Novel Cytotoxic 3′-(*tert*-Butyl) 3′-Dephenyl Analogs of Paclitaxel and Docetaxel

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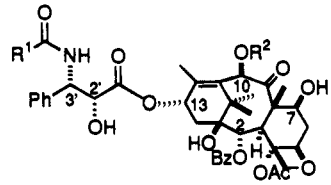
3′-(*tert*-Butyl) 3′-dephenyl analogs of paclitaxel were synthesized from 10-deacetylbaccatin III and oxazolidinecarboxylic acid **7** followed by acylation of intermediate amines **10** and **11**. Oxazolidinecarboxylic acid **7** was prepared in five steps and in good overall yield from L-*tert*-leucine. Twelve analogs were synthesized and evaluated for their *in vitro* ability to stimulate the formation of microtubules and for their cytotoxicity against B16 melanoma cells. Amide, carbamate, urea, and thiourea congeners were prepared. The most potent derivatives found in this study are the docetaxel analog **13**, the *N*-[(*tert*-amyloxy)carbonyl] analog **17**, and the 3′-phenylurea and 3′-*tert*-butylurea derivatives **20** and **23**. Six of these analogs were shown to be ca. 90 times more soluble in water than paclitaxel and ca. 4–5 times more water-soluble than docetaxel.

Paclitaxel (**1**), a complex diterpenoid isolated in small quantities from the bark of *Taxus brevifolia*,[1] is regarded as the most promising anticancer agent[2] developed in this decade for the treatment of ovarian[3] and breast[4] cancer. Recent clinical trials have demonstrated that paclitaxel may also be of utility for the chemotherapy of head and neck cancer, lung cancer, and esophageal carcinomas.[4] Paclitaxel is an antimitotic agent with a unique mode of action, promoting the assembly of stable microtubules, which cannot be depolymerized by calcium, cold, or microtubule-disassembling drugs.[5,6] Docetaxel (**2**), a semisynthetic analog[7] of paclitaxel, has a similar mechanism of action.[8] However, docetaxel is two times as active as paclitaxel in an *in vitro* tubulin assay as an inhibitor of microtubule depolymerization.[8] Preclinical *in vivo* studies in murine and human xenografts demonstrated that docetaxel is more cytotoxic than paclitaxel in the same tumor models.[8,9] Its clinical activity is similar to that of paclitaxel, but it apparently possesses a somewhat different activity profile than paclitaxel.[2] A phase II study of docetaxel with pancreatic cancer patients provided encouraging response rates (28%), whereas paclitaxel was not effective against this type of cancer.[2]



1 R^1 = Ph, R^2 = Ac (Paclitaxel)
2 R^1 = *tert*-BuO, R^2 = H (Docetaxel)

The excellent clinical activity of paclitaxel prompted intense research aimed at understanding the influence of structural modifications at the paclitaxel molecule on biological activity.[10–12] Modifications at positions 7–10 of the diterpene moiety are tolerated very well,[10,11,13] whereas removal and alterations of the substituents at C-2[14–18] and C-4[17–21] significantly influenced biological activity.[22] The presence of the C-13 side chain is an absolute requirement for activity.[1] Since NMR data indicate that bioactive taxanes assume a hydrophobically clustered conformation in aqueous solvents, involving the 2-benzoyl group, the 4-acetyl group, and the 3′-phenyl group,[23] we have suggested that the presence of these or structurally related groups is necessary to promote solution conformations important for bioactivity.[24]

Investigations by several groups have provided extensive data on structure-activity relationships of the C-13 *N*-benzoyl-3′-phenylisoserine side chain.[10,11,13] The natural stereochemistry at the C-13 moiety (2′*R*,3′*S*) and the presence of the 2′-hydroxyl group are required for strong microtubule binding.[7] Homologs of the C-13 side chain were found to be virtually inactive.[25–27] The *N*-benzoyl group tolerates a wide range of modifications,[7,24,27,28] and the 3′-phenyl moiety can be substituted[24,27,29] or heteroaromatic.[24,30,31] Recent reports from several groups have detailed that replacement of the 3′-phenyl group with aliphatic groups such as isobutyl or cyclohexyl moieties provides analogs with excellent bioactivity.[31–34]

We now wish to disclose chemical and biological studies on novel highly cytotoxic 3′-(*tert*-butyl) 3′-dephenyl analogs of paclitaxel and docetaxel. The 3′-*tert*-butyl analogs were prepared from commercially available 10-deacetylbaccatin III[35] and oxazolidinecarboxylic acid **7** followed by acylation of intermediate amines **10** and **11**.[36] The novel analogs were evaluated for their ability to stimulate microtubule assembly, for cytotoxicity against B16 melanoma cells, and for water solubility.

Oxazolidine **7**, which is the precursor for the C-13 *tert*-butylisoserine side chain, was prepared from L-*tert*-leucine (**3**) by a known procedure (Scheme 1).[25,36,37] Reduction of **3** with lithium aluminum hydride was followed by protection of the amino group with di-*tert*-butyl dicarbonate to yield alcohol **4**. Swern oxidation

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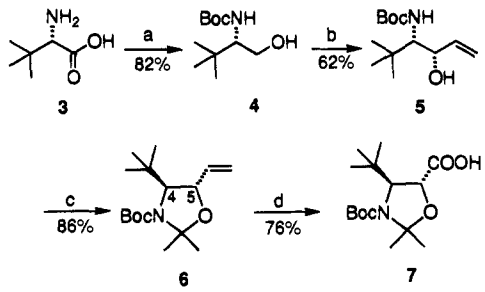
Scheme 1[a]



[a] (a) $LiAlH_4$, THF, $(Boc)_2O$; (b) Swern oxidation, $H_2C{=}CHMgBr$; (c) dimethoxypropane, PPTS; (d) $NaIO_4$, $RuCl_3$, H_2O, $NaHCO_3$.

of 4 to the corresponding aldehyde was followed by *in situ* treatment with vinylmagnesium bromide (Ireland–Norbeck protocol)[38] to provide allylic alcohol **5** as a single isomer. Compound **5** was converted to oxazolidine **6** with dimethoxypropane in the presence of catalytic amounts of PPTS. The stereochemistry of **6** was verified by an NOE experiment ($CDCl_3$ at 50 °C, 500 MHz). An observed NOE of 2% is indicative of a trans relationship of the two protons at the oxazolidine ring system.[25,39] Oxazolidine **6** gave the desired oxazolidinecarboxylic acid **7** upon oxidation with sodium periodate and $RuCl_3$. It is of note that these reactions can be performed at large scale, thus providing a sufficient supply of the key oxazolidinecarboxylic acid **7** for further transformations to bioactive taxanes and structure–activity studies.

10-Deacetylbaccatin III derivative **8**[7] was reacted with oxazolidinecarboxylic acid **7** in the presence of DCC and DMAP to yield coupled product **9** in 71% yield (Scheme 2).[36] Compound **9**, on hydrolysis using formic acid at room temperature, gave amine **10**. Further deprotection of the Troc groups in **10** with Zn/acetic acid provided amine **11** (Scheme 3). Both derivatives (**10** and **11**) can be used as intermediates for the synthesis of bioactive taxanes. When amine **10** was treated with benzoyl chloride under Schotten–Baumann conditions,[40] or with di-*tert*-butyl dicarbonate in the presence of base, followed by deprotection of the Troc groups, paclitaxel analog **12** and docetaxel analog **13**, respectively, were obtained (Scheme 2).

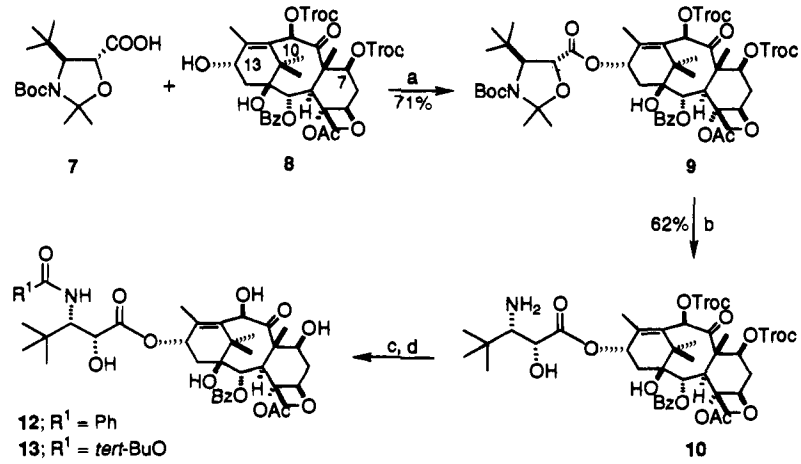
Compounds **12** and **13** were tested in comparison to paclitaxel for their ability to promote microtubule assembly and for their cytotoxicity against B16 melanoma cells (Table 1).[40] Analog **12** showed one-half the activity of paclitaxel in the microtubule assembly assay and was ca. 6 times less cytotoxic than paclitaxel against B16 melanoma cells. Of interest is the finding that docetaxel analog **13** is ca. 2 times as active as paclitaxel and as active as docetaxel in both assays.

The promising biological properties of the 3′-*tert*-butyl analogs **12** and **13** prompted us to initiate an investigation aimed at identifying optimal substituents for the amino group at the C-13 *tert*-butylisoserine side chain. Derivatives **14**–**23** were prepared either by acylation of amine **10** with the appropriate reagents followed by deprotection of the Troc groups at C-7 and C-10 or in one step by acylation of derivative **11** (Scheme 3).

Initially, we prepared carbamates **14**–**17** and amides **18** and **19** which are structurally closely related to the highly cytotoxic docetaxel analog **13**. The isobutoxy analog[41] **14** and the *n*-butoxy analog **15**,[42] constitutional isomers of **13**, were more active than paclitaxel in the microtubule assembly assay but slightly less cytotoxic than paclitaxel against B16 melanoma cells (Table 2). Further extension of the carbon chain, exemplified by *n*-hexyloxy derivative **16**, led to reduced activity in both assays in comparison to paclitaxel and *n*-butoxy derivative **15**. The *N*-[(*tert*-amyloxy)carbonyl] derivative **17**,[41] a homolog of **13**, showed better activity than paclitaxel in the microtubule assembly assay (ED_{50}/ED_{50}(paclitaxel) = 0.45) and was ca. 2 times as cytotoxic as paclitaxel against B16 melanoma cells (ED_{50}/ED_{50}(paclitaxel) = 0.58). Deletion of the oxygen of the *N*-*tert*-Boc group, as in pivaloyl derivative **18**, led to greatly reduced cytotoxicity against B16 melanoma cells (ED_{50}/ED_{50}(paclitaxel) = 32). Since **18** demonstrated good microtubule-assembly properties (ED_{50}/ED_{50}(paclitaxel) = 1.3), it must be assumed that its diminished cytotoxicity is due to unfavorable uptake or metabolism. This outcome corroborates similar results obtained from investigations on related *N*-pivaloyl paclitaxel analogs.[24,28] Compound **19**, in which the oxygen of the *N*-*tert*-Boc group is replaced by a methylene group,[43] showed excellent activity in the microtubule-assembly assay (ED_{50}/ED_{50}(paclitaxel) = 0.48) and better activity against B16 melanoma cells (ED_{50}/ED_{50}(paclitaxel) = 3.6) than pivaloyl derivative **18**.

Bioisostere **20**, a urea derivative in which the oxygen of the *N*-*tert*-Boc group is replaced by a nitrogen, was

Scheme 2[a]



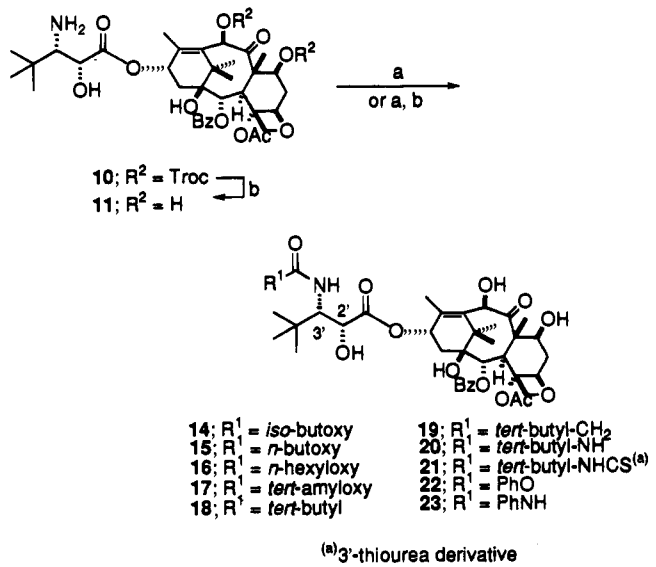
[a] (a) DCC, DMAP, toluene, 60–85 °C, 24 h, 71%; (b) HCOOH 24 °C, 24 h, 62%; (c) for **12** PhCOCl, EtOAc, aqueous $NaHCO_3$, 24 °C, 20 min, 95%; (d) for **13** di-*tert*-butyl dicarbonate, THF, $NaHCO_3$, 24 °C, 6 h, 96%; (d) Zn, AcOH, MeOH, 60 °C, 2–3 h, 55–63%.

Table 1. Biological Evaluation of Paclitaxel Analogs **12–23** in the Microtubule-Assembly Assay and for Their Cytotoxicity against B16 Melanoma Cells in Comparison to Paclitaxel and Docetaxel

		microtubule assembly			B16 melanoma cells		
		ED_{50} (μM)[a]			ED_{50} (μM)[b]		
compd	R^1	paclitaxel	analog	ED_{50}/ED_{50}(paclitaxel)[a]	paclitaxel	analog	ED_{50}/ED_{50}(paclitaxel)[b]
2 (docetaxel)		1.14	0.51	0.45	27	11	0.41
12	Ph	0.93	1.7	1.8	31.3	23.5	7.5
13	*tert*-butoxy	0.93	0.35	0.38	31.3	12.5	0.40
14	isobutoxy	0.93	0.50	0.54	31.3	47	1.5
15	*n*-butoxy	0.93	0.80	0.86	31.3	64	2.1
16	*n*-hexyloxy	0.93	2.1	2.3	31.3	370	12
17	*tert*-amyloxy	0.93	0.42	0.45	31.3	18	0.58
18	*tert*-butyl	1.05	1.35	1.3	29	930	32
19	*tert*-butyl-CH_2	1.05	0.50	0.48	29	104	3.6
20	*tert*-butyl-NH	1.05	0.63	0.60	29	26	0.90
21	*tert*-butyl-NHCS[c]	0.90	3.2	3.6	24.4	>1000	>41
22	PhO	0.93	1.3	1.4	31.3	>1000	>32
23	PhNH	1.04	0.33	0.32	26.8	18.8	0.70

[a] ED_{50} is the concentration which causes polymerization of 50% of the tubulin present in 15 min at 37 °C. [b] ED_{50} refers to the concentration which produces 50% inhibition of proliferation after 40 h incubation. [c] 3′-Thiourea derivative.

Scheme 3[a]



[a] (a) R^1COCl/R^1OCOCl, aqueous $NaHCO_3$, H_2O, EtOAc, or $R^1OCOOCOOR^1$, $NaHCO_3$, THF, 24 °C, 4–6 h, or R^1NCO or R^1NCS, acetonitrile, 24 °C, 4–6 h; (b) Zn, AcOH, MeOH, 60 °C, 2 h.

Table 2. Water Solubility of Paclitaxel, Docetaxel, and Analogs **12–15**, **17**, **19**, **20**, and **23**

compd	R^1	water solubility (μg/mL)	analog solubility/paclitaxel solubility
1 (paclitaxel)		0.30	1
2 (docetaxel)		5.0–6.0	17–20
12	Ph	2.8	9.3
13	*tert*-butoxy	28–33	93–110
14	isobutoxy	28–32	93–107
15	*n*-butoxy	27–29	90–97
17	*tert*-amyloxy	26	87
19	*tert*-butyl-CH_2	26	87
20	*tert*-butyl-NH	29	97
23	PhNH	1.4	4.7

found to possess better activity in both assays than paclitaxel. The thiourea derivative **21**, however, showed greatly diminished activity, especially in the assay for B16 melanoma cytotoxicity (ED_{50}/ED_{50}(paclitaxel) = >41). These results suggest that the effects of the thiocarbonyl group,[44] which involve a decrease in hydrogen bonding and an increase in polarizability and bulk as compared to a carbonyl group, are deleterious to cytotoxicity.

Since 3′-carbamates are excellent 3′-substituents for bioactive taxanes, we also prepared phenoxy derivative **22** as a carbamate analog of paclitaxel. Although **22** showed good microtubule-assembly properties, it was found to possess very little cytotoxicity (ED_{50}/ED_{50}(paclitaxel) = >32) compared to the parent. Surprisingly, the corresponding urea derivative **23** displayed better activity than paclitaxel in both assays (ED_{50}/ED_{50}(paclitaxel) = 0.32 in the microtubule-assembly assay and ED_{50}/ED_{50}(paclitaxel) = 0.70 in the cytotoxicity test against B16 melanoma cells).

Of interest is the finding that urea derivatives **20** and **23** prepared in this study and a related analog prepared by the Abbott group[28] displayed excellent cytotoxicity. Thus it appears that moieties such as 3′-*tert*-butylurea and 3′-phenylurea can be regarded as 3′-substituents providing taxanes with excellent cytotoxicity. It is also of note that replacement of the natural paclitaxel 3′-benzamide group in **12** with a 3′-phenylurea moiety, compound **23**, resulted in an 8-fold increase of cytotoxicity against B16 melanoma cells.

The lack of sufficient aqueous solubility (Table 2)[45] was one of the major problems associated with paclitaxel's formulation for clinical applications.[22,46] Currently, the drug is administered in a Cremophor EL/ethanol mixture, which is diluted with saline or dextrose. However, exposure of patients to a large amount of Cremophor EL results in severe acute allergic reactions.[2] Therefore, patients have to be pretreated with corticosteroids and antihistamines prior to paclitaxel treatment to avoid hypersensitivity reactions.[2] Docetaxel is ca. 20 times (Table 2)[45] more water-soluble than paclitaxel.[46] This is due to the presence of a hydroxyl group at C-10, instead of the 10-acetoxy group as found in paclitaxel, and the replacement of the paclitaxel *N*-benzoyl group with the *N*-Boc group in docetaxel. Nonetheless, docetaxel is also formulated using a surfactant, polysorbate 80/ethanol in dextrose.[47] Since our novel derivatives possess a 3′-*tert*-butyl group, which is less lipophilic[48] than the 3′-phenyl group present in paclitaxel and docetaxel, we expected that these analogs would be more soluble in water. All active derivatives were therefore tested for their water solubility (Table 2). As expected, they displayed superior solubility compared to paclitaxel and docetaxel. Most analogs were ca. 90 times more water-soluble than paclitaxel and ca. 4–5 times more soluble than docetaxel (Table

2). The degree of solubility of these compounds is attractively enhanced, however, not high enough to allow for drug formulation in aqueous solutions without the addition of a surfactant.

In summary, we have prepared novel highly cytotoxic 3′-*tert*-butyl analogs of paclitaxel with attractively enhanced water solubility properties. The most active derivatives found in this study are the docetaxel analog **13**, the docetaxel homolog **17**, and the urea analogs **20** and **23**. All four analogs were more cytotoxic than paclitaxel, and derivatives **13** and **17** had activity similar to docetaxel against B16 melanoma cells. The analogs were ca. 90 times more water-soluble than paclitaxel and ca. 4−5 times more soluble than docetaxel.

Experimental Section[49]

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3,3-dimethyl-1-butanol (4), L-*tert*-Leucine (**3**) (15.0 g, 115 mmol) was slowly added under reflux to a suspension of lithium aluminum hydride (8.64 g, 229 mmol, 2 equiv) in THF (375 mL). After the addition was completed, the reaction mixture was refluxed for an additional 6 h and cooled to room temperature. Excess of lithium aluminum hydride was quenched by adding an aqueous solution of 10% NaOH (15 mL) followed by slow addition of water (15 mL) with external cooling (ice bath). The reaction mixture was stirred at 24 °C for 10 min and then treated with a solution of di-*tert*-butyl dicarbonate (27.33 g, 126.0 mmol, 1.1 equiv) in methylene chloride (100 mL). The reaction mixture was stirred at 60 °C for 6 h, cooled to room temperature, and filtered through sodium sulfate. Removal of the solvent under reduced pressure afforded a solid which was recrystallized from hexane (15 mL) to give 4 (17 g) as white crystals, mp 105 °C. The mother liquor was concentrated and purified by flash column chromatography on silica gel (hexane/ethyl acetate, 80:20) to give 4 (3.3 g). Total yield of 4: 20.3 g 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.45 (s, 9H), 2.69 (br s, 1H), 3.49 (d, J = 7.4 Hz, 2H), 3.84 (t, J = 7.5 Hz, 1H), 4.65 (br s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.2, 79.6, 63.1, 61.0, 31.6, 28.4, 26.8; IR ($CHCl_3$) 3350, 3270, 1680, 1560, 1470, 1360, 1290, 1250, 1180 cm^{-1}; MS (CI) *m/e* 218 (M^+ + 1), 162, 144, 118, 86, 60, 57; $[\alpha]_D$ −7.9° (*c* = 0.26, $CHCl_3$).

(3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-5,5-dimethyl-3-hydroxy-1-hexene (**5**). A solution of oxalyl chloride (2 M in CH_2Cl_2, 70.2 mL, 140 mmol, 1.5 equiv) in methylene chloride (250 mL) was cooled to −78 °C. To this was added dimethyl sulfoxide (10.6 mL, 150 mmol, 1.6 equiv), keeping the internal temperature at −78 °C, over a period of 10 min. The reaction mixture was stirred at −78 °C for 5 min, and then the temperature was raised to −65 °C over 20 min. To this solution at −65 °C was added a solution of 4 (20.30 g, 93.54 mmol) in methylene chloride (200 mL) over 20 min. After the addition was completed, the temperature was brought to −35 °C. Diisopropylethylamine (100 mL) was added at −35 °C, and the reaction mixture was allowed to warm to 0 °C over 20 min. The reaction mixture was transferred through a cannula to a solution of vinylmagnesium bromide (1 M solution in THF, 608 mL, 608 mmol, 6.5 equiv) at 24 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 2 h and treated with ethanol (200 mL) and then with saturated aqueous ammonium chloride solution (200 mL). Then the pH was adjusted to 3−4 using HCl (10% aq). Methylene chloride (150 mL) was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted further with methylene chloride (150 mL), and the organic layers were collected. The combined organic layers were washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a crude product which was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 97:3) to give **5** as a colorless viscous oil (14.0 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.42 (s, 9H), 2.10 (br s, 1H), 3.33 (d, J = 10.2 Hz, 1H), 4.49 (br s, 1H), 5.12 (d, J = 10.5 Hz, 2H), 5.25 (d, J = 17 Hz, 1H), 5.90 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.6, 140.19, 114.6, 78.8, 70.7, 60.9, 35.1, 28.3, 27.3; IR ($CHCl_3$) 3415, 1710, 1690 (br, 1500, 1390, 1360, 1240, 1170, 1060, 1000, 920 cm^{-1}; MS (CI) *m/e* 244 (M^+ + 1), 188, 170, 144, 86, 57; $[\alpha]_D$ −61.8° (*c* = 0.485, $CHCl_3$).

(4*S*,5*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-*tert*-butyl-5-vinyl-1,3-oxazolidine (**6**). A solution of **5** (14.0 g, 57.6 mmol) in toluene (180 mL) was treated with pyridinium *p*-toluenesulfonate (0.60 g, 2.4 mmol) and 2,2-dimethoxypropane (73.0 mL, 600 mmol, 10 equiv) at 24 °C. The reaction mixture was stirred at 80 °C for 4 h and cooled to 24 °C. Removal of the solvent under reduced pressure provided a colorless oil which was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 95:5) to afford **6** (14.0 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.47 (s, 9H), 1.59 (s, 6H), 3.92 (br s, 1H), 4.47 (d, J = 6.2 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 5.23 (d, J = 17.1 Hz, 1H), 6.05 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 140.1, 115.8, 79.8, 78.1, 69.1, 28.2, 27.9, 27.1; IR ($CHCl_3$) 1700, 1470, 1360, 1250, 1170, 1080, 1060, 950, 910, 860 cm^{-1}; MS (CI) *m/e* 284 (M^+ + 1), 279, 240, 226, 212, 184, 126, 73, 57; $[\alpha]_D$ −19.4° (*c*= 0.598, $CHCl_3$).

(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-4-*tert*-butyl-2,2-dimethyl-1,3-oxazolidine-5-carboxylic Acid (**7**). To a stirred mixture of **6** (1.2 g, 4.2 mmol) in acetonitrile (8 mL), carbon tetrachloride (8 mL), and water (12 mL) were added $NaHCO_3$ (2.3 g, 27 mmol, 6.5 equiv) at room temperature and $NaIO_4$ (4.9 g, 23 mmol, 5.5 equiv) in portions over a period of 5 min. The reaction mixture was stirred for 10 min and treated with $RuCl_3 \cdot H_2O$ (0.15 g, 0.72 mmol, 0.17 equiv). After stirring for 48 h at 24 °C, the reaction mixture was diluted with water (50 mL) and ether (50 mL) and stirred for 5 min. The mixture was filtered through Celite and the residue was washed with water. The aqueous layer was collected and acidified with HCl (pH = 3−4) and extracted with methylene chloride (2 × 25 mL). Combined extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude product was crystallized from hexane (2−3 mL) to give acid **7** (0.97 g, 76%): mp 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.47 (s, 9H), 1.63 (s, 6H), 4.47 (br s, 1H), 4.48 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.6, 154.7, 97.5, 80.8, 75.1, 67.7, 36.3, 28.2, 27.9, 26.9; IR ($CHCl_3$) 3500 (br), 1700 (br), 1470, 1360, 1240, 1160, 1130, 1080, 850 cm^{-1}; MS (CI) *m/e* 302 (M^+ + 1), 263, 246, 202, 156, 144, 128, 100, 58; $[\alpha]_D$ −30° (*c* = 0.53, $CHCl_3$). Anal. ($C_{15}H_{27}NO_5$: C, H, N.

13-[[(4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-4-*tert*-butyl-2,2-dimethyl-1,3-oxazolidin-5-yl]carbonyl]-10-deacetyl-7,10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]baccatin III (**9**). A mixture of 10-deacetylbaccatin III derivative **8** (2.2 g, 2.4 mmol) and oxazolidinecarboxylic acid **7** (0.79 g, 2.6 mmol, 1.1 equiv) in anhydrous toluene (80 mL) was treated with 1,3-dicyclohexylcarbodiimide (0.79 g, 3.8 mmol, 1.6 equiv) and 4-(dimethylamino)pyridine (0.15 g, 1.2 mmol, 0.50 equiv). The reaction mixture was heated at 60 °C for 20 h. Then the temperature was raised to 85 °C. After 4 h the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure, and the residue was taken into ethyl acetate (25 mL) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 4:1) to give **9** as a white amorphous solid (2.0 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.19 (s, 3H), 1.26 (s, 3H), 1.48 (s, 9H), 1.60 (s, 3H), 1.62 and 1.66 (2s, 6H), 1.85 (s, 3H), 2.09 (m, 2H), 2.25 (m, 1H), 2.42 (s, 3H), 2.62 (m, 1H), 3.98 (d, J = 6.8 Hz, 1H), 4.15 and 4.36 (2d, J = 8.5, 8.7 Hz, 2H), 4.41 (br s, 1H), 4.60 and 4.92 (2d, J = 11.8 Hz, 2H), 4.76 and 4.78 (2s, 2H), 4.99 (d, J = 8.4 Hz, 1H), 5.61 (dd, J = 7, 11 Hz, 1H), 5.71 (d, J = 7 Hz, 1H), 6.24 (t, J = 8 Hz, 1H), 6.27 (s, 1H), 7.50, 7.63, and 8.09 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.7, 171.8, 170.2, 166.7, 153.9, 153.6, 153.2, 142.9, 133.8, 131.6, 130.0, 128.9, 128.6, 94.2, 94.1, 83.7, 80.5, 79.0, 78.8, 77.3, 76.3, 76.2, 74.2, 71.3, 66.1, 60.3, 56.1, 49.8, 46.9, 43.0, 35.8, 33.2, 32.7, 32.6, 30.7, 30.2, 28.2, 28.1, 27.2, 27.0, 26.1, 26.0, 25.4, 25.3, 24.6, 21.8, 20.9, 15.5, 14.1, 10.6; IR ($CHCl_3$) 3480, 1755, 1725, 1700, 1450, 1350, 1280, 1170, 970, 730 cm^{-1}; MS (FAB$^+$) *m/e* calcd for $C_{50}H_{63}Cl_6NO_{18}Li$ 1182.2336, found 1182.2384, 1182 (M^+ + Li); $[\alpha]_D$ −41° (*c* = 0.71, $CHCl_3$).

3′-*tert*-Butyl-10-deacetyl-*N*-debenzoyl-3′-dephenyl-7,-

10-bis[[(2,2,2-trichloroethyl)oxy]carbonyl]paclitaxel (10). Oxazolidine adduct **9** (2.0 g, 1.7 mmol) was dissolved in formic acid (90%, 30 mL) and stirred at room temperature for 24 h. Formic acid was removed under reduced pressure at 24 °C. The residue was taken into dichloromethane (25 mL). The organic layer was washed with aqueous $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by column chromatography on silica gel (ethyl acetate/hexane, 1:1) gave **10** as a white amorphous solid (1.1 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.19 (s, 3H), 1.27 (s, 3H), 1.86 (s, 3H), 2.03 (m, 1H), 2.07 (s, 3H), 2.29 (m, 2H), 2.43 (s, 3H), 2.63 (m, 1H), 3.93 (d, J = 6.8 Hz, 1H), 4.17 and 4.34 (2d, J = 8.6 and 8.3 Hz, 2H), 4.42 (br s, 2H), 4.60 and 4.91 (2d, J = 11.7 Hz, 2H), 4.78 (br s, 2H), 4.98 (d, J = 7.9 Hz, 1H), 5.57 (m, 1H), 5.69 (d, J = 6.8 Hz, 1H), 6.22 (m, 1H), 6.26 (s, 1H), 7.49, 7.63, and 8.08 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.8, 174.6, 170.5, 166.7, 153.2, 153.1, 143.0, 133.8, 131.7, 130.0, 129.0, 128.7, 94.2, 94.1, 83.6, 80.6, 79.1, 78.8, 77.3, 76.4, 76.3, 74.1, 70.9, 70.8, 61.3, 60.4, 56.2, 46.9, 43.1, 35.5, 34.6, 33.2, 26.9, 26.3, 22.2, 21.0, 20.9, 15.0, 14.2, 10.7; IR ($CHCl_3$) 3500, 1760, 1720, 1450, 1380, 1250, 1080, 980, 830 cm^{-1}; MS (FAB$^+$) m/e calcd for (M^+ + H) $C_{42}H_{52}Cl_6NO_{16}$ 1036.1417, found 1036.1368, 1036 (M^+ + 1); $[\alpha]_D$ −39.9° (c = 0.975, $CHCl_3$).

General Procedure for the Removal of the [(2,2,2-Trichloroethyl)oxy]carbonyl (Troc) Protecting Groups: Synthesis of 3′-*tert*-Butyl-10-deacetyl-*N*-debenzoyl-3′-dephenylpaclitaxel (11). Method A. A mixture of amine **10** (0.30 g, 0.29 mmol), zinc dust (0.30 g), methanol (8 mL), and acetic acid (8 mL) was heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and filtered. The solvents were removed under reduced pressure, and the residue was taken into ethyl acetate (15 mL). The heterogeneous mixture was washed with aqueous saturated sodium bicarbonate solution (10 mL) and brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 8:2) gave **11** as an amorphous white solid (0.15 g): ^{1}H NMR (300 MHz, $CDCl_3$ + MeOH (1 drop)) δ 1.02 (s, 9H), 1.12 (s, 3H), 1.23 (s, 3H), 1.75 (s, 3H), 1.97 (s, 3H), 2.24 (d, J = 8.8 Hz, 2H), 2.38 (s, 3H), 2.59 (m, 1H), 2.89 (br s, 1H), 3.93 (d, J = 7.3 Hz, 1H), 4.19 and 4.32 (2d, J = 8.4, 8.3 Hz, 2H), 4.24 (m, 1H), 4.41 (br s, 1H), 4.96 (d, J = 8.4 Hz, 1H), 5.22 (s, 1H), 5.67 (d, J = 6.9 Hz, 1H), 6.18 (t, J = 9.0 Hz, 1H), 7.48, 7.62, and 8.00 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.1, 174.7, 170.3, 166.7, 138.7, 135.7, 133.6, 129.9, 129.3, 128.5, 84.3, 81.1, 78.6, 74.9, 74.3, 71.6, 71.5, 70.8, 61.1, 57.6, 46.4, 43.0, 36.5, 35.8, 34.5, 26.9, 26.4, 22.3, 20.7, 14.3, 9.8; IR ($CHCl_3$) 3450 (br), 1710 (br), 1450, 1370, 1250, 1070, 980, 910, 740 cm^{-1}; HRMS (FAB$^+$) m/z calcd for (M^+ + H) $C_{36}H_{50}NO_{12}$ 688.3333, found 688.3310, 710 (M^+ + Na), 688 (M^+ + H), 670, 597, 549, 509, 429, 399, 369, 327, 307, 277, 257, 243, 237, 226, 215; $[\alpha]_D$ −30.6° (c = 0.445, methanol).

General Procedure for the *N*-Acylation of 10 and 11, Method B. The chloroformate, or acid chloride (1.2 equiv), was added dropwise to a solution of amine **10** or **11** (0.2 mmol) in ethyl acetate (7 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and water (10 mL). The mixture was stirred at 24 °C for 30 min and extracted with ethyl acetate (2 × 30 mL). The organic extracts were washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel to provide 3′-*N*-acylated products.

3′-*tert*-Butyl-10-deacetyl-3′-dephenylpaclitaxel (12). Amine **10** (30 mg, 0.029 mmol) was treated with benzoyl chloride (3.7 μL, 0.032 mmol, 1.1 equiv) as described in method B followed by removal of the protecting groups at positions 7 and 10 using method A to give **12** as a white amorphous solid (14 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.06 (s, 9H), 1.15 (s, 3H), 1.69 (s, 3H), 1.79 (s, 3H), 2.24 (m, 2H), 2.43 (s, 3H), 2.50 (m, 1H), 3.83 (d, J = 7 Hz, 1H), 4.14 (m, 1H), 4.17 and 4.26 (2d, J = 8.4, 8.7 Hz, 2H), 4.35 (d, J = 10 Hz, 1H), 4.61 (br d, J = 2.8 Hz, 1H), 4.89 (d, J = 7.5 Hz, 1H), 5.10 (br s, 1H), 5.62 (d, J = 7.2 Hz, 1H), 6.12 (t, J = 9.0 Hz, 1H), 6.44 (d, J = 9.9 Hz, 1H), 7.30, 7.43, 7.52, 7.59, and 8.10 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.6, 174.9, 170.3, 167.1, 155.8, 138.9, 135.7, 133.7, 130.3, 129.2, 128.8, 84.2, 81.1, 79.6, 78.9, 77.3, 77.2, 75.0, 74.6, 73.1, 72.1, 70.6, 59.5, 57.6, 46.4, 43.2, 37.0, 35.9, 35.2, 28.3, 27.5, 26.4, 22.9, 21.0, 14.4, 10.0; IR ($CHCl_3$) 3440 (br), 1720 (br), 1500, 1360, 1250, 1160, 1100 cm^{-1}; MS (FAB$^+$) m/e calcd for $C_{43}H_{53}NO_{13}$ 792.3614, found 792.3614, 792 (M^+ + H), 774, 527; $[\alpha]_D$ +4.0° (c = 0.34, $CHCl_3$).

3′-*tert*-Butyl-3′-dephenyldocetaxel (13). Di-*tert*-butyl dicarbonate (0.030 g, 0.14 mmol, 1.5 equiv) was added to a stirred solution of **10** (0.096 g, 0.93 mmol) in THF (4 mL) followed by the addition of sodium bicarbonate (0.011 g, 0.14 mmol, 1.5 equiv). The heterogeneous mixture was stirred at 24 °C for 6 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:1). This product (0.101 g, 96%) was deprotected using method A to provide **13** (0.044 g, 63%) as white crystals, mp 183 °C dec: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.12 (s, 3H), 1.23 (s, 3H), 1.31 (s, 9H), 1.74 (s, 3H), 1.91 (s, 3H), 2.31 (m, 2H), 2.42 (s, 3H), 2.57 (m, 1H), 3.81 (d, J = 10 Hz, 1H), 3.91 (d, J = 6.8 Hz, 1H), 4.20 and 4.33 (2d, J = 8.4 Hz, 2H), 4.24 (m, 1H), 4.56 (br s, 1H), 4.94 (d, J = 9.0 Hz, 1H), 4.96 (d, J = 7.8 Hz, 1H), 5.21 (s, 1H), 5.68 (d, J = 6.8 Hz, 1H), 6.17 (t, J = 9.0 Hz, 1H), 7.49, 7.61, and 8.12 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.6, 174.9, 170.3, 167.1, 155.8, 138.9, 135.7, 133.7, 130.3, 129.2, 128.8, 84.2, 81.1, 79.6, 78.9, 77.3, 77.2, 75.0, 74.6, 73.1, 72.1, 70.6, 59.5, 57.6, 46.4, 43.2, 37.0, 35.9, 35.2, 28.4, 27.6, 26.5, 22.9, 21.0, 14.4, 10.0; IR ($CHCl_3$) 3460 (br), 1710, 1500, 1365, 1250, 1165, 1100, 910 cm^{-1}; MS (FAB$^+$) m/e calcd for (M^+ + H) $C_{41}H_{58}NO_{14}$ 788.3857, found 788.3863, 811 (M^+ + 1 + Na), 788 (M^+ + H); $[\alpha]_D$ −41.69° (c = 0.65, $CHCl_3$).

***N*-(Isobutoxycarbonyl)-3′-*tert*-butyl-10-deacetyl-*N*-debenzoyl-3′-dephenylpaclitaxel (14).** Amine **11** (0.025 g, 0.036 mmol) was treated with isobutyl chloroformate (6.2 μL, 0.047 mmol, 1.3 equiv) according to method A yielding **14** (0.023 g, 81%) as white crystals, mp 150 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 and 0.79 (2d, J = 6.6 Hz, 6H), 1.05 (s, 9H), 1.11 (s, 3H), 1.23 (s, 3H), 1.74 (s, 3H), 1.90 (s, 3H), 2.24 (m, 2H), 2.44 (s, 3H), 2.57 (m, 1H), 3.69 (m, 2H), 3.89 (br d, 2H), 4.21 and 4.31 (2d, J = 8.3 Hz, 3H), 4.59 (br s, 1H), 4.95 (d, J = 9.5 Hz, 1H), 5.21 (s, 1H), 5.67 (d, J = 6.8 Hz, 1H), 6.21 (t, J = 8.7 Hz, 1H), 7.50, 7.60, and 8.11 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.4, 170.4, 167.0, 156.6, 138.6, 135.7, 133.6, 130.3, 129.2, 128.7, 84.2, 81.0, 78.9, 74.9, 74.4, 72.7, 71.9, 71.1, 70.6, 59.7, 57.5, 46.3, 43.1, 37.0, 35.8, 35.3, 27.9, 27.3, 26.4, 22.7, 21.0, 18.8, 18.7, 14.2, 9.9; IR ($CHCl_3$) 3440 (br), 1720 (br), 1500, 1360, 1250, 1100, 1060, 1010, 970 cm^{-1}; HRMS (FAB$^+$) m/z calcd for (M^+ + H) $C_{41}H_{58}NO_{14}$ 788.3857, found 788.3825, 810 (M^+ + Na), 788 (M^+ + H), 770, 752, 728, 688, 583, 527, 509, 491, 467, 449, 405, 387, 359, 345, 327, 311, 299, 284, 262, 216; $[\alpha]_D$ −32.6° (c = 0.565, $CHCl_3$).

***N*-(*n*-Butoxycarbonyl)-3′-*tert*-butyl-10-deacetyl-*N*-debenzoyl-3′-dephenylpaclitaxel (15).** A mixture of amine **11** (0.025 g, 0.036 mmol) was reacted with *n*-butyl chloroformate (5.3 μL, 0.043 mmol, 1.2 equiv) as described in method B to give **15** as white crystals (0.022 g, 77%), mp 151−156 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, 3H), 1.05 (s, 9H), 1.12 (s, 3H), 1.24 (s, 3H), 1.47 (m, 4H), 1.74 (s, 3H), 1.86 (m, 1H), 1.90 (s, 3H), 2.28 (m, 2H), 2.43 (s, 3H), 2.57 (m, 1H), 3.36 (d, J = 4.8 Hz, 1H), 3.89 (m, 3H), 4.21 and 4.31 (2d, J = 8.3, 9.2 Hz, 2H), 4.25 (m, 1H), 4.59 (d, J = 4.3 Hz, 1H), 4.95 (d, J = 8.1 Hz, 1H), 5.14 (d, J = 10 Hz, 1H), 5.21 (s, 1H), 5.67 (d, J = 6.8 Hz, 1H), 6.21 (t, J = 8.8 Hz, 1H), 7.49, 7.60, and 8.13 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.4, 170.4, 166.9, 156.6, 138.5, 135.7, 133.6, 130.2, 129.2, 128.6, 84.2, 81.0, 78.9, 74.9, 74.4, 72.7, 71.9, 70.5, 65.0, 59.7, 57.5, 46.3, 43.1, 36.8, 35.8, 35.2, 30.9, 27.3, 26.4, 22.7, 21.0, 18.8, 14.2, 13.6, 09.9; IR ($CHCl_3$) 3450 (br), 1710 (br), 1510, 1450, 1360, 1240, 1060, 980, 910 cm^{-1}; HRMS (FAB$^+$) m/z calcd for $C_{41}H_{57}NO_{14}Li$ 794.3939, found 794.3934, 810 (M^+ + Na), 788 (M^+ + 1), 770, 752, 688, 583, 549, 509, 408, 387, 345, 327, 309, 284, 262, 216; $[\alpha]_D$ −34° (c = 0.90, $CHCl_3$).

3′-*tert*-Butyl-10-deacetyl-*N*-debenzoyl-3′-dephenyl-*N*-[(*n*-hexyloxy)carbonyl]paclitaxel (16). Amine **11** (0.040 g, 0.58 mmol)was reacted with *n*-hexyl chloroformate (12 μL, 1.2 equiv) using method B to furnish **16** as white crystals in 80% yield (0.038 g), mp 146 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H), 1.12 (s, 3H), 1.19 (m, 4H),

1.24 (s, 3H), 1.48 (m, 4H), 1.76 (s, 3H), 1.91 (s, 3H), 2.29 (m, 2H), 2.44 (s, 3H), 2.59 (m, 1H), 3.36 (br s, OH), 3.89 (m, 4H), 4.21 and 4.31 (2d, J = 8.3, 8.4 Hz, 2H), 4.23 (m, 1H), 4.58 (br d, J = 3.0 Hz, 1H), 4.95 (d, J = 8.2 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 5.20 (s, 1H), 5.68 (d, J = 7.1 Hz, 1H), 6.21 (t, J = 9.2 Hz, 1H), 7.49, 7.60, and 8.14 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 174.4, 170.4, 166.9, 156.6, 138.5, 135.7, 133.6, 130.3, 129.2, 128.6, 84.2, 81.0, 78.9, 74.9, 74.4, 72.6, 71.9, 70.5, 65.3, 59.7, 57.5, 46.3, 43.1, 36.8, 35.8, 35.3, 31.3, 28.9, 27.3, 26.4, 25.3, 22.7, 22.5, 21.0, 14.2, 13.9, 9.9; IR ($CHCl_3$) 3440 (br), 1720, 1500, 1510, 1365, 1250, 1100, 1020 cm^{-1}; MS (FAB$^+$) m/e calcd for $C_{43}H_{61}NO_{14}Li$ 822.4249, found 822.4252, 839 (M^+ + Na), 822 (M^+ + Li), 816 (M^+ + H), 707, 549, 533, 509, 424, 411, 327, 312, 296 (base peak), 290, 244; $[\alpha]_D$ −31° (c = 0.98, $CHCl_3$).

N-[(*tert*-Amyloxy)carbonyl]-3′-*tert*-butyl-10-deacetyl-N-debenzoyl-3′-dephenylpaclitaxel (17). A mixture of di-*tert*-amyl dicarbonate (0.113 mL, 0.462 mmol, 1.5 equiv) and amine **10** (0.320 g, 0.308 mmol) in THF (15 mL) was treated with $NaHCO_3$ (0.039 g, 0.46 mmol, 1.5 equiv). The reaction mixture was stirred at 24 °C for 4 h. After 4 h the solvent was removed under reduced pressure, and the residue was taken into methylene chloride (15 mL). The organic layer was washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:3) giving the N-amyl derivative (0.265 g, 82%), which was deprotected using method A to give **17** (0.098 g, 54%) as white crystals, mp 177–182 °C dec: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, J = 7.5 Hz, 3H), 1.05 (s, 9H), 1.13 (s, 3H), 1.23 (s, 3H), 1.26 (2s, 6H), 1.67 (q, J = 7.5 Hz, 2H), 1.75 (s, 3H), 1.91 (s, 3H), 2.31 (m, 2H), 2.42 (s, 3H), 2.58 (m, 1H), 3.81 (d, J = 10 Hz, 1H), 3.90 (d, J = 6.9 Hz, 1H), 4.20 and 4.33 (2d, J = 8.3 Hz, 2H), 4.24 (m, 1H), 4.57 (br s, 1H), 4.95 (m, 1H), 5.21 (s, 1H), 5.69 (d, J = 6.9 Hz, 1H), 6.17 (t, J = 10 Hz, 1H), 7.50, 7.61, and 8.12 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.5, 174.9, 170.2, 167.0, 155.7, 138.8, 135.6, 133.6, 130.2, 129.1, 128.7, 84.1, 81.9, 81.0, 78.8, 74.9, 74.5, 73.0, 71.9, 70.5, 59.3, 57.5, 46.3, 43.1, 36.9, 35.7, 35.1, 33.0, 27.4, 26.3, 25.8, 22.8, 21.0, 14.2, 9.9, 8.2; MS (FAB$^+$) m/e calcd for $C_{42}H_{59}NO_{14}Li$ 808.4096, found 808.4123, 824 (M^+ + Na), 802 (M^+ + H); $[\alpha]_D$ −38.6° (c = 0.505, $CHCl_3$).

3′-*tert*-Butyl-10-deacetyl-N-debenzoyl-3′-dephenyl-N-pivaloylpaclitaxel (18). A mixture of 11 (0.019 g, 0.028 mmol) was treated with pivaloyl chloride (4.4 μL, 0.035 mmol, 1.3 equiv) as described in general procedure B to give **18** as a white amorphous solid (0.017 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.11 (s, 3H), 1.13 (s, 9H), 1.22 (s, 3H), 1.73 (s, 3H), 1.88 (s, 3H), 2.31 (m, 2H), 2.43 (s, 3H), 2.58 (m, 1H), 3.32 (br s, 1H), 3.87 (d, J = 7 Hz, 1H), 4.14 (d, J = 9.7 Hz, 1H), 4.22 and 4.31 (2d, J = 8.4 Hz, 2H), 4.27 (m, 1H), 4.58 (br s, 1H), 4.95 (d, J = 7.8 Hz, 1H), 5.19 (s, 1H), 5.69 (d, J = 6.9 Hz, 1H), 6.06 (d, J = 10.3 Hz, 1H), 6.08 (t, J = 9.3 Hz, 1H), 7.50, 7.61, and 8.13 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4 178.3, 174.9, 170.2, 166.8, 138.5, 135.8, 133.6, 130.2, 129.4, 128.7, 84.1, 81.0, 78.5, 74.9, 74.4, 73.3, 71.9, 70.3, 57.5, 57.0, 46.2, 43.2, 38.9, 36.9, 35.8, 35.0, 27.5, 27.4, 26.3, 22.8, 21.1, 14.2, 9.9; HRMS (FAB$^+$) m/z calcd for $C_{41}H_{57}NO_{13}Li$ 778.3990, found 778.4021, 794 (M^+ + Na), 772 (M^+ + H), 756, 742, 736, 726, 650, 617, 549, 527, 509, 491, 480, 467, 449, 431, 405, 387, 345, 327, 309, 246, 220, 200; $[\alpha]_D$ −52° (c = 0.81, $CHCl_3$).

3′-*tert*-Butyl-10-deacetyl-N-debenzoyl-3′-dephenyl-N-(3,3-dimethylbutanoyl)paclitaxel (19). 3,3-Dimethylbutyric acid (13 μL, 0.096 mmol, 1.3 equiv) in anhydrous THF (1.5 mL) was cooled to −20 °C. To this was added 4-methylmorpholine (11 μL, 0.10 mmol, 1.3 equiv) followed by the addition of isobutyl chloroformate (15 μL, 0.12 mmol, 1.5 equiv) at −20 °C. The reaction mixture was stirred at −20 °C for 2 min and treated with a solution of amine **10** (0.080 g, 0.077 mmol) in THF (1.5 mL). Stirring was continued at −20 °C for 20 min and at 24 °C for 30 min. The solvent was removed under reduced pressure, and the residue was taken into ethyl acetate (10 mL). The heterogeneous mixture was washed with aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crude product which was purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:2). This product was deprotected using general method A to give **19** (0.023 g) as a white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.05 (s, 9H), 1.12 (s, 3H), 1.23 (s, 3H), 1.74 (s, 3H), 1.88 (s, 3H), 2.04 (s, 2H), 2.31 (m, 2H), 2.42 (s, 3H), 2.56 (m, 1H), 2.38 (br s, 1H), 3.87 (d, J = 6.8 Hz, 1H), 4.19 (d, J = 10.7 Hz, 1H), 4.21 and 4.31 (2d, J = 8.7, 8.4 Hz, 2H), 4.25 (m, 1H), 4.59 (br s, 1H), 4.95 (d, J = 7.9 Hz, 1H), 5.21 (s, 1H), 5.69 (d, J = 7.1 Hz, 1H), 5.75 (d, J = 10.1 Hz, 1H), 6.13 (t, J = 8.5 Hz, 1H), 7.49, 7.60, and 8.11 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.5, 174.9, 171.5, 170.2, 166.8, 138.5, 135.8, 133.6, 130.2, 129.2, 128.7, 84.1, 81.0, 78.6, 74.9, 74.4, 73.2, 71.9, 70.1, 57.5, 50.6, 46.2, 43.2, 36.9, 35.9, 35.0, 30.7, 29.8, 27.5, 26.4, 22.8, 21.1, 14.2, 9.9; HRMS (FAB$^+$) m/z calcd for $C_{42}H_{59}NO_{13}Li$ 792.4147, found 792.4158, 792 (M^+ + Li), 786 (M^+ + H), 768, 677, 626, 619, 603, 577, 551, 533, 523, 466, 443, 391, 379, 313, 289, 154, 136; $[\alpha]_D$ −39° (c = 0.72, $CHCl_3$).

3′-*tert*-Butyl-N′-[(*tert*-butylamino)carbonyl]-10-deacetyl-N-debenzoyl-3′-dephenylpaclitaxel (20). Amine 11 (0.010 g, 0.015 mmol) in acetonitrile (1 mL) was treated with *tert*-butyl isocyanate (2.0 μL, 0.017 mmol, 1.2 equiv) at room temperature and then stirred for 6 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel ($MeOH/CH_2Cl_2$, 3:97) to give **20** as an amorphous solid (0.0093 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.12 (s, 3H), 1.20 (s, 9H), 1.21 (s, 3H), 1.73 (s, 3H), 1.90 (s, 3H), 2.34 (m, 2H), 2.41 (s, 3H), 2.58 (m, 1H), 3.89 (d, J = 6.8 Hz, 1H), 3.93 (d, J = 9.8 Hz, 1H), 4.19 and 4.32 (2d, J = 8.2, 8.4 Hz, 2H), 4.25 (m, 1H), 4.55 (br s, 1H), 4.66 (d, J = 9.3 Hz, 1H), 4.95 (d, J = 8.3 Hz, 1H), 5.22 (s, 1H), 5.69 (d, J = 6.9 Hz, 1H), 6.12 (t, J = 9.2 Hz, 1H), 7.49, 7.61, and 8.11 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.7, 175.3, 170.2, 166.8, 156.8, 138.9, 135.6, 133.6, 130.3, 129.1, 128.7, 84.1, 81.0, 78.5, 74.8, 74.5, 73.1, 71.9, 70.7, 58.6, 57.6, 50.4, 46.3, 43.1, 37.0, 35.9, 35.2, 29.39, 27.5, 26.3, 22.7, 20.9, 14.3, 9.9; HRMS (FAB$^+$) m/z calcd for $C_{41}H_{58}N_2O_{13}Li$ 793.4099, found 793.4079, 793 (M^+ + Li), 533, 466, 313, 289, 267, 245, 22; $[\alpha]_D$ −43° (c = 0.37, $CHCl_3$).

3′-*tert*-Butyl-[(N′-*tert*-butylamino)thiocarbonyl]-10-deacetyl-N-debenzoyl-3′-dephenylpaclitaxel (21). Amine **10** was allowed to react with *tert*-butyl isothiocyanate (1.2 equiv) in acetonitrile using the standard method (see experimental for compound **20**) followed by removal of the protecting groups using method A to give **21** (0.0030 g, 25% overall) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.12 (s, 9H), 1.23 (s, 3H), 1.41 (s, 9H), 1.74 (s, 3H), 1.87 (s, 3H), 2.42 (m, 2H), 2.45 (m, 1H), 2.49 (s, 3H), 3.86 (d, J = 7.3 Hz, 1H), 4.25 (m, 3H), 4.61 (s, 1H), 4.93 (br d, J = 8.7 Hz, 2H), 5.18 (s, 1H), 5.66 (d, J = 6.9 Hz, 1H), 6.15 (unsymm d, J = 9.2 Hz, 2H), 6.34 (t, J = 8.8 Hz, 1H), 7.50, 7.59 and 8.08 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.5, 181.3, 174.8, 170.3, 166.8, 138.6, 135.8, 133.6, 130.2, 129.3, 128.7, 84.1, 80.9, 78.9, 75.1, 74.4, 73.2, 71.9, 69.9, 63.5, 57.5, 52.6, 46.1, 43.0, 36.8, 36.6, 36.4, 29.7, 27.8, 26.6, 23.1, 21.2, 14.2, 10.01; HRMS (FAB$^+$) m/z calcd for (M^+ + H) $C_{41}H_{59}N_2O_{12}S$ 803.3789, found 803.3772, 803 (M^+ + H), 785, 769, 549, 299, 277, 259, 243, 221; $[\alpha]_D$ −26.0° (c = 0.695, $CHCl_3$).

3′-*tert*-Butyl-10-deacetyl-N-debenzoyl-3′-dephenyl-N-(phenoxycarbonyl)paclitaxel (22). Compound **22** was synthesized by treating amine 11 (0.035 g, 0.051 mmol) with phenyl chloroformate (8.4 μL, 066 mmol, 1.3 equiv) under the conditions described in general procedure B to provide **22** in 71% yield (0.029 g) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.13 (s, 3H), 1.24 (s, 3H), 1.72 (s, 3H), 1.91 (s, 3H), 2.10–2.30 (m, 2H), 2.35 (s, 3H), 2.54 (m, 1H), 3.84 (d, J = 7 Hz, 1H), 3.90 (d, J = 11 Hz, 1H), 4.25 (m, 3H), 4.66 (br s, 1H), 4.95 (d, J = 8.8 Hz, 1H), 5.29 (s, 1H), 5.61 (d, J = 10.5 Hz, 1H), 5.64 (d, J = 7.2 Hz, 1H), 6.22 (t, J = 8.8 Hz, 1H), 7.01, 7.15 (m, 5H), 7.35, 7.51, and 8.00 (m, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.4, 175.1, 170.1, 166.8, 155.1, 150.9, 138.5, 135.8, 133.5, 130.1, 129.2, 129.0, 128.5, 125.3, 121.4, 84.1, 81.1, 78.7, 74.8, 74.5, 73.0, 71.8, 70.5, 60.4, 57.6, 46.3, 43.2, 36.8, 35.8, 35.2, 27.4, 26.3, 22.7, 21.1, 14.3, 9.9; IR ($CHCl_3$) 3420 (br), 1730 (br), 1480, 1360, 1250, 1200, 1100, 1040, 910 cm^{-1}; HRMS (FAB$^+$) m/z calcd for $C_{43}H_{53}NO_{14}Li$ 814.3626, found 814.3643, 830 (M^+ + Na), 814 (M^+ + Li), 808 (M^+ + H), 790, 726, 587, 549, 533, 509, 473, 411, 379, 365, 345, 329, 313, 288, 236, 226, 205, 176, 160, 136; $[\alpha]_D$ −20° (c = 0.59, $CHCl_3$).

3′-*tert*-Butyl-10-deacetyl-N-debenzoyl-3′-dephenyl-N-

(phenylamino)carbonyl]paclitaxel (23). Amine **10** (0.10 g, 0.096 mmol) was allowed to react with phenyl isothiocyanate (12 μL, 11 mmol, 1.2 equiv) in acetonitrile (10 mL) using our standard method (see experimental for compound **20**). Removal of the protecting groups using method A gave product **23** (31 mg, 40% overall) as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.08 (s, 3H), 1.15 (s, 3H), 1.73 (s, 3H), 1.84 (s, 3H), 2.23 (m, 3H), 2.43 (s, 3H), 2.56 (m, 1H), 3.85 (d, J = 6.9 Hz, 1H), 4.10 (d, J = 9.7 Hz, 1H), 4.20 (m, 1H), 4.30 (m, 2H), 4.58 (d, J = 4.5 Hz, 1H), 4.91 (d, J = 9.3 Hz, 1H), 5.21 (s, 1H), 5.36 (d, J = 9.7 Hz, 1H), 5.67 (d, J = 6.9 Hz, 1H), 6.17 (t, J = 8.0 Hz, 1H), 6.77 (br s, 1H, NH), 6.92, 7.04, 7.18, 7.50, 7.60, and 8.13 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 211.5, 174.8, 170.4, 166.7, 155.3, 138.6, 138.3, 135.7, 133.7, 130.2, 129.2, 128.7, 123.8, 120.7, 84.2, 81.0, 78.5, 77.3, 76.4, 74.7, 74.4, 72.7, 71.9, 70.8, 60.4, 58.7, 57.6, 46.3, 43.0, 36.81, 36.9, 36.1, 35.3, 27.5, 26.4, 22.7, 21.0, 14.2, 14.1, 9.9; HRMS (FAB^+) m/z calcd for $(M^+ + 1)$ $C_{43}H_{55}N_2O_{13}$ 807.3704, found 807.3691; 807 (M^+ + H), 785, 391, 307, 281, 263, 255; $[\alpha]_D$ −8.7° (c = 1.4, $CHCl_3$).

Biological Evaluation. Microtubule-assembly assay: Bovine brain tubulin was prepared by the three cycles of a temperature-dependent assembly–disassembly procedure[50] followed by the phosphocellulose-biogel P-10 chromatography.[51] Tubulin was drop-frozen in liquid nitrogen and stored at 80 °C. Prior to use, it was thawed and centrifuged at 27000g for 10 min to remove aggregated protein. Tubulin polymerization induced by paclitaxel and the paclitaxel analogs was performed in PEM buffer (0.1 M Pipes, pH 6.9, containing 1 mM $MgSO_4$ and 1 mM EGTA). A centrifugation assay was used to determine the effectiveness of the paclitaxel analogs and paclitaxel in promoting tubulin assembly. Different concentrations of paclitaxel or the analogs were incubated with 10 μM tubulin and 0.5 mM GTP at 37 °C for 15 min followed by centrifugation at 40000g in a Beckman TL-100 ultracentrifuge for 4 min. The volume of the reaction mixture was 0.4 mL. The protein concentration in the supernatant was measured by the Bradford procedure,[52] and the drug concentration causing 50% retention of protein in the supernatant was taken as the ED_{50} value.

B16 melanoma cytotoxicity: ED_{50} refers to the concentration of paclitaxel analogs which produces 50% inhibition of proliferation after 40 h of incubation.

General Procedure for the Assay To Determine the Water Solubility of Paclitaxel Analogs. HPLC conditions: mobile phase A, 50% HPLC grade methanol/50% nanopure water (v/v); mobile phase B, HPLC grade acetonitrile, Dynamax phenyl column, 60A, 8 mm, 4.6 × 250 μm.

Standard Curve Preparation. A standard curve was prepared by placing ca. 0.5 mg of sample to be assayed into a class A, 1 mL, volumetric flask. The flask was brought to volume by HPLC grade methanol and mixed by inversion. The dissolved sample (500 μL) was pipetted into a small amber vial, and to this was added 500 μL of methanol via pipette to bring the total volume of dilution to 1 mL. A continuation of dilution was completed by taking 100 and 10 μL from the original sample of 0.5 mg in 1 mL and diluting with 900 and 990 μL of methanol, respectively. Sample concentrations in mg/mL were calculated, and graphs of sample concentration vs HPLC area units were then prepared on the basis of data obtained.

Sample Preparation. Approximately 0.4 mg of each sample was weighed into a 10 mL volumetric flask and filled with 9 mL of water. The flask was then placed into a beaker containing cold water and sonicated for 15 min. The flask was removed, filled to volume (10 mL) with nanopure water, and allowed to set for at least 24 h. The contents of the flask were then passed through a syringe filter (Gelman Nylon Acrodisc 13, 0.45 μm) and on to the HPLC. Area units were compared to the previously prepared graph to obtain mg/mL concentrations.

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