# Syntheses and Structure−Activity Relationships of the Second-Generation Antitumor Taxoids: Exceptional Activity against Drug-Resistant Cancer Cells

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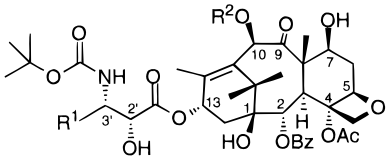
A series of new 3′-(2-methyl-1-propenyl) and 3′-(2-methylpropyl) taxoids with modifications at C-10 was synthesized by means of the *β*-lactam synthon method using 10-modified 7-(triethylsilyl)-10-deacetylbaccatin III derivatives. The new taxoids thus synthesized show excellent cytotoxicity against human ovarian (A121), non-small-cell lung (A549), colon (HT-29), and breast (MCF-7) cancer cell lines. All but one of these new taxoids possess better activity than paclitaxel and docetaxel in the same assay, i.e., the $IC_{50}$ values of almost all the taxoids are in the subnanomolar level. It is found that a variety of modifications at C-10 is tolerated for the activity against normal cancer cell lines, but the activity against a drug-resistant human breast cancer cell line expressing MDR phenotype (MCF7-R) is highly dependent on the structure of the C-10 modifier. A number of the new taxoids exhibit remarkable activity ($IC_{50}$ = 2.1−9.1 nM) against MCF7-R. Among these, three new taxoids, SB-T-1213 (**4a**), SB-T-1214 (**4b**), and SB-T-1102 (**5a**), are found to be exceptionally potent, possessing 2 orders of magnitude better activity than paclitaxel and docetaxel. The observed exceptional activity of these taxoids may well be ascribed to an effective inhibition of P-glycoprotein binding by the modified C-10 moieties. The new taxoid SB-T-1213 (**4a**) shows an excellent activity (T/C = 0% at 12.4 and 7.7 mg/kg/dose, $\log_{10}$ cell kill = 2.3 and 2.0, respectively) against B16 melanoma in $B6D2F_1$ mice via intravenous administration.

## Introduction

Taxol (paclitaxel), a structurally complex diterpenoid,[1] and its semisynthetic analog Taxotère (docetaxel)[2] are currently considered to be the most promising leads in the fight against cancer.[3−7] Both paclitaxel and docetaxel, through their unique antimitotic mechanism of action,[8−10] exhibit significant antitumor activity against various cancers which have not been effectively treated by existing chemotherapeutic drugs.[11,12] Paclitaxel was approved by the FDA for the treatment of advanced ovarian cancer in December 1992 and for the treatment of breast cancer in April 1994. It is also undergoing clinical trials for other cancers. Docetaxel was approved by the FDA for the treatment of breast cancer in May 1996 and is currently undergoing phase II and III clinical trials for breast and lung cancers worldwide.[3,12] Although both paclitaxel and docetaxel possess potent antitumor activity, recent reports have shown that treatment with these drugs often results in a number of undesired side effects as well as multidrug resistance (MDR).[12,13] Therefore, it has become essential to develop new anticancer agents with fewer side effects, superior pharmacological properties, and improved activity against various classes of tumors.

The limited availability of these two drugs, as well as the pursuit for improved analogs, has made them the focus of many synthetic investigations and extensive structure−activity relationship (SAR) studies.[3,14,15] In the course of our SAR study of paclitaxel and docetaxel analogs,[16−21] we have established that the 3′-phenyl group is not an essential component for the potent cytotoxicity and antitumor activity expressed by this class of compounds.[17] We have also reported a series of analogs possessing either a 3′-alkenyl or 3′-alkyl moiety in place of the 3′-phenyl group such as SB-T-1101, -1102, -1211, -1212, and -1302, which possess substantially better cytotoxicity than the parent compounds, especially against a drug-resistant human breast cancer cell line.[18] Two taxoids (SB-T-1101 and SB-T-1211) were shown to possess highly potent *in vivo* antitumor activity equivalent to docetaxel against B16 melanoma in B6D2F1 mice.[18]



**SB-T-1101:** $R^1 = (CH_3)_2CH\text{-}CH_2$; $R^2 = H$
**SB-T-1102:** $R^1 = (CH_3)_2CH\text{-}CH_2$; $R^2 = CH_3CO$
**SB-T-1211:** $R^1 = (CH_3)_2C{=}CH$; $R^2 = H$
**SB-T-1212:** $R^1 = (CH_3)_2C{=}CH$; $R^2 = CH_3CO$
**SB-T-1302:** $R^1 = (E)\text{-}CH_3C{=}CH$; $R^2 = CH_3CO$

In the SAR study of a series of 3′-alkyl and 3′-alkenyl taxoids shown above and others, we recognized that 10-acetyl (R = Ac) analogs exhibited 2−3 times better cytotoxicity than 10-unmodified analogs (R = H) against the doxorubicin-resistant human breast cancer cell line

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**Table 1.** C-10 Modification of 7-TES-DAB

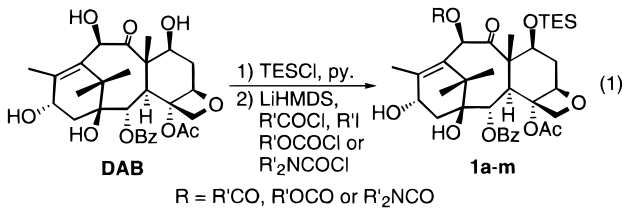
| baccatin | R | yield (%)[a] |
|---|---|---|
| **1a** | $CH_3CH_2$-CO | 72 |
| **1b** | cyclopropane-CO | 91 |
| **1c** | $(CH_3)_2N$-CO | 92 |
| **1d** | $CH_3O$-CO | 90 |
| **1e** | $CH_3$ | 81 |
| **1f** | $CH_3(CH_2)_3$-CO | 83 |
| **1g** | $CH_3(CH_2)_4$-CO | 67 (89) |
| **1h** | $(CH_3)_2CHCH_2$-CO | 63 (79) |
| **1i** | $(CH_3)_3CCH_2$-CO | 87 |
| **1j** | cyclohexane-CO | 78 |
| **1k** | (*E*)-$CH_3CH$=CH-CO | 30 |
| **1l** | $(CH_3CH_2)_2N$-CO | 60 (91) |
| **1m** | morpholine-4-CO | 92 |
| **1n** | $CH_3NH$-CO | 52 |
| **1o** | $CH_3CH_2NH$-CO | 68 |
| **1p** | $CH_3CH_2CH_2NH$-CO | 30 |
| **1q** | $(CH_3)_2CHNH$-CO | 60 |
| **1r** | $CH_2$=$CHCH_2NH$-CO | 50 |
| **1s** | cyclohexyl-NH-CO | 80 |

[a] Isolated yield. The value in parentheses indicates the conversion yield.

MCF-7R (*vide infra*). This observation prompted us to examine the effects of C-10 modification on the cytotoxicity of the 3′-alkyl and 3′-alkenyl taxoids and led us to discover a new series of exceptionally potent taxoids, *the second-generation taxoids*, that possess 2 orders of magnitude higher potency than paclitaxel and docetaxel against the drug-resistant human breast cancer cells MCF7-R. These results are very unexpected since the previous SAR studies on the C-10-modified paclitaxel and taxoids concluded that the modification at C-10 brought about little effects on their cytotoxicity.[14,22] Thus, we would like to describe here the syntheses and SAR study of the second-generation taxoids, i.e., 10-modified 3′-(2-methyl-1-propenyl) and 3′-(2-methylpropyl) taxoids.

## Syntheses of New Taxoids

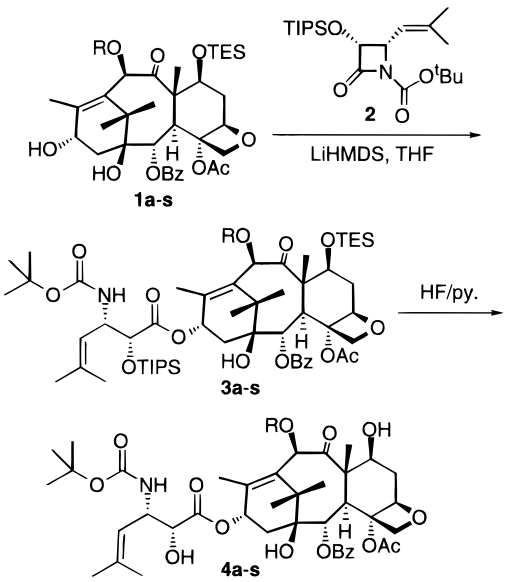
A series of new 3′-(2-methyl-1-propenyl) and 3′-(2-methylpropyl) taxoids with modifications at C-10 was synthesized by means of the *β*-lactam synthon method[14,17−21,23−28] using 10-modified 7-(triethylsilyl)-10-deacetylbaccatin III derivatives. Initial protection at the C-7 position of 10-deacetylbaccatin III (DAB)[29] with a triethylsilyl (TES) group and subsequent modification at the C-10 position with acyl, alkoxycarbonyl, *N*,*N*-dialkylcarbamoyl, and alkyl halides using LiHMDS as the base[22] proceeded uneventfully to give the corresponding 10-modified 7-TES-DABs **1a**−**m** in good yields (eq 1). Results are summarized in Table 1.

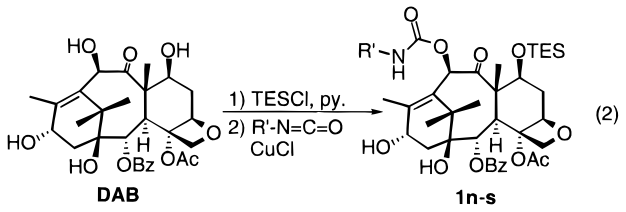



(1)

The C-10 modification with *N*-alkyl and *N*-allyl isocyanates under the same conditions resulted in the formation of a mixture of C-10 (minor) and C-13 (major) carbamoyl-DABs. The attempted introduction of a carbamoyl group at C-7 by Chen et al. through the reaction with isocyanates was reported to have failed.[30] Accordingly, we examined cuprous chloride as the activator, following up a general procedure for the reactions of isocyanates and alcohols reported by Duggan and Imagire.[31] This turned out to be a good choice, and we obtained the desired 10-carbamoyl-DABs. However, this procedure yields a side product, an allophanate, arising from the second addition of isocyanate to the carbamate nitrogen. In order to minimize this side reaction, a slow addition of isocyanates to 7-TES-DAB was employed in the presence of CuCl (1.0 equiv) in dry dichloromethane. Although the reaction conditions were not fully optimized, we were able to obtain the desired 10-carbamoyl-DABs **1n**−**s** in moderate to high yields (eq 2). Results are listed in Table 1.

**Scheme 1**




(2)

The coupling reactions of the baccatins **1a**−**s** with enantiomerically pure (3*R*,4*S*)-1-*t*-Boc-3-TIPSO-4-(2-methyl-1-propenyl)azetidin-2-one (**2**)[18] were carried out based on the Ojima−Holton protocol[24−27,32,33] to give 2′-TIPS-7-TES taxoids **3a**−**s** in fair to good yields (Scheme 1, Table 2). Treatment of **3a**−**s** with HF/pyridine (70:30) afforded the taxoids **4a**−**s** in good to excellent yields (Scheme 1). Results are summarized in Table 2.

The observed lower yields in the coupling of 10-carbamoylbaccatins **1n**−**p**,**r** are ascribed to the side reaction causing the loss of the 10-carbamoyl group through a rather unexpected retro-addition process caused by the deprotonation of the carbamoyl NH by LiHMDS and/or a lithium amide base generated upon coupling of **1** with the *β*-lactam **2**. This side reaction is not serious in the case of **1** with bulky C-10 carbamoyl groups, i.e., **1q**,**s**.

10-Modified 3′-(2-methylpropyl) taxoids **5** were synthesized in quantitative yields simply by hydrogenating the 3′-(2-methyl-1-propenyl) group of selected **4** on 10%

**Table 2.** Syntheses of C-10-Modified 3′-(2-Methyl-1-propenyl) Taxoids **4**

| | | **3** | | **4** | |
|---|---|---|---|---|---|
| 7-TES-baccatin | R | yield (%)[a] | | yield (%)[a] | |
| **1a** | $CH_3CH_2$-CO | **3a** | 75 | **4a** | 69 |
| **1b** | cyclopropane-CO | **3b** | 87 | **4b** | 70 |
| **1c** | $(CH_3)_2N$-CO | **3c** | 74 | **4c** | 70 |
| **1d** | $CH_3O$-CO | **3d** | 76 | **4d** | 61 |
| **1e** | $CH_3$ | **3e** | 66 | **4e** | 69 |
| **1f** | $CH_3(CH_2)3$-CO | **3f** | 88 | **4f** | 82 |
| **1g** | $CH_3(CH_2)_4$-CO | **3g** | 80 | **4g** | 39 (60) |
| **1h** | $(CH_3)_2CHCH_2$-CO | **3h** | 89 | **4h** | 84 |
| **1i** | $(CH_3)_3CCH_2$-CO | **3i** | 89 | **4i** | 87 |
| **1j** | cyclohexane-CO | **3j** | 88 | **4j** | 46 (58) |
| **1k** | (*E*)-$CH_3CH$=CH-CO | **3k** | 75 | **4k** | 63 |
| **1l** | $(CH_3CH_2)_2N$-CO | **3l** | 84 | **4l** | 85 |
| **1m** | morpholine-4-CO | **3m** | 68 (78) | **4m** | 88 |
| **1n** | $CH_3NH$-CO | **3n** | 43 | **4n** | 80 |
| **1o** | $CH_3CH_2NH$-CO | **3o** | 27 | **4o** | 83 |
| **1p** | $CH_3CH_2CH_2NH$-CO | **3p** | 38 | **4p** | 62 |
| **1q** | $(CH_3)_2CHNH$-CO | **3q** | 88 | **4q** | 98 |
| **1r** | $CH_2$=$CHCH_2NH$-CO | **3r** | 35 | **4r** | 70 |
| **1s** | cyclohexyl-NH-CO | **3s** | 67 | **4s** | 98 |

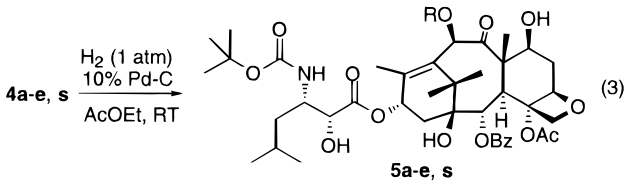
[a] Isolated yield (conversion yield).

**Table 3.** Syntheses of 3′-(2-Methylpropyl) Taxoids **5**

| taxoid **5** | R | yield[a] (%) |
|---|---|---|
| **5a** | $CH_3CH_2$-CO | 100 |
| **5b** | cyclopropane-CO | 100 |
| **5c** | $(CH_3)_2N$-CO | 100 |
| **5d** | $CH_3O$-CO | 100 |
| **5e** | $CH_3$ | 100 |
| **5s** | cyclohexyl-NH-CO | 100 |

[a] Isolated yield.

Pd−C at ambient temperature and hydrogen pressure in ethyl acetate (eq 3). Results are listed in Table 3.




## Cytotoxicity of New Taxoids

The *in vitro* cytotoxicity of these new taxoids thus synthesized was evaluated against several human tumor cell lines, A121 (ovarian carcinoma), A549 (non-small-cell lung carcinoma), HT-29 (colon carcinoma), and MCF-7 (mammary carcinoma) as well as the drug-resistant cell line MCF7-R (mammalian carcinoma 180-fold resistant to doxorubicin) using the method developed by Skehan et al.[34] Results are summarized in Table 4 with the values of paclitaxel, docetaxel, SB-T-1102,[18] and SB-T-1212[18] shown for comparison.

As Table 4 shows, the new taxoids **4** and **5** possess excellent activity against human cancer cell lines, which are better than paclitaxel and docetaxel except for **5s**. A number of the new taxoids **4** and **5** show 1 order of magnitude stronger activity than paclitaxel and docetaxel, and the most cytotoxic taxoid against normal human cancer cell lines is **4m** (SB-T-12162) that exhibits the $IC_{50}$ value of 0.09 nM against ovarian (A121) and breast (MCF7) cancer cell lines. The most significant result, however, is the remarkable activity ($IC_{50}$ = 2.1−9.1 nM) against the doxorubicin-resistant breast cancer cell line MCF7-R expressed by a number of new taxoids **4** and **5**. Among these, the three new taxoids, **4a** (SB-T-1213), **4b** (SB-T-1214), and **5a** (SB-T-1102), are exceptionally potent, possessing *2 orders of magnitude better activity than paclitaxel and docetaxel.* It is noteworthy that the observed exceptional activity is clearly ascribed to the modification at C-10 in comparison with the activity of the corresponding 10-acetyl taxoids SB-T-1212 (12 nM) and SB-T-1102 (36 nM). This fact forms a sharp contrast to the result reported for the SAR study of paclitaxel.[14,22]

**Table 4.** Cytotoxicity ($IC_{50}$, nM)[a] of Taxoids **4** and **5**

| taxoid | A121 (ovarian) | A549 (NSCL) | HT-29 (colon) | MCF-7 (breast) | MCF7-R (breast) |
|---|---|---|---|---|---|
| paclitaxel | 6.3 | 3.6 | 3.6 | 1.7 | 299 |
| docetaxel | 1.2 | 1.0 | 1.2 | 1.0 | 235 |
| SB-T-1102 | 3.8 | 0.98 | 3.2 | 4.0 | 36 |
| SB-T-1212 | 0.46 | 0.27 | 0.63 | 0.55 | 12 |
| **4a** | 0.12 | 0.29 | 0.31 | 0.18 | 2.2 |
| **4b** | 0.26 | 0.57 | 0.36 | 0.20 | 2.1 |
| **4c** | 0.30 | 0.60 | 0.5 | 0.13 | 4.9 |
| **4d** | 0.23 | 0.32 | 0.30 | 0.14 | 5.3 |
| **4e** | 0.70 | 0.90 | 0.90 | 0.37 | 123 |
| **4f** | 0.60 | 0.60 | 0.60 | 0.50 | 30 |
| **4g** | 0.50 | 0.57 | 0.90 | 0.40 | 17.3 |
| **4h** | 0.60 | 0.40 | 0.60 | 0.40 | 8.5 |
| **4i** | 0.34 | 0.50 | 0.50 | 0.40 | 10.5 |
| **4j** | 0.50 | 0.75 | 1.05 | 0.46 | 22.3 |
| **4k** | 0.45 | 1.70 | 0.60 | 0.26 | 3.4 |
| **4l** | 0.17 | 0.20 | 0.40 | 0.20 | 9.1 |
| **4m** | 0.09 | 0.22 | 0.18 | 0.09 | 12.5 |
| **4n** | 1.2 | 0.7 | 1.2 | 0.4 | 20 |
| **4o** | 0.29 | 0.15 | 0.41 | 0.31 | 162 |
| **4p** | 0.34 | 0.22 | 0.55 | 0.36 | 87 |
| **4q** | 0.34 | 0.36 | 0.52 | 0.46 | 65 |
| **4r** | 0.44 | 0.35 | 0.53 | 0.44 | 76 |
| **4s** | 0.28 | 0.20 | 0.46 | 0.33 | 48 |
| **5a** | 0.41 | 0.53 | 0.53 | 0.35 | 2.8 |
| **5b** | 0.51 | 1.1 | 0.78 | 0.51 | 4.3 |
| **5c** | 0.40 | 0.50 | 0.60 | 0.36 | 5.8 |
| **5d** | 0.18 | 0.35 | 0.44 | 0.28 | 6.4 |
| **5e** | 0.70 | 0.60 | 0.60 | 0.33 | 214 |
| **5s** | 5.0 | 3.7 | 5.0 | 1.6 | 33 |

[a] The concentration of compound which inhibits 50% ($IC_{50}$, nM) of the growth of human tumor cell line after 72 h drug exposure.[34]

With respect to the SAR of new taxoids **4** and **5** *against MCF7-R*, the bulkiness of the C-10 modifier has a considerable effect on activity. It appears that the *n*-propanoyl and cyclopropanecarbonyl groups are more or less optimal as demonstrated by the exceptionally high potency of **4a** (SB-T-1213), **4b** (SB-T-1214), and **5a** (SB-T-1102). As the size of the C-10 modifier increases, the activity shows a fairly steady decline as exemplified by the comparison of the dimethylcarbamoyl analog **4c** (4.9 nM) with the diethylcarbamoyl analog **4l** (9.1 nM) as well as the *n*-hexanoyl analog **4g** (17.3 nM) with the cyclohexanecarbonyl analog **4j** (22.3 nM). However, it is worthy of note that the electronic and conformational factors also exert substantial influence on the activity as observed in the comparison of the cyclohexanecarbonyl analog **4j** (22.3 nM) with the morpholine-*N*-carbonyl analog **4m** (12.5 nM). It should also be pointed out that the activity of **4m** against MCF7-R is not among the most potent analogs, although its activity against normal cancer cell lines is the highest of the new taxoids assayed (*vide supra*). The C-10 methyl analogs **4e** (123 nM) and **5e** (214 nM) resulted in 2 orders of magnitude decrease in activity. This result implies the importance of a carbonyl functionality at this position for exceptionally high activity. Although the *N,N*-dialkylcarbamoyl analogs **4c**,**l** show nanomolar

**Table 5.** Cytotoxicities of Selected Antitumor Agents against Ovarian and Drug-Resistant Ovarian Cancer Cell Lines

| | A2780-WT[a] | A2780-DX5[b] | A2780-C25[c] | A2780-CP3[d] |
|---|---|---|---|---|
| cisplatin | 450 | 280 | 1600 | 9000 |
| doxorubicin | 5 | 357 | 63 | 56 |
| paclitaxel | 2.7 | 547 | 3.4 | 4.1 |
| docetaxel | 1.2 | 122 | 1.0 | 1.4 |
| SB-T-1212 | 0.4 | 5.7 | 0.3 | 0.36 |

[a] A2780-WT, human ovarian carcinoma. [b] A2780-DX5, doxorubicin-resistant ovarian carcinoma. [c] A2780-C25, oxaliplatin-resistant ovarian carcinoma. [d] A2780-CP3, cisplatin-resistant ovarian carcinoma.

level $IC_{50}$ values, the analogs bearing *N*-monoalkyl and *N*-monoallyl groups, **4n**−**s** and **5s**, show, uniformly, a substantial decrease in activity (20−162 nM). It should be noted that cyclohexylcarbamoyl, a bulky carbamoyl group, brings about better activity than small size carbamoyl groups as exemplified by the comparison of **4s** (20 nM) or **5s** (33 nM) with **4n** (R = $CH_3NHCO$, 162 nM).

*It is worth mentioning that the activity against MCF7-R, a drug-resistant cell line expressing MDR phenotype, is very sensitive to the structure of the C-10 modifier, while this structural variation has little effects, in general, on the activity against the normal cancer cell lines, i.e., there is no apparent correlation between the activity against the normal cancer cell lines and that against the drug-resistant cell line.*

It has been shown that multidrug resistance, i.e., the cross-resistance to various structurally different cytotoxic agents, is caused by increased outward transport of these agents through the plasma membrane by the action of P-glycoprotein.[35] The photoaffinity label of P-glycoprotein with tritiated photoreactive paclitaxel analog has recently been reported.[36] Accordingly, it is reasonable to assume that the observed SAR that is unique to the drug-resistant cell line MCF7-R is related, at least in part, to the binding ability of these new taxoids to P-glycoprotein. All the new taxoids **4** and **5**, except **5s**, possess subnanomolar level $IC_{50}$ values against the normal cancer cell lines (as an average value for four cell lines). This means that most of the C-10 modifications we made are tolerated for cytotoxicity. On the contrary, the binding of these taxoids to P-glycoprotein is strongly affected by the structure of the C-10 modifier, i.e., it appears that the C-10 position is crucial for P-glycoprotein to recognize and bind taxoid antitumor agents.

In order to certify the relevance of using MCF7-R as the probe cell line to evaluate activity against various drug-resistant cancer cell lines, we looked at the activity of SB-T-1212 against doxorubicin-resistant (A2780-DX5), oxaliplatin-resistant (A2780-C25), and cisplatin-resistant (A2780-CP3) ovarian cancer cell lines. Results are listed in Table 5. As Table 5 clearly shows, taxane antitumor agents, paclitaxel, docetaxel, and SB-T-1212, maintain their excellent activity against the oxaliplatin- and cisplatin-resistant cancer cells. However, paclitaxel and docetaxel suffer from a substantial (100−200 times) cross-resistance against the doxorubicin-resistant cancer cell. In stark contrast to these two drugs, SB-T-1212 keeps excellent activity ($IC_{50}$ = 5.7 nM). These results clearly indicate the validity of the use of MCF7-R assay for the evaluation of the cytotoxicity of the new taxoids **4** and **5** against drug-resistant cancer cells expressing MDR phenotype.

## Antitumor Activity of 4a (SB-T-1213) *in Vivo*

The *in vivo* antitumor activity of **4a** (SB-T-1213) was evaluated against B16 melanoma implanted subcutaneously in $B6D2F_1$ mice.[37] Taxoid **4a** (0.4 mL/mouse) was administered intravenously (iv) on days 5, 7, and 9. Results are as follows: T/C (tumor growth inhibition) = 0% (12.4 mg/kg/day), T−C (tumor growth delay) = 10.9 days, $\log_{10}$ cell kill = 2.3; T/C = 0% (7.7 mg/kg/day), T−C = 9.3 days, $\log_{10}$ cell kill = 2.0; T/C = 34% (4.8 mg/kg/day), T−C = 3.0 days, $\log_{10}$ cell kill = 0.6. (For detailed explanation about T/C, T−C, and $\log_{10}$ cell kill values, see the Experimental Section. A T/C value of <10% is considered excellent antitumor activity by the National Cancer Institute; a larger number for T−C as well as for log cell kill values indicates higher activity.) Under the same conditions, docetaxel showed the following activity: T/C = 0% (20 mg/kg/day, optimal dose), T−C = 15.2 days, $\log_{10}$ cell kill = 3.3; T/C = 7% (12.4 mg/kg/day), T−C = 7.1 days, $\log_{10}$ cell kill = 1.5; T/C = 8% (7.7 mg/kg/day), T−C = 4.3 days, $\log_{10}$ cell kill = 0.9. The results clearly indicate that **4a** (SB-T-1213) is extremely active *in vivo* against this tumor. Although docetaxel shows a higher log cell kill value at optimal dosage, **4a** is more potent than docetaxel on a mg/kg basis, reflecting the exceptional activity of this agent in the *in vitro* cell line assay (*vide supra*). These observations warrant further investigation on **4a** and other exceptionally potent new taxoids such as **4b** (SB-T-1214) and **5a** (SB-T-1102). Accordingly, we are currently preparing for *in vivo* assay against a series of drug-resistant tumors (human cancer xenografts) in nude mice. Results will be reported in due course.

## Conclusions

We have found that the proper modifications at the C-10 position of 3′-(2-methyl-1-propenyl) and 3′-(2-methylpropyl) taxoids result in significant increase in their cytotoxicity, particularly against drug-resistant human breast cancer cell line MCF7-R expressing MDR phenotype. New taxoids possessing exceptionally high potency against MCF7-R, which is *2 orders of magnitude* better than those of paclitaxel and docetaxel, have been developed. The observed exceptional activity against the drug-resistant cancer cells appears to be ascribed to the blocking of P-glycoprotein binding to these C-10-modified analogs. A variety of C-10 acyl groups is tolerated in terms of the cytotoxicity against normal cancer cells, although there is a limitation toward the optimal size of the acyl group. On the contrary, the structure of the C-10 modifier is very sensitive to the activity against the drug-resistant cancer cells. One of the most active new taxoids thus developed, SB-T-1213 (**4a**), shows extremely strong *in vivo* antitumor activity against B16 melanoma in nude mice. Further studies on the development of the second-generation taxoids that possess strong activity against drug-resistant tumors are actively underway in these laboratories.

## Experimental Section

**General Methods.** Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1600 FT-IR spectrophotometer with neat samples. $^1H$,$^{13}C$, and 2D nuclear magnetic resonance (NMR) spectra were measured using a General Electric QE-300 or a Bruker AC-250 spectrometer using tetramethylsilane as the internal

standard. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Thin layer chromatography was performed on Merck DC-alufolien with Kieselgel 60F-254. Column chromatography was carried out on silica gel 60 (230−400 mesh ASTM; Merck). Elemental analyses were performed at M-H-W Laboratories, Phoenix, AZ, and Supersun Technology Analytical Laboratory, Stony Brook, NY. FAB HRMS were performed at UCR Mass Spectrometry Facility, Riverside, CA.

**Materials.** The chemicals were purchased from Aldrich Co. and Sigma and purified before use by standard methods. THF was freshly distilled over sodium and benzophenone. 7-(Triethylsilyl)-10-deacetylbacctain III (7-TES-DAB) was prepared by the literature method.[26,38] (3*R*,4*S*)-3-[(Triisopropylsilyl)-oxy]-4-isobutenyl-1-(*tert*-butoxycarbonyl)azetidin-2-one (**2**) was prepared by the literature procedure.[18]

**General Procedures for the Synthesis of a C-10-Modified 7-(Triethylsilyl)-10-deacetylbaccatin III (1). Method A:** To a solution of 7-TES-DAB in THF (0.055 M) was added 1.1−1.3 equiv of LiHMDS at −40 °C. After the reaction mixture was stirred for 10 min, 1.0−1.2 equiv of an alkanoyl chloride, an *N,N*-dialkylcarbamoyl chloride, or methyl iodide (freshly distilled) was added dropwise at −40 °C. The mixture was warmed to 0 °C over a period of 30−60 min and then concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (hexane/EtOAc = 4:1−1:1) afforded the 10-modified 7-TES-baccatin III **1a**−**m** as a white solid.

**Method B:** To a solution of 7-TES-DAB (0.10 M) in dry dichloromethane was added 1.0 equiv of copper(I) chloride with stirring. A freshly distilled isocyanate (1.5−3.0 equiv) was added dropwise to the resulting green-yellow suspension, and the mixture was stirred at room temperature for 22−72 h. The reaction was quenched with saturated $NH_4Cl$ and the mixture extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography with dichloromethane/methanol (98:2−96:4) as the eluant to give the 10-modified 7-TES-baccatin III **1n**−**s** as a white solid. Identification data for these 10-modified baccatin III derivatives are given in the Supporting Information.

**General Procedure for the Syntheses of Taxoids 4 and SB-T-1212.** To a solution of a baccatin **1** (0.02 M) and 1.3−1.5 equiv of 4-isobutenyl-1-(*tert*-butoxycarbonyl)-3-[(triisopropylsilyl)oxy]azetidin-2-one (**2**) in dry THF was added dropwise 1.0−1.5 equiv of LiHMDS (1.0 M in THF) at −40 °C. The reaction mixture was allowed to warm to −15 ° to −10 °C and stirred for 30−60 min. Then, the reaction was quenched with saturated $NH_4Cl$. The mixture was extracted with ethyl acetate and the organic layers were washed with saturated $NH_4Cl$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (hexane/EtOAc = 4:1) afforded the corresponding taxoid **3** with protecting groups as a white solid. The deprotection was carried out using the following two methods.

**Method A:** To a solution of **3** (0.015 M) in a 1:1 mixture of pyridine and acetonitrile was added HF/pyridine (70:30) (0.1 mL/10 mg of starting material) at 0 °C. After the reaction mixture was warmed to 30 °C for 4−5 h, the reaction was quenched with water and the mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (hexane/EtOAc = 1:1) afforded the corresponding taxoid **4a**−**e** as well as SB-T-1212 as a white solid.

**Method B:** To a solution of **3** (0.015 M) in a 1:1 mixture of pyridine and acetonitrile was added HF/pyridine: (70:30) (0.1 mL/10 mg of starting material) at 0 °C. After the reaction mixture was allowed to warm to room temperature and stir for 12−16 h, the reaction was quenched with water and the mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (hexane/EtOAc = 1:1) afforded the corresponding taxoid **4f**−**s** as a white solid.

**10-Acetyl-3′-dephenyl-3′-(2-methyl-2-propenyl)docetaxel (SB-T-1212):** 90% yield; mp 157−160 °C; $[\alpha]_D$ −76.3° (*c* 0.76, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (s, 3 H), 1.26 (s, 3 H), 1.36 (s, 9 H), 1.68 (s, 3 H), 1.77 (br s, 6 H), 1.90 (br s, 4 H), 2.25 (s, 3 H), 2.36 (s, 3 H), 2.39 (br s, 1 H), 2.53 (m, 2 H), 3.44 (d, *J* = 6.7 Hz, 1 H), 3.82 (d, *J* = 7.0 Hz, 1 H), 4.20 (d, *J* = 8.5 Hz, 1 H), 4.24 (m, 1 H), 4.31 (d, *J* = 8.5 Hz, 1 H), 4.43 (m, 1 H), 4.78 (dq, *J* = 8.5, 2.6 Hz, 1 H), 4.83 (br s, 1 H), 4.96 (d, *J* = 8.1 Hz, 1 H), 5.32 (d, *J* = 8.3 Hz, 1 H), 5.67 (d, *J* = 7.0 Hz, 1 H), 6.17 (t, *J* = 8.6 Hz, 1 H), 6.31 (s, 1 H), 7.45 (d, 2 H), 7.60 (t, 1 H), 8.10 (d, 2 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 9.6, 14.9, 18.5, 20.8, 22.4, 25.7, 26.6, 28.2, 35.6, 43.2, 45.7, 51.6, 58.5, 72.1, 72.2, 73.8, 75.1, 75.6, 76.4, 79.1, 79.9, 81.0, 84.4, 120.7, 128.6, 129.3, 130.1, 132.8, 133.6, 137.7, 145.6, 155.5, 166.9, 170.1, 171.2, 173.7, 203.7. Anal. Calcd for $C_{43}H_{55}NO_{15}$: C, 62.38; H, 6.94; N, 1.69. Found: C, 62.47; H, 6.71; N, 1.60.

**3′-Dephenyl-3′-(2-methyl-2-propenyl)-10-*n*-propanoyldocetaxel (4a):** 69% yield; $[\alpha]_D$ −40.0° (*c* 1.00, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.08 (s, 3 H), 1.13−1.18 (m, 6 H), 1.28 (s, 9 H), 1.60 (s, 3 H), 1.69 (br s, 6 H), 1.72 (m, 1 H), 1.83 (s, 3 H), 2.29 (s, 3 H), 2.31 (s, 2 H), 2.44 (m, 3 H), 3.38 (br s, 1 H), 3.74 (d, *J* = 6.9 Hz, 1 H), 4.10 (d, *J* = 8.1 Hz, 1 H), 4.13 (br s, 1 H), 4.22 (d, *J* = 8.1 Hz, 1 H), 4.33 (dd, *J* = 10.1, 7.5 Hz, 1 H), 4.67 (m, 2 H), 4.88 (d, *J* = 9.3 Hz, 1 H), 5.23 (d, *J* = 8.4 Hz, 1 H), 5.59 (d, *J* = 6.9 Hz, 1 H), 6.06 (m, 1 H), 6.24 (s, 1 H), 7.37 (t, 2 H), 7.51 (t, 1 H), 8.01 (d, 2 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 9.0, 9.5, 14.9, 18.5, 21.8, 22.3, 25.7, 26.6, 27.5, 28.2, 35.5, 43.1, 45.6, 51.6, 55.5, 58.5, 72.1, 72.3, 73.7, 75.0, 75.4, 76.4, 76.5, 77.0, 77.5, 79.1, 79.9, 81.0, 84.3, 120.6, 128.6, 129.2, 130.1, 132.9, 133.6, 137.8, 142.4, 155.4, 166.9, 170.1, 173.0, 174.6, 203.8; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{44}H_{59}O_{15}NH^+$ 842.3962, found 842.4007.

**10-(Cyclopropylcarbonyl)-3′-dephenyl-3′-(2-methyl-2-propenyl)docetaxel (4b):** 70% yield; $[\alpha]_D$ −160° (*c* 1.00, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.10 (m, 2 H), 1.14 (s, 3 H), 1.25 (s, 3 H), 1.34 (s, 9 H), 1.65 (s, 3 H), 1.71 (s, 2 H), 1.75 (br s, 6 H), 1.84 (m, 1 H), 1.88 (s, 3 H), 2.34 (s, 3 H), 2.37 (s, 2 H), 2.46 (m, 1 H), 2.56 (d, *J* = 3.3 Hz, 1 H), 3.36 (m, 1 H), 3.78 (d, *J* = 6.9 Hz, 1 H), 4.13 (d, *J* = 8.4 Hz, 1 H), 4.18 (br s, 1 H), 4.27 (d, *J* = 8.4 Hz, 1 H), 4.40 (m, 1 H), 4.72 (m, 2 H), 4.93 (d, *J* = 8.6 Hz, 1 H), 5.28 (d, *J* = 7.6 Hz, 1 H), 5.64 (d, *J* = 6.9 Hz, 1 H), 6.16 (m, 1 H), 6.28 (s, 1 H), 7.43 (t, 2 H), 7.56 (t, 1 H), 8.07 (d, 2 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 9.1, 9.4, 9.5, 13.0, 14.9, 18.5, 21.9, 22.4, 25.7, 26.7, 28.2, 35.5, 35.6, 43.2, 45.6, 51.6, 58.5, 72.2, 72.3, 73.7, 75.0, 75.4, 76.5, 77.0, 77.5, 79.2, 79.7, 81.0, 84.4, 120.6, 128.6, 129.2, 130.1, 132.9, 133.6, 137.9, 142.6, 155.4, 166.9, 170.1, 175.1, 203.9; IR (neat, $cm^{-1}$) $\nu$ 3368, 2989, 2915, 1786, 1754, 1725, 1709, 1641, 1630, 1355, 1315, 1109; HRMS (FAB, DCM/NBA/NaCl) *m/z* calcd for $C_{45}H_{59}O_{15}NNa^+$ 876.3784, found 876.3782.

**3′-Dephenyl-10-(*N,N*-dimethylcarbamoyl)-3′-(2-methyl-2-propenyl)docetaxel (4c):** 70% yield; $[\alpha]_D$ −50.0° (*c* 2.00, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.13 (s, 3 H), 1.23 (s, 3 H), 1.33 (s, 9 H), 1.64 (s, 3 H), 1.74 (br s, 6 H), 1.85 (m, 1 H), 1.89 (s, 3 H), 2.33 (s, 3 H), 2.36 (s, 2 H), 2.45 (m, 1 H), 2.93 (s, 3 H), 3.02 (s, 3 H), 3.20 (br s, 1 H), 3.45 (m, 1 H), 3.78 (d, *J* = 6.9 Hz, 1 H), 4.14 (d, *J* = 8.4 Hz, 1 H), 4.18 (br s, 1 H), 4.26 (d, *J* = 8.4 Hz, 1 H), 4.40 (dd, *J* = 10.2, 6.7 Hz, 1 H), 4.69 (m, 1 H), 4.80 (s, 1 H), 4.93 (d, *J* = 8.6 Hz, 1 H), 5.27 (d, *J* = 7.6 Hz, 1 H), 5.62 (d, *J* = 6.9 Hz, 1 H), 6.12 (m, 1 H), 6.23 (s, 1 H), 7.41 (t, 2 H), 7.55 (t, 1 H), 8.06 (d, 2 H); $^{13}C$ NMR (63 MHz, $CDCl_3$) $\delta$ 9.3, 15.0, 18.5, 22.2, 22.3, 25.7, 26.8, 28.2, 35.3, 35.6, 36.0, 36.6, 43.1, 45.6, 51.6, 58.4, 72.3, 72.4, 73.7, 75.2, 76.2, 76.4, 76.5, 77.0, 77.5, 79.2, 81.0, 84.6, 128.6, 129.2, 130.1, 133.1, 133.6, 137.8, 142.9, 155.4, 156.1, 166.9, 170.0, 173.0, 205.6; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{44}H_{60}O_{15}N_2Na^+$ 879.3891, found 879.3870.

**3′-Dephenyl-10-(methoxycarbonyl)-3′-(2-methyl-2-propenyl)docetaxel (4d):** 61% yield; $[\alpha]_D$ −15.0° (*c* 2.00, $CHCl_3$); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.14 (s, 3 H), 1.23 (s, 3 H), 1.33 (s, 9 H), 1.68 (s, 3 H), 1.71 (br s, 6 H), 1.87 (m, 1 H), 1.92 (s, 3 H), 2.34 (s, 3 H), 2.47 (m, 2 H), 2.55 (m, 1 H), 3.40 (br s, 1 H), 3.76 (d, *J* = 6.9 Hz, 1 H), 3.85 (s, 3 H), 4.15 (d, *J* = 8.3 Hz, 1 H), 4.19 (br s, 1 H), 4.28 (d, *J* = 8.3 Hz, 1 H), 4.38 (m, 1 H), 4.72 (m, 2 H), 4.93 (d, *J* = 8.6 Hz, 1 H), 5.29 (d, *J* = 7.8 Hz, 1 H), 5.64 (d, *J* = 6.9 Hz, 1 H), 6.11 (s, 1 H), 6.15 (s, 1 H), 7.43 (t, 2 H), 7.56 (t, 1 H), 8.07 (d, 2 H); $^{13}C$ NMR (75 MHz, $CDCl_3$)

$\delta$ 9.4, 15.0, 18.5, 21.7, 22.3, 25.7, 26.5, 28.2, 35.5, 43.1, 45.6, 51.6, 55.5, 58.6, 72.0, 72.2, 73.7, 75.0, 76.4, 76.5, 77.0, 77.2, 77.4, 78.3, 79.1, 79.9, 81.0, 84.3, 120.6, 128.6, 129.2, 130.1, 132.5, 133.6, 137.9, 143.4, 155.4, 155.7, 166.9, 170.1, 172.9, 203.9; HRMS (FAB, DCM/NBA/PPG) *m/z* calcd for $C_{43}H_{57}O_{16}NH^+$ 844.3710, found 844.3755.

**3′-Dephenyl-10-methyl-3′-(2-methyl-2-propenyl)docetaxel (4e):** 69% yield; $[\alpha]_D$ −16.7° (*c* 3.00, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.08 (s, 3 H), 1.13 (s, 3 H), 1.18 (s, 3 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 (m, 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 (75 MHz, $CDCl_3$) $\delta$ 9.7, 14.6, 18.5, 20.8, 22.4, 25.7, 26.3, 28.2, 35.4, 37.0, 43.1, 46.7, 51.5, 56.8, 57.8, 71.9, 72.3, 73.7, 74.9, 76.5, 77.0, 77.2, 77.5, 78.8, 79.9, 81.2, 82.6, 84.2, 120.6, 128.6, 129.2, 130.1, 133.6, 134.9, 139.5, 155.4, 166.9, 170.1, 172.9, 206.7; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{42}H_{57}O_{14}NNa^+$ 822.3676, found 822.3705.

**3′-Dephenyl-3′-(2-methyl-2-propenyl)-10-*n*-pentanoyldocetaxel (4f):** 82% yield; mp 130−133°C; $[\alpha]_D$ −78.8° (*c* 0.33, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.13 (s, 3 H), 1.24 (s, 3 H), 1.33−1.48 (m, 11 H), 1.63−1.82 (m, 9 H), 1.85−1.90 (m, 4 H), 2.37 (br s, 4 H), 2.43−2.59 (m, 3 H), 3.40 (d, *J* = 6.4 Hz, 1 H), 3.80 (d, *J* = 7.0 Hz, 1 H), 4.14−4.21 (m, 2 H), 4.29 (d, *J* = 8.4 Hz, 1 H), 4.38−4.44 (m, 1 H), 4.68−4.81 (m, 2 H), 4.95 (d, *J* = 8.1 Hz, 1 H), 5.30 (d, *J* = 7.8 Hz, 1 H), 5.65 (d, *J* = 7.0 Hz, 1 H), 6.15 (t, *J* = 8.9 Hz, 1 H), 6.29 (s, 1 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 8.09 (d, *J* = 7.4 Hz, 2 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 9.56, 13.74, 14.98, 18.59, 21.90, 22.23, 22.41, 25.75, 26.65, 26.90, 28.23, 33.91, 35.57, 43.16, 45.63, 51.59, 58.56, 72.22, 72.36, 73.76, 75.03, 75.39, 79.15, 80.00, 81.04, 84.45, 120.61, 128.65, 129.19, 130.16, 132.94, 133.71, 137.94, 142.51, 155.45, 166.95, 170.10, 171.19, 173.10, 174.07, 203.81. Anal. Calcd for $C_{46}H_{63}NO_{15}$: C, 63.51; H, 7.30; N, 1.61. Found: C, 63.74; H, 7.13; N, 1.63.

**3′-Dephenyl-10-*n*-hexanoyl-3′-(2-methyl-2-propenyl)-docetaxel (4g):** 39% yield (60% conversion yield); mp 126−128°C; $[\alpha]_D$ −72.0° (*c* 0.50, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.90 (t, *J* = 6.8 Hz, 3 H), 1.13 (s, 3 H), 1.24 (s, 3 H), 1.34 (br s, 13 H), 1.65−1.92 (m, 16 H), 2.34−2.39 (m, 4 H), 2.42−2.61 (m, 3 H), 3.42 (d, *J* = 6.1 Hz, 1 H), 3.79 (d, *J* = 7.0 Hz, 1 H), 4.09−4.21 (m, 2 H), 4.29 (d, *J* = 8.4 Hz, 1 H), 4.36−4.46 (m, 1 H), 4.67−4.83 (m, 2 H), 4.94 (d, *J* = 8.1 Hz, 1 H), 5.30 (d, *J* = 8.4 Hz, 1 H), 5.65 (d, *J* = 7.0 Hz, 1 H), 6.15 (t, *J* = 8.7 Hz, 1 H), 6.29 (s, 1 H), 7.46 (t, *J* = 7.4 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 8.09 (d, *J* = 7.4 Hz, 2 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 9.56, 13.92, 14.96, 18.57, 21.89, 22.29, 22.41, 24.51, 25.73, 26.66, 28.02, 28.23, 31.21, 34.15, 35.55, 35.60, 43.18, 45.64, 51.61, 58.56, 72.20, 72.34, 73.76, 75.39, 76.46, 79.14, 79.98, 81.06, 84.45, 120.64, 128.64, 129.22, 130.16, 132.96, 133.68, 137.90, 142.48, 155.46, 166.94, 170.10, 173.09, 174.07, 203.76. Anal. Calcd for $C_{47}H_{65}NO_{15}$: C, 63.86; H, 7.41; N, 1.58. Found: C, 63.63; H, 7.31; N, 1.64.

Identification data for taxoids **4h**−**s** are given in the Supporting Information.

**General Procedure for the Syntheses of 3′-(2-Methylpropyl) Taxoids 5 and SB-T-1102.** A solution of a 3′-(2-methyl-1-propenyl) taxoid **4** in ethyl acetate (0.01*M*) was subjected to hydrogenation in the presence of 10% Pd−C (30−50% by weight of starting material) at ambient temperature and pressure for 24 h. The solution was filtered through silica gel to remove the catalyst and concentrated *in vacuo* to afford the corresponding 3′-(2-methylpropyl) taxoid **5** or SB-T-1102 as a white solid.

**10-Acetyl-3′-dephenyl-3′-(2-methylpropyl)docetaxel (SB-T-1102):** 85% yield; $[\alpha]_D$ −81.2° (*c* 1.00, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.98 (s, 3 H), 1.01 (s, 3 H), 1.16 (s, 3 H), 1.26 (s, 3 H), 1.32 (s, 9 H), 1.30−1.34 (m, 1 H), 1.65−2.05 (m, 3 H), 1.70 (s, 3 H), 1.90 (s, 3 H), 2.38 (s, 3 H), 2.42 (m, 2 H), 2.56 (m, 1 H), 3.82 (d, *J* = 7.0 Hz, 1 H), 4.10−4.25 (m, 3 H), 4.31 (d, *J* = 8.4 Hz, 1 H), 4.41 (dd, *J* = 10.7, 7.2 Hz, 1 H), 4.97 (d, *J* = 8.0 Hz, 1 H), 5.67 (d, *J* = 7.0 Hz, 1 H), 6.19 (br t, *J* = 8.8 Hz, 1 H), 6.31 (s, 1 H), 7.48 (t, 2 H), 7.61 (t, 1 H), 8.12 (d, 2 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 9.6, 14.9, 20.8, 21.9, 22.5, 23.2, 24.7, 26.6, 27.9, 28.2, 35.6, 41.3, 43.2, 45.6, 51.4, 58.6, 72.2, 73.0, 75.1, 75.6, 76.5, 77.2, 79.2, 79.7, 81.1, 84.4, 128.6, 129.3, 130.2, 132.9, 133.6, 142.6, 155.5, 167.0, 170.0, 171.2, 174.0, 203.7. Anal. Calcd for $C_{43}H_{57}NO_{15}$: C, 62.23; H, 7.17; N, 1.69. Found: C, 62.18; H, 6.82; N, 1.51.

**3′-Dephenyl-3′-(2-methylpropyl)-10-*n*-propanoyldocetaxel (5a):** 100% yield; $[\alpha]_D$ −30.0° (*c* 1.00, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.96 (m, 6 H), 1.13 (s, 3 H), 1.22−1.27 (m, 6 H), 1.30 (s, 9 H), 1.63 (s, 3 H), 1.73 (s, 2 H), 1.82 (m, 1 H), 1.88 (s, 3 H), 2.36 (s, 3 H), 2.40 (s, 2 H), 2.46 (m, 1 H), 2.49 (m, 2 H), 3.25 (br s, 1 H), 3.79 (d, *J* = 7.0 Hz, 1 H), 4.09 (d, *J* = 8.3 Hz, 1 H), 4.16 (br s, 1 H), 4.27 (d, *J* = 8.3 Hz, 1 H), 4.38 (dd, *J* = 10.2, 6.7 Hz, 1 H), 4.57 (d, *J* = 9.5 Hz, 1 H), 4.94 (d, *J* = 8.0 Hz, 1 H), 5.64 (d, *J* = 7.0 Hz, 1 H), 6.13 (m, 1 H), 6.30 (s, 1 H), 7.43 (t, 2 H), 7.56 (t, 1 H), 8.08 (d, 2 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 9.0, 9.5, 14.9, 21.8, 21.9, 22.5, 23.2, 24.6, 26.5, 27.5, 28.1, 29.6, 35.5, 41.2, 43.1, 45.6, 51.3, 58.5, 72.1, 72.6, 73.0, 75.1, 75.4, 76.4, 76.5, 77.0, 77.5, 79.1, 79.7, 81.0, 84.4, 128.6, 129.2, 130.1, 132.9, 133.6, 142.4, 155.5, 166.9, 169.9, 173.9, 174.6, 203.8; HRMS (FAB, DCM/NBA) *m/z* calcd for $C_{44}H_{61}O_{15}NH^+$ 844.4119, found 844.4157.

**10-(Cyclopropylcarbonyl)-3′-dephenyl-3′-(2-methylpropyl)docetaxel (5b):** 100% yield; $[\alpha]_D$ −30.0° (*c* 1.00, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.96 (m, 6 H), 1.09 (m, 2 H), 1.14 (s, 3 H), 1.24 (s, 3 H), 1.30 (s, 9 H), 1.62−1.70 (m, 4 H), 1.66 (s, 3 H), 1.73 (m, 1 H), 1.88 (s, 3 H), 2.36 (s, 3 H), 2.39 (s, 1 H), 2.48 (m, 1 H), 2.50 (m, 1 H), 3.20 (m, 1 H), 3.78 (d, *J* = 6.9 Hz, 1 H), 4.16 (d, *J* = 8.3 Hz, 1 H), 4.20 (br s, 1 H), 4.27 (d, *J* = 8.3 Hz, 1 H), 4.40 (m, 1 H), 4.55 (m, 1 H), 4.93 (d, *J* = 8.1 Hz, 1 H), 5.64 (d, *J* = 7.0 Hz, 1 H), 6.14 (m, 1 H), 6.29 (s, 1 H), 7.43 (t, 2 H), 7.56 (t, 1 H), 8.09 (d, 2 H); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 9.1, 9.4, 9.5, 13.0, 14.9, 21.9, 22.0, 22.5, 23.2, 24.7, 26.6, 28.1, 35.4, 35.5, 41.2, 43.1, 45.6, 51.3, 58.5, 72.2, 72.7, 72.9, 75.1, 75.4, 76.5, 77.0, 77.5, 79.2, 79.7, 81.0, 84.4, 128.6, 129.2, 130.2, 132.9, 133.6, 142.6, 155.5, 166.9, 169.9, 173.9, 175.1, 203.9; HRMS (FAB, DCM/NBC/NaCl) *m/z* calcd for $C_{45}H_{61}O_{15}NNa^+$ 878.3938, found 878.3926.

**3′-Dephenyl-10-(*N*,*N*-dimethylcarbamoyl)-3′-(2-methylpropyl)docetaxel (5c):** 100% yield; $[\alpha]_D$ −80.0° (*c* 2.00, $CHCl_3$); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.95 (m, 6 H), 1.14 (s, 3 H), 1.23 (s, 3 H), 1.29 (s, 9 H), 1.66 (s, 3 H), 1.68 (m, 2 H), 1.82 (m, 1 H), 1.90 (s, 3 H), 2.36 (s, 3 H), 2.39 (s, 2 H), 2.50 (m, 1 H), 2.95 (s, 3 H), 3.03 (s, 3 H), 3.22 (m, 1 H), 3.78 (d, *J* = 7.0 Hz, 1 H), 4.10 (d, *J* = 8.3 Hz, 1 H), 4.16 (br s, 1 H), 4.27 (d, *J* = 8.3 Hz, 1 H), 4.41 (dd, *J* = 10.2, 6.5 Hz, 1 H), 4.56 (m, 1 H), 4.95 (d, *J* = 8.1 Hz, 1 H), 5.63 (d, *J* = 7.0 Hz, 1 H), 6.14 (m, 1 H), 6.24 (s, 1 H), 7.42 (t, 2 H), 7.56 (t, 1 H), 8.08 (d, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 9.8, 15.3, 22.3, 22.7, 22.9, 23.6, 25.1, 27.2, 28.5, 35.8, 36.0, 36.4, 37.0, 41.6, 43.6, 46.0, 51.7, 58.9, 72.8, 73.1, 75.7, 76.6, 76.8, 76.9, 77.1, 77.4, 77.6, 77.8, 79.6, 80.0, 81.5, 85.0, 128.7, 129.0, 129.7, 130.6, 133.6, 133.9, 143.3, 155.9, 156.5, 167.3, 170.3, 174.3, 206.0; HRMS (FAB) *m/z* calcd for $C_{44}H_{62}O_{15}N_2Na^+$ 881.4074, found 881.4047.

Identification data for taxoids **5d**,**e**,**s** are given in the Supporting Information.

**Cytotoxicity Assay *in Vitro*.**[39] Tumor cell growth inhibition was determined according to the method established by Skehan et al.[34] Human tumor cells (A121a, ovarian carcinoma, HT-29, colon carcinoma; A549, non-small-cell lung carcinoma; MCF-7, breast carcinoma) were plated at a density of 400 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). Taxanes were solubilized in DMSO and further diluted with RPMI-1640 medium. Triplicate wells were exposed to various treatments. After 72 h incubation, 100 $\mu$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 $\mu$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 $IC_{50}$ values were then calculated by fitting the concentration−effect curve data with the sigmoid-$E_{max}$ model using nonlinear regression, weighted by the reciprocal of the square of the predicted effect.[40]

**Antitumor Activity Assay *in Vivo*.**[37,41] Tumor fragments of B16 melanoma (1 $mm^3$, 30−60 mg) were grafted subcutaneously (sc) on day 0 in $B6D2F_1$ mice (5 mice/group). Taxoid SB-T-1213 was first dissolved in ethanol, then polysorbate 80 was added, and the final dilution was made with 5% glucose in water (5/5/90, v/v/v). The pH of the final solution was 5. Taxoid SB-T-1213 (0.4 mL/mouse) was administered intravenously (i.v.) on days 5, 7, and 9. Animals were observed for toxicity and tumor growth. Tumors were measured with a caliper. Tumor weights were calculated from 2-dimensional measurements: tumor weight (mg) = $(l \times w^2)/2$, where $l$ and $w$ are the tumor length and width (mm), respectively. Antitumor activity was expressed by the tumor growth inhibition (T/C) value obtained at the maximal tolerated dose (no lethality, body weight loss < 20%), wherein T is the median tumor weight of treated animals and C is the median tumor weight of control animals. A T/C value of 42% or less is considered significant antitumor activity and 10% or less is regarded as excellent by the National Cancer Institute. The other end point used was the tumor growth delay (T−C), where T and C are the median time in days required for the treatment group (T) and the control group (C) to reach 750 mg, respectively. The log cell kill values are derived from the T−C value using the formula: log cell kill = T−C (in days)/3.32 × Td, where Td is the tumor doubling time in days (1.4 days in this assay).

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**Supporting Information Available:** Identification data for the 10-modified baccatin III derivatives **1a**−**s**, the protected taxoids **3a**−**s**, taxoids **4h**−**s**, and taxoids **5d**,**e**,**s** (14 pages). Ordering information is given on any current masthead page.

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