Supporting Information

Enantioselective Syntheses of FR901464 and Spliceostatin A: Potent Inhibitors of Spliceosome

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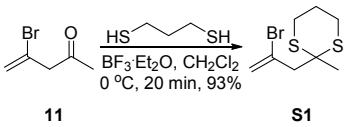
General Information: Those reactions which required anhydrous conditions were carried out under an argon atmosphere using oven-dried glassware (120 ^{o}C). All chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained as follows: anhydrous tetrahydrofuran and diethyl ether were distilled from sodium metal under argon, anhydrous dichloromethane was dried via distillation from CaH_2 immediately prior to use under argon, and anhydrous methanol and ethanol were distilled from activated magnesium under argon. All other solvents were reagent grade. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 Å, 250 μm thickness, F-254 indicator). Flash chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. ^{1}H NMR spectra were recorded at 400 or 500 MHz. ^{13}C NMR spectra were recorded at 100 or 150 MHz. Chemical shifts 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, brs = broad singlet). IR spectra were recorded on a Varian 2000 Infrared spectrophotometer and are reported as cm^{-1}. LRMS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center. Melting point was measured on a melting point apparatus and was

uncorrected.

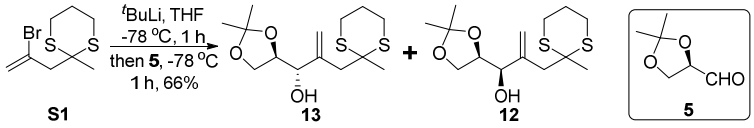
*Synthesis of compound **S1**:*



11 **S1**

To a solution of **11** (3.43 g, 21.07 mmol) and 1.3-propanedithiol (2.54 mL, 25.28 mmol) in anhydrous dichloromethane (55 mL) at 0 °C under argon was added $BF_3{\cdot}Et_2O$ (2.60 mL, 21.07 mmol) dropwise over 5 min. The reaction mixture was stirred for an additional 15 min and then quenched with 5% NaOH (120 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (30:1 to 15:1 hexane/ethyl acetate) to afford **S1** (4.939 g, 93%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 5.68 (d, J = 1.2 Hz, 1H), 3.12 (s, 2H), 2.97-2.75 (m, 4H), 2.08-1.85 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.5, 122.5, 51.3, 47.8, 27.7, 26.8, 24.7; IR (neat) 1622, 1423, 1372, 1276, 1139, 1071, 906, 816 cm^{-1}; LRMS (ESI), *m/z* 275.0 $(M+Na)^+$.

*Synthesis of compounds **12** and **13**:*

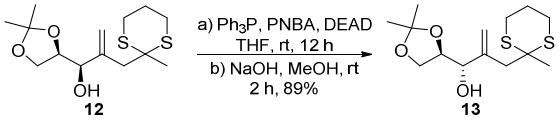


S1 **13** **12** **5**

To a solution of **S1** (2.27 g, 9.02 mmol) in anhydrous THF (45 mL) at -78 °C under argon was added *tert*-butyllithium (1.7 M, 13.3 mL, 22.6 mmol). After stirring at -78 °C for 1 h, a solution of aldehyde **5** (1.75 g. 13.5 mmol) in THF (15 mL) was added. The resulting mixture was stirred for 1 h and then quenched with water (20 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (20:1 to 15:1 hexane/ethyl acetate) to afford **13** (932 mg, 34%) and **12** (877 mg, 32%) as a colorless oil. Compound **13**: $[\alpha]_D^{20}$ -5.6 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (s, 1H), 5.16 (s, 1H), 4.41 (d, J = 5.2 Hz, 1H), 4.20 (q, J = 6.0 Hz, 1H), 4.00-3.90 (m, 2H), 2.97-2.69 (m, 6H), 2.52 (brs, 1H), 2.05-1.78 (m, 2H),

1.63 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 117.8, 109.4, 77.7, 73.3, 65.3, 48.3, 45.1, 28.0, 26.9, 26.8, 26.6, 25.1, 24.9; IR (neat) 3460, 2907, 1643, 1424, 1372, 1213, 1157, 1066, 909 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{14}H_{24}O_3S_2Na$: 327.1065, found 327.1067. Compound **12**: $[\alpha]_D^{20}$ +8.8 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1H), 5.21 (s, 1H), 4.30-4.23 (m, 2H), 4.01 (t, *J* = 8.0 Hz, 1H), 3.80 (t, *J* = 7.2 Hz, 1H), 3.02-2.78 (m, 5H), 2.75-2.62 (m, 2H), 2.08-1.89 (m, 2H), 1.65 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 118.5, 109.7, 77.8, 74.5, 66.3, 48.3, 44.8, 27.9, 26.8, 26.6, 25.3, 24.9; IR (neat) 3467, 2922, 1643, 1455, 1372, 1212, 1157, 1067, 909 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{14}H_{24}O_3S_2Na$: 327.1065, found 327.1068.

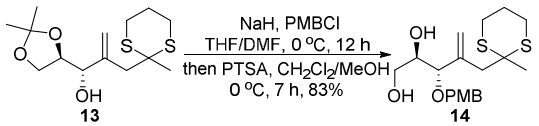
*Conversion of compound **12** into **13**:*



To a solution of **12** (230 mg, 0.76 mmol) in anhydrous THF (4 mL) at room temperature under argon was added triphenylphosphine (397 mg, 1.5 mmol) and *p*-nitrobenzoic acid (253 mg, 1.52 mmol), which was stirred for a period of 10 min. DEAD (239 μL, 1.5 mmol) was then added dropwise. After stirring at room temperature for an additional 12 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and quenched with 10% $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give crude product as a yellow oil.

The aforementioned crude product was dissolved in anhydrous MeOH (5 mL) at room temperature under argon and NaOH (91 mg, 2.3 mmol) was then added. After stirring at room temperature for 2 h, the reaction mixture was concentrated to give a yellow oil which was then purified via silica gel chromatography (10:1 to 5:1 hexane/ethyl acetate) to afford **13** (205 mg, 89%) as a colorless oil.

*Synthesis of compound **14**:*



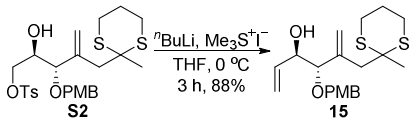
To a solution of **13** (893 mg, 2.9 mmol) in anhydrous THF (8 mL) and DMF (4 mL) at 0 ^{o}C under argon was added NaH (60%, 353 mg, 8.8 mmol). After stirring at 0 ^{o}C for 1 h, PMBCl (797 μL, 5.88 mmol) was added dropwise. The resulting mixture was stirred for 11 h at this temperature and then concentrated. The residue was then dissolved in anhydrous CH_2Cl_2 (15 mL) and MeOH (10 mL) at 0 ^{o}C, to which PTSA (1.677 g, 8.8 mmol) was added. After stirring at 0 ^{o}C for 7 h, the reaction mixture was concentrated to give a yellow oil which was purified via silica gel chromatography (4:1 to 1:2 hexane/ethyl acetate) to afford **14** (936 mg, 83%) as a light yellow oil: $[\alpha]_D^{20}$ +32.1 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.50 (s, 1H), 5.41 (s, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.37-4.25 (m, 2H), 3.80 (s, 3H), 3.82-3.67 (m, 2H), 3.64 (d, *J* = 7.6 Hz, 1H), 3.00-2.75 (m, 5H), 2.64 (d, *J* = 14.8 Hz, 1H), 2.29 (brs, 1H), 2.05-1.89 (m, 2H), 1.72 (s, 3H), 1.62 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 140.9, 130.1, 129.4, 118.5, 113.8, 84.3, 71.4, 71.3, 62.7, 55.2, 48.4, 43.5, 28.4, 26.9, 26.8, 24.9; IR (neat) 3418, 2909, 1613, 1514, 1423, 1248, 1034, 909 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{19}H_{28}O_4S_2Na$: 407.1327, found 407.1322.

*Synthesis of compound **S2**:*

To a solution of **14** (2.43 g, 6.3 mmol) in anhydrous dichloromethane (50 mL) at room temperature under argon was added Et_3N (1.33 mL, 9.54 mmol), Bu_3SnO (95 mg, 0.4 mmol), and TsCl (1.443 g, 7.6 mmol) subsequently. The reaction mixture was stirred for 24 h and then concentrated. The residue was purified via silica gel chromatography (4:1 to 3:1 hexane/ethyl acetate) to afford **S2** (3.27 g, 96%) as a light yellow oil: $[\alpha]_D^{20}$ +22 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.43 (s, 1H), 5.40 (s, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.30-4.19 (m, 2H), 4.19-4.05 (m, 2H), 3.87 (s, 1H), 3.80 (s, 3H), 2.95-2.75 (m, 5H), 2.62 (d, *J* = 15.2 Hz, 1H), 2.44 (s, 3H), 2.05-1.86 (m, 2H), 1.68 (s, 3H), 1.66 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 144.7, 140.7, 132.7, 129.9, 129.7, 129.3, 127.8, 119.2, 113.6, 81.4, 71.2, 70.8, 55.1, 48.2, 43.3, 28.1, 26.7, 24.8, 21.5; IR (neat) 3516, 2908, 1613, 1514, 1360, 1249, 1176, 1096, 984 cm^{-1}; LRMS (ESI), *m/z*

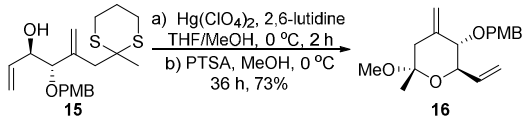
561.1 $(M+Na)^+$.

*Synthesis of compound **15**:*



To a suspension of trimethylsulfonium iodide (5.18 g, 25.4 mmol) in anhydrous THF (50 mL) at 0 °C under argon was added ^{n}BuLi (1.6 M, 13.2 mL, 21.2 mmol) dropwise. After stirring at 0 °C for 1 h, a solution of **S2** (2.276 g. 4.2 mmol) in THF (20 mL) was added. The resulting mixture was stirred for an additional 2 h and then quenched with water (10 mL). After warming up to room temperature, the reaction mixture was diluted with CH_2Cl_2 (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (5:1 to 3:1 hexane/ethyl acetate) to afford **15** (1.415 g, 88%) as a colorless oil: $[\alpha]_D^{20}$ +42.4 (*c* 1.09, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.92 (ddd, *J* = 16.8, 10.8, 5.2 Hz, 1H), 5.44 (s, 1H), 5.37 (s, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 4.22 (s, 2H), 3.80 (s, 3H), 3.00-2.72 (m, 5H), 2.63 (d, *J* = 14.8 Hz, 1H), 2.32 (d, *J* = 4.8 Hz, 1H), 2.05-1.90 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 140.4, 136.5, 130.4, 129.3, 118.6, 116.2, 113.7, 84.2, 73.3, 70.8, 55.2, 48.5, 43.9, 28.2, 26.8, 24.9; IR (neat) 3468, 2907, 1613, 1514, 1423, 1248, 1034, 920 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{20}H_{28}O_3S_2Na$: 403.1378, found 403.1381.

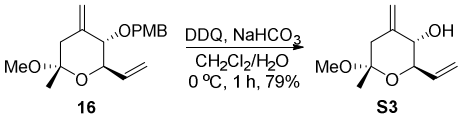
*Synthesis of compound **16**:*



To a solution of **15** (460 mg, 1.2 mmol) in anhydrous THF (4 mL) and MeOH (4 mL) at 0 °C under argon was added 2,6-lutidine (564 μL, 4.8 mmol) and $Hg(ClO_4)_2$ (969 mg, 2.4 mmol). After stirring at 0 °C for 2 h, the mixture was quenched with saturated $Na_2S_2O_3$ (10 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic phase

was washed with 10% $CuSO_4$ (20 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was then dissolved in anhydrous MeOH (4 mL) at 0 °C under argon and PTSA (12 mg, 0.06 mmol) was added. The resulting mixture was stirred at 0 °C for 36 h and then concentrated. The residue was purified via silica gel chromatography (15:1 to 10:1 hexane/ethyl acetate) to afford **16** (269 mg, 73%) as a light yellow oil: $[\alpha]_D^{20}$ +163.0 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.94 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 5.19 (s, 1H), 4.92 (s, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 3.90 (t, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 3.60 (d, *J* = 9.2 Hz, 1H), 3.19 (s, 3H), 2.55 (d, *J* = 9.6 Hz, 1H), 2.36 (d, *J* = 14.0 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 141.4, 136.2, 130.2, 129.5, 117.5, 113.7, 108.6, 99.0,79.7, 75.1, 72.7, 55.3, 48.2, 45.0, 22.8; IR (neat) 1698, 1600, 1513, 1463, 1260, 1160, 1033, 833 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{18}H_{24}O_4Na$: 327.1572, found 327.1576.

*Synthesis of compound **S3**:*

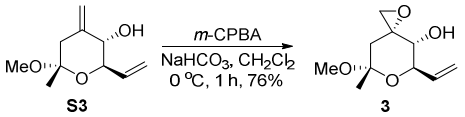


16 **S3**

To a solution of **16** (113 mg, 0.4 mmol) in dichloromethane (3 mL) at 0 °C was added $NaHCO_3$ (64 mg, 0.8 mmol), water (30 μL), and DDQ (85 mg, 0.4 mmol). After stirring at 0 °C for 30 min, $NaHCO_3$ (64 mg, 0.8 mmol), water (30 μL), and DDQ (85 mg, 0.8 mmol) were added again. After an additional 30 min, the mixture was quenched with saturated $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was then purified via silica gel chromatography (8:1 to 5:1 hexane/ethyl acetate) to afford **S3** (54 mg, 79%) as a colorless oil: $[\alpha]_D^{20}$ +190.6 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.16 (s, 1H), 4.93 (s, 1H), 3.88-3.70 (m, 2H), 3.21 (s, 3H), 2.56 (d, *J* = 14.0 Hz, 1H), 2.41 (d, *J* = 13.6 Hz, 1H), 1.75 (d, *J* = 4.8 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 136.0, 119.3, 107.7, 99.0, 77.1, 71.7, 48.3, 44.8, 22.8; IR (neat) 3435, 2992, 1379, 1230, 1184, 1060, 890, 668 cm^{-1}; LRMS (ESI), *m/z* 207.1

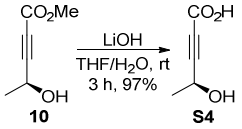
$(M+Na)^+$.

*Synthesis of compound **3**:*



To a solution of **S3** (55 mg, 0.3 mmol) in anhydrous dichloromethane (3 mL) at 0 °C under argon was added $NaHCO_3$ (101 mg, 1.2 mmol) and *m*-CPBA (62 mg, 0.36 mmol). After stirring at 0 °C for 30 min, *m*-CPBA (62 mg, 0.4 mmol) was again added. After an additional 30 min, the mixture was quenched with 5% NaOH (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was then purified via silica gel chromatography (2:1 to 1:1 hexane/ethyl acetate) to afford **3** (46 mg, 76%) as a white powder: mp 53-57 °C; $[\alpha]_D^{20}$ +187.2 (*c* 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.4 Hz, 1H), 3.98 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.57 (t, *J* = 10.4 Hz, 1H), 3.26 (s, 3H), 2.99 (d, *J* = 4.4 Hz, 1H), 2.49 (d, *J* = 4.4 Hz, 1H), 2.29 (d, *J* = 14.8 Hz, 1H), 1.75 (d, *J* = 3.2 Hz, 1H), 1.72 (d, *J* = 6.4 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 117.8, 98.5, 73.1, 67.3, 56.4, 48.3, 47.1, 41.9, 23.0; IR (KBr) 3418, 2910, 1646, 1378, 1236, 1160, 1012, 919cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{10}H_{16}O_4Na$: 223.0946, found 223.0948.

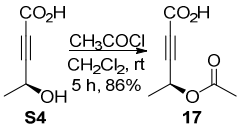
*Synthesis of compound **S4**:*



To a solution of **10** (539 mg, 4.2 mmol) in THF (5 mL) and water (1 mL) at room temperature was added LiOH (303 mg, 12.6 mmol). After stirring for 3 h, hydrochloride acid (37%, 1.2 mL) was added at 0 °C to adjust the pH to a range of ~1-2. The resulting mixture was concentrated and the residue was purified via silica gel chromatography (10:1 to 5:1 dichloromethane/methanol) to afford **S4** (466 mg, 97%) as a colorless oil: $[\alpha]_D^{20}$ -48.5 (*c* 1.08, ethyl acetate); ^{1}H NMR (400 MHz, CD_3OH) δ 5.06 (brs, 2H), 4.58 (q, *J* = 6.8 Hz, 1H), 1.44 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OH) δ 156.2, 90.0, 76.4, 58.2, 23.7; IR (KBr) 3379, 2990,

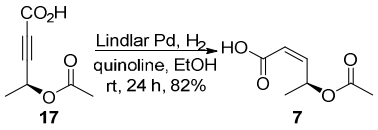
2237, 1699, 1376, 1269, 1057 cm^{-1}; LRMS (ESI), *m/z* 137.0 $(M+Na)^+$.

*Synthesis of compound **17**:*



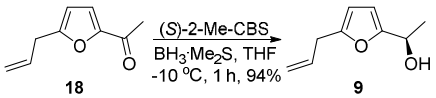
To a solution of **S4** (477 mg, 4.2 mmol) in anhydrous dichloromethane (10 mL) at room temperature under argon was added an excess of acetylchloride (5 mL). After stirring for 5 h, the resulting mixture was concentrated and the residue was purified via silica gel chromatography (1:1 to 1:2 hexane/ethyl acetate) to afford **17** (561 mg, 86%) as a colorless oil: $[\alpha]_D^{20}$ -114.4 (*c* 1.06, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (brs, 1H), 5.51 (q, *J* = 6.8 Hz, 1H), 2.09 (s, 3H), 1.54 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 156.4, 86.9, 75.7, 59.5, 20.8, 20.1; IR (neat) 3501, 2996, 2249, 1732, 1374, 1233, 1050 cm^{-1}; LRMS (ESI), *m/z* 179.0 $(M+Na)^+$.

*Synthesis of compound **7**:*



To a solution of **17** (500 mg, 3.2 mmol) in anhydrous ethanol (10 mL) was added Lindlar catalyst (58 mg) and quinoline (38 μL, 0.3 mmol). The mixture was exposed to an atmosphere of H_2 at room temperature. After 24 h, the resulting mixture was filtered and concentrated. The residue was purified via silica gel chromatography (10:1 to 8:1 hexane/ethyl acetate) to afford **7** (415 mg, 82%) as a colorless oil: $[\alpha]_D^{20}$ +20.6 (*c* 1.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30-6.19 (m, 2H), 5.86-5.78 (m, 1H), 2.05 (s, 3H), 1.38 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 150.4, 119.3, 68.7, 21.1, 19.5; IR (neat) 2986, 1732, 1652, 1434, 1372, 1244, 1121, 1049, 826 cm^{-1}; LRMS (ESI), *m/z* 181.0 $(M+Na)^+$.

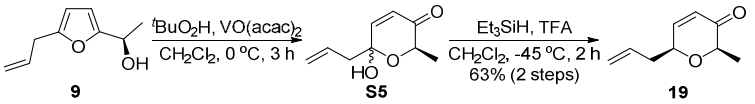
*Synthesis of compound **9**:*



To a solution of (*S*)-2-Me-CBS catalyst (4.357 g, 15.7 mmol) in anhydrous THF (80 mL) at 0

°C under argon was added $BH_3 \cdot Me_2S$ (3.3 mL, 34.6 mmol). After stirring for 30 min, the mixture was cooled to -10 °C and a solution of **18** (4.716 g, 31.4 mmol) in THF (20 mL) was added. The resulting mixture was stirred for 30 min and then quenched with MeOH (10 mL) and water (20 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (10:1 to 6:1 hexane/ethyl acetate) to afford **9** (4.492 g, 94% yield, 93% *ee*) as a colorless oil: $[\alpha]_D^{20}$ +20.6 (*c* 1.10, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, *J* = 2.8 Hz, 1H), 6.00-5.86 (m, 2H), 5.21-5.05 (m, 2H), 4.83 (q, *J* = 6.0 Hz, 1H), 3.37 (d, *J* = 6.4 Hz, 2H), 2.02 (s, 1H), 1.51 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 153.4, 133.8, 116.9, 106.0, 105.8, 63.6, 32.6, 21.1; IR (neat) 3366, 2361, 1643, 1558, 1371, 1181, 1077, 919 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_9H_{12}O_2Na$: 175.0735, found 175.0736.

*Synthesis of compound **19**:*

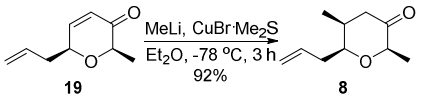


To a solution of **9** (2.37 g, 15.6 mmol) in dichloromethane (60 mL) at 0 °C was added $VO(acac)_2$ (414 mg, 1.6 mmol) and ^{t}BuOOH (5.5 M, 3.7 mL, 20.4 mmol). After stirring for 3 h, the mixture was treated with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give **S5** as a yellow oil.

The aforementioned crude product **S5** was dissolved in anhydrous dichloromethane (60 mL) at -45 °C under argon. Et_3SiH (12.47 mL, 78.1 mmol) and TFA (17.40 mL, 234.2 mmol) were then added subsequently. After stirring at -45 °C for 2 h, the mixture was treated with 30% $NaHCO_3$ to adjust the pH to a range of ~8-9. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (40:1 to 20:1 hexane/ethyl acetate) to afford **19** (1.497 g, 63%, 2 steps) as a light yellow oil: $[\alpha]_D^{20}$ +34.4 (*c* 1.03, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 10.0 Hz, 1H), 6.09 (dd, *J* = 10.0, 2.4 Hz, 1H), 5.92-5.77 (m, 1H), 5.25-5.09 (m, 2H), 4.40 (t, *J* = 5.6 Hz, 1H), 4.07 (dt, *J* = 6.4, 5.2 Hz, 1H), 2.55-2.33 (m, 2H), 1.38

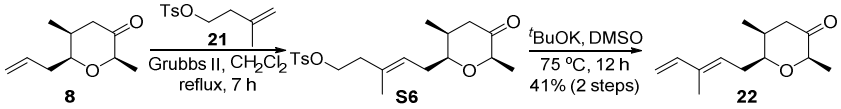
(d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 150.6, 133.0, 126.7, 118.4, 77.0, 73.5, 39.0, 15.4; IR (neat) 1732, 1694, 1446, 1374, 1237, 1097, 924, 741 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_9H_{12}O_2Na$: 175.0735, found 175.0737.

Synthesis of compound ***8****:*



To a suspension of $CuBr{\cdot}Me_2S$ (1.3 g, 6.3 mmol) in anhydrous Et_2O (10 mL) at -78 °C under argon was added MeLi (3 M, 3.9 mL, 11.70 mmol). After stirring for 1 h, a solution of **19** (594 mg, 3.90 mmol) in Et_2O (5 mL) was added. The resulting mixture was stirred for an additional 2 h and then quenched with water (5 mL). After warming to room temperature, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (50:1 to 30:1 hexane/ethyl acetate) to afford **8** (604 mg, 92%) as a colorless oil: $[\alpha]_D^{20}$ -75.1 (*c* 1.01, ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.73 (m, 1H), 5.15-4.99 (m, 2H), 3.95-3.83 (m, 2H), 2.61 (dd, J = 11.2, 6.0 Hz, 1H), 2.43-2.23 (m, 3H), 2.15 (dt, J = 14.4, 7.2 Hz, 1H), 1.23 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 134.5, 117.0, 79.3, 78.5, 46.6, 36.8, 34.8, 14.9, 12.9; IR (neat) 1732, 1715, 1417, 1379, 1244, 1078, 984, 921 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{10}H_{16}O_2Na$: 191.1048, found 191.1050.

Synthesis of compound ***22****:*

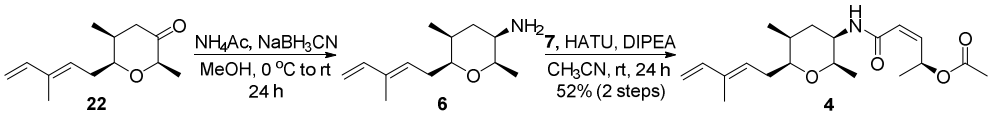


A solution of **8** (240 mg, 1.43 mmol) was prepared in anhydrous dichloromethane (4 mL) at room temperature under argon. To a stirred solution of **21** (3.428 g, 14.3 mmol) in anhydrous dichloromethane (10 mL) was added an aliquot of solution **8** (1 mL) followed by Grubbs' 2nd generation catalyst (121 mg, 0.14 mmol) under argon. The resulting mixture was heated up at reflux for 1.5 h, after which an additional aliquot of solution **8** (1 mL) was added. This

additional process was repeated after 3 h and 5 h. Following 7 h of reaction time, the mixture was concentrated under reduced pressure. The residue was purified via silica gel chromatography (10:1 to 5:1 hexane/ethyl acetate) to afford crude **S6** as a yellow oil.

The aforementioned crude **S6** was then dissolved in DMSO (4 mL) followed by addition of ^{t}BuOK (320 mg, 2.9 mmol). The resulting mixture was heated to 75 ^{o}C for 12 h, cooled to room temperature, and diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (50:1 to 40:1 hexane/acetone) to afford **22** (122 mg, 41%, 2 steps) as a colorless oil: $[\alpha]_D^{20}$ -33.4 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.50 (t, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 14.8 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.00-3.85 (m, 2H), 2.64 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.53-2.41 (m, 1H), 2.38-2.25 (m, 3H), 1.78 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 141.2, 135.9, 127.9, 111.4, 79.5, 78.8, 46.7, 34.9, 31.4, 15.0, 13.1, 11.9; IR (neat) 1724, 1643, 1607, 1444, 1385, 1260, 1228, 1111, 894 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{13}H_{20}O_2Na$: 231.1361, found 231.1355.

*Synthesis of compound **4**:*

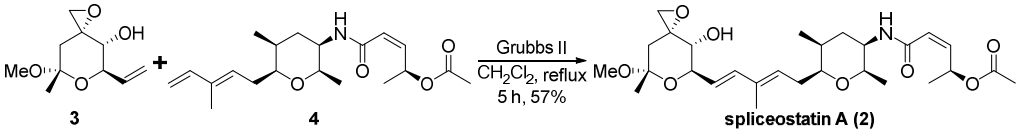


To a solution of **22** (65 mg, 0.3 mmol) in anhydrous methanol (3 mL) at 0 ^{o}C under argon was added ammonium acetate (482 mg, 6.2 mmol) and $NaBH_3CN$ (99 mg, 1.6 mmol). The reaction mixture was then gradually warmed to room temperature. After stirring for 24 h, the reaction mixture was added to aqueous NaOH (4 M, 1.2 mL) to adjust the pH to a range of ~8-9 and then diluted with ethyl acetate (10 mL). The resulting mixture was directly dried over $MgSO_4$, filtered, and concentrated to give crude **6** as a light yellow oil.

To a stirred solution of acid **7** (59 mg, 0.4 mmol) in anhydrous acetonitrile (2 mL) at room temperature under argon was added HATU (143 mg, 0.4 mmol) and DIPEA (273 µL, 1.6 mmol). The resulting mixture was then transferred via cannula to a stirred solution of crude **6** in acetonitrile (2 mL) at room temperature and rinsed with additional acetonitrile (1 mL). After

stirring for 24 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (3 mL) and then diluted with ethyl acetate (15 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (5:1 to 3:1 hexane/ ethyl acetate) to afford **4** (57 mg, 52%, 2 steps) and its C-14 epimer (9 mg) as colorless oil. Compound **4**: $[\alpha]_D^{20}$ -58.6 (*c* 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.26 (dt, *J* = 13.6, 6.8 Hz, 1H), 6.00 (d, *J* = 8.8 Hz, 1H), 5.89 (dd, *J* = 11.6, 8.0 Hz, 1H), 5.70 (d, *J* = 11.6 Hz, 1H), 5.46 (t, *J* = 6.8 Hz, 1H), 5.10 (d, *J* = 17.6 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 3.94 (t, *J* = 3.2 Hz, 1H), 3.67 (dd, *J* = 6.4, 2.0 Hz, 1H), 3.54 (dt, *J* = 7.6, 2.8 Hz, 1H), 2.45-2.32 (m, 1H), 2.30-2.17 (m, 1H), 2.04 (s, 3H), 2.00-1.86 (m, 2H), 1.84-1.75 (m, 1H), 1.75 (s, 3H), 1.39 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 164.8, 143.6, 141.3, 135.7, 128.1, 122.5, 111.1, 80.8, 76.0, 68.9, 47.1, 35.8, 31.9, 28.9, 21.2, 20.0, 17.8, 15.0, 11.9; IR (neat) 3358, 2977, 2934, 1739, 1668, 1634, 1520, 1369, 1243, 1049, 1011 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{20}H_{31}NO_4Na$: 372.2151, found 372.2152.

*Synthesis of spliceostatin A (**2**):*

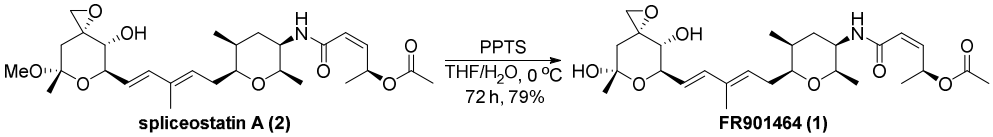


To a solution of **4** (45 mg, 0.13 mmol) in anhydrous dichloromethane (1 mL) at room temperature under argon was added a solution of **3** (31 mg, 0.16 mmol) in anhydrous dichloromethane (500 μL) and Grubbs' 2nd generation catalyst (11 mg, 0.01 mmol). The resulting mixture was heated to reflux for 5 h and then concentrated. The residue was purified via silica gel chromatography (2:1 to 1:2 hexane/ ethyl acetate) to afford spliceostatin A (**2**) (29 mg) as a white powder, in addition to recovered of **3** and **4**.

The combined recovery of **3** and **4** was dissolved in anhydrous dichloromethane (1 mL) at room temperature under argon, to which Grubbs' 2nd generation catalyst (5 mg) was added. The resulting mixture was heated to reflux for 5 h and then concentrated. The residue was purified via silica gel chromatography (2:1 to 1:2 hexane/ ethyl acetate) to afford spliceostatin A (**2**) (9 mg) as a white powder. The combined yield of spliceostatin A (**2**) after one cycle is 38 mg (57%).

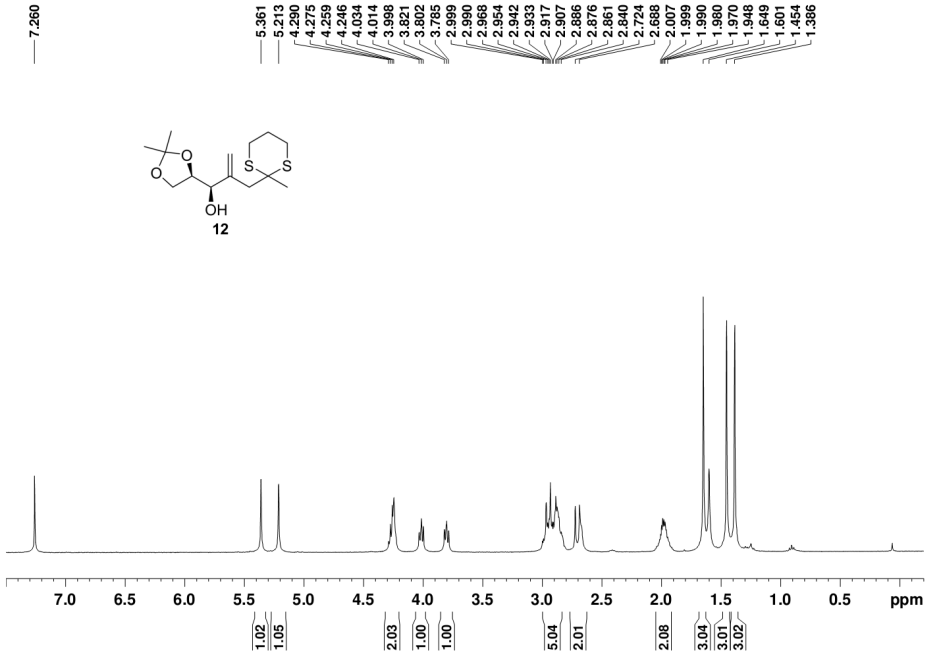
Spliceostatin A (**2**): mp 64-68 °C; $[\alpha]_D^{20}$ +25.3 (*c* 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 15.6 Hz, 1H), 6.26 (dt, *J* = 13.6, 6.8 Hz, 1H), 6.01 (d, *J* = 9.2 Hz, 1H), 5.89 (dd, *J* = 11.2, 8.0 Hz, 1H), 5.75-5.65 (m, 2H), 5.51 (t, *J* = 6.8 Hz, 1H), 4.05 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.94 (d, *J* = 7.6 Hz, 1H), 3.66 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.60 (t, *J* = 10.2 Hz, 1H), 3.52 (dt, *J* = 6.8, 2.0 Hz, 1H), 3.28 (s, 3H), 2.99 (d, *J* = 4.8 Hz, 1H), 2.50 (d, *J* = 4.4 Hz, 1H), 2.42-2.19 (m, 3H), 2.04 (s, 3H), 1.99-1.85 (m, 2H), 1.79 (s, 3H), 1.78-1.68 (m, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.38 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 164.8, 143.6, 138.1, 134.7, 128.9, 124.1, 122.5, 98.6, 80.8, 75.9, 73.2, 68.9, 67.6, 56.5, 48.4, 47.1, 42.0, 35.8, 32.0, 28.9, 23.0, 21.2, 19.9, 17.8, 15.0, 12.6; IR (KBr) 3450, 2977, 1739, 1669, 1635, 1522, 1368, 1245, 1049, 1010 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{28}H_{43}NO_8Na$: 544.2887, found 544.2886.

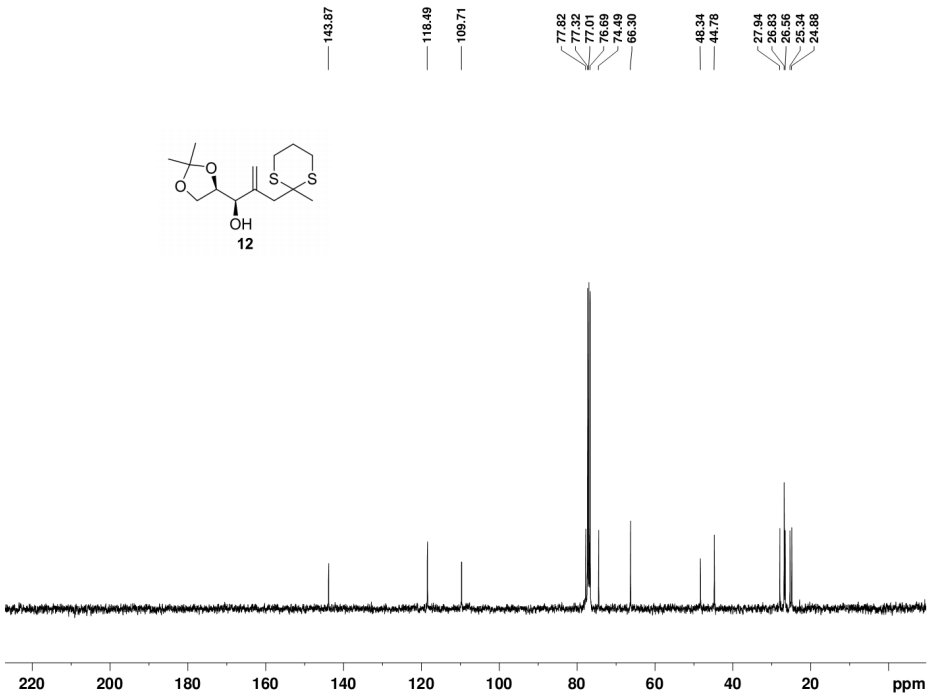
*Synthesis of FR901464 (**1**):*



To a solution of spliceostatin A (**2**) (6.2 mg, 0.01 mmol) in THF/H_2O (3 mL/ 0.75 mL) at 0 °C under argon was added PPTS (17.9 mg, 0.07 mmol). The resulting solution was stirred for 72 h and was then diluted with ethyl acetate (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified via silica gel chromatography (1:1 to 1:4 hexane/ ethyl acetate) to afford FR901464 (**1**) (4.8 mg, 79%) as a white powder: mp 64-67 °C; $[\alpha]_D^{23}$ -13.0 (*c* 0.45, CH_2Cl_2); ^1H NMR (500 MHz, CD_2Cl_2) δ 6.38 (d, *J* = 15.5 Hz, 1H), 6.26 (m, 1H), 5.98 (d, *J* = 9.0 Hz, 1H), 5.90 (dd, *J* = 11.5, 8.0 Hz, 1H), 5.71 (dd, *J* = 11.5, 1.0 Hz, 1H), 5.65 (dd, *J* = 15.7, 7.0 Hz, 1H), 5.54 (t, *J* = 7.0 Hz, 1H), 4.24 (dd, *J* = 9.3, 7.0 Hz, 1H), 3.93-3.87 (m, 1H), 3.66 (qd, *J* = 6.5, 2.1 Hz, 1H), 3.57 (t, *J* = 10.0 Hz, 1H), 3.57-3.50 (m, 1H), 3.34 (s, 1H), 3.06 (d, *J* = 4.5 Hz, 1H), 2.55 (d, *J* = 4.5 Hz, 1H), 2.40-2.31 (m, 1H), 2.34 (d, *J* = 14.3 Hz, 1H), 2.28-2.20 (m, 1H), 2.01 (s, 3H), 1.95-1.91 (m, 2H), 1.78 (s, 3H), 1.78-1.76 (m, 1H), 1.64 (d, *J* = 14.5 Hz, 1H), 1.62 (d, *J* = 10.3 Hz, 1H), 1.43 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 170.6, 164.9, 143.9, 138.3, 134.8, 129.9, 124.6, 122.8,

96.7, 81.1, 76.2, 73.8, 68.9, 68.1, 58.1, 48.1, 47.3, 41.8, 36.2, 32.3, 29.5, 29.1, 21.4, 20.1, 17.9, 15.2, 12.7; IR (KBr) 3449, 2976, 1738, 1667, 1636, 1524, 1369, 1244, 1049, 1010 cm^{-1}; HRMS (ESI), *m/z* $(M+Na)^+$ Calcd for $C_{27}H_{41}NO_8Na$: 530.2730, found 530.2729.

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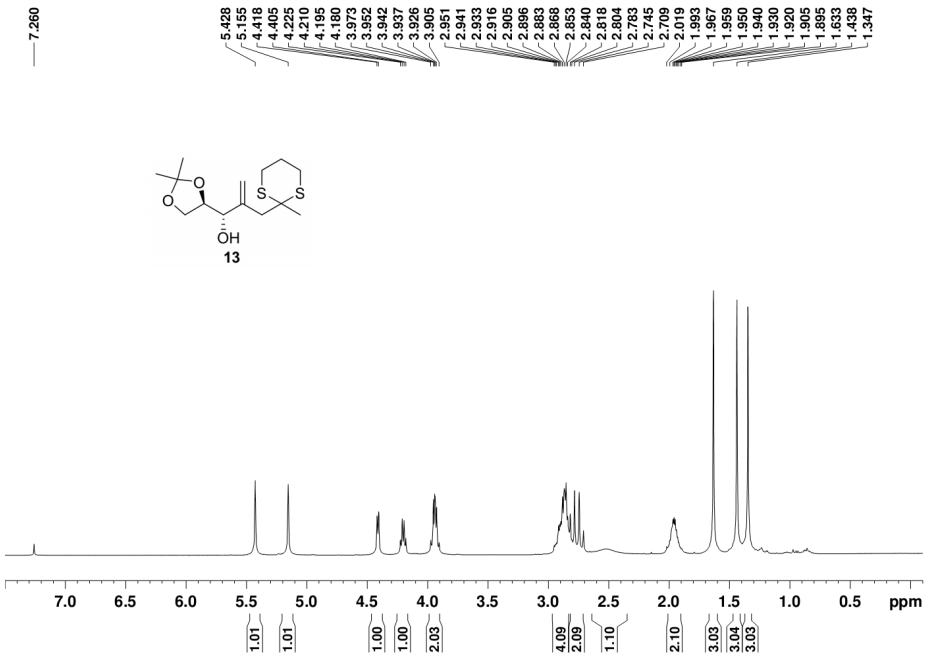
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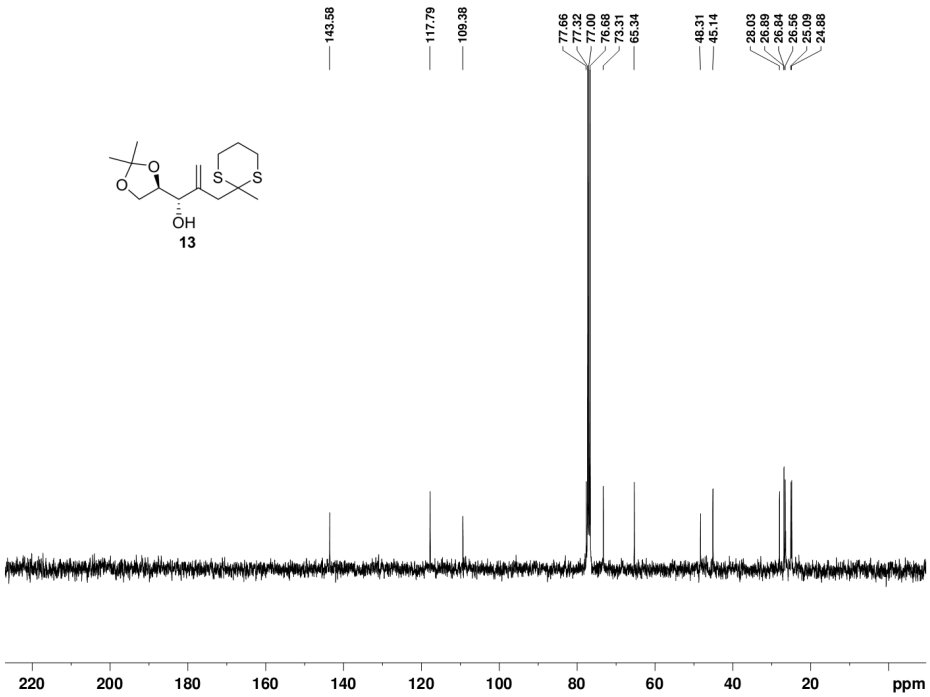
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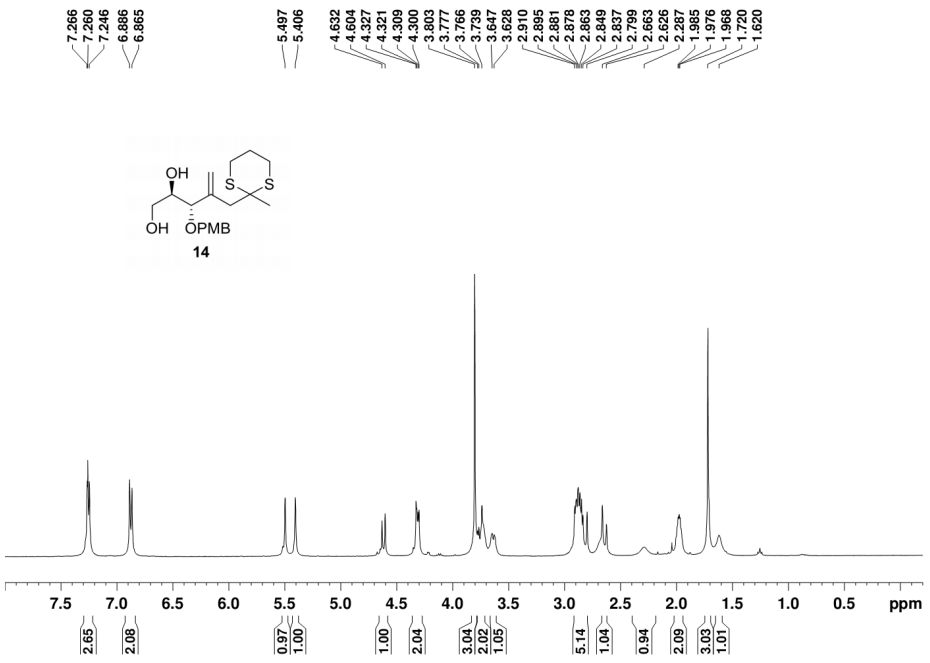
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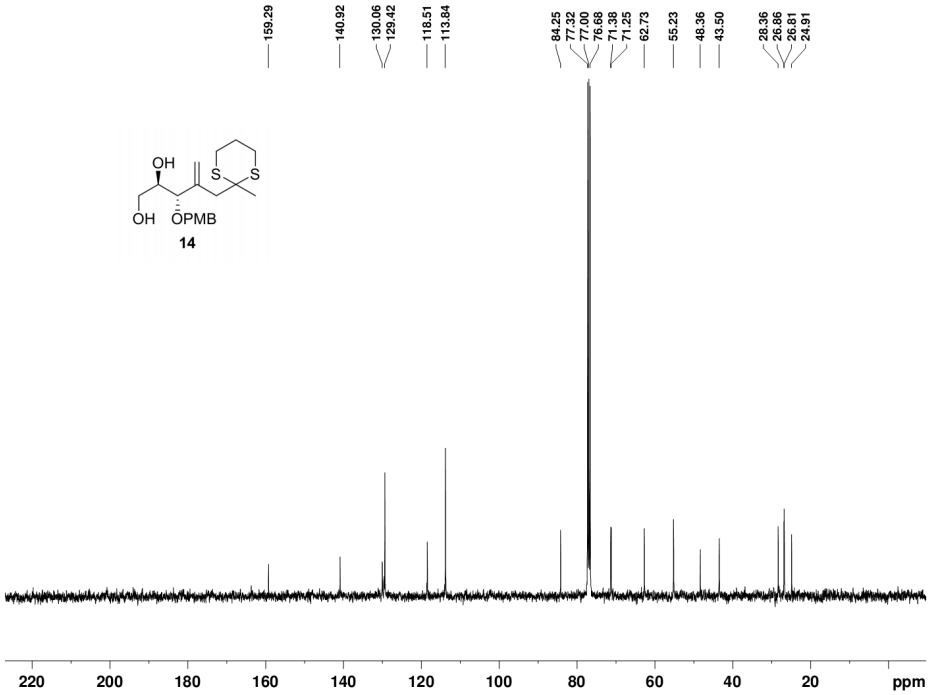
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26.81
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S
OH
OPMB
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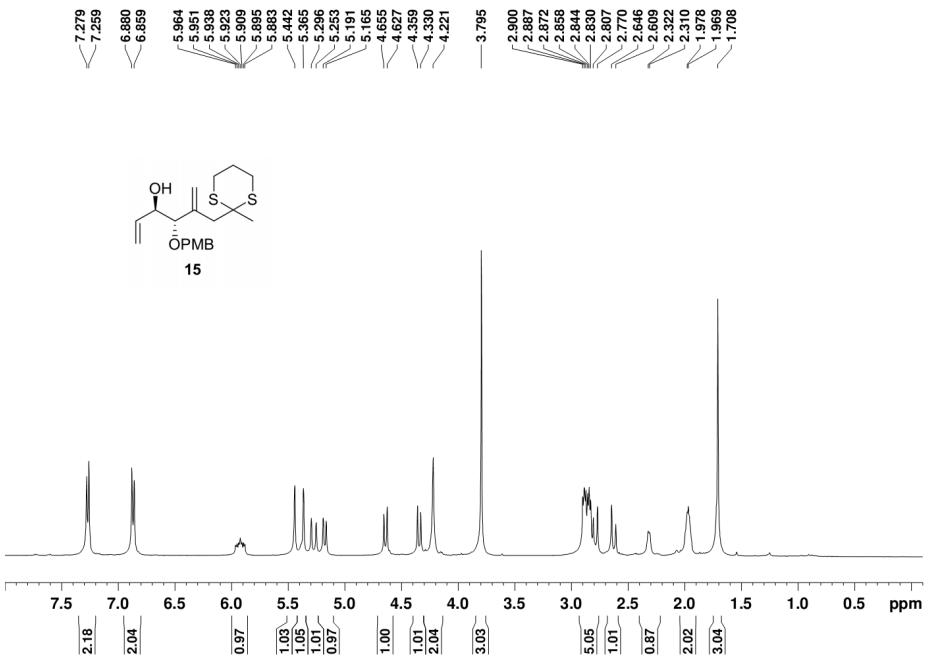
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5.253
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5.165
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4.627
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4.221
3.795
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2.609
2.322
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OH
S
S
OPMB
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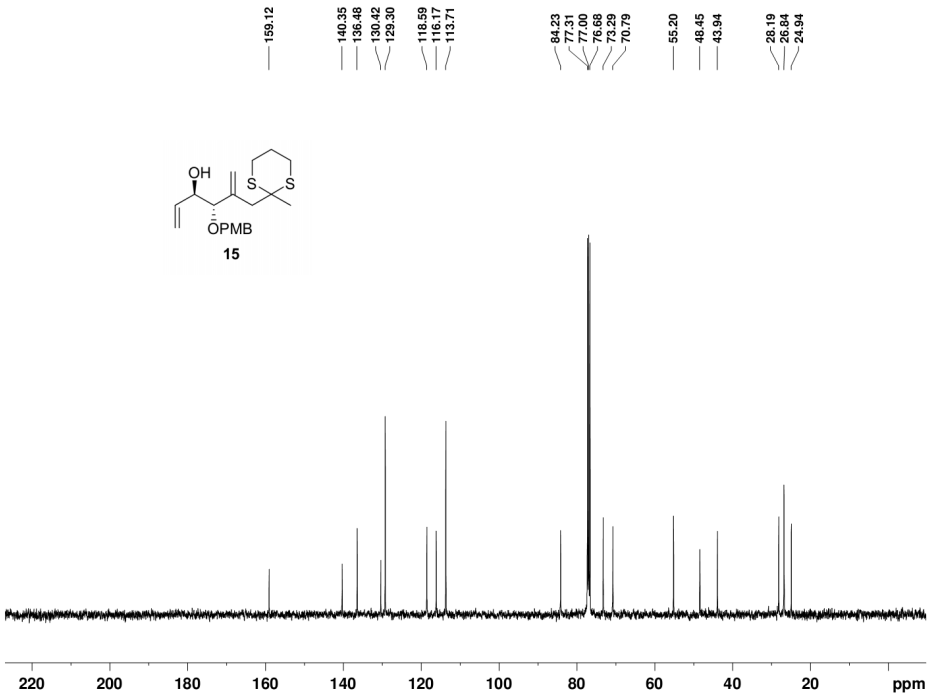
3.04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S
OPMB
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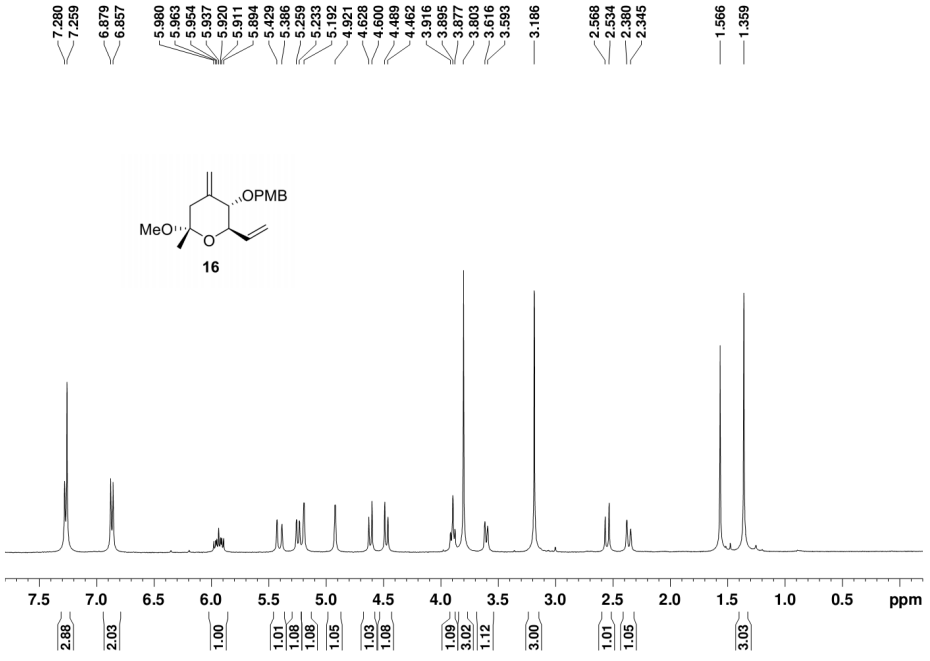
ppm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1.359
OPMB
MeO
O
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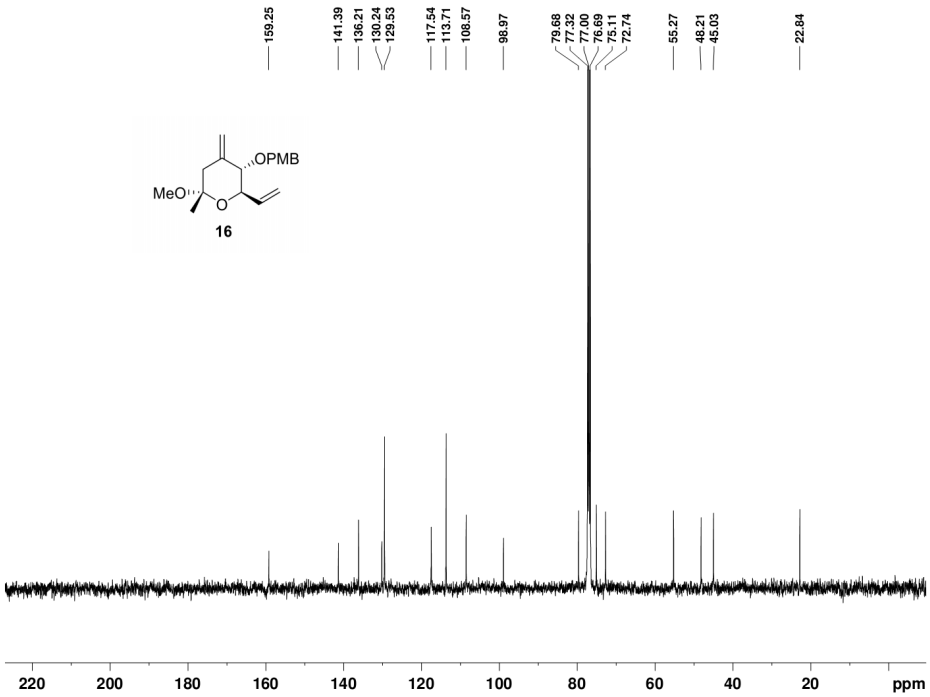
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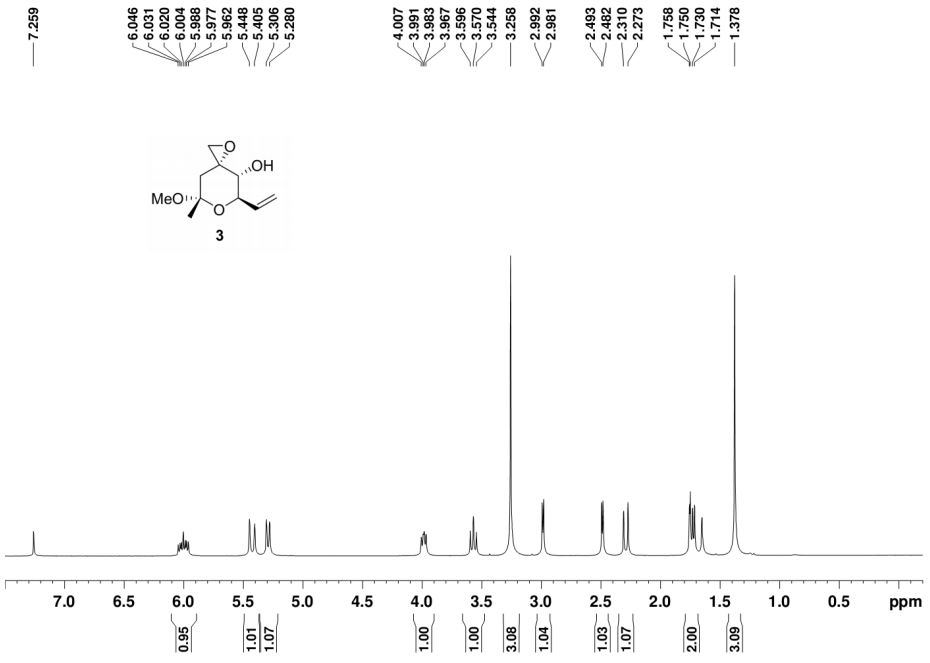
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3.967
3.596
3.570
3.544
3.258
2.992
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2.482
2.310
2.273
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1.750
1.730
1.714
1.378
O
OH
MeO
O
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6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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1.0
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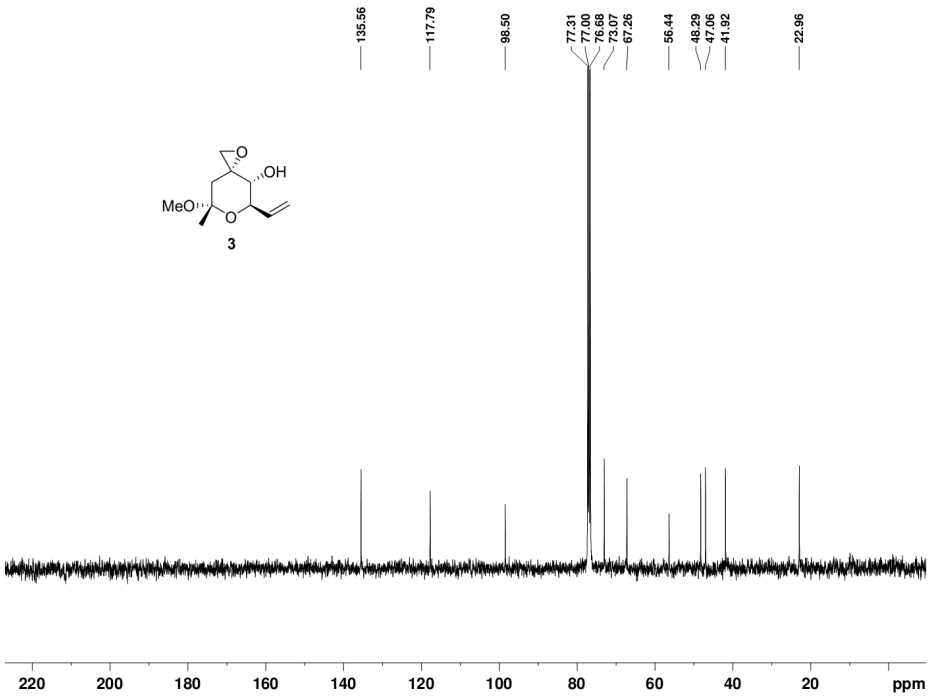
3.09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67.26
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47.06
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OH
MeO
O
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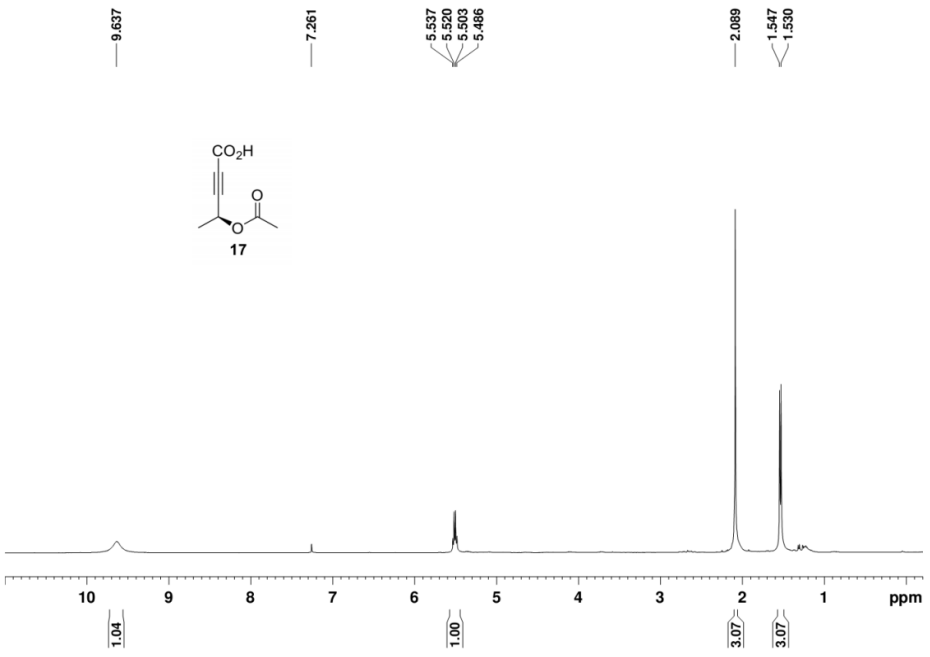
20
ppm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5.486
2.089
1.547
1.530
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O
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9
8
7
6
5
4
3
2
1
ppm
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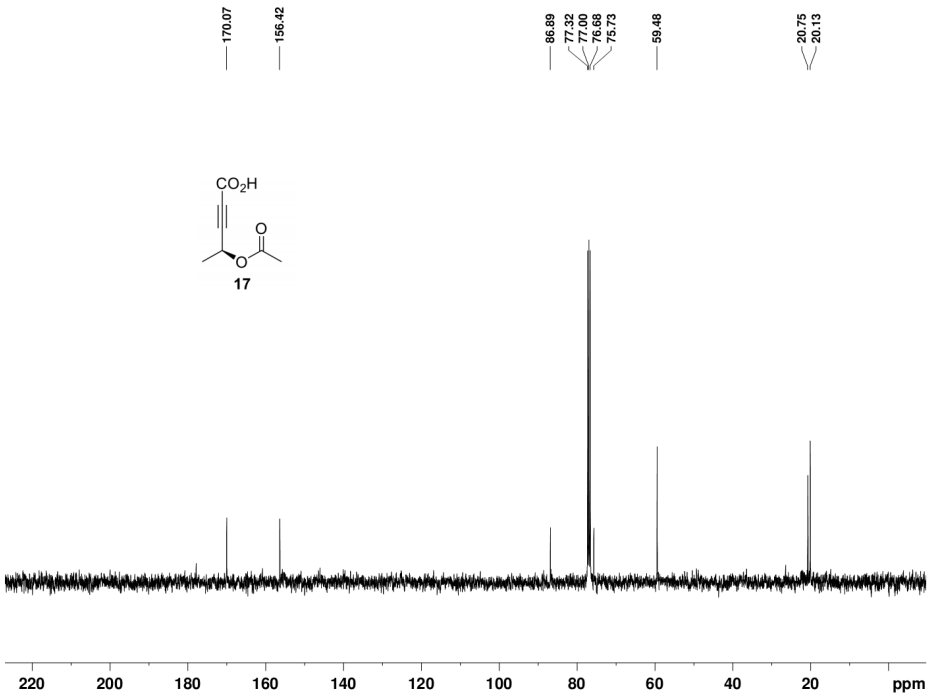
1.00
3.07
3.07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CO2H
O
O
17
220
200
180
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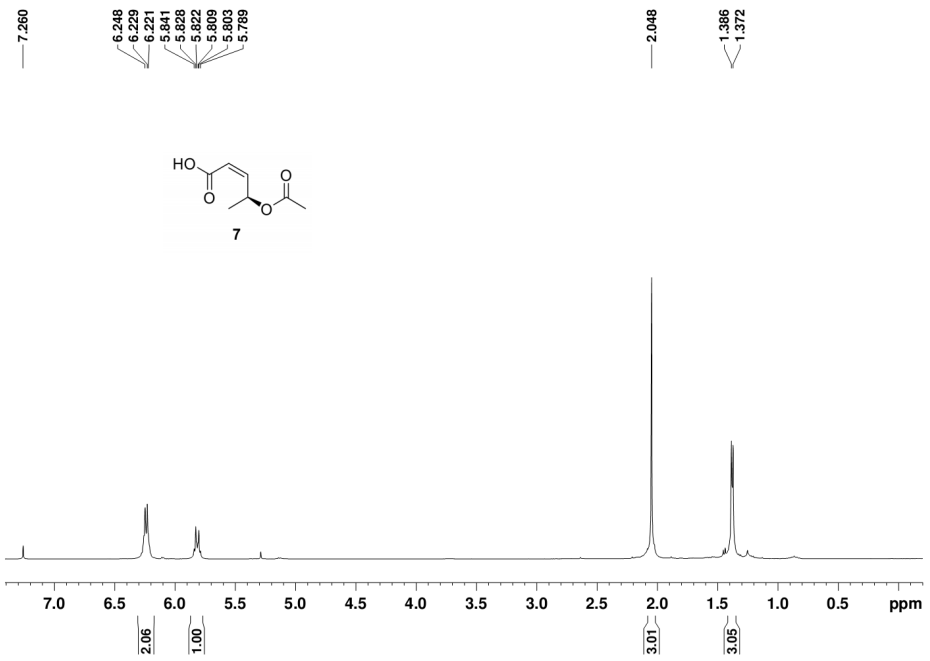
140
120
100
80
60
40
20
ppm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5.809
5.803
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1.372
HO
O
O
O
7
7.0
6.5
6.0
5.5
5.0
4.5
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2.5
2.0
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1.0
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ppm
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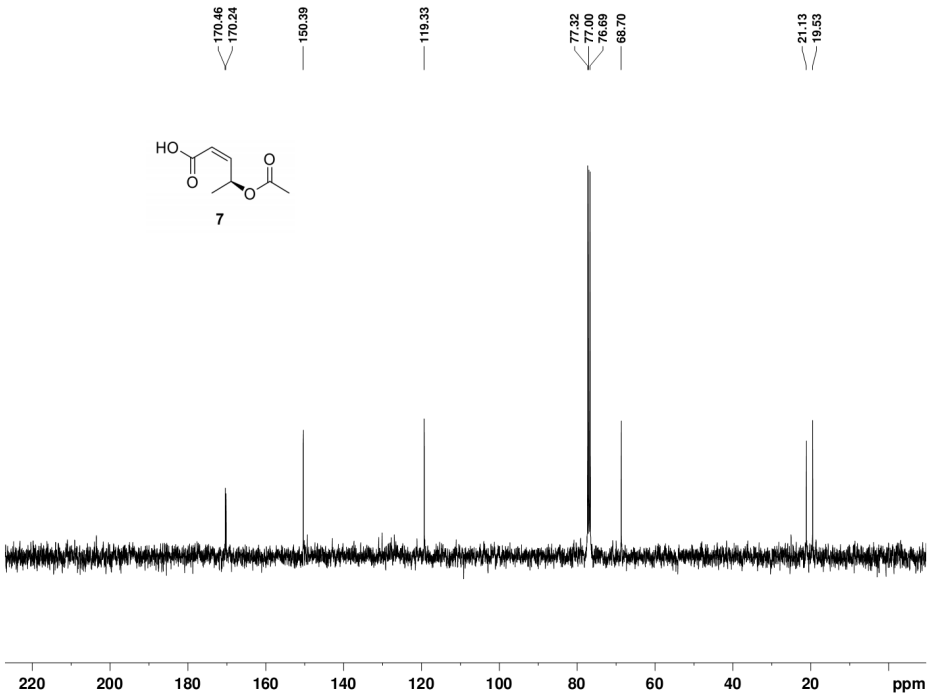
1.00
3.01
3.05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HO
O
O
O
7
220
200
180
160
140
120
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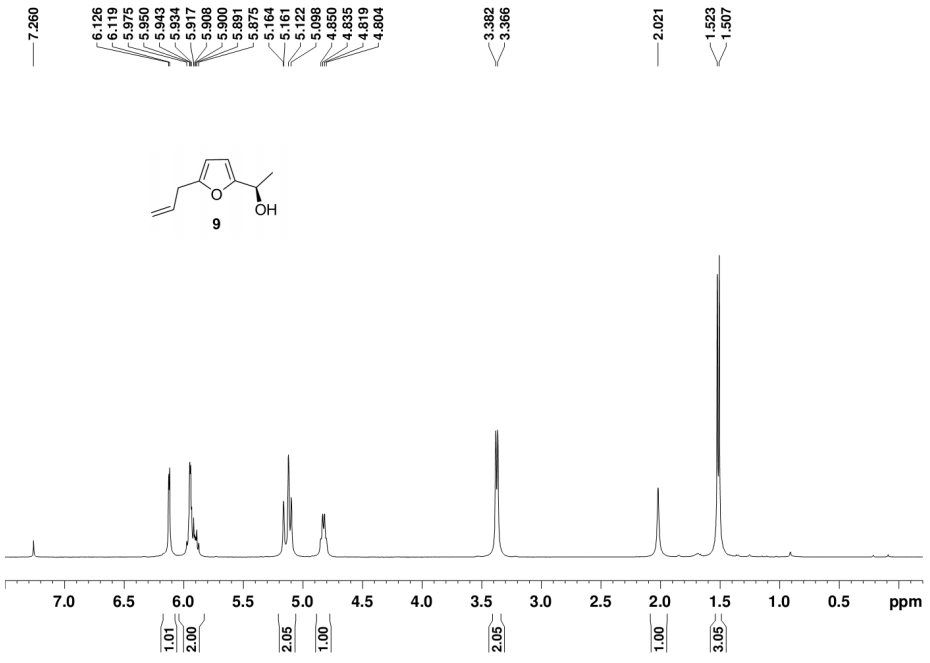
80
60
40
20
ppm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5.161
5.122
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4.819
4.804
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3.366
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1.523
1.507
O
OH
9
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
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1.0
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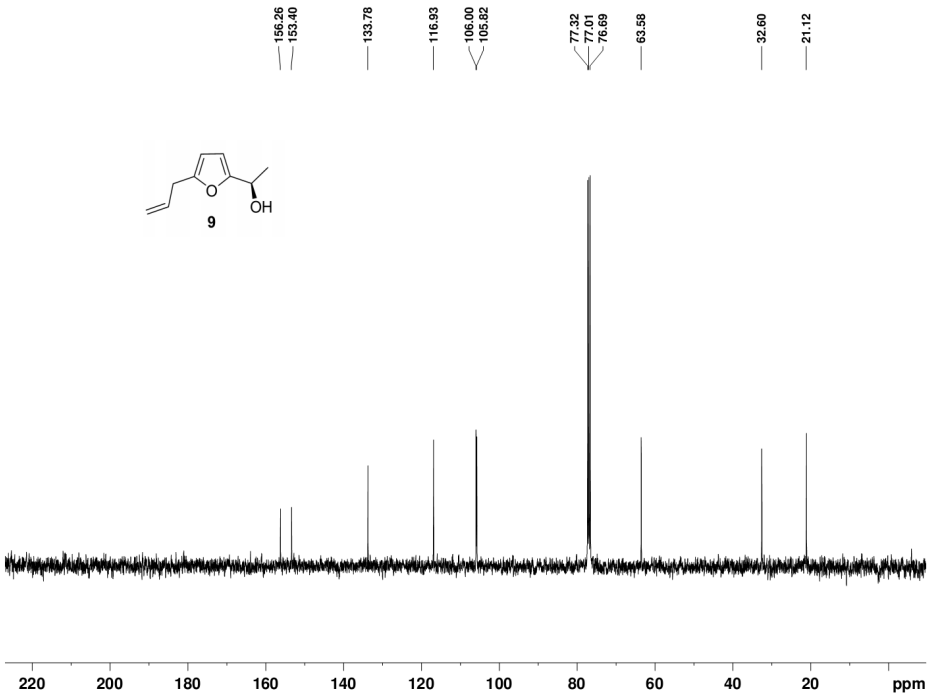
1.00
2.05
1.00
3.05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OH
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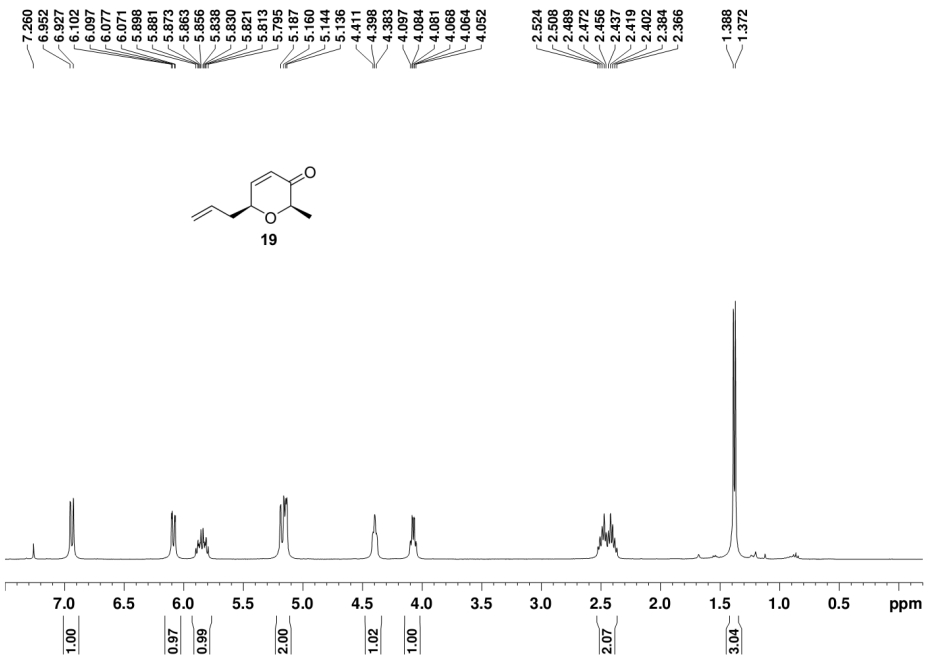
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5.856
5.838
5.830
5.821
5.813
5.795
5.187
5.160
5.144
5.136
4.411
4.398
4.383
4.097
4.084
4.081
4.068
4.064
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2.508
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2.472
2.456
2.437
2.419
2.402
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2.366
1.388
1.372
O
O
19
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6.0
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4.5
4.0
3.5
3.0
2.5
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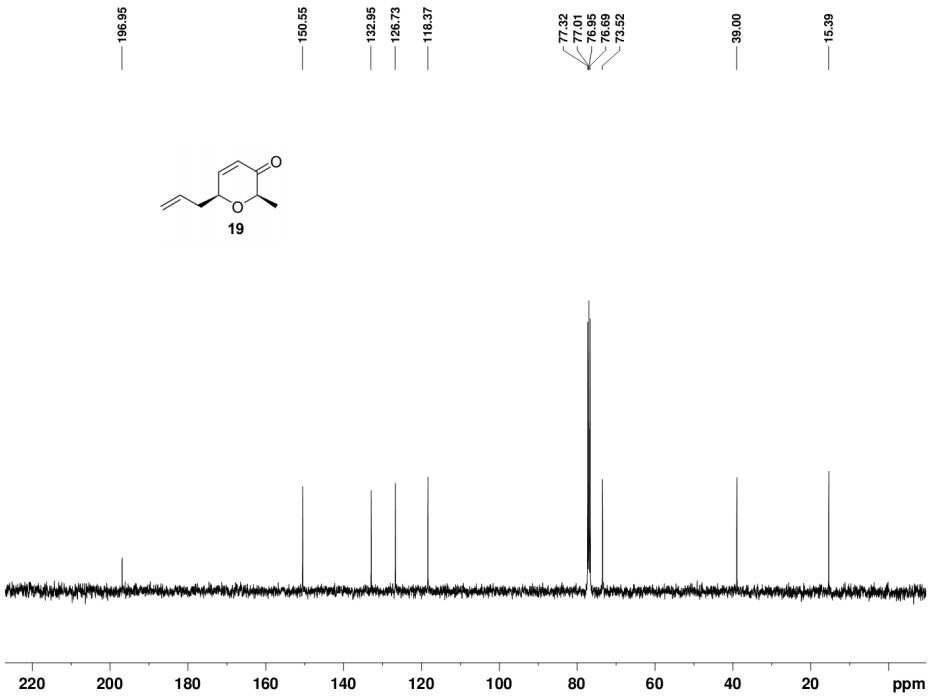
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140
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60
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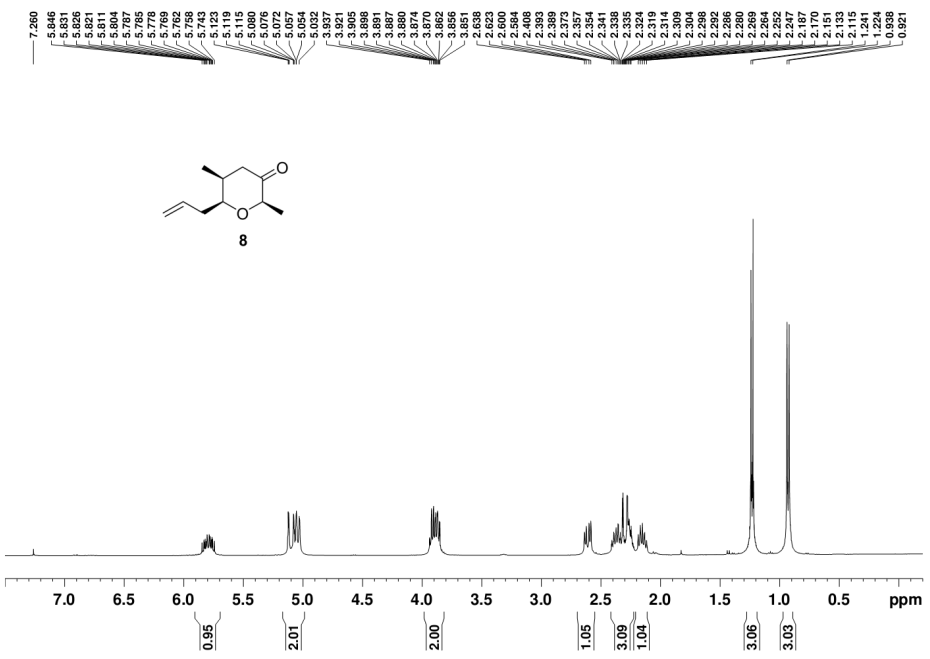
20
ppm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3.905
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3.856
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2.623
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2.298
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5.0
4.5
4.0
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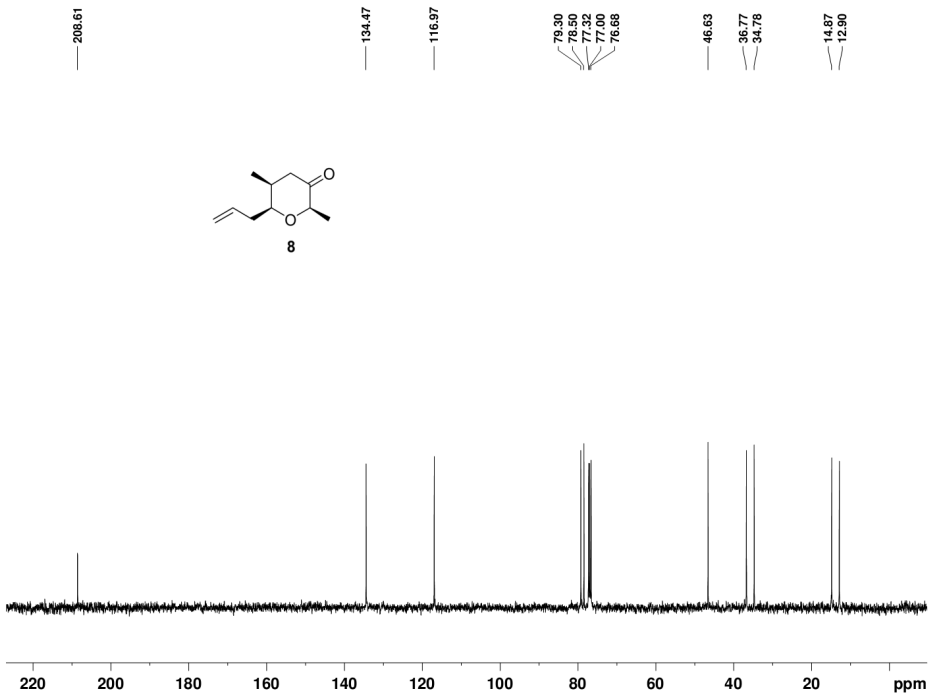
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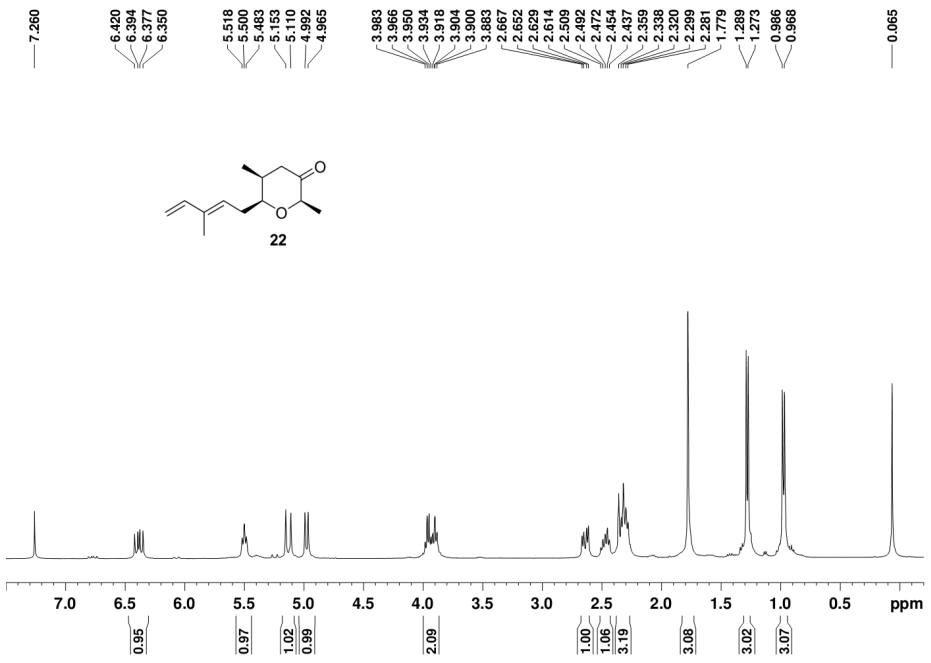
20
ppm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3.966
3.950
3.934
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3.904
3.900
3.883
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2.492
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2.338
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1.289
1.273
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O
O
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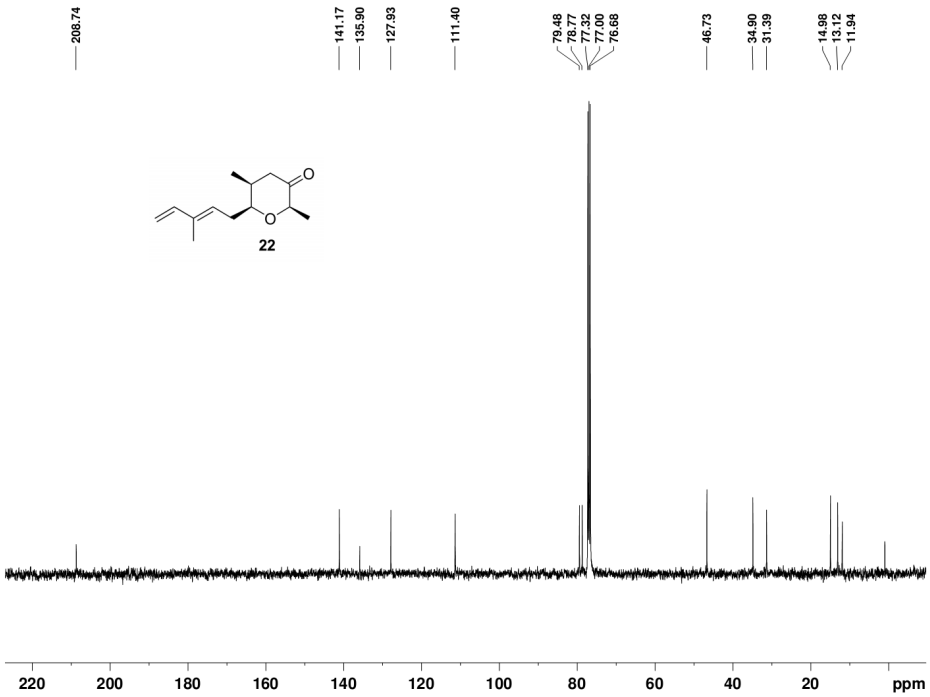
3.07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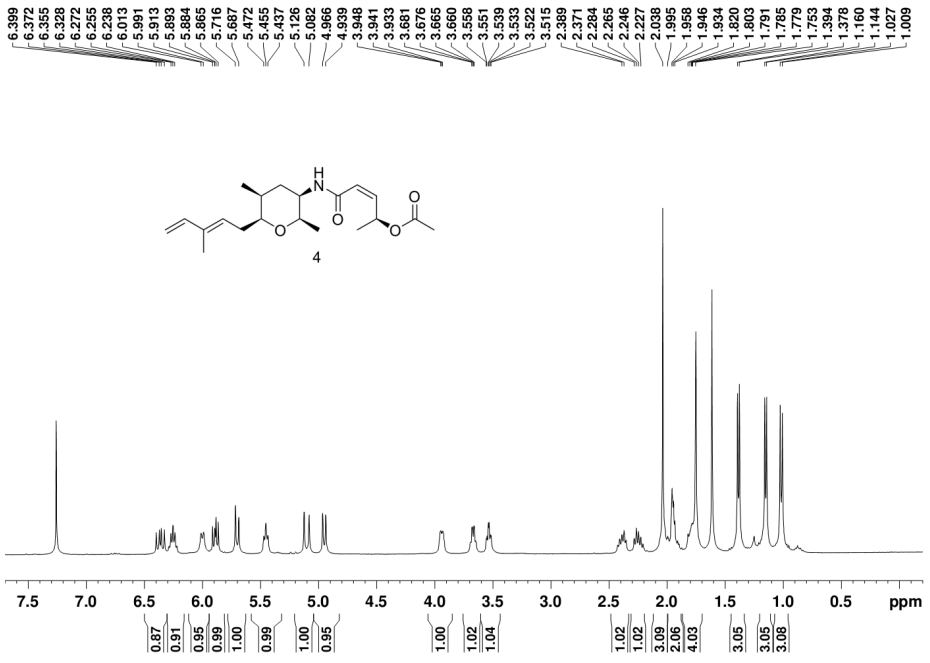
ppm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N
O
O
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3.0
2.5
2.0
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1.0
0.5
ppm
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0.95
0.99
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0.99
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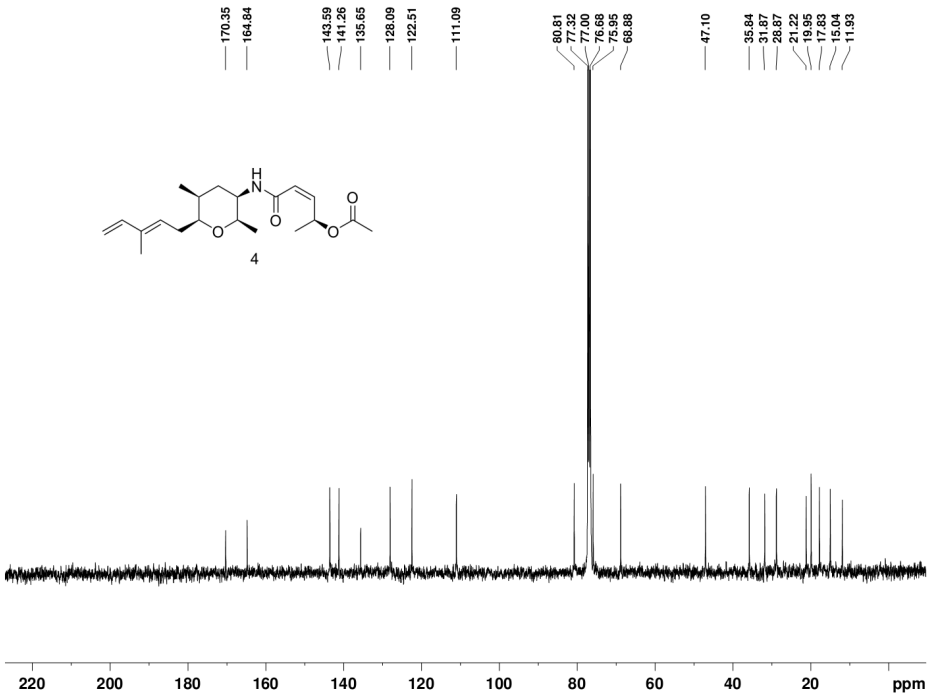
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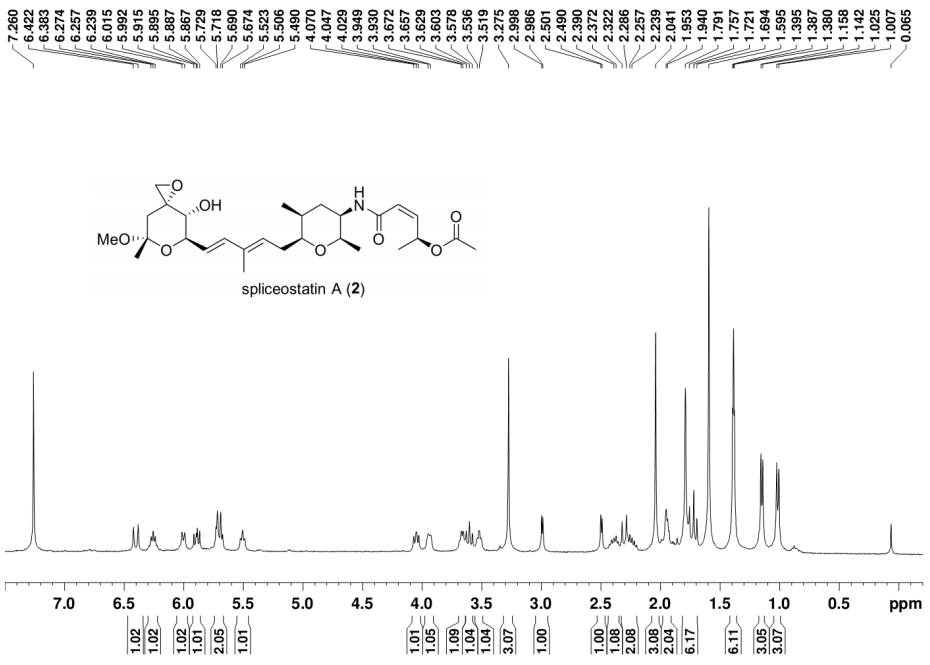
20
ppm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spliceostatin A (2)
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6.0
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3.0
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2.0
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1.0
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1.02
1.02
1.01
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1.01
1.01
1.05
1.09
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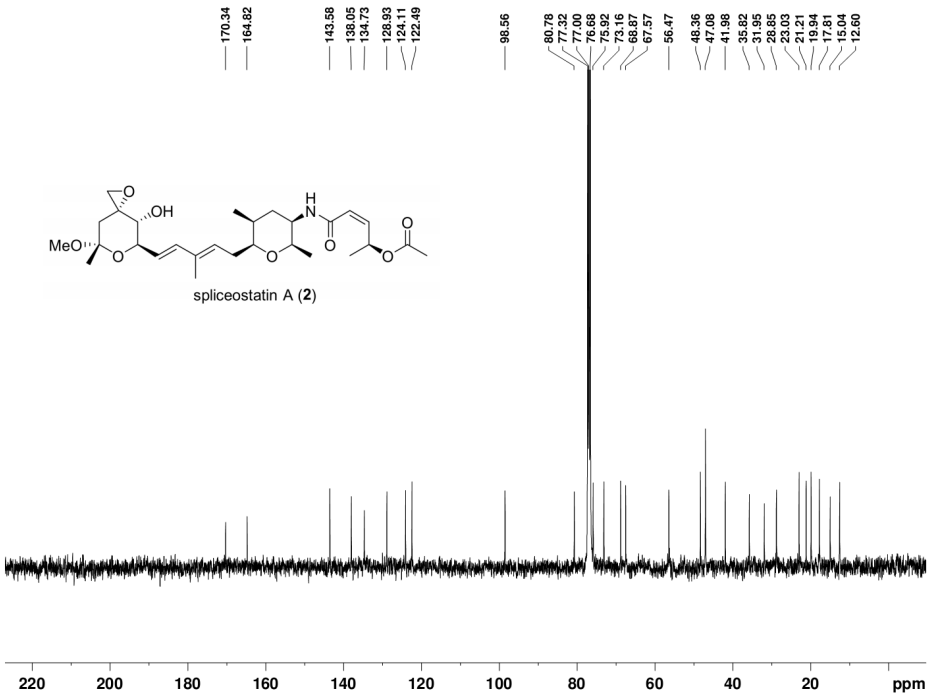
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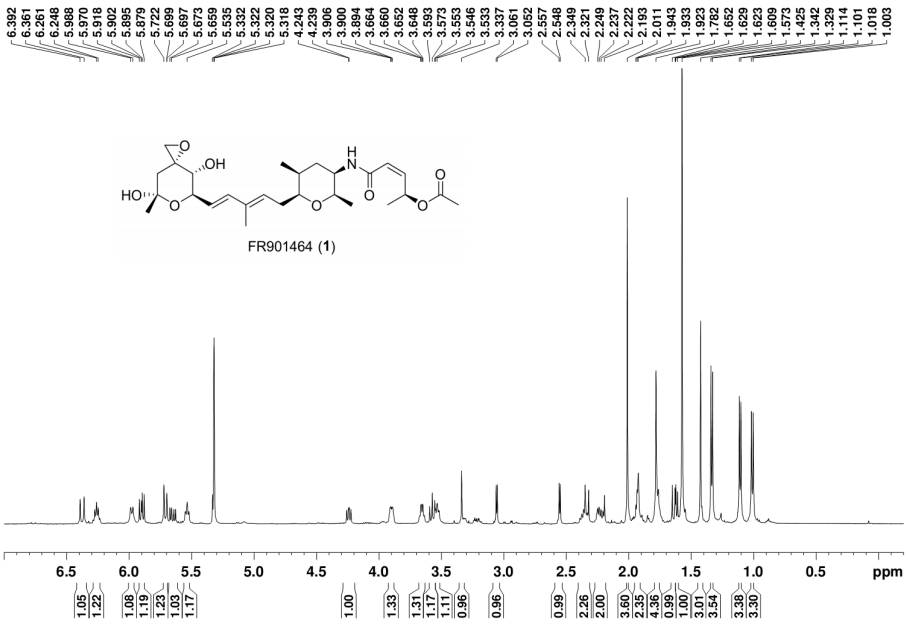
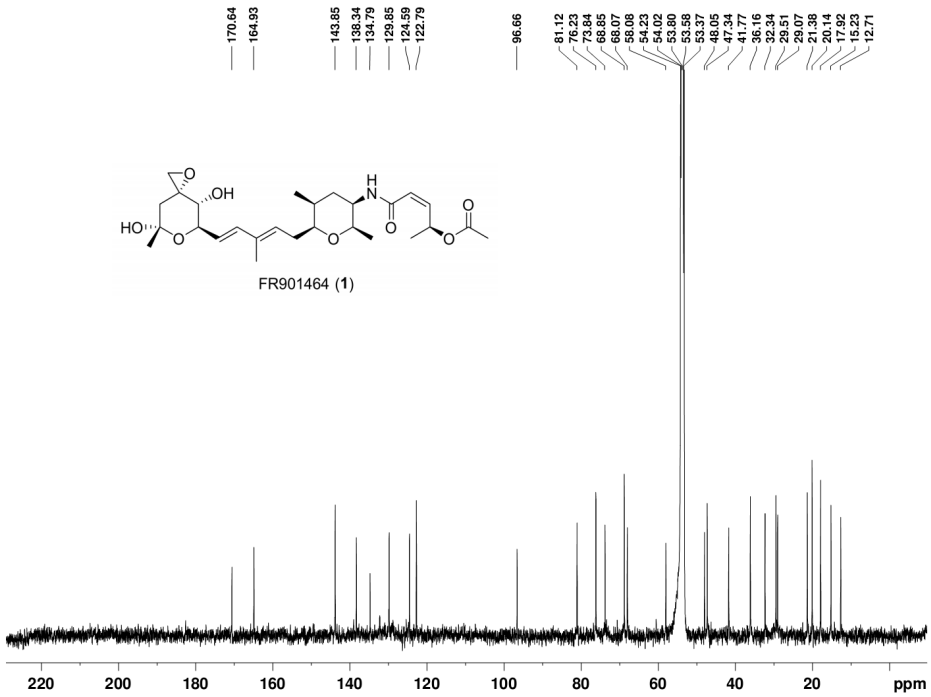
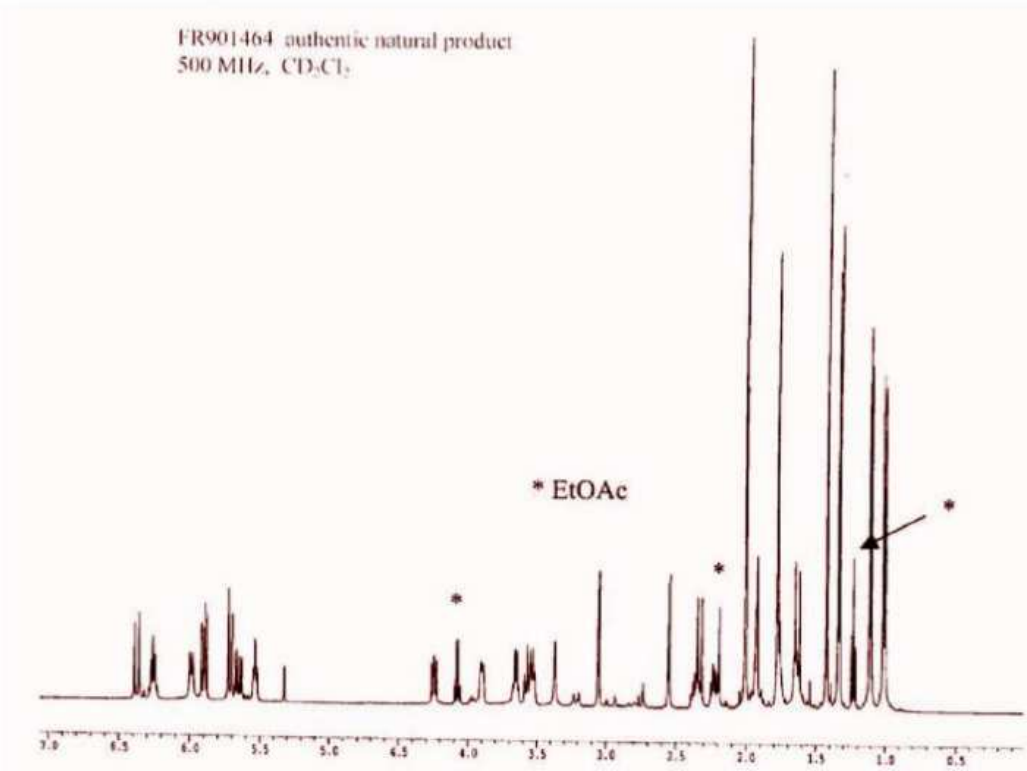
68.87
67.57
56.47
48.36
47.08
41.98
35.82
31.95
28.85
23.03
21.21
19.94
17.81
15.04
12.60
MeO
OH
spliceostatin A (2)
220
200
180
160
140
120
100
80
60
40
20
ppm


6.392
6.361
6.261
6.248
5.988
5.970
5.918
5.902
5.895
5.879
5.722
5.699
5.697
5.673
5.659
5.535
5.332
5.322
5.320
5.318
4.243
4.239
3.906
3.900
3.894
3.664
3.660
3.652
3.648
3.593
3.573
3.553
3.546
3.533
3.337
3.061
3.052
2.557
2.548
2.349
2.321
2.249
2.237
2.222
2.193
2.011
1.943
1.933
1.923
1.782
1.652
1.629
1.623
1.609
1.573
1.425
1.342
1.329
1.114
1.101
1.018
1.003
HO
OH
FR901464 (1)
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
1.05
1.22
1.08
1.19
1.23
1.03
1.17
1.00
1.33
1.31
1.17
1.11
0.96
0.96
0.99
2.26
2.00
3.60
2.35
4.36
0.99
1.00
3.01
3.54
3.38
3.30

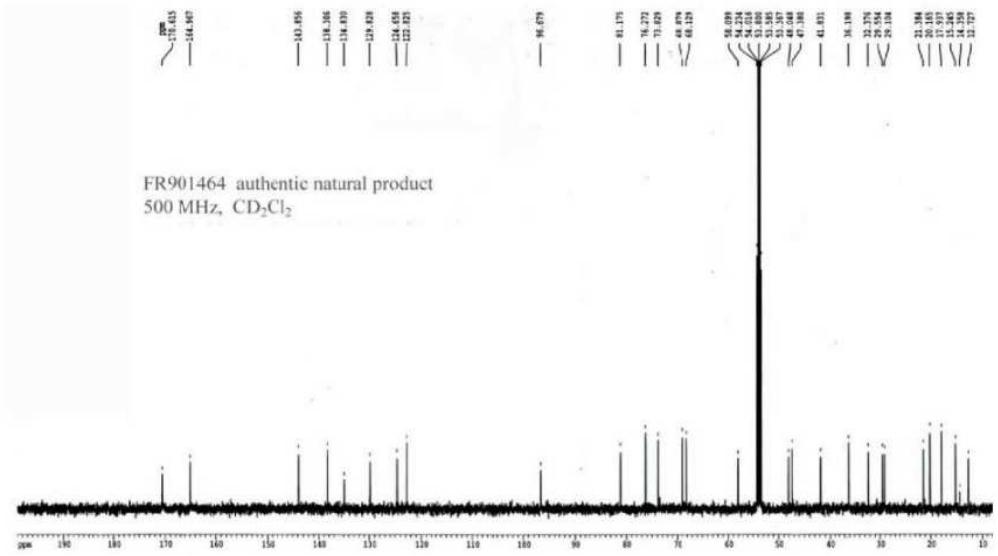


FR901464 (**1**)

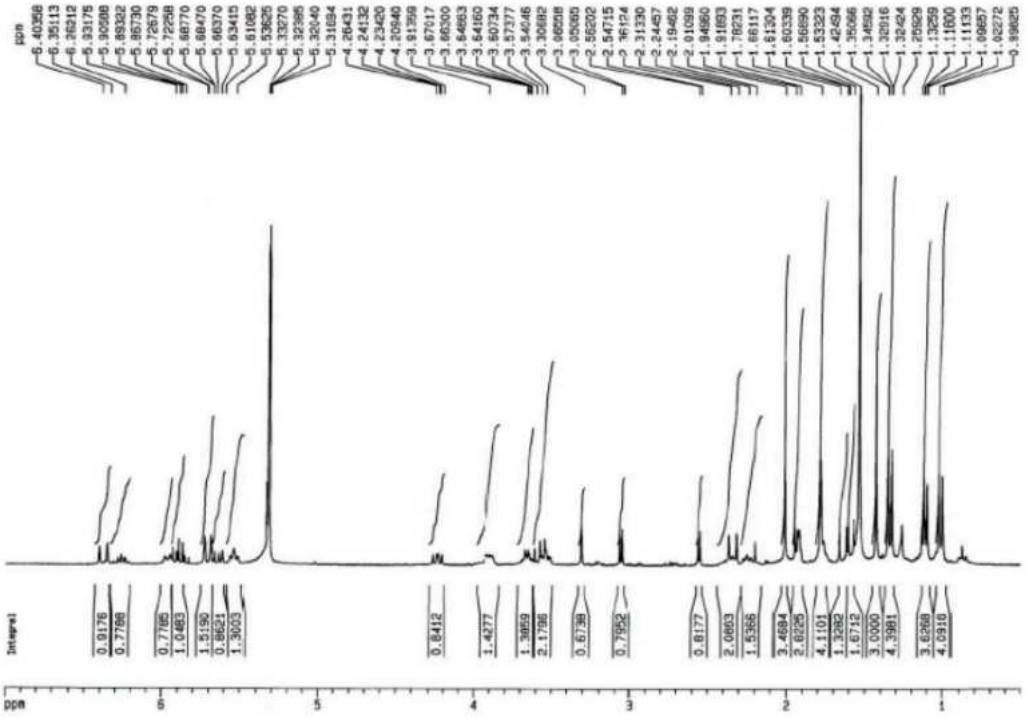
^{1}H NMR of Fujisawa's FR901464 (*J. Antibiot.* **1997**, *50*, 96)



^{13}C NMR



^{1}H NMR of Koide's synthetic FR901464 (*J. Am. Chem. Soc.* **2006**, *128*, 2792-2793.)



^{13}C NMR of Koide's synthetic FR901464 (*J. Am. Chem. Soc.* **2006**, *128*, 2792-2793.)