Synthesis of 13-*epi*-Taxol via a Transannular Delivery of a Borohydride Reagent

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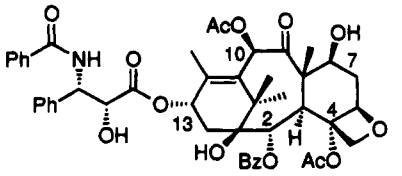
Taxol (1), isolated from the bark of the Pacific yew,[1] is the most important anticancer agent developed in the last decade for the treatment of ovarian and breast cancer.[2] Of particular interest are structure–activity relationships associated with the highly functionalized terpenoid skeletal system.[3] The conformation of taxol is cup-shaped, with the northern hemisphere functionalities C-7 and C-10 oriented on the convex side while the southern hemisphere functionalities at C-2, C-4, and the C-13 ester are located underneath on the concave side. In general, modifications to the northern hemisphere of the molecule[4–6] have little effect on biological activity, whereas modifications to the southern hemisphere[7,8] have a marked impact. A recent proposal by us suggests that a vital feature for biological activity of taxol analogues is the ability to undergo hydrophobic collapse in aqueous media, thus positioning the 4-acetate, the 2-benzoyl, and the 3′-phenyl groups in proximity of one another.[9] While the phenylisoserine side chain has been extensively modified for structure–activity relationship studies, the orientation of the side chain has not. We were interested in preparing 13-*epi*-taxol, in which the C-13 side chain would no longer be situated on the concave side of the tricyclic taxane nucleus, to evaluate this derivative's ability to enhance tubulin assembly.



Taxol (1)

Our plan was to invert the stereochemistry of the 13-hydroxyl group of a suitable baccatin III analogue and then attach the phenylisoserine side chain. Unfortunately, the C-13 hydroxyl group of baccatin III is positioned in a sterically congested region. We felt this could complicate standard displacement chemistry intended to invert the stereochemistry. Therefore, we decided to utilize a nearby hydroxyl group to assist in the delivery of a borohydride reducing agent to a 13-oxobaccatin III.[10] The reagent of choice for this strategy was tetramethylammonium triacetoxyborohydride [$Me_4NBH(OAc)_3$], initially utilized by Saksena for the intramolecular delivery of a hydride to β- and γ-substituted hydroxy ketones.[11] Additionally, Evans took advantage of this reagent for the stereoselective reduction of β-hydroxy ketones,[12] and several reports of directed reductions for α-[13] and γ-hydroxy ketones[14] soon followed. We wish to report a transannular delivery of [$Me_4NBH(OAc)_3$] from a *remote* hydroxyl group as the key step in the synthesis of 13-*epi*-taxol.[15]

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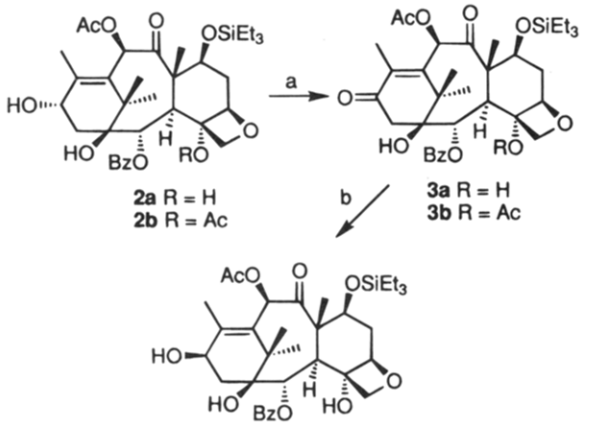
Scheme 1[a]



[a] (a) CrO_3, pyridine, CH_2Cl_2 25 °C (99%); (b) $Me_4NBH(OAc)_3$, CH_3CN/AcOH 1:1, 25 °C (78%).

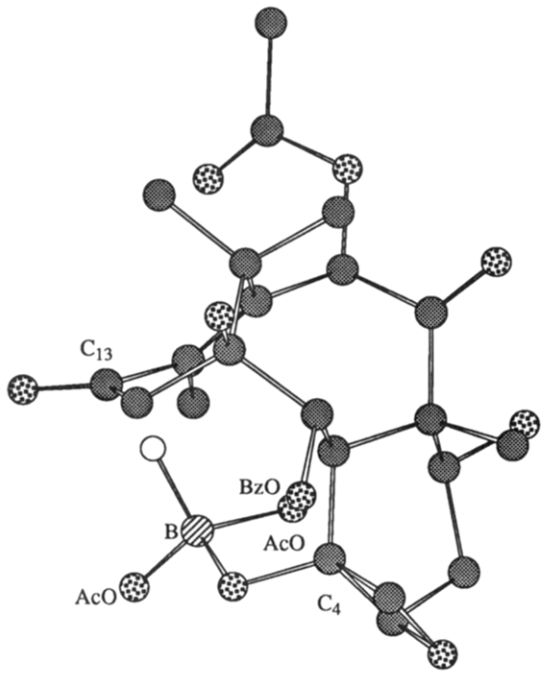


Figure 1. Ball-and-stick representation of the proposed delivery of hydride in compound **3a**. The entire diterpene skeleton is shown but extraneous hydrogen atoms and the C-2 benzoyl group have been removed for clarity; in addition, only the proximal oxygen atoms of the acetate groups in the borohydride reagent are explicitly shown.

Results

The synthesis started with 4-deacetyl-7-(triethylsilyl)-baccatin III (**2a**), readily available utilizing chemistry developed by our group (Scheme 1).[16] Oxidation of **2a** with chromium trioxide–pyridine provided ketone **3** in quantitative yield (99%). Treatment of this ketone in a 1:1 mixture of acetonitrile and acetic acid with three sequential additions of borohydride reagent (4.0 equiv) at 4 h intervals at 25 °C resulted solely in hydride delivery from the bottom face to give 4-deacetyl-7-(triethylsilyl)-13-*epi*-baccatin III (**4**) in 75% yield (Figure 1).

The inverted stereochemistry at C-13 was supported by the altered coupling constants between H_{13} and both $H_{14\alpha}$ and $H_{14\beta}$ (both $J_{13,14\alpha}$ and $J_{13,14\beta} \sim 8.0$ Hz for taxol; for **4**, $J_{13,14\beta} = 4.8$ Hz; $J_{13,14\alpha} = 9.6$ Hz), and a large chemical shift change for $H_{14\alpha}$ (δ 2.95 in **4** vs δ 1.80 in taxol; $H_{14\beta}$ remains near 1.8 ppm in **4**). Also, NOE difference experiments were performed supporting the same conclusion (Figure 2). Irradiation of H_{16} significantly enhanced $H_{14\beta}$, but H_{13} (and $H_{14\alpha}$) showed only minimal enhancement. In taxol, H_{16} and H_{13} show a strong NOE interaction in 2-dimensional NMR studies.[17] In **4**, irradiation of H_{13} strongly enhanced $H_{14\alpha}$, weakly enhanced $H_{14\beta}$, and strongly enhanced H_3 (this NOE is not observed in taxol).

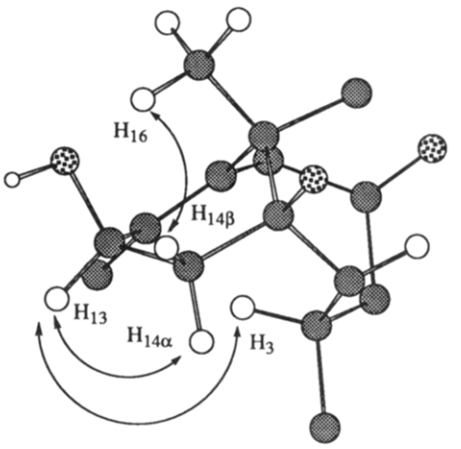


Figure 2. Important NOE's observed for compound **4**. Only the A and B rings of the diterpene skeleton are shown, with the C-10 acetyl group and nonessential hydrogen atoms removed for clarity.

To investigate that a transannular delivery was indeed taking place, two experiments were conducted. The first was treatment of 13-oxo-7-(triethylsilyl)baccatin III (**3b**), in which the 4-position is blocked by an acetyl group, to identical conditions as **3a**. However, only starting material was recovered after 48 h at 25 °C, suggesting that the 4-hydroxy group was necessary to deliver the hydride. This is in agreement with Saksena's profile for this reagent, since it cannot reduce ketones unless it is activated by a nearby hydroxyl group.[11a] Additionally, ketone **3a** was treated with sodium borohydride in 1:1 acetonitrile and methanol resulting in a 2:1 mixture of 4-deacetyl-7-(triethylsilyl)baccatin III (**2a**) and 4-deacetyl-7-(triethylsilyl)-13-*epi*-baccatin III (**4**). This result indicates that a standard borohydride reduction appears to favor approach from the less sterically congested top face.

The phenylisoserine side chain was attached to **4** using a slight modification of the method developed by Commerçon (Scheme 2).[18] Treatment of 13-*epi*-baccatin III **4** with oxazolidinecarboxylic acid **9**, DCC, and DMAP in toluene at 25 °C gave coupled product **5** in 88% yield. It is of note that these conditions are milder and the yields higher than those reported by Commerçon, perhaps indicating that the 13-hydroxyl in compound **4** is now more sterically accessible than in baccatin III. Finally, deprotection of the oxazolidine and triethylsilyl groups was accomplished simultaneously by treatment with formic acid. The crude material was immediately sub-

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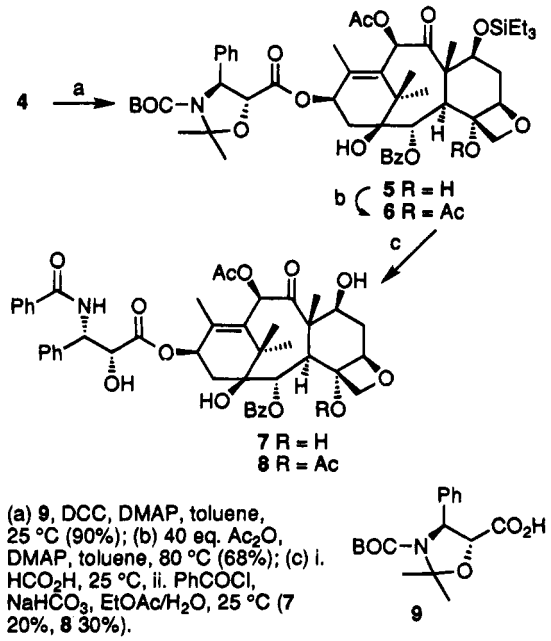
Scheme 2



(a) **9**, DCC, DMAP, toluene, 25 °C (90%); (b) 40 eq. Ac_2O, DMAP, toluene, 80 °C (68%); (c) i. HCO_2H, 25 °C, ii. PhCOCl, $NaHCO_3$, EtOAc/H_2O, 25 °C (**7** 20%, **8** 30%).

9

jected to Schotten-Baumann conditions,[19] yielding the desired 4-deacetyl-13-*epi*-taxol (**7**) in 19% yield over two steps.

Replacement of the acetate on the 4-hydroxyl was a cause for concern since previous results from several groups along with efforts toward the total synthesis of taxol indicated that reacylation could be problematic.[8ae,20] It was our hope that inversion of the C-13 stereocenter would decrease the steric congestion sufficiently to allow reacylation at the 4-position without further modification to the baccatin system. It was found that compound **5** could be acylated under the vigorous conditions of acetic anhydride (40 equiv) with DMAP (2.0 equiv) in toluene at 80 °C for 12 h. This treatment afforded a satisfactory 68% yield of **6**.

Simultaneous deprotection of the oxazolidine and triethylsilyl groups with formic acid followed by immediate treatment of the crude material with benzoyl chloride under Schotten–Baumann conditions yielded 13-*epi*-taxol **8** in 28% yield over two steps. The carbon spectrum of **8** was assigned, and the positions of the two acetate groups were determined to be C-4 and C-10, by an HMBC experiment. 13-*epi*-Taxol **8** contains only two acetates; the C-10 acetate is assigned from the correlation of H_{10} with the carbonyl at δ 170.7. Since C-1 and C-4 are both quaternary centers, there are unfortunately no long-range couplings from taxane protons to the other acetate carbonyl. However, C-4 was identified at 81.0 ppm by its characteristic long-range couplings to H_5 (4.94 ppm) and H_{20} (4.28 and 4.11 ppm), virtually identical to C-4 in taxol indicating that it is acylated. C-1 was identified at δ 82.8 by couplings to H_2 (5.60 ppm), H_3 (3.60 ppm), H_{14} (2.92 ppm), H_{16}, and H_{17}. This represents a downfield shift of 5 ppm from C-1 in taxol, which is attributed to the inversion of stereochemistry at C-13, not to acylation.

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Table 1. Activity of Taxol Derivatives 7 and 8 versus Taxol (1) in a Tubulin Binding Assay[a]

compound	tubulin assembly, ED_{50}[b]	ED_{50}/ED_{50} taxol
taxol (1)	1.04	–
7	>20	>19.6
8	>20	>19.6

[a] Tubulin at 1 mg/mLwas incubated with various concentrations of the compounds at 37 °C for 15 min in 0.5 mL of PEM buffer (0.1 M Pipes, 1 mM EGTA, 1mM $MgSO_4$, pH 6.9). Samples were centrifuged and the protein concentration in the supernatant was determined. [b] The concentration in mM which reduces the supernatant protein concentration by 50%.

Both 4-deacetyl-13-*epi*-taxol (**7**) and 13-*epi*-taxol (**8**) were compared directly to taxol by evaluation of the concentrations necessary for the polymerization of 50% of the tubulin present (ED_{50}) in solution.[21] The ratios of ED_{50} values for **7** and **8** versus that of taxol were both found to be greater than 19.6, indicating that the orientation of the C-13 side chain is essential for the biological activity of taxol.

Experimental Procedures

General.[21] Dichloromethane (CH_2Cl_2) and acetonitrile were distilled from calcium hydride prior to use. Toluene was distilled from sodium prior to use.

4-Deacetyl-13-oxo-7-(triethylsilyl)baccatin III (3). To a solution of 4-deacetyl-7-(triethylsilyl)baccatin III (**2**) (83 mg, 0.13 mmol) in CH_2Cl_2 (2.5 mL) and pyridine (2.5 mL) was added chromium trioxide (45 mg, 0.45 mmol). The reaction mixture was stirred for 90 min. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with water (25 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude oil was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to give 82 mg (99% yield) of 4-deacetyl-13-oxo-7-(triethylsilyl)-baccatin III (**3**) as a white solid: mp 145–150 °C; R_f 0.35 (hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.4 Hz, 2H), 6.54 (s, 1H), 5.68 (d, J = 5.9 Hz, 1H), 4.71 (dd, J = 9.4, 3.5 Hz, 1H,), 4.35 (d, J = 8.8 Hz, 1H), 4.07 (d, J = 8.8 Hz, 1H), 4.03 (dd, J = 11.2, 5.9 Hz, 1H), 3.58 (d, J = 19.5 Hz, 1H), 3.31 (s, 1H), 3.30 (d, J = 5.9 Hz, 1H), 2.63 (d, J = 19.5 Hz, 1H), 2.42 (m, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 1.99 (s, 1H), 1.95 (m, 1H), 1.58 (s, 3H), 1.27 (s, 3H), 1.24 (s, 1H), 1.19 (s, 3H), 0.90 (t, J = 8.0 Hz, 9H), 0.54 (q, J = 8.0 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 200.5, 199.9, 169.0, 166.7, 152.5, 139.7, 133.8, 129.9, 128.9, 128.7, 87.8, 81.0, 78.2, 75.9, 74.3, 73.6, 72.5, 58.9, 50.2, 43.6, 42.9, 37.0, 32.7, 20.8, 18.2, 13.7, 9.8, 6.7, 5.2; IR (neat) 3580, 3520, 3390, 2960, 2910, 2870, 1715, 1684, 1220, 1105, 1080, 901, 735 cm^{-1}; MS (FAB positive) m/z calcd for $C_{35}H_{49}O_{10}Si$ 657.3095, found 657.3084; 657 ([M + H]$^+$, 2), 550 (2), 457 (3), 199 (5), 145 (20), 115 (30), 105 (100), 87 (82), 59 (58); $[\alpha]^{20}_D$ −79.8 (c = 1.434, $CHCl_3$). Anal. Calcd for $C_{35}H_{48}O_{10}Si$: C, 64.00; H, 7.37. Found: C, 63.93; H, 7.50.

4-Deacetyl-7-(triethylsilyl)-13-*epi*-baccatin III (4). To a solution of of 4-deacetyl-13-oxo-7-(triethylsilyl)baccatin III (**3**) (373 mg, 0.57 mmol) in CH_3CN (6 mL) and anhydrous acetic acid (6 mL) was added $Me_4NBH(OAc)_3$ (600 mg, 2.2 mmol). The reaction mixture was stirred for 4 h at 25 °C. The addition of $Me_4NBH(OAc)_3$ (600 mg, 2.2 mmol) was repeated twice more at 4 h intervals. The reaction mixture was quenched slowly with saturated $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with saturated $NaHCO_3$ (3 × 50 mL), saturated NaCl (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude oil was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to give 282 mg (75% yield) of 13-*epi*-4-deacetyl-7-(triethylsilyl)baccatin III (**4**): mp 215–220 °C dec; R_f 0.12 (hexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.3 Hz, 2H), 6.44 (s, 1H), 5.66 (d, J = 6.3

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Hz, 1H), 4.74 (dd, J = 9.5, 3.7 Hz, 1H), 4.38 (d, J = 8.3 Hz, 1H), 4.30 (dd, J = 9.2, 4.4 Hz, 1H), 4.06 (d, J = 8.3 Hz, 1H), 4.02 (dd, J = 11.6, 6.0 Hz, 1H), 3.05 (d, J = 6.4 Hz, 1H), 3.00 (bs, 1H), 2.88 (dd, J = 14.9, 9.4 Hz, 1H), 2.42 (m, 1H), 2.21 (s, 3H), 2.16 (s, 3H), 1.95 (m, 2H), 1.59 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H), 0.91 (t, J = 7.7 Hz, 9H), 0.59 (q, J = 7.7 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 202.1, 169.4, 166.5, 140.6, 137.8, 133.8, 129.7, 129.3, 128.8, 86.8, 82.8, 80.8, 76.2, 74.4, 73.7, 72.5, 70.4, 58.4, 50.6, 42.1, 37.2, 37.1, 32.0, 21.0, 18.8, 18.6, 9.8, 6.8, 5.2; IR (neat) 3560, 2460, 2960, 2940, 2920, 1745, 1710, 1690, 1445, 1365, 1260, 1205, 1110, 1090, 1010, 960, 815, 735 cm^{-1}; MS (FAB positive) m/z calcd for $C_{35}H_{51}O_{10}Si$ 659.3252, found 659.3246; 659 ([M + H]$^+$, 1), 641 (2), 599 (3), 585 (5), 459 (4), 429 (4), 401 (1), 115 (30), 105 (98), 87 (100), 77 (40), 59 (81); $[\alpha]^{20}_D$ −113.1 (c = 0.685, $CHCl_3$). Anal. Calcd for $C_{35}H_{51}O_{10}Si$: C, 63.80; H, 7.65. Found: C, 63.56; H, 7.58.

13-*O*-((4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-phenyloxazolidin-5-yl)carbonyl)-4-deacetyl-7-(triethylsilyl)-13-*epi*-baccatin III (5). To a solution of compound **4** (500 mg, 0.76 mmol) in toluene (50 mL) at 25 °C was added oxazolidinecarboxylic acid **9** (268 mg, 0.83 mmol), DCC (251 mg, 1.2 mmol), and DMAP (46 mg, 0.38 mmol). The reaction mixture was stirred for 3 h at 25 °C, and then the solvent was removed under vacuum. The crude slurry was diluted with EtOAc (50 mL), filtered, and concentrated in vacuo. The crude oil was purified by flash chromatography (silica gel, hexane/EtOAc 2:1) to give 640 mg (88% yield) of coupled product **5**: mp 139−144 °C; R_f 0.27 (hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.8 Hz, 2H, 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.31 (m, 5H), 6.42 (s, 1H), 5.61 (d, J = 5.9 Hz, 1H), 5.48 (m, 1H), 4.95 (bm, 1H), 4.70 (bm, 1H), 4.51 (d, J = 5.0 Hz, 1H), 4.33 (d, J = 8.2 Hz, 1H), 4.08 (d, J = 8.0 Hz, 1H), 4.04 (dd, J = 10.1, 8.0 Hz, 1H), 3.14 (m, 1H), 3.07 (d, J = 5.9 Hz, 1H), 2.39 (m, 1H), 2.20 (s, 3H), 2.03 (s, 3H), 1.76 (s, 3H), 1.67 (s, 3H), 1.54 (s, 3H), 1.16 (bs, 9H), 0.89 (t, J = 7.8 Hz, 9H), 0.57 (q, J = 7.8 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.6, 169.3, 166.6, 151.5, 141.3, 140.8, 136.8, 133.7, 129.9, 128.7, 128.5, 127.6, 126.3, 96.7, 87.4, 82.2, 81.1, 80.9, 75.8, 74.1, 73.5, 73.3, 72.5, 63.9, 60.4, 58.6, 50.5, 42.0, 37.1, 34.3, 31.0, 28.0, 27.9, 26.8, 21.0, 20.9, 18.7, 14.2, 9.8, 6.7, 5.2; IR (neat) 3460, 2960, 2940, 1720, 1680, 1435, 1375, 1235, 1100, 901, 735 cm^{-1}; MS (FAB positive with Li) m/z calcd for $C_{52}H_{71}NO_{14}SiLi$ 968.4804, found 968.4813; 968 [M + Li]$^+$ (3), 647 (7), 581 (5), 459 (4), 327 (6), 222 (8), 206 (10), 176 (100), 133 (90), 104 (100), 85 (30), 54 (42); $[\alpha]^{20}_D$ −78.1 (c = 0.80, $CHCl_3$).

13-*O*-((4*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-phenyloxazolidin-5-yl)carbonyl)-7-(triethylsilyl)-13-*epi*-baccatin III (6). To a solution of 4-deacetyltaxol derivative **5** (463 mg, 0.48 mmol) in toluene (5 mL) at 80 °C was added Ac_2O (908 μL, 9.6 mmol) and DMAP (118 mg, 0.96 mmol). The reaction mixture was allowed to stir for 14 h at 80 °C. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel; hexane/EtOAc 2:1) to give 327 mg (68% yield) of acylated baccatin III **6**: mp 137−140 °C; R_f 0.45 (hexane/EtOAc 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.2 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.9 Hz, 2H), 7.26 (m, 5H), 6.44 (s, 1H), 5.61 (d, J = 6.9 Hz, 1H), 5.11 (dd, J = 9.9, 3.4 Hz, 1H), 4.99 (b, 1H), 4.96 (d, J = 8.2 Hz, 1H), 4.48 (d, J = 5.8 Hz, 1H), 4.44 (dd, J = 10.3, 6.8 Hz, 1H), 4.30 (d, J = 8.3 Hz, 1H), 4.12 (d, J = 8.3 Hz, 1H), 3.61 (d, J = 6.9 Hz, 1H), 2.87 (dd, 1H), 2.54 (m, 1H), 2.48 (s, 3H), 2.22 (s, 3H), 2.05 (s, 3H), 1.89 (m, 1H), 1.75 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.61 (m, 1H), 1.16 (s, 3H), 1.13 (bs, 9H), 1.04 (s, 3H), 0.91 (t, 9H), 0.57 (q, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 201.2, 171.1, 169.2, 167.0, 140.8, 136.8, 133.8, 130.1, 129.0, 128.7, 128.6, 127.7, 126.4, 96.7, 84.0, 82.5, 81.1, 76.2, 75.8, 72.7, 72.4, 72.3, 64.0, 60.4, 59.2, 47.0, 41.9, 37.3, 34.0, 30.8, 28.0, 22.1, 21.0, 18.9, 18.1, 9.7, 6.7, 5.3; IR (neat) 3480, 2970, 2930, 1725, 1370, 1240, 1100, 901, 735 cm^{-1}; MS (FAB positive) m/z calcd for $C_{54}H_{74}NO_{15}Si$ 1004.4828, found 1004.4805; 1004 [M + H]$^+$ (1), 683 (2), 623 (1); $[\alpha]^{20}_D$ −21.2 (c = 0.73, $CHCl_3$). Anal. Calcd for $C_{54}H_{73}NO_{15}Si$: C, 64.58; H, 7.33; N, 1.39. Found: C, 64.78; H, 7.38; N, 1.28.

4-Deacetyl-13-*epi*-taxol (7). A solution of compound **5** (170 mg, 0.18 mmol) in HCO_2H (5 mL) at 25 °C was stirred for 4 h. The solvent was removed under vacuum and the crude oil dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with saturated $NaHCO_3$ (3 × 50 mL), saturated NaCl (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude amino alcohol (ca. 0.18 mmol) was dissolved in a mixture of EtOAc (5 mL), H_20 (7 mL), and saturated $NaHCO_3$ (7 mL) at 25 °C. The mixture was stirred vigorously, and benzoyl chloride (20 mg, 0.14 mmol) was added. The reaction mixture was stirred an additional 20 min and then extracted with EtOAc (2 × 25 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL), saturated NaCl (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to give 28 mg (19% yield) of 4-deacetyl-13-*epi*-taxol (**7**): R_f 0.61 (EtOAc); IR (neat) 3450, 3010, 1715, 1265, 735, 695 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (d, J = 7.4 Hz, 2H), 7.84 (d, J = 7.1 Hz, 2H), 7.62−7.21 (m, 11H), 6.45 (s, 1H), 5.60 (d, 4.1H), 5.57 (d, 6.2H), 5.40 (dd, J = 9.4, 3.7 Hz, 1H), 4.76 (dd, J = 9.4, 3.0 Hz, 1H), 4.63 (d, J = 4.2 Hz, 1H), 4.25 (d, J = 8.1 Hz, 1H), 4.14 (d, J = 8.1 Hz, 1H), 3.87 (dd, J = 11.8, 6.0 Hz, 1H), 3.33 (dd, 1H), 3.05 (d, J = 6.8 Hz, 1H), 2.38 (m, 1H), 2.21 (s, 3H), 2.19 (m, 1H), 1.80 (s, 3H), 1.78 (m, 1H), 1.53 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.0, 169.3, 166.4, 140.5, 137.8, 133.8, 129.7, 129.2, 128.8, 86.7, 82.7, 80.8, 77.0, 76.2, 74.3, 73.7, 72.5, 70.3, 58.4, 50.6, 42.0, 37.2, 37.1, 32.0, 29.7, 21.0, 18.8, 18.6, 9.8, 6.7, 5.2; MS (FAB positive) m/z 834 [M + Na]$^+$ (25), 549 (4), 308 (10), 286 (8), 240 (8), 165 (13), 136 (28), 105 (56), 89 (60), 74 (100), 63 (97); HRMS (FAB positive) calcd 818.3346, found 818.3386.

13-*epi*-Taxol (8). Compound **6** (130 mg, 0.13 mmol) was dissolved in HCO_2H (5 mL) and stirred at 25 °C for 6 h . The solvent was removed under vacuum and the crude oil dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with saturated $NaHCO_3$ (3 × 50 mL) and saturated NaCl (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude amino alcohol (ca. 0.129 mmol) was dissolved in EtOAc (5 mL), H_2O (10 mL), and saturated $NaHCO_3$ (10 mL) at 25 °C followed by the addition of benzoyl chloride (27 mg, 0.193 mmol). The reaction mixture was stirred for 20 min at 25 °C and then extracted with EtOAc (2 × 25 mL). The organic layer was washed with saturated. NaCl (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, hexane/EtOAc 1:2) to give 30 mg (28% yield) of 13-*epi*-taxol (**8**): mp 165−171 °C; R_f 0.15 (hexane/EtOAc 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.3 Hz, 2H), 7.77 (d, J = 7.1 Hz, 2H), 7.62−7.28 (m, 11H), 6.99 (d, J = 8.9 Hz, 1H), 6.29 (s, 1H), 5.72 (dd, J = 9.0, 2.0 Hz, 1H), 5.60 (6.8, 1H), 5.06 (dd, J = 9.6, 3.6 Hz, 1H), 4.94 (d, 8.2H), 4.64 (d, J = 2.0 Hz, 1H), 4.38 (m, 1H), 4.28 (d, J = 8.4 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 3.61 (d, J = 6.9 Hz, 1H), 3.41 (bs, 1H), 2.92 (dd, 1H), 2.56 (m, 2H), 2.34 (s, 3H), 2.27 (s, 3H), 1.93 (s, 3H), 1.65 (s, 3H), 1.25 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.0, 169.3, 166.4, 140.5, 137.8, 133.8, 129.7, 129.2, 128.8, 86.7, 82.7, 80.8, 76.2, 74.4, 73.7, 72.5, 70.3, 58.4, 50.6, 42.0, 37.2, 37.1, 32.0, 29.7, 21.0, 18.8, 18.6, 9.8, 6.7, 5.2; IR (neat) 3500, 3415, 3030, 1720, 1655, 1260, 1100, 1060, 735, 699 cm^{-1}; MS (FAB positive) m/z calcd for $C_{47}H_{52}NO_{14}$ 854.3388, found 854.3383; 854 [M + H]$^+$ (1), 569 (1), 509 (1), 307 (2), 286 (3), 216 (2), 154 (20), 136 (20), 89 (60), 77 (70), 63 (100); $[\alpha]^{20}_D$ −34.8 (c = 0.22, $CHCl_3$).

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Supplementary Material Available: The proton and carbon NMR spectra of compounds **4**, **5**, **7**, and **8** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the micofilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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