# Synthesis and Biological Evaluation of Novel Macrocyclic Paclitaxel Analogs

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**Supporting Information: Synthesis and characterization data for key intermediates and products.**

**General Experimental Methods**: Unless otherwise mentioned, all chemicals and materials were used as received from commercial suppliers without further purification. Moisture sensitive reactions were performed in oven dried glassware under argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone under nitrogen. Dichloromethane was distilled from calcium hydride. Thin layer chromatography (TLC) plates (silica gel 60 GF, with aluminum support) from E. Merck were used for monitoring progress of a reaction and visualized with 254 nm UV light and/or vannilin/sulfuric acid spray in some cases by dipping in a phosphomolybidic acid/ethanol solution. Silica gel for column chromatography was purchased from E. Merck (230-400 mesh). Preparative thin layer chromatography (PTLC) plates (silica gel 60 GF) were procured from Analtech. $^{1}$H and $^{13}$C NMR spectra were obtained from a Varian Unity 400 spectrometer in $CDCl_3$ at 399.951 and 100.578 MHz frequency respectively. Chemical shifts are reported as δ-values relative to tetramethylsilane (TMS) as internal reference. High resolution mass spectra were obtained by Nebraska Center for Mass Spectrometry. The starting material 1-dimethylsilyl-7,10,13-tris(triethylsilyl)-4,10-deacetyl-4-hydroxybaccatin III (**7**) was prepared according to previously reported procedures.[1]

**(3R, 4S)-1-Benzoyl-3-TIPSO-4 -(m-allyloxyphenyl)azetidin-2-one (6).** $[\alpha]^{20}_{D}$ = +40.2° (c 0.0146, CHCl3); $^{1}$H NMR δ 0.92 (m, 18 H), 0.99 (m, 3H), 4.52 (m, 2H), 5.24 (d, J = 6 Hz, 1H), 5.26 (dd, J = 12 Hz, J = 1.6 Hz, 1H), 5.40 (d, J = 6 Hz, 1H), 5.4 (dd, J = 1.6 Hz, 1H), 6.04 (m, 1H), 6.87 (ddd, J = 8.4 Hz, J = 3.6 Hz, J= 1.2 Hz, 1H), 6.98 (m, 2H), 7.27 (dd, J = 8 Hz, J = 15.5 Hz, 1H), 7.48 (m, 2H), 7.59 (m, 1H), 8.04 (dd, J = 1.2 Hz, J = 2.1 Hz, 2H) 13C NMR δ 11.77, 17.55, 61.14, 68.94, 114.71, 117.68, 120.90, 128.23, 129.25, 129.95, 132.16, 133.36, 133.42, 135.44, 158.66, 165.45, 166.32; HRFAB m/z calcd for C28H37NO4Si: 479.2492. Found for [C28H37NO4SiLi]+: 486.2669 (Δ = 3.6 ppm)]

**(3*R*,4*S*)-1-Benzoyl-3-TIPSO-4-(*m*-vinylphenyl)azetidin-2-one (11).** $[\alpha]^{20}_{D}$ = +117.8° (c 2.567, $CHCl_3$); $^{1}$H NMR δ 0.92 (m, 18 H), 0.97-1.04 (m, 3H), 5.24 (dd, J= 0.8 Hz, J = 8 Hz, 1H), 5.26 (d, J = 6 Hz, 1H), 5.43 (d, J= 6 Hz, 1H), 5.74 (dd, J = 0.8 Hz, J = 16.8 Hz, 1H), 6.72 (dd, J = 6.8 Hz, J = 17.6 Hz, 1H), 7.29-7.38 (m, , 3H), 7.41 (bs, 1H), 7.48 (t, J = 5.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 8.04 (d, J = 7.2 Hz, 2H) $^{13}$C NMR δ 11.60, 17.35, 61.01, 76.52, 114.05, 126.16, 127.58, 128.12, 128.30, 129.82, 132.00, 133.32, 134.04, 136.56, 137.49, 165.35, 166.20.

**Preparation of 7a**- To a solution of **7** (500 mg, 0.55 mmol) in dry THF (5 mL) at $0^{o}$C was added LiHMDS (0.60 mL, 0.60 mmol) and stirred for 30 min. followed by the addition 4-pentenoyl chloride (71 μL, 0.60 mmol) and stirred for 1.5 h. The reaction mixture was quenched with saturated solution of $NH_4Cl$ and the aqueous phase was extracted with ethyl acetate (25 mL x 3). The combined organic phase is washed with water and brine and dried over anhydrous sodium sulfate and concentrated under *vacuo*. Purification on PTLC (1.5:8.5 EtOAc/Hexanes) afforded the desired intermediate C-4 modified compound

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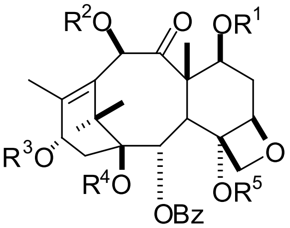
[1] Chen, S-H; Kadow, J. F.; Farina, V. *J. Org. Chem.* **1994**, *59*, 6156-6158.

as a white solid in 78% (425 mg) yield. A minor product with a loss of dimethylsilyl group was also isolated and used in the subsequent step.

**Preparation of 7b**- To a solution of **7a** (417 mg, 0.42 mmol), in 10 mL of THF at 0°C was added 1 mL of pyridine and 2.1 mL of HF/Py dropwise and stirred for 15 min and allowed to stir further for 12 h at room temperature. The reaction mixture is diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The organic phase is then washed with water and brine and concentrated under reduced pressure. The crude product is then purified on PTLC (6.5:3.5, EtOAc/Hexanes) and gave the desired deprotected product in 91% (225 mg) yield.



7, $R^1 = R^2 = R^3$ = TES, $R^4$ = DMS, $R^5$ = H

7a, $R^1 = R^2 = R^3$ = TES, $R^4$ = DMS, $R^5$ = 4-pentenoyl

7b, $R^1 = R^2 = R^3 = R^4$ = H, $R^5$ = 4-pentenoyl

7c, $R^1 = R^3 = R^4$ = H, $R^2$ = acetyl, $R^5$ = 4-pentenoyl

8, $R^3 = R^4$ = H, $R^1$ = TES, $R^2$ = acetyl, $R^5$ = 4-pentenoyl

**Preparation of 7c**- To a solution of **7b** (220 mg, 0.38 mmol) in THF and 0.1 mmol% $CeCl_3$ at room temperature was stirred for 5 min. and 10 equivalents of acetic anhydride was added and reacted for 3 hr and after the completion of the reaction by TLC analysis the reaction mixture was diluted with EtOAc and washed twice with $NaHCO_3$ and the combined organic phase was washed with water, brine, dried over sodium sulfate and concentrated under *vacuo.* Purification of the crude product on PTLC (5:5, EtOAc/Hexanes) yielded the desired a white solid product (222 mg, 94%).

**Preparation of Compound 8**- To a solution of **7c** (215 mg, 0.34 mmol) in anhydrous 2 mL of N,N-dimethylformamid at 0°C and imidazole (69 mg, 1.02 mmol) was added chlorotriethylsilane (86 μL, 0.51 mmol) dropwise via syringe. The reaction mixture was stirred for 4 h and after TLC analysis indicated the completion of the reaction, 3 mL of saturated methanol/$NaHCO_3$ solution was added and stirred for 10 min.. The reaction mixture was then diluted with ethylacetate (75 mL), washed with water (15 mL x 2), brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The crude product was purified with PTLC (3:7, EtOAc/Hexanes) afforded the desired product as a white solid in 92%(234 mg) yield: $^1H$ NMR ($CDCl_3$) δ 0.58 (m, 6H), 0.92 (m, 9H), 1.03 (s, 3H), 1.19 (s, 3H), 1.62 (s, 3H), 1.87 (dt, J = 2 Hz, 12.4 Hz, 1H), 2.03(d, J = 5.2, 1H), 2.17 (s, 3H), 2.26 (m, 2H), 2.51 (m, 3H), 2.68 (t, J = 8 Hz, 2H), 3.87 (d, J = 7.2 Hz, 1H), 4.14 (d, J = 8.0 Hz, 1H), 4.30 (d, J = 8.0, 1H), 4.49 (dd, J = 6.8 Hz, 1H), 4.82 (m, 1H), 4.91 (d, J = 7.6 Hz, 1H), 5.07 (dd, J = 1.2 Hz, J = 9.2 Hz, 1H), 5.14 (d, J = 14 Hz, 1H), 5.63 (d, J = 7.2, 1H), 5.91 (m, 1H), 6.45 (s, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 8.11 (d, J = 7.2 Hz, 2H); $^{13}C$ NMR δ 5.49, 6.98, 10.17, 15.13, 20.32, 21.19, 27.04, 28.96, 34.90, 37.47, 38.48, 43.01, 47.56, 58.90, 68.20, 72.56, 74.97, 76.00, 76.77, 78.97, 81.09, 84.54, 116.07, 128.79, 129.61, 130.34, 132.92, 133.87, 136.88, 144.14, 167.33, 169.60, 172.66, 202.39; HRFAB *m/z* calcd for $C_{40}H_{56}O_{11}Si$: 740.3592. Found for $[C_{40}H_{56}O_{11}SiLi]^+$: 747.3747 ($\Delta$ = 0.6 ppm).

**Preparation of Compound 9**- To a solution of **8** (120 mg, 0.16 mmol) in anhydrous THF (1.5 mL) at –40°C was added LiHMDS ( 0.18 mL, 0.18 mmol) and stirred for 5 min and then β-lactam **6** (153 mg, 0.32 mmol) was added and allowed to stir for 45 min. and the reaction mixture was quenched with saturated solution of $NH_4Cl$ and diluted with ethyl acetate (40 mL). The aqueous phase was extracted twice and the organic layer was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under *vacuo*. The crude coupled product then is purified with PTLC (2.5:7.5, EtOAc/Hexanes) to afford the taxoid-ω,ω’-diene **9** (182 mg, 92%) as a white solid: $^1H$ NMR ($CDCl_3$) δ 0.59 (m, 6H), 0.91 (m, 30H), 1.17 (s, 3H), 1.21 (s, 3H), 1.70 (s, 3H), 1.89 (dt, J = 2 Hz, 12 Hz, 1H), 2.04 (s, 3H), 2.17 (s, 3H), 2.39 (m, 2H), 2.48-2.71 (m, 4H), 3.05 (m, 1H), 3.83 (d, J = 7.2 Hz, 1H), 4.20 (d, J = 8.4 Hz, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.48 (dd, J = 6.8 Hz, J = 4 Hz, 1H), 4.54 (d, J = 2.4 Hz, 2H), 4.88 (m, 1H), 4.90 (s, 1H), 5.04 (d, J = 10.4 Hz, 1H), 5.13 (d, J = 15.6 Hz, 1H), 5.28 (dd, J = 9.2 Hz, J = 1.6 Hz, 1H), 5.39 (d, J = 16 Hz, 1H), 5.64 (d, J = 9.2 Hz, 1H), 5.70 (d, J = 7.2 Hz, 1H), 5.85 (m, 1H), 6.03 (m, 1H), 6.17 (t, J = 10 Hz), 6.46 (s, 1H), 6.84

(d, J = 5.6 Hz, 1H), 6.94 (s, 1H), 7.08 (d, J = 8.8 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 7.34-7.63 (m, 7H), 7.74 (d, J = 7.2 Hz, 2H), 8.16 (d, J = 7.2 Hz, 1H); $^{13}$C NMR δ 5.52, 6.97, 10.34, 12.81, 14.58, 17.98, 18.03, 18.12, 21.10, 26.75, 30.01, 35.76, 37.44, 43.55, 47.00, 56.30, 58.63, 69.01, 72.13, 72.46, 75.14, 75.21, 75.70, 79.09, 81.43, 84.61, 113.30, 114.58, 117.06, 117.90, 119.12, 127.17, 128.931, 129.49, 129.92, 131.98, 133.86, 135.96, 140.24, 140.49, 159.28, 167.01, 167.23, 169.55, 172.11, 172.23, 210.81; HRFAB *m/z* calcd for $C_{68}H_{93}NO_{15}Si_2$: 1219.6083. Found for $[C_{68}H_{93}NO_{15}Si_2Li]^+$: 1226.6192 (Δ = 4.2 ppm).

**Ring Closing Metathesis; Macrocyclic Taxoid 1**- To a solution of **9** (70 mg, 0.06 mmol) in 30 mL of anhydrous $CH_2Cl_2$ at room temperature was added bis(tricyclohexylphosphine)-benzylideneruthenium(IV) dichloride (Grubbs' catalyst) (7.4 mg, 15 mol%) in 15 mL of $CH_2Cl_2$ *via* a Harvard Apparatus syringe pump at 0.08 mL/min flow rate. The reaction mixture was stirred for 20 h and the solvent was removed under reduced pressure and the concentrated residue was purified with PTLC (2.5:7.5, EtOAc/Hexanes) to give the protected intermediate compound **10** (HRFAB *m/z* calcd for $C_{66}H_{89}NO_{15}Si_2$: 1191.5770. Found for $[C_{66}H_{89}NO_{15}Si_2Li]^+$: 1198.5757 (Δ = 2.2 ppm)) in 72% (49 mg) yield.

To a solution of **10** (45 mg, 0.038 mmol), in 4 mL THF at 0°C was added 0.1 mL of pyridine and 0.23 mL of HF/Py dropwise and allowed to stir further for 12 h at room temperature. The reaction mixture is diluted with EtOAc and washed with saturated $NaHCO_3$ solution. The organic phase is then washed with water and brine and concentrated under reduced pressure. The crude product was purified on PTLC (6:4, EtOAc/Hexanes) and gave the desired macrocyclic taxoid **1** in 78% (27 mg) yield. $^1$H NMR δ 1.16 (s, 3H), 1.30 (s, 3H), 1.69 (s, 3H), 1.84 (s, 3H), 1.89 (m, 1H), 2.41 (s, 3H), 2.34-2.56 (m, 5H), 2.68 (m, 1H), 2.88 (dt, J = 3.6 Hz, J = 7.2 Hz, 1H), 3.77 (d, J = 6.8 Hz, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.34 (d, J = 8.4 Hz, 1H), 4.41 (m, 1H), 4.68 (dd, J = 6 Hz, 1H), 4.78 (bd, 1H), 4.9 (d, J = 9.6 Hz, 1H), 5.57 (d, J = 8.8 Hz, 1H), 5.71 (d, J = 7.2 Hz, 1H), 5.75 (m, 1H), 5.84 (m, 1H), 6.27 (bs, 2H), 6.81 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 5.2 Hz, 1H), 7.06 (bs, 1H), 7.30-7.56 (m, 7H), 7.67 (d, J = 6.4 Hz, 1H), 7.71 (d, J = 7.2 Hz, 2H), 8.18 (d, J = 7.2 Hz, 2H); $^{13}$C NMR δ 9.6, 14.71, 20.95, 22.36, 26.99, 29.26, 29.74, 35.50, 35.79, 36.07, 37.58, 43.35, 45.71, 55.55, 58.57, 70.09, 72.26, 72.77, 72.84, 75.15, 75.59, 76.34, 79.41, 81.17, 84.61, 116.39, 119.06, 119.32, 119.52, 127.13, 127.86, 128.75, 128.80, 129.31, 130.29, 130.41, 132.00, 133.14, 133.74, 133.80, 133.90, 139.23, 142.43, 158.44, 167.00, 171.37, 173.38, 203.71; HRFAB *m/z* calcd for $C_{51}H_{55}NO_{15}$: 921.3571. Found for $[C_{51}H_{55}NO_{15}Li]^+$: 928.3746 (Δ = 1.6 ppm)

**Macrocyclic Taxoid 2**. This compound was prepared using a similar procedure to that for compound **1**. Compound **2:** $^1$H NMR δ 1.14 (s, 3H), 1.31 (s, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.78 (m, 1H), 1.89 (m, 1H), 2.1 (m, 2H), 2.23 (s, 3H), 2.53 (m, 3H), 2.64-2.86 (m, 3H), 3.70 (d, J = 7.2 Hz, 2H), 4.19 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.37 (m, 1H), 4.52 (t, J = 5.6 Hz), 4.88 (d, J = 8 Hz, 1H), 5.60 (m, 1H), 5.69 (d, J = 7.2 Hz, 1H), 5.88 (m, 1H), 6.25 (s, 1H), 6.27 (m, 1H), 6.70 (d, J = 11.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.27 (m, 1H), 7.35-7.55 (m, 7H), 7.63 (t, J = 7.6 Hz, 1H), 7.81 (d, J = 7.2, 2H), 8.07 (d, J = 7.2 Hz, 2H) ; $^{13}$C NMR δ 9.89, 14.51, 21.09, 22.84, 24.09, 27.50, 34.97, 35.79, 35.95, 43.55, 46.12, 71.76, 72.48, 75.33, 75.67, 76.04, 79.61, 82.00, 84.94, 125.12, 126.38, 127.38, 128.82, 128.92, 129.30, 129.74, 131.48, 132.33, 132.84, 133.79, 134.067, 138.19, 138.87, 142.88, 167.38, 168.24, 171.63, 172.08, 173.22, 203.86.