Supporting Information

Synthesis of Novel C2-C3'N-linked Macrocyclic Taxoids by Means of Highly Regioselective Heck Macrocyclization

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General Methods. ^1H and ^{13}C NMR spectra were measured on a Bruker AC-250 NMR spectrometer or a Varian 300 NMR spectrometer using tetramethylsilane as the internal standard. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and column chromatography was carried out on silica gel 60 (Merck; 230-400 mesh ASTM). High resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility, Riverside, CA; or Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL.

(3*R*,4*S*)-1-(3-Iodobenzoyl)-3-triisopropylsilyloxy-4-(3-butenyl)azetidin-2-one (**4**):

To a solution of *N*-H- β -lactam **16**^{1,2} (140 mg, 0.43 mmol), triethylamine (0.60 mL, 4.3 mmol) and DMAP (55 mg, 0.4 mmol) in 15 mL dichloromethane, was added 3-iodobenzoyl chloride (573 mg, 2.155 mmol) dropwise at room temperature. The mixture was stirred for 20 h at room temperature and the reaction was quenched with aqueous saturated ammonium chloride solution (25 mL). The mixture was then extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using 10 % ethyl acetate in hexane as the eluant to afford **4** as a colorless oil (239 mg, 92% yield): Colorless oil; $[\alpha]_{\text{D}}^{25} +77.0$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 1.07 (m, 21H), 1.80 (s, 3H), 1.86 (s, 3H), 5.05 (d, $J = 2.7$ Hz, 1H), 5.07 (s, 1H), 5.35 (m, 1H), 7.17 (t, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.94 (d, $J = 7.8$ Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (75.0 MHz, CDCl_3) δ 11.8, 17.5, 18.3, 26.1, 56.0, 76.4, 93.3, 117.5, 128.9, 129.6, 134.2, 138.4, 140.9, 141.7, 164.7, 165.3. HRMS (FAB) m/z calcd. for $\text{C}_{23}\text{H}_{34}\text{INO}_3\text{SiH}^+$: 528.1434, found: 528.1441 ($\Delta = +0.6$ ppm).

(3*R*,4*S*)-1-(3-Iodobenzoyl)-3-triethylsiloxy-4-phenylazetidin-2-one (**5**):

To a solution of *N*-H- β -lactam **17**^{3,4} (66 mg, 0.23 mmol), triethylamine (0.1 mL, 0.69 mmol) and DMAP (6 mg, 0.05 mmol) in 2 mL dichloromethane, was added 3-iodobenzoyl chloride (127 mg, 0.46 mmol) dropwise at room temperature. The mixture was stirred for 4 h at room temperature and the reaction was quenched with aqueous saturated ammonium chloride solution (2 mL). The mixture was then extracted with

dichloromethane (10 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (9/1) as the eluant to afford **5** as a colorless oil (101 mg, 88% yield): ^1H NMR (300 MHz, CDCl_3) δ 0.31-0.54 (m, 6H), 0.68-0.79 (m, 9H), 5.06 (d, $J = 6.0$ Hz, 1H), 5.29 (d, $J = 6.0$ Hz, 1H), 7.21 (t, $J = 7.8$ Hz, 1H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 8.23 (s, 1H). ^{13}C NMR (75.0 MHz, CDCl_3) δ 4.4, 6.2, 61.0, 70.0, 76.3, 93.5, 128.0, 128.1, 128.3, 128.9, 129.7, 133.4, 133.9, 138.4, 142.0, 164.6, 165.1. HRMS (EI) m/z calcd. for $\text{C}_{23}\text{H}_{27}\text{INO}_3\text{Si}^+$: 508.0805, found: 508.0805 ($\Delta = 0.0$ ppm).

7,10,13-Tri(triethylsilyl)-2-debenzoyl-2-(3-ethenylbenzoxy)-10-deacetylbaccatin III (**21**):

To a solution of **15** (352 mg, 0.449 mmol), 3-ethenylbenzoic acid (200 mg, 1.349 mmol) and DMAP (217 mg, 1.780 mmol) in dichloromethane (3 mL) was added 1,3-diisopropylcarbodiimide (DIC, 0.278 mL, 1.780 mmol), and the reaction mixture was stirred for 4 days at room temperature. The precipitate was filtered off and washed with ethyl acetate (30 mL), the filtrate was diluted with ethyl acetate (30 mL), washed with a saturated aqueous sodium bicarbonate (15 mL x 2), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (8/1 followed by 4/1) as the eluant to give **21** as a white solid (267 mg, 65% yield); mp 189-191 °C; $[\alpha]_D^{25} -24.0$ (c 0.5, CHCl_3); ^1H NMR (250 MHz, CDCl_3) δ 0.63 (m, 18H), 0.97 (m, 27H), 1.06 (s, 3H), 1.10 (s, 3H), 1.49 (bs, 1H), 1.58 (s, 3H), 1.86 (m, 1H), 1.93 (s, 3H), 2.00 (s, 1H), 2.04 (s, 1H), 2.16 (s, 3H), 2.46 (m, 1H), 3.84 (d, $J = 7.0$ Hz, 1H), 4.14 (d, $J = 7.8$ Hz, 1H), 4.28 (d, $J = 10.4, 6.6$ Hz, 1H), 4.40 (d, $J = 7.9$ Hz, 1H), 4.91-4.95 (m, 2H), 5.20 (s, 1H), 5.30 (d, $J = 16.0$ Hz, 1H), 5.60 (d, 1H), 5.80 (d, $J = 17.5$, 1H); 6.72 (dd, 1H); 7.40 (m, 1H) 7.57 (d, 1H); 7.95 (d, 1H); 8.15 (d, 1H). ^{13}C NMR (62.9 MHz, CDCl_3) δ 0.3, 0.7, 1.5, 2.3, 2.4, 2.5, 5.9, 10.0, 16.1, 17.9, 21.8, 32.8, 35.3, 38.5, 42.4, 53.7, 63.8, 68.1, 71.0, 71.2, 72.1, 72.5, 72.9, 75.0, 76.3, 79.5, 110.6, 123.1, 124.2, 124.8, 125.4, 126.7, 131.3, 131.7, 133.4, 134.9, 162.5, 165.3, 201.1. HRMS (FAB) m/z calcd. for $\text{C}_{49}\text{H}_{80}\text{O}_{10}\text{Si}_3\text{H}^+$: 914.4182, found: 914.4187 ($\Delta = +0.3$ ppm).

2-Debenzoyl-2-(3-ethenylbenzoxy)-10-deacteyl-baccatin III (**23**):

To a solution of **22** (375 mg, 0.41 mmol) in 10 mL of acetonitrile and 10 mL of pyridine was added 4 mL of HF/Pyridine at 0 °C. The solution was allowed to stir for overnight, at which point the reaction was complete by tlc. The reaction was treated with ethyl acetate and sodium bicarbonate. The organic layer was washed with copper sulfate, water, dried over sodium sulfate and concentrated *in vacuo*. Column chromatography using hexane/ethyl acetate (1/3) gave the desired product **22** (235 mg, 99%) as a white solid. mp 229-231 °C; ^1H NMR (300 MHz, CDCl_3) δ 1.10 (s, 6H), 1.75 (s, 3H), 1.83 (s, 1H), 2.08 (s, 3H), 2.27 (m, 2H), 2.29 (s, 3H), 2.61 (m, 1H), 4.01 (d, $J = 7.1$ Hz, 1H), 4.16 (d, $J = 8.2$ Hz, 1H), 4.27 (dd, $J = 6.3, 11.0$ Hz, 1H), 4.34 (d, $J = 8.5$ Hz, 1H), 4.86 (t, $J = 7.7$ Hz, 1H), 4.98 (d, $J = 7.7$ Hz, 1H), 5.25 (s, 1H), 5.36 (d, $J = 10.7$ Hz, 1H), 5.64 (d, $J = 7.1$ Hz, 1H), 5.84 (d, $J = 17.6$ Hz, 1H), 6.76 (dd, $J = 10.7, 17.3$ Hz, 1H), 7.44 (t, $J = 7.7$ Hz, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.99 (d, $J = 7.4$ Hz, 1H), 8.18 (s, 1H). HRMS (FAB) m/z calcd. for $\text{C}_{31}\text{H}_{38}\text{O}_{10}\text{H}^+$: 571.2544, found: 571.2543 ($\Delta = -0.1$ ppm).

7-Triethylsilyl-2-debenzoyl-2-(3-ethenylbenzoyl)-10-deacetylbaccatin III (22):

To a solution of **23** (240 mg, 0.411 mmol) and imidazole (112 mg, 1.64 mmol) in dry DMF (10 mL) was added chlorotriethylsilane (187 μ L 1.11 mmol) dropwise via syringe at 0 °C. The reaction mixture was stirred for 3 h and diluted with ethyl acetate (75 mL). The mixture was then washed with aqueous ammonium chloride (25 mL x 3), brine (25 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/1) as the eluant to give **22** as a white solid (235 mg, 82%). mp 120-122 °C; $[\alpha]_D^{25}$ -32.0 (*c* 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.55 (m, 6H), 0.92 (m, 9H), 1.05 (s, 6H), 1.71 (s, 3H), 1.88 (m, 1H), 2.06 (s, 3H), 2.22 (m, 2H), 2.26 (s, 3H), 2.46 (m, 1H), 3.93 (d, *J* = 6.9 Hz, 1H), 4.14 (d, *J* = 8.1 Hz, 1H), 4.26 (br s, 1H), 4.30 (d, *J* = 8.7 Hz, 1H), 4.39 (dd, *J* = 6.6, 10.5 Hz, 1H), 4.82 (t, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 8.4 Hz, 1H), 5.16 (s, 1H), 5.33 (d, *J* = 11.1 Hz, 1H), 5.57 (d, *J* = 6.9 Hz, 1H), 5.82 (d, *J* = 17.7 Hz, 1H), 6.76 (dd, *J* = 11.1, 17.7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 8.16 (s, 1H). ¹³C NMR (75.0 MHz, CDCl₃) δ 5.1, 6.7, 9.9, 15.1, 19.5, 22.6, 26.8, 37.2, 38.6, 42.7, 47.0, 57.9, 67.8, 72.9, 74.6, 74.8, 76.5, 78.7, 80.7, 84.2, 115.3, 127.7, 128.8, 129.2, 129.7, 131.3, 135.0, 135.9, 137.9, 141.9, 166.8, 170.6, 210.3. HRMS (FAB) *m/z* calcd. for C₃₇H₅₂O₁₀SiH⁺: 685.3407, found: 685.3408 (Δ = + 0.1 ppm)

7-Triethylsilyl-2-debenzoyl-2-(3-ethenylbenzoyl)baccatin III (3):

To a solution of **22** (200 mg, 0.292 mmol) in dry THF (20 mL) was added 1.0 M LiHMDS in THF (0.343 mL, 0.343 mmol) dropwise via syringe at -40 °C. The mixture was stirred at -40 °C for 15 min, and freshly distilled acetyl chloride (244 μ L, 0.343 mmol) was added dropwise. After 2 h, the reaction was quenched with saturated aqueous ammonium chloride (30 mL), extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (3/2) as the eluant to afford **3** as a white solid (175 mg, 83% yield). mp 135-137 °C; $[\alpha]_D^{25}$ -63.20 (*c* 1.06, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.57 (m, 6H), 0.90 (m, 9H), 1.01 (s, 6H), 1.17 (s, 3H), 1.65 (s, 3H), 1.85 (m, 1H), 2.16 (s, 6H), 2.23 (m, 2H), 2.26 (s, 3H), 2.48 (m, 1H), 3.86 (d, *J* = 6.9 Hz, 1H), 4.11 (d, *J* = 7.8 Hz, 1H), 4.29 (d, *J* = 8.1 Hz, 1H), 4.47 (dd, *J* = 6.6, 10.2 Hz, 1H), 4.79 (t, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 8.7 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.60 (d, *J* = 7.2 Hz, 1H), 5.82 (d, *J* = 17.4 Hz, 1H), 6.44 (s, 1H), 6.73 (dd, *J* = 10.8, 17.4 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 8.15 (s, 1H). ¹³C NMR (75.0 MHz, CDCl₃) δ 5.2, 6.7, 9.9, 14.9, 20.0, 20.9, 22.6, 26.7, 37.2, 38.3, 42.7, 47.2, 58.6, 67.8, 72.3, 74.7, 75.8, 76.5, 78.6, 80.8, 84.2, 115.3, 127.7, 128.8, 129.2, 129.7, 131.2, 135.9, 138.0, 144.1, 166.9, 169.3, 170.6, 202.2. HRMS (FAB) *m/z* calcd. for C₃₉H₅₄O₁₁SiH⁺: 727.3512, found: 727.3514 (Δ = + 0.2 ppm).

2-Debenzoyl-2-(3-ethenylbenzoyl)-3'-N-debenzoyl-3'-N-(3-iodobenzoyl)-2'-triisopropylsilyl-3'-dephenyl-3'-(2-methylprop-1-enyl)-7-triethylsilylpaclitaxel (1a):

To a solution of **3** (18 mg, 0.026 mmol) and β -lactam **4** (16 mg, 0.039 mmol) in dry THF (2 mL) was added a solution of 1.0 M LiHMDS in THF (0.040 mL, 0.040 mmol) dropwise at $-40\text{ }^{\circ}\text{C}$, and the solution was stirred at $-40\text{ }^{\circ}\text{C}$ for 35 min. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the aqueous layer was extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (7/3) as the eluant to afford the coupled product **1a** as a white solid (70 mg, 81%). mp $112\text{--}114\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -41.0$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.58 (m, 6H), 0.91 (m, 9H), 1.14 (s, 3H), 1.22 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 1.83 (s, 3H), 1.95 (m, 1H), 2.03 (s, 3H), 2.16 (s, 3H), 2.30 (m, 2H), 2.37 (s, 3H), 2.49 (m, 1H), 3.84 (d, $J = 6.9$ Hz, 1H), 4.20 (d, $J = 8.7$ Hz, 1H), 4.32 (d, $J = 8.4$ Hz, 1H), 4.47 (dd, $J = 6.6, 10.2$ Hz, 1H), 4.57 (d, $J = 2.1$ Hz, 1H), 4.93 (d, $J = 8.4$ Hz, 1H), 5.22 (t, $J = 6.9$ Hz, 1H), 5.32 (d, $J = 10.8$ Hz, 1H), 5.46 (d, $J = 8.4$ Hz, 1H), 5.69 (d, $J = 6.9$ Hz, 1H), 5.84 (d, $J = 17.4$ Hz, 1H), 6.07 (t, $J = 8.4$ Hz, 1H), 6.41 (s, $J = 9.9$ Hz, 1H), 6.45 (s, 1H), 6.75 (dd, $J = 10.8, 17.4$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 7.41 (t, $J = 7.7$ Hz, 1H), 7.59 (d, $J = 7.2$ Hz, 1H), 7.62 (d, $J = 7.2$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.98 (d, $J = 8.2$ Hz, 1H), 8.01 (s, 1H), 8.16 (s, 1H). ^{13}C NMR (75.0 MHz, CDCl_3) δ 5.3, 6.7, 10.0, 14.2, 18.0, 18.7, 20.8, 21.2, 22.6, 25.7, 26.5, 35.6, 37.2, 43.2, 46.7, 50.9, 58.4, 71.9, 72.2, 74.8, 74.9, 75.1, 78.7, 81.2, 84.3, 94.2, 115.2, 121.1, 125.9, 127.8, 128.8, 129.3, 129.7, 130.2, 131.2, 133.6, 136.0, 137.9, 138.0, 140.3, 140.4, 164.9, 166.7, 169.3, 169.7, 171.7, 201.7. HRMS (DCM/NBA/NaCl) calcd. for $\text{C}_{62}\text{H}_{88}\text{INO}_{14}\text{Si}_2\text{Na}^+$: 1276.4741, found: 1276.4686 ($\Delta = -4.3$ ppm).

2-Debenzoyl-2-(3-ethenylbenzoyl)-3'-N-debenzoyl-3'-N-(3-iodobenzoyl)-2'-triethylsilyl-7-triethylsilylpaclitaxel (2a):

To a solution of **3** (102 mg, 0.14 mmol) and β -lactam **5** (107 mg, 0.21 mmol) in THF (15 mL) was added LiHMDS (1.0 M in THF, 182 μL , 0.21 mmol) at $-40\text{ }^{\circ}\text{C}$. Reaction mixture was stirred for 40 min before quenched by saturated aqueous ammonium chloride (10 mL) and extracted by ethyl acetate. The organic layers were combined and dried by anhydrous magnesium sulfate, filtered, solvent removed by reduced pressure vacuum. The residue was purified by column using hexanes/ethyl acetate (15/1) as the eluant to afford **2a** as a white solid (154 mg, 88%). ^1H NMR (CDCl_3) δ 0.41-0.61 (m, 12H), 0.80-0.95 (m, 18H), 1.19 (s, 3H), 1.22 (s, 3H), 1.69 (s, 3H), 1.74 (m, 2H), 2.01 (s, 3H), 2.10-2.30 (m, 3H), 2.17 (s, 3H), 2.52 (s, 3H), 3.84 (d, $J = 7.2$ Hz, 1H), 4.19 (d, $J = 8.7$ Hz, 1H), 4.32 (d, $J = 8.7$ Hz, 1H), 4.47, (dd, $J = 10.2, 6.3$ Hz, 1H), 4.69 (d, $J = 7.8$ Hz, 1H), 4.94 (d, $J = 8.4$ Hz, 1H), 5.32 (d, $J = 10.8$ Hz, 1H), 5.67-5.71 (m, 2H), 5.84 (d, $J = 17.7$ Hz, 1H), 6.24 (t, $J = 8.4$ Hz, 1H), 6.45 (s, 1H), 6.80 (dd, $J = 17.7, 10.8$ Hz, 1H), 7.03 (d, $J = 9.3$ Hz, 1H), 7.12 (m, 1H), 7.34-7.38 (m, 5H), 7.47 (m, 1H), 7.66 (m, 1H), 7.79 (d, $J = 7.8$ Hz, 1H), 8.02 (d, $J = 7.5$ Hz, 1H), 8.07 (s, 1H), 8.18 (s, 1H). ^{13}C NMR (CDCl_3) δ 4.4, 5.3, 6.5, 6.7, 10.0, 14.1, 20.8, 21.4, 23.0, 26.6, 35.5, 37.2, 43.3, 46.6, 55.7, 58.4, 71.5, 72.1, 74.8, 74.9, 78.8, 81.2, 84.2, 94.3, 115.3, 126.0, 126.5, 128.0, 128.7, 128.9, 129.0, 129.4, 129.5, 120.2, 131.2, 133.6, 135.9, 136.2, 138.1, 138.2, 140.1, 140.6, 165.4, 166.9, 169.3, 170.0, 171.5. HRMS calcd. for $\text{C}_{61}\text{H}_{80}\text{INO}_{14}\text{Si}_2\text{H}^+$: 1234.4240, found 1234.4238 ($\Delta = 0.2$ ppm).

Macrocyclic taxoid (6):

To a solution of **1a** (30 mg, 0.023 mmol) in acetonitrile (7 mL) and triethylamine (1 mL) was added a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (2 mg) and the resulting mixture was allowed to stir at 50 °C overnight. The mixture was cooled to rt, passed through a pad of celite, and the solvent was removed *in vacuo*. The crude residue was purified on silica gel using hexane/ethyl acetate (3/1) as the elutant to give **6** (17 mg, 65%) as a white solid. mp 179-182 °C; $[\alpha]_D^{25}$ -22.0 (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.56 (m, 6H), 0.90 (m, 9H), 1.14 (m, 24H), 1.25 (s, 3H), 1.63 (s, 3H), 1.73 (s, 3H), 1.84 (s, 3H), 1.88 (m, 1H), 1.97 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.21 (m, 2H), 2.46 (m, 1H), 3.62 (d, J = 6.9 Hz, 1H), 4.00 (d, J = 8.4 Hz, 1H), 4.13 (d, J = 8.1 Hz, 1H), 4.40 (dd, J = 6.6, 10.2 Hz, 1H), 4.57 (d, J = 2.1 Hz, 1H), 4.93 (d, J = 8.4 Hz, 1H), 5.22 (t, J = 6.9 Hz, 1H), 5.32 (d, J = 10.8 Hz, 1H), 4.82 (d, J = 8.1 Hz, 1H), 4.96 (d, J = 6.0 Hz, 1H), 5.13 (dd, J = 6.9, 13.8 Hz, 1H), 5.38 (s, 1H), 5.51 (d, J = 6.9 Hz, 1H), 5.66 (s, 1H), 5.88 (d, J = 7.8 Hz, 1H), 5.96 (t, J = 7.2 Hz, 1H), 6.42 (s, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.23 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.85 (m, 2H), 7.99 (s, 1H). ^{13}C NMR (75.0 MHz, CDCl_3) δ 5.3, 6.7, 10.0, 12.4, 14.4, 17.8, 17.9, 18.5, 20.8, 21.2, 22.5, 25.8, 26.5, 35.1, 37.1, 43.0, 46.7, 51.0, 58.3, 70.6, 71.6, 72.2, 75.0, 76.3, 78.4, 80.4, 84.2, 115.8, 119.0, 124.6, 128.0, 129.0, 129.1, 129.3, 129.8, 131.1, 132.6, 133.2, 133.4, 140.4, 140.6, 142.2, 143.9, 148.7, 165.5, 166.9, 169.1, 170.1, 172.3, 201.9. HRMS (DCM/NBA/NACL) calcd. for $\text{C}_{62}\text{H}_{87}\text{NO}_{14}\text{Si}_2\text{Na}^+$: 1148.5504, observed 1148.5554 (Δ = 4.9 ppm).

Macrocyclic taxoid (7-exo):

To a solution of **6** (25 mg, 0.021 mmole) in 1.4 mL of acetonitrile and 1.4 mL of pyridine was added 0.6 mL of HF/Pyridine at 0 °C. The solution was allowed to stir for overnight. Then the reaction mixture was diluted with ethyl acetate washed with aqueous saturated sodium bicarbonate solution. The organic layer was washed with copper sulfate, water, dried over sodium sulfate and concentrated *in vacuo*. Column chromatography using hexane/ethyl acetate (1/3) gave the desired product **7-exo** (13 mg, 70%) as a white solid. mp 215-219 °C; $[\alpha]_D^{25}$ -51.4 (c 0.7, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 1.06 (s, 3H), 1.22 (s, 3H), 1.62 (s, 3H), 1.81 (s, 3H), 1.84 (s, 3H), 1.89 (s, 3H), 2.04 (m, 2H), 2.06 (s, 3H), 2.21 (s, 3H), 2.47 (m, 2H), 2.72 (br s, 1H), 3.62 (d, J = 6.9 Hz, 1H), 4.03 (d, J = 8.1 Hz, 1H), 4.15 (d, J = 8.1 Hz, 1H), 4.35 (dd, J = 6.3, 10.8 Hz, 1H), 4.74 (br d, 1H), 4.83 (d, J = 8.7 Hz, 1H), 5.28 (m, 2H), 5.39 (s, 1H), 5.54 (d, J = 6.9 Hz, 1H), 5.65 (s, 1H), 6.02 (d, J = 6.6 Hz, 1H), 6.15 (t, J = 9.0 Hz, 1H), 6.22 (s, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.31 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.88 (m, 3H). ^{13}C NMR (75.0 MHz, CDCl_3) δ 9.6, 14.4, 19.0, 20.8, 22.2, 22.4, 26.2, 26.8, 29.7, 35.1, 35.4, 43.0, 45.4, 50.7, 58.4, 71.0, 71.2, 71.9, 75.5, 76.2, 78.9, 80.4, 84.4, 116.1, 116.7, 125.3, 127.4, 128.7, 128.8, 129.2, 129.5, 129.7, 131.5, 132.6, 133.0, 133.2, 142.1, 142.4, 143.5, 143.8, 148.6, 165.6, 167.1, 170.4, 171.2, 173.7, 203.7. HRMS (DCM/NBA/NACL) calcd. for $\text{C}_{47}\text{H}_{53}\text{IO}_{14}\text{Na}^+$: 878.3322, observed: 878.3363 (Δ = 4.8 ppm).

Macrocyclic taxoid (9-*exo*):

To a degassed solution of **2a** (10 mg, 0.08 mmol), AsPh_3 (2 mg, 0.06 mmol) and triethylamine 1 mL in 2.3 mL acetonitrile was added $\text{Pd}_2(\text{dba})_3$ (0.37 mg, 0.004 mmol). The reaction mixture was heated up to 55 °C for 1 d and then solvent was removed by reduced pressure vacuum. The residue was passed through a short silica gel column to afford a crude solid. Then to a solution of solid thus obtained in 0.2 mL acetonitrile and 0.2 mL pyridine was added HF-pyridine (0.1 mL). The solution was allowed to stir for overnight. Then the reaction mixture was diluted with ethyl acetate washed with aqueous saturated sodium bicarbonate solution. The organic layer was washed with copper sulfate, water, dried over sodium sulfate and concentrated *in vacuo*. Column chromatography using hexane/ethyl acetate (1/3) gave the desired product **9-*exo*** (4 mg, 56% for two steps) as a white solid. mp >195 °C [α]_D²² –50.0 (c 0.2, CHCl_3); ¹H NMR (CDCl_3) δ 0.85 (m, 9H), 1.1 (s, 3H), 1.38 (s, 3H), 1.58 (b, 6H), 1.65 (s, 3H), 1.79 (s, 3H), 1.86 (m, 1H), 2.00 (b, 3H), 2.21 (s, 3H), 2.23 (s, 3H), 2.40–2.58 (m, 3H), 3.63 (m, 1H), 4.13 (d, J = 8.1 Hz, 1H), 4.23 (d, J = 8.1 Hz, 1H), 4.37 (m, 1H), 4.82 (m, 2H), 5.60 (s, 1H), 5.62 (s, 1H), 5.67 (m, 1H), 6.20 (m, 2H), 6.68 (d, J = 9.0 Hz, 1H), 7.36–7.54 (m, 9H), 7.66–7.78 (m, 2H), 7.84–7.90 (m, 2H). ¹³C NMR (CDCl_3) δ 1.2, 9.9, 10.0, 14.3, 14.6, 21.0, 22.6, 22.8, 22.9, 27.2, 29.9, 33.1, 35.5, 35.7, 35.8, 43.3, 45.5, 45.6, 58.5, 58.6, 58.64, 71.9, 72.3, 72.4, 75.6, 76.3, 76.4, 76.5, 77.6, 77.7, 77.9, 81.5, 84.8, 113.4, 115.7, 117.8, 126.4, 127.1, 127.3, 127.6, 128.2, 128.3, 128.6, 128.8, 128.9, 129.0, 129.2, 129.4, 129.5, 129.6, 129.7, 129.8, 129.9, 130.3, 130.4, 142.4, 143.0, 148.3, 166.0, 170.5, 171.2, 171.8, 203.5. HRMS calcd. for $\text{C}_{49}\text{H}_{51}\text{NO}_{14}\text{H}^+$: 878.3388, found 878.3392 (Δ = 0.2 ppm).

(3*R*,4*S*)-1-(3-Ethenylbenzoyl)-3-triisopropylsiloxy-4-(2-methylprop-1-enyl)azetidin-2-one (**11**):

To a solution of β -lactam **4** (120 mg, 0.23 mmol) was added tributylvinyltin (91 μL , 0.312 mmol), $\text{Pd}_2(\text{dba})_3$ (10 mg, 0.011 mmol), and PPh_3 (12 mg, 0.046 mol) in 8 mL of dioxane. The resulting mixture was stirred at 50 °C for 2 days. The reaction was cooled to room temperature and 1.0 M potassium fluoride (10 mL) was added and the mixture was stirred an additional 30 minutes. The solid which precipitated was filtered through a pad of celite and extracted into ethyl acetate. The organic layer was washed with aqueous 1.0 M potassium fluoride, once with water and dried over anhydrous magnesium sulfate. After filtration and removal of the solvent *in vacuo*, the residue was purified on a silica gel column using hexane/ethyl acetate (9/1) as the eluant to afford **11** as a colorless oil (70 mg, 86% yield): Colorless oil; [α]_D²⁵ + 82 (c 1.0, CHCl_3); ¹H NMR (300 MHz, CDCl_3) δ 0.8 (m, 21 H), 1.81 (s, 3H), 1.86 (s, 3H), 5.06 (m, 2H), 5.32 (d, J = 10.7 Hz, 1H), 5.37 (m, 1H), 5.81 (d, J = 17.2 Hz, 1H), 6.76 (dd, J = 10.7, 17.2 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H); ¹³C NMR (75 MHz, CDCl_3) δ 11.6, 17.4, 18.3, 26.1, 56.2, 76.4, 112.2, 117.3, 126.7, 128.9, 129.6, 134.2, 135.4, 138.4, 140.9, 141.7, 164.7, 165.3. HRMS (FAB) m/z calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_3\text{SiH}^+$: 427.2545, found: 427.2547 (Δ = + 0.5 ppm).

(3*R*,4*S*)-1-(3-Iodobenzoyl)-3-triisopropylsiloxy-4-phenylazetidin-2-one (**19**):

To a solution of *N*-H- β -lactam **18**^{3,4} (90 mg, 0.282 mmol) in 10 mL dichloromethane was added dropwise triethylamine (0.480 mL, 3.45 mmol) at room temperature followed by the addition of the acid chloride of

3-iodobenzoic acid (0.46 g, 1.730 mmol). The mixture was stirred for 1 h at room temperature and the reaction was quenched with aqueous saturated ammonium chloride solution (25 mL). The mixture was then extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (9/1) as the eluant to afford **19** as a colorless oil (126 mg, 81% yield). $[\alpha]_D^{25} +86.0$ (c 1.27, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.91 (m, 21H), 5.26 (d, *J* = 6.3 Hz, 1H), 5.41 (d, *J* = 6.1 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.36 (m, 5H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 8.30 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 11.6, 17.4, 61.3, 76.7, 93.5, 118.3, 122.2, 128.2, 128.4, 129.0, 129.7, 133.5, 138.4, 142.0, 164.6, 165.3. HRMS (FAB) *m/z* calcd. for C₂₅H₃₂INO₃SiH⁺: 550.1277, found: 550.1275 (Δ = -0.5 ppm).

(3*R*,4*S*)-1-(3-Ethenylbenzoyl)-3-triisopropylsiloxy-4-(3-ethenylphenyl)azetidin-2-one (20):

To a solution of β-lactam **19** (100 mg, 0.18 mmol) in 6 mL dioxane, was added Pd₂(dba)₃ (8 mg, 0.01 mmol), triphenylphosphine (5 mg, 0.02 mmol), and tributylvinyltin (0.080 mL, 0.27 mmol). The mixture was then heated to 60 °C and stirred overnight. The reaction was cooled to room temperature, quenched with aqueous 1.0 M potassium fluoride, and stirred for an additional 30 min. The solution was passed through a pad of celite and suspended in a mixture of ethyl acetate (20 mL) and water (20 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (9/1) as the eluant to afford **20** as a colorless oil (62 mg, 77% yield): $[\alpha]_D^{25} +102.0$ (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.92 (m, 21H), 5.25 (d, *J* = 6.1 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.42 (d, *J* = 6.3 Hz, 1H), 5.83 (d, *J* = 17.4 Hz, 1H), 6.76 (dd, *J* = 10.8, 17.4 Hz, 1H), 7.38 (m, 5H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.05 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 11.7, 17.4, 61.2, 76.6, 115.4, 118.4, 122.3, 127.6, 128.1, 128.2, 128.3, 128.4, 129.1, 130.8, 133.8, 135.8, 165.4, 166.1. HRMS (FAB) *m/z* calcd. for C₂₇H₃₅NO₃SiH⁺: 450.2464, found: 450.2464 (Δ = 0.1 ppm).

(3*R*,4*S*)-1-(3-Ethenylbenzoyl)-3-triethylsiloxy-4-phenylazetidin-2-one (12):

To a solution of **20** (60 mg, 0.134 mmol) in 1.8 mL of acetonitrile and 1.8 mL of pyridine was added 1 mL of HF/Pyridine at 0 °C, and the resulting solution was allowed to stir for 24 h. The reaction was quenched with sodium bicarbonate and ethyl acetate. The organic layer was washed with copper sulfate, water, dried over sodium sulfate, and concentrated *in vacuo*. Column chromatography of the crude product using hexane/ethyl acetate (3/2) gave (3*R*,4*S*)-1-(3-ethenylbenzoyl)-3-hydroxy-4-phenylazetidin-2-one (38 mg, 99%) as a white solid: $[\alpha]_D^{25} +146$ (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 5.19 (d, *J* = 6.1 Hz, 1H), 5.35 (d, *J* = 11.1 Hz, 1H), 5.53 (d, *J* = 6.3 Hz, 1H), 5.84 (d, *J* = 17.7 Hz, 1H), 6.77 (dd, *J* = 10.8, 17.4 Hz, 1H), 7.40 (m, 5H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 8.09 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 60.2, 75.9, 115.5, 127.2, 127.6, 128.8, 128.9, 129.0, 131.1, 132.0, 132.8, 135.7, 137.8, 165.0, 166.1.

To a solution of the 3-hydroxy-β-lactam (20 mg, 0.069 mmol), thus obtained, in 2 mL dichloromethane was added DMAP (4 mg, 0.0343 mmol), triethylamine (0.03 mL, 0.2 mmol), and TESCl (0.015 mL, 0.0891 mmol). The resulting mixture was allowed to stir for 2 h and was then quenched with aqueous ammonium chloride. The organic layer was separated and dried over anhydrous magnesium sulfate to give **12** (26 mg, 93%): ¹H NMR (300 MHz, CDCl₃) δ 0.56 (m, 6H), 0.91 (m, 9H), 5.15 (d, *J* = 6.0 Hz, 1H), 5.33 (d, *J* = 11.0 Hz, 1H), 5.40 (d, *J* = 6.0 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 6.76 (dd, *J* = 17.6 Hz, 11.0 Hz, 1H), 7.36 (m, 5H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 8.06 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 4.4, 6.4, 60.9, 76.2, 115.4, 127.7, 128.0, 128.1, 128.2, 128.3, 129.1, 130.9, 132.3, 133.7, 135.8, 137.7, 165.2, 166.1. HRMS (FAB) *m/z* calcd. for C₂₄H₂₉NO₃SiH⁺: 406.1837, found: 406.1838 (Δ = +0.4 ppm).

7,10,13-Tris(triethylsilyl)-2-debenzoyl-2-(3-iodobenzoyl)-10-deacetylbaccatin III (16):

To a solution of 7,10,13-tris(triethylsilyl)-10-deacetylbaccatin III (**15**, 270 mg, 0.346 mmol), 3-iodobenzoic acid (343 mg, 1.384 mmol) and DMAP (128 mg, 1.038 mmol) in dichloromethane (5 mL) was added 1,3-diisopropylcarbodiimide (DIC, 217 μ L, 1.384 mmol), and the reaction mixture was stirred for 16 h at room temperature. The precipitate was filtered off and washed with dichloromethane (30 mL), the filtrate was diluted with methylene chloride (30 mL), washed with a saturated aqueous sodium bicarbonate (15 mL x 2), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (9/1) as the eluant to give **16** as a white solid (338 mg, 95% yield): mp 195-197 °C; $[\alpha]_D^{25}$ -15.0 (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.62 (m, 18H), 0.98 (m, 27H), 1.11 (s, 3H), 1.16 (s, 3H), 1.63 (s, 3H), 1.87 (m, 1H), 1.97 (s, 3H), 2.15 (m, 2H), 2.31 (s, 3H), 2.50 (m, 1H), 3.84 (d, J = 6.9 Hz, 1H), 4.10 (d, J = 8.1 Hz, 1H), 4.23 (d, J = 8.1 Hz, 1H), 4.40 (dd, J = 10.5, 6.6 Hz, 1H), 4.90 (t, J = 8.7 Hz, 1H), 4.94 (d, J = 9.0 Hz, 1H), 5.18 (s, 1H), 5.53 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 4.8, 5.2, 5.9, 6.8, 6.9, 10.3, 14.5, 20.5, 22.4, 26.2, 32.2, 39.8, 42.9, 46.9, 58.1, 68.2, 72.6, 75.7, 75.9, 76.4, 79.7, 80.7, 83.9, 93.8, 129.2, 130.2, 131.6, 135.6, 139.2, 139.4, 142.0, 165.3, 169.9, 205.5. HRMS (FAB) m/z calcd. for $\text{C}_{47}\text{H}_{77}\text{IO}_{10}\text{Si}_3\text{H}^+$: 1013.3952, found: 1013.3948 (Δ = -0.4 ppm).

7-Triethylsilyl-2-debenzoyl-2-(3-iodobenzoyl)-10-deacetylbaccatin III (18):

To a solution of **14** (335 mg, 0.326 mmol) in pyridine-acetonitrile (1/1, 20 mL) was added dropwise HF/pyridine (70:30, 3.5 mL) at 0 °C, and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate. The reaction mixture was then diluted with ethyl acetate (60 mL), washed with saturated aqueous copper sulfate (10 mL x 3) and water (10 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to afford a white solid.

To a solution of the white solid thus obtained (125 mg, 0.183 mmol) and imidazole (50 mg, 733 mmol) in dry DMF (6 mL) was added chlorotriethylsilane (92 μ L, 0.545 mmol) dropwise via syringe at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and diluted with ethyl acetate (50 mL). The mixture was washed with aqueous ammonium chloride (25 mL x 3), brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/1) as the eluant to give **18** as a white solid (120 mg, 83%): mp 142-144 °C; $[\alpha]_D^{25}$ -35 (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.54 (m, 6H), 0.92 (m, 9H), 1.05 (s, 6H), 1.71 (s, 3H), 1.88 (m, 1H), 2.06 (s, 3H), 2.21 (m, 2H), 2.30 (s, 3H), 2.45 (m, 1H), 3.91 (d, J = 6.9 Hz, 1H), 4.14 (d, J = 8.1 Hz, 1H), 4.26 (d, J = 8.1 Hz, 1H), 4.38 (dd, J = 10.5, 6.6 Hz, 1H), 4.82 (t, J = 7.8 Hz, 1H), 4.95 (d, J = 8.1 Hz, 1H), 5.14 (s, 1H), 5.51 (d, J = 6.9 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 5.1, 6.7, 9.8, 15.1, 19.5, 22.5, 26.8, 37.2, 38.6, 42.6, 47.0, 57.8, 67.7, 72.9, 74.4, 74.6, 75.2, 76.4, 78.8, 80.6, 84.2, 129.2, 130.2, 131.4, 134.9, 139.1, 142.0, 142.2, 165.2, 170.6, 210.2. HRMS (FAB) m/z calcd. for $\text{C}_{35}\text{H}_{49}\text{IO}_{10}\text{SiH}^+$: 785.2215, found: 785.2218 (Δ = + 0.4 ppm).

7-Triethylsilyl-2-debenzoyl-2-(3-iodobenzoyl)baccatin III (**10**):

To a solution of **19** (90 mg, 0.132 mmol) in dry THF (9 mL) was added 1.0 M LiHMDS in THF (0.152 mL, 0.152 mmol) dropwise via syringe at $-40\text{ }^{\circ}\text{C}$. The mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 5 min, and freshly distilled acetyl chloride (10.8 μL , 0.152 mmol) was added dropwise. After 2 h, the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with dichloromethane (20 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (3/2) as the eluant to afford **10** as a white solid (95 mg, 99% yield): mp $214\text{--}216\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -49.0$ (c 0.96, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.55 (m, 6H), 0.90 (m, 9H), 1.01 (s, 3H), 1.15 (s, 3H), 1.64 (s, 1H), 1.84 (m, 1H), 2.15 (s, 3H), 2.23 (m, 2H), 2.30 (m, 3H), 2.49 (m, 1H), 3.84 (d, $J = 6.9$ Hz, 1H), 4.07 (d, $J = 8.1$ Hz, 1H), 4.25 (d, $J = 8.1$ Hz, 1H), 4.46 (dd, $J = 9.6, 7.2$ Hz, 1H), 4.79 (t, $J = 7.8$ Hz, 1H), 4.95 (d, $J = 9.3$ Hz, 1H), 5.53 (d, $J = 6.9$ Hz, 1H), 6.43 (s, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 7.5$ Hz, 1H), 8.02 (d, $J = 7.5$ Hz, 1H), 8.47 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 5.2, 6.7, 9.8, 14.9, 20.0, 20.9, 22.6, 26.7, 37.1, 38.2, 42.6, 47.2, 58.5, 67.7, 72.3, 75.1, 75.7, 76.3, 78.8, 80.7, 84.1, 93.9, 129.2, 130.2, 131.3, 132.3, 139.1, 142.1, 144.1, 165.3, 169.3, 170.6, 202.1. HRMS (FAB) m/z calcd. for $\text{C}_{37}\text{H}_{51}\text{IO}_{11}\text{SiH}^+$: 827.2326, found: 827.2323 ($\Delta = -0.3$ ppm).

2-Debenzoyl-2-(3-iodobenzoyl)-3'-dephenyl-3'-(2-methylprop-1-enyl)-3'-N-debenzoyl-3'-N-(3-ethenylbenzoyl)-2'-triisopropylsilyl-7-triethylsilylpacitaxel (**1b**):

To a solution of **10** (48 mg, 0.055 mmol) and β -lactam **11** (45 mg, 0.099 mmol) in dry THF (6 mL) was added a solution of 1.0 M LiHMDS in THF (0.100 mL, 0.099 mmol) dropwise at $-40\text{ }^{\circ}\text{C}$, and the resulting solution was stirred at $-40\text{ }^{\circ}\text{C}$ for 35 min. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the aqueous layer was extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (7/3) as the eluant to afford the coupled product **1b** as a white solid (52 mg, 78%): mp $95\text{--}97\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -42.0$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.57 (m, 6H), 0.92 (m, 9H), 1.15 (m, 27H), 1.68 (s, 3H), 1.77 (s, 3H), 1.86 (s, 3H), 1.88 (m, 1H), 2.01 (s, 3H), 2.15 (s, 3H), 2.36 (m, 2H), 2.41 (s, 3H), 2.56 (m, 1H), 3.83 (d, $J = 6.6$ Hz, 1H), 4.16 (d, $J = 8.1$ Hz, 1H), 4.30 (d, $J = 8.1$ Hz, 1H), 4.46 (dd, $J = 6.3, 9.9$ Hz, 1H), 4.58 (s, 1H), 4.96 (d, $J = 8.7$ Hz, 1H), 5.26 (m, 2H), 5.47 (d, $J = 8.4$ Hz, 1H), 5.64 (d, $J = 6.9$ Hz, 1H), 5.75 (d, $J = 17.7$ Hz, 1H), 6.04 (t, $J = 8.4$ Hz, 1H), 6.45 (s, $J = 9.9$ Hz, 1H), 6.495 (d, $J = 8.7$ Hz, 1H), 6.66 (dd, $J = 11.1, 17.4$ Hz, 1H), 7.21 (t, $J = 8.1$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 7.8$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 1H), 7.71 (s, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 8.07 (d, $J = 7.8$ Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (75.0 MHz, CDCl_3) δ 5.3, 6.7, 10.0, 14.4, 17.9, 19.2, 20.8, 21.2, 22.5, 25.7, 26.4, 35.5, 37.1, 43.2, 46.7, 50.9, 58.3, 71.9, 72.3, 74.9, 74.9, 75.1, 75.2, 76.4, 76.6, 81.1, 84.2, 93.8, 115.1, 121.2, 124.7, 125.9, 128.8, 129.1, 129.4, 130.3, 131.4, 133.4, 134.8, 135.9, 137.8, 138.0, 139.0, 145.4, 142.2, 165.0, 166.5, 169.2, 169.7, 171.8, 201.7. HRMS (FAB) m/z calcd. for $\text{C}_{62}\text{H}_{88}\text{INO}_{14}\text{Si}_2\text{H}^+$: 1254.0805, found: 1254.0800 ($\Delta = +0.5$ ppm).

2-Debenzoyl-2-(3-iodobenzoyl)-3'-N-debenzoyl-3'-N-(3-ethenylbenzoyl)-2'-triethylsilyl-7-triethylsilylpaclitaxel (2b**):**

To a solution of **10** (48 mg, 0.055 mmol) and β -lactam **12** (40 mg, 0.099 mmol) in dry THF (6 mL) was added a solution of 1.0 M LiHMDS in THF (0.100 mL, 0.099 mmol) dropwise at $-40\text{ }^{\circ}\text{C}$, and the solution was stirred at $-40\text{ }^{\circ}\text{C}$ for 35 min. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), and the aqueous layer was extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (7/3) as the eluant to afford the coupled product **1b** as a white solid (52 mg, 77%). mp $121\text{--}122\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} -43$ (c 1.0, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.48 (m, 6H), 0.58 (m, 6H), 0.84 (t, $J = 7.8\text{ Hz}$, 9H), 0.92 (t, $J = 7.8\text{ Hz}$, 9H), 1.18 (s, 3H), 1.21 (s, 3H), 1.69 (s, 3H), 1.81 (m, 1H), 2.01 (s, 3H), 2.17 (s, 3H), 2.35 (m, 2H), 2.51 (m, 1H), 2.55 (s, 3H), 3.84 (d, $J = 7.2\text{ Hz}$, 1H), 4.17 (d, $J = 8.1\text{ Hz}$, 1H), 4.30 (d, $J = 8.1\text{ Hz}$, 1H), 4.46 (dd, $J = 6.6, 10.5\text{ Hz}$, 1H), 4.69 (d, $J = 1.8\text{ Hz}$, 1H), 4.96 (d, $J = 8.4\text{ Hz}$, 1H), 5.27 (d, $J = 11.1\text{ Hz}$, 1H), 5.63 (d, $J = 6.9\text{ Hz}$, 1H), 5.67 (m, 1H), 5.73 (d, $J = 17.4\text{ Hz}$, 1H), 6.20 (t, $J = 8.7\text{ Hz}$, 1H), 6.45 (s, 1H), 6.66 (dd, $J = 11.1, 17.4\text{ Hz}$, 1H), 7.09 (d, $J = 9.0\text{ Hz}$, 1H), 7.26 (t, $J = 7.8\text{ Hz}$, 1H), 7.36 (m, 6H), 7.51 (d, $J = 7.8\text{ Hz}$, 1H), 7.61 (d, $J = 7.5\text{ Hz}$, 1H), 7.77 (s, 1H), 7.91 (d, $J = 7.8\text{ Hz}$, 1H), 8.11 (d, $J = 7.8\text{ Hz}$, 1H), 8.51 (s, 1H); ^{13}C NMR (75.0 MHz, CDCl_3) δ 4.4, 5.3, 6.5, 10.1, 14.2, 20.8, 21.4, 23.0, 26.5, 35.5, 37.2, 43.2, 46.7, 55.7, 58.3, 71.5, 72.2, 74.8, 74.9, 75.3, 76.4, 79.0, 81.1, 84.2, 94.0, 115.2, 125.1, 126.0, 126.6, 128.0, 128.7, 128.8, 129.3, 129.4, 130.5, 131.2, 133.5, 134.5, 135.8, 138.1, 138.5, 139.1, 140.3, 142.3, 165.3, 166.8, 169.2, 170.0, 171.6, 201.5. HRMS (FAB) m/z calcd. for $\text{C}_{61}\text{H}_{80}\text{INO}_{14}\text{Si}_2\text{H}^+$: 1234.4242, found: 1234.4240 ($\Delta = -4.3\text{ ppm}$).

Macrocyclic taxoid 7-endo:

To a solution of **1b** (30 mg, 0.023 mmole) in acetonitrile (7 mL) and triethylamine (1 mL) was added a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (2 mg) and the resulting mixture was allowed to stir at $50\text{ }^{\circ}\text{C}$ overnight. The mixture was cooled to room temperature, passed through a pad of celite, and the solvent was removed *in vacuo*. The crude product was purified on silica gel using 25% ethyl acetate in hexane as the elutant to give a mixture of two isomers (18 mg, 68%) as a white solid. To a solution of the mixture of two isomers (18 mg, 0.021 mmole) in 1.4 mL of acetonitrile and 1.4 mL of pyridine was added 0.6 mL of HF/Pyridine at $0\text{ }^{\circ}\text{C}$. The solution was allowed to stir overnight. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate. The organic layer was washed with copper sulfate, water, dried over sodium sulfate, and concentrated *in vacuo*. Column chromatography of the crude product using hexane/ethyl acetate (1/3) followed by HPLC separation using a semi-preparative Phenomenex Curosil-B 5μ column (250 x 4.60 mm/mm) ($\text{CH}_3\text{CN}/\text{H}_2\text{O} = 1:1$) gave **7-exo** (8 mg, 56%; *vide supra*) and **7-endo** (2.5 mg, 19%) as white solids.

7-endo: ^1H NMR (300 MHz, CDCl_3) δ 1.16 (s, 3H), 1.25 (s, 3H), 1.57 (s, 3H), 1.73 (s, 3H), 1.83 (s, 3H), 1.88 (m, 1H), 1.92 (s, 3H), 2.04 (m, 2H), 2.13 (s, 3H), 2.26 (s, 3H), 2.48 (m, 2H), 2.81 (br s, 1H), 3.82 (d, $J =$

6.9 Hz, 1H), 4.26 (d, $J = 8.4$ Hz, 1H), 4.34 (d, $J = 8.4$ Hz, 1H), 4.42 (m, 2H), 4.92 (d, $J = 7.2$ Hz, 1H), 5.41 (m, 2H), 5.62 (d, $J = 7.2$ Hz, 1H), 6.02 (t, $J = 9.0$ Hz, 1H), 6.33 (s, 1H), 6.67 (d, $J = 9.9$ Hz, 1H), 7.11 (s, 2H), 7.47 (m, 3H), 7.67 (d, $J = 9.0$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.78 (d, $J = 7.8$ Hz, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 8.24 (s, 1H).

Macrocyclic taxoid **7-*exo*(H)**:

A solution of **7-*exo*** (17.0 mg, 0.019 mmol) in ethyl acetate (2 mL) was added to a reaction vessel containing 10% palladium on carbon (10 mg) under a hydrogen atmosphere, and the reaction mixture was stirred overnight (18 h) at room temperature. The reaction mixture was filtered through a pad of celite and concentrated. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/2) as the eluant afford macrocyclic taxoid **7-*exo*(H)** as a white solid (14 mg, 83%; a 1:3.5 mixture of diastereomers): ^1H NMR (300 MHz, CDCl_3) δ 1.06 (s, 0.23H), 1.07 (s, 0.77H), 1.18 (s, 0.33H), 1.21 (s, 0.77H), 1.26 (m, 4H), 1.62 (s, 0.77H), 1.63 (s, 0.33H), 1.76 (m, 4H), 1.86 (m, 6H), 1.91 (s, 3H), 2.07 (m, 2H), 2.21 (m, 1H), 2.22 (s, 3H), 2.35 (m, 2H), 2.42 (m, 1H), 2.43 (s, 3H), 2.53 (m, 2H), 3.54 (d, $J = 6.9$ Hz, 0.23H), 3.66 (d, $J = 6.9$ Hz, 0.77H), 4.13 (m, 2H), 4.30 (m, 1H), 4.41 (m, 1H), 4.83 (d, $J = 8.4$ Hz, 0.33H), 4.87 (d, $J = 8.4$ Hz, 0.77H), 4.93 (m, 1H), 5.13 (m, 1H), 5.36 (d, $J = 10.2$, 1H), 5.58 (d, $J = 6.8$ Hz, 0.77H), 5.61 (d, $J = 6.8$ Hz, 0.33 H), 5.88 (d, $J = 6.6$ Hz, 0.33H), 5.90 (d, $J = 6.6$ Hz, 0.77H), 6.14 (t, $J = 9.0$ Hz, 1H), 6.25 (m, 2H), 7.18 (d, $J = 7.8$ Hz, 0.77H), 7.21 (d, $J = 7.8$ Hz, 0.33H), 7.30 (m, 1H), 7.37 (d, $J = 7.8$ Hz, 0.77H), 7.39 (d, $J = 7.8$ Hz, 0.33H), 7.41-7.48 (m, 2H), 7.64 (m, 1H), 7.84 (t, $J = 7.8$ Hz, 1H), 8.11 (s, 0.77H), 8.17 (s, 0.33H). HRMS (FAB) m/z calcd. for $\text{C}_{47}\text{H}_{57}\text{NO}_{14}\text{H}^+$: 860.3854, found: 860.3857 ($\Delta = +0.4$ ppm).

Macrocyclic taxoid **9-*endo***:

To a solution of **2b** (20 mg, 0.015 mmole) in acetonitrile (3 mL) and triethylamine (0.2 mL) was added a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (3 mg) and the resulting mixture was allowed to stir at 50°C overnight. The mixture was cooled to room temperature, passed through a pad of celite, and the solvent was removed *in vacuo* giving a yellow solid as crude product. This crude product was dissolved in pyridine/acetonitrile (1/1, 5 mL) and $\text{HF}/\text{Pyridine}$ (70/30, 0.4 mL) was added dropwise at 0°C . The mixture was allowed to gradually warm to room temperature and stirred for 11 h at room temperature. The reaction was quenched with saturated sodium bicarbonate (5 mL). The mixture was then diluted with ethyl acetate (50 mL), washed with aqueous saturated copper sulfate (3 x 10 mL), water, and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was purified on a silica gel column using hexane/ethyl acetate (1/3) as the eluant to afford **9-*endo*** as a white solid (12 mg, 87% for 2 steps): mp $>220^\circ\text{C}$; $[\alpha]_D^{22} -38$ (c 0.5, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 1.11 (s, 3H), 1.19 (s, 3H), 1.72 (s, 3H), 1.90 (m, 1H), 1.98 (s, 3H), 2.17 (s, 3H), 2.27 (s, 3H), 2.45 (m, 1H), 2.54 (m, 1H), 2.94 (m, 1H), 3.79 (d, $J = 7.2$ Hz, 1H), 4.26 (d, $J = 8.1$ Hz, 1H), 4.35 (d, $J = 8.1$ Hz, 1H), 4.41 (dd, $J = 6.3, 9.9$ Hz, 1H), 4.66 (d, $J = 1.8$ Hz, 1H), 4.91 (d, $J = 9.6$ Hz, 1H), 5.59 (d, $J = 6.6$ Hz, 1H), 5.80 (m, 2H), 6.28 (s, 1H), 7.14 (s, 2H), 7.32 (d, $J = 6.0$ Hz, 1H), 7.36 (t, $J = 6.0$ Hz, 2H), 7.50 (m, 4H), 7.57 (d, $J = 10.2$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.69 (s, 1H), 7.76 (d, $J = 7.8$

Hz, 1H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.92 (d, $J = 7.8$ Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (75.0 MHz, CDCl_3) δ 9.7, 15.2, 20.8, 21.8, 22.2, 27.1, 29.7, 35.5, 37.3, 42.7, 45.4, 54.6, 58.5, 72.1, 73.9, 75.5, 76.3, 80.1, 84.2, 124.7, 127.9, 128.1, 128.3, 129.0, 129.2, 130.0, 130.1, 133.7, 135.6, 135.7, 136.7, 137.0, 141.9, 166.5, 167.7, 169.8, 171.2, 172.2, 203.6. HRMS (FAB) m/z calcd. for $\text{C}_{49}\text{H}_{51}\text{NO}_{14}\text{H}^+$: 878.3392, found: 878.3388 ($\Delta = -0.5$ ppm).

2-Debenzoyl-2-(3-iodobenzoyl)-3'-N-debenzoyl-3'-N-(pent-4-enoyl)-3'-dephenyl-3'-(2-phenylethenyl)-2'-triethylsilyl-7-triethylsilylpaclitaxel (13):

To a solution of baccatin **10** (145 mg, 0.175 mmol) and β -lactam **21** (101.4 mg, 0.263 mmol) in 6 mL dry THF was added dropwise 1.0 M LiHMDS in THF (0.263 mL, 0.263 mmol) at -40°C , and the solution was stirred at -40°C for 40 min. The reaction was quenched with aqueous saturated ammonium chloride solution (10 mL), and the aqueous layer was extracted with dichloromethane (25 mL x 3). The combined extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (10/1 followed by 6/1, 3/1, then 1/1) as the eluant to afford the unreacted baccatin **10** (29 mg, 20%) and the coupling product **13** (158 mg, 74%; 93% based on 80% conversion) as a white solid: ^1H NMR (300 MHz, CDCl_3) δ 0.55 (m, 6 H), 0.65 (m, 6 H), 0.89 (m, 9 H), 0.96 (m, 9 H), 1.12 (s, 3 H), 1.20 (s, 3 H), 1.67 (s, 3 H), 1.90 (m, 1 H), 2.00 (s, 3 H), 2.15 (s, 3 H), 2.15 (m, 2 H), 2.30 (m, 4 H), 2.44 (s, 3 H), 2.51 (m, 1 H), 3.81 (d, $J = 7.2$ Hz, 1 H), 4.13 (d, $J = 8.2$ Hz, 1 H), 4.27 (d, $J = 8.2$ Hz, 1 H), 4.44 (dd, $J = 10.2, 6.6$ Hz, 1 H), 4.48 (d, $J = 2.1$ Hz, 1 H), 4.92-5.04 (m, 3 H), 5.10 (t, $J = 7.8$ Hz, 1 H), 5.61 (d, $J = 6.9$ Hz, 1 H), 5.76 (m, 1 H), 6.04 (d, $J = 9.0$ Hz, 1 H), 6.10 (t, $J = 9.3$ Hz, 1 H), 6.17 (dd, $J = 15.9, 6.6$ Hz, 1 H), 6.43 (s, 1 H), 6.57 (d, $J = 15.9$ Hz, 1 H), 7.20-7.33 (m, 6 H), 7.89 (d, $J = 7.8$ Hz, 1 H), 8.05 (d, $J = 7.8$ Hz, 1 H), 8.48 (s, 1 H); ^{13}C NMR (75.0 MHz, CDCl_3) δ 4.5, 5.2, 6.6, 9.9, 14.1, 14.2, 20.8, 20.9, 21.1, 22.8, 26.4, 29.3, 35.3, 35.6, 37.1, 43.2, 46.6, 53.8, 58.3, 71.3, 72.2, 73.7, 74.9, 75.2, 76.3, 78.7, 81.0, 84.1, 93.9, 115.5, 125.7, 126.3, 128.0, 128.6, 129.3, 130.4, 131.2, 132.6, 133.5, 136.0, 136.8, 139.1, 140.3, 142.1, 165.1, 169.1, 169.7, 171.3, 171.6, 201.5.

Macrocyclic taxoids 14-*exo* and 14-*endo*:

To a solution of **13** (150 mg, 0.124 mmol) in acetonitrile (20 mL) and triethylamine (2 mL, excess) was added $\text{Pd}(\text{PPh}_3)_4$ (14.3 mg, 0.012 mmol), and the resulting mixture was allowed to stir at 70°C for 25 h. The mixture was cooled to room temperature, and volatiles were removed under reduced pressure. The crude residue was purified on a silica gel column using hexane/ethyl acetate (4:1 followed by 2:1) as the eluant to afford a mixture of products (122 mg) as an off-white solid. To a solution of the mixture of products thus obtained in 5 mL of pyridine/acetonitrile (1/1) was added dropwise HF/pyridine (70/30, 0.8 mL) at 0°C , and the mixture was stirred at room temperature for 22 h. The reaction was quenched with aqueous saturated sodium carbonate (5.0 mL). The reaction mixture was then diluted with ethyl acetate (70 mL), washed with aqueous saturated copper sulfate (10 mL x 3) and water (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified on a silica gel column using hexane/ethyl acetate (1/1 followed by 1/2, then 1/3) as the eluant to afford a mixture of macrocyclic taxoids **14-*exo*** and **14-*endo*** (3/1 as indicated by ^1H NMR) as a white solid (72 mg, 67% for two steps). The two products were separated by

HPLC using a reverse-phase semi-preparative column (Phenomenex, Curosil-D, 250 x 4.6 mm; CH₃CN/H₂O = 1/1; flow rate 10 mL/min; T_R = 13.0 min for **14-endo** and 14.5 min for **14-exo**).

14-exo: mp 214-217 °C; [α]_D²² -10.0 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.25 (s, 6H), 1.68 (s, 3H), 1.86 (m, 1H), 1.89 (s, 3H), 2.18 (m, 2H), 2.24 (s, 3H), 2.31 (m, 2H), 2.32 (s, 3H), 2.50 (m, 2H), 2.82 (m, 1H), 3.86 (d, *J* = 7.2 Hz, 1H), 4.25 (d, *J* = 8.4 Hz, 1H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.51 (dd, *J* = 4.2, 10.2 Hz, 1H), 4.61 (m, 4H), 4.93 (m, 2H), 5.30 (s, 1H), 5.46 (d, *J* = 7.2 Hz, 1H), 5.56 (s, 1H), 5.65 (d, *J* = 7.8 Hz, 1H), 6.06 (dd, *J* = 8.1, 15.6 Hz, 1H), 6.23 (m, 3H), 6.70 (d, *J* = 15.6 Hz, 1H), 7.33 (m, 5H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (75.0 MHz, CDCl₃) δ 9.9, 14.7, 20.8, 23.1, 26.8, 29.7, 30.4, 35.1, 35.3, 36.4, 43.0, 45.5, 70.8, 71.6, 71.9, 75.4, 75.8, 76.2, 80.3, 81.0, 84.7, 114.8, 117.7, 121.0, 126.0, 128.6, 128.7, 129.2, 129.4, 130.1, 131.4, 133.3, 135.4, 136.7, 139.6, 142.1, 144.4, 166.9, 170.6, 171.1, 171.3, 172.9, 203.6. HRMS (FAB) *m/z* calcd. for C₄₇H₅₃NO₁₄H⁺: 856.3541, found: 856.3544 (Δ = +0.4 ppm).

14-endo: mp >220 °C; [α]_D²² +10.0 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.29 (s, 6H), 1.71 (s, 3H), 1.86 (m, 1H), 1.96 (s, 3H), 2.23 (s, 3H), 2.32 (m, 2H), 2.36 (m, 2H), 2.40 (s, 3H), 2.50 (m, 2H), 2.84 (m, 1H), 3.76 (d, *J* = 7.5 Hz, 1H), 4.59 (d, *J* = 2.1 Hz, 1H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.96 (t, *J* = 7.5 Hz, 1H), 5.65 (d, *J* = 7.8 Hz, 1H), 6.11 (d, *J* = 7.8 Hz, 1H), 6.20 (m, 1H), 6.32 (dd, *J* = 7.5, 15.9 Hz, 1H), 6.33 (t, *J* = 7.6 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.67 (d, *J* = 16.2 Hz, 1H), 7.32 (m, 7H), 7.86 (d, *J* = 8.1 Hz, 1H), 8.11 (s, 1H); ¹³C NMR (75.0 MHz, CDCl₃) δ 9.9, 14.6, 20.8, 23.1, 23.5, 27.12, 27.2, 29.7, 34.6, 35.3, 36.8, 43.1, 45.3, 53.9, 58.3, 71.9, 72.0, 72.6, 75.3, 76.1, 76.3, 80.3, 80.7, 84.5, 124.6, 124.8, 126.7, 128.2, 128.6, 128.9, 129.0, 129.7, 130.5, 133.0, 133.2, 133.9, 135.9, 137.9, 142.0, 167.1, 171.1, 171.3, 171.6, 172.7, 203.7. HRMS (FAB) *m/z* calcd. for C₄₇H₅₃NO₁₄H⁺: 856.3541, found: 856.3544 (Δ = +0.4 ppm).

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