Supporting Information

Design, Synthesis and Biological Evaluation of EF- and ABEF- Analogs of (+)-Spongistatin 1

Amos B. Smith, III,[a*] Christina A. Risatti,[a] Onur Atasoylu,[a] Clay S. Bennett,[a] Karen TenDyke,[b] and Qunli Xu[c]

[a] *Department of Chemistry, Laboratory for Research on the Structure of Matter, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.*

[b] *Next Generation Systems, Eisai Inc., 4 Corporate Drive, Andover, MA 01810*

[c] *Oncology Product Creation Unit, Eisai Inc., 4 Corporate Drive, Andover, MA 01810*

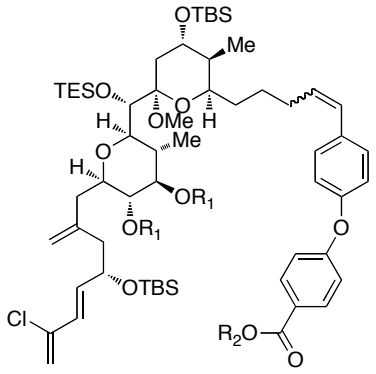
Table of Contents

A. General Methods and Experimental Procedures

i. Materials and Methods

Except as otherwise indicated, all reactions were run under an argon atmosphere in flame- or oven-dried glassware, and solvents were freshly distilled. The argon was deoxygenated and dried by passage through an OXICLEAR™ filter from Aldrich and Drierite tube, respectively. Diethyl ether (Et_2O), tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Aldrich (HPLC purity) and further purified by using the Pure Solve™ PS-400. All other reagents were purchased from Aldrich or Acros and used as received. Reactions were monitored by thin layer chromatography (TLC) either with 0.25-mm Silicycle or 0.25-mm E. Merck (Kieselgel $60F_{254}$, Merck) pre-coated silica gel plates. Silica gel for flash chromatography (particle size 0.040-0.063 mm) was supplied by Silicycle or Sorbent Tehnologies. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^1H and ^{13}C spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26), acetonitrile (δ 1.94) or benzene (δ 7.15) for ^1H and either chloroform (δ 77.0), acetonitrile (δ 1.4, 118.7) or benzene (δ 128.0) for ^{13}C. Infrared spectra were recorded Jasco FTIR-480plus spectrometer. Optical rotations were measured on a Jasco P-2000 polarimeter in the solvent indicated. High resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Center by Dr. Rakesh Kohli on either a VG Micromass 70/70H or VG ZAB-E spectrometer.

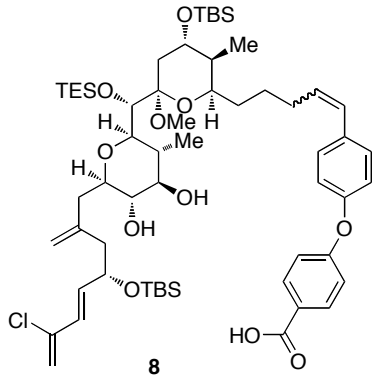
ii. Experiment Section



7 R_1 = TES, R_2 = TIPS

To a flame dried round bottom flask containing activated 4Å molecular sieves was added which was then degassed using the freeze-pump-thaw method (3X) before use in the following reactions. In a separate flask, Wittig salt (+)-**4** (94%, 143.7 mg, 0.096 mmol), which was previously azeotroped with benzene (3X) and dried on high vacuum at 50 °C for 18 h, was dissolved in THF (1.5 mL), cooled to –78 °C. MeLi LiBr complex (1.22 M in ether, 87 μL, 0.11 mmol) was added dropwise, and the resulting orange solution was allowed to stir for 30 min. Aldehyde **5** (78 mg, 0.20 mmol), also azeotroped with benzene (3X) and dried on high vacuum for 2 h, dissolved in THF (1 mL) and added dropwise, via cannula, to the ylide solution. The resulting mixture was allowed to stir for an additional hour at –78 °C and then warmed to room temperature over 2 h. The resulting red solution was diluted with ether and then quenched by the addition of combination of saturated NH_4Cl-saturated $Na_2S_2O_3$ (4:1). The aqueous phase was extracted with ether (3X) and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (5:95) as an elutant afforded Wittig product **7** (66 mg, 49%) as a mixture of olefin isomers, (*Z*:*E* = 4:1). (* indicates data for minor isomer): IR (neat) 2952 (s), 2876 (s), 1701 (m), 1595 (m), 1500 (m), 1464 (m), 1290 (m), 1244 (m), 834 (m), 739 (m) cm^{-1};

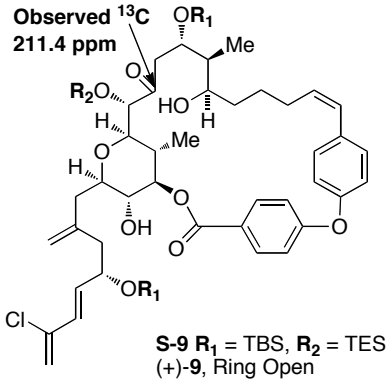
^{1}H NMR (500 MHz, C_6D_6) δ 8.18-8.14 (m, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.86-6.82* (m, 4H), 6.73* (d, *J* = 8.9 Hz, 2H), 6.50 (dd, *J* = 14.9, 4.8 Hz, 1H), 6.45 (d, *J* = 14.9 Hz, 1H), 6.41 (d, *J* = 11.5 Hz, 1H), 6.12* (ddd, *J* = 15.8, 7.1, 7.1 Hz, 1H), 5.67 (ddd, *J* = 11.5, 7.2, 7.2 Hz, 1H), 5.17 (s, 1H), 5.14 (s, 1H), 5.13 (s, 1H), 5.06 (s, 1H), 4.54-4.49 (m, 1H), 4.36-4.32* (m, 1H), 4.27 (ddd, *J* = 8.6, 4.7, 2.0 Hz, 1H), 3.97-3.86 (m, 2H), 3.61-3.48 (m, 4H), 3.19* (s, 3H), 3.14 (s, 3H), 2.76-2.67 (m, 2H), 2.56 (dd, *J* = 13.0, 7.4 Hz, 1H), 2.42-2.30 (m, 4H), 2.25-2.19* (m), 1.97 (ddd, *J* = 10.7, 7.0, 7.0 Hz, 1H), 1.82-1.70 (m, 3H), 1.58-1.27 (m, 6H), 1.19-1.07 (m, 57H), 1.04 (s, 9H), 0.97 (d, 3H), 0.84-0.77 (m, 18H), 0.29* (s, 3H), 0.25* (s, 3H), 0.24 (s, 3H), 0.17 (s, 3H), 0.15* (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 166.0, 162.6, 155.3, 144.7, 139.2, 134.8, 133.2, 133.1, 131.1, 127.0, 126.9, 126.2, 120.9, 120.4, 119.4, 118.2, 118.0, 115.9, 115.4, 102.0, 82.1, 81.1, 78.1, 77.7, 72.2, 72.0, 71.6, 67.8, 47.5, 47.3, 40.7 (2), 39.4, 39.3, 33.4, 30.8, 30.6, 30.6, 29.6, 27.5, 26.5 (2), 18.9, 18.7, 18.5, 16.5, 12.8, 11.0, 7.9, 7.8, 7.8, 6.5, 6.5, -3.7, -3.9, -4.1, -4.2; high resolution mass spectrum (ESI$^+$) *m/z* 1505.8826 [(M+Na)$^+$; calcd for $C_{80}H_{143}ClO_{11}Si_6Na$: 1505.8832].



8

To a solution of Wittig product **7** (80 mg, 0.054 mmol) in THF (10.8 mL) at 0 °C was added TBAF (1M in THF, 0.16 mL, 0.16 mmol) over 1 hour via syringe pump. After an additional 2 h at 0 °C, the reaction mixture was diluted with ether and washed with 1M $KHSO_4$ and brine. The combined aqueous phases were then back extracted with ether (2X). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (20:80-40:60) with 0.5 % AcOH as an elutant afforded *seco*-acid **8** (40 mg, 67%) as a mixture of olefin isomers. Note: toluene was added to the collection flask before concentrating to avoid the *seco*-acid being exposed to neat AcOH (* Indicates data for minor isomer): IR (neat) 3391 (br s), 2924 (s), 1692 (m), 1245 (m), 1097 (m), 835 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.11-8.03 (m, 2H), 7.22-7.18 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.79* (d, *J* = 8.9 Hz, 2H), 6.48-6.36 (m, 3H), 6.13* (ddd, *J* = 15.4, 7.5, 7.5 Hz, 1H), 5.68 (ddd, *J* = 11.4, 7.0, 7.0 Hz, 1H), 5.18 (s, 1H), 5.10 (s, 1H), 5.06 (s, 1H), 5.05 (s, 1H), 4.48-4.42 (m, 1H), 4.34-4.30* (m, 1H), 4.28-4.23 (m, 1H), 3.98-3.96* (m, 1H), 3.96-3.92 (m, 1H), 3.88* (s, 1H), 3.85 (s, 1H), 3.35-3.26 (m, 2H), 3.18-3.12 (m, 1H), 3.08 (s, 3H), 2.95 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.71 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.59-2.48 (m, 2H), 2.44-2.28 (m, 4H), 2.25-2.19* (m, 1H), 1.85-1.66 (m, 5H), 1.63-1.20 (m, 5H), 1.12 (t, *J* = 8.0 Hz, 9H), 1.09 (s, 9H), 1.03 (s, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 7.4 Hz, 3H), 0.84-0.71 (m, 6H), 0.26* (s, 3H), 0.24 (s, 3H), 0.16* (s, 3H), 0.15 (s, 6H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.2, 163.2, 155.0, 144.2, 139.3, 139.2, 135.0, 133.3, 133.2, 131.2, 131.1, 130.1, 126.8, 124.6, 121.0, 120.6, 118.1, 117.8, 116.1, 115.5, 102.0, 79.6, 79.2, 79.1, 76.1, 72.6, 71.6, 71.5, 67.7, 67.6, 47.3, 46.7, 40.0, 39.4, 33.4, 30.9, 30.6, 29.5, 27.5, 26.5, 26.5, 18.9, 18.7, 4.1, 11.0, 7.9, 6.5, -3.7, -3.9, -4.1, -4.2; high resolution

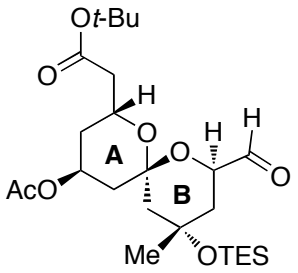
mass spectrum (ESI$^+$) *m/z* 1121.5763 [(M+Na)$^+$; calcd for $C_{59}H_{95}ClO_{11}Si_3Na$: 1121.5768].



Step a. To *seco*-acid **8** (30.3 mg, 0.028 mmol) dissolved in toluene (2.8 mL) was added a solution of *i*-Pr_2NEt (0.4 M in toluene, 1.05 mL, 0.42 mmol) followed by a solution of 2,4,6-TBCCl (0.4 M in toluene, 0.63 mL, 0.25 mmol). The reaction mixture was allowed to stir at room temperature for 5.5 h before being further diluted with toluene (8.0 mL) and than added dropwise, via syringe pump over 24 h to a second flask containing DMAP (68 mg, 0.56 mmol) and toluene (40.5 mL) heated to 90 °C. After the addition, the flask containing seco-acid residue was rinsed with toluene (2.8 mL) and transferred over 12 h to the reaction mixture via a syringe pump, followed by a third time rinsing with toluene (1.9 mL) and adding over 2 h. After the third rinse, the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with ether and then quenched by the addition of saturated $NaHCO_3$. The layers were separated and the organic layer rinsed with brine.. The combined aqueous layers were then back extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:99 to 9:91) as an elutant afforded lactone **S-9** (18.2 mg, 62%) with an impurity which could not

be separated. **Step b.** To macrolactone **S-9** (24.3 mg, 0.022 mmol) in acetonitrile (1.6 mL). At –20 °C was added a freshly prepared solution of aqueous HF in acetonitrile (1.6 mL) via syringe pump over 2 hours. Note: The HF solution was prepared by the dilution of aqueous HF (48%, 2.5 mL) with acetonitrile (10 mL). After the addition was complete, the reaction mixture was allowed to stir for an additional 17 h at –20 °C, before being quenched by the dropwise addition of Et_3N (2.0 mL). The reaction mixture was then warmed to room temperature, at which point it was diluted with a mixture of ethyl acetate and methylene chloride (2:1) and washed with saturated $NaHCO_3$ and brine. The aqueous layers were back extracted with ethyl acetate and methylene chloride (2:1 X2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using methanol-methylene chloride (2:98 to 3:97) as an elutant afforded EF analog (+)-**9** (9.6 mg, 42%). $[\alpha]_D^{20}$ +8.57 (*c* 0.035, C_6H_6); IR (neat) 3420 (br s), 2929 (s), 1708 (s), 1594 (m), 1498 (s), 1234 (s), 1097 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.11 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 11.3 Hz, 1H), 6.37 (dd, *J* = 14.9, 1.2 Hz, 1H), 6.27 (dd, *J* = 15.0, 4.7 Hz, 1H), 5.70 (ddd, *J* = 11.3, 7.5, 7.5 Hz, 1H), 5.16 (s, 1H), 5.01 (s, 1H), 4.99 (s, 1H), 4.91 (s, 1H), 4.67 (dd, *J* = 7.4, 6.8 Hz, 1H), 4.30-4.25 (m, 3H), 3.54-3.47 (m, 2H), 3.45-3.41 (m, 1H), 3.29 (ddd, *J* = 8.2, 8.2, 3.5 Hz, 1H), 3.22 (dd, *J* = 17.2, 9.5 Hz, 1H), 2.87-2.72 (m, 1H), 2.64 (dd, *J* = 14.8, 3.1 Hz, 1H), 2.32-2.13 (m, 6H), 1.74 (dd, *J* = 17.2, 3.2 Hz, 1H), 1.41-1.19 (m, 5H), 1.05-0.80 (m, 7H), 0.74 (d, *J* = 7.4 Hz, 3H); ^1H NMR (500 MHz, CD_3CN) δ 7.93 (d, *J* = 8.9 Hz, 2H), 8.52 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 11.3 Hz, 1H), 6.41 (dd, *J* = 15.0, 1.1 Hz, 1H), 6.15 (dd, *J* = 15.0, 5.3 Hz, 1H), 5.79 (ddd, *J* = 11.3, 7.4, 7.4 Hz, 1H), 5.45 (s,

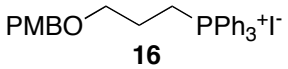
1H), 5.36 (s, 1H), 4.95 (s, 1H), 4.91 (s, 1H), 4.66 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.42-4.36 (m, 2H), 4.26-4.24 (m, 1H), 4.30 (d, *J* = 4.3 Hz, 1H), 3.66-3.61 (m, 1H), 3.59 (d, *J* = 3.7 Hz, 1H), 3.54-3.45 (m, 3H), 3.42-3.36 (m, 2H), 3.21 (dd, *J* = 17.4, 9.0 Hz, 1H), 3.09-3.05 (m, 1H), 2.99 (d, *J* = 4.5 Hz, 1H), 2.63 (dd, *J* = 15.0, 2.2 Hz, 1H), 2.39-2.18 (m, 4H), 1.50-1.28 (m, 4H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.4, 167.1, 165.3, 155.4, 143.1, 139.2, 138.2, 136.1, 134.1, 132.8, 133.1, 129.6, 126.9, 124.7, 122.2, 117.4, 116.2, 115.8, 82.1, 81.8, 80.3, 79.3, 76.6, 74.0, 72.3, 70.2, 45.7, 45.1, 42.3, 39.4, 37.2, 34.6, 28.9, 27.2, 15.6, 6.2; ^{13}C NMR (125 MHz, CD_3CN) δ 211.7, 166.6, 165.2, 155.7, 144.3, 139.3, 139.2, 136.8, 135.0, 132.8, 131.6, 129.4, 129.3, 126.8, 125.7, 122.4, 117.7, 116.4, 115.5, 82.3, 81.5, 80.4, 79.4, 76.1, 73.6, 71.2, 70.0, 45.7, 45.6, 43.3, 39.3, 38.5, 35.2, 29.2, 27.4, 14.7, 7.1; high resolution mass spectrum (ESI$^+$) *m*/*z* 747.2923 [(M-H_2O+Na)$^+$; calcd for $C_{40}H_{47}ClO_9Na$: 747.2912].



(–)-S-17

To a solution of alcohol (–)-**17** (399 mg, 0.79 mmol) in CH_2Cl_2 (4.3 mL) was added anhydrous DMSO (0.41 mL, 5.3 mmol) and *i*-Pr_2NEt (0.56 mL, 3.2 mmol). The reaction mixture was cooled to –10 °C and SO_3•Py (512 mg, 2.42 mmol) was added in a single portion. After 1 h, the reaction mixture was diluted with ether and then washed with water, 1M $KHSO_4$, water and brine, dried over Na_2SO_4, filtered and concentrated *in*

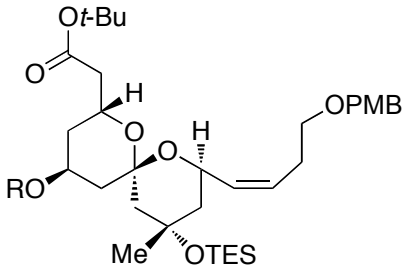
vacuo. The isolated aldehyde (–)-**S-17** (376 mg, 95%) was azeotroped with benzene (3X) and used without further purification in the following reaction. $[\alpha]_D^{20}$ –90.9 (*c* 1.48, C_6H_6); IR (neat) 2956 (m), 2876 (m), 1735 (s), 1245 (m), 1152 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.75 (s, 1H), 4.96-4.93 (m, 1H), 4.72 (dd, *J* = 11.6, 1.9 Hz, 1H), 4.64 (ddt, *J* = 11.6, 5.9, 5.9 Hz, 1H), 2.62 (dd, *J* = 16.4, 6.5 Hz, 1H), 2.20 (dd, *J* = 16.3, 6.1 Hz, 1H), 2.06-2.00 (m, 1H), 1.87-1.81 (m, 4H), 1.75-1.69 (m, 1H), 1.59 (d, *J* = 14.3 Hz, 1H), 1.34 (s, 9H), 1.27-1.19 (m, 2H), 1.05 (dd, *J* = 12.6, 12.6 Hz, 1H), 1.02-0.96 (m, 10H), 0.95 (s, 3H), 0.59 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 201.9, 98.2, 80.6, 72.4, 70.3, 67.4, 62.4, 48.1, 42.1, 39.8, 38.3, 34.5, 32.1, 28.5, 21.4, 7.8, 7.5; high resolution mass spectrum (ESI^+) *m/z* 523.2682 [$(M+Na)^+$; calcd for $C_{25}H_{44}O_8SiNa$: 523.2703].



16

To a flame dried flask containing PMB protected 3-iodopropanol (3.52 g, 11.5 mmol) was added anhydrous acetonitrile (115 mL) followed by PPh_3 (30.2 g., 115 mmol) and *i*-Pr_2NEt (6.0 mL, 35 mmol) and the reaction mixture was then heated to 83°C. After 18 h, the mixture was cooled to room temperature, concentrated *in vacuo*, and purified by column chromatography using methanol-methylene chloride (1:99 to 5:95) as an elutant to afford Wittig salt **16** (6.0 g, 92%). IR (neat) 3423 (br w), 3052 (w), 3006 (w), 2932 (w), 2863 (m), 1513 (s), 1437 (s), 1247 (s), 1113 (s), 722 (s), 689 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78-7.70 (m, 8H), 7.67-7.60 (m, 7H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.38 (s, 2H), 3.75-3.66 (m, 7H), 1.96-1.88 (m, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 134.9 (d, *J* = 2.8 Hz), 133.4 (d, *J* = 9.9 Hz), 130.3 (d, *J* = 12.7 Hz),

129.9, 129.3, 117.8 (d, J = 86.3 Hz), 113.6, 72.7, 68.4 (d, J = 16.1 Hz), 55.1, 23.1, 19.8 (d, J = 52.6 Hz); high resolution mass spectrum (ESI$^+$) m/z 441.1967 [(M-I)$^+$; calcd for $C_{29}H_{30}O_2P$: 441.1983].



R = Ac, (–)-**18** (66%)

R = H, (–)-**19** (15%)

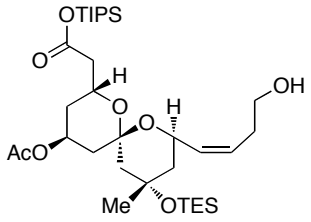
To a flame dried round bottom flask containing activated 4Å molecular sieves was added which was then degassed using the freeze-pump-thaw method (3X) before use in the following reactions. In a separate flask, Wittig salt (+)-**4** (816.7 mg, 1.44 mmol) which was previously azeotroped with benzene (3X) and dried on high vacuum at 50 °C for 18 h, was dissolved in THF (29 mL), cooled to –78 °C. MeLi LiBr complex (1.22 M in ether, 1.2 mL, 1.44 mmol) was added dropwise, and the resulting orange solution was allowed to stir for 30 min. Aldehyde **5** (376 mg, 0.79 mmol), also azeotroped with benzene (3X) and dried on high vacuum for 2 h, dissolved in THF (10 mL) and added dropwise, via cannula, to the ylide solution. The resulting mixture was allowed to stir for an additional hour at –78 °C and then warmed to 10 C over 90 min. The resulting red solution was diluted with ether and then quenched by the addition of combination of saturated NH_4Cl-saturated $Na_2S_2O_3$ (4:1). The aqueous phase was extracted with ether (3X) and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and

concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (1:10 to 1:4) as an elutant afforded Wittig product (–)-**18** (344 mg, 66%) and C(5) deacetylated (–)-**19** (74 mg, 15%).

Wittig Product (–)-**18**: $[\alpha]_D^{20}$ –115.0 (*c* 0.26, C_6H_6); IR (neat) 2953 (s), 2875 (m), 1734 (s), 1514 (w), 1367 (w), 1248 (m), 1150 (m), 1098 (w), 1020 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.74-5.66 (m, 2H), 5.19 (ddd, *J* = 11.1, 7.3, 1.9 Hz, 1H), 5.00-4.97 (m, 1H), 4.75-4.69 (m, 1H), 4.42 (s, 2H), 3.58 (dt, *J* = 9.0, 6.5 Hz, 1H), 3.53 (dt, *J* = 9.0, 6.7 Hz, 1H), 3.31 (s, 3H), 2.80 (dd, *J* = 15.9, 5.2 Hz, 1H), 2.78-2.66 (m, 2H), 2.37 (dd, *J* = 15.8, 7.8 Hz, 1H), 2.12 (ddd, *J* = 14.8, 2.2, 2.2 Hz, 1H), 1.89-1.83 (m, 4H), 1.68-1.63 (m, 1H), 1.62 (ddd, *J* = 13.2, 1.8, 1.8 Hz, 1H), 1.37 (s, 9H), 1.35-1.22 (m, 4H), 1.05 (t, *J* = 7.8 Hz, 9H), 1.02 (s, 3H), 0.70-0.63 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.6, 170.4, 160.0, 133.3, 131.8, 129.6, 128.7, 114.4, 97.7, 80.3, 73.0, 70.9, 70.5, 67.8, 63.0, 62.3, 55.1, 47.7, 45.9, 42.4, 38.8, 34.8, 32.5, 29.4, 28.5, 21.5, 8.0, 7.7; high resolution mass spectrum (ESI^+) *m/z* 685.3715 [$(M+Na)^+$; calcd for $C_{36}H_{58}O_9SiNa$: 685.3748].

C(5) Deacetylated (–)-**19**: $[\alpha]_D^{20}$ –115.4 (*c* 2.16, C_6H_6); IR (neat) 3521 (br w), 2953 (s), 2875 (s), 1733 (s), 1514 (m), 1367 (m), 1248 (s), 1148 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.61 (dt, *J* = 10.8, 7.4 Hz, 1H), 5.53-5.47 (m, 1H), 5.22-5.15 (m, 1H), 4.66 (dddd, *J* = 12.4, 7.3, 5.0, 2.2 Hz, 1H), 4.40 (s, 2H), 4.24 (d, *J* = 10.4 Hz, 1H), 4.06-4.00 (m, 1H), 3.52 (dt, *J* = 9.0, 6.4 Hz, 1H), 3.46 (dt, *J* = 9.2, 6.8 Hz, 1H), 3.34 (s, 3H), 2.79 (dd, *J* = 15.4, 5.0 Hz, 1H), 2.74-2.67 (m, 1H), 2.66-2.58 (m, 1H), 2.40 (dd, *J* = 15.4, 7.6 Hz, 1H), 1.99-1.93 (m, 1H), 1.72 (ddd, *J* =

14.1, 2.2, 2.2, 1H), 1.68 (dd, *J* = 14.3, 2.0 Hz, 1H), 1.54 (ddd, *J* = 13.4, 2.0, 2.0 Hz, 1H), 1.40-1.32 (m, 10H), 1.23 (d, *J* = 11.2 Hz, 1H), 1.20 (d, *J* = 11.2 Hz, 1H), 1.09 (d, *J* = 14.5 Hz, 1H), 1.03 (t, *J* = 7.8 Hz, 9H), 1.00 (s, 3H), 0.65-0.59 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.4, 160.0, 131.9, 131.8, 130.2, 129.7, 114.4, 99.7, 80.4, 73.1, 70.5, 70.3, 65.4, 63.5, 62.3, 55.1, 47.5, 45.8, 42.7, 41.8, 38.4, 32.4, 29.4, 28.5, 7.9, 7.6; high resolution mass spectrum (ESI$^+$) *m/z* 643.3648 [(M+Na)$^+$; calcd for $C_{34}H_{56}O_8SiNa$: 643.3642].

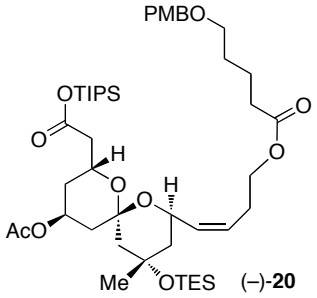


(–)-**12**

Step a. To a flask containing *t*-Butyl ester (–)-**18** (45 mg, 0.068 mmol) in CH_2Cl_2 (1.1 mL) at room temperature was added 2,6-lutidine (0.12 mL, 1.0 mmol) followed by TMSOTf (59μL, 0.31 mmol). After stirring for 1 h, the reaction mixture was diluted with ether and quenched with 1M $KHSO_4$. The organic layer was washed with water then brine. dried over Na_2SO_4, filtered and concentrated *in vacuo*.

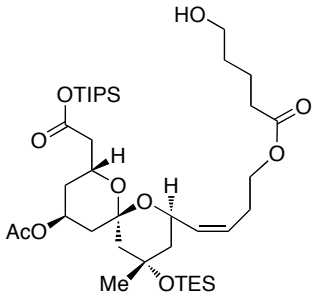
Step b. The resulting crude mixture was dissolved in MeOH (6.8 mL) and THF (1.7 mL) and treated with KF (119 mg, 2.04 mmol). After stirring 30 min at room temperature, the reaction mixture was quenched by the addition of brine. The resulting salts were dissolved in water and the aqueous layer was extracted with ethyl acetate (3X) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the desired hydroxy acid which was used without further purification.

Step c. To a flask containing the hydroxy acid in CH_2Cl_2 (0.68 mL) at 0 °C was added Et_3N (94 μL, 0.67 mmol) followed by TIPSCl (70μL, 0.33 mmol). The resulting mixture was allowed to stir for an additional 1h 0 °C, before it was diluted with ether and quenched by the addition of saturated $NaHCO_3$. The aqueous phase was extracted with ether (3X), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (20:80) as an elutant afforded TIPS-ester (–)-**12** (42 mg, 96% over 3 steps). $[\alpha]_D^{20}$ –95.1 (*c* 1.03, C_6H_6); IR (neat) 3502 (br w), 2950 (s), 2871 (s), 1736 (s), 1369 (w), 1247 (s), 1184 (s), 1065 (m), 1019 (s), 728 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.60 (dd, *J* = 10.4, 9.3 Hz, 1H), 5.48 (dt, *J* = 10.0, 6.2 Hz, 1H), 5.10-5.04 (m, 1H), 5.00-4.96 (m, 1H), 4.73 (dddd, *J* = 9.5, 9.5, 3.8, 1.9 Hz, 1H), 3.72-3.65 (m, 2H), 3.01 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.73-2.64 (m, 1H), 2.53 (dd, *J* = 16.1, 9.5, 1H), 2.41-2.33 (m, 1H), 2.24-2.18 (m, 1H), 2.12 (ddd, *J* = 14.8, 1.9, 1.9 Hz, 1H), 2.00-1.95 (m, 1H), 1.89 (s, 3H), 1.64 (dd, *J* = 14.2, 2.0 Hz, 1H), 1.57 (ddd, *J* = 13.3, 1.8, 1.8 Hz, 1H), 1.30-1.19 (m, 7H), 1.11-1.01 (m, 30H), 0.70-0.57 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.1, 170.7, 133.5, 129.3, 97.8, 70.8, 67.6, 62.7, 62.4, 62.4, 47.6, 45.7, 43.1, 38.7, 35.1, 32.9, 32.4, 21.5, 18.3, 12.6, 7.9, 7.7; high resolution mass spectrum (ESI^+) *m/z* 665.3892 [$(M+Na)^+$; calcd for $C_{33}H_{62}O_8Si_2Na$: 665.3881].



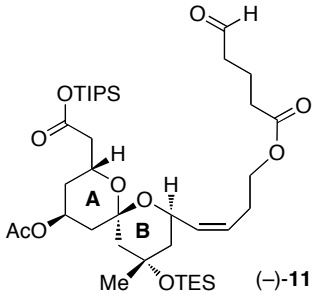
(–)-**20**

To alcohol (–)-**12** (238 mg, 0.37 mmol) in CH_2Cl_2 (3 ml) was added acid **13** (108 mg, 0.48 mmol) and DMAP (4.5 mg, 0.037 mmol). The resulting mixture was cooled to 0 °C and a solution of DCC (1M in CH_2Cl_2, 0.56 mL, 0.56 mmol) was added. The reaction mixture was then allowed to warm to room temperature and stir for 18 h. Column chromatography directly on the reaction mixture using ethyl acetate-hexanes (1:9 to 1:3) as an elutant afforded PMB ether (–)-**20** (280 mg, 88%). $[\alpha]_D^{20}$ –0.858 (*c* 0.99, C_6H_6); IR (neat) 2949 (s), 1735 (s), 1514 (w), 1248 (s), 1182 (m), 1019 (m), 734 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.65 (dd, *J* = 10.8, 8.6 Hz, 1H), 5.46 (dt, *J* = 10.9, 7.4 Hz, 1H), 5.12-5.05 (m, 1H), 4.99-4.96 (m, 1H), 4.67 (dddd, *J* = 11.4, 9.3, 4.1, 2.0 Hz, 1H), 4.31 (s, 2H), 4.22 (dt, *J* = 10.7, 6.6 Hz, 1H), 4.16 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.33 (s, 3H), 3.29 (t, *J* = 6.3 Hz, 2H), 2.99 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.64-2.57 (m, 2H), 2.53 (dd, *J* = 16.2, 9.4 Hz, 1H), 2.23 (t, *J* = 7.8 Hz, 2H), 2.15-2.09 (m, 1H), 2.03-1.96 (m, 1H), 1.87 (s, 3H), 1.80-1.72 (m, 2H), 1.67-1.52 (m, 4H), 1.38-1.20 (m, 7H), 1.12 (d, *J* = 7.4 Hz, 18 H), 1.07 (t, *J* = 7.9 Hz, 9H), 1.02 (s, 3H), 0.73-0.59 (m, 6H) ; ^{13}C NMR (125 MHz, C_6D_6) δ 173.2, 170.9, 170.5, 160.0, 134.3, 131.7, 129.6, 126.8, 114.4, 97.7, 73.1, 70.8, 70.0, 67.7, 64.1, 63.0, 62.3, 55.1, 47.6, 45.8, 43.0, 38.7, 35.0, 34.4, 32.4, 30.0, 28.3, 22.6, 21.5, 18.4, 12.6, 8.0, 7.7; high resolution mass spectrum (ESI^+) *m/z* 885.4999 [$(M+Na)^+$; calcd for $C_{46}H_{78}O_{11}Si_2Na$: 885.4980].



(–)-**S-11**

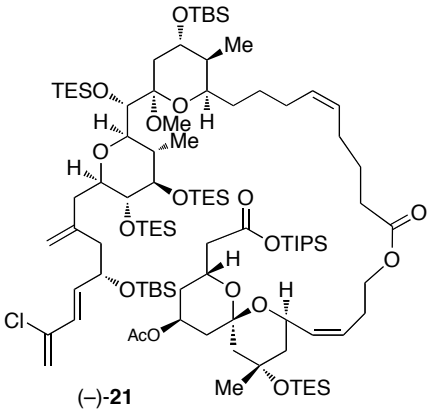
To a flask containing PMB ether (–)-**20** (280 mg, 0.32 mmol) was added CH_2Cl_2 (5.8 mL) and a solution of pH 7 phosphate buffer solution (0.58 mL). The solution was cooled to 0 °C and DDQ (147 mg, 0.65 mmol) was added in a single portion. After 90 min, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with ethyl acetate (3X). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:4 to 1:1) as an elutant afforded the alcohol (–)-S-**11** (213 mg, 89%). $[\alpha]_D^{20}$ –0.664 (*c* 0.69, C_6H_6); IR (neat) 3429 (br w), 2949 (s), 2871 (m), 1736 (s), 1379 (w), 1248 (m), 1183 (m), 1018 (m), 884 (w), 737 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.68-5.62 (m, 1H), 5.46 (dt, *J* = 11.0, 7.4 Hz, 1H), 5.11-5.05 (m, 1H), 5.00-4.96 (m, 1H), 4.70-4.63 (m, 1H), 4.22 (dt, *J* = 10.6, 6.7 Hz, 1H), 4.16 (dt, *J* = 10.7, 7.0 Hz, 1H), 3.31 (t, *J* = 6.3 Hz, 2H), 2.99 (dd, *J* = 16.1, 4.2 Hz, 1H), 2.66-2.50 (m, 3H), 2.19 (t, *J* = 7.4 Hz, 2H), 2.15-2.10 (m, 1H), 2.03-1.97 (m, 1H), 1.88 (s, 3H), 1.67-1.60 (m, 3H), 1.57-1.53 (m, 1H), 1.39-1.20 (m, 9H), 1.12 (d, *J* = 7.4 Hz, 18H), 1.08 (t, *J* = 8.0 Hz, 9H), 1.05-1.01 (m, 4H), 0.73-0.60 (m, 6H) ; ^{13}C NMR (125 MHz, C_6D_6) δ 173.4, 171.0, 170.6, 134.3, 126.8, 97.7, 70.8, 67.7, 64.2, 63.0, 62.4, 62.3, 47.6, 45.8, 43.0, 38.7, 35.0, 34.3, 32.8, 32.4, 28.3, 21.9, 21.5, 18.4, 12.6, 8.0, 7.7; high resolution mass spectrum (ESI$^+$) *m/z* 765.4439 [(M+Na)$^+$; calcd for $C_{38}H_{70}O_{10}Si_2Na$: 765.4405].



(–)-**11**

To a flask containing alcohol (–)-**S-11** (88 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added anhydrous DMSO (43 μL, 0.60 mmol) and *i*-Pr_2NEt (62 μL, 0.36 mmol). The flask was cooled to –5 °C and SO_3•Py (57 mg, 0.36 mmol) was added in a single portion. After 30 min, the reaction mixture was diluted with ether and then quenched with water. The organic phase was washed with 1M $KHSO_4$, water and brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*, to afford aldehyde (–)-**11** (87 mg, 99%) was azeotroped with benzene (3X) and used in the next step without further purification. $[\alpha]_D^{20}$ –105.67 (*c* 0.6, C_6H_6); IR (neat) 2950 (m), 2871 (m), 1735 (s), 1247 (m), 1183 (m), 1019 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.23 (t, *J* = 1.2 Hz, 1H), 5.65 (dddd, *J* = 11.1, 8.4, 1.5, 1.5 Hz, 1H), 5.41 (dddd, *J* = 11.0, 7.4, 7.4, 0.9 Hz, 1H), 5.09-5.04 (m, 1H), 4.99-4.95 (m, 1H), 4.66 (dddd, *J* = 11.3, 9.2, 4.2, 2.0 Hz, 1H), 4.18 (dt, *J* = 10.7, 6.7 Hz, 1H), 4.13 (dt, *J* = 10.7, 7.0 Hz, 1H), 2.98 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.64-2.50 (m, 3H), 2.12 (ddd, *J* = 15.0, 2.2, 2.2 Hz, 1H), 2.07 (t, *J* = 7.2 Hz, 2H), 2.01-1.96 (m, 1H), 1.89-1.84 (m, 5H), 1.68 (p, *J* = 7.0 Hz, 2H), 1.64 (dd, *J* = 14.2, 2.0 Hz, 1H), 1.54 (ddd, *J* = 13.1, 1.9, 1.9 Hz, 1H), 1.34-1.21 (m, 6H), 1.12 (d, *J* = 7.9 Hz, 18H), 1.07 (t, *J* = 7.9 Hz, 9H), 1.04-1.01 (m, 4H), 0.72-0.59 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.1, 172.7, 171.0, 170.5, 134.4, 126.7, 97.7, 70.8, 67.6, 64.3, 63.0, 62.3, 47.6, 45.8, 43.2, 43.0, 38.7,

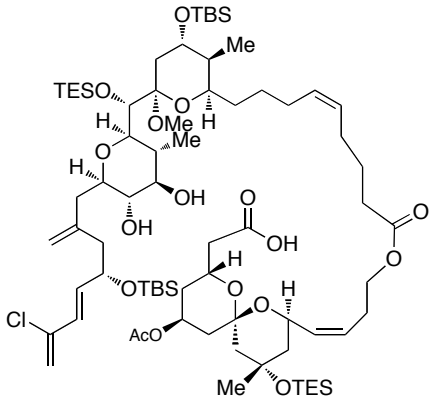
35.0, 33.5, 32.4, 28.3, 21.5, 18.4, 17.9, 12.6, 8.0, 7.7; high resolution mass spectrum (ESI^+) *m*/*z* 763.4274 [$(M+Na)^+$; calcd for $C_{38}H_{68}O_{10}Si_2Na$: 763.4249].



(–)-**21**

To a flame dried round bottom flask containing activated 4Å molecular sieves was added which was then degassed using the freeze-pump-thaw method (3X) before use in the following reactions. In a separate flask, Wittig salt (+)-**4** (94%, 170 mg, 0.107 mmol), which was previously azeotroped with benzene (3X) and dried on high vacuum at 50 °C for 18 h, was dissolved in THF (1.1 mL), cooled to –78 °C. MeLi LiBr complex (0.8 M in ether, 0.14 mL, 0.11 mmol) was added dropwise, and the resulting orange solution was allowed to stir for 30 min. Aldehyde (–)-**11** (102 mg, 0.137 mmol), also azeotroped with benzene (3X) and dried on high vacuum for 2 h, dissolved in THF (1.1 mL) and added dropwise, via cannula, to the ylide solution. The flask which contained the aldehyde was then rinsed with THF (0.55 mL) and the solution was transferred to the reaction flask dropwise via cannula. The resulting mixture was allowed to stir for an additional hour at –78 °C and then warmed to room temperature over 2 h. The resulting red solution was diluted with ether and then quenched by the addition of combination of saturated NH_4Cl-saturated $Na_2S_2O_3$ (4:1). The aqueous phase was extracted with ether (3X) and the

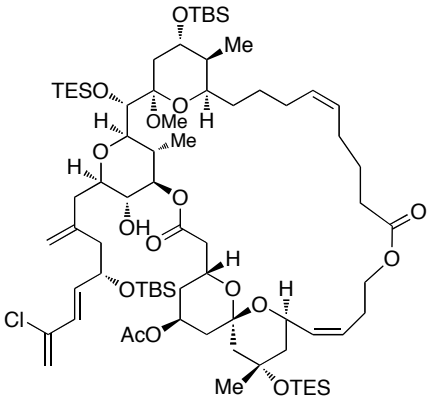
combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate-hexanes (1:9 to 2:3) as an elutant afforded *Z* olefin (–)-**21** (124 mg, 64%. $[\alpha]_D^{20}$ –15.51 (*c* 0.56, C_6H_6); IR (neat) 2953 (s), 2875 (s), 1738 (m), 1462 (w), 1368 (w), 1248 (m), 1113 (m), 1006 (m), 738 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.50 (dd, *J* = 14.9, 5.0 Hz, 1H), 6.44 (d, *J* = 15.0 Hz, 1H), 5.67-5.61 (m, 1H), 5.53-5.36 (m, 3H), 5.17 (s, 1H), 5.13 (s, 1H), 5.12 (s, 1H), 5.11-5.04 (m, 2H), 4.98-4.95 (m, 1H), 4.69-4.63 (m, 1H), 4.53-4.48 (m, 1H), 4.32-4.26 (m, 1H), 4.23 (ddd, *J* = 10.7, 6.7, 6.7 Hz, 1H), 4.17 (ddd, *J* = 10.7, 7.1, 7.1 Hz, 1H), 3.96-3.93 (m, 1H), 3.89 (s, 1H), 3.60-3.47 (m, 4H), 3.17 (s, 3H), 2.98 (dd, *J* = 16.0, 4.2 Hz, 1H), 2.76-2.66 (m, 2H), 2.63-2.48 (m, 4H), 2.39-2.30 (m, 2H), 2.29-2.21 (m, 2H), 2.14-2.05 (m, 5H), 2.03-1.92 (m, 2H), 1.87 (s, 3H), 1.79-1.68 (m, 5H), 1.64 (dd, *J* = 14.2, 1.8 Hz, 1H), 1.62-1.52 (m, 2H), 1.48-1.21 (m, 14H), 1.20-0.99 (m, 76H), 0.86-0.76 (m, 18H), 0.71-0.61 (m, 6H), 0.24 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.1, 170.9, 170.5, 144.7, 139.2, 139.2, 134.3, 131.3, 129.6, 126.8, 126.8, 115.9, 115.4, 101.9, 97.7, 82.1,81.1, 78.1, 77.8, 72.1, 71.9, 71.6, 70.8, 67.8, 67.6, 64.2, 63.0, 62.3, 47.6, 47.4, 45.9, 43.0, 40.8, 40.7, 39.4, 38.7, 35.0, 34.2, 33.3, 32.4, 30.8, 30.6, 30.6, 28.4, 28.2, 27.4, 27.2, 26.5, 25.7, 21.5, 18.9, 18.7, 18.4, 16.5, 12.6, 11.1, 8.0, 7.9, 7.8, 7.8, 7.7, 6.5, 6.5, -3.7, -3.9, -4.1, -4.2; high resolution mass spectrum (ESI^+) *m/z* 1848.1361 [$(M+Na)^+$; calcd for $C_{95}H_{181}ClO_{17}Si_7Na$: 1848.1270].



(–)-**22**

To a solution of Wittig product (–)-**21** (70 mg, 0.038 mmol) in THF (7.6 mL) at 0 °C was added TBAF (1M in THF, 0.12 mL, 0.115 mmol) over 1 hour via syringe pump. After stirring for an additional 2 h at 0 °C, the reaction mixture was diluted with ether and quenched with 1M $KHSO_4$, and washed with brine. The combined aqueous phases were then back extracted with ether (2X). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:4-1:1) with 0.5 % AcOH as an elutant afforded *seco*-acid (–)-**22** (30.5 mg, 56%). . Note : toluene was added the collection before concentrating to avoid the *seco*-acid being exposed to neat AcOH. $[\alpha]_D^{20}$ –18.06 (*c* 1.5, C_6H_6); IR (neat) 3441 (br s), 2952 (s), 1737 (s), 1461 (w), 1383 (w), 1250 (m), 1111 (s), 1019 (m), 836 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.45 (dd, *J* = 14.8, 5.0 Hz, 1H), 6.39 (d, *J* = 14.9 Hz, 1H), 5.67 (dd, *J* = 10.8, 8.4 Hz, 1H), 5.53-5.36 (m, 3H), 5.18 (s, 1H), 5.18-5.11 (m, 2H), 5.08 (s, 1H), 5.06 (s, 1H), 4.94-4.90 (m, 1H), 4.68-4.62 (m, 1H), 4.49-4.44 (m, 1H), 4.36-4.26 (m, 2H), 4.10 (ddd, *J* = 10.7, 7.3, 7.3 Hz, 1H), 3.97-3.94 (m, 1H), 3.90 (s, 1H), 3.39-3.31 (m, 2H), 3.23 (dd, *J* = 8.9, 8.8 Hz, 1H), 3.17 (s, 3H), 3.04 (dd, *J* = 9.8, 9.0 Hz, 1H), 2.79-2.70 (m, 2H), 2.62 (dd, *J* = 16.4, 7.3 Hz, 1H), 2.59-2.45 (m, 3H), 2.38-2.20 (m, 5H), 2.15-2.03 (m, 6H), 1.88 (s, 3H), 1.87-1.53 (m, 10H), 1.47-1.20 (m, 7H), 1.20-0.97 (m, 46H), 0.86-

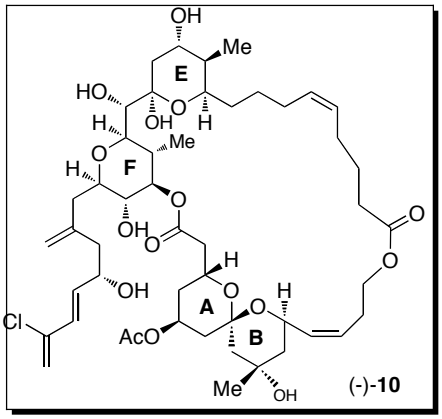
0.76 (m, 6H), 0.75-0.64 (m, 6H), 0.26 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.9, 173.7, 170.8, 144.2, 139.3, 139.2, 134.5, 131.3, 129.5, 126.7, 126.4, 116.1, 115.5, 102.1, 97.7, 79.7, 79.2, 79.1, 76.1, 72.6, 71.6, 71.6, 70.8, 67.7, 67.5, 64.5, 63.1, 62.1, 47.6, 47.4, 46.8, 45.8, 40.8, 39.9, 39.4, 39.4, 38.7, 34.7, 34.3, 33.2, 32.5, 30.8, 28.4, 28.1, 27.4, 27.1, 26.5 (2), 25.7, 21.5, 18.9, 18.8, 14.1, 11.0, 8.0, 7.9, 7.6, 6.5, -3.7, -3.9, -4.1, -4.3; high resolution mass spectrum (ESI$^+$) *m*/*z* 1463.8246 [(M+Na)$^+$; calcd for $C_{74}H_{133}ClO_{17}Si_4Na$: 1463.8206].



(–)-**S-10**

To a flask containing *seco*-acid (–)-**22** (15 mg, 0.010 mmol) dissolved in toluene (1 mL) was added a solution of *i*-Pr_2NEt (0.4 M in toluene, 0.39 mL, 0.156 mmol) followed by a solution of 2,4,6-TBCCl (0.4 M in toluene, 0.23 mL, 0.090 mmol). The reaction mixture was allowed to stir at room temperature for 5.5 h before being further diluted with toluene (2.9 mL) and then added dropwise, via syringe pump, over 24 h to a second flask containing DMAP (24 mg, 0.2 mmol) and toluene (14.3 mL) heated to 90 °C. After the addition, the flask containing seco-acid residue was rinsed with toluene (1 mL) and this solution was transferred over 12 hours via syringe pump, to the reaction mixture, followed by rinsing a third time of the first flask with toluene (0.67 mL) and adding over

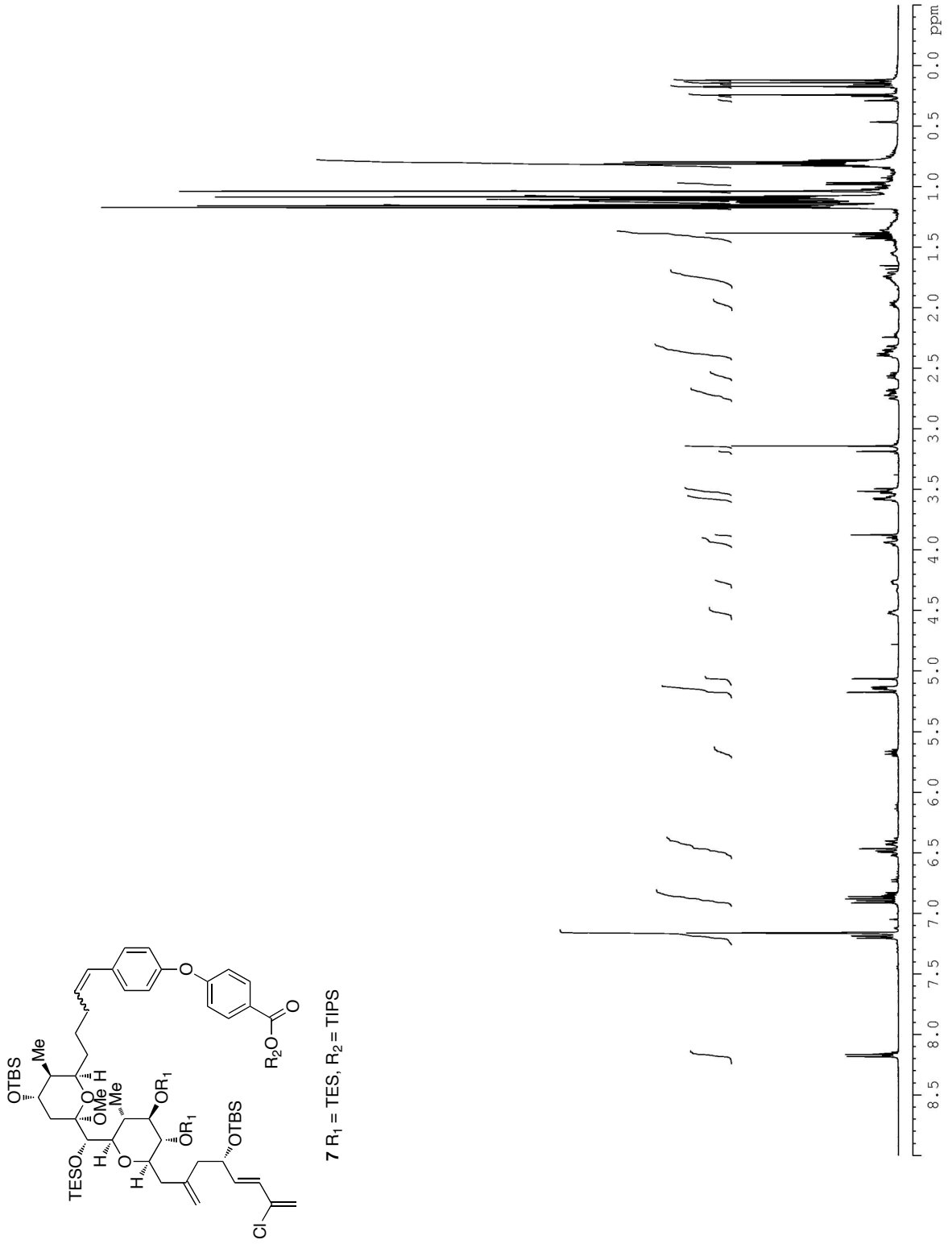
2 h. After the third rinse, the reaction mixture was allowed to cool to room temperature, before being diluted with ether and then quenched by the addition of saturated $NaHCO_3$. The layers were separated and the organic layer was rinsed with saturated NaCl and the combined aqueous layers were back extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using ethyl acetate-hexanes (1:19-1:9-1:4) as an elutant afforded the desired lactone (–)-S-**10** with a minor impurity. $[\alpha]_D^{20}$ –38.4 (*c* 1.15, C_6H_6); IR (neat) 3480 (br w), 2952 (s), 2932 (s), 2876 (m), 2856 (m), 1737 (s), 1251 (s), 1168 (m), 1147 (m), 1115 (s), 1077 (m), 1019 (m), 835 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.45 (dd, *J* = 15.0, 5.1 Hz, 1H), 6.38 (d, *J* = 15.1 Hz, 1H), 5.68-5.60 (m, 2H), 5.60-5.24 (m, 1H), 5.41-5.33 (m, 1H), 5.16 (s, 1H), 5.13-5.05 (m, 3H), 5.04 (s, 1H), 4.91-4.88 (m, 1H), 4.71(dd, *J* = 10.1, 9.1 Hz, 1H), 4.67-4.60 (m, 1H), 4.48-4.43 (m, 1H), 4.30-4.22 (m, 2H), 4.10 (ddd, *J* = 10.7, 7.7, 5.0 Hz, 1H), 3.94-3.88 (m, 2H), 3.45-3.31 (m, 3H), 3.26 (s, 3H), 2.94 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.91-2.85 (m, 1H), 2.61-2.45 (m, 4H), 2.37 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.30-2.08 (m, 6H), 2.03-1.91 (m, 6H), 1.89-1.83 (m, 2H), 1.73-1.58 (m, 5H), 1.56-1.43 (m, 3H), 1.25-1.17 (m, 2H), 1.17-0.94 (m, 50H), 0.85-0.73 (m, 6H), 0.71-0.59 (m, 6H), 0.24 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.3, 172.4, 170.5, 143.8, 139.4, 139.2, 133.8, 131.2, 129.7, 127.3, 126.7, 116.2, 115.4, 101.6, 97.8, 82.3, 80.1, 78.3, 74.1, 73.1, 72.6, 71.7, 70.8, 68.5, 67.8, 64.7, 63.0, 62.0, 48.6, 47.5, 46.9, 45.7, 42.1, 40.4, 39.4, 38.6, 38.4, 35.2, 34.3, 34.0, 32.4, 30.6, 30.4, 29.3, 28.8, 28.1, 27.6, 26.5, 26.5, 26.2, 21.6, 18.8, 18.7, 14.7, 11.2, 8.0, 7.9, 7.7, 6.5, -3.8, -3.9, -4.1, -4.3; high resolution mass spectrum (ESI^+) *m/z* 1445.8168 [$(M+Na)^+$; calcd for $C_{74}H_{131}ClO_{16}Si_4Na$: 1445.8101].



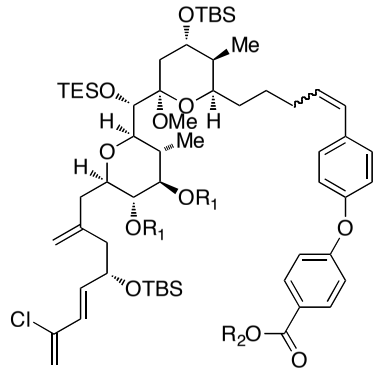
To flask macrolactone (–)-**S-10** (23 mg, 0.016 mmol) in acetonitrile (1.2 mL) at –20 °C was added a freshly prepared solution of aqueous HF in acetonitrile (1.2 mL) via syringe pump over 2 h. [HF solution prepared by dilution of aqueous HF (48%, 2.5 mL) with acetonitrile (10 mL)] Following the addition, the reaction mixture was allowed to stir for an additional 14 h at –20 °C before being quenched by the dropwise addition of Et_3N (1.5 mL). The reaction mixture was then warmed to room temperature, at which point it was diluted with a mixture of ethyl acetate and methylene chloride (2:1) and washed with saturated $NaHCO_3$ then brine. The aqueous layers were back extracted with ethyl acetate and methylene chloride (2:1 X2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography using methanol-methylene chloride (2:98 to 3:97) as an elutant afforded the desired ABEF analog (–)-**10** (9.2 mg, 48% over 2 steps). $[\alpha]_D^{20}$ –20.0 (*c* 0.2, C_6H_6); IR (neat) 3419 (br s), 2939 (br s), 1735 (s), 1402 (w), 1383 (w), 1325 (w), 1252 (m), 1207 (w), 1175 (s), 1090 (m), 1064 (m), 1024 (w), 991 (w) cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 6.42 (d, *J* = 15.0 Hz, 1H), 6.16 (dd, *J* = 15.0, 5.4 Hz, 1H), 5.53-5.42 (m, 4H), 5.39-5.32 (m, 2H), 5.00-4.94 (m, 2H),

4.94-4.90 (m, 1H), 4.89 (s, 1H), 4.84 (d, J = 2.3 Hz, 1H), 4.80 (dd, J = 10.2, 9.4 Hz, 1H), 4.49-4.42 (m, 1H), 4.39 (s, 1H), 4.37-4.31 (m, 1H), 4.31-4.22 (m, 2H), 4.22-4.17 (m, 1H), 3.92-3.84 (m, 2H), 3.80 (d, J = 10.4 Hz, 1H), 3.70-3.64 (m, 1H), 3.43-3.37 (m, 1H), 3.32 (d, J = 10.4 Hz, 1H), 3.16-3.11 (m, 2H), 2.85 (d, J = 10.7 Hz, 1H), 2.77 (d, J = 14.6 Hz, 1H), 2.69-2.57 (m, 2H), 2.52 (dd, J = 16.2, 10.6 Hz, 1H), 2.44-2.23 (m, 6H), 2.14 (s, 3H), 2.13-1.97 (m, 5H), 1.93-1.88 (m, 1H), 1.79-1.73 (m, 1H), 1.70-1.57 (m, 7H), 1.54-1.41 (m, 4H), 1.41-1.30 (m, 4H), 1.08 (s, 3H), 0.80 (d, J = 7.2 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.41 (d, J = 15.3 Hz, 1H), 6.08 (dd, J = 15.2, 5.3 Hz, 1H), 5.56 (s, 1H), 5.49 (dd, J = 10.2, 8.6 Hz, 1H), 5.45-5.36 (m, 3H), 5.34-5.26 (m, 2H), 5.18-5.12 (m, 2H), 5.02 (d, J = 5.2 Hz, 1H), 4.88-4.84 (m, 2H), 4.81 (s, 1H), 4.73 (d, J = 8.3 Hz, 1H), 4.65 (dd, J = 10.8, 9.0 Hz, 1H), 4.41 (d, J = 6.9 Hz, 1H), 4.37-4.30 (m, 1H), 4.29-4.23 (m, 1H), 4.23-4.14 (m, 2H), 4.13 (s, 1H), 3.79 (ddd, J = 10.4, 7.9, 7.9 Hz, 1H), 3.66-3.61 (m, 2H), 3.31-3.26 (m, 1H), 3.21 (d, J = 8.1 Hz, 1H), 3.02 (ddd, J = 9.1, 9.1, 5.5, 1H), 2.74-2.64 (m, 2H), 2.59-2.51 (m, 2H), 2.42-2.34 (m, 2H), 2.31-2.24 (m, 1H), 2.23-2.17 (m, 1H), 2.15-2.04 (m, 2H), 2.04-1.81 (m, 11H), 1.74-1.69 (m, 1H), 1.64-1.28 (m, 13H) 1.03 (s, 3H), 0.74 (d, J = 7.1 Hz, 3H), 0.69 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 174.5, 173.0, 171.4, 144.5, 139.2, 134.5, 131.6, 130.2, 129.4, 127.8, 126.9, 116.5, 115.9, 99.9, 99.4, 80.9, 80.9, 78.4, 73.4, 73.1, 71.5, 71.1, 69.3, 67.9, 67.6, 64.0, 63.8, 63.8, 46.1, 44.2 (2), 40.8, 40.6, 39.1, 37.7, 37.4, 34.6, 34.6, 33.8, 33.3, 30.3, 28.5, 28.4, 28.0, 27.3, 26.2, 21.6, 12.7, 11.0; high resolution mass spectrum (ESI$^+$) m/z 975.4518 [(M+Na)$^+$; calcd for $C_{49}H_{73}O_{16}NaCl$: 975.4485].

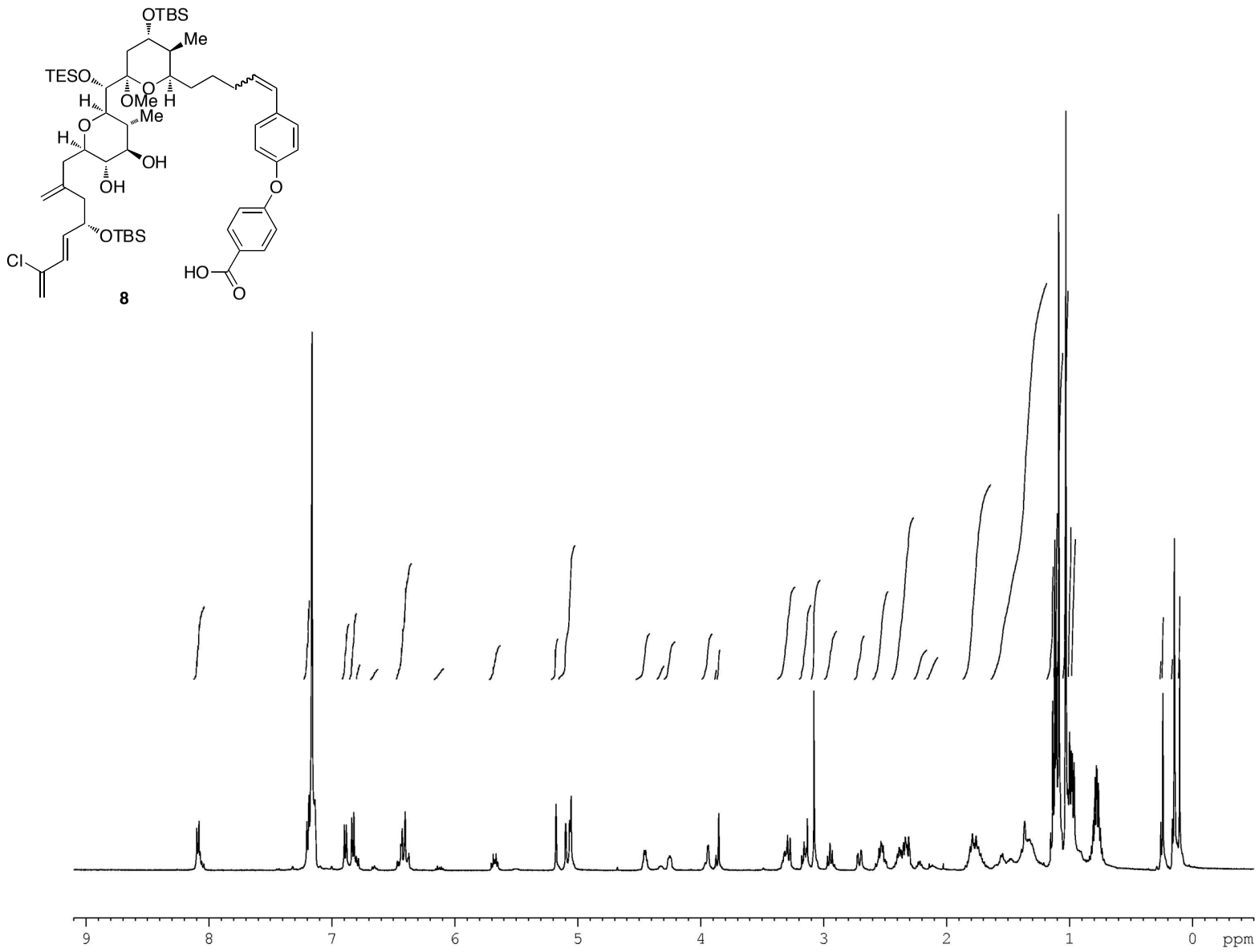
B. ^{1}H and ^{13}C NMR Spectra



7 R_1 = TES, R_2 = TIPS



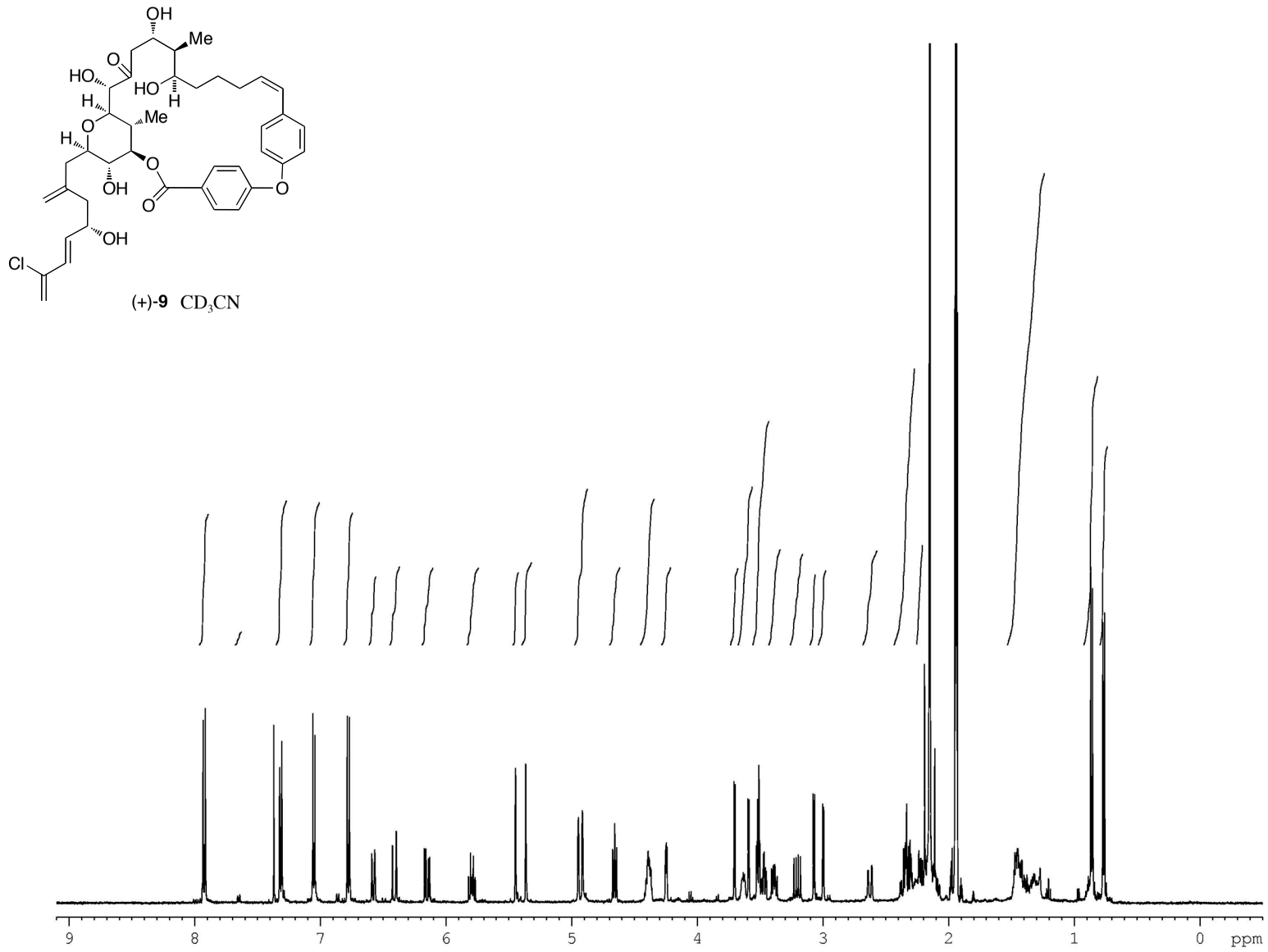
7 R_1 = TES, R_2 = TIPS


OTBS
Me
TESO
O
H
OMe H
Me
O
H
OH
OH
OTBS
Cl
HO
O
O
8
9
8
7
6
5
4
3
2
1
0
ppm

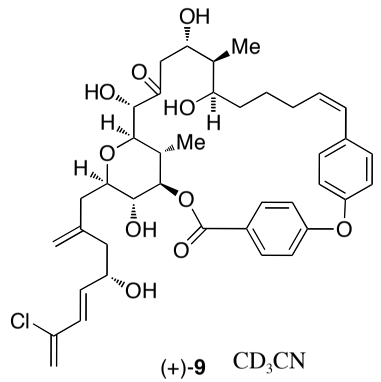
OTBS
Me
OMe H
Me
TESO
H
O
H
O
OH
OH
OTBS
Cl
HO
O
O
8
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

(+)-9
C6D6
ppm

(+)-9 C6D6
0 ppm
20
40
60
80
100
120
140
160
180
200
220
240

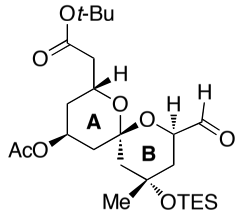


(+)-**9** CD_3CN

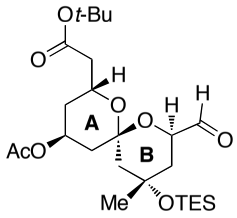

OH
Me
O
HO
HO
H
H
Me
O
H
O
OH
O
O
OH
Cl

(+)-**9** CD_3CN

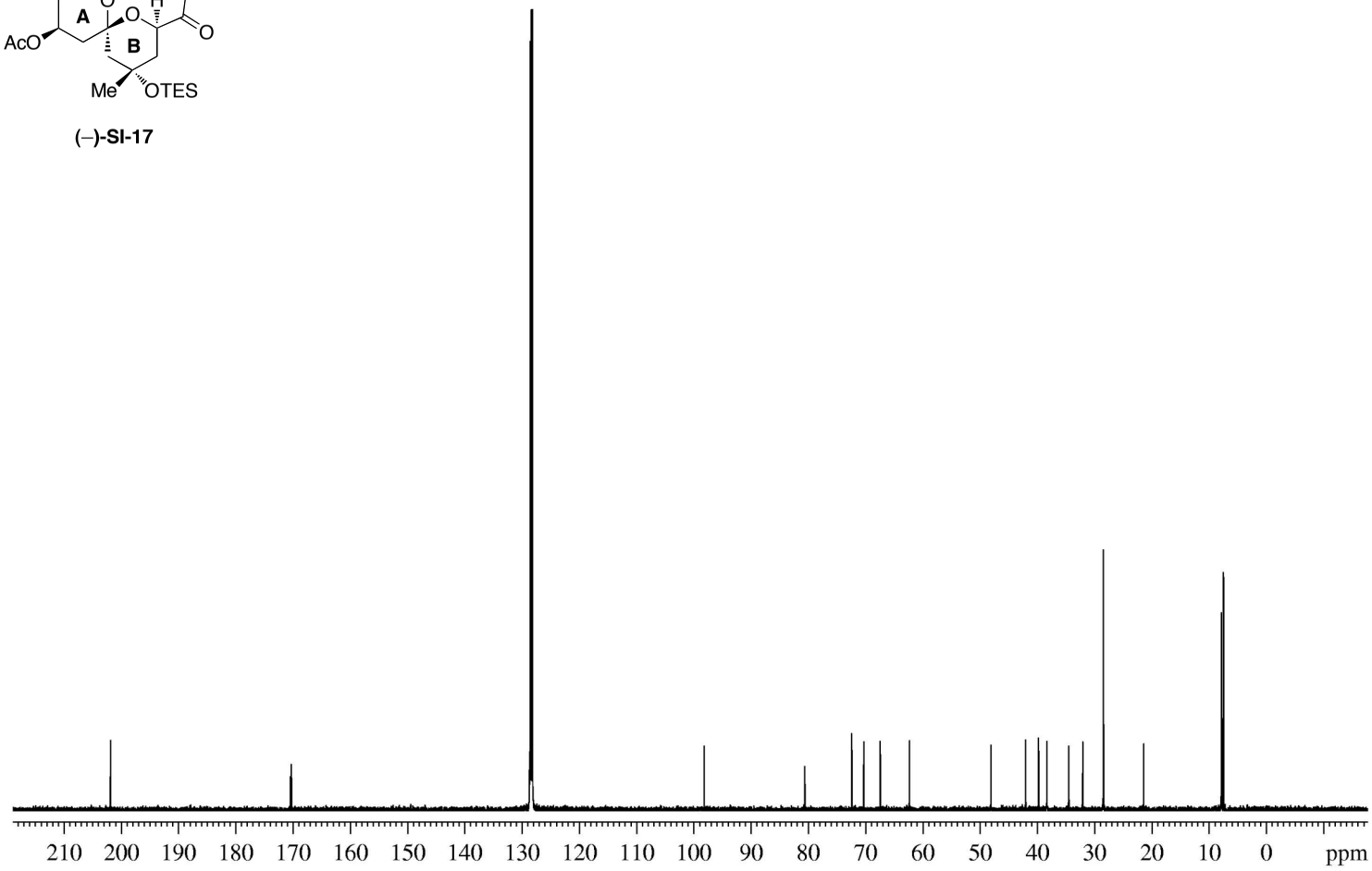
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

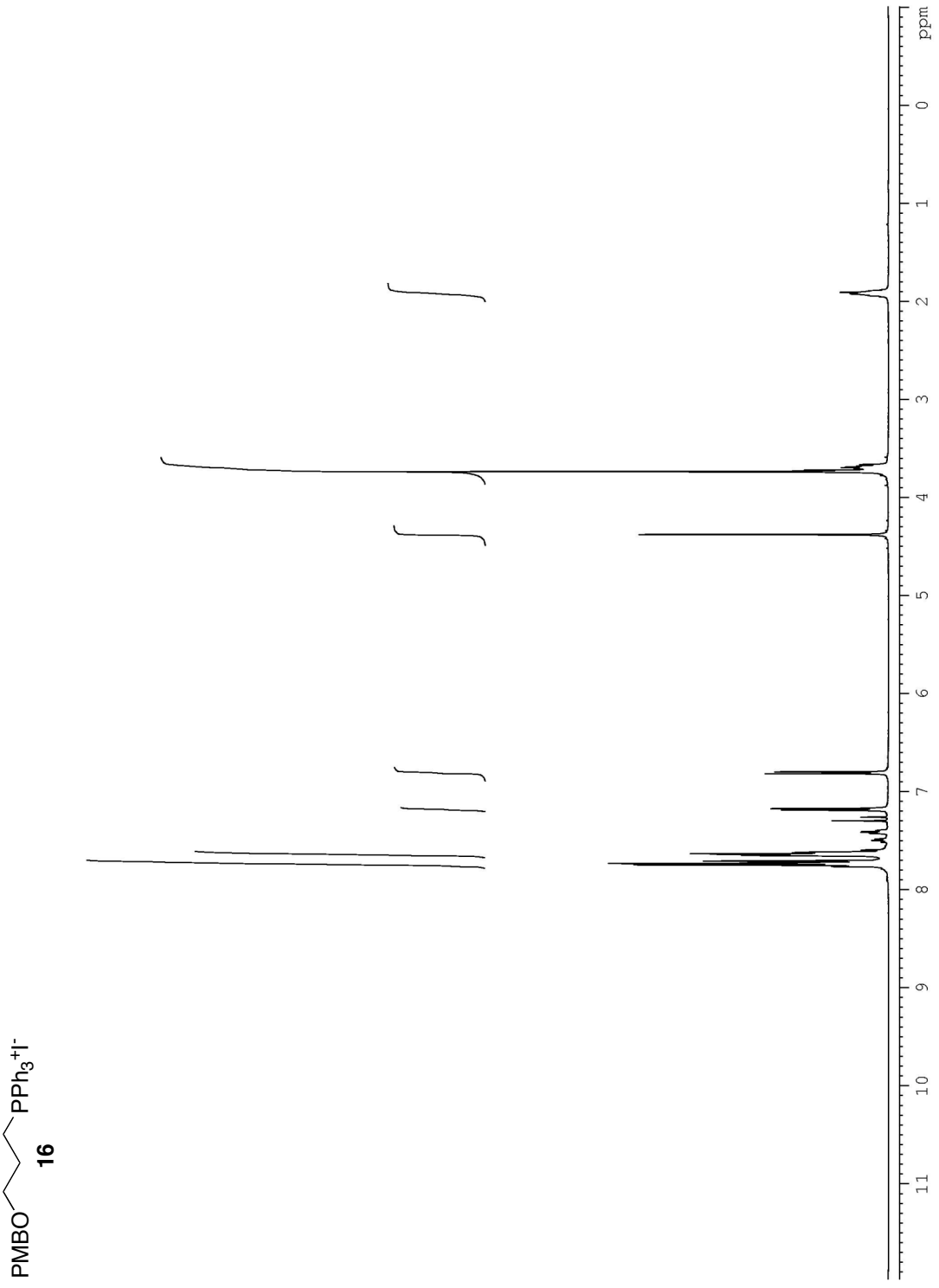


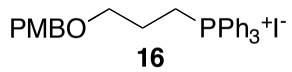
(–)-SI-17


Ot-Bu
O
H
O
A
O
H
H
O
AcO
B
Me
OTES

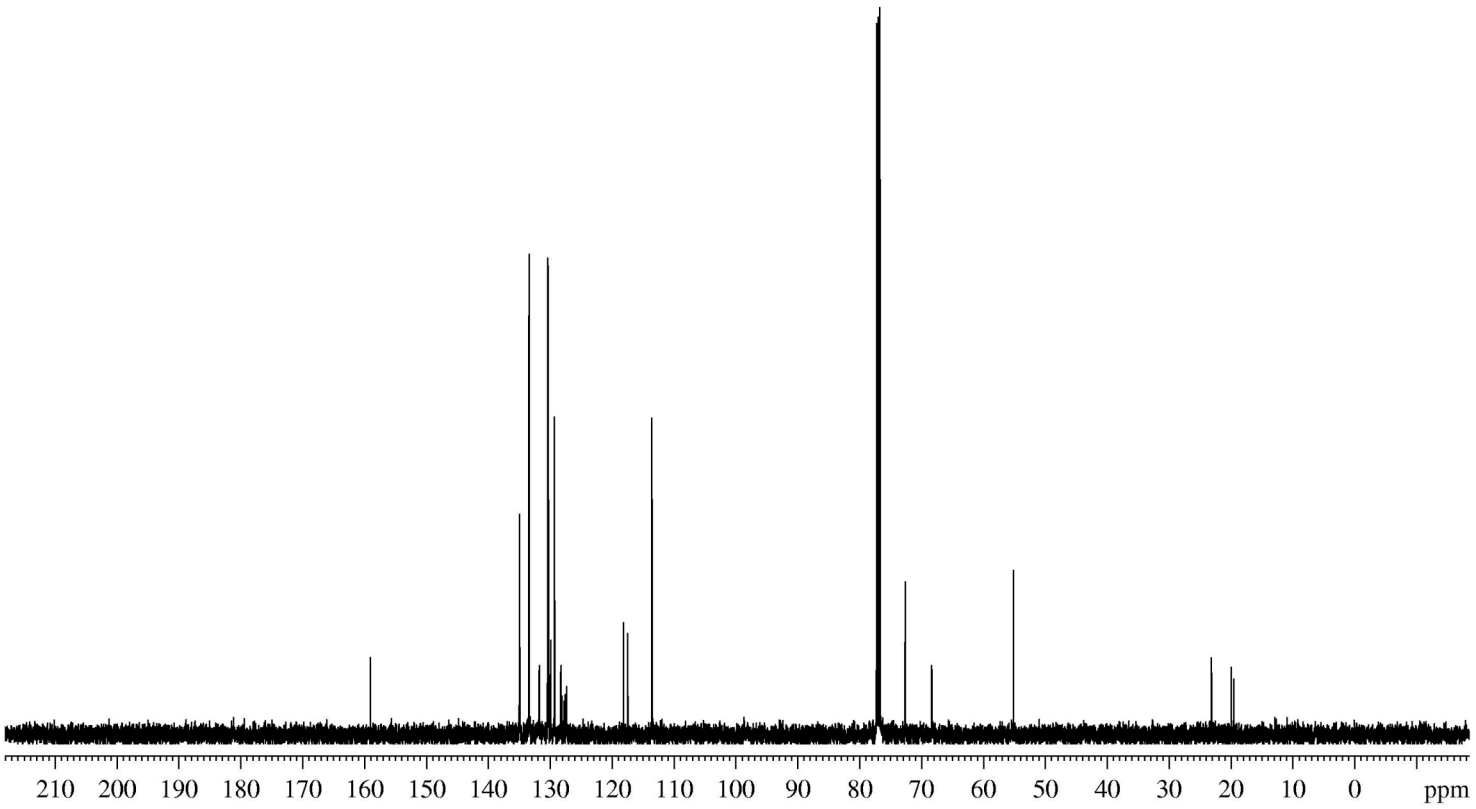
(–)-SI-17

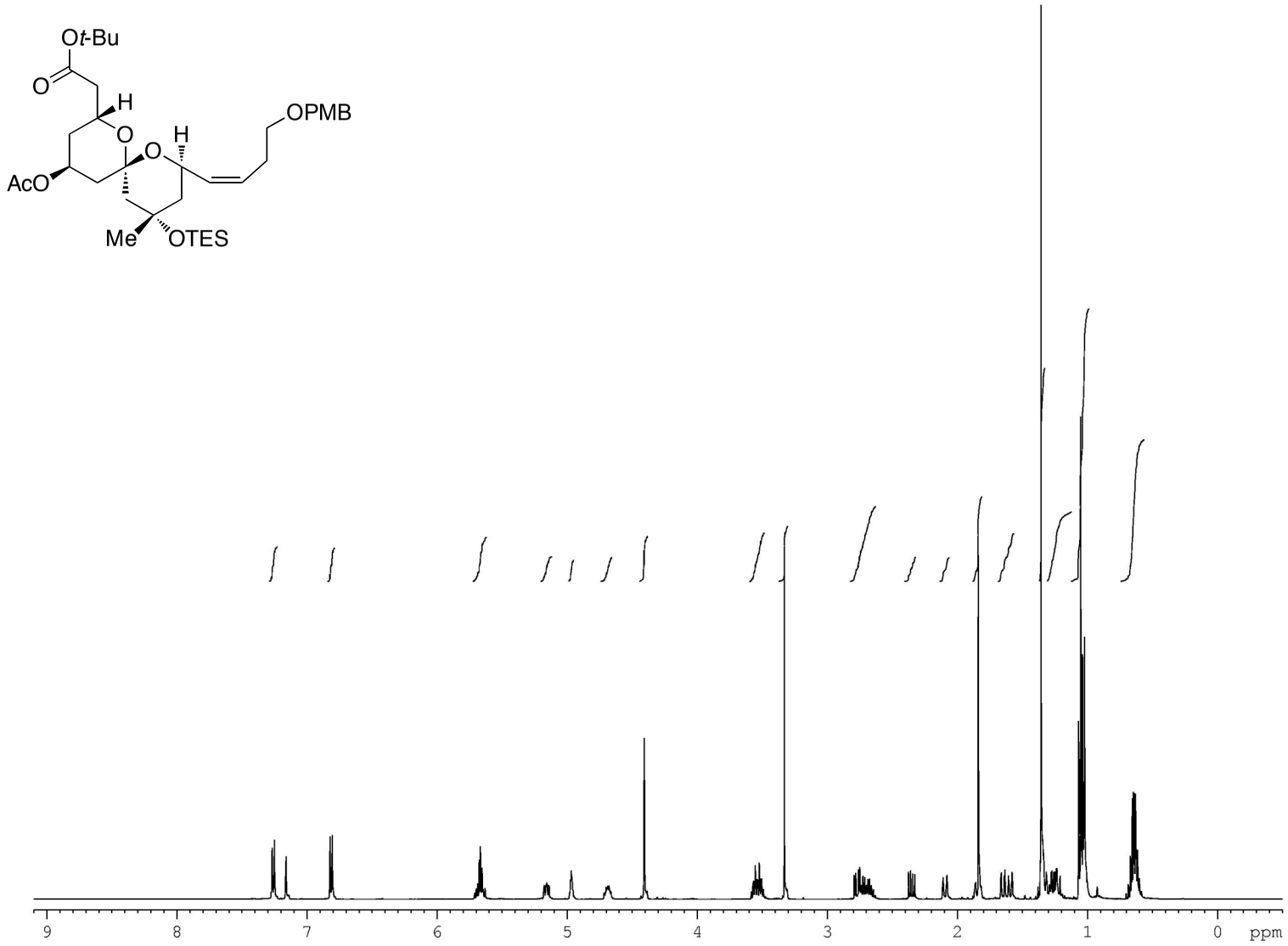

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

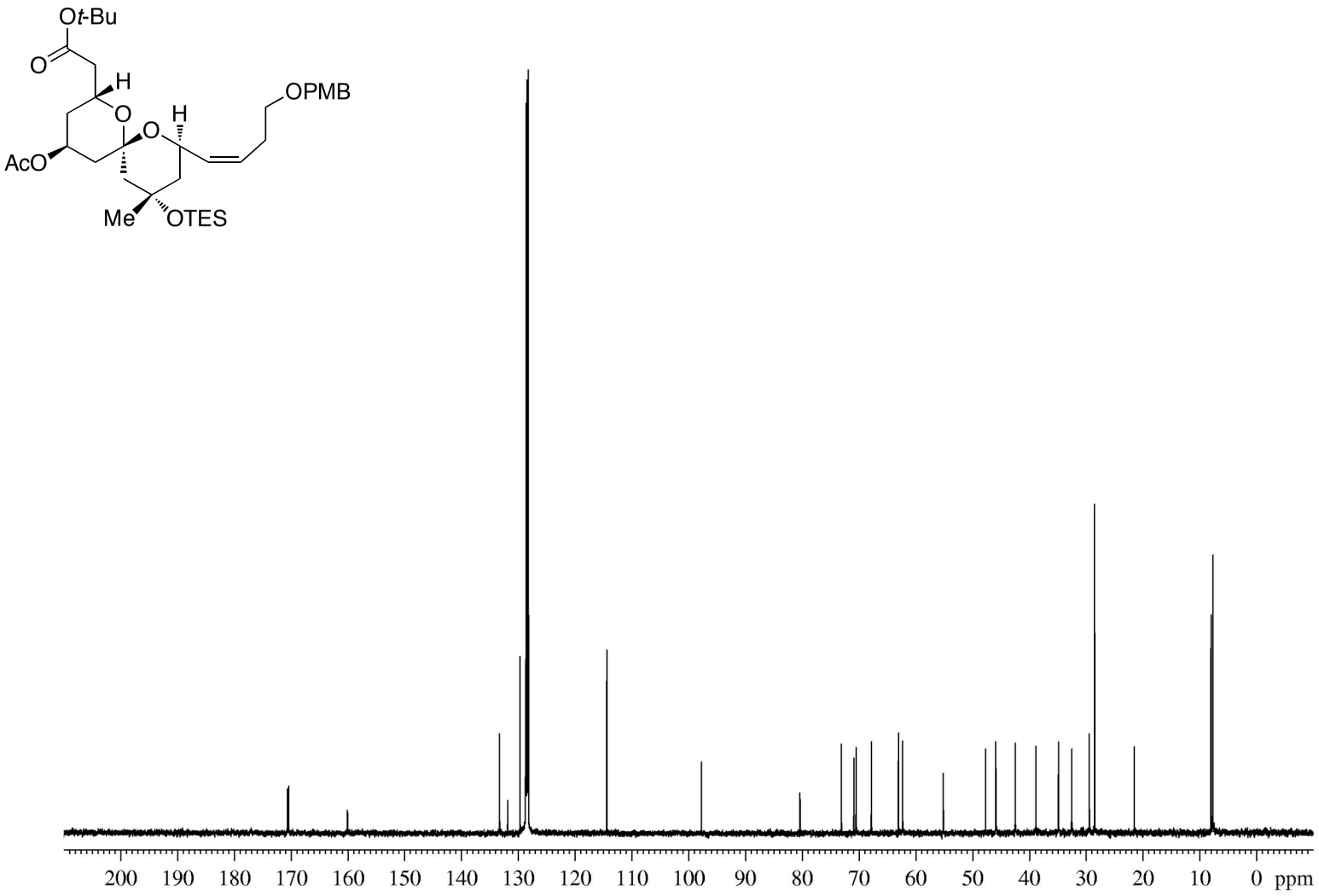

PMBO
PPh3+I-
16
ppm

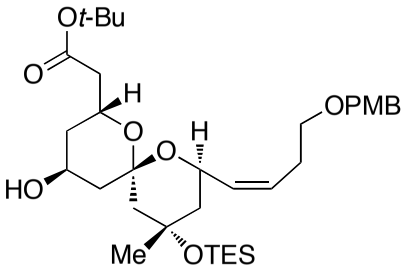

PMBO
PPh3+I-

16

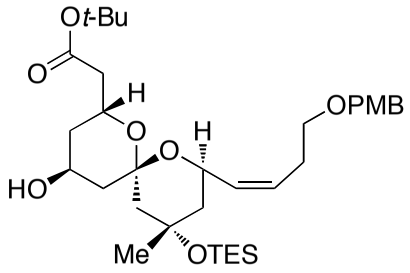

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


Ot-Bu
O
H
O
H
O
OPMB
AcO
Me
OTES
9
8
7
6
5
4
3
2
1
0
ppm

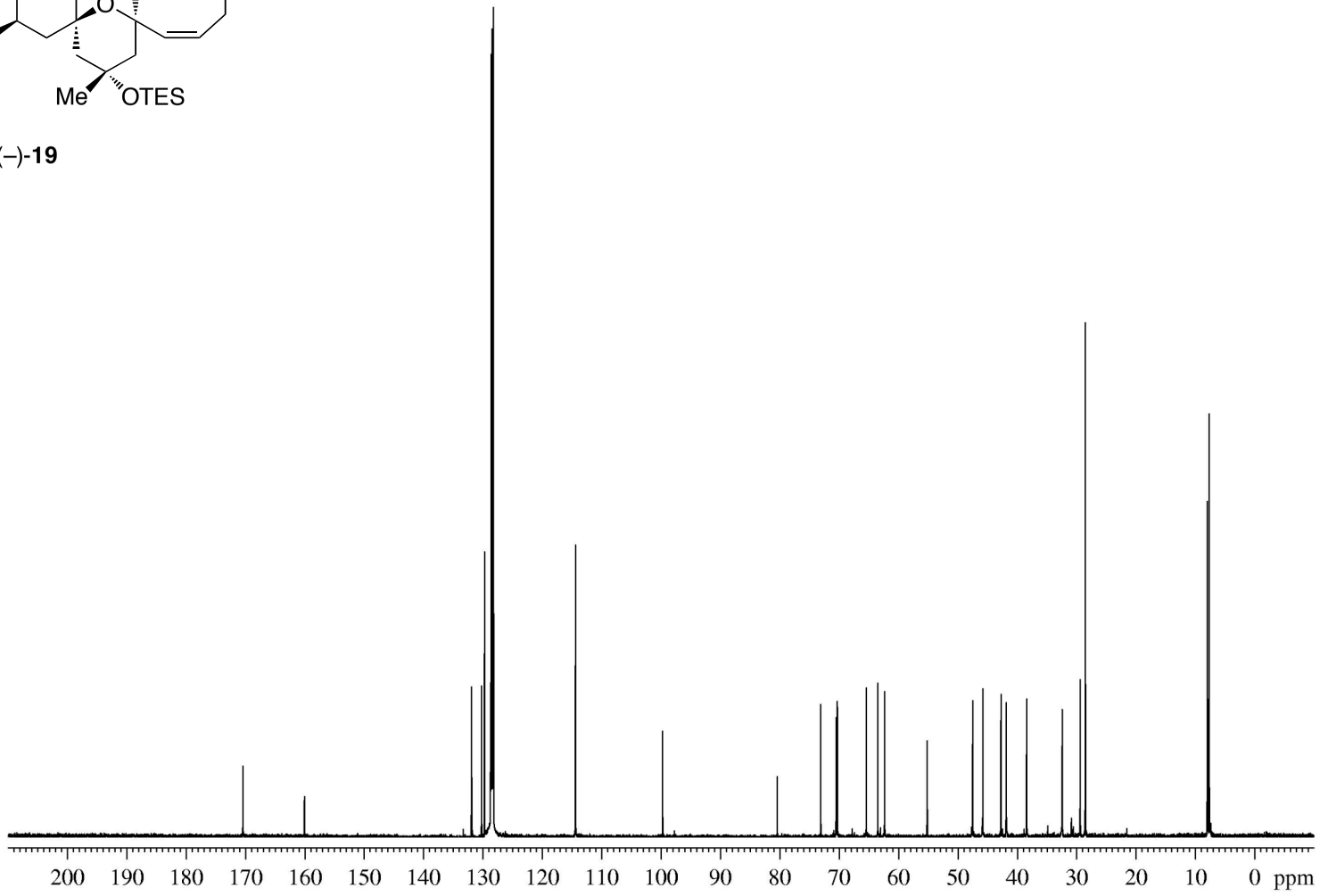

Ot-Bu
O
H
O
O
H
OPMB
AcO
Me
OTES
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

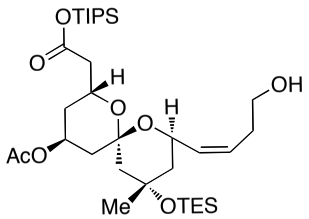


(–)-**19**

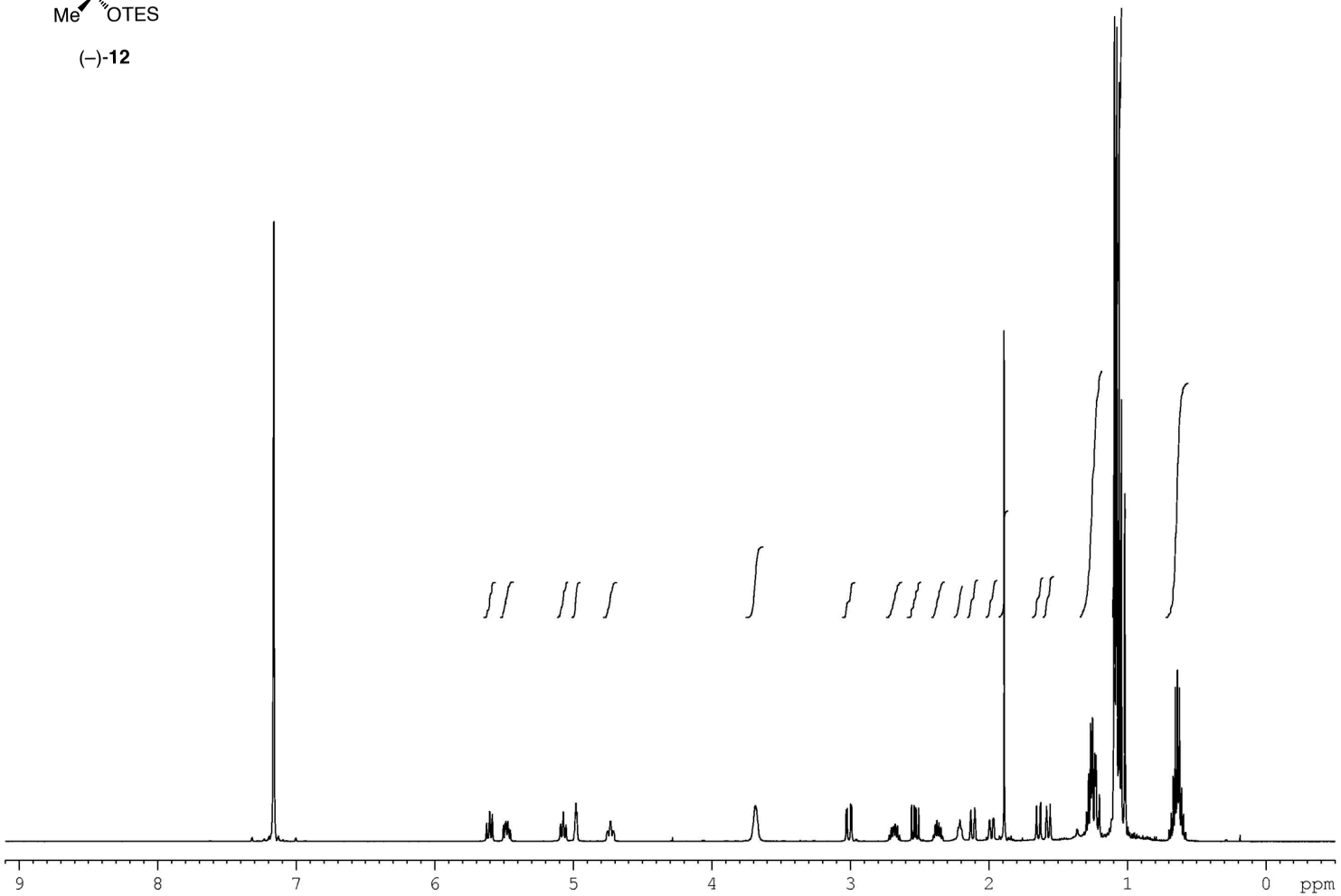

Ot-Bu
O
H
O
O
H
OPMB
HO
Me
OTES

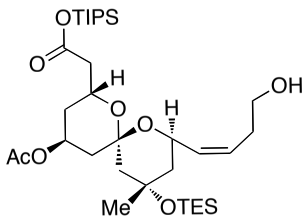
(–)-**19**


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



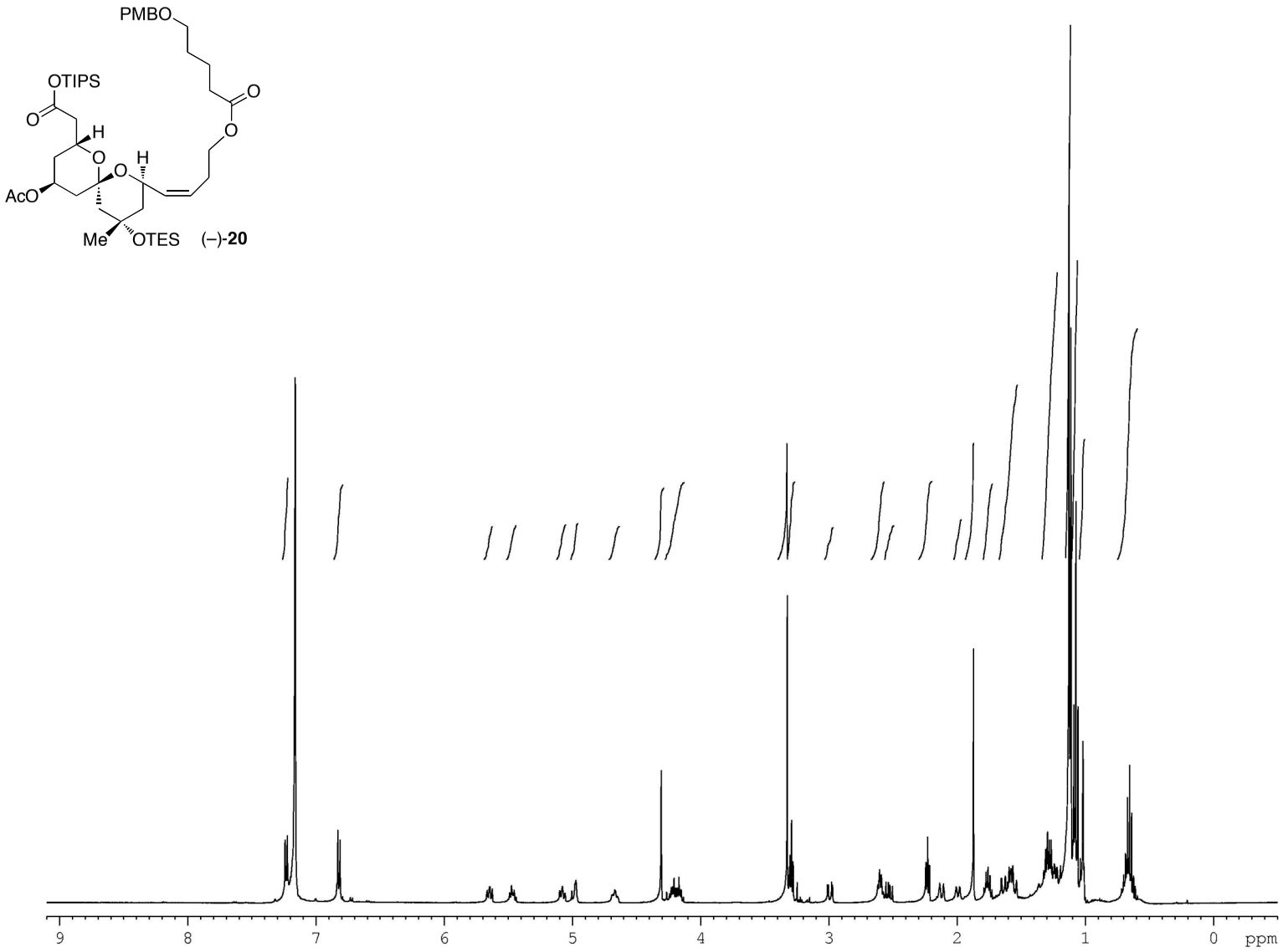
(–)-**12**

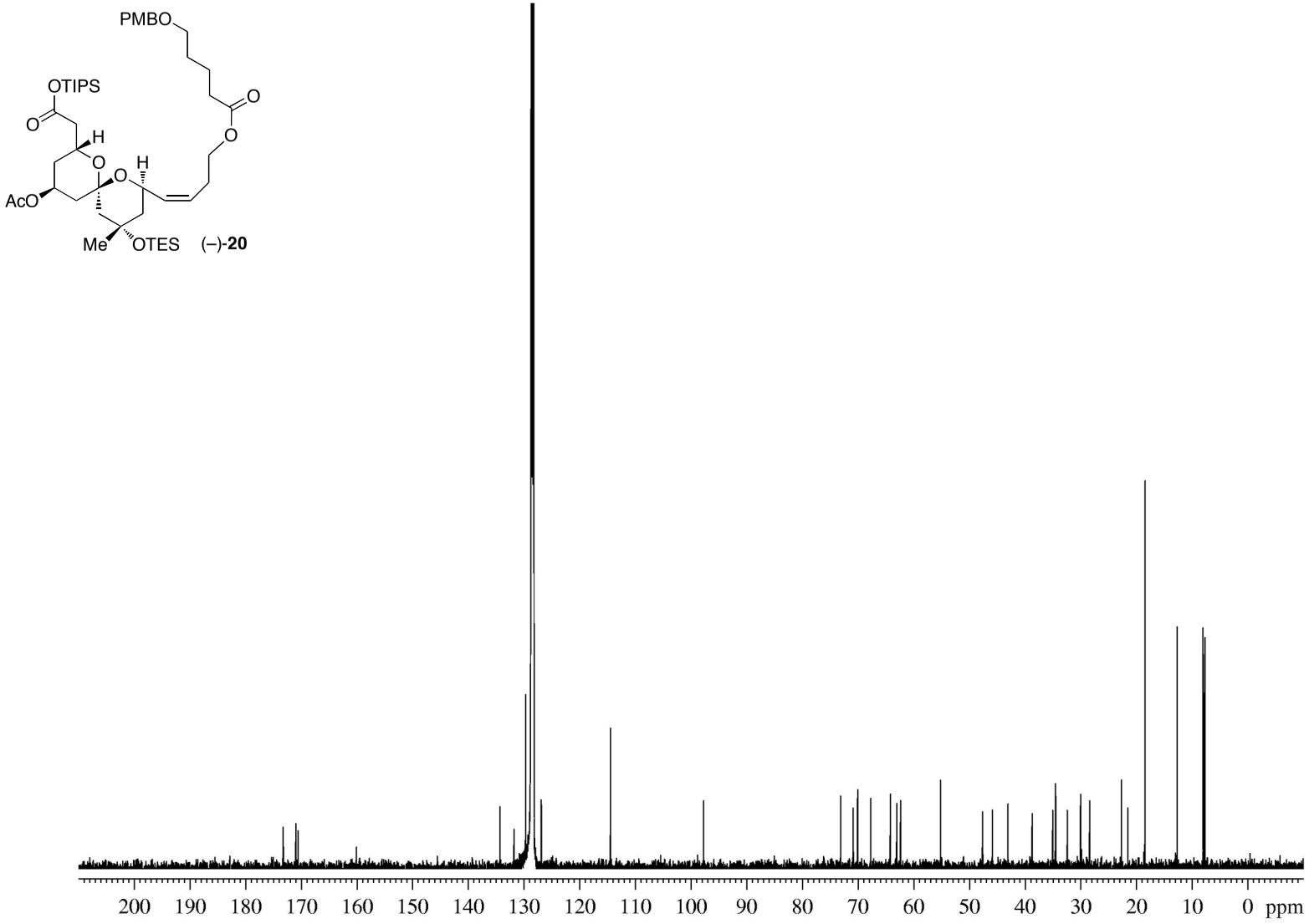


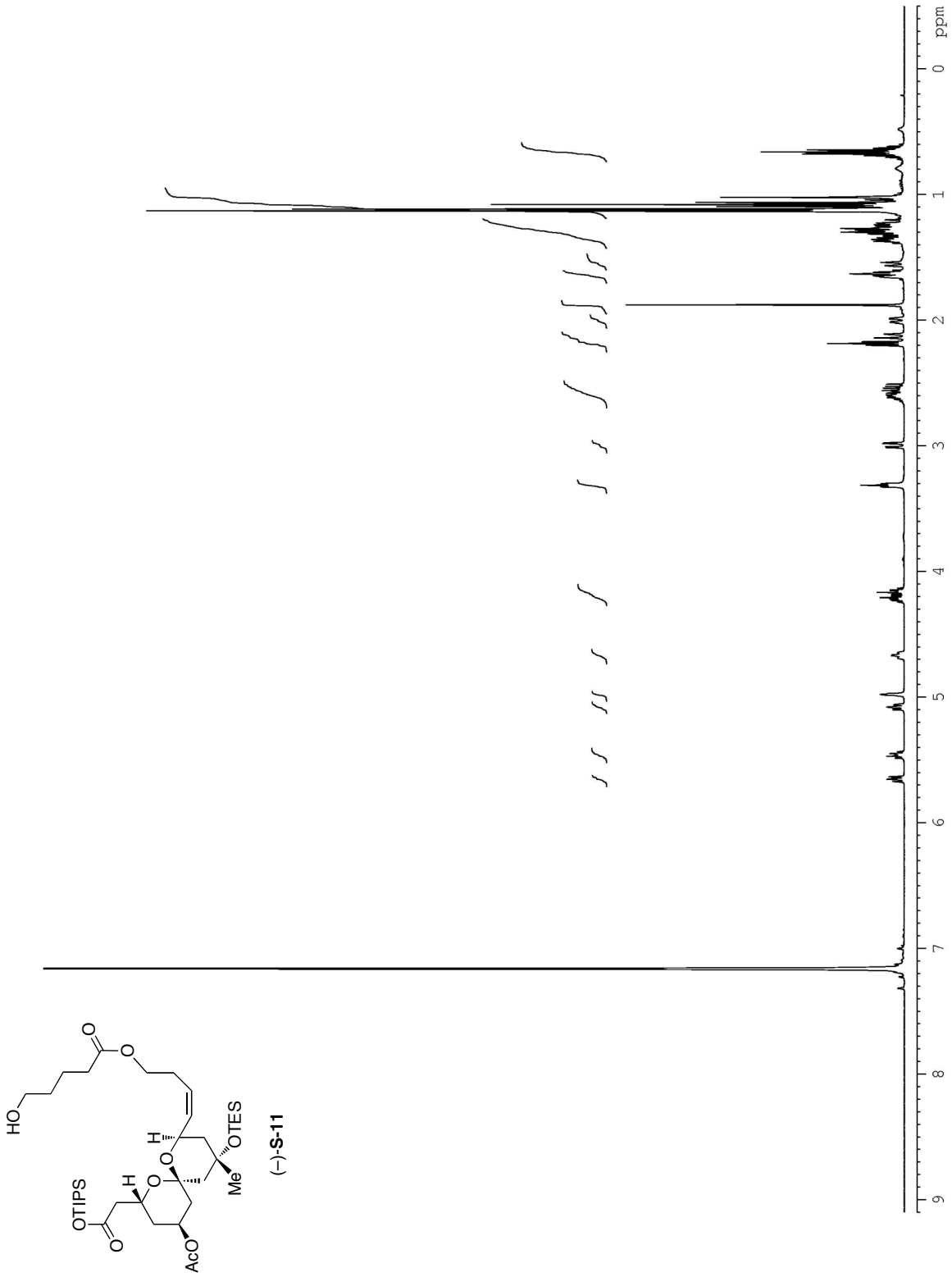

OTIPS
O
H
O
O
H
OH
AcO
Me
OTES

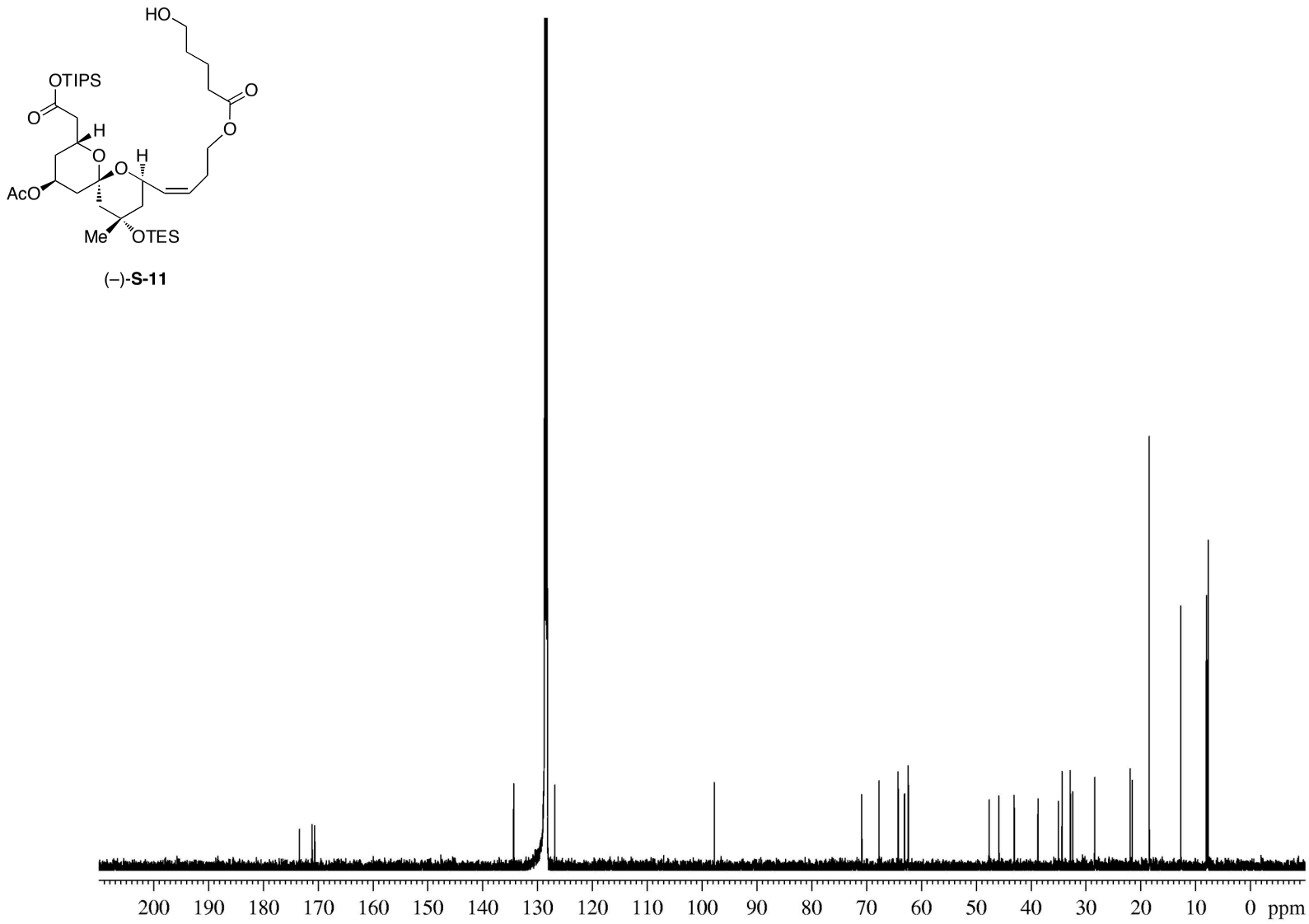
(–)-**12**

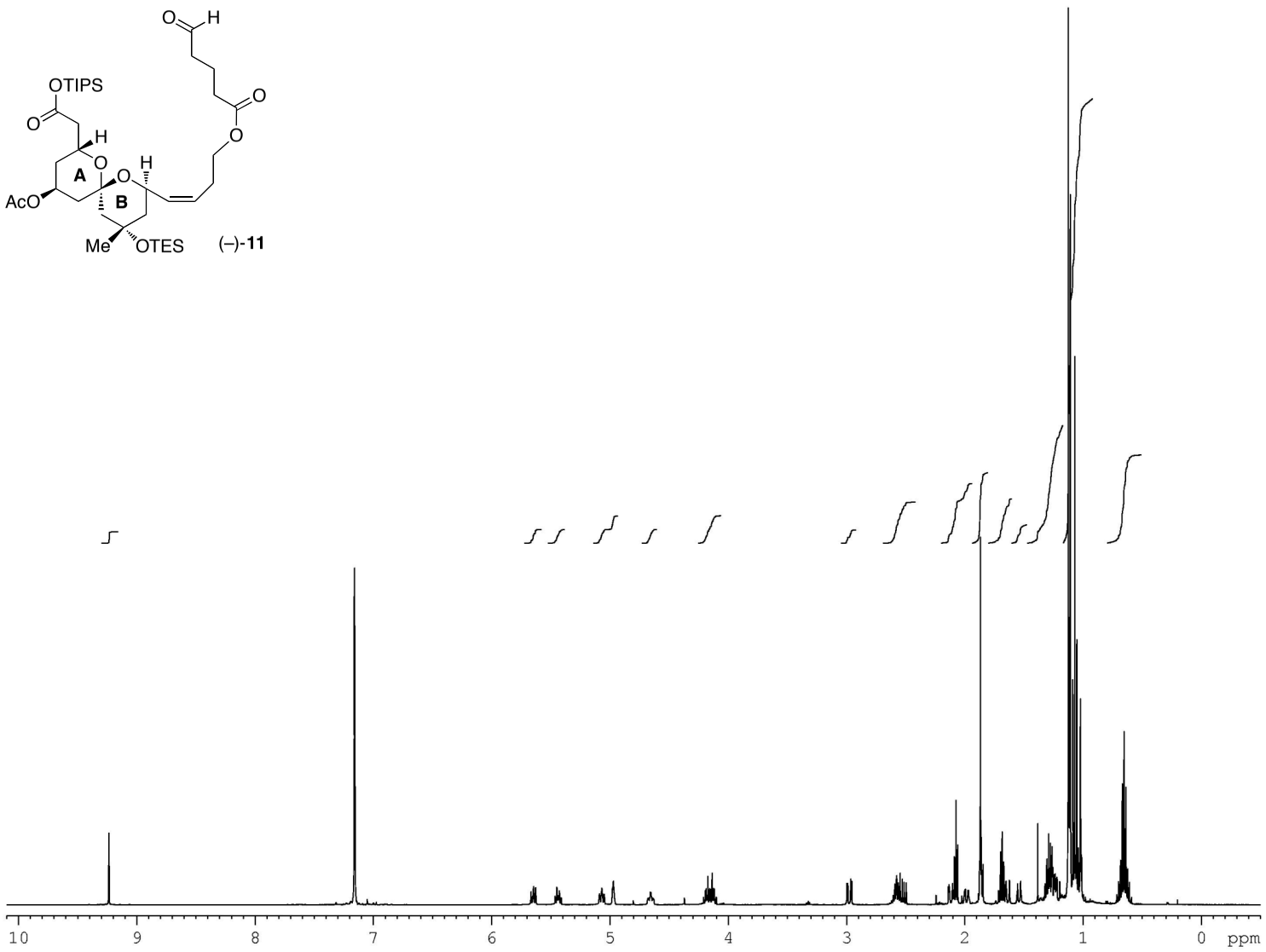
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

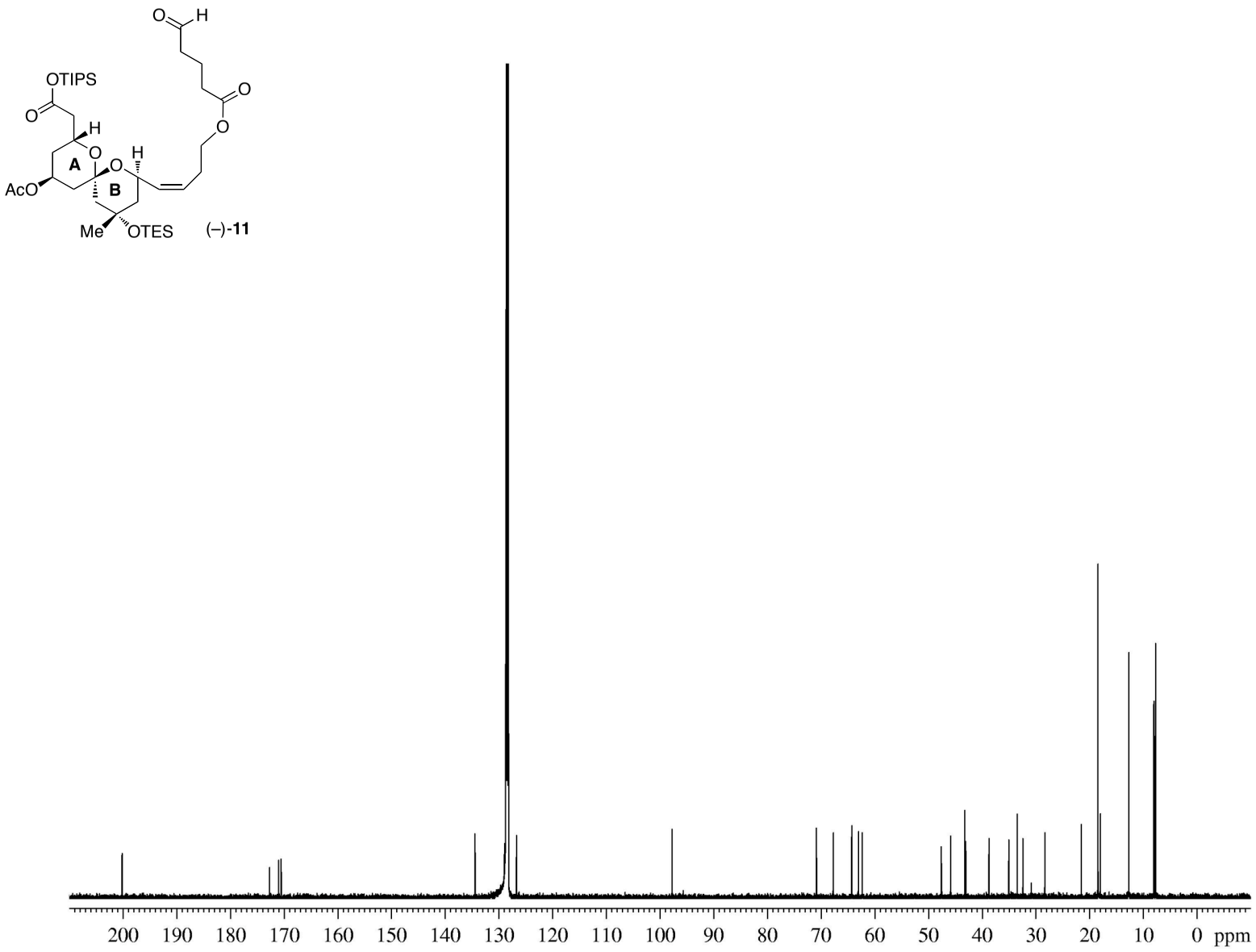

PMBO
OTIPS
O
O
H
O
O
H
AcO
Me
OTES
(–)-20
9
8
7
6
5
4
3
2
1
0
ppm

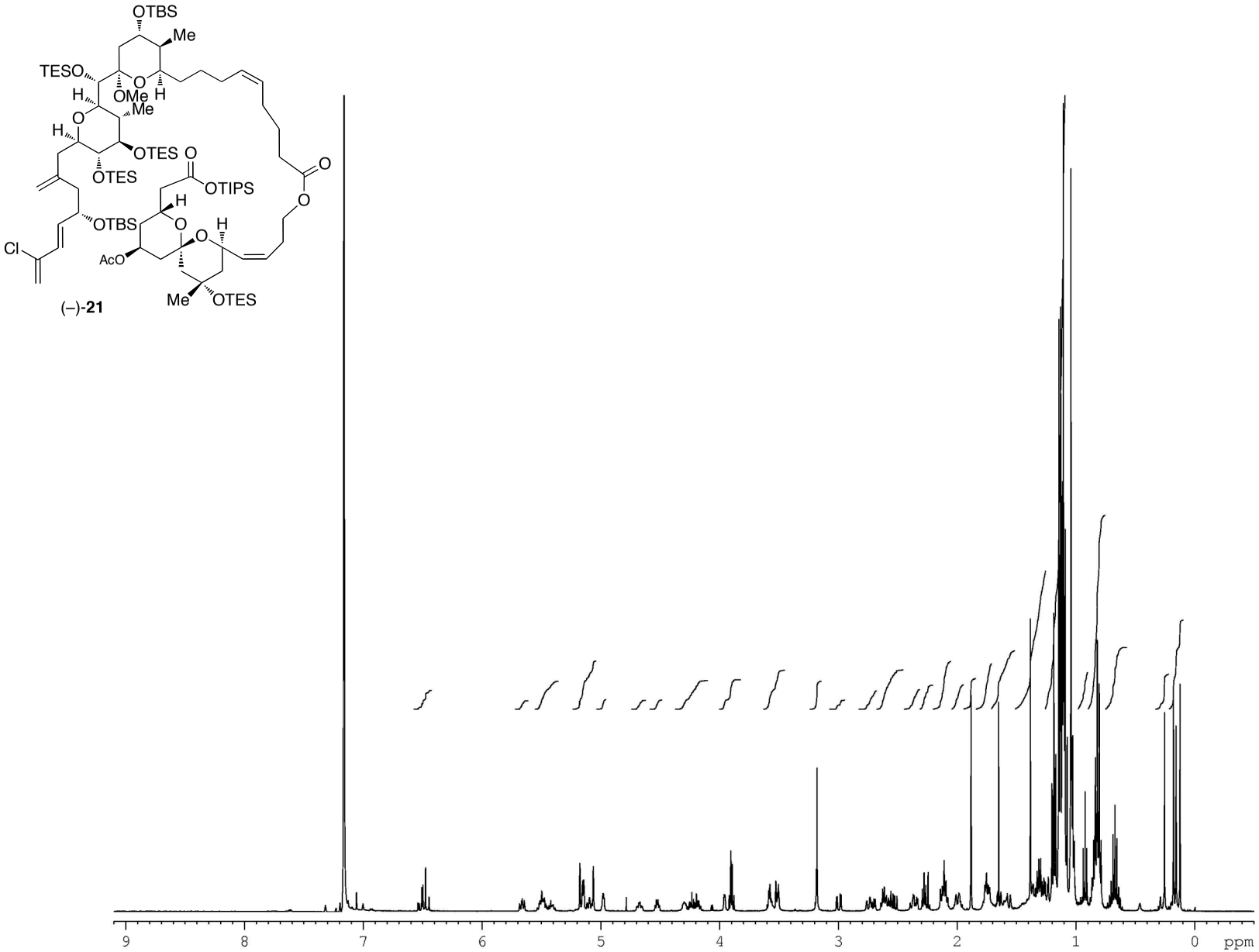

PMBO
OTIPS
O
O
H
O
O
H
AcO
Me
OTES
(–)-20
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HO
OTIPS
AcO
Me
OTES
H
H
O
O
O
O
O
O
(–)-S-11
9
8
7
6
5
4
3
2
1
0
ppm

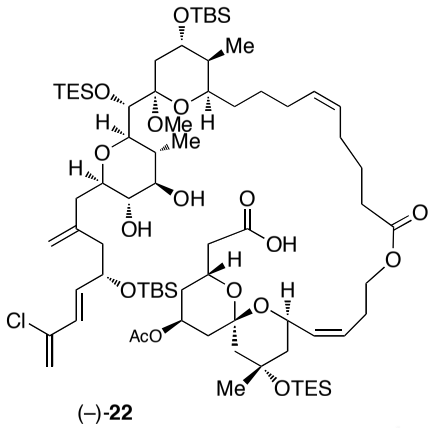

HO
OTIPS
O
O
H
O
O
H
O
AcO
Me
OTES
(–)-S-11
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OTIPS
O
H
O
A
O
H
O
B
AcO
Me
OTES
O
H
O
O
(–)-11
10
9
8
7
6
5
4
3
2
1
0
ppm


OTIPS
O
H
A
O
O
H
AcO
B
Me
OTES
(–)-11
O
H
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

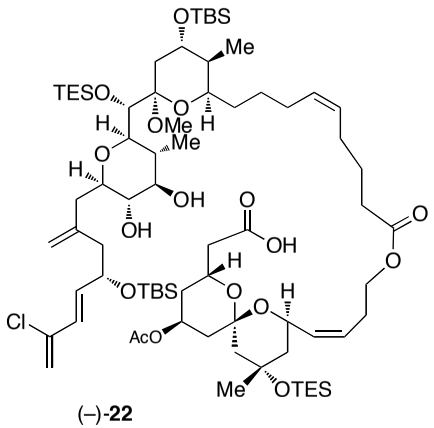

OTBS
Me
TESO
O
H
OMe
H
Me
O
H
OTES
O
OTES
OTES
O
OTIPS
H
O
OTBS
O
H
Cl
AcO
Me
OTES
(–)-21
9
8
7
6
5
4
3
2
1
0
ppm

OTBS
Me
OMe H
Me
TESO
H
O
H
O
OTES
OTES O
OTES
OTBS
OTIPS
H
O
H
O
AcO
Me
OTES
Cl
(–)-21
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OTBS
Me
TESO
O
H
OMe H
Me
H
O
OH
OH
O
OH
O
O
H
OTBS
O
H
Cl
O
AcO
Me
OTES

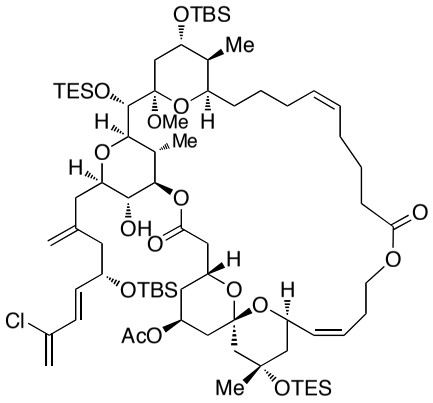
(–)-**22**

9
8
7
6
5
4
3
2
1
0
ppm


OTBS
Me
TESO
O
H
OMe
H
Me
O
H
OH
OH
O
OH
O
H
O
OTBS
O
H
Cl
AcO
O
Me
OTES

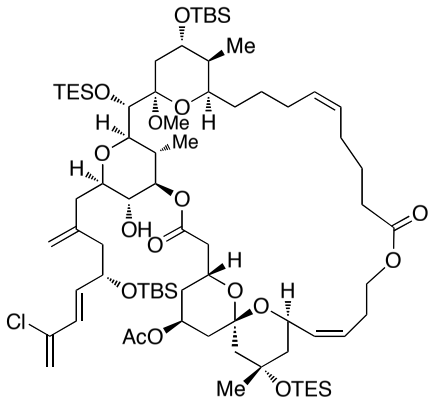
(–)-**22**

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OTBS
Me
TESO
O
H
OMe
H
O
Me
H
O
OH
O
O
O
H
OTBS
O
O
H
Cl
AcO
Me
OTES

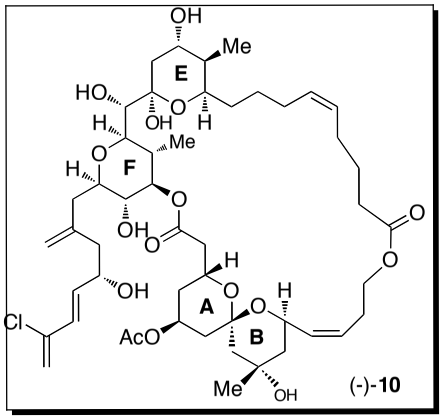
(–)-**S-10**

9
8
7
6
5
4
3
2
1
0
ppm


OTBS
Me
TESO
O
H
OMe
H
Me
O
H
O
OH
O
O
O
H
OTBS
O
H
O
Cl
AcO
Me
OTES

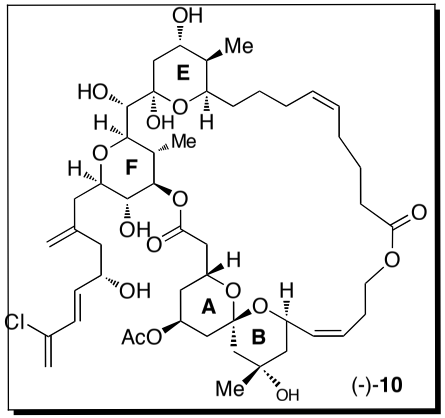
(–)-**S-10**

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


OH
Me
E
HO
O
H
OH
H
Me
F
O
O
OH
O
H
O
O
O
H
OH
A
O
H
Cl
AcO
B
Me
OH
(-)-10

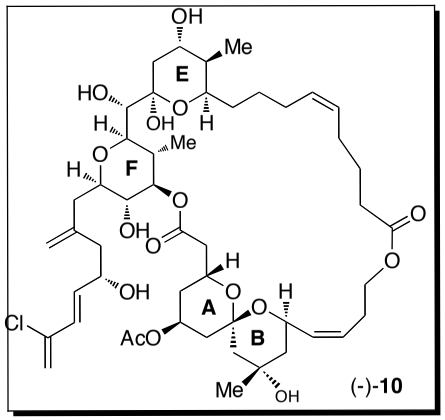
CD_3CN

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OH
Me
E
HO
OH
H
O
H
Me
H
O
F
O
OH
O
O
O
H
H
O
OH
A
O
H
Cl
AcO
B
Me
OH
(-)-10

CD_3CN

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OH
Me
E
HO
OH
H
O
H
Me
O
F
H
O
OH
O
O
O
H
OH
A
O
H
Cl
O
AcO
B
Me
OH
(-)-10

DMSO-d_6

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm