Synthesis and Biological Evaluation of 1-Deoxypaclitaxel Analogues

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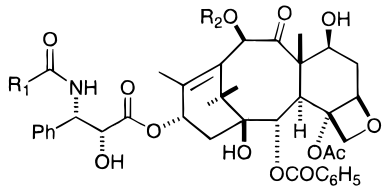
The naturally occurring taxoid baccatin VI has been converted to various 1-deoxypaclitaxel derivatives by selective deacylation followed by attachment of the C-13 side chain. The bioactivities of the resulting analogues were determined in both tubulin polymerization and cytotoxicity assays, and several analogues with activity comparable to that of paclitaxel were discovered. It thus appears that the 1-hydroxyl group is not necessary for the activity of paclitaxel.

Introduction

Interest in the novel diterpenoid paclitaxel (Taxol®) (**1**) continues at a high level from chemical, biological, and clinical viewpoints. First isolated from the bark of the western yew, *Taxus brevifolia*,[1] its development as a clinical candidate was slowed by concerns about its supply and its lack of aqueous solubility. Positive results in new in vivo models in the mid 1970s and the discovery of its novel mechanism of action[2] greatly increased interest in the compound, and clinical trials ultimately demonstrated its clinical effectiveness. It is now approved for treatment of ovarian and breast cancers, with promise also for treatment of lung, skin, and head and neck cancers;[3] the paclitaxel analogue docetaxel (**2**) is also in clinical use.[4]

A large number of structure−activity studies of paclitaxel have been carried out, particularly in recent years,



1 $R_1 = C_6H_5$, R_2 = Ac
2 $R_1 = Me_3CO$, R_2 = H

and have led to the general conclusion that the C-13 ester side chain is essential for activity but that modifications to the "northern hemisphere" (C-7, C-9, and C-10) have modest but often beneficial effects on its bioactivity, while changes to the "southern hemisphere" (C-4, C-2, and the oxetane ring) can have larger effects on activity, usually negative but occasionally positive.[5] Thus opening of the oxetane ring leads to loss of activity,[6] as does deacetylation or deacetoxylation at C-4;[7] replacement of the C-4

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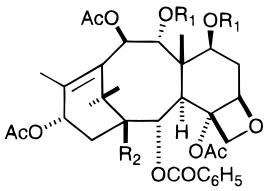
acetate with other acyl groups does, however, lead to restoration or even enhancement of activity.[8]

Among the analogues of paclitaxel that have been prepared are several that lack one or more hydroxyl or acetoxyl groups. Thus analogues have been synthesized lacking the 2-benzoyloxy group,[9,10] lacking the 4-acetoxyl group,[7b] lacking the 7-hydroxyl group,[11] and lacking the 10-acetoxyl group.[12] Despite all the work that has been done in this area, however, it has not proved possible to prepare 1-deoxypaclitaxel analogues from paclitaxel; various attempts to do so by the Barton deoxygenation method used successfully in other examples led only to deoxygenation at C-2.[9,13]

The preparation of 1-deoxy analogues of paclitaxel was an important objective, since the relevance of this functional group to paclitaxel's activity as an anticancer agent was unknown, and since introduction of this group requires additional steps in some synthetic approaches to paclitaxel.[14] Conceivably, if the C-1 hydroxyl group is not required for activity, or if its removal even enhances activity, then such a simplified paclitaxel analogue might be amenable to total synthesis on an industrial scale. Since direct deoxygenation of paclitaxel appeared to be an impractical route to the preparation of 1-deoxypaclitaxel analogues, we elected to make use of the availability of 1-deoxybaccatin VI (**3**) as a starting material for the preparation of selected 1-deoxyanalogues.

1-Deoxybaccatin VI (**3**) was first isolated by one of us from the heartwood of *T. mairei*[15] and was later reisolated by another one of us from the same source.[16] Since it contains the oxetane ring system known to be essential for the activity of paclitaxel,[6] it was the crucial starting material for this work.



3 R_1 = Ac, R_2 = H
4 R_1 = H, R_2 = OH

Results and Discussion

The key problem in the conversion of 1-deoxybaccatin VI (**3**) to paclitaxel analogues is that of selective deacylation of the 7, 9, 10, and 13 acetoxyl groups (and especially of the C-13 group) without concomitant deacylation of the C-2 and C-4 acyloxy groups. A similar situation was faced by Klein in the conversion of 13-acetyl-9(*R*)-dihydrobaccatin III (**4**) to dihydropaclitaxel analogues[17] and was solved by the use of methyllithium, which gave an 82% yield of the desired 13-deacetyl derivative of **4**. The original mechanism proposed for this conversion involved a possible complexation of the alkyllithium reagent with the C-1 oxyanion,[18] but it was later proposed that selective deacetylation occurred by a ketene elimination pathway.[17] Other bases have also been found to be selective for different positions on paclitaxel. Thus in our work on the debenzoylation of paclitaxel at the C-2 position we found that phase-transfer catalysis[19] or Triton B[20] worked well, while the reducing agent Red-Al has been found to be effective in selective debenzoylation of baccatin III derivatives.[21]

On the other hand, the C-4 acetyl group can be removed selectively from 7-*O*-(triethylsilyl)baccatin III by treatment with potassium *tert*-butoxide, presumably via an internal transesterification process.[22] We thus elected to investigate several routes to the selective deacylation of 1-deoxybaccatin VI.

The first route developed (Scheme 1) proved to be very efficient for the synthesis of analogues retaining the 7, 9, and 10 acetyl groups. Treatment of 1-deoxybaccatin VI (**3**) with Red Al at −20 °C gave 13-deacetyl-1-deoxybaccatin VI (**5a**) in 77% yield, together with 12% of the 4-deacetyl derivative **5b**. The formation of small amounts of **5b** was expected in view of earlier experience,[22a] but the amounts formed were acceptable in light of the good yield of the major product **5a**.

Conversion of the 13-deacetyl derivative **5a** to various paclitaxel and docetaxel analogues proceeded by the

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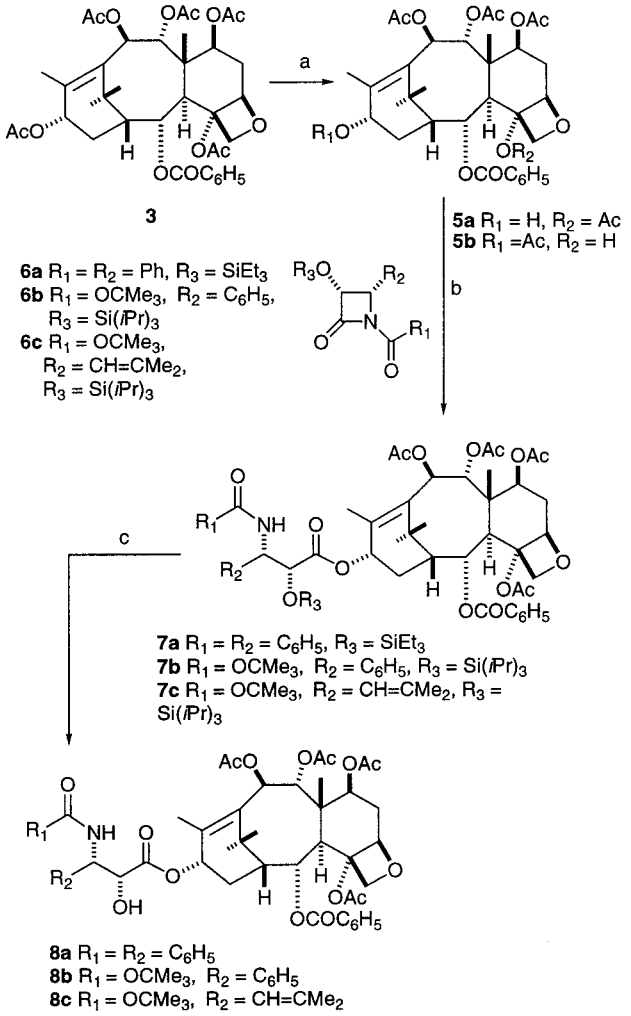
Scheme 1[a]



[a] Key: (a) Red Al, THF; **5a**, 77%; **5b**, 12%; (b) **5a**, NaH, THF, **6a**−**6c**, 0 °C− rt, **6a**, 77%; **6b**, 86%; **6c**, 77%; (c) HF/pyridine, −20 °C, **7a**, 96%; **7b**, 87%; **7c**, 96%.

β-lactam chemistry that has been described previously. The β-lactam derivatives **6a**−**6c** were prepared by literature methods[23] and used to acylate 13-deacetyl-1-deoxybaccatin VI (**5a**); the 2′-silylated 1-deoxypaclitaxel analogues **7a**−**7c** were prepared by this method in good yields and were converted to the final analogues **8a**−**8c** by deprotection of the 2′-hydroxyl group with HF/pyridine.

Although the route described above provided an efficient means of converting **3** into acetate-protected 1-deoxypaclitaxel analogues, it could not provide derivatives with free hydroxyl groups at the 7, 9, and 10 positions. Since changes in the nature of the substituents at these positions can affect the bioactivity of the resulting analogue in small but nevertheless significant ways,[17,24] we desired to develop a route that gave access to free hydroxyl groups at these positions.

Treatment of **3** with Triton B in dichloromethane or with methanolic sodium hydroxide gave the tris-deacetyl derivative **9** in good to excellent yield (Scheme 2). Compound **9** was then selectively protected as its 7,9-acetonide **10a** or its 7,9-benzylidene acetal **10b** by treatment with 2-methoxypropene or benzaldehyde in the presence of acid. Protection of the C-10 hydroxyl group as its triethylsilyl ether gave the fully protected analogues **11a** and **11b**, and these could be deacetylated to the key intermediates **12a** and **12b** by treatment with methyllithium at low temperature. The yields of this selective deacylation step were only modest, but this route had the advantage already noted of additional flexibility for the substituents at C-7, 9, and 10.

Treatment of the 13-deacetyl derivatives **12a** and **12b** with β-lactams **6b** and **6d** respectively gave the protected paclitaxel analogues **13a** and **13b**, which were deprotected in the usual way to give the final products **14a** and **14b** (Scheme 2). Attempted deprotection of the acetal or ketal protecting groups by acidic hydrolysis gave only poor yields of deprotected products accompanied byproducts with an opened oxetane ring, and so the ketals **14a** and **14b** were evaluated as such for their bioactivity.

After the development of the route described above, we developed an improved route to the preparation of the 7, 9, 10 trihydroxy analogues that avoided the protection/deprotection chemistry of Scheme 2. In this route (Scheme 3) the 7,9,10-triacetyl derivative **7b** was converted to the 2′-protected 7,9,10-triol **15** with either Triton B in dichloromethane or with methanolic potassium hydroxide. Deprotection of the TIPS group then gave the triol derivative **16**.

The protected triol **15** was a useful intermediate for the synthesis of other analogues. Thus reaction with DMP/acetone in the presence of PPTS, followed by deprotection at the 2′-position, gave the additional cyclic ketal **14c**. Finally, methylation with methyl iodide in THF gave the 7-*O*-methyl ether **17** and the 7-*O*-methyl-10-*O*-methoxybutyl derivative **19**, both in low yields. Compound **19** is presumably formed by initial attack of THF on methyl iodide to give a methyl oxonium iodide, which then undergoes nucleophalic attack by the 10-alkoxide derivative of **15**. Presumably small amounts of other alkylation products related to **17** and **19** were also formed in the reaction but were not isolated by one workup procedure.

The bioactivities of the 1-deoxypaclitaxel analogues **8a**−**8c**, **14a**−**14c**, **16**, **18**, and **20** were determined both in a tubulin-assembly assay and in a cytotoxicity assay. The tubulin-assembly assay was carried out with calf brain tubulin prepared following the procedure of Williams and Lee,[25] and cytotoxicity was determined using the human colon carcinoma HCT 116 cell line (Table 1). The general conclusion to emerge from these data is that the C-1 hydroxyl group of paclitaxel does not have a major effect on the tubulin assembly activity or cytotoxicity of paclitaxel. In support of this statement, simple 1-deoxy analogues (excluding those with large substituents on the "northern hemisphere" such as **14b** and **20**) all had tubulin-assembly activity within a factor of 3 of that of paclitaxel, and most also had a cytotoxicity to HCT 116 cells within a factor of 3.

A direct comparison with paclitaxel was not possible,

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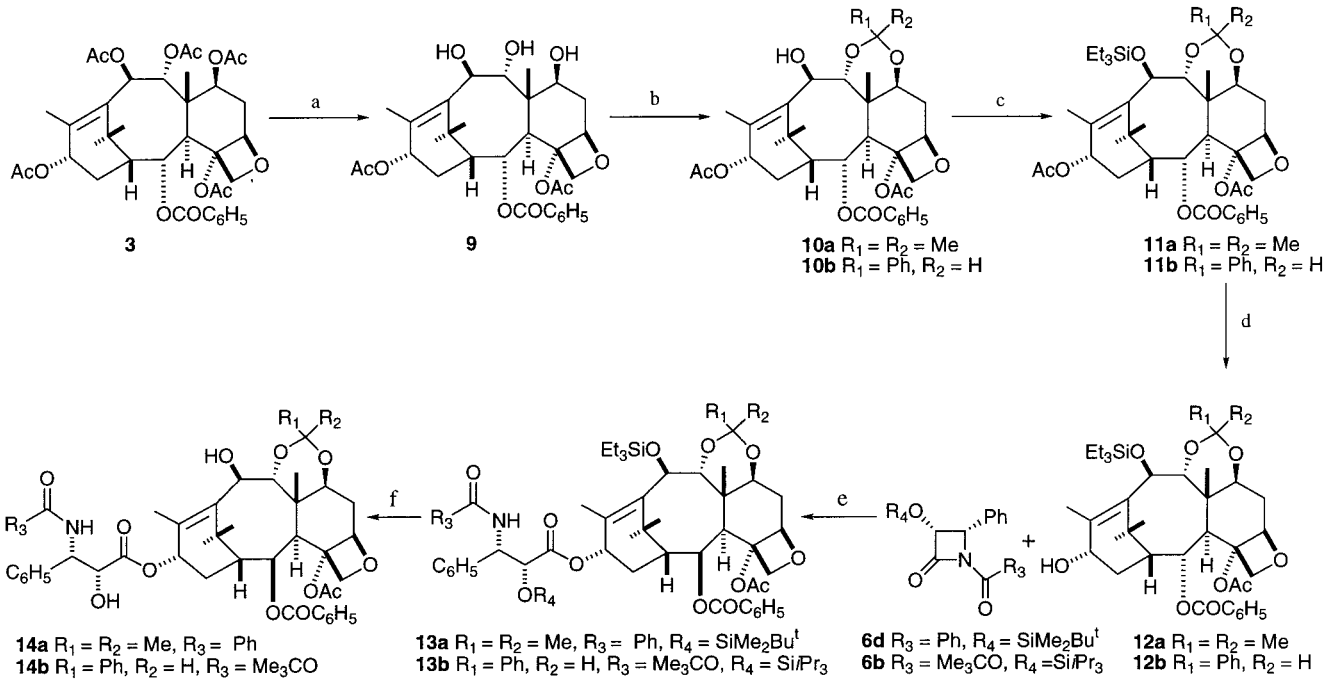
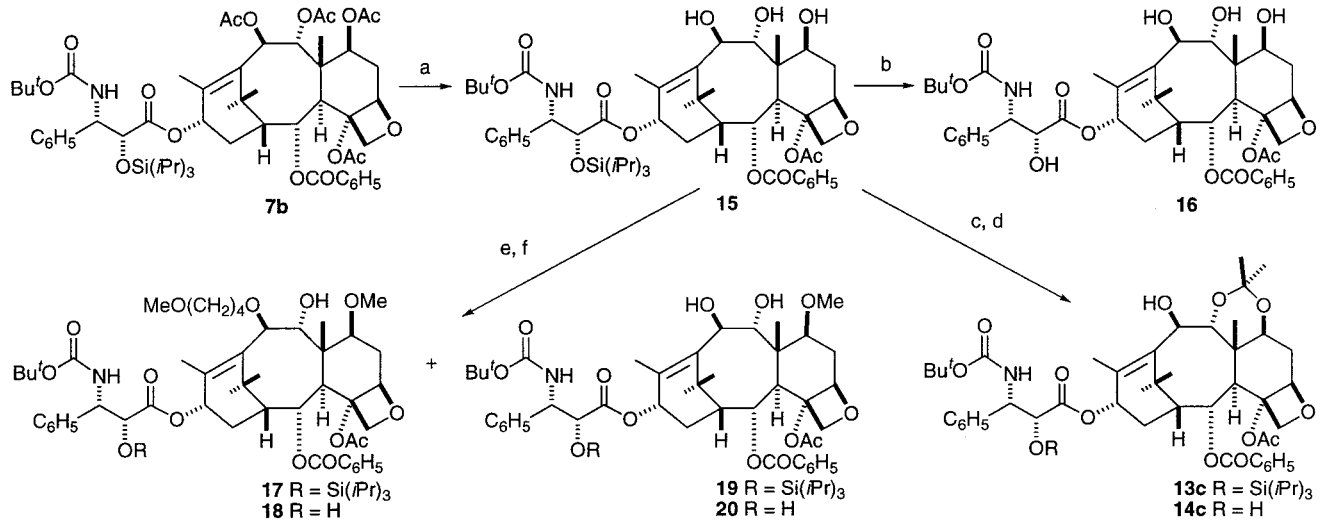
Scheme 2[a]



[a] Key: (a) Triton B, CH_2Cl_2, 65% or 1 N NaOH, MeOH, 84%; (b) 2-methoxypropene, PPTS, CH_2Cl_2, **10a**, 55% or PhCHO, CSA, toluene, **10b**, 63%; (c) Et_3SiCl, Im, CH_2Cl_2 or DMF, **11a**, 74% and **11b**, 72%; (d) MeLi, THF, **12a**, 63% and **12b**, 37%; (e) *n*-BuLi, THF, **12a**, −78 °C; then **6d**, yields **13a** (23%); NaH, THF, **12b**, 0 °C to rt, then **6b**, yields **13b** (69%) (f) HF−Py, THF, **14a**, 99%; **14b**, 33%

Scheme 3[a]



[a] Key: (a) Triton B, CH_2Cl_2, 42%; or KOH, MeOH, 52%; (b) TBAF, THF, −20 °C, 80%; (c) DMP, TsOH, Me_2CO, rt, 97%; (d) TBAF, THF, −20 °C, 78% (e) MeI, Ag_2O, THF, 65 °C, 12h; (f) TBAF, THF, **17**, 12%; **18**, 15%.

because we did not prepare 1-deoxypaclitaxel itself. However, 7,9-diacetyl-9(*R*)-dihydropaclitaxel (**21**) was prepared by Klein and his collaborators,[17] and our compound **8a** is the 1-deoxy analogue of **21**. Although the data were obtained under different conditions, Klein reported that compound **21** is slightly more active than paclitaxel in a tubulin-assembly assay, while compound **8a** is slightly less active than paclitaxel. The cytotoxicity data is even more difficult to compare since different cell lines were used; in the four cell lines evaluated by Klein, compound **21** had IC_{50} values that were, on average, 4.7-, 1.4-, 3.0-, and 2.3-fold greater than those of paclitaxel, while compound **8a** has an IC_{50} value 11-fold greater than that of paclitaxel in the one cell line evaluated. Removal of the C-1 hydroxyl group thus results in a small but significant loss in both tubulin-assembly activity and cytotoxicity for 7,9-diacetyl-9(*R*)-dihydropaclitaxel, and by extension it is likely that removal of the C-1 hydroxyl group from paclitaxel itself would also cause a slight reduction in activity.

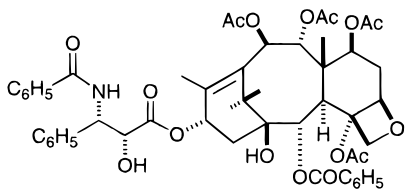


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Table 1. Bioactivity Data for 1-Deoxypaclitaxel Analogues

	tubulin data		cytotoxicity to HCT116 human colon carcinoma	
no.	$EC_{0.01}$	$EC_{0.01}$/$EC_{0.01}$(PT)[a]	IC_{50} (μM)	IC_{50}/IC_{50}(PT)[a]
1	5.3 ± 1.1	1.0	0.0018 ± 0.0002	1
8a	12.2 ± 4.0	2.0	0.0315[b]	11.2
8b	12.0 ± 5.4	2.4	0.0046	2.9
8c	18 ± 2	5.8	0.0047	2.7
14a	9.1 ± 3.7	2.0	0.0043	2.3
14b	>1000	>200	0.0105	6.6
14c	8.5 ± 3.3	1.6	0.0022	1.2
16	9.1 ± 1.4	1.8	0.003	2.0
18	>1000	>200	>0.12	>70
20	12.8 ± 3.3	2.2	0.0049	2.8
21		0.9[c]		0.9−1.8[d]

[a] The $EC_{0.01}$/$EC_{0.01}$(PT) and IC_{50}/IC_{50}(PT) values were obtained by dividing the $EC_{0.01}$ or IC_{50} value observed for the analogue by the $EC_{0.01}$ or IC_{50} value observed for paclitaxel in the same run, and this value varied slightly from run to run; the data thus cannot be obtained by dividing the observed $EC_{0.01}$ value by 5.3 or the observed IC_{50} value by 0.0018. [b] In the case of **8a** the paclitaxel IC_{50} value was 0.0028 μM. [c] ED_{50}/ED_{50}(PT): data from ref 17. [d] Data for human colon adenocarcinoma HT-29 from ref 17.

The analogue **8b** was also tested in vivo against the subcutaneous M109 murine tumor model by the IV route of administration. It reached a maximum tolerated dose (MTD) at 20 mg/Kg/injection on a qd5-8 schedule, and any dose above this was toxic. The delay in the treated animals as compared with control animals reaching a tumor size of 1.0 g was 5.5 days; the comparable value for paclitaxel at its MTD of 40 mg/Kg/injection was 8.8 days.

Experimental Section

General Methods. All chemicals were obtained from Aldrich Chemical Co. and were used without further purification. All anhydrous reactions were performed under argon. THF was dried over sodium/benzophenone. All reactions were monitored by TLC (silica gel, GF) and analyzed with UV light and developed with vanillin spray. ^{1}H NMR spectra were obtained in $CDCl_3$ at 400 MHz and were assigned by comparison of chemical shifts and coupling constants with those of related compounds and by appropriate 2D NMR techniques; coupling constants are reported in hertz. ^{13}C NMR spectra were assigned with the aid of HETCOR and DEPT spectra. Some of the ^{1}H NMR spectra showed the presence of traces of ethyl acetate; paclitaxel and its derivative retain ethyl acetate very tightly, and it cannot be removed completely even on prolonged treatment in vacuo at 38 °C. Exact mass measurements were performed at the Nebraska Center for Mass Spectroscopy. Elemental analysis were performed by National Chemical Consulting, Inc., Tenafly, NJ.

13-Deacetylbaccatin VI (5a) and 4-Deacetylbaccatin VI (5b). Baccatin VI (**3**) (54 mg, 0.007 mmol) was dissolved in THF (2 mL); to this solution was added Red-Al (50 μL, 65% solution in toluene, 0.014 mmol) at −20 °C, and the solution was stirred for 20 min. The solution was then quenched with a saturated solution of potassium tartrate (10 mL), and the reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration under reduced pressure furnished a residue which was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 1/1) to afford unreacted **3** (6.0 mg), **5a** (35 mg, 77% on the basis of unrecovered starting material), and **5b** (5.3 mg, 12%). **5a**: ^{1}H NMR δ 1.00 (s, 3H), 1.58 (s, 3H), 1.81 (s, 3H), 1.84−1.98 (m, 2H), 1.98 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 2.21 (s, 3H), 2.28 (s, 3H), 2.48−2.56 (m, 3H), 3.07 (d, J = 6.1 Hz, 1H), 4.14 (d, J = 8.2 Hz, 1H), 4.40 (d, J = 8.4 Hz, 1H), 4.59 (m, 1H), 4.95 (d, J = 8.7 Hz, 1H), 5.53−5.57 (dd, J = 9.1 and 8.0 Hz, 1H), 5.84 (m, 1H), 5.98 (d, J = 11.4 Hz, 1H), 6.15 (d, J = 11.1 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.60 (m, 1H), 8.08 (dd, J = 1.3 and 8.4 Hz, 2H); ^{13}C NMR δ 12.9, 15.1, 20.8, 21.0, 21.4, 22.9, 26.6, 29.7, 30.1, 31.4, 34.6, 37.7, 44.1, 45.8, 47.1, 67.5, 71.4, 71.6, 71.9, 75.5, 81.7, 82.0, 128.6, 129.8, 132.7, 133.5, 142.0, 164.9, 169.1, 169.8, 170.1, 171.7; HRFABMS calcd for $C_{35}H_{44}O_{12}$ [M + H]$^+$ m/z 679.2730, found 679.2718. **5b**: ^{1}H NMR δ 1.01 (s, 3H), 1.48 (s, 3H), 1.79 (s, 3H), 1.71−2.00 (m, 1H), 2.00 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.17 (s, 3H), 2.18−2.22 (m, 2H), 2.40 (m, 1H), 2.62−2.72 (m, 2H), 4.25 (d, J = 7.7 Hz, 1H), 4.31 (d, J = 8.0 Hz, 1H), 4.78−4.81 (dd, J = 2.8 and 8.6 Hz, 1H), 5.29 (m, 1H), 5.65 (m, 1H), 5.91−5.95 (m, 2H), 6.06 (d, J = 10.9 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.59 (m, 1H), 8.01 (dd, J = 1.4 and 8.4 Hz, 2H); ^{13}C NMR δ 13.1, 16.4, 20.7, 20.9, 21.2, 21.3, 25.5, 27.6, 33.3, 34.1, 37.3, 45.3, 46.4, 47.9, 69.5, 70.6, 71.2, 71.3, 74.9, 75.1, 79.5, 87.0, 128.6, 129.5, 129.7, 133.5, 136.3, 137.8, 164.9, 169.9, 169.2, 169.7, 170.0, 170.1; HRFABMS calcd for $C_{35}H_{44}O_{12}$ [M + H]$^+$ m/z 679.2730, found 679.2725.

7,9-Diacetyl-9(*R*)-dihydro-2′-triethylsilyl-1-deoxypaclitaxel (7a). To a solution of **5a** (10.0 mg, 0.015 mmol) and **6a** (9.3 mg, 0.022 mmol) in THF (1.0 mL) was added NaH (7.0 mg, 60% dispersion in mineral oil, 20 equiv) at 0 °C, and the mixture was allowed to stir at room temperature for 2 h. The mixture was then quenched with AcOH (0.2 mL) at 0 °C and diluted with EtOAc (5 mL). This mixture was diluted with water and extracted with EtOAc (2 × 10 mL), and the organic layer was washed with a saturated solution of $NaHCO_3$, water, and brine, followed by drying over Na_2SO_4. The residue obtained after evaporation under reduced pressure was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/4) to provide **7a** (13.8 mg, 86%): ^{1}H NMR δ 0.38 − 0.51 (m, 6H), 0.78−0.81 (m, 9H), 1.14 (s, 3H), 1.60 (s, 3H), 1.74−1.80 (m, 1H), 1.87 (s, 3H), 1.90−1.92 (m, 1H), 1.97 (s, 3H), 2.02−2.04 (m, 1H), 2.07 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 2.41−2.58 (m, 2H), 2.49 (s, 3H), 3.03 (d, J = 5.50 Hz, 1H), 4.15 (d, J = 8.39 Hz, 1H), 4.40 (d, J = 8.24 Hz, 1H), 4.72 (d, J = 1.83 Hz, 1H), 4.99 (d, J = 8.39 Hz, 1H), 5.57 (dd, J = 9.31 and 7.93 Hz, 1H), 5.66 (d, J = 8.7 Hz, 1H), 5.89 (m, 1H), 5.99−6.04 (m, 2H), 6.24 (d, J = 11.29 Hz, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.29−7.51 (m, 10H), 7.60 (t, J = 7.47 Hz, 1H), 7.74 (d, J = 7.02 Hz, 2H), 8.07 (d, J = 7.17 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 4.4, 6.5, 13.0, 14.4, 20.8, 20.9, 21.4, 23.3, 27.5, 31.4, 34.7, 38.3, 44.1, 45.8, 47.3, 55.6, 71.4, 71.5, 71.9, 74.4, 75.6, 81.4, 83.9, 126.5, 127.0, 127.8, 128.6, 128.7, 129.4, 129.9, 131.7, 133.3, 133.5, 134.3, 138.4, 138.5, 165.0, 167.2, 169.0, 169.3, 170.0, 170.1, 172.0; HRFABMS calcd for $C_{57}H_{72}NO_{15}Si$ [M + H]$^+$ m/z 1038.4671, found 1038.4657.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-7,9-diacetyl-9(*R*)-dihydro-2′-triisopropylsilyl-1-deoxypaclitaxel (7b). To a solution of **5a** (30 mg, 0.045 mmol) and **6b** (23.0 mg, 0.054 mmol) in THF (2.5 mL) was added NaH (23.0 mg, 60% dispersion in mineral oil, 22 equiv) at 0 °C, and the mixture was stirred at room temperature for 6 h. The mixture was then quenched with AcOH (1.0 mL) at 0 °C, diluted with EtOAc (5 mL) and water (5 mL), and extracted with EtOAc (10 mL). The organic layer was washed with a saturated solution of $NaHCO_3$, water, and brine and dried over Na_2SO_4. The residue obtained after concentration of the organic layer under reduced pressure was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 3/7) to yield **7b** (38 mg, 77%): ^{1}H NMR δ 0.90−0.91 (m, 21H), 1.18 (s, 1H), 1.34 (s, 9H), 1.58 (s, 3H), 1.76−1.82 (m, 3H), 1.89 (s, 3H), 1.98 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.46 (s, 3H), 2.48−2.56 (m, 2H), 3.34 (d, J = 5.9 Hz, 1H), 4.14 (d, J = 8.3 Hz, 1H), 4.41 (d, J = 8.0 Hz, 1H), 4.81 (d, J = 1.3 Hz, 1H), 4.98 (d, J = 8.4 Hz, 1H), 5.24 (d, J = 9.9 Hz, 1H), 5.42 (d, J = 9.3 Hz, 1H), 5.56−5.61 (dd, J = 7.9 and 9.6 Hz, 1H), 5.87−5.92 (m, 2H), 6.03 (d, J = 11.4 Hz, 1H), 6.25 (d, J = 11.2 Hz, 1H), 7.24−7.36 (m, 5H), 7.47 (t, J = 7.7 Hz, 2H), 7.59 (m, 1H), 8.08 (dd, J = 1.2 and 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) d 12.5, 12.6, 12.9, 15.0, 17.8, 17.9, 20.8, 20.9, 21.4, 23.3, 27.7, 28.2, 29.7, 31.4, 34.6, 38.2, 44.1, 45.7, 47.4, 70.8, 71.7, 71.9, 75.4, 75.6, 79.7, 81.4, 84.0, 126.5, 127.6, 128.5, 128.6, 129.5, 129.9, 132.9, 133.5, 165.0, 168.9, 169.2, 169.9, 170.1; HRFABMS calcd for $C_{58}H_{81}NO_{16}Si$ [M + Na]$^+$ m/z 1098.5222, found 1098.5267.

9(*R*)-Dihydro-7,9-diacetyl-1-deoxypaclitaxel (8a). To a solution of **7a** (11.0 mg, 0.010 mmol) in THF (1 mL) and pyridine (100 μL) was added HF/pyridine (100 μL), and the mixture was stirred at room temperature for 30 min. It was then diluted with EtOAc (5 mL), and the EtOAc layer was washed succesively with saturated $NaHCO_3$, 0.1 N HCl, again with saturated $NaHCO_3$, water, and brine, and dried over Na_2SO_4. The residue obtained after evaporation was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/1) to yield **8a** (8.11 mg, 87%): ^{1}H NMR δ 1.08 (s, 3H), 1.58 (s, 6H), 1.84 (s, 3H), 1.86−1.90 (m, 2H), 1.96 (s, 3H), 2.00−2.02 (m, 2H), 2.08 (s, 3H), 2.10 (s, 3H), 2.28 (s, 3H), 2.53−2.68 (m, 2H), 2.96 (d, J = 5.80 Hz, 1H), 4.16 (d, J = 8.09 Hz, 1H), 4.38 (d, J = 8.24 Hz, 1H), 4.42 (dd, J = 1.68 and 2.4 Hz, 1H), 4.74 (dd, J = 2.59 and 2.44 Hz, 1H), 4.96 (d, J = 8.09 Hz, 1H), 5.47 (dd, J = 8.70 and 8.39 Hz, 1H), 5.85−5.87 (m, 3H), 5.96 (d, J = 11.14 Hz, 1H), 6.10 (d, J = 11.14 Hz, 1H), 7.32−7.51 (m, 10H), 7.60 (t, J = 7.47 Hz, 1H), 7.81 (d, J = 7.05 Hz, 2H), 8.06 (d, J = 7.18 Hz, 2H); ^{13}C NMR d 13.0, 15.2, 20.7, 20.9, 21.4, 22.6, 26.6, 26.7, 31.3, 34.6, 37.9, 44.0, 46.0, 47.1, 54.3 70.8, 70.9, 71.6, 73.9, 75.4, 82.0, 83.6, 127.0, 127.2, 128.0, 128.6, 128.7, 129.4, 129.7, 131.8, 133.6, 133.8, 134.2, 137.5, 138.5, 164.8, 166.4, 169.0, 169.8, 170.0, 170.9, 171.1; HRFABMS calcd for $C_{51}H_{57}NO_{15}$ [M + Na]$^+$ m/z 946.3625, found 946.3655.

3′-*N*-Debenzoyl-*N*-*tert*-butoxycarbonyl-9(*R*)-dihydro-7,9-diacetyl-1-deoxypaclitaxel (8b). To a well-stirred solution of **7b** (12.0 mg, 0.011 mmol) in THF (1.2 mL) was added HF/pyridine (0.3 mL), and the mixture was stirred at room temperature for 3 h. The mixture was then diluted with EtOAc (5 mL), and this EtOAc layer was washed successively with saturated $NaHCO_3$, 0.1 N HCl, again with saturated $NaHCO_3$, water, and brine. It was then dried over Na_2SO_4 and concentrated under reduced pressure, and the residue obtained was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 9/11) to furnish recovered **7b** (3.0 mg) and **8b** (7.3 mg, 96% on the basis of unrecovered starting material): ^{1}H NMR δ 1.10 (s, 3H), 1.39 (s, 9H), 1.58 (s, 3H), 1.85 (s, 3H), 1.96−2.40 (m, 3H), 1.96 (s, 3H), 1.98 (s, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 2.24 (s, 3H), 2.48−2.68 (m, 2H), 2.98 (d, J = 5.8 Hz, 1H), 4.16 (m, 2H), 4.37 (d, J = 8.2 Hz, 1H), 4.60 (s, 1H), 4.94 (d, J = 8.1 Hz, 1H), 5.28 (m, 1H), 5.49 (dd, J = 9.1 and 8.0 Hz, 1H), 5.63 (d, J = 9.6 Hz, 1H), 5.86 (m, 2H), 5.97 (d, J = 11.2 Hz, 1H), 6.14 (d, J = 11.1 Hz, 1H), 7.26−7.48 (m, 7H), 7.58 (m, 1H), 8.05 (dd, J = 1.2 and 8.4 Hz, 2H); ^{13}C NMR d 13.0, 20.8, 20.9, 21.4, 22.5, 26.7, 28.3, 31.2, 34.6, 37.9, 44.0, 46.0, 47.2, 71.1, 71.6, 75.5, 77.8, 79.9, 81.9, 83.7, 127.0, 127.7, 128.5, 128.6, 129.5, 129.8, 133.6, 164.9, 168.9, 169.8, 170.0; HRFABMS calcd for $C_{49}H_{61}NO_{16}$-Na [M + Na]$^+$ m/z 942.3888, found 942.3883. Anal. Calcd for $C_{49}H_{61}NO_{16}$: C, 63.97; H, 6.65; N, 1.52. Found: C, 64.21; H, 6.98; N, 1.50.

9(*R*)-Dihydro-7,9-diacetyl-3′-dephenyl-3′-(3,3-dimethylpropenyl)-1-deoxypaclitaxel (8c). To a solution of **5a** (10.0 mg, 0.015 mmol) and **6c** (5.0 mg, 0.007 mmol) in THF (0.5 mL) was added NaH (15 mg, 60% dispersion in mineral oil) at 0 °C, and the mixture allowed to stir at room temperature for 3 h. The mixture was then quenched with AcOH (0.2 mL) at 0 °C and diluted with EtOAc (5 mL). This reaction mixture was diluted with water and extracted with EtOAc (2 × 10 mL), and the organic layer was washed with a saturated solution of $NaHCO_3$, water, and brine, followed by drying over Na_2SO_4. The residue obtained after evaporation under reduced pressure was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/4) to provide 9(*R*)-dihydro-7,9-diacetyl-2′-triethylsilyl-3′-dephenyl-3′-(3,3-dimethylpropenyl)-1-deoxy taxol (**7c**, 5.6 mg,77%) which was used directly for the next reaction. To a solution of **7c** (5.0 mg, 0.004 mmol) in THF (1 mL) was added TBAF (100 μL) at −20 °C, and the mixture was stirred for 10 min. It was then diluted with EtOAc (5 mL), and the EtOAc layer was washed successively with saturated $NaHCO_3$, 0.1 N HCl, again with saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The residue obtained after evaporation was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/1) to yield **8c** (4.10 mg, 96%): ^{1}H NMR δ 1.11 (s, 3H), 1.39 (s, 9H), 1.59 (s, 3H), 1.75 (s, 3H), 1.76 (s, 3H), 1.86 (s, 3H), 1.98 (s, 3H), 2.01−2.05 (m, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 2.28 (s, 3H), 2.52−2.64 (m, 2H), 3.00 (d, J = 5.79 Hz, 1H), 3.88 (bs, 1H), 4.16 (d, J = 8.54 Hz, 1H), 4.28−4.30 (dd, J = 2.6 and 4.27 Hz, 1H), 4.39 (d, J = 8.24 Hz, 1H), 4.82 (m, 1H), 4.97 (d, J = 7.78 Hz, 1H), 5.02 (d, J = 9.16 Hz, 1H), 5.24 (d, J = 9.00 Hz, 1H), 5.51 (dd, J = 8.69 and 8.55 Hz, 1H), 5.86−5.90 (m, 2H), 5.98 (d, J = 11.14 Hz, 1H), 6.17 (d, J = 11.14 Hz, 1H), 7.47 (dd, J = 7.94 and 7.47 Hz, 2H), 7.60 (dd, J = 7.48 and 7.32 Hz, 1H), 8.06 (d, J = 7.02 Hz, 2H); ^{13}C NMR d 13.0, 15.3, 18.7, 20.8, 20.9, 21.4, 22.4, 25.8, 26.6, 26.8, 28.3, 31.1, 34,6, 37.9, 44.0, 46.0, 47.2, 71.2, 71.7, 73.9, 75.5, 83.7, 120.9, 128.6, 129.5, 129.8, 133.6, 164.9, 168.9, 169.8, 170.1; HRFABMS calcd for $C_{47}H_{63}NO_{16}$ [M + H]$^+$ m/z 898.4225, found 898.4219.

7,9,10-Trideacetylbaccatin VI (9). Procedure A. To a solution of baccatin VI (**3**) (15.00 mg, 0.021 mmol) in MeOH (2.0 mL) was added 1 N NaOH (120 μL) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. CO_2 was bubbled through the reaction mixture, and the residue obtained after evaporation was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 3/2) to yield **9** (9.00 mg, 84%). **Procedure B.** To a solution of baccatin VI (**3**) (50 mg, 0.071 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added benzyltrimethylammonium hydroxide (30 μL, 40% w/w solution in MeOH, 0.07 mmol) at 0 °C. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC until it showed maximum formation of the polar product. The reaction mixture was diluted with cold CH_2Cl_2 (5 mL) at 0 °C and quenched with 0.1 N HCl (5 mL). The organic layer was separated, washed successively with water, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Concentration of the organic layer under reduced pressure gave a crude residue, which was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 3/2) to yield unreacted **3** (17 mg), **9** (21.5 mg, 79% on the basis of unrecovered starting material), and a small amount of a UV-inactive product which was not characterized. **9**: ^{1}H NMR δ 1.20 (s, 3H), 1.63−1.69 (m, 1H), 1.76 (s, 3H), 1.79 (s, 3H), 1.85 (s, 3H), 1.88−1.96 (m, 2H), 2.18 (s, 3H), 2.27 (s, 3H), 2.42−2.61 (m, 2H), 2.88 (d, J = 5.96 Hz, 1H), 3.08 (s, 1H), 3.42 (s, 1H), 4.16 (d, J = 8.39 Hz, 1H), 4.32−4.41 (m, 3H), 4.76 (s, 1H), 4.91 (d, J = 10.38 Hz, 1H), 4.98 (d, J = 8.09 Hz, 1H), 5.75 (dd, J = 2.14 and 5.95 Hz, 1H), 5.96 (d, J = 10.5 Hz, 1H), 7.48 (t, J = 7.94 Hz, 2H), 7.59 (t, J = 7.32 Hz, 1H), 8.05 (dd, J = 8.39 and 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.5, 14.8, 21.3, 22.8, 26.7, 26.8, 31.7, 38.1, 38.2, 44.1, 44.3, 47.2, 69.3, 71.2, 71.7, 74.5, 78.8, 81.8, 83.9, 128.6, 129.8, 133.5, 135.3, 137.4, 165.0, 169.3, 170.7; HRFABMS calcd for $C_{31}H_{40}O_{10}$ [M + H]$^+$ m/z 573.2699, found 573.2703.

7,9,10-Trideacetylbaccatin VI 7,9-Acetonide (10a). To a solution of **9** (59 mg) in CH_2Cl_2 (3 mL) were added 2-methoxypropene (10 μL, 1.0 mmol) and pyridinium tosylate (2 mg), and the resulting solution was stirred at room temperature for 12 h. After completion of the reaction, it was diluted with CH_2Cl_2 (10 mL), washed with a saturated $NaHCO_3$ solution and brine, and concentrated under vacuo. The residue obtained was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 1/3) to yield **10a** (30 mg, 55%): ^{1}H NMR δ 1.11 (s, 3H), 1.48−2.00 (m, 3H), 1.52 (s, 6H), 1.75 (s, 3H), 1.79 (s, 3H), 1.82 (s, 3H), 2.21 (s, 3H), 2.29 (s, 3H), 2.45−2.65 (m, 2H), 2.76 (d, J = 5.4 Hz, 1H), 4.14 (d, J = 8.2 Hz, 1H), 4.28−4.39 (m, 2H), 4.58 (d, J = 8.5 Hz, 1H), 4.96 (d, J = 8.7 Hz, 1H), 5.06 (d, J = 10 Hz, 1H), 5.81 (d, J = 8.8 Hz, 1H), 6.01 (m, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 8.2 Hz, 1H), 8.08 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.9, 15.3, 21.2, 22.7, 26.2, 26.9, 27.1, 31.7, 36.7, 38.4, 42.0, 42.3, 47.7, 69.4, 71.6, 72.2, 74.5, 76.4, 81.4, 83.7, 84.4, 107.4, 128.5, 129.6, 129.8, 133.2, 133.6, 139.6, 165.0, 169.1, 170.6.

7,9,10-Trideacetylbaccatin VI 7,9-Benzylidene Acetal (10b). To a solution of **9** (21.5 mg) in toluene (2 mL) were added camphor sulfonic acid (1 mg), molecular sieves (4A size), and benzaldehyde (0.2 mL, 1.96 mmol), and the mixture was stirred at 40 °C for 15 h. The reaction mixture was filtered through a pad of Celite and washed with EtOAc, and the organic layer was washed thoroughly with a saturated $NaHCO_3$ solution and brine and dried over Na_2SO_4. The residue obtained after evaporation was purified by PTLC (silica gel,

1000 μm, EtOAc/hexane 2/3) to yield recovered **9** (5.5 mg) and **10b** (12 mg, 63% based on unrecovered starting material): ^{1}H NMR δ 1.19 (s, 3H), 1.65 (s, 3H), 1.79 (s, 3H), 1.64 (m, 1H), 1.93 (s, 1H), 1.99 (d, J = 9.3 Hz, 1H), 2.19 (s, 3H), 2.28 (s, 3H), 2.53 (s, 3H), 2.44−2.70 (m, 2H), 2.76 (d, J = 5.4 Hz, 1H), 4.12 (d, J = 8.2 Hz, 1H), 4.36 (d, J = 8.5 Hz, 1H), 4.38 (d, J = 8.9 Hz, 1H), 4.70 (d, J = 10.1 Hz, 1H), 4.97 (d, J = 8.7 Hz, 1H), 5.13 (s, 1H), 5.19 d, J = 10 Hz, 1H), 5.80 (m, 1H), 6.00 (dd, J = 8.8 and 8.7 Hz, 1H), 6.11 (s, 1H), 7.13−7.27 (m, 3H), 7.40−7.50 (m, 4H), 7.60 (m, 1H), 8.04 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.1, 15.5, 21.3, 22.7, 26.0, 26.9, 31.7, 36.8, 38.2, 42.0, 42.5, 47.6, 69.4, 71.5, 71.5, 72.1, 81.4, 84.0, 84.4, 101.8, 125.3, 126.1, 128.2, 128.6, 128.6, 128.9, 129.0, 129.3, 129.5, 129.8, 133.0, 133.6, 137.8, 140.4, 165.0, 169.2, 170.6.

7,9,10-Trideacetyl-10-triethylsilylbaccatin VI 7,9-Acetonide (11a). To a solution of **10a** (30 mg, 0.049 mmol) in dry CH_2Cl_2 (1 mL) was added imidazole (23.3 mg, 0.34 mmol) followed by Et_3SiCl (50 μL, 0.29 mmol). The mixture was stirred for 2 h at room temperature and diluted with EtOAc (10 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 1/4) to yield **11a** (26 mg, 74%): ^{1}H NMR δ 0.65 (q, J = 8.3 Hz, 6H), 0.99 (t, J = 8.3 Hz, 9H), 1.18 (s, 3H), 1.46 (s, 3H), 1.60 (m, 1H), 1.61 (s, 3H), 1.65 (s, 3H), 1.82 (s, 3H), 1.84 (s, 3H), 1.88−1.95 (m, 2H), 2.18 (s, 3H), 2.25 (s, 3H), 2.41−2.65 (m, 2H), 2.70 (d, J = 5.9 Hz, 1H), 4.13 (d, J = 8.7 Hz, 1H), 4.29 (t, J = 8.6 Hz, 1H), 4.31−4.36 (m, 2H), 4.86 (d, J = 10.1 Hz, 1H), 4.95 (d, J = 8.5 Hz, 1H), 5.85 (m, 1H), 5.95 (m, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 8.07 (dd, J = 1.3 and 8.2 Hz 2H); ^{13}C NMR δ 5.9, 7.12, 13.4, 15.2, 21.2, 22.7, 26.9, 27.0, 27.2, 28.2, 31.5, 38.5, 38.9, 42.6, 44.1, 48.2, 69.5, 71.8, 72.3, 74.2, 76.6, 81.3, 82.5, 84.4, 106.5, 128.6, 129.8, 133.5, 134.5, 137.2, 165.1, 169.2, 170.7; HRFABMS calcd for $C_{40}H_{58}O_{11}SiLi$ $[M + Li]^+$ m/z 733.3959, found 733.3960.

7,9,10-Trideacetyl-10-triethylsilylbaccatin VI 7,9-Benzylidene Acetal (11b). To a solution of **10b** (12 mg, 0.018 mmol) in dry DMF (1 mL) were added imidazole (11 mg, 0.16 mmol) and Et_3SiCl (15 μL, 0.09 mmol) at room temperature. The mixture was stirred overnight and diluted with EtOAc (10 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/3) to yield **11b** (10.1 mg, 72%): ^{1}H NMR δ 0.68 (q, J = 8.4 Hz, 6H), 1.01 (t, J = 8.4 Hz, 9H), 1.18 (s, 3H), 1.62 (m, 1H), 1.72 (s, 3H), 1.76 (s, 3H), 1.91 (s, 3H), 2.00 (s, 3H), 2.20 (s, 3H), 2.27 (s, 3H), 2.42−2.60 (m, 2H), 2.71 (d, J = 5.9 Hz, 1H), 4.13 (d, J = 8.7 Hz, 1H), 4.37 (m, 2H), 4.61 (d, J = 10.5 Hz, 1H), 4.97 (d, J = 8.5 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 5.81−5.84 (dd, J = 2.1 and 5.9 Hz, 1H), 5.97 (s, 1H), 5.99 (m, 1H), 7.36−7.61 (m, 8H), 8.06 (dd, J = 1.3 and 8.5 Hz, 2H); ^{13}C NMR δ 6.0, 7.1, 12.8, 15.5, 21.3, 22.7, 26.2, 26.9, 31.9, 38.4, 38.7, 43.1, 44.1, 47.8, 69.6, 71.6, 72.8, 76.3, 76.4, 81.5, 82.4, 84.7, 102.0, 126.4, 128.4, 128.5, 128.9, 129.8, 133.5, 134.7, 138.7, 138.9, 165.0, 169.3, 170.6.

7,9,10,13-Tetradeacetyl-10-triethylsilylbaccatin VI 7,9-Acetonide (12a). To a solution of **11a** (26 mg, 0.035 mmol) in THF (1.5 mL) was added methyllithium (75 μL, 1.4 M solution in ether, 0.06 mmol) at −78 °C, and the resulting solution was stirred at the same temperature for 10 min. The mixture was then quenched with saturated NH_4Cl, diluted with EtOAc (5 mL), and warmed to room temperature. The organic layer was washed with water and brine and dried over Na_2SO_4. The residue obtained after concentration of the organic layer under reduced pressure was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/3) to yield recovered **11a** (10.2 mg) and **12a** (9.5 mg, 63% on the basis of unrecovered **11a**): ^{1}H NMR δ 0.66 (q, J = 8.4 Hz, 6H), 1.00 (t, J = 8.4 Hz, 9H), 1.06 (s, 3H), 1.46 (s, 3H), 1.48 (s, 3H), 1.64 (s, 3H), 1.78 (s, 3H), 1.86−1.93 (m, 3H), 2.01 (s, 3H), 2.18 (d, J = 10.4 Hz, 1H), 2.27 (s, 3H), 2.51−2.59 (m, 2H), 2.79 (d, J = 5.9 Hz, 1H), 4.16 (d, J = 8.8 Hz, 1H), 4.28−4.38 (m, 4H), 4.59 (m, 1H), 4.83 (d, J = 10.4 Hz, 1H), 4.90 (d, J = 8.4 Hz, 1H), 5.83 (m, 1H), 7.47 (t, J = 8.4 Hz, 2H), 7.59 (t, J = 8.3 Hz, 1H), 8.08 (dd, J = 1.3 and 8.3 Hz, 2H); ^{13}C NMR δ 5.8, 7.2, 13.8, 15.6, 23.0, 26.6, 27.2, 28.2, 30.7, 31.4, 38.4, 38.7, 42.0, 44.4, 48.1, 67.9, 71.8, 71.9, 74.6, 82.0, 82.6, 84.9, 106.5, 128.6, 129.8, 129.9, 133.4, 133.9, 140.9, 165.1, 172.4; HRFABMS calcd for $C_{38}H_{56}O_9SiLi$ $[M + Li]^+$ m/z 691.3853, found 691.3847.

7,9,10,13-Tetradeacetyl-10-triethylsilylbaccatin VI 7,9-Benzylidene Acetal (12b). To a solution of **11b** (16.3 mg, 0.021 mmol) in THF (1.5 mL) was added methyllithium (100 μL, 1.4 M solution in ether, 0.13 mmol) at −78 °C; the solution was stirred at the same temperature for 15 min. The mixture was quenched with a buffer solution (pH 7.2) and diluted with EtOAc (5 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a residue which was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/1) to provide **12b** (5.5 mg, 37%): ^{1}H NMR δ 0.68 (q, J = 8.2 Hz, 6H), 1.02 (t, J = 8.2 Hz, 9H), 1.55 (s, 3H), 1.68 (s, 3H), 1.75 (s, 3H), 1.91−2.22 (m, 3H), 2.07 (s, 3H), 2.27 (s, 3H), 2.56 (m, 2H), 2.89 (d, J = 5.6 Hz, 1H), 4.16 (d, J = 8.2 Hz, 1H), 4.37 (m, 2H), 4.60 (m, 2H), 4.93 (d, J = 9.1 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 5.81 (dd, J = 2.4 and 6.2 Hz, 1H), 5.97 (s, 1H), 7.30−7.62 (m, 8H), 8.08 (dd, J = 1.2 and 8.4 Hz, 2H); ^{13}C NMR δ 5.9, 7.13, 12.9, 15.9, 23.0, 25.8, 30.5, 31.9, 38.0, 38.6, 42.8, 44.2, 47.6, 67.8, 71.6, 72.8, 82.0, 82.5, 84.9, 102.0, 126.5, 128.4, 128.5, 128.9, 129.8, 133.4, 134.2, 139.0, 142.1, 165.0, 171.9.

10-Deacetyl-9(*R*)-dihydro-10-triethylsilyl-2′-*tert*-butyldimethylsilyl-1-deoxypaclitaxel 7,9-Acetonide (13a). To a solution of **12a** (20 mg, 0.029 mmol) in THF (1.0 mL) was added *n*-butyllithium (20 μL, 2 M solution in the hexane, 0.5 mmol) at −78 °C, followed by the addition of **6d** (16 mg, 0.043 mmol) in dry THF (0.2 mL), and the mixture was stirred at the same temperature for 10 min. The mixture was then quenched with saturated NH_4Cl at −10 °C, diluted with EtOAc (5 mL), and warmed to room temperature. The mixture was extracted with EtOAc (2 × 10 mL), and the organic layer was washed with water and brine and dried over Na_2SO_4. The residue obtained after concentration under reduced pressure was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 1/4) to yield **13a** (7.2 mg, 23%): ^{1}H NMR δ −0.15 (s, 3H), 0.01 (s, 3H), 0.65 (q, J = 8.4 Hz, 6H), 0.82 (s, 9H), 1.00 (t, J = 8.4 Hz, 9H), 1.21 (s, 3H), 1.46 (s, 3H), 1.52 (s, 3H), 1.68 (s, 3H), 1.71−2.00 (m, 3H), 1.84 (s, 3H), 1.86 (s, 3H), 2.38−2.65 (m, 2H), 2.48 (s, 3H), 2.74 (d, J = 5.8 Hz, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.34 (dd, J = 9.1 and 8.0 Hz, 1H), 4.39 (m, 2H), 4.72 (s, 1H), 4.84 (d, J = 9.2 Hz, 1H), 4.98 (d, J = 8.6 Hz, 1H), 5.74 (d, J = 8.2 Hz, 1H), 5.90 (m, 1H), 6.08 (m, 1H), 7.16 (d, J = 7.0 Hz, 1H), 7.28−7.55 (m, 10H), 7.62 (t, J = 8.4 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 8.09 (dd, J = 1.3 and 8.4 Hz, 2H); ^{13}C NMR δ −5.8, −5.2, 5.9, 7.2, 14.0, 14.8, 18.1, 23.4, 25.6, 26.4, 27.2, 27.5, 28.2, 31.7, 38.7, 38.9, 42.2, 44.2, 48.4, 55.6, 71.7, 72.0, 74.2, 74.8, 81.3, 82.6, 84.7, 106.5, 126.5, 127.0, 127.9, 128.6, 128.8, 129.6, 129.9, 131.7, 133.5, 134.2, 134.5, 137.0, 138.4, 165.3, 167.1, 169.6, 171.9; HRFABMS calcd for $C_{60}H_{83N}O_{12}Si_2Li$ $[M + Li]^+$ m/z 1073.5605, found 1073.5605.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-10-deacetyl-10-triethylsilyl-9(*R*)-dihydro-2′-triisopropylsilyl-1-deoxypaclitaxel 7,9-Benzylidene Acetal (13b). To a solution of **12b** (20 mg, 0.029 mmol) and **6b** (5.0 mg, 0.011 mmol) in THF (1.0 mL) was added NaH (3.5 mg, 60% dispersion in mineral oil, 20 equiv) at 0 °C, and the mixture was allowed to stir at room temperature for 2.5 h. The mixture was then quenched with AcOH (0.2 mL) at 0 °C and diluted with EtOAc (5 mL). This mixture was then diluted with H_2O and extracted with EtOAc (2 × 10 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine, followed by drying over Na_2SO_4. The residue obtained after evaporation under reduced pressure was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/4) to provide **13b** (6.0 mg, 69%): ^{1}H NMR δ 0.68 (q, J = 8.2 Hz, 6H), 0.94 (m, 21H), 1.02 (t, J = 8.2 Hz, 9H), 1.21 (s, 3H), 1.34 (s, 9H), 1.74 (s, 3H), 1.76 (s, 3H), 1.92 (s, 3H), 1.86−2.42 (m, 3H), 2.45 (s, 3H), 2.56 (m, 2H), 2.74 (d, J = 5.6 Hz, 1H), 4.15 (d, J = 8.3 Hz, 1H), 4.36−4.41 (m, 2H), 4.63 (d, J = 10.2 Hz, 1H), 4.82 (s, 1H), 4.96 (d, J = 8.8 Hz, 1H), 5.13 (d, J = 10.2 Hz, 1H), 5.23 (d, J = 9.7 Hz, 1H), 5.40 (d, J = 10.5 Hz, 1H), 5.85 (dd, J = 2.4 and 6.2 Hz, 1H), 5.95

(s, 1H), 7.27−7.60 (m, 13H), 8.08 (dd, J = 1.2 and 8.4 Hz, 2H); ^{13}C NMR δ 6.0, 7.1, 12.6, 13.0, 15.0, 17.8, 17.9, 23.3, 26.3, 26.8, 28.2, 32.0, 38.6, 38.7, 43.0, 44.0, 48.1, 71.8, 72.7, 72.9, 76.0, 79.8, 81.6, 82.4, 84.9, 102.0, 126.4, 126.6, 127.6, 128.3, 128.5, 128.6, 128.8, 129.6, 129.9, 133.4, 134.1, 138.8, 139.0, 165.2, 169.4, 170.9, 172.3.

10-Deacetyl-9(*R*)-dihydro-1-deoxypaclitaxel 7,9-Acetonide (14a). To a solution of **13a** (7.0 mg, 0.006 mmol) in THF (0.5 mL) and pyridine (100 μL) was added HF/pyridine (100 μL), and the mixture was stirred at room temperature for 1.5 h. The mixture was then diluted with EtOAc (5 mL), and the EtOAc layer was washed succesively with saturated $NaHCO_3$, 0.1 N HCl, again with saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue obtained was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/1) to yield **14a** (6.0 mg, 99%): ^{1}H NMR δ 1.16 (s, 3H), 1.52 (s, 6H), 1.56 (s, 3H), 1.69 (s, 3H), 1.78 (s, 3H), 1.81−1.98 (m, 3H), 2.28 (s, 3H), 2.58−2.66 (m, 2H), 2.71 (d, J = 5.8 Hz, 1H), 3.78 (m, 1H), 4.18 (d, J = 8.4 Hz, 1H), 4.21 (dd, J = 9.1 and 8.0 Hz, 1H), 4.36 (m, 2H), 4.54 (d, J = 10.2 Hz, 1H), 4.78 (m, 1H), 4.96 (m, 2H), 5.81 (m, 1H), 5.85−5.96 (m, 2H), 7.11−7.58 (m, 10H), 7.60 (t, J = 8.3 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 8.09 (dd, J = 1.3 and 8.3 Hz, 2H); ^{13}C NMR δ 13.0, 15.6, 22.6, 25.7, 26.9, 27.0, 31.8, 36.73 38.3, 41.8, 42.6, 47.5, 54.44, 71.1, 71.3, 72.2, 73.8, 74.4, 76.4, 82.2, 83.6, 84.3, 107.5, 127.0, 127.1, 127.3, 128.1, 128.7, 128.9, 129.4, 129.8, 131.8, 133.7, 133.8, 134.3, 138.3, 138.4, 165.0, 166.3, 170.9, 171.3; HRFABMS calcd for $C_{48}H_{55}NO_{12}Li$ [M + Li]$^+$ m/z 844.3884, found 844.3913.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-10-deacetyl-9(*R*)-dihydro-1-deoxypaclitaxel 7,9-Benzylidene Acetal (14b). To a solution of **13b** (6.0 mg, 0.005 mmol) in THF (1.0 mL) was added HF/pyridine (200 μL), and the mixture was stirred at room temperature for 2 h. The mixture was then diluted with EtOAc (15 mL), and the EtOAc layer was washed succesively with saturated $NaHCO_3$, 0.1 N HCl, again with saturated $NaHCO_3$, water, and brine. It was then dried over Na_2SO_4 and concentrated under reduced pressure, and the residue obtained was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 9/11) to yield **14b** (1.5 mg, 33%): ^{1}H NMR δ 1.16 (s, 3H), 1.39 (s, 9H), 1.65 (s, 3H), 1.78 (s, 3H), 1.79 (s, 3H), 1.91−2.00 (m, 2H), 1.99 (d, J = 9.0 Hz, 1H),2.25 (s, 3H), 2.62−2.66 (m, 2H), 2.74 (d, J = 5.3 Hz, 1H), 4.01 (s, 1H), 4.15 (d, J = 7.6 Hz, 1H), 4.30−4.36 (m, 2H), 4.62−4.68 (m, 2H), 4.93 (d, J = 9.4 Hz, 1H), 4.96 (d, J = 10. 9 Hz, 1H), 5.15 (d, J = 9.6 Hz, 1H), 5.29 (m, 1H), 5.60 (m, 1H), 5.80 (m, 1H), 5.91 (m, 1H), 6.12 (s, 1H), 7.28−7.60 (m, 13H), 8.04 (dd, J = 1.2 and 8.6 Hz, 2H); HRFABMS calcd for $C_{50}H_{59}NO_{13}Li$ [M + Li]$^+$ m/z 888.4146, found 888.4159.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-9(*R*)-dihydro-10-deacetyl-2′-triisopropylsilyl-1-deoxypaclitaxel (15). Procedure A. To a solution of **7b** (26 mg, 0.024 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added benzyltrimethylammonium hydroxide (10 μL, 40% w/w solution in methanol, 0.024 mmol) at 0 °C. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC until a polar spot developed at the base of the chromatogram. The reaction mixture was then diluted with cold CH_2Cl_2 (5 mL) at 0 °C and quenched with 0.1 N HCl (5 mL). The organic layer was separated, washed succesively with water, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Concentration of the organic layer under reduced pressure gave crude residue which was purified by PTLC (silica gel, 1000 μm, MeOH/CH_2Cl_2 1/24) to furnish recovered **7b** (10 mg) and **15** (6.0 mg, 42% on the basis of unrecovered starting material). **Procedure B.** To a solution of **7b** (35.00 mg) in MeOH (2.0 mL) was added 1 N KOH (250 μL) at 0 °C, and the reaction mixture was stirred at room temperature for 16 h. CO_2 was then bubbled through the reaction mixture, and the residue obtained after evaporation was purified by PTLC (silica gel, 500 μm, 4% MeOH/CH_2Cl_2) to yield unreacted **7b** (7.5 mg) and **15** (12.0 mg, 52% based on unrecovered starting material): ^{1}H NMR δ 0.91 (m, 21H), 1.25 (s, 3H), 1.35 (s, 9H), 1.78 (s, 3H), 1.79 (s, 3H), 1.87 (s, 3H), 1.91−2.04 (m, 2H), 2.45 (s, 3H), 2.49−2.61 (m, 2H), 2.91 (d, J = 5.8 Hz, 1H), 4.17 (d, J = 8.2 Hz, 1H), 4.35−4.42 (m, 3H), 4.79 (s, 1H), 4.92−4.98 (m, 2H), 5.23 (d, J = 10.2 Hz, 1H), 5.77 (m, 1H), 5.94 (m, 1H), 7.24−7.36 (m, 5H), 7.47 (t, J = 7.4 Hz, 2H), 7.59 (m, 1H), 8.05 (dd, J = 1.3 and 8.5 Hz, 2H); ^{13}C NMR δ 12.6, 14.5, 17.8, 17.9, 23.4, 26.2, 27.5, 28.2, 38.2, 38,5, 43.9, 44.2, 45.9, 47.2, 47.4, 71.7, 71.9, 74.4, 75.5, 78.2, 79.2, 81.8, 84.1, 126.5, 127.6, 128.5, 128.6, 129.6, 129.9, 133.5, 148.6, 167.9, 169.3, 170.1; HRFABMS calcd for $C_{52}H_{76}NO_{13}$ [M + H]$^+$ m/z 950.5085, found 950.5045.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-9(*R*)-dihydro-10-deacetyl-9,10-dihydroxy-1-deoxypaclitaxel (16). To a solution of **15** (3.0 mg, 0.003 mmol) in THF (1.0 mL) was added tetrabutylammonium fluoride (25 μL, 1 M solution in THF) at −20 °C, and the mixture was stirred at the same temperature for 5 min and then at room temperature for 10 min. The mixture was then diluted with EtOAc (5 mL), and the EtOAc layer was washed successively with saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The residue obtained after concentration of the organic layer was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 3/2) to yield **16** (1.9 mg, 80%): ^{1}H NMR δ 1.19 (s, 3H), 1.39 (s, 9H), 1.68 (s, 3H), 1.76 (s, 3H), 1.80 (s, 3H), 1.86−1.96 (m, 2H), 2.24 (s, 3H), 2.52−2.66 (m, 2H), 2.84 (d, J = 5.3 Hz, 1H), 4.11 (m,1H), 4.19 (d, J = 8.5 Hz, 1H), 4.25−4.35 (m, 3H), 4.61 (s, 1H), 4.88(d, J = 10.2 Hz, 1H), 4.93 (d, J = 8.3 Hz, 1H), 5.28 (d, J = 9.4 Hz, 1H), 5.66 (d, J = 9.6 Hz, 1H), 5.76 (m, 1H), 5.87 (m, 1H), 7.27−7.48 (m, 7H), 7.59 (t, J = 7.4 Hz, 1H), 8.03 (dd, J = 1.3 and 8.5 Hz, 2H); ^{13}C NMR δ 12.5, 15.1, 22.6, 26.7, 28.3, 31.6, 38.2, 43.9, 44.6, 47.2, 55.9, 71.3, 71.4, 74.1, 74.4, 79.0, 83.8, 127.0, 127.8, 128.5, 128.6, 129.5, 133.6, 165.0; HRFABMS calcd for $C_{43}H_{55}NO_{13}$ [M + H]$^+$ m/z 794.3751, found 794.3740. Anal. Calcd for $C_{52}H_{55}NO_{13}$: C, 65.06; H, 6.97; N, 1.76. Found: C, 65.09; H, 6.59; N, 1.92.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-9(*R*)-dihydro-10-deacetyl-7-*O*-methyl-10-*O*-(4-methoxybutyl)-1-deoxypaclitaxel (18) and 3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-9(*R*)-dihydro-10-deacetyl-7-*O*-methyl-1-deoxypaclitaxel (20). To a solution of **15** (20 mg, 0.021 mmol) in THF (1.0 mL) were added methyl iodide (1 mL) and Ag_2O (20 mg), and the mixture was stirred at 65 °C for 16 h. The reaction mixture was diluted with EtOAc (5 mL), and the EtOAc layer was washed succesively with buffer solution (pH 7.2), saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The residue obtained after concentration of the organic layer was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 3/2) to yield a mixture of **17** and **19** (4.6 mg) and recovered starting material (6 mg). This mixture was dissolved in THF (1 mL), treated with TBAF (50 μL) at −20 °C, and stirred at the same temperature for 15 min. The residue obtained after the usual workup was purified by PTLC (silica gel, 500 μm, 2.5%, MeOH/CH_2Cl_2) to yield **18** (1.6 mg, 12%) and **20** (1.7 mg, 15%).

Compound 18: ^{1}H NMR δ 1.15 (s, 3H), 1.39 (s, 9H), 1.68 (s, 3H), 1.75 (s, 3H), 1.81 (s, 3H), 1.91−2.04 (m, 3H), 2.10 (s, 3H), 2.16−2.18 (m, 2H), 2.22 (s, 3H), 2.60 (m, 2H), 2.80 (d, J = 6.11 Hz, 1H), 3.34 (s, 3H), 3.39−3.41 (m, 2H), 3.69−3.71 (m, 2H), 3.72 (s, 3H), 3.99 (d, J = 10.37 Hz, 1H), 4.17 (m, 1H), 4.33 (d, J = 8.24 Hz, 1H), 4.61 (m, 1H), 4.68 (d, J = 10.38 Hz, 1H), 4.93 (d, J = 8.85 Hz, 1H), 5.58 (m, 1H), 5.73 (m, 1H), 5.89 (m, 1H), 7.29−7.61 (m, 8H), 8.05 (d, J = 6.71 Hz, 2H); HRFABMS calcd for $C_{49}H_{68}NO_{14}$ [M + H]$^+$ m/z 894.4639, found 894.4621.

Compound 20: ^{1}H NMR δ 1.17 (s, 3H), 1.40 (s, 9H), 1.50−1.51 (m, 1H), 1.70 (s, 3H), 1.76 (s, 3H), 1.82 (s, 3H), 1.85−1.95 (m, 3H), 2.24 (s, 3H), 2.68 (m, 2H), 2.86 (d, J = 5.49 Hz, 1H), 3.42 (s, 3H), 3.43 (d, J = 9.31 Hz, 1H), 3.89 (dd, J = 9.61 and 7.02 Hz, 1H), 4.20 (d, J = 8.70 Hz, 1H), 4.34 (d, J = 8.39 Hz, 1H), 4.61 (m, 1H), 4.70 (d, J = 10.37 Hz, 1H), 4.96 (d, J = 8.39 Hz, 1H), 5.20 (d, J = 9.61 Hz, 1H), 5.29 (m, 1H), 5.67 (d, J = 9.01 Hz, 1H), 5.85 (m, 1H), 7.28−7.61 (m, 8H), 8.03 (d, J = 7.17 Hz, 2H); HRFABMS calcd for $C_{44}H_{58}NO_{13}$ [M + H]$^+$ m/z 808.3908, found 808.3885.

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-10-deacetyl-9(*R*)-dihydro-2′-triisopropylsilyl-1-deoxypaclitaxel 7,9-Acetonide (13c). To a solution of **15** (7.0 mg, 0.007 mmol) in acetone (1 mL) were added dimethoxypropane (200 μL, 1.0

mmol) and pyridinium tosylate (2 mg), and the mixture was stirred at room temperature for 15 min. After completion of the reaction, it was diluted with EtOAc (10 mL), washed with a saturated $NaHCO_3$ solution and brine, and concentrated in vacuo. The residue obtained was purified by PTLC (silica gel, 1000 μm, EtOAc/hexane 1/3) to yield **13c** (7.0 mg, 97%): ^{1}H NMR δ 0.90 (m, 21H), 1.34 (s, 9H), 1.51 (s, 6H), 1.69 (s, 3H), 1.73−1.85 (m, 2H), 1.81 (s, 3H), 1.88 (s, 3H), 2.04 (s, 3H), 2.09 (m, 1H), 2.44 (s, 3H), 2.59−2.65 (m, 2H), 2.75 (d, J = 5.95 Hz, 1H), 4.09−4.13 (m, 2H), 4.22−4.38 (m, 2H), 4.58 (d, J = 10.22 Hz, 1H), 4.79 (m, 1H), 4.94 (d, J = 8.85 Hz, 1H), 5.03 (d, J = 9.77 Hz, 1H), 5.13 (m, 1H), 5.23 (m, 1H), 5.42 (d, J = 8.85 Hz, 1H), 5.81 (m, 1H), 5.95 (m,1H), 7.25−7.39 (m, 5H), 7.47 (dd, J = 7.93 and 7.79 Hz, 2H), 7.59 (t, J = 7.48 Hz, 1H), 8.07, (d, J = 7.32 Hz, 2H).

3′-*N*-Debenzoyl-3′-*N*-*tert*-butoxycarbonyl-10-deacetyl-9(*R*)-dihydro-1-deoxypaclitaxel 7,9-Acetonide (14c). To a solution of **13c** (4.5 mg, 0.0045 mmol) in THF (1 mL) was added TBAF (25 μL) at −20 °C, and the mixture was stirred at the same temperature for 10 min. The residue obtained after usual workup was purified by PTLC (silica gel, 500 μm, EtOAc/hexane 1/1) to yield **14c** (2.9 mg, 78%): ^{1}H NMR δ 1.17 (s, 3H), 1.39 (s, 9H), 1.51 (s, 6H), 1.54 (m, 1H), 1.69 (s, 6H), 1.78 (s, 3H), 1.85−2.00 (m, 3H), 2.23 (s, 3H), 2.57−2.65 (m, 2H), 2.69 (d, J = 5.34 Hz, 1H), 4.04 (bs, 1H), 4.14 (d, J = 8.4 Hz, 1H), 4.21−4.25 (dd, J = 8.09 and 8.24 Hz, 1H), 4.33 (d, J = 8.54 Hz, 1H), 4.52 (d, J = 10.07 Hz, 1H), 4.61 (m, 1H), 4.90−4.99 (m, 3H), 5.28 (d, J = 9.61 Hz, 1H), 5.63 (d, J = 10.68 Hz, 1H), 5.78−5.80 (dd, J = 1.83 and 5.99 Hz, 1H), 5.88 (dd, J = 8.69 and 8.55 Hz, 1H), 7.27−7.62 (m, 9H), 8.04 (d, J = 7.02 Hz, 2H); ^{13}C NMR δ 13.0, 15.6, 22.5, 25.9, 26.3, 26.9, 27.0, 28.3, 31.7, 36.7, 38.4, 41.8, 42.5, 47.6, 55.9, 71.2, 71.6, 72.1, 74.1, 74.4, 79.9, 82.0, 83.7, 84.3, 107.5, 127.0, 127.8, 128.5, 128.6, 129.4, 129.8, 133.7, 138.7, 165.0, 170.7, 171.4; HRFABMS calcd for $C_{46}H_{59}NO_{13}$ $[M + H]^+$ m/z 834.4064, found 834.4063. Anal. Calcd for $C_{46}H_{59}NO_{13}$: C, 66.28; H, 7.09; N, 1.68. Found: C, 66.46; H, 6.88; N, 1.64.

Tubulin Assembly Assays. Twice-cycled microtubule protein was prepared by following the procedure of Williams and Lee[25] and stored in liquid nitrogen before use. Quantification of tubulin polymerization potency was accomplished following a modified procedure of Swindell et al.[26] These modifications, in part, result in the expression of tubulin polymerization potency as an effective concentration for any given compound. For this method, different compound concentrations in polymerization buffer (0.1 M MES, 1 mM EGTA, 0.5 mM $MgCl_2$, pH 6.6) were added to microtubule protein in polymerization buffer at 37 °C in microcuvette wells of a Beckman (Beckman Instruments) Model DU 7400 UV spectrophotometer. A final microtubule protein concentration of 1.0 mg/mL and compound concentrations of 2.5, 5.0, and 10 μM were used. Initial slopes of absorbance change measured every 10 s were calculated by the program accompanying the instrument after initial and final times of the linear region encompassing at least 3 time points were manually defined. Under these conditions linear variances were generally < 10^{-6}, slopes ranged from 0.03 to 0.002 A unit/min, and maximum absorbance was 0.15 A unit. Effective concentration ($EC_{0.01}$) is defined as the interpolated concentration capable of inducing an initial slope of 0.01 A unit/min and is calculated using the formula $EC_{0.01}$ = concentration/slope.

Cytotoxicity Assays. Cells of the human colon carcinoma line HCT116 were grown in 96-well titer plates for 48 h at 37 °C under 5% CO_2 in 0.1 mL of medium. The IC_{50} value was the drug concentration required to inhibit by 50% the increase in cell protein. The average IC_{50} values for paclitaxel in the experiments presented here were in the range 2.0−2.5 μM.

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Supporting Information Available: ^{1}H NMR spectra of compounds **8a**−**8c**, **14a**−**14c**, **16**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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