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Design, Synthesis and Biological Evaluation of New Generation Taxoids

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Abstract

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 drug-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 as well, wherein the drug-resistance is mediated by 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 4 pancreatic cancer cell lines, expressing 3–4 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 USA 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

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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 encounters 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) studies on paclitaxel and its congeners have been performed in different laboratories, to date, 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, N₃, 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

A series of second-generation taxoids bearing different aromatic acyl groups at the C10 position was 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 triethyl silyl chloride (TESCl) and 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.

A series of novel second-generation taxoids, bearing substituents at the *meta* position of the C-2-benzoyl group, was synthesized (Scheme 5) from the corresponding C2-modified DABs **10** (see Scheme 3 and Scheme 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 ($R^1 = F, Cl, MeO, Me, N_3, \text{vinyl}$) 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.

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 C-13 position of **10b** using TPAP and NMO provided 13-oxobaccatin **12**. The C10 position was then acylated with 2-methoxybenzoyl chloride in the presence of DMAP to afford 10-(2-methoxybenzoyl)-13-oxobaccatin **13**. Reduction of the C13 ketone with NaBH_4 gave 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 resolution²⁷. 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, taxoids **14g** (SB-T-121303) ($R^1 = \text{MeO}$, $R^2 = \text{propanoyl}$, $R^3 = 2\text{-methylpropen-1-yl}$) was subjected to hydrogenation on Pd/C to afford **15g** ($R^3 = 2\text{-methylpropyl}$) 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 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-propanoylbaccatin III or baccatin **11b** using 1.5–2 equivalents 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 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–6o**, 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 two 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 vs. 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 the R/S ratio of 1.2. In general, taxoids with a substituted or unsubstituted benzoyl group (**6a–6e**) or 2-phenylpropanoyl group (**6m–6o**) are highly potent against LCC6-MDR, while taxoids with an arylacetyl substituents (**6i–6k**) show reduced activity against LCC6-MDR although 4 out of 7 taxoids in this group (**6h–6k**) 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 (IC₅₀ values of 4.8 and 4.7 nM, respectively). Taxoid **6k**, bearing a 4-methoxyphenyl acetyl group at C10 is the least potent (IC₅₀ = 38.4 nM) against LCC6-MDR, but **6k** possesses the highest potency against LCC6-WT. Interestingly, elongation of the alkyl chain of **6i–6k** 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 one to two orders of magnitude higher potency against drug-resistant LCC6-MDR and NCI/ADR cell lines as compared with paclitaxel. Two taxoids (**17d** and **17e**), bearing cyclopent-2-en-1-yl and cyclohex-2-en-1-yl groups, 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 IC₅₀ 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 as well as **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 **14i** 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; **14i**: 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 cycloalkenoyl or carbalkoxy groups at the C3'N position, do not have recognizable effects on potency, except for taxoids **18h** and **18m**, which exhibit sub-nanomolar IC₅₀ 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 as well.

For the effects of the *meta* substituents of the C2-benzoyl moiety, the potency decreases in the order: F > Cl > N₃ > MeO >> CH₂=CH- against LCC6-WT (Pgp[−]), while the order changes to MeO > N₃ > Cl > F >> CH₂=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 *meta*-vinyl substitution of the C2-benzoyl moiety (**14f**) resulted in the least potent taxoid in this comparison. The introduction of a *meta*-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~14p**), especially (*S*)-2,2-dimethylcyclopropyl group (**14p**) appears 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(C₆H₄)CH₂CO~2-MeO(C₆H₄)CO > MeOCO~Ac > cyclo-PrCO ~ EtCO > PhCH₂OCO (Cbz) against LCC6-WT, while the order changes to 4-MeO(C₆H₄)CH₂CO > 2-MeO(C₆H₄)CO~EtCO > MeOCO > Cbz > Ac < cyclo-Pr against LCC6-MDR. However, the decreasing order further changes against MCF7 and NCI/ADR, i.e., Cbz > EtCO > MeOCO > 4-MeO(C₆H₄)CH₂CO > Ac > 2-MeO(C₆H₄)CO~EtCO against MCF7, while EtCO >> MeOCO > Cbz > 4-MeO(C₆H₄)CH₂CO > Ac > 2-MeO(C₆H₄)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 against drug-resistant cell lines 1A9PTX10 and 1A9PTX22, with two 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 five 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 4 pancreatic cancer cell lines, MIA PaCa-2, CFPAC-1, BxPC-3 and PANC-1.

As Table 9 shows, new generation taxoids **19** and **14g** exhibit excellent cytotoxicity against four pancreatic cancer cell lines with sub-nanomolar to single-digit nanomolar IC₅₀ 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) than 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 nM 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 μ M 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. 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 mm³ on day 19, three intravenous injections of **19** (20 mg/kg $\times$ 3, 60 mg/kg total dose in Tween 80/EtOH/PBS) were made in three days interval, 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. Changes in absorbance in this spectrophotometric assay provide a direct measure of turbidity, hence indicate 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 Figure 1 and Figure 2). The microtubules formed with these new generation taxoids as well as paclitaxel were stable against Ca²⁺-induced depolymerization. As Figure 1 shows, taxoids **19** and **14g** promote rapid polymerization of tubulin at a faster rate than that of paclitaxel. The turbidity of the tubulin solution treated by **19** or **14g** reaches 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 ca. 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 slightly different protocol for tubulin preparation 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 Figure 3A and 3B 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 (Figure 3D and 3E). The microtubules 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 similar characteristics with 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 omega-3 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 3 days regimen (q3d×3, on day 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 (20mg/kg × 3), wherein complete regression of the DLD-1 tumor was achieved in five of five mice (tumor growth delay >150 days). Systemic toxicity profile shows that there was only 3–5% weight loss during the period of 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 due to drug's toxicity. Nevertheless, three animals survived till the end of the experiment on day 167 (tumor growth delay >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 **19** warrants further preclinical evaluation of this second-generation taxoid.

Experimental Section

General Methods

^1H 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 $\text{CH}_3\text{CN}/\text{water}$ (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 4A molecular sieves under reduced pressure. 4-(*N,N*-Dimethylamino)pyridine (DMAP) was used as received. 10-Deacetylbaecatin III (DAB, **1**) was obtained from Indena, SpA, Italy. 7-Triethylsilylbaecatin 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-deacetylbaecatin III (**7**),^{23,49} 7,10,13-tri(triethylsilyl)-2-debenzoyl-10-deacetylbaecatin III (**8**),^{49,50} 7-triethylsilyl-10-deacetyl-10-propanoylbaecatin,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 that 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-triethylsilylbaecatin 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 dry THF was added 1M 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 (hex:EtOAc = 6:1) to afford **4** (125 mg, 95% yield) as a white solid: ^1H (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, $J = 8.1$, 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 EtOH was added 1 mL $N_2H_4 \cdot H_2O$, and the mixture was allowed to stir for 1 h. The reaction was quenched with saturated aqueous NH_4Cl , and extracted 2 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: 1H (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 equivalents of DMAP, and 3 equivalents of triethylamine in CH_2Cl_2 , were added 3 equivalents 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 equivalents of DMAP, and 3 equivalents of the corresponding acid in CH_2Cl_2 , was added 3 equivalents 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, $CDCl_3$); 1H 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 $C_{49}H_{61}NO_{16}H^+$: 920.4069. Found: 920.4068 ($\Delta = 0.1$ 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% (2 steps), white solid; mp 140–143 °C; ^1H 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 $\text{C}_{48}\text{H}_{59}\text{NO}_{15}\cdot\text{H}^+$: 890.3963. Found: 890.3966 (Δ = -0.3 ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(3-methoxybenzoyl)docetaxel (6c)

87% (2 steps); white solid; mp 154–159 °C; $[\alpha]_{\text{D}}^{20}$ -75 (c 0.010, CDCl_3); ^1H 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 $\text{C}_{49}\text{H}_{61}\text{NO}_{16}\cdot\text{H}^+$: 920.4069. Found: 920.4068 (Δ = 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 nm and 254 nm) showed $\geq 95\%$ purity.

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(4-methoxybenzoyl)docetaxel (6d)

80%; white solid; mp 148–156 °C; $[\alpha]_{\text{D}}^{20}$ -45 (c 0.010, CDCl_3); ^1H 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 $\text{C}_{49}\text{H}_{61}\text{NO}_{16}\cdot\text{H}^+$: 920.4069. Found: 920.4068 (Δ = 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 nm and 254 nm) showed $\geq 95\%$ purity.

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(3,4-dimethoxybenzoyl)docetaxel (6e)

92% (for 2 steps); white solid; mp 159–165 °C; ^1H 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 (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 $\text{C}_{50}\text{H}_{63}\text{NO}_{17}\cdot\text{H}^+$: 950.4174. Found: 950.4174 (Δ = 0.0 ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(1-naphthoyl)docetaxel (6f)

90% (2 steps); white solid; mp 162–164 °C; ^1H 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 (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 $\text{C}_{52}\text{H}_{61}\text{NO}_{15}\cdot\text{H}^+$: 940.4128. Found: 940.4124 ($\Delta = 0.4$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(2-naphthoyl)docetaxel (6g)

92%; white solid; mp 165–170 °C; ^1H 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 $\text{C}_{52}\text{H}_{61}\text{NO}_{15}\cdot\text{H}^+$: 940.4128. Found: 940.4124 ($\Delta = 0.4$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-benzoyloxycarbonyl docetaxel (6h)

97%, white solid; mp 145–150 °C; ^1H 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 $\text{C}_{49}\text{H}_{61}\text{NO}_{16}\cdot\text{H}^+$: 920.4069. Found: 920.4068 ($\Delta = 0.1$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(2-methoxyphenylacetyl)docetaxel (6i)

80% (for 2 steps); white solid; mp 148–149 °C; ^1H 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 $\text{C}_{50}\text{H}_{63}\text{NO}_{16}\cdot\text{H}^+$: 934.4225. Found: 934.4229 ($\Delta = -0.4$ ppm). HPLC analysis using a Phenomenex Curosil-B column ($\text{CH}_3\text{CN}/\text{water}$ (2/3)) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ purity.

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(3-methoxyphenylacetyl)docetaxel (6j)

80% (for 2 steps); white solid; mp 145–150 °C; ^1H 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 $\text{C}_{50}\text{H}_{63}\text{NO}_{16}\cdot\text{H}^+$: 934.4225. Found: 934.4229 ($\Delta = -0.4$ ppm). HPLC analysis using a Phenomenex Curosil-B column ($\text{CH}_3\text{CN}/\text{water}$ (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ purity.

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-(4-methoxyphenylacetyl)docetaxel (6k)

60% (for 2 steps); white solid; mp 145–150 °C; ^1H 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 $\text{C}_{50}\text{H}_{63}\text{NO}_{16}\cdot\text{H}^+$: 934.4225. Found: 934.4229 ($\Delta = -0.4$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-hydrocinnamoyldocetaxel(6l)

85% (for 2 steps); white solid; mp 150–155 °C; ^1H 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), 3.7m (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 (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 $\text{C}_{50}\text{H}_{63}\text{NO}_{15}\cdot\text{H}^+$: 918.4276. Found: 918.4276 ($\Delta = 0.0$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-[3-(2-methoxyphenyl)propanoyl]docetaxel (6m)

97%; white solid; mp 155–159 °C; $[\alpha]_{\text{D}}^{20} -45$ (c 0.050, CDCl_3); ^1H 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 (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 $\text{C}_{51}\text{H}_{65}\text{NO}_{16}\cdot\text{H}^+$: 948.4382. Found: 948.4382 ($\Delta = 0.0$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-[3-(3-methoxyphenyl)propanoyl]docetaxel (6n)

80%; white solid; mp 159–164 °C; ^1H 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 (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 $\text{C}_{51}\text{H}_{65}\text{NO}_{16}\cdot\text{H}^+$: 948.4382. Found: 948.4382 ($\Delta = 0.0$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-10-[3-(4-methoxyphenyl)propanoyl]docetaxel (6o)

80%; white solid; mp 169–172 °C; ^1H 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 (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 $\text{C}_{51}\text{H}_{65}\text{NO}_{16}\cdot\text{H}^+$: 948.4382. Found: 948.4382 ($\Delta = 0.0$ 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-deacetyl-baccatin 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 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 $\times$ 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; ^1H 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 $\text{C}_{47}\text{H}_{77}\text{O}_{10}\text{SiF}_3\cdot\text{H}^+$: 905.4887. Found: 905.4869 ($\Delta = 2.0$ 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-deacetylbaecatin III (7-OH-**10c**) as a white solid (106 mg, 94%).

(b) To a solution of baecatin 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), brine (10 mL), dried over MgSO₄ 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-deacetylbaecatin III (**10c**) as a white solid (105 mg, 84% yield): mp 118–120 °C; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₃₅H₄₉O₁₀FSi-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 (0.016 L, 0.1844 mmol) was added dropwise and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added aqueous saturated NH₄Cl (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; [α]_D²⁰ −74 (c 0.39, CHCl₃); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₃₈H₅₃O₁₁FSi-H⁺: 733.3419. Found: 733.3418 (Δ = + 0.2 ppm).

Other 7-TES-2-(3-substituted-benzoyl)-10-acylbaecatin (**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)baecatin III (**11k**)

(a) To a solution of 104 mg (0.16 mmol) of 2-debenzoyl-2-(3-methoxybenzoyl)-7-triethylsilyl-10-deacetyl baecatin III (**10b**) in 2 mL of CH₂Cl₂ 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, 1 H), 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, 1 H), 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 $\text{C}_{44}\text{H}_{58}\text{O}_{13}\text{Si}\cdot\text{H}^+$: 823.3725. Found: 823.3723 ($\Delta = -0.2$ 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-methoxybenzoyl 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 3 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 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 3 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 (hex: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, 6H), 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 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 2 steps) as a white solid: White solid; mp 145–148 °C; $[\alpha]_D^{20} - 85$ (c 0.011, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1 H), 6.16 (t, *J* = 8.7 Hz, 1 H), 6.30 (s, 1 H), 7.37 (m, 2 H), 7.90 (m, 2 H); ¹³C (63 MHz, CDCl₃) 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 C₄₄H₅₉NO₁₅·Na⁺: 864.3782. Found: 864.3803 (Δ = - 2.4 ppm).

Other taxoids **14b–p**, **15c–e** and **15g** 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 2 steps); mp 142–144 °C; $[\alpha]_D^{25} - 72$ (c 0.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75.0 MHz, CDCl₃) 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 C₄₄H₅₉NO₁₆Na⁺: 880.3766, obtained: 880.3732 (Δ = -3.9 ppm). HPLC analysis using a Phenomenex Curosil-B column (CH₃CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm 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 2 steps); mp 137–139 °C; $[\alpha]_D^{20} - 78$ (c 0.45, CHCl₃); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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. ¹⁹F NMR (CDCl₃, using Freon as standard) δ -112.1. HRMS (FAB) *m/z* calcd for C₄₄H₅₈O₁₅FN·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 2 steps); mp 142–144 °C; $[\alpha]_D^{20} - 89$ (c 0.090, CHCl₃); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 ($\Delta = 0.0$ ppm).

2-Debenzoyl-2-(3-azidobenzoyl)-10-deacetyl-10-propanoyl-3'-dephenyl-3'-(2-methylprop-1-enyl)docetaxel (14e)

White solid; 71% (for 2 steps); mp 128–130 °C; $[\alpha]_D^{20} - 71$ (c 0.44, $CHCl_3$); 1H 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 ($\Delta = -1.1$ 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 nm and 254 nm) showed $\geq 95\%$ purity.

3'-Dephenyl-3'-(2-methylprop-1-enyl)-2-debenzoyl-2-(3-allylbenzoyl)-10-propanoyldocetaxel (14f)

White solid; 80% (for 2 steps), mp 118–120 °C; 1H 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 ($\Delta = -4.7$ 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 nm and 254 nm) showed $\geq 95\%$ purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-deacetyl-10-propanoyl-3'-dephenyl-3'-(2-methylprop-1-enyl)docetaxel (14g)

White solid; 69% (for 2 steps); mp 130–132 °C; $[\alpha]_D^{20} - 75$ (c 0.080, $CHCl_3$); 1H 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 ($\Delta = -0.4$ 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 nm and 254 nm) showed $\geq 95\%$ purity.

3'-Dephenyl-3'-(2-methylprop-1-enyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(cyclopropane-carbonyl)docetaxel (14h)

77% (for 2 steps); mp 144–146 °C; $[\alpha]_{\text{D}}^{25}$ –74 (c 0.92, CHCl₃); ¹H 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, 1H), 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); ¹³C NMR (75.0 MHz, CDCl₃) 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 C₄₆H₆₁NO₁₆Na⁺: 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 2 steps); mp 132–138 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.15 (s, 3H), 1.25 (m, 12H), 1.68 (m, 6H), 1.89 (m, 1H), 1.93 (s, 3H), 2.17 (s, 3H), 2.35 (s, 3H), 2.57 (m, 1H), 3.78 (d, *J* = 6.9 Hz, 1H), 3.87 (bs, 7H), 4.20 (m, 2H), 4.36 (m, 2H), 4.73 (m, 2H), 4.95 (d, *J* = 7.8 Hz, 1H), 5.31 (d, *J* = 7.0, 1H), 5.65 (d, *J* = 6.9 Hz, 1H), 6.17 (m, 2H), 7.12 (dd, *J* = 7.8 Hz, 2.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 7.68 (d, *J* = 4.5 Hz, 1H), 8.01 (s, 1H); ¹³C NMR (63 MHz, CDCl₃) 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 C₅₁H₆₅NO₁₇·H⁺: 964.4331. Found: 964.4366 (Δ = 3.7 ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(benzyloxy-carbonyl)docetaxel (14j)

White solid; 70% (for 2 steps); mp 145–150 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.15 (s, 3H), 1.25 (m, 12H), 1.69 (m, 6H), 1.89 (m, 1H), 1.95 (s, 3H), 2.16 (s, 3H), 2.35 (s, 3H), 2.56 (m, 1H), 3.36 (d, *J* = 6.9 Hz, 1H), 3.78 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 4.19 (m, 2H), 4.33 (d, *J* = 8.7 Hz, 1H), 4.40 (m, 1H), 4.72 (m, 2H), 4.95 (d, *J* = 7.5 Hz, 1H), 5.23 (s, 2H), 5.31 (d, *J* = 7.8 Hz, 1H), 5.65 (d, *J* = 7.2 Hz, 1H), 6.14 (m, 2H), 7.12 (dd, *J* = 7.2 Hz, 1.8 Hz, 1H), 7.34 (m, 6H), 7.63 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H). HRMS (FAB) *m/z* calcd for C₅₀H₆₃NO₁₇·H⁺: 950.4174. Found: 950.4164 (Δ = –1.1 ppm). HPLC analysis using a Phenomenex Curosil-B column (CH₃CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm 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 2 steps); mp 143–145 °C; ¹H NMR (300 MHz, CDCl₃) δ 1.28 (s, 3H), 1.31 (s, 3H), 1.34 (s, 9H), 1.60 (m, 1H), 1.71 (s, 3H), 1.75 (s, 3H), 1.77 (s, 3H), 1.91 (m, 1H), 1.96 (s, 3H), 2.37 (s, 3H), 2.59 (m, 2H), 3.35 (bs, 1H), 3.88 (s, 3H), 3.91 (s, 3H), 4.22 (m, 2H), 4.35 (d, *J* = 8.4 Hz, 1H), 4.51 (m, 1H), 4.76 (m, 2H), 4.98 (d, *J* = 8.1 Hz, 1H), 5.32 (m, 1H), 5.71 (d, *J* = 6.9 Hz, 1H), 6.21 (m, 1H), 6.57 (s, 1H), 6.99 (m, 2H), 7.13 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.50 (m, 1H), 7.65 (s, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.99 (dd, *J* = 7.8 Hz, 2.1 Hz, 1H); ¹³C NMR (63 MHz, CDCl₃) 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 ($\Delta = -2.7$ ppm).

3'-Dephenyl-3'-(2-methyl-1-propenyl)-2-debenzoyl-2-(3-methoxybenzoyl)-10-(4-methoxyphenylacetyl)docetaxel (141)

White solid; 70% (for 2 steps); mp 152–154 °C; 1H 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 ($\Delta = 3.7$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-(prop-2-enyl)docetaxel (14m)

White solid; 65% (for 2 steps); mp 127–130 °C; $[\alpha]_D^{20} -64$ (c 0.25, $CHCl_3$); 1H 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 ($\Delta = -3.7$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-[(E)-prop-1-enyl]docetaxel (14n)

White solid; 80% (for 2 steps); mp 120–122 °C; $[\alpha]_D^{20} -100$ (c 0.010, $CHCl_3$). 1H 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 ($\Delta = -3.7$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-(but-3-enyl)docetaxel (14o)

White solid; 71% (for 2 steps); mp 116–117 °C; $[\alpha]_D^{20} -37$ (c 0.30, $CHCl_3$); 1H 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 $\text{C}_{45}\text{H}_{61}\text{NO}_{16}\cdot\text{Na}^+$: 894.3870. Found: 894.3904 ($\Delta = -3.1$ ppm).

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-[(S)-2,2-dimethylcyclopropyl]docetaxel (14p)

White solid; 83% (for 2 steps); ^1H NMR (CDCl_3) δ 0.098 (t, $J = 4.6$ Hz, 1H), 0.62 (dd, $J = 8.5, 4.3$ Hz, 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 $\text{C}_{46}\text{H}_{63}\text{NO}_{16}\cdot\text{H}^+$: 886.4225. Found: 886.4237 ($\Delta = -1.3$ ppm).

2-Debenzoyl-2-(3-fluorobenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropyl)docetaxel (15c)

White solid; 89% for 2 steps; mp 138–140 °C; $[\alpha]_{\text{D}}^{20} -79$ (c 0.47, CHCl_3); ^1H 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) $\delta -112.1$. HRMS (FAB) m/z calcd for $\text{C}_{44}\text{H}_{60}\text{O}_{15}\text{FN}\cdot\text{H}^+$: 862.4025. Found: 862.4022 ($\Delta = +0.4$ ppm).

2-Debenzoyl-2-(3-chlorobenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropyl)docetaxel (15d)

White solid; 80% (for 2 steps); mp 143–145 °C; $[\alpha]_{\text{D}}^{20} -83$ (c 0.12, CHCl_3); ^1H 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 $\text{C}_{44}\text{H}_{60}\text{O}_{15}\text{NCl}\cdot\text{H}^+$: 878.3730. Found: 878.3728 ($\Delta = 0.2$ ppm).

2-Debenzoyl-2-(3-azidobenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropyl)docetaxel (15e)

White solid; 70% (for 2 steps); mp 132–134 °C; $[\alpha]_{\text{D}}^{20} -70$ (c 0.47, CHCl_3); ^1H 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 $\text{C}_{44}\text{H}_{60}\text{N}_4\text{O}_{15}\cdot\text{H}^+$: 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 2 steps); mp 132–134 °C; $[\alpha]_{\text{D}}^{20} -110$ (c 0.070, CHCl_3); ^1H 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 $\text{C}_{45}\text{H}_{63}\text{O}_{16}\text{N}\cdot\text{H}^+$: 874.4225. Found: 874.4224 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column ($\text{CH}_3\text{CN}/\text{water}$ (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ 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 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 **15g** (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-one²⁰ (129 mg, 0.435 mmol) and DMAP (53 mg, 0.435 mmol) 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 $\times$ 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; ^1H 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 (^1H 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-propanoylbaccatin¹⁷ 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 2 steps as white solid: mp 149–151 °C [α]_D²⁰ –72.6 (c 2.91, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1 H), 5.35 (d, *J* = 8.7 Hz, 1 H), 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); ¹³C NMR (63 MHz, CDCl₃) 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 C₄₄H₅₇NO₁₄·H⁺: 824.3857. Found: 824.3855 (Δ = 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*-(cyclopentane-carbonyl)docetaxel (17b)

White solid; 78% (for 2 steps); mp 150–152 °C; [α]_D²⁰ –75.7 (c 3.75, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (63 MHz, CDCl₃) 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 C₄₅H₅₉NO₁₄·H⁺: 838.4014. Found: 838.4011 (Δ = 0.3 ppm).

10-Propanoyl-3'-dephenyl-3'-(2-methylprop-1-enyl)-3'-*N*-(cyclohexanecarbonyl)docetaxel (17c)

White solid; 85% (for 2 steps); mp 152–155 °C; [α]_D²⁰ –78.3 (c 3.78, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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 C₄₆H₆₁NO₁₄·H⁺: 852.4170. Found: 852.4172 (Δ = –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 2 steps); mp 148–151 °C [α]_D²⁰ –70.3 (c 1.45, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1 H), 4.31 (m, 2 H), 4.42 (m, 1 H), 4.96 (d, *J* = 4.8 Hz, 1 H), 5.10 (m, 1 H), 5.38 (d, *J* = 9.0 Hz, 1 H), 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); ¹³C NMR (63 MHz, CDCl₃) 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 C₄₅H₅₇NO₁₄·H⁺: 836.3857. Found: 836.3858 (Δ = –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 2 steps); mp 151–154 °C; $[\alpha]_D^{20}$ –67 (c 2.92, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1 H), 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); ¹³C NMR (63 MHz, CDCl₃) 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 C₄₆H₅₉NO₁₄·H⁺: 850.4014. Found: 850.4018 (Δ = –0.5 ppm).

10-Propanoyl-3'-dephenyl-3'-(2-methylprop-1-enyl)-3'-N-debenzoyl-3'-N-(cyclopentylloxycarbonyl)docetaxel (17f)

White solid; 85% (for 2 steps); mp 141–143 °C $[\alpha]_D^{20}$ –74 (c 5.06, CHCl₃); ¹H NMR (300MHz,CDCl₃) δ 1.08(s,3H), 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); ¹³C NMR (63 MHz, CDCl₃) 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 C₄₅H₅₉NO₁₅·H⁺: 854.3963. Found: 854.3960 (Δ = + 0.3 ppm).

10-Propanoyl-3'-dephenyl-3'-(2-methylprop-1-enyl)-3'-N-debenzoyl-3'-N-(cyclohexylloxycarbonyl)docetaxel (17g)

White solid; 80% (for 2 steps); mp 142–144 °C $[\alpha]_D^{20}$ –66.5 (c 5.00, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (63 MHz, CDCl₃) 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 C₄₆H₆₁NO₁₅·H⁺: 868.4120. Found: 868.4120 (Δ = –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 2 steps); mp 141–143 °C; $[\alpha]_D^{20}$ –66.6 (c 11.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 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, 1H), 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* = 2.4Hz, 1 H), 7.3 (t, *J* = 7.8m 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 C₄₄H₅₇NO₁₅·H⁺: 840.3806. Found: 840.3802 (Δ = –0.5 ppm). HPLC

analysis using a Phenomenex Curosil-B column (CH₃CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropen-1-yl)-3'-N-dt-tert-butoxycarbony-3'-N-(cyclobutanecarbonyl)docetaxel (17i)

White solid; 61% (for 2 steps); mp 143–145 °C; $[\alpha]_D^{20} -70.4$ (c 13.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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 C₄₅H₅₉O₁₅N·H⁺: 854.3962. Found: 854.3962 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column (CH₃CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropen-1-yl)-3'-N-de-tert-butoxycarbony-3'-N-(cyclopentanecarbonyl)docetaxel (17j)

White solid; 77% (for 2 steps); mp 136–138 °C; $[\alpha]_D^{20} -74.5$ (c 14.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1H), 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, $J = 7.5$ m Hz, 2 H) 7.63 (s, 1 H), 7.69 (d, $J = 7.5$ Hz, 1 H). HRMS m/e calcd for C₄₆H₆₁O₁₅N·H⁺: 868.4119. Found: 868.4122 ($\Delta = -0.3$ ppm). HPLC analysis using a Phenomenex Curosil-B column (CH₃CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropen-1-yl)-3'-N-de-tert-butoxycarbony-3'-N-(cyclohexanecarbonyl)docetaxel (17k)

White solid; 81% (for 2 steps); mp 151–153 °C; $[\alpha]_D^{20} -73.4$ (c 14.3, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1H), 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 C₄₇H₆₃O₁₅N·H⁺: 882.4276. Found: 882.4275 ($\Delta = 0.1$ ppm). HPLC analysis using a Phenomenex Curosil-B column (CH₃CN/water (2/3) as the solvent system with a flow rate of 1 mL/min; UV 230 nm and 254 nm) showed $\geq 95\%$ purity.

2-Debenzoyl-2-(3-methoxybenzoyl)-10-propanoyl-3'-dephenyl-3'-(2-methylpropen-1-yl)-3'-N-de-tert-butoxycarbony-3'-N-(cyclohexyloxycarbonyl)docetaxel (17l)

White solid; 77% (for 2 steps); mp 141–143 °C; $[\alpha]_D^{20} -68$ (c 10.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 2H), 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 nm and 254 nm) showed $\geq 95\%$ 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 was 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; $[\alpha]_D^{20} -114$ (c 3.70, $CHCl_3$); 1H 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; $[\alpha]_D^{20} -74$ (c 4.21, $CHCl_3$); 1H 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, 1H), 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 nm and 254 nm) showed $\geq 95\%$ purity.

10-Propanoyl-3'-dephenyl-3'-(2-methylpropyl)-3'*N*-debenzoyl-3'*N*-cyclopentylloxycarbonyldocetaxel (**18f**)

White solid; 100%; mp 131–133 °C; $[\alpha]_D^{20} -67$ (c 0.42, $CHCl_3$); 1H 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, 1H), 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; $[\alpha]_D^{20}$ –60 (c 1.28, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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, 1H), 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); ¹³C NMR (63 MHz, CDCl₃) –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 C₄₆H₆₃NO₁₅·H⁺: 870.4273. Found: 870.4276 (Δ = + 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; $[\alpha]_D^{20}$ –74.5 (c 14.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₄₄H₅₉O₁₅·N·H⁺: 842.3963. Found: 842.3941 (Δ = –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; $[\alpha]_D^{20}$ –85 (c 14.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₄₇H₆₅NO₁₅·H⁺: 884.4432. Found: 884.4413 (Δ = –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 3 steps from **11**); mp 143–145 °C; $[\alpha]_D^{20}$ –70 (c 13.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 $C_{46}H_{63}O_{16}N \cdot H^+$: 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 400–2,000 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 incubation, 100 μ L 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 μ L 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 IC₅₀ 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, Virginia). 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 media was changed the following morning and replaced with media containing taxane derivatives or vehicle control. Taxoids were dissolved in DMSO to 10 mM concentration and were further diluted in appropriate media prior to addition to cells. Each dose of drug or vehicle was tested in triplicate, and the experiment is representative of at least 3 independent trials. After 72 hours of treatment the media was aspirated and the cells were washed in warm PBS. MTT reagent (Sigma) was diluted in RPMI-1640 media without phenol red (Invitrogen), and added to the cells at a concentration of 0.5 mg/mL. After 3 hours of incubation, the reagent was aspirated, the plate was washed with PBS and MTT formazan crystals were dissolved in 500 μ L acidified isopropanol (0.1N hydrochloric acid). Subsequently, 100 μ L of the solution was transferred to a microtiter plate. Absorbance at 570 nm was measured on a thermomax plate reader (Molecular Devices). The IC₅₀ 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) was 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 1mg/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 Figure 1 and Figure 22. Microtubule assembly was carried out with 10 μ M taxoid (**19**, **4g** or **14i**). Paclitaxel (10 μ M) 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 3, tubulin stored in liquid nitrogen was centrifuged just before use and protein concentration adjusted to 1 mg/mL, while the experiments in Figure 4 used tubulin stored in liquid nitrogen as it was at 1 mg/mL concentration.

Electron microscopy

Aliquots (50 μ L) were taken from *in vitro* polymerization assays at the end of the reaction and placed onto 300-mesh carbon-coated, formavar-treated copper grids. Samples were then

stained with 20 μ L 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 six to eight weeks were obtained from the National Cancer Institute (Frederick, Maryland), 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 pgg, were 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 mm³ size), 5 days after implantation and continued either every three 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 i.v. 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 mm³, was calculated using the formula: $v = 0.4(l \times w^2)$. The time in days to the pre-determined target tumor volume of 600 mm³ 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 pre-set 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 six to eight weeks obtained from Taconic Farms (Hudson, New York). The human pancreatic cancer cell line CFPAC-1, which expresses high levels of *mdrl*, was used for the experiments. CFPAC-1 cancer cells (1×10^6) were resuspended in 200 μ L 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 mm³ 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 appropriate concentration of each drug could be injected in a final volume of 0.2 mL. The taxoid was administered i.v. using tail vein injection three times at 3 day intervals on day 19, 22 and 25 (20 mg/kg $\times$ 3; total dose 60 mg/kg). The tumor size was measured and the volume calculated in the same manner as that described above.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

DAB, 10-deacetylbaicatin III
IC₅₀, half maximal inhibitory concentration
LiHMDS, lithium hexamethyldisilazide
NMO, *N*-methyldimorpholine-*N*-oxide
PBS, phosphate buffered saline
PDA, photodiode-array
Pgp, P-glycoprotein
R/S, resistance factor (the ratio of the IC₅₀ value against the drug-resistant cell line vs. 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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Figure 1.
Tubulin polymerization with **19**, **14g** and paclitaxel: microtubule protein 1 mg/mL, 37 °C, GTP 1 μ M, Drug 10 μ M

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

Figure 3.
Electromicrographs of microtubules (20,000 $\times$): (A) GTP; (B) paclitaxel; (C) **19**; (D) **14g**; (E) **14i**; (F) discodermolide

Scheme 1.

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.

Reagents and conditions: (i) (a) RCl, TEA, DMAP, CH₂Cl₂ or (b) ROH, DIC, DMAP, CH₂Cl₂ or (c) RCl, LiHMDS, THF, -20 °C (75–98%); (ii) HF/pyridine, pyridine/MeCN (80–97%).

Scheme 3.

Reagents and conditions: (i) TESCl, imidazole, DMF, RT, 96% (ii) sodium bis(2-methoxyethoxy)aluminumhydride, THF, $-10\text{ }^{\circ}\text{C}$, 97% (iii) DIC, DMAP, CH_2Cl_2 , 85–90% (iv) HF/pyridine, pyridine/MeCN; (v) TESCl, imidazole, DMF, RT, 2h; (vi) LiHMDS, R^2COCl , THF.

Scheme 4.

Reagents and conditions: (i) TPAP, NMO, 4Å mol. Sieves, CH₂Cl₂, 25 °C, 99% (ii) 2-MeO-BzCl, DMAP, TEA, CH₂Cl₂, 100% (iii) NaBH₄, MeOH/THF, 80% at 50% conversion.

Scheme 5.

Reagents and conditions: (i) **3a-f** (1.2~1.5 equiv), LiHMDS, THF, $-40\text{ }^\circ\text{C}$, 30 min; (ii) HF/pyridine, pyridine/MeCN, $0\text{ }^\circ\text{C}$ — RT, 18h; (iii) $\text{H}_2/\text{Pd-C}$, EtOAc/MeOH, RT, 24h.

Scheme 6.

Reagents and conditions: (i) LiHMDS, THF, -40 °C, 30 min; (ii) HF/pyridine, pyridine/MeCN, 0 °C — RT, 18 h (61–86% for two steps); (iii) H₂, Pd/C, EtOAc, RT, 24 h (90–92%).

Table 1Synthesis of Taxoids **6**

Taxoid	R	Yield (%) (for 2 steps)
6a	Bz	90
6b	2-MeO(C ₆ H ₄)CO	90
6c	3-MeO(C ₆ H ₄)CO	87
6d	4-MeO(C ₆ H ₄)CO	80
6e	3,4-(MeO) ₂ (C ₆ H ₃)CO	92
6f	1-naphthoyl	90
6g	2-naphthoyl	92
6h	Cbz	97
6i	2-MeO(C ₆ H ₄)CH ₂ CO	80
6j	3-MeO(C ₆ H ₄)CH ₂ CO	80
6k	4-MeO(C ₆ H ₄)CH ₂ CO	60
6l	(C ₆ H ₅)(CH ₂) ₂ CO	85
6m	2-MeO(C ₆ H ₄)(CH ₂) ₂ CO	97
6n	3-MeO(C ₆ H ₄)(CH ₂) ₂ CO	80
6o	4-MeO(C ₆ H ₄)(CH ₂) ₂ CO	80

Table 22,10-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	<i>c</i> -PrCO	84
11i	MeO	MeOCO	92
11j	MeO	PhCH ₂ OCO	94
11k	MeO	2-MeO(C ₆ H ₄)CO	80
11l	MeO	4-MeO(C ₆ H ₄)CH ₂ CO	98

Table 3Second- and third-generation taxoids **14** and **15**.

Taxoid	R ¹	R ²	R ³	Yield (%) (for two steps)
14a	Me	MeCO	Me ₂ C=CH-	80
14b	MeO	MeCO	Me ₂ C=CH-	72
14c	F	EtCO	Me ₂ C=CH-	84
14d	Cl	EtCO	Me ₂ C=CH-	70
14e	N ₃	EtCO	Me ₂ C=CH-	71
14f	CH ₂ C=CH-	EtCO	Me ₂ C=CH-	80
14g	MeO	EtCO	Me ₂ C=CH-	69
14h	MeO	<i>c</i> -PrCO	Me ₂ C=CH-	77
14i	MeO	MeOCO	Me ₂ C=CH-	80
14j	MeO	PhCH ₂ OCO	Me ₂ C=CH-	70
14k	MeO	2-MeO(C ₆ H ₄)CO	Me ₂ C=CH-	95
14l	MeO	4-MeO(C ₆ H ₄)CH ₂ CO	Me ₂ C=CH-	70
14m	MeO	EtCO	CH ₂ =CHCH ₂ -	65
14n	MeO	EtCO	(<i>E</i>)-CH ₃ CH=CH-	80
14o	MeO	EtCO	CH ₂ =CH(CH ₂) ₂ -	71
14p	MeO	EtCO	(<i>S</i>)-2,2-Me ₂ - <i>c</i> -Pr-	83
15c	F	EtCO	Me ₂ CHCH ₂ -	89
15d	Cl	EtCO	Me ₂ CHCH ₂ -	80
15e	N ₃	EtCO	Me ₂ CHCH ₂ -	70
15g	MeO	EtCO	Me ₂ CHCH ₂ -	73

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

^aYield for 2 steps unless otherwise noted.

^bYield for hydrogenation.

^cYield for 3 steps.

Table 5Cytotoxicity of second-generation taxoids with modifications at C10 (IC_{50} nM)^a

Taxoid	R	LCC6
Paclitaxel	--	3.
6a	Bz	1.
6b		2.
6c		2.
6d		3.

Taxoid

R

LCC6

6e

6f

6g

6h

Cbz

Taxoid

R

LCC6

6i

2.

6j

2.

6k

1.

Taxoid

R

LCC6

61

5.

Taxoid

R

LCC6

6m

Taxoid

R

LCC6

6n

3.

6o

1.

^aConcentration of compound which inhibits 50% (IC₅₀, nM) of the growth of human tumor cell line after 72 h drug exposure.

^bLCC6-WT: human breast carcinoma cell line (Pgp⁻).

^cLCC6-MDR: *mdrl* transduced cell line (Pgp⁺).

^dResistance factor = (IC₅₀ for drug resistant cell line, R)/(IC₅₀ for drug-sensitive cell line, S).

Table 6
Cytotoxicity of second-generation taxoids with C3'N modifications (IC₅₀ 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	<i>t</i> -Boc	2-Me-prop-1-enyl	--	--	--	0.18	4.0	22
6'x	<i>t</i> -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

^aSee the footnotes of Table 1

^bSee the footnote of Table 1

^cSee the footnote of Table 1.

^dSee the footnote of Table 1.

^eMCF7: human breast carcinoma cell line.

^fNCI/ADR: multi-drug resistant human ovarian carcinoma cell line.

Table 7
Cytotoxicity of second-generation taxoids with C2-*meta* modifications (IC₅₀ 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	176
Docetaxel	<i>t</i> -BuO	Ph	H	H	1.0	120	120	1.0	235	235
6x	<i>t</i> -BuO	Me ₂ C=CH-	EtCO	H	--	--	--	0.18	4.0	22
6'x	<i>t</i> -BuO	Me ₂ CHCH ₂ -	EtCO	H	--	--	--	0.35	5.1	21
19	<i>t</i> -BuO	Me ₂ C=CH-	<i>c</i> -PrCO	H	--	--	--	0.20	3.9	20
14a	<i>t</i> -BuO	Me ₂ C=CH-	MeCO	Me	1.5	5.8	3.9	0.8	5.0	6.3
14b	<i>t</i> -BuO	Me ₂ C=CH-	MeCO	MeO	0.6	2.7	4.5	0.8	2.3	2.9
14c	<i>t</i> -BuO	Me ₂ C=CH-	EtCO	F	0.5	2.1	4.2	--	--	--
14d	<i>t</i> -BuO	Me ₂ C=CH-	EtCO	Cl	0.8	1.3	1.6	--	--	--
14e	<i>t</i> -BuO	Me ₂ C=CH-	EtCO	N ₃	0.9	1.2	1.3	0.9	1.1	1.2
14f	<i>t</i> -BuO	Me ₂ C=CH-	EtCO	CH ₂ =CH-	2.9	7.1	2.4	--	--	--
14g	<i>t</i> -BuO	Me ₂ C=CH-	EtCO	MeO	1.0	0.9	0.90	0.36	0.33	0.92
14h	<i>t</i> -BuO	Me ₂ C=CH-	<i>c</i> -PrCO	MeO	1.0	2.9	2.9	--	--	--
14i	<i>t</i> -BuO	Me ₂ C=CH-	MeOCO	MeO	0.6	1.6	2.7	0.4	1.4	3.5
14j	<i>t</i> -BuO	Me ₂ C=CH-	PhCH ₂ OCO	MeO	1.2	1.8	1.5	0.2	1.5	7.5
14k	<i>t</i> -BuO	Me ₂ C=CH-	2-MeO(C ₆ H ₄)CO	MeO	0.4	0.9	2.3	1.1	3.3	3.0
14l	<i>t</i> -BuO	Me ₂ C=CH-	4-MeO(C ₆ H ₄)CH ₂ CO	MeO	0.4	0.4	1.0	0.6	1.8	3.0

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
14m	<i>t</i> -BuO	CH ₂ =CHCH ₂ -	EtCO	MeO	1.2	8.4	7.0	0.8	8.7	10.9
14n	<i>t</i> -BuO	(<i>E</i>)-CH ₃ CH=CH-	EtCO	MeO	1.2	4.1	3.4	--	--	--
14o	<i>t</i> -BuO	CH ₂ =CH(CH ₂) ₂ -	EtCO	MeO	0.9	5.4	6.0	2.0	7.7	3.9
14p	<i>t</i> -BuO	(<i>S</i>)-2,2-Me ₂ - <i>c</i> -Pr-	EtCO	MeO	0.48	1.1	2.3	0.6	1.5	2.5
15c	<i>t</i> -BuO	Me ₂ CHCH ₂ -	EtCO	F	0.4	2.4	6.0	--	--	--
15d	<i>t</i> -BuO	Me ₂ CHCH ₂ -	EtCO	Cl	0.8	2.9	3.6	--	--	--
15e	<i>t</i> -BuO	Me ₂ CHCH ₂ -	EtCO	N ³	1.1	2.4	2.2	1.0	2.1	2.1
15g	<i>t</i> -BuO	Me ₂ CHCH ₂ -	EtCO	MeO	0.9	0.8	0.89	0.36	0.43	1.19
17h	<i>c</i> -Pr	Me ₂ C=CH-	EtCO	MeO	1.1	17.2	16	0.5	7.8	15.6
17i	<i>c</i> -Bu	Me ₂ C=CH-	EtCO	MeO	1.6	15	9.4	0.8	8.8	11
17j	<i>c</i> -Pentyl	Me ₂ C=CH-	EtCO	MeO	1.1	11	10	0.3	9.5	32
17k	<i>c</i> -Hexyl	Me ₂ C=CH-	EtCO	MeO	6.9	42	6.1	1.8	17.5	9.7
17l	<i>c</i> -Hex-O	Me ₂ C=CH-	EtCO	MeO	1.23	14.8	12.0	1.44	14	9.7
18h	<i>c</i> -Pr	Me ₂ CHCH ₂ -	EtCO	MeO	0.6	13	22	0.4	11.8	30
18k	<i>c</i> -Hexyl	Me ₂ CHCH ₂ -	EtCO	MeO	1.0	12	12	0.7	6.5	9.3
18m	<i>c</i> -Pent-O	Me ₂ CHCH ₂ -	EtCO	MeO	0.76	2.6	3.4	0.17	1.18	6.9

^a See the footnote of Table 1.

^b See the footnote of Table 1.

^d See the footnote of Table 1.

^e See the footnote of Table 2.

^f See the footnote of Table 2.

Table 8
Cytotoxicity of new generation taxoids against 1A9PTX10 and 1A9PTX22 cell lines (IC₅₀ nM)^a

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 See the footnote of Table 1.

^b See the footnote of Table 1.

Table 9Cytotoxicity of **19** and **14g** against pancreatic cancer cell lines (IC₅₀ 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

^aSee the footnote of Table 1.

Table 10Antitumor effect of taxoid **19** delivered i.v. to SCID mice bearing a Pgp+ human colon tumor xenograft, DLD-1

Treatment ^a (i.v.)	Total Dose (mg/kg)	Growth Delay (days)	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

^aTreatment given IV to SCID mice on day 5 after DLD-1 human colon tumor implant, and continued as noted all drugs formulated in Tween:EtOH^bBased on comparison of each group vs. control using the Cox-Mantel Test^cNumber of animals who either died or lost greater than 20% body weight.^dSCID mice with no palpable tumor on day 167, end of experiment.