Design, Synthesis, and Biological Evaluation of New-Generation Taxoids

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Novel second-generation taxoids with systematic modifications at the C2, C10, and C3′N positions were synthesized and their structure−activity relationships studied. A number of these taxoids exhibited exceptionally high potency against multidrug-resistant cell lines, and several taxoids exhibited virtually no difference in potency against the drug-sensitive and drug-resistant cell lines. These exceptionally potent taxoids were termed "third-generation taxoids". **19** (SB-T-1214), **14g** (SB-T-121303), and **14i** (SB-T-1213031) exhibited excellent activity against paclitaxel-resistant ovarian cancer cell lines with mutations in β-tubulin as well, wherein the drug resistance is mediated by the β-tubulin mutation. These taxoids were found to possess exceptional activity in promoting tubulin assembly, forming numerous very short microtubules similar to those formed by discodermolide. Taxoids **19** and **14g** also showed excellent cytotoxicity against four pancreatic cancer cell lines, expressing three to four multidrug-resistant genes. Moreover, taxoid **19** exhibited excellent in vivo efficacy against highly drug-resistant CFPAC-1 pancreatic as well as DLD-1 human colon tumor xenografts in mice.

Introduction

Cancer is one of the most common lethal diseases in the world. In the U.S. cancer is now the leading cause of death in people under the age of 85.[1,2] Among a variety of chemotherapeutic drugs paclitaxel and docetaxel are currently two of the most widely used drugs in the fight against cancer, especially for the treatment of ovarian, breast, and lung cancers as well as Kaposi's sarcoma.[3,4] Further clinical applications are ongoing against different types of cancers as well as for combination therapies with other anticancer drugs.[3] These "taxane" anticancer drugs bind to the β-tubulin subunit, accelerate the polymerization of tubulin, and stabilize the resultant microtubules, thereby inhibiting their depolymerization.[5,6] This results in the arrest of the cell division cycle mainly at the G2/M stage, leading to apoptosis through the cell-signaling cascade. Although both paclitaxel and docetaxel possess potent antitumor activity, it has been shown that treatment with these drugs often produces undesirable side effects as well as drug resistance.[3] Therefore, it is important to develop new taxane anticancer agents with fewer side effects, superior pharmacological properties, and improved activity against various classes of tumors, especially against drug-resistant human cancer.

Accordingly, extensive structure−activity relationship (SAR[a]) studies on paclitaxel and its congeners have been performed in different laboratories for discovery and development of better taxane anticancer agents.[4,7–16] In the course of our SAR study on taxoids, we found that (i) the C3′-phenyl group was not an essential component for their potent activity and (ii) the modifications of the C10 position with certain acyl groups as well as the replacement of the phenyl group with an alkenyl or alkyl group at the C3′ position made compounds 1−2 orders of magnitude more potent than the parent drugs (paclitaxel and docetaxel) against drug-resistant human breast cancer cell lines. These highly potent taxoids were termed "second-generation taxoids".[17] Furthermore, we found that introduction of a substituent (e.g., MeO, N_3, Cl, F, etc.) to the meta position of the C2-benzoyl group of the second-generation taxoids enhanced the activities 2−3 orders of magnitude higher than the parent drugs against drug-resistant human breast cancer cell lines.[14,15] We describe here a full account of our work on the synthesis, biological evaluations, and SAR of a series of novel new generation taxoids bearing various substituents at the C2, C10, C3′, and C3′N positions.

Chemical Synthesis

Second-generation taxoids bearing different aromatic acyl groups at the C10 position were synthesized by applying the procedure developed by Georg.[18] The C7 hydroxy group of 10-deacetylbaccatin III (DAB, **1**) was selectively protected as a triethylsilyl ether using triethylsilyl chloride (TESCl) and

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[a] Abbreviations: DAB, 10-deacetylbaccatin III; IC_{50}, half-maximal inhibitory concentration; LiHMDS, lithium hexamethyldisilazide; NMO, *N*-methylmorpholine *N*-oxide; PBS, phosphate buffered saline; PDA, photodiode array; Pgp, P-glycoprotein; *R*/*S*, resistance factor (the ratio of the IC_{50} value against the drug-resistant cell line to that against the drug-sensitive cell line); RT-PCR, reverse transcriptase−polymerase chain reaction; SAR, structure−activity relationship; SCID, severe combined immunodeficiency; TEA, triethylamine; TES, triethylsilyl; TIPS, triisopropylsilyl; TLC, thin layer chromatography; TPAP, tetrapropylammonium perruthenate; WT, wild type.

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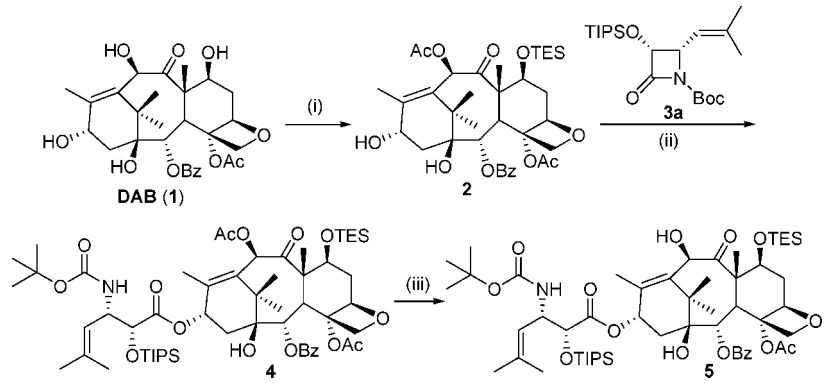
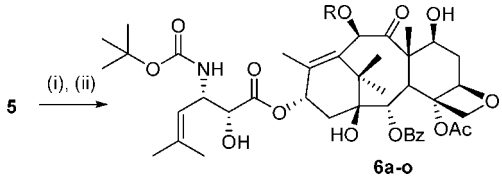
Scheme 1[a]



[a] Reagents and conditions: (i) (a) TESCl, imidazole, (b) LiHMDS, AcCl, 95% in two steps; (ii) LiHMDS, THF, 95%; (iii) $N_2H_4 \cdot H_2O$, EtOH, 85%.

Scheme 2[a]



[a] Reagents and conditions: (i) (a) RCl, TEA, DMAP, CH_2Cl_2 or (b) ROH, DIC, DMAP, CH_2Cl_2 or (c) RCl, LiHMDS, THF, −20 °C (75−98%); (ii) HF/pyridine, pyridine/MeCN (80−97%).

imidazole in DMF. The resulting 7-TES-DAB was acetylated specifically at the C10 position to give 7-TES-baccatin III (**2**) in excellent yield (95% for two steps)[8,17,19] An isoserine moiety was introduced to the C13 position of **2** through the Ojima−Holton coupling of **2** with *N*-*t*-Boc-β-lactam **3a**[7,20] under the standard conditions in the presence of LiHMDS in THF at −40 °C to afford the corresponding taxoid **4** (Scheme 1).[21,22]

The selective removal of the acetyl group at the C10 position of **4** with hydrazine was possible when the hydroxyl group at the C2′ position was protected as a TIPS ester. This selective deacetylation under mild conditions gave the desired C2′-TIPS-7-TES-10-OH-taxoid **5** in high yield (Scheme 1).

Taxoid **5** served as the key intermediate for the syntheses of a number of second-generation taxoids, bearing different acyl groups at the C10 position. The acylation of the C10 position of **5** was carried out using either an acid chloride with triethylamine (TEA) and DMAP or a carboxylic acid with DIC and DMAP (Scheme 2). For the introduction of a Cbz group, CbzCl and LiHMDS were used (Scheme 2). Yields for the acylation reactions were 75−98% (see Supporting Information for details). The deprotection of C2′-TIPS and 7-TES groups with HF−pyridine in pyridine/acetonitrile (1:1) proceeded smoothly to give desired 10-acyl second-generation taxoids **6a**−**o** in 80−97% yields (Scheme 2). Results are summarized in Table 1.

Novel second-generation taxoids, bearing substituents at the meta position of the C-2-benzoyl group, were synthesized (Scheme 5) from the corresponding C2-modified DABs **10** (see Schemes 3 and 4). The protection of the C7, C10, and C13 hydroxy groups of DAB with TES made it possible to selectively remove the C2-benzoyl moiety with sodium bis(2-methoxyethoxy)aluminumhydride, giving 7,10,13-tris-TES-2-debenzoyl-DAB **8** in excellent yield.[23,24] The esterification of the C2-OH of **8** with 3-substituted benzoic acids (R^1 = F, Cl, MeO, Me, N_3, vinyl) with DIC and DMAP gave various C2-modified tris-TES-DABs **9a**−**f** in 80−90% yields. Removal of all TES groups of **9a**−**f** with HF−pyridine followed by selective protection of the C7 hydroxyl group of the resulting baccatin gave 2-modified DABs **10a**−**f**. Subsequent selective acylation at the C10 position of **10a**−**f** afforded the corresponding 2,10-modified DABs **11a**−**l** in 71−95% yields (Scheme 3). Results are summarized in Table 2.

Table 1. Synthesis of Taxoids **6**

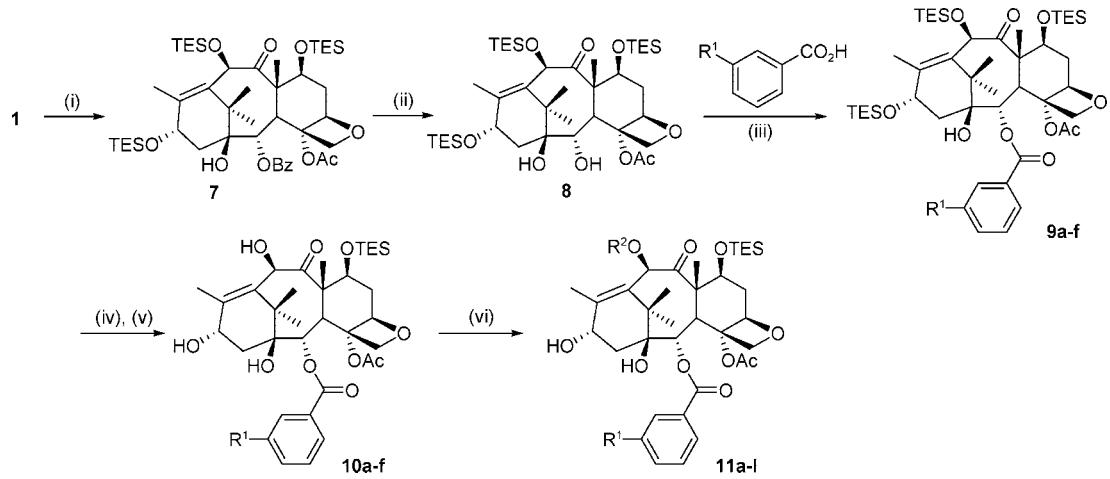
taxoid	R	yield (%) (for two steps)
6a	Bz	90
6b	2-MeO(C_6H_4)CO	90
6c	3-MeO(C_6H_4)CO	87
6d	4-MeO(C_6H_4)CO	80
6e	3,4-$(MeO)_2$(C_6H_3)CO	92
6f	1-naphthoyl	90
6g	2-naphthoyl	92
6h	Cbz	97
6i	2-MeO(C_6H_4)CH_2CO	80
6j	3-MeO(C_6H_4)CH_2CO	80
6k	4-MeO(C_6H_4)CH_2CO	60
6l	(C_6H_5)$(CH_2)_2$CO	85
6m	2-MeO(C_6H_4)$(CH_2)_2$CO	97
6n	3-MeO(C_6H_4)$(CH_2)_2$CO	80
6o	4-MeO(C_6H_4)$(CH_2)_2$CO	80

The same strategy was applied to the introduction of 2-methoxybenzoyl group at the C10 position but did not work well. Thus, we employed an alternative method, which is shown in Scheme 4. Selective oxidation of the C13 position of **10b** using TPAP and NMO provided 13-oxobaccatin **12**. The C10 position was then acylated with 2-methoxylbenzoyl chloride in the presence of DMAP to afford 10-(2-methoxybenzoyl)-13-oxobaccatin **13**. Reduction of the C13 ketone with $NaBH_4$ gave the desired 2-(3-methoxybenzoyl)-10-(2-methoxybenzoyl)baccatin **11k** in reasonable yield.

The Ojima−Holton coupling reactions of baccatins **11a**−**l** with β-lactams **3a**−**f** in the presence of LiHMDS as a base[17,25] proceeded smoothly to give the corresponding taxoids **14** (see Table 3 for structures). Enantiopure β-lactams with various C4 substituents were readily obtained through efficient chiral ester enolate−imine cyclocondensations[15,17,20,22,25,26] or [2 + 2] ketene−imine cycloaddition, followed by enzymatic optical resolution.[27] The deprotection of the silyl groups with HF/pyridine gave desired taxoids **14a**−**p** and **15c**−**e**,**g** in 65−95% yields (for two steps) (Scheme 5). In addition, taxoid **14g** (SB-T-121303) (R^1 = MeO, R^2 = propanoyl, R^3 = 2-methylpropen-1-yl) was subjected to hydrogenation on Pd/C to afford **15g** (R^3 = 2-methylpropyl) in quantitative yield (Scheme 5). Results are summarized in Table 3.

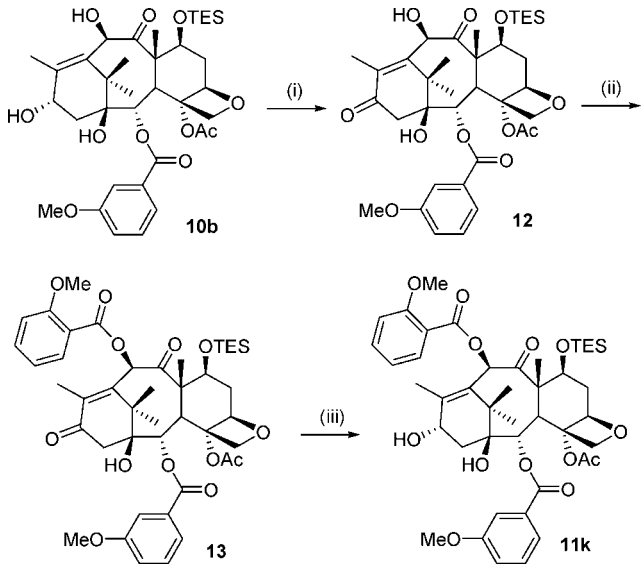
We also investigated the effects of the C3′N substituents on the cytotoxicity of second-generation taxoids. Modification of

Scheme 3[a]



[a] Reagents and conditions: (i) TESCl, imidazole, DMF, room temp, 96%; (ii) sodium bis(2-methoxyethoxy)aluminumhydride, THF, −10 °C, 97%; (iii) DIC, DMAP, CH_2Cl_2, 85−90%; (iv) HF/pyridine, pyridine/MeCN; (v) TESCl, imidazole, DMF, room temp, 2 h; (vi) LiHMDS, R^2COCl, THF.

Scheme 4[a]



[a] Reagents and conditions: (i) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 25 °C, 99%; (ii) 2-MeO-BzCl, DMAP, TEA, CH_2Cl_2, 100%; (iii) $NaBH_4$, MeOH/THF, 80% at 50% conversion.

the C3′N position can be made by using enantiopure β-lactams bearing various *N*-acyl or *N*-carbalkoxy groups. These β-lactams were readily obtained by reacting NH-free 3-TBSO- or 3-TIPSO-β-lactam with acid chlorides or chloroformates. The resulting β-lactams **16a**−**h** were coupled with 10-deacetyl-10-propanoyl-baccatin III or baccatin **11b** using 1.5−2 equiv of β-lactam **16a**−**h** to complete the reactions in excellent yields. Subsequent deprotection of silyl groups with HF/pyridine gave desired taxoids **17a**−**l** in good to excellent yields. Hydrogenation of selected **17** on Pd/C gave the corresponding 3′-(2-methylpropyl)taxoids **18** in quantitative yields (Scheme 6). Results are summarized in Table 4.

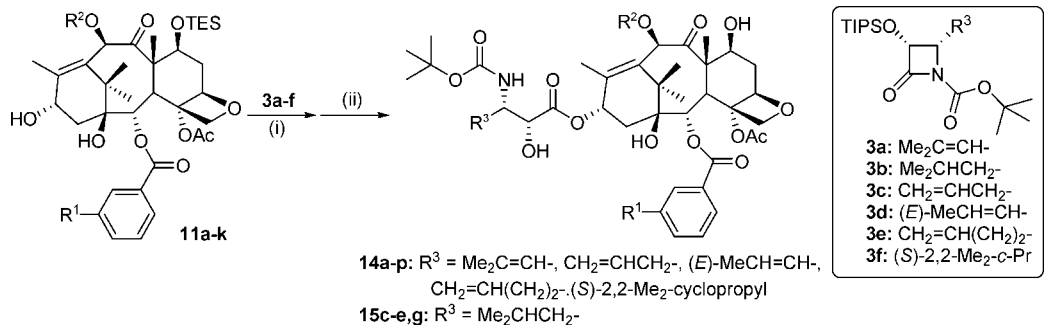
Evaluation of Biological Activities

Cytotoxicity of New Generation Taxoids against Human Breast and Ovarian Cancer Cell Lines. New second-generation taxoids, thus obtained, were evaluated for their cytotoxicity against drug-sensitive (LCC6-WT, P-glycoprotein negative, Pgp−) and drug-resistant (LCC6-MDR, P-glycoprotein positive, Pgp+) human breast cancer cell lines, and selected taxoids were also assayed for their potency against human breast cancer cell line MCF7 (Pgp−) and human ovarian cancer cell line NCI/ADR (Pgp+). Cytotoxicity assay results of taxoids **6a**−**o** bearing various aromatic groups in the acyl moieties at the C10 position against LCC6-WT and LCC6-MDR cell lines are summarized in Table 5.

As Table 5 shows, all taxoids assayed exhibit activities similar to or slightly better than that of paclitaxel against LCC6-WT, while their activities against LCC6-MDR are 2 orders of magnitude better than that of paclitaxel for more than a half of this series of taxoids. The most noteworthy feature revealed in this assay can be seen in the dramatic decrease in the *R*/*S* ratio, i.e., the ratio of the IC_{50} value against the drug-resistant cell line to that against the drug-sensitive cell line (paclitaxel's *R*/*S* value is 112 in this assay), which is an excellent indicator to see the level of drug resistance associated with drugs. A majority of the taxoids in this series exhibit an *R*/*S* ratio at or below 3, and taxoid **6d** demonstrates almost no difference against drug-resistant and drug-sensitive cell lines with an *R*/*S* ratio of 1.2. In general, taxoids with a substituted or unsubstituted benzoyl group (**6a**−**e**) or 2-phenylpropanoyl group (**6m**−**o**) are highly potent against LCC6-MDR, while taxoids with an arylacetyl substituents (**6i**−**k**) show reduced activity against LCC6-MDR although 4 out of 7 taxoids in this group (**6h**−**k**) are more potent than paclitaxel against LCC6-WT. Taxoids **6a** and **6d** that bear a benzoyl group and a 4-methoxybenzoyl group, respectively, at C10 possess highest potencies against LCC6-MDR (IC_{50} values of 4.8 and 4.7 nM, respectively). Taxoid **6k**, bearing a 4-methoxyphenyl acetyl group at C10, is the least potent (IC_{50} = 38.4 nM) against LCC6-MDR, but **6k** possesses the highest potency against LCC6-WT. Interestingly, elongation of the alkyl chain of **6i**−**k** just by one carbon restores high potency against LCC6-MDR.

10-Propanoyl taxoids bearing different acyl or carboalkoxy groups at the C3′N position were assayed for their cytotoxicity against LCC6-WT (Pgp−), LCC6-MDR (Pgp+), MCF7 (Pgp−), and NCI/ADR (Pgp+) human cancer cell lines, and results are summarized in Table 6. As Table 6 shows, most of C3′N-modified taxoids possess better cytotoxicity against LCC6-WT and MCF7 cell lines and 1−2 orders of magnitude higher potency against drug-resistant LCC6-MDR and NCI/ADR cell lines compared with paclitaxel. Two taxoids (**17d** and **17e**), bearing cyclopent-2-en-1-yl and cyclohex-2-en-1-yl groups,

Scheme 5[a]



[a] Reagents and conditions: (i) **3a**−**f** (1.2−1.5 equiv), LiHMDS, THF, −40 °C, 30 min; (ii) HF/pyridine, pyridine/MeCN, 0 °C to room temp, 18 h; (iii) H_2/Pd−C, EtOAc/MeOH, room temp, 24 h.

Table 2. 2,10-Modified Baccatins **11**

baccatin	R^1	R^2	yield (%)
11a	Me	MeCO	94
11b	MeO	MeCO	77
11c	F	EtCO	84
11d	Cl	EtCO	77
11e	N_3	EtCO	84
11f	CH_2=CH−	EtCO	67
11g	MeO	EtCO	95
11h	MeO	*c*-PrCO	84
11i	MeO	MeOCO	92
11j	MeO	$PhCH_2OCO$	94
11k	MeO	2-MeO(C_6H_4)CO	80
11l	MeO	4-MeO(C_6H_4)CH_2CO	98

Table 3. Second- and Third-Generation Taxoids **14** and **15**

txoid	R^1	R^2	R^3	yield for two steps (%)
14a	Me	MeCO	Me_2C=CH−	80
14b	MeO	MeCO	Me_2C=CH−	72
14c	F	EtCO	Me_2C=CH−	84
14d	Cl	EtCO	Me_2C=CH−	70
14e	N_3	EtCO	Me_2C=CH−	71
14f	CH_2=CH−	EtCO	Me_2C=CH−	80
14g	MeO	EtCO	Me_2C=CH−	69
14h	MeO	*c*-PrCO	Me_2C=CH−	77
14i	MeO	MeOCO	Me_2C=CH−	80
14j	MeO	$PhCH_2OCO$	Me_2C=CH−	70
14k	MeO	2-MeO(C_6H_4)CO	Me_2C=CH−	95
14l	MeO	4-MeO(C_6H_4)CH_2CO	Me_2C=CH−	70
14m	MeO	EtCO	CH_2=$CHCH_2$−	65
14n	MeO	EtCO	(*E*)-CH_3CH=CH−	80
14o	MeO	EtCO	CH_2=$CH(CH_2)_2$−	71
14p	MeO	EtCO	(*S*)-2,2-Me_2-*c*-Pr−	83
15c	F	EtCO	Me_2CHCH_2−	89
15d	Cl	EtCO	Me_2CHCH_2−	80
15e	N_3	EtCO	Me_2CHCH_2−	70
15g	MeO	EtCO	Me_2CHCH_2−	73

exhibit high potency against all four cell lines examined, and the *R*/*S* ratios are 9.2−15. The observed cytotoxicity values for **17d** and **17e** are comparable to those for the parent second-generation taxoids, **6x** (SB-T-1213)[17] and **6′x** (SB-T-1103),[17] shown in Table 2 for comparison. These results indicate that the *t*-Boc group at the C3′N position, which is the "gold standard", can be replaced by these cycloalkenoyl groups without losing potency.

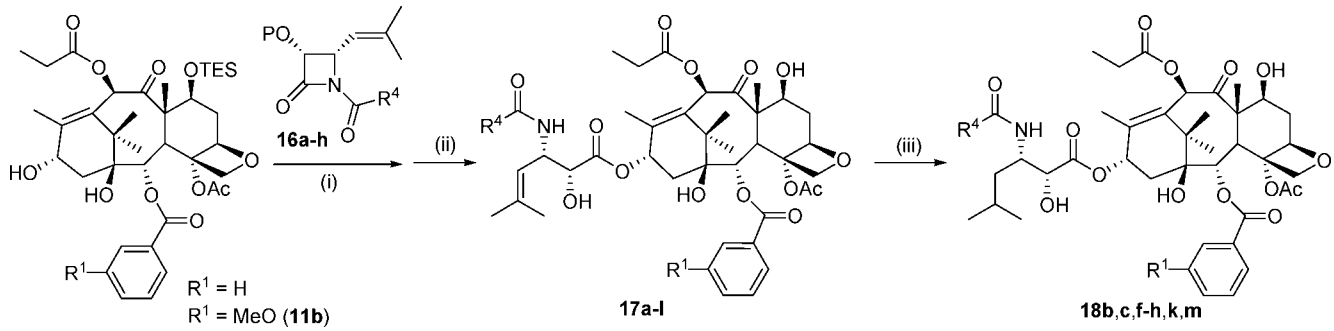
Cytotoxicity assay results of second-generation taxoids bearing a modified C2-benzoyl group at its meta position are summarized in Table 7. The IC_{50} values of paclitaxel, docetaxel, **6x**, **6′x**, and **19** (SB-T-1214) are also listed for comparison.[17] As Table 7 shows, a majority of these new second-generation taxoids (**14** and **15**), bearing a *t*-Boc group at the C3′N position, exhibit remarkable potency against drug-resistant (Pgp+) cancer cell lines, LCC6-MDR, and NCI/ADR, i.e., 2−3 orders of magnitude higher potencies than those of paclitaxel and docetaxel. In more than several cases, the *R*/*S* ratios are less than 3 and even become less than 1 in three cases (**14g** for LCC6-WT:LCC6-MDR and MCF7:NCI/ADR and **15g** for LCC6-WT:LCC6-MDR). In these three cases, it can be said that the Pgp-mediated MDR is completely circumvented by new taxoids **14g** and **15g**. In addition to **14g** and **15g**, **14e** and **14l** also show excellent *R*/*S* ratios, i.e., **14e**, *R*/*S* ratios of 1.3 and 1.2 for LCC6-WT:LCC6-MDR and MCF7:NCI/ADR, respectively; **14l**, *R*/*S* ratios of 1.0 for LCC6-WT:LCC6-MDR. *Accordingly, we have defined these new-generation taxoids, which can virtually circumvent the Pgp-mediated MDR, as the "third-generation" taxoids*. It is interesting to point out that the same C2-benzoyl group modifications to the taxoids, bearing cycloalkanoyl or carbalkoxy groups at the C3′N position, do not have recognizable effects on potency except for taxoids **18h** and **18m**, which exhibit subnanomolar IC_{50} values against LCC6-WT and MCF7. Taxoid **18m** also shows very high potency against drug-resistant LCC6-MDR (2.6 nM) and NCI/ADR (1.18 nM) cell lines.

For the effects of the meta substituents of the C2-benzoyl moiety, the potency decreases in the order F > Cl > N_3 > MeO ≫ CH_2=CH− against LCC6-WT (Pgp−), while the order changes to MeO > N_3 > Cl > F ≫ CH_2=CH− against LCC6-MDR (Pgp+). Apparently, the former order is more or less reflecting the ability of a taxoid with such a modification to bind microtubules. On the other hand, the latter order reflects the effects of these substituents on the MDR reversal activity of taxoids or simply indicates the extent of interaction of taxoids with Pgp in the reverse order. In both case, the *m*-vinyl substitution of the C2-benzoyl moiety (**14f**) resulted in the least potent taxoid in this comparison. The introduction of a *m*-methyl group to the C2-benzoyl moiety (**14a**) does not seem to have a recognizable positive effect.

For the C3′ position, 2-methylprop-1-enyl and 2-methylpropyl are the best substituents for potency so far. However, the introduction of allyl, (*E*)-prop-1-enyl, but-3-enyl, or (*S*)-2,2-dimethylcyclopropyl group provided very potent taxoids (**14m**−**p**), especially with the (*S*)-2,2-dimethylcyclopropyl group (**14p**) appearing to have a beneficial effect, comparable to those of 2-methylprop-1-enyl and 2-methylpropyl groups.

For the C10 modifications, the potency decreases in the order 4-MeO(C_6H_4)CH_2CO ∼ 2-MeO(C_6H_4)CO > MeOCO ∼ Ac > cyclo-PrCO ∼ EtCO > $PhCH_2OCO$ (Cbz) against LCC6-WT, while the order changes to 4-MeO(C_6H_4)CH_2CO > 2-MeO(C_6H_4)CO ∼ EtCO > MeOCO > Cbz > Ac < *c*-Pr against LCC6-MDR. However, the decreasing order further changes against MCF7 and NCI/ADR, i.e., Cbz > EtCO > MeOCO >

Scheme 6[a]



[a] Reagents and conditions: (i) LiHMDS, THF, −40 °C, 30 min; (ii) HF/pyridine, pyridine/MeCN, 0 °C to room temp, 18 h (61−86% for two steps); (iii) H_2, Pd/C, EtOAc, room temp, 24 h (90−92%).

Table 4. C3′N-Modified Second-Generation Taxoids **17** and **18**

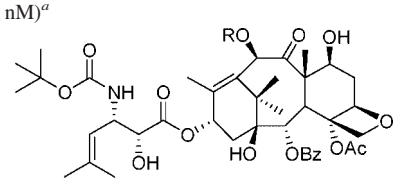
taxoid	R^1	R^4	yield (%)[a]
17a	H	cyclobutyl	86
17b	H	cyclopentyl	78
17c	H	cyclohexyl	85
17d	H	cyclopent-1-enyl	80
17e	H	cyclohex-1-enyl	75
17f	H	cyclopentyloxy	85
17g	H	cyclohexyloxy	80
17h	H	cyclopropyl	66
17i	H	cyclobutyl	61
17j	H	cyclopentyl	77
17k	H	cyclohexyl	81
17l	H	cyclohexyloxy	77
18b	H	cyclopentyl	98[b]
18c	H	cyclohexyl	98[b]
18f	H	cyclopentyloxy	98[b]
18g	H	cyclohexyloxy	98[b]
18h	MeO	cyclopropyl	98[b]
18k	MeO	cyclohexyl	98[b]
18m	MeO	cyclopentyloxy	60[c]

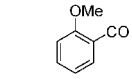
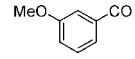
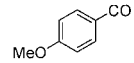
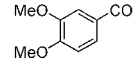
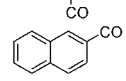
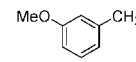
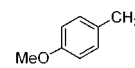
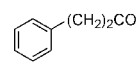
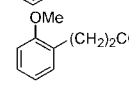
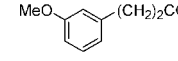
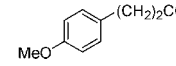
[a] Yield for two steps unless otherwise noted. [b] Yield for hydrogenation. [c] Yield for three steps.

4-MeO(C_6H_4)CH_2CO > Ac > 2-MeO(C_6H_4)CO ∼ EtCO against MCF7, while EtCO ≫ MeOCO > Cbz > 4-MeO(C_6H_4)CH_2CO > Ac > 2-MeO(C_6H_4)CO ∼ EtCO against NCI/ADR. These results suggest that the cancer cell types including Pgp overexpression are sensitive to the C10 substitution. Nevertheless, the difference in potency for these cases is within the factor of 10. Accordingly, all these highly potent new taxoids are very good candidates for further preclinical studies.

Cytotoxicity of New-Generation Taxoids against Paclitaxel-Resistant Cancer Cells with Point Mutations in Tubulin. Multidrug resistance to paclitaxel arises from the overexpression of ATP-binding cassette (ABC) transporters,[28] but other drug-resistance mechanisms are also involved in paclitaxel resistance.[29] One of the significant mechanism is associated with alterations of its cellular target, tubulin/microtubule.[30–35] In this regard, two paclitaxel-resistant sublines 1A9PTX10 and 1A9PTX22, derived from 1A9 cell line, have been reported.[34] The parental 1A9 is a clone of the human ovarian carcinoma cell line A-2780. Point mutations in class I β-tubulin in both 1A9PTX10 and 1A9PTX22 have been identified by sequence analysis.[34] Thus, the cytotoxicity of new-generation taxoids against these two paclitaxel-resistant cell lines would provide critical information about their ability to deal with drug resistance other than MDR. Selected new-generation taxoids, **19**, **14g**, and **15g**, were assayed against both drug-resistant cell lines and the parental cell line. As Table 8 shows, all three taxoids exhibit extremely potent activity, especially

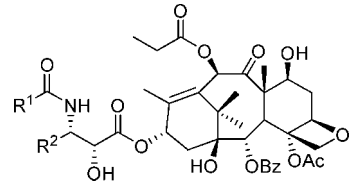
Table 5. Cytotoxicity of Second-Generation Taxoids with Modifications at C10 (IC_{50}, nM)[a]



Taxoid	R	LCC6-WT[b]	LCC6-MDR[c]	R/S
Paclitaxel	--	3.1	346	112
6a	Bz	1.8	4.8	2.7
6b		2.1	5.8	2.7
6c		2.8	5.1	1.8
6d		3.8	4.7	1.2
6e		2.1	5.7	2.7
6f		5.3	15.2	2.9
6g		6.3	15.2	2.4
6h	Cbz	1.8	16.7	9.3
6i		2.3	13.8	6.0
6j		2.1	20.3	9.7
6k		1.4	38.4	27.4
6l		5.1	31.2	6.1
6m		1.5	5.0	3.3
6n		3.7	6.7	1.8
6o		1.7	4.9	2.9

[a] Concentration of compound that inhibits 50% (IC_{50}, nM) of the growth of human tumor cell line after 72 h of drug exposure. *R*/*S*: resistance factor = (IC_{50} for drug resistant cell line, *R*)/(IC_{50} for drug-sensitive cell line, *S*). [b] LCC6-WT: human breast carcinoma cell line (Pgp−). [c] LCC6-MDR: *mdr1* transduced cell line (Pgp+).

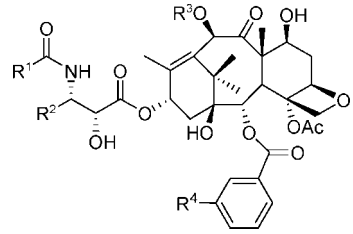
Table 6. Cytotoxicity of Second-Generation Taxoids with C3′N Modifications (IC_{50}, nM)[a]



taxoid	R^1	R^2	LCC6-WT[b]	LCC6-MDR[c]	*R*/*S*[d]	MCF7[e]	NCI/ADR[f]	*R*/*S*[d]
paclitaxel			3.1	346	112	1.7	300	176
6x	*t*-Boc	2-Me-prop-1-enyl				0.18	4.0	22
6′x	*t*-Boc	2-Me-propyl				0.35	5.1	15
17a	cyclobutyl	2-Me-prop-1-enyl	1.3	34	26	1.2	41	34
17b	cyclopentyl	2-Me-prop-1-enyl	1.1	19	17	1.1	22	20
18b	cyclopentyl	2-Me-propyl	6.3	64	10	2.3	29	12
17c	cyclohexyl	2-Me-prop-1-enyl	1.3	13	10	1.0	18	18
18c	cyclohexyl	2-Me-propyl	5.8	32	5.5	1.5	19	13
17d	cyclopent-1-enyl	2-Me-prop-1-enyl	1.2	14	12	0.4	6.0	15
17e	cyclohex-1-enyl	2-Me-prop-1-enyl	1.2	11	9.2	0.3	3.8	13
17f	cyclopentyloxy	2-Me-prop-1-enyl	0.94	12	13	1.4	8.6	6.1
18f	cyclopentyloxy	2-Me-propyl	2.6	14	5.4	1.3	8.8	6.8
17g	cyclohexyloxy	2-Me-prop-1-enyl	1.2	15	13	1.4	8.9	6.4
18g	cyclohexyloxy	2-Me-propyl	4.8	18	3.8	1.4	14	10

[a] Concentration of compound that inhibits 50% (IC_{50}, nM) of the growth of human tumor cell line after 72 h of drug exposure. [b] LCC6-WT: human breast carcinoma cell line (Pgp−). [c] LCC6-MDR: *mdr1* transduced cell line (Pgp+). [d] *R*/*S*: resistance factor = (IC_{50} for drug resistant cell line, *R*)/(IC_{50} for drug-sensitive cell line, *S*). [e] MCF7: human breast carcinoma cell line. [f] NCI/ADR: multidrug resistant human ovarian carcinoma cell line.

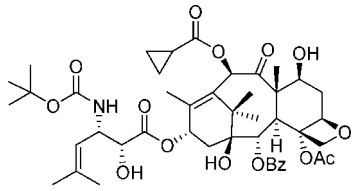
Table 7. Cytotoxicity of Second-Generation Taxoids with C2-Meta Modifications (IC_{50}, nM)[a]



taxoid	R^1	R^2	R^3	R^4	LCC6-WT[b]	LCC6-MDR[c]	*R*/*S*[d]	MCF7[e]	NCI/ADR[f]	*R*/*S*[d]
paclitaxel	Ph	Ph	MeCO	H	3.1	346	112	1.7	300	178
docetaxel	*t*-BuO	Ph	H	H	1.0	120	120	1.0	235	235
6x	*t*-BuO	$Me_2C{=}CH-$	EtCO	H				0.18	4.0	22
6′x	*t*-BuO	Me_2CHCH_2-	EtCO	H				0.35	5.1	21
19	*t*-BuO	$Me_2C{=}CH-$	*c*-PrCO	H				0.20	3.9	20
14a	*t*-BuO	$Me_2C{=}CH-$	MeCO	Me	1.5	5.8	3.9	0.8	5.0	6.3
14b	*t*-BuO	$Me_2C{=}CH-$	MeCO	MeO	0.6	2.7	4.5	0.8	2.3	2.9
14c	*t*-BuO	$Me_2C{=}CH-$	EtCO	F	0.5	2.1	4.2			
14d	*t*-BuO	$Me_2C{=}CH-$	EtCO	Cl	0.8	1.3	1.6			
14e	*t*-BuO	$Me_2C{=}CH-$	EtCO	N_3	0.9	1.2	1.3	0.9	1.1	1.2
14f	*t*-BuO	$Me_2C{=}CH-$	EtCO	$CH_2{=}CH-$	2.9	7.1	2.4			
14g	*t*-BuO	$Me_2C{=}CH-$	EtCO	MeO	1.0	0.9	0.90	0.36	0.33	0.92
14h	*t*-BuO	$Me_2C{=}CH-$	*c*-PrCO	MeO	1.0	2.9	2.9			
14i	*t*-BuO	$Me_2C{=}CH-$	MeOCO	MeO	0.6	1.6	2.7	0.4	1.4	3.5
14j	*t*-BuO	$Me_2C{=}CH-$	$PhCH_2OCO$	MeO	1.2	1.8	1.5	0.2	1.5	7.5
14k	*t*-BuO	$Me_2C{=}CH-$	2-MeO(C_6H_4)CO	MeO	0.4	0.9	2.3	1.1	3.3	3.0
14l	*t*-BuO	$Me_2C{=}CH-$	4-MeO(C_6H_4)CH_2CO	MeO	0.4	0.4	1.0	0.6	1.8	3.0
14m	*t*-BuO	$CH_2{=}CHCH_2-$	EtCO	MeO	1.2	8.4	7.0	0.8	8.7	10.9
14n	*t*-BuO	(*E*)-$CH_3CH{=}CH-$	EtCO	MeO	1.2	4.1	3.4			
14o	*t*-BuO	$CH_2{=}CH(CH_2)_2-$	EtCO	MeO	0.9	5.4	6.0	2.0	7.7	3.9
14p	*t*-BuO	(*S*)-2,2-Me_2-*c*-Pr−	EtCO	MeO	0.48	1.1	2.3	0.6	1.5	2.5
15c	*t*-BuO	Me_2CHCH_2-	EtCO	F	0.4	2.4	3.0			
15d	*t*-BuO	Me_2CHCH_2-	EtCO	Cl	0.8	2.9	3.6			
15e	*t*-BuO	Me_2CHCH_2-	EtCO	N_3	1.1	2.4	2.2	1.0	2.1	2.1
15g	*t*-BuO	Me_2CHCH_2-	EtCO	MeO	0.9	0.8	0.89	0.36	0.43	1.19
17h	*c*-Pr	$Me_2C{=}CH-$	EtCO	MeO	1.1	17.2	16	0.5	7.8	15.6
17i	*c*-Bu	$Me_2C{=}CH-$	EtCO	MeO	1.6	15	9.4	0.8	8.8	11
17j	*c*-pentyl	$Me_2C{=}CH-$	EtCO	MeO	1.1	11	10	0.3	9.5	32
17k	*c*-hexyl	$Me_2C{=}CH-$	EtCO	MeO	6.9	42	6.1	1.8	17.5	9.7
17l	*c*-hex-O	$Me_2C{=}CH-$	EtCO	MeO	1.23	14.8	12.0	1.44	14	9.7
18h	*c*-Pr	Me_2CHCH_2-	EtCO	MeO	0.6	13	22	0.4	11.8	30
18k	*c*-hexyl	Me_2CHCH_2-	EtCO	MeO	1.0	12	12	0.7	6.5	9.3
18m	*c*-pent-O	Me_2CHCH_2-	EtCO	MeO	0.76	2.6	3.4	0.17	1.18	6.9

[a] Concentration of compound that inhibits 50% (IC_{50}, nM) of the growth of human tumor cell line after 72 h of drug exposure. [b] LCC6-WT: human breast carcinoma cell line (Pgp−). [c] LCC6-MDR: *mdr1* transduced cell line (Pgp+). [d] *R*/*S*: resistance factor = (IC_{50} for drug resistant cell line, *R*)/(IC_{50} for drug-sensitive cell line, *S*). [e] MCF7: human breast carcinoma cell line. [f] NCI/ADR: multidrug resistant human ovarian carcinoma cell line.

Table 8. Cytotoxicity of New Generation Taxoids against 1A9PTX10 and 1A9PTX22 Cell Lines (IC_{50}, nM)[a]



19

taxoids	A-2780	1A9PTX10	*R*/*S*[b]	1A9PTX22	*R*/*S*[b]
paclitaxel	1.38 ± 0.05	532.95 ± 3.18	386	160.70 ± 14.70	116
19	0.44 ± 0.04	9.00 ± 0.77	20.4	3.94 ± 0.03	9.0
14g	0.76 ± 0.01	3.65 ± 0.21	4.8	3.88 ± 0.54	5.1
15g	0.25 ± 0.01	4.91 ± 0.53	19.6	2.10 ± 0.13	8.4

[a] Concentration of compound that inhibits 50% (IC_{50}, nM) of the growth of human tumor cell line after 72 h of drug exposure. [b] *R*/*S*: resistance factor = (IC_{50} for drug resistant cell line, *R*)/(IC_{50} for drug-sensitive cell line, *S*).

against drug-resistant cell lines 1A9PTX10 and 1A9PTX22, with 2 orders of magnitude higher potency than paclitaxel. The results clearly demonstrate that these second- and third-generation taxoids possess capability of effectively circumventing the paclitaxel drug resistance arising from point mutations in tubulins/microtubules besides MDR. This makes the new-generation taxoids even more attractive.

Cytotoxicity of New-Generation Taxoids against Pancreatic Cancer Cell Lines. Currently there are no effective chemotherapeutic treatments for pancreatic cancer and the 5-year survival rate is less than 5%.[36] Pancreatic cancer is refractive to conventional therapy, and the expression of various multidrug resistance proteins is believed to be a major factor for the extensive drug resistance.[37–39] We carried out a RT-PCR analysis of the expression of multidrug resistance genes in lysates of pancreatic cancer cell lines and found that CFPAC-1 and PANC-1 cell lines expressed *mdr1*, *mrp1*, *mrp2*, and *lrp* genes, responsible for multidrug resistance, while MIA PaCa-2 and BxPC-3 cell lines expressed *mrp1*, *mrp2*, and *lrp* genes.[40] Accordingly, it was of particular interest for us to examine the efficacy of new generation taxoids against highly multidrug-resistant pancreatic cancer cell lines. Thus, two taxoids, **19** and **14g** were evaluated for their cytotoxicity against four pancreatic cancer cell lines, MIA PaCa-2, CFPAC-1, BxPC-3, and PANC-1.

Table 9. Cytotoxicity of **19** and **14g** against Pancreatic Cancer Cell Lines (IC_{50}, nM)[a]

taxoids	MIA PaCa-2	CFPAC-1	BxPC-3	PANC-1
19	0.92	0.83	1.04	3.68
14g	0.68	0.89	3.03	22.6

[a] Concentration of compound that inhibits 50% (IC_{50}, nM) of the growth of human tumor cell line after 72 h of drug exposure.

As Table 9 shows, new-generation taxoids **19** and **14g** exhibit excellent cytotoxicity against four pancreatic cancer cell lines with subnanomolar to single-digit nanomolar IC_{50} values except one case for **14g** against PANC-1. It is worth mentioning that the third-generation taxoid **14g**, which possesses superior potency (>10 times) over the second-generation taxoid **19** against Pgp+ (i.e., *mdr1*) human ovarian cancer cell line NCI/ADR (see Table 3), exhibits lower potency than taxoid **19** against BxPC-3 and PANC-1 cell lines, especially against the latter (22.6 vs 3.68 nM). The results may suggest that taxoid **14g** cannot modulate a combination of multidrug-resistant proteins so efficiently as Pgp alone. Nevertheless, **14g** is still highly cytotoxic to PANC-1. On the other hand, taxoid **19** demonstrates remarkably high potency against all four pancreatic cancer cell lines. In addition, taxoid **19** did not show any appreciable cytotoxicity against primary pancreatic ductal cells up to 10 μM concentration. This is a very impressive finding.

Preliminary in Vivo Antitumor Activity against Pancreatic Cancer CFPAC-1 Xenograft in Nude Mice. Encouraged by remarkable in vitro cytotoxicity, a preliminary study on the in vivo antitumor activity of taxoid **19** against CFPAC-1 xenograft in nude mice was undertaken. Animals were inoculated with 1 million CFPAC-1 pancreatic cancer cells that express high levels of *mdr1* in each flank. After the tumor size had become 100 mm^3 on day 19, three intravenous injections of **19** (20 mg/kg × 3, 60 mg/kg total dose in Tween-80/EtOH/PBS) were made in 3-day intervals, i.e., days 19, 22, and 25. The treatment was highly efficacious, causing complete reduction in tumor volume. After 8 weeks tumors were recovered from the xenograft and subjected to histopathological analysis. The analysis of the stained tissues revealed that only inflammatory infiltrate and fibrotic issue remained and no trace of cancer cells. Consequently, taxoid **19** can be considered a very promising lead compound for potential treatment of pancreatic cancer.

Microtubule Polymerization Assay. The activities of **19**, **14g**, and **14i** (SB-T-1213031) were evaluated in two in vitro tubulin polymerization assays. Paclitaxel was also used as the standard for comparison purposes. Changes in absorbance in this spectrophotometric assay provide a direct measure of turbidity, hence indicating the extent of tubulin polymerization. Taxoids **19**, **14g**, and **14i** induced tubulin polymerization in the absence of GTP in a manner similar to paclitaxel (see Figures 1 and 2). The microtubules formed with these new generation taxoids as well as paclitaxel were stable against Ca^{2+}-induced depolymerization. As Figure 1 shows, taxoids **19** and **14g** promote rapid polymerization of tubulin at a faster rate than paclitaxel. The turbidity of the tubulin solution treated by **19** or **14g** reaches a plateau quickly and does not change with time. This observation may imply that there is a difference in structure between microtubules formed with the new-generation taxoids and those with paclitaxel. Third-generation taxoid **14g** causes spontaneous tubulin polymerization, reaching >90% of a plateau within 5 min from onset, while it takes about 12 min for second-generation taxoid **19** to reach the same point.

In a similar manner, the activity of taxoid **14i** was compared with that of paclitaxel in a tubulin polymerization assay using a protocol for tubulin preparation slightly different from that used for the experiments presented in Figure 1. As Figure 2 shows, this assay reveals a remarkable difference in the speed of tubulin polymerization between the third-generation taxoid **14i** and paclitaxel. Taxoid **14i** causes instantaneous polymerization of tubulin, completing the polymerization within 2 min, while paclitaxel promotes the polymerization much more slowly.

Electron Microscopy Analysis. The microtubules formed with new-generation taxoids (**19**, **14g**, and **14i**) were analyzed further by electron microscopy for their morphology and structure in comparison with those formed by using GTP and paclitaxel. The electron micrographs of microtubules formed with three taxoids, paclitaxel, and GTP are summarized in Figure 3. As parts A and B of Figure 3 show, GTP and paclitaxel form long and straight microtubules. The microtubules formed with a second-generation taxoid **19** (Figure 3C) are shorter than those with GTP or paclitaxel. In contrast, the morphology of the microtubules formed by the action of third-generation taxoids **14g** and **14i** is unique in that those microtubules are very short and numerous (parts D and E of Figure 3). The microtubules

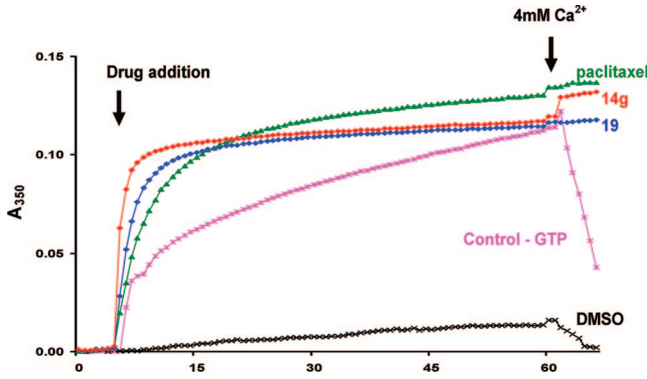


Figure 1. Tubulin polymerization with **19**, **14g**, and paclitaxel: microtubule protein 1 mg/mL, 37 °C, GTP 1 mM, drug 10 μM.

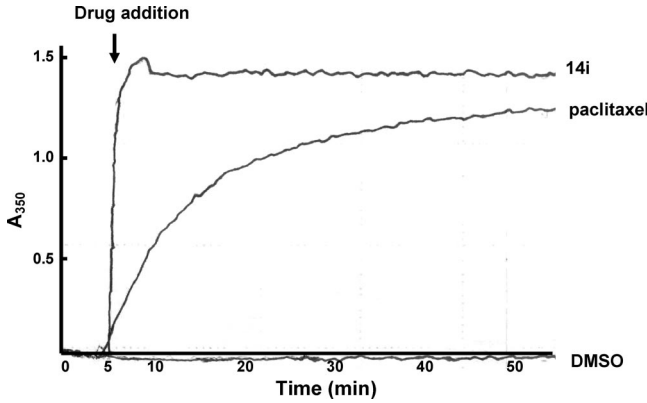


Figure 2. Tubulin polymerization with **14i** and paclitaxel: microtubule protein 1 mg/ml, 37 °C, drug 10 μM.

with taxoid **14g** appear to have more curvature than those with **14i**. It is worth mentioning that discodermolide (another potent anticancer drug candidate, stabilizing microtubules[41–44]) forms microtubules with characteristics similar to those formed with **14g** and **14i**, i.e., short and numerous (Figure 3F). It is strongly suggested that the formation of short and numerous microtubules is related to the instantaneous rapid polymerization of tubulin observed with these third-generation taxoids as well as discodermolide.

Antitumor Activity of Taxoid 19 in Vivo against Pgp+ DLD-1 Human Colon Tumor Xenograft. Taxoid **19** has recently emerged as one of the leading candidates among the second- and third-generation taxoids being studied in the Ojima laboratory, especially in connection with tumor-targeting drug delivery using taxoid conjugates with ω3 fatty acids.[45] Accordingly, this taxoid was evaluated for its efficacy against a drug-resistant human colon tumor xenograft (Pgp+) DLD-1 in severe combined immune deficient mice (SCID). Taxoid was administered intravenously at three doses 3 times using a 3-day regimen (q3d × 3, on days 5, 8, and 11), starting from day 5 after DLD-1 subcutaneous tumor implantation. Results are summarized in Table 10.

As Table 6 shows, taxoid **19** exhibits remarkable antitumor activity in sharp contrast to paclitaxel. As anticipated, paclitaxel is ineffective against this highly drug-resistant (Pgp+) tumor at its optimal dose (60 mg/kg total dose). The best result for taxoid **19** was obtained at 60 mg/kg total dose (20 mg/kg × 3), wherein complete regression of the DLD-1 tumor was achieved in 5 of 5 mice (tumor growth delay greater than 150 days). Systemic toxicity profile shows that there was only 3−5% weight loss during day 15 to day 20, and the drug was very well tolerated by animals. At 30 mg/kg total dose (10 mg/kg × 3), tumor growth delay of 37 days was observed, but all animals died before day 60. At 120 mg/kg total dose (40 mg/kg × 3), two animals died because of the drug's toxicity. Nevertheless, three animals survived till the end of the experiment on day 167 (tumor growth delay less than 150 days). Thus, the total dose of 60 mg/kg (20 mg/kg × 3) appears to be optimal for taxoid **19**. The highly promising in vivo antitumor activity of

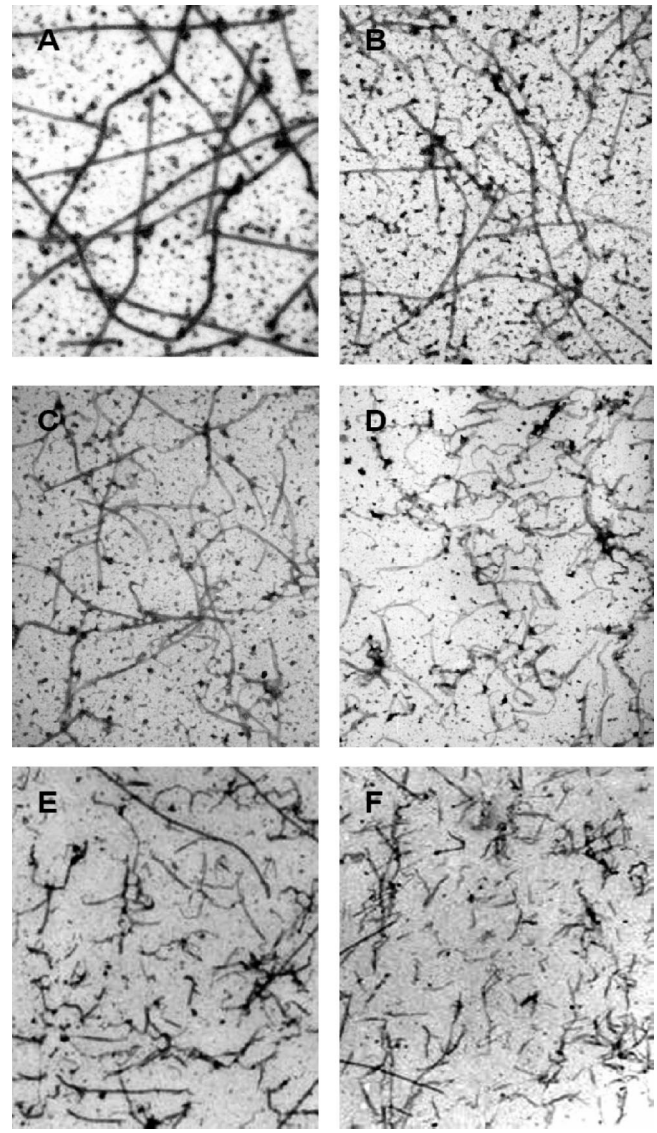


Figure 3. Electromicrographs of microtubules (20000×): (A) GTP; (B) paclitaxel; (C) **19**; (D) **14g**; (E) **14i**; (F) discodermolide.

Table 10. Antitumor Effect of Taxoid **19** Delivered iv to SCID Mice Bearing a Pgp+ Human Colon Tumor Xenograft, DLD-1

iv treatment[a]	total dose (mg/kg)	growth delay[b] (day)	toxicity[c]	cured mice/ group[d]
control	0		0	0/10
vehicle	0	4	0	0/5
paclitaxel	60	8	0	0/5
19	30	37	0	0/5
19	60	>150	0	5/5
19	120	>150	2	3/5

[a] Treatment given iv to SCID mice on day 5 after DLD-1 human colon tumor implant and continued as noted. All drugs were formulated in Tween/EtOH. [b] Based on comparison of each group vs control using the Cox−Mantel test. [c] Number of animals that either died or lost greater than 20% body weight. [d] SCID mice with no palpable tumor on day 167, end of experiment.

19 warrants further preclinical evaluation of this second-generation taxoid.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were measured on a Varian 300, 400, or 500 MHz NMR spectrometer or a Bruker AC-250 NMR spectrometer. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific optical rotations were measured on a Perkin-Elmer model 241 polarimeter. IR spectra were recorded on a Perkin-Elmer model 1600 FT-IR spectrophotometer. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254, and column chromatography was carried out on silica gel 60 (Merck, 230−400 mesh ASTM). Purity was determined with a Waters HPLC assembly consisting of dual Waters 515 HPLC pumps, a PC workstation running Millennium 32, and a Waters 996 PDA detector, using a Phenomenex Curosil-B column, employing CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min. High-resolution mass spectra were obtained at the Mass Spectrometry Laboratory, University of Illinois at Urbana−Champaign, Urbana, IL, or the Mass Spectrometry Facility, University of California, Riverside, Riverside, CA.

Materials. The chemicals were purchased from Aldrich-Sigma Co. and used as received or purified before use by standard methods. Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. *N,N*-Dimethylformamide (DMF) was distilled over 4 Å molecular sieves under reduced pressure. 4-(*N,N*-Dimethylamino)pyridine (DMAP) was uses as received. 10-Deacetylbaccatin III (DAB, **1**) was obtained from Indena, SpA, Italy. 7-Triethylsilylbaccatin III (**2**),[46,47] (3*R*,4*S*)-1-*tert*-butoxycarbonyl-3-triisopropylsiloxy-4-(2-methylprop-1-enyl) azetidin-2-one (**3a**),[7,20] (3*R*,4*S*)-1-*tert*-butoxycarbonyl-3-triisopropylsiloxy-4-(2-methylpropyl)azetidin-2-one (**3b**),[14,48] (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-(prop-2-enyl)azetidin-2-one (**3c**),[49] (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-[(*E*)-prop-1-enyl]azetidin-2-one(**3d**),[7] (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-(3-butenyl)azetidin-2-one (**3e**),[49] (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-[(*S*)-2,2-dimethylcyclopropyl]azetidin-2-one (**3f**),[26] 7,10,13-tri(triethylsilyl)-10-deacetylbaccatin III (**7**),[23,49] 7,10,13-tri(triethylsilyl)-2-debenzoyl-10-deacetylbaccatin III (**8**),[49,50] 7-triethylsilyl-10-deacetyl-10-propanoylbaccatin,[17] and 3′-dephenyl-3′-(2-methyl-1-propenyl)-10-(cyclopropanecarbonyl)docetaxel (**19**)[17] were prepared by the literature methods.

Synthesis of C10-Modified Taxoids 6. C-10 modified second-generation taxoids **6** were synthesized using the route illustrated in Scheme 1 via key intermediates **4** and **5**, followed by acylation and deprotection. Typical procedures for the preparation of **4** and **5** as well as those for acylation and deprotection are described below.

7-Triethylsilyl-10-acetyl-2′-triisopropyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (4). To a solution of 7-triethylsilylbaccatin III (**2**)[46,47] (86 mg, 0.12 mmol) and 4-(2-methylprop-1-enyl)-β-lactam **3**[7,20] (82 mg, 0.20 mmol) in 5 mL of dry THF was added 1 M LiHMDS (0.20 mL, 0.20 mmol) in THF dropwise at −40 °C, and the solution was stirred at the same temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 6:1) to afford **4** (125 mg, 95% yield) as a white solid: ^{1}H (300 MHz, $CDCl_3$) δ 0.54 (m, 6 H), 0.85 (m, 9 H), 1.04 (m, 24 H), 1.15 (s, 3 H), 1.33 (s, 9 H), 1.64 (s, 6 H), 1.74 (m, 4 H), 2.16 (s, 3 H), 2.35 (s, 3 H), 2.49 (m, 1 H), 3.90 (d, J = 7.5 Hz, 1 H), 4.20 (d, J = 8.7 Hz, 1 H), 4.30 (d, 8.7 Hz, 1 H), 4.43 (m, 2 H), 4.80 (m, 2 H), 4.92 (d, J = 8.1 Hz, 1 H), 5.33 (d, J = 8.4 Hz, 1 H), 5.63 (d, J = 7.5 Hz, 1 H), 6.08 (t, J = 8.1 Hz, 1 H), 6.35 (s, 1 H), 7.47 (dd, J = 8.1 Hz, 7.2 Hz, 2 H), 7.59 (dd, J = 7.2 Hz, 8.1 Hz, 1 H), 8.09 (d, J = 7.2 Hz, 2 H).

2′-Triisopropyl-3′-dephenyl-3′-(2-methyl-1-propenyl)-7-triethylsilyldocetaxel (5). To a solution of **4** (31 mg, 0.03 mmol) in 3 mL of EtOH was added 1 mL of $N_2H_4 \cdot H_2O$, and the mixture was allowed to stir for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted two times with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude solid was purified by flash chromatography on silica gel (hexanes/EtOAc = 3/1) to afford **5** (25 mg, 85% yield) as a white solid: ^{1}H (300 MHz, $CDCl_3$) δ 0.54 (m, 6 H), 0.85 (m, 9 H), 1.04 (m, 24 H), 1.15 (s, 3 H), 1.33 (s, 9 H), 1.64 (s, 6 H), 1.74 (m, 4 H), 2.34 (m, 1 H), 2.37 (s, 3 H), 3.90 (d, J = 7.5 Hz, 1 H), 4.20 (d, J = 8.7 Hz, 1 H), 4.30 (d, 8.7 Hz, 1 H), 4.42 (m, 2 H), 4.80 (m, 2 H), 4.92 (d, J = 8.1, 1 H), 5.11 (d, J = 1.8 Hz, 1 H), 5.33 (d, J = 8.4 Hz, 1 H), 5.63 (d, J = 7.5 Hz, 1 H), 6.15 (t, J = 8.1 Hz, 1 H), 7.47 (dd, J = 8.1 Hz, 7.2 Hz, 2 H), 7.59 (dd, J = 7.2 Hz, 8.1 Hz, 1 H), 8.09 (d, J = 7.2 Hz, 2 H).

Preparation of 2′,7-Protected Taxoid 5A. Method A. To a solution of **5**, 3 equiv of DMAP, and 3 equiv of triethylamine in CH_2Cl_2 was added 3 equiv of the corresponding acid chloride. The solution was allowed to stir for 12−72 h at 25−40 °C, diluted with EtOAc, and quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting solid was purified by flash chromatography on silica gel to afford the corresponding coupling product, 2′-triisopropyl-3′-dephenyl-3′-(2-methyl-1-propenyl)-7-triethylsilyl-10-acyldocetaxel (**5A**).

Method B. To a solution of **5**, 3 equiv of DMAP, and 3 equiv of the corresponding acid in CH_2Cl_2 was added 3 equiv of DIC. The solution was allowed to stir for 12−72 h at 25 °C, diluted with EtOAc, and quenched with saturated aqueous $NaHCO_3$. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting solid was purified by flash chromatography on silica gel to afford the desired coupling product **5A**.

Preparation of Taxoids 6 through Deprotection of 5A. A typical procedure is described for the synthesis of 3′-dephenyl-3′-(2-methyl-1-propenyl)-10-(2-methoxybenzoyl)docetaxel (**6b**). To a solution of 10 mg (0.01 mmol) of 2′-triisopropyl-3′-dephenyl-3′-(2-methyl-1-propenyl)-7-triethylsilyl-10-(2-methoxybenzoyl)docetaxel (**5A-b**) in 1 mL of pyridine/acetonitrile (1/1) was added dropwise 0.1 mL of HF/pyridine at 0 °C, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was then diluted with ethyl acetate, washed with saturated $CuSO_4$ solution and water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc = 1/1) to afford 5 mg (90% yield) of taxoid **6b** as a white solid: mp 150−158 °C; $[\alpha]_D^{20}$ −75 (*c* 0.010, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (m, 6 H), 1.31 (s, 9 H), 1.54 (s, 3 H), 1.63 (s, 3 H), 1.82 (m, 1 H), 1.84 (s, 3 H), 2.01 (s, 3 H), 2.36 (s, 3 H), 2.57 (m, 2 H), 3.39 (bs, 1 H), 3.89 (m, 4 H), 4.20 (m, 2 H), 4.31 (d, J = 8.1 Hz, 1 H), 4.48 (m, 1 H), 4.63 (m, 2 H), 4.98 (d, J = 8.7 Hz, 1 H), 5.25 (m, 1 H), 5.70 (d, J = 6.9 Hz, 1 H), 6.12 (m, 1 H), 6.47 (s, 1 H), 7.00 (m, 2 H), 7.54 (m, 4 H), 8.22 (m, 3 H); ^{13}C (63 MHz, $CDCl_3$) δ 9.6, 15.0, 18.6, 21.9, 22.4, 25.7, 26.6, 28.2, 35.6, 43.3, 45.7, 51.6, 55.9, 58.7, 72.2, 72.4, 73.8, 75.2, 75.6, 78.0, 79.3, 80.0, 81.1, 84.5, 112.1, 120.3, 120.63, 128.6, 129.2, 130.2, 132.7, 133.0, 133.7, 134.6, 160.0, 165.8, 167.0, 170.1, 170.5, 203.8. HRMS (FAB) *m/z* calcd for $C_{49}H_{61}NO_{16} \cdot H^+$: 920.4069. Found: 920.4068 (Δ = 0.1 ppm). Other taxoids **6a** and **6c−o** were prepared in the same manner, and characterization data are shown below.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-benzoyldocetaxel (6a). 90% (two steps); white solid; mp 140−143 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.22 (s, 3 H), 1.35 (s, 9 H), 1.58 (s, 3 H), 1.70 (s, 3 H), 1.76 (s, 3 H), 1.85 (m, 1 H), 1.96 (s, 3 H) 2.37 (s, 3 H), 2.60 (m, 2 H), 3.38 (m, 1 H), 3.89 (d, J = 7.0 Hz, 1 H), 4.21 (m, 2 H), 4.32 (d, J = 8.3 Hz, 1 H), 4.52 (m, 1 H), 4.76 (m, 2 H), 4.98 (d, J = 8.0 Hz, 1 H), 5.30 (m, 1 H), 5.71 (d, J = 7.0 Hz, 1 H), 6.21 (m, 1 H), 6.56 (s, 1 H), 7.47 (dd, J = 7.3 Hz, 7.8 Hz, 4

H), 7.58 (m, 2 H), 8.10 (m, 4 H); ^{13}C (63 MHz, $CDCl_3$) δ 9.6, 15.0, 18.6, 22.1, 22.4, 23.5, 25.7, 26.9, 28.2, 35.7, 42.3, 43.3, 45.8, 51.6, 58.7, 72.3, 72.4, 73.8, 75.1, 76.0, 79.2, 80.1, 81.1, 84.5, 120.6, 128.5, 128.7, 129.1, 129.2, 130.0, 130.2, 132.9, 133.7, 142.9, 166.4, 167.0, 170.1, 172.1, 203.6. HRMS (FAB) *m/z* calcd for $C_{48}H_{59}NO_{15}\cdot H^+$: 890.3963. Found: 890.3966 ($\Delta = -0.3$ ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(3-methoxybenzoyl)-docetaxel (6c). 87% (two steps); white solid; mp 154−159 °C; $[\alpha]^{20}_D$ −75 (*c* 0.010, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (s, 3 H), 1.37 (s, 15 H), 1.54 (s, 3 H), 1.63 (s, 3 H), 1.82 (m, 1 H), 1.84 (s, 3 H), 2.36 (s, 3 H), 2.57 (m, 2 H), 3.39 (bs, 1 H), 3.89 (m, 4 H), 4.20 (m, 2 H), 4.31 (d, $J = 8.1$ Hz, 1 H), 4.48 (m, 1 H), 4.63 (m, 2 H), 4.98 (d, $J = 8.7$ Hz, 1 H), 5.25 (m, 1 H), 5.70 (d, $J = 6.9$ Hz, 1 H), 6.12 (m, 1 H), 6.54 (s, 1 H), 7.02 (m, 1 H), 7.44 (m, 6 H), 8.02 (m, 2 H); ^{13}C (63 MHz, $CDCl_3$) δ 9.6, 15.0, 18.6, 22.1, 22.4, 25.7, 26.8, 28.2, 33.4, 35.7, 43.3, 45.8, 51.6, 55.4, 58.7, 72.3, 73.8, 75.1, 76.1, 79.2, 80.0, 81.1, 84.5, 105.1, 114.1, 120.1, 120.6, 122.3, 128.7, 129.2, 129.6, 130.2, 130.4, 132.8, 133.7, 159.6, 166.3, 167.0, 169.7, 169.8, 170.1, 170.4, 203.5. HRMS (FAB) *m/z* calcd for $C_{49}H_{61}NO_{16}\cdot H^+$: 920.4069. Found: 920.4068 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(4-methoxybenzoyl)-docetaxel (6d). 80%; white solid; mp 148−156 °C; $[\alpha]^{20}_D$ −45 (*c* 0.010, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (s, 3 H), 1.35 (s, 9 H), 1.55 (s, 3 H), 1.70 (s, 6 H), 1.77 (s, 3 H), 1.82 (m, 1 H), 1.95 (s, 3 H), 2.37 (s, 3 H), 2.57 (m, 2 H), 3.39 (bs, 1 H), 3.88 (m, 4 H), 4.21 (m, 2 H), 4.31 (d, $J = 8.1$ Hz, 1 H), 4.55 (m, 1 H), 4.76 (m, 2 H), 4.98 (d, $J = 8.7$ Hz, 1 H), 5.23 (m, 1 H), 5.75 (d, $J = 6.6$ Hz, 1 H), 6.21 (m, 1 H), 6.54 (s, 1 H), 6.94 (d, $J = 6.5$ Hz, 2 H), 7.48 (m, 3 H), 8.03 (d, $J = 9$ Hz, 2 H), 8.11 (d, $J = 6.5$ Hz, 2 H); ^{13}C (63 MHz, $CDCl_3$) δ 9.6, 15.0, 18.6, 22.1, 22.4, 25.7, 26.8, 28.2, 33.4, 35.7, 43.3, 45.8, 51.6, 55.4, 58.7, 72.3, 73.8, 75.1, 76.1, 79.2, 80.0, 81.1, 84.5, 105.1, 114.1, 120.1, 120.6, 121.3, 128.7, 129.2, 129.6, 130.2, 131.4, 132.8, 133.7, 159.6, 166.3, 167.4, 169.8, 170.0, 170.1, 170.7, 203.6. HRMS (FAB) *m/z* calcd for $C_{49}H_{61}NO_{16}\cdot H^+$: 920.4069. Found: 920.4068 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(3,4-dimethoxybenzoyl)docetaxel (6e). 92% (for two steps); white solid; mp 159−165 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (s, 6 H), 1.33 (s, 12 H), 1.70 (s, 3 H), 1.76 (s, 3 H), 1.95 (m, 4 H), 2.42 (s, 3 H), 2.66 (m, 2 H), 3.37 (bs, 1 H), 3.88 (m, 1 H), 3.93 (s, 3 H), 3.95 (s, 3 H), 4.18 (m, 2 H), 4.32 (d, $J = 8.5$ Hz, 1 H), 4.51 (m, 1 H), 4.76 (m, 2 H), 4.98 (d, $J = 8.0$ Hz, 1 H), 5.31 (m, 1 H), 5.71 (d, $J = 6.8$ Hz, 1 H), 6.21 (t, $J = 8.0$ Hz, 1 H), 6.53 (s, 1 H), 6.92 (d, $J = 8.5$ Hz, 1 H), 7.44 (dd, $J = 7.3$ Hz, 8.0 Hz, 2 H), 7.57 (m, 2 H), 7.73 (d, $J = 8.5$ Hz, 1 H), 8.11 (d, $J = 7.0$ Hz, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.2, 15.0, 18.6, 22.1, 22.4, 25.7, 26.9, 28.2, 29.7, 35.6, 43.3, 45.8, 51.6, 56.0, 56.1, 58.7, 72.3, 73.8, 75.1, 75.9, 79.2, 80.0, 81.1, 84.5, 110.4, 112.4, 120.6, 121.5, 124.1, 128.7, 129.2, 130.2, 132.9, 133.7, 138.0, 142.8, 148.8, 153.7, 155.5, 166.2, 167.0, 170.1, 173.1, 203.8. HRMS (FAB) *m/z* calcd for $C_{50}H_{63}NO_{17}\cdot H^+$: 950.4174. Found: 950.4174 ($\Delta = 0.0$ ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(1-naphthoyl)docetaxel (6f). 90% (two steps); white solid; mp 162−164 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (s, 3 H), 1.28 (s, 3 H), 1.35 (s, 9 H), 1.73 (s, 3 H), 1.77 (s, 6 H), 1.93 (m, 1 H), 2.00 (s, 3 H), 2.38 (s, 3 H), 2.68 (m, 2 H), 3.37 (bs, 1 H), 3.92 (d, $J = 7.0$ Hz, 1 H), 4.23 (m, 2 H), 4.33 (d, $J = 8.3$ Hz, 1 H), 4.58 (m, 1 H), 4.77 (m, 2 H), 5.00 (d, $J = 8.0$ Hz, 1 H), 5.33 (m, 1 H), 5.73 (d, $J = 7.0$ Hz, 1 H), 6.23 (t, $J = 7.0$ Hz, 1 H), 6.69 (s, 1 H), 7.57 (m, 6 H), 7.90 (d, $J = 7.5$ Hz, 1 H), 8.10 (m, 3 H), 8.32 (d, $J = 6.5$ Hz, 1 H), 8.89 (d, $J = 8.3$ Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.6, 15.1, 15.6, 18.6, 22.2, 22.4, 25.7, 26.8, 28.2, 35.7, 43.3, 45.8, 51.6, 58.7, 72.3, 72.4, 73.8, 75.1, 76.0, 79.2, 80.0, 81.1, 84.5, 120.6, 124.5, 125.7, 126.1, 126.4, 128.0, 128.6, 128.7, 129.2, 130.2, 130.8, 131.4, 133.0, 133.7, 134.1 138.0, 143.0, 155.5, 167.0, 167.5, 170.2, 173.0, 203.9. HRMS (FAB) *m/z* calcd for $C_{52}H_{61}NO_{15}\cdot H^+$: 940.4128. Found: 940.4124 ($\Delta = 0.4$ ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(2-napthoyl)docetaxel (6g). 92%; white solid; mp 165−170 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.35 (s, 9 H), 1.39 (s, 3 H), 1.57 (s, 3 H), 1.72 (s, 3 H), 1.76 (s, 3 H), 1.95 (m, 1 H), 1.98 (s, 3 H), 2.38 (s, 3 H), 2.50 (m, 2 H), 3.39 (bs, 1 H), 3.92 (d, $J = 7.0$ Hz, 1 H), 4.23 (m, 2 H), 4.31 (d, $J = 8.3$ Hz, 1 H), 4.55 (m, 1 H), 4.77 (m, 2 H), 4.99 (d, $J = 8.8$ Hz, 1 H), 5.25 (m, 1 H), 5.73 (d, $J = 6.8$ Hz, 1 H), 6.23 (m, 1 H), 6.63 (s, 1 H), 7.51 (m, 5 H), 7.99 (m, 6 H), 8.65 (s, 1 H); ^{13}C (63 MHz, $CDCl_3$) δ 9.6, 14.2, 15.1, 18.6, 22.2, 22.4, 25.7, 26.9, 28.2, 35.7, 43.3, 45.8, 51.6, 58.7, 72.3, 73.4, 73.8, 75.1, 76.2, 79.2, 80.0, 81.1, 84.5, 120.6, 125.2, 126.3, 126.8, 127.8, 128.4, 128.6, 129.2, 129.5, 130.2, 131.8, 132.4, 132.9, 133.7, 135.9, 138.0, 142.9, 155.5, 166.6, 167.0, 170.1, 203.6. HRMS (FAB) *m/z* calcd for $C_{52}H_{61}NO_{15}\cdot H^+$: 940.4128. Found: 940.4124 ($\Delta = 0.4$ ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-benzyloxycarbonyl-docetaxel (6h). 97%, white solid; mp 145−150 °C; ^{1}H NMR (300 MHz. $CDCl_3$) δ 1.15 (s, 3 H), 1.23 (s, 3 H), 1.34 (s, 9 H), 1.60 (bs, 1 H), 1.70 (s, 3 H), 1.76 (s, 6 H), 1.85 (m, 1 H), 1.89 (s, 3 H), 2.36 (s, 3 H), 2.54 (m, 2 H), 3.36 (bs, 1 H), 4.19 (m, 2 H), 4.30 (d, $J = 8.7$ Hz, 1 H), 4.40 (m, 1 H), 4.76 (m, 2 H), 4.96 (d, $J = 7.8$ Hz, 1 H), 5.23 (s, 2 H), 5.31 (d, $J = 7.5$ Hz, 1 H), 5.67 (d, $J = 6.9$ Hz, 1 H), 6.16 (m, 2 H), 7.40 (m, 7 H), 7.61 (dd, $J = 7.2$ Hz, 7.5 Hz, 1 H), 8.10 (d, $J = 7.5$ Hz, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 15.1, 18.5, 21.8, 22.4, 25.7, 26.5, 28.2, 35.5, 35.6, 43.1, 45.6, 51.6, 58.2, 58.6, 70.6, 72.1, 72.3, 73.8, 75.0, 78.4, 79.2, 80.0, 81.0, 84.4, 120.6, 128.5, 128.6, 128.7, 129.2, 130.1, 132.5, 133.7, 134.7, 137.9, 143.5, 155.3, 155.5, 166.9, 170.1, 173.0, 203.9. HRMS (FAB) *m/z* calcd for $C_{49}H_{61}NO_{16}\cdot H^+$: 920.4069. Found: 920.4068 ($\Delta = 0.1$ ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(2-methoxyphenylacetyl)docetaxel (6i). 80% (for two steps); white solid; mp 148−149 °C; ^{1}H NMR (250 MHz. $CDCl_3$) δ 1.04 (s, 3 H), 1.13 (s, 3 H), 1.35 (s, 9 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.76 (s, 3 H), 1.88 (s, 4 H), 2.34 (s, 3 H), 2.39 (m, 2 H), 2.50 (m, 1 H), 3.39 (bs, 1 H), 3.81 (m, 4 H), 4.19 (m, 2 H), 4.32 (m, 2 H), 4.75 (m, 2 H), 4.94 (d, $J = 7.5$ Hz, 1 H), 5.29 (m, 1 H), 5.64 (d, $J = 6.8$ Hz, 1 H), 6.14 (t, $J = 7.5$ Hz, 1 H), 6.29 (s, 1 H), 6.92 (m, 2 H), 7.27 (m, 2 H), 7.46 (m, 2 H), 7.56 (m, 1 H), 8.09 (d, $J = 7.0$ Hz, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.2, 15.1, 18.5, 21.6, 22.4, 25.7, 26.4, 28.2, 30.9, 35.6, 40.1, 43.1, 45.8, 51.5, 55.7, 58.8, 61.2, 72.0, 72.3, 73.7, 74.9, 75.0, 75.8, 79.1, 81.0, 84.4, 87.5, 114.0, 114.6, 120.1, 120.6, 122.5, 128.6, 129.6, 130.4, 130.5, 132.7, 142.5, 159.6, 169.7, 170.5, 172.9, 203.4. HRMS (FAB) *m/z* calcd for $C_{50}H_{63}NO_{16}\cdot H^+$: 934.4225. Found: 934.4229 ($\Delta = -0.4$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(3-methoxyphenylacetyl)docetaxel (6j). 80% (for two steps); white solid; mp 145−150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 1.18 (s, 3 H), 1.34 (s, 9 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 1.76 (s, 3 H) 1.86 (s, 3 H), 1.86 (m, 1 H), 2.17 (m, 4 H), 2.37 (s, 3 H), 2.39 (m, 2 H), 2.55 (m, 1 H), 3.34 (bs, 1 H), 3.79 (m, 4 H), 4.19 (m, 1 H), 4.32 (d, $J = 8.4$ Hz, 1 H), 4.39 (m, 1 H), 4.73 (m, 2 H), 4.94 (d, $J = 8.1$ Hz, 1 H), 5.30 (m, 1 H), 5.64 (d, $J = 6.8$ Hz, 1 H), 6.13 (t, $J = 8.1$ Hz, 1 H), 6.30 (s, 1 H), 6.88 (m, 2 H), 7.27 (m, 2 H), 7.46 (m, 2 H), 7.60 (m, 1 H), 8.09 (d, $J = 7.3$ Hz, 2 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 9.5, 14.5, 15.1, 18.4, 21.6, 22.4, 25.7, 26.4, 28.2, 30.9, 35.6, 40.1, 43.1, 45.6, 51.5, 55.7, 58.8, 61.2, 72.0, 72.3, 73.7, 74.9, 75.0, 75.8, 79.1, 81.0, 84.4, 87.5, 114.0, 114.6, 120.1, 120.6, 122.7, 128.6, 129.6, 130.2, 130.5, 132.5, 142.5, 159.6, 168.9, 170.5, 172.9, 203.6. HRMS (FAB) *m/z* calcd for $C_{50}H_{63}NO_{16}\cdot H^+$: 934.4225. Found: 934.4229 ($\Delta = -0.4$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-(4-methoxyphenylacetyl)docetaxel (6k). 60% (for two steps); white solid; mp 145−150 °C; ^{1}H NMR (250 MHz. $CDCl_3$) δ 1.07 (s, 3 H), 1.18

(s, 3 H), 1.34 (s, 9 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 1.76 (s, 3 H), 1.86 (s, 3 H), 1.86 (m, 1 H), 2.17 (m, 4 H), 2.37 (s, 3 H), 2.39 (m, 2 H), 2.55 (m, 1 H), 3.34 (bs, 1 H), 3.79 (m, 4 H), 4.19 (m, 1 H), 4.32 (d, J = 8.4 Hz, 1 H), 4.39 (m, 1 H), 4.73 (m, 2 H), 4.94 (d, J = 8.1 Hz, 1 H), 5.30 (m, 1 H), 5.64 (d, J = 6.9 Hz, 1 H), 6.15 (t, J = 8.1 Hz, 1 H), 6.30 (s, 1 H), 7.03 (d, J = 9.0 Hz, 2 H), 7.45 (m, 2 H), 7.58 (m, 1 H), 8.10 (d, J = 7.3 Hz, 2 H), 8.26 (d, J = 9.0 Hz, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.2, 15.1, 18.5, 21.6, 22.4, 25.7, 26.4, 28.2, 30.9, 35.6, 40.1, 43.1, 45.8, 51.5, 55.7, 58.8, 61.2, 72.0, 72.3, 73.7, 74.9, 75.0, 75.8, 79.1, 81.0, 84.4, 87.5, 114.0, 114.6, 120.1, 120.6, 122.5, 128.6, 129.6, 130.4, 130.5, 132.7, 142.5, 159.6, 169.7, 170.5, 172.9, 203.4. HRMS (FAB) m/z calcd for $C_{50}H_{63}NO_{16}\cdot H^+$: 934.4225. Found: 934.4229 (Δ = −0.4 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-hydrocinnamoyldocetaxel (6l). 85% (for two steps); white solid; mp 150−155 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.21 (s, 3 H), 1.56 (s, 12 H), 1.68 (s, 3 H), 1.72 (s, 3 H), 1.86 (s, 3 H), 1.88 (m, 1 H), 2.16 (s, 3 H), 2.38 (m, 2 H), 2.85 (m, 2 H), 3.20 (m, 2 H), 3.35 (bs, 1 H), 3.7 (m, 1 H), 4.20 (m, 2 H), 4.34 (d, J = 8.3 Hz, 1 H), 4.45 (m, 1 H), 4.77 (m, 2 H), 4.94 (d, J = 7.5 Hz, 1 H), 5.31 (bs, 1 H), 5.66 (d, J = 7.0 Hz, 1 H), 6.27 (m, 2 H), 7.17 (m, 5 H), 7.47 (dd, J = 7.8 Hz, 8.3 Hz, 2 H), 7.60 (m, 1 H), 8.09 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 15.0, 18.6, 22.4, 25.7, 26.6, 28.2, 30.0, 35.6, 36.1, 43.2, 45.6, 51.6, 55.3, 58.6, 72.2, 72.3, 73.8, 75.0, 75.5, 79.2, 81.1, 113.9, 117.6, 120.6, 128.6, 129.2, 130.2, 132.2, 133.7, 138.0, 142.6, 158.2, 167.0, 170.1, 173.1, 173.6, 203.8. HRMS (FAB) m/z calcd for $C_{50}H_{63}NO_{15}\cdot H^+$: 918.4276. Found: 918.4276 (Δ = 0.0 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-[3-(2-methoxyphenyl)propanoyl]docetaxel (6m). 97%; white solid; mp 155−159 °C; $[\alpha]^{20}_D$ −45 (c 0.050, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.24 (s, 3 H), 1.35 (s, 9 H), 1.67 (s, 3 H), 1.75 (s, 3 H), 1.88 (s, 4 H), 2.01 (s, 3 H), 2.35 (s, 3 H), 2.48 (m, 2 H), 2.79 (m, 2 H), 2.94 (m, 2 H), 3.33 (m, 1 H), 3.82 (m, 4 H), 4.20 (m, 2 H), 4.30 (d, J = 8.5 Hz, 1 H), 4.38 (m, 1 H), 4.75 (m, 2 H), 4.96 (d, J = 8.0 Hz, 1 H), 5.31 (m, 1 H), 5.64 (d, J = 7.0 Hz, 1 H), 6.19 (m, 1 H), 6.29 (s, 1 H), 6.82 (m, 2 H), 7.19 (m, 2 H), 7.45 (m, 2 H), 7.59 (m, 1 H), 8.10 (d, J = 7.3 Hz 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 15.0, 18.6, 21.9, 22.4, 25.7, 26.0, 26.6, 28.2, 30.9, 31.6, 33.4, 34.0, 35.6, 43.2, 45.7, 51.6, 55.2, 58.6, 72.2, 72.4, 73.8, 75.1, 75.4, 79.2, 80.0, 81.1, 84.4, 87.3, 105.1, 110.2, 120.4, 120.6, 127.7, 128.5, 128.6, 129.2, 130.0, 130.2, 132.9, 133.7, 137.9, 142.5, 155.4, 157.5, 167.0, 170.1, 173.5, 203.8. HRMS (FAB) m/z calcd for $C_{51}H_{65}NO_{16}\cdot H^+$: 948.4382. Found: 948.4382 (Δ = 0.0 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-[3-(3-methoxyphenyl)propanoyl]docetaxel (6n). 80%; white solid; mp 159−164 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.23 (s, 3 H), 1.35 (s, 9 H), 1.55 (s, 3 H), 1.60 (s, 3 H), 1.75 (s, 3 H), 1.87 (s, 3 H), 1.88 (m, 1 H), 2.35 (s, 3 H), 2.49 (m, 2 H), 2.81 (m, 2 H), 2.94 (m, 2 H), 3.34 (m, 1 H), 3.79 (s, 3 H), 3.81 (m, 1 H), 4.20 (m, 2 H), 4.29 (d, J = 8.3 Hz, 1 H), 4.38 (m, 1 H), 4.75 (m, 2 H), 4.92 (d, J = 8.0 Hz, 1 H), 5.30 (bs, 1 H), 5.66 (d, J = 7.0 Hz, 1 H), 6.19 (m, 1 H), 6.29 (s, 1 H), 6.79 (m, 3 H), 7.20 (m, 1 H), 7.47 (m, 2 H), 7.53 (m, 1 H), 8.15 (d, J = 7.5 Hz 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.9, 18.6, 21.9, 22.4, 25.7, 26.6, 28.2, 30.9, 33.4, 35.6, 35.7, 36.3, 43.2, 45.6, 51.6, 55.2, 58.6, 72.2, 73.7, 75.0, 75.6, 79.2, 81.1, 84.4, 105.2, 111.8, 114.0, 120.6, 128.6, 129.2, 129.5, 130.2, 132.8, 133.7, 141.8, 142.7, 166.9, 169.7, 170.1, 171.3, 173.0, 203.8. HRMS (FAB) m/z calcd for $C_{51}H_{65}NO_{16}\cdot H^+$: 948.4382. Found: 948.4382 (Δ = 0.0 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-10-[3-(4-methoxyphenyl)propanoyl]docetaxel (6o). 80%; white solid; mp 169−172 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.23 (s, 3 H), 1.35 (s, 9 H), 1.68 (s, 3 H), 1.76 (s, 3 H), 1.86 (s, 6 H), 1.88 (m, 1 H), 2.35 (s, 3 H), 2.48 (m, 2 H), 2.79 (m, 2 H), 2.94 (m, 2 H), 3.33 (d, J = 6.5 Hz, 1 H), 3.78 (s, 3 H), 3.81 (m, 1 H), 4.20 (m, 2 H), 4.30 (d, J = 8.5 Hz, 1 H), 4.42 (m, 1 H), 4.75 (m, 2 H), 4.96 (d, J = 8.0 Hz, 1 H), 5.31 (bs, 1 H), 5.66 (d, J = 7.0 Hz, 1 H), 6.17 (m, 1 H), 6.29 (s, 1 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 8.5 Hz, 2 H), 7.47 (dd, J = 7.3 Hz, 7.8 Hz, 2 H), 7.60 (m, 1 H), 8.10 (d, J = 7.3 Hz 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.9, 18.6, 22.4, 25.7, 26.6, 28.2, 30.0, 35.6, 36.1, 43.2, 45.6, 51.6, 55.3, 58.6, 72.2, 72.3, 73.8, 75.0, 75.5, 79.2, 81.1, 84.4, 113.9, 117.6, 120.6, 128.6, 129.2, 130.2, 132.2, 132.8, 133.7, 138.0, 142.6, 158.2, 167.0, 170.1, 173.1, 173.6, 203.8. HRMS (FAB) m/z calcd for $C_{51}H_{65}NO_{16}\cdot H^+$: 948.4382. Found: 948.4382 (Δ = 0.0 ppm).

Preparation of 7,10,13-Tri-TES-2-Modified Baccatins (9). A typical procedure is described for the preparation of 7,10,13-tri(triethylsilyl)-2-debenzoyl-2-(3-fluorobenzoyl)-10-deacetylbaccatin III (**9c**). To a solution of baccatin **8** (200 mg, 0.255 mmol), 3-fluorobenzoic acid (179 mg, 1.28 mmol), and DMAP (31 mg, 0.255 mmol) in 4 mL of dichloromethane was added 1,3-diisopropylcarbodiimide (DIC) (193.1 mg, 1.53 mmol), and the mixture was stirred at 40 °C for 40 h. The resulting precipitate was filtered off and washed with ethyl acetate (30 mL). The filtrate was washed with saturated sodium bicarbonate solution (10 mL × 2), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Column chromatography of the residue on silica gel using hexanes/ethyl acetate (7/1) as eluant gave **9c** as a white solid (183 mg, 79%): mp 93−95 °C; ^{1}H NMR ($CDCl_3$) δ 0.60 (m, 18 H), 0.98 (m, 27 H), 1.09 (s, 3 H), 1.16 (s, 3 H), 1.57 (bs, 1 H), 1.62 (s, 3 H), 1.85 (m, 1 H), 1.96 (s, 3 H), 2.14 (m, 2 H), 2.26 (s, 3 H), 2.50 (m, 1 H), 3.83 (d, J = 6.9 Hz, 1 H), 4.10 (d, J = 8.1 Hz, 1 H), 4.24 (d, J = 8.1 Hz, 1 H), 4.39 (dd, J = 10.4, 6.9 Hz, 1 H), 4.92 (m, 2 H), 5.17 (s, 1 H), 5.56 (d, J = 7.0 Hz, 1 H), 7.29 (m, 1 H), 7.43 (dd, J = 13.6, 8.0 Hz, 1 H), 7.76 (d, J = 9.2 Hz, 1 H), 7.87 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 4.8, 5.2, 5.9, 6.9, 10.4, 14.6, 20.6, 22.3, 26.3, 37.2, 39.8, 42.9, 46.9, 58.2, 68.2, 72.6, 75.7, 75.9, 76.5, 79.6, 80.7, 84.0, 116.6, 117.0, 120.3, 120.7, 125.6, 130.1, 130.3, 131.7, 131.9, 132.4, 135.6, 139.5, 160.6, 164.5, 165.6, 169.9, 205.6. HRMS (FAB, DCM/NBA) m/z calcd for $C_{47}H_{77}O_{10}SiF\cdot H^+$: 905.4887. Found: 905.4869 (Δ = 2.0 ppm).

Other 7,10,13-tri-TES-2-modified baccatins **9a**, **9b**, and **9d−f** were prepared in the same manner, and characterization data are summarized in the Supporting Information.

Preparation of 7-TES-2-(3-substituted benzoyl)-10-acylbaccatins 11. A typical procedure is described for the preparation of 7-triethylsilyl-2-debenzoyl-2-(3-fluorobenzoyl)-10-deacetyl-10-propanoylbaccatin III (**11c**). (a) To a solution of **9c** (181 mg, 0.200 mmol) in 10 mL of pyridine/acetonitrile (1:1) was added dropwise HF/pyridine (70:30, 1.5 mL) at 0 °C, and the mixture was stirred at room temperature for 17 h. To the reaction mixture was added ethyl acetate (100 mL) and saturated aqueous sodium carbonate (15 mL). The organic layer was separated and washed with saturated aqueous copper sulfate (10 mL × 3) and water (10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford 2-(3-fluorobenzoyl)-2-debenzoyl-10-deacetylbaccatin III (7-OH-**10c**) as a white solid (106 mg, 94%).

(b) To a solution of baccatin 7-OH-**10c** thus obtained (105 mg, 0.187 mmol) and imidazole (54 mg, 0.789 mmol) in dry DMF (3.1 mL) was added chlorotriethylsilane (0.10 mL, 0.592 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 h and diluted with ethyl acetate (60 mL). The reaction mixture was then washed with water (5 mL × 3) and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. Column chromatography of the residue on silica gel (hexanes/ethyl acetate = 2/1 to 1/1) gave 7-TES-2-(3-fluorobenzoyl)-2-debenzoyl-10-deacetylbaccatin III (**10c**) as a white solid (105 mg, 84% yield): mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 0.55 (m, 6 H), 0.92 (m, 9 H), 1.06 (s, 6 H), 1.61 (bs, 1 H), 1.71 (s, 3 H), 1.89 (m, 1 H), 2.06 (s, 3 H), 2.21 (s, 1 H), 2.25 (s, 1 H), 2.27 (s, 3 H), 2.47 (m, 1 H), 3.93 (d, J = 7.0 Hz, 1 H), 4.13 (d, J = 7.1 Hz, 1 H), 4.28 (m, 2 H), 4.39 (dd, J = 10.5, 6.6 Hz, 1 H), 4.84 (t, J = 7.8 Hz, 1 H), 4.95 (d, J = 8.3 Hz, 1 H), 5.16 (s, 1 H), 5.55 (d, J = 7.0 Hz, 1 H), 7.29 (m, 1 H), 7.44 (dd, J = 13.6, 7.8 Hz, 1 H), 7.77 (d, J = 8.9 Hz, 1 H), 7.88 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 5.1, 6.7, 9.9, 15.2, 18.5, 22.5, 28.8, 37.2, 38.5, 42.6, 46.9, 57.9, 67.8, 72.9, 74.5, 75.2, 76.4, 78.8, 80.6, 84.2, 116.7, 117.0, 120.5, 120.8, 125.8, 125.9, 130.2, 130.3, 134.9, 160.5, 164.5, 165.8, 170.7, 210.2. HRMS (FAB, DCM/NBA) m/z calcd for $C_{35}H_{49}O_{10}FSi\cdot H^+$: 677.3157. Found: 677.3177 (Δ = −2.9 ppm).

(c) To a solution of **10c** (104 mg, 0.154 mmol) in dry THF (11 mL) was added LiHMDS (1.0 M in THF, 0.17 mL, 0.17 mmol) dropwise at −40 °C. The mixture was stirred at −40 °C for 5 min. Then freshly distilled chlorotriethylsilane (0.016L, 0.1844 mmol) was added dropwise and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added aqueous saturated NH_4Cl (10 mL) and ethyl acetate (100 mL), and the organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Column chromatography of the residue on silica gel (hexanes/ethyl acetate = 3/1) gave **11c** as a white solid (95 mg, 84%): mp 194−196 °C; $[\alpha]^{20}_D$ −74 (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.56 (q, J = 7.8 Hz, 6 H), 0.89 (t, J = 7.8 Hz, 9 H), 1.00 (s, 3 H), 1.20 (m, 7 H), 1.64 (s, 3 H), 1.83 (m, 1 H), 2.16 (s, 3 H), 2.25 (m, 3 H), 2.40 (m, 4 H), 3.85 (d, J = 6.8 Hz, 1 H), 4.09 (d, J = 8.2 Hz, 1 H), 4.25 (d, J = 8.2 Hz, 1 H), 4.45 (dd, J = 10.2, 6.7 Hz, 1 H), 4.79 (t, J = 8.0 Hz, 1 H), 4.93 (d, J = 9.4 Hz, 1 H), 5.57 (d, J = 7.1 Hz, 1 H), 6.45 (s, 1 H), 7.29 (m, 1 H), 7.44 (dd, J = 13.6, 8.0 Hz, 1 H), 7.74 (d, J = 8.7 Hz, 1 H), 7.86 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 5.3, 6.7, 6.94, 9.2, 9.9, 14.9, 20.1, 22.5, 26.8, 27.7, 37.2, 38.3, 42.7, 47.2, 58.5, 67.8, 72.3, 75.2, 75.5, 76.4, 78.8, 80.7, 84.2, 116.7, 117.0, 120.5, 120.8, 125.9, 130.2, 130.3, 131.6, 131.7, 132.6, 144.1, 165.8, 170.6, 172.8, 202.3. HRMS (FAB) *m/z* calcd for $C_{38}H_{53}O_{11}FSi\cdot H^+$: 733.3419. Found: 733.3418 (Δ = +0.2 ppm).

Other 7-TES-2-(3-substituted-benzoyl)-10-acylbaccatins (**11a**, **11b**, and **11d**−**k**) were prepared in the same manner, and characterization data are summarized in the Supporting Information.

Preparation of 2-Debenzoyl-2-(3-methoxybenzoyl)-7-triethylsilyl-10-deacetyl-10-(2-methoxybenzoyl)baccatin III (11k). (a) To a solution of 104 mg (0.16 mmol) of 2-debenzoyl-2-(3-methoxybenzoyl)-7-triethylsilyl-10-deacetyl baccatin III (**10b**) in 2 mL of CH_2Cl_2 was added 21 mg (0.17 mmol) of *N*-methylmorpholine *N*-oxide (NMO) and 20 mg of 4 Å molecular sieves. After the mixture was stirred for 10 min, 37 mg (0.01 mmol) of tetrapropylammonium perruthenate (TPAP) was added and the mixture was allowed to stir for 4 h. The reaction mixture was then filtered and concentrated in vacuo to give 2-debenzoyl-2-(3-methoxybenzoyl)-7-triethylsilyl-10-deacetyl-13-oxo-baccatin III (**12**) (104 mg, 99% yield) as a white solid: ^1H (300 MHz, $CDCl_3$) δ 0.49 (m, 6 H), 0.95 (m, 9 H), 1.15 (s, 3 H), 1.22 (s, 3 H), 1.24 (m, 1H), 1.71 (s, 3 H), 1.84 (m, 2 H), 2.10 (s, 3 H), 2.17 (s, 3 H), 2.47 (m, 1 H), 2.60 (d, J = 19.8 Hz, 1 H), 2.89 (d, J = 19.8 Hz, 1H), 3.85 (m, 6 H), 4.11 (d, J = 8.7 Hz, 1 H), 4.35 (m, 4 H), 4.90 (d, J = 8.1 Hz, 1 H), 5.31 (d, J = 1.8 Hz, 1 H), 5.62 (d, J = 6.6 Hz, 1 H), 7.13 (dd, J = 8.4 Hz, 2.7 Hz, 1 H), 7.38 (t, J = 5.4 Hz, 1 H), 7.58 (s, 3 H), 7.64 (d, J = 7.5 Hz, 1 H). HRMS: *m/e* calcd for $C_{44}H_{58}O_{13}Si\cdot H^+$: 823.3725. Found: 823.3723 (Δ = −0.2 ppm).

(b) To a solution of 104 mg (0.159 mmol) of **12**, DMAP (59 mg, 0.477 mmol), and triethylamine (48 mg, 0.477 mmol) in 2 mL of CH_2Cl_2 was added 2-methoxylbenzoyl chloride (81 mg, 0.477 mmol). The mixture was allowed to stir overnight, and the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted three times with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting solid was purified by column chromatography on silica gel (hexanes/EtOAc = 8/1) to give 2-debenzoyl-2-(3-methoxybenzoyl)-7-triethylsilyl-10-deacetyl-10-(2-methoxybenzoyl)-13-oxo-baccatin III (**13**) (125 mg, 100%) as a white solid: ^1H (300 MHz, $CDCl_3$) δ 0.58 (m, 6 H), 0.91 (q, J = 7.8 Hz, 9 H), 1.10 (s, 3 H), 1.12 (s, 3 H), 1.37 (s, 3 H), 1.92 (m, 1 H), 1.97 (bs, 1 H), 2.19 (s, 3 H), 2.30 (s, 3 H), 2.55 (m, 1 H), 2.64 (d, J = 19.8 Hz, 1 H), 2.93 (s, J = 19.8 Hz, 1 H), 3.54 (m, 3 H), 3.85 (m, 8 H), 3.97 (d, J = 6.6 Hz, 1 H), 4.13 (d, J = 8.1 Hz, 1 H), 4.35 (d, J = 8.7 Hz, 1 H), 4.54 (dd, J = 6.6 Hz, 3.9 Hz, 1 H), 4.93 (d, J = 8.1 Hz, 1 H), 5.73 (d, J = 6.6 Hz, 1 H), 6.82 (s, 1 H), 6.66−7.07 (m, 3 H), 7.14−7.19 (m, 2 H), 7.28−7.42 (m, 1 H), 7.48−7.68 (m, 1 H), 8.01 (m, 1 H).

(c) To a solution of **13** (125 mg, 0.159 mmol) in 6 mL of MeOH/THF (3/2) at 0 °C was added $NaBH_4$ (100 mg, 6.36 mmol), and the solution was allowed to stir for 5 h. The reaction was quenched with saturated NH_4Cl and extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting solid was purified by column chromatography on silica gel (hexane/EtOAc = 3:1) to give **10k** (60 mg, 40% yield, 80% yield based on 50% conversion) as a white solid: ^1H (300 MHz, $CDCl_3$) δ 0.58 (m, 6 H), 0.91 (q, J = 7.8 Hz, 9 H), 1.10 (s, 3 H), 1.12 (s, 3 H), 1.37 (s, 3 H), 1.92 (m, 2 H), 1.97 (bs, 1 H), 2.19 (s, 3 H), 2.30 (s, 3 H), 2.55 (m, 1 H), 3.54 (m, 1 H), 3.85 (m, 7 H), 3.94 (d, J = 6.9 Hz, 1 H), 4.15 (d, J = 7.8 Hz, 1 H), 4.34 (d, J = 7.8 Hz, 1 H), 4.53 (dd, J = 6.6 Hz, 3.6 Hz, 1 H), 4.84 (m, 1H), 4.97 (d, J = 7.8 Hz, 1 H), 5.66 (d, J = 6.9 Hz, 1 H), 6.69 (s, 1 H), 6.95−7.07 (m, 2 H), 7.14−7.19 (m, 1 H), 7.28−7.42 (m, 2 H), 7.65−7.73 (m, 2 H), 8.01 (m, 1 H).

Synthesis of Second- and Third-Generation Taxoids 14 through the Ojima−Holton Coupling of Baccatins 11 with β-Lactams 3a−f. A typical procedure is described for the synthesis of 2-debenzoyl-2-(3-methylbenzoyl)-10-acetyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (**14a**). (a) To a solution of baccatin **11a** (50 mg, 0.071 mmol) and β-lactam **3a** (41.1 mg, 0.099 mmol) in 3 mL of dry THF was added a 1.0 M solution of LiHMDS in THF (0.099 mL, 0.099 mmol) dropwise at −40 °C, and the solution was stirred at the same temperature for 30 min. The reaction was quenched with aqueous saturated ammonium chloride, and the aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified on a silica gel column (hexanes/EtOAc = 6/1) to afford the coupling product, 7-TES-2′-TIPS-**14a** (67 mg, 84% yield), as a white solid.

(b) To a solution of 7-TES-2′-TIPS-**14a** (65.0 mg, 0.058 mmol), thus obtained, in 4 mL pyridine/acetonitrile (1/1) was added dropwise HF/pyridine (70/30, 0.5 mL) at 0 °C. The mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was diluted with EtOAc, washed with aqueous saturated $CuSO_4$ and water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc = 1/1) to afford **14a** (47 mg, 96% yield, 81% yield for two steps) as a white solid: mp 145−148 °C; $[\alpha]^{20}_D$ −85 (*c* 0.011, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.25 (s, 3 H), 1.34 (s, 9 H), 1.67 (s, 3 H), 1.75 (d, J = 3.6 Hz, 6 H), 1.89 (s, 3 H), 2.23 (s, 3 H), 2.37 (m, 9 H), 2.52 (m, 2 H), 3.80 (d, J = 7.2 Hz, 1 H), 4.18 (m, 2 H), 4.30 (d, J = 8.7 Hz, 1 H), 4.42 (m, 1 H), 4.75 (m, 2 H), 4.96 (d, J = 7.8 Hz, 1 H), 5.29 (m, 2 H), 5.64 (d, J = 7.2 Hz, 1H), 6.16 (t, J = 8.7 Hz, 1 H), 6.30 (s, 1 H), 7.37 (m, 2 H), 7.90 (m, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 14.9, 18.5, 20.8, 21.3, 21.8, 22.3, 25.7, 26.6, 28.2, 35.6, 43.2, 25.6, 58.4, 72.1, 72.3, 73.7, 74.9, 75.6, 76.46, 79.1, 81.1, 84.4, 120.7, 127.3, 128.5, 129.1, 130.8, 132.8, 134.4, 138.3, 142.6, 155.4, 167.0, 170.0, 171.3, 203.7. HRMS (FAB) *m/z* calcd for $C_{44}H_{59}NO_{15}\cdot Na^+$: 864.3782. Found: 864.3803 (Δ = −2.4 ppm).

Other taxoids **14b**−**p**, **15c**−**e**, and **15 g** were prepared in the same manner, and characterization data are shown below.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-acetyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (14b). White solid; 72% (for two steps); mp 142−144 °C; $[\alpha]^{25}_D$ −72 (*c* 0.70, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.26 (s, 3H), 1.34 (s, 9H), 1.68 (s, 3H), 1.74 (s, 3H), 1.77 (s, 3H), 1.90 (s, 3H), 1.92 (m, 1H), 2.24 (s, 3H), 2.35 (s, 3H), 2.38 (m, 2H), 2.54 (m, 1H), 3.81 (d, J = 6.9 Hz, 1H), 3.87 (s, 3H), 4.18 (d, J = 8.4 Hz, 1H), 4.35 (d, J = 8.4 Hz, 1H), 4.43 (dd, J = 6.6, 10.5 Hz, 1H), 4.75 (br s, 2H), 4.97 (d, J = 8.1 Hz, 1 H), 5.32 (s, 1H), 5.66 (d, J = 7.2 Hz, 1H), 6.18 (t, J = 8.4 Hz, 1H), 6.30 (s, 1H), 7.14 (dd, J = 2.1, 8.1 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 9.5, 15.0, 18.5, 20.9, 21.8, 22.4, 25.7, 26.7, 28.2, 29.7, 35.6, 43.2, 45.6, 51.5, 55.4, 58.6, 72.2, 72.3, 73.7, 75.1, 75.6, 76.4, 79.1, 80.0, 81.1, 84.4, 114.6, 120.2, 122.6, 122.6, 129.6, 130.4, 132.8, 137.9, 142.7, 143.5, 159.7, 166.8, 170.0, 171.3, 173.1, 203.8. HRMS (DCM/NBA/NACL) calcd for $C_{44}H_{59}NO_{16}Na^+$: 880.3766. Obtained: 880.3732 (Δ = −3.9 ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

2-Debenzoyl-2-(3-fluorobenzoyl)-10-deacetyl-10-propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (14c). White solid; 84% (for two steps); mp 137−139 °C; $[\alpha]^{20}_D$ −78 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.19 (m, 6 H), 1.33 (m, 9 H), 1.66 (s, 3 H), 1.75 (s, 6 H), 1.89 (s, 3 H), 2.34 (m, 5 H), 2.52 (m, 4 H), 3.37 (m, 1 H), 3.80 (d, J = 7.0 Hz, 1 H), 4.12 (m, 2 H), 4.29 (d, J = 8.5 Hz, 1 H), 4.42 (m, 1 H), 4.76 (m, 1 H), 4.96 (d, J = 8.1 Hz, 1 H), 5.29 (m, 1 H), 5.63 (d, J = 7.2 Hz, 1 H), 6.16 (t, J = 8.4 Hz, 1 H), 6.30 (s, 1 H), 7.29 (m, 1 H), 7.43 (m, 1 H), 7.77 (d, J = 9.1 Hz, 1 H), 7.89 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.1, 9.5, 14.9, 18.5, 21.8, 22.3, 25.7, 26.6, 27.6, 28.2, 35.5, 43.1, 45.6, 51.6, 58.5, 72.2, 73.7, 75.4, 76.3, 77.6, 79.2, 79.9, 81.0, 84.4, 116.8, 117.1, 120.6, 125.9, 130.3, 130.4, 132.8, 138.0, 142.6, 155.4, 165.7, 170.0, 174.6, 203.7; ^{19}F NMR ($CDCl_3$, using Freon as standard) δ −112.1. HRMS (FAB) *m*/*z* calcd for $C_{44}H_{58}O_{15}FN\cdot H^+$: 860.3869. Found: 860.3870 (Δ = −0.1 ppm).

2-Debenzoyl-2-(3-chlorobenzoyl)-10-deacetyl-10-propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (14d). White solid; 70% (for two steps); mp 142−144 °C; $[\alpha]^{20}_D$ −89 (*c* 0.090, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.21 (m, 7 H), 1.33 (s, 9 H), 1.66 (m, 3 H), 1.74 (m, 7 H), 1.82 (s, 3 H), 2.45 (m, 5 H), 2.52 (m, 3 H), 3.80 (d, J = 7.1 Hz, 1 H), 4.12 (m, 2 H), 4.27 (d, J = 8.3 Hz, 1 H), 4.40 (dd, J = 10.6, 6.5 Hz, 1 H), 4.75 (m, 2 H), 4.96 (d, J = 8.2 Hz, 1 H), 5.30 (d, J = 9.2 Hz, 1 H), 5.60 (d, J = 7.1 Hz, 1 H), 6.13 (t, J = 8.6 Hz, 1 H), 6.30 (s, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.97 (d, J = 7.7 Hz, 1 H), 8.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.5, 14.9, 18.6, 21.8, 22.3, 25.6, 26.5, 27.5, 28.1, 35.5, 41.2, 43.1, 45.6, 51.6, 58.4, 72.2, 72.3, 73.7, 75.4, 75.5, 76.3, 79.2, 79.9, 81.0, 84.4, 120.5, 128.3, 130.0, 130.2, 131.0, 132.7, 133.6, 134.7, 137.9, 142.6, 155.4, 165.5, 169.9, 173.1, 174.6, 203.7. HRMS: *m*/*e* calcd for $C_{44}H_{58}O_{15}NCl\cdot H^+$: 876.3573. Found: 876.3573 (Δ = 0.0 ppm).

2-Debenzoyl-2-(3-azidobenzoyl)-10-deacetyl-10-propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (14e). White solid; 71% (for two steps); mp 128−130 °C; $[\alpha]^{20}_D$ −71 (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.25 (m, 9 H), 1.34 (s, 9 H), 1.66−1.73 (m, 12 H), 1.89 (s, 3 H), 2.37 (m, 5 H), 2.52 (m, 4 H), 3.32 (bs, 1 H), 3.81 (d, J = 6.9 Hz, 1 H), 4.12 (m, 2 H), 4.30 (d, J = 8.1 Hz, 1 H), 4.40 (dd, J = 10.6, 6.8 Hz, 1 H), 4.74 (m, 2 H), 4.96 (d, J = 8.2 Hz, 1 H), 5.29 (m, 1 H), 5.64 (d, J = 7.0 Hz, 1 H), 6.13 (t, J = 9.0 Hz, 1 H), 6.31 (s, 1 H), 7.23 (d, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.9 Hz, 1 H), 7.78 (s, 1 H), 7.86 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.5, 15.0, 18.6, 21.8, 22.5, 25.7, 26.6, 27.6, 28.2, 35.5, 43.2, 45.6, 51.6, 58.6, 72.2, 72.6, 73.7, 75.4, 76.4, 79.2, 81.0, 84.5, 87.3, 120.1, 120.5, 124.3, 126.8, 130.2, 132.7, 140.8, 166.0, 170.1, 174.6, 203.8. HRMS: *m*/*e* calcd for $C_{44}H_{58}O_{15}N_4\cdot H^+$: 883.3977. Found: 883.3987 (Δ = −1.1 ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methylprop-1-enyl)-2-debenzoyl-2-(3-allylbenzoyl)-10-propanoyldocetaxel (14f). White solid; 80% (for two steps), mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.21 (t, J = 7.4 Hz, 3 H), 1.23 (s, 3 H), 1.34 (s, 9 H), 1.68 (s, 3 H), 1.75 (s, 3 H), 1.77 (s, 3 H), 1.86 (m, 1 H), 1.90 (s, 3 H), 2.36 (s, 6 H), 2.39 (m, 2 H), 2.37 (s, 3 H), 2.53 (m, 3 H), 3.36 (bs, 1 H), 3.83 (d, J = 6.9 Hz, 1 H), 4.19 (m, 3 H), 4.32 (d, J = 8.4 Hz, 1 H), 4.43 (dd, J = 6.6, 10.5 Hz, 1 H), 4.74 (d, J = 3.0 Hz, 1 H), 4.97 (d, J = 8.4 Hz, 1 H), 5.34 (br d, J = 10.8 Hz, 2 H), 5.67 (d, J = 6.9 Hz, 1 H), 5.85 (d, J = 17.4 Hz, 1 H), 6.18 (t, J = 8.4 Hz, 1 H), 6.32 (s, 1 H), 6.76 (dd, J = 10.5, 17.4 Hz, 1 H), 7.44 (t, J = 7.8 Hz, 1 H), 7.63 (d, J = 7.5 Hz, 1 H), 7.98 (d, J = 7.8 Hz, 1 H), 8.17 (s, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 15.0, 18.5, 20.9, 22.4, 25.7, 26.7, 28.2, 29.7, 35.5, 35.6, 43.2, 45.6, 51.5, 58.6, 72.2, 72.9, 75.1, 75.4, 79.2, 80.0, 81.1, 84.4, 115.4, 120.6, 127.8, 128.9, 129.4, 131.3, 135.9, 138.1, 155.4, 159.7, 165.4, 166.9, 170.0, 171.9, 178.5, 203.8. HRMS (FAB) *m*/*z* calcd for $C_{46}H_{61}NO_{15}\cdot Na^+$: 890.3981. Found: 890.3939 (Δ = −4.7 ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed 95% purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-deacetyl-10-propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)docetaxel (14g). White solid; 69% (for two steps); mp 130−132 °C; $[\alpha]^{20}_D$ −75 (*c* 0.080, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.28 (m, 8 H), 1.33 (s, 9 H), 1.66 (m, 3 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.89 (m, 5 H), 2.37 (m, 6 H), 2.52 (m, 3 H), 3.80 (d, J = 6.9 Hz, 1 H), 3.86 (s, 3 H), 4.12 (m, 2 H), 4.32 (d, J = 8.5 Hz, 1 H), 4.40 (dd, J = 10.6, 6.8 Hz, 1 H), 4.72 (m, 2 H), 4.96 (d, J = 8.3 Hz, 1 H), 5.30 (d, J = 7.6 Hz, 1 H), 5.64 (d, J = 7.0 Hz, 1 H), 6.16 (t, J = 8.6 Hz, 1 H), 6.30 (s, 1 H), 7.13 (d, J = 7.9 Hz, 1 H), 7.33 (t, J = 8.0 Hz, 1 H), 7.62 (s, 1 H), 7.68 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.5, 14.9, 18.5, 21.8, 22.4, 25.7, 26.6, 27.5, 28.2, 35.5, 43.2, 45.6, 51.5, 55.3, 58.5, 72.2, 72.3, 73.7, 75.1, 75.4, 76.2, 79.1, 79.9, 81.1, 84.4, 114.6, 120.1, 120.6, 122.5, 129.6, 130.4, 132.9, 137.8, 142.5, 155.4, 159.6, 166.8, 170.0, 174.0, 174.6, 203.8. HRMS *m*/*e* calcd for $C_{45}H_{61}O_{16}N\cdot H^+$: 872.4069. Found: 872.4072 (Δ = −0.4 ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methylprop-1-enyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(cyclopropanecarbonyl)docetaxel (14h). 77% (for two steps); mp 144−146 °C; $[\alpha]^{25}_D$ −74 (*c* 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, CDCl3) δ 1.16 (s, 3H), 1.26 (s, 3H), 1.34 (s, 9H), 1.66 (m, 4H), 1.67 (s, 3H), 1.74 (s, 3H), 1.77 (s, 3H), 1.82 (m, 2H), 1.89 (s, 3H), 2.34 (s, 3H), 2.38 (m, 2H), 2.54 (m, 1H), 3.36 (br s, 1H), 3.81 (d, J = 7.2 Hz, 1H), 3.87 (s, 3H), 4.18 (d, J = 9.0 Hz, 1H), 4.20 (s, 1H), 4.34 (d, J = 8.4 Hz, 1H), 4.41 (dd, J = 6.6, 11.1 Hz, 1H), 4.79 (m, 2H), 4.97 (d, J = 9.0 Hz, 1 H), 5.31 (br s, 1H), 5.66 (d, J = 6.9 Hz, 1H), 6.18 (t, J = 9.0 Hz, 1H), 6.30 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 9.5, 13.0, 15.0, 18.5, 21.9, 22.4, 25.7, 26.7, 28.2, 29.7, 35.5, 35.6, 43.2, 45.6, 51.5, 55.4, 58.6, 72.2, 72.4, 73.7, 75.1, 75.4, 76.4, 79.2, 80.0, 81.1, 84.4, 114.6, 120.1, 120.6, 122.6, 129.6, 130.4, 132.9, 137.9, 142.7, 155.4, 159.7, 166.8, 170.0, 171.9, 175.1, 203.9. HRMS (DCM/NBA/NACL) calcd for $C_{46}H_{61}NO_{16}Na^+$: 906.3909. Obtained: 906.3888 (Δ = −2.3 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(methoxycarbonyl)docetaxel (14i). White solid; 80% (for two steps); mp 132−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.25 (m, 12 H), 1.68 (m, 6 H), 1.89 (m, 1 H), 1.93 (s, 3 H), 2.17 (s, 3 H), 2.35 (s, 3 H), 2.57 (m, 1 H), 3.78 (d, J = 6.9 Hz, 1 H), 3.87 (bs, 7 H), 4.20 (m, 2 H), 4.36 (m, 2 H), 4.73 (m, 2 H), 4.95 (d, J = 7.8 Hz, 1 H), 5.31 (d, J = 7.0, 1 H), 5.65 (d, J = 6.9 Hz, 1 H), 6.17 (m, 2 H), 7.12 (dd, J = 7.8 Hz, 2.4 Hz, 1 H), 7.37 (t, J = 7.8 Hz, 1 H), 7.63 (s, 1 H), 7.68 (d, J = 4.5 Hz, 1 H), 8.01 (s, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.4, 15.0, 18.5, 21.7, 22.4, 25.7, 26.6, 28.2, 30.9, 33.3, 35.6, 43.1, 45.6, 51.5, 55.4, 55.6, 58.6, 72.1, 72.3, 73.7, 75.1, 78.3, 79.1, 80.0, 81.1, 84.4, 105.1, 114.6, 120.1, 120.6, 122.5, 129.6, 130.4, 132.5, 137.9, 143.5, 155.8, 159.7, 166.8, 170.1, 176.4, 204.0. HRMS (FAB) *m*/*z* calcd for $C_{51}H_{65}NO_{17}\cdot H^+$: 964.4331. Found: 964.4366 (Δ = 3.7 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(benzyloxycarbonyl)docetaxel (14j). White solid; 70% (for two steps); mp 145−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.25 (m, 12 H), 1.69 (m, 6 H), 1.89 (m, 1 H), 1.95 (s, 3 H), 2.16 (s, 3 H), 2.35 (s, 3 H), 2.56 (m, 1 H), 3.36 (d, J = 6.9 Hz, 1 H), 3.78 (d, J = 7.2 Hz, 1 H), 3.87 (s, 3 H), 4.19 (m, 2 H), 4.33 (d, J = 8.7 Hz, 1 H), 4.40 (m, 1 H), 4.72 (m, 2 H), 4.95 (d, J = 7.5 Hz, 1 H), 5.23 (s, 2 H), 5.31 (d, J = 7.8 Hz, 1 H), 5.65 (d, J = 7.2 Hz, 1 H), 6.14 (m, 2 H), 7.12 (dd, J = 7.2 Hz, 1.8 Hz, 1 H), 7.34 (m, 6 H), 7.63 (s, 1 H), 7.68 (d, J = 7.8 Hz, 1 H). HRMS (FAB) *m*/*z* calcd for $C_{50}H_{63}NO_{17}\cdot H^+$: 950.4174. Found: 950.4164 (Δ = −1.1 ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

3′-Dephenyl-3′-(2-methyl-1-propenyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(2-methoxybenzoyl)docetaxel (14k). White solid; 95% (for two steps); mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3 H), 1.31 (s, 3 H), 1.34 (s, 9 H), 1.60 (m, 1 H), 1.71 (s,

3 H), 1.75 (s, 3 H), 1.77 (s, 3 H), 1.91 (m, 1 H), 1.96 (s, 3 H), 2.37 (s, 3 H), 2.59 (m, 2 H), 3.35 (bs, 1 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.22 (m, 2 H), 4.35 (d, J = 8.4 Hz, 1 H), 4.51 (m, 1 H), 4.76 (m, 2 H), 4.98 (d, J = 8.1 Hz,1 H), 5.32 (m, 1 H), 5.71 (d, J = 6.9 Hz, 1 H), 6.21 (m, 1 H), 6.57 (s, 1 H), 6.99 (m, 2 H), 7.13 (dd, J = 8.4 Hz, 1.8 Hz, 1 H), 7.36 (t, J = 7.5 Hz, 1 H), 7.50 (m, 1 H), 7.65 (s, 1 H), 7.70 (d, J = 7.5 Hz, 1 H), 7.99 (dd, J = 7.8, 2.1 Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.56, 15.0, 18.5, 22.4, 25.7, 26.6, 28.2, 35.6, 43.3, 45.7, 55.4, 55.9, 58.7, 72.2, 72.4, 73.7, 75.2, 75.6, 79.2, 81.2, 84.5, 87.6, 105.0, 105.1, 112.1, 120.2, 120.3, 122.6, 129.7, 130.5, 132.7, 134.6, 159.7, 160.0, 165.9, 166.9, 170.1, 203.8. HRMS (FAB) m/z calcd for $C_{50}H_{63}NO_{17}\cdot H^+$: 950.4174. Found: 950.4149 (Δ = −2.7 ppm).

3′-Dephenyl-3′-(2-methyl-1-propenyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(4-methoxyphenylacetyl)docetaxel (14l). White solid; 70% (for two steps); mp 152−154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 1.18 (s, 3 H), 1.34 (s, 9 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 1.76 (s, 3 H) 1.86 (s, 3 H), 1.86 (m, 1 H), 2.17 (m, 4 H), 2.37 (s, 3 H), 2.39 (m, 2 H), 2.55 (m, 1 H), 3.34 (bs, 1 H), 3.79 (m, 4 H), 3.68 (s, 3 H), 4.19 (m, 1 H), 4.32 (d, J = 8.4 Hz, 1 H), 4.39 (m, 1 H), 4.73 (m, 2 H), 4.94 (d, J = 8.1 Hz, 1 H), 5.30 (m, 1 H), 5.64 (d, J = 6.9 Hz, 1 H), 6.15 (t, J = 8.1 Hz, 1 H), 6.30 (s, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 7.12 (dd, J = 7.8 Hz, 2.1 Hz, 1 H), 7.24 (m, 2 H), 7.37 (t, J = 7.5 Hz, 1 H), 7.63 (s, 1 H), 7.68 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.53, 14.2, 14.9, 18.5, 21.6, 22.4, 25.7, 26.4, 28.2, 30.9, 35.6, 40.1, 43.1, 45.6, 51.5, 55.2, 55.3, 58.5, 72.1, 72.3, 73.7, 75.0, 75.8, 79.0, 79.9, 81.0, 84.4, 87.5, 114.0, 114.6, 120.1, 120.6, 122.5, 129.6, 130.4, 130.5, 132.7, 142.5, 159.6, 166., 170.0, 172.0, 203.4, 206.9. HRMS (FAB) m/z calcd for $C_{51}H_{65}NO_{17}\cdot H^+$: 964.4331. Found: 964.4366 (Δ = 3.7 ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(prop-2-enyl)docetaxel (14m). White solid; 65% (for two steps); mp 127−130 °C; $[\alpha]^{20}_D$ −64 (c 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.21 (m, 26 H), 1.66 (m, 3 H), 1.88 (s, 3 H), 2.20−2.37 (m, 5 H), 2.52 (m, 3 H), 3.39 (bs, 1 H), 3.80 (d, J = 8.8 Hz, 1 H), 3.89 (s, 3 H), 4.12 (m, 2 H), 4.35 (m, 3 H), 4.61 (m, 1 H), 4.96 (m, 2 H), 5.63 (m, 1.25 H), 5.84 (d, J = 5.8 Hz, 0.5 H), 6.06 (d, J = 5.9 Hz, 0.25 H), 6.23 (t, J = 8.8 Hz, 1 H), 6.30 (s, 1 H), 7.13 (d, J = 5.8 Hz, 1 H), 7.38 (t, J = 8.0 Hz, 1 H), 7.63 (s, 1 H), 7.70 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.6, 14.8, 21.9, 22.5, 26.7, 27.6, 28.0, 29.7, 35.5, 43.2, 45.7, 55.3, 58.6, 68.5, 72.2, 73.0, 75.1, 75.3, 79.0, 81.2, 84.5, 87.4, 103.1, 114.1, 120.7, 122.7, 129.8, 130.2, 133.3, 159.7, 167.1, 170.3, 170.7, 174.6, 203.6. HRMS (FAB) m/z calcd for $C_{44}H_{59}NO_{16}\cdot H^+$: 858.3912. Found: 858.3880 (Δ = −3.7 ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-[(*E*)-prop-1-enyl]docetaxel (14n). White solid; 80% (for two steps); mp 120−122 °C; $[\alpha]^{20}_D$ −100 (c 0.010, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.32 (s 3 H), 1.66 (s, 3 H), 1.73 (s 3 H), 1.75 (s, 3 H), 1.88 (s, 3 H), 2.36 (m, 6 H), 3.87 (s, 2 H), 4.12 (d, 2 H), 4.27 (m, 2 H), 4.40 (dd, J = 10.6, 6.8 Hz, 1 H), 4.57 (b, 1 H), 4.86 (d, 1 H), 4.96 (d, J = 8.1 Hz, 1 H), 5.60 (m, 2 H), 6.13 (t, J = 8.8 Hz, 1 H), 6.30 (s, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.97 (d, J = 7.7 Hz, 1 H), 8.10 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 4.5, 5.0, 10.4, 13.3, 17.3, 18.0, 22.2, 23.0, 23.6, 25.2, 31.0, 31.1, 38.7, 41.1, 50.9, 54.1, 67.7, 68.6, 70.6, 70.9, 73.2, 74.5, 76.6, 79.9, 110.0, 115.8, 118.1, 122.8, 124.3, 125.2, 128.0, 138.0, 149.0, 162.0, 165.6, 170.0, 199.0. HRMS m/e calcd for $C_{44}H_{59}NO_{16}H^+$: 858.3912. Found: 858.3880 (Δ = −3.7 ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(but-3-enyl)docetaxel (14o). White solid; 71% (for two steps); mp 116−117 °C; $[\alpha]^{20}_D$ −37 (c 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.23 (t, J = 7.5 Hz, 3 H), 1.25 (s, 3 H), 1.30 (s, 9 H), 1.39 (m, 2 H), 1.67 (m, 3 H), 1.84 (m, 1 H), 1.88 (s, 3 H), 2.15 (m, 2 H), 2.33 (m, 2 H), 2.37 (s, 3 H), 2.53 (m, 3 H), 3.26 (bs, 1 H), 3.81 (d, J = 6.9 Hz, 1 H), 3.89 (s, 3 H), 4.05 (m, 1 H), 4.18 (d, J = 8.1 Hz, 1 H), 4.23 (s, 1 H), 4.36 (d, J = 8.4 Hz, 1 H), 4.44 (dd, J = 7.2, 10.2 Hz, 1 H), 4.64 (d, J = 9.9 Hz, 1 H), 4.97 (d, J = 8.7 Hz, 1 H), 5.05 (d, J = 8.4 Hz, 1 H), 5.08 (d, J = 15.3 Hz, 1 H), 5.66 (d, J = 7.2 Hz, 1 H), 5.82 (m, 1H), 6.21 (t, J = 8.7 Hz, 1 H), 6.31 (s, 1 H), 7.14 (dd, J = 2.4, 8.1 Hz, 1 H), 7.39 (t, J = 8.1 Hz, 1 H), 7.65 (s, 1 H), 7.72 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 21.9, 22.6, 26.7, 27.6, 28.1, 29.7, 30.1, 31.4, 35.5, 35.6, 43.2, 45.6, 55.4, 58.6, 72.2, 72.5, 75.1, 75.4, 79.1, 79.8, 81.1, 84.4, 114.4, 115.8, 120.3, 122.7, 129.7, 130.4, 137.2, 155.4, 159.6, 166.9, 170.3, 170.0, 173.9, 174.6, 203.8. HRMS (FAB) m/z calcd for $C_{45}H_{61}NO_{16}\cdot Na^+$: 894.3870. Found: 894.3904 (Δ = −3.1 ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-[(*S*)-2,2-dimethylcyclopropyl]docetaxel (14p). White solid; 83% (for two steps); ^{1}H NMR ($CDCl_3$) δ 0.098 (t, J = 4.6 Hz, 1 H), 0.62 (dd, J = 8.5, 4.3 H), 1.11 (m, 10 H), 1.24 (s, 6 H), 1.31 (s, 9 H), 1.66 (s, 3 H), 1.83 (s, 1 H), 1.89 (s, 3 H), 2.34 (s, 3 H), 2.37 (m, 2 H), 2. 54 (m, 3 H), 3.34 (d, J = 6.6 Hz, 1 H), 3.51 (t, J = 9.3 Hz, 1 H), 3.80 (d, J = 7.0 Hz, 1 H), 3.85 (s, 3 H), 4.18 (d, J = 8.4 Hz, 1 H), 4.32 (s, 1 H), 4.34 (d, J = 8.4 Hz, 1 H), 4.43 (m, 1 H), 4.80 (d, J = 8.9 Hz, 1 H), 4.97 (d, J = 8.4 Hz, 1 H), 5.65 (d, J = 7.0 Hz, 1 H), 6.15 (t, J = 8.6 Hz, 1 H), 6.30 (s, 1 H), 7.13 (dd, J = 8.0, 2.2 Hz, 1 H), 7.36 (t, J = 8.0 Hz, 1 H), 7.63 (s, 1 H), 7.69 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.5, 14.9, 17.1, 19.3, 20.1, 22.0, 22.6, 26.2, 26.5, 27.1, 27.5, 28.1, 33.2, 35.5, 43.2, 45.5, 55.3, 55.4, 58.5, 72.1, 72.7, 73.0, 75.1, 75.4, 76.4, 79.1, 79.8, 81.1, 84.4, 87.4, 114.4, 120.3, 122.6, 129.6, 130.4, 132.8, 142.6, 155.0, 159.6, 166.7, 169.7, 170.6, 174.6, 203.8. HRMS (FAB) m/z calcd for $C_{46}H_{63}NO_{16}H^+$: 886.4225. Found: 886.4237 (Δ = −1.3 ppm).

2-Debenzoyl-2-(3-fluorobenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)docetaxel (15c). White solid; 89% (for two steps): mp 138−140 °C; $[\alpha]^{20}_D$ −79 (c 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 0.97 (s, 3 H), 1.13 (s, 3 H), 1.28 (m, 18 H), 1.66 (m, 5 H), 2.37 (m, 6 H), 2.52 (m, 4 H), 3.21 (bs, 1 H), 3.80 (d, J = 7.0 Hz, 1 H), 4.12 (m, 2 H), 4.29 (d, J = 8.5 Hz, 1 H), 4.42 (m, 1 H), 4.57 (d, J = 9.7 Hz, 1 H), 4.96 (d, J = 10.1 Hz, 1 H), 5.61 (d, J = 6.8 Hz, 1 H), 6.16 (t, J = 8.4 Hz, 1 H), 6.30 (s, 1 H), 7.29 (m, 1 H), 7.43 (m, 1 H), 7.77 (d, J = 9.1 Hz, 1 H), 7.89 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.1, 9.5, 14.9, 21.8, 22.4, 23.2, 24.7, 26.5, 27.6, 28.1, 35.5, 41.2, 43.2, 45.6, 51.3, 57.6, 72.2, 72.6, 73.0, 75.4, 75.5, 76.2, 79.2, 79.6, 81.0, 84.4, 116.8, 117.2, 120.6, 120.9, 126.0, 130.3, 130.4, 142.6, 155.5, 169.9, 174.0, 174.6, 203.7; ^{19}F NMR ($CDCl_3$, using Freon as the standard) δ −112.1. HRMS (FAB) m/z calcd for $C_{44}H_{60}O_{15}FN\cdot H^+$: 862.4025. Found: 862.4022 (Δ = + 0.4 ppm).

2-Debenzoyl-2-(3-chlorobenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)docetaxel (15d). White solid; 80% (for two steps); mp 143−145 °C; $[\alpha]^{20}_D$ −83 (c 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 6 H), 1.12 (s, 3 H), 1.28 (m, 26 H), 1.66 (m, 6 H), 1.88 (s, 3 H), 2.37 (m, 6 H), 2.52 (m, 4 H), 3.21 (bs, 1 H), 3.80 (d, J = 7.1 Hz, 1 H), 4.12 (m, 2 H), 4.27 (d, J = 8.3 Hz, 1 H), 4.40 (dd, J = 10.6, 6.8 Hz, 1 H), 4.57 (d, J = 9.6 Hz, 1 H), 4.96 (d, J = 8.1 Hz, 1 H), 5.60 (d, J = 7.1 Hz, 1 H), 6.13 (t, J = 8.8 Hz, 1 H), 6.30 (s, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.97 (d, J = 7.7 Hz, 1 H), 8.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.5, 14.9, 21.8, 22.3, 23.2, 24.6, 26.5, 27.5, 28.1, 35.5, 41.2, 43.1, 45.6, 51.3, 58.4, 72.2, 72.6, 73.0, 75.4, 75.5, 76.2, 79.2, 79.6, 81.0, 84.4, 128.3, 130.0, 130.3, 131.0, 132.7, 133.6, 134.7, 142.6, 155.5, 165.5, 169.8, 174.0, 174.6, 203.7. HRMS m/e calcd for $C_{44}H_{60}O_{15}NCl\ H^+$: 878.3730. Found: 878.3728 (Δ = 0.2 ppm).

2-Debenzoyl-2-(3-azidobenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)docetaxel (15e). White solid; 70% (for two steps); mp 132−134 °C; $[\alpha]^{20}_D$ −70 (c 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 6 H), 1.12 (s, 3 H), 1.28 (m, 26 H), 1.66 (m, 6 H), 1.88 (s, 3 H), 2.37 (m, 5 H), 2.52 (m, 4 H), 3.18 (bs, 1 H), 3.82 (d, J = 6.9 Hz, 1 H), 4.12 (m, 4 H), 4.31 (d, J = 8.4 Hz, 1 H), 4.40 (dd, J = 10.2, 6.6 Hz, 1 H), 4.56 (d, J = 9.6 Hz, 1 H), 4.97 (d, J = 8.7 Hz, 1 H), 5.65 (d, J = 6.9 Hz, 1 H), 6.14 (t, J = 8.4 Hz, 1 H), 6.31 (s, 1 H), 7.23 (m, 1 H), 7.46 (t, J = 7.8 Hz, 1 H), 7.88 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.5, 14.9, 21.8, 22.5, 23.2, 24.7, 26.6, 27.6, 28.1, 35.5, 41.2, 43.2, 45.6, 51.4, 58.5, 72.2, 72.6, 73.0, 75.4, 75.5, 76.3, 78.0, 79.2, 79.7, 81.0, 84.4, 120.2, 124.3,

126.8, 130.1, 132.8, 140.8, 142.6, 155.5, 166.0, 170.1, 174.0, 174.6, 203.8. HRMS *m/e* calcd for $C_{44}H_{60}N_4O_{15}\cdot H^+$: 885.4133. Found: 885.4134 ($\Delta = -0.1$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)docetaxel (15g). White solid; 73% (for two steps); mp 132−134 °C; $[\alpha]^{20}_D$ −110 (*c* 0.070, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 6 H), 1.13 (s, 3 H), 1.28 (m, 8 H), 1.66 (m, 6 H), 1.88 (s, 3 H), 2.37 (m, 6 H), 2.52 (m, 4 H), 3.21 (bs, 1 H), 3.80 (d, $J = 6.9$ Hz, 1 H), 3.86 (s, 3 H), 4.12 (m, 2 H), 4.30 (d, $J = 8.4$ Hz, 1 H), 4.40 (dd, $J = 10.6$, 6.8 Hz, 1 H), 4.57 (d, $J = 9.6$ Hz, 1 H), 4.96 (d, $J = 8.1$ Hz, 1 H), 5.63 (d, $J = 7.0$ Hz, 1 H), 6.16 (t, $J = 8.4$ Hz, 1 H), 6.30 (s, 1 H), 7.13 (d, $J = 7.9$ Hz, 1 H), 7.33 (t, $J = 8.0$ Hz, 1 H), 7.62 (s, 1 H), 7.68 (d, $J = 7.6$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.0, 9.6, 14.9, 21.8, 22.5, 23.3, 24.7, 26.6, 27.6, 28.1, 35.5, 41.2, 43.2, 45.6, 51.2, 55.3, 58.5, 72.2, 72.6, 73.0, 75.4, 75.5, 76.2, 79.1, 79.7, 81.1, 84.4, 114.1, 120.4, 122.7, 129.6, 130.4, 132.9, 142.5, 155.4, 159.6, 166.8, 169.9, 174.0, 174.6, 203.8. HRMS *m/e* calcd for $C_{45}H_{63}O_{16}N\cdot H^+$: 874.4225. Found: 874.4224 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

Alternative Method for the Synthesis of 15g through Hydrogenation of 14g. To a reaction flask with activated Pd/C (33 mg, 0.014 mmol) was added a solution of **14g** (250 mg, 0.287 mmol) in 10 mL of EtOAc with several drops of MeOH under hydrogen atmosphere. The suspension was stirred overnight, and the reaction mixture was filtered through Celite. The filtrate was condensed by a rotary evaporator and the residue was purified on a silica gel column using hexanes/EtOAc (1/1) as the eluant to afford **15 g** (250 mg, 99.8% yield) as a white solid.

Preparation of (3*R*,4*S*)-1-Acyl-3-trialkylsiloxy-4-(2-methylprop-1-enyl)azetidin-2-ones (16). A typical procedure is described for the preparation of (3*R*,4*S*)-1-cyclohexanecarbonyl-3-triisopropylsiloxy-4-(2-methylprop-1-enyl)azetidin-2-one (**16h**). To a solution of (3*R*,4*S*)-3-triisopropylsiloxy-4-(2-methylprop-1-enyl)azetidin-2-one[20] (129 mg, 0.435mmol) and DMAP (53 mg, 0.435mmol) in 1 mL of CH_2Cl_2 was added triethylamine (0.6 mL, 4.35 mmol) followed by the dropwise addition of cyclohexyl chloroformate (0.14 mL, 0.652 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature, quenched with NH_4Cl (5 mL), and extracted with EtOAc (10 mL × 3), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography of the residue on silica gel (hexanes/EtOAc = 20/1) afforded **16h** (177 mg, 94% yield) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (m, 21 H). 1.14−1.50 (m, 6 H), 1.64−1.93 (m, 4 H), 1.76 (s, 3 H), 1.78 (s, 3 H), 2.91 (m, 1 H), 4.80 (dd, $J = 6.3$ Hz, $J = 9.9$ Hz, 1 H), 4.99 (d, $J = 6.3$ Hz, 1 H), 5.22 (d, $J = 9.9$ Hz, 1 H).

Other N-modified β-lactams **16a**−**g** were prepared in the same manner. (3*R*,4*S*)-3-*tert*-butyldimethylsiloxy-4-(2-methylprop-1-enyl)azetidin-2-one was prepared in the same manner as that described for the corresponding 3-triisopropylsiloxy-β-lactam.[20,22] Characterization data (^{1}H NMR) for **16a**−**g** are summarized in the Supporting Information.

Synthesis of Taxoids 17. Taxoids **17a**−**l** were synthesized through the Ojima−Holton coupling of 7-TES-10-deacetyl-10-propanoylbaccatin[17] or baccatin **11b** with β-lactams **16a**−**h** in the same manner as that described above for the synthesis of **14a**−**p**. For example, 3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-debenzoyl-3′*N*-cyclobutanecarbonyl-10-propanoyldocetaxel (**17a**) was obtained in 86% yield for two steps as a white solid: mp 149−151 °C; $[\alpha]^{20}_D$ −72.6 (*c* 2.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 3 H), 1.21−1.26 (m, 15 H), 1.69 (s, 3 H), 1−2.00 (m, 10 H), 1.83 (s, 3 H), 2.09−2.21 (m, 5 H), 2.44−2.60 (m, 4 H), 2.92 (m, 1 H), 3.82 (d, $J = 6.6$ Hz, 1 H), 4.32−4.19 (m, 3 H), 4.43 (m, 1 H), 4.97 (d, $J = 8.4$ Hz, 1 H), 5.04 (m, 1H), 5.35 (d, $J = 8.7$ Hz, 1H), 5.58 (d, $J = 8.4$ Hz, 1 H), 5.68 (d, $J = 7.2$ Hz, 1 H), 6.20 (t, 1 H), 6.31 (s, 1 H), 7.47 (t, 2 H), 7.61 (t, 1 H), 8.11 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 0, 9.5, 14.9, 18.6, 21.9, 22.4, 25.2, 25.5, 25.7, 26.7, 27.6, 29.7, 35.7, 39.7, 43.2, 45.6, 50.2, 58.6, 72.1, 72.2, 73.8, 75.0, 75.4, 76.4, 79.1, 81.0, 84.4, 120.0, 128.6, 129.2, 130.1, 133.1, 133.7, 139.0, 142.3, 166.9, 170.2, 172.8, 174.6, 174.9, 203.8. HRMS *m/e* calcd for $C_{44}H_{57}NO_{14}\cdot H^+$: 824.3857. Found: 824.3855 ($\Delta = 0.3$ ppm).

Other taxoids **17b**−**l** were synthesized in the same manner, and characterization data are shown below.

10-Propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-(cyclopentanecarbonyl)docetaxel (17b). White solid; 78% (for two steps); mp 150−152 °C; $[\alpha]^{20}_D$ −75.7 (*c* 3.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (m, 6H), 1.16 (s, 3 H), 1.23 (m, 3 H), 1.26 (s, 9 H), 1.84−1.41 (m, 13 H), 1.88 (s, 3 H), 2.39 (s, 3 H), 2.43−2.59 (m, 3 H), 3.37 (d, $J = 5.7$ Hz, 1 H), 3.80 (d, $J = 7.2$ Hz, 1 H), 4.20 (m, 2 H), 4.30 (d, $J = 8.1$, 1 H), 4.42 (m, 2 H), 4.97 (d, $J = 7.5$ Hz, 1 H), 5.47 (d, $J = 9.4$ Hz, 1 H), 5.68 (d, $J = 7.2$ Hz, 1 H), 6.14 (m, 1 H), 6.30 (s, 1 H), 7.47 (t, 2 H), 7.60 (t, 1 H), 8.12 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.6, 14.9, 21.9, 22.0, 22.5, 23.3, 24.8, 25.8, 25.8, 26.7, 27.6, 29.7, 30.7, 35.6, 35.8, 41.0, 43.2, 45.6, 45.7, 49.6, 58.6, 72.2, 72.6, 72.9, 75.0, 75.4, 76.5, 79.1, 81.1, 84.4, 128.7, 129.2, 130.2, 133.1, 133.6,142.2, 166.9, 170.1, 173.8, 174.6, 176.3, 203.8. HRMS *m/e* calcd for $C_{45}H_{59}NO_{14}\cdot H^+$: 838.4014. Found: 838.4011 ($\Delta = 0.3$ ppm).

10-Propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-(cyclohexanecarbonyl)docetaxel (17c). White solid; 85% (for two steps); mp 152−155 °C; $[\alpha]^{20}_D$ −78.3 (*c* 3.78, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br, s, 6 H) 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, $J = 6.9$ Hz, 1 H), 4.10 (d, $J = 8.1$ Hz, 1 H), 4.13 (br s 1 H), 4.22 (d, $J = 8.1$ Hz, 1 H), 4.33 (dd, $J = 10.1$, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, $J = 9.3$ Hz, 1 H), 5.23 (d, $J = 8.4$ Hz, 1 H), 5.59 (d, $J = 6.9$ Hz, 1 H), 6.06 (m, 1 H), 6.24 (s, 1 H), 7.37 (t, 2 H), 7.51 (t, 1 H), 8.01 (d, 2 H). HRMS *m/e* calcd for $C_{46}H_{61}NO_{14}\cdot H^+$: 852.4170. Found: 852.4172 ($\Delta = -0.2$ ppm).

10-Propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-debenzoyl-3′*N*-(cyclopent-1-ene-1-carbonyl)docetaxel (17d). White solid; 80% (for two steps); mp 148−151 °C; $[\alpha]^{20}_D$ −70.3 (*c* 1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br, s, 6 H), 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.82 (d, $J = 6.6$ Hz, 1 H), 4.19 (d, $J = 8.7$ Hz, 1H), 4.31 (m, 2H), 4.42 (m, 1 H), 4.96 (d, $J = 4.8$ Hz, 1H), 5.10 (m, 1H), 5.38 (d, $J = 9.0$ Hz, 1H), 5.67 (d, $J = 7.2$ Hz, 1 H), 5.89 (d, $J = 8.1$ Hz, 1 H), 6.19 (t, 1 H), 6.31 (s, 1 H), 6.51 (dd, 1 H), 7.47 (t, 2 H), 7.61 (t, 1 H), 8.09 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 18.6, 21.8, 22.4, 23.2, 25.8, 26.8, 27.6, 31.4, 33.1, 35.6, 35.8, 43.2, 45.6, 50.4, 58.6, 72.0, 72.2, 73.8, 75.0, 75.4, 76.5, 79.0, 81.0, 84.4, 87.5, 120.0, 128.6, 129.2, 130.1, 133.1, 133.7, 138.4, 139.2, 139.5, 142.2, 165.0, 166.8, 170.3, 172.7, 174.6, 203.8. HRMS *m/e* calcd for $C_{45}H_{57}NO_{14}\cdot H^+$: 836.3857. Found: 836.3858 ($\Delta = -0.1$ ppm).

10-Propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-debenzoyl-3′*N*-(cyclohex-1-ene-1-carbonyl)docetaxel (17e). White solid; 75% (for two steps); mp 151−154 °C; $[\alpha]^{20}_D$ −67 (*c* 2.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.13−1.18 (m, 6 H), 1.26 (s, 9 H), 1.60 (s, 3 H), 1.69 (br, s, 6 H), 1.72 (m, 1 H), 1.81 (s, 3H), 1.93 (s, 3 H), 2.16 (m, 4 H), 2.38 (s, 3 H), 2.45−2.59 (m, 3 H), 3.74 (d, $J = 6.9$ Hz), 3.82 (d, $J = 6.6$ Hz, 1H), 4.20 (d, $J = 8.4$ Hz, 1 H), 4.30 (m, 2H), 4.41 (m, 1 H), 4.96 (d, $J = 7.8$ Hz, 1 H), 5.06 (m, 1H), 5.11 (d, $J = 3.6$ Hz, 1H), 5.37 (d, $J = 9.0$ Hz, 1 H), 5.67 (d, $J = 7.2$ Hz, 1 H), 5.93 (d, $J = 7.8$ Hz, 1H), 6.18 (t, 1 H), 6.31 (s, 1 H), 6.60 (dd, 1H), 7.46 (t, 2 H), 7.60 (t, 1 H), 8.09 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 18.6, 21.4, 21.8, 22.0, 22.4, 24.2, 25.4, 25.8, 26.8, 27.6, 29.7, 30.9, 35.6, 35.8, 43.2, 45.6, 50.5, 58.6, 71.9, 72.2, 73.9, 75.0, 75.4, 79.1, 81.0, 84.4, 120.1, 128.6, 129.2, 130.1, 132.5, 133.0, 133.7, 134.7, 139.2, 142.3, 166.9, 168.4, 170.3, 172.8, 174.6, 203.8. HRMS *m/e* calcd for $C_{46}H_{59}NO_{14}\cdot H^+$: 850.4014. Found: 850.4018 ($\Delta = -0.5$ ppm).

10-Propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-debenzoyl-3′*N*-(cyclopentyloxycarbonyl)docetaxel (17f). White solid; 85% (for two steps); mp 141−143 °C; $[\alpha]^{20}_D$ −74 (*c* 5.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br, s, 6 H) 1.72 (m, 1 H), 1.83

(s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, $J = 6.9$ Hz, 1 H), 4.10 (d, $J = 8.1$ Hz, 1 H), 4.13 (br s 1 H), 4.22 (d, $J = 8.1$ Hz, 1 H), 4.33 (dd, $J = 10.1$, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, $J = 9.3$ Hz, 1 H), 5.23 (d, $J = 8.4$ Hz, 1 H), 5.59 (d, $J = 6.9$ Hz, 1 H), 6.06 (m, 1 H), 6.24 (s, 1 H), 7.37 (t, 2 H), 7.51 (t, 1 H), 8.01 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 18.5, 21.9, 22.4, 23.6, 23.6, 25.7, 26.7, 27.5, 29.7, 32.6, 32.6, 35.6, 35.6, 43.2, 45.7, 51.9, 58.5, 72.1, 72.2, 73.7, 75.0, 75.4, 76.4, 77.9, 79.2, 81.1, 84.4, 120.5, 128.6, 129.2, 130.1, 133.0, 133.7, 138.2, 142.3, 156.1, 166.9, 170.2, 172.8, 174.6, 203.8. HRMS *m/e* calcd for $C_{45}H_{59}NO_{15}\cdot H^+$: 854.3963. Found: 854.3960 ($\Delta = +0.3$ ppm).

10-Propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-debenzoyl-3′*N*-(cyclohexyloxycarbonyl)docetaxel (17g). White solid; 80% (for two steps); mp 142−144 °C; $[\alpha]^{20}_D$ −66.5 (*c* 5.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br, s, 6 H) 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, $J = 6.9$ Hz, 1 H), 4.10 (d, $J = 8.1$ Hz, 1 H), 4.13 (br s 1 H), 4.22 (d, $J = 8.1$ Hz, 1 H), 4.33 (dd, $J = 10.1$, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, $J = 9.3$ Hz, 1 H), 5.23 (d, $J = 8.4$ Hz, 1 H), 5.64 (d, $J = 7.0$ Hz, 1 H), 6.18 (m, 1 H), 6.30 (s, 1 H), 7.46 (t, 2 H), 7.59 (t, 1 H), 8.09 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 18.5, 21.9, 22.4, 23.6, 23.7, 25.3, 25.7, 26.7, 27.5, 31.8, 35.6, 35.6, 43.2, 45.7, 51.8, 58.5, 72.1, 72.2, 73.7, 75.0, 75.4, 76.4, 79.2, 81.0, 84.4, 120.6, 128.6, 129.2, 130.1, 133.0, 133.7, 138.1, 142.3, 155.8, 166.9, 170.2, 172.8, 174.6, 203.8. HRMS *m/e* calcd for $C_{46}H_{61}NO_{15}\cdot H^+$: 868.4120. Found: 868.4120 ($\Delta = -0.1$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylprop-1-enyl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclopropanecarbonyl)docetaxel (17h). White solid; 66% (for two steps); mp 141−143 °C; $[\alpha]^{20}_D$ −66.6 (*c* 11.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 3 H), 1.28 (m, 9 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 1.77 (s, 3 H), 1.88 (m, 5 H), 2.35 (m, 5 H), 2.52 (m, 3 H), 3.80 (d, $J = 6.8$ Hz, 1 H), 3.85 (s, 3 H), 4.17 (d, $J = 8.7$, 1 H), 4.25 (d, $J = 3.2$ Hz, 1 H), 4.33 (d, $J = 8.7$ Hz), 4.41 (dd, $J = 10.5$ Hz, $J = 6.3$ Hz, 1 H), 4.96 (d, $J = 8.1$ Hz, 1 H), 5.03 (td, $J = 3.2$, 8.8 Hz, 1 H), 5.37 (d, $J = 8.8$ Hz, 1 H), 5.66 (d, $J = 6.8$ Hz, 1 H), 5.92 (d, $J = 8.1$ Hz, 1 H), 6.15 (t, $J = 8.4$ Hz, 1 H), 6.30 (s, 1 H), 7.13 (dd, $J = 7.8$ Hz, $J = 2.4$ Hz, 1 H), 7.3 (t, $J = 7.8$ Hz, 2 H) 7.62 (d, 2.4 Hz, 1 H), 7.68 (d, $J = 7.8$ Hz, 1 H). HRMS *m/e* calcd for $C_{44}H_{57}NO_{15}\cdot H^+$: 840.3806. Found: 840.3802 ($\Delta = -0.5$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropen-1-yl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclobutanecarbonyl)docetaxel (17i). White solid; 61% (for two steps); mp 143−145 °C; $[\alpha]^{20}_D$ −70.4 (*c* 13.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.28 (m, 8 H), 1.33 (s, 9 H), 1.67 (m, 3 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.89 (m, 5 H), 2.37 (m, H), 2.52 (m, 3 H), 2.91 (m, 1 H), 3.80 (d, $J = 6.9$ Hz, 1 H), 3.85 (s, 3 H), 4.19 (d, $J = 8.4$, 1 H), 4.25 (s, 1 H), 4.34 (d, $J = 8.4$ Hz), 4.42 (t, $J = 7.2$, 1 H), 4.96 (d, $J = 8.1$ Hz, 1 H), 5.03 (dt, $J = 3.3$, 8.9 Hz, 1 H), 5.35 (d, $J = 8.9$ Hz, 1 H), 5.57 (d, $J = 8.1$ Hz, 1 H), 5.67 (d, $J = 7.2$ Hz, 1 H), 6.16 (t, $J = 8.7$ Hz, 1 H), 6.31 (s, 1 H), 7.13 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1 H), 7.37 (t, $J = 7.8$ Hz, 1 H) 7.63 (s, 1 H), 7.70 (d, $J = 7.8$ Hz, 1 H). HRMS *m/e* calcd for $C_{45}H_{59}O_{15}N\cdot H^+$: 854.3962. Found: 854.3962 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed 95% purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropen-1-yl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclopentanecarbonyl)docetaxel (17j). White solid; 77% (for two steps); mp 136−138 °C; $[\alpha]^{20}_D$ −74.5 (*c* 14.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.28 (m, 8 H), 1.33 (s, 9 H), 1.67 (m, 3 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.89 (m, 5 H), 2.37 (m, H), 2.52 (m, 3 H), 3.80 (d, $J = 6.9$ Hz, 1 H), 3.85 (s, 3 H), 4.19 (d, $J = 8.4$, 1 H), 4.21 (s, 1 H), 4.32 (d, $J = 8.4$ Hz), 4.41 (t, J=10.2, 1 H), 4.96 (d, $J = 8.4$ Hz, 1 H), 5.03 (dt, $J = 3.0$, 8.7 Hz, 1 H), 5.36 (d, $J = 9.0$ Hz, 1 H), 5.66 (d, $J = 6.9$ Hz, 1 H), 5.72 (d, $J = 8.1$ Hz, 1 H), 6.13 (t, $J = 8.7$ Hz, 1 H), 6.31 (s, 1 H), 7.13 (dd, $J = 7.5$ Hz, $J = 2.1$ Hz, 1 H), 7.37 (d, $J = 7.5$ Hz, 2 H), 7.63 (s, 1 H), 7.69 (d, $J = 7.5$ Hz, 1 H). HRMS *m/e* calcd for $C_{46}H_{61}O_{15}N\cdot H^+$: 868.4119. Found: 868.4122 ($\Delta = -0.3$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropen-1-yl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclohexanecarbonyl)docetaxel (17k). White solid; 81% (for two steps); mp 151−153 °C; $[\alpha]^{20}_D$ −73.4 (*c* 14.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.28 (m, 8 H), 1.33 (s, 9 H), 1.67 (m, 3 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.89 (m, 5 H), 2.37 (m, H), 2.52 (m, 3 H), 3.80 (d, $J = 6.9$ Hz, 1 H), 3.86 (s, 3 H), 4.18−4.23 (m, 2 H), 4.33 (d, $J = 8.7$ Hz, 1 H), 4.41 (dt, $J = 11.1$, 6.6 Hz, 1 H), 4.95 (d, $J = 7.8$, 1 H), 5.03 (dt, $J = 2.7$, 8.4 Hz, 1 H), 5.35 (d, $J = 8.4$ Hz, 1 H), 5.67 (d, $J = 6.9$ Hz, 1 H), 5.72 (d, $J = 8.1$ Hz, 1 H), 6.12 (t, $J = 9.0$ Hz, 1 H), 6.31 (s, 1 H), 7.13 (dd, $J = 7.8$ Hz, $J = 2.1$ Hz, 1 H), 7.37 (d, $J = 7.8$ Hz, 2 H), 7.63 (s, 1 H), 7.69 (d, $J = 7.8$ Hz, 1 H). HRMS *m/e* calcd for $C_{47}H_{63}O_{15}N\cdot H^+$: 882.4276. Found: 882.4275 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed 95% purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropen-1-yl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclohexyloxycarbonyl)docetaxel (17l). White solid; 77% (for two steps); mp 141−143 °C; $[\alpha]^{20}_D$ −68 (*c* 10.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.28 (m, 8 H), 1.33 (s, 9 H), 1.66 (m, 3 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.89 (m, 5 H), 2.37 (m, H), 2.52 (m, 3 H), 3.81 (d, $J = 7.2$ Hz, 1 H), 3.87 (s, 3 H), 4.17 (d, 8.7 Hz, 1 H), 4.23 (d, $J = 3.0$ Hz, 1 H), 4.34 (d, $J = 8.7$ Hz), 4.42 (dd, $J = 10.8$, 7.5 Hz, 1 H), 4.49 (m, 1 H), 4.79 (dt, $J = 3.0$, 8.0 Hz, 1 H), 4.88 (d, $J = 8.7$ Hz, 1 H), 4.96 (d, $J = 7.5$ Hz, 2 H), 5.32 (d, $J = 8.0$ Hz, 1 H), 5.66 (d, $J = 7.2$ Hz, 1 H), 6.19 (t, $J = 8.1$ Hz, 1 H), 6.31 (s, 1 H), 7.13 (dd, $J = 7.8$ Hz, $J = 2.1$ Hz, 1 H), 7.37 (d, J =7.8 Hz, 2 H) 7.63 (s, 1 H), 7.69 (d, $J = 7.8$ Hz, 1 H). HRMS *m/e* calcd for $C_{47}H_{63}O_{16}N\cdot H^+$: 898.4225. Found: 898.4226 ($\Delta = -0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed 95% purity.

Synthesis of Taxoids 18 through Hydrogenation of 17. A typical procedure is described for the synthesis of 10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)-3′*N*-debenzoyl-3′*N*-(cyclopentanecarbonyl)docetaxel (**18b**). To a flask charged with activated 10% Pd/carbon (2 mg, 0.002 mmol) and **17b** (13 mg, 0.02 mmol) under hydrogen atmosphere were added EtOAc (12.0 mL) and MeOH (0.02 mL), and the suspension was stirred at room temperature for 24 h. The reaction mixture was filtered over Celite and the filtrate was concentrated in vacuo to afford **18b** in quantitative yield as white solid: mp 149−152 °C; $[\alpha]^{20}_D$ −114 (*c* 3.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (m, 6H), 1.16 (s, 3 H), 1.23 (m, 3 H), 1.26 (s, 9 H), 1.84−1.41 (m, 13 H), 1.88 (s, 3 H), 2.39 (s, 3 H), 2.43−2.59 (m, 3 H), 3.37 (d, $J = 5.7$ Hz, 1 H), 3.80 (d, $J = 7.2$ Hz, 1 H), 4.20 (m, 2 H), 4.30 (d, $J = 8.1$, 1 H), 4.42 (m, 2 H), 4.97 (d, $J = 7.5$ Hz, 1 H), 5.47 (d, $J = 9.4$ Hz, 1 H), 5.68 (d, $J = 7.2$ Hz, 1 H), 6.14 (m, 1 H), 6.30 (s, 1 H), 7.47 (t, 2 H), 7.60 (t, 1 H), 8.12 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.6, 14.9, 21.9, 22.0, 22.5, 23.3, 24.8, 25.8, 25.8, 26.7, 27.6, 29.7, 30.7, 35.6, 35.8, 41.0, 43.2, 45.6, 45.7, 49.6, 58.6, 72.2, 72.6, 72.9, 75.0, 75.4, 76.5, 79.1, 81.1, 84.4, 128.7, 129.2, 130.2, 133.1, 133.6, 142.2, 166.9, 170.1, 173.8, 174.6, 176.3, 203.8. HRMS *m/e* calcd for $C_{45}H_{61}NO_{14}\cdot H^+$: 840.4170. Found: 840.4174 ($\Delta = -0.4$ ppm).

Other taxoids **18c**, **18f**−**h**, **18k**, and **18m** were synthesized in the same manner, and characterization data are shown below.

10-Propanoyl-3′-dephenyl-3′-(2-methylpropyl)-3′*N*-debenzoyl-3′*N*-cyclohexanecarbonyldocetaxel (18c). White solid; 100%; mp 133−135 °C; $[\alpha]^{20}_D$ −74 (*c* 4.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s,

3 H), 1.69 (br, s, 6 H) 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, $J = 6.9$ Hz, 1 H), 4.10 (d, $J = 8.1$ Hz, 1 H), 4.13 (br s 1 H), 4.22 (d, $J = 8.1$ Hz, 1 H), 4.33 (dd, $J = 10.1$, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, $J = 9.3$ Hz, 1 H), 5.23 (d, $J = 8.4$ Hz, 1 H), 5.59 (d, $J = 6.9$ Hz, 1 H), 6.06 (m, 1 H), 6.24 (s, 1 H), 7.37 (t, 2 H), 7.51 (t, 1 H), 8.01 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.6, 14.9, 21.8, 22.0, 22.5, 23.3, 24.8, 25.6, 26.7, 27.6, 29.7, 35.6, 35.7, 41.0, 43.2, 45.5, 45.6, 49.2, 58.5, 72.2, 72.6, 72.8, 75.1, 75.4, 79.0, 81.1, 84.4, 128.6, 129.3, 130.2, 133.1, 133.6, 142.2, 166.8, 170.0, 173.8, 174.6, 176.1, 203.8. HRMS *m/e* calcd for $C_{45}H_{61}NO_{14}\cdot H^+$: 840.4170. Found: 840.4174 ($\Delta = -0.4$ ppm). HPLC analysis using a Phenomenex Curosil-B column: CH_3CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV (230 and 254 nm) showed ≥95% purity.

10-Propanoyl-3′-dephenyl-3′-(2-methylpropyl)-3′*N*-debenzoyl-3′*N*-cyclopentyloxycarbonyldocetaxel (18f). White solid; 100%; mp 131−133 °C; $[\alpha]^{20}_D$ −67 (*c* 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br s, 6 H) 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, $J = 6.9$ Hz, 1 H), 4.10 (d, $J = 8.1$ Hz, 1 H), 4.13 (br s 1 H), 4.22 (d, $J = 8.1$ Hz, 1 H), 4.33 (dd, $J = 10.1$, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, $J = 9.3$ Hz, 1 H), 5.23 (d, $J = 8.4$ Hz, 1 H), 5.59 (d, $J = 6.9$ Hz, 1 H), 6.06 (m, 1 H), 6.24 (s, 1 H), 7.37 (t, 2 H), 7.51 (t, 1 H), 8.01 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 18.5, 21.9, 22.4, 23.6, 23.6, 25.7, 26.7, 27.5, 29.7, 32.6, 32.6, 35.6, 35.6, 43.2, 45.7, 51.9, 58.5, 72.1, 72.2, 73.7, 75.0, 75.4, 76.4, 77.9, 79.2, 81.1, 84.4, 120.5, 128.6, 129.2, 130.1, 133.0, 133.7, 138.2, 142.3, 156.1, 166.9, 170.2, 172.8, 174.6, 203.8. HRMS: *m/e* calcd for $C_{45}H_{61}NO_{15}\cdot H^+$: 856.4119. Found: 854.4121 ($\Delta = -0.2$ ppm).

10-Propanoyl-3′-dephenyl-3′-(2-methylpropyl)-3′*N*-debenzoyl-3′*N*-cyclohexyloxycarbonyldocetaxel (18g). White solid; 100%; mp 142−144 °C; $[\alpha]^{20}_D$ −60 (*c* 1.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br, s, 6 H), 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, $J = 6.9$ Hz, 1 H), 4.10 (d, $J = 8.1$ Hz, 1 H), 4.13 (br s 1 H), 4.22 (d, $J = 8.1$ Hz, 1 H), 4.33 (dd, $J = 10.1$, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, $J = 9.3$ Hz, 1 H), 5.23 (d, $J = 8.4$ Hz, 1 H), 5.64 (d, $J = 7.0$ Hz, 1 H), 6.18 (m, 1 H), 6.30 (s, 1 H), 7.46 (t, 2 H), 7.59 (t, 1 H), 8.09 (d, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 9.0, 9.5, 14.9, 18.5, 21.9, 22.4, 23.6, 23.7, 25.3, 25.7, 26.7, 27.5, 31.8, 35.6, 35.6, 43.2, 45.7, 51.8, 58.5, 72.1, 72.2, 73.7, 75.0, 75.4, 76.4, 79.2, 81.0, 84.4, 120.6, 128.6, 129.2, 130.1, 133.0, 133.7, 138.1, 142.3, 155.8, 166.9, 170.2, 172.8, 174.6, 203.8. HRMS *m/e* calcd for $C_{46}H_{63}NO_{15}H^+$: 870.4273. Found: 870.4276 ($\Delta = +0.3$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclopropanecarbonyl)docetaxel (18h). White solid; 100%; mp 139−141 °C; $[\alpha]^{20}_D$ −74.5 (*c* 14.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (m, 2H), 0.86 (m, 2H), 0.95 (dd, $J_1 = 6.4$ Hz, $J_2 = 16.4$ Hz, 6 H), 1.15 (s, 3H), 1.21−1.41 (m, 8 H), 1.62−1.78 (m, 5 H), 1.88 (m, 3H), 2.38 (m, 4H), 2.54 (m, 4H), 3.66 (bs, 1H), 3.79 (d, $J = 7.2$ Hz, 1 H), 3.87 (s, 1H), 4.20 (m, 2 H), 4.32 (d, $J = 8.4$ Hz, 1 H), 4.42 (m, 2 H), 4.96 (dd, $J_1 = 2$ Hz, $J_2 = 9.6$ Hz, 1 H), 5.67 (d, $J = 7.2$ Hz, 1H), 5.78 (d, $J = 9.2$ Hz, 1H), 6.14 (m, 1 H), 6.30 (s, 1 H), 7.14 (bdd, 1 H), 7.37 (bt, $J = 8$ Hz, 1 H), 7.63 (bs, 1H), 7.70 (bd, $J = 7.6$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 7.5, 9.0, 9.6, 14.5, 14.8, 21.8, 22.0, 22.5, 23.2, 24.7, 26.7, 27.6, 35.6, 35.7, 40.9, 43.2, 45.5, 50.0, 55.3, 58.5, 72.1, 72.4, 73.0, 75.1, 75.4, 76.4, 78.9, 81.1, 84.4, 114.3, 120.4, 122.6, 129.6, 130.5, 133.0, 142.2, 159.6, 166.7, 170.0, 173.7, 173.8, 174.6, 203.8. HRMS *m/e* calcd for $C_{44}H_{59}O_{15}N\cdot H^+$: 842.3963. Found: 842.3941 ($\Delta = -2.6$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropan-1-yl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclohexanecarbonyl)docetaxel (18k). White solid; 100%; mp 143−145 °C; $[\alpha]^{20}_D$ −85 (*c* 14.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (dd, $J_1 = 6.4$ Hz, $J_2 = 16.4$ Hz, 6 H), 1.15−1.37 (m, 16 H), 1.57−1.40 (m, 10 H), 1.87 (m, 5H), 2.38 (m, 5H), 2.54 (m, 4H), 3.81 (d, $J = 6.8$ Hz, 1 H), 3.87 (s, 3H), 4.20 (m, 2 H), 4.33 (d, $J = 8.4$ Hz, 1 H), 4.43 (m, 2H), 4.97 (bd, $J = 9.6$ Hz, 1 H), 5.47 (d, $J = 9.6$ Hz, 1H), 5.68 (d, $J = 7.2$ Hz, 1H), 6.12 (m, 1 H), 6.30 (s, 1 H), 7.14 (dd, $J_1 = 2$ Hz, $J_2 = 8.4$ Hz, 1 H), 7.37 (bt, $J = 8$ Hz, 1 H), 7.64 (bs, 1H), 7.70 (bd, $J = 7.6$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 9.5, 14.8, 21.7, 22.0, 22.5, 23.3, 24.8, 25.5, 25.6, 26.7, 27.6, 29.7, 35.6, 35.7, 41.0, 43.2, 45.4, 45.5, 49.2, 55.3, 58.5, 72.2, 72.6, 72.9, 75.1, 75.4, 76.4, 78.8, 81.2, 84.4, 114.2, 120.4, 122.7, 129.6, 130.5, 133.2, 142.1, 159.6, 166.6, 170.0, 173.7, 174.6, 176.1, 203.8. HRMS *m/e* calcd for $C_{47}H_{65}NO_{15}H^+$: 884.4432. Found: 884.4413 ($\Delta = -2.1$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3′-dephenyl-3′-(2-methylpropyl)-3′*N*-de-*tert*-butoxycarbonyl-3′*N*-(cyclopentyloxycarbonyl)docetaxel (18m). White solid; 60% yield (for three steps from **11b**); mp 143−145 °C; $[\alpha]^{20}_D$ −70 (*c* 13.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (dd, $J_1 = 6.4$ Hz, $J_2 = 10$ Hz, 6 H), 1.14 (s, 3 H), 1.25 (m, 7 H), 1.35−1.72 (m, 15 H), 1.85 (s, 3H), 2.36 (m, 5H), 2.54 (m, 4H), 3.81 (d, $J = 8$ Hz, 1 H), 3.87 (s, 1H), 4.12−4.20 (m, 3 H), 4.33 (d, $J = 8.4$ Hz, 1 H), 4.42 (m, 1 H), 4.69 (d, $J = 9.6$ Hz, 1 H), 4.89 (m, 1 H), 4.98 (d, $J_1 = 8$ Hz, 1 H), 5.66 (d, $J = 7.2$ Hz, 1H), 6.20 (m, 1 H), 6.30 (s, 1 H), 7.13 (dd, $J_1 = 2.8$ Hz, $J_2 = 8.4$ Hz, 1 H), 7.37 (bt, $J = 8$ Hz, 1 H), 7.64 (bs, 1H), 7.70 (bd, $J = 7.6$ Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 9.5, 14.8, 21.7, 22.0, 22.5, 23.2, 23.5, 23.6, 24.6, 26.7, 27.5, 32.5, 32.6, 35.5, 41.2, 43.2, 45.6, 51.6, 55.3, 58.5, 72.1, 72.5, 73.0, 75.1, 75.4, 76.4, 77.8, 79.1, 81.1, 84.4, 114.2, 120.5, 122.7, 129.6, 130.4, 133.0, 142.3, 156.1, 159.7, 166.8, 170.0, 173.7, 174.6, 203.8. HRMS *m/e* calcd for $C_{46}H_{63}O_{16}NH^+$: 886.4225. Found: 886.4211 ($\Delta = -1.6$ ppm).

In Vitro Cell Growth Inhibition Assay. (a) Tumor cell growth inhibition was determined according to the method established by Skehan et al.[51] Human cancer cells LCC6-WT (Pgp−), MCF-7 (Pgp−), LCC6-MDR (Pgp+), and NCI/ADR (Pgp+) were plated at a density of 400−2000 cells/well in 96-well plates and allowed to attach overnight. These cell lines were maintained in RPMI-1640 medium (Roswell Park Memorial Institute growth medium) supplemented with 5% fetal bovine serum and 5% Nu serum (Collaborative Biomedical Product, MA). Taxoids were dissolved in DMSO and further diluted with RPMI-1640 medium. Triplicate wells were exposed to various treatments. After 72 h of incubation, 100 μL of ice-cold 50% trichloroacetic acid (TCA) was added to each well, and the samples were incubated for 1 h at 4 °C. Plates were then washed five times with water to remove TCA and serum proteins, and 50 μL of 0.4% sulforhodamine B (SRB) was added to each well. Following a 5 min incubation, plates were rinsed five times with 0.1% acetic acid and air-dried. The dye was then solubilized with 10 mM Tris base (pH 10.5) for 5 min on a gyratory shaker. Optical density was measured at 570 nm. The IC_{50} values were then calculated by fitting the concentration−effect curve data with the sigmoid-E_{max} model using nonlinear regression, weighted by the reciprocal of the square of the predicted effect.[52]

(b) Human pancreatic cancer cell lines MIA PaCa-2, CFPAC-1, BxPC-3, and PANC-1 were cultured as specified by ATCC (Manassas, VA). For cytotoxicity assays the cells were plated at a density of 2.5×10^4 cells/well in 24-well plates and allowed to adhere overnight. The medium was changed the following morning and replaced with medium containing taxane derivatives or vehicle control. Taxoids were dissolved in DMSO to 10 mM and were further diluted in appropriate medium prior to addition to cells. Each dose of drug or vehicle was tested in triplicate, and the experiment is representative of at least three independent trials. After 72 h of treatment, the medium was aspirated and the cells were washed in warm PBS. MTT reagent (Sigma) was diluted in RPMI-1640 medium without phenol red (Invitrogen) and added to the cells at 0.5 mg/mL. After 3 h of incubation, the reagent was aspirated, the plate was washed with PBS, and MTT formazan crystals were dissolved in 500 μL of acidified isopropanol (0.1 N hydrochloric acid). Subsequently, 100 μL of the solution was transferred to a microtiter plate. Absorbance at 570 nM was measured on a ThermoMax plate reader (Molecular Devices). The

IC_{50} values were obtained by using the same method as that described for (a).

Tubulin Polymerization Assay. Assembly and disassembly of calf brain microtubule protein (MTP) were monitored spectrophotometrically (Beckman Coulter DU 640, Fullerton, CA) by recording changes in turbidity at 350 nm at 37 °C.[53,54] MTP was diluted to 1 mg/mL in MES buffer containing 3 M glycerol. The concentration of tubulin in MTP is 85%, and that is taken into consideration when the ratios of tubulin to drug are presented in Figures 1 and 2. Microtubule assembly was carried out with 10 μM taxoid (**19**, **14g**, or **14i**). Paclitaxel (10 μM) was also used for comparison purpose. Calcium chloride (6 mM) was added to the assembly reaction after 50 min to follow the calcium-induced microtubule depolymerization. For the experiments shown in Figure 1, tubulin stored in liquid nitrogen was centrifuged just before use and protein concentration adjusted to 1 mg/mL, while the experiments in Figure 2 used tubulin stored in liquid nitrogen as it was at 1 mg/mL concentration.

Electron Microscopy. Aliquots (50 μL) were taken from in vitro polymerization assays at the end of the reaction and placed onto 300-mesh carbon-coated, Formvar treated copper grids. Samples were then stained with 20 μL of 2% uranyl acetate and viewed with a JEOL model 100CX electron microscope.

Animals and Tumor Xenografts. Female severe combined immune deficient (SCID) mice aged 6−8 weeks were obtained from the National Cancer Institute (Frederick, Maryland) and were housed and monitored at the Medical Research Complex at Roswell Park Cancer Institute. All experimental procedures and protocols were approved by the Institutional Animal Care and Use Committee. The human colon tumor DLD-1, which expresses Pgp, was initiated by implantation of approximately 50 mg of non-necrotic tumor fragments on the right flank using a 12-gauge trocar needle. Chemotherapy was started when the tumor was established as a palpable mass, (approximately 50−100 mm^3 size), 5 days after implantation and continued either every 3 days or weekly. Each drug treatment group or drug-free vehicle consisted of 5 mice per group; untreated controls contained 10 mice per group.

Drug Preparation for in Vivo Experiments. Taxoid **19** was prepared as a 30 mg/mL stock solution in equal parts of Tween-80 (polyoxyethylene-sorbitan monooleate, purchased from Sigma Chemical Company) and absolute ethanol. Each stock solution was further diluted before use in 0.9% NaCl (saline) so that the appropriate concentration of each drug could be injected iv via the tail vein, in a volume of approximately 0.4 mL for a 20 g mouse.

In Vivo Tumor Growth Inhibition Assay against DLD-1 Tumor Xenograft. For each animal, the tumor length (l) and width (w), each in mm, were measured using electronic calipers and recorded every 3−4 days. Tumor volume (v), in mm^3, was calculated using the formula $v = 0.4(l)(w^2)$. The time in days to the predetermined target tumor volume of 600 mm^3 was linearly interpolated from a plot of log(volume) versus time. Statistically significant differences in tumor volumes between control and drug-treated mice were determined by the Cox−Mantel test. For the Cox−Mantel test, the time-to-event data for animals that did not reach the target tumor volume, either because of long-term cure (defined as those animals that were still alive at the conclusion of the experiment whose tumors either completely regressed or did not reach the preset target volume) or early death due to drug toxicity, were treated as censored data. All statistical tests were two-sided.

In Vivo Efficacy Assay of Taxoid 19 against CFPAC-1 Tumor Xenograft. A preliminary in vivo efficacy evaluation of taxoid **19** was also performed against human pancreatic cancer xenograft in male Swiss nude mice aged 6−8 weeks obtained from Taconic Farms (Hudson, New York). The human pancreatic cancer cell line CFPAC-1, which expresses high levels of *mdr1*, was used for the experiments. CFPAC-1 cancer cells (1×10^6) were resuspended in 200 μL of PBS and injected bilaterally into the flanks of mice using a 26 gauge needle. Treatment started when the tumor was established as a palpable mass (approximately 100 mm^3 in size) 19 days after the injection. Taxoid **19** was prepared as a 30 mg/mL stock solution in Tween-80 and absolute ethanol (1:1). Each stock solution was further diluted by PBS prior to administration so that the appropriate concentration of each drug could be injected in a final volume of 0.2 mL. The taxoid was administered iv using tail vein injection three times at 3-day intervals on days 19, 22, and 25 (20 mg/kg × 3, total dose of 60 mg/kg). The tumor size was measured and the volume calculated in the same manner as that described above.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of new taxoids and characterization data for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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