Supporting Information for:

Gram-Scale Synthesis of (+)-Spongistatin 1. Development of an Improved, Scalable Synthesis of the F-Ring Subunit, Fragment Union, and Final Elaboration

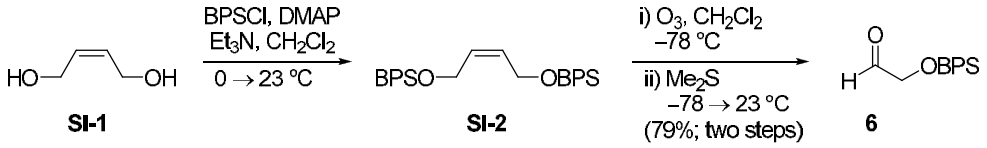
Amos B. Smith, III*, Takashi Tomioka, Christina A. Risatti, Jeffrey B. Sperry, and Chris Sfouggatakis

Department of Chemistry, Monell Chemical Senses Center, and Laboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, Pennsylvania19104

General Experimental

All non-aqueous reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise noted. All solvents were filtered under argon through activated alumina and copper solvent purification system supplied by Innovative Technology. All argon was deoxygenated by passing it through an "OXICLEAR" tube from Aldrich. Triethylamine, hexamethylphophoramide, hexamethyldisilazane, and diisopropylamine were freshly distilled from calcium hydride. *n*-Butyllithium and *t*-butyllithium were purchased from Aldrich and titrated immediately before use with diphenylacetic acid. Cerium(III) chloride hydrate was dried under vacuum at 110 °C overnight and stored in a dessicator. All other commercially available reagents were used as received. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 230 - 400 mesh) supplied by either Sorbent Technologies or Silicycle. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Infrared spectra were recorded on a Perkin-Elmer Model 283B FT/IR spectrometer. ^{1}H and ^{13}C NMR data was obtained on a Bruker AM-500 spectrometer and chemical shifts are reported (ppm) relative to chloroform (d 7.26), benzene (d 7.15), or acetonitrile (d 1.94) for ^{1}H NMR and either chloroform (d 77.0), benzene (d 128.0), acetonitrile (d 118.69) for ^{13}C NMR.

Large-Scale Preparation of Aldehyde (+)-7

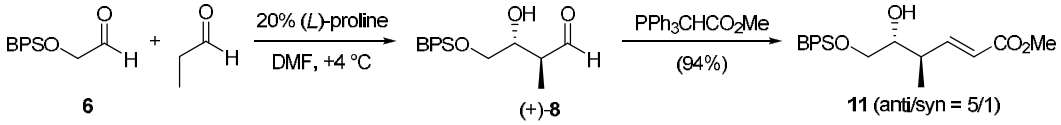


SI-1 **SI-2** **6**

Aldehyde 6. To a 0 °C solution of *cis*-2-butene-1,4-diol **SI-1** (16.5 g, 15.4 mL, 0.187 mol, 1.0 equiv.) in 400 mL of dry CH_2Cl_2 was added DMAP (2.27 g, 1.87 mmol, 0.10 equiv.) and triethylamine (56 mL, 0.56 mol, 3.0 equiv.). To this solution was added dropwise BPSCl (108 g, 102 mL, 0.392 mol, 2.1 equiv.) via addition funnel. Once addition is complete (ca. 1.5 hours), the addition funnel was rinsed with 50 mL of CH_2Cl_2. The cloudy reaction was allowed to slowly warm to 23 °C and allowed to stir at this temperature overnight (~14 hours total reaction time). The reaction was quenched with 200 mL of saturated $NaHCO_3$, diluted with 200 mL of water and extracted. The aqueous layer was extracted with two 250 mL portions of CH_2Cl_2 and the combined organics were washed with 200 mL of brine. The organics were dried over sodium sulfate and concentrated to yield alkene **SI-2** as a pale-yellow oil that was used in the next reaction without further purification.

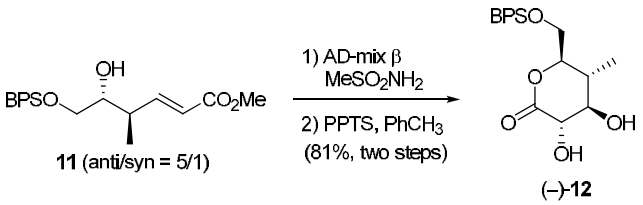
A solution of the above **SI-2** in 300 mL of CH_2Cl_2 was cooled to –78 °C. Ozone was bubbled through until the solution remained blue (ca. 4 hours on this scale). Argon was then bubbled through the solution to remove the excess ozone for approximately 20-30 minutes. Methylsulfide (64 mL, 871 mmol, 4.6 equiv.) was added dropwise via addition funnel over 1 hour. The reaction was removed from the –78 °C bath and allowed to warm to ambient temperature. The decomposition of the ozonide was monitored by TLC until complete (usually 3 days before ozonide decomposition was judged complete by TLC). The reaction was diluted with 750 mL of diethyl ether and washed with brine (2 x 150 mL). The organics were dried over sodium sulfate and concentrated. Silica gel chromatography (98/2 Hex/EtOAc to 90/10 Hex/EtOAc) provided 88.0 g of *tert*-

butyldiphenylsilyloxyacetaldehyde **6** as a colorless oil (79%; two steps) with spectral data consistent with values reported in the literature.[21]



Ester 11. Into a 4 °C suspension of *tert*-butyldiphenylsilyloxyacetaldehyde (**6**) (107.5 g, 0.360 mol, 1.0 equiv.) and *L*-proline (8.29 g, 72 mmol, 0.2 equiv.) in dioxane (350 mL) and DMF (55 mL) was added dropwise a solution of propionaldehyde (131 mL, 1.8 mol, 5.0 equiv.) in dioxane (350 mL) over 28 hours via addition funnel. The mixture was allowed to stir for an additional 28 hours at the same temperature. Following completion, the reaction was diluted with a 1:1 hexanes:diethyl ether mixture (2 L) and vigorously washed with 20 portions of water (400 mL) and one portion of brine (400 mL). The organics were dried over Na_2SO_4 and concentrated. The crude oil was used directly for the next reaction. Attempts to purify this material led to significant depreciation of the yield, presumably due to the instability of (+)-**8** to silica gel.

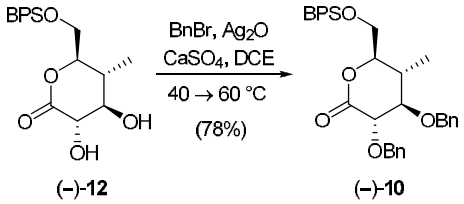
Into a solution of unpurified (+)-**8** in 250 mL of CH_2Cl_2 was added dropwise a solution of PPh_3=$CHCO_2Me$ (180.5 g, 0.54 mol, in 540 mL CH_2Cl_2, 1.5 equiv.) via addition funnel over 5 hours, keeping the internal temperature of the solution below 30 °C. The addition funnel was rinsed with an additional 100 mL of CH_2Cl_2 and the reaction was stirred for 10 hours at room temperature. The solvent was removed under reduced pressure and the crude material dissolved in300 mL of hexanes. The mixture was cooled to 0 °C to precipitate the triphenylphosphine oxide and filtered. The hexanes was evaporated and the material purified by silica gel chromatography (Hex/EtOAc = 95/5 to 85/15) to afford 139.6 g (94%; two steps) of **11** as an inseparable 5/1 mixture of anti/syn diastereomers.



Lactone (–)-12. A mixture of $K_2OsO_2(OH)_2$ (317 mg, 0.862 mmol, 0.006 equiv.), $(DHQD)_2PHAL$ (1.68 g, 2.16 mmol, 0.015 equiv.), $K_3Fe(CN)_6$ (142 g, 431.1 mmol, 3.0 equiv.), K_2CO_3 (59.6 g, 431.1 mmol, 3.0 equiv.), and $MeSO_2NH_2$ (13.7 g, 143.7 mmol, 1.0 equiv.) in 1:1 *t*-BuOH/H_2O (440 mL) was stirred for 30 minutes at room temperature. This mixture was slowly poured into a4 °C solution of **11** (59.3 g, 143.7 mmol, 1.0 equiv.) in *t*-BuOH/H_2O (1 L). The reaction was stirred via mechanical stirrer at 4 °C for 48 hours. When complete, solid $Na_2S_2O_3$ (34 g) was added and the mixture stirred for 1.5 hours after warming to room temperature (color change from orange to dark green). After phase separation (upper: *t*-BuOH, lower: H_2O), the aqueous layer was extracted five times with EtOAc (500 mL). The combined organics were dried over Na_2SO_4 and concentrated. The unpurified triol was used directly for the next reaction.

The unpurified triol was azeotroped twice with benzene (200 mL) and dissolved in toluene (1 L). PPTS (38.4 g, 0.153 mmol, 1.0 equiv.) was added and the reaction was stirred for 2 hours at room temperature. When complete, the reaction was quenched with a saturated $NaHCO_3$ solution (300 mL). The organics were washed with brine (300 mL) and concentrated. The crude oil was purified by silica gel chromatography (Hex/EtOAc = 3/1 to 2/3) to afford (–)-**12** as a colorless, thick paste (40.2 g, 81%; two steps, based on *anti* diastereomer). $[a]^{20}_D$ –33.8 (*c* 0.56, $CHCl_3$); IR (neat) 3419, 3071, 2930, 1739, 1471, 1428, 1390, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 7.67-7.63 (m, 4H), 7.47-7.37 (m, 6H), 4.04 (d, *J* = 10.0 Hz, 1H), 4.00 (dt, *J* = 10.1, 2.4 Hz, 1H), 3.94 (dd, *J* = 11.8, 2.3 Hz, 1H), 3.76 (dd, *J* = 11.8, 2.5 Hz, 1H), 3.62 (t, *J* = 10.3 Hz, 1H), 3.40-3.30 (br, 1H), 2.80-2.70 (br, 1H), 2.42 (m, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.06 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) d 173.1, 135.6,

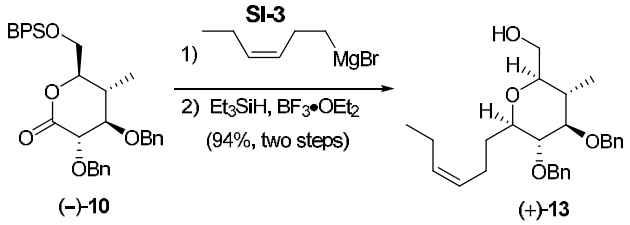
135.5, 132.8, 132.5, 129.9, 129.8, 127.8, 127.7, 84.3, 73.3, 72.9, 62.9, 34.8, 26.8, 19.2, 13.2; High resolution mass spectrum (+ESI) *m/z* 437.1757 $[(M+Na)]^+$; calcd for $C_{23}H_{30}O_5SiNa$ 437.1760].



Bis-Benzylether (–)-10. *This reaction is carried out in the absence of light*. To a solution of (–)-**12** (42.1 g, 101.5 mmol, 1.0 equiv.) in anhydrous 1,2-dichloroethane (210 mL) was added freshly prepared[1] silver(I) oxide (46.9 g, 213 mmol, 2.0 equiv.), followed by anhydrous $CaSO_4$ (69.1 g, 507 mmol, 5.0 equiv.) and freshly distilled benzyl bromide (23.8 mL, 213 mmol, 2.0 equiv.). The suspension was heated to 40 °C and stirred vigorously for 24 hours. The reaction was allowed to cool to room temperature and an additional portion of silver(I) oxide (46.9 g, 213 mmol, 2.0 equiv.) and benzyl bromide (23.8 mL, 213 mmol, 2.0 equiv.) were added. The suspension was heated to 60 °C and stirred vigorously for an additional 8 to 10 hours until judged complete by TLC. Once complete, the mixture was cooled to room temperature, filtered through Celite and concentrated. The residue was purified by silica gel chromatography (Hex/EtOAc = 9/1) to afford 47.1 g (78%) of (–)-**10** as a colorless paste. Any additional monobenzylated product (17-20 %) can be recycled according to these described conditions. $[a]^{20}_D$ –45.6 (*c* 1.07, $CHCl_3$); IR (neat) 3068, 2930, 1749, 1454, 1428, 1390, 1360, 1231, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 7.69-7.26 (m, 20H), 5.09 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.09 (d, *J* = 7.3 Hz, 1H), 4.04 (dt, *J* = 10.1, 2.6, Hz, 1H), 3.91 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.75 (dd, *J* = 11.8, 3.0

[1] Silver(I) oxide can be easily prepared by dissolving 90 g of NaOH in 1.0 L of water and adding this solution SLOWLY over 3 hours to a solution of 370 g of $AgNO_3$ in 1.0 L of water at ambient temperature. This mixture is stirred via mechanical stirrer in a 4 L flask covered with aluminum foil overnight. The suspension is filtered and the solid washed with 2 L of water and 1 L of diethyl ether. The solid silver(I) oxide is collected and placed into a 1 L flask and placed under vacuum on a rotary evaporator overnight (flask protected from light with foil). The following morning, the flask is placed under high vacuum until a free-flowing solid remains and no water collects in vacuum trap (approximately 2 days). Silver(I) oxide is stored in dark bottles in a dessicator.

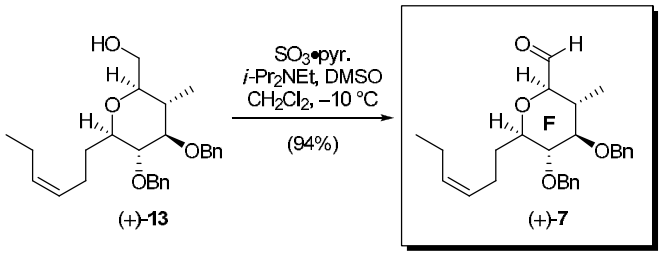
Hz, 1H), 3.50 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.38-2.30 (m, 1H), 1.05 (s, 9H), 1.03 (d, *J* = 3.4 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) d 170.4, 137.7, 137.3, 135.7, 135.5, 133.0, 132.6, 129.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 82.2, 80.8, 79.8, 74.1, 63.1, 35.4, 26.8, 19.3, 14.1; High resolution mass spectrum (+ESI) *m/z* 617.2718 $[(M+Na)]^+$; calcd for $C_{37}H_{42}O_5SiNa$ 617.2699].



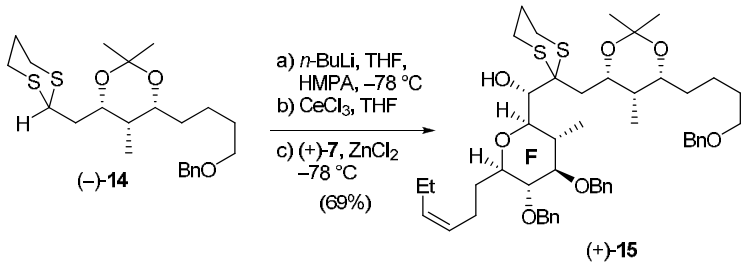
A solution of (–)-**10** (25.0 g, 42 mmol, 1.0 equiv.) in THF (250 mL) was cooled to –78 °C and a 1M solution of **SI-3** (84 mmol, 84 mL) was added dropwise over 30 minutes. After stirring for 1.5 hours at the same temperature, the reaction was warmed to 0 °C and quenched with a saturated NH_4Cl solution (150 mL) and diluted with water (50 mL). After phase separation, the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The hemiketal was taken on to the next step without further purification.

To a solution of the intermediate hemiketal in 380 mL of CH_3CN at –40 °C was added Et_3SiH (20.3 mL, 126 mmol, 3.0 equiv.) followed by $BF_3 \cdot OEt_2$ (16.0 mL, 126 mmol, 3.0 equiv.) dropwise under argon. After stirring for 30 minutes at the same temperature, the reaction was allowed to slowly warm to 0 °C over 1.25 hours. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (250 mL) and diluted with water (100 mL). After phase separation, the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (Hex/EtOAc = 95/5 to 80/20) to

yield 16.76 g of (+)-**13** as a colorless oil (94%; two steps) with spectral data matching our previous reports.[15]



Aldehyde (+)-7. To a solution of alcohol (+)-**13** (35.0 g, 82.4 mmol, 1.0 equiv.) in methylene chloride (600 mL) at –10 °C was added diisopropylethylamine (43.0 mL, 247 mmol, 3.0 equiv.), followed by DMSO (31.8 mL, 412 mmol, 5.0 equiv.) and sulfur trioxide/pyridine complex (39.4 g, 247 mmol, 3.0 equiv.). The reaction was stirred for 45 minutes at –10 °C and allowed to warm slowly to –5 °C over 1 hour. The reaction was quenched with saturated $NaHCO_3$ (600 mL) and extracted three times with 400 mL portions of CH_2Cl_2. The combined organic extracts were washed with water (150 mL), brine (150 mL), and dried over sodium sulfate. After filtration and concentration, silica gel chromatography (90/10, Hex/EtOAc) provided the desired aldehyde (+)-**7** (33.4 g, 94%) as a colorless oil: $[\alpha]^{20}_D$ +61.2 (*c* 1.86, $CHCl_3$); IR (neat) 2962, 1740, 1453, 1359, 1096, 697 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.40 (d, *J* = 2.5 Hz, 1H), 7.29-7.08 (m, 3H), 5.47-5.37 (m, 2H), 4.75 (dd, *J* = 11.3, 5.6 Hz, 2H), 4.46 (dd, *J* = 5.3, 8.1 Hz, 2H), 3.20 (app dt, *J* = 2.6, 9.3 Hz, 1H), 3.12-3.06 (m, 2H), 2.93 (dd, *J* = 8.7, 1.4 Hz, 1H), 2.27 (m, 2H), 2.04 (m, 2H), 1.94 (m, 1H), 1.68 (m, 1H), 1.56 (m, 1H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 138.2, 138.0, 132.5, 128.5, 128.4, 128.4, 128.2, 127.8, 127.8, 86.4, 84.3, 83.1, 78.4, 76.7, 75.7, 75.3, 38.2, 31.7, 22.9, 20.5, 14.3, 12.0; High resolution mass spectrum (+ESI) *m/z* 445.2361 [$(M+Na)^+$; calcd for $C_{27}H_{34}O_4Na$ 445.2457].

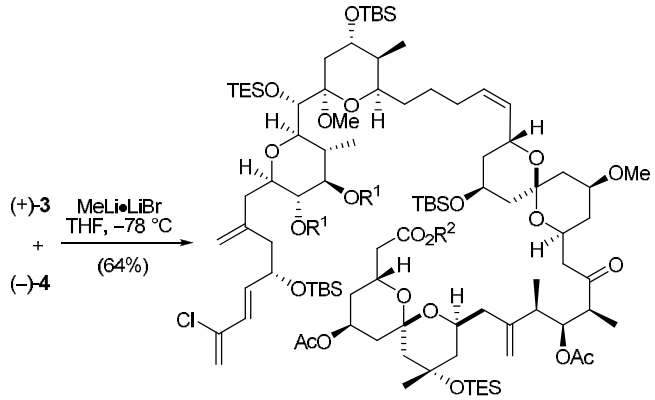


Flask A: A flame-dried flask was charged with anhydrous $CeCl_3$ (16.9 g, 68.6 mmol, 3.5 equiv.), heated to 110 ºC (oil bath temp) under high vacuum for 16 hours with vigorous stirring. The system was then purged with argon, charged with THF (100 mL) and the resulting white slurry was stirred vigorously for a further 2 hours.

Flask B: To a –78 ºC solution of dithiane (–)-**14** (25.0 g, 58.9 mmol, 3.0 equiv.; dried under high vacuum for 16 hours) in THF (300 mL) and HMPA (16.4 mL, 88.2 mmol, 4.5 equiv.) was added *n*-BuLi (2.5 M in hexanes, 23.5 mL, 58.9 mmol, 3.0 equiv.) slowly via syringe over 1 hour. The resulting deep red solution was stirred at –78 ºC for 1 hour. The contents of *Flask A* were then added to *Flask B* via a thick gauge cannula, and the resulting red slurry was stirred at–78 ºC for 1.5 hours.

Flask C: To a –78 ºC solution of aldehyde (+)-**7** (8.3 g, 19.6 mmol, 1.0 equiv.; dried under high vacuum for 16 hours) in THF (100 mL) was added $ZnCl_2$ (1 M in Et_2O, 21.6 mL, 21.6 mmol, 1.1 equiv.). After stirring for 30 minutes, the –78 ºC bath was removed and the solution was transferred via cannula into *Flask B* over 30 minutes. The resulting yellow slurry was stirred at –78 ºC for 3 hours, then diluted with 300 mL diethyl ether, quenched with 200 mL of saturated NH_4Cl solution and allowed to warm to room temperature. The aqueous phase was extracted three times with 250 mL portions of diethyl ether, the combined organic phases were then washed twice with 150 mL water, and 150 mL of brine, dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (Hex/EtOAc, 95/5 to 90/10 to 85/15) afforded alcohol (+)-**15** (11.4 g, 69%) as a pale yellow oil: $[\alpha]^{20}_D$ +1.9 (*c* 0.7, $CHCl_3$); IR (neat) 3356, 3029, 2934, 2859, 1454, 1387, 1358, 1270, 1094 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 15H), 5.37-5.34 (m, 2H), 4.91 (d, *J* =

11.0 Hz, 1H), 4.86 (d, *J* = 10.9 Hz, 1H), 4.66 (d, *J* = 2.3 Hz, 1H), 4.64 (d, *J* = 2.1 Hz, 1H), 4.50 (s, 2H), 4.43 (d, *J* = 8.2 Hz, 1H), 4.33 (d, *J* = 10.2 Hz, 1H), 3.91 (d, *J* = 10.1 Hz, 2H), 3.71 (d, *J* = 10.1 Hz, 1H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.33-3.30 (m, 1H), 3.23 (m, 2H), 2.81-2.67 (m, 5H), 2.31-2.28 (m, 1H), 2.23-2.20 (m, 1H), 2.11-1.95 (m, 6H), 1.86-1.84 (m, 1H), 1.67-1.61 (m, 2H), 1.56-1.47 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 1.35-1.33 (m, 4H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 5.2 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.5, 138.3, 132.0, 128.8, 128.4, 128.3, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 99.2, 86.5, 83.2, 78.9, 78.4, 75.1, 74.9, 73.4, 72.8, 72.4, 70.6, 70.1, 57.4, 40.3, 39.2, 36.7, 32.3, 31.9, 29.8, 29.6, 26.2, 25.9, 25.1, 23.5, 22.0, 20.6, 19.4, 14.4, 13.3, 5.0; High resolution mass spectrum (+ESI) *m/z* 869.4432 [$(M+Na)^+$; calcd for $C_{50}H_{70}O_7S_2Na$ 869.4563].

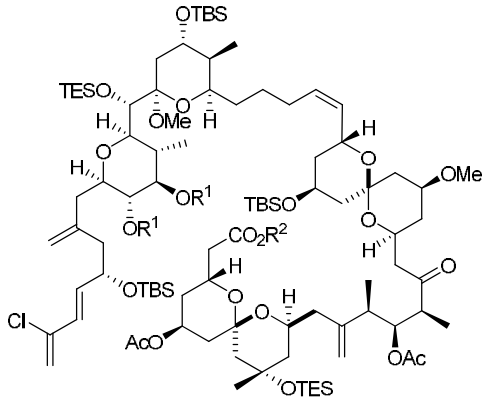


(+)-**19**: R^1 = TES, R^2 = TIPS

Alkene (+)-19. To a flame dried round bottom containing activated 4Å molecular sieves was added THF. The THF was degassed using the freeze-pump-thaw method (3X) before use in the pending reaction. To a –78 °C solution of Wittig salt (+)-**3** [azeotroped with benzene 3X then dried on high vacuum at 50 °C for 18 hours before use] (454 mg, 0.304 mmol, 1.4 equiv.) in THF (3.0 mL) was added MeLi as a complex with LiBr (1.3 M in ether, 0.25 mL, 0.320 mmol, 1.4 equiv.) dropwise and the resulting orange solution was allowed to stir for 30 minutes. A solution of aldehyde (–)-**4**

[azeotroped with benzene 3X then dried on high vacuum at room temperature for 2 hours before use] (237 mg, 0.21 mmol, 1.0 equiv.) in THF (3.0 mL) was added dropwise via cannula. The flask which had contained the aldehyde was then rinsed with THF (1.5 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 then warmed to room temperature over 2 hours. The resulting red solution was diluted with ether (15 mL) and then quenched by the addition of 10 mL of a saturated NH_4Cl/saturated $Na_2S_2O_3$ (4/1) solution. The aqueous phase was extracted three times with ether (15 mL) and the combined organic phases washed with saturated NaCl(10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate/hexanes (10/90 to 30/70) as an elutant afforded Wittig product (+)-**19** (412 mg, 64%). Subsequent elution with methanol/methylene chloride (5/95) allowed for recovery of the excess EF Wittig salt (+)-**3**. $[\alpha]^{25}_{D}$ +4.6 (*c* 1.0, C_6H_6); IR (thin film) 2953, 1733, 1464, 1370, 1251, 1111 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) d 6.48 (dd, *J* = 14.8, 5.1 Hz, 1H), 6.40 (d, *J* = 14.8 Hz, 1H), 5.72 (m, 1H), 5.59 (m, 2H), 5.50 (m, 1H), 5.15 (s, 2H), 5.09 (s, 2H), 5.05 (s, 1H), 5.01 (s, 1H), 4.97 (s, 1H), 4.49 (m, 2H), 4.27 (m, 2H), 4.18 (br t, *J* = 10.2 Hz, 1H), 3.92 (b rs, 2H), 3.90 (s, 1H), 3.48-3.37 (m, 3H), 3.31-3.25 (m, 2H), 3.16 (s, 3H), 3.09 (m, 1H), 3.05 (s, 3H), 2.96-2.89 (m, 2H), 2.79 (d, *J* = 13.6 Hz, 1H), 2.74 (dd, *J* = 18.5, 10.0 Hz, 1H), 2.66 (d, *J* = 6.9 Hz, 1H), 2.62 (dd, *J* = 13.3, 5.8 Hz, 1H), 2.57-2.30 (m, 8H), 2.21 (dd, *J* = 13.2, 9.5 Hz, 1H), 2.11 (m, 3H), 1.95 (br s, 2H), 1.92 (s, 3H), 1.78 (s, 3H), 1.76-1.55 (m, 8H), 1.48-1.19 (m, 13H), 1.17-1.12 (m, 29H), 1.08-0.98 (m, 36H), 0.85-0.75 (m, 6H), 0.67-0.57 (m, 6H), 0.28 (s, 9H), 0.25 (s, 9H), 0.22 (s, 3H), 0.18 (s, 9H), 0.13 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) d 209.5, 170.6, 170.1, 168.6, 147.9, 144.2, 138.8, 138.7, 132.2, 130.9, 126.4, 115.3, 115.1, 113.7, 101.5, 98.3, 97.1, 81.0, 80.3, 78.6, 77.9, 74.7, 73.8, 71.9, 71.3, 71.2, 70.7, 67.6, 66.9, 66.6, 65.3, 64.5, 62.3, 61.7, 55.1, 51.1, 47.9, 47.0, 46.6, 45.5, 44.5, 42.9, 42.7, 40.7, 40.0, 39.4, 38.9, 38.8, 38.4, 38.0, 35.0, 34.5, 33.0, 32.1, 30.4, 30.1, 28.7, 26.8, 26.2, 26.1, 21.3, 20.5, 18.4, 18.3, 18.0, 15.2, 13.8, 12.3, 12.1, 10.7, 7.6,

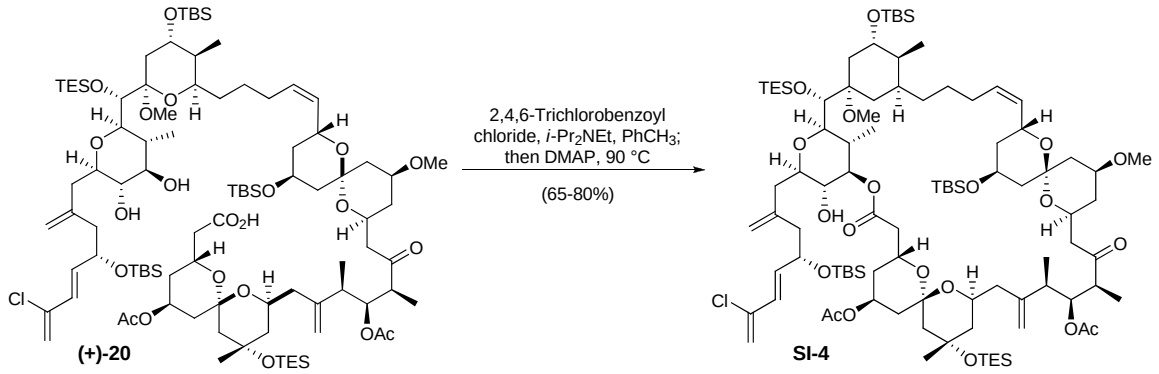
7.5, 7.3, 6.1, 1.7, 1.6, 0.36, 4.2, 4.5, 4.8, 4.9; high resolution mass spectrum (+ESI) *m/z* 2106.2068 [$(M+Na)^+$; calcd for $C_{106}H_{199}ClO_{22}NaSi_8$ 2106.2194].



(+)-**20** $R^1 = R^2 = H$

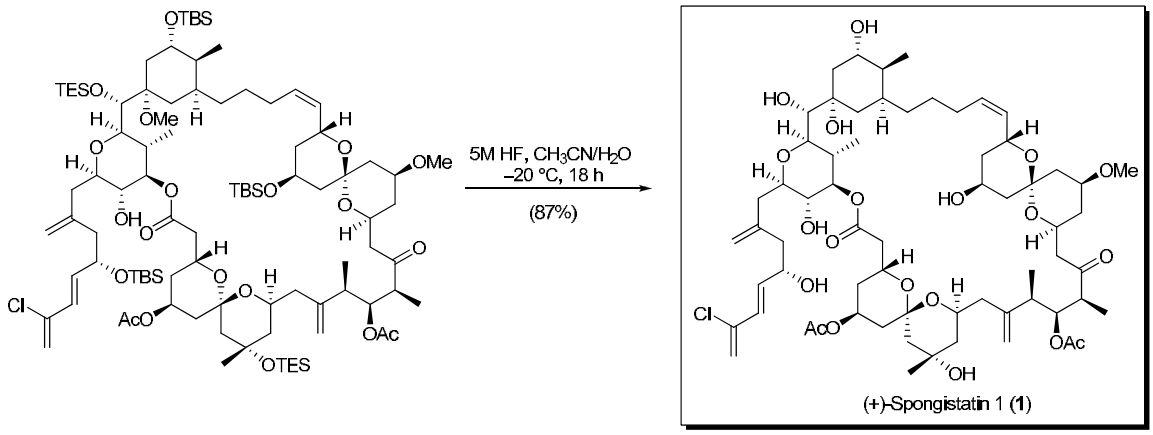
***Seco*-acid (+)-20**. To a solution of Wittig product (+)-**19** (412 mg, 0.187 mmol, 1 equiv.) in THF (10.8 mL) cooled to 0 °C was added TBAF (1M in THF, 0.56 mL, 0.56 mmol, 3 equiv.) over 1 hour via syringe pump. After an additional 2 hours at 0 °C, the reaction mixture was diluted with ether (25 mL) and washed with 1M $KHSO_4$ (15 mL) then brine (15 mL). The combined aqueous phases were then extracted twice with ether (25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography using ethyl acetate/hexanes (20/80 to 40/60) with 0.5 % AcOH as an elutant [the collection flask was diluted with 50 mL of toluene before concentrating to avoid the *seco*-acid being exposed to neat AcOH] afforded *seco*-acid (+)-**20** (249 mg, 73%). $[\alpha]^{25}_D$ +6.52 (*c* 1.4, C_6H_6); IR (thin film) 3447, 2953, 2856, 1733, 1464, 1372, 1250, 1110 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) d 6.44 (dd, *J* = 14.9, 4.9 Hz, 1H), 6.38 (d, *J* = 15.0 Hz, 1H), 5.71 (m, 1H), 5.59 (dd, *J* = 9.5, 2.6 Hz, 1H), 5.57-5.48 (m, 2H), 5.18 (s, 1H), 5.14 (s, 2H), 5.11 (s, 1H), 5.06 (s, 1H), 4.97 (s, 1H), 4.48-4.42 (m, 2H), 4.30-4.26 (m, 2H), 4.17 (m, 1H), 3.95 (m, 1H), 3.92 (s, 2H), 3.37-3.34 (m, 2H), 3.28-3.20 (m, 2H), 3.18 (s, 3H), 3.10 (dd, *J* = 18.4, 2.9 Hz, 1H), 3.05 (s, 3H), 3.03-2.99 (m, 1H), 2.84 (dd, *J* = 18.4, 5.1 Hz, 1H), 2.76-2.69 (m, 2H), 2.60 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.56-2.51 (m, 1H), 2.50-2.31 (m, 10H), 2.26-2.19 (m, 3H), 1.94 (s, 3H), 1.90-1.83 (m, 2H), 1.81 (s, 3H), 1.78-1.55 (m, 12H), 1.53-1.41 (m, 3H), 1.37 (s, 2H), 1.29 (d, *J* = 6.9, 3H), 1.23 (d, *J* = 7.0

Hz, 3H), 1.15 (t, *J* = 8.0 Hz, 9H), 1.09-0.99 (m, 45H), 0.85-0.75 (m, 6H), 0.66-0.59 (m, 6H), 0.23 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) d 209.5, 172.5, 170.4, 169.0, 147.9, 143.7, 138.9, 138.8, 132.1, 130.9, 126.4, 115.8, 115.1, 113.7, 101.7, 98.4, 97.4, 79.2, 78.9, 78.8, 75.8, 75.0, 73.9, 72.2, 71.2, 71.2, 70.8, 67.4, 67.0, 66.8, 66.6, 65.2, 64.3, 62.4, 61.5, 55.1, 51.2, 48.0, 47.9, 47.0, 46.3, 45.4, 44.2, 42.8, 40.6, 39.5, 39.3, 39.0, 38.8, 38.7, 38.4, 37.9, 35.1, 34.3, 32.9, 32.1, 30.6, 30.4, 28.5, 26.6, 26.2, 21.3, 20.6, 18.5, 13.9, 12.4, 10.7, 7.6, 7.6, 7.2, 6.2, 1.3, –4.1, –4.3, –4.5, –4.6, –4.80; High resolution mass spectrum (+ESI) *m/z* 1848.0687 [$(M+Na)^+$; calcd for $C_{94}H_{169}ClO_{22}NaSi_5$ 1848.0640].

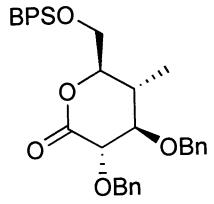


Macrocycle SI-4. To a solution of *seco*-acid (+)-**20** (180.0 mg, 0.099 mmol, 1.0 equiv.) in toluene (9.0 mL) was added *i*-Pr_2NEt (1.03 mL, 5.91 mmol, 60 equiv.) and 2,4,6-trichlorobenzoyl chloride (0.31 mL, 1.98 mmol, 20 equiv.) at room temperature under argon. The reaction mixture was stirred at ambient temperature for 4 hours, and diluted with additional toluene (28.3 mL). This solution was added via syringe pump (100 mL gas-tight glass syringe) to a solution of DMAP (605 mg, 4.95 mmol, 50 equiv.) in toluene (146 mL) at 90 ºC over 24 h. The flask was rinsed with 9.9 mL toluene and this solution was added via the same syringe over 12 hours. The flask containing the *seco*-acid was rinsed a second time with 6.6 mL of toluene and this solution was added via syringe pump over 4 hours. After stirring for and additional 9 hours, the reaction mixture was cooled to room temperature, and diluted with 120 mL of diethyl ether. The reaction was then quenched by the addition of 120 mL of saturated $NaHCO_3$ solution and extracted. The aqueous phase was extracted

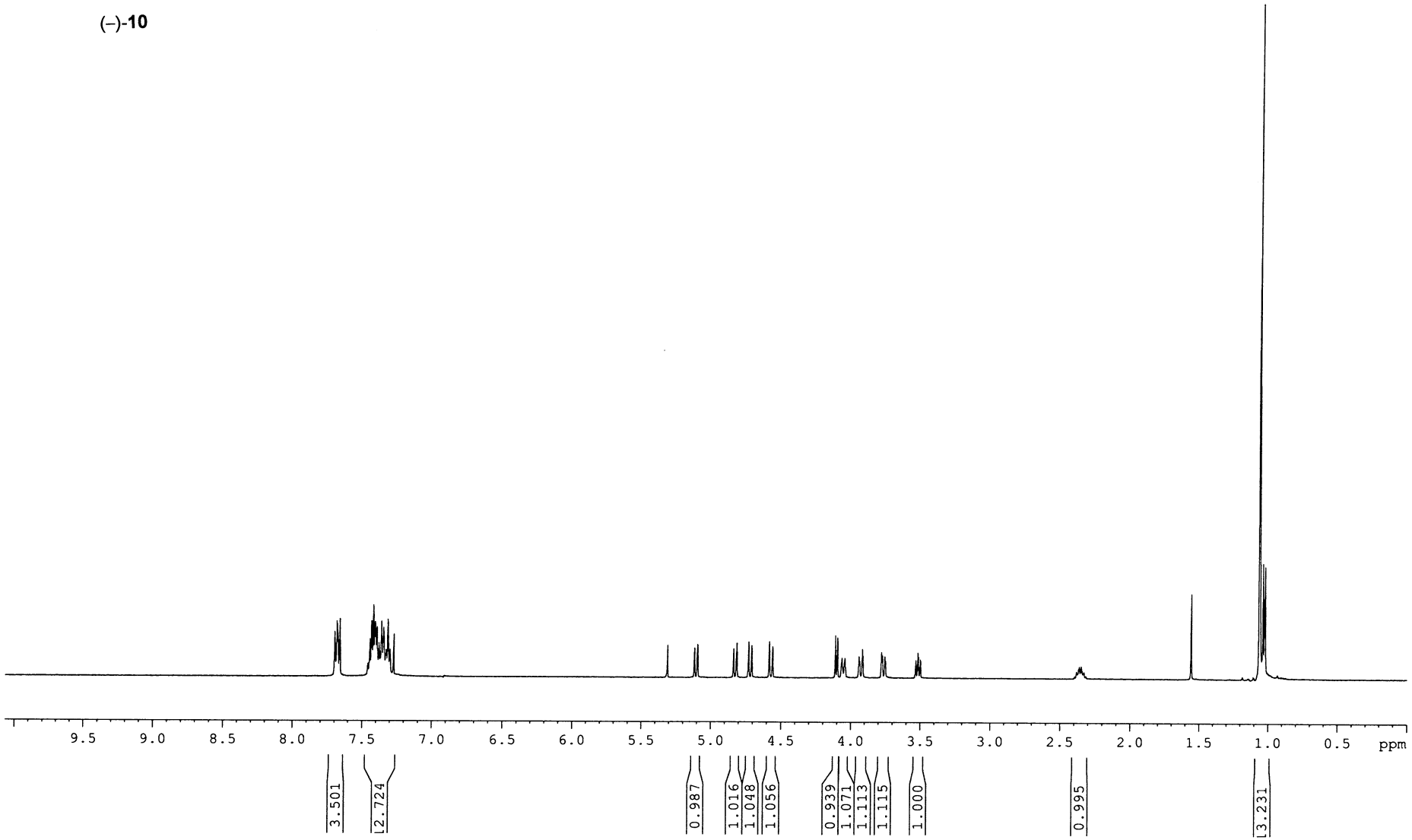
twice with 120 mL portions of EtOAc and the combined organic solutions were washed with brine, dried over Na_2SO_4, and concentrated. Silica gel chromatography, using a gradient of EtOAc/Hex (10/90 to 40/60) as eluant, provided 132 mg (74%; 81% on 24.0 mg scale) of the macrolide as a colorless oil. $[\alpha]^{25}_D$ +21.5 (*c* 1.05, C_6D_6); IR (thin film) 3482, 2931, 1751, 1733, 1652, 1590, 1464, 1373, 1252, 1112, 962, 836, 742 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) d 6.43 (dd, *J* = 14.9, 5.1 Hz, 1H), 6.37 (d, *J* = 15.0 Hz, 1H), 5.76 (dd, *J* = 11.2, 6.9 Hz, 1H), 5.61 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.46 (m, 1H), 5.37 (m, 1H), 5.17 (s, 1H), 5.15 (s, 1H), 5.08 (s, 1H), 5.05 (s, 1H), 5.04 (s, 1H), 4.94 (m, 2H), 4.83 (dd, *J* = 10.4, 8.8 Hz, 1H), 4.50 (m, 1H), 4.43 (dd, *J* = 12.1, 6.0 Hz, 1H), 4.37-4.35 (m, 2H), 4.12 (m, 1H), 4.00 (s, 1H), 3.94-3.91 (m, 2H), 3.51 (d, *J* = 10.4 Hz, 1H), 3.44-3.41 (m, 2H), 3.37 (s, 3H), 3.27 (m, 2H), 3.16-3.12 (m, 1H), 3.10-3.05 (m, 2H), 3.04 (s, 3H), 2.89-2.84 (m, 2H), 2.73-2.68 (m, 1H), 2.58-2.50 (m, 5H), 2.38-2.29 (m, 4H), 2.23-2.16 (m, 2H), 2.08 (m, 1H), 2.01-2.00 (m, 2H), 1.99 (s, 3H), 1.85 (s, 3H), 1.80-1.59 (m, 12H), 1.52-1.42 (m, 3H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 8.0 Hz, 10H), 1.12-1.10 (m, 13H), 1.04-0.99 (m, 33H), 0.89-0.79 (m, 6H), 0.62-0.57 (m, 7H), 0.21 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) d 208.9, 171.5, 170.3, 168.5, 147.9, 143.4, 138.9, 138.8, 132.7, 129.9, 126.4, 116.0, 115.1, 113.5, 101.7, 98.5, 97.0, 81.1, 80.1, 78.6, 75.0, 74.0, 73.4, 72.3, 71.8, 71.4, 70.4, 67.2, 66.6, 66.2, 65.3, 63.7, 63.4, 60.6, 55.2, 52.2, 48.3, 47.7, 47.6, 46.6, 45.6, 43.9, 43.4, 40.9, 39.8, 39.2, 38.9, 38.4, 38.0, 36.8, 36.3, 34.4, 32.6, 32.3, 30.4, 27.9, 26.2, 26.1, 21.4, 21.0, 20.6, 18.5, 18.4, 18.3, 14.4, 14.2, 12.9, 10.8, 7.6, 7.5, 7.2, 6.2, 4.1, 4.3, 4.5, 4.7, 4.9; High resolution mass spectrum (+ESI) *m/z* 1829.8524 [$(M+Na)^+$; calcd for $C_{94}H_{167}ClO_{21}NaSi_5$ 1830.0433].

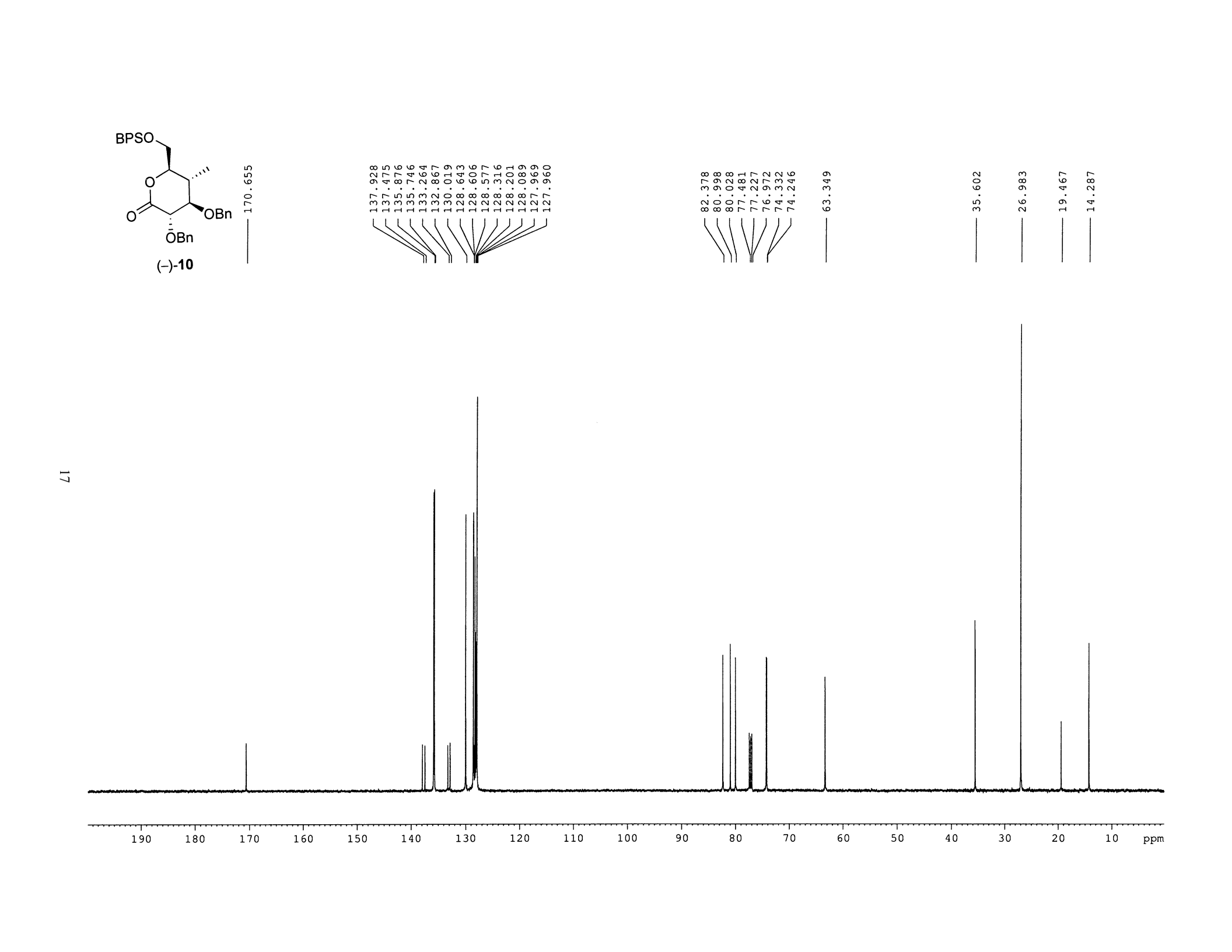


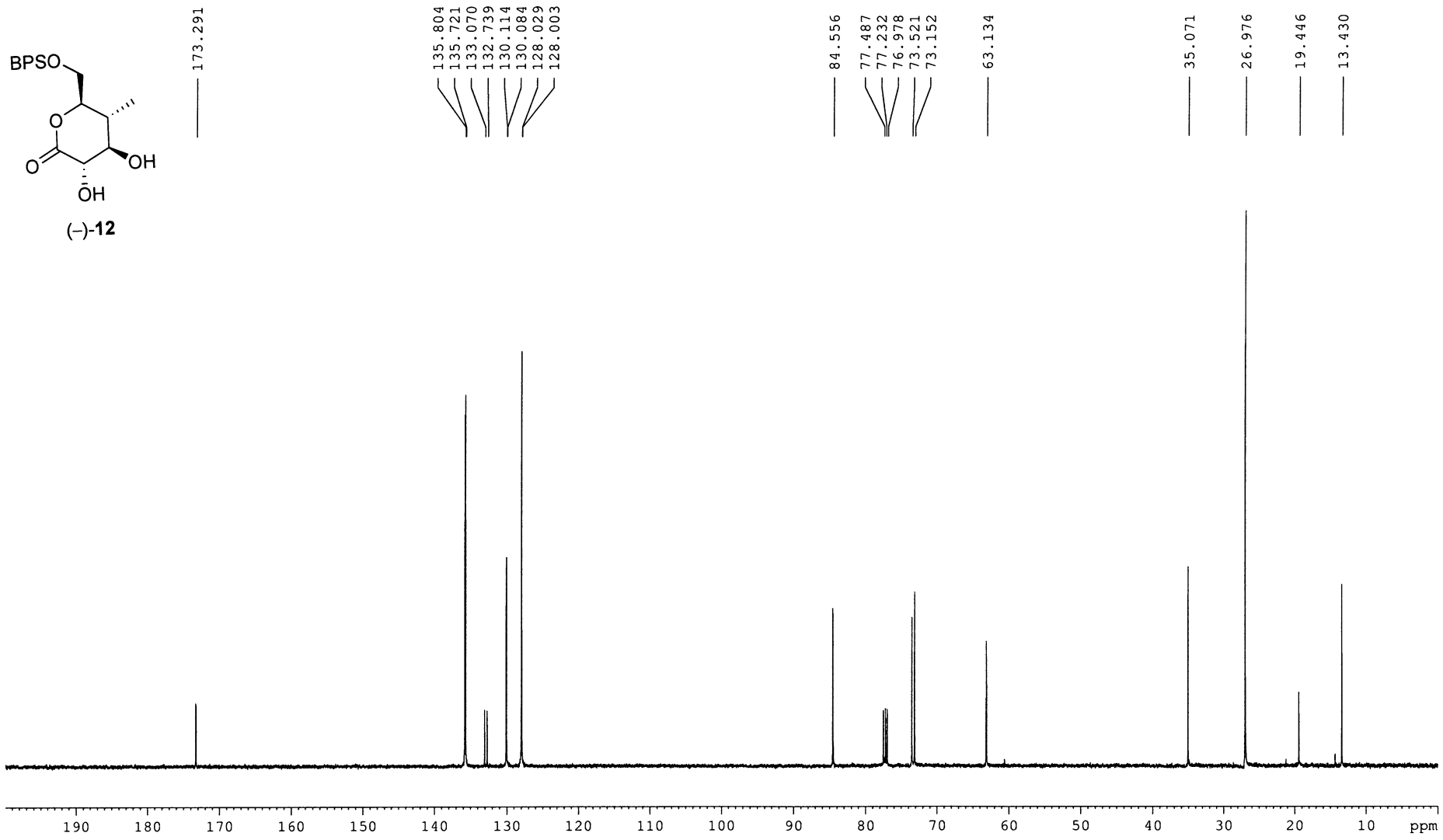
(+)-Spongistatin 1. To macrolactone (130 mg, 0.071 mmol) in acetonitrile (5.1 mL) cooled to –20 °C was added a freshly prepared solution of aqueous HF in acetonitrile (5.1 mL) via syringe pump over 2 hours. [HF solution prepared by dilution of aqueous HF (48%, 2.5 mL) with acetonitrile (10 mL)] Following addition, the reaction mixture was allowed to stir for an additional 18 hours at –20 °C. The reaction was quenched by the dropwise addition of Et_3N (6.5 mL). The reaction mixture was then warmed to room temperature, at which point it was diluted with a 2:1 mixture of ethyl acetate and methylene chloride (60 mL) and washed with saturated $NaHCO_3$ (60 mL) then brine (60 mL). The aqueous layers were extracted twice with ethyl acetate and methylene chloride (2:1, 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Column chromatography using methanol/methylene chloride (1:99/5:95) as an eluant afforded (+)-spongistatin 1 (76 mg, 87%; 93% on 180 mg scale) as a white amorphous solid with spectral data matching our previous reports.[8]


BPSO
O
O
OBn
OBn

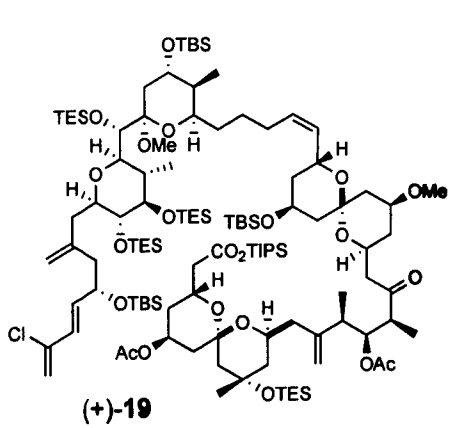
(–)-**10**


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.501
2.724
0.987
1.016
1.048
1.056
0.939
1.071
1.113
1.115
1.000
0.995
3.231

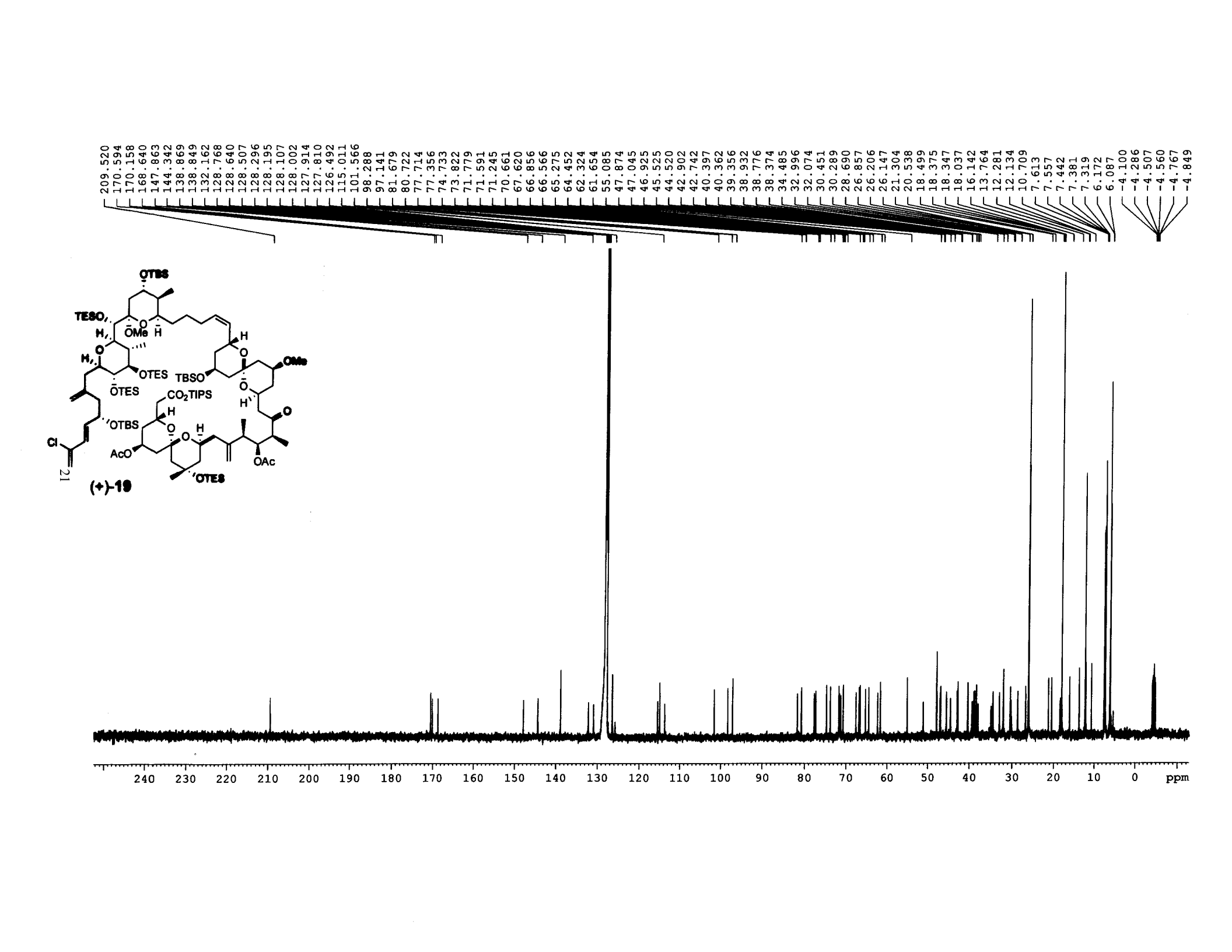

BPSO
O
O
OBn
OBn
(–)-10
170.655
137.928
137.475
135.876
135.746
133.264
132.867
130.019
128.643
128.606
128.577
128.316
128.201
128.089
127.969
127.960
82.378
80.998
80.028
77.481
77.227
76.972
74.332
74.246
63.349
35.602
26.983
19.467
14.287
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

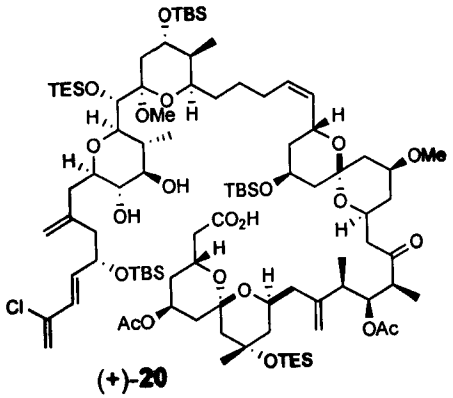

BPSO
O
O
OH
OH
(–)-12
173.291
135.804
135.721
133.070
132.739
130.114
130.084
128.029
128.003
84.556
77.487
77.232
76.978
73.521
73.152
63.134
35.071
26.976
19.446
13.430
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

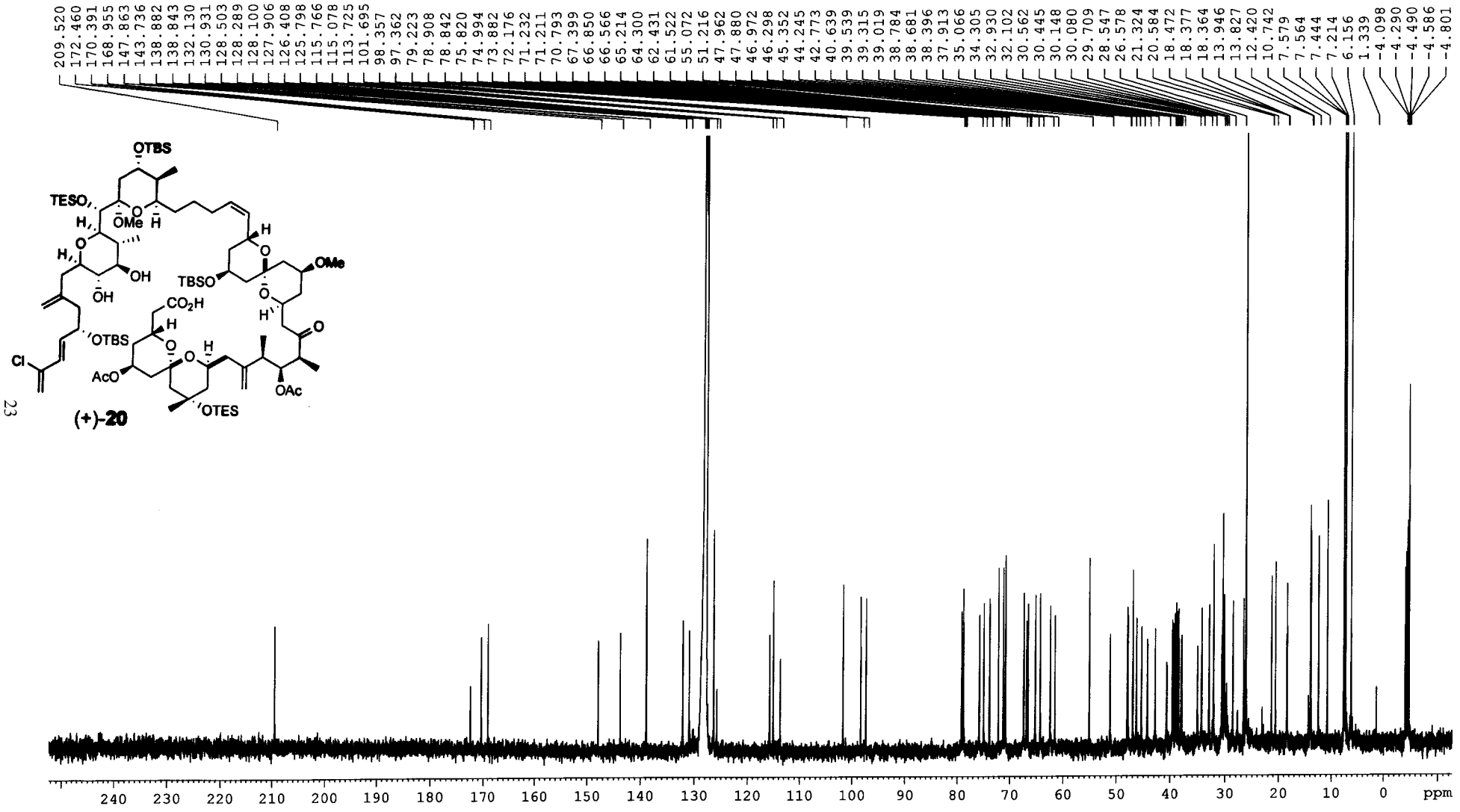
7.672
7.669
7.666
7.660
7.656
7.653
7.459
7.454
7.448
7.444
7.443
7.441
7.439
7.436
7.425
7.424
7.421
7.412
7.409
7.399
7.396
7.393
7.271
4.066
4.046
4.017
4.012
3.997
3.992
3.962
3.958
3.938
3.934
3.783
3.778
3.760
3.755
3.652
3.631
3.611
2.056
1.271
1.107
1.102
1.093
1.077
1.072
1.066
1.060
1.046
BPSO
OH
OH
O
O
(−)-12
3.534
5.174
3.000
8.184
0.870
0.539
0.899
1.101
1.031
0.968
0.847
ppm

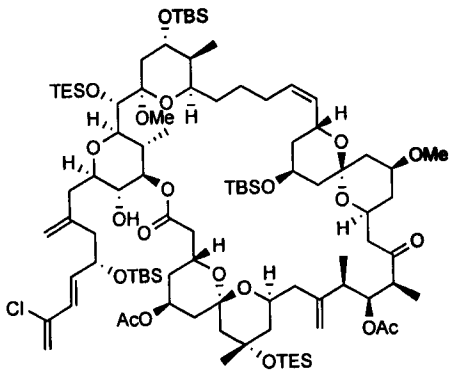


(+)-19


209.520
170.594
170.158
168.640
147.863
144.342
138.869
138.849
132.162
128.768
128.640
128.507
128.296
128.195
128.107
128.002
127.914
127.810
126.492
115.011
101.566
98.288
97.141
81.679
80.722
77.714
77.356
74.733
73.822
71.779
71.591
71.245
70.661
67.620
66.856
66.566
65.275
64.452
62.324
61.654
55.085
47.874
47.045
46.925
45.525
44.520
42.902
42.742
40.397
40.362
39.356
38.932
38.776
38.374
34.485
32.996
32.074
30.451
30.289
28.690
26.857
26.206
26.147
21.304
20.538
18.499
18.375
18.347
18.037
16.142
13.764
12.281
12.134
10.709
7.613
7.557
7.442
7.381
7.319
6.172
6.087
-4.100
-4.286
-4.507
-4.560
-4.767
-4.849
OTBS
TESO
OMe
H
OTES
TBSO
OMe
CO2TIPS
OTBS
Cl
AcO
OAc
OTES
21
(+)-19
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

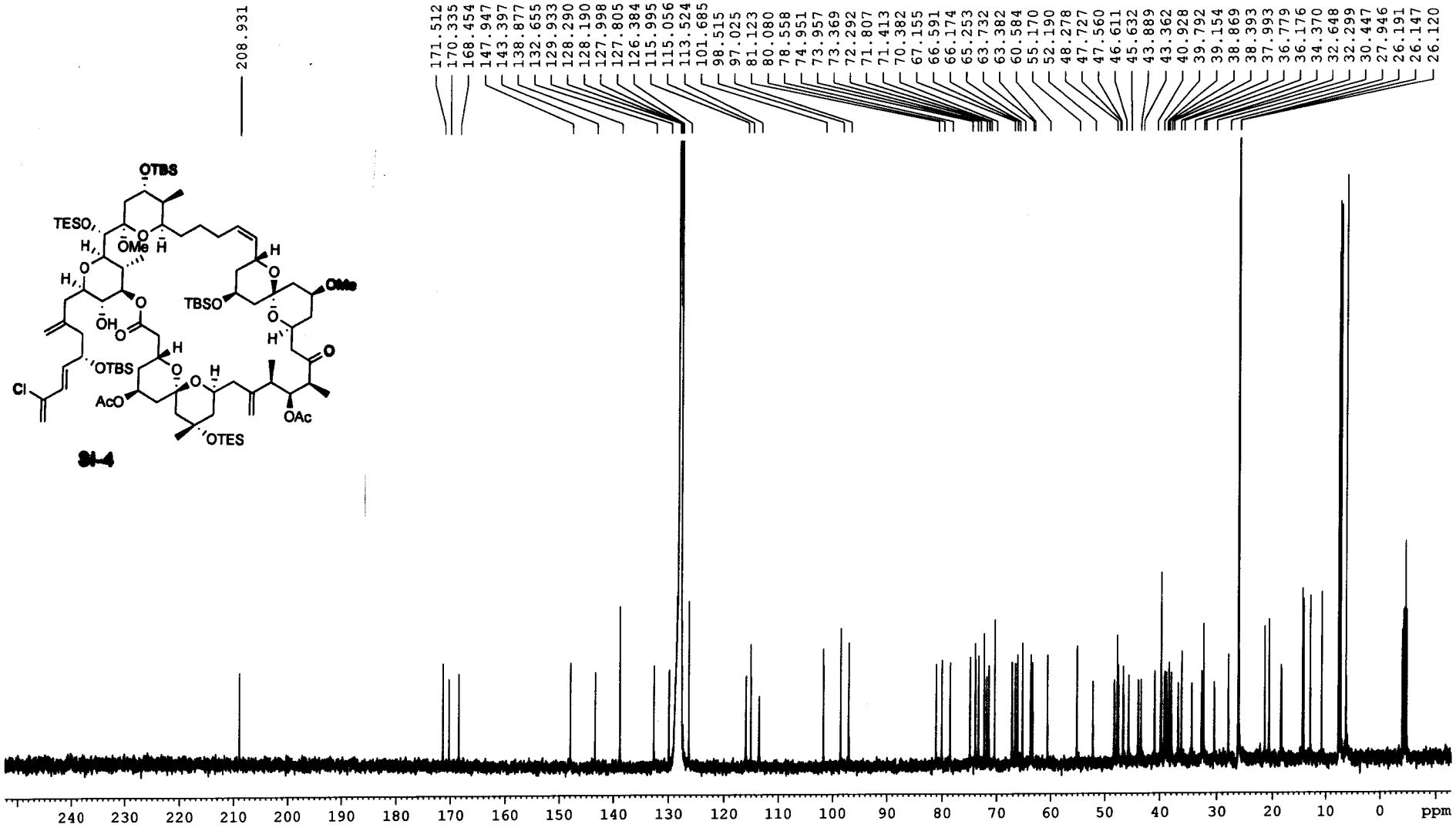

OTBS
TESO
OMe
H
OH
OH
TBSO
OMe
CO2H
OTBS
Cl
AcO
OAc
OTES
(+)-20


209.520
172.460
170.391
168.955
147.863
143.736
138.882
138.843
132.130
130.931
128.503
128.289
128.100
127.906
126.408
125.798
115.766
115.078
113.725
101.695
98.357
97.362
79.223
78.908
78.842
75.820
74.994
73.882
72.176
71.232
71.211
70.793
67.399
66.850
66.566
65.214
64.300
62.431
61.522
55.072
51.216
47.962
47.880
46.972
46.298
45.352
44.245
42.773
40.639
39.539
39.315
39.019
38.784
38.681
38.396
37.913
35.066
34.305
32.930
32.102
30.562
30.445
30.148
30.080
29.709
28.547
26.578
21.324
20.584
18.472
18.377
18.364
13.946
13.827
12.420
10.742
7.579
7.564
7.444
7.214
6.156
1.339
-4.098
-4.290
-4.490
-4.586
-4.801
OTBS
TESO
OMe
H
O
OH
TBSO
OMe
CO2H
OTBS
Cl
AcO
OAc
OTES
(+)-20
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

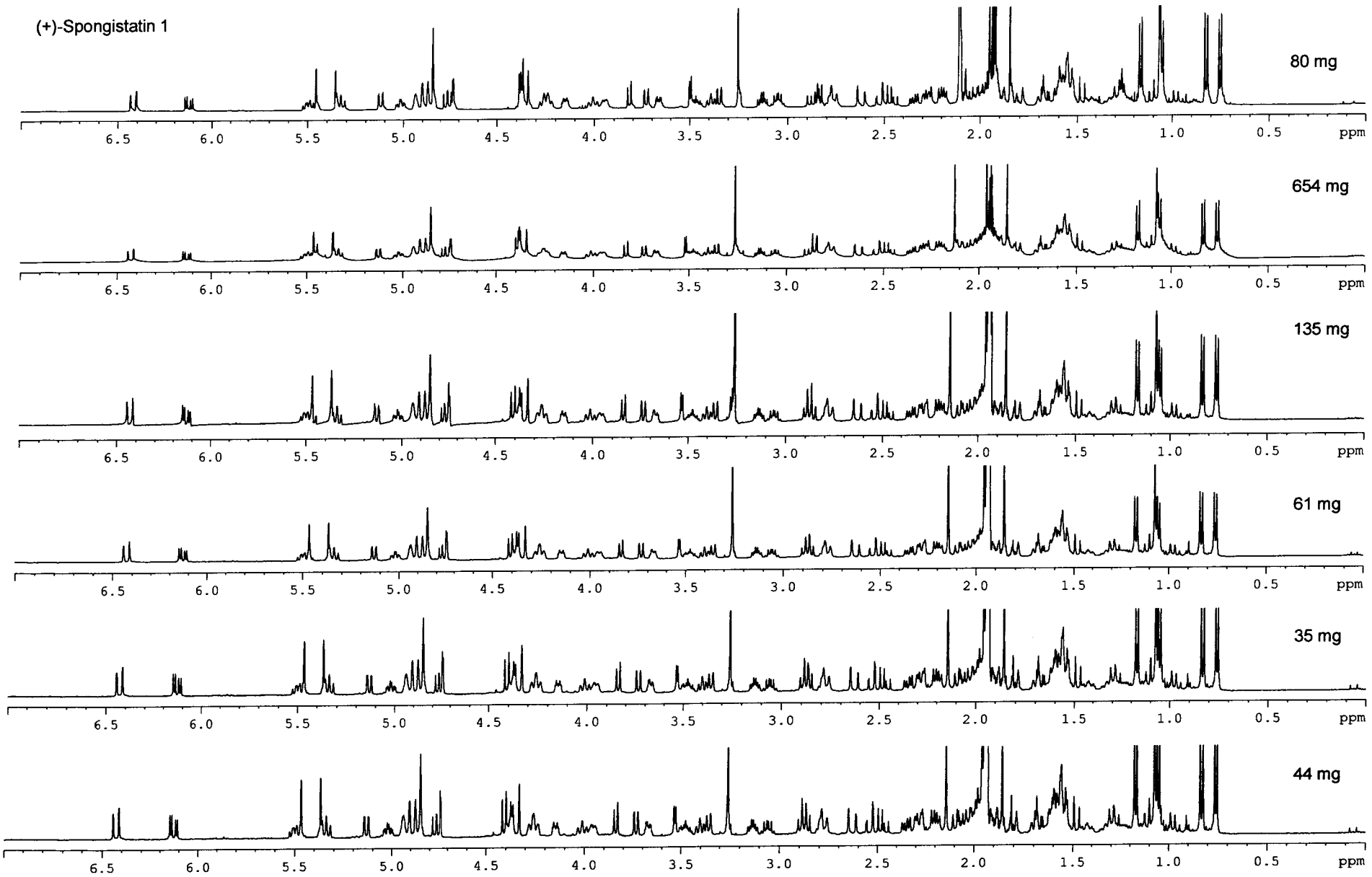

OTBS
TESO
OMe
H
O
H
O
H
OH
O
TBSO
OMe
O
H
O
H
O
OTBS
H
O
O
H
Cl
AcO
OAc
OTES

SI-4

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
1.798
0.886
0.939
0.948
1.000
1.895
2.862
1.768
0.913
0.972
1.020
1.885
0.990
0.868
1.906
0.963
1.782
2.468
1.246
0.893
4.386
1.872
1.202
4.540
3.904
2.044
1.222
4.714
12.588
3.110
3.192
2.944
9.912
12.419
33.240
5.955
7.107
2.302
4.957
7.624


208.931
171.512
170.335
168.454
147.947
143.397
138.877
132.655
129.933
128.290
128.190
127.998
127.805
126.384
115.995
115.056
113.524
101.685
98.515
97.025
81.123
80.080
78.558
74.951
73.957
73.369
72.292
71.807
71.413
70.382
67.155
66.591
66.174
65.253
63.732
63.382
60.584
55.170
52.190
48.278
47.727
47.560
46.611
45.632
43.889
43.362
40.928
39.792
39.154
38.869
38.393
37.993
36.779
36.176
34.370
32.648
32.299
30.447
27.946
26.191
26.147
26.120
OTBS
TESO
OMe
TBSO
OMe
OTBS
Cl
AcO
OAc
OTES
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

31-4


(+)-Spongistatin 1
80 mg
654 mg
135 mg
61 mg
35 mg
44 mg
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