# Synthesis and Evaluation of the Cytotoxicity of Apoptolidinones A and D

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Supporting Information

**General Methods**: Unless indicated, all commercial reagents were used as received without further purification. All non-aqueous reactions were carried out under an argon atmosphere using glassware that had been dried overnight at 120 °C and cooled to room temperature under an argon atmosphere. Tetrahydrofuran was distilled over Na/benzophenone, while dichloromethane, toluene, diethyl ether and dimethylformamide were dried by being passed through a column of neutral alumina under an atmosphere of nitrogen. Benzene was distilled from calcium hydride and stored over 4 Å molecular sieves. All solvents were determined to contain less than 50 ppm water by Karl Fisher coulometric moisture analysis. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck pre-coated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was performed using silica gel 60 (particle size 230-400 mesh) with the indicated solvent system. An automated chromatography system was also employed, chromatography methods being created based on $R_f$ values. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were taken on a micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon-13 ($^{13}$C NMR) spectra were recorded on a 300, 400 or 500 MHz spectrometer at ambient temperature. $^1$H and $^{13}$C NMR data are reported as δ values relative to tetramethylsilane δ 0 ppm ($CDCl_3$) or residual non-deuterated solvent δ 7.26 ppm from $CHCl_3$, δ 7.15 ppm for $C_6D_6$. For $^{13}$C spectra, chemical shifts are reported relative to the δ 77.23 ppm resonance of $CDCl_3$ or

the δ 128.39 resonance of $C_6D_6$. Infrared (IR) spectra were recorded as thin films or solutions in the indicated solvent.

**TBS Ether 3**: To a solution of alcohol **2** (3.26 g, 15.7 mmol) in DMF (140 mL) at 0 °C was added imidazole (3.20 g, 47.0 mmol), TBSCl (7.10 g, 47.0 mmol), and 4-dimethylaminopyridine (38 mg, 0.31 mmol). The solution was warmed to room temperature and stirred for 3 h and quenched with $H_2O$ (50 mL). The aqueous layer was extracted with $Et_2O$ (3 X 40 mL). The combined organic layers were washed with $H_2O$ (60 mL), brine (60 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 50:1) to afford 4.81 g (95%) of TBS ether **3** as a colorless oil: $[\alpha]^{25}_D$ +20.8° (c 1.0, $CHCl_3$); IR (neat) 3053, 2986, 2305, 1424, 1276, 892, 764 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.11 (dd, J = 10.5, 4.5 Hz, 1H), 4.07-4.02 (m, 1H), 3.29 (s, 3H), 3.28 (dd, J = 9.5, 5.5 Hz, 1H), 3.23 (d, J = 9.5, 5.5 Hz, 1H), 2.88-2.71 (m, 4H), 2.06 (m , 1H), 1.92-1.77 (m, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); $^{13}C$ NMR (125 MHz, CDCl3) δ 77.2, 67.8, 59.0, 43.5, 40.1, 30.4, 29.7, 26.0, 25.9, 18.1, -4.3, -4.9; HRMS (ESI) m/z 329.1632 [$(M + Li)^+$, calculated for $C_{14}H_{30}LiO_2S_2Si$: 329.1617].

**Aldehyde 4:** To a solution of **3** (3.91 g, 12.1 mmol) in $CH_3CN/H_2O$ (132 mL, 10:1) was added $K_2CO_3$ (3.34 g, 24.2 mmol), followed by iodomethane (17.2 g, 121 mmol). The slurry was stirred for 8 h at 40 °C and quenched with saturated $NaHCO_3$ (40 mL). The aqueous layer was extracted with $Et_2O$ (3 X 40 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc , 40:1) to afford 2.54 g (90%) of aldehyde **4** as a colorless oil: $[\alpha]^{25}_D$ +8.6° (c 1.0, $CHCl_3$); IR (neat)

2930, 2857, 1728 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): 9.75 (t, J = 2.5 Hz, 1H), 4.28 (quintet, J = 5.5 Hz, 1H), 3.36 (dd, J = 9.5, 5.0 Hz, 1H), 3.30 (s, 3H), 3.26 (dd, J = 9.5, 5.5 Hz, 1H), 2.54 (ddq, J = 16.0, 5.5, 2.5 Hz, 2H), 0.82 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}C$ NMR (125 MHz, CDCl3): δ 201.4, 76.5, 67.2, 59.1, 48.7, 25.7, 18.0, -4.5, - 5.0; HRMS (ESI) m/z 233.1590 [$(M+H)^+$ calculated for $C_{11}H_{25}O_3Si$: 233.1573].

**Aldol 5**: To a solution of acyloxazolidinethione **9** (1.12 g, 4.48mmol) in dichloromethane (20 mL) at 0 °C was added a solution of $TiCl_4$ (4.48 mL, 1 M in dichloromethane). The solution was allowed to stir for 15 min before the addition of (-)-sparteine (1.32 mL, 5.76 mmol). After 15 min, the reaction mixture was cooled to -78 °C, and aldehyde **4** (0.990 g, 4.27 mmol) in dichloromethane (4 mL) was added dropwise. The reaction mixture was maintained at -78 °C for 1 h, warmed to 0 °C and stirring continued for 1 h. The reaction was quenched with saturated $NH_4Cl$ (15 mL) and the aqueous layer was extracted with dichloromethane (3 X 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc, 6:1) to afford 1.95 g (95%) of aldol **5** as a colorless oil: $[\alpha]^D_{25}$ +52.5° (c 4.4, $CHCl_3$); IR ($CHCl_3$) 2960, 2851, 1695, 1367, 1185 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.37-7.23 (m, 5H), 4.98-4.94 (m, 1H), 4.71 (dq, J = 7.0, 4.0 Hz, 1H), 4.35-4.28 (m, 3H), 4.10 (quintet, J = 5.0 Hz, 1H), 3.56 (s, 1H), 3.44-3.29 (m, 3H), 3.37 (s, 3H), 2.77 (dd, J = 13.0, 10.0 Hz, 1H), 1.83-1.77 (m, 1H), 1.65 (ddd, J = 14.0, 6.0, 1.5 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 185.4, 177.3, 135.5, 129.6, 129.2, 127.6, 70.4, 69.9, 68.9, 60.6, 59.4, 43.4, 38.6, 37.8, 26.1, 18.3, 11.0,

-4.3, -4.7; HRMS (ESI) m/z 482.2402 [(M+H)+ calculated for $C_{24}H_{40}NO_5SSi$: 482.2396].

**Silyl ether 6**: To a solution of aldol **5** (0.535 g, 1.11 mmol) in DMF (5 mL) at 0 °C was added imidazole (0.227 g, 3.33 mmol) and TESCl (0.559 mL, 3.33 mmol). The reaction was stirred at 0 °C for 3 h, at which time the reaction was quenched with $H_2O$ (5 mL). The mixture was extracted with $Et_2O$ (3 X 7 mL). The combined organic layers were washed with $H_2O$ (8 mL), brine (8 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (Hexanes/EtOAc, 20:1,) to afford 0.635 g (95%) of ether **6** as an oil: $[\alpha]^D_{25}$ +49.8° (c 3.6, $CHCl_3$); IR ($CHCl_3$) 2960, 2880, 1702, 1367, 1185, 749 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.37-7.22 (m, 5H), 4.84-4.78 (m, 2H), 4.30 (dd, J = 9.0, 1.5 Hz, 1H), 4.21-4.14 (m, 2H), 3.93-3.88 (m, 1H), 3.34-3.30 (m, 3H), 3.32 (s, 3H), 2.75 (dd, J = 13.0, 10.5 Hz, 1H), 1.82-1.72 (m, 2H), 1.26 (d, J = 6.5 Hz, 3H), 0.93 (t, J = 8.0 Hz, 9H), 0.89 (s, 9H), 0.59 (q, J = 8.0 Hz, 6H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 185.3, 176.3, 135.7, 129.7, 129.2, 127.6, 78.0, 71.7, 70.2, 69.3, 61.1, 59.0, 43.8, 40.6, 37.6, 26.2, 18.5, 12.8, 7.2, 5.5, -3.5, -4.3; HRMS (ESI) m/z 596.3265 $[(M+H)^+$ calculated for $C_{30}H_{54}NO_5SSi_2$: 596.3261].

**Alcohol 7:** To a solution of aldol **6** (1.97 g, 3.30 mmol) in $Et_2O$ (30 mL) at 0 °C was added MeOH (0.20 mL, 4.96 mmol) followed by $LiBH_4$ (2M solution in THF, 2.48 mL, 4.96 mmol). The reaction was stirred at 0 °C for 1.5 h and quenched with $H_2O$ (5 mL) followed by saturated $NH_4Cl$ (5 mL). The mixture was extracted with $Et_2O$ (3 X 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc on Biotage SP1) to afford 1.20 g (90%) of alcohol **7** as an oil: $[\alpha]^D_{25}$

+8.9° (c 1.8, $CHCl_3$); IR ($CHCl_3$) 3396, 2953, 2873, 1462, 1251, 1105, 836 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 4.02-3.99 (m, 1H), 3.92-3.87 (m, 1H), 3.71- 3.67 (m, 1H), 3.55-3.51 (m, 1H), 3.34 (s, 3H), 3.33-3.28 (m, 1H), 2.83 (dd, J = 6.5, 3.5 Hz, 1H), 2.04-2.00 (m, 1H), 1.62 (t, J = 5.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 9H), 0.89 (s, 9H), 0.81 (d, J = 7.0 Hz, 3H), 0.65 (q, J = 7.5 Hz, 6H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 78.1, 73.8, 69.6, 66.2, 59.0, 40.4, 38.2, 26.2, 18.5, 12.5, 7.1, 5.4, -3.5, -4.4 ; HRMS (ESI) m/z 407.3047 [(M+H)+ calculated for $C_{20}H_{47}O_4Si_2$: 407.3013].

**Aldehyde 8**: To a solution of $(COCl)_2$ (0.043 mL, 0.493 mmol) in dichloromethane (1 mL) was added DMSO (0.070 mL, 0.986 mmol). The resulting mixture was stirred at -78 °C for 15 min before alcohol **7** (125 mg, 0.308 mmol) in dichloromethane (1 mL) was added. The mixture was stirred 15 min at -78 °C, and $Et_3N$ (0.216 ml, 1.54 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for another 15 min before it was warmed to 0 °C for 45 min. The reaction was quenched with $H_2O$ (10 mL) and the aqueous layer was extracted with dichloromethane (3 X 20 mL). The combined organic layers were washed with 0.1 N HCl (20 mL), $H_2O$ (15 mL), saturated $NaHCO_3$ (15 mL), $H_2O$ (15 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc, 20:1) to afford 0.11 g (88%) of aldehyde **8** as a colorless oil: $[\alpha]^D_{25}$ +26.3° (c 6.0, $CHCl_3$); IR (neat) 2953, 2873, 1709, 1462, 1251 $cm^{-1}$; 1H NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 4.31-4.28 (m, 1H), 3.89- 3.85 (m, 1H), 3.30 (dd, J = 5.5, 2.0 Hz, 2H), 3.33 (s, 3H), 2.52 (dq, J = 7.0, 3.5 Hz, 1H), 1.68-1.65 (m, 2H), 1.07 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.89 (s, 9H), 0.62 (q, J = 8.0 Hz, 6H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 205.5, 77.8, 70.1, 69.5, 59.1, 52.4, 40.3,

26.1, 18.4, 8.1, 7.1, 5.4, -3.7, -4.4; HRMS (ESI) m/z 427.2664 [(M+Na)+ calculated for $C_{20}H_{44}NaO_4Si_2$: 427.2676].

**Silyl ether 11**: To a solution of 1-hydroxybutan-2-one (0.021 g, 2.384 mmol) in dichloromethane (24 mL) cooled to 0 °C was added imidazole (0.032 g, 4.767 mmol, 2 equiv) followed by TESCl (0.60 mL, 3.575 mmol, 1.5 equiv). The mixture was stirred overnight at room temperature and quenched with $H_2O$ (10 mL). The aqueous layer was extracted with dichloromethane (3 X 20 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc, 40:1 to 10:1) to afford 0.338 g (70%) of TES ether **11** as a colorless oil: IR (neat) 2955, 2878, 1720 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 4.18 (s, 2H), 2.54 (q, J = 7.0 Hz, 2H), 1.07 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.64 (q, J = 8.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 211.7, 68.7, 31.5, 7.2, 6.6, 4.3; HRMS (ESI) m/z 209.1571 [(M+Li)+ calculated for $C_{10}H_{22}LiO_2Si$: 209.1549].

**Silyl enol ether 12:** To a solution of diisopropylamine (4.0 mL, 29.2 mmol) in THF (100 mL) was added n-BuLi (2.5 M in hexanes, 11.7 mL, 29.2 mmol) at 0 °C. After 15 min at 0 °C, the mixture was cooled to –78 °C and a solution of silyl ether **11** (4.9 g, 24.3 mmol) in THF (20 mL) was added dropwise. The resulted solution was stirred for 30 min at –78 °C. TMSCl (3.7 mL, 29.2 mmol) was added dropwise and the resulted solution was stirred for 2 h at –78 °C. The reaction was quenched with $NaHCO_3$ (20 mL) and extracted with $Et_2O$ (3 X 100 mL). The combined organic layer were dried ($Na_2SO_4$), filtered and concentrated *in vacuo.* The residue was purified by distillation under reduced pressure (85-90 °C, 1 mm Hg) to afford 5.3 g (80%) isolated as a light yellow and

mixture of silyl enol ethers (Z)-**12**/(E)-**12**/(Z)-**13** (ca. 15:73:12 as determined by GC analysis). The double bond geometry of (E)-**12** and (Z)-**13** was assigned by NOESY NMR analysis: IR (neat) 2958, 2879, 1266, 1162, 1078, 1008, 940, 908, 840, 744 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$): δ 6.32 (s, 1H), 2.42 (q, J = 7.5 Hz, 2H), 1.17 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H), 0.17 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 143.4, 125.3, 21.9, 11.0, 6.5, 4.4, 4.3, 0.3; HRMS (ESI) *m/z* 281.1946 [$(M+Li)^+$ calculated for $C_{13}H_{30}LiO_2Si_2$: 281.1944].

**Silyl enol ether (Z)-13:** To a solution of silyl ether **11** (0.54 g, 2.67 mmol) in THF (10 mL) at 0 °C, triethyl amine (0.6 mL, 1.6 equiv) was added dropwise followed by TMSOTf (0.72 mL, 1.5 equiv). Stirred at 0 °C for 30 min then quenched with water (10 mL). The mixture was extracted with $Et_2O$ (3 x 50 mL). The combined organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo to afford 0.67 g (92%) of (Z)**-13** as a yellow oil: IR (neat) 2956, 2914, 2878, 1678, 1460, 1414, 1386, 1336, 1295, 1251, 1209, 1111, 1064, 1041, 1003, 903, 843, 821, 744, 673 $cm^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$): δ 4.90 (q, J = 6.7 Hz, 1H), 4.01 (s, 2H), 1.62 (d, J = 6.9 Hz, 3H), 0.99 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.8 Hz, 6H), 0.23 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 103.1, 65.1, 10.7, 7.0, 6.8, 4.8, 0.8; HRMS (ESI) *m/z* 281.1948 [$(M+Li)^+$ calculated for $C_{13}H_{30}LiO_2Si_2$: 281.1944].

**Vinyl iodide 16 via Brown syn crotylation:** To a solution of t-BuOK (4.31g, 36.5 mmol, 1.1 equiv) in THF (50 mL) at –78 °C was added *cis*-2-butene (15 mL, 165.9 mmol, 5 equiv, condensed in a graduated cylinder at –78 °C). After 5 min, n-BuLi (1.8 M in hexanes, 20.3 mL, 36.5 mmol, 1.1 equiv) was added. The mixture was warmed to -

45 °C for 15 min, cooled to –78 °C and (-)-$Ipc_2BOMe$ (12.6 g, 39.8 mmol, 1.2 equiv) in THF (50 mL) was added. The resultant solution was stirred at –78 °C for 30 min and $BF_3$•$OEt_2$ (5.42 mL, 43.13 mmol, 1.3 equiv) was added. After 15 min a solution of aldehyde **14** (ca. 33 mmol) was added. The resultant solution was stirred at –78 °C for 16 h before warmed to room temperature. The reaction was quenched with water (100 mL) and concentrated aqueous NaOH (50 mL), diluted with $Et_2O$ (ca. 50 mL) and hydrolysis progress monitored by TLC. After the organic layer was separated, the aqueous layer was extracted with $Et_2O$ (3 x 50 mL). Combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography purification (Hexane/EtOAc on Biotage SP1) afforded ca. 6 g (25 mmol, 75%) of the alcohol as a colorless oil. To a solution of the alcohol (6.0 g, 25.2 mmol) in dichloromethane (140 mL) at 0 °C 2,6-lutidine (4.4 mL, 37.8 mmol, 1.5 equiv) was added followed by TESOTf (6.27 mL, 27.7 mmol, 1.1 equiv). The resultant solution was stirred at 0 °C for 1 h, quenched with $H_2O$ (50 mL), extracted with dichloromethane (50 mL x 3), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Hexane/EtOAc 100:1) to afford 4.07 g (67%) of **16** as a colorless oil. Enantiomeric excess was determined by chiral GC analysis to be 90%: $[\alpha]^{D}_{25}$ -18.6° (*c* 1.7, $CHCl_3$); IR (neat) 2955, 2876, 1239, 1166, 1072, 1006, 947, 915, 828, 742, 727, 671 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 6.50 (dd, J = 14.4, 6.8 Hz, 1H), 6.19 (d, J = 14.4 Hz, 1H), 5.78 (ddd, J = 17.2, 10.8, 7.2 Hz, 1H), 5.04-4.99 (m, 2H), 3.94 (t, J = 6.2 Hz, 1H), 2.29-2.24 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 8 Hz, 9H), 0.58 (q, J = 7.7 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 147.5, 139.9, 114.9, 78.9, 76.6, 43.9, 14.8, 6.8, 4.9; HRMS (ESI) *m/z* 359.0885 [$(M+Li)^+$ calculated for $C_{13}H_{25}ILiOSi$: 359.0879].

**Vinyl boronate 17:** To a solution of **16** (1.49 g, 4.23 mmol, 1 equiv) in THF (40 mL) at -78 °C n-BuLi (1.8 M in hexanes, 3.53 mL, 6.34 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h and 2-isopropoxy-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1.18 g, 6.34 mmol, 1.5 equiv) was added neat. After 10 min the mixture was diluted with $Et_2O$ (50 mL), washed with water (50 mL), brine (50 mL), dried ($MgSO_4$.) and concentrated *in vacuo* to afford **17** (1.37 g, 92%) as a slightly yellow oil: $[\alpha]^D_{25}$ +7.0° (*c* 2.0, $CHCl_3$); IR (neat) 3018, 2953, 2865, 1738, 1709, 1636, 1360, 1215 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): δ 6.92 (dd, J = 18.0, 5.5 Hz, 1H), 5.96 (dd, J = 18.0, 1.0 Hz, 1H), 5.91-5.80 (m, 1H), 4.97-4.95 (m, 1H), 4.94-4.93 (m, 1H), 4.06 (dt, J = 6.0, 1.0 Hz, 1H), 2.31-2.25 (m, 1H), 1.03 (s, 12H), 1.01 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.56 (dq, J = 8.0, 2.5 Hz, 6H); $^{13}C$ NMR (125 MHz, $C_6D_6$): δ 154.8, 141.1, 114.4, 83.0, 78.5, 44.3, 42.8, 42.7, 14.6, 7.1, 5.3; HRMS (ESI) *m/z* 359.2792 [$(M+Li)^+$ calculated for $C_{19}H_{37}BLiO_3Si$: 359.2765].

**Alcohol 23**: To a solution of lactone **21** (7.27 g, 62.6 mmol) in dichloromethane (100 mL) at -78 °C was added DIBAl-H (neat, 16.74 mL, 93.9 mmol, 1.5 equiv) dropwise. The resulting solution was stirred at -78 °C for 3 h and quenched with MeOH (ca. 5 mL; until no more gas evolution can be observed). The mixture was allowed to warm to room temperature and poured into a saturated solution of potassium sodium tartrate (100 mL). Dichloromethane (200 mL) was added to the solution and the mixture stirred for 3 h. The aqueous layer was extracted with dichloromethane (extensive extraction is necessary and TLC monitoring is recommended; the resulting lactol appears to be fairly soluble in the aqueous phase). The combined organic layers were dried ($MgSO_4$). About half of the solvent was evaporated to ca. 400 mL. 1,3-propanedithiol

(18.9 mL, 187.8 mmol, 3 equiv) and $BF_3 \cdot OEt_2$ (9.5 mL, 75.12 mmol, 1.2 equiv) were then added sequentially dropwise. The resulting solution was stirred at room temperature for 12 h. The reaction was quenched with $H_2O$ (100 mL), and the aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 2:1-1.5:1-1:1) to afford 11.2 g (86%) of alcohol **23** as colorless oil: $[\alpha]_D^{25}$ +14.4° (c 5.2, $CHCl_3$); IR (neat) 3448, 2981, 2895, 1425, 1113, 756 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.18 (dd, J = 8.1, 6.3 Hz, 1H), 3.82 (ddd, J = 11.4, 6.0, 3.6 Hz, 1H), 3.65-3.50 (m, 2H), 3.47 (s, 3H), 2.99-2.82 (m, 4H), 2.21-2.04 (m, 2H), 1.96-1.83 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 78.1, 63.6, 57.8, 43.9, 37.1, 30.6, 30.4, 26.1; HRMS (ESI) *m/e* 231.0500 [ $(M+Na)^+$ calcd for $C_8H_{16}O_2S_2Na$: 231.0483].

**Aldehyde 24**: To a solution of $(COCl)_2$ (0.228 mL, 2.61 mmol, 1.6 equiv) in dichloromethane (6 mL) was added a solution of DMSO (0.403 mL, 5.22 mmol, 3.2 equiv) in dichloromethane (2 mL). The resulting mixture was stirred at -78 °C for 15 min before alcohol **23** (0.34 g, 1.63 mmol) in dichloromethane (1 mL) was added. The mixture was stirred for 15 min at -78 °C, and *i*-$Pr_2NEt$ (1.42 mL, 8.15 mmol, 5.0 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for another 15 min, warmed to 0 °C and stirred for 45 min. The reaction was quenched with $H_2O$ (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with 0.1 N HCl (5 mL), $H_2O$ (10 mL), saturated $NaHCO_3$ (10 mL), $H_2O$ (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 5:1) to afford 0.33 g (98%) of the aldehyde **24** as a colorless oil: $[\alpha]_D^{25}$ –36.5° (*c* 3.8 , $CHCl_3$); IR (neat) 3418, 2931, 2902,

2822, 1724, 1418, 1113 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): δ 9.37 (d, J = 1.5 Hz, 1H), 4.05 (t, J = 7.0 Hz, 1H), 3.54 (ddd, J = 8.0, 5.0, 1.5 Hz, 1H), 2.99 (s, 3H), 2.30-2.22 (m, 2H), 2.19-2.13 (m, 2H), 2.09-2.00 (m, 2H), 1.48-1.36 (m, 2H); $^{13}C$ NMR (125 MHz, $C_6D_6$): δ 201.7, 82.6, 57.9, 41.7, 36.2, 28.6, 28.5, 25.6; HRMS (ESI) *m/z* 207.0514 [$(M+H)^+$ calcd for $C_8H_{15}O_2S_2$: 207.0513].

**Alcohol 26**: To a suspension of freshly cut magnesium ribbon (10.53 g, 433.3 mmol, 20 equiv) in $Et_2O$ (100 mL) at room temperature was added 1,2-dibromoethane (2.80 mL, 32.49 mmol, 1.5 equiv). Addition was dropwise at a rate to maintain a gentle reflux. A solution of bromide **25** (28.47 g, 65 mmol, 3 equiv) in $Et_2O$ (40 mL) was added to the resulting solution over 2 h. The mixture was stirred at room temperature for 1 h, transferred via cannula to a second flask and cooled to -78 °C. A solution of aldehyde **24** (4.47 g, 21.66 mmol, 1 equiv) in $Et_2O$ (40 mL) was then added dropwise. The reaction mixture was stirred at -78 °C for 3 h, quenched with saturated $NaHCO_3$ (100 mL), extracted with $Et_2O$ (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc/$Et_3N$, 40:5:1) to afford 10.4 g (85%) of alcohol **26** as a colorless oil: $[\alpha]_D^{25}$ -4.6° (c 4.3, $CHCl_3$); IR (neat ) 3440, 2953, 2924, 1462, 1418, 1375, 1098 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) δ 6.76 (tq, J = 6.5, 1.5 Hz, 1H), 4.19 (t, J = 7.0 Hz, 1H), 3.55-3.51 (m, 1H), 3.41 (dd, J = 11.5, 4.5 Hz, 1H), 3.21 (s, 3H), 2.48-2.27 (m, 6H), 2.08 (t, J = 6.5 Hz, 2H), 1.97 (d, J = 1.5 Hz, 3H), 1.71 (d, J = 6.5 Hz, 1H), 1.63-1.51 (m, 9H), 1.41-1.35 (m, 7H), 1.00-0.92 (m, 15H); $^{13}C$ NMR (125 MHz, $C_6D_6$) δ 141.2, 138.3, 80.8, 72.4, 58.6, 44.3, 37.1, 33.5, 30.2, 30.0, 29.5, 27.7, 25.9, 25.0, 19.2, 13.8, 9.4 ; HRMS (ESI) *m/e* 567.2353 [ $(M)^+$ calcd for $C_{25}H_{50}O_2S_2Sn$: 567.2352].

**Vinyl iodide 28**: To a solution of alcohol **26** (2.43 g, 4.3 mmol) in dichloromethane (10 mL) at 0 °C was added a solution of iodine (1.1 g, 4.3 mmol) in dichloromethane (5 mL) slowly until a yellow color persisted. After 5 min, imidazole (0.878 g, 12.9 mmol, 3 equiv) was added to the solution followed by TESCl (2.1 mL, 12.9 mmol, 3 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated $Na_2S_2O_3$ (10 mL) and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc, 25:1) to afford 2.0 g (90%) of vinyl iodide **28** as a colorless oil: $[\alpha]_D^{25}$ -11.6° (c 4.6, $CHCl_3$); IR (neat ) 2950, 2873, 1419, 1240, 1102, 1004, 779 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$) δ 6.09 (tq, J = 7.5, 1.5 Hz, 1H), 4.34 (dd, J = 10.5, 4.0 Hz, 1H), 3.79-3.76 (m, 1H), 3.63 (ddd, J = 10.0, 4.5, 2.0 Hz, 1H), 3.28 (s, 3H), 2.44-2.38 (m, 3H), 2.20 (ddd, J = 14.5, 10.5, 2.5 Hz, 1H), 2.15 (d, J = 1.5 Hz, 3H), 2.08-2.02 (m, 1H), 1.97 (ddd, J = 14.5, 10.0, 4.0 Hz, 1H), 1.84-1.76 (m, 1H), 1.61-1.48 (m, 3H), 1.42-1.37 (m, 1H), 1.25-1.20 (m, 1H), 0.99 (t, J = 8.0 Hz, 9H), 0.62 (dq, J = 8.0, 2.5 Hz, 6H) ; $^{13}C$ NMR (125 MHz, $C_6D_6$) δ 141.2, 93.8, 80.3, 71.2, 58.1, 44.7, 35.6, 30.8, 30.4, 29.9, 27.5, 27.3, 26.1, 7.1, 5.4; HRMS (ESI) *m/e* 523.1193 [ $(M+Li)^+$ calcd for $C_{19}H_{37}ILiO_2S_2Si$: 523.1173].

**Aldehyde 29**: To a solution of dithiane **28** (1.58 g, 3.06 mmol) in MeCN/pH 7 buffer (70 mL 4:1) at 0 °C was added $K_2CO_3$ (1.06 g, 7.65 mmol, 2.5 equiv) and MeI (1.90 mL, 30.58 mmol, 10 equiv) dropwise over 5 min. The reaction mixture was warmed to 30 °C and stirred for 24 h. The reaction mixture was diluted with $Et_2O$ (50 mL) and the aqueous layer was extracted with $Et_2O$ (3 x 50 mL). The combined organic

layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane/EtOAc, 25:1-20:1-15:1) to afford 1.20 g (92%) of aldehyde **29** as a colorless oil: $[\alpha]_D^{25}$ –15.0° (*c* 4.4 , $CHCl_3$); IR (neat) 2953, 2873, 1724, 1455, 1375, 1113, 742 $cm^{-1}$; $^1H$ NMR (500 MHz $C_6D_6$): δ 9.47 (s, 1H), 6.14-6.10 (m, 1H), 3.68-3.62 (m, 2H), 3.04 (s, 3H), 2.31 (ddt, J = 12.0, 3.5, 1.0 Hz, 1H), 2.16-2.12 (m, 1H), 2.11 (s, 3H), 2.04-1.96 (m, 1H), 1.79-1.71 (m, 1H), 1.54-1.47 (m, 1H), 1.16-1.09 (m, 1H), 0.90 (t, J = 8.0 Hz, 9H), 0.50 (q, J = 8.0 Hz, 6H); $^{13}C$ NMR (125 MHz, $C_6D_6$): δ 199.2, 141.0, 93.9, 78.8, 71.3, 57.5, 43.6, 30.9, 27.3, 27.2, 6.9, 5.2; HRMS (ESI) *m/z* 427.1131 [$(M+H)^+$ calcd for $C_{16}H_{32}IO_3Si$: 427.1166].

**Diene 30**: To a solution of aldehyde **29** (0.63 g, 1.48 mmol) and vinyl borate **17** (0.63 g, 1.77 mmol, 1.2 equiv) in THF/$H_2O$ (60 mL, 3:1, degassed by three freeze-thaw cycles) at room temperature was added $Pd(Ph_3P)_4$ (171 mg, 0.15 mmol, 0.1 equiv). The mixture was stirred for 5 min, TlOEt (157 μL, 2.22 mmol, 1.5 equiv) was added. The reaction was quenched after 15 min with saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with $Et_2O$ (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc on Biotage SP1) to afford 0.67 g (86%) of diene **30** as a colorless oil: $[\alpha]_D^{25}$ –11.0° (*c* 1.2 , $CHCl_3$); IR (neat) 2960, 2873, 1731, 1462, 1236, 1105 $cm^{-1}$; $^1H$ NMR (500 MHz $C_6D_6$): δ 9.53 (s, 1H), 6.27 (d, J = 15.5 Hz, 1H), 6.04-5.97 (m, 1H), 5.64 (dd, J = 15.5, 7.5 Hz, 1H), 5.51 (t, J = 7.0 Hz, 1H), 5.07-5.02 (m, 2H), 4.08 (t, J = 6.0 Hz, 1H), 3.83-3.79 (m, 1H), 3.72-3.68 (m, 1H), 3.10 (s, 3H), 2.42-2.37 (m, 2H), 2.36-2.29 (m, 1H), 2.21 (ddd, J = 16.5, 8.0, 2.0 Hz, 1H), 2.14 –2.06 (m, 1H), 1.74 (s, 3H), 1.73-1.66 (m, 1H), 1.36-1.28 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.02 (t, J =

8.0 Hz, 9H), 0.95 (t, J = 8.0 Hz, 9H), 0.64 (dq, J = 8.0, 1.5 Hz, 6H), 0.56 (q, J = 8.0 Hz, 6H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 199.5, 141.3, 135.6, 133.8, 132.2, 128.8, 114.2, 78.9, 78.0, 71.6, 57.6, 45.1, 43.7, 31.6, 25.2, 15.1, 12.6, 7.1, 7.0, 5.4, 5.3; HRMS (ESI) *m/z* 531.3869 [$(M+Li)^+$ calcd for $C_{29}H_{56}O_4Si_2Li$: 531.3877].

**Ester 33**: To a solution of aldol **31** (0.39 g, 0.55 mmol) and acid **32** (0.17 g, 0.68 mmol, 1.25 equiv) in toluene (50 mL) was added DMAP (1 g, 8.2 mmol, 15 equiv). After DMAP dissolved completely the mixture was cooled to -78 °C, and $Et_3N$ (0.84 mL, 6 mmol, 11 equiv) was added followed by 2,4,6-trichlorobenzoyl chloride (0.86 mL, 5.5 mmol, 10 equiv). The resulting slurry was slowly warmed to room temperature over 2.5 h. The reaction was stirred overnight at room temperature, quenched with saturated aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc on Biotage SP1) to afford 0.37 g (71%) of ester **33** as a colorless oil: $[\alpha]_D^{25}$ –8.2° (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2932, 2882, 1719, 1468, 1420, 1219, 1128, 1017 cm$^{-1}$; $^1$HMR (500 MHz, $C_6D_6$): δ 7.23 (s, 1H), 6.24 (d, J = 15.5 Hz, 1H), 6.17 (s, 1H), 6.03-5.96 (m, 1H), 5.80 (ddd, J = 6.0, 2.5, 1.5 Hz, 1H), 5.62 (dd, J = 15.5, 7.5 Hz, 1H), 5.51 (t, J = 6.5 Hz, 1H), 5.06-5.01 (m, 2H), 4.25 (d, J = 4.5 Hz, 1H), 4.05 (dd, J = 7.0, 5.5 Hz, 1H), 3.94-3.91 (m, 1H), 3.32 (s, 3H), 3.31-3.28 (m, 1H), 2.58 (dq, J = 17.5, 7.5 Hz, 1H), 2.42 -2.30 (m, 3H), 2.24-2.13 (m, 2H), 1.85 (s, 3H), 1.85-1.80 (m, 2H), 1.74 (s, 3H), 1.70 (s, 3H), 1.57-1.49 (m, 1H), 1.10 (d, J = 6.5 Hz, 3H), 1.02-0.92 (m, 30H), 0.64-0.53 (m, 18H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 209.5, 167.5, 143.8, 141.3, 139.3,135.6, 133.8, 132.3, 128.7, 128.4, 114.2, 86.1, 80.6, 80.1, 78.0, 72.3, 70.9, 58.2, 45.1, 32.0, 31.5, 30.5, 25.3, 24.2, 15.0, 14.2, 12.7, 7.5,

7.1, 7.1, 6.9, 5.4, 5.4, 5.0; HRMS (ESI) *m/z* 967.4882 [$(M+Li)^+$ calcd for $C_{46}H_{85}IO_7Si_3Li$: 967.4808].

**Aldol 35**: To a solution of LHMDS (0.87 mL, 0.87 mmol, 1M in THF, 2 equiv) in THF (6 mL) at -78 °C was added a solution of ketone **33** (0.42 g, 0.43 mmol) and HMPA (0.23 mL, 1.31 mmol, 3 equiv) in THF (9 mL). The reaction mixture was stirred at -78 °C for 2 h before a solution of aldehyde **8** (0.53 g, 1.31 mmol, 3 equiv) in THF (5 mL) was added dropwise. The solution was stirred at -78 °C for 3 h, quenched with saturated $NH_4Cl$ (50 mL) and warmed to room temperature. The aqueous layer was extracted with $Et_2O$ (3 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc on Biotage SP1, 40M column, 0-3% gradient over 40 column volumes) to afford 0.29 g (48%) of aldol **35** as a colorless oil: $[\alpha]_D^{25}$ –15.8° (*c* 2.1, $CHCl_3$); IR (neat) 3455, 2953, 2865, 1702, 1455, 1375, 1222, 1098 $cm^{-1}$; $^1$HMR (500 MHz, $C_6D_6$): δ 7.24 (s, 1H), 6.24 (d, J = 15.5 Hz, 1H), 6.21 (s, 1H), 6.04-5.97 (m, 1H), 5.62 (dd, J = 15.5, 7.5 Hz, 1H), 5.51 (t, J = 7.0 Hz, 1H), 5.06-5.02 (m, 2H), 4.84 (d, J = 3.5 Hz, 1H), 4.40 (d, J = 10.0 Hz, 1H), 4.33-4.30 (m, 1H), 4.07-4.05 (m, 2H), 3.95-3.92 (m, 1H), 3.36 (s, 3H), 3.33-3.30 (m, 1H), 3.29-3.24 (m, 2H), 3.23-3.19 (m, 1H), 3.06 (s, 3H), 2.42-2.31 (m, 3H), 2.22-2.15 (m, 1H), 2.08-2.02 (m, 1H), 1.98-1.84 (m, 3H), 1.87 (d, J = 1.5 Hz, 3H), 1.84-1.79 (m, 1H), 1.74 (s, 3H), 1.73 (s, 3H), 1.60-1.52 (m, 1H), 1.30-1.26 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.05-0.97 (m, 45H), 0.88 (d, J = 7.5 Hz, 3H), 0.78-0.67 (m, 24H), 0.21 (s, 3H), 0.18 (s, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 210.3, 167.7, 143.8, 141.3, 139.3, 135.7, 133.7, 132.4, 128.6, 128.4, 128.2, 114.2, 86.2, 80.9, 79.2, 75.4, 72.6, 72.5, 71.0, 70.0, 58.3, 58.1, 45.2, 45.1, 40.9, 38.9, 31.6, 31.2, 30.1,

30.1, 26.2, 25.9, 25.2, 24.2, 18.5, 15.0, 14.3, 12.7, 12.1, 7.5, 7.1, 7.0, 7.0, 5.4, 5.3, 5.3, -3.5, -4.5; HRMS (MALDI) *m/z* 1387.7399 [$(M+Na)^+$ calcd for $C_{66}H_{129}IO_{11}Si_5Na$: 1387.7319].

**Silyl ether 36**: To a solution of alcohol **35** (0.29 g, 0.21 mmol) in dichloromethane (4 mL) at -78 °C was added 2,6-lutidine (0.19 mL, 1.67 mmol, 8 equiv) followed by TESOTf (0.28 mL, 1.25 mmol, 6 equiv). The mixture was stirred for 30 min at -78 °C, then 30 min at 0 °C and quenched with $H_2O$ (15 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/EtOAc on Biotage SP1) to afford 0.30 g (97%) of TES ether **36** as a colorless oil: $[\alpha]_D^{25}$ –37.9° (*c* 0.7, $CHCl_3$); IR (neat) 2955, 2932, 2877, 1707, 1457, 1245, 1123, 1017 $cm^{-1}$; $^1$HMR (500 MHz, $C_6D_6$): δ 7.27 (s, 1H), 6.27 (d, J = 15.5 Hz, 1H), 6.26 (s, 1H), 6.07-5.97 (m, 2H), 5.65 (dd, J = 15.5, 7.5 Hz, 1H), 5.56 (t, J = 6.5 Hz, 1H), 5.09-5.05 (m, 2H), 4.88 (d, J = 3.5 Hz, 1H), 4.32 (ddd, J = 9.5, 5.0, 1.5 Hz, 1H), 4.22 (dd, J = 8.5, 1.5 Hz, 1H), 4.09 (t, J = 6.5 Hz, 1H), 4.00-3.92 (m, 2H), 3.51-3.46 (m, 1H), 3.41-3.38 (m, 2H), 3.37 (s, 3H), 3.30 (dd, J = 10.0, 4.5 Hz, 1H), 3.20 (s, 3H), 2.48-2.38 (m, 3H), 2.26-2.18 (m, 1H), 2.13-2.08 (m, 1H), 2.05-1.95 (m, 2H), 1.92-1.87 (m, 1H), 1.89 (d, J = 1.0 Hz, 3H), 1.79-1.75 (m, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 1.63-1.56 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H), 1.18-1.00 (m, 57 H), 0.99-0.90 (m, 9H), 0.84 (q, J = 8.0 Hz, 6H), 0.75 (q, J = 8.0 Hz, 6H), 0.68-0.60 (m, 12H), 0.22 (s, 3H), 0.20 (s, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): δ 209.5, 167.7, 143.7, 141.3, 139.4, 135.7, 133.8, 132.3, 128.7, 128.2, 128.1, 114.2, 86.4, 80.6, 79.8, 78.1, 77.0, 74.6, 72.4, 70.8, 70.3, 70.0, 58.8, 58.2, 47.1, 45.1, 43.8, 40.6, 31.5, 31.1, 26.0, 25.3, 24.2, 18.3, 15.0, 14.3, 12.7, 10.1, 7.5, 7.4,

7.2, 7.1, 7.1, 6.6, 5.8, 5.7, 5.4, 5.4, -4.0, -4.5; HRMS (ESI) *m/z* 1485.8426 [$(M+Li)^+$ calcd for $C_{72}H_{143}IO_{11}Si_6Li$: 1485.8451].

**Vinyl boronate 37**: To a solution of alkene **36** (20.5 mg, 13.8 μmol) in toluene (0.5 mL) was added iso-propenyl pinacol boronic ester (12 mg, 69 μmol, 5 equiv) followed by Grubbs second-generation catalyst **34** (0.6 mg, 0.7 μmol, 0.05 equiv). The resulting solution was stirred at 50 °C for 46 h, cooled to room temperature and diluted with dichloromethane (5 mL). The resultant solution was filtered through a short silica gel plug. The solvent was removed *in vacuo* and the residue was purified by HPLC (Hexanes/EtOAc, 0-5% gradient over 50 min) to afford 5 mg (22%) vinyl boronate **37** as a colorless oil: $[\alpha]_D^{25}$ –32.84° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 3684, 3600, 3029, 2926, 2868, 1706, 1597, 1481, 1456, 1385, 1101 $cm^{-1}$; $^1$HMR (500 MHz, $C_6D_6$): δ 7.24 (s, 1H), 6.73 (dq, J = 10.0, 1.5 Hz, 1H), 6.29 (d, J = 16.0 Hz, 1H), 6.23 (s, 1H), 5.96 (d, J = 9.5 Hz, 1H), 5.69 (dd, J = 16.0, 6.5 Hz, 1H), 5.50 (t, J = 7.0 Hz, 1H), 4.86 (d, J = 3.0 Hz, 1H), 4.30-4.37 (m, 1H), 4.20-4.13 (m, 2H), 3.96-3.91 (m, 2H), 3.48-3.44 (m, 1H), 3.38-3.35 (m, 2H), 3.34 (s, 3H), 3.28-3.25 (m, 1H), 3.17 (s, 3H), 2.98-2.92 (m, 1H), 2.42-2.35 (m, 2H), 2.22-2.14 (m, 1H), 2.11-2.04 (m, 2H), 2.02-1.97 (m, 1H), 1.97 (d, J = 2.0 Hz, 3H), 1.94-1.92 (m, 1H), 1.86 (d, J = 1.0 Hz, 3H), 1.86-1.80 (m, 1H), 1.74 (d, J = 1.0 Hz, 3H), 1.71 (s, 3H), 1.64-1.50 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 1.15-0.98 (m, 69 H), 0.96-0.86 (m, 9H), 0.82 (q, J = 8.0 Hz, 6H), 0.74 (q, J = 8.0 Hz, 6H), 0.65 (q, J = 8.0 Hz, 6H), 0.59 (q, J = 8.0 Hz, 6H), 0.19 (s, 3H), 0.17 (s, 3H) ; $^{13}$C NMR (125 MHz, $C_6D_6$): δ 209.4, 167.7, 149.7, 143.8, 139.4, 135.1, 133.9, 132.0, 129.2, 128.6, 86.4, 83.0, 80.6, 77.6, 77.0, 74.6, 72.4, 70.7, 70.3, 70.0, 58.5, 58.1, 47.1, 43.8, 40.6, 31.4, 31.1, 30.1, 26.0, 25.3, 25.0, 24.8, 24.2, 18.3, 15.4, 14.5, 14.3, 12.6, 12.0, 10.1, 7.5, 7.4, 7.2, 7.2, 6.6,

5.8, 5.7, 5.5, 5.4, -4.0, -4.5; HRMS (ESI) *m/z* 1625.9207 [$(M+Li)^+$ calcd for $C_{79}H_{156}BIO_{13}Si_6Li$: 1625.9459].

**Silyl enol ether 39:** To a solution of aldehyde **8** (0.15 g, 0.37 mmol) in dichloromethane (5 mL) at 0 °C $K_2CO_3$ (77 mg, 0.56 mmol, 1.5 equiv) was added. The reaction mixture was cooled to -78 °C at which time $BF_3$•$OEt_2$ (9 μL, 0.074 mmol, 0.2 equiv) was added dropwise followed by (Z)-**13** silyl enol ether (0.2 g, 0.74 mmol, 2 equiv). The resultant solution was stirred for 3 h at -78 °C, quenched with saturated $NaHCO_3$ aqueous solution (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexanes/Ethyl Acetate, 25/1) to afford 0.17 g (68%) of silyl enol ether **39** as a slightly yellow oil: $[\alpha]_D^{25}$ -45.5°(*c* 0.69, $CHCl_3$); IR (neat) 2956, 2878, 1682, 1460, 1248, 1154, 1102, 1042, 1003, 973, 837, 813, 775, 744, 668 $cm^{-1}$; $^1H$ NMR (500 MHz, $C_6D_6$): δ 5.72 (s, 1H), 4.24 (td, J = 6.8, 2.5 Hz, 1H), 4.08 (d, J = 8.5 Hz, 1H), 4.02-3.98 (m, 1H), 3.37-3.31 (m, 2H), 3.17 (s, 3H), 3.08 (d, J = 1.5 Hz, 1H), 2.26 (quintet, J = 7 Hz, 1H), 2.05-1.95 (m, 3H), 1.44 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 6.5 Hz, 3H), 1.05-1.02 (m, 18H), 0.98 (t, J = 8 Hz, 9H), 0.70 (q, J = 8 Hz, 6H), 0.61 (q, J = 8 Hz, 6H), 0.33 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); $^{13}C$ NMR (100 MHz, $C_6D_6$): δ 139.4, 120.8, 77.5, 77.1, 75.6, 69.8, 58.8, 41.2, 40.6, 38.9, 26.2, 18.4, 16.0, 7.2, 6.8, 6.6, 5.8, 4.7, 1.1, -3.9, -4.4; HRMS (ESI) *m/z* 701.4455 [$(M+Na)^+$ calculated for $C_{33}H_{74}NaO_6Si_4$: 701.4460].

**Pyran 40:** A solution of silyl enol ether **39** (4 mg, 5.9 μmol) and p-TsOH (1 mg, 5.2 μmol) in 1 mL MeOH was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography ($CH_2Cl_2$/MeOH,

25/1) to afford 1 mg (69%) of pyran **40** as a colorless oil: $^1$H NMR (600 MHz, $CD_3OD$): δ 4.02 (t, J = 5.4 Hz, 1H), 3.95 (ddt, J = 12, 5.4, 4.2 Hz, 1H), 3.59 (t, J = 9.9 Hz, 1H), 3.41 (d, J = 12 Hz, 1H), 3.36 (d, J = 11.4 Hz, 1H), 3.35 (s, 3H), 3.33 – 3.31 (m, 1H), 1.99 (dqd, J = 10.2, 7.2, 5.4 Hz, 1H), 1.96 (dq, J = 9.6, 6.6 Hz, 1H), 1.71 (ddd, J = 13.8, 12.6, 6 Hz, 1H), 1.64 (ddd, J = 13.8, 3.6, 0.6 Hz, 1H), 1.05 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 7.2 Hz, 3H); HRMS (ESI) *m/z* 253.1625 [$(M+Li)^+$ calculated for $C_{12}H_{22}LiO_5$: 253.1627].

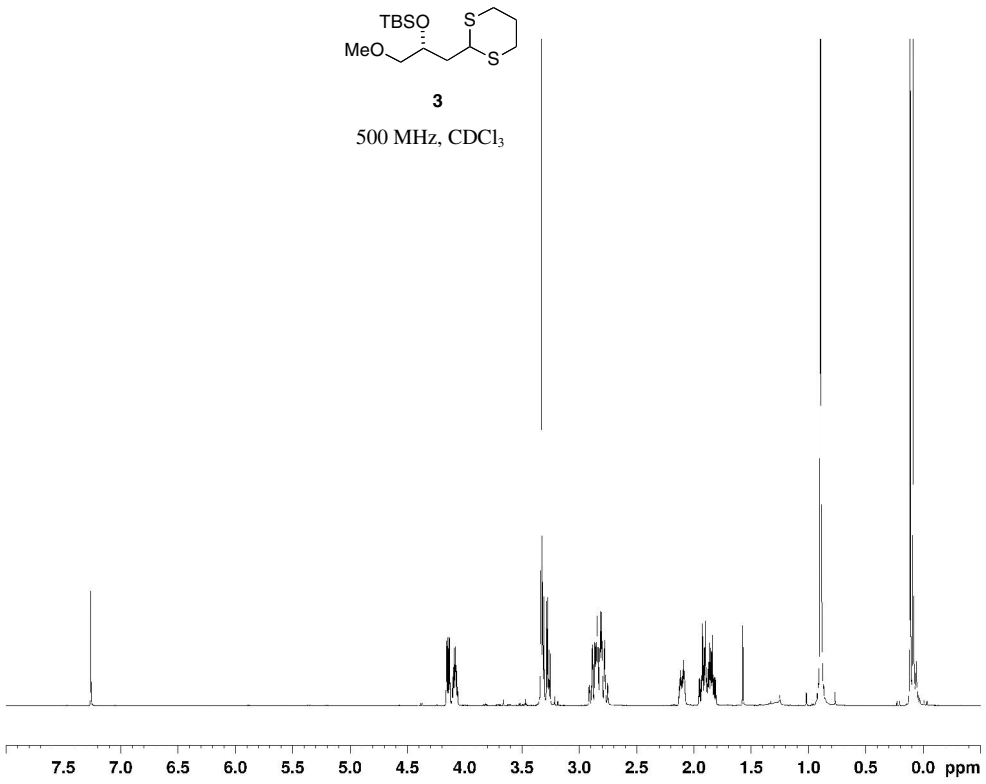
**Vinyl boronate 41**: To a solution of alkene **36** (28.9 mg, 19.5 μmol) in toluene (0.2 mL) was added 1-propenyl pinacol boronic ester (33 mg, 195 μmol, 10 equiv) followed by Grubbs second-generation catalyst **34** (1.7 mg, 1.95 μmol, 0.1 equiv). The resulting solution was stirred at 80 °C for 6 h, then 0.2 mL toluene were added and the mixture stirred at 40 °C for 24 h. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (5 mL). The resultant solution was filtered through a short silica gel plug. The solvent was removed *in vacuo* and the residue was purified by HPLC (Hexanes/EtOAc, 0-5% gradient over 50 min) to afford 16.6 mg (53%) vinyl boronate **41** as a colorless oil: IR (neat) 3467, 2954, 2365, 2343, 1708, 1638, 1459, 1362, 1242, 1112, 1007, 834, 740 $cm^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): δ 7.27 (s, 1H), 7.12 (d, J = 7 Hz, 1H), 6.27 (s, 1H), 6.26 (d, J = 15.5 Hz, 1H), 5.98 (d, J = 11 Hz, 1H), 5.85 (d, J = 18 Hz, 1H), 5.64 (dd, J = 15.5, 7 Hz, 1H), 5.52 (t, J = 6.8 Hz, 1H), 4.88 (d, J = 3 Hz, 1H), 4.32 (dd, J = 8.5, 5.5 Hz, 1H), 4.22 (d, J = 8 Hz, 1H), 4.18 (t, J = 5.8 Hz, 1H), 4.00-3.92 (m, 2H), 3.48 (q, J = 7 Hz, 1H), 3.43-3.40 (m, 2H), 3.38 (s, 3H), 3.30 (dd, J = 11, 4 Hz, 1H), 3.21 (s, 3H), 2.49-2.36 (m, 3H), 2.26-2.15 (m, 1H), 2.14-2.07 (m, 1H), 2.05-1.92 (m, 2H), 1.90 (s, 3H), 1.89-1.82 (m, 1H), 1.78 (s, 3H), 1.75-1.73 (m, 1H), 1.72 (s, 3H), 1.64-1.53 (m, 1H), 1.37 (d, J = 7 Hz, 3H), 1.20-1.00 (m, 72H), 0.99-0.89 (m, 6H),

0.88-0.82 (m, 6H), 0.79-0.73 (m, 6H), 0.68-0.59 (m, 12H), 0.22 (s, 3H), 0.20 (s, 3H); $^{13}$C NMR (150 MHz, $C_6D_6$): δ 209.5, 167.8, 157.2, 143.9, 139.5, 135.6, 133.9, 132.3, 128.8, 86.5, 82.9, 80.7, 79.9, 77.6, 77.1, 74.7, 72.5, 70.9, 70.4, 70.1, 58.9, 58.3, 47.2, 47.0, 43.9, 40.7, 31.5, 31.2, 25.4, 24.9, 24.8, 24.3, 14.4, 14.2, 12.7, 12.1, 10.2, 7.6, 7.5, 7.3, 7.2, 6.7, 5.9, 5.8, -3.9, -4.4; HRMS (MALDI) *m/z* 1627.9080 [$(M+Na)^+$ calcd for $C_{78}H_{154}BINaO_{13}Si_6$: 1627.9040].

**Macrolactone 42**: To a solution of vinyl boronate **41** (16.6 mg, 10.3 μmol) in THF/$H_2O$ (12 mL, 3:1, degassed) was added $Pd(Ph_3P)_4$ (2.4 mg, 2.06 μmol, 0.2 equiv). The resulting yellow solution was stirred for 5 min before Tl(OEt) (1.1 μL, 15.45 μmol, 1.5 equiv) was added. The solution was stirred for 15 min (color turns from yellow to grey). The reaction was quenched with saturated $NaHCO_3$ (5 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was diluted with Hexanes and filtrated through a small silica gel plug (washed with Hexanes until no more product eluted) to afford 13.3 mg (95%) of macrolactone **42** as a colorless oil: IR (neat) 2954, 2876, 1723, 1699, 1458, 1239, 1110, 1007, 961, 835, 740 $cm^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$): δ 7.53 (s, 1H), 6.27 (d, J = 11 Hz, 1H), 6.05 (dd, J = 14.5, 11 Hz, 1H), 5.92 (d, J = 16 Hz, 1H), 5.75 (d, J = 8 Hz, 1H), 5.53 (t, J = 7.3 Hz, 1H), 5.40-5.30 (m, 2H), 5.00 (d, J = 4 Hz, 1H), 4.33 (dd, J = 8.5, 4.5 Hz, 1H), 4.27 (d, J = 8 Hz, 1H), 3.98-3.92 (m, 1H), 3.82 (t, J = 8.5 Hz, 1H), 3.65 (t, J = 6.5 Hz, 1H), 3.57-3.51 (m, 1H), 3.54 (s, 3H), 3.43-3.39 (m, 2H), 3.20 (s, 3H), 3.03 (t, J = 7.8 Hz, 1H), 2.54-2.46 (m, 1H), 2.41-2.34 (m, 1H), 2.16-1.93 (m, 6H), 2.09 (s, 3H), 1.84-1.78 (m, 1H), 1.72 (s, 3H), 1.70-1.64 (m, 1H), 1.61 (s, 3H), 1.46 (d, J = 7 Hz, 3H), 1.44-1.36 (m, 1H), 1.27 (d, J =

6.5 Hz, 3H), 1.22-1.03 (m, 56H), 1.02-0.86 (m, 12H), 0.79-0.65 (m, 18H), 0.22 (s, 3H), 0.19 (s, 3H); $^{13}C$ NMR (150 MHz, $C_6D_6$): δ 209.9, 168.2, 144.9, 144.5, 140.9, 136.2, 133.6, 132.6, 131.9, 131.0, 126.1, 123.9, 82.2, 80.6, 78.3, 77.2, 76.2, 74.1, 73.1, 70.5, 70.1, 61.0, 58.8, 47.3, 46.7, 43.7, 40.9, 35.6, 34.9, 26.1, 24.8, 18.6, 15.4, 14.1, 12.2, 11.3, 10.4, 7.6, 7.5, 7.4, 7.3, 7.2, 6.7, 6.0, 5.9, 5.6, 5.5, -3.9, -4.4; HRMS (MALDI) *m/z* 1373.9100 [$(M+Na)^+$ calcd for $C_{72}H_{142}NaO_{11}Si_6$: 1373.9065].

**Cytotoxicity Assay:** H292 lung carcinoma cells were plated at a density of 500/well in 96-well plates in RPMI 1640 medium containing 10% fetal bovine serum. Compounds were dissolved in DMSO, and cells were treated with DMSO alone (control); apoptolidin A; apoptolidonone A; or apoptolidonone D from 3 nM - 10 mM (0.5% DMSO final concentration in culture medium). Viability was measured after 7 days by adding 2 μM Calcein-AM, and measuring fluorescence on a Spectramax (Molecular Dynamics) plate reader, λabs = 494; λem = 517. Effective concentration 50 ($EC_{50}$) values for apoptolidin A, apoptolidonone A, and apoptolidonone D are defined as the concentration of compound at which Calcein-AM fluorescence is inhibited by 50%.


TBSO
MeO
S
S
3
500 MHz, CDCl3
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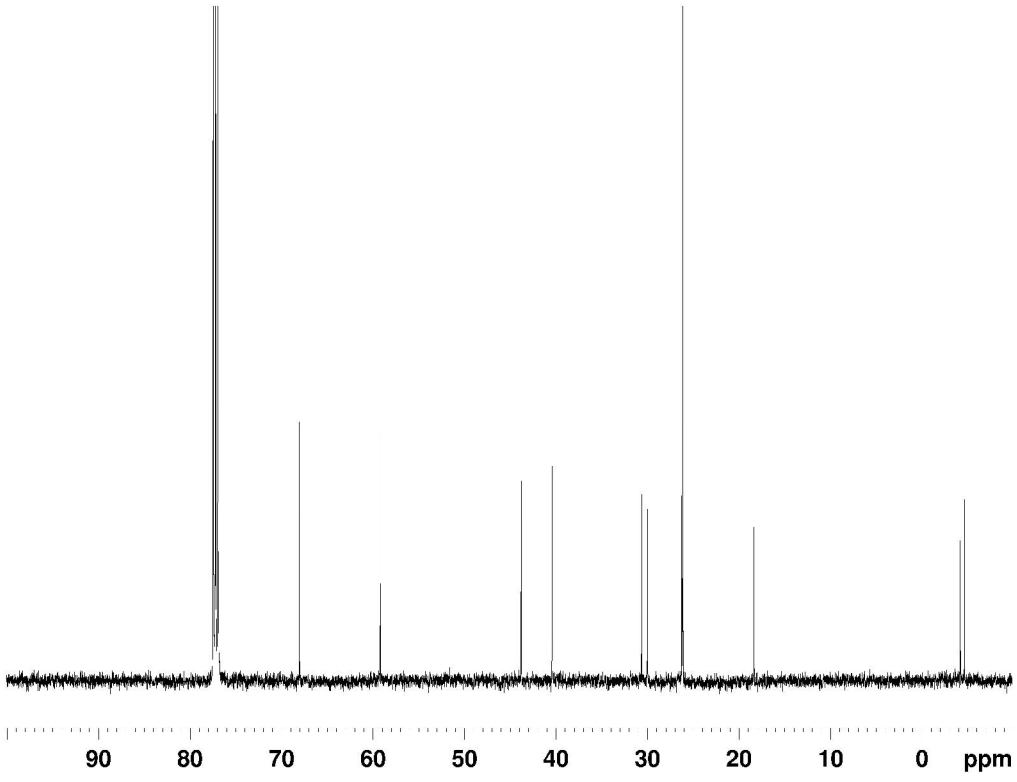
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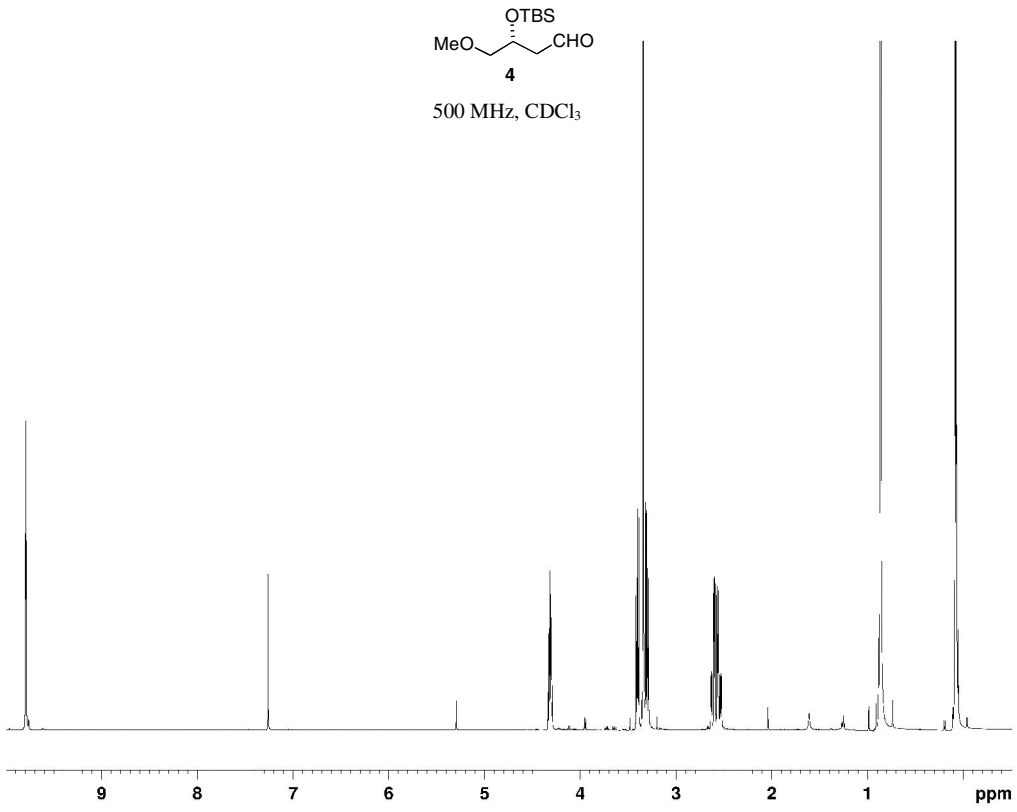
OTBS
MeO
CHO
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500 MHz, CDCl3
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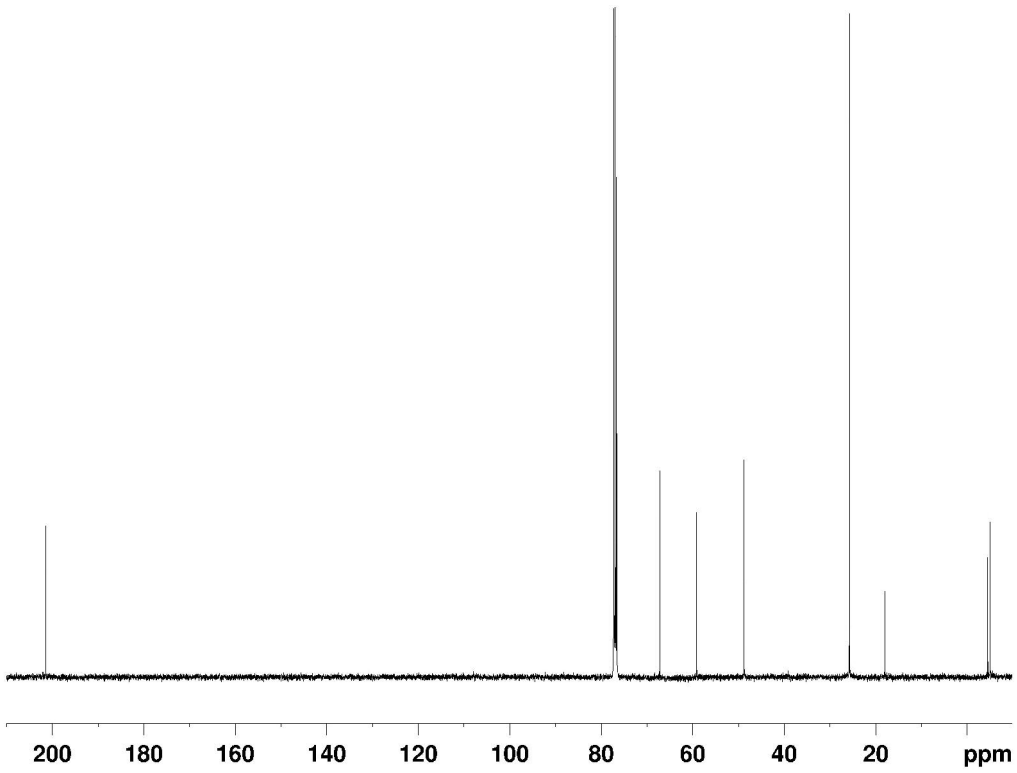
8
7
6
5
4
3
2
1
ppm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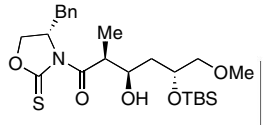
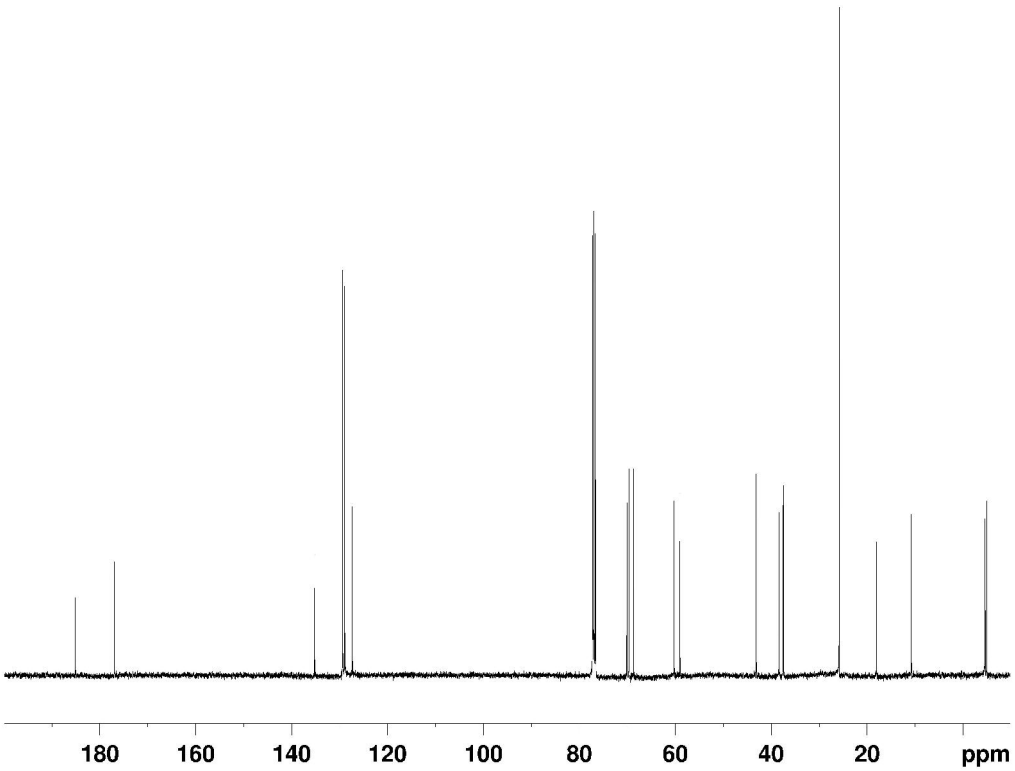
80
60
40
20
ppm

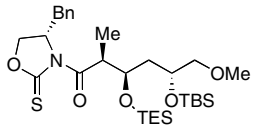



**5**

500 MHz, $CDCl_3$

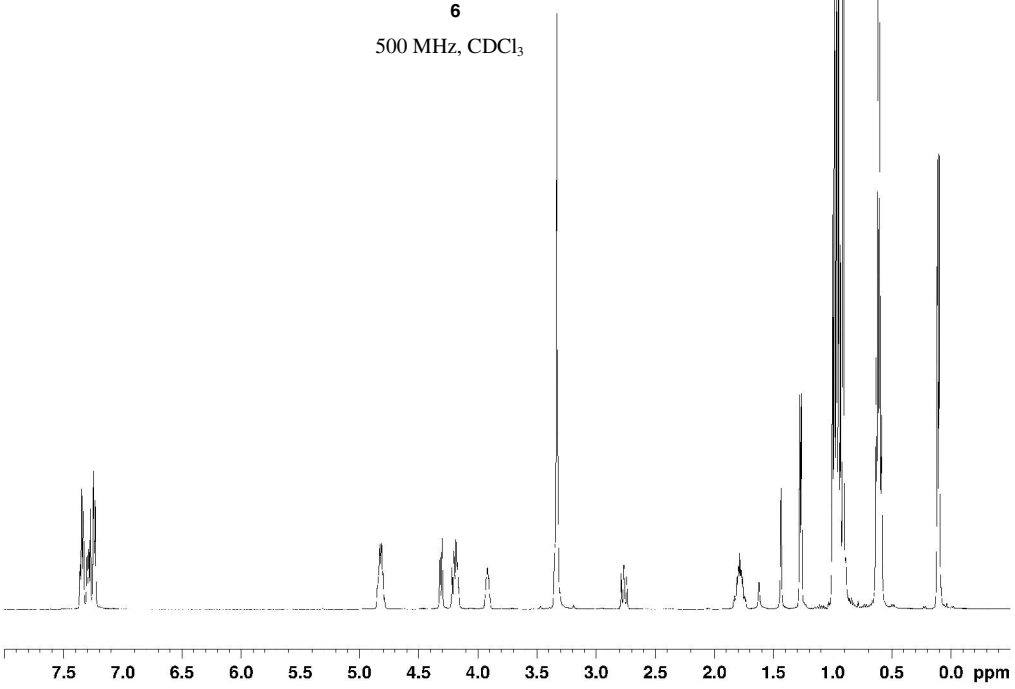


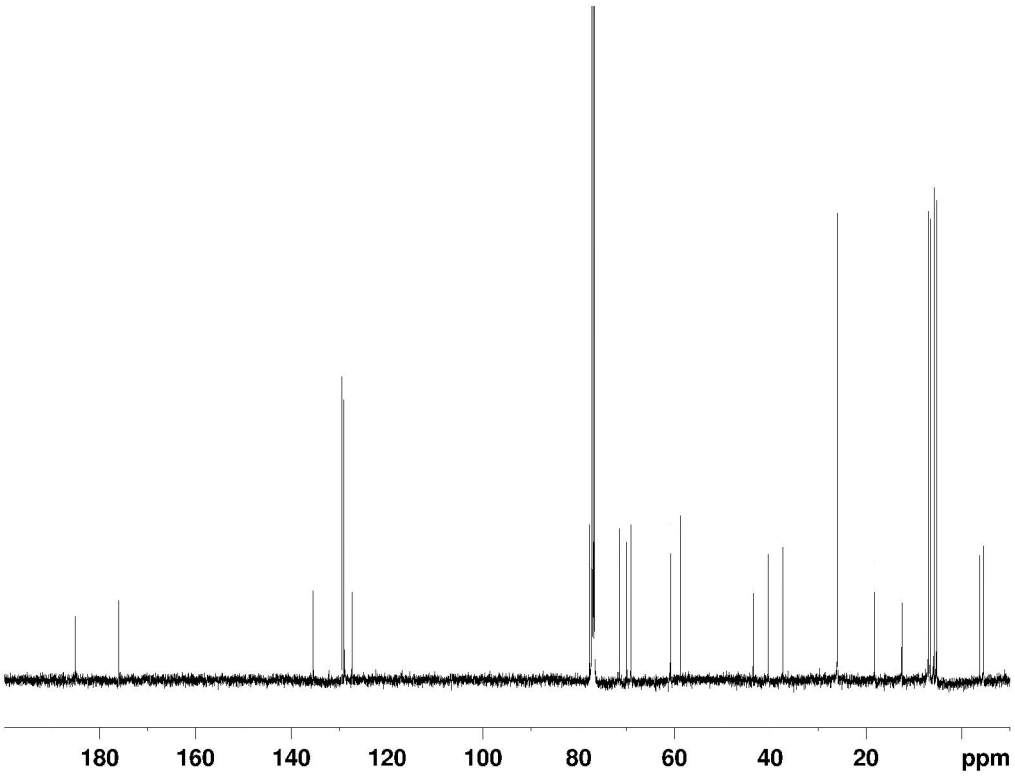



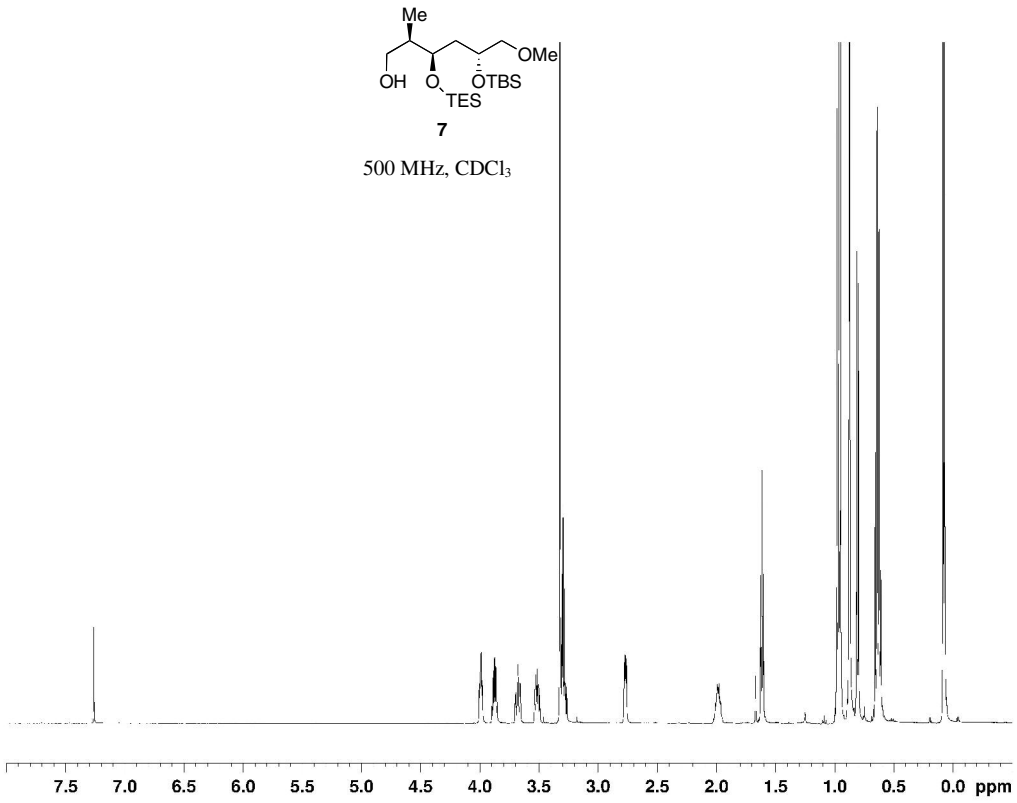


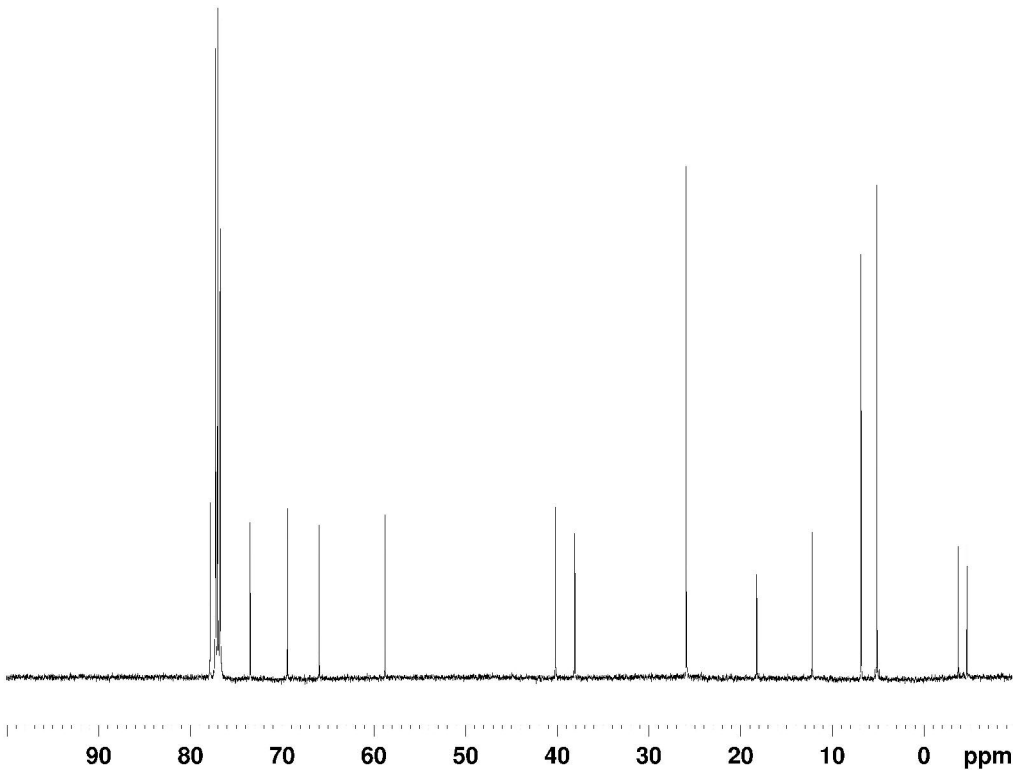

**6**

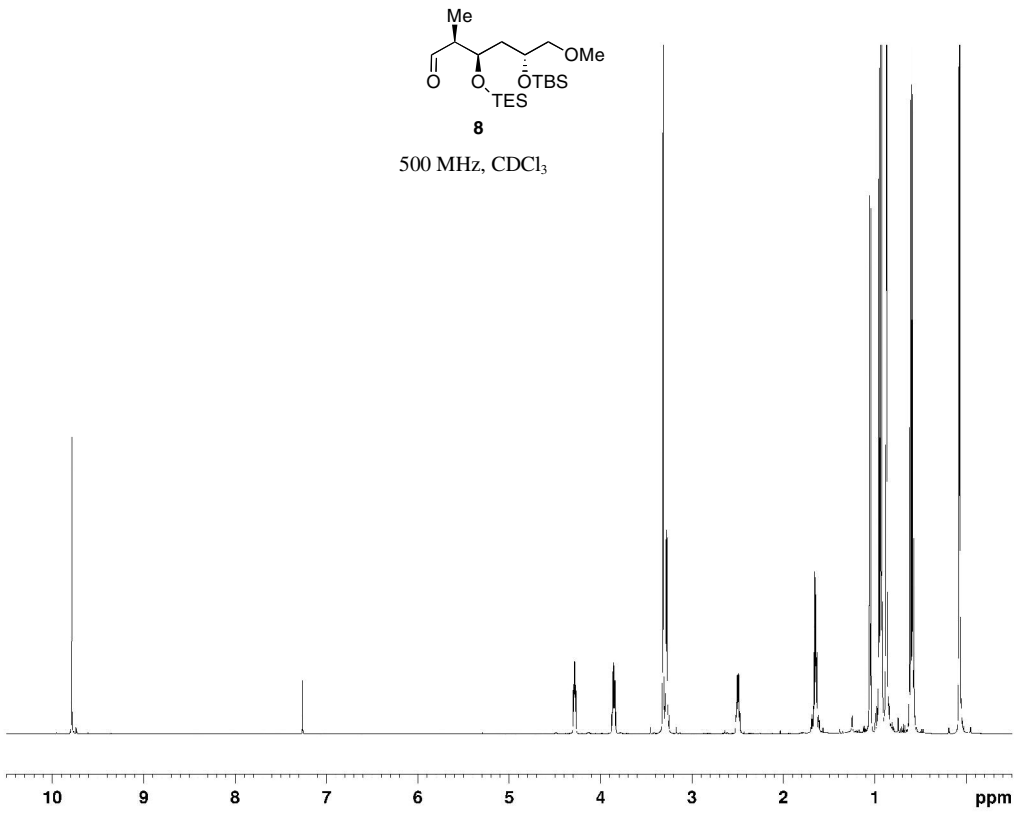
500 MHz, $CDCl_3$

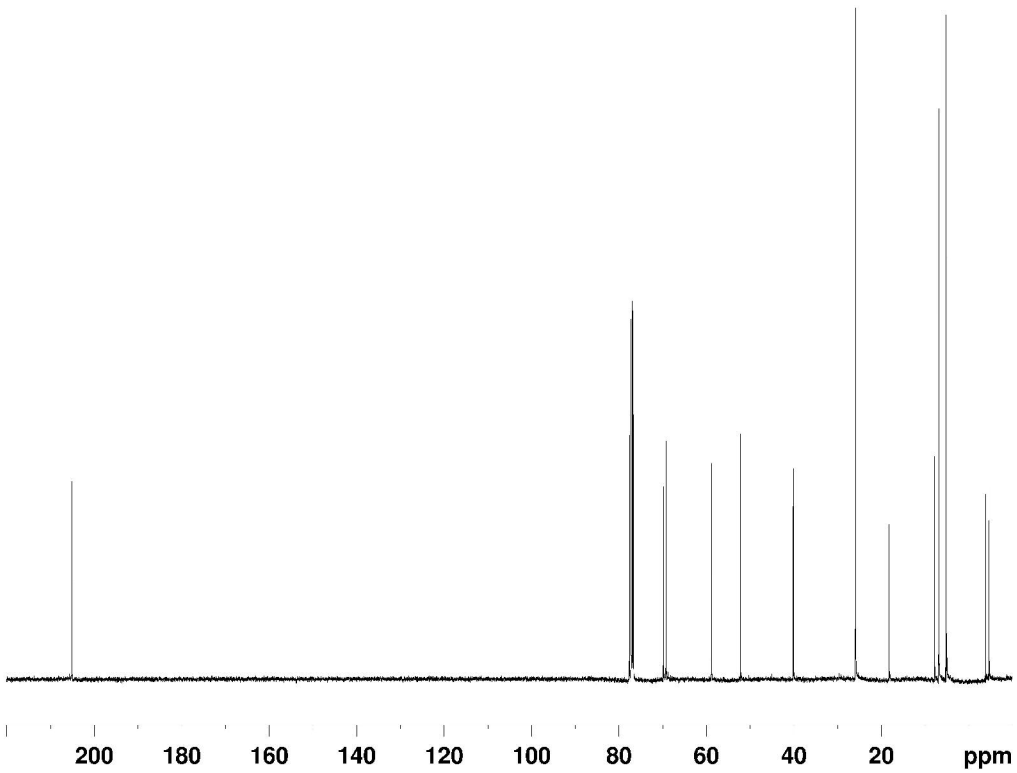


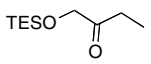




Me
OMe
OH
O
OTBS
TES
7
500 MHz, CDCl3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


90 80 70 60 50 40 30 20 10 0 ppm

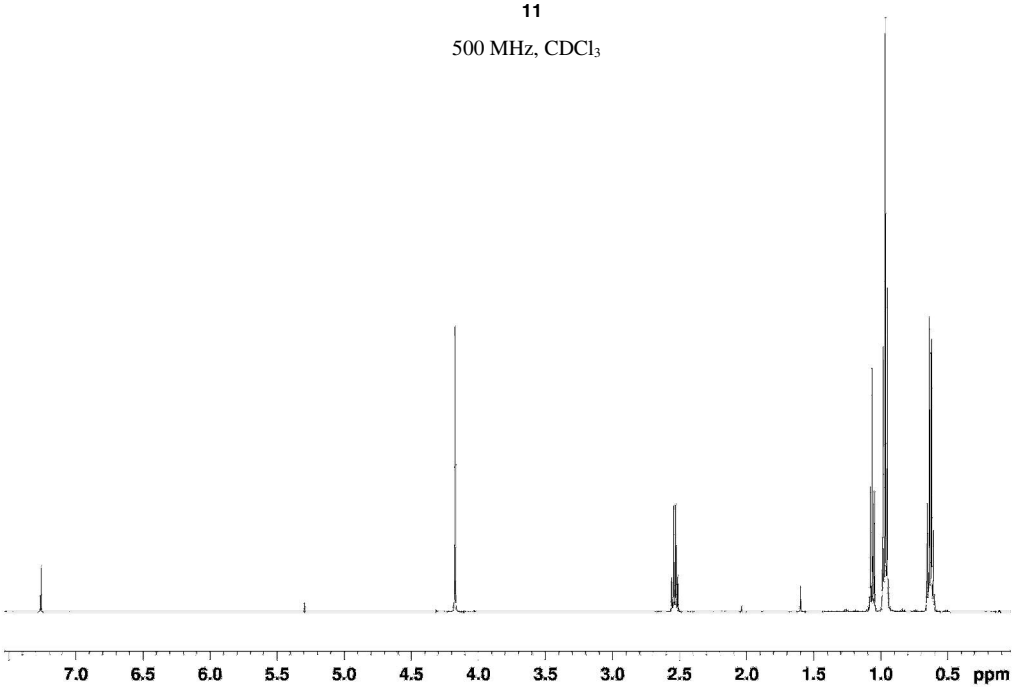

Me
OMe
O
O
OTBS
TES
8
500 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
ppm

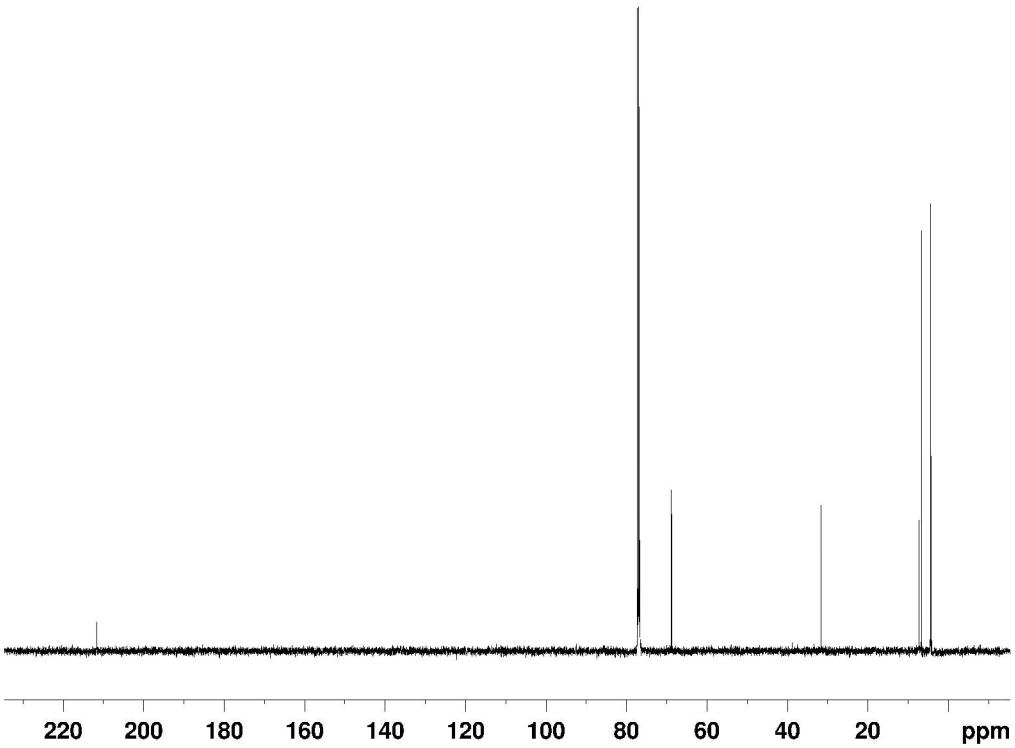

200
180
160
140
120
100
80
60
40
20
ppm

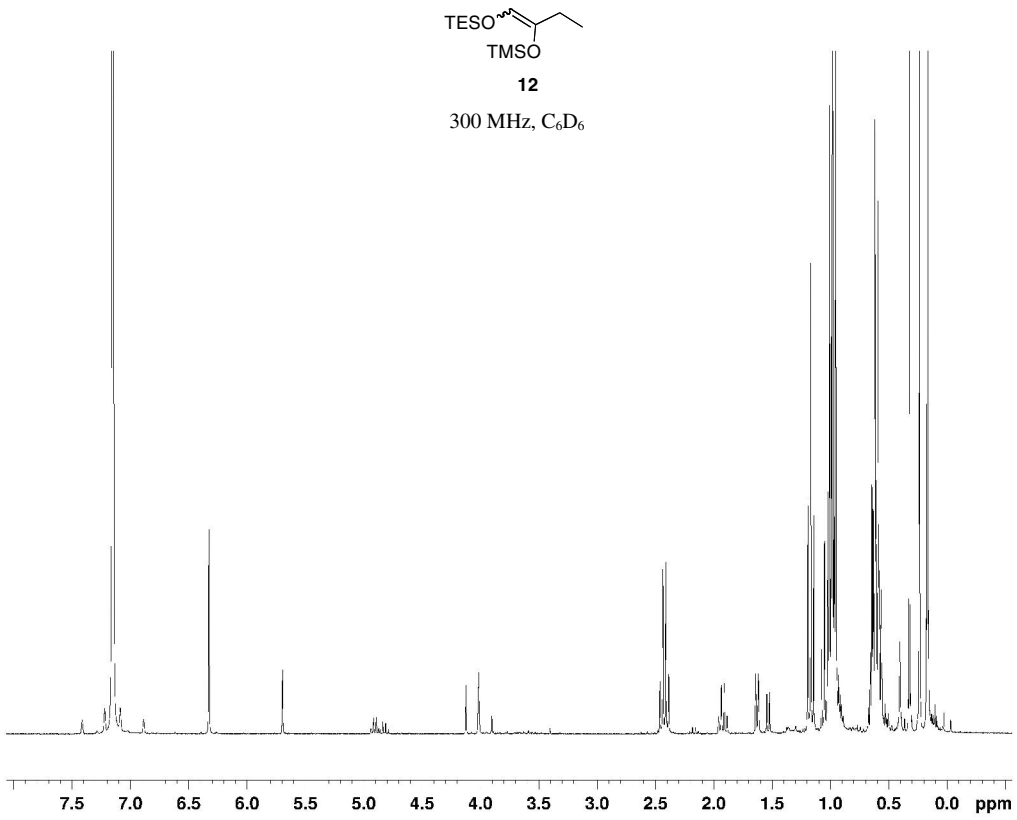



**11**

500 MHz, $CDCl_3$




TESO
TMSO
12
300 MHz, C6D6
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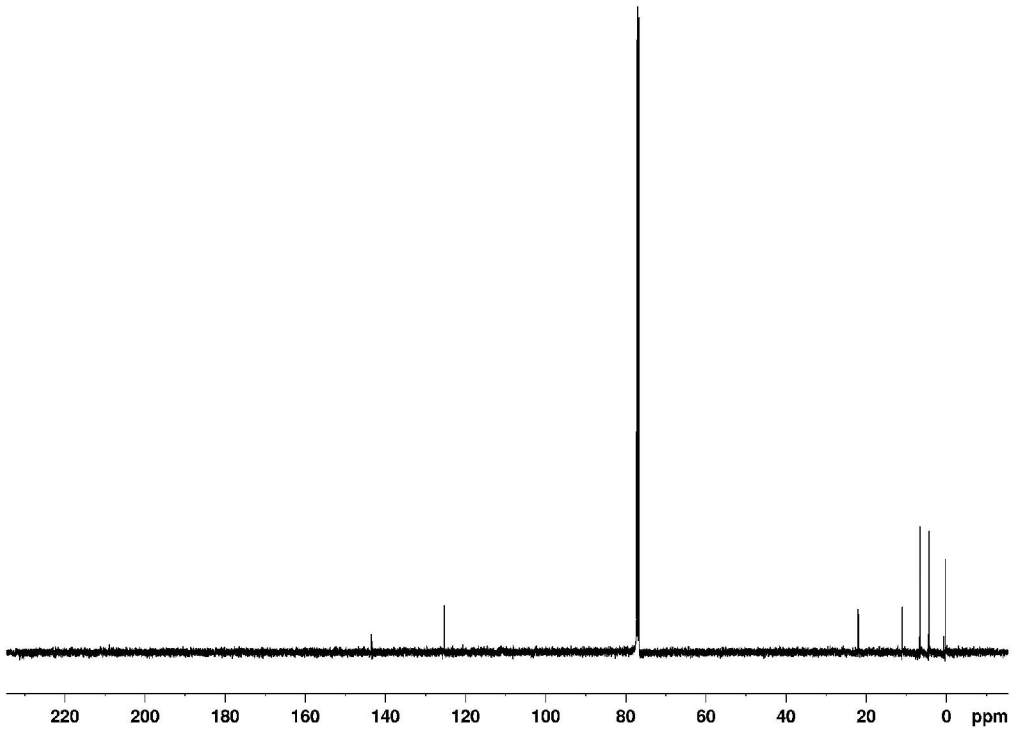
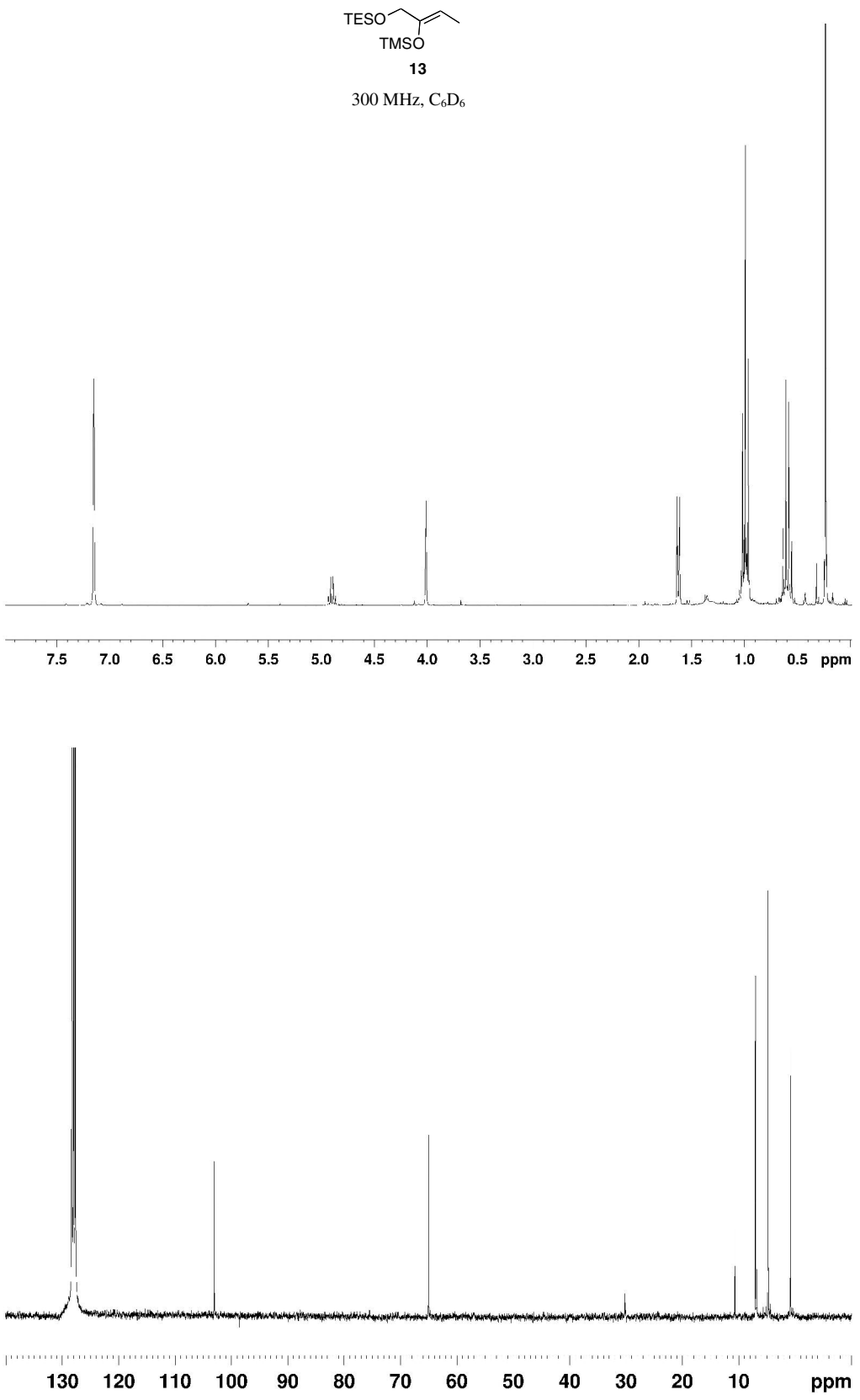
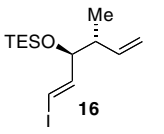
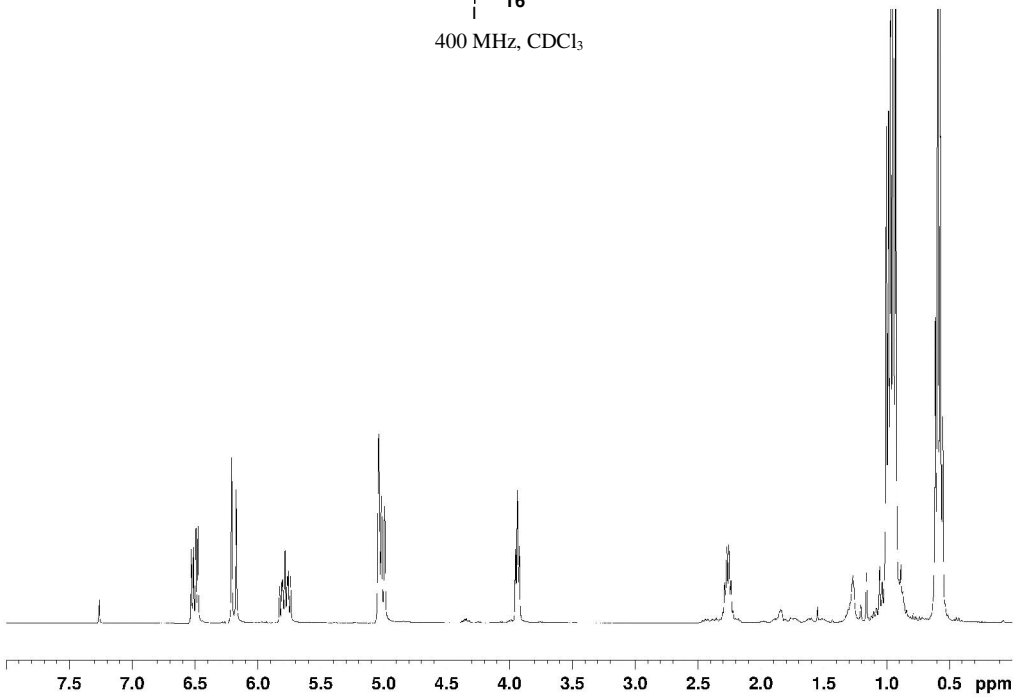
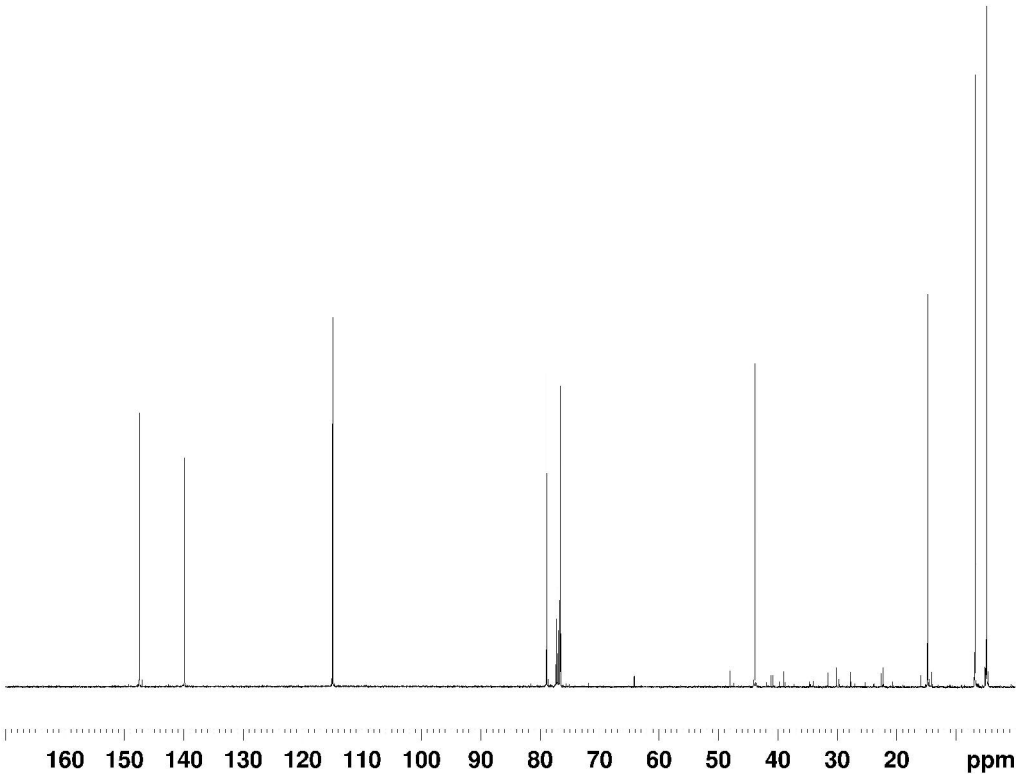

220 200 180 160 140 120 100 80 60 40 20 0 ppm

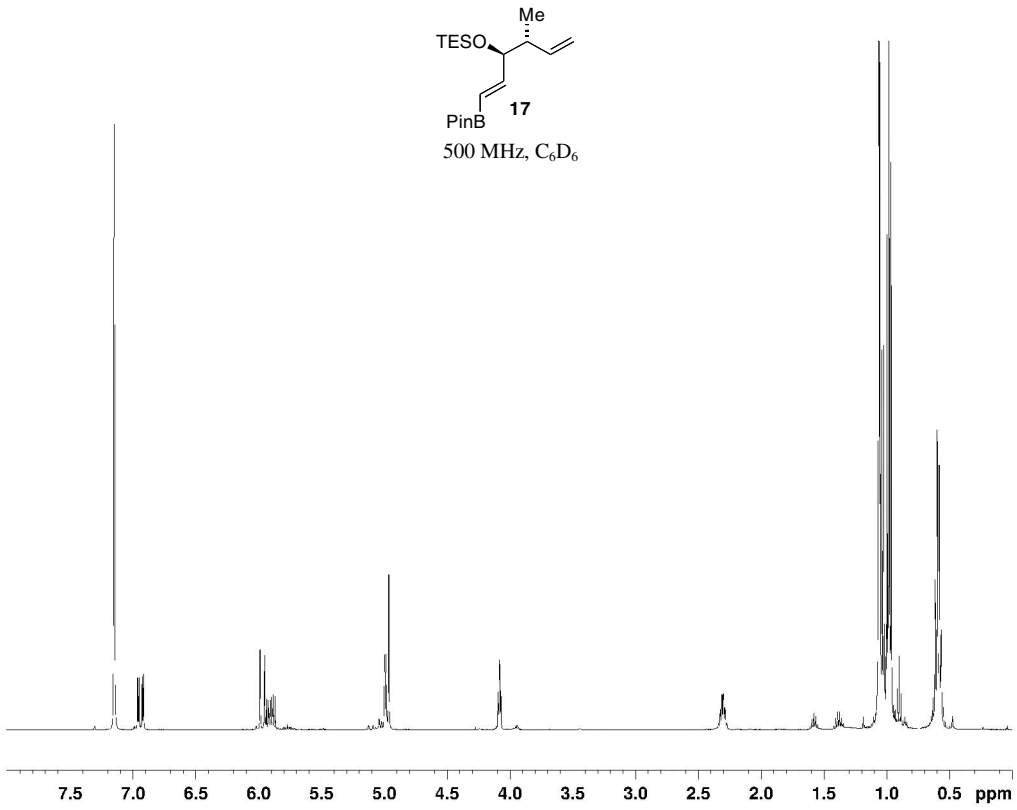

TESO
TMSO
13
300 MHz, C6D6
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

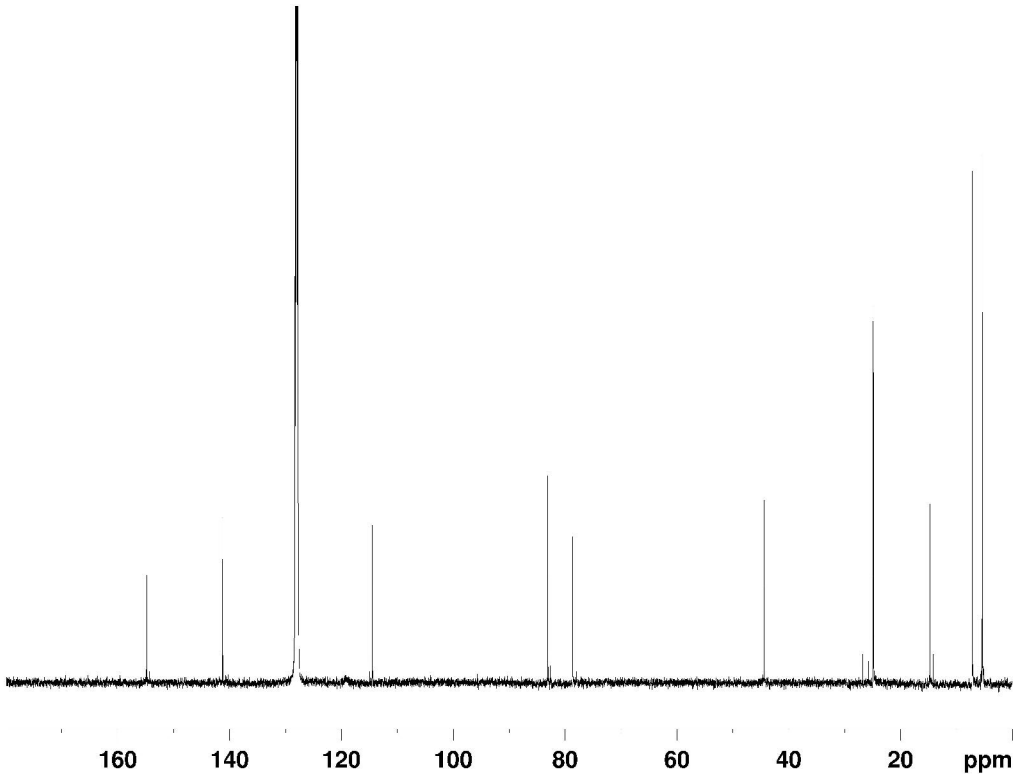


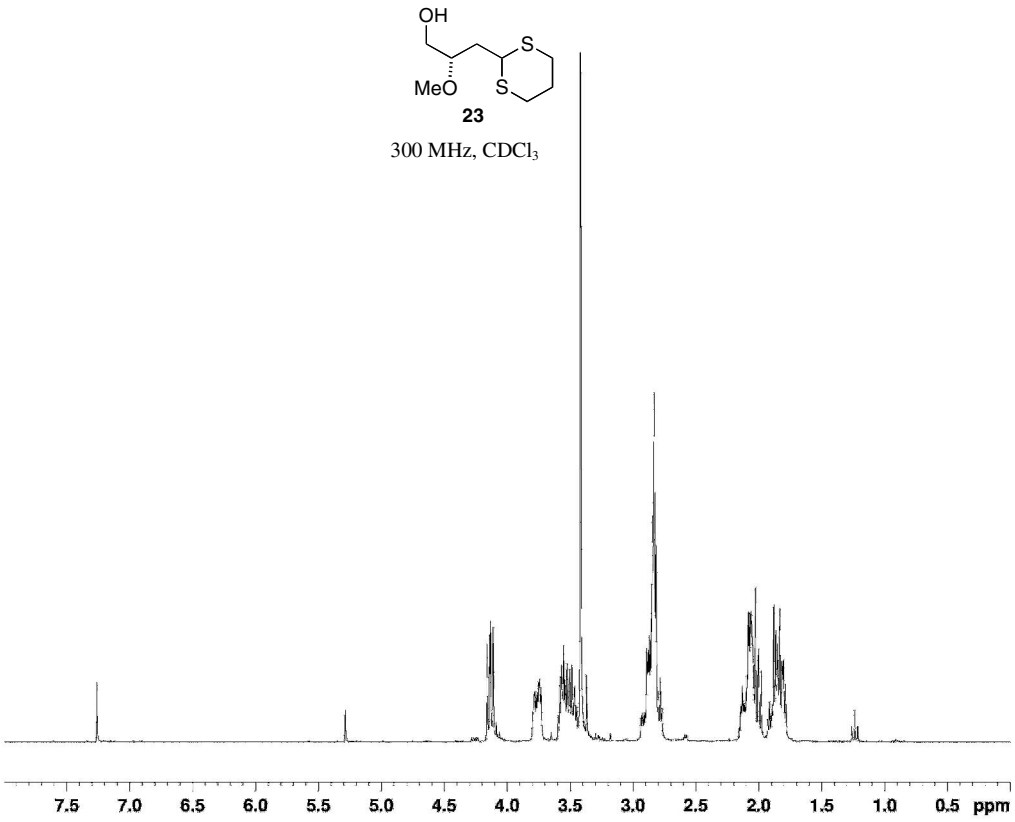

400 MHz, $CDCl_3$

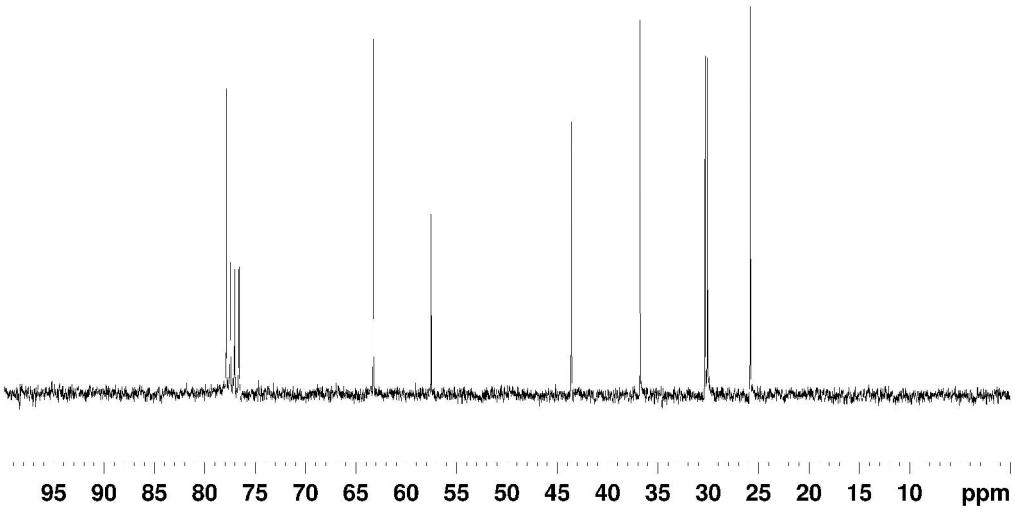


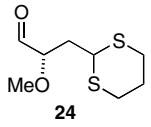




Me
TESO
PinB
17
500 MHz, C6D6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


160
140
120
100
80
60
40
20
ppm


OH
S
MeO
S
23
300 MHz, CDCl3
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 ppm

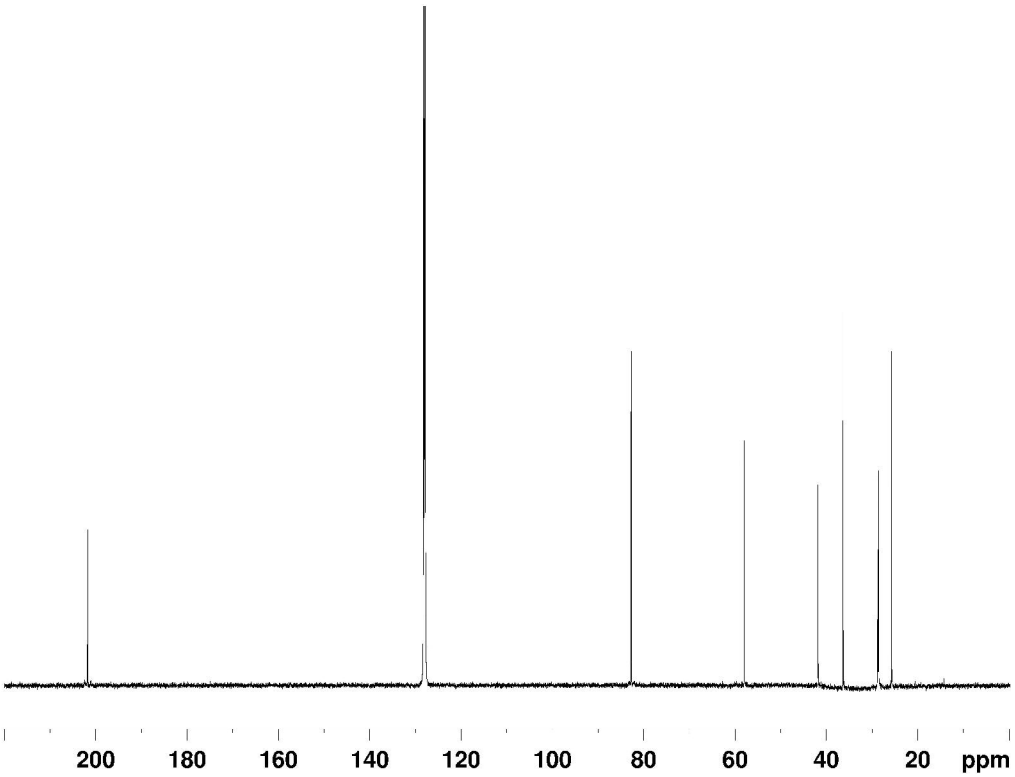

95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm

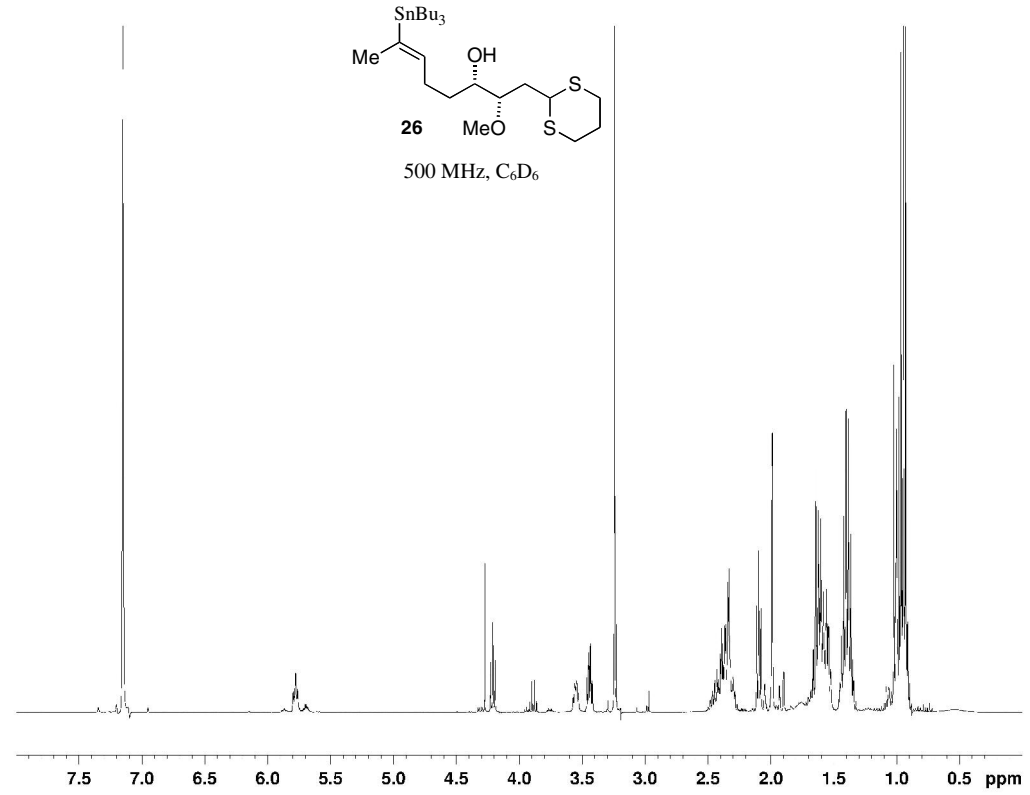


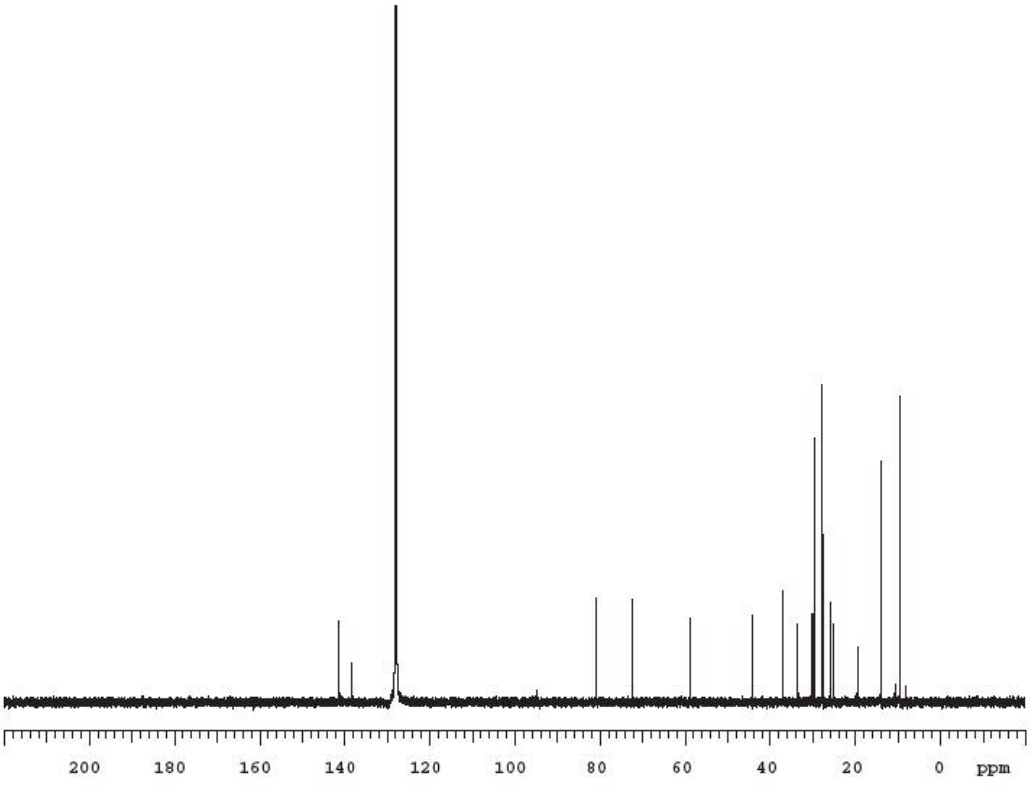

**24**

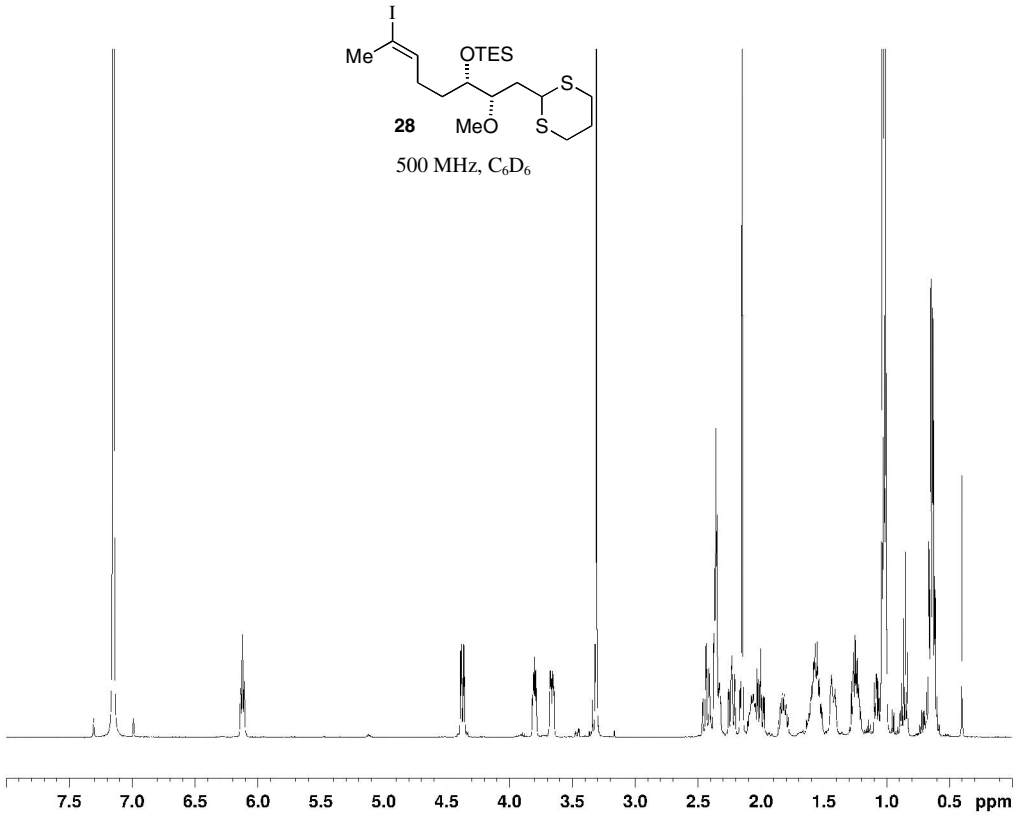
500 MHz, $C_6D_6$

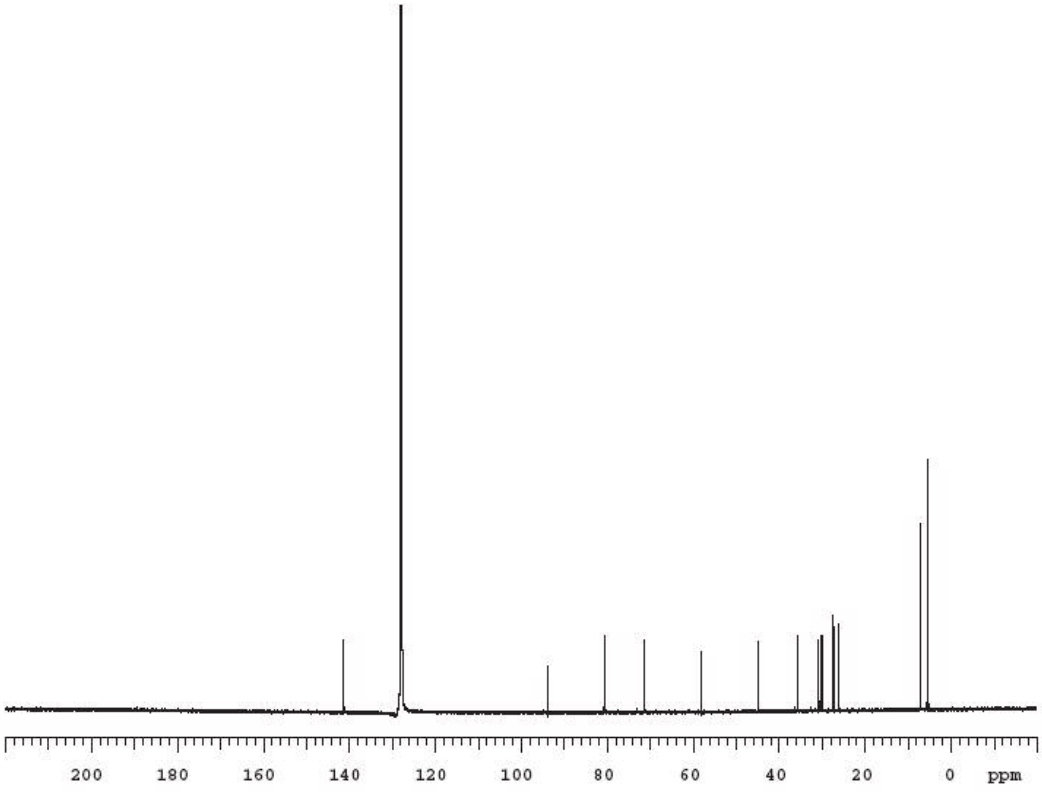


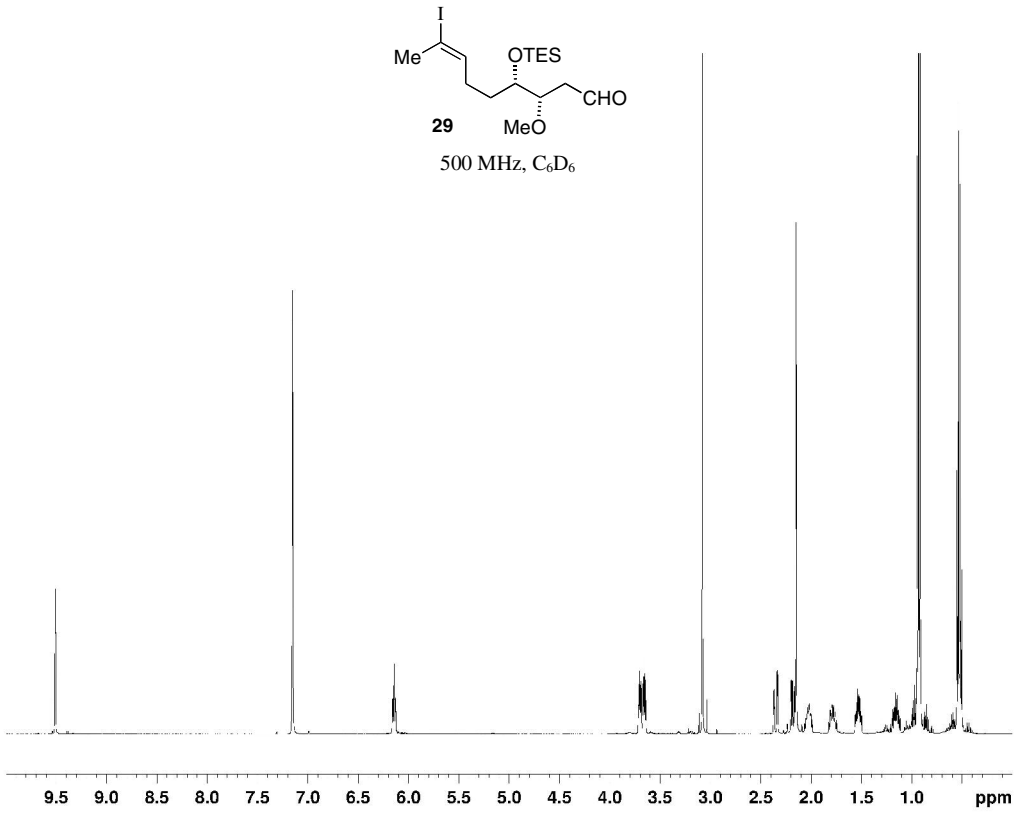



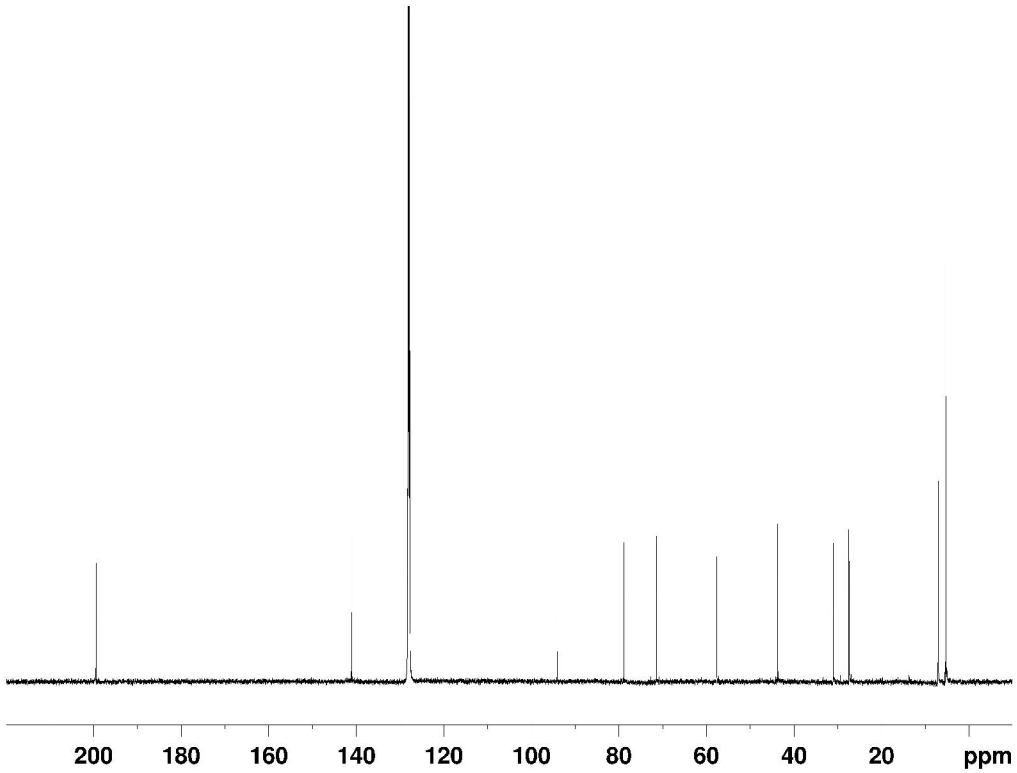

SnBu3
Me
OH
S
S
26
MeO
500 MHz, C6D6
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

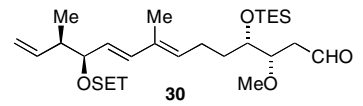

200 180 160 140 120 100 80 60 40 20 0 ppm


I
Me
OTES
S
S
28
MeO
500 MHz, C6D6
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 ppm


200 180 160 140 120 100 80 60 40 20 0 ppm


I
Me
OTES
CHO
MeO
29
500 MHz, C6D6
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
ppm

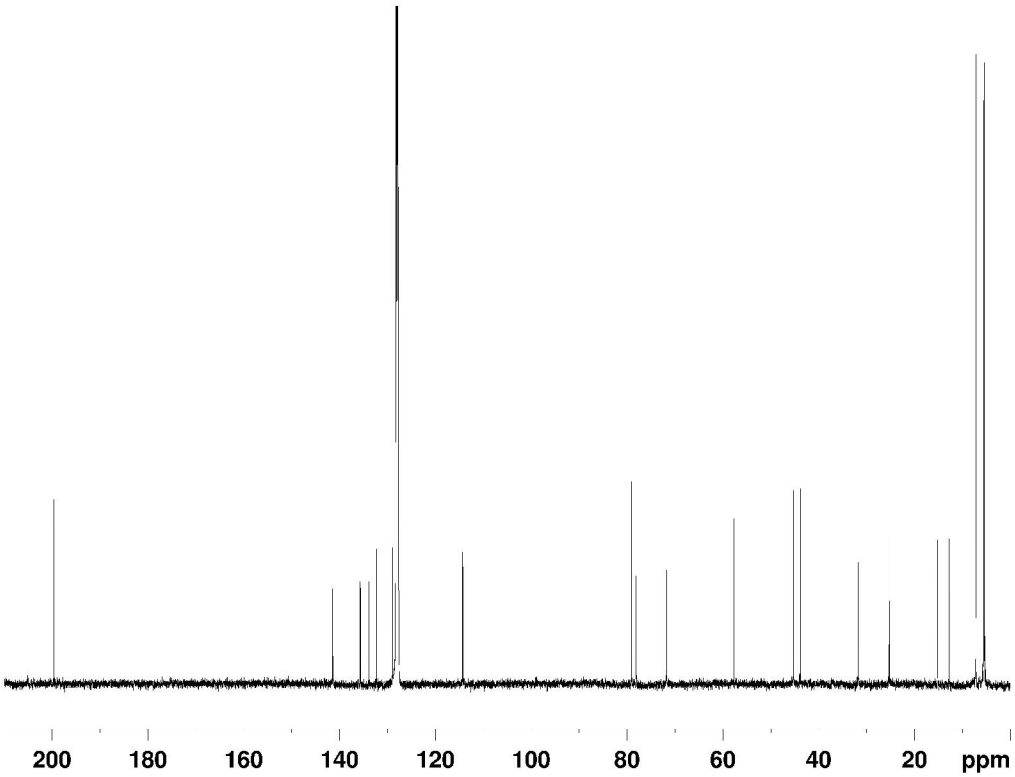

200 180 160 140 120 100 80 60 40 20
ppm

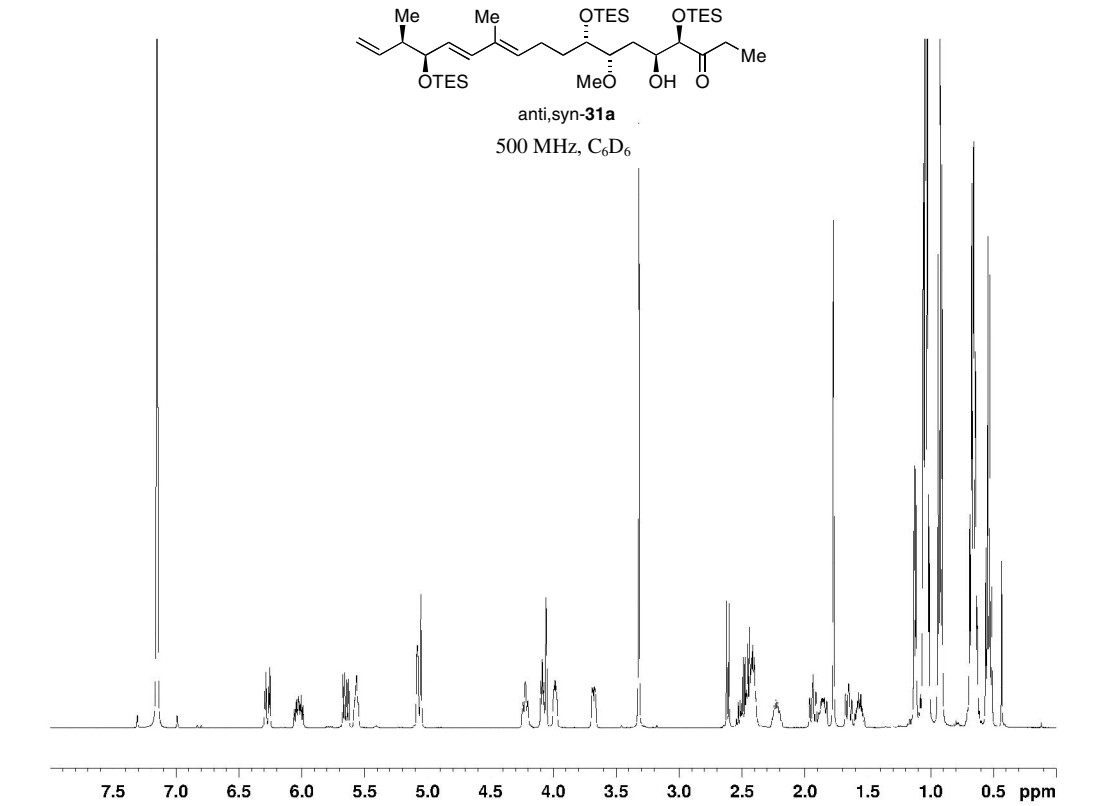


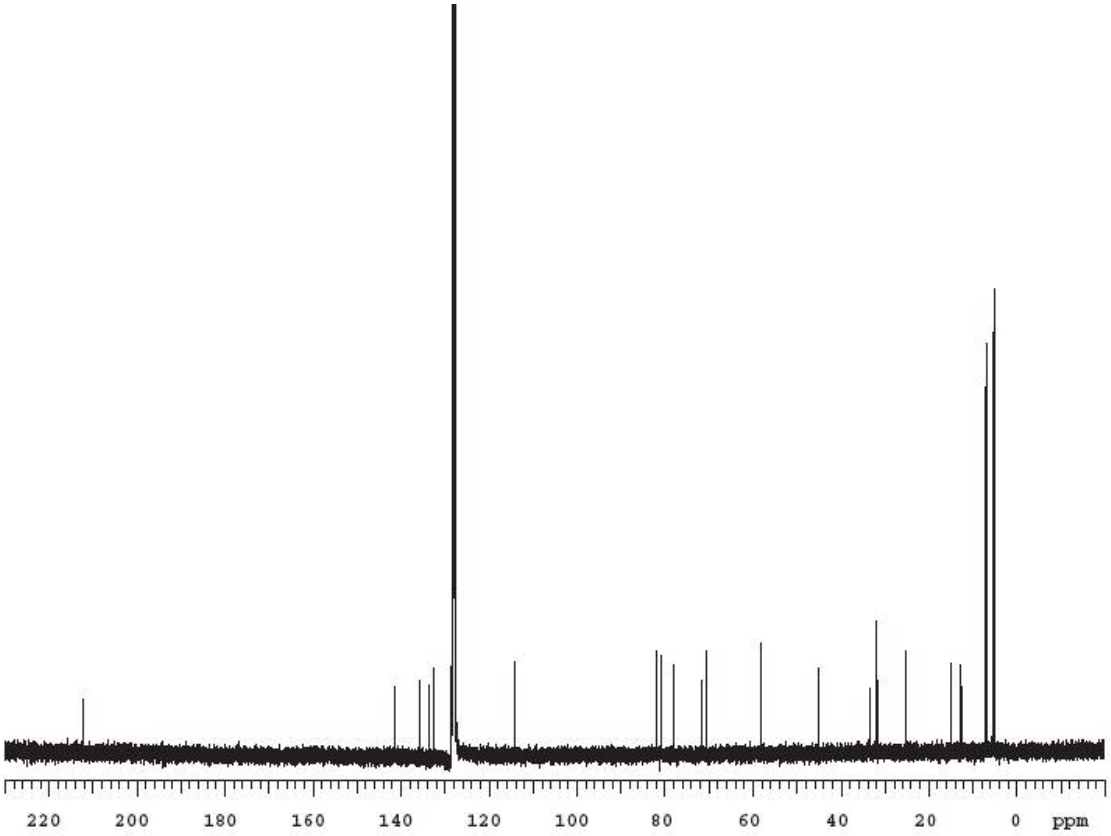

**30**

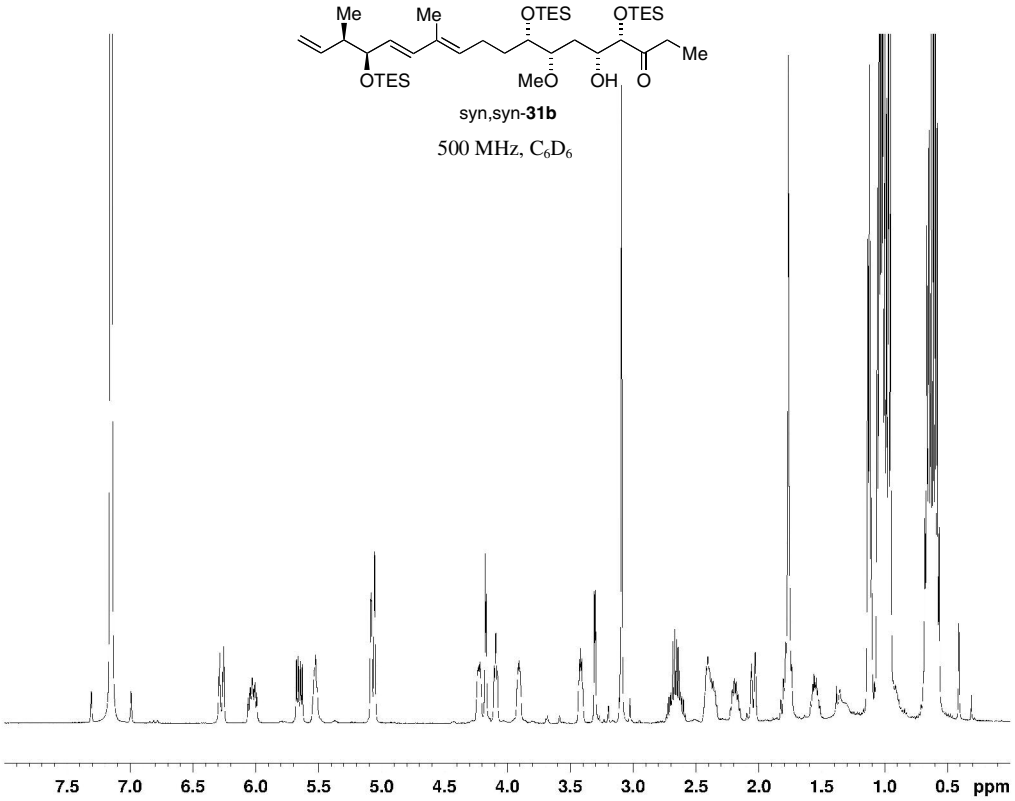
500 MHz, $C_6D_6$

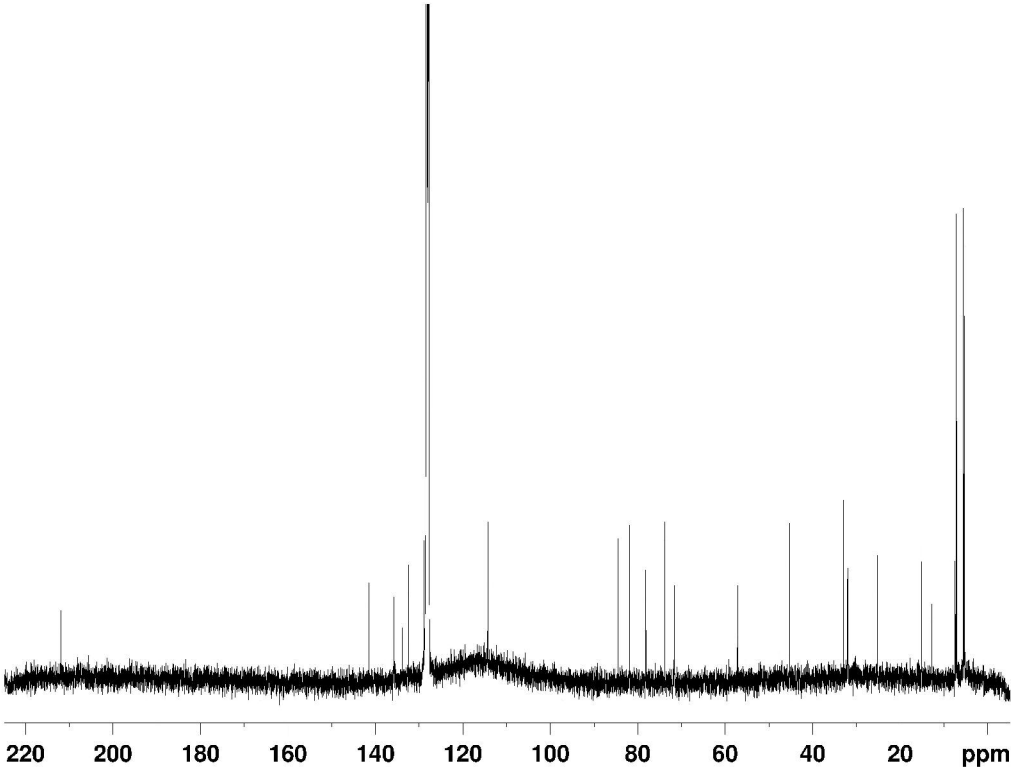


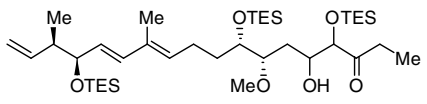




Me
Me
OTES
OTES
Me
OTES
MeO
OH
O
anti,syn-31a
500 MHz, C6D6
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
Me
OTES
OTES
Me
OTES
MeO
OH
O
syn,syn-31b
500 MHz, C6D6
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
ppm


220
200
180
160
140
120
100
80
60
40
20
ppm

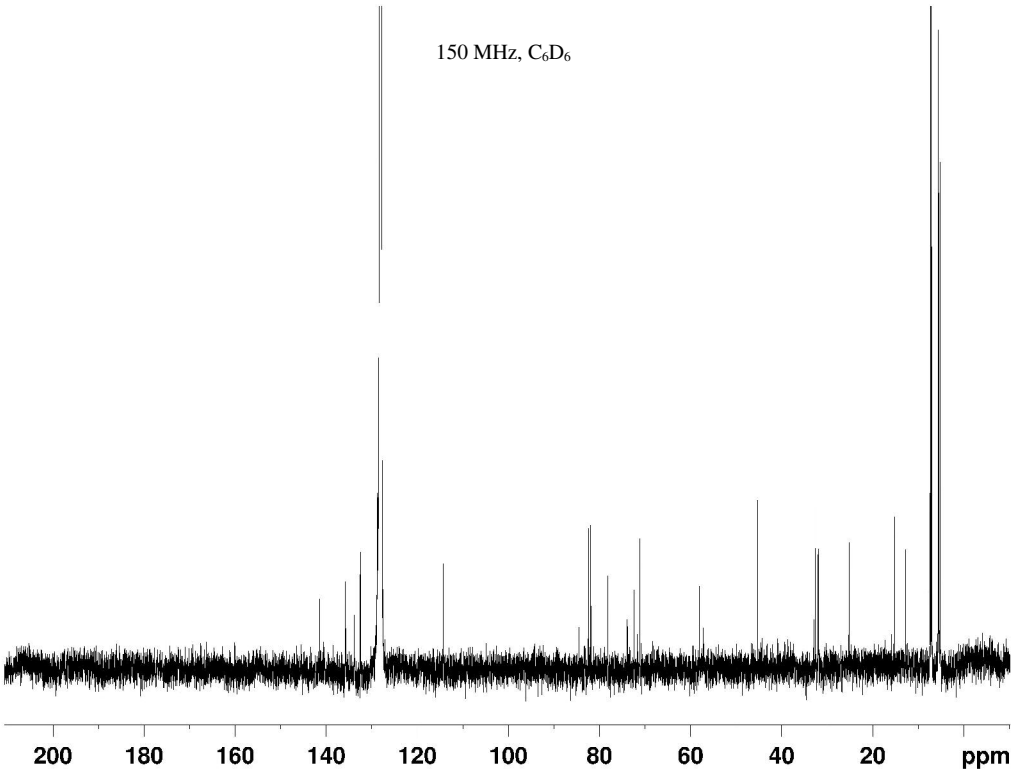


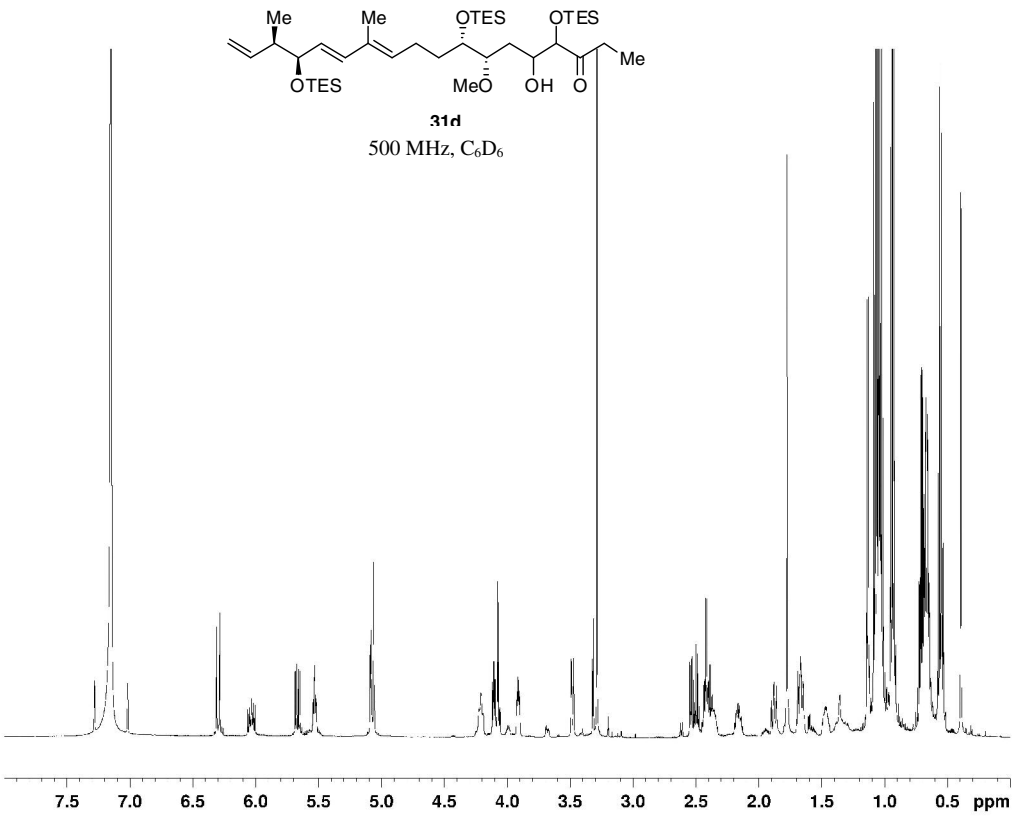

**31c**

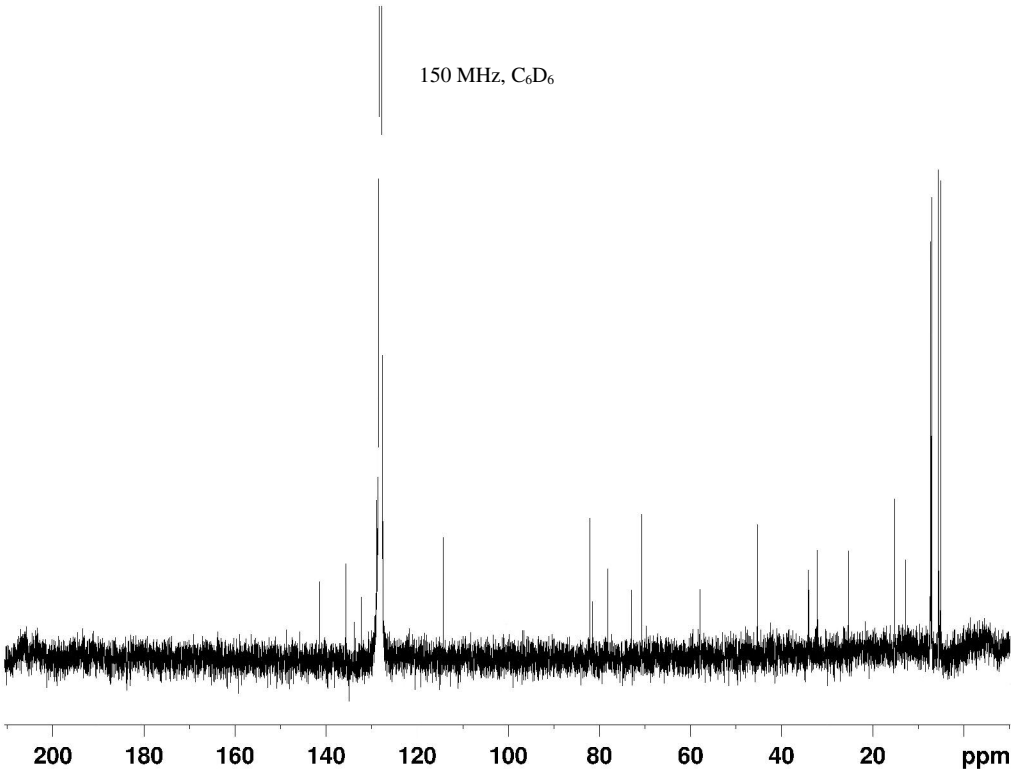
500 MHz, $C_6D_6$

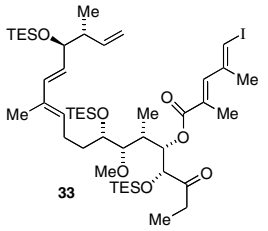



150 MHz, $C_6D_6$




Me
Me
OTES
OTES
Me
OTES
MeO
OH
O
31d
500 MHz, C6D6
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
ppm

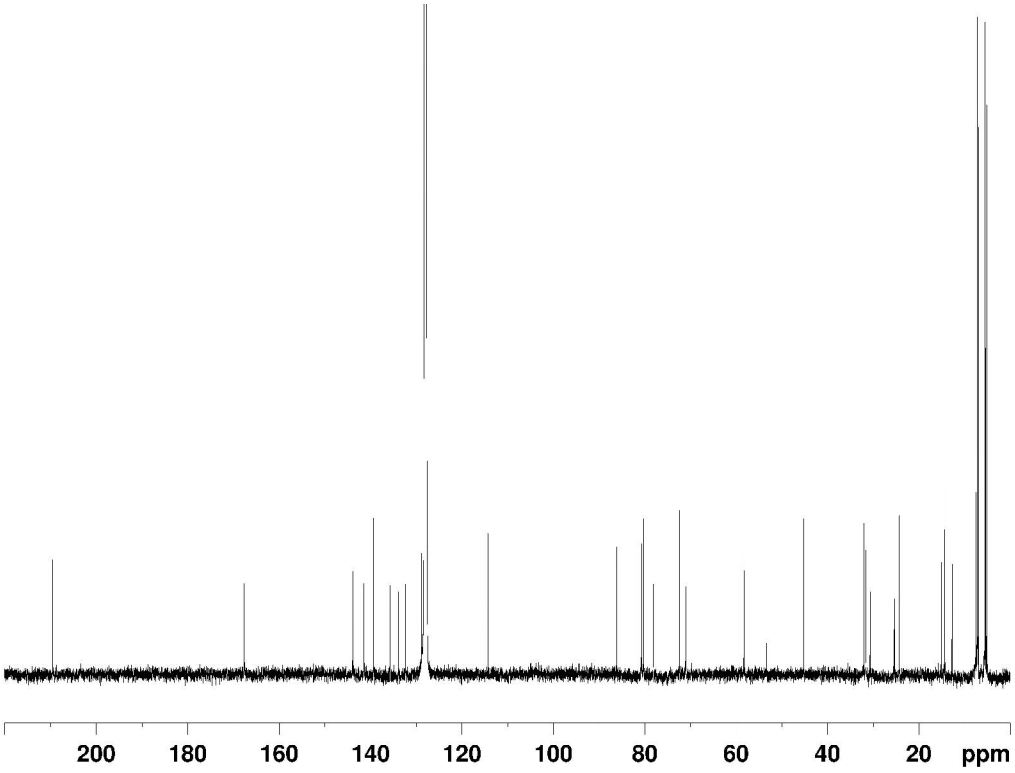

150 MHz, C6D6
200
180
160
140
120
100
80
60
40
20
ppm

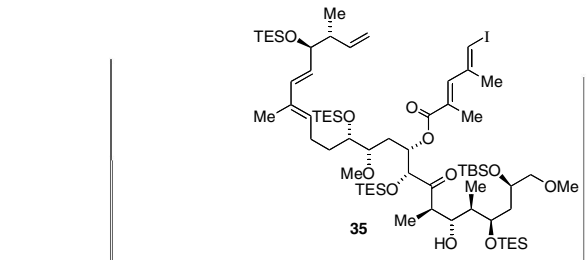



33

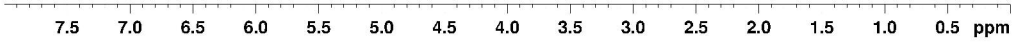
500 MHz, $C_6D_6$

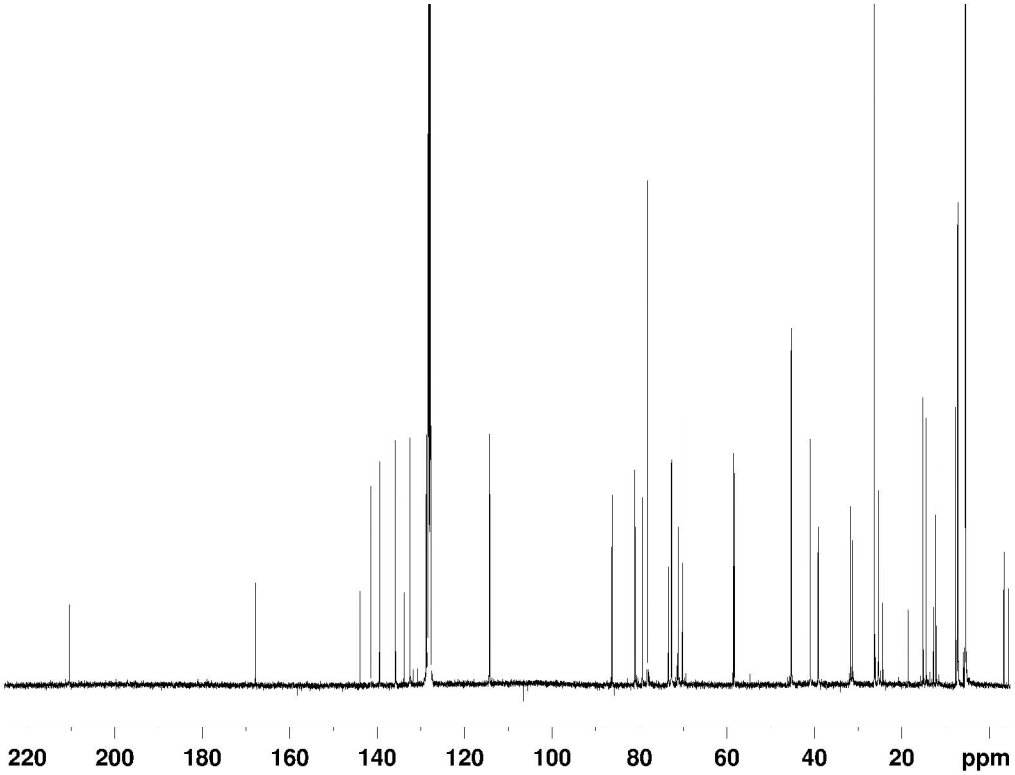


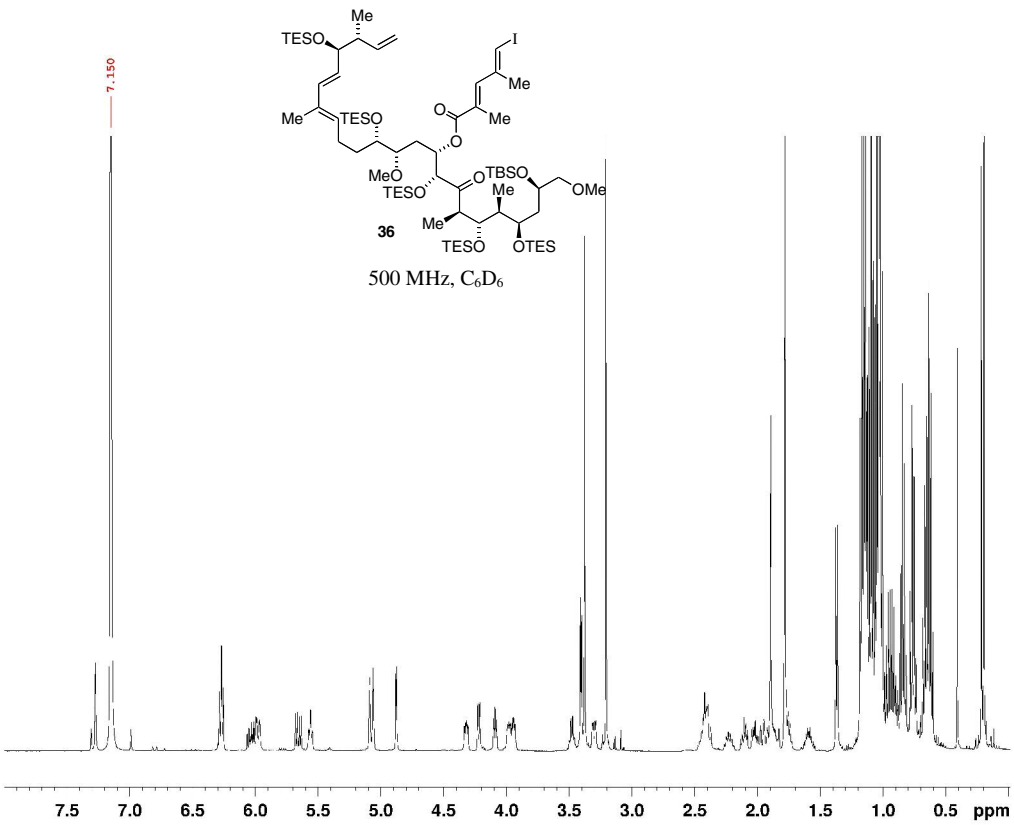




Me
TESO
I
Me
Me
TESO
O
Me
O
MeO
TESO
O
TBSO
Me
OMe
Me
35
HO
OTES

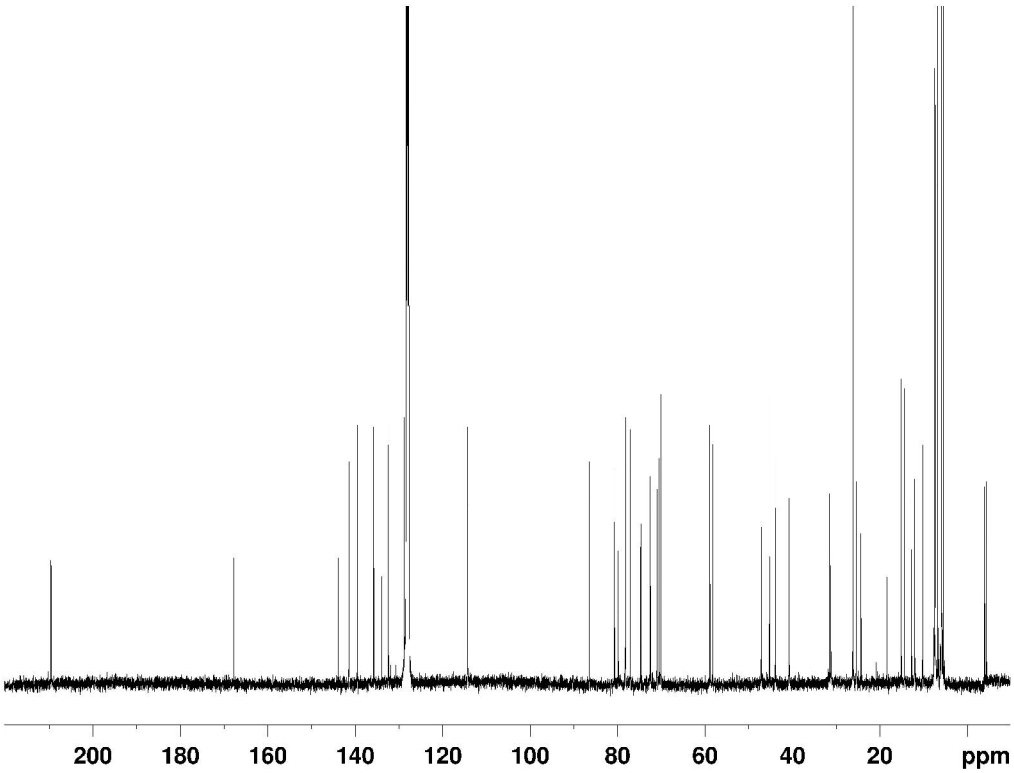
500 MHz, $C_6D_6$

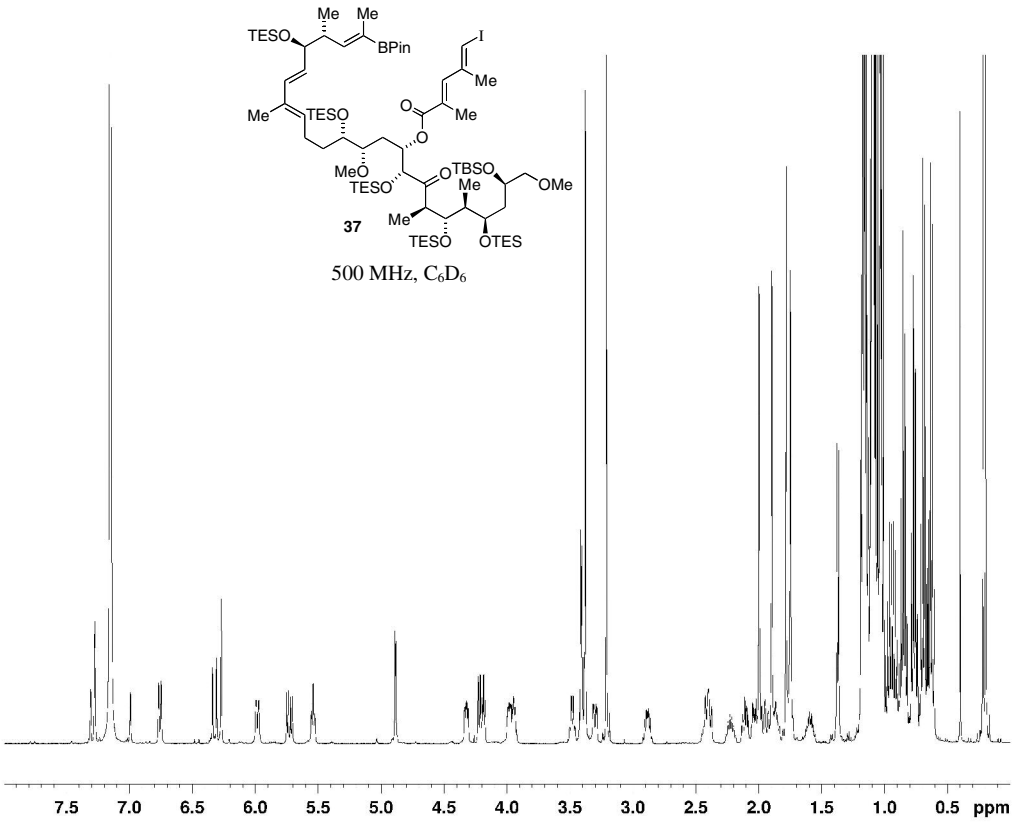

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


220
200
180
160
140
120
100
80
60
40
20
ppm

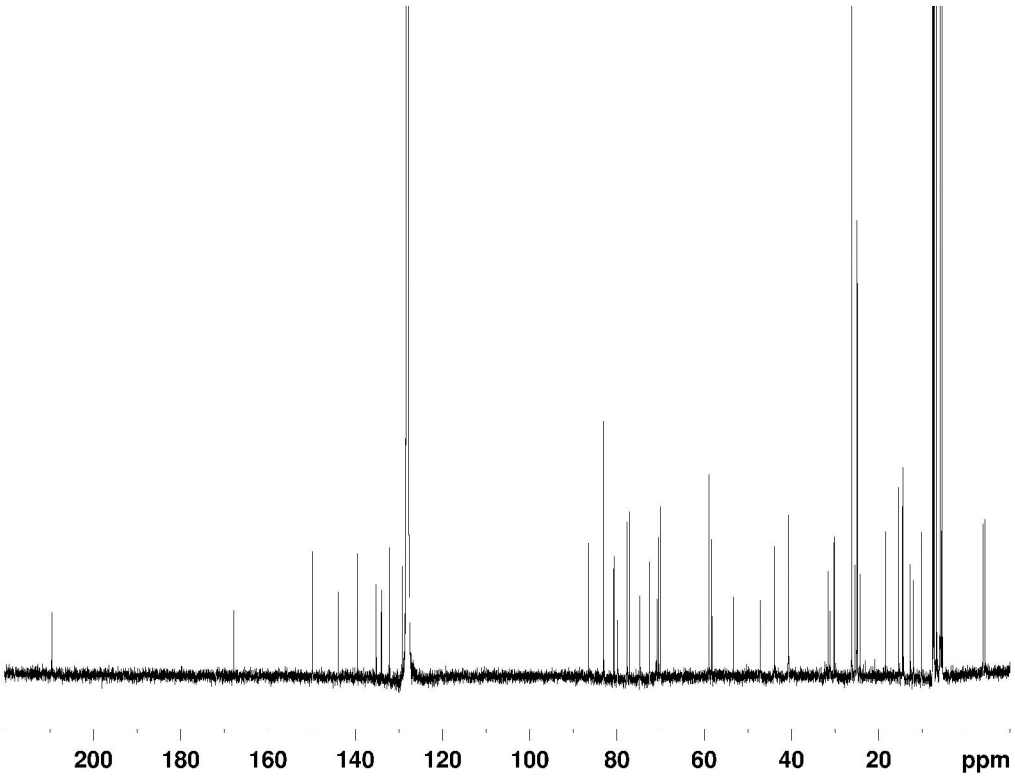

7.150
Me
TESO
I
Me
Me
TESO
O
Me
O
MeO
TESO
O
TBSO
Me
OMe
Me
TESO
OTES
36
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

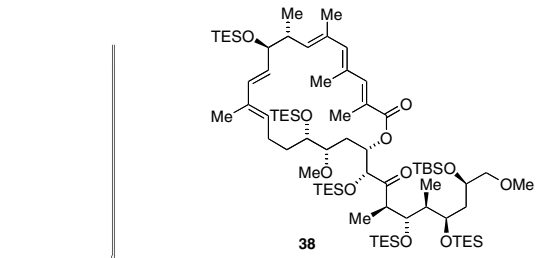
500 MHz, $C_6D_6$


200
180
160
140
120
100
80
60
40
20
ppm


Me
Me
TESO
BPin
I
Me
Me
TESO
O
Me
O
MeO
TESO
O
TBSO
Me
OMe
37
Me
TESO
OTES
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
ppm

500 MHz, $C_6D_6$

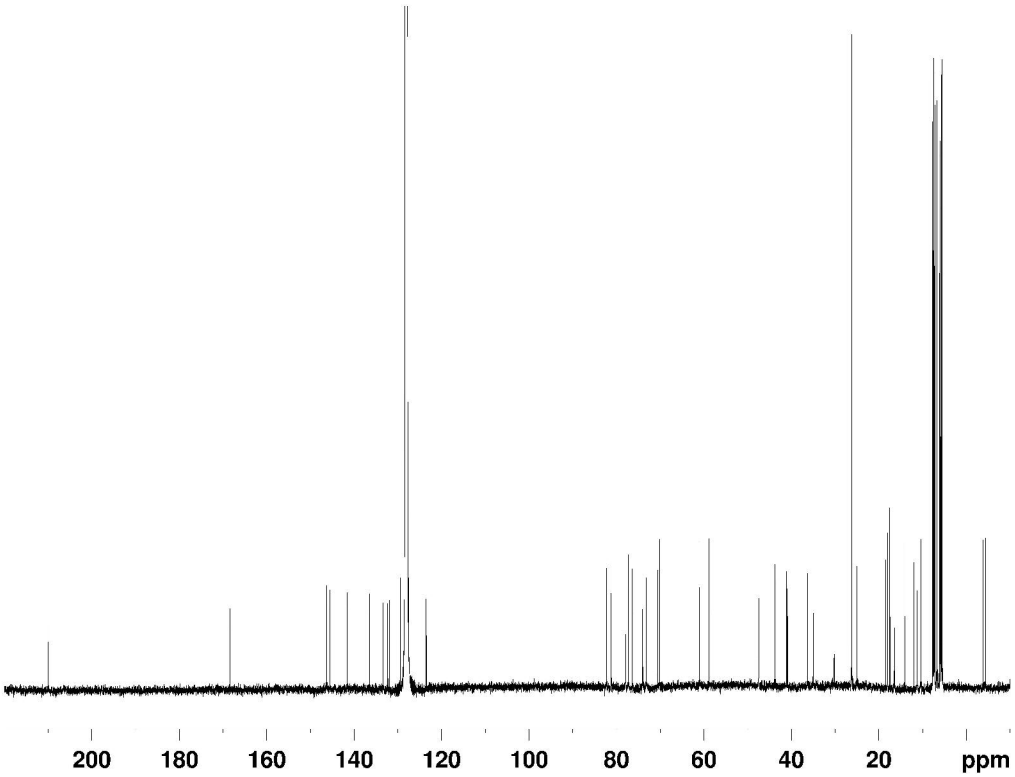

200
180
160
140
120
100
80
60
40
20
ppm

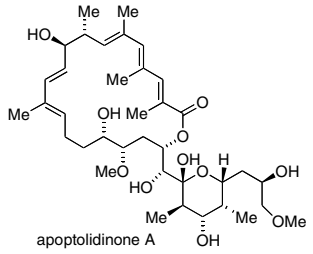



**38**

500 MHz, $C_6D_6$



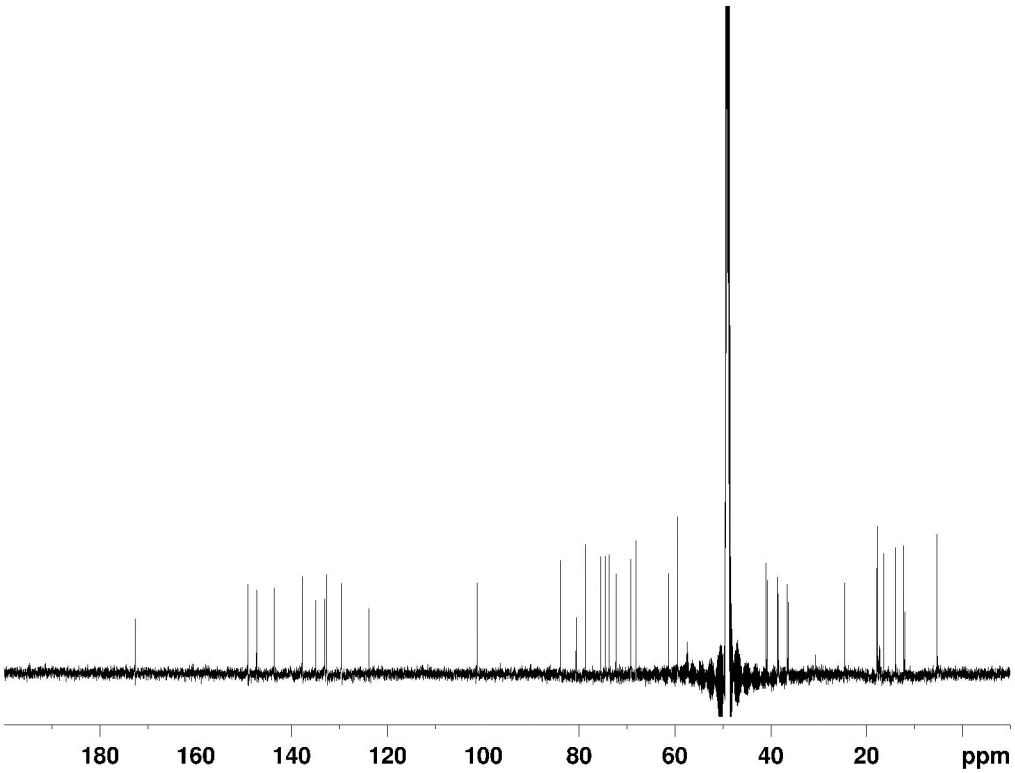



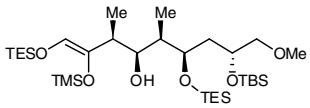



apoptolidinone A

500 MHz, $CD_3OD$



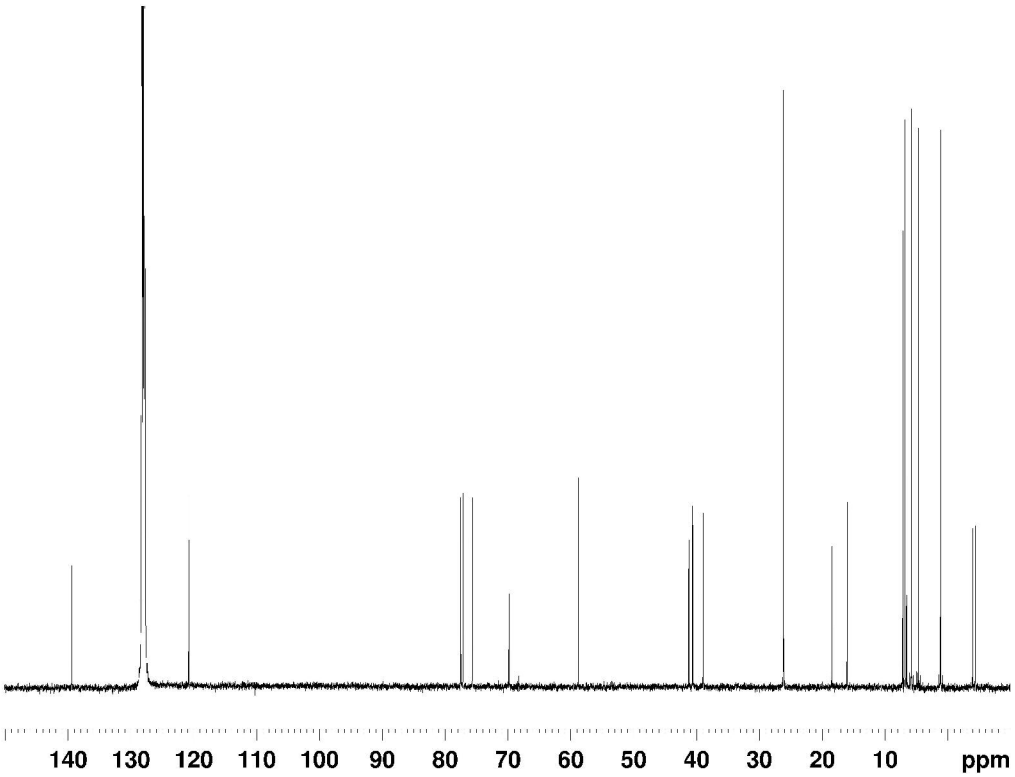



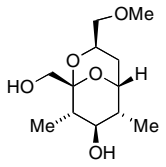



**39**

500 MHz, $C_6D_6$

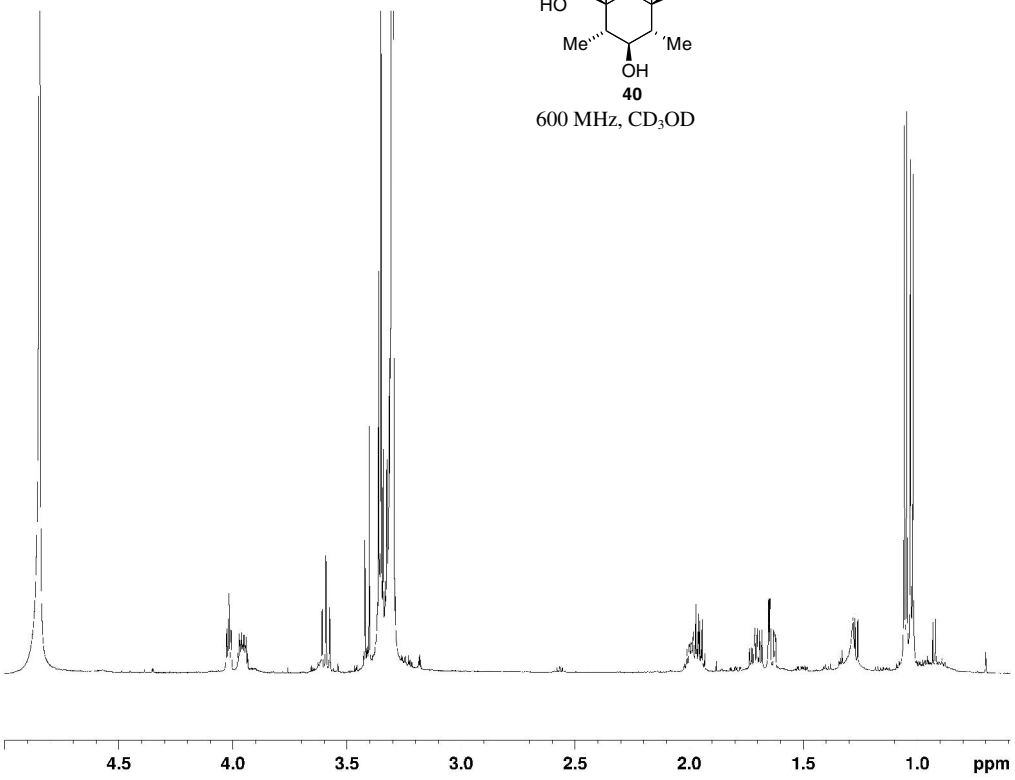


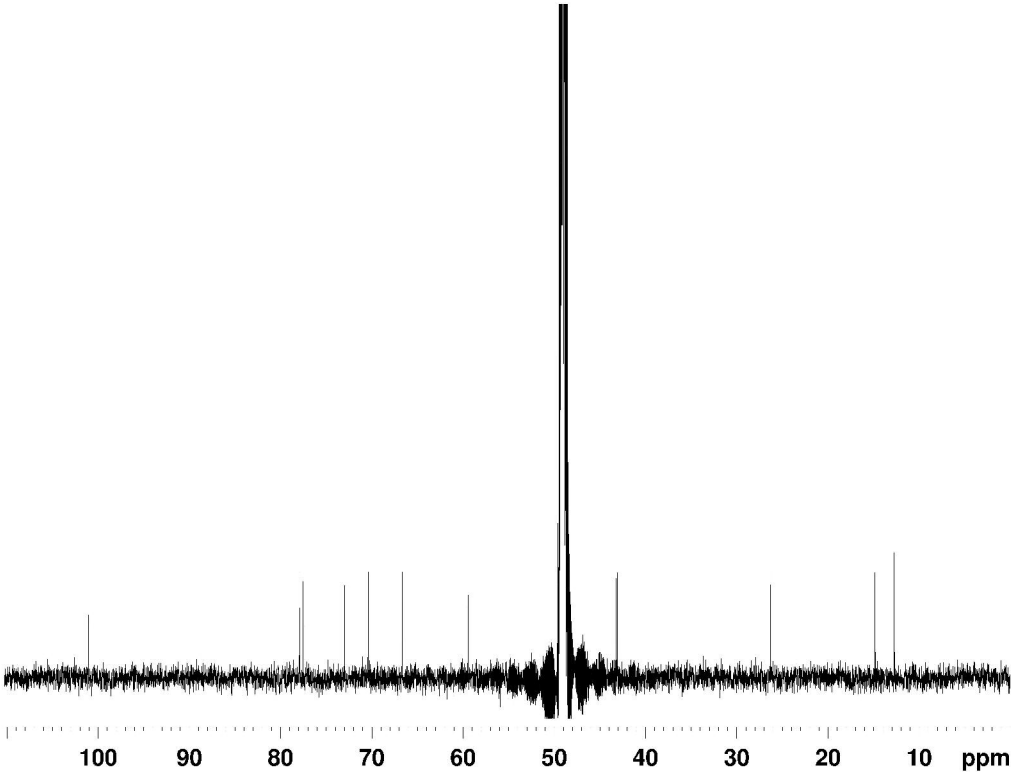



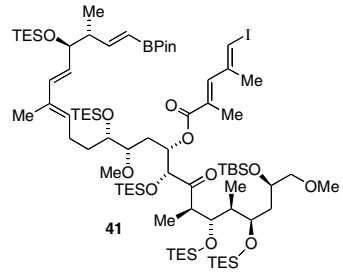



**40**

600 MHz, $CD_3OD$

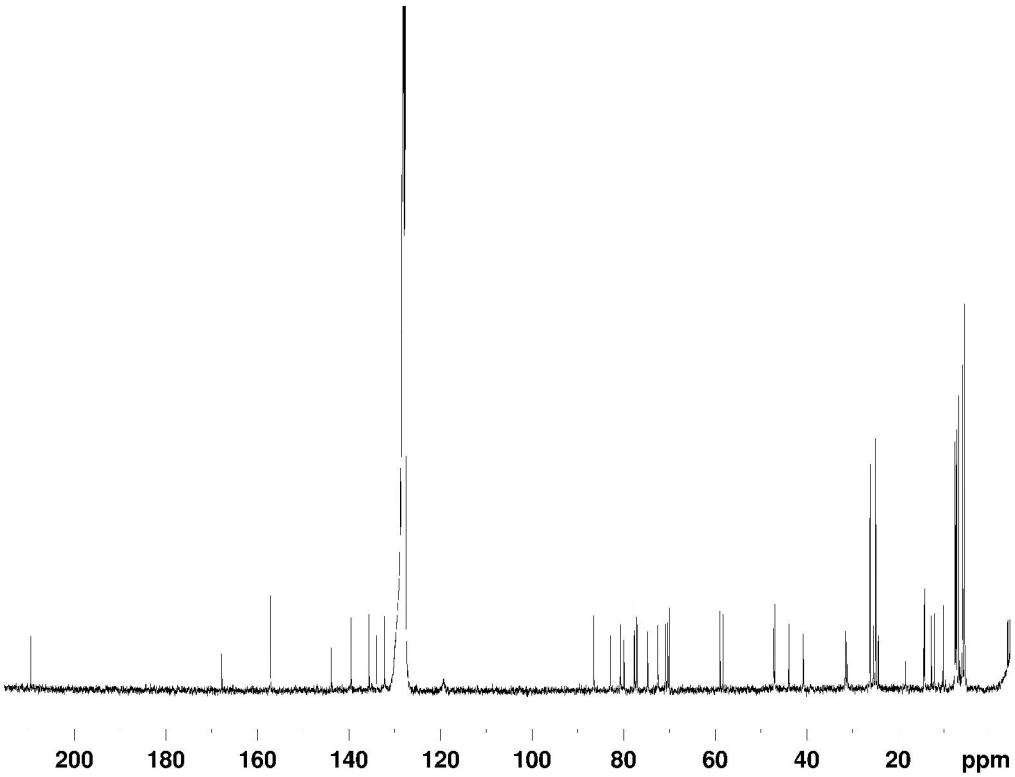


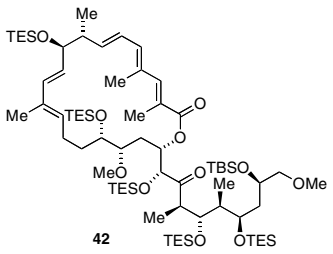




Me
TESO
BPin
I
Me
Me
TESO
O
Me
O
MeO
TESO
O
TBSO
Me
OMe
Me
41
TES
O
TES
O

500 MHz, $C_6D_6$


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
ppm

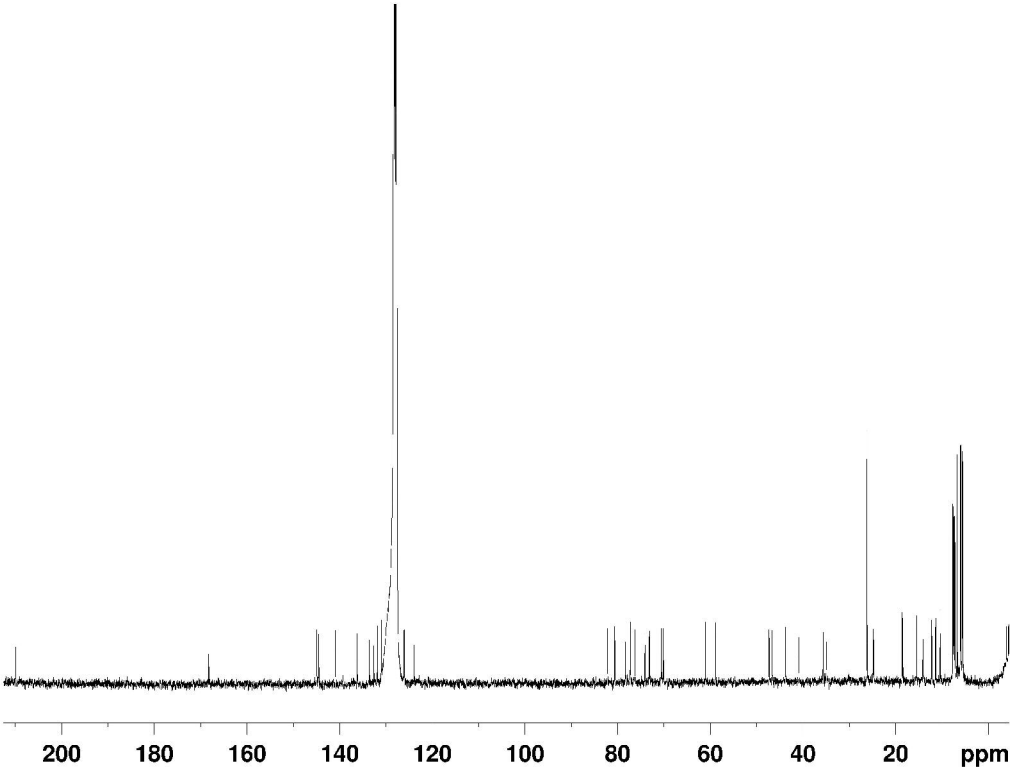

200
180
160
140
120
100
80
60
40
20
ppm

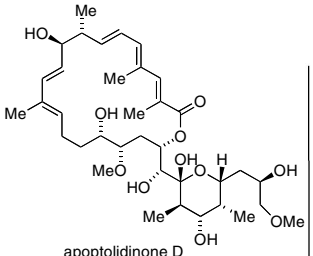



**42**

500 MHz, $C_6D_6$






apoptolidinone D

500 MHz, $CD_3OD$