Electronic Supplementary Information. Further Experimental Details

Design, synthesis and biological evaluation of bridged epothilone D analogues

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Experimental

Genaral synthetic procedures

Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter. Infrared spectra were measured using a SENSIR ATR on MIDAC M2004 Series spectrometer. NMR spectra were obtained on a JEOL Eclipse 500 or a Varian Unity 400 or Varian Inova 400 spectrometer in $CDCl_3$ or CD_3CN. The chemical shifts are given in δ (ppm), and coupling constants are reported in Hz. High-resolution FAB mass spectra were obtained on a JEOL HX110 Dual Focusing Mass Spectrometer. THF was distilled from sodium-benzophenone and dichloromethane was distilled from calcium hydride. Other reagents and solvents were purchased from commercial sources and were used without further purification. Silica gel column chromatography was performed using flash silica gel (32-63μ). Preparative thin-layer chromatography (PTLC) separations were carried out on 500μ or 1000μ Uniplate thin layer chromatography plates. All reactions were carried out under a nitrogen atmosphere unless otherwise noted.

Methyl (3*S*)-3-hydroxy-5-(ᵗbutyldimethylsilyloxy)-pentanoate (14b). Pd-C (10%, 0.6 g) was added to the solution of benzyl ether **13**[1] (3.4 g, 14.2 mmol) in CH_3OH (20 mL), and the resulting mixture was hydrogenated in a sealed tube at 35 psi for 4 h. The insoluble material was removed by filtration through a silica gel pad, and the filtrate was concentrated *in vacuo* to give

residue, which was subjected to silica gel chromatography with 50% ethyl acetate in hexanes to provide diol **14a** (2.1 g, 100%). $[\alpha]_D$ + 19.13 (*c* 1.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 3.90 (br.s, 1H), 3.75 (m, 2H), 3.65 (s, 3H), 3.40 (br.s, 1H), 2.46 (dd, *J* = 5.8, 1.2 Hz, 2H), 1.65 (q, *J* = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 67.4, 60.5, 51.9, 41.7, 38.1.

To a solution of diol **14a** (1.9 g, 6.75 mmol) in CH_2Cl_2 (15 mL) was sequentially added imidazole (0.69 g, 10 mmol, 1.5eq) and TBSCl (1 g, 6.75 mmol, 1eq), and the reaction was allowed to proceed at 25 ^oC with stirring for 30 min. A saturated solution of aqueous $NaHCO_3$ was added to quench the reaction and the mixture was extracted with EtOAc (20 mL × 3). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude product obtained was subjected to silica gel column chromatography eluting with 20-25% EtOAc in hexanes to afford **14b** (1.7 g, 95% yield) as a colorless oil. $[\alpha]_D$ + 9.6 (*c* 0.74, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 3.80 (m, 2H), 3.62 (s, 3H), 3.60 (d, *J* = 1.2 Hz, 1H), 2.44 (m, 2H), 1.63 (m, 2H), 0.82 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 67.7, 61.6, 51.7, 41.8, 38.3, 26.0, 18.3, -5.35, -5.37. HRFABMS: calcd for $C_{12}H_{27}O_4Si$ (M+H) 263.1679, found 263.1669.

Methyl (*S*)-2-((*S*)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)-propyl)pent-4-enoate. A solution of LDA (2 M, 3.96 mmol, 2.6 eq) in THF was added to a solution of **14b** (0.4 g, 1.52 mmol) in THF (15 mL) at -78 ^oC, and the resulting solution was allowed to warm to -20 ^oC and stir for 30 min at -20 ^oC. Allyl iodide (0.2 mL, 2.28 mmol, 1.5 eq) in HMPA (0.76 mL, 4.27 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was recooled to -78 ^oC. The subsequent reaction mixture was warmed to -20 ^oC and the reaction was allowed to proceed at -20 ^oC with stirring for 1 h prior to being quenched by the addition of saturated NH_4Cl solution (50 mL). The two layers were separated and aqueous phase was extracted with ether (20 × 3). The combined organic extracts were washed with water and brine, the organic fraction was dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure to give the crude mass. Purification of the product by silica gel column chromatographyeluting with 10% ethyl acetate in hexanes yielded methyl (*S*)-2-((*S*)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)-propyl)pent-4-enoate (0.336 g, 72%). $[\alpha]_D$ + 5.4 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.04 (dd, *J* = 17.2, 1.6 Hz, 1H),

5.96 (dt, *J* = 10.0, 0.8 Hz, 1H), 3.92 (m, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 3.64 (s, 3H), 3.40 (d, *J* = 4.4 Hz, 1H), 2.51 (m, 1H), 2.32 (m, 2H), 1.66 (m, 2H), 0.83 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 135.2, 117.1, 71.6, 61.9, 51.7, 51.4, 36.6, 33.2, 26.0, 18.3, -5.3. HRFABMS: calcd for $C_{15}H_{31}O_4Si$ (M+H) 303.1992, found 303.2002.

Methyl (*R*)-2-((*S*)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)propyl)-2-methylpen-4-enoate (15). To a freshly prepared solution of LDA (0.6 M, 15.73 mmol, 2.6 eq) in THF (24 mL), a solution of (*S*)-2-((*S*)-1-hydroxy-3-(*tert*-butyl-dimethylsilyloxy)-propyl)pent-4-enoate, obtained from the previoius reaction, (1.83 g, 6 mmol) in THF (15 mL) was added at -78 ^{o}C, and the resulting solution was warmed to -20 ^{o}C ans stirred for 4 h at that temperature. Then a solution of methyl iodide (0.6 mL, 9.69 mmol, 1.6 eq) in HMPA (17 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was re-cooled to -78 ^{o}C. The subsequent reaction mixture was re-warmed to -20 ^{o}C and allowed to stir at that temperature for 2 h. The reaction was quenched by the addition of saturated ammonium chloride (50 mL). The two layers were separated and aqueous phase was re-extracted with ether (20 mL × 3). The combined organic phases were washed with water and brine, the organic fraction was dried (Na_2SO_4), and the solvents were removed under reduced pressure. The crude oil obtained was subjected to silica gel column chromatography using 5% ether in hexane as eluent to provide **15** as the major product (1.09 g, 57% yield), together with a minor diastereomeric product (0.35 g, 18% yield). Compound **15**: $[\alpha]_D$ + 17.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.04 (dd, *J* = 17.2, 1.6 Hz, 1H), 3.98 (dd, *J* = 10.8, 0.8 Hz, 1H), 3.93 (br.d, *J* = 10.4, 1H), 3.85-3.71 (m, 2H), 3.60 (s, 3H), 3.43 (d, *J* = 2.4 Hz, 1H), 2.47 (dd, *J* = 13.6, 7.2 Hz,, 1H), 2.26 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.66-1.54 (m, 1H), 1.45(dt, *J* = 12.8, 1.0 Hz, 1H), 1.19 (s, 3H), 1.08 (s, 9H), 0.8 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 134.4, 118.0, 75.7, 63.0, 51.7, 51.3, 40.8, 34.3.2, 26.0, 18.3, 16.2, -5.3. HRFABMS: calcd for $C_{16}H_{33}O_4Si$ (M+H) 317.2148, found 317.2166.

Methyl (*R*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)-propyl)-2-methylpent-4-enoate. To a solution of **15** (1.97 g, 6.23 mmol) in dichloromethane (25 mL) was added 2,6-lutidine (1.15 mL, 9.96 mmol, 1.6 eq) and TBSOTf (2.24 mL, 9.35 mmol, 1.5 eq) at -78 ^{o}C and the resulting reaction mixture was allowed to stir at -78 ^{o}C over 6 h. Saturated ammonium chloride (50 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase

was re-extracted with dichloromethane (20 mL × 3). The combined dichloromethane phase was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was subjected to silica gel chromatography eluting with 5% ether in hexanes to furnish bis-TBS ether (2.22 g, 83%). $[\alpha]_D$ + 5.1 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 1H), 4.99-4.95 (m, 2H), 3.98 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.58 (s, 3H), 3.61-3.51 (m, 2H), 2.38 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.22 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.62-1.44 (m, 2H), 1.04 (s, 3H), 0.85 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), -0.009 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 134.5, 117.9, 73.6, 60.0, 52.8, 51.6, 42.3, 37.7, 26.2, 26.0, 18.5, 18.4, 14.8, -3.6, -3.8, -5.1.

(*S*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpen-4-en-1-ol (16). A solution of DIBAL-H (1 M, 17 mmol, 3.5 eq) was added dropwise to a solution of bis-TBS ether (2.08 g, 4.83 mmol), obtained from the above reaction, in dichloromethane (45 mL) at -78 ^{o}C. The reaction was allowed to proceed at -78 ^{o}C with stirring for 45 min. Methanol (5 mL) was added and the solution was allowed to warm to 25 ^{o}C. Then a saturated solution of sodium/potassium tartrates (50 mL) was added to the mixture, which was stirred at 25 ^{o}C until the two layers were clearly separated. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (30 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvents was evaporated under reduced pressure. Purification of the crude product obtained by silica gel column chromatography with 3 % EtOAc in hexanes as eluent to yield **16** (1.83 g, 94%). $[\alpha]_D$ -16.9 (*c* 0.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.05-5.01 (m, 2H), 3.77-3.63 (m, 4H), 3.32 (dd, *J* = 11.2, 6.8 Hz,, 1H), 2.97 (t, *J* = 4.4 Hz, 1H), 2.25-1.91 (m, 3H), 1.67-1.58 (m, 1H), 0.98 (s, 3H), 0.90 (s, 18H), 0.099 (s, 3H), 0.092 (s, 3H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 117.8, 76.1, 68.5, 60.8, 42.2, 39.7, 36.2, 26.3, 26.1, 19.4, 18.4, -3.7, -3.9, -5.0, -5.1.

(*R*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal. To a solution of **16** (1.8 g, 4.5 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (40 mL), was added triethylamine (3.16 mL, 22.7 mmol, 5eq) followed by SO_3.Py (3.16 g, 22.78 mmol, 5 eq) at 0 ^{o}C and the resulting reaction mixture was stirred for 30 min. The reaction was quenched by the addition of saturated NH_4Cl solution (50 mL). Organic layer was separated and the aqueous phase was

extracted with dichloromethane (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvents was removed under reduced pressure. The crude product was purified *via* silica gel column chromatography eluting with 5 % ether in hexanes to yield (*R*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (1.75 g, 97%). $[\alpha]_D$ -3.8 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 5.65 (m, 1H), 5.08-5.03 (m, 2H), 4.00 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.68-3.56 (m, 2H), 2.50 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.25 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.76-1.66 (m, 1H), 1.65-1.56 (m, 1H), 1.00 (s, 3H), 0.885 (s, 9H), 0.880 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 133.7, 118.4, 72.9, 59.7, 54.3, 37.2, 37.0, 26.2, 26.1, 18.5, 18.4, 15.7, -3.6, -4.0, -5.11, -5.13.

(4*S*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol. To a solution of (*R*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (1.5 g, 3.75 mmol), obtained from the above reaction, in THF (20 mL) was added ethyl magnesium bromide (1 M, 6.56 mL, 6.56 mmol, 1.7 eq) at 0 ^{o}C and the resulting reaction mixture was allowed to stir at 0 ^{o}C for 1 h. Saturated NH_4Cl solution (50 mL) was added to quench the reaction. Organic layer was separated and the aqueous phase was re-extracted with dichloromethane (20 mL × 3). The organic extracts were combined and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The crude product obtained was purified *via* silica gel column chromatography eluting with 2.5 % ether in hexanes to produce the product as a diastereomeric mixture (9:1) (68%) and alcohol **16** as an undesired byproduct (31%). The diastereomeric mixture of (4*S*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy) propyl)-4-methylhept-6-en-3-ol was subjected to the next reaction without further purification. HRFABMS: calcd for $C_{23}H_{51}O_3Si_2$ (M+H) 431.3371, found 431.3372.

(*R*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-one (9). To a solution of (4*S*)-4-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol (1.545 g, 3.59 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (36 mL), was added triethylamine (2.50 mL, 17.97 mmol, 5 eq) followed by SO_3.Py complex (2.82 g, 17.96 mmol, 5 eq) at 0 ^{o}C. The reaction was allowed to proceed at 0 ^{o}C with stiring for 2 h prior to being quenched by the addition of saturated NH_4Cl solution (50 mL). Organic layer was separated and the aqueous phase was extracted with dichloromethane (20 mL × 3). The combined organic extracts were

dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give crude product, which was purified via silica gel chromatography eluting with 3 % ether in hexanes to give **9** (1.16 g, 75%). $[\alpha]_D$ -0.0 (*c* 1.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.00-4.97 (m, 2H), 4.05 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.58 (dd, *J* = 8.0, 4.8 Hz, 2H), 2.55-2.35 (m, 3H), 2.22 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.52-1.35 (m, 2H), 1.09 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 134.3, 117.9, 73.3, 59.8, 57.4, 42.3, 37.8, 32.8, 26.3, 26.0, 18.6, 18.4, 14.9, 7.6, -3.5, -3.6, -5.13, -5.15. HRFABMS: calcd for $C_{23}H_{49}O_3Si_2$ (M+H) 429.3220, found 429.3208.

Aldol Product 18. A solution of ketone **9** (1.4 g, 3.27 mmol, 1.8 eq to aldehyde **8**) in THF (8 mL) was added to a solution of freshly prepared LDA (~ 0.6 M, 3.76 mmol, 1.15 eq to **9**) in THF at -78 ^oC. After stirring for 1 h at -78 ^oC, the solution was allowed to warm up to -40 ^oC and stir at that temperature for 30 min. The reaction mixture was then recooled to -78 ^oC and a cold (-78 ^oC) solution of aldehyde **8**[2,3] (1.3 g, 1.81 mmol) in THF (18 mL) was rapidly introduced to the above reaction mixture. Upon completion of the addition, stirring was continued for a further 5 min before the reaction was quenched by the rapid injection of AcOH (0.521 mL, 4.8 eq) as a solution in THF (1.8 mL). The whole reaction mixture was warmed to 25 ^oC and partitioned between ether and saturated aqueous NH_4Cl solution. The aqueous phase was re-extracted with ether (50 mL × 3), and the combined organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 1.5 to 20% ether in hexanes) of crude product obtained provided **18** (1.77 g, 80%) as a colorless oil. $[\alpha]_D$ -21.1 (c 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.2, 1.6 Hz, 6H), 7.22 (m, 9H), 6.17 (s, 1H), 5.60 (m, 1H), 5.49 (t, *J* = 7.2 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 4.97 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.16 (t, *J* = 6.0 Hz, 1H), 3.80 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.64-3.56 (m, 2H), 3.43 (br.s, 2H), 3.25 (br.s, 1H), 3.16 (m, 2H), 2.42 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.26 (m, 2H), 2.08-1.98 (m, 3H), 1.80 (s, 3H), 1.65 (m, 2H), 1.42 (m, 2H), 1.24 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.86 (2 singlets, 27H), 0.67 (d, *J* = 6.8 Hz, 3H), 0.08 (2 singlets, 6H), 0.02 to -0.02 (3 singlets, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 150.4, 144.5, 138.9, 134.2, 128.8, 127.9, 127.0, 121.4, 118.5, 86.7, 77.7, 77.6, 74.4, 73.8, 67.3, 60.4, 57.7, 42.4, 41.6, 38.0, 35.5, 34.8, 33.2, 29.3, 26.3, 26.1, 25.8, 19.9, 18.6, 18.49, 18.41, 17.3, 15.4, 9.1, -3.4, -3.8, -4.6, -4.7,

-5.02, -5.05; HRFABMS: calcd for $C_{62}H_{99}O_6Si_3INa$ (M+Na) 1173.5692, found 1173.5741.

Tetrakis-[*tert*-butyldimethylsilyl]-ether 19a. To a solution of **18** (2.8 g, 2.43 mmol) in dichloromethane (35 mL) was added 2,6-lutidine (1.21 mL, 10.5 mmol, 4.3 eq) followed by TBSOTf (1.78 mL, 7.79 mmol, 3.2 eq) at 0 ^oC and the reaction was allowed to proceed with stirring for 4 h at 0 ^oC. Saturated $NaHCO_3$ solution was added to quench the reaction. Two layers were separated and the aqueous layer was re-extracted with dichloromethane (50 mL × 3). The combined organic extracts were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The crude mass obtained was subjected to column chromatography over silica gel, eluting with 1.5% ether in hexanes, to yield tetrakis-TBS ether **19a** (2.82 g, 94%). $[\alpha]_D$ -18.0 (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.2, 1.6 Hz, 6H), 7.30-7.22 (m, 9H), 6.21 (s, 1H), 5.60 (m, 1H), 5.52 (t, *J* = 7.2 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.96 (dd, *J* = 17.0, 1.6 Hz, 1H), 4.20 (t, *J* = 6.0 Hz, 1H), 3.79 (dd, *J* = 7.8, 2.4 Hz, 1H), 3.63 (m, 3H), 3.47 (dd, *J* = 17.0, 12.0 Hz, 2H), 3.06 (dd, *J* = 6.8, 4.8 Hz, 1H), 2.42 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.28 (m, 2H), 2.0 (m, 3H), 1.82 (s, 3H), 1.72 (m, 1H), 1.40 (m, 1H), 1.28 (m, 3H), 1.22 (s, 3H), 1.06 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91 (2 singlets, 36H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.12-0.02 (8 singlets, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.2, 150.4, 144.5, 138.9, 134.6, 128.9, 127.9, 127.0, 121.7, 118.1, 86.7, 77.6, 76.6, 74.7, 67.3, 60.6, 56.9, 45.5, 41.1, 39.9, 37.7, 34.9, 31.7, 29.5, 26.8, 26.44, 26.40, 26.1, 26.0, 19.9, 18.7, 18.6, 18.5, 18.4, 17.2, 14.3, 1.21, -3.3, -3.4, -3.6, -3.8, -4.6, -4.7, -5.0; HRFABMS: calcd for $C_{68}H_{113}O_6Si_4ILi$ (M+Li) 1271.6820, found 1271.6862.

Tris-[*tert*-butyldimethylsilyl]-ether 19b. To a solution of **19a** (2.8 g, 2.21 mmol) in THF (50 mL) was added a stock solution of HF.Py (this stock solution was prepared by addition of 4 mL HF.Py to 11 mL pyridine in 22 mL THF) at 0 ^oC. The resulting reaction mixture was warmed to 25 ^oC by removing the ice-bath and allowed to stir at that temperature for 2 h. Saturated $NaHCO_3$ solution was added to quench the reaction and two layers were seperated. The aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The crude product obtained was subjected to column chromatography over silica gel employing 12% EtOAc in hexanes as eluent to yield the desired primary alcohol **19b** (2.2 g, 86%). $[\alpha]_D$ -9.1 (*c*

0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.2 , 1.6Hz, 6H), 7.32-7.22 (m, 9H), 6.20 (s, 1H), 5.60 (m, 1H), 5.52 (t, *J* = 7.2 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 4.94 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.20 (t, *J* = 6.0 Hz, 1H), 3.98 (m, 1H), 3.72-3.64 (m, 3H), 3.46 (dd, *J* = 17.0, 12.0 Hz, 2H), 3.00 (dd, *J* = 7.0, 4.8 Hz, 1H), 2.45 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.28 (m, 2H), 2.00 (m, 3H), 1.80 (s, 3H), 1.64 (m, 1H), 1.58 (m, 1H), 1.28 (m, 3H), 1.26 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.90 (2 singlets, 27H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.12-0.02 (6 singlets, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 150.4, 144.5, 138.9, 133.8, 128.8, 128.1, 127.9, 127.4, 127.0, 121.7, 118.3, 86.7, 76.2, 73.1, 67.3, 60.4, 57.2, 45.4, 41.0, 39.9, 38.1, 34.9, 31.6, 29.5, 26.7, 26.4, 26.3, 26.0, 25.8, 19.9, 18.7, 18.6, 18.4, 17.6, 17.1, 14.6, -3.5, -3.6, -3.8, -4.6, -4.7; HRFABMS: calcd for $C_{62}H_{99}O_6Si_3ILi$ (M+Li) 1157.5956, found 1157.5931.

Oxidation of primary alcohol 19b to aldehyde 19c. To a solution of primary alcohol **19b** obtained in the preceding step (2.15 g, 1.86 mmol) in 1:1 mixture of dichloromethane and DMSO (22 mL), was added triethylamine (1.33 mL, 9.34 mmol, 5 eq) followed by SO_3.Py (1.5 g, 9.34 mmol, 5 eq) at 0 ^{o}C and the reaction was allowed to proceed at 0 ^{o}C with stirring for 1 h. Saturated NH_4Cl solution (50 mL) was added to quench the reaction, and the mixture was extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and the organic solvents were removed under reduced pressure. The crude product obtained was subjected to silica gel column chromatography eluting with 1-2% ether in hexanes to give **19c** (1.87 g, 87%). $[\alpha]_D$ -14.6 (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H, C*H*O), 7.45 (dd, *J* = 7.2, 1.6 Hz, 6H), 7.25 (m, 9H), 6.20 (s, 1H), 5.60 (m, 1H), 5.51 (t, *J* = 7.2 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.95 (d, *J* = 16.8 Hz, 1H), 4.38 (t, *J* = 5.6 Hz, 1H), 4.19 (t, *J* = 6.4 Hz, 1H), 3.63 (dd, *J* = 5.0, 2.4 Hz, 1H), 3.45 (dd, *J* = 17.4, 12.0 Hz, 2H), 3.03 (dd, *J* = 7.0, 5.6 Hz, 1H), 2.64 (dd, *J* = 17.0, 4.4 Hz, 1H), 2.44 (dd, *J* = 5.2, 2.4 Hz, 1H), 2.38-2.23 (m, 3H), 1.97 (m, 3H), 1.80 (s, 3H), 1.25 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.88 (2 singlets, 27H), 0.8 (d, *J* = 6.8 Hz, 3H), 0.11-0.008 (6 singlets, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4, 200.8, 150.4, 144.5, 138.8, 133.4, 128.8, 127.9, 127.0, 121.7, 118.8, 86.7, 77.6, 76.5, 71.3, 67.3, 56.5, 49.3, 45.5, 40.6, 39.8, 34.9, 31.6, 29.4, 26.7, 26.4, 26.1, 26.0, 19.9, 18.7, 18.4, 18.2, 17.2, 14.5, -3.5, -3.7, -3.8, -4.1, -4.6, -4.7; HRFABMS: calcd for $C_{62}H_{97}O_6Si_3ILi$ (M+Li) 1155.5799, found 1155.5792.

Further oxidation of aldehyde 19c to carboxylic acid 19d. To a solution of **19c** (1.87 g, 1.62 mmol) in *t*-BuOH:H_2O (4.5:1, 11 mL) was added sequentially, 2-methyl-2-butene (12 mL, 120 mmol, 75 eq) in THF (33 mL), NaH_2PO_4 (678 mg, 5.7 mmol, 3.5 eq), and $NaClO_2$ (1 g, 11.4 mmol, 7 eq). The reaction was allowed to proceed with stirring at 25 ^oC for 1 h, then volatiles were removed under reduced pressure, and the residue was partitioned between ethyl acetate and brine solution. Two layers were separated and aqueous layer was re-extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and the organic solvents were removed in vacuo. Purification of the crude product *via* silica gel column chromatography employing 20% ether in hexanes as eluent furnished **19d** (1.8 g, 98%). $[\alpha]_D$ -22.5 (*c* 0.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 6H), 7.27 (m, 9H), 6.20 (s, 1H), 5.60 (m, 1H), 5.51 (t, *J* = 7.6 Hz, 1H), 5.00 (d, *J* = 10.4 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.27 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.19 (t, *J* = 6.0 Hz, 1H), 3.63 (dd, *J* = 5.2, 2.0 Hz, 1H), 3.45 (dd, *J* = 17.4, 12.0 Hz, 2H), 3.05 (dd, *J* = 7.0, 5.6 Hz, 1H), 2.62 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.41 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.31 (m, 3H), 1.99 (m, 3H), 1.81 (s, 3H), 1.28 (m, 3H), 1.24 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 27H), 0.8 (d, *J* = 6.4 Hz, 3H), 0.11-0.01 (6 singlets, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.2, 177.8, 150.4, 144.5, 138.8, 133.5, 128.8, 127.9, 127.0, 121.7, 118.8, 86.7, 77.6, 76.7, 73.9, 67.3, 56.6, 45.6, 40.4, 39.8, 39.7, 34.9, 31.5, 29.5, 26.7, 26.4, 26.2, 26.0, 19.9, 18.7, 18.47, 18.41, 17.3, 14.6, -3.4, -3.6, -4.0, -4.3, -4.6, -4.7; HRFABMS: calcd for $C_{62}H_{97}O_7Si_3ILi$ (M+Li) 1171.5748, found 1171.5822.

Hydroxy acid 19e. A solution of the carboxylic acid **19d** (880 mg, 0.757 mmol) in THF (15 mL) at 0 ^oC was treated with TBAF (4.54 mL, 1 M in THF, 4.54 mmol, 6 eq) and then the mixture was allowed to warm up to 25 ^oC. The reaction was quenched after being stirred for 20 h at 25 ^oC by the addition of saturated aqueous NH_4Cl solution (50 mL), and the mixture was extracted with EtOAc (30 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure to give crude product. Column chromatography of this crude product over silica gel, eluting with 40% ethyl acetate in hexanes, yielded hydroxyl acid **19e** (767 mg, 96%). $[\alpha]_D$ -21.0 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.0, 0.8 Hz, 6H), 7.27-7.20 (m, 9H), 6.30 (s, 1H), 5.55 (m, 1H), 5.43 (t, *J* = 6.8 Hz, 1H), 4.97 (d, *J* = 9.2 Hz, 1H), 4.93 (d, *J* = 17.2 Hz, 1H), 4.25 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 3.61 (d, *J* = 3.2 Hz, 1H), 3.52 (d, *J* = 12.4 Hz, 2H), 3.46 (d, *J* = 12.4 Hz,

1H), 3.00 (m, 1H), 2.54 (dd, *J* = 17.0, 1.6 Hz, 1H), 2.40 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.32 (t, *J* = 6.8 Hz, 2H), 2.24 (dd, *J* = 17.2, 6.4 Hz, 1H), 1.99 (m, 3H), 1.81 (s, 3H), 1.24 (m, 3H), 1.20 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 18H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.07-0.01 (4 singlets, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 176.9, 149.1, 144.1, 140.7, 133.4, 128.6, 127.7, 126.9, 120.1, 118.5, 86.7, 78.4, 77.2, 76.5, 76.0, 73.5, 67.1, 56.5, 45.4, 40.1, 39.6, 39.3, 33.4, 31.2, 29.2, 26.5, 26.1, 25.9, 20.1, 18.4, 18.2, 18.1, 17.2, 14.5, -3.7, -3.9, -4.2, -4.6; HRFABMS: calcd for $C_{56}H_{82}O_7Si_2I$ (M+H) 1049.4644, found 1049.4554.

Macrolactone 20a. To a solution of hydroxyl acid **19e** (832 mg, 0.792 mmol) in THF (8.2 mL, 0.1 M) was added triethylamine (0.661 mL, 4.75 mmol, 6 eq), followed by 2,4,6-trichlorobenzoyl chloride (0.3 mL, 1.9 mmol, 2.4 eq) at 0 ^{o}C and the resulting reaction mixture was stirred for 1 h at that temperature. The mixture was then added to a solution of DMAP (212 mg, 1.74 mmol, 2.2 eq) in toluene (160 ml, 0.005 M based on **19e**) at 75 ^{o}C over 3 h, *via* syringe pump. After addition was complete, the reaction mixture was stirred for an additional 2 h. Toluene was removed under reduced pressure and the residue was filtered through a short plug of silica gel, eluting with 60% ether in hexanes, to give a crude product. Purification of this product by column chromatography over silica gel, eluting with 2% ether in hexanes, furnished lactone **20a** (645 mg, 78%). $[\alpha]_D$ -10.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.0, 1.6 Hz, 6H), 7.30-7.21 (m, 9H), 6.38 (s, 1H), 5.63 (m, 1H), 5.53 (dd, *J* = 9.8, 5.6 Hz, 1H), 5.16 (m, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 5.04 (d, *J* = 17.2 Hz, 1H), 4.13 (m, 1H), 3.84 (d, *J* = 8.0 Hz, 1H), 3.48, 3.40 (ABq, *J* = 11.6 Hz, 2H), 3.00 (m, 1H), 2.72 (m, 2H), 2.58 (m, 1H), 2.38 (m, 3H), 2.18 (m, 1H), 2.00 (m, 1H), 1.90 (s, 3H), 1.50 (m, 3H), 1.20 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1. 07 (s, 3H), 0.93 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.72 (s, 9H), 0.08-0.05 (4 singlets, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 170.6, 146.4, 144.3, 133.2, 128.8, 127.9, 127.1, 118.9, 86.6, 79.9, 77.9, 77.4, 74.3, 66.9, 56.9, 41.1, 32.2, 31.2, 28.8, 27.1, 26.6, 26.3, 20.7, 18.8, 18.7, 1.2, -3.0, -3.3; HRFABMS: calcd for $C_{56}H_{80}O_6Si_2I$ (M+H) 1031.4531, found 1031.4489.

Macrolactone iodide 21. To a solution of macrolactone **20a** (426 mg, 0.423 mmol) in THF (30 mL) was added HF.Py (70%, 10 mL) at 0 ^{o}C. The resulting reaction mixture was allowed to warm up to 25 ^{o}C and the reaction was allowed to proceed with stirring at 25 ^{o}C for 36 h prior to

being quenched by careful portionwise addition into saturated aqueous $NaHCO_3$ solution with further addition of sufficient solid $NaHCO_3$ to ensure complete neutralization. The mixture was then extracted with EtOAc (50 mL × 3), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the crude product obtained by column chromatography over silica gel eluting with 55% ethyl acetate in hexanes gave **21** (224 mg, 94%). $[\alpha]_D$ -43 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 5.62 (m, 1H), 5.38 (m, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.22 (dd, *J* = 11.0, 2.4 Hz, 2H), 4.05, 3.95 (ABq, *J* = 13.6 Hz, 2H), 3.65 (dd, *J* = 5.2, 1.6 Hz, 1H), 3.15 (dq, *J* = 7.2, 1.6 Hz, 1H), 2.68 (m, 1H), 2.52 (m, 4H), 2.38 (m, 1H), 2.20 (m, 2H), 2.00 (m, 2H), 1.88 (s, 3H), 1.76 (m, 1H), 1.60 (m, 1H), 1.38 (m, 2H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.3, 170.1, 146.4, 145.6, 142.5, 133.3, 121.4, 119.5, 80.5, 77.7, 73.5, 72.5, 66.5, 57.2, 42.0, 40.0, 39.5, 37.8, 31.9, 28.1, 25.2, 21.0, 15.9, 15.8, 12.6; HRFABMS: calcd for $C_{25}H_{40}O_6I$ (M+H) 563.1870, found 563.1881.

26-Acryloyloxy-macrolactone 7. To a solution of triol **21** (28 mg, 0.049 mmol) in dichloromethane (2 mL) was added sequentially Et_3N (35 μL, 0.25 mmol, 5eq), acryloyl chloride (7.2 μL, 0.088 mmol, 1.8eq) and DMAP (2 mg) at 0 ^{o}C. The resulting reaction mixture was allowed to stir for 30 min prior to being quenched by addition into saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with EtOAc (10 mL × 3), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the crude product obtained by preparative thin layer chromatography over silica gel eluting with 18% ethyl acetate in hexanes gave **7** (18 mg, 60%). $[\alpha]_D$ -50.0 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (t, *J* = 0.8 Hz, 1H), 6.40 (dd, *J* = 17.4, 1.2 Hz, 1H), 6.13 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.84 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.63 (m, 1H), 5.38 (m, 2H), 5.16 (d, *J* = 10.4 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 4.60 (d, *J* = 12.8 Hz, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.26 (m, 1H), 3.66 (m, 1H), 3.17 (dq, *J* = 5.8, 2.0 Hz, 1H), 2.94 (d, *J* = 2.0 Hz, 1H), 2.69-2.44 (m, 4H), 2.39 (m, 2H), 2.25 (m, 2H), 2.05 (m, 1H), 1.88 (s, 3H), 1.76 (m, 1H), 1.38-1.24 (m, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.3, 169.9, 166.1, 145.3, 137.3, 133.4, 131.3, 128.4, 124.0, 119.4, 80.3, 73.6, 72.4, 67.5, 57.2, 41.9, 40.0, 39.4, 38.1, 32.0, 31.9, 29.9, 28.3, 25.1, 21.1, 15.9, 15.7, 12.8; HRFABMS:

calcd for $C_{28}H_{42}O_7I$ (M+H) 617.1975, found 617.2003.

26-(3-Butenoyloxy)-macrolactone 22. A similar procedure was employed as that described above for the conversion of **21** to **7** (19 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 5.92 (m, 1H), 5.64 (m, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 5.36 (t, *J* = 6.0 Hz, 1H), 5.18 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.08 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.52 (d, *J* = 13.2 Hz, 1H), 4.43 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.66 (dd, *J* = 4.8, 2.0 Hz, 1H), 3.16 (dq, *J* = 5.8, 2.0 Hz, 1H), 3.11 (dt, *J* = 7.2, 1.2 Hz, 2H), 2.68-2.46 (m, 4H), 2.38 (dd, *J* = 15.2, 2.4 Hz, 1H), 2.20 (m, 2H), 2.00 (m, 1H), 1.88 (s, 3H), 1.78 (m, 1H), 1.64 (m, 1H), 1.38-1.26 (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.2, 171.4, 169.9, 145.3, 137.4, 133.4, 130.3, 123.8, 119.4, 119.0, 80.3, 73.6, 72.4, 67.6, 57.2, 41.9, 40.8, 39.4, 39.3, 38.0, 31.96, 31.91, 29.9, 25.0, 21.1, 15.9, 15.7, 12.8; HRFABMS: calcd for $C_{29}H_{44}O_7I$ (M+H) 631.2132, found 631.2095.

26-(4-Pentenoyloxy)-macrolactone 23. A similar procedure was employed as that described above for the conversion of **21** to **7** (21.7 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 5.80 (m, 1H), 5.62 (m, 1H), 5.38 (d, *J* = 1.2 Hz, 1H), 5.35 (t, *J* = 6.0 Hz, 1H), 5.16 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.14 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.05 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.02 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H), 4.42 (d, *J* = 12.8 Hz, 1H), 4.25 (m, 1H), 3.66 (m, 1H), 3.16 (dq, *J* = 5.8, 2.0 Hz, 1H), 2.93 (d, *J* = 2.4 Hz, 1H), 2.68-2.46 (m, 4H), 2.40 (m, 6H), 2.22 (m, 2H), 2.02 (m, 1H), 1.88 (s, 3H), 1.78 (m, 1H), 1.38-1.24 (m, 4H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 3H), 1.00 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.2, 172.7, 169.7, 145.1, 137.3, 136.5, 133.1, 123.5, 119.2, 115.2, 80.1, 77.0, 73.3, 72.2, 67.1, 56.9, 41.7, 39.8, 39.2, 37.8, 33.4, 31.74, 31.70, 28.7, 27.9, 24.8, 20.8, 15.7, 15.5, 12.5; HRFABMS: calcd for $C_{30}H_{46}O_7I$ (M+H) 645.2288, found 645.2258.

(4*R*)-4-Allyl-4-demethyl-26-(acryloyloxy)epothilone D 31. Epothilone derivative **31** was prepared (20 mg, 60%) by a silimar procedure to that described above for the conversion of **21** to **22**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.55 (s, 1H), 6.36 (dd, *J* = 17.2, 1.6 Hz, 1H), 6.09 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.80 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.60 (m, 1H), 5.45 (dd, *J* = 10.2, 4.8 Hz, 1H), 5.27 (d, *J* = 8.0 Hz, 1H), 5.11 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dd, *J* = 10.4,

1.6 Hz, 1H), 4.58 (d, *J* = 12.8 Hz, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 4.41 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.64 (d, *J* = 5.6 Hz, 1H), 3.49 (br.s, 1H), 3.19 (qd, *J* = 5.6, 1.2 Hz, 1H), 3.08 (d, *J* = 1.6 Hz, 1H), 2.66 (m, 1H), 2.65 (s, 3H), 2.60-2.42 (m, 3H), 2.38-2.26 (m, 3H), 2.04 (s, 1H), 2.03 (s, 3H), 1.77 (m, 2H), 1.63 (m, 1H), 1.40 (m, 1H), 1.28 (m, 1H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.00 (s, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.6, 170.2, 165.9, 151.7, 138.9, 137.0, 133.4, 131.0, 128.4, 125.3, 119.2, 118.9, 115.8, 78.2, 73.3, 71.6, 67.6, 57.7, 41.4, 40.1, 39.6, 37.6, 32.4, 31.5, 28.3, 24.6, 19.0, 16.0, 15.5, 14.6, 12.1; HRFABMS: calcd for $C_{32}H_{46}NO_7S$ (M+H) 588.2995, found 588.3007.

Methyl (*R*)-2-((*S*)-1-hydroxy-3-(*t*-butyl-dimethylsilyloxy) propyl)-2-methylpen-4-enoate 37. A solution of LDA (~0.6 M, 69.7 mmol, 2.6 eq) in THF was added to a solution of **14b** (7.02 g, 26.8 mmol) in THF (55 mL) at -78 ^{o}C, and the resulting solution was allowed to warm to -20 ^{o}C and stir for 30 min at -20 ^{o}C. Methyl iodide (2.5 mL, 40.2 mmol, 1.5 eq) in HMPA (13 mL, 75.04 mmol, 1.08 eq to LDA) was added to the above reaction mixture that was recooled to -78 ^{o}C. The subsequent reaction mixture was warmed to -20 ^{o}C and the reaction was allowed to proceed at -20 ^{o}C with stirring for 1 h prior to being quenched by the addition of saturated NH_4Cl solution (200 mL). The two layers were separated and aqueous phase was extracted with ether (100 × 3). The combined organic extracts were washed with water and brine, the organic fraction was dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure to give the crude mass. Purification of the product by silica gel column chromatography eluting with 10% ethyl acetate in hexanes yielded methyl-2-(*R*)-methyl-3-(*S*)-hydroxy-5-O-*t*butyldimethylsilyloxy pentanoate (3.5 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91-3.70 (m, 2H), 3.70-3.50 (m, 2H), 3.66 (s, 3H), 2.59-2.48 (m, 1H), 1.71-1.55 (m, 2H), 1.11 (d, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 73.0, 62.1, 51.8, 45.7, 35.8, 26.0, 18.3, 13.6, -5.34, -5.35. HRFABMS: calcd for $C_{13}H_{29}O_4Si$ (M+H) 277.1835, found 277.1818.

To a freshly prepared solution of LDA (0.6 M, 27.3 mmol, 2.6 eq) in THF (50 mL), a solution of methyl-2-methyl-3-hydroxy-5-*O*-*t*butyldimethylsilyloxy pentanoate, obtained from the above reaction, (2.90 g, 10.51 mmol) in THF (20 mL) was added at -78 ^{o}C, and the resulting solution was warmed to -20 ^{o}C ans stirred for 2 h at that temperature. Then a solution of allyl iodide (1.45 mL, 15.76 mmol, 1.5 eq) in HMPA (29.53 mmol, 1.08 eq to LDA) was added to the above

reaction mixture that was re-cooled to -78 ^{o}C. The subsequent reaction mixture was re-warmed to -20 ^{o}C and allowed to stir at that temperature for 2 h. The reaction was quenched by the addition of saturated ammonium chloride (150 mL). The two layers were separated and aqueous phase was re-extracted with ether (100 mL × 3). The combined organic phases were washed with water and brine, the organic fraction was dried (Na_2SO_4), and the solvents were removed under reduced pressure. The crude oil obtained was subjected to silica gel column chromatography using 10% ethyl acetate in hexanes as eluent to provide **37** (2.07 g, 62.3% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.64 (m, 1H), 5.05 (d, *J* = 18.4 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 3.92 (d, *J* = 10.4, 1H), 3.88-3.79 (m, 2H), 3.68 (s, 3H), 3.32 (br.s, 1H), 2.43 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.18 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.68-1.48 (m, 2H), 1.13 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 133.8, 118.4, 75.4, 62.4, 52.0, 51.2, 40.6, 33.7, 26.1, 18.4, 17.0, -5.2.

(*R*)-2-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-2-methylpen-4-en-1-ol (38). To a solution of **37** (2.35 g, 7.43 mmol) in dichloromethane (37 mL) was added 2,6-lutidine (1.38 mL, 11.90 mmol, 1.6 eq) and TBSOTf (2.58 mL, 11.15 mmol, 1.5 eq) at -78 ^{o}C and the resulting reaction mixture was allowed to warm to -20 ^{o}C over 6 h. Saturated ammonium chloride (60 mL) was added to quench the reaction. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (30 mL × 3). The combined dichloromethane phase was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure. The crude product obtained was subjected to silica gel chromatography eluting with 5% ether in hexanes to furnish methyl (*S*)-2-((*S*)-1,3-bis(tert-butyldimethylsilyloxy) propyl)-2-methylpen-4-enoate (3.08 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.60 (m, 1H), 5.00 (d, *J* = 18.0 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.11 (dd, *J* = 8.0, 2.8 Hz, 1H), 3.72-3.56 (m, 2H), 3.61 (s, 3H), 2.37 (dd, *J* = 16.5, 8.5 Hz, 1H), 2.08-2.02 (m, 1H), 1.78-1.64 (m, 1H), 1.59-1.50 (m, 1H), 1.12 (s, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 6H), -0.006 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 134.3, 117.9, 73.9, 60.5, 52.7, 51.6, 40.5, 36.4, 26.1, 18.5, 18.4, 16.4, -3.7, -4.3, -5.0.

A solution of DIBAL-H (1 M, 25 mmol, 3.5 eq) was added dropwise to a solution of methyl (*S*)-2-((*S*)-1,3-bis(tert-butyldimethylsilyloxy) propyl)-2-methylpen-4-enoate (3.08 g, 7.16 mmol), obtained from the above reaction, in dichloromethane (72 mL) at -78 ^{o}C. The reaction

was allowed to proceed at -78 ^{o}C with stirring for 1 h. Methanol (8 mL) was added and the solution was allowed to warm to 25 ^{o}C. Then a saturated solution of sodium/potassium tartrates (80 mL) was added to the mixture, which was stirred at 25 ^{o}C until the two layers were clearly separated. The organic layer was separated and the aqueous phase was re-extracted with dichloromethane (50 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvents was evaporated under reduced pressure. Purification of the crude product obtained by silica gel column chromatography with 3 % EtOAc in hexanes as eluent to yield **38** (2.66 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.80 (m, 1H), 5.08 (d, *J* = 16.8 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 3.77-3.60 (m, 4H), 4.33 (dd, *J* = 11.2, 8.5 Hz, 1H), 3.03 (dd, *J* = 8.0, 3.3 Hz, 1H), 2.38 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.06 (dd, *J* = 13.5, 7.4 Hz, 1H), 1.98-1.90 (m, 1H), 1.70-1.62 (m, 1H), 0.88 (s, 18H), 0.71 (s, 3H), 0.10 (s, 6H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 117.6, 76.4, 67.5, 60.7, 42.0, 39.2, 36.3, 26.1, 25.9, 18.7, 18.3, -4.2, -5.21, -5.24.

(*S*)-4-((*S*)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-one (39). To a solution of **38** (2.64 g, 6.57 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (66 mL), was added triethylamine (4.6 mL, 32.8 mmol, 5eq) followed by SO_3.Py (5.22 g, 32.8 mmol, 5 eq) at 0 ^{o}C and the resulting reaction mixture was stirred for 30 min. The reaction was quenched by the addition of saturated NH_4Cl solution (100 mL). Organic layer was separated and the aqueous phase was extracted with ethyl ether (50 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvents was removed under reduced pressure. The crude product was purified via silica gel column chromatography eluting with 5 % ethyl acetate in hexanes to yield (*S*)-2-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal (2.47 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 5.65-5.55 (m, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 4.98 (d, *J* = 13.6 Hz, 1H), 4.02 (dd, *J* = 7.6, 2.8 Hz, 1H), 3.64-3.59 (m, 2H), 2.38 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.10 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.76-1.71 (m, 1H), 1.58-1.53 (m, 1H), 0.97 (s, 3H), 0.85 (s, 9H), 0.82 (s, 9H), 0.03 (s, 3H), 0.005 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 132.9, 118.3, 72.3, 59.5, 54.2, 37.9, 36.1, 25.9, 25.8, 18.2, 18.1, 14.2, -3.9, -4.3, -5.3.

To a solution of (*S*)-2-((*S*)-1,3-bis(tert-butyldimethyl-silyloxy)propyl)-2-methylpent-4-enal (1.55 g, 3.87 mmol), obtained from the above reaction, in THF (39 mL) was added ethyl magnesium bromide (1 M, 11.6 mL, 11.6 mmol, 2.5 eq) at 0 ^{o}C and the resulting reaction

mixture was allowed to stir at 0 ^{o}C for 20 min. Saturated NH_4Cl solution (100 mL) was added to quench the reaction. Organic layer was separated and the aqueous phase was re-extracted with dichloromethane (50 mL × 3). The organic extracts were combined and dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. The crude product obtained was purified via silica gel column chromatography eluting with 3 % ether in hexanes and 10 % ethyl acetate in hexanes to produce the product as a diastereomeric mixture (9:1) (660 mg, 39%), together with alcohol **38** (480 mg, 31%) as an undesired byproduct (31%) and starting material (420 mg, 27%). The diastereomeric mixture of (4*R*)-4-((S)-1,3-bis(tert-butyldimethylsilyloxy)propyl)-4-methylhept-6-en-3-ol was subjected to the next reaction without further purification.

To a solution of (4*R*)-4-((*S*)-1,3-bis(tert-butyldimethyl-silyloxy)propyl)-4-methylhept-6-en-3-ol (1.6 g, 3.72 mmol) in a 1:1 mixture of CH_2Cl_2 and DMSO (38 mL), was added triethylamine (2.60 mL, 18.6 mmol, 5 eq) followed by SO_3.Py complex (2.96 g, 18.6 mmol, 5 eq) at 0 ^{o}C. The reaction was allowed to proceed at 0 ^{o}C with stiring for 2 h prior to being quenched by the addition of saturated NH_4Cl solution (60 mL). Organic layer was separated and the aqueous phase was extracted with ethyl ether (30 mL × 3). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give crude product, which was purified via silica gel chromatography eluting with 2 % ether in hexanes to give **39** (1.05 g, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65-5.50 (m, 1H), 4.99 (d, *J* = 16.4 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.05 (dd, *J* = 7.6, 2.4 Hz, 1H), 3.70-3.52 (m, 2H), 2.56-2.36 (m, 3H), 2.00 (q, *J* = 6.8 Hz, 1H), 1.72-1.60 (m, 1H), 1.49-1.42 (m, 1H), 1.10 (s, 3H), 0.96 (t, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.005 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 134.3, 117.9, 74.2, 60.2, 56.5, 40.3, 36.8, 33.4, 26.2, 26.1, 18.5, 18.4, 17.4, 7.6, -3.92, -3.96, -5.10. HRFABMS: calcd for C23H49O3Si2 (M+H) 429.3220, found 429.3194.

Aldol product 40. The 4*S*, 6*S*, 7*R* aldol product **40** was obtained from the aldol reaction of ketone **39** and aldehyde **11**, according to the procedure described previously for the synthesis of aldol product **18**, as a major product (680 mg, 46%, colorless oil), together with other two minor products (28% total yield for both). Compound **40:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.1 Hz, 6H), 7.27 (t, *J* = 7.1 Hz, 6H), 7.20 (t, *J* = 7.1 Hz, 3H), 6.89 (s, 1H), 6.50 (s, 1H),

5.62-5.53 (m, 2H), 4.99 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 16.4 Hz, 1H), 4.17 (t, *J* = 6.8 Hz, 1H), 3.68-3.59 (m, 3H), 3.47 (br.s, 2H), 3.33 (d, *J* = 8.2 Hz, 1H), 3.13 (q, *J* = 6.9 Hz, 1H), 2.69 (s, 3H), 2.43-2.31 (m, 3H), 2.13 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.03-1.99 (m, 1H), 2.03 (s, 3H), 1.82-1.78 (m, 1H), 1.66-1.60 (m, 1H), 1.54-1.38 (m, 2H), 1.15 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.89-0.87 (overlap, 21H), 0.12 (s, 3H), 0.10 (s, 3H), 0.036 (s, 3H), 0.030 (s, 3H), 0.027 (s, 3H), 0.024 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.5, 164.4, 153.2, 144.4, 142.4, 138.1, 133.9, 128.7, 127.7, 126.9, 122.9, 118.9, 118.1, 115.2, 86.6, 78.7, 74.9, 72.1, 67.4, 60.1, 57,8, 41.6, 39.2, 36.9, 35.4, 35.2, 32.9, 29.0, 26.2, 26.0, 25.9, 19.2, 18.5, 18.4, 18.35, 18.32, 15.5, 14.1, 10.2, -3.5, -4.0, -4.5, -4.7, -5.1; HRFABMS: calcd for $C_{66}H_{104}NO_6SSi_3$ (M+Na) 1122.6892, found 1122.6927.

Tetrakis-[*tert*-butyldimethylsilyl]-ether 41a. 4*S*, 6*S*, 7*R* tetrakis-TBS ether **41a** was prepared (510 mg, 94%) as a colorless oil by a silimar procedure to that described above for the conversion of **18** to **19a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 6H), 7.25 (t, *J* = 8.2 Hz, 6H), 7.21 (t, *J* = 7.4 Hz, 3H), 6.89 (s, 1H), 6.50 (s, 1H), 5.62-5.54 (m, 2H), 4.92 (d, *J* = 17.0 Hz, 1H), 4.87 (d, *J* = 10.1 Hz, 1H), 4.18 (t, *J* = 6.9 Hz, 1H), 4.10 (d, *J* = 8.8 Hz, 1H), 3.74 (d, *J* = 7.4 Hz, 1H), 3.66-3.58 (m, 2H), 3.46, 3.42 (ABq, *J* = 11.8 Hz, 2H), 3.05-2.98 (m, 1H), 2.69 (s, 3H), 2.48-2.27 (m, 3H), 2.99 (dd, *J* = 14.3, 7.7 Hz, 1H), 2.04 (s, 3H), 2.03-1.95 (m, 1H), 1.91-1.82 (m, 1H), 1.74-1.69 (m, 1H), 1.62-1.46 (m, 4H), 1.19-1.11 (m, 2H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.83 (s, 18H), 0.73 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.038 (s, 3H), 0.031 (s, 3H), 0.026 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 164.3, 153.3, 144.4, 142.4, 138.1, 134.8, 128.7, 127.7, 126.8, 122.5, 118.8, 117.4, 115.2, 86.5, 78.7, 76.9, 71.7, 67.3, 60.1, 57.5, 45.2, 38.3, 36.9, 36.2, 35.2, 35.1, 34.7, 31.6, 29.0, 26.6, 26.3, 26.2, 26.0, 25.9, 22.7, 20.7, 19.9, 19.2, 18.66, 18.60, 18.38, 18.31, 16.2, 14.2, 14.0, 13.5, 11.5, -3.2, -3.3, -3.6, -3.9, -4.5, -4.7, -4.9, -5.0; HRFABMS: calcd for $C_{72}H_{118}NO_6SSi_4$ (M+H) 1236.7757, found 1236.7793.

Tris-[tert-butyldimethylsilyl]-ether 41b. 4*S*, 6*S*, 7*R* tris-TBS ether **41b** was prepared (390 mg, 87%) as a colorless oil from tetrakis-TBS ether **41a** using a silimar procedrure as described previously for the conversion of **19a** to **19b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.9 Hz, 6H), 7.28-7.22 (m, 6H), 7.19 (t, *J* = 7.9 Hz, 3H), 6.88 (s, 1H), 6.49 (s, 1H), 5.64-5.52 (m, 2H),

4.94 (d, *J* = 17.0 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 4.17 (t, *J* = 5.5 Hz, 1H), 4.11 (d, *J* = 8.0 Hz, 1H), 3.74 (d, *J* = 7.4 Hz, 1H), 3.73-3.58 (m, 2H), 3.45, 3.41 (ABq, *J* = 11.8 Hz, 2H), 3.06-3.00 (m, 1H), 2.68 (s, 3H), 2.41-2.27 (m, 3H), 2.15 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.03 (s, 3H), 2.00-1.94 (m, 3H), 1.72-1.52 (m, 4H), 1.18 (s 3H), 1.15-1.05 (m, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.73 (d, *J* = 6.4 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H), 0.028 (s, 3H), 0.022 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.1, 164.3, 153.2, 144.4, 142.5, 138.1, 134.4, 128.7, 127.7, 126.8, 122.5, 118.8, 117.6, 115.1, 86.5, 78.7, 71.7, 67.4, 59.9, 57.2, 45.2, 38.4, 37.2, 36.2, 35.2, 35.1, 29.0, 26.6, 26.3, 26.2, 25.9 19.8, 19.2, 18.6, 18.5, 18.3, 16.1, 14.1, 13.6, -3.3, -3.6, -4.1, -4.5, -4.7; HRFABMS: calcd for $C_{66}H_{104}NO_6SSi_3$ (M+H) 1122.6892, found 1122.6949.

Oxidation of 41b to aldehyde 41c. A similar procedure was employed to prepare aldehyde **41c** (353.5 mg, 90%, colorless oil) as that described previously for the conversion of **19b** to **19c**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.42 (d, *J* = 7.1 Hz, 6H), 7.25 (t, *J* = 7.1 Hz, 6H), 7.17 (t, *J* = 7.1 Hz, 3H), 6.88 (s, 1H), 6.50 (s, 1H), 5.59 (t, *J* = 7.1 Hz, 1H), 5.57-5.48 (m, 1H), 4.93 (d, *J* = 14.8 Hz, 1H), 4.91 (d, *J* = 8.2 Hz, 1H), 4.64 (dd, *J* = 6.0, 3.8 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 1H), 3.74 (d, *J* = 7.7 Hz, 1H), 3.45, 3.41 (ABq, *J* = 11.5 Hz, 2H), 3.05-2.97 (m, 1H), 2.69 (s, 3H), 2.56-2.50 (m, 2H), 2.38-2.25 (m, 3H), 2.14 (dd, *J* = 14.5, 6.6 Hz, 1H), 2.03 (s, 3H), 1.99-1.93 (m, 1H), 1.21 (s, 3H), 1.15-0.98 (m, 4H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.84 (s, 9H), 0.72 (d, *J* = 6.3 Hz, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.027 (s, 6H), 0.021 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 201.3, 164.3, 153.3, 144.4, 142.4, 138.1, 133.4, 128.7, 127.7, 126.8, 122.6, 118.9, 118.3, 115.2, 86.5, 78.7, 76.6, 69.3, 67.4, 56.9, 47.9, 45.3, 38.4, 37.6, 35.19, 35.15, 29.0, 26.6, 26.3, 26.0, 25.9, 19.2, 19.0, 18.6, 18.3, 16.0, 14.1, 13.5, -3.3, -3.6, -4.1, -4.2, -4.5, -4.7; HRFABMS: calcd for $C_{66}H_{100}NO_6SSi_3$ (M-H) 1118.6579, found 1118.6549.

Hydroxy acid 41d. A similar procedure was employed to prepare hydroxy acid **41d (**300 mg, 91% for two steps, colorless oil) from aldehyde **41c** as previously described for the conversion of **19c** to **19e**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.4 Hz, 6H), 7.21 (t, *J* = 7.4 Hz, 6H), 7.19 (t, *J* = 7.4 Hz, 3H), 6.91 (s, 1H), 6.60 (s, 1H), 5.69-5.57 (m, 1H), 5.56 (t, *J* = 7.1 Hz, 1H), 4.97 (d, *J* = 18.6 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 4.48 (dd, *J* = 7.4, 2.2 Hz, 1H), 4.18 (t, *J* =

6.6 Hz, 1H), 3.76 (d, *J* = 7.1 Hz, 1H), 3.53, 3.49 (ABq, *J* = 12.1 Hz, 2H), 3.15-3.09 (m, 1H), 2.71 (s, 3H), 2.47-2.29 (m, 4H), 2.23-2.15 (m, 1H), 2.03 (s, 3H), 2.05-1.99 (m, 1H), 1.16 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.76 (d, *J* = 6.6 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 175.6, 165.2, 152.5, 144.3, 142.1, 140.3, 134.1, 128.7, 127.8, 126.9, 121.5, 118.6, 117.9, 115.3, 86.8, 77.0, 76.6, 72.5, 67.5, 57.1, 45.9, 39.2, 38.7, 37.1, 35.3, 33.9, 28.9, 26.7, 26.3, 26.1, 19.9, 18.8, 18.6, 18.3, 16.2, 14.8, 13.6, -3.4, -3.6, -4.1, -4.5. HRFABMS: calcd for $C_{60}H_{88}NO_7SSi_2$ (M+H) 1022.5820, found 1022.5824.

Macrolactone 42. 4*S*, 6*S*, 7*R* macrolactone **42** was prepared (135 mg, 46.6%) as a colorless oil from hydroxy acid **41d** by a silimar procedrure as described previously for the synthesis of macrolactone **20a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.38 (m, 6H), 7.26-7.13 (m, 9H), 6.83 (s, 1H), 6.38 (s, 1H), 5.73-5.60 (m, 1H), 5.59 (t, *J* = 7.6 Hz, 1H), 5.22 (br.s, 1H), 5.08 (d, *J* = 14.0 Hz, 1H), 5.07 (d, *J* = 7.9 Hz, 1H), 4.17 (br.d, *J* = 7.4 Hz, 1H), 3.90 (br.s, 1H), 3.48, 3.40 (ABq, 2H), 2.70-2.64 (m, 1H), 2.68 (s, 3H), 2.58-2.45 (m, 3H), 2.25-2.12 (m, 2H), 2.18 (s, 3H), 1.76-1.70 (m, 1H), 1.55-1.45 (m, 1H), 1.38-1.32 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 3H), 0.86 (s, 18 H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.03 (s, 3H), -0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.1, 170.4, 164.4, 152.7, 144.3, 140.4, 136.8, 134.1, 129.1, 127.8, 126.9, 119.1, 118.9, 118.0, 116.4, 86.7, 75.0, 73.6, 67.6, 60.4, 56.5, 48.6, 42.3, 40.0, 38.8, 34.8, 31.0, 29.7, 28.5, 28.0, 26.4, 19.3, 18.8, 18.7, 16.1, 15.9, -3.5, -3.9, -4.5, -4.7. HRFABMS: calcd for $C_{60}H_{86}NO_6SSi_2$ (M+H) 1004.5714, found 1004.5754.

Primary Alcohol 43. To a solution of macrolactone **42** (132.5 mg, 0.13 mmol) in ether (3 mL) at -5 ^{o}C was added formic acid (3 mL) and the reaction was allowed to proceed with stirring for 5 h at -5 ^{o}C. Water (20 mL) and then solid $NaHCO_3$ were sequently added until cessation of effervescence. The mixture was extracted with ether (20 mL × 3), the combined organic extracts were dried (Na_2SO_4), and the solvents were removed in vacuo. Purification of the crude product via preparative thin layer chromatography eluting with 50% ether in hexanes to yield primary alcohol **43** (62 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.33 (s, 1H), 5.74-5.64 (m, 1H), 5.33 (t, *J* = 7.6 Hz, 1H), 5.17 (br.s, 1H), 5.07 (d, *J* = 17.6 Hz, 1H), 5.06 (d, *J* = 9.6 Hz, 1H), 4.17 (d, *J* = 8.8 Hz, 1H), 4.05-3.91 (m, 2H), 3.98 (br.s, 2H), 3.46-3.36 (m,

1H), 2.72-2.62 (m, 2H), 2.68 (s, 3H), 2.51-2.40 (m, 5H), 2.25-2.19 (m, 2H), 2.09 (s, 3H), 1.92-1.72 (m, 2H), 1.15-1.00 (m, 2H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.91 (s, 9 H), 0.89 (s, 9H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.19 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125 MHz, CDC_{l3}) δ 214.4, 170.5, 164.7, 152.6, 143.0, 136.7, 134.2, 119.9, 119.4, 118.1, 116.2, 78.5, 75.0, 73.8, 67.5, 56.6, 48.7, 42.3, 40.3, 38.7, 35.0, 30.9, 28.2, 26.5, 26.4, 19.4, 18.9, 18.7, 16.2, 16.1, 14.3, -3.4, -3.8, -4.2, -4.6. HRFABMS: calcd for $C_{41}H_{72}NO_6SSi_2$ (M+H) 762.4619, found 762.4601.

(4*S*)-4-Allyl-4-demethyl-26-hydroxy-6*S*,7*R*-epothilone D 54. A similar procedure was used to prepare triol **54** (14.5 mg, 51%, colorless oil), as well as 48% mono-TBS ether, from lactone **42** following the procedure described previously for the conversion of **20a** to **21**. Compound **54**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.53 (s, 1H), 5.66-5.60 (m, 2H), 5.46 (dd, *J* = 9.6, 3.0 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 5.12 (d, *J* = 11.3Hz, 1H), 4.15-4.11 (m, 1H), 4.05, 4.02 (ABq, *J* = 13.5 Hz, 2H), 3.65-3.54 (m, 1H), 3.50 (d, *J* = 9.6 Hz, 1H), 3.45-3.39 (m, 1H), 3.36 (br.s, 1H), 3.31 (d, *J* = 3.3 Hz, 1H), 2.73-2.66 (m, 1H), 2.69 (s, 3H), 2.55 (dd, *J* = 15.7, 2.2 Hz, 1H), 2.50 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.41-2.26 (m, 4H), 2.07 (s, 3H), 2.04-1.94 (m, 1H), 1.70-1.43 (m, 5H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 3H), 0.96-0.91 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.2, 171.0, 165.2, 152.7, 141.5, 137.0, 132.5, 122.6, 120.2, 119.4, 116.5, 78.4, 74.7, 72.3, 66.1, 56.1, 43.0, 39.3, 38.5, 35.5, 33.4, 32.5, 28.4, 24.5, 19.2, 17.2, 16.0, 15.5, 11.8.

12β,13β-Epoxide 55. To a solution of allylic alcohol **54** (14.5 mg, 0.027 mmol) and 4 Å molecular sieves (40 mg) in CH_2Cl_2 (0.5 mL) at -20 ^{o}C was added diethyl-L-tartrate (6.7 mg, 0.0326 mmol, 1.2 eq) in CH_2Cl_2 (0.1 mL) and titanium isopropoxide (7.7 mg, 0.027 mmol, 1.0 eq) in CH_2Cl_2 (0.1 mL). After stirring at that temperature for 1 h, *t*-butyl hydroperoxide (16 μL, 5 M in decane, 0.0081 mmol, 3.0 eq) was added and the resulting reaction mixture was stirred at -20 ^{o}C for an additional 2 h. The reaction mixture was then filtered through celite into saturated aqueous Na_2SO_4 solution (10 mL), rinsing with EtOAc (10 mL). The subsequent biphasic mixture was stirred for 1 h and two layers were separated. The aqueous phase was re-extracted with EtOAc (10 mL × 3), and the combined organic extracts were dried over anhydrous Na_2SO_4, and the solvents were removed *in vacuo* to give a crude oil. Purification of

this oil by preparation thin layer chromatography over silica gel using 70% EtOAc in hexanes as eluent furnished β-epoxide triol **55** (8.5 mg, 84%) as a syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.63 (s, 1H), 5.67 (br.s, 1H), 5.52-5.47 (m, 1H), 5.10 (d, *J* = 9.3 Hz, 1H), 5.09 (d, *J* = 17.3 Hz, 1H), 4.31-4.28 (m, 2H), 3.74 (d, *J* = 9.3 Hz, 1H), 3.69 (br.s, 2H), 3.53 (br.s, 1H), 3.45-3.30 (m, 3H), 2.69 (s, 3H), 2.58-2.37 (m, 3H), 2.20-2.18 (m, 2H), 2.13 (s, 3H), 1.97-1.93 (m, 1H), 1.86-1.58 (m, 4H), 1.54-1.40 (m, 2H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.6, 171.5, 164.9, 152.2, 134.7, 132.2, 119.8, 119.2, 116.6, 76.0, 74.0, 73.2, 63.3, 62.3, 57.6, 56.8, 40.7, 39.7, 39.6, 35.9, 34.4, 33.4, 30.1, 28.6, 26.6, 19.3, 16.3, 15.8, 14.2, 11.4.

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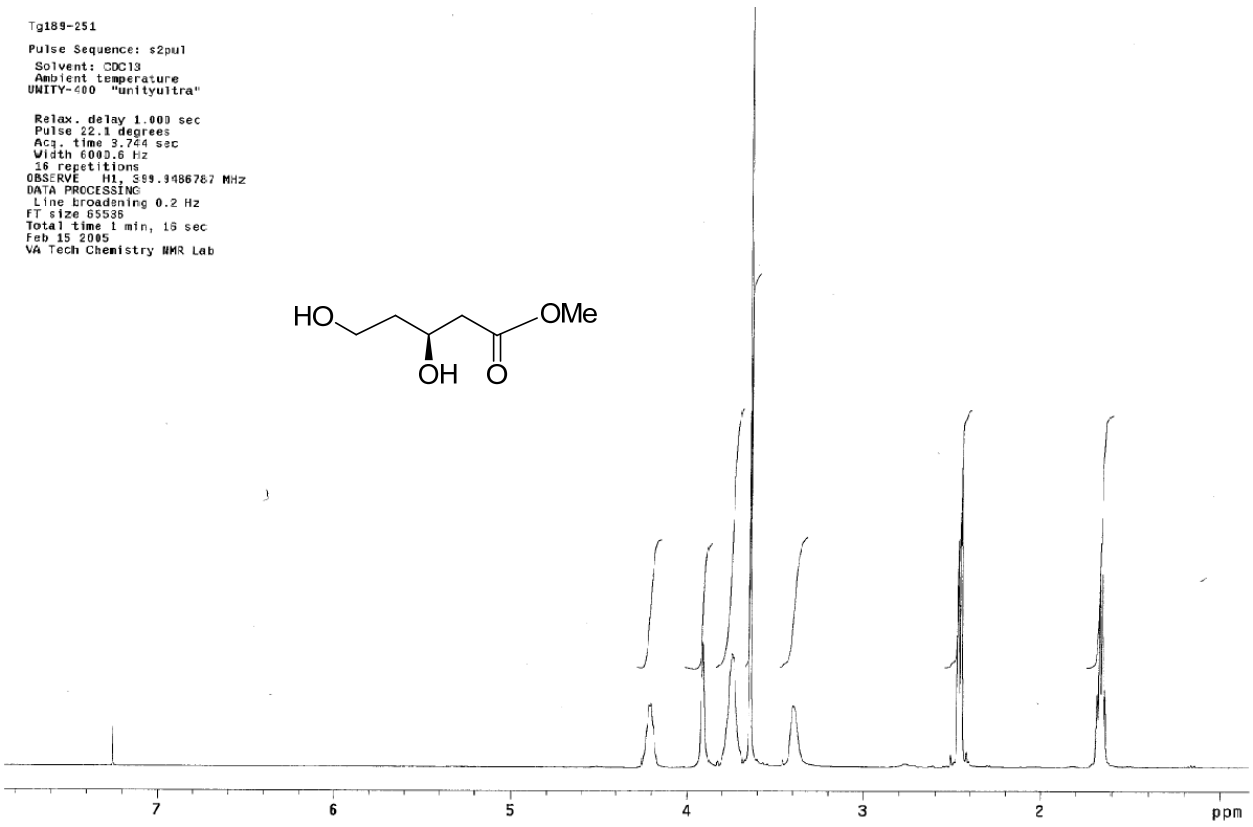
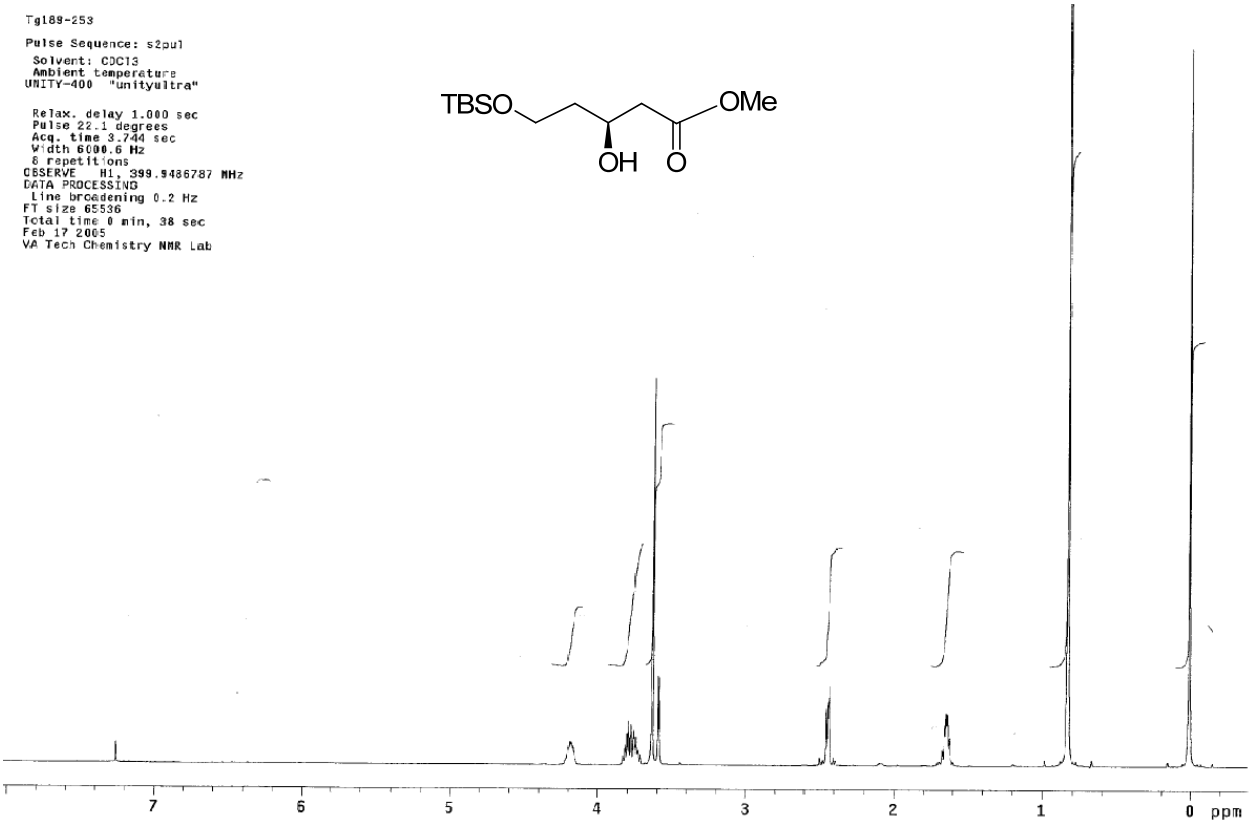


^{1}HNMR spectrum of compound **14a**



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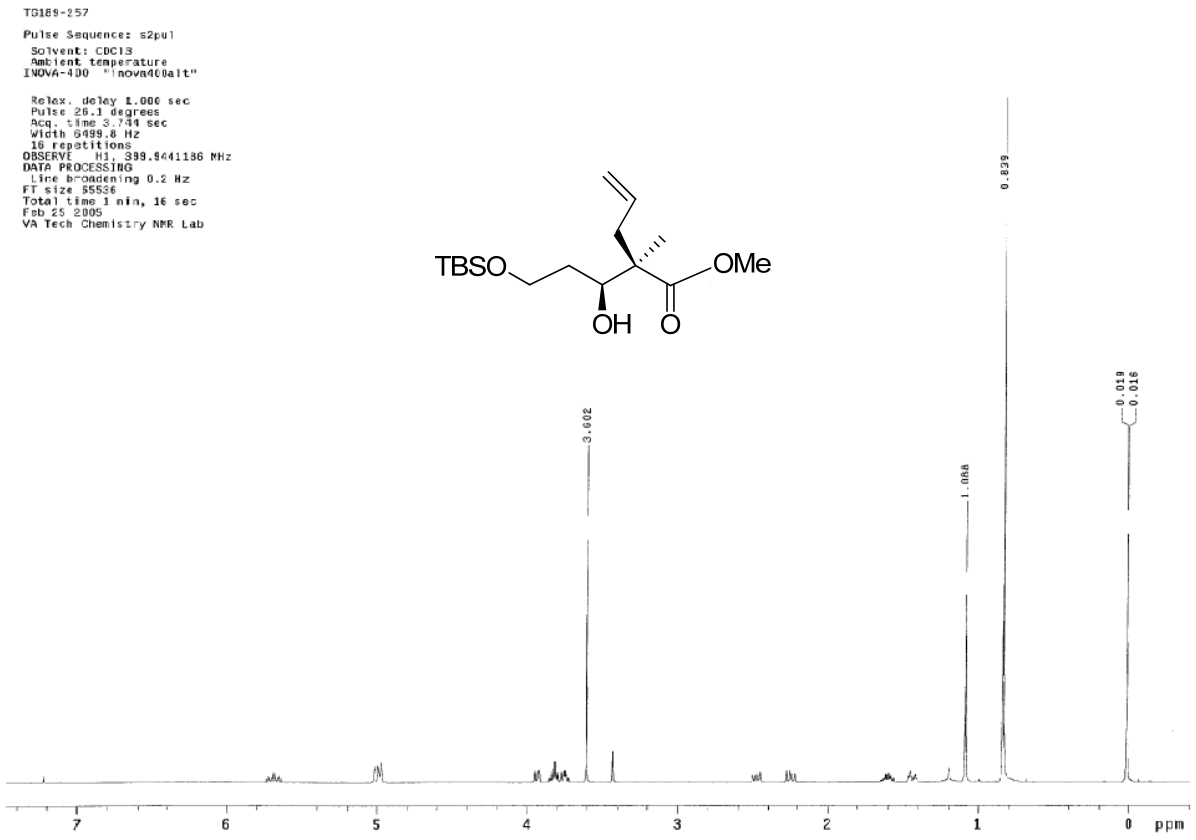
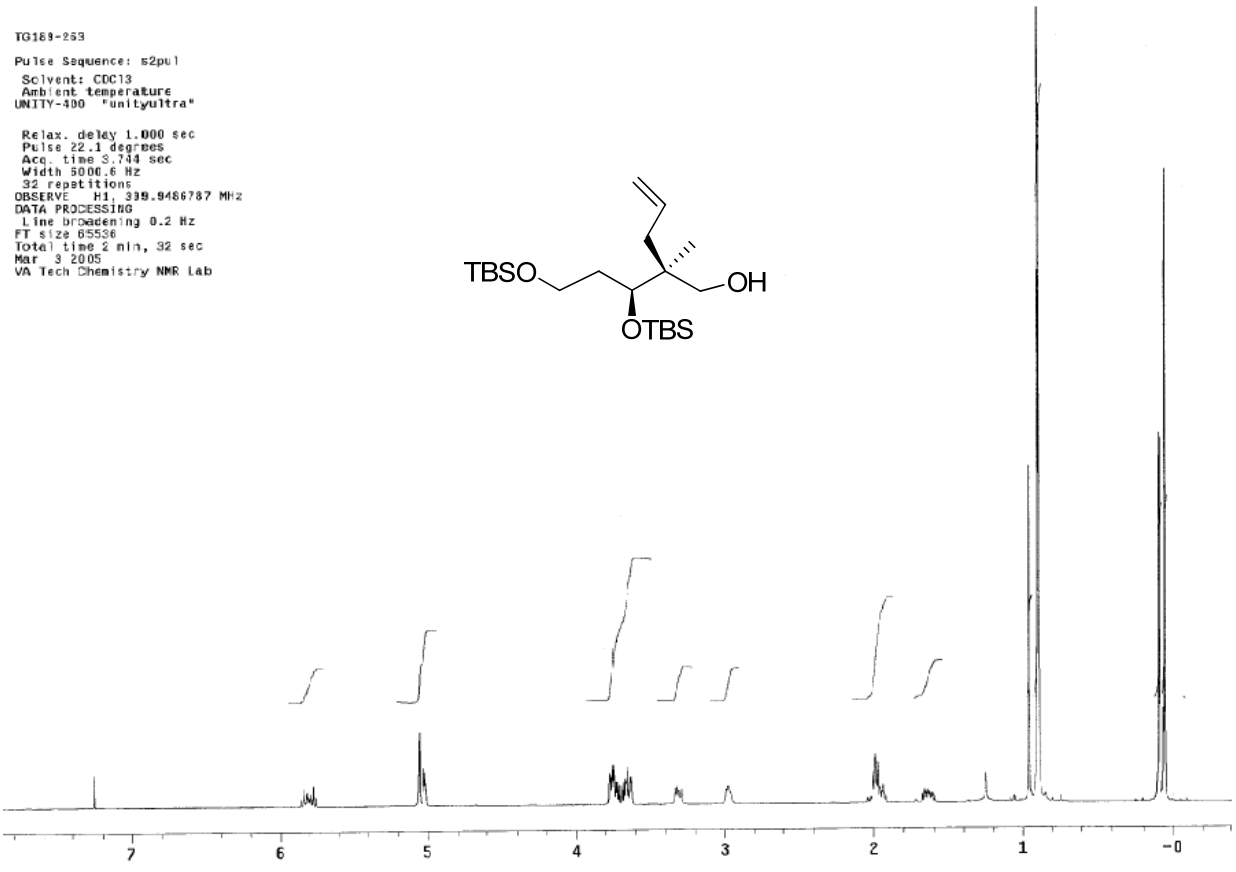
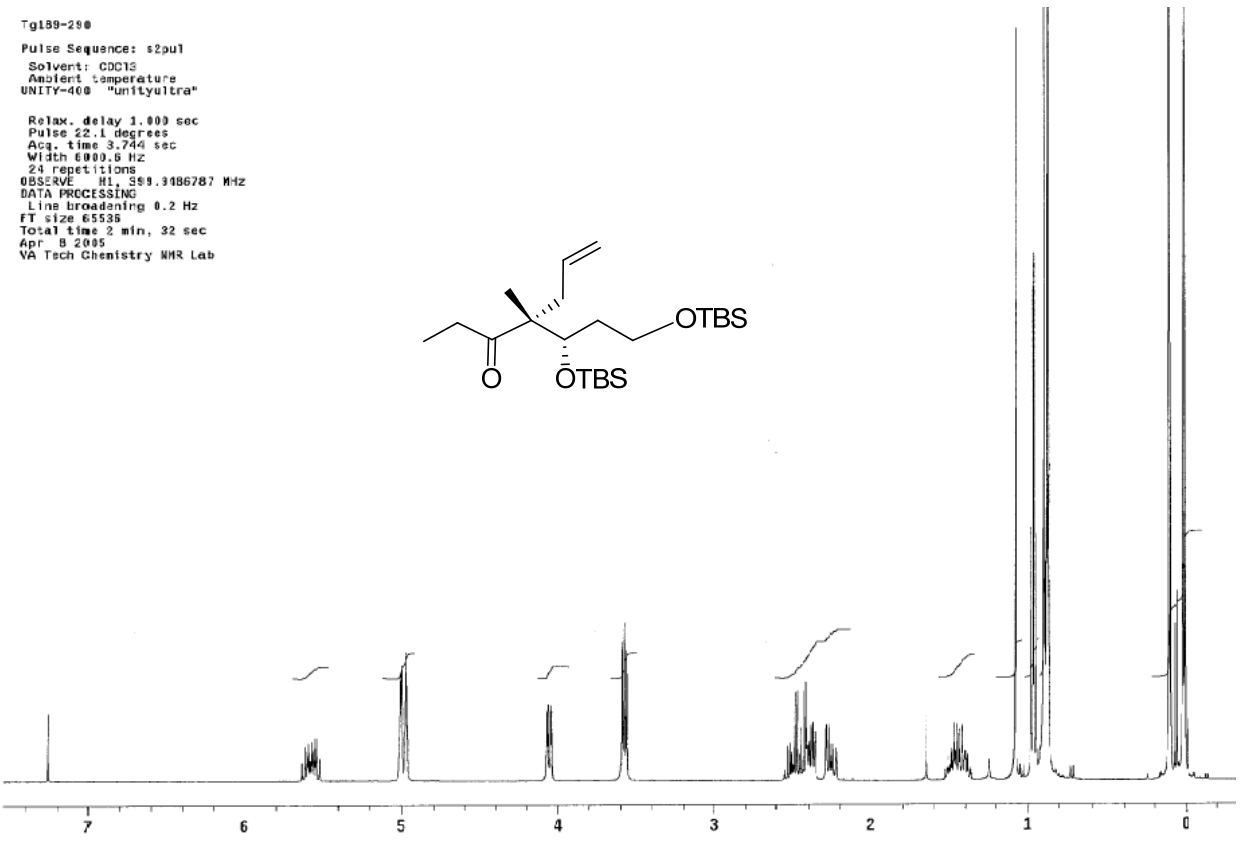


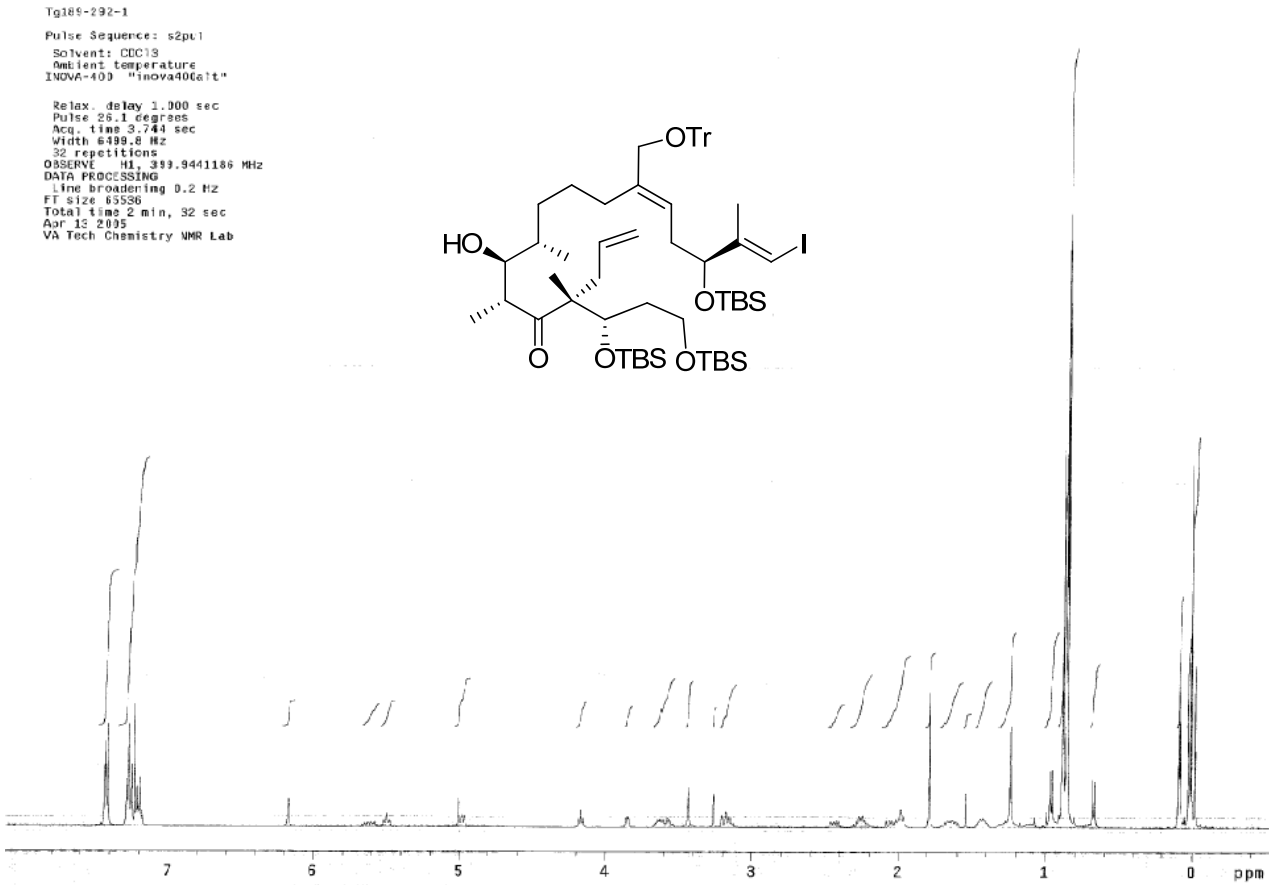
[1]HNMR spectrum of compound **15**



[1]HNMR spectrum of compound **16**



[1]HNMR spectrum of compound **9**



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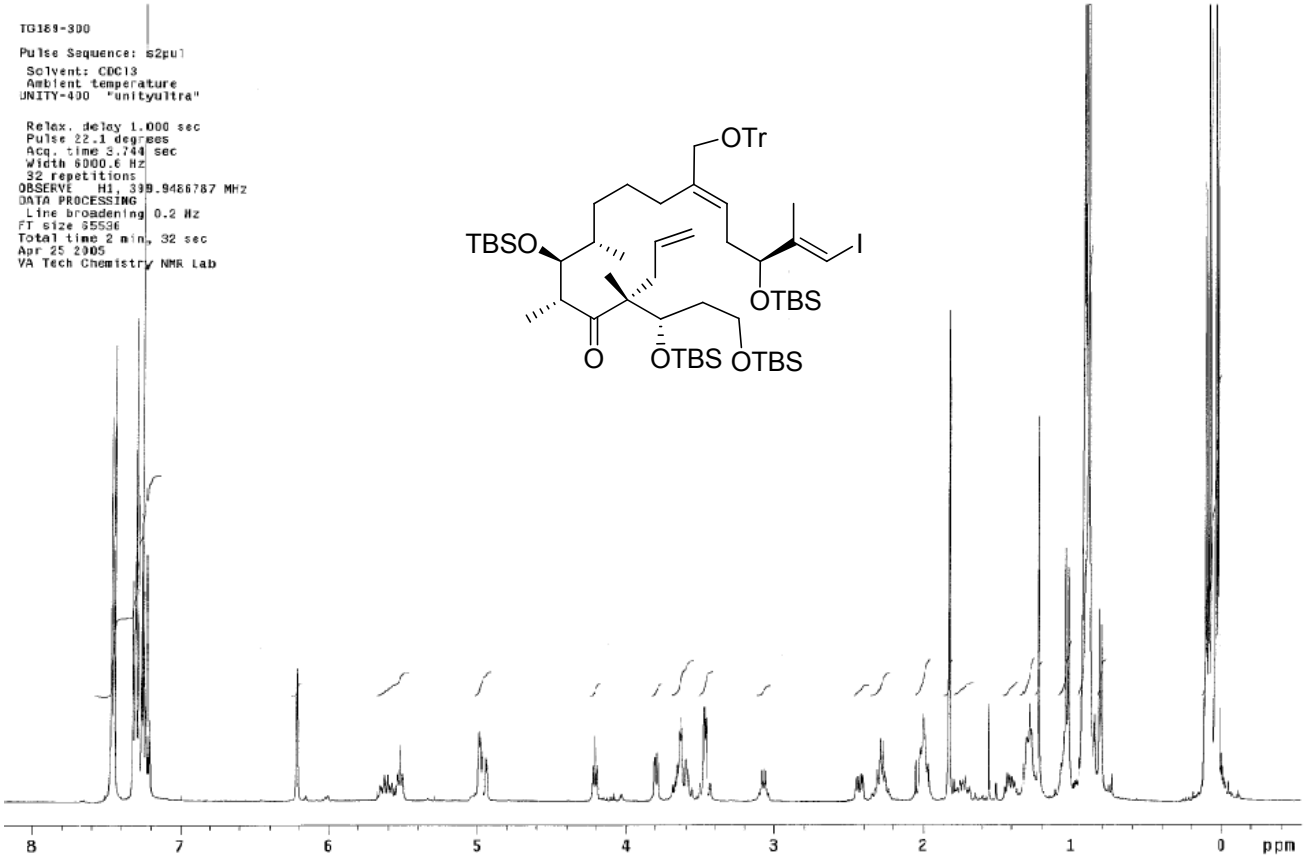
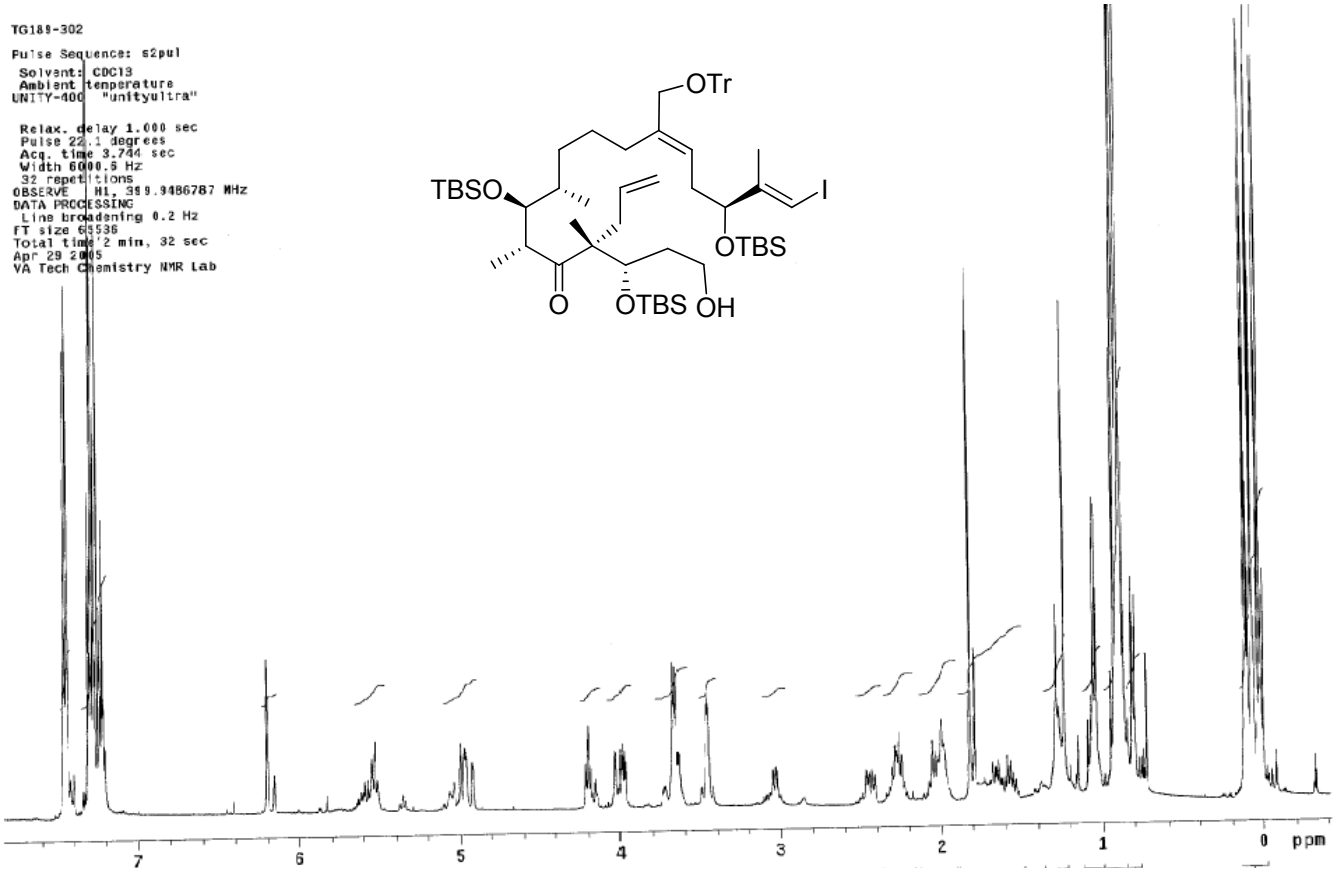
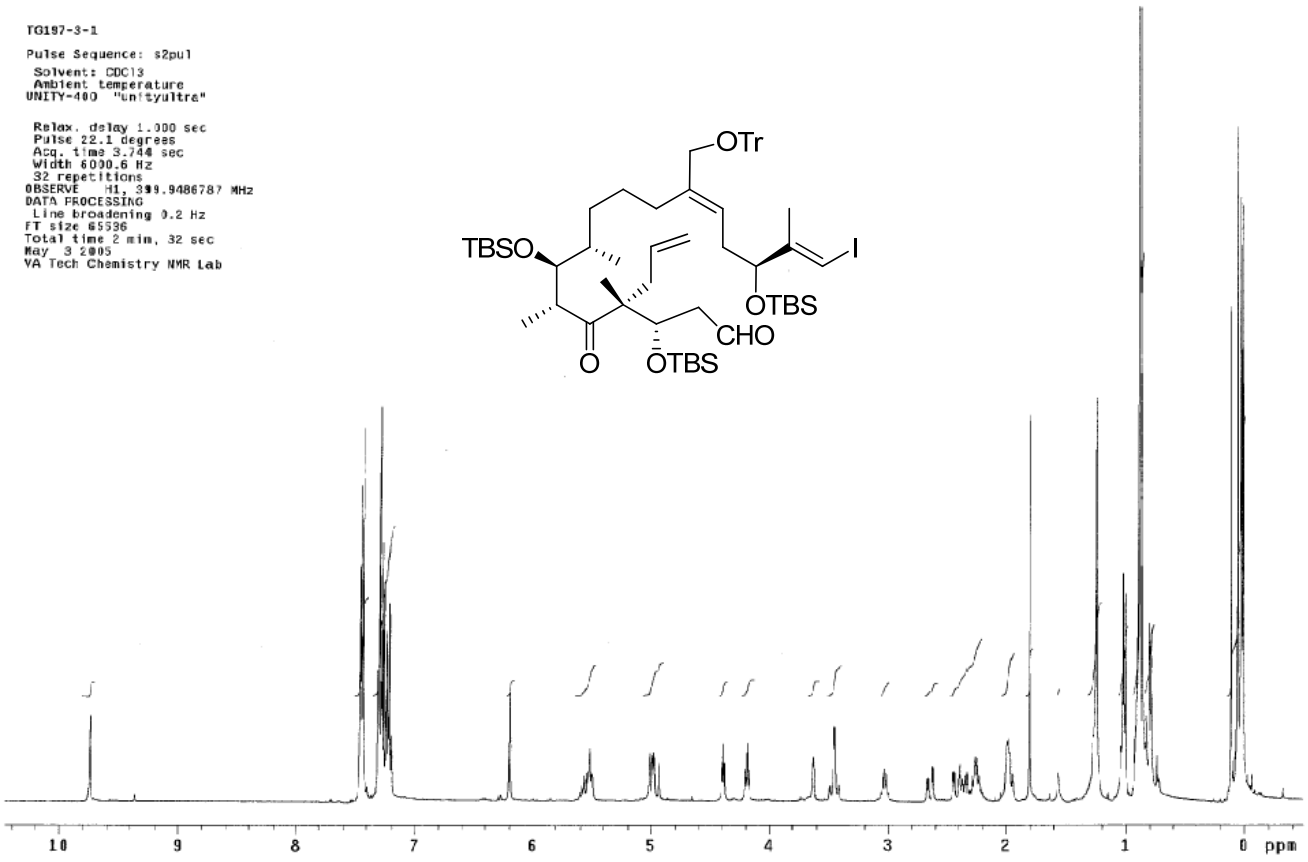


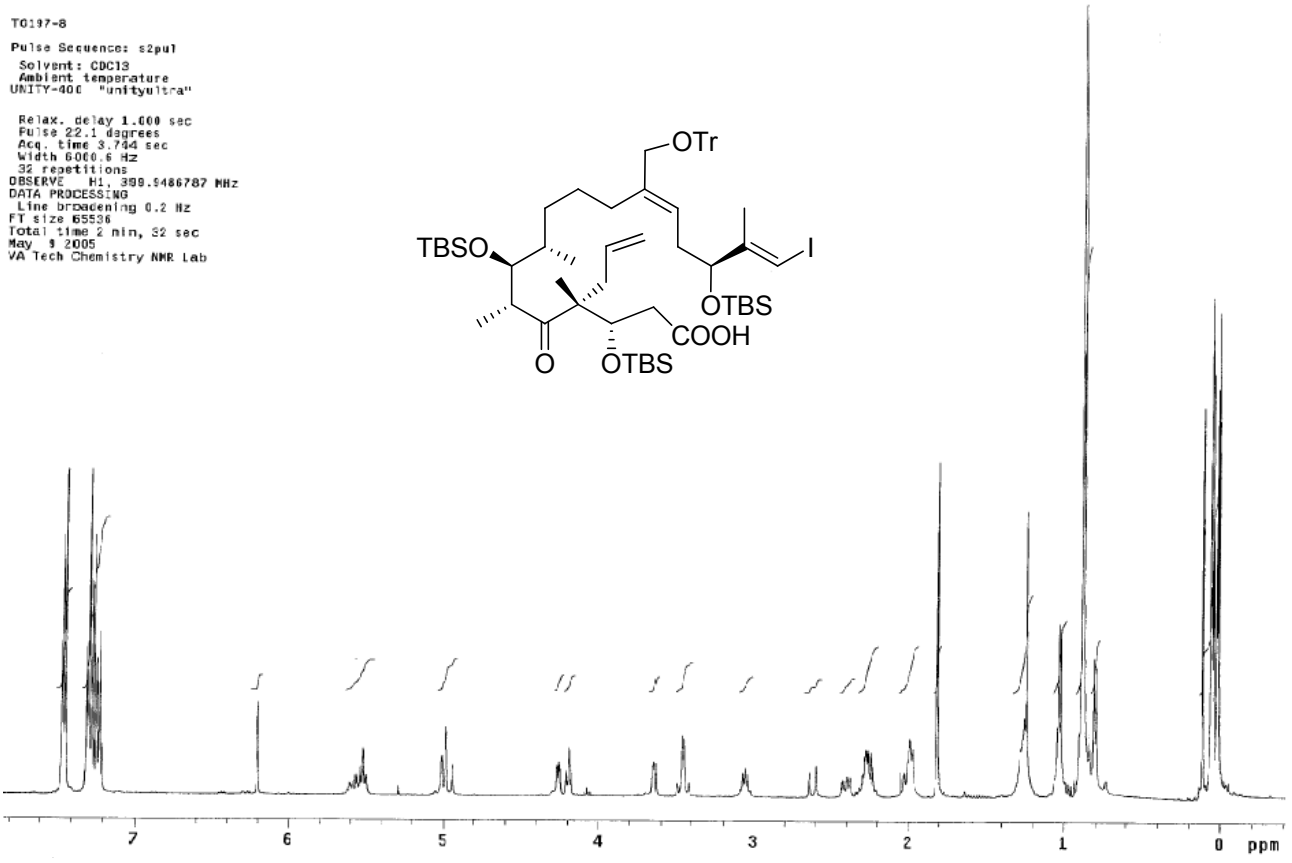
^{1}HNMR spectrum of compound **19a**



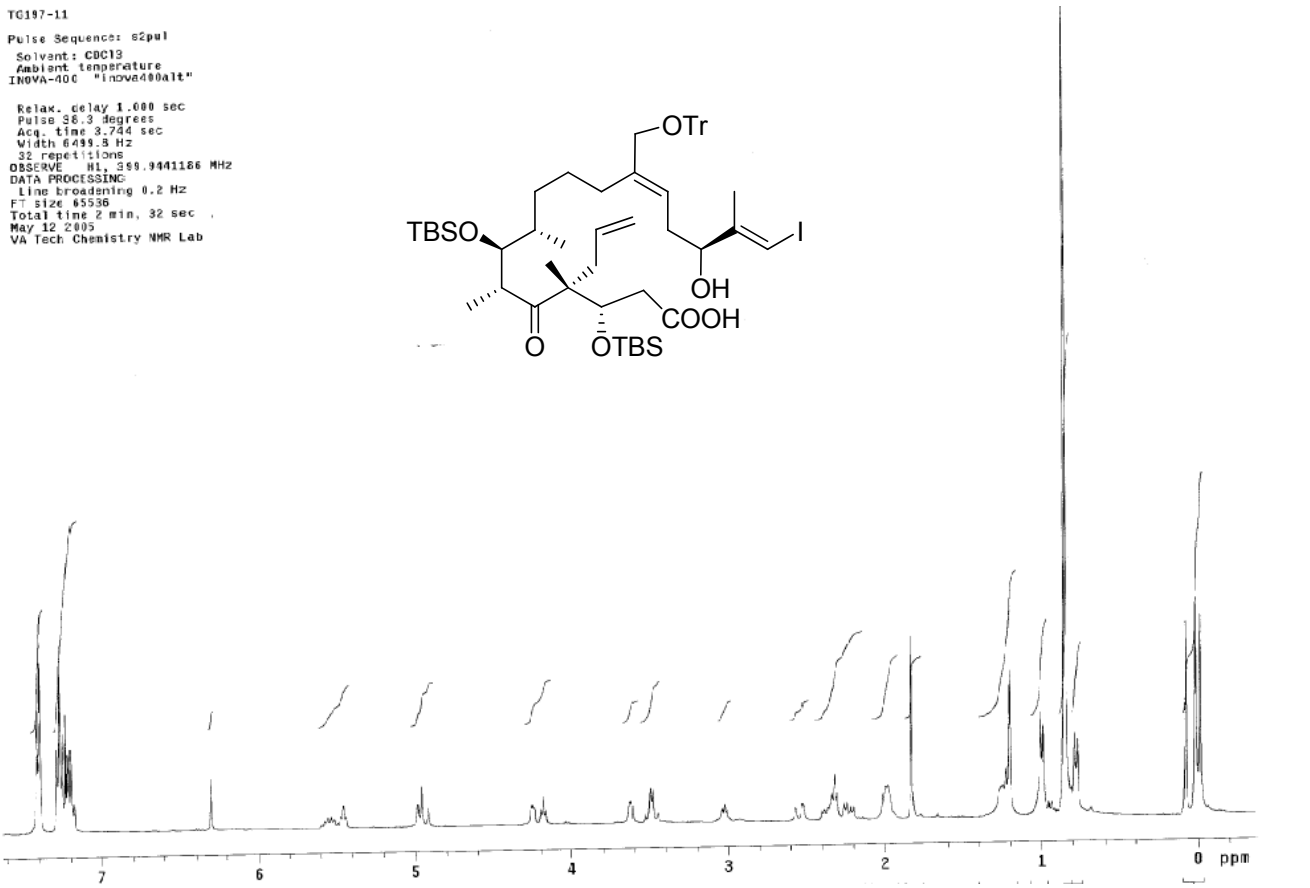
^{1}HNMR spectrum of compound **19b**



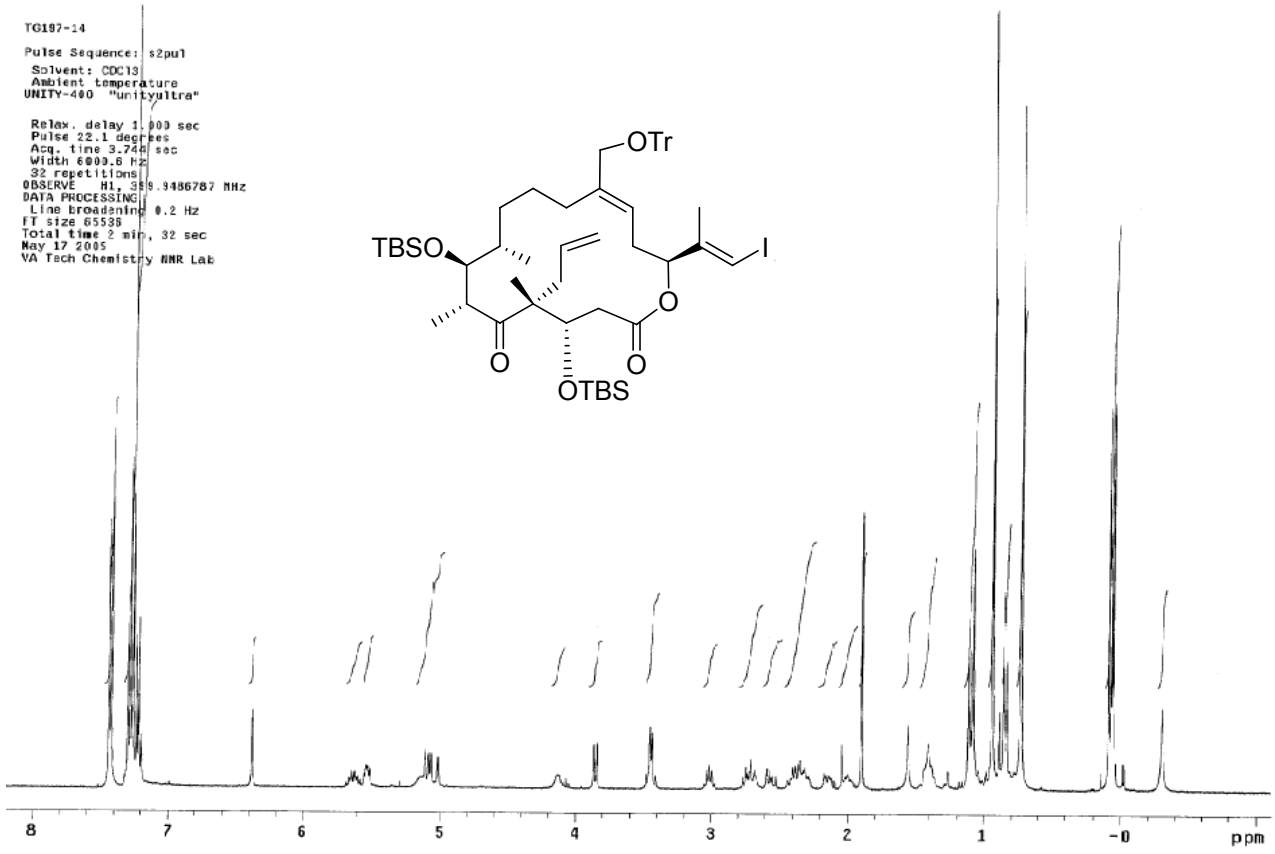
^{1}HNMR spectrum of compound **19c**



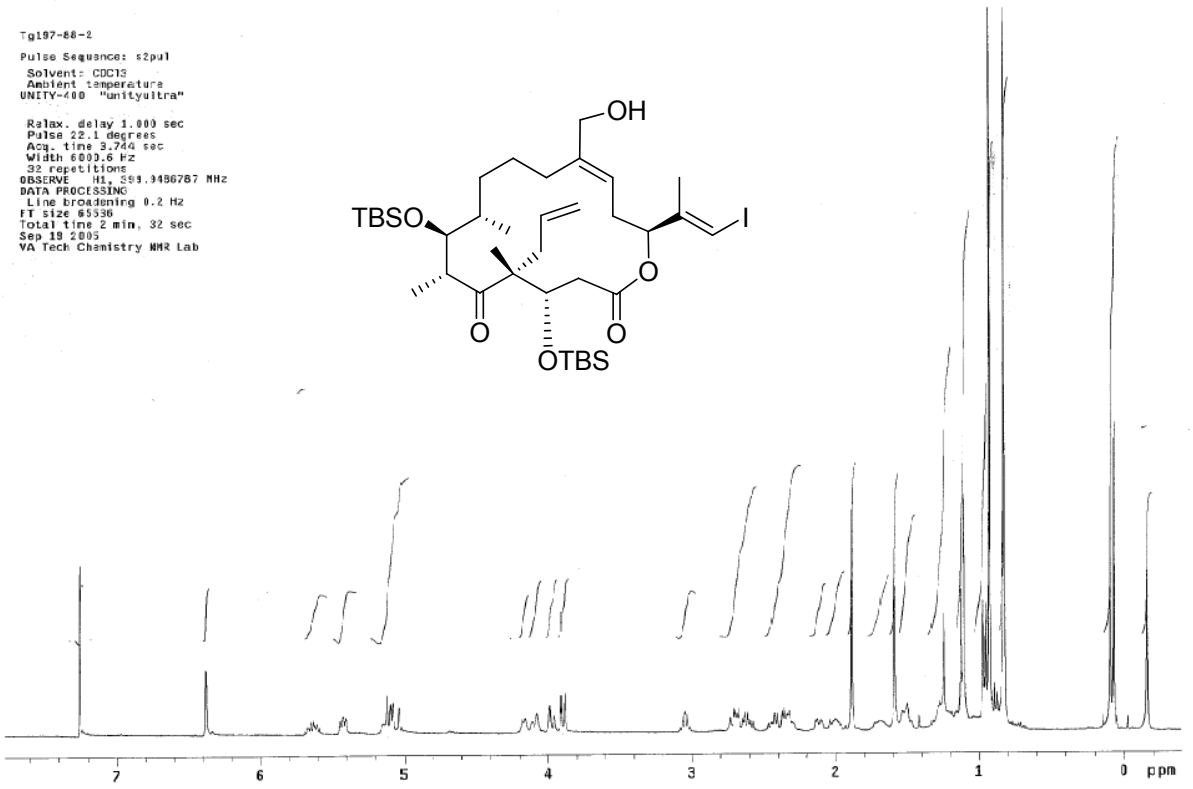
^{1}HNMR spectrum of compound **19d**



^{1}HNMR spectrum of compound **19e**



^{1}HNMR spectrum of compound **20a**



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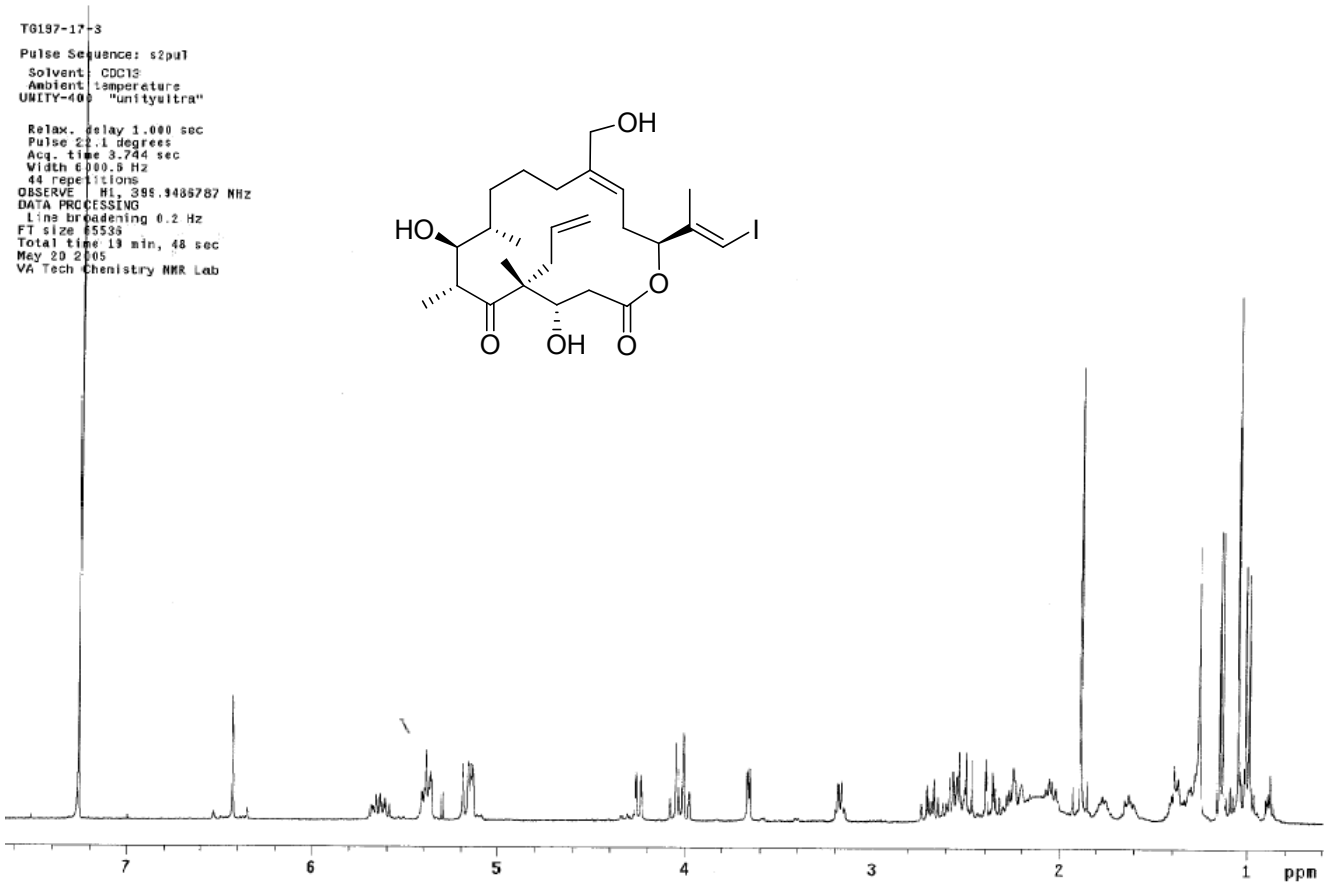

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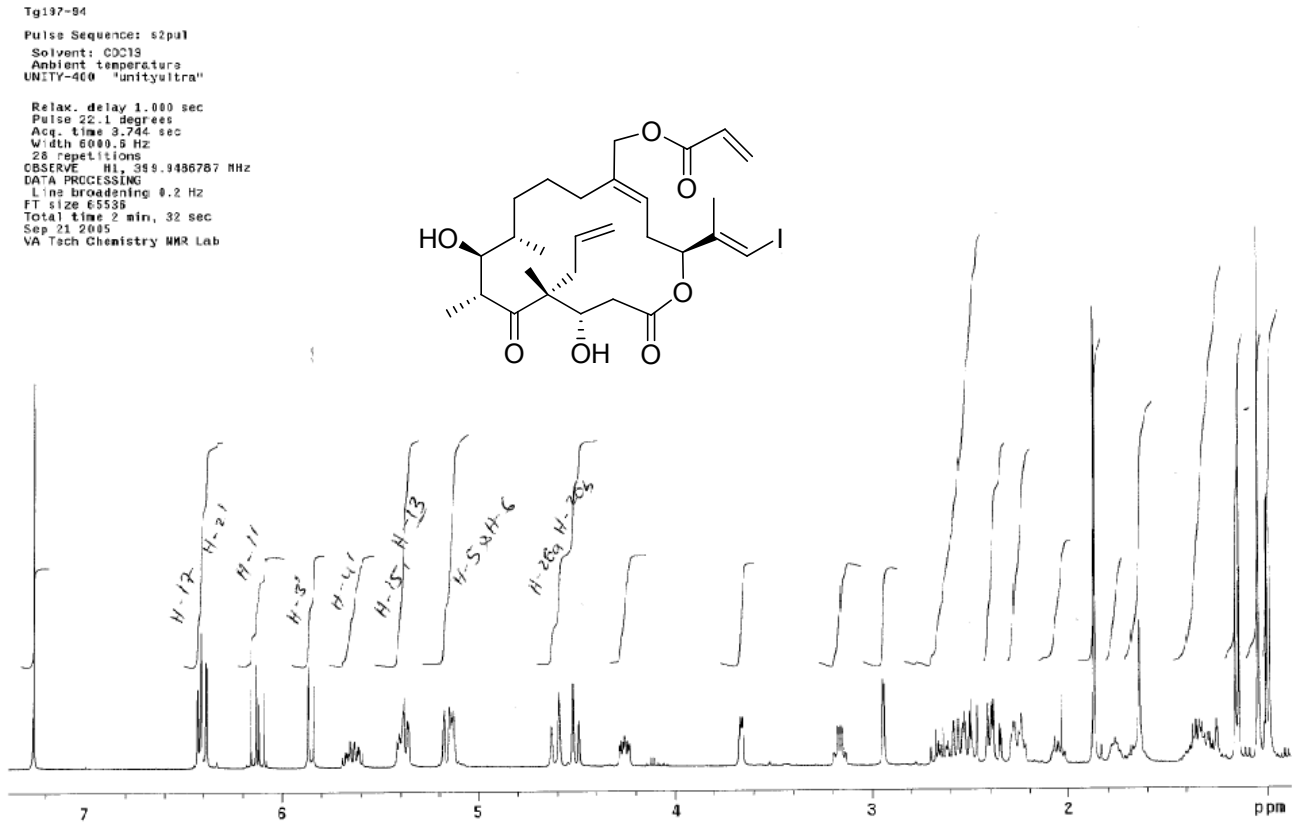
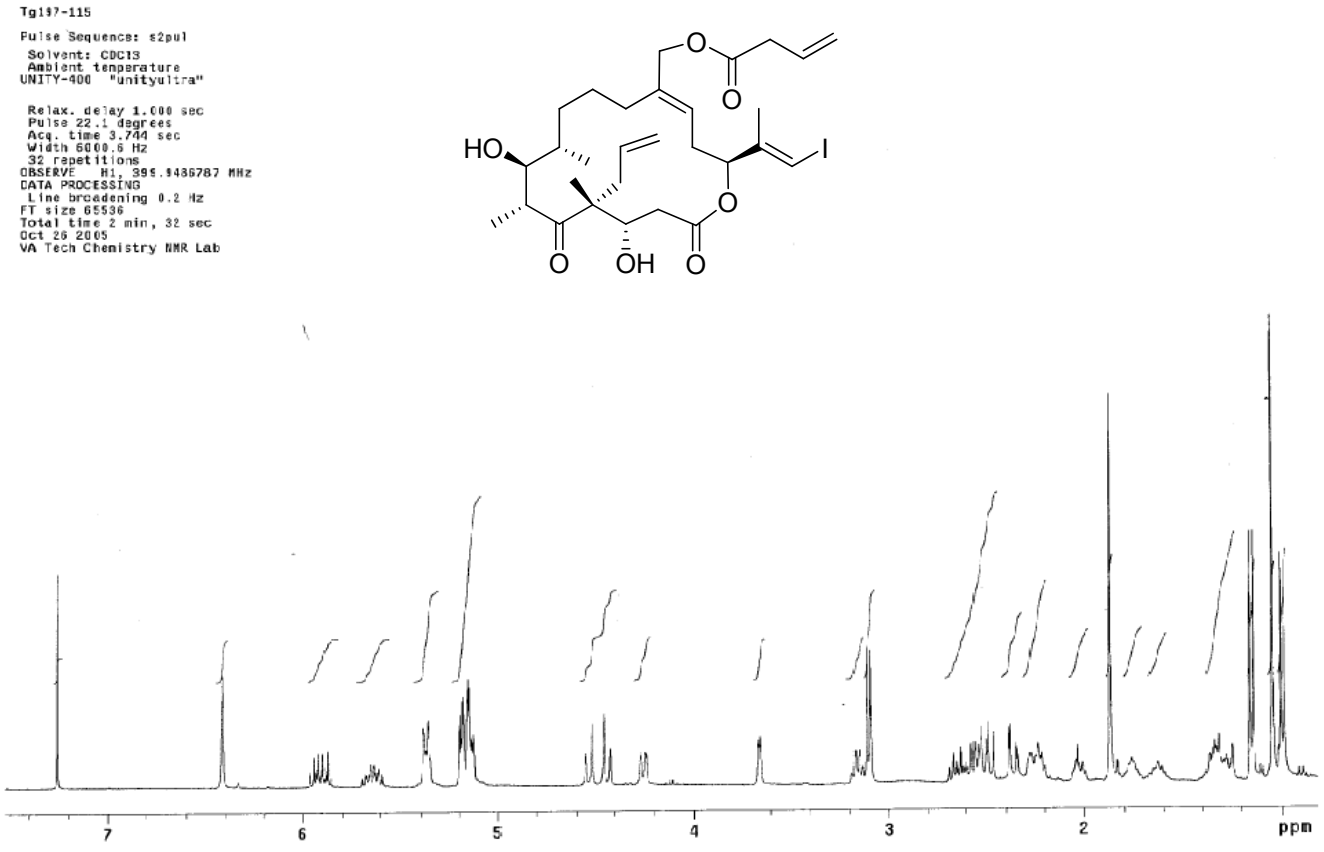


^{1}HNMR spectrum of compound **7**



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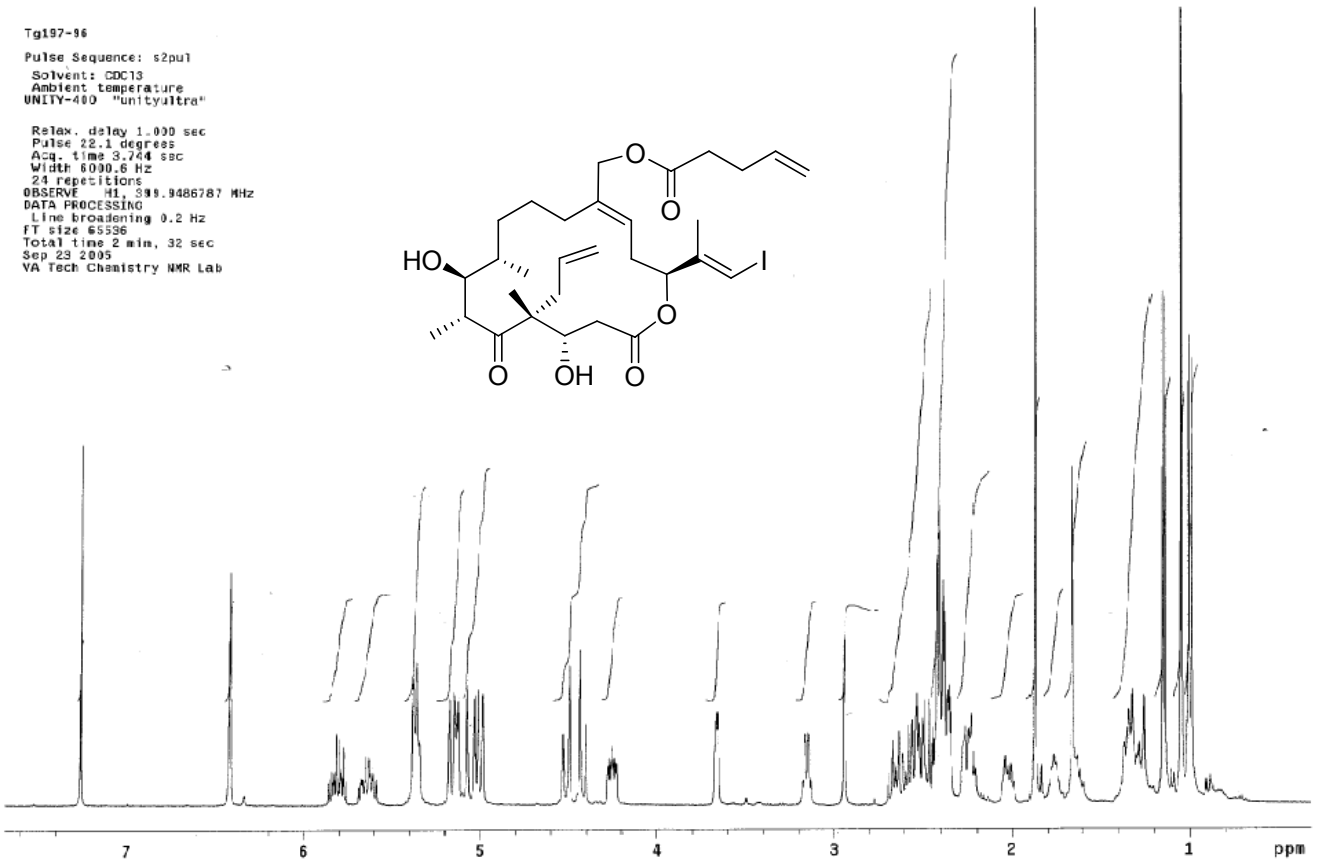
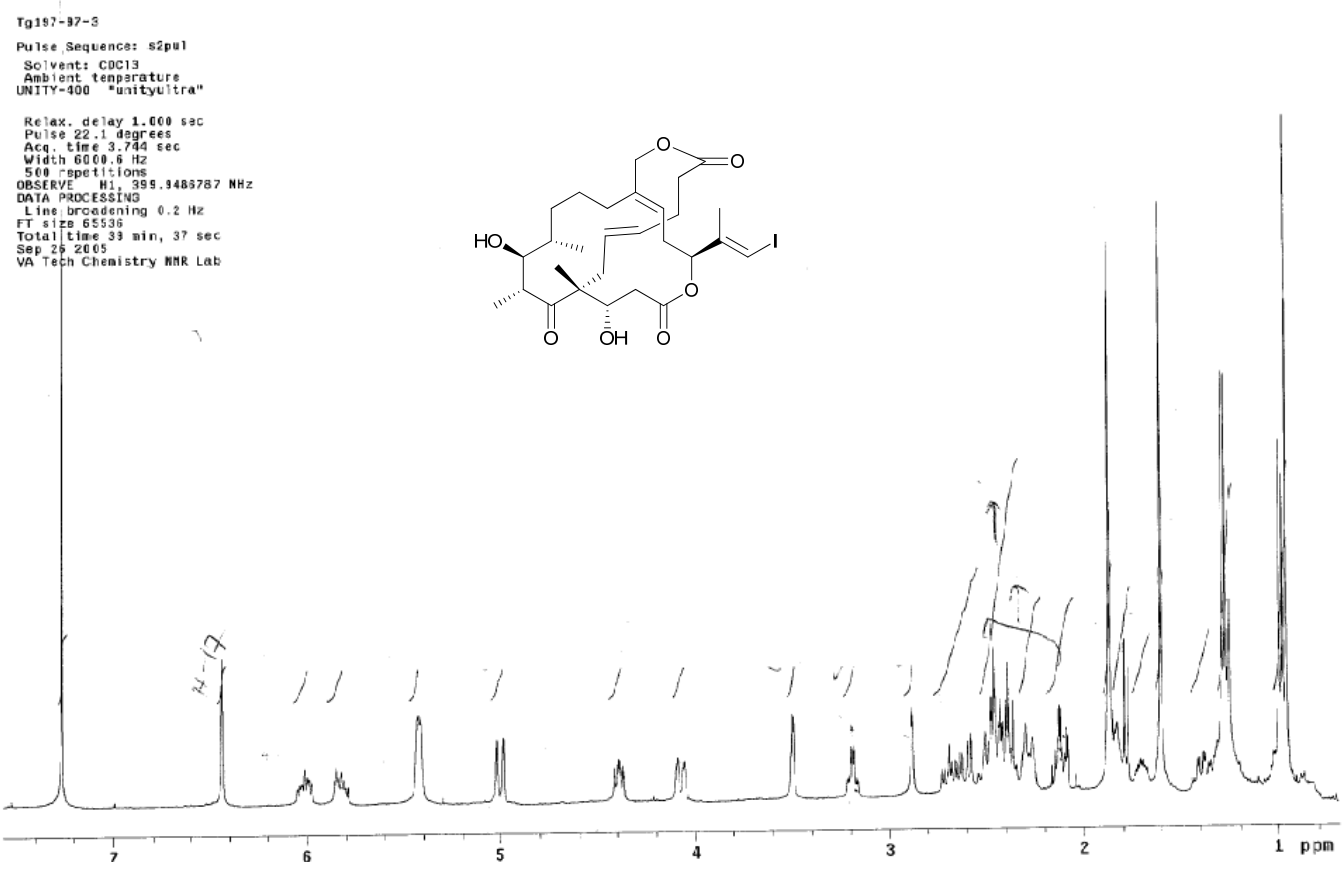
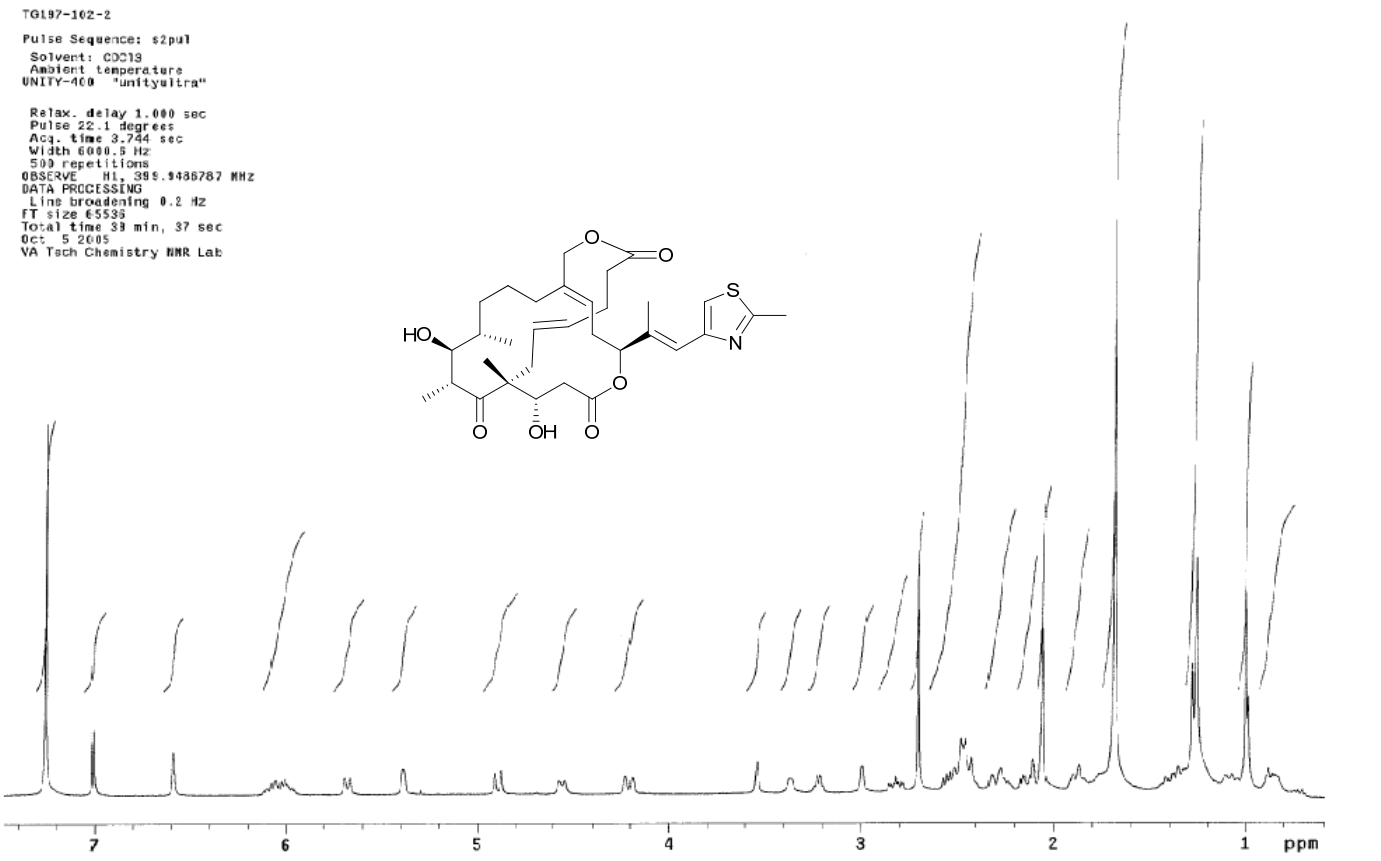


^{1}HNMR spectrum of compound **23**



^{1}HNMR spectrum of compound **25**



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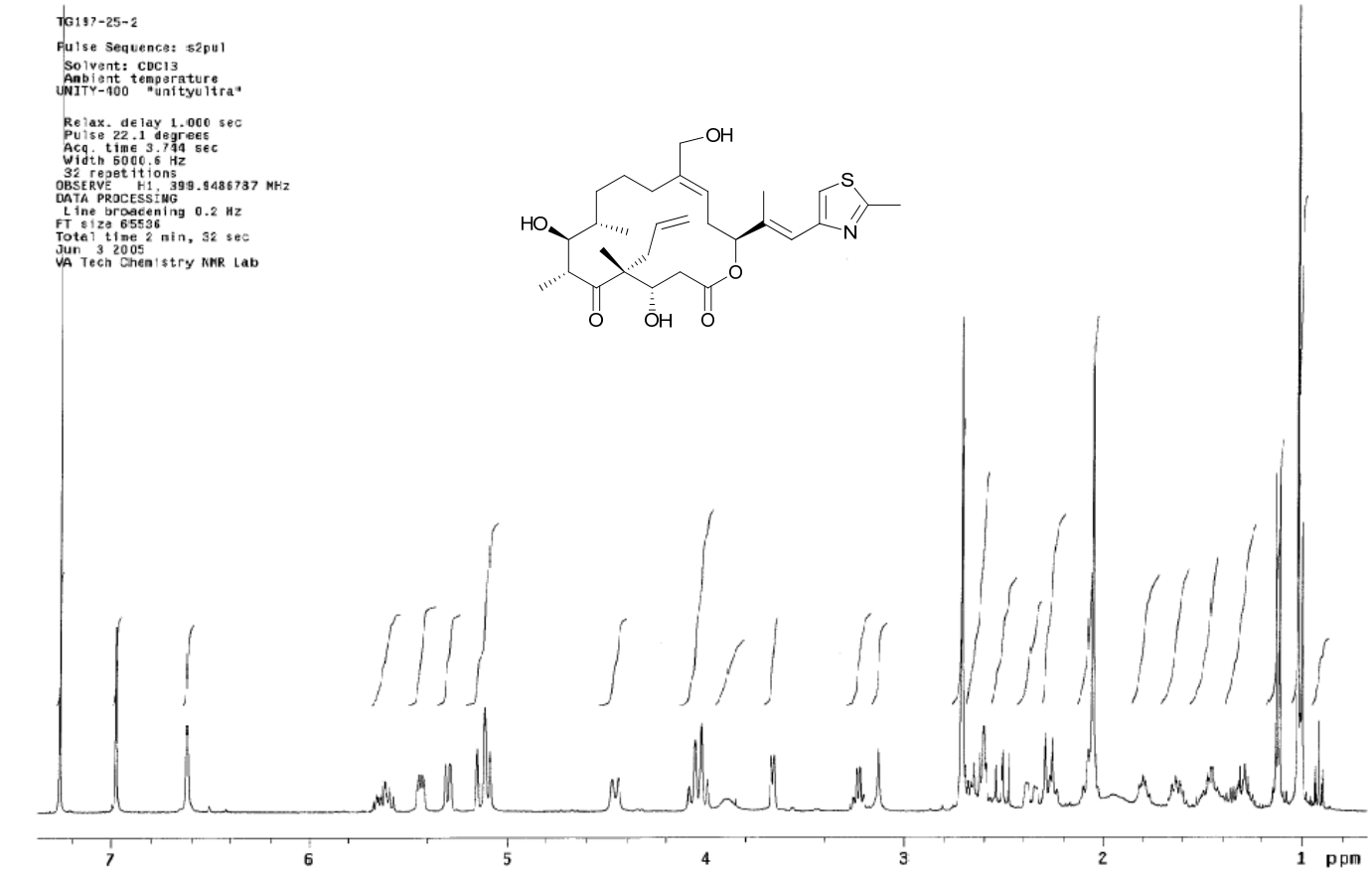

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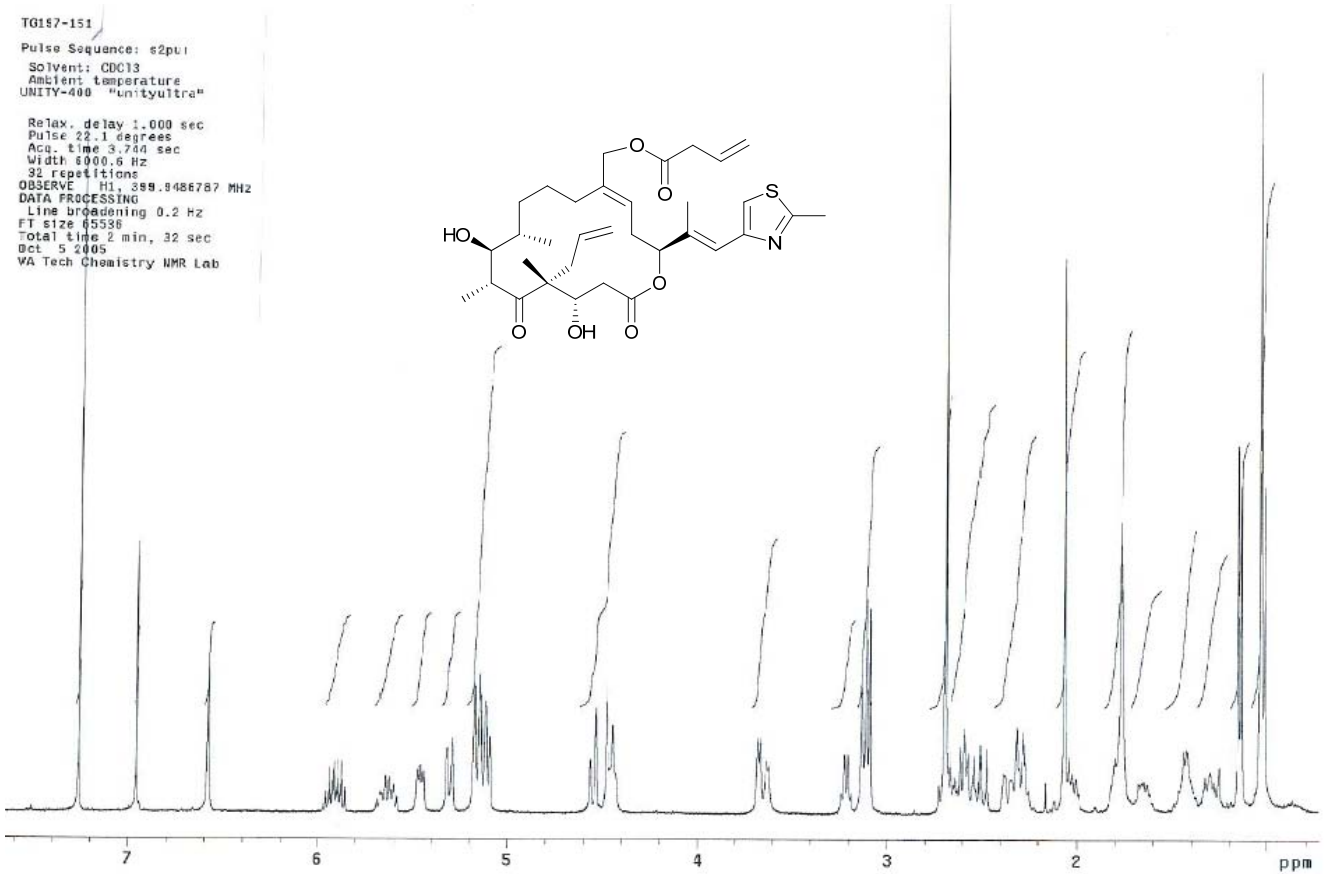

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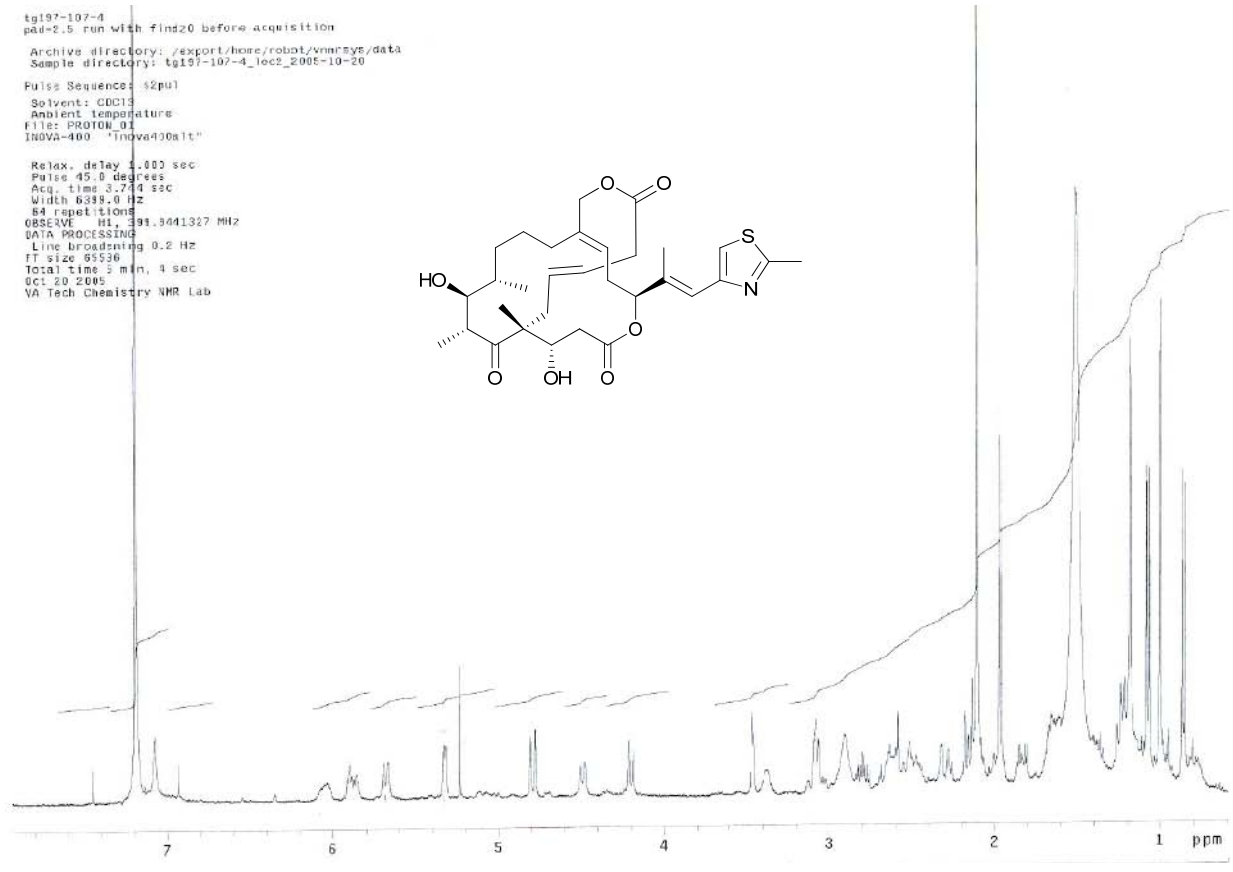

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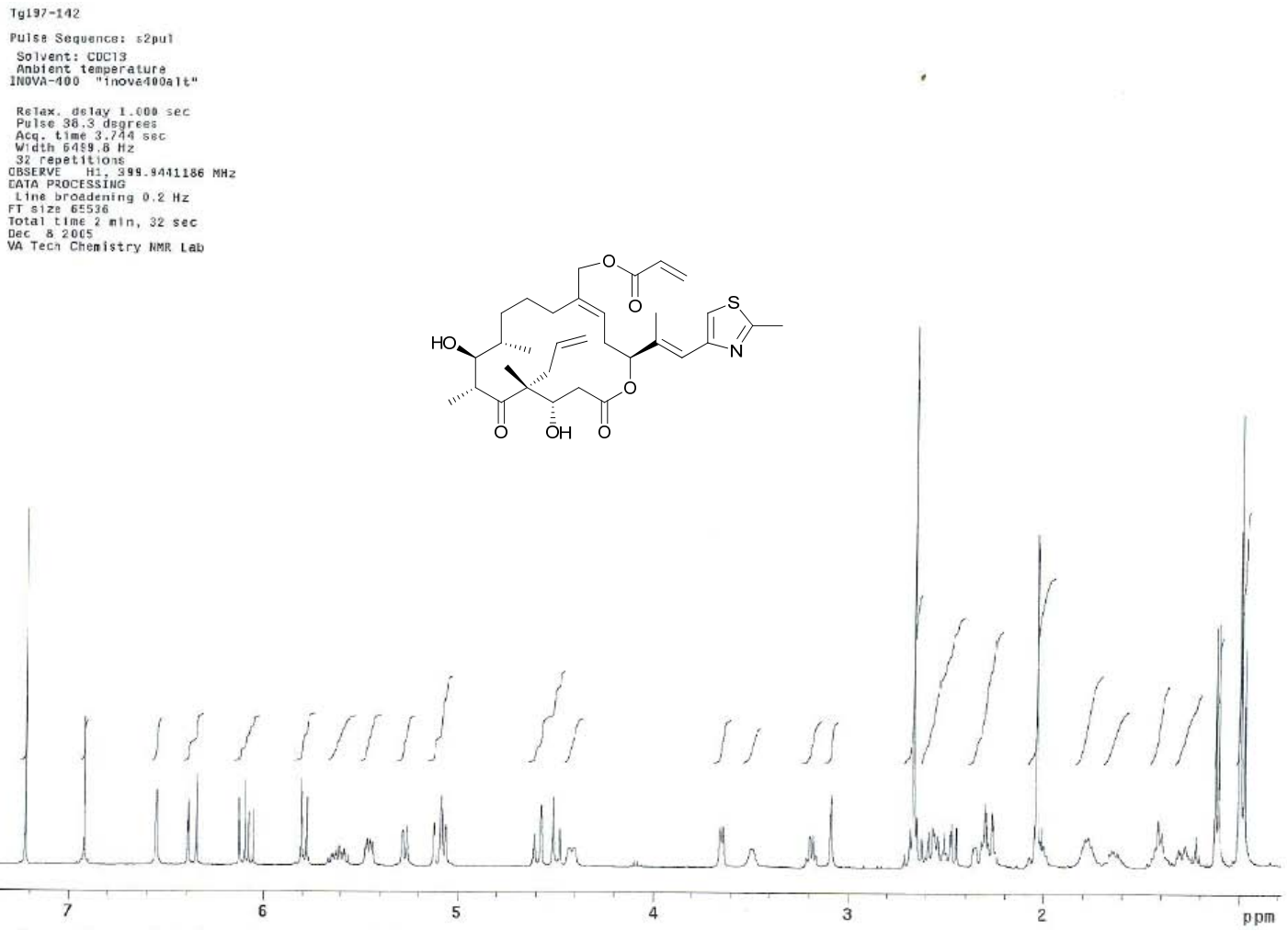

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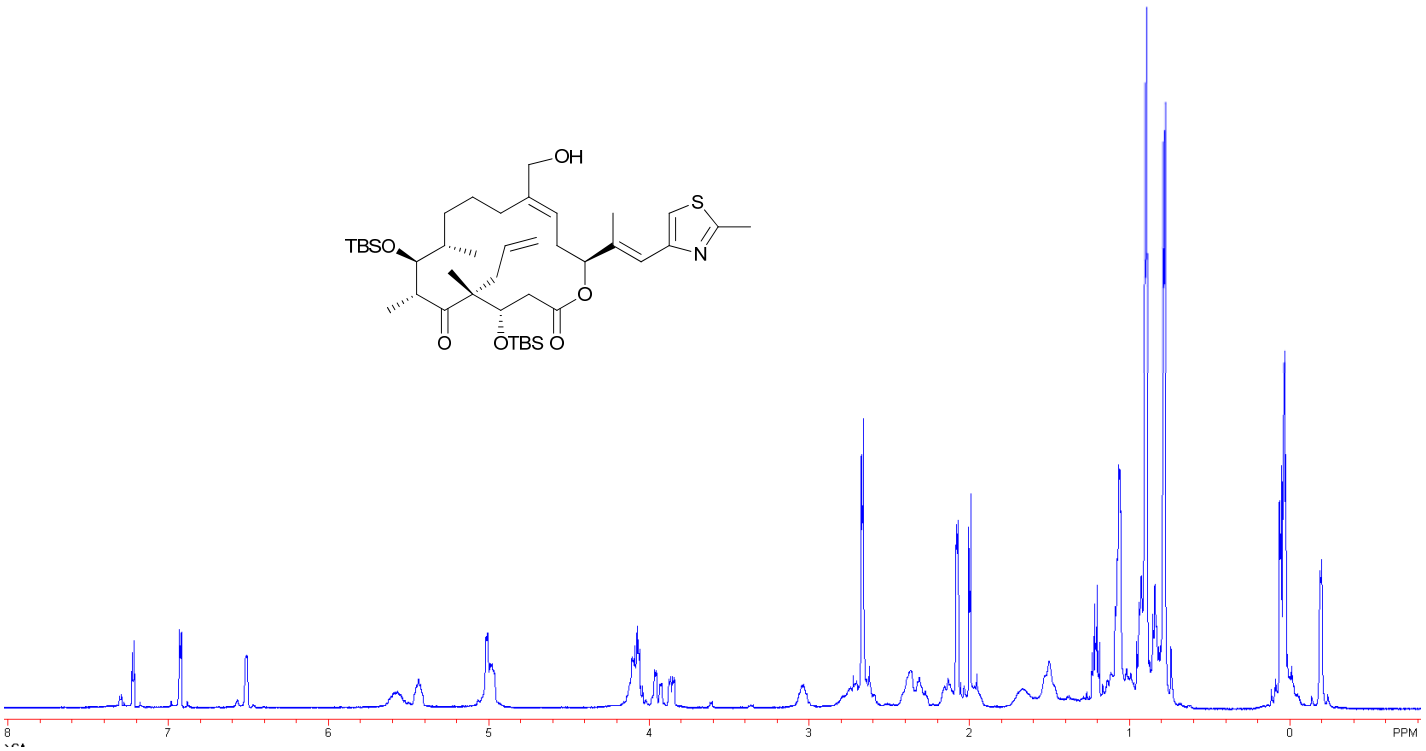

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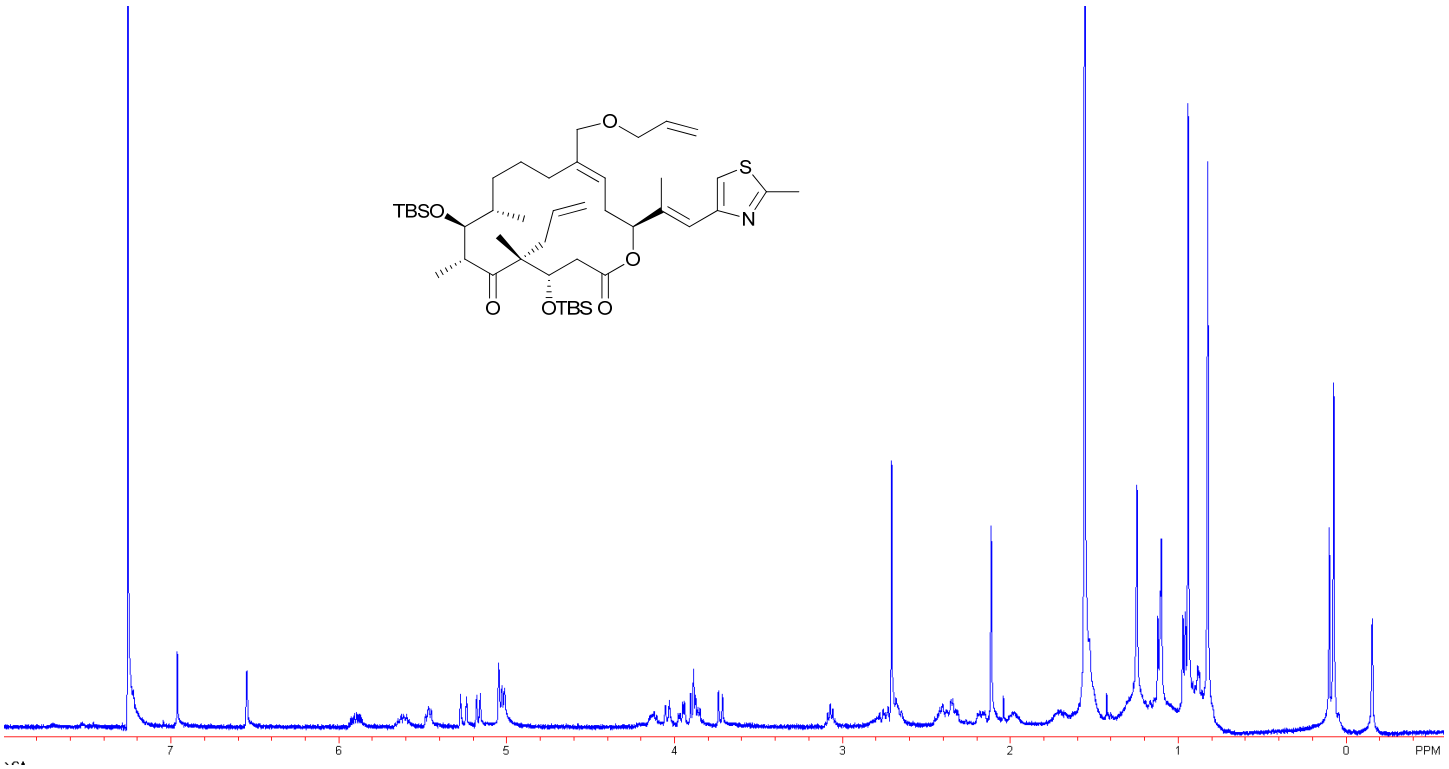
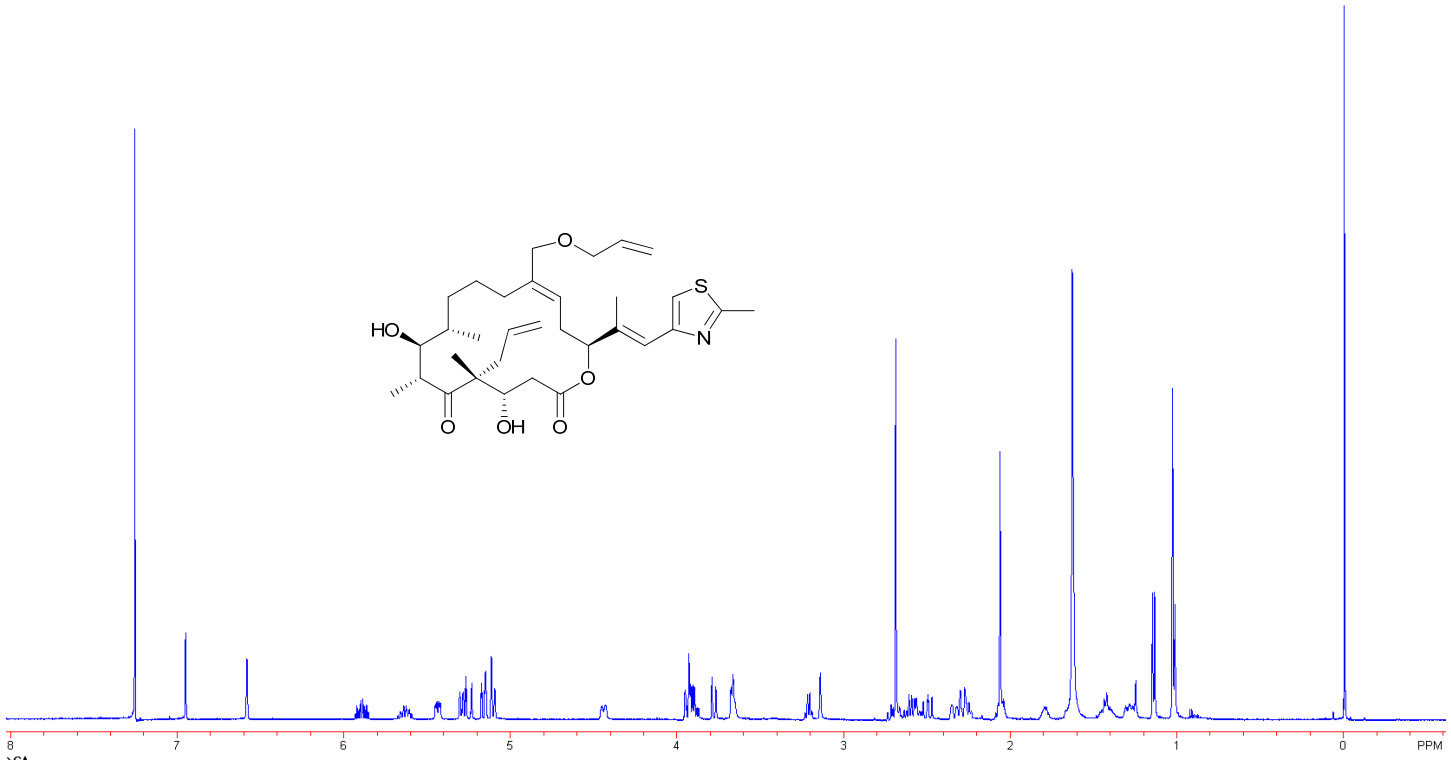
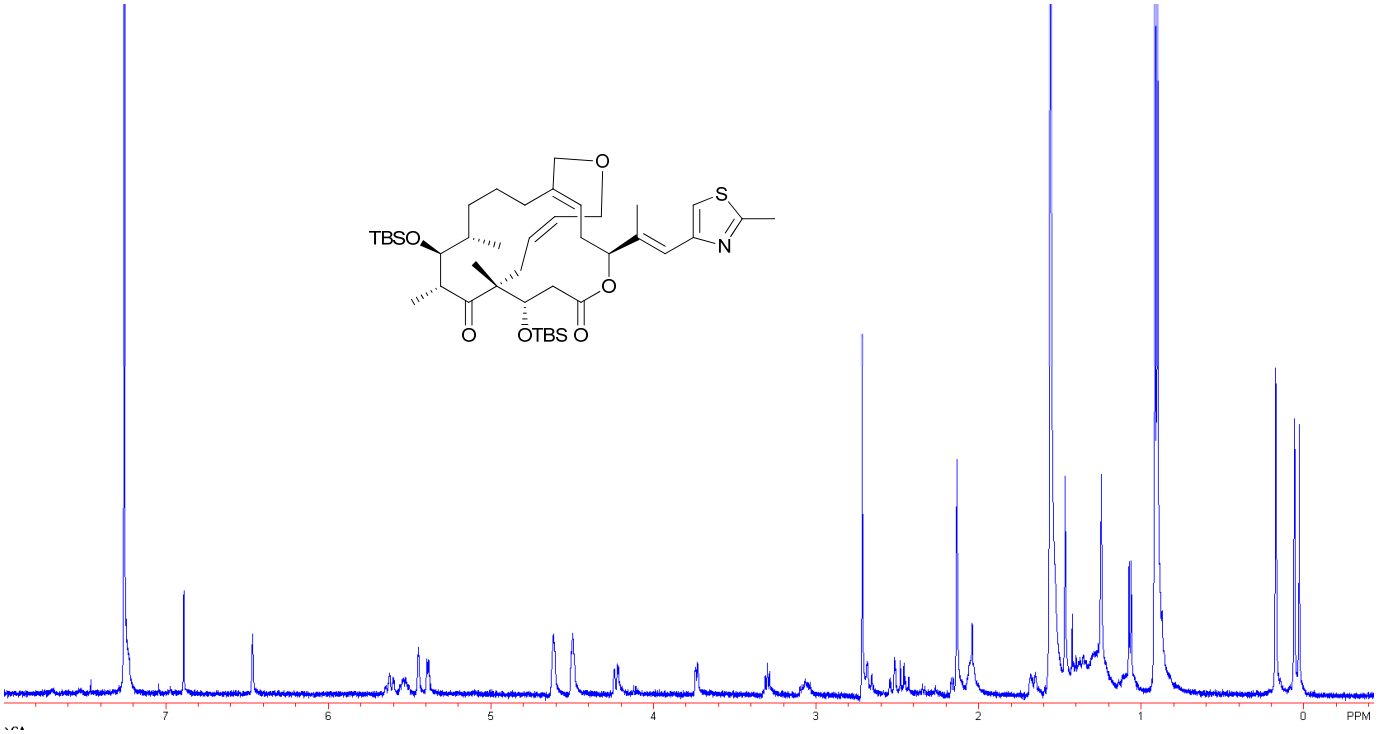


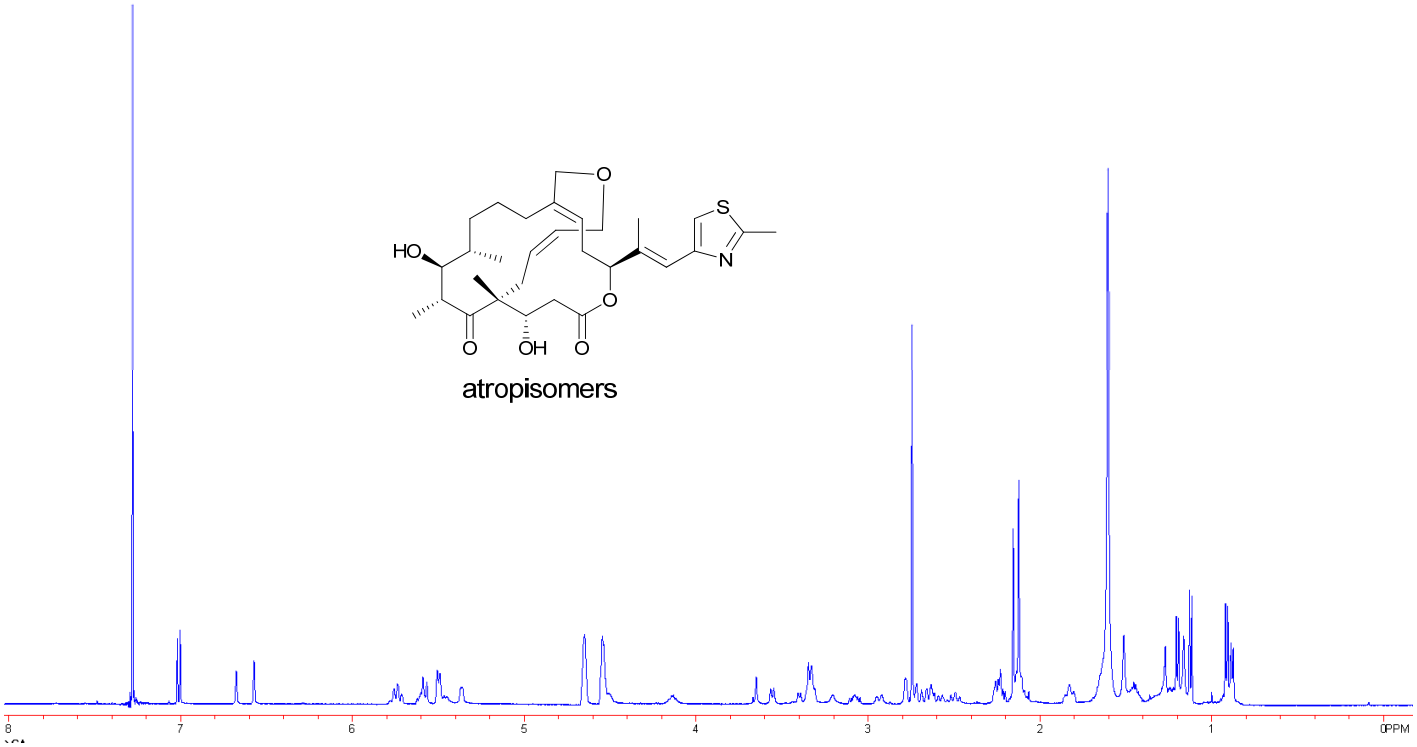
^{1}HNMR spectrum of compound **33**



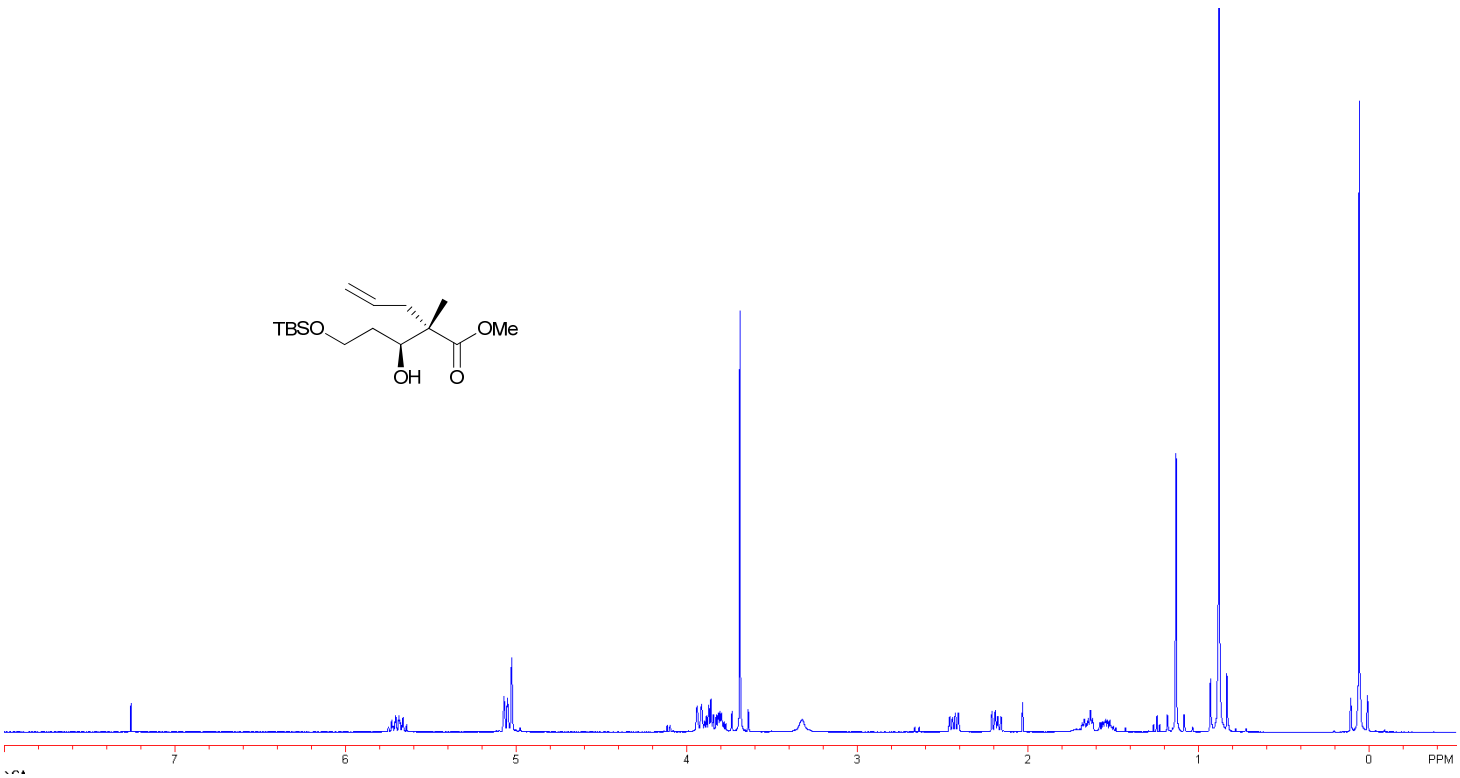
^{1}HNMR spectrum of compound **34**



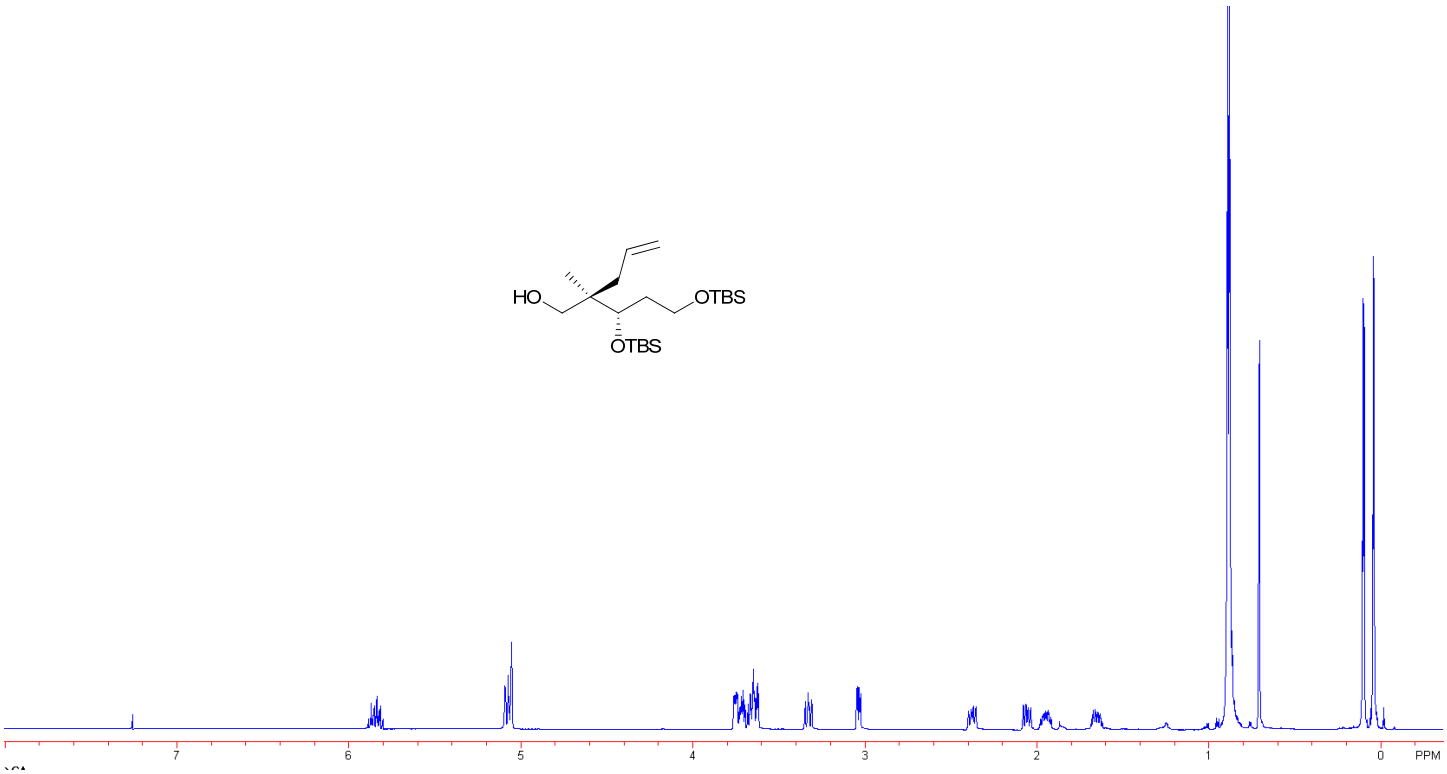
^{1}HNMR spectrum of compound **35**



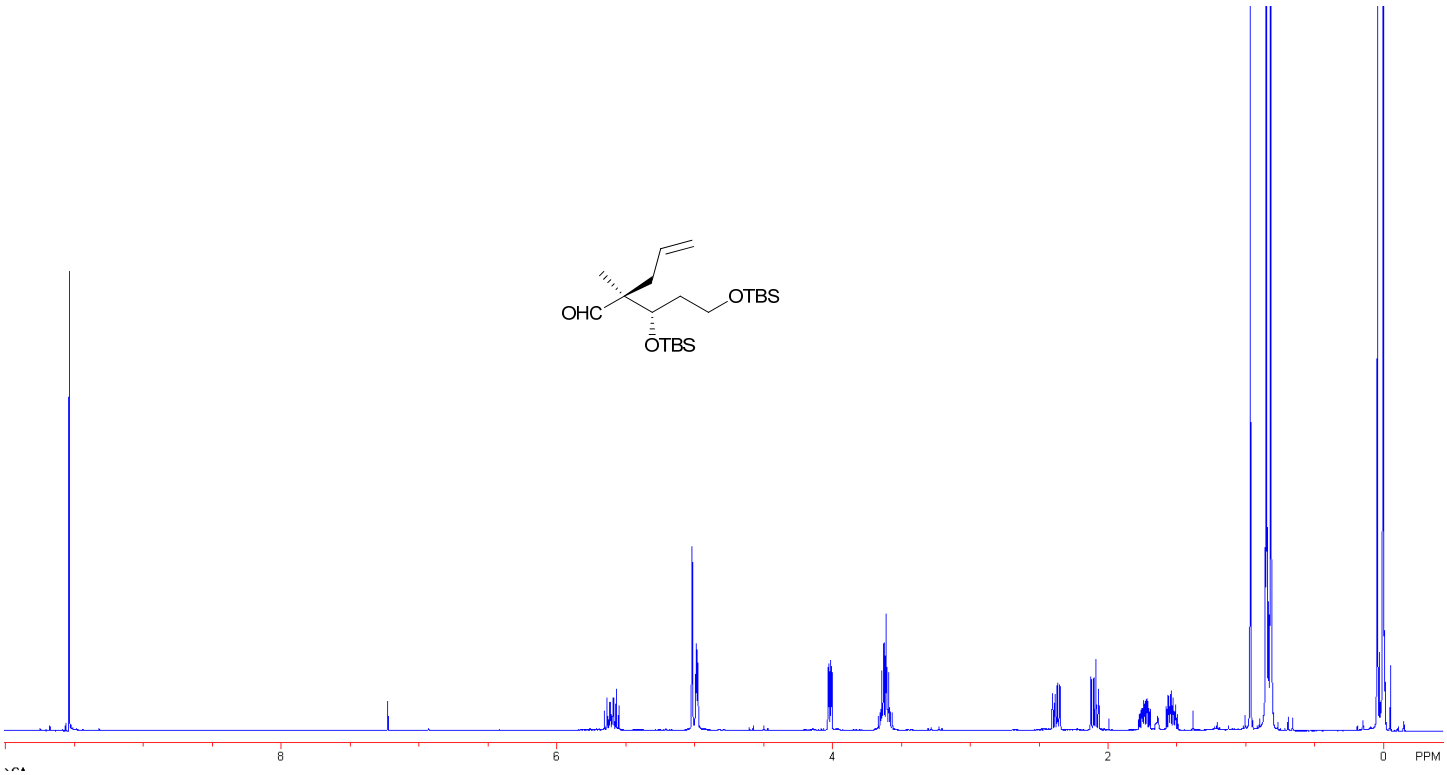
^{1}HNMR spectrum of compound **36**



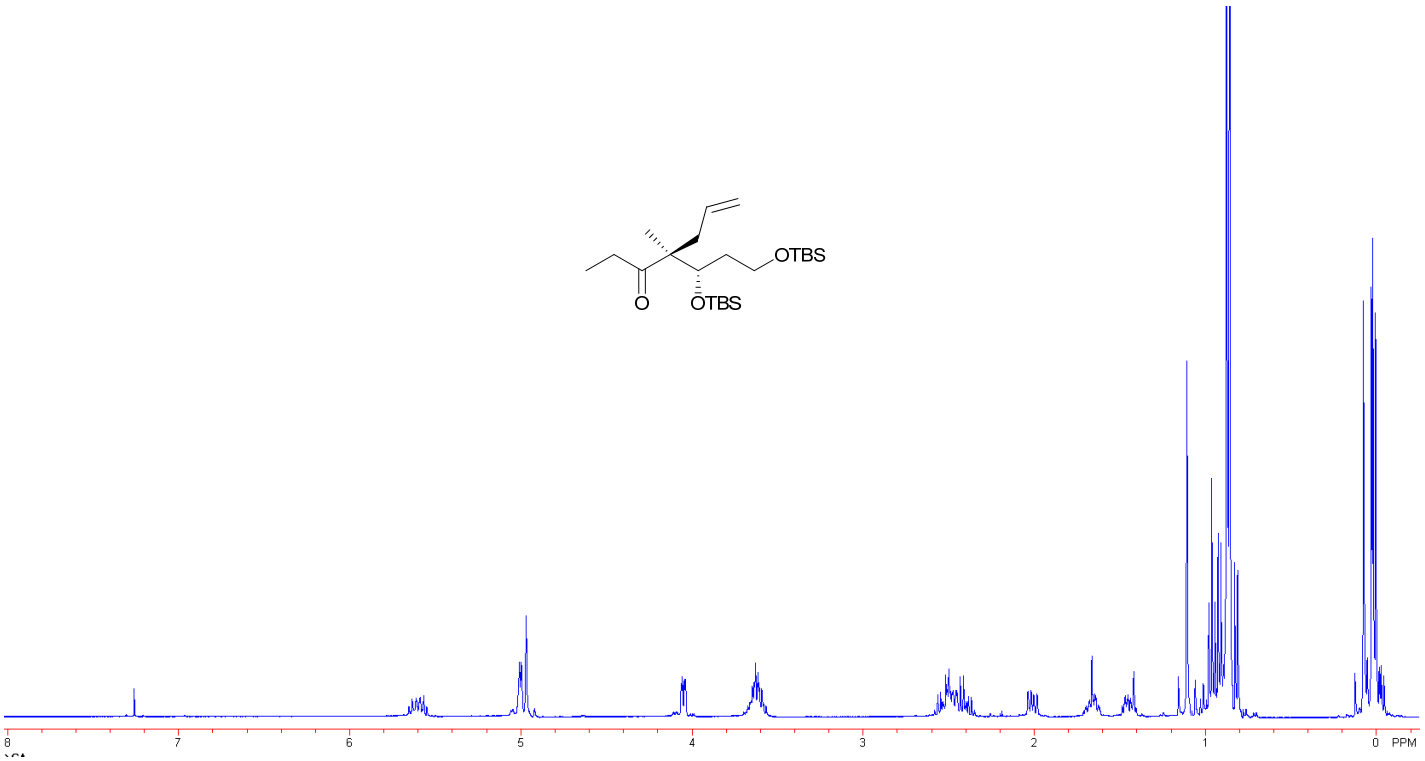
^{1}HNMR spectrum of compound **37**



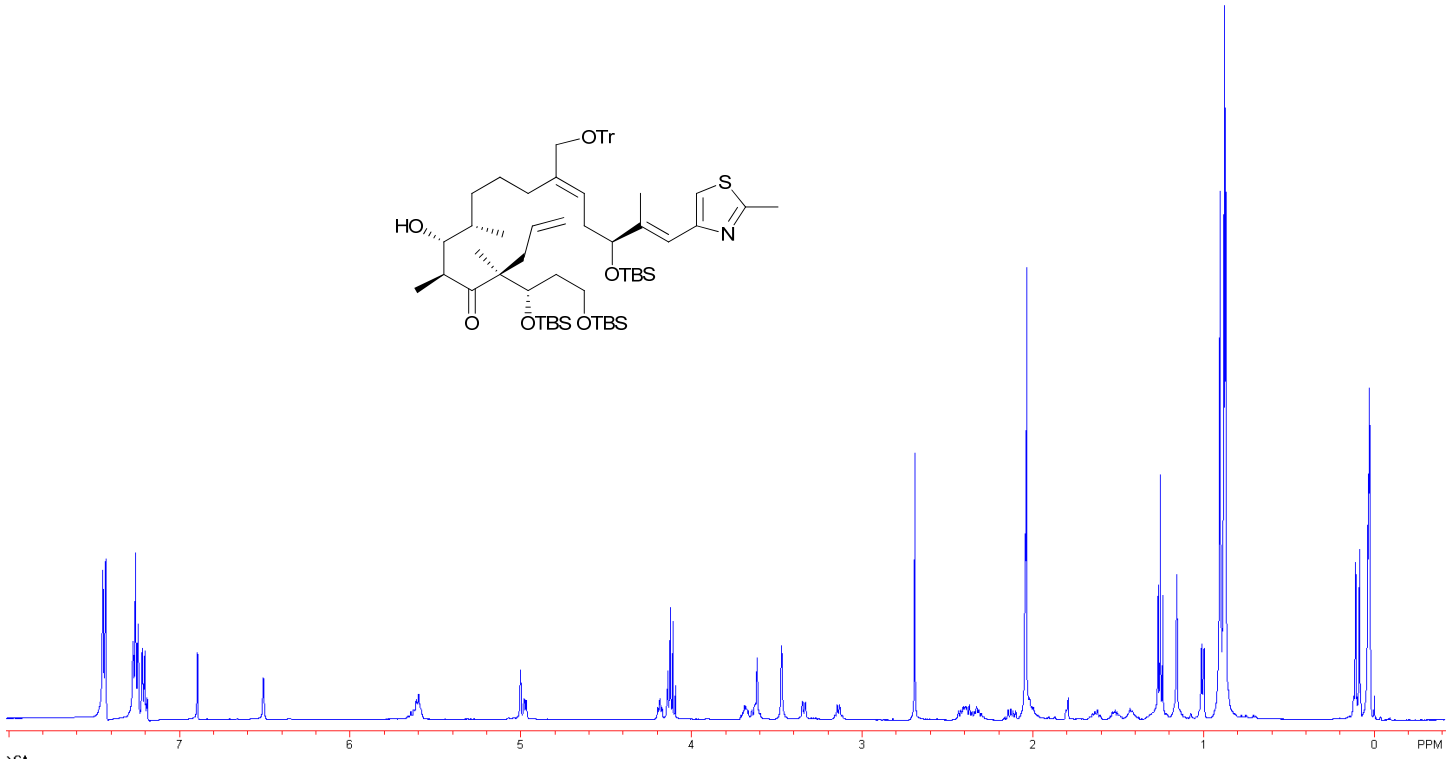
^{1}HNMR spectrum of compound **38**



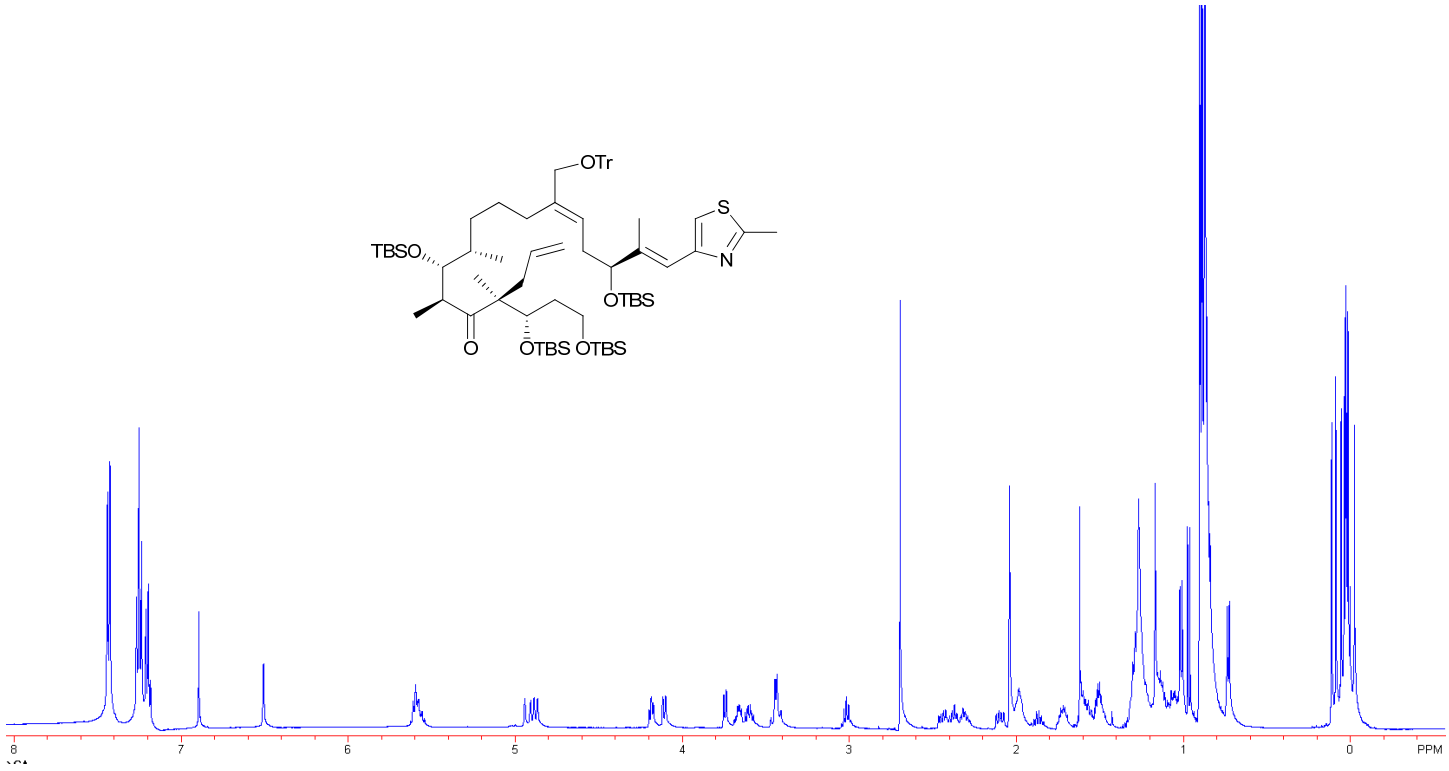
^{1}HNMR spectrum of **(*S*)-2-((*S*)-1,3-bis(*tert*-butyldimethylsilyloxy)propyl)-2-methylpent-4-enal**



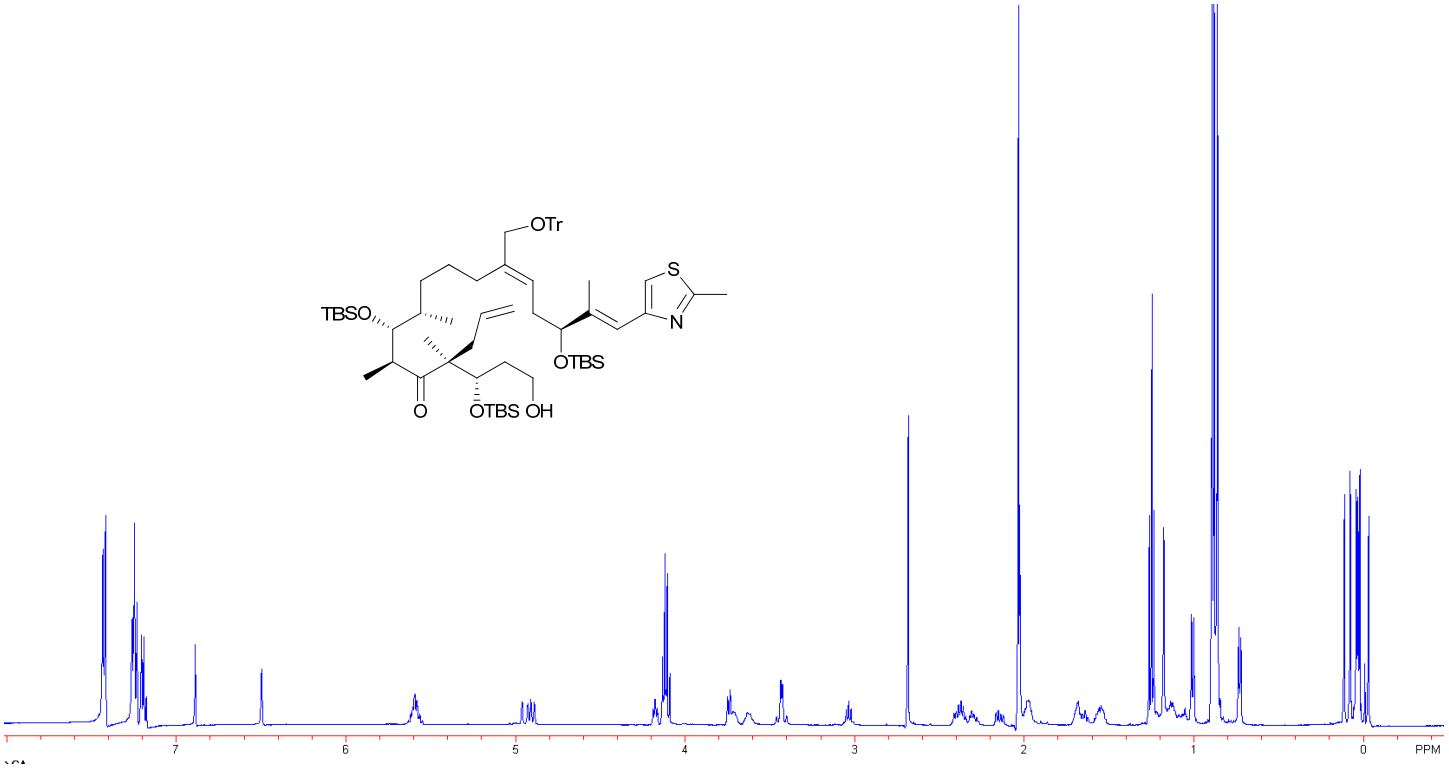
^{1}HNMR spectrum of compound **39**



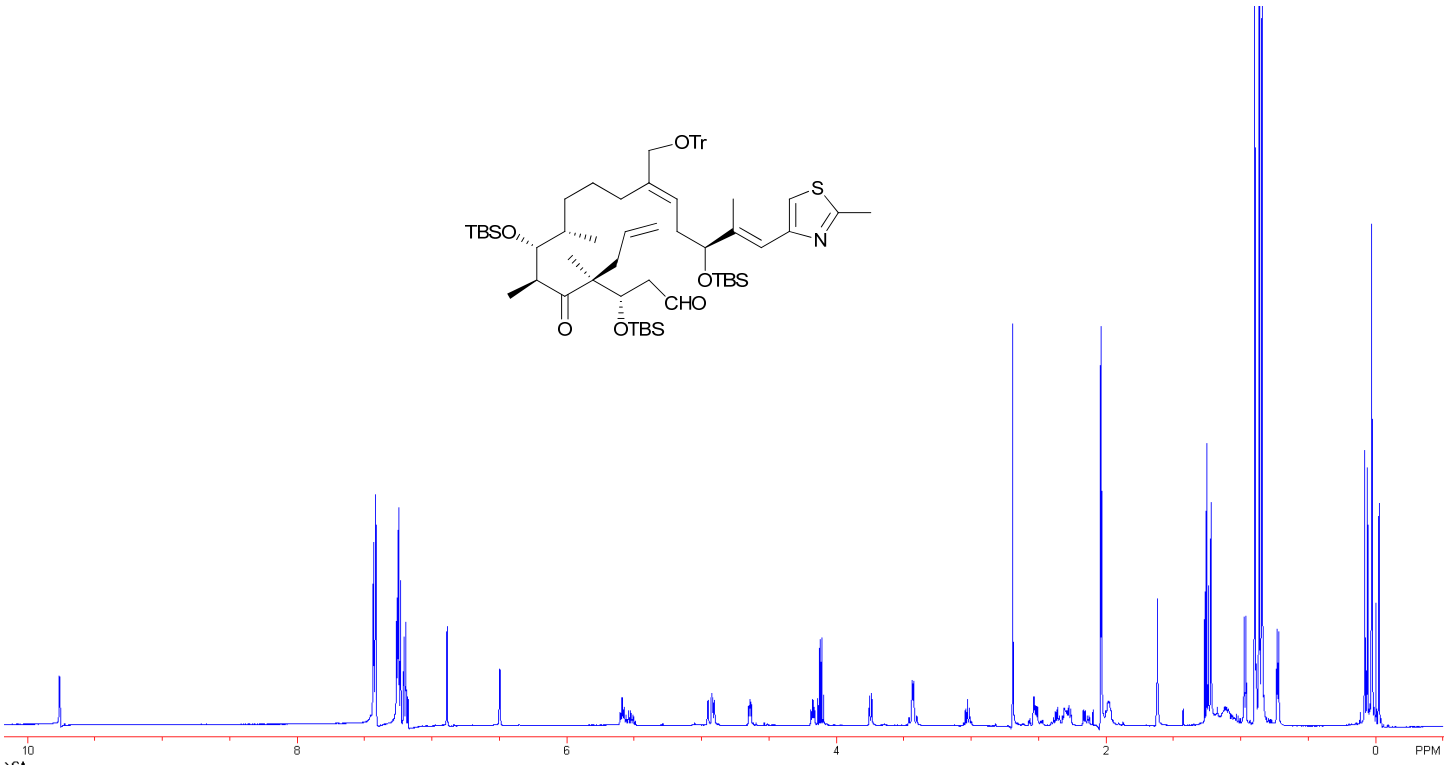
^{1}HNMR spectrum of compound **40**



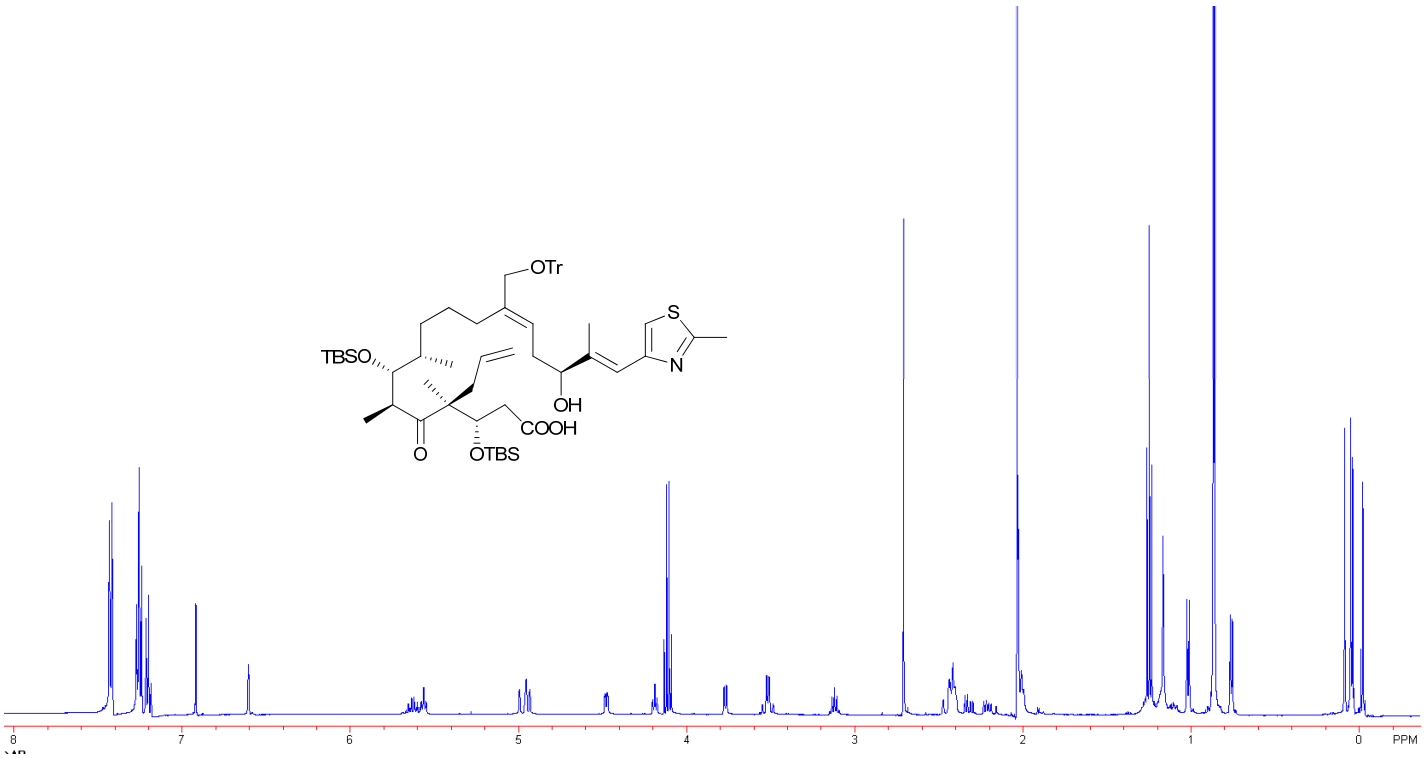
^{1}HNMR spectrum of compound **41a**



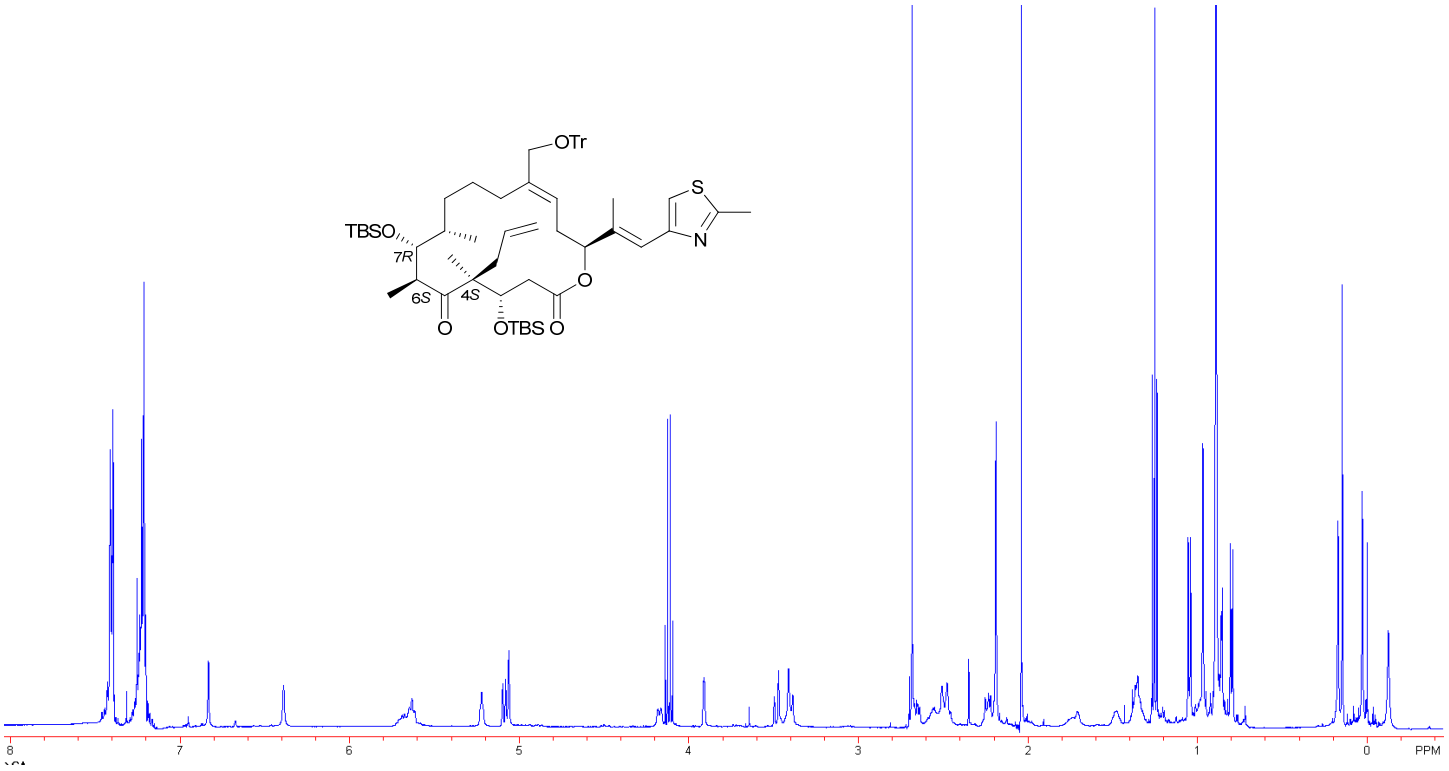
^{1}HNMR spectrum of compound **41b**



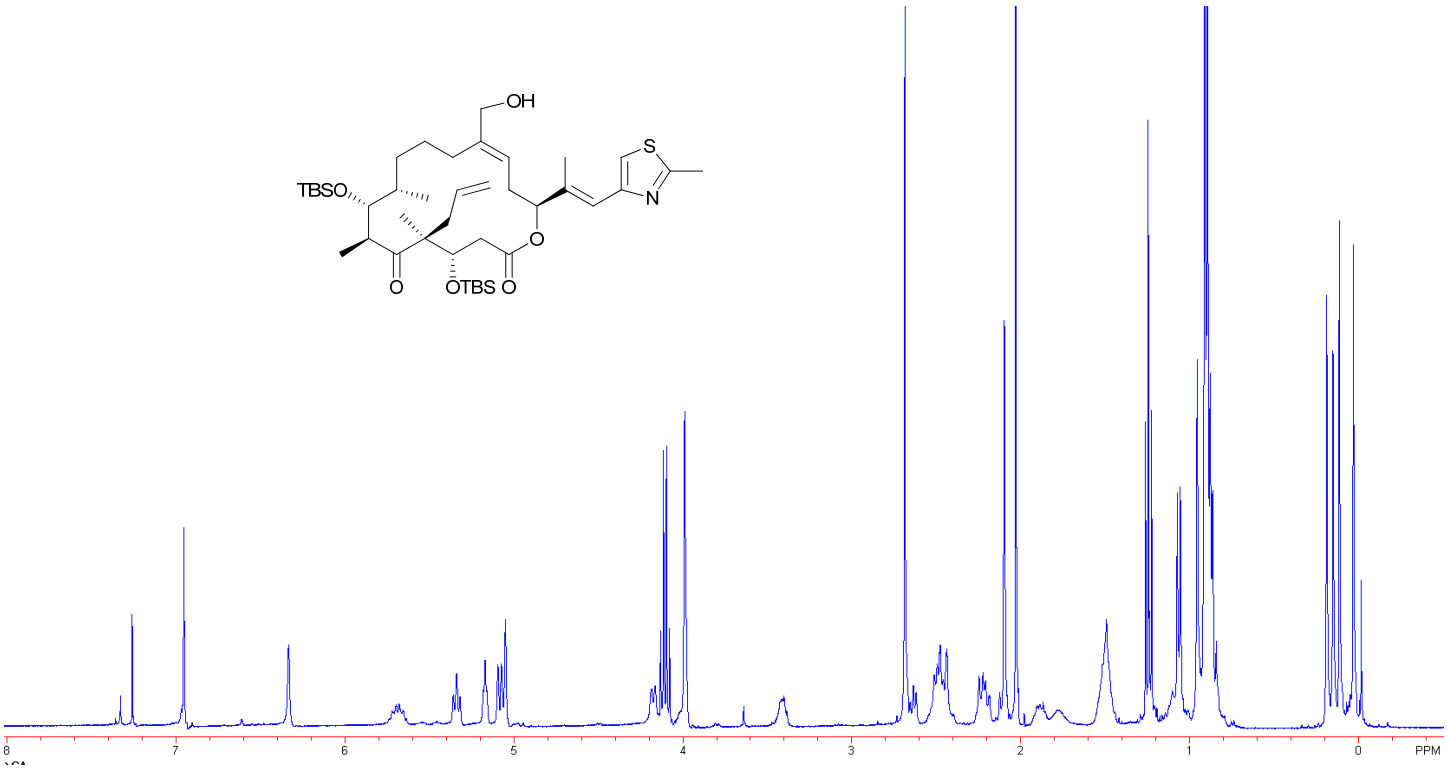
^{1}HNMR spectrum of compound **41c**



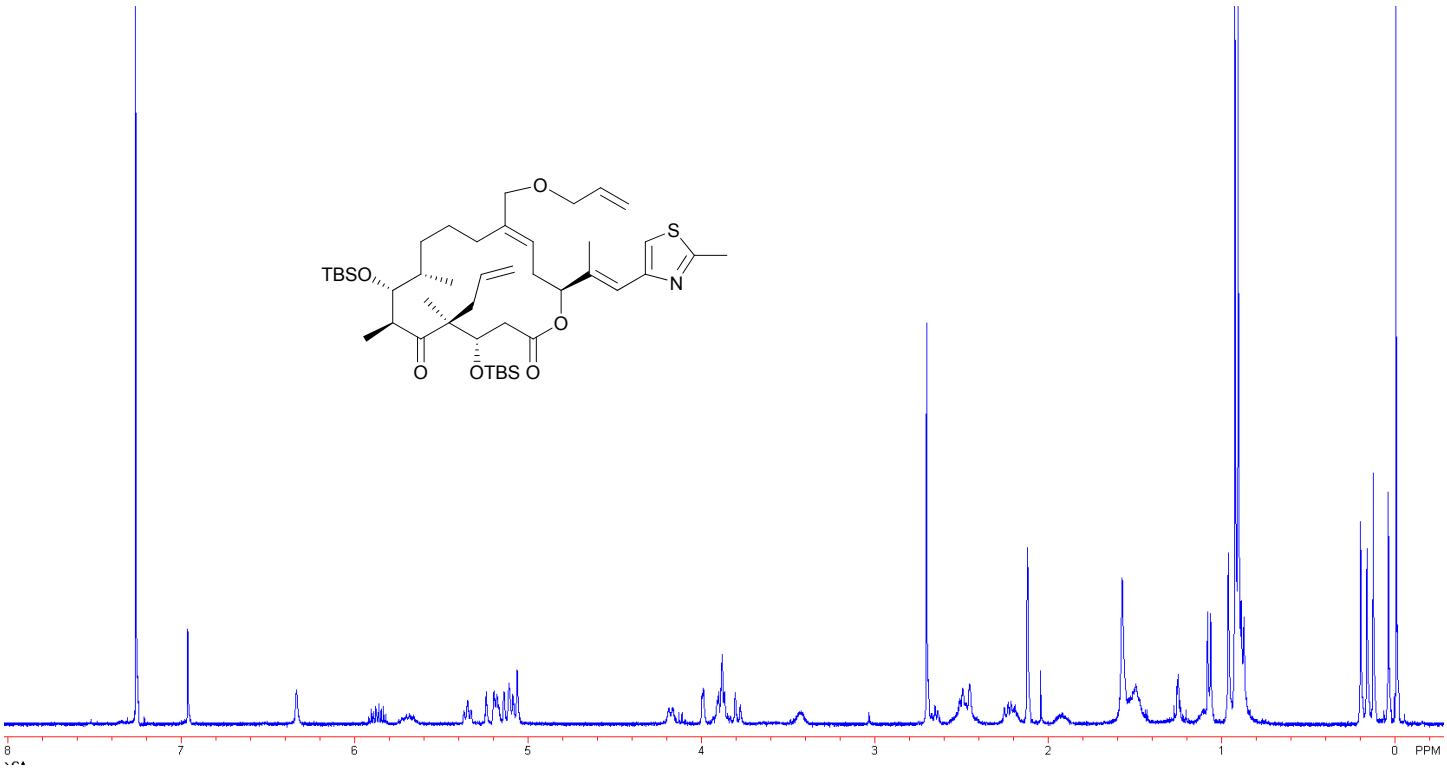
^{1}HNMR spectrum of compound **41d**



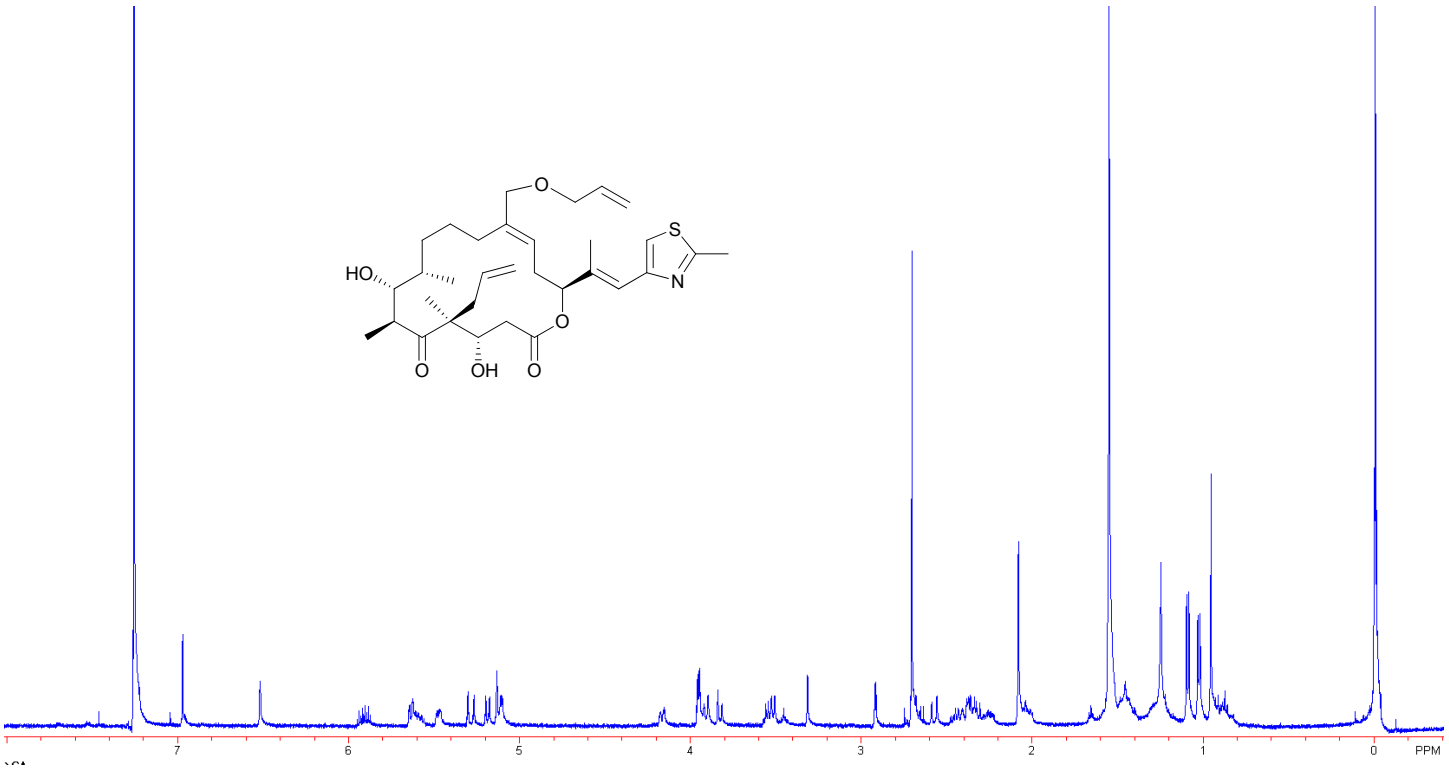
^{1}HNMR spectrum of compound **42**



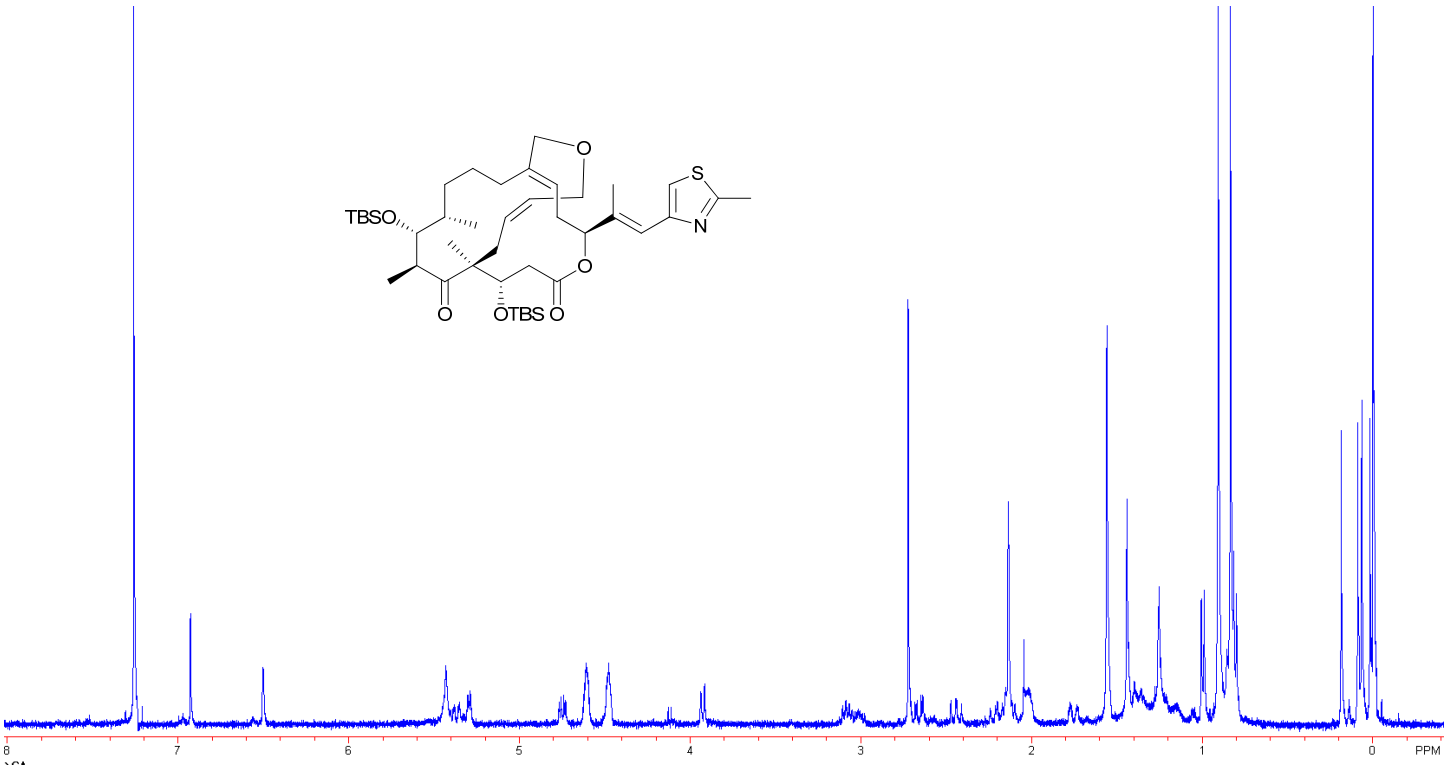
^{1}HNMR spectrum of compound **43**



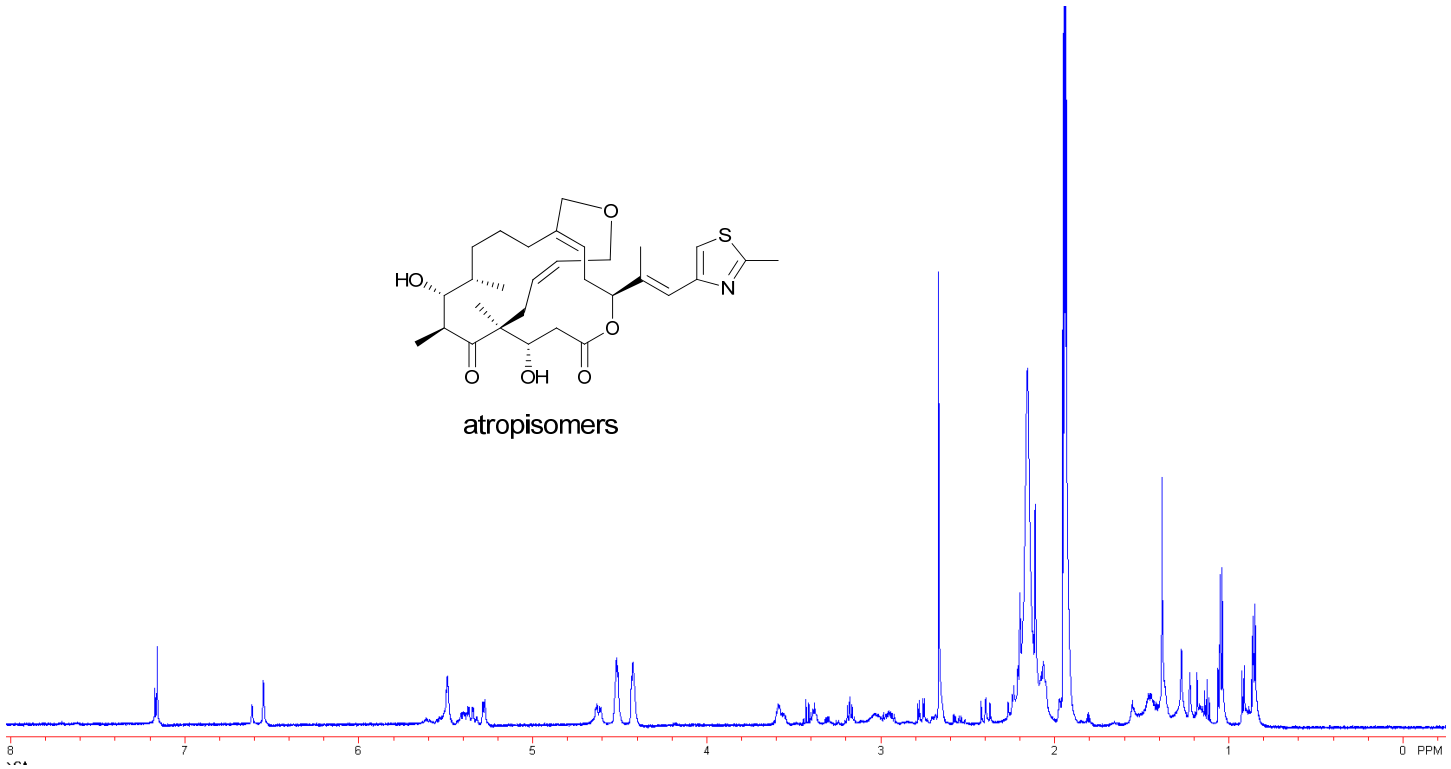
^{1}HNMR spectrum of compound **44**



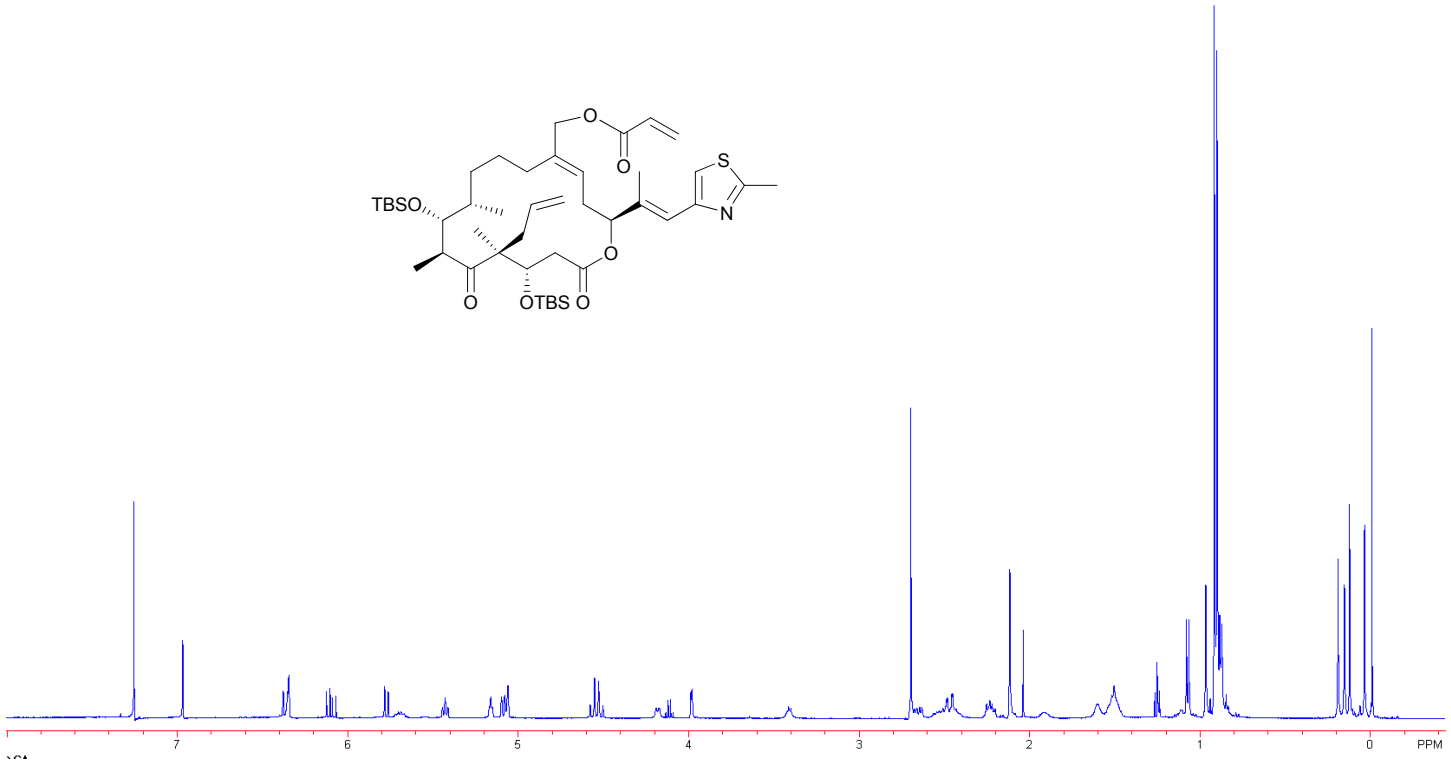
^{1}HNMR spectrum of compound **45**



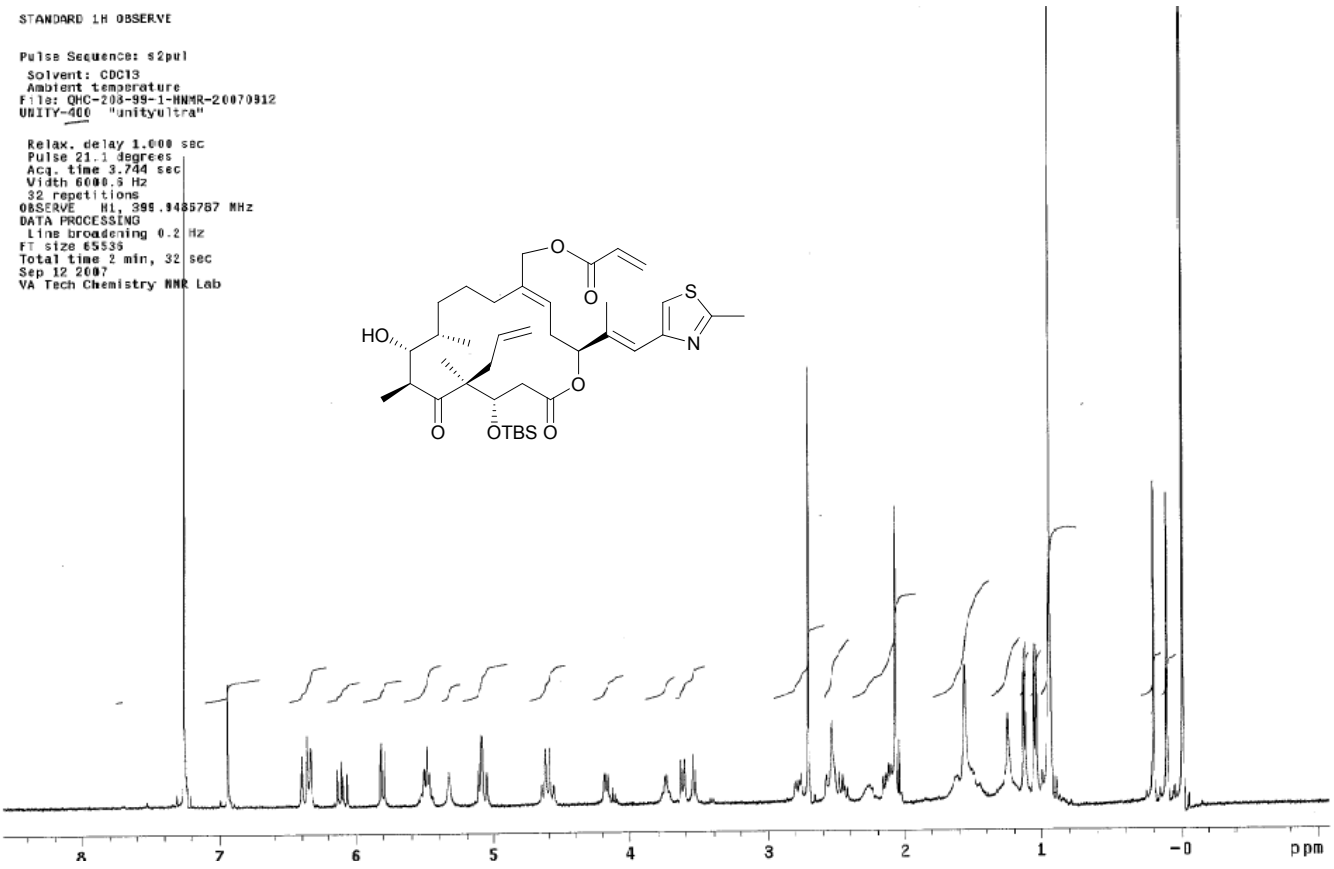
^{1}HNMR spectrum of compound **46**



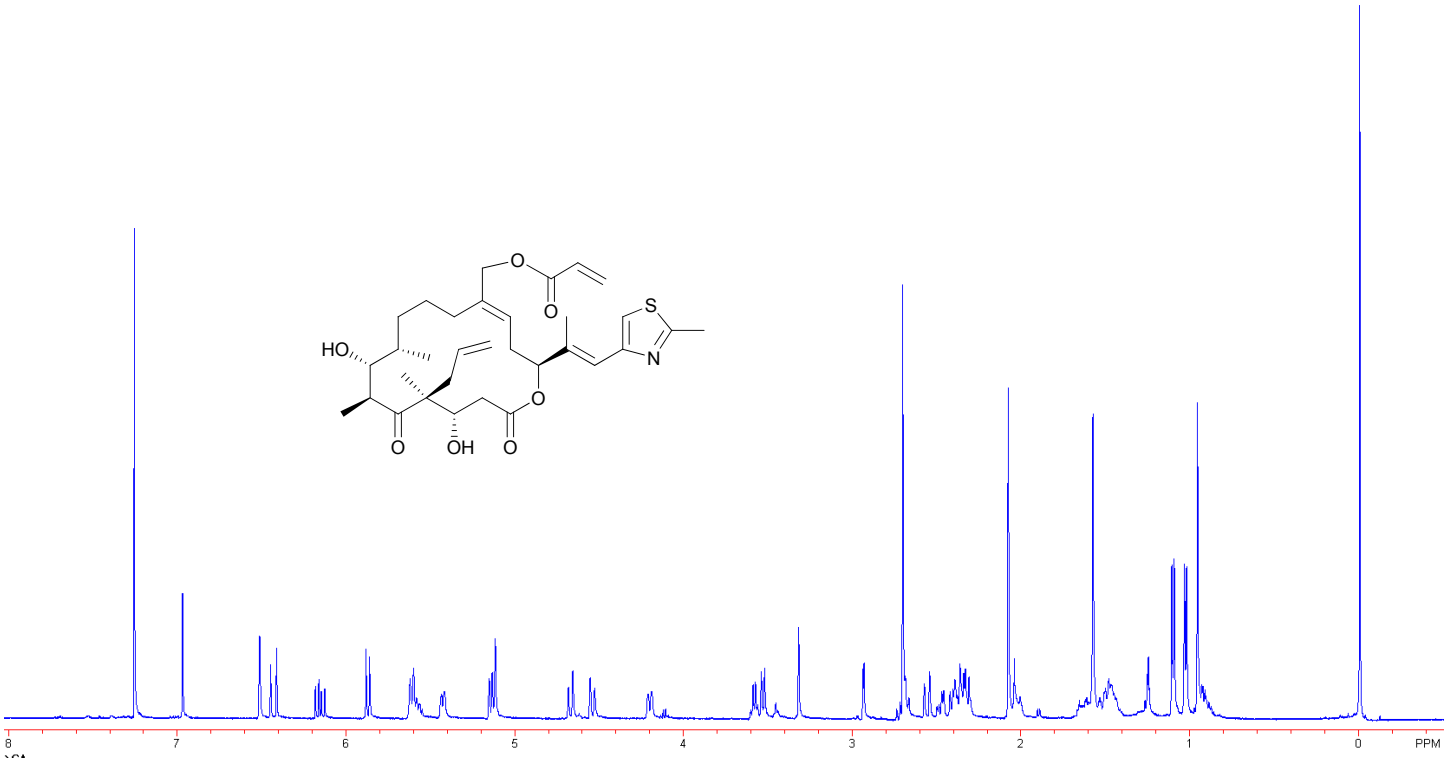
^{1}HNMR spectrum of compound **47**



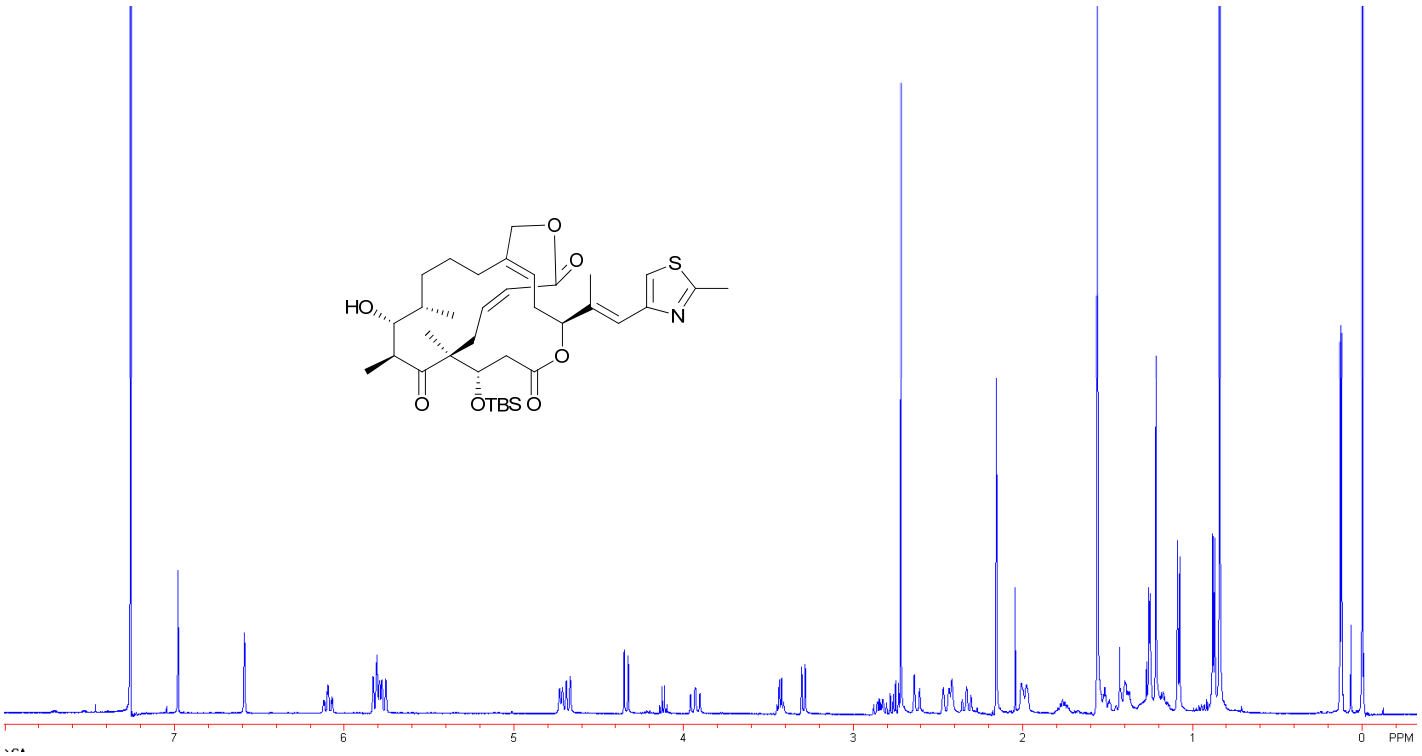
^{1}HNMR spectrum of compound **48**



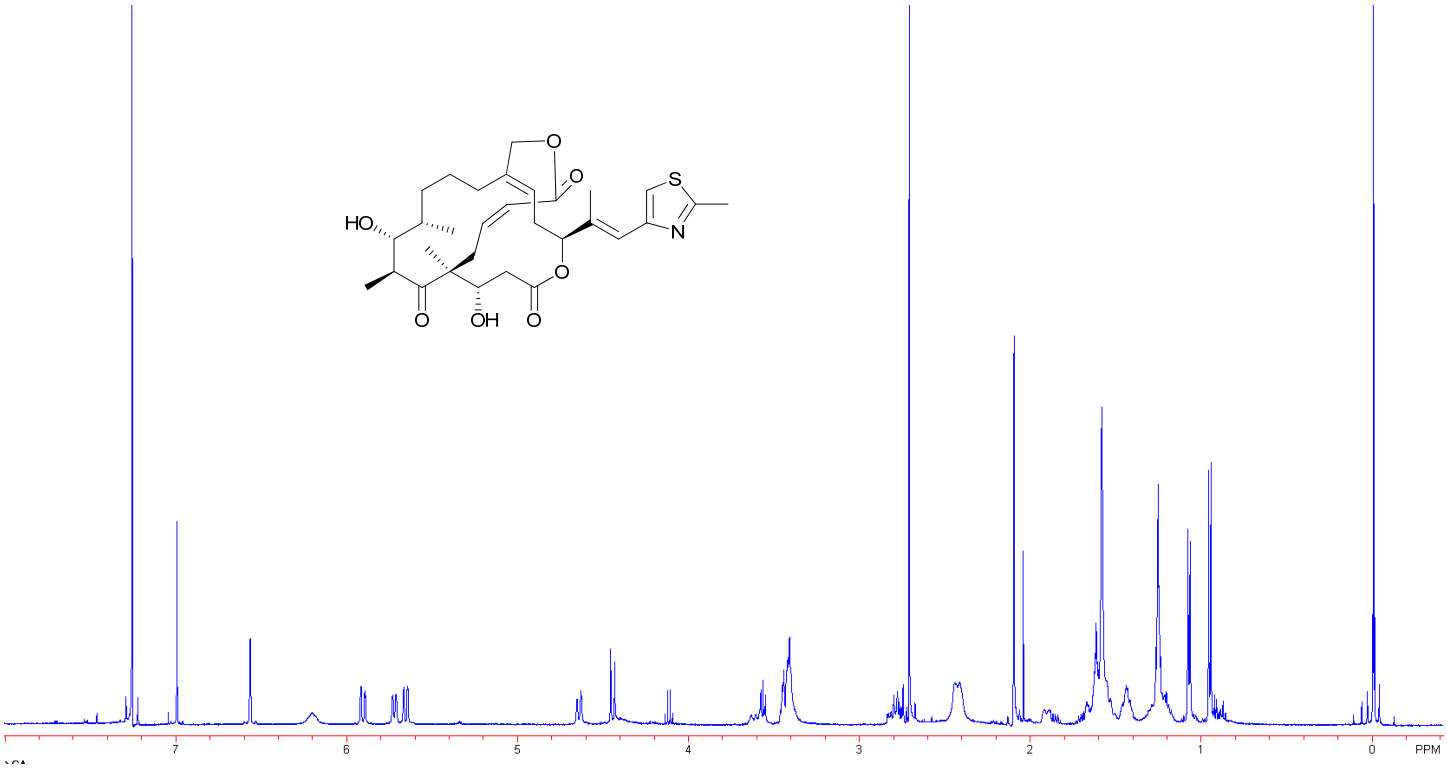
^{1}HNMR spectrum of compound **49**



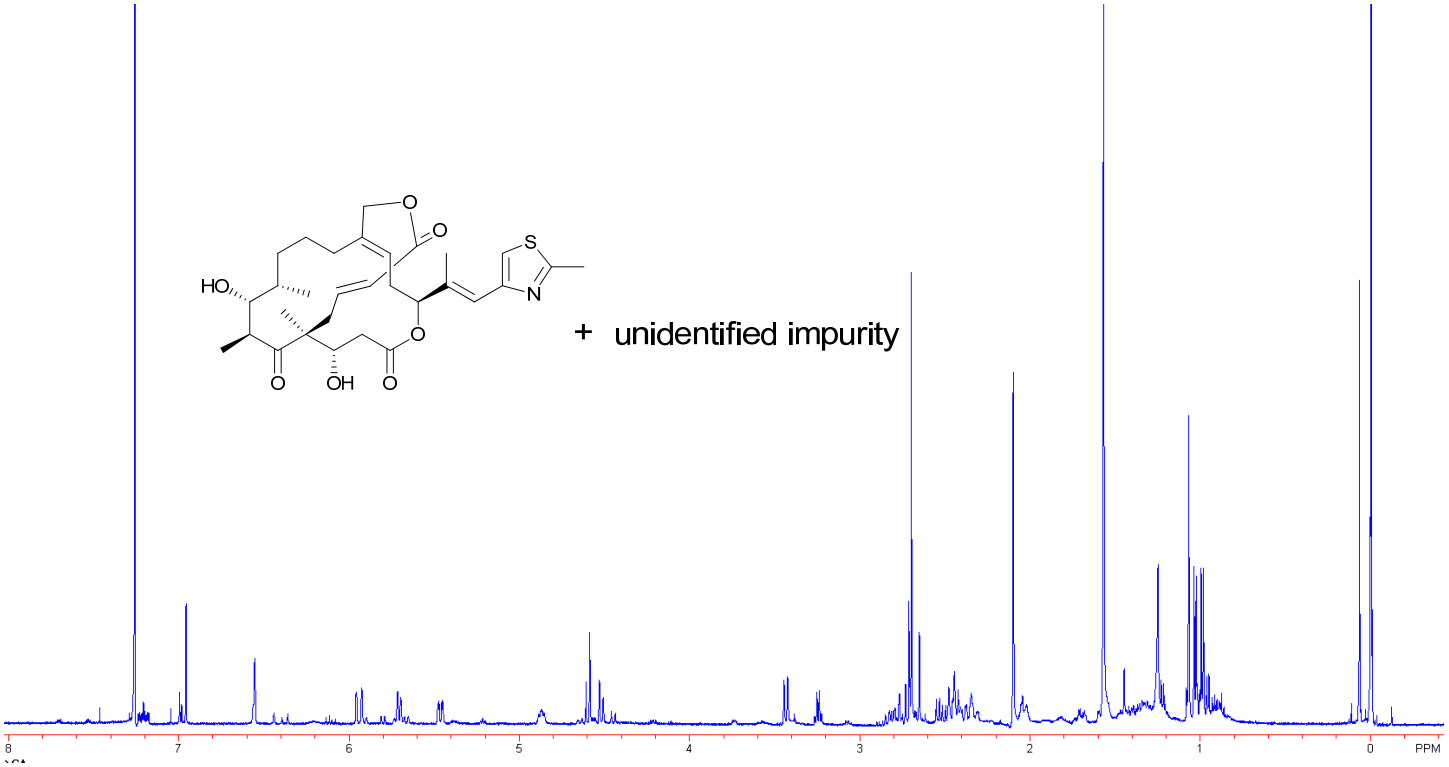
^{1}HNMR spectrum of compound **50**



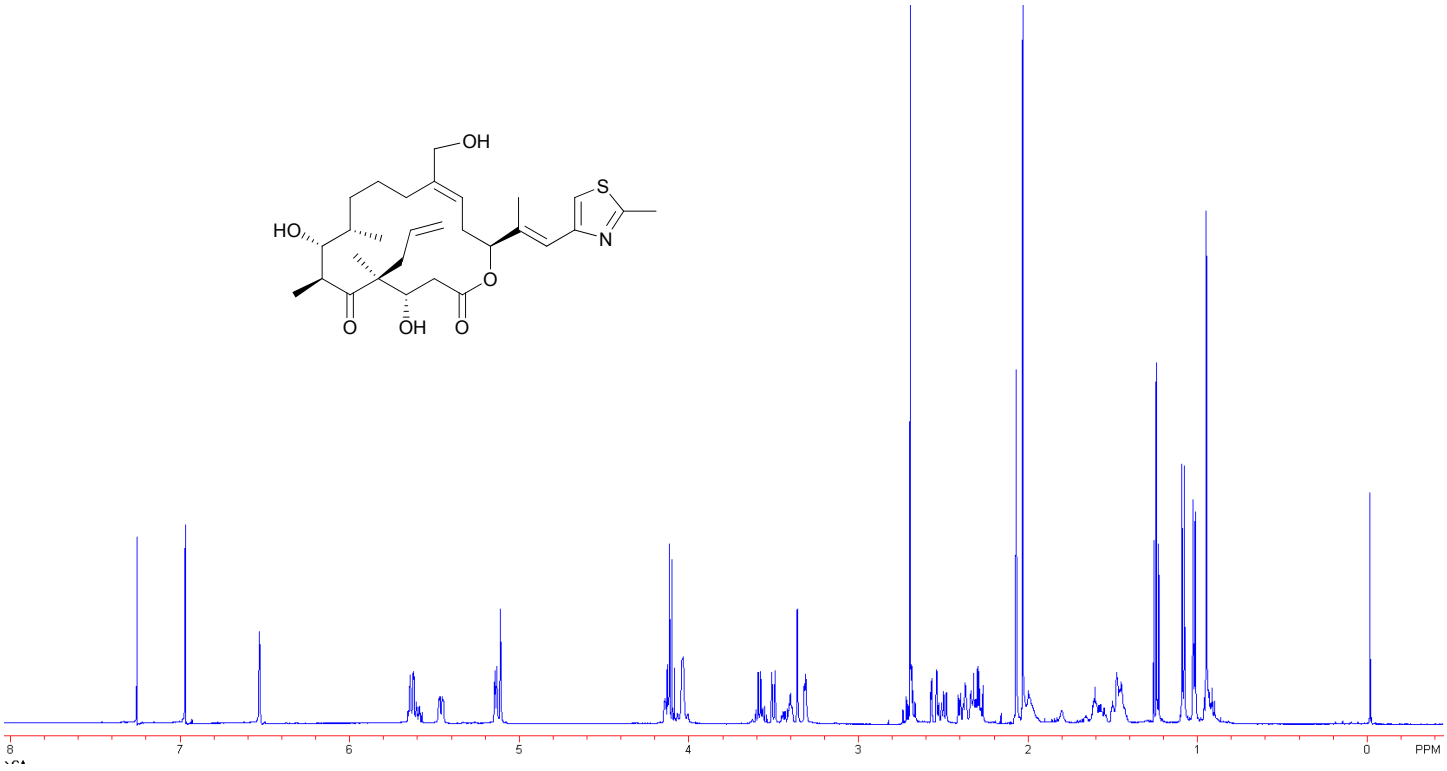
^{1}HNMR spectrum of compound **51**



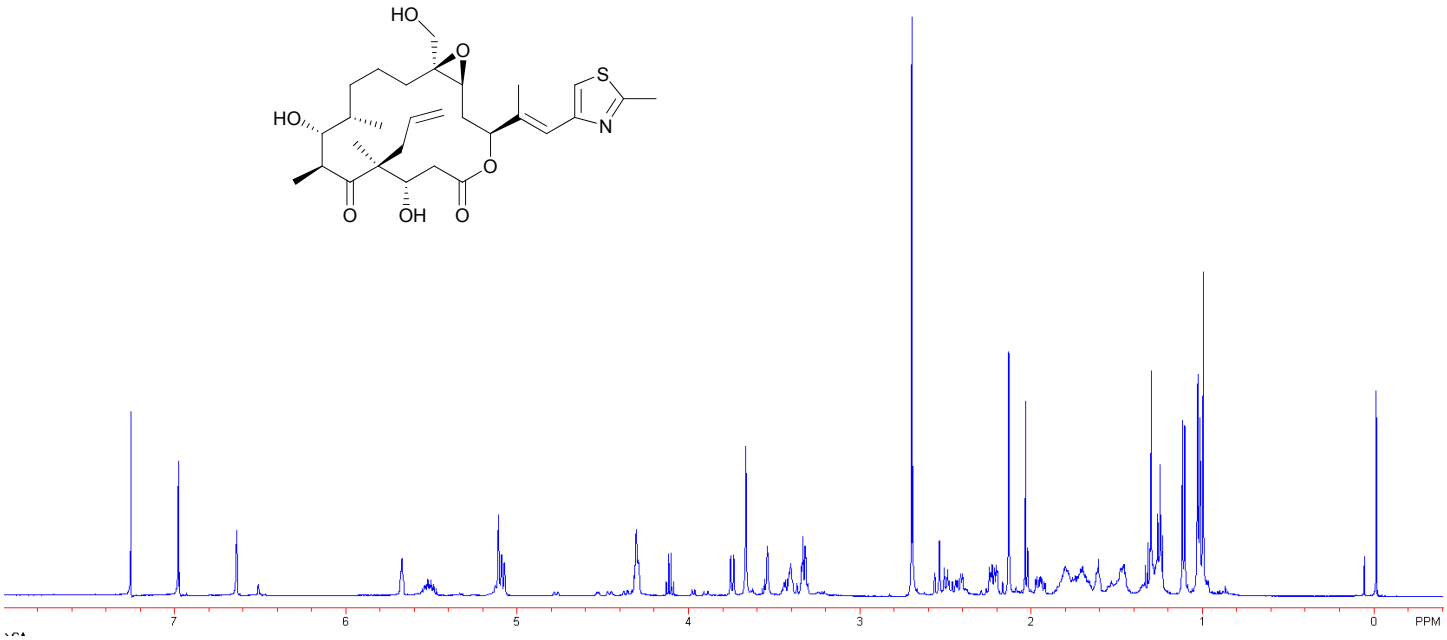
^{1}HNMR spectrum of compound **52**



[1]HNMR spectrum of compound **53**



[1]HNMR spectrum of compound **54**



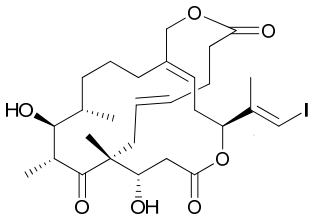
^{1}H NMR spectrum of compound **55**

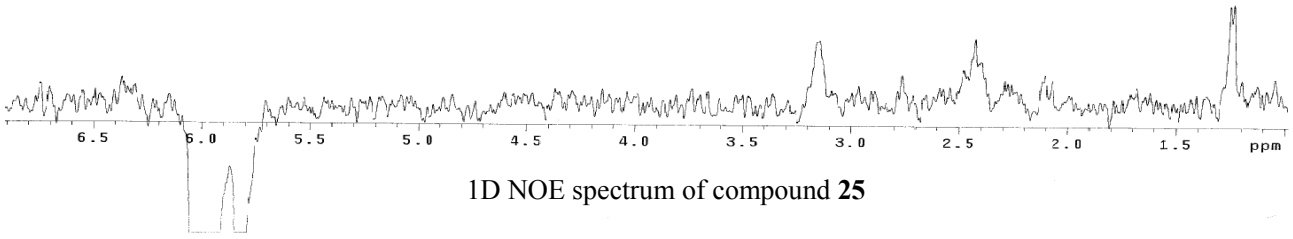
TG197-93-3

Pulse Sequence: NOESY1D
Solvent: CDCl3
Ambient temperature
File: TG197-97-3-6.0-NOE-
INOVA-400 "inova400alt"

Relax. delay 1.000 sec
Pulse 90.0 degrees
Mixing 0.300 sec
Acq. time 3.744 sec
Width 6499.8 Hz
500 repetitions
OBSERVE H1, 399.9441185 MHz
DATA PROCESSING
Line broadening 4.0 Hz
FT size 65536
Total time 49 min, 44 sec
Oct 7 2005
VA Tech Chemistry NMR Lab

TG197-97-3



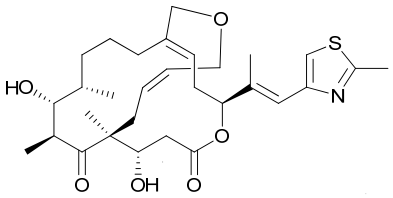


1D NOE spectrum of compound **25**

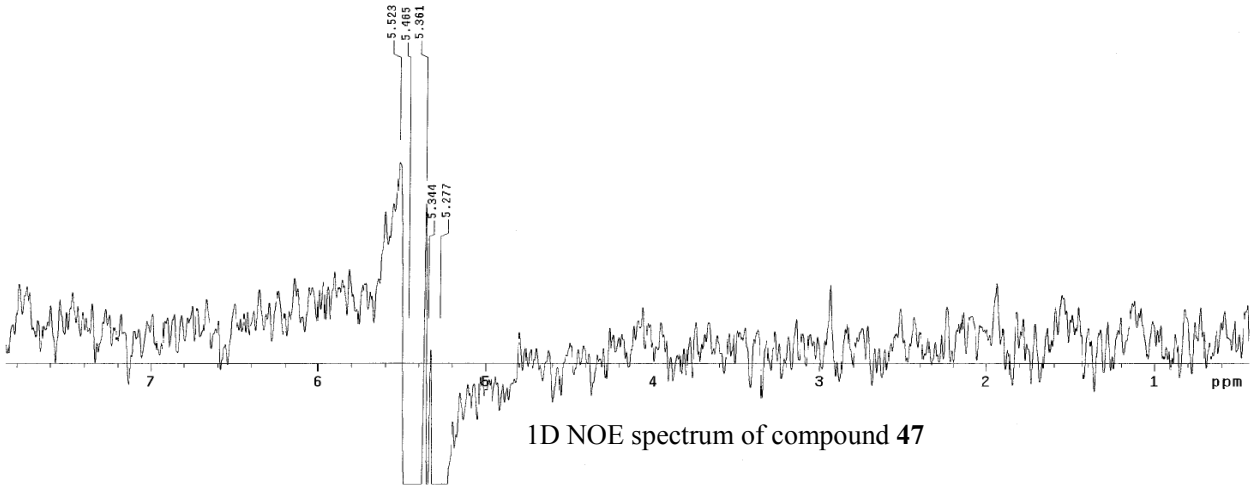
STANDARD 1H OBSERVE

Pulse Sequence: NOESY1D
Solvent: CD3CN
Ambient temperature
INOVA-400 "inova400alt"

Relax. delay 1.000 sec
Pulse 90.0 degrees
Mixing 0.500 sec
Acq. time 3.744 sec
Width 6499.8 Hz
9396 repetitions
OBSERVE H1, 399.9462343 MHz
DATA PROCESSING
Line broadening 5.0 Hz
FT size 65536
Total time 19 hr, 18 min, 28 sec
Feb 22 2008
VA Tech Chemistry NMR Lab



atropisomers



1D NOE spectrum of compound **47**