Supporting Information

An Efficient Total Synthesis of (-)-Epothilone B

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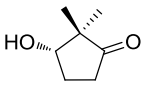
1. General Information

All non-aqueous reactions were run under a positive pressure of nitrogen. Anhydrous solvents were obtained using standard drying techniques. Commercial grade reagents were used without further purification unless stated otherwise. Flash chromatography was performed on 300-400 mesh silica gel with the indicated solvent systems. ^{1}H NMR spectra were recorded on a Bruker 400 (400 MHz) spectrometer and chemical shifts are reported in ppm down field from TMS, using TMS (0.00 ppm) or residual chloroform (7.26 ppm) as an internal standard. Data are reported as: (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, hept = heptalet, m = multiplet; *J* = coupling constant in Hz, integration.). ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) spectrometer, using proton decoupling unless otherwise noted. Chemical shifts are reported in ppm down field from TMS, using the central resonance of $CDCl_3$ (77.00 ppm) as the internal standard. ^{19}F NMR spectra were recorded on a Bruker 300 (282 MHz) spectrometer and chemical shifts were determined relative to $CFCl_3$ at 0.0. $[\alpha]_D$ values were given in 10^{-1} deg cm^2 g^{-1}.HRMS were recorded by using either FTMS-7 or IonSpec 4.7 spectrometers.

2. Experimental Procedures and Spectral Data

1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane was purchased from J&K. Grubbs II catalyst was purchased from Aldrich. $TiCl_4$ (1.0 M in CH_2Cl_2) and 2,4,6-trichlorobenzoyl chloride were purchased from TCI. Chiral auxiliary **S5**[1] was prepared as described in literature.

(S)-3-hydroxy-2,2-dimethylcyclopentanone (10)

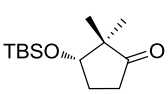


10

Compound **10** was prepared by the method of Corey[2]. A 50 mL flask equipped with a stir bar and a 50 mL pressure-equalizing addition funnel (containing a cotton plug and ca. 5 g of 4Å molecular sieves) fitted on top with a reflux condenser and a nitrogen inlet adaptor was charged with (*R*)-(–)-α,α-diphenyl-2-pyrrolidine-methanol (253 mg, 1.0 mmol, 10%), *n*-butylboronic acid (102 mg, 1.0 mmol, 10%) and 25 mL of toluene. The resulting solution was heated to reflux. After 3 h, the reaction mixture was cooled to *ca.* 60 ℃ and the addition funnel and condenser were quickly replaced with a short-path distillation head. The mixture was concentrated by distillation to a volume of *ca.* 10 mL. This distillation protocol was repeated three times by re-charging with 3 x 20 mL of toluene. The solution was then allowed to cool to room temperature and the distillation head was quickly replaced with a vacuum adaptor. Concentration *in vacuo* afforded the corresponding catalyst as clear oil which was used directly for the reduction reaction.

To a solution of freshly prepared catalyst (1.0 mmol, 10%) in toluene (20 mL) was added 2,2-dimethylcyclopentane-1,3-dione (**9**, 1.76 g, 14 mmol) and *N*,*N*-diethylaniline (0.8 mL, 5 mmol, 0.5 equiv). The resulting solution was cooled to –60 ℃ (chloroform/dry-ice bath) and a solution of catecholborane (2.16 g, 18 mmol, 1.8 equiv, dissolved in 18 mL of toluene) was added slowly along the side of the reaction flask by using a syringe pump over 2 h with vigorous stirring. After the addition and 2 h further reaction at –60 ℃, MeOH (3 mL) was added slowly down the side wall of the flask and the solution was allowed to warm to room temperature. The resulting solution was vigorously stirred with saturated $NaHCO_3$ (20 mL) and 3 N NaOH (20 mL) for 1 h. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The residue was purified by flash column chromatography (5:1 hexane/EtOAc) to afford the product (**10**, 764 mg, 61% yield, 96% ee) as a colorless oil. $[\alpha]_D^{24}$ +13.7 (c 1.2 in $CHCl_3$), lit.,[2] $[\alpha]_D^{25}$ -14.0 (c 1.0 in $CHCl_3$) for the enatiomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.05 (m, 1H), 2.52-2.41 (m, 1H), 2.31-2.20 (m, 2H), 1.97-1.86 (m, 1H), 1.04, (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 221.4, 78.2, 50.1, 34.2, 27.7, 22.2, 16.8; LRMS (ESI): 151 $(M+Na)^+$.

(S)-3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylcyclopentanone (11)

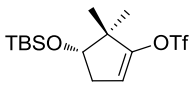


11

To a solution of **10** (729 mg, 5.7 mmol) in CH_2Cl_2/DMF (10/1, 4.4 mL) was added imidazole (1.16 g, 17.1 mmol, 3.0 equiv). After stirring at ambient temperature for 10 min, TBSCl (1.72g, 11.4 mmol, 2.0 equiv) was added and the resulting mixture was stirred overnight before diluted with CH_2Cl_2 (30 mL). The organic

layer was washed successively with saturated $NaHCO_3$, brine, and water. The organic layer was then dried over Na_2SO_4, concentrated, and purified by flash chromatography (200:1 hexane/EtOAc) to give **11** (1.258 g, 91% yield) as colorless oil. $[\alpha]_D^{25}$ +28.0 (c 0.9 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.95 (m, 1H), 2.49-2.38 (m, 1 H), 2.25-2.09 (m, 2H), 1.88-1.78 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 221.3, 78.6, 50.3, 34.2, 28.4, 25.7(3), 22.1, 18.0, 17.5, -4.6, -5.0; IR (KBr film): ν 2958, 2930, 2858, 1745, 1471, 1408, 1291, 1127, 1085, 1066, 798, 777 cm^{-1}; LRMS (EI): 242 (M^+) ; HRMS (EI) calcd for $C_{13}H_{26}O_2Si$ (M^+) : 242.1702, found: 242.1705.

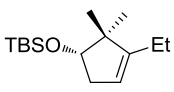
(S)-4-((tert-butyldimethylsilyl)oxy)-5,5-dimethylcyclopent-1-en-1-yl trifluoromethanesulfonate (12)



12

A 150 mL flask charged with the substrate (**11**, 1.13 g, 4.66 mmol) and THF (32 mL) was cooled to -78 ^oC and a solution of KHMDS (14.0 mL, 1.0 M in THF, 3.0 equiv) was added in dropwise. The resulting solution was kept stirring at that temperature for 1 hour. $PhN(Tf)_2$ in THF (18 mL) was added in dropwise. After stirring 20 min at -78 ^oC, 10 mL of saturated $NaHCO_3$ (aq) was added in. The resulting mixture was then allowed to warm to room temperature and extracted with CH_2Cl_2 (20 mL x 3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane) to give **12** (1.597 g, 92% yield). $[\alpha]_D^{25}$ +9.5 (c 0.9 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.43 (br dd, J_1 = 3.0Hz, J_2 = 2.0Hz, 1H), 4.00 (dd, J_1 = 7.3Hz, J_2 = 6.8Hz, 1 H), 2.53 (ddd, J_1 = 15.6Hz, J_2 = 7.3Hz, J_3 = 3.0Hz, 1H), 2.21 (ddd, J_1 = 15.6Hz, J_2 = 6.8Hz, J_3 = 2.0Hz, 1H), 1.08 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 118.6 (q, J_{C-F} = 320.3 Hz), 109.9, 78.1, 46.3, 35.6, 25.7(3), 23.6, 18.4, 18.0, -4.6, -5.0; IR (KBr film): ν 2958, 2932, 2887, 1652, 1465, 1425, 1251, 1213, 1143, 1066, 884, 838, 793 cm^{-1}; LRMS (ESI): 397 $(M+Na)^+$; HRMS (ESI) calcd for $C_{14}H_{25}F_3O_4SSiNa$ $(M+Na)^+$: 397.1087, found: 397.1104.

(S)-tert-butyl((3-ethyl-2,2-dimethylcyclopent-3-en-1-yl)oxy)dimethylsilane

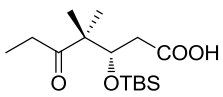


5

A 100 mL flask charged with the substrate (**12**, 623 mg, 1.66 mmol) and THF (33 mL) was cooled to 0 ^oC and $Pd(PPh_3)_4$ (96 mg, 0.05 equiv) was added in one portion. The resulting solution was stirred at that temperature for less than 5 min before a solution of Et_2Zn (2.50 mL, 1.0 M in hexane, 1.5 equiv) was added in dropwise. After kept stirring for 10 min, the reaction was quenched with saturated NaCl (aq,

30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by chromatography (hexane) to give **5** without futher purification.

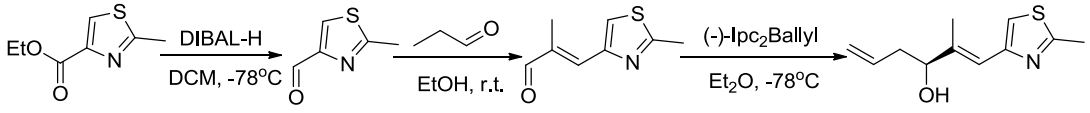
(S)-3-((tert-butyldimethylsilyl)oxy)-4,4-dimethyl-5-oxoheptanoic acid



3

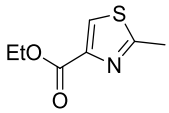
A solution of crude **5** (described above) in CH_2Cl_2 (20 mL) was cooled to -78 ^oC and subjected to ozone until the solution color turned blue. The mixture was then flushed with Ar gas until turned colorless. Et_3N (0.47 mL, 2.0 equiv) was added and the mixture was allowed to war to room temperature and kept stirring for another 3 hours before HCl (aq, 1N, 30 mL) was added in. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by chromatography (5:1 hexane/EtOAc) to give **3** (293 mg, 58% yield for 2 steps) as colorless oil. $[\alpha]_D^{26}$ -18.4 (c 0.95 in $CHCl_3$), lit.,[3] $[\alpha]_D^{22}$ -17.6 (c 1.0 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.48 (dd, J_1 = 3.6Hz, J_2 = 7.0Hz, 1H), 2.56-2.48 (m, 2 H), 2.37-2.31 (m, 1H), 1.14 (s, 3H), 1.09 (s, 3H), 1.01 (t, J = 7.0Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.3, 177.7, 73.5, 52.4, 39.1, 31.8, 25.8, 20.8, 20.4, 18.0, 7.5, -4.6, -5.0.

Compound **7** was prepared according to literatures[4, 5, 6]:



S1 84% **S2** 92% E:Z>20:1 **S3** 99%, 94%ee **7**

Ethyl 2-methylthiazole-4-carboxylate (S1)



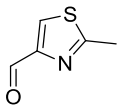
S1

A 250 mL three-necked flask equipped with a reflux condenser, a thermometer and a 25 mL pressure-equalizing addition funnel was charged with ethyl pyruvate (11.6 g, 100 mmol) and Et_2O (65 mL). Bromine (5.13 mL, 100mmol, 1.0 equiv) was added in dropwise through the funnel and the temperature was controlled below 35 ^oC. The resulting mixture was kept stirring at room temperature for another 1 hour to give a slightly yellow solution. Solvent was removed under reduced pressure and the resulting ethyl bromopyruvate was used without further purification.

To a solution of thioacetamide (9.02 g, 120 mmol, 1.2 equiv) in absolute ethanol (55 mL) was added freshly prepared ethyl bromopyruvate (100 mmol) dropwise in 30 min. After being stirred overnight at room temperature, the reaction mixture was poured onto 2.5 *N* HCl (45 mL), stirred 30 min, and extracted with diethyl ether (3 x 100 mL). The aqueous solution was cautiously neutralized with excess, solid $NaHCO_3$ and extracted with diethyl ether (3 x 100

mL). The combined extracts were washed with brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (hexanes/EtOAc, 8/1) to give **S1** (14.4 g, 84% for 2 steps) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (s, 1H), 4.42 (q, *J* = 7.1Hz, 2 H), 2.76 (s, 3H), 1.40 (t, *J* = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 161.4, 147.0, 127.2, 61.4, 19.2, 14.2.

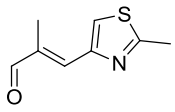
2-methylthiazole-4-carbaldehyde (S2)



S2

To a solution of **S1** (5.14 g, 30 mmol) in dry CH_2Cl_2 (250 mL) was added DIBAL-H (45 mL, 1.0 M in hexane, 1.5 equiv) via syringe pump over 1 h at -78 ^{o}C. After being stirred for 1.5 h at that temperature, an additional portion of DIBAL-H (15 mL, 1.0 M in hexane, 0.5 equiv) was added over 15 min and the clear solution stirred until its completion was verified by TLC (ca. 1-2 h). After addition of methanol (2 mL) at -78 ^{o}C to quench the reaction, the mixture was warmed to room temperature and saturated aqueous Rochelle salt (100 mL) was added. The biphasic mixture was rapidly stirred overnight whereupon two clear, colorless layers formed. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL x 3). The combined organic solutions were washed with brine (500 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 5/1) to provide the aldehyde **S2** (3.22 g, 84% yield) as slightly yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.95 (s, 1H), 8.04 (s, 1H), 2.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.3, 167.6, 154.8, 128.3, 19.2.

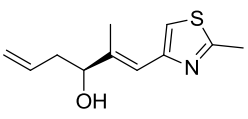
(E)-2-methyl-3-(2-methylthiazol-4-yl)acrylaldehyde (S3)



S3

To a 250 mL flask equipped with a stir bar was added **S2** (2.96 g, 23.3 mmol) and absolute ethanol (60 mL). After the solid disappeared, propanal (1.78 mL, 24.5 mmol, 1.05 eqiuv) and 5% aqueous NaOH (1 mL) was added in successively and the resulting solution was stirred overnight. The solvent was removed under reduced pressure and the crude mixture was directly purified by flash column chromatography (hexanes/EtOAc, 10/1) to provide the aldehyde **S3** (3.90 g, 92% yield) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.54 (s, 1H), 7.45 (s, 1H), 7.22 (s, 1H), 2.74 (s, 3H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.3, 165.9 151.6, 141.1, 138.4, 122.9, 19.3, 11.0.

(S,E)-2-methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-ol (7)

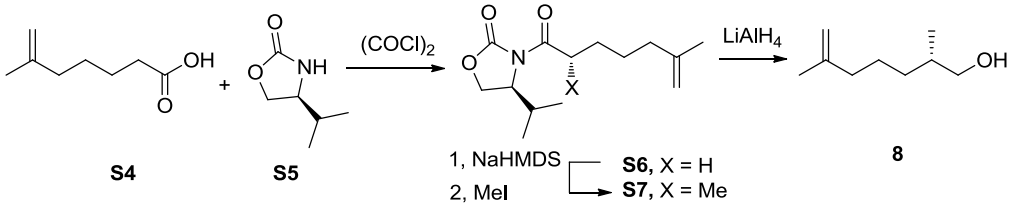


7

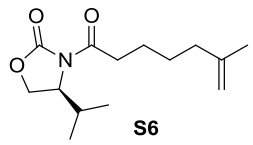
(-)-Diisopinocampheylborane chloride (4.33 g, 13.5 mmol, 1.35 equiv) was dissolved in anhydrous diethyl ether (5 mL) under nitrogen in a Schlenk flask. Then, after the mixture had been cooled to -40 ℃, a

solution of allylmagnesium bromide (12.0 mL, 1.0 M in diethyl ether, 1.2 equiv) was added dropwise and the mixture was warmed to room temperature over 1 hour. The resulting solution of (allyl)diisopinocampheylborane was then cooled to -78 ℃, and the aldehyde **S3** (1.67 g, 10 mmol) in diethyl ether (15 mL) was added in over 30 min. After stirring for 2.5 hours at -78 ℃, the reaction mixture was quenched by addition of MeOH (5 mL) and allowed to warm to 0 ℃. A mixture of NaOAc (2.48 g, 27 mmol), H_2O (10 mL), and H_2O_2 (6 mL, 30%, aq) was then added in dropwise. After that, the mixture was allowed to warm to room temperature and stirred for 20 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 4/1) to provide the alcohol **7** (2.07 g, 99% yield, 94% ee) as yellowish oil. (Chiral OD-H, 0.46 x 25 cm, eluent: hexane/2-propanol, 70:30, 1.0 mL/min, UV detection, 254 nm). $[\alpha]_D^{26}$ -18.1 (c 1.05 in $CHCl_3$), lit.,[6] $[\alpha]_D^{20}$ -18.6 (c 0.58 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (s, 1H), 6.57 (s, 1H), 5.84 (ddt, J_1 = 17.1Hz, J_2 = 10.1Hz, J_3 = 7.1Hz, 1H), 5.19-5.11 (m, 2H), 4.23 (t, J = 6.3Hz, 1H), 2.72 (s, 3H), 2.57 (br, 1H), 2.48-2.35 (m, 2H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 152.8, 141.6, 141.1, 134.7, 119.0, 117.8, 115.5, 76.5, 40.0, 19.1, 14.4.

Compound **8** was prepared according to literature[7]:



(S)-4-isopropyl-3-(6-methylhept-6-enoyl)oxazolidin-2-one (S6)

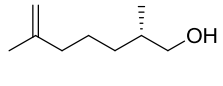


To a 50 mL flask charged with **S4** (1.60 g, 11.3 mmol) and benzene (17 mL) was added oxalyl chloride (2.14 mL, 29.8 mmol, 2.6 equiv) dropwise. The resulting solution was kept stirring at room temperature for 2 hours and evaporated under reduced pressure to give a slightly yellow oil which is used directly without further purification.

To a 50 mL flask charged with **S5** (1.22 g, 9.4 mmol) and THF (20 mL) was added *n*BuLi (4.15 mL, 2.5 M in hexane, 10.3 mmol, 1.1 equiv) dropwise at -78 ^{o}C. After stirred at that temperature for 30 min, freshly prepared acyl chloride of **S4** (11.3 mmol, 1.2 equiv) in THF (7 mL) was added in dropwise. The reaction mixture was allowed to warm to room temperature and stirrd overnight before brine (30 mL) was added in. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined

organic layers were washed with brine (100 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 15/1) to provide the product **S6** (2.07 g, 87% yield) as colorless oil.

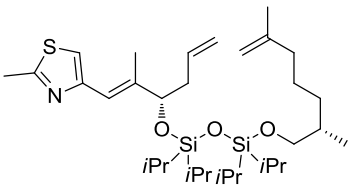
(S)-2,6-dimethylhept-6-en-1-ol (8)



8

Alcohol **8** was prepared from **S6** identical to the literature[7]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.70-4.67 (m, 2H), 3.53-3.40 (m, 2H), 2.03-1.99 (m, 2H), 1.71 (s, 3H), 1.66-1.35 (m, 5H), 1.15-1.06 (m, 1H), 0.93 (d, *J* = 6.8Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.0, 109.8, 68.3, 38.0, 35.7, 32.8, 24.9, 22.3, 16.6. The analytical data are in agreement with those reported in the literature[7].

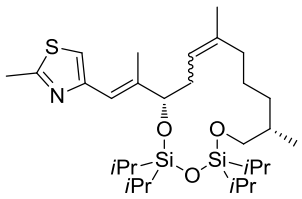
4-((S,E)-3-((3-(((S)-2,6-dimethylhept-6-en-1-yl)oxy)-1,1,3,3-tetraisopropyldisiloxanyl)oxy)-2-methylhexa-1,5-dien-1-yl)-2-methylthiazole (6)



6

In a 100 mL flask equipped with a stir bar, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.26 g, 3.99 mmol, 1.2 equiv) was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 ^{o}C. A solution of **7** (695 mg, 3.32 mmol) and DBU (1.24 mL, 2.5 quiv) in CH_2Cl_2 (15 mL) was added in dropwise over 20 min. Then the reaction was allowed to warm to room temperature and stirred for another 2 hours. A solution of **8** (708 mg, 4.98 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) was added in and the resulting solution was kept stirring at room temperature overnight. The mixture was diluted with CH_2Cl_2 (30 mL) and HCl (0.5 N, 50 mL) was added in. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 200/1) to provide the product **6** (1.62 g, 82% yield) as colorless oil. $[\alpha]_D^{30}$ -3.5 (c 0.93 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (s, 1H), 6.45 (s, 1H), 5.73 (ddt, J_1 = 17.4Hz, J_2 = 10.3Hz, J_3 = 7.0Hz, 1H), 5.04-4.96 (m, 2H), 4.67 (m, 2H), 4.42 (t, *J* = 6.4Hz, 1H), 3.57 (dd, J_1 = 9.5Hz, J_2 = 5.7Hz, 1H), 3.49 (dd, J_1 = 9.5Hz, J_2 = 6.5Hz, 1H), 2.70 (s, 3H), 2.43 (m, 2H), 2.01 (br d, *J* = 1.0Hz, 3H), 2.01-1.96 (m, 2H), 1.70 (s, 3H), 1.66-1.59 (m, 2H), 1.50-1.36 (m, 3H), 1.06-1.00 (m, 28H), 0.88 (d, *J*=6.8Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ164.2, 153.2, 146.2, 141.1, 134.6, 119.4, 116.7, 115.0, 109.6, 77.5, 67.8, 41.2, 38.1, 35.7, 32.9, 25.1, 22.4, 19.2, 17.53(2), 17.52(2), 17.46, 17.40(4), 16.7, 14.0, 13.41, 13.37, 13.1; LRMS (ESI): 616 $(M+Na)^+$; HRMS (ESI) calcd. for $C_{32}H_{59}NO_3SSi_2Na$ $(M+Na)^+$: 616.3646, found: 616.3645.

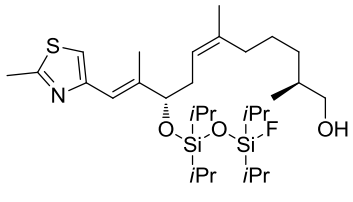
2-methyl-4-((1E)-2-((6S,13S)-2,2,4,4-tetraisopropyl-9,13-dimethyl-1,3,5-trioxa-2,4-disilacyclotetradec-8-en-6-yl)prop-1-en-1-yl)thiazole (16)



16 (Z/E = 1.7/1)

A 250 mL flask charged with **6** (396 mg, 0.67 mmol) and CH_2Cl_2 (130 mL) was added Grubbs II catalyst (28 mg, 5%) quickly. The resulting solution was warmed to 40 ^oC and stirred at that temperature for 5 hours. The solvent was evaporated under reduced pressure and the resulting brown oil was purified by flash column chromatography (hexanes/EtOAc, 200/1) directly to provide the product **16** (358 mg, 95% yield, 1.7/1 of Z/E mixture) as colorless oil. It is used in the next step without further purification. For **Z-isomer**: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.92 (s, 1H), 6.45 (s, 1H), 5.02-4.98 (m, 1H), 4.37 (dd, J_1 = 8.5Hz, J_2 = 5.0Hz, 1H), 3.68 (dd, J_1 = 9.6Hz, J_2 = 5.1Hz, 1H), 3.61 (dd, J_1 = 9.6Hz, J_2 = 5.8Hz, 1H), 2.71 (s, 3H), 2.53-2.50 (m, 1H), 2.32-2.26 (m, 1H), 2.08-1.92 (m, 2H), 2.03 (br d, J = 0.6Hz, 3H), 1.71-1.62 (m, 2H),1.64 (s, 3H), 1.53-1.43 (m, 3H), 1.09-1.00 (m, 28H), 0.91 (d, J=6.6Hz, 3H); LRMS (ESI): 588 $(M+Na)^+$; HRMS (ESI) calcd. for $C_{30}H_{55}NO_3SSi_2Na$ $(M+Na)^+$: 588.3333, found: 588.3336. For **E-isomer**: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.89 (s, 1H), 6.53 (s, 1H), 5.37 (m, 1H), 4.41 (dd, J_1 = 8.0Hz, J_2 = 3.2Hz, 1H), 3.67 (dd, J_1 = 9.5Hz, J_2 = 4.5Hz, 1H), 3.50 (dd, J_1 = 9.2Hz, J_2 = 7.5Hz, 1H), 2.71 (s, 3H), 2.31-2.23 (m, 2H), 2.14-1.97 (m, 2H), 2.06 (br d, J = 0.7Hz, 3H), 1.76-1.69 (m, 2H), 1.56 (s, 3H), 1.48-1.39 (m, 3H), 1.06-0.97 (m, 28H), 0.85 (d, J=6.8Hz, 3H); LRMS (ESI): 588 $(M+Na)^+$; HRMS (ESI) calcd. for $C_{30}H_{55}NO_3SSi_2Na$ $(M+Na)^+$: 588.3333, found: 588.3336.

(2S,6Z,9S,10E)-9-((3-fluoro-1,1,3,3-tetraisopropyldisiloxanyl)oxy)-2,6,10-trimethyl-11-(2-methylthiazol-4-yl)undeca-6,10-dien-1-ol (Z-S8)



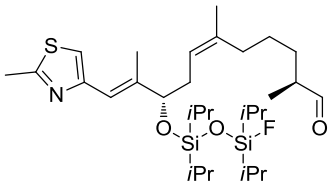
Z-S8

In a 100 mL flask equipped with a stir bar, **16** (352 mg, 0.62 mmol, Z/E mixture) was dissolved in CH_2Cl_2 (35 mL) and cooled to 0 ^oC. HF-Pyridine (0.6 mL) was added in dropwise and the resulting mixture was kept stirring at that temperature for 1 hour. The reaction was quenched with saturated $NaHCO_3$ (30 mL) and the resulting mixture was allowed to warm to room temperature and stirred vigorously for 1 hour. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 6/1) to provide the product **S8** (297 mg, 82% yield, 1.7/1 of Z/E mixture) as colorless oil. The mixture was separated by preparative HPLC (CH_3CN/ H_2O, 25/1) to give

the Z-isomer (**Z-S8**, 180 mg, 49% yield). For **Z-isomer**: $[\alpha]_D^{27}$ -1.9 (c 1.65 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.94 (s, 1H), 6.48 (s, 1H), 5.17 (t, *J* = 7.0 Hz, 1H), 4.37 (t, *J* = 6.5 Hz, 1H), 3.50 (dd, J_1 = 10.4 Hz, J_2 = 5.9 Hz, 1H), 3.42 (dd, J_1 = 10.4 Hz, J_2 = 6.5 Hz, 1H), 2.73 (s, 3H), 2.39-2.35 (m, 2H), 2.08-1.96 (m, 3H), 2.03 (s, 3H), 1.67 (s, 3H), 1.65-1.59 (m, 1H), 1.47-1.31 (m, 3H), 1.08-0.99 (m, 28H), 0.92 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.4, 153.1, 141.8, 136.9, 120.9, 119.2, 114.9, 78.5, 68.1, 35.8, 35.4, 33.1, 32.2, 25.3, 23.4, 19.1, 17.15(2), 17.12(2), 16.75(2), 16.69(2), 16.6, 14.0, 13.11, 13.09, 12.7, 12.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -149.9 (s); IR (KBr film): ν 3385, 2946, 2868, 1464, 1056, 885, 842, 700 cm^{-1}; LRMS (ESI): 608 $(M+Na)^+$; HRMS (ESI) calcd. for $C_{30}H_{56}FNO_3SSi_2Na$ $(M+Na)^+$: 608.3396, found: 608.3378.

For **E-isomer**: $[\alpha]_D^{27}$ +7.8 (c 0.81 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (s, 1H), 6.46 (s, 1H), 5.06 (t, *J* = 7.0 Hz, 1H), 4.36 (dd, J_1 = 8.0 Hz, J_2 = 5.3 Hz, 1H), 3.46-3.39 (m, 2H), 2.73 (s, 3H), 2.46-2.34 (m, 2H), 2.03-1.97 (m, 2H), 2.01 (s, 3H), 1.85 (br, 1H), 1.60 (s, 3H), 1.57-1.29 (m, 5H), 1.08-0.99 (m, 28H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 152.9, 141.3, 136.7, 120.1, 119.6, 114.8, 78.3, 68.2, 39.6, 35.7, 35.0, 32.3, 24.7, 18.9, 17.14(2), 17.11(2), 16.74(2), 16.68(2), 16.3, 15.9, 13.7, 13.11, 13.08, 12.6, 12.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -150.0 (s); IR (KBr film): ν 3339, 2945, 2868, 1464, 1056, 885, 842, 700 cm^{-1}; LRMS (ESI): 608 $(M+Na)^+$; HRMS (ESI) calcd. for $C_{30}H_{56}FNO_3SSi_2Na$ $(M+Na)^+$: 608.3396, found: 608.3382.

(2S,6Z,9S,10E)-9-((3-fluoro-1,1,3,3-tetraisopropyldisiloxanyl)oxy)-2,6,10-trimethyl-11-(2-methylthiazol-4-yl)undeca-6,10-dienal (4)

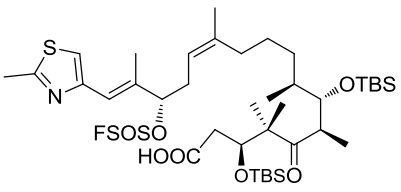


4

Dess-Martin periodinane (100 mg, 0.24 mmol, 1.5 equiv) was added to a solution of alcohol **Z-S8** (92 mg, 0.16 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 40 min at room temperature before saturated Na_2SO_3 (2 mL) and $NaHCO_3$ (5 mL) was added. The resulting mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 20/1) to provide the aldehyde **4** (78 mg, 85% yield) as colorless oil. $[\alpha]_D^{25}$ +8.5 (c 1.47 in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.61 (d, J = 1.7 Hz, 1H), 6.94 (s, 1H), 6.48 (s, 1H), 5.18 (t, *J* = 7.1 Hz, 1H), 4.37 (t, *J* = 6.4 Hz, 1H), 2.73 (s, 3H), 2.38-2.29 (m, 3H), 2.06-2.03 (m, 2H), 2.04 (s, 3H), 1.72-1.65 (m, 1H), 1.67 (s, 3H), 1.45-1.31 (m, 3H), 1.10-0.1.03 (m, 31H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.1, 164.2, 153.2, 141.5, 136.2, 121.3, 119.3, 115.1, 78.3, 46.3, 35.3, 31.9,

30.4, 25.2, 23.3, 19.2, 17.15(2), 17.12(2), 16.75(2), 16.69(2), 14.0, 13.3, 13.12, 13.09, 12.7, 12.5; IR (KBr film): ν 2946, 2868, 1728, 1464, 1097, 1056, 885, 841, 700 cm^{-1}; LRMS (ESI): 606 $(M+Na)^+$; HRMS (ESI) calcd. for $C_{30}H_{54}FNO_3SSi_2Na$ $(M+Na)^+$: 606.3239, found: 606.3212.

(3S,6R,7S,8S,12Z,15S,16E)-3-((tert-butyldimethylsilyl)oxy)-15-((fluorosulfonothioyl)oxy)-4,4,6,7,8,12,16-heptamethyl-17-(2-methylthiazol-4-yl)-5-oxoheptadeca-12,16-dienoic acid (S9)



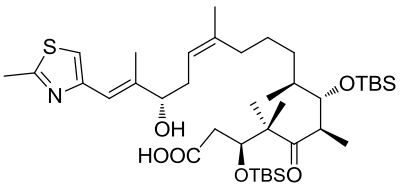
S9

To a solution of **3** (25 mg, 83 μmol, 1.2 equiv) in CH_2Cl_2 (1 mL) at -78 ℃ was added dropwise a solution of $TiCl_4$ (0.18 mL, 1.0 M in CH_2Cl_2, 0.18 mmol, 2.6 equiv). The bright yellow-orange solution was stirred for 5 min before Et*N*i*Pr*$_2$ (31 μL, 2.6 equiv) was added and the dark red reaction was stirred at -78 ℃ for 1h. Then a solution of of **4** (39 mg, 67 μmol) in CH_2Cl_2 (1 mL) was added dropwise via cannula. The reaction was allowed to warm to room temperature over 1 hour and kept stirring for another 2 hours before quenched with phosphate buffer (pH 7.0, 5 mL). The resulting mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 4/1) to provide the acid **17** (30 mg, 51% yield, 73% yield brsm) as single diastereomer along with 12 mg of **4** recovered.

To a solution of **17** (12.0 mg, 13.5 μmol) in CH_2Cl_2 (0.5 mL) at 0 ℃ was added dropwise 2,6-lutidine (8 μL, 5 equiv) and TBSOTf (9 μL, 3 equiv). The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and HCl (aq, 1N, 3 mL) was added in. The resulting mixture was stirred vigorously for 50 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 8/1) to provide the acid **S9** (11.8 mg, 87% yield) as colorless oil. $[\alpha]_D^{27}$ -18.2 (c 0.45 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.91 (s, 1H), 6.54 (s, 1H), 5.17 (t, J = 7.2 Hz, 1H), 4.41-4.35 (m, 2H), 3.76 (dd, J_1 = 6.1 Hz, J_2 = 1.8 Hz, 1H), 3.13 (m, 1H), 2.71 (s, 3H), 2.48 (dd, J_1 = 16.6 Hz, J_2 = 3.3 Hz, 1H), 2.36-2.29 (m, 3H), 2.07-2.03 (m, 1H), 1.97 (s, 3H), 1.94-1.88 (m, 2H), 1.68-1.62 (m, 1H), 1.65 (s, 3H), 1.42-1.36 (m, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 1.07-1.01 (m, 31H), 0.90-0.88 (m, 21H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 218.1, 174.5, 165.0, 152.8, 142.7, 137.1, 121.0, 118.7,

114.7, 78.5, 73.4, 53.8, 44.5, 39.9, 39.3, 35.5, 32.6, 31.5, 30.3, 29.7, 26.2(3), 26.0(3), 23.52, 23.49, 19.0, 18.8, 18.5, 18.2, 17.16, 17.13(4), 16.80, 16.75(2), 16.70(2), 15.7, 14.1, 13.13, 13.10, 12.7, 12.5, -3.8, -4.0, -4.1, -4.6; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -149.9 (s); IR (KBr film): ν 3108, 2929, 2858, 1713, 1688, 1464, 1254, 1093, 1057, 989, 837, 775, 700 cm^{-1}; LRMS (ESI): 1001 $(M+H)^+$; HRMS (ESI) calcd. for $C_{51}H_{98}FNO_7SSi_4Na$ $(M+Na)^+$: 1022.6017, found: 1022.6002.

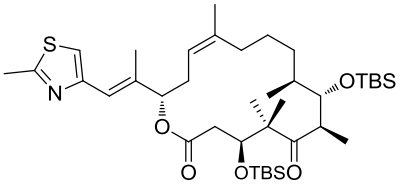
(3S,6R,7S,8S,12Z,15S,16E)-3,7-bis((tert-butyldimethylsilyl)oxy)-15-hydroxy-4,4,6,8,12,16-hexamethyl-17-(2-methylthiazol-4-yl)-5-oxoheptadeca-12,16-dienoic acid (18)



18

To a solution of **S9** (11.8 mg, 11.8 μmol) in THF (1.0 mL) was added dropwise a solution of TBAF (71 μL, 1.0 M in THF, 6.0 equiv). The resulting solution was allowed to stirred at room temperature for 10 min before quenched with HCl (aq, 0.5 N, 10 mL). The mixture was extacted with with CH_2Cl_2 (10 mL x 3) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 1/1) to provide the hydroxy acid **18** (7.8 mg, 90% yield) as colorless oil. $[\alpha]_D^{27}$ -12.2 (c 1.05 in $CHCl_3$), lit.,[8] $[\alpha]_D^{22}$ -10.4 (c 0.4 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (s, 1H), 6.64 (s, 1H), 5.18 (t, J = 7.1 Hz, 1H), 4.40 (dd, J_1 = 6.3 Hz, J_2 = 3.5 Hz, 1H), 4.15 (t, J = 6.6 Hz, 1H), 3.79 (br d, J = 6.5 Hz, 1H), 3.13 (m, 1H), 2.71 (s, 3H), 2.48 (dd, J_1 = 16.5 Hz, J_2 = 3.4 Hz, 1H), 2.36-2.29 (m, 3H), 2.14-2.07 (m, 1H), 2.04-1.95 (m, 1H), 2.01 (s, 3H), 1.71 (s, 3H), 1.55-1.46 (m, 1H), 1.41-1.32 (m, 2H), 1.21 (s, 3H), 1.13 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.03-0.96 (m, 2H), 0.92-0.90 (m, 12H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.9, 175.5, 165.1, 152.6, 142.2, 139.3, 120.4, 118.7, 115.2, 73.5, 53.8, 44.8, 40.1, 39.1, 34.2, 32.5, 31.3, 29.7, 26.3, 26.2(3), 26.0(3), 23.6, 23.5, 19.2, 18.8, 18.5, 18.2, 17.1, 15.9, 14.6, -3.8, -3.9, -4.2, -4.6; LRMS (ESI): 738 $(M+H)^+$.

(4S,7R,8S,9S,16S,Z)-4,8-bis((tert-butyldimethylsilyl)oxy)-5,5,7,9,13-pentamethyl-16-((E)-1-(2-methylthiazol-4-yl)prop-1-en-2-yl)oxacyclohexadec-13-ene-2,6-dione (19)

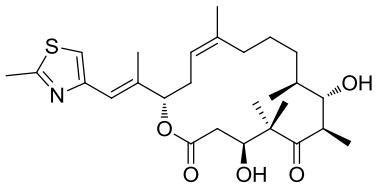


19

A solution of hydroxy acid **18** (31.0 mg, 42 μmol) in THF (5.0 mL) was treated at 0 ℃ with Et_3N (36 μL, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (32 μL, 5.0 equiv). The reaction mixture was stirred at 0 ℃ for 40 min and then added to a solution of 4-DMAP (50 mg, 0.42 mmol, 10.0 equiv) in toluene (22 mL, 0.002 M) over 20 min at 25 ℃ and stirred at that temperature

overnight. The solvents were removed *in vacuo*, and the crude product obtained was diluted with CH_2Cl_2 (10 mL) and HCl (aq, 0.5N, 8 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 40/1) to provide the lactone **19** (24.7 mg, 81% yield) as colorless oil. $[\alpha]_D^{28}$ -16.2 (c 0.6 in $CHCl_3$), lit.,[8] $[\alpha]_D^{22}$ -11.8 (c 0.8 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (s, 1H), 6.56 (s, 1H), 5.17 (m ,1H), 4.98 (d, *J* = 9.8 Hz, 1H), 4.04 (d, *J* = 9.8 Hz, 1H), 4.89 (d, *J* = 8.8 Hz, 1H), 3.03 (m, 1H), 2.83-2.79 (m, 1H), 2.73-2.65 (m, 2H), 2.71 (s, 3H), 2.50-2.44 (m, 1H), 2.11 (s, 3H), 2.08-2.04 (m, 1H), 1.77-1.71 (m, 2H), 1.68 (s, 3H), 1.55-1.43 (m, 2H), 1.19 (s, 3H), 1.14 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H), 0.91-0.87 (m, 2H), 0.85 (s, 9H), 0.11 (s, 6H), 0.08 (s, 3H), -0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.1, 171.2, 164.6, 152.6, 140.6, 138.8, 119.4, 119.2, 115.9, 79.9, 76.3, 53.5, 39.3, 32.5, 32.0, 31.5, 29.7, 27.4, 26.4(3), 26.2(3), 24.4, 24.3, 23.1, 19.2, 18.7, 18.6, 17.7, 15.3, -3.3, -3.68, -3.70, -5.6; LRMS (ESI): 721 $(M+H)^+$.

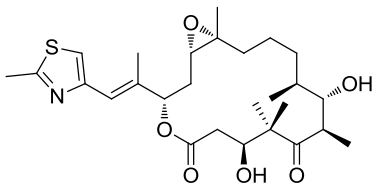
Epothilone D (2)



Epothilone D (2)

To a solution of lactone **19** (24.7 mg, 34.3 μmol) in CH_2Cl_2 (2 mL) at 0 ℃ was added CF_3COOH (0.4 mL) dropwise. The resulting mixture was allowed to stir at that temperature for 45 min before diluted with CH_2Cl_2 (15 mL) and quenched with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 3/1) to provide Epothilone D (**2**, 15.4 mg, 91% yield) as colorless oil. $[\alpha]_D^{23}$ -89.7 (c 0.75 in $CHCl_3$), lit.,[8] $[\alpha]_D^{22}$ -91.5 (c 0.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.96 (s, 1H), 6.59 (s, 1H), 5.22 (d, *J* = 8.8 Hz, 1H), 5.14 (dd, J_1 = 9.9 Hz, J_2 = 4.6 Hz, 1H), 4.30 (dd, J_1 = 11.1 Hz, J_2 = 2.3 Hz, 1H), 3.72 (m, 1H), 3.57 (br, 1H), 3.16 (ddd, J_1 = 13.6 Hz, J_2 = 6.8 Hz, J_3 = 2.0 Hz, 1H), 3.07 (br, 1H), 2.70-2.59 (m, 1H), 2.69 (s, 3H), 2.46 (dd, J_1 = 14.7 Hz, J_2 = 11.2 Hz, 1H), 2.36-2.22 (m, 3H), 2.06 (s, 3H), 1.93-1.85 (m, 1H), 1.77-1.70 (m, 2H), 1.66 (s, 3H), 1.35 (s, 3H), 1.32-1.24 (m, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.7, 170.4, 165.0, 152.1, 139.2, 138.5, 120.9, 119.2, 115.6, 78.9, 74.2, 72.3, 53.6, 41.7, 39.7, 38.5, 32.6, 31.8, 31.6, 25.4, 22.94, 22.91, 19.0, 18.0, 15.9, 15.7, 13.4; LRMS (ESI): 514 $(M+Na)^+$.

Epothilone B (1)



Epothilone B (1)

To a solution of **2** (17.1 mg, 34.8 μmol) in $CHCl_3$ (1.5 mL) was added *m*-CPBA (9.0 mg, 85% purity, 44.3 μmol, 1.3 equiv) at -20 ℃. After stirring 1 hour at that temperature, *m*-CPBA (18.0 mg, 2.6 equiv) was added in. 2 hours later, more *m*-CPBA (9.0 mg, 1.3 equiv) was added in. The mixture was allowed to stir for another 1 hour at -20 ℃ before diluted with CH_2Cl_2 (15 mL) aquenched with saturated Na_2SO_3 (2 mL) and $NaHCO_3$ (5 mL). The resulting mixture was stirred vigorously for 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (hexanes/EtOAc, 1/1) to provide Epothilone B (**1**) and its β-epoxy isomer (15.0 mg, 83% yield) as a 4/1 mixture of colorless oil. The mixture was further separated by preparative HPLC (MeOH/H_2O, 60/40) to afford Epothilone B (**1**) (9.2 mg) which is dissolved in CH_2Cl_2 (0.5 mL) and treated with petroleum ether (10 mL) to give a white solid. $[\alpha]_D^{20}$ -34.3 (c 0.43 in MeOH), lit.,[8] $[\alpha]_D^{22}$ -34.3 (c 0.2 in MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (s, 1H), 6.59 (s, 1H), 5.42 (dd, J_1 = 7.8 Hz, J_2 = 2.8 Hz, 1H), 4.23 (br s, 1H), 4.22 (br s, 1H), 3.78 (t, J = 4.3 Hz, 1H), 3.32-3.29 (m, 1H), 2.81 (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1H), 2.72-2.64 (m, 1H), 2.70 (s, 3H), 2.55 (dd, J_1 = 13.8 Hz, J_2 = 9.0 Hz, 1H), 2.39-2.35 (m, 1H), 2.13-2.09 (m, 1H), 2.09 (s, 3H), 1.96-1.88 (m, 1H), 1.75-1.68 (m, 2H), 1.54-1.34 (m, 5H), 1.37 (s, 3H), 1.28 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.09 (s, 3H), 1.01 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 220.6, 170.6, 165.2, 151.7, 137.6, 119.6, 116.1, 76.6, 74.0, 72.8, 61.7, 61.4, 53.1, 42.8, 39.2, 36.4, 32.3, 32.0, 30.7, 22.7, 22.3, 21.4, 19.6, 19.1, 17.1, 15.8, 13.6; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.35 (s, 1H), 6.51 (s, 1H), 5.29 (d, J = 8.3 Hz, 1H), 5.10 (d, J = 7.1 Hz, 1H), 4.48 (d, J = 6.3 Hz, 1H), 4.12-4.07 (m, 1H), 3.48 (t, J = 7.3 Hz, 1H), 3.12 (m, 1H), 2.85 (dd, J_1 = 9.5 Hz, J_2 = 2.9 Hz, 1H), 2.65 (s, 3H), 2.40-2.36 (m, 2H), 2.11 (s, 3H), 2.07-2.04 (m, 1H), 1.88-1.80 (m, 1H), 1.64-1.46 (m, 2H), 1.38-1.24 (m, 5H), 1.19 (s, 6H), 1.07 (d, J = 6.5 Hz, 3H), 0.91 (d, 3H), 0.90 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 217.9, 170.6, 164.7, 152.6, 137.7, 119.7, 118.2, 77.0, 76.0, 71.0, 62.0, 61.5, 53.7, 45.4, 36.0, 33.4, 32.6, 30.1, 23.5, 23.0, 22.5, 20.2, 19.3, 18.9, 17.0, 14.6; LRMS (ESI): 530 $(M+Na)^+$.

3. References

(1) Gennäs, G. B.; Talman, V.; Aitio, O.; *et al. J. Med. Chem.* **2009,** *52*, 3969–3981.

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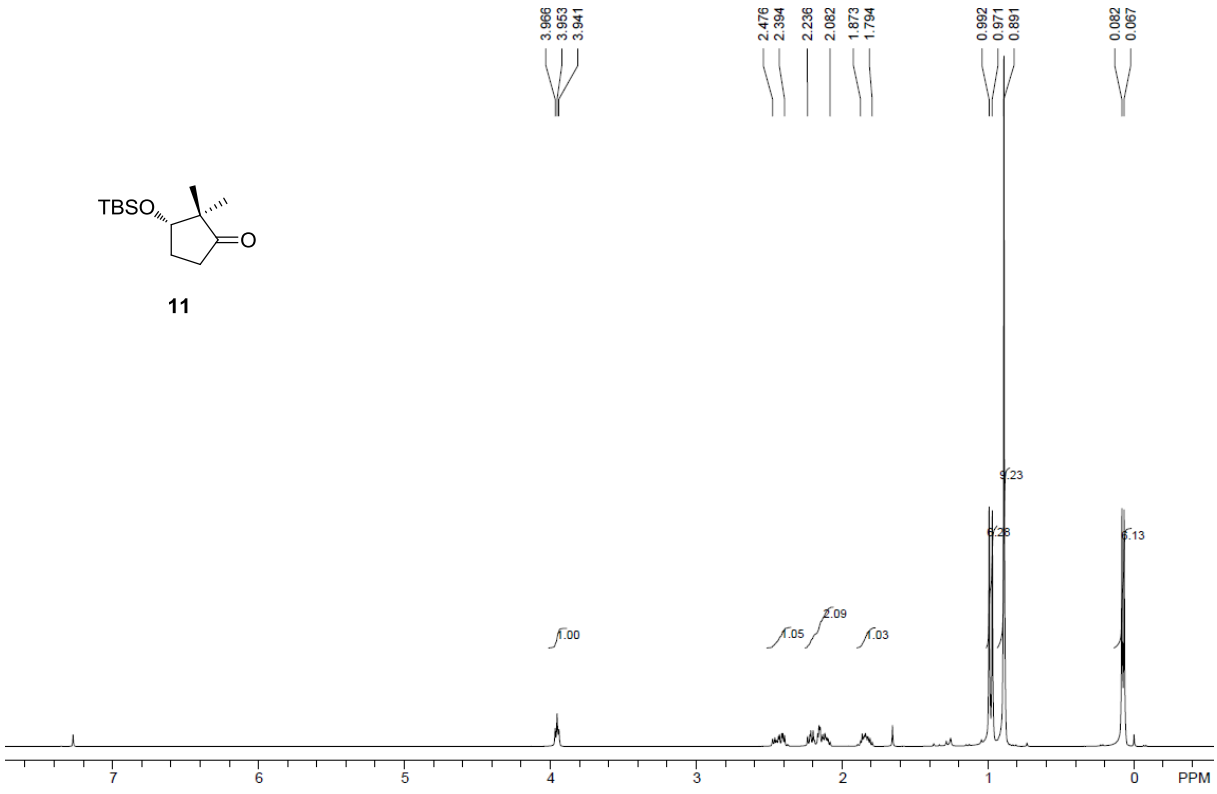
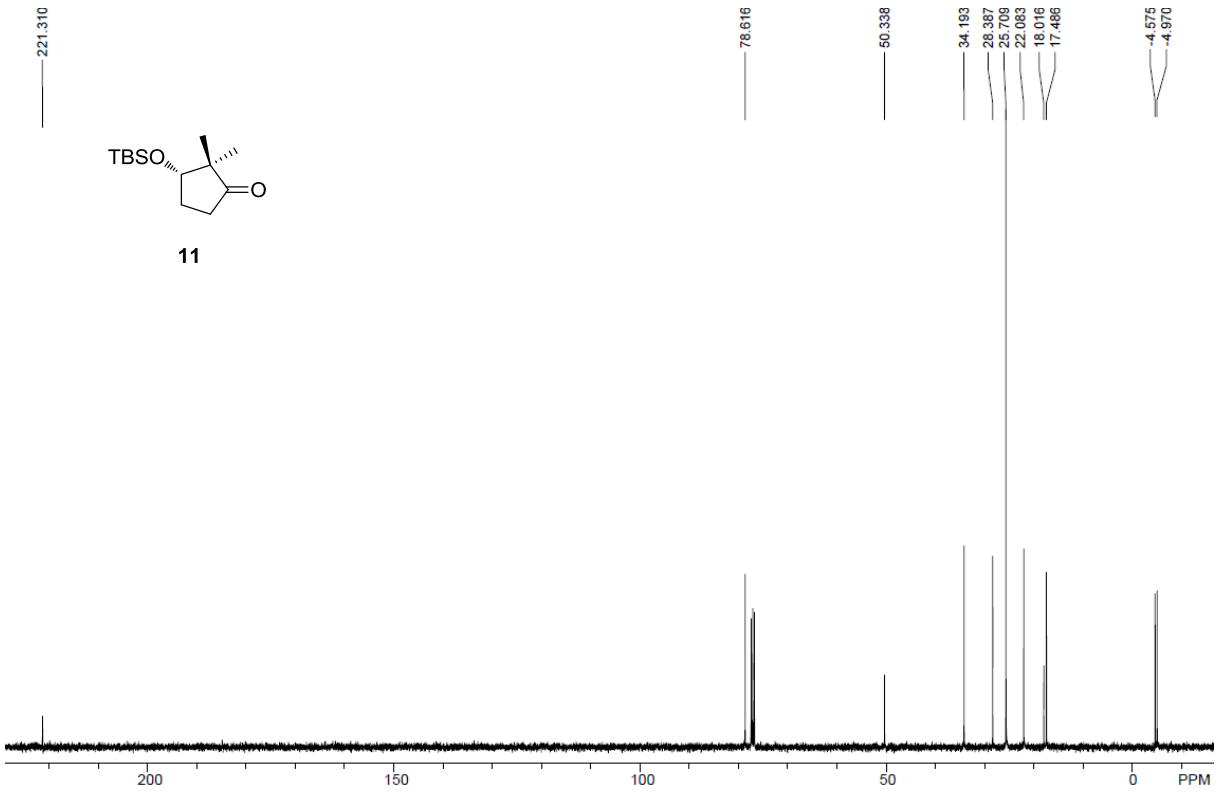
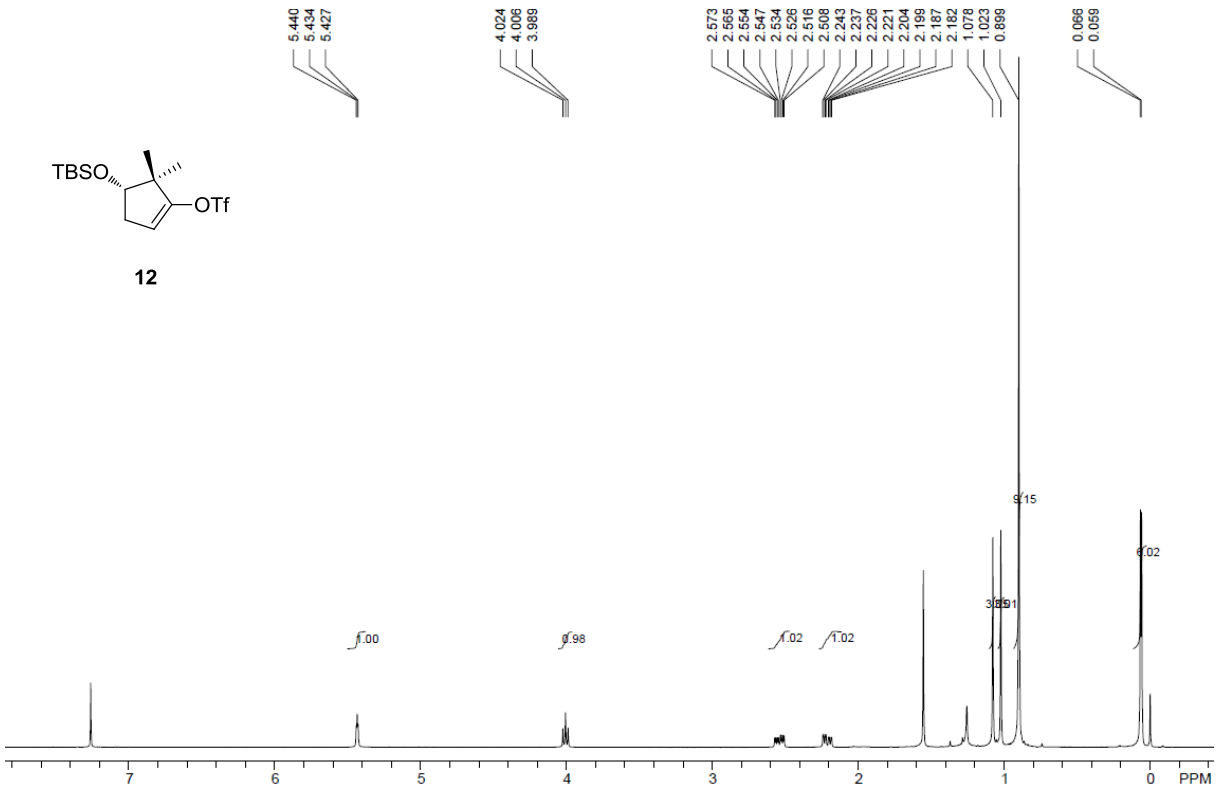
(7) Schinzer, K. C.; Bauer, A.; Schieber, J. *Chem. Eur. J.* **1999**, *5*, 2492-2500.

(8) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; et al. *J. Am. Chem. Soc.* **1997**, *119*, 7974-7991.

4 NMR Spectra



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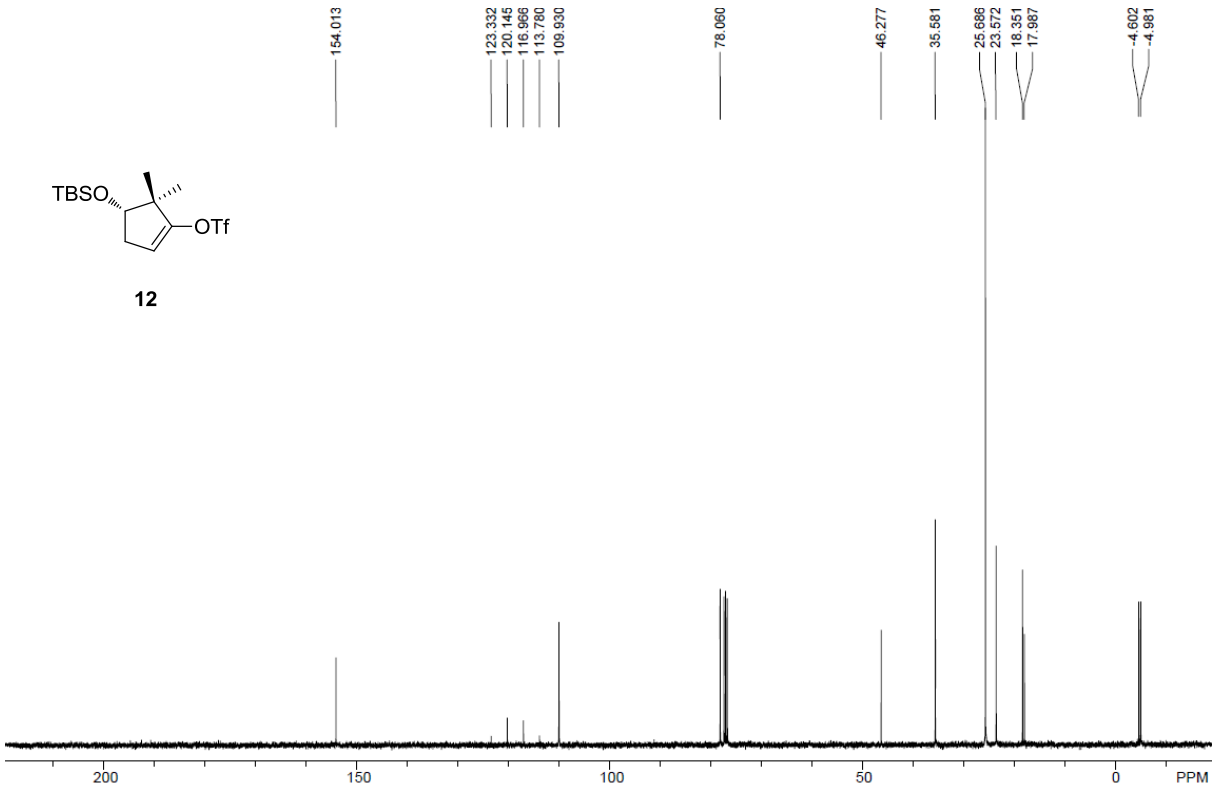
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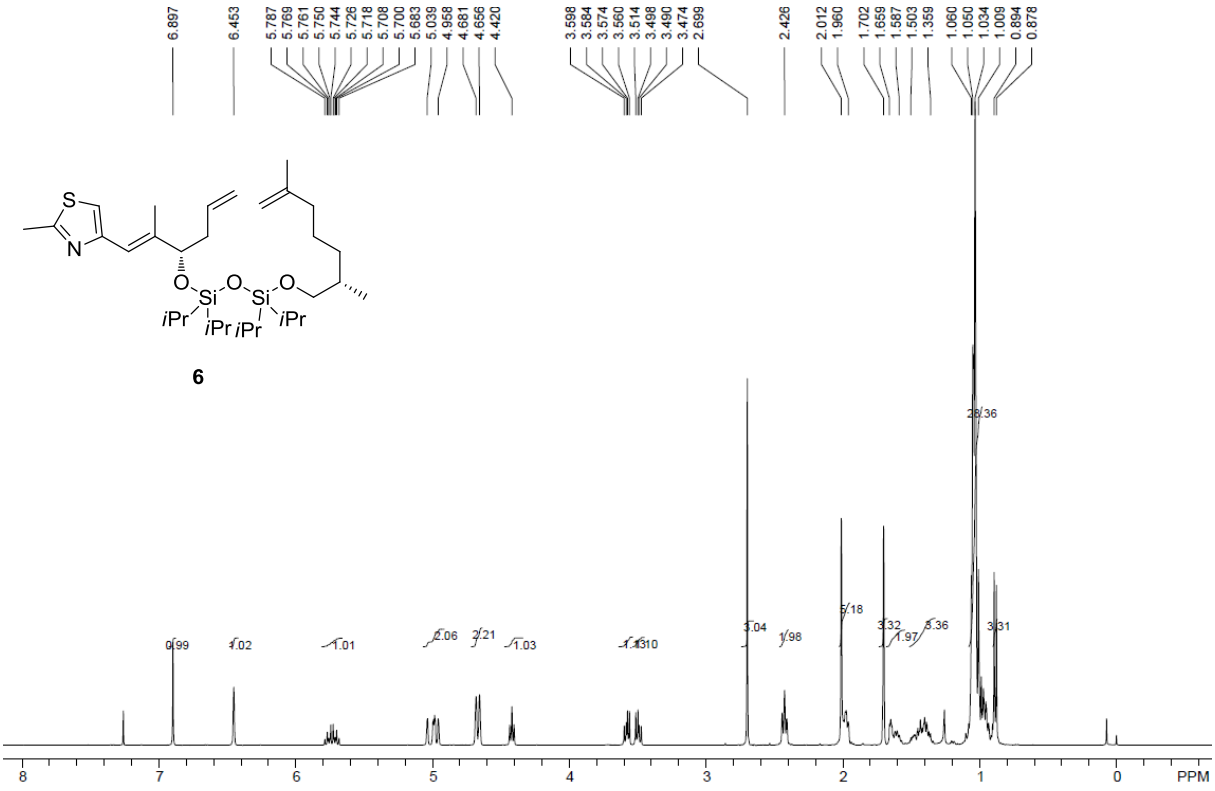
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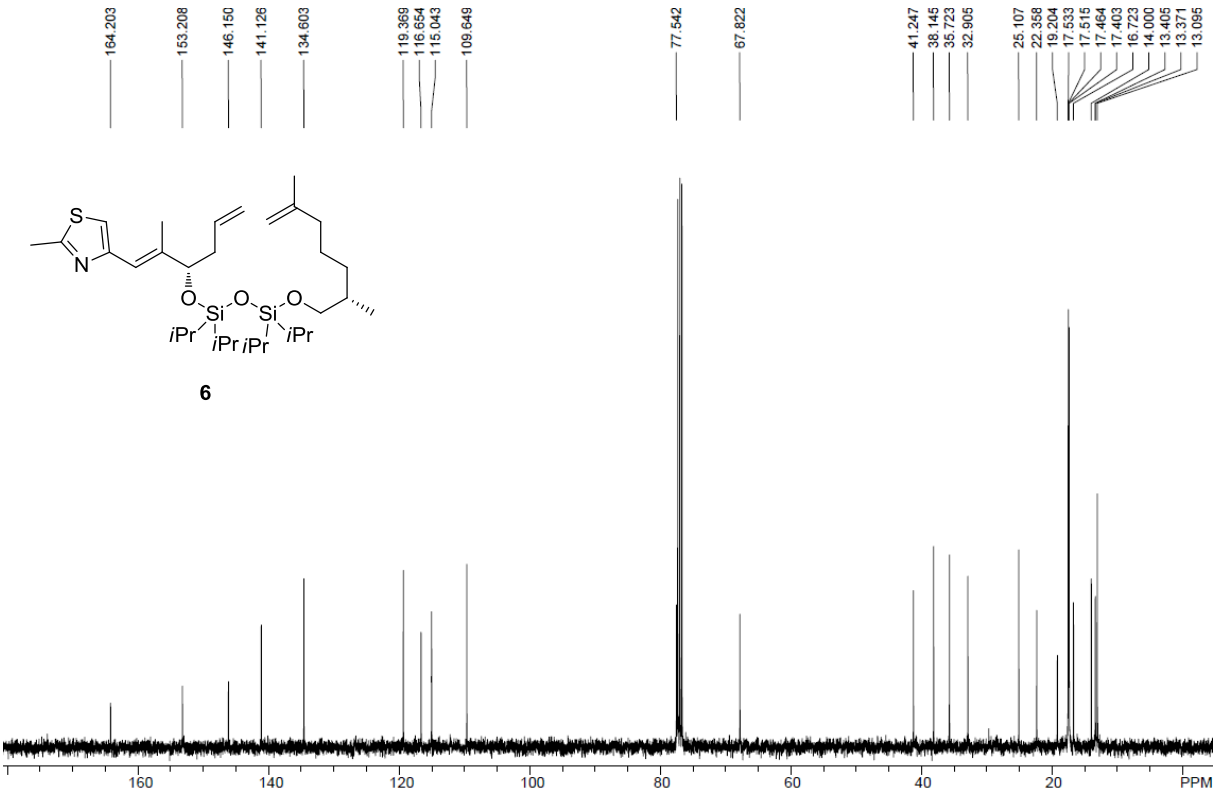
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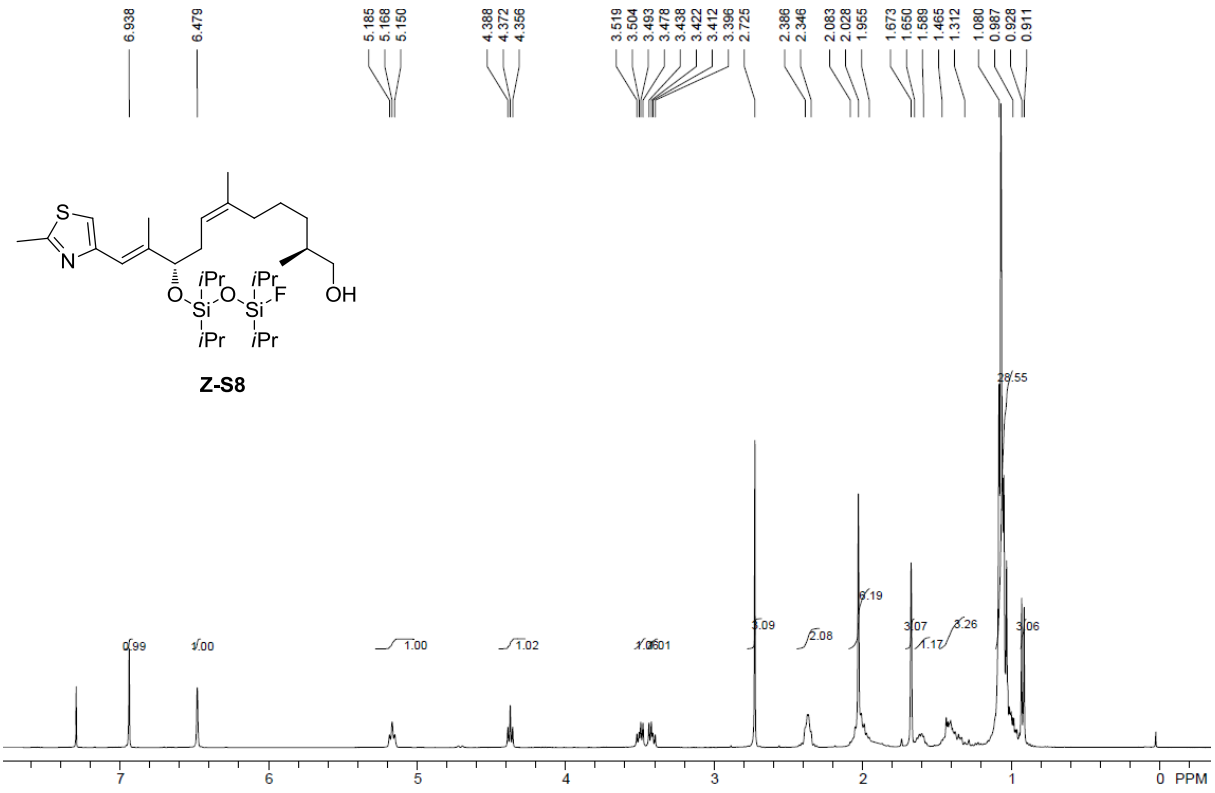
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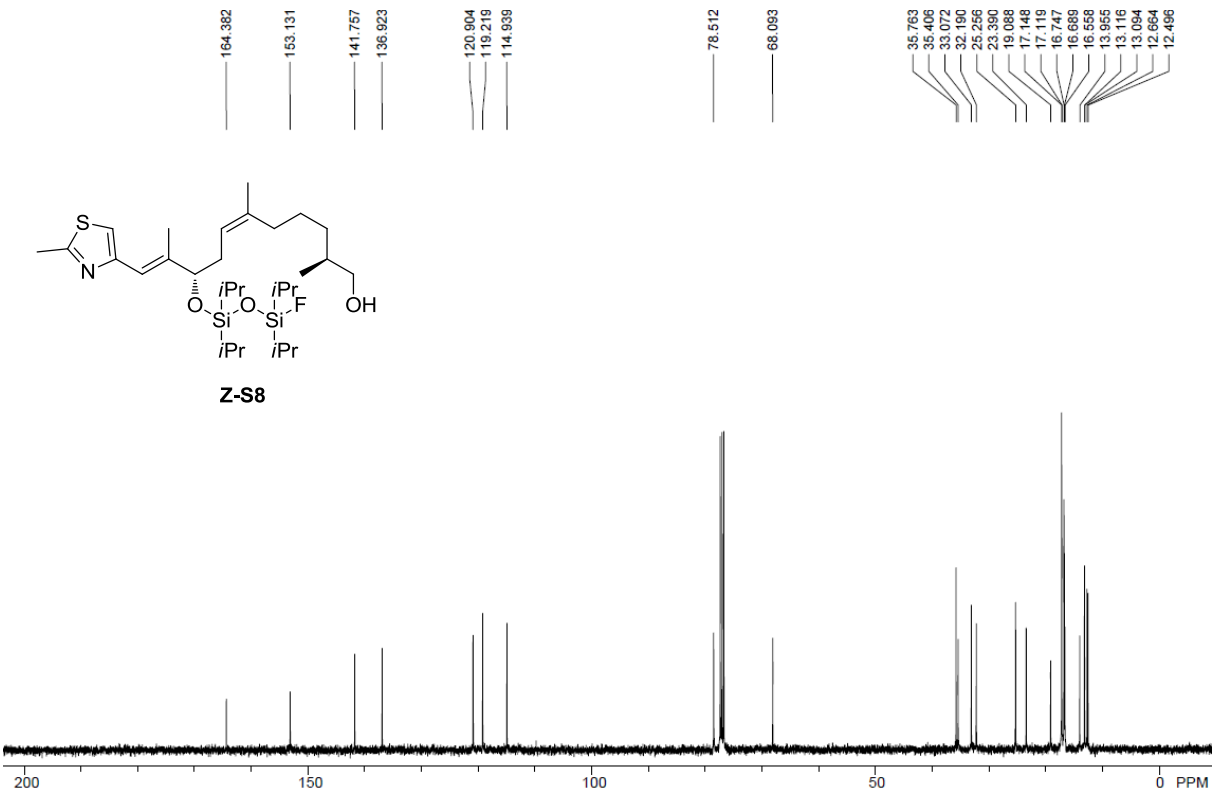
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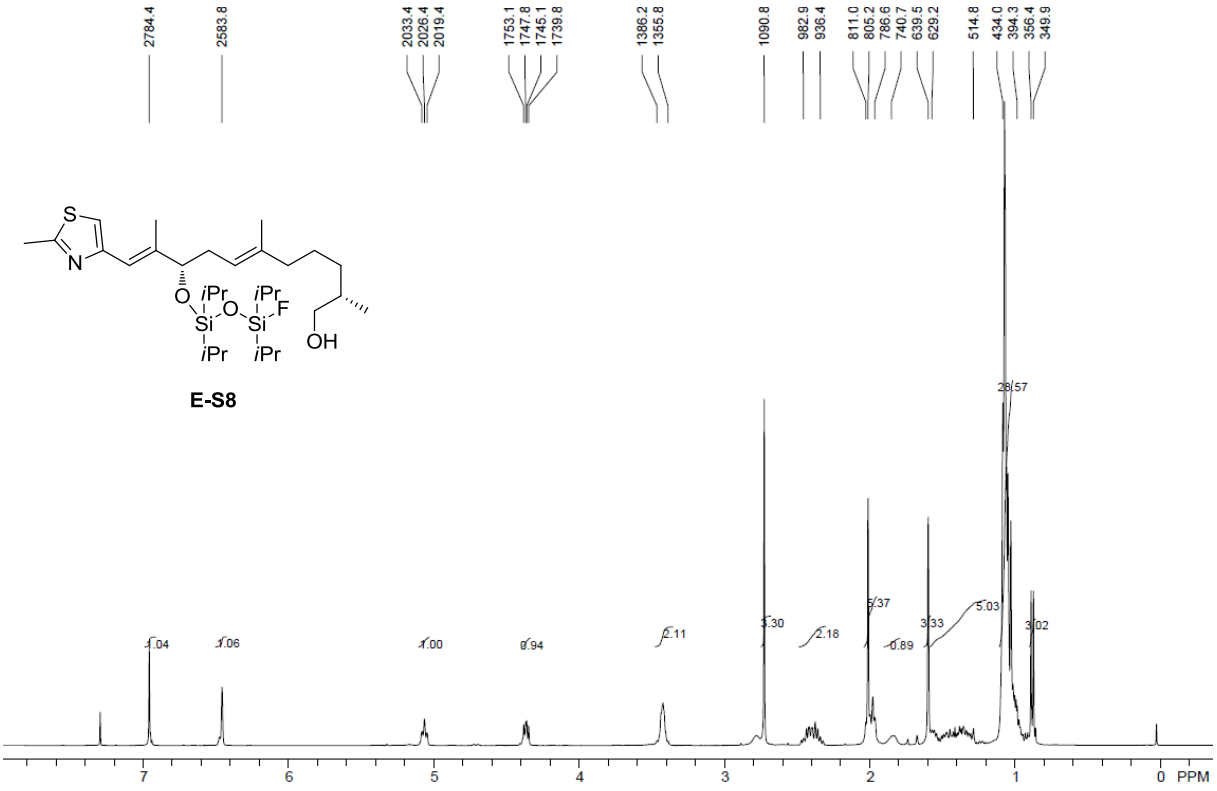
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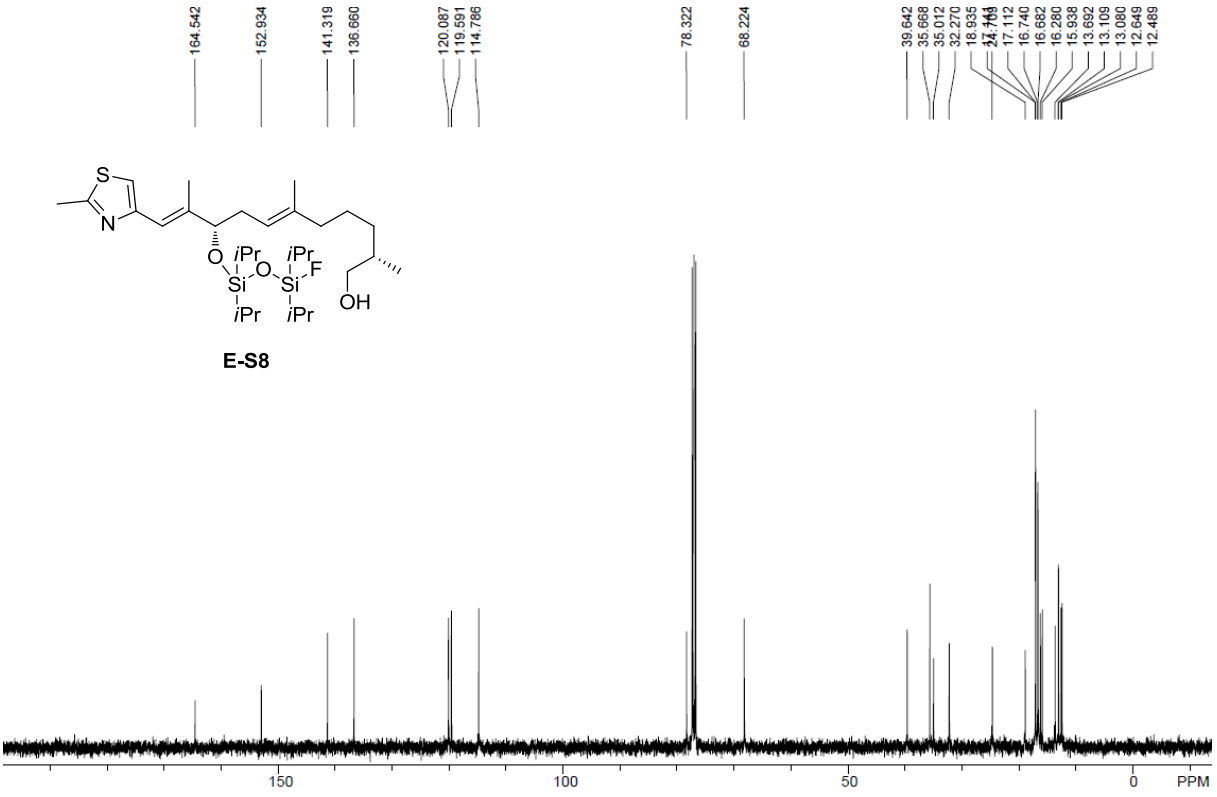
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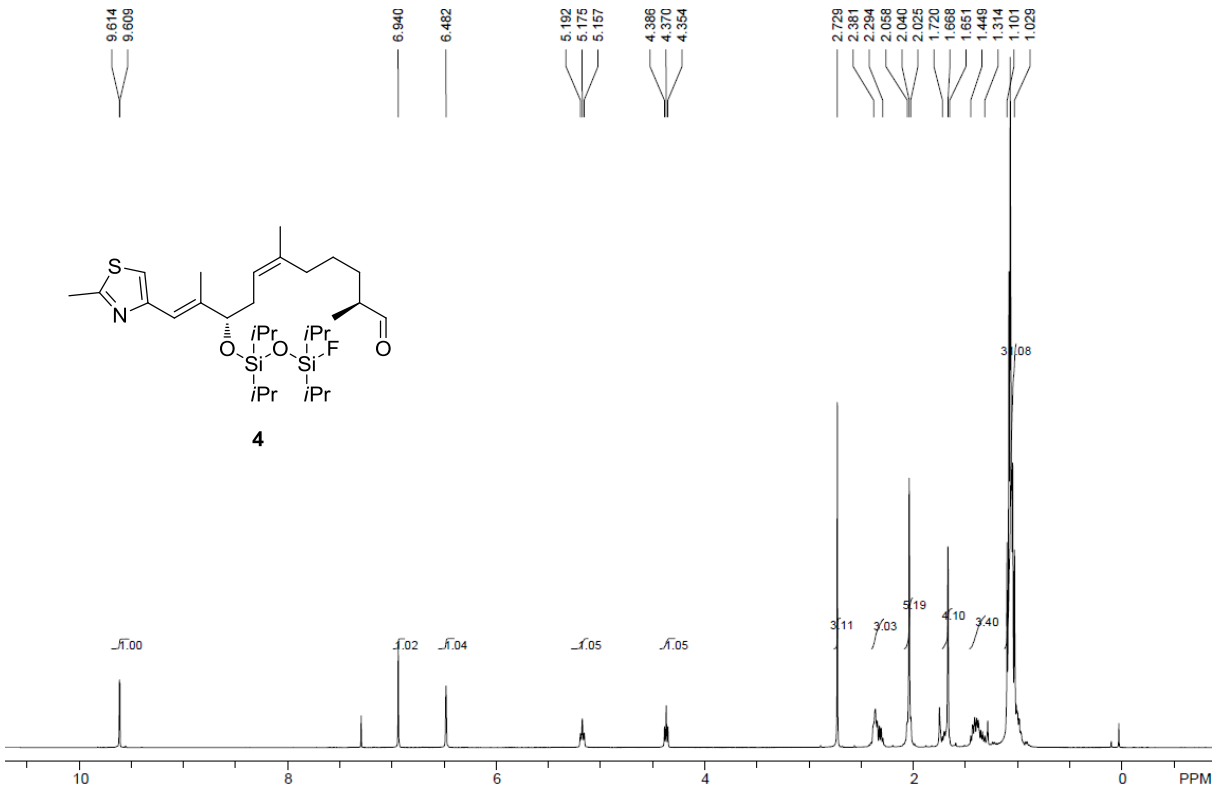
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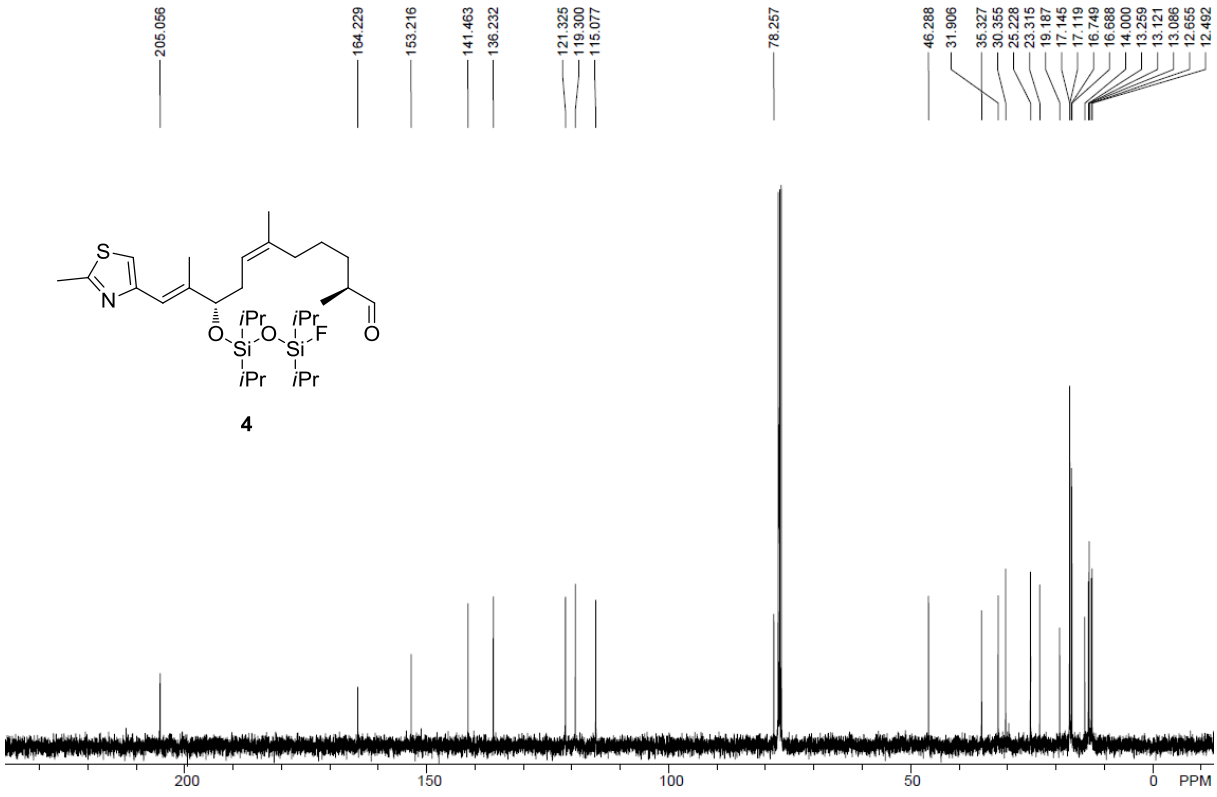
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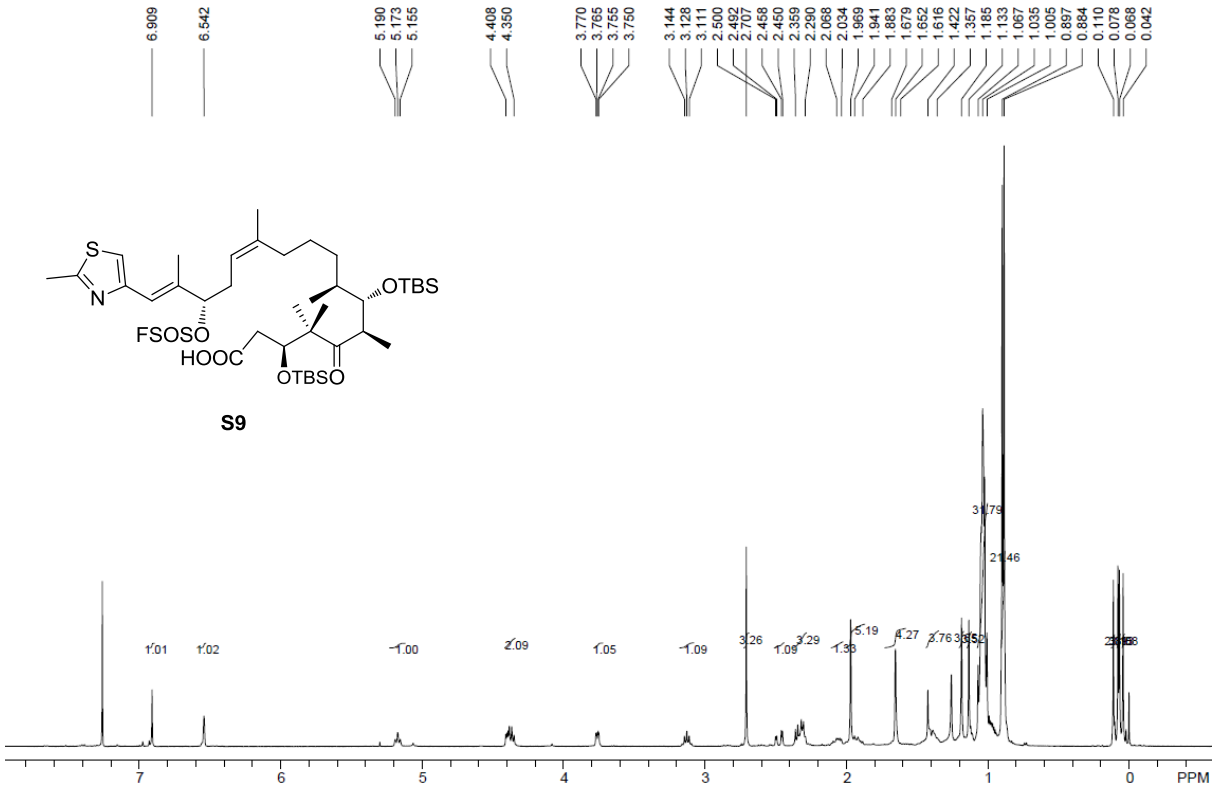
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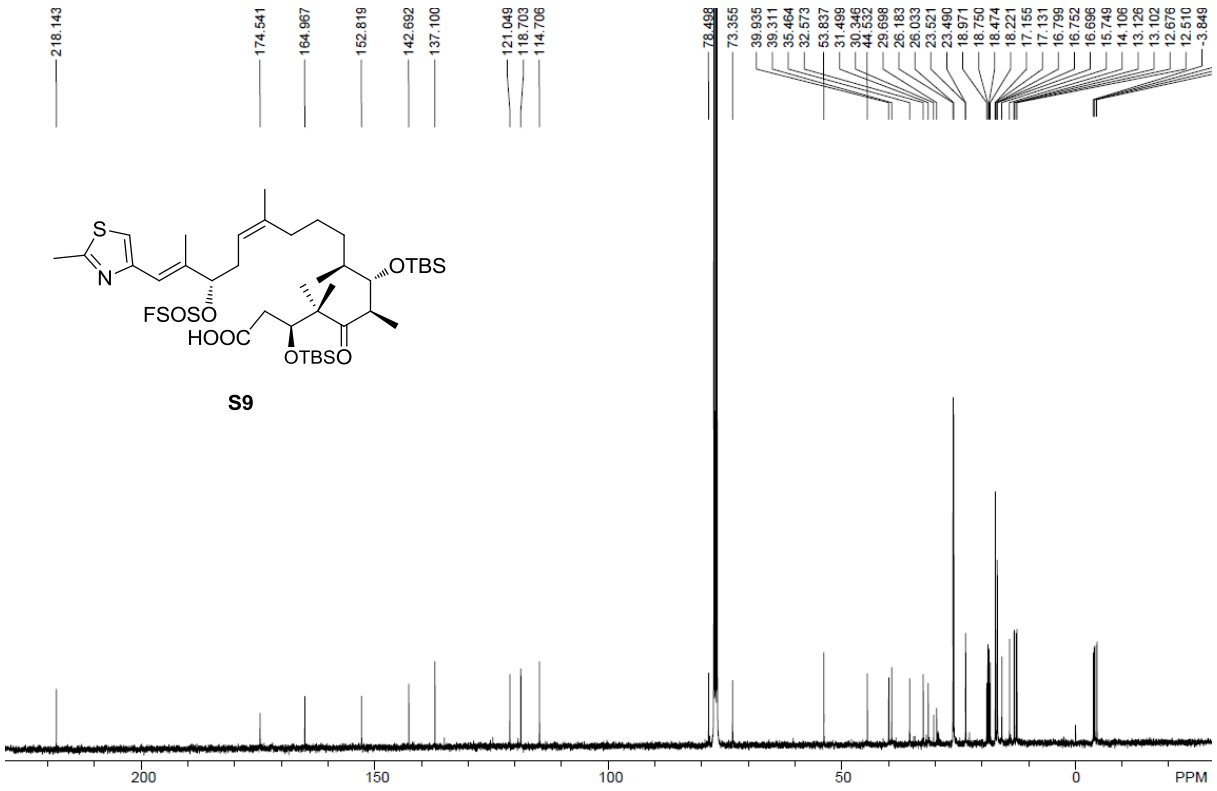
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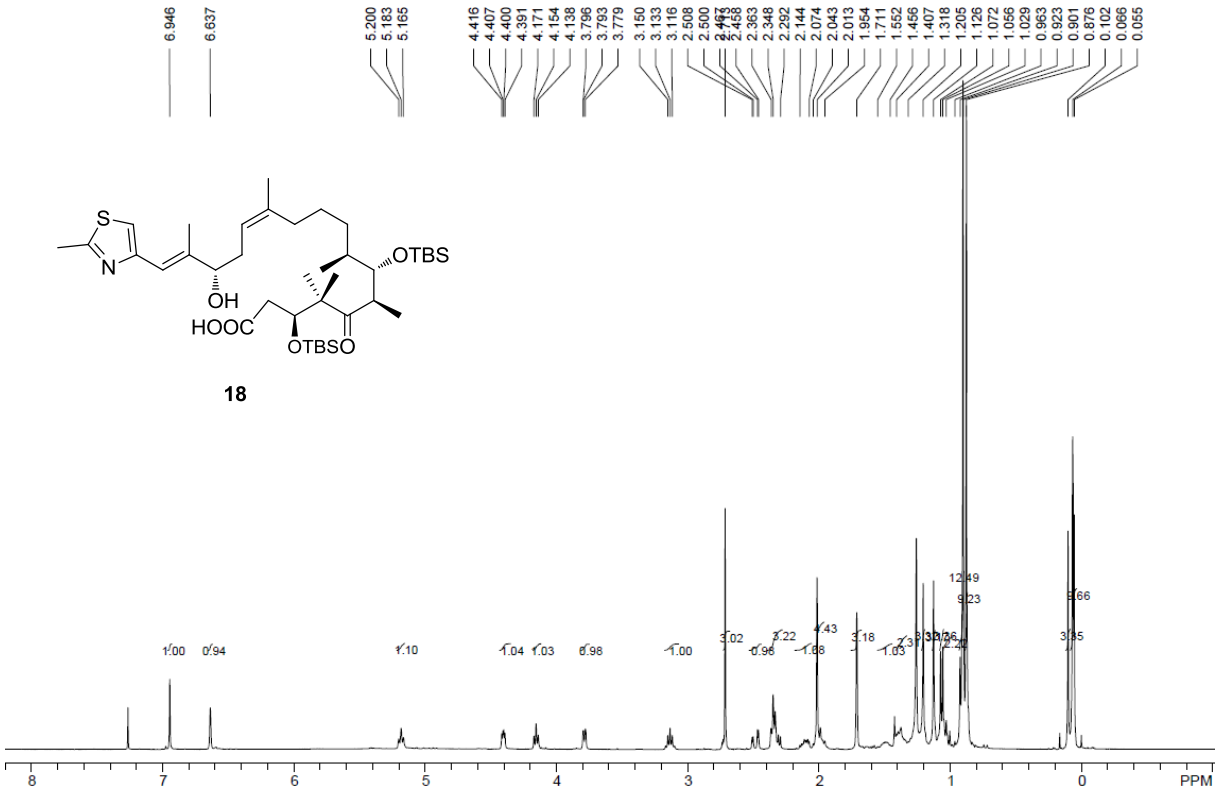
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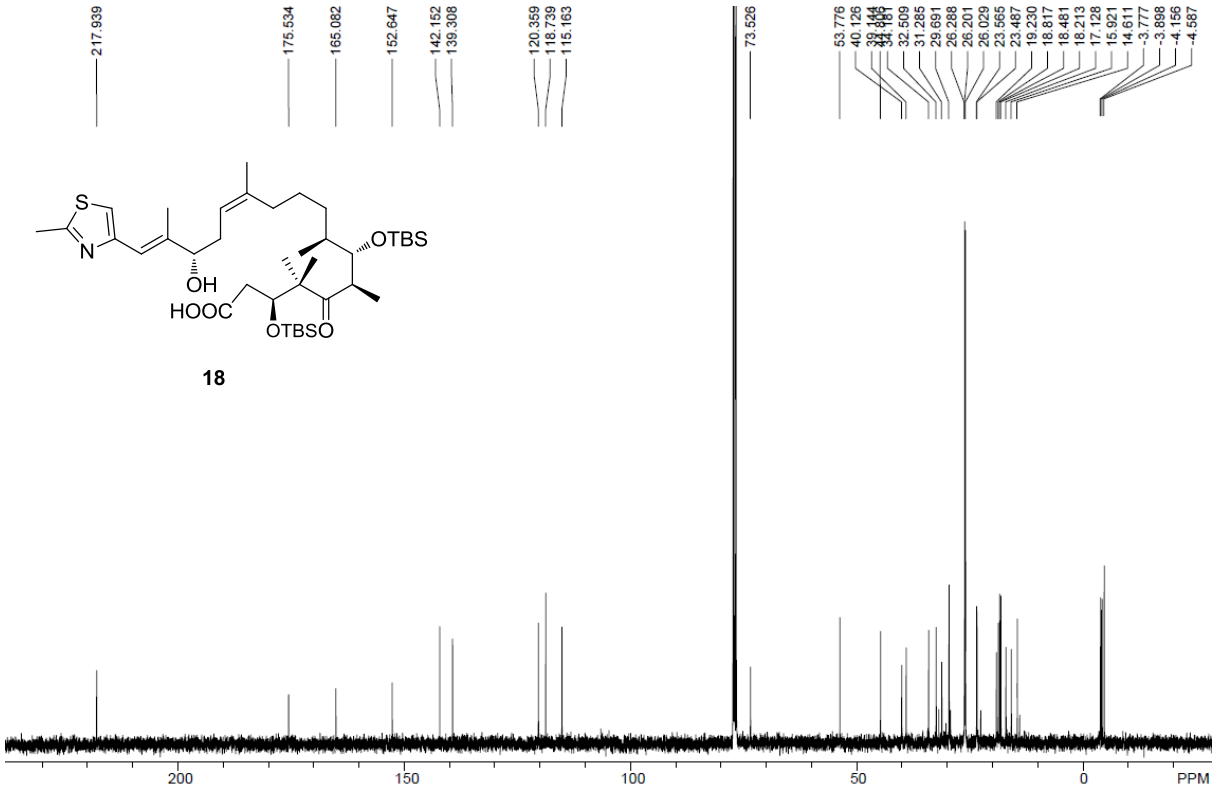
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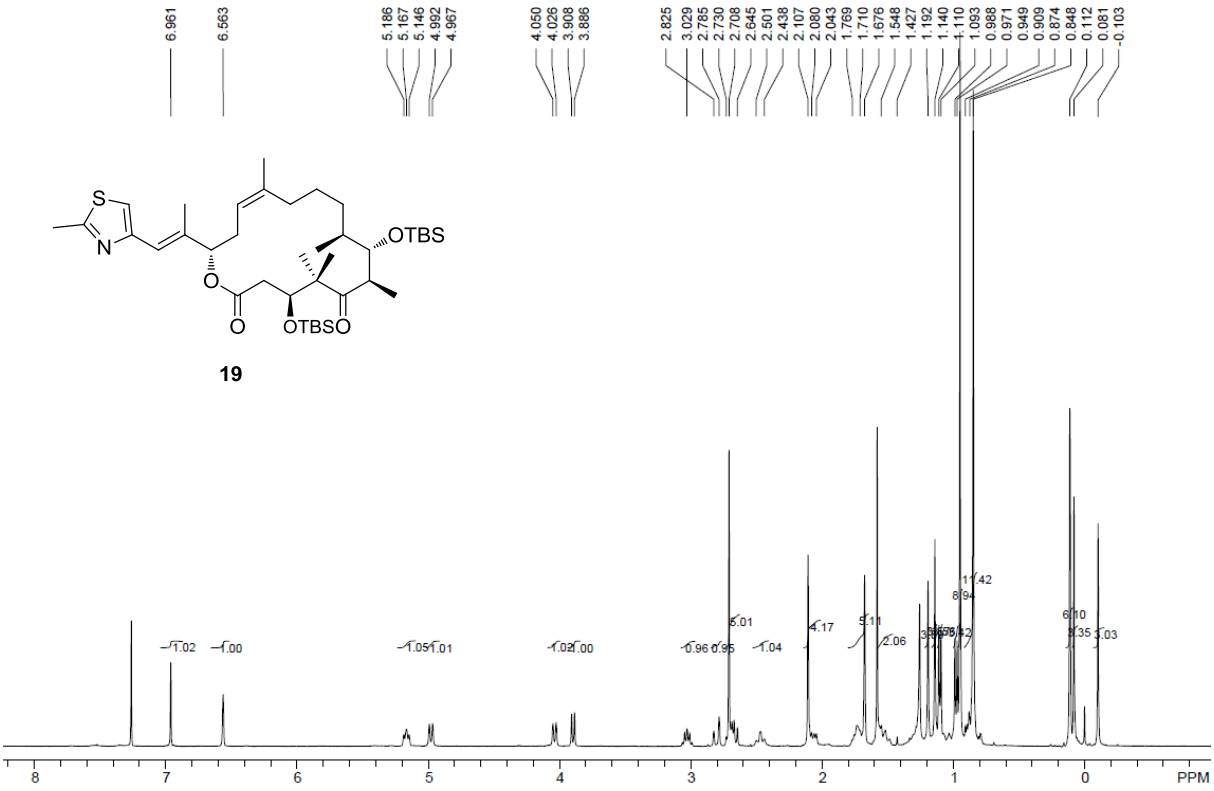
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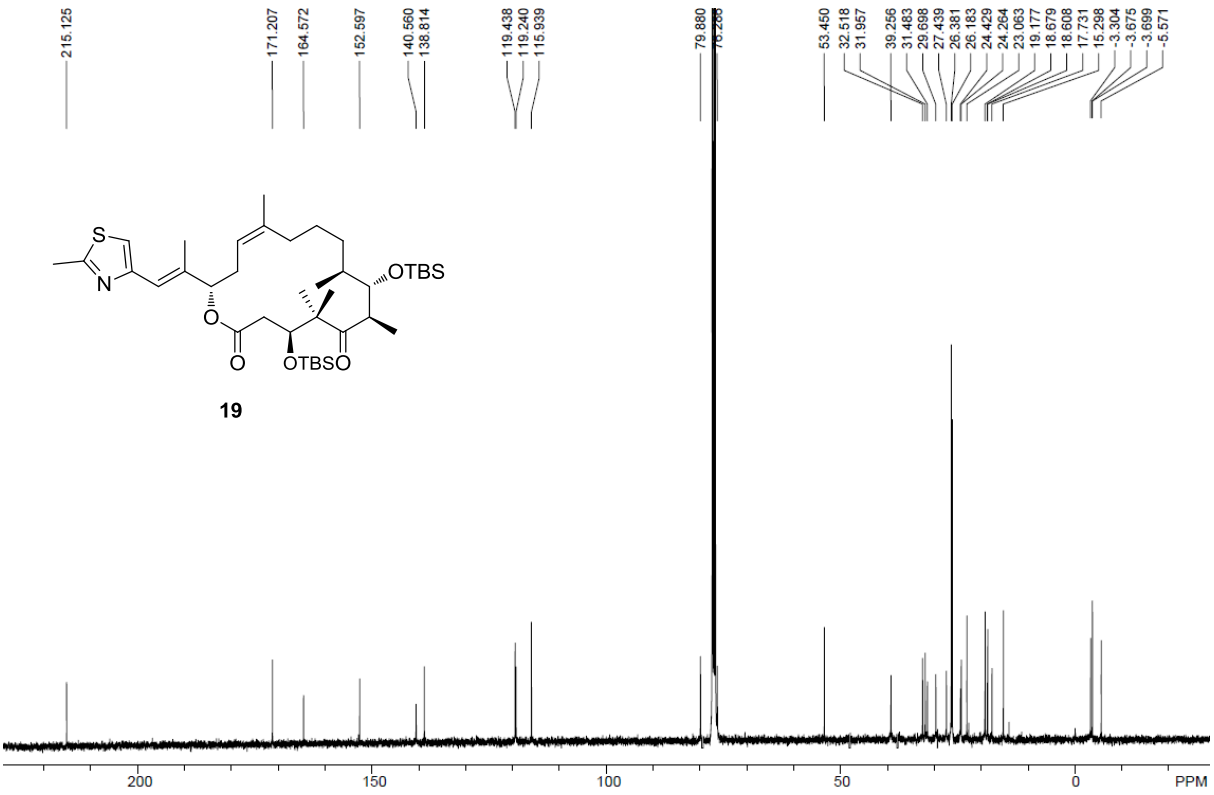
6.563
5.186
5.167
5.146
4.992
4.967
4.050
4.026
3.908
3.886
2.825
3.029
2.785
2.730
2.708
2.645
2.501
2.438
2.107
2.080
2.043
1.769
1.710
1.676
1.548
1.427
1.192
1.140
1.110
1.093
0.988
0.971
0.949
0.909
0.874
0.848
0.112
0.081
-0.103
S
N
O
OTBS
O
OTBSO
1.02
1.00
1.05
1.01
1.02
1.00
0.96
0.95
1.04
5.01
4.17
5.11
2.06
11.42
8.94
6.10
5.35
3.03
8
7
6
5
4
3
2
1
0
PPM

19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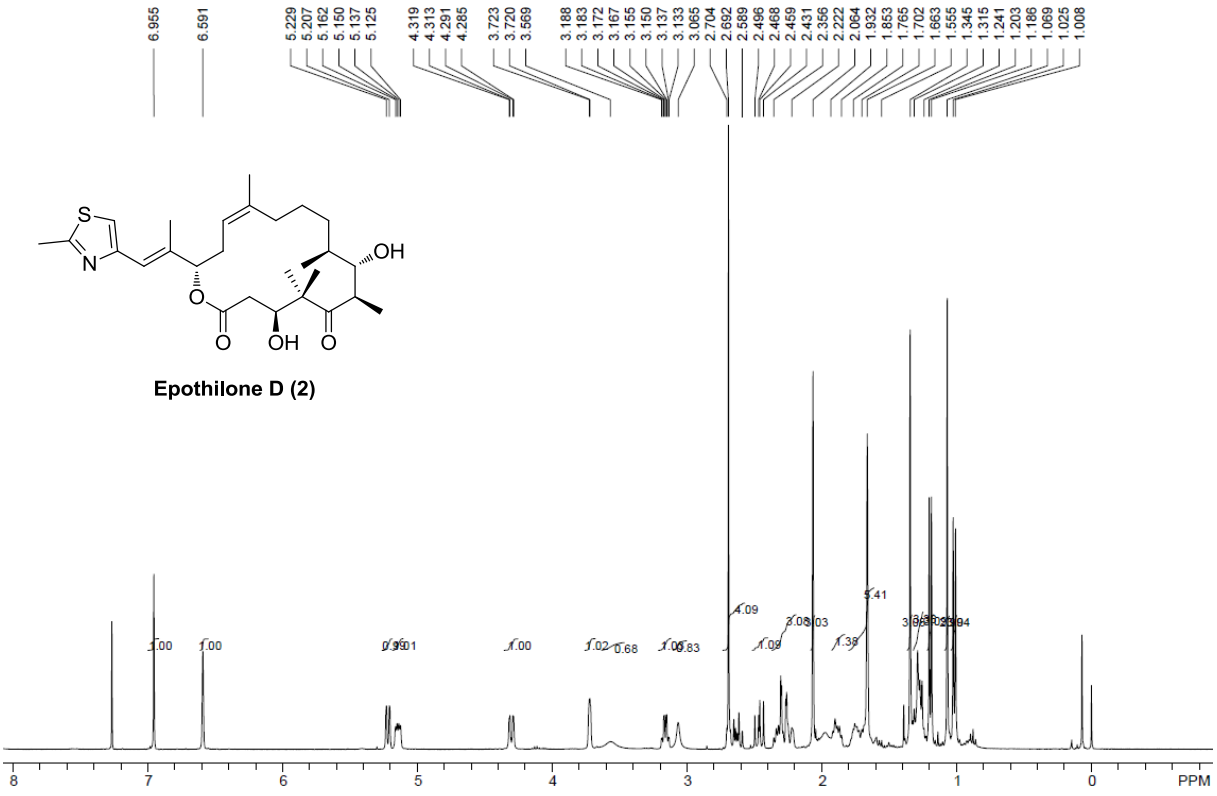
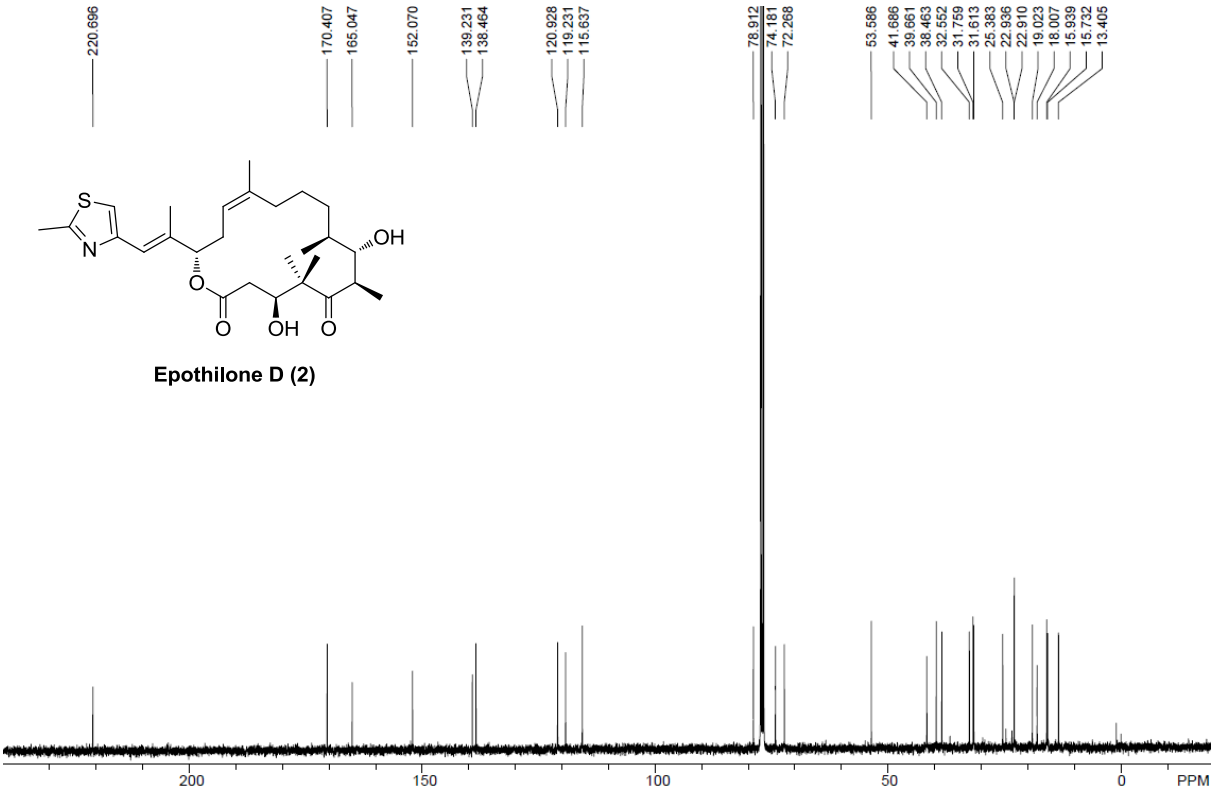
171.207
164.572
152.597
140.560
138.814
119.438
119.240
115.939
79.880
53.450
32.618
31.957
39.256
31.483
29.698
27.439
26.381
26.183
24.429
24.264
23.063
19.177
18.679
18.608
17.731
15.298
-3.304
-3.675
-3.699
-5.571
S
N
O
OTBS
O
OTBSO
200
150
100
50
0
PPM

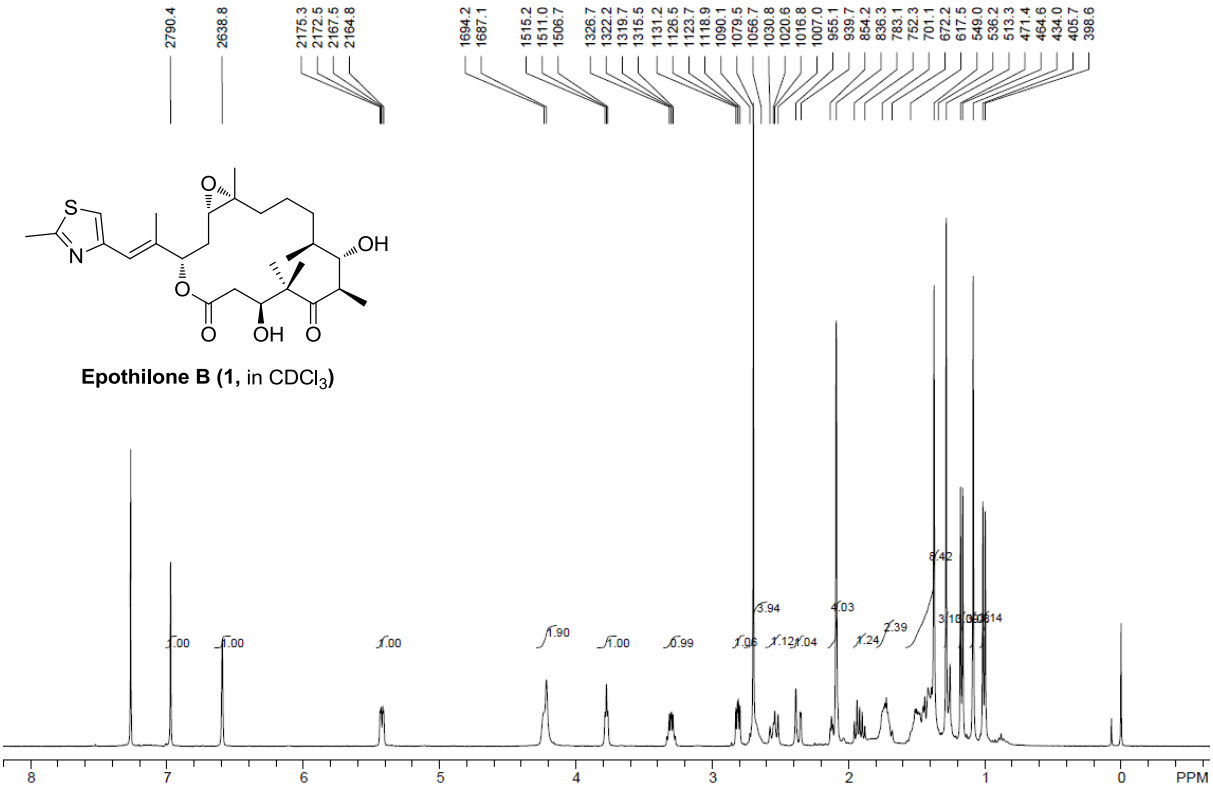
19



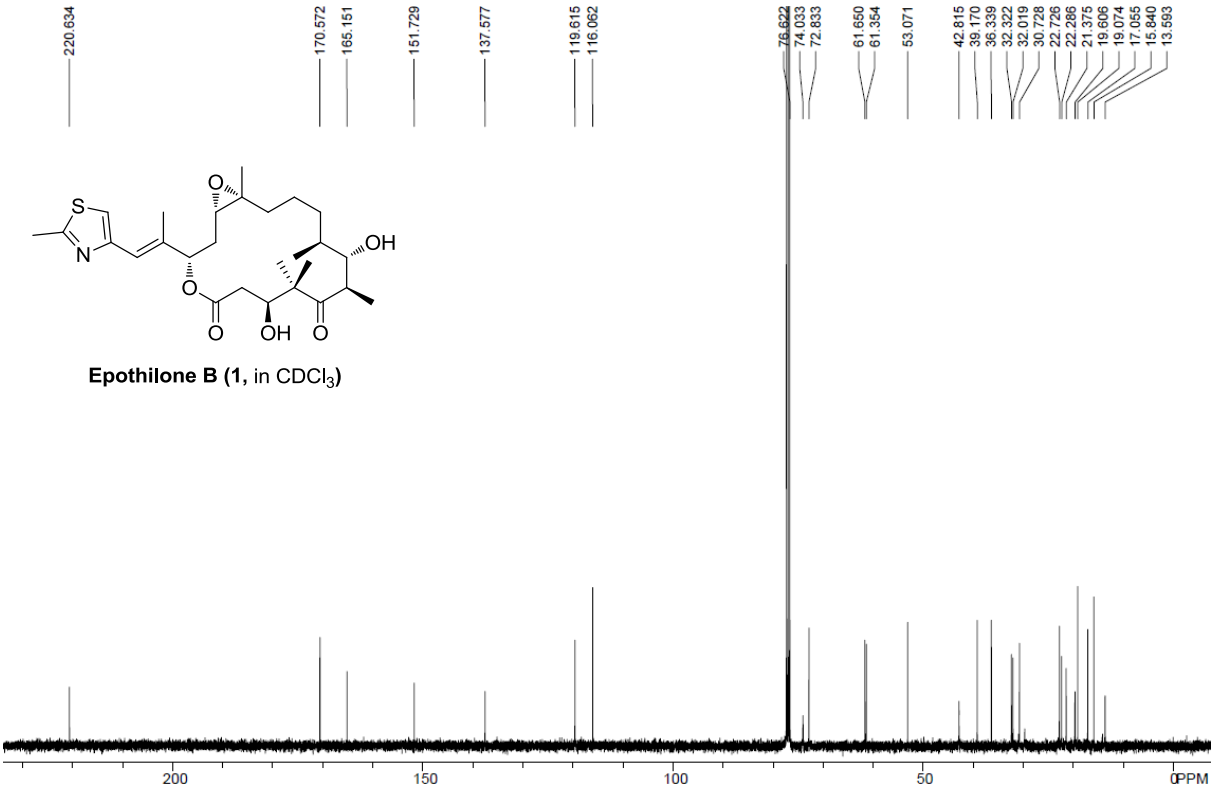
Epothilone D (2)



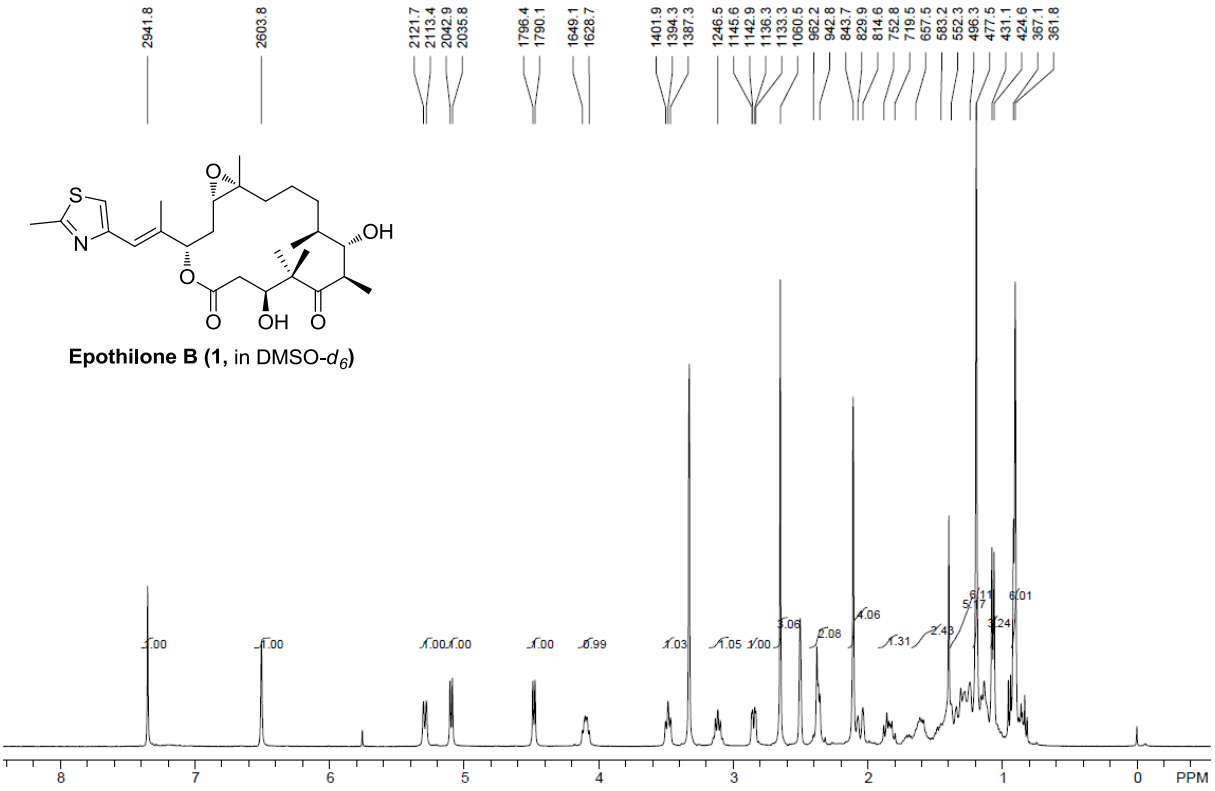
Epothilone D (2)



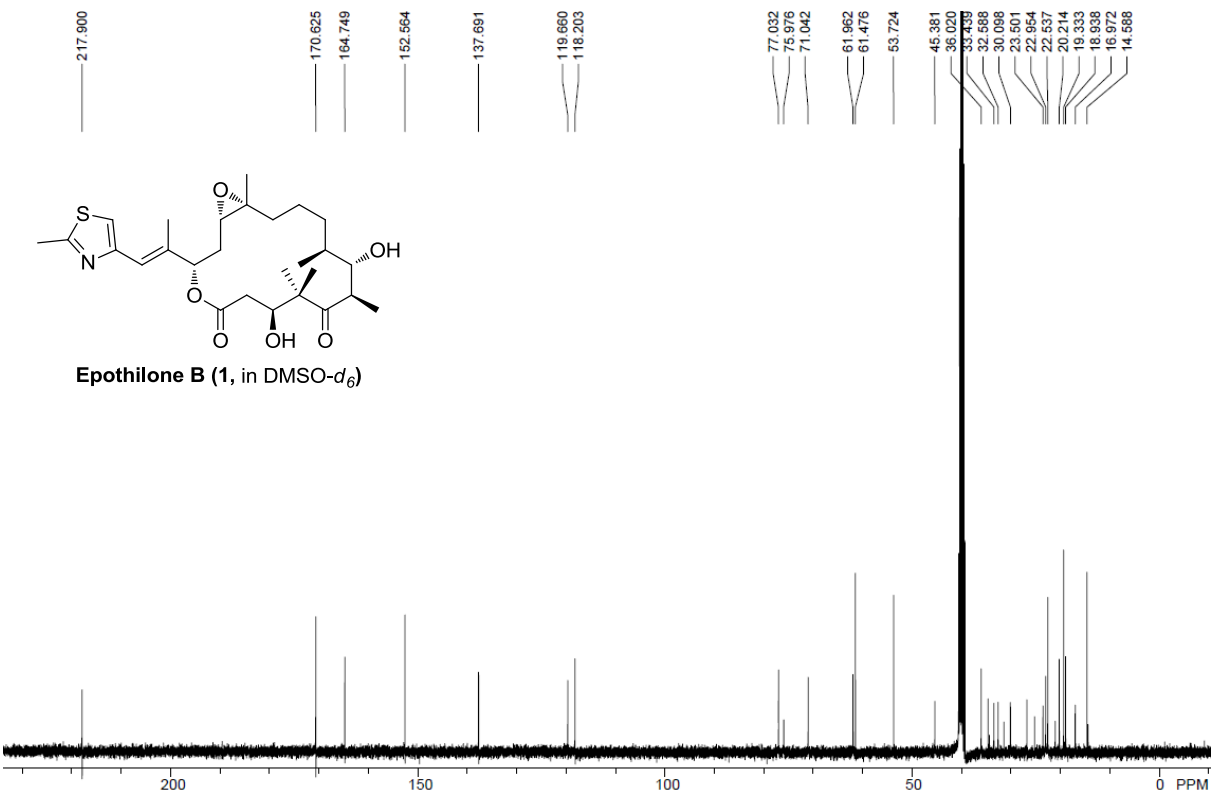
Epothilone B (1, in $CDCl_3$**)**



Epothilone B (1, in $CDCl_3$**)**



Epothilone B (1, in DMSO-d_6**)**



Epothilone B (1, in DMSO-d_6**)**