Supporting Information

Enantioselective Synthesis of Spliceostatin G and Evaluation of Bioactivity of Spliceostatin G and its Methyl ester

Arun K. Ghosh*,[†] Guddeti Chandrashekar Reddy,[†] Andrew J. MacRae,[‡] and Melissa S. Jurica[‡]

†Department of Chemistry and Department of Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907; ‡Department of Molecular Cell and Developmental Biology and Center for Molecular Biology of RNA, University of California, Santa Cruz, California 95064

E-mail: akghosh@purdue.edu

Table of Contents:

General Information…… S1

Experimental Details……..... S2-S15

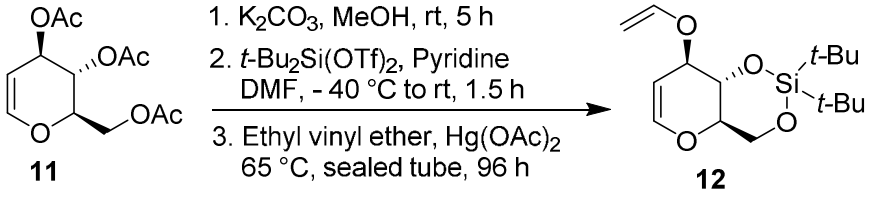
^{1}H NMR and ^{13}C NMR Spectra of compounds…….....S16-S30

General Information:

All chemical and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The following reaction solvents were distilled prior to use: Dichloromethane, 1,2-dichloroethane, dimethylformamide and toluene from calcium hydride, diethyl ether and tetrahydrofuran from Na/Benzophenone. All reactions were carried out under an argon atmosphere. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 A, 250 μm thickness, F-254 indicator). Column chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AV-III-400-HD with 5mm BBFO Z-gradient SmartProbe and Bruker DRX-500 with 5mm TXI Z-gradient cryoprobe. Chemical shifts (δ values) are reported in parts per million, and are referenced to the deuterated residual solvent peak. NMR data is reported as: δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet). Optical rotations were recorded on a Perkin Elmer 341 polarimeter. LRMS spectra were recorded on Agilent 6120 Quadrupole LC-MS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

Experimental Details:

Synthesis of vinyl ether 12:



To a solution of **11** (10 g, 36.73 mmol) in MeOH (50 mL) was added K_2CO_3 (0.101 g, 0.73 mmol) at room temperature, reaction mixture was stirred for 5 h and then the solvent was evaporated under reduced pressure and then directly chromatographed (5% MeOH in EtOAc) to afford D-glucal (5 g, 93%) as a white solid.

To a solution of D-glucal (5 g, 34.23 mmol) in dry DMF (10 mL) was added pyridine (13.54 g, 171.17 mmol), to the mixture was added *t*-$Bu_2Si(OTf)_2$ (16.59 g, 37.66 mmol) at -40 ºC, reaction mixture was allowed to room temperature over 1.5 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with 10% $CuSO_4$ solution (30 mL) followed by water (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (10% EtOAc in hexane) to give allyl alcohol (7.5 g, 77%) as a white solid.

To a solution of allylic alcohol (7 g, 24.46 mmol) in ethyl vinyl ether (40 mL) was added $Hg(OAc)_2$ (2.33 g, 7.31 mmol), the reaction mixture was heated at 65 ºC in a sealed tube for 96 h, $Hg(OAc)_2$ (2.33 g, 7.31 mmol) was added every 24 h. The reaction mixture was diluted with EtOAc (200 mL), washed with water (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (2% EtOAc in hexane) to give vinyl ether **12** (5.3 g, 70%) as a colorless oil. The starting allylic alcohol (1.4 g, 20%) was recovered.

$[\alpha]_D^{20}$ = -80 (*c* 1.0, MeOH).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.53 (dd, *J* = 14.0, 6.4 Hz, 1H), 6.32 (dd, *J* = 6.1, 1.7 Hz, 1H), 4.78 (dd, *J* = 6.1, 2.0 Hz, 1H), 4.42-4.37 (m, 2H), 4.19 (dd, *J* = 10.3, 5.0 Hz, 1H), 4.13 (dd, *J* =

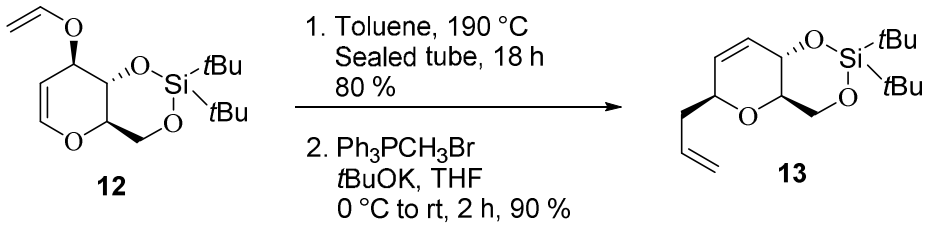
10.3, 7.1 Hz, 1H), 4.03 (dd, *J* = 6.5, 1.6 Hz, 1H), 3.98 (t, *J* = 10.4 Hz, 1H), 3.89-3.82 (m, 1H), 1.06 (s, 9H), 1.00 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 151.3, 144.8, 100.7, 89.0, 77.5, 75.3, 72.6, 66.0, 27.5, 27.0, 22.8, 19.9.

LRMS-ESI (*m/z*): 313.1 $(M+H)^+$

References for vinyl ether **12**: (1) Mori, Y.; Hayashi, H. *J. Org. Chem.* **2001**, *66*, 8666-8668 and (2) Pazos, G.; Pérez, M.; Gándara, Z.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009**, *50*, 5285-5287.

Synthesis of diene 13:



A solution of **12** (5.0 g, 16.02 mmol) in toluene (40 mL) was heated at 190 ºC in a sealed tube for 18 h, solvent was removed under reduced pressure. The crude was purified via silica gel chromatography (10% EtOAc in hexane) to afford aldehyde (4.0 g, 80%) as a white solid.

To a suspension of methyl triphenylphosphonium bromide (13.38 g, 37.5 mmol) in dry THF (120 mL) at 0 ºC was added by dropwise a 1.0 M solution of potassium *tert*-butoxide (31.25 mL, 31.25 mmol). The mixture was stirred at same temperature for 30 min, and then a solution of the above aldehyde (3.9 g, 12.5 mmol) in dry THF (60 mL) was added dropwise at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 2 h, reaction mixture was quenched with water, extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified via silica gel chromatography (2 % EtOAc in hexane) to afford **13** (3.5 g, 90%) as a white solid.

$[\alpha]_D^{20}$ = +47.2 (*c* 1.0, $CHCl_3$)

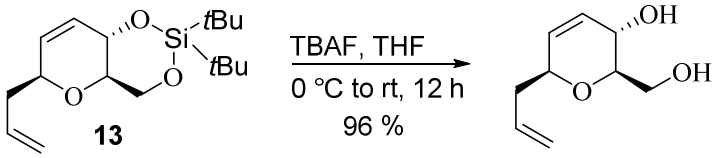
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.88-5.84 (m, 1H), 5.83-5.75 (m, 1H), 5.64 (dt, J = 10.4, 1.9 Hz, 1H), 5.13-5.06 (m, 2H), 4.41-4.36 (m, 1H), 4.28-4.23 (m, 1H), 4.17 (dd, J = 9.9, 5.0 Hz, 1H), 3.88 (t, J = 10.2 Hz, 1H), 3.50 (ddd, J = 10.5, 8.5, 5.0 Hz, 1H), 2.34-2.22 (m, 2H), 1.05 (s, 9H), 0.99 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 133.8, 130.1, 129.1, 117.6, 75.0, 74.8, 70.4, 67.3, 39.7, 27.6, 27.2, 22.8, 20.2.

LRMS-ESI (*m/z*): 311.1 $(M+H)^+$
HRMS-APCI (*m/z*): $(M+H)^+$ calcd for $C_{17}H_{30}O_3SiH$, 311.2042; found 311.2033

Reference for aldehyde: (2) Pazos, G.; Pérez, M.; Gándara, Z.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009**, *50*, 5285-5287.

Synthesis of diol:



To a solution of **13** (3.25 g, 10.4 mmol) in dry THF (80 mL) at 0 ºC was added a 1.0 M TBAF in THF (20.83 mL, 20.83 mmol), reaction mixture was allowed to room temperature and it was stirred for 12 h. The reaction mixture was diluted with water and extracted with EtOAc (3 x 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified via silica gel chromatography (50% EtOAc in hexane) to give diol (1.7 g, 96%) as a colorless oil.

$[\alpha]_D^{20}$ = +106.1 (*c* 2.13, $CHCl_3$)

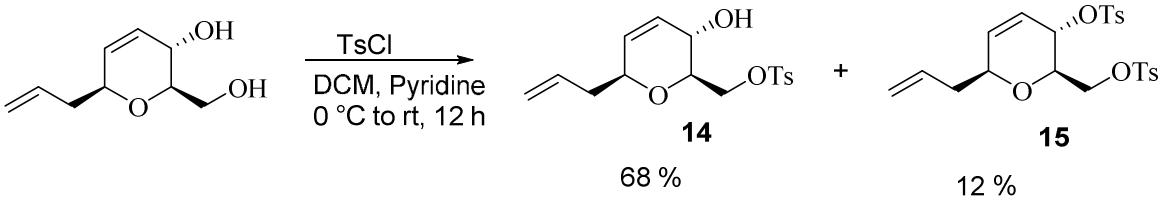
^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.85-5.76 (m, 2H), 5.77-5.72 (m, 1H), 5.13-5.05 (m, 2H), 4.22-4.13 (m, 2H), 3.90-3.84 (m, 1H), 3.82-3.74 (m, 1H), 3.39-3.34 (m, 1H), 2.68 (d, J = 5.6 Hz, 1H), 2.58 (brs, 1H), 2.36-2.22 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 133.8, 130.8, 129.2, 117.7, 78.9, 74.1, 64.3, 63.2, 39.7.

LRMS-ESI (*m/z*): 193.1 $(M+Na)^+$

HRMS-APCI (*m/z*): $(M+H)^+$ calcd for $C_9H_{14}O_3H$, 171.1021; found 171.1013

Synthesis of sulfonates 14 and 15:



To a solution of diol (0.05 g, 0.291 mmol) in dry CH_2Cl_2 (1 mL) at 0 ºC was added pyridine (0.3 mL) and *p*-toluenesulfonyl chloride (0.067 g, 0.352 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h, and then another portion of *p*-toluenesulfonyl chloride (0.027 g, 0.145 mmol) was added at 0 ºC and warmed to room temperature and stirred for 6 h. The reaction mixture was diluted with water (2 mL) and CH_2Cl_2 (20 mL), washed with 1.0 N HCl and a saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (30% EtOAc in hexane) to give **14** (0.064 g, 68%) as a colorless oil and **15** (0.016g, 12%) as a white solid.

Compound 14:

$[\alpha]_D^{20}$ = +43.4 (*c* 1.05, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.80-5.69 (m, 3H), 5.11-5.06 (m, 1H), 5.05 (t, *J* = 1.3 Hz, 1H), 4.32-4.23 (m, 2H), 4.16-4.08 (m, 2H), 3.51-3.43 (m, 1H), 2.45 (s, 3H), 2.31-2.14 (m, 2H), 1.81 (d, *J* = 7.1 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.9, 133.7, 132.9, 131.0, 129.9, 128.6, 128.1, 117.5, 77.1, 74.3, 69.9, 63.5, 39.5, 21.7.

LRMS-ESI (*m/z*): 347.0 $(M+Na)^+$

Compound 15:

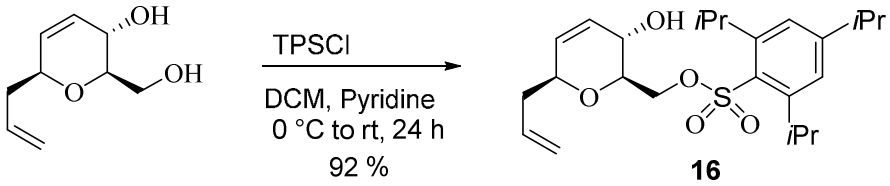
$[\alpha]_D^{20}$ = +71.9 (*c* 1.2, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.80 (dt, *J* = 10.4, 1.6 Hz, 1H), 5.71-5.59 (m, 2H), 5.06 (s, 1H), 5.04-5.00 (m, 1H), 4.84-4.78 (m, 1H), 4.10-4.02 (m, 2H), 3.83 (dd, *J* = 11.0, 5.8 Hz, 1H), 3.64-3.58 (m, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 2.24-2.09 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.7, 144.8, 133.8, 133.1, 132.9, 130.3, 129.8, 128.1, 127.9, 124.2, 117.9, 74.3, 73.7, 71.4, 68.3, 39.2, 21.8, 21.7.

LRMS-ESI (*m/z*): 501.0 $(M+Na)^+$

Synthesis of sulfonate 16:



16

To a solution of diol (1.7 g, 10.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 ºC was added pyridine (10 mL) and 2,4,6-triisopropylbenzenesulfonyl chloride (3.93 g, 13.0 mmol). The reaction mixture was warmed to room temperature and stirred for 12 h, then another portion of 2,4,6-triisopropylbenzenesulfonyl chloride (0.908 g, 3.0 mmol) was added at 0 ºC and warmed to room temperature and stirred for 12 h. The reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (100 mL), washed with 1.0 N HCl and a saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20% EtOAc in hexane) to give **16** (4.0 g, 92%) as a white solid.

$[\alpha]_D^{20}$ = +38.5 (*c* 1.5, $CHCl_3$)

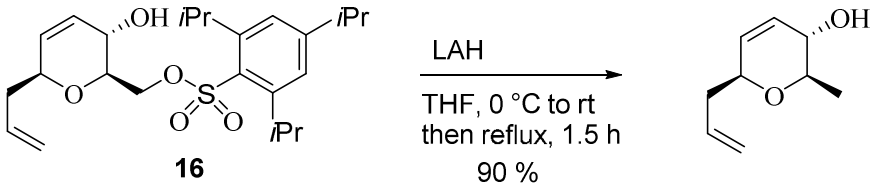
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2H), 5.80-5.69 (m, 3H), 510-5.01 (m, 2H), 4.36-4.24 (m, 2H), 4.21-4.09 (m, 4H), 3.56-3.47 (m, 1H), 2.96-2.86 (m, 1H), 2.32-2.14 (m, 2H), 1.89 (d, J = 47.1 Hz, 1H), 1.30-1.23 (m, 18H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.8, 150.9, 133.7, 131.1, 129.4, 128.6, 123.8, 117.6, 74.4, 68.9, 63.7, 39.5, 34.3, 29.7, 24.8, 23.6.

LRMS-ESI (*m/z*): 459.1 $(M+Na)^+$

HRMS-ESI (*m/z*): $(M+Na)^+$ calcd for $C_{24}H_{36}O_5SNa$, 459.2181; found 459.2175

Synthesis of pyranol:



16

To a suspension of LAH (1.74 g, 45.87 mmol) in dry THF (100 mL) at 0 ºC under argon a solution of **16** (4.0 g, 9.17 mmol) in THF (20 mL) was added dropwise. The reaction mixture was warmed to room temperature and refluxed for 1.5 h, EtOAc was added dropwise at 0 ºC to quench excess of LAH, and then water was added at 0 ºC dropwise. The mixture was warmed to room temperature and stirred for 0.5 h, then filtered through a layer of celite, rinsed with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20% EtOAc in hexane) to give pyranol (1.27 g, 90%) as a colorless oil.

$[\alpha]_D^{20}$ = +97.7 (*c* 1.56, $CHCl_3$)

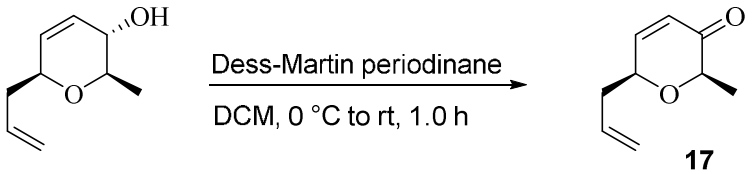
^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (m, 1H), 5.76 (s, 2H), 5.15-5.05 (m, 2H), 4.18-4.11 (m, 1H), 3.86 (td, J = 87.9, 3.0 Hz, 1H), 3.39-3.30 (m, 1H), 2.38-2.29 (m, 1H), 2.29-2.20 (m, 1H), 1.55 (d, J = 87.4 Hz, 1H), 1.34 (d, J = 6.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 134.1, 131.3, 129.2, 117.5, 75.8, 74.1, 69.8, 39.9, 18.5.

LRMS-ESI (*m/z*): 177.1 $(M+Na)^+$

HRMS-ESI (*m/z*): $(M+Na)^+$ calcd for $C_9H_{14}O_2Na$, 177.0891; found 177.0889

Synthesis of enone 17:



17

To a solution of pyranol (0.8 g, 5.19 mmol) in dry CH_2Cl_2 (32 mL) at 0 ºC was added DMP (3.30 g, 7.79 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h, and then quenched with a saturated $Na_2S_2O_3$ and saturated $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20% Et_2O in hexane) to give **17** (0.64 g, 80%) as a colorless oil.

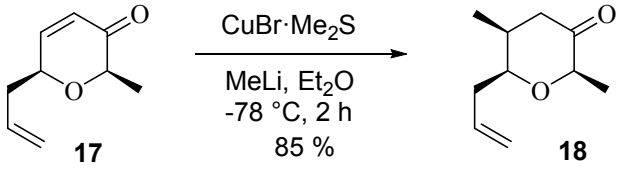
$[\alpha]_D^{20}$ = +38.2 (*c* 2.55, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 10.3, 1.5 Hz, 1H), 6.09 (dd, *J* = 10.3, 2.5 Hz, 1H), 5.91-5.80 (m, 1H), 5.21-5.13 (m, 2H), 4.43-4.37 (m, 1H), 4.08 (qd, *J* = 6.6, 2.0 Hz, 1H), 2.45-2.36 (m, 1H), 2.54-2.45 (m, 1H), 1.39 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.0, 150.6, 133.1, 126.9, 118.5, 77.1, 73.6, 39.1, 15.5.

LRMS-ESI (*m/z*): 153.1 $(M+H)^+$

Synthesis of ketone 18:



To a suspension of CuBr·Me_2S (1.62 g, 7.89 mmol) in anhydrous Et_2O (20 mL) at -78 ºC under argon was added MeLi (3.1 M, 5.17 mL, 16.05 mmol). The mixture was stirred for 1 h, a solution of **17** (0.4 g, 2.63 mmol) in Et_2O (4 mL) was added at the same temperature and stirring was continued for 3 h. The reaction mixture was quenched with EtOAc (1mL) and water (1mL), the reaction mixture was extracted with Et_2O, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (5% EtOAc in hexane) to give **18** (0.378 g, 85%) as a colorless oil.

$[\alpha]_D^{20}$ = -58.7 (*c* 2.13, EtOAc)

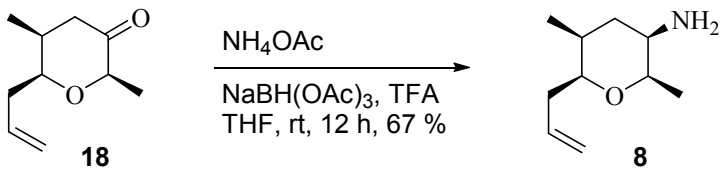
^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.91-5.76 (m, 1H), 5.14 (dq, J = 17.1, 1.7 Hz, 1H), 5.11-5.06 (m, 1H), 3.99-3.85 (m, 2H), 2.69-2.58 (m, 1H), 2.46-2.37 (m, 1H), 2.37-2.25 (m, 2H), 2.23-2.15 (m, 1H), 1.28 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 7.3 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.9, 134.7, 117.2, 79.5, 78.7, 46.8, 36.9, 34.9, 15.1, 13.1.

LRMS-ESI (*m/z*): 169.1 $(M+H)^+$

References for ketone **18**: (3) Ghosh, A. K.; Chen, Z. H. *Org. Lett*. **2013**, *15*, 5088-5091 and (4) Ghosh, A. K.; Chen, Z. H.; Effenberger, K. A.; Jurica, M. S. *J. Org. Chem*. **2014**, *79*, 5697-5709.

Synthesis of amine 8:



To a solution of **18** (0.3 g, 1.78 mmol) in THF (15 mL) were added NH_4OAc (2.75 g, 35.71 mmol), $NaBH(OAc)_3$ (1.89 g, 8.93 mmol) and TFA (0.20 g, 1.78 mmol) at room temperature. The reaction mixture was stirred for 12 h, and then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 40 mL).The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (10% MeOH in CH_2Cl_2) to give **8** (0.2 g, 67%) as a white semisolid.
$[\alpha]_D^{20}$ = -19.83 (*c* 1.2, $CHCl_3$)

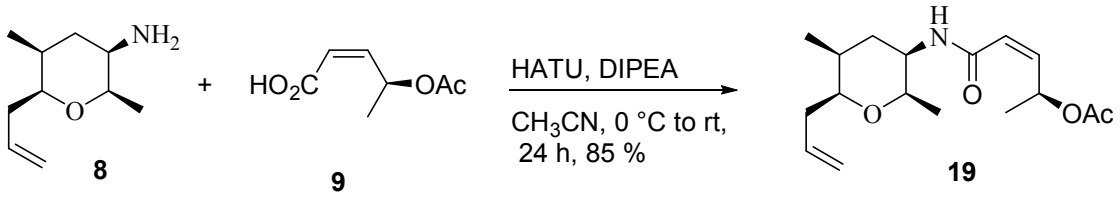
^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.86-5.73 (m, 1H), 5.10 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.06-4.99 (m, 1H), 3.57 (qd, *J* = 6.5, 2.0 Hz, 1H), 3.48 (td, *J* = 7.1, 2.8 Hz, 1H), 3.26 (brs, 2H), 2.77 (brs, 1H), 2.38-2.29 (m, 1H), 2.18-2.08 (m, 1H), 2.02-1.92 (m, 2H), 1.91-1.84 (m, 1H), 1.77-1.67 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.1, 116.6, 80.8, 76.6, 49.4, 38.0, 37.5, 29.0, 17.9, 15.2.

LRMS-ESI (*m/z*): 170.1 $(M+H)^+$

HRMS-ESI (*m/z*): $(M+H)^+$ calcd for $C_{10}H_{19}NOH$, 170.1545; found 170.1537

Synthesis of amide 19:



To a solution of **9** (0.089 g, 0.568 mmol) in dry acetonitrile (2 mL) at 0 ºC was added HATU (0.215 g, 0.568 mmol) followed by DIPEA (0.244 g, 1.893 mmol). A solution of **8** (0.08 g, 0.473 mmol) in acetonitrile (2 mL) was added to the mixture. The resulting mixture was warmed to room temperature and stirred for 24 h, and then the reaction was quenched with saturated NH_4Cl, diluted with water, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified

via silica gel chromatography (30% EtOAc in hexane) to provide **19** (0.124 g, 85%) as a colorless oil.

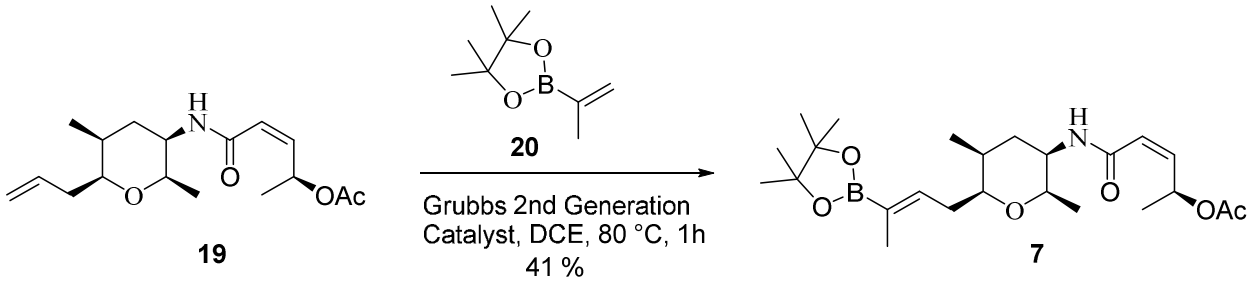
$[\alpha]_D^{20}$ = -69.3 (*c* 1.22, CH_2Cl_2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.31-6.21 (m, 1H), 5.97 (d, *J* = 9.1 Hz, 1H), 5.89 (dd, *J* = 11.6, 7.9 Hz, 1H), 5.84-5.72 (m, 1H), 5.69 (dd, *J* = 11.6, 1.3 Hz, 1H), 5.11 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.07-5.01 (m, 1H), 3.98-3.90 (m, 1H), 3.66 (qd, *J* = 6.5, 2.3 Hz, 1H), 3.53 (ddd, 7.5, 6.7, 2.3 Hz, 1H), 2.38-2.28 (m, 1H), 2.17-2.08 (m, 1H), 2.03 (s, 3H), 1.98-1.93 (m, 2H), 1.82-1.73 (m, 1H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 164.9, 143.8, 134.8, 122.6, 116.8, 80.9, 76.1, 69.0, 47.2, 37.5, 36.0, 28.9, 21.3, 20.1, 17.9, 15.1.

LRMS-ESI (*m/z*): 310.1 $(M+H)^+$

Synthesis of boronate 7:



To a solution of **19** (0.1 g, 0.323 mmol) and isopropenylboronic acid pinacol ester **20** (0.271 g, 1.615 mmol) in 1,2 dichloroethane (3 mL) was added Grubbs 2nd generation catalyst (0.027, 0.032 mmol), and then the reaction mixture was refluxed for 1 h under argon. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (30% EtOAc in hexane) to provide **7** (0.06 g, 41%) as a white solid.

$[\alpha]_D^{20}$ = -47.3 (*c* 0.66, $CHCl_3$)

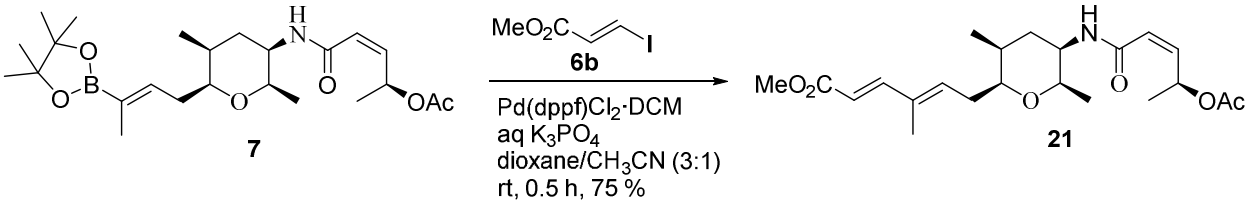
^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.31-6.21 (m, 2H), 5.99 (d, J = 9.0 Hz, 1H), 5.93-5.84 (m, 1H), 5.73-5.66 (m, 1H), 3.98-3.89 (m, 1H), 3.72-3.63 (m, 1H), 3.60 (td, 7.1, 2.4 Hz 1H), 2.41-2.31 (m, 1H), 2.31-2.22 (m, 1H), 2.03 (d, J = 1.1 Hz, 3H), 1.99-1.91 (m, 2H), 1.85- 1.77 (m, 1H), 1.69 (s, 3H), 1.38 (d, J = 6.5 Hz, 3H), 1.25 (brs, 12H), 1.15 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 164.9, 143.6, 141.0, 122.6, 83.2, 80.4, 76.1, 76.0, 68.9, 47.2, 35.9, 32.4, 28.8, 24.9, 24.8, 21.3, 20.0, 17.9, 15.1, 14.3.

LRMS-ESI (*m/z*): 450.3 $(M+H)^+$

Reference for boronate **7**: (5) Nicolaou, K. C.; Rhoades, D.; Lamani, M.; Pattanayak, M. R.; Kumar, S. M. *J. Am. Chem. Soc*. **2016**, *138*, 7532−7535.

Synthesis of diester 21:



Compound **6b** (0.028 g, 0.133 mmol) and **7** (0.04 g, 0.089 mmol) were dissolved in rigorously degassed (freeze-pump-thaw technique x 3) 1,4-dioxane/MeCN ((3:1), 4 mL). To the obtained solution was added rigorously degassed (freeze-pump-thaw technique x 3) 1 mL of K_3PO_4 stock solution (stock solution: K_3PO_4 (0.112 g, 0.527 mmol) was dissolved in H_2O (2 mL)). To the above mixture was added Pd(dppf)Cl_2·DCM (0.0145 g, 0.0178 mmol) at room temperature, stirred for 0.5 h, filtered through a layer of celite and rinsed with EtOAc. The organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (40% EtOAc in hexane) to provide **21** (0.027 g, 75%) as a colorless oil.

$[\alpha]_D^{20}$ = -66.3 (*c* 1.7, $CHCl_3$)

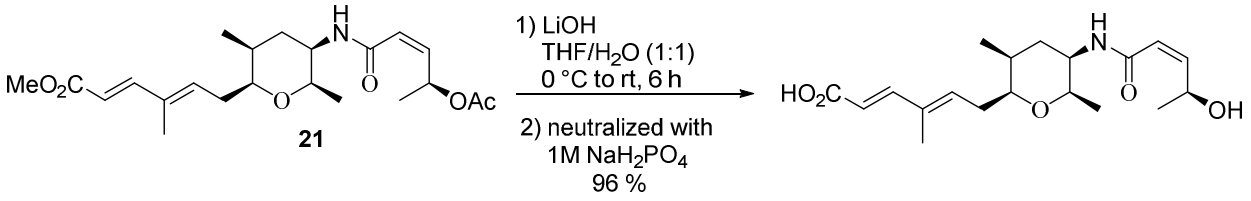
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 15.7 Hz, 1H), 6.27-6.19 (m, 1H), 6.01(d, *J* = 9.0 Hz, 1H), 5.93-5.84 (m, 2H), 5.80 (d, *J* = 15.7 Hz, 1H), 5.71 (dd, *J* = 11.6, 1.3 Hz, 1H), 3.97-3.90 (m, 1H), 3.73 (s, 3H), 3.68-3.63 (m, 1H), 3.59-3.52 (m, 1H), 2.48-2.38 (m, 1H), 2.32-2.23 (m, 1H), 2.02 (s, 3H), 1.98-1.91 (m, 2H), 1.77 (brs, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.22 (s, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 168.0, 164.9, 149.5, 143.6, 137.6, 134.3, 122.6, 115.6, 80.5, 76.1, 69.0, 51.5, 47.1, 35.9, 32.6, 29.3, 21.3, 20.0, 17.8, 15.1, 12.5.

LRMS-ESI (*m/z*): 430.1 $(M+Na)^+$

HRMS-ESI (*m/z*): $(M+Na)^+$ calcd for $C_{22}H_{33}NO_6Na$, 430.2206; found 430.2198

Synthesis of hydroxyl acid:



To a stirred solution of **21** (0.02 g, 0.049 mmol) in THF/H_2O (1:1) at 0 ºC was added LiOH·H_2O (0.012 g, 0.294 mmol), and then the reaction was allowed to warm to room temperature, and stirred for 6 h. The reaction mixture was neutralized with 1.0 M NaH_2PO_4 (1.5 mL), extracted with CH_2Cl_2 (20 mL x 5), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (5% MeOH in CH_2Cl_2) to provide hydroxyl acid (0.0165 g, 96%) as a colorless oil, R_f = 0.2 (silica gel, 60% EtOAc in hexane).

$[\alpha]_D^{20}$ = -14.1 (*c* 1.1, $CHCl_3$)

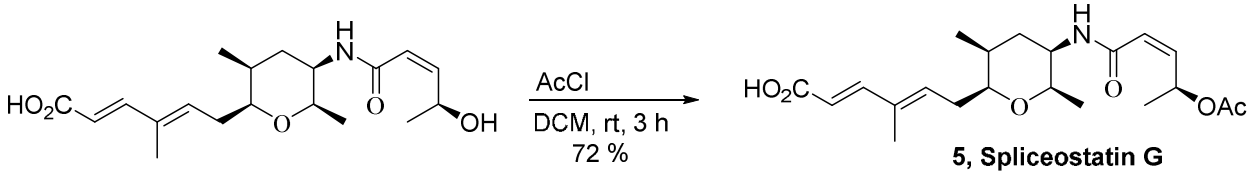
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 15.6 Hz, 1H), 6.34 (d, J = 8.9 Hz, 1H), 6.18 (dd, J = 11.9, 5.4 Hz, 1H), 5.94 (t, J = 7.1 Hz, 1H), 5.86-5.75 (m, 2H), 4.85-4.74 (m, 1H), 4.00-3.91 (m, 1H), 3.71 (qd, J = 6.4, 2.2 Hz, 1H), 3.66-3.58 (m, 1H), 2.53-2.40 (m, 1H), 2.36-2.24 (m, 1H), 2.03-1.90 (m, 2H), 1.81 (brs, 4H), 1.35 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 2.0 Hz, 1H), 1.16 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 7.4 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.7, 166.4, 151.1, 150.6, 138.2, 134.5, 122.7, 115.6, 80.9, 76.4, 64.7, 47.4, 35.7, 32.6, 29.4, 22.8, 17.8, 15.2, 12.5.

LRMS-ESI (*m/z*): 352.1 $(M+H)^+$

HRMS-ESI (*m/z*): $(M+H)^+$ calcd for $C_{19}H_{29}NO_5H$, 352.2124; found 352.2121

Synthesis of spliceostatin G (5):



5, Spliceostatin G

To a stirred solution of hydroxyl acid (0.01 g, 0.028 mmol) in CH_2Cl_2 (1mL) at room temperature under argon was added excess of acetyl chloride (0.04 mL). After stirring for 3 h, the reaction mixture was quenched with water (0.5 mL), extracted with CH_2Cl_2 (20 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (2% MeOH in CH_2Cl_2) to provide spliceostatin G (**5**) (0.008 g, 72%) as a colorless oil, R_f = 0.3 (silica gel, 60% EtOAc in hexane).

$[\alpha]_D^{20}$ = -71.7 (*c* 0.53, $CHCl_3$)

^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.11 (brs, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 115.6 Hz, 1H), 6.41-6.31 (m, 1H), 6.11 (dd, J = 11.6, 1.4 Hz, 1H), 6.00 (t, 7.2 Hz, 1H), 5.87 (dd, J = 11.6, 7.5 Hz, 1H), 5.74 (d, J = 15.6 Hz, 1H), 3.70-3.62 (m, 1H), 3.59-3.53 (m, 1H), 2.43-2.32 (m,

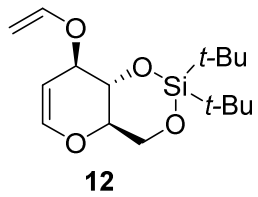
1H), 2.32-2.22 (m, 1H), 1.98 (s, 3H), 1.86-1.79 (m, 2H), 1.75 (brs, 3H), 1.72-1.64 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 7.3 Hz, 3H).

^{13}C-NMR (100 MHz, DMSO-d_6) δ 169.6, 167.8, 164.5, 148.6, 142.7, 138.0, 133.4, 122.8, 116.6, 79.6, 74.9, 68.1, 46.3, 35.2, 32.2, 28.8, 21.0, 19.9, 17.7, 14.3, 12.2.

LRMS-ESI (*m/z*): 394.1 $(M+H)^+$

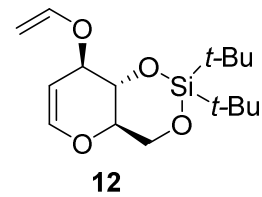
HRMS-ESI (*m/z*): $(M+Na)^+$ calcd for $C_{21}H_{31}NO_6Na$, 416.2049; found 416.2042

^{1}H NMR (500 MHz, $CDCl_3$)



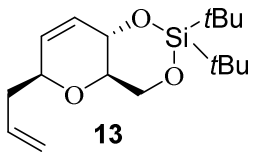
12

^{13}C NMR (125 MHz, $CDCl_3$)



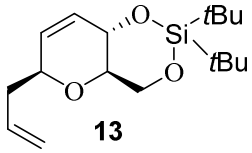
12

^{1}H NMR (500 MHz, $CDCl_3$)

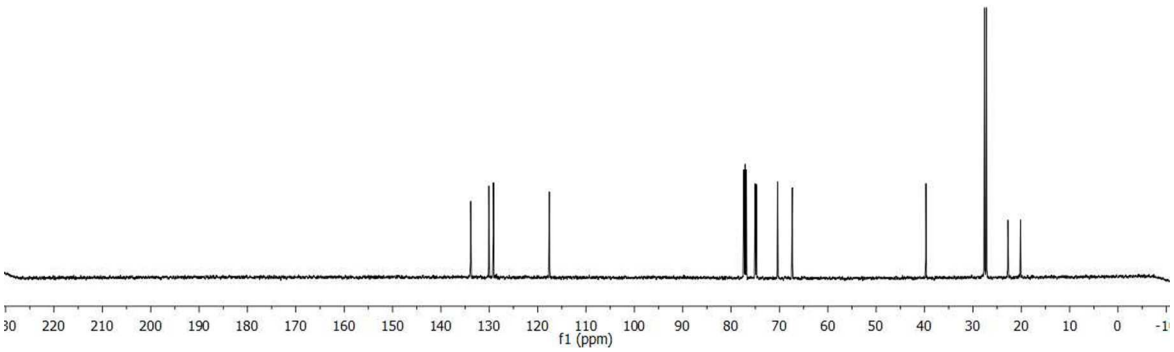


13

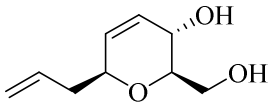
^{13}C NMR (125 MHz, $CDCl_3$)

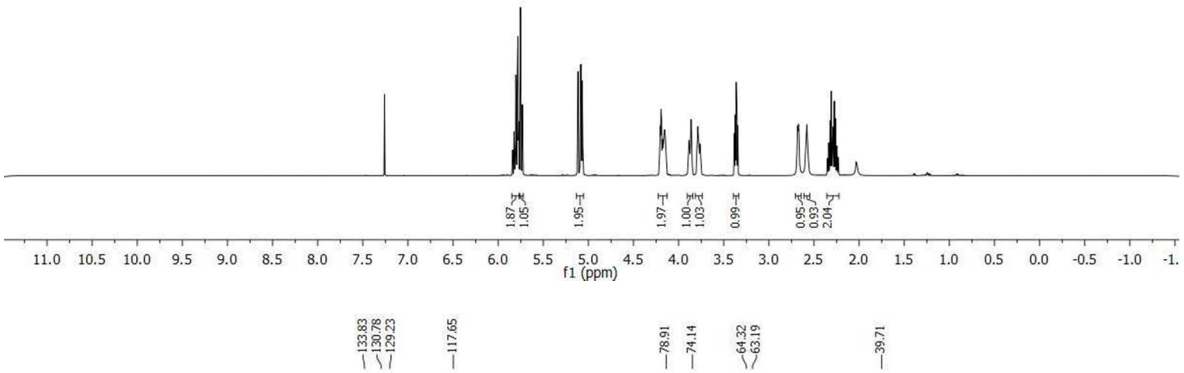


13

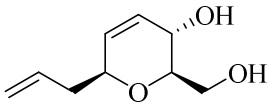


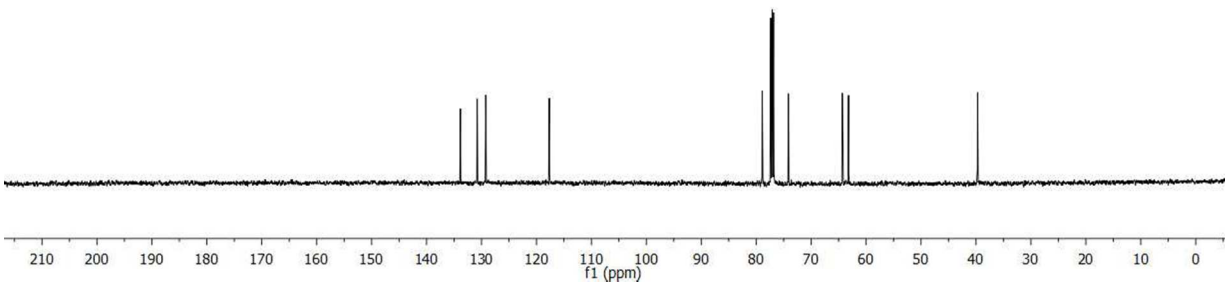
^{1}H NMR (500 MHz, $CDCl_3$)



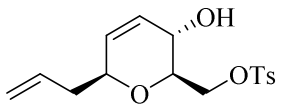


^{13}C NMR (125 MHz, $CDCl_3$)



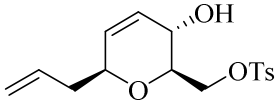


^{1}H NMR (400 MHz, $CDCl_3$)

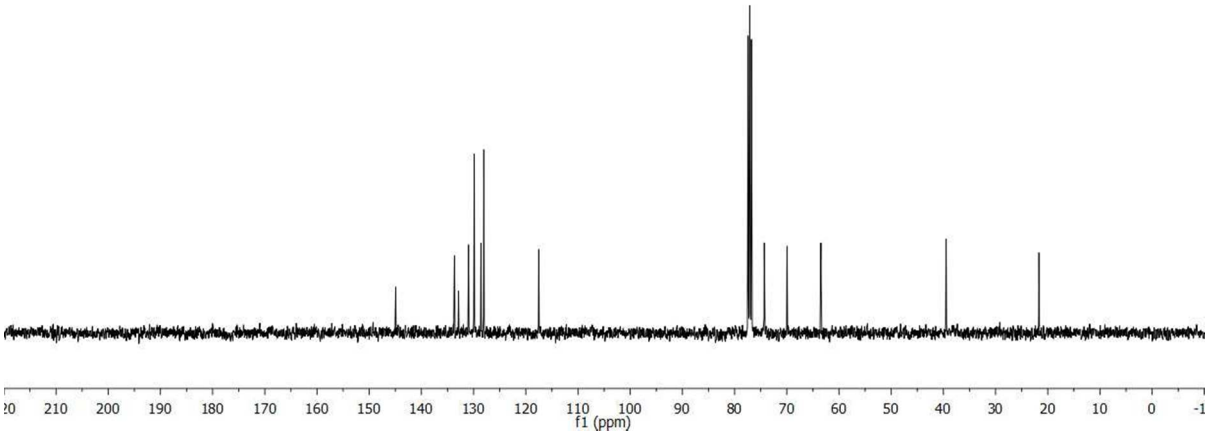


14

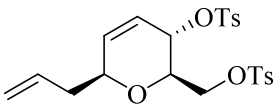
^{13}C NMR (100 MHz, $CDCl_3$)



14

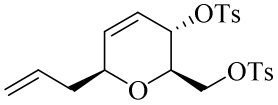


^{1}H NMR (400 MHz, $CDCl_3$)



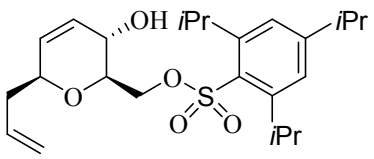
15

^{13}C NMR (100 MHz, $CDCl_3$)



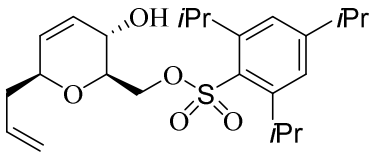
15

^{1}H NMR (400 MHz, $CDCl_3$)

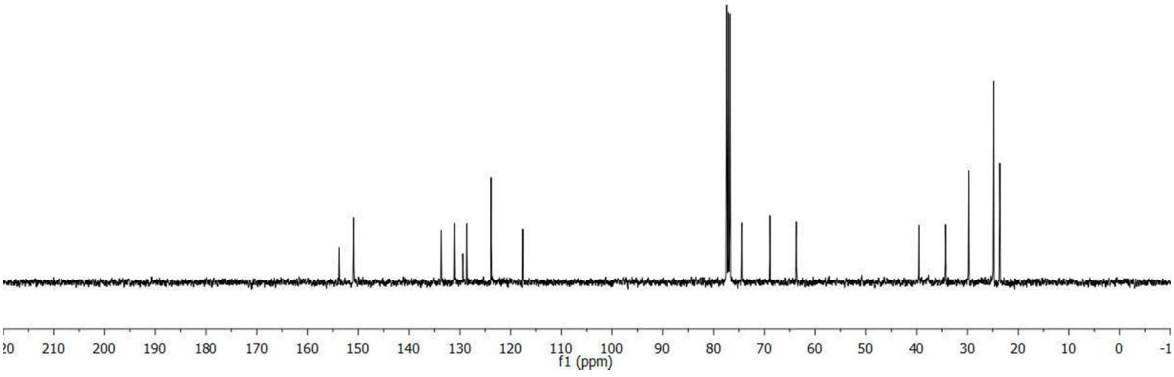


16

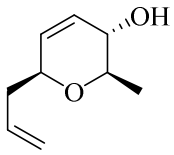
^{13}C NMR (100 MHz, $CDCl_3$)



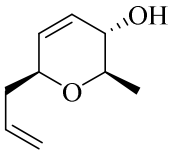
16

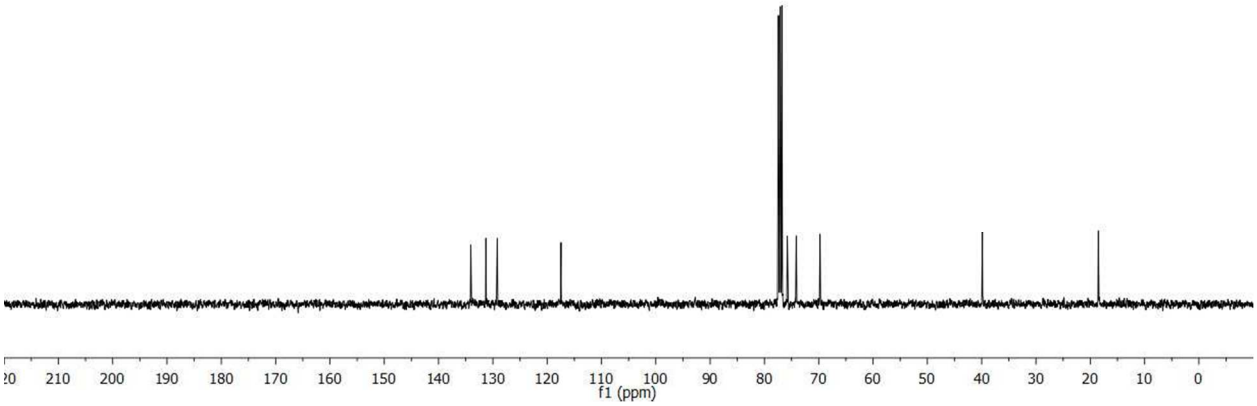


^{1}H NMR (400 MHz, $CDCl_3$)

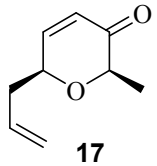


^{13}C NMR (100 MHz, $CDCl_3$)



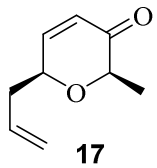


^{1}H NMR (400 MHz, $CDCl_3$)

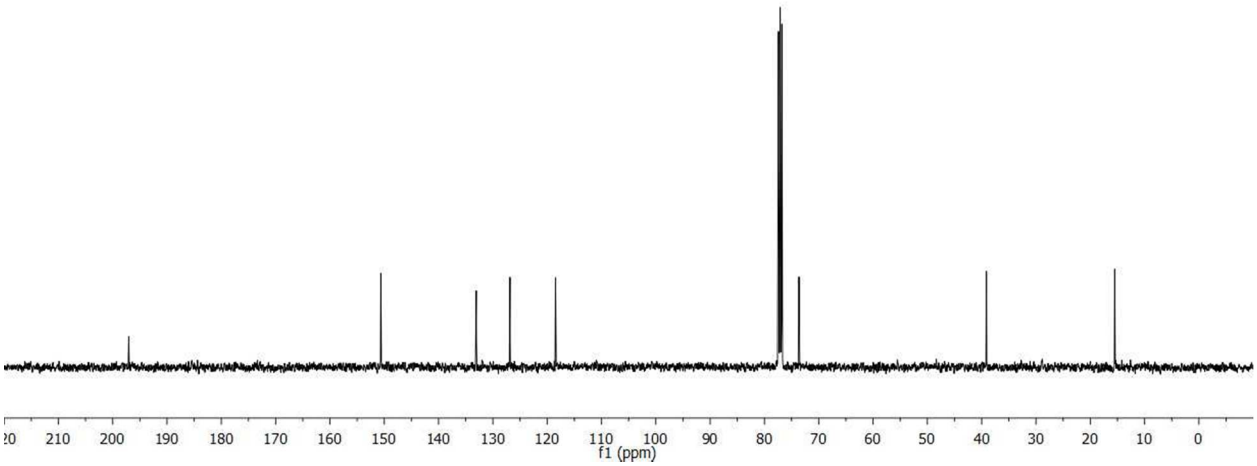


17

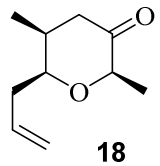
^{13}C NMR (100 MHz, $CDCl_3$)



17

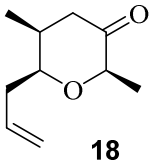


^{1}H NMR (400 MHz, $CDCl_3$)

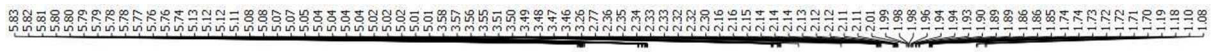


18

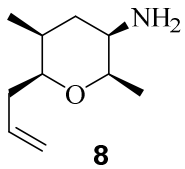
^{13}C NMR (100 MHz, $CDCl_3$)



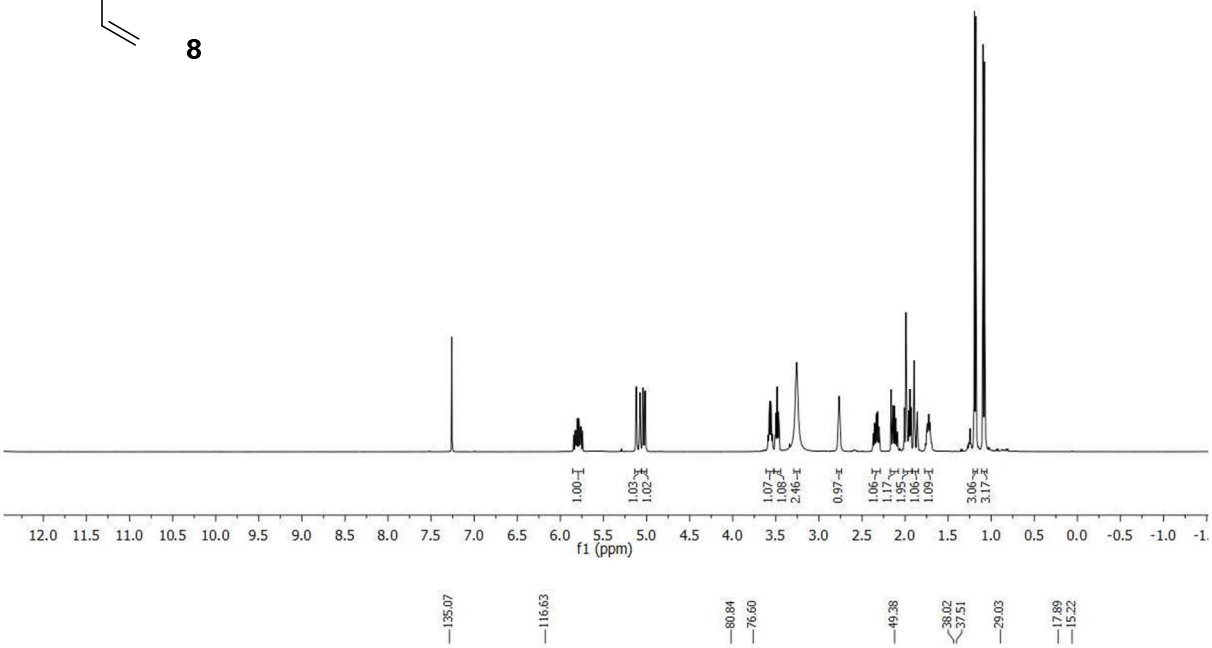
18



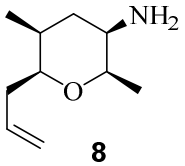
^{1}H NMR (400 MHz, $CDCl_3$)



8

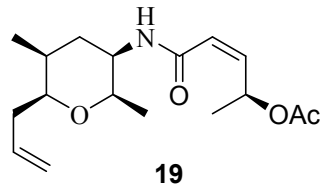


^{13}C NMR (100 MHz, $CDCl_3$)



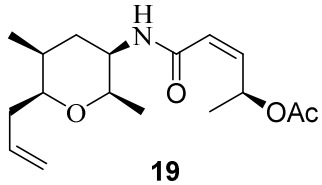
8

^{1}H NMR (400 MHz, $CDCl_3$)



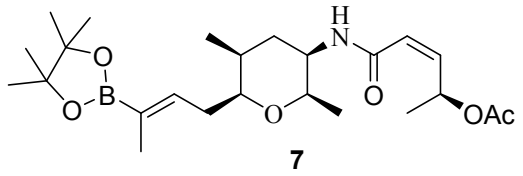
19

^{13}C NMR (100 MHz, $CDCl_3$)



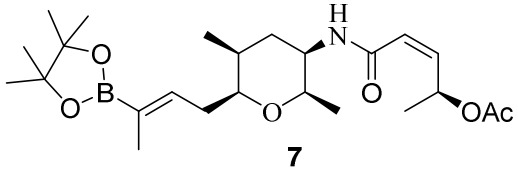
19

^{1}H NMR (400 MHz, $CDCl_3$)

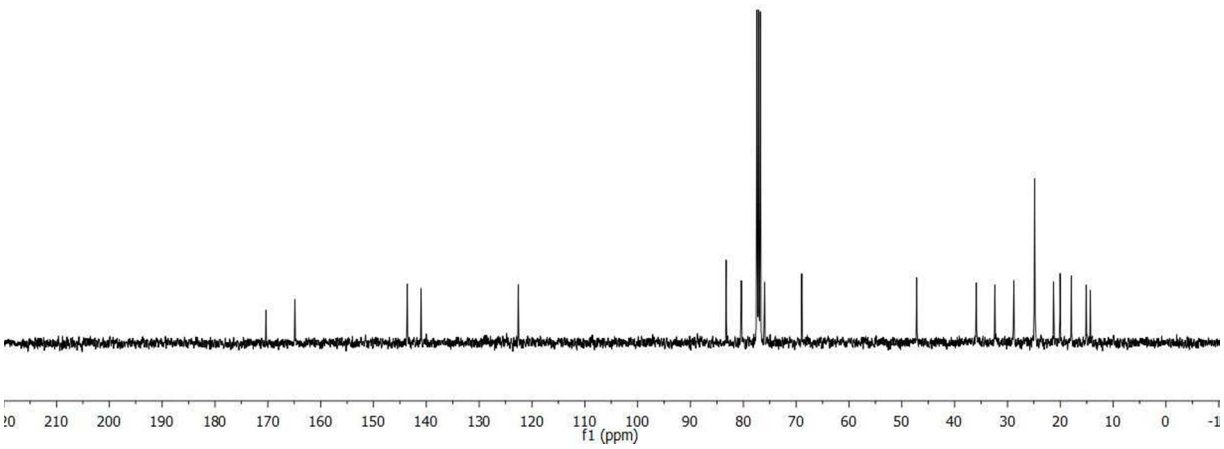


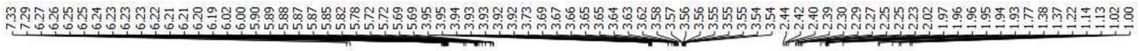
7

^{13}C NMR (100 MHz, $CDCl_3$)

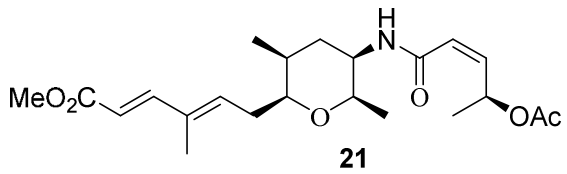


7



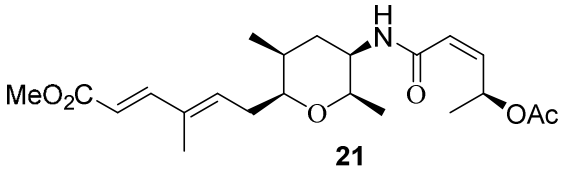


^{1}H NMR (400 MHz, $CDCl_3$)

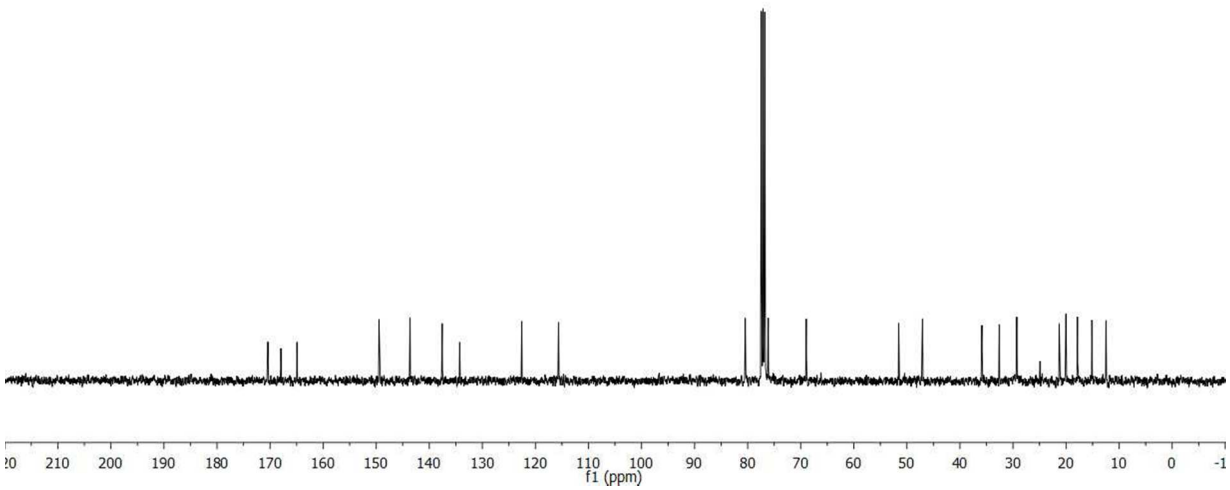


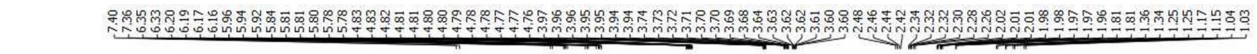
21

^{13}C NMR (100 MHz, $CDCl_3$)

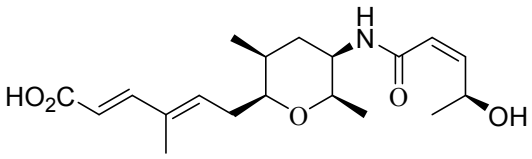


21

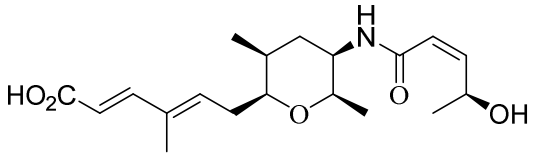




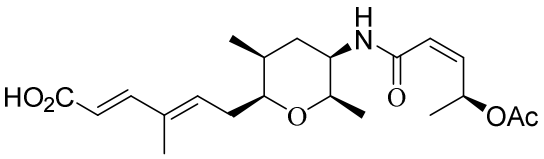
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

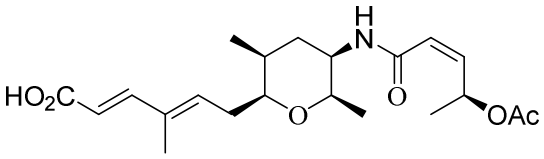


^{1}H NMR (400 MHz, DMSO-d_6)



5, Spliceostatin G

^{13}C NMR (100 MHz, DMSO-d_6)



5, Spliceostatin G