Supporting Information

Total Synthesis of (−)-Vindoline and (+)-4-*epi*-Vindoline Based on a 1,3,4-Oxadiazole Tandem Intramolecular [4 + 2]/[3 + 2] Cycloaddition Cascade Initiated by an Allene Dienophile

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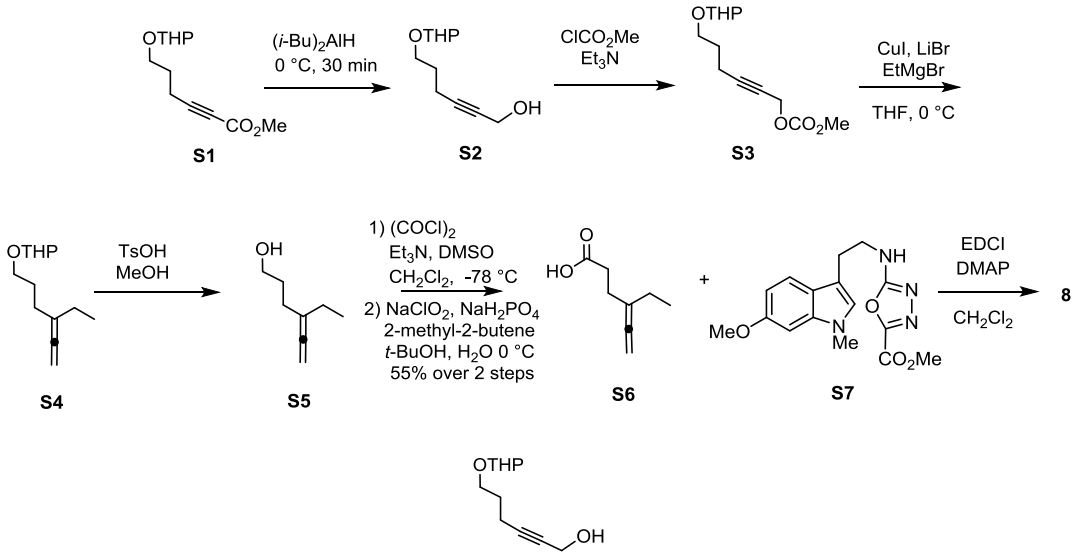
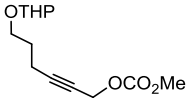
Synthesis of 8:

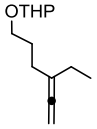


Compound S2. Diisobutylaluminum hydride (42 mmol, 42 mL of a 1 M solution in hexanes) was added dropwise to a solution of **S1**[S1] (4.32 g, 19 mmol) in toluene (60 mL) at 0 ºC. The resulting mixture was stirred for 30 min at 0 ºC. The reaction was quenched by addition of MeOH (100 mL) and the mixture was filtered through Celite. Silica gel flash chromatography (25–50% EtOAc/hexanes gradient) gave **S2** (3.10 g, 82%) as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 4.3, 2.8 Hz, 1H), 4.24 (br s, 2H), 3.88–3.79 (m, 2H), 3.52–3.45 (m, 2H), 2.33 (tt, *J* = 7.1, 2.2 Hz, 2H), 1.83–1.77 (m, 4H), 1.73–1.68 (m, 1H), 1.60–1.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.0, 85.9, 78.9, 66.0, 62.4, 51.5, 30.8, 28.9, 25.6, 19.7, 15.8; IR (neat) ν_{max} 3422, 2939, 2869, 1440, 1136, 1021 cm^{-1}; HRMS-ESI-TOF *m/z* 199.1324 ($C_{11}H_{18}O_3$ + H^+ requires 199.1329).

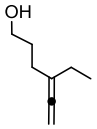


Compound S3. Compound **S2** (2.04 g, 10 mmol) was added dropwise to a solution of methyl chloroformate (2.3 mL, 30 mmol) in CH_2Cl_2 (60 mL) at 0 ºC. Then Et_3N (5.6 mL, 40 mmol) was added dropwise and the resulting mixture was stirred at 0 ºC for 3 h. The reaction was quenched by addition of water (30 mL). The aqueous layer was extracted with CH_2Cl_2, dried with Na_2SO_4, and concentrated under reduced pressure. Silica gel flash chromatography (20% EtOAc/hexanes) gave **S3** (2.47 g, 94%) as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (br s, 2H), 4.58 (br s, 1H), 3.87–3.79 (m, 2H), 3.80 (s, 3H), 3.51–3.43 (m, 2H), 2.36–2.33 (m, 2H), 1.81–1.78 (m, 3H) 1.70–1.68 (m, 1H), 1.58–1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 98.9, 88.0, 73.8, 66.0, 62.3, 56.4, 55.1, 30.8, 28.7,

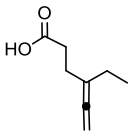
25.6, 19.7, 15.9; IR (neat) ν_{max} 2942, 2870, 1751, 1443, 1255, 1136, 1033 cm^{-1}; HRMS-ESI-TOF *m/z* 257.1385 ($C_{13}H_{20}O_5 + H^+$ requires 257.1383).



Compound S4. Ethylmagnesium bromide (13.8 mmol, 15.3 mL of a 0.9 M solution in THF) was added dropwise to a suspension of CuI (2.63 g, 13.8 mmol) and LiBr (1.20 g, 13.8 mmol) in THF (48 mL) at 0 ºC. The resulting mixture was cooled to –5 °C and **S3** was added dropwise as a solution in THF (6 mL). The resulting mixture was stirred for 30 min at 0 ºC and quenched with the addition of 30 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel flash chromatography (0–5% EtOAc/hexanes gradient) gave **S4** (430 mg, 89%) as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (p, *J* = 3.4 Hz, 2H), 4.57 (dd, *J* = 4.5, 2.9 Hz, 1H), 3.85 (td, *J* = 8.1, 4.0 Hz, 1H), 3.75 (dt, *J* = 9.6, 6.6 Hz, 1H), 3.51–3.47 (m, 1H), 3.40 (dt, *J* = 9.7, 6.5 Hz, 1H), 2.04–1.99 (m, 2H), 1.97–1.91 (m, 2H), 1.83–1.81 (m, 1H), 1.76–1.68 (m, 3H) 1.60–1.49 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 104.8, 99.0, 76.5, 67.3, 62.4, 30.9, 28.8, 27.8, 25.7, 25.3, 19.8, 12.3; IR (neat) ν_{max} 2938, 2870, 1981, 1440, 1135, 1031 cm^{-1}; HRMS-ESI-TOF *m/z* 211.1688 ($C_{13}H_{22}O_2 + H^+$ requires 211.1692).

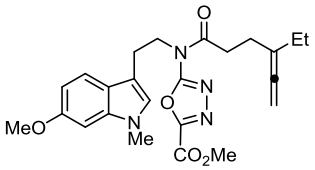


Compound S5. *p*-Toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added to a mixture of **S4** (430 mg, 2 mmol) in MeOH (10 mL). After stirring for 2 h at room temperature, the mixture was diluted with saturated NH_4Cl (4 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel flash chromatography (20–40% Et2O/hexanes gradient) gave **S5** (240 mg, 95%) as a clear, colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (p, *J* = 3.4 Hz, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.03–1.99 (m, 2H), 1.97–1.91 (m, 2H), 1.74–1.67 (m, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 104.7, 76.5, 62.6, 30.6, 28.4, 25.3, 12.2; IR (neat) ν_{max} 3327, 2965, 2934, 2876, 1957, 1434, 1058 cm^{-1}; HRMS-ESI-TOF *m/z* 127.112 ($C_8H_{14}O + H^+$ requires 127.117).

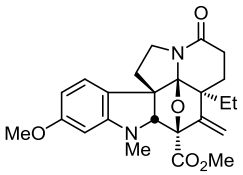


Compound S6. DMSO (568 μL, 8 mmol) was added to a mixture of oxalyl chloride (338 μL, 4 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 30 min, **S5** (240 mg, 1.9 mmol) was added in 5 mL CH_2Cl_2 and after a further 30 min, Et_3N (1.7 mL, 12 mmol) was added. The mixture was allowed to warm to room temperature over 1 h, then poured into water (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed sequentially with aqueous 0.1 N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic extracts were dried over Na_2SO_4 and carefully concentrated under reduced pressure. The crude aldehyde was used immediately. A solution of $NaClO_2$ (678 mg, 6 mmol) and NaH_2PO_4 (1.25 g, 8 mmol) in water (2 mL) was added to a mixture of aldehyde (1.9 mmol), 2-methyl-2-butene (12 mL) and *t*-BuOH (36 mL) at 0 °C. The mixture was warmed to room temperature over 2 h, then poured into water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel flash chromatography (10–20% EtOAc/hexanes gradient) gave **S6** (165 mg, 62%) as a clear, pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (t, *J* = 3.6 Hz, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 2.25–2.23

(br m, 2H), 1.97–1.95 (br m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 179.9, 104.2, 78.0, 32.3, 26.4, 25.5, 12.2; IR (neat) ν_{max} 3500–2933 (br), 2001, 1710, 1430, 1284 cm^{-1}; HRMS-ESI-TOF *m/z* 141.0908 ($C_8H_{12}O_2$ + H^+ requires 141.0916).



Compound 8. EDCI (655 mg, 3.42 mmol) and DMAP (417 mg, 3.42 mmol) were added to a solution of **S6** (478 mg, 3.42 mmol) in CH_2Cl_2 (38 mL) at 0 °C. Compound **S7**[S2] (374 mg, 1.13 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature overnight. After 14 h, the mixture was concentrated under reduced pressure. Silica gel flash chromatography (40% EtOAc/hexanes) gave **8** (480 mg, 94%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.6 Hz, 1H), 6.78 (dd, J = 8.6, 2.2 Hz, 1H), 6.74 (s, 1H), 6.69 (d, J = 2.2 Hz, 1H), 4.69 (t, J = 3.6 Hz, 2H), 4.22–4.20 (m, 2H), 4.00 (s, 3H), 3.87 (s, 3H), 3.65 (s, 3H), 3.07 (t, J = 7.6 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H), 2.34–2.32 (m, 2H), 1.99–1.97 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 172.1, 162.2, 156.6, 154.2, 153.4, 137.8, 126.5, 121.9, 119.7, 110.1, 109.2, 104.5, 92.8, 77.9, 55.8, 53.7, 47.9, 34.5, 32.7, 26.7, 25.5, 24.5, 12.2; IR (neat) ν_{max} 2962, 1933, 1748, 1702, 1561, 1438, 1152 cm^{-1}; HRMS-ESI-TOF *m/z* 453.2138 ($C_{24}H_{28}N_4O_5$ + H^+ requires 453.2132).



Compound 9. Argon was bubbled through a solution of **8** (100 mg, 0.222 mmol) in 1,3,5-triisopropylbenzene (110 mL). The vessel was sealed and warmed at 230 °C for 48 h. Upon cooling to room temperature, the reaction mixture was filtered through a column of silica gel which was washed thoroughly with hexanes before products were eluted with 70% EtOAc/hexanes, providing **9** (86 mg, 92%) as a pale yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, J = 8.2 Hz, 1H), 6.11 (dd, J = 8.1, 2.3 Hz, 1H), 5.93 (d, J = 2.2 Hz, 1H), 5.17 (s, 1H), 5.09 (s, 1H), 4.22, (s, 1H), 3.99 (dd, J = 10.4, 4.4 Hz, 2H), 3.89 (s, 3H), 3.77 (s, 3H), 2.95 (s, 3H), 2.50–2.42 (m, 2H), 2.38–2.26 (m, 2H), 2.21 (dt, J = 12.4, 4.3 Hz, 1H), 1.82–1.78 (m, 1H), 1.06–0.97 (m, 1H), 0.82 (t, J = 7.3 Hz, 3H), 0.75–0.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.5, 161.8, 154.6, 151.9, 123.9, 120.6, 107.8, 105.8, 101.6, 93.4, 90.9, 82.6, 64.5, 55.5, 52.9, 47.4, 47.1, 37.1, 33.8, 29.9, 28.5, 23.7, 9.9; IR (neat) ν_{max} 2956, 1734, 1667, 1621, 1399, 1247, 1119 cm^{-1}; HRMS-ESI-TOF *m/z* 425.2086 ($C_{24}H_{28}N_2O_5$ + H^+ requires 425.2071).

The structure and stereochemistry of **9** were established by a single crystal X-ray structure determination conducted on plates grown from a layered mixture of EtOAc and hexanes. (CDCC 1412216).

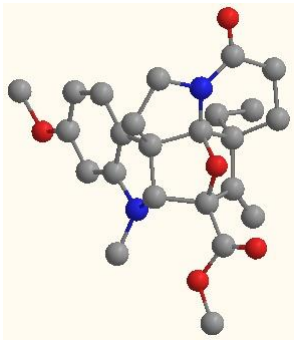
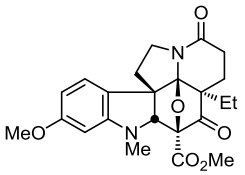
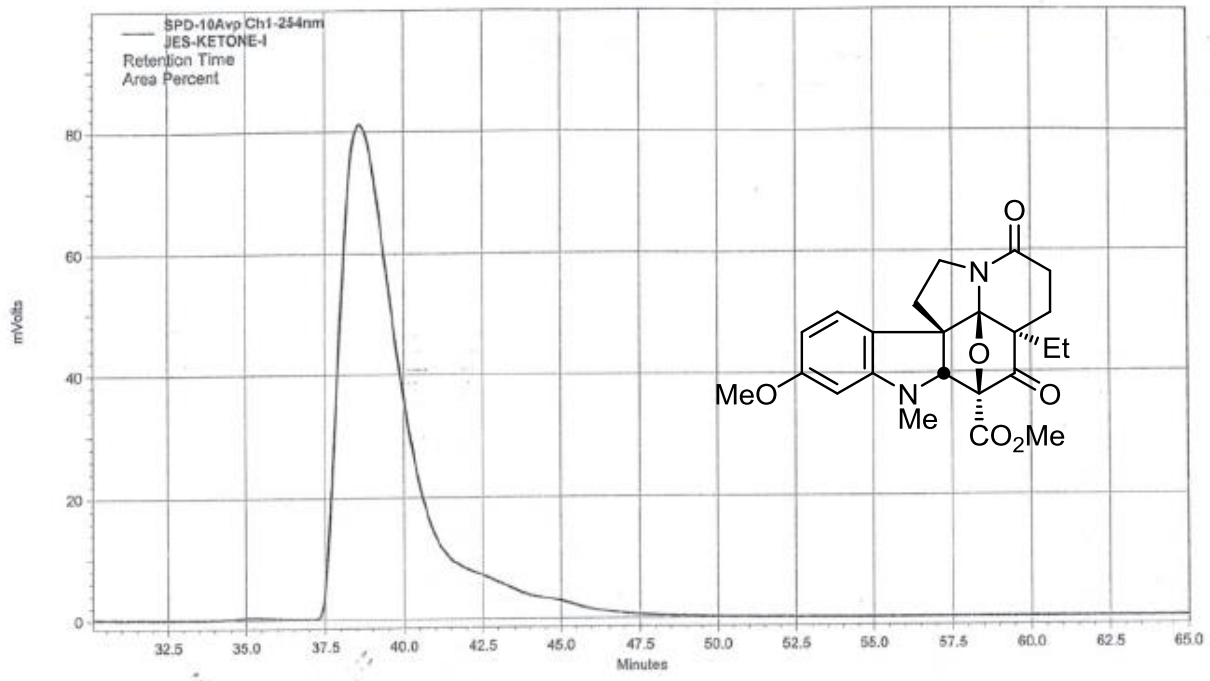


Figure S1. X-ray structure of **9**.



Compound 11. DMAP (85 mg, 0.70 mmol) was added to a solution of **9** (145 mg, 0.342 mmol) in *t*-BuOH (1.7 mL) at 23 °C. OsO_4 (4% in H_2O, 2.15 mL, 0.345 mmol) was added and the mixture was allowed to stir vigorously. After 2 h, $NaHSO_3$ (360 mg, 3.45 mmol) was added and the mixture was allowed to stir for 30 min. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layers were combined, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated. The organic residue was dissolved in a 1:1 mixture of PhMe/MeOH (180 mL). The solution was cooled to –78 °C and $Pb(OAc)_4$ (1.52 g, 3.42 mmol) was added in one portion and the mixture was allowed to stir for 5 min. At this time, the reaction mixture was transferred to a 0 °C ice bath and allowed to stir for 5 min before it was quenched by the addition of aqueous $NaHCO_3$. The reaction mixture was extracted with EtOAc and the organic layers were combined, dried over Na_2SO_4, and concentrated. Silica gel flash chromatography (70% EtOAc/hexanes) afforded **11** as a white foam (106 mg, 73%): $[\alpha]_D$ +12 (*c* 0.35, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.46 (d, *J* = 8.1 Hz, 1H), 6.17 (d, *J* = 8.1 Hz, 1H), 5.87 (s, 1H), 4.15 (s, 1H), 3.95−3.88 (m, 2H), 3.35 (s, 3H), 3.32 (s, 3H), 2.75 (s, 3H), 2.32 (td, *J* = 13.5, 6.0 Hz, 1H), 2.13−1.98 (m, 3H), 1.72−1.65 (m, 1H), 1.57 (dd, *J* = 6.0, 1.4 Hz, 1H), 1.40−1.30 (m, 1H), 0.92−0.85 (m, 1H), 0.64 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 205.4, 168.6, 167.1, 162.6, 155.1, 124.2, 120.7, 106.0, 103.7, 94.6, 93.8, 80.9, 64.6, 55.0, 52.6, 51.2, 47.8, 36.3, 34.2, 29.0, 24.2, 20.1, 9.0; IR (neat) ν_{max} 2951, 1774, 1745, 1672, 1620, 1501, 1439, 1396, 1323, 1241, 1204, 1143, 1120, 1095, 1059, 1020, 864, 792, 735 cm^{-1}; HRMS-ESI-TOF *m/z* 427.1863 ($C_{23}H_{26}N_2O_6 + H^+$ requires 427.1864).

The enantiomers of **11** were separated (α = 1.55) on a semipreparative ChiralCel OD column (2 × 25 cm, 15% *i*-PrOH–hexanes, 7 mL/min flow rate).



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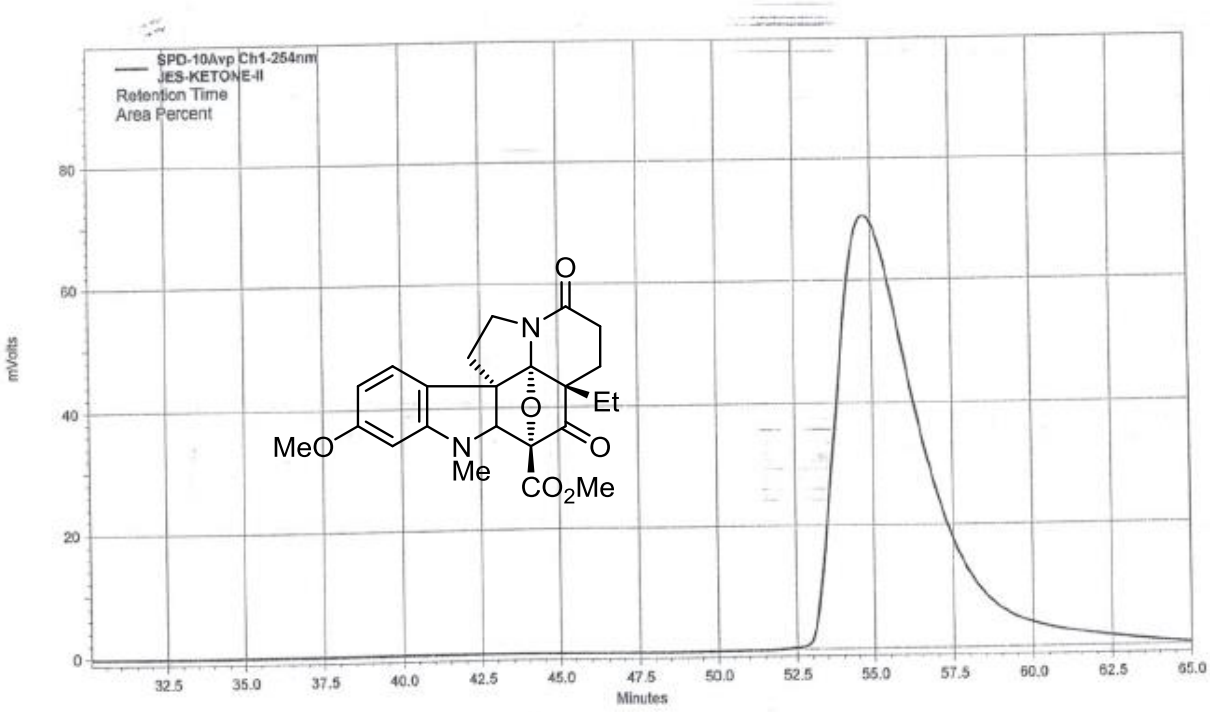

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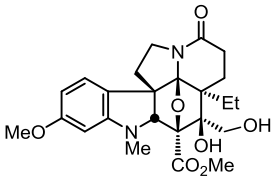
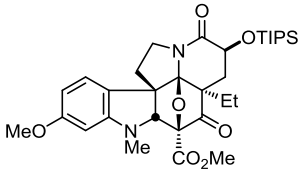
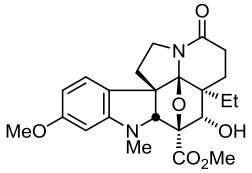


Isolation and Characterization of Intermediate Diol 10. The organic residue resulting from the dihydroxylation reaction could be purified to yield compound **10**. PTLC (SiO_2,70% EtOAc/hexanes) afforded the intermediate diol as a white solid (81%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, *J* = 6.8 Hz, 1H), 6.23 (dd, *J* = 1.8, 6.7 Hz, 1H), 6.08 (d, *J* = 1.8 Hz, 1H), 4.40 (d, *J* = 9.7 Hz, 1H), 4.03 (s, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.70−3.66 (m, 2H), 3.19 (d, *J* = 6.9, 1H), 2.99 (s, 3H), 2.55−2.39 (m, 3H), 2.30−2.17 (m, 3H), 2.05 (s, 2H), 1.84 (dd, *J* = 4.9, 11.7, 2H), 0.93−0.88 (m, 1H), 0.74 (t, *J* = 7.3 Hz, 3H), .0.71−0.67 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 172.0, 170.6, 161.7, 154.1, 124.4, 121.1, 105.8, 103.5, 95.0, 93.1, 64.2, 62.1, 60.4, 55.4, 50.6, 46.9, 39.1, 35.8, 28.9, 22.8, 21.05, 19.8, 14.2, 9.7; IR (neat) ν_{max} 3449 (br), 2951, 1731, 1644, 1620, 1501, 1436, 1403, 1121, 1072 cm^{-1}; HRMS-ESI-TOF *m/z* 459.2125 ($C_{24}H_{30}N_2O_7$ + H^+ requires 459.2126).

The structure and stereochemistry of **10** were established by a single crystal X-ray structure determination conducted on needles grown from CH_2Cl_2/hexanes (CDCC 1412217).



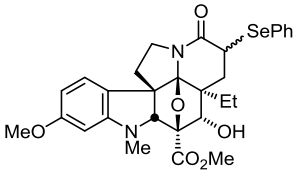
Compound 13. A stirred solution of **11** (21 mg, 0.049 mmol) in anhydrous THF (3.5 mL) under Ar at –40 °C was treated with bis(trimethylsilyl)peroxide (170 µL, 0.196 mmol), followed by NaHMDS (98 µL of a 1 M solution in THF, 0.098 mmol). After stirring for 1 h at –40 °C, the reaction mixture was treated with triisopropylsilyl trifluoromethanesulfonate (0.118 mL, 0.440 mmol) and Et_3N (14 µL, 0.28 mmol) at this temperature, and the mixture was allowed to warm slowly to room temperature. The mixture was diluted with saturated aqueous NH_4Cl and was extracted with EtOAc. The extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 20% EtOAc/hexanes) gave **13** (15.4 mg, 51%) as a white solid identical in all respects with authentic material:[S2] $[\alpha]_D$ +46 (*c* 0.15, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.39 (d, *J* = 8.0 Hz, 1H), 6.14 (dd, *J* = 2.0, 8.2 Hz, 1H), 5.87 (d, *J* = 2.2 Hz, 1H), 4.54 (dd, *J* = 5.8, 11.3 Hz, 1H), 4.14 (s, 1H), 3.92–3.87 (m, 1H), 3.78–3.72 (m, 1H), 3.32 (s, 3H), 3.29 (s, 3H), 3.01–2.96 (m, 1H), 2.74 (s, 3H), 2.51 (dd, *J* = 5.7, 13.4 Hz, 1H), 2.07–2.00 (m, 1H), 1.67–1.62 (m, 1H), 1.27–1.14 (m, 22H), 1.07–0.98 (m, 1H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 204.3, 169.8, 166.8, 162.5, 154.9, 123.9, 120.4, 105.5, 103.5, 94.4, 93.9, 80.7, 67.8, 64.2, 54.8, 52.4, 51.7, 47.3, 36.4, 34.2, 34.0, 20.9, 18.3 (3C), 18.2 (3C), 12.9 (3C), 9.2; IR (neat) ν_{max} 2949, 2855, 1775, 1740, 1693, 1622, 1499, 1458, 1399, 1381, 1349, 1234, 1199, 1152, 1135, 1097, 1036, 1007, 883, 734, 682 cm^{-1}; HRMS-ESI-TOF *m/z* 599.3144 ($C_{32}H_{46}N_2O_7Si$ + H^+ requires 599.3147).



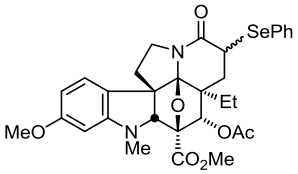
Compound 14. Method A: A solution of **11** (60 mg, 0.14 mmol) in a 1:1 mixture of MeOH/CH_2Cl_2 (12 mL) was cooled to –78 °C. $NaBH_4$ (27 mg, 0.70 mmol) was added in one portion. After 10 min, the reaction was quenched by the addition of aqueous 1 N HCl and allowed to warm to room temperature. The biphasic mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated. PTLC (SiO_2, 70% EtOAc/hexanes) afforded **14** as a white foam (50.7 mg,

84%) identical in all respects to previously reported material:[S2] $[\alpha]_D$ +77 (*c* 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.48 (d, *J* = 8.2 Hz, 1H), 6.28 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.26 (d, *J* = 10.8 Hz, 1H), 5.95 (d, *J* = 2.3 Hz, 1H), 4.29 (dd, *J* = 10.8, 1.7 Hz, 1H), 4.07 (d, *J* = 1.7 Hz, 1H), 3.95−3.80 (m, 2H), 3.38 (s, 3H), 3.27 (s, 3H), 2.60 (s, 3H), 2.30−2.20 (m, 1H), 2.23−1.90 (m, 3H), 1.70−1.55 (m, 2H), 0.98−0.90 (m, 1H), 0.80−0.70 (m, 1H), 0.61 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.8, 169.1, 161.8, 154.5, 124.4, 123.8, 108.1, 107.1, 98.1, 84.4 (2C), 82.5, 64.2, 54.9, 52.1, 46.4, 45.3, 38.0, 37.5, 29.7, 28.9, 19.0, 9.7; IR (neat) ν_{max} 3256, 2955, 1737, 1666, 1620, 1501, 1453, 1399, 1378, 1332, 1270, 1224, 1166, 1123, 1087, 1061, 1032, 1000, 866, 733 cm^{-1}; HRMS-ESI-TOF *m/z* 429.2017 ($C_{23}H_{28}N_2O_6$ + H^+ requires 429.2020).

Method B: A solution of **11** (20 mg, 0.047 mmol) in THF (0.2 mL) at 0 °C was treated with a solution of LiAlH(O*t*-Bu)$_3$ (12 mg, 0.047 mmol) in THF (0.2 mL). The reaction mixture was allowed to stir at this temperature for 30 min, at which point an additional aliquot of LiAlH(O*t*-Bu)$_3$ (12 mg, 0.047 mmol) in THF (0.2 mL) was added. This sequence was repeated a third time, and the reaction was allowed to stir for an additional 2 h. After this time, the reaction was quenched by the addition of aqueous 1 N HCl and allowed to warm to room temperature. This mixture was then made basic with the addition of saturated aqueous $NaHCO_3$ and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried of Na_2SO_4 and concentrated. PTLC (SiO_2, 70% EtOAc/hexanes) afforded **14** as white foam (14.3 mg, 71%).

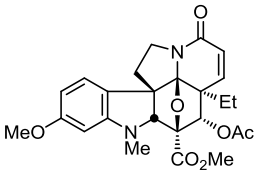


Compound 15. A cooled (–78 °C) solution of **14** (40 mg, 0.093 mmol) and diphenyl diselenide (159 mg, 0.512 mmol) in THF (3.9 mL) was treated dropwise with freshly prepared lithium diisopropylamide (LDA, 3.55 mL, 0.130 M in THF, 0.462 mmol). The mixture was stirred for 2 h at –78 °C. The resulting yellow mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. PTLC (SiO_2, 50% EtOAc/hexanes) provided an isomeric mixture of **15** (44.5 mg, 82%) as a light yellow foam (ca. 8:1 β:α diastereomers): ^{1}H NMR (600 MHz, C_6D_6) δ 7.66−7.63 (m, 2H), 6.96−6.93 (m, 3H), 6.52 (d, *J* = 8.2 Hz, 1H), 6.30 (dd, *J* = 2.2, 8.2 Hz, 1H), 6.15 (d, *J* = 10.8 Hz, 1H), 5.93 (d, *J* = 2.3 Hz, 1H), 4.20 (dd, *J* = 1.8, 10.8 Hz, 1H), 4.07 (q, *J* = 5.6 Hz, 1H), 4.03 (d, *J* = 1.8 Hz, 1H), 3.88 (td, *J* = 8.0, 10.7 Hz, 1H), 3.70 (t, *J* = 9.8 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 3H), 2.62 (t, *J* = 13.4 Hz, 1H), 2.56 (s, 3H), 2.18 (dd, *J* = 5.6, 13.6 Hz, 1H), 2.03 (q, *J* = 2.2 Hz, 1H), 1.65−1.60 (m, 1H), 0.87−0.81 (m, 1H), 0.73−0.68 (m, 1H), 0.50 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 170.2, 168.5, 161.5, 154.1, 135.6, 128.8, 128.0, 127.5, 124.0, 123.1, 107.6, 106.7, 97.7, 84.0, 83.6, 82.2, 63.7, 54.5, 51.6, 49.9, 46.6, 46.4, 39.7, 37.8, 37.5, 37.1, 18.9, 9.2; IR (neat) ν_{max} 3734, 2921, 2851, 1668, 1604, 1475, 1456, 1398, 1124, 1063 cm^{-1}; HRMS-ESI-TOF *m/z* 585.1500 ($C_{29}H_{32}N_2O_6Se$ + H^+ requires 585.1498).

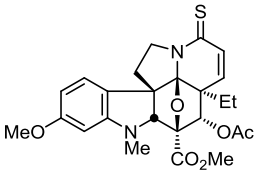


Compound 16. DMAP (4.5 mg, 0.037 mmol) was added to a solution of **15** (43 mg, 0.074 mmol) in pyridine (1.0 mL) and cooled to 0 °C. An excess of Ac_2O (1.0 mL) was added and the reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched with the addition of saturated NH_4Cl and the mixture was diluted with EtOAc. The organic layer was separated

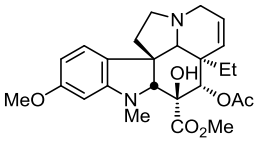
and washed with water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over Na_2SO_4 and concentrated. The residue was purified by PTLC (SiO_2, 50% EtOAc/hexanes) to provide an isomeric mixture of **16** (β:α = 7:1, 40.2 mg, 87%) as a light yellow foam: ^{1}H NMR (600 MHz, C_6D_6) δ 7.70−7.68 (m, 2H), 6.95−6.94 (m, 3H), 6.50 (d, *J* = 8.1 Hz, 1H), 6.11 (dd, *J* = 2.3, 8.1 Hz, 1H), 5.89 (d, *J* = 2.2 Hz, 1H), 5.01 (s, 1H), 4.30 (d, *J* = 1.4 Hz, 1H), 3.95 (q, *J* = 5.9 Hz, 1H), 3.89−3.84 (m, 1H), 3.72 (t, *J* = 11.3 Hz, 1H), 3.47 (s, 3H), 3.35 (s, 3H), 2.75 (t, *J* = 12.9 Hz, 1H), 2.63 (s, 3H), 2.11 (dd, *J* = 6.1, 13.6 Hz, 1H), 1.99 (q, *J* = 11.2 Hz, 1H), 1.71−1.65 (m, 1H), 1.49 (s, 3H), 0.92−0.87 (m, 1H), 0.72−0.65 (m, 1H), 0.48 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 168.8, 167.9, 161.4, 153.9, 135.3, 128.3, 127.5, 123.7, 120.6, 107.2, 100.9, 93.2, 84.0, 81.1, 78.8, 63.3, 53.9, 52.5, 51.5, 49.3, 46.7, 45.7, 38.9, 38.0, 36.6, 33.2, 19.2, 18.7, 8.3; IR (neat) ν_{max} 3308, 2921, 2851, 1668, 1604, 1399, 1123, 1063 cm^{-1}; HRMS-ESI-TOF *m/z* 627.1603 ($C_{31}H_{34}N_2O_7Se$ + H^+ requires 627.1604).



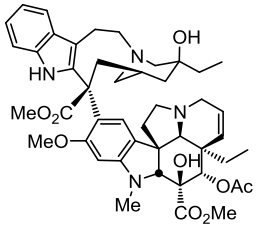
Compound 17. A solution of a mixture of the isomeric phenylselenides **16** (40.2 mg, 0.064 mmol) in THF (4 mL) was treated with a solution of H_2O_2 (35% in H_2O, 0.018 mL, 0.194 mmol) at room temperature. The reaction mixture allowed to stir for 30 min. The reaction mixture was extracted with EtOAc, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by PTLC (SiO_2, 70% EtOAc/hexanes) to afford **17** (27.8 mg, 92%) as a white solid: $[\alpha]_D^{23}$ +41 (*c* 0.24, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.61 (d, *J* = 8.0 Hz, 1H), 6.04 (dd, *J* = 2.2, 8.0 Hz, 1H), 5.97 (d, *J* = 9.8 Hz, 1H), 5.91 (d, *J* = 2.2, 1H), 5.87 (d, *J* = 9.8 Hz, 1H), 4.34 (s, 1H), 4.06 (t, *J* = 10.8 Hz, 1H), 3.70 (td, *J* = 7.8, 11.3 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.66 (s, 3H), 2.09−2.04 (m, 1H), 1.72 (dd, *J* = 7.6, 12.3 Hz, 1H), 1.54 (s, 3H), 1.02−0.95 (m, 1H), 0.93−0.90 (m, 1H), 0.78−0.72 (m, 1H), 0.47 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 169.1, 162.3, 161.7, 153.7, 145.9, 123.5, 122.8, 119.4, 107.3, 99.6, 92.1, 82.9, 80.7, 78.2, 63.8, 53.9, 51.4, 48.7, 45.7, 37.3, 32.1, 29.2, 20.8, 19.2, 7.5; IR (neat) ν_{max} 2926, 2813, 1707, 1681, 1254 cm^{-1}; HRMS-ESI-TOF *m/z* 469.1971 ($C_{25}H_{28}N_2O_7$ + H^+ requires 469.1969).



Compound 18. A solution of **17** (15.0 mg, 0.032 mmol) in toluene (2 mL) was treated with Lawesson's reagent (14.1 mg, 0.035 mmol, 1.1 equiv). The reaction mixture was warmed at 80 °C under Ar for 30 min, cooled to room temperature and concentrated under reduced pressure. The residue was purified by PTLC (SiO_2, 60% EtOAc/hexanes) to afford **18** (12.1 mg, 77%) as a yellow foam: $[\alpha]_D^{23}$ +151 (*c* 0.17, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 6.58 (d, *J* = 9.5 Hz, 1H), 6.57 (d, *J* = 8.1 Hz 1H), 6.01 (dd, *J* = 2.3, 8.1 Hz, 1H), 5.90 (d, *J* = 2.2 Hz, 1H), 5.54 (d, *J* = 9.5 Hz, 1H), 5.51 (d, *J* = 1.4 Hz, 1H), 4.40 (dd, *J* = 9.9, 13.5 Hz, 1H), 4.33 (s, 1H), 3.99−3.94 (m, 1H), 3.37 (s, 6H), 2.65 (s, 3H), 2.07−2.03 (m, 1H), 1.7 (dd, *J* = 7.5, 12.7 Hz), 1.52 (s, 3H), 0.99−0.95 (m, 1H), 0.76−0.72 (m, 1H), 0.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 190.5, 168.9, 168.8, 161.8, 153.8, 137.1, 129.9, 123.5, 119.1, 99.8, 92.2, 82.8, 81.0, 78.2, 64.4, 54.0, 52.3, 51.5, 49.3, 36.9, 32.3, 31.5, 29.4, 19.2, 13.5, 7.5; IR (neat) ν_{max} 2919, 1714, 1615, 1421, 1253 cm^{-1}; HRMS-ESI-TOF *m/z* 485.1739 ($C_{25}H_{28}N_2O_7$ + H^+ requires 485.1741).



4-*epi*-Vindoline (19). A solution of **18** (10.0 mg, 0.020 mmol) in CH_2Cl_2 (0.8 mL) was cooled to 0 °C and treated with trimethyloxonium tetrafluoroborate (8.9 mg, 0.060 mmol) under Ar. After stirring for 2 h at 0 °C, the reaction mixture was concentrated under a stream of N_2, and anhydrous MeOH (6 mL) was added. After 15 min, $NaBH_4$ (7.5 mg, 0.20 mmol) was added, and the mixture was stirred at 0 °C for 30 min. The resulting mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by PTLC (SiO_2, 2.5% MeOH/CH_2Cl_2) to provide **19** (5.7 mg, 63%) as a white solid identical to previously reported material:[S3] $[\alpha]_D^{23}$ +13 (*c* 0.45, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ 9.09 (br s, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 7.9 Hz, 1H), 6.10 (s, 1H), 5.86 (s, 1H), 5.66 (d, *J* = 9.8 Hz, 1H), 5.36 (m, 1H), 4.17 (s, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 2.78 (m, 2H), 2.76 (s, 3H), 2.48 (s, 1H), 2.23 (d, *J* = 15.6 Hz, 1H), 2.11 (m, 1H), 1.89 (dd, *J* = 10.6, 18.3 Hz, 2H), 1.66 (s, 3H), 1.50 (dq, *J* = 7.4 Hz, *J* = 14.0 Hz, 1H), 1.16 (dq, *J* = 6.7 Hz, *J* = 13.4 Hz, 1H), 0.55 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 171.4, 169.8, 161.8, 154.9, 135.5, 126.7, 122.6, 122.5, 102.7, 94.8, 78.4, 78.1, 76.1, 66.3, 55.0, 52.8, 51.6, 51.4, 50.6, 43.2, 42.8, 36.3, 26.0, 20.5, 8.3; IR (neat) ν_{max} 2961, 2878, 1740, 1618, 1502, 1460, 1434, 1369, 1237, 1174, 1138, 1118, 1092, 1034 cm^{-1}; HRMS ESI−TOF *m/z* 457.2337 ($C_{25}H_{32}N_2O_6 + H^+$ requires 457.2333).



4-*epi*-Vinblastine (21). Iron(III) chloride hexahydrate (18 mg, 0.065 mmol) was added to a solution of (+)-**19** (6.4 mg, 0.014 mmol) and catharanthine sulfate (**20**, 6.1 mg, 0.012 mmol) in CF_3CH_2OH (50 µL), aqueous 0.1 N HCl (0.3 mL) and H_2O (0.3 mL) at 23 °C under Ar. The reaction mixture was stirred for 2 h at 23 °C. Meanwhile, in a separate flask, a mixture of iron(III) oxalate hexahydrate (68 mg, 0.14 mmol) in H_2O (56 mL) was stirred at room temperature for 2 h. The resulting clear solution was cooled to 0 °C and air was vigorously bubbled through the mixture for 10 min. The coupling reaction solution was transferred by syringe to this aqueous $Fe_2(ox)_3$ solution and $NaBH_4$ (10.6 mg, 0.28 mmol) in H_2O (0.6 mL) was added to the mixture at 0 °C. The resulting mixture was stirred for 30 min before being quenched by the addition of 28−30% aqueous NH_4OH (18 mL). The mixture was extracted with 10% MeOH in CH_2Cl_2 (4 × 60 mL) and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. PTLC (SiO_2, 3% Et_3N in 3% MeOH–EtOAc) provided 4-*epi*-vinblastine (+)-**21** (4.6 mg) and the corresponding leurosidine analogue (2.5 mg). For (+)-**21**: $[\alpha]^{23}_D$ +52 (*c* 0.27, $CDCl_3$); ^{1}H NMR (C_6D_6, 600 MHz) δ 8.46 (br s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.11 (m, 2H), 6.90 (s, 1H), 5.95 (s, 1H), 5.91 (s, 1H), 5.63 (d, *J* = 9.8 Hz, 1H), 5.30 (br s, 1H), 4.46 (t, *J* = 13.5 Hz, 1H), 4.12 (s, 1H), 4.08 (t, *J* = 12.8 Hz, 1H), 3.89 (m, 2H), 3.59 (m, 1H), 3.44 (m, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.32 (s, 3H), 3.22 (d, *J* = 14.9 Hz, 1H), 3.11 (m, 1H), 3.04 (s, 1H), 2.82 (m, 2H), 2.79 (s, 3H), 2.70 (d, *J* = 13.7 Hz, 1H), 2.50 (m, 2H), 2.38 (s, 1H), 2.25 (m, 2H), 2.05 (m, 1H), 1.84 (m, 2H), 1.80 (s, 3H), 1.59 (dd, *J* = 7.1, 13.8 Hz, 1H), 1.49 (d, *J* = 13.4 Hz, 1H), 1.42−1.18 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.78 (m, 6H); IR (film) 3469, 2927, 1737, 1616, 1503, 1459, 1432, 1370, 1233, 1139, 1099, 1037 cm^{-1}; HRESI-TOF *m/z*: 811.4286 ($C_{46}H_{58}N_4O_9 + H^+$ requires 811.4276).

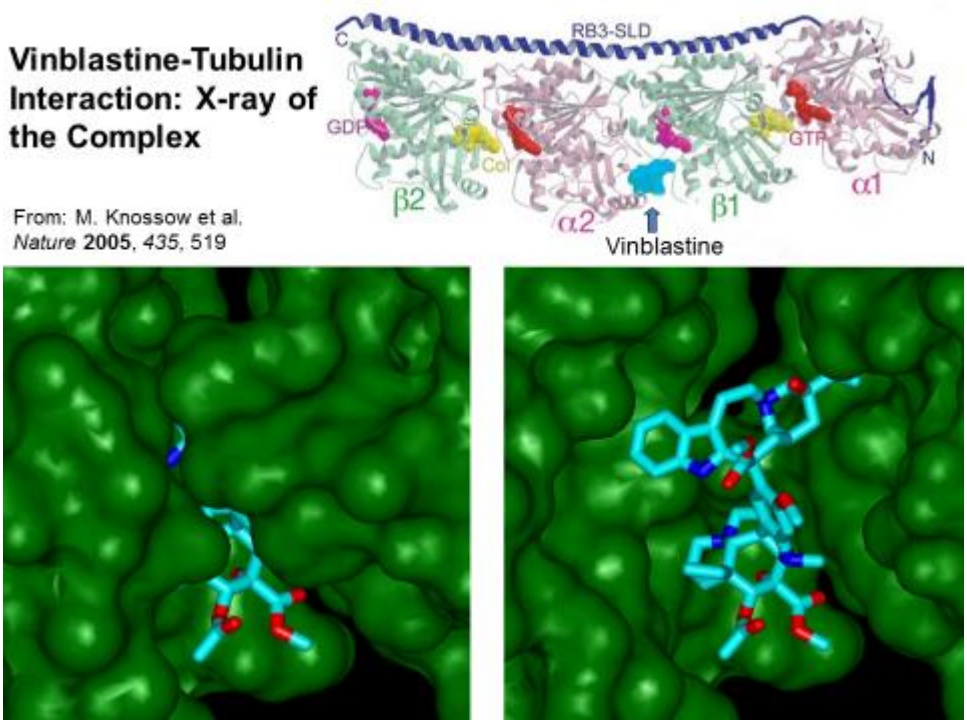


Figure S2. (Top) X-ray crystal structure of vinblastine bound to tubulin. (Bottom left) Expanded region of the X-ray highlighting the dimer interface where vinblastine is bound. (Bottom right) Protein removed to reveal vinblastine bound at the dimer interface. The C4 acetoxy group, C3 alcohol, and C3 methyl ester form an interface between the bound complex and solvent.

References

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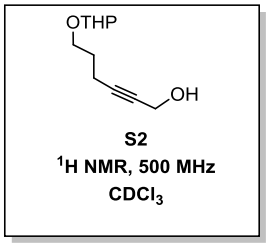
S2. Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596.
S3. Schleicher, K. D.; Sasaki, Y.; Tam, A.; Kato, D.; Duncan, K. K.; Boger, D. L. *J. Med. Chem.* **2013**, *56*, 483.



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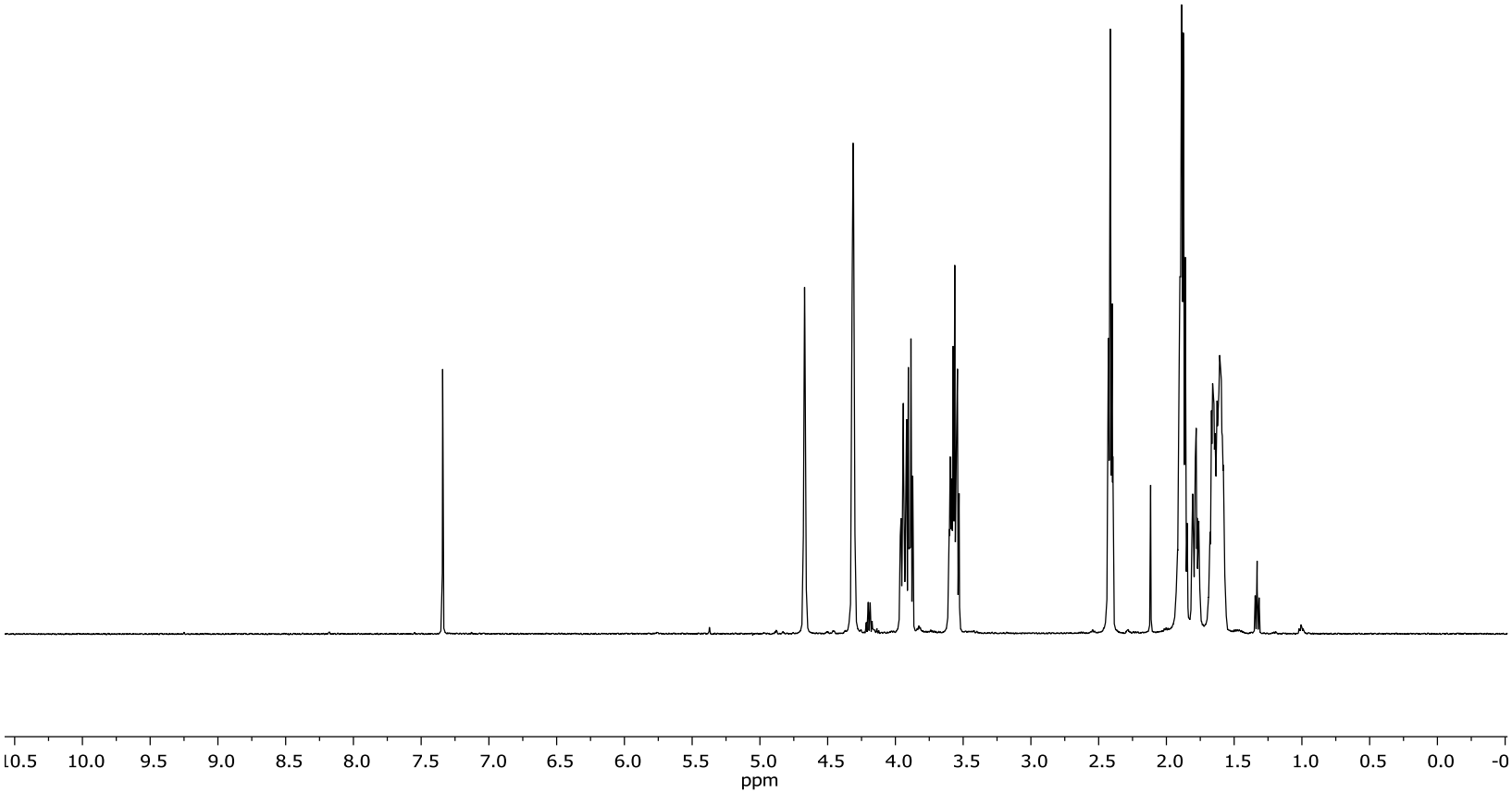

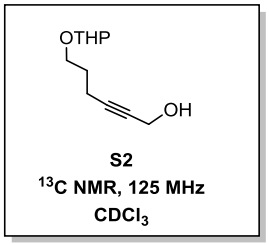

S2
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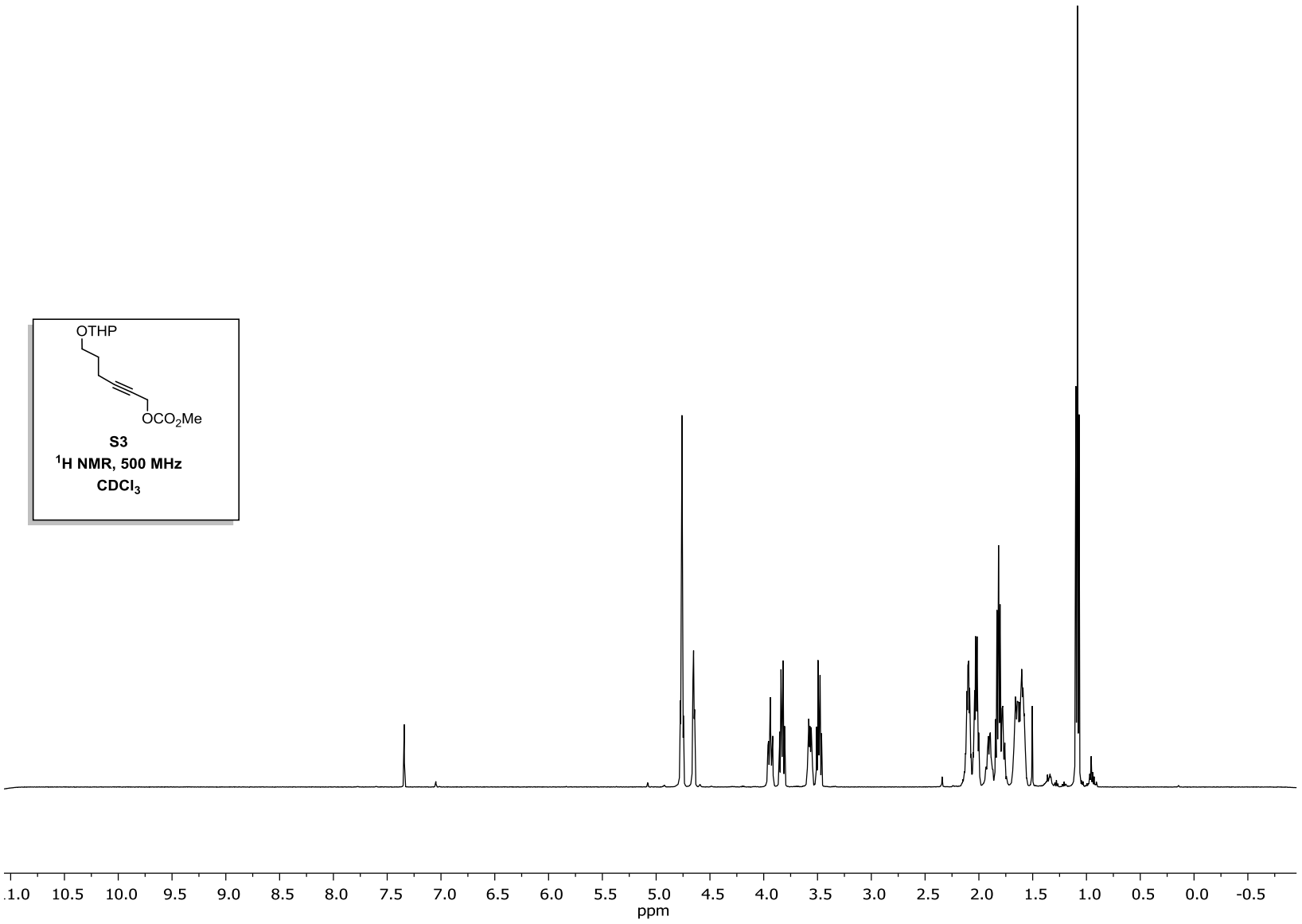
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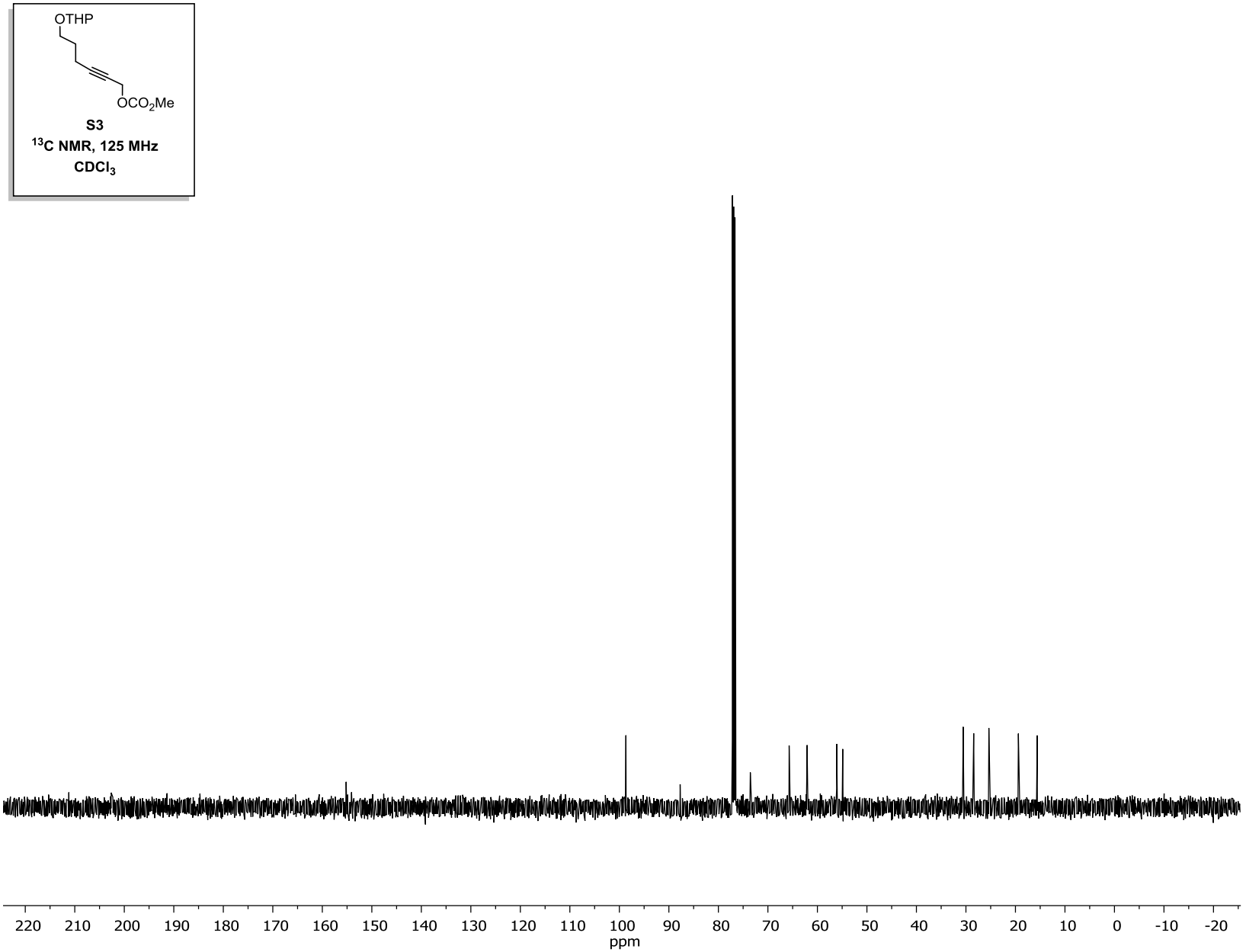
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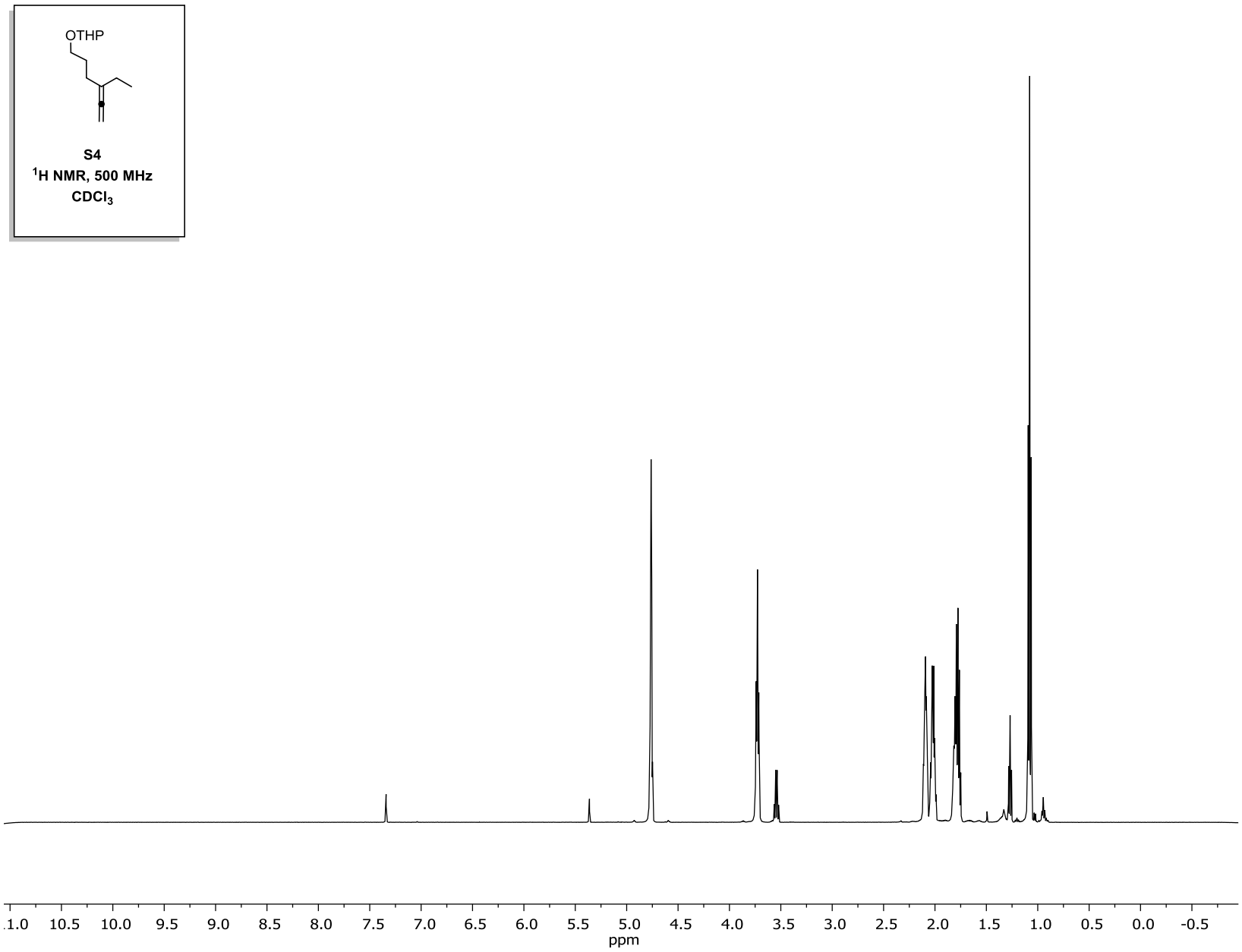
ppm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6.5
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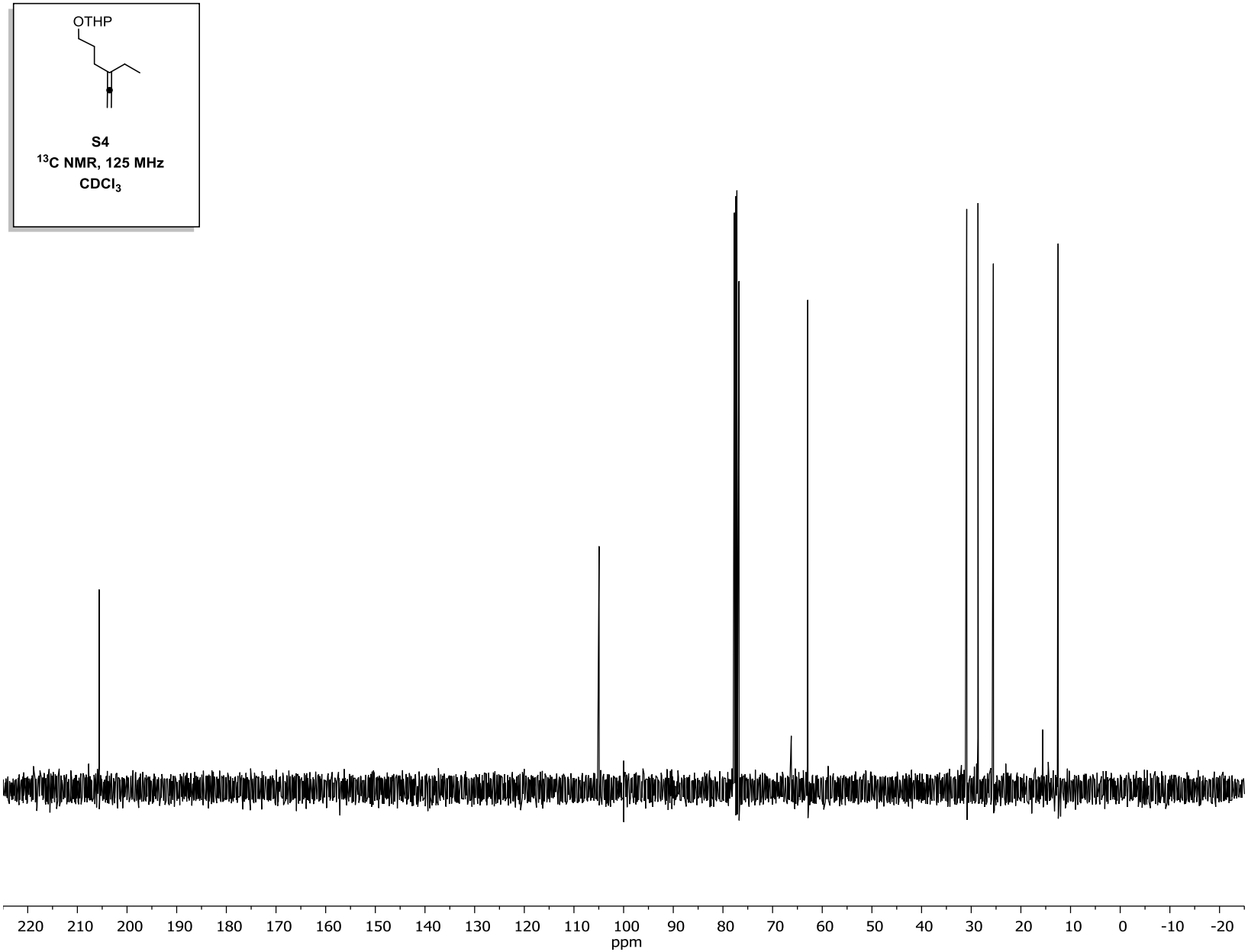
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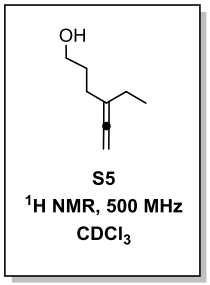
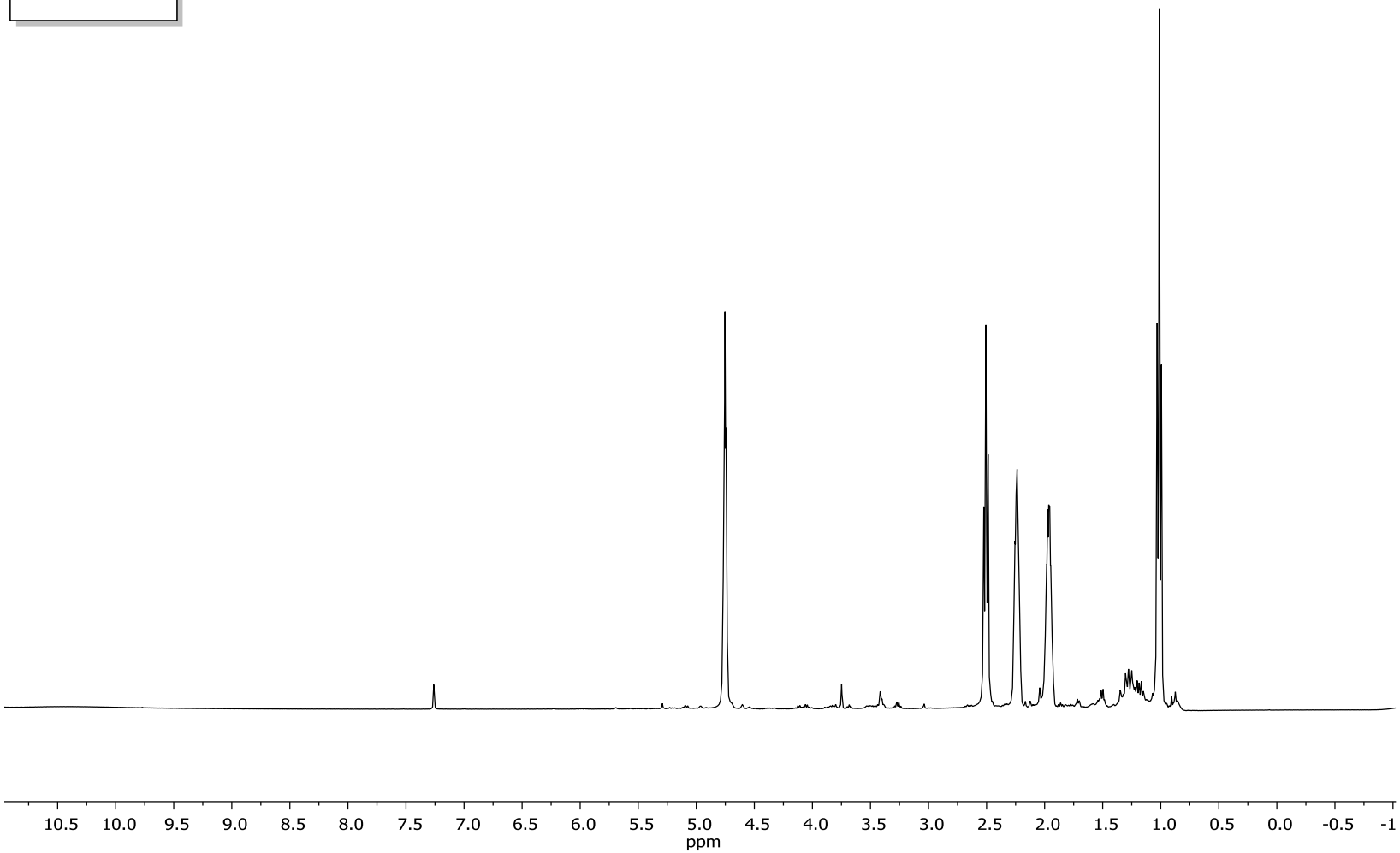
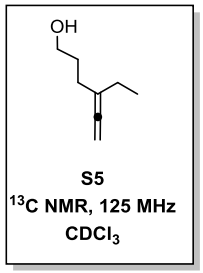
S4
13C NMR, 125 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm

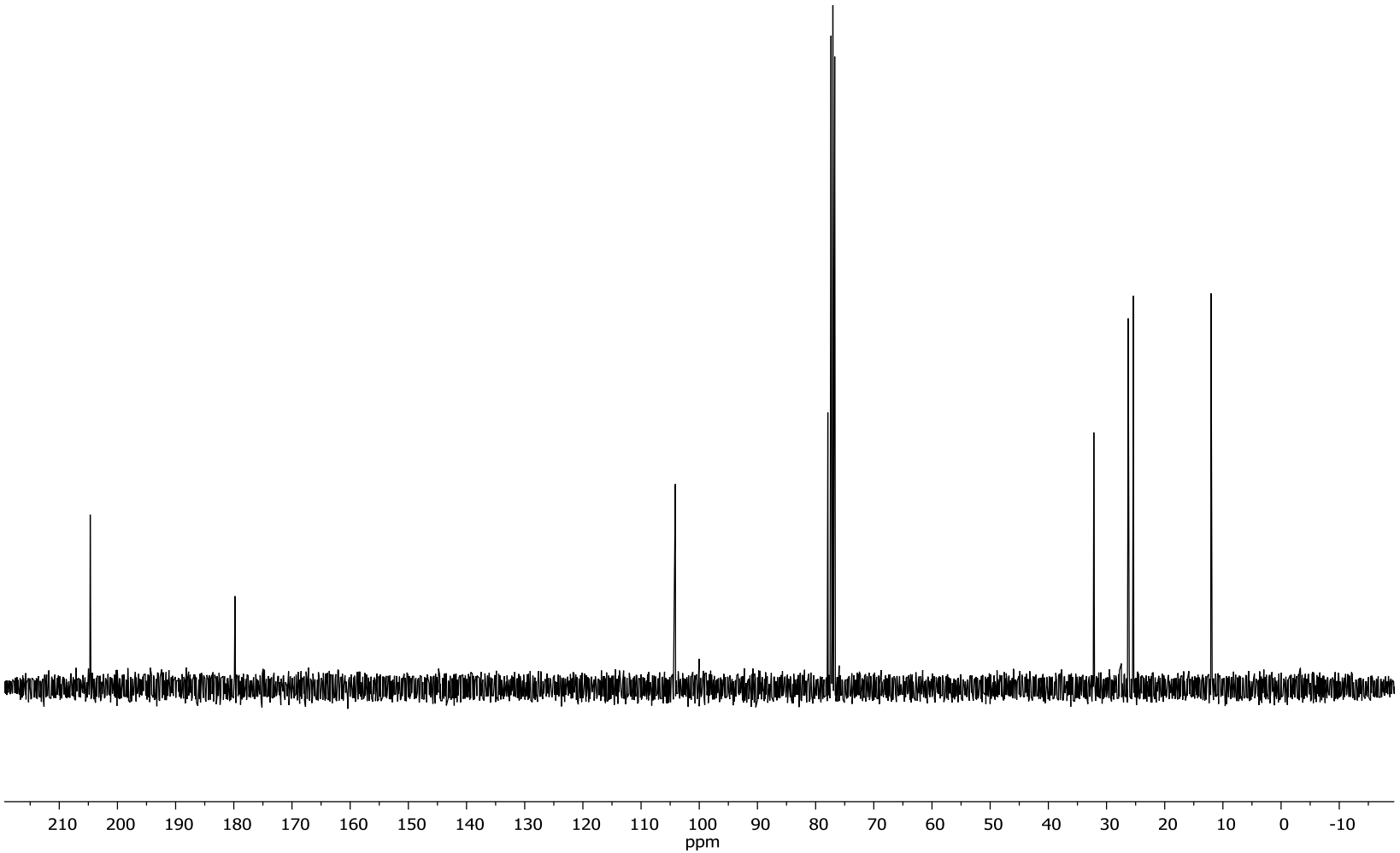


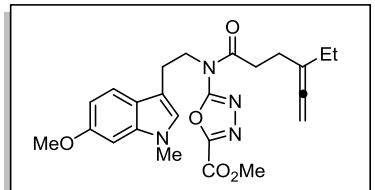
S5
^{1}H NMR, 500 MHz
$CDCl_3$





S5
^{13}C NMR, 125 MHz
$CDCl_3$

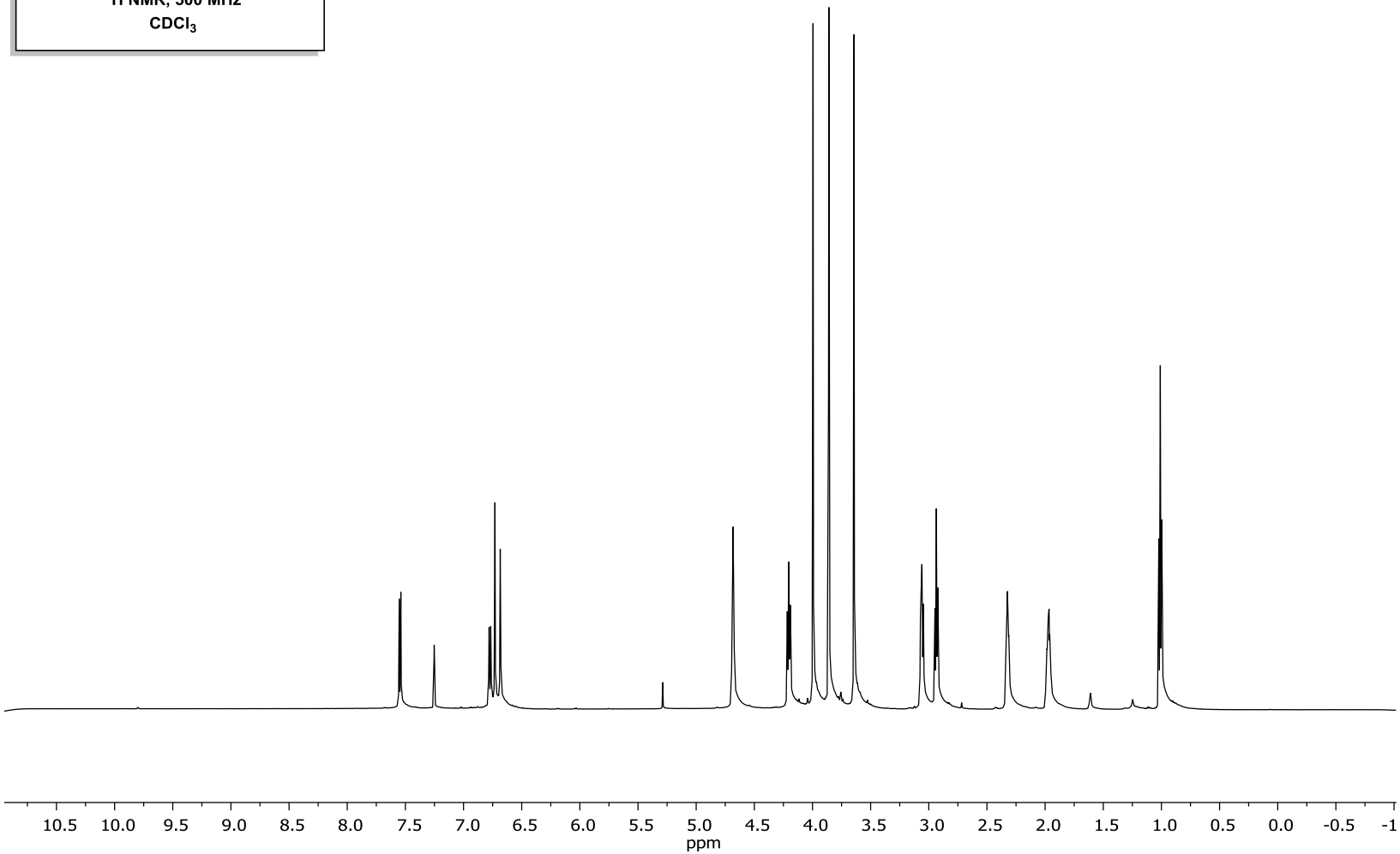


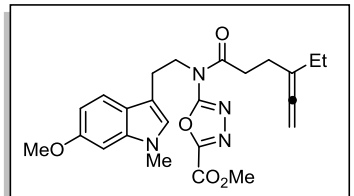


8

^{1}H NMR, 500 MHz

$CDCl_3$

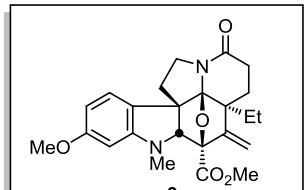




8

^{13}C NMR, 125 MHz

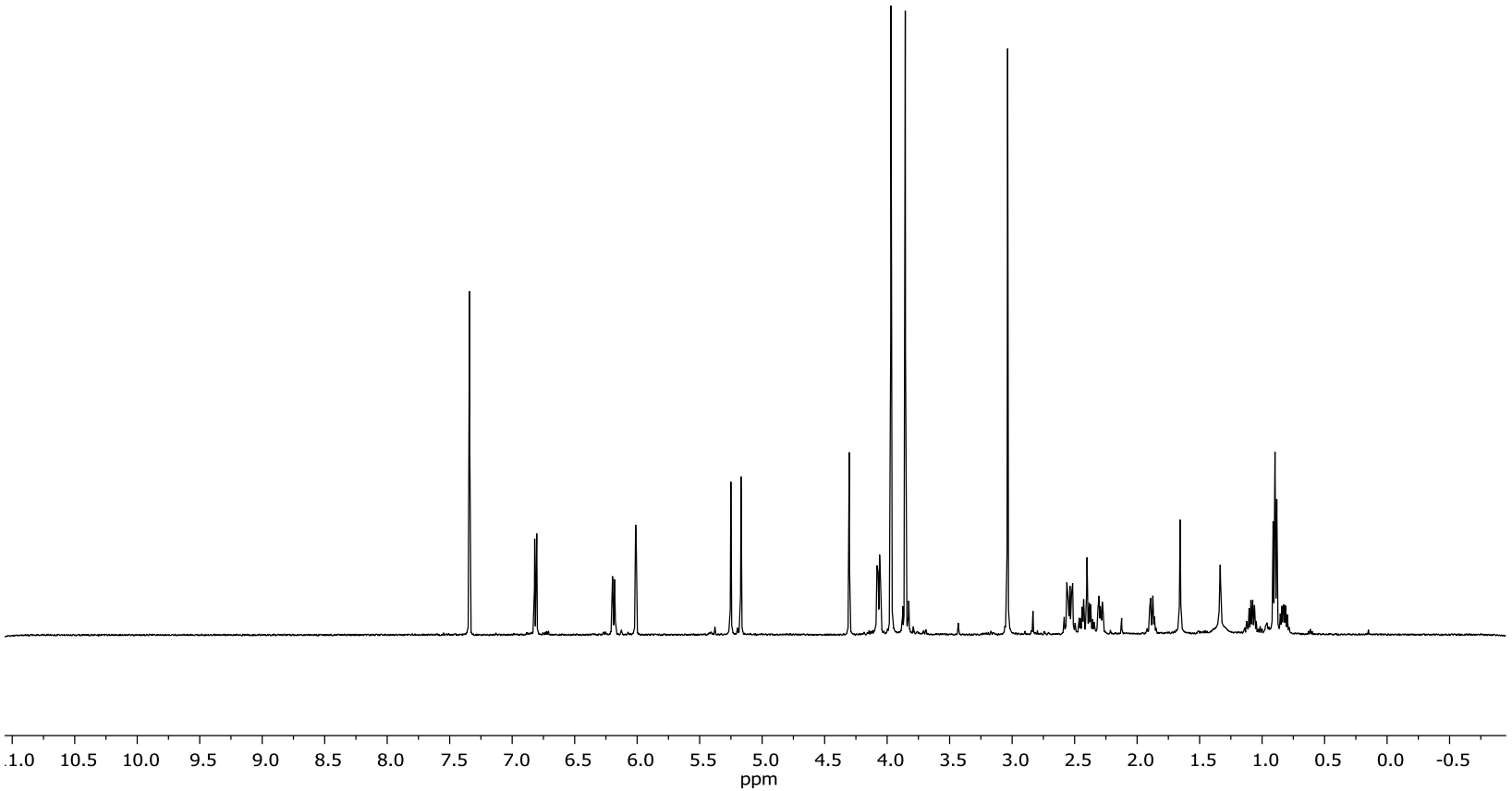
$CDCl_3$

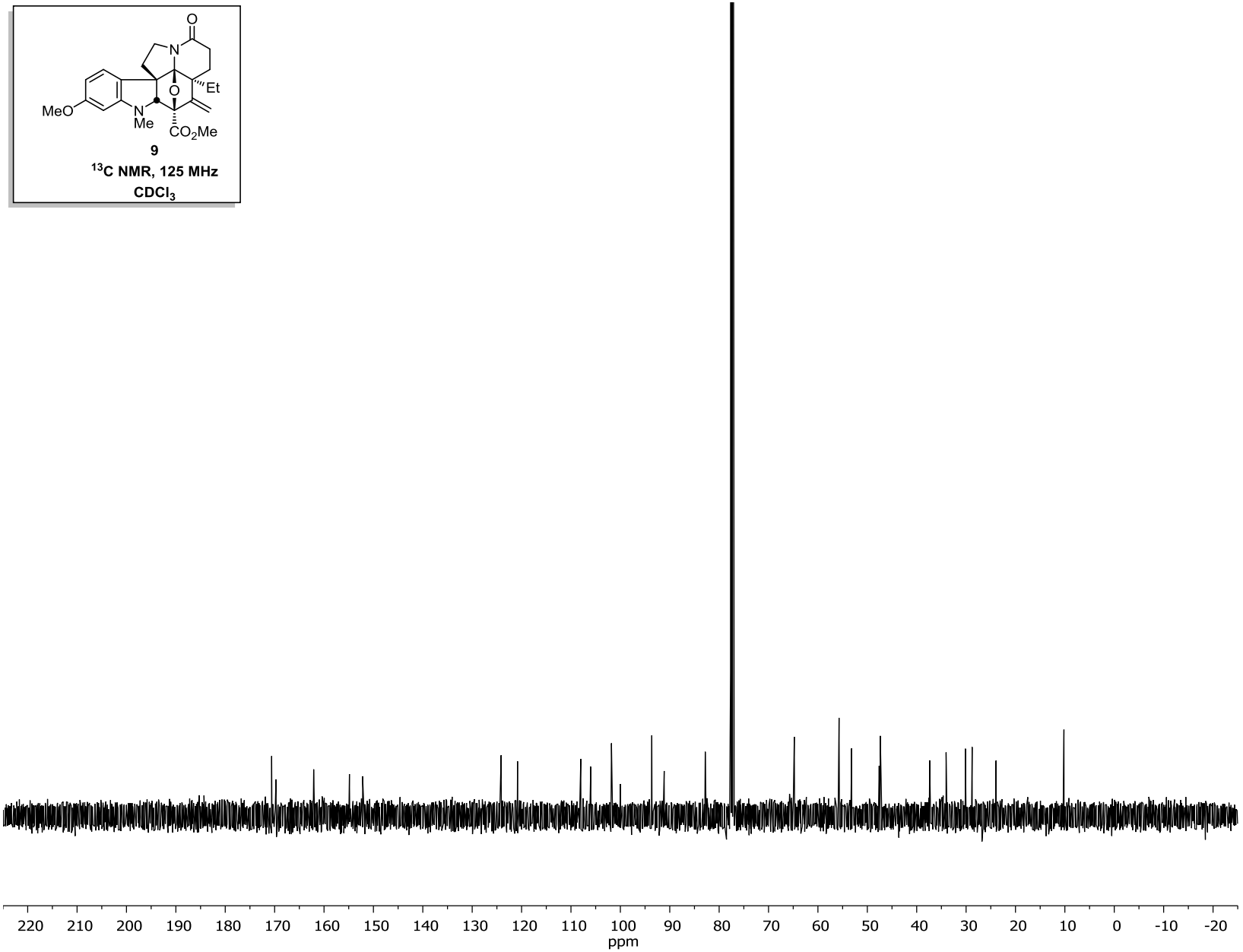


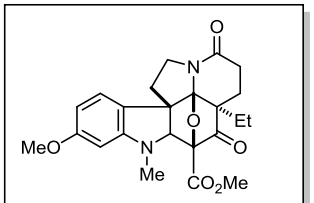
9

^{1}H NMR, 500 MHz

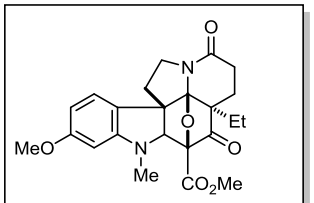
$CDCl_3$




O
N
Et
MeO
O
N
Me
CO2Me
9
13C NMR, 125 MHz
CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
ppm



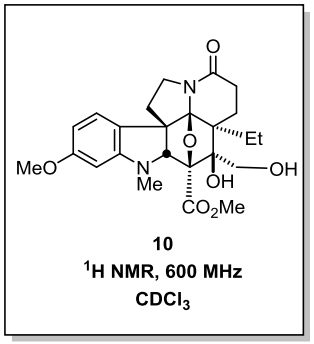
11
^{1}H NMR, 600 MHz
C_6D_6



11

^{13}C NMR, 150 MHz

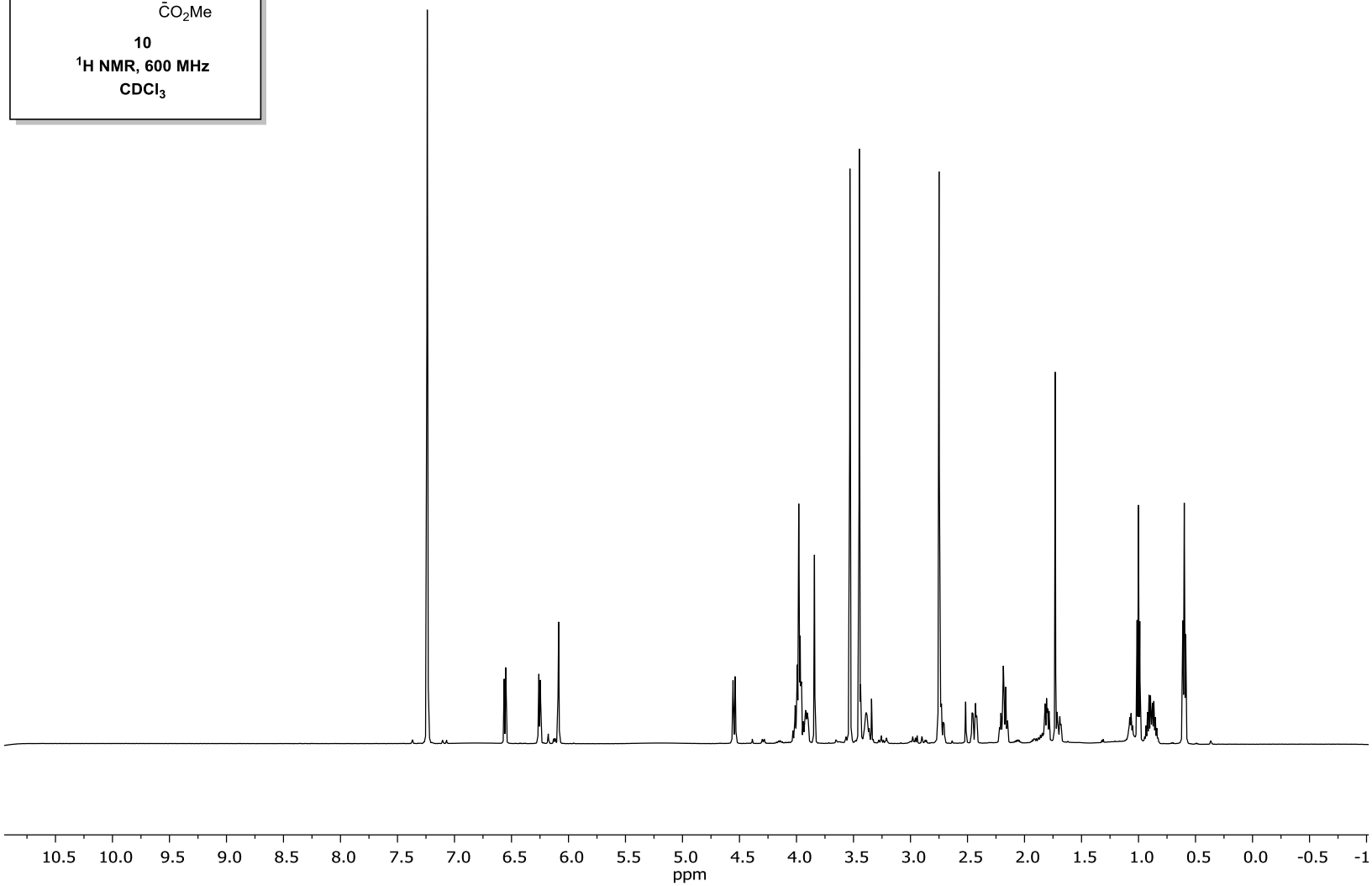
C_6D_6

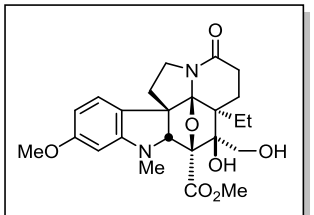


10

^{1}H NMR, 600 MHz

$CDCl_3$

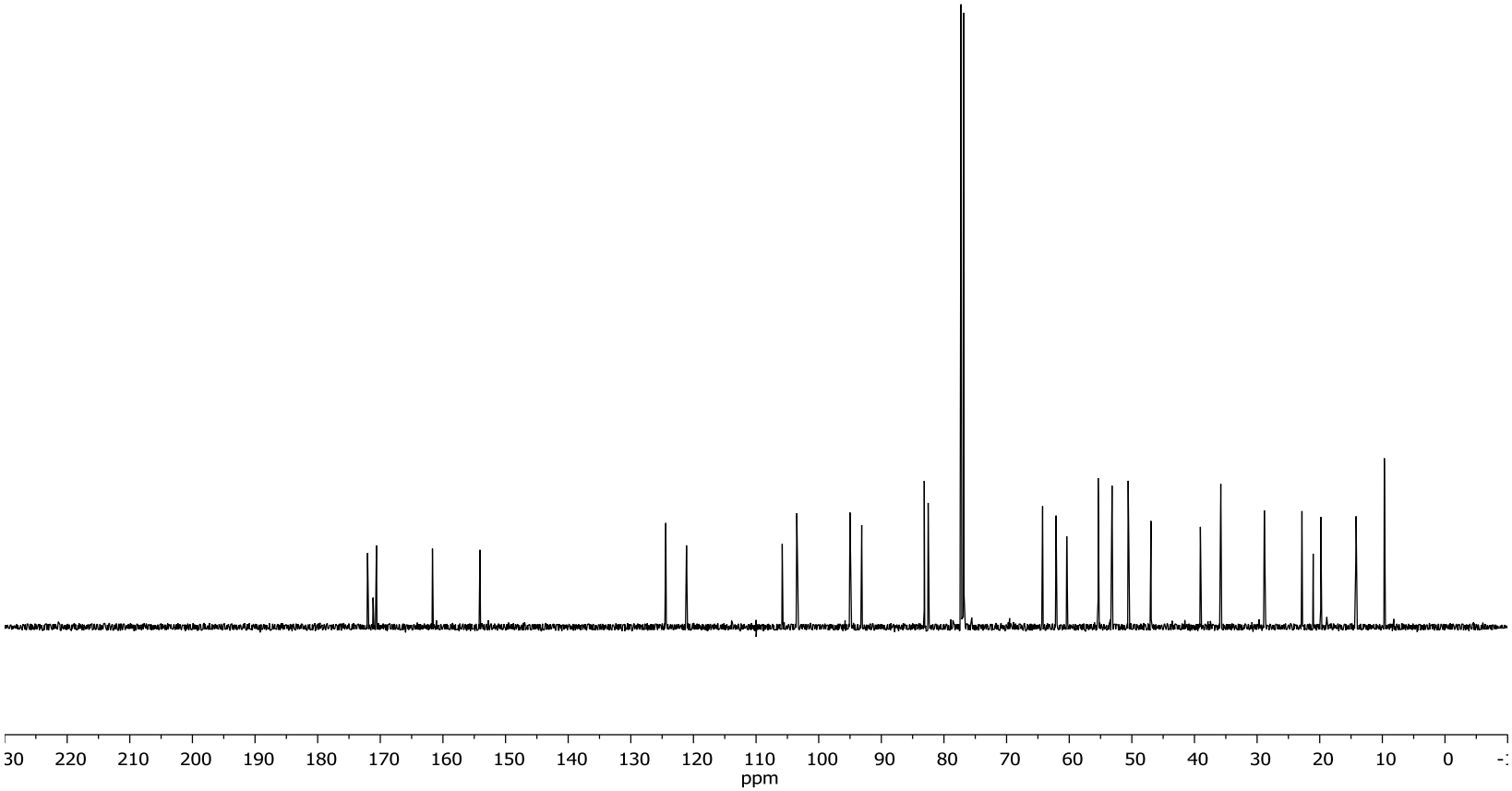


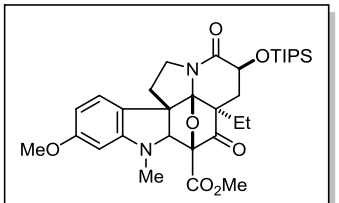


10

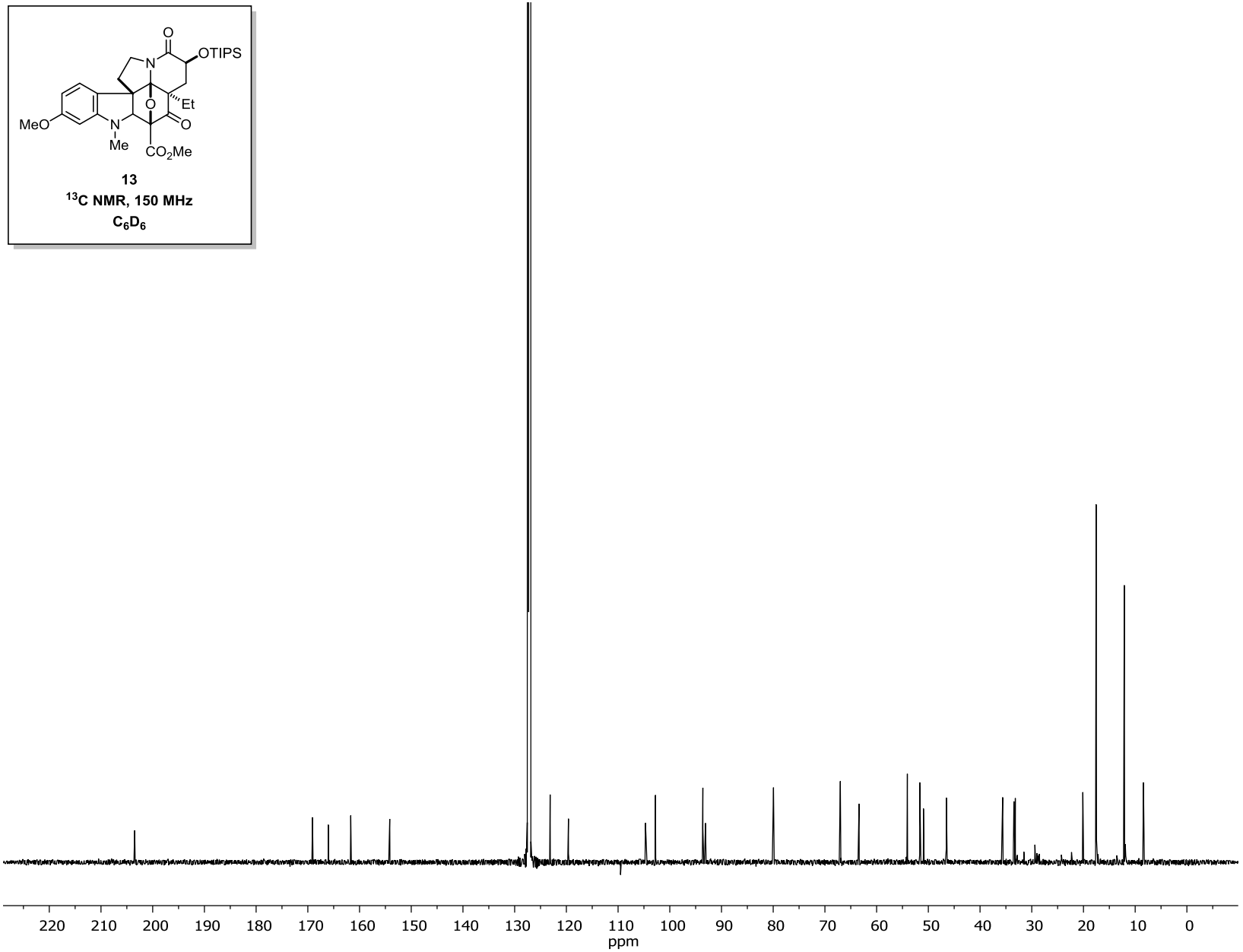
^{13}C NMR, 150 MHz

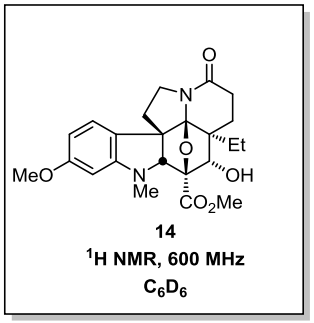
$CDCl_3$





13
^{1}H NMR, 600 MHz
C_6D_6

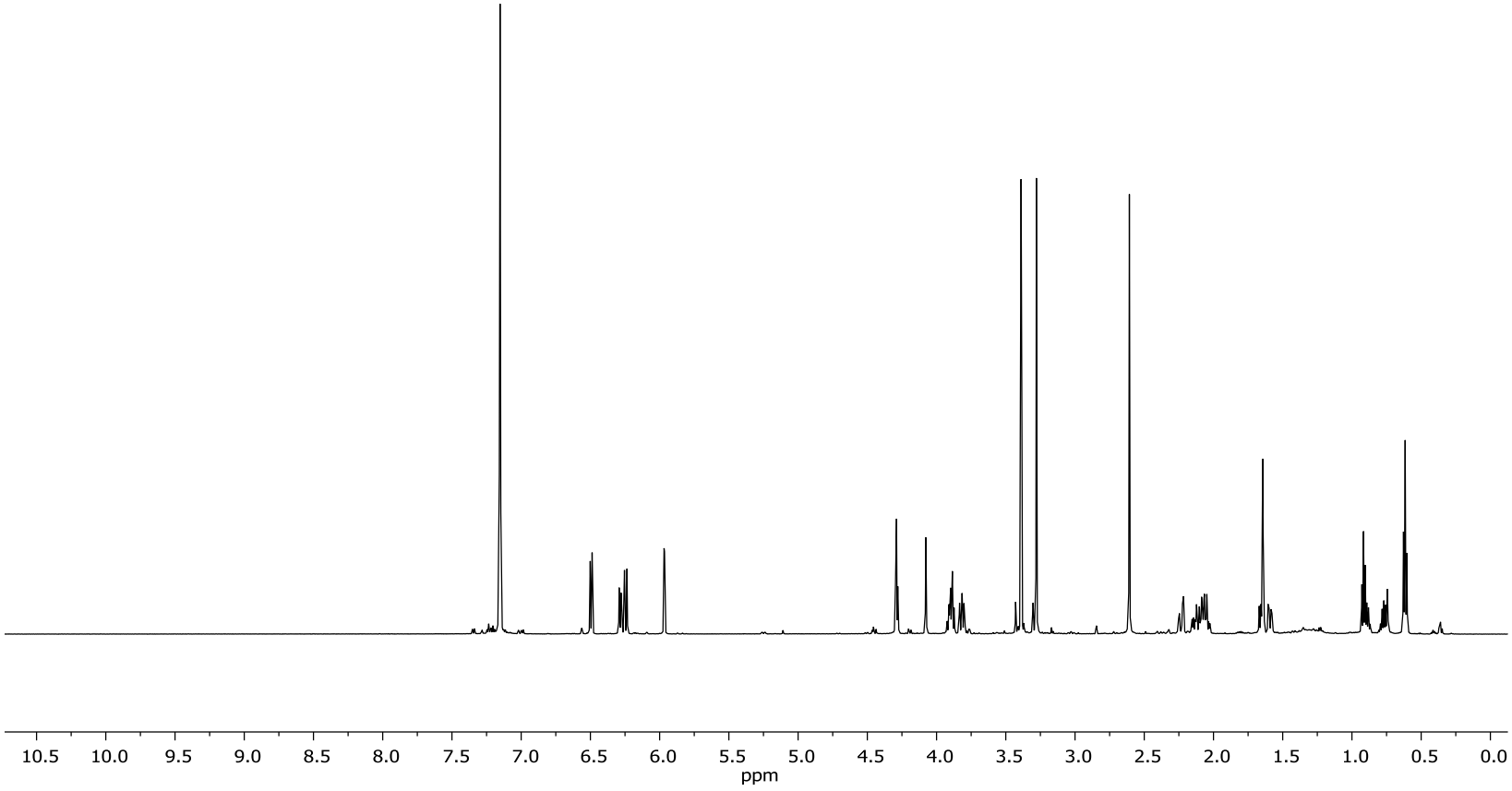

O
OTIPS
N
O
Et
MeO
N
O
Me
CO2Me
13
13C NMR, 150 MHz
C6D6
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

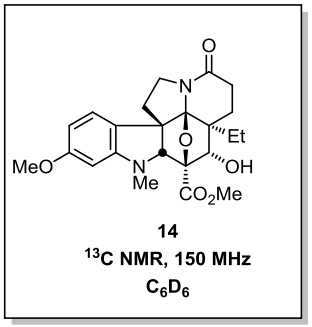


14

^{1}H NMR, 600 MHz

C_6D_6

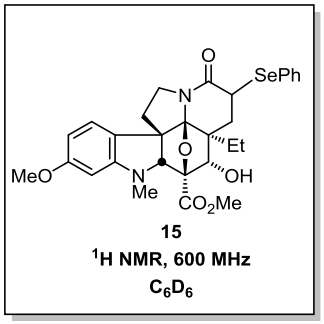




14

^{13}C NMR, 150 MHz

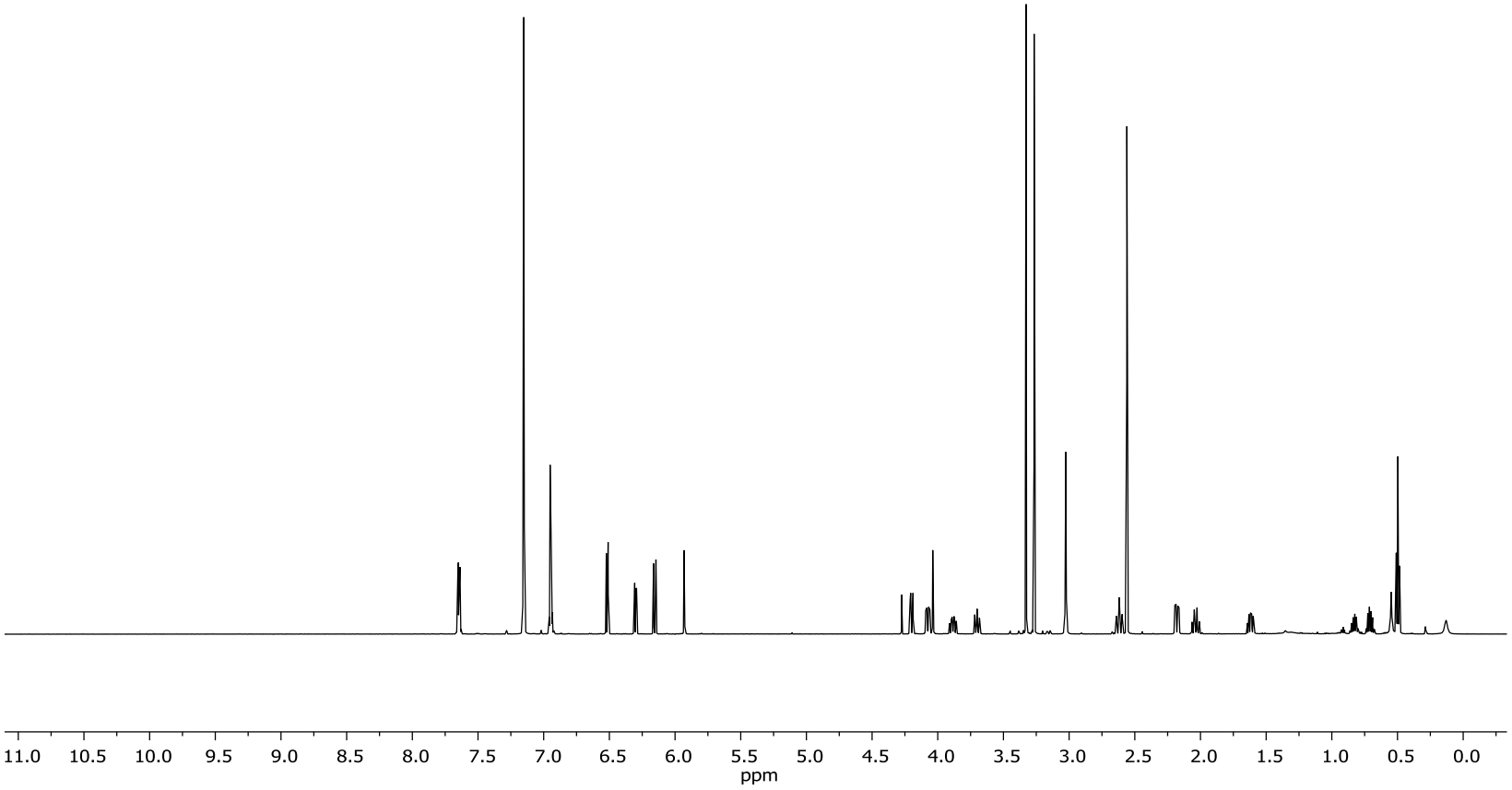
C_6D_6

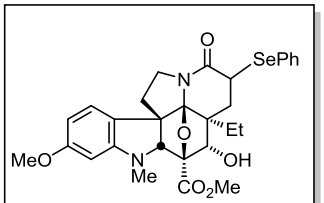


15

^{1}H NMR, 600 MHz

C_6D_6

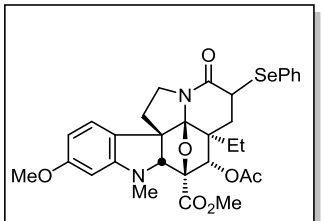




15

^{13}C NMR, 150 MHz

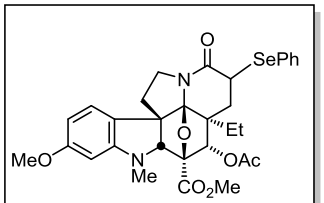
C_6D_6



16

^{1}H NMR, 600 MHz

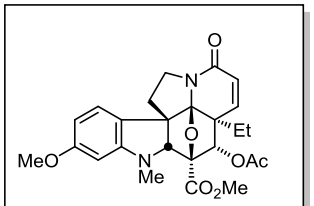
C_6D_6



16

^{13}C NMR, 150 MHz

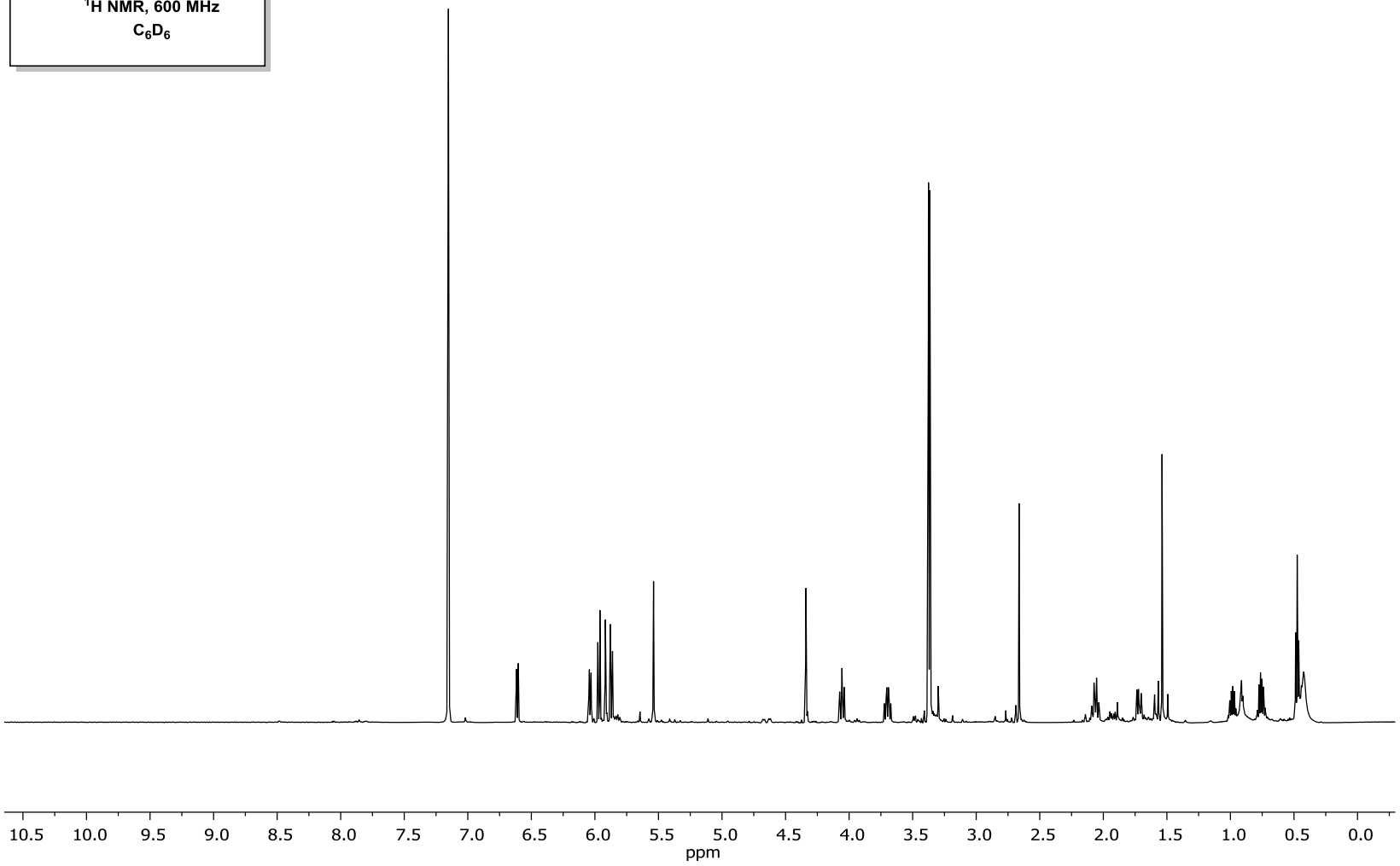
C_6D_6

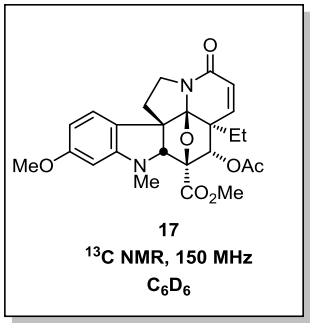


17

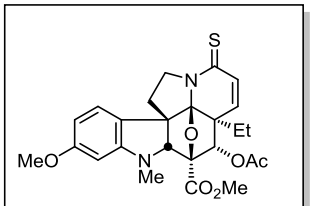
^{1}H NMR, 600 MHz

C_6D_6





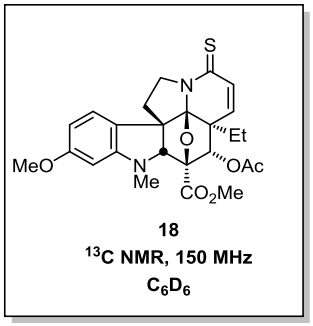
17
^{13}C NMR, 150 MHz
C_6D_6



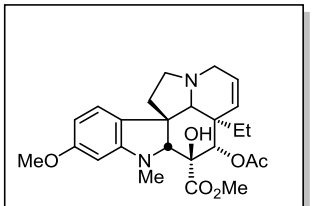
18

^{1}H NMR, 600 MHz

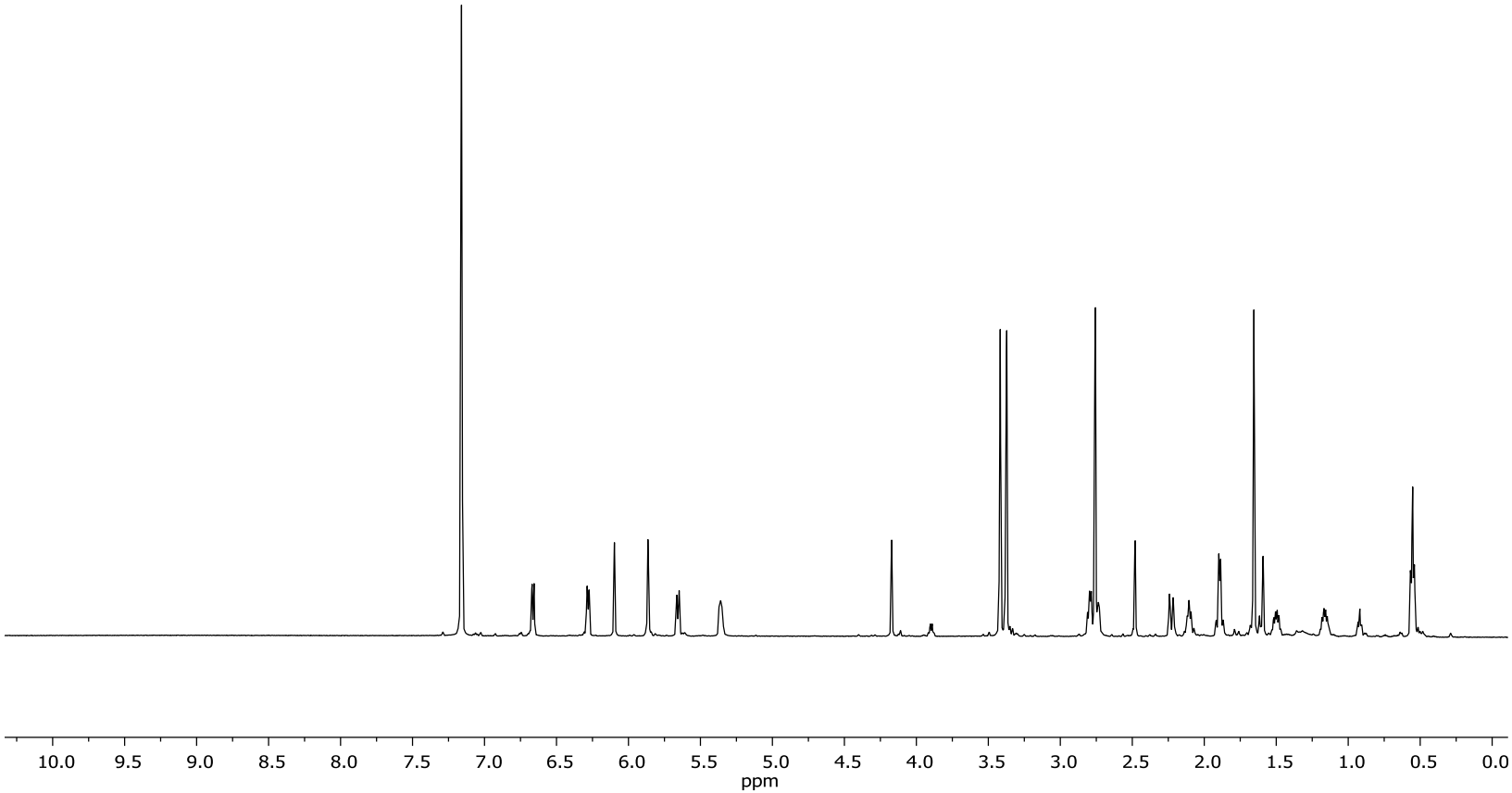
C_6D_6

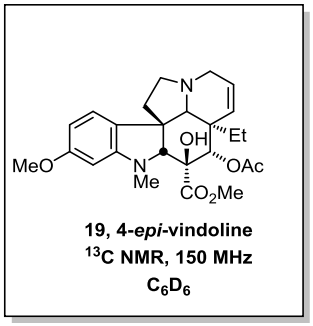


18
^{13}C NMR, 150 MHz
C_6D_6

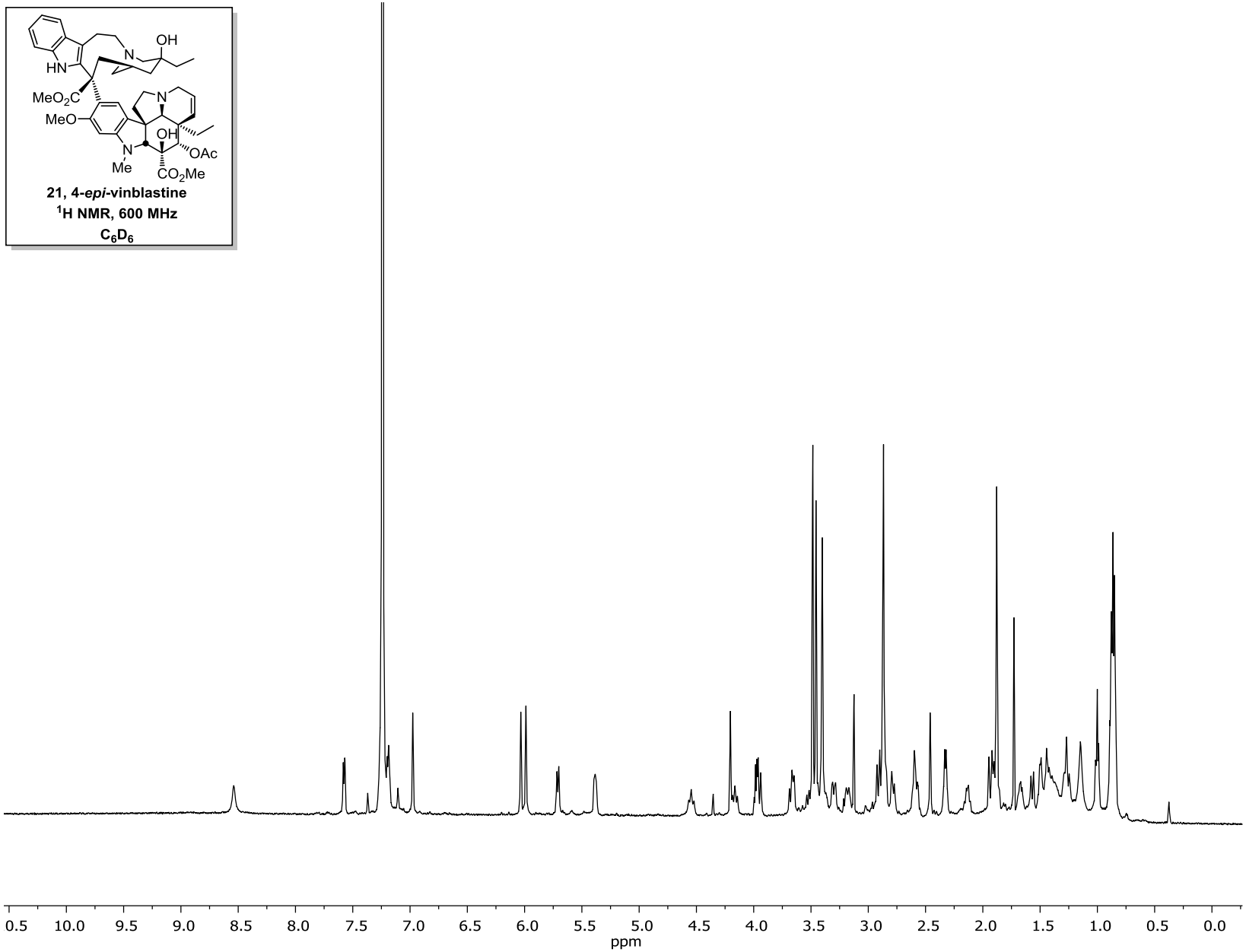


19, 4-*epi*-vindoline
^{1}H NMR, 600 MHz
C_6D_6





19, 4-*epi*-vindoline
^{13}C NMR, 150 MHz
C_6D_6


OH
HN
N
MeO2C
MeO
N
OH
OAc
Me
CO2Me
21, 4-epi-vinblastine
1H NMR, 600 MHz
C6D6
0.5
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