Supporting information

Novel C-seco-taxoids possessing high potency against paclitaxel-resistant cancer cell lines overexpressing class III β-tubulin

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Contents:

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 MHz NMR spectrometer or a Varian 300, 400 or 500 MHz NMR spectrometers using tetramethylsilane as the internal standard. The ^{1}H and ^{13}C NMR spectra of C-seco-baccatins and C-seco-taxoids were assigned based on Appendino's attribution.[1] 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. Thin layer chromatotraphy (TLC) was performed on Merck DC-alufolien with Kieselgel 60F-254, Column chromatography was carried out on silica gel 60 (Merck; 230-400 mesh ASTM). The purity of the final taxoids was analyzed by HPLC with a Shimadzu LC-2010A/2010C, using a Novapack C-18 column and acetonitrile-water (1:1) as the solvent system with a flow rate of 0.5 ml/min. Low resolution mass spectrometric analysis was carried out on an Agilent G1956 1100 Series LC-MS system. High resolution mass spectrometry (HRMS) was performed at the Mass Spectrometry Laboratory, University of Illinois at Urbana-Champaign, Urbana, IL.

Materials. Chemicals were purchased from Sigma Aldrich Co. or Fisher Scientific, and used as received. Tetrahydrofuran was freshly distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride immediately before use. In addition, a PureSolv^{TM} solvent purification system SPS-400 (Innovative Technology, Inc.) was used for the purification of HPLC grade solvents. (3*R*,4*S*)-1-*tert*-Butoxycarbonyl-3-triisopropylsiloxy-4-(2-methylprop-1-enyl)azetidin-2-one (**1**)[2], (3*R*,4*S*)-1-*tert*-butoxycarbonyl-3-triisopropylsiloxy-4-(2-methylpropyl)azetidin-2-one (**2**),[3] 2-debenzoyl-2-(3-methoxybenzoyl)-10-deacetylbaccatin III (**3a**)[4, 5], 2-debenzoyl-2-(3-chlorobenzoyl)-10-deacetyl-baccatin III (**3b**),[4, 5] and 2-debenzoyl-2-(3-fluorobenzoyl)-10-deacetylbaccatin III (**3c**)[4, 5] were prepared by the literature methods.

Synthesis of 2-debenzoyl-2-(3-methoxybenzoyl)-10-dehydro-10-deacetylbaccatin III (4a).

To a solution of 2-(3-OMe-benzoyl)-DAB **3a** (606 mg 1.04 mmol) in MeOH (20 mL) was added $Cu(OAc)_2.H_2O$ (630 mg, 3 equiv.). The suspension was stirred at room temperature overnight (open air). The reaction mixture was concentrated *in vacuo*, and the crude product was passed through a short silica gel column, using dichloromethane-methanol(3%) as eluant, to remove the Cu salts. Then, **4a** was collected as yellowish solid (458 mg, 77% yield as a 4:1 mixture of two epimers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dt, 1 H, J = 1.2, 8 Hz, 6-H_{Ar}), 7.70 (t, 1 H, J = 3 Hz, 2-H_{Ar}), 7.44 (t, 1 H, J = 8 Hz, 5-H_{Ar}), 7.20 (ddd, 1 H, J = 1.2, 3, 8 Hz, 4-H_{Ar}), 5.83 (d, 1 H, J = 7 Hz, 2-H), 4.95 (m, 2 H, 13-H, 5-H), 4.65 (d, 1 H, J = 11 Hz, 7-H), 4.47 (d, 1 H, J = 8 Hz, 20-Ha), 4.34 (d, 1 H, J = 8 Hz, 20-Hb), 4.10 (d, 1 H, J = 7 Hz, 3-H), 3.90 (s, 3 H, OMe), 2.40 (m, 4 H, 4-Ac, 6-Ha), 2.30 (m, 2 H, 14-Ha, 14-Hb), 2.14 (m, 1 H, 6-Hb), 2.00 (d, 3 H, J = 1.5 Hz, 18-CH_3), 1.70 (s, 3 H, 19-CH_3), 1.10 (m, 6 H, 17-CH_3, 16-CH_3).

*In the same manner, 2-(3-chloro- and fluorobenzoyl) analogues, **4b** and **4c**, were synthesized.*

2-Debenzoyl-2-(3-chlorobenzoyl)-7-epi-10-dehydro-10-deacetylbaccatin III (4b): 77% yield as a 4:1 mixture of two epimers; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (d, 1 H, J = 7 Hz, H-2, epimer A), 5.52 (d, 1 H, J = 7 Hz, H-2, epimer B), 497-4.89 (m, 4 H, H-13 +H-5 epimer A, H-13 +H-5 epimer B), 4.63 (d, 1 H, J = 11 Hz 7-H), 4.58 (d, 1 H, J = 8 Hz, H-20 epimer A), 4.49 (d, 1 H, J = 8 Hz, H-20 epimer B), 4.28 (d, 1 H, J = 8 Hz, H-20 epimer A), 4.13 (m, 1 H, J = 8 Hz, H-20 epimer B), 4.03 (dd, 1 H, J = 7, 11 Hz, H-7), 3.53 (d, 1 H, J = 7 Hz, H-3), 2.60 (m, 1H), 2.2-1.0 (m, 20 H for both epimers).

2-Debenzoyl-2-(3-fluorobenzoyl)-10-dehydro-10-deacetylbaccatin III (4c): 86 % yield; a yellowish solid, a 4:1 mixture of epimers**:**

Epimer A (less polar epimer)**.** ^{1}H NMR (300 MHz $CDCl_3$) δ 7.99 (d, 1 H, J = 8 Hz, 6-H_{Ar}), 7.84 (m, 1 H, 2-H_{Ar}), 7.56 (m, 1 H, 5-H_{Ar}), 7.41 (m, 1 H, 4-H_{Ar}), 5.85 (d, 1 H, J = 7 Hz, 2-H), 5.00 (m, 2 H, 5-H, 13-H), 4.69 (d, 1 H, J = 11 Hz, 7-H), 4.47 (d, 1 H, J = 8 Hz, 20-Ha), 4.35 (d, 1 H, J = 8 Hz, 20-Hb), 4.15 (d, 1 H, J = 7 Hz, 3-H), 3.88 (m, 1 H, OH), 2.44 (s, 3 H, 4-Ac), 2.40 (m, 1 H, 6-Ha), 2.32 (m, 2 H, 14-Ha, 14-Hb), 2.00 (s, 4 H, 18-CH_3, 6-Hb), 1.75 (s, 3 H, 19-CH_3), 1.14 (s, 3 H, 16-CH_3), 1.12 (s, 3 H, 17-CH_3); ^{13}C NMR (75 MHz $CDCl_3$) δ 208.6 (9-C), 196.4 (10-C), 172.7 (4-Ac), 166.1 (2-benz), 163.0 (d, J_{CF} = 246 Hz, CF), 147.0 (12-C), 140.7 (11-C), 131.7 (J_{CF} = 7 Hz, 1-C_{Ar}), 130.7 (J_{CF} = 8 Hz, 5-CH_{Ar}), 126.2 (J_{CF} = 3 Hz, 6-CH_{Ar}), 121.4 (J_{CF} = 21 Hz, 4-CH_{Ar}), 117.3 (J_{CF} = 23 Hz, 2-CH_{Ar}), 82.8 (5-CH), 81.5 (4-C), 79.4 (1-C), 77.3 (7-CH), 76.9 (20-CH_2), 75.7 (2-CH), 67.7 (13-CH), 57.6 (8-C), 40.0 (15-C), 39.9 (3-CH), 39.1 (14-CH_2), 35.6 (6-CH_2), 26.6 (16-CH_3), 22.7 (4-Ac), 22.3 (17-CH_3), 15.2 (18-CH_3), 14.8 (19-CH_3).

Epimer B (more polar epimer)**.** ^{1}H NMR (300 MHz $CDCl_3$) δ 7.98 (m, 1 H, 6-H_{Ar}), 7.80 (m, 1 H, 2-H_{Ar}), 7.56 (m, 1 H, 5-H_{Ar}), 7.40 (m, 1 H, 4-H_{Ar}), 5.80 (d, 1 H, J = 7 Hz, 2-H), 5.03 (m, 2 H, 5-H, 13-H), 4.39 (d, 1 H, J = 8 Hz, 20-Ha), 4.21 (d, 1 H, J = 8 Hz, 20-Hb), 4.14 (dd, 1 H, J = 7, 10 Hz, 7-H), 4.13 (d, 1 H, J = 7 Hz, 3-H), 2.60 (m, 1 H, 6-Ha), 2.42 (m, 2 H, 14-Ha, 14-Hb), 2.39 (s, 3 H, 4-Ac), 1.90 (m, 2 H, 6-Hb, OH), 1.78 (s, 3 H, 19-CH_3), 1.27 (s, 3 H, 17-CH_3), 1.21 (s, 3 H, 16-CH_3); ^{13}C NMR (75 MHz $CDCl_3$) δ, 206.8 (9-C), 194.4 (10-C), 170.7 (4-Ac), 166.0 (2-benz.), 163.0 (J_{CF} = 246 Hz, CF), 150.7 (12-C), 141.4 (11-C), 131.7 (1-C_{Ar}), 130.6 (d, J_{CF} = 8 Hz, 5-CH_{Ar}), 126.1 (d, J_{CF} = 3 Hz, 6-CH_{Ar}), 121.1 (d, J_{CF} = 21 Hz, 4-CH_{Ar}), 117.2 (d, J_{CF} = 23 Hz, 2-CH_{Ar}), 84.5 (5-CH), 80.5 (4-C), 79.5 (1-C), 76.1 (20-CH_2), 75.2 (2-CH), 69.0 (7-CH), 68.3 (13-CH), 58.7 (8-C), 45.9 (3-C), 40.6 (15-C), 38.6 (14-CH_2), 35.8 (6-CH_2), 27.1 (16-CH_3), 23.4 (4-Ac), 22.6 (17-CH_3), 14.6 (18-CH_3), 8.4 (19-CH_3).

Synthesis of 2-debenzoyl-2-(3-methoxybenzoyl)-10-dehydro-7-8-seco-10-deacetylbaccatin (5a).

L-selectride (1M solution in THF, 4 eq) was added, dropwise to a solution of 10-oxo-2-*m*-OMe-benzoyl-DAB (**4a**) (130 mg, 0.227 mmol) in THF (2.5 mL) at –70 ^{o}C. After 10 min, the reaction was quenched by addition of ethyl acetate (2.5 mL) and a 2 *N* H_2SO_4 (1.0 mL). The reaction mixture was extracted with ethyl acetate and the combined organic phases were washed with a saturated aqueous $NaHCO_3$ and brine. The resulting solution was dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure to give a crude product. The crude product was purified on a short silica gel column, using dichloromethane/methanol(3%) as eluant to afford **5a** (90 mg, 70% yield) as a white solid: ^{1}H NMR (400 MHz $CDCl_3$) δ 7.60 (m, 2 H, 6, 2–H_{Ar}), 7.37 (t, 1 H, J = 7 Hz, 5-H_{Ar}), 7.10 (m, 1 H, 4–H_{Ar}), 6.48 (s, 1 H, 9-OH), 5.55 (d, 1 H, J = 9 Hz, 2-H), 5.20 (m, 2 H, 5-H, 20-Ha), 4.90 (m, 1 H, 13-H), 4.40-4.20 (m, 2 H, 3-H, 20-Hb), 3.85 (s, 3 H, OMe), 3.80-3.60 (m, 2 H, 7-Ha, 7-Hb), 3.20 (m, 1 H, 14-Ha), 2.7-1.6 (m, 12 H, 6-Ha, 14-Hb, 6-Hb, 4-Ac, 18-CH_3, 19-CH_3), 1.12 (s, 3 H, 17-CH_3), 1.05 (s, 3 H, 16-CH_3).

In the same manner, 2-(3-chloro- and fluorobenzoyl) analogues, ***5b*** *and* ***5c****, were synthesized.*

2-Debenzoyl-2-(3-chlorobenzoyl)-10-dehydro-7-8-seco-10-deacetylbaccatin (5b): 70% yield; white solid; mp 156-158 ^{o}C; $[\alpha]_D^{25}$ 63^o (c 0.43, $CHCl_3$); ^{1}H NMR (400 MHz $CDCl_3$) δ 8.90 (m, 2 H, arom), 7.60 (m, 1 H, arom), 7.40 (m, 1 H, arom), 6.52 (s, 1 H, 9-OH), 5.58 (bd, 1 H, 2-H), 5.20 (bs, 1 H, 5-H), 4.90 (m, 2 H, 20-Ha, 13-H), 4.30 (m, 2 H, 3-H, 20-Hb), 3.70 (m, 2 H, 7-Ha, 7-Hb), 1.70-2.80 (m, 14 H, 14-Ha, 6-Ha, 14-Hb, 6-Hb, 4-Ac, 18-CH_3, 19-CH_3, OH), 1.20 (s, 3 H, 16-CH_3), 1.12 (s, 3 H, 17-CH_3); ^{13}C NMR (100 MHz $CDCl_3$) δ 192.0 (10-C), 170.0 (4-Ac), 166.0 (2-benz), 149.1 (9-C), 141.3 (11-C), 141.2 (12-C), 135.2 (4-CH_{Ar}), 134.0 (3-C_{Ar}), 131.5 (1-C_{Ar}), 130.4 (2-CH_{Ar}), 129.7 (5-CH_{Ar}), 127.9 (6-

CH_{Ar}), 123.9 (8-CH), 87.2 (5-CH), 86.6 (4-C), 80.1 (1-C), 75.3 (20-CH_2), 75.2 (2-CH), 67.3 (13-CH), 59.5 (7-CH), 44.5 (3-CH), 42.9 (15-C), 39.8 (14-CH_2), 38.2 (6-CH_2), 25.3 (16-CH_3), 22.4 (4-Ac), 21.0 (17-CH_3), 14.7 (18-CH_3), 14.6 (19-CH_3).

2-Debenzoyl-2-(3-fluorobenzoyl)-10-dehydro-7-8-seco-10-deacethylbaccatin (5c): 50% yield; white solid; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.80 (m, 1 H, arom), 7.60 (m, 1 H, arom), 7.40 (m, 1 H, arom), 7.30 (m, 1 H, arom), 6.52 (s, 1 H, 9-OH), 5.54 (d, J = 9 Hz, 2-H), 5.10 (bs, 2 H, 5-H, 20-Ha), 4.90 (m, 1 H, 13-H), 4.29 (m, 2 H, 20-Hb, 3-H), 3.70 (m, 2 H, 7-Ha, 7-Hb), 1.80-2.80 (m, 14 H, 14-Ha, 6-Ha, 14-Hb, 6-Hb, 4-Ac, 18-CH_3, 19-CH_3, OH), 1.10 (s, 3 H, 16-CH_3), 1.04 (s, 3 H, 17-CH_3); ^{13}C NMR (100 MHz $CDCl_3$) δ 192.1 (10-C), 169.2 (4-Ac), 166.0 (2-benz.), 163.0 (d, J_{CF} = 247 Hz, CF_{Ar}), 149.0 (9-C), 141.1 (11-C), 140.0 (12-C), 131.9 (d, J_{CF} = 7 Hz, 1-C_{Ar}), 130.8 (5-CH_{Ar}), 125.4 (8-C), 123.4 (6-CH_{Ar}), 121.2 (d, J_{CF} = 21 Hz, 4-CH_{Ar}), 116.7 (2-CH_{Ar}), 87.0 (5-CH), 86.5 (4-C), 80.6 (1-C), 76.9 (20-CH_2), 75.4 (2-CH), 67.1 (13-CH), 59.2 (7-C), 44.5 (3-CH), 42.8 (15-C), 39.8 (14-CH_2), 39.7 (6-CH_2), 25.3 (16-CH_3), 22.4 (4-Ac), 21.1 (17-CH_3), 14.5 (18-CH_3), 11.1 (19-CH_3).

Synthesis of 2-debenzoyl-2-(3-methoxybenzoyl)-7,9-ditriethylsilyl-10-dehydro-7-8-seco-10-deacethylbaccatin (6a).

Chlororiethylsilane (147 μL, 0.88 mmol) and methylimidazole (80 μL, 1.0 mmol) were added dropwise to a solution of **5a** (230 mg, 0.40 mmol) in freshly distilled DMF (0.133 M) at 0 ^{o}C and the mixture was stirred at 0 ^{o}C for 40 min in an ice/water bath. The reaction mixture was washed with a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic phases were washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified on a silica gel column using a mixture of petroleum ether and ethyl ether (1:1) to afford **6a** (217 mg, 67 % yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2 H, 6, 2–H_{Ar}), 7.37 (t, 1 H, J = 7 Hz, 5-H_{Ar}), 7.10 (m, 1 H, 4–H_{Ar}), 5.55 (d, 1 H, J = 9 Hz, 2-H), 5.20 (m, 2 H, 5-H, 20-Ha), 4.90 (m, 1 H, 13-H), 4.40 (m, 1 H, 3-H), 4.20 (m, 1 H, 20-Hb), 3.85 (s, 3 H, OMe), 3.80 (m, 1 H, 7-Ha), 3.60 (m, 1 H, 7-Hb), 2.70-2.10 (m, 3 H, 14-Ha, 6-Ha, 14-Hb), 2.00-1.40 (m, 10 H, 4-Ac, 6-Hb, 18-CH_3, 19-CH_3), 1.24 (s, 3 H, 17-CH_3), 1.10 (m, 3 H, 16-CH_3) 0.90 (m, 18 H, 2*Si($CH_2C\underline{H_3})_3$), 0.80 (m, 6 H, Si($\underline{CH_2}CH_3)_3$), 0.60 (m, 6 H, Si($\underline{CH_2}CH_3)_3$).

In the same manner, 2-(3-chloro- and fluorobenzoyl) analogues, ***6b*** *and* ***6c****, were synthesized.*

2-Debenzoyl-2-(3-chlorobenzoyl)-7,9-triethylsilyl-10-dehydro-7-8-seco-10-deacethylbaccatin (6b): 50 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (bs, 2 H, 2, 6-H_{Ar}), 7.60 (d, 1 H, J = 6 Hz, 4-H_{Ar}), 7.40 (t, 1 H, J = 6 Hz 5-H_{Ar}), 5.60 (bd, 1 H, J = 7 Hz 2-H), 5.40-5.20 (m, 2 H, 5-H, 20-Ha), 4.95 (m, 1 H, 13-H), 4.20 (m, 2 H, 3-H, 20-Hb), 3.90-3.60 (m, 2 H, 7-Ha, 7-Hb), 2.70 (m, .60 (m, 10 H, 6-Hb, 18-CH_3, 4-Ac, 19-CH_3), 1.10 (s, 3 H, 17-CH_3), 1.15 (s, 3 H, 16-CH_3), 0.90 (m, 18 H, 2*Si($CH_2C\underline{H_3})_3$), 0.75 (m, 6 H, Si($\underline{CH_2}CH_3)_3$), 0.60 (m, 6 H, Si($\underline{CH_2}CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3 (10-C), 172.2 (4-Ac), 166.0 (2-benz.),149.0 (9-C), 142.7 (11-C), 137.0 (12-C), 135.2 (4-CH_{Ar}), 133.0 (3-C_{Ar}), 131.6 (1-C_{Ar}), 130.4 (2-CH_{Ar}), 129.7 (5-CH_{Ar}), 128.0 (6-CH_{Ar}), 87.2 (5-CH), 86.6 (4-C), 80.1 (1-C), 76.9 (20-CH_2) 75.2 (2-CH), 68.1 (13-CH), 57.6 (7-CH_2), 51.4 (3-CH), 42.7 (15-C), 41.1 (6-CH), 35.7 (14-CH_2), 26.6 (16-CH_3), 22.3 (4-Ac), 21.9 (17-CH_3), 15.1 (18-CH_3), 13.1 (19-CH_3), 7.2 (($Si(CH_2\underline{C}H_3)_3$), 7.1 ($Si(CH_2\underline{C}H_3)_3$), 6.4 ($Si(\underline{C}H_2CH_3)_3$), 5.0 ($Si(\underline{C}H_2CH_3)_3$). MS-ES$^+$ (*m*/*z*):calcd for $C_{41}H_{63}ClO_{10}Si_2H^+$ 807.36; found 807.4.

2-Debenzoyl-2-(3-fluorobenzoyl)-7,9-bis(triethylsilyl)-10-dehydro-7-8-seco-10-deacethylbaccatin (6c): white solid; 52 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 1 H, arom), 7.70 (m, 1 H, arom), 7.50 (m, 1 H, arom), 7.35 (m, 1 H, arom), 5.58 (d, 1 H, J = 9 Hz, 2-H), 5.20 (bs, 1 H, 5-H), 4.90 (m, 2 H, 20-Ha, 13-H), 4.20 (m, 2 H, 20-Hb, 3-H), 3.80 (m, 1 H, 7-Ha), 3.60 (m, 1 H, 7-Hb), 1.70-2.60 (m, 14 H,

14-Ha, 6-Ha, 14-Hb, 6-Hb, 4-Ac, 18-CH_3, 19-CH_3, OH), 1.15 (s, 3 H, 16-CH_3), 1.10 (s, 3 H, 17-CH_3), 0.95 (m, 18 H, 2*Si($CH_2C\underline{H_3})_3$), 0.80 (m, 6 H, Si($\underline{CH_2}CH_3)_3$), 0.60 (m, 6 H, Si($\underline{CH_2}CH_3)_3$).

Synthesis of 2-debenzoyl-2-(3-methoxybenzoyl)-2'-triisopropylsilyl-3'-dephenyl-3'-(2-methyl-1-propyl)-7,9-ditriethylsilyl-10-dehydro-7-8-seco-docetaxel (7a).

LiHMDS (1M solution in THF, 279 μL, 1.5 equiv) was added to a solution of 7-9-diTES-*m*-OMe-benzoyl-DAB **6a** (147 mg, 0.177 mmol) and β-lactam **2** (106 mg, 1.5 eq) in THF (20 mL) at -40 ^oC and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with brine, extracted with ethyl acetate, and the organic layer was dried over anhydrous $MgSO_4$. The crude mixture was purified by column chromatography on silica gel using hexanes/ethyl acetate (6/1) as eluant to afford **7a** (168 mg, 80 % yield) as a white solid: ^1H NMR (400 MHz $CDCl_3$) δ 7.60 (m, 1 H, 6-H_{Ar}), 7.50 (m, 1 H, 2-H_{Ar}), 7.40 (t, 1 H, *J* = 8 Hz, 5-H_{Ar}), 7.15 (ddd, 1 H, *J* = 1.2, 3, 8 Hz, 4-H_{Ar}), 6.05 (m, 1 H, 13-H), 5.60 (d, 1 H, *J* = 9 Hz, 5-H),5.30 (m, 1 H, 2-H), 5.20 (m, 1 H, 20-Ha), 4.65 (d, 1H, *J* = 10 Hz, NH), 4.37 (m, 1 H, 2'-H), 4.30-4.10 (m, 3 H, 3-H, 20-Hb, 3'-H), 3.85 (s, 3 H, OMe), 3.70 (m, 2 H, 7-Ha, 7-Hb), 2.40 (m, 2 H, 14-Ha, 6-Ha), 1.80-1.60 (m, 14 H, 14-Hb, 6-Hb, 4-Ac, 18-CH_3, 19-CH_3, 5'-CH, 4'-Ha, 4'-Hb), 1.30 (s, 9 H, Boc), 1.20 (s, 3 H, 17-CH_3), 1.14 (s, 3 H, 16-CH_3), 0.99 (m, 27 H, 6'-CH_3, 7'-CH_3, TIPS), 0.95 (m, 18 H, 2*Si($CH_2C\underline{H_3})_3$), 0.70 (m, 6 H, Si($C\underline{H_2}CH_3)_3$), 0.55 (m, 6 H, Si($C\underline{H_2}CH_3)_3$); ^{13}C NMR (100 MHz $CDCl_3$) δ 191.8 (10-C), 172.1 (1'-C), 169.2 (4-Ac), 168.9 (2-benz.), 159.9 (3-C_{Ar}), 155.8 (NCCO), 149.0 (9-C), 142.4 (11-C), 137.1 (12-C), 131.0 (1-C_{Ar}), 129.9 (5-CH_{Ar}), 124.6 (8-C), 122.1 (6-CH_{Ar}), 120.1 (4-CH_{Ar}), 114.7 (2-CH_{Ar}), 87.5 (5-CH), 85.8 (4-C), 80.6 (1-C), 79.4 (C, Boc), 75.2 (20-CH_2), 74.9 (2-CH), 73.8 (2'-CH), 71.1 (13-CH), 60.0 (7-CH_2), 55.6 (OMe), 52.4 (3'-CH), 44.6 (3-CH), 43.1 (15–C), 42.4 (4'-CH_2), 37.7 (6-CH_2), 36.6 (14-CH_2), 28.4 (CH_3, Boc), 25.0 (5'-CH), 23.4 (17-CH_3), 22.5 (6'-CH_3), 22.4 (7'-CH_3), 22.2 (4-Ac), 21.8 (16-CH_3), 18.3 (SiCH($\underline{C}H_3)_2$), 14.8 (18-CH_3), 14.6 (19-CH_3), 12.9 (Si$\underline{C}H(CH_3)_2$), 7.2 (Si($CH_2\underline{C}H_3)_3$), 6.9 (Si($CH_2\underline{C}H_3)_3$), 6.4 (Si($\underline{C}H_2CH_3)_3$), 4.5 (Si($\underline{C}H_2CH_3)_3$).

*In the same manner, 2-(3-chlorobenzoyl) analogue **7b** was synthesized.*

2-Debenzoyl-2-(3-chlorobenzoyl)-2'-triisopropylsilyl-3'-dephenyl-3'-(2-methyl-1-propyl)-7,9-ditriethylsilyl-10-dehydro-7-8-seco-docetaxel (7b): 75% yield; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (m, 1 H, 2-H_{Ar}), 8.00 (m, 1 H, 6-H_{Ar}), 7.60 (m, 1 H, 4-H_{Ar}), 7.44 (m, 1 H, 5-H_{Ar}), 6.03 (m, 1 H, 13-H), 5.57 (d, *J* = 9 Hz, 2-H), 5.30 (m, 1 H, 5-H), 4.66 (d, 1 H, NH), 4.50-4.10 (m, 2'-H, 3'-H, 20-Ha, 20-Hb), 3.70 (m, 2 H, 7-Ha, 7-Hb), 2.80-1.80 (m, 13 H, 14-Ha, 6-Ha, 14-Hb, 6-Hb, 4-Ac, 19-CH_3, 18-CH_3), 1.70-1.40 (m, 3 H, 5'-H, 4'-Ha, 4'-Hb), 1.30 (s, 9 H, Boc), 1.20 (s, 3 H, 17-CH_3), 1.13 (s, 3 H, 16-CH_3), 1.10 (m, 27 H, 7'-CH_3, 6'-CH_3, TIPS), 0.90 (m, 18 H, 2*Si($CH_2C\underline{H_3})_3$), 0.70 (m, 6 H, Si($\underline{CH_2}CH_3)_3$), 0.56 (m, 6 H, Si($\underline{CH_2}CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7 (10-C), 172.1 (1'-C), 168.8 (4-Ac), 167.0 (2-benz.), 155.8 (NCOO), 150.4 (9-C), 143.6 (11-C), 137.0 (12-C), 136.6 (4-CH_{Ar}), 135.0 (3-CH_{Ar}), 133.6 (1-C_{Ar}), 131.6 (2-CH_{Ar}), 130.2 (5-CH_{Ar}), 129.4 (6-CH_{Ar}), 125.8 (8-C), 88.5 (5-CH), 87.6 (4-C), 82.0 (1-C), 81.5 (C, Boc), 76.9 (20-CH_2), 76.5 (2-CH), 74.9 (2'-CH), 71.0 (13-CH), 61.2 (7-CH_2), 52.4 (3'-CH), 46.0 (3-CH), 43.1 (15-C), 42.4 (6-CH_2), 36.6 (14-CH_2), 28.4 (CH_3, Boc), 25.0 (6'-CH_3), 23.4 (7'-CH_3), 22.8 (17-CH_3), 22.4 (4-Ac), 21.8 (16-CH_3), 18.3 (SiCH($\underline{C}H_3)_2$), 14.7 (18-CH_3), 14.5 (19-CH_3), 12.9 (Si$\underline{C}H(CH_3)_2$), 7.2 (Si($CH_2\underline{C}H_3)_3$), 6.9 (Si($CH_2\underline{C}H_3)_3$), 6.4 (Si($\underline{C}H_2CH_3)_3$), 4.5 (Si($\underline{C}H_2CH_3)_3$).

2-Debenzoyl-2-(3-methoxybenzoyl)-2'-triisopropylsilyl-3'-dephenyl-3'-(2-methyl-1-propenyl)-7,9-bis(triethylsilyl)-10-dehydro-7-8-seco-docetaxel (8a)

LiHMDS (1.0 M in THF, 0.68 mL, 0.68 mmol) was added to a solution of **6a** (355 mg, 0.45 mmol) and *β*-lactam **1** (270 mg, 0.68 mmol) in THF cooled to -40 ^oC with a dry ice/acetone bath. After 1 h, the

reaction was quenched with 30 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted for 3 times with 20 mL of EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Column chromatography of the residue on silica gel (hexanes/EtOAc= 15/1 to 5/1) afforded **8a** as a white solid in 71 % yield: ^{1}H NMR (400 MHz $CDCl_3$) δ 7.60 (m, 2 H, 6, 2–H_{Ar}), 7.32 (m, 1 H, 5-H_{Ar}), 7.10 (m, 1 H, 4–H_{Ar}), 6.05 (m, 1 H, 13-H), 5.60 (d, 1 H, *J* = 9 Hz, 2-H), 5.30 (d, 1 H, *J* = 9 Hz, 5-H), 4.80 (m, 3 H, NH, 4'-H, 20-Ha), 4.40-4.10 (m, 4 H, 2'–H, 3-H, 20-Hb, 3'-H), 3.85 (s, 3 H, OMe), 3.70 (bs, 2 H, 7-Ha, 7-Hb), 2.40 (bs, 2 H, 14-Ha, 6-Ha), 2.20-1.70 (m, 11 H, 14-Hb, 6-Hb, 4-Ac, 18-CH_3, 19-CH_3), 1.31 (s, 9 H, Boc), 1.20 (s, 3 H, 17-CH_3), 1.13 (s, 3 H, 16-CH_3), 1.08 (m, 27 H, 6'-CH_3, 7'-CH_3, TIPS), 0.90 (m, 18 H, 2*Si($CH_2C\underline{H_3}$)$_{\underline{3}}$), 0.70 (m, 6 H, Si($\underline{CH_2}CH_3$)$_{\underline{3}}$), 0.60 (m, 6 H, Si($\underline{CH_2}CH_3$)$_{\underline{3}}$); ^{13}C NMR (100 MHz $CDCl_3$) δ 191.9 (10-C), 171.7 (1'-C), 169.0 (4-Ac), 167.5 (2-benz.), 159.9 (3-C_{Ar}), 155.4 (NCOO), 149.0 (9-C), 144.4 (11-C), 137.0 (12-C), 135.7 (4'-C), 131.0 (1-C_{Ar}), 129.9 (5-CH_{Ar}), 124.6 (8-C), 122.9 (6-CH_{Ar}), 122.1 (5'-C), 119.9 (4-CH_{Ar}), 114.9 (2-CH_{Ar}), 87.5 (5-CH), 85.8 (4-C), 80.6 (1-C), 79.6 (C, Boc), 75.5 (20-CH_2), 74.9 (2-CH), 73.8 (2'-CH), 71.3 (13-CH), 60.0 (7-CH_2), 55.6 (OMe), 52.6 (3'-CH), 44.6 (3-CH), 43.1 (15–C), 37.7 (6-CH_2), 36.6 (14-CH_2), 28.4 (CH_3, Boc), 25.8 (17-CH_3), 22.5 (6'-CH_3), 22.4 (4-Ac), 21.9 (16-CH_3), 18.6 (SiCH($\underline{C}H_3$)$_2$), 14.8 (18-CH_3), 13.0 (19-CH_3), 12.7 (Si$\underline{C}$H(CH_3)$_2$), 7.2 (Si($CH_2\underline{C}H_3$)$_3$), 6.9 (Si($CH_2\underline{C}H_3$)$_3$), 6.4 (Si($\underline{C}H_2CH_3$)$_3$), 4.5 (Si($\underline{C}H_2CH_3$)$_3$).

*In the same manner, 2-(3-chloro- and fluorobenzoyl) analogues **8b** and **8c** were synthesized.*

2-Debenzoyl-2-(3-chlorobenzoyl)-2'-triisopropylsilyl-3'-dephenyl-3'-(2-methyl-1-propenyl)-7,9-ditriethylsilyl-10-dehydro-7-8-seco-docetaxel (8b): 74% yield; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (m, 1 H, 2-H_{Ar}), 8.00 (m, 1 H, 6-H_{Ar}), 7.63 (m, 1 H, 4-H_{Ar}), 7.44 (m, 1 H, 5-H_{Ar}), 6.10 (m, 1 H, H-13), 5.64 (d, 1 H, *J* = 9 Hz, 2-H), 5.40 (m, 2 H, *J* = 8 Hz, 5-H, 20-Ha), 5.00 (m, 3 H, 3'-H, 4'-H, NH), 4.40-4.20 (bs, 3 H, 2'-H, 20-Hb, 3-H), 3.8 (m, 2 H, 7-Ha, 7-Hb), 2.60-2.20 (m, 4 H, 6-Ha, 6-Hb, 14-Ha, 14-Hb), 1.85 (m, 6 H, 19-CH_3, 4-Ac), 1.79 (s, 3 H, 18-CH_3), 1.39 (s, 9 H, Boc), 1.28 (s, 3 H, 17-CH_3), 1.20 (s, 16-CH_3), 1.15 (m, 21 H, TIPS), 0.90 (m, 24 H, 7'-CH_3, 6'-CH_3, 2*Si($CH_2C\underline{H_3}$)$_{\underline{3}}$), 0.80 (m, 6 H, Si($\underline{CH_2}CH_3$)$_{\underline{3}}$), 0.60 (m, 6 H, Si($\underline{CH_2}CH_3$)$_{\underline{3}}$).

2-Debenzoyl-2-(3-fluorobenzoyl)-2'-triisopropylsilyl-3'-dephenyl-3'-(2-methylprop-1-enyl)-7,9-ditriethylsilyl-10-dehydro-7-8-seco-docetaxel (8c): 78% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (m, 6 H), 0.75 (m, 6 H), 0.89 (m, 9 H), 0.95 (m, 9 H), 1.04 (m, 4 H), 1.13 (s, 2 H), 1.21 (s, 2 H), 1.26 (m, 2 H), 1.32 (s, 9 H), 1.73 (s, 2 H), 1.79 (m, 6 H), 3.71 (m, 2 H), 4.15 (m, 1 H), 4.39 (s, 1 H), 4.82 (m, 1 H), 4.88 (m, 1 H), 5.31 (d, *J* = 8.4 Hz, 1 H), 5.59 (d, *J* = 9.2 Hz, 1 H), 6.02 (m, 1 H), 7.23 (m, 1 H), 7.39 (m, 1 H), 7.75 (m, 1 H), 7.86 (m, 1 H).

Synthesis of 2-debenzoyl-2-(3-methoxybenzoyl)-3'-dephenyl-3'-(2-methylprop-1-enyl)-10-dehydro-7-8-seco-docetaxel (SB-CST-10201).

To an acetonitrile/pyridine solution (1/1, 17 mL) of **8a** (417 mg, 0.35 mmol) was added HF/pyridine (70%, 4.2 mL) dropwise at 0 ^{o}C in an ice/water bath. The mixture was stirred at 0 ^{o}C for 1 h and then at room temperature overnight. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 35 mL). The aqueous layers were extracted with ethyl acetate, and the combined organic layers were washed with saturated aqueous $CuSO_4$ (2 × 40 mL) and brine (20 mL), and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by purification of the crude product by flash chromatography on silica gel (hexane/EtOAc = 3/1 to 1/1) afforded **SB-CST-10201** (202 mg, 71% yield) as a white solid: m.p. 147-149 °C; $[\alpha]^{20}_D$ -26.90 ($CHCl_3$, c 2.12); ^{1}H NMR (500 MHz $CDCl_3$) δ 7.60 (m, 1 H, 6-H_{Ar}), 7.50 (m, 1 H, 2-H_{Ar}), 7.40 (t, 1 H, *J* = 8 Hz, 5-H_{Ar}), 7.15 (ddd, 1 H, *J* = 1.2, 3, 8 Hz, 4-H_{Ar}), 6.48 (s, 1 H, 9-OH), 6.18 (m, 1 H, 13-H), 5.61 (d, 1 H, *J* = 9 Hz, 2-H), 5.25 (m, 2 H, 5-H, 20-Ha), 4.95 (m, 1 H, NH), 4.80 (m, 1 H, 4'-H), 4.40-4.10 (m, 3 H, 2'-H, 3'-H, 20-Hb),

3.90 (m, 1 H, 7-Ha), 3.85 (s, 3 H, OMe), 3.75 (m, 1 H, 7-Hb), 2.80 (m, 1 H, 14-Ha), 2.60 (m, 1 H, 6-Ha), 2.45 (dd, 1 H, J = 9, 15 Hz, 14-Hb), 2.20 (m, 2 H, 6-Hb, OH), 1.87 (m, 9^{13}C NMR (125 MHz $CDCl_3$) δ 191.8 (10-C), 172.8 (1'-C), 170.0 (4-Ac), 167.7 (2-benz.), 160.5 (3-C_{Ar}), 156.2 (NCOO), 149.0 (9-C), 142.7 (11-C), 137.1 (12-C), 136.5 (4'-CH), 131.3 (1-C_{Ar}), 130.6 (5-CH_{Ar}), 125.0 (8-C), 122.4 (5'-C), 121.5 (6-CH_{Ar}), 120.0 (4-CH_{Ar}), 115.2 (2-CH_{Ar}), 87.5 (5-CH), 86.7 (4-C), 81.0 (1-C), 80.7 (C, Boc), 75.5 (20-CH_2), 75.4 (2-CH), 71.7 (2'-CH), 71.6 (13-CH), 60.3 (7-CH_2), 56.1 (OMe), 52.0 (3'-CH), 45.5 (3-CH), 43.2 (15-C), 39.1 (6-CH_2), 37.2 (14-CH_2), 28.9 (CH_3, Boc), 26.4 (6'-CH_3), 25.4 (7'-CH_3), 22.8 (16-CH_3), 21.8 (4-Ac), 15.3 (17-CH_3), 15.0 (18-CH_3), 14.8 (19-CH_3). MS-ES$^+$ (*m/z*) calcd for $C_{42}H_{57}NO_{15}H^+$ 816.37; found 816.4. HRMS (ES$^+$, *m/z*) calcd. for $C_{42}H_{57}NO_{15}H^+$, 816.3806; Found, 816.3777 (Δ = 3.5 ppm).

In the same manner, C-seco-taxoids, ***SB-CST-10101****,* ***SB-CST-10102****,* ***SB-CST-10104****;* ***SB-CST-10202*** *and* ***SB-CST-10204****, were synthesized.*

2-Debenzoyl-2-(3-methoxybenzoyl)-3'-dephenyl-3'-(2-methyl-1-propyl)-10-dehydro-7-8-seco-docetaxel (**SB-CST-10101**): 76% yield; white solid**;** m.p. 147-145 °C; $[\alpha]^{20}_D$ -28.80 ($CHCl_3$, c 1.98); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.60 (m, 1 H, 6-H_{Ar}), 7.50 (m, 1 H, 2-H_{Ar}), 7.40 (t, 1 H, J = 8 Hz, 5-H_{Ar}), 7.15 (ddd, 1 H, J = 1.2, 3, 8 Hz, 4-H_{Ar}), 6.48 (s, 1 H, 9-OH), 6.17 (m, 1 H, 13-H), 5.58 (d, 1 H, J = 9 Hz, 2-H), 5.20 (m, 2 H, 5-H, 20-Ha), 4.80 (bs, 1 H, NH), 4.40 (m, 1 H, 3-H), 4.30-4.05 (m, 4 H, 20-Hb, 2'-H, 3'-H), 3.90 (m, 1 H, 7-Ha), 3.80 (s, 3 H, OMe), 3.70 (m, 1 H, 7-Hb), 3.40 (bs, 1 H, 2'-OH), 2.80 (m, 1 H, 14-Ha), 2.48 (m, 1 H, 6-Ha), 2.40 (dd, 1 H, J = 15, 9 Hz, 14-Hb), 2.24 (m, 1 H, OH), 2.10 (m, 1 H, 6-Hb), 1.88 (s, 3 H, 4-Ac), 1.82 (s, 3 H, 18-CH_3), 1.78 (s, 3 H, 19-CH_3), 1.70 (m, 1 H, 5'-H), 1.60 (m, 1 H, 4'-Ha), 1.40 (m, 1 H, 4'-Hb), 1.30 (s, 9 H, Boc), 1.20 (m, 4 H, OH, 17-CH_3), 1.08 (s, 3 H, 16-CH_3), 0.95 (d, 6H, J = 6 Hz, 6'-CH_3, 7'-CH_3); ^{13}C NMR (100 MHz $CDCl_3$) δ 191.4 (10-C), 173.4 (1'-C), 169.3 (4-Ac), 167.4 (2–benz.), 160.0 (3-C_{Ar}), 156.1 (NCOO), 149.0 (9-C), 142.4 (11-C), 137.1 (12-C), 130.9 (1-C_{Ar}), 130.3 (5-CH_{Ar}), 124.6 (8-C), 122.1 (6-CH_{Ar}), 119.8 (4-CH_{Ar}), 114.9 (2-CH_{Ar}), 87.5 (5-CH), 86.3 (4-C), 80.6 (1-C), 80.2 (C, Boc), 75.2 (20-CH_2), 75.1 (2-CH), 73.8 (2'-CH), 70.6 (13-CH), 60.0 (7-CH_2), 55.7 (OMe), 51.7 (3'-CH), 44.6 (3-CH), 43.2 (15–C), 40.9 (4'-CH_2), 37.7 (6-CH_2), 36.7 (14-CH_2), 28.4 (CH_3, Boc), 25.1 (5'-CH), 23.4 (17-CH_3), 22.4 (6'-CH_3), 22.4 (7'-CH_3), 22.3 (4-Ac), 21.4 (16-CH_3), 15.0 (18-CH_3), 14.6 (19-CH_3). MS-ES$^+$ (*m/z*) calcd for $C_{42}H_{59}NO_{15}H^+$ 818.4; found 818.5. HRMS (ES$^+$, *m/z*) calcd. for $C_{42}H_{59}NO_{15}H^+$, 818.3963; Found, 818.3931 (Δ = 3.9 ppm).

2-Debenzoyl-2-(3-chlorobenzoyl)-3'-dephenyl-3'-(2-methyl-1-propyl)-10-dehydro-7-8-seco-docetaxel (SB-CST-10102): 80% yield; white solid**;** mp. 138-140 °C; $[\alpha]^{20}_D$ -18.70 ($CHCl_3$, c 0.91); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.96 (m, 2 H, 2-H_{Ar}, 6-H_{Ar}), 7.58 (d, 1 H, J = 8 Hz, 4-H_{Ar}), 7.42 (t, J = 8 Hz, 5-H_{Ar}), 6.47 (9-OH), 6.20 (13-H), 5.58 (d, J = 9.6 Hz, 2-H), 5.20 (m, 2 H, 5-H, 20-Ha), 4.80 (m, 1 H, NH), 4.40-4.10 (m, -Hb, 2'-H, 3'-H), 3.90 (m, 1 H, 7-Hb), 3.70 (m, 1 H, 7-Hb), 3.20 (2'-OH), 2.80 (m, 1 H, 14-Ha), 2.55 (m, 1 H, 14-Hb), 2.40 (m, 1 H, 6-Hb), 2.10 (s, 3 H, 4-Ac), 1.88 (s, 3 H, 18-CH_3), 1.82 (s, 4 H, 6-Hb, 19-CH_3), 1.65 (m, 1 H, 5'-H), 1.60 (m, 1 H, 4'-Ha), 1.40 (m, 1 H, 4'-Hb), 1.33 (s, 9 H, Boc), 1.09 (s, 6 H, 16-CH_3, 17-CH_3), 0.96 (s, 3 H, 6'-CH_3), 0.95 (s, 3 H, 7'-CH_3); ^{13}C NMR (100 MHz $CDCl_3$) δ 191.3 (10-C), 173.5 (1'-C), 169.1 (4-Ac), 166.3 (2-benz.), 156.0 (NCOO), 149.0 (9-C), 142.3 (11-C), 137.0 (12-C), 135.3 (4-CH_{Ar}), 134.0 (3-C_{Ar}), 131.3 (1-C_{Ar}), 130.6 (2-CH_{Ar}), 129.8 (5-CH_{Ar}), 128.0 (6-CH_{Ar}), 124.3 (8-C), 87.5 (5-CH), 86.4 (4-C), 80.5 (1-C), 79.9 (C, Boc), 75.5 (20-CH_2), 75.0 (2-CH), 73.6 (2'-CH), 79.6 (13-CH), 60.0 (7-CH_2), 51.6 (3'-CH), 44.6 (3-CH), 43.2 (15-C), 41.0 (4'-CH_2), 37.6 (6-CH_2), 36.7 (14-CH_2), 28.4 (CH_3, Boc), 25.1 (5'-CH), 23.4 (17-CH_3), 22.4 (7'-CH_3, 6'-CH_3, 4-Ac), 21.4 (16-CH_3), 15.0 (18-CH_3), 14.6 (19-CH_3). HRMS (ES$^+$, *m/z*) calcd. for $C_{41}H_{56}NO_{14}ClH^+$, 822.3468; Found, 822.3452 (Δ = 1.9 ppm).

2-Debenzoyl-2-(3-fluorobenzoyl)-3'-dephenyl-3'-(2-methyl-1-propyl)-10-dehydro-7-8-seco-docetaxel (SB-CST-10104): 75% yield; white solid; mp. 139-141 °C; $[\alpha]^{20}_{D}$ -20.10 ($CHCl_3$, c 1.44); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.90 (m, 1 H, 6-H_{Ar}), 7.78 (m, 1 H, 2-H_{Ar}), 7.56 (m, 1 H, 4-H_{Ar}), 7.41 (m, 1 H, 5-H_{Ar}), 6.58 (s, 1 H, 9-OH), 6.20 (m, 1 H, 13-H), 5.50 (d, 1 H, *J* = 9 Hz, 2-H), 5.20 (m, 2 H, 5-H, 20-Ha), 4.80 (m, 1 H, NH), 4.40-4.05 (m, 4 H, 20-Hb, 2'-H, 3'-H, 3-H), 3.90 (m, 1 H, 7-Ha), 3.65 (m, 1 H, 7-Hb), 2.80 (m, 1 H, 14-Ha), 2.50 (m, 2 H, 14-Hb, 6-Ha), 1.90 (m, 9 H, 4-Ac, 18-CH_3, 19-CH_3), 1.70 (m, 1 H, 5'-H), 1.60 (m, 1 H, 4'-Ha), 1.40 (m, 1 H, 4'-Hb), 1.30 (s, 9 H, Boc), 1.21 (s, 3 H, 16-CH_3), 1.10 (s, 3 H, 17-CH_3), 0.96 (m, 6 H, 7'-CH_3, 6'-CH_3); ^{13}C NMR (100 MHz $CDCl_3$) δ 191.3 (10-C), 173.5 (1'-C), 171.4 (4-Ac), 166.3 (2-benz.), 163.0 (d, J_{CF} = 246 Hz, CF), 156.0 (NCOO), 149.0 (9-C), 142.3 (11-C), 137.2 (12-C), 131.8 (d, J_{CF} = 7 Hz, 1-C_{Ar}), 130.8 (5-CH_{Ar}), 125.6 (8-C), 124.4 (6-CH_{Ar}), 121.2 (d, J_{CF} = 21 Hz, 4-CH_{Ar}), 116.7 (2-CH_{Ar}), 87.5 (5-CH), 86.4 (4-C), 80.5 (1-C), 80.0 (C, Boc), 75.5 (20-CH_2), 75.4 (2-CH), 73.6 (2'-CH), 70.6 (13-CH), 60.6 (7-CH_2), 51.6 (3'-CH), 44.6 (3-CH), 43.1 (15-C), 41.0 (4'-CH_2), (4'-CH_2), 37.7 (6-CH_2), 36.8 (14-CH_2), 28.3 (CH_3, Boc), 25.0 (5'-CH), 23.3 (17-CH_3), 22.3 (7'-CH_3, 6-CH_3), 21.3 (4-Ac), 21.2 (16-CH_3), 15.0 (18-CH_3), 14.4 (19-CH_3). MS-ES$^+$ (*m*/*z*):calcd for $C_{41}H_{56}FNO_{14}H^+$ 806.37; found 806.4.

2-Debenzoyl-2-(3-chlorobenzoyl)-3'-dephenyl-3'-(2-methylprop-1-enyl)-10-dehydro-7-8-seco-docetaxel (SB-CST-10202): 70 % yield; white solid; mp 159-161 °C; $[\alpha]_D^{21}$ -25.0 (c 1.16 $CHCl_3$); ^{1}H NMR (400 MHz $CDCl_2CDCl_2$, 70 °C) δ 7.99 (m, 1 H, 2-H_{Ar}), 7.93 (d, 1 H, *J* = 8 Hz, 6-H_{Ar}), 7.61 (m, 1 H, 4-H_{Ar}), 7.42 (d, 1 H, *J* = 8 Hz, 5-H_{Ar}), 6.15 (m, 1 H, 13-H), 5.59 (d, 1 H, *J* = 9 Hz, 2-H), 5.30 (d, 1 H, *J* = 8 Hz, 5-H), 5.17 (bd, 1 *J* = 10 Hz, NH), 4.90 (d, 1 H, *J* = 9 Hz, 20-Ha), 4.79 (ddd, 1 H, *J* = 3, 9, 9 Hz, 3'-H), 4.36 (bs, 1 H, 3-H), 4.31 (d, 1 H, *J* = 8 Hz, 20-Hb), 4.27 (d, 1 H, *J* = 3 Hz, 2'-H), 3.85 (m, 1 H, 7-Ha), 3.66 (m, 1 H, 7-Hb), 2.85 (bs, 1 H, 14-Ha), 2.48 (dd, 1 H, *J* = 9, 15 Hz, 14-Hb), 2.40 (bs, 1 H, 6-Ha), 2.05 (s, 3 H, 4-Ac), 2.00 (m, 1 H, 6-Hb), 1.95 (s, 3 H, 19-CH_3), 1.77 (d, 3 H, *J* = 1.2 Hz, 18-CH_3), 1.37 (s, 9 H, Boc), 1.27 (m, 9 H, 17-CH_3, 6'-CH_3, 7'-CH_3), 1.12 (s, 3 H, 16-CH_3);

^{13}C NMR (100 MHz $CDCl_2CDCl_2$, 25 °C) δ 192.7 (10-C), 174.0 (1'-C), 170.6 (4-Ac), 167.5 (2-benz.), 157.4 (NCOO), 150.4 (9-C), 143.6 (11-C), 140.0 (12-C), 138.6 (4'-C), 136.6 (4-CH_{Ar}), 135.6 (3-C_{Ar}), 132.6 (1-C_{Ar}), 132.1 (2-CH_{Ar}), 130.9 (5-CH_{Ar}), 129.4 (6-CH_{Ar}), 125.8 (8-C), 122.5 (5'-C), 88.5 (5-CH), 87.7 (4-C), 82.0 (1-C), 81.7 (C, Boc), 76.9 (20-CH_2), 76.5 (2-CH), 71.7 (2'-CH), 71.6 (13-CH), 61.2 (7-CH_2), 53.1 (3'-CH), 46.0 (3-CH), 44.5 (15-C), 39.1 (6-CH_2), 38.3 (14-CH_2), 29.9 (CH_3, Boc), 27.4 (6'-CH_3), 26.4 (7'-CH_3), 23.8 (17-CH_3), 22.8 (4-Ac), 20.4 (16-CH_3), 16.4 (18-CH_3), 16.1 (19-CH_3). HRMS (ES$^+$, *m/z*): Calcd. for $C_{41}H_{54}NO_{14}ClH^+$, 820.3311; Found, 820.3316 (Δ = 0.6 ppm).

2-Debenzoyl-2-(3-fluorobenzoyl)-3'-dephenyl-3'-(2-methylprop-1-enyl)-10-dehydro-7-8-seco-docetaxel (SB-CST-10204): 73% yield; white solid; mp 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 4 H), 1.21 (s, 4 H), 1.25 (s, 3 H), 1.34 (s, 9 H), 1.44 (m, 1 H), 1.73 (m, 8 H), 1.85 (m, 8 H), 2.09 (m, 3 H), 2.45 (m, 2 H), 2.80 (m, 1 H), 3.67 (m, 1 H), 3.88 (s, 1 H), 4.24 (d, *J* = 4.0 Hz, 1 H), 4.28 (d, *J* = 7.6 Hz, 1 H), 4.76 (m, 1 H), 4.98 (s, 1 H), 5.18 (m, 2 H), 5.26 (d, *J* = 9.0 Hz, 1 H), 5.59 (d, *J* = 7.0 Hz, 1 H), 6.14 (m, 1 H), 6.50 (s, 1 H), 7.31 (dt, *J* = 10.5 Hz, 3.5 Hz, 1 H), 7.45 (m, 1 H), 7.67 (d, *J* = 7.2 Hz, 1 H), 7.80 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100.5 MHz, CDCl3) δ 10.0, 14.1, 14.7, 18.6, 21.1, 22.1, 22.6, 25.7, 28.2, 29.6, 31.5, 36.5, 42.9, 51.4, 59.5, 70.1, 74.5, 75.2, 79.9, 86.1, 116.6, 120.8, 121.0, 124.1 125.2, 130.7, 131.5, 131.6, 142.0, 148.8, 155.7, 157.9, 161.4, 163.9, 166.0, 169.0, 172.4, 191.1, 202.4. HRMS (FAB/DCM/NaCl) m/z calcd. for $C_{41}H_{54}FNO_{14}H^+$ 804.3607; found 804.3605 (Δ = -0.2 ppm).

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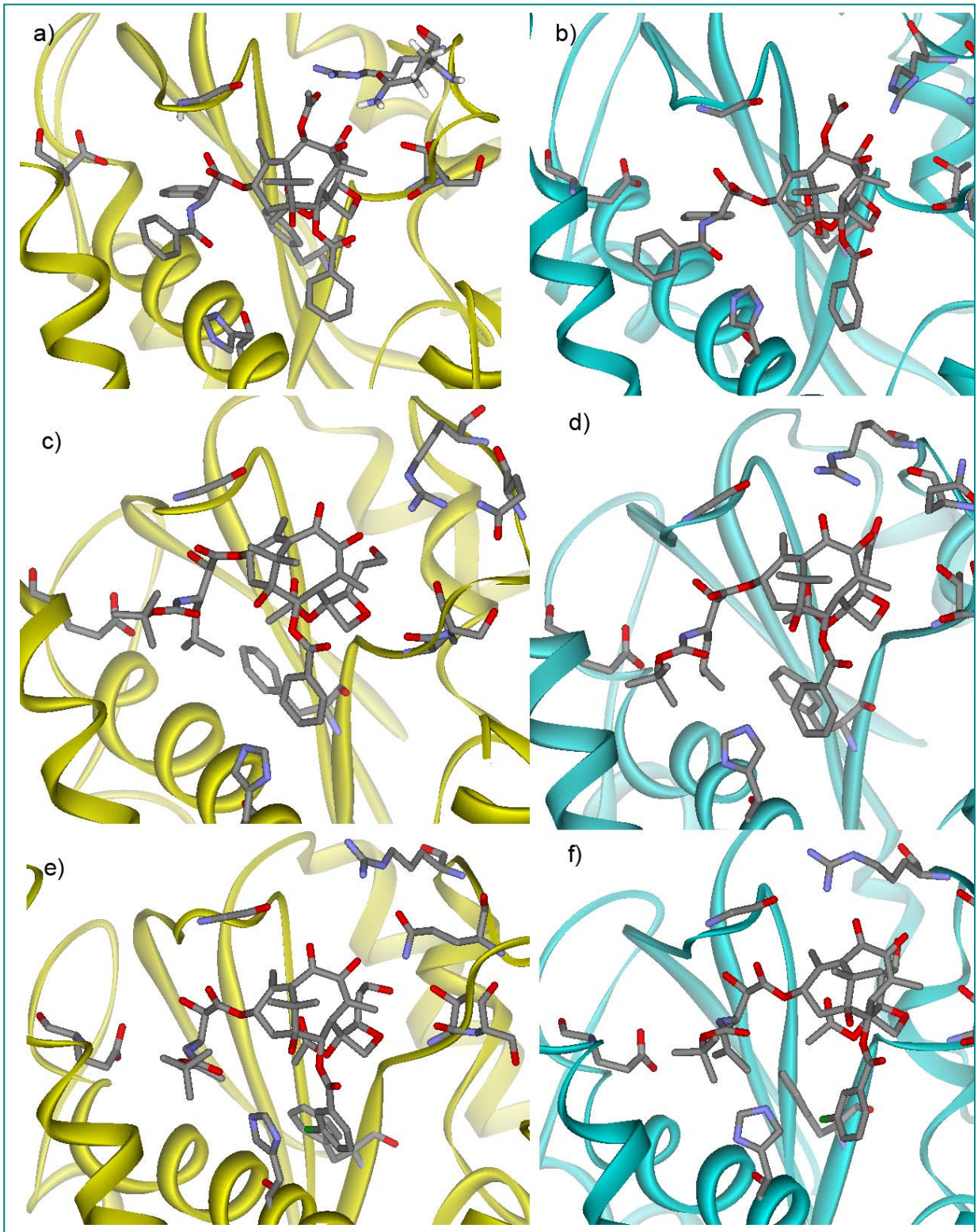

Figure S1. Snapshots of paclitaxel (a,b), **IDN-5390** (c,d) and **SB-CST-10202** (e,f) in TBB1 (a,c,e) and TBB3 (b,d,f)