Total Syntheses of Bryostatins. Completion of the Synthesis of Bryostatin 16 using a Pd-Catalyzed Diyne-coupling as a Macrocyclization Method and Synthesis of C20-*epi*-Bryostatin 7 as a Potent Anticancer Agent

Barry M. Trost* and Guangbin Dong

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

Supporting Information (Part I)

General:

All reactions were run under an atmosphere of nitrogen unless otherwise indicated. Anhydrous solvents were transferred via oven-dried syringe or cannula. Flasks were flame-dried under vacuum and cooled under a stream of nitrogen or argon. Tetrahydrofuran (THF), and dimethoxyethane (DME), Benzene, pyridine, diisopropylamine, triethylamine, diisopropylethylamine, and dimethylsulfoxide, acetonitrile, hexane, toluene, diethyl ether, and dichloromethane were purified with a Solv-Tek solvent purification system by passing through a column of activated alumina. Acetone was distilled from calcium sulfate. Methanol was distilled from magnesium methoxide.

Where indicted, solvents are degassed via freezing in liquid nitrogen and thawing under high vacuum. The above cycle is repeated three times, unless otherwise indicated.

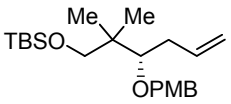
Analytical thin layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}).

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded using a Varian UI-600 (600 MHz), UI-500 (500 MHz) or Varian MERC-400 (400 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) or in ppm relative to the singlet at 7.26 ppm for

deuterochloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet.

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Varian UI-600 (150 MHz), Varian UI-500 (125 MHz) or Varian MERC-400 (100 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at 77.1 ppm for deuterochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

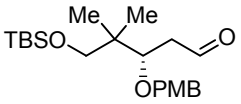
Optical rotation data was obtained with a Jasco DIP-360 digital polarimeter at the sodium D line (589 nm) in the solvent and concentration indicated.



11

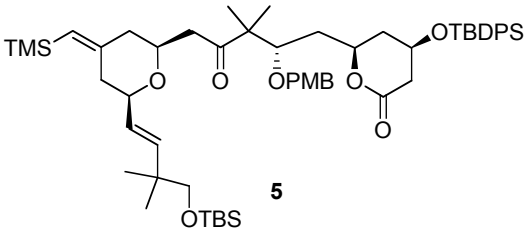
Compound 11: To a solution of aldehyde **10** (0.86 g, 4.0 mmol) in dry Et_2O (14 ml) at –90 ^{o}C under N_2, was added a solution of (–)-$(Ipc)_2B$(allyl) (3.5 ml, 3.5 mmol, 1M in pentane) dropwisely. The reaction mixture was stirred at –90 ^{o}C for 1h, before MeOH (0.8 ml) was added carefully. The mixture was allowed to warm to rt, and a mixture of THF-water (ca. 1:1, 15 ml) was added, followed by $NaBO_3 \cdot H_2O$ (1.6 g, 16 mmol). The mixture was stirred vigorously overnight, before water (ca. 20 ml) was added. The mixture was extracted with ether three times and the combined organic fractions were dried over $MgSO_4$. The known homoallyl alcohol[32] was purified via silica gel flash column chromatography (5% ether/petroleum ether, then 5% ethyl acetate/petroleum ether) to give a colorless oil (0.61 g, 67%, 94% ee, determined by chiral GC, 2 ^{o}C/min). NaH (0.46 g, 11 mmol) was added to a solution of the above homoallyl alcohol (1.0 g, 3.9 mmol) in DMF (22 ml) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 10 min, and then PMBBr (1.17 g, 5.81 mmol) was added slowly. The reaction mixture was stirred at the same temperature for 2 h, before saturated aqueous NH_4Cl was added. The mixture was extracted with ether four times and the combined organic fractions were dried over $MgSO_4$. The PMB ether **11** was purified via silica gel flash column chromatography (2%, then 5% ether/petroleum ether) to give a colorless oil (1.3 g, 90%). R_F: 0.5 (ether/petroleum ether, 1:9 v/v); $[\alpha]^{D}_{20}$(deg cm^3 g^{-1} dm^{-1}): +2.33 (c 2.1 g cm^{-3} in DCM);

^{1}H NMR (C_6D_6, 500 MHz) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.96 (m, 1H), 5.11 (ddd, *J* = 1.5, 3.5, 17 Hz, 1H), 5.02 (ddd, *J* = 1.0, 2.0, 10 Hz, 1H), 4.55 (1H, *J* = 10.5 Hz, 1H), 4.48 (d, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.52 (d, *J* = 14.5 Hz, 1H), 3.43 (dd, *J* = 3.5, 9.0 Hz, 1H), 2.32 (m, 1H), 2.25 (m ,1H), 0.91 (s, 9H), 0.88 (s, 3H), 0.86 (s, 3H), 0.040 (s, 3H), 0.036 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 159.0, 137.6, 131.6, 113.7, 82.7, 74.0, 69.8, 55.3, 40.7, 35.6, 26.0, 21.7, 20.2, 18.3, –5.4, –5.5; IR (film):2955, 2931, 2857, 1614, 1514, 1471, 1249, 1172, 1093, 1040, 851, 837, 775 cm^{-1}.



9

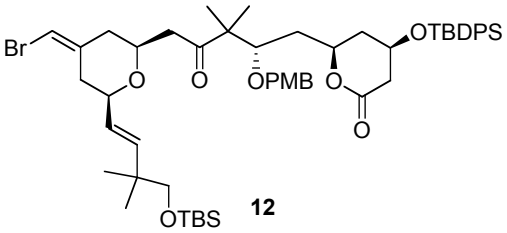
Compound 9: To a solution of PMB ether **11** (1.3 g, 3.4 mmol) in 1,4-dioxane/water (30 ml, 3:1) was added 2,6-lutidine (0.74 g, 6.9 mmol), OsO_4 (0.4 ml, 0.068 mmol, 4% in water) and $NaIO_4$ (2.9 g, 13.6 mmol) at rt. The reaction mixture was stirred at rt for 1.5 h, before water (20 ml) and DCM (40 ml) was added. The mixture was extracted with DCM three times and the combined organic fractions were dried over Na_2SO_4. The known aldehyde **9** was purified via silica gel flash column chromatography (5%, then 10% ether/petroleum ether) to give a colorless oil (1.02 g, 87%). R_F: 0.3 (ether:petroleum ether, 1:9 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +5.9 (c 1.1 g cm^{-3} in DCM); Reported: $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +6.1 (c 1.8 g cm^{-3} in CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, J = 2.0 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.51 (2H), 3.98 (t, J = 6.0 Hz, 1H), 3.80 (s, 3H), 3.52 (d, J = 9.5 Hz, 1H), 3.27 (d, J = 10.0 Hz, 1H), 2.63 (dd, J = 2.0, 6.0 Hz, 2H), 0.91 (s, 9H), 0.89 (s, 3H), 0.85 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 159.2, 130.8, 129.3, 113.8, 77.7, 73.4, 69.3, 55.3, 45.7, 40.4, 26.0, 21.5, 20.2, 18.3, -5.4, -5.5; IR (neat film): 2955, 2857, 1726, 1613, 1514, 1470, 1249, 1092, 1037, 837, 776 cm^{-1}. ^{1}H NMR, ^{13}C NMR and IR are identical to those previously reported.[1]



5

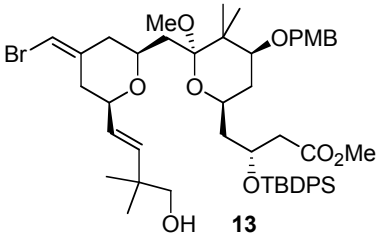
Compound 5: $CpRu(CH_3CN)_3PF_6$ (4.0 mg, 0.0092 mmol) was added to a solution of compound **6** (50 mg, 0.080 mmol) and compound **7** (24.5 mg, 0.069 mmol) in DCM (0.4 ml) at 0 ^oC. The resulting yellow solution was stirred at rt for 12 h. Compound **5** was purified directly via silica gel flash column chromatography (10%, then 15% ethyl acetate/petroleum ether) to give a colorless foam (23.1 mg, 34%; 80% brsm, 45.6 mg **6** + **7** can be recovered).

At a larger scale, compound **6** (969 mg, 1.59 mmol) and compound **7** (471 mg, 1.33 mmol) with $CpRu(CH_3CN)_3PF_6$ (86 mg, 0.199 mmol) in DCM (3 ml), according to the same procedure, gave compound **5** (0.45 g, 35%, 0.19 g, **7** was recovered). R_F: 0.3 (ethyl acetate:petroleum ether, 1:9 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): –21.1 (c 1.27 g cm^{-3} in DCM); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.59 (m, 4H), 7.47-7.44 (m, 2H), 7.43-7.37 (m, 4H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.63 (dd, *J* = 0.5, 16 Hz, 1H), 5.40 (dd, *J* = 7.0, 16 Hz, 1H), 5.26 (s, 1H), 4.55 (d, *J* = 11 Hz, 1H), 4.34 (d, *J* = 11 Hz, 1H), 4.03-3.98 (m, 2H), 3.88-3.80 (m, 2H), 3.73 (m, 1H), 3.73 (s, 3H), 3.25 (s, 2H), 3.00 (dd, *J* = 5.5, 17 Hz, 1H), 2.53 (dd, *J* = 7.0, 18 Hz, 1H), 2.47-2.38 (m, 3H), 2.23 (br d, *J* = 13 Hz, 1H), 1.97 (br dd, *J* = 12, 24 Hz, 2H), 1.90 (ddd, *J* = 2.5, 5.5, 14 Hz, 1H), 1.58-1.55 (m, 2H), 1.48 (dd, *J* = 1.5, 10.5, Hz, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 1.03 (s, 9H), 0.93 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.09 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.3, 170.4, 159.2, 152.9, 139.2, 135.73, 135.69, 133.4, 133.2, 130.7, 130.12, 130.06, 129.6, 128.0, 127.9, 127.7, 123.7, 113.8, 79.4, 79.3, 75.1, 74.6, 73.2, 71.8, 65.2, 55.3, 52.6, 45.3, 45.2, 40.6, 39.7, 38.9, 38.1, 37.9, 30.4, 26.9, 26.0, 24.0, 23.7, 20.9, 20.8, 19.1, 18.3, 0.4, –5.4; IR (film): 2956, 2858, 1744, 1702, 1612, 1514, 1249, 1094, 838 cm^{-1}; HRMS ($C_{57}H_{86}O_8Si_3$): Calc'd. 1005.5528 ($M+Na^+$), Found 1005.5520.



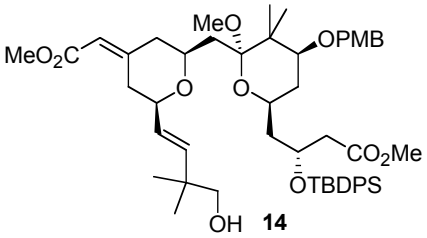
12

Compound 12: NBS (156 mg, 0.876 mmol) was added to a solution of compound **5** (172 mg, 0.175 mmol) in DMF (1.8 ml) at 0 ^{o}C. The resulting solution was stirred in the dark for 3 h, before it was poured into a solution of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with ethyl acetate and the combined organic fractions were dried over Na_2SO_4. Compound **12** was purified via silica gel flash column chromatography (10%, then 15% ethyl acetate/petroleum ether) to give a colorless oil (171 mg, 98%). R_F: 0.5 (ethyl acetate:petroleum ether, 1:4 v/v); $[\alpha]^{D}_{20}$(deg cm^3 g^{-1} dm^{-1}): –13.18 (c 0.72 g cm^{-3} in DCM); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63-7.59 (m, 4H), 7.47-7.43 (m, 2H), 7.41-7.37 (m, 4H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.98 (s, 1H), 5.67 (dd, *J* = 1.0, 16 Hz, 1H), 5.41 (dd, *J* = 6.5, 16 Hz, 1H), 4.56 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.02-3.97 (m, 2H), 3.84-3.74 (m, 3H), 3.73 (s, 3H), 3.26 (s, 2H), 3.03 (dd, *J* = 5.5, 18 Hz, 1H), 2.80 (br d, *J* = 13.5 Hz, 1H), 2.55 (dd, *J* = 7.0, 18 Hz, 1H), 2.47-2.36 (m, 3H), 1.91 (ddd, *J* = 3.5, 5.5, 14 Hz, 1H), 1.88-1.78 (m, 2H), 1.60-1.54 (m, 2H), 1.47 (m, 1H), 1.18 (s, 3H), 1.09 (s, 3H), 1.03 (s, 9H), 0.95 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.1, 170.4, 159.3, 139.8, 139.6, 135.72, 135.67, 133.4, 133.2, 130.6, 130.1, 130.07, 129.5, 127.95, 127.9, 127.2, 113.8, 100.4, 79.5, 78.0, 75.1, 73.7, 73.1, 71.8, 65.2, 55.3, 52.6, 44.9, 40.4, 39.6, 38.9, 38.2, 38.0, 37.1, 30.4, 26.8, 26.0, 23.9, 23.6, 20.9, 20.8, 19.1, 18.4, –5.4; IR (film): 2957, 2858, 1744, 1706, 1612, 1514, 1472, 1250, 1094, 838 cm^{-1}; HRMS ($C_{54}H_{77}O_8BrSi_2$): Calc'd. 1011.4238 (M+Na$^+$), Found 1011.4239.



13

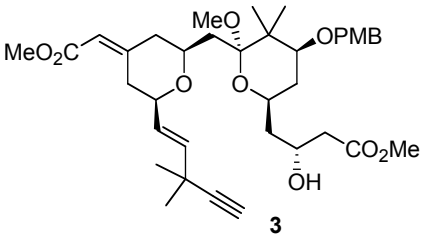
Compound 13: CSA (18 mg, 0.080 mmol) was added to a solution of compound **12** (0.88 g, 0.89 mmol) in MeOH (dry, 18 ml) at 0 ^{o}C. The resulting solution was stirred at rt for 12 h, before it was poured into saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate three times and the combined organic fractions were dried over Na_2SO_4. Compound **13** was purified via silica gel flash column chromatography (15%, then 30% ethyl acetate/petroleum ether) to give a colorless oil (0.76 g, 93%). R_F: 0.2 (ethyl acetate:petroleum ether, 1:4 v/v); $[\alpha]^{D}_{20}$(deg cm^3 g^{-1} dm^{-1}): +27.5 (c 0.85 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.84-7.80 (m, 4H), 7.26-7.21 (m, 6H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.98 (s, 1H), 5.71 (dd, *J* = 1.2, 16 Hz, 1H), 5.52 (dd, *J* = 5.2, 16 Hz, 1H), 4.58 (m, 1H), 4.38 (d, *J* = 11.2, 1H), 4.18 (d, *J* = 11.2 Hz, 1H), 3.71-3.64 (m, 2H), 3.57 (m, 1H), 3.45 (m, 1H), 3.38 (s, 3H), 3.31 (s, 3H), 3.13 (s, 2H), 2.97 (m, 1H), 2.90 (s, 3H), 2.75-2.65 (m, 2H), 2.26 (brd, *J* = 12 Hz, 1H), 2.18 (dd, *J* = 4.8, 16 Hz, 1H), 1.89 (m, 1H), 1.81-1.65 (m, 4H), 1.51 (m, 1H), 1.20 (s, 3H), 1.17 (s, 9H), 1.14 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 171.6, 159.6, 140.8, 138.2, 136.30, 136.26, 134.4, 134.2, 131.8, 130.1, 129.3, 129.2, 128.0, 127.9, 114.0, 104.3, 100.5, 78.1, 77.2, 74.6, 71.4, 71.2, 69.7, 66.5, 54.7, 51.2, 48.0, 44.7, 43.6, 43.5, 42.4, 39.0, 38.2, 37.6, 33.2, 27.1, 23.9, 23.7, 21.1, 19.5, 16.8; IR (film): 3444, 2933, 1738, 1614, 1514, 1248 cm^{-1}; HRMS ($C_{50}H_{69}O_9BrSi$): Calc'd. 943.3792 ($M+Na^+$), Found 943.3801.



14

Compound 14: A solution of DMF/MeOH/Et_3N (4:2:0.06, 23 ml), which was degassed via freeze-pump-thaw technique, was added to a mixture of compound **13** (0.76 g, 0.83 mmol), $PdCl_2(CH_3CN)_2$ (16 mg, 0.062 mmol) and dppf (103 mg, 0.19 mmol) under CO. The resulting solution was stirred vigorously under CO (1 atm) at 80 ^{o}C for 12 h, before it was poured into a brine/water (1:1) solution. The mixture was extracted with ethyl acetate three times and the combined organic fractions were dried over Na_2SO_4. Compound **14** was purified via silica gel flash column chromatography (20%, then 30% ethyl

acetate/petroleum ether) to give a colorless oil (0.62 g, 83%; 90% brsm: ca 85 mg compound **13** was recovered). R_F: 0.35 (ethyl acetate:petroleum ether, 2:3 v/v); $[\alpha]^{D}_{20}$(deg cm^3 g^{-1} dm^{-1}) +22.5 (c 0.80 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 500 MHz) δ 7.84 (m, 4H), 7.25-7.16 (m, 8H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.86 (s, 1H), 5.76 (d, *J* = 16 Hz, 1H), 5.57 (dd, *J* = 5.0, 16 Hz, 1H), 4.60 (m, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 13.5 Hz, 1H), 4.17 (d, *J* = 11.5 Hz, 1H), 3.80 (dd, *J* = 5.0, 11 Hz, 1H), 3.70-3.63 (m, 2H), 3.42 (s, 3H), 3.41 (s, 3H), 3.31 (s, 3H), 3.13 (s, 2H), 2.91 (s, 3H), 2.75 (m, 2H), 2.22-2.16 (m, 2H), 1.98-1.83 (m, 3H), 1.77-1.67 (m, 2H), 1.50 (dt, *J* = 3.5, 12.5 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 9H), 1.14 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 171.6, 166.7, 159.5, 158.0, 138.2, 136.31, 136.28, 135.2, 134.4, 134.2, 131.8, 130.1, 129.4, 129.2, 128.3, 128.2, 114.0, 104.3, 78.1, 78.0, 74.9, 71.5, 71.1, 69.8, 66.6, 54.7, 51.2, 50.6, 48.0, 44.6, 44.2, 43.6, 43.5, 39.4, 38.2, 36.6, 33.1, 30.4, 27.1, 23.8, 23.7, 21.1, 19.5, 16.8; IR (film): 3475 (br), 2952, 2859, 1738, 1718, 1648, 1514, 1430, 1363, 1248 cm^{-1}; HRMS ($C_{52}H_{72}O_{11}Si$): Calc'd. 923.4742 (M+Na$^+$), Found 923.4753.



3

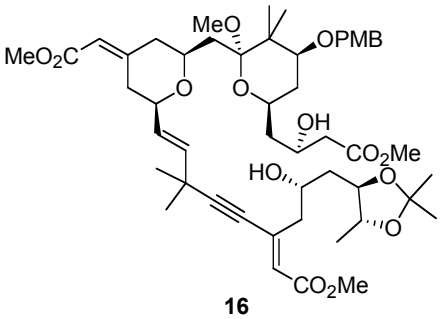
Compound 3: Dess–Martin periodinane (1.17 g, 2.76 mmol) was added to a mixture of coupound **14** (0.83 g, 0.92 mmol) and $NaHCO_3$ (1.5 g, 18.4 mmol) in DCM (18 ml) at 0 ^{o}C. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate and the combined organic fraction was dried over Na_2SO_4. The solvent was removed under vacuum, and aldehyde **15** was purified via silica gel flash column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give a colorless oil (0.73 g, 88%).

The aldehyde was dissolved with freshly distilled MeOH (1.5 ml). Ohira–Bestmann reagent (55.6 mg, 0.289 mmol) and K_2CO_3 (60 mg, 0.435 mmol) were added to above solution at 0 ^{o}C. The resulting mixture was stirred for 1h, before it was poured

into pH 7.0 buffer. The mixture was extracted with ethyl acetate and the combined organic fractions were dried over Na_2SO_4. The terminal acetylene was purified via silica gel flash column chromatography (10%, then 15% ethyl acetate/petroleum ether) to give a colorless oil (125 mg, 97%).

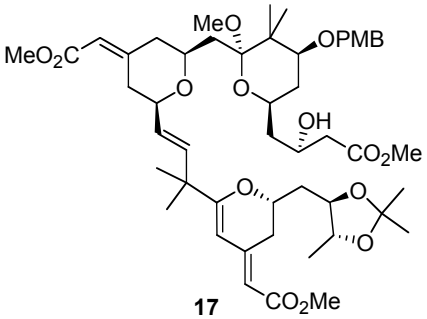
TBAF (1 M buffered with 20 mol % HOAc in THF, 0.24 ml) was added to a solution of the above terminal acetylene (193 mg, 0.216 mmol) in THF (4.0 ml) at rt under N_2. The resulting red solution was stirred at rt for 10 h, before it was poured into pH 7.0 buffer. The mixture was extracted with ethyl acetate and the combined organic fractions were dried over Na_2SO_4. Compound **3** was purified via silica gel flash column chromatography (15%, 30% then 40% ethyl acetate/petroleum ether) to give a colorless oil (127 mg, 90%, brsm 96%, 13 mg starting material was recovered). R_F: 0.35 (ethyl acetate:petroleum ether, 2:3 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +65.7 (c 0.16 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.10 (dd, *J* = 5.2, 15.6 Hz, 1H), 5.85 (s, 1H), 5.79 (dd, *J* = 1.6, 15.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.43 (m, 1H), 4.31 (m, 1H), 4.27 (d, *J* = 11.6 Hz, 1H), 3.96-3.89 (m, 2H), 3.81 (dd, *J* = 4.4, 11.2 Hz, 1H), 3.76 (m, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.30 (s, 3H), 3.13 (s, 3H), 2.34-2.28 (m, 4H), 2.01 (m, 1H), 2.00 (s, 1H), 1.91 (t, *J* = 12 Hz, 1H), 1.79 (dd, *J* = 6.0, 16 Hz, 1H), 1.63 (m, 1H), 1.46-1.36 (m, 4H), 1.26 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 171.7, 166.9, 159.8, 158.1, 136.9, 136.6, 136.5, 134.7, 134.4, 132.0, 130.3, 129.4, 129.0, 128.3, 128.1, 115.0, 114.2, 104.5, 89.7, 78.4, 77.6, 75.2, 71.4, 70.7, 70.0, 66.8, 55.0, 51.4, 50.8, 48.2, 44.9, 44.5, 43.8, 43.7, 39.6, 36.7, 33.7, 33.4, 27.3, 21.4, 19.7, 17.0; IR (film): 3292 (br), 2950, 2858, 1739, 1718, 1651, 1513, 1435, 1247, 1110, 705 cm^{-1}; HRMS ($C_{37}H_{52}O_{10}$): Calc'd. 679.3458 ($M+Na^+$), Found 679.3448.

Compounds **16-18**, the intermediates in the end of an unproductive route, were not fully characterized due to limited availability. Experimental procedures, R_f value, and ^{1}H NMR data were provided for compounds **16** and **17** in the following.



16

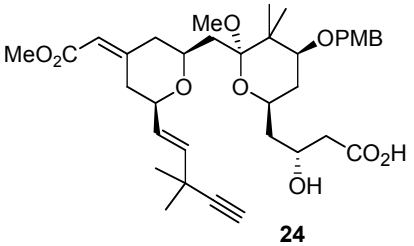
Compound 16: To a mixture of $Pd(OAc)_2$ (3.2 mg, 0.028 mmol) and TDMPP [tris(2,6-dimethoxyphenyl)phosphine] (6.4 mg, 0.028 mmol) was added freshly distilled benzene (0.2 ml). The mixture was stirred at rt for 30 min. The resulting red solution (0.016 ml, ca. 0.0011 mmol) was slowly added a mixture of **3** (7.5 mg, 0.011 mmol) and **4** (2.9 mg, 0.011 mmol) at rt under N_2. The reaction was stirred at rt for 24 h, before it was filtered through a short plug of silica gel and washed with ethyl acetate. The solvent was removed under vacuum and the coupling product **16** was purified via silica gel flash column chromatography (40% then 60% ethyl acetate/petroleum ether) to give a yellow oil (8.4 mg, 81%): R_f: 0.20 (50% ethyl acetace in petroleum ether); ^{1}H NMR (C_6D_6, 400 MHz): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.32 (s,1H), 6.06 (dd, *J* = 4.8, 15.2 Hz, 1H), 5.86 (s, 1H), 5.81 (dd, *J* = 0.8 Hz, 15.2 Hz, 1H), 4.53-4.45 (2H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.33 (d, *J* = 14 Hz, 1H), 4.02-3.89 (3H), 3.82 (dd, *J* = 4.4, 11.2 Hz, 1H), 3.77 (m, 1H), 3.70 (dd, *J* = 6.0, 8.4 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 3.32 (1H), 3.30 (s, 3H), 3.24 (s, 3H), 3.22 (1H), 3.15 (s, 3H), 2.34-2.27 (5H), 2.05 (t, *J* = 12.8 Hz, 1H), 1.95 (t, *J* = 12.4 Hz, 1H), 1.80 (dd, *J* = 5.6, 16 Hz, 1H), 1.73 (t, *J* = 6.0 Hz, 2H), 1.64 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.21 (6H), 1.14 (d, *J* = 6.0 Hz, 3H).



17

Compound 17: To a mixture of $Au(PPh_3)_3Cl$ (10.2 mg, 0.020 mmol) and $AgSbF_6$ (7.0 mg, 0.020 mmol) was added dry DCM (0.5 ml) at rt under N_2. The resulting mixture was

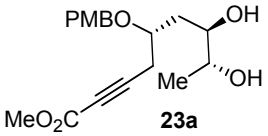
stirred in the dark for 15 min, and a purple precipitate was formed. The supernatant solution (0.025 ml, ca 0.0010 mmol, 20 mol%) was added to a mixture of compound **16** (4.6 mg, 0.0050 mmol) and $NaHCO_3$ (1.3 mg, 0.021 mmol) in DCM/CH_3CN (8:1, 1.5 ml) at 0 ^oC under N_2. The resulting reaction mixture was stirred vigorously in the dark for 6 h. The suspension was poured into saturated aqueous $NaHCO_3$, and the mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. Dihydropyran **17** were isolated via silica gel flash column chromatography (30%, 40% then 50% ethyl acetate/petroleum ether) (3.0 mg, 65%): R_f: 0.65 (40% ethyl acetace in petroleum ether); ^1H NMR (C_6D_6, 400 MHz): δ 7.26 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.00 (d, J = 16 Hz, 1H), 5.85 (s, 1H), 5.75 (s, 1H), 5.66 (dd, J = 4.8, 16 Hz, 1H), 5.47 (s, 1H), 4.47 (d, J = 11.2 Hz, 1H), 4.44 (2H), 4.30 (d, J = 11.2 Hz, 1H), 4.30 (m ,1H), 4.20 (m, 1H), 3.94-3.72 (ca. 6H), 3.48 (s, 3H), 3.42 (s, 3H), 3.36 (s, 3H), 3.34 (m, 1H), 3.31 (s, 3H), 3.26 (m, 1H), 3.17 (s, 3H), 2.61 (m, 1H), 2.33-2.25 (ca. 4H), 2.10-1.75 (ca. 5H), 1.46 (s, 3H), 1.43 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.23 (6H), 1.17 (d, J = 5.6 Hz, 3H).



24

Compound 24: Trimethyltin hydroxide (10 mg, 0.055 mmol) was added to a solution of compound **3** (16.5 mg, 0.025 mmol) in dry DCE (0.7 ml) at rt under N_2. The resulting mixture was stirred at 80 ^oC for 12 h. Compound **24** was purified directly via silica gel flash column chromatography (40%, 60%, 80% ethyl acetate/petroleum ether, then 5%, 10% MeOH in DCM) to give a colorless oil (13.5 mg, 84%). R_F: 0.25 (ethyl acetate:petroleum ether, 4:1 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +70.7 (c 0.07 g cm^{-3} in DCM); ^1H NMR (C_6D_6, 400 MHz) δ 7.26 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.10 (dd, J = 4.8, 15.6 Hz, 1H), 5.88 (s, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.46 (d, J = 11.2 , 1H), 4.37–4.24 (m, 2H), 4.29 (d, J = 11.2 Hz, 1H), 3.94-3.73 (m, 4H), 3.47 (s, 3H), 3.31 (s, 3H), 3.10 (s, 3H), 2.35-2.23 (m, 3H), 2.03 (s, 1H), 2.00-1.88 (m, 2H), 1.75 (dd, J = 5.2,

16 Hz, 1H), 1.59 (br d, J = 13.6 Hz, 1H), 1.44 (t, J = 12.4 Hz, 1H), 1.36-1.28 (m, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz) δ 176.6, 166.8, 159.6, 157.7, 136.9, 131.8, 129.3, 128.7, 127.8, 125.8, 114.8, 114.0, 104.3, 89.5, 78.3, 77.5, 75.2, 71.4, 70.5, 65.5, 64.7, 54.7, 50.8, 48.2, 44.2, 43.7, 42.1, 39.4, 36.5, 33.5, 32.6, 21.0, 16.9; IR (film): 3446 (br), 3296, 2949, 1715, 1651, 1514, 1247, 1088 cm^{-1}; HRMS ($C_{36}H_{50}O_{10}$): Calc'd. 665.3302 (M+Na$^+$), Found 665.3301.



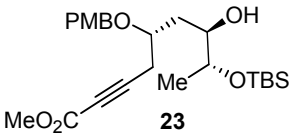
23a

Compound 23a: $Cu(OTf)_2$ (0.05 mg, 0.00014 mmol) was added to a solution of compound **4** (3.7 mg, 0.014 mmol) and $PMBOC(NH)CCl_3$ (5.8 mg, 0.022 mmol) in toluene (0.2 ml) at –10 ^{o}C. The reaction mixture was stirred at –10 ^{o}C for 30 min, before it was quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate three times and the combined organic fractions were dried over Na_2SO_4. The PMB ether was isolated with impurities via silica gel flash column chromatography (10 %, 15% then 20% ethyl acetate/petroleum ether) to give a light yellow oil. The impure PMB ether was then dissolved with freshly distilled MeOH (0.15 ml), and PPTS (3.5 mg, 0.014 mmol) was added. The resulting solution was heated at 60 ^{o}C for 4 h, before it was poured into aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate three times and the combined organic fractions were dried over Na_2SO_4. Compound **23a** was purified via silica gel flash column chromatography (60% ethyl acetate/petroleum ether) to give a colorless oil (4.5 mg, 93% over two steps).

The same reaction was also carried out with $Cu(OTf)_2$ (5.6 mg, 0.016 mmol), **4** (0.4 g, 1.56 mmol), $PMBOC(NH)CCl_3$ (460 mg, 1.72 mmol) and toluene (10 ml) in the first operation, and MeOH (10 ml), and PPTS (377 mg, 1.5 mmol) to give **23a** (223.7 mg, 43% yield over two steps).

R_F: 0.25 (ethyl acetate:petroleum ether, 3:2 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +47.9 (c 0.06 g cm^{-3} in DCM); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.62 (d, J = 11 Hz, 1H), 4.46 (d, J = 11 Hz, 1H), 3.93 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.57 (m, 2H), 2.69 (dd, J = 5.0, 16.5 Hz, 1H), 2.59 (dd, J = 7.0, 17Hz,

1H), 2.60 (br, 1H), 2.32 (br, 1H), 1.75 (dd, J = 7.0 Hz, 2H), 1.17 (d, J = 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.6, 154.0, 129.8, 129.6, 114.1, 85.8, 77.3, 73.4, 72.5, 71.7, 70.9, 37.5, 24.2, 19.4; IR (film): 3410 (br), 2955, 2921, 1712, 1259, 1073, 820 cm^{-1}; HRMS ($C_{18}H_{24}O_6$): Calc'd. 359.1471 (M+Na$^+$), Found 359.1478.

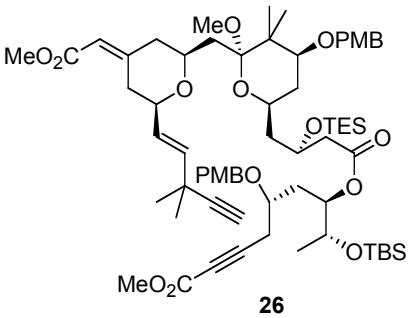


23

Compound 23: TBSOTf (3.5 mg, 0.013 mmol) was added to a solution of compound **23a** (4.5 mg, 0.013 mmol) and 2,6-lutidine (2.1 mg, 0.020 mmol) in DCM (0.13 ml) at –78 ^{o}C under N_2. The reaction mixture was stirred at –78 ^{o}C for 1 h, before it was poured into saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate and the combined organic fractions were dried over Na_2SO_4. Compound **23** was purified via silica gel flash column chromatography (10%, then 15% ethyl acetate/petroleum ether) to give a colorless oil (4.3 mg, 71%).

The same reaction was also carried out with TBSOTf (176 mg, 0.67 mmol), **23a** (223.7 mg, 0.67 mmol) and 2,6-lutidine (107 mg, 1.0 mmol) in DCM (6.6 ml) gave **23** (210 mg, 70% yield, 31.4 mg **23a** was recovered, 82% brsm).

R_F: 0.6 (ethyl acetate:petroleum ether, 3:2 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +23.8 (c 0.48 g cm^{-3} in DCM); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (dd, J = 2.0, 6.8 Hz, 2H), 6.87 (dd, J = 2.0, 6.8 Hz, 2H), 4.61 (d, J = 10.8, 1H), 4.50 (d, J = 10.8, 1H), 3.96 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.62 (m, 1H), 3.56 (m, 1H), 2.63 (dd, J = 5.6, 17.2 Hz, 1H), 2.55 (dd, J = 6.4, 17.2 Hz, 1H), 2.34 (d, J = 5.6 Hz, 1H), 1.67-1.63 (m, 2H), 11.5 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.082 (s, 3H), 0.075 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 154.1, 130.3, 129.7, 113.9, 86.4, 77.3, 73.7, 72.2, 72.0, 55.4, 52.7, 39.3, 30.4, 25.9, 24.9, 20.2, 18.1, –4.1, –4.8; IR (film): 3552 (br), 2954, 2930, 2857, 1716, 1613, 1514, 1253, 1074, 836 cm^{-1}; HRMS ($C_{24}H_{38}O_6Si$): Calc'd. 473.2335 (M+Na$^+$), Found 473.2335.

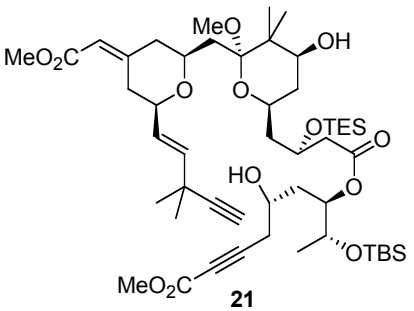


26

Compound 26: To a solution of hydroxyacid **24** (74 mg, 0.12 mmol) in DCM (2.5 ml) was added freshly distilled 2,6-lutidine (62 mg, 0.58 mmol) at –10 ^{o}C, followed by dropwise addition of freshly distilled TESOTf (67 mg, 0.25 mmol). The resulting solution was stirred at the same temperature for 20 min, before poured into pH 7.0 buffer. The mixture was extracted with ethyl acetate five times and the combined organic fractions were dried over Na_2SO_4. The TES ether-acid **22** was purified via **quick** silica gel flash column chromatography (10%, 20% then 30% ethyl acetate/petroleum ether) to give a colorless foam (73 mg, 79%). (Significant decomposition has been observed when slower chromatography was applied.)

To a solution of TES ether-acid **22** (17.0 mg, 0.0225 mmol) in dry toluene (0.5 ml) was added Et_3N (4.8 mg, 0.047 mmol) at rt under N_2, followed by dropwise addition of freshly distilled 2,4,6-trichlorobenzoyl chloride (5.6 mg, 0.024 mmol) at rt. The resulting solution was stirred at rt for 1 h, before a solution of alcohol **23** (10.1 mg, 0.0225 mmol) and DMAP (6.9 mg, 0.056 mmol) in toluene (0.75 ml) was added. The resulting mixture was stirred at rt for another 1h, before poured into pH 7.0 buffer. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The ester **26** was purified via silica gel flash column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give a colorless foam (25 mg, 92%). R_F: 0.35 (ethyl acetate:petroleum ether, 1:4 v/v); $[\alpha]^{D}_{20}$(deg cm^3 g^{-1} dm^{-1}): +62.6 (c 0.11 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 500 MHz) δ 7.41 (d, J =8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.07 (dd, J = 5.0, 15.5 Hz, 1H), 5.93 (s, 1H), 5.79 (dd, J = 1.5, 15.5 Hz, 1H), 5.48 (ddd, J = 2.0, 4.0, 10.5 Hz, 1H), 4.60 (m, 1H), 4.53 (d, J = 10.5, 1 H), 4.47 (d, J = 11.5 Hz, 1H), 4.42 (d, J = 10.5 Hz, 1H), 4.32 (brd, J = 15.5 Hz, 1H), 4.27 (d, J = 11.5 Hz, 1H), 3.97 (m, 1H), 3.88-3.83 (2H), 3.79 (m, 1H),

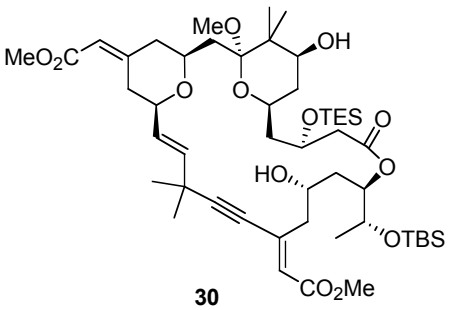
3.67 (m ,1H), 3.45 (s, 3H), 3.33 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.70 (br s, 1H), 2.69 (d, J = 2.0 Hz, 1H), 2.38-2.25 (4H), 2.07-1.89 (6H), 2.01 (s, 1H), 1.84 (dd, J = 5.0, 16 Hz, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.57 (dd, J = 9.5, 19.5 Hz, 2H), 1.29 (s, 3H), 1.22 (s, 3H), 1.21 (s, 6H), 1.18 (d, J = 6.0 Hz, 3H), 1.07 (t, J = 6.5 Hz, 9H), 1.00 (3, 9H), 0.72 (m, 6H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 170.9, 166.7, 159.8, 159.6, 157.7, 153.9, 136.8, 131.7, 130.5, 130.1, 129.3, 128.7, 128.3, 128.1, 127.9, 114.9, 114.1, 114.03, 113.96, 104.5, 89.4, 85.8, 78.5, 77.5, 75.6, 75.1, 73.6, 73.4, 72.1, 71.5, 70.5, 68.7, 67.8, 66.2, 54.74, 54.70, 52.0, 50.6, 48.3, 44.9, 44.3, 43.7, 43.6, 39.5, 36.4, 34.4, 33.8, 33.5, 29.8, 26.01, 25.96, 24.5, 21.2, 18.6, 18.2, 17.0, 7.3, 5.7, –4.6, –4.7; IR (film): 2927, 2240, 1717, 1651, 1614, 1514, 1463, 1377, 1250, 1075 cm^{-1}; HRMS ($C_{66}H_{100}O_{15}Si_2$): Calc'd. 1211.6499 (M+Na$^+$), Found 1211.6484.



21

Compound 21: DDQ (14 mg, 0.063 mmol) was added to a mixture of ester **26** (15.0 mg, 0.0126 mmol) in DCM (2.6 ml) and pH 7.0 buffer (0.26 ml) at 0 ^{o}C, and then the ice-bath was removed. The resulting mixture was stirred for 1.5 h, before another portion of DDQ (7.5 mg, 0.033 mmol) and pH 7.0 phosphate buffer (0.15 ml) was added at rt. The resulting mixture was stirred at rt for 1 h, before saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ was added. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by silica gel flash column chromatography (20%, 30% then 40% ethyl acetate/petroleum ether) to give diol **21** (~5.5 mg, ~46%) and mono-PMB ether **28** (~7.0 mg, ~52%). **28** can be re-subjected to the same DDQ deprotection procedure to give diol **21** in ca 50% yield. The overall yield of diol **21** from ester **26** was ca 72% after two iteration. R_F: 0.35 (ethyl acetate:petroleum ether, 3:7 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): –43.8 (c 0.21 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.09 (dd, J = 5.0, 15.5 Hz, 1H), 5.90 (s, 1H), 5.82 (d, J = 15.5 Hz, 1H), 5.29

(m, 1H), 4.50 (m, 1H), 4.28 (d, J = 13.5 Hz, 1H), 4.01 (dd, J = 4.5, 11 Hz, 1H), 4.00-3.73 (6H), 3.44 (s, 3H), 3.22 (s, 3H), 3.21 (s, 3H), 2.67 (dd, J = 6.5, 10.5 Hz, 2H), 2.36-2.24 (3H), 2.16 (dd, J = 5.5, 17 Hz), 2.02 (s, 1H), 2.02-1.91 (4H), 1.83 (dd, J = 5.5 15.5 Hz, 1H), 1.80-1.74 (3H), 1.59-1.45 (4H), 1.23 (s, 3H), 1.22 (s, 3H), 1.17 (s, 6H), 1.13 (d, J = 6.0 Hz, 3H), 1.04 (t, J = 8.0 Hz, 9H), 0.99 (s, 9H), 0.66 (m, 6H), 0.17 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 171.7, 166.8, 157.8, 154.4, 136.8, 128.7, 128.3, 128.1, 127.9, 125.8, 114.8, 104.4, 89.4, 87.2, 77.5, 75.3, 75.2, 74.3, 70.7, 70.5, 68.6, 67.4, 65.9, 65.8, 52.0, 50.7, 48.2, 44.4, 44.1, 43.6, 42.9, 39.5, 37.0, 36.5, 36.0, 33.5, 30.4, 29.8, 28.0, 26.01, 25.96, 20.9, 18.5, 18.2, 15.8, 7.2, 5.6, 5.5, –4.6, –4.7; IR (film): 3453 (br), 2927, 2240, 1718, 1650, 1614, 1435, 1378, 1254, 1075 cm^{-1}; HRMS ($C_{50}H_{84}O_{13}Si_2$): Calc'd. 971.5348 (M+Na$^+$), Found 971.5354.

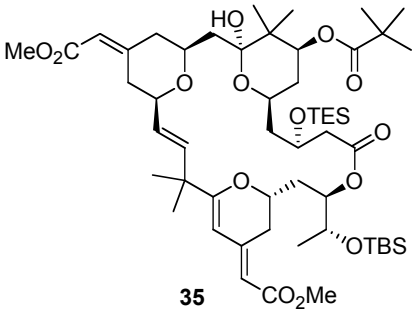


30

Compound 30: To a mixture of $Pd(OAc)_2$ (4.4 mg, 0.02 mmol) and TDMPP [tris(2,6-dimethoxyphenyl)phosphine] (11.2 mg, 0.025 mmol) was added freshly distilled toluene (1 ml). The mixture was stirred at rt for 30 min, and the resulting red solution (0.02 ml, ca. 0.0004 mmol) was slowly added a solution of diyne **21** (3.2 mg, 0.0034 mmol) in freshly distilled toluene (1.6 ml) under N_2. The reaction was stirred at rt for 3 days, before it was filtered through a short plug of silica gel. The solvent was removed under vacuum and the macrocycle **30** was purified via silica gel flash column chromatography (20%, 30% then 40% ethyl acetate/petroleum ether) to give a white paste (1.8 mg, 56%).

The same reaction was also carried out with $Pd(OAc)_2$ (1.1 mg, 0.0048 mmol), TDMPP (1.6 mg, 0.0075 mmol), diyne **21** (45 mg, 0.048 mmol) in toluene (20 ml) to give macrocycle **30** (16.0 mg, 36% yield; 16.7 mg **21** was recover, 57% yield brsm). R_F: 0.35 (ethyl acetate:petroleum ether, 3:7 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): –43.8 (c 0.21 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.32 (s, 1H), 6.12 (dd, J = 3.5, 15.5 Hz, 1H),

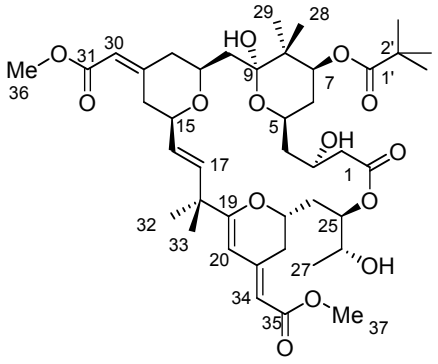
5.89 (d, J = 15 Hz, 1H), 5.73 (s, 1H), 5.34 (d, J = 10.5 Hz, 1H), 4.67 (m, 1H), 4.36 (d, J = 13 Hz, 1H), 4.31 (m, 1H), 4.12 (d, J = 11 Hz, 1H), 4.03-4.00 (2H), 3.91 (m ,1H), 3.86 (m ,1H), 3.40 (s, 3H), 3.38 (t, J = 7.5 Hz, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 3.16 (dd, J = 5.0, 14.5 Hz, 1H), 2.68 (dd, J = 3.0, 16 Hz, 1H), 2.62 (dd, J = 9.0, 16 Hz, 1H), 2.21 (dd, J = 8.0, 16 Hz, 1H), 2.00 (m 1H), 1.92-1.84 (4H), 1.65-1.53 (3H), 1.46 (m, 1H), 1.36-1.29 (2H), 1.24 (s, 3H), 1.22 (s, 3H), 1.19 (d, J = 6.5 Hz, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 1.07 (t, J = 8.0 Hz, 9H), 0.98 (s, 9H), 0.66 (m, 6H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 172.3, 166.5, 157.7, 140.2, 134.9, 129.1, 128.2, 127.9, 125.1, 114.8, 103.5, 102.0, 83.9, 76.4, 75.1, 74.3, 70.0, 68.7, 67.4, 66.9, 65.9, 50.9, 50.6, 49.1, 46.5, 44.6, 43.2, 42.8, 40.6, 40.2, 37.2, 36.8, 36.4, 34.6, 30.2, 29.8, 29.6, 26.0, 20.6, 18.5, 18.3, 16.6, 7.35, 6.0, –4.68, –4.72; IR (film): 3442 (br), 2924, 2853, 1717, 1650, 1614, 1435, 1376, 1256, 1151, 1107 cm^{-1}; HRMS ($C_{50}H_{84}O_{13}Si_2$): Calc'd. 971.5348 ($M+Na^+$), Found 971.5341.



35

Compound 35: To a mixture of $Au(PPh_3)_3Cl$ (10.2 mg, 0.020 mmol) and $AgSbF_6$ (7.0 mg, 0.020 mmol) was added dry DCM (0.5 ml) at rt under N_2. The resulting mixture was stirred in the dark for 15 min, and a purple precipitate was formed. The supernatant solution (0.01 ml, ca 0.0004 mmol) was transferred to a mixture of compound **30** (1.8 mg, 0.0017 mmol) and $NaHCO_3$ (1.8 mg, 0.021 mmol) in DCM/CH_3CN (10:1, 0.5 ml) at 0 ^oC under N_2. The resulting reaction mixture was stirred vigorously overnight, before it was poured into a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (ca 1:1), and then the mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The dihydropyran intermediate (**34**) was purified via **quick** silica gel flash column chromatography (10%, 20% then 30% ethyl acetate/petroleum ether) to give a colorless foam (1.4 mg, 73%).

To a solution of **34** (1.9 mg, 0.0020 mmol) in DCM (0.10 ml) was added DMAP (20 mg, 0.16 mmol) and Piv_2O (18 mg, 0.10 mmol) at rt under N_2. The resulting solution was sealed and stirred at 52 ^oC for 2 h, before it was cooled to rt and MeOH (0.10 ml) was added. The solution was stirred at rt for 10 min, and the solvent was removed under vacuum. The pivalate ester **35** was purified directly via silica gel flash column chromatography (10%, 15% then 20% ethyl acetate/petroleum ether) to give a white paste (1.3 mg, 62%). R_F: 0.30 (ethyl acetate:petroleum ether, 1:9 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +52.6 (c 0.12 g cm^{-3} in DCM); ^{1}H NMR (C_6D_6, 400 MHz) δ 6.06 (d, *J* = 16.2 Hz, 1H), 5.81 (s, 1H), 5.79 (s, 1H), 5.60 (brs, 1H), 5.52 (dd, *J* = 6.0, 15.4 Hz, 1H), 5.33 (dd, *J* = 3.6, 11.5 Hz, 1H), 5.24 (brs, 1H), 5.10 (dd, *J* = 4.7, 11.6 Hz, 1H), 4.48-4.42 (2H), 4.30 (d, *J* = 14 Hz, 1H), 4.20 (m, 1H), 3.81-3.71 (2H), 3.62 (t, *J* = 12 Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 3.39-3.28 (2H), 2.50 (dd, *J* = 10, 16.6 Hz, 1H), 2.30 (t, *J* = 16 Hz, 1H), 2.02-1.93 (2H), 1.80-1.40 (9H), 1.26 (s, 3H), 1.21(s, 3H), 1.18 (s, 9H), 1.11 (t, *J* = 7.7 Hz, 9H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.06 (s, 6H), 1.05 (s, 9H), 0.75-0.69 (m, 6H), 0.26 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz) δ 177.6, 172.3, 168.7, 167.3, 166.1, 156.0, 150.4, 138.4, 127.9, 127.3, 115.3, 109.6, 101.4, 78.8, 75.2, 74.0, 73.9, 73.0, 72.2, 69.2, 68.4, 67.3, 50.6, 50.4, 45.2, 45.0, 42.4, 42.2, 41.1, 39.1, 36.5, 36.3, 34.0, 32.8, 32.1, 30.2, 27.3, 26.4, 26.1, 23.3, 18.4, 17.1, 15.3, 7.3, 5.5, 1.4, –4.7, –4.8; IR (film): 3442 (br), 2954, 2927, 2855, 1729, 1612, 1434, 1376, 1231, 1152, 1044 cm^{-1}; HRMS ($C_{50}H_{84}O_{13}Si_2$): Calc'd. 1041.5761 (M+Na$^+$), Found 1041.5764.



bryostatin 16 (**1**)

Bryostatin 16: To a solution of pivalate ester **35** (1.0 mg, 0.001 mmol) in THF (0.05 ml) was added TBAF (0.005 ml, 0.005 mmol, 1M) at 0 ^oC. The resulting solution was allowed to slowly warm to rt and stirred for 4 h. The reaction mixture was diluted with ethyl acetate and pH 7.0 buffer was added. The mixture was extracted with ethyl acetate

five times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by reverse phase HPLC (RP C-18 column, CH_3CN in H_2O from 65% to 95%) to give **1** as a white paste (0.4 mg, ca 52%). R_F: 0.35 (ethyl acetate:petroleum ether, 4:1 v/v); $[\alpha]^D_{20}$(deg cm^3 g^{-1} dm^{-1}): +81 (c 0.04 g cm^{-3} in MeOH); IR (film): 3359 (br), 2958, 2917, 2849, 1722, 1702, 1605, 1614, 1433, 1375, 1259, 1154, 1099 cm^{-1}; HRMS ($C_{42}H_{62}O_{14}$): Calc'd. 913.4037 (M+Na$^+$), Found 913.4038.

^{1}H NMR (CD_3CN, 600 MHz) (δ, ppm) [reported (CD_3CN, 400 MHz)]

Reported	Found
5.92 (d, *J* = 16 Hz, 1H)	5.92 (d, *J* = 15.8 Hz, 1H)
5.75 (brs, 1H)	5.75 (brs, 1H)
5.50 (brs, 1H)	5.50 (brs, 1H)
5.47 (brs, 1H)	5.47 (brs, 1H)
5.41 (dd, *J* = 7.3, 16 Hz, 1H)	5.41 (dd, *J* = 7.2, 15.9 Hz, 1H)
5.20 (brd, *J* = 11 Hz, 1H)	5.20 (ddd, *J* = 1.8, 4.2, 11.6 Hz, 1H)
5.10 (dd, *J* = 5, 12 Hz, 1H)	5.10 (dd, *J* = 5.1, 11.9 Hz, 1H)
4,16 (m, 1H),* 4.12 (m, 1H)*	4.20-4.08 (m, 2H)*
3.98 (brdd, *J* = 7.3, 12 Hz, 1H)	3.99 (ddd, *J* = 2.0, 7.2, 11.7 Hz, 1H)
3.82 (brt *J* = 11 Hz, 1H), 3.78 (1H)*	
3.76 (1H)*	3.86-3.75 (m, 3H)*
3.68 (1H)*	3.68 (1H)*
3.66 (s, 3H)	3.66 (s, 3H)
3.61 (s, 3H)	3.61 (s, 3H)
3.57 (brd, *J* = 17 Hz, 1H)	3.57 (brd, *J* = 17.1 Hz, 1H)
unreported	3.06 (d, *J* = 9.2 Hz, 1H) [C(3)HO**H**]
unreported	2.91 (d, *J* = 5.8 Hz, 1H) [C(26)HO**H**]
2.47 (2H) *	2.48 (d, *J* = 3.2 Hz, 1H)
	2.46 (d, *J* = 10.1 Hz, 1H)
2.25 (brdd, *J* = 11, 17 Hz, 1H)	2.26 (1H)*
2.23 (1H)*	2.23 (1H)*
2.18 (1H)*	2.18 (1H)*
1.98 (brt, *J* = 11 Hz, 1H)	1.98 (1H)**
1.89 (1H)*	1.89 (1H)*
1.88 (m, 1H)*	1.87 (m, 1H)*
1.86 (1H)*	1.85 (1H)*
1.78 (dd, *J* = 3, 15 Hz, 1H)	1.78 (dd, *J* = 3.4, 15.2 Hz, 1H)
1.67 (m, 1H)*, 1.64 (m, 2H)*	1.68-1.62 (m, 3H)*
1.40 (dt, *J* = 12, 12 Hz, 1H)	1.40 (dt, *J* = 12.1, 12.1 Hz, 1H)
1.21 (s, 3H)	1.21 (s, 3H)
1.19 (s, 3H)	1.19 (s, 3H)
1.16 (s, 9H)	1.16 (s, 9H)
1.10 (d, *J* = 6.6 Hz, 3H)	1.10 (d, *J* = 6.6 Hz, 3H)
0.97 (s, 3H)	0.97 (s, 3H)
0.89 (s, 3H)	0.89 (s, 3H)

*Couplings for these signals were obscured.

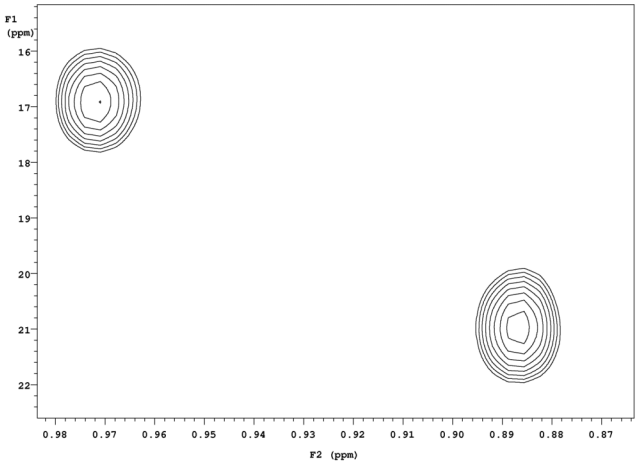
**Overlapping with the peak of CH_3CN, detectable from gCOSY.

^{13}C NMR (CD_3CN, 150 MHz), determined from gHSQC and gHMBC (δ, ppm) [reported (CD_3CN, 100 MHz)]

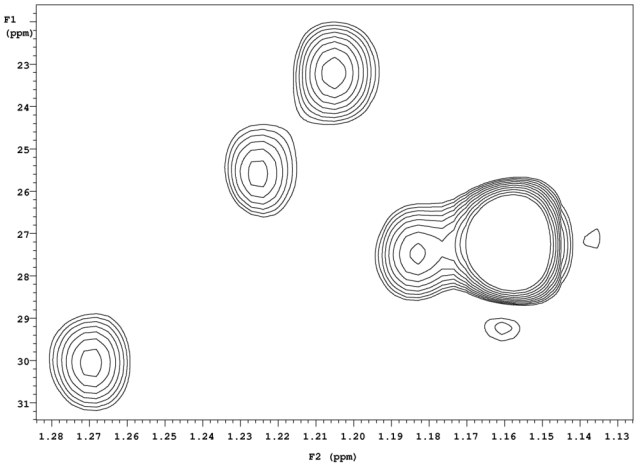
Position	Reported	Found[a]	Found[b]
1	172.8	172.7	172.7
2	42.9	42.7	42.7
3	67.4	67.4	67.4
4	42.5	42.4	42.4
5	66.0	65.8	65.8
6	34.3	34.1	34.1
7	73.5	73.5	73.5
8	41.9	41.9	41.9
9	102.5	102.4	102.4
10	43.0	42.8	42.8
11	74.4	74.2	74.2
12	45.3	45.2	45.2
13	158.9	158.5	158.5
14	36.5	36.3	36.3
15	79.9	79.4	79.4
16	128.2	128.1	128.1
17	139.5	139.4	139.4
18	42.1	42.0	42.0
19	151.9	151.9	169.8 (see 21, 35)
20	101.6	101.5	101.5
21	168.2	168.2	151.9 (see 19, 35)
22	32.8	32.7	32.7
23	73.5	73.2	73.2
24	36.5	36.3	36.3
25	73.5	73.4	73.4
26	69.0	68.9	68.9
27	19.1	18.9	18.9
28	21.3	21.0	17.0 (see 29)
29	17.2	17.0	21.0 (see 28)
30	114.8	114.8	114.8
31	167.8	167.5	167.5
32	27.7	27.5	23.2 (see 33)
33	23.4	23.2	27.5 (see 32)
34	108.9	108.8	108.8
35	170.0	169.8	168.2 (see 19, 21)
36	51.6	51.4	51.4
37	51.2	51.1	51.1
1’	178.5	178.5	178.5
2’	39.6	39.5	39.5
3’-5’	27.5	27.3	27.3

a) Chemical shift according to the original assignment
b) Chemical shift according to our new assignment

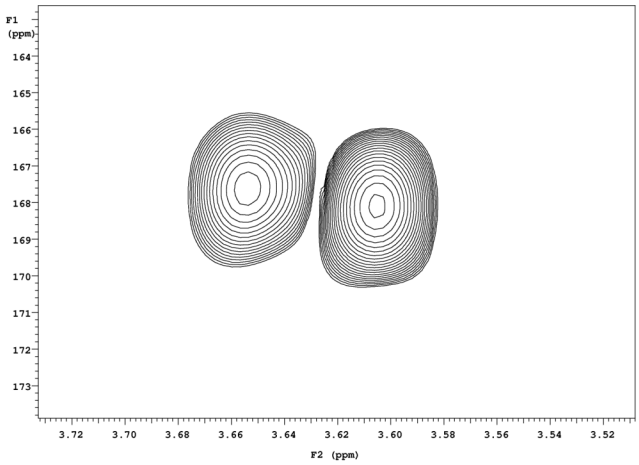
From gHSQC, correlations from 0.97 (H28) to 17.0, and from 0.89 (H29) to 21.0 were observed to support our C28-29 assignment.



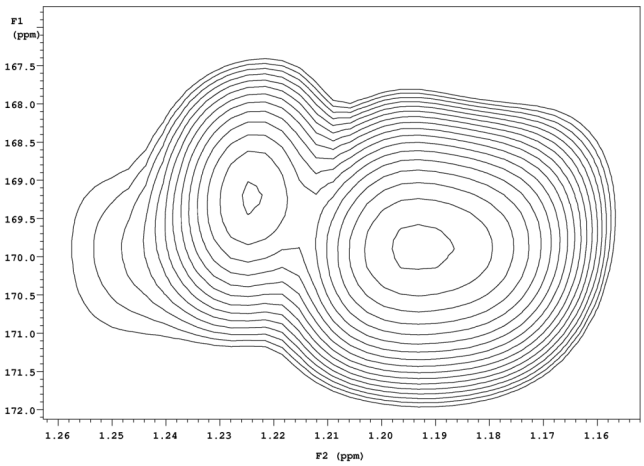
From gHSQC, correlations from 1.21 (H32) to 23.2, and from 1.19 (H33) to 27.5 were observed to support our C32-33 assignment.



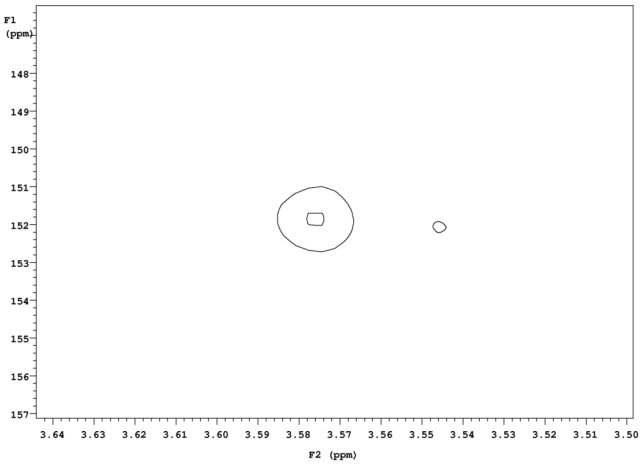
From gHMBC, correlations from 3.61 (H37) to 168.2 was observed to support our C35 assignment.



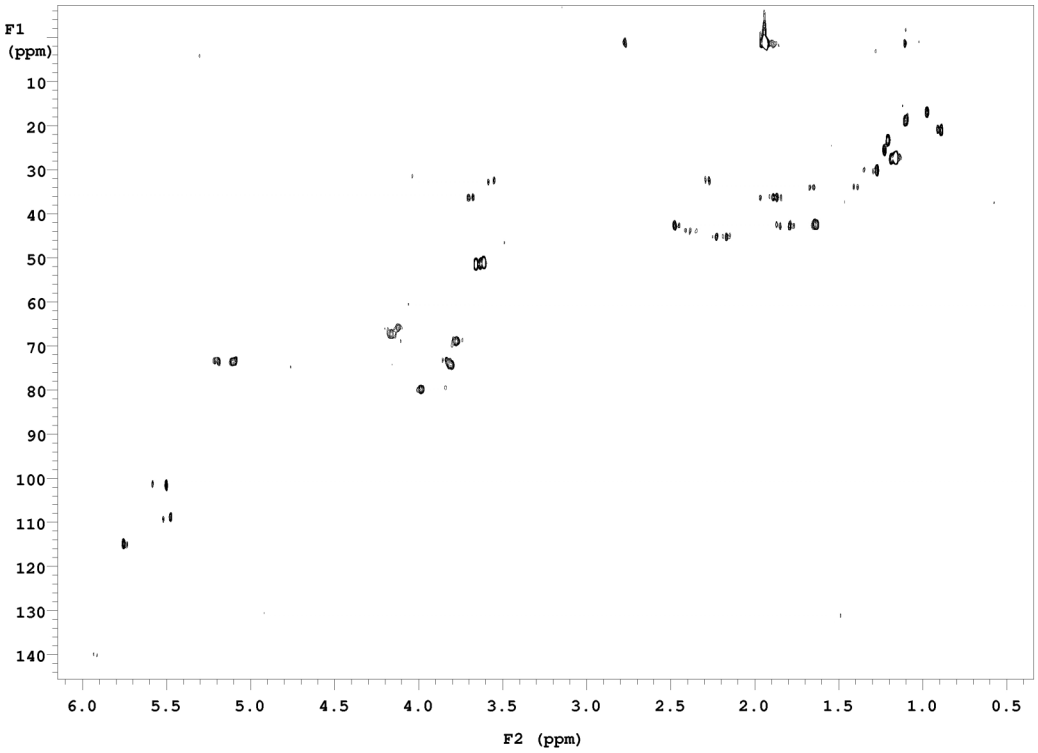
From gHMBC, correlations from 1.21 (H32) and 1.19 (H33) to 169.8 was observed to support our C19 assignment.



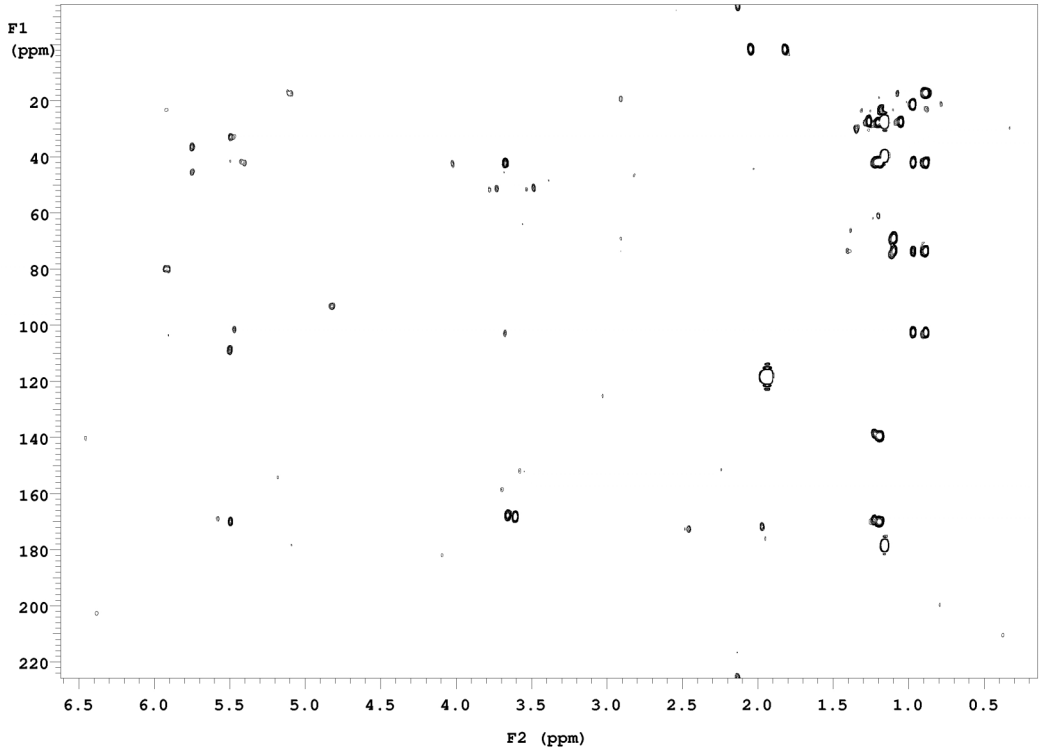
From gHMBC, correlation from 3.57 (H22) to 151.9 was observed to support our C21 assignment.

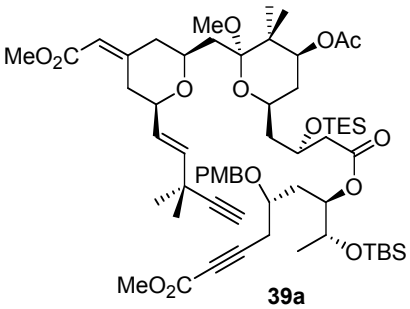


Full gHSQC spectrum:



Full gHMBC spectrum:

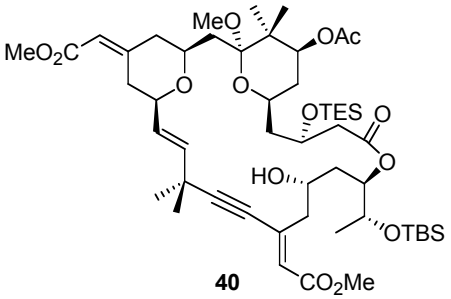




39a

Compound 39a: DDQ (7.7 mg, 0.034 mmol) was added to a mixture of ester **26** (20.0 mg, 0.017 mmol) in DCM (1.7 ml) and pH 7.0 buffer (0.17 ml) at 0 ^{o}C. The resulting mixture was stirred in the dark at 0 ^{o}C for 2 h, before saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ was added. The mixture was extracted with diethyl ether five times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by silica gel flash column chromatography (20%, then 30% ethyl acetate/petroleum ether) to give mono-PMB ether **28** (13.9 mg, 77%).

To a solution of the above mono-PMB ether **28** (13.9 mg, 0.013 mmol) in pyridine (0.1 ml) at 0 ^{o}C was added acetic anhydride (0.1 ml). The resulting solution was stirred at 4 ^{o}C overnight before quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by silica gel flash column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give compound **39a** (13.2 mg, 91%) as a colorless thick oil: R_f: 0.35 (20% ethyl acetace in petroleum ether); $[\alpha]_D$: 42.9 (c 0.55, DCM); ^{1}H NMR (C_6D_6, 400 MHz): δ 7.41 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.08 (dd, *J* = 4.8, 15.2 Hz, 1H), 5.93 (s, 1H), 5.79 (d, *J* = 15.2 Hz, 1H), 5.60 (dd, *J* = 4.8, 12 Hz, 1H), 5.46 (brd, *J* = 9.2 Hz, 1H), 4.53 (d, *J* = 10 Hz, 1H), 4.49 (m, 1H), 4.40 (d, *J* = 10.4 Hz, 1H), 3.97-3.84 (m, 3H), 3.74 (m, 1H), 3.66 (m, 1H), 3.46 (s, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 3.19 (s, 3H), 2.65-2.62 (m, 2H), 2.39-2.21 (4H), 2.07-1.89 (8H), 1.81 (dd, *J* = 5.2, 16 Hz, 1H), 1.74 (m, 1H), 1.69 (s, 3H), 1.56 (dd, *J* = 12, 24 Hz, 1H), 1.23 (s, 3H), 1.22 (s, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.05 (t, *J* = 8.0 Hz, 9H), 0.99 (s, 9H), 0.68 (m, 6H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C-NMR(C_6D_6, 100 MHz) δ 171.1, 170.0, 166.9, 160.1, 157.8, 154.1, 137.1, 130.8, 130.4, 128.9, 115.2, 114.3, 104.6, 89.6, 86.0, 77.7, 75.8, 75.3, 74.0, 73.8, 73.6, 72.4, 70.8, 68.9, 67.9, 66.3, 55.0, 52.2, 50.9, 48.5, 44.6, 43.6, 42.7, 39.5, 36.6, 34.7, 34.1, 33.7, 30.6, 30.03, 30.00, 26.2, 24.7, 21.1, 20.9, 18.8, 18.5, 17.3, 7.5, 5.8, –4.3, –4.5; IR (film) 2954, 1719, 1435, 1366, 1249, 1074 cm^{-1}; HRMS ($C_{60}H_{94}O_{15}Si_2$): Calc'd. 1133.6029 ([M+Na]$^+$), Found 1133.6011.

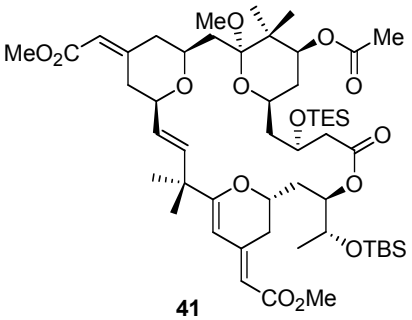


40

Compound 40: DDQ (13.6 mg, 0.12 mmol) was added to a mixture of acetate **39a** (13.2 mg, 0.012 mmol) in DCM (1.2 ml) and pH 7.0 buffer (0.12 ml) at rt. The resulting mixture was stirred for 1.5 h, before another portion of DDQ (13.6 mg, 0.12 mmol) and pH 7.0 buffer (0.12 ml) was added at rt. The resulting mixture was stirred at rt for 2 h,

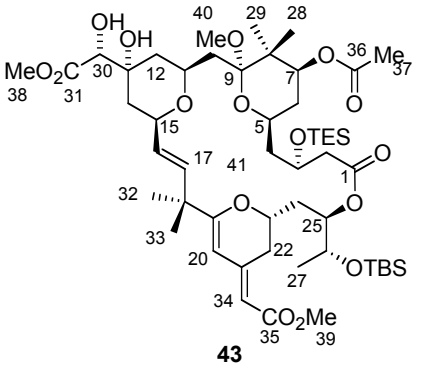
before saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ was added. The mixture was extracted with diethyl ether five times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by silica gel flash column chromatography (20%, then 30% ethyl acetate/petroleum ether) to give alcohol **39** (10.5 mg, 90%) as a colorless thick oil.

To a mixture of $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and TDMPP [tris(2,6-dimethoxyphenyl)phosphine] (7.5 mg, 0.017 mmol) was added freshly distilled toluene (1 ml). The mixture was stirred at rt for 30 min, and part of the resulting red solution (0.2 ml, ca. 0.002 mmol) was transferred to a flask containing toluene (2.0 ml). To the above-diluted catalyst solution was added freshly distilled MeOH (0.1 ml), followed by slow addition of a solution of diyne **39** (20 mg, 0.020 mmol) in freshly distilled toluene (2.0 ml) via syringe pump (0.2 ml/h) for 10 h. The reaction was stirred at rt for another 30 h, before it was purified directly via silica gel flash column chromatography (20% then 30% ethyl acetate/petroleum ether) to give a white foam (13.0 mg, 65%, 2.0 mg **39** was recovered, 72% yield brsm): R_f: 0.35 (20% ethyl acetace in petroleum ether); $[\alpha]_D$: 34.7 (c 0.24, DCM); ^{1}H NMR (C_6D_6, 500 MHz): δ 6.31 (s, 1H), 6.14 (dd, *J* = 3.5, 15.5 Hz, 1H), 5.89 (dd, *J* =2.0, 15.5 Hz, 1H), 5.73 (s, 1H), 5.69 (dd, *J* = 5.0, 12 Hz, 1H), 5.31 (dt, *J* = 3.0, 10 Hz, 1H), 4.64 (m, 1H), 4.36 (d, *J* = 13 Hz, 1H), 4.29 (m, 1H), 4.14 (brd, *J* = 11 Hz, 1H), 4.02-3.89 (m, 3H), 3.41 (s, 3H), 3.39 (m, 1H), 3.27 (s, 3H), 3.15 (m, 1H), 3.14 (s, 3H), 2.60 (d, *J* = 6.0 Hz, 2H), 2.17 (dd, *J* = 8.5, 16 Hz, 1H), 1.99 (ddd, *J* = 2.5, 11, 14 Hz, 1H), 1.93-1.81 (m, 5H), 1.73 (s, 3H), 1.61 (m, 1H), 1.57-1.51 (2H) 1.24 (s, 3H), 1.23 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.17 (s, 3H), 1.06 (s, 3H), 1.04 (t, *J* = 8.0 Hz, 9H), 0.98 (s, 9H), 0.68 (m, 6H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR(C_6D_6, 125 MHz) δ 172.2, 169.7, 166.5, 166.4, 157.5, 140.2, 134.9, 129.2, 128.3, 127.9, 125.0, 114.9, 103.5, 102.0, 83.9, 76.4, 74.8, 74.3, 73.3, 68.7, 67.1, 66.9, 65.6, 50.9, 50.6, 49.1, 46.3, 44.6, 42.7, 42.2, 40.6, 39.9, 36.8, 36.4, 34.6, 34.0, 30.2, 29.9, 29.5, 26.0, 20.7, 20.6, 18.5, 18.2, 17.8, 7.3, 5.9, –4.70, –4.72; IR (film) 3487 (br), 2953, 2929, 1721, 1652, 1614, 1435, 1365, 1238, 1108 cm^{-1}; HRMS ($C_{52}H_{86}O_{14}Si_2$): Calc'd. 1013.5454 ([M+Na]$^+$), Found 1013.5456.



41

Compound 41: To a mixture of $Au(PPh_3)_3Cl$ (10.2 mg, 0.020 mmol) and $AgSbF_6$ (7.0 mg, 0.020 mmol) was added dry DCM (0.5 ml) at rt under N_2. The resulting mixture was stirred in the dark for 15 min, and a purple precipitate was formed. The supernatant solution (0.015 ml, ca 0.0006 mmol) was transferred to a mixture of compound **40** (2.9 mg, 0.0030 mmol) and $NaHCO_3$ (2.4 mg, 0.03 mmol) in DCM/CH_3CN/2,2-dimethoxypropane, (10:1:2, 0.4 ml) at 0 ^oC under N_2. The resulting reaction mixture was stirred vigorously overnight, before it was poured into a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (ca 1:1), and then the mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. Dihydropyran **41** was purified via **quick** silica gel flash column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give a colorless foam (2.4 mg, 83%): R_f: 0.3 (10% ethyl acetace in petroleum ether); $[\alpha]_D$: 42.5 (c 0.17, DCM); ^{1}H NMR (C_6D_6, 500 MHz): δ 6.13 (d, *J* = 15.5 Hz, 1H), 5.74 (s, 1H), 5.73 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.67 (dd, *J* = 5.0, 12 Hz, 1H), 5.61 (s, 1H), 5.46 (dd, *J* = 4.5, 11 Hz, 1H), 5.37 (s, 1H), 4.63 (m, 1H), 4.37 (d, *J* = 13 Hz, 1H), 4.02-3.91 (m, 4H), 3.77 (t, *J* = 12 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.11 (s, 3H), 2.68 (dd, *J* = 5.0, 15 Hz, 1H), 2.42-2.34 (m, 2H), 2.18 (dd, *J* = 8.5, 16 Hz, 1H), 2.05-1.84 (m, 5H), 1.78 (m, 1H), 1.75 (s, 3H), 1.65-1.45 (5H) 1.30 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 9H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.57 (m, 6H), 0.23 (s, 3H), 0.13 (s, 3H); ^{13}C-NMR(C_6D_6, 125 MHz) δ 170.0, 169.8, 169.3, 167.3, 158.2, 150.5, 136.2, 129.1, 128.5, 127.8, 125.0, 114.7, 108.9, 103.2, 100.9, 77.0, 73.8, 73.7, 73.4, 72.4, 68.1, 66.8, 64.7, 50.5, 50.4, 48.2, 44.8, 44.0, 42.7, 42.2, 41.0, 39.7, 37.0, 33.8, 33.7, 32.4, 30.2, 26.0, 25.0, 24.9, 20.72, 20.70, 18.3, 18.0, 17.9, 7.2, 6.0, –4.7; IR (film) 2953, 2929, 1734, 1608, 1614, 1435, 1375, 1245, 1150, 1102 cm^{-1}; HRMS ($C_{52}H_{86}O_{14}Si_2$): Calc'd. 1013.5454 ($[M+Na]^+$), Found 1013.5453.



43

Compound 43: To a mixture of AD-mix-α (17.6 mg) and $KHCO_3$ (13.2 mg, 0.13 mmol) in *t*-BuOH (0.05 ml) and water (0.05 ml) was added $Me_2SO_2NH_2$ (1.0 mg, 0.011 mmol). The resulting mixture was vigorously stirred at rt for 20 minutes, before compound **41** (2.0 mg, 0.0021 mmol) was added at 4 °C. The reaction mixture was stirred at 4 °C for 1 h before being quenched with solid Na_2SO_3. The mixture was stirred for another 30 min before it was extracted with EtOAc. The combined organic phases were concentrated under vacuum and purified by silica gel flash column chromatography (20%, then 30 % EtOAc/ petroleum ether) to give diol **43** (1.4 mg, 70 %) as a thick oil: R_f: 0.30 (30% ethyl acetace in petroleum ether); $[\alpha]_D$: 26.9 (c 0.14, DCM); IR (film): 3380 (br), 2953, 2920, 2851, 1737, 1722, 1655, 1639, 1608, 1461, 1320, 1248, 1150 cm^{-1}; HRMS ($C_{52}H_{88}O_{16}Si_2$): Calc'd. 1047.5509 ($[M+Na]^+$), Found 1047.5529.

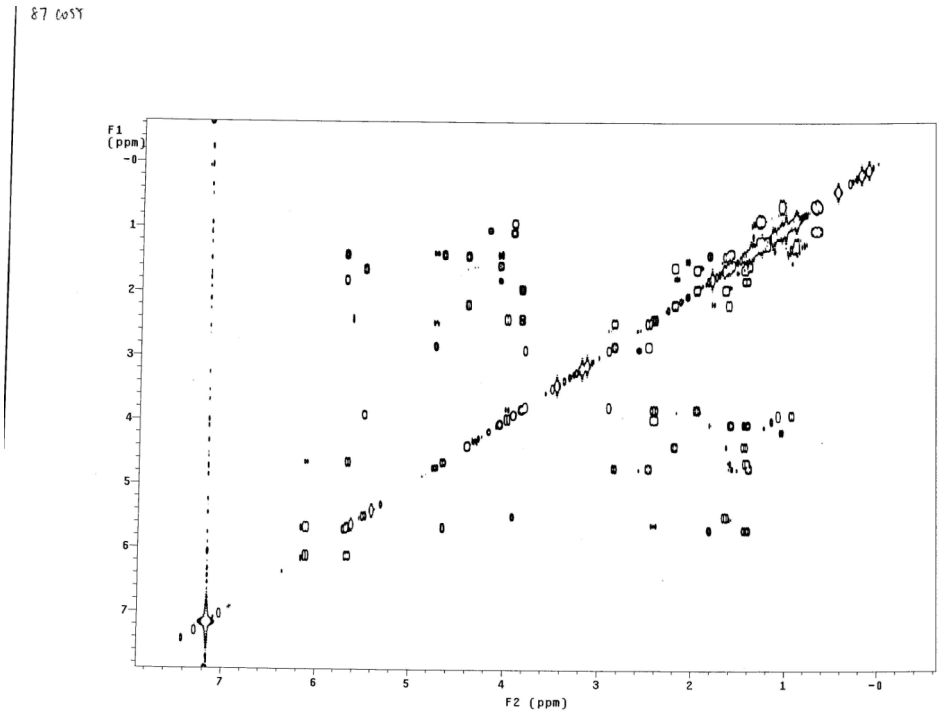
^1H NMR (C_6D_6, 600 MHz) (δ, ppm)

^{13}C NMR (C_6D_6, 150 MHz), determined from gHSQC and gHMBC (δ, ppm)

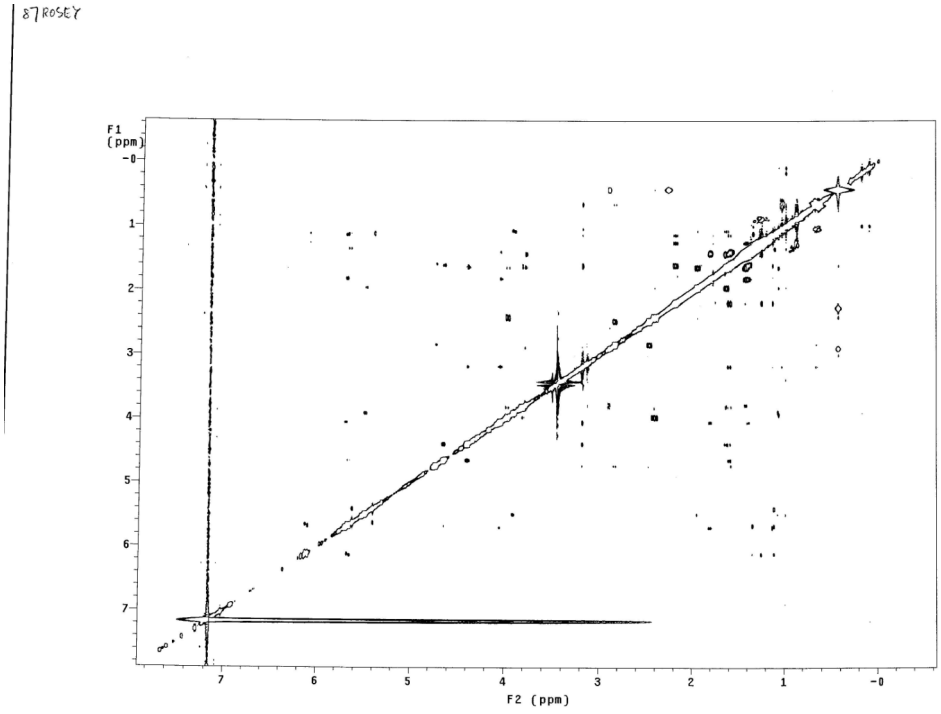
NMR data for compound 43 (note: bryostatin numbering)

Position	^{1}H	^{13}C
1		170.1
2a	2.83 (dd, *J* = 4.8, 14.4 Hz, 1H)	44.2
2b	2.47 (dd, *J* = 9.0, 14.4 Hz, 1H)	
3	4.73 (m, 1H)	66.6
4a	1.58 (1H)	44.8
4b	1.39 (1H)	
5	4.05 (t, *J* = 10.8, 1H)	64.1
6a	1.80 (1H)	33.1
6b	1.41 (1H)	
7	5.69 (dd, *J* = 4.8, 11.4 Hz, 1H)	73.7
8		42.3
9		103.4
10a	1.60 (d, *J* = 15.6 Hz, 1H)	42.3
10b	2.18 (dd, *J* = 9.0, 16.2 Hz, 1H)	
11	4.39 (t, *J* = 10.2 Hz, 1H)	68.2
12a	1.44 (1H)	34.1
12b	1.62 (1H)	
13		72.6
14a	1.58 (1H)	36.4
14b	1.42 (1H)	
15	4.64 (d, *J* = 7.8 Hz, 1H)	71.5
16	5.66 (dd, *J* = 4.8, 15.6 Hz, 1H)	129.1
17	6.11 (d, *J* = 15.6 Hz, 1H)	135.4
18		41.0
19		169.5
20	5.40 (s, 1H)	100.7
21		154.6
22a	2.40 (t, *J* = 14.4 Hz, 1H)	32.3
22b	3.97 (d, *J* = 15.6 Hz, 1H)	
23	3.81 (t, *J* = 12 Hz, 1H)	73.1
24a	1.94 (dd, *J* = 11.4, 14.4 Hz, 1H)	34.2
24b	1.63 (1H)	
25	5.49 (dd, *J* = 4.8, 10.8, 1H)	71.9
26	3.90 (m, 1H)	68.1
27	1.07 (d, *J* = 6.6 Hz, 3H)	18.0
28	1.25 (s, 3H)	18.0
29	1.13 (s, 3H)	20.6
30	3.78 (d?, 1H)	77.5
OH	2.89 (s?, 1H)	
31		173.2
32	1.11 (s, 3H)	25.1
33	1.34 (s, 3H)	24.0
34	5.62 (s, 1H)	108.6
35		167.3
38	3.12 (s, 3H)	51.4
39	3.44 (s, 3H)	49.9
40	3.18 (s, 3H)	47.9
TES:	0.65 (m, 6H)	5.9
TES:	1.03 (9H)	7.1
TBS	0.08 (s, 3H)	–4.8
TBS	0.17 (s, 3H)	–5.1
TBS:	0.99 (s, 9H)	25.8
TBS:		18.3

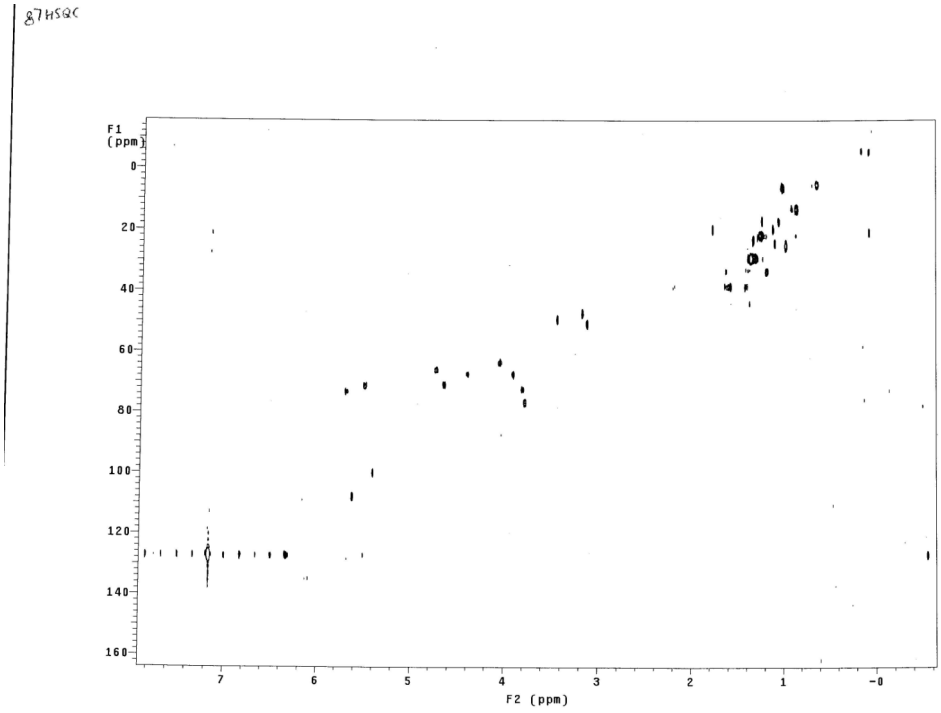
gCOSY of Compound 43



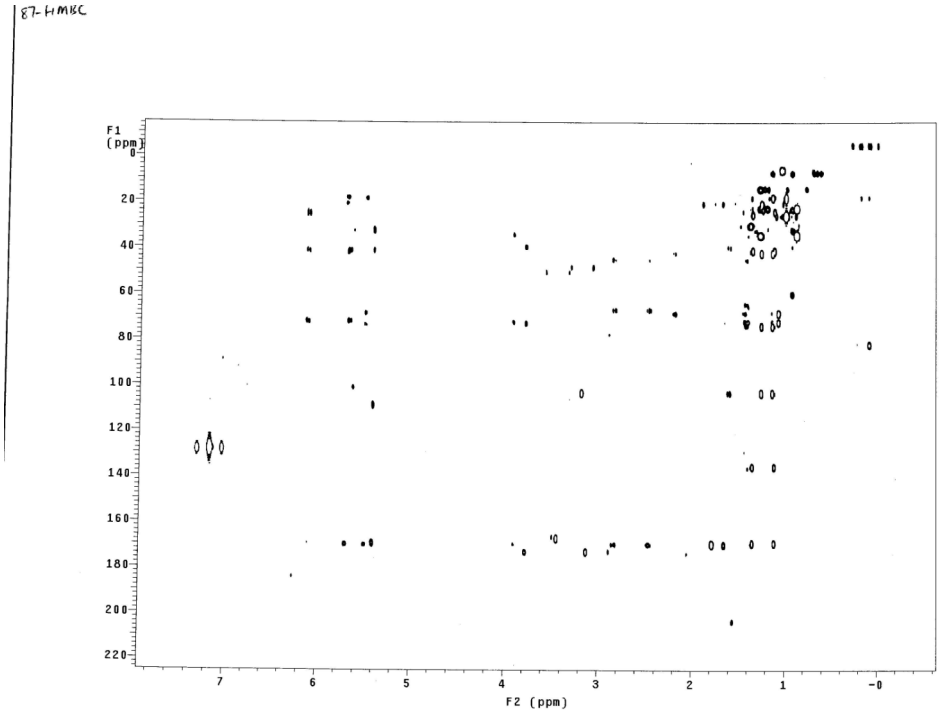
ROSEY of Compound 43

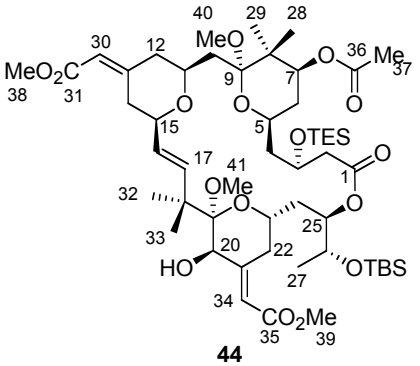


gHSQC of Compound 43



gHMBC of Compound 43





44

Compound 44: UHP (37.6 mg, 0.4 mmol) was added to a solution of MTO (5.0 mg, 0.02 mmol), *N*-methylimidazole (8.2 mg, 0.1 mmol) in freshly distilled MeOH (2 ml) at rt. The resulting solution was stirred at rt for 5 min, during which the color of the reaction turned to yellow. A portion of the above solution (0.026 ml) was added to a solution of **41** (2.5 mg, 0.0026 mmol) in MeOH (0.2 ml) at 0 ^{o}C. The resulting reaction mixture was stirred at ^{o}C for 6h (monitored by TLC) before it was quenched with saturate aqueous $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The crude epoxide product was obtained after the solvent was removed under vacuum. To the above crude epoxide was added a solution of HOAc in MeOH (0.2 ml, obtained from 1 drop of HOAc in 1 ml MeOH) at 0 ^{o}C. The resulting solution was stirred at 0 ^{o}C for 3 h (monitored by TLC), before it was quenched with saturate aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. Compound **44** was purified via silica gel flash column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give a colorless foam (1.7 mg, 64%).

A one-pot protocol: UHP (19 mg, 0.2 mmol) was added to a solution of MTO (5.0 mg, 0.02 mmol), *N*-methylimidazole (8.2 mg, 0.1 mmol) in freshly distilled MeOH (1 ml) at rt. The resulting solution was stirred at rt for 5 min, during which the color of the reaction turned to yellow. A portion of the above solution (0.021 ml, 10 mol% MTO) was added to a solution of **41** (4.3 mg, 0.0044 mmol) in MeOH (0.3 ml) and DCM (0.2 ml) at 0 ^{o}C for 30 min, before another portion of the oxidant (0.022 ml) was added. The resulting reaction mixture was stirred at ^{o}C for 3h (monitored by TLC) before it was cooled to –78 ^{o}C and $ZnCl_2$ (0.020 ml, 1.0 M in ether) was added. The resulting solution was stirred at 4 ^{o}C for 4 h (monitored by TLC), before it was quenched with saturate

aqueous $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. Compound **44** was purified via silica gel flash column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give a colorless foam (2.2 mg, 48%): R_f: 0.33 (15% ethyl acetace in petroleum ether); $[\alpha]_D$: 57.7 (c 0.17, DCM); IR (film): 3400 (br), 2954, 2928, 2856, 1722, 1651, 1378, 1247, 1098 cm^{-1}; HRMS ($C_{53}H_{90}O_{16}Si_2$): Calc'd. 1061.5665 ($[M+Na]^+$), Found 1061.5640.

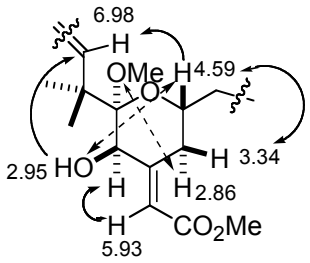
^1H NMR (C_6D_6, 600 MHz) (δ, ppm)

^{13}C NMR (C_6D_6, 150 MHz), determined from gHSQC and gHMBC (δ, ppm)

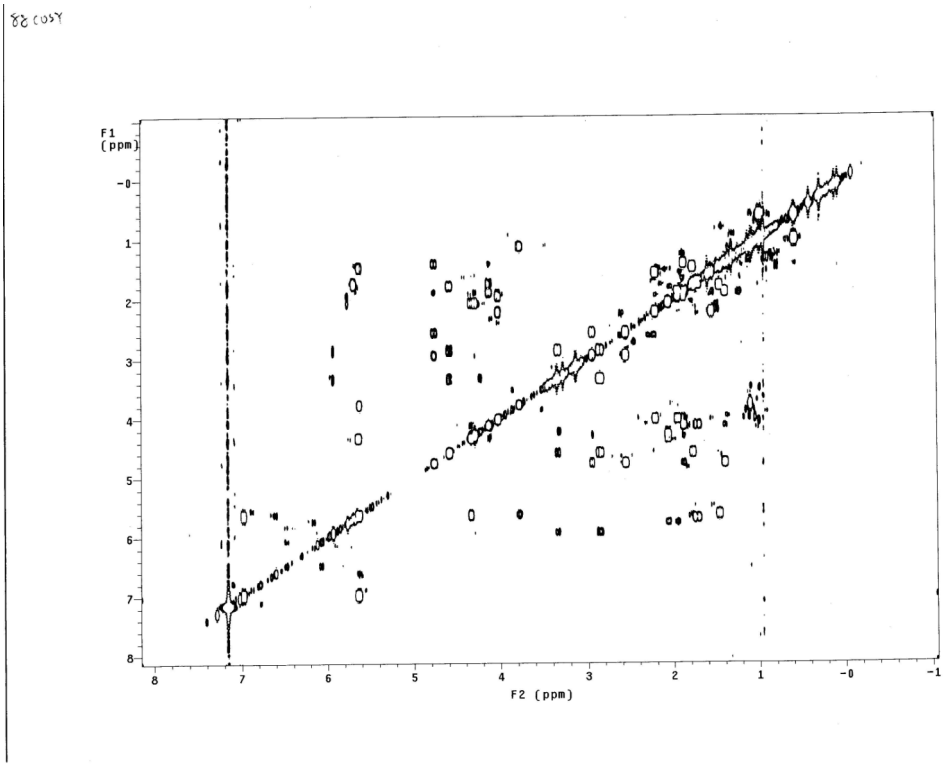
NMR data for compound 44 (note: bryostatin numbering)

Position	^{1}H	^{13}C
1		169.5
2a	2.56 (dd, *J* = 10.8, 14.4 Hz, 1H)	44.2
2b	2.95 (dd, *J* = 3.6, 14.4 Hz, 1H)	
3	4.76 (t, *J* = 10.2 Hz, 1H)	66.9
4a	1.41 (1H)	43.5
4b	1.88 (1H)	
5	4.13 (t, *J* = 10.8, 1H)	64.3
6a	1.75 (1H)	33.2
6b	1.70 (1H)	
7	5.69 (dd, *J* = 5.4, 11.4 Hz, 1H)	73.9
8		42.4
9		103.2
10a	1.56 (d, *J* = 16.2 Hz, 1H)	42.3
10b	2.22 (dd, *J* = 8.4, 16.2 Hz, 1H)	
11	4.02 (t, *J* = 9.0 Hz, 1H)	73.4
12a	1.88 (1H)	42.3
12b	1.94 (t, *J* = 12 Hz, 1H)	
13		157.3
14a	2.06 (t, *J* = 12.6 Hz, 1H)	36.4
14b	4.29 (d, *J* = 13.8 Hz, 1H)	
15	4.34 (t, *J* = 9.6 Hz, 1H)	78.4
16	5.64 (dd, *J* = 8.4, 16.2 Hz, 1H)	128.9
17	6.98 (d, *J* = 16.2 Hz, 1H)	142.0
18		46.4
19		101.5
20	4.29 (s, 1H)	75.1
OH	2.94 (s, 1H)	
21		154.6
22a	2.86 (ddd, *J* = 2.4, 13.2, 19.8 Hz, 1H)	34.4
22b	3.34 (1H)	
23	4.59 (m, 1H)	66.4
24a	1.47 (dd, *J* = 10.8, 14.4 Hz, 1H)	36.6
24b	1.78 (1H)	
25	5.63 (dd, *J* = 6.0, 10.8, 1H)	73.1
26	3.78 (m, 1H)	68.9
27	1.11 (d, *J* = 6.6 Hz, 3H)	18.8
28	1.33 (s, 3H)	17.6
29	1.11 (s, 3H)	20.8
30	5.76 (s, 1H)	114.7
31(or 35)		166.3
32	1.14 (s, 3H)	20.4
33	1.08 (s, 3H)	24.2
34	5.93 (s, 1H)	118.6
35(or 31)		166.4
38(or 39)	3.35 (s, 3H)	50.2
39(or 38)	3.28 (s, 3H)	50.2
40	3.14 (s, 3H)	47.8
41	3.13 (s, 3H)	50.8
TES:	0.60 (m, 6H)	6.2
TES:	1.00 (9H)	7.08
TBS	0.08 (s, 3H)	–1.5
TBS	0.12 (s, 3H)	–5.4
TBS:	0.96 (s, 9H)	25.7
TBS:		18.2

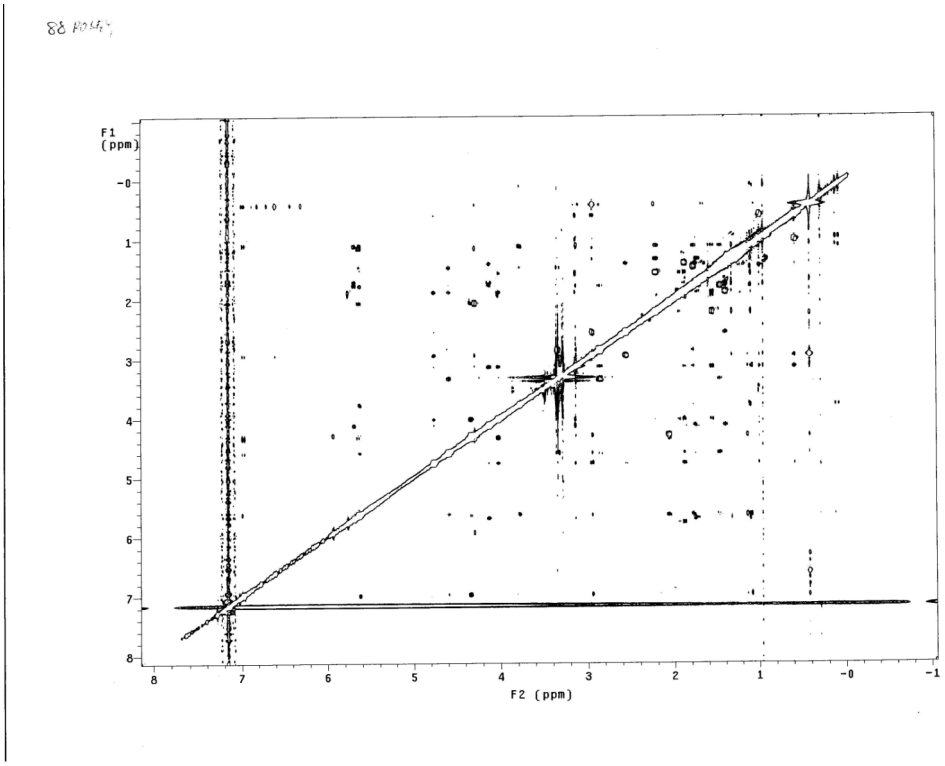
Key ROESY Correlations Observed for 44



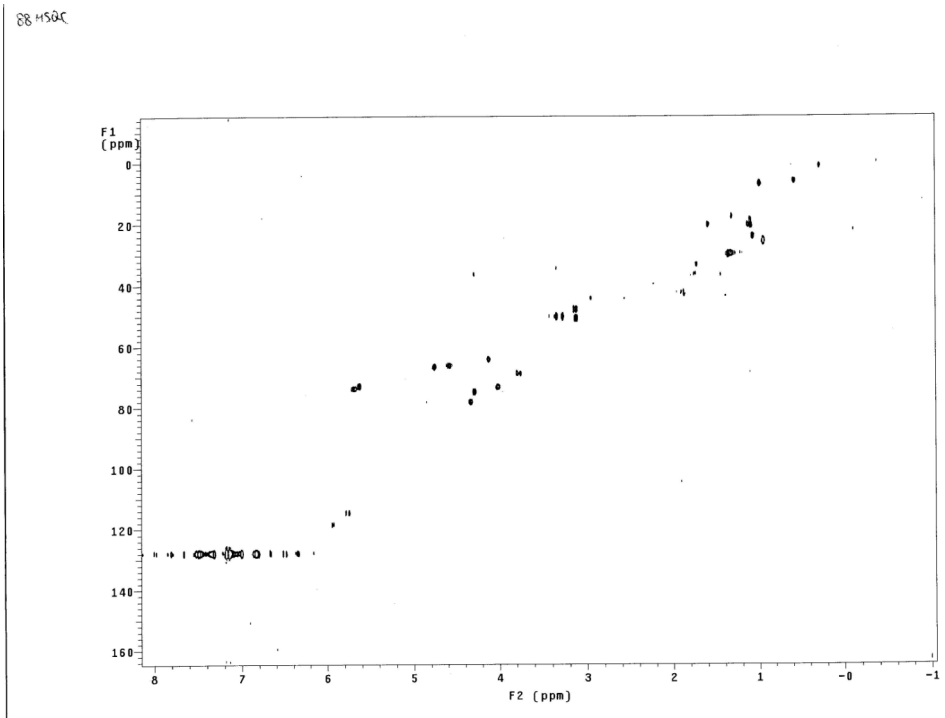
gCOSY of Compound 44



ROSEY of Compound 44

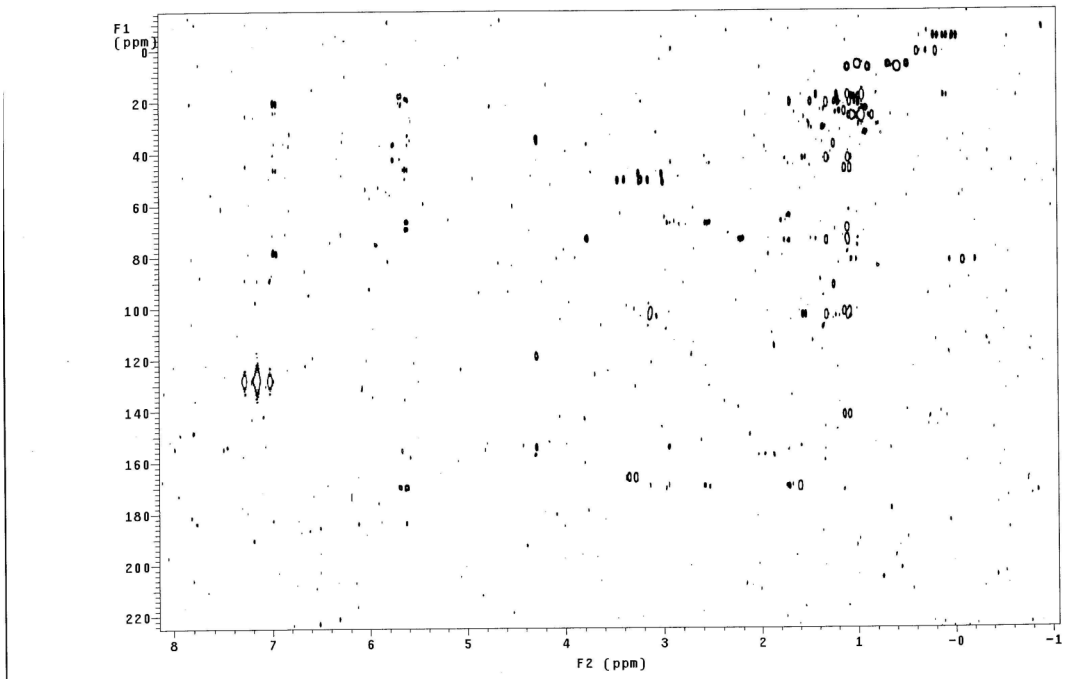


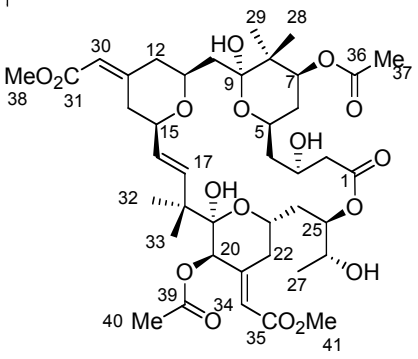
gHSQC of Compound 44



gHMBC of Compound 44

88 HMBC





20-*epi*-bryostatin (**47**)

Compound 47: To a solution of alcohol **44** (1.0 mg, 0.001 mmol) in pyridine (0.15 ml) was added acetic anhydride (0.1 ml) at 0 ^{o}C, followed by DMAP (1.0 mg, 0.008 mmol). The resulting solution was stirred at rt for 4 h, before it was quenched with MeOH (0.1 ml), followed by pH 7.0 Buffer at 0 ^{o}C. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by silica gel column chromatography (10%, then 20% ethyl acetate/petroleum ether) to give compound **46** (ca 1.0 mg) as a colorless thick oil.

To a solution of the above acetate (**46**, ca 1.0 mg) in CH_3CN (0.2 ml) was added aqueous HF (2 drops, conc. 48-53%) at 0 ^oC. The resulting solution was stirred at a warming ice-bath for 2.5 h, before solid K_2HPO_4 and saturated aqueous $NaHCO_3$ were added. The mixture was extracted with ethyl acetate four times and the combined organic fractions were dried over Na_2SO_4. The residue was purified by preparative TLC (60% ethyl acetace in petroleum ether) to give 20-*epi*-bryostatin 7 (**47**) as a white paste (0.5 mg, ca 63% over two steps): R_f: 0.30 (60% ethyl acetace in petroleum ether); $[\alpha]_D$: 27.6 (c 0.07, DCM); IR (film): 3455, 3300(br), 2924, 2853, 1722, 1652, 1374, 1243, 1153, 1077 cm^{-1}; HRMS ($C_{41}H_{60}O_{17}$): Calc'd. 847.3728 ($[M+Na]^+$), Found 847.3741.

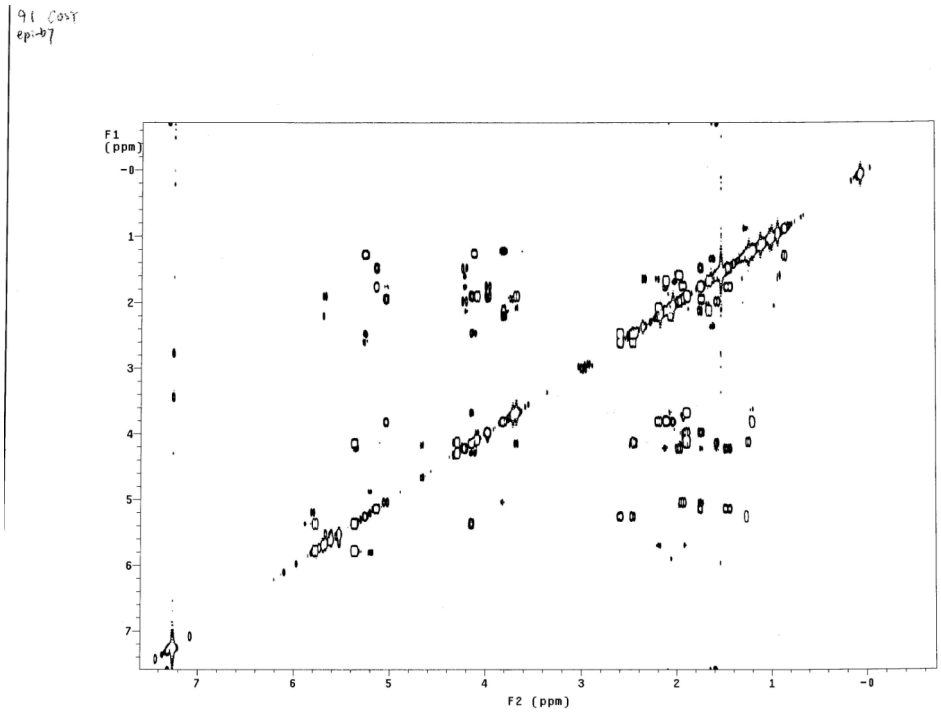
^1H NMR (C_6D_6, 600 MHz) (δ, ppm)

^{13}C NMR (C_6D_6, 150 MHz), determined from gHSQC and gHMBC (δ, ppm)

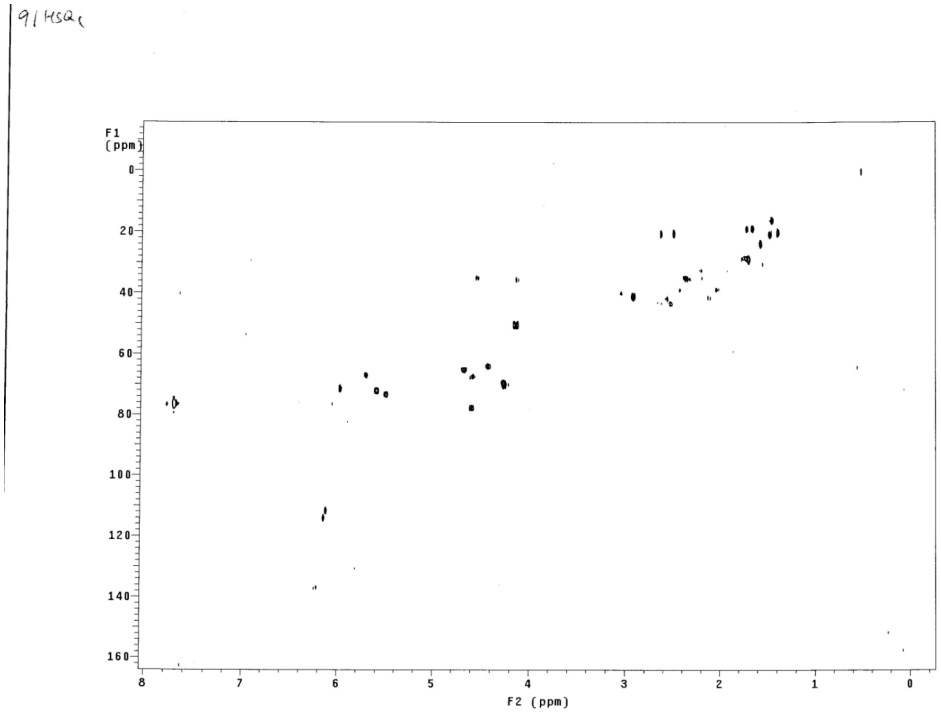
NMR data for compound 47 (note: bryostatin numbering)

Position	^{1}H	^{13}C
1		172.2
2a	2.45 (1H)	41.9
2b	2.48 (1H)	
3	4.13 (1H)	67.9
4a	1.59 (1H)	39.5
4b	1.98 (1H)	
5	4.22 (t, *J* = 10.8 Hz, 1H)	65.8
6a	1.47 (1H)	33.2
6b	1.76 (d, *J* = 11.4 Hz, 1H)	
7	5.14 (dd, *J* = 4.8, 11.4 Hz, 1H)	72.7
8		41.2
9		101.0
10a	1.67 (d, *J* = 15.0 Hz, 1H)	42.2
10b	2.11 (1H)	
11	3.81 (1H)	70.5
12a	2.09 (1H)	43.8
12b	2.20 (1H)	
13		156.0
14a	1.90 (t, *J* = 13.2 Hz, 1H)	36.1
14b	3.68 (1H)	
15	4.14 (1H)	78.3
16	5.36 (dd, *J* = 7.8, 15.6 Hz, 1H)	131.1
17	5.78 (d, *J* = 15.6 Hz, 1H)	137.6
18		45.3
19		101.2
20	5.53(1H)	71.9
21		154.1
22a	1.90 (1H)	35.7
22b	4.09 (d, *J* = 13.2 Hz, 1H)	
23	3.97 (t, *J* = 11.4 Hz, 1H)	64.6
24a	1.75 (1H)	35.6
24b	1.94 (1H)	
25	5.04 (m, 1H)	73.9
26	3.82 (m, 1H)	70.1
27	1.22 (d, *J* = 6.6 Hz, 3H)	19.5
28	0.95 (s, 3H)	20.8
29	1.01 (s, 3H)	16.8
30	5.69 (1H)	114.5
31(or 35)		166.6
32	1.13 (s, 3H)	24.6
33	1.04 (s, 3H)	21.5
34	5.67(s, 1H)	112.1
35(or 31)		166.7
36		170.6
37	2.04 (s, 3H)	21.1
38(or 41)	3.71 (s, 3H)	50.4
39		169.8
40	2.18 (s, 3H)	21.2
41(or 38)	3.40 (s, 3H)	51.0

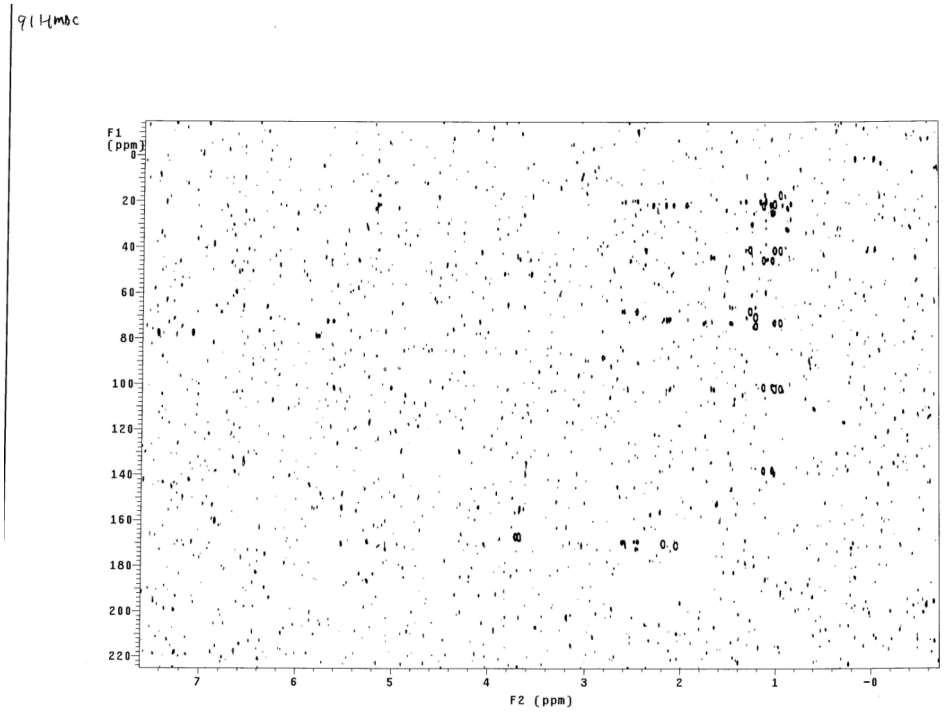
gCOSY of Compound 47



gHSQC of Compound 47



gHMBC of Compound 47



Reference:

[1] Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007**, *129*, 2206-2207