Notes

Efficient Synthesis of the 3′-Phenolic Metabolite of Paclitaxel

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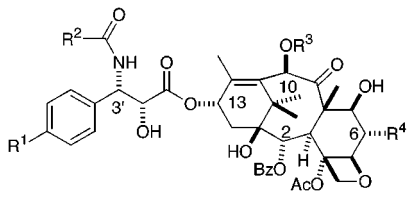
Paclitaxel (**1**; Taxol) and docetaxel (**2**; Taxotere) have emerged as two of the most effective antitumor agents in a variety of malignancies.[1−5] Acting via a similar mechanism of action, both these drugs bind to tubulin, leading to microtubule stabilization, mitotic arrest, and subsequent cell death. Despite the great similarity in the chemical structures and their mode of action, the metabolic profile of paclitaxel and docetaxel was found to be quite different.[6,7] These taxanes are metabolized in the liver by the cytochrome P-450 enzymes and are eliminated in the bile. Extensive in vitro and in vivo studies in animals and humans have resulted in the isolation and identification of the various metabolites of paclitaxel and docetaxel.[6,7] Thus, the two major human metabolites of paclitaxel were found to be 6-α-hydroxypaclitaxel (**3**) and the phenolic 3′-(4-hydroxyphenyl)paclitaxel **4** derivative (Figure 1), whereas the primary metabolites of docetaxel results from hydroxylation of the *tert*-butyl group of the C3′ carbamate. Because of the limited availability of pure metabolites, several research groups including ours have undertaken synthesis of the various paclitaxel and docetaxel metabolites.[8−11] In a recent project, however, we needed to synthesize multigram quantities of the 3′-phenolic metabolite **4** of paclitaxel, and as our earlier reported method lacked efficiency in terms of larger scale synthesis, we decided to explore and develop an alternative pathway more suited to our present requirement. The details of the synthesis thus undertaken are reported herein.



Paclitaxel (**1**) R^1 = H; R^2 = Ph; R^3 = Ac; R^4 = H
Docetaxel (**2**) R^1 = H; R^2 = *t*-BuO; R^3 = H; R^4 = H
3, R^1 = H; R^2 = Ph; R^3 = Ac; R^4 = OH
4, R^1 = OH; R^2 = Ph; R^3 = Ac; R^4 = H

Figure 1. Structures of paclitaxel, docetaxel, and paclitaxel metabolites.

The Sharpless asymmetric aminohydroxylation protocol has been shown to be among the most efficient methods for the large scale synthesis of enantiomerically pure 3-phenylisoserine side chain of taxanes.[12a] We therefore decided to employ the above aminohydroxylation reaction to synthesize the required 4-hydroxy substituted phenylisoserine side chain precursor followed by its coupling with a baccatin III derivative to form the target phenolic metabolite of paclitaxel.

Toward this end, Wittig olefination of commercially available substrates, 4-benzyloxybenzaldehyde (**5**) and (carboethoxymethylene)triphenylphosphorane, provided the corresponding adduct **6** (Scheme 1) in high yield and good *E*-selectivity (*E*/*Z* = 9/1). This cinnamate derivative **6**, when subjected to the Sharpless aminohydroxylation reaction under known conditions,[12] formed the expected 3-(4-benzyloxyphenyl)isoserinate derivative **7** in good yield and high enantiomeric excess (94% by HPLC). For the determination of the enantiomeric excess achieved in this reaction, *ent*-**7**, the enantiomer of compound **7** was prepared as well.

Selective deacylation of the acetamide functionality and subsequent Boc-protection of the amine yielded the corresponding *N*-Boc derivative **8** in 90% yield. Acetonide protection of the amino alcohol moiety to form the fully protected oxazolidine carboxylate **9**, followed by hydrolysis of the ester linkage, afforded the required C13 side chain precursor amino acid **10** in good overall yield. Esterification of the acid **10** with 7-Cbz-baccatin III (**11**)[13] under standard conditions[14] uneventfully afforded the

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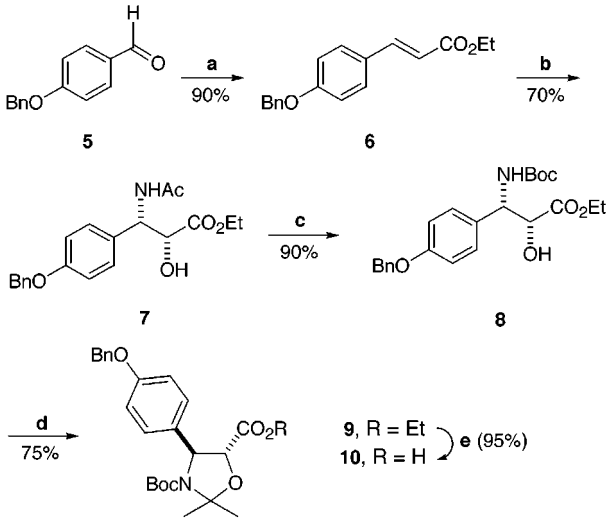
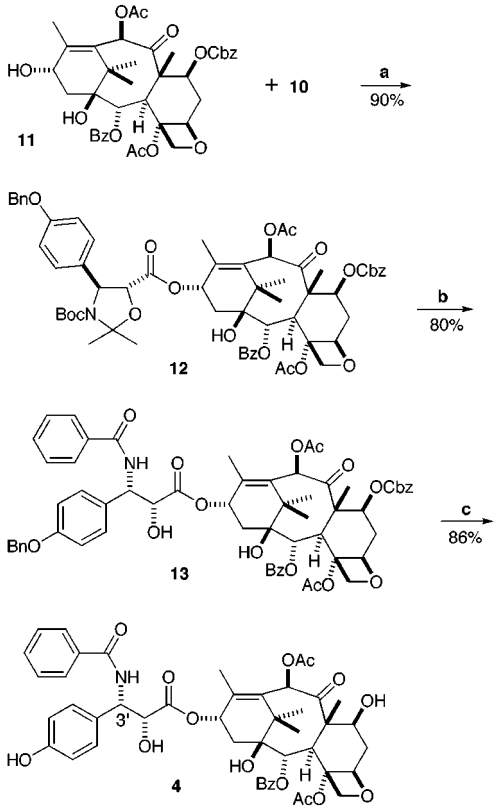
Scheme 1[a]



[a] (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; [b] $K_2[OsO_2(OH)_4]$, LiOH, $(DHQ)_2$-PHAL, AcNHBr, MeCN−H_2O, 4 °C; [c] (i) HCl−EtOH, 90 °C; (ii) Boc_2O, $NaHCO_3$, THF; [d] $Me_2C(OMe)_2$, PPTS, toluene, 90 °C; [e] LiOH, MeOH−THF−H_2O.

Scheme 2[a]



[a] DCC, DMAP, toluene, 90 °C; [b] (i) HCO_2H; (ii) PhCOCl, aq $NaHCO_3$, EtOAc; [c] 10% Pd−C, H_2, MeOH.

coupled product **12** (Scheme 2) in 90% yield. Subsequent formic acid assisted simultaneous removal of the *N*,*O*-acetonide and the Boc-protecting group, followed by reaction of the resulting free amine with benzoyl chloride, formed the diprotected taxane derivative **13** in 80% overall yield. Finally, a one-flask reductive debenzylation of the *O*7-Cbz and 3′-phenolic hydroxy protecting groups cleanly afforded the required paclitaxel metabolite **4** in high yield.

The above reaction sequence is easily amenable to large scale synthesis and by following the described route we could efficiently prepare multigram quantities of the target paclitaxel derivative **4** in high overall yield.

Experimental Section[15]

Ethyl *E*-(4-Benzyloxy)cinnamate (6). A solution of 4-benzyloxybenzaldehyde (50.0 g, 0.236 mol) and (carboethoxymethylene)triphenylphosphorane (98.5 g, 0.282 mol) in anhydrous CH_2Cl_2 (650 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel. Elution with 10% EtOAc/hexane afforded the *E*-cinnamate [R_f (10% EtOAc/hexane): *Z*-**6** = 0.58; *E*-**6** = 0.47], which was crystallized from EtOAc−hexane providing the pure product **6** as a white solid (60 g, 90%): mp 65−67 °C; IR (KBr) 1712, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 4.25 (q, J = 7.0 Hz, 2H), 5.09 (s, 2H), 6.31 (d, J = 15.8 Hz, 1H), 6.97 (d, J = 8.6 Hz, 2H), 7.45−7.28 (m, 5H), 7.47 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.32, 160.49, 144.20, 136,46, 129.72, 128,67, 128.16, 127.48, 127.42, 115,87, 115.18, 70.04, 60.35, 14.38; HRMS (FAB+) *m*/*z* calcd for $C_{18}H_{19}O_3$ [MH^+]: 283.1334, found 283.1334.

Ethyl (2*R*,3*S*)-3-(Acetylamino)-3-[4-(benzyloxy)phenyl]-2-hydroxypropanoate (7). In 335 mL of an aqueous solution of LiOH·H_2O (7.59 g, 181 mmol) was dissolved $K_2[OsO_2(OH)_4]$ (2.6 g, 7.1 mmol, 4 mol %) with stirring. After addition of t-BuOH (665 mL), $(DHQ)_2$PHAL (6.91 g, 8.87 mmol, 5 mol %) was added, and the mixture was stirred for 10 min to give a clear solution. The solution was then diluted with additional water (665 mL) and immersed in a cooling bath set to 0 °C. A solution of the cinnamate **6** (50.0 g, 177 mmol) in acetonitrile (335 mL) was then added to the mixture, followed by addition of *N*-bromoacetamide (26.91 g, 195.1 mmol) in one lot, and the mixture was vigorously stirred between 0 and 5 °C. After stirring for 24 h, the reaction mixture was treated with Na_2SO_3 (89 g) and stirred at room temperature for 30 min, and ethyl acetate (1 L) was added to it. The organic layer was separated, and the water layer was extracted three times with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel. Elution with EtOAc/hexane (1:1) afforded 10% of the diol byproduct followed by 40 g (70%) of the required amino alcohol **7** as a white crystalline solid: mp 124−126 °C; IR (KBr) 3359, 1716, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 2.02 (s, 3H), 3.26 (d, J = 4.0 Hz, 1H, exchangeable with D_2O), 4.28−4.33 (m, 2H), 4.49 (dd, J = 3.6, 2.1 Hz, 1H), 5.08 (s, 2H), 5.51 (d, J = 9.2 Hz, 1H), 6.24 (d, J = 9.2 Hz, 1H, exchangeable with D_2O), 6.98 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.29−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.94, 169.65, 158.32, 136.87, 131.30, 128.61, 128.21, 128.00, 127.44, 127.16, 114.91, 114.64, 73.38, 69.99, 62.44, 54.07, 23.13, 14.10; HRMS (FAB+) *m*/*z* calc′d for $C_{20}H_{24}NO_5$ [MH^+]: 358.1654, found 358.1647; $[\alpha]^{22}_D$ +33 (*c* = 1.0, $CHCl_3$). HPLC: Chiralcel ODH, 40% *i*-PrOH/hexane, 0.5 mL/min, 254 nm, retention time for the major isomer = 7.5 min, 94% ee; retention time for the minor isomer = 6.8 min.

Ethyl (2*S*,3*R*)-3-(Acetylamino)-3-[4-(benzyloxy)phenyl]-2-hydroxypropanoate (*ent*-7). $K_2[OsO_2(OH)_4]$ (8.12 mg., 0.022 mmol, 4% equiv) was dissolved in a 5 mL of aqueous solution of LiOH (24 mg, 0.56 mmol). After addition of t-BuOH (10 mL), $(DHQD)_2$PHAL (21 mg, 0.026 mmol) was added to give a cloudy solution. The reaction mixture was then diluted with water (10 mL) and subsequently cryocooled in a bath set to 0 °C and stirred for 30 min at that temperature. Then, a solution of cinnamate

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6 (150 mg, 0.53 mmol) in acetonitrile (5 mL) was added to the mixture, followed by the addition of *N*-bromoacetamide (88 mg, 0.63 mmol) in one portion. More water (3−5 mL) was poured into the reaction mixture, and stirring was continued for 22 h at 0 °C. Then the mixture was treated with solid Na_2SO_3 (300 mg) and stirred at room temperature for 30 min. The reaction mixture was extracted with EtOAc three times. The combined extracts were washed with water and brine and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the crude product was immediately purified by flash column chromatography on silica gel (EtOAc/hexane = 1:1) to give 96 mg (51%) of a colorless solid product: mp 124−126 °C; ^{1}H NMR and ^{13}C NMR ($CDCl_3$) were identical to **7**. HRMS (FAB+) *m*/*z* calcd for $C_{20}H_{24}NO_5$ [MH^+]: 358.1654, found 358.1670; $[\alpha]^{23}_D$ −32 (*c* = 1.0, $CHCl_3$). HPLC: Chiralcel ODH, 40% *i*-PrOH/hexane, 0.5 mL/min, 254 nm, retention time for the major isomer = 6.8 min, >99% ee; retention time for the minor isomer = 7.5 min.

Ethyl (2*R*,3*S*)-3-(*tert*-Butoxycarbonylamino)-3-[4-(benzyloxy)phenyl]-2-hydroxypropanoate (8). To a solution of the amino alcohol **7** (22.0 g, 61.6 mmol) in ethanol (200 mL) was added 50 mL of EtOH/HCl (saturated) and the resulting solution refluxed at 90 °C for 4 h. Ethanol was removed under reduced pressure, and the resulting amine hydrochloride was dried under vacuum for 1 h. The salt was then taken up into anhydrous THF (100 mL), and solid $NaHCO_3$ (52 g, excess) was added to it. The resulting heterogeneous mixture was stirred for 5 min followed by addition of Boc-anhydride (20.18 g, 92.46 mmol, 1.5 equiv). The mixture was then stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc (500 mL), quenched with 10% HCl, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo, and the residue was purified by column chromatography on silica gel. Elution with EtOAc/methylene chloride (1:19) furnished 23 g (90%) of the *N*-Boc-amino alcohol **8** as a white solid: mp 130−131 °C; IR (KBr) 3384, 1718, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.40 (s, 9H), 3.27 (br d, *J* = 3.4 Hz, 1H), 4.20−4.35 (m, 2H), 4.40 (br s, 1H), 5.04 (s, 2H), 5.17 (d, *J* = 8.7 Hz, 1H), 5.40 (d, *J* = 9.3 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.25−7.44 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.99, 158.31, 155.11, 136.99, 131.77, 128.61, 127.99, 127.48, 114.89, 79.76, 73.69, 70.04, 62.42, 55.49, 28.30, 14.15; HRMS (FAB+) *m*/*z* calcd for $C_{23}H_{30}NO_6$ [MH^+]: 416.2073, found 416.2085. [$[\alpha]^{22}_D$ +16.4 (*c* = 1.05, $CHCl_3$).

Ethyl (4*S*,5*R*)-4-[4-(Benzyloxy)phenyl]-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine-5-carboxylate (9). A solution of the amino alcohol **8** (21.0 g, 50.6 mmol), 2,2-dimethoxypropane (18.64 mL, 151.8 mmol), and a catalytic amount of pyridinium *p*-toluenesulfonate (100 mg) in toluene (100 mL) was stirred at 90 °C for 8 h. Removal of the solvent under vacuum and purification of the resulting oily residue by flash column chromatography (silica gel) using EtOAc/hexane (1:19) as eluent afforded the pure oxazolidine derivative **9** (17 g, 75%) as a light yellow viscous liquid: IR (KBr)1756, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (br s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.72 (s, 3H), 1.79 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.47 (d, *J* = 5.4 Hz, 1H), 5.04 (br s, 1H), 5.10 (s, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 7.22−7.48 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.20, 158.12, 151.58, 136.89, 133.44, 128.50, 127.88, 127.51, 127.39, 114.80, 96.37, 81.01, 80.09, 69.96, 63.32, 61.55, 28.06, 26.56, 25.83, 14.08. HRMS (FAB+) *m*/*z* calcd for $C_{26}H_{34}NO_6$ [MH^+]: 456.2386, found 456.2371; $[\alpha]^{22}_D$ −10. (*c* = 1.0, $CHCl_3$).

(4*S*,5*R*)-4-[4-(Benzyloxy)phenyl]-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine-5-carboxylic Acid (10). To an ice-cooled solution of the ester **9** (19.8 g, 43.5 mmol) in 1.7 L of THF/MeOH/water (10:5:4) was added solid $LiOH·H_2O$ (3.65 g, 87.0 mmol, 2.0 equiv) in small portions, and the resulting mixture was stirred for 2 h at 22 °C. The reaction mixture was then diluted with EtOAc (2 L) acidified with dil HCl (pH = 5), and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue dried for 12 h under high vacuum to yield the oxazolidine carboxylic acid **10** (17.7 g, 95%) as a white solid and was used as such without further purification: mp 111−112 °C; IR (KBr) 2977, 1725, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (br s, 9H), 1.75 (s, 3H), 1.80 (s, 3H), 4.54 (d, *J* = 5.3 Hz, 1H), 5.09 (s, 3H), 6.98 (1/2 ABq, *J* = 8.6 Hz, 2H), 7.50−7.25 (series of m, 7H), 8.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.98, 158.30, 151.66, 136,88, 133.14, 128.63, 128.04, 127.58, 127.53, 114.95, 96.86, 80.55, 70.07, 63.38, 28.13, 26.62, 25.97; HRMS (FAB+) *m*/*z* calcd for $C_{24}H_{30}NO_6$ [MH^+]: 428.2073, found 428.2051; $[\alpha]^{22}_D$ +2.4 (*c* = 1.0, $CHCl_3$).

7-Benzyloxycarbonylbaccatin III 13-*O*-[(4*S*,5*R*)-4-{4-(Benzyloxy)phenyl}-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidine-5-carboxylate] (12). To a stirred solution of 7-Cbz-baccatin III (**11**)[12] (2.81 g, 3.90 mmol) and the oxazolidine carboxylic acid **10** (2.50 g, 5.86 mmol) in dry toluene (60 mL) were added DCC (1.43 g, 6.95 mmol) and a catalytic amount of DMAP (40 mg). The resulting mixture was stirred at 90 °C for 90 min, when TLC monitoring revealed completion of the reaction. Toluene was then removed under reduced pressure, and the residue was purified by silica gel flash column chromatography. Elution with EtOAc/methylene chloride (1:19) afforded the pure coupled product **12** as a white solid (4.0 g, 90%): mp 153−156 °C; IR (KBr) 3428, 3326, 1746, 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.23 (s, 6H), 1.72 (s, 3H), 1.75 (s, 3H), 1.79 (s, 3H), 1.89 (s, 3H),1.95−1.98 (m, 1H), 2.05 (s, 3H), 2.21 (s, 3H), 2.23 (br s, 2H), 2.58−2.65 (m, 1H), 3.96 (d, *J* = 7.0 Hz, 1H), 4.13 (d, *J* = 9.3 Hz, 1H), 4.30 (d, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 6.7 Hz, 1H), 4.93 (d, *J* = 8.5 Hz, 1H), 5.04 (br s, 1H), 5.13 (s, 2H), 5.19 (ABq, *J* = 12.0 Hz, 1H), 5.26 (ABq, *J* = 11.9 Hz, 1H), 5.55 (dd, *J* = 10.7, and 7.1 Hz, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 6.27 (t, *J* = 8.6 Hz, 1H), 6.43 (s, 1H), 7.01 (d, *J* = 8.1 Hz, 2H), 7.28−7.58 (m, 15H), 8.0 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.67, 170.03, 168.95, 166.96, 158.40, 154.12, 151.62, 141.12, 136.81, 135.37, 133.85, 132.83, 129.10, 128.79, 128.68, 128.65, 128.46, 128.34, 128.14, 127.74, 127.58, 115.13, 96.83, 83.97, 81.07, 80.53, 79.01, 77.29, 76.23, 75.37, 75.29, 74.49, 71.30, 70.17, 63.71, 50.02, 47.01, 43.26, 35.48, 33.31, 28.11, 21.45, 21.21, 20.83, 14.72, 10.77; HRMS (CI) *m*/*z* calcd for $C_{63}H_{75}N_2O_{18}$ [$M^+ + NH_4$]: 1147.5015, found 1147.4991; $[\alpha]^{22}_D$ −34 (*c* = 1.0, $CHCl_3$).

7-Benzyloxycarbonyl-3′-(4-benzyloxyphenyl)-3′-dephenylpaclitaxel (13). The baccatin III-coupled product **12** (7.80 g, 6.92 mmol) was dissolved in 96% formic acid (300 mL) and stirred for 2 h at 22 °C. Excess formic acid was removed under reduced pressure at room temperature and the residual solid dried under high vacuum for 12 h. The crude free amine salt was then dissolved in EtOAc (150 mL), and saturated aq $NaHCO_3$ solution (200 mL) was added to it carefully. To the resulting solution was added benzoyl chloride (0.88 mL, 7.6 mmol, 1.1 equiv) slowly at 0 °C. After stirring for 5 min, TLC examination indicated the disappearance of starting material. The reaction mixture was diluted with more EtOAc (100 mL), and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography. Gradient elution with EtOAc/methylene chloride (1:9 to 1:5) furnished the protected paclitaxel derivative **13** as a white solid (6.1 g, 80%): mp 153−156 °C; IR (KBr) 3432, 2949, 1739, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.24 (s, 3H), 1.83 (s, 3H), 1.91 (s, 3H), 1.94−2.01 (m, 1H), 2.21 (s, 3H), 2.35−2.38 (m, 2H), 2.40 (s, 3H), 2.58−2.66 (m, 1H), 3.70 (br d, *J* = 3.9 Hz, 1H), 3.96 (d, *J* = 7.0 Hz, 1H), 4.20 (d, *J* = 8.5 Hz, 1H), 4.33 (d, *J* = 8.5 Hz, 1H), 4.78 (br s, 1H), 4.96 (d, *J* = 9.0 Hz, 1H), 5.09 (s, 2H), 5.19 (ABq, *J* = 12.0 Hz, 1H), 5.26 (ABq, *J* = 11.9 Hz, 1H), 5.52 (dd, *J* = 10.7 and 7.1 Hz, 1H), 5.70 (d, *J* = 7.2 Hz, 1H), 5.76 (d, *J* = 8.4 Hz, 1H), 6.19 (t, *J* = 8.6 Hz, 1H), 6.43 (s, 1H), 7.03 (m, 3H), 7.34−7.54 (m, 17H), 7.61 (m, 1H), 7.77 (d, *J* = 7.6 Hz, 2H), 8.13 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.57, 172.49, 170.35, 168.96, 167.23, 166.70, 158.61, 154.07, 136.68, 135.24, 133.64, 133.01, 131.84, 130.30, 130.09, 128.67, 128.60, 128.53, 128.39, 128.37, 128.02, 127.43, 127.05, 115.15, 83.82, 80.86, 78.41, 76.85, 75.44, 75.30, 74.28, 73.26, 72.01, 70.11, 70.02, 56.11, 54.54, 46.93, 43.19, 26.49, 22.47, 20.92, 20.77, 14.64, 10.66; HRMS (FAB+) *m*/*z* calc′d for $C_{62}H_{64}NO_{17}$ [MH^+]: 1094.4174, found 1094.4183; $[\alpha]^{22}_D$ −52 (*c* = 1.0, $CHCl_3$).

3′-Dephenyl-3′-(4-hydroxyphenyl)paclitaxel (4). The diprotected paclitaxel derivative **13** (4.80 g, 4.39 mmol) was dissolved in dry methanol (50 mL), and a catalytic amount of 10% Pd/C was added to it. The resulting heterogeneous mixture was stirred at 22 °C for 24 h under a hydrogen atmosphere at atmospheric pressure. The reaction mixture was then filtered through a small

pad of silica gel, solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography. Elution with EtOAc/methylene chloride (1:5) afforded a white solid, which was further purified by crystallization (methylene chloride/hexane) affording the pure 3′-phenolic metabolite of paclitaxel **4** as a white solid (3.3 g, 86%): mp 192−194 °C (dec) [lit.[8] mp 184−189 °C]; IR (KBr) 3416, 1728, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.24 (s, 3H), 1.69 (s, 3H), 1.79 (s, 3H), 1.80−1.93 (m, 2H), 2.24 (s, 3H), 2.26−2.37 (m, 2H), 2.38 (s, 3H), 2.46 (br d, J = 3.7 Hz, 1H), 2.48−2.60 (m, 1H), 3.55 (d, J = 5.3 Hz, 1H), 3.80 (d, J = 7.0 Hz, 1H), 4.20 (1/2 ABq, J = 8.6 Hz, 1H), 4.31 (1/2 ABq, J = 8.5 Hz, 1H), 4.38−4.47 (m, 1H), 4.75 (dd, J = 5.1, 2.70 Hz, 1H), 4.95 (d, J = 7.6 Hz, 1H), 5.23 (s, 1H), 5.62−5.75 (m, 2H), 6.22 (t, J = 9.2 Hz, 1H), 6.27 (s, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.7 Hz, 1H), 7.28−7.64 (m, 8H), 7.74 (1/2 ABq, J = 7.1 Hz, 2H), 8.13 (1/2 ABq, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.68, 172.59, 171.33, 170.75, 167.92, 166.84, 156.31, 141.79, 133.77, 133.45, 133.12, 132.09, 130.13, 129.11, 128.72, 128.27, 127.15, 115.85, 84.37, 81.08, 78.77, 77.29, 75.63, 74.82, 73.34, 72.05, 58.43, 54.99, 45.84, 43.12, 35.70, 26.73, 22.55, 21.70, 20.88, 14.77, 9.65; HRMS (FAB+) m/z calcd for $C_{47}H_{52}NO_{15}$ $[MH^+]$: 870.3337, found 870.3318; $[\alpha]^{22}_D$ −53 (c = 1.0, $CHCl_3$) {lit.[8] $[\alpha]^{22}_D$ −54 (c = 0.70, $CHCl_3$)}.

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Supporting Information Available: Proton and carbon NMR spectra of compounds **6**, **7**, **8**, **9**, **10**, **12**, **13**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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