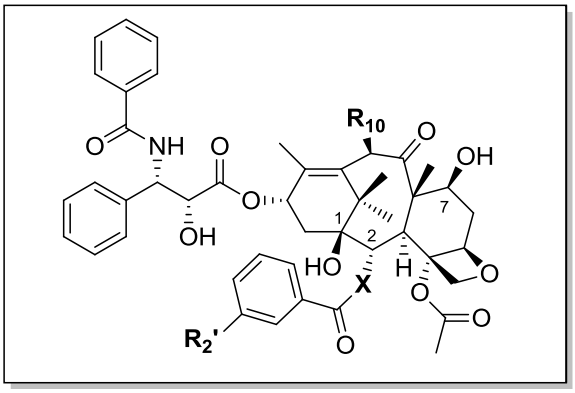
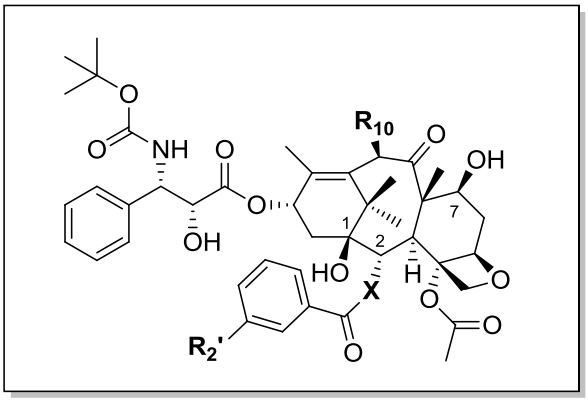
Electronic Supporting Information

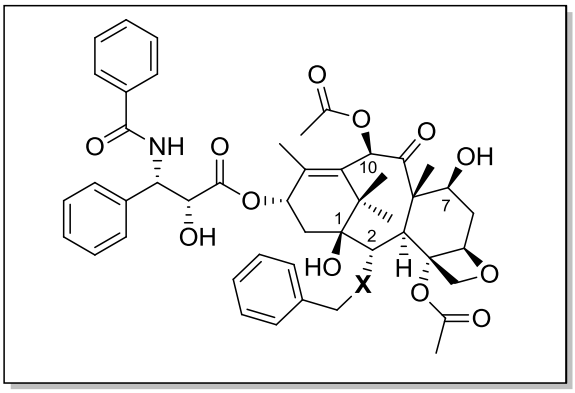
Scheme S1. Chemical structures of the training set of taxanes (from ref. 8 in the main text).



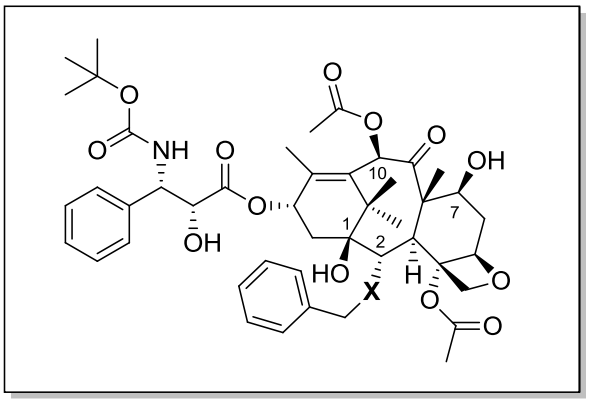
	R_2'	R_{10}	X
PXL	H	$OCOCH_3$	O
CTX11	OCH_3	$OCOCH_3$	O
CTX12	N_3	$OCOCH_3$	O
CTX15	H	OH	O
CTX23	H	$OCOCH_3$	S



	R_2'	R_{10}	X
DXL	H	OH	O
CTX21	H	$OCOCH_3$	O
CTX22	H	$OCOCH_3$	S
CTX40	N_3	$OCOCH_2CH_3$	O
CTX42	H	$OCOCH_3$	NH
CTX43	OCH_3	$OCOCH_3$	NH
CTX44	Cl	$OCOCH_3$	NH

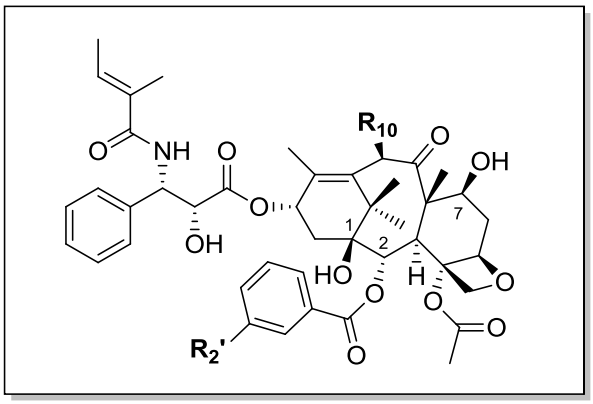


	X
CTX25	O
CTX27	S
CTX38	NH

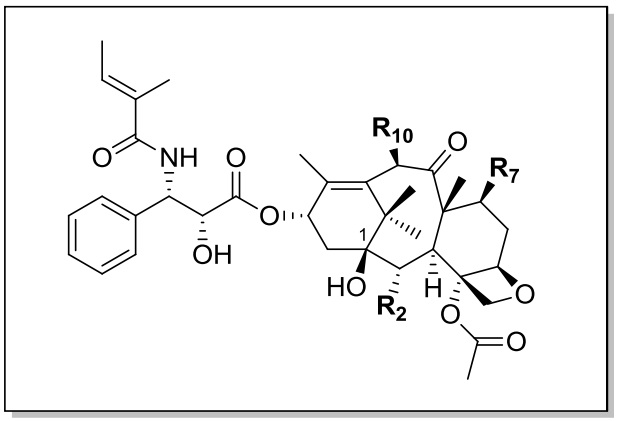


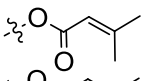
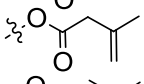
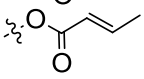
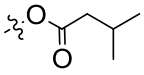
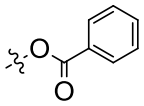
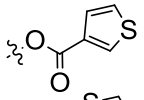
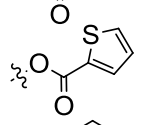
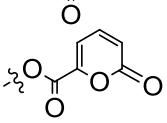
	X
CTX24	O
CTX26	S
CTX39	NH

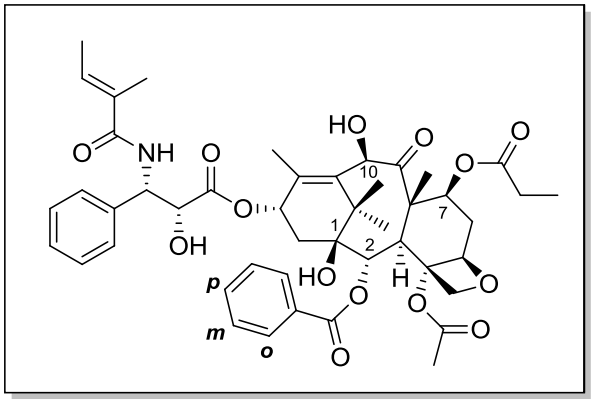
Scheme S1 (continued).



	R_2'	R_{10}
CPM	H	$OCOCH_3$
CTX13	OCH_3	$OCOCH_3$
CTX14	N_3	$OCOCH_3$
CTX18	H	$OCOCH_2CH_3$
CTX19	OCH_3	$OCOCH_2CH_3$
CTX20	N_3	$OCOCH_2CH_3$
CTX37	OH	$OCOCH_2CH_3$



	R_2	R_7	R_{10}
CTX2		$OCOCH_2CH_3$	OH
CTX3		$OCOCH_2CH_3$	OH
CTX9		$OCOCH_2CH_3$	OH
CTX10		$OCOCH_2CH_3$	OH
CTX17		OH	$OCOCH_3$
CTX31		$OCOCH_2CH_3$	OH
CTX32		$OCOCH_2CH_3$	OH
CTX41		$OCOCH_2CH_3$	OH



	o	*m*	*p*		*o*	*m*	*p*
CTX1	H	H	H	**CTX28**	F	H	F
CTX4	H	N_3	H	**CTX29**	Cl	H	Cl
CTX5	H	OCH_3	H	**CTX30**	H	I	H
CTX6	H	Cl	H	**CTX33**	H	CHO	H
CTX7	H	CN	H	**CTX34**	H	Br	H
CTX8	H	CH_3	H	**CTX35**	H	OCH_3	OCH_3
				CTX36	H	CH_2OH	H

CTX16

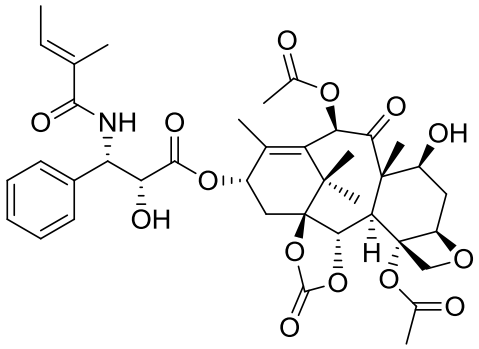


Table S1. Selected PLS pseudocoefficients (absolute value ≥ |0.1|) for the energy terms that contribute the most to explaining the predicted binding free energy differences in the exploratory COMBINE model derived from the original series (Figure 3 in the main text).

Residue	vdW	Ele	Residue	vdW	Ele
Lys19		0.11	Phe272	0.60	
Glu22	-0.1	0.16	Pro274	0.1	
Val23	0.15		Leu275	0.24	
Asp26	0.30		Thr276	-0.1	0.1
Glu27		0.14	Arg278		0.31
Cys213	-0.21		Gln282	-0.1	0.1
Leu217	-0.33		Pro360	0.1	-0.1
Leu219	-0.26		Arg369	0.1	
Asp226	0.25	-0.49	Gly370	-0.23	-0.15
His229	0.55	0.50	WAT2	-0.52	0.62
Leu230	0.14				
Ala233	0.48		DesolvL		-0.16

The computational studies were undertaken considering a pH of 6.5 for the calculation of the protonation state of ionizable groups in β-tubulin to mimic the experimental conditions (ref. 8). At this pH the side-chain imidazole of His229 (found in the middle of helix 7 and positionally equivalent to Arg229 in α-tubulin) is likely to be protonated on both Nδ and Nε giving rise to (i) a MEP in the taxane-binding site that is quite distinct from that obtained with a neutral imidazole side chain (ref. 8), and (ii) different hydrogen-bonding possibilities.

To consider an alternative scenario, we also refined the whole set of complexes with a β-tubulin in which His229 was protonated exclusively on Nε. The corresponding COMBINE model (Figure S1) turned out to be of inferior quality (average r^2 and q^2 over 10 runs of 0.75±0.02 and 0.63±0.02, respectively, using 2±1 LV) and was unable to predict accurately the binding free energy of CTX40 when this compound was taken out of the training set. The largest change in the PLS pseudocoefficients affected precisely the electrostatic interaction energy with His229 (Table S2).

From this comparison we surmise that His229 is indeed more likely to be protonated of both imidazole nitrogens.

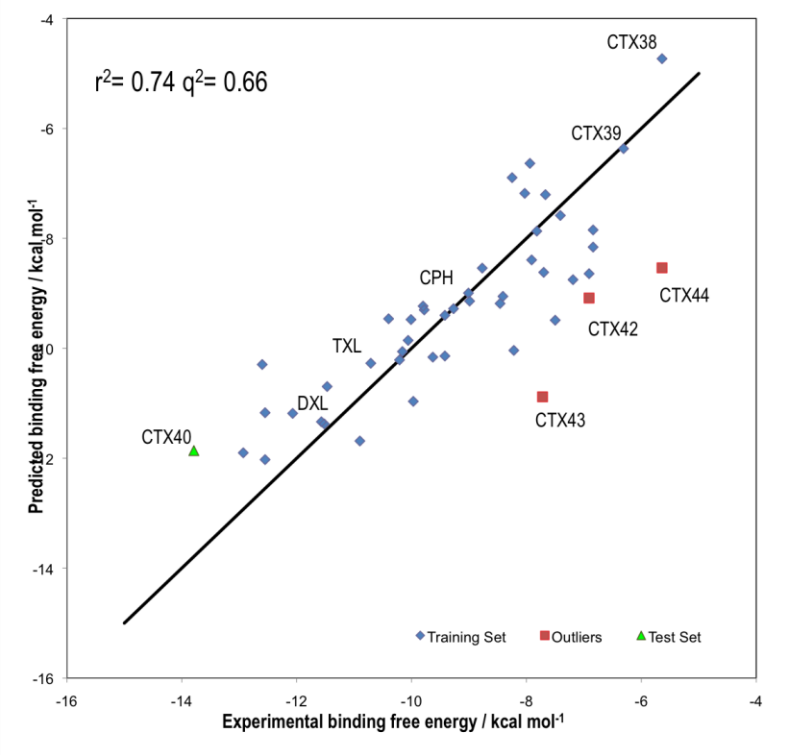


Figure S1. Correlation between the binding free energies calculated in the cross-validated COMBINE model generated from complexes in which β-tubulin was built with a neutral His229 and the experimental values for compounds in the original training set (◆) upon exclusion of the three outliers (■). This model, with only 2 LV and worse quality than that presented in Figure 3 in the main text, fails to accurately predict the affinity of **CTX40** (▲), which was not included in model derivation.

Table S2. Selected PLS pseudocoefficients (absolute value ≥ |0.1|) for the energy terms that contribute the most to explaining the predicted binding free energy differences in the COMBINE model generated from complexes in which β-tubulin was built with a neutral His229.

Residue	vdW	Ele	Residue	vdW	Ele
Glu22		-0.1	Leu230	0.27	
Val23	-0.1		Ala233	0.1	
Asp26	0.1	-0.16	Phe272	0.23	
Glu27		0.1	Leu275	0.19	
Leu217	-0.12		Arg278		0.1
Leu219	-0.1		Arg369		0.12
Asp226	0.1	-0.39	WAT2	-0.15	0.13

His229	0.64	DesolvR	0.13

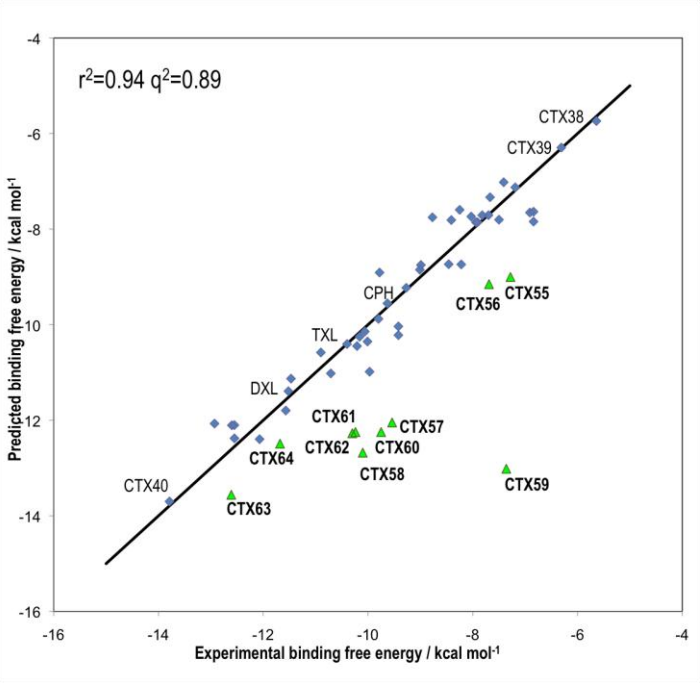


Figure S2. Correlation between the binding free energies calculated in the cross-validated COMBINE model (5 LV) and the experimental values for compounds in the training set (◆) and an external set consisting of the newly synthesized taxanes (▲).

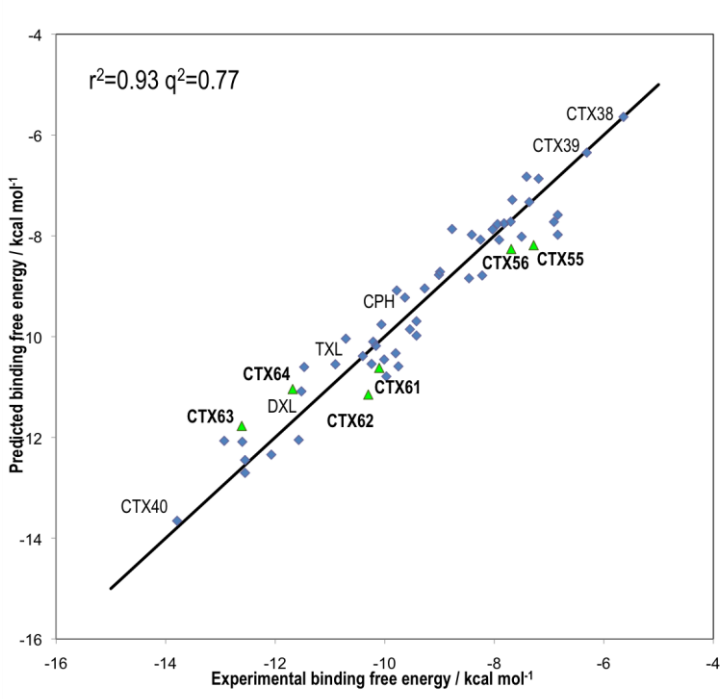


Figure S3. Correlation between calculated and experimental binding free energies in the updated COMBINE model that now includes in the training set (◆) the 3'N-substituted derivatives **CTX57** to **CTX60** and correctly predicts the external set (▲) consisting of the fourth 3'N derivative **CTX61**, the new C2-substituted taxanes **CTX55** and **CTX56**, and the C3'-substituted analogs **CTX62** to **CTX64**.

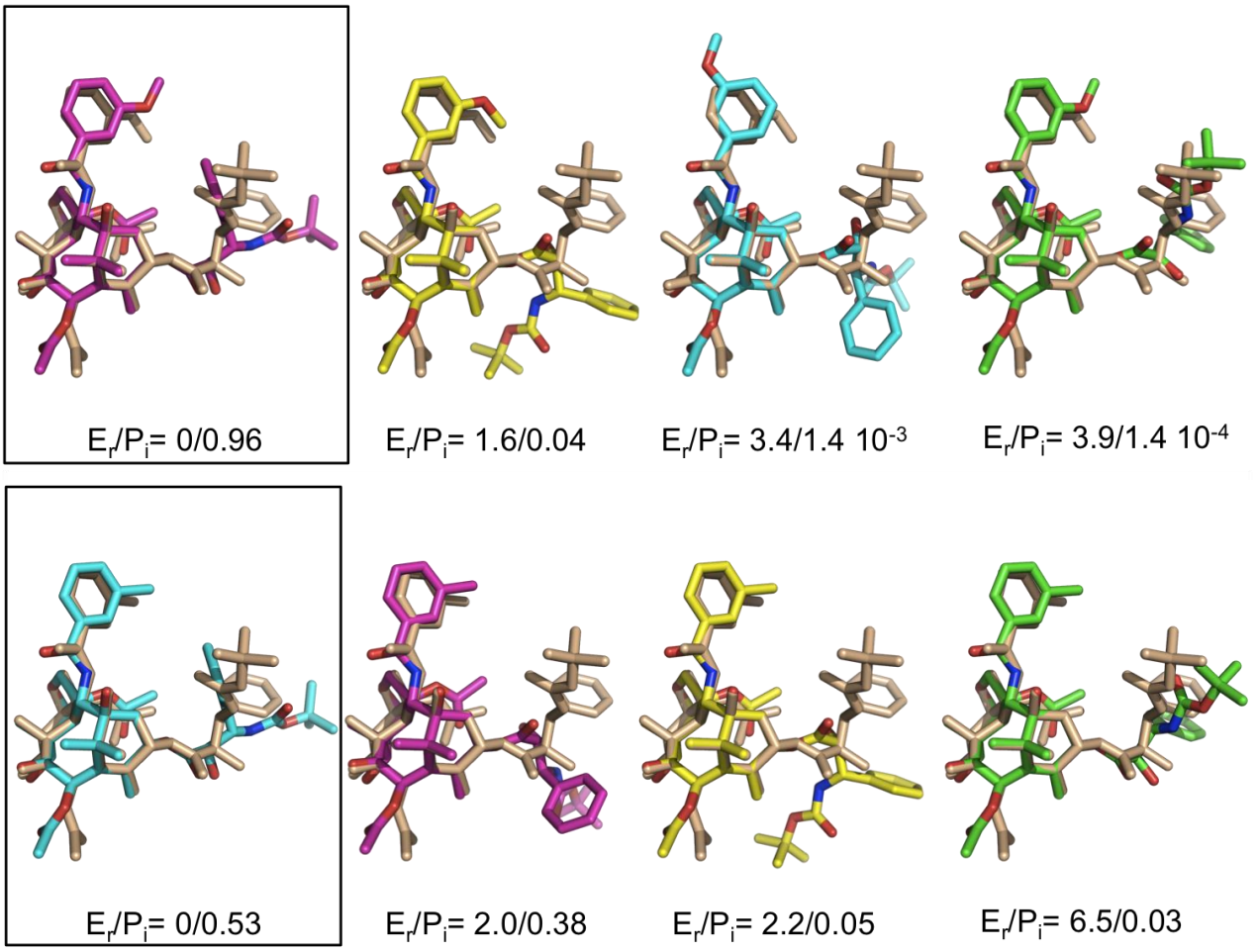


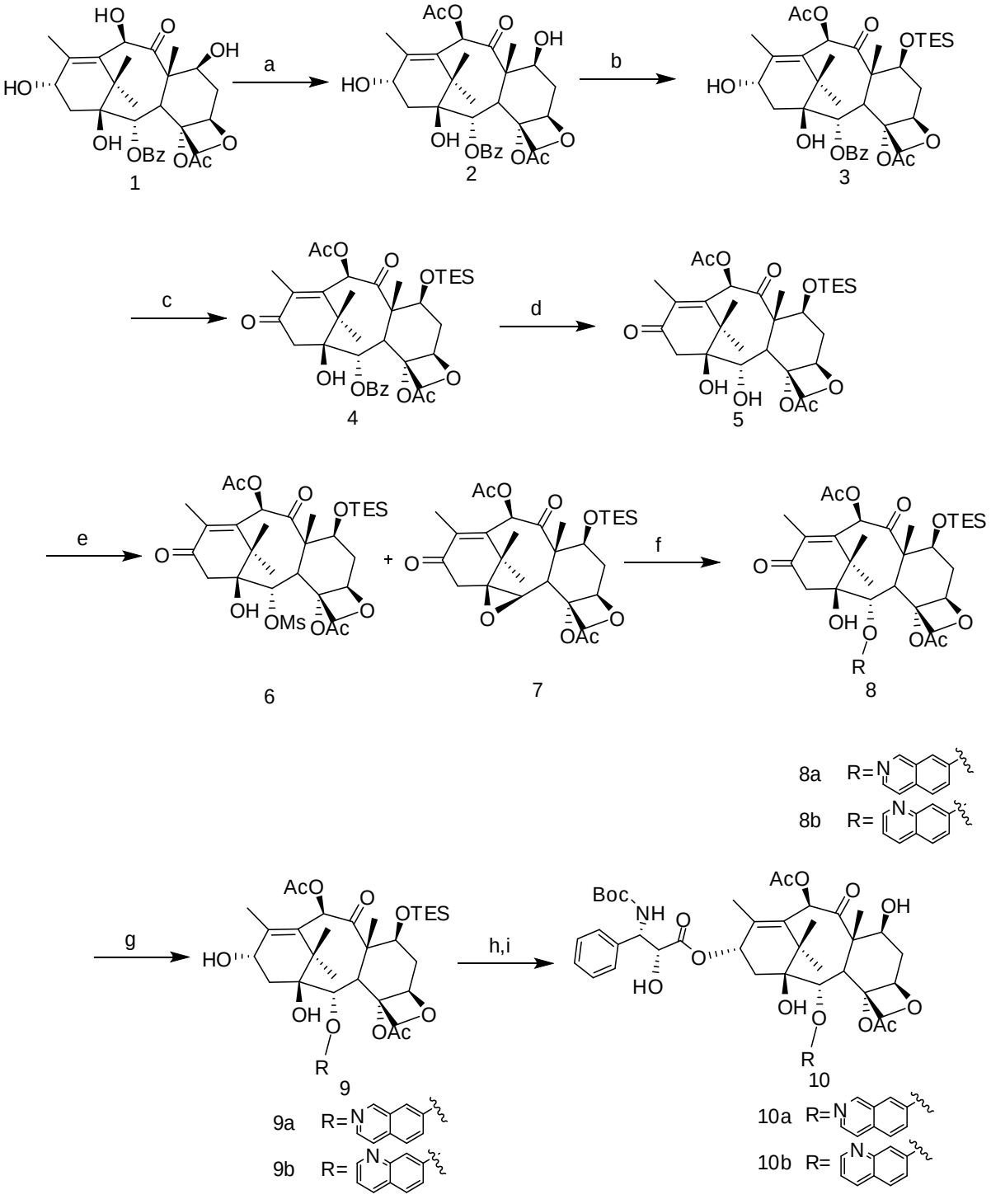
Figure S4. Structural comparison of the tubulin-bound conformations (pale pink sticks) and the four conformations found in the MD simulations of free **CTX43** (top) and **CTX44** (bottom). The lowest-energy and most populated conformer is boxed and that corresponding to the bound conformation is shown with C atoms colored in green. E_r is the energy of the average structure extracted from each cluster relative to the minimum energy conformation whereas P_i is the probability of a microstate as given by a Boltzmann distribution (see the Theoretical Methods section in the main text). Note that the bound conformation is unlikely for **CTX43** and **CTX44** in solution but it corresponds to the major conformer in the case of **CTX40** (Figure 9 in the main text).

Synthetic Procedures

General. ^{1}H and ^{13}C NMR spectra were measured on a Varian 300, 400, or 500 MHz NMR spectrometer. Mass spectra (ESI) were measured on JEOL Accu TOF CS (JMS T100CS). High-resolution mass spectrometry (HR-MS) spectra were measured on an Agilent 1100 Series LC-MSD-Trap-SL. All chemicals other than anhydrous solvents were obtained from Aldrich and Acros and used directly without further purification. All anhydrous reactions were performed under Ar, and anhydrous THF was dried over sodium (benzophenone as indicator). Reactions were monitored by TLC (silica gel, GF254) with UV light and H_2SO_4-anisaldehyde spray visualization. The stated HPLC purities and retention times were measured at the specified wavelengths under the following conditions: Instrument: Agilent 1100; Column: Agilent XDB-C8 (Φ4.6 x 150mm).

Synthesis.

C-2 modified taxol analogues



(a) $CeCl_3$, Ac_2O, THF, room temp, 3 h, 83%; (b) Im, TESCl, DMF, room temp, 40 min, 80.2%; (c) PDC, DCM, 1.5 h, room temp, 99%; (d) Triton-B, DCM, -25^{o}C, 15 min, 94%; (e) Mesyl chloride, triethylamine, DCM, -15^{o}C, 40 min; (f) RONa, DMF, room temp, 12-16 h, **8a** (58.3%), **8b** (28%); (g) $NaBH_4$, THF, 24 h, room temp, **9a** (83.4%), **9b** (52%); (h) β-lactam, LHMDS, THF, -45^{o}C ~-35^{o}C, 90-130 min; (i) HF/Py, CH_3CN, room temp, 7-12 h, **10a** (9.75%), **10b** (30.9%) (for h, i two steps).

13-oxo-7-O-triethylsilyl-2-debenzoyl-2-methylsulfonyl-baccatin III (6) and 13-oxo-7-O-triethylsilyl-2-debenzoyl-(1S, 2R)-[1, 2]-oxiranyl-baccatin III (7)[1]

The preparation of **5** from 10-deacetyl baccatin III (**1**) followed the literature procedure.[1] To a stirred solution of **5** (23 mg, 0.039 mmol) in dry methylene chloride (0.65 mL), was added triethylamine (0.1 mL, 0.72 mmol) and methanesulfonyl chloride (0.03 mL, 0.4 mmol) at -15^{o}C, and the mixture was stirred at room temperature for 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL), and the mixture was diluted with ethyl acetate (10 mL), washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:10) gave the mixture of compound **6** and **7** as sticky solids (22 mg).

13-oxo-7-O-triethylsilyl-2-debenzoyl-2-(isoquinolin-7-yl) baccatin III (8a).

To a stirred solution of **6** and **7** (19 mg, 0.030 mmol) in dry DMF (0.9 mL) was added newly prepared sodium quinolin-7-olate (10 mg, 0.06 mmol), and the mixture was stirred at room

temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (1 mL), and the mixture was diluted with ethyl acetate (20 mL), washed with a saturated aqueous Na_2CO_3 solution (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:1) gave compound **8a** as sticky solids (12.6 mg, 60.1% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.55-0.63 (m, 6H), 0.93 (t, *J* = 8.1 Hz, 9H), 1.20 (s, 3H), 1.48 (s, 3H), 1.71 (s, 3H), 1.88-1.96 (m, 1H), 2.10 (s, 3H), 2.15 (s, 3H), 2.23 (s, 3H), 2.50-2.61 (m, 1H), 2.90 (d, *J* = 4.5 Hz, 1H), 2.98 (d, *J* = 6.0 Hz, 1H), 3.68 (d, *J* = 5.7 Hz, 1H), 4.37 (t, *J* = 5.1 Hz, 1H), 4.49 (dd, *J* = 6.9, 10.2 Hz, 1H), 4.69 (d, *J* = 9.3 Hz, 1H), 4.74 (d, *J* = 9.0 Hz, 1H), 4.96 (d, *J* = 8.7 Hz, 1H), 6.57 (s, 1H), 7.45 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.52 (s, 1H), 7.58 (d, *J* = 5.7 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 4.2 Hz, 1H), 9.13 (s, 1H); MS (ESI) $C_{39}H_{51}NO_{10}Si$ *m/z* 722.5 ($M + H^+$), 744.5 ($M + Na^+$).

13-oxo-7-O-triethylsilyl-2-debenzoyl-2-(quinolin-7-yl) baccatin III (8b).

To a stirred solution of **6** and **7** (18 mg, 0.028 mmol) in dry DMF (0.87 mL) was added newly prepared sodium quinolin-7-olate (10 mg, 0.06 mmol), and the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (1 mL), and the mixture was diluted with ethyl acetate (20 mL), washed with a saturated aqueous Na_2CO_3 solution (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:5) gave compound **8b** as sticky solids (6 mg, 28.7% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55-0.65 (m, 6H), 0.93 (t, *J* = 7.8 Hz, 9H), 1.19 (s, 3H), 1.47 (s, 3H), 1.73 (s, 3H), 1.87-1.99 (m, 1H), 2.10 (s, 3H), 2.15 (s, 3H), 2.23 (s, 3H), 2.50-2.63 (m, 1H), 2.90 (d, *J* =

19.2 Hz, 1H), 3.01 (d, *J* = 19.2 Hz, 1H), 3.69 (d, *J* = 6.0 Hz, 1H), 4.42 (t, *J* = 4.8 Hz, 1H), 4.50 (dd, *J* = 6.8, 10.0 Hz, 1H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.78 (d, *J* = 8.8 Hz, 1H), 4.97 (d, *J* = 8.8 Hz, 1H), 6.58 (s, 1H), 7.17 (d, *J* = 9.2 Hz, 1H), 7.34 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.77 (s, 1H), 8.01 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.85 (d, *J* = 1.2 Hz, 1H); MS (ESI) $C_{39}H_{51}NO_{10}Si$ *m/z* 722.5 $(M + H)^+$, 744.4 $(M + Na^+)$.

7-O-triethylsilyl-2-debenzoyl-2-(isoquinolin-7-yl) baccatin III (9a).

To a stirred solution of **8a** (9 mg, 0.013 mmol) in CH_3OH (0.66 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) at -15^oC by portions, and the reaction was stirred at room temperature for 24 h. The reaction was quenched with brine (1 mL), and the mixture was diluted with ethyl acetate (20 mL), washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:2) gave compound **9a** as white solids (5mg, 55.4%) and recovered start material (4 mg): ^1H NMR (400 MHz, $CDCl_3$) δ 0.52-0.64 (m, 6H), 0.93 (t, *J* = 8.0 Hz, 9H), 1.10 (s, 3H), 1.37 (s, 3H), 1.68 (s, 3H), 1.86-1.97 (m, 1H), 2.04-2.24 (m, 1H), 2.17, 2.18 (s, 6H), 2.20 (s, 3H), 2.49-2.61 (m, 1H), 2.73 (dd, *J* = 9.6, 15.6 Hz, 1H), 3.65 (d, *J* = 6.4 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 1H), 4.50 (dd, *J* = 6.8, 10.0 Hz, 1H), 4.62-4.72 (m, 3H), 5.00 (d, *J* = 9.2 Hz, 1H), 6.45 (s, 1H), 7.46-7.62 (m, 3H), 7.73 (d, *J* = 8.8 Hz, 1H), 8.39 (s, 1H), 9.12 (s, 1H); MS (ESI) $C_{39}H_{53}NO_{10}Si$ *m/z* 724.4 $(M + H^+)$, 746.4 $(M + Na^+)$.

7-O-triethylsilyl-2-debenzoyl-2-(quinolin-7-yl) baccatin III (9b).

To a stirred solution of **8b** (6 mg, 0.008 mmol) in CH_3OH (0.4 mL) was added $NaBH_4$ (15.5 mg, 0.4 mmol) at -15^oC by portions, and the reaction was stirred at room temperature for 22 h. The reaction was quenched with brine (1 mL), and the mixture was diluted with ethyl acetate (20 mL), washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:5) gave compound **9b** as white solids (2 mg, 33.1%) and recovered start material (2 mg): ^1H NMR (400 MHz, $CDCl_3$) δ 0.55-0.68 (m, 6H), 0.94 (t, *J* = 7.2 Hz, 9H), 1.10 (s, 3H), 1.36 (s, 3H), 1.68 (s, 3H), 1.86-1.97 (m, 1H), 2.08-2.25 (m, 1H), 2.16, 2.18 (s, 6H), 2.21 (s, 3H), 2.48-2.61 (m, 1H), 2.84 (dd, *J* = 9.6, 15.6 Hz, 1H), 3.66 (d, *J* = 5.6 Hz, 1H), 4.36 (t, *J* = 4.8 Hz, 1H), 4.50 (dd, *J* = 6.0, 9.8 Hz, 1H), 4.72 (s, 3H), 4.99 (d, *J* = 8.8 Hz, 1H), 6.45 (s, 1H), 7.23-7.29 (m, 1H), 7.33 (dd, *J* = 4.4, 7.8 Hz, 1H), 7.63-7.73 (m, 1H), 7.84 (s, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 8.82 (s, 1H); MS (ESI) $C_{39}H_{53}NO_{10}Si$ *m/z* 724.4 ($M + H^+$), 746.4 ($M + Na^+$).

10-acetoxyl-2-debenzoyl-2-(isoquinolin-7-yl) docetaxel (10a, CTX55).

To a solution of **9a** (45 mg, 0.062 mmol) in dry THF (1.5 mL) at -50 ^oC under argon was added LHMDS (1.06 M in THF) (0.23 mL, 0.155mmol). After being stirred at this temperature for 40 min, the reaction mixture was added the solution of (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triethylsilyloxy-4-phenyl-azetidin-2-one (32 mg, 0.087 mmol) in dry THF (0.7 mL), and the reaction was stirred at -45^{o}C~-35^{o}C for 90 min. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), and the mixture was diluted with ethyl acetate (40 mL), washed with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by

silica gel chromatography (acetone: petroleum ether = 1:5) afford the intermediate subjected to the next step reaction.

To a stirred solution of the intermediate in CH_3CN (0.34 mL) was added Py (0.38 mL) and 40% aqueous HF solution (0.19 mL), and the reaction was stirred at room temperature for 7 h. The mixture was poured into the saturated aqueous $NaHCO_3$ solution (10 mL), extracted with ethyl acetate (20 mL), washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:1) gave compound **10a** as white solids (5 mg, 9.2% for two steps): HPLC purity: 98%, 20.15 min (227 nm). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.32 (s, 3H), 1.33 (s, 3H), 1.69 (s, 3H), 1.84 (s, 3H), 1.90-1.94 (m, 1H), 2.15-2.32 (m, 1H), 2.27 (s, 3H), 2,28 (s, 3H), 2.54-2.60 (m, 1H), 3.11 (dd, *J* = 9.6, 15.6 Hz, 1H), 3.61 (d, *J* = 7.2 Hz, 1H), 4.40 (t, *J* = 6.0 Hz, 1H), 4.43 (dd, *J* = 7.2, 10.8 Hz, 1H), 4.55 (s, 1H), 4.69 (d, *J* = 9.0 Hz, 1H), 4.71 (d, *J* = 9.6 Hz, 1H), 5.00 (dd, *J* = 1.8, 9.6 Hz, 1H), 5.12 (d, *J* = 9.0 Hz, 1H), 5.18 (d, *J* = 9.6 Hz, 1H), 6.00 (t, *J* = 8.4 Hz, 1H), 6.30 (s, 1H), 7.26-7.37 (m, 5H), 7.43-7.59 (m, 2H), 7.66 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 14.9, 20.8, 22.7, 22.8, 27.5, 29.7, 31.9, 35.7, 44.9, 45.0, 45.8, 55.5, 58.7, 72.4, 72.7, 74.7, 74.9, 75.6, 78.1, 79.5, 82.3, 84.2, 106.3, 109.8, 117.9, 120.3, 126.8, 128.0, 128.1, 128.5, 128.8, 132.9, 138.2, 143.6, 153.3, 154.7, 154.9, 162.3, 171.0, 180.5, 204.2; MS (ESI) $C_{47}H_{56}N_2O_{14}$ *m/z* 873.5 ($M + H^+$), 895.5 ($M + Na^+$).

10-Acetoxyl-2-debenzoyl-2-(quinolin-7-yl) docetaxel (10b, CTX56).

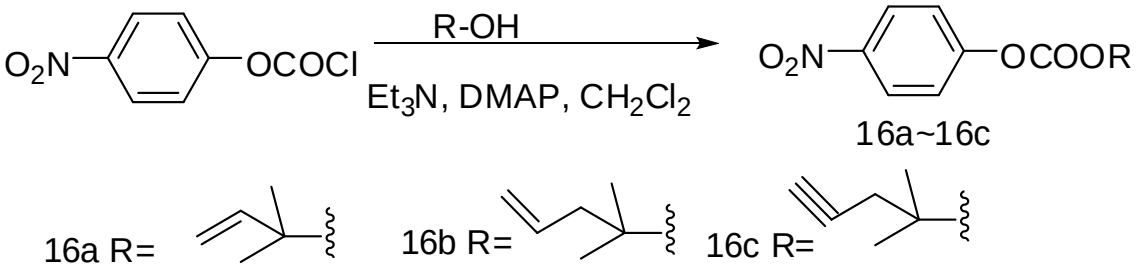
To a stirred solution of **9b** (69 mg, 0.096 mmol) in dry THF (2.5 mL) at -50^{o}C under argon, was added LHMDS (1.06 M in THF) (0.23 mL, 0.24 mmol). After being stirred at this temperature for

40 min, the reaction mixture was added the solution of (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triethylsilyloxy-4-phenyl-azetidin-2-one (45 mg, 0.125 mmol) in dry THF (0.9 mL), and the reaction was stirred at -45 ^{o}C – -35 ^{o}C for 130 min. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), and the mixture was diluted with ethyl acetate (40 mL), washed with saturated aqueous NH_4Cl solution (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:5) afforded the intermediate subjected to the next step reaction.

To a stirred solution of the intermediate in CH_3CN (1 mL), was added Py (1.1 mL) and 40% aqueous HF solution (0.55 mL), and the reaction was stirred at room temperature for 12 h. The mixture was poured into the saturated aqueous $NaHCO_3$ solution (10 mL), extracted with ethyl acetate (20 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:1) gave compound **10b** as white solids (26 mg, 31.2% for two steps): HPLC purity: 92%, 17.73 min (254 nm). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.31 (s, 3H), 1.32 (s, 3H), 1.70 (s, 3H), 1.81 (s, 3H), 1.89-1.95 (m, 1H), 2.14-2.30 (m, 1H), 2.24 (s, 3H), 2,28 (s, 3H), 2.52-2.60 (m, 1H), 3.07 (dd, *J* = 10.2, 15.6 Hz, 1H), 3.60 (d, *J* = 6.6 Hz, 1H), 4.40-4.44 (m, 2H), 4.49 (s, 1H), 4.74 (m, 2H), 4.99 (dd, *J* = 1.8, 9.6 Hz, 1H), 5.10 (d, *J* = 9.0 Hz, 1H), 5.20 (d, *J* = 8.4 Hz, 1H), 5.97 (t, *J* = 7.8 Hz, 1H), 6.29 (s, 1H), 7.23-7.31 (m, 7H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.78 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 8.82 (dd, *J* = 1.2, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 14.9, 20.9, 22.7, 22.8, 27.7, 29.7, 33.6, 35.7, 44.9, 45.8, 45.9, 56.3, 58.8, 72.4, 72.6, 72.6, 74.7, 75.7, 78.2, 82.3, 84.2, 91.0, 119.6, 124.0, 124.5, 126.9, 128.0, 128.5, 128.7, 132.9, 136.2, 138.0, 140.7, 142.7, 147.6,

149.8, 151.5, 154.9, 170.2, 171.1, 179.4, 204.3; MS (ESI) $C_{47}H_{56}N_2O_{14}$ *m/z* 873.8 ($M + H^+$), 895.5 ($M + Na^+$).

3'N-modified taxol analogues



General experimental procedure for compounds 16a~16c

2-methylbut-3-en-2-yl 4-nitrophenyl carbonate (16a)

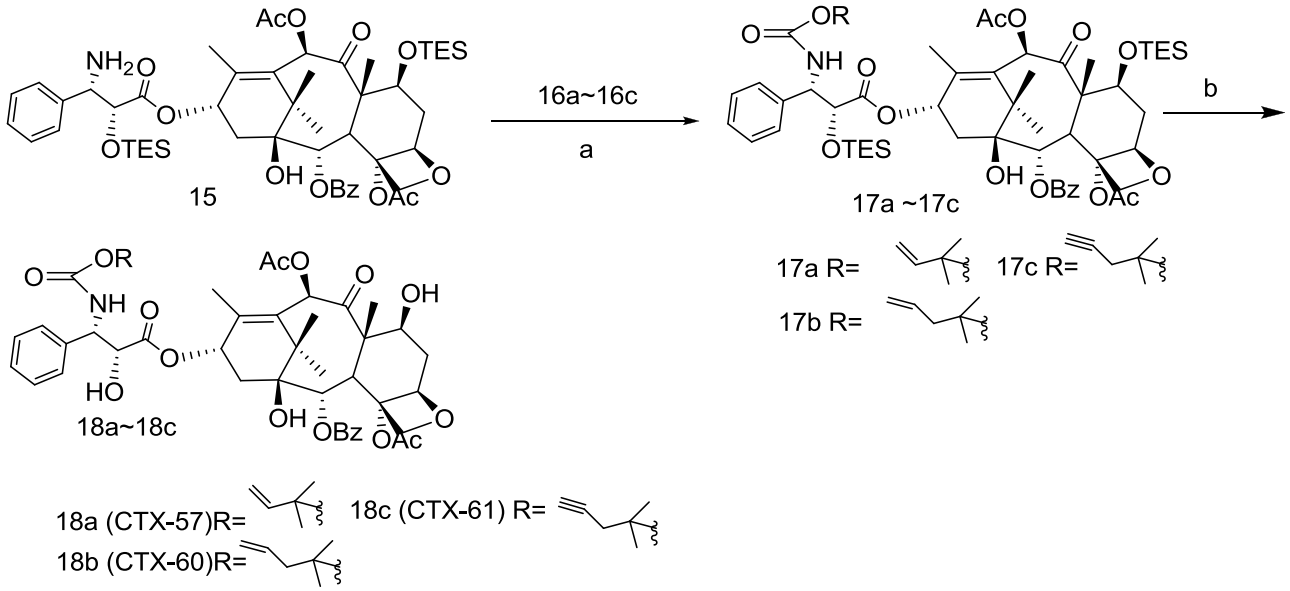
To a solution of 2-methylbut-3-en-2-ol (73 mg, 0.8 mmol), pyridine (72 μL, 0.9mmol) and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (0.8 mL). PNP chloroformate (161 mg, 0.8 mmol) dissolved in 0.8 mL of methylene chloride was added. The reaction mixture was stirred for 5 h at room temperature and then was diluted with Et_2O (30 mL). The mixture was washed with 0.5 M HCl (2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL) and saturated aqueous NaCl (2 x 10 mL). The organic layer dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (methylene chloride: petroleum ether = 1: 3) gave product **16a** as white solids (30 mg, 14.9% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78(s, 3H), 1.81(s, 3H), 4.78(d, *J* = 7.2Hz, 2H), 5.45(m, 1H), 7.38(d, *J* = 9.3Hz, 2H), 8.27(d, *J* = 9.3Hz, 2H); MS (ESI) $C_{12}H_{13}NO_5$ *m/z* 274.2($M + Na^+$).

2-methylpent-4-en-2-yl 4-nitrophenyl carbonate (16b)

Yield of 37.1% (123 mg) from 2-methylpent-4-en-2-ol (125 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55(s, 6H), 2.62(d, 2H), 5.17(m, 2H), 5.85(m, 1H), 7.34(d, *J* = 8.8Hz, 2H), 8.27(d, *J* = 8.8Hz, 2H); HRMS (ESI, [M + Na^+]) m/z calcd for $C_{13}H_{15}NO_5Na$, 288.0848; Found: 288.0845.

2-methylpent-4-yn-2-yl 4-nitrophenyl carbonate (16c)

Yield of 10.7% (28 mg) from 2-methylpent-4-yn-2-ol (98 mg), sticky solids; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65(s, 6H), 2.10(s, 1H), 2.81(d, *J* = 2.1Hz, 2H), 7.37(d, *J* = 8.7Hz, 2H), 8.27(d, *J* = 8.7Hz, 2H); HRMS (ESI, [M + Na^+]) m/z calcd for $C_{13}H_{13}1NO_5Na$, 286.0691; Found: 286.0691.



(a) Et_3N, DMAP, CH_2Cl_2, carbonate, room temp, 72 h, (30–45%); (b) HF/pyridine, CH_3CN, room temp, 24 h, (80–84%).

General procedure for the syntheses of compounds 17a~17c

7,2'-di(O-triethylsilyl)-3'-N-debenzoyl-3'-N-[(2-methylbut-3-en-2-yloxyl)carbonyl]-paclitaxel (17a)

To a solution of 7,2'-di(O-triethylsilyl)-3'-N-debenzoylpaclitaxel[4] (**5**, 71 mg, 0.073 mmol), DMAP (4 mg, 0.033 mmol), and carbonate (24 mg, 0.096 mmol) in methylene chloride (0.8 mL), triethylamine (20μL, 0.146 mmol) was added. The reaction mixture was stirred for 36h and then another potion of DMAP (3 mg, 0.025 mmol), triethylamine (10 μL, 0.073 mmol) and carbonate (12 mg, 0.048 mmol) was added. The reaction mixture was stirred for another 36h and then was diluted with ethyl acetate (30 mL). The mixture was washed with 0.5 M HCl (2 x 10 mL), saturated aqueous Na_2CO_3 (6 x 10 mL), and saturated aqueous NaCl (2 x 10 mL). The organic layer dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:5) gave product **17a** as white solids (25 mg, 31.6% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28-0.49(m, 6H), 0.54-0.62(m, 6H), 0.78(t, *J* = 8.0Hz, 9H), 0.93(t, *J* = 7.8Hz), 1.24(s, 6H), 1.53(s, 3H), 1.66(s, 3H), 1.70(s, 3H), 1.86-1.95(m, 1H), 1.99(s, 3H), 2.06-2.14(m, 1H), 2.18(s, 3H), 2.34-2.42(m, 1H), 2.52(s, 3H), 2.47-2.58(overlap, 1H), 3.84(d, *J* = 6.6Hz, 1H), 4.19, 4.31(ABq, *J* = 8.4Hz, 2H), 4.42(d, *J* = 6.9 Hz, 2H), 4.49(dd, *J* = 10.8, 6.6 Hz, 1H), 4.57(d, *J* = 2.7 Hz, 1H), 4.94(d, *J* = 9.3 Hz, 1H), 5.23-5.31(m, 2H), 5.64(d, *J* = 8.7 Hz, 1H), 5.70(d, *J* = 6.9 Hz, 1H), 6.29(t, *J* = 9.2 Hz, 1H), 6.46(s, 1H), 7.29-7.39(m, 5H), 7.49(t, *J* = 7.4 Hz, 2H), 7.59(t, *J* = 6.8Hz, 1H), 8.14(d, *J* = 7.5 Hz, 2H); MS (ESI) $C_{58}H_{83}NO_{15}Si_2$ *m/z* 1112.9 ($M + Na^+$).

7,2'-di(O-triethylsilyl)-3'-N-debenzoyl-3'-N-[(2-methylpent-4-en-2-yloxyl)carbonyl]-

paclitaxel (17b)

Yield of 45.5% (37mg) from 1**5** (72mg), white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.31-0.50(m, 6H), 0.55-0.62(m, 6H), 0.78(t, *J* = 8.0 Hz, 9H), 0.93(t, *J* = 8.0 Hz, 9H), 1.23(s, 6H), 1.27(brs, 6H), 1.70(s, 3H), 1.90(m, 1H), 2.01(s, 3H), 2.18(s, 3H), 2.41(m, 2H) 2.08-2.46(overlap, 2H), 2.52(s, 3H), 2.44-2.58 (overlap, 1H), 3.84(d, *J* = 6.6 Hz, 1H), 4.19, 4.31(ABq, *J* = 8.3 Hz, 1H), 4.48(dd, *J* = 10.5, 6.8 Hz, 1H), 4.57(s, 1H), 4.90-5.01(m, 3H), 5.30(brd, 1H), 5.49(d, *J* = 8.4 Hz, 1H), 5.58-5.68(overlap, 1H), 5.70(d, *J* = 6.9 Hz, 1H), 6.29(t, *J* = 8.6 Hz, 1H), 6.47(s, 1H), 7.28-7.40(m, 5H), 7.48(t, *J* = 7.5 Hz, 2H), 7.56-7.61(m, 1H), 8.12(d, *J* = 6.9 Hz, 2H); MS (ESI) $C_{59}H_{85}NO_{15}Si_2$ *m/z* 1126.4 ($M + Na^+$).

7,2'-di(O-triethylsilyl)-3'-N-debenzoyl-3'-N-[(2-methylpent-4-yn-2-yloxyl)carbonyl]-paclitaxel (17c)

Yield of 40.2% (24 mg) from **15** (53 mg), white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30-0.49 (m, 6H), 0.55-0.65(m, 6H), 0.77(t, *J* = 7.8 Hz, 9H), 0.94(t, *J* = 7.8 Hz, 9H), 1.24(s, 6H), 1.35(s, 3H), 1.38(s, 3H), 1.71(s, 3H), 1.87-1.96(m, 2H), 2.01(s, 3H), 2.14-2.67(overlap, 5H), 2.19(s, 3H), 2.54(s, 3H), 3.85(d, *J* = 6.9 Hz 1H), 4.21,4.32(ABq, *J* = 8.3 Hz, 2H), 4.49(dd, *J* = 10.2, 6.8 Hz, 1H), 4.58(s, 1H), 4.95(d, *J* = 8.7 Hz, 1H), 5.33(d, *J* = 9.0 Hz, 1H), 5.56(d, *J* = 9.6 Hz, 1H), 5.71(d, *J* = 7.2 Hz, 1H), 6.33(t, *J* = 8.6 Hz, 3H), 6.46(s, 1H), 7.26-7.40(overlap, 5H), 7.48(t, *J* = 7.5 Hz, 2H), 7.58(t, *J* = 7.4 Hz, 1H), 8.12-8.14(d, *J* = 7.5 Hz, 2H); MS (ESI) $C_{59}H_{83}NO_{15}Si_2$ *m/z* 1102.6 ($M + H^+$), 1124.5 ($M + Na^+$).

General procedure for the syntheses of compounds 18a~18c

3'-N-debenzoyl-3'-N-[(2-methylbut-3-en-2-yloxyl)carbonyl]-paclitaxel (18a, CTX57)

To a solution of **17a** (25 mg, 0.023 mmol) in acetonitrile (1.0 mL) was added dropwise 0.25 mL of HF/pyridine (v/v 1:2) at 0°C, and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate, washed with saturated NH_4Cl. The organic layer dried over anhydrous Na_2SO4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:1.2) gave product **18a** (CTX57) as white solids (16mg, 80.9% yield): HPLC purity: 98%, 12.72 min (220 nm). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15(s, 3H), 1.27(s, 3H), 1.57(overlap, 3H), 1.68(s, 6H), 1.83(s, 3H), 1.85-1.91(m, 1H), 2.25(s, 3H), 2.20-2.31(overlap, 2H), 2.37(s, 3H), 2.52-2.58(m, 1H), 3.34(brs, 1H), 3.80(d, *J* = 6.5 Hz, 1H), 4.18, 4.29(ABq, *J* = 8.5 Hz, 2H), 4.41(dd, *J* = 10.5, 6.8 Hz, 1H), 4.45-4.50(m, 2H), 4.64(s, 1H), 4.94(d, *J* = 8.5 Hz, 1H), 5.24(m, 1H), 5.30(brd, 1H), 5.54(d, *J* = 9.5 Hz, 1H), 5.67(d, *J* = 7.0 Hz, 1H), 6.26(overlap, 1H), 6.28(s, 1H), 7.31-7.34(m, 1H), 7.39-7.42(m, 4H), 7.50(t, *J* = 7.8 Hz, 2H), 7.61(t, *J* = 7.3 Hz, 1H), 8.12(d, *J* = 7.0 Hz, 2H); ^{13}C NMR (125MHz, acetone-d_6) δ 10.2, 14.8, 18.0, 20.8, 22.4, 23.0, 25.7, 27.1, 36.7, 37.1, 44.2, 47,2, 58.5, 59.0, 62.1, 71.7, 72.3, 75.1, 75.8, 76.2, 76.7, 78.7, 79.0, 79.3, 81.7, 85.0, 120.5, 128.1, 128.4, 129.2, 129.4, 130.9, 131.2, 138.0, 140.5, 142.1, 157.1, 166.6, 170.7, 171.1, 173.5, 203.7; MS (ESI) $C_{46}H_{55}NO_{15}$ *m/z* 884.4(M + Na^+).

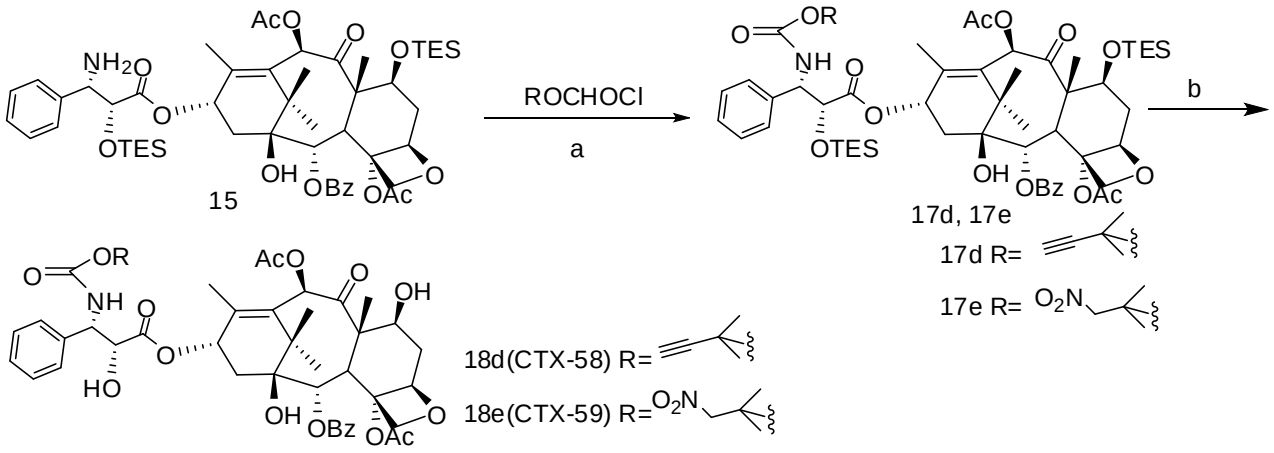
3'-N-debenzoyl-3'-N-[(2-methylpent-4-en-2-yloxyl)carbonyl]-paclitaxel (18b, CTX60)

Yield of 81.0% (27 mg) from **17b** (42 mg), white solid; HPLC purity: 100%, 9.25 min (227 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (s, 3H), 1.27 (s, 3H), 1.31(s, 3H), 1.32(s, 3H), 1.68(s, 3H),

1.85(s, 3H), 1.85-1.92(overlap, 1H), 2.25(s, 3H), 2.23-2.32(m, 2H), 2.37(s, 3H) , 2.43(m, 2H), 2.51-2.59(m, 1H), 3.80(d, *J* = 6.8 Hz, 1H), 4.18, 4.30(ABq, *J* = 8.5 Hz, 2H), 4.41(dd, *J* = 10.8, 6.8 Hz, 1H), 4.63(s, 1H), 4.94-5.03(m, 3H), 5.27(brd, 1H), 5.38(d, *J* = 9.6 Hz, 1H), 5.60-5.75(overlap, 1H) , 5.67(d, *J* = 7.2 Hz, 1H), 6.24(t, *J* = 8.6 Hz 1H), 6.29(s, 1H), 7.31-7.43(m, 5H), 7.50(t, *J* = 7.6Hz, 2H), 7.61(t, *J* = 7.4Hz, 1H), 8.11(d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125MHz, $CDCl_3$) 9.5, 14.9, 20.8, 21.9, 22.6, 26.06, 26.11, 26.8, 35.5, 35.6, 43.2, 44.8, 45.6, 56.1, 58.6, 72.2, 72.4, 73.5, 74.9, 75.6, 76.5, 79.1, 81.1, 81.6, 84.4, 118.2, 126.7, 128.1, 128.7, 128.9, 129.1, 130.2, 133.0, 133.4, 133.7, 138.2, 142.3, 155.1, 167.0, 170.1, 171.3, 172.9, 203.7; MS (ESI) $C_{47}H_{57}NO_{15}$ *m/z* 898.5 (M + Na^+).

3'-N-debenzoyl-3'-N-[(2-methylpent-4-yn-2-yloxyl)carbonyl]-paclitaxel (18c, CTX61)

Yield of 84.1% (20 mg) from **17c** (30 mg), white solid: HPLC purity: 96%, 6.09 min (254 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16(s, 3H), 1.27(s, 3H), 1.38(s, 3H), 1.40(s, 3H), 1.69(s, 3H), 1.78-1.98(m, 2H), 1.93(s, 3H), 2.25 (s, 3H), 2.29-2.72(overlap, 5H, H-14a, H-14b, H-6a), 2.40(s, 3H), 3.31(s, 1H), 3.81(d, *J* = 7.2 Hz, 2H), 4.19,4.30 (ABq, *J* = 8.7 Hz, 2H), 4.42(dd, *J* = 10.8, 6.3 Hz, 1H), 4.66(s, 1H), 4.95(d, *J* = 7.8 Hz, 1H), 5.31(d, *J* = 8.7 Hz, 1H), 5.49(d, *J* = 9.9 Hz, 1H), 5.68(d, *J* = 6.9 Hz, 1H), 6.29(s, 1H), 6.33(overlap, 1H) 7.33-7.41(m, 5H), 7.50(t, *J* = 7.5Hz, 2H), 7.61(t, *J* = 7.5Hz, 1H), , 8.12(d, *J* =7.5 Hz 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 9.6, 14.8, 20.8, 22.0, 22.7, 25.9, 26.0, 26.8, 30.4, 35.6, 35.7, 43.3, 45.6, 55.9, 58.6, 70.6, 72.1, 72.4, 73.5, 75.0, 75.6, 76.5, 79.1, 80.0, 80.5, 81.2, 84.4, 126.7, 128.1, 128.7, 128.9, 129.2, 130.2, 133.2, 133.7, 138.2, 142.2, 154.9, 167.0, 170.2, 171.2, 172.8, 203.6; MS (ESI) $C_{47}H_{55}NO_{15}$ *m/z* 874.3(M + H^+).



(a) chloroformate, DMAP, CH_2Cl_2, 4^oC, 4 h ; (b) HF/pyridine, CH_3CN, room temp, 24 h (50%~70%, two steps).

General procedure for the syntheses of compounds 18d and 18e

3'-N- debenzoyl-3'-N-[(2-methylbut-3-yn-2-yloxy)carbonyl]-paclitaxel (18d, CTX58)

A solution of triphosgene (27 mg, 0.092 mmol) in methylene chloride (0.4 mL) was cooled in an ice bath and added pyridine (28 μL, 0.35 mmol). The reaction mixture was stirred for 30 min at 0 ^oC and then 2-methylbut-3-yn-2-ol (26 μL, 0.27 mmol) was added. The reaction was stirred for another 6 h at 0 ^oC and then most of the solvent and excess phosgene were removed under reduced pressure. The remains were added 0.6 mL of methylene chloride and retained at 0^oC.

To a solution of 7,2'-di(O-triethylsilyl)-3'-N- debenzoylpaclitaxel (23 mg, 0.024 mmol) and DMAP (10 mg ,0.08 mmol) in methylene chloride (0.5 mL) was added a solution of chloroformate (0.15 mL) in methylene chloride prepared above, the reaction mixture was stirred for 4 h at 4 ^oC and then was diluted with ethyl acetate (30 mL), washed with saturated aqueous NH_4Cl (3x10 mL).

The organic layer dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude product was used for the next step reaction without further purification.

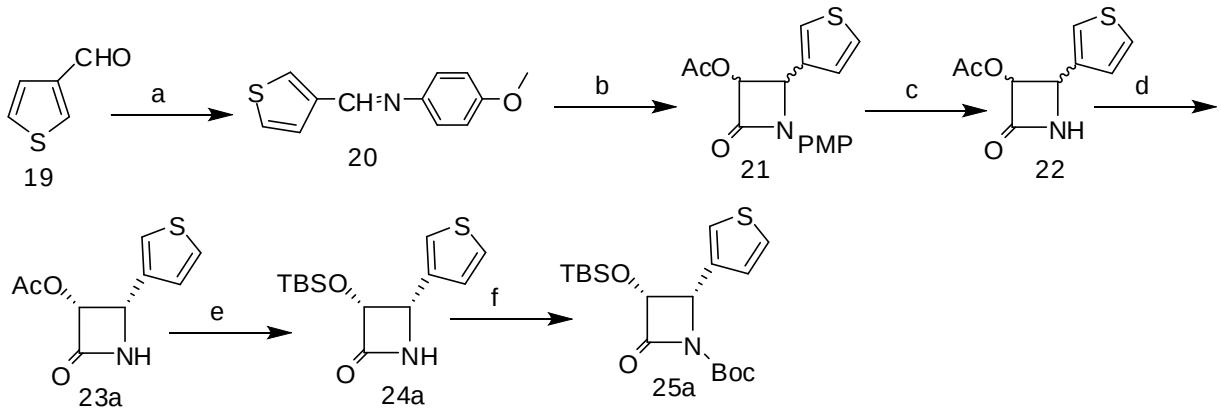
To a solution of crude product obtained above in acetonitrile (0.9 mL) was added dropwise 0.21 mL of HF/pyridine (v:v = 1:2) at 0°C, and the reaction mixture was stirred at room temperature for 24h. The reaction was quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate, washed with saturated NH_4Cl. The organic layer dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:1.3) gave product **18d** (CTX58) as white solids (11mg, 54.4% yield for two steps): HPLC purity: 99%, 17.53 min (227 nm). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15(s, 3H), 1.27(s, 3H), 1.57 (s, 3H), 1.61(s, 3H), 1.68(s, 3H), 1.84(s, 3H), 1.84-1.91(overlap, 1H), 2.25(s, 3H), 2.34(m, 2H), 2.38(s, 3H), 2.48(s, 1H), 2.55-2.58(m, 1H), 3.31(brs, 1H), 3.80(d, *J* = 7.0 Hz, 1H), 4.18, 4.29(ABq, *J* = 8.5 Hz, 2H), 4.41(dd, *J* = 10.0, 6.8 Hz, 1H), 4.66(s, 1H). 4.94(d, *J* = 8.5 Hz, 1H), 5.33(d, *J* = 8.5 Hz 1H), 5.51(d, *J* = 9.5 Hz, 1H), 5.66(d, *J* = 7.5 Hz, 1H), 6.27(overlap, 1H), 6.29(s, 1H), 7.32-7.34(m, 1H), 7.39-7.42(m, 4H), 7.50(t, *J* = 7.5 Hz, 2H), 7.61(t, *J* = 7.3Hz, 1H), 8.11(d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 9.5, 14.8, 20.8, 21.9, 22.7, 26.8, 28.9, 29.2, 35.3, 35.6, 43.2, 45.6, 56.1, 58.6, 60.4, 72.2, 72.4, 72.5, 73.4, 75.0, 75.6, 76.5, 79.2, 81.1, 84.4, 84.8, 126.7, 128.2, 128.7, 128.9, 129.1, 130.2, 133.0, 133.7, 138.0, 142.2, 154.2, 167.1, 170.2, 171.3, 172.8. 203.7; MS (ESI) $C_{46}H_{53}NO_{15}$ *m/z* 877.7 (M + NH_4^+), 882.7 (M + Na^+).

3'-N- debenzoyl-3'-N-[(2-methyl-1-nitropropan-2-yloxy)carbonyl]-paclitaxel (18e, CTX59)

Yield of 70.3% (9 mg) from **5** (14 mg) (for two steps), white solid: HPLC purity: 96%, 4.52 min (254 nm). ^{1}H NMR (300MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 1.68

(s, 3H), 1.85 (s, 3H), 2.25 (s, 3H), 2.29-2.32 (m, 2H), 2.38 (s, 3H), 2.50-2.60 (m, 2H), 3.31 (s, 1H), 3.81 (d, *J* = 6.9Hz, 1H), 4.18, 4.30 (ABq, *J* = 8.4Hz, 2H), 4.42 (m, 1H), 4.57, 4.78 (ABq, *J* = 11.3Hz, 2H), 4.69 (s 1H), 4.95 (d, *J* = 8.4Hz, 1H), 5.33 (d, *J* = 9.3Hz, 1H), 5.61-5.67 (m, 2H), 6.28 (s, 1H), 6.33 (t, *J* = 8.4Hz, 1H), 7.34-7.43 (m, 5H), 7.49 (t, *J* = 7.5Hz, 2H), 7.61 (t, *J* = 7.2Hz, 1H) , 8.12 (d, *J* = 7.5Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 9.8, 15.0, 21.1, 22.2, 22.9, 25.2, 25.4, 27.0, 35.8, 43.4, 45.8, 56.2, 58.8, 72.4, 72.8, 73.5, 75.3, 75.8, 76.7, 77.8, 79.4, 81.0, 81.4, 84.6, 126.8, 128.4, 128.9, 129.2, 129.4, 130.4, 138.1, 133.3, 133.8, 142.4, 154.6, 167.2, 170.3, 171.5, 172.8, 203.8; MS (ESI) $C_{45}H_{54}N_2O_{17}$ *m/z* 912.4 ($M + NH_4^+$), 917.2 ($M + Na^+$).

C-3' modified taxol analogues



(a) 4-methoxyaniline, Na_2SO_4, room temp, 8 h, CH_2Cl_2, 78.1%; (b) CH_3COOCH_2COCl, Et_3N, CH_2Cl_2, room temp, 12 h, 87.6%; (c) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, -15 ^oC, 30min, 77.6%; (d) lipase, buffer, $(C_2H_5)_2O$, 25 ^oC, 43.7%; (e) pyrrolidine, pyridine, 25 ^oC, 8 h, and then TBSCl, Im, THF, 25 ^oC, 6 h, 86.4%; (f) $(BOc)_2O$, Et_3N, DMAP, CH_2Cl_2, 25 ^oC, 8 h, 85.6%.

(*E*)-4-methoxy-N-(thiophen-3-ylmethylene)aniline (20)

To a solution of **19** (985 mg, 8 mmol) in 16 mL CH_2Cl_2 was added 4-methoxyaniline (897 mg, 8 mmol) and Na_2SO_4 (8 g), the reaction was stirred for 8 hours at room temperature and filtered. After the solvent was removed, the production **20** (1352 mg, 78.1% yield) was obtained by recrystallization in petroleum ether.

***cis*-(±)-1-(4-methoxyphenyl)-3-acetoxy-4-(thiophen-3-yl)azetidin-2-one (21)**

To a solution of **20** (1352 mg, 6.222 mmol) in 24 mL CH_2Cl_2 was added CH_3COOCH_2COCl (997 mg, 7.466 mmol), Et_3N (756 mg, 7.466 mmol). The reaction was stirred for 12 hours at room temperature, washed by saturated aqueous $NaHCO_3$, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The production **21** (1729 mg, 87.6% yield) was obtained by recrystallization with ethyl acetate: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.70 (s, 3H), 3.74 (s, 3H), 5.64 (d, *J* = 4.8 Hz, 1H), 5.96 (d, *J* = 4.8 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 7.05 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 2H),7.51 – 7.44 (m, 2H).

***cis*-(±)-3-acetoxy-4-(thiophen-3-yl)azetidin-2-one (22)**

To a solution of **21** (1745 mg, 5.5 mmol) in 45 mL of acetonitrile at -15^{o}C was slowly added a solution of ceric ammonium nitrate (6030 mg, 11 mmol in 3 mL of water) over a 30-min period. The mixture was stirred for 30 minutes at -15^{o}C and saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous $NaHSO_3$ (20 mL) was added. The aqueous layer was extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The production **22** (901 mg, 77.6% yield) was obtained by recrystallization with ethyl acetate: ^{1}H NMR (300 MHz, acetone-d_6) δ 1.70

(s, 3H), 5.12 (d, *J* = 4.8 Hz, 1H), 5.81 (dd, *J* = 4.8, 2.7 Hz, 1H), 7.02 (d, *J* = 3.9 Hz, 1H), 7.37 (s, 1H), 7.47 (dd, *J* = 4.9, 3.1 Hz, 1H), 7.91 (s, 1H).

(3*R*,4*S*)-3-acetoxy-4-(thiophen-3-yl)azetidin-2-one (23a)

To a solution of **5** (900 mg, 4.261 mmol) in 30 mL ethoxyethane was added 20 mL of 0.2 M sodium phosphate buffer (pH 7.5) and 5 mL crude pig lipase and the mixture was stirred vigorously at 25 ^{o}C until approximately 50% of the substrate was consumed. Acetone (15 mL) was added and the mixture was filtered, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : ethyl acetate = 3 : 1) to afford **6** (393 mg, 43.7% yield) as white solids: α_D^{20}=-86.84 (*c* 1.14 mg/ mL,$CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.70 (s, 3H), 5.12 (d, *J* = 4.8 Hz, 1H), 5.81 (dd, *J* = 4.8, 2.7 Hz, 1H), 7.02 (d, *J* = 3.9 Hz, 1H), 7.37 (s, 1H), 7.47 (dd, *J* = 4.9, 3.1 Hz, 1H), 7.91 (s, 1H); MS (ESI) $C_9H_9NO_3S$ *m/z* 212.0 (M + H^+), 234.0 (M + Na^+).

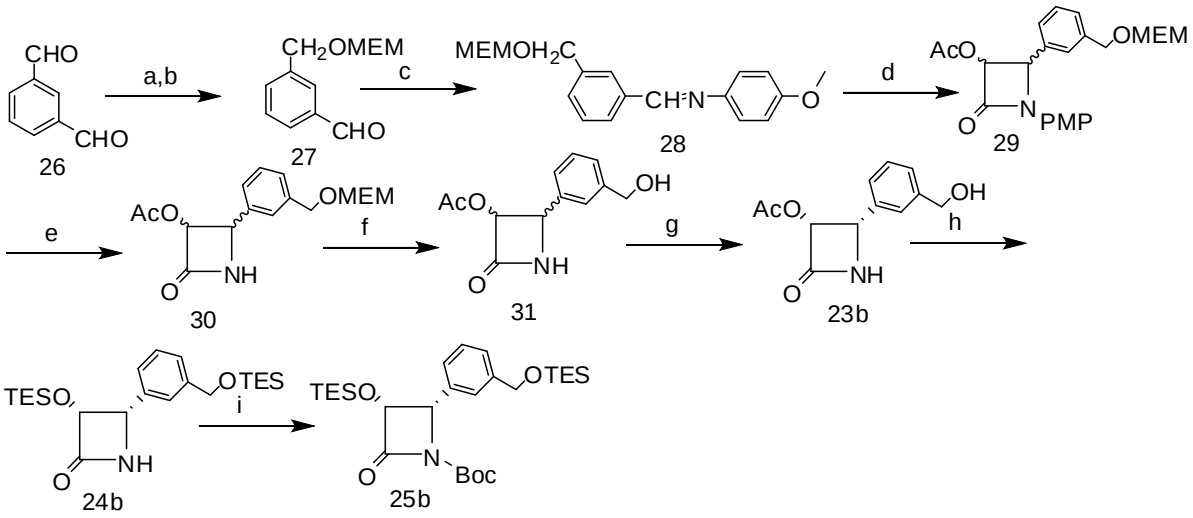
(3*R*,4*S*)-3-(tert-butyldimethylsilyloxy)-4-(thiophen-3-yl)azetidin-2-one (24a)

To a solution of **23a** (211 mg, 1 mmol) in 4 mL THF was added pyrrolidine (213 mg, 3 mmol) and pyridine (237 mg, 3 mmol) and the mixture was stirred for 8 hours at 25 ^{o}C. TBSCl (904 mg, 6 mmol) and imidazole (206 mg, 3 mmol) was added and the mixture was stirred for another 6 hours at 25 ^{o}C. The mixture was diluted by 20 mL saturated aqueous NH_4Cl , extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : ethyl acetate = 5 : 1) to afford **24a** (245 mg, 86.4% yield) as white solids: ^{1}H NMR (300 MHz, acetone-d_6) δ -0.09 (s, 3H), 0.06 (s, 3H), 0.72 (s, 9H),

2.04 (s, 3H), 4.93 (d, *J* = 4.8 Hz, 1H), 5.09 (dd, *J* = 4.8, 2.4 Hz, 1H), 7.08 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.58 (s, 1H); MS (ESI) $C_{13}H_{21}NO_2SSi$ *m/z* 284.0 ($M + H^+$).

(3*R*,4*S*)-1-(tert-Butoxycarbonyl)-3-(tert-butyldimethylsilyloxy)-4-(thiophen-3-yl)azetidine-2 one (25a)

To a solution of **24a** (28 mg, 0.073 mmol) in 0.4 mL CH_2Cl_2 was added $(Boc)_2O$ (32 mg, 0.146 mmol) DMAP (1 mg, 0.008 mmol) and Et_3N (18 mg, 0.175 mmol), the mixture was stirred for 8 hours at 25oC. Saturated aqueous $NaHCO_3$ (2 mL) was added and the aqueous phase was extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether : ethyl acetate = 30:1) to afford **25a** (33 mg, 85.6% yield) as white solids: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.32 (s, 3H), -0.15 (s, 3H), 0.49 (s, 9H), 1.19 (s, 9H), 4.79 (d, *J* = 5.6 Hz, 1H), 4.92 (d, *J* = 5.6 Hz, 1H), 6.83 (d, *J* = 4.8 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 4.8, 2.4 Hz, 1H); MS (ESI) $C_{18}H_{29}NO_4SSi$ *m/z* 384.1 ($M + H^+$), 406.1 ($M + Na^+$).



(a) $NaBH_4$, C_2H_5OH, room temp, 1h; (b) MEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 55.5%, room temp, 12 h; (c) Na_2SO_4, CH_2Cl_2, 4-methoxyaniline, room temp, 12 h; (d) $AcOCH_2COCl$, Et_3N, CH_2Cl_2, room temp, 20 h, 70.1%, for two steps c and d; (e) CAN, CH_3CN, -15°C~-10°C, 15 min, 69.7%; (f) PPTS, *t*-BuOH, reflux, 4 h, 37.4%; (g) lipase, ether, buffer solution, 24 °C, 70 min, 26.7%; (h) pyrrolidine, pyridine, THF, room temp, 7 h and then TESCl, pyridine, room temp, 8h, 72.5%; (i) $(Boc)_2O$, $(Et)_3N$, DMAP, CH_2Cl_2, room temp, 12 h, 86.5% .

3-(((2-methoxyethoxy)methoxy)methyl)benzaldehyde (27)

The 3-(hydroxymethyl)benzaldehyde **(26**) was prepared according to the literature.[5] The crude product can be used directly. A solution of 3-(hydroxymethyl)benzaldehyde (4.40 g crude material) in methylene chloride (100 mL) was cooled to 0 °C, $(i\text{-}Pr)_2NEt$ (9.96 mL, 58.3 mmol) and MEMCl (6.25 mL, 55.0 mmol) were added. The reaction mixture was stirred for 12 h at room temperature and then diluted with methylene chloride (100 mL). The mixture was washed with 0.5 M HCl (2 x 80 mL), saturated aqueous $NaHCO_3$ (2 x 80 mL) and saturated aqueous NaCl (2 x 80 mL). The organic layer dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1: 4.5) gave product **27** as an oil (4.02g, 55.5% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 3.40(s, 3H), 3.57(m, 2H), 3.75(m, 2H), 4.70(s, 2H), 4.83(s, 2H), 7.52(m, 1H), 7.61(m, 1H), 7.80(m, 1H), 7.88(s, 1H), 10.03(s, 1H).

4-methoxy-N-(3-(((2-methoxyethoxy)methoxy)methyl)benzylidene)aniline (28)

To a solution of **27** (2.74 g, 12.2 mmol) in methylene chloride (15 mL), anhydrous Na_2SO_4 (3.00 g, 21.1 mmol) was added and then 4-methoxyaniline (1.35 g, 11 mmol) in 15 mL of methylene chloride was added dropwise. The reaction mixture was stirred for 12h at room temperature and filtered. The solvent was removed under reduced pressure and the crude product (3.90 g) could be used directly without purifying.

cis-(±)-1-(4-methoxyphenyl)-3-acetoxy-4-[3-(((2-methoxyethoxy)methoxy)methyl)phenyl] azetidin-2-one (29)

To a solution of 2-chloro-2-oxoethyl acetate (2.17g, 17.8mmol) and triethylamine (3.0 mL, 21.6mmol) in methylene chloride (18 mL) was added dropwise **28** (3.90 g, crude material) in 18 mL of methylene chloride. The reaction mixture was stirred for 20h at room temperature and then was diluted with ethyl acetate (150 mL). The mixture washed with saturated aqueous NaCl (1 x 100 mL), 0.5M HCl (1 x 100 mL), saturated aqueous $NaHCO_3$ (1 x 100 mL) and saturated aqueous NaCl again (2x100 mL). The organic layer dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether=1:3) gave product **29** as a sticky solid (3.68 g, 70.1% yield, for two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71(s, 3H), 3.42(s, 3H), 3.58(m, 2H), 3.72(m ,2H), 3.76(s, 3H), 4.62(s, 2H), 4.80(s, 2H), 5.35(m, 1H), 5.97(m, 1H), 6.82(m, 2H), 7.29-7.35(m, 6H).

cis-(±)-3-acetoxy-4-[3-(((2-methoxyethoxy)methoxy)methyl)phenyl]azetidin-2-one (30)

A solution of **29** (1.84 g, 4.29 mmol) in acetonitrile (40.0 mL) was cooled to -15°C. A solution of CAN (6.03 g, 1.10 mmol) in water (30.0 mL) was added dropwise in 8 min. The reaction mixture

was stirred at -15°C to -10 °C for 15min. The mixture was added saturated aqueous $NaHCO_3$ (33 mL) and stirred for 5 min and then was added aqueous $NaHSO_3$ and stirred for another 5 min. At last, aqueous $NaHCO_3$ was added to the reaction mixture until the pH was up to 8. The reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl (2x100 mL), dried over anhydrous Na_2SO4 and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1: 3) gave product **30** as a sticky solid (0.965 g, 69.7% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64(s, 3H), 3.35(s, 3H), 3.53(m, 2H), 3.69(m, 2H), 4.56(s, 2H), 4.73(s, 2H), 4.97(d, *J* = 8.0Hz, 1H), 5.82(m, 1H), 6.61(brs, 1H), 7.17-7.29(m, 4H).

cis-(±)-3-acetoxy-4-(3-hydroxymethyl) phenylazetidin-2-one (31)

30 (1.74 g, 5.39 mmol) and anhydrous PPTS (13.5 g, 53.8 mmol) in 2-methylpropan-2-ol (60 mL) were boiled under reflux in an argon atmosphere for 4h. The reaction mixture was diluted with ethyl acetate (250 mL) and washed with saturated aqueous NaCl (5x150 mL). The organic layer was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:2) gave product **31** as white solids (0.474g, 37.4% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 1.63(s, 3H), 4.62(s, 2H), 5.04(d, *J* = 4.5 Hz, 1H), 5.86(m, 1H), 7.16(m, 1H), 7.31(m, 3H), 7.93(s, 1H).

(3*R*,4*S*)-3-acetoxy-4-(3-hydroxymethyl)phenylazetidin-2-one (23b)

$K_2HPO_4 \cdot 3H_2O$ (28.5 g, 125 mmol) and KH_2PO_4 (1.22 g, 9.00 mmol) were dissolved in H_2O (250 mL) to prepare buffer solution. **31** (570 mg, 2.43 mmol), ether (18 mL) and buffer solution (12 mL)

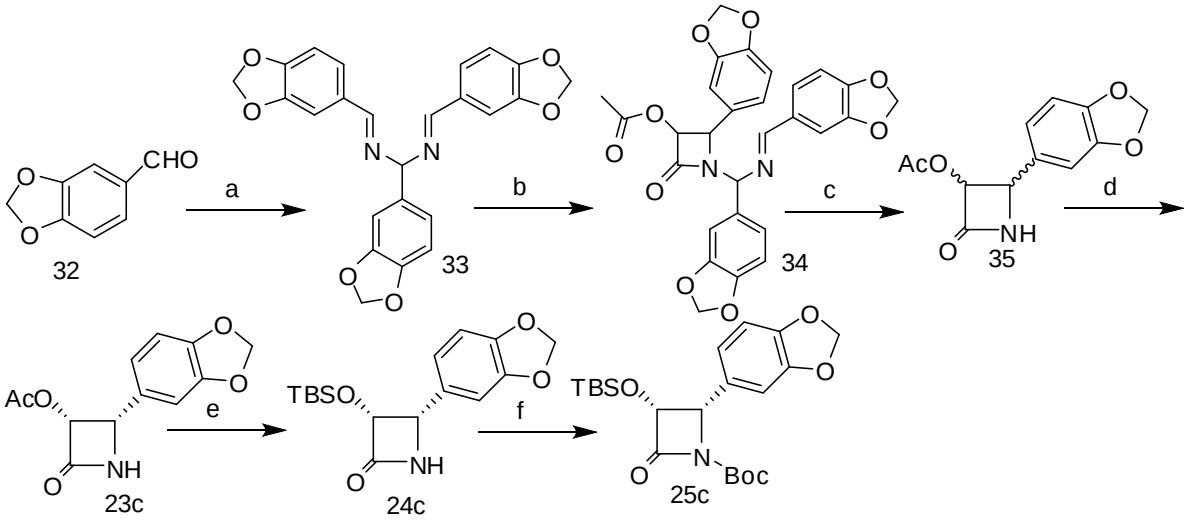
were mixed and a pig liver homogenate (3 mL) was added. The reaction mixture was stirred vigorously at 24^{o}C for 70 min and then quenched with acetone. Ethyl acetate (80 mL) was added and the mixture was filtered. The filter residue was washed with ethyl acetate (3x30 mL). The organic layer was washed with saturated aqueous NaCl (2x50 mL), dried over anhydrous Na_2SO4, and then concentrated under reduced pressure. α_D^{20}= -7.14 (*c* 1.40 mg/mL, CH_3OH). Purification of the crude product by silica gel chromatography (acetone: petroleum ether = 1:2) gave product **23b** as a white solid (152 mg, 26.7% yield). α_D^{20}= -7.14 (c=1.40 mg/ml, CH_3OH): ^{1}H NMR (300 MHz, acetone-d_6) δ 1.63(s, 3H), 4.62(s, 2H), 5.04(d, *J* = 4.8 Hz, 1H), 5.86(d, *J* = 4.4 Hz, 1H), 7.16(brs, 1H), 7.31(m, 3H), 7.93(s, 1H); MS (ESI) $C_{12}H_{13}NO_4$ *m/z* 258.1 (M + Na^+).

(3*R*,4*S*)-3-triethylsilyloxy-4-(3- triethylsilyloxymethyl)phenylazetidin-2-one (24b)

To a solution of **23b** (87 mg, 0.370 mmol) in dry THF (1.0 mL) was added pyridine (60 μL, 0.748 mmol) and pyrrolidine (62 μL, 0.748 mmol). The reaction mixture was stirred at room temperature for 7 h and then pyridine (180 μL, 2.24 mmol) and TESCl (376 μL, 2.24 mmol) were added. The reaction mixture was stirred at room temperature for another 8 h and then diluted with ethyl acetate (30 mL). The mixture was washed with saturated aqueous NH_4Cl (5x15 mL). The organic layer dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:5.5) afforded product **24b** as an oil (113mg, 72.5% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37-0.51(m, 6H), 0.650(q, *J* = 8.0 Hz, 6H), 0.76(t, *J* = 7.8 Hz, 9H), 0.98(t, *J* = 7.8 Hz, 9H), 4.73(s, 2H), 4.78(d, *J* = 4.8 Hz, 1H), 5.07(dd, *J* = 4.8, 2.8 Hz, 1H), 6.12(s, 1H), 7.18-7.20(m, 1H), 7.26-7.33(m, 3H); MS (ESI) $C_{22}H_{39}NO_3Si_2$ *m/z* 422.2 (M + H^+), 439.2(M + NH_4^+).

(3*R*,4*S*)-1-(tert-Butoxycarbonyl)-3-triethylsilyloxy-4-(3-triethylsilyloxymethyl)phenyl-azetidin-2-one (25b)

To a solution of **24b** (113 mg, 0.268 mmol), triethylamine (90 μL, 0.648 mmol) and DMAP (15 mg 0.123 mmol) in methylene chloride (0.8 mL), di-tert-butyl dicarbonate (117 mg, 0.536 mmol) dissolved in 0.4 mL of methylene chloride was added. The reaction mixture was stirred at room temperature for 12 h, diluted with ethyl acetate (30 mL). The mixture was washed with saturated aqueous NH_4Cl (3x15 mL). The organic layer dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:15) gave product **25b** as an oil (121mg, 86.5% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.36-0.50(m, 6H), 0.64(q, *J* = 7.9 Hz, 6H,), 0.76(t, *J* = 8.0 Hz, 9H), 0.97(t, *J* = 8.0 Hz, 9H), 1.39(s, 9H), 4.72(brs, 2H), 5.04(m, 2H), 7.15-7.22(m, 2H), 7.29-7.31(m, 2H); MS (ESI) $C_{27}H_{47}NO_5Si_2$ *m/z* 539.4 ($M + NH_4^+$), 544.2($M + Na^+$).



(a) NH_3, C_2H_5OH, room temp, 12 h, 86.9%; (b) CH_3COOCH_2COCl, Et_3N, CH_2Cl_2; room temp, 12 h; (c) CH_3COOH, 42 ^oC, 4 h, 78.6% for two steps (b and c); (d) lipase, buffer, Et_2O, 25 ^oC,

40.7%; (e) pyrrolidine, pyridine, 25 ^{o}C, 8 h and then TBSCl, Im, THF, 25 ^{o}C, 6 h, 84.6%; (f) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 25 ^{o}C, 8 h, 84.3%.

(NE,NE)-1-(benzo[d][1,3]dioxol-5-yl)-N,N'-bis(benzo[d][1,3]dioxol-5-ylmethylene) methanediamine (33)

To a solution of saturated NH_3 in ethanol (75 mL) was added **32** (2252 mg, 15 mmol) and the reaction was stirred for 12 hours at room temperature. The mixture was concentrated *in vacuo*. The residue was purified by recrystallization with ethanol to afford **13** (1870 mg, 86.9% yield) as white solids: ^{1}H NMR (300 MHz, acetone-d_6) δ 5.85 (s, 1H) , 5.95 (s, 2H) , 6.06 (s, 4H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 1H), 7.02 (s, 1H), 7.28 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.45 (d, *J* = 1.2 Hz, 2H), 8.51 (s, 2H).

(E)-2-(benzo[d][1,3]dioxol-5-yl)-1-(benzo[d][1,3]dioxol-5-yl(benzo[d][1,3]dioxol-5-ylmethyleneamino)methyl)-4-oxoazetidin-3-yl acetate (34)

To a solution of **33** (2516 mg, 5.846 mmol) in 50 mL CH_2Cl_2 was added CH_3COOCH_2COCl (878 mg, 6.430 mmol) at 0^{o}C, and the reaction was stirred for 12 hours at room temperature. CH_2Cl_2 (150 mL) was added and the organic phase was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The residue was treated for the next step. ^{1}H NMR (300 MHz, acetone-d_6): δ 1.70 (s, 3H), 2.82 (s, 6H), 4.83 (d, *J* = 4.8 Hz, 1H), 5.22 (d, *J* = 4.8 Hz, 1H), 5.78 (dd, *J* = 4.8, 2.1 Hz, 1H), 5.90-5.85 (m, 1H), 6.09-5.84 (m, 5H), 6.66-6.50 (m, 2H), 6.97-6.73 (m, 6H), 7.34-7.18 (m, 1H), 8.40 (s, 1H).

2-(benzo[d][1,3]dioxol-5-yl)-4-oxoazetidin-3-yl acetate (35)

To a solution of the residue obtained above in 30 mL CH_2Cl_2 was added 3 mL CH_3COOH and 1 mL water. The mixture was stirred for 4 hours at 42^oC and 30 mL CH_2Cl_2 was added. The mixture was washed by saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate = 2:1) to afford **15** (1071 mg, 78.6% yield for two steps) as white solids: ^1H NMR (300 MHz, acetone-d_6) δ 1.73 (s, 3H), 4.99 (d, *J* = 4.8 Hz, 1H), 4.99 (d, *J* = 4.8 Hz, 2H), 5.81 (dd, *J* = 4.8, 2.7 Hz, 1H), 6.00 (s, 2H), 6.94 – 6.67 (m, 3H), 7.88 (s, 1H); MS (ESI) *m/z* $C_{12}H_{11}NO_5$ 250.1 ($M + H^+$), 272.0 ($M + Na^+$).

(3*R*,4*S*)-3-acetoxy-4-(benzo[d][1,3]dioxol-5-yl)azetidin-2-one (23c)

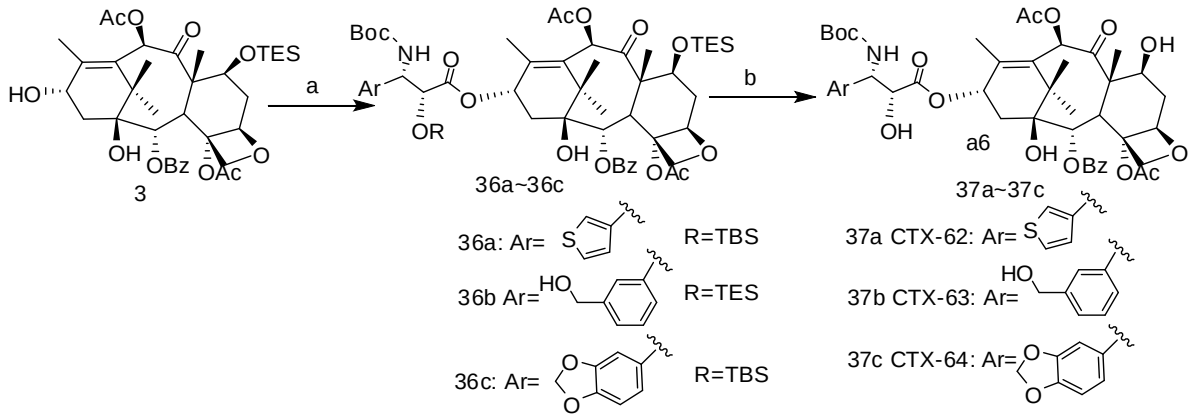
To a solution of **15** (997 mg, 4 mmol) in 30 mL ethoxyethane was added 20 mL of 0.2 M sodium phosphate buffer (pH 7.5) and 5 mL of crude pig lipase and the mixture was stirred vigorously with a magnetic stirrer at 25 ^oC until approximately 50% of the substrate was transformed into production. Acetone (15 mL) was added and the mixture was filtered, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate = 2:1) to afford **16** (406 mg, 40.7% yield) as white solids. α_D^{20} = -14.014 (*c* 1.04 mg/mL, $CHCl_3$): ^1H NMR (300 MHz, acetone-d_6) δ 1.73 (s, 3H), 4.99 (d, *J* = 4.8 Hz, 1H), 4.99 (d, *J* = 4.8 Hz, 2H), 5.81 (dd, *J* = 4.8, 2.7 Hz, 1H), 6.00 (s, 2H), 6.94-6.67 (m, 3H), 7.88 (s, 1H); MS (ESI) $C_{12}H_{11}NO_5$ *m/z* 250.1 ($M + H^+$), 272.0 ($M + Na^+$).

(3*R*,4*S*)-3-((tert-butyldimethylsilyl)oxy)-4-(benzo[d][1,3]dioxol-5-yl)azetidin-2-one (24c)

To a solution of **23c** (199 mg, 0.8 mmol) in 3.2 mL THF was added pyrrolidine (171 mg, 2.4 mmol) and pyridine (190 mg, 2.4 mmol) and the mixture was stirred for 8 hours at 25^{o}C. TBSCl (724 mg, 4.8 mmol) and imidazole (163 mg, 2.4 mmol) was added and the mixture was stirred for another 6 hours at 25 ^{o}C. The mixture was diluted by 20 mL saturated aqueous NH_4Cl , extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate = 5:1) to afford **24c** (218 mg, 84.6% yield) as white solids: ^{1}H NMR (300 MHz, acetone-d_6) δ -0.11 (s, 3H), 0.05 (s, 3H), 0.70 (s, 9H), 4.80 (d, *J* = 4.8 Hz, 1H), 5.06 (dd, *J* = 4.8, 2.7 Hz, 1H), 6.82 (s, 3H), 5.96 (s, 2H), 7.56 (s, 1H); MS (ESI) $C_{16}H_{23}NO_4Si$ *m/z* 322.0 (M + H^+), 344.2 (M + Na^+).

(3*R*,4*S*)-1-(tert-Butoxycarbonyl)-3-((tert-butyldimethylsilyl)oxy)-4-(benzo[d][1,3]dioxol-5-yl)azetidin-2-one (25c)

To a solution of **24c** (55 mg, 0.169 mmol) in 0.4 mL THF was added $(Boc)_2O$ (74 mg, 0.338 mmol), DMAP (1 mg, 0.008 mmol) and Et_3N (35 mg, 0.340 mmol). The mixture was stirred for 8 hours at 25 ^{o}C. Saturated aqueous $NaHCO_3$ (2 mL) was added and the aqueous phase was extracted with ethyl acetate, dried by anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate = 10:1) to afford **25c** (60 mg, 84.3% yield) as white solids: ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.12 (s, 3H), 0.70 (s, 3H), 0.69 (s, 9H), 1.43 (s, 9H), 4.96 (d, *J* = 5.7 Hz, 1H), 4.99 (d, *J* = 5.7 Hz, 1H), 5.98 (s, 2H), 6.89 – 6.64 (m, 3H); MS (ESI) $C_{21}H_{31}NO_6Si$ *m/z* 421.1 (M + Na^+).



(a) β-lactam, LHMDS, THF; (b) HF/pyridine, CH_3CN.

2'-O-(t-Butyldimethylsilyl)-3'N-debenzoyl-3'N-BOC-3'C-dephenyl-3'C-(thiophen-3-yl)- 7-O-(triethylsilyl)-taxol (36a)

To a solution of 7-triethylsilylbaccatinIII **3** (33 mg, 0.043 mmol) and **25a** (33 mg ,0.086 mmol) in 1 mL dry THF was added 0.086 mL LHMDS (1.06 M in THF) dropwise at -40^{o}C and the solution was stirred at the same temperature for 1h. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was treated for the next step.

7,2'-di(triethylsilyl)-10-acetoxyl-3'-debenzoyl-3'-[3-((triethylsilyloxy)methyl)phenyl] docetaxel (36b)

A solution of 7-O-(triethylsilyl)baccatin III **3** (46 mg, 0.0657 mmol) in THF (0.8 mL) under argon was cooled to -50°C and a solution of LHMDS (140 μL, 0.148 mmol, 1.06 M in THF) was added. The reaction mixture was stirred for 25 min at -45 °C and then **25b** (57 mg, 0.109 mmol) in

0.6 mL of THF was added and the reaction mixture was stirred for 1h at the same temperature and then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with saturated aqueous NH_4Cl (5 x 15 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude product by silica gel chromatography (ethyl acetate: petroleum ether = 1:6) gave product **36b** as a sticky solid (54 mg, 67.3% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.30-0.46(m 6H), 0.54-0.71(m, 12H), 0.75-0.80(m, 9H), 0.90-1.02(m, 18H), 1.23(s, 6H), 1.30(s, 9H), 1.70(s, 3H), 1.87-1.95(m, 1H), 2.02(s, 3H), 2.18(s, 3H), 2.09-2.48(overlap, 2H), 2.52(s, 3H), 2.48-2.58(overlap, 1H), 3.85(d, *J* = 6.9 Hz, 1H), 4.19, 4.32(ABq, *J* = 7.7 Hz, 2H), 4.49(dd, *J* = 10.2, 6.8 Hz, 1H), 4.57(s, 1H), 4.74(s, 2H), 4.95(d, *J* = 8.7 Hz, 1H), 5.29(brd, 1H 5.45(d, *J* = 8.7 Hz, 1H), 5.70(d, *J* = 6.9 Hz, 1H), 6.28(t, *J* = 9.0 Hz, 1H), 6.47(s, 1H), 7.13-7.16(m, 1H), 7.27-7.35(m, 3H), 7.48(t, *J* = 7.2Hz, 2H), 7.59(t, *J* = 6.3Hz, 1H), 8.12(d, *J* = 7.5 Hz, 2H); MS (ESI) $C_{64}H_{99}NO_{16}Si_3$ *m/z* 1222.5 ($M + H^+$), 1244.5 ($M + Na^+$).

2'-O-(t-Butyldimethylsilyl)-3'N-debenzoyl-3'N-Boc-3'C-dephenyl-3'C-((benzo[d][1,3]dioxol-5-yl)- 7-O-(triethylsilyl)-taxol (36c)

To a solution of 7-triethylsilylbaccatinIII **3** (42 mg, 0.059 mmol) and **25c** (50 mg , 0.118 mmol) in 1.38 mL dry THF was added 0.118 mL LHMDS (1.06 M in THF) dropwise at -40^{o}C and the solution was stirred at the same temperature for 1h. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was treated for the next step.

3'N-debenzoyl-3'N-Boc-3'C-dephenyl-3'C-(thiophen-3-yl)-taxol (37a, CTX62)

To a solution of the residue obtained above in 0.26 mL pyridine and 0.98 mL acetonitrile was added dropwise 0.15 mL HF (wt 40%) at 0 ^{o}C, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4, concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate = 1:1) to afford **37a** (CTX62) as white solids (24 mg, 67.0% yield, for two steps): HPLC purity: 96%, 5.71 min (254 nm). ^{1}H NMR (300 MHz, $CDCl_3$) 1.16 (s, 3H), 1.24 (s, 3H), 1.34 (s, 9H), 1.68 (s, 3H), 1.86 (s, 3H), 1.80 – 1.86 (m, 1H, overlapped), 2.24 (s, 3H), 2.32 - 2.35 (m, 2H, overlapped), 2.35 (s, 3H), 2.53 (ddd, *J* = 14.4, 9.6, 7.5 Hz, 1H), 3.49 (s, 1H), 3.81 (d, *J* = 6.9 Hz, 1H), 4.17 (d, *J* = 8.7 Hz, 1H), 4.30 (d, *J* = 8.7 Hz, 1H), 4.46 – 4.35 (dd, *J* = 10.5, 6.6 Hz 1H), 4.63 (d, *J* = 1.8 Hz 1H), 4.95 (d, *J* = 8.7 Hz, 1H), 5.32 (s, 2H), 5.67 (d, *J* = 6.9 Hz, 1H), 6.23 (t, *J* = 8.4 Hz, 1H), 6.30 (s, 1H), 7.11 (d, *J* = 5.1 Hz, 1H), 7.30 (s, 1H), 7.38 – 7.33 (m, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 14.2, 14.8, 20.8, 21.0, 22.5, 26.7, 28.1, 35.4, 43.2, 45.6, 58.5, 60.4, 72.1, 72.4, 73.1, 74.9, 75.6, 76.4, 79.0, 80.2, 81.1, 84.4, 122.4, 126.5, 126.6, 128.7, 129.1, 130.2, 133.0, 133.6, 139.3, 142.3, 155.3, 167.0, 170.1, 171.2, 172.8, 203.6; MS (ESI) $C_{43}H_{53}NO_{15}S$ *m/z* 856.3 ($M + H^+$), 878.2 ($M + Na^+$).

10-acetoxyl-3'-debenzoyl-3'-[(3-hydroxymethyl)phenyl]-docetaxel (37b, CTX63)

To a solution of **36b** (44 mg, 0.0360 mmol) in acetonitrile (1.2 mL) was added dropwise 0.3 mL of HF/pyridine (v:v = 1:2) at 0°C. The reaction mixture was stirred at room temperature for 23 h, quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate, and washed with saturated NH_4Cl. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel chromatography (dichloromethane:

methanol = 20:1) gave product **37b** (CTX63) as white solids (25mg, 79.0% yield): HPLC purity: 95%, 5.48 min (254 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14(s, 3H), 1.26(s, 3H), 1.34(s, 9H), 1.67(s, 3H), 1.84(s, 3H), 1.85-1.91(overlap, 1H), 2.24(s, 3H), 2.15-2.25(m, 2H), 2.36(s, 3H), 2.48-2.58(m, 1H), 3.77(d, *J* = 6.6 Hz, 1H), 4.16, 4.30(ABq, *J* = 8.3 Hz, 1H), 4.39(dd, *J* = 10.5, 6.2 Hz, 1H), 4.57(s, 1H), 4.69(s, 2H), 4.94(d, *J* = 8.4 Hz, 1H), 5.21(brd, 1H), 5.41(d, *J* = 9.0 Hz, 1H), 5.66(d, *J* = 6.9 Hz, 1H), 6.19(t, *J* = 8.7 Hz, 1H), 6.28(s, 1H), 7.26-7.42(m, 5H), 7.51(t, *J* = 7.5 Hz, 2H), 7.62(t, *J* = 7.1 Hz, 1H), 8.10(d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 9.6, 14.8, 20.8, 21.9, 22.6, 26.7, 28.2, 35.4, 35.6, 43.2, 45.6, 56.6, 58.5, 65.0, 72.1, 72.3, 74.0, 74.9, 75.5, 76.4, 79.0, 80.3, 81.1, 84.3, 109.7, 125.5, 125.8, 126.8, 128.7, 129.0, 129.1, 130.2, 133.0, 133.7, 141.6, 142.2, 155.4, 167.0, 170.2, 171.3, 172.9, 203.6; MS (ESI) $C_{46}H_{57}NO_{16}$ *m/z* 880.4 ($M + H^+$), 902.4 ($M + Na^+$).

3'N-debenzoyl-3'N-Boc-3'C-dephenyl-3'C-((benzo[d][1,3]dioxol-5-yl)-paclitaxel (37c, CTX64)

To a solution of the residue obtained above in 0.311 mL pyridine and 0.593 mL acetonitrile was added dropwise 0.185 mL HF (wt 40%) at 0 ^{o}C, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate = 1:1) to afford **37c** (CTX64) as white solids (24 mg, 35.0% yield for two steps): HPLC purity: 97%, 3.75 min (254 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.29 (s, 3H), 1.33 (s, 9H), 1.68 (s, 3H), 1.85 – 1.76 (m, 1H), 1.87 (s, 3H), 2.25 (s, 3H), 2.23 – 2.32 (m, 2H), 2.38 (s, 3H), 2.55 (ddd, *J* = 15.9, 12.6, 7.8 Hz, 1H), 3.80 (d, *J* = 8.7 Hz, 1H), 4.17 (d, *J* = 8.7 Hz, 1H), 4.31 (d, *J* = 8.7 Hz, 1H),

4.41 (dd, *J* = 10.5, 6.6 Hz 1H), 4.56 (s, 1H), 4.95 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 6.9 Hz, 1H), 5.33 (d, *J* = 8.7 Hz, 1H), 5.67 (d, *J* = 7.2 Hz, 1H), 6.23 (t, *J* = 8.4 Hz 1H), 6.30 (s, 1H), 6.82 (s, 1H), 6.89 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.5, 14.8, 20.9, 21.8, 22.6, 26.7, 28.2, 35.5, 35.6, 43.2, 45.6, 56.0, 58.6, 72.2, 72.4, 73.7, 74.9, 75.6, 76.5, 79.0, 80.3, 81.1, 84.4, 101.3, 107.4, 108.4, 109.8, 120.1, 128.7, 129.1, 130.2, 133.0, 133.7, 142.2, 147.4, 148.2, 155.4, 167.1, 170.2, 171.3, 178.9, 203.7; MS (ESI) $C_{46}H_{55}NO_{17}$ *m/z* 916.3 ($M + Na^+$).

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