The Chemistry of the Taxane Diterpene: Stereoselective Reductions of Taxanes

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Stereoselective reductions of taxanes are detailed. Chelation-controlled reductions employing SmI_2 are described for the stereoselective reduction of the 9-keto functionality of the diterpene moiety of several taxanes. In all cases the 9β-hydroxy stereochemistry was obtained exclusively. In addition to C9 reduction, partial C10-deoxygenation via β-elimination was observed. Lower reaction temperatures favored the reduction pathway without β-elimination. Acetic acid as the proton source gave higher yields and cleaner reaction products. This chemistry provided access to taxanes with 9β-hydroxy, 10β-hydroxy stereochemistry. Evidence is presented, suggesting that chelation of samarium with the 7β-hydroxyl group is required for the reduction of the C9 ketone moiety. The synthesis of paclitaxel analogues, possessing the 9α-hydroxy, 10α-hydroxy stereochemistry was also achieved. Reduction of the 10-ketone group of 10-oxopaclitaxel employing $NaBH_4$ produced 10-deacetyl-10-epipaclitaxel stereoselectively. Using an excess of $NaBH_4$ in this reaction gave exclusively the 9α-hydroxy, 10α-hydroxy paclitaxel analogue.

Paclitaxel (**1**, Figure 1) and its semisynthetic analogue docetaxel (**7**, Scheme 2), have been found to be effective in the treatment of drug resistant ovarian cancer, metastatic breast cancer, and Kaposi's sarcoma.[1] Additional clinical trials with these two anticancer agents have shown promising results in patients with squamous cell carcinoma, malignant melanoma, nonsmall cell lung and small cell lung cancer, germ cell cancer, urothelial cancer, esophageal cancer, and non-Hodgkin's lymphoma.[1] Paclitaxel's success as an antitumor agent in the treatment of a variety of cancers has made this molecule one of the most important finds[2] in the area of cancer chemotherapy over the last few decades.[3−5]

The target of paclitaxel is the microtubule cytoskeleton.[6] Paclitaxel promotes the formation of stable microtubules, a process which interferes with cell division. Photoaffinity labeling studies[7−9] and a recently published electron crystallographic structure of a polymerized tubulin−docetaxel complex[10] have demonstrated that the taxol binding site is located in the β-subunit of tubulin.

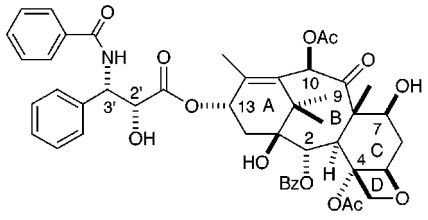
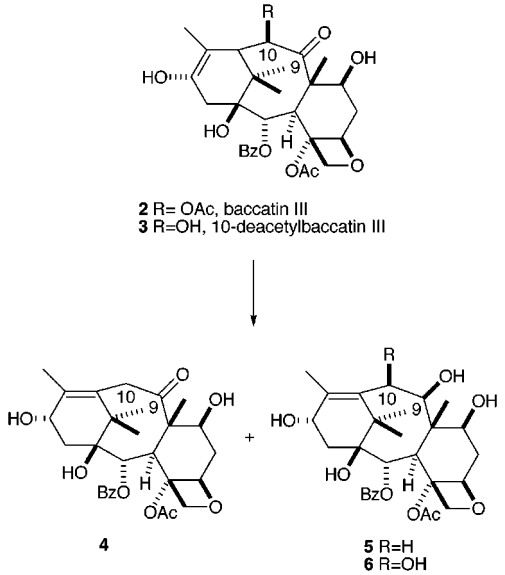


Figure 1. Structure of paclitaxel (**1**).

Scheme 1



Paclitaxel and related analogues may also be of therapeutic value for other disease states. It has been found to induce regression of collagen-induced arthritis,[11] to inhibit congenital polycystic kidney disease,[12] and to

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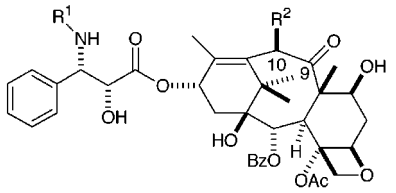
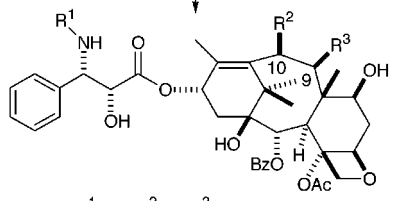
Scheme 2



1 R^1=Bz, R^2=OAc, paclitaxel
7 R^1=t-BuOCO, R^2=OH, docetaxel
8 R^1=Bz, R^2=OH



9 R^1=Bz, R^2=H, R^3= ketone (=O)
10 R^1=t-BuOCO, R^2=H, R^3=ketone (=O)
11 R^1=Bz, R^2=H, R^3=OH
12 R^1=t-BuOCO, R^2=H, R^3=OH
13 R^1=Bz, R^2=OH, R^3=OH
14 R^1=t-BuOCO, R^2=OH, R^3=OH

protect primary neurons against the β-amyloid protein, implicated in Alzheimer's disease.[13]

The chemistry of the antitumor agent paclitaxel (**1**, Figure 1) has been under investigation since its isolation from the bark of the Pacific yew.[14] This highly oxygenated diterpene contains an array of functionalities and interesting chemical reactivity, making it an exciting synthetic target. Information on the SAR of the C13-side chain[15] of the diterpene,[16−19] including the total syntheses of the molecule, affords important insights for the development of new taxanes with increased biological activity.[3−5,17,18,20,21]

Chemistry on the diterpene portion of the molecule includes selective deacylations at the 2-benzoate and 4-acetate, deoxygenation studies at C2, C4, C7, and C10, modifications at C13, and D-ring chemistry.[3−5,20,22,23] We have reported preliminary data on stereoselective reductions[24,25] at the C9 keto group and on the inversion of stereochemistry at the C10 position of the diterpene of paclitaxel. We are now providing the full details of this chemistry and other new findings.

For the targeted reduction of the 9-ketone there were certain issues to consider, reduction of the ketone without effecting reductive cleavage of the ester functionalities[26] (including the phenylisoserine side chain[27]) and epimerization at the C7 position via retro-aldol chemistry.[28,29] Initially, the chemistry was performed on the more available diterpenes baccatin III (**2**, Scheme 1) or 10-deacetylbaccatin III (**3**, Scheme 1). 10-Deacetylbaccatin III (**3**) contains hydroxyl groups both α and β to the ketone (C10 and C7 hydroxyls, respectively) to afford possible five- or six-membered coordinated transition states for chelation-controlled ketone reduction or to facilitate hydroxyl-directed reductions. To effect the reduction, a variety of hydride delivering reagents were unsuccessfully used including $LiAlH_4$, $LiBH_4$, $NaBH_4$, Me_4NBH_4, $Me_4NBH(OAc)_3$, Bu_4NBH_4, and $NaBH(OAc)_3$. The results of these reactions included multiple ester cleavage products, epimerization at C7, or recovery of the starting diterpene. No ketone reduction products were detected. It appeared from these results that hydride delivery to the 9-ketone was not attainable due to the sterically congested environment around the C9 carbonyl group and to the chemical sensitivity of this highly functionalized molecule. To effect the reduction, we also investigated mild, one-electron-reducing reagents, in particular the lanthanide series of reducing reagents.[30] These reagents, such as samarium(II) iodide, have a high degree of chemoselectivity, with reductions occurring at ketones over ester functionalities.[31−33]

The advantages in utilizing lanthanide-mediated reductions resides in their chemoselectivity and their utility in the reaction of sterically crowded carbonyls,[32] which was necessary in the reduction of the taxanes. The divalent lanthanide, SmI_2, smoothly effects α-deoxygenations of α-acetoxy ketones.[31−33] Utilizing this chemistry, we have reported the synthesis of 10-deacetoxybaccatin III (**4**, Scheme 1) and 10-deacetoxypaclitaxel (**9**, Scheme 2) in 95% and 90% yield, respectively.[34] Similar results were reported by other groups.[35−37] Earlier, we reported also on the importance of the proton source in avoiding

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Lewis acid-mediated retro-aldol chemistry at the C7 position.[34] The retro-aldol chemistry is catalyzed by the trivalent lanthanide byproduct of the reduction.[34] Mechanistically, the α-deoxygenation must proceed via ketyl formation, further reduction to the carbanion, and subsequent enolate formation with the acetoxy moiety as the formal leaving group.[32] This suggested that since the ketone underwent the first step of the reaction that ketone reduction could be accomplished in the absence of a good leaving group α to the C9 ketone. Initially, we believed the ketone would be more difficult to reduce, and to accomplish the reduction we employed ytterbium metal, which has precedence in reducing ketones where samarium(II) was unsuccessful.[38] Thus, we utilized activated ytterbium(0) in the presence of H_2O as the proton source to effect the reduction of 10-deacetoxybaccatin III (**4**). This chemistry proved unsuccessful. However, when **4** was subjected to treatment with SmI_2, the C9 keto group was reduced to provide the 9β-hydroxy product **5** in 90% yield. Baccatin III (**2**) and paclitaxel (**1**) were also exposed to these reaction conditions (using 6.0 equiv of SmI_2) and, subsequently, afforded the 10-deoxygenated, C9-reduced products **5** (88% yield) and **11** (83% yield), respectively (Schemes 1 and 2).

It was then further rationalized that a decrease in the leaving group ability of the α-substituent (replacement of the acetoxy group with a hydroxy group) on the taxane may result in ketone reduction alone, if protonation of the samarium ketyl (or the carbanion) was faster than enolization, which induces the β-elimination. To this end, reaction of 10-deacetylbaccatin III (**3**) in the presence of 6.0 equiv of freshly prepared SmI_2 with water as the proton source[39] resulted in the formation of 10-deacetoxy-9-dihydrobaccatin III (**5**) and 10-deacetyl-9-dihydrobaccatin III (**6**) in 45% and 36% yield, respectively (Scheme 1). When the same reaction conditions were applied to 10-deacetylpaclitaxel (**8**), 32% of 9-hydroxypaclitaxel **11**, and 28% of 9,10-dihydroxypaclitaxel **13** were obtained. Reaction of docetaxel (**7**, Scheme 2) provided 9-hydroxydocetaxel **12** and 9,10-dihydroxydocetaxel **14** in 50% and 40% yield, respectively (2.5 equiv of SmI_2).

When we further investigated the reaction between 10-deacetylbaccatin III (**3**) and SmI_2, we noted that varying ratios of the products were obtained in this reaction for **5** and **6**, ranging from 1.3:1 to 3:7, depending on the exact reaction conditions. We also noted that the use of acetic acid as the proton source instead of water gave a higher yield and a cleaner reaction. To capitalize on these observations and to favor the ketone reduction pathway, the reaction temperature was lowered from room temperature to −5 to −10 °C. Addition of the THF solution of starting diterpene **3** and acetic acid to a cold solution of SmI_2 (6.0 equiv) resulted in the formation of 10-deacetyl-9-dihydrobaccatin III (**6**) in 85% and 10-deacetoxy-9-dihydrobaccatin III (**5**) in 10% yield (Scheme 1.) This chemistry was then successfully applied to 10-deacetylpaclitaxel (**8**) to afford 10-deacetyl-9-dihydropaclitaxel (**13**) in 83% yield.

The stereochemistry of the hydroxyl groups at C9 of the 9-hydroxy derivatives was determined through NOE studies. Irradiation of the protons at C9 showed an NOE to the protons at C3. Therefore, the stereochemistry of the C9 hydroxyl groups was assigned as 9β.

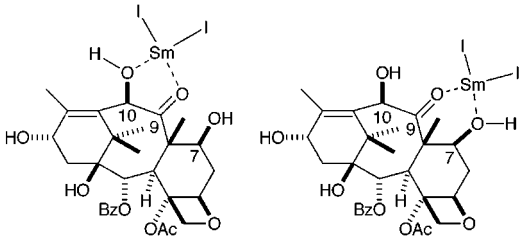
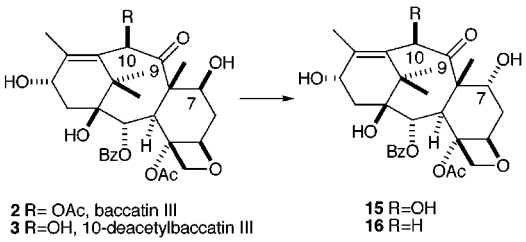


Figure 2. Possible coordination sites for chelation-controlled reductions.

Scheme 3



2 R= OAc, baccatin III
3 R=OH, 10-deacetylbaccatin III

15 R=OH
16 R=H

Since the SmI_2-mediated reductions produced solely 9β-hydroxy diterpenes, we postulated that coordination of the lanthanide at either of the two flanking hydroxyl groups would result in a coordinated transition state, placing the metal on the β-face of the molecule (Figure 2), thus favoring the delivery of the proton from the α-face of the molecule.

Although a coordinated transition state from the α-face is possible, this seems highly improbable from the standpoint of the molecule's conformation. The diterpene, being cup or "cage-like", has a sterically shielded underside or α-face. This suggests that the approach of the quite large lanthanide from this face would be improbable.

To investigate further the nature of the stereoselectivity of the reaction, we addressed the following. Coordination could be occurring through either the C7 hydroxyl or the C10 hydroxyl at the β-face resulting in the one-electron delivery to the C9 carbonyl (Figure 2). To aid in the mechanistic understanding of the reaction, we investigated the reduction of a 7-epitaxane. Capitalizing on the facile conversion of **3** to **15** (Scheme 3) via retro-aldol chemistry,[28,29] we subjected 10-deacetylbaccatin III (**3**) to 1.5 equiv of LiHMDS at −78 ° C for 0.5 h resulting in the formation **15** in 50% yield. 10-Deacetyl-7-epibaccatin III (**15**) was then subjected to 6.0 equiv of SmI_2 at room temperature for 0.5 h. This resulted in the formation of 10-deacetoxy-7-epibaccatin III (**16**) as the sole product. This implies that coordination at the β-C7 hydroxyl group is crucial for reduction to occur at the C9 carbonyl. Deoxygenation at C10 still occurs because a C10 hydroxyl/C9 keto five-membered coordination can exist to aid in the α-deoxygenation. After deoxygenation, the ability of the samarium reagent to coordinate between the C7 hydroxyl (now on the α-face) and the 9-ketone no longer exists, and the ketone remains untouched. To confirm this finding, the product **16** was placed back into a freshly prepared SmI_2 solution (6.0 equiv) resulting in complete recovery of starting material. No ketone reduction products were observed.

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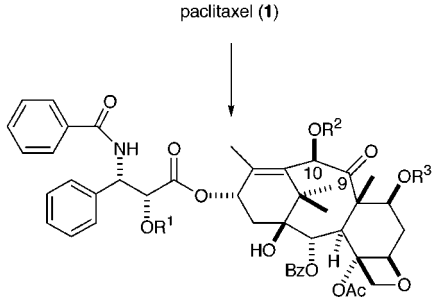
In the context of this discussion on the chelation-controlled deoxygenation and reduction chemistry, it is of interest to note that we[34] and others[35−37] have found that baccatin III, when protected as the 7-triethylsilyl ether, does not undergo samarium diiodide-mediated α-deoxygenation of the C10 acetoxy group. However, Py et al.[36,37] demonstrated that deoxygenation takes place when the 7-hydroxyl group carries an acetyl moiety or a Troc protecting group. It appears that the sterically demanding 7-triethylsilyl group interferes with the coordination of the samarium ion to the C9 keto group and the 10-acetoxy group, thus preventing α-deoxygenation. Smaller groups such as 7-acetyl and 7-Troc as well as the 7-epi hydroxy moiety apparently do not interfere with chelation. As a result α-deoxygenation of the C10 acetoxy group can take place.

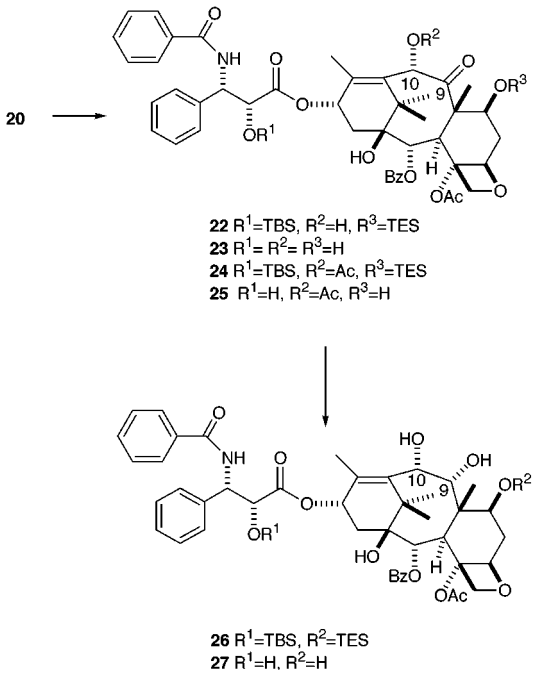
As mentioned before, the C9 carbonyl group is highly unreactive toward hydride reductions due to its sterically crowded environment. However, the delivery of a hydride to the C9 carbonyl group is desirable since it is expected to provide reaction products with the C9 α-stereochemistry, due to the cup shape of the molecule. It would nicely complement the samarium diiodide reduction method, which exclusively yields the C9 *β*-stereochemistry. Klein and collaborators have reported on the semisynthesis of 9α-hydroxypaclitaxel and related analogues from naturally occurring 13-acetyl-9α-hydroxybaccatin III.[40] To achieve our goal to develop a chemical method to prepare and to evaluate 9α-hydroxytaxanes, we decided to use the C10 hydroxy (acetoxy) group of taxanes toward activation of the C9 carbonyl. We rationalized that oxidation of the C10 hydroxy group to a ketone group would not only reduce the steric congestion around the C9 carbonyl group but would also enhance its reactivity toward nucleophilic attack of the reducing agent.[24] Thus, we prepared 10-oxopaclitaxel (**21**). The isolation of a similar taxane, 10-oxo-7-epipaclitaxel, from the bark of *Taxus brevifolia* has been reported.[41] The synthetic approach to this molecule began with the regioselective silylation of paclitaxel (**1**, Scheme 4). Selective silylation at the more reactive 2′-hydroxyl in the presence of TBSCl and imidazole resulted in the formation of **17** in 93% yield, which can be deacylated regioselectively at the C10 position utilizing hydrazine hydrate to form **18** in 82% yield.[42] This approach was quite nice as deacylation at C10 could be effected without protection at the 7-hydroxyl moiety, a position prone to racemization due to retro-aldol chemistry. No epimerization occurs under these conditions. Subsequent silylation at the C7 hydroxyl resulted in the formation of the protected taxane **19** in 90% yield.[42] Alternatively, taxane **19** was obtained from 10-deacetylpaclitaxel in a one-flask procedure by sequential double silylation. Treatment with TBSCl provided selective silylation at the 2′-hydroxyl group of the C13 side chain and was followed by selective silylation of the C7 hydroxyl group with TESCl. Oxidation of the C10 hydroxyl group with *N*-methylmorpholine *N*-oxide and a catalytic quantity of $(n\text{-Pr})_4NRuO_4$[43] resulted in the formation of the protected diketone **20** in 79% yield. The removal of the protecting groups at the 2′- and 7-hydroxyls was effected by pyridinium HF to afford the free diketone **21** in 74% yield.

Stereoselective reduction of **20** with $NaBH_4$ (5.0 molar equiv) resulted, after 45 min, in the formation of the 10α-hydroxy taxane **22** in 65% yield, due to hydride delivery from the more accessible *β*-face (Scheme 5). The inversion of stereochemistry at C10 relative to paclitaxel was

Scheme 4



Scheme 5



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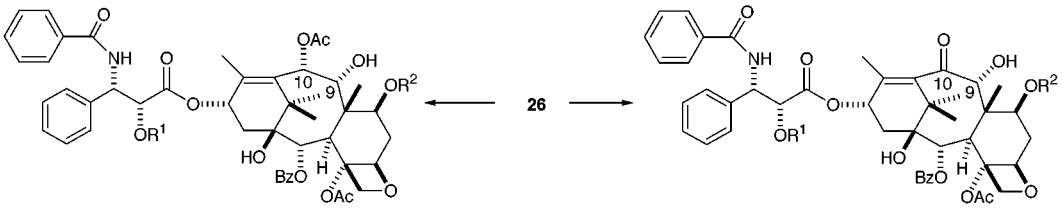
Scheme 6



confirmed by an NOE difference experiment. Irradiation of the signal from the 16 methyl strongly enhanced H13, but gave almost no enhancement of H10. Irradiation of the 17 methyl signal strongly enhanced H2 and H10; in paclitaxel, there is basically no enhancement of H10 from H17. This demonstrates that H10 is now in the α-face of the molecule, on the same side of the molecule as H2 but on the opposite side from H13.

When excess reducing agent was used and after longer reaction times, a more polar minor reduction product was formed, which was identified as the doubly reduced analogue, 9α,10α-dihydroxy taxane **26**. The yield of **26** could be improved by first isolating 10α-hydroxy taxane **22** and then subjecting **22** to reduction with $NaBH_4$ (5 molar equiv) for 3 h to provide **26** in 71% yield (Scheme 5). The cis relationship between the hydroxy groups at C9 and C10 was confirmed by their large NOE and the coupling constant between H9 and H10 ($J_{H9,H10} = 3.7$ Hz). The ease of reduction of the C9 carbonyl under these conditions can be traced to the inversion of stereochemistry at C10. The C10 group is now located in the α-face of the molecule, reducing the steric congestion on the *β*-face. This allows the attack of the reducing agent on the C9 carbonyl from the *β*-face to provide the reaction product with the C9 α-hydroxyl stereochemistry. Fluoride-mediated deprotection of the C7 and C2′ hydroxyls of both **22** and **26** was accomplished in the presence of pyridinium hydrogen fluoride in pyridine to afford **23** and **27** in 70 and 71% yield, respectively (Scheme 5).

10α-Hydroxy taxane **22** was also subjected to acylation conditions (Scheme 5). Acylation in the presence of acetic anhydride and DMAP afforded 10-acetyltaxane **24** in 83% yield. Deprotection of the acylated taxane with pyridinium HF afforded 10-epipaclitaxel (**25**) in 79% yield. It is worth noting that our attempts to prepare 10-epipaclitaxel (**25**) through Mitsunobu chemistry were not successful.

Taxane **26** was utilized in the formation of 9-dihydro-10-epipaclitaxel (**29**) (Scheme 6). Regioselective acylation of 9α,10α-dihydroxytaxane **26** in the presence of Ac_2O and DMAP resulted in the formation of 10-acetyltaxane **28** in 80%. The selectivity in the reaction could be due to the presence of the 7-*O*-triethylsilyl group, which may be responsible for sterically shielding the 9-hydroxyl preventing its acylation. Subsequent fluoride-mediated deprotection afforded the final taxane **29** in 77% yield.

The 9α,10α-dihydroxy taxane **26** was also subjected to the mild oxidation conditions with $(n\text{-Pr})_4NRuO_4$ and NMO resulting selectively in allylic oxidation producing the 9α-hydroxy-10-oxotaxane **30** in 81% yield (Scheme 6). Removal of the silyl protecting groups with pyridinium HF in pyridine afforded **31** in 78% yield.

The biological evaluation of the paclitaxel analogues for their ability to promote the formation of microtubules and for their cytotoxicity against B16 melanoma cells has been published.[24,25] The results of these studies were in agreement with earlier observations that structural modifications at the northern part of the paclitaxel molecule do not significantly alter its bioactivity.[19]

Experimental Procedures

General. The 1D NOE difference experiments were performed at 25 °C on a 500 MHz instrument. The sample concentration was approximately 5 mg/mL in $CDCl_3$. In the experiment, a 1-s delay was followed by irradiation of the peak of interest (16- or 17-methyl) for 2 s, a 90° observe pulse, and a 2.7 s acquisition delay. The samples were not degassed prior to use, nor were the T_1s of the peaks measured to verify that the NOE had reached steady state after 2 s. Consequently, percentage enhancements were not meaningful and are not reported; however, nearby protons were judged to be those with a >10% enhancement in the difference spectrum, and distant protons to be those with <2% enhancement. SmI_2 was either freshly prepared from samarium metal and 1,2-diiodoethane using the procedure described by Kagan[44] or a 0.1 M solution of SmI_2 in THF (Aldrich) was used. Paclitaxel (**1**), 10-deacetylpaclitaxel (**8**), baccatin III (**2**), and 10-deacetylbaccatin III (**3**) are commercially available. 10-Deacetoxybaccatin III (**4**) was prepared as described before.[34]

10-Deacetoxy-9*β*-hydroxybaccatin III (5). To a stirred solution of 10-deacetoxybaccatin III (**4**, 29 mg, 0.055 mmol) in THF (0.5 mL) was added H_2O (1.34 mL) followed by the addition of the SmI_2 solution (1.34 mL, 0.1 M solution in THF) at room temperature. After stirring at room temperature for 3 h, the reaction mixture was treated with a saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water and dried (Na_2SO_4). Purification by silica gel flash column chromatography (EtOAc/hexane 1:1 to 3:2) gave 10-deacetoxy-9*β*-hydroxybaccatin III (**5**, 26.1 mg, 90%): mp 142−144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.51 (s, 3H), 1.64 (s, 3H), 1.84−2.34 (m, 1H), 1.90 (s, 3H), 2.07 (m, 1H), 2.22 (m, 1H), 2.22−2.24 (m, 1H), 2.33 (s, 3H), 2.44 (dd, $J = 3.6$, 11 Hz, 2H), 2.92 (d, $J = 9.7$ Hz, 1H), 3.03 (d, $J = 4.6$ Hz, 1H), 3.71 (dd, $J = 5.6$, 10.6 Hz, 1H), 4.35 (q, $J = 8.6$ Hz, 1H), 4.41 (q, $J = 8.6$ Hz, 1H), 4.59 (s, 1H), 4.73 (s, 1H), 5.08 (s, 1H), 5.91 (d, $J = 4$, 7 Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 2H), 7.61 (t, 7.4 1H), 8.13 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 166.8, 137.3, 133.6, 133.3, 130.1, 129.4, 128.6, 88.7, 83.1, 78.4, 75.8, 72.9, 71.0, 68.6, 50.2, 43.6, 43.3, 40.2, 34.9, 29.4, 25.8, 23.3, 22.6, 15.8, 14.8; FAB HRMS *m/z* calcd for $C_{19}H_{39}O_9$ (M + 1) 531.2595, found 531.2606; $[\alpha]^{20}_D$ +16° (*c* = 0.21, $CHCl_3$).

10-Deacetyl-9*β*-hydroxybaccatin III (6). To a stirred solution of 10-deacetylbaccatin III (**3**, 20 mg, 0.037 mmol) in THF (2.0 mL) under an argon atmosphere was added acetic acid (0.020 mL), and the reaction was cooled to −5 to −10 °C and stirred for 10 min at this temperature. To the cooled solution, SmI_2 (2.9 mL, 8 equiv, 0.1 M solution in THF) was added dropwise in 5 min. The reaction was stirred at −10 °C for 2 h and then brought to 0 °C. The reaction mixture was treated with a saturated $NaHCO_3$ solution and extracted with

(44) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.

EtOAc. The organic layer was washed with water and dried (Na_2SO_4). Purification by silica gel flash column chromatography (EtOAc/hexane 3:2) gave 10-deacetoxy-9β-hydroxybaccatin III (**5**, 2 mg, 10%) and 10-deacetyl-9β-hydroxy baccatin III (**6**, 17 mg, 85%): mp 120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.56 (s, 3H), 1.69 (s, 3H), 1.93 (s, 3H), 2.00 (m, 1H), 2.24 (m, 1H), 2.46 (m, 1H), 2.58 (m, 1H), 2.31 (s, 3H), 3.14 (d, J = 4.8 Hz, 1H), 4.17 (s, 1H), 4.18 (dd, J = 8.2, 16 Hz, 1H), 4.24 (d, J = 8.4 Hz, 1H), 4.27 (m, 1H), 4.35 (d, J = 8.4 Hz, 1H), 4.97 (d, J = 5.6 Hz, 1H), 5.25 (d, J = 4.3 Hz, 1H), 6.16 (d, J = 4.5 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 8.11 (d, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 167.1, 139.1, 137.8, 133.5, 130.1, 129.6, 128.6, 86.0, 83.1, 78.8, 77.5, 74.5, 74.3, 71.7, 71.4, 68.9, 47.7, 44.4, 43.1, 39.3, 34.9, 28.6, 23.2, 22.7, 15.4, 13.9; FAB HRMS *m/z* calcd for $C_{29}H_{39}O_{10}$ (M + 1) 547.2543, found 547.2561; $[\alpha]^{20}_D$ +8.8° (c = 0.40, $CHCl_3$).

10-Deacetoxy-9β-hydroxypaclitaxel (11). To a stirred solution of paclitaxel (**1**, 20 mg, 0.023 mmol) in THF (0.5 mL) was added H_2O (0.015 mL) followed by the addition of the SmI_2 solution (0.58 mL, 0.1 M solution in THF) at room temperature. After stirring at room temperature for 3 h, the reaction mixture was treated with a saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water and dried (Na_2SO_4). Purification by silica gel flash column chromatography (EtOAc/hexane 1:1 to 3:2) gave 10-deacetoxy-9β-paclitaxel (**11**, 15.4 mg, 83%). mp 146−148 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.41 (s, 3H), 1.48 (s, 3H), 1.94 (m, 1H), 2.05 (m, 1H), 2.22 (m, 1H), 2.30 (s, 3H), 2.41 (dd, J = 11.2 and 14.9 Hz, 1H), 2.82 (d, J = 4.3 Hz, 1H), 2.87 (br s, 1H), 3.59 (dd, J = 5.5 and 10.0 Hz, 1H), 3.71 (d, J = 3.7 and 10.8 Hz, 1H), 4.33 (d, J = 8.6 Hz, 1H), 4.40 (d, J = 8.6 Hz, 1H), 4.56 (br s, 1H), 4.70 (m, 1H), 4.74 (br s, 1H), 4.85 (br s, 1H), 5.14 (br s, 1H), 5.86 (d, J = 9.1 Hz, 1H), 5.94 (d, J = 4.5 Hz, 1H), 6.0 (br t, J = 7.2 Hz, 1H), 7.29−7.53 (m, 10H), 7.83 (d, J = 7.5 Hz, 2H), 8.09 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 170.9, 166.7, 138.7, 135.1, 133.9, 133.7, 132.6, 131.8, 130.1, 129.2, 128.7, 128.6, 128.5, 127.9, 127.2, 127, 88.1, 83.0, 78.1, 77.6, 75.4, 74.3, 73.0, 71.6, 70.8, 54.4, 50.4, 43.7, 36.4, 34.6, 31.9, 29.7, 29.6, 29.3, 29.2, 26.1, 22.8, 22.4, 15.8, 14.8; FAB HRMS *m/z* calcd for $C_{45}H_{52}NO_{12}$ (M + 1) 798.3490, found 798.3483; 799 (M + 1), 781, 513, 495, 286, 185, 93; $[\alpha]^{20}_D$ −13° (c = 0.50, $CHCl_3$).

10-Deacetyl-9β-hydroxypaclitaxel (13). To a solution of SmI_2 (18 mg, 0.12 mmol) and 1,2-diiodoethane (25 mg, 0.089 mmol) in THF (1 mL) at −5 °C was added dropwise a THF solution (1 mL) of 10-deacetylpaclitaxel (**8**, 12 mg, 0.015 mmol) and glacial acetic acid (0.05 mL). After stirring for 1 h at −5 °C, the reaction was quenched with a saturated solution of $NaHCO_3$. After extraction with EtOAc, the organic layer was dried with Na_2SO_4. Silica gel flash column chromatography (EtOAc/hexane 1:1 to 3:2) provided 10 mg (83%) of 10-deacetyl-9β-hydroxypaclitaxel (**13**) as colorless solid: mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.39 (s, 3H), 1.64 (s, 3H), 1.74 (s, 3H), 1.94 (m, 1H), 2.18 (m, 1H), 2.28 (s, 3H), 2.40 (m, 1H), 2.97 (d, J = 4.4 Hz, 1H), 3.14 (br, 1H), 4.12 (br m, 1H), 4.24 (d, J = 8.6 Hz, 1H), 4.38 (d, J = 8.3 Hz, 1H), 4.83 (br s, 1H), 4.9 (br s, 1H), 5.01 (d, J = 4.9 Hz, 1H), 5.12 (d, J = 5 Hz, 1H), 8.88 (dd, J = 2.0 and 9 Hz, 1H), 6.11 (t, J = 6.8 Hz, 1H), 6.19 (d, J = 4.8 Hz, 1H), 7.29−8.1 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 170.9, 167.0, 166.0, 139.7, 138.6, 133.9, 133.8, 133.6, 131.8, 130.0, 129.3, 128.7, 128.6, 128.0, 127.3, 127.0, 85.5, 83.4, 78.6, 74.5, 74.2, 74.1, 71.9, 71.3, 71.2, 54.3, 47.9, 44.7, 43.3, 35.5, 34.7, 30.9, 28.7, 23.1, 22.8, 15.3, 14.2; FAB HRMS *m/z* calcd for $C_{45}H_{52}NO_{13}$ (M + 1) 814.3439, found 814.3420; 814 (M + 1), 705, 643, 521, 491, 307, 217; $[\alpha]^{20}_D$ +5.20° (c = 0.174, $CHCl_3$).

10-Deacetoxy-9β-hydroxydocetaxel (12) and 9β-Hydroxydocetaxel (14).[45] To a stirred solution of docetaxel (**7**, 20 mg, 0.025 mmol) in THF (0.5 mL) was added H_2O (0.015 mL) followed by the addition of the SmI_2 solution (0.58 mL, 0.1 M solution in THF) at room temperature. After stirring at room temperature for 3 h, the reaction mixture was treated with a saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water and dried (Na_2SO_4). Purification by silica gel flash column chromatography (EtOAc/hexane 1:1 to 3:2) gave 10-deacetoxy-9β-hydroxydocetaxel (**12**, 9.13 mg, 50%) and 9β-hydroxydocetaxel (**14**, 7.5 mg, 40%) as colorless solids. Compound **12**: mp 137−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.39 (s, 3H), 1.47 (s, 3H), 1.49 (s, 3H), 1.58 (s, 3H), 2.0−2.5 (m, 2H), 2.25 (s, 3H), 2.3 (m, 2H), 2.45 (dd, J = 11, 15 Hz, 1H), 2.86 (d, 4.2H), 2.93 (m, 1H), 3.66 (m, 1H), 4.40 (d, J = 8.6 Hz, 1H), 4.33 (d, J = 8.6 Hz, 1H), 4.59 (s, 1H), 4.95 (s, 1H), 5.12 (s, 1H), 5.3 (d, 9.3 1H), 5.7 (d, J = 10 Hz, 1H), 6.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 170.9, 155.0, 139.2, 135.0, 133.7, 133.0, 130.1, 129.2, 128.7, 128.5, 127.7, 127.0, 88.2, 82.9, 79.8, 78.2, 77.6, 75.5, 74.6, 73.0, 71.6, 70.8, 55.9, 50.4, 43.8, 43.6, 36.4, 34.7, 29.3, 28.4, 26.1, 22.8, 22.7, 14.8, 14.1; FAB HRMS *m/z* calcd for $C_{43}H_{55}NO_{13}$ 793.3673, found 793.3621; $[\alpha]^{20}_D$ −4.3° (c = 0.46, $CHCl_3$). Compound **14**: mp 155−157 °C; ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.25 (s, 3H), 1.40 (s, 9H), 1.59 (s, 3H), 1.66 (s, 3H), 1.76 (s, 3H), 1.9 (m, 1H), 2.05 (m, 1H), 2.25 (s, 3H), 2.39 (m, 1H), 2.45 (m, 1H), 3.12 (s, 1H), 4.12 (m, 1H), 4.20 (m, 1H), 4.24 (d, J = 8.3 Hz, 1H), 4.35 (d, J = 8.3 Hz, 1H), 4.64 (d, J = 11 Hz, 1H), 4.99 (d, J = 5.8 Hz, 1H), 5.23 (s, 1H), 5.31 (d, J = 9 Hz, 1H), 6.10 (s, 1H), 6.21 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.0, 167.0, 155.0, 139.5, 139.0, 134.4, 133.6, 130.1, 129.4, 128.6, 128.5, 127.7, 127.0, 85.5, 83.2, 79.9, 78.7, 77.5, 75.0, 74.9, 74.6, 74.2, 72.0, 71.3, 55.9, 47.8, 44.7, 43.3, 35.6, 34.8, 28.8, 28.4, 23.2, 22.7, 15.4, 14.2; FAB HRMS *m/z* calcd for $C_{43}H_{56}NO_{14}$ (M + 1) 810.3701, found 810.3699; $[\alpha]^{20}_D$ −14° (c = 0.37, $CHCl_3$).

10-Deacetyl-7-epibaccatin III (15). To a −78 °C solution of 10-deacetylbaccatin III (**3**, 100 mg, 0.184 mmol) in THF (2 mL) was added LiHMDS (0.20 mL, 1.10 equiv). The reaction mixture was stirred at that temperature for 30 min and then warmed to 0 °C for another 30 min. The reaction was quenched at 0 °C with brine and extracted with ethyl ether. The organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The resulting residue was subjected to silica gel chromatography on the Chromatotron (EtOAc/hexane 3:2) to provide **15** (47 mg, 45%) as a colorless solid. Starting material was also recovered (45 mg, 43%). Stored in a freezer, **15** is stable but partial epimerization to 10-deacetylbaccatin III is observed at room temperature: mp 165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.62 (s, 1H), 1.69 (s, 3H), 1.98 (s, 3H), 2.29−2.34 (m, 2H), 2.33−2.39 (m, 2H), 2.37 (s, 3H), 3.65 (dd, J = 3 and 12, 1H), 4.04 (d, J = 7, 1H), 4.11 (s, 1H), 4.40 (AB, 2H), 4.84 (t, J = 8, 1H), 4.87 (d, J = 12, 1H), 4.94 (dd, J = 4 and 9, 1H), 5.48 (s, 1H), 5.70 (d, J = 7, 1H), 7.50 (t, J = 9, 2H), 7.62 (t, J = 9, 1H), 8.12 (dd, J = 2 and 9, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 172.6, 167.1, 141.8, 134.6, 133.7, 130.1, 129.1, 128.7, 82.6, 81.8, 79.2, 78.5, 77.8, 75.7, 75.4, 67.8, 57.4, 42.1, 40.6, 38.7, 35.4, 26.5, 22.5, 19.6, 16.7, 15.4; FAB MS *m/z* calcd for $C_{29}H_{37}O_{10}$ (M + 1) 545, found 545; $[\alpha]^{20}_D$ −22° (c = 0.40, MeOH).

2′-TBS-10-deacetyl-7-TES-10-ketopaclitaxel (20). To a solution of 2′-TBS-10-deacetyl-7-TES-paclitaxel (**19**, 200 mg, 0.192 mmol) and NMO (33 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature, TPAP (10 mg, 0.028 mmol) was added and the mixture stirred for 2 h, after which another portion of TPAP (10 mg, 0.028 mmol) was added to the mixture and stirring continued for 2 h. The solution was then filtered, and the residue was washed with CH_2Cl_2 (10 mL). The combined filtrates were concentrated and purified by flash column chromatography (silica gel, EtOAc/hexane = 3:7) affording the product as a colorless solid. Yield, 156 mg (78%): mp 129−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.27 (s, 3H), −0.02 (s, 3H), 0.61 (q, J = 7.8 Hz, 6H), 0.81 and 0.82 (2s, 9H), 0.97 (t, J = 7.8 Hz, 9H), 1.22 (s, 3H), 1.24 (s, 3H), 1.73 (s, 3H), 1.94 (s, 3H), 2.05−2.52 (m, 3H), 2.59 (s, 3H), 3.68 (d, J = 6.7 Hz, 1H), 4.22 (m, 2H), 4.36 (d, J = 8.4 Hz, 1H), 4.69 (d, J = 2.0 Hz, 1H), 4.92 (d, J = 9.4 Hz, 1H), 5.77 (br d, J = 8.8 Hz, 1H), 5.83 (d, J = 6.8 Hz, 1H), 6.27 (t, J = 8.7 Hz,

(45) The synthesis of 9β-hydroxydocetaxel (**14**) from docetaxel (**7**) through electrochemical reduction has been described: Pulicani, J.-P.; Bourzat, J.-D.; Bouchard, H.; Commerçon, A. *Tetrahedron Lett.* **1994**, *35*, 4999−5002.

1H), 7.09 (d, J = 9.4 Hz, 1H), 7.32−7.64 (m, 11H), 7.75 (d, J = 7.8 Hz, 2H), 8.16 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.3, 5.2, 6.4, 6.8, 8.8, 18.1, 22.9, 23.8, 25.4, 26.8, 35.5, 37.1, 40.9, 45.6, 55.6, 58.1, 69.7, 71.1, 74.7, 75.1, 76.3, 79.2, 80.7, 84.2, 126.3, 126.4, 126.9, 128.0, 128.7, 128.8, 129.0, 130.2, 131.8, 133.7, 133.9, 138.1, 142.2, 144.5, 166.9, 167.0, 170.1, 171.1, 194.1, 204.4; IR (neat) 3425, 1740, 1725, 1700, 1660 cm^{-1}; FAB HRMS m/z calcd for $C_{57}H_{75}NO_{13}Si_2$ 1038.4855 (M + 1), found 1038.4859; $[\alpha]^{20}_D$ −73° (c = 0.24, CH_2Cl_2).

10-Deacetyl-10-ketopaclitaxel (21). To an ice-cooled solution of 2′-TBS-10-deacetyl-7-TES-10-ketopaclitaxel (**20**, 50 mg, 0.048 mmol) in anhydrous pyridine (3 mL) was added HF·Py (10 drops), was added and the mixture was stirred at room temperature for 3.5 h. After diluting with EtOAc (50 mL), the solution was washed sequentially with a saturated $NaHCO_3$ solution, water, and brine. Drying (Na_2SO_4), removal of the solvent, and flash column chromatography (silica gel, EtOAc/hexane = 3:2 to 3:1) afforded the pure product as a colorless solid, 28.5 mg (74%): mp 181−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.29 (s, 3H), 1.76 (s, 3H), 1.81 (m, 1H), 1.89 (s, 3H), 2.40 (m, 1H), 2.41 (s, 3H), 2.57 (m, 1H), 3.64 (d, J = 6.8 Hz, 1H), 3.69 (d, J = 5.4 Hz, 1H, exch. with D_2O), 4.04 (m, 1H), 4.22 and 4.35 (2d, J = 8.6 Hz, 2H), 4.84 (dd, J = 2.5 and 5.2 Hz, 1H), 4.92 (d, J = 7.9 Hz, 1H), 5.79 (dd, J = 2.2 and 8.7 Hz, 1H), 5.84 (d, J = 6.8 Hz, 1H), 6.24 (t, J = 8.8 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 7.38−7.69 (m, 11H), 7.75 (d, J = 7.1 Hz, 2H), 8.17 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 14.1, 22.5, 23.8, 26.9, 35.5, 35.6, 40.8, 45.3, 55.1, 58.3, 68.7, 72.0, 73.0, 74.5, 76.1, 79.1, 80.6, 84.1, 127.0, 128.4, 128.7, 128.8, 128.9, 129.0, 130.2, 132.0, 133.5, 133.9, 137.8, 141.7, 146.6, 166.8, 167.2, 170.3, 172.6, 193.9, 206.1; IR (neat) 3420, 1725, 1710, 1695, 1645 cm^{-1}; FAB HRMS m/z calcd for $C_{45}H_{47}NO_{13}$ 810.3126 (M + 1), found 810.3115; $[\alpha]^{20}_D$ −66° (c = 1.1, $CHCl_3$).

2′-TBS-10-deacetyl-7-TES-10α-hydroxypaclitaxel (22). A solution of 2′-TBS-10-deacetyl-7-TES-10-ketopaclitaxel (**20**, 80 mg, 0.077 mmol) in ethanol (95%, 8 mL) was treated with $NaBH_4$ (15 mg, 0.385 mmol), and the mixture was stirred at room temperature for 45 min. The solution was diluted with EtOAc (50 mL), washed with water and brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography (silica gel, EtOAc/hexane = 1:2), yielding the product as a colorless solid, 52 mg (65%); starting material recovered = 9 mg (11%): mp 158−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.28 (s, 3H), 0.02 (s, 3H), 0.64 (m, 6H), 0.82 (s, 9H), 0.99 (t, J = 7.8 Hz, 9H), 1.11 (s, 3H), 1.25 (s, 3H), 1.69 (s, 3H), 2.0 (m, 2H), 2.14 (s, 3H), 2.51 (m, 1H), 2.61 (s, 3H), 2.66 (d, J = 4.3 Hz, 1H, exch. with D_2O), 4.25 (d, J = 8.3 Hz, 1H), 4.30 (d, J = 6.8 Hz, 1H), 4.35 (d, J = 8.3 Hz, 1H), 4.68 (d, J = 1.9 Hz, 1H), 4.89 (dd, J = 6.5 and 11.0 Hz, 1H), 5.03 (br d, J = 7.8 Hz, 1H), 5.16 (d, J = 2.5 Hz, 1H), 5.69 (d, J = 6.8 Hz, 1H), 5.76 (br d, J = 8.8 Hz, 1H), 6.27 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.32−7.64 (m, 11H), 7.77 (d, J = 7.1 Hz, 2H), 8.16 (d, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz) $CDCl_3$ δ 5.2, 5.3, 5.9, 6.8, 6.9, 11.2, 12.9, 18.1, 23.1, 25.5, 26.4, 35.8, 36.9, 42.6, 45.7, 53.6, 55.7, 60.1, 71.8, 72.3, 75.1, 75.3, 76.8, 78.7, 81.1, 82.6, 84.2, 126.4, 127.0, 127.8, 128.6, 128.7, 128.8, 129.2, 130.2, 131.7, 132.2, 132.8, 133.6, 134.1, 138.4, 167.0, 169.8, 169.9, 171.4, 206.2; IR (neat) 3430, 1725, 1660 cm^{-1}; FAB HRMS m/z calcd for $C_{57}H_{77}NO_{13}Si_2$ (M + 1) 1040.5012, found 1040.5028; $[\alpha]^{20}_D$ −66° (c = 0.47, CH_2Cl_2).

10-Deacetyl-10α-hydroxypaclitaxel (23). To an ice-cooled solution of 2′-TBS-10-deacetyl-7-TES-10α-hydroxypaclitaxel (**22**, 55 mg, 0.053 mmol) in anhydrous pyridine (3 mL), HF·Py (10 drops) was added, and the mixture was stirred at room temperature for 3.5 h. After diluting with EtOAc (50 mL), the solution was washed sequentially with saturated $NaHCO_3$ solution, water, and brine. Drying (Na_2SO_4), removal of the solvent, and flash column chromatography (silica gel, EtOAc/hexane = 3:2 to 3:1) afforded the pure product as a colorless solid, 30 mg (70%): mp 188−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.67 (s, 3H), 1.86 (m, 1H), 1.91 (s, 3H), 2.29 (m, 2H), 2.39 (s, 3H), 2.49 (m, 1H), 2.81 (br s, 1H, exchangeable with D_2O), 4.01 (d, J = 4.7 Hz, 1H, exchangeable with D_2O), 4.14 (d, J = 6.8 Hz, 1H), 4.21 (br d, J = 7.8 Hz, 2H), 4.32 (d, J = 8.3 Hz, 1H), 4.67 (m, 1H), 4.81 (br s, 1H), 5.01 (d, J = 7.7 Hz, 1H), 5.11 (br s, 1H), 5.71 (d, J = 6.8 Hz, 1H), 5.82 (br d, J = 7.1 Hz, 1H), 6.14 (t, J = 8.6 Hz, 1H), 7.28 (d, J = 9.3 Hz, 1H), 7.35−7.66 (m, 11H), 7.78 (d, J = 7.3 Hz, 2H), 8.14 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 13.1, 22.6, 26.3, 35.3, 35.8, 42.6, 45.4, 54.8, 59.9, 70.6, 72.5, 73.3, 75.0, 78.4, 80.7, 81.3, 84.7, 127.0, 127.1, 128.2, 128.6, 128.7, 128.9, 129.1, 130.1, 131.9, 132.8, 133.3, 133.7, 138.1, 166.8, 167.1, 170.2, 172.5, 208.3; IR (neat) 3420, 1715, 1640 cm^{-1}; FAB HRMS m/z calcd for $C_{45}H_{49}NO_{13}$ (M + 1) 812.3282, found 812.3299; $[\alpha]^{20}_D$ −56° (c = 0.85, $CHCl_3$).

2′-TBS-10-epi-7-TES-paclitaxel (24). To an ice-cooled solution of 2′-TBS-7-TES-10α-hydroxypaclitaxel (**22**, 65 mg, 0.063 mmol) and DMAP (70 mg, 0.6 mmol) in anhydrous pyridine (4 mL) was added dropwise freshly distilled acetic anhydride (0.5 mL), and the mixture was stirred at room temperature for 1.5 h. The mixture was then poured into EtOAc (50 mL), washed with water, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, EtOAc/hexane = 1:2) affording the product as a colorless solid, 54 mg (80%): mp 127−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.31 (s, 3H), −0.02 (s, 3H), 0.60 (m, 6H), 0.79 (s, 9H), 0.95 (t, J = 7.8 Hz, 9H), 1.25 (s, 6H), 1.69 (s, 3H), 1.87 (s, 3H), 2.0 (m, 2H), 2.16 (s, 3H), 2.45 (m, 2H), 2.57 (s, 3H), 4.08 (d, J = 6.7 Hz, 1H), 4.26 and 4.32 (2d, J = 8.3 Hz, 2H), 4.66 (d, J = 1.8 Hz, 1H), 4.71 (dd, J = 6.2 and 10.1 Hz, 1H), 4.95 (d, J = 6.7 Hz, 1H), 5.75 (br d, J = 6.9 Hz, 2H), 6.08 (s, 1H), 6.13 (t, J = 8.3 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 7.31−7.62 (m, 11H), 7.74 (d, J = 7.2 Hz, 2H), 8.14 (d, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, 5.7, 7.1, 10.5, 14.6, 21.2, 21.9, 23.5, 25.9, 27.0, 37.6, 43.7, 47.1, 56.0, 58.8, 71.8, 72.6, 75.4, 75.5, 76.9, 79.2, 81.6, 84.6, 126.8, 127.3, 128.3, 128.7, 129.1, 130.5, 130.6, 132.5, 133.9, 134.5, 138.3, 140.6, 167.4, 169.6, 172.0, 175.0, 204.8; IR (neat) 3420 (br), 1720, 1660 cm^1; FAB HRMS m/z calcd for $C_{59}H_{79}NO_{14}Si_2$ (M + 1) 1082.5117, found 1082.5136.

10-Epipaclitaxel (25). To an ice-cooled solution of 2′-TBS-10-epi-7-TES-paclitaxel (**24**, 50 mg, 0.046 mmol) in anhydrous pyridine (3 mL) was added HF·Py (15 drops), and the mixture was stirred at room temperature for 3.5 h. After diluting with EtOAc (50 mL), the solution was washed sequentially with saturated $NaHCO_3$ solution, water, and brine. Drying (Na_2SO_4), removal of the solvent, and flash column chromatography (silica gel, EtOAc/hexane = 3:2 to 3:1) afforded the pure product as a colorless solid, 31 mg (79%): mp 173−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.46 (s, 3H), 1.59 (s, 3H), 1.79 (s, 3H), 2.13 (m, 1H), 2.15 (s, 3H), 2.20 (m, 2H), 2.38 (s, 3H), 2.42 (m, 1H), 3.14 (d, J = 7.1 Hz, 1H, exchangeable with D_2O), 3.56 (d, J = 5.9 Hz, 1H), 4.16 (d, J = 3.6 Hz, 1H, exchangeable with D_2O), 4.27 (d, J = 8.4 Hz, 1H), 4.37 (d, J = 8.4 Hz, 1H), 4.57 (m, 1H), 5.05 (dd, J = 3.03 and 6.18 Hz, 1H), 5.85 (dd, J = 2.2 and 9.1 Hz, 1H), 5.98 (d, J = 5.9 Hz, 1H), 6.10 (t, J = 8.3 Hz, 1H), 6.15 (s, 1H), 7.21 (d, J = 9.1 Hz, 1H), 7.34−7.85 (m, 11H), 7.79 (d, J = 7.1 Hz, 2H), 8.14 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 14.8, 20.9, 22.5, 22.7, 25.9, 33.4, 35.8, 43.3, 45.5, 54.6, 58.4, 69.8, 71.6, 73.6, 74.7, 75.8, 78.2, 81.8, 85.9, 127.0, 128.1, 128.6, 128.7, 128.8, 128.9, 130.1, 130.9, 131.8, 133.7, 133.8, 138.1, 138.3, 166.7, 169.1, 170.8, 171.8, 202.8; IR (neat) 3430 (br), 1730 (br), 1645 cm^{-1}; FAB HRMS m/z calcd for $C_{47}H_{51}NO_{14}$ (M + 1) 854.3388, found 854.3393; $[\alpha]^{20}_D$ −20° (c = 0.70, $CHCl_3$).

2′-TBS-10-deacetyl-10-epi-7-TES-9α-hydroxypaclitaxel (26). A solution of 2′-TBS-10-deacetyl-7-TES-10α-hydroxypaclitaxel (**22**, 65 mg, 0.063 mmol) in ethanol (95%, 8 mL) was treated with $NaBH_4$ (10 mg, 0.28 mmol), and the mixture was stirred at room temperature for 2.5 h. The solution was then diluted with EtOAc (50 mL) washed with water and brine, dried over Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, EtOAc/hexane = 2:3), yielding the product **26** as a colorless solid, 41 mg (63%): mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.28 (s, 3H), 0.01 (s, 3H), 0.74 (m, 6H), 0.81 (s, 9H), 1.03 (t, J = 7.8 Hz, 9H), 1.34 (s, 3H), 1.48 (s, 3H), 1.81 (s, 3H), 1.95 (m, 2H), 2.16 (s, 3H), 2.41 (m, 1H), 2.54 (s, 3H), 2.99 (br s, 1H, exch. with D_2O), 3.50 (d, J = 5.5 Hz, 1H), 4.24 (m, 2H), 4.35 (d, J = 8.3 Hz, 1H), 4.72 (d, J

= 1.7 Hz, 1H), 4.86 (m, 1H), 4.88 (d, J = 3.7 Hz, 1H), 4.97 (d, J = 8.9 Hz, 1H), 5.69 (br d, J = 7.3 Hz, 1H), 5.76 (d, J = 5.7 Hz, 1H), 6.15 (d, J = 7.3 Hz, 1H, exch. with D_2O), 6.24 (t, J = 8.2 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.31−7.67 (m, 1H), 7.79 (d, J = 7.0 Hz, 2H), 8.13 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.5, 6.8, 13.2, 13.6, 18.1, 23.3, 23.5, 25.5, 28.1, 35.4, 38.2, 43.2, 46.1, 46.3, 55.7, 72.2, 73.7, 74.7, 76.4, 78.0, 78.4, 81.9, 83.9, 126.5, 126.9, 127.8, 128.6, 128.7, 129.2, 130.1, 131.7, 132.4, 133.6, 133.7, 138.3, 166.7, 167.1, 169.5, 171.7; IR (neat) 3420 (br), 1715, 1650 cm^{-1}; FAB HRMS m/z calcd for $C_{57}H_{79}NO_{13}Si_2$ (M + 1) 1042.5168, found 1042.5181.

10-Deacetyl-10-epi-9α-hydroxypaclitaxel (27). To an ice-cooled solution of 2′-TBS-10-deacetyl-10-epi-7-TES-9α-hydroxypaclitaxel (**26**, 58 mg, 0.056) in anhydrous pyridine (3 mL) was added HF·Py (15 drops), and the mixture was stirred at room temperature for 3.5 h. After diluting with EtOAc (50 mL), the solution was washed sequentially with saturated $NaHCO_3$ solution, water, and brine. Drying (Na_2SO_4), removal of solvent, and flash column chromatography (silica gel, EtOAc/hexane = 3:2 to 3:1) afforded the pure product as a colorless solid, 32 mg (71%): mp 163−166 °C; ^{1}H NMR (300 MHz, MeOH-d_4) δ 1.31 (s, 3H), 1.48 (s, 3H), 1.73 (s, 3H), 1.80 (m, 1H), 2.04 (m, 2H), 2.13 (s, 3H), 2.34 (s, 3H), 2.45 (m, 1H), 3.53 (d, J = 5.3 Hz, 1H), 4.2 (br t, J = 8.6 Hz, 2H), 4.28 (br s, 1H), 4.73 (m, 1H), 4.78 (d, J = 4.4 Hz, 1H), 4.86 (br s, 1H), 5.0 (d, J = 8.6 Hz, 1H), 5.73 (m, 2H), 6.16 (t, J = 8.8 Hz, 1H), 7.33−7.65 (m, 11H), 7.87 (d, J = 7.3 Hz, 2H), 8.15 (d, J = 7.3 Hz, 2H), 8.72 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 13.7, 23.6, 24.4, 28.6, 36.4, 44.6, 47.4, 57.4, 57.5, 73.6, 74.6, 75.0, 75.4, 75.5, 77.8, 79.8, 83.4, 86.0, 128.5, 128.6, 128.9, 129.6, 129.7, 131.3, 131.5, 132.9, 134.5, 136.9, 140.1, 167.7, 170.5, 171.5, 174.8; IR (neat) 3420 (br), 1740, 1710, 1645 (br) cm^{-1}; FAB HRMS m/z calcd for $C_{45}H_{51}NO_{13}$ (M + 1) 814.3439, found 814.3476; $[\alpha]^{20}_D$ +14° (c = 0.80, MeOH).

2′-TBS-10-epi-7-TES-9α-hydroxypaclitaxel (28). To an ice-cooled solution of 2′-TBS-10-deacetyl-10-epi-7-TES-9α-hydroxypaclitaxel (**26**, 50 mg, 0.048 mmol) and DMAP (60 mg, 0.49 mmol) in anhydrous pyridine (3 mL) was added dropwise freshly distilled acetic anhydride (0.5 mL), and the mixture was stirred at room temperature for 1.5 h. The mixture was then poured into EtOAc (50 mL), washed with water, saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, EtOAc/hexane = 3:7), affording the product as a colorless solid, 40 mg (77%): mp 143−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.29 (s, 3H), −0.01 (s, 3H), 0.75 (m, 6H), 0.80 (s, 9H), 1.03 (t, J = 7.7 Hz, 9H), 1.31 (s, 3H), 1.58 (s, 3H), 1.81 (s, 3H), 1.88 (s, 3H), 2.10 (m, 2H), 2.17 (s, 3H), 2.41 (m, 2H), 2.54 (s, 3H), 3.45 (d, J = 5.4 Hz, 1H), 4.24 (d, J = 8.3 Hz, 1H), 4.36 (m, 2H), 4.69 (d, J = 1.8 Hz, 1H), 4.82 (br t, J = 9.4 Hz, 1H), 4.96 (d, J = 9.2 Hz, 1H), 5.39 (d, J = 9.4 Hz, 1H, exch. with D_2O), 5.69 (br d, J = 8.7 Hz, 1H), 5.77 (d, J = 5.4 Hz, 1H), 5.86 (br d, J = 1.7 Hz, 1H), 6.09 (t, J = 8.4 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 7.31−7.65 (m, 11H), 7.77 (d, J = 7.1 Hz, 2H), 8.12 (d, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.8, −5.1, 5.1, 5.9, 6.8, 12.7, 13.6, 18.0, 21.6, 22.8, 23.5, 25.5, 27.1, 35.3, 38.3, 43.3, 46.6, 46.9, 55.7, 72.0, 73.5, 74.8, 76.1, 76.5, 78.5, 82.0, 83.8, 126.3, 126.5, 126.9, 127.8, 128.6, 128.7, 128.8, 129.1, 130.1, 131.6, 131.8, 132.8, 133.6, 134.1, 138.2, 166.6, 167.1, 169.4, 169.6, 171.6; IR (neat) 3430, 1740, 1725, 1660 cm^{-1}; FAB HRMS m/z calcd for $C_{59}H_{82}NO_{14}Si_2$ (M + 1) 1084.5274, found 1084.5240.

10-Epi-9α-hydroxypaclitaxel (29). To an ice-cooled solution of 2′-TBS-10-epi-7-TES-9α-hydroxypaclitaxel (**28**, 55 mg, 0.051 mmol) in anhydrous pyridine (3 mL) was added HF·Py (15 drops), and the mixture was stirred at room temperature for 3 h. After diluting with EtOAc (50 mL), the solution was washed sequentially with saturated $NaHCO_3$ solution, water, and brine. Drying (Na_2SO_4), removal of solvent, and flash column chromatography (silica gel, EtOAc/hexane = 3:2 to 3:1) afforded the pure product as a colorless solid, 30 mg (70%): mp 169−172 °C; ^{1}H NMR (300 MHz, MeOH-d_4) δ 1.30 (s, 3H), 1.54 (s, 3H), 1.72 (s, 3H), 1.83 (s, 3H), 2.04 (m, 2H), 2.14 (s, 3H), 2.28 (m, 1H), 2.33 (s, 3H), 2.45 (m, 1H), 3.47 (d, J = 5.7 Hz, 1H), 4.18 (dd, J = 3.9 and 8.1 Hz, 2H), 4.45 (d, J = 3.93 Hz, 1H), 4.66 (br t, J = 8.31 Hz, 1H), 4.76 (d, J = 4.4 Hz, 1H), 4.97 (d, J = 8.8 Hz, 1H), 5.68 (d, J = 4.4 Hz, 1H), 5.72 (d, J = 5.4 Hz, 1H), 5.95 (br s, 1H), 6.09 (br t, J = 7.7 Hz, 1H), 7.31−7.69 (m, 11H), 7.84 (d, J = 7.2 Hz, 2H), 8.12 (d, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 13.7, 21.3, 23.6, 24.3, 28.4, 36.2, 38.6, 44.7, 47.4, 57.5, 73.1, 74.7, 75.2, 77.2, 77.8, 77.9, 78.8, 83.3, 85.8, 128.5, 128.6, 128.9, 129.6, 129.7, 131.3, 131.4, 132.9, 133.2, 134.1, 134.6, 135.6, 140.0, 167.6, 171.6, 171.9, 174.7, 192.5; IR (neat) 3400 (br), 1720 (br), 1640 (br) cm^{-1}; FAB HRMS m/z calcd for $C_{47}H_{53}NO_{14}$ (M + 1) 856.3544, found 856.3515; $[\alpha]^{20}_D$ +21° (c = 0.55, MeOH).

2′-TBS-10-deacetyl-7-TES-9α-Hydroxy-10-ketopaclitaxel (30). To a solution of 2′-TBS-10-deacetyl-10-epi-7-TES-9α-hydroxypaclitaxel (**26**, 50 mg, 0.048 mmol) and NMO (8 mg, 0.068 mmol) in anhydrous CH_2Cl_2 (10 mL) at room temperature was added TPAP (10 mg, 0.028 mmol), and the mixture was stirred for 2 h, after which another portion of TPAP (5 mg, 0.014 mmol) was added to the mixture and stirring was continued for 2 h. The solution was filtered, and the residue was washed with CH_2Cl_2 (10 mL). The combined filtrates were concentrated and purified by flash column chromatography (silica gel, EtOAc/hexane = 3:7), affording the product as a colorless solid. Yield, 40 mg (81%): mp 156−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.22 (s, 3H), 0.02 (s, 3H), 0.76 (q, J = 7.8 Hz, 6H), 0.86 (s, 9H), 1.07 (t, J = 7.8 Hz, 9H), 1.39 (s, 3H), 1.62 (s, 3H), 1.91 (s, 6H), 1.98 (m, 1H), 2.32 (m, 1H), 2.47 (m, 2H), 2.58 (s, 3H), 3.02 (d, J = 5.6 Hz, 1H), 4.18 (dd, J = 7.3 and 10.2 Hz, 1H), 4.30 and 4.41 (2d, J = 8.3 Hz, 2H), 4.76 (d, J = 1.9 Hz, 1H), 4.89 (d, J = 10.7 Hz, 1H), 4.96 (d, J = 8.8 Hz, 1H), 5.10 (d, J = 10.7 Hz, 1H, exchangeable with D_2O), 5.75 (dd, J = 1.9 and 8.9 Hz, 1H), 6.01 (d, J = 5.8 Hz, 1H), 6.29 (t, J = 8.7 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 7.36−7.72 (m, 11H), 7.82 (d, J = 7.1 Hz, 2H), 8.18 (d, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.4, 6.7, 12.1, 14.7, 18.1, 23.5, 25.5, 25.7, 28.1, 35.1, 38.1, 41.7, 46.6, 47.2, 55.6, 71.8, 73.5, 74.6, 79.1, 81.7, 81.9, 84.0, 126.5, 126.9, 127.9, 128.6, 128.7, 128.8, 128.9, 130.1, 131.8, 133.8, 134.0, 138.1, 142.6, 144.0, 166.7, 167.1, 169.7, 171.5, 201.3; IR (neat) 3480, 3430, 1750, 1725, 1685, 1660 cm^{-1}; FAB HRMS m/z calcd for $C_{57}H_{77}NO_{13}Si_2$ (M + 1) 1040.5012, found 1040.5014.

10-Deacetyl-9α-hydroxy-10-ketopaclitaxel (31). To an ice-cooled solution of 2′-TBS-7-TES-9α-hydroxy-10-ketopaclitaxel (**30**, 40 mg, 0.039 mmol) in anhydrous pyridine (3 mL) was added HF·Py (10 drops), and the mixture was stirred at room temperature for 3 h. After diluting with EtOAc (50 mL), the solution was washed sequentially with a saturated $NaHCO_3$ solution, water, and brine. Drying (Na_2SO_4), removal of solvent, and flash column chromatography (silica gel, EtOAc/hexane = 3:2 to 3:1) afforded the pure product as a colorless solid, 24 mg (77%): mp 184−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.45 (s, 3H), 1.57 (s, 3H), 1.78 (m, 1H), 1.87 (s, 3H), 2.24 (m, 1H), 2.31 (s, 3H), 2.49 (m, 2H), 2.92 (d, J = 5.3 Hz, 1H), 3.85 (t, J = 7.4 Hz, 1H), 4.20 (d, J = 8.2 Hz, 1H), 4.34 (d, J = 8.2 Hz, 1H), 4.44 (br s, 1H, exchangeable with D_2O), 4.65 (d, J = 3 Hz, 1H), 4.78 (d, J = 3 Hz, 1H, exchangeable with D_2O), 4.80 (br s, 1H), 4.90 (d, J = 6.9 Hz, 1H), 5.85 (dd, J = 1.95 and 9.15 Hz, 1H), 6.0 (d, J = 5.3 Hz, 1H), 6.17 (t, J = 8.2 Hz, 1H), 7.28 (d, J = 9.2 Hz, 1H), 7.33−7.85 (11), 7.79 (d, J = 7.1 Hz, 2H), 8.12 (7.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.6, 22.7, 24.1, 27.1, 35.6, 36.6, 41.3, 45.4, 47.9, 54.5, 71.1, 72.8, 73.1, 73.5, 76.2, 78.3, 82.2, 83.5, 84.3, 126.9, 127.1, 127.2, 127.3, 128.1, 128.7, 128.8, 130.1, 131.9, 133.6, 133.9, 138.2, 141.6, 142.4, 166.6, 169.8, 170.9, 171.4, 201.7; IR (neat) 3400 (br), 1725, 1710, 1680, 1630 cm^{-1}; FAB HRMS m/z calcd for $C_{45}H_{50}NO_{13}$ 812.3282 (M + 1), found 812.3272; $[\alpha]^{20}_D$ −44° (c = 0.3, MeOH).

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Supporting Information Available: Procedures for the formation of **5**, **6**, **11**, and **13** using H_2O as the proton source and at room temperature for the samarium diiodide-mediated reactions; the experimental procedures for the synthesis of **16** and **19**; ^1H and ^{13}C NMR spectra for 20 new compounds (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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