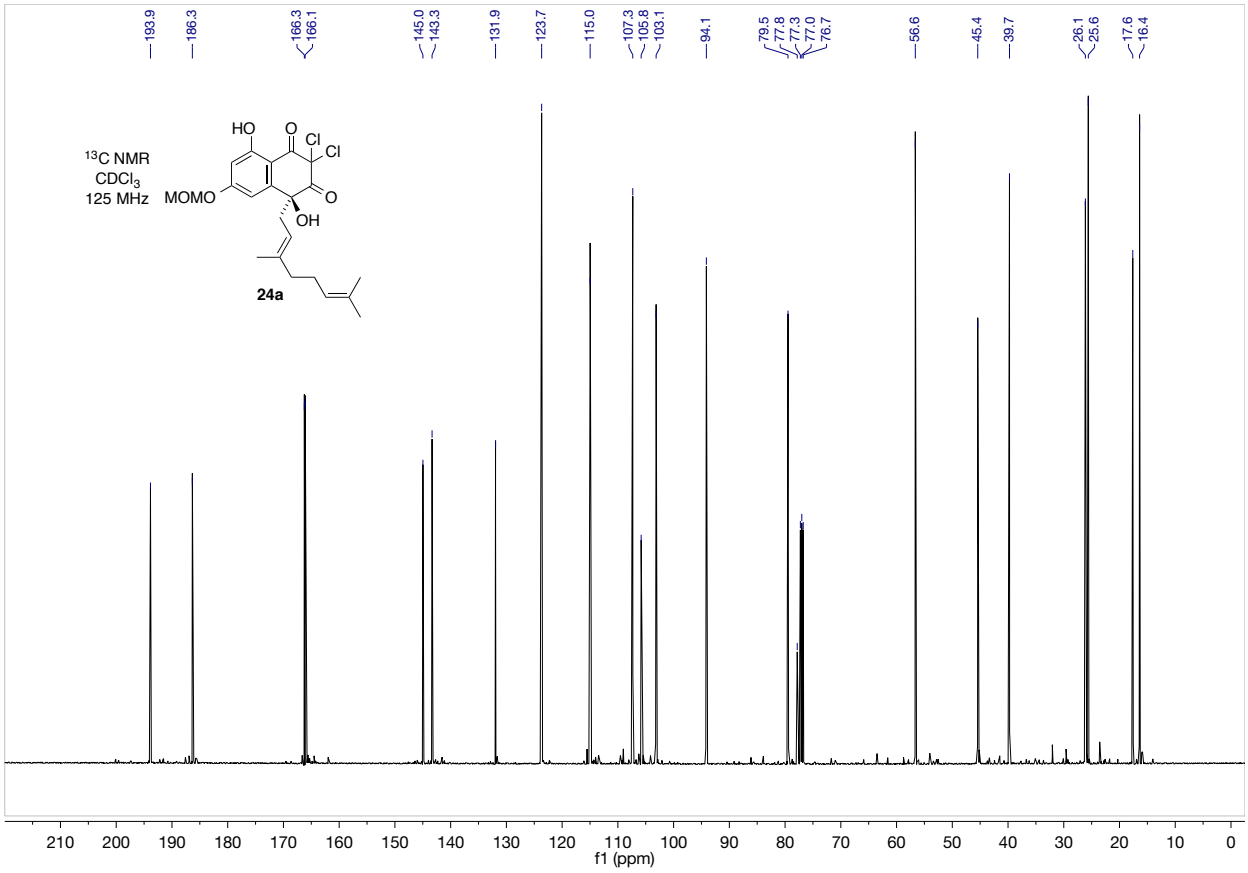


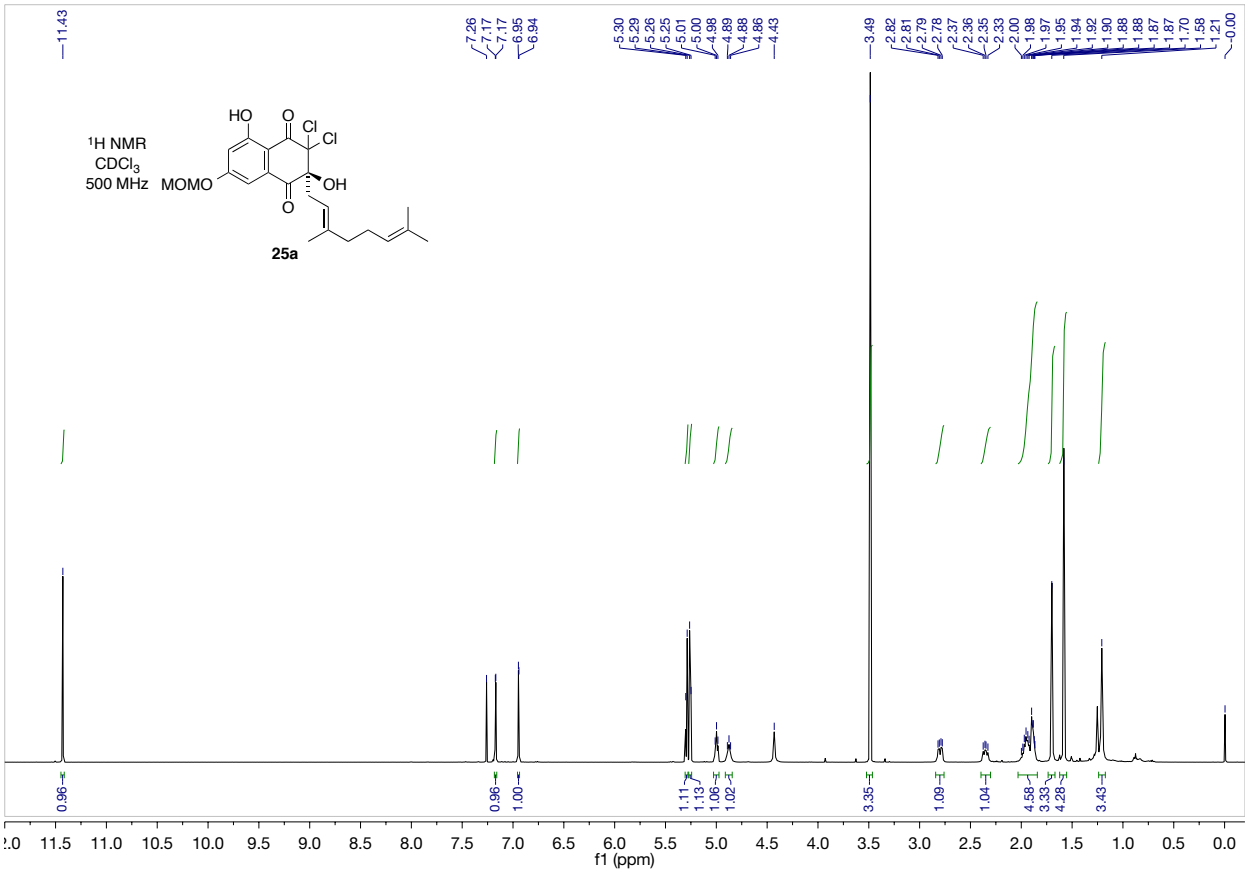



^{1}H NMR
$CDCl_3$
500 MHz
MOMO
MOMO
Cl
Cl
O
O
OAc
22a
7.26
6.91
6.90
6.73
6.72
5.31
5.30
5.29
5.28
5.27
5.24
5.22
5.20
5.19
5.04
5.03
5.02
5.02
5.02
5.01
5.01
4.94
4.94
4.93
4.92
4.92
4.91
4.91
3.53
3.53
3.48
2.98
2.96
2.95
2.93
2.75
2.74
2.72
2.71
2.14
2.01
1.99
1.94
1.93
1.92
1.66
1.66
1.58
1.57
1.41
1.41
0.00
1.02
0.94
4.57
1.01
1.04
5.51
1.14
1.12
2.74
3.78
2.83
2.72
2.50
ppm


^{13}C NMR
$CDCl_3$
125 MHz
MOMO
MOMO
Cl
Cl
O
O
OAc
22a
190.70
178.46
169.19
162.78
159.77
143.35
141.92
131.65
123.80
113.66
113.57
105.36
104.00
94.93
94.36
82.14
81.43
77.25
77.00
76.74
56.67
56.56
40.35
39.77
26.01
25.65
20.43
17.64
16.29
ppm

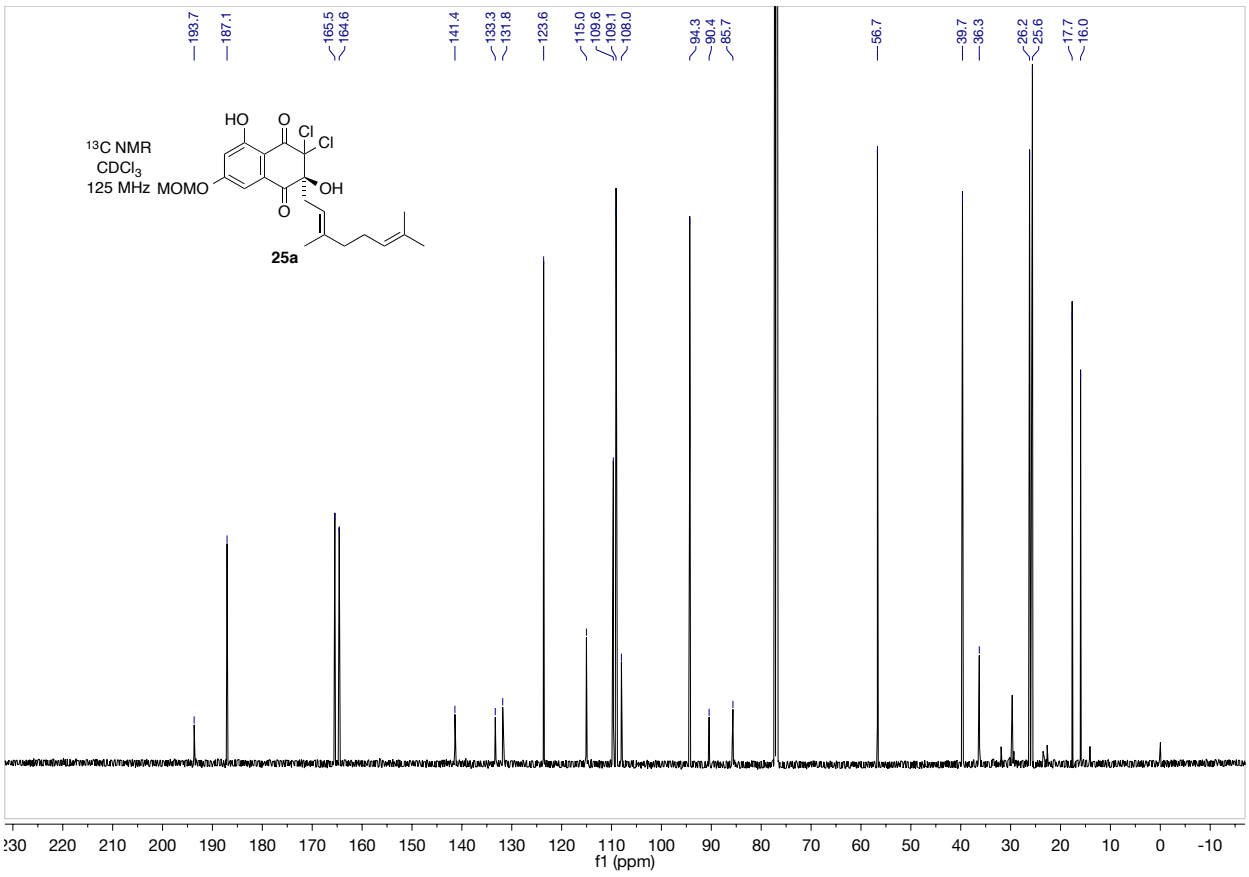

^{1}H NMR
$CDCl_3$
500 MHz
HO
O
Cl
Cl
MOMO
O
OH
24a
f1 (ppm)


^{13}C NMR
$CDCl_3$
125 MHz
HO
O
Cl
Cl
MOMO
O
OH
24a
f1 (ppm)



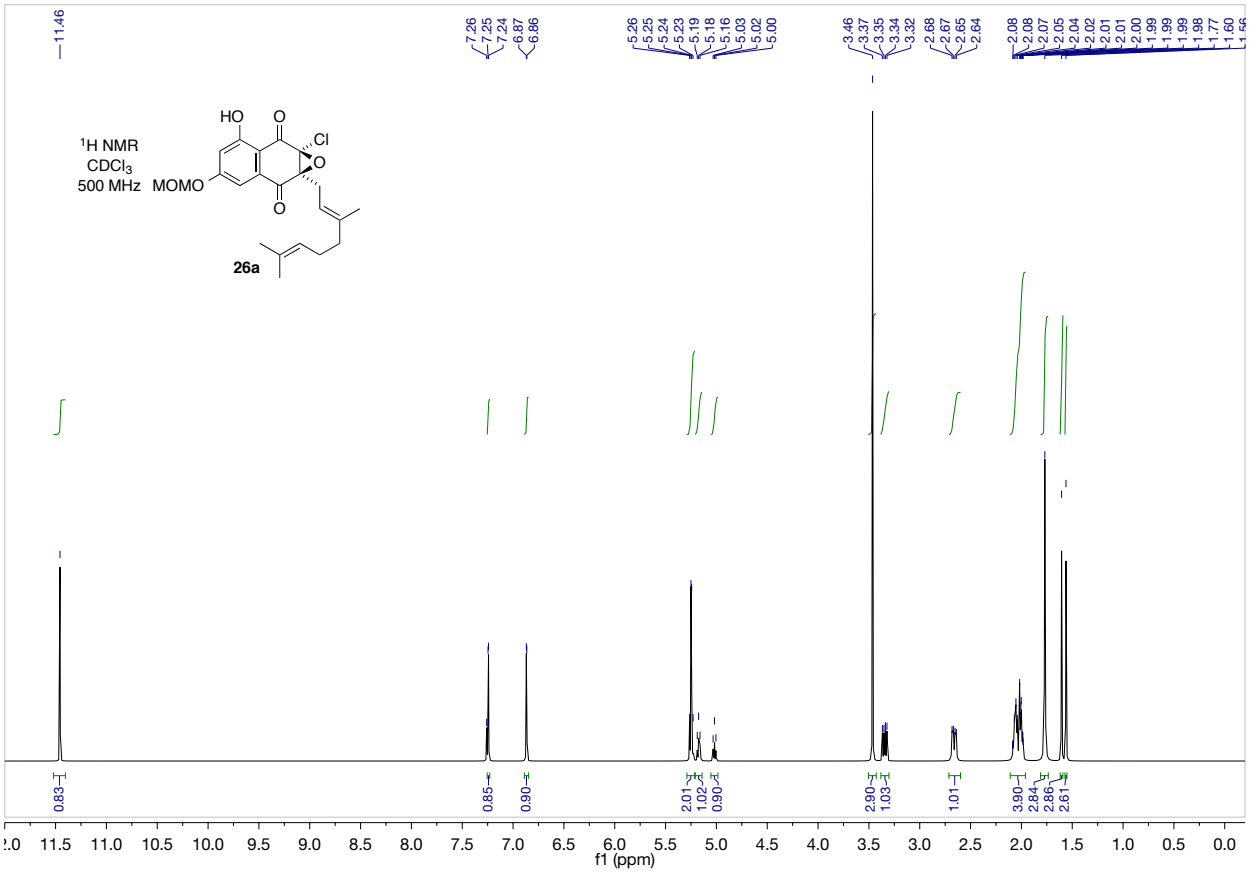
^{1}H NMR
$CDCl_3$
500 MHz

25a



^{13}C NMR
$CDCl_3$
125 MHz

25a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7.25
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5.25
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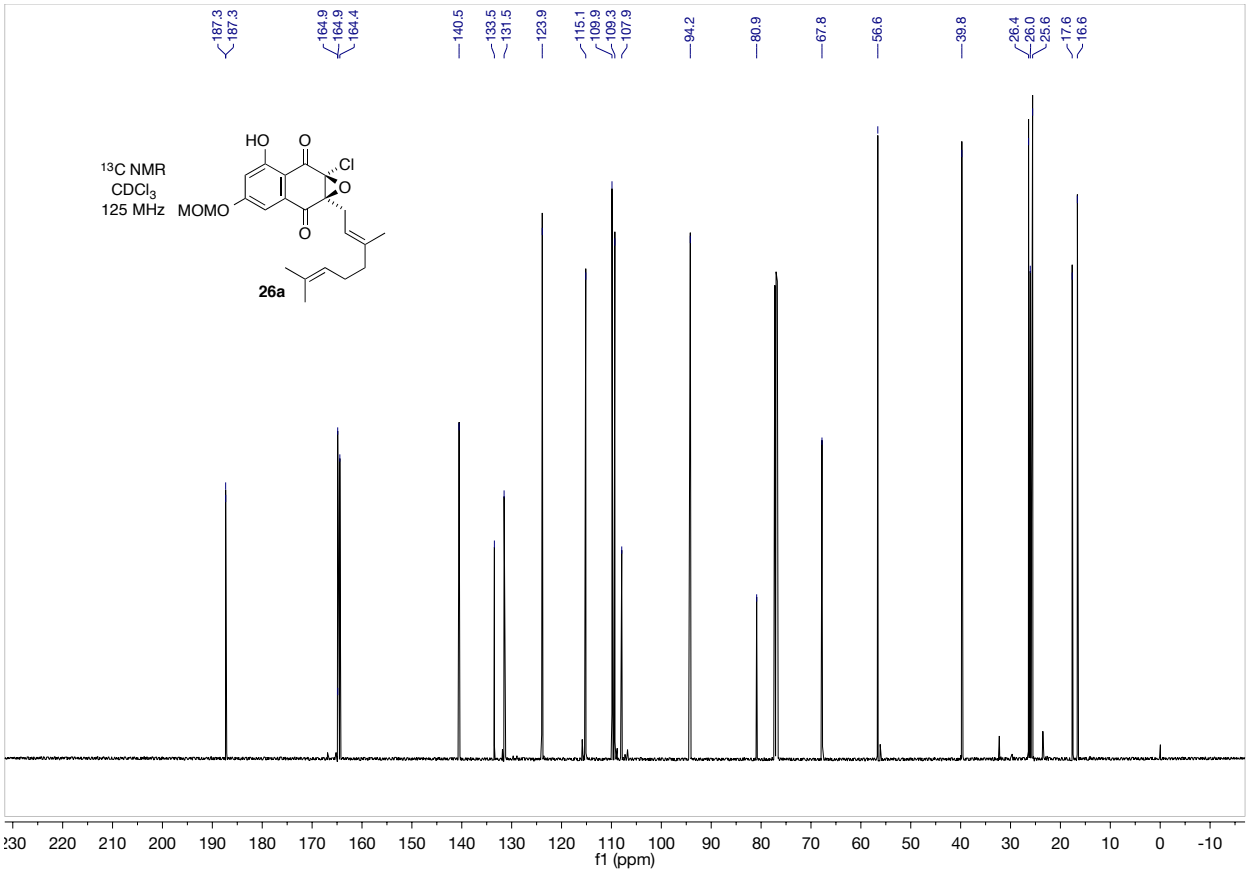
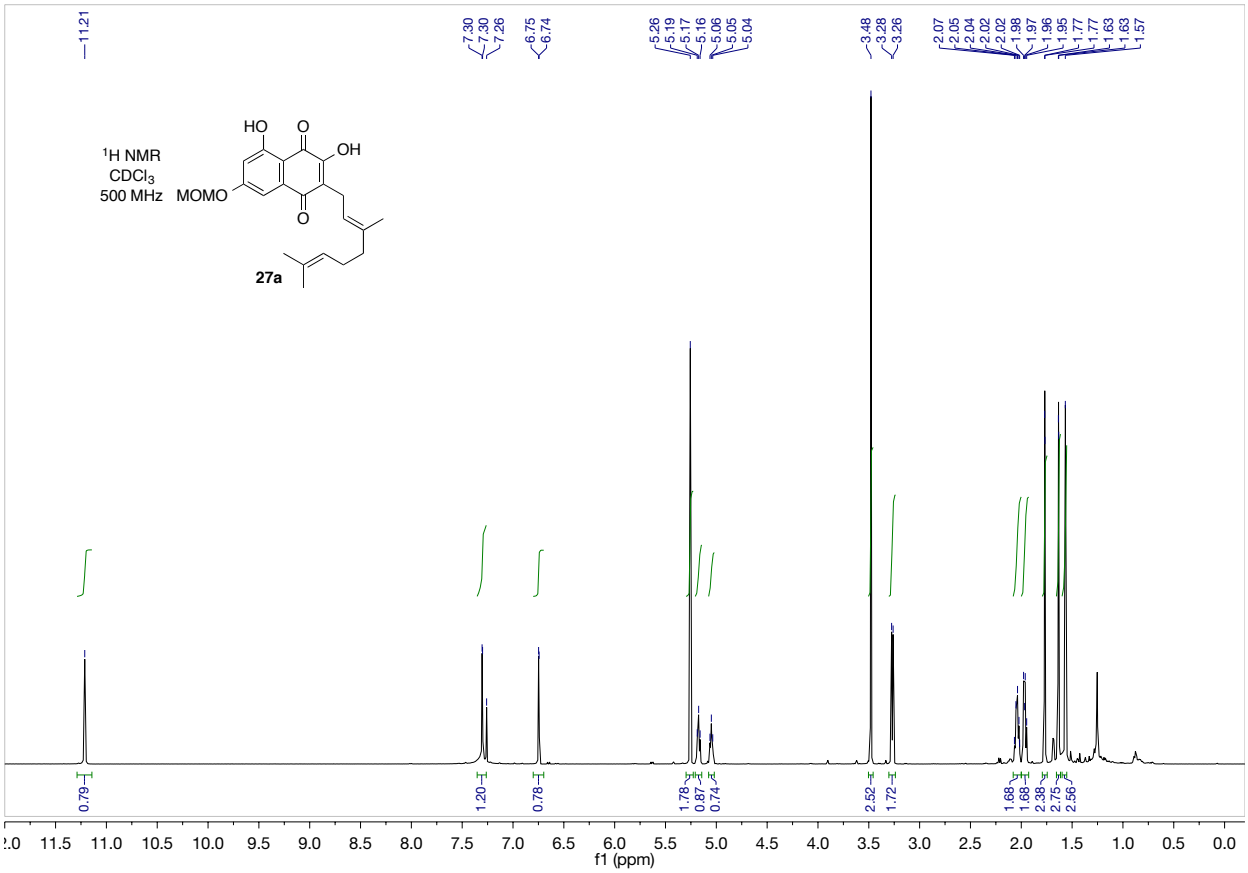
5.23
5.19
5.18
5.16
5.03
5.02
5.00
3.46
3.37
3.35
3.34
3.32
2.68
2.67
2.65
2.64
2.08
2.08
2.07
2.05
2.04
2.02
2.01
2.01
2.00
1.99
1.99
1.99
1.98
1.77
1.60
1H NMR
CDCl3
500 MHz
HO
O
Cl
O
MOMO
O
26a
0.83
0.85
0.90
2.01
1.02
0.90
2.90
1.03
1.01
3.90
2.84
2.86
2.61
f1 (ppm)


187.3
187.3
164.9
164.9
164.4
140.5
133.5
131.5
123.9
115.1
109.9
109.3
107.9
94.2
80.9
67.8
56.6
39.8
26.4
26.0
25.6
17.6
16.6
13C NMR
CDCl3
125 MHz
HO
O
Cl
O
MOMO
O
26a
f1 (ppm)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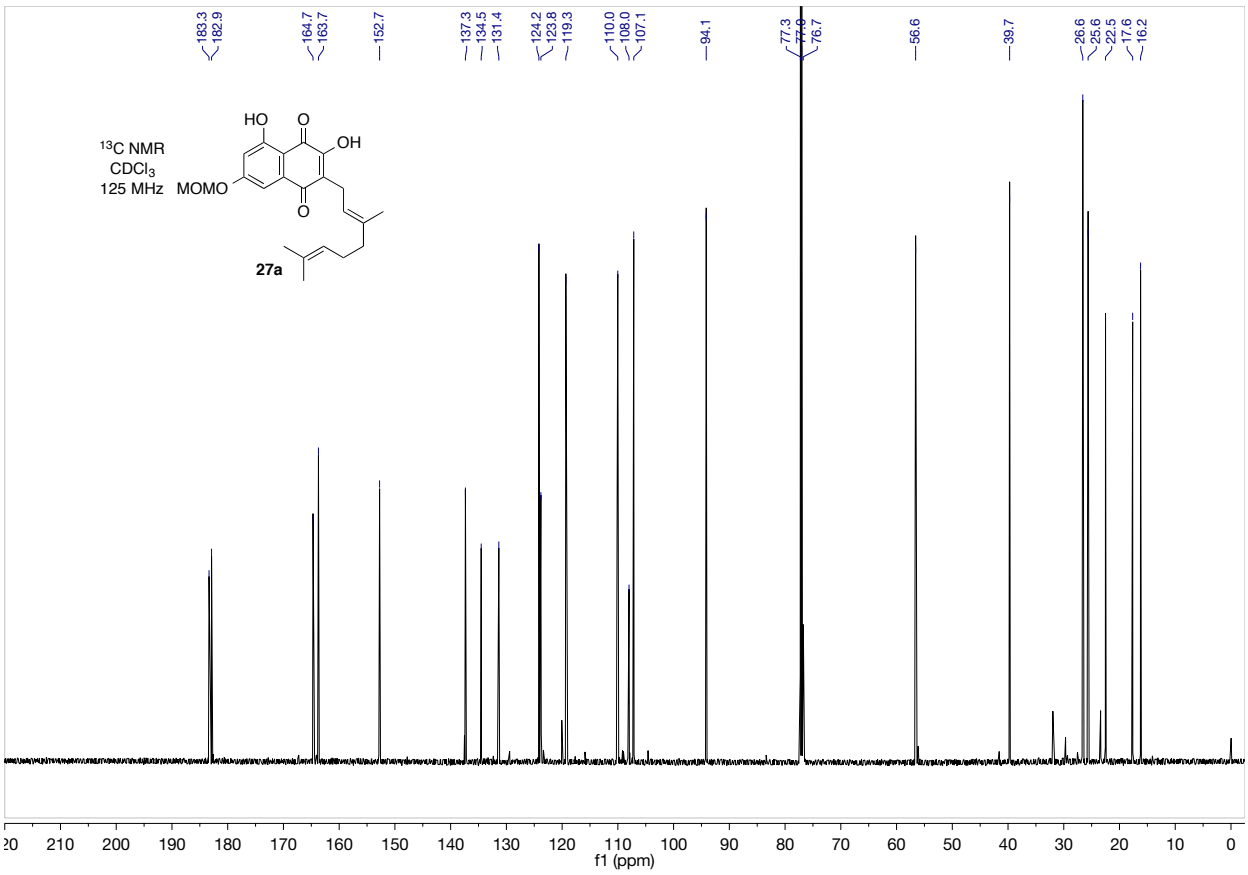
7.30
7.30
7.26
6.75
6.74
5.26
5.19
5.17
5.16
5.06
5.05
5.04
3.48
3.28
3.26
2.07
2.05
2.04
2.02
2.02
1.98
1.97
1.96
1.95
1.77
1.77
1.63
1.63
1.57
HO
O
OH
MOMO
O
1H NMR
CDCl3
500 MHz
27a
0.79
1.20
0.78
1.78
0.87
0.74
2.52
1.72
1.68
1.68
2.38
2.75
2.56
f1 (ppm)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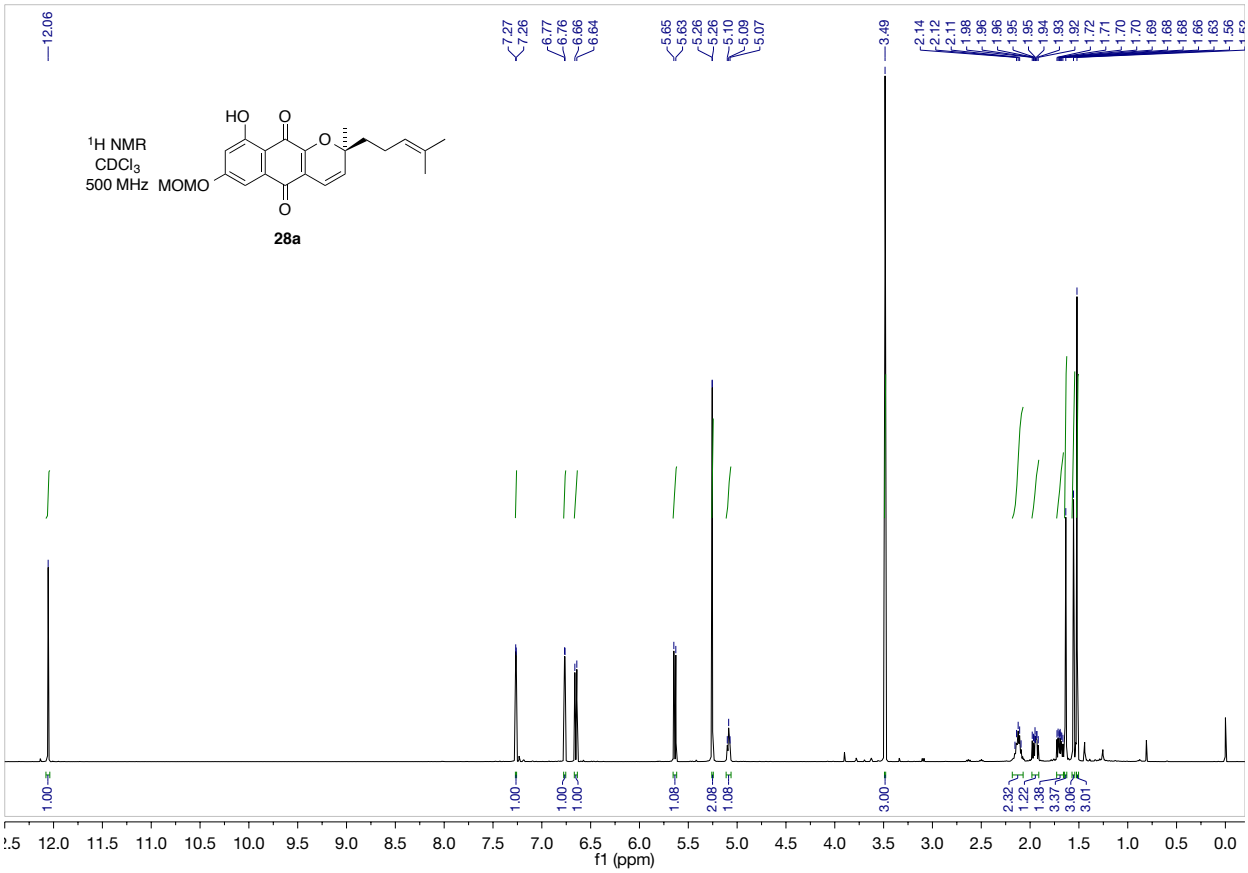
182.9
164.7
163.7
152.7
137.3
134.5
131.4
124.2
123.8
119.3
110.0
108.0
107.1
94.1
77.3
77.0
76.7
56.6
39.7
26.6
25.6
22.5
17.6
16.2
HO
O
OH
MOMO
O
13C NMR
CDCl3
125 MHz
27a
f1 (ppm)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7.27
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6.77
6.76
6.66
6.64
5.65
5.63
5.26
5.26
5.10
5.09
5.07
3.49
2.14
2.12
2.11
1.98
1.96
1.96
1.95
1.95
1.94
1.93
1.92
1.72
1.71
1.70
1.70
1.69
1.68
1.68
1.66
1.63
1.56
1H NMR
CDCl3
500 MHz
HO
O
O
MOMO
O
28a
1.00
1.00
1.00
1.00
1.08
2.08
1.08
3.00
2.32
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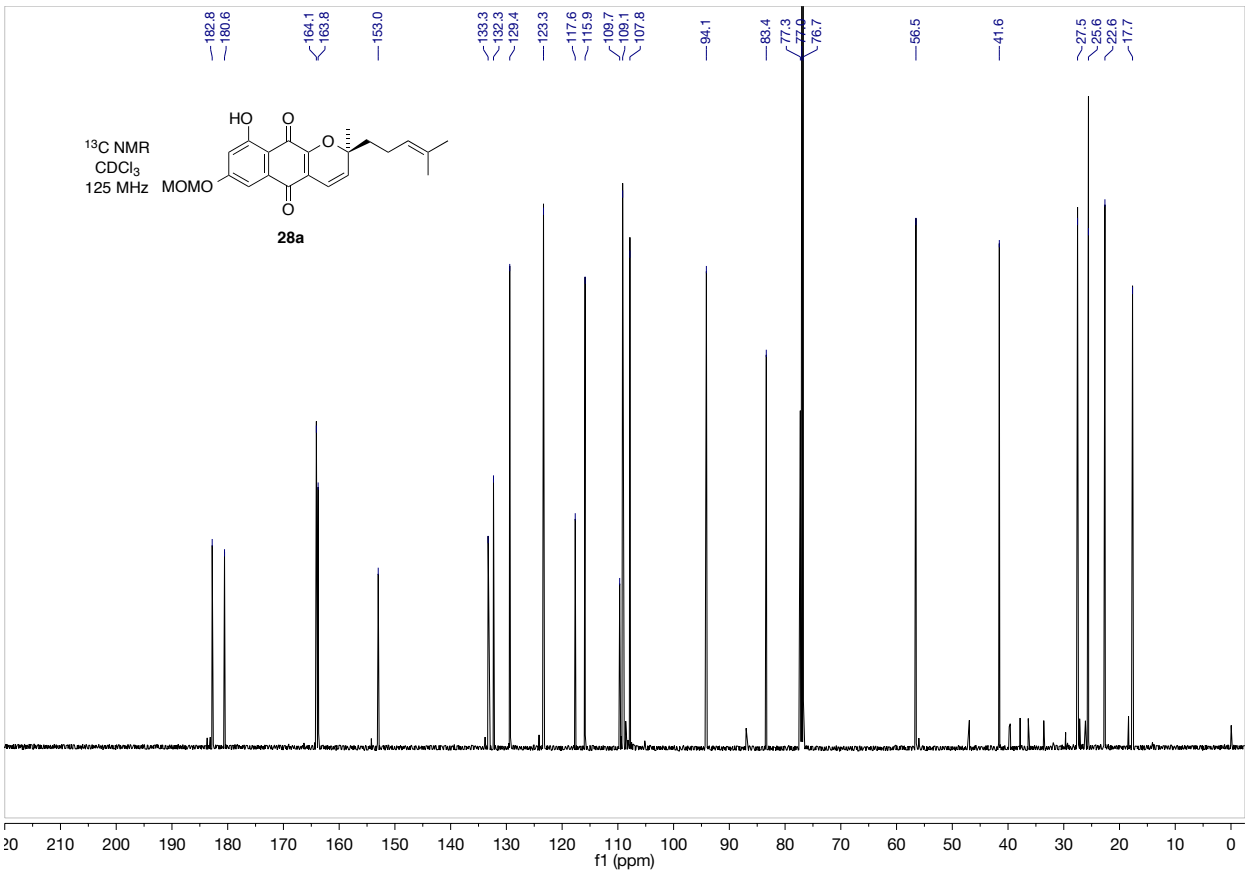
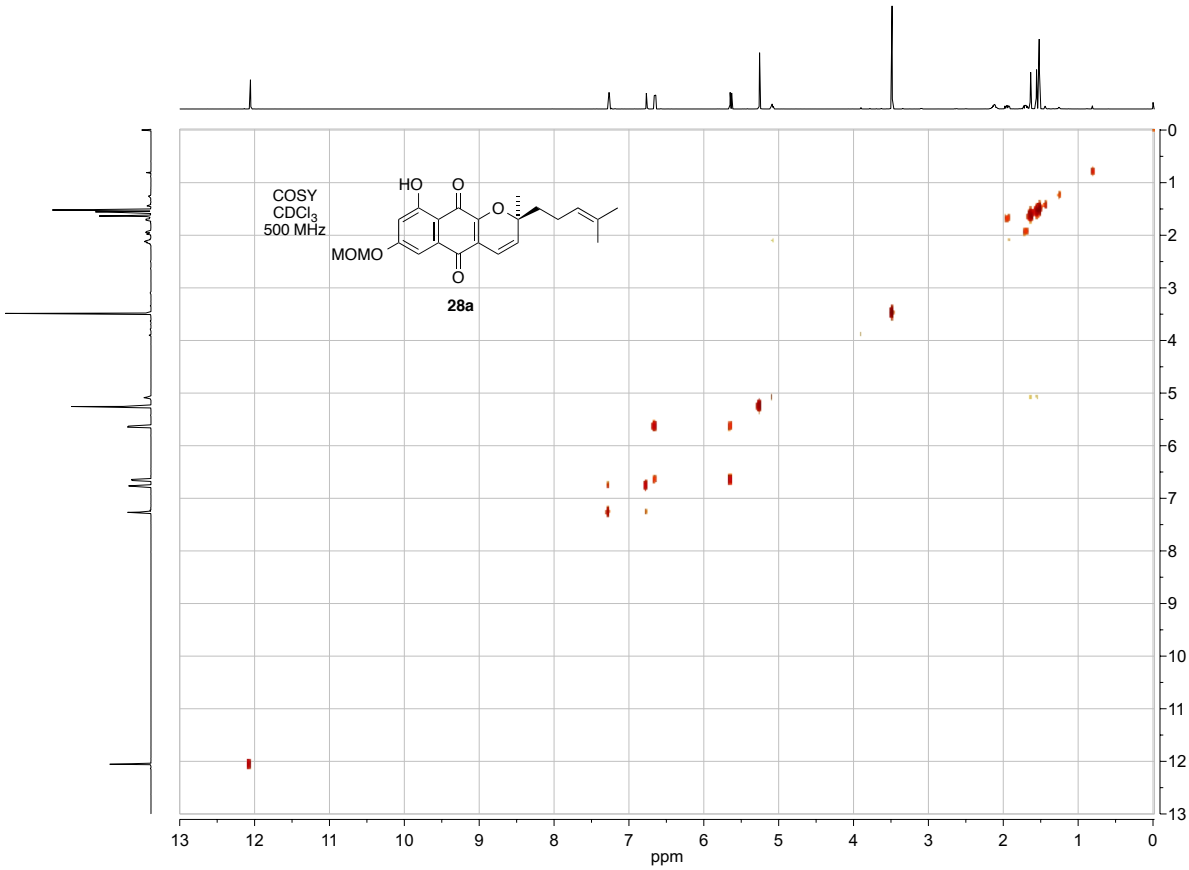
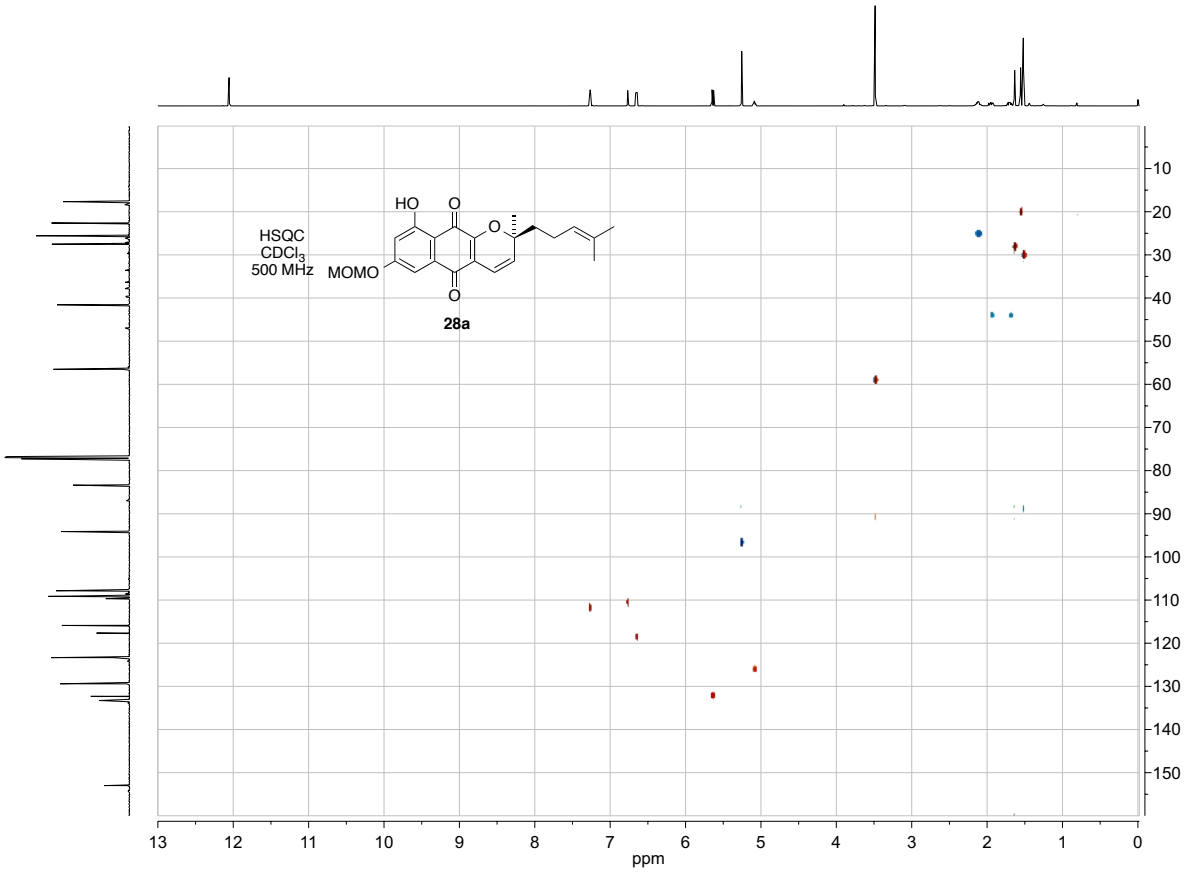
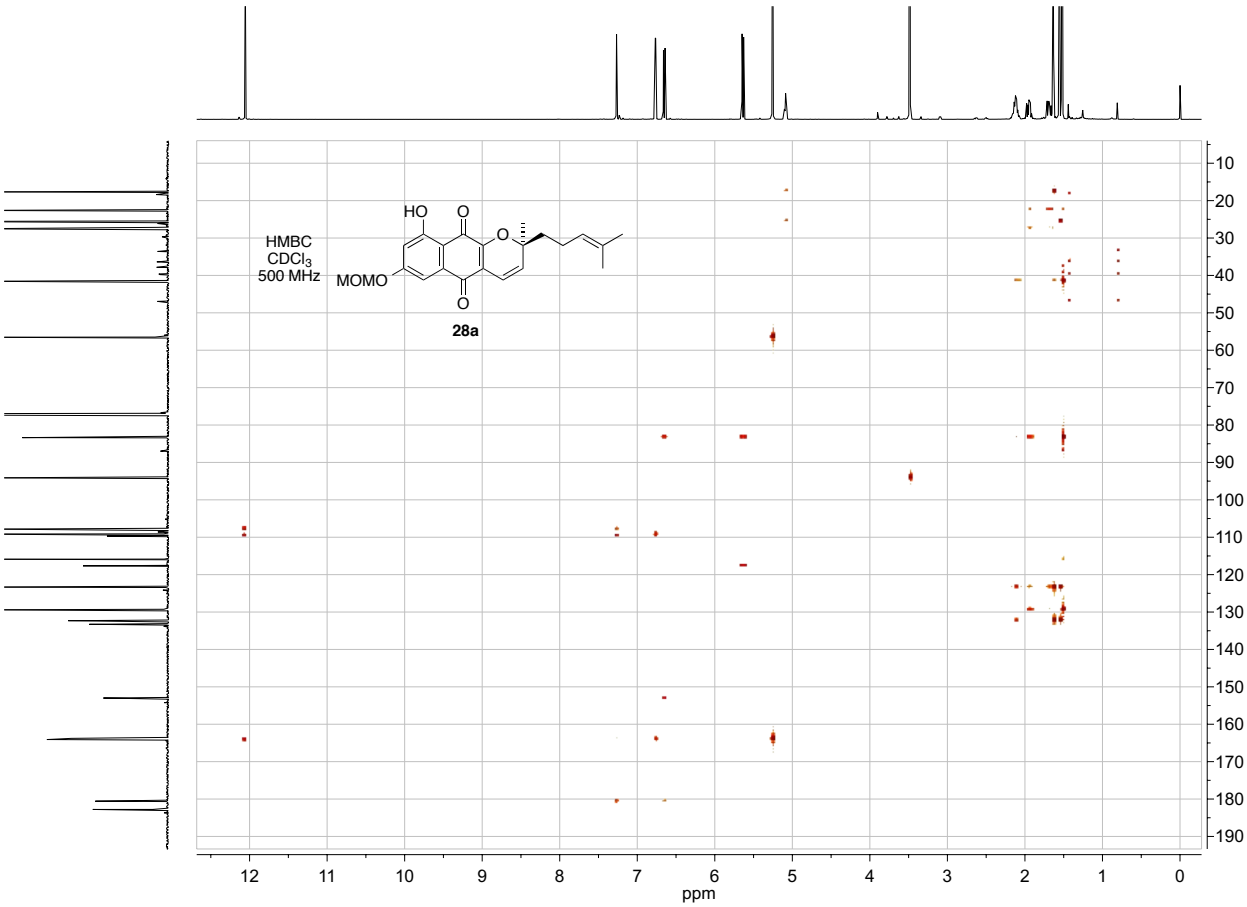
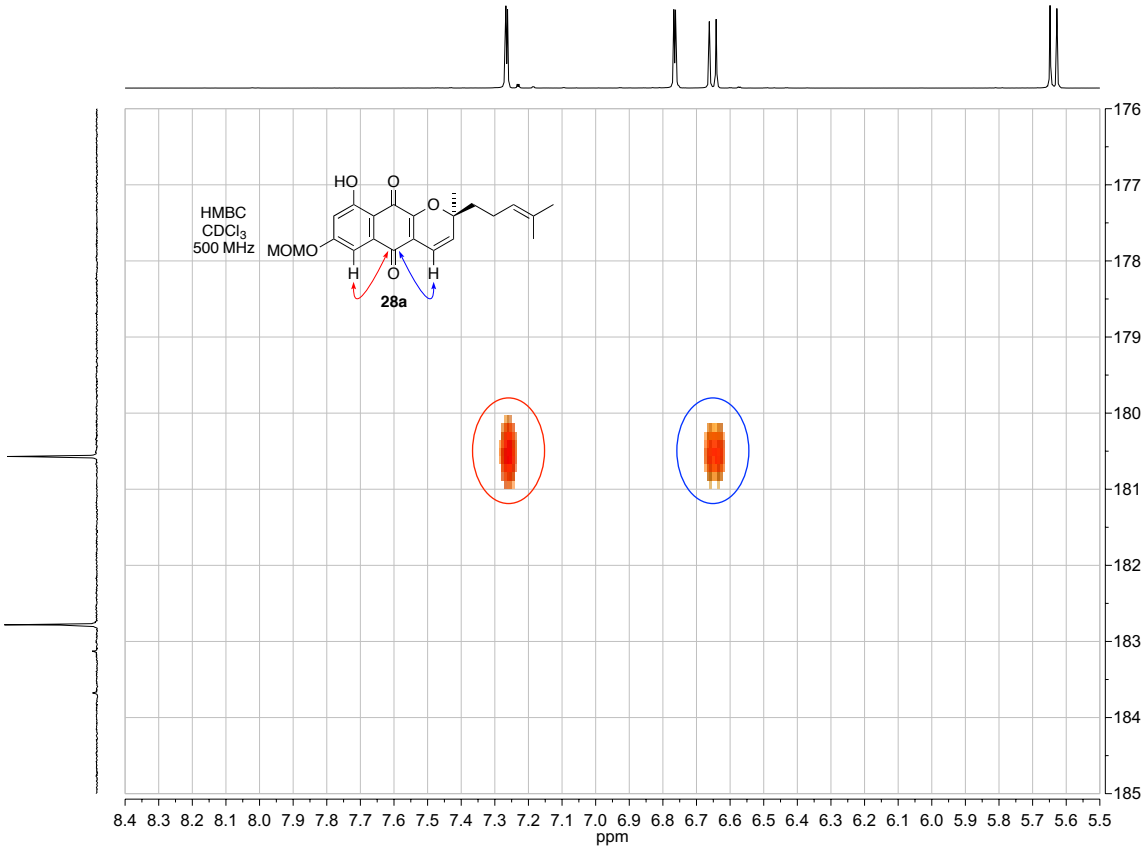
1.38
3.37
3.06
3.01
f1 (ppm)

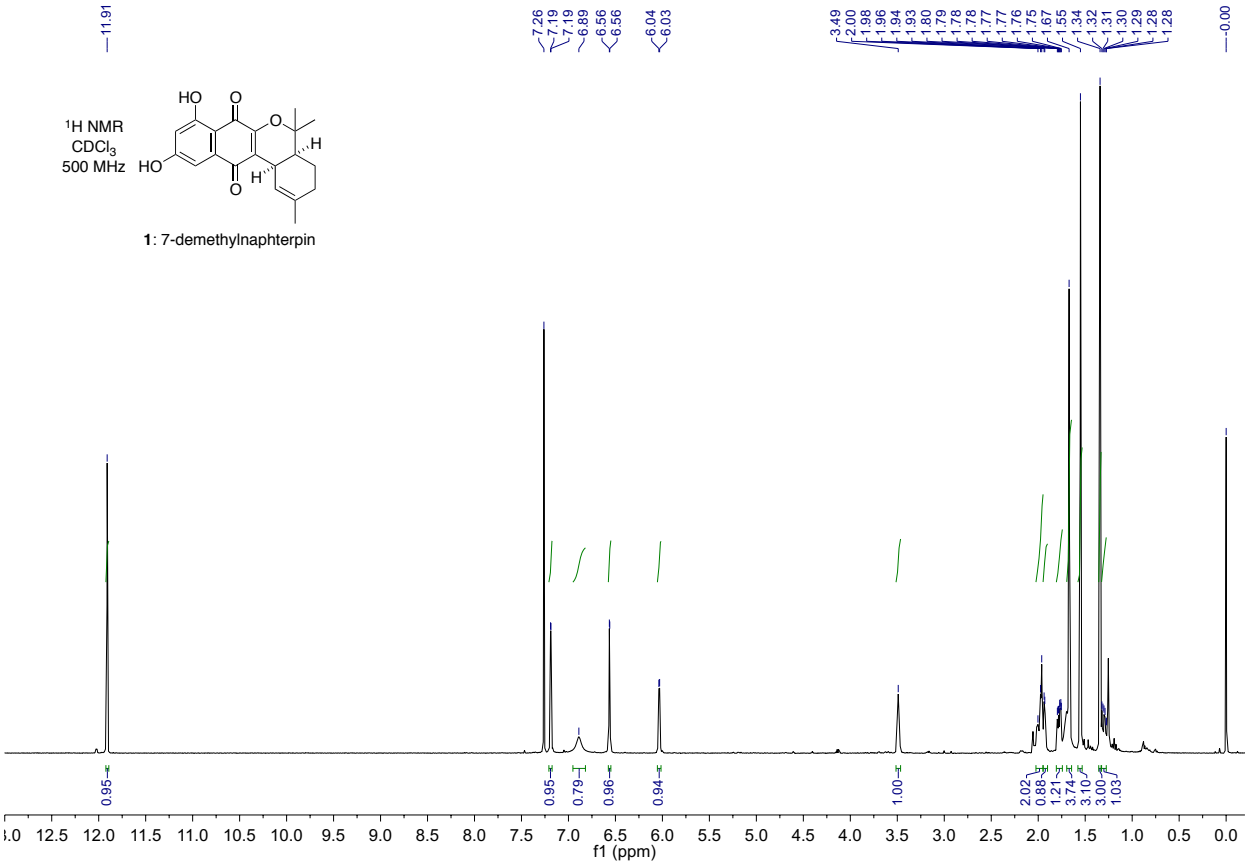

182.8
180.6
164.1
163.8
153.0
133.3
132.3
129.4
123.3
117.6
115.9
109.7
109.1
107.8
94.1
83.4
77.3
77.0
76.7
56.5
41.6
27.5
25.6
22.6
17.7
13C NMR
CDCl3
125 MHz
HO
O
O
MOMO
O
28a
f1 (ppm)

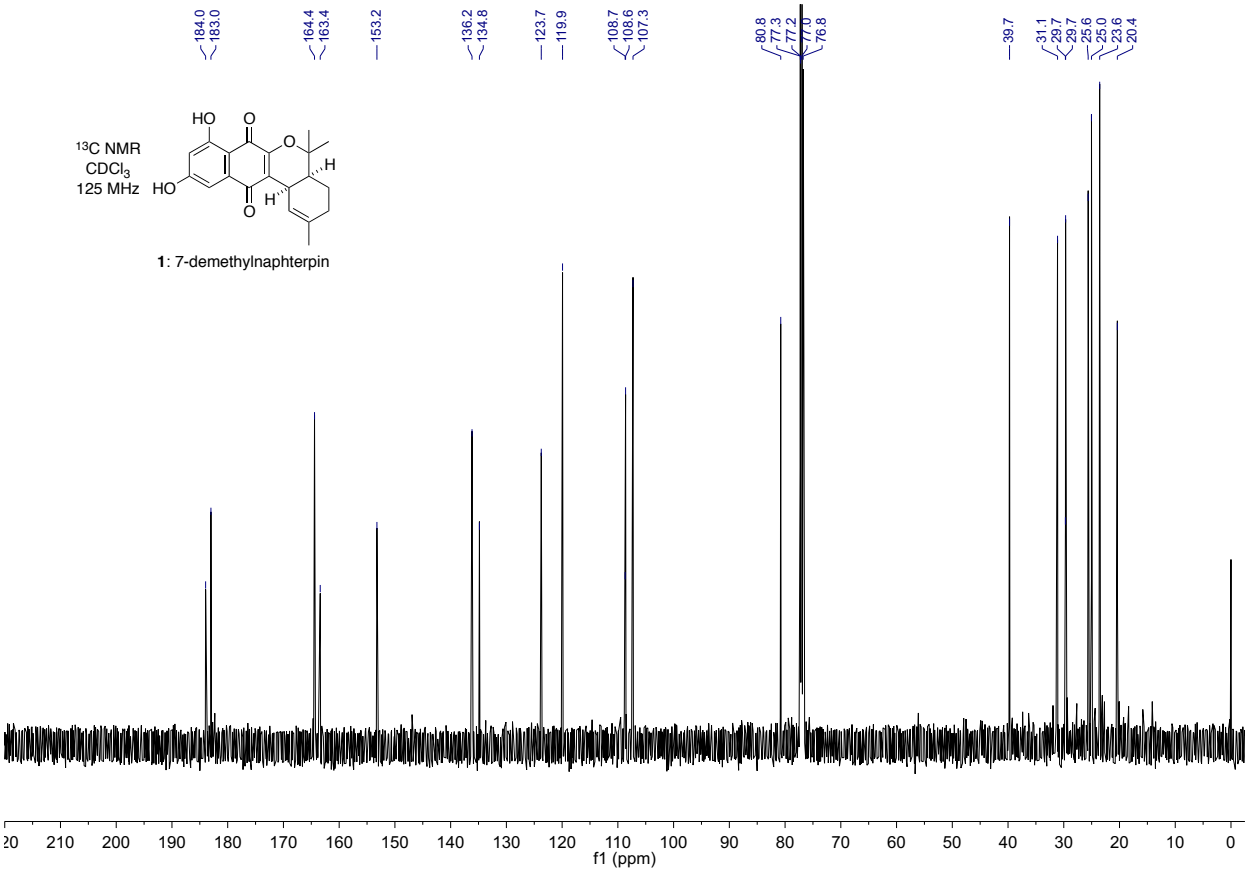

COSY
CDCl3
500 MHz
HO
O
O
MOMO
O
28a
ppm

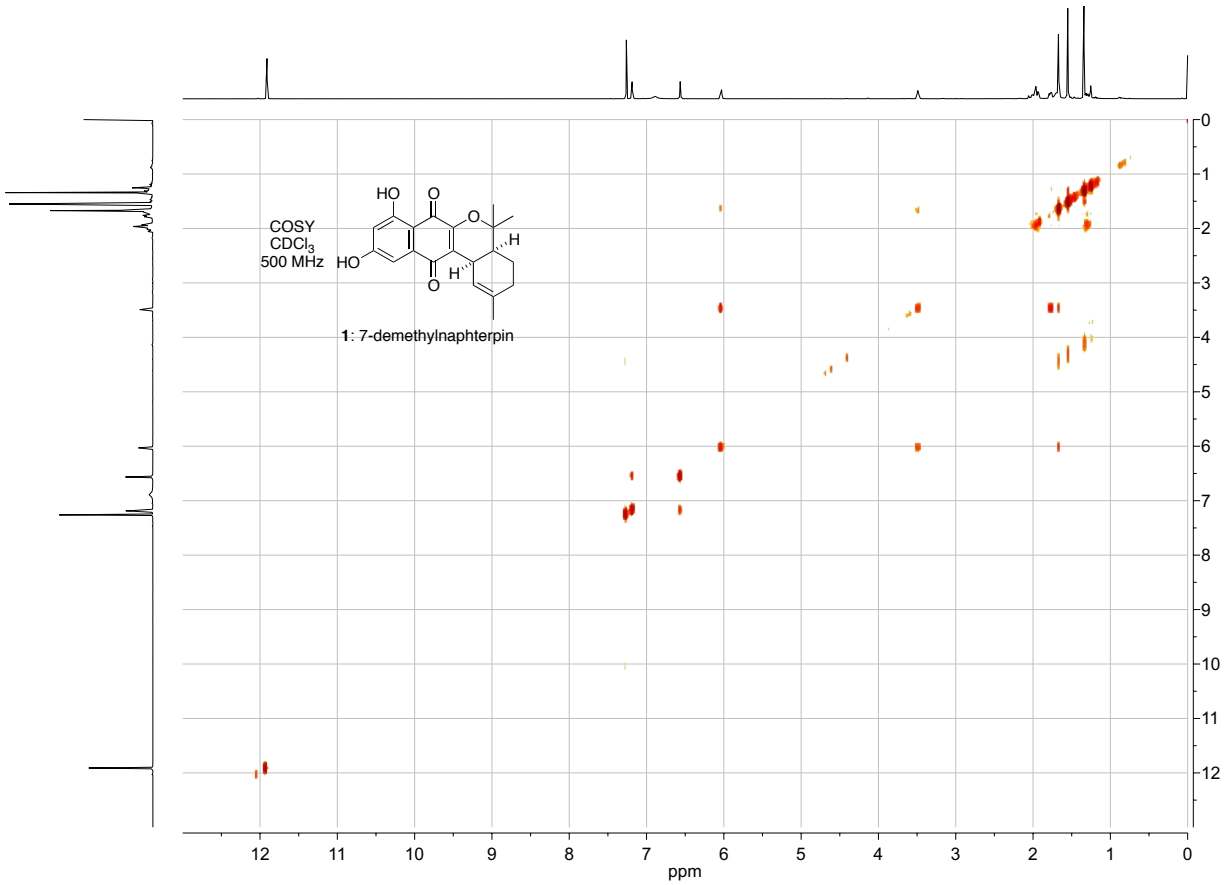

HSQC
CDCl3
500 MHz
HO
O
O
MOMO
O
28a
ppm


HMBC
CDCl3
500 MHz
HO
O
O
MOMO
O
28a
ppm


HMBC
CDCl3
500 MHz
HO
O
O
MOMO
H
O
H
28a
ppm


11.91
7.26
7.19
7.19
6.89
6.56
6.56
6.04
6.03
3.49
2.00
1.98
1.96
1.94
1.93
1.80
1.79
1.78
1.78
1.77
1.77
1.76
1.75
1.67
1.55
1.34
1.32
1.31
1.30
1.29
1.28
1.28
0.00
1H NMR
CDCl3
500 MHz
HO
O
O
H
HO
O
H
1: 7-demethylnaphterpin
0.95
0.95
0.79
0.96
0.94
1.00
2.02
0.88
1.21
3.74
3.10
3.00
1.03
f1 (ppm)


184.0
183.0
164.4
163.4
153.2
136.2
134.8
123.7
119.9
108.7
108.6
107.3
80.8
77.3
77.2
77.0
76.8
39.7
31.1
29.7
29.7
25.6
25.0
23.6
20.4
13C NMR
CDCl3
125 MHz
HO
O
O
H
HO
O
H
1: 7-demethylnaphterpin
f1 (ppm)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CDCl3
500 MHz
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O
O
H
HO
H
O
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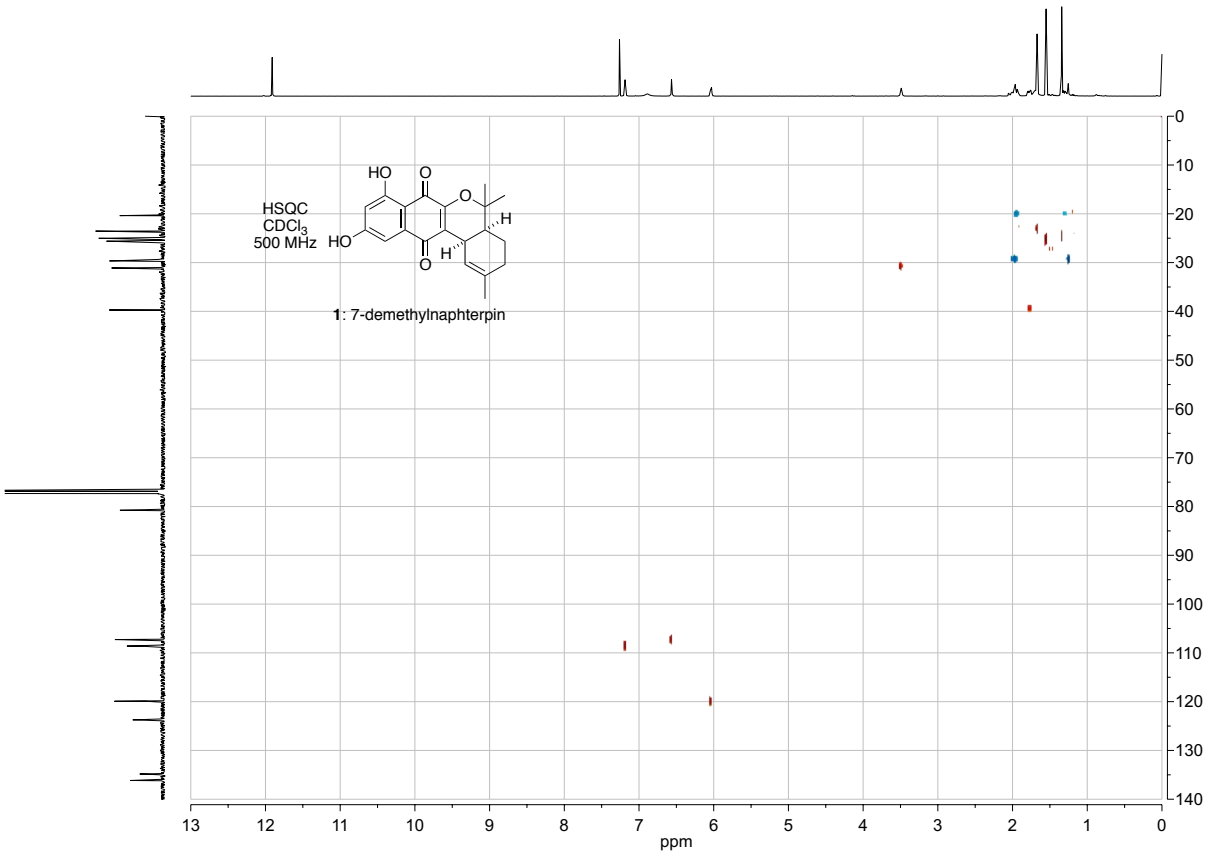
ppm


HSQC
CDCl3
500 MHz
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O
O
H
HO
H
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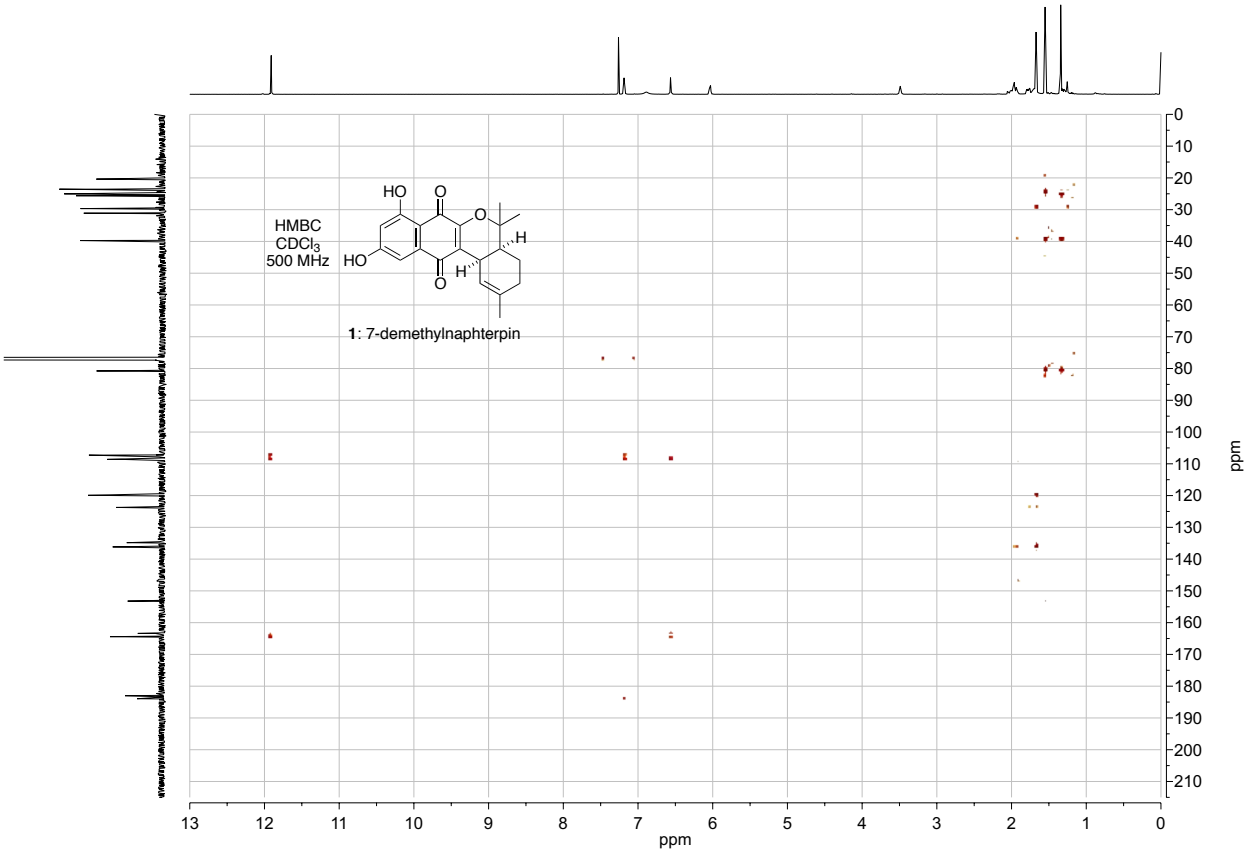
ppm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CDCl3
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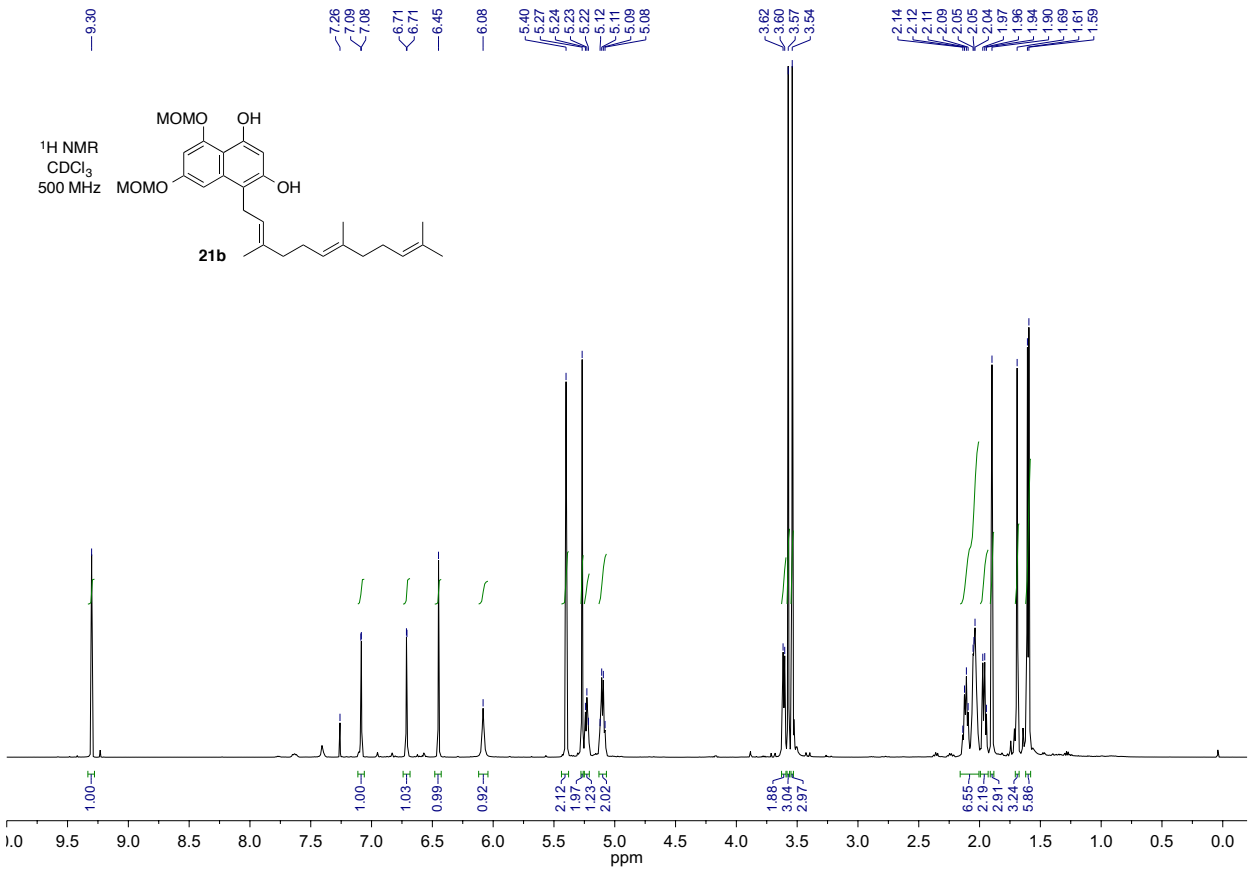
O
O
H
H
O
1: 7-demethylnaphterpin
ppm
ppm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7.09
7.08
6.71
6.71
6.45
6.08
5.40
5.27
5.24
5.23
5.22
5.12
5.11
5.09
5.08
3.62
3.60
3.57
3.54
2.14
2.12
2.11
2.09
2.05
2.05
2.04
1.97
1.96
1.94
1.90
1.69
1.61
1.59
1H NMR
CDCl3
500 MHz
MOMO
OH
MOMO
OH
21b
1.00
1.00
1.03
0.99
0.92
2.12
1.97
1.23
2.02
1.88
3.04
2.97
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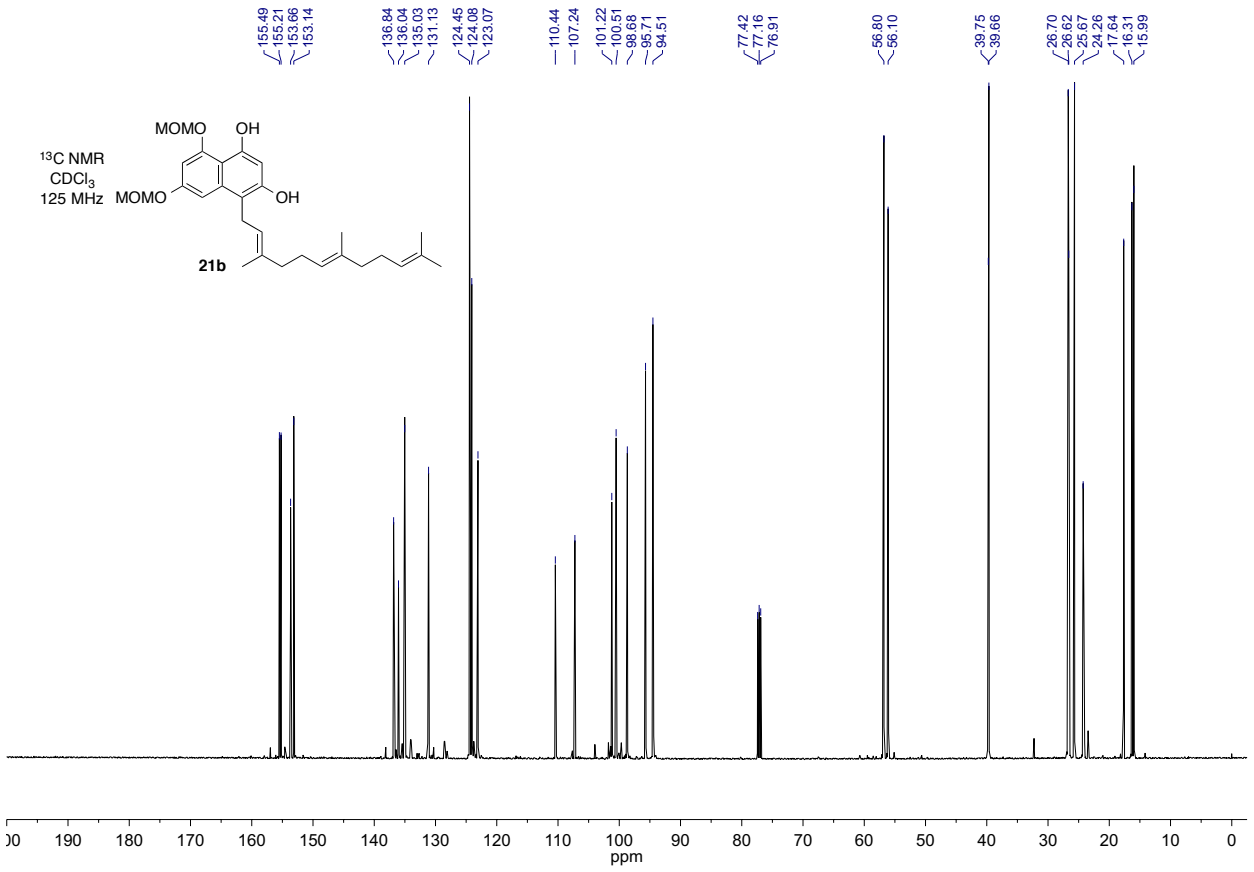
5.86
ppm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153.14
136.84
136.04
135.03
131.13
124.45
124.08
123.07
110.44
107.24
101.22
100.51
98.68
95.71
94.51
77.42
77.16
76.91
56.80
56.10
39.75
39.66
26.70
26.62
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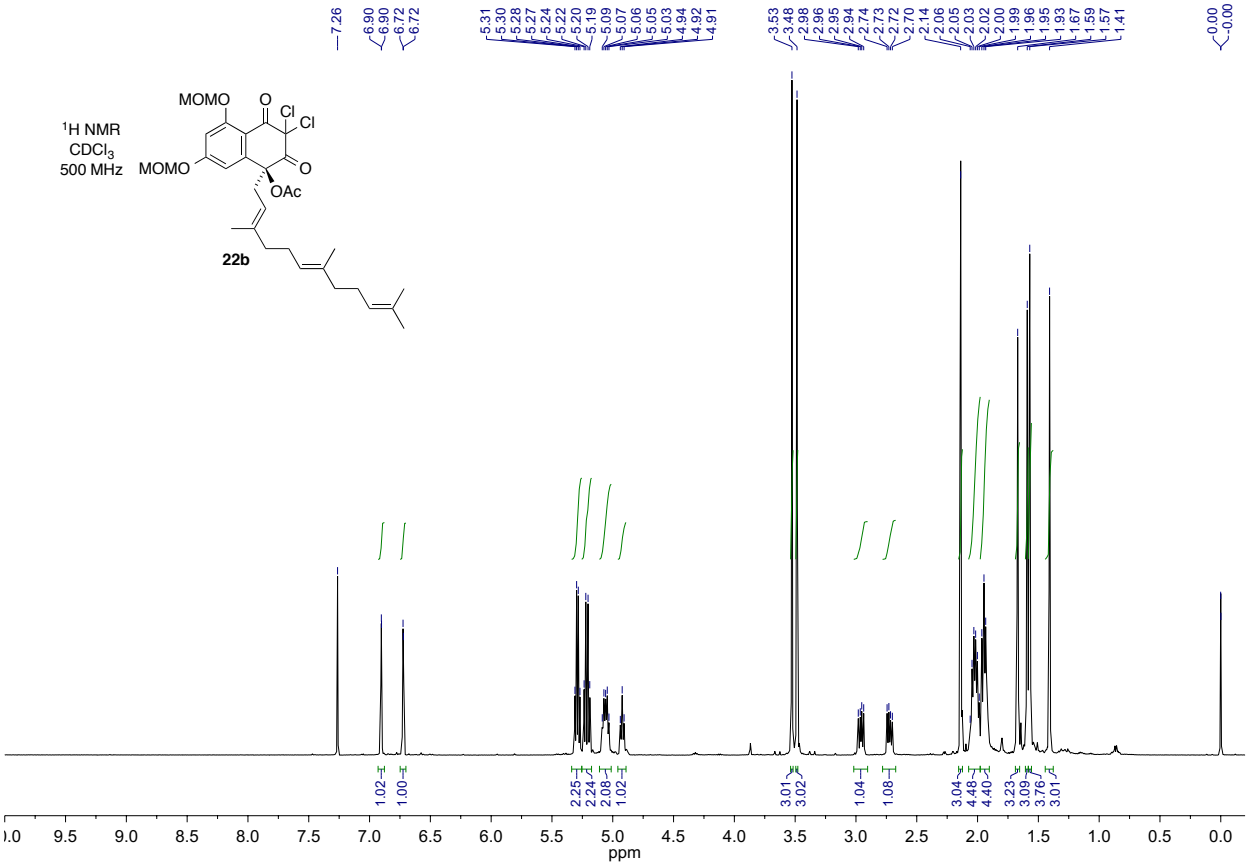
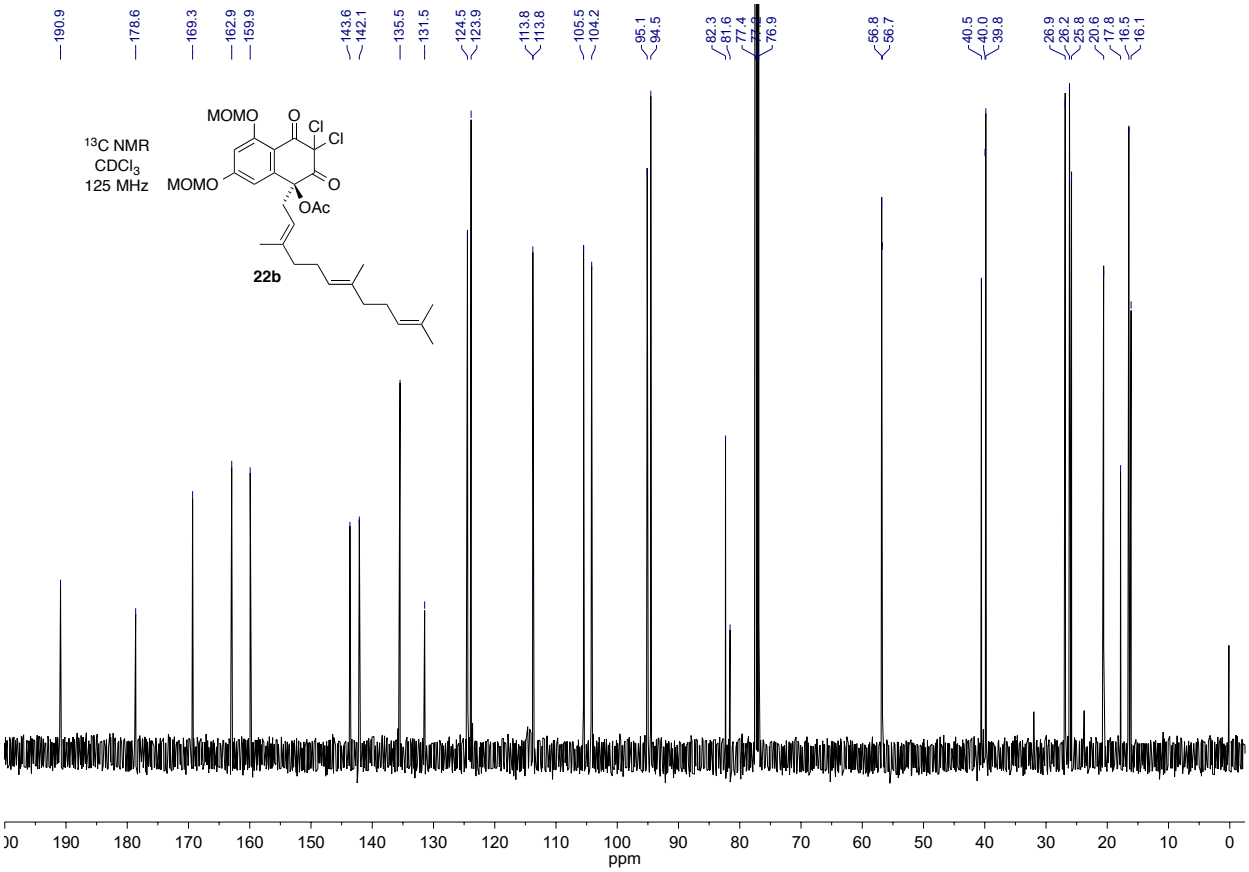
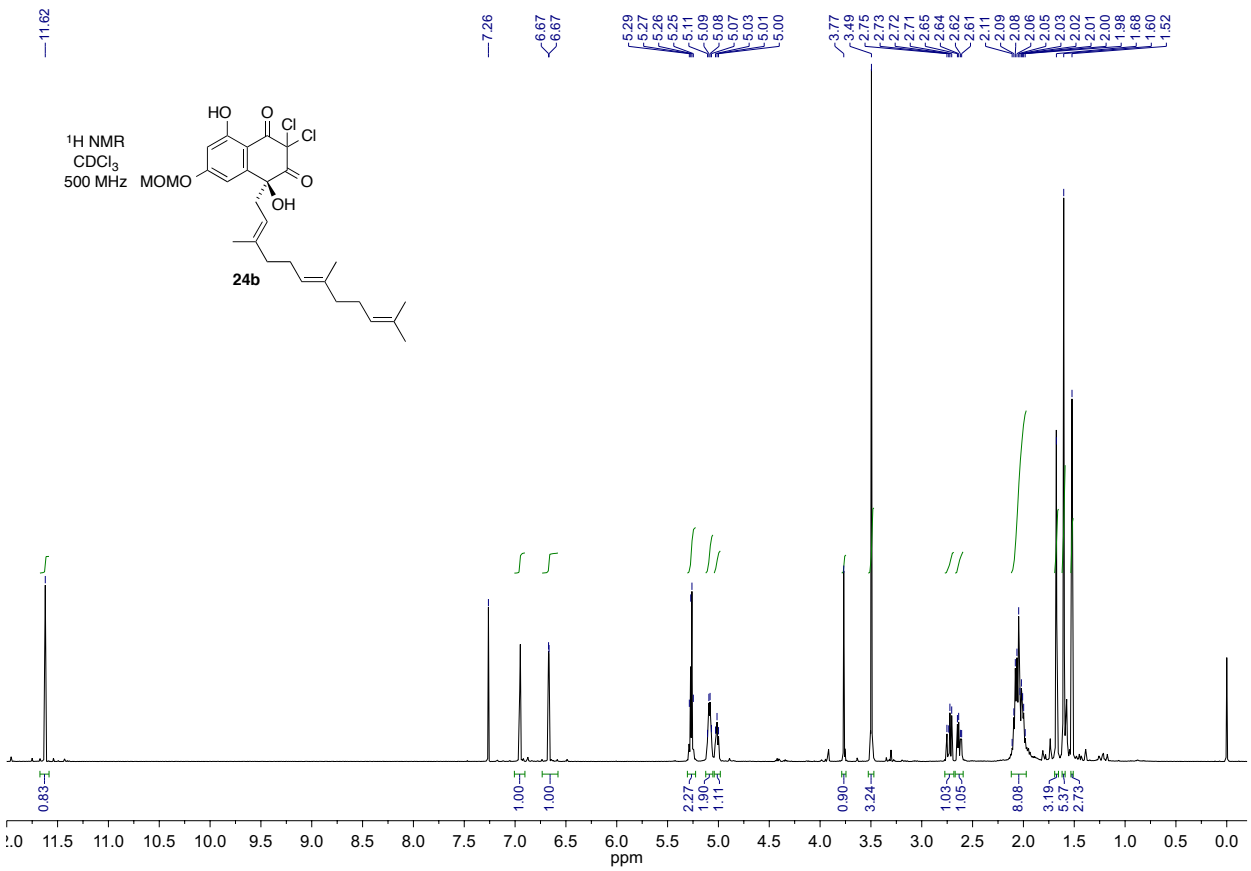
CDCl3
125 MHz
MOMO
OH
MOMO
OH
21b
ppm


^{1}H NMR
$CDCl_3$
500 MHz
MOMO
MOMO
O
Cl
Cl
O
OAc
22b
ppm


^{13}C NMR
$CDCl_3$
125 MHz
MOMO
MOMO
O
Cl
Cl
O
OAc
22b
ppm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5.08
5.07
5.03
5.01
5.00
3.77
3.49
2.75
2.73
2.72
2.71
2.65
2.64
2.62
2.61
2.11
2.09
2.08
2.06
2.05
2.03
2.02
2.01
2.00
1.98
1.68
1.60
1.52
1H NMR
CDCl3
500 MHz
HO
O
Cl
Cl
MOMO
O
OH
24b
0.83
1.00
1.00
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1.11
0.90
3.24
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8.08
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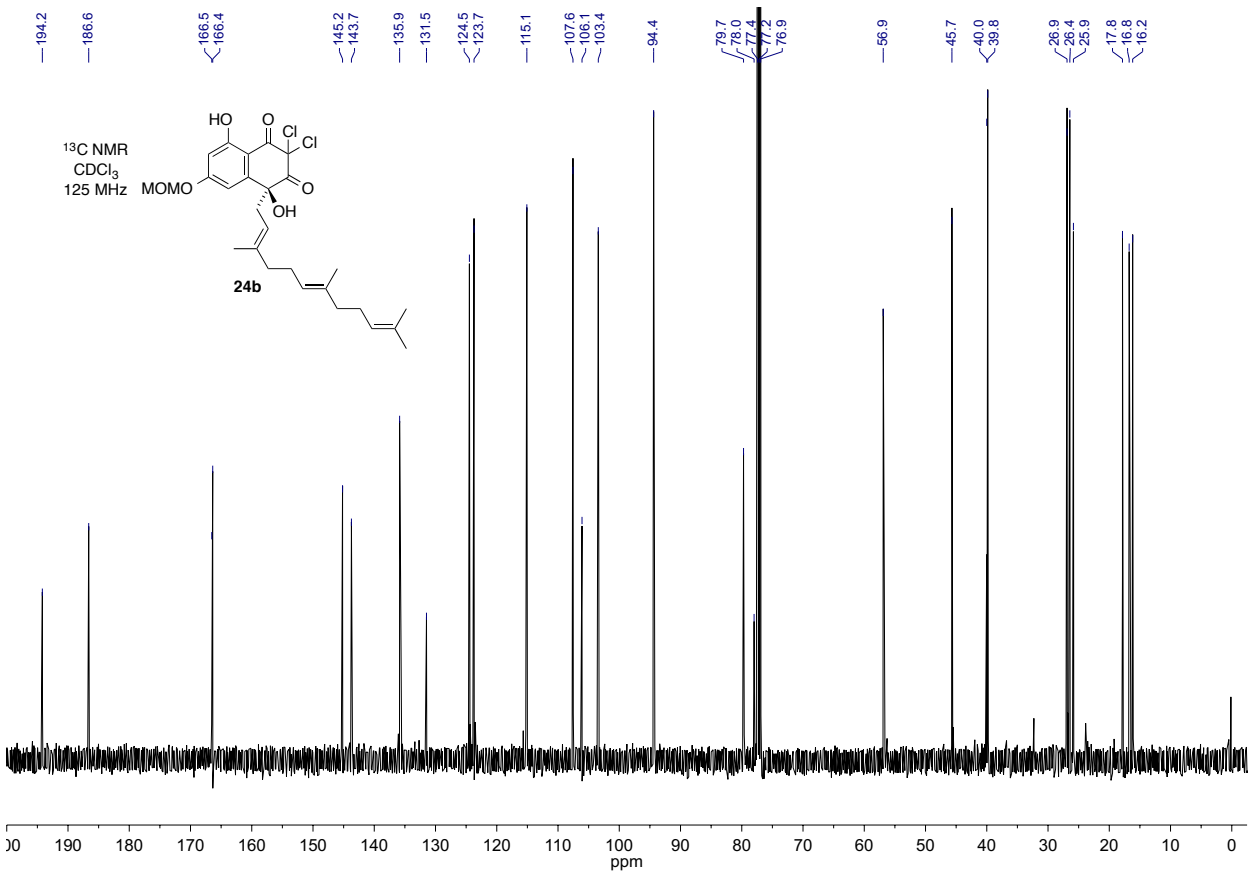
5.37
2.73
ppm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166.4
145.2
143.7
135.9
131.5
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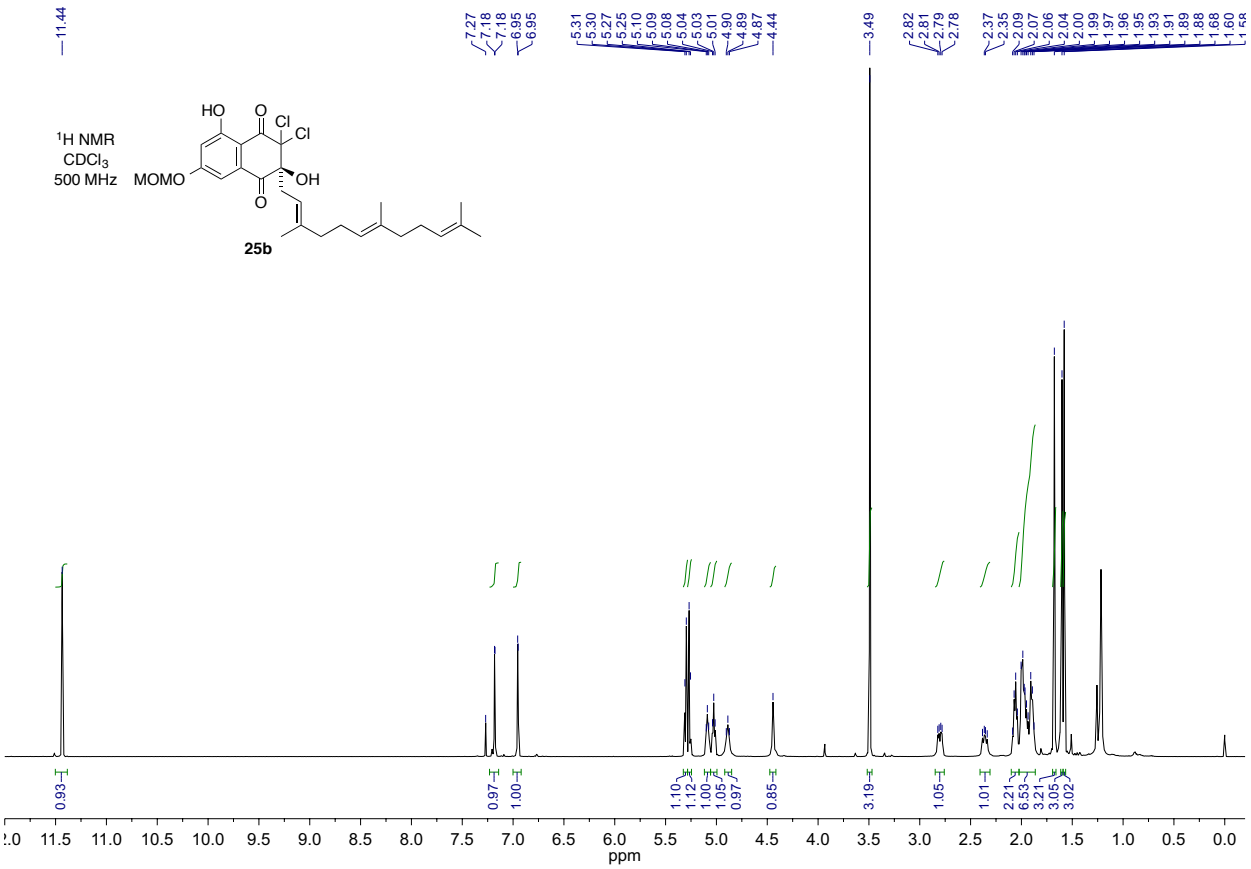
115.1
107.6
106.1
103.4
94.4
79.7
78.0
77.4
77.2
76.9
56.9
45.7
40.0
39.8
26.9
26.4
25.9
17.8
16.8
16.2
13C NMR
CDCl3
125 MHz
HO
O
Cl
Cl
MOMO
O
OH
24b
ppm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7.18
7.18
6.95
6.95
5.31
5.30
5.27
5.25
5.10
5.09
5.08
5.04
5.03
5.01
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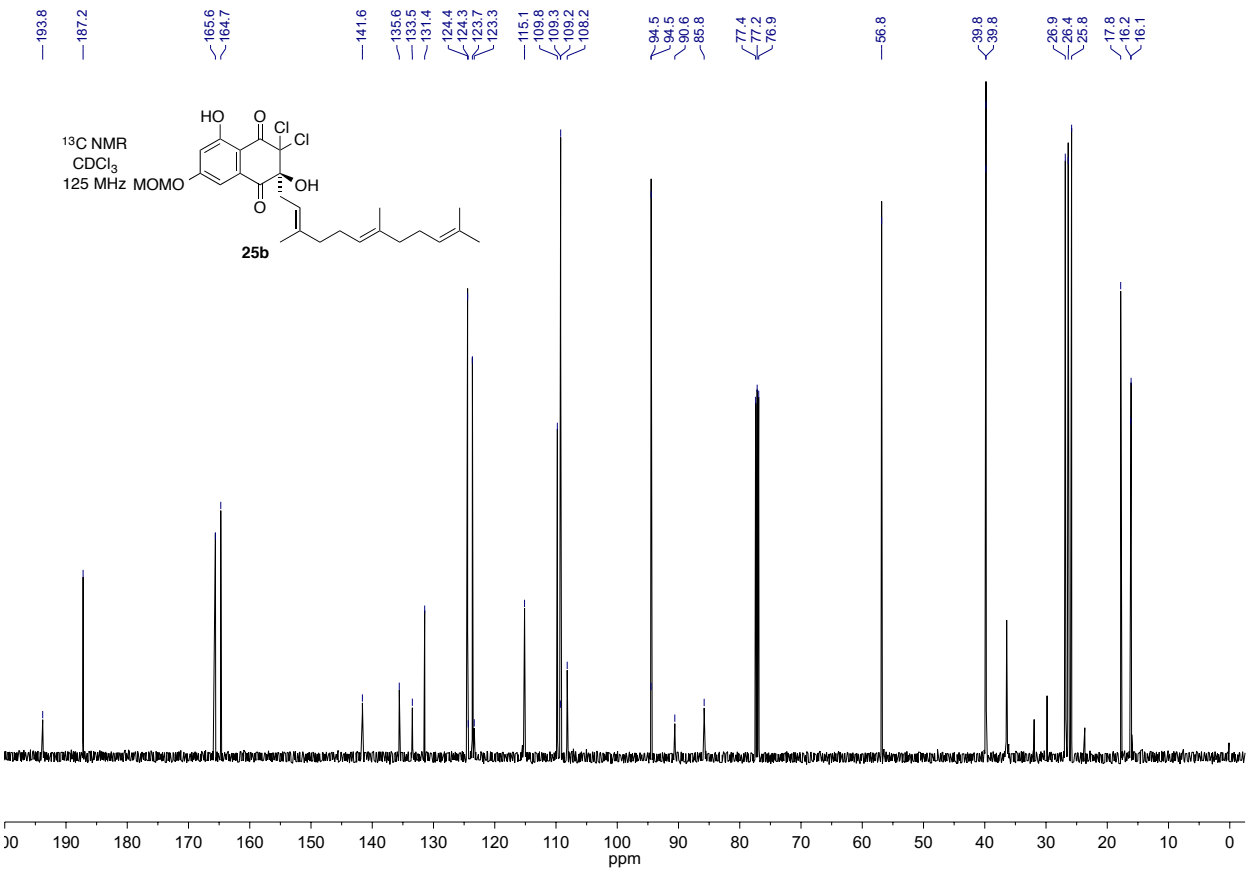
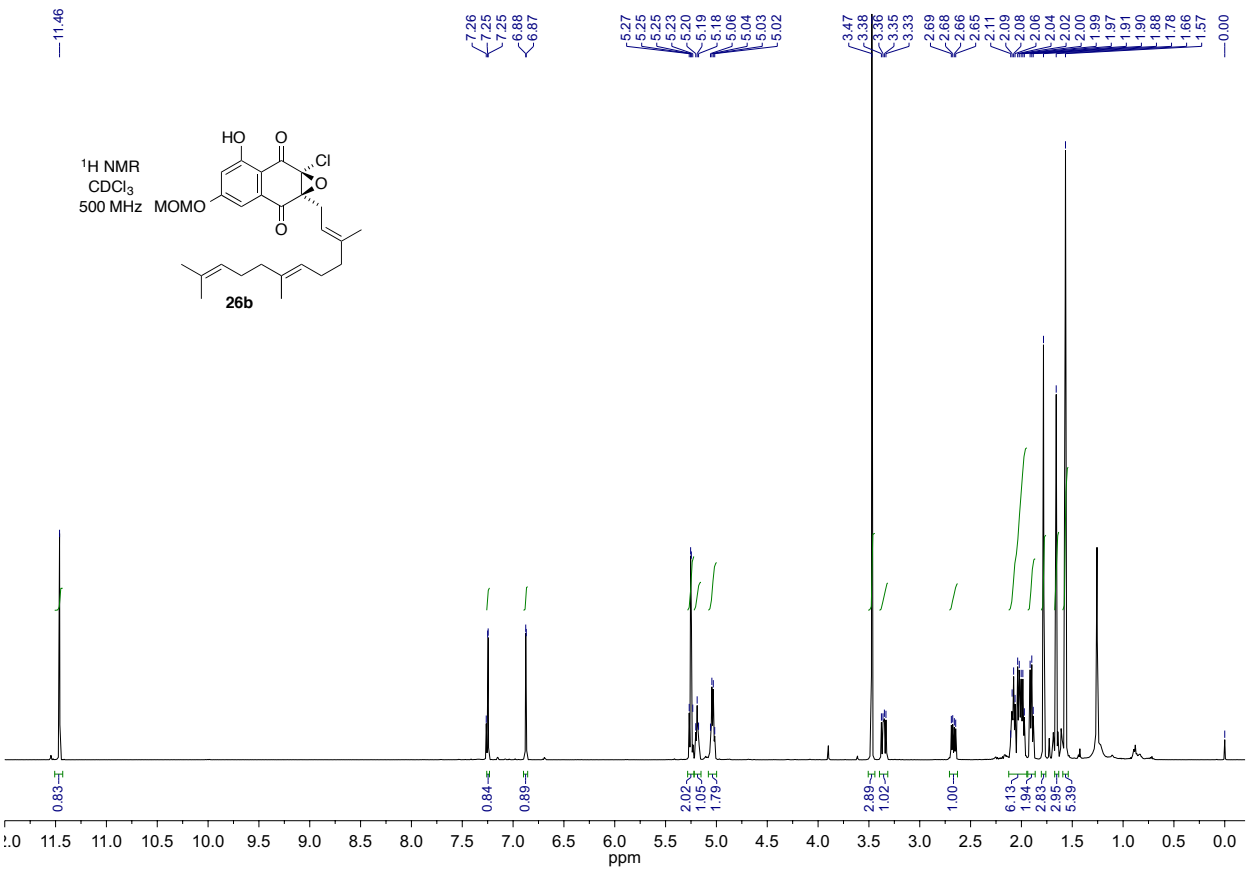
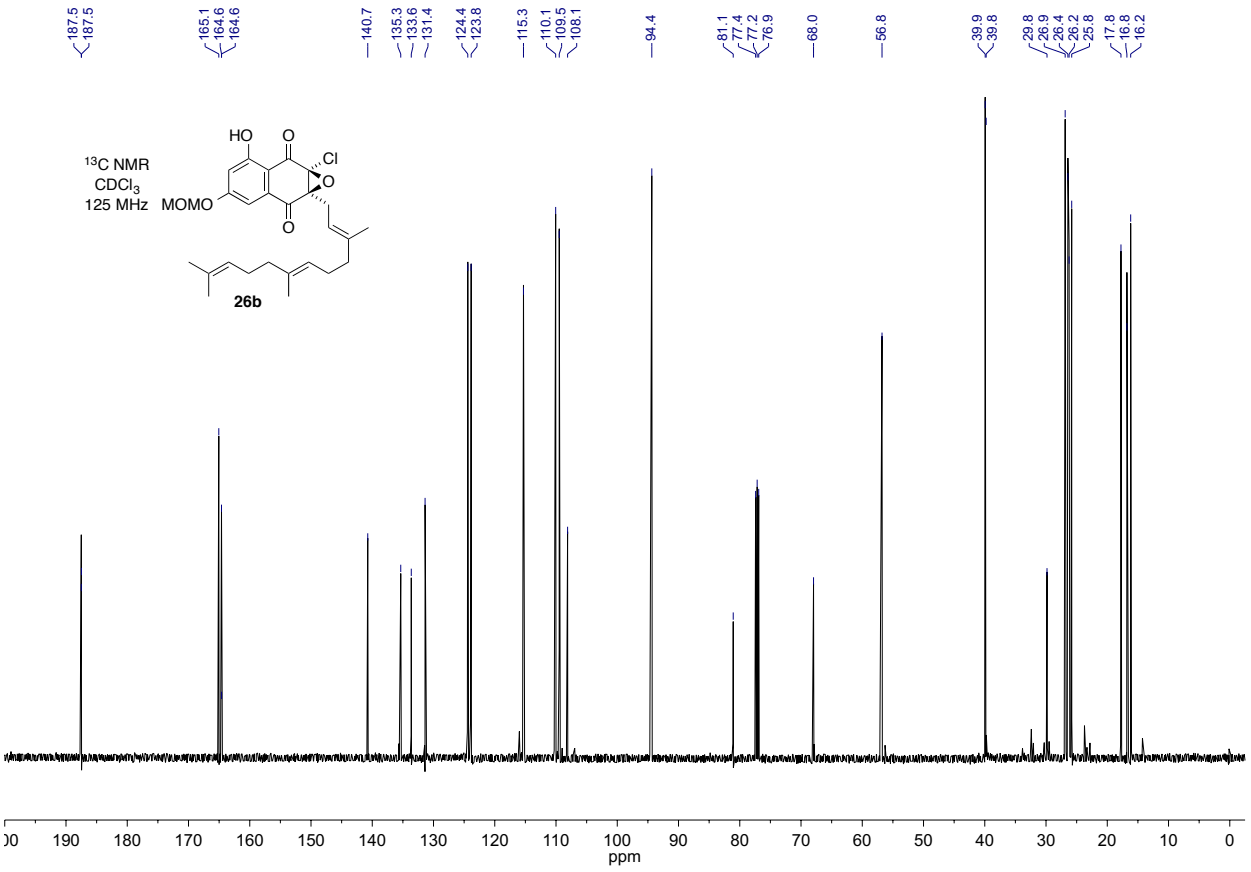
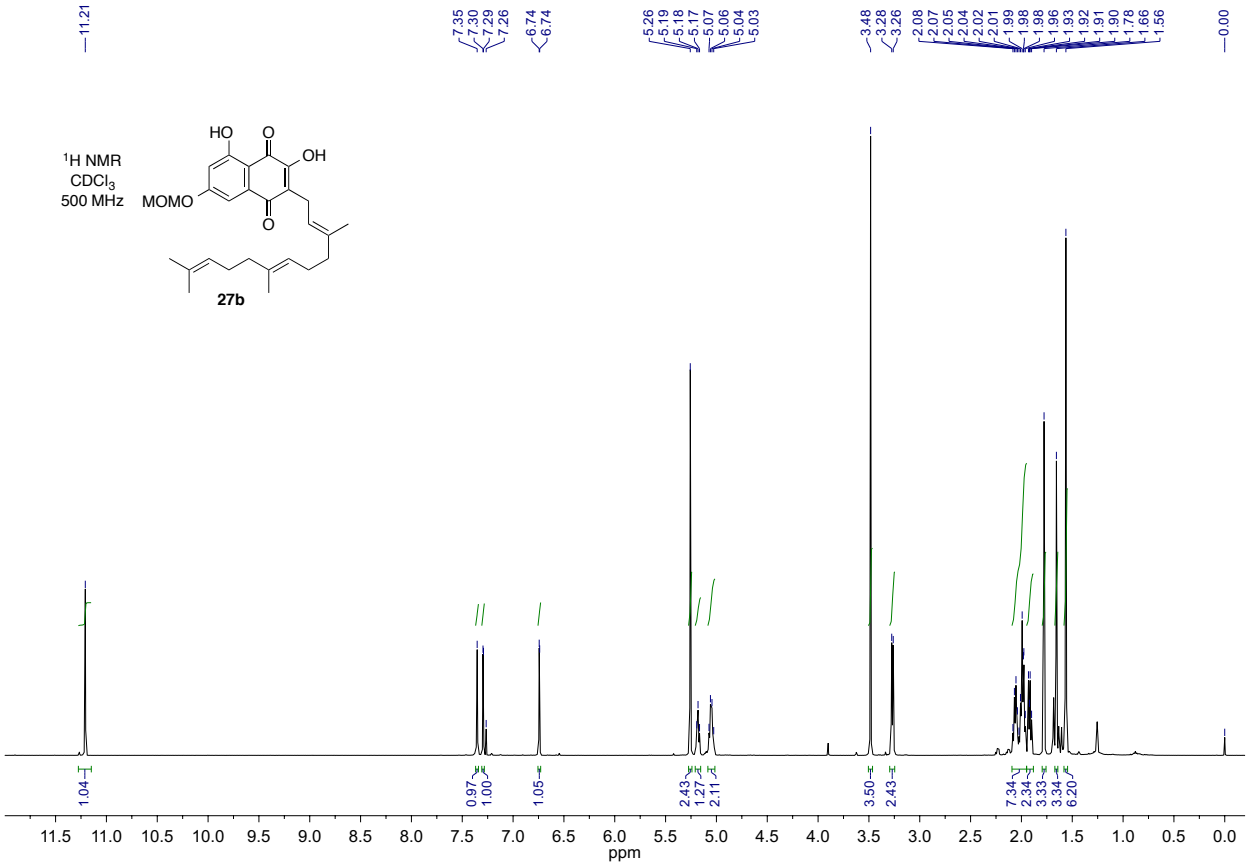
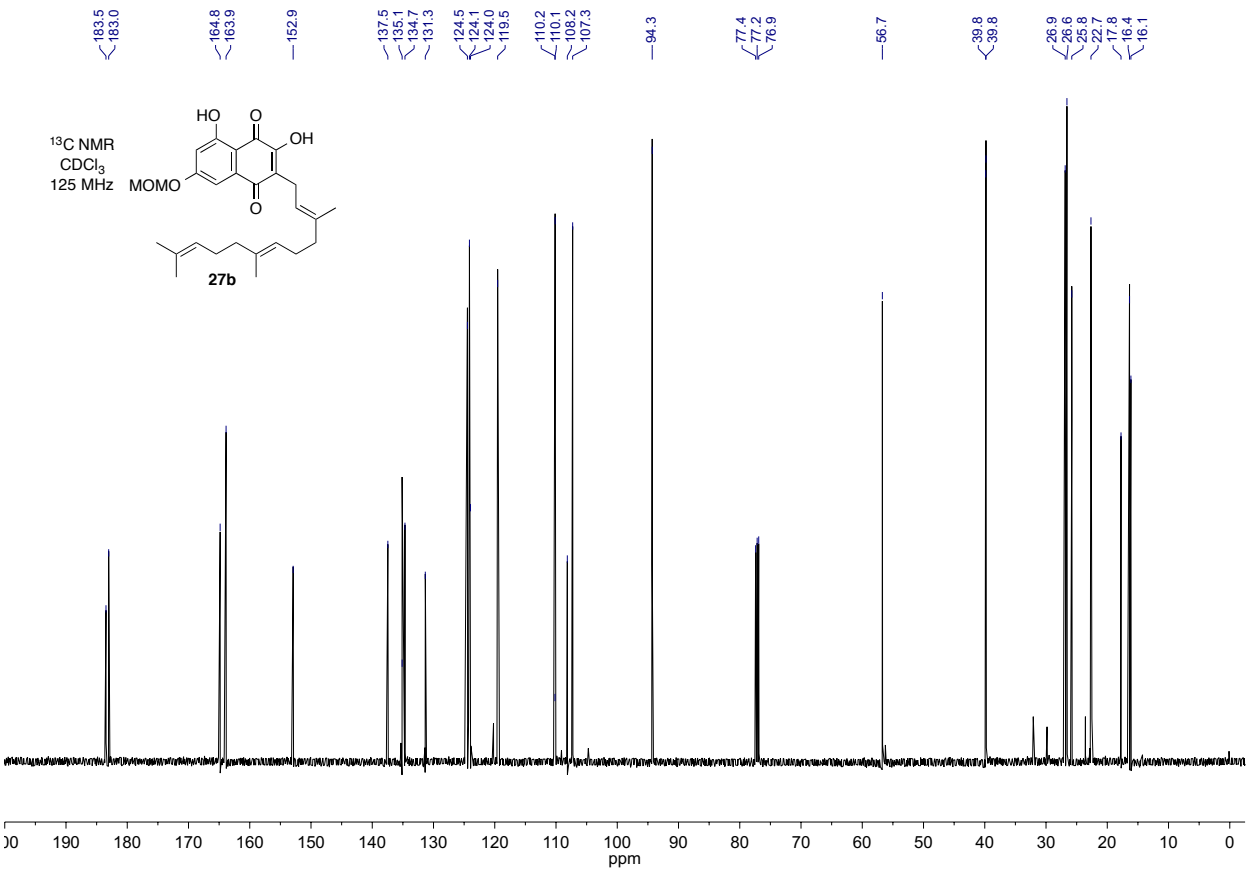
2.04
2.00
1.99
1.97
1.96
1.95
1.93
1.91
1.89
1.88
1.68
1.60
0.93
0.97
1.00
1.10
1.12
1.00
1.05
0.97
0.85
3.19
1.05
1.01
2.21
6.53
3.21
3.05
3.02
ppm
1H NMR
CDCl3
500 MHz
HO
O
Cl
Cl
MOMO
OH
O
25b

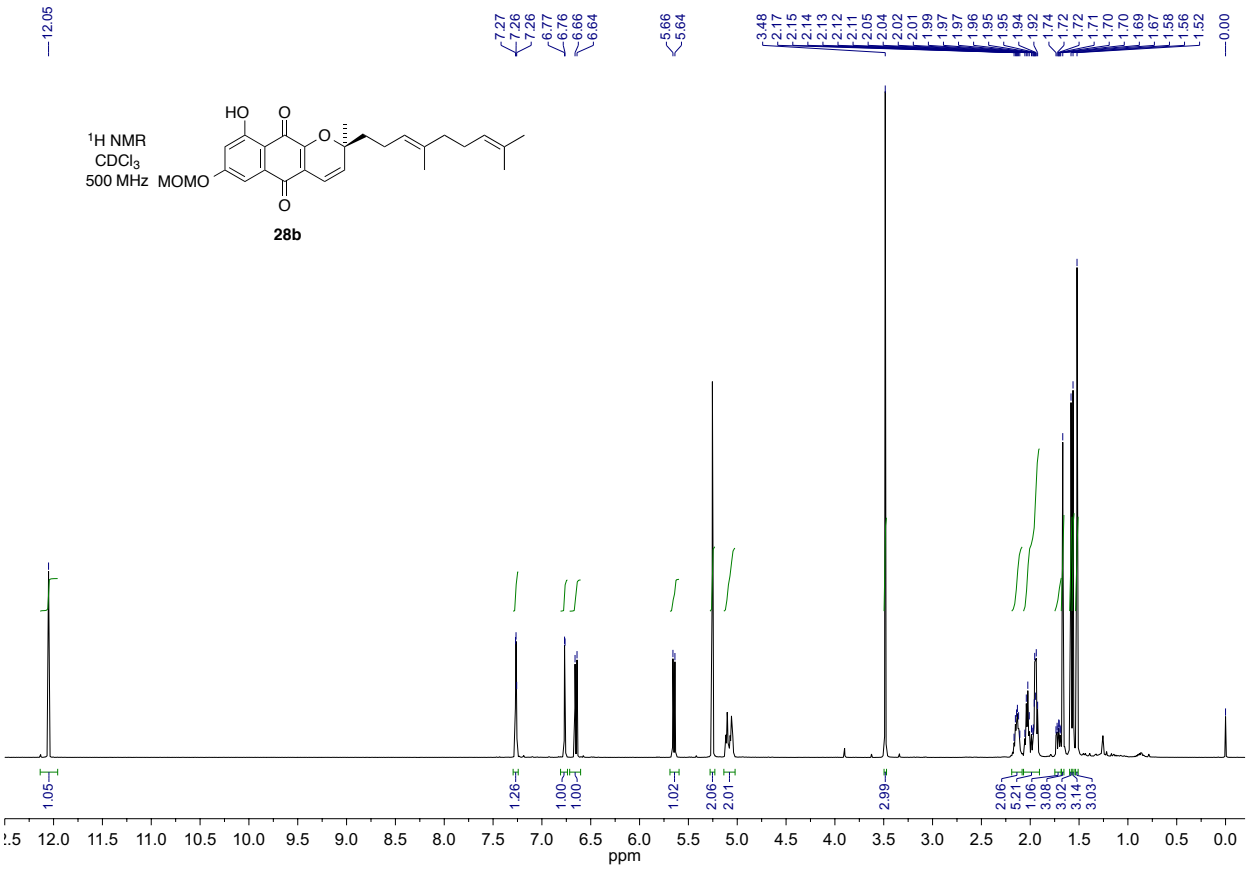

193.8
187.2
165.6
164.7
141.6
135.6
133.5
131.4
124.4
124.3
123.7
123.3
115.1
109.8
109.3
109.2
108.2
94.5
94.5
90.6
85.8
77.4
77.2
76.9
56.8
39.8
39.8
26.9
26.4
25.8
17.8
16.2
16.1
ppm
13C NMR
CDCl3
125 MHz
HO
O
Cl
Cl
MOMO
OH
O
25b

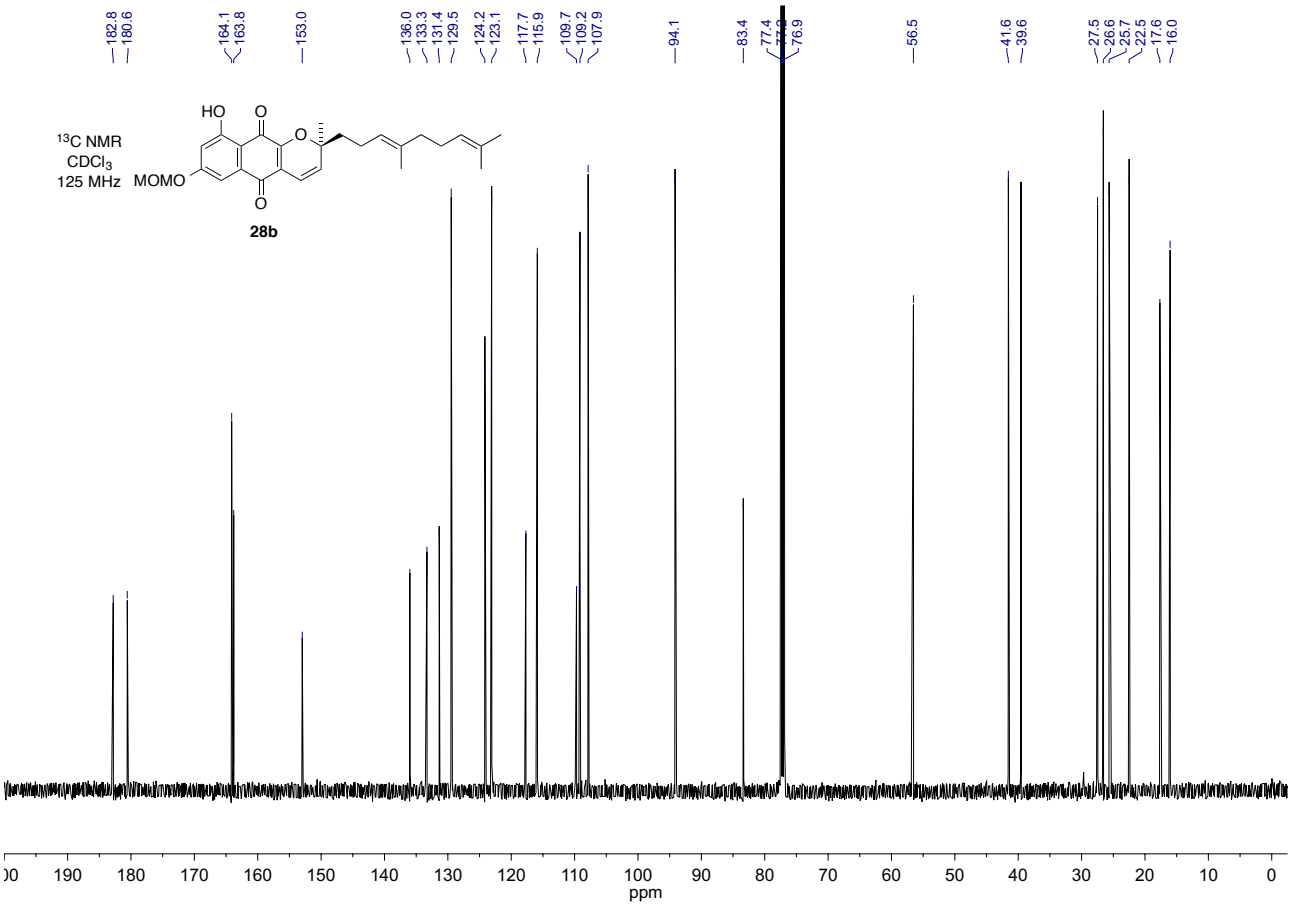

^{1}H NMR
$CDCl_3$
500 MHz
HO
O
Cl
O
MOMO
O
26b
11.46
7.26
7.25
7.25
6.88
6.87
5.27
5.25
5.25
5.23
5.20
5.19
5.18
5.06
5.04
5.03
5.02
3.47
3.38
3.36
3.35
3.33
2.69
2.68
2.66
2.65
2.11
2.09
2.08
2.06
2.04
2.02
2.00
1.99
1.97
1.91
1.90
1.88
1.78
1.66
1.57
0.00
0.83
0.84
0.89
2.02
1.05
1.79
2.89
1.02
1.00
6.13
1.94
2.83
2.95
5.39
ppm

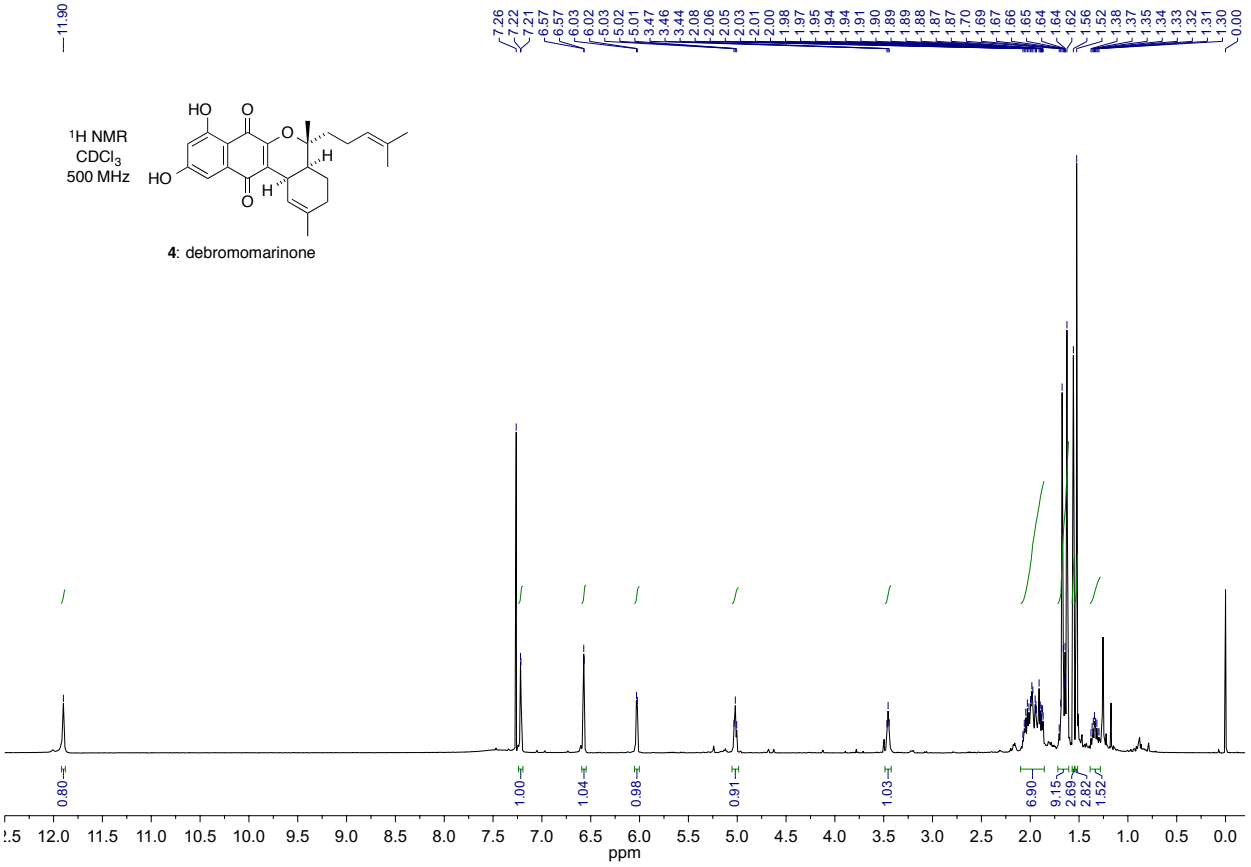

^{13}C NMR
$CDCl_3$
125 MHz
HO
O
Cl
O
MOMO
O
26b
187.5
187.5
165.1
164.6
164.6
140.7
135.3
133.6
131.4
124.4
123.8
115.3
110.1
109.5
108.1
94.4
81.1
77.4
77.2
76.9
68.0
56.8
39.9
39.8
29.8
26.9
26.4
26.2
25.8
17.8
16.8
16.2
ppm

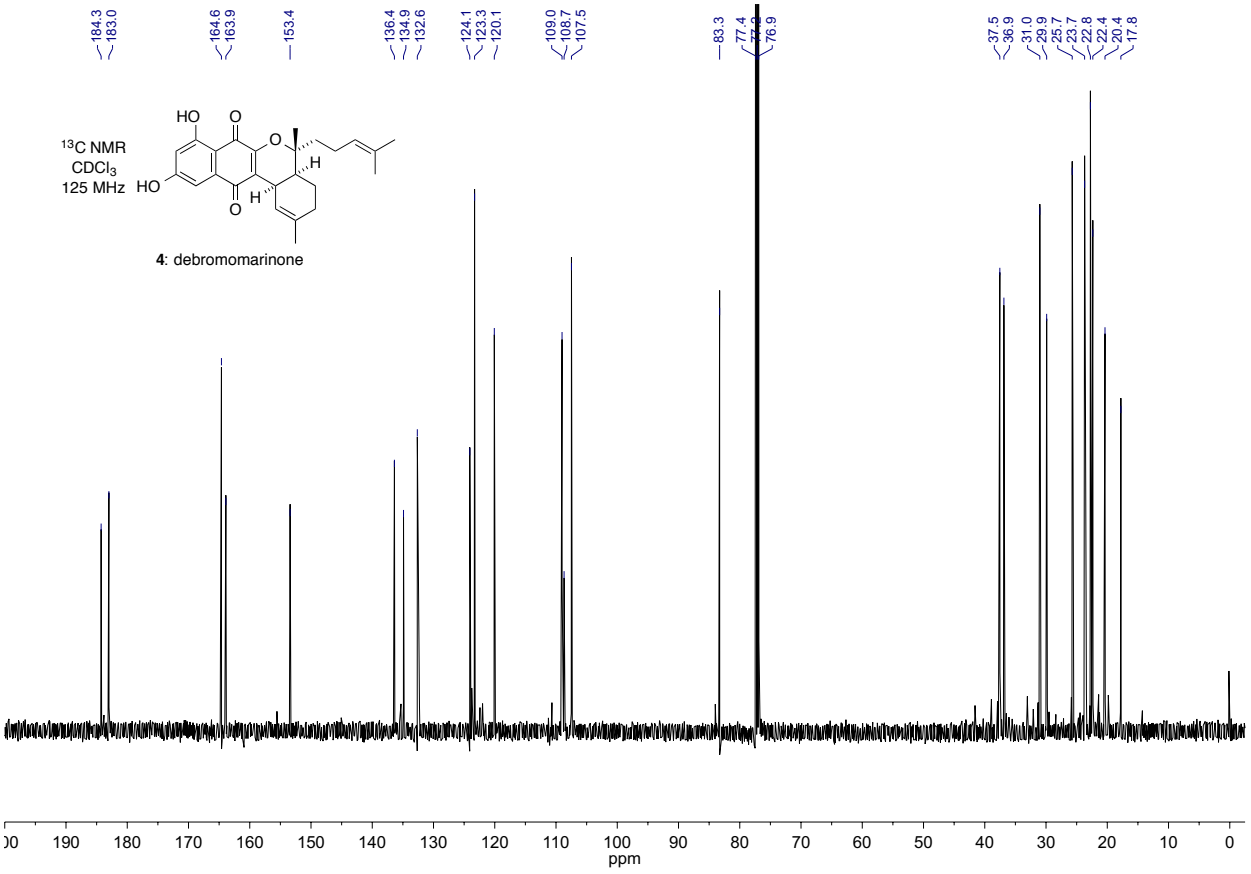

11.21
7.35
7.30
7.29
7.26
6.74
6.74
5.26
5.19
5.18
5.17
5.07
5.06
5.04
5.03
3.48
3.28
3.26
2.08
2.07
2.05
2.04
2.02
2.01
1.99
1.98
1.98
1.96
1.93
1.92
1.91
1.90
1.78
1.66
1.56
0.00
1H NMR
CDCl3
500 MHz
HO
O
OH
MOMO
O
27b
1.04
0.97
1.00
1.05
2.43
1.27
2.11
3.50
2.43
7.34
2.34
3.33
3.34
6.20
11.5 11.0 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 0.5 0.0
ppm

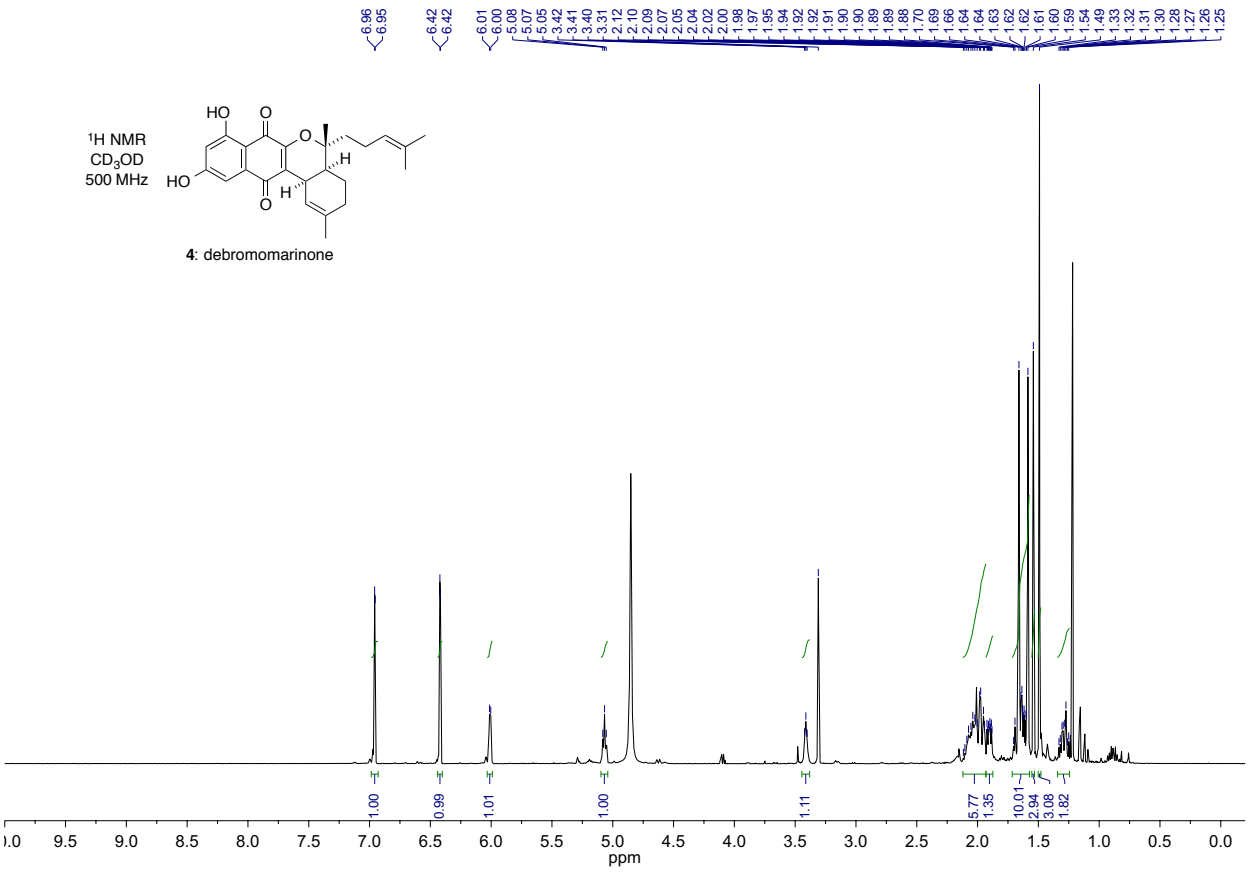

183.5
183.0
164.8
163.9
152.9
137.5
135.1
134.7
131.3
124.5
124.1
124.0
119.5
110.2
110.1
108.2
107.3
94.3
77.4
77.2
76.9
56.7
39.8
39.8
26.9
26.6
25.8
22.7
17.8
16.4
16.1
13C NMR
CDCl3
125 MHz
HO
O
OH
MOMO
O
27b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

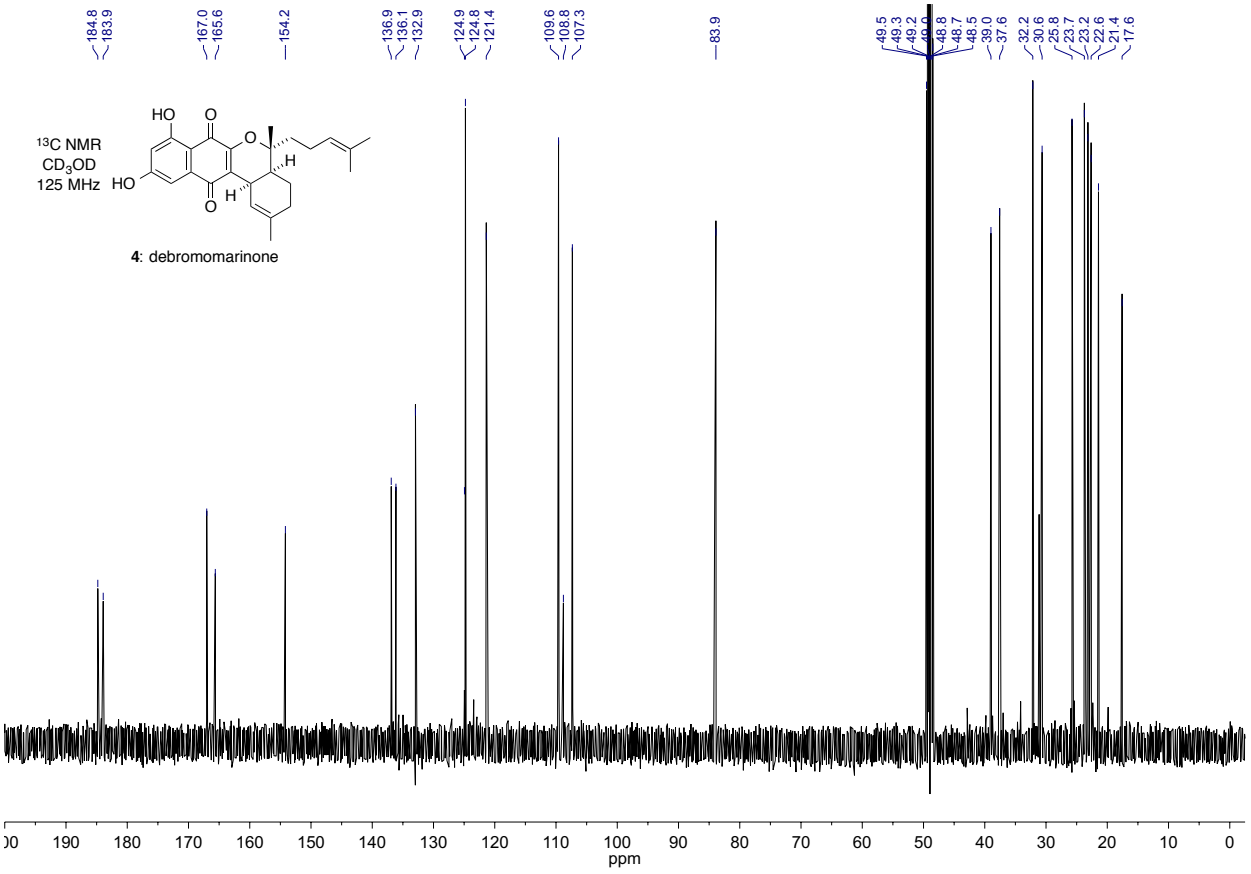

12.05
7.27
7.26
7.26
6.77
6.76
6.66
6.64
5.66
5.64
3.48
2.17
2.15
2.14
2.13
2.12
2.11
2.05
2.04
2.02
2.01
1.99
1.97
1.97
1.96
1.95
1.95
1.94
1.92
1.74
1.72
1.72
1.71
1.70
1.70
1.69
1.67
1.58
1.56
1.52
0.00
1H NMR
CDCl3
500 MHz
HO
O
O
MOMO
O
28b
1.05
1.26
1.00
1.00
1.02
2.06
2.01
2.99
2.06
5.21
1.06
3.08
3.02
3.14
3.03
12.0 11.5 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 0.5 0.0
ppm

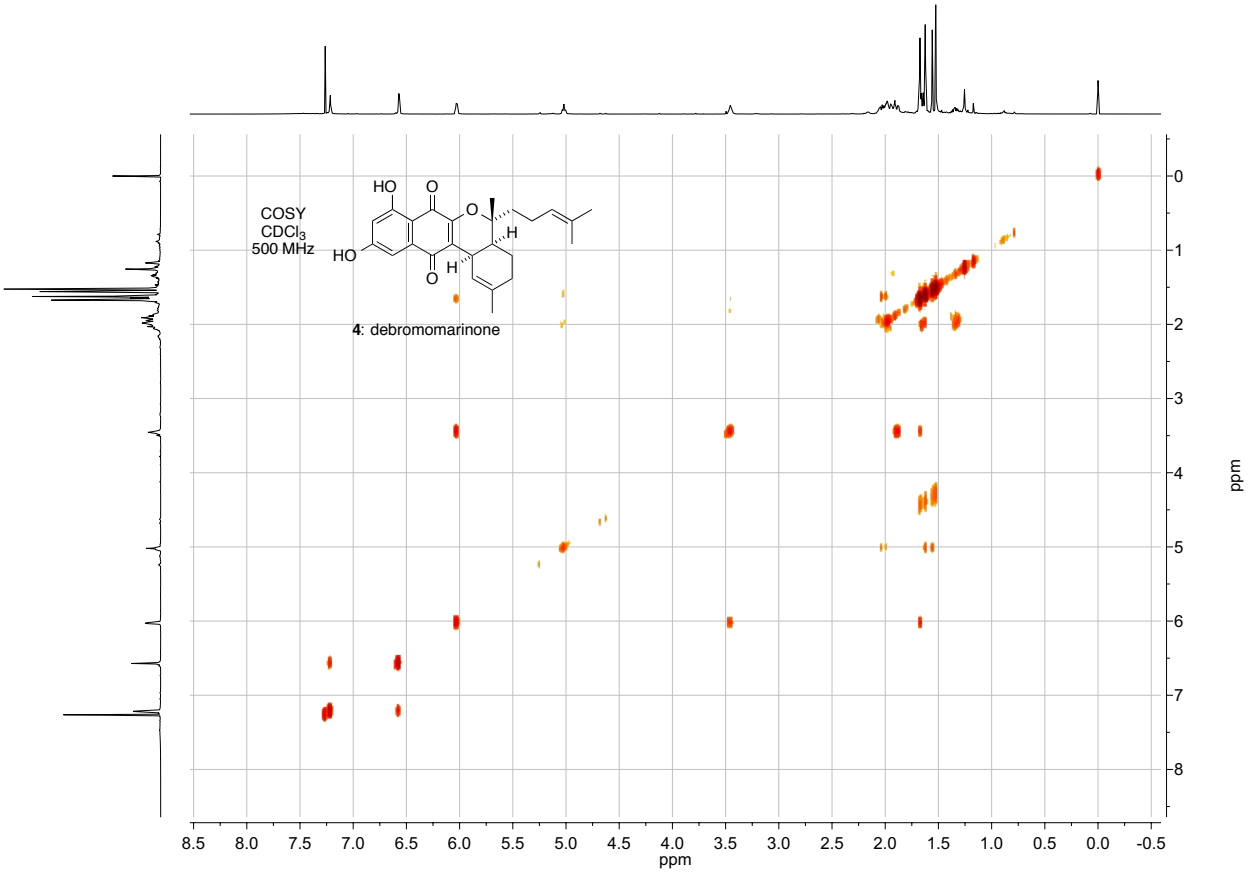

182.8
180.6
164.1
163.8
153.0
136.0
133.3
131.4
129.5
124.2
123.1
117.7
115.9
109.7
109.2
107.9
94.1
83.4
77.4
77.0
76.9
56.5
41.6
39.6
27.5
26.6
25.7
22.5
17.6
16.0
13C NMR
CDCl3
125 MHz
HO
O
O
MOMO
O
28b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

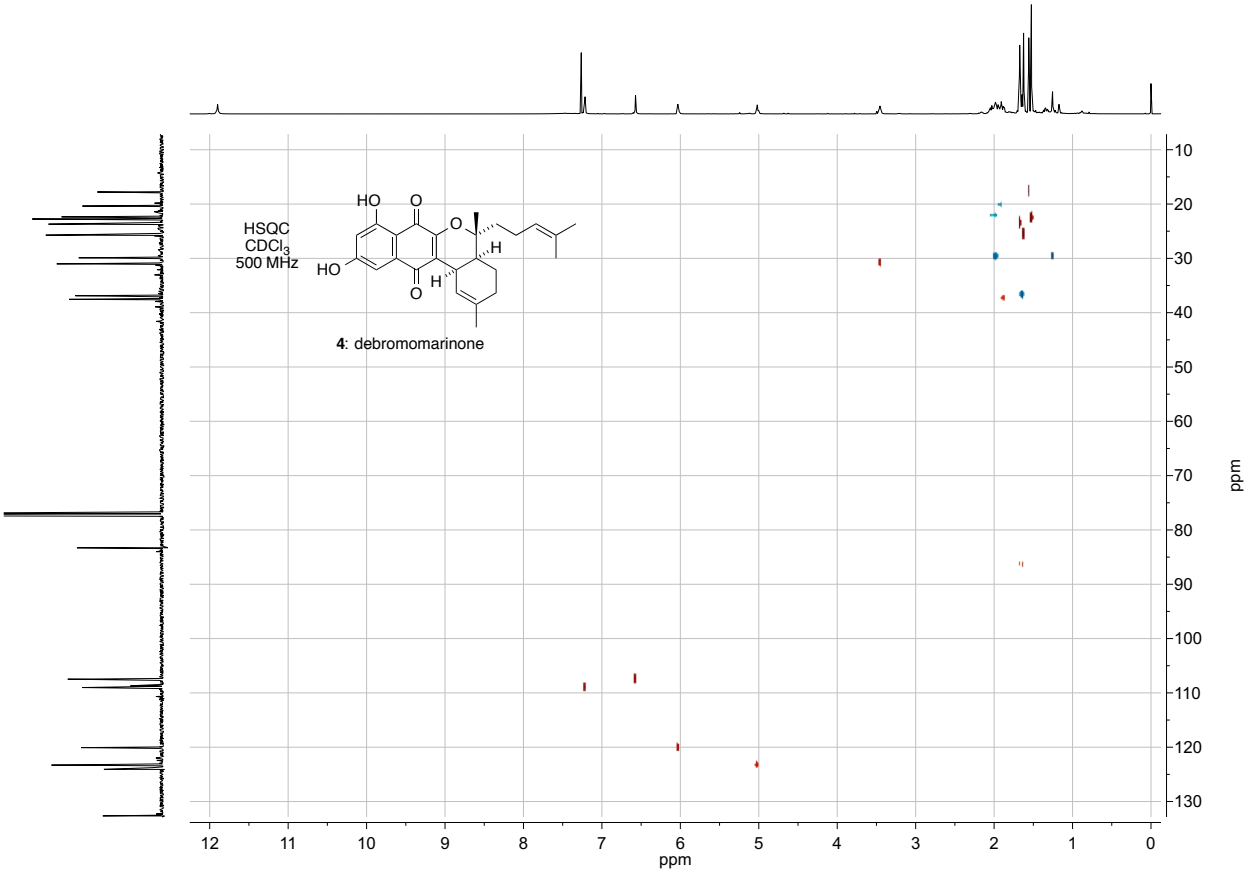

11.90
7.26 7.22 7.21 6.57 6.57 6.03 6.02 5.03 5.02 5.01 3.47 3.46 3.44 2.08 2.06 2.05 2.03 2.01 2.00 1.98 1.97 1.95 1.94 1.94 1.91 1.90 1.89 1.89 1.88 1.87 1.87 1.70 1.69 1.67 1.66 1.65 1.64 1.64 1.62 1.56 1.52 1.38 1.37 1.35 1.34 1.33 1.32 1.31 1.30 0.00
1H NMR
CDCl3
500 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
0.80 1.00 1.04 0.98 0.91 1.03 6.90 9.15 2.69 2.82 1.52
12.0 11.5 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 0.5 0.0
ppm

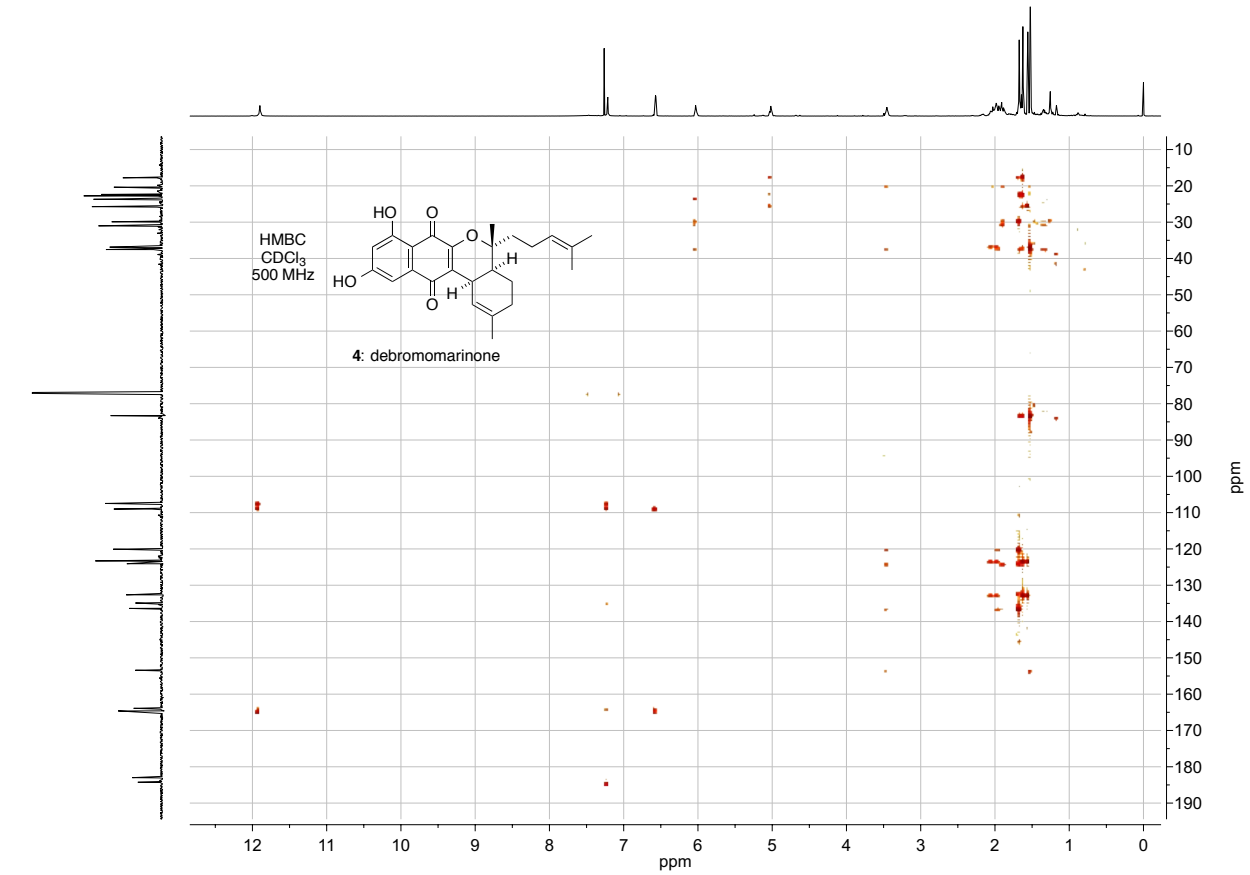

184.3 183.0 164.6 163.9 153.4 136.4 134.9 132.6 124.1 123.3 120.1 109.0 108.7 107.5 83.3 77.4 77.0 76.9 37.5 36.9 31.0 29.9 25.7 23.7 22.8 22.4 20.4 17.8
13C NMR
CDCl3
125 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

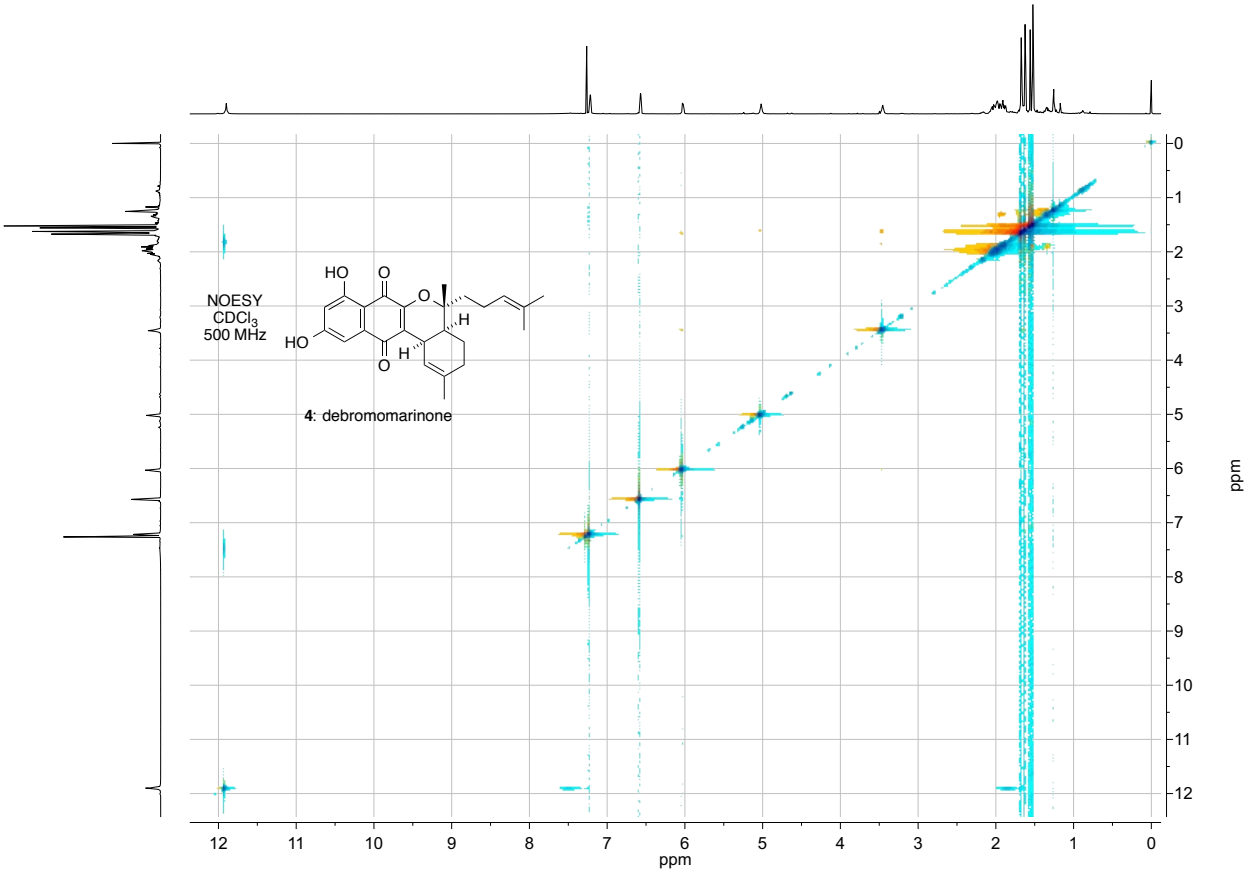

6.96
6.95
6.42
6.42
6.01
6.00
5.08
5.07
5.05
3.42
3.41
3.40
3.31
2.12
2.10
2.09
2.07
2.05
2.04
2.02
2.00
1.98
1.97
1.95
1.94
1.92
1.92
1.91
1.90
1.90
1.89
1.89
1.88
1.70
1.69
1.66
1.64
1.64
1.63
1.62
1.62
1.61
1.60
1.59
1.54
1.49
1.33
1.32
1.31
1.30
1.28
1.27
1.26
1.25
1H NMR
CD3OD
500 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
1.00
0.99
1.01
1.00
1.11
5.77
1.35
10.01
2.94
3.08
1.82
ppm

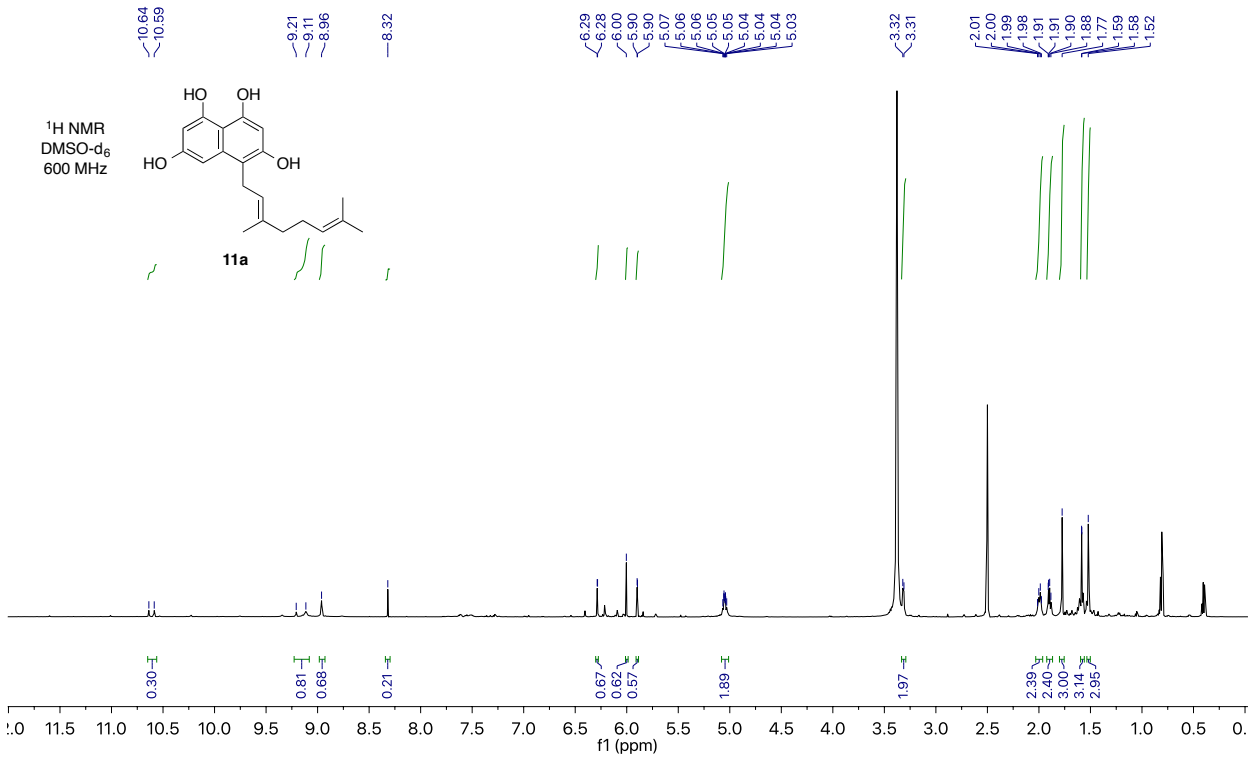

184.8
183.9
167.0
165.6
154.2
136.9
136.1
132.9
124.9
124.8
121.4
109.6
108.8
107.3
83.9
49.5
49.3
49.2
48.8
48.7
48.5
39.0
37.6
32.2
30.6
25.8
23.7
23.2
22.6
21.4
17.6
13C NMR
CD3OD
125 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
ppm

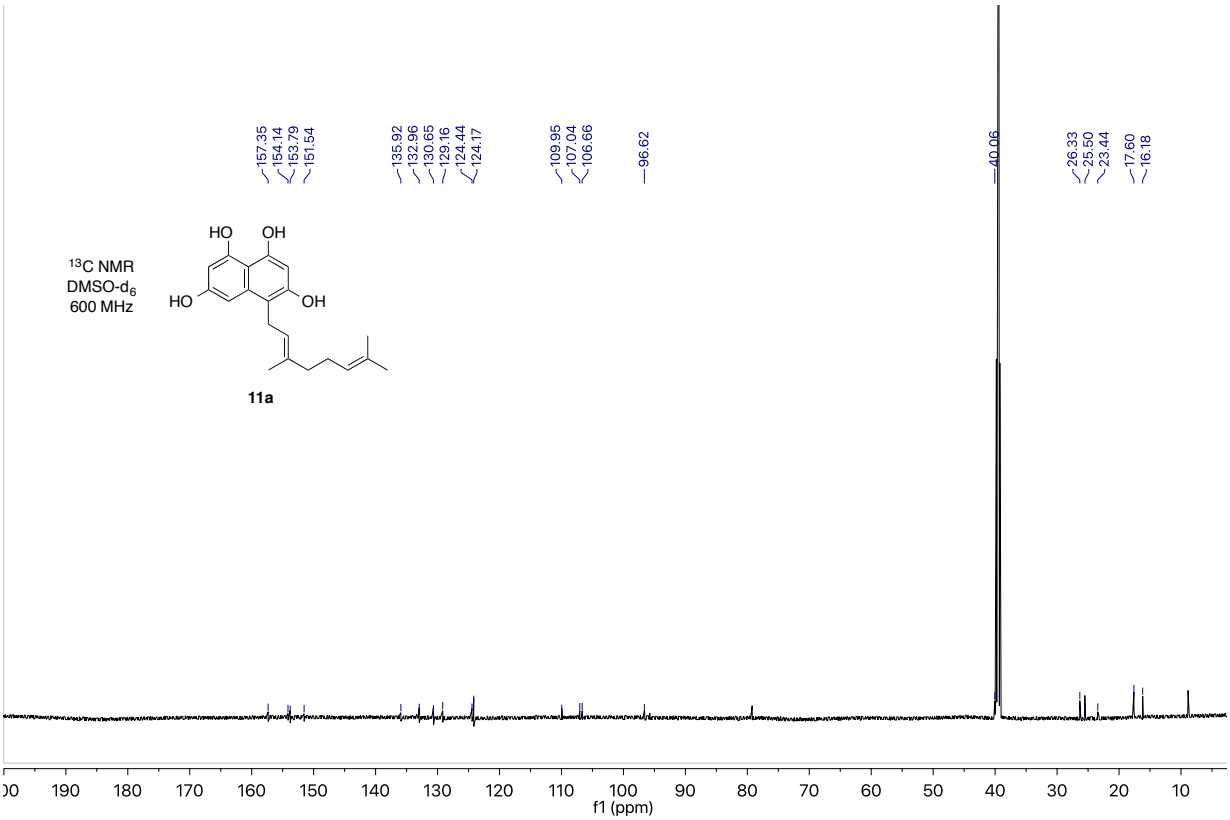

COSY
CDCl3
500 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
ppm
ppm

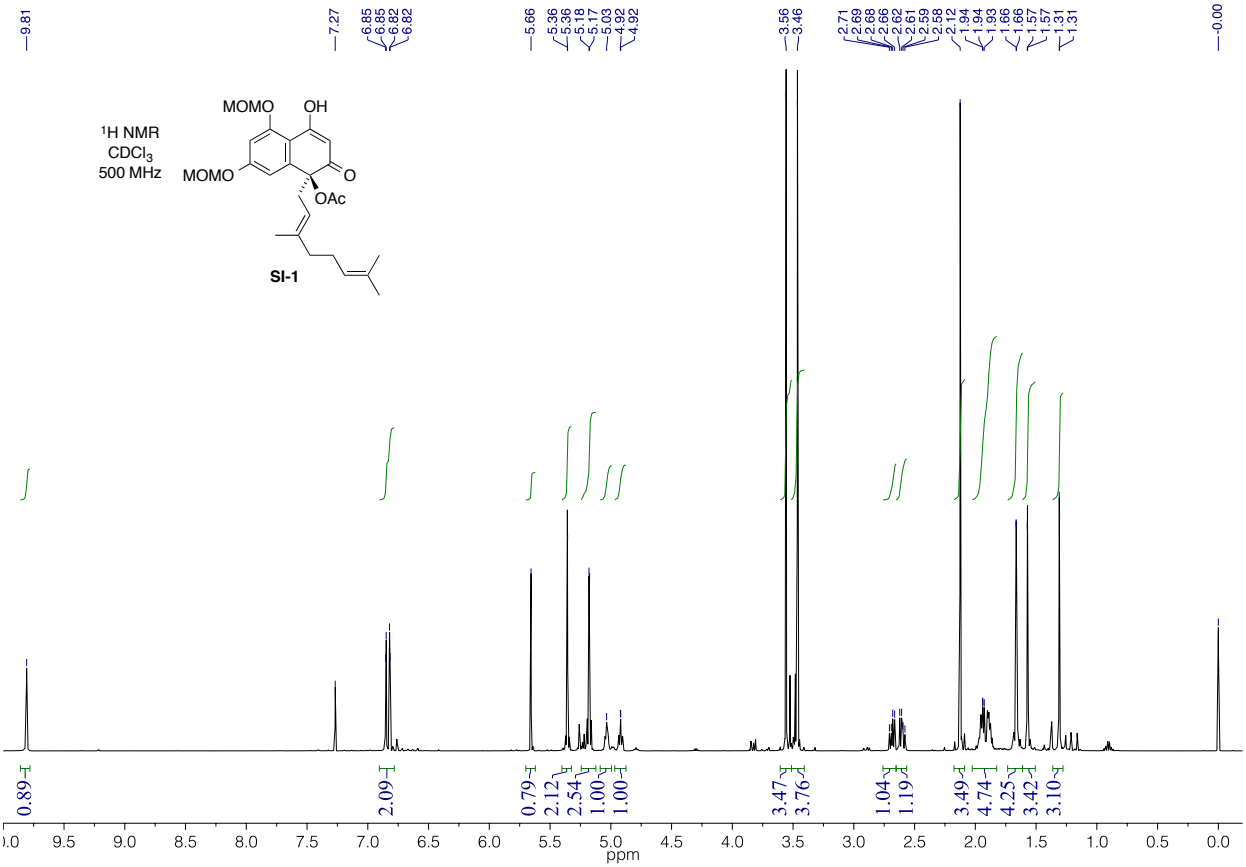

HSQC
CDCl3
500 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
ppm
ppm

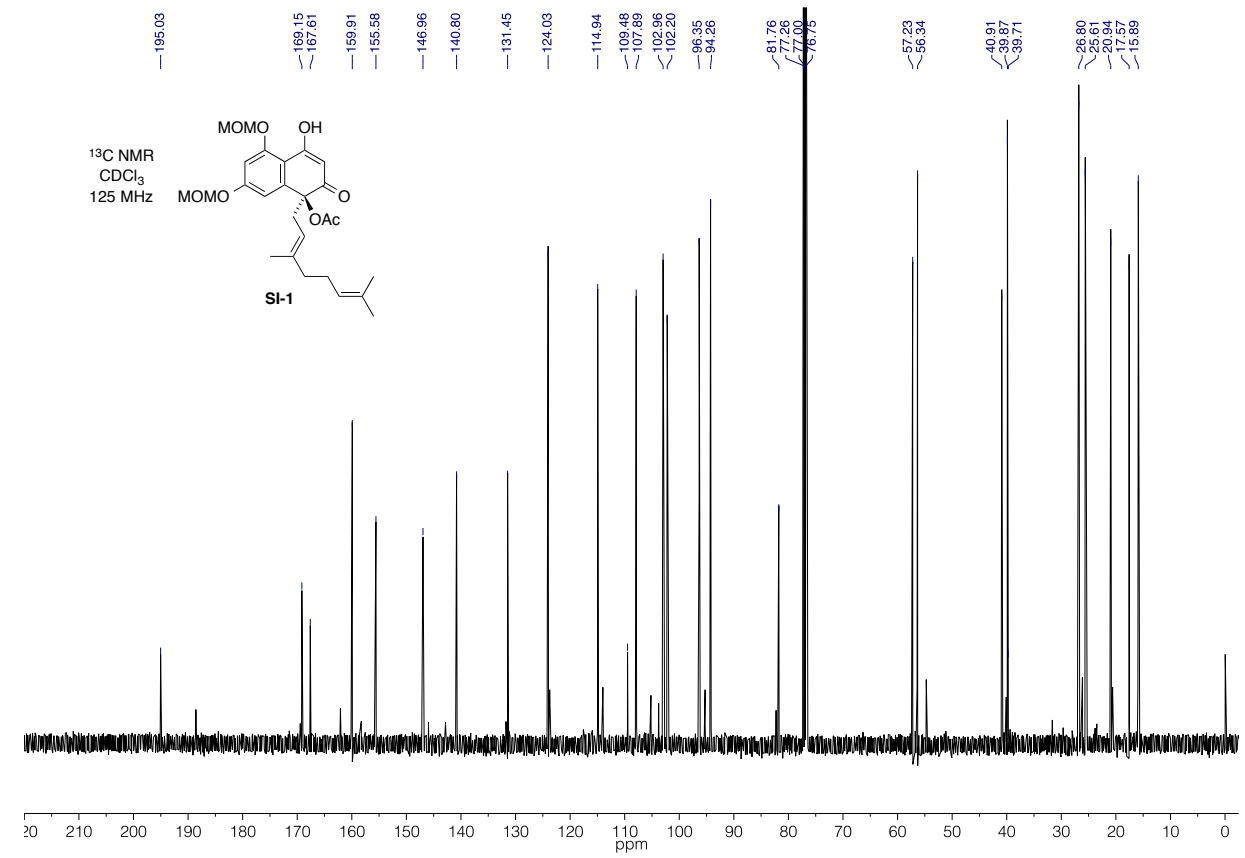

HMBC
CDCl3
500 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
ppm
ppm

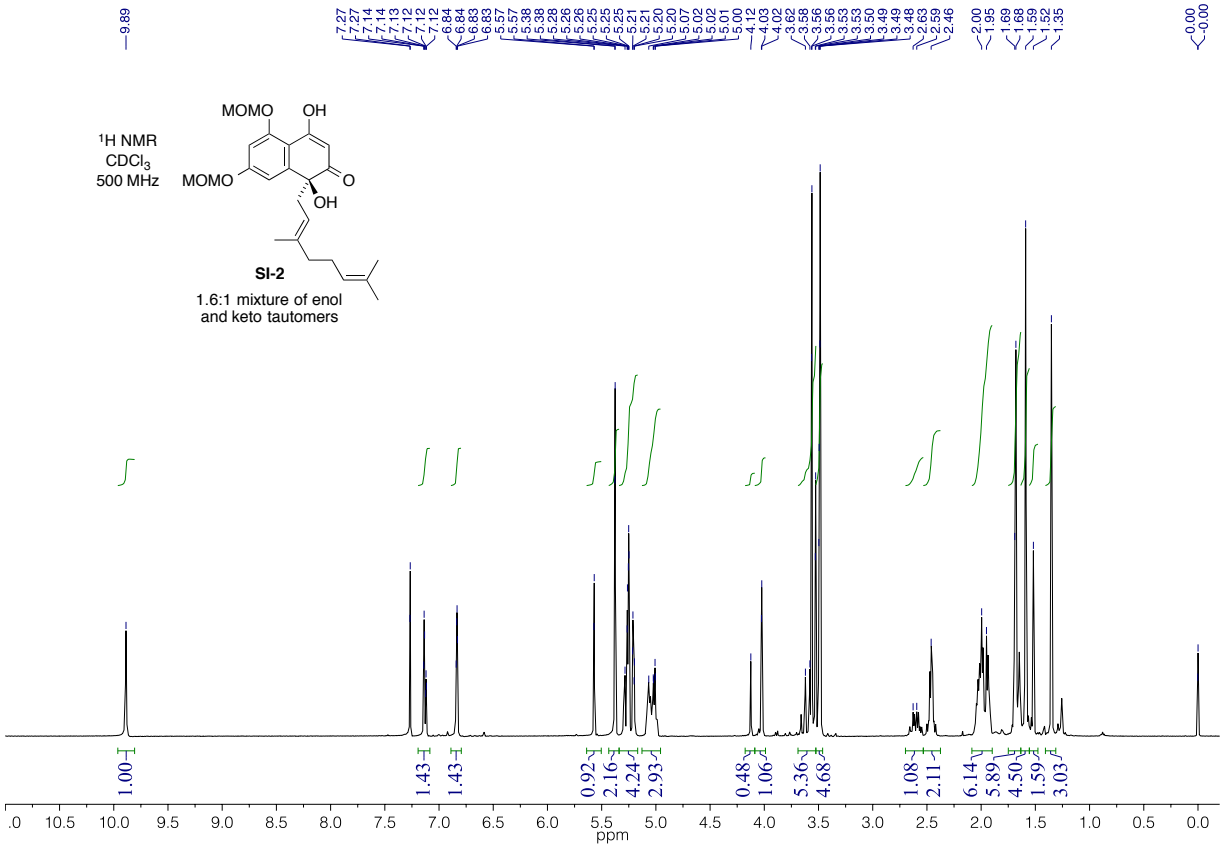

NOESY
CDCl3
500 MHz
HO
O
O
H
HO
H
O
4: debromomarinone
ppm
ppm

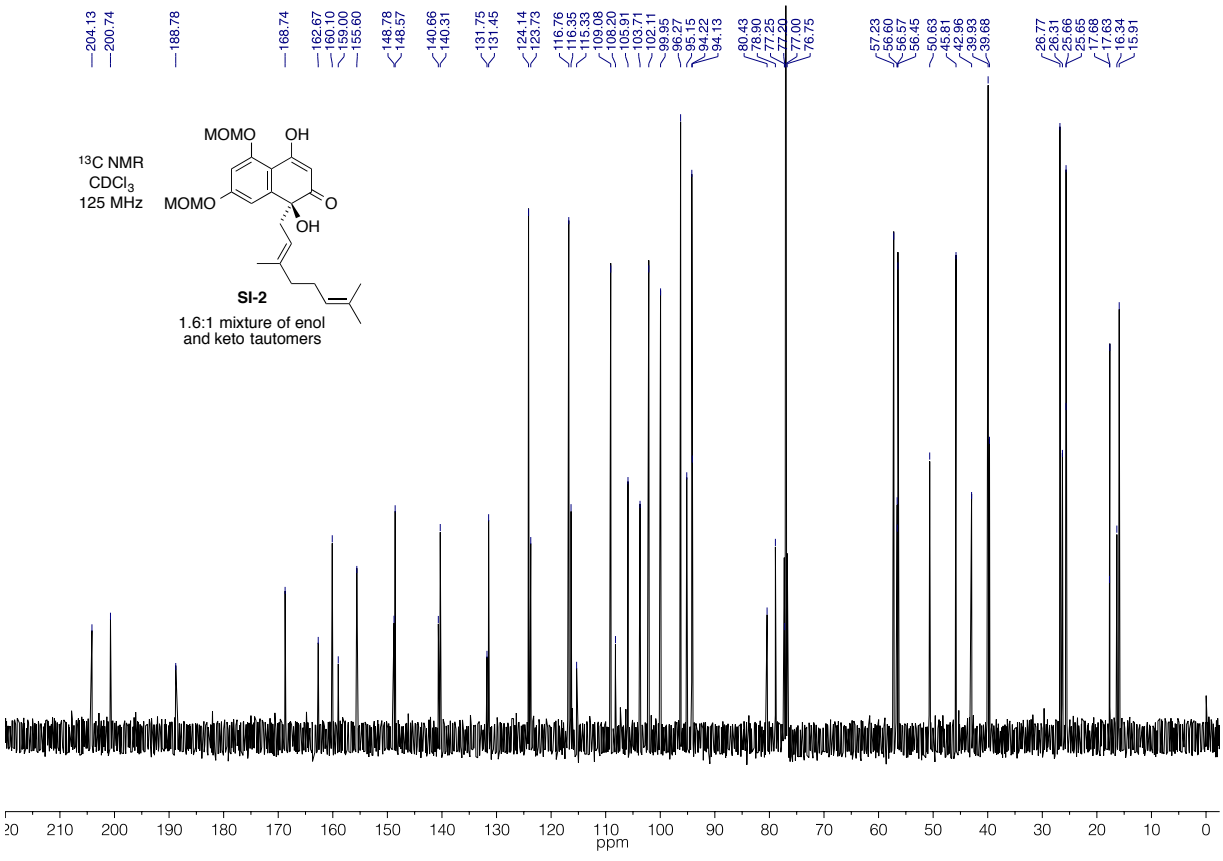

^{1}H NMR
DMSO-d$_6$
600 MHz
HO
OH
HO
OH
11a
10.64
10.59
9.21
9.11
8.96
8.32
6.29
6.28
6.00
5.90
5.90
5.07
5.06
5.06
5.05
5.05
5.04
5.04
5.04
5.03
3.32
3.31
2.01
2.00
1.99
1.98
1.91
1.91
1.90
1.88
1.77
1.59
1.58
1.52
0.30
0.81
0.68
0.21
0.67
0.62
0.57
1.89
1.97
2.39
2.40
3.00
3.14
2.95
f1 (ppm)

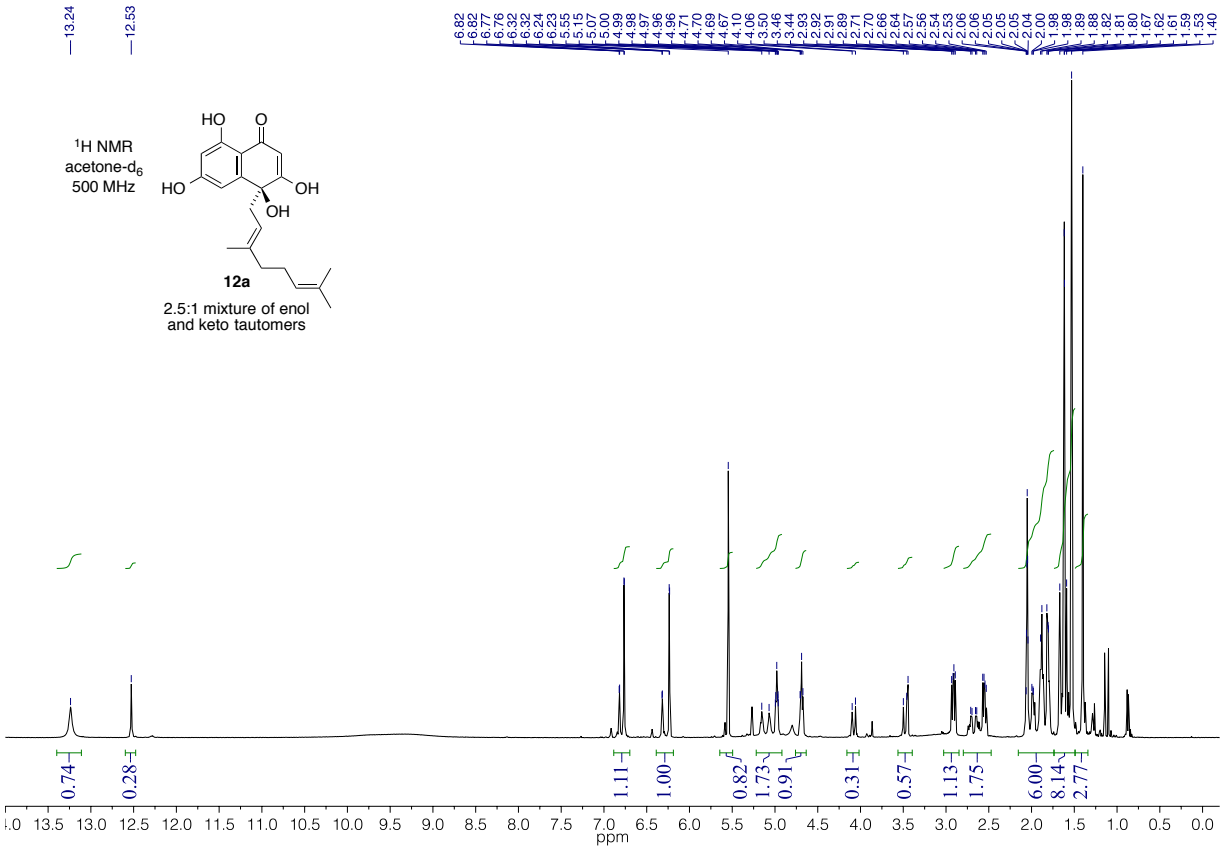

^{13}C NMR
DMSO-d$_6$
600 MHz
HO
OH
HO
OH
11a
157.35
154.14
153.79
151.54
135.92
132.96
130.65
129.16
124.44
124.17
109.95
107.04
106.66
96.62
40.06
26.33
25.50
23.44
17.60
16.18
f1 (ppm)

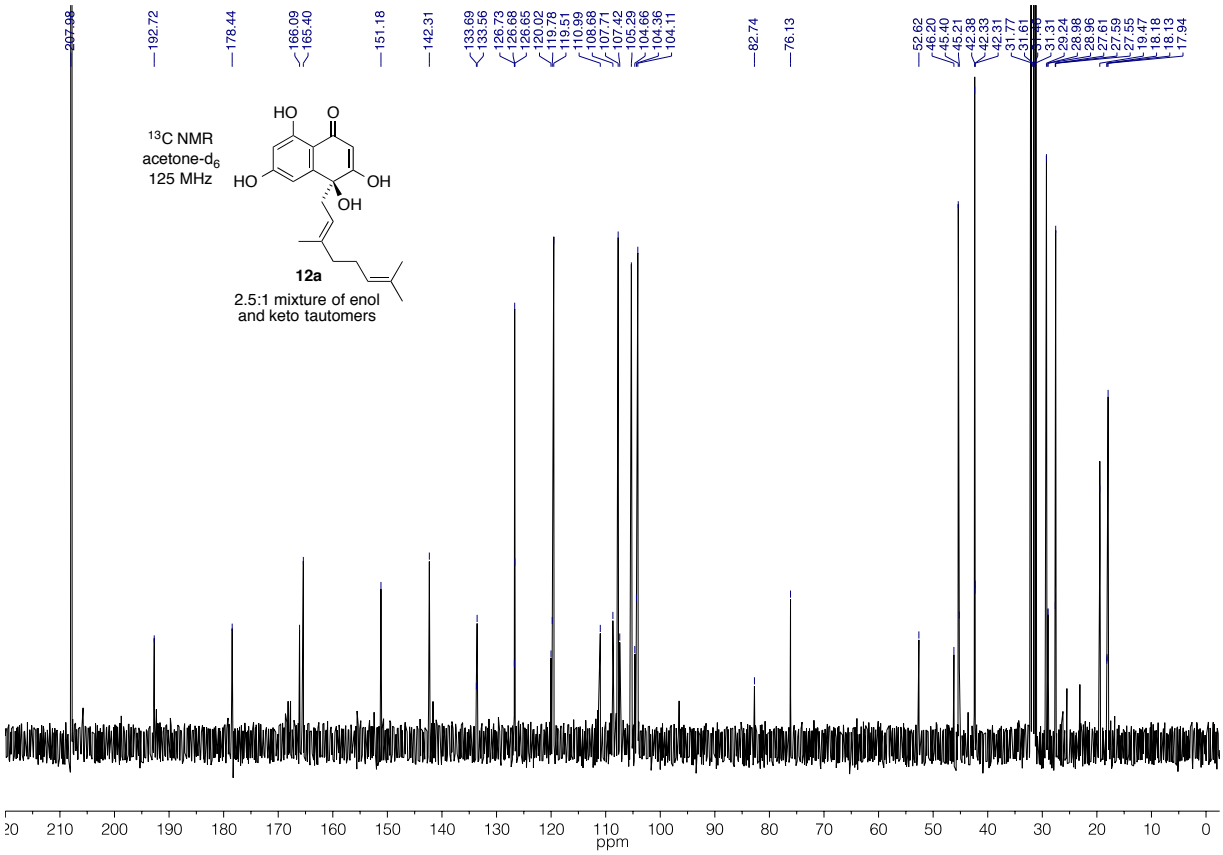

9.81
7.27
6.85
6.85
6.82
6.82
5.66
5.36
5.36
5.18
5.17
5.03
4.92
4.92
3.56
3.46
2.71
2.69
2.68
2.66
2.62
2.61
2.59
2.58
2.12
1.94
1.94
1.93
1.66
1.66
1.57
1.57
1.31
1.31
0.00
1H NMR
CDCl3
500 MHz
MOMO
OH
MOMO
O
OAc
SI-1
0.89
2.09
0.79
2.12
2.54
1.00
1.00
3.47
3.76
1.04
1.19
3.49
4.74
4.25
3.42
3.10
ppm

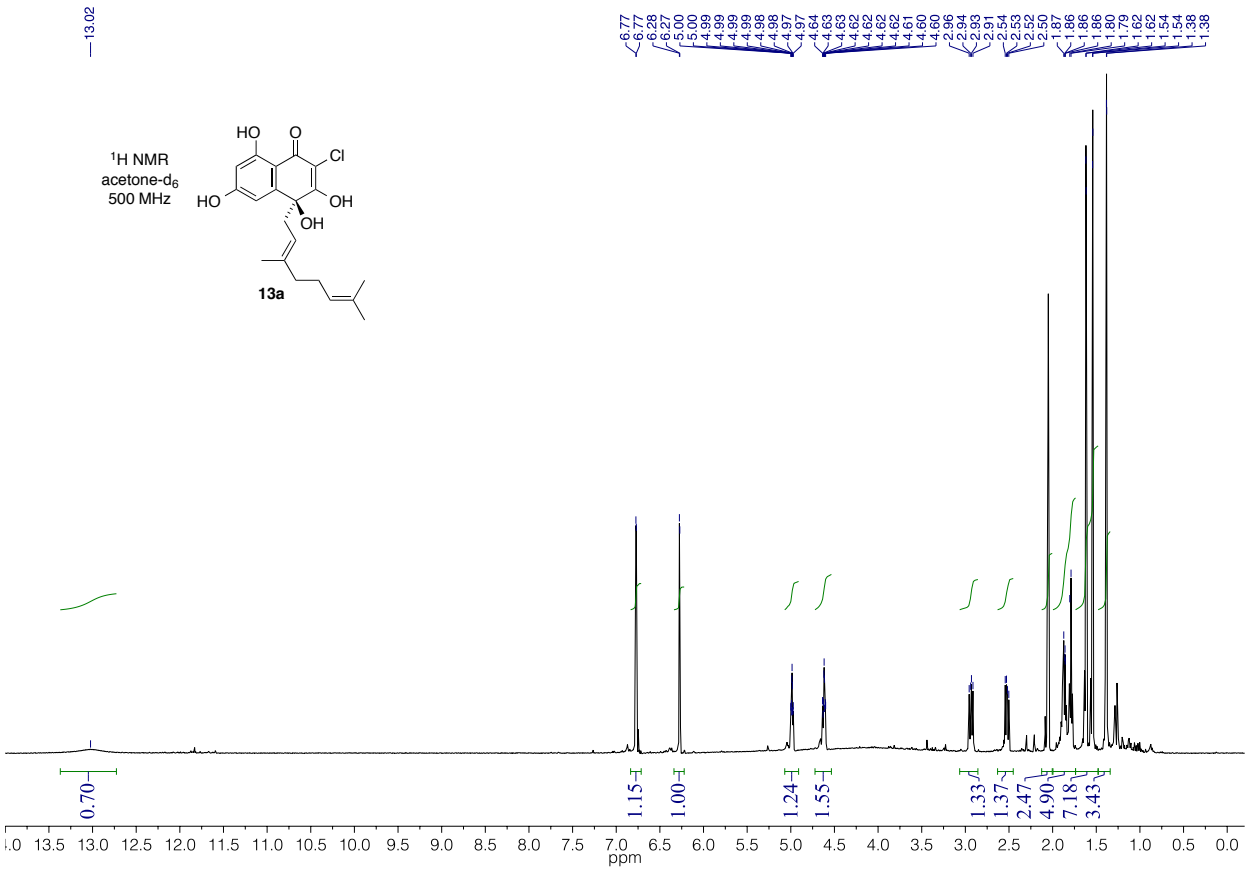

195.03
169.15
167.61
159.91
155.58
146.96
140.80
131.45
124.03
114.94
109.48
107.89
102.96
102.20
96.35
94.26
81.76
77.26
77.00
76.75
57.23
56.34
40.91
39.87
39.71
26.80
25.61
20.94
17.57
15.89
13C NMR
CDCl3
125 MHz
MOMO
OH
MOMO
O
OAc
SI-1
ppm


9.89
7.27 7.27 7.14 7.14 7.13 7.12 7.12 7.12 6.84 6.84 6.83 6.83 5.57 5.57 5.38 5.38 5.26 5.26 5.25 5.25 5.25 5.21 5.21 5.20 5.20 5.07 5.02 5.02 5.01 5.00 4.12 4.03 4.02 3.62 3.58 3.56 3.56 3.53 3.53 3.50 3.49 3.49 3.48 2.63 2.59 2.46 2.00 1.95 1.69 1.68 1.59 1.52 1.35
0.00 -0.00
1H NMR
CDCl3
500 MHz
MOMO
OH
MOMO
O
OH
SI-2
1.6:1 mixture of enol
and keto tautomers
1.00 1.43 1.43 0.92 2.16 4.24 2.93 0.48 1.06 5.36 4.68 1.08 2.11 6.14 5.89 4.50 1.59 3.03
ppm


204.13
200.74
188.78
168.74
162.67
160.10
159.00
155.60
148.78
148.57
140.66
140.31
131.75
131.45
124.14
123.73
116.76
116.35
115.33
109.08
108.20
105.91
103.71
102.11
98.95
96.27
95.15
94.22
94.13
80.43
78.90
77.25
77.20
77.00
76.75
57.23
56.60
56.57
56.45
50.63
45.81
42.96
39.93
39.68
26.77
26.31
25.66
25.65
17.68
17.63
16.34
15.91
13C NMR
CDCl3
125 MHz
MOMO
OH
MOMO
O
OH
SI-2
1.6:1 mixture of enol
and keto tautomers
ppm


^{1}H NMR
acetone-d$_6$
500 MHz
HO
O
HO
OH
OH
12a
2.5:1 mixture of enol
and keto tautomers
ppm


^{13}C NMR
acetone-d$_6$
125 MHz
HO
O
HO
OH
OH
12a
2.5:1 mixture of enol
and keto tautomers
ppm


^{1}H NMR
acetone-d$_6$
500 MHz
HO
O
Cl
HO
OH
OH
13a
13.02
6.77
6.28
6.27
5.00
4.99
4.98
4.97
4.64
4.63
4.62
4.61
4.60
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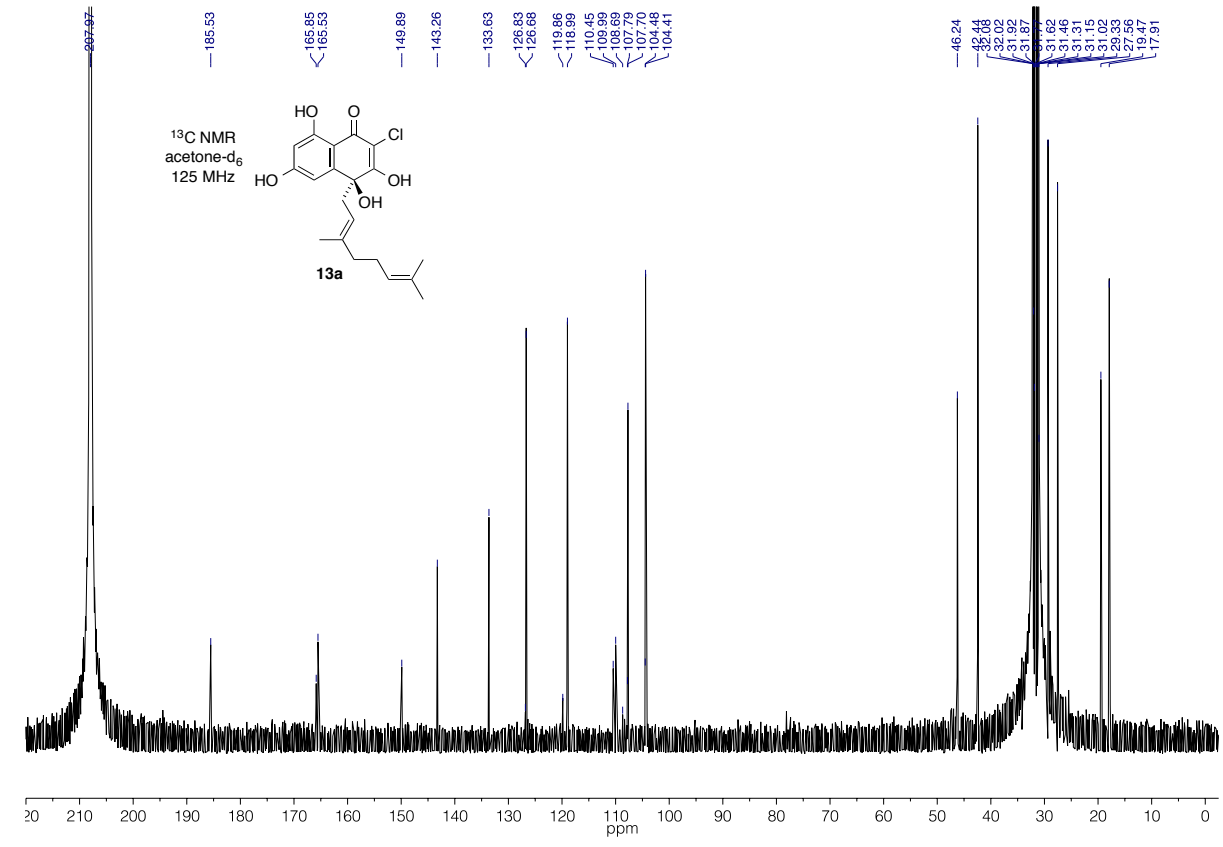
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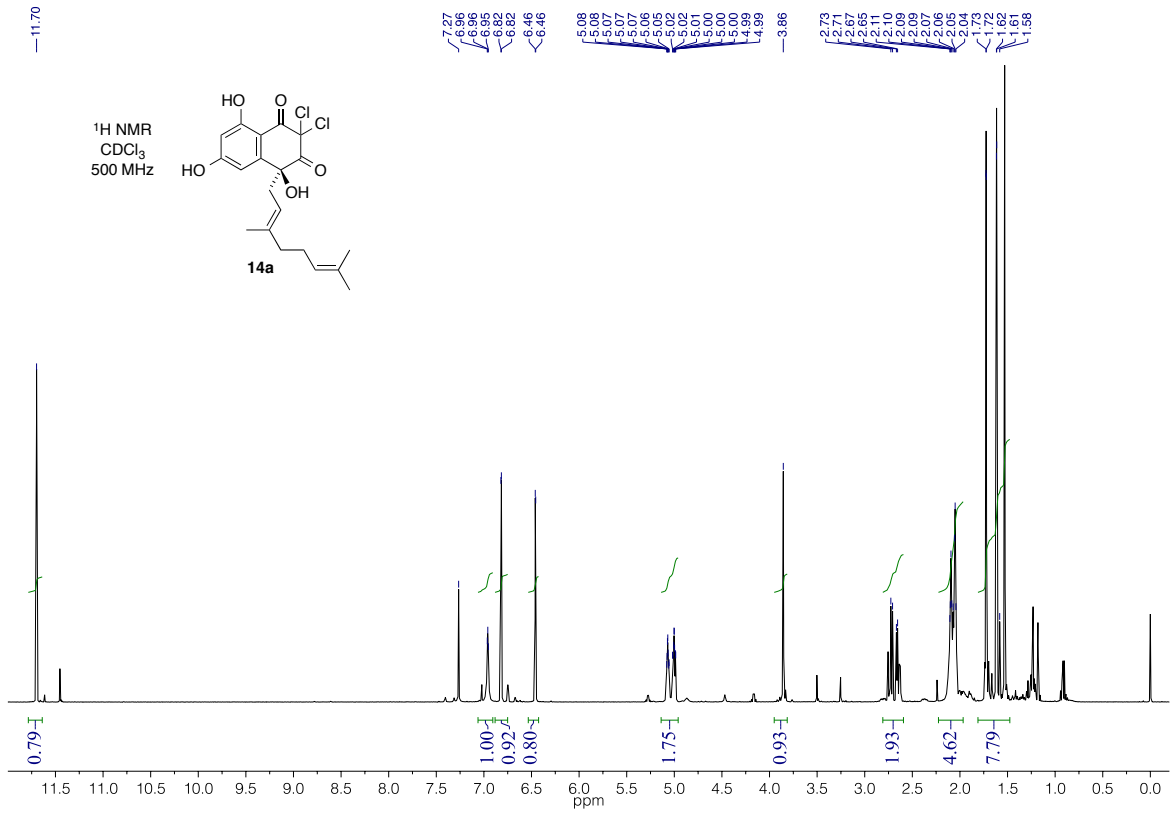
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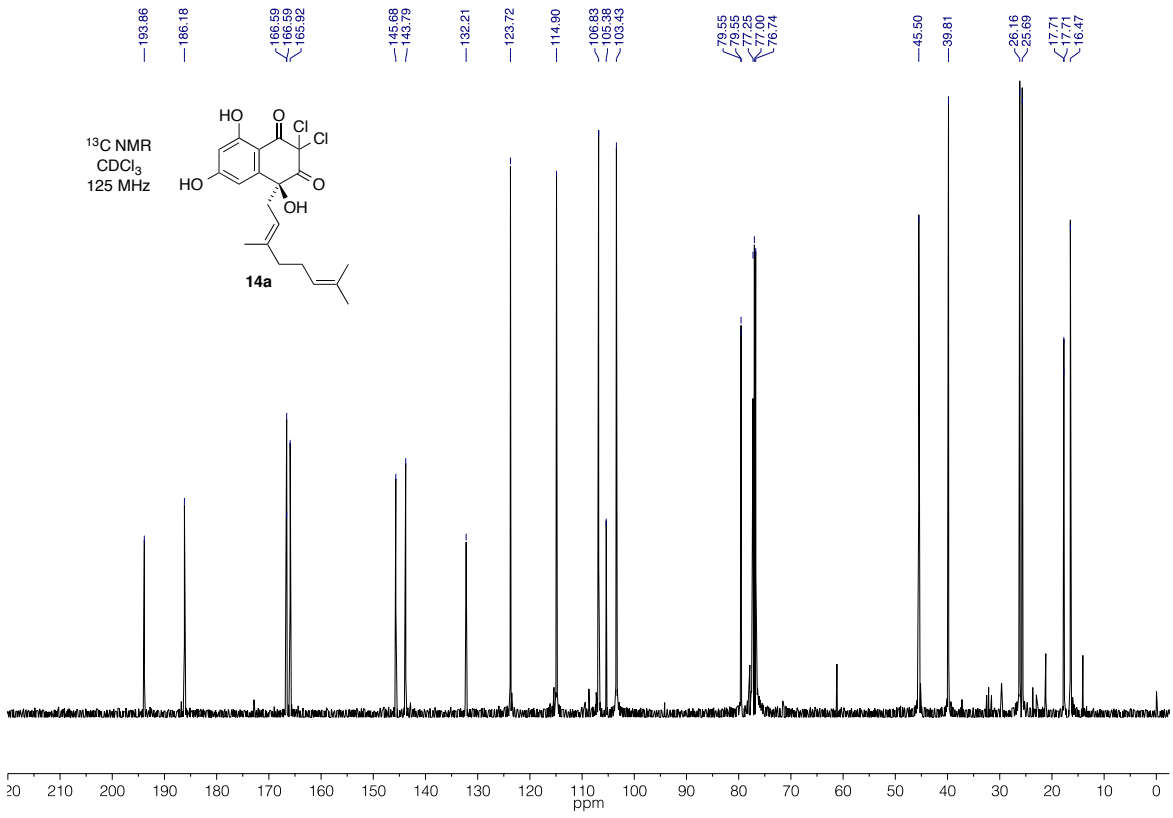
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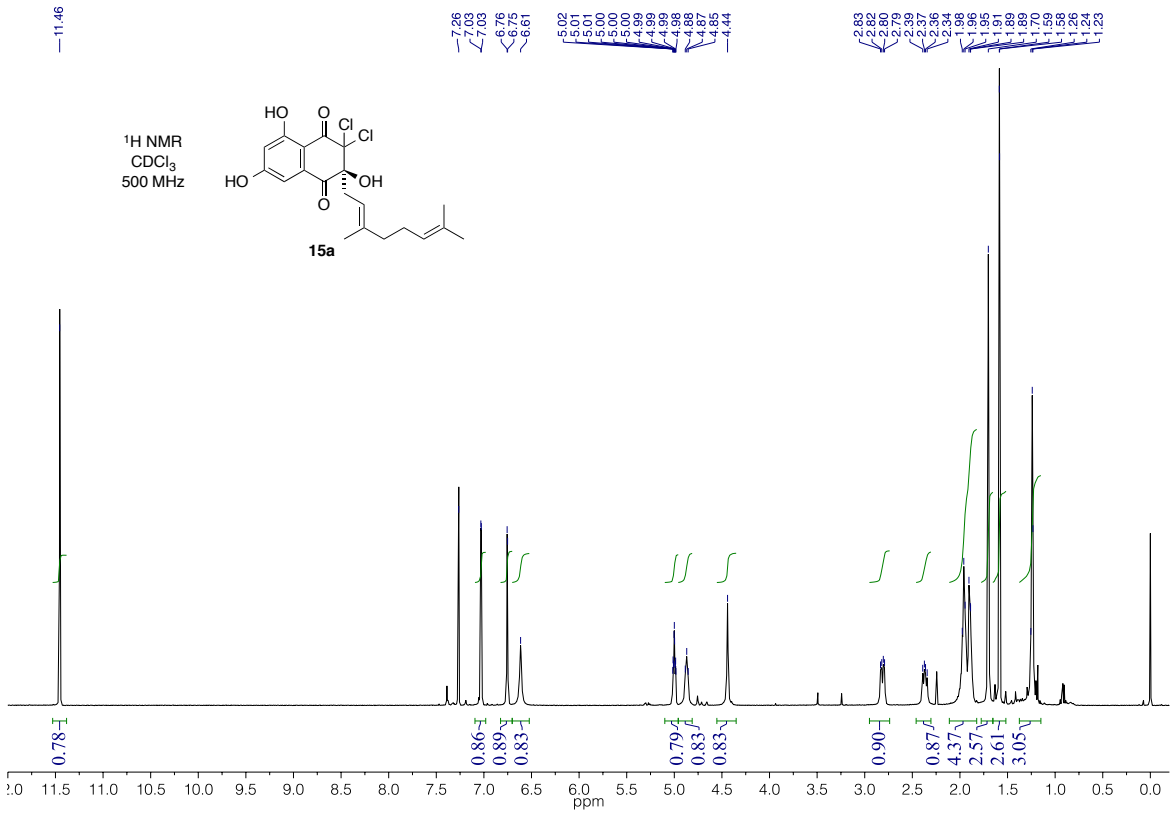
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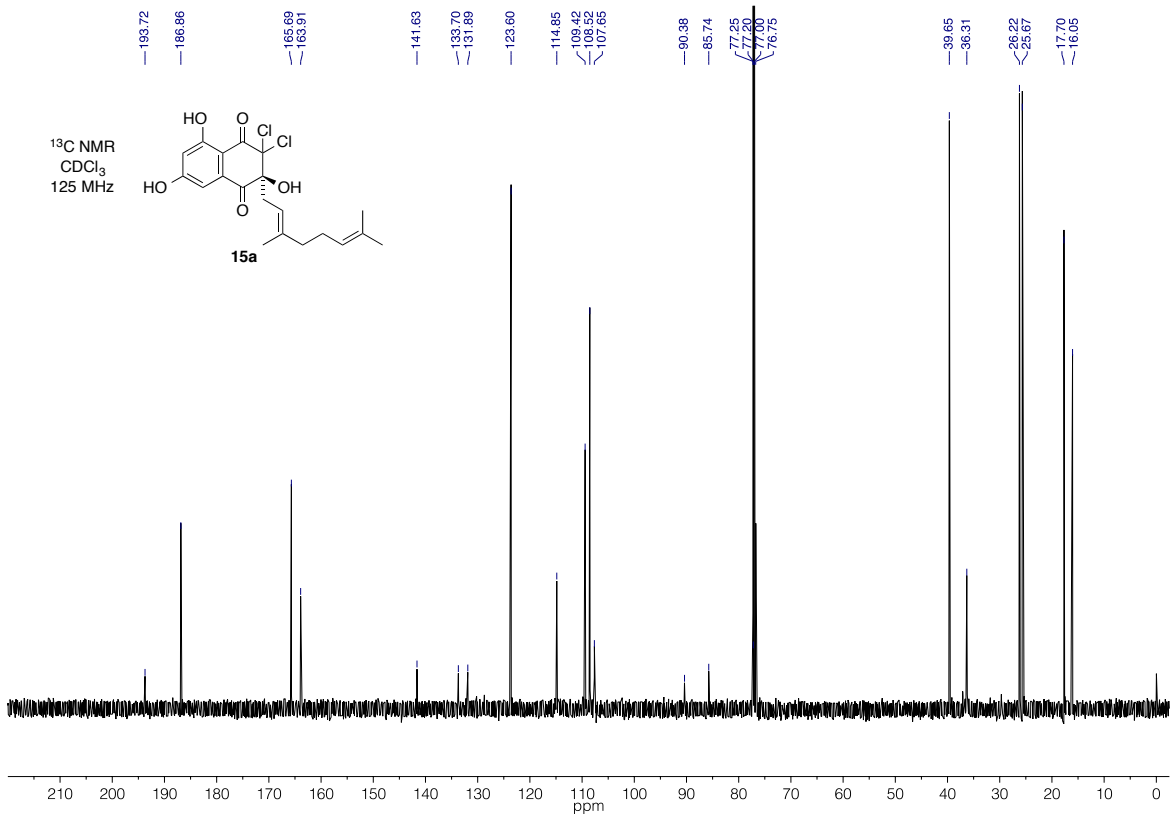
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36.31
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Cl
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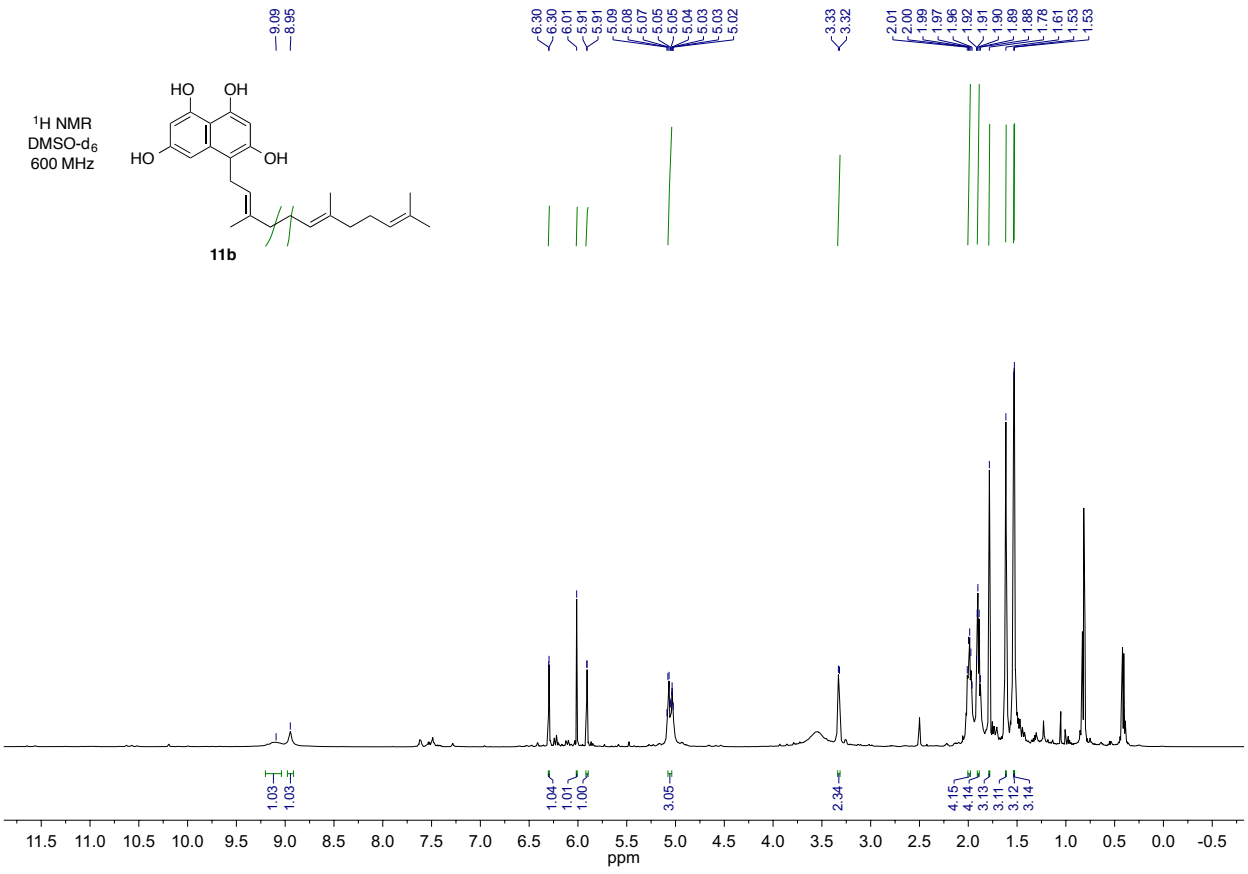
ppm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DMSO-d6
600 MHz
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OH
HO
OH
11b
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1.03
1.04
1.01
1.00
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4.15
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3.14
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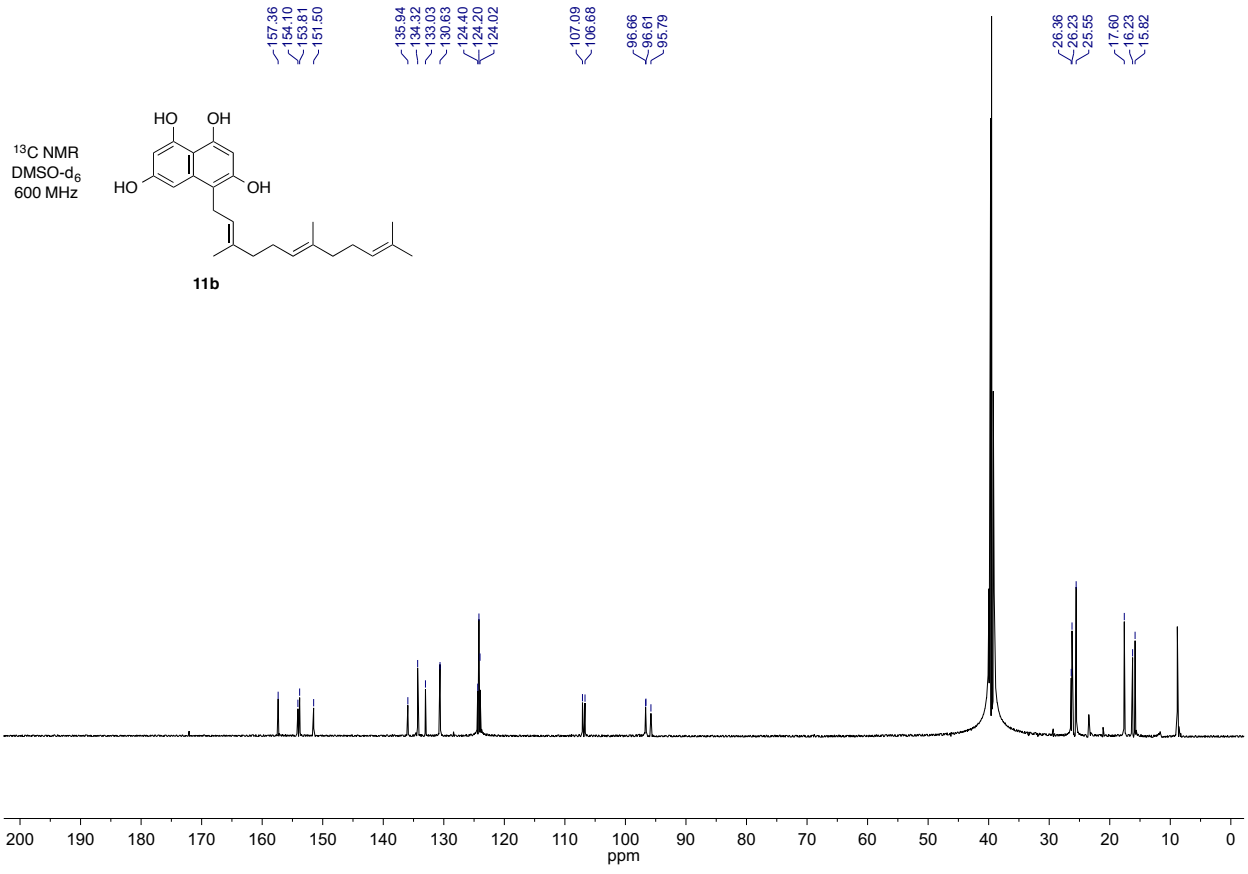
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17.60
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11b
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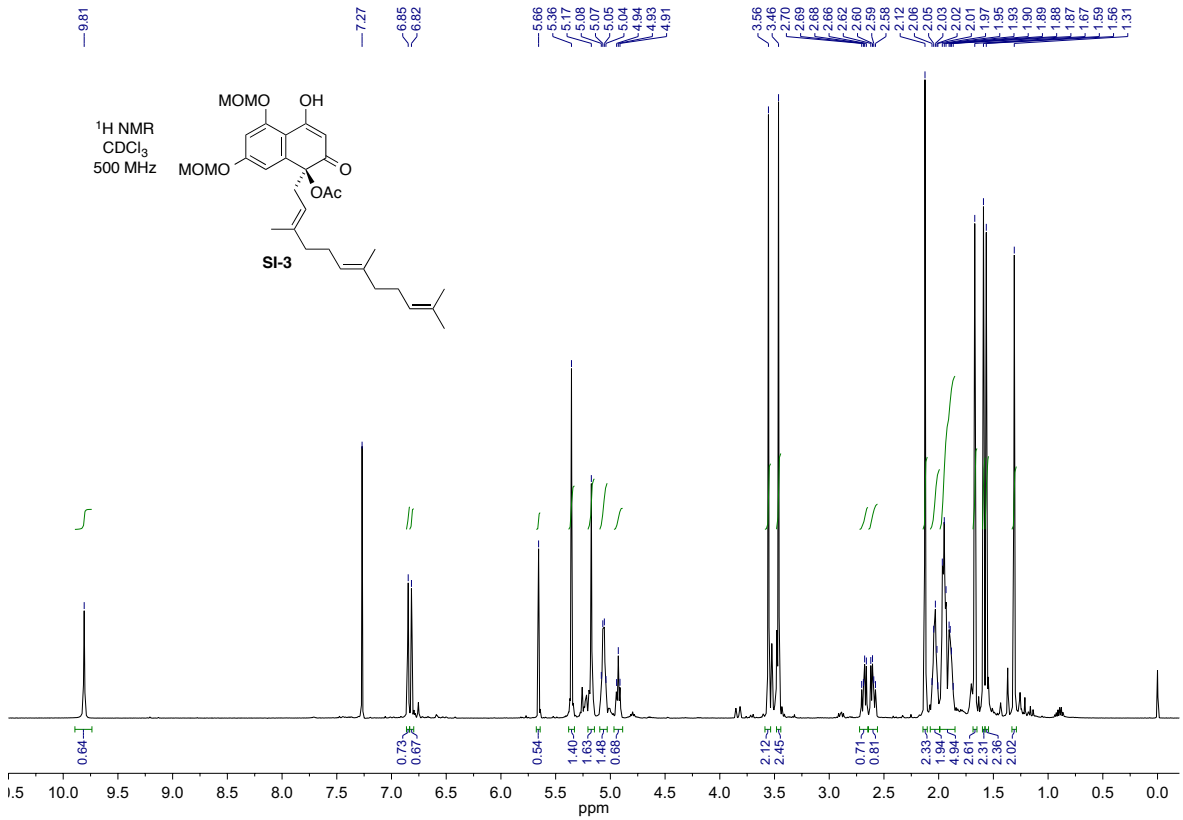
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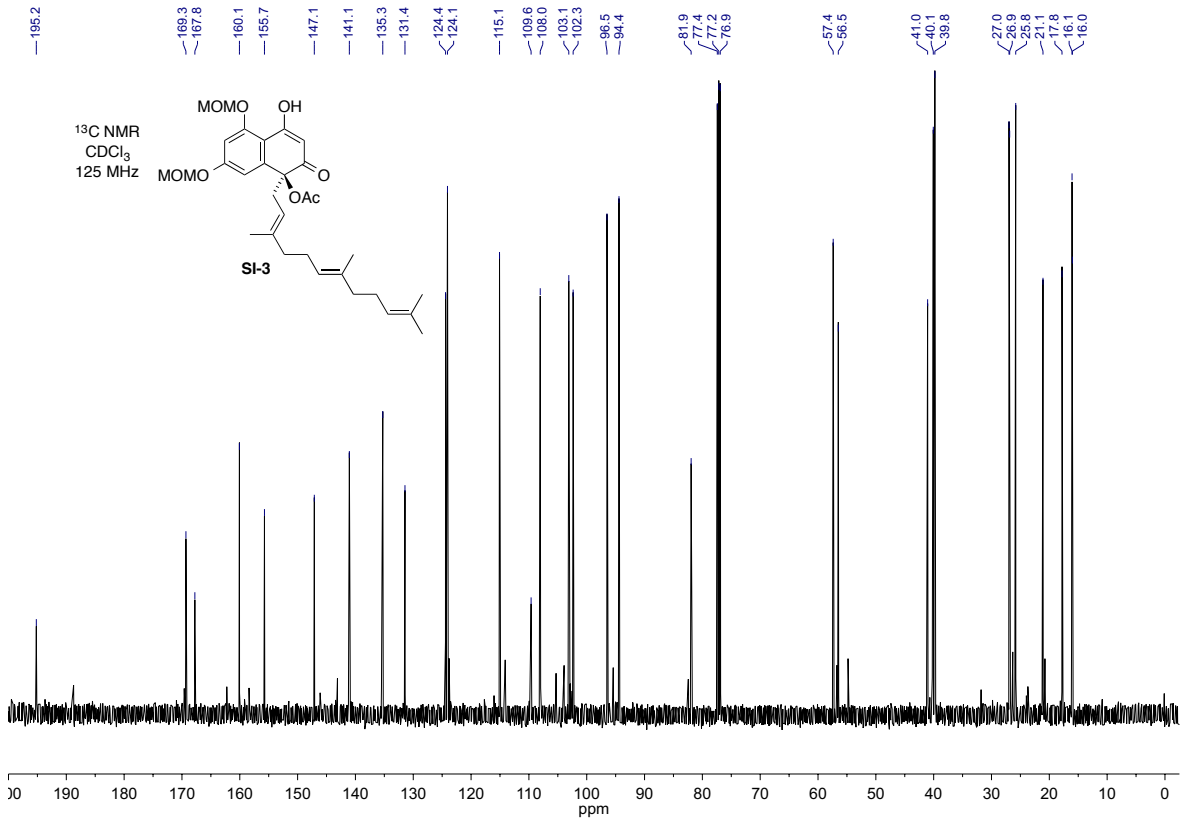
OAc
SI-3
ppm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125 MHz
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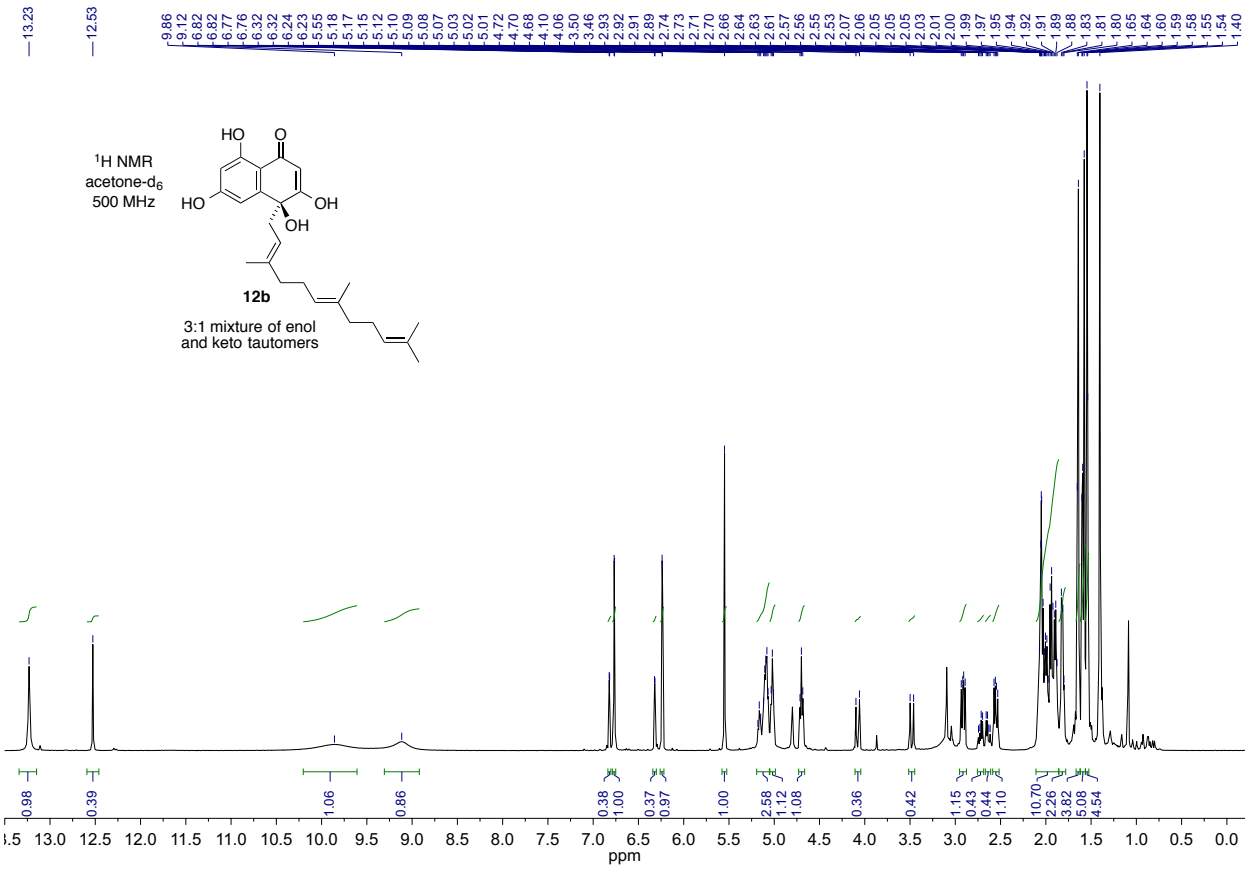
OAc
SI-3
ppm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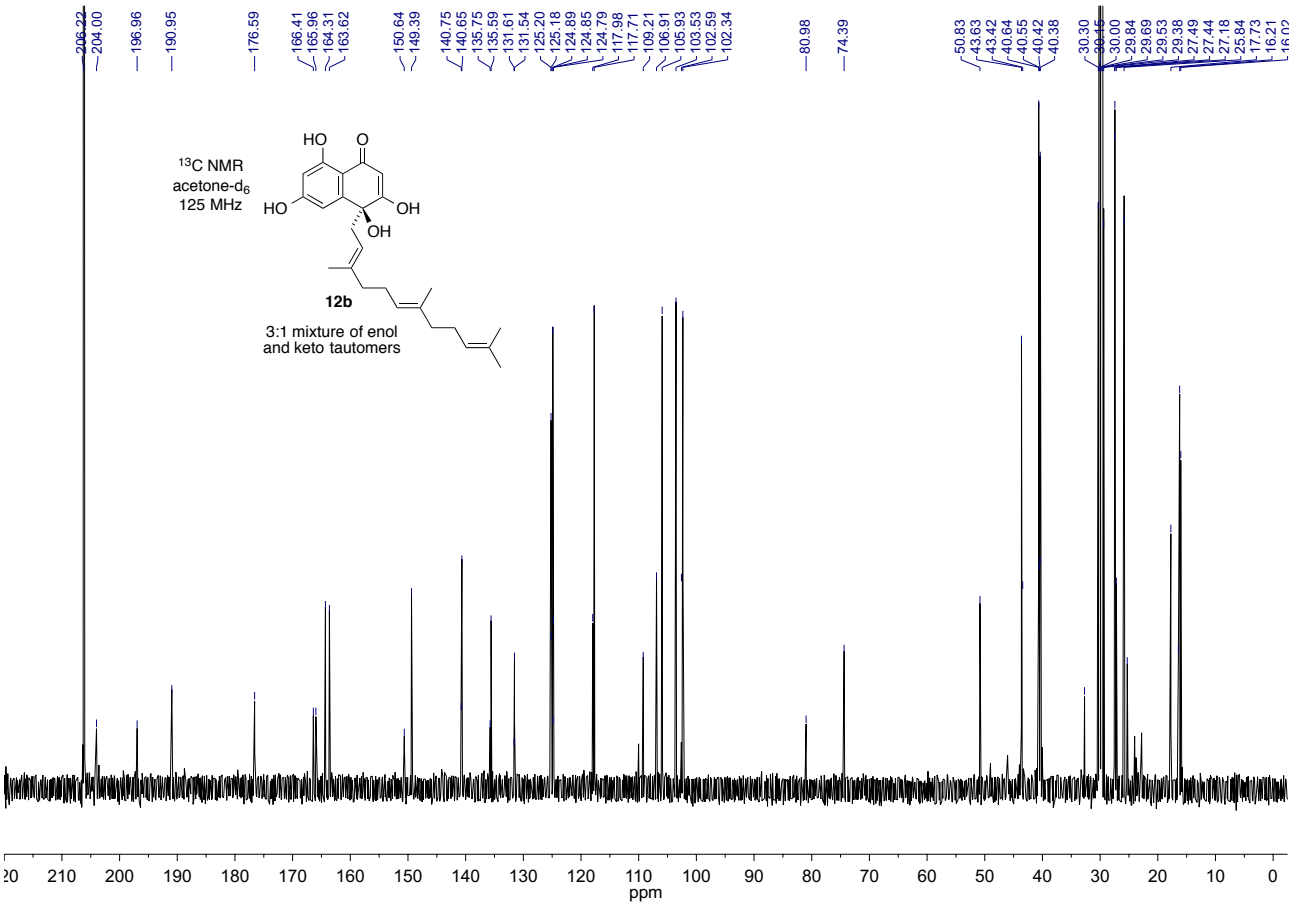
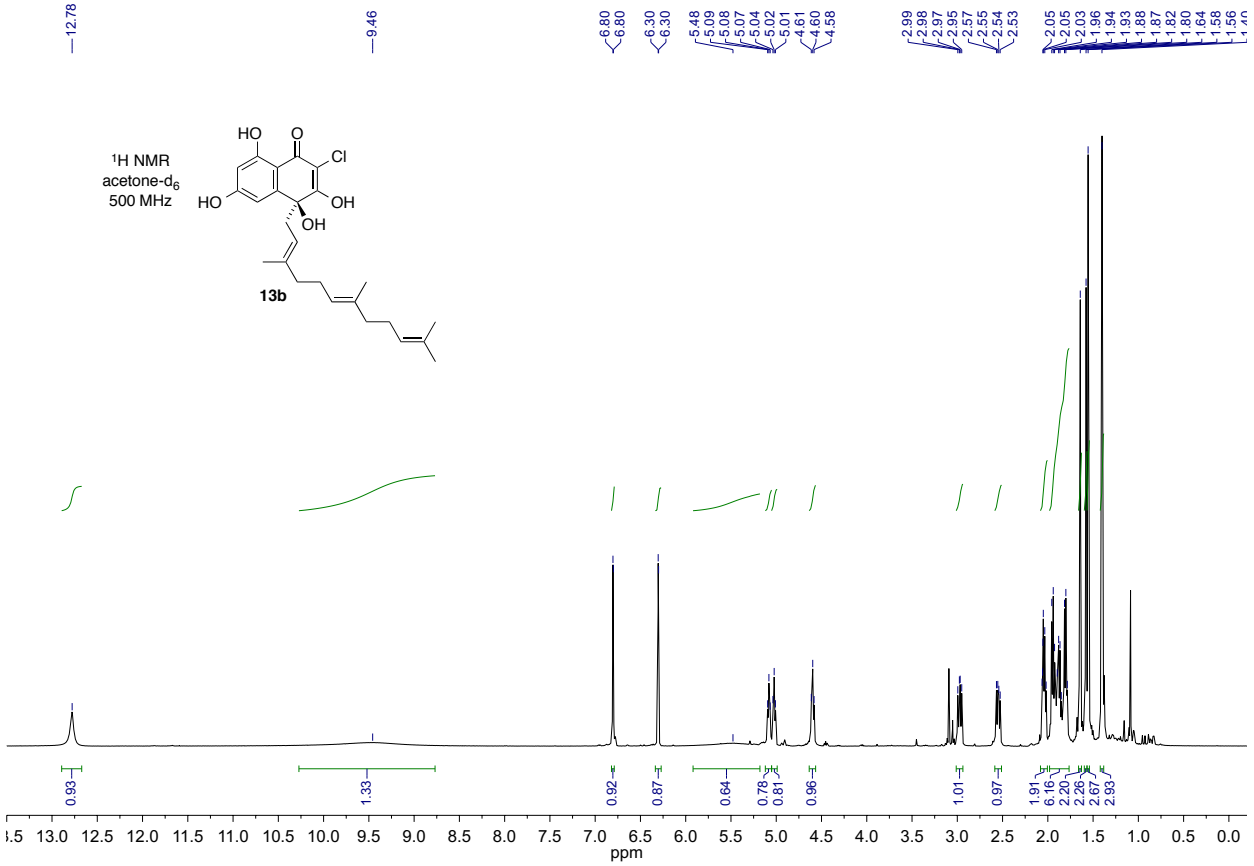
500 MHz
12b
3:1 mixture of enol
and keto tautomers
ppm


^{13}C NMR
acetone-d$_6$
125 MHz
12b
3:1 mixture of enol
and keto tautomers
ppm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¹H NMR
acetone-d6
500 MHz
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O
Cl
HO
OH
OH
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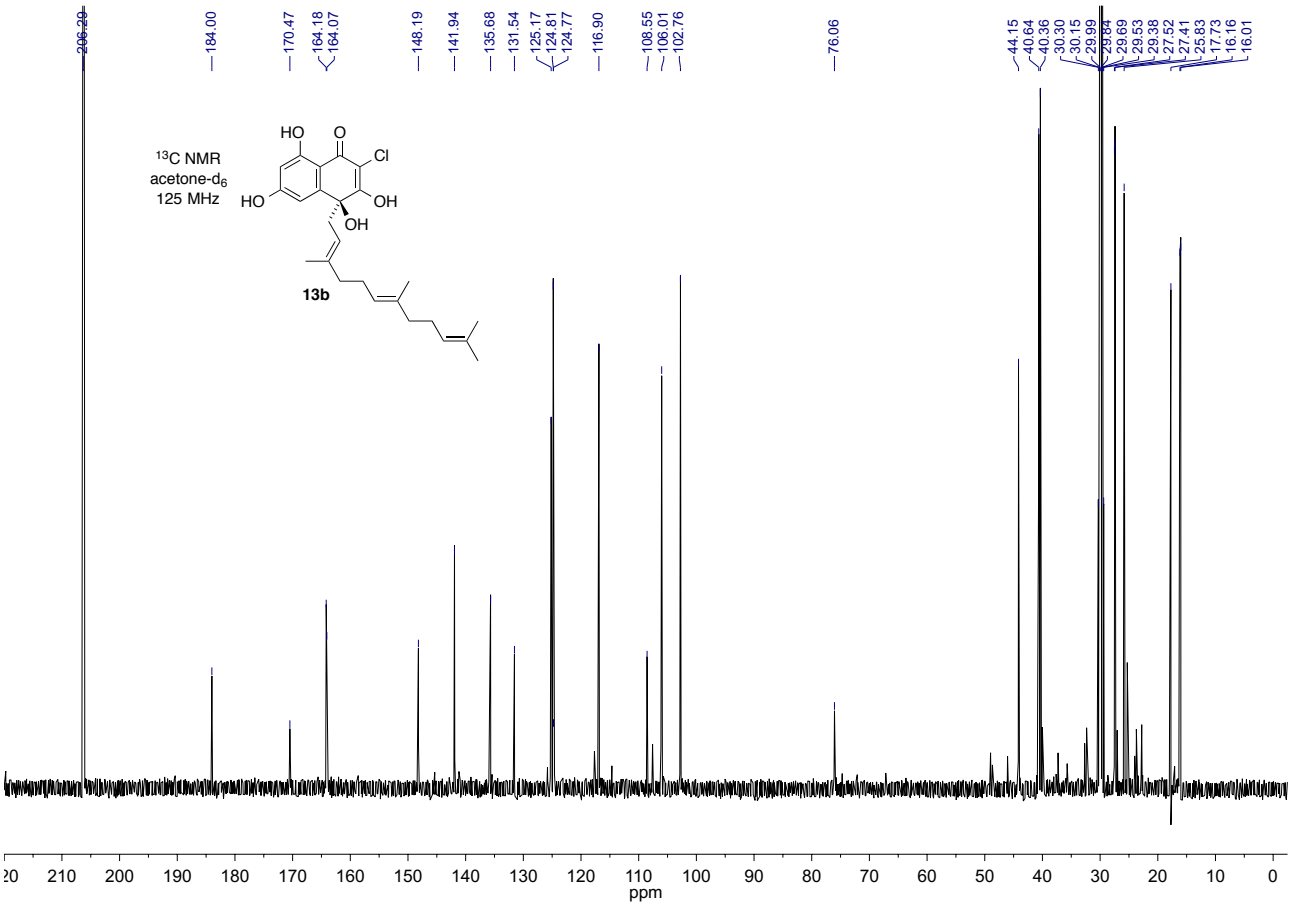
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¹³C NMR
acetone-d6
125 MHz
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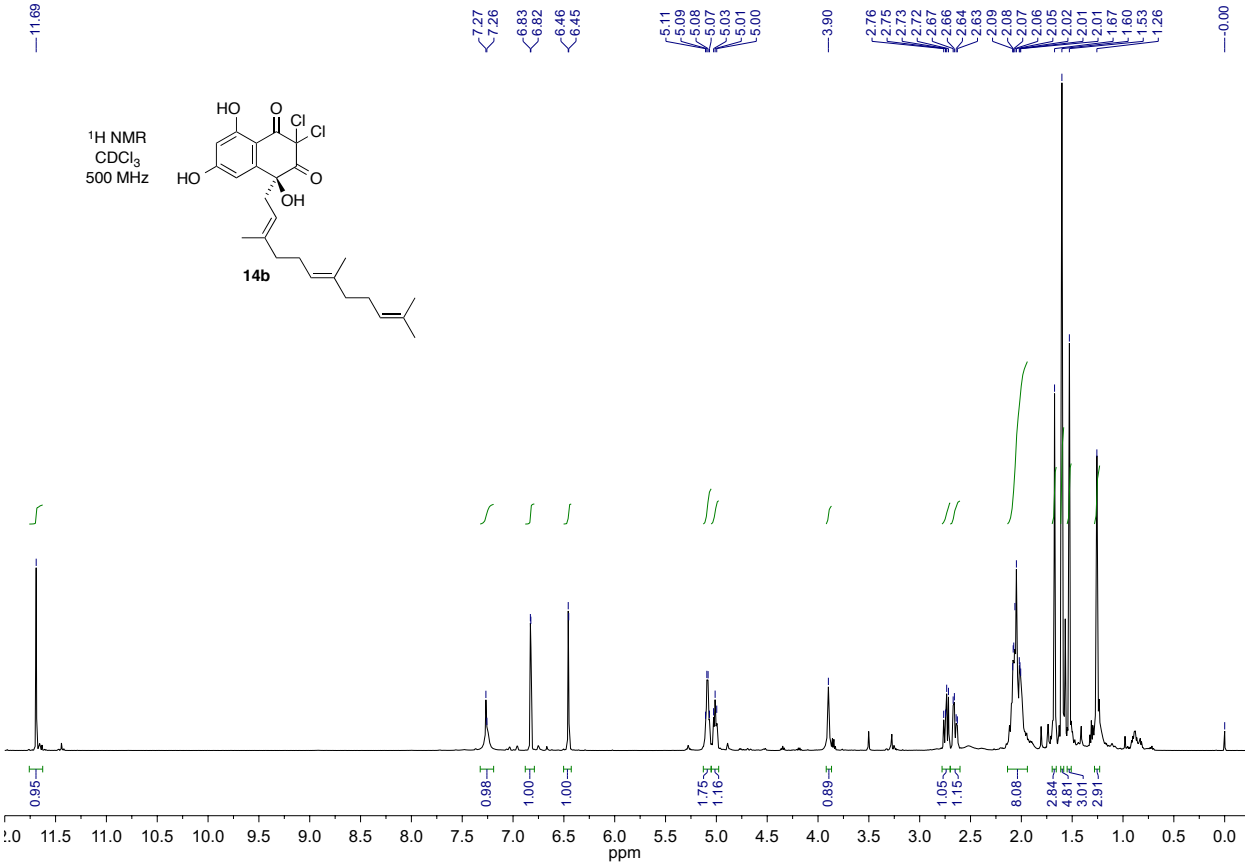
ppm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1.26
0.00
1H NMR
CDCl3
500 MHz
HO
O
Cl
Cl
HO
O
OH
14b
0.95
0.98
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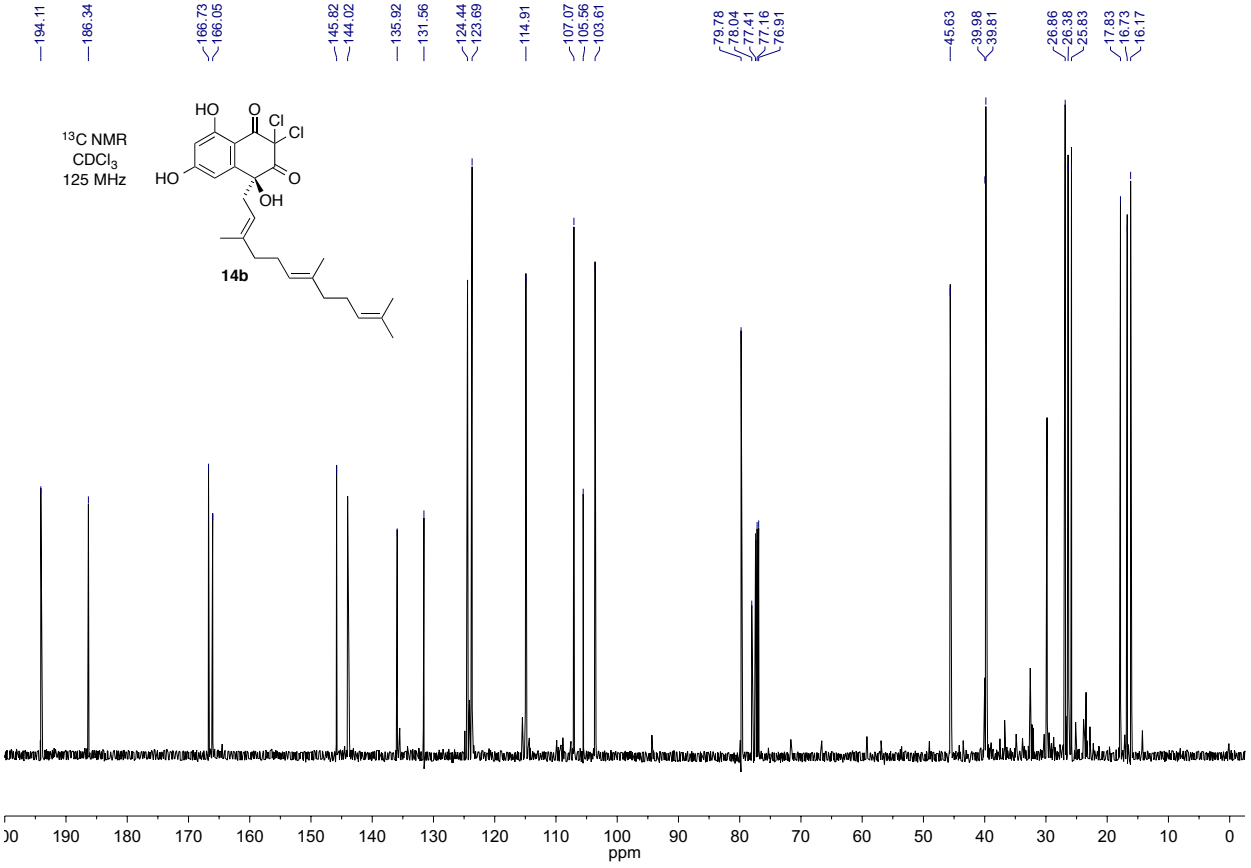
2.84
4.81
3.01
2.91
ppm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26.86
26.38
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13C NMR
CDCl3
125 MHz
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Cl
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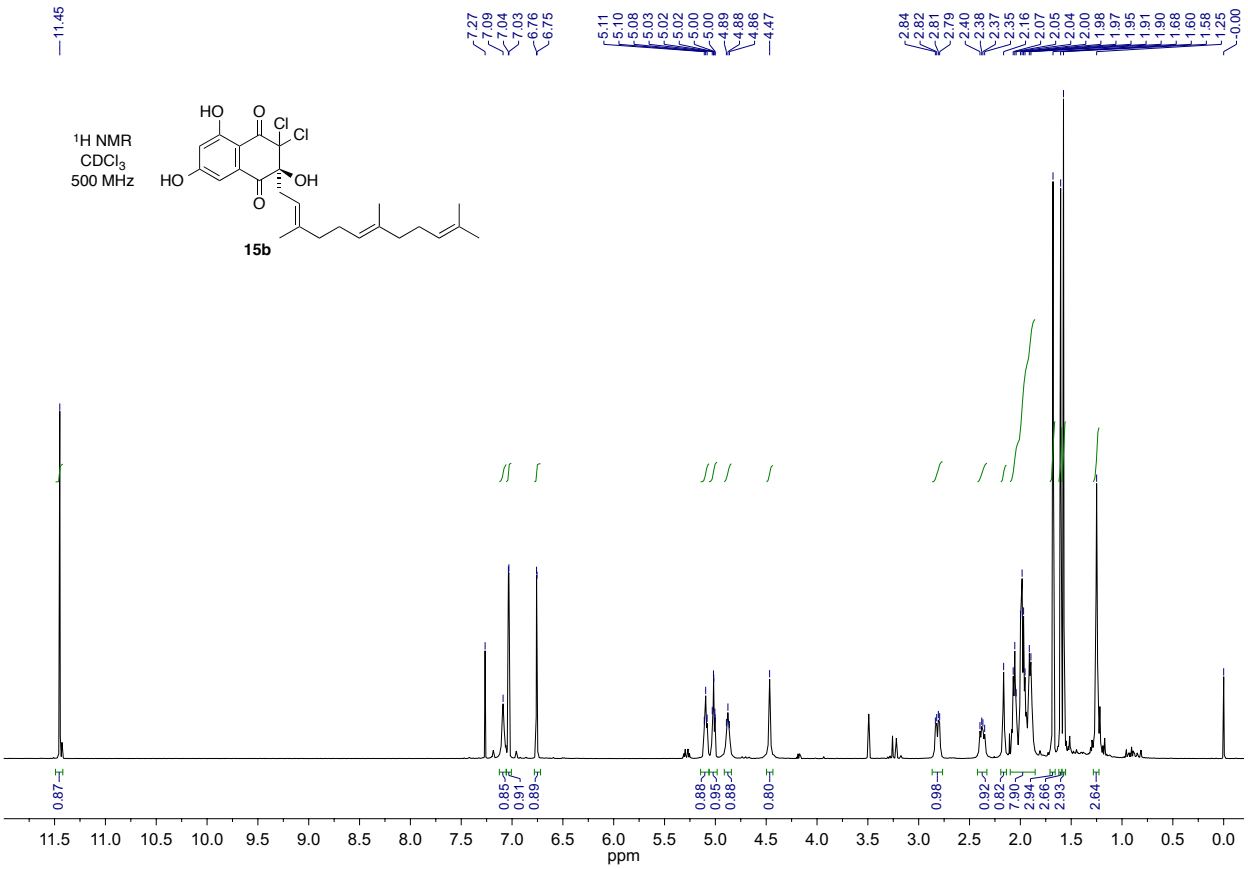
OH
14b
ppm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500 MHz
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Cl
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HO
OH
O
15b
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7.27
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7.04
7.03
6.76
6.75
5.11
5.10
5.08
5.03
5.02
5.02
5.00
5.00
4.89
4.88
4.86
4.47
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7.90
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2.64
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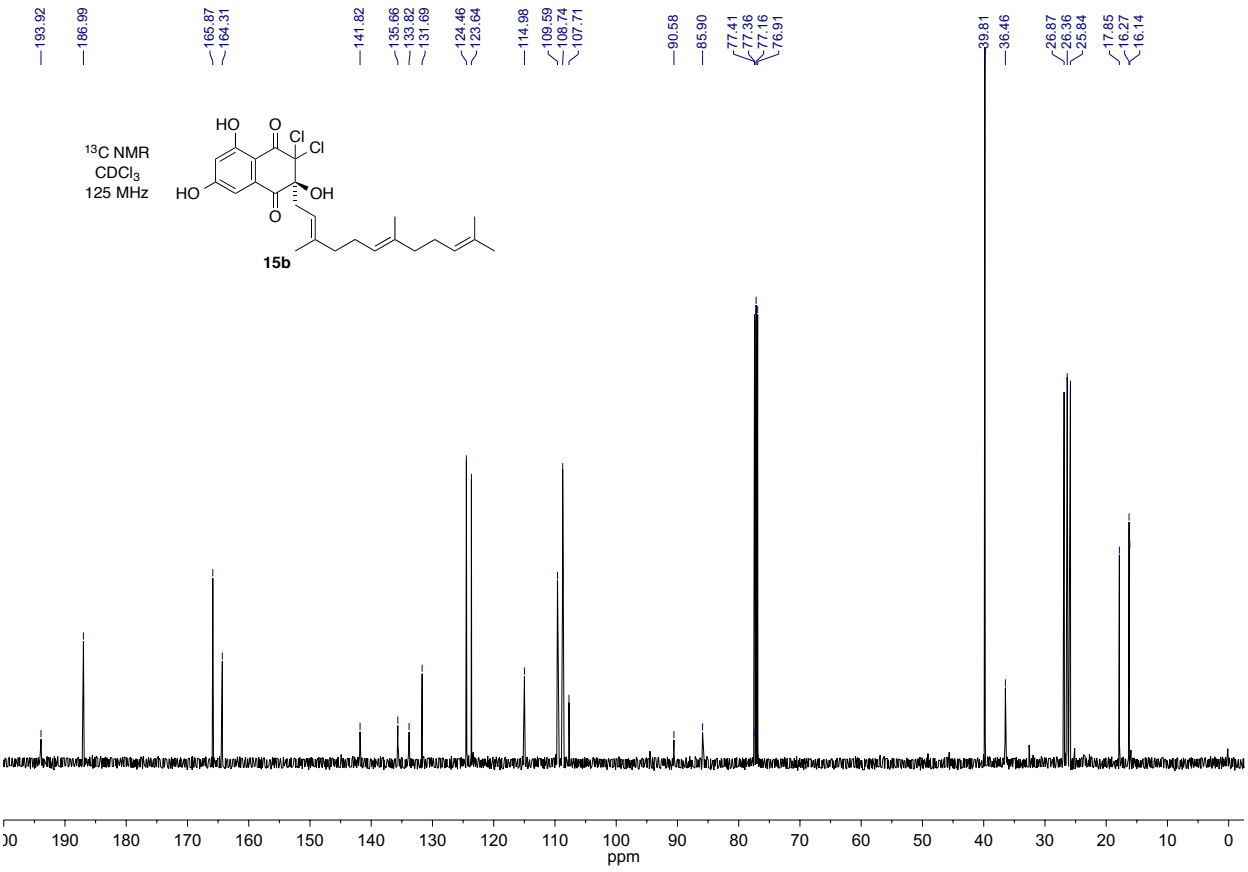
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$CDCl_3$
125 MHz
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O
Cl
Cl
HO
OH
O
15b
193.92
186.99
165.87
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141.82
135.66
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123.64
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109.59
108.74
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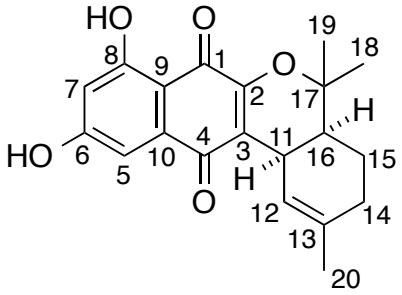
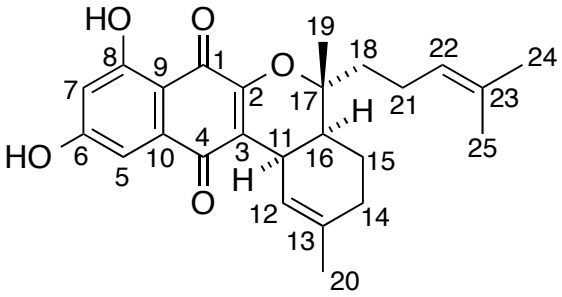
39.81
36.46
26.87
26.36
25.84
17.85
16.27
16.14
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

4. Comparison between synthetic and natural ^{1}H and ^{13}C NMR data

7-Demethylnaphterpin (**1**) and debromomarinone (**4**) atoms numbered as follows:



1: 7-demethylnaphterpin



4: debromomarinone

Table SI-1: ^{1}H NMR comparison between synthetic and natural[3] 7-demethylnaphterpin (**1**)

Position	^{1}H data of natural 7-demethylnaphterpin (**1**) ($CDCl_3$)	^{1}H data of synthetic 7-demethylnaphterpin (**1**) ($CDCl_3$)
OH-8	11.92	11.91 (s, 1H)
OH-6	6.37	6.89 (s, 1H)
H-5	7.09	7.19 (d, J = 2.1 Hz, 1H)
H-7	6.53	6.56 (d, J = 2.1 Hz, 1H)
H-11	3.48	3.49 (m, 1H)
H-12	6.04	6.03 (d, J = 4.0 Hz, 1H)
H-14	1.95	1.95 (m, 2H)
H-15	1.95, 1.28	1.95 (m, 1H) 1.28 (m, 1H)
H-16	1.76	1.77 (ddd, J = 12.1, 6.1, 2.8 Hz, 1H),
H-18	1.55	1.55 (s, 3H),
H-19	1.33	1.34 (s, 3H),
H-20	1.66	1.67 (s, 3H)

Table SI-2: ^{13}C NMR comparison between synthetic and natural[3] 7-demethylnaphterpin (**1**)

Position	^{13}C NMR data of natural 7-demethylnaphterpin (**1**) ($CDCl_3$)	^{13}C NMR data of synthetic 7-demethylnaphterpin (**1**) ($CDCl_3$)
C-1	183.1	183.0
C-2	153.0	153.2
C-3	123.8	123.7
C-4	183.6	184.0
C-5	108.3	108.6
C-6	162.9	163.4
C-7	107.2	107.3
C-8	164.3	164.4
C-9	108.9	108.7
C-10	135.0	134.8
C-11	31.1	31.1
C-12	120.0	119.9
C-13	136.1	136.2
C-14	29.7	29.7
C-15	20.4	20.4
C-16	39.7	39.7
C-17	80.6	80.8
C-18	25.7	25.6
C-19	25.0	25.0
C-20	23.5	23.6

[3] K. Shin-ya, A. Shimazu, Y. Hayakawa, H. Seto, *J. Antibiot.* **1992**, *45*, 124.

Table SI-3: ^{1}H NMR comparison between synthetic and natural[4] debromomarinone (**4**)

Position	^{1}H data of natural debromomarinone (**4**) (CD_3OD)	^{1}H data of synthetic debromomarinone (**4**) (CD_3OD)
H-5	6.83 (d, *J* = 2.5 Hz)	6.96 (d, *J* = 2.4 Hz)
H-7	6.10 (d, *J* = 2.5 Hz)	6.42 (d, *J* = 2.4 Hz,)
H-11	3.39 (t, *J* = 5.0 Hz)	3.42 (t, *J* = 6.0 Hz)
H-12	6.03 (d, *J* = 5.0 Hz)	6.01 (d, *J* = 5.0 Hz)
H-14	2.00 m	2.00 m
H-15	1.31 (dt, *J* = 6.0, 12.0 Hz) 2.00 m	1.29 m 2.00 m
H-16	1.88 (ddd, *J* = 3.0, 6.0, 12.0 Hz)	1.90 (ddd, *J* = 3.0, 6.0, 12.0 Hz)
H-18	1.63 m	1.64 m
H-19	1.49 s	1.49 s
H-20	1.66 s	1.66 s
H-21	2.00 m	2.00 m
H-22	5.08 (t, *J* = 7.0)	5.07 (t, *J* = 7.2 Hz)
H-24	1.60 s	1.59 s
H-25	1.55 s	1.54 s

Table SI-4: ^{13}C NMR comparison between synthetic and natural[5] debromomarinone (**4**)

Position	^{13}C NMR data of natural debromomarinone (**4**) ($CDCl_3$)	^{13}C NMR data of synthetic debromomarinone (**4**) ($CDCl_3$)
C-1	182.5	182.8
C-2	153.0	153.3
C-3	123.8	123.9
C-4	184.0	184.1
C-5	107.8	108.5
C-6	164.4	163.7
C-7	106.9	107.3
C-8	165.1	164.5
C-9	109.0	108.9
C-10	134.5	134.7
C-11	30.7	30.9
C-12	119.9	119.9
C-13	135.9	136.2
C-14	29.6	29.7
C-15	20.0	20.2
C-16	37.2	37.4
C-17	82.9	83.1
C-18	36.5	36.7
C-19	22.4	22.6
C-20	23.3	23.5
C-21	22.0	22.2
C-22	123.0	123.1
C-23	132.3	132.5
C-24	25.4	25.6
C-25	17.4	17.6

[4] C. Pathirana, P. R. Jensen, W. Fenical, *Tetrahedron Lett.* **1992**, *33*, 7663

[5] J. A. Kalaitzis, Y. Hamano, G. Nilsen, B. S. Moore, *Org. Lett.* **2003**, *5*, 4449

5. Biochemical methods

Cloning of *Streptomyces* sp. CNQ-509 *marH1*, *marH2*, and *marH3*:

Putative *mar* VCPO genes from *Streptomyces* sp. CNQ-509 (GenBank accession number CP011492)[6] were amplified from genomic DNA using standard PCR conditions using the following primers at the indicated annealing temperatures:

MarH1: Fwd - 5′– AAACATATGACGACCGGACACTCTCC–3′

MarH1: Rev - 5′– ATAAAGCTTTCAGTCCTCGACCTCACCCTTG–3′ (annealing temp. 59 °C)

MarH2: Fwd - 5′– ATACATATGATGACGACGTCCGGAAGCTCCTCC–3′

MarH2: Rev - 5′– ATTAAGCTTTCAGTCCTCGGCCTCGCCCGAG–3′ (annealing temp. 71 °C)

MarH3: Fwd - 5′– ATACATATGACGTCCGGAAACTCCTCCTCCGC–3′

MarH3: Rev - 5′– ATTAAGCTTTCAGTCCTCCACGTCGCCCTTGATG–3′(annealing temp. 66 °C)

The resulting PCR products were digested with restriction enzymes NdeI and HindIII, and subsequently ligated into a similarly digested pET28a vector (Novagen) for expression of N-terminally His_6-tagged MarH1, MarH2, and MarH3.

Expression of *Streptomyces* sp. CNQ-509 VCPO enzymes

VCPO enzymes were expressed, purified, and assayed following a general literature procedure.[7] *E. coli* BL21-Gold(DE3) cells (Agilent Technologies) containing the pET28a:*marH* genes were individually grown in 1L of TB broth containing 50 μg/mL kanamycin with shaking (200 rpm) at 37 °C until an OD_{600} of approximately 0.6. The temperature was decreased to 18 °C and cells were grown for an additional 1 h. Protein expression was induced by the addition of 0.1 mM IPTG (final concentration) and allowed to grow overnight at 18 °C. The next day, cells were harvested by centrifugation (7000 x *g*), resuspended in buffer A (50 mM Tris-HCl (pH 8.0), 0.5 M NaCl, and 25 mM imidazole) and stored at -80 °C.

General purification of *Streptomyces* sp. CNQ-509 VCPO enzymes

Cell pellets were thawed and sonified on ice with stirring using a Branson digital sonifier (40% amplitude) and a 15 s on/45 s off cycle over 40 minutes. The lysate was centrifuged for 40 minutes at 17000 x *g* at 4 °C to pellet insoluble material. Clarified lysate was loaded onto a 5 mL HisTrap FF column (GE Healthcare) previously equilibrated with buffer A. The column was washed with 25 mL of buffer A, and then washed with a gradient of 0-10% buffer B (50 mM Tris-HCl (pH 8.0), 0.5 M NaCl, and 500 mM imidazole) over 10 mL. The column was washed with 50 mL of 10% buffer B to elute weakly bound proteins, then *mar* VCPO enzymes were eluted in a gradient of 10-100%

[6] C. Rückert, F. Leipoldt, P. Zeyhle, W. Fenical, P. R. Jensen, J. Kalinowski, L. Heide, L. Kaysser, *J. Biotechnol*. **2015**, 140.

[7] S. M. K. McKinnie, Z. D. Miles, B. S. Moore, *Methods Enzymol.*, **2018**, *604*, 405.

buffer B over 60 mL. Fractions containing MarH enzymes were identified by SDS-PAGE (12%), pooled, and concentrated to under 2.5 mL using an Amicon Ultra-15 30 kDa cutoff concentrator (EMD Millipore) by centrifugation at 3500 x *g*, 4 °C. Concentrated protein was loaded onto a PD-10 desalting column (GE Healthcare) pre-equilibrated with >5 column volumes of cold storage buffer (25 mM HEPES-NaOH (pH 8.0), 200 mM NaCl, 5% glycerol), and eluted in 3.5 mL of the same buffer. Proteins were concentrated as described above and their concentration determined using the Bradford method and bovine serum albumin as a standard.

MarH VCPO enzyme aliquots were frozen on dry ice and stored at -80 °C until needed.

Typical production yields: MarH1 10 - 20 mg/L; MarH2 30 - 40 mg/L; MarH3 20 - 45 mg/L.

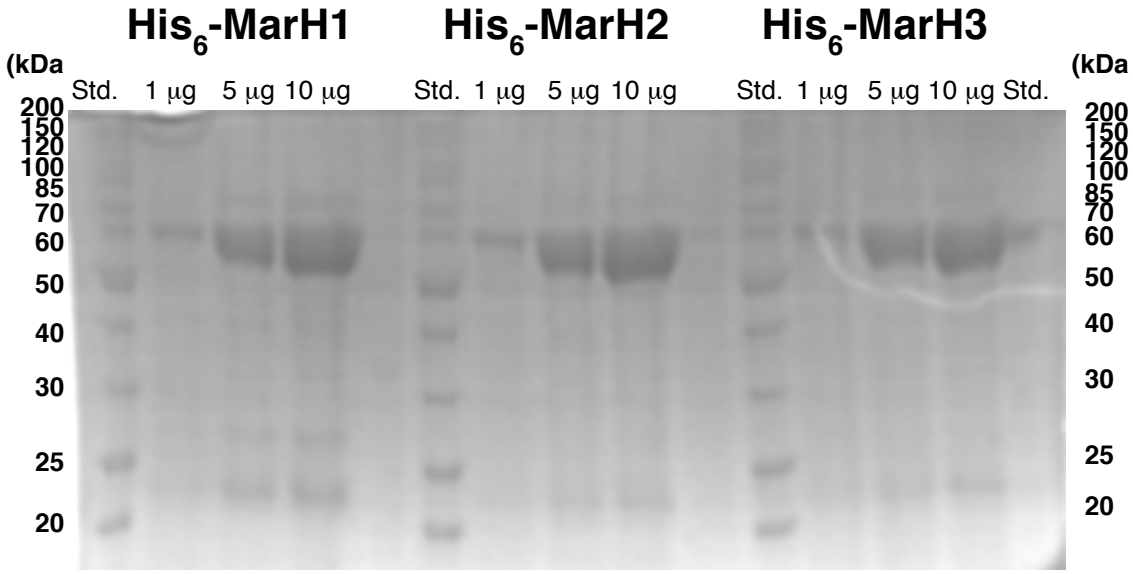


Figure SI-1. SDS-PAGE gel (12%) of purified MarH1, MarH2, and MarH3. The bands are consistent with the predicted molecular weights of His_6-MarH1 (59.6 kDa), His_6-MarH2 (58.3 kDa), and His_6-MarH3 (58.8 kDa). All proteins were judged to be ~90% pure based on band intensities.

```
MarH1       -MTTGHSPVSGFSPRRRSLLIGGASAAALLPLGHAG-----T-AAAAEGGKAAQAEFDLD     53
Mcl40       MKTSGHTSASDLSLGRRSLLLGGSSAALMLALPH-------P-ANAGTSEEPPTFDFDLD     52
NapH1       MTTSGHTSFSDYSPRRRSMLLGGLGGAAALSAAGFTGMASAS-PRGSAGSKAAAIEFDLD     59
NapH4       ------------------------------------------------------------     0
NapH3       ----------------------------------------------VTTSAPAQQIPFDFD     15
MarH2       MTTSGSSSVPGFSPRRRSLLLGGGSAAALTALGHAGTAAA---EPGPAAEPPP--AFDLD     55
MarH3       -MTSGNSSSAGFSPARRSLLLGGASTAALATLGTGTAAA-AGQGTGPAAKPAAAAEFDFD     58
Mcl24       MTTSERSSVSDFSPRRRSLLIGSASAAALATLGSTGTAAAAGA-----ADEPPTVDFDFD     55

MarH1       KDNYIEWFQPE-DDGAGISPSSEIFGPMDVTVFLWINHLTGLGWFDAVAPYHETAVGVHS     112
Mcl40       TDNYIKWVKPATDEQASQSPLWESVGSMDVTVILWMSRVGNLAVFDAVAPYHETAVGVYS     112
NapH1       KDNYIKWAQPT-DENAGQSPTLAILGPMDVTVFLWINRVVWLAAFDALAPYHETAVGVYS     118
NapH4       ------------------------------------------------------------     0
NapH3       NGNFIRDLITT--HGGGGYPPADAMAPGDVSSYTWVTHLLQTSWFDALAPYHPTAVGVYS     73
MarH2       KGNFVRDLLTV--A-GDSSGETQDLGPADVTLIFWIQDVMQTAWFDALAPYHPTAVGVRT     112
MarH3       TGNFHRDLLST--AA---NPSEEPLGPMDATVLVYLTHLTMTAWFDALAPYHPTAVGRHS     113
Mcl24       NGNFIRDLIIT--RAGGVFPEEGVIGPMDASVYIWITSLFQLSWFDALAPYHPTAVGIHS     113

MarH1       RIPRRPSSESATNRNMNIACIYSQYQLVKQVIPSRV----KPMRDLLTSIGLDPDDDSMD     168
Mcl40       RIPRRPSSESATNRNMNIAILYTQLHTFERLLPLGLRGPAGSLRAMMVGLGLDPDNKSED     172
NapH1       QIPRRPSSESATNRNLNIAALHAQHGVWKRVLPQQV----DQLRELMTALGLDPSDETEN     174
NapH4       ---------------MNIACIHAQNAIWSRLLPPIV----AGLRELMVALGLDPDDKSED     41
NapH3       RIPRRPAEESATNRNKNIAGLYAMFQVVKAAFTERV----PVLRQALGALGLDPDDESQD     129
MarH2       RLPRRPAGESETNRNKNIAGLYATYHVVSVAYPERG----YILRGLLEAIGLDPDDESED     168
MarH3       RIPRRPASESNTNRNKNVAAFHAANVVFQSVFKERV----AAFRQLMTTLGLDPDDQSTD     169
Mcl24       RIARRPAGEAATNRNKNIAGLYAALRVLEGVFEERV----PVMRAGFTAAGLDPDDRSED     169

MarH1       PADPVGVGNIAGKSVFEALKNDGMNFLGHDGGRKYNPRPWADYTGYRPVNTAFDVVNPSR     228
Mcl40       LTTPVGIGNVAFKSVWNALKNDGMNVLGYEGGRKYNPLPWADYTGYEPVNTPFRLNNPSR     232
NapH1       LSSPVGIGNVAAKNAFNALKNDGMNFLGYE-GRKYNPRPWADYTGYEPVNTAFKVNNPSR     233
NapH4       VTTPVGIGNVAAKAVWNVLKNDGMNVLGHEGGRKYNPRPWADYTGYVPTNTAFKLNNPSR     101
NapH3       LSTAVGIGNTAGKAVAAARMGDGMNALGGK-DRTHNGQPYEDYTGYRPVNTADELVDPSR     188
MarH2       PATPAGIGNLAGKAAVEARRRDGMNFLGDE-GRRYHPQPFEDYTGYEPVNTAYKLVDPSK     227
MarH3       PTSPVGIGNLAARGVLKAKARDGMNLFGDE-GRKYHGQPYEDYTGFEPVNTAYKLVNPSK     228
Mcl24       PTTPIGIGNIAGKAVVRARANDGMNHLGNV-GRKYHGKPYEDYTGYQPVNSPYKLVNPSK     228

MarH1       WQPQLQAHNGRRVGGGPGDLGIWVAQHFVTPQMRMVKPHIYADPREFTVPPPKHVDHTRP     288
Mcl40       WQPQLHAHNGRRPGGGPGDLGIYVSQHFVTPQIALTKPHIFTDPAQFPLAAPKHSDHTRP     292
NapH1       WQPQLQAHNARRAGGGPGDLGIYVTQHFVTPQTARTKAHIFRDPSRFRIPRPEFSDHTNT     293
NapH4       WQPQLQAHNGRRAGGGPGDLGIYVTQHFVTPQIAVTLPHIFKDPTAFPLPRPDFTDHTDR     161
NapH3       WQPAVEPHR-RRTDGGPGDKGIFTAQRFATPQLGLVAPQTYRDPARFKLAAPDHLDHNDA     247
MarH2       WQPARTPHR-RRVGGGPGDKGIFTVQQFATPQLRLVEGHTFRDPGRFELPPPDHSDHTAP     286
MarH3       WQPARHPHR-RRVGGGPGDKGIFVVQHMVTPQMALVKPDTYRHPSQFPLAPPDHLDHTDP     287
Mcl24       WQPALHPHQ-RRVGGGPGDKGIWVIQAFVTPQLALVKPYTYRNPGQFTVPVPDHSTHTNV     287

MarH1       RDFKRSADEVLEASAALTDEQKAIAEVMDNKIWGIGHSALVIARKHDQNGELGVQGWAHF     348
Mcl40       RDYKRSVDEILEASASLNDERKALAEVMDNKLWGIGYTSTVIGRKYDENNEMGVFGWAAW     352
NapH1       RAYKRSVDEIIDASANLNDERKALAEIMENKLWGIGHSSIVIANKYDQNNEMGVHGWCHW     353
NapH4       RAYKRSVDEIIEASAALDDERKALAEIMENKLWGIGHSSIEIGLKNDQNNELGVHGWAQW     221
NapH3       GAYRQAVDEVLAASAGLTDEQKVKAEFFEHTPLSVTLSPRAAAMAH----DLDLDGWAQL     303
MarH2       GRYKRAVDEILRASAALTDEQKAKAEFFSNNYQGILLATRAAAIAH----DLDLDGWVHL     342
MarH3       RRYKRSVDEILEASATLDDEQKVKAEFFDNKFLGIGQSTKAAGIAH----DLELDDWVHL     343
Mcl24       RKYKQSVDQILEASATLTDEKKLMAEWFDNKLAGIALAPSAAALSH----DLDLDGWCHL     343

MarH1       ILEHLLATFDPLIAVWNEKTKYDAARPVTVIQHVYGKKKVTSWGGPGMGTVDDMPAGEWS     408
Mcl40       SLQHFLATFDALIAVWRNKRKYDTVRPVSAVRHVYGHSKVTAWGGAGMGTVNDIRATEWM     412
NapH1       MLAHVLATFEPLIAAWHHKTRFDAVRPVTAIRHVYGNRKIRAWGGVGMGTVD-IRASEWS     412
NapH4       MLQHILATFDTLIAAWGYKRKYEAVRPITAVRHVYGNRKIRAWGGVGMGTVDDIPANEWA     281
NapH3       FLVCSTARFDSLIAAWHHKRAYDTVRPFSAVRHVYGSKPVTAWGGPGKGTVESIPADEWT     363
MarH2       YMTSSVAQLDNLIASWHLKHAYDAVRPFSAVRHVYGRQKVRAWGGPGKGTV-ELRADEWA     401
MarH3       IYTSSLAQVEDLIAAWHYKVKYQAPRPFSAIRHVYGKKKVSAWGGPGIGTVHDMPADEWA     403
Mcl24       YAVTALARLDDLIAAWHWKTKFNSVRPFTAVHHVYGRKKISAWGGVGKGTVHDMPANEWS     403

MarH1       SYLPVGDHPEYPSGSTTLCSAASQCARRYFGSDELDWKFTFPAGSTRTEPGVVPAKDIEL     468
Mcl40       PYLPTGDHPEYPSGSTSLCAAGAQTARRYFNSEELDWTLEFNAGTSAVEPETTPAKNLQL     472
NapH1       SYLPVGDHPEYPSGSTSLCSATSQAARRYFDSDELDWTINYPAGSTVVEPGITPGKDLSI     472
NapH4       GYLPVGDHPEYPSGSTTVGSAASQAARRFFDSDDLNWEFDFEVGKSIVEPGITPVENVRV     341
NapH3       GYLPVGNHPEYPSGFTTLIAAQAQAARSFLGDDVLNWTHAFPAGSGQREPGAVPASDLEL     423
MarH2       GYLPVNDHPEYPSGSTALCAAMAQGARRFLGDDVLEWTYTFKAGSTQTEPGLVPARDIEL     461
MarH3       SFLPVGDHPDYPSGSTTLCAAEAQAARRFLGDDRLDWTWPIPAGWTLTEPGITPARDMEL     463
Mcl24       SYLPVGDHPEYISGSTTLCSAEAQAARRFLGDDVLDWTYSFPAGSGLTEPGLVPAKDTEL     463

MarH1       HFPTWTDFTQKCGASRVWGGVHFRKTVETSIAFGEQFGDMAHEFVQKHIKGEVED----     523
Mcl40       HFHTWAEFNKACAESRVWGGVHFRKTVQQSLIYGEQFGDLAHEFVNRHVKGNIKTDTRN     531
NapH1       HIPTWTDFTRTCATSRVWGGVHFQTTVDRTIDFGEQFGDLAHEFVQRHVKGDVKD----     527
NapH4       SFPTWTDFNKRCAYSRLDGGVHFKKTVERSMAFGEQFGDLAHDFIQRHVKGEGDG----     396
NapH3       TWATWTDFENDCATSRVWAGAHFTKTAETSLAFGTQFGDLAHTFVQRHINGDVKD----     478
MarH2       NYGTWTTFVRDAALSRVWAGVNFTKTAERSVEFGKQFGDLAHEFVQRHVSGEAED----     516
MarH3       HYGTWTEFVKDCGYSRLWAGVHFTTTVERSMEFGTQFGDLAYEFAQKYIKGDVED----     518
Mcl24       HWDTWTRFTRDCADSRVWGGVHFQTTVDRSIEWGAQFGDRAHQFLQRHIKGEVS-----     517
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Figure SI-2. Multiple sequence alignment of VHPO homologues from *Streptomyces* spp. meroterpenoid gene clusters: NapH1, H3 and H4 from the napyradiomycin cluster in *Streptomyces* sp. CNQ-525; Mcl24 and 40 from the merochlorin cluster in *Streptomyces* sp. CNH-189; and MarH1, H2 and H3 from the putative marinone cluster in *Streptomyces* sp. CNQ-509. The key vanadate-coordinating histidine residue [His494 in NapH1 sequence – PDB 3W36] highlighted in red is mutated to an asparagine residue in MarH2. Sequence alignment was performed using Clustal Omega.[8]

[8] F. Sievers, A. Wilm, D. G. Dineen, T. J. Gibson, K. Karplus, W. Li, R. Lopez, H. McWilliam, M. Remmert, J. Söding, J. D. Thompson, D. G. Higgins, *Mol. Syst. Biol.* **2011**, *7*, 539.

marH1: (GenBank accession number: CP011492.1 region 5599806 to 5601377)

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marH2: (GenBank accession number: CP011492.1 region 5596313 to 5597863)

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marH3: (GenBank accession number: CP011492.1 region 5593882 to 5595438)

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Figure SI-3. *marH* gene sequences used in this study.

Monochlorodimedone (MCD) assays – pH experiments:

To a 1 mL solution of 50 mM buffer (MES-NaOH, pH 6.0 or HEPES-NaOH, pH 8.0), 200 mM KCl, 50 μM MCD, and 10 μM sodium orthovanadate, MarH enzyme (10 μg) was added and transferred to a quartz cuvette. The absorbance at 290 nm of the solution was recorded every 1 second using a kinetic scanning program (Cary 60 UV-Vis spectrophotometer, Agilent) for 2 minutes to obtain a baseline MCD absorbance. At 2 minutes, 1 mM hydrogen peroxide (final concentration) was added and monitored for 5 additional minutes. If no decrease in absorbance was observed after this time, 200 mM potassium bromide (final concentration) was added and monitored for an additional 8 minutes.

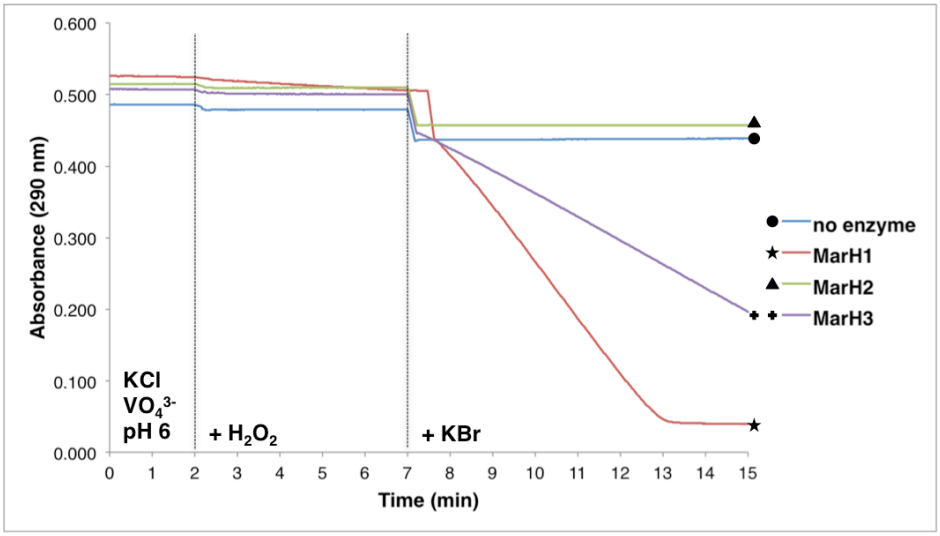


Figure SI-4. Monochlorodimedone (MCD) assay of MarH VCPO homologues at pH 6. Only MarH1 and MarH3 showed halogenation activity in the presence of bromide anions, consistent with other *Streptomyces* spp. VCPO enzymes.

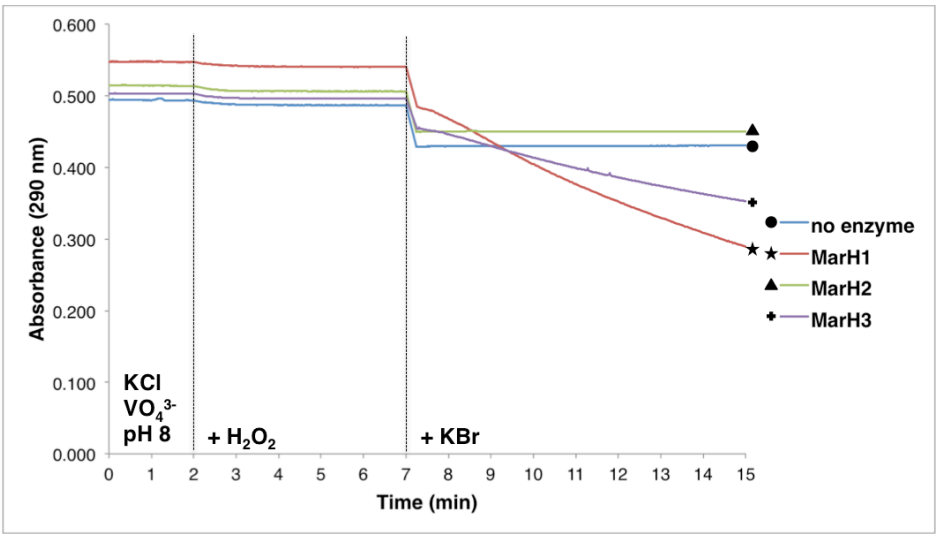


Figure SI-5. Monochlorodimedone (MCD) assay of MarH VCPO homologues at pH 8. Only MarH1 and MarH3 showed halogenation activity in the presence of bromide anions, consistent with other *Streptomyces* spp. VCPO enzymes.

Monochlorodimedone (MCD) assays – vanadium dependency experiments:

To a 1 mL solution of 50 mM buffer (MES-NaOH, pH 6.0), 200 mM KCl, 200 mM KBr, 50 μM MCD, and 1 mM hydrogen peroxide, MarH enzyme (10 μg) was added and transferred to a quartz cuvette. The absorbance at 290 nm of the solution was recorded every 1 second using a kinetic scanning program (Cary 60 UV-Vis spectrophotometer, Agilent) for 2 minutes to obtain a baseline MCD absorbance. At 2 minutes, 10 μM sodium orthovanadate (final concentration) was added and monitored for 13 additional minutes.

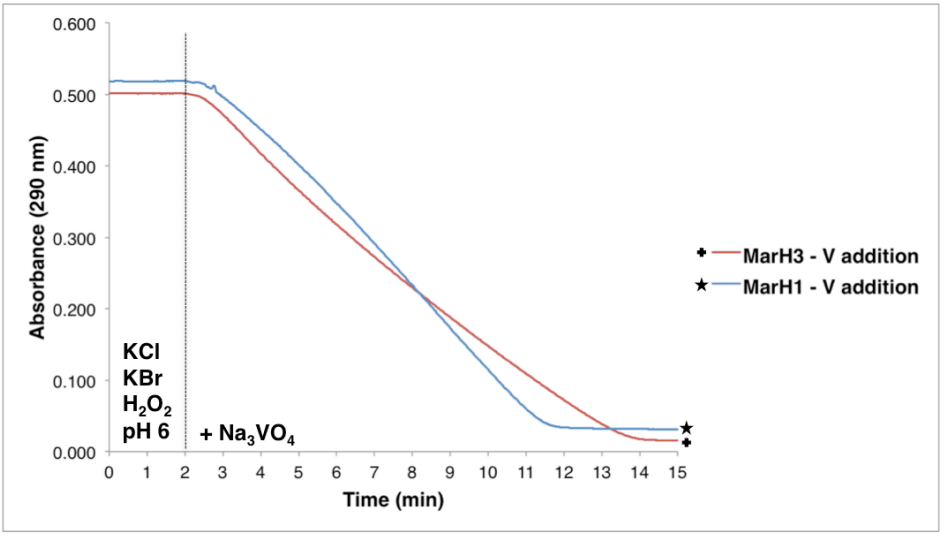


Figure SI-6. Monochlorodimedone (MCD) assay of MarH1 and MarH3 VCPO homologues at pH 6 adding sodium vanadate at 2 minutes. A decrease in absorbance at 290 nm is only observed following the addition of exogenous sodium vanadate. This indicates that recombinant MarH1 and MarH3 enzymes do not have bound vanadium in their active sites and there is negligible time required to incorporate vanadate in order to restore catalysis.

General VCPO activity assay procedure:

To a 1 mL solution of 50 mM buffer solution (MES-NaOH, pH 6.0 or HEPES-NaOH, pH 8.0), 100 mM KCl, 100 μM sodium orthovanadate, 1 mM hydrogen peroxide (1 equivalent), and 20 μM MarH enzyme(s), a DMSO solution of 1 mM substrate (final concentration) was added and incubated at 20 °C. Aliquots (50 μL) were removed at 1, 3 and 18 h intervals, quenched with 50 μL of acetonitrile, centrifuged for 2 minutes at 13000 x *g* to pellet proteins, and the clarified supernatant was analyzed by RP-HPLC-MS in negative ionization mode using the following method: 10 - 100% B (20 min), 100% B (4 min), 100 - 10% B (3 min), 10% B (3 min), where A = 0.1% aqueous formic acid, and B = 0.1% formic acid in acetonitrile (flow rate: 0.75 mL/min; column: Agilent Eclipse XDB-C18 5 μm, 4.6 x 150 mm; LC: Agilent Technologies 1200 series system with a diode-array detector; MS: Bruker Amazon SL ESI-Ion Trap mass spectrometer; data processing: Bruker Compass Data Analysis 4.2 SR2). VCPO assay analytes showing comparable retention times and *m/z* to synthetic standards are highlighted in grey boxes (*m/z* values ± 0.2 Da of synthetic standards: **12a** – 343.2; **12b** – 411.2; **13a** – 377.1; **13b** – 445.2; **15a** – 411.1; **15b** – 479.1).

Activity of MarH1 on pre-marinone (11b) at pH 8:

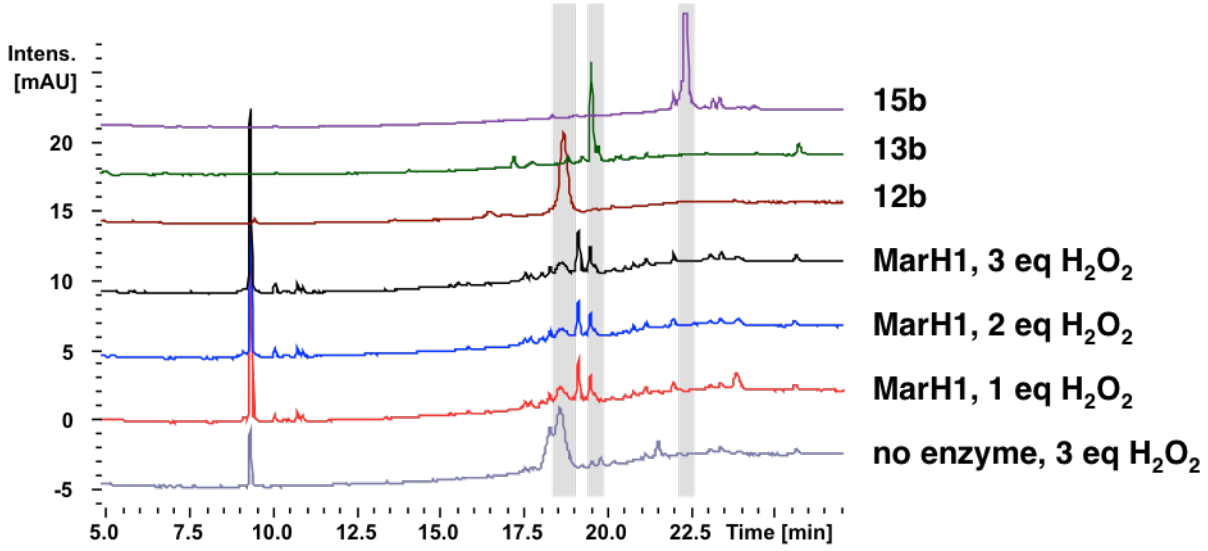


Figure SI-7. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH1 incubation with **11b** in the presence of variable equivalents of hydrogen peroxide (pH 8, 18 h), and comparison to synthetic standards **12b**, **13b**, and **15b**.

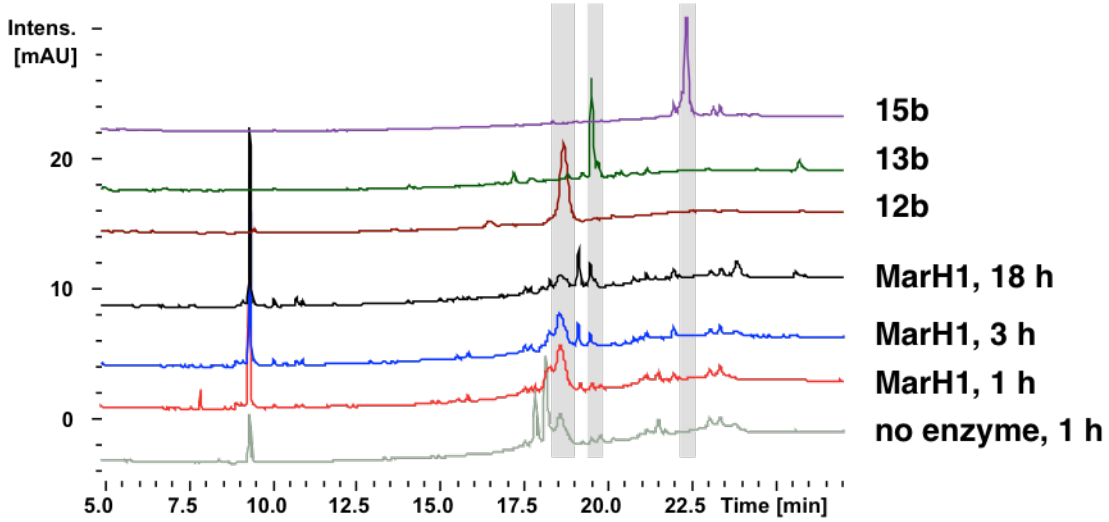


Figure SI-8. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH1 incubation with **11b** over time (pH 8, 1 equiv. hydrogen peroxide), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Activity of MarH1 on pre-marinone (11b) at pH 6:

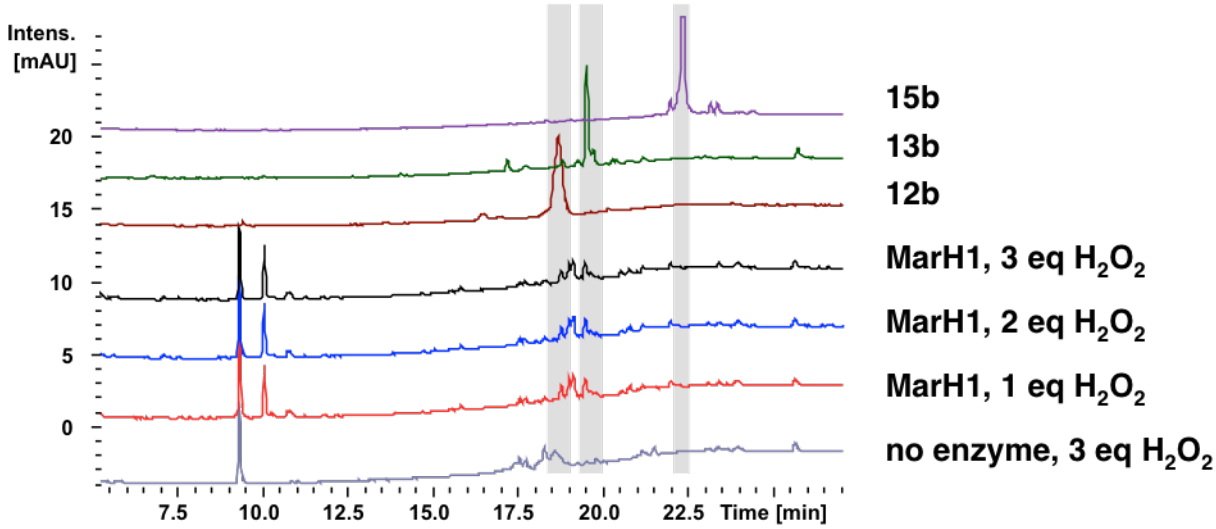


Figure SI-9. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH1 incubation with **11b** in the presence of variable equivalents of hydrogen peroxide (pH 6, 18 h), and comparison to synthetic standards **12b**, **13b**, and **15b**.

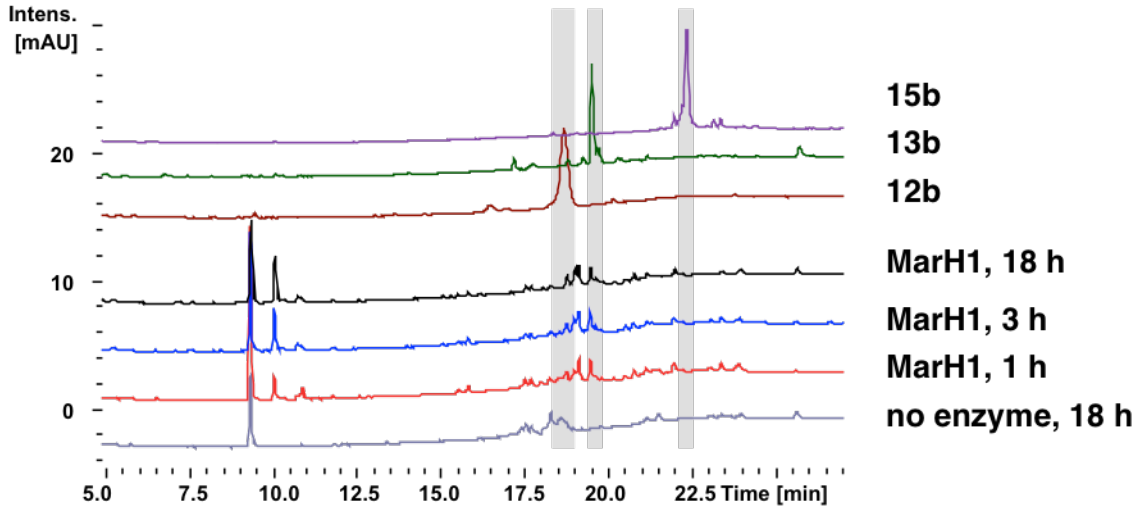


Figure SI-10. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH1 incubation with **11b** over time (pH 6, 1 equiv. hydrogen peroxide), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Activity of MarH3 on pre-marinone (11b) at pH 8:

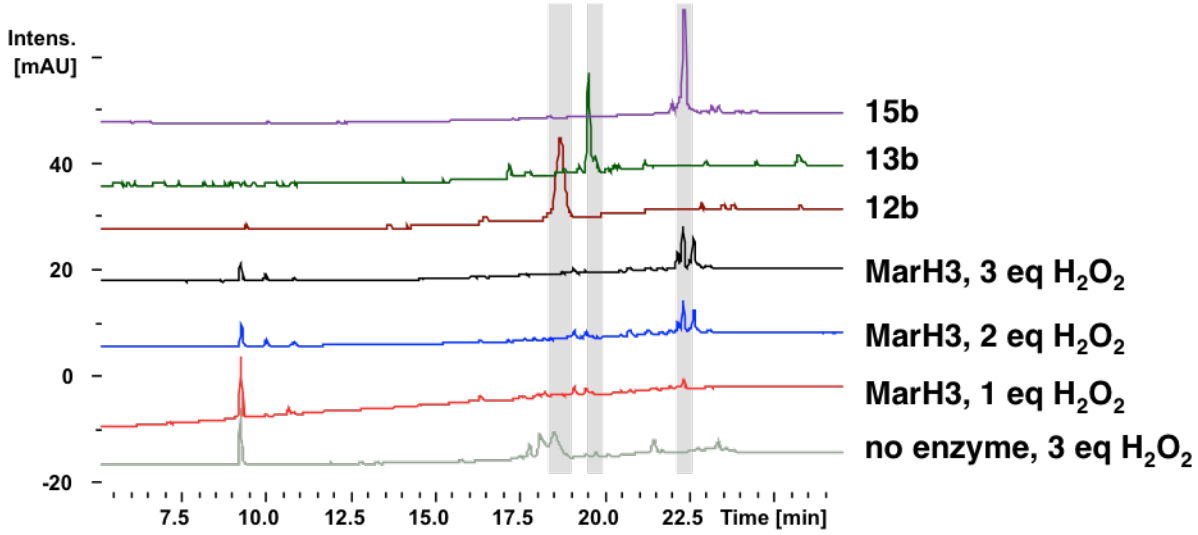


Figure SI-11. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH3 incubation with **11b** in the presence of variable equivalents of hydrogen peroxide (pH 8, 18 h), and comparison to synthetic standards **12b**, **13b**, and **15b**.

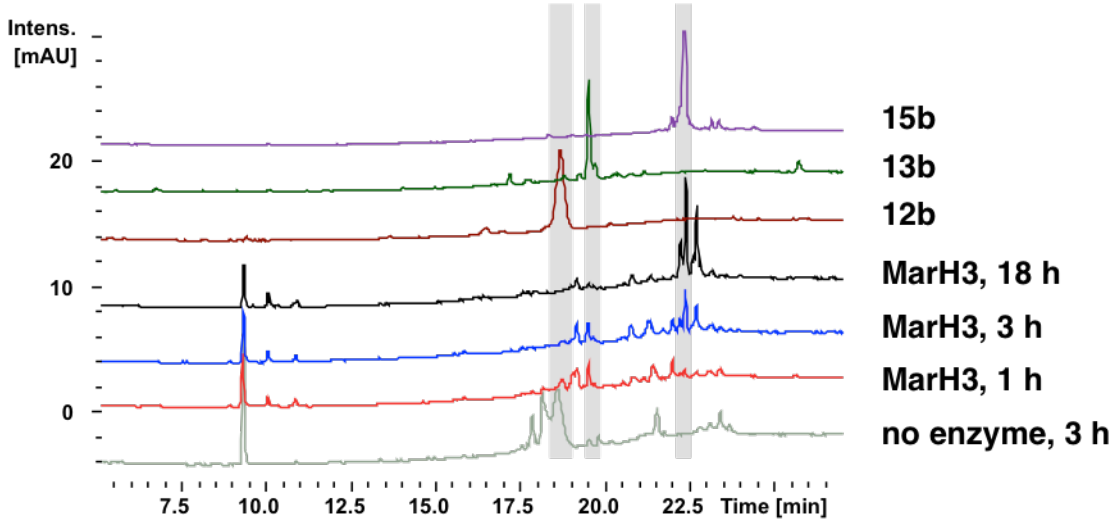


Figure SI-12. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH3 incubation with **11b** over time (pH 8, 3 equiv. hydrogen peroxide), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Activity of MarH3 on pre-marinone (11b) at pH 6:

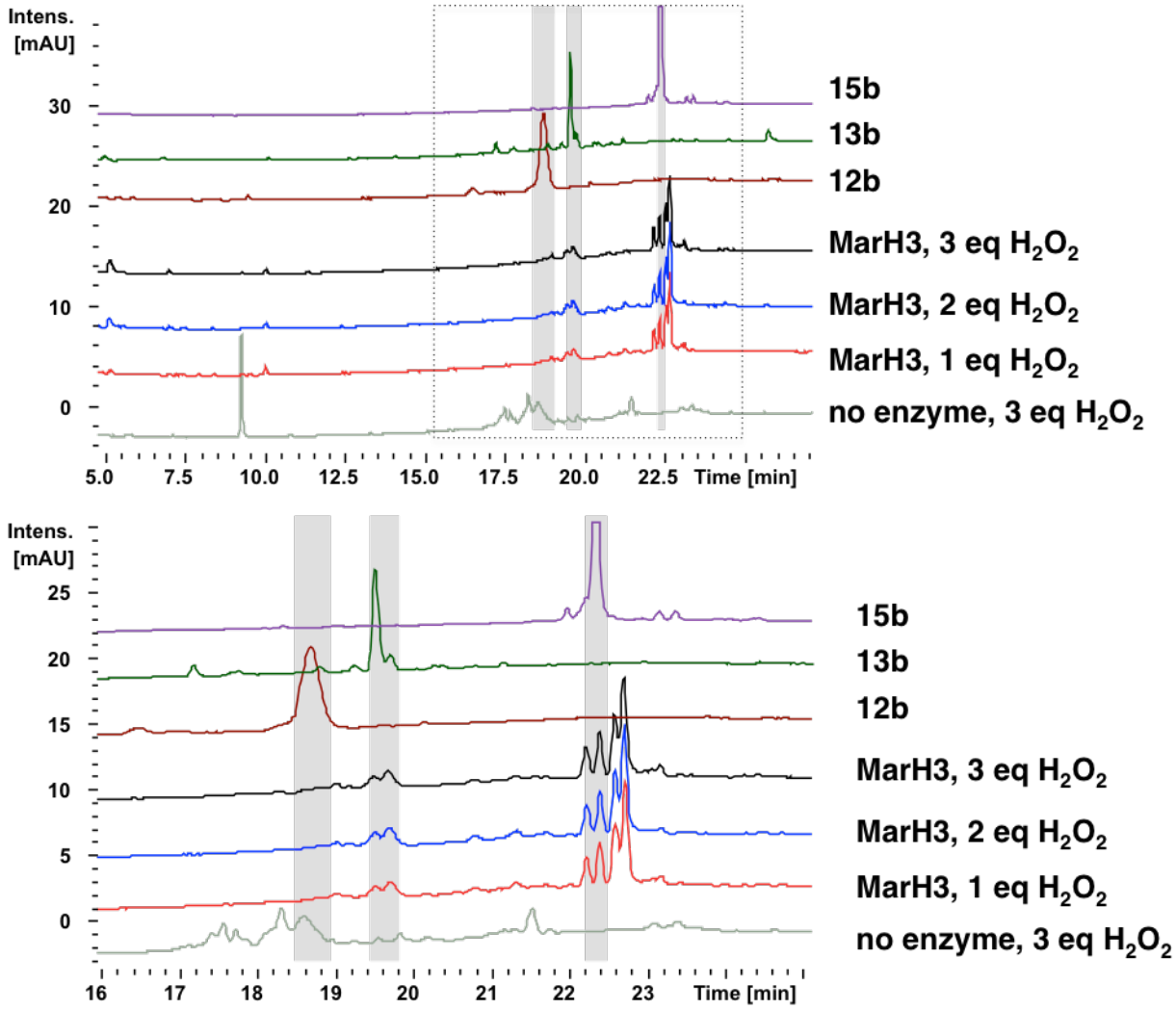


Figure SI-13. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH3 incubation with **11b** in the presence of variable equivalents of hydrogen peroxide (pH 6, 18 h), and comparison to synthetic standards **12b**, **13b**, and **15b**.

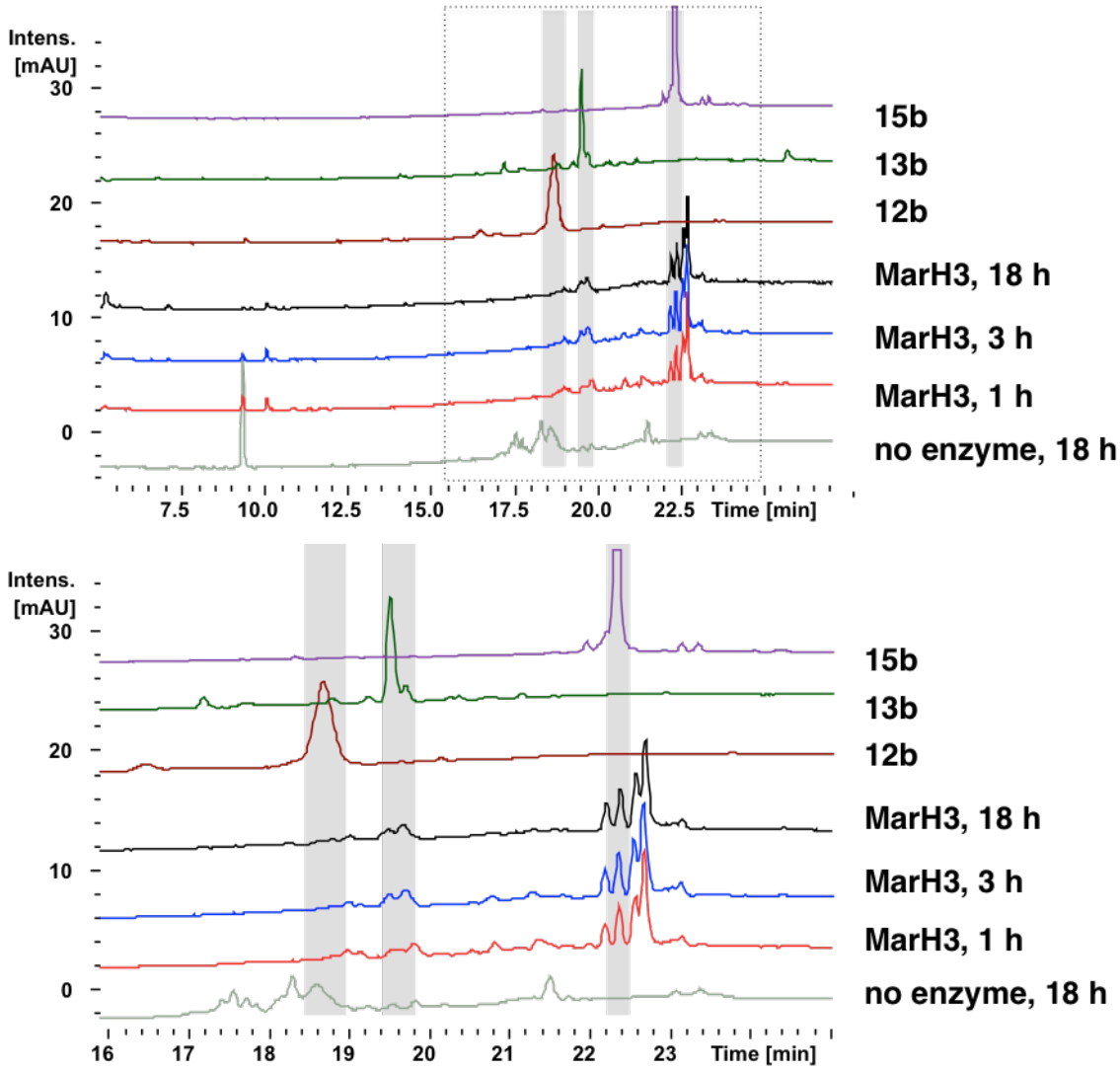


Figure SI-14. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH3 incubation with **11b** over time (pH 6, 3 equiv. hydrogen peroxide), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Sequential activities of MarH1, then MarH3 on pre-marinone (11b):

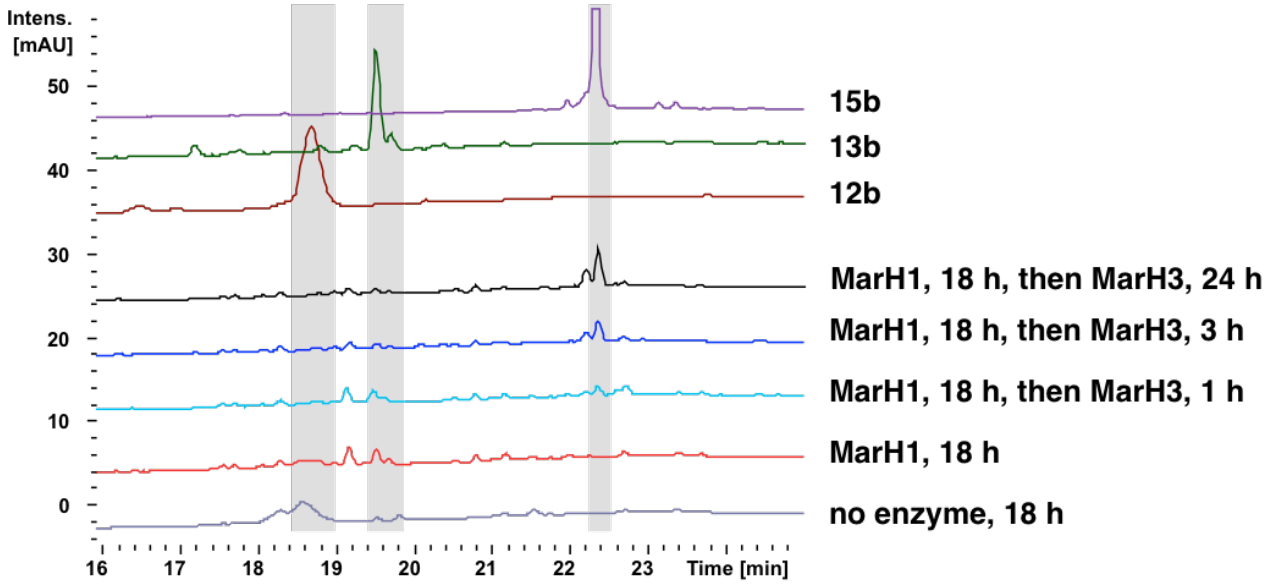


Figure SI-15. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11b** with MarH1 (pH 8, 2 equiv. hydrogen peroxide, 18 h) followed by MarH3 (1 additional equiv. hydrogen peroxide, variable time), and comparison to synthetic standards **12b**, **13b**, and **15b**.

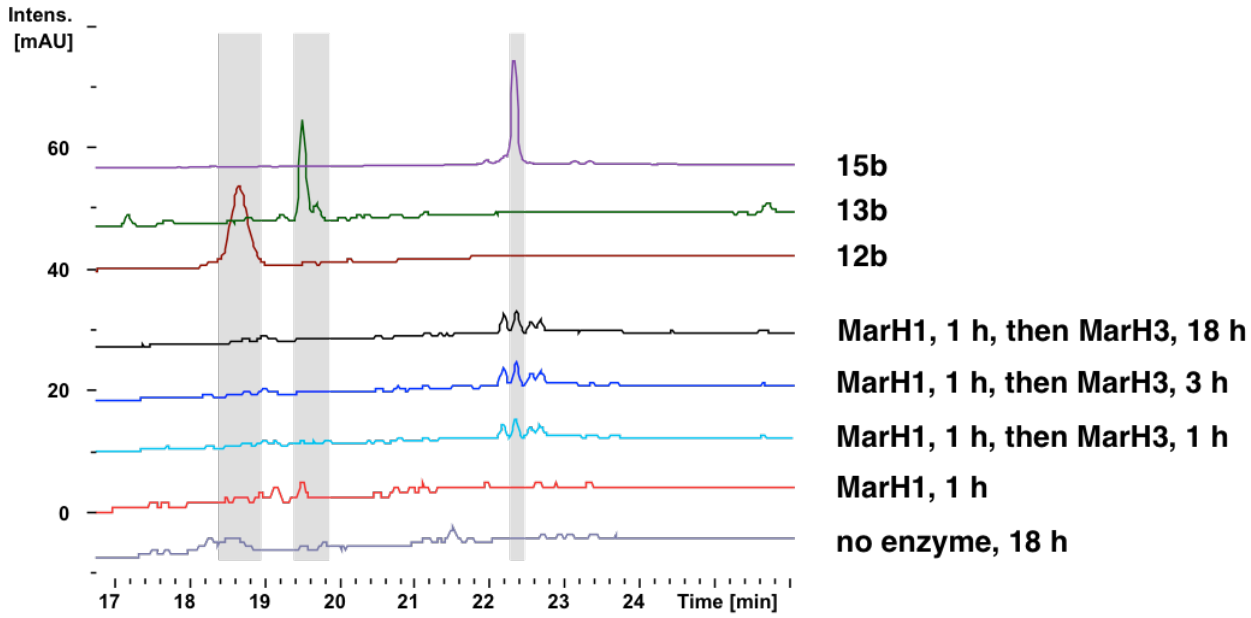


Figure SI-16. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11b** with MarH1 (pH 6, 2 equiv. hydrogen peroxide, 1 h) followed by MarH3 (1 additional equiv. hydrogen peroxide, variable time), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Comparison of *in vitro* activities of MarH1 and MarH3 on pre-marinone (11b) with and without MarH2 co-incubation.

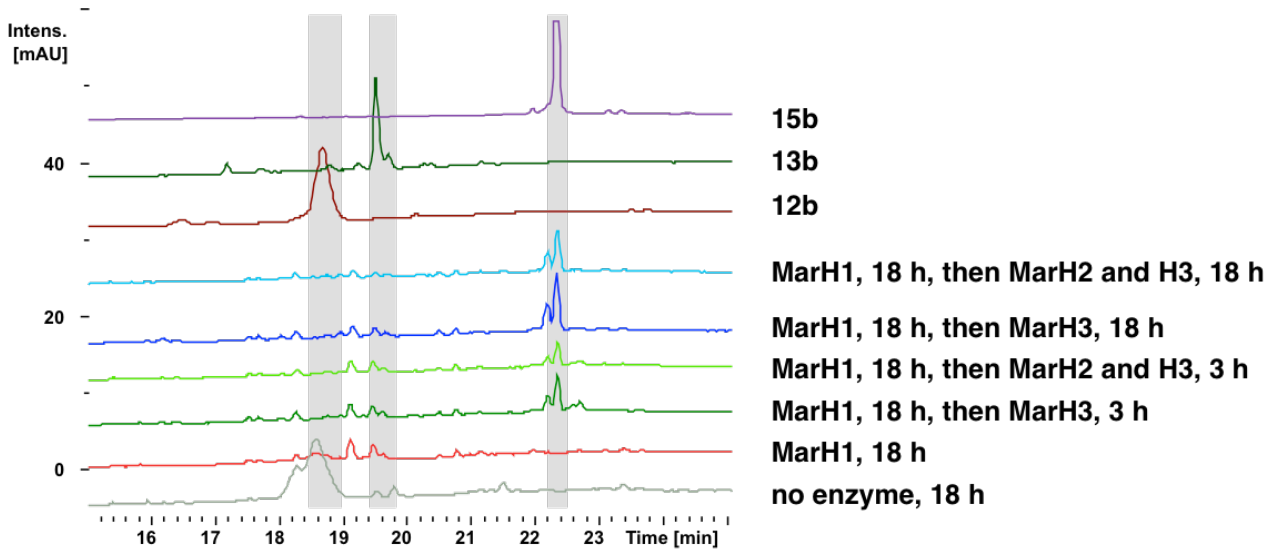


Figure SI-17. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11b** with MarH1 (pH 8, 2 equiv. hydrogen peroxide, 18 h) followed by MarH3 with or without MarH2 (1 additional equiv. hydrogen peroxide, variable time), and comparison to synthetic standards **12b**, **13b**, and **15b**.

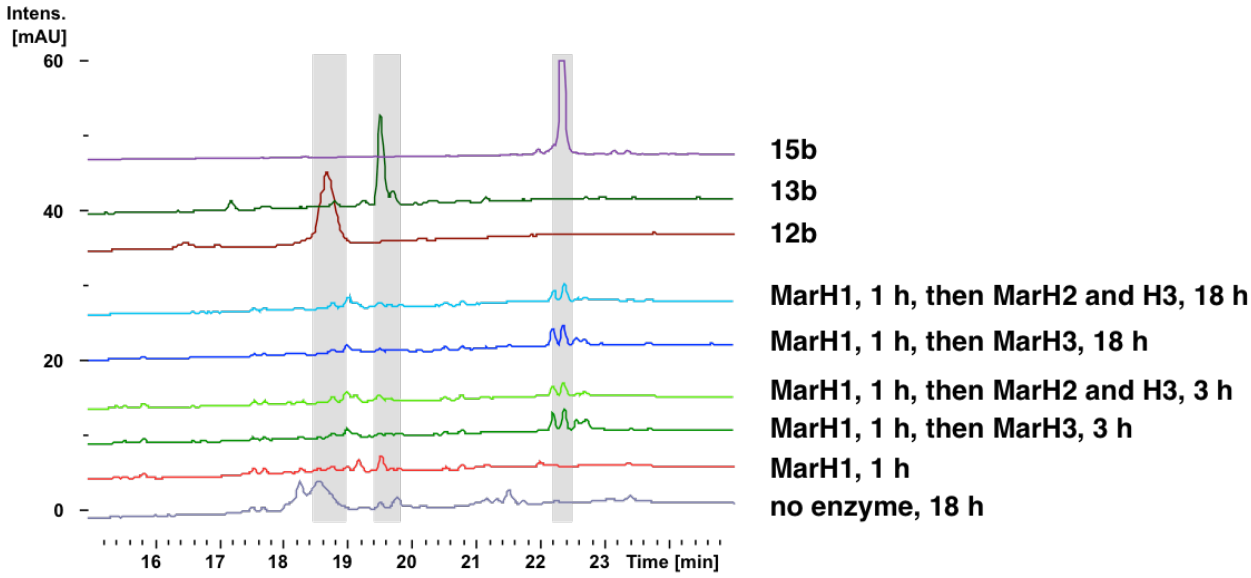


Figure SI-18. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11b** with MarH1 (pH 6, 2 equiv. hydrogen peroxide, 18 h) followed by MarH3 with or without MarH2 (1 additional equiv. hydrogen peroxide, variable time), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Comparison of *in vitro* activity of MarH3 on pre-marinone (11b) with and without MarH2 co-incubation:

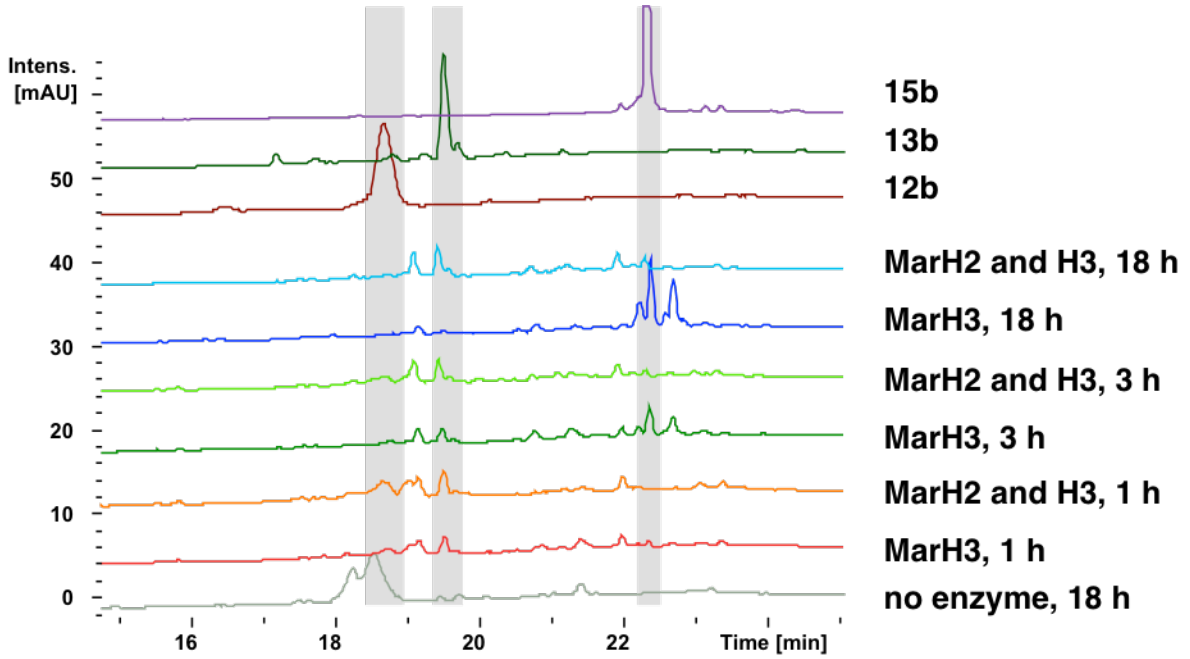


Figure SI-19. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11b** with MarH3 over time (pH 8, 3 equiv. hydrogen peroxide) with or without MarH2, and comparison to synthetic standards **12b**, **13b**, and **15b**.

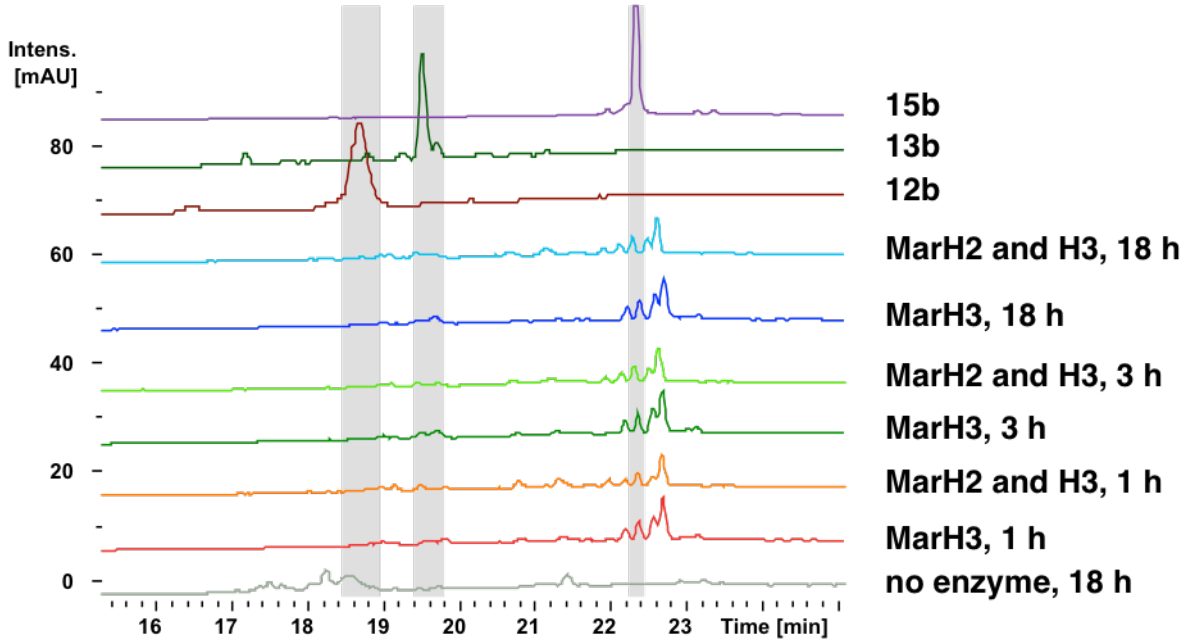


Figure SI-20. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11b** with MarH3 over time (pH 6, 3 equiv. hydrogen peroxide) with or without MarH2, and comparison to synthetic standards **12b**, **13b**, and **15b**.

Activity of MarH1 on pre-naphterpin (11a) at pH 8:

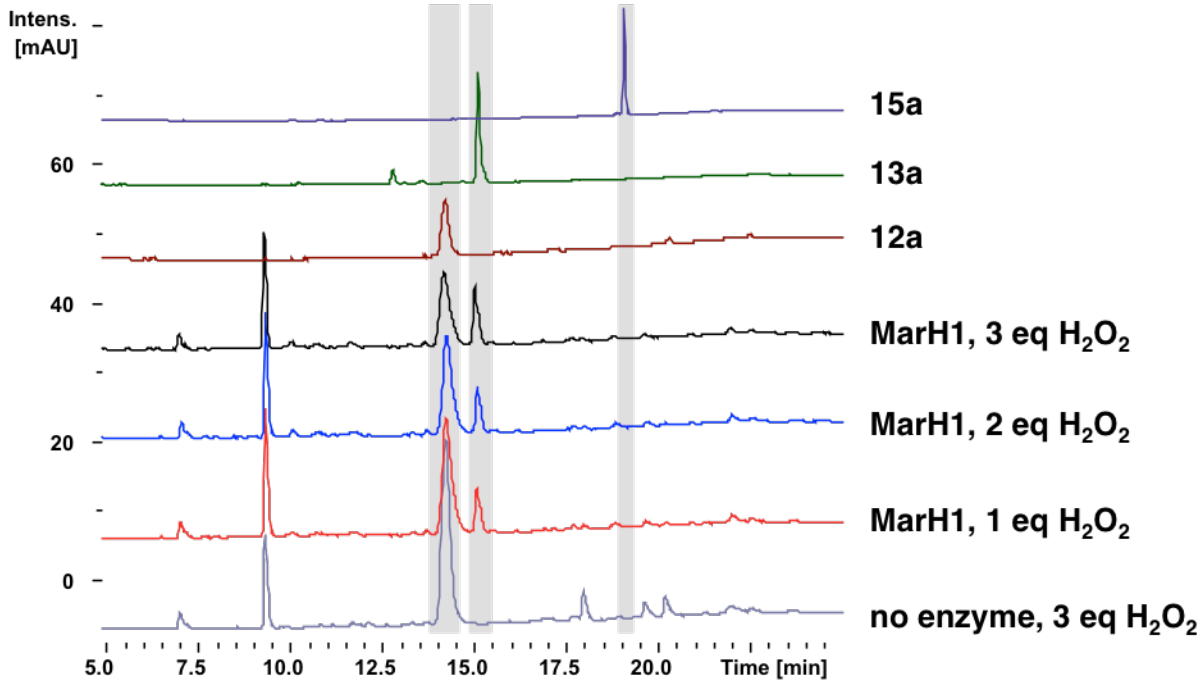


Figure SI-21. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH1 incubation with **11a** in the presence of variable equivalents of hydrogen peroxide (pH 8, 18 h), and comparison to synthetic standards **12a**, **13a**, and **15a**.

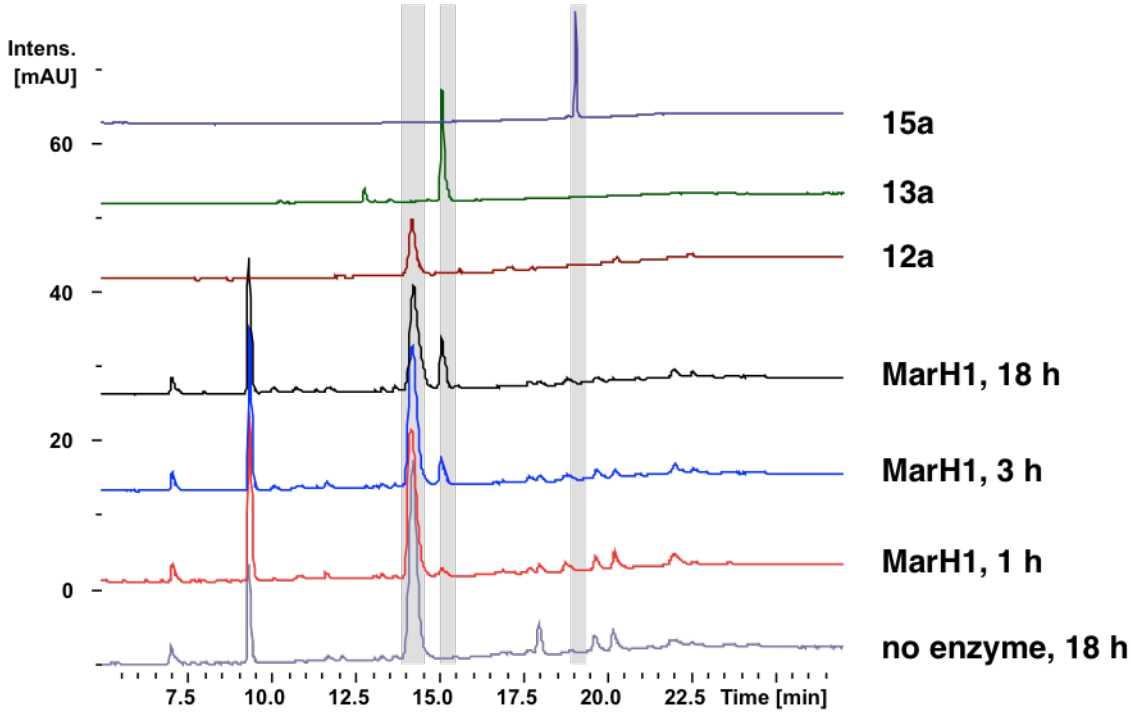


Figure SI-22. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH1 incubation with **11a** over time (pH 8, 3 equiv. hydrogen peroxide), and comparison to synthetic standards **12a**, **13a**, and **15a**.

Activity of MarH3 on pre-naphterpin (11a) at pH 8:

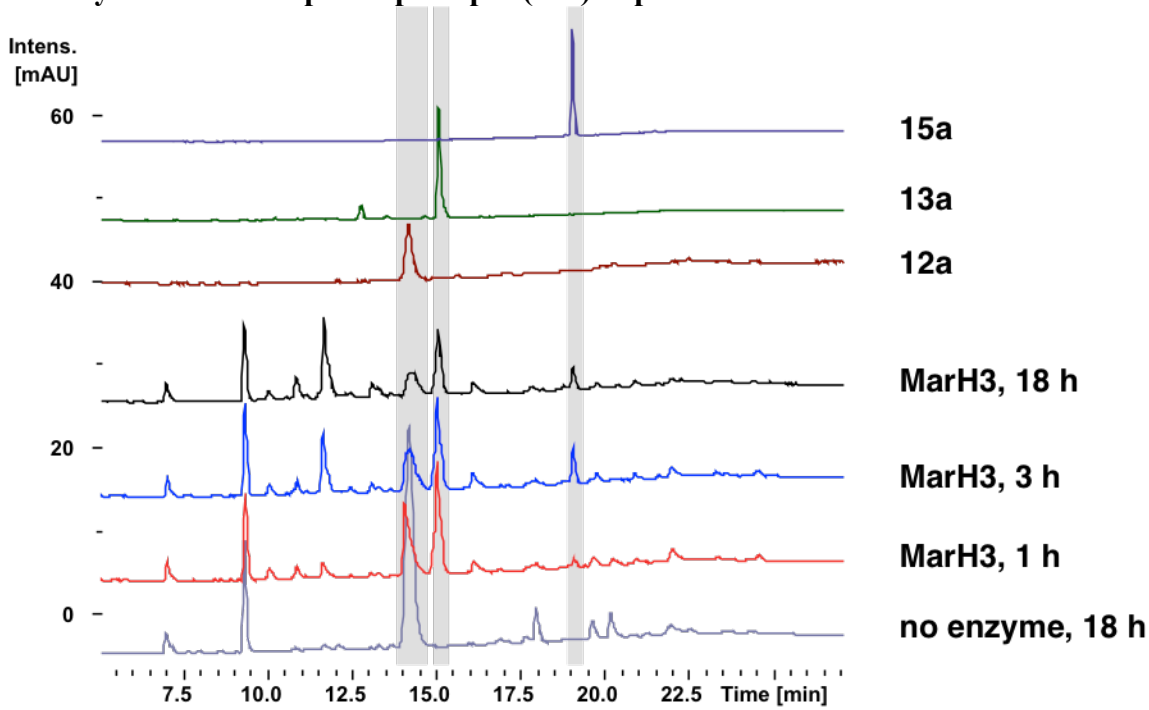


Figure SI-23. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* MarH3 incubation with **11a** in the presence of variable equivalents of hydrogen peroxide (pH 8, 18 h), and comparison to synthetic standards **12a**, **13a**, and **15a**.

Sequential activities of MarH1, then MarH3 on pre-naphterpin (11a):

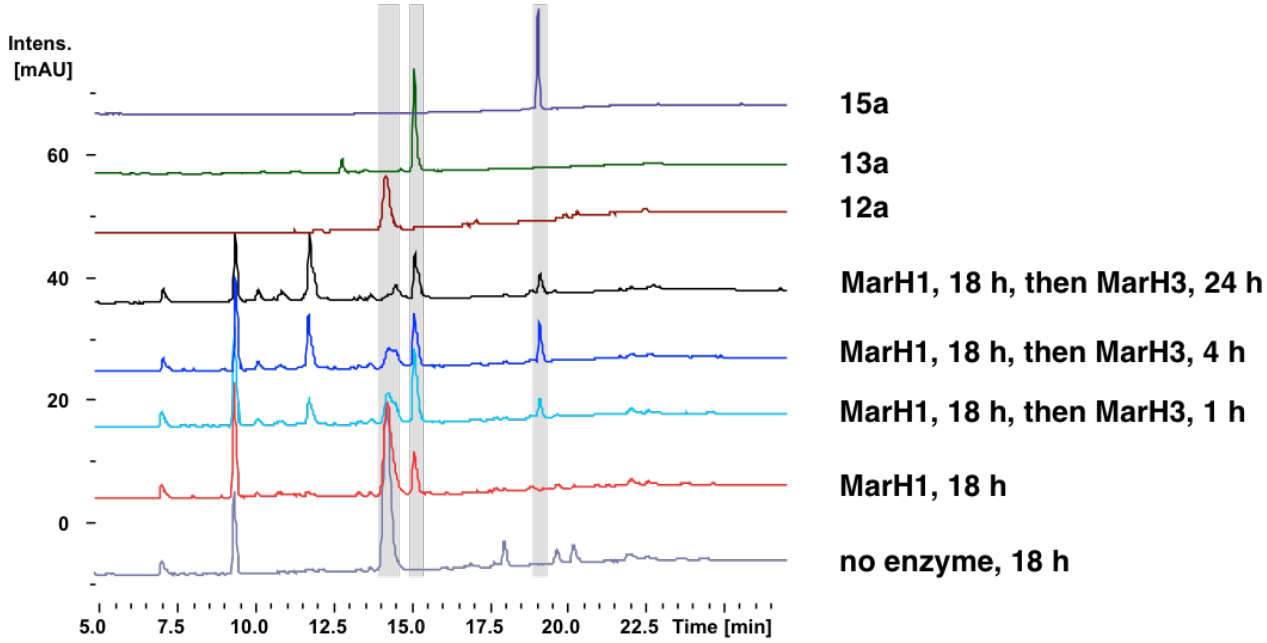


Figure SI-24. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of **11a** with MarH1 (pH 8, 3 equiv. hydrogen peroxide, 18 h) followed by MarH3 (1 additional equiv. hydrogen peroxide, variable time), and comparison to synthetic standards **12a**, **13a**, and **15a**.

Activity of MarH3 on racemic dearomatized substrates 12b and 13b:

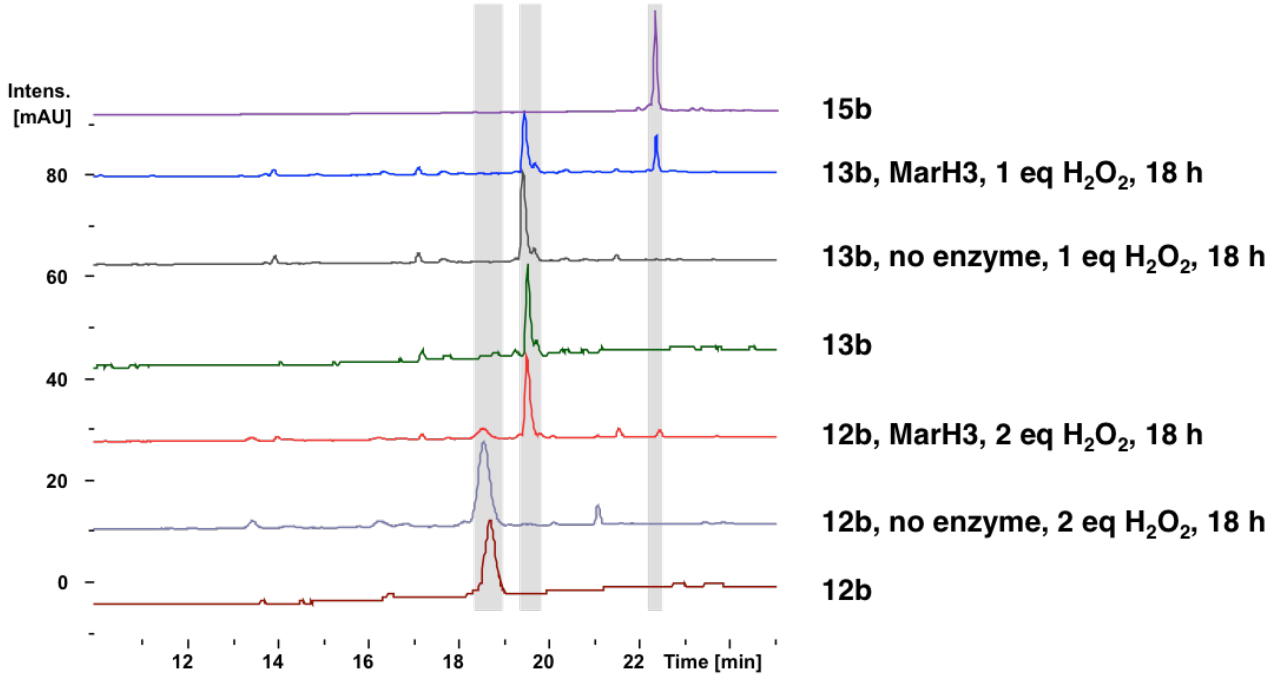


Figure SI-25. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of racemic synthetic substrates (**12b**/**13b**) with MarH3 (pH 8, variable quantities of hydrogen peroxide, 18 h), and comparison to synthetic standards **12b**, **13b**, and **15b**.

Activity of MarH3 on racemic dearomatized substrates 12a and 13a:

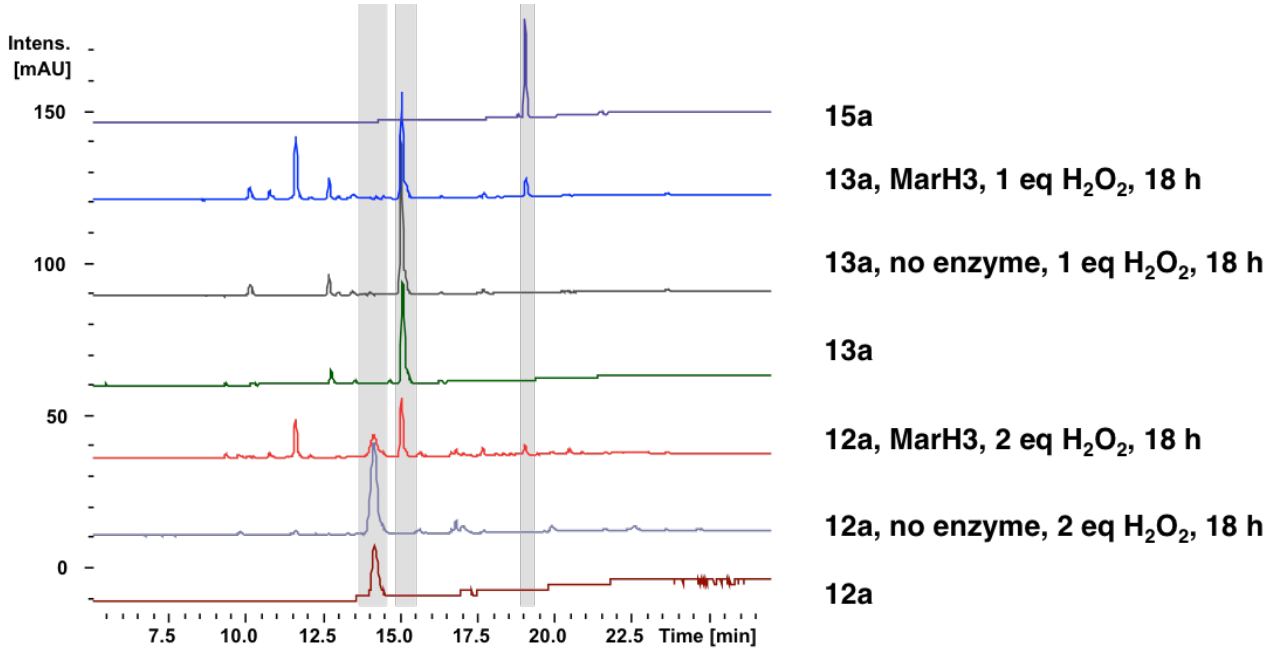
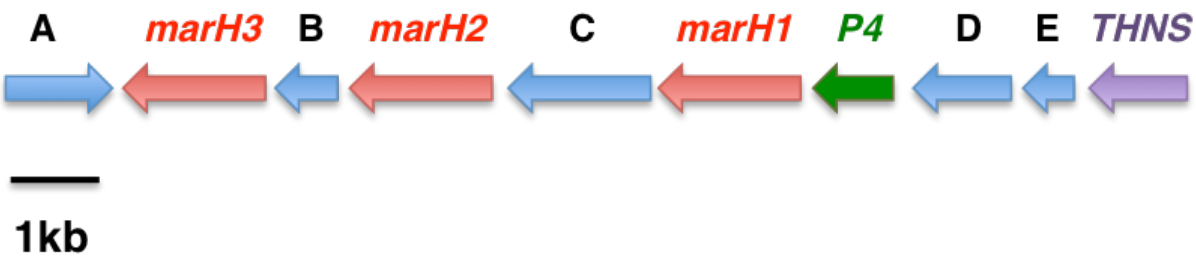


Figure SI-26. RP-HPLC-MS analysis (λ = 300 nm) of *in vitro* incubation of racemic synthetic substrates (**12a**/**13a**) with MarH3 (pH 8, variable quantities of hydrogen peroxide, 18 h), and comparison to synthetic standards **12a**, **13a**, and **15a**.



Gene Product	Amino acids	Proposed function	Protein accession number
A	381	myo-inositol-1-phosphate synthase	WP_047018061.1
MarH3	518	VCPO	WP_047020372.1
B	219	prenyl diphosphate synthase/ isoprenyl transferase	WP_047018062.1
MarH2	516	VCPO	WP_047020373.1
C	512	MFS transporter	AKH87007.1
MarH1	523	VCPO	AKH84811.1
P4	303	prenyltransferase	WP_047018064.1
D	357	C-methyltransferase	WP_047018065.1
E	190	isopentenyl-diphosphate delta-isomerase	AKH84814.1
THNS	355	THN synthase (type III PKS)	WP_047020375.1

Figure SI-27. Putative marinone biosynthetic gene cluster.