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Supporting Information

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Synthesis of the Sporolide Ring Framework Through a Cascade Sequence Involving a Novel Intramolecular [4+2] Cycloaddition Reaction of an *o*-Quinone

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I) Experimental

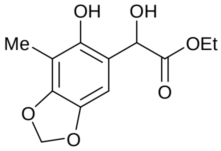
General Procedures. All reactions were carried out under an argon atmosphere with dry solvent under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), *N*,*N*-dimethylformamide (DMF), CH_3CN, CH_3OH and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

NMR spectra were recorded on Bruker DRX-600, DRX-500 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, b = broad, td = triple doublet, dt = double triplet.

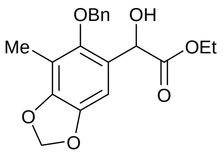
Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

Hydroxy ester 11: To a stirred solution of 2-methyl sesamol (**9**)[1] (8.18 g, 53.7 mmol) in THF (80 mL) at 0 ºC was added MeMgBr (3.0 M in Et_2O, 21.5 mL, 64.4 mmol, 1.2 equiv.) carefully and the reaction mixture was stirred at this temperature for 0.5 h. Then ethyl glyoxolate **10** (50% in toluene, 16.0 mL, 80.6 mmol, 1.5 equiv.) was added at 0 ºC and the reaction mixture was stirred at this temperature for an additional 0.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (60 mL) and the resulting mixture was extracted with EtOAc (60 mL × 3). The combined organic phase



11

was washed with H_2O (50 mL) and brine (50 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:2) to give pure hydroxy ester **11** (13.4 g, 52.6 mmol, 98%). **11**: R_f = 0.37 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3414bw, 2920w, 1734s, 1475m, 1248m, 1093s, 1027m, 926w cm^{-1}; ^1H NMR: ($CDCl_3$, 500 MHz) δ = 7.00 (s, 1 H), 6.52 (s, 1 H), 5.90 (d, J = 3.5 Hz, 2 H), 5.18 (d, J = 2.5 Hz, 1 H), 4.34 – 4.18 (m, 2 H), 3.48 (d, J = 2.5 Hz, 1 H), 2.12 (s, 3 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 173.1, 148.9, 147.0, 140.4, 113.6, 109.4, 104.9, 101.0, 72.6, 62.6, 14.0, 8.7 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{12}H_{14}O_6Na$ [$M+Na^+$]: 277.0683; found 277.0677.



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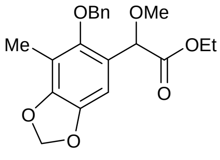
Benzyl ether 12: To a stirred solution of hydroxy ester **11** (4.06 g, 16.0 mmol) in DMF (40 mL) at 0 ºC was added BnBr (5.73 mL, 47.9 mmol, 3.0 equiv.), Cs_2CO_3 (10.4 g, 31.9 mmol, 2.0 equiv.) and NaI (2.39 g, 16.0 mmol, 1.0 equiv.) sequentially and the mixture was stirred at 25 ºC for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (40 mL) and the resulting mixture was extracted with EtOAc (40 mL × 3). The combined organic phase was washed with H_2O (40 mL × 3) and brine (40 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:4) to give pure benzyl ether **12** (5.06 g, 14.7 mmol, 92%). **12**: R_f = 0.26 (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 3484bw, 2903w, 1733m, 1474m, 1257m, 1208m, 1090s, 1025m, 939w, 736w, 698w cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 7.48 (d, J = 7.2 Hz, 2 H), 7.42 – 7.39 (m, 2 H), 7.37 – 7.34 (m, 1 H), 6.60 (s, 1 H), 5.96 (d, J = 2.4 Hz, 2 H), 5.39 (d, J = 5.4 Hz, 1 H), 4.94 (d, J = 11.1 Hz, 1 H), 4.86 (d, J = 11.1 Hz, 1 H), 4.28 – 4.15 (m, 2 H), 3.34 (d, J = 5.4 Hz, 1 H), 2.21 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 174.1, 150.7, 147.2, 143.5, 137.1, 128.5, 128.1, 127.9, 124.4, 113.9, 104.6, 101.4, 76.4, 68.5, 62.1, 14.1, 9.7 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{19}H_{21}O_6$ [$M+H^+$]: 345.1333; found 345.1330.

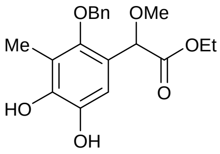
Methyl ether 13: To a stirred solution of benzyl ether **12** (1.19 g, 3.45 mmol) and HBF_4 (49% in H_2O, 0.620 mL, 3.45 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) at 0 ºC was added



13

TMSCHN$_2$ (2.0 M in hexanes, 3.45 mL, 6.91 mmol, 2.0 equiv.) dropwise (carefully!) and the reaction mixture was stirred at 25 ºC for 2 h. The reaction mixture was quenched with H_2O (20 mL) and the resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic phase was washed with H_2O (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:4) to give pure methyl ether **13** (1.00 g, 2.79 mmol, 81%). **13**: $R_f = 0.46$ (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2903w, 1745m, 1473m, 1426m, 1386m, 1261m, 1188m, 1091s, 1027m, 979w, 858w, 735w, 698m cm^{-1}; ^{1}H NMR: (CDCl$_3$, 400 MHz) δ = 7.52 – 7.49 (m, 2 H), 7.44 – 7.34 (m, 3 H), 6.77 (s, 1 H), 5.96 (s, 2 H), 5.15 (s, 1 H), 4.97 (d, *J* = 11.2 Hz, 1 H), 4.82 (d, *J* = 11.2 Hz, 1 H), 4.27 – 4.15 (m, 2 H), 3.31 (s, 3 H), 2.21 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 171.0, 151.0, 147.3, 143.6, 137.2, 128.5, 128.1, 127.8, 122.2, 113.5, 104.5, 101.4, 76.5, 76.4, 61.2, 57.0, 14.1, 9.6 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{23}O_6$ [M+H$^+$]: 359.1489; found 359.1490.

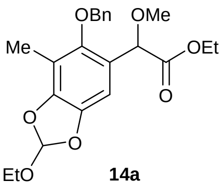
Catechol 14: To a stirred solution of methyl ether **13** (1.88 g, 5.25 mmol) in benzene (25 mL) at 25 ºC was added Pb(OAc)$_4$ (3.49 g, 7.87 mmol, 1.5 equiv.) and the reaction mixture was heated to 80 ºC and stirred at this temperature for 16 h. The reaction mixture was diluted with EtOAc (75 mL) and washed with H_2O (50 mL × 5) and brine (50 mL). The organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to the next reaction without further purification.



14

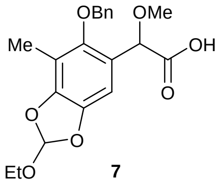
To a stirred solution of the residue obtained above in THF/H_2O (5:1, 9.0 mL) at 25 ºC was added AcOH (15 mL, excess) and the reaction mixture was stirred at this temperature for 6 h. The reaction mixture was quenched with saturated aqueous NaHCO$_3$ solution (60 mL) and the resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic phase was washed with saturated aqueous NaHCO$_3$ solution (40 mL × 4), H_2O (40 mL) and brine (40 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:2) to give pure catechol **14** (1.73 g, 4.99 mmol, 95%). **14**: R_f = 0.37 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3400bm, 2935w, 1729s, 1607w, 1455m, 1375m, 1300s, 1213s, 1114s, 1027m, 861w, 698m cm^{-1}; ^{1}H NMR: (CDCl$_3$, 500 MHz) δ = 7.55 – 7.48 (m, 2 H), 7.44 – 7.40 (m, 2 H), 7.38 – 7.36 (m, 1 H), 7.17 (bs, 1 H), 6.89 (s, 1 H), 5.79 (bs, 1 H), 5.24 (s, 1 H), 4.95 (d, *J* = 11.0 Hz, 1 H), 4.84 (d, *J* = 11.0 Hz, 1 H), 4.27 - 4.13 (m, 2 H), 3.24 (s, 3 H), 2.26 (s, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 172.0, 150.1, 144.6, 140.2, 137.4, 128.6, 128.1, 127.8, 119.6, 118.0, 110.5, 76.2, 75.8, 61.6, 56.4, 14.0, 9.6 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{19}H_{22}O_6Na$ [M+Na$^+$]: 369.1309; found 369.1307.

Ethyl orthoester 14a: To a stirred mixture of catechol **14** (170 mg, 0.491 mmol), CH(OEt)$_3$ (0.164 mL, 0.983 mmol, 2.0 equiv.) and 4 Å MS (40 mg, 80 mg per mmol **13**) in benzene (5.0 mL) at 25 ºC was added TsOH·H$_2$O (18.6 mg, 0.098 mmol, 0.20 equiv.) and the reaction mixture was heated to 80 ºC and stirred at this temperature for 16 h. The reaction mixture was filtered through a celite pad and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:4) to give pure ethyl orthoester **14a** (189 mg, 0.470 mmol, 96%) as a *ca.* 1:1 mixture of two chromatographically inseparable diastereomers. **14a**: R_f = 0.51 (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2982w, 1847w, 1747m, 1479m, 1430m, 1376m, 1267w, 1189m, 1088s, 1032m, 736w, 698w cm^{-1}; ^{1}H NMR: (CDCl$_3$, 600 MHz) δ = 7.51 – 7.49 (m, 2 H), 7.43 – 7.41 (m, 2 H), 7.38 – 7.35 (m, 1 H), 6.80 – 6.85 (s × 2, 1 H), 6.82 – 6.81 (s × 2, 1 H), 5.16 (s × 2, 1 H), 4.97 (d, *J* = 11.1 Hz, 1 H), 4.82 (d, *J* = 11.1 Hz, 1 H), 4.26 – 4.14 (m, 2 H), 3.79 – 3.72 (m, 2 H), 3.32 – 3.30 (s × 2, 3 H), 2.24 (s × 2, 3 H), 1.30 – 1.22 (m, 6 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 171.0, 151.0, 151.0, 145.7, 145.6, 142.1, 142.1, 137.2, 128.6, 128.1, 127.8, 127.8, 122.5, 119.5, 119.4, 113.3, 113.2, 104.4, 104.2, 76.5, 76.5, 76.4, 61.2, 61.2, 60.0, 59.5, 57.2, 57.0, 14.8, 14.1, 9.7 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{22}H_{27}O_7$ [M+H$^+$]: 403.1751; found 403.1749.



14a

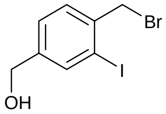
Carboxylic acid 7: To a stirred solution of ethyl orthoester **14a** (850 mg, 2.11 mmol) in dioxane/H$_2$O (5:1, 18.0 mL) at 25 ºC was added LiOH (1.01 g, 42.2 mmol, 20 equiv.) and the reaction mixture was heated to 80 ºC and stirred at this temperature for 3 h. The



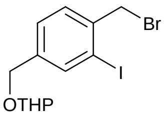
7

reaction mixture was quenched with 10% aqueous citric acid solution (50 mL) and the resulting mixture was extracted with EtOAc (30 mL × 3). The combined organic phase was washed with H_2O (40 mL × 4) and brine (40 mL), dried with Na_2SO_4 and concentrated *in vacuo* to give pure carboxylic acid **7** (786 mg, 2.10 mmol, 99%) as a *ca.* 1:1 mixture of two chromatographically inseparable diastereomers. **7**: $R_f = 0.10$ (silica gel, EtOAc:hexanes 1:1); IR ν_{max} (film): 2932w, 1720m, 1480m, 1376m, 1181m, 1087s, 1004m, 916w, 734w, 698w cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 7.49 – 7.46 (m, 2 H), 7.42 – 7.38 (m, 2 H), 7.37 – 7.34 (m, 1 H), 6.87 – 6.86 (s × 2, 1 H), 6.73 (s, 1 H), 5.09 (s × 2, 1 H), 5.02 – 5.00 (d × 2, *J* = 13.2 Hz, 1 H), 4.86 – 4.82 (d × 2, *J* = 13.2 Hz, 1 H), 3.77 – 3.70 (m, 2 H), 3.31 – 3.29 (s × 2, 3 H), 2.26 – 2.25 (s × 2, 3 H), 1.30 – 1.27 (m, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 172.9, 151.2, 151.1, 146.1, 142.3, 142.2, 136.8, 128.6, 128.3, 127.9, 121.3, 121.3, 119.6, 119.6, 113.5, 113.5, 104.2, 104.2, 76.6, 76.5, 76.5, 59.8, 59.7, 57.0, 56.9, 14.8, 14.8, 9.8 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{22}O_7Na$ [$M+Na^+$]: 397.1263; found 397.1267.

Benzylic alcohol 15a: To a stirred solution of 4-bromomethyl-3-iodobenzoic acid (**15**)[2] (27.2 g, 80.0 mmol) in THF (200 mL) at 25 ºC was added $BH_3 \cdot THF$ (1.0 M in THF, 160 mL, 160 mmol, 2.0 equiv.) dropwise and the reaction mixture was stirred at this temperature for 2 h. The reaction was quenched with H_2O (20 mL) (carefully!), saturated aqueous $NaHCO_3$ solution (50 mL) and the resulting mixture was extracted with EtOAc (100 mL × 3). The combined organic phase was washed with H_2O (200 mL) and brine (200 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:4) to give pure benzylic alcohol **15a** (20.9 g, 64.1 mmol, 80%). **15a**: $R_f = 0.50$ (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3261bw, 2853w, 1400m, 1273m, 1224m, 1202m, 1044s, 873m, 820m, 760m cm^{-1}; ^1H NMR: ($CDCl_3$, 600 MHz) δ = 7.88 (s, 1 H), 7.45 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 4.67 (d, *J* = 4.2 Hz, 2 H), 4.60 (s, 2 H), 1.71 (t, *J* = 4.2 Hz, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 143.1, 139.4, 138.2, 130.4, 127.2, 100.1, 63.8, 38.4 ppm; HRMS (ESI TOF): *m/z* calcd for C_8H_9BrIO [$M+H^+$]: 326.8881; found 326.8880.

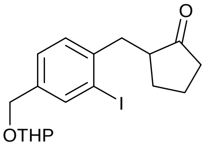


15a



16

THP ether 16: To a stirred solution of benzylic alcohol **15a** (19.0 g, 58.3 mmol) and DHP (4.0 mL, 70 mmol, 1.2 equiv.) in CH_2Cl_2 (120 mL) at 25 ºC was added TsOH·H_2O (1.10 g, 5.83 mmol, 0.1 equiv.) and the reaction mixture was stirred at this temperature for 0.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (60 mL) and the resulting mixture was extracted with CH_2Cl_2 (60 mL × 3). The combined organic phase was washed with H_2O (60 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:8) to give pure THP ether **16** (22.7g, 55.4 mmol, 95%). **16**: $R_f = 0.69$ (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2939m, 2867w, 1385m, 1344m, 1199m, 1120s, 1032s, 971s, 905s, 869s, 815m cm^{-1}; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 7.85 (s, 1 H), 7.43 (d, *J* = 6.4 Hz, 1 H), 7.32 (d, *J* = 6.4 Hz, 1 H), 4.73 – 4.68 (m, 2 H), 4.60 – 4.53 (m, 2 H), 4.43 (d, *J* = 10.0 Hz, 1 H), 3.90 – 3.85 (m, 1 H), 3.56 – 3.52 (m, 1 H), 1.88 – 1.84 (m, 1 H), 1.78 – 1.72 (m, 1 H), 1.67 – 1.54 (m, 4 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 140.8, 139.2, 138.9, 130.2, 128.0, 100.0, 97.9, 67.2, 62.1, 38.5, 30.4, 25.3, 19.2 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{16}BrIO_2Na$ [M+Na^{+}]: 432.9271; found 432.9271.

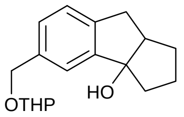


18

Cyclopentanone 18: To a stirred solution of *i*Pr_2NH (8.00 mL, 57.2 mmol, 1.3 equiv.) in THF (100 mL) at –78 ºC was added *n*BuLi (2.5 M in hexanes, 22.9 mL, 57.2 moL, 1.3 equiv.) dropwise and the reaction mixture was warmed to 0 ºC for 0.5 h. Then cyclopentanone (**17**, 5.10 mL, 57.2 mmol, 1.3 equiv.) was added at −78 ºC and the mixture was warmed to 0 ºC over 1 h. Then HMPA (25 mL) and THP ether **16** (18 g, 44 mmol, 1.0 equiv.) in THF (30 mL) were added sequentially at −78 ºC and the reaction mixture was stirred at 25 ºC for additional 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (40 mL) and the resulting mixture was extracted with Et_2O (60 mL × 3). The combined organic phase was washed with H_2O (60 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:4) to give pure cyclopentanone **18** (11.8 g, 28.6 mmol, 65%) as a *ca.* 1:1 mixture of two chromatographically inseparable diastereomers.

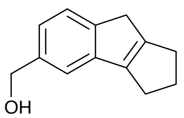
18: R$_f$ = 0.50 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 2941m, 2869w, 1737s, 1452w, 1345w, 1120m, 1035s, 974w, 906w, 816w cm^{-1}; ^{1}H NMR: (CDCl$_3$, 600 MHz) δ = 7.83 (s, 1 H), 7.26 (d, *J* = 7.8 Hz, 1 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 4.71 – 4.68 (m, 2 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 3.89 (t, *J* = 9.9 Hz, 1 H), 3.56 – 3.53 (m, 1 H), 3.28 (dd, *J* = 14.4, 4.8 Hz, 1 H), 2.62 (dd, *J* = 13.8, 9.6 Hz, 1 H), 2.49 – 2.44 (m, 1 H), 2.36 (dd, *J* = 19.2, 8.4 Hz, 1 H), 2.18 – 2.12 (m, 1 H), 2.07 – 1.98 (m, 2 H), 1.90 – 1.82 (m, 1 H), 1.77 – 1.72 (m, 2 H), 1.68 – 1.52 (m, 5 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 219.5, 141.9, 138.8, 138.4, 129.8, 127.8, 100.6, 97.9, 67.5, 62.1, 49.8, 39.8, 37.9, 30.5, 29.2, 25.4, 20.5, 19.3 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{18}H_{24}IO_3$ [M+H$^+$]: 415.0765; found 415.0758.

Tertiary alcohol 19: To a stirred solution of cyclopentanone **18** (4.40 g, 10.6 mmol) in DMF (30 mL) at 25 ºC was added $CrCl_2$ (5.40 g, 42.7 mmol, 4.0 equiv.) and $NiCl_2$ (27 mg, 0.21 mmol, 0.02 equiv.) and the reaction mixture was heated to 100 ºC and stirred at this temperature for 16 h. The reaction mixture was cooled to ambient temperature and quenched with H_2O (10 mL). The resulting mixture was extracted with Et_2O (40 mL × 3) and the combined organic phase was washed with H_2O (30 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:4) to give pure tertiary alcohol **19** (2.30 g, 8.00 mmol, 76%) as a *ca.* 1:1 mixture of two chromatographically inseparable diastereomers. **19**: R$_f$ = 0.30 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3398bw, 2942m, 1441w, 1347m, 1200m, 1117s, 1025s, 907m, 813m cm^{-1}; ^{1}H NMR: (CDCl$_3$, 600 MHz) δ = 7.38 (s, 1 H), 7.25 (d, *J* = 4.8 Hz, 1 H), 7.14 (d, *J* = 4.8 Hz, 1 H), 4.78 (dd, *J* = 12.0, 3.0 Hz, 1 H), 4.72 (dd, *J* = 7.2, 3.6 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 3.96 – 3.90 (m, 1 H), 3.58 – 3.53 (m, 1 H), 3.31 (dd, *J* = 16.8, 9.0 Hz, 1 H), 2.68 – 2.63 (m, 1 H), 2.54 (dd, *J* = 16.8, 3.6 Hz, 1 H), 2.19 – 2.13 (m, 1 H), 2.08 – 2.06 (m, 2 H), 1.95 (d, *J* = 6.6 Hz, 1 H), 1.90 – 1.78 (m, 2 H), 1.76 – 1.71 (m, 1 H), 1.67 – 1.42 (m, 5 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 147.7, 142.5, 137.4, 128.3, 124.8, 123.2, 123.2, 97.9, 97.8, 93.7, 69.0, 68.9, 62.1, 62.1, 51.8, 41.2, 37.7, 34.1, 30.5, 25.7, 25.5, 19.3 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{18}H_{24}O_3Na$ [M+Na$^+$]: 311.1618; found 311.1618.



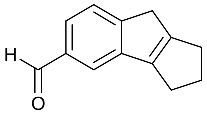
19

Hydroxy indene 20: To a stirred solution of tertiary alcohol **19** (1.90 g, 6.60 mmol) in benzene (30 mL) at 25 ºC was added TsOH·H_2O (125 mg, 0.66 mmol, 0.1 equiv.) and the reaction mixture was heated to 80 ºC and stirred at this temperature for 0.5 h. The reaction mixture was cooled to ambient temperature and CH_3OH (10 mL) was added. The reaction mixture was stirred at 25 ºC for additional 0.5 h before quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with Et_2O (20 mL × 3) and the combined organic phase was washed with H_2O (20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes: 1:4) to give pure hydroxy indene **20** (1.00 g, 5.38 mmol, 82%). **20**: R_f = 0.25 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3337bm, 2843m, 1736w, 1620w, 1440m, 1351m, 1278m, 1163m, 1039s, 864s, 816s cm^{-1}; ^1H NMR: ($CDCl_3$, 400 MHz) δ = 7.35 (d, *J* = 7.6 Hz, 1 H), 7.21 (s, 1 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 4.70 (s, 2 H), 3.19 (s, 2 H), 2.63 – 2.59 (m, 4 H), 2.45 – 2.39 (m, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 152.1, 147.8, 147.4, 142.5, 139.0, 123.9, 122.3, 117.5, 65.8, 34.9, 29.7, 28.2, 26.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{15}O$ [$M+H^+$]: 187.1117; found 187.1114.



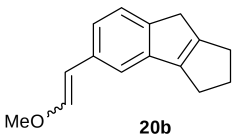
20

Aldehyde 20a: To a stirred solution of hydroxy indene **20** (750 mg, 4.03 mmol) in CH_2Cl_2 (10 mL) at 25 ºC was added $NaHCO_3$ (1.01 g, 12.0 mmol, 3.0 equiv.) and DMP (2.05 g, 4.83 mmol, 1.2 equiv.) sequentially and the reaction mixture was stirred at this temperature for 0.5 h. The reaction mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:8) to give pure aldehyde **20a** (700 mg, 3.80 mmol, 95%). **20a**: R_f = 0.60 (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2950w, 2846w, 1691s, 1612w, 1448w, 1175w cm^{-1}; ^1H NMR: ($CDCl_3$, 400 MHz) δ = 10.01 (s, 1 H), 7.67 (s, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 3.27 (s, 2 H), 2.66 – 2.61 (m, 4 H), 2.47 – 2.39 (m, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 192.8, 155.5, 153.3, 147.1, 142.9, 135.3, 126.9, 124.2,



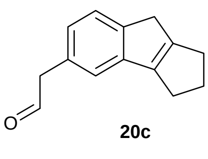
20a

118.3, 35.6, 29.8, 28.1, 26.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{13}O$ [M+H$^+$]: 185.0961; found 185.0961.



20b

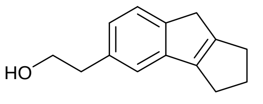
Methyl enol ether 20b: To a stirred suspension of $MeOCH_2PPh_3Br$ (1.48 g, 4.30 mmol, 1.5 equiv.) in THF (20 mL) at 0 ºC was added KHMDS (0.5 M in toluene, 8.60 mL, 4.30 mmol, 1.5 equiv.) dropwise and the reaction mixture was stirred at this temperature for 1 h. Then a solution of aldehyde **20a** (530 mg, 2.88 mmol) in THF (3 mL) was added at 0 ºC and the reaction mixture was stirred at 25 ºC for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and the resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was washed with H_2O (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:10) to give pure methyl enol ether **20b** (590 mg, 2.78 mmol, 96%) as a *ca.* 1:1 mixture of *E/Z*- isomers. **20b**: R_f = 0.80 (silica gel, EtOAc:hexanes 1:10); IR ν_{max} (film): 2933m, 2893m, 2843m, 1638s, 1464m, 1437m, 1392w, 1262m, 1222s, 1148s, 1090s, 930m, 872m, 820m, 720s cm^{-1}; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 7.42 – 7.28 (m, 4 H), 7.10 – 7.05 (m, 2 H), 6.98 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.11 (d, *J* = 7.2 Hz, 1 H), 5.99 (d, *J* = 13.2 Hz, 1 H), 5.28 (d, *J* = 7.2 Hz, 1 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 3.17 (s, 4 H), 2.64 – 2.58 (m, 8 H), 2.45 – 2.39 (m, 4 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 151.9, 151.3, 148.1, 147.7, 147.4, 147.0, 145.9, 145.8, 142.5, 142.1, 134.3, 133.9, 133.8, 133.6, 128.7, 128.5, 128.4, 124.0, 123.7, 123.6, 120.8, 118.5, 115.2, 106.4, 105.7, 60.6, 56.4, 34.9, 34.9, 29.7, 28.2, 26.5, 26.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{15}H_{17}O$ [M+H$^+$]: 213.1274; found 213.1273.



20c

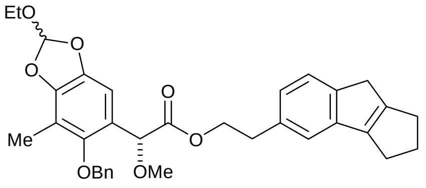
Aldehyde 20c: To a stirred solution of methyl enol ether **20b** (500 mg, 2.36 mmol) in THF (15 mL) at 25 ºC was added aqueous HCl solution (2.0 N, 4.70 mL, 9.40 mmol, 4.0 equiv.) and the reaction mixture was heated to 60 ºC and stirred at this temperature for 3 h. The reaction mixture was cooled to ambient temperature and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with Et_2O (10 mL × 3) and the combined organic phase was washed with H_2O (10 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:8) to give pure aldehyde **20c** (410 mg, 2.07 mmol, 88%). **20c**: R_f = 0.60 (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2895w, 2845w, 1723s, 1619w, 1467w, 1395w, 1033w, 811w, 725w cm^{-1}; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 9.75 (t, *J* = 2.8 Hz, 1 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.04 (s, 1 H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 1 H), 3.69 (d, *J* = 2.8 Hz, 2 H), 3.20 (s, 2 H), 2.63 – 2.58 (m, 4 H), 2.43 – 2.36 (m, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 200.0, 152.6, 147.4, 147.3, 143.1, 130.0, 124.7, 124.4, 119.8, 50.8, 35.0, 29.7, 28.2, 26.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{14}H_{15}O$ [M+H$^+$]: 199.1117; found 199.1115.

Alcohol 8: To a stirred solution of aldehyde **20c** (400 mg, 2.02 mmol) in THF/CH_3OH (5:1, 6.0 mL) at 25 ºC was added $NaBH_4$ (84 mg, 2.2 mmol, 1.1 equiv.) portionwise and the reaction mixture was stirred at this temperature for 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and the resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic phase was washed with H_2O (10 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:4) to give pure alcohol **8** (383 mg, 1.92 mmol, 95%). **8**: R_f = 0.25 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3346bm, 2945s, 2846s, 1621w, 1467m, 1397w, 1045s, 810m, 725m cm^{-1}; ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 7.31 (d, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 1.2 Hz, 1 H), 6.96 (dd, *J* = 7.6, 1.2 Hz, 1 H), 3.90 – 3.85 (dd, *J* = 12.4, 6.4 Hz, 2 H), 3.17 (s, 2 H), 2.90 (t, *J* = 6.4 Hz, 2 H), 2.62 – 2.58 (m, 4 H), 2.44 – 2.38 (m, 2 H) ppm; ^{13}C NMR: ($CDCl_3$, 100 MHz) δ = 152.1, 147.4, 146.5, 142.6, 136.2, 124.1, 124.0, 119.3, 64.0, 39.3, 34.9, 29.7, 28.2, 26.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{14}H_{17}O$ [M+H$^+$]: 201.1274; found 201.1270.



8

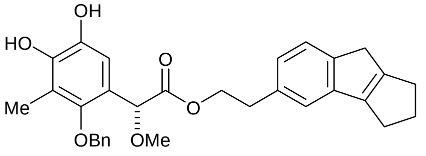
Ester 21: To a stirred solution of carboxylic acid **7** (85.2 mg, 0.228 mmol, 1.25 equiv.) and alcohol **8** (36.7 mg, 0.183 mmol, 1.0 equiv.) in CH_2Cl_2 (1.5 mL) at 25 ºC was added DCC (49.1 mg, 0.238 mmol, 1.3 equiv.) and 4-DMAP (4.5 mg, 0.037 mmol, 0.2 equiv.) and the reaction mixture was stirred at this temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue so obtained was subjected to flash column



21

chromatography (EtOAc:hexanes, 1:6) to give pure ester **21** (85.5 mg, 0.154 mmol, 84%) as a *ca.* 1:1 mixture of two chromatographically inseparable diastereomers. **21**: R_f = 0.47 (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2931m, 1747m, 1621w, 1478m, 1376m, 1345w, 1261m, 1185m, 1087s, 1034m, 1005m, 735m, 697m cm^{-1}; ^{1}H NMR: ($CDCl_3$, 600 MHz) δ = 7.42 – 7.34 (m, 5 H), 7.19 – 7.17 (d × 2, *J* = 7.8 Hz, 1 H), 6.97 – 6.94 (s × 2, 1H), 6.86 (s, 1 H), 6.81 – 6.77 (m, 2 H), 5.13 (s, 1 H), 4.82 – 4.80 (m, 1 H), 4.64 – 4.62 (s × 2, 1 H), 4.42 – 4.36 (m, 2 H), 3.80 – 3.71 (m, 2 H), 3.29 – 3.27 (s × 2, 3 H), 3.12 (s, 2 H), 2.95 – 2.89 (m, 2 H), 2.59 – 2.56 (m, 2 H), 2.53 – 2.51 (m, 2 H), 2.41 – 2.36 (m, 2 H), 2.21 – 2.20 (s × 2, 3 H), 1.31 – 1.26 (m, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 171.0, 171.0, 151.9, 151.8, 151.0, 150.9, 147.4, 146.5, 146.5, 145.7, 145.7, 142.5, 142.4, 142.1, 137.2, 135.2, 135.2, 128.5, 128.0, 127.7, 127.7, 124.0, 124.0, 123.8, 123.8, 122.4, 122.4, 119.5, 119.4, 119.0, 119.0, 113.2, 113.1, 104.4, 103.1, 76.3, 76.3, 76.2, 76.2, 65.9, 65.8, 60.0, 59.4, 57.2, 57.0, 35.0, 35.0, 34.8, 29.7, 28.2, 26.3, 14.8, 9.7 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{34}H_{36}O_7Na$ [M+Na$^+$]: 579.2353; found 579.2350.

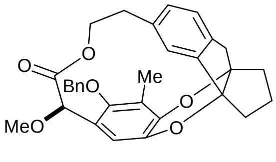
Catechol 6: To a stirred solution of ester **21** (64.2 mg, 0.115 mmol) in CH_3OH (1.0 mL) at 25 ºC was added $TsOH{\cdot}H_2O$ (1.1 mg, 0.0058 mmol, 0.05 equiv.) and the mixture was stirred at this temperature for 16 h. The reaction reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and the resulting mixture was extracted with EtOAc (3 × 3 mL). The combined organic phase was washed with H_2O (5 mL) and brine (5 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:2) to give pure catechol **6** (56.7 mg, 0.113 mmol, 98%). **6**: R_f = 0.25 (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3380bm, 2924s, 1731s, 1609w, 1460s, 1378s, 1302s, 1187s, 1114s, 1039m, 1009s, 911w, 809w, 731m, 697m cm^{-1}; ^{1}H NMR: ($CDCl_3$, 600 MHz) δ = 7.42 – 7.33 (m, 5 H), 7.16 (d, *J* = 7.2 Hz, 1 H), 6.93 (s, 1 H), 6.77 (s, 1 H), 6.75 (d, *J* = 7.2 Hz, 1 H), 6.42 (s, 1 H), 5.65 (s, 1 H), 5.18 (s,



6

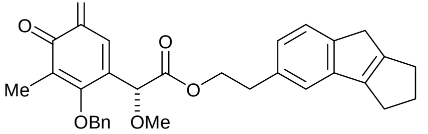
1 H), 4.76 (d, *J* = 11.4 Hz, 1 H), 4.62 (d, *J* = 11.4 Hz, 1 H), 4.43 – 4.35 (m, 2 H), 3.22 (s, 3 H), 3.11 (s, 2 H), 3.91 – 2.87 (m, 2 H), 2.58 – 2.55 (m, 2 H), 2.53 – 2.48 (m, 2 H), 2.40 – 2.35 (m, 2 H), 2.21 (s, 3 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 171.8, 152.0, 150.2, 147.3, 146.5, 144.4, 142.4, 139.8, 137.4, 135.1, 128.5, 128.0, 127.7, 124.0, 123.8, 119.9, 119.0, 118.0, 110.6, 76.1, 75.8, 66.0, 56.5, 34.8, 29.7, 28.2, 26.3, 9.6 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{31}H_{32}O_6Na$ [M+Na$^+$]: 523.2091; found 523.2093.

Macrocycle 4a (one-step procedure): To a stirred solution of catechol **6** (25.0 mg, 50 μmol) in toluene (10 mL, 0.005 M concentration) at 120 ºC was added Ag_2O (23.1 mg, 100 μmol, 2.0 equiv.) and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:4) to give pure macrocycle **4a** (15.0 mg, 30 μmol, 60%). **4a**: R$_f$ = 0.35 (silica gel, EtOAc:hexanes 1:4); IR ν$_{max}$ (film): 2959m, 1732s, 1473m, 1260m, 1108s, 1061s, 731m cm^{-1}; ^{1}H NMR: (CDCl$_3$, 600 MHz) δ = 7.40 – 7.30 (m, 5 H), 6.97 (s, 1 H), 6.82 – 6.78 (m, 3 H), 4.89 (s, 1 H), 4.71 (d, *J* = 13.8 Hz, 1 H), 4.58 (d, *J* = 13.8 Hz, 1 H), 4.27 – 4.16 (m, 2 H), 3.27 (s, 3 H), 3.09 (d, *J* = 20.4 Hz, 1 H), 3.01 – 2.94 (m, 2 H), 2.84 (dt, J^d = 17.4 Hz, J^t = 3.3 Hz, 1 H), 2.61 – 2.55 (m, 1 H), 2.48 – 2.42 (m, 1 H), 2.38 – 2.32 (m, 2 H), 2.23 – 2.16 (m, 1 H), 2.03 (s, 3 H), 1.80 – 1.73 (m, 1 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 170.1, 150.3, 148.3, 144.0, 142.4, 140.4, 136.9, 136.7, 129.0, 128.5, 128.2, 128.1, 127.7, 124.5, 122.1, 120.8, 119.4, 101.5, 98.3, 77.9, 76.1, 65.8, 57.2, 44.1, 37.3, 36.3, 34.5, 23.2, 9.2 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{31}H_{31}O_6$ [M+H$^+$]: 499.2115; found 499.2116.



4a

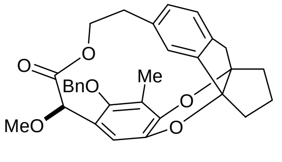
***o*-Quinone indene 5** (two-step procedure): To a stirred solution of catechol **6** (207.5 mg, 0.414 mmol) in CH_2Cl_2 (5.0 mL) at 25 ºC was added Ag_2O (192.1 mg, 0.829 mmol, 2.0 equiv.) and the reaction mixture was stirred at this temperature for 5 min. The reaction mixture was filtered through a celite pad and washed with EtOAc (5 mL × 2). The filtrate was concentrated *in vacuo* to give pure *o*-quinone indene **5** (206.5 mg, 0.414 mmol, 99%). **5**: R$_f$ = 0.43 (silica gel,



5

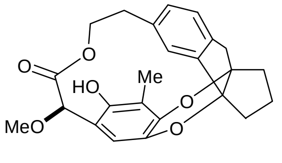
EtOAc:hexanes 1:2); IR ν_{max} (film): 2924m, 2852w, 1739m, 1683w, 1653m, 1627w, 1579m, 1455m, 1377m, 1316s, 1260m, 1185s, 1105s, 1045m, 1011m, 913m, 805m, 734m, 698m cm^{-1}; ^{1}H NMR: (CDCl$_3$, 600 MHz) δ = 7.40 – 7.37 (m, 3 H), 7.32 – 7.30 (m, 2 H), 7.16 (d, J = 7.8 Hz, 1 H), 6.95 (s, 1 H), 6.82 (d, J = 7.2 Hz, 1 H), 6.35 (s, 1 H), 4.92 (d, J = 11.4 Hz, 1 H), 4.85 (d, J = 11.4 Hz, 1 H), 4.47 (s, 1 H), 4.33 – 4.28 (m, 2 H), 3.37 (s, 3 H), 3.12 (s, 2 H), 2.90 – 2.87 (m, 2 H), 2.60 – 2.58 (m, 2 H), 2.54 – 2.52 (m, 2 H), 2.42 – 2.38 (m, 2 H), 1.89 (s, 3 H) ppm; ^{13}C NMR: (CDCl$_3$, 150 MHz) δ = 179.9, 179.4, 167.9, 162.5, 152.5, 149.5, 147.1, 146.7, 142.5, 135.3, 135.0, 128.8, 128.8, 127.8, 125.0, 124.0, 124.0, 123.1, 118.9, 78.4, 75.7, 66.3, 58.9, 34.9, 34.7, 29.7, 28.2, 26.4, 10.2 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{31}H_{31}O_6$ [M+H$^+$]: 499.2115; found 499.2112.

Macrocycle 4a: A solution of *o*-quinone indene **5** (67.6 mg, 0.135 mmol) in toluene (27 mL, 0.005 M concentration) was heated in a sealed flask at 120 ºC for 3 h. The reaction mixture was concentrated *in vacuo* and subjected to flash column chromatography (EtOAc:hexanes, 1:4) to give pure title compound **4a** (33.8 mg, 0.0678 mmol, 50%). All the spectroscopic data of the product were identical to the data of the product obtained by the one-step procedure as described above.



4a

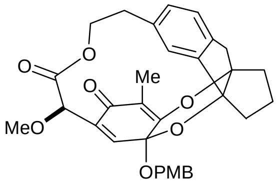
Phenol 22: To a solution of macrocycle **4a** (22.9 mg, 45.9 μmol) in EtOH (1.0 mL) at 25 ºC was added Pd(OH)$_2$ (20% on carbon, 2.3 mg, 10% wt) and the reaction flask was charged with H$_2$ (balloon, ~ 1 atm). The reaction mixture was stirred at this temperature for 16 h. The reaction mixture was filtered through celite and washed with EtOAc (2 × 2 mL). The filtrate was concentrated *in vacuo* and the resulting residue was subjected to flash column chromatography (EtOAc:hexanes, 1:2) to give pure phenol **22** (16.0 mg, 39.1 μmol, 85%). **22**: R$_f$ = 0.11 (silica gel, EtOAc:hexanes 1:4); mp. 233 – 234 ºC (acetone/hexanes); IR ν_{max} (film): 3464bm, 2949w, 1714s, 1477m, 1437m, 1357w, 1253m, 1226m, 1175s, 1116s, 1059s, 989m, 952w, 821w cm^{-1}; ^{1}H NMR: (CDCl$_3$, 600 MHz) δ = 6.97 (s, 1 H), 6.82 – 6.79 (m, 3 H), 5.03 (s, 1 H), 4.49 (s, 1 H), 4.41 (td, J^{t} = 11.7 Hz, J^{d} = 2.4 Hz, 1 H), 4.14 – 4.10 (m, 1 H), 3.40 (s, 3 H), 3.07 (d, J = 16.8 Hz, 1 H),



22

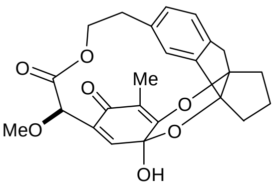
2.99 (td, $J^t = 13.5$ Hz, $J^d = 4.2$ Hz, 1 H), 2.94 (d, $J = 17.4$ Hz, 1 H), 2.85 (d, $J = 14.4$ Hz, 1 H), 2.59 – 2.53 (m, 1 H), 2.47 – 2.41 (m, 1 H), 2.35 – 2.30 (m, 2 H), 2.21 – 2.16 (m, 1 H), 1.98 (s, 3 H), 1.80 – 1.72 (m, 1 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) $\delta = 170.8$, 148.0, 146.7, 142.5, 141.9, 140.5, 136.7, 128.1, 127.7, 124.5, 118.7, 115.9, 114.6, 101.6, 98.4, 77.6, 65.8, 57.2, 43.9, 37.3, 36.2, 34.8, 23.3, 8.0 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{24}H_{24}O_6Na$ [M+Na$^+$]: 431.1465; found 431.1458.

PMB ketal 23: To a stirred mixture of phenol **22** (10.9 mg, 26.7 µmol), PMBOH (33 µL, 0.27 mmol, 10 equiv.) and K_2CO_3 (18.5 mg, 0.133 mmol, 5.0 equiv.) in CH_3CN (1.0 mL) at 0 °C was added $PhI(CO_2CF_3)_2$ (12.1 mg, 28.0 µmol, 1.05 equiv.) and the reaction mixture was stirred at this temperature for 5 min. The reaction mixture was quenched with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with H_2O (5 mL) and brine (5 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc/hexanes, 1:4) to give pure PMB ketal **23** (12.6 mg, 23.1 µmol, 87%). **23**: $R_f = 0.34$ (silica gel, EtOAc:hexanes 1:4); IR ν_{max} (film): 2949m, 1742s, 1679m, 1633s, 1514m, 1443w, 1372m, 1301m, 1248s, 1173s, 1109m, 1022s, 821m, 731w cm^{-1}; ^{1}H NMR: ($CDCl_3$, 600 MHz) $\delta = 7.22$ (d, $J = 8.4$ Hz, 2 H), 7.00 – 6.95 (m, 2 H), 6.90 (s, 1 H), 6.87 (s, 1 H), 6.84 (d, $J = 9.0$ Hz, 2 H), 4.84 (s, 1 H), 4.58 – 4.54 (m, 2 H), 4.50 (d, $J = 10.8$ Hz, 1 H), 3.90 (td, $J^t = 12.0$ Hz, $J^d = 3.6$ Hz, 1 H), 3.79 (s, 3 H), 3.40 (s, 3 H), 3.19 (d, $J = 16.8$ Hz, 1 H), 3.13 (d, $J = 16.8$ Hz, 1 H), 3.03 (td, $J^t = 13.2$ Hz, $J^d = 4.8$ Hz, 1 H), 2.79 (d, $J = 14.4$ Hz, 1 H), 2.52 – 2.47 (m, 1 H), 2.38 – 2.32 (m, 2 H), 2.31 – 2.24 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.52 (s, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) $\delta = 185.0$, 168.9, 161.6, 159.2, 142.9, 138.1, 137.0, 136.4, 133.8, 129.9, 129.4, 128.9, 125.5, 124.4, 120.3, 113.7, 103.0, 91.8, 90.9, 75.5, 65.6, 65.2, 58.0, 55.3, 44.3, 38.2, 34.1, 33.7, 23.9, 7.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{32}H_{33}O_8$ [M+H$^+$]: 545.2175; found 545.2173.



23

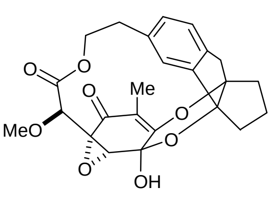
Hemiketal 24: To a stirred solution of PMB ketal **23** (12.6 mg, 23.1 µmol) in CH_2Cl_2/H_2O (10:1, 1.1 mL) at 25 °C was added DDQ (7.9 mg, 35 µmol, 1.5 equiv.) and



24

the reaction mixture was stirred at this temperature for 16 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution (3 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with saturated aqueous $Na_2S_2O_3$ solution (2 × 5 mL), H_2O (10 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to flash column chromatography (EtOAc:hexanes, 1:2) to give pure hemiketal **24** (9.4 mg, 22 μmol, 96%). **24**: $R_f = 0.18$ (silica gel, EtOAc:hexanes 1:2); IR ν_{max} (film): 3350bm, 2924s, 1743s, 1633s, 1373w, 1297m, 1261m, 1191s, 1108s, 1004s, 801m cm^{-1}; ^{1}H NMR: ($CDCl_3$, 600 MHz) δ = 6.99 – 6.96 (m, 2 H), 6.87 (s, 1 H), 6.83 (s, 1 H), 4.81 (s, 1 H), 4.57 (ddd, *J* = 10.8, 5.4, 2.4 Hz, 1 H), 3.89 (ddd, *J* = 12.6, 11.7, 3.6 Hz, 1 H), 3.44 (s, 3 H), 3.26 (bs, 1 H), 3.22 (d, *J* = 17.4 Hz, 1 H), 3.13 (d, *J* = 17.4 Hz, 1 H), 3.02 (ddd, *J* = 18.0, 14.4, 5.4 Hz, 1 H), 2.79 (d, *J* = 13.8 Hz, 1 H), 2.44 – 2.39 (m, 2 H), 2.30 – 2.24 (m, 2 H), 1.92 – 1.88 (m, 2 H), 1.54 (s, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 184.8, 168.8, 162.0, 142.5, 138.4, 137.0, 136.5, 133.4, 129.0, 125.5, 124.2, 119.5, 103.4, 90.9, 88.7, 75.4, 65.3, 58.2, 44.1, 38.5, 34.5, 34.1, 24.0, 7.4 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{24}H_{25}O_7$ [M+H$^+$]: 425.1595; found 425.1599.

Epoxide 3: To hemiketal **24** (5.4 mg, 13 μmol) at 25 ºC was added TBHP (55 mM in CH_2Cl_2, 1.13 mL, 62 μmol, 5.0 equiv.) and DBU (0.4 μL, 3 μmol, 0.2 equiv.) sequentially and the reaction mixture was heated to 40 ºC and stirred at this temperature in a sealed tube for 24 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution (1 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was washed with H_2O (5 mL) and brine (5 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue so obtained was subjected to preparative TLC (EtOAc:hexanes, 1:2, twice) to give pure epoxide **3** (3.4 mg, 7.7 μmol, 60%). **3**: $R_f = 0.26$ (silica gel, EtOAc:hexanes 1:2); mp. 218 – 219 ºC (acetone/hexanes); IR ν_{max} (film): 3350bm, 2924s, 2853m, 1741s, 1643m, 1463m, 1379m, 1260s, 1177s, 1105s, 1055s cm^{-1}; ^{1}H NMR: ($CDCl_3$, 600 MHz) δ = 7.07 – 7.04 (m, 2 H), 6.96 (d, *J* = 7.2 Hz, 1 H), 4.61 (ddd, *J* = 10.8, 4.8, 2.4 Hz, 1 H), 4.45 (s, 1 H), 4.05 (s, 1



3

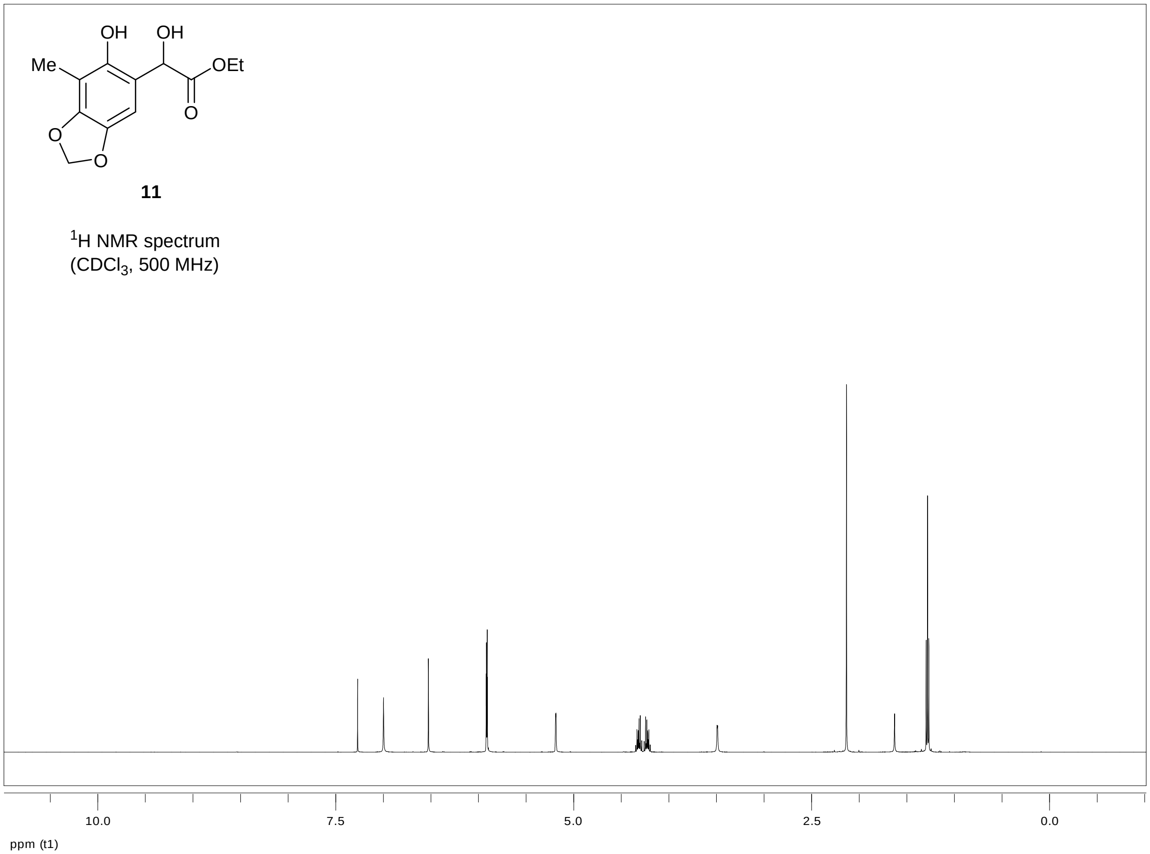
H), 3.70 – 3.65 (m, 1 H), 3.51 (s, 3 H), 3.19 – 3.13 (m, 3 H), 3.02 (td, J^t = 13.2 Hz, J^d = 4.8 Hz,1 H), 2.83 (d, J = 13.8 Hz, 1 H), 2.61 – 2.55 (m, 1 H), 2.40 – 2.29 (m, 3 H), 2.06 – 2.00 (m, 1 H), 1.96 – 1.91 (m, 1 H), 1.32 (s, 3 H) ppm; ^{13}C NMR: ($CDCl_3$, 150 MHz) δ = 189.6, 167.5, 161.8, 143.7, 137.2, 136.6, 128.5, 125.5, 125.3, 116.7, 105.0, 96.1, 89.5, 76.5, 66.1, 60.4, 60.0, 59.1, 44.9, 37.1, 34.2, 32.2, 23.8, 7.1 ppm; HRMS (ESI TOF): *m/z* calcd for $C_{24}H_{25}O_8$ [M+H$^+$]: 441.1544; found 441.1555.

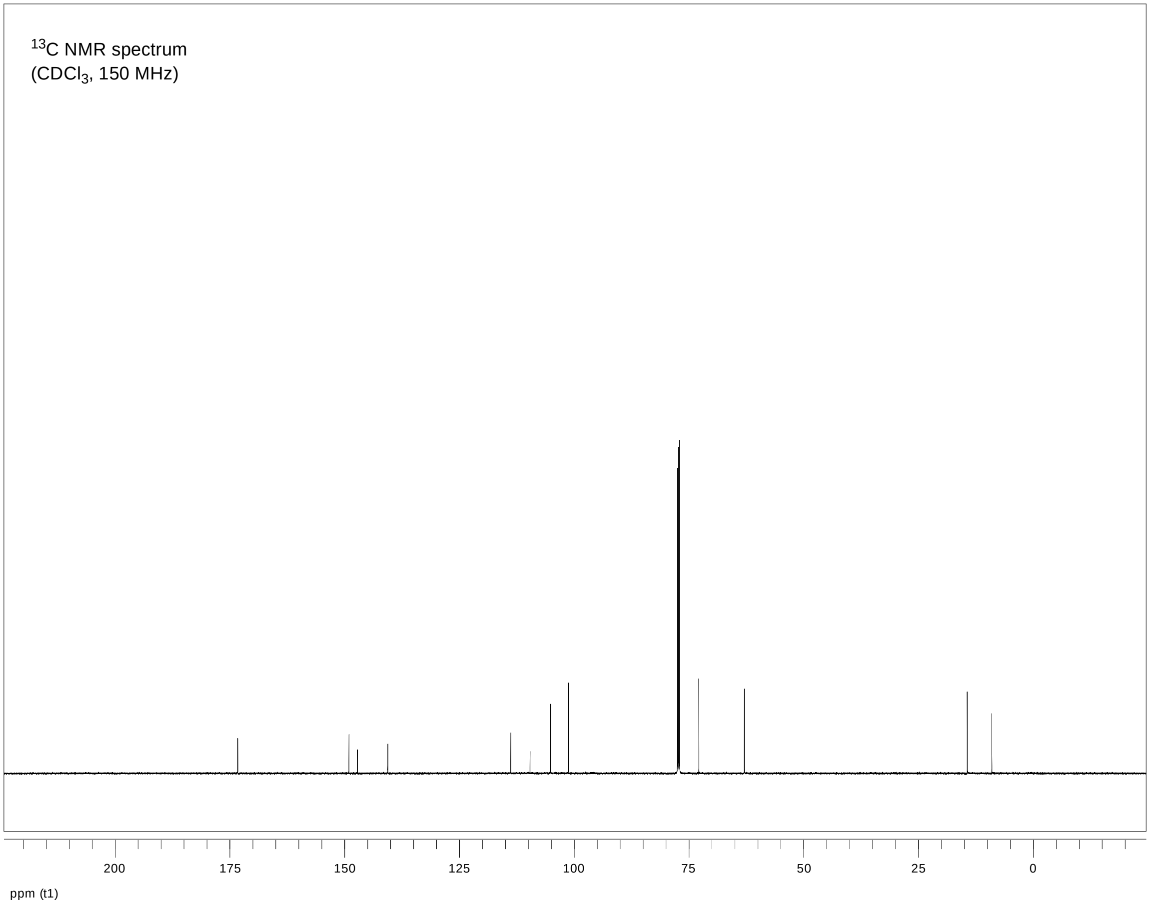
References:

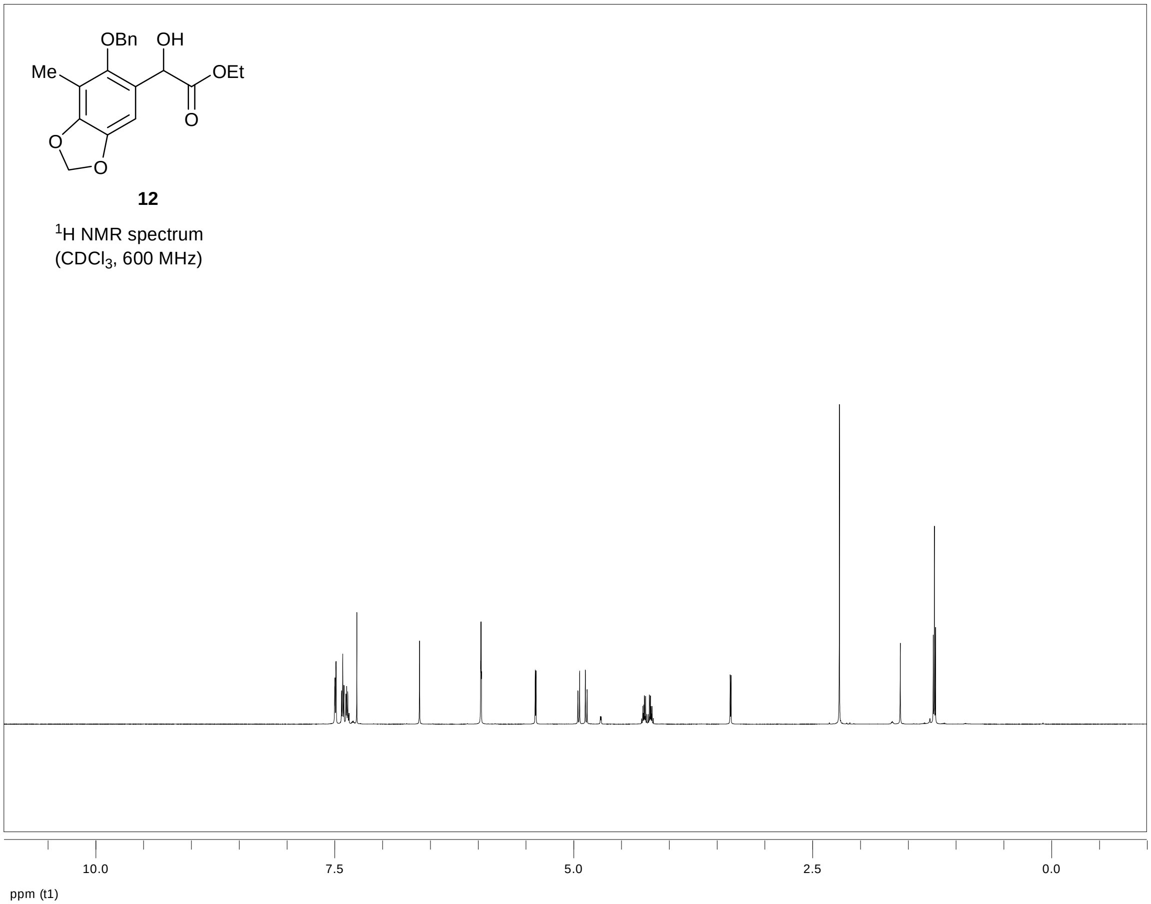
[1] X. Chen, J. Chen, M. De Paolis, J. Zhu, *J. Org. Chem.* **2005**, *70*, 4397.

[2] S. Shankar, G. Vaidyanathan, D. Affleck, P. C. Welsh, M. R. Zalutsky, *Bioconjugate Chem.* **2003**, *14*, 331.

II) ^{1}H and ^{13}C NMR spectra of compounds:

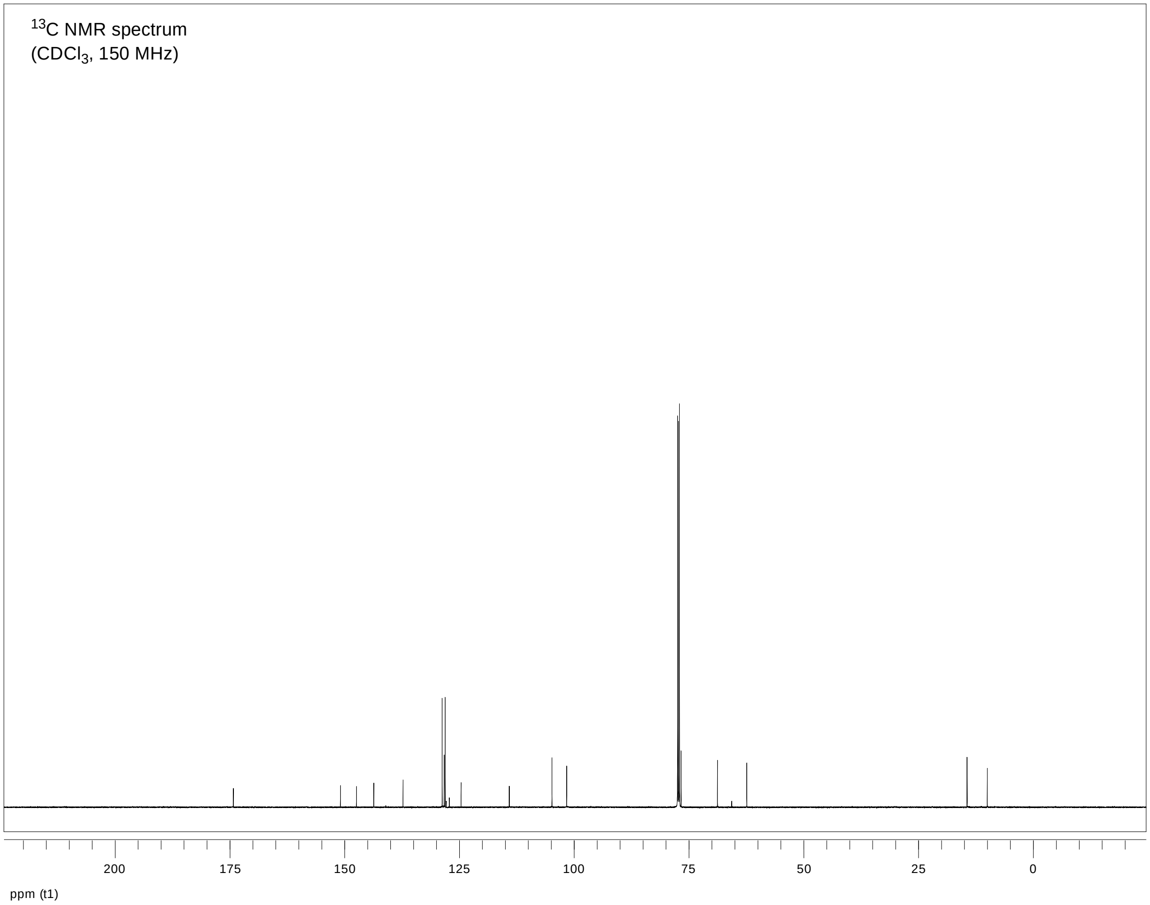




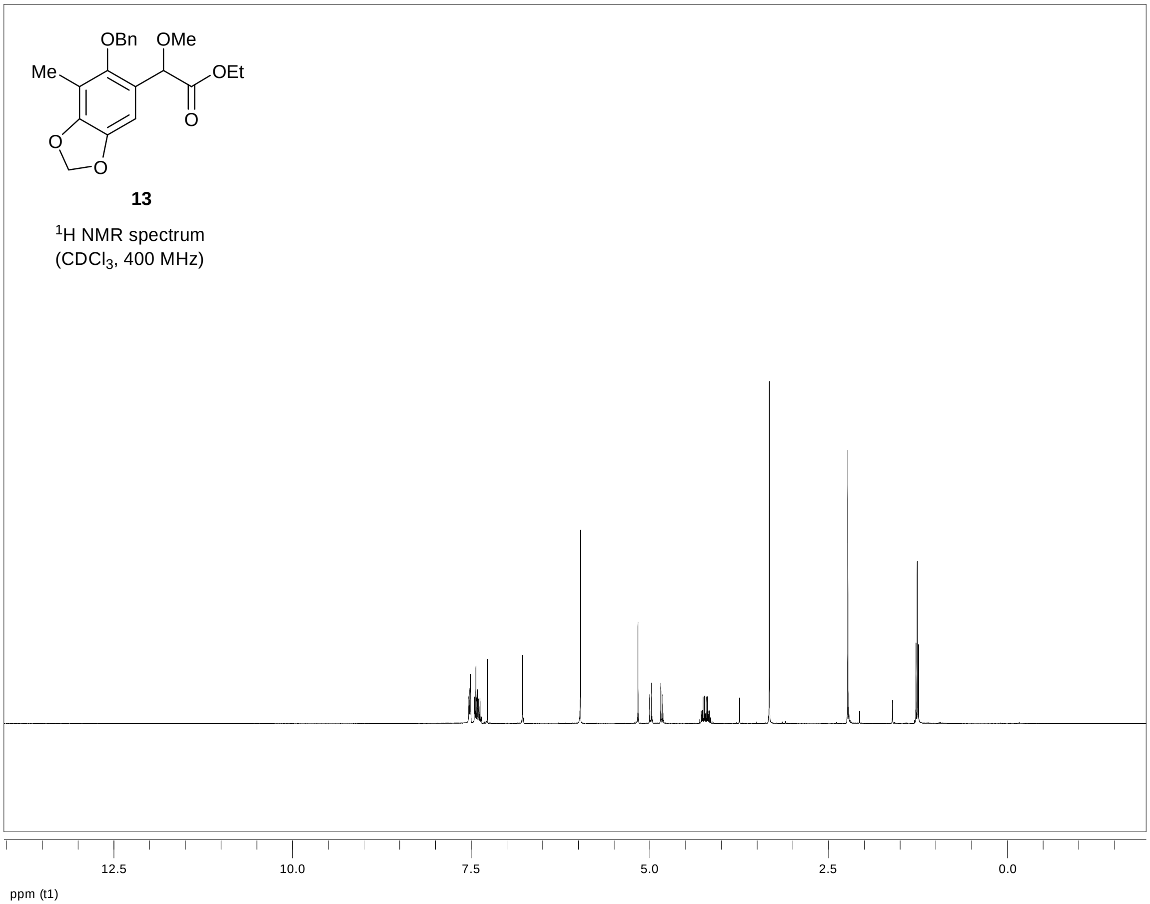


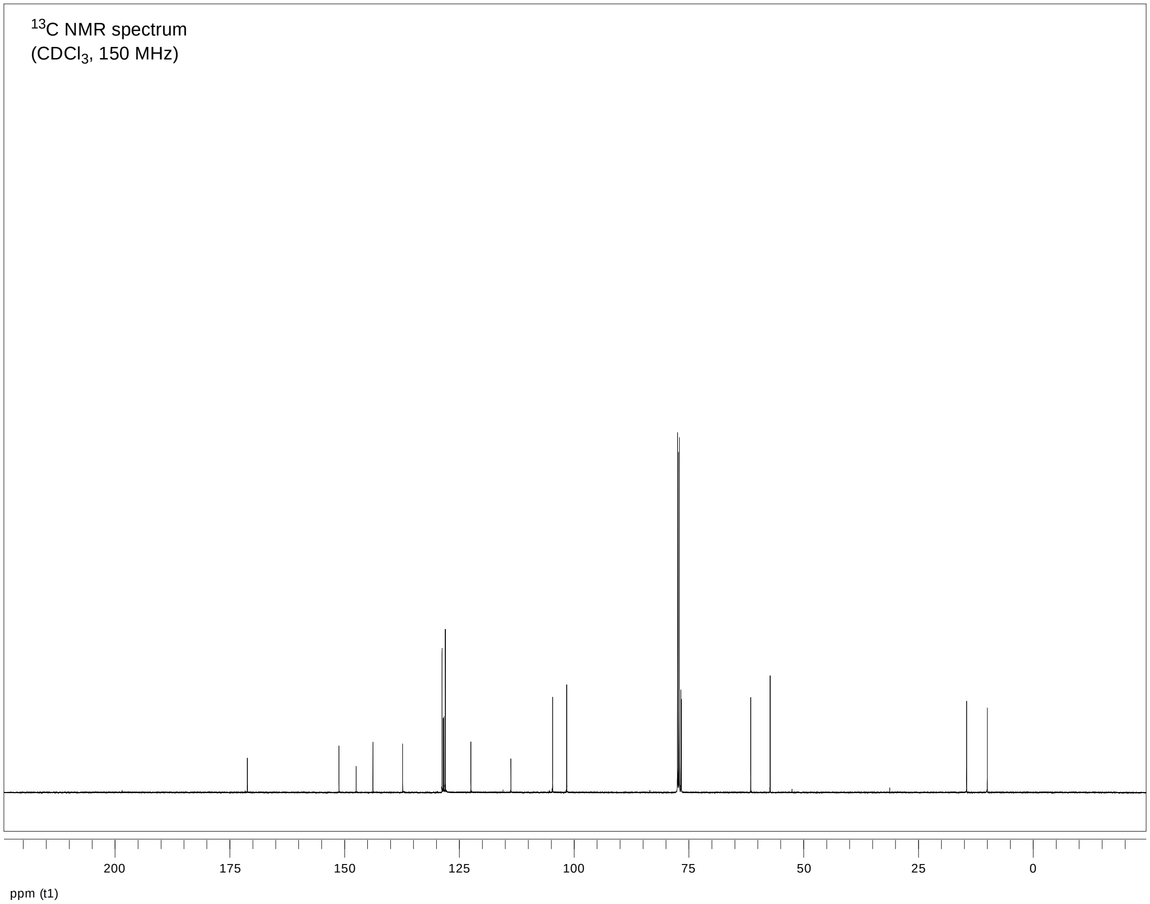
12

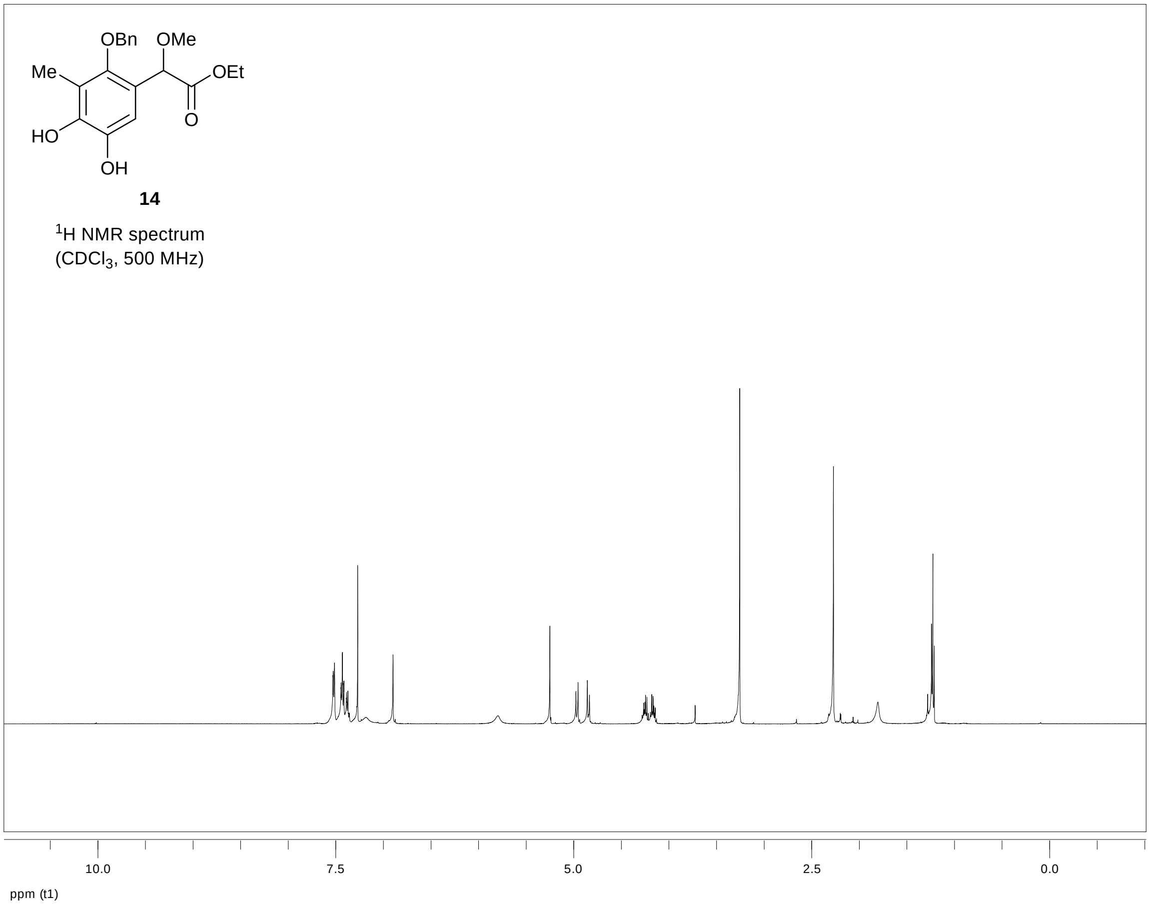
^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

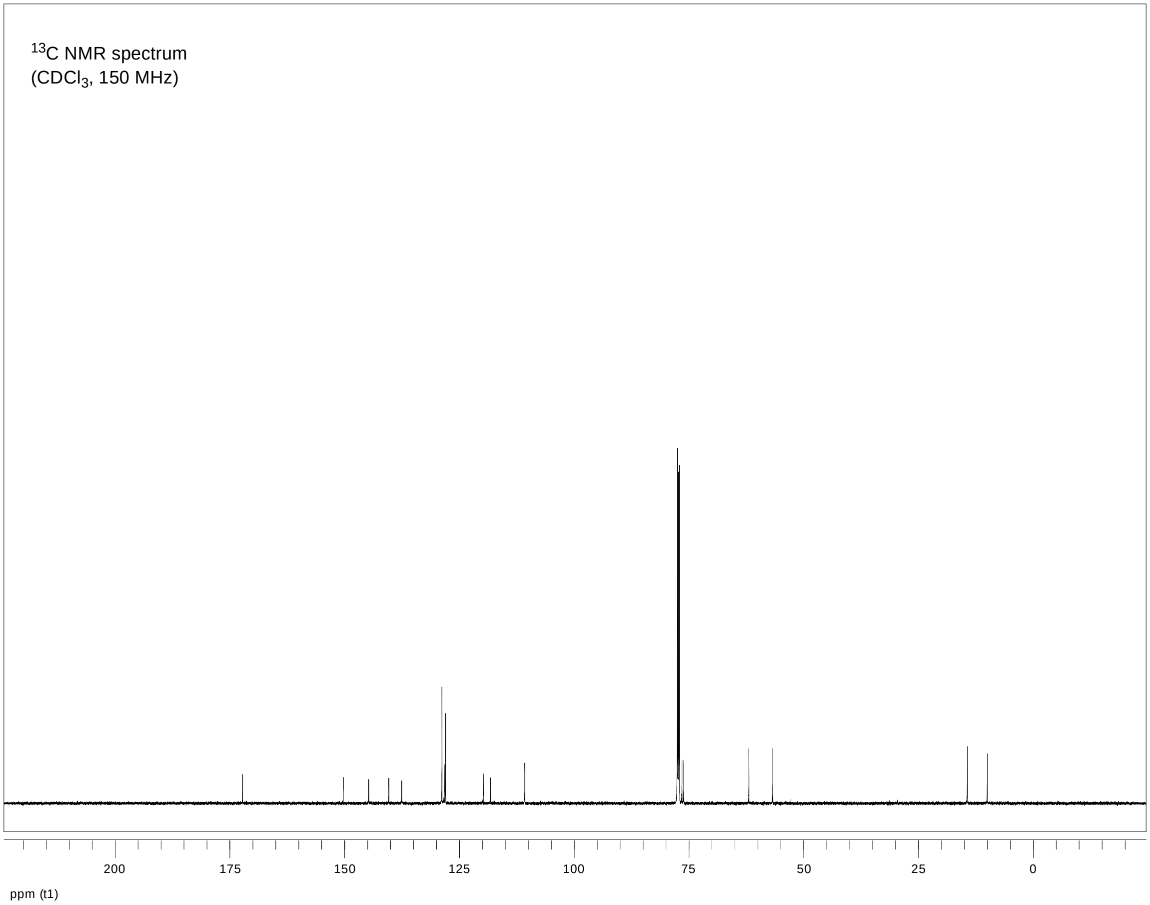

OBn
OMe
Me
OEt
O
O
O
13
^{1}H NMR spectrum
(CDCl$_3$, 400 MHz)
12.5
10.0
7.5
5.0
2.5
0.0
ppm (t1)


^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)

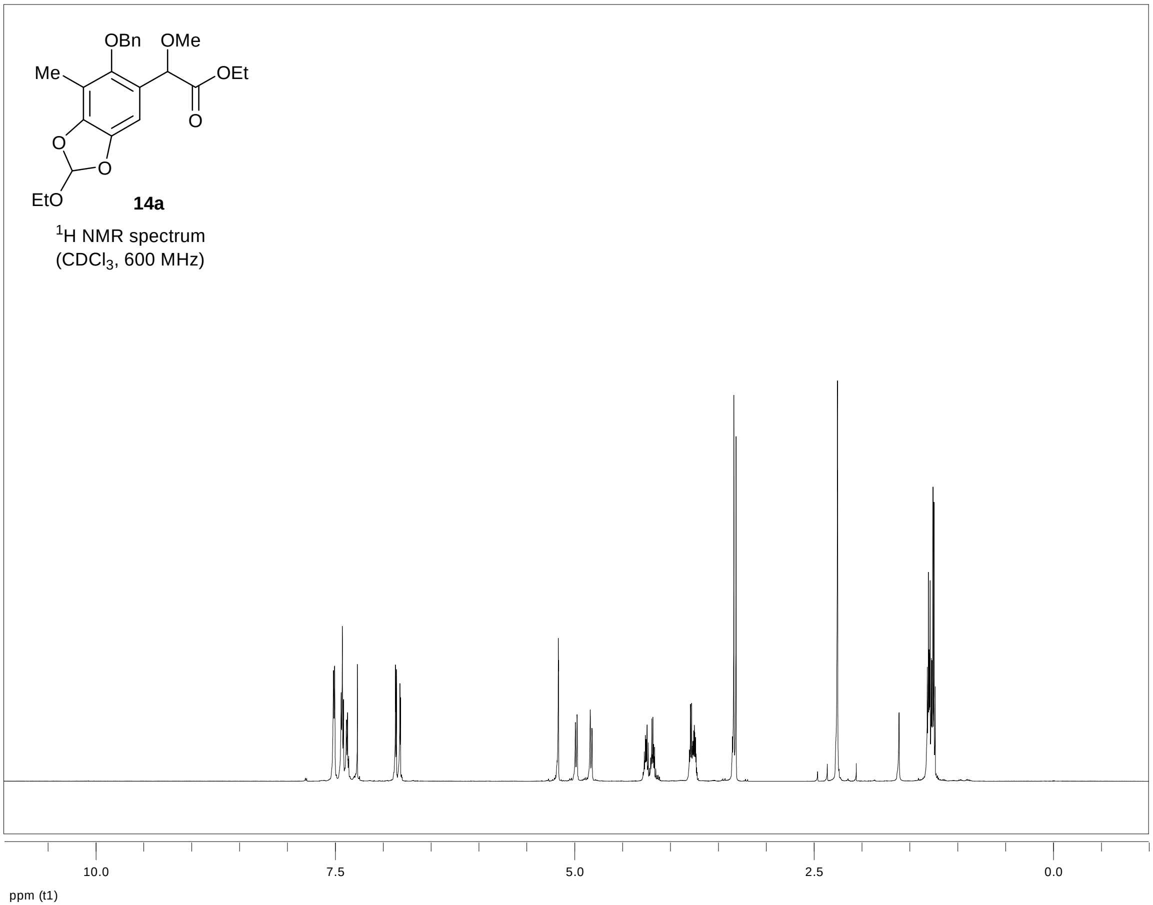


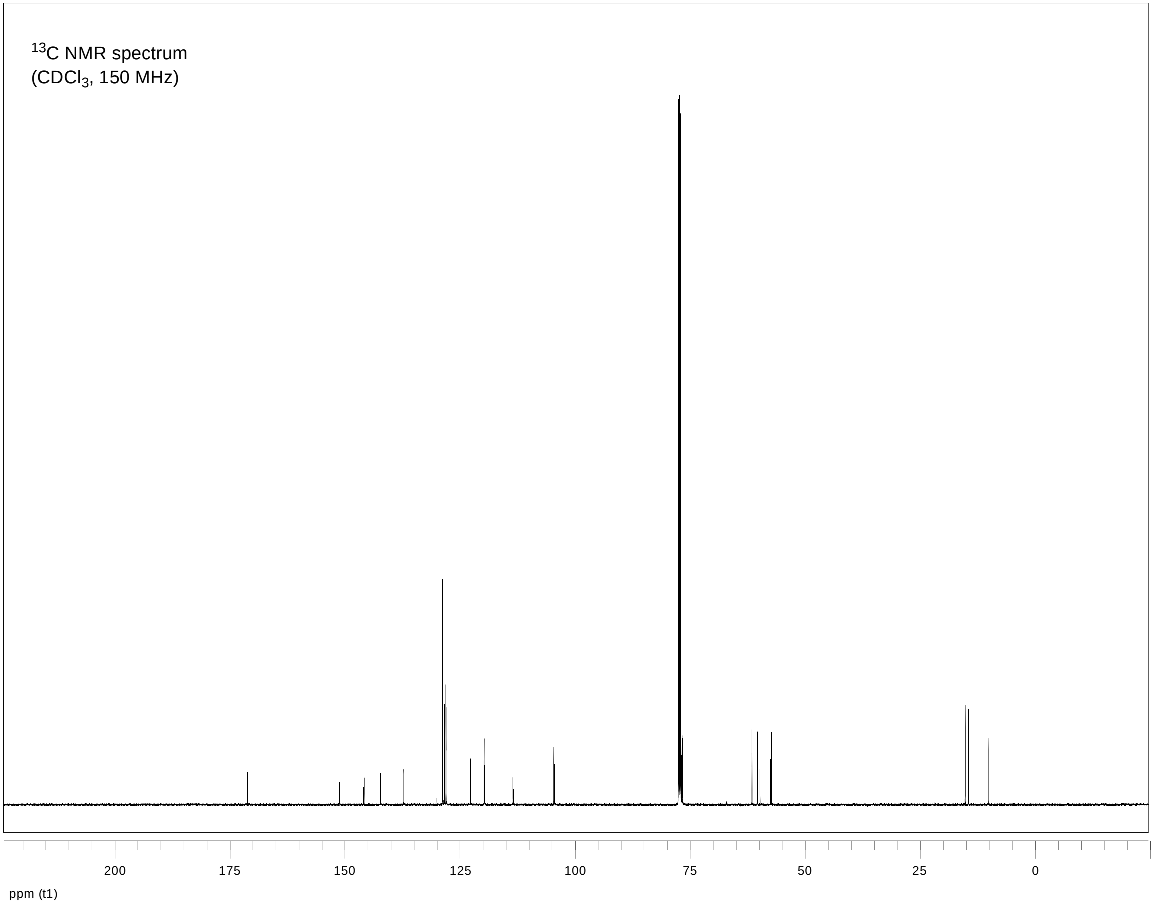
14

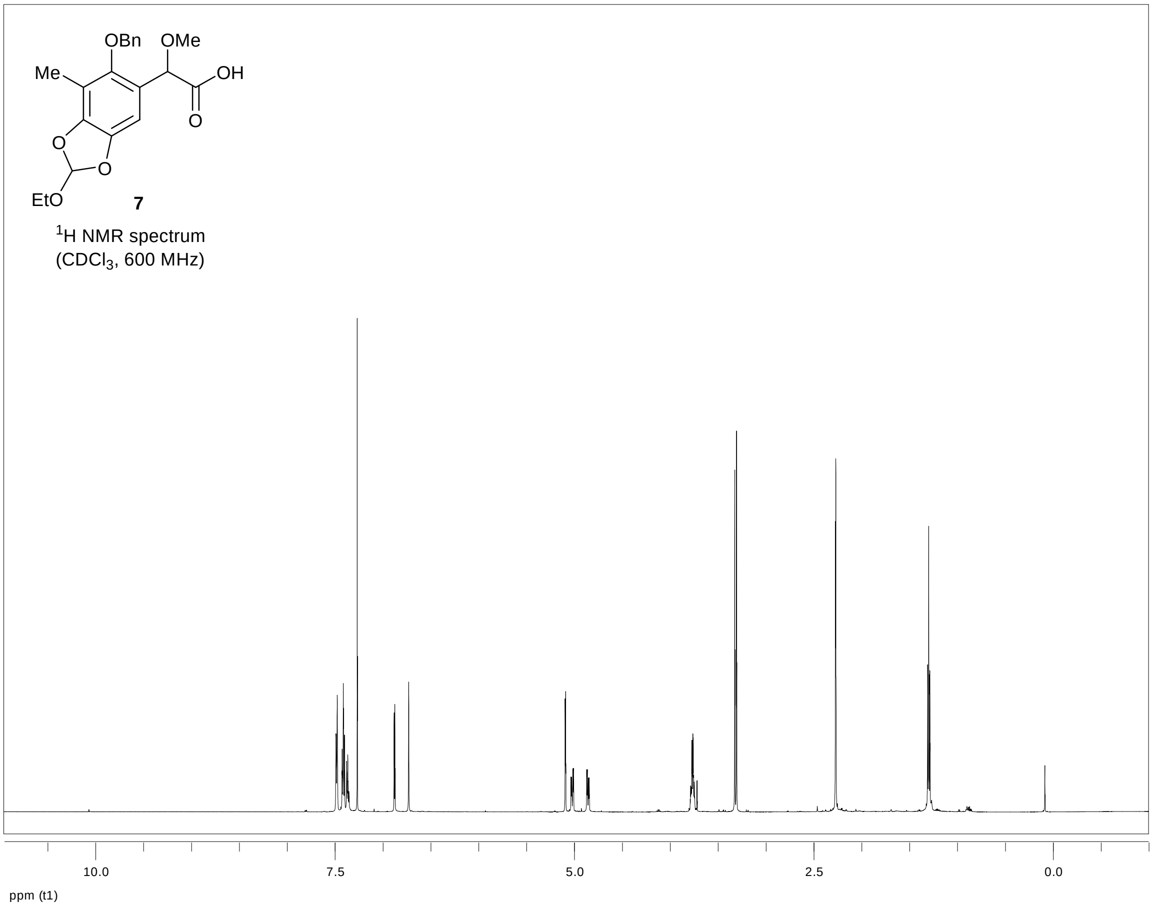
^{1}H NMR spectrum
(CDCl$_3$, 500 MHz)



^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)

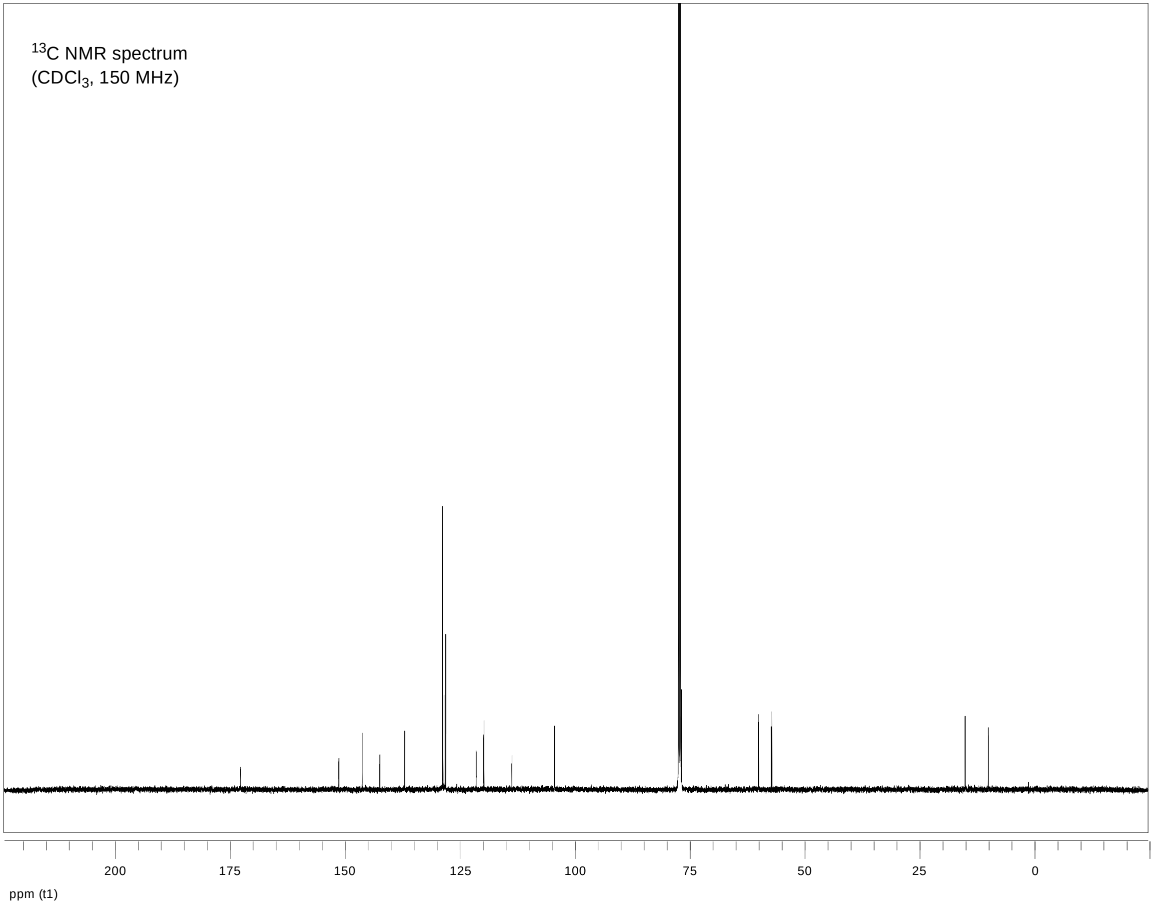

OBn
OMe
Me
OEt
O
O
O
EtO
14a
1H NMR spectrum
(CDCl3, 600 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)


13C NMR spectrum
(CDCl3, 150 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)

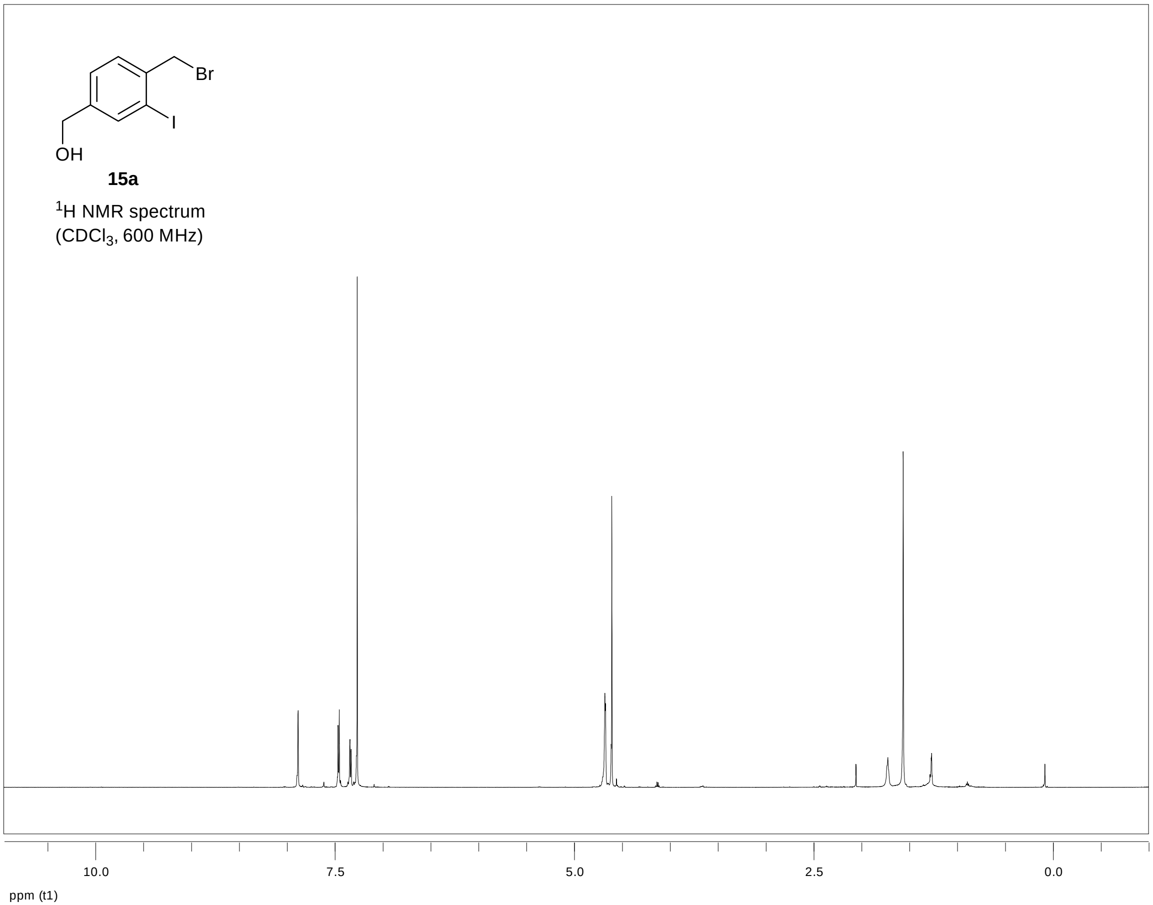


7

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

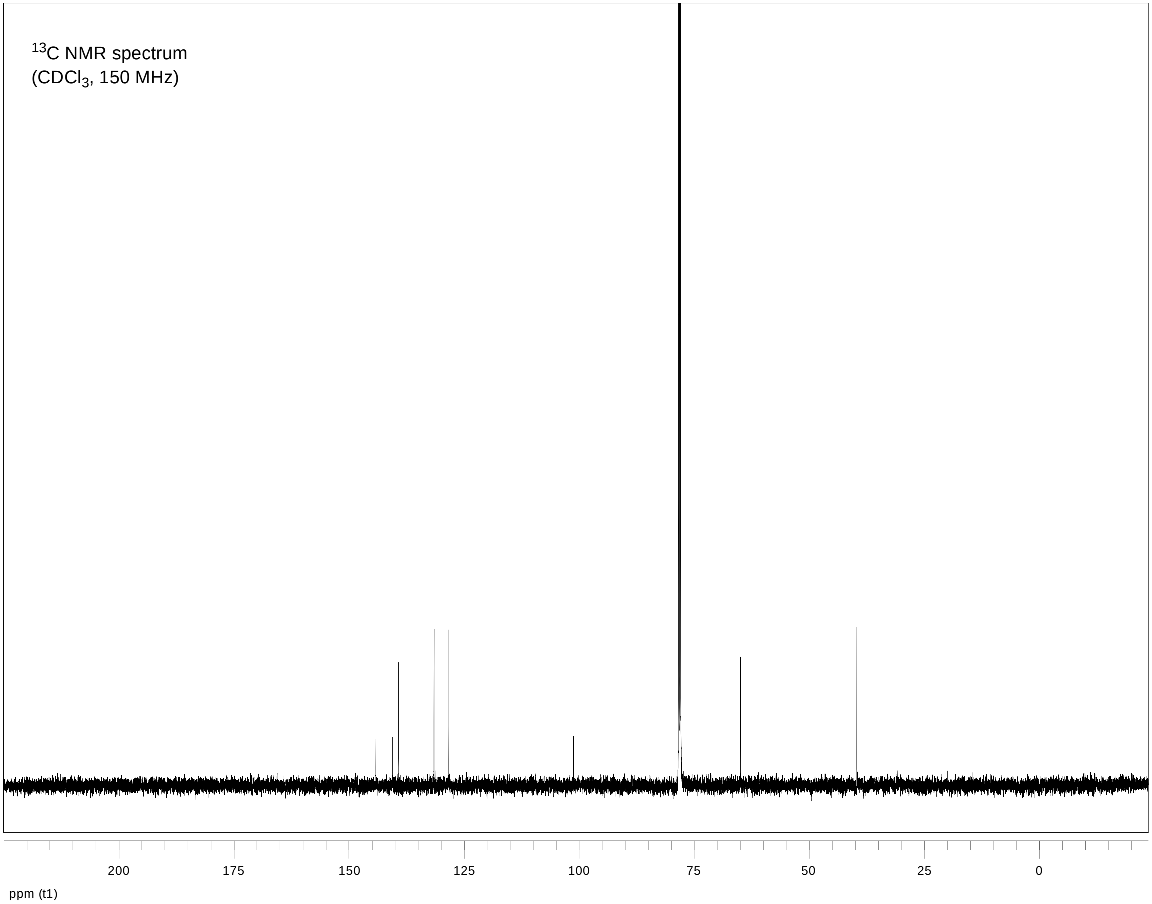


^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

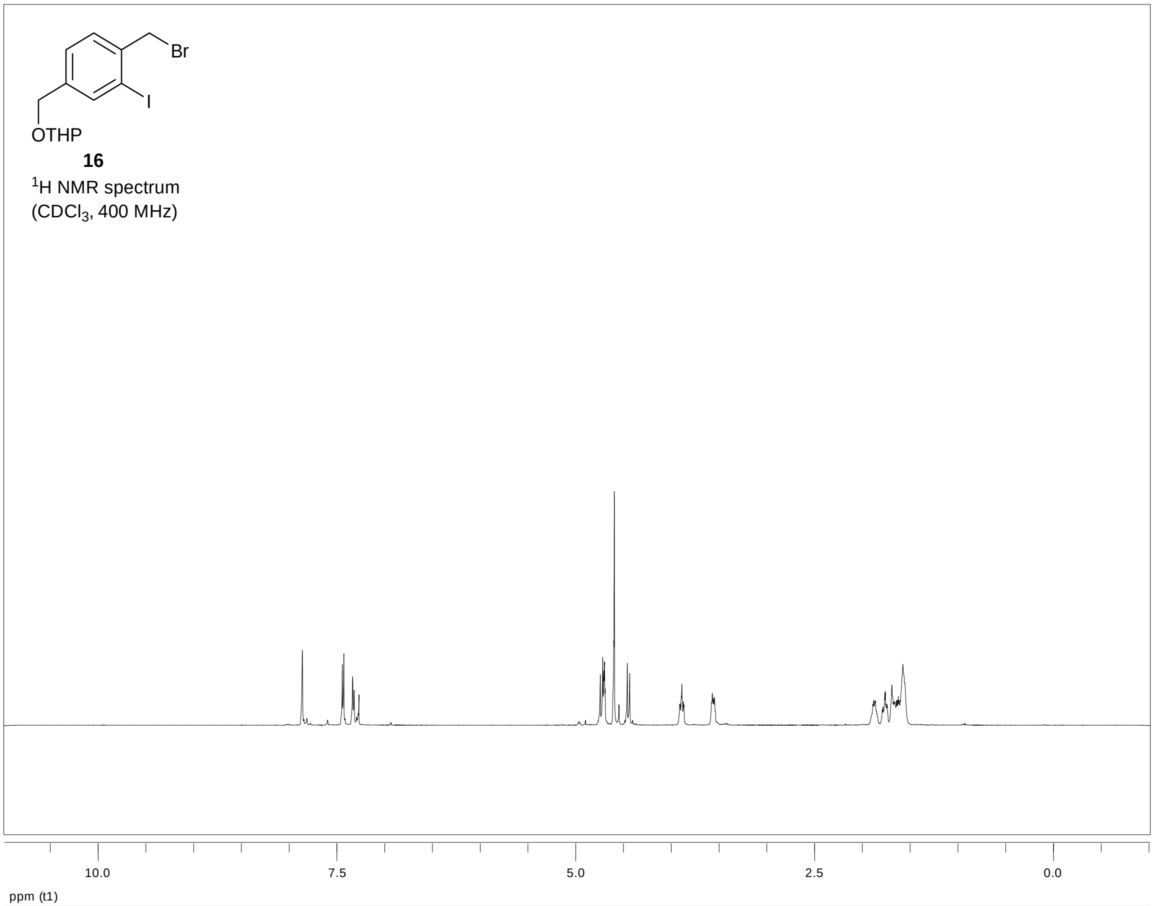


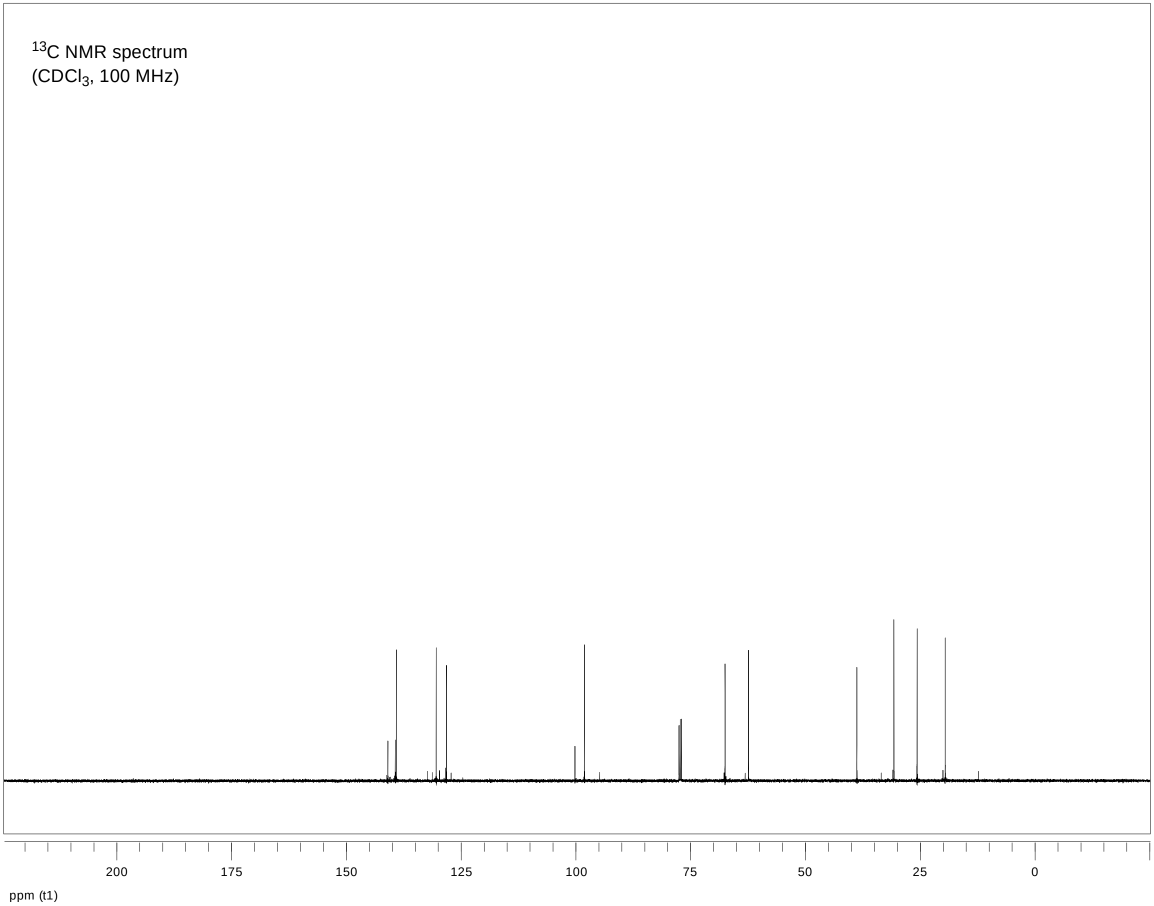
15a

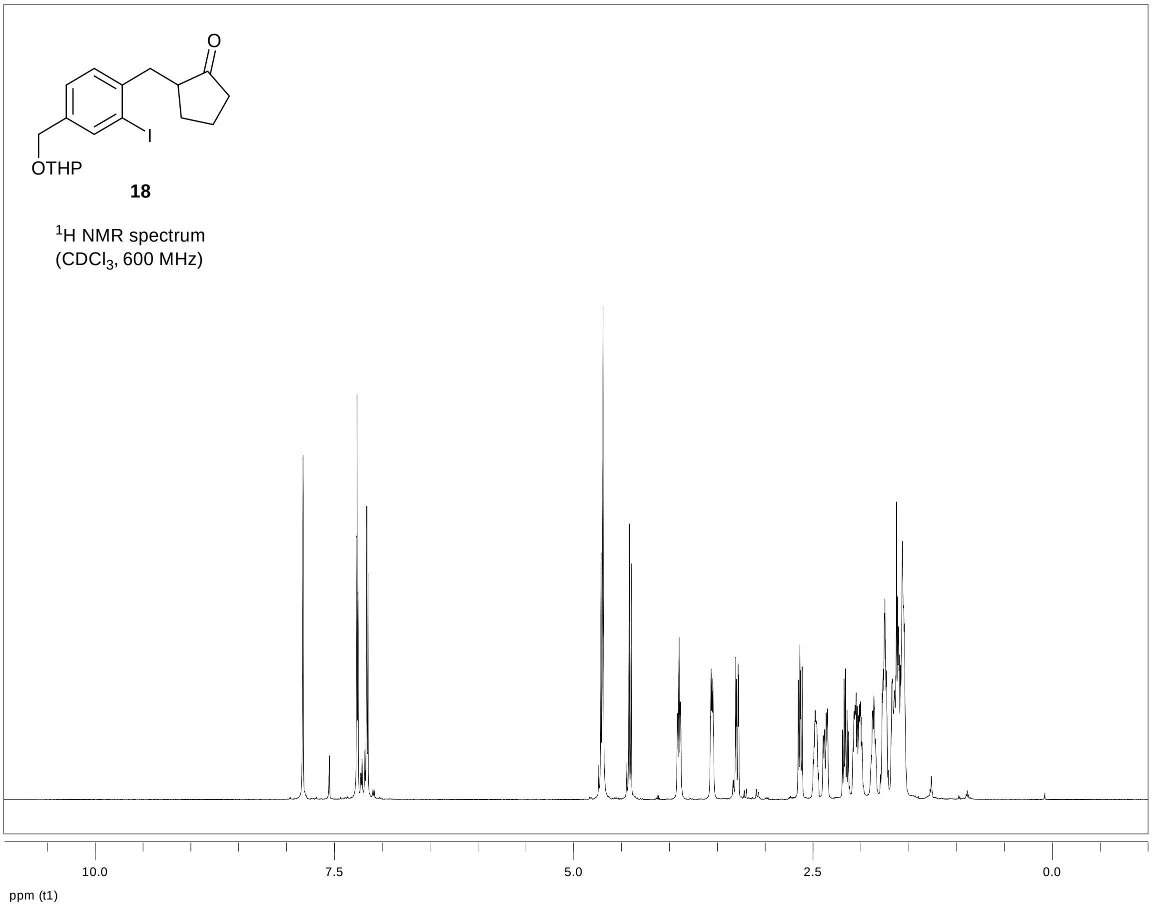
^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

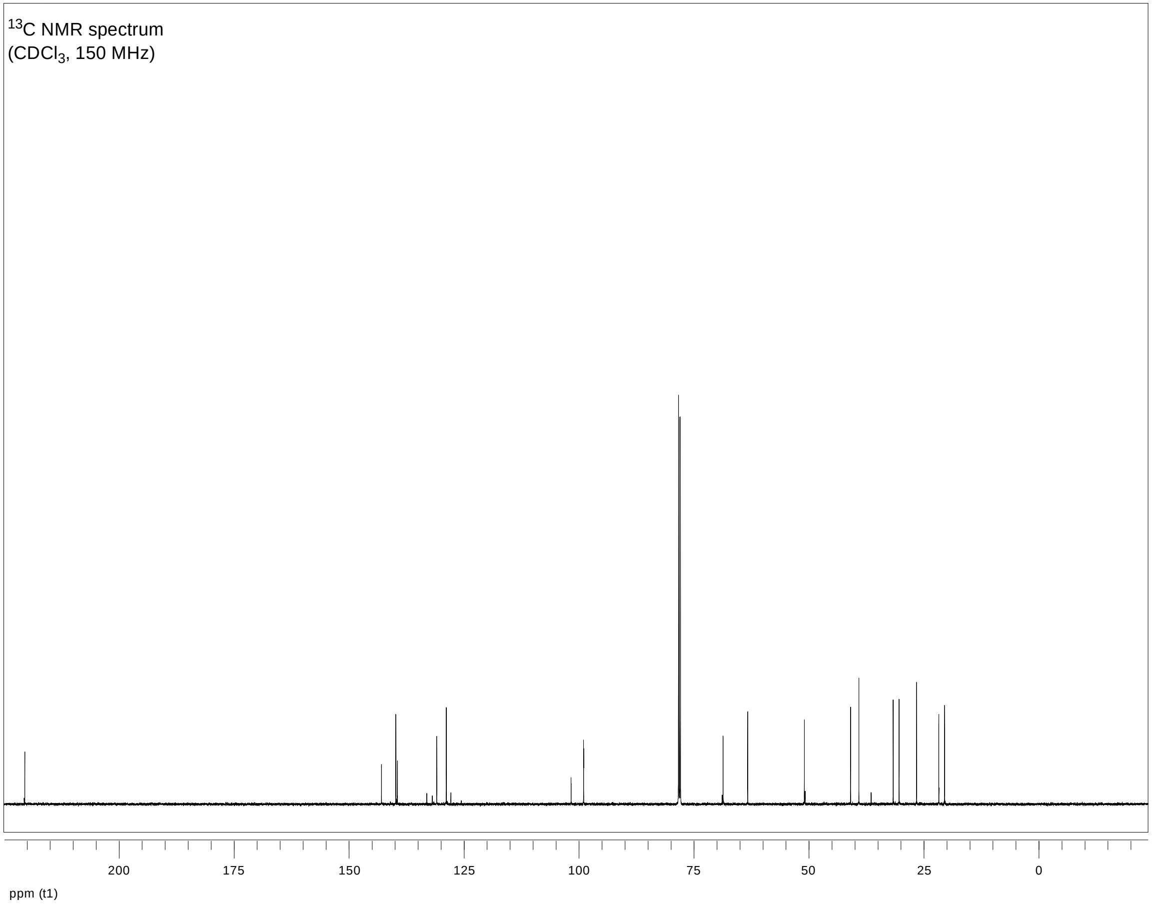


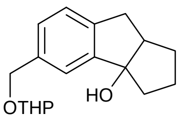
^{13}C NMR spectrum
($CDCl_3$, 150 MHz)


Br
I
OTHP
16
^{1}H NMR spectrum
(CDCl$_3$, 400 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)

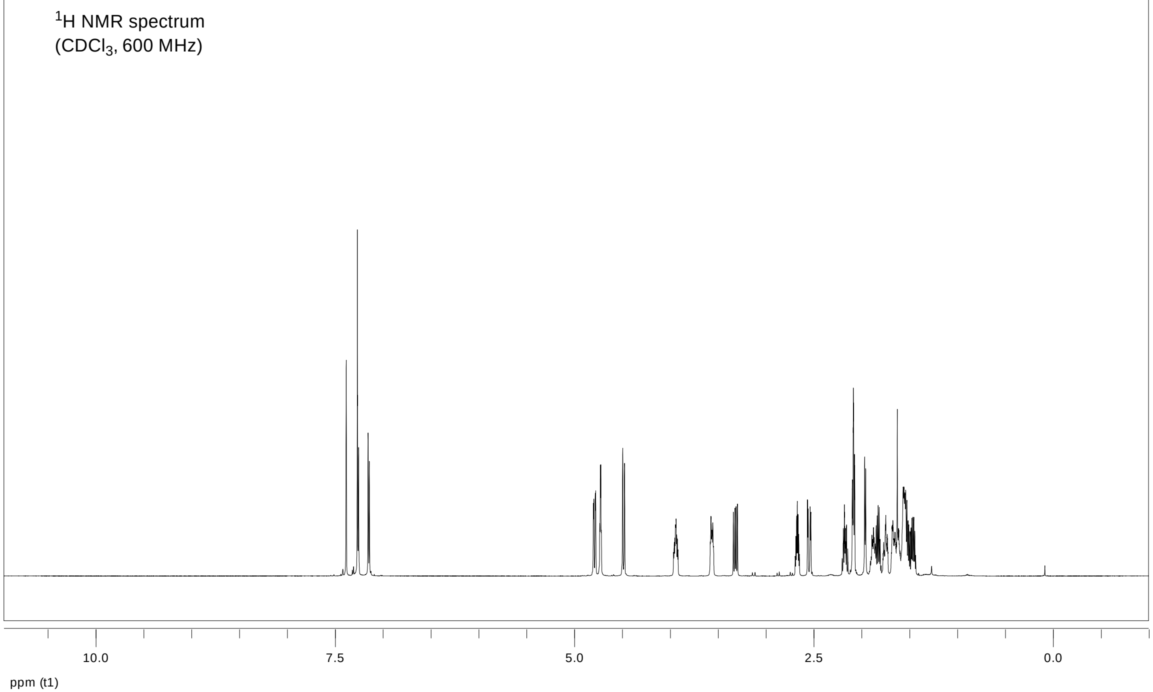

^{13}C NMR spectrum
(CDCl$_3$, 100 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)


O
I
OTHP
18
^{1}H NMR spectrum
(CDCl$_3$, 600 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)

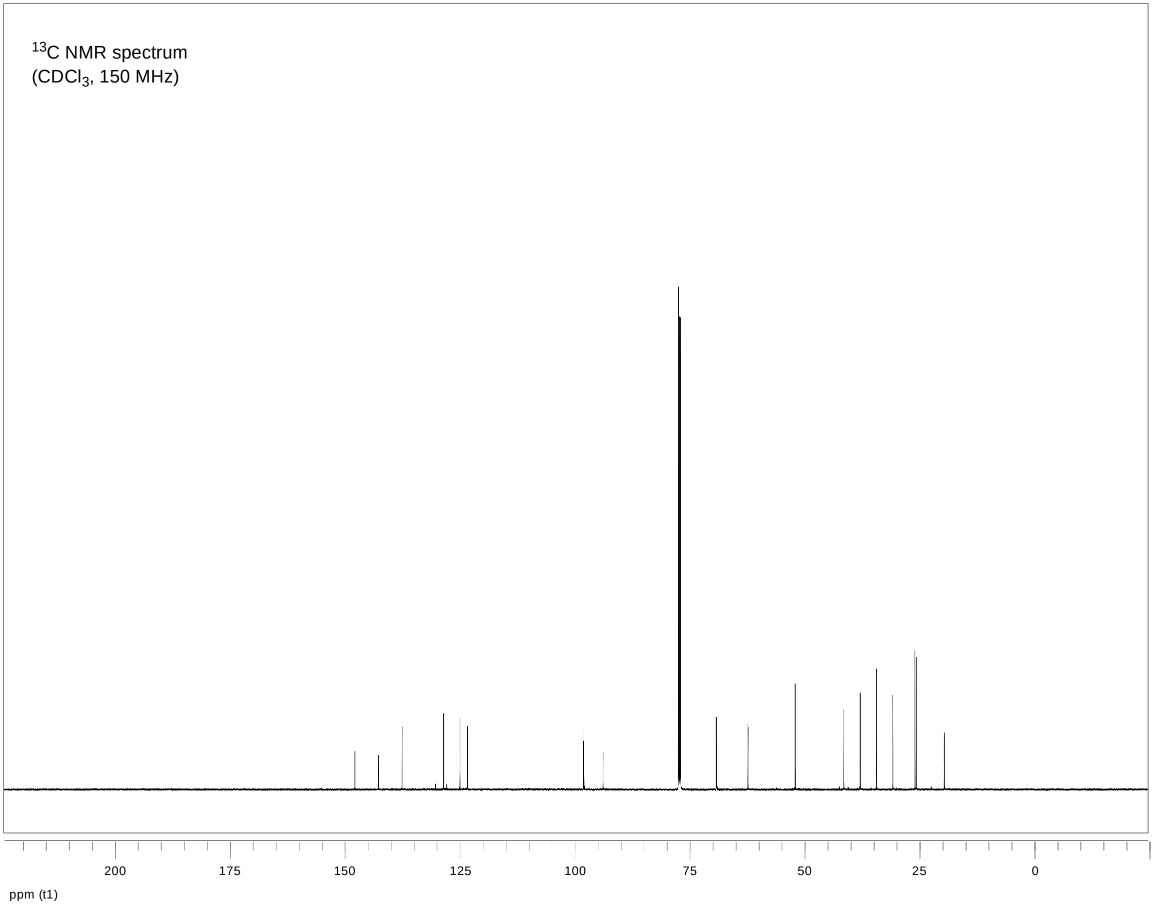

^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)



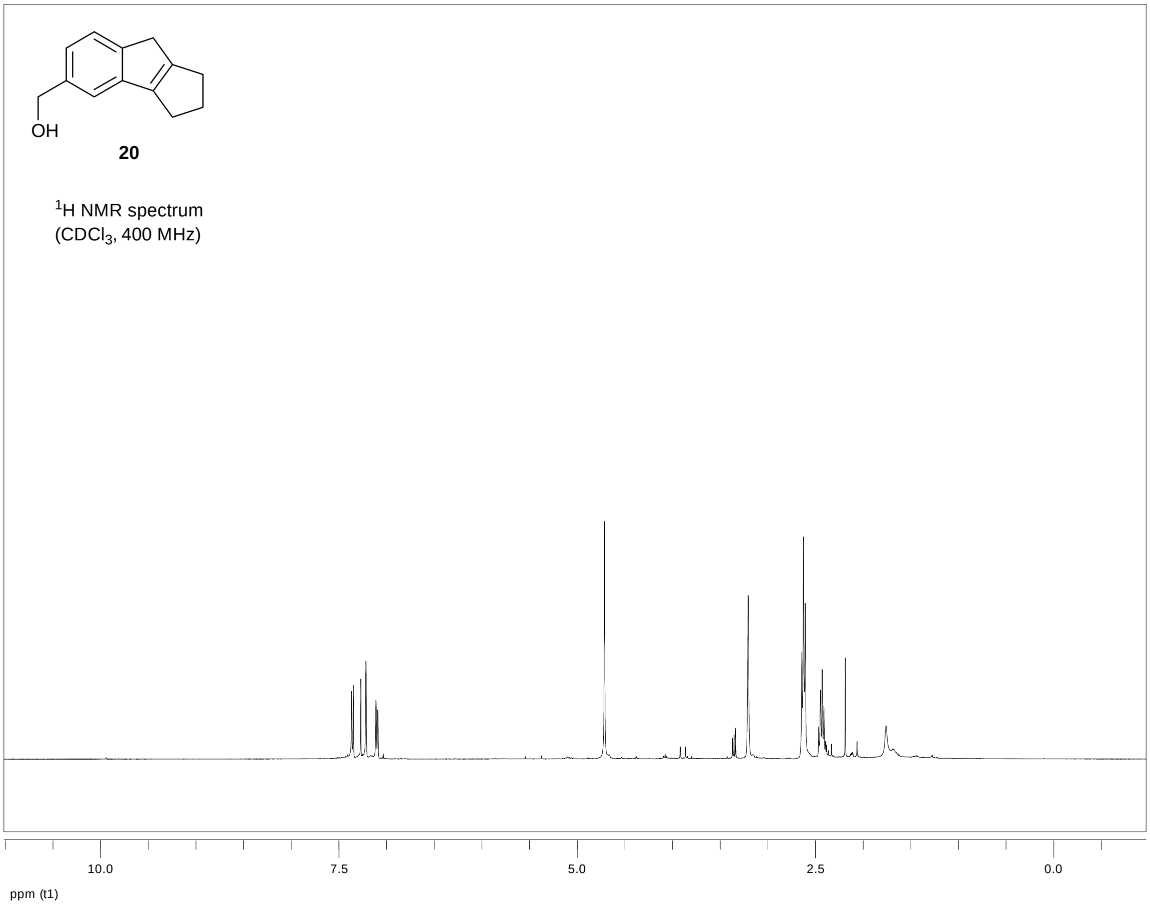
19



^{1}H NMR spectrum
($CDCl_3$, 600 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)

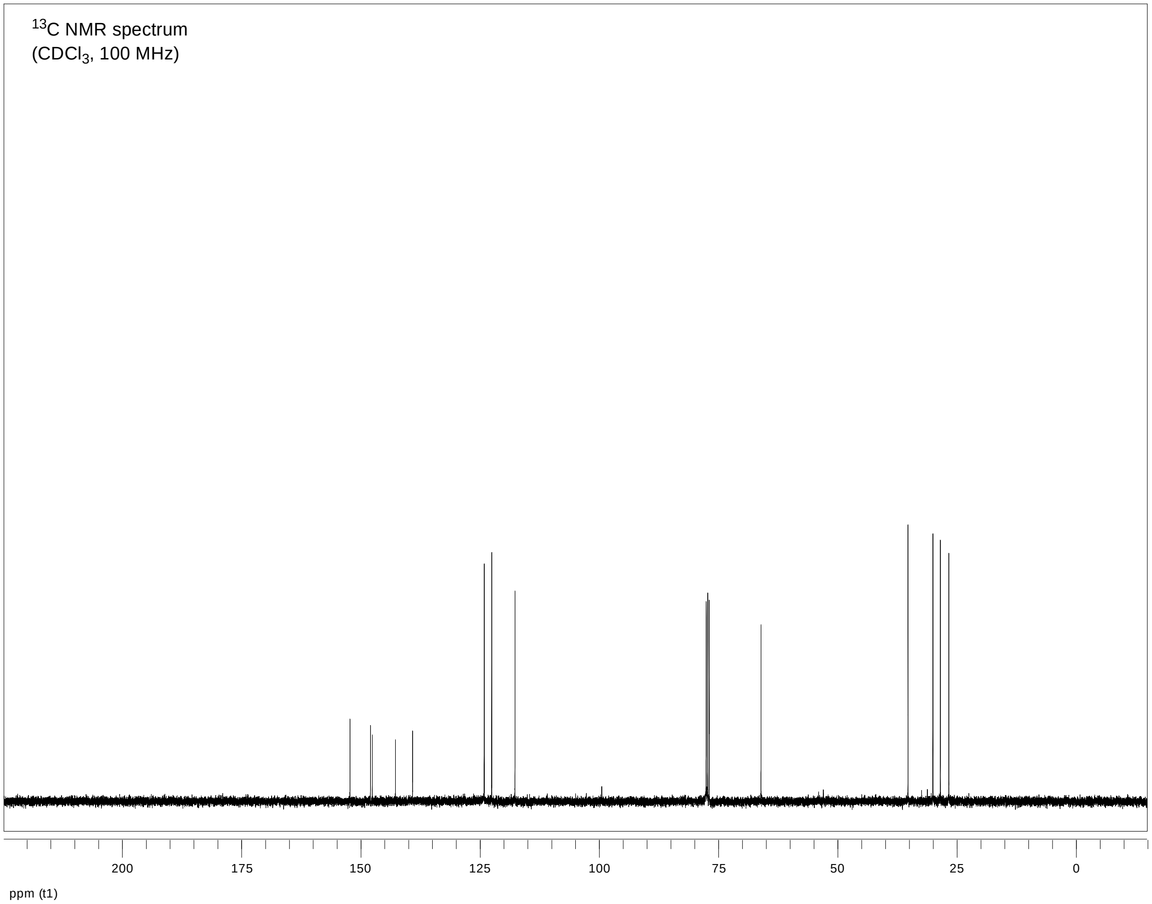


^{13}C NMR spectrum
($CDCl_3$, 150 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)

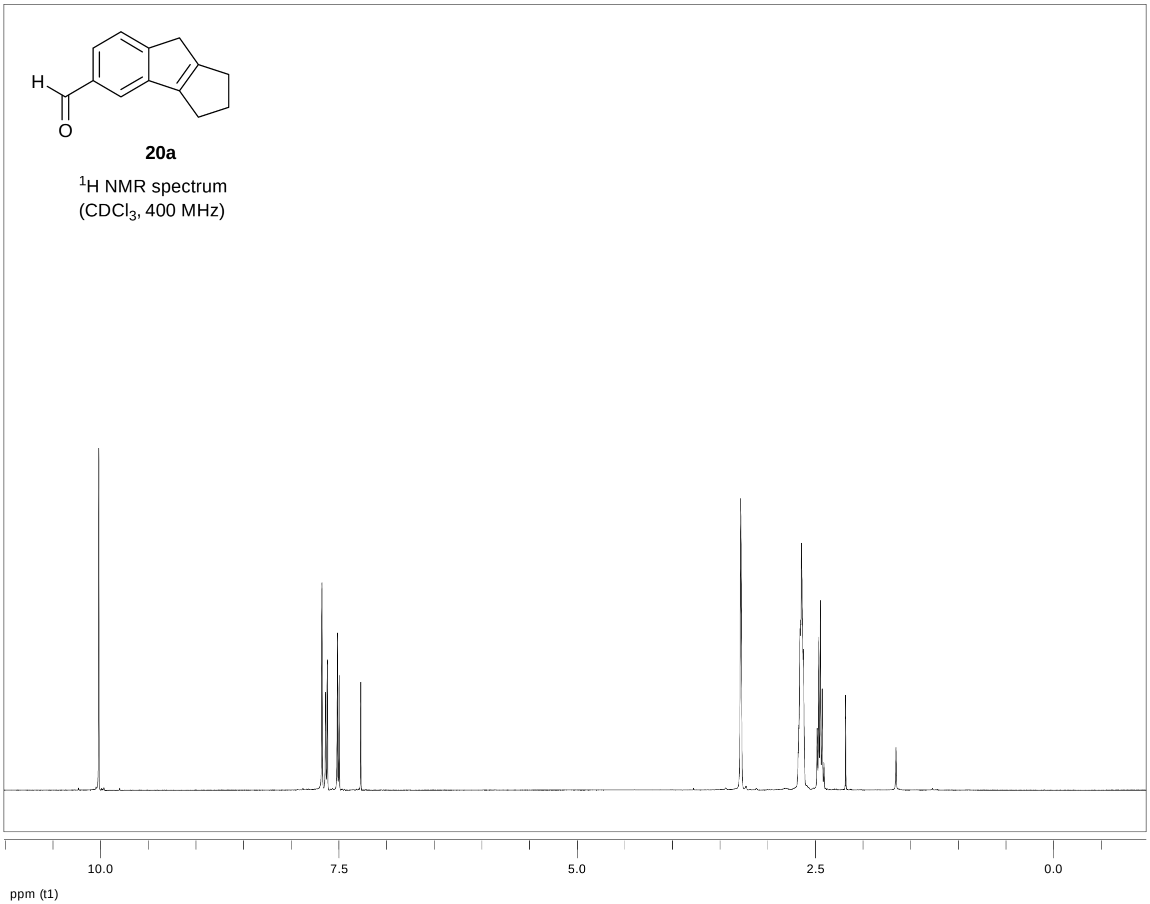


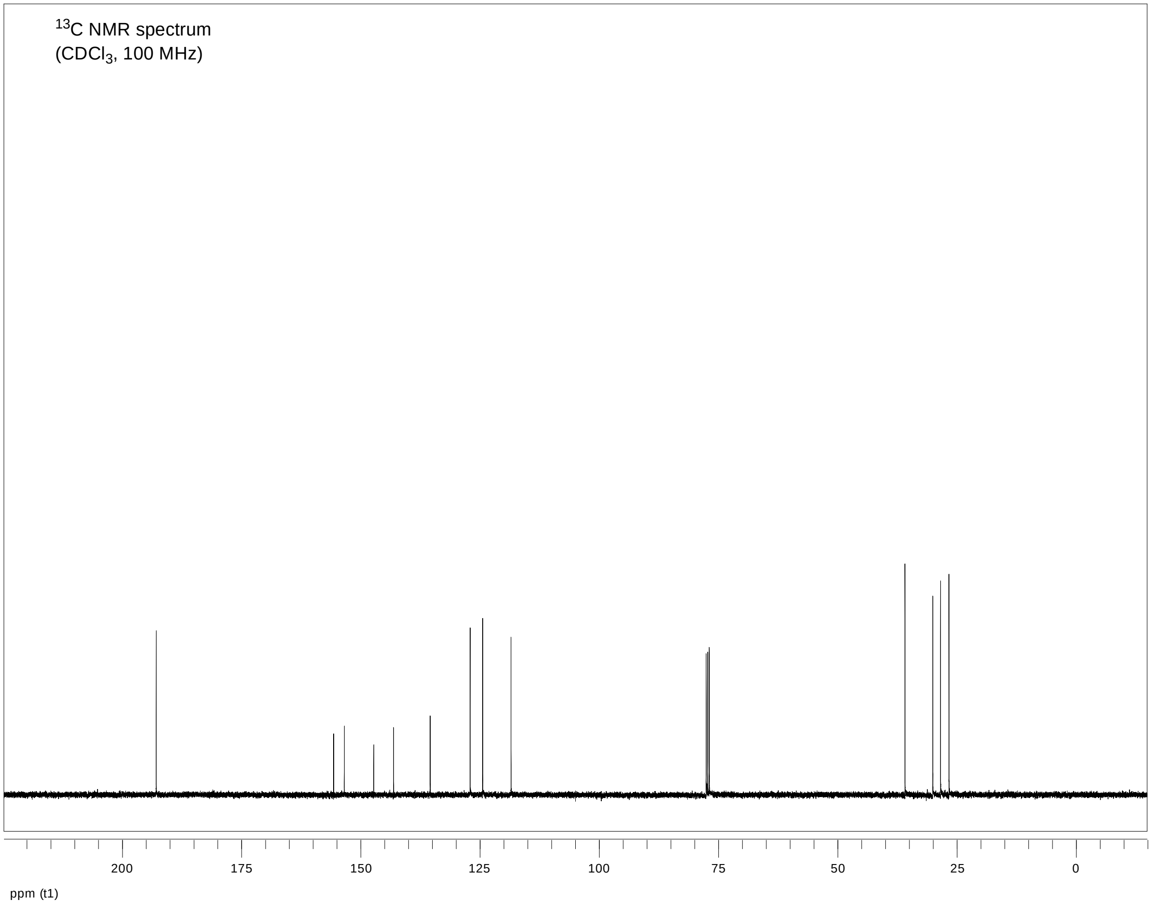
20

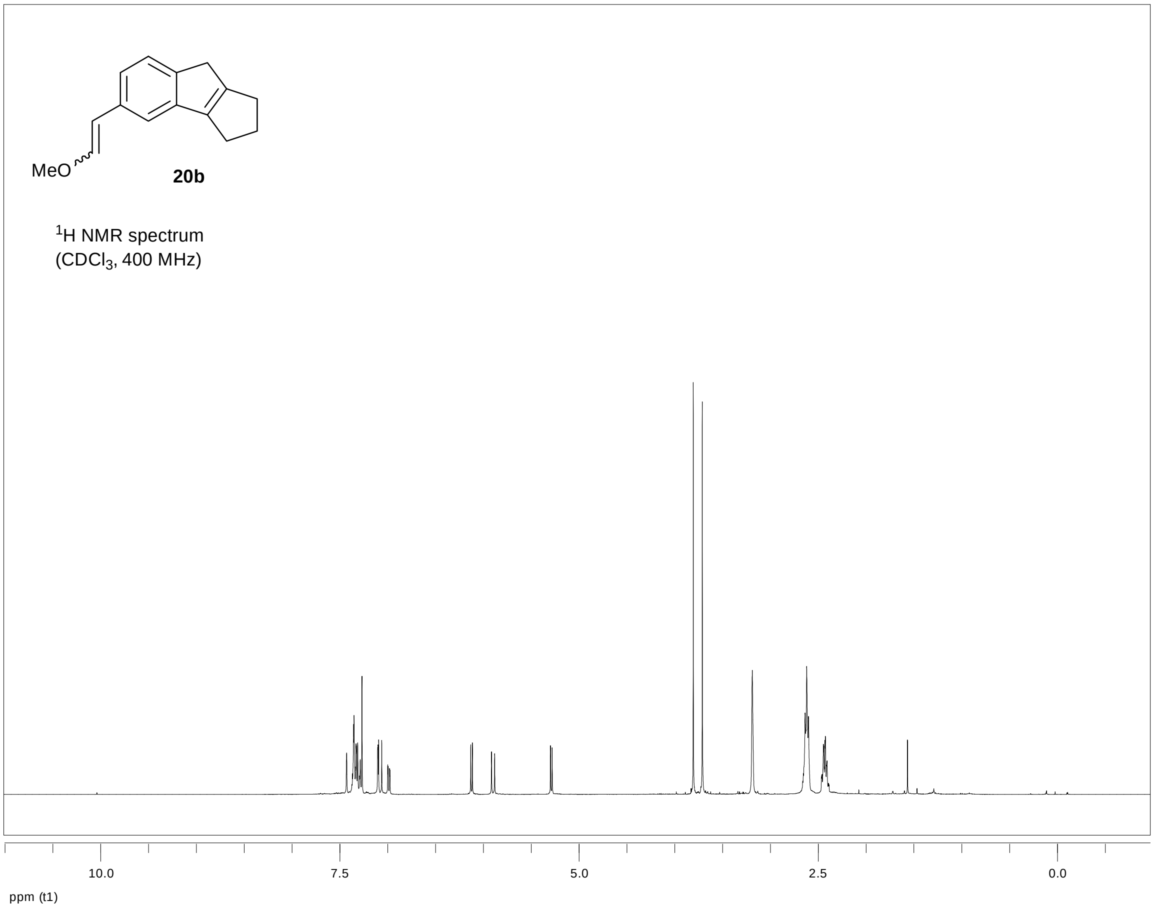
^{1}H NMR spectrum
($CDCl_3$, 400 MHz)

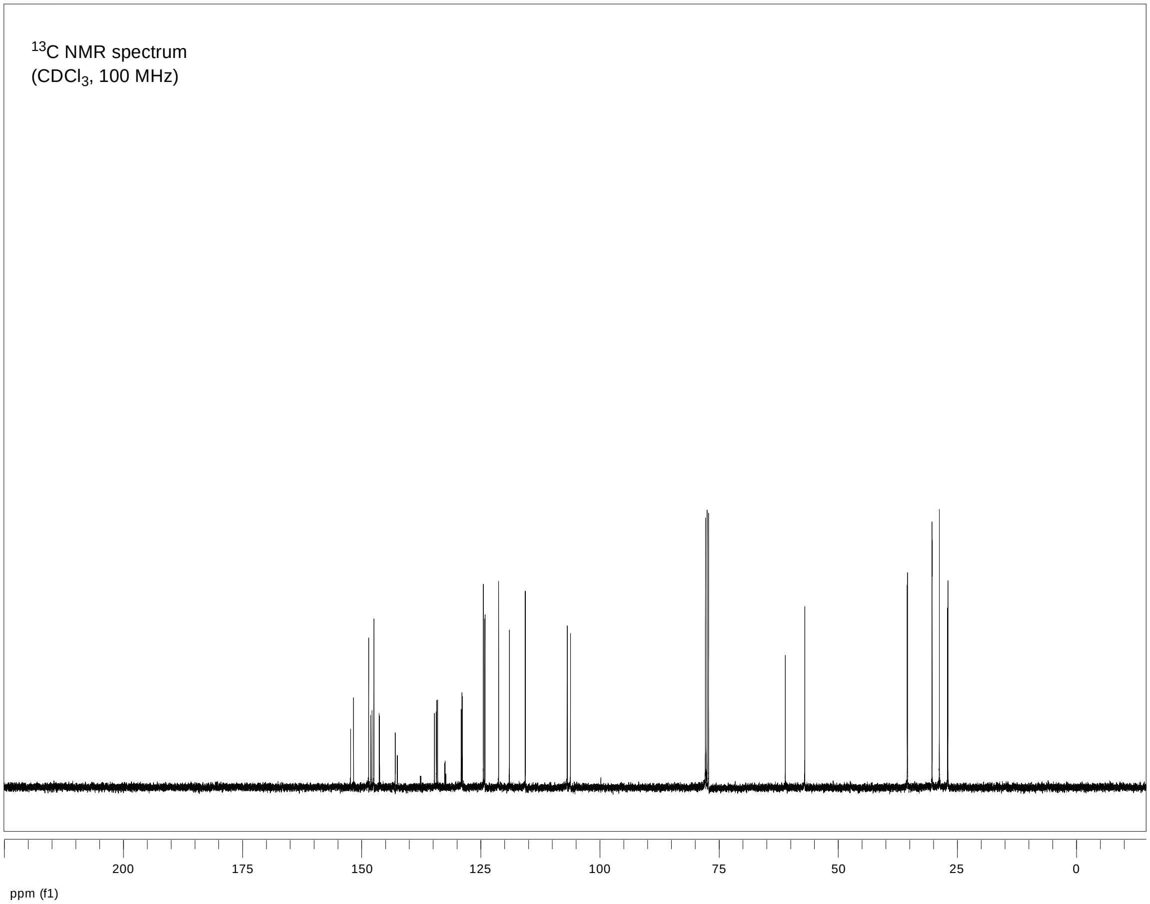


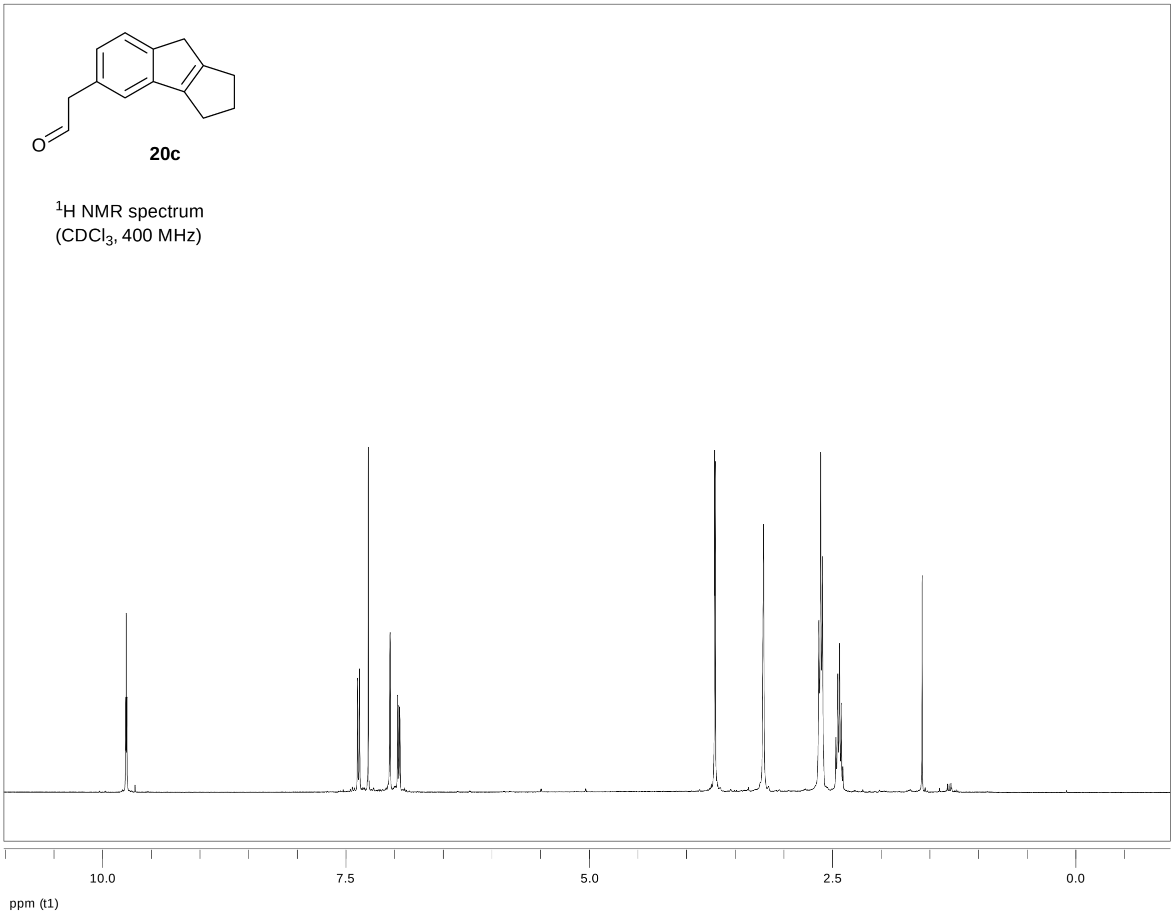
^{13}C NMR spectrum
($CDCl_3$, 100 MHz)


H
O
20a
^{1}H NMR spectrum
(CDCl$_3$, 400 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)


^{13}C NMR spectrum
(CDCl$_3$, 100 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)

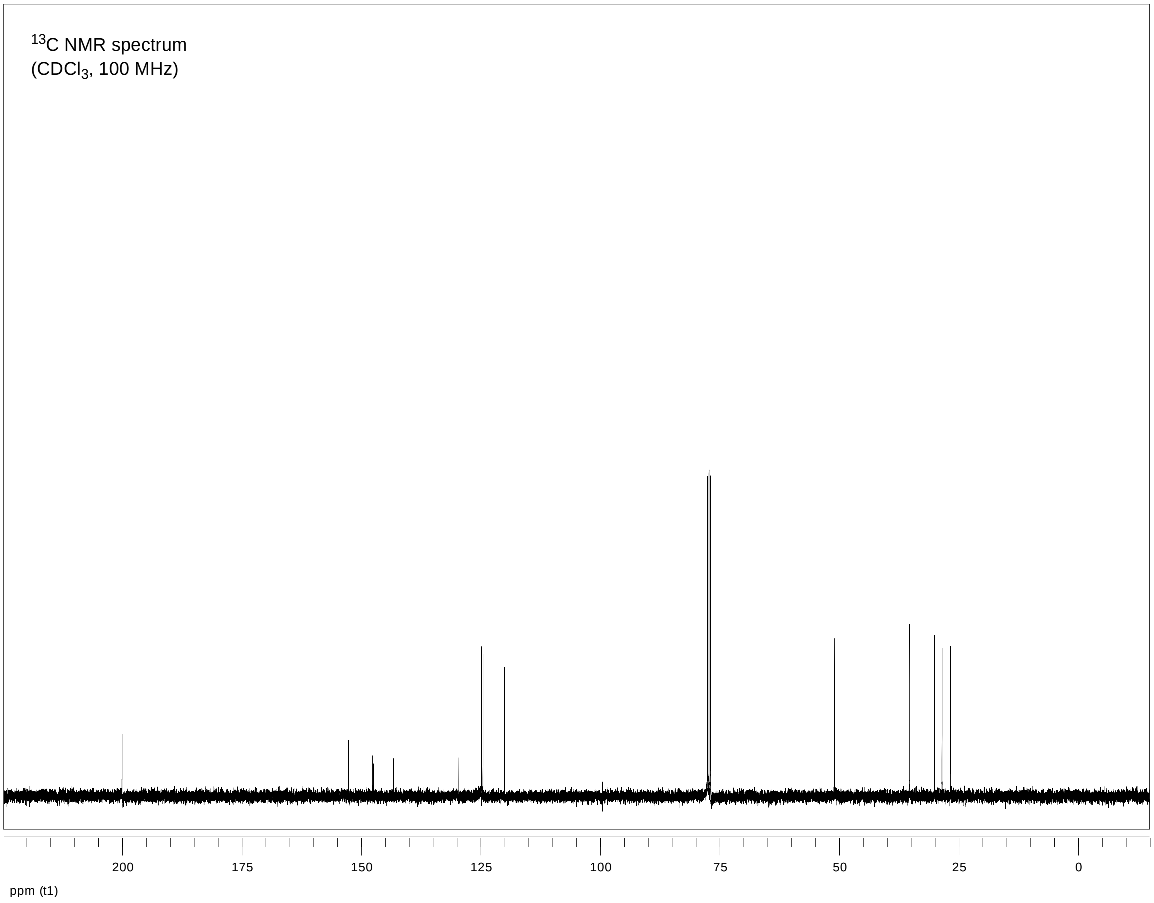

MeO
20b
^{1}H NMR spectrum
(CDCl$_3$, 400 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)


^{13}C NMR spectrum
(CDCl$_3$, 100 MHz)
200
175
150
125
100
75
50
25
0
ppm (f1)

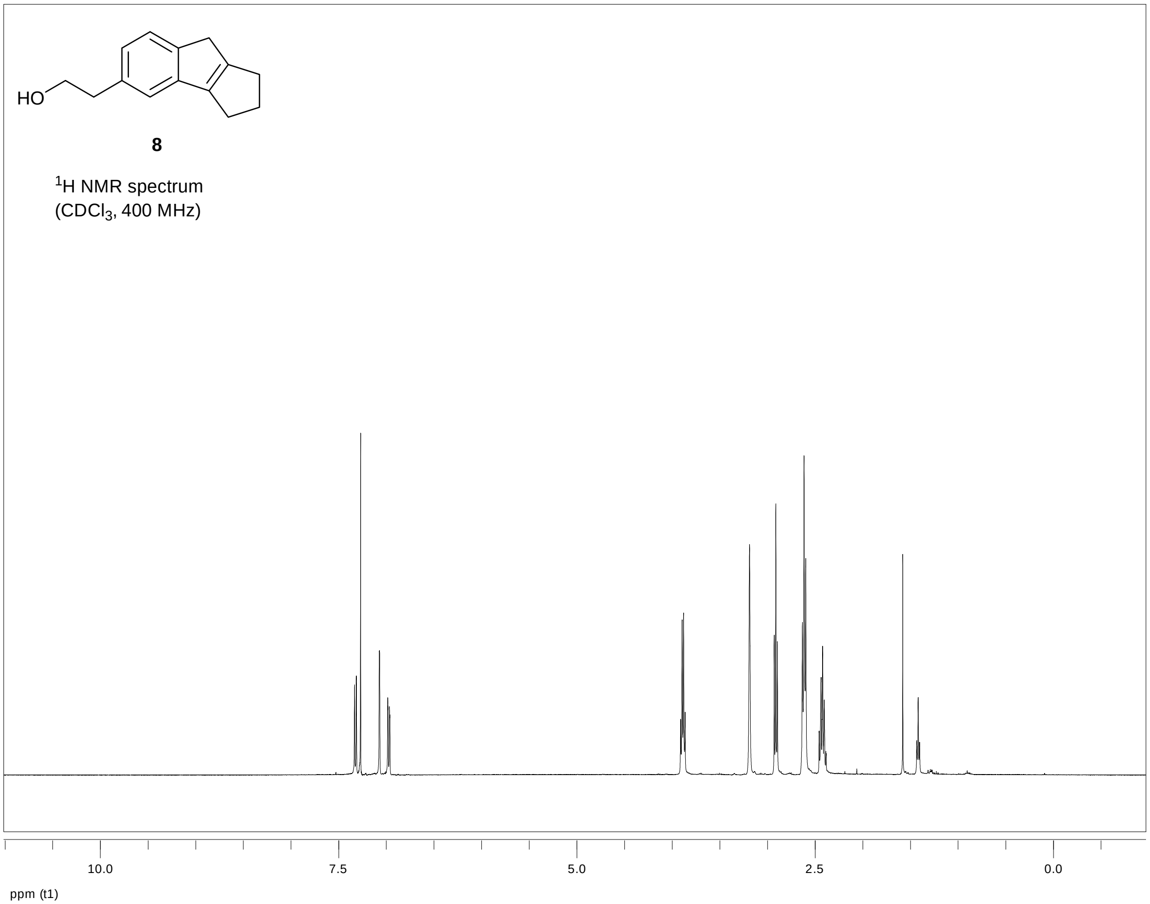


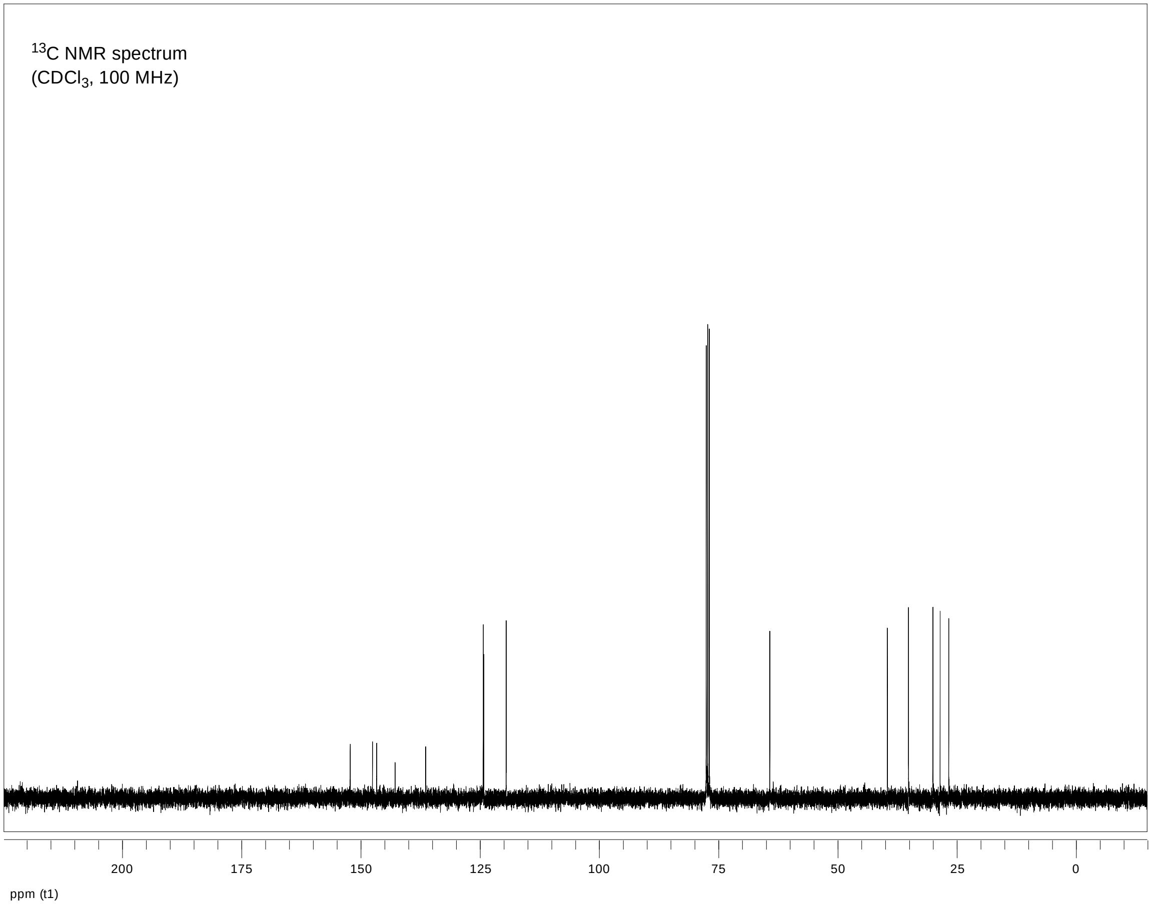
20c

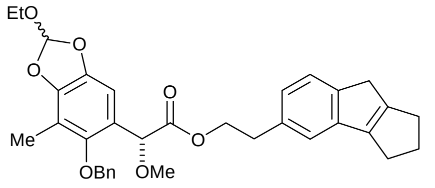
^{1}H NMR spectrum
($CDCl_3$, 400 MHz)



^{13}C NMR spectrum
($CDCl_3$, 100 MHz)

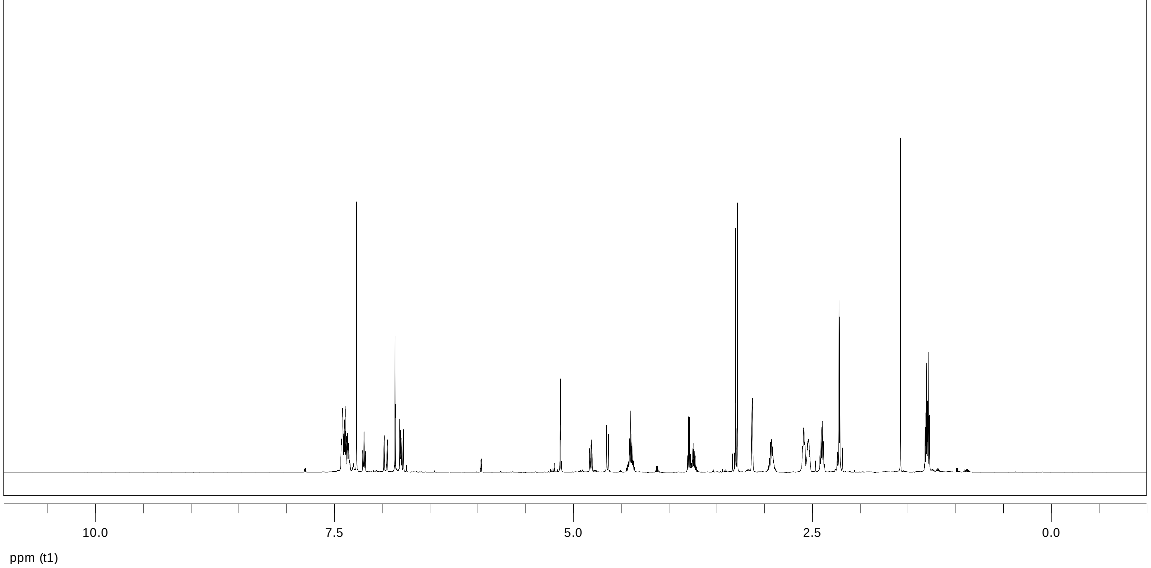

HO
8
^{1}H NMR spectrum
(CDCl$_3$, 400 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)

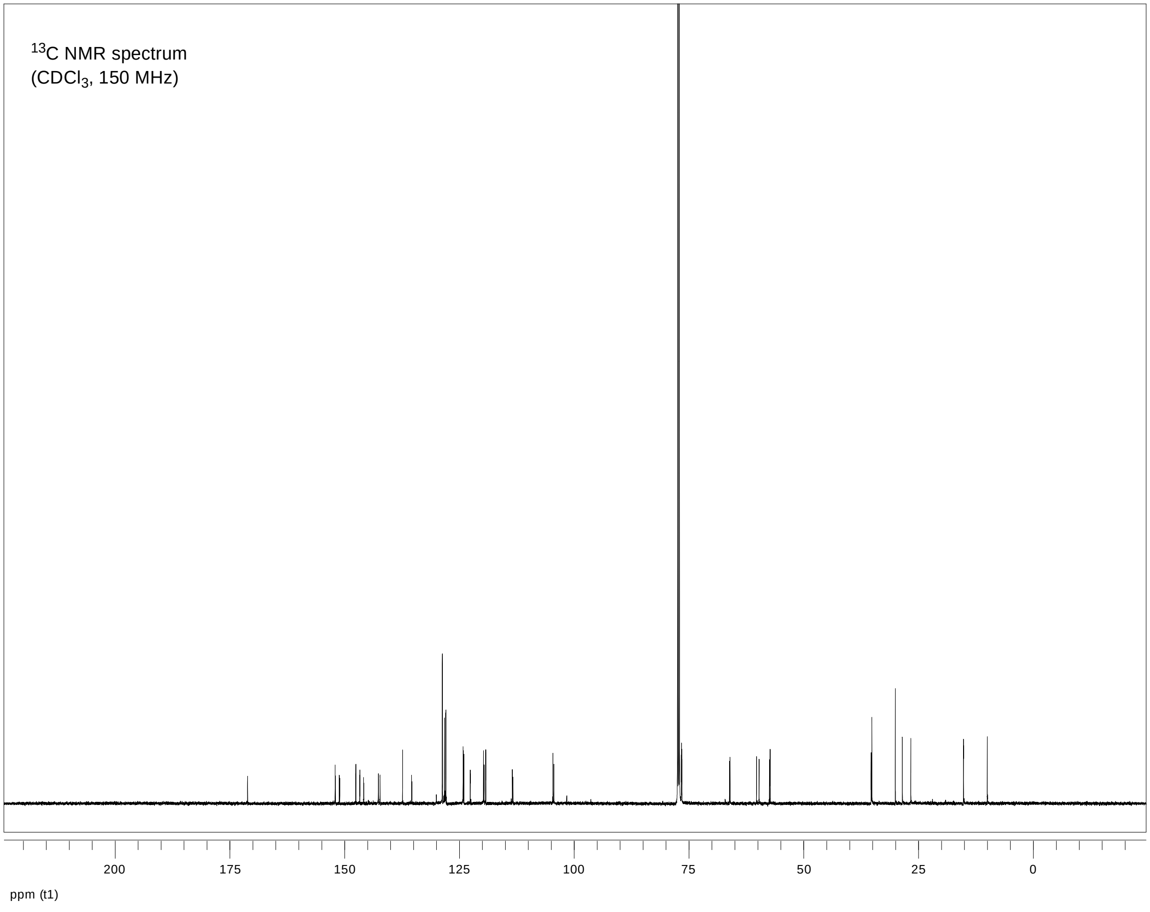

^{13}C NMR spectrum
(CDCl$_3$, 100 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)



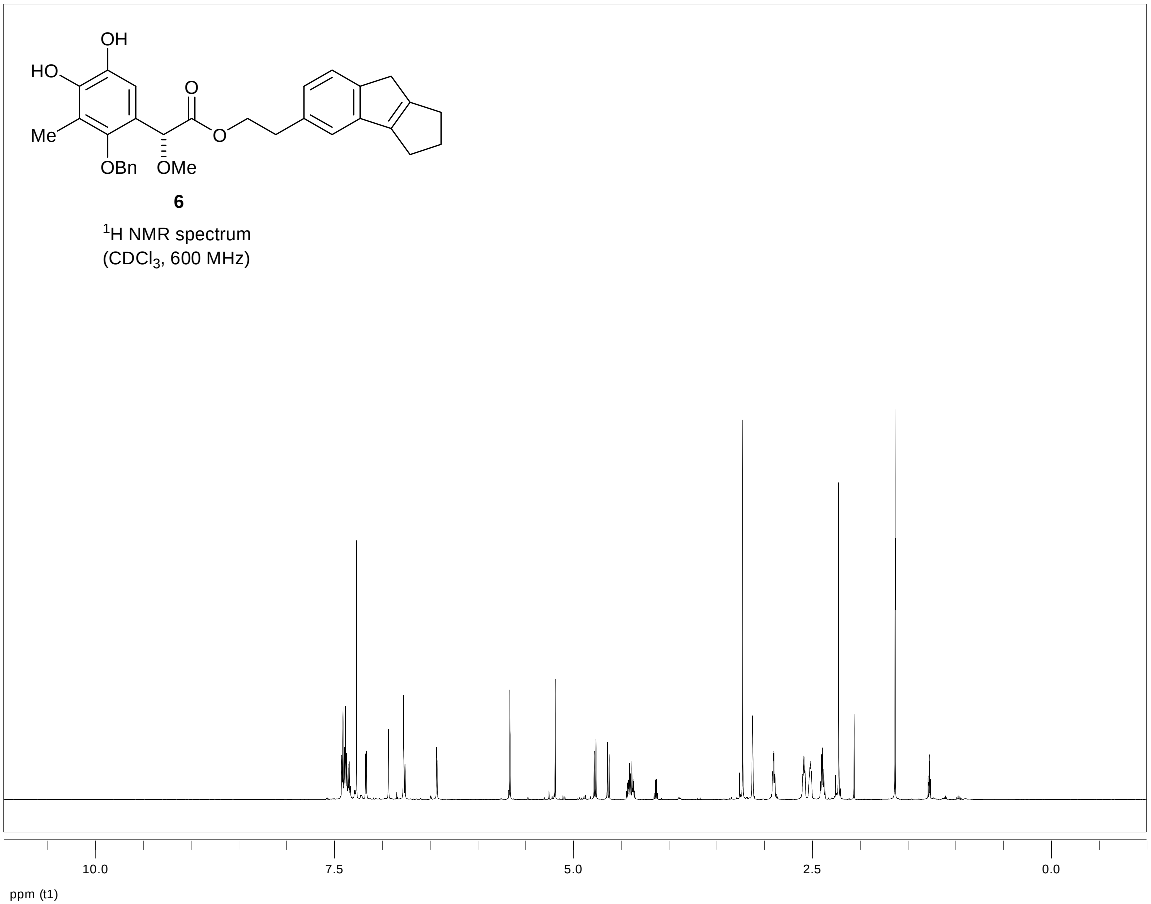
21

^{1}H NMR spectrum
(CDCl$_3$, 600 MHz)



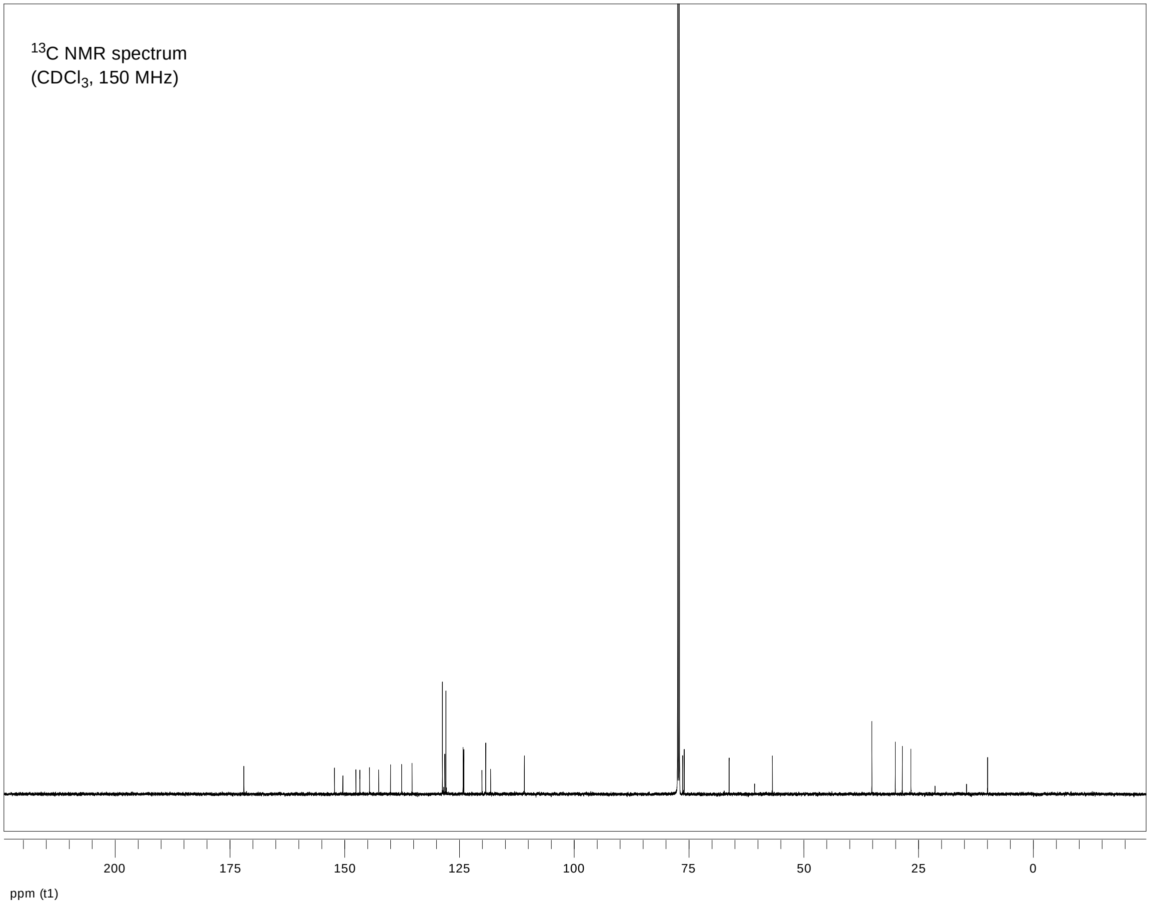


^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)

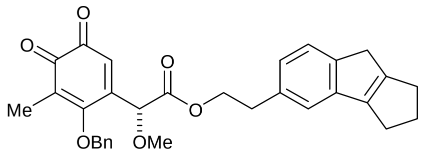


6

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)

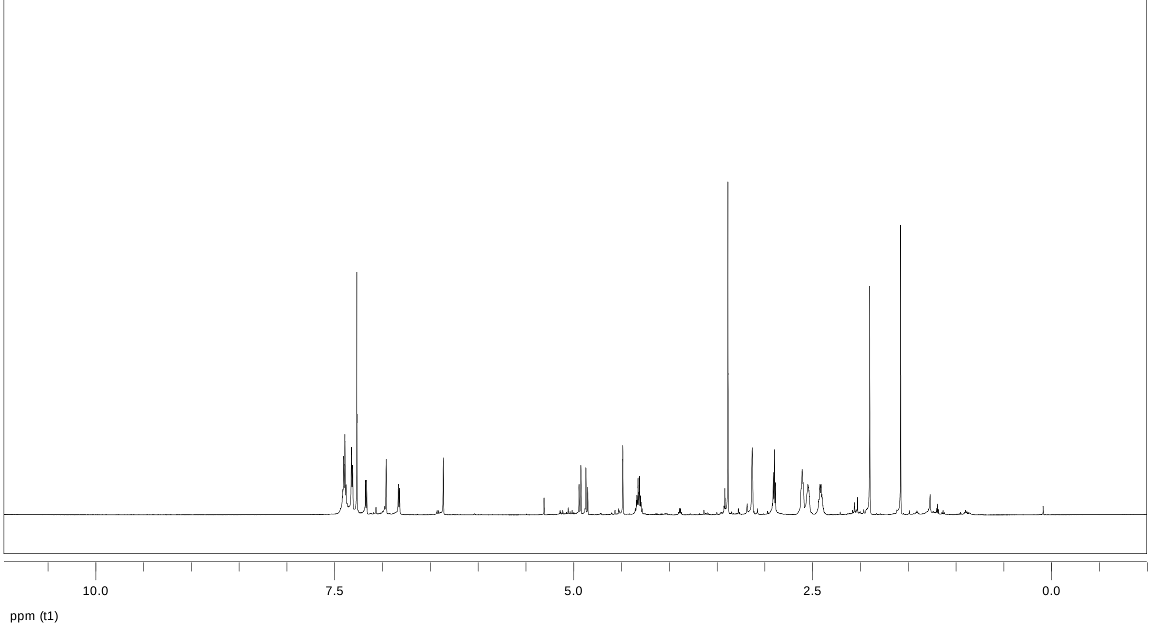


^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

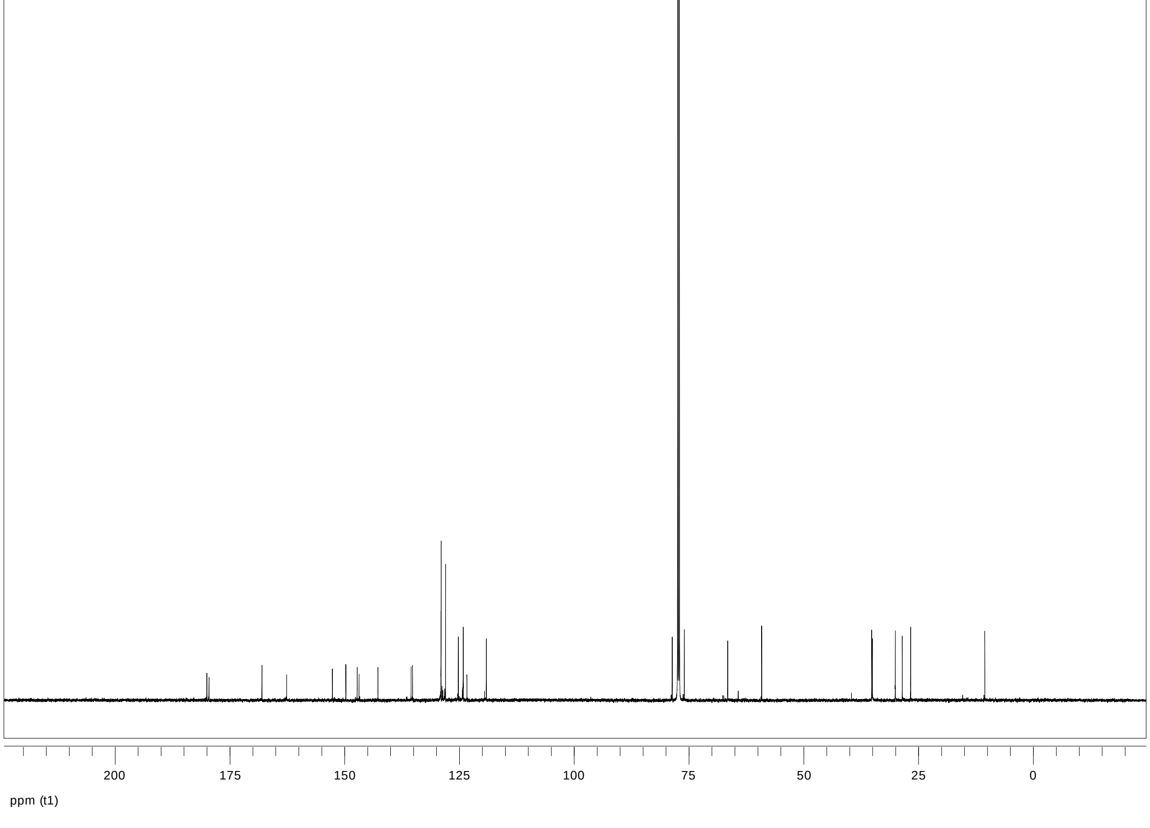


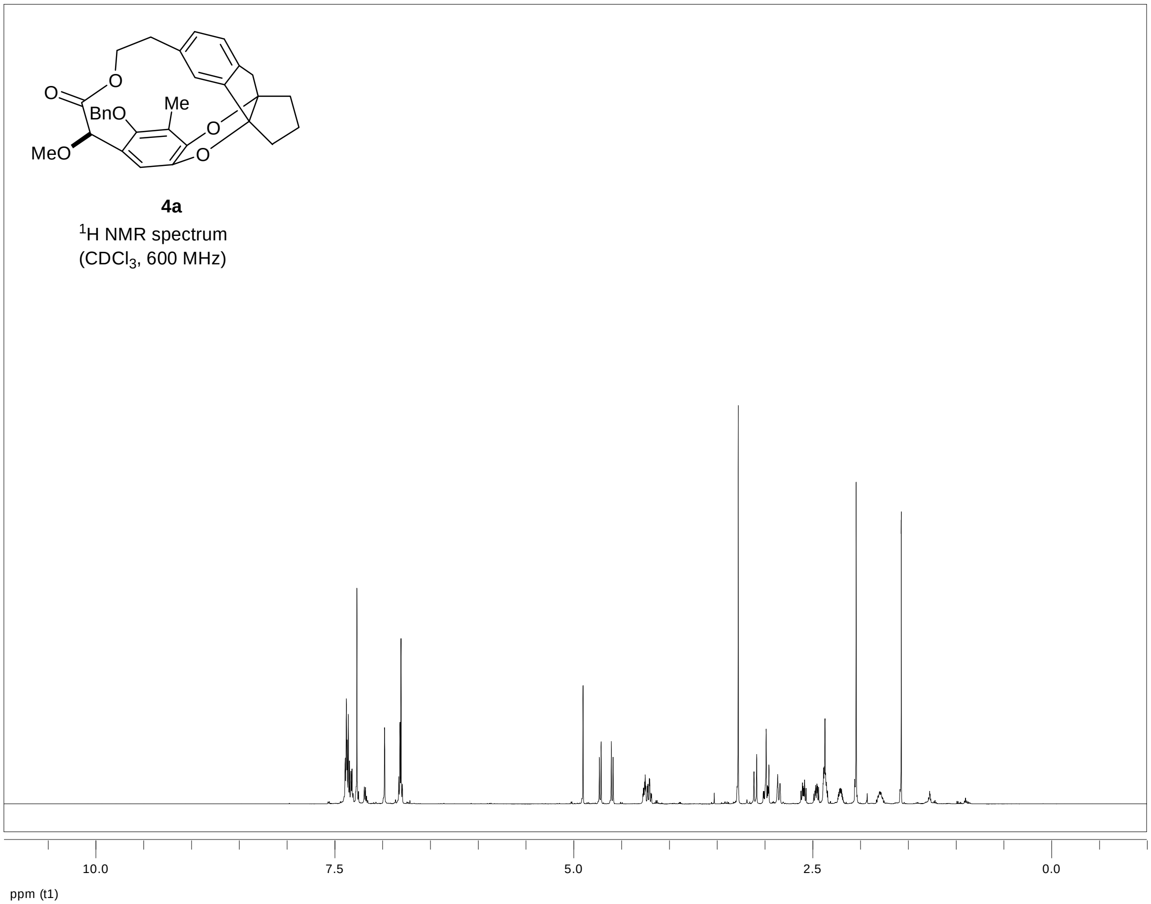
5

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



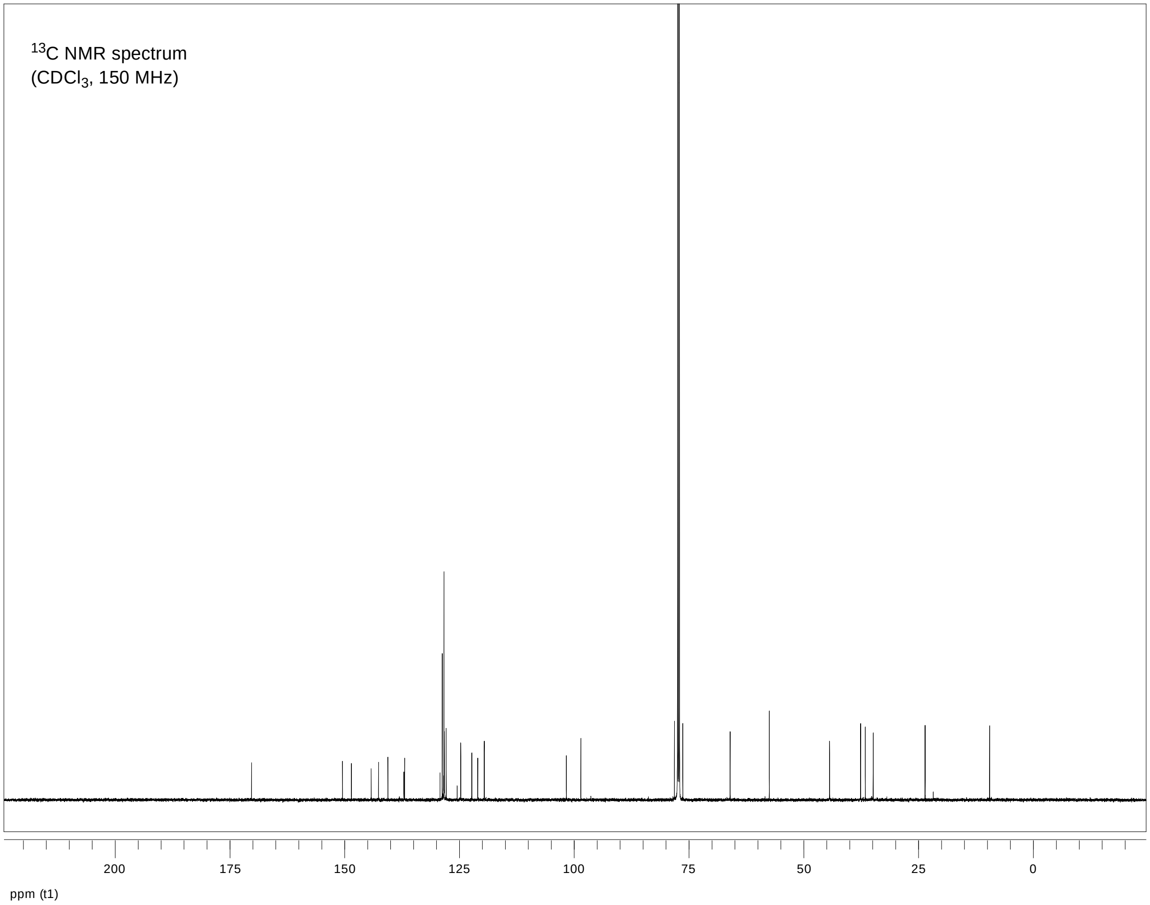
^{13}C NMR spectrum
($CDCl_3$, 150 MHz)



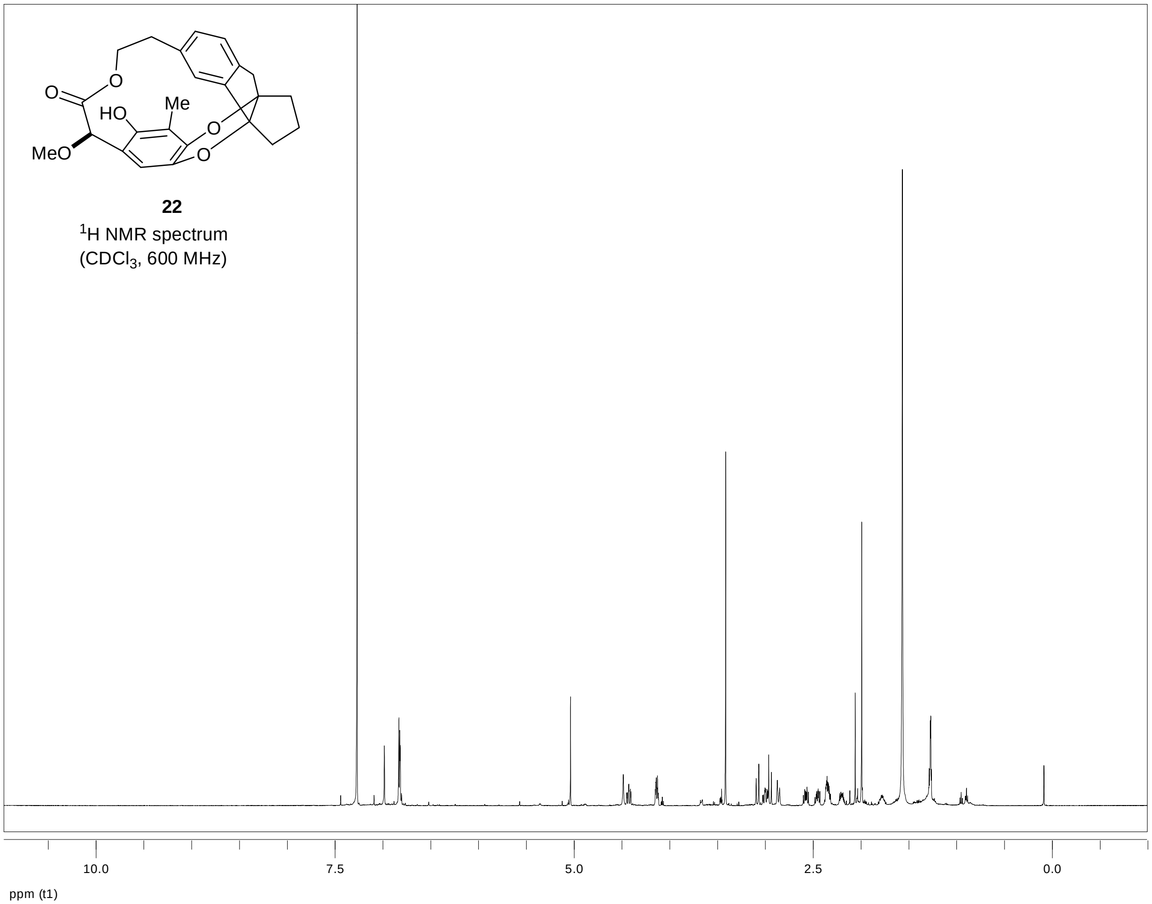


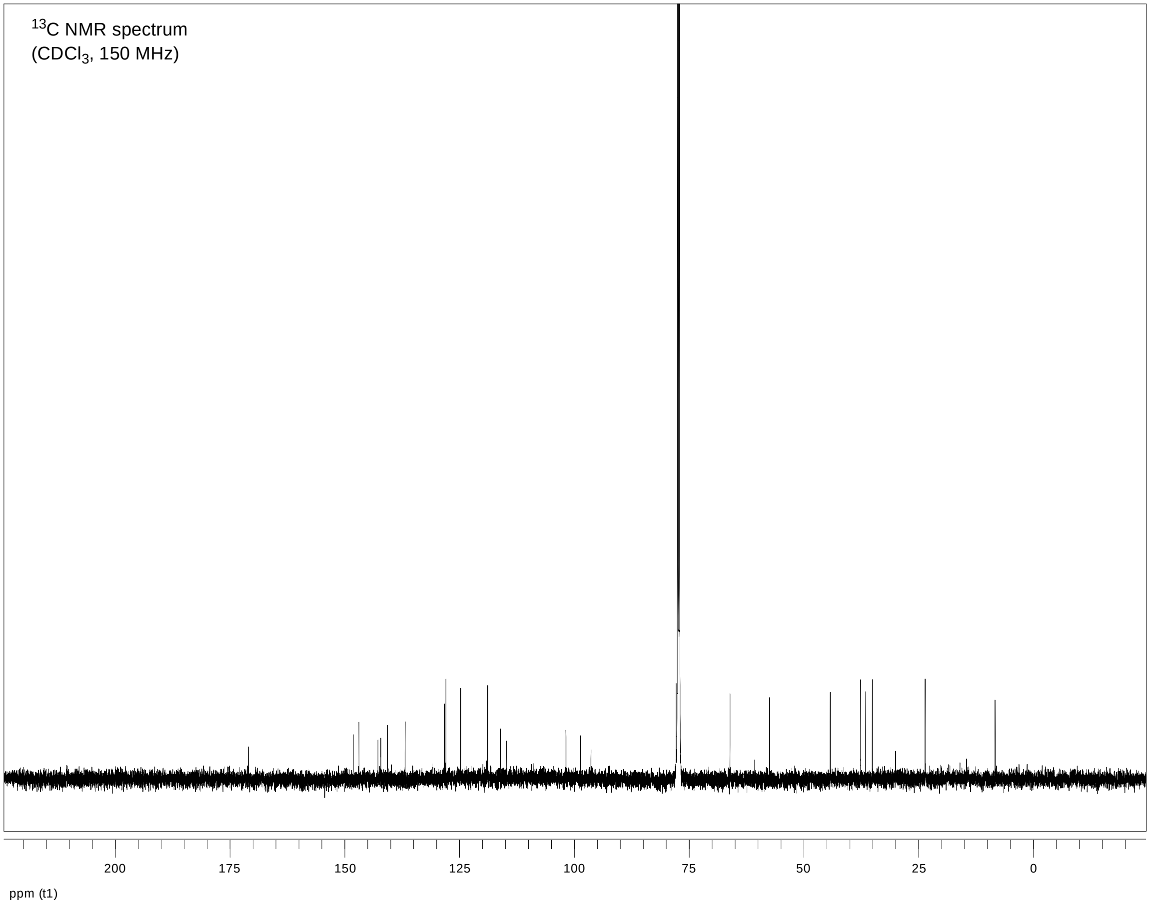
4a

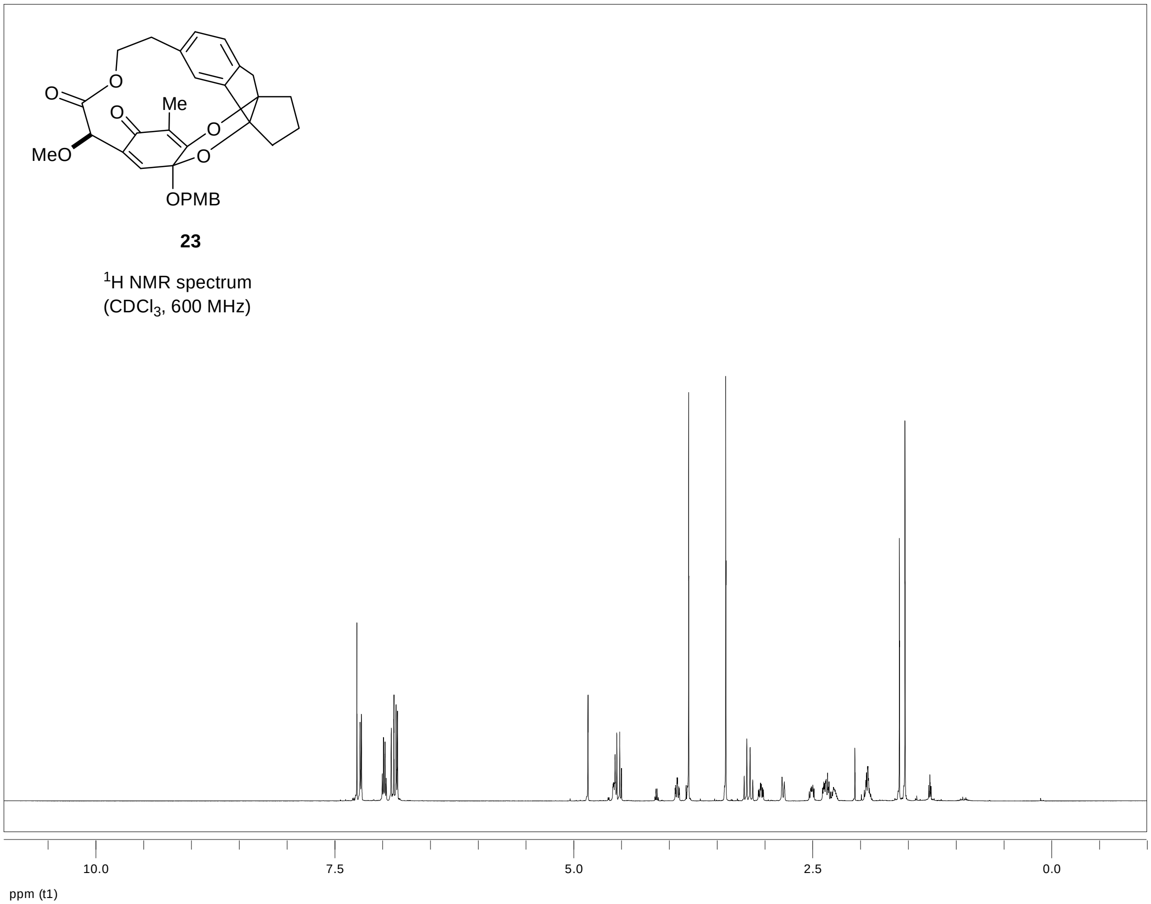
^{1}H NMR spectrum
(CDCl$_3$, 600 MHz)



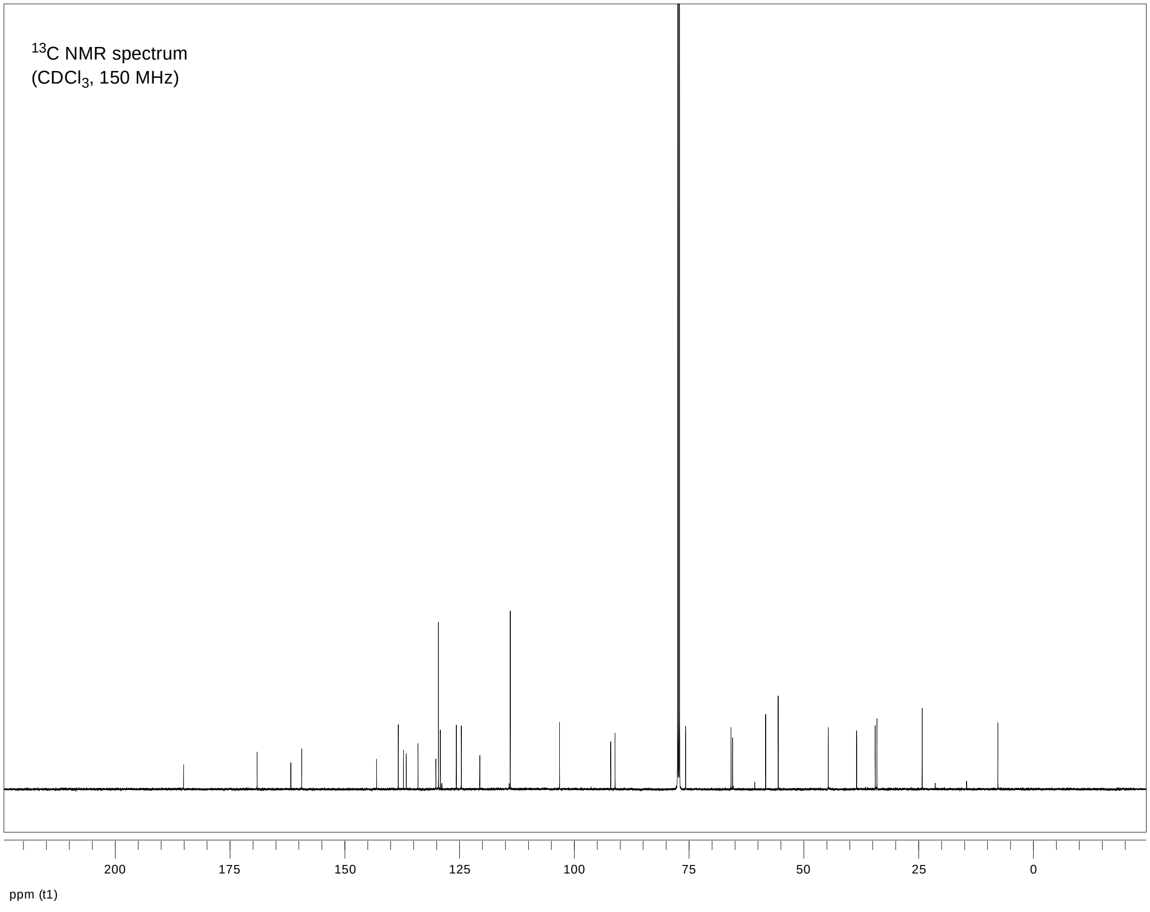
^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)

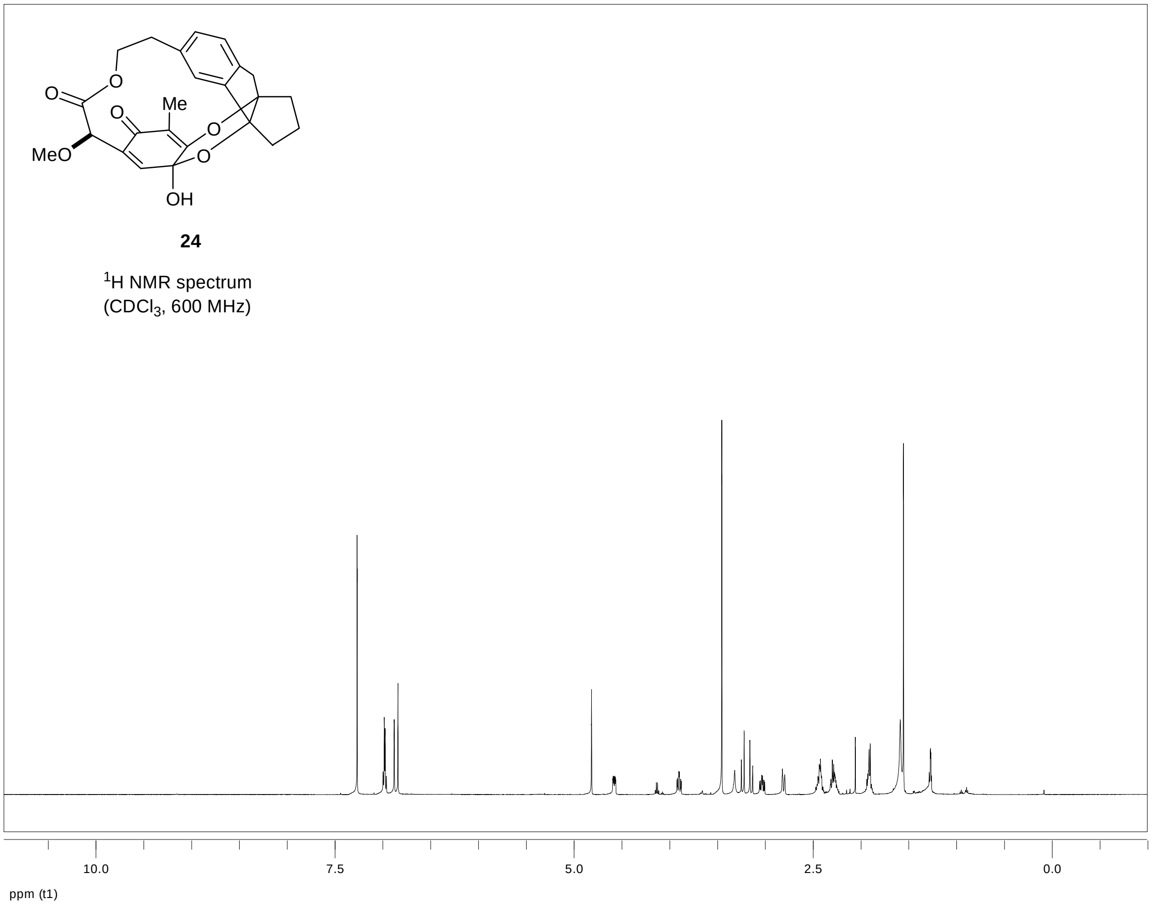

O
O
HO
Me
O
MeO
O
22
^{1}H NMR spectrum
(CDCl$_3$, 600 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)


^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)


23

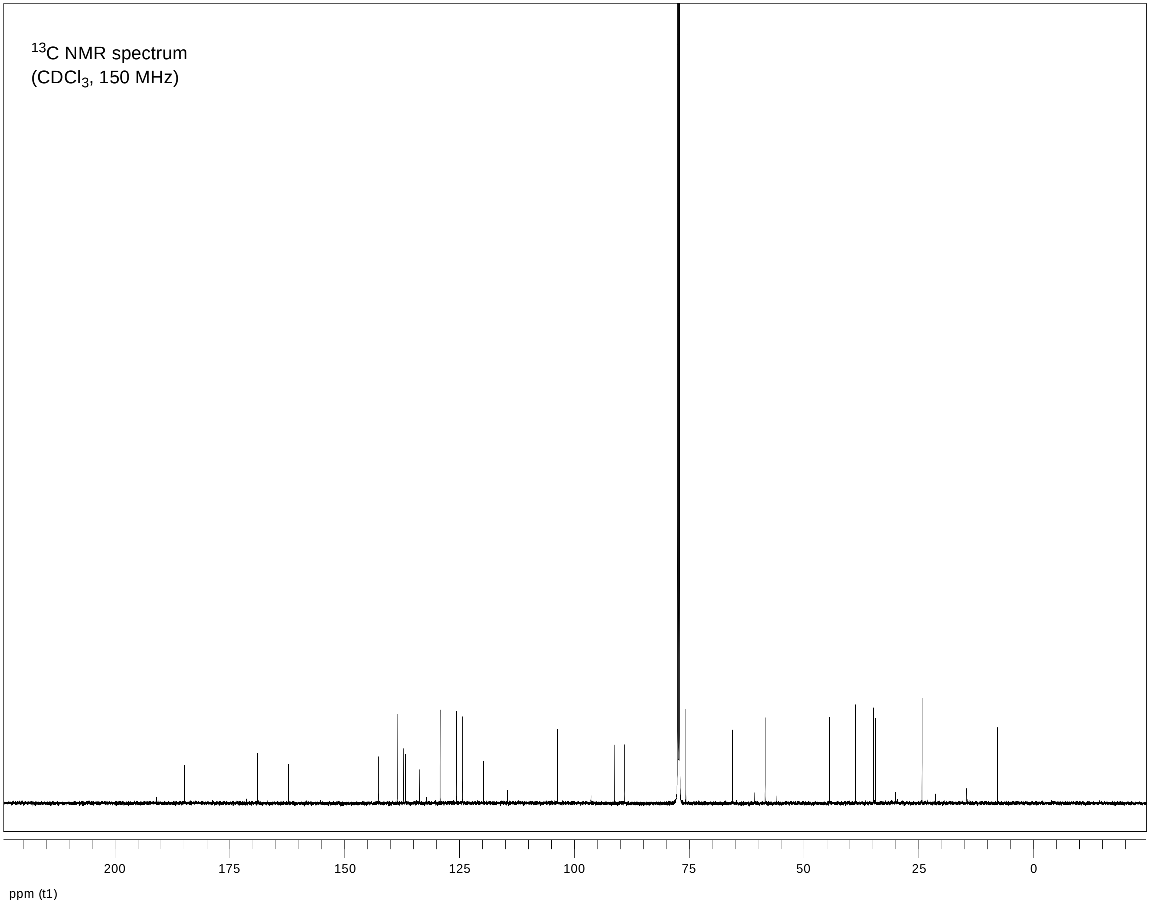
^{1}H NMR spectrum
($CDCl_3$, 600 MHz)


^{13}C NMR spectrum
($CDCl_3$, 150 MHz)

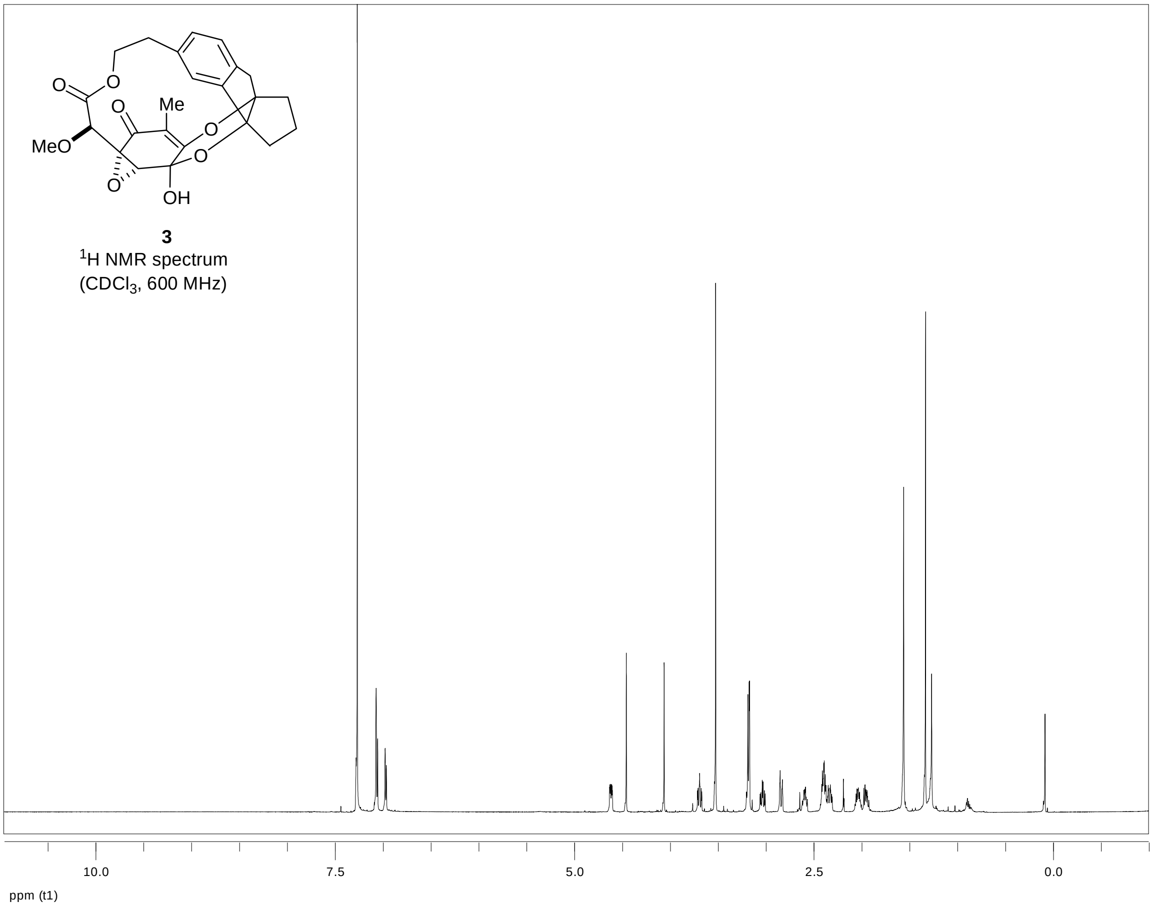


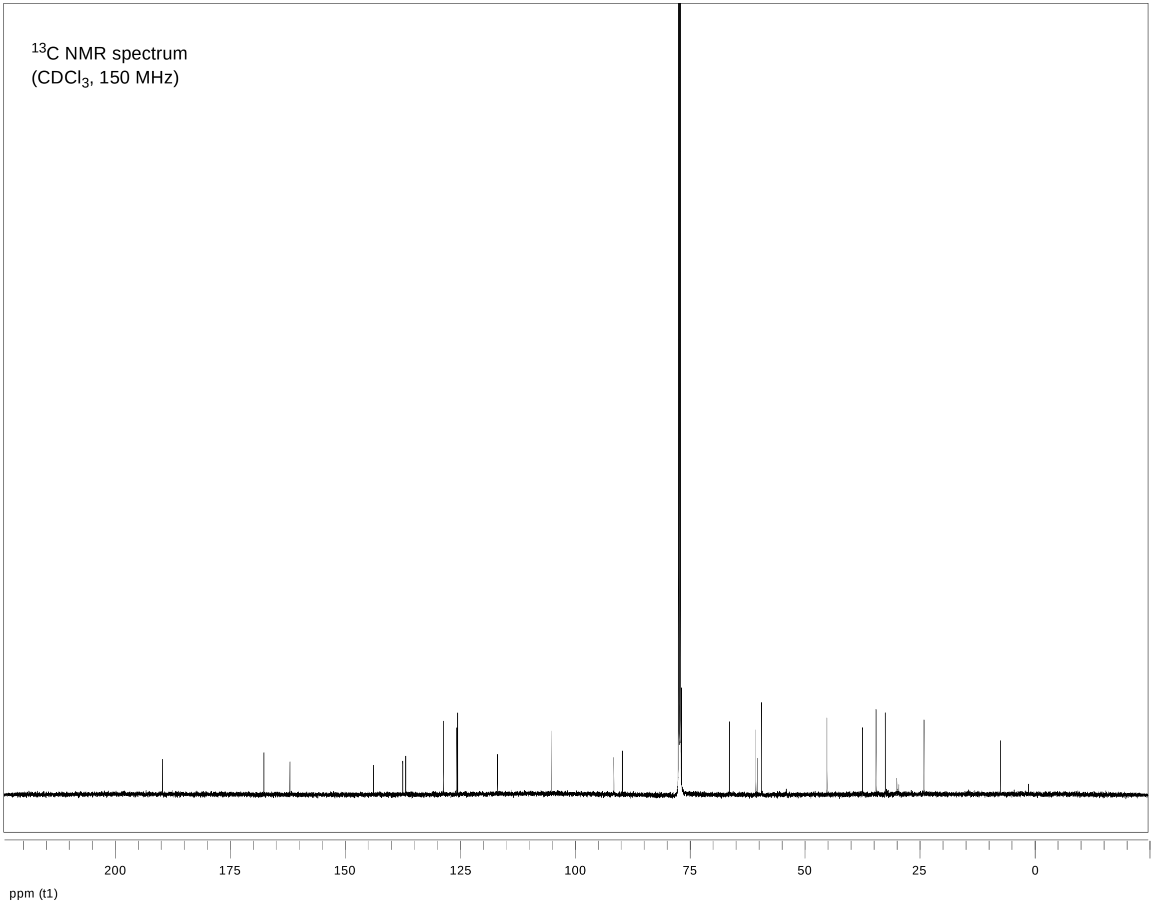
24

^{1}H NMR spectrum
($CDCl_3$, 600 MHz)



^{13}C NMR spectrum
($CDCl_3$, 150 MHz)


O
O
O
Me
MeO
O
O
O
OH
3
^{1}H NMR spectrum
(CDCl$_3$, 600 MHz)
10.0
7.5
5.0
2.5
0.0
ppm (t1)


^{13}C NMR spectrum
(CDCl$_3$, 150 MHz)
200
175
150
125
100
75
50
25
0
ppm (t1)