Electronic Supporting Information

Total Synthesis of a Library of Designed Hybrids of the Microtubule-Stabilising Anticancer Agents Taxol, Discodermolide and Dictyostatin

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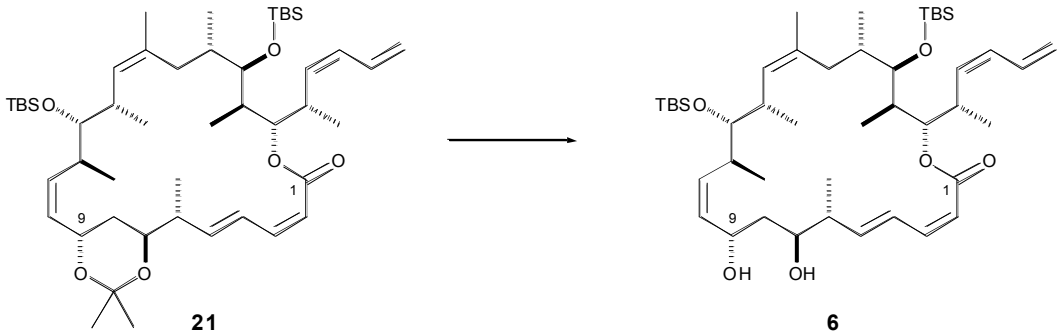
General Experimental Details

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 deuteriobenzene (C_6D_6), deuteriomethylene chloride (CD_2Cl_2), deuteriochloroform ($CDCl_3$) or deuteriodimethyl formamide ($(CD_3)_2NCDO$) 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; $(CD_3)_2NCDO$: 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.

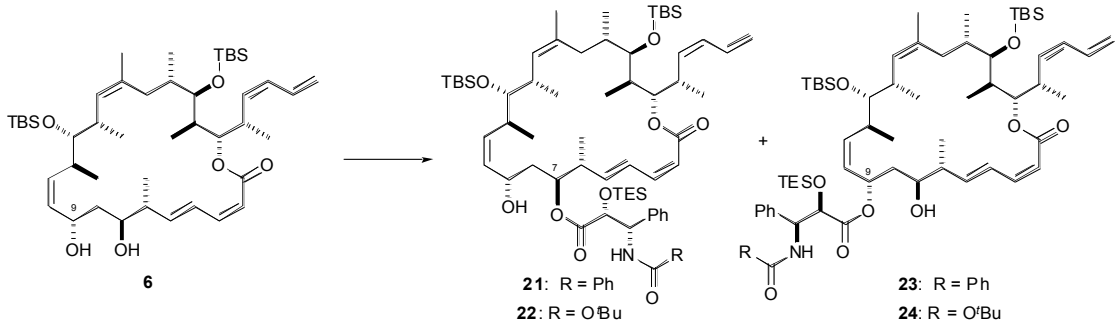


14,20-*Bis*-(*tert*-butyl-dimethyl-silanyloxy)-8,10-dihydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (6)

To a stirred solution of acetonide **21**[1] (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 **6** as a colourless oil (40.0 mg, 98%). $\mathbf{R}_f$ 0.05 (20% EtOAc / P. E.); $[\alpha]_D^{20}$ +23.4 (*c* 0.27, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3383 (*br*), 2928, 1713, 1639, 1598, 1462; **^{1}H NMR** (500MHz, 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** (125MHz, 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.

1.) I. Paterson, G. J. Naylor and A. E. Wright, *Chem. Commun*., 2008, 4628.



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 **7** or **8** (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 (3x), 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-Benzoylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-10-hydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (21)

3-Benzoylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (23)

General procedure A was followed with alcohol **6** (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 **7** (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 **21** and **23** (colourless oil) which was subjected to

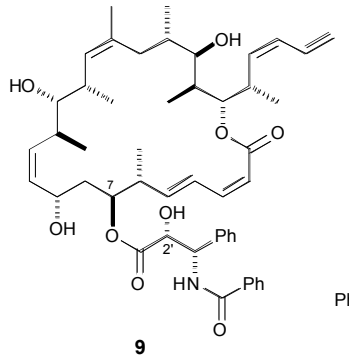
deprotection without further purification. $\mathbf{R_f}$ 0.52 (20% EtOAc / P.E.). **HRMS** (ES^+) calc. for $C_{67}H_{111}N_2O_9Si_3$ $[M+NH_4]^+$: 1171.7592. Found: 1171.7590.

3-*tert*-Butoxycarbonylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-10-hydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (22)

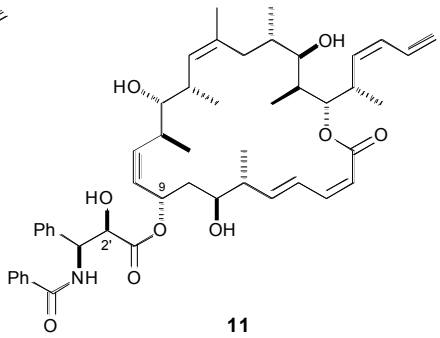
3-*tert*-Butoxycarbonylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (24)

General procedure A was followed with alcohol **6** (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 **8** (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 **22** and **24** (colourless oil) which was subjected to deprotection without further purification. $\mathbf{R_f}$ 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.

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 (3x). The organic phases were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (25% → 50% EtOAc / P.E.) then afforded the desired final compound.



9



11

3-Benzoylamino-2-hydroxy-3-phenyl-propionic acid 10,14,20-trihydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (9)

3-Benzoylamino-2-hydroxy-3-phenyl-propionic acid 8,14,20-trihydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (11)

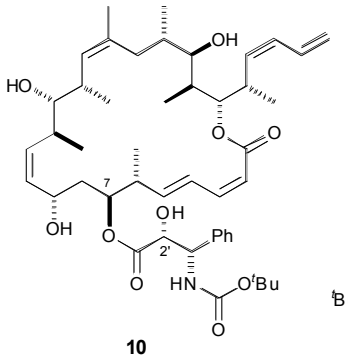
A mixture of silylated compounds **21** and **23** in THF (300 μL) was subjected to general procedure B using 450 μL of the HF·py stock solution. Following flash chromatography, an inseparable mixture of triple hybrids **9** and **11** (1.6 mg, 46% over two steps) was isolated as a white powder. Subsequent HPLC purification isolated regiomerically pure **9** and **11**.

7-Taxol Triple Hybrid **9**: $\mathbf{R}_f$ 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 (*br*), 2923, 2853, 1711, 1647, 1520, 1461; **^{1}H NMR** (500MHz, 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-OH), 4.62 (1H, d, *J* = 4.1 Hz, C19-OH), 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 **9**'s tendency to rapidly transesterify, we were unable to successfully measure a ^{13}C NMR spectrum for this compound.

9-Taxol Triple Hybrid **11**: $\mathbf{R}_f$ 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 (*br*), 2922, 2853, 1715, 1655, 1517, 1457; **^{1}H NMR** (500MHz, 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′-OH), 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-OH), 4.71 (1H, d, *J* = 5.3 Hz, C19-OH), 4.63 (1H, t, *J* = 4.4 Hz, H2′), 4.53 (1H, d, *J* = 5.3 Hz, C7-OH), 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** (125MHz, 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.



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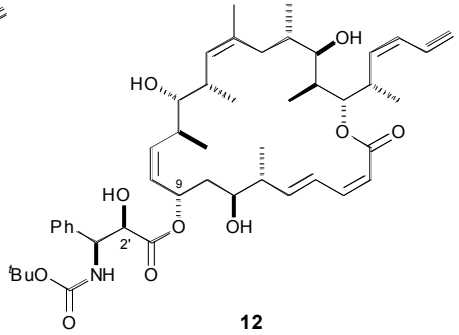


12

3-*tert*-Butoxycarbonylamino-2-hydroxy-3-phenyl-propionic acid 10,14,20-trihydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (10)

3-*tert*-Butoxycarbonylamino-2-hydroxy-3-phenyl-propionic acid 8,14,20-trihydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (12)

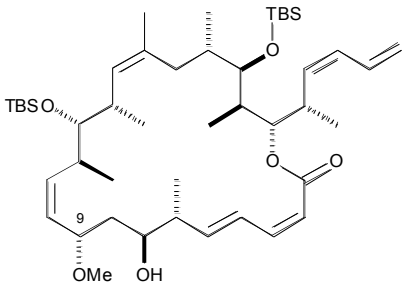
A mixture of silylated compounds **22** and **24** in THF (300 μL) was subjected to general procedure B using 450 μL of the HF·py stock solution. Following flash chromatography, an inseparable mixture of triple hybrids **10** and **12** (2.2 mg, 57% over two steps) was isolated as a white powder. Subsequent HPLC purification isolated regiomerically pure **10** and **12**.

7-Taxotere Triple Hybrid **10**: $\mathbf{R}_f$ 0.56 (70% EtOAc / P.E.); $\mathbf{R}_t$ 13.5 mins (7% IPA / hexane); $[\alpha]_D^{20}$ –20.0 (*c* 0.02, $CHCl_3$); **IR** (neat, cm^{-1}) ν_{max} = 3450 (*br*), 2963, 2918, 1696, 1498, 1457; **^{1}H NMR** (500MHz, 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′-OH), 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** (125MHz, CD_2Cl_2) δ = 173.2 (C1′), 166.3 (C1), 156.3 (^{t}BuO<u>C</u>(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 (<u>C</u>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, C<u>Me</u>$_3$), 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 $C_{47}H_{69}NO_{10}Na$ $[M+Na]^+$: 830.4819. Found: 830.4858.

9-Taxotere Triple Hybrid **12**: $\mathbf{R}_f$ 0.56 (70% EtOAc / P.E.); $\mathbf{R}_t$ 9.5 mins (7% IPA / hexane); $[\alpha]_D^{20}$ +6.0 (*c* 0.03, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3433 (*br*), 2963, 2920, 1694, 1498, 1456; **^{1}H NMR** (500MHz, CD_2Cl_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′-OH), 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** (125MHz, CD_2Cl_2) δ = 173.0 (C1′), 166.4 (C1), 156.3 (^{t}BuO<u>C</u>(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 (<u>C</u>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 (C<u>Me</u>$_3$), 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.

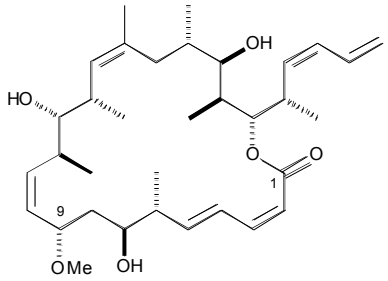


25

14,20-*Bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-10-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (25)

To a stirred solution of alcohol **6** (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 x 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 **25** (3.2 mg, 46%, 100% brsm) as a colourless oil. $\mathbf{R_f}$ 0.41 (20% EtOAc / P.E.); $[\alpha]_D^{20}$ +8.1 (*c* 0.31, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3460 (*br*), 2961, 2929, 1713, 1639, 1597, 1462; **^{1}H NMR** (500MHz, 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** (125MHz, 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.

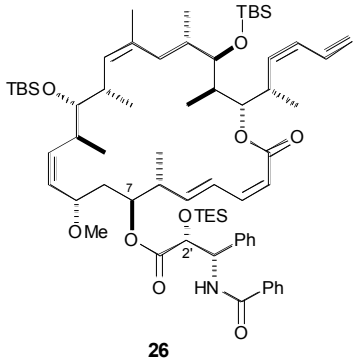


14

8,14,20-Trihydroxy-10-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (14)

Protected precursor **25** (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, analogue **14** (1.0 mg, 72%) was isolated as a white powder. $\mathbf{R}_f$ 0.54 (70% EtOAc / P.E.); $\mathbf{R}_t$ 20.0 mins (4.5% IPA / hexane); $[\alpha]_D^{20}$ –109.4 (*c* 0.17, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3456 (*br*), 2961, 2928, 1699, 1638, 1457; **^{1}H NMR** (500MHz, 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** (125MHz, 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.

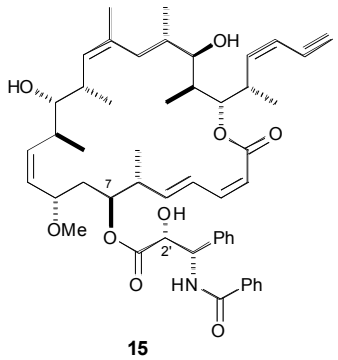


26

3-Benzoylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-10-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (26)

General procedure A was followed with alcohol **25** (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 **7** (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 **26** as a colourless oil contaminated with trace amounts of unreacted β-lactam **7**. 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** (500MHz, C_6D_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, $Si(CH_2C\underline{H}_3)_3$), 0.45 – 0.56 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.17 (3H, s, $Si(CH_3)_2$), 0.16 (9H, s, $Si(CH_3)_2$); **^{13}C NMR** (125MHz, C_6D_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.

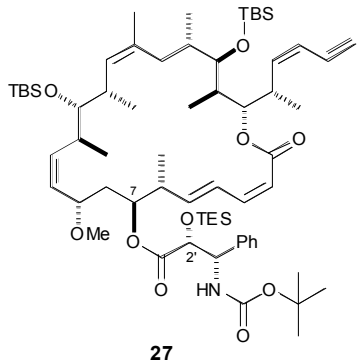


15

3-Benzoylamino-2-hydroxy-3-phenyl-propionic acid 14,20-dihydroxy-10-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (15)

Protected precursor **26** in THF (450 μL) was subjected to general procedure B using 425 μL of the HF·py stock solution. Following flash chromatography, analogue **15** (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. $\mathbf{R}_f$ 0.41 (60% EtOAc / P.E.); $\mathbf{R}_t$ 15.5 mins (6% IPA / hexane); $[\alpha]_D^{20}$ –56.9 (*c* 0.13, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3415 (*br*), 2962, 2926, 1713, 1654, 1603, 1518, 1485, 1454;

^{1}H NMR (500MHz, 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′-OH), 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** (125MHz, CD_2Cl_2) δ = 172.3 (PhC(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.

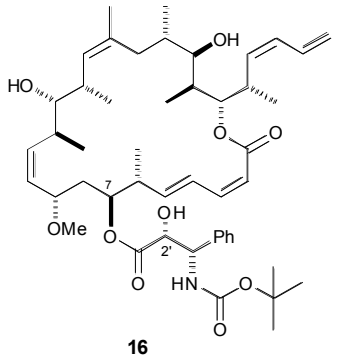


27

3-*tert*-Butoxycarbonylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-10-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (27)

General procedure A was followed with alcohol **25** (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 **8** (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 protected analogue **27** (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** (500MHz, 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** (125MHz, 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.

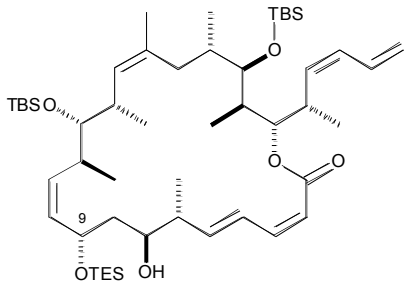


16

3-*tert*-Butoxycarbonylamino-2-hydroxy-3-phenyl-propionic acid 14,20-dihydroxy-10-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-8-yl ester (16)

Protected precursor **27** (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, analogue **16** (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 (*br*), 2925, 2853, 1716, 1497, 1457; **^{1}H NMR** (500MHz, 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′-OH), 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** (125MHz, 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</u>$_3$), 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.

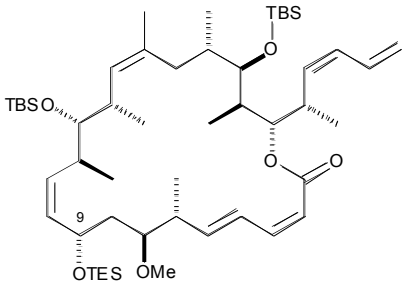


28

14,20-*Bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-10-triethylsilanyloxy-oxacyclodocosa-3,5,11,16-tetraen-2-one (28)

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 **6** (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 x 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 desired product **28** (3.9 mg, 71%) and the

corresponding *bis*-TES protected compound (1.1 mg, 17%) as colourless oils. $\mathbf{R}_f$ 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** (500MHz, 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 x $SiC(CH_3)_3$, $Si(CH_2C\underline{H}_3)_3$), 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 (3 H, s, $Si(CH_3)_2$), 0.17 (3 H, s, $Si(CH_3)_2$); **^{13}C NMR** (125MHz, 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.

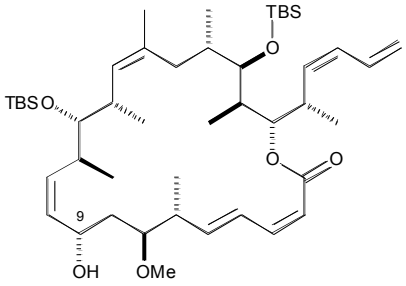


29

14,20-*Bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-10-triethylsilanyloxy-oxacyclodocosa-3,5,11,16-tetraen-2-one (29)

Proton sponge (36.2 mg, 0.169 mmol, 10 eq.) was added to a stirred solution of alcohol **28** (15.0 mg, 16.9 μmol) in DCM (1.7 mL) and then stirred at r.t. for 10 min

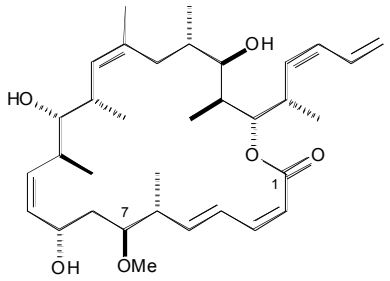
before Meerwein's salt (15.0 mg, 0.101 mmol, 6 eq.) was added. After 1 h, a further portion of Meerwein's salt (7.5 mg, 0.05 mmol, 3 eq.) was added and stirring continued for 30 min. The reaction was quenched with 10% citric acid solution then diluted with water (5 mL) and DCM (5 mL). After separating the phases, the aqueous phase was extracted with DCM (3 x 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 **29** (11.7 mg, 77%) and recovered starting material (3.2 mg, 21%) as colourless oils. $\mathbf{R}_f$ 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** (500MHz, 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, H26b), 5.05 (1H, d, *J* = 10.3 Hz, H26a), 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, $Si(C\underline{H}_2CH_3)_3$), 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** (125MHz, 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.



30

14,20-*Bis*-(*tert*-butyl-dimethyl-silanyloxy)-10-hydroxy-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (30)

PPTS (2 crystals) was added to a stirred solution of TES ether **29** (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 **30** (11.3 mg, 99%) was isolated as a colourless oil. $\mathbf{R}_f$ 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** (500MHz, 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** (125MHz, 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.

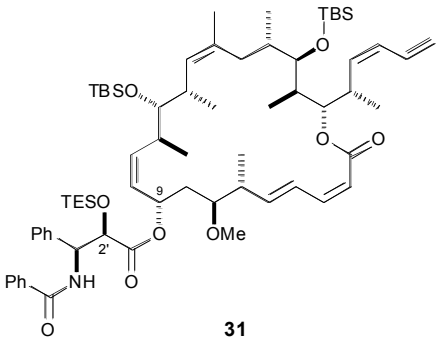


18

10,14,20-Trihydroxy-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (18)

Protected precursor **30** (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 analogue **18** (1.6 mg, 68%) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. $\mathbf{R}_f$ 0.37 (70% EtOAc / P.E.); $\mathbf{R}_t$ 34.9 mins (6% IPA / hexane); $[\alpha]_D^{20}$ –24.4 (*c* 0.09, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3402 (*br*), 2928, 1672, 1638, 1451; **^{1}H NMR** (500MHz, 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** (125MHz, 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.

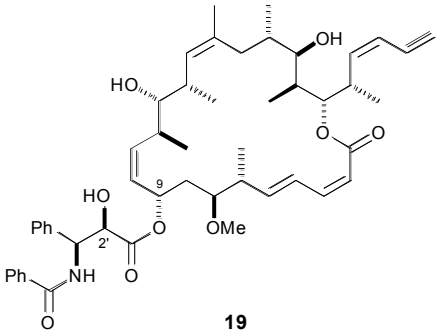


31

3-Benzoylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (31)

General procedure A was followed with alcohol **30** (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 **7** (2.2 mg, 5.7 μmol, 1.5 eq.) in THF (500 μL) was added *via* syringe. After stirring at –78 ˚C for 45 minutes, a further portion of NaHMDS (5 μL, 1M in THF, 1.2 eq.) was added before warming to 0 ˚C for 30 mins. The standard work-up procedure and subsequent flash chromatography yielded protected analogue **31** (3.4 mg, 77%) as a colourless oil. $\mathbf{R}_f$ 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** (500MHz, C_6D_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,

$Si(CH_2C\underline{H}_3)_3$), 0.36 – 0.45 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.24 (3H, s, $Si(CH_3)_2$), 0.20 (3H, s, $Si(CH_3)_2$), 0.12 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125MHz, C_6D_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.

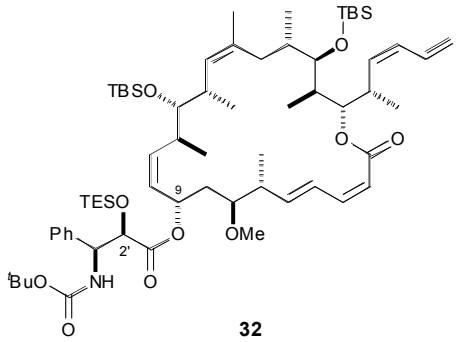


19

3-Benzoylamino-2-hydroxy-3-phenyl-propionic acid 14,20-dihydroxy-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (19)

Protected precursor (**31**) (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, analogue **19** (1.8 mg, 85%) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. $\mathbf{R}_f$ 0.45 (60% EtOAc / P.E.); $\mathbf{R}_t$ 102 mins (2% IPA / hexane); $[\alpha]_D^{20}$ +46.0 (*c* 0.05, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3427 (*br*), 2959, 2934, 1711, 1651, 1518, 1486; **^{1}H NMR** (500MHz, 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′-OH), 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** (125MHz, CD_2Cl_2) δ = 172.3 (C1′), 166.7 (PhC(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.

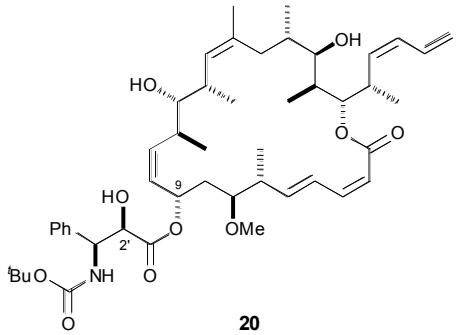


32

3-*tert*-Butoxycarbonylamino-3-phenyl-2-triethylsilanyloxy-propionic acid 14,20-*bis*-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (32)

General procedure A was followed with alcohol **30** (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 **7** (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 protected analogue

31 (3.4 mg, 77%) as a colourless oil. $\mathbf{R}_f$ 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** (500MHz, 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** (125MHz, 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 $C_{66}H_{117}NO_{10}$ $[M+NH_4]^+$: 1181.8011. Found: 1181.8013.

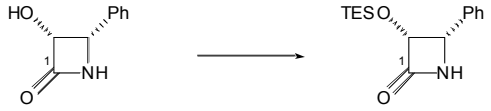


20

3-*tert*-Butoxycarbonylamino-2-hydroxy-3-phenyl-propionic acid 14,20-dihydroxy-8-methoxy-7,13,15,17,19,21-hexamethyl-22-(1-methyl-penta-2,4-dienyl)-2-oxo-oxacyclodocosa-3,5,11,16-tetraen-10-yl ester (20)

Protected precursor **32** (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, analogue **20** (2.2 mg, quant.) was isolated as a white powder. Subsequent HPLC purification was used to prepare the compound for biological testing. $\mathbf{R}_f$ 0.51 (60% EtOAc / P.E.); $\mathbf{R}_t$ 44 mins (2% IPA / hexane); $[\alpha]_D^{20}$ +40.9 (*c* 0.11, $CHCl_3$); **IR** (neat, cm^{-1}) υ_{max} = 3421 (*br*), 2964, 2925, 1710, 1639, 1496, 1454; **^{1}H NMR** (500MHz, 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′-OH), 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** (125MHz, CD_2Cl_2) δ = 172.2 (C1′), 166.4 (C1), 155.7 (^{t}BuOC(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

(CMe_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, CMe_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.



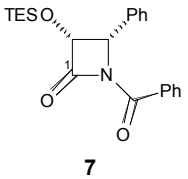
33 **34**

4-Phenyl-3-triethylsilanyloxy-azetidin-2-one (34)

To a stirred solution of alcohol **33**[2] (51.0 mg, 0.313 mmol, 1.0 eq.) in pyridine (1.0 mL) at r.t. was added TESCl (63 μL, 0.375 mmol, 1.2 eq.). The mixture was stirred for 50 min before the solvents were removed *in vacuo*. Flash chromatography of the crude residue (20 % EtOAc / P.E.) yielded the TES ether **34** (76.9 mg, 89%) as a colourless oil. $\mathbf{R_f}$ 0.08 (20% EtOAc / P.E.); **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.28 – 7.37 (5H, m, Ar), 6.43 – 6.49 (1H, m, NH), 5.07 (1H, dd, *J* = 2.7, 4.7 Hz, H3), 4.78 (1H, d, *J* = 4.7 Hz, H2), 0.76 (9H, t, *J* = 8.1 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.35 – 0.49 (6H, m, $Si(C\underline{H}_2CH_3)_3$).

Compound was previously synthesised: G. I. Georg, Z. S. Cheruvallath, G. C. B. Harriman, M. Hepperle and H. Park, *Bioorg. & Med. Chem, Lett.*, 1993, **3**, 2467.

2.) V. Farina, S. I. Hauck and D. G. Walker, *Synlett*, 1992, 761.



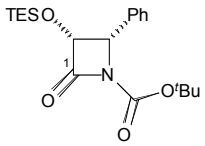
7

1-Benzoyl-4-phenyl-3-triethylsilanyloxy-azetidin-2-one (7)

β-Lactam **34** (105 mg, 0.377 mmol, 1.0 eq.) and DMAP (4.6 mg, 0.038 mmol, 0.1 eq.) were dissolved in DCM (5 mL) and cooled to 0 ˚C. Triethylamine (0.105 mL,

0.753 mmol, 2.0 eq.) and benzoyl chloride (0.066 mmol, 0.565 mmol, 1.5 eq.) were then added and the mixture warmed to r.t. for 1 h. Solvents were removed *in vacuo* and the crude mixture purified by flash chromatography (10 % EtOAc / P.E.) to afford coupling precursor **7** (118 mg, 82%) as a colourless oil. $\mathbf{R}_f$ 0.42 (20% EtOAc / P.E.); **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.04 (2H, d, *J* = 7.6 Hz, Ar), 7.59 (1H, t, *J* = 7.6 Hz, Ar), 7.48 (2H, t, *J* = 7.6 Hz, Ar), 7.29 – 7.38 (5H, m, Ar), 5.42 (1H, d, *J* = 6.3 Hz, H3), 5.15 (1H, d, *J* = 6.3 Hz, H2), 0.81 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.42 – 0.56 (6H, m, $Si(C\underline{H}_2CH_3)_3$).

Compound was previously synthesised: S.-C. Kim and H.-K. Kim, *Bull. Kor. Chem. Soc*., 2000, **21**, 1047.

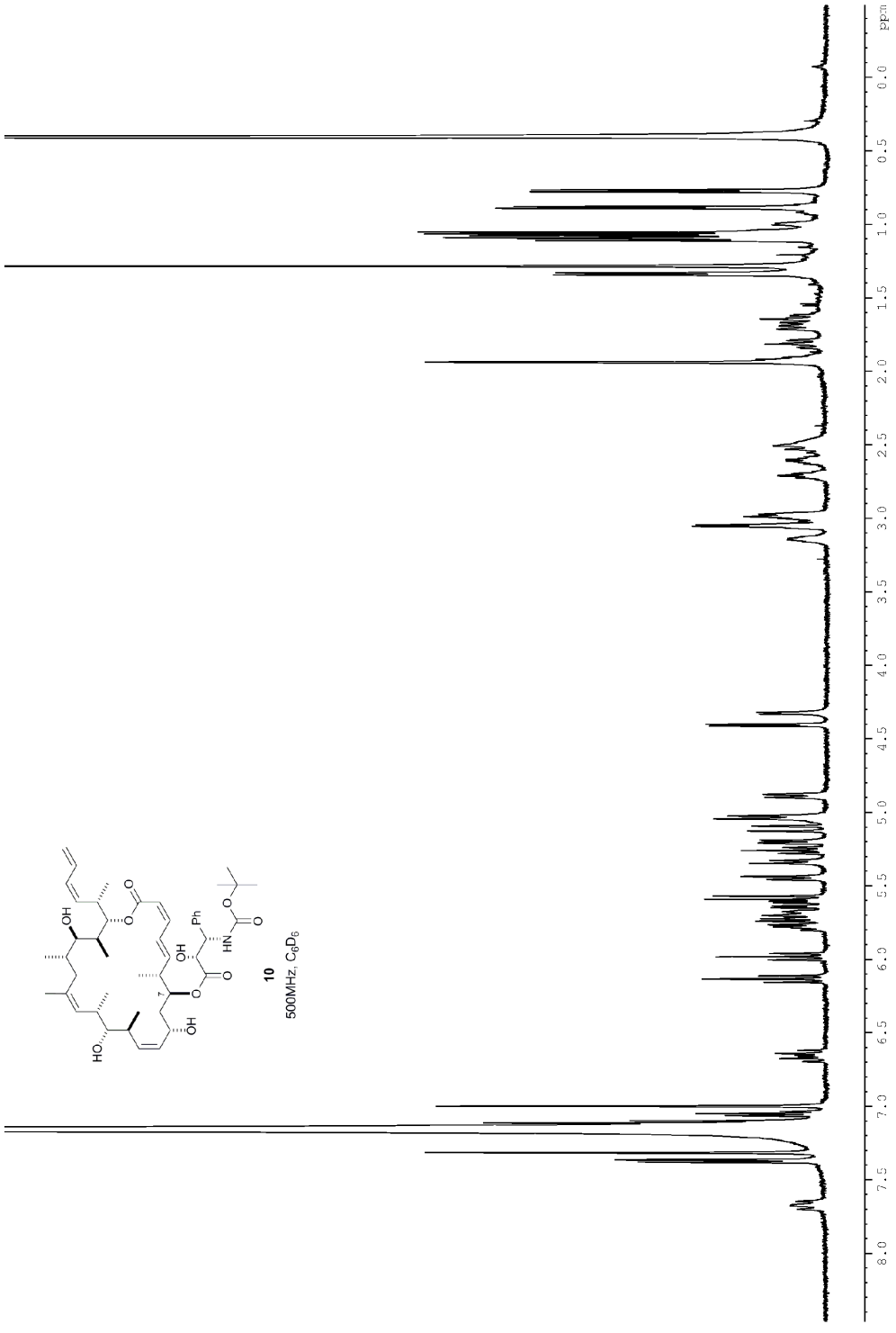


8

2-Oxo-4-phenyl-3-triethylsilanyloxy-azetidine-1-carboxylic acid *tert*-butyl ester (8)

β-Lactam **34** (77 mg, 0.277 mmol, 1.0 eq.) and DMAP (4.8 mg, 0.039 mmol, 0.15 eq.) were dissolved in DCM (4 mL) and cooled to 0 ˚C. Triethylamine (0.077 mL, 0.554 mmol, 2.0 eq.) and pivalic anhydride (0.084 mmol, 0.416 mmol, 1.5 eq.) were then added and the mixture warmed to r.t. for 2 h. Solvents were removed *in vacuo* and the crude mixture purified by flash chromatography (10 % EtOAc / P.E.) to afford coupling precursor **8** (93 mg, 89%) as a colourless oil. $\mathbf{R}_f$ 0.43 (20% EtOAc / P.E.); **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.25 – 7.35 (5H, m, Ar), 5.05 (1H, d, *J* = 5.7 Hz, H3), 5.02 (1H, d, *J* = 5.7 Hz, H2), 1.39 (9H, s, $C(CH_3)_3$), 0.76 (9H, t, *J* = 7.8 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.36 – 0.50 (6H, m, $Si(C\underline{H}_2CH_3)_3$).

Compound was previously synthesised: I. Ojima, C. M. Sun, M. Zucco, Y. H. Park, O. Duclos and S. Kuduk, *Tetrahedron Lett*., 1993, **34**, 4149.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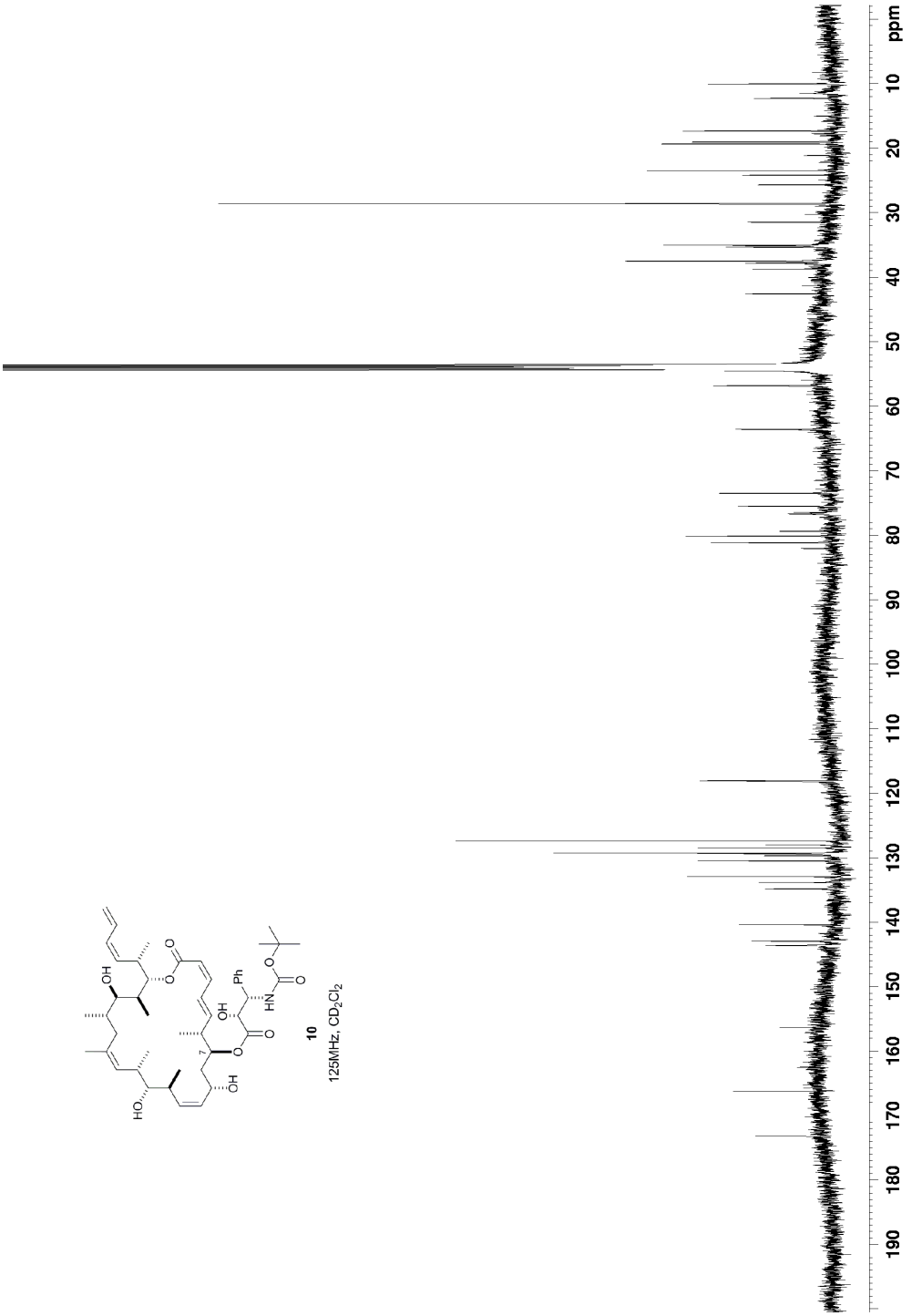
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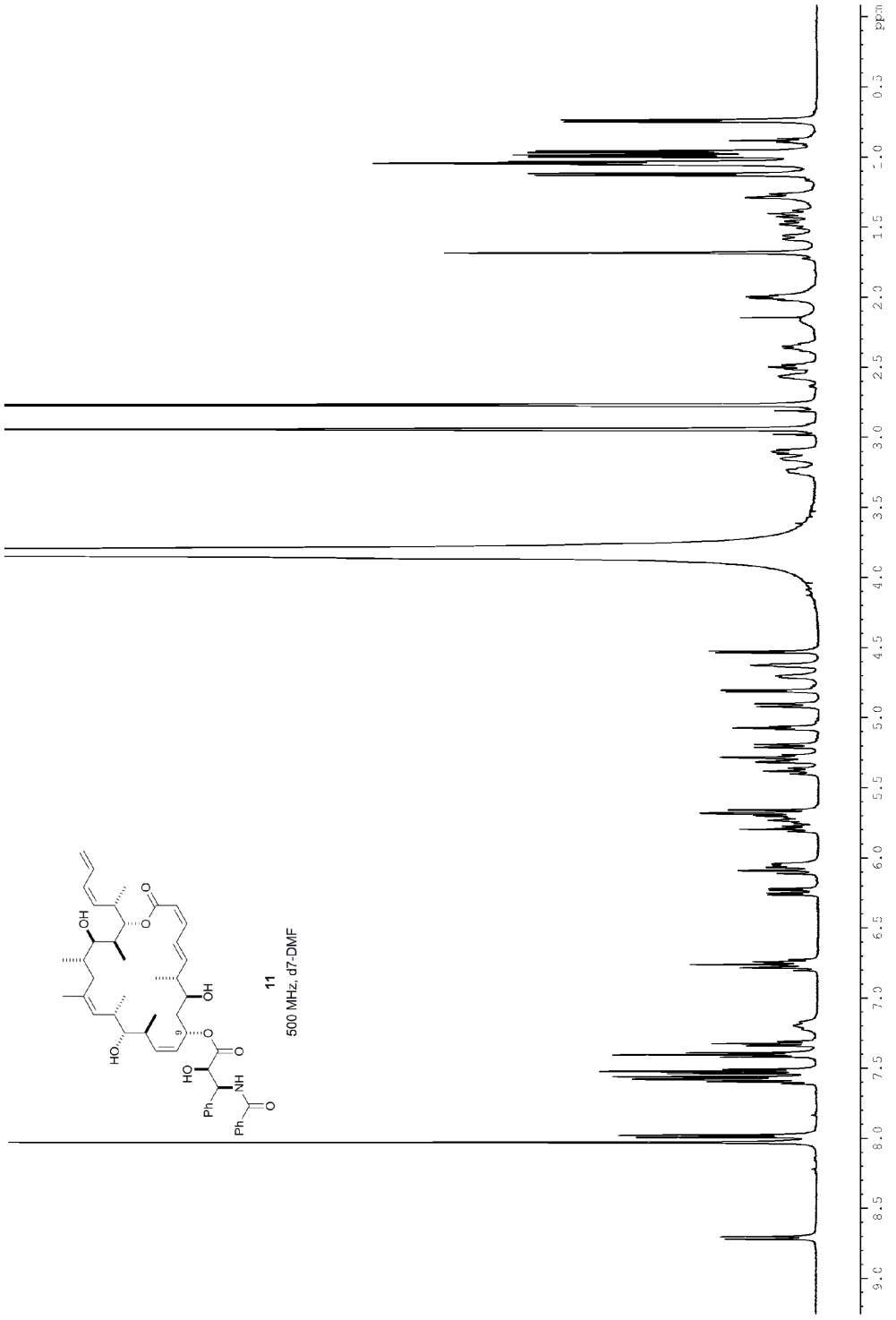
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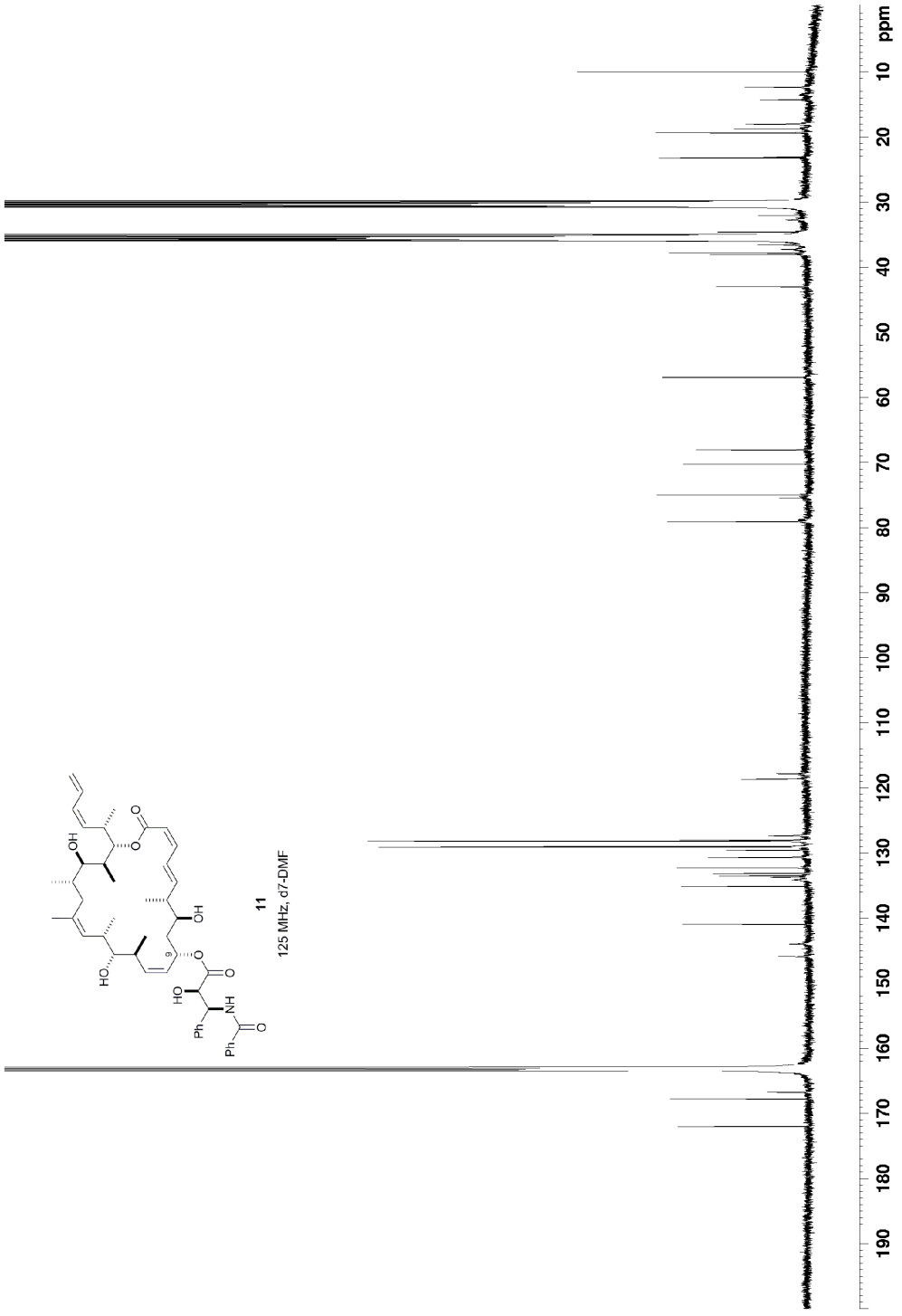
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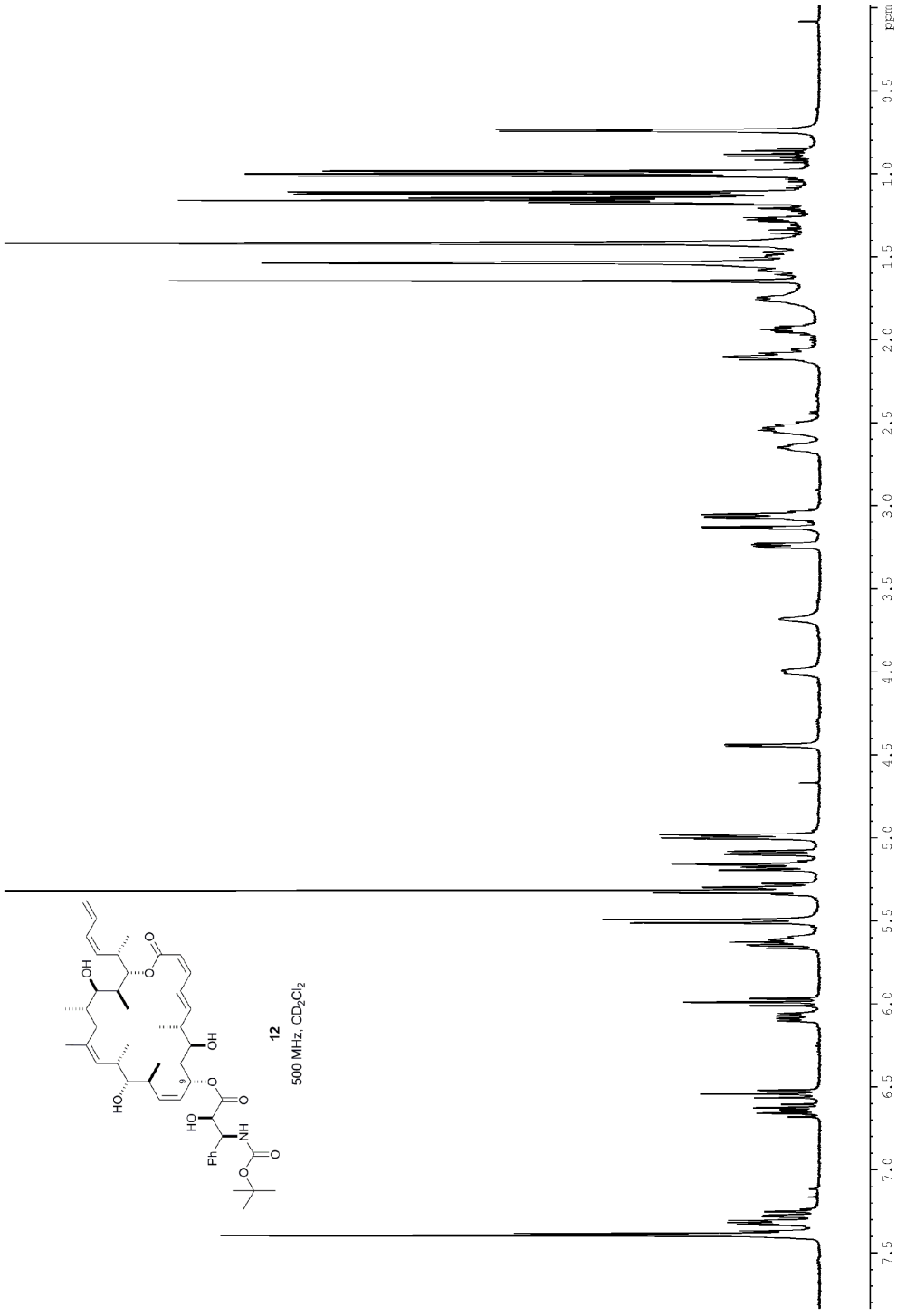
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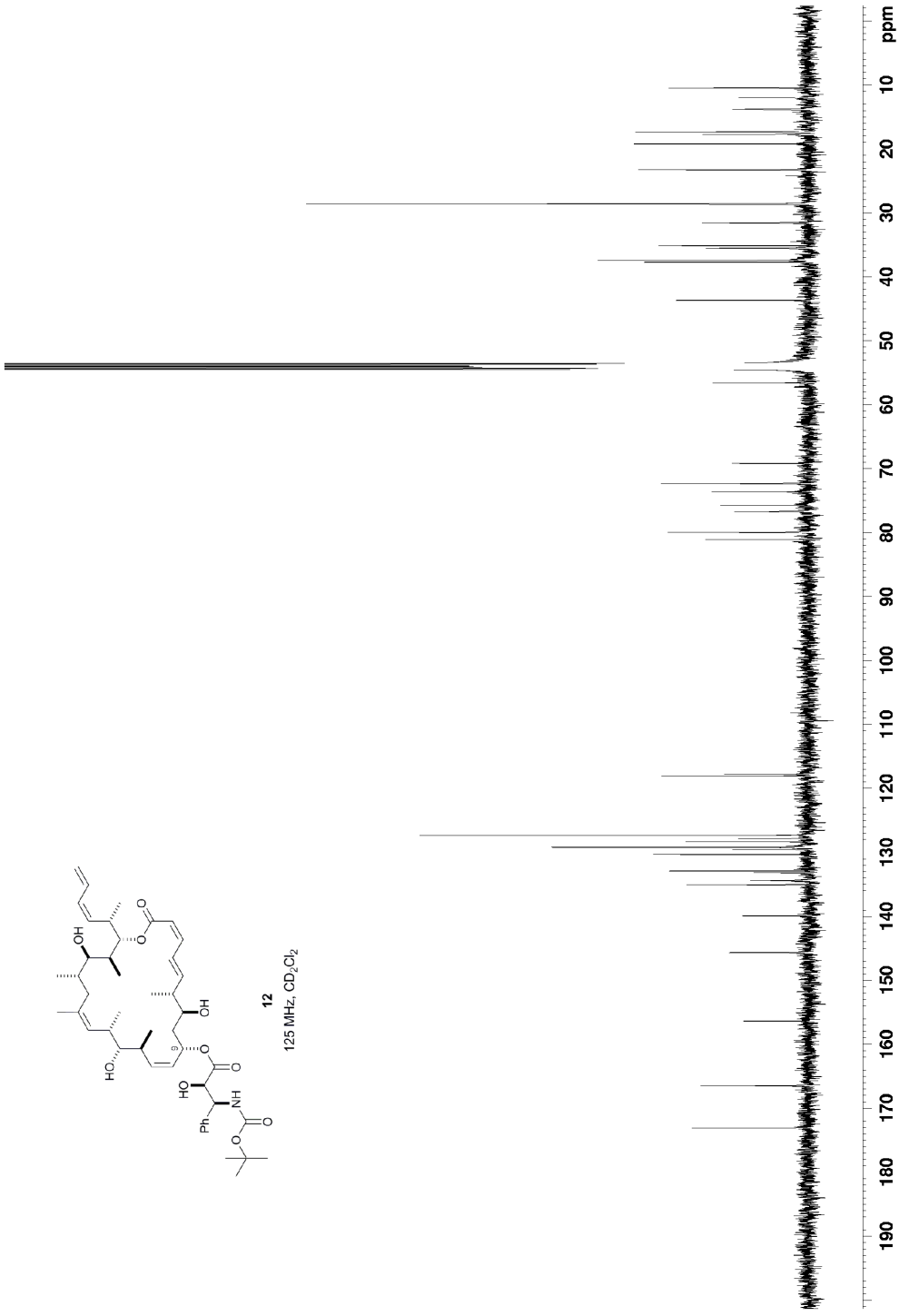
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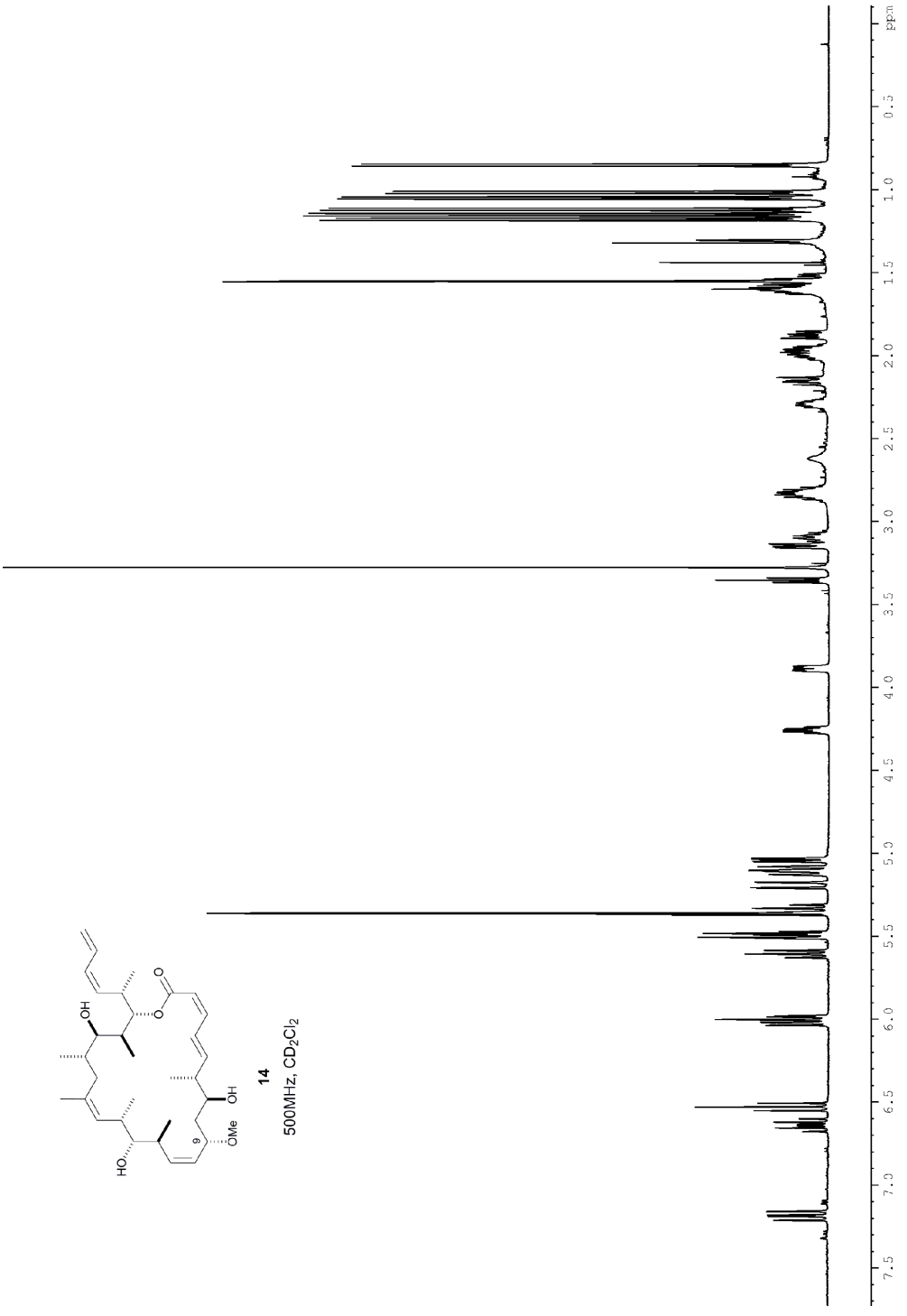
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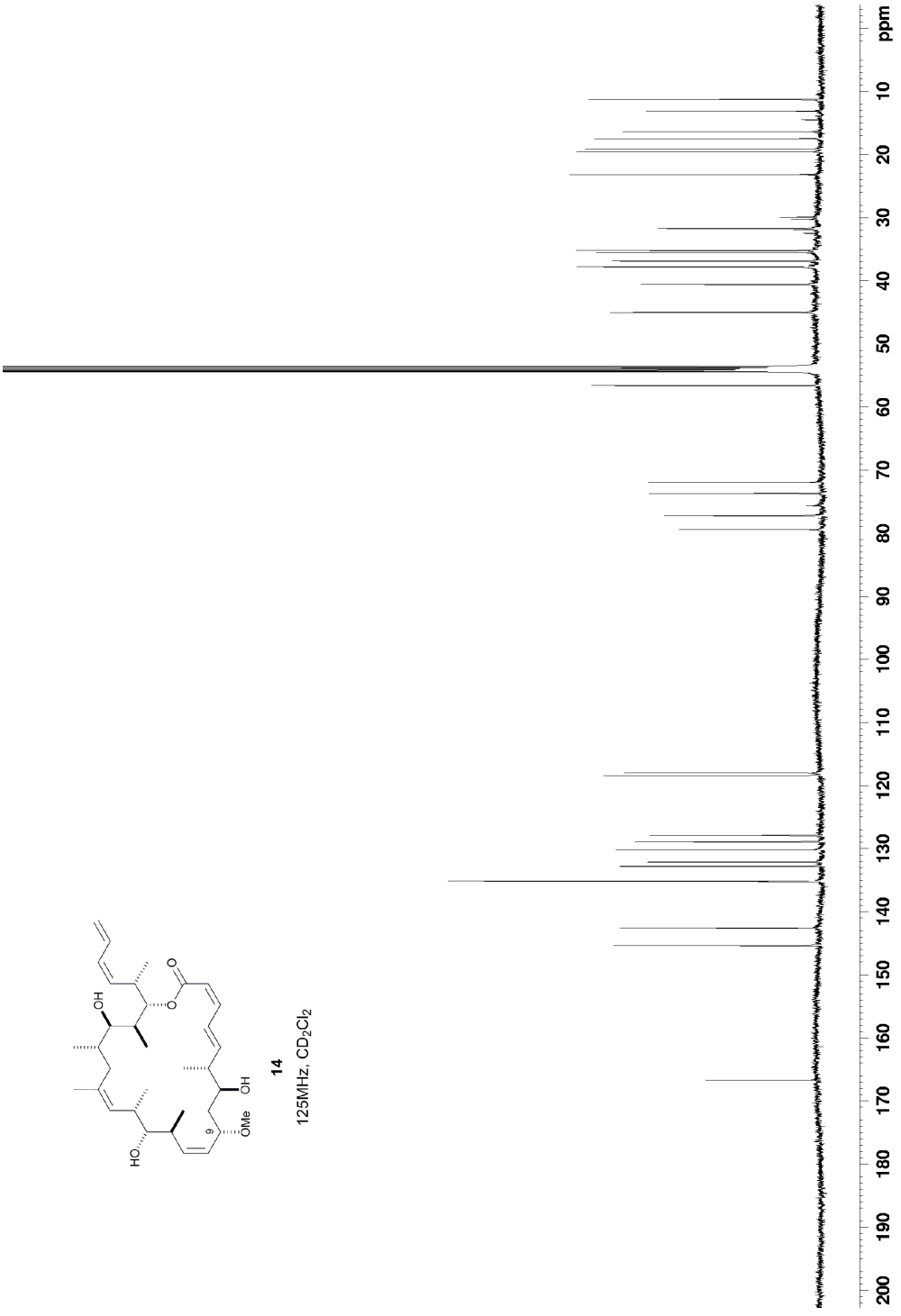
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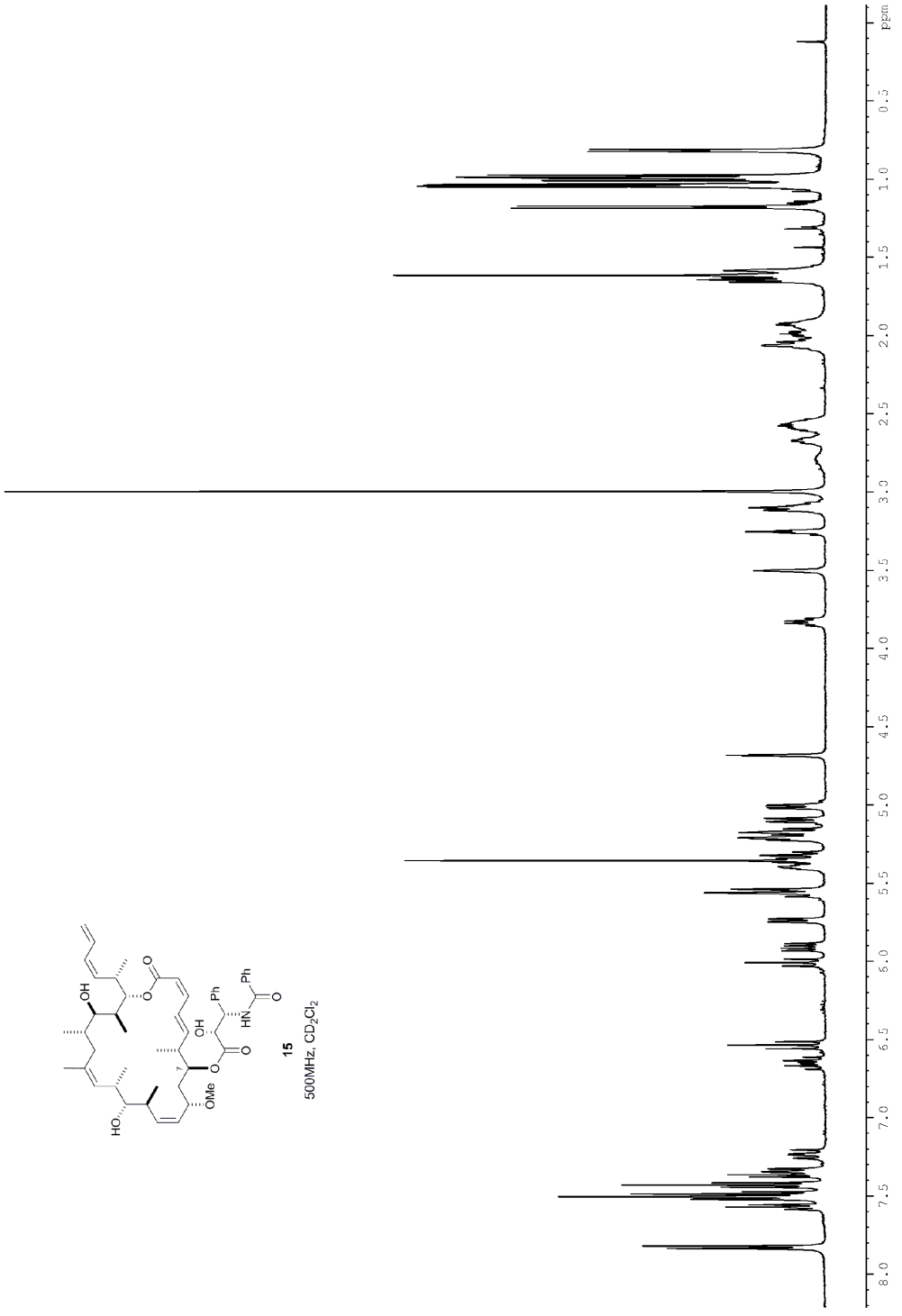
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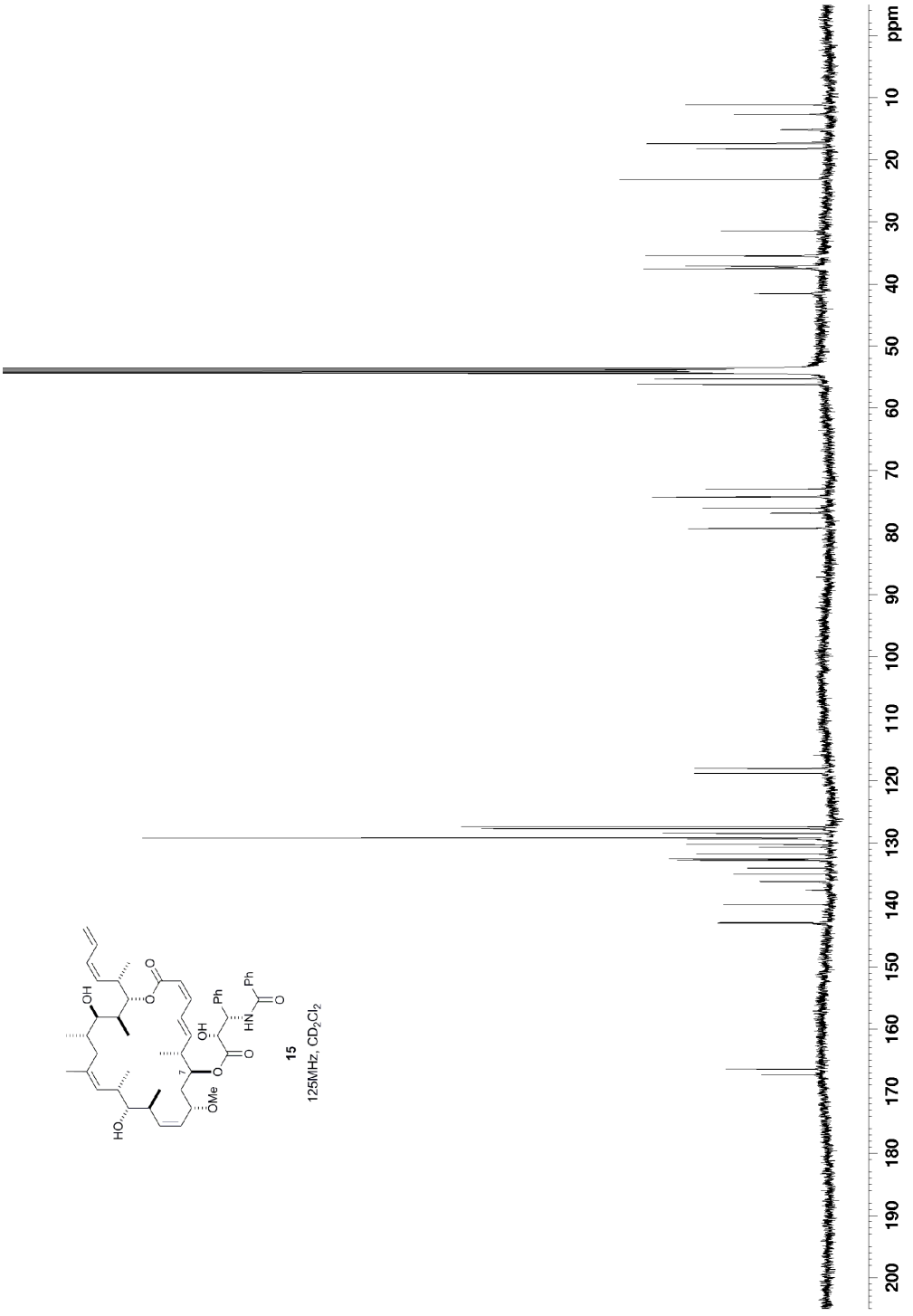
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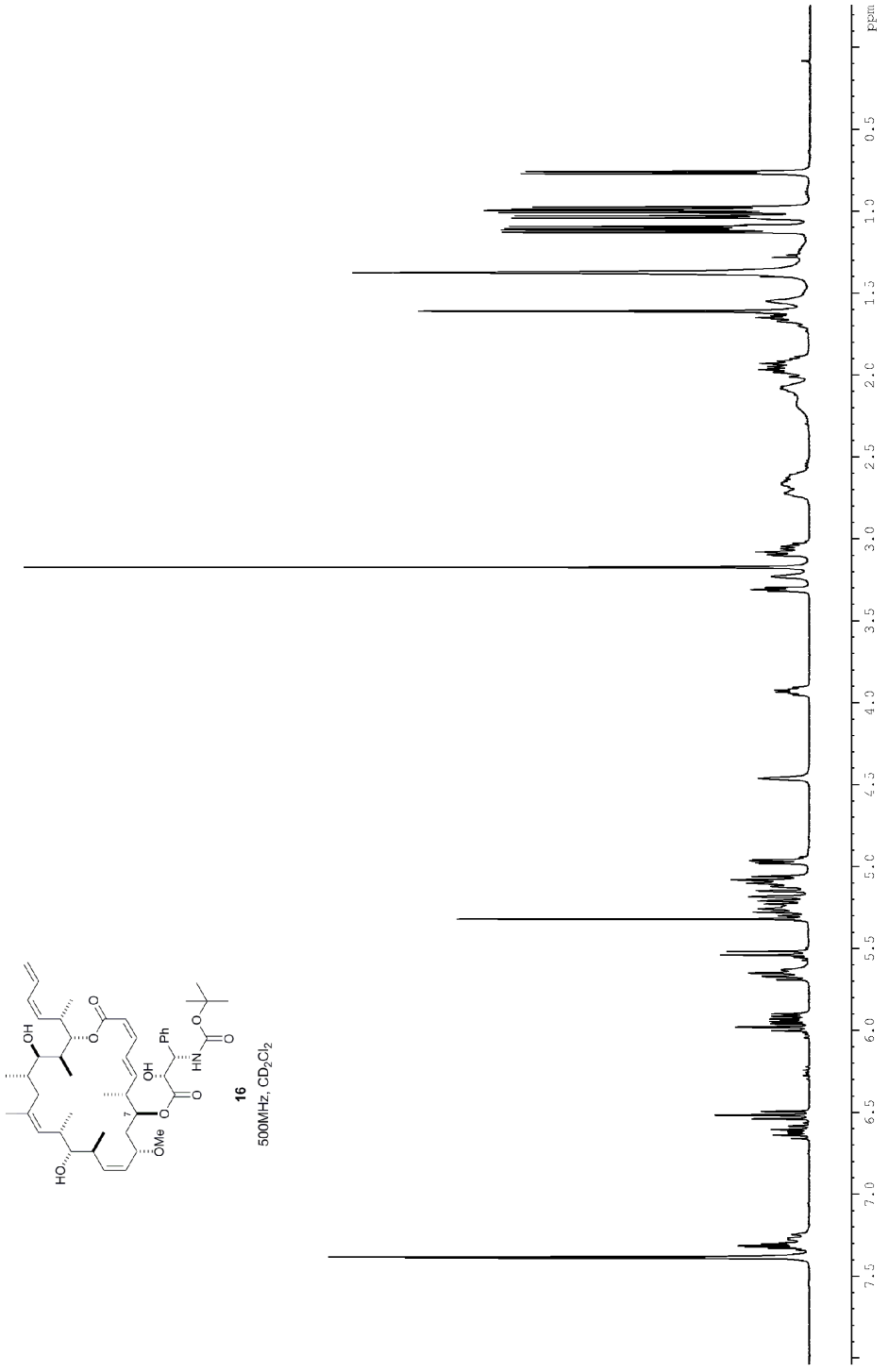
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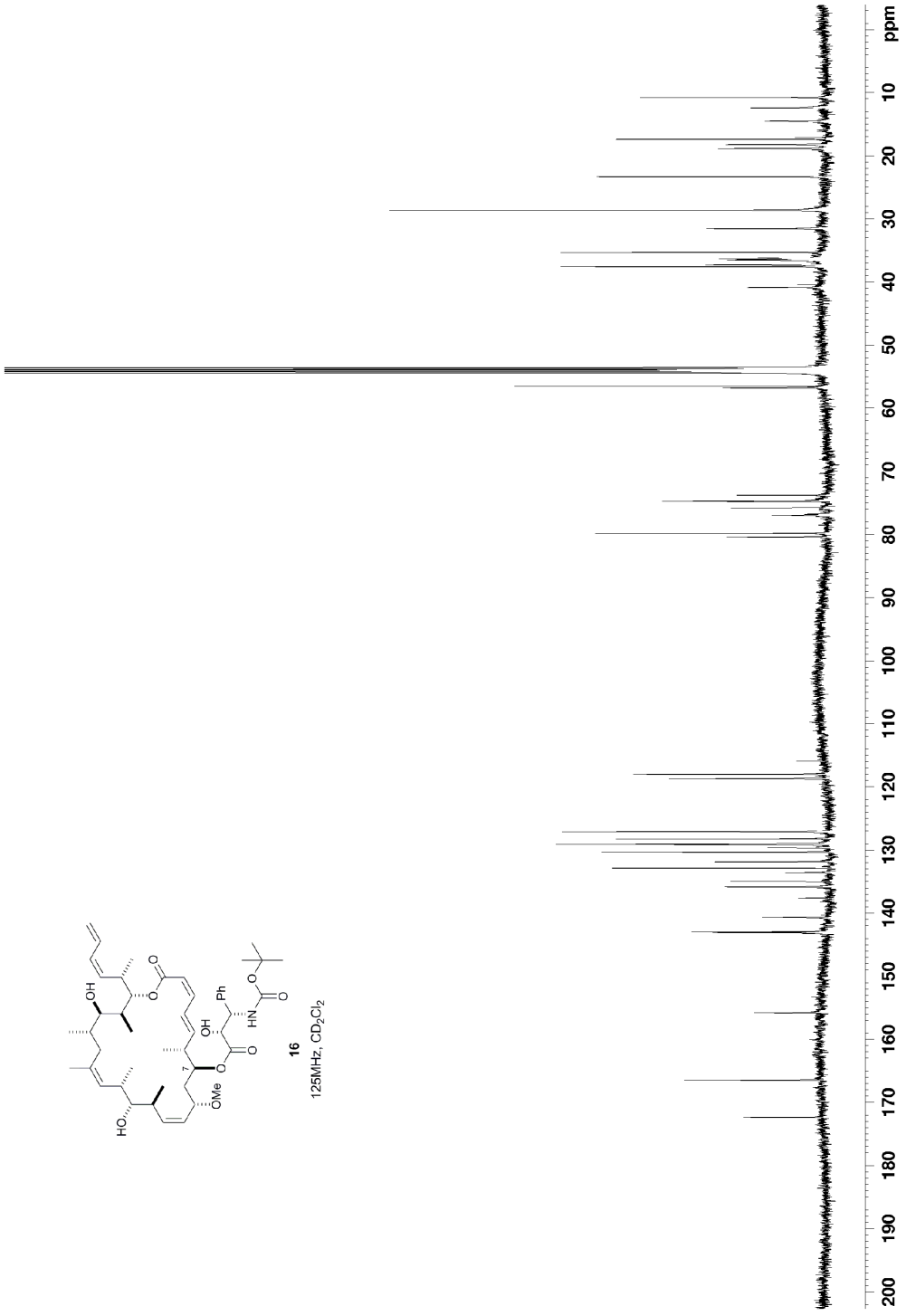
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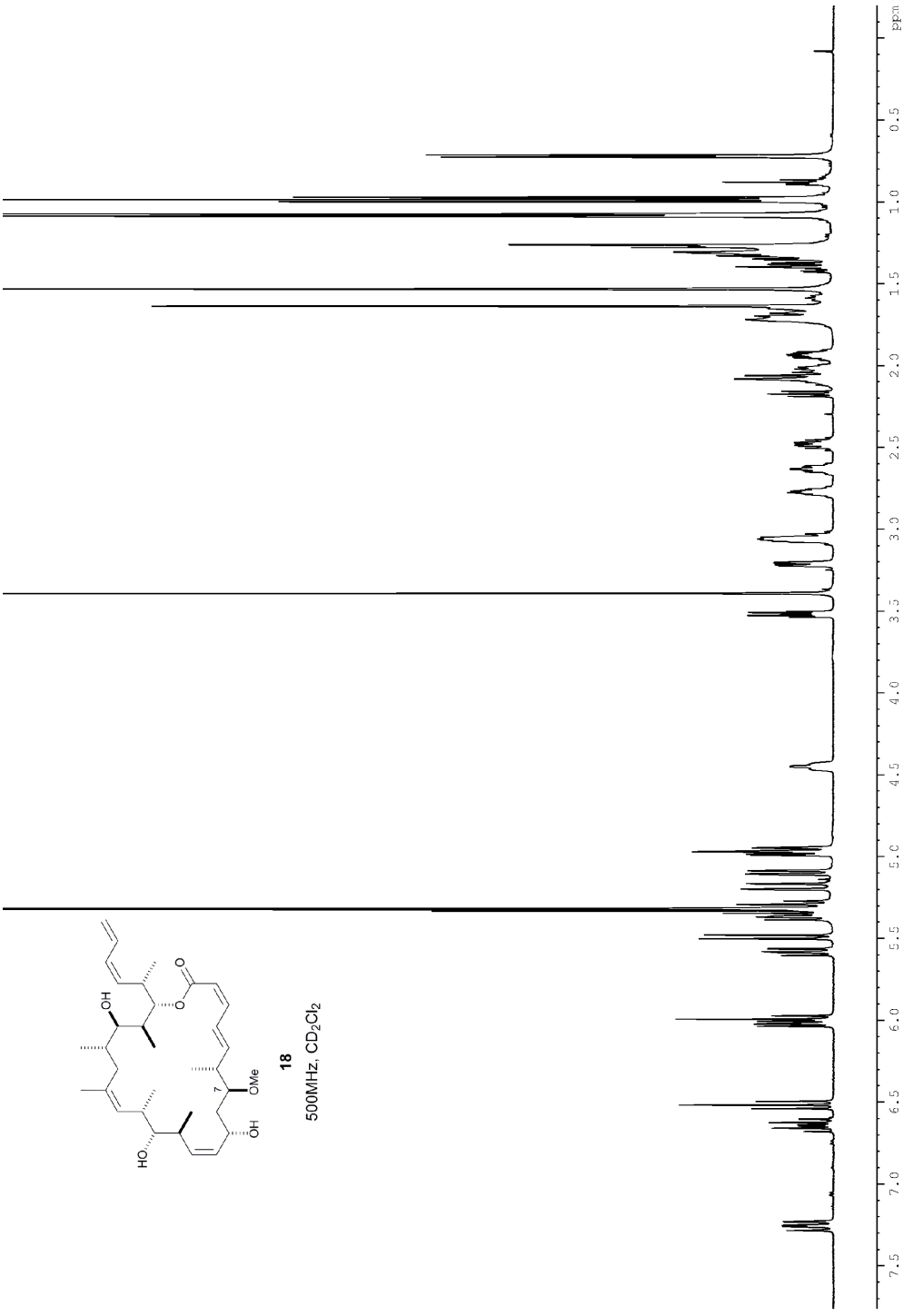
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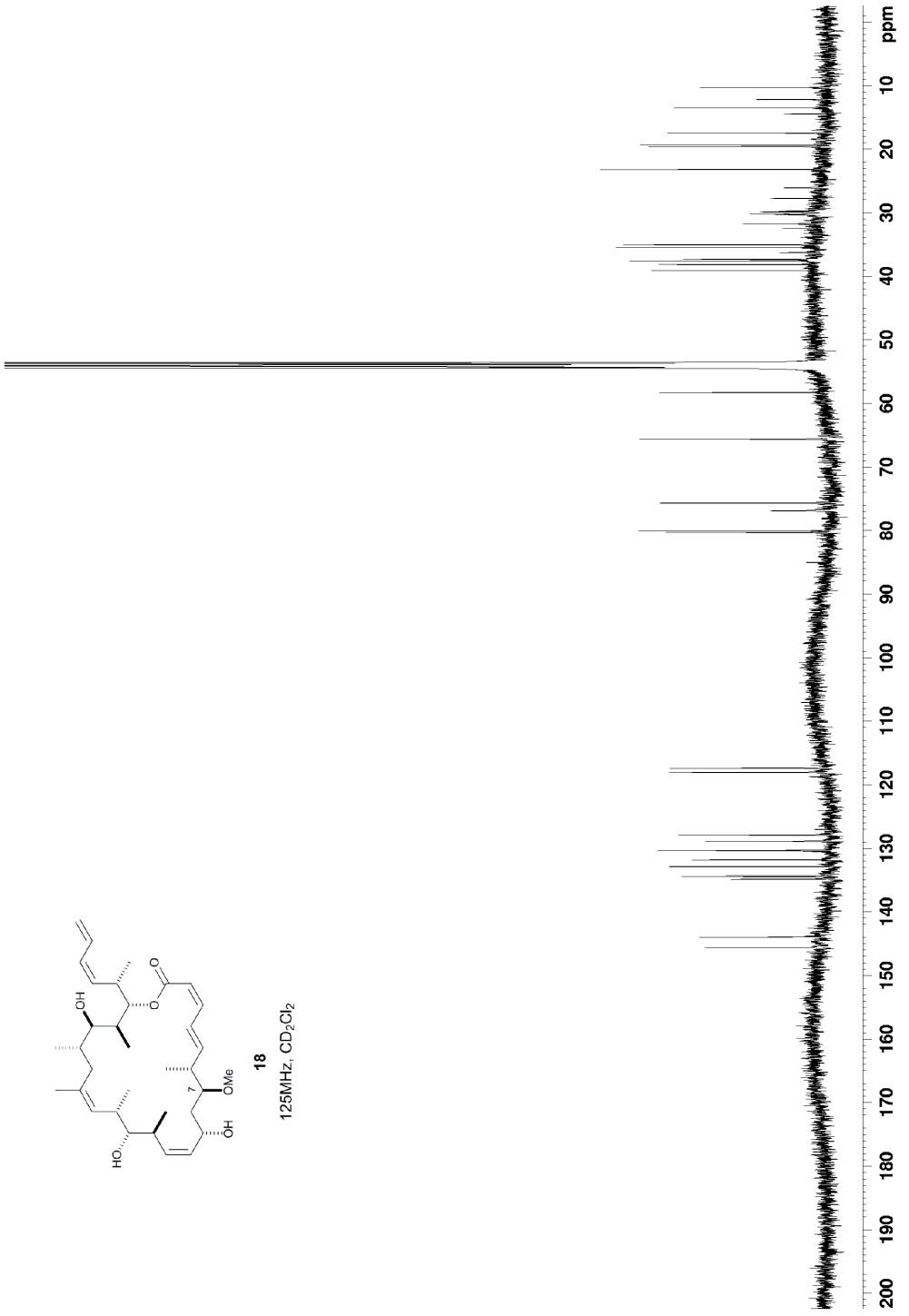
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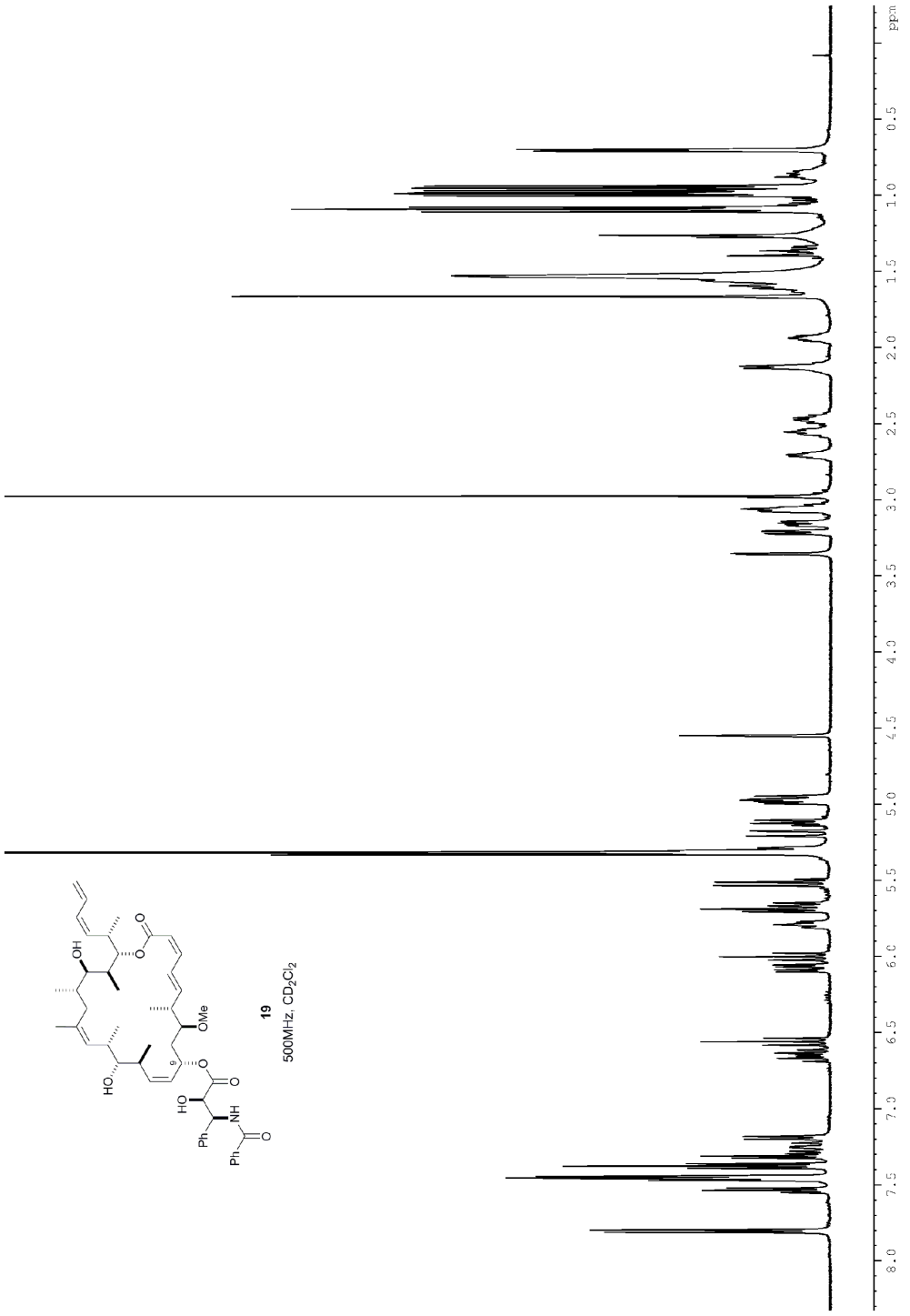
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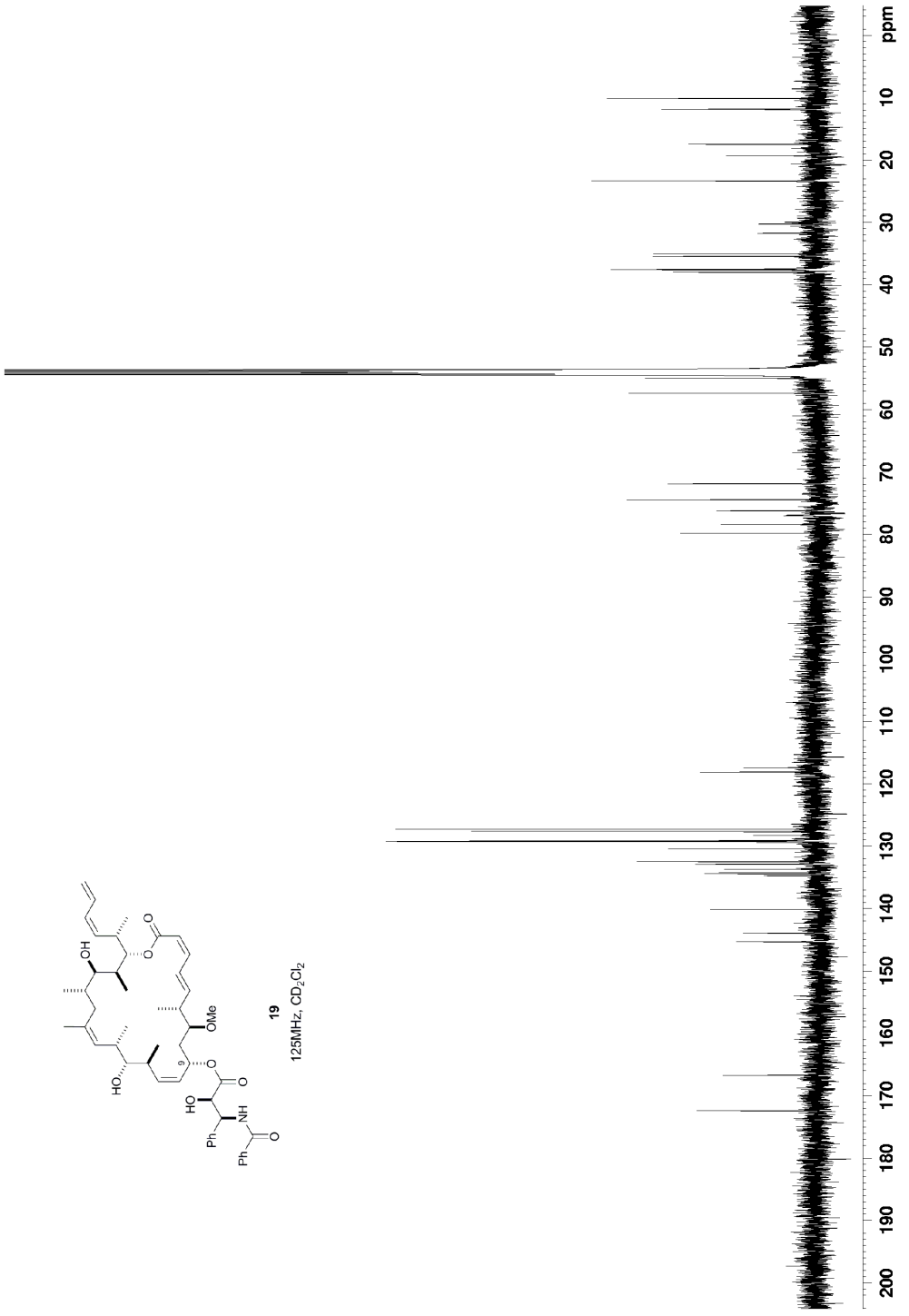
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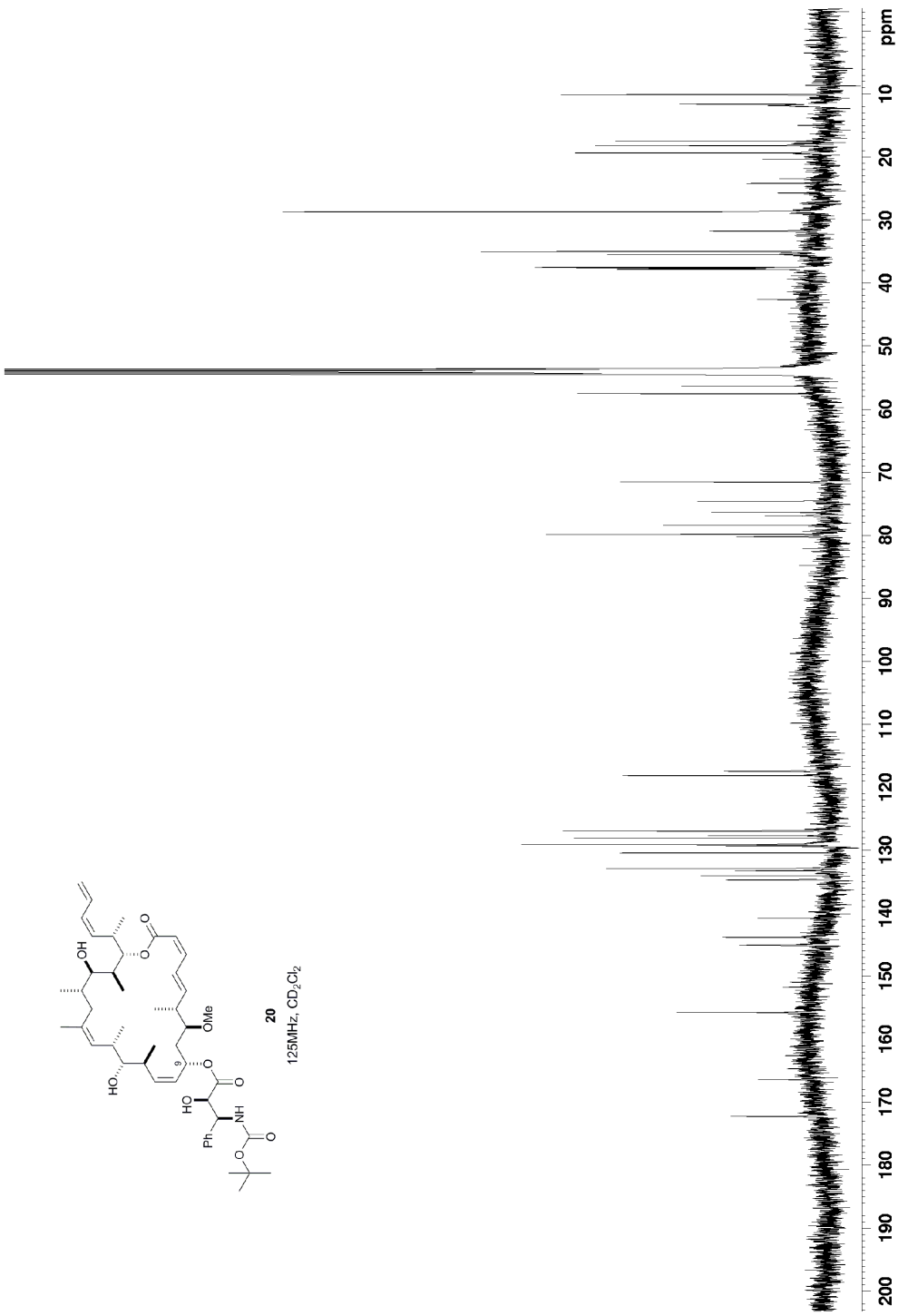
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