Exploiting Pseudo C2-Symmetry for an Efficient Synthesis of the F-Ring of the Spongistatins

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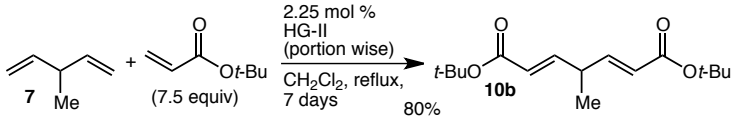
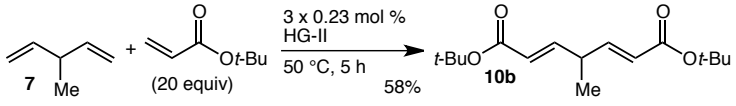
Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring unless otherwise indicated. Degassed solvents were purified by passage through an activated alumina column. Buffered silica gel (pH 7) was prepared by adding 10% (by weight) pH 7 aqueous phosphate buffer solution to silica gel and mixing until homogeneous. ^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 MHz), Bruker DPX-400 (400 MHz), or Bruker Avance III 500 (500 MHz) spectrometer and are reported relative to protiated solvent signals ($CDCl_3$ = 7.27 ppm; C_6D_6 = 7.16 ppm; DMSO-d_6 = 2.50). Data are based on apparent multiplicities and are reported as follows: (bs= broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets; coupling constant(s) in Hz). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz), Bruker DPX-400 (100 MHz), or Bruker Avance III 500 (126 MHz) spectrometer and are reported in ppm from $CDCl_3$ internal standard (77.23 ppm), C_6D_6 (128.39 ppm) or DMSO-d_6 (39.52 ppm). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. Melting points were recorded on a SRS DigiMelt MPA160 melting point apparatus and are uncorrected.

Procedure 1:



Procedure 2:

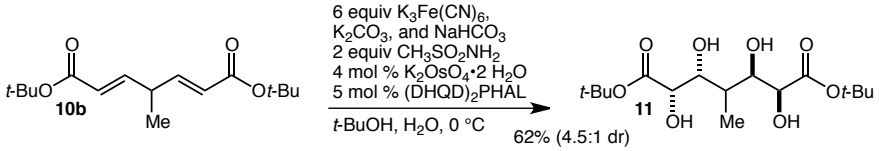


Procedure 1: To a solution of 3-methyl-1,4-pentadiene **7** (12 mL, 98 mmol) and *tert*-butyl acrylate (36 mL, 246 mmol, 2.5 equiv) in CH_2Cl_2 (480 mL) was added Hoveyda-Grubbs 2nd

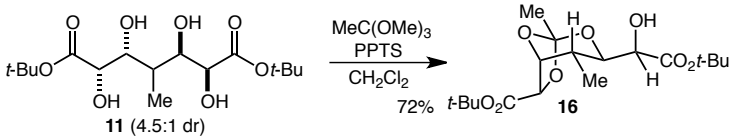
Generation catalyst (308 mg, 0.492 mmol, 0.5 mol %). After 16h, an additional portion of *tert*-butyl acrylate (18 mL, 123 mmol, 1.25 equiv) was added followed by an additional portion of the HG-II catalyst (154 mg, 0.25 mmol, 0.25 mol %), and the reaction mixture was heated to 30 °C. After 30h, an additional portion of *tert*-butyl acrylate (18 mL, 123 mmol, 1.25 equiv) was added followed by an additional portion of the HG-II catalyst (154 mg, 0.25 mmol, 0.25 mol %), and the temperature was raised to 45 °C. Each day for the next two days, an additional portion of *tert*-butyl acrylate (18 mL, 123 mmol, 1.25 equiv) was added followed by an additional portion of the HG-II catalyst (154 mg, 0.25 mmol, 0.25 mol %). Each day for the following three days, an additional portion of the HG-II catalyst (154 mg, 0.25 mmol, 0.25 mol %) was added. The reaction mixture was cooled to ambient temperature and concentrated. The residue was treated with hexanes and the mixture was concentrated. The residue was purified by silica gel flash column chromatography (5% EtOAc/Hex) to yield diene **10b** (22 g, 78 mmol, 80%) as a pale yellow oil.

Procedure 2: To a solution of 3-methyl-1,4-pentadiene **7** (5.62 mL, 45 mmol, 1 equiv) and 4-methoxyphenol (25 mg, 0.199 mmol, 0.47 mol %) (**Note**: 4-methoxyphenol is a stabilizer for the *t*-butyl acrylate, and we have found that we get slightly better results by adding additional stabilizer in this fashion) in *t*-butyl acrylate (135 ml, 0.9 mol, 20 equiv) was added Hoveyda-Grubbs 2nd Generation catalyst (65.6 mg, 0.105 mmol, 0.23 mol %). The flask was fitted with a reflux condenser and the reaction mixture was heated to 50 °C (oil bath, external temperature). After 1.5 h, an additional portion of the HG-II catalyst (65.6 mg, 0.105 mmol, 0.23 mol %) was added. After 1.5 h, an additional portion of the HG-II catalyst (65.6 mg, 0.105 mmol, 0.23 mol %) was added. After 2 h, the reaction mixture was cooled to ambient temperature and concentrated. The residue was treated with toluene and the mixture was concentrated. The residue was purified by silica gel flash column chromatography (4% EtOAc/Hex) to yield diene **10b** (7.55 g, 26.7 mmol, 58%) as a pale yellow oil.

Data for **10b**: TLC R_f = 0.45 (10% EtOAc/Hex); IR (thin film) 2977, 2933, 1713, 1614, 1392, 1318, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 15.7, 7.0 Hz, 2H), 5.73 (dd, *J* = 15.7, 1.3 Hz, 2H), 3.17-3.08 (m, 1H), 1.47 (s, 18H), 1.20 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 148.4, 123.2, 80.6, 38.5, 28.3, 18.6; HRMS for $C_{16}H_{27}O_4$ (FAB+): calcd 283.1904 ($[M+H]^+$), found 283.1910 ($[M+H]^+$).

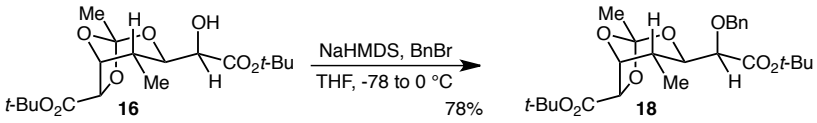


To a mechanically-stirred solution of $K_3Fe(CN)_6$ (148 g, 450 mmol, 6 equiv), K_2CO_3 (62.1 g, 450 mmol, 6 equiv), $NaHCO_3$ (37.8 g, 450 mmol, 6 equiv) and $CH_3SO_2NH_2$ (14.3 g, 150 mmol, 2 equiv) in H_2O (750 mL) was added a solution of $(DHQD)_2PHAL$ (3.00 g, 3.85 mmol, 0.05 equiv) in *t*-BuOH (500 mL). The mixture was cooled to 0 °C and $K_2OsO_4 \bullet 2H_2O$ (1.10 g, 3.00 mmol, 0.04 equiv) was added, followed 10 minutes later by a solution of diene **10b** (21.2 g, 74.9 mmol) in *t*-BuOH (250 mL). The bright orange suspension was stirred vigorously at 0 °C for 18 h. Solid Na_2SO_3 (94 g, 749 mmol, 10 equiv) was added and the reaction mixture was stirred for a further 45 min. The layers of the cold reaction mixture were separated, and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic layers were stirred with solid NaCl, the resulting brine layer was removed. The organic phase was washed with additional brine (350 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (50% EtOAc/Hex) to yield tetraol **11** (16.4 g, 46.7 mmol, 62%) as the major product of a 4.5:1 mixture of diastereomers (as judged by ^1H NMR spectroscopy – see below) as a colorless gum that solidified to a colorless solid on standing. This mixture was used as is in the next step, but for the purposes of characterization, an analytically pure sample was obtained by careful flash chromatography: TLC R_f = 0.3 (60% EtOAc/Hex); mp 87-89 °C; $[\alpha]^{21}_D$ = -12.7° (*c* = 0.56, $CHCl_3$); IR (thin film) 3473, 2978, 2934, 1716, 1394, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (dd, *J* = 5.7, 3.0 Hz, 1H), 4.12 (dd, *J* = 5.7, 1.6 Hz, 1H), 4.06 (dt, *J* = 8.4, 3.3 Hz, 1H), 3.99 (td, *J* = 8.9, 1.3 Hz, 1H), 3.55 (d, *J* = 8.5 Hz, 1H), 3.52 (d, *J* = 5.7 Hz, 1H), 3.34 (d, *J* = 5.7 Hz, 1H), 3.22 (d, *J* = 9.1 Hz, 1H), 2.26-2.14 (m, 1H), 1.50 (s, 18H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 83.5, 83.3, 75.0, 74.2, 72.2, 71.9, 40.0, 28.2, 13.1; HRMS for $C_{16}H_{31}O_8$ (FAB+): calcd 351.2013 ($[M+H]^+$), found 351.2018 ($[M+H]^+$).

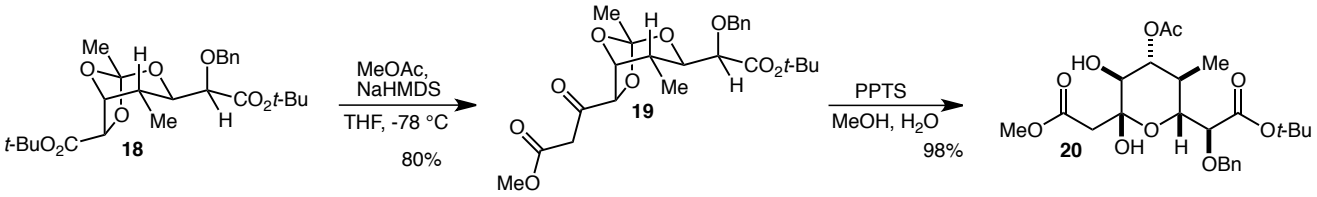


To a solution of tetraol **11** (12.7 g, 36.2 mmol) and trimethyl orthoacetate (8.90 mL, 54.3 mmol, 1.5 equiv) in CH_2Cl_2 (630 mL) was added pyridinium *p*-toluenesulfonate (PPTS) (9.10 g, 36.2 mmol, 1 equiv). After 16 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (400 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (20% EtOAc/Hex) to yield orthoacetate **16** as a pale yellow gum (9.77 g, 26.1 mmol, 72%). TLC R_f = 0.65 (50% EtOAc/hex); $[\alpha]^{22}_D$ = +18.0° (*c* = 1.53, $CHCl_3$);

IR (thin film) 3512, 3004, 1752, 1728, 1403, 1293, 1131 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49 (s, 1H), 4.47 (d, *J* = 3.5 Hz, 1H), 4.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.86 (dd, *J* = 10.4, 1.7 Hz, 1H), 2.92 (d, *J* = 8.3 Hz, 1H), 2.51 (dqd, *J* = 10.4, 6.9, 3.5 Hz, 1H), 1.64 (s, 3H), 1.48 (s, 9H), 1.48 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 169.7, 120.7, 83.1, 82.5, 81.7, 76.7, 74.1, 69.6, 30.7, 28.18, 28.15, 21.6, 12.1; HRMS for $C_{18}H_{31}O_8$ (FAB+): calcd 375.2013 ($[M+H]^+$), found 375.2014 ($[M+H]^+$).



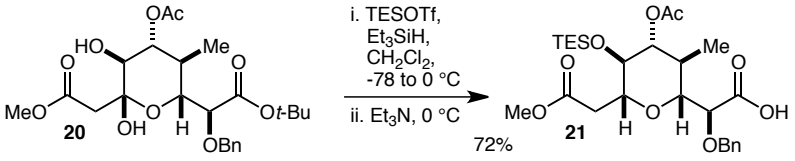
To a cooled (-78 °C) solution of alcohol **16** (5.54 g, 14.8 mmol) in THF (150 mL) was added a solution of NaHMDS (2.66 g, 14.5 mmol, 0.98 equiv) in THF (15 mL) by syringe pump over 30 min. Five minutes following complete addition, benzyl bromide (3.52 mL, 29.6 mmol, 2 equiv) was added in one portion and the reaction mixture was warmed to 0 °C. After 3.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (10% EtOAc/Hex) to yield orthoacetate **18** (5.40 g, 11.6 mmol, 78%) as a colorless gum. TLC R_f = 0.35 (20% EtOAc/hex); $[\alpha]^{20}_D$ = -42.3° (*c* = 0.64, $CHCl_3$); IR (thin film) 2976, 1751, 1723, 1403, 1368, 1151, 1135 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.96 (d, *J* = 12.3 Hz, 1H), 4.40 (s, 2H), 4.39 (d, *J* = 15.0 Hz, 1H), 3.91 (dd, *J* = 10.5, 2.6 Hz, 1H), 3.83 (d, *J* = 2.7 Hz, 1H), 2.44 (dqd, *J* = 10.3, 6.9, 3.5 Hz, 1H), 1.68 (s, 3H), 1.50 (s, 9H), 1.46 (s, 9H), 0.57 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 169.3, 137.4, 128.9, 128.6, 128.3, 120.9, 82.4, 82.2, 81.8, 76.4, 75.2, 74.1, 72.7, 30.8, 28.3, 28.2, 21.7, 11.7; HRMS for $C_{25}H_{37}O_8$ (FAB+): calcd 465.2483 ($[M+H]^+$), found 465.2501 ($[M+H]^+$).



To a cooled (-78 °C) solution of NaHMDS (7.78 g, 42.4 mmol, 4.5 equiv) in THF (200 mL) was added a solution of MeOAc (3.75 mL, 47.1 mmol, 5 equiv) in THF (16.5 mL) by syringe pump over 40 min. Upon complete addition, the reaction mixture was stirred for a further 2 h, and then a

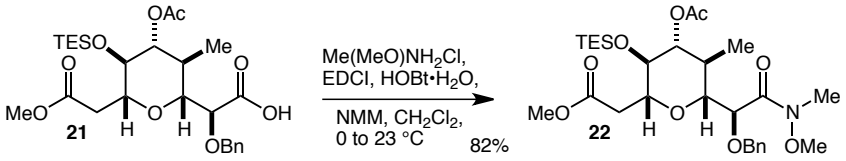
solution of orthoacetate **18** (4.38 g, 9.43 mmol) in THF (25 mL) was added by syringe pump over 15 min. After 5 h, the still cold reaction mixture was poured into saturated aqueous NH_4Cl (400 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine (300 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (20% EtOAc/Hex) to yield β-ketoester **19** (3.50 g, 7.53 mmol, 80%) as a pale yellow oil. Analysis by ^{1}H NMR spectroscopy revealed a complex mixture of tautomers, and the material was taken into the next step without further characterization.

To a solution of β-ketoester **19** (5.20 g, 11.2 mmol) in MeOH (85 mL) was added H_2O (30 mL) and pyridinium *p*-toluenesulfonate (2.81 g, 11.2 mmol, 1 equiv). After 39 h, solid $NaHCO_3$ (excess) was added and the reaction mixture was stirred until bubbling ceased. The reaction mixture was diluted with brine (300 mL) and extracted with EtOAc (4 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel flash column chromatography (40% EtOAc/Hex) to yield hemiketal **20** (5.32 g, 11.0 mmol, 98%) as a pale yellow oil that solidified to a colorless solid on standing. TLC R_f = 0.25 (50% EtOAc/Hex); mp 144-146 °C; $[\alpha]^{22}_D$ = -48.5° (*c* = 0.45, $CHCl_3$); IR (thin film) 3435, 2977, 2934, 1743, 1497, 1369, 1236, 1158, 1053 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.99 (s, 1H), 4.96 (t, *J* = 10.3 Hz, 1H), 4.95 (d, *J* = 12.9 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.08 (d, *J* = 10.2 Hz, 1H), 3.89 (s, 1H), 3.68 (s, 3H), 3.21 (t, *J* = 10.4 Hz, 1H), 3.01 (d, *J* = 16.4 Hz, 1H), 2.68 (d, *J* = 16.4 Hz, 1H), 2.13 (s, 3H), 2.17-2.07 (m, 1H), 2.04 (d, *J* = 12.0 Hz, 1H), 1.50 (s, 9H), 0.54 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 172.0, 169.0, 137.2, 129.1, 128.7, 128.4, 98.1, 82.1, 75.9, 75.9, 75.2, 74.4, 73.1, 52.2, 39.0, 36.1, 28.3, 21.3, 12.1; HRMS for $C_{24}H_{35}O_{10}$ (FAB+): calcd 483.2225 ([M+H]$^+$), found 483.2238 ([M+H]$^+$).



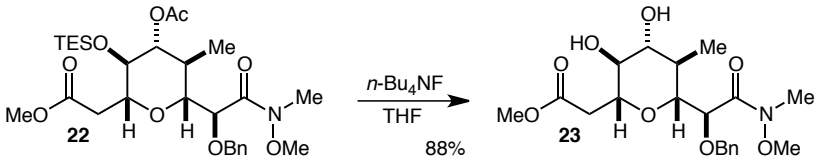
To a cooled (-78 °C) solution of hemiketal **20** (0.90 g, 1.9 mmol) and triethylsilane (3.0 mL, 19 mmol, 10 equiv) in CH_2Cl_2 (27 mL) was added triethylsilyl trifluoromethanesulfonate (1.7 mL, 7.5 mmol, 4 equiv) slowly down the side of the flask. After 10 min, the reaction mixture was warmed to 0 °C. After 1.3 h, triethylamine (2.6 mL, 19 mmol, 10 equiv) was added slowly down the side of the

flask. After 1 h, saturated aqueous $NaHCO_3$ (30 mL) was added and the resulting mixture was vigorously stirred. The layers were separated, and the aqueous layer was acidified with AcOH before being extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Excess AcOH was removed by azeotroping with hexanes, and the remaining volatiles were removed *in vacuo* overnight. The residue was purified by silica gel flash column chromatography (gradient 20 to 40 to 100% EtOAc/Hex) to yield carboxylic acid **21** (0.71 g, 1.4 mmol, 72%) as a colorless solid. TLC R_f = 0.07 (EtOAc); mp 104-110 °C; $[\alpha]^{20}_D$ = -13.3° (*c* = 0.51, $CHCl_3$); IR (thin film) 3378, 2954, 2878, 1740, 1615, 1497, 1231, 1131, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (m, 5H), 4.99 (d, *J* = 12.2 Hz, 1H), 4.74 (dd, *J* = 9.8, 8.9 Hz, 1H), 4.32 (d, *J* = 12.3 Hz, 1H), 3.86 (s, 1H), 3.73 (s, 3H), 3.62 (d, *J* = 10.2 Hz, 1H), 3.56-3.44 (m, 2H), 2.84 (d, *J* = 14.1 Hz, 1H), 2.64 (dd, *J* = 14.3, 6.5 Hz, 1H), 2.14 (s, 3H), 2.04-1.97 (m, 1H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.44 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 173.5, 170.6, 137.6, 129.1, 128.6, 128.2, 82.4, 79.4, 77.6, 77.4, 73.2, 72.2, 52.6, 37.2, 36.8, 21.6, 12.2, 7.0, 5.4; HRMS for $C_{26}H_{40}NaO_9Si$ (FAB+): calcd 547.2334 ($[M+Na]^+$), found 547.2354 ($[M+Na]^+$).

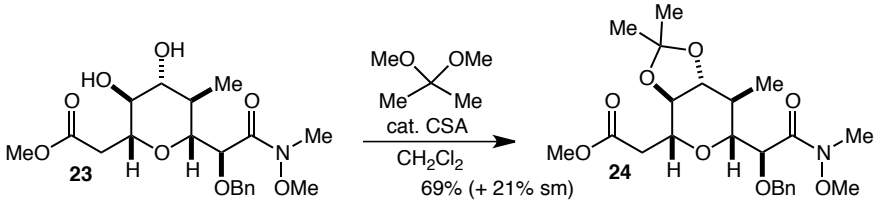


To a cooled (0 °C) solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (543 mg, 2.83 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL) was added HOBt•H_2O (394 mg, 2.57 mmol, 1 equiv) and *N*-methylmorpholine (0.62 mL, 5.66 mmol, 2.2 equiv), followed by a solution of carboxylic acid **21** (1.35 g, 2.57 mmol) in CH_2Cl_2 (15 mL) slowly. After 30 min, the reaction mixture was cooled to 0 °C and Me(OMe)NH•HCl (276 mg, 2.83 mmol, 1.1 equiv) was added. After 5 min, the cooling bath was removed and the reaction mixture was allowed to warm to ambient termperature. After 16 h, 40 h, and 48 h, additional portions of *N*-methylmorpholine (62 μL, 0.22 equiv) and Me(OMe)NH•HCl (50 mg, 0.2 equiv) were added. After 64 h total, the reaction mixture was poured into H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (30 mL), and the aqueous layer was back-extracted with EtOAc (20 mL). The combined organic layers were washed with brine (80 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (50% EtOAc/Hex) to yield Weinreb amide **22** (1.20 g, 2.11 mmol, 82%)

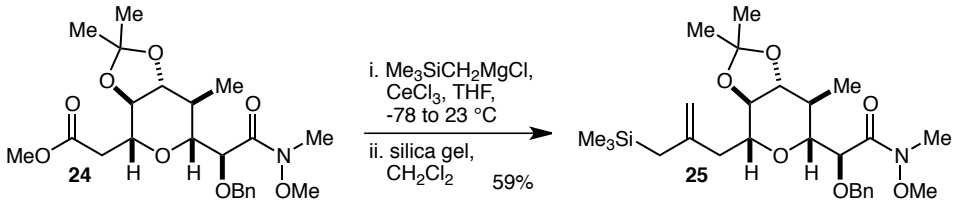
as a colorless gum that slowly crystallized to colorless crystals. TLC R_f = 0.6 (EtOAc); mp 108-110 °C; $[\alpha]^{20}_D$ = -18.4° (*c* = 0.52, $CHCl_3$); IR (thin film) 2954, 2878, 1741, 1686, 1619, 1232, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.87 (d, *J* = 11.9 Hz, 1H), 4.77 (dd, *J* = 10.1, 9.3 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.24 (s, 1H), 3.65 (s, 3H), 3.65-3.60 (m, 2H), 3.59 (s, 3H), 3.47 (t, *J* = 9.0 Hz, 1H), 3.24 (s, 3H), 2.69 (d, *J* = 15.1 Hz, 1H), 2.49 (dd, *J* = 15.0, 10.9 Hz, 1H), 2.19-2.10 (m, 1H), 2.13 (s, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.60-0.52 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.8, 169.5, 137.1, 129.1, 128.5, 128.3, 79.9, 79.6, 78.0, 75.0, 73.4, 72.4, 61.3, 51.7, 37.2, 37.1, 32.9, 21.6, 12.3, 7.0, 5.4; HRMS for $C_{28}H_{46}NO_9Si$ (FAB+): calcd 568.2936 ($[M+H]^+$), found 568.2936 ($[M+H]^+$).



To a solution of Weinreb amide **22** (1.20 g, 2.11 mmol) in THF (10.6 mL) was added tetrabutylammonium fluoride (10.6 mL of a 1M solution in THF, 10.6 mmol, 5 equiv). After 16 h, the reaction mixture was poured into saturated aqueous NH_4Cl (40 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc) to yield diol **23** (0.760 g, 1.86 mmol, 88%) as a colorless gum. TLC R_f = 0.1 (EtOAc); $[\alpha]^{20}_D$ = -35.5° (*c* = 0.50, $CHCl_3$); IR (thin film) 3444, 2936, 2876, 1736, 1660, 1438, 1164, 1066 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.33-7.27 (m, 2H), 7.15-7.03 (m, 3H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 2.9 Hz, 1H), 4.21 (d, *J* = 11.6 Hz, 1H), 3.90-3.76 (m, 2H), 3.68 (dd, *J* = 10.2, 2.9 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 1H), 3.34 (td, *J* = 8.9, 3.9 Hz, 1H), 3.24 (s, 3H), 3.29-3.15 (m, 1H), 3.11 (s, 3H), 3.02 (dd, *J* = 15.6, 2.6 Hz, 1H), 2.64 (dd, *J* = 15.6, 9.8 Hz, 1H), 2.36-2.17 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 172.8, 170.5, 138.1, 129.5, 129.0, 128.7, 81.3, 79.2, 78.0, 77.3, 75.6, 72.9, 61.2, 51.7, 38.6, 38.3, 33.8, 13.1; HRMS for $C_{20}H_{30}NO_8$ (FAB+): calcd 412.1966 ($[M+H]^+$), found 412.1978 ($[M+H]^+$).

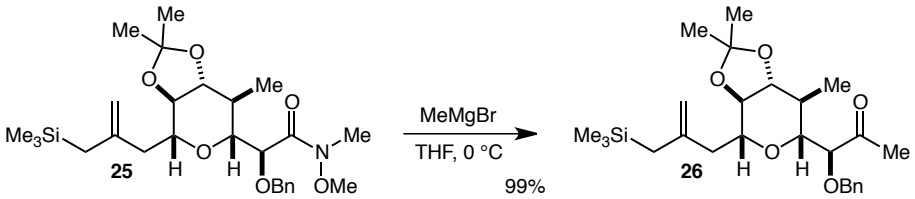


To a solution of diol **23** (0.67 g, 1.6 mmol) and 2,2-dimethoxypropane (8 mL) in CH_2Cl_2 (8 mL) was added (±)-camphorsulfonic acid (16 mg, 0.065 mmol, 4 mol %). After 3 d, saturated aqueous $NaHCO_3$ (10 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (4 x 4 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel flash column chromatography (gradient 50 to 100% EtOAc/Hex) to yield acetonide **24** (0.51 g, 1.13 mmol, 69%) as a colorless oil, along with recovered diol **23** (0.14 g, 0.34 mmol, 21%). TLC R_f = 0.4 (EtOAc); $[\alpha]^{20}_D$ = -32.6° (*c* = 0.61, $CHCl_3$); IR (thin film) 2983, 2936, 1739, 1678, 1371, 1171, 1087, 1065, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.84 (d, *J* = 11.9 Hz, 1H), 4.29 (d, *J* = 12.1 Hz, 1H), 4.24 (s, 1H), 3.90-3.81 (m, 1H), 3.62 (s, 3H), 3.57 (s, 3H), 3.52 (d, *J* = 9.4 Hz, 1H), 3.22 (s, 3H), 3.20-3.13 (m, 2H), 2.63 (d, *J* = 15.1 Hz, 1H), 2.57 (dd, *J* = 15.3, 10.1 Hz, 1H), 2.35-2.22 (m, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 0.74 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 169.6, 137.1, 128.9, 128.5, 128.3, 110.6, 83.9, 81.2, 78.3, 76.0, 74.8, 72.4, 61.1, 51.7, 37.6, 36.6, 33.3, 27.0, 26.7, 12.7; HRMS for $C_{23}H_{34}NO_8$ (FAB+): calcd 452.2279 ($[M+H]^+$), found 452.2294 ($[M+H]^+$).



To a cooled (0 °C) flask containing dry $CeCl_3$ (0.87 g, 3.5 mmol, 8 equiv) was added THF (4.5 mL) slowly with vigorous stirring, and the resulting suspension was sonicated for 15 min. The ice water bath was removed and the resulting suspension was stirred overnight. The mixture was sonicated again for 20 min and then cooled to -78 °C. $TMSCH_2MgCl$ (1.87 mL, 2.44 mmol, 5.5 equiv) was then added dropwise over 5 min. After 3 h, a solution of acetonide **24** (197 mg, 0.436 mmol) in THF (4 mL) was added dropwise. After 2 h, the mixture was allowed to warm to ambient temperature. After 6 h, saturated aqueous NH_4Cl (15 mL) was added, and the biphasic mixture was poured into H_2O (15 mL) and EtOAc (15 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), silica gel (4 g) was added, and the resulting suspension was stirred for 14 h. The reaction mixture was filtered, and the silica gel was washed with EtOAc. The filtrate was concentrated and the residue was purified by silica gel flash column chromatography (30% EtOAc/Hex) to yield allylsilane **25** (131 mg, 0.259 mmol, 59%) as a

colorless oil. TLC R_f = 0.7 (60% EtOAc/Hex); $[\alpha]^{20}_D$ = -20.6° (*c* = 0.63, $CHCl_3$); IR (thin film) 2983, 2938, 2877, 1741, 1685, 1370, 1231, 1156, 1087, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.67 (br s, 1H), 4.56 (br s, 1H), 4.33 (d, *J* = 12.1 Hz, 1H), 4.26 (s, 1H), 3.59 (s, 3H), 3.51 (d, *J* = 8.8 Hz, 2H), 3.25 (s, 3H), 3.21-3.13 (m, 2H), 2.30 (d, *J* = 14.9 Hz, 2H), 2.21 (dd, *J* = 15.2, 9.4 Hz, 1H), 1.56 (d, *J* = 13.5 Hz, 1H), 1.50 (d, *J* = 13.5 Hz, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 0.77 (d, *J* = 6.2 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.6, 144.1, 137.2, 129.0, 128.6, 128.3, 110.2, 109.1, 84.1, 81.4, 79.2, 79.0, 75.3, 72.5, 61.1, 40.6, 36.8, 33.3, 27.8, 27.1, 26.9, 13.0, -1.1; HRMS for $C_{27}H_{44}NO_6Si$ (FAB+): calcd 506.2932 ($[M+H]^+$), found 506.2929 ($[M+H]^+$).



To a cooled (-78 °C) solution of allylsilane **25** (28 mg, 0.056 mmol) in THF (0.65 mL) was added MeMgBr (79 μL, 0.11 mmol, 2 equiv) slowly down the side of the flask. After 5 min, the reaction mixture was warmed to 0 °C. After 45 min, the reaction mixture was recooled to -78 °C and an additional portion of MeMgBr (79 μL, 0.11 mmol, 2 equiv) was added slowly down the side of the flask. After 5 min, the reaction mixture was warmed to 0 °C. After 15 min, saturated aqueous NH_4Cl (2 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 0.75 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), filtered and concentrated to yield methyl ketone **12** (26 mg, 0.056 mmol, 99%) as a colorless oil. TLC R_f = 0.7 (30% EtOAc/Hex); $[\alpha]^{22}_D$ = -32.6° (*c* = 0.86, $CHCl_3$); IR (thin film) 2954, 2876, 1713, 1635, 1371, 1230, 1087, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 4.82 (d, *J* = 11.9 Hz, 1H), 4.61 (br s, 1H), 4.57 (br s, 1H), 4.32 (d, *J* = 11.9 Hz, 1H), 3.78 (d, *J* = 1.7 Hz, 1H), 3.53 (t, *J* = 8.4 Hz, 1H), 3.27 (dd, *J* = 9.7, 1.6 Hz, 1H), 3.16 (p, *J* = 8.7 Hz, 2H), 2.34 (d, *J* = 15.4 Hz, 1H), 2.26 (s, 3H), 2.25-2.17 (m, 2H), 1.54 (d, *J* = 14.2 Hz, 1H), 1.46 (d, *J* = 13.7 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 0.68 (d, *J* = 6.4 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.8, 143.5, 136.9, 129.0, 128.9, 128.7, 110.4, 109.5, 83.7, 83.7, 82.5, 79.1, 78.4, 73.7, 41.0, 37.0, 28.0, 27.2, 27.1, 26.9, 13.0, -1.1; HRMS for $C_{26}H_{41}O_5Si$ (FAB+): calcd 461.2718 ($[M+H]^+$), found 461.2737 ($[M+H]^+$).

X-ray Structure of 22:

X-ray quality crystals of **22** were obtained as described above, and its structure was solved by Dr. Aaron Sattler (Parkin Group). This structure confirms the stereostructure of **22** is as shown (Fig. S1).

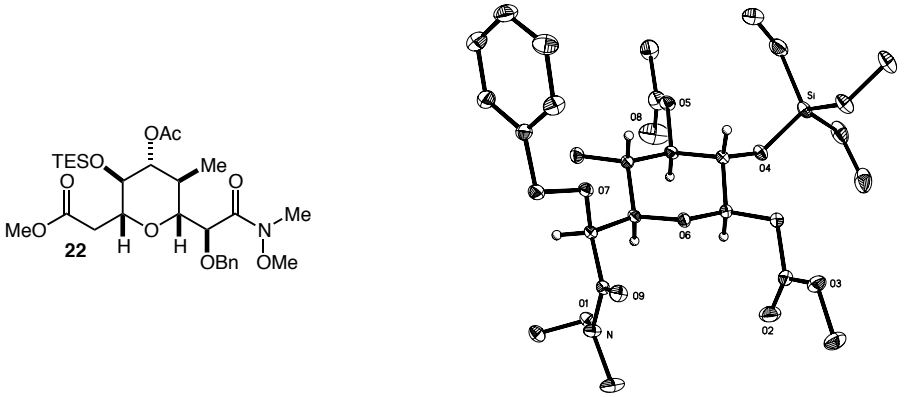


Figure S1. X-ray structure of **22**.

NMR Structure of 15:

The structure of compound **15** was assigned from a series of NMR experiments, including ^{1}H and ^{13}C spectra, as well as COSY, HSQC, and NOESY spectra. The key nOe interactions are shown in Fig. S2, and the spectra are reproduced below.

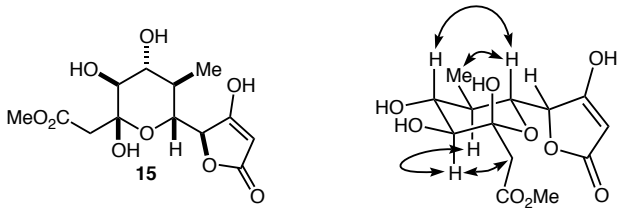
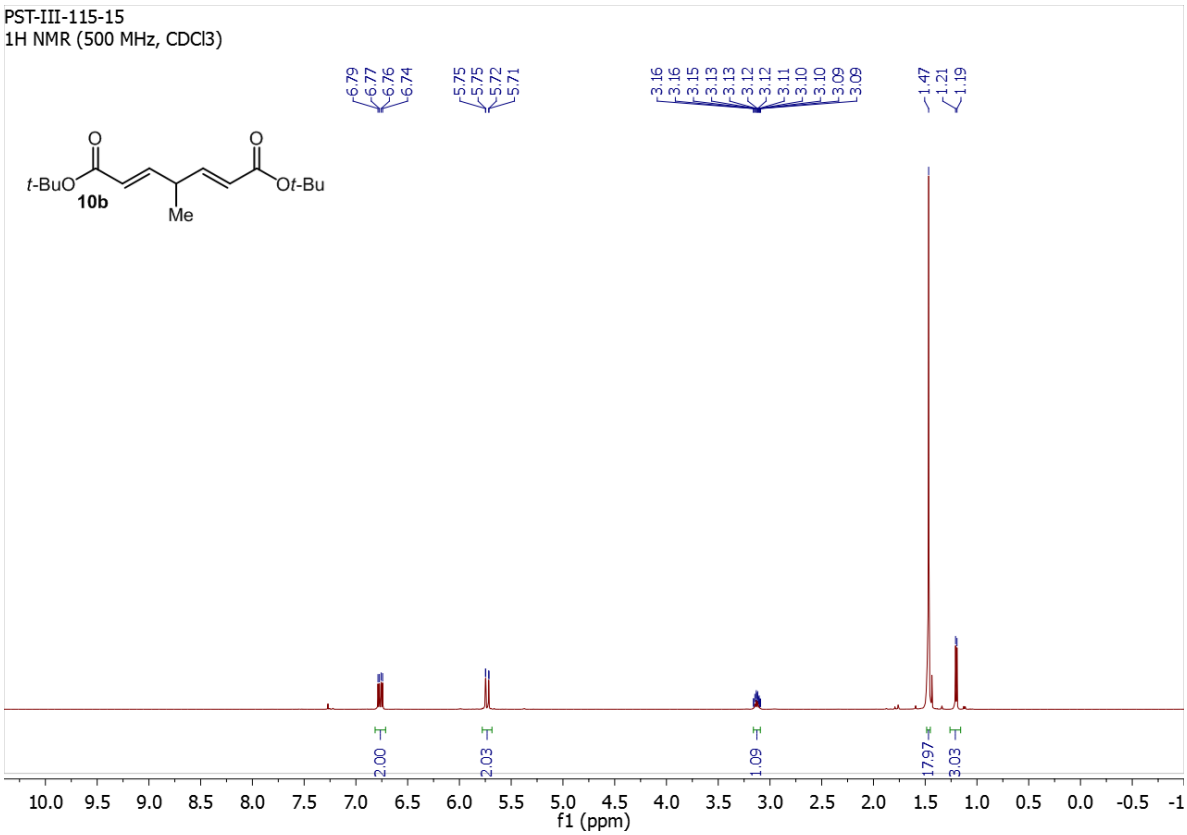
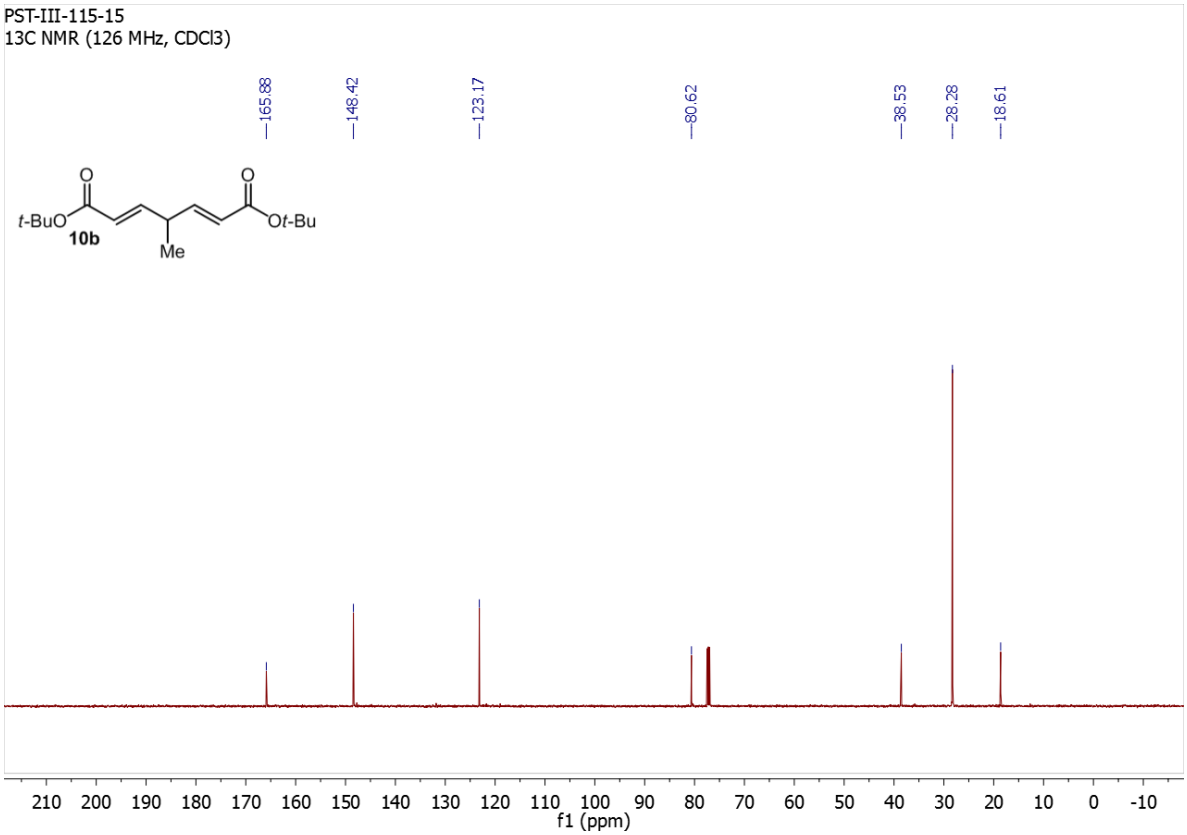
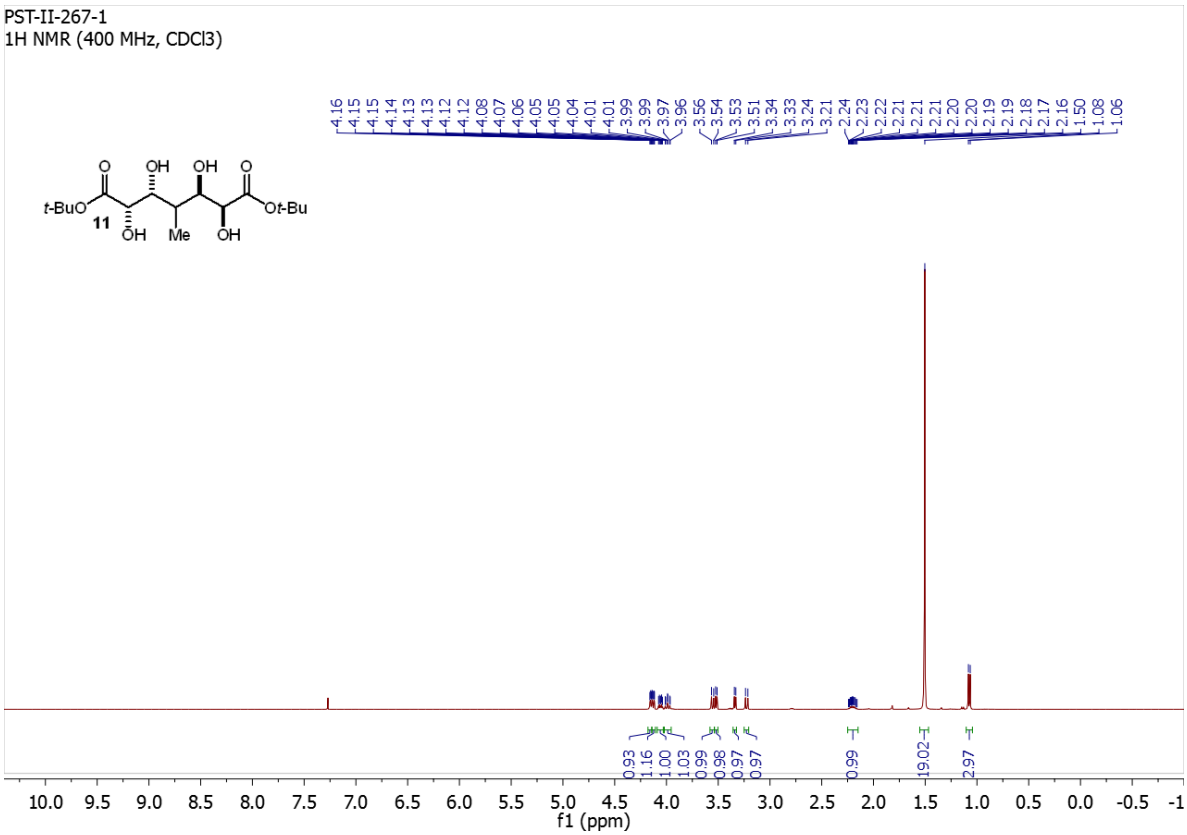
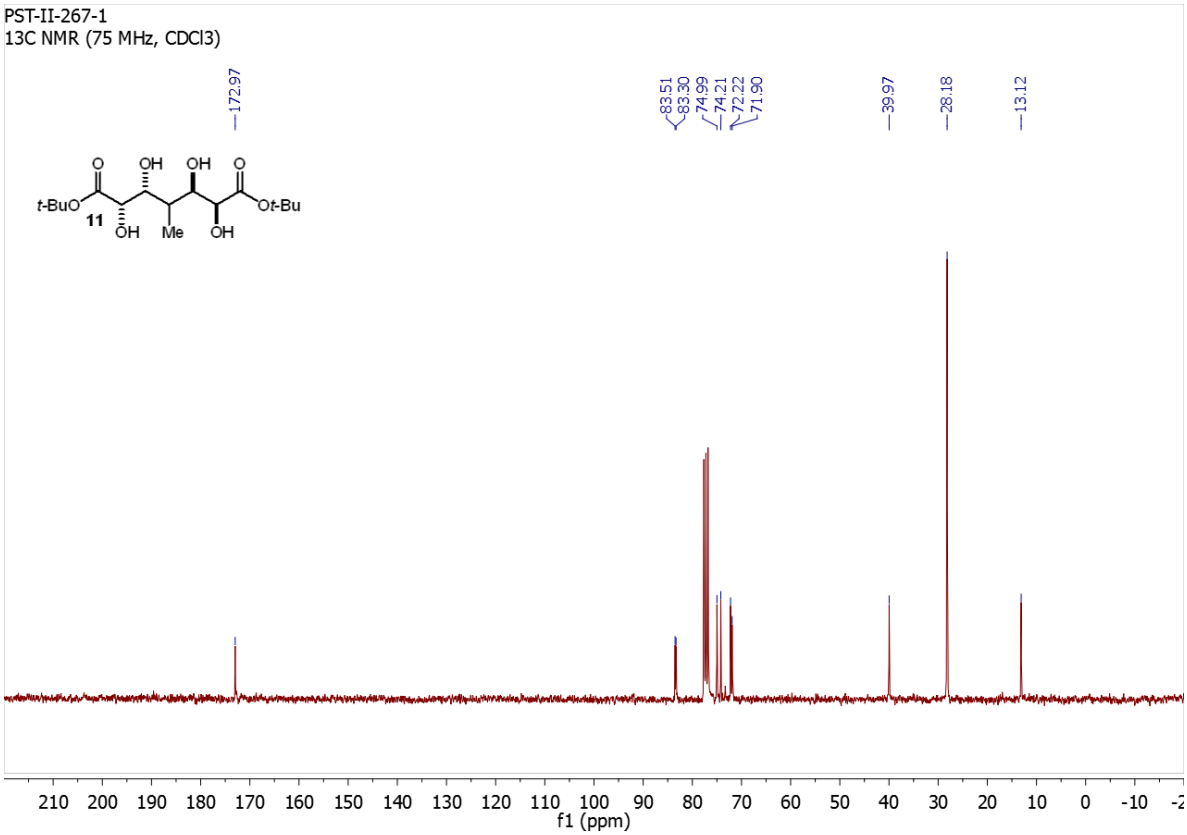


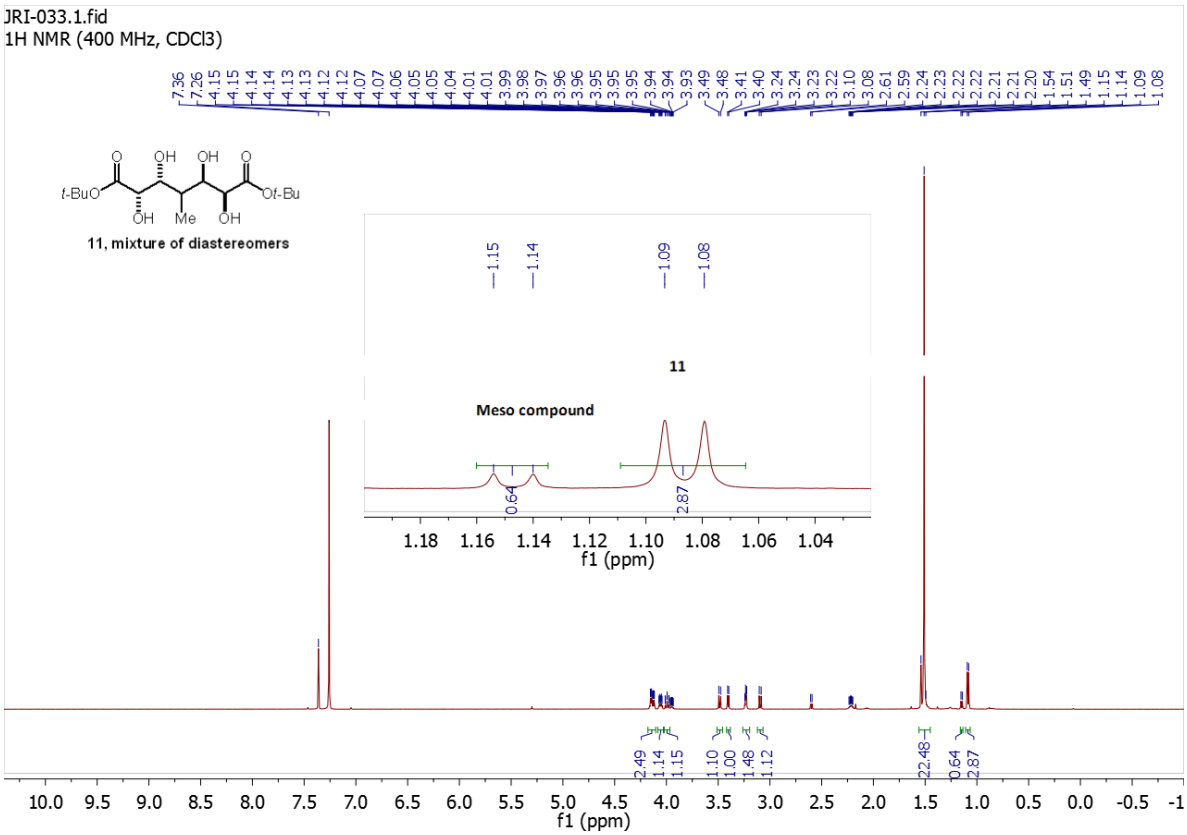
Figure S2. NOESY enhancements observed for **15** establish its stereostructure.


PST-III-115-15
1H NMR (500 MHz, CDCl3)
6.79
6.77
6.76
6.74
5.75
5.75
5.72
5.71
3.16
3.16
3.15
3.13
3.13
3.12
3.12
3.11
3.10
3.10
3.09
3.09
1.47
1.21
1.19
t-BuO
10b
Me
Ot-Bu
2.00
2.03
1.09
17.97
3.03
10.0 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 0.0 -0.5 -1
f1 (ppm)

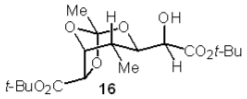

PST-III-115-15
13C NMR (126 MHz, CDCl3)
165.88
148.42
123.17
80.62
38.53
28.28
18.61
t-BuO
10b
Me
Ot-Bu
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


PST-II-267-1
1H NMR (400 MHz, CDCl3)
4.16
4.15
4.15
4.14
4.13
4.13
4.12
4.12
4.08
4.07
4.06
4.05
4.05
4.04
4.01
4.01
3.99
3.99
3.97
3.96
3.56
3.54
3.53
3.51
3.34
3.33
3.24
3.21
2.24
2.23
2.22
2.21
2.21
2.21
2.20
2.20
2.19
2.19
2.18
2.17
2.16
1.50
1.08
1.06
t-BuO
11
OH
OH
OH
Me
OH
Ot-Bu
0.93
1.16
1.00
1.03
0.99
0.98
0.97
0.97
0.99
19.02
2.97
10.0 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 0.0 -0.5 -1
f1 (ppm)


PST-II-267-1
13C NMR (75 MHz, CDCl3)
172.97
83.51
83.30
74.99
74.21
72.22
71.90
39.97
28.18
13.12
t-BuO
11
OH
OH
OH
Me
OH
Ot-Bu
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -2
f1 (ppm)

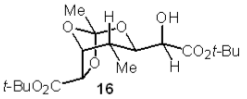

JRI-033.1.fid
1H NMR (400 MHz, CDCl3)
11, mixture of diastereomers
11
Meso compound
f1 (ppm)

PST-II-174-1
1H NMR (500 MHz, CDCl3)



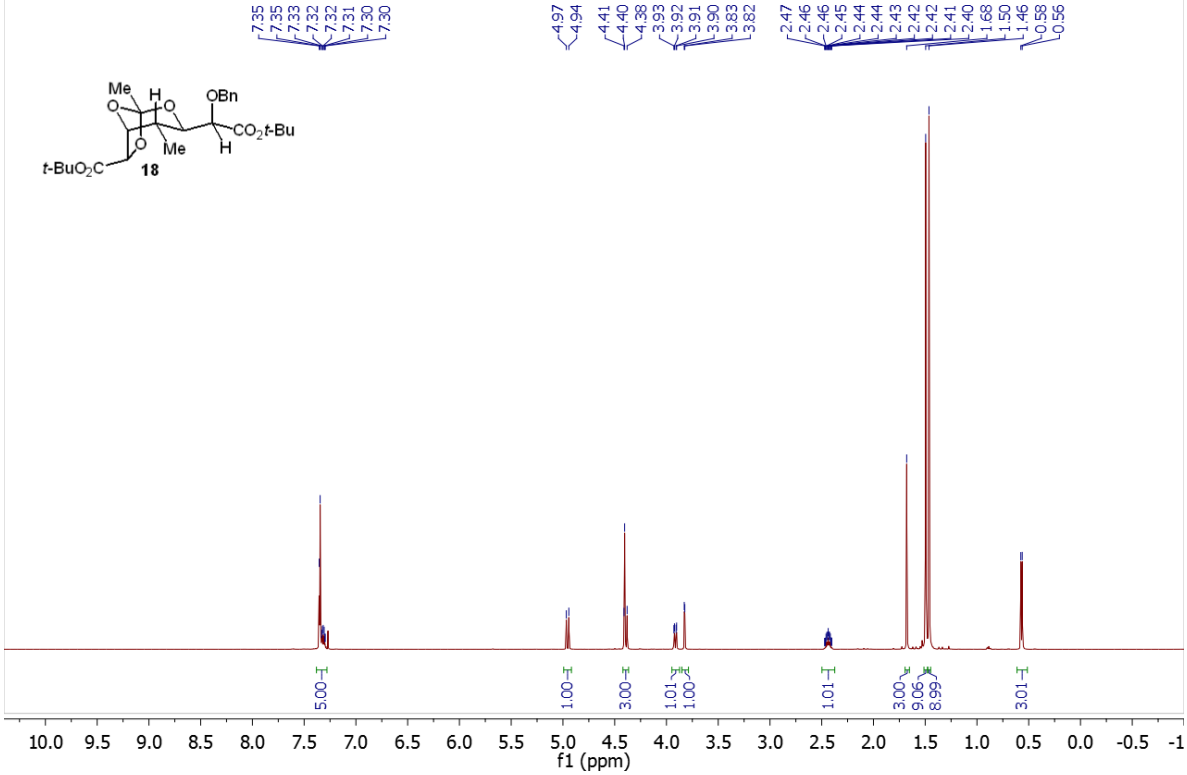
16

PST-II-174-1
13C NMR (126 MHz, CDCl3)

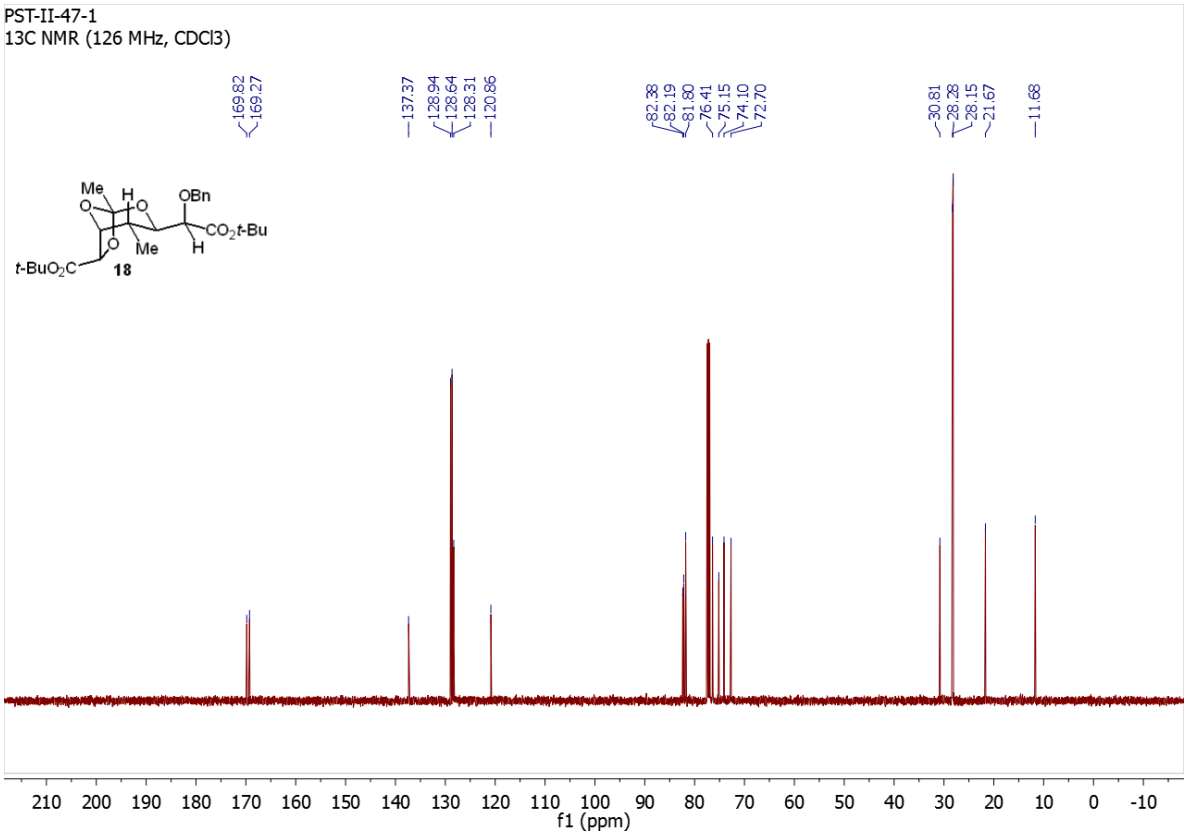


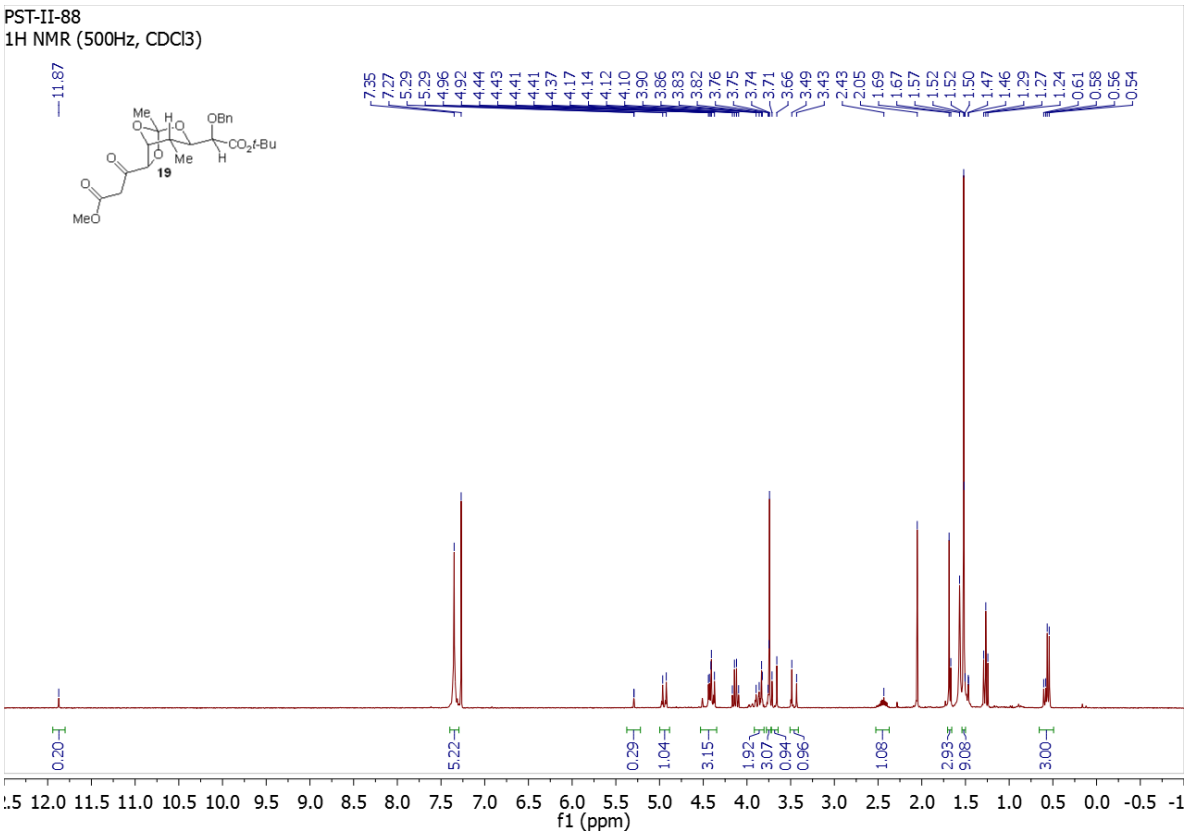
16

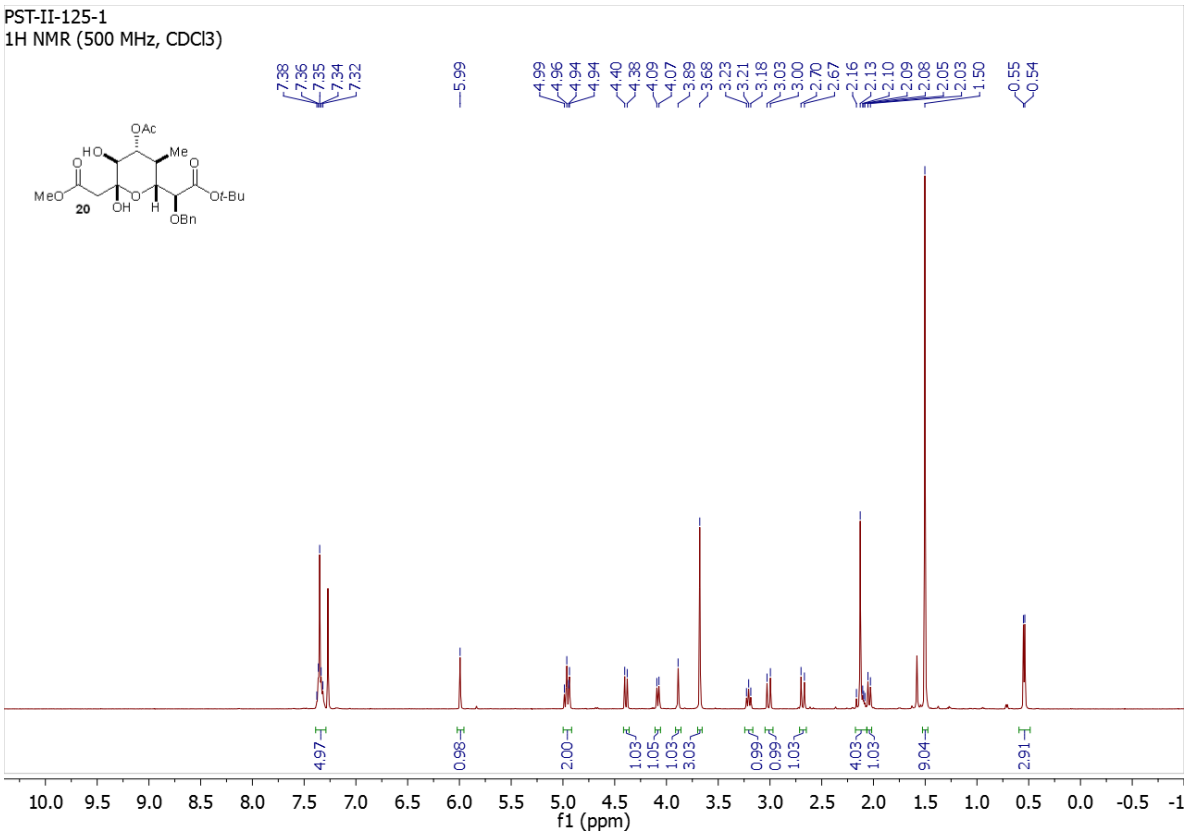
PST-II-47-1
1H NMR (500 MHz, CDCl3)

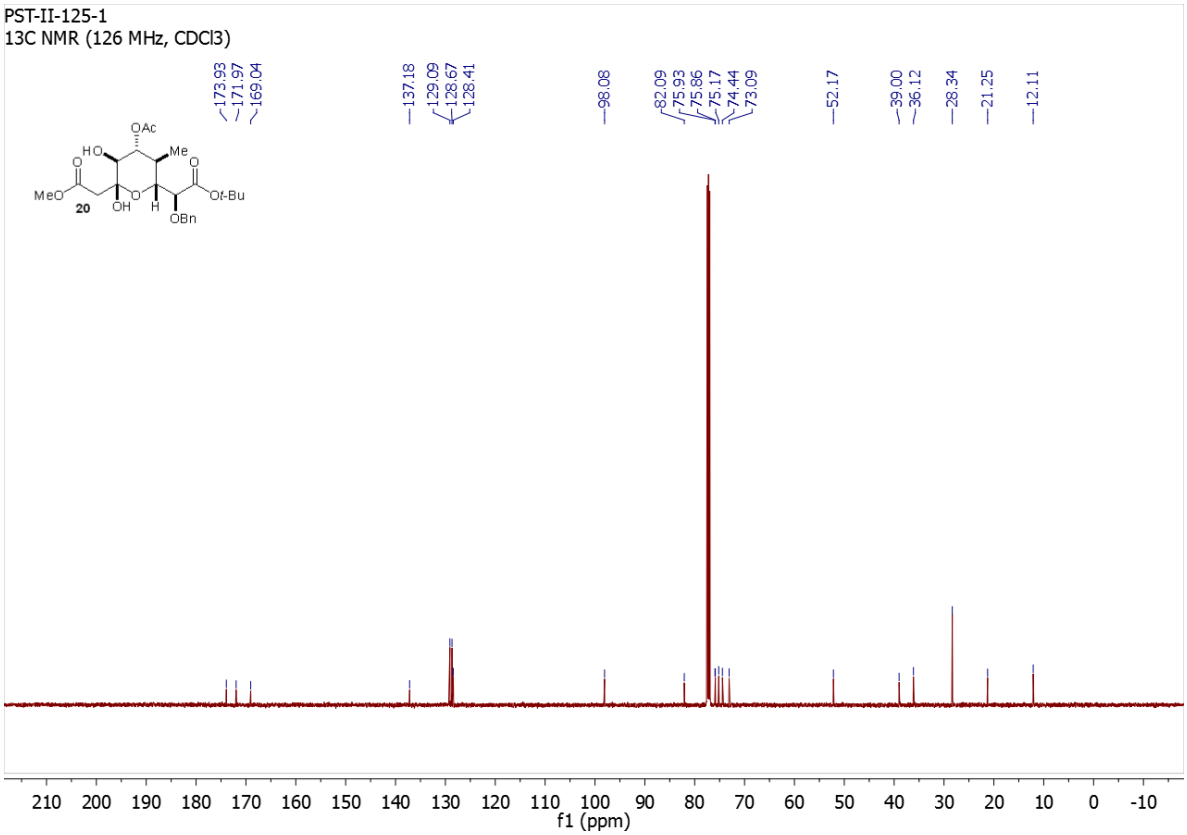


PST-II-47-1
13C NMR (126 MHz, CDCl3)

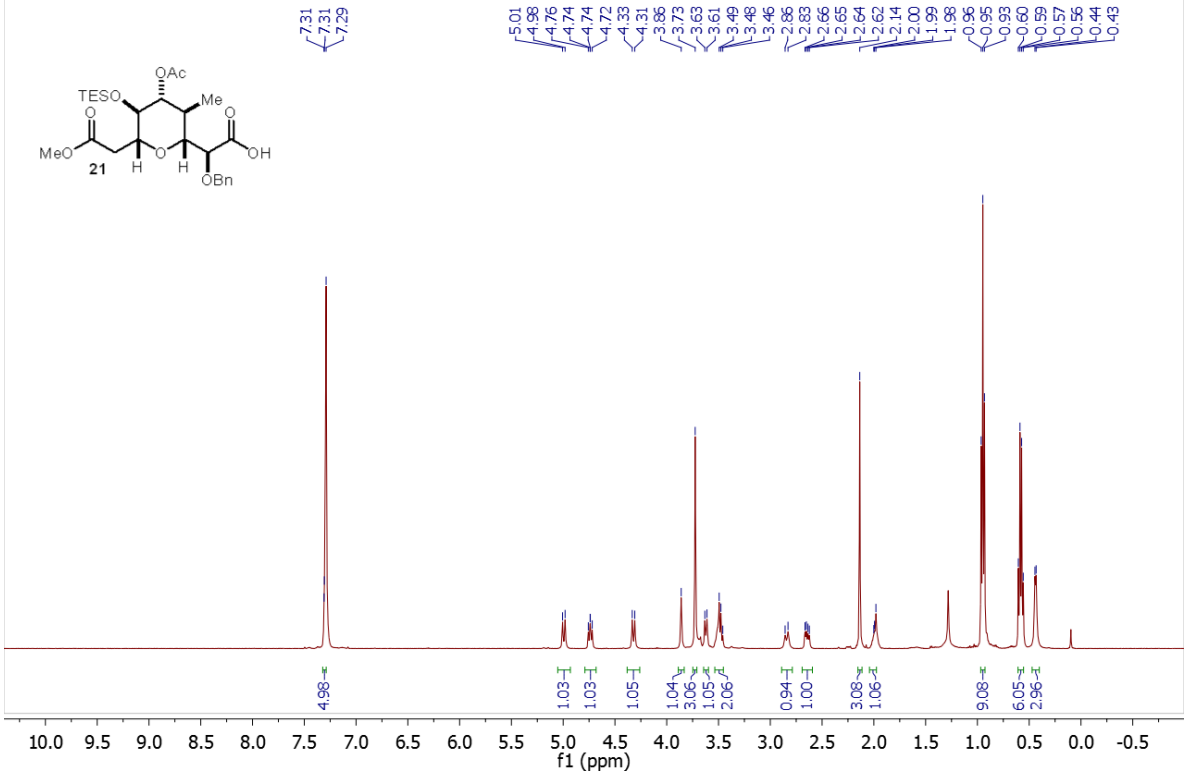



PST-II-88
1H NMR (500Hz, CDCl3)
11.87
7.35
7.27
5.29
5.29
4.96
4.92
4.44
4.43
4.41
4.41
4.37
4.17
4.14
4.12
4.10
3.90
3.86
3.83
3.82
3.76
3.75
3.74
3.71
3.66
3.49
3.43
2.43
2.05
1.69
1.67
1.57
1.52
1.52
1.50
1.47
1.46
1.29
1.27
1.24
0.61
0.58
0.56
0.54
Me
H
OBn
CO2t-Bu
Me
19
MeO
0.20
5.22
0.29
1.04
3.15
1.92
3.07
0.94
0.96
1.08
2.93
9.08
3.00
f1 (ppm)

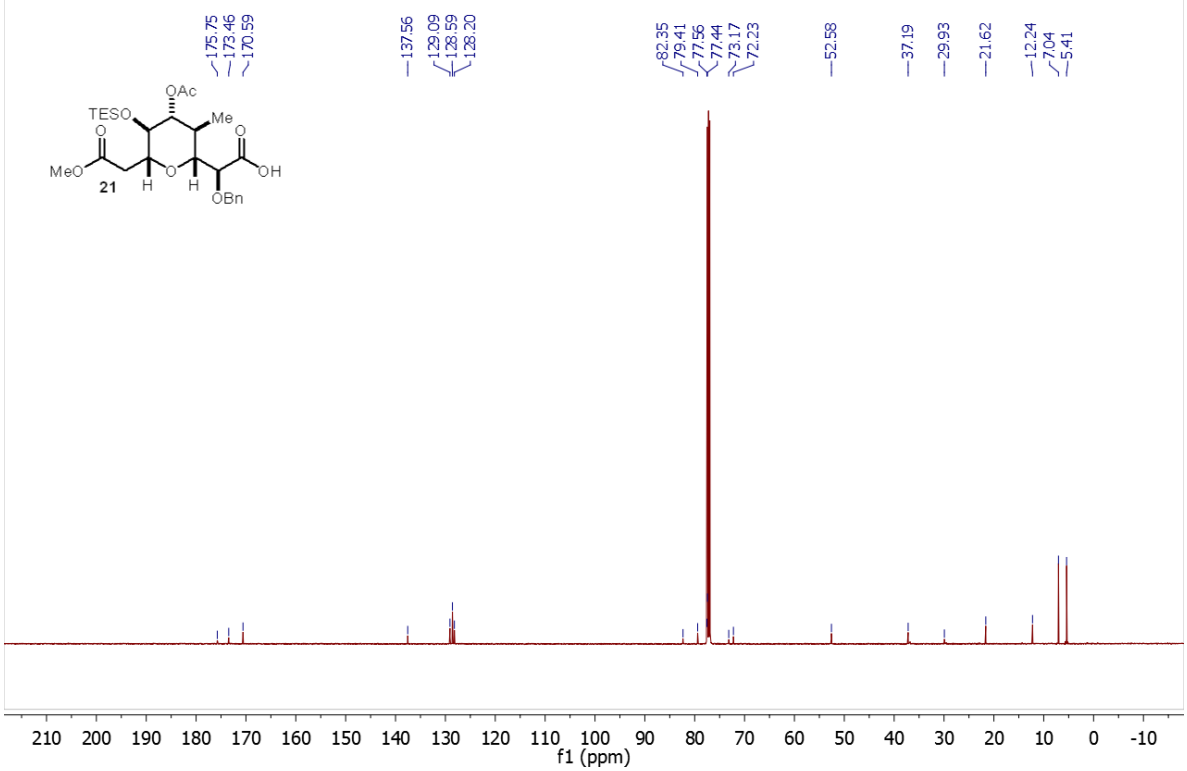

PST-II-125-1
1H NMR (500 MHz, CDCl3)
7.38
7.36
7.35
7.34
7.32
5.99
4.99
4.96
4.94
4.94
4.40
4.38
4.09
4.07
3.89
3.68
3.23
3.21
3.18
3.03
3.00
2.70
2.67
2.16
2.13
2.10
2.09
2.08
2.05
2.03
1.50
0.55
0.54
OAc
HO
Me
MeO
O
Ot-Bu
20
OH
H
OBn
4.97
0.98
2.00
1.03
1.05
1.03
3.03
0.99
0.99
1.03
4.03
1.03
9.04
2.91
10.0 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 0.0 -0.5 -1
f1 (ppm)

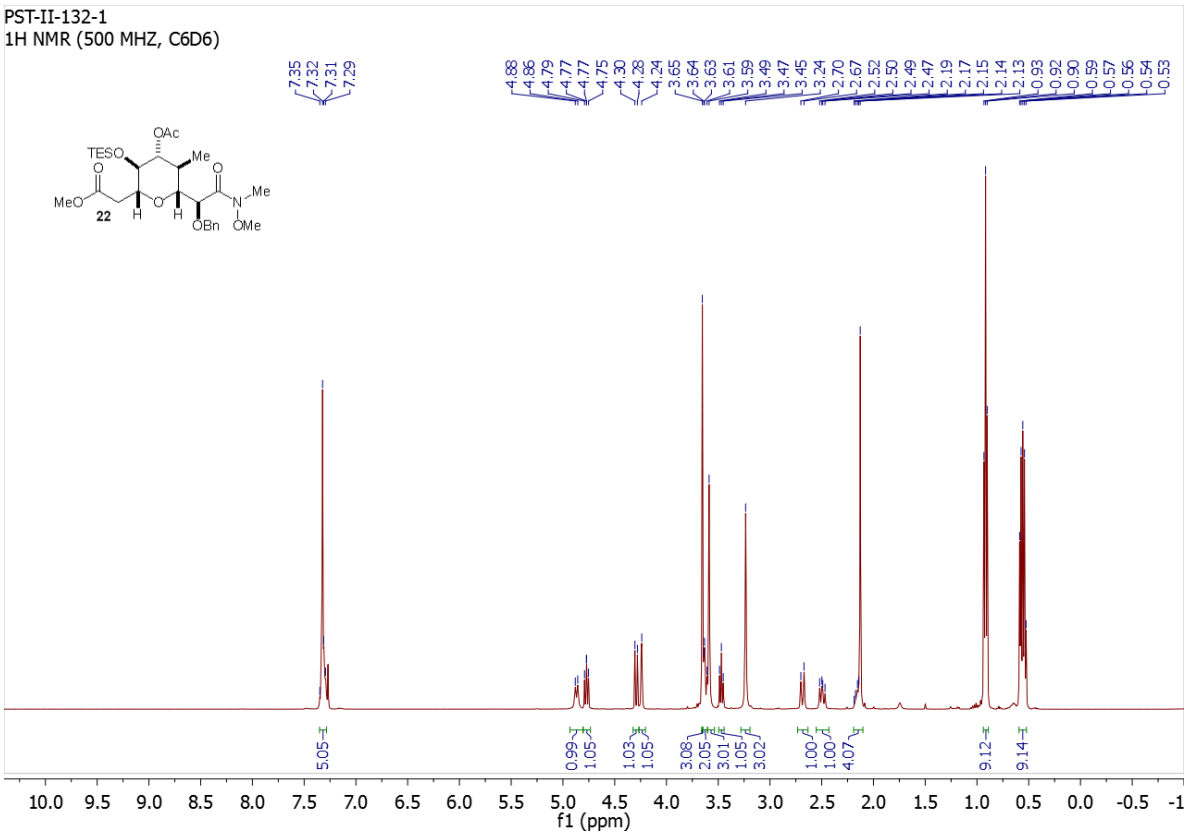

PST-II-125-1
13C NMR (126 MHz, CDCl3)
173.93
171.97
169.04
137.18
129.09
128.67
128.41
98.08
82.09
75.93
75.86
75.17
74.44
73.09
52.17
39.00
36.12
28.34
21.25
12.11
OAc
HO
Me
MeO
O
Ot-Bu
20
OH
H
OBn
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

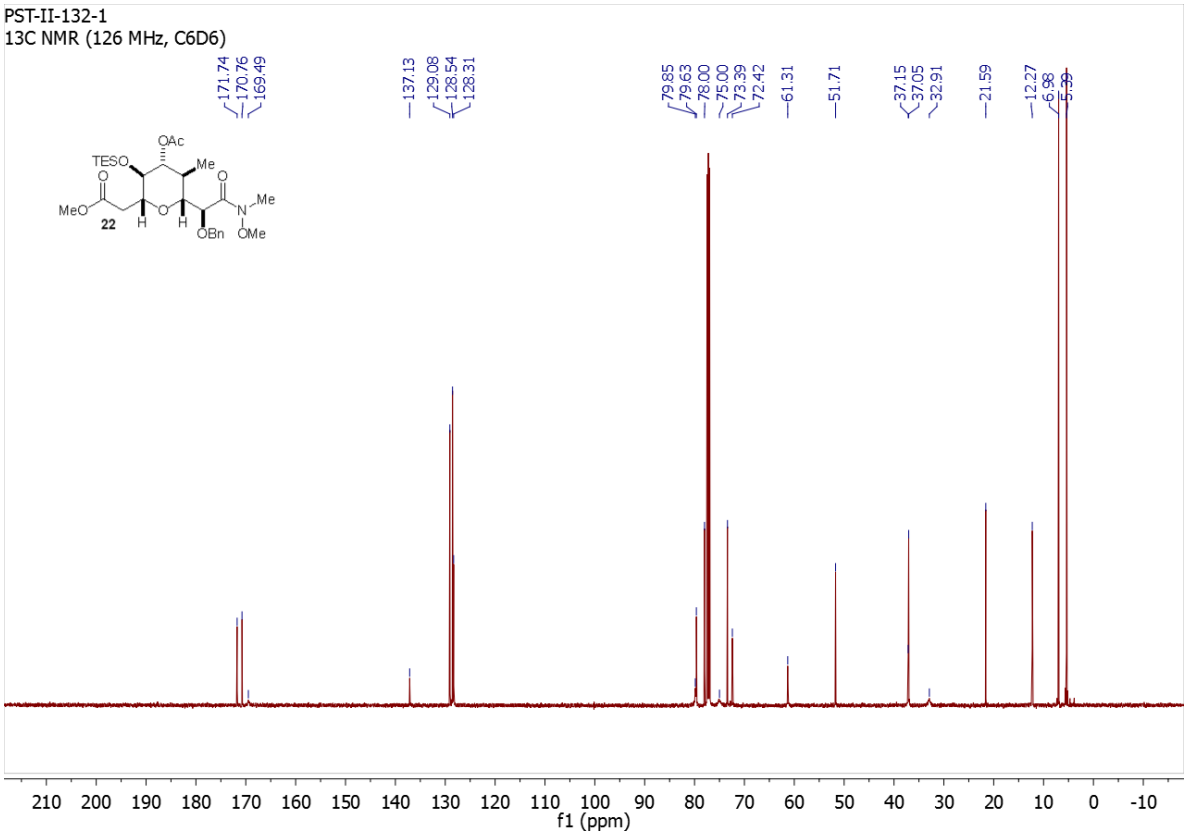
PST-II-129-1
1H NMR (500 MHz, CDCl3)

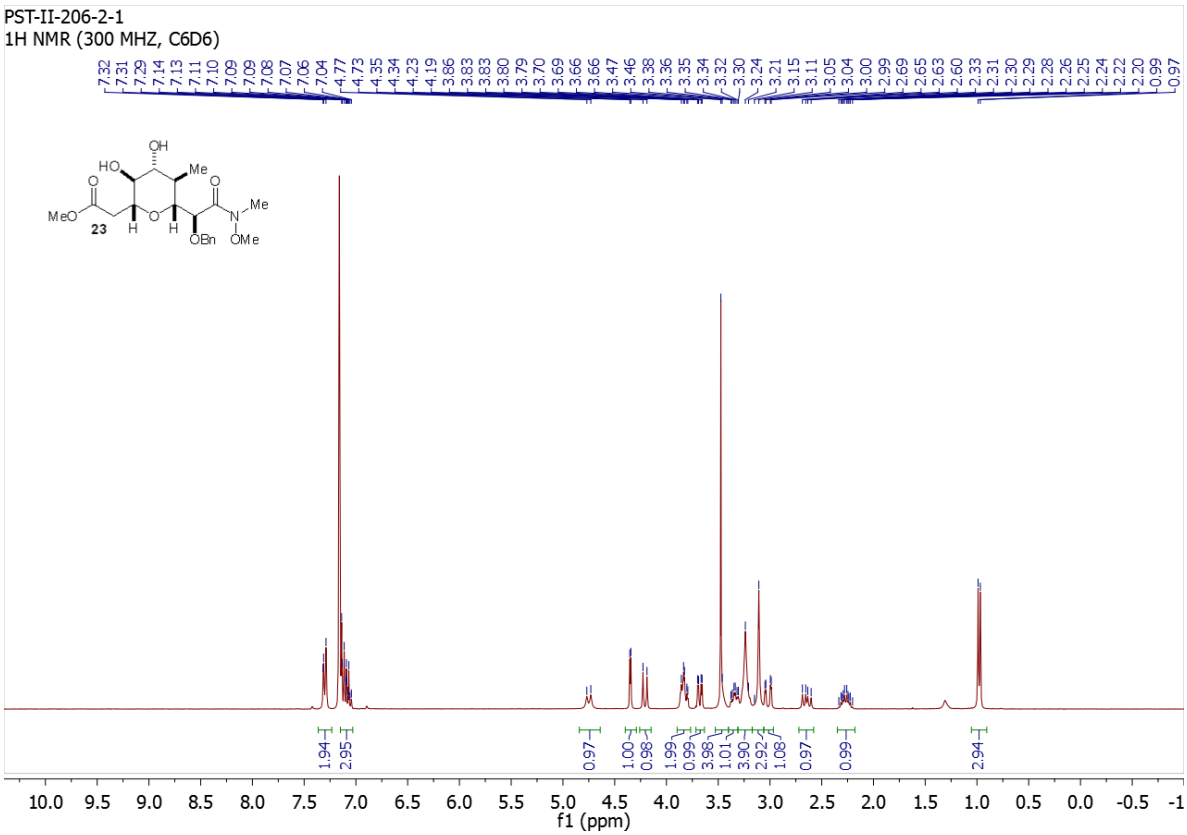


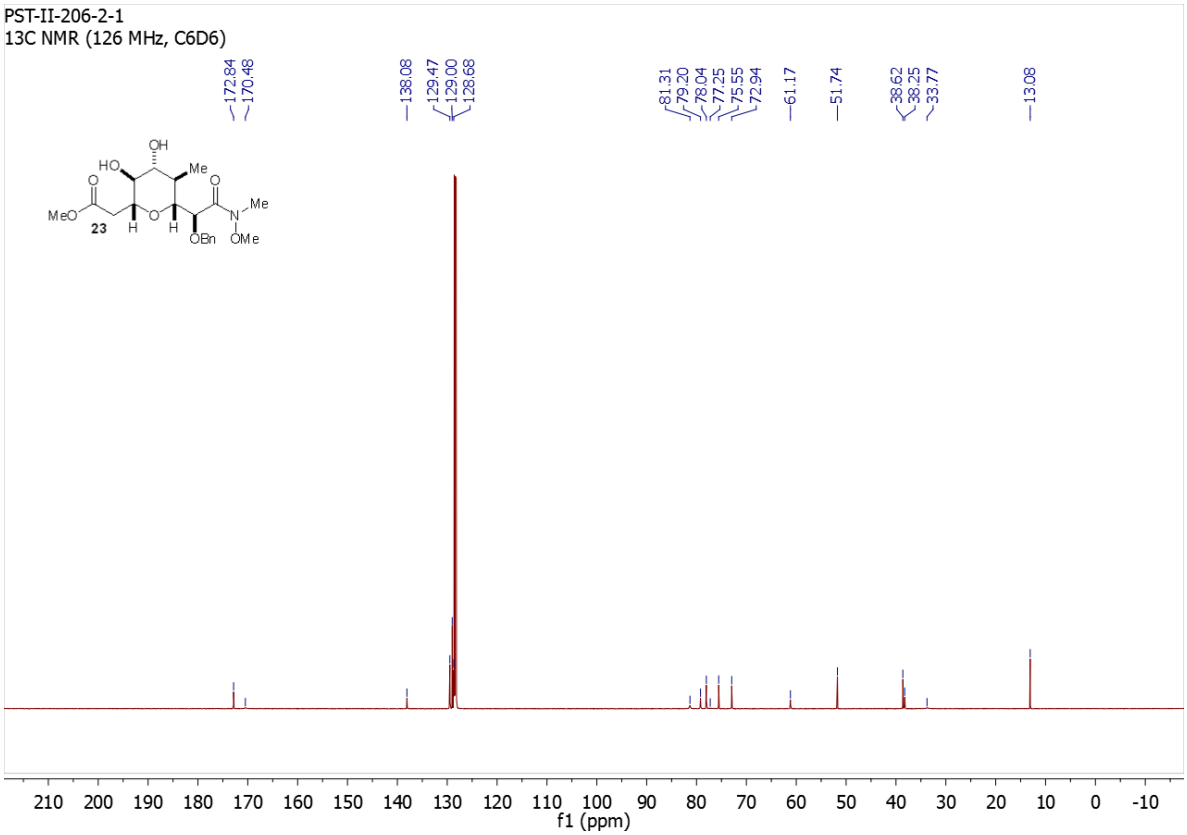
PST-II-129-1
13C NMR (126 MHz, CDCl3)



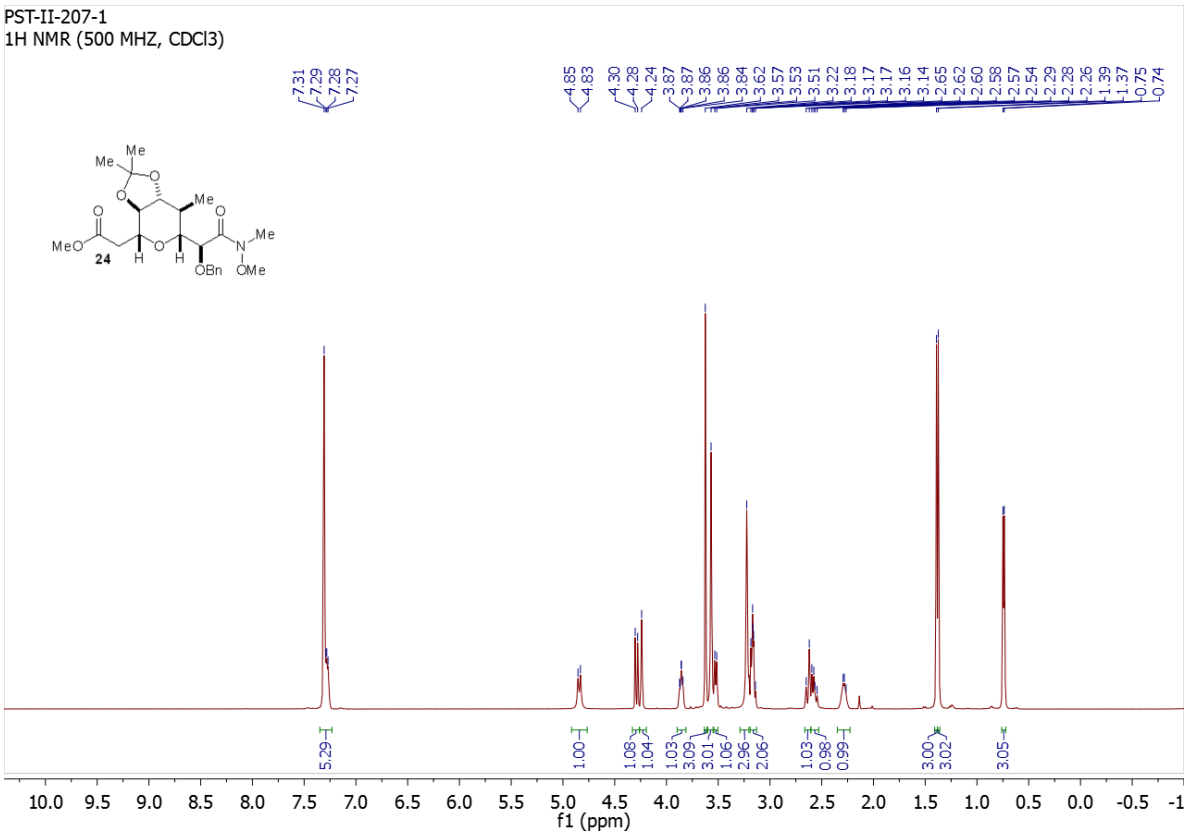

PST-II-132-1
1H NMR (500 MHZ, C6D6)
7.35
7.32
7.31
7.29
4.88
4.86
4.79
4.77
4.77
4.75
4.30
4.28
4.24
3.65
3.64
3.63
3.61
3.59
3.49
3.47
3.45
3.24
2.70
2.67
2.52
2.50
2.49
2.47
2.19
2.17
2.15
2.14
2.13
0.93
0.92
0.90
0.59
0.57
0.56
0.54
0.53
OAc
TESO
Me
MeO
22
OBn
OMe
N
Me
5.05
0.99
1.05
1.03
1.05
3.08
2.05
3.01
1.05
3.02
1.00
1.00
4.07
9.12
9.14
f1 (ppm)


PST-II-132-1
13C NMR (126 MHz, C6D6)
171.74
170.76
169.49
137.13
129.08
128.54
128.31
79.85
79.63
78.00
75.00
73.39
72.42
61.31
51.71
37.15
37.05
32.91
21.59
12.27
6.98
5.99
OAc
TESO
Me
MeO
22
OBn
OMe
N
Me
f1 (ppm)

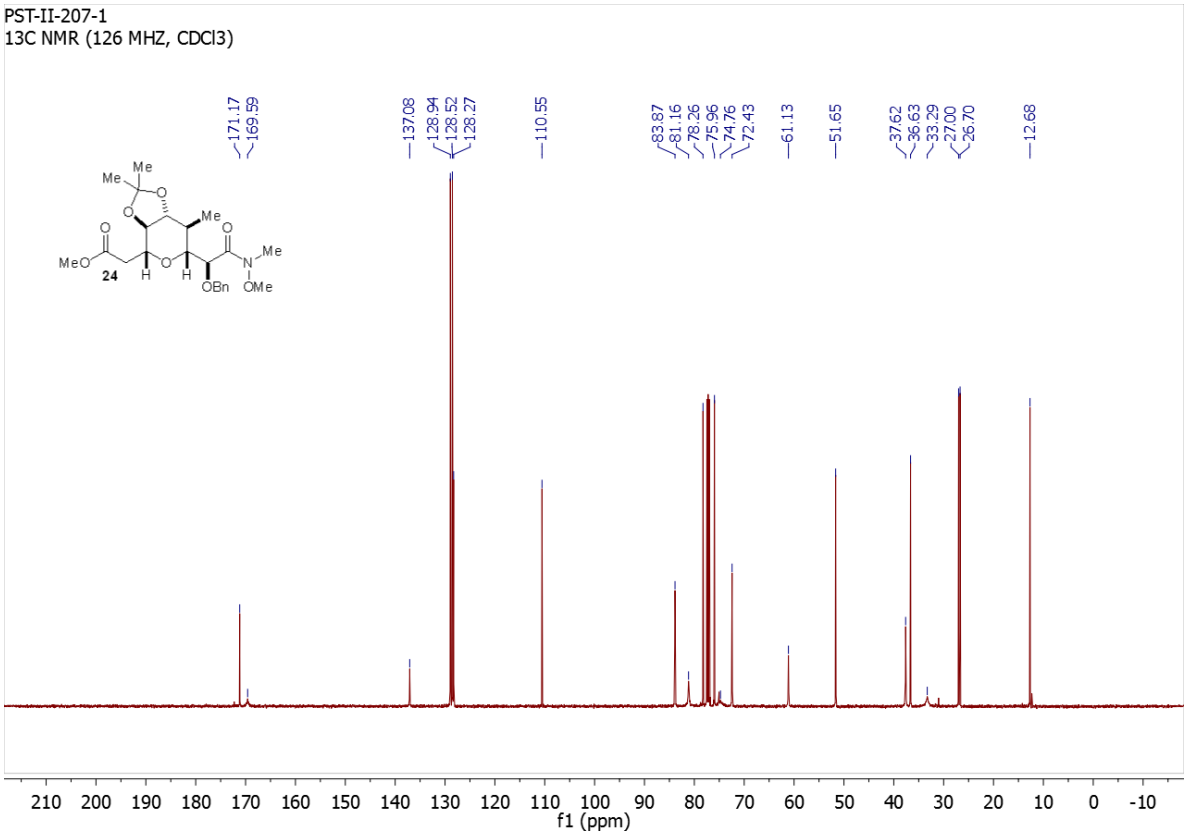

PST-II-206-2-1
1H NMR (300 MHZ, C6D6)
7.32 7.31 7.29 7.14 7.13 7.11 7.10 7.09 7.09 7.08 7.07 7.06 7.04 4.77 4.73 4.35 4.34 4.23 4.19 3.86 3.83 3.83 3.80 3.79 3.70 3.69 3.66 3.66 3.47 3.46 3.38 3.36 3.35 3.34 3.32 3.30 3.24 3.21 3.15 3.11 3.05 3.04 3.00 2.99 2.69 2.65 2.63 2.60 2.33 2.31 2.30 2.29 2.28 2.26 2.25 2.24 2.22 2.20 0.99 0.97
OH
HO
Me
O
MeO
O
N
Me
OMe
OBn
H
H
O
23
1.94 2.95 0.97 1.00 0.98 1.99 0.99 3.98 1.01 3.90 2.92 1.08 0.97 0.99 2.94
10.0 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 0.0 -0.5 -1
f1 (ppm)

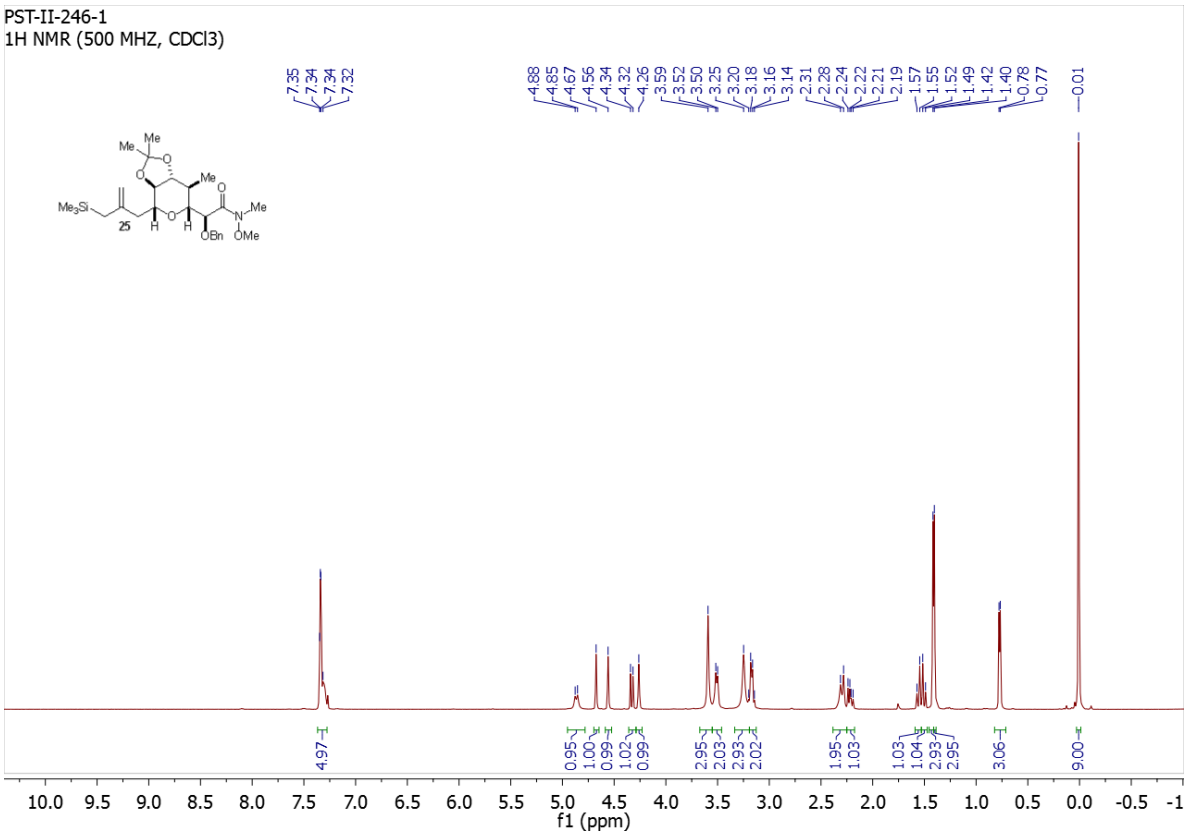

PST-II-206-2-1
13C NMR (126 MHz, C6D6)
172.84 170.48 138.08 129.47 129.00 128.68 81.31 79.20 78.04 77.25 75.55 72.94 61.17 51.74 38.62 38.25 33.77 13.08
OH
HO
Me
O
MeO
O
N
Me
OMe
OBn
H
H
O
23
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

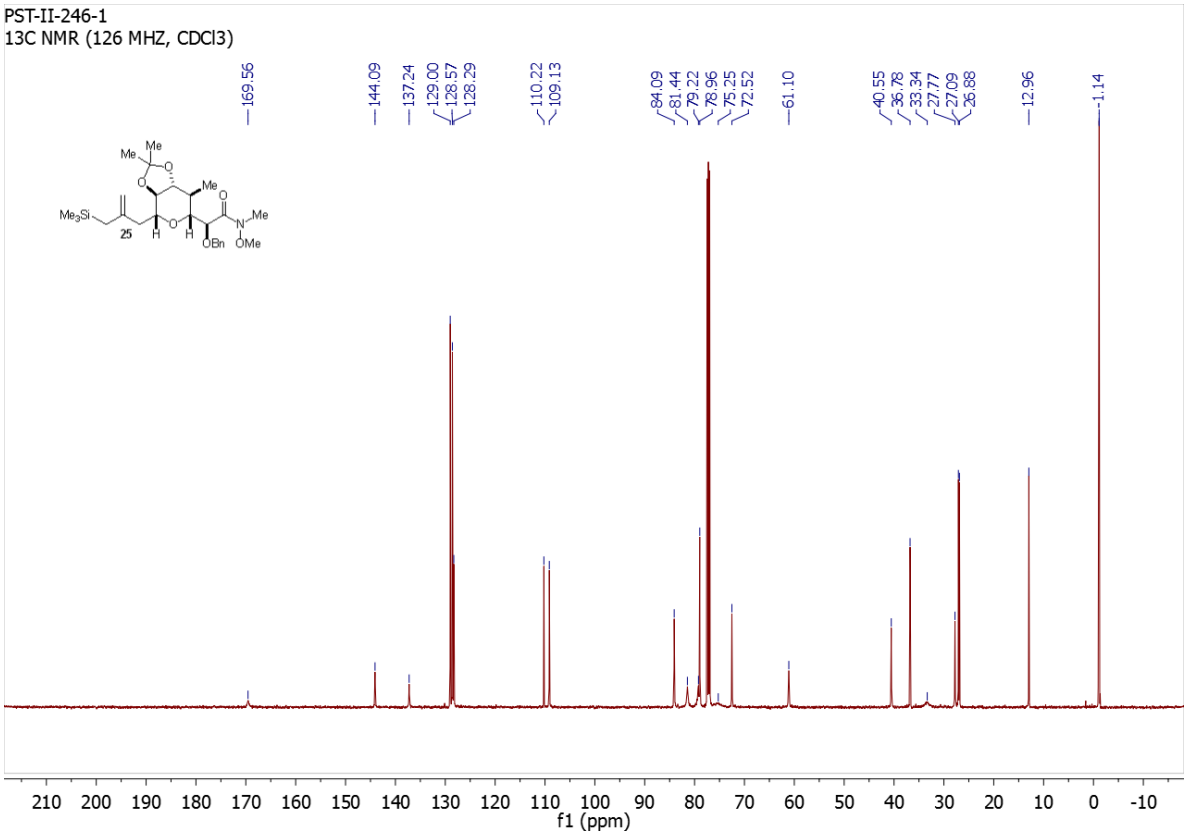
PST-II-207-1
1H NMR (500 MHZ, CDCl3)

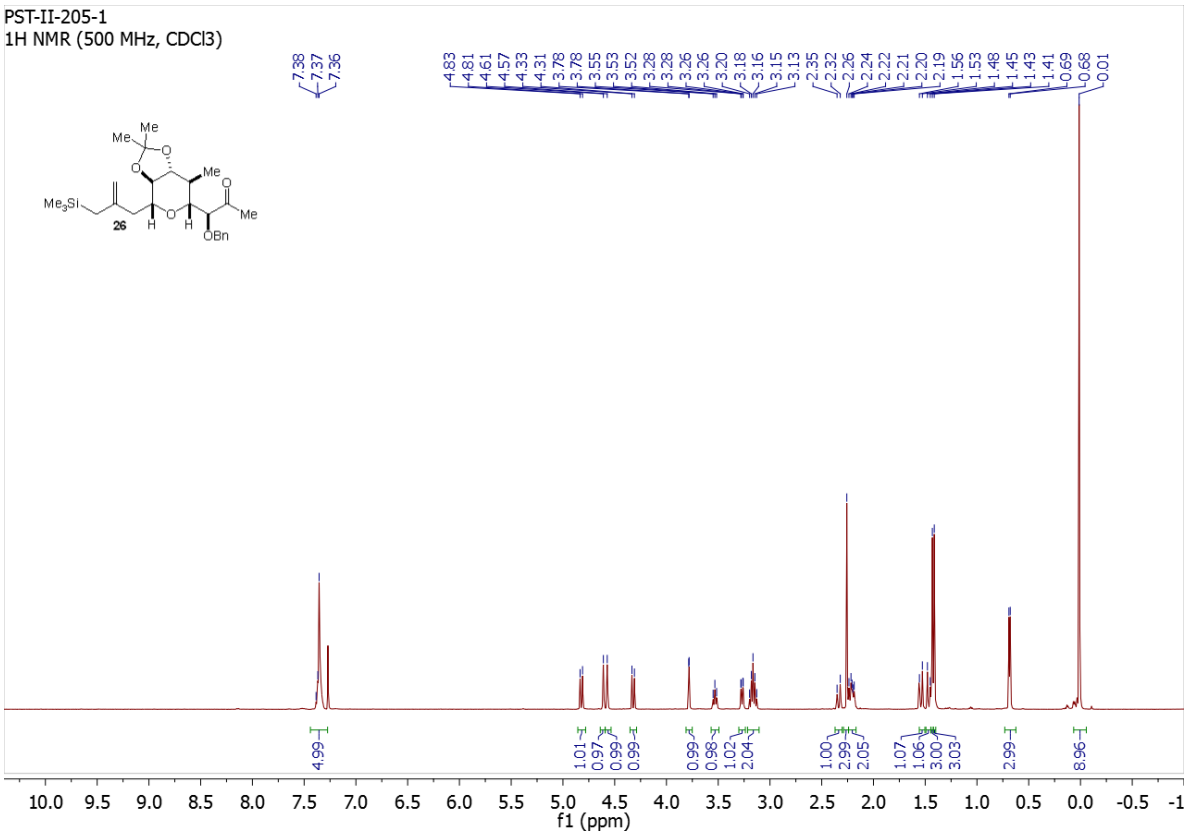


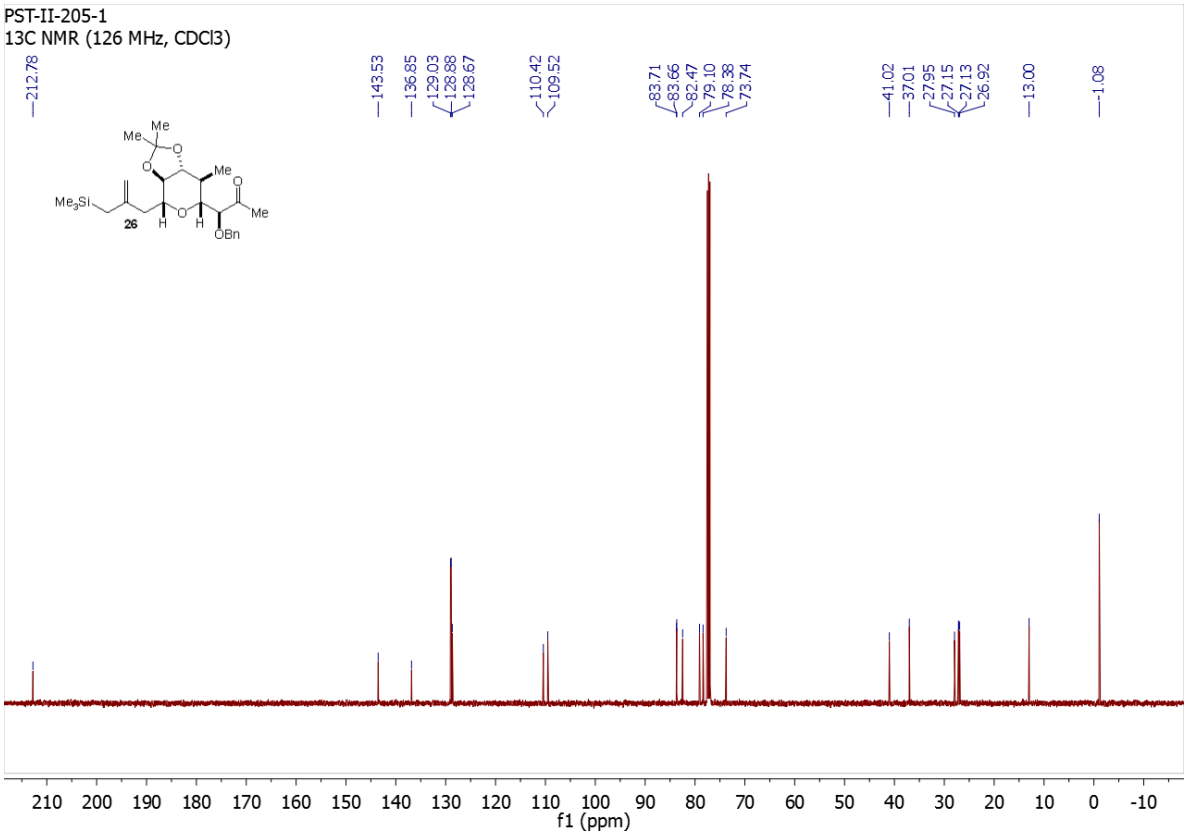
PST-II-207-1
13C NMR (126 MHZ, CDCl3)



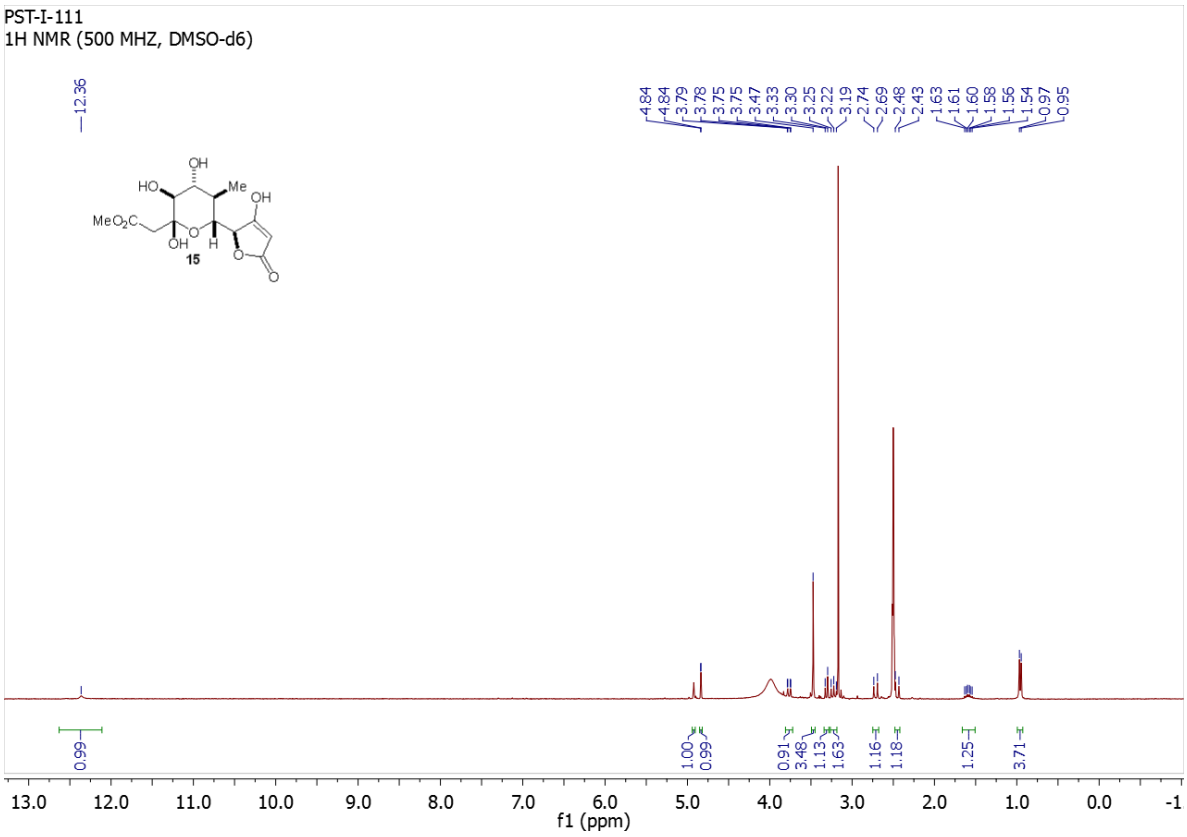

PST-II-246-1
1H NMR (500 MHZ, CDCl3)
7.35
7.34
7.34
7.32
4.88
4.85
4.67
4.56
4.34
4.32
4.26
3.59
3.52
3.50
3.25
3.20
3.18
3.16
3.14
2.31
2.28
2.24
2.22
2.21
2.19
1.57
1.55
1.52
1.49
1.42
1.40
0.78
0.77
0.01
4.97
0.95
1.00
0.99
1.02
0.99
2.95
2.03
2.93
2.02
1.95
1.03
1.03
1.04
2.93
2.95
3.06
9.00
f1 (ppm)


PST-II-246-1
13C NMR (126 MHZ, CDCl3)
169.56
144.09
137.24
129.00
128.57
128.29
110.22
109.13
84.09
81.44
79.22
78.96
75.25
72.52
61.10
40.55
36.78
33.34
27.77
27.09
26.88
12.96
1.14
f1 (ppm)

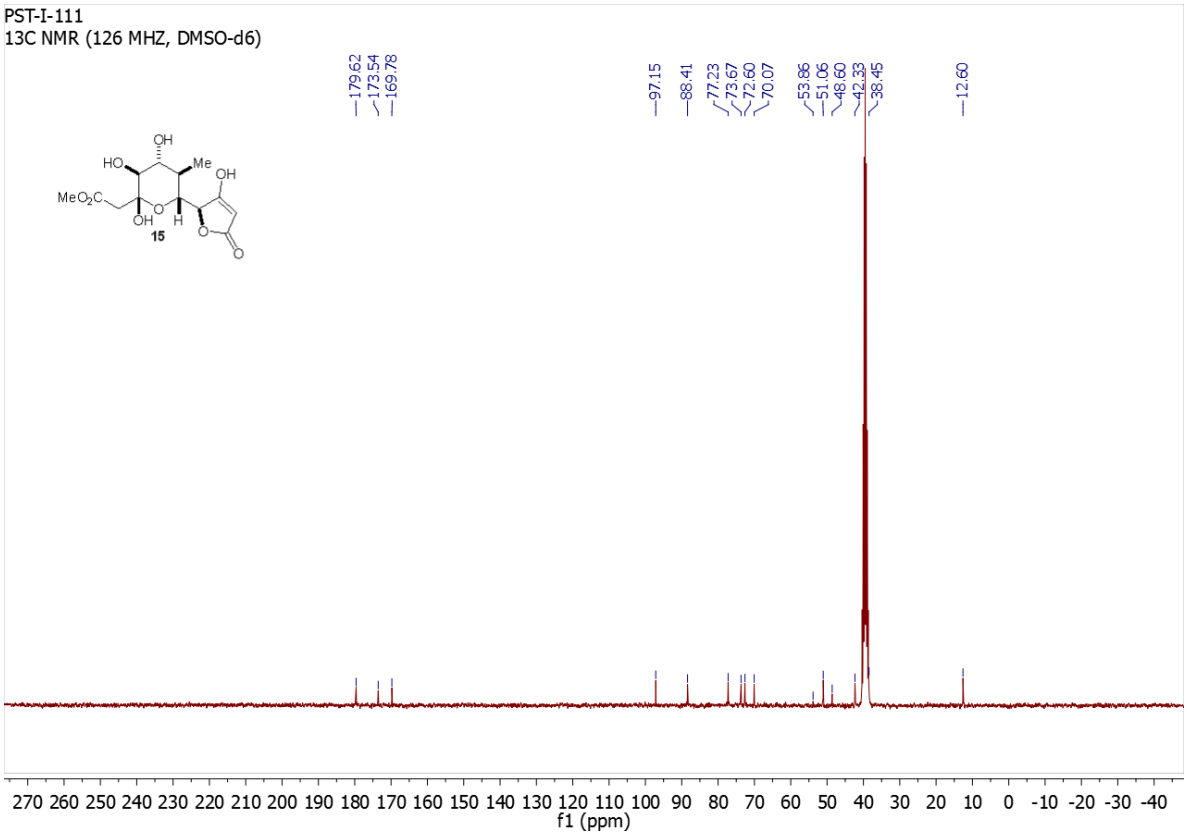

PST-II-205-1
1H NMR (500 MHz, CDCl3)
f1 (ppm)

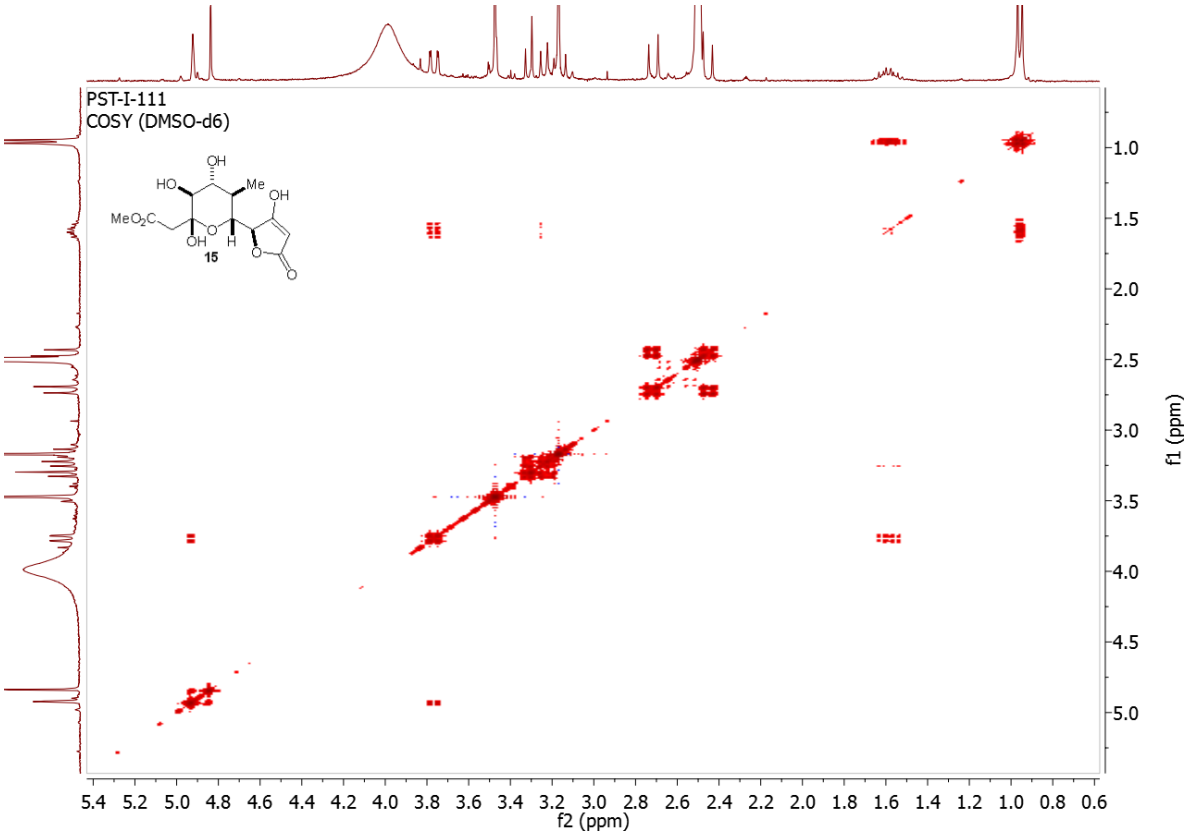

PST-II-205-1
13C NMR (126 MHz, CDCl3)
f1 (ppm)

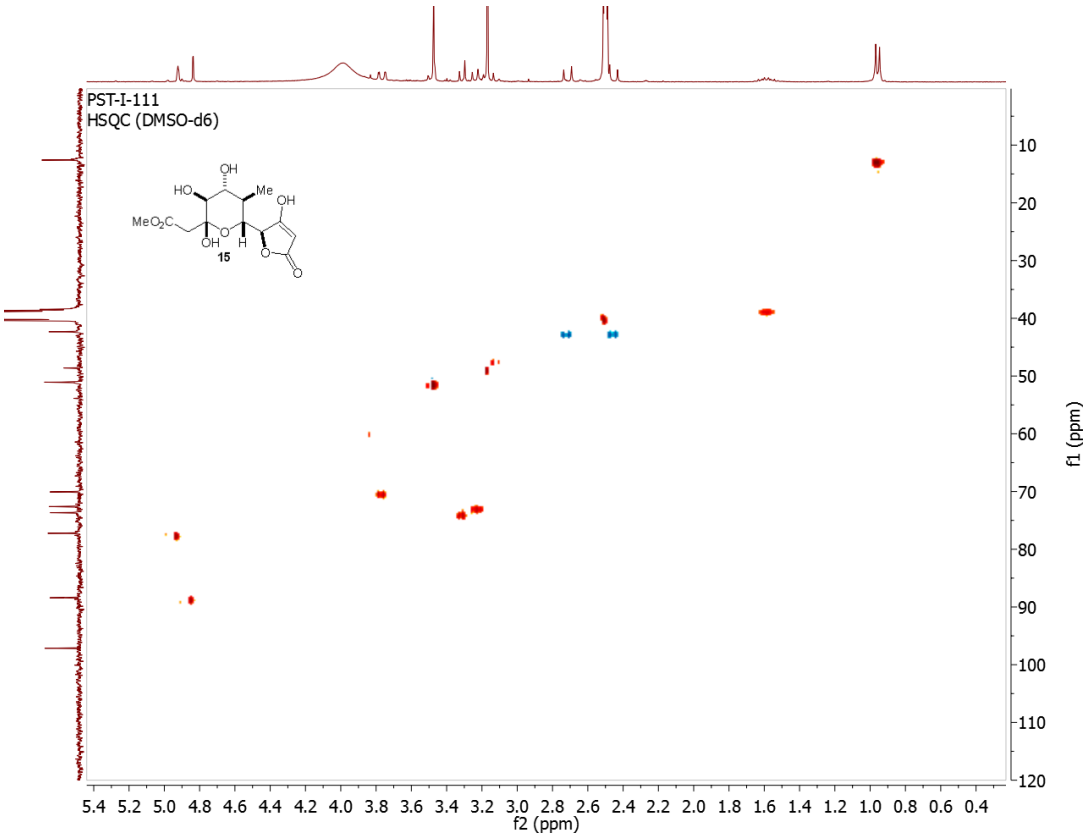
PST-I-111
1H NMR (500 MHZ, DMSO-d6)

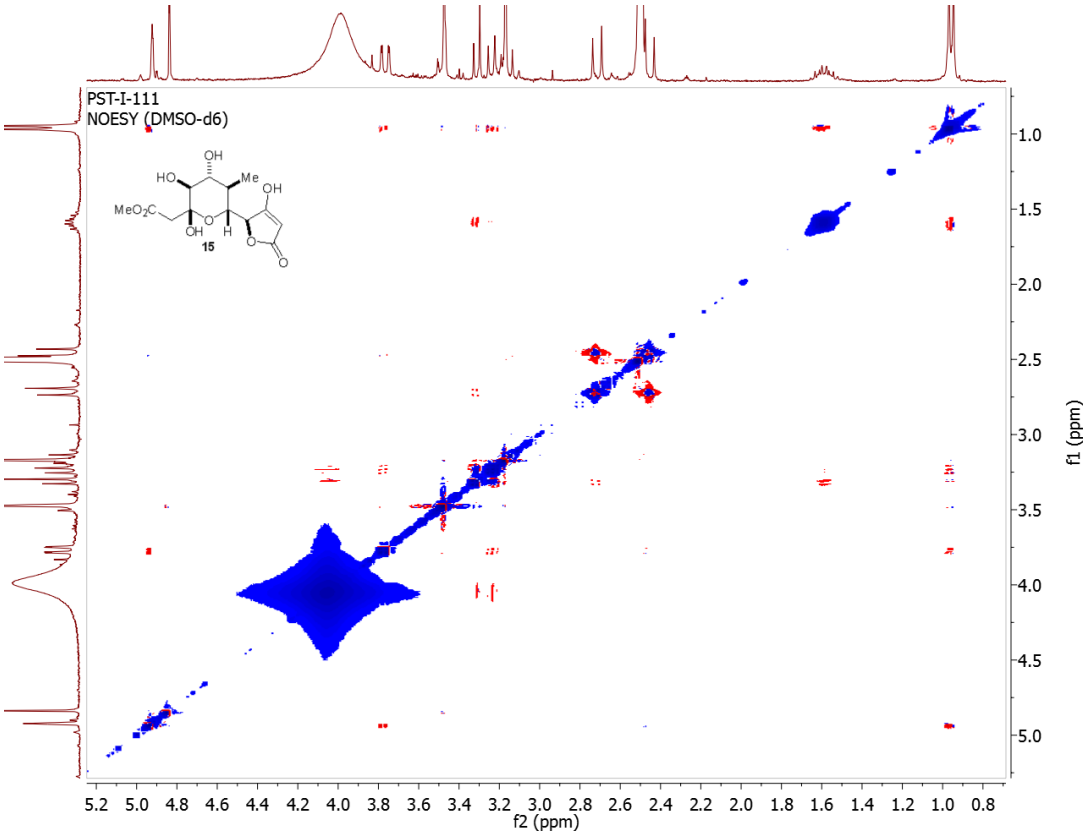


PST-I-111
13C NMR (126 MHZ, DMSO-d6)




PST-I-111
COSY (DMSO-d6)
15
f2 (ppm)
f1 (ppm)


PST-I-111
HSQC (DMSO-d6)
15
f2 (ppm)
f1 (ppm)


PST-I-111
NOESY (DMSO-d6)
OH
HO
Me
OH
MeO2C
O
OH
H
O
O
15
f1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)