C-3′-Cyclopropanated Taxol Analogs: Synthesis, Bioassay and Biostructural Analysis[‡]

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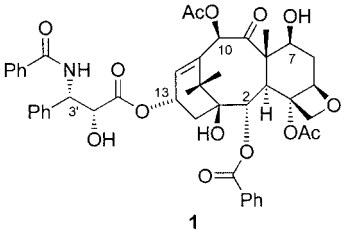
Ten taxoids with a cyclopropanated side chain were synthesized by coupling a spirocyclopropanated oxazoline-5-carboxylic acid with 7-(triethylsilyl)baccatin III, followed by hydrolytic ring opening and benzoyl migration. The absolute configuration of the 2′-position was determined by NMR analysis of the corresponding Mosher esters. These paclitaxel analogs were active in A2780 mammalian and PC-3 prostate cancer cell lines, and also in a tubulin-assembly assay, but all the analogs were less active than paclitaxel itself. To probe the basis for the uniform potency reduction shown by the cyclopropanated taxoid series, we have examined the conformational properties of compound **3b** alone by molecular mechanics and in complex with tubulin by molecular dynamics. In addition, we have performed an NMR/NAMFIS conformer deconvolution analysis for compound **3b**. Both modeling and NAMFIS approaches provide a satisfying understanding of the biological behavior of the series of cyclopropanated taxoids and provide further, though indirect, support for the T-form as characteristic of taxoids bound to β-tubulin.

Introduction

Taxol[1] (**1**), originally isolated from the Pacific yew (*Taxus brevifolia*),[2] has become an important anticancer drug, especially for the treatment of refractory ovarian cancer, small-cell lung cancer, and metastatic breast disease.[3] Extensive structure-activity relationship (SAR) studies of taxol have been carried out and several new analogs are in clinical trials.[4] Cyclopropyl groups have proved to be highly effective in improving the activity of many biologically active compounds,[5,6] and several cyclopropyl-bearing analogs of taxol[7] and epothilone[8] have previously been synthesized and shown to have improved or retained anticancer activity. Recently, a new simple access to the spirocyclopropanated oxazoline-5-carboxylic acid **4a** was disclosed, and **4a** was considered to be a potential precursor to taxol analogs with a cyclopropane-containing side chain.[9]

The synthesis of a taxol analog with a cyclopropane-containing side chain was of interest, since it was hoped that the 1,1-disubstituted cyclopropyl group in the side chain would restrain the conformational mobility of the side chain and bring it closer to the biologically active binding conformation of paclitaxel. The synthetic strategy, the principle of which had been successfully executed before,[10] is to couple an oxazolinecarboxylic acid of general type **4** to



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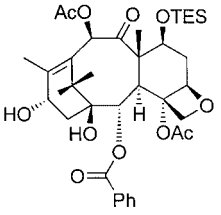

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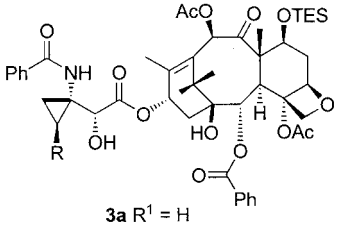
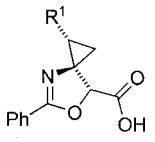


3a R^1 = H
3b R^1 = Me
3c R^1 = *i*Pr



(+/–)-**4a** R^1 = H
(+/–)-**4b** R^1 = Me
(+/–)-**4c** R^1 = *i*Pr

[‡] For one of us (A. d. M.) this is to be considered as Part 115 in the series "Cyclopropyl Building Blocks for Organic Synthesis". Part 114: M. Kordes, M. Brands, M. Es-Sayed, A. de Meijere, *Eur. J. Org. Chem.*, submitted. Part 113: M. Schelper, O. Buisine, S. I. Kozhushkov, C. Aubert, A. de Meijere, M. Malacria, *Eur. J. Org. Chem.*, submitted.

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7-(triethylsilyl)baccatin III (7-TES-baccatin III) (**2**), and then hydrolytically open the oxazoline moiety to the desired side chain.

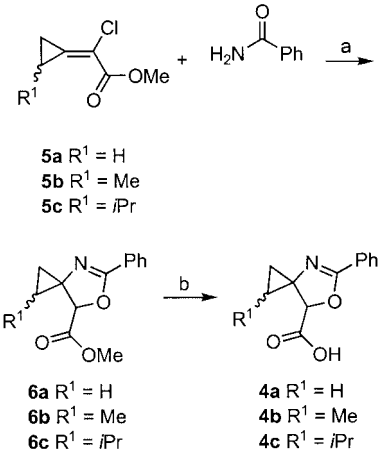
Molecular modeling has proved to be a powerful tool to elucidate the biologically active conformation of taxol, the T-taxol conformation.[11] The initial computationally refined electron crystallographic model[11] was employed in the design, synthesis and subsequent bioanalysis of a novel and highly active series of C-4 to C-3′ bridged analogs providing clearcut experimental confirmation of the model.[12] A synthetic approach employing less constrained C-2 to C-3′ linkers complemented by protein docking, conceived around the same time by the French group, furnishes parallel support for the T-concept,[13] while another recent approach based on a REDOR-taxol structure gives support to aspects of the T-concept.[14] An additional successful application of the model was inspired by the observation that tubulin from yeast (*S. cerevisiae*) is not polymerized by taxol.[15] Mutation of five key residues in contact with T-taxol in the tubulin binding site as portrayed by the electron crystallographic model restored the ability of the drug to stabilize yeast microtubules.[16] It can be added that the relative cytotoxicity of paclitaxel and docetaxel in a cell line made resistant by the Asp26Glu mutation can likewise be explained by a model in which both compounds adopt the β-tubulin-bound T-conformation.[17] In this paper, the conformational properties of a cyclopropyl-bearing taxoid were examined in isolation by molecular mechanics and in complex with tubulin by molecular dynamics. As a complement, an NMR/NAMFIS conformer deconvolution analysis was performed. The combined computational approaches provide a better understanding of the biological behavior of this series of cyclopropanated taxoids and offer further insight into how taxol binds to β-tubulin.

Synthesis

The synthesis of (±)-2-phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylic acids **4a**–**c** was performed according to the previously developed procedures (Scheme 1).[9,18]

The coupling of 7-TES-baccatin III (**2**) with (±)-2-phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylic acid (**4a**) using DCC/4-PP occurs in good yield (85%). The two diastereomers **7a** and **8a** were obtained in a ratio of 2:3 and were easily separated by column chromatography (Scheme 2f).

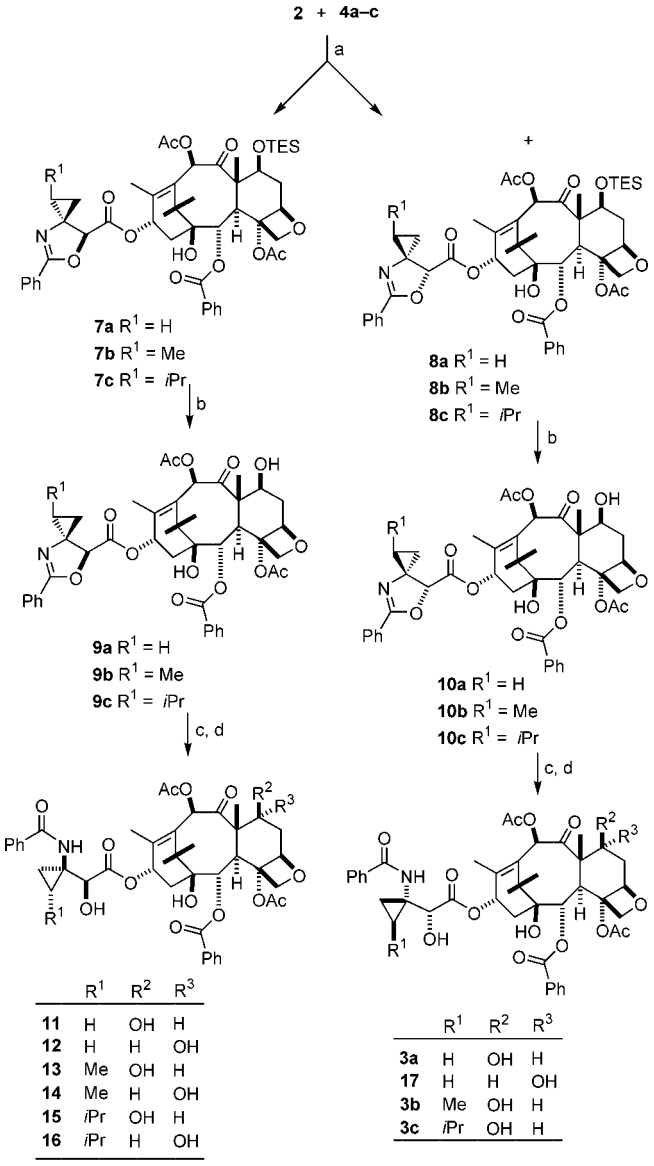
The products **7a** and **8a** proved to be resistant to hydrolysis under the conditions previously used [0.1 N HCl/dioxane (1:1)].[10] Only starting material and various decomposition products could be detected under the literature conditions, while prolonged reaction times led to cleavage of the side chain. Surprisingly, however, when the triethylsilyl groups in **7a** and **8a** were first removed by treatment with HF/pyridine, and the product subsequently hydrolyzed with 0.1 N HCl/dioxane (1:1) at 50 °C, the 3′-amino-2′-*O*-benzoyl derivatives were obtained. These compounds proved to be less prone than other related taxol analogs to rearrangement by



Scheme 1. Synthesis of cyclopropanes **4a**–**4c**. (a) NaH, MeCN, 0 °C to room temp., 20 h, 16–60%; (b) NaOH, THF, room temp., 20 h, 58–100%.

benzoyl migration from the 2′-hydroxy group to the 3′-amino group.[19] Thus, benzoyl group migration did not take place under neutral aqueous conditions and basic non-aqueous conditions, and the 2′-*O*-benzoyl derivative was formed (structure not shown). Treatment of the 2′-*O*-benzoyl derivative with 0.1 N $NaHCO_3$/dioxane (1:1) led to clean rearrangement, however, and the four cyclopropane-containing paclitaxel analogs **11**, **12**, **3a**, and **17** were obtained. High-resolution FAB mass spectra (HRFABMS) showed that all four compounds had the same mass and elemental composition. The chemical shift differences between the 7-H and 10-H protons in the ^{1}H NMR spectra of compounds **11** and **12** (or **3a** and **17**) were quite large. By comparison with literature values,[20] it could be concluded that **12** and **17** sustain the (7*R*) (7-*epi*) configuration rather than the normal (7*S*) configuration. The epimerization to form small amounts of the C-7 epimers is an expected occurrence under the slightly basic conditions of the reaction.[4a]

Syntheses of the related taxol analogs **3b**–**c** and **13**–**16** were similar to those described above, except that the DCC/4-PP coupling conditions were replaced by EDC/DMAP conditions for easier workup. Small amounts of the C-7 epimers of **3b** and **3c** were also formed, but the quantities were too small for complete characterization. With a methyl or isopropyl group on the cyclopropane ring, compounds **9b**–**9c** and **10b**–**10c** turned out to be slightly more resistant to acid hydrolysis, but reaction could be achieved by raising the temperature and prolonging the reaction time. The benzoyl migration from the 2′-hydroxy group to the 3′-amino group also occurred less readily, and a longer time was needed. In the case of compounds **9b** and **9c**, the final products **13**–**16** underwent epimerization at the taxol 7-OH group under slightly basic aqueous conditions, like compounds **9a** and **10a**. Compounds **10b** and **10c**, on the other hand, gave only **3b** and **3c** with the normal taxol C-7 configuration.

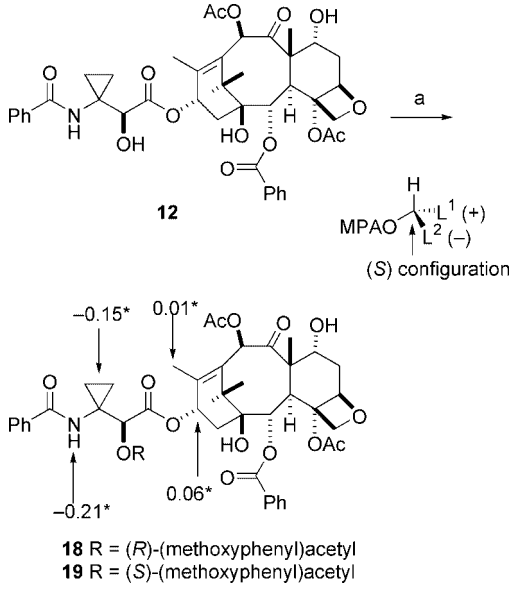


Scheme 2. Synthesis of C-3′-cyclopropanated taxol analogs. (a) DCC or EDC, 4-PP, toluene, room temp., 24 h, 85%; (b) HF/pyridine, THF, 0 °C to room temp., 24 h, 90%; (c) 0.1 N HCl/1,4-dioxane (1:1), 50 °C, 1–3 h, 85%; (d) 0.1 N $NaHCO_3$/1,4-dioxane (1:1), room temp., 6–24 h, 80%.

Results and Discussion

Determination of the Absolute Configuration at the 2′-Position

In order to determine the absolute configuration at the 2′-position, compound **12** was converted to two esters with (*R*)- or (*S*)-α-methoxyphenylacetic acid (MPA), using the EDC/DMAP coupling conditions. Since the hydroxy groups at C-1 and C-7 in this compound are highly hindered,[21] reaction occurred only at the 2′-OH position to yield the Mosher esters **18** and **19**. This observation also supports the assigned configuration being (*R*) at C-7 for **12** and **17**. The resulting 2′-MPA esters **18** and **19** were subjected to NMR analysis.[22] Fortunately, the chemical shift differences $\Delta\delta^{RS}$ were significant (Scheme 3). From these data it was concluded that the taxoid **12** must have the (*S*) configuration at C-2′, which is the configuration of 2′-*epi*-paclitaxel. Thus, the diastereomers **3a** and **17** must be (2′*R*), and **11** must be (2′*S*).



Scheme 3. Determination of the absolute configuration of **12**. (a) (*R*)-α-Methoxyphenylacetic acid or (*S*)-α-methoxyphenylacetic acid, EDC, DMAP, CH_2Cl_2, room temp., 24 h, 85%. $*\Delta\delta^{RS} = \delta^R(\mathbf{18}) - \delta^S(\mathbf{19})$.

The absolute configurations at C-2′ for **13**–**16** and **3b**–**c** were also checked using the Mosher ester analysis. From these data it was concluded that taxoids **14** and **16** have the (*S*) configuration at C-2′. The diastereomers **3b** and **3c** must thus be (2′*R*), while **13** and **15** must be (2′*S*).

Cytotoxicity and Tubulin Assembly Assays

The bioactivities of taxoids **3a**–**c** and **11**–**17** were compared in the tubulin-assembly assay, the A2780 ovarian cancer cell line, and the PC-3 prostate cancer cell line (Table 1). In general, taxoids with the unnatural configuration at the 2′ position were much less active, while configuration at the C-7 position plays a less important role for activity. The most active compounds were the taxoids **3b** and **3c** with the naturally occurring configuration at both C-2′ and C-7. In the tubulin-assembly assay, both compounds are less active than taxol by a factor of 4–5. The cytotoxicities of compounds **3b** and **3c** in the A2780 and PC-3 cell lines were also less than that of taxol itself. In the A2780 cell line, all of the cyclopropanated taxoids are much less active than taxol (50–1000×), but **3b** and **3c** were only about an order of magnitude less active in the PC-3 cell line. The activities appear to be related to the substituents on the cyclopropane ring. As the proton was changed to methyl, activity increases by factors of 5 and 3 were observed in the tubulin-assembly assay and the A2780 ovarian cancer cell line, respectively. The same trend was observed for the change from methyl to isopropyl, although the activity does not

increase as dramatically in the same two assays. A plausible explanation lies in the greater hydrophobicity of the ligands accompanied by an entropy gain in the binding free energy as the ligand leaves the aqueous milieu and associates with the hydrophobic binding pocket within the protein.

Table 1. Tubulin polymerization (ED_{50} values) and cytotoxicities (IC_{50} values) of compounds **3a–c** and **11–17**.

Compound	Tubulin assembly ED_{50} [μM]	A2780 IC_{50} [μM]	PC-3 IC_{50} [μM]
Taxol (**1**)	0.25	0.024 ± 0.012	0.052
3a	6.7	8.2 ± 0.6	>6.6
3b	1.3	2.9 ± 0.8	0.69
3c	0.92	1.2 ± 0.1	0.69
11	>30	>25	>6.6
12	>30	22 ± 1	>6.6
13	9.5	19 ± 1	6.45
14	8.4	21 ± 1	10.0
15	1.8	3.4 ± 1.0	0.88
16	1.7	5.4 ± 0.2	0.95
17	12	9.5 ± 0.3	>6.6

The observation that compounds **11–17** are even less active than diastereomeric **3b** and **3c** is consistent with the above-mentioned configurational assignments, as taxoids with a (2′*S*) configuration are usually less active than those with a (2′*R*) configuration.[19,23]

The Conformation of Taxol on β-Tubulin: The C-3′ Problem

The electron crystallographic (EC) analysis of zinc-stabilized microtubule sheets has provided a clear picture of the secondary elements of the α,β-tubulin dimer[24] and confirmed the location of the taxoid binding site originally located by photoaffinity labeling.[25] Subsequent analysis of the EC structure and the corresponding density allowed derivation of a model of the paclitaxel-binding conformation, namely T-taxol.[11] Several follow-up studies provided support for this conformation, but the most definitive evidence came from the design, synthesis and bioassay of a series of paclitaxel analogs bridged between the 4-OAc methyl group and the *ortho* position of the phenyl moiety at C-3′.[26] Figure 1a illustrates the near-space alignment of the C-4 and C-3′ centers in the T-taxol form. Figure 1b shows how a short bridge maintains the integrity of the conformation while permitting the terminal phenyl rings from the benzamido unit at C-3′ and the benzoyl unit at C-2 to surround His227 in β-tubulin.[11] Bridging in this manner is highly effective at stabilizing the T-taxol shape. The compounds proved to match and surpass taxol in both their microtubule-stabilizing capacity and cytotoxicity.[12,13] More recently, the French team reported an efficient route to a highly active series of taxol analogs bridged between the C-2 benzoyl phenyl group and an alkyl replacement of the 3′-benzamido functionality.[14] While all the compounds were significantly weaker cytotoxins than docetaxel, unsaturated (*E*) and (*Z*) analogs with a C_7 spacer linking the 3′-NHC(=O) carbon atom and the *meta* position of the terminal 2-phenyl group proved to be as active as PTX in the tubulin aggregation assay. A docking study concluded that the T-conformer is the preferred form for optimal binding to β-tubulin.

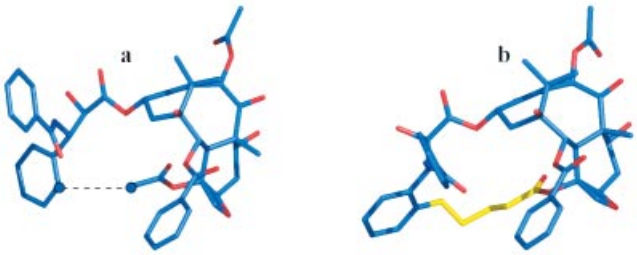


Figure 1. Taxol analog conformations at the β-tubulin binding site. a) T-Taxol conformer illustrating the close contact between the 4-OAc methyl group and the *ortho* position of the phenyl group at C-3′; b) A C-4–C3′-bridged taxane with activity equivalent to parent taxol.

One of the consequences of this conformation as the bioactive one is that the proton at C-3′ is directed into the concave cavity of paclitaxel when the molecule is bound to the protein. As depicted by Figure 2a, 3′-H is well above van der Waals contact with the 4-OAc methyl protons (i.e. 2.7 Å[27]). Were this proton to be replaced by an alkyl group, it would have difficulty achieving the T-taxol local minimum energy conformation as a result of steric repulsion. Indeed, 3′-methyltaxotere is devoid of activity in microtubule-stabilization assays.[28]

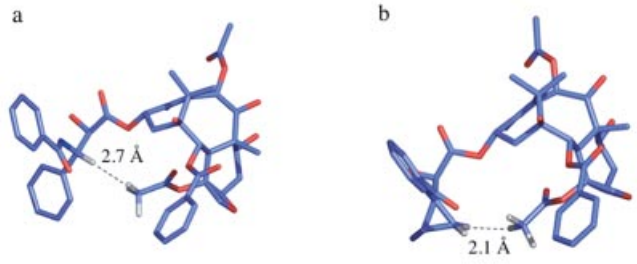


Figure 2. T-Taxol conformations illustrating the potential for steric congestion between the 4-OAc methyl group and the C-3′ center. a) The H···H distances between 3′-H and the 4-OAc methyl group in T-taxol are above the sum of the van der Waals radii (2.7 Å); b) cyclopropyl H atoms as in **3b** engage in severe van der Waals contacts with the 4-OAc methyl group (2.1 Å).

Internal Strain in the C-3′-Cyclopropanated Taxoids

In the cyclopropyl series of Table 1, the 3′-phenyl group of paclitaxel is replaced by CHR^1, namely the edge of the cyclopropane that would formally confer the (*S*) configuration on C-3′. It is well known that alkyl and alkenyl substitutions at this center are well tolerated.[29–31] However, for **3a–c** and **11–17** the 3′-H atom is also replaced with CH_2 of the cyclopropane to generate a quaternary center. While tetrasubstitution at C-2′ has been shown to provide taxanes with activity comparable to taxol,[32,33] to the best of our knowledge the C-3′ variant has not been previously re-

ported to deliver effective *anti*-tubulin agents. In fact, as speculated for the 3′-methyl group mentioned above, the cyclopropane CH_2 group most likely experiences a strongly disfavored steric clash with the 4-OAc methyl group in the T-taxol conformation (Figure 2b). While cyclopropanes **3a**–**c** and **11**–**17** cannot undergo full torsional relaxation within the tubulin binding site, a molecular dynamics treatment of the **3b**–tubulin complex demonstrates that, although the cyclopropyl methyl group overlaps nicely with the 3′-phenyl group, the ligand's reaction to internal steric compression is to uncoil to a sufficient extent to reposition the 3′-benzamidophenyl group 2.0–2.2 Å further away from the baccatin core by comparison with taxol. As a result, the terminal phenyl group of the taxoid suffers conflict with tubulin side chains in the hydrophobic binding pocket similar to what we reported for a pair of low-activity bridged taxoids,[34] although the conflict is with the side rather than the bottom of the taxoid pocket (Figure 3).

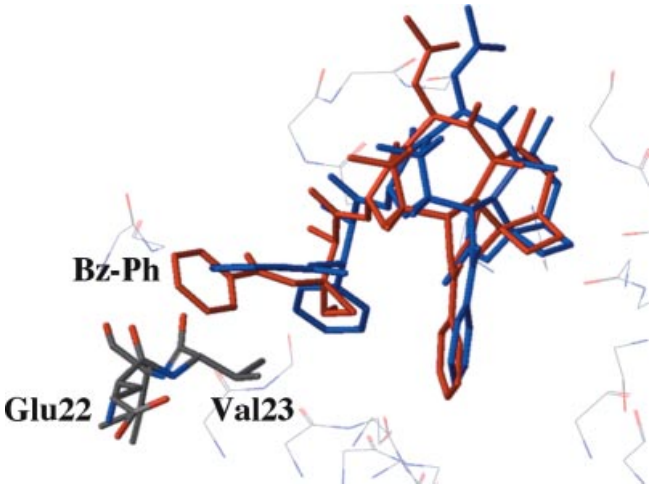


Figure 3. T-Taxol (blue) and cyclopropyl analog **3b** (red) docked in the β-tubulin binding pocket and relaxed by low-temperature molecular dynamics. In response to internal steric strain in the concave region of the molecule, the molecular volume of the **3b** expands by 2.0–2.2 Å from C-4 to C-3′ and places the 3′-benzamido phenyl group (Bz-Ph) in unfavorable contact with tubulin's Glu22 and Val23 residues.

One possible resolution of the problem is to retain the substituted cyclopropyl group, but eliminate the acetate substituent at C-4. Both 4-deacetyl-[35,36] and 4-deacetoxytaxol[37] are known, but the compounds are ineffective in tubulin assembly and cytotoxicity bioassays. By contrast, the compound incorporating the simple and less congested 4-methoxy compound is nearly as active as parents taxol and docetaxel.[38] Conceivably, the combination of 4-OR (R = H, Me) and C-3′-cyclopropanated taxol modifications might induce activity in the analog series of Table 1.

Solution Conformations of Cyclopropane 3b: NMR/NAMFIS Analysis

In the original proposal for a T-shaped taxol conformation as the bioactive binding form on β-tubulin[11] and in several subsequent studies with taxane derivatives,[33,34,39,40] conformational analyses were performed on the compounds in solution. The combination of a 2D NMR NOESY or ROESY experiment, an exhaustive conformational analysis and a NAMFIS (*N*MR *a*nalysis of *m*olecular *f*lexibility *i*n *s*olution)[41,42] deconvolution of the averaged NMR spectrum provided minimum-energy conformers assigned specific populations in the dynamic conformational equilibrium. In all these cases involving active taxanes, T-forms were found among the set of solution conformations and presumed to serve as the bioactive forms.

Above, we have rationalized the lack of activity of the C-3′-cyclopropanated taxanes as due to an excessive energy penalty associated with achieving the T-taxol conformation. To substantiate this interpretation, we have performed a 2D ROESY analysis for **3b** in $CDCl_3$, the results of which are given in Table 2. Sixteen well-resolved ROE cross-peak amplitudes provided the same number of intramolecular separations by comparison with the *r*[H(3)–H(10)] standard distance of 2.9 Å. Two additional weak cross peaks (see Table 2) were arbitrarily assigned internal separations of 4.0 Å. Conformers of **3b** were generated by an MMFF/GBSA/H_2O conformational search in MacroModel yielding 139 fully optimized conformers, the global minimum having been located 109 times during the 10000 step search. NAMFIS intersection of the NMR spectroscopic data and the conformational dataset identified five conformations with populations of 31, 25, 24, 17 and 4% that match the data quite well (SSD[41,42] = 29). None correspond to the T-taxane conformation. The first, second and fifth forms involve hydrophobic collapse of the terminal phenyl rings of 3′-NHCOPh and 2-OCOPh as expected for the non-polar taxol conformer.[43] The third and fourth forms locate the side chain terminal phenyl and cyclopropyl groups in very different regions of space by comparison with the corresponding side chain phenyl groups of taxol.

Figure 4 illustrates the relationship of the five NAMFIS-derived conformers with T-taxol. Four atoms of the rigid baccatin rings of all six structures have been superimposed. At the right of the graphical composite, the baccatin cores, the 2-benzoyl groups and the 10-acetyl groups are nicely aligned. By contrast, at the terminus of the C-13 side chain in the foreground of the graphic, serious misalignment with the phenyl rings of T-taxol rendered in blue is observed. In two cases, the methyl groups on the cyclopropanes are situated near the center of the 3′-phenyl ring of taxol (Figure 4, yellow and red). In all of the conformations, the benzamido side chains of the same taxoids occupy entirely different regions of space in comparison with the parent ligand. If the T-taxol conformation of **3b** is a torsional partner in the conformer equilibrium mixture in solution, it would appear to fall in the NMR noise; i.e. at or below a population of 3%.

To ascertain whether T-forms exist at all within the 139 conformer dataset, we searched the latter against T-taxol by requiring a 3-D match of five baccatin core atoms, the centroids of the 3′-NHCOPh and 2-OCOPh phenyl rings and the 3-Ph vs. the cyclopropyl–Me group, respectively.

Table 2. Interproton distances [Å] for **3b** calculated from 2D NMR ROESY measurements in $CDCl_3$.

Proton interactions	ROESY distances	NAMFIS average distances	Difference
H(5′α or β)–H(2′)	2.70	2.52	0.18
H(6′)–H(2′)	2.50	2.76	0.26
H(4-OAc)–H(2′)	3.10	3.26	0.16
H(10)–H(3)	(2.90)[a]	–	–
H(CONH)–H(5′)	3.00	3.77	0.77
H(6α)–H(6β)	2.00	1.73	0.27
H(3)–H(7)	2.50	2.35	0.15
H(2)–H(16)	2.50	2.59	0.09
H(10)–H(7)	2.40	2.36	0.04
H(10)–H(18)	2.30	2.57	0.27
H(13)–H(17)	2.40	2.58	0.18
H(2)–H(19)	2.60	2.80	0.20
H(6α)–H(7)	3.00	2.40	0.60
H(6α)–H(5)	2.40	2.24	0.16
H(CONH)–H(3′-Ph-*o*-H)	2.80	2.79	0.01
H(20β)–H(19)	3.10	4.23	1.13
H(20α)–H(19)	2.40	2.55	0.15
H(20α,β)–H(2-Ph-*o*-H)	weak[b] (4.00)	4.04	0.04
H(20β)–H(2)	weak[b] (4.00)	3.04	0.96

[a] Standard cross peak/distance from which all other distances were obtained. [b] These weak peaks could not be quantified accurately. Thus, the distances were assumed to be 4.0 Å.

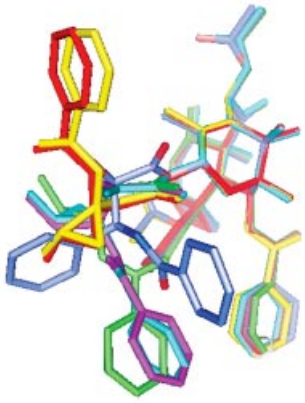


Figure 4. Five NAMFIS conformations of cyclopropane **3b** in $CDCl_3$ (green, magenta, yellow, red, cyan) superimposed on the T-taxol conformer (blue) within the baccatin core. At the C-13 termini, neither the phenyl rings nor the cyclopropane rings of the synthetic taxoids match the phenyl rings of taxol. Two methyl groups (yellow and red) fall near the middle of taxol's 3′-phenyl group.

No structures fall within an overall root mean square deviation of 1.0 Å. Graphical inspection of those exhibiting a 1.0 to 1.5 Å rms deviation from the T-taxol target illustrates sufficient structural deviation to eliminate these conformers from consideration as the bioactive form within the β-tubulin binding site. In sum, neither the NAMFIS-determined conformations in $CDCl_3$ nor the MMFF database of minimized torsional rotamers contains the T-taxoid form.

Conclusions

A series of C-3′-cyclopropanated taxols was synthesized and assayed for microtubule stabilization and cytotoxicity against two cell lines. While the tubulin assembly measurements demonstrate compound activities ranging from 4 to >120-fold poorer than taxol, the cell-based assessments show IC_{50}(cyclopropane)/IC_{50}(taxol) ratios from 13–1000 (Table 1). Although a number of interplaying factors can account for both the differences between the isolated tubulin and cell-based assays and the range of responses as a function of cyclopropane substitution, the common factor for all compounds is the incorporation of a quaternary center at C-3′. In the C-13 side chain rotamer believed to represent the bioactive T-taxoid conformation, the methylene group (CH_2) of a cyclopropanated taxane would encounter the methyl group of the 4-acetyl group to produce structures incompatible with productive binding to the protein. This scenario explains the uniformly lowered activity for the C-3′-cyclopropanated taxanes cited in Table 1. Relative to taxol, the best compounds, **3b** and **3c**, are 4–6-fold and 10–120-fold less potent in the tubulin polymerization and cytotoxicity assays, respectively. The activity reduction is very similar to that observed for bridged taxols incorporating less than optimal linkers between C-4 and C-3′ (10-fold).[34] In that case, the loss of activity was traceable to an unfavorable interaction between ligand and protein analogous to that depicted in Figure 3. An added perturbation for the C-3′-cyclopropanated derivatives is the internal strain caused by the short interatomic contacts shown in the constrained T-form of Figure 2b. According to MD relaxation within the tubulin binding pocket, the structure of **3b** does not remain in this rotameric state. The cyclopropyl group twists away from the 4-acetyl group, displaces the 3′-benzamido phenyl group and causes the unfavorable interactions with the protein depicted in Figure 3. Thus, while the cyclopropanated taxane ligand can still fit within the β-tubulin binding pocket, there is an energy penalty contributing to the reduced activity. These considerations are also consistent with the failure of the NAMFIS treatment to detect T-taxoid forms for **3b** in solution. The latter observation contrasts with previous NMR/NAMFIS solution analyses of taxanes with moderate to high activity, all of

which evidence at least a low population contribution of the T-conformer.[33,34,39,40] The analysis for **3b** implies that a distorted T-form (Figures 3 and 4) is most likely the best binding compromise for C-3′-cyclopropanated analogs, but that it leads to weak activity in the most favorable cases. The result provides indirect confirmation that the T-geometry is the bound form for unstrained taxanes on α,β-tubulin. Within the context of the classic baccatin core, the loss of activity by C-3′ substitution would seem to be general. It suggests, however, that taxol-like activity for the cyclopropanoids might be recoverable in 4-deacetylated analogs or in the corresponding ethers.

Experimental Section

General: ^{1}H and ^{13}C NMR: Spectra were recorded at 600 (^{1}H), and 62.9, 75.5 (^{13}C, additional DEPT or APT) MHz with Varian INOVA 600, Bruker AM 250 and Varian Mercury 300 instruments in $CDCl_3$, C_6D_6 or [D_6]acetone solution and, if not otherwise specified, solvent residual signals used as internal reference; δ in ppm, J in Hz. ^{1}H-NOE experiments were recorded at 600 MHz with a Varian INOVA 600 instrument in C_6D_6 solution. IR: Bruker IFS 66 (FT-IR) instrument, measured as KBr pellets, oils as films between KBr plates. MS (EI) and HRMS (EI): Finnigan MAT 95 spectrometer. M.p.: Büchi 510 capillary melting point apparatus, values are uncorrected. TLC: Macherey & Nagel precoated sheets, 0.20 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 70–230 mesh ASTM. Starting materials: Anhydrous acetonitrile was distilled from CaH_2. Tetrachlorocyclopropene[44] and methyl (*E*/*Z*)-2-chloro-2-(2′-methylcyclopropylidene)acetate[45] were prepared according to published procedures. All other chemicals were used as commercially available from Merck/VWR, Aldrich, Acros and Bayer. For the synthesis of all other compounds, chemicals were obtained from Aldrich Chemical Co. and were used without further purification. All solvents were of reagent grade or HPLC grade. THF was distilled from sodium/benzophenone, and CH_2Cl_2 was distilled from calcium hydride. All ^{1}H NMR spectroscopic data were obtained in $CDCl_3$ or CD_3OD with Varian Unity 400 spectrometer (operating at 399.951 MHz for ^{1}H and 100.578 MHz for ^{13}C). Mass spectra were obtained at the Analytical Service in the Department of Chemistry (HRFABMS) or Department of Biochemistry (MALDI-TOF MS) at Virginia Tech.

Methyl (*E*/*Z*)-2-Chloro-2-(2′-isopropylcyclopropylidene)acetate (5c):[44] A sampling cylinder (320 mL, monel alloy) was charged with tetrachlorocyclopropene.[44] (80.0 g, 0.449 mol), 3-methyl-1-butene (94.6 g, 1.35 mol) and anhydrous potassium carbonate (8.9 g, 64 mmol). The carefully sealed cylinder was heated at 170 °C for 20 h. After cooling to ambient temperature, the cylinder was emptied and rinsed with dichloromethane (2 × 30 mL). The brown reaction mixture was filtered to remove inorganic salts. The excess of 3-methyl-1-butene and the dichloromethane were removed under reduced pressure and the liquid residue was bulb-to-bulb-distilled (70 °C, 0.01 mbar) to yield 86.2 g (77%) of (*E*/*Z*)-1-chloro-2-isopropyl-1-(trichlorovinyl)cyclopropane as a pale yellow liquid, (*E*)/(*Z*) ratio 1.37:1 according to GC (column: CP-SIL 5 CB, 25 m). This product was used for the subsequent transformation without further purification. Into a stirred solution of sodium methoxide [freshly prepared by disolving sodium (39.4 g, 1.71 mol) in anhydrous methanol (400 mL)] was added dropwise a solution of (*E*/*Z*)-1-chloro-2-isopropyl-1-(trichlorovinyl)cyclopropane (53.1 g, 0.214 mol) in anhydrous methanol (60 mL) at 5 °C. The mixture was stirred at ambient temperature for 17 h and then heated under reflux for an additional 2 d. After cooling to ambient temperature, cold water (900 mL) was added. The brown solution was extracted with dichloromethane (6 × 150 mL), and the combined organic layers, containing trimethyl (*E*/*Z*)-2-chloro-2-(2′-isopropylcyclopropylidene)orthoacetate, were concentrated to a volume of ca. 600 mL. Strongly acidic ion exchange resin (46 g) (Bayer) catalyst K 2621, (styrene-divinylbenzene copolymer with sulfonic acid groups) was added, and the mixture stirred vigorously for 21 h. The catalyst was filtered off and washed with dichloromethane (100 mL). After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel (200 g, 3.8 × 35 cm) eluting with pentane/ether (20:1), R_f = 0.32, to yield 23.1 g (57%) of (*E*/*Z*)-2-chloro-2-(2′-isopropylcyclopropylidene)acetate as a pale yellow liquid, (*E*)/(*Z*) ratio 2.64:1 according to GC (column: CP-SIL 5CB, 25 m). IR (KBr, film): $\tilde{\nu}$ = 2959 cm^{-1}, 2872, 1732, 1436, 1264, 1065, 908, 760. ^{1}H NMR (600 MHz, C_6D_6): Major isomer (*E*): δ = 0.76 (d, ^3J = 6.6 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.91–0.96 (m, 1 H), 1.07–1.12 (m, 1 H), 1.17–1.25 (m, 2 H), 3.37 (s, 3 H); minor isomer (*Z*): δ = 0.65 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 1.08–1.11 (m, 1 H), 1.28–1.34 (m, 1 H), 1.45–1.53 (m, 1 H), 1.53–1.58 (m, 1 H), 3.33 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, add. APT): Major isomer (*E*): δ = 13.7 (–), 21.5 (+), 21.7 (+), 26.0 (+), 30.7 (+), 52.9 (+), 114.1 (–), 143.5 (–), 162.9 (–); minor isomer (*Z*): δ = 8.9 (–), 19.9 (+), 21.4 (+), 29.7 (+), 29.9 (+), 52.7 (+), 112.9 (–), 143.9 (–), 162.6 (–) ppm. MS (EI, 70 eV): *m*/*z* (%) = 189/187 (11/26) [M]$^+$, 175 (40), 173 (100), 157 (12), 121 (22), 105 (28), 93 (81), 91 (60), 77 (49), 69 (21), 59 (13).

Methyl (5′*S)-2′-Isopropyl-2-phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylate (6c):** A solution of methyl (*E*/*Z*)-2-chloro-2-(2′-isopropylcyclopropylidene)acetate [ratio (*E*)/(*Z*) 2.64:1] (3.773 g, 20.0 mmol) and benzamide (2.423 g, 20.0 mmol) in anhydrous acetonitrile (90 mL) was treated with NaH (0.920 g, 23.0 mmol, 60% dispersion in mineral oil) at 0 °C. The suspension was subsequently stirred at ambient temperature for 20 h. The whole reaction mixture was filtered through silica gel (10 g, 2.5 × 4 cm), the silica gel was rinsed with diethyl ether (250 mL), and the solvents were removed. The oily residue was subjected to column chromatography on silica gel (170 g, 3.7 × 30 cm) eluting with pentane/ether (10:1), R_f = 0.23, to yield 834 mg (16%) of **6c** as a colorless oil. The stereochemical assignments rest on NOE experiments. IR (KBr): $\tilde{\nu}$ = 2956 cm^{-1}, 1763, 1745, 1653, 1636, 1451, 1287, 1061, 695. ^{1}H NMR (600 MHz, C_6D_6): δ = 0.66 (dd, ^3J = 5.6, 6.7 Hz, 1 H), 0.83 (d, J = 6.7 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 1.09–1.19 (m, 1 H), 1.31 (ddd, J = 6.7, 9.6, 10.7 Hz, 1 H), 1.44 (dd, J = 5.5, 9.4 Hz, 1 H), 3.23 (s, 3 H), 4.90 (s, 1 H), 7.02–7.06 (m, 3 H), 8.19–8.23 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, add. DEPT): δ = 15.3 (–), 21.9 (+), 28.0 (+), 32.0 (+), 52.1 (+), 57.9 (C_{quat}), 76.1 (+), 126.9 (C_{quat}), 127.8 (+), 128.2 (+), 131.2 (+), 162.1 (C_{quat}), 169.8 (C_{quat}) ppm. MS (EI, 70 eV): *m*/*z* (%) = 273 (17) [M$^+$], 230 (100), 217 (17), 186 (26), 158 (21), 105 (27), 77 (10). $C_{16}H_{19}NO_3$: calcd. C 70.31, H 7.01, N 5.13; found C 70.17, H 6.84, N 5.05.

(5*S)-2′-Isopropyl-2-phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylic Acid (4c):** A solution of **6c** (600 mg, 2.2 mmol) in tetrahydrofuran (41 mL) was stirred vigorously with 5 N aqueous sodium hydroxide (6.2 mL) at ambient temperature for 22 h. After addition of acetic acid (10 mL) and stirring for an additional 10 min, all solvents were removed under reduced pressure. The residue was taken up in water (25 mL) and the aqueous solution was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with water (25 mL). After removal of the solvent, the residual colorless solid was filtered through silica gel (11 g,

1.5 × 6 cm) eluting with dichloromethane to remove residual acetic acid, then eluting the product with ether/methanol (10:1). Yield, after careful drying under reduced pressure, 388 mg (68%) of **4c** as a colorless solid, m.p. 70–72 °C. IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 1734, 1646, 1452, 1264, 1069, 694. ^1H NMR (600 MHz, [D$_6$]acetone): δ = 0.73 (dd, ^3J = 5.7, 5.9 Hz, 1 H), 1.04 (d, ^3J = 6.6 Hz, 3 H), 1.07 (d, ^3J = 6.6 Hz, 3 H), 1.10–1.30 (m, 3 H), 4.91 (s, 1 H), 7.44–7.49 (m, 2 H), 7.51–7.55 (m, 1 H), 7.91–7.95 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, add. DEPT): δ = 14.9 (–), 22.0 (+), 27.9 (+), 31.8 (+), 56.9 (C_{quat}), 76.3 (+), 126.0 (C_{quat}), 128.2 (+), 128.4 (+), 131.9 (+), 163.8 (C_{quat}), 172.0 (C_{quat}) ppm. MS (EI, 70 eV): *m*/*z* (%) = 259 (18) [M$^+$], 216 (100), 203 (20), 158 (17), 144 (13), 105 (54), 77 (17). HRMS (EI, 70 eV) calcd. for $C_{15}H_{17}NO_3$ [M$^+$] 259.1208, found 259.1208.

General Procedure for Acylation at C-13 of 7-TES-Baccatin III: To a solution of **4a** (70 mg, 0.32 mmol) in toluene (4 mL) was added DCC (68 mg, 0.32 mmol). After stirring at room temperature for 15 min, 4-PP (3 mg, cat.) was added and stirring was continued for 5 min before 7-TES-baccatin III (**2**) (75 mg, 0.11 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. It was then diluted with ethyl acetate (50 mL). The organic phase was washed with sodium hydrogencarbonate, water, brine, dried with sodium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (30% EtOAc/hexane) to give **7a** (35 mg, 36%) and **8a** (48 mg, 49%). Compounds **7b** (65%), **7c** (50%), and **8b** (35%) and **8c** (34%) were prepared similarly using EDC.

(7-TES-baccatin III)-13-yl (5*S*)-2-Phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylate (7a): ^1H NMR (400 MHz, $CDCl_3$): δ = 0.64 (dq, *J* = 7.9, 2.3 Hz, 6 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 1.05 (m, 1 H), 1.18–1.36 (m, 2 H, overlapped), 1.23 (s, 3 H), 1.26 (s, 3 H), 1.71 (s, 3 H), 1.90 (m, 1 H), 2.13 (d, *J* = 1.1 Hz, 3 H), 2.20 (s, 3 H), 2.21 (s, 3 H), 2.17–2.25 (m, 1 H), 2.40–2.58 (m, 2 H, overlapped), 3.81 (d, *J* = 7.1 Hz, 1 H), 4.17 (d, *J* = 8.3 Hz, 1 H), 4.31 (d, *J* = 8.3 Hz, 1 H), 4.48 (dd, *J* = 10.7, 6.6 Hz, 1 H), 4.91 (dd, *J* = 9.4, 1.6 Hz, 1 H), 5.07 (s, 1 H), 5.71 (d, *J* = 7.1 Hz, 1 H), 6.17 (dt, *J* = 8.9, 1.3 Hz, 1 H), 6.48 (s, 1 H), 7.44–7.58 (m, 5 H, Ar, overlapped), 7.64 (m, 1 H, Ar), 7.99 (m, 2 H, Ar), 8.09 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.5, 6.9, 10.2, 11.5, 14.3, 14.8, 21.0, 21.4, 22.5, 26.8, 36.3, 37.4, 43.5, 46.9, 53.5, 58.7, 72.1, 72.4, 75.0, 75.1, 76.6, 79.4, 80.2, 81.2, 84.3, 126.9, 128.2, 128.7, 128.8, 129.4, 130.2, 131.9, 133.9, 134.2, 139.6, 163.6, 167.2, 168.9, 169.5, 169.8, 201.8 ppm. HRFABMS: calcd. for $C_{49}H_{62}NO_{13}S$ [M + H$^+$] 900.3990, found: 900.3983.

(7-TES-baccatin III)-13-yl (5*R*)-2-Phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylate (8a): ^1H NMR (400 MHz, $CDCl_3$): δ = 0.57 (m, 6 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 1.21 (s, 3 H), 1.25 (s, 3 H), 1.19–1.44 (m, 4 H, overlapped), 1.71 (s, 3 H), 1.91 (m, 1 H), 1.99 (d, *J* = 1.2 Hz, 3 H), 2.18 (s, 3 H), 2.19–2.29 (m, 1 H), 2.35 (s, 3 H), 2.43–2.59 (m, 2 H, overlapped), 3.80 (d, *J* = 7.0 Hz, 1 H), 4.17 (d, *J* = 8.3 Hz, 1 H), 4.34 (d, *J* = 8.3 Hz, 1 H), 4.47 (dd, *J* = 10.5, 6.6 Hz, 1 H), 4.98–5.00 (2 H, overlapped), 5.71 (d, *J* = 7.0 Hz, 1 H), 6.00 (dt, *J* = 8.9, 1.3 Hz, 1 H), 6.42 (s, 1 H), 7.45–7.57 (m, 5 H, Ar, overlapped), 7.64 (m, 1 H, Ar), 8.09 (m, 2 H, Ar), 8.11 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.4, 6.9, 10.2, 10.3, 14.7, 15.3, 21.0, 21.2, 22.2, 26.9, 36.2, 37.4, 43.4, 47.1, 53.9, 58.6, 72.5, 72.7, 75.0, 75.2, 76.6, 79.3, 79.5, 81.1, 84.3, 126.9, 128.4, 128.6, 128.8, 129.4, 130.2, 131.8, 133.9, 134.0, 140.2, 163.7, 167.2, 169.32, 169.33, 169.7, 201.9 ppm. HRFABMS: calcd. for $C_{49}H_{62}NO_{13}Si$ [M + H$^+$] 900.3999, found 900.3990.

General Procedure for Silyl Deprotection: To a solution of **7a** (15.1 mg, 0.0106 mmol), in 0.6 mL of dried THF, was added 0.1 mL of anhydrous pyridine, then the solution was cooled to 0 °C, and 0.1 mL of HF/pyridine (70% HF, 30% pyridine) was added. The reaction mixture was allowed to warm to room temperature, and stirred overnight. The reaction mixture was then diluted with EtOAc, the organic phase was washed with sodium hydrogencarbonate, water, and brine, dried with sodium sulfate, and concentrated in vacuo. The residue was applied to preparative TLC (50% EtOAc/hexane) to give **9a** (12.3 mg, 97%). Compounds **9b** (99%), **9c** (94%), **10a** (99%), **10b** (71%), and **10c** (98%) were prepared similarly.

(Baccatin III)-13-yl (5*S*)-2-Phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylate (9a): ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (m, 2 H, overlapped), 1.17 (s, 3 H), 1.26–1.30 (m, 1 H), 1.30 (s, 3 H), 1.47–1.52 (m, 1 H), 1.69 (s, 3 H), 1.88 (m, 1 H), 2.01 (d, *J* = 1.3 Hz, 3 H), 2.12 (s, 3 H), 2.18–2.25 (m, 1 H), 2.27 (s, 3 H), 2.37–2.58 (m, 2 H, overlapped), 3.79 (d, *J* = 7.1 Hz, 1 H), 4.17 (d, *J* = 8.4 Hz, 1 H), 4.30 (d, *J* = 8.4 Hz, 1 H), 4.44 (m, 1 H), 4.92 (dd, *J* = 7.6, 2.1 Hz, 1 H), 5.09 (s, 1 H), 5.68 (d, *J* = 7.1 Hz, 1 H), 6.26 (td, *J* = 8.9, 1.3 Hz, 1 H), 6.32 (s, 1 H), 7.46–7.59 (m, 5 H, Ar, overlapped), 7.64 (m, 1 H, Ar), 7.99 (m, 2 H, Ar), 8.08 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 11.2, 14.0, 15.1, 20.9, 22.16, 22.20, 26.9, 35.5, 36.3, 43.2, 45.5, 53.2, 58.5, 71.8, 72.1, 75.1, 75.4, 76.3, 79.6, 80.1, 80.9, 84.4, 126.7, 128.0, 128.6, 128.7, 129.1, 130.0, 131.9, 133.2, 133.8, 141.9, 163.5, 166.9, 168.7, 169.8, 171.3, 203.6 ppm. HRFABMS: calcd. for $C_{43}H_{48}NO_{13}$ [M + H$^+$] 786.3126, found 786.3108.

(Baccatin III)-13-yl (5*R*)-2-Phenylspiro[cyclopropane-1′,4-oxazoline]-5-carboxylate (10a): ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (m, 1 H), 1.16 (s, 3 H), 1.17–1.24 (m, 1 H), 1.28 (s, 3 H), 1.25–1.34 (m, 1 H), 1.38–1.45 (m, 1 H), 1.69 (s, 3 H), 1.88 (d, *J* = 1.3 Hz, 3 H), 1.85–1.93 (m, 1 H, overlapped), 2.20–2.30 (m, 1 H, overlapped), 2.24 (s, 3 H), 2.31 (s, 3 H), 2.40–2.60 (m, 2 H, overlapped), 3.79 (d, *J* = 7.1 H, 1 Hz), 4.18 (d, *J* = 8.3 Hz, 1 H), 4.32 (d, *J* = 8.3 Hz, 1 H), 4.42 (m, 1 H), 4.99 (dd, *J* = 7.6, 2.0 Hz, 1 H), 5.02 (s, 1 H), 5.69 (d, *J* = 7.1 Hz, 1 H), 6.08 (dt, *J* = 8.9, 1.3 Hz, 1 H), 6.27 (s, 1 H), 7.46–7.60 (m, 5 H, Ar, overlapped), 7.64 (m, 1 H, Ar), 8.04 (m, 2 H, Ar), 8.08 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 10.3, 15.00, 15.04, 20.8, 21.9, 22.0, 26.9, 35.5, 36.2, 43.2, 45.6, 53.7, 58.5, 72.1, 72.4, 75.0, 75.5, 76.4, 79.5, 80.9, 84.4, 126.7, 128.1, 128.6, 128.7, 129.1, 130.1, 131.8, 133.1, 133.8, 142.3, 163.5, 167.0, 169.0, 169.6, 171.2, 203.7 ppm. HRFABMS: calcd. for $C_{43}H_{48}NO_{13}$ [M + H$^+$] 786.3126, found 786.3115.

General Procedure for Hydrolysis of the Oxazoline Ring: To a solution of compound **9a** (25 mg, 0.032 mmol) in 1,4-dioxane (5 mL) was added HCl (0.1 N, 5 mL) and stirring was continued at 50 °C for 1 h. TLC showed that all the starting material was consumed, and a much more polar compound was formed. Then, 84 mg of $NaHCO_3$ powder was added at room temperature. The reaction mixture was stirred overnight until the TLC showed the highly polar intermediate was converted to two less polar compounds. The reaction mixture was diluted with EtOAc (20 mL), and then washed with water, brine, and dried with sodium sulfate. The organic phase was concentrated under reduced pressure, and the residue was applied to PTLC (50% EtOAc/hexane) to give **11** (7.7 mg, 48%) and **12** (5.1 mg, 32%). Compounds **3a** (50%), **3b** (80%), **3c** (78%), **13** (34%), **14**, (48%), **15** (29%), **16** (45%), and **17** (40%) were prepared by a similar procedure.

3′-(*N*-Debenzoyl)-3′-dephenyl-3′,3′-ethylene-2′-*O*-benzoyl-2′-*epi*-taxol: ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 10 Hz), 1.00 (s, 2 H), 1.18 (s, 3 H), 1.22 (m, 2 H), 1.27 (s, 3 H), 1.72 (s, 3 H), 1.90 (m, 4 H), 2.06 (s, 3 H) 2.28 (s, 3 H), 2.32 (m, 1 H), 2.38 (s, 3 H), 2.44 (m, 1 H), 2.60 (m, 1 H), 3.88 (d, *J* = 6.8 Hz, 1 H), 4.21 (d, *J*

= 8.4 Hz, 1 H), 4.33 (d, *J* = 8.4 Hz, 1 H), 4.48 (dd, *J* = 10, 6.8 Hz, 1 H), 4.55 (s, 1 H), 5.0 (d, *J* = 8 Hz, 1 H), 5.70 (d, *J* = 6.8 Hz, 1 H), 6.34 (t, *J* = 8.8 Hz, 1 H), 6.35 (s, 1 H), 7.52 (m, 4 H), 7.65 (t, *J* = 7.6 Hz), 8.14 (m, 4 H, 2 H) ppm.

3′-Dephenyl-3′,3′-ethylene-2′-*epi*-taxol (11): $[\alpha]_D^{20}$ = –60 (*c* = 0.23). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.24 (s, 3 H), 1.05–1.40 (m, 4 H), 1.68 (s, 3 H), 1.88 (m, 1 H), 2.12 (d, *J* = 1.1 Hz, 3 H), 2.15–2.35 (m, 2 H), 2.24 (s, 3 H), 2.28 (s, 3 H), 2.51–2.61 (m, 1 H), 3.68 (s, 1 H), 3.84 (d, *J* = 7.1 Hz, 1 H), 4.16 (d, *J* = 8.3 Hz, 1 H), 4.29 (d, *J* = 8.3 Hz, 1 H), 4.45 (dd, *J* = 10.7, 6.6 Hz, 1 H), 4.96 (dd, *J* = 7.7, 1.8 Hz, 1 H), 5.66 (d, *J* = 7.1 Hz, 1 H), 6.15 (td, *J* = 8.9, 1.3 Hz, 1 H), 6.34 (s, 1 H), 6.66 (s, 1 H), 7.33–7.52 (m, 5 H), 7.61 (m, 1 H), 7.67 (m, 2 H), 8.05 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 13.7, 14.7, 15.9, 21.1, 21.9, 22.8, 26.9, 35.8, 36.3, 36.8, 43.3, 46.0, 58.8, 72.0, 72.5, 75.1, 75.9, 76.6, 77.3, 79.6, 81.2, 84.6, 127.2, 128.93, 128.94, 129.3, 130.3, 132.5, 132.8, 133.4, 134.0, 143.0, 167.2, 170.3, 170.4, 171.5, 172.3, 204.0 ppm. HRFABMS: calcd. for $C_{43}H_{50}NO_{14}$ [M + H$^+$] 804.3231, found 804.3197.

3′-Dephenyl-3′,3′-ethylene-2′,7-*epi*-taxol (12): $[\alpha]_D^{20}$ = –56 (*c* = 0.41). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.17 (s, 3 H), 1.07–1.31 (m, 4 H), 1.65 (s, 3 H), 1.65–1.75 (m, 1 H), 2.00 (d, *J* = 1.3 Hz, 3 H), 2.19 (s, 3 H), 2.20–2.39 (m, 3 H), 2.39 (s, 3 H), 3.66–3.73 (m, 1 H), 3.72 (s, 1 H), 3.94 (d, *J* = 7.4 Hz, 1 H), 4.33 (d, *J* = 8.6 Hz, 1 H), 4.38 (d, *J* = 8.6 Hz, 1 H), 4.70 (d, *J* = 10.3 Hz, 1 H), 4.92 (dd, *J* = 5.7, 3.3 Hz, 1 H), 5.73 (d, *J* = 7.4 Hz, 1 H), 6.11 (td, *J* = 8.9, 1.5 Hz, 1 H), 6.71 (s, 1 H), 6.83 (s, 1 H), 7.32–7.52 (m, 5 H), 7.62 (m, 1 H), 7.68 (m, 2 H), 8.06 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.6, 15.9, 16.4, 21.1, 21.3, 22.7, 26.2, 35.6, 36.6, 37.0, 40.6, 42.8, 57.8, 71.5, 75.4, 75.9, 77.8, 78.4, 79.5, 82.2, 82.9, 127.3, 128.96, 129.00, 129.4, 130.2, 132.6, 133.1, 133.4, 134.0, 140.3, 167.2, 169.7, 170.9, 172.1, 172.3, 207.5 ppm. HRFABMS: calcd. for $C_{43}H_{49}NO_{14}Na$ [M + Na$^+$] 826.3050, found 826.3050;

3′-Dephenyl-3′,3′-ethylenetaxol (3a): $[\alpha]_D^{20}$ = –68 (*c* = 0.30). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 3 H), 1.27 (s, 3 H), 1.07–1.35 (m, 4 H), 1.69 (s, 3 H), 1.79 (d, *J* = 1.3 Hz, 3 H), 1.88 (m, 1 H), 2.23 (s, 3 H), 2.25–2.38 (m, 2 H), 2.46 (s, 3 H), 2.57 (m, 1 H), 3.82 (d, *J* = 7.1 Hz, 1 H), 3.91 (s, 1 H), 4.18 (d, *J* = 8.5 Hz, 1 H) 4.33 (d, *J* = 8.5 Hz, 1 H), 4.44 (dd, *J* = 10.8, 6.7 Hz, 1 H), 4.99 (dd, *J* = 7.5, 2.1 Hz, 1 H), 5.68 (d, *J* = 7.1 Hz, 1 H), 6.24 (td, *J* = 9.2, 1.5 Hz, 1 H), 6.25 (s, 1 H) 6.83 (s, 1 H), 7.44–7.60 (m, 5 H), 7.64 (m, 1 H), 7.74 (m, 2 H), 8.10 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 13.6, 14.3, 14.8, 20.9, 22.01, 22.04, 26.7, 35.5, 35.9, 37.2, 43.2, 45.6, 58.5, 71.0, 72.1, 75.1, 75.6, 76.4, 77.9, 79.5, 80.7, 84.5, 127.2,128.7, 128.9, 129.2, 129.3, 130.1, 132.59, 132.60, 132.7, 132.8, 133.8, 142.8, 167.0, 170.6, 170.8, 171.2, 172.3, 203.8, 207.4 ppm. HRFABMS: calcd. for $C_{43}H_{50}NO_{14}$ [M + H$^+$] 804.3231, found 804.3239.

3′-Dephenyl-3′,3′-ethylene-7-*epi*-taxol (17): $[\alpha]_D^{20}$ = –70 (*c* = 0.24). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.22 (s, 3 H), 1.08–1.37 (m, 4 H) 1.66 (s, 3 H), 1.71 (d, *J* = 1.4 Hz, 3 H), 2.18 (s, 3 H), 2.23–2.41 (m, 3 H), 2.57 (s, 3 H), 3.69 (m, 1 H), 3.89 (s, 1 H), 3.92 (d, *J* = 7.5 Hz, 1 H), 4.35 (d, *J* = 8.5 Hz, 1 H), 4.41 (d, *J* = 8.5 Hz, 1 H), 4.78 (d, *J* = 11.7 Hz, 1 H), 4.96 (dd, *J* = 5.7, 3.4 Hz, 1 H), 5.76 (d, *J* = 7.5 Hz, 1 H), 6.21 (td, *J* = 9.0, 1.4 Hz, 1 H), 6.74 (s, 1 H) 6.80 (s, 1 H) 7.44–7.60 (m, 5 H) 7.65 (m, 1 H), 7.73 (m, 2 H), 8.12 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 14.6, 14.8, 16.2, 20.9, 21.3, 22.1, 25.9, 35.3, 36.2, 37.5, 40.4, 42.7, 57.6, 70.9, 75.4, 75.7, 77.5, 78.2, 78.6, 79.5, 81.6, 82.8, 127.2, 128.7, 128.9, 129.3, 130.1, 132.5, 132.7, 133.8, 140.3, 167.1, 169.3, 171.2, 172.3, 172.6, 207.4 ppm. HRFABMS: calcd. for $C_{43}H_{50}NO_{14}$ [M + H$^+$] 804.3231, found 804.3226.

(3′*R*)-3′-Dephenyl-3′,3′-[(1*R*)-methylethylene]-2′-*epi*-taxol (13): $[\alpha]_D^{20}$ = –76 (*c* = 0.61). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (m, 1 H), 1.16 (s, 3 H), 1.26 (s, 3 H), 1.34–1.47 (5 H, overlapped), 1.71 (s, 3 H), 1.78 (s, 1 H), 1.87–1.96 (m, 1 H), 2.14 (d, *J* = 1.2 Hz, 3 H), 2.19–2.26 (m, 1 H), 2.27 (s, 3 H), 2.29–2.36 (m, 1 H, overlapped), 2.35 (s, 3 H), 2.54–2.64 (2 H, overlapped), 3.87 (d, *J* = 7.1 Hz, 1 H), 4.00 (br. s, 1 H), 4.19 (d, *J* = 8.4 Hz, 1 H), 4.32 (d, *J* = 8.4 Hz, 1 H), 4.48 (m, 1 H), 4.99 (dd, *J* = 9.4, 1.8 Hz, 1 H), 5.17 (br. s, 1 H), 5.68 (d, *J* = 7.1 Hz, 1 H), 6.18 (dt, *J* = 8.9, 1.2 Hz, 1 H), 6.37 (s, 1 H), 6.68 (s, 1 H), 7.39 (m, 2 H, Ar), 7.46–7.54 (m, 3 H, Ar), 7.64 (m, 1 H, Ar), 7.69 (m, 2 H, Ar), 8.07 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 14.4, 15.7, 20.9, 21.0, 21.8, 22.6, 26.7, 35.6, 36.2, 39.9, 43.1, 45.8, 58.6, 71.6, 72.3, 74.2, 74.9, 75.7, 76.4, 79.4, 81.0, 84.4, 127.0, 128.71, 128.73, 129.1, 130.0, 132.3, 132.6, 133.2, 133.8, 142.8, 166.9, 170.0, 170.4, 171.3, 172.6, 203.8 ppm. HRFABMS: calcd. for $C_{44}H_{52}NO_{14}$ [M + H$^+$] 818.3388, found 818.3392.

(3′*R*)-3′-Dephenyl-3′,3′-[(1*R*)-methylethylene]-2′,7-*epi*-taxol (14): $[\alpha]_D^{20}$ = –58 (*c* = 0.29). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 6.1 Hz, 1 H), 1.17 (s, 3 H), 1.20 (s, 3 H), 1.28–1.33 (m, 1 H), 1.39–1.47 (m, 1 H), 1.47 (d, *J* = 5.7 Hz, 3 H), 1.68 (s, 3 H), 1.74 (s, 1 H), 2.02 (d, *J* = 1.3 Hz, 3 H), 2.22 (s, 3 H), 2.24–2.42 (4 H, overlapped), 2.45 (s, 3 H), 3.73 (m, 1 H), 3.98 (d, *J* = 7.4 Hz, 1 H), 4.03 (d, *J* = 6.7 Hz, 1 H), 4.34 (d, *J* = 8.7 Hz, 1 H), 4.41 (d, *J* = 8.7 Hz, 1 H), 4.74 (d, *J* = 11.6 Hz, 1 H), 4.96 (dd, *J* = 8.9, 3.3 Hz, 1 H), 5.68 (d, *J* = 6.7 Hz, 1 H), 5.76 (d, *J* = 7.4 Hz, 1 H), 6.16 (dt, *J* = 8.7, 1.3 Hz, 1 H), 6.69 (s, 1 H), 6.87 (s, 1 H), 7.39 (m, 2 H, Ar), 7.48–7.54 (m, 3 H, Ar, overlapped), 7.66 (m, 1 H, Ar), 7.71 (m, 2 H, Ar), 8.09 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 15.7, 16.1, 20.9, 21.1, 21.3, 22.2, 22.6, 26.0, 35.4, 36.5, 40.1, 40.4, 42.6, 57.6, 71.0, 75.0, 75.2, 75.7, 77.6, 78.2, 79.3, 82.1, 82.7, 127.1, 128.76, 128.78, 129.2, 130.0, 132.4, 132.9, 133.1, 133.8, 140.2, 167.0, 169.4, 171.0, 172.1, 172.2, 207.3 ppm. HRFABMS: calcd. for $C_{44}H_{52}NO_{14}$ [M + H$^+$] 818.3388, found 818.3405.

(3′*S*)-3′-Dephenyl-3′,3′-[(1*S*)-methylethylene]taxol (3b): $[\alpha]_D^{20}$ = –57 (*c* = 0.43). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t,, *J* = 6.1 Hz 1 H), 1.11 (s, 3 H), 1.20–1.26 (4 H, overlapped), 1.33–1.41 (m, 1 H), 1.43 (d, *J* = 6.1 Hz, 3 H), 1.65 (s, 3 H), 1.71 (d, *J* = 1.3 Hz, 3 H), 1.79 (s, 1 H), 1.80–1.89 (m, 1 H), 2.19 (s, 3 H), 2.21–2.36 (m, 2 H, overlapped), 2.43 (d, *J* = 4.2 Hz, 1 H), 2.45 (s, 3 H), 2.48–2.58 (m, 1 H), 3.78 (d, *J* = 7.1 Hz, 1 H), 4.08 (d, *J* = 7.1 Hz, 1 H), 4.15 (d, *J* = 8.5 Hz, 1 H), 4.30 (d, *J* = 8.5 Hz, 1 H), 4.40 (m, 1 H), 4.96 (dd, *J* = 9.6, 2.0 Hz, 1 H), 5.65 (d, *J* = 7.1 Hz, 1 H), 5.94 (d, *J* = 7.1 Hz, 1 H), 6.19 (s, 1 H), 6.22 (dt, *J* = 8.9, 1.3 Hz, 1 H), 6.75 (s, 1 H), 7.42–7.64 (m, 6 H, Ar, overlapped), 7.71 (m, 2 H, Ar), 8.08 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8, 14.9, 15.0, 21.1, 22.0, 22.2, 22.3, 22.4, 27.0, 35.7, 36.1, 40.9, 43.4, 45.8, 58.6, 71.2, 72.3, 75.4, 75.8, 76.4, 76.6, 79.8, 80.8, 84.7, 127.4, 128.9, 127.1, 129.4, 130.3, 132.7, 132.8, 132.9, 134.0, 143.1, 167.2, 170.8, 171.4, 171.5, 173.0, 204.1 ppm. HRFABMS: calcd. for $C_{44}H_{52}NO_{14}$ [M + H$^+$] 818.3388, found 818.3392.

(3′*R*)-3′-Dephenyl-3′,3′-[(1*R*)-isopropylethylene]-2′-*epi*-taxol (15): $[\alpha]_D^{20}$ = –74 (*c* = 0.54). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.16 (8 H, overlapped), 1.23 (s, 3 H), 1.27–1.39 (5 H, overlapped), 1.88 (m, 1 H), 2.10 (d, *J* = 1.1 Hz, 3 H), 2.15–2.33 (m, 2 H, overlapped), 2.23 (s, 3 H), 2.30 (s, 3 H), 2.56 (m, 1 H), 3.84 (d, *J* = 7.1 Hz, 1 H), 3.95 (d, *J* = 5.5 Hz, 1 H), 4.16 (d, *J* = 8.3 Hz, 1 H), 4.28 (d, *J* = 8.3 Hz, 1 H), 4.45 (dd, *J* = 10.8, 6.8 Hz, 1 H), 4.96 (dd, *J* = 9.5, 1.9 Hz, 1 H), 5.17 (d, *J* = 6.1 Hz, 1 H), 5.65 (d, *J* = 7.1 Hz, 1 H), 6.16 (dt, *J* = 8.9, 1.1 Hz, 1 H), 6.33 (s, 1 H), 6.60 (s, 1 H), 7.36 (m,

2 H, Ar), 7.42–7.52 (m, 3 H, Ar, overlapped), 7.60 (m, 1 H, Ar), 7.67 (m, 2 H, Ar), 8.04 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7, 15.9, 18.8, 21.1, 22.0, 22.8, 22.9, 23.0, 26.9, 29.8, 35.8, 36.3, 36.5, 40.8, 43.3, 46.0, 58.8, 71.8, 72.5, 74.3, 75.1, 75.9, 76.6, 79.6, 81.3, 84.6, 127.3, 128.91, 128.92, 129.3, 130.2, 132.5, 132.7, 133.5, 134.0, 143.0, 167.1, 170.3, 170.5, 171.5, 172.9, 204.0 ppm. HRFABMS: calcd. for $C_{46}H_{56}NO_{14}$ [M + H$^+$] 846.3701, found 846.3725.

(3′*R*)-3′-Dephenyl-3′,3′-[(1*R*)-isopropylethylene]-2′,7-*epi*-taxol (16): $[\alpha]_D^{20}$ = –58 (c = 0.17). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 1 H), 1.11 (d, J = 6.1 Hz, 3 H), 1.13 (s, 3 H), 1.08–1.14 (m, 1 H, overlapped), 1.16 (s, 3 H), 1.20–1.26 (m, 1 H), 1.32–1.42 (4 H, overlapped), 1.62 (s, 1 H), 1.65 (s, 3 H), 1.98 (d, J = 1.0 Hz, 3 H), 2.10–2.45 (4h, overlapped), 2.19 (s, 3 H), 2.40 (s, 3 H), 3.69 (m, 1 H), 3.94 (d, J = 7.6 Hz, 1 H), 3.98 (s, 1 H), 4.33 (d, J = 8.7 Hz, 1 H), 4.38 (d, J = 8.7 Hz, 1 H), 4.93 (dd, J = 9.1, 3.4 Hz, 1 H), 5.72 (d, J = 7.6 Hz, 1 H), 6.13 (dt, J = 8.8, 1.0 Hz, 1 H), 6.67 (s, 1 H), 6.82 (s, 1 H), 7.36 (m, 2 H, Ar), 7.44–7.51 (m, 3 H, Ar, overlapped), 7.62 (m, 1 H, Ar), 7.68 (m, 2 H, Ar), 8.05 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 16.3, 19.1, 21.1, 21.3, 22.77, 22.82, 23.1, 26.1, 29.8, 35.6, 36.6, 36.8, 40.6, 41.0, 42.8, 57.8, 71.2, 75.1, 75.4, 75.9, 77.8, 78.4, 79.5, 82.3, 82.9, 127.3, 128.95, 128.98, 129.4, 130.2, 132.6, 133.2, 134.0, 140.4, 167.2, 169.6, 171.1, 172.3, 172.5, 207.5 ppm. HRFABMS: calcd. for $C_{46}H_{56}NO_{14}$ [M + H$^+$] 846.3701, found 846.3725.

(3′*S*)-3′-Dephenyl-3′,3′-[(1*S*)-isopropylethylene]-taxol (3c): $[\alpha]_D^{20}$ = –66 (c = 0.66). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (m, 1 H), 1.07 (d, J = 6.2 Hz, 3 H), 1.10 (s, 3 H), 1.04–1.12 (m, 1 H, overlapped), 1.15–1.20 (m, 1 H), 1.23 (s, 3 H), 1.32–1.42 (4 H, overlapped), 1.65 (s, 3 H), 1.70 (s, 1 H), 1.71 (d, J = 1.1 Hz, 3 H), 1.80–1.88 (m, 1 H), 2.19 (s, 3 H), 2.20–2.38 (m, 2 H, overlapped), 2.43 (s, 3 H), 2.27–2.57 (m, 1 H), 3.77 (d, J = 7.1 Hz, 1 H), 4.06 (s, 1 H), 4.15 (d, J = 8.3 Hz, 1 H), 4.29 (d, J = 8.3 Hz, 1 H), 4.39 (dd, J = 10.9, 6.6 Hz, 1 H), 4.95 (d, J = 9.6, 1.9 Hz, 1 H), 5.64 (d, J = 7.1 Hz, 1 H), 6.18 (s, 1 H), 6.20 (dt, J = 9.0, 1.1 Hz, 1 H), 6.79 (s, 1 H), 7.40–7.64 (m, 6 H, Ar, overlapped), 7.71 (m, 2 H, Ar), 8.07 (m, 2 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 14.7, 19.3, 20.9, 22.0, 22.2, 22.6, 23.1, 26.7, 29.6, 35.5, 35.9, 36.5, 41.5, 43.2, 45.6, 58.5, 71.0, 72.0, 75.2, 75.6, 76.1, 76.4, 79.6, 80.6, 84.5, 127.2, 128.7, 128.9, 129.2, 130.1, 132.5, 133.7, 142.9, 167.0, 170.5, 171.18, 171.24, 172.9, 203.9 ppm. HRFABMS: calcd. for $C_{46}H_{56}NO_{14}$ [M + H$^+$] 846.3701, found 846.3708.

[1] The chemical compound represented by structure **1** was named taxol in 1971 by its discoverers, but the name taxol was subsequently registered as a trademark by Bristol-Myers Squibb to refer to their formulation of taxol. The original chemical name taxol is used in this paper to refer to compound **1**; no infringement of the Bristol–Myers Squibb trademark is implied.

[2] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.

[3] a) F. A. Holmes, R. S. Walters, R. L. Theriault, A. D. Forman, L. K. Newton, M. N. Raber, A. U. Buzdar, D. K. Frye, G. N. Hortobagyi, *J. Nat. Cancer Inst.* **1991**, *83*, 1797–1805; b) M. Markman, *Yale J. Biol. Med.* **1991**, *64*, 583–590; c) S. M. Swain, S. F. Honig, M. C. Tefft, L. Walton, *Invest. New Drugs* **1995**, *13*, 217–222.

[4] a) D. G. I. Kingston, P. G. Jagtap, H. Yuan, L. Samala, in: *Progress in the Chemistry of Organic Natural Products*, vol. 84 (Eds.:W. Herz, H. Falk, G. W. Kirby), Springer, Wien, **2002**, p. 53–225; b) D. G. I. Kingston, in: *Antitumor Agents from Natural Sources* (Eds.: G. M. Cragg, D. G. I. Kingston, D. J. Newman), Taylor and Francis, London, **2005**; c) R. Geney, J. Chen, I. Ojima, *Med. Chem.* **2005**, *1*, 125–139.

[5] Reviews see: a) J. Salaün, M. S. Baird, *Curr. Med. Chem.* **1995**, *2*, 511–542; b) J. Salaün, in: *Topics in Current Chemistry*, vol. 207 (Ed.: A. de Meijere), Springer, Heidelberg, **2000**, p. 1–67.

[6] W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589–8627.

[7] I. Ojima, S. Lin, *J. Org. Chem.* **1998**, *63*, 224–225.

[8] J. Johnson, S.-H. Kim, M. Bifano, J. DiMarco, C. Fairchild, J. Gougoutas, F. Lee, B. Long, J. Tokarski, G. Vite, *Organic Lett.* **2000**, *2*, 1537–1540.

[9] M. W. Nötzel, M. Tamm, T. Labahn, M. Noltemeyer, M. Es-Sayed, A. de Meijere, *J. Org. Chem.* **2000**, *65*, 3850–3852.

[10] D. G. I. Kingston, A. G. Chaudhary, A. A. L. Gunatilaka, M. L. Middleton, *Tetrahedron Lett.* **1994**, *35*, 4483–4484.

[11] J. P. Snyder, J. H. Nettles, B. Cornett, K. H. Downing, E. Nogales, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 5312–5316.

[12] a) T. Ganesh, R. C. Guza, S. Bane, R. Ravindra, N. Shanker, A. S. Lakdawala, J. P. Snyder, D. G. I. Kingston, *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 1006–10011; b) D. G. I. Kingston, S. Bane, J. P. Snyder, *Cell Cycle* **2005**, *4*, 279–289.

[13] O. Querolle, J. Dubois, S. Thoret, F. Roussi, F. Guéritte, D. J. Guénard, *J. Med. Chem.* **2004**, *47*, 5937–5944.

[14] R. Geney, L. Sun, P. Pera, R. J. Bernacki, S. Xia, S. B. Horwitz, C. L. Simmerling, I. Ojima, *Chem. Biol.* **2005**, *12*, 339–348.

[15] G. Barnes, K. A. Louie, D. Botstein, *Mol. Biol. Cell* **1992**, *3*, 29–47.

[16] a) C. J. Bode, M. L. Gupta, Jr., E. A. Reiff, K. A. Suprenant, G. I. Georg, R. H. Himes, *Biochemistry* **2002**, *41*, 3870–3874; b) M. L. Gupta, C. J. Bode, G. I. Georg, R. H. Himes, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 6394–6397.

[17] M. Hari, F. Loganzo, T. Annable, X. Tan, S. Musto, D. B. Morilla, J. H. Nettles, J. P. Snyder, L. M. Greenberger, submitted.

[18] T. Liese, S. Teichmann, A. de Meijere, *Synthesis* **1988**, 25–32.

[19] W. Cabri, M. Curini, M. C. Marcotullio, O. Rosati, *Tetrahedron Lett.* **1996**, *37*, 4785–4786.

[20] G. N. Chmurny, B. D. Hilton, S. Brobst, S. A. Look, K. M. Witherup, J. A. Beutler, *J. Nat. Prod.* **1992**, *55*, 414–423.

[21] A. G. Chaudhary, J. M. Rimoldi, D. G. I. Kingston, *J. Org. Chem.* **1993**, *58*, 3798–3799.

[22] R. Riguera, E. Quiñoá, J. M. Seco, *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.

[23] F. Gueritte-Voegelein, D. Guenard, F. Lavelle, M.-T. Le Goff, L. Mangatal, P. Potier, *J. Med. Chem.* **1991**, *34*, 992–998.

[24] E. Nogales, S. G. Wolf, K. H. Downing, *Nature* **1998**, *391*, 199–203.

[25] a) S. Rao, N. E. Krauss, J. M. Heerding, C. S. Swindell, I. Ringel, G. A. Orr, S. B. Horwitz, *J. Biol. Chem.* **1994**, *269*, 3132–3134; b) S. Rao, G. A. Orr, A. G. Chaudhary, D. G. I. Kingston, S. B. Horwitz, *J. Biol. Chem.* **1995**, *270*, 20235–20238; c) C. Combeau, A. Commercon, C. Mioskowski, B. Rousseau, F. Aubert, M. Goeldner, *Biochemistry* **1994**, *33*, 6676–6683.

[26] T. Ganesh, R. C. Guza, S. Bane, R. Ravindra, N. Shanker, A. S. Lakdawala, J. P. Snyder, D. G. I. Kingston, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 10006–10011.

[27] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441–451.

[28] C. Lucatelli, F. Viton, Y. Gimbert, A. E. Greene, *J. Org. Chem.* **2002**, *67*, 9468–9470.

[29] G. I. Georg, G. C. B. Harriman, D. G. Vander Velde, T. C. Boge, Z. S. Cheruvallath, A. Datta, M. Hepperle, H. Park, R. H. Himes, L. Jayasinghe, in: *Taxane Anticancer Agents* (Eds.: G. I. Georg, T. T. Chen, I. Ojima, D. M. Vyas), American Chemical Society, Washington, **1995**, p. 217–232.

[30] I. Ojima, Y. H. Park, I. Fenoglio, O. Duclos, C.-M. Sun, S. D. Kuduk, M. Zucco, G. Appendino, P. Pera, J. M. Veith, R. J. Bernacki, M.-C. Bissery, C. Combeau, P. Vrignaud, J. G. Riou, F. Lavelle, in: *Taxane Anticancer Agents: Basic Science and Current Status*, ACS Symposium Series vol. 583 (Eds.: G. I. Georg, T. T. Chen, I. Ojima, D. M. Vyas), American Chemical Society, Washington, DC, **1995**, p. 262–275.

[31] L. Li, S. A. Thomas, L. L. Klein, C. M. Yeung, C. J. Maring, D. J. Grampovnik, P. A. Lartey, J. J. Plattner, *J. Med. Chem.* **1994**, *37*, 2655–2663.

[32] a) J.-N. Denis, A. Fkyerat, Y. Gimbert, C. Coutterez, P. Mantellier, S. Jost, A. E. Greene, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1811–1815; b) J. Kant, W. S. Schwartz, C. Fairchild, Q. Gao, S. Huang, B. H. Long, J. F. Kadow, D. R. Langley, V. Farina, D. Vyas, *Tetrahedron Lett.* **1996**, *37*, 6495–6498.
[33] L. Barboni, C. Lambertucci, G. Appendino, D. G. Vander Velde, R. H. Himes, E. Bombardelli, M. Wang, J. P. Snyder, *J. Med. Chem.* **2001**, *44*, 1576–1587.
[34] B. B. Metaferia, J. Hoch, T. E. Glass, S. L. Bane, S. K. Chatterjee, J. P. Snyder, A. Lakdawala, B. Cornett, D. G. I. Kingston, *Org. Lett.* **2001**, *3*, 2461–2464.
[35] K. A. Neidigh, M. M. Gharpure, J. M. Rimoldi, D. G. I. Kingston, Y. Q. Jiang, E. Hamel, *Tetrahedron Lett.* **1994**, *35*, 6839–6842.
[36] S.-H. Chen, J.-M. Wei, B. H. Long, C. A. Fairchild, J. Carboni, S. W. Mamber, W. C. Rose, K. Johnston, A. M. Casazza, J. F. Kadow, V. Farina, D. Vyas, T. W. Doyle, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2741–2746.
[37] M. D. Chordia, A. G. Chaudhary, D. G. I. Kingston, Y. Q. Jiang, E. Hamel, *Tetrahedron Lett.* **1994**, *35*, 6843–6846.
[38] S.-H. Chen, *Tetrahedron Lett.* **1996**, *37*, 3935–3938.
[39] J. P. Snyder, N. Nevins, D. O. Cicero, J. Jansen, *J. Am. Chem. Soc.* **2000**, *122*, 724–725.
[40] L. Barboni, A. Datta, D. Dutta, G. I. Georg, D. G. Vander Velde, R. H. Himes, M. Wang, J. P. Snyder, *J. Org. Chem.* **2001**, *66*, 3321–3329.
[41] D. O. Cicero, G. Barbato, R. Bazzo, *J. Am. Chem. Soc.* **1995**, *117*, 1027–1033.
[42] N. Nevins, D. Cicero, J. P. Snyder, *J. Org. Chem.* **1999**, *64*, 3979–3986.
[43] a) J. Dubois, D. Guenard, F. Gueritte-Voeglein, N. Guedira, P. Potier, B. Gillet, J.-C. Betoeil, *Tetrahedron* **1993**, *49*, 6533–6544; b) H. J. Williams, A. I. Scott, R. A. Dieden, C. S. Swindell, L. E. Chirlian, M. M. Francl, J. M. Heerding, N. E. Krauss, *Tetrahedron* **1993**, *49*, 6545–6560; c) R. E. Cachau, R. Gussio, J. A. Beutler, G. N. Chmurny, B. D. Hilton, G. M. Muschik, J. W. Erickson, *Supercomputer Applications and High Performance Computing* **1994**, *8*, 24–34.
[44] C. Glück, V. Poignee, H. Schwager, *Synthesis* **1987**, 260–262.
[45] T. Liese, F. Jaekel, A. de Meijere, *Org. Synth.* **1990**, *69*, 144–153.

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