General Experimental Details

Thin layer chromatography was carried out on commercial glass backed silica gel 60 F254 plates. Visualization of chromatograms was accomplished using ultraviolet light (254 nm) and/or heating the plate after staining with either a solution of 20% ceric ammonium molybdate w/v in H_2O or 20% potassium permanganate w/v in H_2O. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 589 nm (sodium D line) and concentrations (c) are reported in g/100 mL. Infrared (IR) spectra were recorded on a Perkin-Elmer 1620 FT-IR spectrophotometer with internal calibration. Only selected characteristic IR absorption data, in wavenumbers (cm^{-1}) are provided for each compound. NMR spectra were recorded using C_6D_6, CD_2Cl_2, $CDCl_3$, CD_3OD or $(CD_3)_2NCDO$ as the solvent. Chemical shifts (δ) are given in parts per million (ppm) from tetramethylsilane (δ = 0) and were measured relative to the signal of the solvent in which the sample was analyzed (C_6D_6: δ 7.16, ^{1}H NMR; δ 128.1, ^{13}C NMR; CD_2Cl_2: δ 5.32, ^{1}H NMR; δ 54.00, ^{13}C NMR; $CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.16, ^{13}C NMR; CD_3OD: δ 3.34, ^{1}H NMR; δ 49.0, ^{13}C NMR; $(CD_3)_2NCDO$: δ 8.03, ^{1}H NMR; δ 163.15, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: number of protons, multiplicity (br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; qu, quintet; m, multiplet; *obs*, obscured), coupling constant and proton assignment where applicable. High resolution mass specta (HRMS) were recorded by the EPSRC Mass Spectrometry Service (Swansea, UK) and the Departmental Mass Spectrometry Service (University Chemical Laboratory, Cambridge) using Electron Impact (EI) and electrospray (ESI) techniques. The parent ion $[M+H]^+$, $[M+NH_4]^+$ or $[M+Na]^+$ is quoted.

Cytotoxicity Assays

Test materials were analyzed as to their effects on the proliferation of a panel of tumor cell lines including both cell lines which are sensitive and resistant to paclitaxel. The NCI-ADR-RES, PANC-1, AsPC-1, and DLD-1 cell lines are maintained in Roswell Park Memorial Institute (RPMI) medium 1640 supplemented with 100 U/mL penicillin 100 μg/mL streptomycin, 60 μg/mL L-glutamine, 18 mM HEPES, 0.05 mg/mL gentamycin and 10% fetal bovine serum (for the PANC-1, AsPC-1 and DLD-1 cell lines the media is also supplemented with 100 μg/mL sodium pyruvate and 2.5 mg/mL glucose). Cell lines are cultured in plastic tissue culture flasks and kept in an incubator at 37 °C in humidified air containing 5% CO_2. To assess the antiproliferative effects of agents against the various cell lines, 200 μL cultures (96-well tissue culture plates, Nunc, Denmark) are first established at 3×10^4 cells/mL and incubated for 24 hr at 37°C in 10% CO_2 in air in order to allow cells to attach. A volume of 100 μL of medium is removed from each test well and 100 μL of medium containing serial, two-fold dilutions of the test agent is added to each well containing tumor cells. Medium without drug is also added to wells containing tumor cells which serve as no drug controls. Positive drug controls are included to monitor drug sensitivity of each of the cell lines. These include varying dilutions of 5-fluorouracil, doxorubicin and paclitaxel. After 72 h exposures, tumor cells are enumerated using 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (M. C. Alley *et al., Cancer Res.* **1988**, *48*, 589) as follows: A volume of 75 μL of warm growth media containing 5 mg/mL MTT is added to each well, cultures returned to the incubator, and left undisturbed for 3 hours. To spectrophotometrically quantitate formation of reduced formazan, plates are centrifuged (900 x g, 5 minutes), culture fluids removed by aspiration, and 200 μL of acidified isopropanol (2 mL concentrated HCl/Litre isopropanol) added per well. The absorbance of the resulting solutions is measured at 570 nm with a plate reader ((NOVOstar, BMG Labtech Inc., Durham, NC). The absorbance of tests wells is divided by the absorbance of drug-free wells, and the concentration of agent that results in 50% of the absorbance of untreated cultures (IC_{50}) is determined by linear regression using Microsoft Excel.

Cell Cycle Analysis

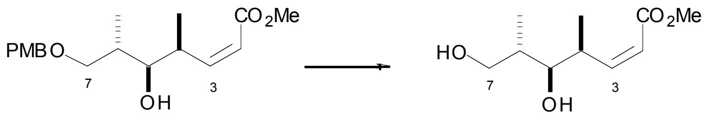
PANC-1 human pancreatic carcinoma cells were used as targets to observe the effects of compounds on the cell cycle. Cell cycle analysis was performed as follows: PANC-1 cells were incubated in tissue culture media (TCM = Roswell Park Memorial Institute (RPMI) medium 1640 supplemented with 100 U/mL penicillin, 100 mg/ mL streptomycin, 60 mg/ mL L-glutamine, 18 mM HEPES, 0.05 mg/ mL gentamicin, 100 μg/ mL sodium pyruvate, 2.5 mg/ mL glucose and 10% fetal bovine serum) at 37 °C in 5% CO_2 in air in the presence or absence of varying concentrations of test compound, methanol (vehicle control) or paclitaxel (positive control) for 24 h. At the end of this incubation, cells were harvested, fixed in ethanol and stained with 0.02 mg/ mL of propidium iodide (P.I.) together with 0.1 mg/ mL of RNAse A. Stained preparations were analyzed on a BD FACSCanto. 10,000 events were collected per sample. Raw histogram data was further analyzed using the DNA analysis software ModFit (Verity, Topsham, ME).

Immunofluorescent Detection of Effects on the Microtubule Matrix in Tumor Cells

PANC-1 human pancreatic carcinoma cells were maintained as described above. Stock cultures of PANC-1 cells were subcultured 1:10 every 3 to 4 days. On day 1, 1.25 x 10^5 PANC-1 cells were sub-cultured in TCM overnight at 37 °C in 5% CO_2 on 22 mm^2 coverslips in 6-well microtiter plates. On day 2, TCM was removed and replaced with various concentrations of natural dictyostatin, synthetic dictyostatin or paclitaxel, in TCM or TCM without drug (control) and incubated overnight at 37 °C in 5% CO_2. On day 3, TCM was removed and cells attached to coverslips were fixed with a 3.7% formaldehyde solution in Dulbecco's PBS for 10 min at room temperature. Cells were permeabilized with a 2% Triton X-100 solution, 2 mL per well, for 5 min at room temperature and washed twice in Dulbecco's PBS prior to staining.

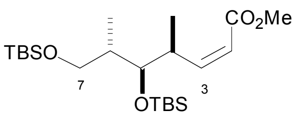
To each well containing cells attached to coverslips. a 2 mL volume of mouse monoclonal anti-alpha-tubulin (Cat # T-5168, Sigma Chemical Co.) diluted 1:1000 in Dulbeccos phosphate buffered saline (D-PBS) was added and the cells incubated at room temperature for 45 min. A 2 mL volume of goat-anti-mouse-IgG-FITC conjugate (Cat # T-5262, Sigma Chemical Co.) diluted 1:1000 in D-PBS was added and the cells incubated at room temperature for 45 min. Coverslips were rinsed three times with sterile distilled water, air-dried and mounted on slides and observed using an Olympus confocal microscope using epifluorescence illumination for the presence of abnormal aster and microtubule formation.

Synthesis of Discodermolide/Dictyostatin Hybrid **5**



8a **8b**

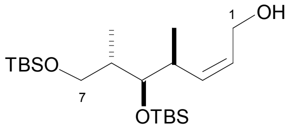
Diol **8b**: To a stirred solution of PMB ether **8a** (11.9 mg, 36.9 μmol, 1.0 eq.) in CH_2Cl_2 (1.5 mL) at –78 °C was added $BCl_3{\cdot}DMS$ (37.0 μL, 73.9 μmol, 2.0 eq.) dropwise. After warming to –40 °C, the mixture was stirred for 35 min, before being quenched by the addition of a saturated solution of NH_4Cl (2 mL) and warmed to r.t. The phases were separated, the aqueous phase extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (20% → 80% EtOAc / P.E.) afforded diol **8b** (6.4 mg, 86%) as a colourless oil. **R*f*** 0.26 (60% EtOAc / hexane); $[\alpha]_D^{20}$ +106.3 (*c* 0.56, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max}= 3360, 2964, 2880, 1719, 1642, 1437, 1408; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.22 (1H, dd, *J* = 11.6, 10.3 Hz, H3), 5.79 (1H, dd, *J* = 11.3, 0.7 Hz, H2), 3.82 (1H, dd, *J* = 10.8, 3.7 Hz, H7a), 3.77 - 3.70 (1H, m, H4), 3.70 (3H, s, OMe), 3.62 (1H, dd, *J* = 10.7, 7.1 Hz, H7b), 3.53 (1H, t, *J* = 6.3 Hz, H5), 3.11 (1H, *br* s, OH), 2.59 (1H, *br* s, OH), 1.85 - 1.77 (1H, m, H6), 1.07 (3H, d, *J* = 6.6 Hz, Me4), 0.95 (3H, d, *J* = 7.0 Hz, Me6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.9, 153.5, 118.6, 80.4, 67.6, 51.2, 37.3, 36.4, 14.1, 14.0; **HRMS** (ES+) Calcd. for $C_{10}H_{19}O_4$ $[M+H]^+$: 203.1278. Found: 203.1280.



8c

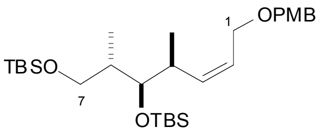
TBS Ether **8c**: To a solution of diol **8b** (11.9 mg, 58.9 μmol, 1.0 eq.) in CH_2Cl_2 (500 μL) at –78 °C was added 2,6-lutidine (33.0 μL, 283 μmol, 4.8 eq.) then TBSOTf (33.0 μL, 141 μmol, 2.4 eq.). After 3 h the reaction was quenched by the addition of a saturated solution of NH_4Cl (1 mL) and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification using flash column chromatography (60% EtOAc / hexane) afforded TBS ether **8c** (18.0 mg, 71%) as a colourless oil. **R*f*** 0.61 (25% EtOAc / hexane); $[\alpha]_D^{20}$ +46.0 (*c* 2.26, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max}= 2954, 2929, 2857, 1726, 1643, 1472, 1463, 1407; **^{1}H NMR**

(500 MHz, $CDCl_3$) δ = 6.17 (1H, dd, J = 16.8, 10.5 Hz, C3), 5.69 (1H, d, J = 11.6 Hz, H2), 3.73 - 3.68 (4H, m, H4, OMe), 3.65 - 3.59 (2H, m, H5, H7a), 3.38 (1H, dd, J = 9.9, 7.5 Hz, H7b), 1.79 (1H, sep, J = 5.7 Hz, H6), 0.99 (3H, d, J = 6.7 Hz, Me4), 0.93 (3H, d, J = 3.9 Hz, Me6), 0.90 (9H, s, $SiC(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$), 0.01 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 166.6, 154.8, 117.5, 77.1, 76.6, 65.1, 51.0, 41.2, 35.6, 26.1, 25.9, 25.7, 15.2, 13.4, –3.9, –4.0, –5.3, –5.4; **HRMS** (ES+) Calcd. for $C_{22}H_{47}O_4Si_2$ $[M+H]^+$: 431.3007. Found: 431.3009.



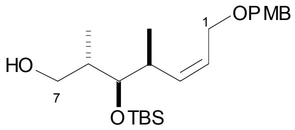
8d

Alcohol **8d**: To a stirred solution of methyl ester **8c** (50.0 mg, 0.116 mmol, 1.0 eq.) in CH_2Cl_2 (0.5 mL) at –78 °C was added DIBALH (255 μL of a 1 M solution in CH_2Cl_2, 0.255 mmol, 2.2 eq.) *via* syringe. The reaction was quenched after 1 h with a saturated solution of sodium potassium tartrate (5 mL) and stirred vigorously for 2 h. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification with flash column chromatography (20% EtOAc / hexane) afforded allylic alcohol **8d** (46.8 mg, 99%) as a clear oil. **R$_f$** 0.47 (20% EtOAc / hexane); $[\alpha]_D^{20}$ +3.2 (c 8.09, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max}= 3316, 2955, 2857, 1472; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.56 (1H, dtd, J = 11.2, 7.1, 0.6 Hz, H2), 5.43 (1H, d, J = 10.2 Hz, H3), 4.21 - 4.17 (1H, m, H1a), 4.15 - 4.10 (1H, m, H1b), 3.70 (1H, dd, J = 12.8, 5.7 Hz, H7a), 3.46 (1H, dd, J = 11.9, 3.7 Hz, H5), 3.38 (1H, dd, J = 7.3, 7.2 Hz, H7b), 2.74 - 2.70 (1H, m, H4), 1.89 - 1.84 (1H, m, H6), 1.65 (1H, *br* s, OH), 0.95 (3H, d, J = 6.7 Hz, Me4), 0.90 (3H, d, J = 6.8 Hz, Me6), 0.89 - 0.88 (18H, m, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, CDCl3) δ = 137.4, 127.3, 77.9, 65.3, 58.6, 40.6, 35.6, 26.2, 26.0, 18.4, 18.3, 17.3, 14.5, –3.8, –3.9, –5.3, –5.4; **HRMS** (ES+) Calcd. for $C_{21}H_{47}O_3Si_2$ $[M+H]^+$: 403.3058. Found: 403.3055.



8e

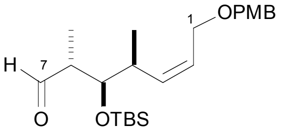
PMB Ether **8e**: To a stirred solution of allylic alcohol **8d** (162 mg, 400 µmol, 1.0 eq.) in THF (1 mL) at r.t. was added PMBTCA (171 mg, 600 µmol, 1.5 eq.) and then Sc(OTf)$_3$ (59.0 mg, 120 µmol, 0.3 eq.). After 45 min the reaction was quenched by the addition of a saturated NaHCO$_3$ solution (3 mL) and the phases separated. The aqueous phase was extracted with Et$_2$O (3 × 4 mL), the combined organic extracts dried (MgSO$_4$) and concentrated *in vacuo*. Flash column chromatography (7% EtOAc / hexane) afforded PMB ether **8e** (159 mg, 76%) as a colourless oil. **R*f*** 0.70 (30% EtOAc / hexane); $[\alpha]_D^{20}$ +15.4 (*c* 7.51, CHCl$_3$); **IR** (neat, cm^{-1}) ν_{max}= 2955, 2929, 2856, 1614, 1513, 1463; **^{1}H NMR** (400 MHz, CDCl$_3$) δ = 7.25 (2H, d, *J* = 6.5 Hz, Ar), 6.87 (2H, d, *J* = 8.3 Hz, Ar), 5.51 - 5.46 (2H, m, H2, H3), 4.43 (2H, s, OCH$_2$Ar), 4.02 (1H, dd, *J* = 12.1, 4.4 Hz, H1a), 4.07 (1H, dd, *J* = 12.1, 4.4 Hz, H1b), 3.79 (3H, s, OMe), 3.63 (1H, dd, *J* = 9.8, 5.8 Hz, H7a), 3.48 (1H, dd, *J* = 11.3, 10.0 Hz, H5), 3.37 (1H, dd, *J* = 13.5, 7.6 Hz, H7b), 2.58 (1H, sex, *J* = 6.8 Hz, H4), 1.81 (1H, sep, *J* = 6.6 Hz, H6), 0.93 (3H, d, *J* = 6.7 Hz, Me4), 0.89 (9H, s, SiC(CH$_3$)$_3$), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.86 (3H, d, *J* = 7.0 Hz, Me6), 0.03 (6H, s, Si(CH$_3$)$_2$), 0.01 (6H, s, Si(CH$_3$)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ = 159.2, 137.8, 130.5, 129.3, 125.0, 113.8, 77.3, 71.9, 65.8, 65.2, 55.3, 41.0, 35.4, 26.1, 25.9, 18.4, 18.3, 16.6, 13.7, –3.8, –4.0, –5.3, –5.4; **HRMS** (ES+) Calcd. for C$_{29}$H$_{55}$O$_4$Si$_2$ [M+H]$^+$: 523.3633. Found: 523.3636.



8f

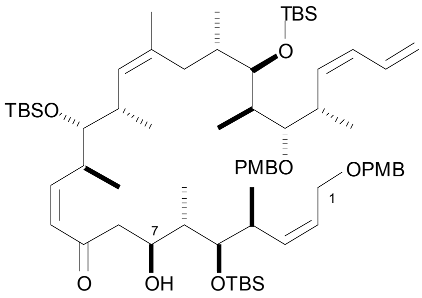
Alcohol **8f**: To a stirred solution of TBS ether **8e** (1.48 g, 3.65 mmol, 1.0 eq.) in CH$_2$Cl$_2$ / MeOH (1.5 : 1, 30 mL) at 0 °C was added CSA (84.6 mg, 0.365 mmol, 0.1 eq.). After 10 min the reaction was warmed to r.t. and stirred for a further 3 h. The reaction was quenched by the addition of a saturated solution of NaHCO$_3$ (20 mL) and the phases separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% EtOAc / hexane) to afford alcohol **8f** (946 mg, 89%) as a colourless oil. **R*f*** 0.36 (15% EtOAc / hexane); $[\alpha]_D^{20}$ +10.9

(*c* 2.38, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max}= 3436, 2956, 2930, 2856, 1613, 1587, 1513, 1463; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.25 (2H, d, *J* = 6.3 Hz, Ar), 6.87 (2H, d, *J* = 8.6 Hz, Ar), 5.56 (1H, dt, *J* = 11.2, 6.5 Hz, H2), 5.43 (1H, t, *J* = 10.9 Hz, H3), 4.43 (2H, s, OCH_2Ar), 4.08 - 4.00 (2H, m, H1a, H1b), 3.79 (3H, s, OMe), 3.65 - 3.60 (1H, m, H7a), 3.60 - 3.52 (1H, m, H7b), 3.44 (1H, dd, *J* = 6.8, 3.5 Hz, H5), 2.72 - 2.68 (1H, m, H4), 2.37 - 2.34 (1H, m, OH), 1.85 - 1.81 (1H, m, H6), 0.98 (3H, d, *J* = 6.9 Hz, Me4), 0.96 (3H, d, *J* = 7.2 Hz, Me6), 0.91 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $Si(CH_3)_2$), 0.07 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 159.2, 136.8, 130.3, 129.4, 125.7, 113.8, 81.0, 72.1, 65.8, 65.2, 55.3, 38.2, 37.2, 26.1, 18.3, 17.6, 16.0, –3.7, –3.8; **HRMS** (ES+) Calcd. for $C_{23}H_{41}O_4Si$ $[M+H]^+$: 409.2769. Found: 409.2770.



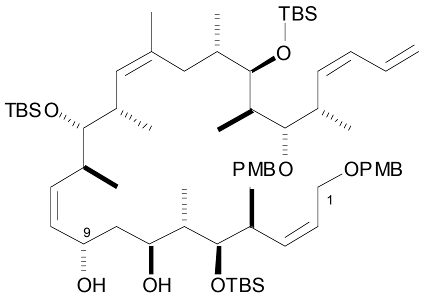
7

Aldehyde **7**: To a stirred solution of alcohol **8f** (67.0 mg, 163 μmol, 1.0 eq) in CH_2Cl_2 (2 mL) at r.t. was added Dess-Martin periodinane (104 mg, 245 μmol, 1.5 eq.). After 45 min the reaction mixture was loaded directly onto a column and purified by flash column chromatography (10% EtOAc / hexane) to afford aldehyde **7** (66.0 mg, 100%) as a colourless oil. **R*f*** 0.24 (15% EtOAc / hexane); $[\alpha]_D^{20}$ –5.3 (*c* 0.60, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max}= 2930, 2856, 1724, 1613, 1514, 1463; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 9.68 (1H, d, *J* = 1.8 Hz, H7), 7.24 (2H, d, *J* = 5.5 Hz, Ar), 6.87 (2H, d, *J* = 5.4 Hz, Ar), 5.59 (1H, dt, *J* = 11.3, 6.4 Hz, H2), 5.31 (1H, t, *J* = 10.7 Hz, H3), 4.40 (1H, d, *J* = 11.6 Hz, $OC\underline{H}_aH_bAr$), 4.41 (1H, d, *J* = 11.6 Hz, $OCH_a\underline{H}_bAr$), 4.05 - 3.98 (2H, m, H1a, H1b), 3.79 (3H, s, OMe), 3.71 (1H, dd, *J* = 7.1, 3.6 Hz, H5), 2.69 - 2.64 (1H, m, H4), 2.54 - 2.50 (1H, m, H6), 1.07 (3H, d, *J* = 7.1 Hz, Me6), 0.99 (3H, d, *J* = 6.7 Hz, Me4), 0.88 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $Si(CH_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 204.1, 159.2, 135.4, 130.3, 129.3, 129.2, 113.8, 78.2, 72.1, 65.7, 55.3, 50.8, 37.0, 25.9, 18.2, 17.4, 11.0, –4.0, –4.1; **HRMS** (ES+) Calcd. for $C_{23}H_{39}O_4Si$ $[M+H]^+$: 407.2612. Found: 407.2614.



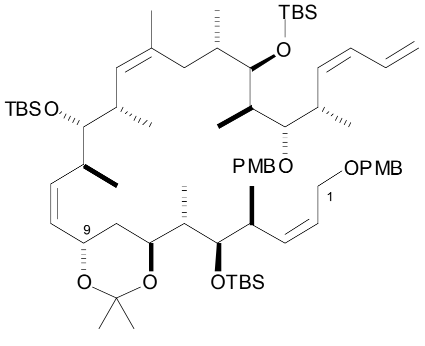
10

Aldol Adduct **10**: To a stirred solution of ketone **6** (1.89 g, 2.50 mmol, 3.0 eq.) in Et_2O (2.1 mL) at – 78 °C was added *c*-Hex_2BCl (584 µL, 2.67 mmol, 3.2 eq.) then immediately Et_3N (407 µL, 2.92 mmol, 3.5 eq.). After warming to 0 °C and stirring for 1 h, the reaction mixture was then re-cooled to –78 °C and aldehyde **7** (339 mg, 0.834 mmol) in Et_2O (2.4 mL) added *via* cannula. After 15 min, the reaction was quenched by the addition of an aqueous pH 7 buffer solution (3 mL) and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (3% EtOAc / hexane) afforded solely aldol adduct **10** (436 mg, 45%) as a pale yellow oil. $\boldsymbol{R_f}$ 0.59 (20% EtOAc / hexane); $[\alpha]_D^{20}$ +61.6 (*c* 2.4, MeOH); **IR** (neat, cm^{-1}) υ_{max} = 3396, 2961, 1613, 1514, 1457, 1301; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.34 (2H, d, *J* = 8.6 Hz, Ar), 7.29 (2H, d, *J* = 8.6 Hz, Ar), 6.86 (2H, d, *J* = 8.6 Hz, Ar), 6.82 (2H, d, *J* = 8.8 Hz, Ar), 6.73 (1H, dt, *J* = 17.0, 11.0 Hz, H25), 6.32 (1H, dd, *J* = 11.4, 9.7 Hz, H11), 6.13 (1H, t, *J* = 11.1 Hz, H24), 5.98 (1H, d, *J* = 11.6 Hz, H10), 5.74 (1H, t, *J* = 10.7 Hz, H23), 5.70 - 5.60 (2H, m, H2, H3), 5.28 (1H, d, *J* = 16.8 Hz, H26a), 5.15 (1H, d, *J* = 9.5 Hz, H26b), 4.97 (1H, d, *J* = 10.3 Hz, H15), 4.61 (1H, d, *J* = 10.6 Hz, ArC$\underline{H}_a$H$_b$O), 4.57 (1H, d, *J* = 10.6 Hz, ArCH$_a\underline{H}_b$O), 4.43 (1H,d, *J* = 11.6 Hz, ArC$\underline{H}_a$H$_b$O), 4.40 (1H, d, *J* = 11.6 Hz, ArCH$_a\underline{H}_b$O), 4.35 - 4.27 (1H, m, H7), 4.14 (1H, dd, *J* = 11.7, 5.2 Hz, H1a), 4.05 (1H, dd, *J* = 11.8, 5.0 Hz, H1b), 3.97 - 3.89 (2H, m, H5, H12), 3.67 (1H, d, *J* = 2.9 Hz, H19), 3.63 (1H, t , *J* = 4.1 Hz, OH), 3.49 (1H, dd, *J* = 8.0, 2.8 Hz, H13), 3.38 (1H, dd, *J* = 7.4, 3.8 Hz, H21), 3.34 (3H, s, ArOMe), 3.32 (3H, s, ArOMe), 3.14 - 3.10 (1H, m, H22), 2.86 - 2.81 (1H, m, H4), 2.62 - 2.59 (1H, dd, *J* = 17.1, 2.1 Hz, H8a), 2.60 - 2.52 (1H, m, H14), 2.40 (1H, dd, *J* = 17.4, 9.3 Hz, H8a), 2.22 (1H, t, *J* = 12.5 Hz, H17a), 2.06 - 2.02 (1H, m, H20), 1.97 - 1.92 (2H, m, H6, H18), 1.81 (1H, d, *J* = 11.4 Hz, H17b), 1.68 (3H, s, Me16), 1.28 (3H, d, *J* = 6.8 Hz, Me20), 1.17 (6H, d, *J* = 6.1 Hz, Me12, Me22), 1.10 - 0.92 (36H, m, Me4, Me6, Me14, 3 × $SiC(CH_3)_3$), 0.88 (3H, d, *J* = 7.1 Hz, Me6), 0.21 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 201.2, 159.6, 159.5, 137.5, 135.4, 134.7, 132.7, 132.5, 131.3, 131.1, 130.8, 129.4, 129.2, 125.9, 125.4, 117.7, 113.9, 84.7, 80.8, 77.8, 75.2, 72.1, 72.1, 69.3, 65.9, 54.5, 48.6, 44.8, 40.4, 38.5, 37.8, 36.5, 35.9, 35.6, 35.5, 26.4, 26.3, 26.1, 25.9, 22.9, 18.7, 18.6, 18.5, 18.3, 17.9, 17.8, 17.6, 14.8, 11.8, 11.0, –3.1, –3.3, –3.5, –3.9, –4.0, –4.2; **HRMS** (ES+) Calcd. for $C_{68}H_{116}O_9Si_3Na$ $[M+Na]^+$: 1183.7819. Found: 1183.7786.



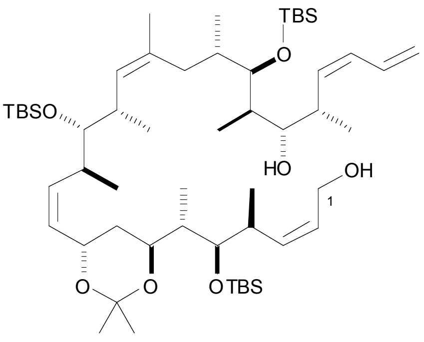
10a

Diol **10a**: To a solution of β-hydroxyketone **10** (9.7 mg, 8.5 μmol, 1.0 eq.) in CH_2Cl_2 (750 μL) at 0 °C was added (*R*)-methyl-oxazaborolidine (8.5 μL, 8.5 μmol of 1 M solution in toluene, 1.0 eq.) then BH_3·THF (8.5 μL, 8.5 μmol of 1 M solution in THF, 1.0 eq.). After 1 h another equivalent of (*R*)-methyl-oxazaborolidine (8.5 μL, 8.5 μmol of 1 M solution in toluene, 1.0 eq.) and BH_3·THF (8.5 μL, 8.5 μmol of 1 M solution in THF, 1.0 eq.) was added. After 3 h at 0 °C, the reaction was quenched by the addition of MeOH (1 mL) and concentrated *in vacuo*. The crude material was evaporated from MeOH (1 mL) three times before purification using flash column chromatography (10% → 20% EtOAc / hexane) affording 1,3-*anti* diol **10a** (6.0 mg, 62%) and the corresponding 1,3-*syn* diol (2.0 mg, 21%) as colourless oils. $\boldsymbol{R_f}$ 0.32 (20% EtOAc / hexane); $[\alpha]_D^{20}$ +49.7 (*c* 0.68, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3477, 2957, 2930, 2856, 1614, 1515, 1462, 1375; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.32 (2H, d, *J* = 8.6 Hz, Ar), 7.30 (2H, d, *J* = 8.6 Hz, Ar), 6.84 (4H, t, *J* = 11.4 Hz, Ar), 6.73 (1H, dt, *J* = 16.8, 10.4 Hz, H25), 6.11 (1H, t, *J* = 11.0 Hz, H24), 5.71 (1H, t, *J* = 10.6 Hz, H2), 5.69 (1H, t, *J* = 11.2 Hz, H23), 5.66 - 5.64 (2H, m, H10, H11), 5.57 (1H, t, *J* = 10.4 Hz, H3), 5.26 (1H, d, *J* = 16.9 Hz, H26a), 5.19 (1H, d, *J* = 10.3 Hz, H15), 5.13 (1H, d, *J* = 10.1 Hz, H26b), 4.91 (1H, *br* s, H9), 4.60 (1H, d, *J* = 10.6 Hz, ArC$\underline{H}_a$H$_b$O), 4.54 (1H, d, *J* = 10.6 Hz, ArCH$_a\underline{H}_b$O), 4.47 (1H, d, *J* = 11.5 Hz, ArC$\underline{H}_a$H$_b$O), 4.41 (1H, d, *J* = 11.5 Hz, ArCH$_a\underline{H}_b$O), 4.17 (1H, dd, *J* = 12.2, 10.1 Hz, H1a), 4.04 (1H, dd, *J* = 12.2, 10.1 Hz, H1b), 4.10 (1H, t, *J* = 8.5 Hz, H7), 3.80 (1H, dd, *J* = 6.4, 3.4 Hz, H5), 3.65 (1H, t, *J* = 4.6 Hz, H19), 3.46 (1H, *br* s, OH), 3.41 (1H, dd, *J* = 6.3, 4.6 Hz, H13), 3.36 (1H, dd, *J* = 6.8, 4.2 Hz, H21), 3.33 (3H, s, ArOMe), 3.32 (3H, s, ArOMe), 3.16 - 3.09 (1H, m, H22), 3.03 - 2.96 (1H, m, H12), 2.90 - 2.82 (1H, m, H4), 2.74 - 2.67 (1H, m, H14), 2.58 (1H, *br* s, OH), 2.32 (1H, t, J = 12.5 Hz, H17a), 2.08 - 1.98 (3H, m, H6, H18, H20), 1.91 - 1.86 (2H, m, H8a, H17a), 1.77 - 1.72 (1H, m, H8b), 1.73 (3H, s, Me16), 1.26 (3H, d, J = 6.9 Hz, Me20), 1.17 (3H, d, J = 6.9 Hz, Me14), 1.15 (3H, d, J = 6.5 Hz, Me22), 1.13 (3H, d, J = 6.6 Hz, Me12), 1.12 (3H, d, J = 6.9 Hz, Me4), 1.09 (9H, s, $SiC(CH_3)_3$), 1.05 (9H, s, $SiC(CH_3)_3$), 1.00 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, d, J = 6.1 Hz, Me18), 0.94 (3H, d, J = 7.3 Hz, Me6), 0.21 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.15 (6H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 159.55, 159.50, 137.0, 135.0, 133.6, 133.2, 132.8, 132.7, 131.4, 131.2, 130.8, 129.37, 129.35, 126.1, 125.6, 117.6, 113.90, 113.87, 84.7, 81.2, 79.1, 77.6, 75.0, 74.8, 72.2, 69.3, 65.9, 54.58, 54.56, 44.5, 42.1, 40.4, 37.4, 37.0, 36.8, 35.6, 35.5, 30.2, 26.4, 26.3, 26.1, 22.9, 19.0, 18.7, 18.6, 18.3, 18.1, 17.7, 14.2, 14.0, 11.3, –3.0, –3.1, –3.2, –3.7, –3.9, –4.2; **HRMS** (ES+) Calcd. for $C_{68}H_{118}O_9Si_3Na$ $[M+Na]^+$: 1185.7976. Found: 1185.7975.



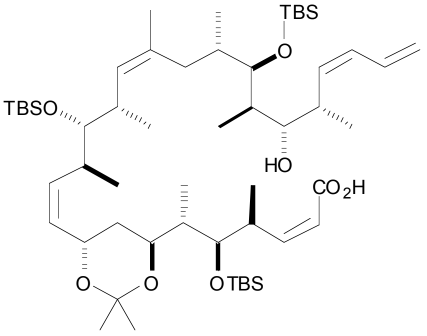
10b

Acetonide **10b**: To a stirred solution of diol **10a** (29.3 mg, 25.2 μmol, 1.0 eq.) in dimethoxypropane (1 mL) at r.t. was added a crystal of PPTS. After 2 h, the solvent was removed *in vacuo* and the product purified using flash column chromatography (10% EtOAc / hexane) to yield acetonide **10b** (29.5 mg, 97%) as a colourless oil. ***R$_f$*** 0.53 (10% EtOAc / hexane); $[\alpha]_D^{20}$ +35.8 (*c* 0.15, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2956, 2929, 2857, 1613, 1514, 1462; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.31 (2H, d, J = 8.5 Hz, Ar), 7.29 (2H, d, J = 8.9 Hz, Ar), 6.85 (2H, d, J = 8.4 Hz, Ar), 6.82 (2H, d, J = 8.4 Hz, Ar), 6.71 (1H, dt, J = 16.8, 10.6 Hz, H25), 6.11 (1H, t, J = 11.0 Hz, H24), 5.83 (1H, t, J = 11.9 Hz, H11), 5.72 - 5.66 (2H, m, H2, H23), 5.63 - 5.57 (2H, m, H10, H3), 5.26 (1H, d, J = 16.6 Hz, H26a), 5.13 (1H, d, J = 10.0 Hz, H26b), 5.09 (1H, d, J = 10.2 Hz, H15), 4.73 (1H, *br* q, J = 8.3 Hz, H9), 4.59 (1H, d, J = 10.5 Hz, $ArC\underline{H}_aH_bO$), 4.54 (1H, d, J = 10.5 Hz, $ArCH_a\underline{H}_bO$), 4.43 (2H, s, $ArCH_2O$), 4.18 - 4.13 (2H, m, H1a, H1b), 4.03 (1H, dt, J = 9.3, 6.0 Hz, H7), 3.96 (1H, dd, J = 10.0, 2.6 Hz, H5), 3.62 (1H, t, J = 4.1 Hz, H19), 3.38 - 3.34 (2H, m, H21, H13), 3.35 (3H, s, ArOMe), 3.32 (3H, s, ArOMe), 3.14 - 3.08 (1H, m, H22), 2.92 - 2.84 (2H, m, H12, H4), 2.66 - 2.59 (1H, m, H14), 2.26 (1H, t, J = 10.5 Hz, H17a), 2.04 - 2.00 (3H, m, H6, H18, H20), 1.87 - 1.80 (2H, m, H8a, H17b), 1.75 - 1.69 (1H, H8b), 1.72 (3H, s, Me16), 1.47 (3H, s, $C(CH_3)$), 1.45 (3H, s, $C(CH_3)$), 1.25 (3H, d, J = 6.8 Hz, Me18), 1.19 (3H, d, J = 7.0 Hz, Me4), 1.15 (3H, d, J = 6.8 Hz, Me22), 1.13 (3H, d, J = 6.4 Hz, Me12), 1.10 (3H, d, J = 6.6 Hz, Me14), 1.08 (9H, s, $SiC(CH_3)_3$), 1.04 (18H, s, 2 × $SiC(CH_3)_3$), 0.99 - 0.95 (6H, m, Me6, Me20), 0.22 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.15 (6H, s, $Si(CH_3)2$), 0.14 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6), δ = 159.73, 159.71, 137.1, 135.9, 134.7, 132.6, 132.4, 131.53, 131.48, 131.2, 130.7, 129.6, 129.5, 129.4, 125.7, 117.9, 114.1, 114.0, 100.2, 84.7, 81.5, 77.9, 75.9, 75.4, 72.3, 67.9, 66.4, 63.4, 54.76, 54.73, 46.5, 40.6, 38.8, 38.0, 37.3, 36.7, 35.8, 35.7, 35.6, 30.4, 26.6, 26.4, 26.3, 25.8, 25.4, 23.2, 19.1, 19.0, 18.9, 18.7, 18.5, 18.4, 15.3, 11.0, 10.6, 2.8, 3.0, 3.1, 3.4, 3.7, 4.1; **HRMS** (ES+) Calcd. for $C_{71}H_{122}O_9Si_3Na$ $[M+Na]^+$: 1225.8289. Found: 1225.8245.



11

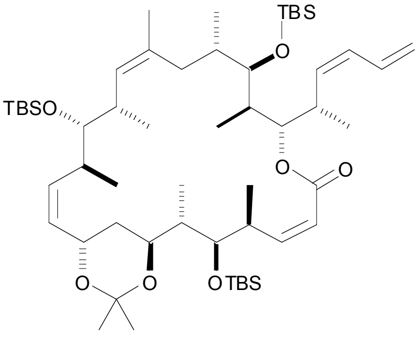
Diol **11**: To a solution of **10b** (28.7 mg, 23.8 μmol, 1.0 eq.) in CH_2Cl_2 / pH 7 buffer (10:1, 1.1 mL) at r.t. was added DDQ (16.2 mg, 71.5 μmol, 3.0 eq.). The mixture was stirred for 3 h before diluting with an aqueous solution of pH 7 buffer (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% EtOAc / hexane) to afford diol **11** (16.3 mg, 70%). ***R_f*** 0.20 (20% EtOAc / hexane); $[\alpha]_D^{20}$ +18.4 (c 0.13, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3418, 2957, 2930, 2856, 1515, 1462, 1376; **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.65 (1H, dt, J = 16.9, 10.9 Hz, H25), 6.06 (1H, t, J = 10.9 Hz, H24), 5.91 (1H, t, J = 10.4 Hz, H11), 5.65 (1H, dd, J = 10.9, 8.0 Hz, H10), 5.57 (1H, dt, J = 11.0, 6.9 Hz, H2), 5.43 (1H, t, J = 10.4 Hz, H3), 5.21 (1H, t, J = 10.5 Hz, H23), 5.17 (1H, d, J = 17.6 Hz, H26a), 5.12 (1H, d, J = 10.1 Hz, H15), 5.06 (1H, d, J = 10.2 Hz, H26b), 4.75 (1H, q, *J* = 7.5 Hz, H9), 4.19 - 4.13 (2H, m, H1a, H7), 3.99 (1H, *br* dd, *J* = 11.7, 5.8 Hz, H1b), 3.79 - 3.75 (2H, m, H5, H19), 3.38 - 3.34 (2H, H13, H21), 3.00 - 2.88 (2H, m, H4, H12), 2.84 - 2.79 (1H, m, H22), 2.70 - 2.65 (1H, m, H14), 2.44 (1H, t, *J* = 12.4 Hz, H17a), 2.13 - 2.06 (2H, m, H18, H6), 1.92 - 1.84 (3H, m, H8a, H17b, H20), 1.83 - 1.82 (1H, m, H8b), 1.80 (3H, s, Me16), 1.51 (3H, s, $C(CH_3)$), 1.48 (3H, s, $C(CH_3)$), 1.20 (3H, d, *J* = 7.0 Hz, Me12), 1.14 (3H, d, *J* = 6.7 Hz, Me14), 1.12 (3H, d, *J* = 6.9 Hz, Me20), 1.08 (9H, s, $SiC(CH_3)_3$), 1.06 (3H, d, *J* = 7.0 Hz, Me4), 1.041 (9H, s, $SiC(CH_3)_3$), 1.036 (9H, s, $SiC(CH_3)_3$), 1.01 (3H, d, *J* = 7.2 Hz, Me6), 0.98 (3H, d, *J* = 6.7 Hz, Me18), 0.87 (3H, d, *J* = 6.8 Hz, Me22), 0.21 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 136.9, 135.7, 134.7, 132.8, 132.5, 131.5, 131.3, 130.8, 118.5, 100.5, 81.5, 79.1, 77.5, 76.0, 67.7, 63.7, 58.5, 44.8, 39.1, 38.2, 37.8, 37.7, 37.3, 36.6, 36.0, 35.1, 26.6, 26.5, 26.4, 25.6, 25.4, 23.4, 19.5, 18.85, 18.76, 18.7, 18.5, 17.3, 14.2, 14.0, 11.8, 10.0, – 3.0, –3.11, –3.13, –3.4, –3.5, –3.8; **HRMS** (ES+) Calcd. for $C_{55}H_{106}O_7Si_3Na$ $[M+Na]^+$: 985.7139. Found: 985.7126.



11a

Seco-acid **11a**: To a solution of diol **11** (16.0 mg, 16.6 µmol, 1.0 eq.) in CH_2Cl_2 (750 µL) at 0 °C was added $PhI(OAc)_2$ (10.7 mg, 37.2 µmol, 2.0 eq.) then a crystal of TEMPO. After 10 min, the reaction was warmed to r.t. and stirred for a further 1 h before quenching with saturated solutions of $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (1 mL). The phases were separated, the aqueous phase extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography through a plug of silica (10% EtOAc / hexane) afforded the intermediate enal.

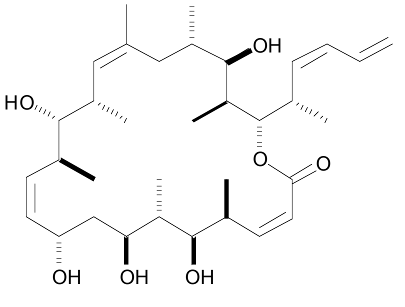
This aldehyde (12.5 mg, 13.0 µmol, 1.0 eq.) was immediately dissolved in *t*-BuOH / 2-methyl-2-butene (10:1, 825 µL). To the reaction was added a solution of $NaClO_2$ (4.7 mg, 52 µmol, 4.0 eq.) and NaH_2PO_4 (6.0 mg, 52 µmol, 4.0 eq.) in H_2O (750 µL). After 4 h the reaction was diluted by the addition of brine (3 mL) and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. *Seco*-acid **11a** (14.0 mg, 86% over 2 steps) was isolated as a colourless oil and was used without further purification. ***R*$_f$** 0.42 (20% EtOAc / hexane); **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.60 (1H, dt, *J* = 16.6, 10.5 Hz, H25), 6.11 (1H, dd, *J* = 11.4, 10.2 Hz, H3), 6.06 (1H, t, *J* = 10.2 Hz, H11), 6.02 (1H, t, *J* = 10.5 Hz, H24), 5.82 (1H, d, *J* = 11.5 Hz, H2), 5.70 (1H, dd, *J*, = 10.7, 8.2 Hz, H10), 5.16 (1H, dd, *J* = 16.7, 0.9 Hz, H26a), 5.09 - 5.03 (3H, m, H15, H23, H26b), 4.68 (1H, *br* q, *J* = 8.3 Hz, H9), 4.32 (1H, dt, *J* = 9.5, 5.9 Hz, H7), 3.96 (1H, dd, *J* = 7.4, 3.5 Hz, H5), 3.88 - 3.84 (2H, m, H4, H19), 3.43 (1H, *br* dd, *J* = 5.1, 1.2 Hz, H21), 3.30 (1H, dd, *J* = 8.6, 1.3 Hz, H13), 2.92 (1H, *br* qn, *J* = 7.0 Hz, H12), 2.82 - 2.75 (1H, m, H22), 2.66 - 2.58 (1H, m, H14), 2.53 (1H, t, t, *J* = 12.4 Hz, H17a), 2.18 (1H, sex, *J* = 6.8 Hz, H6), 2.14 - 2.09 (1H, m, H18), 2.02 - 1.90 (2H, m, H8a, H20), 1.85 (3H, s, Me16), 1.83 - 1.76 (2H, m, H8b, H17b), 1.52 (3H, s, $C(CH_3)$), 1.49 (3H, s, $C(CH_3)$), 1.21 (3H, d, *J* = 7.0 Hz, Me12), 1.20 (3H, d, *J* = 6.9 Hz, Me6), 1.15 (3H, d, *J* = 7.9 Hz, Me14), 1.12 (3H, d, *J* = 6.9 Hz, Me20), 1.10 (9H, s, $SiC(CH_3)_3$), 1.05 (9H, $SiC(CH_3)_3$), 1.03 (3H, d, *J* = 7.8 Hz, Me4), 1.01 (9H, s, $SiC(CH_3)_3$), 0.96 (3H, d, *J* = 6.6 Hz, Me18), 0.78 (3H, d, *J* = 6.6 Hz, Me22), 0.26 (3H, s, $SiCH_3$), 0.23 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 168.1, 156.4, 135.2, 134.1, 133.1, 132.2, 131.7, 131.2, 130.8, 127.5, 118.9, 100.4, 81.7, 78.8, 76.7, 76.4, 66.6, 63.5, 43.8, 38.8, 38.3, 37.8, 37.1, 36.3, 35.3, 34.6, 34.3, 26.6, 26.5, 26.4, 25.44, 25.39, 23.2, 20.4, 19.6, 18.9, 18.8, 18.7, 16.9, 14.2, 13.0, 10.2, 9.9, –2.7, –2.9, –3.1, –3.4, –3.6; **HRMS** (ES+) Calcd. for $C_{55}H_{104}O_8Si_3Na$ $[M+Na]^+$: 999.6931. Found: 999.6934.



11b

Macrolactone **11b**: To a solution of acid **11a** (7.0 mg, 7.2 μmol, 1.0 eq.) in toluene (2 mL) at r.t. was added Et_3N (7.0 μL, 50 μmol, 7.0 eq.) then 2,4,6-trichlorobenzoyl chloride (6.0 μL, 36 μmol, 5.0 eq.). The solution was diluted after 40 min with toluene (12 mL) and DMAP

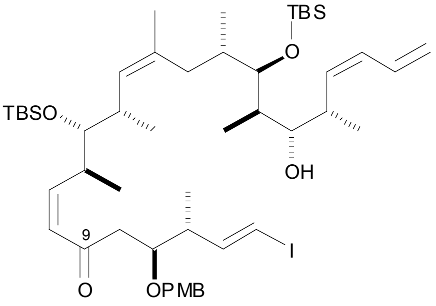
(4.0 mg, 36 μmol, 5.0 eq.) added. After 20 min, the reaction mixture was filtered through a plug of silica (100% Et_2O) and concentrated *in vacuo*. Flash column chromatography (3% EtOAc / hexane) afforded macrolactone **11b** (6.0 mg, 87%) as a colourless oil. ***R**$_f$* 0.32 (5% EtOAc / hexane); $[\alpha]_D^{20}$ +40.9 (*c* 0.11, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2959, 2928, 2857, 1721, 1462, 1380; **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.67 (1H, dt, *J* = 16.8, 10.6 Hz, H25), 6.13 (1H, t, *J* = 12.0 Hz, H3), 6.11 (1H, t, *J* = 10.7 Hz, H11), 5.93 (1H, t, *J* = 11.3 Hz, H24), 5.72 (1H, d, *J* = 11.4 Hz, H2), 5.68 (1H, t, *J* = 10.3 Hz, H10), 5.13 - 5.05 (4H, m, H21, H23, H26a, H26b), 4.99 (1H, d, *J* = 9.3 Hz, H15), 4.72 (1H, *br* q, *J* = 9.2 Hz, H9), 4.51 - 4.45 (1H, m, H7), 4.02 (1H, qn, *J* = 7.6 Hz, H4), 3.75 (1H, d, *J* = 10.0 Hz, H5), 3.39 (1H, d, *J* = 10.2 Hz, H19), 3.28 (1H, d, *J* = 9.1 Hz, H13), 3.00 - 2.92 (2H, m, H12, H22), 2.69 (1H, t, *J* = 13.0 Hz, H17a), 2.66 - 2.52 (2H, m, H14, H18), 2.30 - 2.25 (1H, m, H6), 2.15 - 2.09 (1H, m, H20), 1.99 - 1.94 (1H, m, H8a), 1.97 (3H, s, Me16), 1.79 (1H, d, *J* = 12.5 Hz, H17b), 1.71 - 1.66 (1H, m, H8b), 1.50 (3H, s, $C(CH_3)$), 1.49 (3H, s, $C(CH_3)$), 1.29 (3H, d, *J* = 6.8 Hz, Me6), 1.17 (3H, d, *J* = 7.3 Hz, Me12), 1.14 (3H, d, *J* = 6.9 Hz, Me14), 1.13 - 1.10 (12H, m, Me20, $SiC(CH_3)_3$), 1.04 (9H, s, $SiC(CH_3)_3$), 1.01 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, d, *J* = 6.7 Hz, Me18), 0.92 (3H, d, *J* = 6.6 Hz, Me4), 0.75 (3H, d, *J* = 6.5 Hz, Me22), 0.27 (3H, s, $SiCH_3$), 0.26 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 165.5, 159.0, 134.8, 133.5, 131.5, 130.5, 130.3, 127.5, 125.8, 119.0, 117.8, 100.6, 81.4, 78.0, 77.8, 76.1, 65.8, 63.7, 41.8, 38.8, 38.1, 36.2, 34.8, 34.6, 34.3, 32.4, 26.53, 26.49, 26.45, 25.3, 24.9, 22.7, 22.6, 21.3, 20.2, 18.9, 17.1, 14.2, 11.6, 11.4, 10.9, 10.7, 10.0, –2.2, –2.4, –2.7, –2.9, –3.0, –3.1; **HRMS** (ES+) Calcd. for $C_{55}H_{102}O_7Si_3Na$ $[M+Na]^+$: 981.6826. Found: 981.6866.



5

Discodermolide/Dictyostatin Hybrid **5**: To a stirred solution of macrocycle **11b** (10.4 mg, 10.8 μmol, 1.0 eq.) in MeOH (1 mL) at 0 °C was added acidified MeOH (3:1, MeOH: concentrated HCl, 500 μL). After stirring at r.t. for 8 h, the reaction mixture was diluted with water (4 mL) and EtOAc (4 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% EtOAc) and then by HPLC (10% IPA / hexane) to yield macrolactone **5** (3.3 mg, 53%) as an amorphous white solid. ***R**f* 0.39 (100% EtOAc); $\mathbf{R_t}$ 28 min (10% IPA / hexane); $[\alpha]_D^{20}$ +71.6 (*c* = 0.27); **IR** (neat, cm^{-1}) υ_{max} = 3385, 2963, 2929, 2873, 1713, 1640, 1454, 1413, 1379; **^{1}H NMR** (700 MHz, CD_3OD) δ = 6.62 (1H, dt, *J* = 17.0, 10.6 Hz, H25), 6.08 (1H, t, *J* = 10.9 Hz, H3), 5.98 (1H, t, *J* = 10.9 Hz, H24), 5.65 (1H, d, *J* = 11.8 Hz, H2), 5.57 (1H, dd, *J* = 9.0, 10.9 Hz, H11), 5.30 (1H, t, *J* = 10.1 Hz, H10), 5.19 (1H, *br* t, *J* = 9.0 Hz, H23), 5.16 (1H, d, *J* = 17.0 Hz, H26a), 5.08 (1H, d, *J* = 10.1 Hz, H26b), 4.88 (1H, *br* d, *J* = 4.9 Hz, H21), 4.83 (1H, d, *J* = 10.2 Hz, H15), 4.50 (1H, *br* d, *J* = 8.3 Hz, H9), 4.12 (1H, *br* dd, *J* = 3.9, 9.7 Hz, H7), 3.55 (1H, *br* s, H4), 3.37 – 3.32 (1H, m, H5), 3.07 – 3.02 (2H, m, H13, H22), 2.98 (1H, *br* s, H19), 2.56 (1H, quin., *J* = 7.7 Hz, H12), 2.40 – 2.35 (1H, m, H14), 2.32 (1H, *br* s, H17a), 2.11 (1H, *br* s, H18), 1.96 – 1.91 (1H, m, H20), 1.78 (1H, sex., *J* = 7.2 Hz, H6), 1.65 (3H, s, Me16), 1.53 (1H, d, *J* = 12.6 Hz, H17b), 1.36 (1H, ddd, *J* = 2.6, 11.4, 13.8 Hz, H8a), 1.24 (1H, dd, *J* = 2.9, 10.7 Hz, H8b), 1.05 (3H, d, *J* = 7.2 Hz, Me12), 0.97 (3H, d, *J* = 6.8 Hz, Me20), 0.95 (3H, d, *J* = 6.8 Hz, Me4), 0.93 (3H, d, *J* = 6.8 Hz, Me14), 0.91 (3H, d, *J* = 6.8 Hz, Me22), 0.84 (3H, d, *J* = 7.0 Hz, Me6), 0.64 (3H, d, *J* = 6.3 Hz, Me18); **^{13}C NMR** (175 MHz, CD_3OD) δ = 173.0 (C1), 167.6 (C16), 135.3 (C10), 134.5 (C23), 133.6 (C25), 131.4 (C24), 131.3 (C15), 131.0 (C11), 119.6 (C2), 118.4 (C26), 80.8 (C13), 78.6 (C5), 78.1 (C21), 77.0 (C19), 68.2 (C7), 65.1 (C9), 43.4 (C6), 38.6 (C17), 38.4 (C8), 38.3 (2C, C14, C20), 37.2 (C4), 35.8 (C12), 35.5 (C22), 32.8 (C18), 23.2 (Me16), 19.9 (Me12), 19.3 (Me22), 17.8 (Me14), 12.8 (Me4), 12.0 (Me6), 11.7 (Me18), 10.1 (Me20); **HRMS** (ES+) Calcd. for $C_{34}H_{56}O_7Na$ $[M+Na]^+$ 599.3918. Found: 599.3923.

Synthesis of Discodermolide/Dictyostatin Hybrid **12** and Acetonide **18**



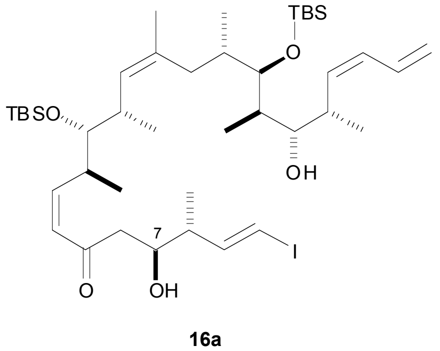
16

(*Z*)-Enone **16**: Freshly azeotroped 18-crown-6 (357 mg, 1.35 mmol, 10 eq.) and vacuum dried potassium carbonate (56 mg, 0.405 mmol, 3 eq.) were suspended in PhMe / HMPA (10 : 1, 39 mL : 3.9 mL) at 0 ˚C and stirred for 1 h. A solution of freshly azeotroped aldehyde **13**[1] (970 mg, 1.67 mmol, 1.0 eq.) and freshly azeotroped phosphonate **14**[2] (1.58 mg, 2.50 mmol, 1.5 eq.) in PhMe / HMPA (10 : 1, 39 mL : 3.9 mL) was then added *via* cannula. The reaction mixture was then stirred at 0 °C for 7 days before being quenched by the addition of NH_4Cl (50 mL). The layers were separated and the aqueous phase extracted with DCM (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (10% EtOAc / PhMe) yielded (*Z*)-enone **16** (1.01 g, 67%) as a colourless oil, with isomeric (*E*)-enone **24** (150 mg, 10%) as a colourless oil. **16**: $\boldsymbol{R_f}$ 0.64 (10% EtOAc / PhMe); $[\alpha]_D^{20}$ +46.1 (*c* 0.90, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2960, 2930, 2857, 1688, 1614, 1585, 1514, 1458; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.23 (2H, d, *J* = 8.6 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.63 (1H, ddd, *J* = 10.4, 10.6, 16.8 Hz, H25), 6.50 (1H, dd, *J* = 8.4, 14.4 Hz, H5), 6.21 (1H, dd, *J* = 9.5, 11.6 Hz, H11), 6.14 (1H, t, *J* = 11.1 Hz, H24), 6.04 (2H, t, *J* = 11.5 Hz, H4, H10), 5.33 (1H, t, *J* = 10.5 Hz, H23), 5.25 (1H, d, *J* = 16.8 Hz, H26a), 5.16 (1H, d, *J* = 10.3 Hz, H26b), 4.92 (1H, d, *J* = 10.2 Hz, H15), 4.51 (1H, d, *J* = 10.9 Hz, $OC\underline{H}_aH_bAr$), 4.39 (1H, d, *J* = 10.9 Hz, $OCH_a\underline{H}_bAr$), 3.87 (1H, q, *J* = 5.4 Hz, H7), 3.70 (3H, s, ArOMe), 3.62 – 3.65 (1H, m, H12), 3.61 (1H, dd, *J* = 3.2, 5.5 Hz, H19), 3.44 (1H, dd, *J* = 3.2, 6.7 Hz, H13), 3.34 (1H, t, *J* = 3.7 Hz, H21), 2.77 – 2.84 (1H, m, H22), 2.68 (1H, dd, *J* = 6.8, 16.5 Hz, H8a), 2.52 (1H, dd, *J* = 5.4, 16.5 Hz, H8b), 2.38 – 2.45 (2H, m, H6, H14), 2.18 (1H, t, *J* = 12.5 Hz, H17a), 1.84 – 1.91 (1H, m, H18), 1.80 (1H, dq, *J* = 3.4, 6.3 Hz, H20), 1.68 (1H, d, *J* = 12.6 Hz, H17b), 1.57 (3H, s, Me16), 1.58 (1H, d, *J* = 2.8 Hz, C21-O$\underline{H}$), 1.04 (3H, d, *J* = 6.9 Hz, Me6), 1.00 (3H, d, *J* = 6.9 Hz, Me22), 0.96 (6H, t, *J* = 7.0 Hz, Me16, Me20), 0.93 (9H, s, $SiC(CH_3)_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.90 (3H, d, *J* = 6.6 Hz, Me14), 0.72 (3H, d, *J* = 6.5 Hz, Me18), 0.11 (3H, s, $Si(CH_3)_2$), 0.10 (6H, s, $Si(CH_3)_2$), 0.09 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 198.9, 159.3, 152.1, 148.0, 134.8, 132.7, 132.3, 131.2, 130.8, 130.7, 129.6, 129.2, 128.4, 125.7, 125.6, 118.6, 113.9, 80.6, 78.9, 78.0, 76.3, 75.9, 72.3, 55.4, 46.7, 44.8, 38.3, 37.4, 36.6, 36.5, 34.9, 26.4, 26.4, 23.3, 18.6, 18.6, 18.0, 17.7, 17.4, 15.7, 13.5, 9.7, –3.2, –3.3, –3.3, –3.7; **HRMS** (ESI+) Calcd. for $C_{50}H_{89}NIO_6Si_2$ $[M+NH_4]^+$: 982.5268. Found: 928.5275.

[1] I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, *Angew. Chem.* **2000**, *112*, 385; *Angew. Chem. Int. Ed.* **2000**, *39*, 377.

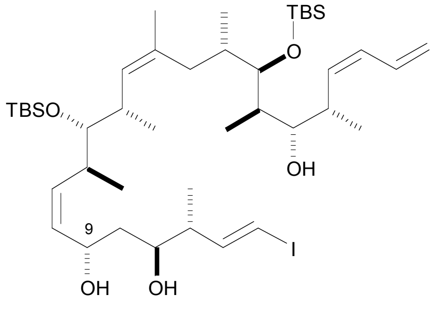
[2] I. Paterson, R. Britton, O. Delgado, N. M. Gardner, A. Meyer, G. J. Naylor, K. G. Poullennec, *Tetrahedron* **2010**, *66,* 6534.

(E)-Enone **24**: ***R**$_f$* 0.60 (10% EtOAc / PhMe); $[\alpha]_D^{20}$ +41.3 (*c* 0.15, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2929, 2872, 1617, 1514, 1462; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.25 (2H, d, *J* = 8.6 Hz, Ar), 7.02 (1H, dd, *J* = 7.8, 16.0 Hz, H11), 6.81 (2H, d, *J* = 8.6 Hz, Ar), 6.67 (1H, dt, *J* = 10.6, 16.8 Hz, H25), 6.60 (1H, dd, *J* = 8.6, 14.5 Hz, H5), 6.04 – 6.11 (2H, m, H10, H24), 5.83 (1H, dd, *J* = 0.7, 14.5 Hz, H4), 5.23 (1H, t, *J* = 10.6 Hz, H23), 5.16 (1H, d, *J* = 16.8 Hz, H26a), 5.05 (2H, d, *J* = 10.2 Hz, H15, H26b), 4.52 (1H, d, *J* = 11.1Hz, $OC\underline{H}_aH_bAr$), 4.34 (1H, d, *J* = 11.1Hz, $OCH_a\underline{H}_bAr$), 4.04 (1H, ddd, *J* = 3.8, 5.0, 8.7 Hz, H7), 3.81 (1H, dd, *J* = 3.5, 5.3 Hz, H19), 3.40 (1H, dd, *J* = 3.9, 7.1 Hz, H13), 3.36 (1H, qn, *J* = 3.6 Hz, H21), 3.31 (3H, s, OMe), 2.78 – 2.86 (2H, m, H8a, H22), 2.71 (1H, dt, *J* = 6.8, 9.9 Hz, H14), 2.52 (2H, dd, *J* = 5.1, 16.7 Hz, H8b, H12), 2.41 (1H, t, *J* = 12.2 Hz, H17a), 2.22 – 2.27 (1H, m, H6), 2.08 – 2.14 (1H, m, H17b), 2.01 (1H, d, *J* = 13.1 Hz, H18), 1.88 – 1.94 (1H, m, H20), 1.77 (3H, s, Me16), 1.14 (3H, d, *J* = 6.9 Hz, Me20), 1.10 (3H, d, *J* = 7.3 Hz, Me14), 1.07 (3H, d, *J* = 7.5 Hz, Me12), 1.09 (9H, s, $SiC(CH_3)_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, *J* = 6.7 Hz, Me18), 0.91 (3H, d, *J* = 6.9 Hz, Me6), 0.89 (3H, d, *J* = 6.6 Hz, Me22), 0.21 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.10 (3H, s, $Si(CH_3)_2$), 0.07 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 197.5, 159.8, 150.0, 148.3, 134.8, 133.7, 132.6, 131.5, 131.3, 131.0, 130.3, 129.7 (2C), 118.6, 114.1, 81.0, 79.0, 78.1, 76.3, 76.2, 72.6, 54.8, 45.2, 43.1, 42.8, 39.2, 37.2, 36.9, 36.7, 35.5, 26.62 (3C), 26.58, 26.4 (3C), 26.2, 23.6, 18.9, 18.6, 18.1, 17.4, 16.2, 15.9, 14.2, 10.1, –3.1, –3.2, –3.5, –3.6; **HRMS** (ESI+) Calcd. for $C_{50}H_{89}NIO_6Si_2$ $[M+NH_4]^+$: 982.5268. Found: 928.5265.



16a

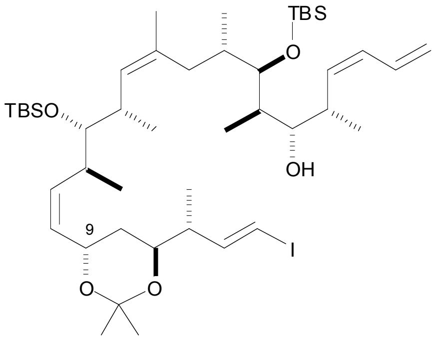
Ketone **16a**: To a stirred biphasic solution of PMB ether **16** (185 mg, 0.192 mmol, 1.0 eq.) in DCM (8.4 mL) and pH 7 buffer (1.7 μL) at 0 °C was added DDQ (61 mg, 0.269 mmol, 1.4 eq.). After 2.5 h, the reaction was quenched by the addition of $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (10% EtOAc / P.E.) afforded ketone **16a** (143 mg, 88%) as a colourless oil. $\boldsymbol{R_f}$ 0.52 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +31.3 (*c* 0.52, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3432, 2930, 2856, 1688, 1614, 1462; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.63 (1H, ddd, *J* = 10.7, 10.9, 17.0 Hz, H25), 6.57 (1H, dd, *J* = 8.4, 14.4 Hz, H5), 6.30 (1H, dd, *J* = 9.6, 11.5 Hz, H11), 6.14 (1H, t, *J* = 10.8 Hz, H24), 6.08 (1H, d, *J* = 14.5 Hz, H4), 6.05 (1H, d, *J* = 11.4 Hz, H10), 5.35 (1H, t, *J* = 10.6 Hz, H23), 5.25 (1H, d, *J* = 16.4 Hz, H26a), 5.16 (1H, d, *J* = 10.1 Hz, H26b), 4.88 (1H, d, *J* = 10.2 Hz, H15), 3.95 (1H, qn, *J* = 4.5 Hz, H7), 3.62 (1H, d, *J* = 6.9 Hz, H19), 3.58 (1H, dd, *J* = 3.5, 5.5 Hz, H12), 3.39 (1H, dd, *J* = 2.8, 7.3 Hz, H13), 3.35 (1H, dd, *J* = 3.4, 7.2 Hz, H21), 3.27 (1H, s, C7-O<u>H</u>), 2.77 – 2.86 (1H, m, H22), 2.46 – 2.60 (2H, m, H8a, H8b), 2.25 – 2.36 (2H, m, H6, H14), 2.12 (1H, t, *J* = 12.3 Hz, H17a), 1.82 – 1.88 (1H, m, H18), 1.77 (1H, q, *J* = 5.8 Hz, H20), 1.63 (1H, d, *J* = 11.6 Hz, H17b), 1.57 (3H, s, Me16), 1.55 (1H, s, C21-O<u>H</u>), 1.07 (3H, d, *J* = 6.9 Hz, Me6), 1.00 (3H, d, *J* = 7.1 Hz, Me12), 0.98 (3H, d, *J* = 6.8 Hz, Me22), 0.96 (3H, d, *J* = 6.9 Hz, Me20), 0.93 (18H, s, $SiC(CH_3)_3$), 0.89 (3H, d, *J* = 6.5 Hz, Me14), 0.70 (3H, d, *J* = 6.8 Hz, Me18), 0.10 (6H, s, $Si(CH_3)_2$), 0.09 (3H, s, $Si(CH_3)_2$), 0.08 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 201.3, 152.9, 147.8, 134.7, 133.0, 132.3, 131.1, 130.5, 128.4, 125.5, 118.6, 80.7, 78.7, 76.3, 76.0, 70.5, 47.7, 45.9, 38.5, 38.3, 38.0, 36.4, 34.7, 29.9, 26.4, 26.4, 23.3, 22.8, 22.5, 18.7, 18.6, 18.3, 18.0, 17.4, 15.8, 14.2, 13.6, 9.7, –3.2, –3.2, –3.3, –3.6; **HRMS** (ESI+) Calcd. for $C_{42}H_{81}NIO_5Si_2$ $[M+NH_4]^+$: 862.4692. Found: 862.4677.



16b

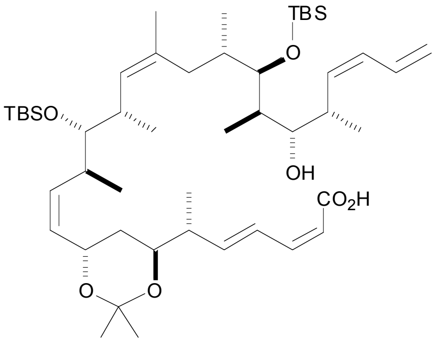
1,3-Diol **16b**: To a stirred solution of (*R*)-CBS (250 μL of a 1 M solution in PhMe) at 0 °C was added $BH_3{\cdot}THF$ (250 μL of a 1 M solution in THF), the mixture was then stirred for 1 h at 0 °C. To a stirred solution of ketone **16a** (110 mg, 0.130 mmol, 1.0 eq.) in THF (11 mL) at

–30 ˚C was added the pre-mixed solution of (*R*)-CBS / BH_3 (350 μL of a 0.5 M solution, 1.5 eq.). After stirring for 4 h, the reaction was quenched with the slow addition of MeOH (500 μL). The crude product was azeotroped with MeOH five times, before being loaded directly onto a column and purified by flash chromatography (25% EtOAc / P.E.) to yield 1,3-diol **16b** as a colourless oil. ***R**f* 0.17 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +24.1 (*c* 0.39, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3432, 2959, 2929, 2856,1692, 1462, 1378; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.63 (1H, ddd, *J* = 10.8, 11.0, 17.0 Hz, H25), 6.54 (1H, dd, *J* = 8.4, 14.4 Hz, H5), 6.15 (1H, t, *J* = 11.0 Hz, H24), 6.10 (1H, d, *J* = 14.4 Hz, H4), 5.51 (1H, t, *J* = 10.6 Hz, H11), 5.43 (1H, dd, *J* = 7.8, 11.3 Hz, H10), 5.33 (1H, t, *J* = 10.5 Hz, H23), 5.25 (1H, d, *J* = 16.6 Hz, H26a), 5.16 (1H, d, *J* = 10.3 Hz, H26b), 5.04 (1H, d, *J* = 9.8 Hz, H15), 4.67 (1H, ddd, *J* = 3.4, 3.9, 7.8 Hz, H9), 3.81 – 3.75 (1H, m, H7), 3.61 (1H, dd, *J* = 3.1, 5.9 Hz, H19), 3.34 (1H, d, *J* = 7.5 Hz, H21), 3.29 (1H, dd, *J* = 5.0, 5.3 Hz, H13), 2.75 – 2.85 (2H, m, H12, H22), 2.58 (1H, d, *J* = 2.7 Hz, C7-O<u>H</u>), 2.47 (1H, ddq, *J* = 6.1, 10.2, 12.1 Hz, H14), 2.24 – 2.35 (2H, m, H6, C9-O<u>H</u>), 2.18 (1H, t, *J* = 12.4 Hz, H17a), 1.84 – 1.93 (1H, m, H18), 1.77 – 1.84 (1H, m, H20), 1.73 (1H, d, *J* = 12.5 Hz, H17b), 1.60 – 1.69 (2H, m, H8a, H8b), 1.62 (3H, *obs* s, Me16), 1.04 (3H, d, *J* = 6.9 Hz, Me6), 1.00 (3H, d, *J* = 6.9 Hz, Me22), 0.97 (3H, d, *J* = 6.6 Hz, Me12), 0.96 (3H, d, *J* = 6.9 Hz, Me20), 0.93 (9H, s, $SiC(CH_3)_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.90 (3H, d, *J* = 6.9 Hz, Me14), 0.74 (3H, d, *J* = 6.7 Hz, Me18), 0.09 (3H, s, $Si(CH_3)_2$), 0.09 (3H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 148.2, 135.7, 134.8, 132.5, 132.2, 131.3, 131.0, 128.9, 126.1, 118.7, 80.7, 78.9, 76.3, 71.5, 66.6, 47.1, 40.3, 38.2, 37.2, 36.6, 36.5, 36.3, 34.9, 29.9, 26.4, 23.4, 19.2, 18.6, 17.3, 16.8, 16.1, 13.4, 9.7, –2.9, –3.1, –3.3, –3.7; **HRMS** (ESI+) Calcd. for $C_{42}H_{79}O_5NaSi_2I$ $[M+Na]^+$: 869.4409. Found: 869.4441.



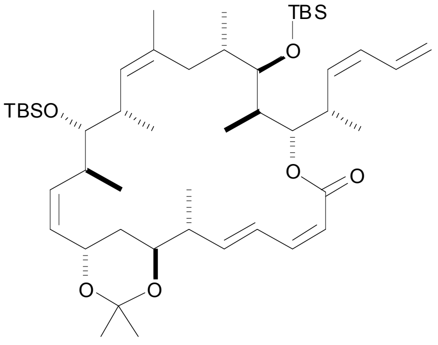
17

Acetonide **17**: To a stirred solution of 1,3-diol **16b** (110 mg, 1.0 eq.) in DCM (6.5 mL) and 2,2-dimethoxypropane (17 mL) at 0 °C was added PPTS (1 crystal). The reaction mixture was stirred overnight and allowed to slowly warm to r.t.. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (5% EtOAc / P.E.) to afford acetonide **17** (99 mg, 86% over two steps) as a colourless oil. ***R_f*** 0.49 (10% EtOAc / P.E.); $[\alpha]_D^{20}$ +18.6 (*c* 0.30, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2958, 2929, 2854, 1732, 1461, 1377; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 6.63 (1H, ddd, *J* = 10.6, 10.9, 16.8 Hz, H25), 6.55 (1H, dd, *J* = 8.0, 14.6 Hz, H5), 6.15 (1H, t, *J* = 10.9 Hz, H24), 6.04 (1H, d, *J* = 14.6 Hz, H4), 5.66 (1H, t, *J* = 10.3 Hz, H11), 5.27 – 5.35 (2H, m, H10, H23), 5.25 (1H, d, *J* = 16.8 Hz, H26a), 5.16 (1H, d, *J* = 10.2 Hz, H26b), 4.99 (1H, d, *J* = 10.2 Hz, H15), 4.46 (1H, dd, *J* = 6.5, 8.6 Hz, H9), 3.65 (1H, ddd, *J* = 5.9, 6.1, 9.4 Hz, H7), 3.59 (1H, dd, *J* = 3.1, 5.9 Hz, H19), 3.35 (1H, d, *J* = 7.8 Hz, H21), 3.27 (1H, dd, *J* = 3.3, 6.9 Hz, H13), 2.81 (1H, ddq, *J* = 6.6, 7.0, 9.9 Hz, H22), 2.61 – 2.66 (1H, m, H12), 2.40 (1H, ddq, *J* = 6.6, 9.9, 11.9 Hz, H14), 2.25 (1H, q, *J* = 6.9 Hz, H6), 2.19 (1H, t, *J* = 12.4 Hz, H17a), 1.85 – 1.92 (1H, m, H18), 1.79 (1H, ddq, *J* = 3.0, 6.4, 7.4 Hz, H20), 1.58 – 1.69 (3H, m, H8a, H8b, H17b), 1.63 (3H, *obs* s, Me16), 1.37 (3H, s, $C(CH_3)_2$), 1.32 (3H, s, $C(CH_3)_2$), 1.01 (3H, d, *J* = 7.0 Hz, Me6), 0.99 (3H, d, *J* = 7.1 Hz, Me12), 0.97 (3H, d, *J* = 6.7 Hz, Me22), 0.95 (3H, d, *J* = 7.0 Hz, Me20), 0.92 (9H, s, $SiC(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.86 (3H, d, *J* = 6.6 Hz, Me14), 0.72 (3H, d, *J* = 6.9 Hz, Me18), 0.09 (3H, s, $Si(CH_3)_2$), 0.08 (3H, s, $Si(CH_3)_2$), 0.05 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 148.3, 136.7, 134.8, 132.5, 132.2, 131.3, 131.0, 129.3, 118.7, 100.7, 81.0, 78.9, 76.2, 75.5, 69.3, 63.3, 45.0, 38.3, 37.4, 37.1, 36.6, 36.5, 34.6, 29.9, 26.4, 26.4, 25.1, 24.5, 23.4, 19.1, 18.6, 18.0, 17.3, 15.5, 13.5, 9.7, –3.0, –3.1, –3.3, –3.5; **HRMS** (ESI+) Calcd. for $C_{45}H_{83}O_5NaSi_2I$ $[M+Na]^+$: 909.4722. Found: 909.4750.



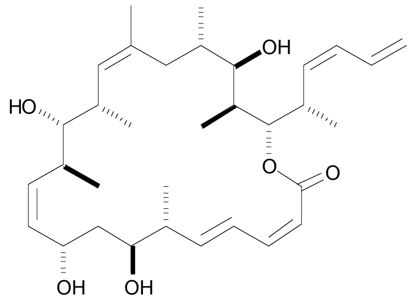
17a

Seco-Acid **17a**: To a deoxygenated (freeze-thaw) solution of vinyl iodide **17** (48 mg, 54 μmol, 1.0 eq.) and stannane **15** (114 mg, 0.216 mmol, 4.0 eq.) in NMP (1.2 mL) at r.t. was added CuTC (108 mg, 0.541 mmol, 10 eq.). The reaction mixture was stirred overnight before quenching with NH_4Cl (5 mL). The mixture was then extracted with DCM (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford crude TIPS ester. This ester was then dissolved in THF / MeOH (3.6 mL : 1.2 mL) and KF (62.7 mg, 1.08 mmol, 20 eq.) added at r.t.. The mixture was stirred for 2 h before quenching with NH_4Cl (5 mL). The mixture was extracted with DCM (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (5% EtOAc / P.E. → 30% EtOAc / P.E.) yielded *seco*-acid **17a**, contaminated with stannane impurity, which was taken on directly to the next step. $\boldsymbol{R_f}$ 0.23 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ –18.3 (*c* 0.49, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2928, 2856, 1692, 1636, 1462; ^{1}**H NMR** (500 MHz, C_6D_6) δ = 7.58 (1H, dd, *J* = 11.2, 15.4 Hz, H4), 6.62 (1H, ddd, *J* = 10.4, 10.8, 16.9 Hz, H25), 6.32 (1H, t, *J* = 11.3 Hz, H3), 6.09 (2H, t, *J* = 11.1 Hz, H11, H24), 5.98 (1H, dd, *J* = 8.7, 15.3 Hz, H5), 5.66 (1H, dd, *J* = 9.0, 10.6 Hz, H10), 5.60 (1H, d, *J* = 11.3 Hz, H2), 5.25 (1H, t, *J* = 10.4 Hz, H23), 5.13 (1H, d, *J* = 16.7 Hz, H26a), 5.03 (2H, t, *J* = 9.0 Hz, H15, H26b), 4.64 (1H, dd, *J* = 6.9, 8.4 Hz, H9), 3.85 (1H, dd, *J* = 2.0, 7.9 Hz, H19), 3.78 (1H, ddd, *J* = 3.2, 5.5, 9.5 Hz, H7), 3.56 (1H, dd, *J* = 2.1, 8.6 Hz, H21), 3.29 (1H, dd, *J* = 1.4, 5.2 Hz, H13), 2.88 (1H, t, *J* = 7.4 Hz, H12), 2.79 (1H, dq, *J* = 7.3, 8.4 Hz, H22), 2.64 (1H, dq, *J* = 7.1, 9.2 Hz, H14), 2.59 (1H, t, *J* = 12.3 Hz, H17a), 2.16 – 2.23 (2H, m, H6, H18), 1.89 – 1.96 (2H, m, H8a, H20), 1.83 (1H, d, *J* = 13.6 Hz, H17b), 1.80 (3H, s, Me16), 1.55 – 1.63 (1H, m, H8b), 1.45 (3H, s, $C(CH_3)_2$), 1.38 (3H, s, $C(CH_3)_2$), 1.19 (3H, d, *J* = 7.1 Hz, Me12), 1.16 (3H, d, *J* = 6.6 Hz, Me14), 1.12 (9H, s, $SiC(CH_3)_3$), 1.11 (3H, d, *J* = 6.9 Hz, Me20), 1.10 (3H, d, *J* = 6.9 Hz, Me18), 1.05 (9H, s, $SiC(CH_3)_3$), 0.97 (3H, d, *J* = 6.8 Hz, Me6), 0.78 (3H, d, *J* = 6.8 Hz, Me18), 0.26 (3H, s, $Si(CH_3)_2$), 0.22 (3H, s, $Si(CH_3)_2$), 0.14 (3H, s, $Si(CH_3)_2$), 0.11 (3H, s, $Si(CH_3)_2$); ^{13}**C NMR** (125 MHz, C_6D_6) δ = 168.7, 146.4, 145.7, 134.8, 134.4, 133.6, 132.4, 131.9, 131.3, 130.5, 118.8, 116.8, 100.6, 81.0, 79.2, 75.7, 70.1, 63.6, 50.3, 41.8, 38.8, 38.1, 36.9, 36.7, 34.6, 33.5, 30.2, 26.7, 26.5, 25.1, 24.8, 23.5, 20.6, 19.6, 19.0, 16.8, 14.4, 13.8, 12.2, 10.4, 1.4, –2.5, –2.5, –2.9, –3.1; **HRMS** (ESI+) Calcd. for $C_{48}H_{86}O_7NaSi_2$ $[M+Na]^+$: 853.5810. Found: 853.5848.



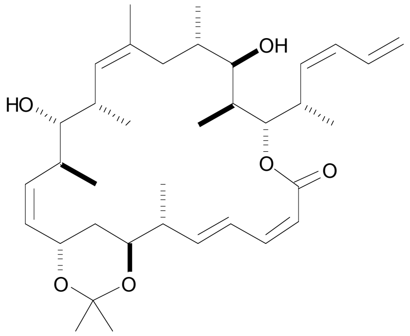
27

Macrolactone **27**: Triethylamine (53 μL, 0.378 mmol, 7.0 eq.) was added to a solution of freshly azeotroped *seco*-acid **17a** (48 mg, 54 μmol, 1.0 eq.) in PhMe (6.6 mL) at r.t.. After stirring for 10 min, 2,4,6-trichlorobenzoylchloride (42 μL, 0.270 mmol, 5.0 eq.) was added and the mixture was stirred for a further hour before first diluting with PhMe (26.5 mL) and then adding DMAP (660 μL of a 0.08 M solution in PhMe, 1.0 eq.); a white suspension formed. A further aliquot of DMAP (660 μL of a 0.08 M solution in PhMe, 1.0 eq.) was added each day for 4 days, before the reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. Flash chromatography (100% PhMe) yielded macrolactone **27** (34 mg, 77% over two steps) as a colourless oil. **R_f** 0.31 (100% PhMe); $[\alpha]_D^{20}$ +55.6 (*c* 0.28, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2928, 2856, 1715, 1642, 1461; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.78 – 7.88 (1H, m, H4), 6.70 (1H, ddd, *J* = 10.4, 10.6, 16.9 Hz, H25), 6.24 (1H, t, *J* = 11.2 Hz, H3), 6.14 (1H, dd, *J* = 8.6, 10.6 Hz, H11), 5.98 (1H, t, *J* = 10.6 Hz, H24), 5.66 (1H, dd, *J* = 5.7, 15.7 Hz, H5), 5.61 (1H, *obs* d, *J* = 11.2 Hz, H2), 5.60 (1H, *obs* d, *J* = 10.1 Hz, H10), 5.21 – 5.28 (2H, m, H21, H23), 5.11 (1H, d, *J* = 16.5 Hz, H26a), 5.06 (1H, d, *J* = 9.9 Hz, H26b), 4.96 (1H, d, *J* = 10.3 Hz, H15), 4.61 (1H, dq, *J* = 4.7, 5.2 Hz, H9), 3.95 (1H, ddd, *J* = 3.8, 7.0, 10.6 Hz, H7), 3.32 (1H, d, *J* = 9.2 Hz, H19), 3.26 (1H, d, *J* = 9.3 Hz, H13), 2.97 – 3.06 (1H, m, H22), 2.86 (1H, qn, *J* = 7.5 Hz, H12), 2.69 – 2.75 (1H, m, H6), 2.56 – 2.67 (3H, m, H14, H18, H17a), 2.11 (1H, t, *J* = 7.2 Hz, H20), 1.37 – 1.40 (1H, *obs* m, H8b), 2.05 (3H, s, Me16), 1.59 (1H, d, *J* = 10.5 Hz, H17b), 1.49 (3H, s, $C(CH_3)_2$), 1.43 (3H, s, $C(CH_3)_2$), 1.31 (3H, d, *J* = 6.9 Hz, Me6), 1.18 (3H, d, *J* = 7.3 Hz, Me12), 1.15 (3H, d, *J* = 7.1 Hz, Me20), 1.12 (3H, d, *J* = 5.6 Hz, Me18), 1.10 (9H, s, $SiC(CH_3)_3$), 1.05 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, *J* = 6.0 Hz, Me14), 0.78 (3H, *br* s, Me22), 0.15 (3H, s, $Si(CH_3)_2$), 0.13 (3H, s, $Si(CH_3)_2$), 0.12 (3H, s, $Si(CH_3)_2$), 0.10 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 165.7, 152.1, 145.0, 144.2, 136.0, 133.8, 132.9, 131.0, 130.4, 129.8, 125.9, 117.7, 100.6, 81.5, 78.3, 68.1, 67.0, 64.1, 39.7, 39.2, 38.7, 38.0, 36.3, 34.7, 34.4 32.3, 30.5, 26.7 (3C), 26.5 (3C), 25.5, 24.7, 23.4, 21.4, 20.3, 18.9, 16.8, 14.4, 10.8, –2.3, –2.8, –3.0; **HRMS** (ESI+) Calcd. for $C_{48}H_{84}O_6NaSi_2$ $[M+Na]^+$: 835.5704. Found: 835.5731.



12

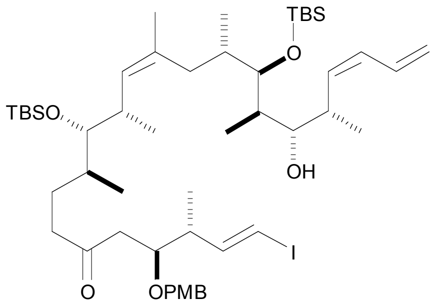
Double Hybrid **12**: To a stirred solution of macrolactone **27** (10.0 mg, 12.3 μmol) in MeOH (1.6 mL) at 0 °C was added acidified MeOH (3.2 mL, 3:1 MeOH:3N HCl). The reaction mixture was allowed to warm to r.t. and stirred for 48 h before being diluted with H_2O (5 mL) and extracted with EtOAc (4 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (25% EtOAc → 50% EtOAc → 75% EtOAc → 100% EtOAc) yielded macrolactone **12** (4.8 mg, 72%) as a colourless oil. $\boldsymbol{R_f}$ 0.48 (100% EtOAc); $\mathbf{R_t}$ 15 mins (10% IPA / hexane); $[\alpha]_D^{20}$ –106.9 (*c* 0.38, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3406, 2965, 2931, 1687, 1638, 1453; ^{1}**H NMR** (500 MHz, C_6D_6) δ = 7.51 (1H, dd, *J* = 11.2, 15.6 Hz, H4), 6.64 (1H, ddd, *J* = 10.5, 10.6, 16.8 Hz, H25), 6.25 (1H, t, *J* = 11.6 Hz, H3), 6.02 (1H, t, *J* = 11.0 Hz, H24), 5.88 (1H, dd, *J* = 7.7, 15.5 Hz, H5), 5.63 (1H, d, *J* = 11.7 Hz, H2), 5.53 – 5.64 (2H, m, H10, H11), 5.40 (1H, t, *J* = 10.5 Hz, H23), 5.30 (1H, dd, *J* = 3.0, 8.6 Hz, H21), 5.12 (1H, d, *J* = 17.0 Hz, H26a), 5.00 (2H, t, *J* = 12.0 Hz, H15, H26b), 4.66 (1H, dq, *J* = 4.0, 7.8 Hz, H9), 4.01 (1H, d, *J* = 10.6 Hz, H7), 3.27 (1H, dd, *J* = 2.4, 8.6 Hz, H19), 3.04 – 3.13 (2H, m, H13, H22), 2.65 – 2.78 (2H, m, H12, H14), 2.30 – 2.38 (2H, m, H6, H18), 2.00 – 2.18 (3H, m, H17a, H17b, H20), 1.79 (3H, s, Me16), 1.67 (1H, ddd, *J* = 3.8, 10.4, 14.3 Hz, H8a), 1.46 (1H, ddd, *J* = 2.3, 7.8, 14.1 Hz, H8b), 1.25 (3H, d, *J* = 6.7 Hz, Me20), 1.17 (3H, d, *J* = 6.8 Hz, Me6), 1.07 (3H, d, *J* = 6.9 Hz, Me12), 1.05 (3H, d, *J* = 7.0 Hz, Me14), 0.96 (3H, d, *J* = 6.6 Hz, Me18), 0.87 (3H, d, *J* = 6.6 Hz, Me22); ^{13}**C NMR** (125 MHz, C_6D_6) δ = 166.2 (C1), 144.9 (C5), 143.2 (C3), 134.8 (C23), 134.5 (C10), 134.0 (C11), 132.7 (C25), 132.6 (C16), 130.4 (C24), 128.6 (C15), 127.9 (C4), 118.1 (C2), 118.0 (C26), 79.5 (C13), 76.8 (C21), 74.8 (C19), 71.1 (C7), 66.0 (C9), 43.3 (C6), 40.8 (C8), 37.8 (C14), 37.6 (C17), 37.2 (C20), 35.4 (C22), 35.2 (C12), 31.8 (C18), 23.2 (Me16), 20.0 (Me12), 19.3 (Me14), 17.2 (Me22), 15.6 (Me6), 12.7 (Me18), 10.8 (Me20); **HRMS** (ESI+) Calcd. for $C_{33}H_{53}O_6$ $[M+H]^+$: 545.3842. Found: 545.3864.



18

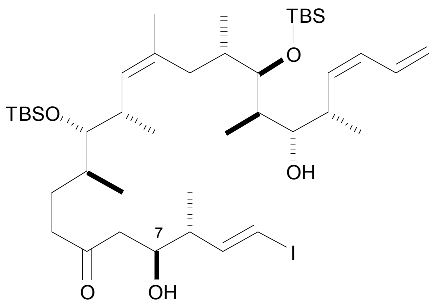
Acetonide **18**: To a stirred solution of hybrid **12** (0.7 mg, 1.3 μmol) in 2,2-dimethoxypropane (300 μL) at 0 ˚C was added PPTS (1 crystal). The reaction mixture was stirred overnight and allowed to slowly warm to r.t.. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (20% → 40% EtOAc / P.E.) to afford acetonide **18** (0.7 mg, quant) as a colourless oil. $\boldsymbol{R_f}$ 0.66 (40% EtOAc); $\mathbf{R_t}$ 16 mins (25% EtOAc / hexane); $[\alpha]_D^{20}$ –20.0 (*c* 0.06, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3395, 2923, 2853, 1713, 1641, 1456; ^{1}**H NMR** (500 MHz, C_6D_6) δ = 7.60 (1H, dd, *J* = 11.0, 15.0 Hz, H4), 6.67 (1H, ddd, *J* = 9.5, 10.6, 16.5 Hz, H25), 6.24 (1H, t, *J* = 11.0 Hz, H3), 5.99 (1H, t, *J* = 10.9 Hz, H24), 5.77 (1H, dd, *J* = 7.0, 15.9 Hz, H5), 5.53 – 5.68 (3H, m, H2, H10, H11), 5.31 (1H, t, *J* = 10.9 Hz, H23), 5.23 (1H, dd, *J* = 2.3, 9.1 Hz, H21), 5.10 (1H, d, *J* = 16.8 Hz, H26a), 5.03 (1H, d, *J* = 10.5 Hz, H26b), 4.95 (1H, d, *J* = 10.5 Hz, H15), 4.58 (1H, dq, *J* = 6.4, 9.9 Hz, H9), 3.87 (1H, ddd, *J* = 3.2, 6.4, 9.0 Hz, H7), 3.08 (1H, d, *J* = 9.5 Hz, H19), 3.03 (1H, dq, *J* = 6.4, 14.9 Hz, H22), 2.95 (1H, dd, *J* = 3.7, 7.8 Hz, H13), 2.66 – 2.74 (1H, m, H12), 2.62 (1H, q, *J* = 8.2 Hz, H14), 2.50 – 2.56 (1H, m, H6), 2.43 – 2.50 (1H, m, H18), 2.28 (1H, t, *J* = 12.3 Hz, H17a), 1.98 (1H, ddd, *J* = 2.8, 7.3, 9.6 Hz, H20), 1.89 – 1.95 (1H, m, H17b), 1.86 (3H, s, Me16), 1.79 (1H, ddd, *J* = 5.9, 9.1, 14.9 Hz, H8a), 1.41 (3H, s, $C(CH_3)_2$), 1.38 (3H, s, $C(CH_3)_2$), 1.28 – 1.35 (1H, m, H8b), 1.24 (3H, d, *J* = 6.8 Hz, Me6), 1.15 (3H, d, *J* = 7.2 Hz, Me20), 1.06 (3H, d, *J* = 6.9 Hz, Me12), 1.03 (3H, d, *J* = 6.9 Hz, Me14), 0.95 (3H, d, *J* = 6.8 Hz, Me18), 0.80 (3H, d, *J* = 7.3 Hz, Me22); ^{13}**C NMR** (125 MHz, C_6D_6) δ = 165.8, 144.3, 143.8, 135.0, 134.6, 132.9, 132.8, 131.9, 130.3, 127.8, 117.8, 117.7, 100.6, 79.9, 76.0, 75.2, 68.2, 67.9, 63.9, 40.6, 37.6, 37.5, 36.2, 35.1, 34.2, 31.3, 25.9, 25.2, 24.7, 23.3, 19.5, 19.3, 17.0, 11.6, 10.4; **HRMS** (ESI+) Calcd. for $C_{36}H_{56}O_6Na$ $[M+Na]^+$: 607.3975. Found: 607.3994.

Synthesis of 10,11-Dihydro Double Hybrid **23**



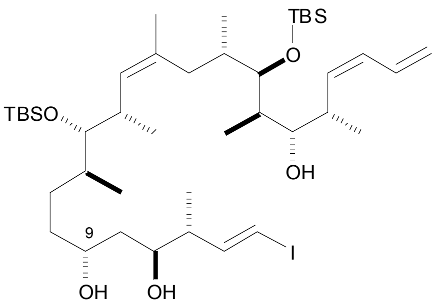
24a

Ketone **24a**: (*E*)-Enone **24** (23.0 mg, 0.24 mmol, 1.0 eq.) was dissolved in PhMe : H_2O (400:1, 1.2 mL) and degassed (freeze-thaw) before Stryker's reagent (18.3 mg, 9.5 μmol, 0.4 eq.) was added at r.t. and stirred for 16 h. The solvent was removed *in vacuo* and the reaction mixture was loaded onto a column and purified by flash chromatography to yield the ketone **24a** (18.6 mg, 80%) as a colourless oil. $\boldsymbol{R_f}$ 0.72 (10% EtOAC / PhMe); $[\alpha]_D^{20}$ +12.1 (*c* 0.70, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2957, 2928, 2855, 1713, 1613, 1514, 1462; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.21 (2H, d, *J* = 8.3 Hz, Ar), 6.85 (2H, d, *J* = 8.3 Hz, Ar), 6.63 (1H, dt, *J* = 10.5, 16.8 Hz, H25), 6.49 (1H, dd, *J* = 8.3, 14.5 Hz, H5), 6.14 (1H, t, *J* = 11.0 Hz, H24), 6.04 (1H, d, *J* = 14.5 Hz, H4), 5.34 (1H, t, *J* = 10.5 Hz, H23), 5.24 (1H, d, *J* = 16.8 Hz, H26a), 5.15 (1H, d, *J* = 10.4 Hz, H26b), 5.02 (1H, d, *J* = 10.2 Hz, H15), 4.42 (2H, q, *J* = 10.7 Hz, $OC\underline{H_2}Ar$), 3.88 (1H, dt, *J* = 4.2, 8.3, Hz, H7), 3.79 (3H, s, OMe), 3.62 (1H, dd, *J* = 3.5, 5.2 Hz, H19), 3.32 – 3.36 (1H, m, H21), 3.25 (1H, dd, *J* = 4.3, 5.8 Hz, H13), 2.81 (1H, dt, *J* = 7.2, 9.7 Hz, H22), 2.65 (1H, dd, *J* = 7.6, 16.5 Hz, H8a), 2.51 (1H, dt, *J* = 6.6, 10.2 Hz, H14), 2.37 – 2.46 (3H, m, H6, H8b, H10a), 2.29 (1H, ddd, *J* = 6.0, 9.9, 16.1 Hz, H10b), 2.21 (1H, t, *J* = 12.1 Hz, H17a), 1.86 – 1.93 (1H, m, H18), 1.72 – 1.84 (3H, m, H11a, H17b, H20), 1.61 (3H, s, Me16), 1.48 – 1.54 (1H, m, H12), 1.27 – 1.34 (1H, m, H11b), 1.04 (3H, d, *J* = 7.0 Hz, Me6), 0.97 (3H, d, *J* = 7.1 Hz, Me22), 0.95 (3H, d, *J* = 7.2 Hz, Me20), 0.92 (9H, s, $SiC(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.89 (3H, d, *J* = 6.6 Hz, Me14), 0.85 (3H, d, *J* = 6.7 Hz, Me12), 0.74 (3H, d, *J* = 6.8 Hz, Me18), 0.09 (6H, s, $Si(CH_3)_2$), 0.042 (3H, s, $Si(CH_3)_2$), 0.038 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (500 MHz, $CDCl_3$) δ = 209.6, 159.4, 148.0, 134.9, 132.3, 132.1, 131.6, 131.2, 130.6, 129.7 (2C), 118.6, 113.9 (2C), 80.9, 78.9, 77.9, 76.5, 76.0, 72.7, 55.5, 45.1, 44.6, 43.1, 38.3, 38.2, 36.5, 35.8, 35.0, 26.42 (3C), 26.38 (3C), 23.4, 18.67, 18.63, 17.5, 17.4, 16.5, 15.4, 13.7, 9.7, –3.1, –3.35, –3.4, –3.7; **HRMS** (ESI+) calc. for $C_{50}H_{91}NIO_6Si_2$ $[M+NH_4]^+$: 984.5424. Found: 984.5422.



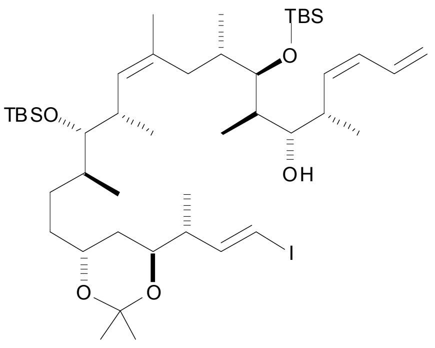
25

Diol **25**: To a stirred biphasic solution of PMB ether **24a** (27.5 mg, 0.028 mmol, 1.0 eq.) in DCM (1.1 mL) and pH 7 buffer (250 µL) at 0 ˚C was added DDQ (9.0 mg, 0.040 mmol, 1.4 eq.). After 2.5 h, the reaction was quenched by the addition of $NaHCO_3$ (3 mL). The layers were separated and the aqueous phase extracted with DCM (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (5% → 10% EtOAc / P.E.) afforded diol **25** (20.6 mg, 87%) as a colourless oil. ***R$_f$*** 0.36 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +7.3 (*c* 0.90, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2958, 2630, 2856, 1709, 1462, 1377; **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.66 (1H, dt, *J* = 10.8, 17.1 Hz, H25), 6.56 (1H, dd, *J* = 8.5, 14.1 Hz, H5), 6.08 (1H, t, *J* = 10.8 Hz, H24), 5.78 (1H, dd, *J* = 0.8, 14.6 Hz, H4), 5.24 (1H, t, *J* = 10.6 Hz, H23), 5.15 – 5.20 (2H, m, H15, H26a), 5.06 (1H, d, *J* = 10.1 Hz, H26b), 3.81 (1H, dd, *J* = 3.6, 5.2 Hz, H19), 3.74 (1H, dt, *J* = 3.0, 9.9 Hz, H7), 3.34 – 3.39 (2H, m, H13, H21), 2.95 (1H, s, OH), 2.77 – 2.87 (2H, m, H14, H22), 2.46 (1H, t, *J* = 12.1 Hz, H17a), 2.04 – 2.18 (4H, m, H8a, H10a, H17b, H18), 1.87 – 2.01 (4H, m, H8b, H10b, H11a, H20), 1.83 – 1.87 (1H, m, H6), 1.78 (3H, s, Me16), 1.61 – 1.67 (1H, m, H12), 1.47 (1H, s, OH), 1.38 – 1.45 (1H, m, H11b), 1.16 (3H, d, *J* = 6.6 Hz, Me14), 1.14 (3H, d, *J* = 6.9 Hz, Me20), 1.09 (9H, s, $SiC(CH_3)_3$), 1.06 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, *J* = 6.7 Hz, Me18), 0.95 (3H, d, *J* = 7.1 Hz, Me12), 0.90 (3H, d, *J* = 6.6 Hz, Me22), 0.85 (3H, d, *J* = 6.9 Hz, Me6), 0.22 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.15 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (500 MHz, C_6D_6) δ = 210.8, 148.0, 134.8, 132.6 (2C), 131.9, 131.4, 128.6, 118.5, 81.6, 79.0, 76.3, 76.0, 70.2, 46.6, 46.2, 42.1, 39.1, 38.2, 37.0, 36.6, 36.3, 35.6, 26.6 (3C), 26.5 (3C), 26.1, 23.6, 18.9, 18.8, 18.2, 17.4, 16.9, 15.9, 14.3, 10.1, –3.1, –3.16, –3.24, –3.5; **HRMS** (ESI+) calc. for $C_{42}H_{83}NIO_5Si_2$ $[M+NH_4]^+$: 864.4849. Found: 864.4839.



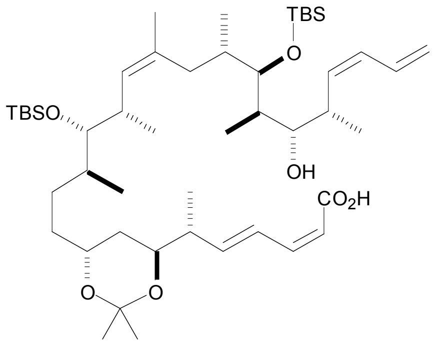
26

Triol **26**: A solution of sodium triacetoxyborohydride (38.8 mg, 0.147 mmol, 5 eq.) in MeCN / AcOH (2:1, 760 μL : 380 μL) at 0 °C was treated with a solution of β-hydroxyketone **25** (12.5 mg, 0.015 mmol, 1.0 eq) in MeCN (380 μL). After stirring for 16 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) then a saturated solution of Na/K tartrate (5 mL). After 1 h at r.t., the aqueous layer was extracted with DCM (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by column chromatography (15% → 30% EtOAc / P.E.) to afford the triol **26** (6.9 mg, 55%) as a colourless oil and unreacted starting material (4.5 mg, 36%, 91% brsm). ***R_f*** 0.29 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +13.8 (*c* 0.85, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2958, 2929, 2856, 1461, 1376, 1370, 1251; **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.67 (1H, dt, *J* = 10.7, 16.7 Hz, H25), 6.48 (1H, dd, *J* = 8.5, 14.3 Hz, H5), 6.09 (1H, t, *J* = 11.2 Hz, H24), 5.80 (1H, d, *J* = 14.5 Hz, H4), 5.16 – 5.28 (3H, m, H15, H23, H26a), 5.07 (1H, d, *J* = 10.3 Hz, H26b), 3.82 (1H, t, *J* = 4.0 Hz, H19), 3.73 – 3.78 (1H, m, H9), 3.51 – 3.56 (1H, m, H7), 3.42 (1H, dd, *J* = 3.6, 6.2 Hz, H13), 3.37 (1H, dd, *J* = 4.4, 6.8 Hz, H21), 2.80 – 2.87 (2H, m, H14, H22), 2.46 (1H, t, *J* = 12.5 Hz, H17a), 2.06 – 2.14 (2H, m, H18, H17b), 1.89 – 1.95 (2H, m, H6, H20), 1.78 (3H, s, Me16), 1.70 – 1.75 (1H, m, H12), 1.42 – 1.48 (2H, m, H8a, H11a), 1.24 – 1.34 (4H, m, H8b, H10a, H10b, H11b), 1.18 (3H, d, *J* = 6.4 Hz, Me14), 1.15 (3H, d, *J* = 7.0 Hz, Me20), 1.09 (9H, s, $SiC(CH_3)_3$), 1.07 (9H, s, $SiC(CH_3)_3$), 1.06 (3H, d, *J* = 7.1 Hz, Me12), 1.02 (3H, d, *J* = 6.5 Hz, Me18), 0.91 (3H, d, *J* = 6.8 Hz, Me22), 0.79 (3H, d, *J* = 6.8 Hz, Me6), 0.23 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.17 (3H, s, $Si(CH_3)_2$), 0.15 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (500 MHz, C_6D_6) δ = 148.6, 134.8, 132.7, 132.4, 132.2, 131.4, 128.6, 118.6, 81.6, 79.0, 76.3, 76.1, 71.4, 70.0, 47.3, 40.5, 39.2, 39.1, 37.0, 36.7, 36.3, 35.7, 28.9, 26.62 (3C), 26.59 (3C), 23.6, 18.91, 18.87, 18.2, 17.5, 17.3, 15.9, 14.4, 14.3, 10.2, –3.1, –3.17, –3.21, –3.4; **HRMS** (ESI+) calc. for $C_{42}H_{85}NIO_5Si_2$ $[M+NH_4]^+$: 866.5005. Found: 866.4994.



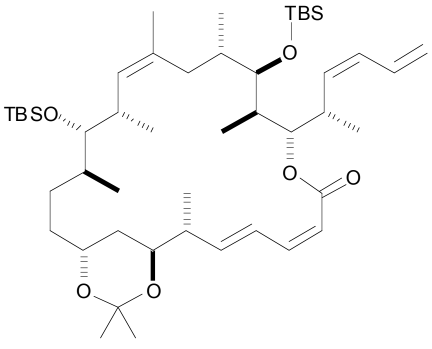
26a

Acetonide **26a**: To a stirred solution of 1,3-diol **26** (15.9 mg, 19 μmol, 1.0 eq.) in DCM (900 μL) and 2,2-dimethoxypropane (2.5 mL) at 0 °C was added PPTS (1 crystal). The reaction mixture was stirred overnight and allowed to slowly warm to r.t.. The solvent was removed *in vacuo* and the crude product purified by flash column chromatography (5% EtOAc / P.E.) to afford acetonide **26a** (16.7 mg, quant.) as a colourless oil. $\boldsymbol{R_f}$ 0.68 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +3.9 (*c* 0.84, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2958, 2929, 2856, 1462, 1378, 1251, 1224; **^{1}H NMR** (500 MHz, C_6D_6) δ = 6.60 – 6.70 (2H, m, H5, H25), 6.05 (1H, t, *J* = 11.0 Hz, H24), 5.83 (1H, d, *J* = 14.6 Hz, H4), 5.27 (1H, d, *J* = 10.3 Hz, H15), 5.19 (1H, *obs* t, *J* = 10.3 Hz, H23), 5.15 (1H, *obs* d, *J* = 17.0 Hz, H26a), 5.05 (1H, d, *J* = 10.2 Hz, H26b), 3.82 – 3.85 (1H, m, H19), 3.68 (1H, dt, *J* = 5.7, 8.7 Hz, H9), 3.52 (1H, dt, *J* = 3.8, 6.1 Hz, H7), 3.42 (1H, t, *J* = 5.1 Hz, H13), 3.32 – 3.37 (1H, m, H21), 2.78 – 2.87 (2H, m, H14, H22), 2.50 (1H, t, *J* = 12.2 Hz, H17a), 2.09 – 2.17 (1H, m, H18), 2.04 (1H, d, *J* = 14.3 Hz, H17b), 1.99 (1H, q, *J* = 6.9 Hz, H6), 1.90 – 1.95 (1H, m, H20), 1.84 – 1.90 (1H, m, H11a), 1.79 (3H, s, Me16), 1.70 – 1.77 (1H, m, H12), 1.46 – 1.57 (3H, m, H8a, H10a, H11b), 1.36 (3H, s, $C(CH_3)_2$), 1.33 (3H, s, $C(CH_3)_2$), 1.27 – 1.40 (2H, *obs* m, H8a, H10b), 1.17 (3H, d, *J* = 7.1 Hz, Me14), 1.13 (3H, d, *J* = 7.1 Hz, Me20), 1.08 (3H, *obs* d, Me12), 1.08 (9H, s, $SiC(CH_3)_3$), 1.07 (9H, s, $SiC(CH_3)_3$), 1.01 (3H, d, *J* = 6.6 Hz, Me18), 0.88 (3H, d, *J* = 6.9 Hz, Me22), 0.82 (3H, d, *J* = 6.9 Hz, Me6), 0.23 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.16 (3H, s, $Si(CH_3)_2$), 0.14 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (500 MHz, C_6D_6) δ = 148.6, 148.5, 134.8, 132.6, 132.4, 132.1, 131.5, 118.6, 100.5, 81.3, 79.1, 76.2, 75.7, 69.6, 67.5, 45.3, 39.2, 39.0, 37.0, 36.7, 36.1, 35.7, 35.1, 29.2, 26.63 (3C), 26.57 (3C), 24.9, 24.8, 23.6, 18.9, 18.8, 17.7, 17.3, 16.8, 15.3, 14.1, 10.1, –3.1, –3.2, –3.3, –3.5; **HRMS** (ESI+) calc. for $C_{45}H_{89}NIO_5Si_2$ $[M+NH_4]^+$: 906.5318. Found: 906.5327.



26b

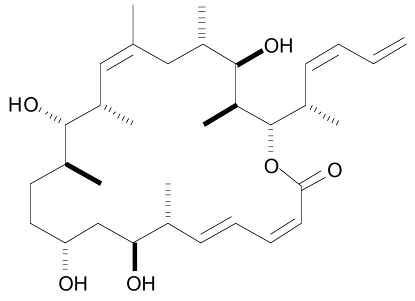
Seco-Acid **26b**: To a deoxygenated (freeze-thaw) solution of vinyl iodide **26a** (8.0 mg, 9 μmol, 1.0 eq.) and stannane **15** (19 mg, 36 μmol, 4.0 eq.) in NMP (200 μL) at r.t. was added CuTC (18 mg, 0.090 mmol, 10 eq.). The reaction mixture was stirred overnight before quenching with NH_4Cl (5 mL). The mixture was then extracted with DCM (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford the TIPS ester. The crude ester was then dissolved in THF / MeOH (600 μL : 200 μL) and KF (10.5 mg, 0.180 mmol, 20 eq.) added at r.t.. The mixture was stirred for 2 h before quenching with NH_4Cl (5 mL). The mixture was extracted with DCM (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (10% → 25% EtOAc / P.E.) yielded *seco*-acid **26b** contaminated with stannane impurity, which was taken on directly to the next step. ***R_f*** 0.17 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ –6.1 (*c* 0.80, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2957, 2928, 2856, 1690, 1637, 1600, 1461, 1378; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.70 (1H, t, *J* = 12.1 Hz, H4), 6.65 (1H, dt, *J* = 10.6, 16.5 Hz, H25), 6.33 (1H, t, *J* = 9.7 Hz, H3), 6.03 – 6.11 (2H, m, H5, H24), 5.57 (1H, d, *J* = 10.6 Hz, H2), 5.18 – 5.27 (2H, m, H15, H23), 5.16 (1H, d, *J* = 17.0 Hz, H26a), 5.05 (1H, d, *J* = 10.2 Hz, H26b), 3.83 – 3.89 (1H, m, H19), 3.72 – 3.79 (1H, m, H9), 3.65 – 3.71 (1H, m, H7), 3.38 – 3.45 (2H, m, H13, H21), 2.78 – 2.87 (2H, m, H14, H22), 2.49 – 2.58 (1H, m, H17a), 2.21 – 2.29 (1H, m, H6), 2.11 – 2.19 (1H, m, H18), 2.03 (1H, dd, *J* = 12.4 Hz, H17b), 1.90 – 1.97 (1H, m, H20), 1.80 (3H, s, Me16), 1.71 – 1.77 (1H, m, H12), 1.63 – 1.71 (3H, m, H8a, H10a, H11a), 1.42 – 1.47 (2H, *obs* m, H8b, H10b), 1.43 (3H, s, $C(CH_3)_2$), 1.39 (3H, s, $C(CH_3)_2$), 1.37 – 1.41 (1H, *obs* m, H11b), 1.18 (3H, d, *J* = 6.2 Hz, Me14), 1.13 (3H, d, *J* = 6.8 Hz, Me20), 1.10 (3H, *obs* d, Me12), 1.09 (15H, *br* s, Me6, Me18, $SiC(CH_3)_3$), 1.07 (9H, s, $SiC(CH_3)_3$),1.02 (3H, d, *J* = 6.4 Hz, Me22), 0.24 (3H, s, $Si(CH_3)_2$), 0.21 (3H, s, $Si(CH_3)_2$), 0.16 (3H, s, $Si(CH_3)_2$), 0.14 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (500 MHz, C_6D_6) δ = 171.0, 148.1, 147.4, 142.1, 134.8, 132.5, 132.4, 131.6, 118.7, 115.9, 100.5, 81.4, 79.1, 76.2, 70.2, 67.6, 42.2, 39.4, 38.9, 37.3, 37.1, 36.7, 36.0, 35.3, 30.3, 29.2, 28.4, 27.5, 26.7 (3C), 26.5 (3C), 24.95, 24.85, 23.6, 18.9, 18.8, 17.4, 17.3, 16.8, 16.5, 14.0, 10.1, –2.9, –3.1, –3.4, –3.5; **HRMS** (ESI+) calc. for $C_{48}H_{88}O_7Si_2$ $[M+Na]^+$: 855.5966. Found: 855.6004.



26c

Macrolactone **26c**: Triethylamine (3.4 µL, 24 µmol, 2.7 eq.) was added to a solution of freshly azeotroped *seco*-acid **26b** (8.0 mg, 9 µmol, 1.0 eq.) in PhMe (750 µL) at r.t.. After stirring for 10 min, 2,4,6-trichlorobenzoylchloride (2.5 µL, 16 µmol, 1.8 eq.) was added and the mixture was stirred for a further hour before first diluting with PhMe (11 mL) and then adding DMAP (110 µL of a 0.08 M solution in PhMe, 1.0 eq.); a white suspension formed. A further aliquot of DMAP (55 µL of a 0.08 M solution in PhMe, 0.5 eq.) was added after 8 h. The reaction mixture was then stirred for 16 h before it was filtered through a plug of silica and concentrated *in vacuo*. Flash chromatography (100% PhMe) yielded macrolactone **26c** (5.9 mg, 79% over two steps) as a colourless oil. $\boldsymbol{R_f}$ 0.50 (100% PhMe); $[\alpha]_D^{20}$ +73 (*c* 0.59, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2958, 2929, 2857, 1714, 1641, 1602, 1462, 1378; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.82 (1H, *br* s, H4), 6.70 (1H, dt, *J* = 10.8, 17.1 Hz, H25), 6.24 (1H, t, *J* = 11.3 Hz, H3), 5.98 – 6.08 (1H, m, H24), 5.66 (1H, dd, *J* = 5.0, 15.6 Hz, H5), 5.06 (1H, d, *J* = 11.2 Hz, H2), 5.32 – 5.39 (1H, m, H23), 5.25 – 5.32 (1H, m, H21), 5.12 (1H, d, *J* = 16.6 Hz, H26a), 5.06 (1H, d, *J* = 10.1 Hz, H26b), 5.01 (1H, d, *J* = 10.6 Hz, H15), 3.92 (1H, td, *J* = 3.2, 6.6 Hz, H9), 3.76 – 3.82 (1H, m, H7), 3.44 – 3.50 (1H, m, H19), 3.35 (1H, dd, *J* = 2.3, 9.0 Hz, H13), 3.00 – 3.09 (1H, m, H22), 2.78 (1H, q, *J* = 6.7 Hz, H14), 2.56 – 2.63 (1H, m, H6), 2.46 – 2.55 (1H, m, H18), 2.08 (1H, t, *J* = 6.1 Hz, H20), 1.98 (3H, *br* s, Me16), 1.74 – 1.86 (4H, m, H8a, H10a, H12, H17a), 1.58 – 1.64 (2H, m, H8b, H11a), 1.45 (3H, s, C(Me)$_2$), 1.42 (3H, s, C(Me)$_2$), 1.27 – 1.36 (3H, m, H10b, H11b, H17b), 1.24 (3H, d, *J* = 7.0 Hz, Me6), 1.17 (3H, d, *J* = 7.0 Hz, Me20), 1.15 (3H, d, *J* = 6.9 Hz, Me14), 1.09 (3H, d, *J* = 7.1 Hz, Me12), 1.08 (9H, s, $SiC(CH_3)_3$), 1.03 (9H, s, $SiC(CH_3)_3$), 1.01 (3H, d, *J* = 6.8 Hz, Me18), 0.75 – 0.83 (3H, *br* s, Me22), 0.19 (3H, s, $Si(CH_3)_2$), 0.18 (3H, s, $Si(CH_3)_2$), 0.12 (3H, s,

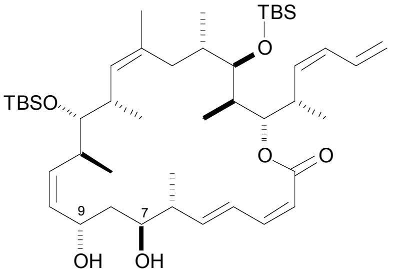
$Si(CH_3)_2$), 0.09 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (500 MHz, C_6D_6) δ = 165.7, 145.6, 135.0, 132.9, 132.0, 131.8, 130.5, 129.4, 126.8, 117.8, 116.4, 100.5, 81.9, 78.8, 76.0, 68.0, 67.1, 60.2, 40.2, 39.0, 38.2, 36.3, 35.8, 35.0, 33.0, 30.7, 30.3, 26.7 (3C), 26.4 (3C), 25.2, 24.8, 23.2, 22.8, 20.6, 20.5, 19.0, 18.7, 16.9, 14.3, 11.0, –2.6, –3.2, –3.5, –3.8; **HRMS** (ESI+) calc. for $C_{48}H_{87}O_6Si_2$ $[M+H]^+$: 815.6041. Found: 815.6008.



23

Double Hybrid **23**: To a stirred solution of protected macrolactone **26c** (1.4 mg, 1.7 μmol) in MeOH (250 μL) at 0 ˚C was added acidified MeOH (500 μL, 3:1 MeOH:3N HCl). The reaction mixture was allowed to warm to r.t. and stirred for 24 h before being diluted with H_2O (3 mL) and extracted with EtOAc (4 × 3 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (33% EtOAc → 66% EtOAc → 100% EtOAc) yielded macrolactone **23** (0.7 mg, 74%) as a colourless oil. ***R_f*** 0.37 (100% EtOAc); **R_t** 12 mins (10% IPA / hexane); –64.6 $[\alpha]_D^{20}$ (*c* 0.3, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3395, 2963, 2928, 1683, 1638, 1454, 1407, 1378; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.43 (1H, dd, *J* = 11.2 Hz, H4), 6.56 (1H, dt, *J* = 10.9, 16.9 Hz, H25), 6.21 (1H, t, *J* = 11.5 Hz, H3), 6.10 (1H, t, *J* = 10.7 Hz, H24), 5.74 (1H, dd, *J* = 8.8, 15.4 Hz, H5), 5.67 (1H, d, *J* = 11.7 Hz, H2), 5.60 (1H, t, *J* = 10.7 Hz, H23), 5.49 (1H, t, *J* = 6.2 Hz, H21), 5.19 (1H, d, *J* = 16.8 Hz, H26b), 5.04 (1H, d, *J* = 10.4 Hz, H26a), 4.92 (1H, d, *J* = 10.6 Hz, H15), 3.65 – 3.71 (2H, m, H7, H9), 3.35 (1H, t, *J* = 5.4 Hz, H19), 3.14 (1H, *ddd*, J = 6.7, 13.4, 18.0 Hz, H22), 3.04 (1H, dd, *J* = 1.7, 7.7 Hz, H13), 2.62 (1H, ddd, *J* = 6.6, 13.7, 17.2 Hz, H14), 2.35 – 2.43 (1H, m, H6), 2.08 – 2.15 (1H, m, H20), 2.05 (2H, d, *J* = 6.8 Hz, H17a, H17b), 1.93 (12H, dt, *J* = 7.0, 13.5 Hz, H18), 1.87 (1H, *br* s, H10a), 1.71 (2H, t, *J* = 7.2 Hz, H10b, H11a), 1.65 (3H, s, Me16), 1.49 – 1.55 (2H, m, H11b, H12), 1.40 – 1.45 (1H, m, H8a), 1.17 – 1.22 (1H, m, H8b), 1.14 (3H, d, *J* = 6.8 Hz, Me20), 1.01 (3H, *obs* d, *J* = 6.3 Hz, Me14), 1.00 (3H, *obs* d, *J* = 6.9 Hz, Me6), 0.98 (3H, *obs* d, *J* = 7.1 Hz, Me22), 0.93 (3H, *obs* d, *J* = 6.8 Hz, Me12), 0.92 (3H, *obs* d, *J* = 6.4 Hz, Me18); **^{13}C NMR** (500 MHz, C_6D_6) δ = 166.5 (C1), 145.0 (C5), 142.2 (C3), 34.4 (C23), 133.4 (C16), 132.6 (C25), 130.2 (C24), 129.9 (C15), 129.3 (C4), 118.7 (C2), 118.2 (C26), 81.0 (C13), 78.1 (C21), 75.3 (C19), 72.5 (C7), 70.0 (C9), 44.0 (C6), 40.7 (C12), 37.9 (C20), 37.1 (C14), 36.3 (C8), 35.8 (C17), 34.8 (C22), 32.9 (C18), 32.0 (C10), 25.3 (C11), 23.0 (Me16), 18.8 (Me14), 17.7 (Me22), 17.2 (Me16), 14.4 (Me18), 14.0 (Me12), 10.4 (Me20); **HRMS** (ESI+) calc. for $C_{33}H_{55}O_6$ $[M+H]^+$: 547.3999. Found: 547.4013.

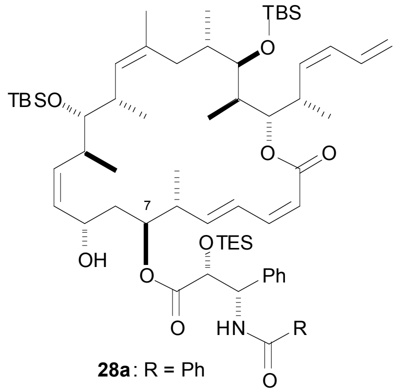
Synthesis of Triple Hybrids **31-34** and Methoxy Analogues **36**, **38-40** and **44-46**



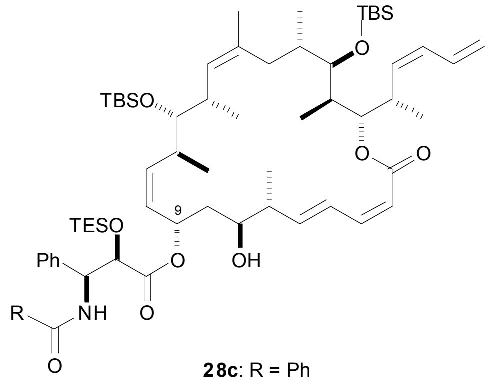
28

Diol **28**: To a stirred solution of acetonide **27** (43.1 mg, 0.0529 mmol) in DCM / MeOH (1:1) at 0 ˚C was added PPTS (1 crystal). The solution was allowed to warm to r.t. and stirred for 16 hr. Solvent was removed *in vacuo* and the crude product purified by flash chromatography (15% → 25% EtOAc / P. E.) to afford diol **28** as a colourless oil (40.0 mg, 98%). **R*f*** 0.05 (20% EtOAc / P. E.); $[\alpha]_D^{20}$ +23.4 (*c* 0.27, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3383, 2928, 1713, 1639, 1598, 1462; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.67 – 7.84 (1H, m, H4), 6.70 (1H, ddd, *J* = 10.5, 10.8, 16.8 Hz, H25), 6.21 (1H, t, *J* = 11.1 Hz, H3), 6.00 (1H, t, *J* = 11.1 Hz, H24), 5.91 (1H, t, *J* = 9.8 Hz, H11), 5.77 (1H, dd, *J* = 6.2, 15.7 Hz, H5), 5.62 (1H, d, *J* = 11.0 Hz, H2), 5.51 (1H, dd, *J* = 8.6, 10.4 Hz, H10), 5.25 – 5.36 (2H, m, H21, H23), 5.14 (1H, d, *J* = 16.8 Hz, H26a), 5.04 – 5.10 (2H, m, H15, H26b), 4.61 (1H, t, *J* = 7.7 Hz, H9), 4.00 (1H, d, *J* = 10.0 Hz, H7), 3.39 (1H, d, *J* = 7.7 Hz, H19), 3.31 (1H, dd, *J* = 2.0, 7.9 Hz, H13), 3.00 – 3.09 (1H, m, H22), 2.74 (1H, t, *J* = 7.3 Hz, H12), 2.61 – 2.68 (1H, m, H14), 2.40 – 2.56 (1H, *br* s, OH), 2.34 (1H, *br* d, *J* = 5.1 Hz, H6), 2.10 (1H, t, *J* = 7.3 Hz, H20), 1.94 – 2.01 (4H, m, H18, Me16), 1.83 – 1.89 (1H, m, H17a), 1.69 (1H, t, *J* = 11.4 Hz, H17b), 1.60 (1H, t, *J* = 11.2 Hz, H8a), 1.30 – 1.36 (1H, m, H8b), 1.12 – 1.16 (12H, m, Me6, Me12, Me14, Me20), 1.10 (9H, s, $SiC(CH_3)_3$), 1.07 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, *J* = 6.7 Hz, Me18), 0.78 – 0.85 (3H, m, Me22), 0.18 (3H, s, $Si(CH_3)_2$), 0.17 (3H, s, $Si(CH_3)_2$), 0.15 (3H, s, $Si(CH_3)_2$), 0.14

(3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 166.0, 145.0, 135.0, 133.7, 133.3, 132.9, 130.5, 130.4, 128.6, 127.2, 117.9, 117.0, 81.2, 78.3, 76.2, 70.3, 65.5, 42.4, 39.5, 38.5, 37.9, 37.1, 34.8, 33.3, 32.4, 30.5, 29.9, 26.8 (3C), 26.6 (3C), 23.2, 23.0, 20.4, 19.5, 19.0, 18.9, 17.1, 10.9, –2.5, –2.9, –3.0, –3.2; **HRMS** (ES^+) calc. for $C_{45}H_{81}NO_6Si_2$ $[M+H]^+$: 773.5566. Found: 773.5565.



28a: R = Ph
28b: R = O^{t}Bu



28c: R = Ph
28d: R = O^{t}Bu

General Procedure A: Alcohol **6** (1.0 eq.) was dissolved in THF and cooled to –78 ˚C before NaHMDS (1M in THF, 1.2 eq.) was added. After 10 min, a solution of β-lactam **29**[3] or **30**[3] (1.5 eq.) in THF was added *via* syringe and stirring continued for 30 min. The reaction mixture was then allowed to warm to 0 ˚C and stirred for an additional 30 min. Following addition of NH_4Cl and separation of the layers, the aqueous phase was extracted with EtOAc (3×), the organic phases were then combined, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (1 % → 5% → 10% EtOAc / P.E.) afforded the desired protected triple hybrids as an inseparable mixture.

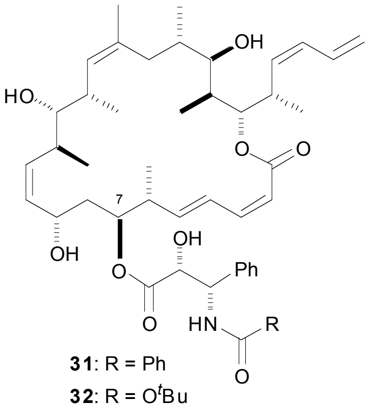
[3] Prepared by adapting the method of Farina *et al.*, see V. Farina, S. I. Hauck, D. G. Walker, *Synlett*, **1992**, 761.

Protected Triple Hybrids **28a** and **28c**: General procedure A was followed with alcohol **28** (3.2 mg, 4.1 μmol, 1.0 eq.) in THF (400 μL). Following addition of NaHMDS (4.9 μL, 1M in THF, 1.2 eq.), β-lactam **29** (2.4 mg, 6.2 μmol, 1.5 eq.) in THF (400 μL) was added *via* syringe. After the standard work-up procedure, flash chromatography yielded an inseparable 3:1 mixture of regioisomers **28a** and **28c** (colourless oil) which was subjected to deprotection without further purification.

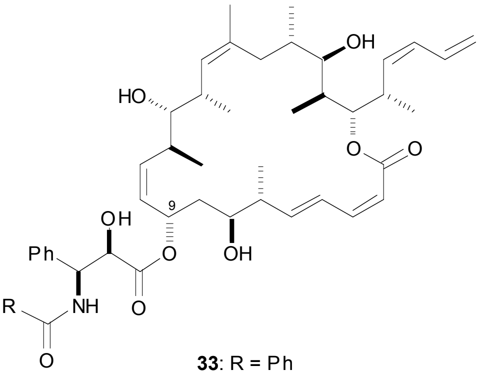
R_f 0.52 (20% EtOAc / P.E.). **HRMS** (ES$^+$) calc. for $C_{67}H_{111}N_2O_9Si_3$ [M+NH$_4$]$^+$: 1171.7592. Found: 1171.7590.

Protected Triple Hybrids **28b** and **28d**: General procedure A was followed with alcohol **28** (3.8 mg, 4.9 μmol, 1.0 eq.) in THF (400 μL). Following addition of NaHMDS (6 μL, 1M in THF, 1.2 eq.), β-lactam **30** (2.8 mg, 7.3 μmol, 1.5 eq.) in THF (400 μL) was added *via* syringe. After the standard work-up procedure, flash chromatography yielded an inseparable 3:2 mixture of regioisomers **28b** and **28d** (colourless oil) which was subjected to deprotection without further purification.

R_f 0.69 (20% EtOAc / P.E.). **HRMS** (ES$^+$) calc. for $C_{65}H_{115}N_2O_{10}Si_3$ [M+NH$_4$]$^+$: 1167.7854. Found: 1167.7851.



31: R = Ph
32: R = O^{t}Bu



33: R = Ph
34: R = O^{t}Bu

General Procedure B: HF·py (400 μL) was added to stirred mixture of pyridine (150 μL) and THF (400 μL) at 0 ˚C. An aliquot of this stock solution was then added to a stirred solution of the silylated compound in THF at 0 ˚C before allowing to warm to r.t.. After stirring for 4 days, the reaction was re-cooled to 0 ˚C and diluted with EtOAc. The mixture was then added dropwise to a stirred solution of NaHCO$_3$ at 0 ˚C *via* pipette. The phases were separated and the aqueous phase was extracted with EtOAc (3×). The organic phases were combined, dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Flash chromatography (25% → 50% EtOAc / P.E.) then afforded the desired final compound.

A mixture of silylated compounds **28a** and **28c** in THF (300 μL) was subjected to general procedure B using 450 μL of the HF·py stock solution. Following flash chromatography, an inseparable mixture of triple hybrids **31** and **33** (1.6 mg, 46% over two steps) was isolated as a white powder. Subsequent HPLC purification isolated regiomerically pure **31** and **33**.

Triple Hybrid **31**: $\mathbf{R_f}$ 0.63 (80% EtOAc / P.E.); $\mathbf{R_t}$ 15.0 mins (8% IPA / hexane); $[\alpha]_D^{20}$ +23.3 (*c* 0.03, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3348, 2923, 2853, 1711, 1647, 1520, 1461; ^{1}**H NMR** (500 MHz, d7-DMF) δ = 8.83 (1H, d, *J* = 8.9 Hz, NH), 8.00 (2H, d, *J* = 8.3 Hz, Ar), 7.60 (2H, d, *J* = 7.8 Hz, Ar), 7.57 (2H, d, *J* = 7.6 Hz, Ar), 7.50 (2H, t, *J* = 7.7 Hz, Ar), 7.37 – 7.43 (1H, m, Ar), 7.32 (1H, t, *J* = 7.5 Hz, Ar), 7.23 (1H, t, *J* = 12.3 Hz, H4), 6.70 – 6.80 (2H, m, H3, H25), 6.24 (1H, dd, *J* = 5.8, 15.6 Hz, H5), 6.05 – 6.13 (1H, m, H24), 5.77 (1H, dd, *J* = 2.9, 9.0 Hz, H11), 5.65 – 5.72 (2H, m, H2, H3′), 5.36 (1H, d, *J* = 9.0 Hz, H23), 5.31 – 5.35 (1H, m, H7), 5.28 (2H, d, *J* = 16.3 Hz, H10, H26a), 5.18 (1H, d, *J* = 10.2 Hz, H26b), 5.07 (1H, t, *J* = 5.8 Hz, H21), 4.98 (1H, d, *J* = 10.2 Hz, H15), 4.70 (1H, d, *J* = 2.8 Hz, C13-O$\underline{\text{H}}$), 4.62 (1H, d, *J* = 4.1 Hz, C19-O$\underline{\text{H}}$), 4.55 – 4.61 (2H, m, H9, H2′), 3.18 – 3.26 (1H, m, H22), 3.08 – 3.16 (2H, t, *J* = 10.2 Hz, H13, H19), 2.54 – 2.61 (1H, m, H6), 2.41 – 2.49 (1H, m, H12), 2.24 – 2.32 (1H, m, H14), 2.02 – 2.08 (1H, m, H18), 1.99 (1H, q, *J* = 6.1 Hz, H20), 1.74 (3H, s, Me16), 1.55 (2H, q, *J* = 11.2 Hz, H8a, H17a), 1.37 – 1.43 (1H, m, H8b), 1.33 – 1.37 (1H, m, H17b), 1.15 (3H, d, *J* = 7.1 Hz, Me12), 1.06 (3H, d, *J* = 6.9 Hz, Me20), 1.05 (3H, d, *J* = 6.9 Hz, Me6), 0.99 (6H, t, *J* = 6.3 Hz, Me14, Me22), 0.74 (3H, d, *J* = 6.3 Hz, Me18); **HRMS** (ES^+) calc. for $C_{49}H_{66}NO_9$ $[M+H]^+$: 812.4738. Found: 812.4736.

Due to hybrid **31**’s tendency to rapidly transesterify, we were unable to successfully measure a ^{13}C NMR spectrum for this compound.

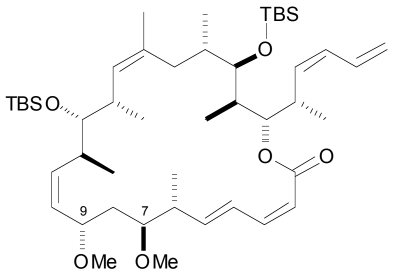
Triple Hybrid **33**: $\mathbf{R_f}$ 0.63 (80% EtOAc / P.E.); $\mathbf{R_t}$ 9.1 mins (8% IPA / hexane); $[\alpha]_D^{20}$ +6.6 (*c* 0.03, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3363, 2922, 2853, 1715, 1655, 1517, 1457; ^{1}**H NMR** (500 MHz, d7-DMF) δ = 8.71 (1H, d, *J* = 9.1 Hz, NH), 7.99 (2H, d, *J* = 7.3 Hz, Ar), 7.55 – 7.61 (3H, m, Ar), 7.52 (2H, t , *J* = 7.8 Hz, Ar), 7.41 (2H, t, *J* = 7.5 Hz, Ar), 7.33 (1H, t, *J* = 7.3 Hz, Ar), 7.20 (1H, t, *J* = 13.1 Hz, H4), 6.72 – 6.81 (2H, m, H3, H25), 6.24 (1H, dd, *J* = 6.1, 15.8 Hz, H5), 6.09 (1H, t, *J* = 10.9 Hz, H24), 6.05 (1H, d, *J* = 9.5 Hz, C2′-O$\underline{\text{H}}$), 5.79 (1H, t, *J* = 9.5 Hz, H11), 5.73 (1H, t, *J* = 9.2 Hz, H9), 5.68 – 5.71 (1H, *obs* m, H3′), 5.67 (1H, *obs* d, *J* = 10.4 Hz, H2), 5.38 (1H, t, *J* = 10.7 Hz, H23), 5.30 (1H, *obs* d, *J* = 15.8 Hz, H26a), 5.29 (1H, *obs* t, *J* = 9.6 Hz, H10), 5.20 (1H, d, *J* = 10.4 Hz, H26b), 5.07 (1H, t, *J* = 5.8 Hz, H21), 4.91 (1H, d, *J* = 10.2 Hz, H15), 4.81 (1H, d, *J* = 5.6 Hz, C13-O$\underline{\text{H}}$), 4.71 (1H, d, *J* = 5.3 Hz, C19-O$\underline{\text{H}}$), 4.63 (1H, t, *J* = 4.4 Hz, H2′), 4.53 (1H, d, *J* = 5.3 Hz, C7-O$\underline{\text{H}}$), 3.21 – 3.28 (1H, m, H22), 3.13 – 3.18 (1H, m, H19), 3.10 (1H, dd, *J* = 6.1, 9.5 Hz, H13), 2.57 (1H, q, *J* = 6.1 Hz, H6), 2.50 (1H, t, *J* = 7.5 Hz, H12), 2.36 (1H, q, *J* = 8.5 Hz, H14), 2.00 (2H, q, *J* = 6.1

Hz, H18, H20), 1.69 (3H, s, Me16), 1.57 (1H, d, *J* = 12.1 Hz, H17a), 1.48 (1H, t, *J* = 11.2 Hz, H8a), 1.41 (1H, dt, *J* = 3.2, 10.4 Hz, H8b), 1.25 – 1.31 (1H, m, H17b), 1.13 (3H, d, *J* = 7.1 Hz, Me12), 1.05 (6H, t, *J* = 6.3 Hz, Me6, Me20), 0.99 (3H, d, *J* = 6.8 Hz, Me22), 0.96 (3H, d, *J* = 6.6 Hz, Me14), 0.74 (3H, d, *J* = 6.7 Hz, Me18); **^{13}C NMR** (125 MHz, d7-DMF) δ = 172.0, 167.8, 166.8, 145.9, 144.0, 140.9, 135.1, 134.1, 133.7, 133.5, 133.1, 132.3, 130.7, 130.6, 129.5, 129.1 (2C), 129.0 (2C), 128.2 (2C), 128.1 (2C), 128.0, 127.3, 118.2, 117.8, 79.1, 78.8, 75.4, 75.0, 70.2, 68.1, 56.9, 43.0, 38.0, 37.8, 37.3, 36.6, 34.6, 32.7, 23.2 (2C), 23.1, 19.4, 18.7, 18.0, 14.3, 13.6, 12.3, 10.0; **HRMS** (ES$^+$) calc. for $C_{49}H_{66}NO_9$ $[M+H]^+$: 812.4738. Found: 812.4734.

A mixture of silylated compounds **28b** and **28d** in THF (300 μL) was subjected to general procedure B using 450 μL of the HF·py stock solution. Following flash chromatography, an inseparable mixture of triple hybrids **32** and **34** (2.2 mg, 57% over two steps) was isolated as a white powder. Subsequent HPLC purification isolated regiomerically pure **32** and **34**.

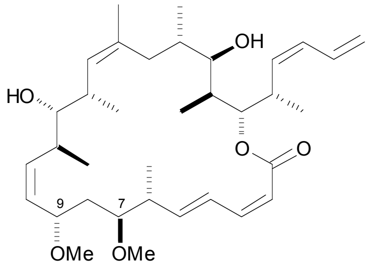
Triple Hybrid **32**: **R*f*** 0.56 (70% EtOAc / P.E.); **Rt** 13.5 mins (7% IPA / hexane); $[\alpha]_D^{20}$ –20.0 (*c* 0.02, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max} = 3450, 2963, 2918, 1696, 1498, 1457; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.68 (1H, t, *J* = 13.5 Hz, H4), 7.38 (2H, d, *J* = 7.4 Hz, Ar), 7.11 (2H, *obs* d, *J* = 7.7 Hz, Ar), 7.05 (1H, t, *J* = 7.4 Hz, Ar), 6.66 (1H, ddd, *J* = 10.7, 10.8, 16.8 Hz, H25), 6.13 (1H, t, *J* = 11.0 Hz, H3), 5.98 (1H, t, *J* = 11.0 Hz, H24), 5.66 – 5.81 (2H, m, H7, H11), 5.63 (1H, dd, *J* = 6.1, 16.2 Hz, H5), 5.58 (1H, d, *J* = 11.3 Hz, H2), 5.45 (1H, d, *J* = 10.1 Hz, NH), 5.34 (1H, d, *J* = 10.1 Hz, H3′), 5.26 (1H, t, *J* = 10.4 Hz, H23), 5.20 (1H, dd, *J* = 2.5, 8.9 Hz, H21), 5.11 (1H, d, *J* = 16.8 Hz, H26a), 5.03 (2H, d, *J* = 10.6 Hz, H10, H26b), 4.89 (1H, d, *J* = 10.1 Hz, H15), 4.41 (1H, d, *J* = 5.5 Hz, H2′), 4.33 (1H, d, *J* = 5.1 Hz, H9), 3.11 – 3.18 (1H, m, H6), 3.05 (2H, d, *J* = 5.5 Hz, H13, C2′-O$\underline{H}$), 2.99 (2H, t, *J* = 9.2 Hz, H19, H22), 2.71 (1H, t, *J* = 2.7 Hz, H12), 2.61 (1H, q, *J* = 6.4 Hz, H14), 2.45 – 2.56 (2H, m, H17a, H18), 1.94 (3H, s, Me16), 1.89 – 1.93 (1H, *obs* m, H20), 1.81 (1H, dt, *J* = 2.8, 13.1 Hz, H8a), 1.70 (1H, d, *J* = 11.1 Hz, H8a), 1.65 (1H, dt, *J* = 2.8, 13.0 Hz, H17b), 1.34 (3H, d, *J* = 7.1 Hz, Me12), 1.28 (9H, s, $C(CH_3)_3$), 1.10 (3H, d, *J* = 7.1 Hz, Me6), 1.08 (3H, d, *J* = 6.9 Hz, Me20), 1.06 (3H, d, *J* = 6.7 Hz, Me14), 0.88 (3H, d, *J* = 6.5 Hz, Me18), 0.77 (3H, d, *J* = 6.7 Hz, Me22); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 173.2 (C1′), 166.3 (C1), 156.3 (^{t}BuO$\underline{C}$(O)NHR), 143.9 (C3), 142.9 (C5), 140.4 (Ar), 134.8 (C10, C23), 133.8 (C16), 132.9 (C25), 130.5 (C24), 129.7 (C11), 129.4 (C15), 129.3 (Ar), 128.5 (Ar), 128.0 (C4), 127.4 (2 x C, Ar), 118.15 (C2), 118.10 (C26), 81.1 ($\underline{\text{C}}\text{Me}_3$), 80.1 (C13), 76.7 (C21), 76.5 (C19), 75.7 (C7), 73.5 (C2′), 63.9 (C9), 56.8 (C3′), 38.7 (C6), 37.8 (C17), 37.51 (C20), 37.47 (C14), 35.3 (C12), 35.1 (C8), 35.0 (C6), 31.5 (C18), 28.6 (3 x C, $\text{C}\underline{\text{Me}_3}$), 23.5 (Me16), 19.3 (Me14), 19.0 (Me12), 17.3 (Me22), 12.3 (Me6), 11.5 (Me18), 10.0 (Me20); **HRMS** (ES$^+$) calc. for $C_{47}H_{69}N\ O_{10}Na$ [M+Na]$^+$: 830.4819. Found: 830.4858.

Triple Hybrid **34**: **R$_f$** 0.56 (70% EtOAc / P.E.); **R$_t$** 9.5 mins (7% IPA / hexane); $[\alpha]_D^{20}$ +6.0 (*c* 0.03, CHCl$_3$); **IR** (neat, cm^{-1}) υ_{max} = 3433, 2963, 2920, 1694, 1498, 1456; **^{1}H NMR** (500 MHz, CD$_2$Cl$_2$) δ = 7.36 – 7.42 (4H, m, Ar), 7.29 – 7.34 (1H, m, Ar), 7.28 (1H, dd, *J* = 4.4, 15.4 Hz, H4), 6.64 (1H, ddd, *J* = 10.9, 11.0, 16.9 Hz, H25), 6.54 (1H, t, *J* = 11.0 Hz, H3), 6.08 (1H, dd, *J* = 7.0, 15.6 Hz, H5), 5.99 (1H, t, *J* = 11.0 Hz, H24), 5.65 (1H, *obs* dd, *J* = 8.6, 11.0 Hz, H11), 5.58 – 5.63 (1H, m, H9), 5.50 (2H, d, *J* = 11.2 Hz, H2, NH), 5.27 – 5.35 (2H, m, H10, H23), 5.15 – 5.20 (2H, m, H26a, H3′), 5.09 (1H, d, *J* = 10.0 Hz, H26b), 4.99 (2H, dd, *J* = 2.7, 9.0 Hz, H15, H21), 4.44 (1H, d, *J* = 4.5 Hz, H2′), 4.00 (1H, d, *J* = 9.8 Hz, H7), 3.68 (1H, *br* s, OH), 3.24 (1H, dd, *J* = 3.4, 8.5 Hz, H13), 3.13 (1H, d, *J* = 4.6 Hz, C2′-O$\underline{\text{H}}$), 3.06 (2H, d, *J* = 7.6 Hz, H19, H22), 2.62 – 2.68 (1H, m, H12), 2.49 – 2.58 (2H, m, H6, H14), 2.05 – 2.13 (2H, m, H17a, H18), 1.95 (1H, ddd, *J* = 2.5, 3.0, 6.7 Hz, H20), 1.75 (1H, d, *J* = 7.8 Hz, H17b), 1.65 (3H, s, Me16), 1.47 – 1.60 (2H, m, H8a, H8b), 1.42 (9H, s, C(CH$_3$)$_3$), 1.16 (6H, t, *J* = 6.9 Hz, Me6, Me12), 1.12 (3H, d, *J* = 6.7 Hz, Me20), 1.01 (3H, d, *J* = 6.7 Hz, Me22), 0.99 (3H, d, *J* = 6.8 Hz, Me14), 0.74 (3H, d, Me18); **^{13}C NMR** (125 MHz, CD$_2$Cl$_2$) δ = 173.0 (C1′), 166.4 (C1), 156.3 (^{t}BuO$\underline{\text{C}}$(O)NHR), 145.7 (C5), 143.8 (C3), 139.9 (Ar), 135.1 (C23), 134.4 (C16), 133.2 (C11), 132.9 (C25), 130.3 (C24), 129.5 (C10), 129.2 (2 x C, Ar), 129.0 (C15), 128.3 (Ar), 127.9 (C4), 127.3 (2 x C, Ar), 118.0 (C26), 117.7 (C2), 81.1 ($\underline{\text{C}}\text{Me}_3$), 79.9 (C13), 76.7 (C21), 75.7 (C19), 73.6 (C2′), 72.3 (C9), 69.2 (C7), 56.6 (C3′), 43.7 (C6), 37.7 (C20), 37.4 (3C, C8, C14, C17), 35.5 (C12), 35.1 (C22), 31.6 (C18), 28.6 ($\text{C}\underline{\text{Me}_3}$), 23.3 (Me16), 19.2 (Me14), 17.7 (Me12), 17.4 (Me22), 13.8 (Me6), 12.0 (Me18), 10.5 (Me20); **HRMS** (ES$^+$) calc. for $C_{47}H_{70}NO_{10}$ [M+H]$^+$: 808.5000. Found: 808.5028.



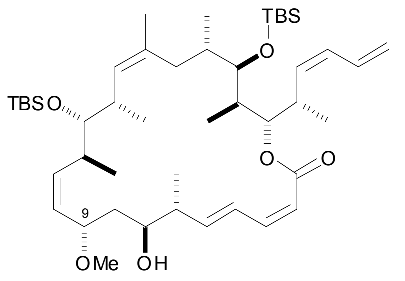
35

*Bis*methyl Ether **35**: To a stirred solution of alcohol **28** (22.5 mg, 29.1 μmol, 1.0 eq.) in DCM (2.5 mL) at r.t. was added proton sponge (62 mg, 0.291 mmol, 10 eq.) and then Meerwein's salt (13 mg, 87 μmol, 3.0 eq.). The mixture was stirred for 70 min before 10% citric acid solution (3 mL) was added and the phases separated. The aqueous phase was extracted with EtOAc (3 × 3 mL) before the organic phases were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10% → 25% EtOAc / P.E.) provided the monomethylated product **37** (13.8 mg, 60%), the *bis*methylated product **35** (4.5 mg, 19%) and recovered starting material **28** (4.0 mg, 18%) as colourless oils. **35**: R_f 0.68 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +45.1 (*c* 0.45, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2928, 2856, 1714, 1639, 1598; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.79 – 7.94 (1H, m, H4), 6.71 (1H, ddd *J* = 10.5, 10.8, 17.1 Hz, H25), 6.22 (1H, t, *J* = 11.1 Hz, H3), 6.00 (1H, t, *J* = 9.6 Hsz, H24), 5.93 (1H, t, *J* = 9.3 Hz, H11), 5.68 (1H, dd, *J* = 4.8, 15.9 Hz, H5), 5.61 (1H, d, *J* = 11.1 Hz, H2), 5.52 (1H, t, *J* = 10.2 Hz, H10), 5.28 – 5.34 (2H, m, H21, H23), 5.17 (1H, d, *J* = 9.3 Hz, H15), 5.13 (1H, *br* d, *J* = 16.8 Hz, H26a), 5.06 (1H, d, *J* = 9.9 Hz, H26b), 4.33 (1H, q, *J* = 6.9 Hz, H9), 3.75 (1H, q, *J* = 5.7 Hz, H7), 3.35 – 3.42 (2H, m , H13, H19), 3.29 (3H, s, OMe), 3.21 (3H, s, OMe), 3.00 – 3.08 (1H, m, H22), 2.75 – 2.81 (1H, m, H14), 2.68 – 2.75 (2H, m, H6, H12), 2.48 – 2.64 (2H, m, H18, H20), 2.00 – 2.11 (4H, m, H17a, Me16), 1.66 (1H, d, *J* = 10.2 Hz, H17b), 1.45 (1H, t, *J* = 6.0Hz, H8a), 1.31 – 1.39 (1H, m, H8b), 1.22 (3H, d, *J* = 7.2 Hz, Me6), 1.19 (3H, d, *J* = 6.7 Hz, Me20), 1.15 (6H, d, *J* = 6.9 Hz, Me12, Me14), 1.11 (9H, s, $SiC(CH_3)_3$), 1.08 (9H, s, $SiC(CH_3)_3$), 0.99 (3H, d, *J* = 6.3 Hz, Me18), 0.75 – 0.83 (3H, m, Me22), 0.17 (12H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 166.0, 145.4, 135.2, 134.0, 133.0, 132.5, 131.3, 130.4, 126.7, 117.3, 116.3, 80.4, 78.5, 78.1, 75.5, 74.0, 56.9, 56.4, 38.9, 38.4, 37.24, 37.17, 36.7, 35.5, 34.9, 32.5, 30.3, 30.2, 29.9, 26.8 (3C), 26.5 (3C), 23.19, 23.15, 19.0, 18.9, 18.8, 18.5, 16.8, 10.9, 10.4, –2.3, –2.9, –3.1, –3.6; **HRMS** (ES^+) calc. for $C_{47}H_{88}NO_6Si_2N$ $[M+NH_4]^+$: 818.6145. Found: 818.6139.



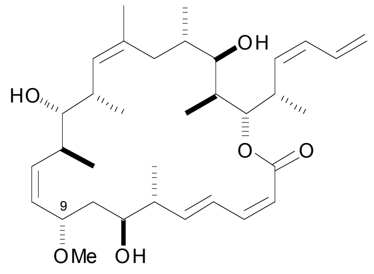
36

Double Hybrid **36**: To a stirred solution of protected macrolactone **35** (3.0 mg, 3.7 μmol) in MeOH (400 μL) at 0 ˚C was added acidified MeOH (800 μL, 3:1, MeOH / 3N HCl). The reaction mixture was allowed to warm to r.t. and stirred for 48 h before being diluted with H_2O (4 mL) and extracted with EtOAc (3 × 4 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (30% EtOAc / P.E.) yielded macrolactone **36** (1.5 mg, 70%) as a colourless oil. ***R*** R_f 0.50 (50% EtOAc); **R_t** 32 mins (2.5% IPA / hexane); $[\alpha]_D^{20}$ –5.0 (*c* 0.10, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3435, 2962, 2930, 1713, 1639, 1599; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.23 (1H, dd, *J* = 10.9, 15.2 Hz, H4), 6.64 (1H, dddd, *J* = 1.0, 10.7, 10.8, 16.8 Hz, H25), 6.52 (1H, t, *J* = 11.3 Hz, H3), 6.02 (1H, dd, *J* = 6.6, 9.1 Hz, H5), 5.99 (1H, t, *J* = 10.7 Hz, H24), 5.69 (1H, t, *J* = 8.4, 11.2 Hz, H11), 5.48 (1H, d, *J* = 11.3 Hz, H2), 5.29 (1H, t, *J* = 10.3 Hz, H23), 5.16 – 5.21 (1H, m, H10), 5.10 (1H, d, *J* = 10.3 Hz, H26a), 4.98 (1H, dd, *J* = 3.5, 8.4 Hz, H21), 4.94 (1H, d, *J* = 10.1 Hz, H15), 3.96 (1H, dt, *J* = 3.9, 9.6 Hz, H9), 3.50 (1H, dt, *J* = 3.4, 10.4 Hz, H7), 3.36 (3H, s, OMe), 3.21 (3H, s, OMe), 3.20 – 3.24 (1H, *obs* m, H13), 3.02 – 3.08 (2H, m, H19, H22), 2.78 (1H, q, *J* = 6.2 Hz, H6), 2.46 – 2.55 (2H, m, H12, H14), 2.11 (2H, d, *J* = 7.8 Hz, H17a, H17b), 1.94 (1H, ddd, *J* = 1.7, 3.8, 7.0 Hz, H20), 1.59 – 1.67 (1H, *obs* m, H18), 1.64 (3H, s, Me16), 1.19 – 1.29 (2H, m, H8a, H8b), 1.11 (3H, d, *J* = 7.1, Me12) 1.09 (3H, d, *J* = 6.9 Hz, Me20) 1.05 (3H, d, *J* = 6.9 Hz, Me6), 0.99 (3H, d, *J* = 6.6 Hz, Me22), 0.98 (3H, d, *J* = 6.6 Hz, Me14), 0.71 (3H, d, *J* = 6.2 Hz, Me18); **^{13}C NMR** (125 MHz, CD2Cl2) δ = 166.4 (C1), 145.7 (C5), 143.9 (C3), 134.8 (C23), 134.1 (C16), 133.5 (C10), 132.9 (C25), 132.5 (C11), 130.4 (C24), 129.0 (C15), 127.6 (C4), 118.0 (C26), 117.4 (C2), 80.2 (C13), 79.4 (C7), 76.4 (C21), 75.9 (C19), 74.1 (C9), 58.1 (OMe), 56.4 (OMe), 38.9 (C6), 37.53 (C18, C20), 37.48 (C17), 37.3 (C14), 36.2 (C8), 35.1 (C22), 34.9 (C12), 23.3 (Me16), 19.3 (Me14), 18.9 (Me12), 17.4 (Me22), 12.6 (Me6), 12.0 (Me18), 10.3 (Me20); **HRMS** (ESI+) Calcd. for $C_{35}H_{56}O_6Na$ $[M+Na]^+$: 595.3975. Found: 595.3990.



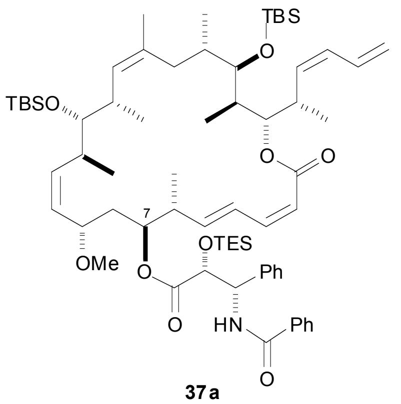
37

9-Methoxy Macrolactone **37**: To a stirred solution of alcohol **28** (7.0 mg, 9.1 μmol, 1.0 eq.) in DCM (800 μL) at r.t. was added proton sponge (19 mg, 91 μmol, 10 eq.) and then Meerwein's salt (4.0 mg, 27 μmol, 3.0 eq.). After 15 min, a further portion of Meerwein's salt (2.7 mg, 18 μmol, 2.0 eq.) was added. The mixture was stirred for 30 min before 10% citric acid solution (3 mL) and DCM (3 mL) were added and the phases separated. The aqueous phase was extracted with EtOAc (3 × 3 mL) before the organic phases were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10% → 25% EtOAc / P.E.) provided the macrolactone **37** (3.2 mg, 46%, 100% brsm) as a colourless oil. ***R*** R_f 0.41 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +8.1 (*c* 0.31, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3460, 2961, 2929, 1713, 1639, 1597, 1462; ^{1}**H NMR** (500 MHz, C_6D_6) δ = 7.62 – 7.71 (1H, m, H4), 6.69 (1H, ddd, *J* = 10.5, 10.6, 16.7 Hz, H25), 6.20 (1H, t, *J* = 11.0 Hz, H3), 5.95 – 6.03 (2H, m, H11, H24), 5.84 (1H, dd, *J* = 6.1, 15.9 Hz, H5), 5.60 (1H, d, *J* = 11.0 Hz, H2), 5.47 (1H, t, *J* = 11.0 Hz, H10), 5.27 – 5.38 (2H, m, H21, H23), 5.15 (1H, d, *J* = 9.4 Hz, H15), 5.12 (1H, d, *J* = 15.9 Hz, H26a), 5.05 (1H, d, *J* = 10.2 Hz, H26b), 4.26 (1H, dt, *J* = 2.8, 8.9 Hz, H9), 4.10 (1H, d, *J* = 10.6 Hz, H7), 3.41 – 3.46 (1H, m, H19), 3.38 (1H, d, *J* = 5.9 Hz, H13), 3.14 (3H, s, OMe), 3.02 – 3.09 (1H, m, H22), 2.63 – 2.74 (2H, m, H12, H14), 2.41 – 2.51 (2H, m, H6, H18), 2.09 (1H, t, *J* = 7.6 Hz, H20), 1.97 (3H, *br* s, Me16), 1.87 – 1.92 (1H, m, H17a), 1.72 – 1.78 (1H, m, H17b), 1.57 (1H, t, *J* = 11.7 Hz, H8a), 1.47 (1H, t, *J* = 10.4 Hz, H8b), 1.21 (3H, d, *J* = 6.9 Hz, Me6), 1.15 (9H, t, *J* = 6.7 Hz, Me12, Me14, Me20), 1.09 (9H, s, $SiC(CH_3)_3$), 1.07 (9H, s, $SiC(CH_3)_3$), 0.99 (3H, d, *J* = 6.5 Hz, Me18), 0.83 (3H, *br* d, *J* = 6.7 Hz, Me22), 0.18 (3H, s, $Si(CH_3)_2$), 0.165 (6H, s, $Si(CH_3)_2$), 0.158 (3H, s, $Si(CH_3)_2$); ^{13}**C NMR** (125 MHz, C_6D_6) δ = 166.1, 145.2, 144.2, 134.9, 134.5, 132.88, 132.85, 132.2, 130.0, 130.4, 128.6, 126.9, 117.9, 117.1, 81.0, 78.6, 76.2, 74.6, 69.6, 56.0, 42.8, 38.4, 37.4 (2C), 37.1, 34.9, 30.3, 26.7 (3C), 26.5 (3C), 23.2, 19.4, 19.0 (2C), 18.9, 17.1, 12.4, 11.1, –2.5, –2.9 (2C), –3.4; **HRMS** (ES^+) calc. for $C_{46}H_{86}NO_6Si_2$ $[M+NH_4]^+$: 804.5988. Found: 804.5986.



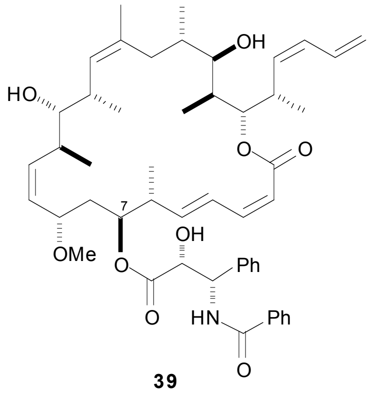
38

Double Hybrid **38**: Protected precursor **37** (2.0 mg, 2.5 μmol) in THF (375 μL) was subjected to general procedure B using 400 μL of the HF·py stock solution. Following flash chromatography and HPLC purification, macrolactone **38** (1.0 mg, 72%) was isolated as a white powder. **R_f** 0.54 (70% EtOAc / P.E.); **R_t** 20.0 mins (4.5% IPA / hexane); $[\alpha]_D^{20}$ –109.4 (*c* 0.17, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3456, 2961, 2928, 1699, 1638, 1457; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.14 (1H, dd, *J* = 11.3, 15.8 Hz, H4), 6.60 (1H, dddd, *J* = 0.9, 10.6, 11.0, 16.9 Hz, H25), 6.49 (1H, dt, *J* = 0.6, 11.4 Hz, H3), 5.98 (1H, *obs* dd, *J* = 6.4, 8.9 Hz, H5), 5.94 (1H, *obs* t, *J* = 4.1 Hz, H24), 5.57 (1H, t, *J* = 10.0 Hz, H11), 5.45 (1H, *obs* d, *J* = 11.6 Hz, H2), 5.45 (1H, *obs* dd, *J* = 9.4, 11.2 Hz, H10), 5.29 (1H, t, *J* = 10.4 Hz, H23), 5.15 (1H, dt, *J* = 2.0, 16.7 Hz, H26a), 5.06 (2H, t, *J* = 12.4 Hz, H15, H26b), 5.00 (1H, dd, *J* = 3.0, 8.8 Hz, H21), 4.22 (1H, qu, *J* = 4.5 Hz, H9), 3.84 (1H, ddd, *J* = 2.3, 4.5, 10.3 Hz, H7), 3.31 (1H, t, *J* = 6.3 Hz, H13), 3.24 (3H, s, OMe), 3.10 (1H, dd, *J* = 2.8, 8.9 Hz, H19), 3.05 (1H, q, *J* = 7.4 Hz, H22), 2.75 – 2.83 (2H, m, H12, H14), 2.49 – 2.63 (1H, *br* s, OH), 2.22 – 2.28 (1H, m, H6), 2.11 (1H, dd, *J* = 8.8, 13.5 Hz, H17a), 1.89 – 1.99 (2H, m, H18, H20), 1.83 (1H, dd, *J* = 7.2, 13.2 Hz, H17b), 1.52 – 1.57 (2H, m, H8a, H8b), 1.51 (3H, s, Me16), 1.14 (3H, d, *J* = 6.8 Hz, Me20), 1.11 (3H, d, *J* = 6.8 Hz, Me6), 1.08 (3H, d, *J* = 6.8 Hz, Me12), 1.01 (3H, d, *J* = 6.7 Hz, Me 22), 0.97 (3H, d, *J* = 6.9 Hz, Me14), 0.81 (3H, d, *J* = 6.5 Hz, Me18); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 166.7 (C1), 145.4 (C5), 142.6 (C3), 135.25 (C16),135.19 (2 x C, C11, C23), 132.8 (C25), 132.1 (C10), 130.2 (C24), 128.9 (C4), 127.9 (C15), 118.4 (C2), 118.0 (C26), 79.4 (C13), 77.2 (C21), 75.6 (C9), 73.7 (C19), 71.9 (C7), 56.6 (OMe), 45.0 (C6), 40.6 (C8), 37.82 (C20), 37.76 (C14), 36.9 (C17), 35.5 (C22), 35.2 (C12), 31.7 (C18), 23.1 (Me16), 19.5 (Me12), 19.1 (Me14), 17.5 (Me22), 16.3 (Me6), 13.1 (Me8), 11.2 (Me20); **HRMS** (ES^+) calc. for $C_{34}H_{55}O_6$ $[M+H]^+$: 559.3999. Found: 599.3998.



37a

Ester **37a**: General procedure A was followed with alcohol **37** (4.3 mg, 5.5 μmol, 1.0 eq.) in THF (450 μL). Following addition of NaHMDS (6.6 μL, 1M in THF, 1.2 eq.), β-lactam **29** (3.1 mg, 8.3 μmol, 1.5 eq.) in THF (450 μL) was added *via* syringe. After the standard work-up procedure, flash chromatography yielded protected analogue **37a** as a colourless oil contaminated with trace amounts of unreacted β-lactam **29**. This material was subjected to deprotection without further purification. **R$_f$** 0.55 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +13.6 (*c* 0.25, CHCl$_3$); **IR** (neat, cm^{-1}) υ_{max} = 2957, 2929, 1751, 1713, 1675, 1509, 1483, 1462; **^{1}H NMR** (500 MHz, C$_6$D$_6$) δ = 7.98 (2H, d, *J* = 7.1 Hz, Ar), 7.82 – 7.94 (1H, m, H4), 7.59 (1H, d, *J* = 7.6 Hz, NH), 7.44 (2H, d, *J* = 7.4 Hz, Ar), 7.04 – 7.09 (2H, m, Ar), 6.96 – 7.04 (4H, m, Ar), 6.69 (1H, ddd, *J* = 10.4, 10.7, 16.8 Hz, H25), 6.08 (2H, t, *J* = 11.1 Hz, H3, H11), 6.02 (1H, d, *J* = 8.2 Hz, H3′), 5.93 – 6.00 (1H, m, H24), 5.85 (1H, d, *J* = 11.7 Hz, H7), 5.65 (1H, dd, *J* = 5.0, 15.9 Hz, H5), 5.58 (1H, d, *J* = 10.8 Hz, H2), 5.43 (1H, t, *J* = 9.5 Hz, H10), 5.24 – 5.34 (2H, m, H21, H23), 5.12 (2H, d, *J* = 9.8 Hz, H15, H26a), 5.02 – 5.09 (1H, m, H26b), 4.80 (1H, s, H2′), 4.41 (1H, t, *J* = 9.0 Hz, H9), 3.42 (1H, d, *J* = 7.7 Hz, H13), 3.33 – 3.39 (1H, m, H19), 3.31 (3H, s, OMe), 3.12 – 3.20 (1H, m, H6), 2.98 – 3.07 (1H, m, H22), 2.80 – 2.87 (1H, m, H12), 2.72 – 2.80 (1H, m, H14), 2.48 – 2.60 (1H, m, H20), 1.99 – 2.13 (4H, m, H18, Me16), 1.81 – 1.91 (1H, m, H8a), 1.57 – 1.69 (1H, m, H8b), 1.46 (3H, d, *J* = 7.4 Hz, Me12), 1.25 – 1.35 (5H, m, H17a, H17b, Me6), 1.13 (9H, d, *J* = 6.6 Hz, Me14, Me18, Me22), 1.10 (9H, s, SiC(CH$_3$)$_3$), 1.06 (9H, s, SiC(CH$_3$)$_3$), 0.98 (3H, d, *J* = 6.8 Hz, Me20), 0.87 (9H, t, *J* = 7.8 Hz, Si(CH$_2$C$\underline{H}_3$)$_3$), 0.45 – 0.56 (6H, m, Si(C$\underline{H}_2$CH$_3$)$_3$), 0.17 (3H, s, Si(CH$_3$)$_2$), 0.16 (9H, s, Si(CH$_3$)$_2$); **^{13}C NMR** (125 MHz, C$_6$D$_6$) δ = 171.4, 166.4, 165.9, 144.7, 143.3, 140.4, 135.3, 133.9, 133.4, 133.0, 132.8, 131.6, 130.6, 130.5, 128.9, 128.7, 128.6, 127.6, 127.5, 127.1, 125.9, 117.8, 116.9, 81.3, 78.5, 75.9, 75.6, 73.4, 73.0, 57.2, 56.4, 39.2, 38.7, 38.2, 37.9, 36.6, 34.9, 33.5, 32.4, 30.5, 30.3, 26.8 (3C), 26.6 (3C), 23.5, 23.2, 20.0, 19.5, 19.0, 18.9, 16.7, 14.4, 11.2, 11.0, 7.1, 6.9 (3C), 4.9 (3C), 1.5, –2.3, –2.6, –2.9, –3.2; **HRMS** (ES^+) calc. for $C_{68}H_{110}NO_9Si_3$ $[M+H]^+$: 1168.7483. Found: 1168.7482.

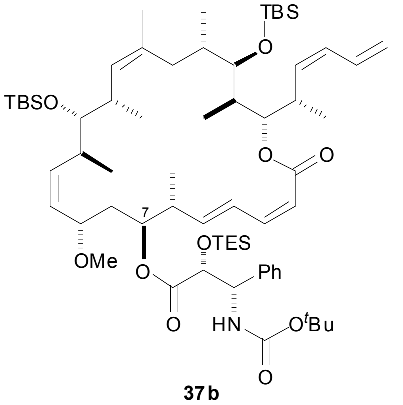


39

Triple Hybrid **39**: Protected precursor **37a** in THF (450 μL) was subjected to general procedure B using 425 μL of the HF·py stock solution. Following flash chromatography, macrolactone **39** (3.5 mg, 78% over two steps) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing.

R*f* 0.41 (60% EtOAc / P.E.); **R$_t$** 15.5 mins (6% IPA / hexane); $[\alpha]_D^{20}$ –56.9 (*c* 0.13, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3415, 2962, 2926, 1713, 1654, 1603, 1518, 1485, 1454; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.79 (2H, d, *J* = 7.7 Hz, Ar), 7.54 (1H, t, *J* = 7.6 Hz, Ar), 7.43 – 7.49 (4H, m, Ar), 7.40 (2H, t, *J* = 7.6 Hz, Ar), 7.34 (1H, d, *J* = 7.6 Hz, Ar), 7.30 (1H, d, *J* = 8.8 Hz, NH), 7.19 (1H, dd, *J* = 11.3, 15.6 Hz, H4), 6.61 (1H, ddd, *J* = 10.5, 10.8, 16.7 Hz, H25), 6.50 (1H, t, *J* = 11.6 Hz, H3), 5.97 (1H, t, *J* = 11.0 Hz, H24), 5.87 (1H, dd, *J* = 8.2, 15.8 Hz, H5), 5.70 (1H, dd, *J* = 1.5, 8.8 Hz, H3′), 5.52 (1H, *obs* t, *J* = 9.3 Hz, H11), 5.51 (1H, *obs* d, *J* = 11.8 Hz, H2), 5.34 – 5.38 (1H, m, H7), 5.28 (1H, t, *J* = 10.1 Hz, H23), 5.18 (1H, d, *J* = 7.4 Hz, H15), 5.15 (1H, *obs* t, *J* = 9.6 Hz, H10), 5.13 (1H, d, *J* = 14.5 Hz, H26a), 5.06 (1H, d, *J* = 10.2 Hz, H26b), 4.97 (1H, dd, *J* = 2.6, 9.1 Hz, H21), 4.64 (1H, s, H2′), 3.79 (1H, dd, *J* = 7.8, 14.7 Hz, H9), 3.47 (1H, d, *J* = 2.0 Hz, C2′-O$\underline{H}$), 3.21 (1H, t, *J* = 4.8 Hz, H13), 3.02 – 3.08 (2H, m, H19, H22), 2.95 (3H, s, OMe), 2.63 (1H, dt, *J* = 2.8, 7.1 Hz, H6), 2.48 – 2.58 (2H, m, H12, H14), 1.98 – 2.05 (2H, m, H17a, H18), 1.95 (1H, ddd, *J* = 2.5, 6.8, 9.0 Hz, H20), 1.86 – 1.91 (1H, m, H17b), 1.60 (2H, t, *J* = 7.1 Hz, H8a, H8b), 1.57 (3H, d, *J* = 1.0 Hz, Me16), 1.14 (3H, d, *J* = 6.8 Hz, Me20), 1.00 (6H, d, *J* = 6.8 Hz, Me6, Me22), 0.95 (6H, t, *J* = 7.2 Hz, Me12, Me14), 0.78 (3H, d, *J* = 6.5 Hz, Me18); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 172.3 (Ph$\underline{C}$(O)NHR), 167.3 (C1′), 166.5 (C1), 142.9 (C3), 142.7 (C5), 139.9 (Ar), 136.3 (C11), 135.0 (C23), 134.0 (Ar), 132.8 (C25), 132.7 (C16), 132.6 (Ar), 131.8 (C10), 130.7

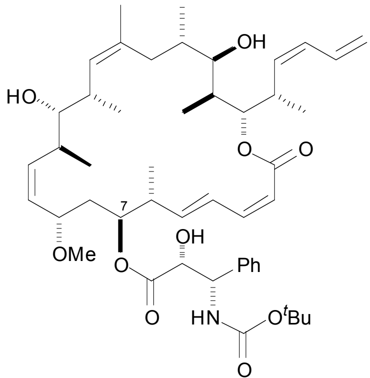
(C15), 130.3 (C24), 129.4 (C4), 129.2 (3 x C, Ar), 128.5 (Ar), 127.7 (2 x C, Ar), 127.3 (2 x C, Ar), 118.8 (C2), 118.0 (C26), 79.3 (C13), 76.9 (C21), 76.1 (C7), 74.3 (C2′), 74.2 (C19), 73.0 (C9), 56.2 (OMe), 55.3 (C3′), 41.5 (C6), 37.6 (C20), 37.3 (C8), 37.2 (C12), 37.1 (C17), 35.5 (C14), 35.4 (C22), 31.5 (C18), 23.1 (Me16), 18.2 (Me14), 17.4 (Me12), 17.3 (Me22), 15.2 (Me6), 12.7 (Me18) 11.1 (Me20); **HRMS** (ES^+) calc. for $C_{50}H_{68}NO_9$ $[M+H]^+$: 826.4894. Found: 826.4908.



37b

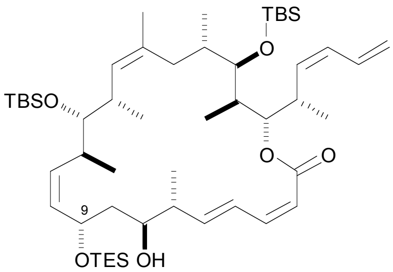
Ester **37b**: General procedure A was followed with alcohol **37** (5.0 mg, 6.4 μmol, 1.0 eq.) in THF (450 μL). Following addition of NaHMDS (7 μL, 1M in THF, 1.1 eq.), β-lactam **30** (3.6 mg, 9.5 μmol, 1.5 eq.) in THF (450 μL) was added *via* syringe. After the standard work-up procedure, flash chromatography yielded ester **37b** (6.8 mg, 91%) as a colourless oil. $\mathbf{R_f}$ 0.59 (15% EtOAc / P.E.); $[\alpha]_D^{20}$ +21.0 (*c* 0.27, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2957, 2931, 1755, 1715, 1642, 1492, 1461; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.83 – 7.92 (1H, m, H4), 7.54 (2H, d, *J* = 8.2 Hz, Ar), 7.12 (1H, *obs*, Ar), 7.06 (2H, t, *J* = 7.3 Hz, Ar), 6.70 (1H, ddd, *J* = 10.3, 10.7, 17.0 Hz, H25), 6.11 (2H, t, *J* = 10.7 Hz, H3, H11), 6.03 (1H, d, *J* = 8.7 Hz, NH), 5.94 – 6.00 (1H, m, H24), 5.80 – 5.89 (1H, m, H7), 5.65 (1H, dd, *J* = 3.6, 15.4 Hz, H5), 5.80 (2H, d, *J* = 9.1 Hz, H2, H3′), 5.52 (1H, t, *J* = 9.5 Hz, H10), 5.24 – 5.33 (2H, m, H21, H23), 5.12 (2H, d, *J* = 10.3 Hz, H15, H26a), 5.02 – 5.08 (1H, m, H26b), 4.66 (1H, s, H2′), 4.39 (1H, t, *J* = 8.7 Hz, H9), 3.52 (3H, s, OMe), 3.42 (1H, d, *J* = 7.6 Hz, H13), 3.33 – 3.40 (1H, m, H19), 3.13 – 3.20 (1H, m, H6), 2.99 – 3.07 (1H, m, H22), 2.76 – 2.85 (2H, m, H12, H14), 2.50 – 2.59 (1H, m, H20), 2.01 – 2.13 (4H, *br* s, H18, Me16), 1.82 – 1.90 (1H, m, H8a), 1.61 – 1.73 (1H, m, H8b), 1.41 (3H, d, *J* = 7.1 Hz, Me14), 1.26 – 1.37 (5H, m, H17a, H17b, Me6), 1.33 (9H, s, $OCMe_3$), 1.09 – 1.18 (9H, m, Me12, Me18, Me20), 1.06 (18H, s, $SiC(CH_3)_3$), 0.99 (3H, d, *J* = 7.0 Hz, Me20), 0.82 (9H, t, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.35 – 0.51 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.19 (6H, s, $Si(CH_3)_2$), 0.15 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ

= 171.0, 166.0, 155.4, 145.0, 143.6, 141.2, 135.1, 133.7, 133.6, 133.3, 132.9, 130.5, 127.0, 125.9, 117.8, 116.8, 81.4, 79.4, 78.6, 76.1, 75.6, 73.4, 73.2, 58.2, 56.8, 39.2, 38.7, 38.2, 38.0, 36.4, 34.9, 33.4, 32.4, 30.5, 29.9, 28.4 (3C), 26.8 (3C), 26.6 (3C), 23.5, 23.2, 20.0, 19.0, 19.6, 18.9, 16.7, 14.4, 11.1, 10.9, 6.9 (3C), 4.8 (3C), 1.5, –2.3, –2.6, –2.9, –3.1; **HRMS** (ES^+) calc. for $C_{66}H_{117}N_2O_{10}Si_3$ $[M+NH_4]^+$: 1181.8011. Found: 1181.8014.



40

Triple Hybrid **40**: Protected precursor **37b** (3.8 mg, 3.3 μmol) in THF (375 μL) was subjected to general procedure B using 400 μL of the HF·py stock solution. Following flash chromatography, macrolactone **40** (2.7 mg, quant.) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. $\mathbf{R}_f$ 0.54 (60% EtOAc / P.E.); $\mathbf{R}_t$ 15.5 mins (6% IPA / hexane); $[\alpha]_D^{20}$ –22.1 (*c* 0.14, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3432, 2925, 2853, 1716, 1497, 1457; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.38 (4H, d, *J* = 4.4 Hz, Ar), 7.32 (1H, m, Ar), 7.27 (1H, dd, *J* = 11.1, 15.4 Hz, H4), 6.62 (1H, ddd, *J* = 10.4, 10.7, 16.8 Hz, H25), 6.52 (1H, t, *J* = 11.4 Hz, H3), 5.98 (1H, t, *J* = 10.9 Hz, H24), 5.92 (1H, dd, *J* = 7.3, 15.4 Hz, H5), 5.68 (1H, d, *J* = 10.2 Hz, NH), 5.65 (1H, t, *J* = 9.3 Hz, H11), 5.53 (1H, d, *J* = 11.6 Hz, H2), 5.28 (1H, t, *J* = 10.6 Hz, H23), 5.23 – 5.26 (1H, *obs* m, H7), 5.22 (1H, d, *J* = 9.4 Hz, H10), 5.17 (1H, dd, *J* = 2.0, 16.9 Hz, H26a), 5.11 (1H, d, *J* = 10.1 Hz, H15), 5.08 – 5.12 (1H, *obs* m, H3′), 5.07 (1H, d, *J* = 10.3 Hz, H26b), 4.97 (1H, dd, *J* = 3.0, 9.1 Hz, H21), 4.46 (1H, s, H2′), 3.93 (1H, dt, *J* = 5.3, 9.2 Hz, H9), 3.31 (1H, dd, *J* = 4.5, 6.1 Hz, H13), 3.23 (1H, s, C2′-O$\underline{H}$), 3.17 (3H, s, OMe), 3.09 (1H, d, *J* = 9.0 Hz, H19), 3.05 (1H, dq, *J* = 7.3, 9.0 Hz, H22), 2.70 – 2.75 (1H, m, H6), 2.58 – 2.70 (2H, m, H12, H14), 2.13 – 2.22 (1H, *br* s, OH), 2.08 (1H, d, *J* = 6.9 Hz, H18), 1.88 – 2.02 (3H, m, H17a, H17b, H20), 1.63 – 1.71 (2H, m, H8a, H8b), 1.61 (3H, s, Me16), 1.38 (9H, s, $C(CH_3)_3$), 1.12 (3H, d, *J* = 6.7 Hz, Me20), 1.10 (3H, d, *J* = 6.9 Hz, Me12), 1.04 (3H, d, *J* = 7.0 Hz, Me6), 1.00 (3H, d, *J* = 6.8 Hz, Me22), 0.98 (3H, d, *J* = 6.8 Hz, Me14), 0.77 (3H, d, *J* = 6.7 Hz, Me18); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 172.3 (C1′), 166.5 (C1), 155.8 (^{t}BuO<u>C</u>(O)NHR), 143.1 (C3), 142.9 (C5), 140.7 (Ar), 135.8 (C11), 135.0 (C23), 133.6 (C16), 132.9 (C25), 131.9 (C10), 130.3 (C24), 129.7 (C15), 129.1 (Ar), 129.0 (Ar), 128.2 (C4), 127.1 (Ar), 118.7 (C2), 118.0 (C26), 80.4 (<u>C</u>Me$_3$), 79.8 (C13), 77.0 (C21), 75.8 (C19), 74.8 (C7), 74.7 (C2′), 74.0 (C9), 56.8 (C3′), 56.5 (OMe), 40.9 (C6), 37.6 (C20), 37.3 (C14), 36.5 (C8), 36.3 (C12), 36.2 (C17), 35.3 (C22), 31.5 (C18), 28.6 (3 x C, C<u>Me$_3$</u>), 23.3 (Me16), 18.8 (Me14), 18.2 (Me12), 17.4 (Me22), 14.5 (Me6), 12.4 (Me18), 10.7 (Me20); **HRMS** (ES$^+$) calc. for $C_{48}H_{72}NO_{10}$ $[M+H]^+$: 822.5156. Found: 822.5158.

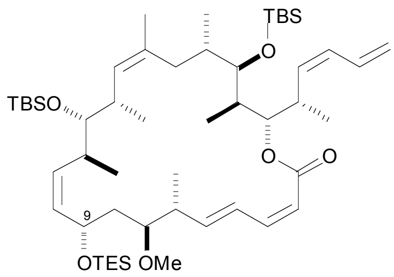


42

Alcohol **42**: TESOTf (30 μL, 137 μmol) was added to 170 μL of DCM to make a stock solution. 2,6-lutidine (3.6 μL, 31 μmol, 5.0 eq.) was added to a stirred solution of alcohol **28** (4.8 mg, 6.2 μmol, 1.0 eq.) in DCM (475 μL) at r.t.. The mixture was immediately cooled to –98 °C and stirred vigorously before 10 μL of the TESOTf stock solution (6.8 μmol, 1.1 eq.) was added. After 1 h a further 3 μL of the TESOTf stock solution (2.3 μmol, 0.3 eq.) was added. The mixture was stirred for a further 30 min before NH_4Cl (1 mL) was added and allowed to warm to r.t.. The reaction mixture was diluted with water (5 mL) and DCM (5 mL) and the phases separated. The aqueous phase was extracted with DCM (3 × 5 mL), before the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (2% → 10% → 50% EtOAc / P.E.) yielded the *mono*-TES ether **42** (3.9 mg, 71%) and the corresponding *bis*-TES protected compound **41** (1.1 mg, 17%) as colourless oils.

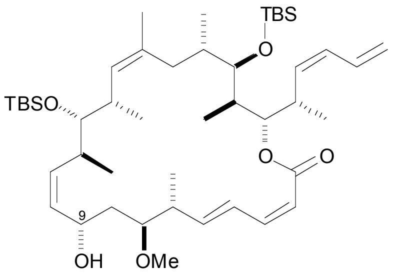
Mono-TES Ether **42**: **R$_f$** 0.64 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +42.4 (*c* 0.17, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2957, 2930, 1713, 1639, 1596, 1461; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.67 (1H, t, *J* = 12.7 Hz, H4), 6.69 (1H, ddd, *J* = 10.4, 10.5, 16.8 Hz, H25), 6.21 (1H, t, *J* = 11.3 Hz, H3), 5.98 (1H, t, *J* = 11.2 Hz, H24), 5.96 (1H, dd, *J* = 5.6, 15.3 Hz, H5), 5.75 (1H, dd, *J* = 8.6, 11.2 Hz, H10), 5.65 (1H, t, *J* = 9.9 Hz, H11), 5.60 (1H, d, *J* = 10.9 Hz, H2), 5.33 (3H, t, *J* = 10.3 Hz, H15, H21, H23), 5.11 (1H, d, *J* = 16.9 Hz, H26a), 5.04 (1H, d, *J* = 10.3Hz, H26b), 4.92 (1H, q, *J* = 6.5 Hz, H9), 4.07 (1H, q, *J* = 6.3 Hz, H7), 3.49 (1H, t, *J* = 4.1 Hz, H13), 3.38 (1H, d, *J* = 7.9 Hz, H19), 3.05 (1H, q, *J* = 9.0 Hz, H22), 2.71 – 2.81 (2H, m, H12, H14), 2.49 – 2.58 (1H, m, H18), 2.40 (1H, t, *J* = 5.7 Hz, H6), 2.07 (2H, t, *J* = 6.8 Hz, H17a, H20), 1.99 (3H, s, Me16), 1.79 (1H, d, *J* = 10.3 Hz, H17b), 1.51 (2H, t, *J* = 6.2 Hz, H8a, H8b), 1.24 (3H, d, *J* = 7.2 Hz, Me12), 1.16 (3H, d, *J* = 6.8 Hz, Me14), 1.15 (3H, d, *J* = 7.0 Hz, Me6), 1.14 (3H, d, *J* = 6.9 Hz, Me19), 1.06 – 1.08 (27H, m, 2 × $SiC(CH_3)_3$, $Si(CH_2C\underline{H}_3)_3$), 0.98 (3H, d, *J* = 6.6 Hz, Me18), 0.80 – 0.84 (3H, m, Me22), 0.67 – 0.73 (6H, $Si(C\underline{H}_2CH_3)_3$), 0.19 (6H, s, $Si(CH_3)_2$), 0.18 (3H, s, $Si(CH_3)_2$), 0.17 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 165.8, 145.1, 143.9, 135.3, 134.6, 132.6, 132.0, 131.6, 131.0, 130.1, 126.1, 117.5, 116.8, 79.8, 78.1, 75.8, 70.4, 70.0, 42.5, 39.6, 38.3, 38.2, 37.8, 35.5, 34.6, 32.9, 26.4 (3C), 26.1 (3C), 22.6, 18.6, 18.5, 17.2, 16.8, 11.5, 10.7, 6.9 (3C), 5.3 (3C), –2.9, –3.2, –3.7, –4.1; **HRMS** (ES^+) calc. for $C_{51}H_{98}NO_6Si_3$ $[M+NH_4]^+$: 904.6696. Found: 904.6700.

Bis-TES Ether **41**: **R_f** 0.68 (5% EtOAc / P.E.); +35.0 (*c* 0.12, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2955, 2925, 2853, 1716, 1639, 1596, 1461, 1377; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.79 – 7.94 (1H, m, H4), 6.71 (1H, dt, *J* = 10.5, 16.6 Hz, H25), 6.18 (1H, t, *J* = 11.1 Hz, H3), 5.96 – 6.07 (1H, m, H24), 5.81 (1H, dd, J = 4.5, 15.6 Hz, H5), 5.71 – 5.76 (2H, m, H10, H11), 5.60 (1H, d, *J* = 11.1 Hz, H2), 5.31 (3H, d, *J* = 8.7 Hz, H15, H21, H23), 5.12 (1H, *br* d, *J* = 14.6 Hz, H26a), 5.05 (1H, d, *J* = 10.1 Hz, H26b), 4.89 – 4.95 (1H, m, H9), 4.36 (1H, dt, *J* = 3.7, 8.7 Hz, H7), 3.48 – 3.53 (1H, m, H13), 3.36 – 3.42 (1H, m, H19), 3.00 – 3.09 (1H, m, H22), 2.78 – 2.89 (2H, m, H12, H14), 2.64 – 2.69 (1H, m, H6), 2.46 – 2.54 (1H, m, H18), 1.99 – 2.13 (3H, m, H17a, H20 Me16), 1.72 – 1.80 (1H, m, H17b), 1.54 – 1.63 (2H, m, H8a, H8b), 1.25 (3H, d, *J* = 6.9 Hz, Me12), 1.16 (3H, d, *J* = 6.4 Hz, Me14), 1.09 – 1.13 (24H, Me6, Me20, 2 × $Si(CH_2C\underline{H}_3)_3$), 1.09 (3H, d, *J* = 7.0 Hz, Me18), 1.07 (18H, s, 2 × $SiC(CH_3)_3$), 0.91 (3H, *br* s, Me22), 0.78 (6H, *obs* t, *J* = 7.7 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.77 (6H, *obs* t, *J* = 7.7 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.30 (6H, s, $Si(CH_3)_2$), 0.22 (3H, s, $Si(CH_3)_2$), 0.21 (3H, s, $Si(CH_3)_2$); **HRMS** (ES^+) calc. for $C_{57}H_{108}NO_6Si_4$ $[M+H]^+$: 1001.7223. Found: 1001.7234.



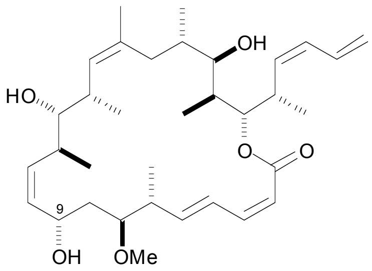
42a

Methyl Ether **42a**: Proton sponge (36.2 mg, 0.169 mmol, 10 eq.) was added to a stirred solution of alcohol **42** (15.0 mg, 16.9 μmol) in DCM (1.7 mL) and then stirred at r.t. for 10 min before Meerwein's salt (15.0 mg, 0.101 mmol, 6 eq.) was added. After 1 h, a further portion of Meerwein's salt (7.5 mg, 0.05 mmol, 3 eq.) was added and stirring continued for 30 min. The reaction was quenched with 10% citric acid solution then diluted with water (5 mL) and DCM (5 mL). After separating the phases, the aqueous phase was extracted with DCM (3 × 5 mL), the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified *via* flash chromatography (1% → 10% EtOAc / P.E.) to afford methyl ether **42a** (11.7 mg, 77%) and recovered starting material **42** (3.2 mg, 21%) as colourless oils. **R_f** 0.40 (5% EtOAc / P.E.); $[\alpha]_D^{20}$ +31.1 (*c* 0.27, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2956, 2924, 2853, 1715, 1640, 1597, 1462; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.84 (1H, t, *J* = 12.2 Hz, H4), 6.71 (1H, ddd, *J* = 10.5, 10.8, 17.0 Hz, H25), 6.16 (1H, t, *J* = 11.0 Hz, H3), 5.99 (1H, t, *J* = 10.5 Hz, H24), 5.70 (1H, t, *J* = 9.8 Hz, H10), 5.65 (1H, dd, *J* = 4.2, 15.5 Hz, H5), 5.59 (2H, d, *J* = 11.0 Hz, H2, H11), 5.37 (1H, d, *J* = 10.0 Hz, H15), 5.31 (2H, *br* d, *J* = 9.0 Hz, H21, H23), 5.10 (1H, d, *J* = 16.8 Hz, H26a), 5.05 (1H, d, *J* = 10.3 Hz, H26b), 4.92 (1H, t, *J* = 9.0 Hz, H9), 3.70 (1H, ddd, *J* = 4.5, 6.2, 8.3 Hz, H7), 3.52 (1H, *br* s, H13), 3.31 – 3.36 (1H, m, H19), 3.16 (3H, s, OMe), 2.99 – 3.06 (1H, m, H22), 2.82 (2H, t, *J* = 5.0 Hz, H12, H14), 2.76 (1H, d, *J* = 5.5 Hz, H6), 2.47 – 2.57 (1H, m, H18), 2.06 (5H, m, H17a, H20, Me16), 1.68 (1H, d, *J* = 12.8 Hz, H17b), 1.35 – 1.44 (2H, m, H8a, H8b), 1.27 (3H, d, *J* = 7.3 Hz, Me12), 1.17 (3H, d, *J* = 6.8 Hz, Me14), 1.10 – 1.15 (15H, m, Me6, Me20, $Si(CH_2C\underline{H}_3)_3$), 1.09 (9H, s, $SiC(CH_3)_3$), 1.08 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, *J* = 6.4 Hz, Me18), 0.71 – 0.80 (9H, m, Me12, $Si(C\underline{H_2}CH_3)_3$), 0.23 (3H, s, $Si(CH_3)_2$), 0.22 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.18 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 166.0, 145.4, 145.0, 137.0, 135.3, 133.0, 132.5, 131.6, 131.2, 130.4, 126.4, 117.7, 116.2, 79.5, 78.4, 77.7, 75.6, 66.0, 55.7, 38.44, 38.37, 37.7, 36.2, 35.3, 34.8, 32.6, 26.8 (3C), 26.4 (3C), 22.9, 19.0, 18.7, 17.5, 17.1, 16.7, 11.0, 10.8, 9.4, 7.4 (3C), 5.7 (3C), –2.4, –2.8, –3.6, –4.1; **HRMS** (ES$^+$) calc. for $C_{52}H_{100}NO_6Si_3$ $[M+NH_4]^+$: 918.6853. Found: 918.6861.



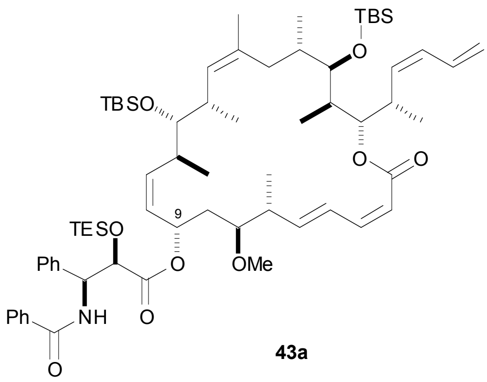
43

Alcohol **43**: PPTS (2 crystals) was added to a stirred solution of TES ether **42a** (13.0 mg, 14.4 μmol) in DCM / MeOH (1:1, 1.8 mL) at 0 °C. After 5 min the reaction mixture was warmed to r.t. for 2 h before the solvent was removed *in vacuo* and the crude mixture loaded directly onto a column where it was purified by flash chromatography (15% EtOAc / P.E.). Alcohol **43** (11.3 mg, 99%) was isolated as a colourless oil. **R*f*** 0.05 (5% EtOAc / P.E.); $[\alpha]_D^{20}$ +15.1 (*c* 0.33, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2959, 2927, 2854, 1713, 1639, 1597, 1462; **^{1}H NMR** (500 MHz, C_6D_6) δ = 7.80 – 7.94 (1H, m, H4), 6.71 (1H, ddd, *J* = 10.5, 10.6, 16.9 Hz, H25), 6.23 (1H, t, *J* = 11.4 Hz, H3), 5.96 – 6.05 (1H, m, H24), 5.80 (1H, t, *J* = 10.2 Hz, H11), 5.66 (1H, dd, *J* = 5.1, 16.1 Hz, H5), 5.61 (1H, d, *J* = 11.0 Hz, H2), 5.51 (1H, t, *J* = 10.2 Hz, H10), 5.26 – 5.35 (2H, m, H21, H23), 5.14 (2H, d, *J* = 8.2 Hz, H15, H26a), 5.06 (1H, d, *J* = 10.6 Hz, H26b), 4.71 (1H, t, *J* = 8.6 Hz, H9), 3.65 (1H, dt, *J* = 3.4, 10.7 Hz, H7), 3.33 – 3.40 (2H, m, H13, H19), 3.19 (3H, s, OMe), 3.00 – 3.08 (1H, m, H22), 2.70 – 2.78 (2H, m, H12, H14), 2.63 (1H, d, *J* = 5.9 Hz, H6), 2.46 – 2.57 (1H, m, H18), 1.95 – 2.12 (5H, m, H17a, H20, Me16), 1.66 (1H, d, *J* = 10.6 Hz, H17b), 1.51 (1H, ddd, *J* = 2.8, 11.1, 14.0 Hz, H8a), 1.31 – 1.37 (1H, m, H8b), 1.19 (3H, d, *J* = 7.2 Hz, Me12), 1.12 – 1.17 (9H, m, Me6, Me14, Me20), 1.11 (9H, s, $SiC(CH_3)_3$), 1.08 (9H, s, $SiC(CH_3)_3$), 0.98 (3H, d, *J* = 6.5 Hz, Me18), 0.75 – 0.83 (3H, m, Me22), 0.18 (6H, s, $Si(CH_3)_2$), 0.16 (3H, s, $Si(CH_3)_2$), 0.15 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ = 165.9, 145.2, 135.2, 132.9, 132.7, 132.1, 130.4, 128.6, 126.9, 117.7, 116.3, 80.6, 78.5, 78.4, 75.7, 65.1, 57.1, 38.7, 38.3, 37.6, 37.3, 37.1, 34.9, 32.7, 30.3, 26.8 (3C), 26.6 (3C), 23.1, 19.2, 19.0, 18.8, 16.9, 10.9, –2.4, –2.9, –3.1, –3.5; **HRMS** (ES^+) calc. for $C_{46}H_{86}NO_6Si_2$ $[M+NH_4]^+$: 804.5988. Found: 804.5987.



44

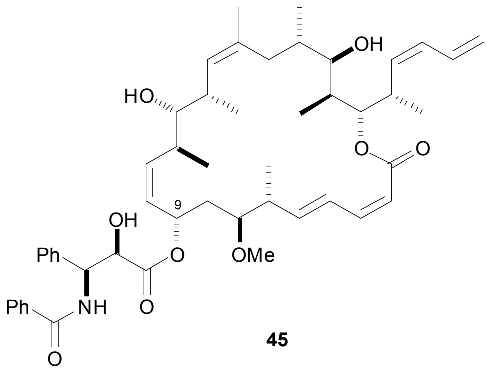
Double Hybrid **44**: Protected precursor **43** (3.3 mg, 4.2 μmol) in THF (400 μL) was subjected to general procedure B using 450 μL of the HF·py stock solution. Following flash chromatography, macrolactone **44** (1.6 mg, 68%) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. **R*f*** 0.37 (70% EtOAc / P.E.); **R$_t$** 34.9 mins (6% IPA / hexane); $[\alpha]_D^{20}$ –24.4 (*c* 0.09, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3402, 2928, 1672, 1638, 1451; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.26 (1H, dd, *J* = 11.3, 15.8 Hz, H4), 6.64 (1H, dddd, *J* = 0.9, 10.7, 10.8, 16.9 Hz, H25), 6.52 (1H, t, *J* = 11.4 Hz, H3), 6.02 (1H, dd, *J* = 6.6, 9.2 Hz, H5), 5.99 (1H, t, *J* = 10.6 Hz, H24), 5.58 (1H, dd, *J* = 9.0, 11.4 Hz, H11), 5.49 (1H, d, *J* = 11.4 Hz, H2), 5.37 (1H, dd, *J* = 8.4, 11.3 Hz, H10), 5.29 (1H, *obs* t, *J* = 10.6 Hz, H23), 5.18 (1H, dd, *J* = 1.9, 16.8 Hz, H26a), 5.10 (1H, d, *J* = 10.2 Hz, H26b), 4.98 (1H, dd, *J* = 3.5, 8.4 Hz, H21), 4.95 (1H, d, *J* = 9.9 Hz, H15), 4.45 (1H, t, *J* = 8.0 Hz, H9), 3.52 (1H, ddd, *J* = 3.5, 6.4, 6.9 Hz, H7), 3.39 (3H, s, OMe), 3.21 (1H, dd, *J* = 3.3, 8.4 Hz, H13), 3.02 – 3.09 (2H, m, H19, H22), 2.77 (1H, q, *J* = 6.4 Hz, H6), 2.63 (1H, tt, *J* = 1.7, 8.0 Hz, H12), 2.48 (1H, q, *J* = 9.5, H14), 1.99 – 2.09 (2H, m, H17a, H18), 1.94 (1H, ddd, *J* = 1.6, 3.6, 6.8 Hz, H20), 1.67 – 1.72 (1H, m, H17b), 1.64 (3H, s, Me16), 1.37 – 1.43 (1H, m, H8a), 1.31 – 1.36 (1H, m, H8b), 1.08 (9H, d, *J* = 7.3 Hz, Me6, Me12, Me20), 0.99 (6H, t, *J* = 6.8 Hz, Me14, Me22), 0.72 (3H, d, *J* = 6.1 Hz, Me18); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 166.5 (C1), 145.6 (C5), 144.0 (C3), 134.8 (C23), 134.5 (C16), 134.3 (C10), 132.9 (C25), 131.8 (C11), 130.4 (C24), 128.9 (C15), 127.9 (C4), 118.1 (C26), 117.4 (C2), 80.3 (C7), 80.1 (C13), 76.9 (C21), 75.7 (C19), 65.6 (C9), 58.3 (OMe), 39.1 (C6), 38.2 (C8), 37.59 (C14), 37.55 (C20), 37.3 (C17), 35.4 (C12), 35.1 (C19), 31.7 (C18), 23.2 (Me16), 19.6 (Me22), 19.3 (Me14), 17.5 (Me20), 13.5 (Me6), 12.2 (Me18), 10.3 (Me20); **HRMS** (ES^+) calc. for $C_{34}H_{55}O_6$ $[M+H]^+$: 559.3999. Found: 559.4005.



43a

Ester **43a**: General procedure A was followed with alcohol **43** (3.0 mg, 3.8 μmol, 1.0 eq.) in THF (500 μL). Following addition of NaHMDS (5 μL, 1M in THF, 1.2 eq.), β-lactam **29** (2.2 mg, 5.7 μmol, 1.5 eq.) in THF (500 μL) was added *via* syringe. After stirring at –78 ˚C for 45 min, a further portion of NaHMDS (5 μL, 1M in THF, 1.2 eq.) was added before warming to 0 ˚C for 30 min. The standard work-up procedure and subsequent flash chromatography yielded ester **43a** (3.4 mg, 77%) as a colourless oil. **R*f*** 0.41 (15% EtOAc / P.E.); $[\alpha]_D^{20}$ +48.8 (*c* 0.35, CHCl$_3$); **IR** (neat, cm^{-1}) υ_{max} = 2929, 1752, 1713, 1671, 1511, 1483; **^{1}H NMR** (500 MHz, C$_6$D$_6$) δ = 7.97 (2H, d, *J* = 7.5 Hz, Ar), 7.93 – 7.99 (1H, *obs* m, H4), 7.55 (1H, d, *J* = 8.4 Hz, NH), 7.30 (2H, *obs* d, *J* = 8.4 Hz, Ar), 7.09 (2H, t, *J* = 8.1 Hz, Ar), 7.05 (2H, dd, *J* = 2.6, 7.1 Hz, Ar), 7.01 (2H, t, *J* = 7.8 Hz, Ar), 6.70 (1H, ddd, *J* = 10.5, 10.7, 16.7 Hz, H25), 6.40 (1H, t, *J* = 10.3 Hz, H9), 6.30 (1H, t, *J* = 11.1 Hz, H3), 6.08 (2H, d, *J* = 8.3 Hz, H2, H3′), 5.96 – 6.04 (2H, m, H11, H24), 5.68 (1H, t, *J* = 9.6 Hz, H10), 5.56 (1H, d, *J* = 12.2 Hz, H5), 5.26 – 5.35 (2H, m, H21, H23), 5.08 – 5.15 (2H, m, H15, H26a), 5.02 – 5.08 (1H, m, H26a), 4.67 (1H, s, H2′), 3.60 – 3.67 (1H, m, H7), 3.33 – 3.39 (2H, m, H13, H19), 3.09 (3H, *br* s, OMe), 2.97 – 3.07 (1H, m, H22), 2.80 – 2.89 (2H, m, H6, H12), 2.70 – 2.79 (1H, m, H14), 2.49 – 2.65 (1H, m, H20), 1.98 – 2.14 (4H, m, H18, Me16), 1.76 – 1.90 (1H, m, H8a), 1.65 (1H, t, *J* = 13.7 Hz, H8b, H17a), 1.26 – 1.38 (1H, *obs*, H17b), 1.10 – 1.18 (12H, m, Me6, Me14, Me18, Me22), 1.10 (9H, *br* s, SiC(CH$_3$)$_3$), 1.05 (9H, s, SiC(CH$_3$)$_3$), 0.98 (3H, d, *J* = 6.5 Hz, Me20), 0.83 (9H, t, Si(CH$_2$C$\underline{\text{H}}_3$)$_3$), 0.36 – 0.45 (6H, m, Si(C$\underline{\text{H}}_2$CH$_3$)$_3$), 0.24 (3H, s, Si(CH$_3$)$_2$), 0.20 (3H, s, Si(CH$_3$)$_2$), 0.12 (6H, s, Si(CH$_3$)$_2$); **^{13}C NMR** (125 MHz, C$_6$D$_6$) δ = 170.4, 166.1, 166.0, 145.3, 140.4, 135.2, 135.0, 134.4, 133.4, 132.9, 132.7, 131.7, 131.1, 130.4, 130.0, 128.9, 128.7, 128.6, 127.6, 127.4, 127.0, 117.8, 116.2, 80.5, 78.7, 77.1, 76.4, 75.5, 70.0, 56.7, 56.5, 39.0, 38.2, 37.3, 37.2, 36.8, 35.2, 34.9, 32.4, 29.9, 26.7 (3C), 26.5 (3C), 23.2 19.2, 19.0, 18.8, 16.7, 10.9, 7.0, 6.8 (3C), 6.3, 4.8 (3C),

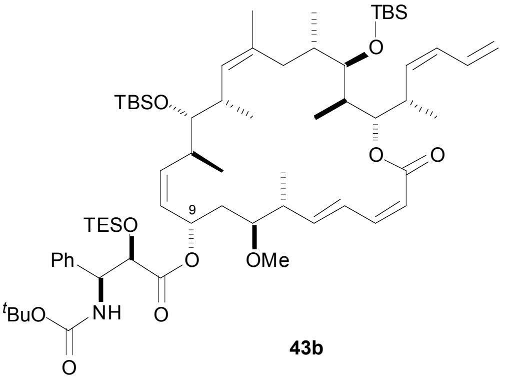
–2.4, –2.9, –3.2, –3.5; **HRMS** (ES$^+$) calc. for $C_{68}H_{113}N_2O_9Si_3$ $[M+NH_4]^+$: 1185.7748. Found: 1185.7749.



45

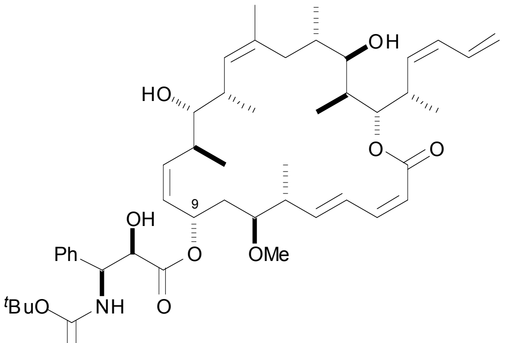
Triple Hybrid **45**: Protected precursor **43a** (3.0 mg, 2.6 μmol) in THF (375 μL) was subjected to general procedure B using 400 μL of the HF·py stock solution. Following flash chromatography, macolactone **45** (1.8 mg, 85%) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. **R$_f$** 0.45 (60% EtOAc / P.E.); **R$_t$** 102 mins (2% IPA / hexane); $[\alpha]_D^{20}$ +46.0 (*c* 0.05, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3427, 2959, 2934, 1711, 1651, 1518, 1486; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.81 (2H, d, *J* = 7.4 Hz, Ar), 7.54 (1H, t, *J* = 7.5 Hz, Ar), 7.46 (4H, t, *J* = 6.7 Hz, Ar), 7.38 (2H, t, *J* = 7.2 Hz, Ar), 7.32 (1H, d, *J* = 7.7 Hz, Ar), 7.25 (1H, dd, *J* = 11.6, 15.4 Hz, H4), 7.19 (1H, d, *J* = 8.9 Hz, NH), 6.65 (1H, ddd, *J* = 10.3, 10.7, 16.6 Hz, H25), 6.56 (1H, t, *J* = 11.3 Hz, H3), 6.08 (1H, dd, *J* = 6.2, 15.7 Hz, H5), 6.00 (1H, t, *J* = 11.0 Hz, H24), 5.79 (1H, dt, *J* = 3.9, 10.4 Hz, H9), 5.70 (1H, d, *J* = 8.6 Hz, H3′), 5.67 (1H, *obs* dd, *J* = 8.9, 11.0 Hz, H11), 5.52 (1H, d, *J* = 11.0 Hz, H2), 5.27 – 5.31 (2H, m, H10, H23), 5.19 (1H, d, *J* = 16.9 Hz, H26a), 5.11 (1H, d, *J* = 10.7 Hz, H26b), 4.98 (1H, dd, *J* = 3.6, 8.2 Hz, H21), 4.96 (1H, d, *J* = 10.5 Hz, H15), 4.55 (1H, s, H2′), 3.36 (1H, d, *J* = 2.4 Hz, C2′-O$\underline{H}$), 3.21 (1H, dd, *J* = 3.0, 8.8 Hz, H13), 3.16 (1H, ddd, *J* = 1.8, 4.2, 10.7 Hz, H7), 3.04 – 3.09 (2H, m, H19, H22), 2.98 (3H, s, OMe), 2.71 (1H, q, *J* = 6.2 Hz, H6), 2.56 (1H, t, *J* = 8.2 Hz, H12), 2.47 (1H, q, *J* = 8.8 Hz, H14), 2.13 (2H, d, *J* = 7.8 Hz, H17a, H18), 1.94 (1H, dt, *J* = 3.8, 7.8 Hz, H20), 1.66 (3H, s, Me16), 1.56 – 1.63 (2H, m, H8a, H17b), 1.37 (1H, ddd, *J* = 3.6, 11.1, 14.5 Hz, H8b), 1.10 (3H, d, *J* = 7.2 Hz, Me12), 1.09 (3H, d, *J* = 7.0 Hz, Me20), 1.00 (3H, d, *J* = 6.8 Hz, Me22), 0.97 (3H, d, *J* = 6.6 Hz, Me14), 0.94 (3H, d, *J* = 6.8 Hz, Me6), 0.70 (3H, d, *J* = 5.6 Hz, Me18); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 172.3 (C1′), 166.7 (Ph$\underline{C}$(O)NHR), 166.4 (C1), 145.4 (C5), 143.9 (C3), 140.1 (Ar), 134.7 (C23), 134.5 (Ar), 134.2 (C16), 133.7 (C11), 132.9 (C25), 132.5 (Ar), 130.4 (C24), 129.4 (C10), 129.23 (2 x C, Ar), 129.17 (2 x C, Ar), 129.1

(C15), 128.3 (Ar), 127.8 (C4), 127.6 (2 x C, Ar), 127.3 (2 x C, Ar), 118.1 (C26), 117.4 (C2), 79.8 (C13), 78.4 (C7), 76.9 (C21), 76.2 (C19), 74.5 (C2′), 71.9 (C9), 57.4 (OMe), 55.0 (C3′), 38.0 (C6), 37.6 (2 x C, C17, C20), 37.5 (C14), 35.5 (C12), 35.4 (C8), 35.0 (C22), 31.7 (C18), 23.3 (Me16), 19.3 (Me22), 18.2 (Me12), 17.5 (Me14), 11.90 (Me18), 11.85 (Me6), 10.2 (Me20); **HRMS** (ES$^+$) calc. for $C_{50}H_{68}NO_9$ $[M+H]^+$: 826.4894. Found: 826.4907.



43b

Ester **43b**: General procedure A was followed with alcohol **43** (3.0 mg, 3.8 μmol, 1.0 eq.) in THF (400 μL). Following addition of NaHMDS (5 μL, 1M in THF, 1.2 eq.), β-lactam **30** (2.2 mg, 5.7 μmol, 1.5 eq.) in THF (200 μL) was added *via* syringe. The standard work-up procedure and subsequent flash chromatography yielded ester **43b** (3.4 mg, 77%) as a colourless oil. **R*f*** 0.64 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +73.8 (*c* 0.34, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 2957, 2931, 2858, 1757, 1719, 1639, 1493, 1462; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.90 – 8.06 (1H, m, H4), 7.32 (2H, *br* s, Ar), 7.12 (2H, t, *J* = 7.6 Hz, Ar), 7.04 (1H, d, *J* = 7.6 Hz, Ar), 6.70 (1H, ddd, *J* = 10.5, 10.6, 16.8 Hz, H25), 6.43 (1H, t, *J* = 9.8 Hz, H 9), 6.25 (1H, t, *J* = 11.0 Hz, H3), 5.98 – 6.08 (2H, m, H11, H24), 5.95 (1H, d, *J* = 9.1 Hz, NH), 5.62 – 5.69 (1H, m, H5), 5.53 – 5.60 (3H, m, H2, H10, H3′), 5.26 – 5.37 (2H, m, H21, H23), 5.14 (2H, d, *J* = 7.4 Hz, H15, H26a), 5.07 (1H, d, *J* = 16.2 Hz, H26b), 4.53 (1H, s, H2′), 3.68 – 3.75 (1H, m, H7), 3.44 (3H, s, OMe), 3.34 – 3.41 (2H, m, H13, H19), 3.01 – 3.08 (1H, m, H22), 2.98 (1H, d, *J* = 5.9 Hz, H6), 2.83 – 2.91 (1H, m, H12), 2.70 – 2.79 (1H, m, H14), 2.55 – 2.67 (1H, m, H20), 2.02 – 2.17 (4H, m, H18, Me16), 1.76 – 1.88 (1H, m, H8a), 1.71 (2H, t, *J* = 11.9 Hz, H8b, H17a), 1.39 (1H, m, H17b), 1.35 (9H, s, $OC(CH_3)_3$), 1.26 – 1.34 (9H, m, Me6, Me12, Me22), 1.11 – 1.17 (6H, m, Me14, Me18), 1.10 (9H, s, $SiC(CH_3)_3$), 1.06 (9H, s, $SiC(CH_3)_3$), 0.99 (3H, d, *J* = 6.4 Hz, Me20), 0.78 (9H, t, *J* = 7.7 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.31 – 0.45 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.24 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.16 (3H, s, $Si(CH_3)_2$), 0.15 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 170.0, 166.0, 155.4, 145.1, 141.3, 135.2, 134.2, 133.4, 132.9, 132.7, 131.1, 130.8, 130.4, 130.1, 126.8, 117.8, 116.3, 80.6, 79.5, 78.7, 77.5, 76.4, 75.5, 69.7, 57.8, 56.9, 39.0, 38.2, 37.4, 37.1, 37.0, 34.9, 32.4, 31.0, 30.2, 29.9, 28.4 (3C), 26.7 (3C), 26.6 (3C), 23.2, 19.4, 19.0, 18.9, 18.4, 16.7, 14.4, 13.9, 11.2, 10.9, 10.3, 6.8 (3C), 4.8 (3C), –2.3, –2.8, –3.1, –3.4; **HRMS** (ES$^+$) calc. for $C_{66}H_{117}NO_{10}Si_3$ $[M+NH_4]^+$: 1181.8011. Found: 1181.8013.



46

Triple Hybrid **46**: Protected precursor **43b** (3.0 mg, 2.6 μmol) in THF (375 μL) was subjected to general procedure B using 400 μL of the HF·py stock solution. Following flash chromatography, macrolactone **46** (2.2 mg, quant.) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. **R*f*** 0.51 (60% EtOAc / P.E.); **R$_t$** 44 mins (2% IPA / hexane); $[\alpha]_D^{20}$ +40.9 (*c* 0.11, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3421, 2964, 2925, 1710, 1639, 1496, 1454; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ = 7.34 – 7.40 (4H, m, Ar), 7.27 – 7.33 (2H, m, Ar), 6.66 (1H, ddd, *J* = 10.4, 10.8, 16.6 Hz, H25), 6.60 (1H, t, *J* = 11.2 Hz, H3), 6.11 (1H, dd, *J* = 6.2, 15.9 Hz, H5), 6.01 (1H, t, *J* = 10.9 Hz, H24), 5.81 (1H, ddd, *J* = 3.2, 8.6, 11.9 Hz, H9), 5.68 (1H, dd, *J* = 8.9, 11.2 Hz, H11), 5.52 – 5.58 (2H, m, H2, NH), 5.26 – 5.31 (2H, m, H10, H23), 5.20 (1H, d, *J* = 16.7 Hz, H26a), 5.12 (2H, d, *J* = 10.2, H26B, H3′), 5.00 (1H, dd, *J* = 3.5, 8.3 Hz, H21), 4.97 (1H, d, *J* = 10.4 Hz, H15), 4.36 (1H, s, H2′), 3.30 (3H, s, OMe), 3.26 – 3.28 (1H, m, H7), 3.23 (1H, dd, *J* = 2.7, 9.0 Hz, H13), 3.15 (1H, d, *J* = 3.1 Hz, C2′-O<u>H</u>), 3.05 – 3.09 (2H, m, H19, H22), 2.86 (1H, q, *J* = 6.3 Hz, H6), 2.57 (1H, t, *J* = 7.7 Hz, H12), 2.47 (1H, q, *J* = 8.1 Hz, H14), 2.13 – 2.20 (2H, m, H17a, H18), 1.95 (1H, dt, *J* = 3.8, 7.8 Hz, H20), 1.74 (3H, s, Me16), 1.66 – 1.68 (1H, m, H17b), 1.63 (1H, d, *J* = 12.7 Hz, H8a), 1.39 (9H, s, $C(CH_3)_3$), 1.34 – 1.38 (1H, *obs* m, H8b), 1.13 (3H, d, *J* = 6.9 Hz, Me12), 1.10 (3H, d, *J* = 6.9 Hz, Me20), 1.05 (3H, d, *J* = 6.9 Hz, Me6), 1.00 (6H, t, *J* = 7.1 Hz, Me14, Me22), 0.71 (3H, d, *J* = 6.1 Hz, Me18); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ = 172.2 (C1′), 166.4 (C1), 155.7 (^{t}BuO<u>C</u>(O)NHR), 145.1 (C5), 143.9

(C3), 140.8 (Ar), 134.7 (C23), 134.1 (C16), 133.3 (C11), 132.9 (C25), 130.5 (C24), 129.4 (C10), 129.2 (Ar), 129.1 (C15), 128.1 (C4), 127.7 (Ar), 126.9 (Ar), 118.2 (C26), 117.5 (C2), 80.3 ($\underline{\mathrm{C}}\mathrm{Me}_3$), 79.9 (C13), 78.4 (C7), 76.9 (C21), 76.4 (C19), 74.6 (C2′), 71.6 (C9), 57.5 (OMe), 56.4 (C3′), 37.8 (C6), 37.7 (C17), 37.6 (C20), 37.5 (C14), 35.4 (C12), 35.0 (2 x C, C8, C22), 31.7 (C18), 28.6 (3 x C, $\mathrm{C}\underline{\mathrm{Me}}_3$), 23.4 (Me16), 19.3 (Me14), 18.2 (Me12), 17.5 (Me22), 11.8 (Me18), 11.6 (Me6), 10.1 (Me20); **HRMS** (ES$^+$) calc. for $C_{48}H_{72}NO_{10}$ [M+H]$^+$: 822.5156. Found: 822.5185.